Difficult Decisions in Surgery:
An Evidence-Based Approach

Christopher L. Skelly
Ross Milner *Editors*

Difficult Decisions in Vascular Surgery

An Evidence-Based Approach

Springer

Difficult Decisions in Surgery: An Evidence-Based Approach

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The complexity of decision making in any kind of surgery is growing exponentially. As new technology is introduced, physicians from nonsurgical specialties offer alternative and competing therapies for what was once the exclusive province of the surgeon. In addition, there is increasing knowledge regarding the efficacy of traditional surgical therapies. How to select among these varied and complex approaches is becoming increasingly difficult. These multi-authored books will contain brief chapters, each of which will be devoted to one or two specific questions or decisions that are difficult or controversial. They are intended as current and timely reference sources for practicing surgeons, surgeons in training, and educators that describe the recommended ideal approach, rather than customary care, in selected clinical situations.

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Preface

Vascular surgeons are bound together through the shared experience of vascular surgical training. As surgical residents, we operate, we labor, we train, we study, we treat, and we endure clinical challenges that shape and ultimately solidify our decision-making skills as a natural extension of our selves. As surgeons who have to make snap decisions because of life-threatening vascular emergencies, the skills of surgical decision making are a crucial talent to master. Over the course of the past three decades, the endovascular era disrupted vascular surgery in a way that has changed the profession forever. The endovascular innovation also disrupted the process of clinical decision making. As a result, many surgeons who had trained in the pre-endovascular era were faced with new tools and techniques that were not a natural extension of their clinical training and therefore not a natural extension of themselves. A new level of complexity was added to the snap decision-making process. Conversely, younger surgeons who came into practice after the establishment of endovascular surgery may lack the open approach skill set or the older tools to adequately include in their clinical decision making. Clinical vascular decision making had effectively been changed forever.

The objectives of this book are to explain the process of decision making, both on the part of the physician and on the part of the patient; to discuss specific clinical problems in vascular surgery; and to provide recommendations regarding their management using. The Society for Vascular Surgery (SVS) recognized that clinical decision making had been changed by the endovascular era and in 2006 published "Guideline methodology of the Society for Vascular Surgery including the experience with the GRADE framework." With this guideline, the profession of vascular surgery effectively entered the realm of evidence-based medicine to help guide vascular surgeons in areas that they may be unfamiliar. This text is a natural extension of the SVS goal to improve upon the process of clinical decision making for the practicing vascular surgeon and to ultimately improve patient outcomes. To accomplish this, it was necessary to assemble a phalanx of authors widely felt to be experts in their fields. They were given the assignment of crucially evaluating evidence on a well-defined topic: one based solely on the existing evidence and another based on their prevailing practice, clinical experience, and teaching. In addition to the analysis of the evidence on the topic, we include a section in each chapter called: **A personal view of the data.** This

section allowed for the authors' personal opinion of the data and the application to the data. This component we found to complement the evidence perfectly because it allows for the expression of the "art" in the "Art and Science of Medicine." In other words, we gave the author license to juxtapose any differences between practicing medicine (the snap decisions based on practice) with research medicine (clinical trials).

This book is intended as a resource for clinical surgeons and other interested readers who wish to understand how experts in the field assess existing knowledge. As part of the process, authors were asked to assess the evidence quality based on the following criteria.

High quality	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality	We are moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of effect, but possibility to be substantially different
Low quality	Our confidence in the effect is limited: The true effect may be substantially different from the estimate of the effect
Very low quality	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

What became apparent in going through the process of editing this text was that the quality of data upon which we base many of our decisions in vascular surgery is low to moderate quality. Therefore, this book is not intended to be used as a clinical pathway for management of our vascular surgical patients. As with all clinical care, consideration must be given to the individual needs of patients in the context of that physician–patient relationship.

My hope is that readers will find the information and recommendations in this book insightful and intellectually stimulating. I encourage the readers who find a particular chapter interesting to read the original source materials to come up with their own objective conclusions. Furthermore, I encourage students and residents and practicing surgeons to realize that there are gaps in our knowledge that can and should be filled with good strong quality evidence.

Producing a book of this caliber in a relatively short time period requires the help of a number of individuals. I would like to thank the students, residents, fellows, and faculty with whom I work on a daily basis for stimulating discussions and the basis for many of the chapters. I would like to thank the authors, co-authors, and their support staff for all of the hard work required to produce this work and my continual pestering and revisions. I am indebted to Michael Sova, Jessica Gonzalez, and Julia Megginson at Springer for keeping my colleagues on track, ushering the manuscripts through to a finished product. I thank my family for their continual patience and unquestioning support. Finally, I am indebted to Mark Ferguson who was my teacher and now my colleague, for his innovative approach to evidence-based medicine and shepherding this concept through the profession of surgery as a whole. Dr. Ferguson has championed a movement away from the time honored traditional training format of "see one, do one, teach one" which as he points out "stifles insight, objectivity and creativity."

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Part I
Aortic Disease

Chapter 1
In Patients with Acute Type B Aortic Dissection, Do Current Operative Therapies Reduce Complications Compared to Medical Management?

Nadia Awad and Joseph Lombardi

Abstract The management of acute type B aortic dissection (TBAD) has largely been dictated by whether or not the case is "complicated," meaning symptomatic or extensive such that no intervention would lead to death. Historically, complicated acute TBAD has been managed with operative intervention and uncomplicated acute TBAD has been managed with medical treatment. Acute complicated TBAD left untreated has mortality rates as high as 50 % in the first month. While uncomplicated acute TBAD has good outcomes with medical management in the short-term, long-term outcomes are discouraging with mortality rates approaching 30–50 % at 5 years, largely due to aneurysmal degeneration of the false lumen. Both open and endovascular treatment strategies have a role in both complicated and uncomplicated acute TBAD and the role of endovascular intervention is ever-expanding as research shows favorable short-term outcomes and long-term aortic remodeling.

Keywords Acute type B aortic dissection • Endovascular • Open • Medical therapy • Complicated • Uncomplicated

Introduction

Aortic dissection is a relatively uncommon disease, with an incidence of 3.5–14 per 100,000 persons per year [1–4]. Acute TBAD accounts for 24–40 % of all aortic dissections and may be classified as complicated or uncomplicated. Complicated acute TBAD refers to the presence of rupture, malperfusion, continued pain, or

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hypertension with maximum medical management. While complicated acute TBAD accounts for a minority of cases, these cases require surgical repair. Uncomplicated acute TBAD has typically been managed medically with blood pressure control and anti-impulse therapy. With this approach, in-hospital mortality rates remain low, typically less than 10 %. However, long-term results remain disappointing due to aneurysmal expansion of the false lumen and late complications [5–7].

Current review of short- and long-term outcomes is showing the increasing role for early repair of both complicated and uncomplicated acute TBAD. In 1999, thoracic endovascular aortic repair (TEVAR) was introduced as an alternative surgical intervention for TBAD and proceeded to obtain FDA approval in 2005. Since the introduction of endovascular techniques for repair, an increasing number of surgical cases have been performed with a resultant decrease in short-term mortality [3, 4, 6]. Long-term results are limited since the recent paradigm shift towards early endovascular repair has only occurred in the last decade, however favorable outcomes with respect to aortic remodeling are promising in decreasing the occurrence of late aneurysmal degeneration [8–10].

Search Strategy

A literature search of English language publications from 2000 to present was performed to identify published data regarding acute type B aortic dissection management and intervention using the PICO outline (Table 1.1). The databases searched were PubMed, OVID Medline, and Cochrane Evidence Based Medicine. Terms searched included “acute aortic dissection,” “descending aortic dissection,” “type B aortic dissection,” AND (“complicated” OR “uncomplicated” OR “surgical treatment” OR “medical treatment”). Articles were excluded if they included type A aortic dissection. One Cochrane review, two randomized trials, one prospective registry review, two expert guidelines, and two review articles were included in our analysis. The data was classified using the GRADE system.

Results

Early Guidelines Summary

Contemporary management of acute type B aortic dissection has evolved over the last 15 years. In 2001 the European Society of Cardiology sought to review current diagnosis and management strategies regarding aortic dissection and provide

Table 1.1 PICO table for treatment of acute Type B aortic dissection

P (patients)	I (intervention)	C (comparator)	O (outcome)
Patients with acute type B aortic dissection	Open and endovascular surgical repair	Medical therapy	Mortality, need for subsequent intervention, aortic remodeling, cost

recommendations and guidelines regarding optimal treatment [11]. This established the first set of society guidelines for aortic dissection. A task force of 11 members included one member appointed by the American College of Cardiology to include endorsement from that group as well. The group recommended strict heart rate and blood pressure control with beta-blockers and nitroprusside upon admission. Emergent operative repair was recommended in instances of hemodynamic instability. Other indications for operative repair in TBAD included persistent or recurrent chest pain, aortic expansion, periaortic hematoma, and mediastinal hematoma. Endovascular therapy was described as an evolving technique with goals of fenestration with or without stent placement for coverage of entry tears and relieving malperfusion due to the tears. However, the supporting evidence for endovascular intervention at this time was largely based on case reports and only awarded a GRADE "very low" quality of evidence. This paper served as the first formal guidelines supported by a society in the treatment of acute type B aortic dissections.

Prospective Registry- International Registry of Acute Aortic Dissection (IRAD)

Interest in better delineating the treatment and outcome of acute aortic dissection led to the need for a robust database, culminating in the creation of the International Registry of Acute Aortic Dissection (IRAD) in 1996. All patients with acute aortic dissection confirmed by imaging, visualization in the operating room, or at autopsy are included and data are enrolled prospectively and a questionnaire of 290 variables is used to collect data. Initially, patients were enrolled from 12 centers in 6 countries, and now this has expanded to 24 referral centers in 11 countries. Reports from the IRAD database are published periodically [5, 12, 13].

In 2008 Fattori et al. analyzed the impact of different treatment strategies on survival in patients in the IRAD database [12]. This review included 571 patients with acute type B aortic dissection who were enrolled in the database between 1996 and 2005. Of these patients, 390 were treated medically and 125 were treated surgically. The surgical treatment group included 59 patients who underwent open repair and 66 patients who were treated with an endovascular approach. All patients were initially treated with aggressive antihypertensive and anti-impulse therapy. The patients undergoing open intervention suffered either extension of dissection, recurrent or refractory pain, visceral ischemia, or limb ischemia. The reasons for endovascular treatment included recurrent or refractory pain, and limb or visceral ischemia. Endovascular techniques employed in this group included stent graft repair as well as endovascular balloon fenestration of the dissection flap. Mortality in the endovascular treatment group was 10.6 %, while mortality in the open surgical group was 33.9 % (P = .002). In-hospital complications, including stroke, spinal cord ischemia, myocardial infarction, acute renal failure, limb ischemia, and mesenteric ischemia were observed in 20.8 % of the patients undergoing endovascular intervention, and in 40.0 % of the patients undergoing open surgical repair (P = .04). Patients with uncomplicated acute TBAD were treated with medical therapy only

and mortality in this group was similar to that of the complicated acute TBAD group treated with endovascular therapy. This report demonstrated the likely better short-term outcomes of endovascular repair versus open surgical repair of complicated acute TBAD with respect to mortality and in-hospital complications. However, long-term follow-up was lacking and no comparison directly between medical therapy and endovascular treatment was available.

As a follow-up to this analysis, Fattori et al. reviewed the IRAD database to compare medical therapy to thoracic endovascular aortic repair (TEVAR) therapy [13]. This review included 1129 patients enrolled between December 26, 1995 and January 20, 2012, 853 of whom were treated exclusively with medical therapy, and 276 of whom were treated with endovascular stent-graft placement in addition to medical therapy. Of note, patients undergoing endovascular treatment were more likely to present with signs of malperfusion, pre-operative renal failure, and pulse deficit. Additionally, endovascular therapy was more frequently used in European centers compared to North American sites. Despite these differences in the patient populations, in-hospital mortality was similar between the two groups with 10.9 % mortality in the endovascular group and 8.7 % in the medically treated group (P = .273). Complications in this acute phase, including renal failure, stroke, spinal cord ischemia, and extension of dissection, were more common in the TEVAR group (38.9 % vs. 17.8 %). At 1-year post-discharge, the mortality was 8.1 % in the patients treated with TEVAR and 9.8 % in the patients treated with medical therapy alone, though this was not statistically significant (P = .604). Kaplan-Meier estimates were modeled for 5-year follow-up and projected a lower mortality rate for those patients undergoing endovascular treatment versus medical therapy alone (15.5 % vs. 29.0 %, P = .018). While late intervention rates were projected to be more common after TEVAR (30.6 % vs. 19.7 %), this was not anticipated to be significant (P = .810). Additionally, projections demonstrated a smaller descending aortic diameter in the group treated with TEVAR as compared to the medical therapy group with median diameter of 4.2 cm for the TEVAR group and 4.6 cm for the medical therapy group (P = .034). The analysis from this review demonstrates similar long-term mortality between patients treated with TEVAR versus medical therapy alone as well as favorable long-term aortic remodeling in patients undergoing TEVAR.

Prospective Trials

While IRAD does provide “real-world” review of acute aortic dissection, it lacks the rigor of a randomized study to provide better comparison of outcomes between medical therapy alone versus medical therapy and operative intervention. The Investigation of Stent Grafts in Aortic Dissection (INSTEAD) Trial was the first randomized trial to compare TEVAR and medical therapy for subacute TBAD [14]. Nienaber et al. recruited 140 patients in stable clinical condition between November 2003 and November 2005 and randomized to elective stent-graft placement in addition to

medical therapy or to medical therapy alone. Seventy-two patients were randomized to the TEVAR group and 68 were randomized to the medical treatment group, with no significant differences noted between the two study groups. Patients undergoing TEVAR had TALENT stent grafts placed (Medtronic, Inc, Santa Rosa, CA). At 2-year follow-up, overall survival was 88.9 % in the TEVAR group and 95.6 % in the medical therapy group (P = .145). Freedom from aorta-related mortality at 2 years was also not significantly different between the two groups, 94.4 % for the TEVAR group and 97.0 % for the medical treatment group (P = .435). Similarly, there was no difference in progression of aortic disease, 77.2 % for the TEVAR group and 72.5 % for the medical treatment group (P = .545). Of note, there was a significant trend towards decreased false-lumen diameter with concomitant increase in true-lumen diameter in the TEVAR group at the 3-month, 1-year, and 2-year follow-up. Additionally, complete false-lumen thrombosis at 2 years was achieved in 91.3 % of patients undergoing TEVAR and only 19.4 % of patients undergoing medical therapy (P < .001). The overall observed mortality rate was lower than expected, leading to the study being underpowered. However, this study did confirm that TEVAR leads to favorable aortic remodeling and false-lumen thrombosis, fostering the argument for the expanded role for operative intervention in subacute TBAD, even in uncomplicated cases traditionally managed with medical therapy alone.

Nienaber et al. followed INSTEAD with INSTEAD-XL, the 5-year follow-up of the randomized study [9]. While all-cause mortality was not significantly different at 2 years, there was a significant survival benefit seen with TEVAR between 2 and 5 years with 100 % of TEVAR patients surviving that time frame compared to 83.1 % of the medical treatment group (P = .0003). Similarly, there was a significant decrease in aorta-specific mortality between 2 and 5 years for the TEVAR group, with no patients from the TEVAR group experiencing aorta-specific mortality between 2 and 5 years. At 5 years, the overall aorta-specific mortality was 6.9 % for the TEVAR group and 19.3 % for the medical treatment group (P = .045). TEVAR also out-performed medical treatment between years 2 and 5 with respect to progression of disease and aorta-specific events, with 95.9 % of TEVAR patients free from these events compared to 71.9 % of medical treatment patients (P = .004). False lumen thrombosis and aortic remodeling was favorable in the TEVAR group with complete thoracic false lumen thrombosis in 90.6 % and morphologic remodeling in 79.2 % at 5 years. The medical treatment group was conversely associated with an increase in aortic diameter in 66.0 % and only demonstrated false lumen thrombosis in 22.0 % at 5 years. INSTEAD-XL demonstrated that while TEVAR was associated with excess early mortality largely due to peri-procedural risks, TEVAR was beneficial in treatment of subacute TBAD with respect to overall mortality, aorta-specific mortality, aortic remodeling, and false lumen thrombosis with a number needed to treat of 13.

While the INSTEAD-XL trial demonstrated long-term improvement in outcomes for patients with subacute uncomplicated TBAD, studies are undergoing to determine the impact of endovascular repair in complicated TBAD. The Study for the Treatment of complicated Type B Aortic Dissection using Endoluminal repair (STABLE) trial is a prospective, multicenter study to evaluate the use of proximal stent grafting with distal bare metal stents (Zenith Dissection Endovascular System;

Cook Medical, Bloomington, IN) in the treatment of complicated TBAD. Lombardi et al. recently reported 2-year results with the system [8]. Eighty-six patients enrolled between December 2007 and February 2012 were reviewed, all of whom underwent treatment within 90 days of symptom onset. Inclusion criteria included impending rupture, resistant hypertension, persistent pain or symptoms, aortic growth greater than 5 mm in 3 months or transaortic diameter greater than 40 mm, and evidence of branch vessel obstruction or compromise. The 30-day mortality was 4.7 %. The freedom from all-cause mortality was 88.3 % at 1 year and 84.7 % at 2 years. The freedom from dissection-related mortality, based on the evaluation of a clinical events committee, was 90.6 % at 1 year and 89.3 % at 2 years. Subgroup analysis of patients with acute and non-acute dissections did not reveal any difference in overall mortality or dissection-related mortality. Overall complication rates were low, with paraplegia only occurring in one patient, renal failure in 9 patients, aortic rupture in 5 patients, stroke in 7 patients, and retrograde dissection in 7 patients during the 2 years studied, although the majority of complications were found among patients treated in the acute phase. Complete false lumen thrombosis was 43.5 % at 2 years ($P < .001$). The study also evaluated the changes in true-lumen, false-lumen, and transaortic diameters. At 2 years, the true lumen diameter increased significantly in the descending thoracic aorta and distal abdominal aorta. The false lumen diameter decreased significantly in these segments as well at 2 years. The authors concluded that the combined stent graft with distal bare metal stent in complicated TBAD leads to favorable mortality and morbidity rates as well as leading to favorable aortic remodeling at 2 years with respect to true lumen size, false lumen size and thrombosis, and transaortic size.

The first prospective randomized trial on acute type B aortic dissection, the Acute Dissection Stentgraft OR Best Medical Treatment (ADSORB) trial, recently published its preliminary findings [15]. Sixty-one patients were recruited from 17 European centers and randomized from December 2008 to December 2010. Thirty-one patients were randomized to best medical therapy (BMT) and 30 patients were randomized to BMT and TEVAR. The Gore TAG device (W. L. Gore & Associates, Inc. Flagstaff, AZ) was used for endovascular repair, which was performed within 48 h of randomization. The composite endpoint studied included incomplete or no false lumen thrombosis, aortic dilatation greater than 5 mm or maximum diameter of the descending thoracic aorta greater than 55 mm, and aortic rupture. No deaths occurred in either group at 30 days. At 1 year, the composite endpoint was met by 100 % of the patients in the BMT group and only 50 % in the TEVAR group ($P < .001$). No aortic rupture occurred in either study group. No false lumen thrombosis occurred in 97 % of the BMT group and only 43 % of the TEVAR group ($P < .001$). Of note, similar rates of aortic dilatation were noted between the two study groups with 37 % of the TEVAR group and 45 % of the BMT group experiencing aortic dilatation ($P = .5$). While the study was not powered for mortality, the authors concluded that the BMT only group results were inferior those seen the TEVAR group, supporting TEVAR for acute uncomplicated TBAD.

Guidelines Summary

Since results from IRAD, INSTEAD and INSTEAD-XL, STABLE, and ADSORB have been available, new reviews and society guidelines regarding treatment recommendations for aortic dissection have been established. Ulug et al. performed a Cochrane review of uncomplicated chronic subacute type B aortic dissection, largely based on INSTEAD results and while unable to make any specific practice recommendations, supported the idea that early endovascular interventions lead to favorable aortic remodeling and may likely be of long-term benefit [16]. Erbel et al. through the Task Force for the Diagnosis and Treatment of Aortic Diseases updated the European Society of Cardiology (ESC) guidelines first set in 2001 [17]. With respect to uncomplicated TBAD, the ESC recommends medical therapy with Class I, Level C support and consideration of TEVAR with Class IIa, Level B support. For complicated TBAD, TEVAR was recommended with Class I, Level C support. Open surgery for complicated TBAD may be considered based on Class IIb, Level C support. The recommendations of the ESC demonstrate the evolving practice patterns and outcomes for TBAD over the last 15 years since the introduction of endovascular thoracic aortic repair for dissection.

Fattori et al. recently provided an interdisciplinary expert consensus document on the management of TBAD [18]. They reviewed data from 63 studies published from 2006 to 2012 with a total of 1548 patients treated medically, 1706 patients treated with open surgery, and 3457 patients treated with TEVAR. The expert panel recommended medical treatment for uncomplicated acute TBAD as there was no good evidence demonstrating a benefit of TEVAR or open surgery over medical treatment. For patients with complicated acute TBAD, the group suggests that TEVAR should be considered as first-line treatment as a survival benefit has been demonstrated over open surgical treatment. Because of aneurysmal degeneration and rupture risk in patients treated medically, as well as the possibility of adverse aortic events after TEVAR, both groups of patients should be followed closely with serial imaging, particularly in the first few months. The group cautioned that the data available currently is lacking in robust randomized trials and there are gaps in reporting standards of the studies available for review.

Recommendations

The management and treatment of acute TBAD has evolved over the last 15 years. Multiple studies and reviews have been performed to evaluate the impact of medical treatment, endovascular repair, and open repair on acute TBAD, and more studies are underway. Randomized controlled studies are few and typically underpowered, leading to recommendations based on imperfect data, and therefore any recommendation must be reviewed with caution.

With respect to acute uncomplicated TBAD, optimum medical treatment is still the standard of care. Low quality evidence exists from the ADSORB trial that demonstrates favorable aortic remodeling and false lumen thrombosis with TEVAR in this group. If using uncomplicated chronic TBAD as a marker for those cases with acute uncomplicated TBAD that continue to be uncomplicated, the INSTEAD-XL trial demonstrates low to moderate quality evidence for the use of TEVAR in this patient population.

For patients with acute complicated TBAD, good evidence exists that TEVAR is superior to open surgical intervention and should be utilized as first-line intervention. Data from IRAD and STABLE have shown decreased mortality, increased false lumen thrombosis, and decreased aortic size with TEVAR in patients with acute complicated TBAD.

Personal View of the Data

Acute TBAD requires consideration of acute events and pathology such as rupture, malperfusion, and ongoing symptomatology as well as anticipation of long-term sequelae and risks such as aneurysmal degeneration, aortic-related death, and recurrent symptoms. All patients require timely and strict medical management with blood pressure control and anti-impulse treatment. While there are good data that demonstrate TEVAR is the intervention of choice in those patients with complicated TBAD, there is a paucity of rigorous randomized trials for uncomplicated TBAD. All of the attempted randomized controlled trials suffer from low enrollment and inability to reach sufficient power as contemporary medical treatment has decreased the overall mortality rate, requiring more patients to be enrolled to detect a difference.

The ADSORB trial provides an opportunity to address this shortcoming, though its first results are lacking and fail to definitively show a survival benefit and, in fact, showed no difference in aortic dilation between the two treatment groups. More time is needed for enrollment to reach adequate numbers, and long-term follow-up will be needed to see the true impact of the study. However, given the evidence from the INSTEAD-XL trial and large analyses, we hypothesize that TEVAR does have a role in the treatment of uncomplicated subacute TBAD, though the extent of that role is yet to be determined.

Currently, much of the research focus regarding endovascular intervention for TBAD is centered on false lumen thrombosis in the thoracic aorta as a marker for aortic remodeling and eventual mitigation of the risk of aneurysmal degeneration. However, we believe that this data is incomplete and does not address the more difficult issue of outcomes related to the abdominal aorta and the difficulty in managing residual disease that may affect the visceral vessels. To date, no study has seriously studied the long-term effects of TEVAR for TBAD on the abdominal aorta, which will be needed to fully appreciate the impact of these interventions.

Summary of Recommendations

- For patients with acute uncomplicated TBAD, we recommend optimum medical therapy and close surveillance to follow progression of disease. (**evidence quality moderate, strong recommendation**)
- For patients with acute complicated TBAD, we recommend TEVAR in addition to optimum medical therapy and close surveillance. (**evidence quality moderate, strong recommendation**)
- TEVAR may be of benefit in subacute uncomplicated TBAD (**evidence quality low, weak recommendation**)

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Chapter 2
In Patients with a Chronic Type B Dissection, Does Endovascular Treatment Reduce Long Term Complications?

Yana Etkin and Ronald M. Fairman

Abstract Aortic dissection is a highly morbid condition. Acute type B dissection is associated with 13 % 30-day mortality and 83 % 5 year survival [1]. The management of type B dissection remains complex and challenging. Since the introduction of TEVAR technology in the 1990's it has become a preferred method of treatment of acute and chronic type B dissections. Medical management of chronic type B dissection continues to be a gold standard therapy while the role and timing of TEVAR remains controversial. The objective of this chapter is to describe treatment options for chronic type B dissection and establish possible benefits of endovascular repair in reducing long term complications of chronic type B dissection.

Keywords Aortic dissection • Chronic type B dissection • TEVAR • Complication of type B dissection • Medical management

Introduction

Aortic dissection is a highly morbid condition. Population-based studies suggest that the incidence of aortic dissection is 2.6–3.5 cases per 100,000 people per year [1]. Hypertension and various genetic disorders which alter connective tissue are the most common risk factors [1]. Acute type B dissection is associated with 13 %

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30-day mortality and 83 % 5 year survival [1]. The management of type B dissection is complex and challenging. Since the first description of thoracic endovascular repair (TEVAR) in 1999, acute and chronic type B dissections have been increasingly treated by an endovascular approach [2, 3]. The introduction of this technology has lead to improved perioperative outcomes as compared to open surgery [4].

Traditionally a 2 week distinction between acute and chronic aortic dissection was established relative to the timing of death in the era of open surgery. The role of TEVAR in management of chronic type B dissection remains controversial. The early results have been satisfactory, however long term outcomes of TEVAR for chronic dissection are variable. It is unclear whether TEVAR can prevent late aortic-related complications and death [5]. The difference in clinical outcomes between acute and chronic dissection can be partly explained by the difference in aortic remodeling in these two phases. TEVAR for acute dissection results in rapid expansion of the compressed true lumen, and potential collapse and thrombosis of false lumen. These changes are not always present in the chronic phase which may lead to adverse clinical outcomes [6, 7].

Only one randomized perspective control trial of TEVAR versus medical management for chronic uncomplicated type B dissection has been published [8, 9]. The majority of publications analyzing TEVAR for type B dissection are uncontrolled prospective or retrospective cohort studies or case series. Timing of interventions, patient baseline comorbidities and severity of the disease are significantly different in these studies, making comparison of the surgical and medical management difficult.

The objective of this chapter is to describe treatment options for chronic type B dissection and establish possible benefits of endovascular repair in reducing long term complications of chronic type B dissection.

Search Strategy

A literature search of computerized databases including PubMed, Ovid Med line and the Cochrane Library was performed using the PICO outline (Table 2.1). The search was limited to the past 6 years from 2009 to 2014 and was used to identity data on management of chronic type B dissection published in English. Terms used in the search included “chronic type B aortic dissection” AND “medical management” OR “endovascular treatment”. After relevant studies were identified, additional searches were conducted using related study links within PubMed and within a reference list of the published studies. The search was limited to studies on humans and adults only with at least 50 or more patients in the cohort. Case reports were excluded. Type A dissection, acute type B dissection, open surgical and hybrid repairs were excluded. The data was classified using the GRADE system. Eleven studies were included in this analysis: 1 prospective randomized controlled trial, 3 prospective nonrandomized trials and 7 case series (Tables 2.2, 2.3, and 2.4).

Table 2.1 PICO table for treatment of chronic Type B aortic dissection

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with Chronic Type B dissection	Endovascular treatment	Medical management (for uncomplicated type B dissection) Open surgical repair (complicated type B dissection)	30 day mortality, early CVA and spinal cord ischemia (SCI), long-term survival, aortic event-free survival and rate of aortic re-interventions.

Table 2.2 Results for TEVAR in chronic complicated Type B aortic dissection

Author, year (ref.#)	n	30 day mortality N (%)	Early CVA N (%)	Early SCI N (%)	Mean f/up (m)	Survival (%)	Aortic event freedom rate	
							Aorta related death, reintervention, expansion free (%)	Aorta related death free (%)
Prospective nonrandomized trials								
Virtue registry (2011, 2014) [10, 11]	50	0	0	1 (3.8)	36	1 year: 96 3 years: 74	1 year: 88 3 years: 68	1 year: 91.3 3 years: 74
Case series								
Alves (2009) [13]	61	2 (3.3)	0	0	35.9	3 years: 94	3 years: 78	n/a
Parsa (2011) [16]	51	0	0	0	27	5 years: 77.7	5 years:77.3	5 years: 98
Kang (2011) [17]	76	4 (5)	1 (1.3)	0	34	1 year: 86 3 years: 80	1 year: 72 3 years: 59	1 year: 89 3 years: 86
Andacheh (2012) [18]	73	10 (14)	1 (1.3)	1 (1.3)	18	1 year: 81	1 year: 85	1 year: 86
Mani (2012) [19]	58	3 (5.2)	0	1 (1.7)	n/a	1 year: 89 3 years: 64	1 year: 85 3 years: 71	
Cumulative	369	5.6 %	0.4 %	1.1 %				

SCI spinal cord ischemia, *CVA* cerebral vascular accident, *f/up* follow up

Table 2.3 Results for medical treatment in chronic uncomplicated Type B aortic dissection

Author, year (ref.#)	n	30 days mortality N (%)	Early CVA N (%)	Early SCI N (%)	Mean f/up (m)	Survival (%)	Aortic event freedom rate	
							Aorta related death, reintervention, expansion free (%)	Aorta related death free (%)
Prospective randomized controlled trials								
Nienaber INSTEAD (2009, 2013) [8, 9]	68	0	0	0	69	1 year: 82.5 15 years: 80.7 years: 97	1 year: 82.5 5 years: 53.9	1 year: 97 5 years: 80.7
Prospective nonrandomized trials								
Jia (2013) [12]	68	0	0	0	69	1 year: 97 5 years: 80.7	1 year: 82.5 5 years: 53.9	1 year: 97 5 years: 80.7
Cumulative	163	0	0	0				

Table 2.4 Results for TEVAR in chronic uncomplicated Type B aortic dissection

Author, year (ref.#)	n	30 days mortality N (%)	Early CVA N (%)	Early SCI N (%)	Mean f/up (m)	Survival (%)	Aortic event freedom rate	
							Aorta related death, reintervention, expansion free (%)	Aorta related death free (%)
Prospective randomized controlled trials								
Nienaber INSTEAD (2009, 2013) [8, 9]	72	2 (2.8)	1 (1.4)	2 (2.9)	69	1 year: 91.3 5 years: 91.3	1 year: 83.3 5 years: 73	1 year: 94.2 5 years: 93.1
Prospective nonrandomized trials								
Zipfel Restore registry (2011) [20]	51	3 (5)	0	2 (3.9)	10	N/a	n/a	n/a
Jia (2013) [12]	208	0	0	2 (0.9)	28.5	2 years: 87.5 4 years: 82.7	2 years: 87.8 4 years: 78.8	2 years: 91.6 4 years: 88.1
Case series								
Kim (2009) [14]	72	0	0	0	64.4	5 years: 92	5 years: 83.9	5 years: 98.3
Xu (2009) [15]	84	1 (1.2)	0	0	33.2	3 years: 91.7	5 years: 84.4	7 years: 75.2
Kim (2009) [14]	72	0	0	0				

The time of type B dissection was defined based on previously established guidelines [21]. Patients treated within 14 days of onset of symptoms were categorized as acute Type B dissection and were excluded from this analysis. Chronic type B dissection was defined as presentation beyond 2 weeks of onset of symptoms. Complicated type B dissection was defined as total thoracic aortic diameter greater than or equal to 55 mm, total aortic diameter yearly increase more than 4 mm or recurrence of symptoms.

The endpoints included in the analysis were 30 day mortality, early CVA and spinal cord ischemia (SCI) as well as long-term survival, aortic event-free survival and rate of aortic reinterventions.

Results

Results for Chronic Complicated Type B Dissections

Five year survival of chronic Type B dissection managed medically are estimated to be around 60–80 % due to development of long term complications [21]. Twenty-five to forty percent of patient with chronic type B dissection treated medically over time will develop aneurysmal degeneration of the false lumen in the thoracic aorta requiring surgical interventions [22–25]. The 5-year survival for patients with 6.0 cm thoracic aneurysms is estimated to be 54 %, with 3.7 % rate of rupture per year, and 12 % risk of death per year [26].

Persistent patency of false lumen has been identified as an independent predictor of aneurysmal degeneration and a predictor of development of dissection-related events [27–30]. Sueyoshi and et al. described 3.3 mm per year dilatation of persistently patent false lumen [31]. Other factors that have been shown to have impact on aneurysm development are poorly controlled hypertension and maximal aortic diameter of at least 40 mm in the acute phase.

Since aneurysmal aortic degeneration greater than 55–60 mm in diameter is associated with significant risk of rupture and mortality elective repair is strongly recommended. Outcomes of TEVAR for chronic complicated type B dissections are summarized in Table 2.2. The analysis included 6 studies with total of 369 patients. These studies suggest that TEVAR can be performed safely with minimal morbidity and mortality. Cumulative early mortality was 5.9 % and early stroke and SCI was 0.4 % and 1.1 %, respectively. One-year survival ranged between 81 and 96 % and 3-year survival between 64 and 94 %. Freedom from re-interventions was around 85 % at 1-year and 65 % in 3 years.

Open surgical repair has been associated with significantly higher early mortality and morbidity as compare to TEVAR. Recent studies demonstrate perioperative mortality as high as 10 %, early stroke rates of 2–6 % and SCI 0–5 %. The 1-year survival is 78 % and 5-year survival is 68–92 %, similar to the rates following TEVAR. The freedom from re-interventions in the open surgical group is significantly higher at 99 % in 1-year and 85–93 % in 5 years [32, 33].

Due to lower early mortality and morbidity, TEVAR is a preferred method of management of complicated chronic type B aortic dissection in a setting of suitable anatomy.

Results for Chronic Uncomplicated Type B Aortic Dissections

Medical management remains a standard of care for uncomplicated chronic type B dissection. The goal of medical therapy is to reduce systolic blood pressure and thereby reduce the forces predisposing to further propagation of dissection or rupture of the dissected aorta. Indications for TEVAR in these patients remain a controversial issue with very limited outcome data available (Tables 2.3 and 2.4). Only two studies were found in recent literature comparing outcomes of medical management vs. TEVAR in uncomplicated type B dissections [9, 12]. Currently, INSTEAD trial is the only prospective randomized controlled trial performed and completed [8, 9].

INSTEAD trial included 68 patients randomized to optimal medical therapy (OMT) and 72 patients treated with TEVAR [8, 9]. TEVAR was successfully performed in 95.7 % of patients with postoperative stroke rate of 1.4 and 2.9 % rate of spinal cord ischemia. Early mortality in the TEVAR group was 2.8 % as compared to no mortality in the medical group. 1-year mortality was also higher in the TEVAR group with 91.3 % vs. 97 % in the medical group [8].

The benefits of TEVAR were observed only after 2 years of follow up. 5-year all-cause mortality trended lower in patient randomized to TEVAR than OMT alone (11.1 ± 3.7 % vs 19.3 ± 4.8 %, p = 0.13). Kaplan-Meier curves demonstrated survival benefit with TEVAR seen between 2 and 5 years, but not within 2 years of follow up. Aorta-specific mortality showed a similar trend with survival benefit of TEVAR compared with OMT between 2 and 5 years (100 % vs. 83.1 ± 4.7 %, p = 0.0005). Kaplan-Meier analysis of the combined end point of disease progression which included aorta-specific death, crossover/conversion and secondary procedures shows a similar pattern. At 5 years cumulative freedom from this cluster endpoint was 53.9 ± 6.1 % with OMT alone and 73.0 ± 5.3 % with TEVAR (p = 0.0004) [9].

Jia et al. [12] also compared medical management vs TEVAR for chronic uncomplicated dissections however assignment to treatment groups in this study was not randomized. Similarly to INSTEAD trial, TEVAR was associated with low morbidity (0 % stroke rate, 0.9 % SCI) and no 30-day mortality. This study did not demonstrate significant overall survival benefit at 2 and 4 years, 87.5 % at 82.7 % with TEVAR, respectively vs. 77.5 % and 69.1 % with OMT, respectively (p = 0.06). However, estimated freedom form aorta-related death at 2 and 4 year was significantly lower in the TEVAR group, 91.6 % and 88.1 %, respectively and 82.8 % and 73.8 % with OMT, respectively (p = 0.03).

Other case series summarized in Table 2.4 shows similar outcomes for TEVAR in chronic uncomplicated type B dissection. Overall, perioperative mortality is 1.8 % with early stroke rate of 0.2 % and early SCI 1.5 %. 1-year survival ranges from 87 to 91 % and 5-year survival 84–92 %. Freedom from aortic related death, reintervention and expansion is 73–84 % in 5 years. Freedom from aortic related death ranges from 75 to 93 %.

Recommendations

Chronic type B dissection managed medically is associated with significant long term complications with about 60–80 % 5 year survival. Delayed rupture due to aneurysmal degeneration of false lumen is a major cause of late mortality. Evidence in recent literature suggests that patients with recurrent symptoms, rapidly growing thoracic aorta (>4 mm/year) and thoracic aortic diameter over 55 mm should be managed with an elective repair. In these patients TEVAR reduces risk of rupture and aorta related mortality. TEVAR can be performed with significantly lower perioperative mortality and morbidity as compared to open repair. Open surgical repair should be reserved only for patients who are not anatomically suitable for TEVAR.

Management of patients with chronic type B dissection without recurrent symptoms or aneurysmal degeneration is not clear at this time. Only one prospective randomized controlled trial available in the literature suggests that TEVAR in these patients will decrease long term complications and mortality but this survival benefit is seen only after 2 years of follow up. Perioperative mortality, risk of stroke and spinal cord ischemia as well as 1-year mortality are significantly higher with TEVAR as compared to optimal medical management. The findings of decreased overall 5-year mortality after TEVAR were not reproduced in the other recent study published by Jia et al. Medical management consisting of optimizing blood pressure control continues to be the treatment of choice in patients with chronic uncomplicated type B dissections.

Summary of Recommendations

- Chronic, uncomplicated type B aortic dissection should be managed medically until complications develop. Optimal blood pressure control should be achieved to limit false lumen aneurysmal dilation over time (**evidence quality high, strong recommendation**).
- TEVAR for chronic, uncomplicated type B aortic dissection may decrease the rate of long term complications and improve 5-year mortality.

However it is associated with higher perioperative morbidity and mortality as well as higher 1-year mortality. Use of TEVAR in this patient population is up to individual surgeon discretion (**evidence quality low, weak recommendation**).

- Complications of type B aortic dissection, such as recurrence of symptoms, aneurysmal dilation of thoracic aorta greater than 55 mm or yearly growth of the aorta greater than 4 mm should be managed with elective TEVAR to decrease long term complications of rupture (**evidence quality high, strong recommendation**).

A Personal View of the Data

The role of TEVAR in management of chronic type B dissection continues to be an area of controversy. Despite some evidence in the literature that TEVAR improves long term aorta related mortality in patient with chronic uncomplicated type B dissection the practice at our institution is to use TEVAR selectively only in patients who present with complications of chronic type B dissection such as aneurysmal degeneration. Further studies are needed to better understand the role of preemptive TEVAR in chronic uncomplicated type B dissections.

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Chapter 3
In Patients with a Retrograde Type A Aortic Dissection, Does Treatment Like a Type B Aortic Dissection Improve Outcomes?

Reilly D. Hobbs, Prashanth Vallabhajosyula, and Wilson Y. Szeto

Abstract Type A aortic dissection is a surgical emergency with mortality approaching 60 % when treated with medical therapy alone. Survival benefit has been consistently demonstrated with emergent surgical repair; however, overall mortality is still reported to be as high as 25 %. Type A aortic dissection most commonly arises from a primary intimal tear just distal to the coronary ostia, followed by primary aortic arch tear. Less commonly, retrograde type A dissection (RTAD) can arise from a primary intimal tear in the descending aorta with retrograde propagation into the ascending aorta. RTAD are categorized as spontaneous or iatrogenic. Spontaneous RTAD account for approximately 10 % of all acute type A dissections. Iatrogenic RTAD have become a topic of increased interest due to their occurrence after thoracic endovascular aortic repair (TEVAR) for type B descending thoracic aortic (DTA) dissections and aneurysms. In addition, open surgical repair of RTAD carries increased perioperative morbidity and mortality due to the necessity of replacing the aortic arch in order to cover the primary dissection flap. Some clinicians have advocated treating RTAD in a similar fashion to type B dissection where the mainstay of treatment is medical management with or without TEVAR. Studies comparing medical and surgical therapies have demonstrated improved medium term outcomes RTAD compared to antegrade dissections. The studies suggest that medical management may be suitable in select patients who have (1) no malperfusion syndromes, (2) false lumen thrombosis, (3) no aneurysmal disease, and (4) no rupture. No long term data is available comparing retrograde versus antegrade aortic dissection, thus,

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the true natural history is unclear. In this report, we review the current literature on the management strategies of RTAD and provide our institutional approach in treating this complex aortic pathology

Keywords Aortic dissection • Retrograde aortic dissection • Acute aortic syndromes • DeBakey type IIId • Iatrogenic type A dissection • Type A aortic dissection TEVAR • Prognosis of retrograde dissection

Introduction

Acute aortic syndrome includes penetrating athromatous ulcers (PAU), intramural hematomas (IMH), and aortic dissections; the most serious of which is aortic dissection. The continuum of severity increases from PAU, to IMH, and aortic dissection. This chapter will focus on IMH and dissection. IMH describes a condition where hematoma is seen in the aortic medial wall without flow through a false lumen. It is believed to be due to rupture of the vasa vasorum. Untreated, IMH may progress to aortic dissection and/or aortic rupture. Aortic dissection differs from IMH in that the inciting event is a disruption in the aortic intima accompanied by degeneration of the aortic media with flow through a false lumen [1–7].

Aortic dissections are classified according to the anatomic DeBakey and Stanford systems [2, 3, 8]. In the DeBakey system a Type I dissection originates in the ascending aorta and extends into the aortic arch and further distally. Type II dissection originates and is confined to the ascending aorta only. Type III dissection originates in the descending aorta and extends distally. Type III dissections have been subcategorized by Ruel et al. according to the distance the dissection extends distally (type IIIa, b, and c); and for proximal retrograde extension into the ascending aorta (type IIId) (Table 3.1) [9].

The Stanford system is categorized as type A or type B. Type A dissection involves the ascending aorta with any variable amount extending into the aortic arch and descending aorta. Type B dissection involves the descending aorta only. The Stanford system has become increasingly popular in recent years due to its ability to predict disease prognosis and guide therapeutic strategies. As our understanding of aortic pathologies have progressed there is an increased need for qualifiers that account for clinical status at the time of presentation as this has been shown to correlate with overall survival [10–12]. The group from the University of Pennsylvania has proposed a PENN classification system of type A dissections that accounts for clinical presentation and extent of dissection. In this system class A refers to dissection without aortic branch malperfusion or circulatory collapse. Class B refers to

Table 3.1 Classification of type A aortic dissections

Ascending and descending	Ascending	Descending
Stanford type A	Stanford type A	Stanford type B
DeBakey type I	DeBakey type II	Debakey type III

Table 3.2 Penn clinical classification of type A dissections

Clinical presentation	Definition of clinical presentation class
Class A	Clinical presentation characterized by *Absence* of branch vessel malperfusion or circulatory collapse
Class B	Clinical presentation characterized by *Branch* vessel malperfusion with ischemia e.g. stroke; ischemia extremity
Class C	Clinical presentation characterized by *Circulatory* collapse with or without cardiac involvement
Class B and C	Clinical presentation characterized by both *Branch* vessel malperfusion and *Circulatory* collapse

branch vessel malperfusion (e.g. stroke, ischemic limb, etc.). Class C refers to circulatory collapse with or without cardiac involvement. Class B and C refers to patients with circulatory collapse with branch vessel malperfusion (Table 3.2). The PENN classification system provides valuable prognosis data for clinicians that the Stanford and DeBakey systems fail to deliver [13, 14].

Emergent surgical repair is the gold standard for management of type A aortic dissection [3, 4, 6, 15, 16]. The standard operation entails aortic root reconstruction, valve resuspension, ascending aorta and hemiarch reconstruction. One of the major principles of repair is resection of the primary tear site, with stabilization of the true lumen flow. Untreated distal extent of dissection has been associated with poorer long-term outcomes. Recently, the use of antegrade stenting and TEVAR as an adjunct has become increasingly utilized and shown to improve long-term survival and decrease the need for subsequent distal aortic intervention [17–23]. RTAD are a subgroup of aortic dissection that can be categorized as spontaneous or iatrogenic. Patients with Spontaneous RTAD have historically been considered a high-risk endeavor. However, as surgical techniques for simultaneous treatment of the ascending and descending aorta have evolved, the surgical risk has decreased accordingly [20, 24, 25]. Iatrogenic RTAD have become an increasingly prevalent condition with an increasing body of literature dedicated to the description and proposed treatment strategies. Iatrogenic RTAD has been described after all forms of endovascular interventions involving the descending aorta; however, it is most commonly described after TEVAR for type B aneurysms and dissections. The rate of RTAD is currently believed to occur in 1–2 % of all patients undergoing TEVAR, and risk factors for its development include oversizing of thoracic stents, balloon manipulation of the proximal stent graft, and wire injury. Presentation of the RTAD can vary from intra-operative detection to several months post-procedure [17, 26–29].

Search Strategy

A literature search of English language publications from 1990 to 2013 was used to identity published data on diagnosis, natural history, and treatment of type A aortic dissection originating distal to the left subclavian artery (Table 3.3). Select studies

Table 3.3 PICO table for management of retrograde type A dissections

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with retrograde type A aortic dissections	Open surgical repair	Medical therapy or endovascular repair	Perioperative mortality and morbidity

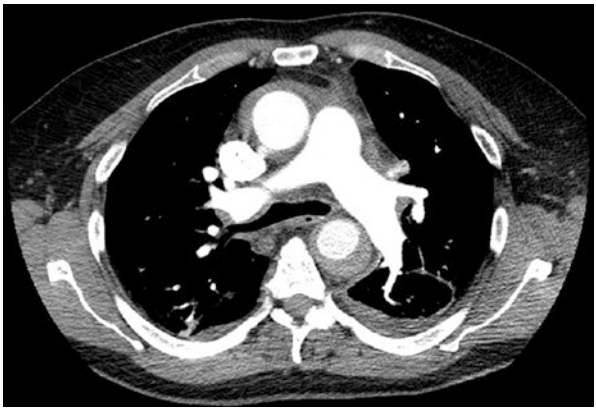

Fig. 3.1 CT scan demonstrating patient with a Type B IMH and retrograde involvement of hematoma in the ascending aorta

dated prior to 1990 were utilized to provide historical context. Databases searched included PubMed, Embase, Medline, and Cochrane Evidence Based Medicine. Terms used in the search were; "type A aortic dissection" OR "type A dissection" OR "retrograde aortic dissection" OR "Debakey type IIId" OR "aortic dissection after TEVAR" OR "iatrogenic aortic dissection" OR "Prognosis of iatrogenic type A dissection" OR "Prognosis of retrograde type A dissection" AND/OR "medical management". The data was classified using the GRADE system.

Results

Clinical Relevance of Type A Aortic Dissections Originating Distal to the Left Subclavian Artery

Spontaneous Type A Retrograde Dissection

Spontaneous RTAD are a subtype of type A dissection whose incidence and natural history are incompletely understood (Fig. 3.1). Studies suggest varying rates of RTAD. Ruel and colleagues published the first series formally classifying RTAD in 1975 showing 9 (10 %) of 91 with type A dissections having intimal flaps in the descending aorta [9]. In 1984 Miller et al. reported 5 (10 %) of 48 cases with descending aorta intimal flaps [30]. More recent studies in 1993 and 1994 by Erbel et al. [31] and Lansman et al. [32] demonstrated rates of 27 % (22 of 82) and 7 % (5 of 69) cases respectively. Lansman published a second report in

Table 3.4 Incidence and mortality of spontaneous type A retrograde dissection

Author (year)	Incidence	Mortality	Study type (evidence quality)
Ruel (1975)	9/91 10 %	8/9 89 %	Case series (low)
Miller (1984)	5/48 10 %	Not recorded	Case series (low)
Erbel (1993)	22/82 27 %	10/22 45 %	Case series (low)
Lansman (1994)	6/69 9 %	0/6 0 %	Case series (low)
Lansman (1999)	8/139 6 %	0/8 0 %	Case series (low)
Kaji (2003)	27/109 25 %	4/27 15 %	Case series (low)
Kim (2014)	49/538 9.1 %	4/49 8 %	Case series (low)
Total:	125/1076 11.6 %	26/121 21 %	

1999 where the rate of RTAD was found to be 6 % [33]. In a 2003 study by Kaji and colleagues comparing outcomes of antegrade and retrograde type A dissection found 27 of 109 (25 %) cases to have intimal tears in the descending aorta (Table 3.4) [34]. The most recent study, performed by Kim and colleagues at a single institution between 1999 and 2011 found the rate of retrograde dissection to be 9.1 % (49 of 538) [35].

Iatrogenic Retrograde Type A Dissections

Iatrogenic RTAD is one of the most catastrophic complications of TEVAR (Figs. 3.2 and 3.3). As indications and overall number of TEVAR cases continues to expand, it is likely that the prevalence of iatrogenic RTAD will increase. Current literature suggests varying incidence between 1 and 6.8 % [36–39]. A review of the European Registry on Endovascular Aortic Repair Complications found an overall rate of iatrogenic dissection to be 1.33 %, with an associated mortality of 42 %. Time of onset in this study varied from intraoperative to 1050 days post-TEVAR [27]. A single center study from the University of Pennsylvania in 2013 examining reintervention after TEVAR found the rate of iatrogenic RTAD to be 1.3 % (9 of 680), with associated operative mortality of 22 % (2 of 9) [39]. In 2008, Langer and colleagues reported the incidence of RTAD after TEVAR to be 1.8 % (2 of 106) [37]. A study by Neuhauser et al. in 2005 showed a rate of type A retrograde dissection after TEVAR to be 6.8 % (5 of 73), with a median time of RTAD detection to be at 20 days (range 2–124 days). The associated mortality in this report was 40 % [38]. In 2011, Dumfarth and colleagues examined 421 patients who underwent TEVAR at two institutions and found that 5 (1.1 %) patients developed RTAD [26]. A 2009

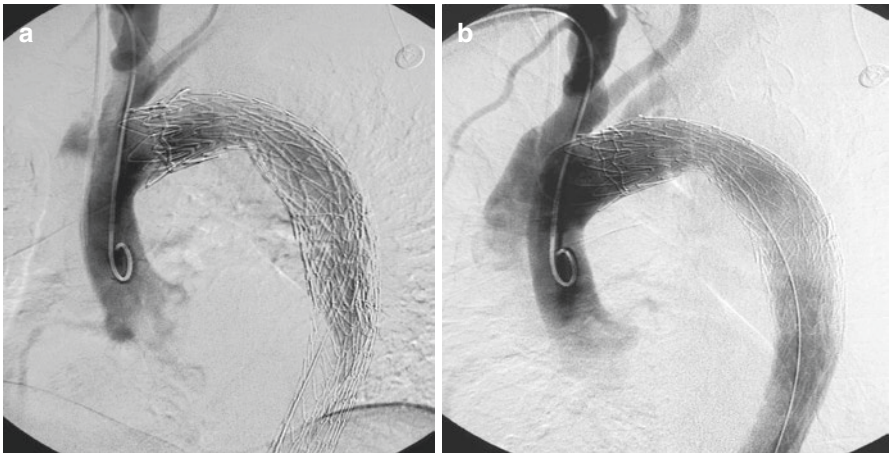

Fig. 3.2 (**a**, **b**) Series of angiograms performed after TEVAR showing retrograde dissection

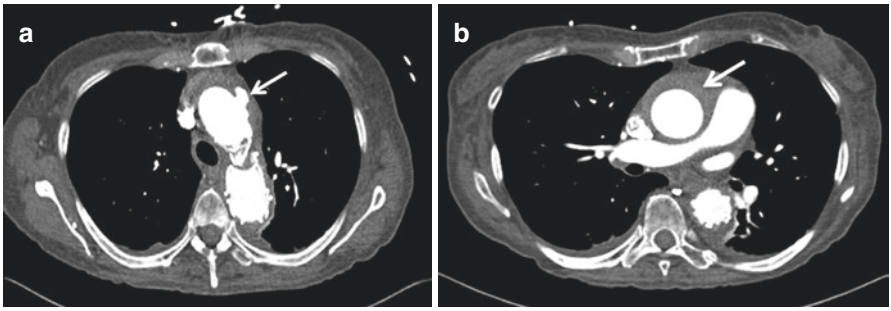

Fig. 3.3 Patient with a retrograde type A IMH who presented 4 weeks after a TEVAR for chronic type B aneurysm with CT scan demonstrating the entry tear (**a**: *arrow*) and extensive IMH (**b**: *arrow*)

study in China by Dong and colleagues examined a single center experience where 11 (2.4 %) of 443 patients undergoing TEVAR developed RTAD with associated mortality of 27.3 % [40].

Risk Factors for Spontaneous Type A Retrograde Dissection

Spontaneous Type A Retrograde Dissection

Known risk factors for Spontaneous RTAD are currently believed to be identical to those of antegrade dissections. Hypertension, atherosclerosis, preexisting aortic aneurysm, aortic ulcer, connective tissue disease, advanced age, and biscuspid aortic valve disease have all been associated with increased risk [1, 6, 12, 16, 41–44]. No literature specifically focusing on patient risk factors for de novo RTAD was found in the preparation of this chapter.

Table 3.5 Risk factors for RTAD during TEVAR

Stent graft injury	Guidewire injury
Sheath injury	Balloon manipulation of stent graft
Proximal stent graft placement	Bare metal stents
Oversizing of the stent graft	Steep aortic arch angulation (>60°)
Connective tissue disease	Aortic fragility
Ascending aorta diameter >40 mm	Progression of aortic disease

Iatrogenic Type A Retrograde Dissection

The primary risk factor for the development of iatrogenic RTAD is endovascular manipulation of the aortic arch and DTA, most commonly, during TEVAR and hybrid surgical procedures [26, 27, 39, 45–48]. A study by Eggebrecht and colleagues examining the European registry on endovascular repair complications found the majority of iatrogenic RTAD to be caused by stent graft injury to the aorta (N = 29, 60 %). Other causes included guidewire/sheath injury (N = 7, 15 %), as well as progression of underlying disease (N = 7, 15 %) [27]. Other factors associated with increased risk for development of iatrogenic RTAD include balloon manipulation of the stent graft (especially in the proximal portion of the graft) the use of proximal stents with bare metal springs, oversizing the stent graft, steep aortic arch angulation (>60°) [49], connective tissue disease [40], fragile aorta, ascending aorta diameter >40 mm, progression of aortic disease [48], and patients with connective tissue disease (Table 3.5) [26, 49].

Treatment Strategies

Treatment of Spontaneous Type A Retrograde Dissections

A wide range of strategies have been proposed for treatment of spontaneous RTAD, including; medical management, endovascular therapies, open repairs, and hybrid procedures. To date, no randomized studies have been performed comparing these therapies. Most institutions advocate for emergent surgical repair for RTAD due to the high risk of malperfusion syndromes, cardiac tamponade, continued aortic dilation, and rupture.

Recent studies have examined the use of initial medical therapy with interventions when appropriate on select patients with spontaneous RTAD if the following conditions are met (1) false lumen thrombosis, (2) no malperfusion syndromes and (3) acceptable aortic diameter (<5.5 cm), no aortic rupture or tamponade [34, 35]. In these studies, the outcome of patients initially treated with medical therapy is superior to the surgically treated groups, however, the medically managed groups presented without malperfusion or cardiovascular collapse (PENN Class A), which has previously been associated with improved survival even when treated with emergent surgical therapy [14].

Endovascular treatment of RTAD has been reported in the literature with increasing frequency over recent years [49–59]. A systematic review written by Lyons et al. 2011 examined the body of literature dedicated to the use of TEVAR for RTAD. In this study, the in-hospital mortality for TEVAR was 1.2–2.4 % [60], a significant improvement compared to open repair, which carries at least 20 % in-hospital mortality [12, 30]. Nevertheless, patient selection bias and lack of long-term follow-up were important study limitations. Therefore, until a randomized study comparing these 3 treatment modalities is performed, open surgical repair remains the gold standard.

The surgical principles of open repair for RTAD are the same as for acute type A dissection, including; (1) Complete excision or coverage (through hybrid techniques) of the primary tear site, (2) Replacement of the affected ascending aorta with repair to the aortic root and arch as clinically indicated, (3) True lumen stabilization, and, (4) Use of neuroprotective strategies to minimize the risk of stroke or cerebral ischemia [24].

Treatment of Iatrogenic Type A Retrograde Dissections

Mortality rates for iatrogenic RTAD is higher than the spontaneous variant, reported mortality up to 42 % [27, 47, 54]. There has been speculation and limited clinical evidence that the type of instrumentation causing the retrograde dissections affects the clinical outcome of patients. Stent graft induced new injuries have been associated with worse prognosis than wire or catheter based injuries [40]. Some groups advocate conservative treatment of iatrogenic RTAD if they are small in size/localized, and not caused by the stent graft injury. Iatrogenic RTAD related to the TEVAR graft is widely considered to be the most serious form. In these patients, the universal consensus is that open surgical repair is the treatment of choice in patients who are medically stable [46].

Recommendations

Spontaneous Type A Retrograde Dissection

Spontaneous RTAD is a lethal condition that deserves prompt surgical intervention in all patients without prohibitive risk. Some studies have been published demonstrating acceptable outcomes for select patients managed with initial medical therapy. However, the patients in these studies presented with PENN Class A clinical status, which is associated with favorable outcomes even when treated with prompt surgical therapy. Medical management leaves these patients at risk for the future development of malperfusion syndromes (and associated increased operative risk),

aneurysmal dilation, and rupture. Prior to recommending medical therapy in patients who are otherwise good surgical candidates, studies comparing the outcomes of medical to surgical therapy in patients with similar clinical status are warranted.

Iatrogenic Type A Retrograde Dissections

Iatrogenic RTAD is a dreaded complication of elective and emergent TEVAR. The current recommendations for iatrogenic RTAD is emergent surgical repair, however, associated operative mortality is greater than 40 %. As the indications for TEVAR continue to broaden and healthier patients are treated with this modality, associated operative mortality for open repair of iatrogenic RTAD may decrease accordingly.

A Personal View of the Data

Spontaneous Type A Retrograde Dissection

De novo RTAD is a life threatening condition that requires prompt surgical repair in all patients able to tolerate open cardiac surgery. Concerns over increased surgical morbidity for RTAD has been largely invalidated as improved surgical techniques for treatment of arch disease and advanced circulation management strategies have evolved. In select patients with prohibitive surgical risk, there may be a role for selective stenting and/or initial medical therapy; however, no randomized trials have compared outcomes between medical, surgical, and endovascular strategies. At this time, it is hard to justify conservative management of RTAD given the well document survival benefit and durability of open surgical repair.

Iatrogenic Type A Retrograde Dissection

Iatrogenic RTAD is a serious complication of TEVAR and is associated with increased morbidity and mortality. The most serious cases seem to arise from stent graft induced aortic injury, which have been associated after all devices currently in use. Iatrogenic RTAD should be managed with open surgical procedures that repair the site of injury as well as the proximal extent of disease. Open surgical repair has been historically associated with increased mortality in iatrogenic cases compared to spontaneous RTAD. This is most likely due to the more extensive aortic arch injury associated with TEVAR, higher patient comorbidity in patients undergoing TEVAR, and greater technical difficulty associated with arch reconstruction in

TEVAR cases. The overall rates of RTAD will likely decrease as provider skill increases and TEVAR technology continues to improve.

Recommendations for Iatrogenic Type A Retrograde Dissection

- Patients with iatrogenic RTAD occurring as a complication of endovascular therapies should undergo emergent open surgical repair with treatment of the proximal extent of disease and the site of intimal tear (**evidence quality very low; strong recommendation**).
- Patients who are poor surgical candidates with iatrogenic RTAD may be managed with medical therapy and/or endovascular modalities if the dissection is asymptomatic without evidence of malperfusion syndromes (**evidence quality very low; weak recommendation**).

Recommendations for Spontaneous Type A Retrograde Dissection

- Patients with acute onset spontaneous RTAD, emergent open surgical repair should be undertaken with treatment of the proximal extent of disease as well as the site of intimal tear (**evidence quality moderate; strong recommendation**).
- Patients who are poor surgical candidates with prohibitive risk may be treated conservatively with medical and/or endovascular modalities if the dissection is asymptomatic without evidence of malperfusion syndromes (**evidence quality very low; weak recommendation**).

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Chapter 4
In Patients with Small AAA, Does Medical Therapy Prevent Growth?

Kenneth R. Ziegler and John A. Curci

Abstract Throughout most of the twentieth and now twenty-first century the dominant treatment paradigm for abdominal aortic aneurysm (AAA) has been mechanical exclusion of the degenerative wall to prevent the consequences of aortic wall failure, namely, rupture and death. The medical literature has been clear that the risks of a procedural intervention on "small" AAA do not exceed the benefits when the maximal diameter is less than 5.5 cm in men. Nevertheless, the underlying pathology of the small aneurysm remains active and nearly always leads to progressive weakening and dilatation of the aortic wall. A large potential exists in this patient class to modify the aneurysmal disease process to slow or halt the growth of small AAA, thereby preventing the need to undergo the procedural risks and costs of mechanical exclusion. Recent progress in our pathobiologic understanding of aneurysmal degeneration has provided specific opportunities for disease process modification. No therapy has yet been proven to alter AAA progression; this chapter reviews the insights available from published clinical studies and summarizes potential therapies in contemporary clinical trials.

Keywords AAA • Abdominal aortic aneurysm • Aneurysm growth • Doxycycline • HMG-CoA reductase inhibitors • Statins • Antihypertensives • Inflammation • Vascular surgery

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Introduction

The current paradigm for the management of small abdominal aortic aneurysms (AAA) is continued observation with serial imaging until the aneurysm reaches a size appropriate for surgical intervention [1]. Though various factors may influence the growth rate of AAAs based on the individual patient's genetic predispositions and comorbidities, the median expansion rate of small AAA appears to hover around 2.5 mm/year [2]. This rate is highly dependent on the initial size of the aneurysm on discovery, and tends to increase with increasing diameter [3]. However, the vast majority of AAA detected through screening programs fall below the minimum diameter threshold of 5.0 cm in women and 5.5 cm in men where the benefits of surgical intervention likely exceed the risks [4]. These small AAA represent a major opportunity for disease-modifying intervention: if a novel therapy could be found to induce a reduction of the growth rate of AAAs, the risk of mechanical wall failure may be reduced or eliminated, thus obviating the need for mechanical intervention. This chapter reviews the ongoing effort to achieve that goal.

Search Strategy

A literature search of articles published in the English language between 2000 and 2014 was undertaken in order to identify reported data on the influence of medical therapies on the growth of small abdominal aortic aneurysms (AAA) using the PICO outline (Table 4.1). In addition, given the dynamic nature of the data in this field, our search was extended into identifying ongoing studies specifically addressing sole medical management of small AAA. The databases searched were PubMed, Medscape, the ClinicalTrials.gov registry, and the EU clinical trials registry. Terms included in the search were "abdominal aortic aneurysm," AND "medical management," "expansion rate/prevention," "growth rate/prevention." Articles were excluded if the aneurysms discussed were larger than 50 mm in maximal diameter, if non-abdominal aortic aneurysms or non-aortic aneurysms were studied, considered surgery as the treatment arm, discussed study effects in non-human populations (animal or laboratory models of aneurysmal disease), or limited the examination to molecular risk factors and mechanisms rather than clinical outcomes of pharmacologic intervention; likewise, preliminary results and articles were excluded if subsequent updated data and studies were published by the same group. Seven original

Table 4.1 PICO table for the prevention of growth of small AAA by medical management

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with abdominal aortic aneurysms measuring less than 5.5 cm in maximal diameter	Pharmacologic therapy, exercise therapy	No pharmacologic therapy	Expansion of AAA, rate of expansion

publications and two meta-analyses were included in this review; nine relevant clinical trials were identified in the registries.

Results

Medical Therapies

Between the theories of aneurysmal disease derived from the observational experience of affected patients and the experimental study of abdominal aneurysms, including the development of various animal models, multiple therapeutic targets have emerged as potential targets for pharmacological intervention. An overview of studied treatments since 2000 is reflected in Table 4.2.

Propranolol

One of the earliest agents to demonstrate decreased aneurysmal growth in preclinical models was propranolol, an effect believed to be related to reduced cardiac contractility and an effect on aortic tensile strength [5–7]. Further nonrandomized human trials suggested a beneficial effect of beta-blockade on aneurysmal growth rates [8, 9]. Based on this background, the Propanolol Aneurysm Trial Investigators conducted a multicenter, double-blind randomized placebo-controlled trial to study the effect of propranolol on the growth rate of AAAs measuring 3.0–5.0 cm. Having recruited 276 patients into the experimental arm and 272 patients into the placebo arm, the study ultimately demonstrated no significant reduction of growth due to the beta-blocker by intention to treat analysis (2.2 mm/year on propranolol vs 2.6 mm/year on placebo, $p = 0.11$) over a mean follow up period of 2.5 years. Furthermore, the propranolol treatment was poorly tolerated by these elderly patients – 39 % of the patients permanently withdrew from the trial due to adverse effects of the drug, namely fatigue, shortness of breath, and bradycardia [10].

Macrolide Antibiotics

Based on studies that demonstrated the presence *Chlamydophilia pneumoniae* in atherosclerotic arterial lesions and AAAs [11–13], as well as an association between IgA positivity against *C. pneumoniae* and expanding small AAA [14], Vammen et al. investigated the role of antibiotic therapy on AAA growth rate. The macrolide antibiotic roxithromycin was compared to placebo in a double-blind randomized controlled trial; pre-recruitment power calculations estimated a need for 100 subjects to detect a 33 % reduction in expansion rate. Ultimately, 92 eligible men were randomized into the trial with a mean follow up of 1.5 years. The trial resulted in a 43 % reduction in overall mean expansion rate in the

Table 4.2 Summary of the efficacy of medical therapeutics in small AAA disease (since 2000)

Intervention	Reference	Effect on AAA growth	Grade of evidence	Strength of recommendation
Propanolol	Propanolol Aneurysm Trial Investigators (2002) *RCT*	No significant inhibition vs placebo (2.2 vs. 2.6 mm/year, p=0.11)	High quality	Strong
Macrolides	Vammen et al. (2001) *RCT*	43 % reduction in growth rate vs. placebo (1.56 vs. 2.75 mm/year, p<0.02)	Moderate quality	Weak
	Karlsson et al. (2009) *RCT*	No significant inhibition vs. placebo (2.2 vs. 2.2 mm/year, p=0.85)	High quality	Strong
Doxycycline	Mosorin et al. (2001) *RCT*	Inhibition at 6–12 and 12–18 month internals vs placebo (p=0.01), but no significant difference for trial	Low quality	Weak
	Meijer et al. (2013) (PHAST trial) *RCT*	Adjusted[a] 0.8 mm increase in aneurysm size vs. placebo at 18 months (4.1 vs. 3.3 mm, p=0.016)	Moderate quality	Weak
HMG-CoA Reductase Inhibitors	Twine et al. (2011) *Meta-analysis*	No significant difference in mean growth rate with statin therapy (–0.14 mm/year, p=0.16)	Low quality	Weak
	Takagi et al. (2012) *Meta-analysis*	Significant inhibition of growth with statin therapy vs. no statin	Moderate quality	Weak
Aspirin	Lindholt et al. (2008) *Cohort*	43 % reduction in growth rate of aneurysms 4.0–4.9 cm vs no therapy (2.92 v 5.18 mm/year, 2.27 mm/year difference, 95 % CI 0.42–4.11)	Low quality	Weak
	Karlsson et al. (2009) *Post-hoc analysis*	31 % reduction in growth rate vs. placebo (1.8 vs. 2.6 mm/year, p=0.004)	Low quality	Weak
Exercise	Myers (2013) *RCT*	No significant inhibition vs. usual care	Moderate quality	Strong

[a]Post-hoc analysis of results using linear mixed modeling

roxithromycin group (1.56 mm/year vs. 2.75 mm/year, p = 0.02). On post-hoc analysis, this was found to be most effective during the first year of treatment; the change in rate during the second year was not significantly different between the two treatment arms [15].

More recently, the effect of azithromycin on small AAA growth rate was tested by Karlsson et al. in a larger double-blind randomized controlled trial; the aims of this study also included assessing the association between titers of *C. pneumoniae* antigen and AAA growth. 247 patients were randomized into the experimental azithromycin regimen (600 mg daily for 3 days, then once weekly for 15 weeks) or placebo and followed for at least 18 months; 34 patients were excluded due to loss to follow up. Between the two treatment arms, no significant difference was found in median AAA expansion rate (2.2 mm/year in the azithromycin group vs. 2.2 mm/year in the placebo group, p = 0.85). Likewise, no correlation was identified between the rate of aneurysm expansion and the level of serological markers for *C. pneumoniae* infection [16].

Doxycycline

The most readily apparent histologic change associated with AAA is the fragmentation and loss of medial elastin. Unlike the rationale for the macrolide antibiotic use, the use of doxycycline is primarily predicated on its capacity to broadly inhibit the activity of elastolytic matrix metalloproteases, which are thought to be responsible for the loss of the elastic fibers [17–19]. Mosorin et al., conducted a pilot double-blind, randomized placebo-controlled trial to elucidate the effect of doxycycline on small aneurysm growth rates. A small study population of 34 patients were randomized into a group of 17 patients receiving 150 mg doxycycline daily for 3 months or a control placebo group of 15 patients (2 patients excluded due to emergent surgery unrelated to AAA and death) and observed with ultrasound scanning for a mean follow up of 18 months. While the overall aneurysm expansion rate was higher in the placebo group than the experimental arm over the course of the trial, this difference did not reach statistical significance (1.5 mm/year vs 3.0 mm/year, p > 0.05). Only on post-hoc analysis of timeframes in this small study does there appeared to be a significant difference: in the 6–12 month follow up period (0.0 mm/year vs. 2.0 mm/year, p = 0.01), as well as the 12–18 month period (0.0 mm/year vs 5.0 mm/year, p = 0.01) [20].

These study results are remarkable in three ways. First, this was the first randomized trial to show a significant effect on AAA growth. Second, the effect on AAA growth appeared to be durable long after the cessation of the doxycycline therapy. Third, the effect of doxycycline on AAA growth did not become evident until after the first 6 months.

Subsequent to this pilot investigation, the PHarmacologic Aneurysm Stabilization Trial (PHAST) study – a double blind, randomized placebo controlled trial - was conducted in 14 Dutch hospitals between 2008 and 2011, as eported by Meijer et al. Two groups of patients were randomized for the trial, one with AAA diameters between 3.0 and 5.0 cm and a second group where the maximal AAA diameter was

>5.0 cm, but the patient was either a poor candidate for surgical intervention or refused surgical repair. A total of 286 patients were recruited and randomized to a daily dose of 100 mg of doxycycline or placebo over 18 months; growth rate was measured by ultrasound in the AP plane only using a single ultrasonographer. This study was closed prematurely at an interim safety review due to apparent futility. There was also a larger than expected loss to follow-up. A revised post-hoc data analysis, conducted under a linear mixed model, indicated that doxycycline treatment was associated with an increase in aneurysm growth (difference in diameter of growth 0.8 mm, 95 % CI 0.1–1.4 mm, p = 0.016) [21].

Careful examination of the PHAST data shows that the majority of the apparent accelerated growth effect of doxycycline occurred in the first 6 months of therapy. Subsequently, the growth curves did not appear to further diverge. Combined with the interval results of the Mosorin study, this finding suggests that the effect of doxycycline may be delayed. It should also me noted that the journal's editorial staff included a boxed note indicating that this study's results, while provocative, could not be considered definitive.

HMG-CoA Reductase Inhibitors

The class of hydroxymethylglutaryl-CoA reductase inhibitors ("statins") are among the most studied in medical literature. With strong evidence of efficacy in other realms of cardiovascular disease including claudication [22], cardiac risk reduction [23], and stroke prevention [24], much attention has been paid to the potential for these drugs in the treatment of aortic aneurysmal disease. All published literature to date consists of cohort studies, most frequently based on re-analysis of the results of longitudinal studies of patients with AAA. Twine and Williams published a meta-analysis of 12 of these cohort studies in 2011, aiming to validate claims of a beneficial effect of statin therapy on AAA growth rates. In their subgroup analysis of high-quality cohort studies examining the growth rate in small AAA, they found no significant difference in AAA expansion rates associated with the drug (SMD -0.14 mm/year, p = 0.16) [25].

More recently, Takagi et al. conducted a separate meta-analysis of 7 "high quality" observational studies, including studies in the Twine analysis, addressing the effect of HMG-CoA reductase inhibitors on AAA growth. Their study demonstrated a statistically significant result favoring statin therapy (SMD −0.367, 95 % CI −0.566 to −0.168, p < 0.001). Because management of patients with small AAA should include statin therapy as part of a program to reduce cardiovascular events in these patients, it is unlikely that the effect of statins on AAA growth will ever be analyzed in a randomized placebo controlled trial. Based on these cohort analyses, these agents can reasonably be administered to patients with small AAA without concern for adverse effects on AAA growth [26].

Aspirin

Compared to the other pharmacological interventions discussed, the data supporting aspirin (ASA) use in AAA disease tends to be of lower quality. Lindholt et al. published an observational cohort study in 2008 that examined the role of low-dose

aspirin. Over a mean follow up of 6.6 years, 148 patients with small AAA were followed annually after a positive screening exam until they were referred to surgery when the aneurysm reached 5.0 cm in diameter. Among those patients with an aortic diameter of 4.0–4.9 cm on initial screening, those on low-dose ASA were found to have a statistically significant 43 % reduction in aneurysmal growth rate compared to non-users (2.92 mm/year vs. 5.18 mm/year; difference 2.27 mm/year, 95 % confidence interval 0.42–4.11) [27].

The Karlsson azithromycin study, discussed above, included a post-hoc analysis that examined the role of ASA in small aneurysmal growth. In the subset of patients that were on chronic ASA therapy, a lower expansion rate was observed compared to those patients who did not take ASA (1.8 mm/year vs 2.6 mm/year, $p=0.004$). While interesting, as a retrospective observation on a study designed to randomize to azithromycin use, the ASA observation is, at best, weak evidence of an inflammatory role in the etiology of aneurysmal disease [16].

Exercise

The growth of an AAA may, in part, depend on locally deranged flow patterns within the distal aorta, including high resistance outflow. Increasing exercise, particularly of the lower body, has been hypothesized to alter distal aortic flow dynamics through decreased resistance, and thereby slow the growth of small AAA [28, 29]. Myers et al. conducted a randomized controlled trial to elucidate the role of exercise training in the prevention of small AAA growth. In this unique study, 140 patients with small AAA were identified and randomized to exercise therapy ($n=72$) or regular care ($n=68$); these patients were followed for up to 3 years, with an average of 23.4 months of follow-up. Though the exercise regimen was well tolerated by the experimental group, no significant difference in aneurysmal growth rate was identified at 1, 2, or 3 years [30].

Active Clinical Investigations

Nine ongoing and recently completed clinical trials examining medical therapy on small AAA were identified in the publically accessible databases; the studies are described by intervention below and summarized in Table 4.3.

Antihypertension

Uncontrolled hypertension can adversely affect aneurysm growth, possibly by simply increasing the stress on the aortic wall [31]. In addition, alterations in BP systems regulation, particularly related to the renin-angiotensin-aldosterone axis, have been shown to have an important effect on many models of AAA. The efficacy of angiotensin-receptor blockers on AAA growth rate are being investigated by the TEDY group (NCT01683084), testing telmisartan against placebo, and in the BASE trial (NCT01904981), where valsartan is being trialed against the beta-adrenergic receptor

Table 4.3 Ongoing clinical trials examining the efficacy of medical therapy in abdominal aortic aneurysms

ClinicalTrials.gov ID number	EudraCT number	Study Title	Intervention	Primary Outcome	Estimated completion date	Surveillance modality
NCT01683084	2012-001859-39	TEDY	Telmisartan vs. placebo	AAA growth rate	April 2015	CT Angiography
NCT01904981		BASE trial	Atenolol vs. Valsartan	AAA growth rate	October 2016	CT Angiography
NCT01118520	2010-020226-17	AARDVARK	Perindopril vs. Amlodipine vs. placebo	AAA growth rate	August 2014	Ultrasound
NCT01425242		PISA	Aliskiren vs. Amlodipine	Change in vessel wall FDG uptake	Sept 2013	PET-CT
NCT02007252	2013-002088-25	ACZ885 Therapy for AAA	ACZ885[a] vs. placebo	Change in baseline AAA size	December 2015	Ultrasound
NCT01354184	2011-000285-35	AORTA	CRD007[b] at 40 mg, 25 mg, 10 mg vs placebo		Completed	
NCT02225756		ACA4	Cyclosporine A vs. placebo	AAA diameter evolution	September 2017	CT Angiography
NCT02070653	2013-002736-24	TicAAA	Ticagrelor vs. placebo	AAA volume growth	June 2015	MRI, Ultrasound
NCT01756833		N-TA^3CT	Doxycycline vs. placebo	AAA maximum diameter	June 2016	CT Angiography

[a]ACZ885 carries the name Canakinumab (trade name Ilaris): human monoclonal IL-1b antibody
[b]CRD007 is a perimolast potassium compound acting as a mast cell stabilizer

antagonist atenolol. Further examinations on the renin-angiotensin-aldosterone pathway are being conducted in the AARDVARK trial (NCT01118520), where both perindopril and the calcium channel blocker amlodipine are being compared to placebo in their effect of AAA growth rate, and in the PISA trial (NCT01425242), where the direct renin inhibitor aliskiren is directly compared to amlodipine on its effect of reducing inflammation of the aneurysm vessel wall, as measured by FDG-avidity on PET-CT.

Anti-inflammation

Directly targeting inflammation as the mediator of aneurysmal growth, NCT02007252 is utilizing the canakinumab (formerly ACZ885), a human monoclonal antibody against interleukin-1b, compared to placebo, to determine if there is a difference in the change of aneurysm growth rates from baseline. The recently completed AORTA trial (NCT01354184) was a safety and efficacy study on CRD007 (perimolast potassium), a mast-cell stabilizer. Along these lines, the ACA4 trial (NCT02225756) is examining whether the immunosuppressant cyclosporine A can prevent aneurysmal diameter growth compared to placebo on CT angiography.

Antiplatelet

The TicAAA trial (NCT02070653) is testing the effect of ticagrelor, a platelet aggregation inhibitor targeting the P2Y12 receptor, on AAA volume growth vs. placebo on MRI and ultrasound.

Doxycycline

A US NIH-sponsored investigation of doxycycline therapy is being undertaken under the title “Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial” (NCT0756833). Patients will be randomized to 100 mg of doxycycline twice daily vs. placebo, with maximum AAA diameter on CT being the primary outcome.

Recommendations

There is currently no satisfactory evidence to support the clinical use of any therapy for the purpose of modifying the aneurysmal disease process and reducing the growth of small AAA. The inclusion of an HMG-CoA Reductase inhibitor and/or ASA as part of the management of overall cardiovascular risk in these patients is recommended and is not likely to be detrimental to aneurysm growth. Similarly, the appropriate management of blood pressure by standard guidelines is essential in patients with AAA, however any advantages of one agent or class of agents over another have not been established.

A Personal View of the Data

While there is no available therapeutic that has been shown to be clearly effective in aneurysm disease modification as measured by maximal diameter growth, there are a large number of ongoing trials which hold great promise to help these patients. The only agents for which we have some weak data, such as statins and ASA, may reduce the rate of growth of the AAA, but may also have salutary effects on lifespan. Paradoxically, this may reduce the effectiveness of these agents to impact the need for mechanical intervention since a reduction in growth rate can be offset by an increase in overall lifespan which still allows the AAA to reach a size at which its rupture risk is high. All caregivers should seriously consider whether their patients with small AAA would be good candidates for clinical trial enrollment.

Recommendations

- Optimization of cardiovascular health through the management of lipids, blood pressure and platelet hyperactivity is appropriate in patients with AAA.
- Patients with small AAA may derive some mild direct growth suppression from HMG-CoA reductase inhibitors (**low quality, weak recommendation**) and aspirin therapy (**low quality evidence, weak recommendation**) should they be prescribed these agents for related indications.
- There are a large number of on-going randomized trials which are designed appropriately to identify an effect on aneurysm growth, and it is reasonable to consider enrollment and randomization in patients with small AAA.

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Chapter 5
Challenging AAA Neck Anatomy: Does the Fenestrated or Snorkel/Chimney Technique Improve Mortality and Freedom from Reintervention Relative to Open Repair?

Brant W. Ullery and Jason T. Lee

Abstract Complex endovascular aneurysm repair (EVAR) most often refers to extension of the proximal seal zone with preservation of branch vessel patency, thereby expanding the applicability of aortic endografts from the infrarenal to the suprarenal aorta. Snorkel/chimney (ch-EVAR) and fenestrated EVAR (f-EVAR) are the two most commonly utilized advanced endovascular techniques to combat hostile proximal neck anatomy. The current literature examining this topic is limited to level II data and therefore should be interpreted with appropriate caution. Nevertheless, available data to date does provide low quality evidence supporting a promising trend towards improved perioperative outcomes, including reduced perioperative mortality, with complex EVAR compared to open surgical repair, although this early clinical benefit may come at the expense of increased need for secondary intervention.

Keywords Abdominal aortic aneurysm • Endovascular aneurysm repair • Fenestrated • Snorkel • Chimney

Introduction

Endovascular aneurysm repair (EVAR) has revolutionized the management of patients with abdominal aortic aneurysm (AAA) disease since its introduction in 1991 [1]. EVAR has steadily become recognized as the standard of care for routine infrarenal AAAs and has supplanted open surgical repair (OSR) as the predominant

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therapeutic modality for such patients over the last decade [2]. The safety and efficacy of this less invasive modality has been reliably demonstrated among those with suitable aneurysm morphology [3]. However, it is estimated that up to 30–40 % of patients are unsuitable anatomic candidates for conventional EVAR, most commonly due to challenging proximal aortic neck anatomy [4]. The inadequate proximal landing zone below the renal arteries precludes EVAR using standard devices, thereby restricting such patients to OSR and the associated risks of suprarenal or supravisceral clamping. With increasing surgeon experience and accompanying technologic advances, a myriad of complex endovascular strategies have evolved to address this issue of proximal neck fixation, ranging from deployment of conventional infrarenal aortic stent-grafts outside the instructions for use of the device, homemade and physician-modified endografts, snorkel/chimney (ch-EVAR) approaches with parallel covered stents, and utilization of customized fenestrated (f-EVAR) endografts.

The conceptual basis for complex EVAR involves extension of the proximal seal zone with preservation of branch vessel patency, thereby expanding the applicability of aortic endografts from the infrarenal to the suprarenal aorta. Ch- and f-EVAR serve as the two most commonly utilized advanced endovascular techniques to combat hostile proximal neck anatomy. Despite excellent early and mid-term outcomes using both of these strategies, uncertainties remain regarding the durability of this approach and optimal management of patients with challenging AAA neck anatomy. This chapter addresses whether complex EVAR using either a fenestrated or snorkel technique for the treatment of challenging AAAs (e.g. juxtarenal, suprarenal, type IV thoracoabdominal) is associated with improved mortality or freedom from reintervention relative to OSR.

Search Strategy

A literature search of English language publications from January 2004 – October 2014 was used to identify published data on open and endovascular repair of complex AAAs using the PICO outline (Table 5.1). Databases searched were PubMed, Embase, Ovid, Science Citation Index/Social sciences Citation Index and Cochrane Evidence Based Medicine. Aortic pathologies encompassed degenerative atherosclerotic aneurysms, post-EVAR type I endoleaks, and para-anastomotic aneurysms extending to the juxtarenal or suprarenal aorta. Search terms were “pararenal/

Table 5.1 PICO table for patients with complex abdominal aortic aneurysms

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with abdominal aortic aneurysms having complex aneurysm neck morphology	Fenestrated or snorkel/chimney endovascular aneurysm repair (EVAR)	Open repair	Mortality and need for re-intervention

juxtarenal/suprarenal abdominal aortic aneurysm", "challenging/hostile/complex aneurysm neck anatomy", "fenestrated endovascular aneurysm repair", "FEVAR", "snorkel/chimney/periscope endovascular aneurysm repair", "fenestrated/chimney/snorkel endograft", "fenestrated device", "double barrel", or "open abdominal aortic aneurysm repair". Only reports specifically addressing mortality, perioperative morbidity, and need for re-intervention were included. Duplicate reports were removed and all manuscripts were appraised critically for eligibility before inclusion. The references of all articles used were further examined to identify additional relevant reports. The data was classified using the GRADE system. Reports pertaining to non-type IV thoracoabdominal aortic aneurysms, aortic dissections, and cases series with fewer than 10 patients were excluded.

Results

Early Mortality and Associated Perioperative Morbidity

While early reports demonstrated OSR of complex AAAs to be associated with increased morbidity and mortality rates compared to infrarenal AAAs [5–7], recent data suggest that OSR of such complex AAAs can be performed with clinical outcomes that are equivalent to those of open infrarenal AAA repair [8–11]. In a retrospective study by Kabbani and colleagues [9] at Henry Ford Hospital, a 30-day mortality of 2.9 % was achieved in a cohort of 245 patients undergoing OSR of pararenal and paravisceral AAAs. Major complications were reported in nearly two-thirds of patients, with acute kidney injury (60 %) and pulmonary complications (22 %) serving as the most common form of perioperative morbidity. Long-term survival rates at 5 and 10 years were 70 % and 43 %, respectively, and compare favorably to those reported in other series involving patients undergoing OSR of infrarenal AAAs. Congestive heart failure, chronic obstructive pulmonary disease, and increased aneurysm size at presentation were associated with worse survival. In addition, the Mayo Clinic group recently reported that OSR of juxtarenal AAAs remains a safe option in the current era of complex EVAR, citing a 0.8 % 30-day mortality rate in their consecutive series of 126 patients undergoing elective OSR requiring suprarenal aortic clamping between 2001 and 2006 [10]. No independent risk factors for mortality were identified in their analysis. One-, three-, and five-year cumulative survival rates were 93.9 %, 78.3 %, and 63.8 %, respectively, and were not significantly different than age or gender-matched normative data of the U.S. population.

Complex EVAR using either the snorkel or fenestrated technique has been performed with excellent technical success and with low morbidity and mortality rates in multiple retrospective and observational studies from high volume referral centers and national registries (Table 5.2). The relative superiority of one technique over the other is unclear at the present time due to a paucity of reports directly comparing these two advanced EVAR techniques. Available data to date have shown

Table 5.2 Overview of data from all included series reporting open or endovascular repair of complex AAAs

Study, date	N	Study type	Mean follow-up	30-day mortality	Late mortality	Reintervention
Open repair						
Komori (2004) [12]	22	Retrospective	50[a]	0.7	NR	NR
Kudo (2004) [13]	18	Retrospective	NR	0.0	NR	NR
Ryan (2004) [14]	44	Retrospective	NR	0.0	NR	NR
Back (2005) [15]	158	Retrospective	NR	7.6	NR	NR
Chiesa (2006) [16]	119	Retrospective	NR	4.2	NR	NR
West (2006) [5]	247	Retrospective	1	2.5	NR	NR
Wahlgren (2007) [17]	38	Retrospective	24 (6–60)	5.3	81.6	NR
Illuminati (2007) [18]	21	Retrospective	27 (2–73)	9.5	33.0	7.7
Ockert (2007) [19]	35	Retrospective	28 (8–96)	8.6[b]	20.0	20.0
Pearce (2007) [20]	150	Retrospective	17.9[a]	3.3	25.0	10.7
Knott (2008) [10]	126	Retrospective	48 (9–80)	0.8	NR	2.4
Yeung (2008) [21]	23	Retrospective	NR	0.0	NR	NR
Marrocco-Trischitta (2009) [22]	32	Retrospective	29	0.0	6.3	NR
Chisci (2009) [23]	61	Retrospective	25 (0–39)	3.3	NR	9.8
Landry (2010) [24]	174	Retrospective	12[a]	3.4	NR	NR
Bruen (2011) [25]	21	Retrospective	12	4.8	14.3	NR
Tsai (2012) [26]	199	Retrospective	56 (0–108)	2.5	32.2	NR
Donas (2012) [27]	31	Prospective	NR	6.4	NR	3.2
Canavati (2013) [28]	54	Retrospective	NR	3.7	9.3	16.7[c]
Kabbani (2014) [9]	245	Retrospective	54[a]	2.9	NR	NR
Raux (2014) [8]	147	Retrospective	NR	2.0	NR	NR
Fenestrated						
Halak (2006) [29]	17	Retrospective	21	0.0	5.9	NR
Muhs (2006) [30]	38	Prospective	26 (9–46)	2.6	13.2	7.9
O'Neill (2006) [31]	119	Prospective	19 (0–48)	0.8	12.6	11.8

Study, date	N	Study type	Mean follow-up	30-day mortality	Late mortality	Reintervention
Semmens (2006) [32]	58	Retrospective	17	3.4	10.3	24.1
Ziegler (2007) [33]	63	Retrospective	23	1.6	22.2	20.6
Scurr (2008) [34]	45	Retrospective	24[a] (1–48)	2.2	8.9	13.3
Bicknell (2008) [35]	11	Retrospective	12[a] (9–14)	0.0	18.2	NR
Kristmundsson (2009) [36]	54	Prospective	25[a] (12–32)	3.7	22.2	13.0
Greenberg (2009) [37]	30	Prospective	24	0.0	6.7	16.7
Chisci (2009) [23]	52	Retrospective	14 (0–37)	5.7	NR	11.5
Amiot (2010) [38]	134	Prospective	15[a] (2–53)	2.2	9.0	9.0
Verhoeven (2010) [39]	100	Retrospective	24[a] (1–87)	1.0	22	9.0
Tambyraja (2011) [40]	29	Retrospective	20[a]	0.0	13.8	37.9
Manning (2011) [41]	20	Retrospective	NR	10.0	NR	NR
Donas (2012) [27]	29	Prospective	NR	0.0	NR	10.3
Canavati (2013) [28]	53	Retrospective	NR	1.9	3.8	11.3[c]
Raux (2014) [8]	42	Retrospective	NR	9.5	NR	NR
Lee (2014) [42]	15	Retrospective	6	0	13	13.3
Banno (2014) [43]	80	Retrospective	14[a] (0–88)	6.3	18.8	20.0[c]
Snorkel/chimney						
Larzon (2008) [44]	13	Retrospective	17 (1–40)	0.0	NR	NR
Bruen (2011) [25]	21	Retrospective	12	4.8	14.3	NR
Coscas (2011) [45]	16	Retrospective	11 (2–19)	12.5	25.0	12.5
Donas (2012) [27]	30	Prospective	24	0.0	0.0	3.3
Lee (2012) [46]	28	Retrospective	11 (3–25)	7.1	10.7	3.6
Banno (2014) [43]	38	Retrospective	12[a] (0–48)	7.9	18.4	15.8[c]
Lee (2015) [56]	517	Retrospective	17 (1–70)	4.9	15.5	6.6

NR not reported
[a]Reported median
[b]In-hospital mortality
[c]Early re-intervention within 30 days of operation

no reliable difference in these two approaches pertaining to cannulation failure, target branch vessel patency, early mortality, type I endoleak, postoperative renal dysfunction, or need for secondary intervention [11, 27, 42, 43]. We recently sought to compare the early learning curve at our institution with both techniques [42]. Consistent with previous reports, our investigation demonstrated comparable postoperative outcomes between ch- and f-EVAR with respect to mortality, perioperative complications, and short-term branch vessel patency. Additional studies have reported a wide range of 30-day mortality rates following f-EVAR, with a pooled 30-day mortality of 2.1 % noted in a recent systematic review that included 9 studies encompassing 629 patients [47]. Wilson et al. [48] conducted a similar systematic review of 14 studies involving 176 patients with complex AAA treated with ch-EVAR and noted an overall pooled 30-day mortality of 3.4 %.

The clinical benefit of EVAR over OSR in patients with infrarenal AAAs has been well established by large randomized controlled trials and is further supported by over two decades of long-term data [49–52]. As endovascular repair of complex AAAs becomes more widespread, surgeons will continue to experience a significant reduction in open surgical volume of uncomplicated infrarenal AAAs and will increasingly be faced with the clinical conundrum of defining the optimal treatment strategy for patients with juxtarenal, suprarenal, and type IV thoracoabdominal aneuryms. Studies directly comparing OSR versus endovascular repair in patients with such complex AAAs are sparse and are further limited by lack of long-term results. Thus, it remains unclear as to whether a similar paradigm shift will occur in the management of complex aortic disease as was observed during the adoption of conventional EVAR.

In the absence of any randomized controlled trial to date exploring this topic, Tsilimparis and colleagues [53] recently reported the first comparative results between OSR and f-EVAR for elective repair of complex AAAs in a large cohort of similar patients using multi-institutional, nationwide real-world data from the American College of Surgeons National Surgical Quality Improvement Program database. Patients undergoing OSR (n = 1,091) had significantly higher risk of morbidity in all combined end points in this observational study, including increased rates of nonsurgical (30 % vs. 8 %, P < .001), pulmonary (21 % vs. 2 %, P < .001), renal (10 % vs. 2 %, P = .001), and cardiovascular complications (8 % vs. 2 %, P < .001). Thirty-day mortality (5.4 % vs. 0.8 %, P = .001) and total length of hospital stay (11 ± 10 vs. 4 ± 5 days, P < .001) was also noted to be significantly lower for the f-EVAR group (n = 264) compared to the OSR group. In a larger systematic review by Nordon et al. [54], pooled results from eight f-EVAR and 12 OSR series showed an increase in both 30-day and absolute mortality following OSR compared to f-EVAR. The investigators acknowledged, however, a host of limitations that prohibited a more robust comparison, including the lack of available randomized data, selection bias inherent in each of the includes series, and their inability to accurately compare patients based on aneurysm morphology and co-morbid status.

To address many of these methodological limitations, Raux and colleages [8] performed a more rigorous analysis using a propensity-matched comparison of outcomes in high-risk patients undergoing either f-EVAR or OSR of complex AAAs at two high-volume centers. After conducting 1:4 propensity matching to closely

approximate patients both anatomically and with similar clinical risk, their analysis included 42 patients undergoing f-EVAR and 147 undergoing OSR. Contrary to previous reports, multivariate analysis demonstrated f-EVAR to be associated with increased 30-day mortality (odds ration [OR] 5.1; 95% confidence interval [CI], 1.1–24; P = .04), any complication (OR, 2.3; 95% CI, 1.1–4.9; P = .01), and graft complications (OR, 24; 95% CI, 4.8–66; P < .01) compared with OSR. The increased mortality observed among f-EVAR patients likely related to patient selection, specifically with regards to aneurysm morphology given that their study took into account actual or anticipated aortic clamp site. Based on these results, the authors cautioned against extension of the endovascular infrarenal AAA treatment paradigm shift to those with more complex AAAs until patient selection for f-EVAR was better defined.

With regard to parallel stent-graft techniques, Bruen and colleagues [25] compared their series of 21 ch-EVARs to 21 anatomically-matched patients that underwent OSR. Patients undergoing ch-EVAR were noted to have worse baseline renal and pulmonary function but no difference in 30-day mortality was observed between the two treatment groups (4.8% in each). Significant reduction in estimated blood loss, transfusion requirements, and length of stay was also noted in the ch-EVAR group.

Two studies have included both advanced endovascular strategies in their comparative analysis of complex EVAR to OSR for the repair of challenging AAAs. Donas et al. [55] prospectively assigned 90 patients with primary degenerative juxtarenal AAAs to different treatment strategies based on morphology and clinical characteristics, including 23 f-EVARs, 30 ch-EVARs, and 31 OSRs. Despite a treatment algorithm that reserved OSR exclusively for low-risk, physiologically fit patients, early procedure-related and all-cause 30-day mortality was 0% for the endovascular group and 6.4% for the OSR group. The second study by Katsargyris et al. [11] explored the feasibility of a paradigm shift in the management of juxtrarenal AAAs by means of a meta-analysis of 20 studies encompassing a total of 1,725 patients undergoing OSR, 10 studies detailing 931 patients undergoing f-EVAR, and 5 studies comprising 94 patients receiving ch-EVAR. Cumulative 30-day mortality was not statistically different across treatment groups, with a 3.4% mortality rate following OSR, 2.4% after f-EVAR, and 5.3% after ch-EVAR. Impaired renal function (18.5% vs. 9.8%, P < .001) and cardiac complications (11.3% vs. 3.7%, P < .001) were more common after OSR compared to f-EVAR. Ischemic stroke was more common following ch-EVAR (3.2%) relative to either f-EVAR (0.3%, P = .01) or OSR (0.1%, P = .002).

Reintervention

Despite increasing reports suggesting an advantage of endovascular repair with f-EVAR or ch-EVAR in high-risk patients, the routine application of this treatment modality among low- and medium-risk patients is hindered by the uncertainty regarding long-term durability of these approaches. In a multi-institutional series by Chisci

et al. [23], freedom from reintervention at 3 years was 91.8 and 79.7 % for patients undergoing OSR and f-EVAR of short, angulated, or otherwise challenging AAAs, although this difference failed to reach statistical significance. The majority of reinterventions following f-EVAR were performed endovascularly, while those following OSR more often required another surgical procedure. In the comparative study by Canavati and colleagues [28], nine of 54 patients undergoing OSR (16.7 %) required a total of 16 early (<30 days postoperatively) reinterventions, most commonly relaparotomy as a result of mesenteric ischemia, abdominal compartment syndrome, bleeding complications, or abdominal wall dehiscence. Only 6 of 53 (11 %) f-EVAR patients required a total of six early reinterventions. These secondary procedures featured one laparotomy and two SMA stents for mesenteric ischemia, one renal stent for declining renal function, and two femorofemoral crossover bypasses.

In the meta-analysis by Nordon et al. [54], the early mortality benefit observed with f-EVAR was noted to be at the tradeoff of increased need for early reinterventions. Fifty-three of 351 (15.1 %) f-EVAR patients across eight studies required reintervention. Indication for reintervention included endoleaks in 48 % (type I, 21 %; type II, 8 %; type III, 19 %), with the remaining related to angioplasty of visceral or peripheral stenosis, access or wound related complications, or laparotomy for mesenteric ischemia. Only 14 of the 532 (2.6 %) patients undergoing OSR across 12 studies required surgical reintervention, usually related to postoperative bleeding, distal embolization, or visceral ischemia. Linsen et al. [47] performed a separate meta-analysis of published reports on pararenal AAAs using f-EVAR and documented a pooled estimated for reinterventions of 17.8 % during a follow-up period of 15–25 months. Multiple other reports have documented reintervention rates after f-EVAR to range from 8 to 24 %.

Limited data exist regarding reinterventions following ch-EVAR. Donas et al. [27] were the first in the literature as a single center report to present results from both sn- and f-EVAR techniques for patients with complex AAAs compared to OSR. The investigators noted similarly low reintervention rates for sn-EVAR (n = 1; 3.3 %) and OSR (n = 1; 3.2 %), whereas 10.3 % (n = 3) of patients required a secondary procedure following f-EVAR. There was one left renal artery occlusion in each endovascular group, which presented as flank pain and was treated by ilio-renal bypass in both cases. We achieved a similarly low reintervention rate of 3.6 % in our early experience with sn-EVAR, citing only one reintervention among a cohort of 28 patients (56 snorkel endografts) which was related to a type III endoleak successfully treated with an iliac extension cuff [46]. In a recent comparative study by Banno and colleages [13], there was no difference in freedom from reintervention rates (72.0 % vs. 71.4 %) or primary patency of branch vessels (87.6 % vs. 97.1 %) between sn-EVAR and f-EVAR patient groups.

Reintervention rates for complication-related events after OSR is variably reported and ranges from 2.4 to 20.0 % in most recent series. In the largest series to report such figures, Pearce et al. [20] described their experience with 150 complex AAAs (134 juxtarenal, 16 suprarenal) during a 10-year period. Secondary perioperative procedures were required in 16 (11 %) patients in their series and did not significantly vary based on aneurysm type or related aortic clamp position.

Recommendations

The safety and therapeutic efficacy of complex EVAR involving snorkel/chimney or fenestrated approaches must be compared to conventional OSR, which arguably in the physiologically fit serves as the gold standard treatment for challenging AAAs. While both advanced endovascular techniques continue to evolve, an expanding body of non-randomized data suggests that both ch- and f-EVAR are technically feasible with regards to successful aneurysmal exclusion and can be performed with low morbidity and mortality among patients deemed high-risk for conventional OSR. The long-term durability of these endovascular approaches, including preservation of graft fixation, branch vessel patency, and device integrity, remains to be determined. The current literature examining this topic is limited to low to moderate quality data and must be interpreted with appropriate caution. Nevertheless, the available data to date does provide low quality evidence supporting a promising trend towards improved perioperative outcomes, including reduced perioperative mortality, with complex EVAR compared to OSR, although this early clinical benefit may come at the expense of increased need for secondary intervention. The most recent registry study (PERICLES) published this year shows that in centers of excellence performing ch-EVAR, the rate of second intervention can be under 7 % [56]. Randomized controlled trials comparing open and endovascular repair of complex AAAs may be needed to confirm a sustained clinical advantage of sn- and/or f-EVAR over OSR in the management of AAAs with challenging proximal neck anatomy, although we are not convinced such a trial could be performed based on patient and physician preferences and biases. We make a weak recommendation for the use of complex EVAR in the management of complex AAAs in those patients at high-risk for OSR, including those with symptomatic or ruptured aneurysms.

A Personal View of the Data

Our initial experience with complex EVAR is consistent with those of others and supports the use of ch- and f-EVAR for patients at high-risk for OSR. It is important to note, however, that optimal patient selection for complex EVAR and the corresponding role this treatment modality has in the management of patients with AAAs possessing challenging proximal neck anatomy has yet to be fully defined. In addition, both techniques require extensive case planning, including advanced interpretation skills in three-dimensional imaging, technical proficiency in salvage maneuvers, anticipation of wire and catheter-related navigation difficulties, and knowledge of device limitations. Given the uncertainty regarding long-term durability of complex EVAR and recent reports demonstrating comparative perioperative results among those with infrarenal and more proximal AAAs undergoing OSR, we believe conventional OSR remains the gold standard therapeutic option for patients of low physiologic risk. For those with challenging AAAs who are at increased

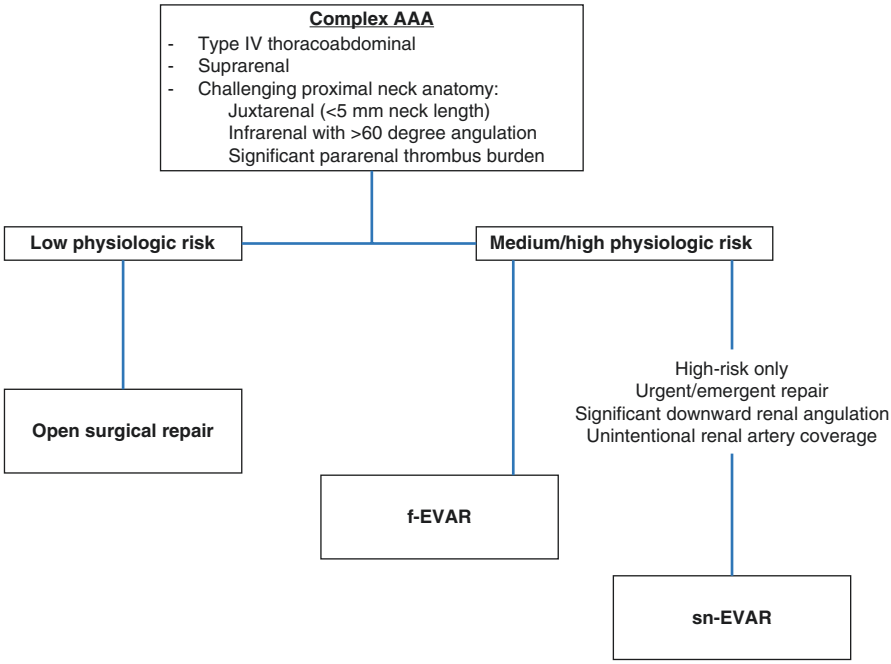

Fig. 5.1 Suggested treatment algorithm for complex AAAs

(medium or high-risk) physiologic risk, f-EVAR represents a viable, FDA-approved therapeutic alternative to OSR and may be associated with decreased perioperative risk in certain patients. Unlike f-EVAR, ch-EVAR remains an endovascular strategy that utilizes devices in an off-label fashion with promising mid-term outcomes and can also be used as an alternative to OSR, particularly in high-risk patients with complex AAAs that require emergent intervention (symptomatic or ruptured), those that possess significant downward renal artery angulation, or those requiring a bail-out option as a result of unintentional renal artery coverage during conventional or fenestrated EVAR (Fig. 5.1).

Recommendations

- Conventional OSR remains the gold standard treatment option for patients with aneurysms involving the juxtarenal, pararenal, or paravisceral aorta who are of low physiologic risk (**evidence quality moderate, strong recommendation**).
- Among those with increased physiologic risk, f-EVAR serves as a valid, FDA-approved therapeutic alternative to OSR and may be associated with an early survival advantage in the perioperative period (**evidence quality low; weak recommendation**).

- Ch-EVAR is an additional alternative form of treatment for patients with complex AAAs that can be used in high-risk patients with complex AAAs that require emergent intervention (symptomatic or ruptured aneurysms), those involving significant downward renal artery angulation, or cases requiring a bailout option as a result of unintentional renal artery coverage during conventional or fenestrated EVAR (**evidence quality low; weak recommendation**).

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Chapter 6
In Patients Who Require Hypogastric Artery Coverage to Treat an AAA with EVAR, Does Preservation Improve Outcomes When Compared to Exclusion of the Vessel?

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Abstract Hypogastric artery exclusion has been utilized as a means to extend applicability of endovascular aortic repair to patients with complex aortoiliac aneurysmal disease. Since its introduction, the technique has been associated with ischemic complications, notably buttock claudication and erectile dysfunction, which can affect quality of life. Both the incidence of buttock claudication and its duration are varied in the literature. Serious complications (gluteal necrosis, colon ischemia, and paraplegia), however, are exceedingly rare even with bilateral hypogastric occlusion. Several patient and technical factors have been studied that may predict those at higher risk of developing ischemic complications, as these patients stand to benefit the most from hypogastric preservation. A variety of open and endovascular techniques are available to preserve hypogastric circulation during aneurysm repair, each with its own limitations. Data regarding the use of these adjunctive techniques comes primarily from small studies with short term follow-up. Further research into the long term efficacy of these techniques is warranted.

Keywords Aorto-iliac aneurysm • Hypogastric artery • Pelvic ischemia • Buttock claudication • EVAR

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Introduction

With the advent of endovascular aortic repair (EVAR) technology, increasing numbers of patients are being offered a minimally invasive approach to aneurysm exclusion. The success of stent graft-mediated exclusion of an aneurysm relies upon adequate proximal and distal landing zones. In nearly 20% of patients, the presence of iliac artery aneurysms precludes the use of commercially available stent grafts [1]. A number of adjunctive procedures, surrounding the management of the hypogastric artery, have been developed to extend endovascular candidacy to these patients. Early on, investigators were able to demonstrate successful aneurysm exclusion by performing coil embolization of the hypogastric artery (HA), either prior to, or in conjunction with EVAR, followed by extension of the ipsilateral iliac limb into the external iliac artery (EIA). Common indications for HA exclusion include the absence of an adequate common iliac artery (CIA) landing zone, the presence of a CIA aneurysm, and/or the presence of a HA aneurysm. Though often successful at aneurysm exclusion, acute HA occlusion can be associated with a host of complications including buttock/thigh claudication, pelvic ischemia, sexual dysfunction and others. As a result, other open and endovascular procedures or technologies were developed in order to preserve pelvic perfusion. This chapter will review the available literature on the complications of HA occlusion, strategies to maintain HA perfusion, and attempt to evaluate these effects on quality of life.

Methods

A literature search of English articles from Medline and PubMed databases from 1990 to 2014 was performed using the PICO outline (Table 6.1). The following search terms were in conjunction with the Boolean operators AND and OR: "hypogastric artery, internal iliac, aneurysm, coil embolization, aortic aneurysm, aortoiliac, EVAR, pelvic ischemia, buttock claudication, preservation, iliac branch device, and stent graft." In addition, references from selected articles were used to identify other relevant citations. The data was classified using the GRADE system.

Table 6.1 PICO table for quality of life in hypogastric artery exclusion

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with aneurysmal common iliac or hypogastric arteries undergoing endovascular aneurysm repair	Hypogastric artery exclusion	Hypogastric artery preservation	Mortality, Incidence of pelvic ischemic (buttock claudication, erectile dysfunction, ischemic colitis, gluteal necrosis, spinal cord ischemia)

Results

Table 6.2 summarizes data compiled from a growing number of published series of over 1,000 patients since the introduction of endovascular/iatrogenic HA occlusion. One of the difficulties in analyzing the effects of HA occlusion lies in the preponderance of single institution, retrospective case series. In summary, HA occlusion (unilateral or bilateral) was associated with extremely low rates of in-hospital death, and the majority of series reported no early deaths. There were, however, a number of ischemic complications identified: buttock claudication, erectile dysfunction (ED), colon ischemia, gluteal necrosis, and spinal cord ischemia.

Buttock Claudication

Undoubtedly the most common complication with HA occlusion is buttock claudication (BC), occurring within 2–55 % (on average 25 %) of patients immediately after occlusion. Potential reasons accounting for the wide variations for the incidence of BC include publication bias, patient factors, and differences in procedural technique.

To better evaluate pelvic circulation in a vascular surgery cohort, Iliopoulos et al. examined HA stump pressures in patients undergoing open revascularization for aortoiliac aneurysmal or occlusive disease [23]. They identified the ipsilateral external iliac and femoral circumflex arteries as more crucial to the maintenance of pelvic circulation than the contralateral HA. Indeed Yano et al. reviewed preoperative angiograms in patients developing pelvic ischemia after HA occlusion [4]. They identified a contralateral HA stenosis and absence of ipsilateral circumflex femoral collaterals as two consistent radiographic findings. Similarly Lin et al. identified a stenotic (defined as greater than 50 %) profunda femoral artery in all patients who developed ischemic symptoms after HC occlusion [7].

Several studies support the fact that the immediate symptoms of BC are not permanent, but rather improve and occasionally resolve over time. Karch et al. reported BC improvement in 43 % of patients [3]. In a larger series, Farahmand demonstrated a 33 % incidence in persistent BC at 6 months follow up [13]. This has been shown in other series highlighting resolution or improvement in varying numbers of patients postoperatively [4–6, 9–12, 14, 19].

Intuitively coil embolization of both HAs would be expected to increase the rate of severity of ischemic complications. This phenomenon, however, has not definitively been proven in the literature. Lin et al. demonstrated lower penile-brachial indices in patients undergoing bilateral HA occlusion compared with those undergoing unilateral HA occlusion, but were unable to demonstrate a significant difference in the incidence of pelvic ischemic complications between the two groups [7]. Mehta et al. reviewed outcomes on 32 patients undergoing bilateral HA occlusion in a staged fashion prior to EVAR, noting a similar incidence of BC and ED as that of other series [10]. In contrast, Rayt et al. demonstrated a higher incidence of both BC

Table 6.2 Incidence of ischemic complications after hypogastric artery coverage

Author	Year	Patients (n)	Follow-up (m)	Bilateral n (%)	30 days Mortality n (%)	Ischemic colitis n (%)	Pelvic necrosis n (%)	Spinal ischemia n (%)	Early BC n (%)	ED n (%)	Quality of evidence
Criado [2]	2000	39	12–24	11 (28)	0	0	0	0	5 (13)	1 (2.6%)	Very low
Karch [3]	2000	22	6–24	2 (9.1)	1 (4.5)	3 (13.6)	0	0	7 (32)	n/a	Very low
Yano [4]	2001	103	12	11 (11)	1 (1)	1 (1)	0	n/a	21 (20)	n/a	Moderate
Lee [5]	2001	23	0.2–39.4	0	n/a	0	0	0	9 (39)	n/a	Low
Mehta [6]	2001	107	n/a	8 (7.5)	n/a	2 (1.9)	0	2 (1.9)	17 (16)	7 (6.5)	Low
Lin [7]	2002	12	4–24	4 (33)	n/a	0	2 (17)	n/a	n/a	5 (42)	Low
Kritpracha [8]	2003	20	24	0	0	0	0	0	9 (45)	1 (5)	Low
Arko [9]	2004	12	20.5	0	0	n/a	n/a	n/a	6 (50)	n/a	Low
Mehta [10]	2004	32	12	32 (100)	n/a	0	0	0	5 (16)	2 (11)	Low
C. Lee [11]	2006	24	1–40	0	n/a	1 (4)	n/a	n/a	4 (17)	n/a	Low
W. Lee [12]	2006	31	18	0	0	n/a	n/a	n/a	12 (39)	n/a	Low
Farahmand [13]	2008	101	5–100	3 (3)	n/a	0	0	n/a	51 (50)	19 (19)	Moderate
Rayt [14]	2008	37	21.5	10 (27)	0	n/a	n/a	n/a	16/29 (55)	6/13 (46)	Low
Bratby [15]	2008	39	1–96	39 (100)	0	0	0	1 (3)	12 (31)	2 (5)	Moderate
Verzini [16]	2009	42	12	n/a	0	0	0	0	8/37 (19)	1/37 (3)	Low
Naughton [17]	2012	94	9–38	0	1 (1.1)	1 (1.1)	0	0	2 (2.1)	n/a	Low
Papazoglou [18]	2012	137	33	5 (3.6)	1 (0.7)	0	1 (0.7)	0	18 (13.1)	n/a	Moderate
Ryer [19]	2012	53	39.3	4 (7.5)	0	0	0	0	16/57 (28)	n/a	Low
Lobato [20]	2013	14	6–30	0	0	0	0	0	8 (57)	1 (2.5)	Low
Stokmans [21]	2013	32	3–31	2 (6)	0	0	0	0	7 (23)	n/a	Low
Jean-Baptiste [22]	2014	71	1–105	9 (13)	3 (4.3)	1 (1.4)	0	1 (1.4)	18 (25.3)	n/a	Moderate

BC buttock claudication, *n/a* not applicable, *ED* erectile dysfunction

and ED in patients undergoing bilateral HA occlusion compared to patients undergoing unilateral occlusion [14].

Technical factors also affect the incidence of pelvic ischemic symptoms. Kritpracha et al. examined the effect of the location of coil placement on pelvic ischemic symptoms [8]. In patients whom coils were placed within the main trunk of the HA (termed proximal embolization), rates of BC and ED were lower compared to patients in whom coils were placed into distal branches of the HA (termed distal embolization). This trend was supported by Bratby et al. as well [15]. Other groups favor the use of endovascular embolization plugs over coils, in order to facilitate proximal HA trunk occlusion and minimize inadvertent distal embolization [19]. This technique is only viable in cases of non-aneurysmal HA, otherwise all branches of the HA require coil embolization to successfully exclude flow from a HA aneurysm.

In order to study the effect of timing of HA occlusion on ischemic outcomes, Lee et al. compared a small group of patients undergoing concomitant HA occlusion and EVAR with those undergoing staged (1 week or greater) HA occlusion followed by EVAR [11]. Despite showing the safety in simultaneous embolization and EVAR, the authors demonstrated higher rates of BC in these patients compared to those that underwent staged repair. In contrast, Bratby was unable to demonstrate a statistically significant difference in rates of pelvic ischemia between patients undergoing simultaneous versus staged HA occlusion [15]. Little data exists on recommending the appropriate time (if any) to delay aneurysm repair after HA occlusion. Some groups report a delay of only 1 day prior to EVAR for unilateral HA occlusion, and a delay of 3 months in those undergoing staged bilateral HA occlusions [13].

Other Complications and Quality of Life

Erectile dysfunction (ED) has been poorly studied in the setting of HA occlusion, having been evaluated as an endpoint in less than half of the studies reviewed in this chapter. Like BC, ED is reported to occur in varying numbers of patients undergoing HA occlusion (between 2 and 40 % of patients, Table 6.2). Complicating matters is the high frequency (nearly 30 %) of pre-existing sexual dysfunction in this patient population [10]. One study was able to correlate the occurrence of postoperative ED with a decrease in postoperative penile-brachial indices [7]. Fortunately more serious complications, such as ischemic colitis, gluteal necrosis, and spinal cord ischemia occur far less frequently. Combined they comprise less than 2 % of all ischemic complications (Table 6.2).

Recently several groups have challenged the notion that HA embolization is required prior to stent graft coverage to prevent a type II endoleak, highlighting the benefits of decreased radiation eposure, operative time, contrast use, and cost. Papazoglou et al. published their series on 112 patients in which the HA was not embolized prior to coverage with a stent graft [18]. The decision not to preemptively embolize was based upon the presence of an adequate seal zone in the EIA or a

small (<5 mm) HA orifice. In fact the total incidence of type II endoleak occurrence (related to the covered HA) was reported at 6.2%. Half of these resolved during follow up and the remaining did not result in aneurysm sac enlargement and, thus, were observed. Similarly Stokmans et al. published their series of 32 patients undergoing stent graft coverage of the HA without coil embolization [21]. They reported no rates of type II endoleaks related to the covered HA, and similar rates of pelvic ischemia as other groups.

Despite the large of prevalence of BC subsequent to HA occlusion, the severity of BC and its impact on a patient's quality of life has not been extensively studied to date. Several authors have attempted to grade the disability caused by BC via subjective descriptions such as "severe" or "life-style limiting" [3, 13]. Two studies attempted to quantify the disability associated with BC using telephone interviews, demonstrating inferior scores in patients with BC compared with those without symptoms [5, 9]. In a well-designed review of patients undergoing HA occlusion prior to stent graft coverage, Jean-Baptiste et al. prospectively evaluated patients using a previously validated assessment tool (the Walking Impairment Questionnaire) to quantify the degree of buttock claudication and its subsequent effects on quality of life [22]. They demonstrated lower quality of life scores in patients who develop persistent BC, in comparison to patients who either 1) did not develop BC or 2) had resolution of immediate postoperative BC. Their study was limited by the lack of preoperative quality of life scores.

Techniques for HA Preservation

In an attempt to preserve antegrade flow into the pelvis, several authors have developed alternative surgical and endovascular techniques to HA occlusion. Open/hybrid techniques include a number of maneuvers to 'relocate' the iliac bifurcation distally to allow for a more suitable landing zone, or creation of retrograde iliac endovascular bypass supplied by a cross femoral bypass. Endovascular techniques include using "bell-bottom" limbs for deploying into the distal CIA, a bifurcated main body graft deployed within the CIA (with one limb directed towards the HA), newer iliac branched devices (IBDs), and chimney/snorkel grafts alongside traditional EVAR devices. Table 6.3 highlights outcomes in patients undergoing HA preservation.

Open/Hybrid Techniques

Originally described by Parodi et al., relocation of the iliac bifurcation allows for deployment of the distal limb of the endograft into a suitable external iliac artery while maintaining flow into the ipsilateral HA [33]. This is performed via a short interposition graft between the distal EIA (beyond the intended distal landing zone)

Table 6.3 Incidence of ischemic complications after hypogastric artery (HA) preservation

Author	Year	Patients (n)	Follow-up (m)	Bilateral n (%)	30 days Mortality n (%)	Ischemic colitis n (%)	Gluteal Ischemia n (%)	Spinal ischemia n (%)	Early BC n (%)	ED n (%)	HA preservation method	Quality of evidence
Faries [24]	2001	10	4–15	1 (10)	0	0	0	0	0	0	EI bypass, HAT	Very low
Bergamini [25]	2002	4	6–17	0	0	0	0	0	1 (25)	n/a	EI endograft	Very low
Arko [9]	2004	9	14.8	0	0	n/a	n/a	n/a	0	n/a	EI bypass	Very low
W. Lee [12]	2006	26	30	0	0	n/a	n/a	n/a	1 (4)	n/a	EI bypass	Low
Minion [26]	2008	5	4–12	0	0	0	0	0	0	0	Trifurcated main body	Very low
Verzini [16]	2009	32	12	0	0	0	0	0	1/23 (4)	0	IBD	Low
Ferreira [27]	2010	37	2–22	10 (27)	0	0	0	0	1 (3)	1 (3)	IBD	Low
Naughton [17]	2012	166	9–38	0	1 (0.6)	0	0	0	0	n/a	Bellbottom limb	Low
DeRubertis [28]	2012	21	1–20	2 (10)	0	n/a	n/a	n/a	0	n/a	Chimney stent	Very low
Parlani [29]	2012	100	1–60	9 (9)	0	0	0	0	4 (4)	n/a	IBD	Moderate
Alvarez Marcos [30]	2013	19	35	2 (11)	0	0	n/a	n/a	n/a	n/a	Bellbottom	Low
Lobato [20]	2013	40	6–30	8 (40)	0	0	0	0	2 (4.2)	1 (2.5)	Sandwich stent	Low
Wong [31]	2013	130	1–72	8 (16)	1 (0.8)	0	0	0	5 (4)	n/a	IBD	Moderate
Wu [32]	2013	5	4–6	0	0	0	0	0	0	n/a	Chimney stent	Very low

Buttock claudication was evaluated only if ipsilateral to side of HA preservation

BC buttock claudication, *ED* erectile dysfunction, *n/a* not applicable, *EI* external to internal iliac, *HAT* hypogastric artery transposition, *IBD* iliac branch device

and the HA. In cases of a redundant HA, full mobilization permits direct anastomosis to the distal EIA without the use of a prosthetic conduit. Each procedure can be performed through a small retroperitoneal incision, and can be used to perform bilateral HA revascularization. The drawback of open HA revascularization is the need for an additional open surgical procedure, potentially negating the minimally invasive benefit that EVAR offers. Faries et al. published their initial results on 10 patients undergoing either bypass or transposition [24]. They reported no incidence of pelvic ischemia, though identified retroperitoneal hematoma formation in half of their patients. Similarly, Arko et al. reported no incidence of pelvic ischemia in a small group of patients who underwent revascularization of the HA compared with a 50 % incidence of BC in patients who underwent coil embolization [9]. Perioperative morbidity rates, blood loss, and lengths of stay were similar for both groups. More importantly, however, they were able to quantify the effects of buttock claudication on quality of life, with patients undergoing coil embolization reporting inferior disability scores postoperatively, compared with patients who underwent HA bypass. Lee et al. retrospectively studied outcomes in 26 patients requiring HA revascularization compared with patients requiring HA embolization [12]. Of note, nearly half of the patients undergoing HA bypass also underwent contralateral HA embolization. Not surprisingly, half of these patients (22 % of all patients undergoing HA bypass) suffered postoperative BC ipsilateral to the side of the embolized HA. Only 1 patient developed BC after thrombosis of the HA bypass graft, resulting in a 91 % primary patency rate at 36 months.

Other groups have attempted an alternative hybrid technique of HA preservation that obviates the need for an additional retroperitoneal incision. Using early commercially available stent grafts, Clarke et al. describe deploying a stent graft from the EIA into the ipsilateral HA, thereby functionally ‘excluding’ the ipsilateral CIA. An aorto-uni-iliac endograft was deployed into the contralateral EIA (after HA occlusion). Perfusion to the lower extremities and pelvis was restored using a cross femoral bypass graft [34]. Several case reports of this technique have since been published [25, 35–38]. Unfortunately the overall numbers of patients being managed with this technique are few, and the duration of follow-up relatively short. Ongoing investigation of this technique will be warranted to confirm its feasibility.

Endovascular Techniques

In patients with an ectatic or aneurysmal CIA, one alternative to HA bypass is to land the stent graft within the CIA itself. In early iterations of EVAR devices, iliac limb diameters were too small to seal effectively within these dilated CIAs, and various groups resorted to using larger aortic cuff extensions to prevent Type IA endoleaks, termed a “bell-bottom limb” [2]. As the devices have matured,

manufacturers have designed larger diameter iliac limb extensions incorporating this larger diameter flared end. Current devices can now accommodate native artery diameters of up to 25 mm (i.e. Medtronic Endurant II) [39]. The rationale behind utilizing bell-bottom limbs is maintaining antegrade pelvic perfusion while minimizing the complexity of the endovascular repair. A concern with this technique is endoleak formation due to deploying a stent graft in an aneurysmal artery. Kirkwood et al. reviewed data from the Cook Zenith registry, evaluating the long term effects of utilizing an aneurysmal iliac artery as a distal landing zone [40]. Patients who underwent placement of a limb within an aneurysmal CIA (defined as a diameter greater than 20 mm) demonstrated no increased rate of native artery diameter increase, secondary interventions, or serious adverse events (rupture, conversion to open repair, or death) when compared to patients with non-aneurysmal distal landing zones. Alvarez Marcos et al. prospectively reviewed 19 patients with aneurysmal CIAs (greater than 18 mm but less than 25 mm at the iliac bifurcation) who underwent placement of an aortic cuff into the CIA, and compared results with historical controls undergoing conventional EVAR. They reported no overt incidence of pelvic ischemia, and no statistically significant difference in endoleak rates by 3 years [30]. In a large retrospective study, Naughton et al. compared outcomes of patients undergoing EVAR with either bell-bottom iliac limbs to patients undergoing HA exclusion [17]. Although patients undergoing HA exclusion demonstrated overall low rates of pelvic ischemia, no patients undergoing HA preservation with bell-bottom limb experienced ischemic symptoms. Moreover the rates of any re-intervention (11.6 % vs. 19 %), rates of endoleak (4 % in each group), and limb patency (3 % vs. 2 %), were not statistically different between the bell-bottom limb or HA exclusion groups.

In cases of a large CIA aneurysm (>25 mm at the iliac bifurcation) not amenable to a bell-bottom technique, several investigational techniques have been described to maintain antegrade pelvic perfusion. An Iliac Branch Device (IBD) is a modification of conventional iliac limb stent grafts with a separate sidearm for the HA. The proximal portion of the stent graft is deployed within the CIA (or into the ipsilateral iliac limb of a traditional bifurcated endograft), and the distal limb is deployed into the EIA. A preloaded wire allows for easier cannulation of the sidearm from the contralateral femoral approach, with the goal to deploy a covered stent to bridge the sidearm and the native HA. A technically successful deployment excludes a CIA aneurysm while maintaining antegrade pelvic perfusion. Typical indications for IBD placement include a distal CIA diameter greater than 24 mm, a patent CIA lumen greater than 18 mm, an EIA landing zone of >15 mm, and a HA landing zone of >10 mm [41]. Currently two IBDs exist, the Zenith Iliac Branch Endovascular Graft (Cook Medical) and recently the Excluder Iliac Branch Endoprosthesis (WL Gore). The Zenith device utilizes a woven sidearm, while the Excluder device mimics an aortic main body graft with the contralateral gate designed for the HA. Within the United States, both are available only for investigational use. The majority of published data, thus, originates primarily from Europe.

Verzini et al. published early and mid-term results of 32 patients receiving IBDs compared with those undergoing HA exclusion in a single institution [16]. Technical success was reported at 94 %. At 1 year, HA branch patency rates were 100 %, persistent BC was reported in 4 %, and Type II endoleak rates occurred in 3 %. This is in contrast to the patients undergoing HA exclusion, where BC occurred in 22 % and endoleaks occurred in 19 %. Ferreira et al. published their work utilizing IBDs in 37 patients, 10 of whom underwent bilateral IBD deployment [27]. Technical success was achieved in 97 % of attempts, and there were no instances of immediate pelvic ischemia. At a follow up time of 22 months, HA branch patency was reported at 85 %, no endoleaks were identified, and BC occurred in 3 % (secondary to HA branch occlusion). In a large European series, Parlani et al. presented 5 year outcomes in 100 patients undergoing IBD usage [29], of whom 9 % underwent bilateral IBD use. As seen with previous reports, there was no incidence of early pelvic ischemia, with a 95 % rate of technical success. At 5 years HA branch patency was 91 %, endoleaks occurring in 3 %, and BC in 4 %. Wong et al. recently published their experience with IBD use in the US [31]. As seen with the European groups, technical success was reported to be high (94 %), 5 year patency was acceptable (81.8 %), and freedom from endoleak was high (96 % at 5 years). The authors discovered the majority (71 %) of patients experiencing late (greater than 1 month postoperatively) HA occlusion developed disabling BC.

Due to the lack of commercial availability of IBDs outside of Europe, several groups have formulated other endovascular options to preserve HA perfusion. One early technique described is placement of a bifurcated proximal aortic endograft within the common iliac artery, with orientation of the contralateral gate towards the HA. This has been referred to as the "trifurcated endograft technique" by some authors [26]. The contralateral gate can be cannulated (and a stent graft ultimately placed into the HA) via a brachial exposure [26], or via use of a surgeon modified preloaded catheter/wire to allow access from the contralateral groin [42]. Unfortunately, there have been few patients being reported undergoing this procedure with only short term follow-up.

Other authors describe the use of parallel stent grafts in tandem with conventional aortic endografts. This technique is often referred to as a "chimney" [32] or "sandwich" technique [43]. Variations on this technique can occur depending on the type of main body endograft selected, be it a modular bifurcated [20] or a modular unibody device [44]. Lobato et al. initially described the feasibility of using a covered self-expanding stent (Viabahn, WL Gore) in conjunction with a modular bifurcated stent graft [43]. The Viabahn is placed via a left brachial approach, deployed into the HA alongside an iliac limb extension in the CIA. Several years later the authors published midterm outcomes on 40 patients undergoing this sandwich technique, with 8 patients undergoing bilateral HA revascularization [20]. Technical success was reported in all patients. Early (within 30 days) HA limb occlusion occurred in 4.3 % of stent grafts, and no late occlusions were identified. Buttock claudication and erectile dysfunction were reported in 4.2 % and 2.5 % of patients, respectively, all secondary to HA stent occlusion. There were no severe cases of pelvic ischemia reported. In a dual

institution review, DeRubertis et al. described a similar sandwich technique in 21 patients utilizing several commercially available main body endografts [28]. Technical success was reported in 88 % of patients, with 6 month primary patency rates of the HA stent graft reported at 88 %. In addition, there were no type I and III endoleak occurrence, with a 14.3 % incidence of type II endoleaks. Importantly, no patient developed any signs of pelvic ischemia as a result of HA preservation. Cuff et al. highlighted the significance of utilizing a unibody aortic endograft in obviating the need for brachial access, in addition to being able to perform bilateral HA preservation [45]. Mosquera Arochena et al. have modified this sandwich technique by utilizing a highly conformable main body endograft to maintain HA circulation in patients with extremely tortuous iliac vessels [46]. Other variations include one by Wu et al., who described a 'crossover chimney' method of deploying a Viabahn from the distal CIA to the contralateral HA in a patient with a unilateral CIA aneurysm [32].

Recommendations

In patients with complex aortoiliac aneurysms undergoing EVAR, occlusion of the HA artery is potentially associated with both immediate and long term pelvic ischemia along with a subsequent decline in quality of life. Retrospective and observational studies that include heterogeneous patient populations likely explain the wide range of incidences reported. For patients felt to be at higher risk of buttock claudication, colon ischemia, and paraplegia (i.e. those with preexisting occlusive disease, those undergoing bilateral HA embolization, and those undergoing distal embolization), we recommend pursuing preservation (by any method) of at least one hypogastric artery (evidence quality moderate, strong recommendation). When embolization is required, the following maneuvers should be performed to minimize ischemic symptoms: embolization of the proximal HA trunk (except in HA aneurysms) and preservation of the ipsilateral iliofemoral collaterals (evidence quality moderate, strong recommendation). Techniques to maintain HA perfusion succeed in doing so and can be associated with an improved quality of life. They are, however, more complex, less widely available, and less well studied in the long term.

Recommendations

- We recommend pursuing hypogastric artery preservation in patients at high risk of pelvic ischemia (**evidence quality moderate, strong recommendation**).
- When embolization is required, adherence to certain principles can minimize ischemic complications (**evidence quality moderate, strong recommendation**).

A Personal View of the Data

Through many observational studies over the last decade, we have learned that iatrogenic hypogastric artery occlusion is not without risk. Immediate complications can occur, though predicting the natural history and identifying patients at higher risk of developing them are less clear. For patients requiring HA preservation whose comorbidities limit their open surgical candidacy, alternative means should be sought. The specific technique utilized should be tailored to each patient's anatomy, and guided by the surgeon's experience with currently available devices. Future research should be aimed at identifying risk factors for pelvic ischemia and improving current endovascular technology to treat patients with complex aortoiliac disease.

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Chapter 7
In Patients with Aortic Graft Infections, Does EVAR Improve Long Term Survival Compared to Open Graft Resection?

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Abstract Primary and secondary aortic infections are uncommon but potentially lethal conditions. It remains uncertain what treatment strategy is best for these patients. This chapter provides an overview of the current literature on different treatment options for primary and secondary infected aortas. No randomized controlled trials have been published and the highest levels of evidence are systematic reviews, retrospective cohort studies and case series. Mortality rates for open and endovascular repair are high (20–50 %) and both show high reinfection rates (20 %). In aortic graft infections, endovascular repair is mostly studied for the treatment of aortoenteric fistulas and seems feasible as a bridge to open surgery or as a definite treatment. In-situ repair has a slightly better outcome in most studies when compared with other open treatment options. No studies compared open with endovascular treatment. Therefore, from the current literature, no recommendations can be made and the best approach should be to weigh the pros and cons of open and endovascular treatment for each individual patient.

Keywords Aortic graft infection • Open repair • Endovascular repair

Introduction

Aortic graft infection is a rare but life-threatening complication. Although several treatment strategies have been proposed and studied, reported mortality rates remain as high as 40 % or more [1–5]. Patients surviving this devastating condition

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are at risk of many complications, especially reinfection (10–27 %) and limb loss (5–27 %) [1–3, 5]. One reason for these poor results is that major vascular surgery is performed in patients who are usually in poor condition with serious signs of systemic infection and significant comorbidity. With rapidly evolving technology, one of the potential ways to lower this complication rate is to switch from open repair towards a far less invasive endovascular option. Endovascular aortic repair (EVAR) has been studied as a treatment solution for patients with primary infected aortic aneurysms. However, without debridement of the infected aneurysm and surrounding tissue, the question remains if this is only a bridge to open surgery, or a definite treatment. Far less reports on EVAR for aortic graft infections have been published. Most of these studies address patients with aortoenteric fistulas [6, 7]. Therefore, the role of EVAR in these patients remains highly uncertain. In order to streamline the difficult decision on what's the best treatment to offer a patient with an infected aortic graft, we will give an overview of the current literature on aortic infections, aortic graft infections, endograft infections as well as the different treatment options. Hopefully, this will help practitioners with an evidence-based approach towards the best management of their patients that present with this highly complex problem.

Search Strategy

We performed a search of English language publications from 2000 to 2014 to find published data on aortic infections, aortic graft infections and endograft infections. We focused our search on articles comparing different treatment strategies, specifically those comparing open with endovascular treatment as proposed in our PICO outline (Table 7.1).

We searched PubMed and the Cochrane Library. Search terms used were:

("aorta" OR "aortic") AND ("transplants" OR "graft") AND ("infection" OR "infection") AND resection.
("aorta" OR "aortic") AND ("transplants" OR "graft") AND ("infection" OR "infection") AND ("endovascular" OR "EVAR").
("aorta") AND ("infection") AND ("therapy" OR "treatment" OR "therapeutics").

Next, we analyzed all references for missed publications. Case reports and papers without full text content were excluded. Data was classified using the GRADE system.

Table 7.1 PICO table for EVAR used in aortic graft infection

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Aortic graft infection	EVAR	Graft resection	Reinfection, mortality, amputation

Table 7.2 Summary of publications studying different treatment modalities for either aortic graft infection or aorta infection

Study	**P**	**EAB**	**RBP**	**ISVR**	**Study type**
O'Connor (2006) [18]	GI	Mean event rate =0.16[a]	Mean event rate =0.07	Mean event rate =0.10	Meta-analysis of 37 studies
Study	**P**	**EAB**	**ISR**	**ISVR**	**Study type**
Charlton-Ouw (2014) [2]	GI	0 % amputation 20 % reinfection 40 % mortality (1-year graft related)	18 % amputation 27 % reinfection 18 % mortality	27 % amputation 27 % reinfection 36 % mortality	Retrospective cohort of 28 patients
Oderich (2006) [1]	GI	12 % amputation 16 % reinfection 12 % mortality (perioperatively)	0 % amputation[b] 10 % reinfection 9 % mortality	– – –	Retrospective cohort of 117 patients
Lee (2011) [3]	AI	27 % mortality (perioperatively) 7 % amputation 33 % late complication	8 % mortality 0 % amputation 0 % late complication[c]		Retrospective cohort of 28 patients

P patients, *GI* aortic graft infection, *EAB* extra-anatomic bypass, *RBP* rifampicin-bonded prosthesis, *ISVR* in-situ venous repair, *ISR* in-situ repair (not specified), *AI* aortic infection
Mean event rate = amputation, conduit failure, reinfection and mortality combined
[a] $p < 0.05$ compared with RBP and ISVR
[b] $p = 0.06$
[c] $p = 0.04$

Results

We found no randomized controlled trails, 1 meta-analysis, 3 systematic reviews, 7 retrospective cohort studies, 15 single center reviews, 2 multicenter reviews and 9 literature reviews/updates of the current literature. Studies with the highest level of evidence according to the GRADE system, comparing different treatment options for primary or secondary aortic infections, are summarized in Table 7.2.

Primary Aortic Infection

Aortitis (inflammation of the aorta) is either infectious or noninfectious [8]. Examples of noninfectious causes are arteritis, vasculitis or sarcoidosis. These conditions usually do not require surgical treatment. Primary aortic infection on the other hand is an infectious aortitis involving bacterial or other organisms. This may lead to an aortic aneurysm, also described as a mycotic aneurysm. Besides

antibiotics, extensive surgery is usually necessary as a definitive treatment. Open and endovascular techniques are possible. Options for open repair are in-situ repair with a prosthetic graft (with or without an omental wrap), with an autologous vein or with an allograft. Another option would be excision of the infected aorta with extra-anatomic reconstruction, either in one or two stages.

Open Repair

A retrospective cohort study by Lee et al. [3] compared in situ repair (ISR, n = 13) versus extra-anatomic bypass (EAB, n = 15) in 28 patients with a mycotic aortic aneurysm (see Table 7.2). Neither perioperative mortality, nor amputation was significantly different between the 2 groups. Late complications did differ significantly (0 % in ISR vs. 33 % in EAB). These included graft occlusion, graft infection and ischemia colitis. The overall reoperation rate for graft salvage was 33 %.

Further studies on this topic included only case reports or case series. Amongst these is an article by van Zitteren et al. [9] describing 5 patients who underwent spiral vein reconstruction with limb salvage after 6–67 months of 100 % and no re-infections. An article by Noel et al. [10] studied 56 patients treated with cryopreserved grafts. The overall mortality was 25 %, persistent infection was 9 %, graft occlusion was 9 % and amputation rate was 5 %. Dubois et al. [11] treated 44 patients with ISR or EAB. In-hospital mortality was 18.9 % and 50 % respectively. Finally, a literature review by Lew et al. [12] on antibiotic-impregnated grafts studying 5 case series shows a 30-day mortality of 7–21 % and graft reinfection of 4–22 %.

Endovascular Repair

The highest level of evidence addressing this topic is a systematic review performed by Kan et al. [13]. The authors report the results of a literature review including 48 cases from 22 studies investigating the outcome after endovascular stent grafting for mycotic aortic aneurysms (either abdominal or thoracic). The 30-day survival rate was 89.6 % and the 2-year survival rate was 82.2 %. Persistent infection occurred in 22.9 % of cases and these patients had a 1-year survival rate of only 39.0 %. In a multivariate logistic regression analysis, rupture of the aneurysm and fever at the time of the operation were the only two independent predictors of persistent infection after EVAR. Additional procedures were performed in 37.1 %, including antibiotics-soaked stents, drainage cannulas and debridement. It is not reported when these procedure were done (at the time of the EVAR or during follow-up). In 45.8 % of patients antibiotics were given more than 1 week before the EVAR. Less than 50 % of the patients received antibiotics postoperatively for more than 4 weeks.

The same authors published their own data on the endovascular treatment of 12 patients with a mycotic aneurysm in 3 hospitals in Taiwan [14]. There was no hospital death in these patients. Three patients received drainage (of whom 1 also underwent a debridement laparotomy) for psoas abscesses. One patient (8.3 %) died after 8 months. Mean follow-up was 2–48 months with no evidence for graft infection. With respect to the antibiotics regimen, their protocol was to start with broad-spectrum antibiotics after blood was drawn for culture followed by endovascular treatment. Bacteria specific intravenous antibiotics were given for at least 4 weeks postoperatively.

A review by Setacci et al. [15] summarizing 6 studies reporting on the role of (T) EVAR in mycotic aneurysms shows a 30-day mortality between 0 and 28.0 % and a 2-year mortality from 16.1 to 45.0 %. Kritpracha et al. [16] reported their results of treating 21 patients with an infected aortic aneurysm using an endovascular stent graft. Five patients presented with an aortoenteric fistula. In this group, the in-hospital mortality was 60 %, whilst in the non-fistula group, this was only 6 %. One conversion was performed in the fistula group. All patients received life-long antibiotics. Sedivy et al. [17] reported their experiences with the endovascular treatment of 32 patients with a mycotic aneurysm. Thirty-day mortality was 19.0 %, 50.0 % after 1 year and 59.4 % after 3 years. All patients received antibiotics prior to the procedure and at least 4 weeks after laboratory results normalized (CRP, white blood count). Salmonella infections were treated indefinitely.

Aortic Graft Infection

When open repair is chosen, treatment options are similar as for primary aortic infection (in-situ repair with a prosthetic graft, an autologous vein, an allograft or extra-anatomic bypass). Endovascular options are far less studied. (T)EVAR is mostly used in patients with an aortoenteric fistula, often when emergency surgery is necessary.

Open Repair

A meta-analysis done by O'Connor et al. [18] compared EAB, rifampicin-bonded prosthesis (RBP), cryopreserved allografts (CA) and autogenous veins (AV) for the treatment of aortic graft infection in a meta-analysis (Table 7.2). They determined pooled estimates of mean event rates for amputation, conduit failure, reinfections and mortality and found that for all outcomes combined, EAB had the highest event rate (0.16), which was significantly worse compared with all other 3 techniques ($p < 0.05$). Amputation rate was highest in EAB and AV, conduit failure in EAB, reinfection in RBP and early and late mortality in EAB.

A retrospective cohort study by Batt et al. [19] (not in Table 7.2) compared ISR, including various conduits (venous and non-venous), with EAB in 82 patients. Perioperative mortality was 32 % for ISR and 45 % for EAB (p = NS). Freedom from recurrent infection and survival rates were estimated using the log-rank test. This showed a lower rate of recurrent infection after ISR (p = 0.04) and a higher survival rate after ISR (p = 0.003) compared with EAB.

The other 2 retrospective studies [1, 2] are presented in Table 7.2. Mortality seems higher in EAB compared with IS(V)R, but not significantly different. Reinfection is also not significantly different between the groups. Oderich et al. [1] found a significantly higher amputation rate in EAB compared with ISR. Charlton-Ouw et al. [2] found higher amputation and reinfection rates in the IS(V)R group which is not in line with the current literature. They address this in their discussion, but cannot give an explanation.

Partial resection of the graft, or nonresectional management, has also been described, although these are only single center reviews. Maze et al. [20] describe a series of 17 patients only treated with antibiotics (because of operative risks, estimated life expectancy from co-morbidities, technical difficulties and patient preference). During a follow-up of 57 months, 59 % relapsed, 59 % died and 24 % underwent graft explantation at a later stage. A review of Lawrence [21] on this topic states that this strategy only works with indolent organisms, excluding infections from Gram-negative organisms like Pseudomonas and Salmonella. They advise drainage (percutaneously or open) of the perigraft space followed by lifelong antibiotics. Hart et al. [4] performed a retrospective analysis of 30 patients with aortic graft infection in which 15 patients underwent partial removal of the graft. Recurrent infection was 13 % in the complete resection group and 27 % in the partial resection group (p = NS). Long-term survival was not different between the two groups.

Vogel et al. [22] tried to identify risk factors for the development of aortic graft infection. A large retrospective cohort study was done in 13902 patients who underwent 12626 open repairs and 1276 EVARs. The 2-year rate of graft infection was 0.19 % for open and 0.16 % for EVAR (p = 0.75). Blood stream septicemia and surgical site infection increased the risk of graft infection significantly. In a multivariate model, only septicemia was significantly associated with graft infection (OR 4.2, 95 % CI: 1.5–11.8).

Endovascular Repair

As mentioned earlier, endovascular repair for graft infections has mostly been studied in patients with an aortoenteric fistula. It can serve as a definite treatment, or as a bridge to open surgery. Antoniou et al. [6] performed a systematic review on the outcome of endovascular stent repair for aortoenteric fistulas. They included 41 patients (either primary or secondary following aortic surgery) and found that persistent infection developed in 44 % of patients. Patients with a secondary fistula

compared with a primary fistula, had a threefold increased risk of persistent infection (p = 0.06). The 30-day mortality was 17 % for patients with a persistent infection and 0 % when no signs of infection after treatment occurred (p = 0.04).

Danneels et al. describe a series of 15 patients with an aortoenteric fistula treated endovascularly [7]. Reinfection occurred in 60 % of the patients. The 30-day mortality was 0 %. Seven patients were reoperated, after which 2 patients died.

Endograft Infection

On this topic, only a few case reports and case series are published and 1 retrospective cohort study. The latter was performed by Cernohorsky et al. [23]. They identified 12 patients with an infected endograft out of 1431 EVARs and TEVARs. The incidence of graft infection was significantly higher in patients treated in an emergency setting (0.56 % vs. 2.79 %, p = 0.002), with similar results for EVAR and TEVAR. Mortality was 27 %. Six patients were treated conservatively with only antibiotics, 2 patients died during follow-up (33 %). The other 6 patients were treated with surgical intervention and antibiotics, 4 of these patients had complete removal of the endograft. Only 1 patient died (17 %).

Other series describe their results on endograft infection with removal of the graft and in-situ or extra-anatomic bypasses with mortality rates from of 21–66 % [24–26].

Recommendations Based on the Data

So far, very few articles have been published that study the treatment of aortic (endo) graft infection. Of the studies that have been done, none reach high quality evidence according to the GRADE system. The highest level of evidence is a meta-analysis of the different treatment modalities for aortic graft infection [18]. However, the studies included in this meta-analysis are all retrospective or observational, none are randomized controlled trials. Also, the authors use a ‘standardized’ scoring system to determine which studies should be in- and excluded in the meta-analysis. They refer to an article by Berman et al. [27]. In this article, the authors state that this scoring system ‘is a model of an evaluation score sheet, it has not been formally tested or externally validated’. In the meta-analysis a threshold is used to exclude studies, but this threshold is not described, and also, the authors do not weigh the results of the individual studies. All and all we can only rate this paper as low quality. The next best article is a systematic review on the use of endovascular treatment for mycotic aortic aneurysms [13]. Again, only retrospective and observational studies are included and no weight was assigned to the different studies included. Furthermore, the authors do not describe how they in- or excluded papers for their analyses and if they were blinded for authors while doing so. This paper can also only be graded as low quality.

Next, several retrospective cohort studies were published, most of these studying which treatment is best when dealing with aortic graft infection. The number of patients included in these studies is low. The diagnosis aortic infection or aortic (endo)graft infection was not standardized. Also, which treatment had been chosen, was done by the surgeon at time of diagnosis and was off course influenced by patients comorbidity, sepsis, anatomy and preference of the surgeon. So also these articles we can only rate as very low quality. All other studies are published data on the experience of a certain treatment strategy performed in one or multiple centers, or literature reviews/updates. Considering the above, we cannot draw any conclusions based on the current literature.

Recommendations

- In patients with aortic graft infections, no best treatment can be clearly advocated based on these data. Therefore each case should take into consideration the risks and benefits of open and endovascular treatment, taking into account the anatomy, preference and comorbidity of the patient (**Quality of evidence, Low; strong recommendation**)

A Personal View of the Data

Infection of an aortic (endo)graft or primary aortic infection is an uncommon, but devastating condition. Because it is rare, most vascular surgeons have very little experience in dealing with this life-threatening problem. With very sick patients that often have extensive comorbidity, invasive vascular surgery is extremely hazardous and quite often even lethal. Less invasive options for treating these patients, like endovascular repair, seems attractive but no firm conclusions on its effectiveness can be drawn from the current literature. For many cases (primary as well as secondary aortic infections) it seems feasible as a bridge to open surgery in order to gain time for improvement of the patients' general condition or to streamline decision making for possible further therapeutic options with the patient and his or her family.

Mortality rates for endovascular repair (in primary aortic infections) range from 10 to 28 % (30-day) and from 18 to 50 % (2-year), with over 20 % of patients having a persistent infection. The same 30-day mortality rates were found for (T)EVAR in patients with an aortoenteric fistula. Is mortality indeed lower when using this less invasive endovascular treatment? Mortality rates published for open repair vary between open techniques and between primary and secondary infected aortas. In-hospital mortality of 25–50 % has been described and 1-year graft related mortality of 40 %. On the other hand, ISR with perioperative mortality of 8 % and 1-year mortality of 18 % is also reported. The percentage of persistent infection is similar as compared to open repair (around 20 %). There is a wide range in these mortality rates and no study compared open with endovascular techniques. Which open technique should be used is also still a matter of debate with conflicting results published so far,

although most studies seem to show that in-situ repair has slightly better outcomes. It is important to realize however, that there is a huge selection bias and that published results are usually from large tertiary centers of excellence resulting in complication rates that are not necessarily comparable with everyday's practice.

Despite many publications on this complex subject, the level of evidence is poor and no best treatment can be clearly advocated based on these data. When confronted with a patient suffering from an uncommon and highly lethal aortic (graft/endograft) infection, the best approach should still be to meticulously weigh the pros and cons of open and endovascular treatment, taking into account the anatomy, preference and comorbidity of the patient.

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Chapter 8
Does EVAR Improve Outcomes or Quality of Life in Patients Unfit for Open Surgery?

Tadaki M. Tomita and Andrew W. Hoel

Abstract Endovascular aneurysm repair (EVAR) has emerged as the preferred treatment for most patients with an abdominal aortic aneurysm (AAA). A less invasive procedure, EVAR would seem to be a suitable method to treat AAAs in patients who are unfit for open surgery. However, recent studies have called into question the utility of EVAR in this patient population. Though there is a group of patients that do not benefit from EVAR because of either unacceptably high perioperative risk or poor long-term survival, this group is not well defined in the literature. Patients who have high-risk anatomy for EVAR and patients who have a decreased quality of life after EVAR may also not benefit. Ultimately, the complex decision making process to proceed with EVAR in any high-risk patient will require a frank discussion of the risks and benefits between the surgeon and the patient.

Keywords Endovascular aneurysm repair • Abdominal aortic aneurysm • Unfit • High-risk • Quality of life

Introduction

When Juan Parodi performed the first endovascular repair of an abdominal aortic aneurysm (AAA) over two decades ago, he did so in a patient who was unfit for an open surgical repair [1]. Since that groundbreaking event, endovascular aneurysm repair (EVAR) has emerged as the preferred treatment for most patients with an AAA [2]. A less invasive procedure, EVAR would seem to be a suitable method to treat AAAs in patients who are unfit for open surgery. These patients must survive the perioperative period with little morbidity and go on to have a long-term survival to benefit from prophylactic EVAR. However, recent studies have suggested that EVAR done in patients unfit for open surgery have poor long-term outcomes calling

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into question the utility of EVAR in this patient population [3, 4]. Patients who have a decreased quality of life after EVAR may also not benefit. Here, we address the question: does EVAR improve outcomes or quality of life in patients unfit for open surgery?

Search Strategy

A literature search of English language publications was performed using a PICO outline (Table 8.1). The PubMed database was searched for "(high-risk or unfit) AND endovascular aneurysm repair"; "("quality of life") AND endovascular aneurysm repair"; "(indications for use) AND endovascular aneurysm repair"; "(concurrent (malignancy or cancer)) AND endovascular aneurysm repair". When appropriate articles were identified, the "Related citations in PubMed" was used to identify additional articles of interest.

Results

The following 7 articles were identified to help understand how patients unfit for open surgery tolerate EVAR (Table 8.2).

EVAR-2

The EVAR trial 2 (EVAR-2) is the only randomized clinical trial evaluating the efficacy of EVAR in patients deemed unfit for open surgery due to significant comorobidities and resulting physiologic high-risk. The study was a multicenter trial conducted in the United Kingdom with 197 patients randomized to EVAR and 207 patients randomized to no-intervention with a primary endpoint of all-cause mortality. There were also secondary endpoints of aneurysm-related mortality, graft-related complications and total hospital cost [4, 5]. Enrolling physicians were given guidelines for patient enrollment (Table 8.3), but the final decision was left to the discretion of the treating physician [10]. This study had a 30-day perioperative mortality rate of 7.3 %. There was no difference in all cause mortality between the study groups with a total mortality of 21.0 deaths per 100 person years in the EVAR group and 22.1 deaths per 100 person years in the no-interventions group (P = 0.97).

Table 8.1 PICO terms

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Patients at high risk for surgery or with limited life expectancy	EVAR	Medical management	Mortality Morbidity Quality of life

Table 8.2 Pertinent articles

Study	Patients	Outcome classification	Outcomes		Quality of evidence
EVAR-2 [4, 5]	Multicenter Trial Randomized to EVAR vs. no treatment in the United Kingdom	All cause mortality	EVAR All cause mortality: 21.0 deaths per 100 person years	No intervention All cause mortality: 22.1 deaths per 100 person years	Low quality
De Martino el al [3]	EVAR patients in a regional vascular database	All cause mortality	Survival: Fit – 80 % at 5 years	Survival: unfit – 61 % At 5 years	Low quality
Hynes et al. [5]	Single center patients assigned to EVAR or medical therapy	All cause mortality	Survival: EVAR – 78.8 % at 4 years	Survival: medical Therapy 27.9 % at 4 years	Low quality
Egorova et al. [6]	EVAR patients from Medicare claims database	Perioperative mortality	Survival: score ≤ 9–>95 %	Survival: score ≥ 13–<90 %	Low quality
Schanzer et al. [7]	Multicenter retrospective study of sac expansion after EVAR	Aneurysm expansion	Aneurysm expansion: 41 % at 5 years	Adherence to anatomic indications for device use 48 %	Low quality
Lin et al. [8]	Single center retrospective study of EVAR vs Open AAA repair in patients with concomitant CRC	All cause mortality	Survival: staged open repair 44 % at 4 years	Survival: staged EVAR 58 % at 4 years	Low quality

EVAR endovascular aneurysm repair, *AAA* abdominal aortic aneurysm, *CRC* colorectal cancer

Table 8.3 Guidelines for inclusion in EVAR-2

	Criteria
Cardiac	MI within last 3 months[a]
	Onset of angina within 3 months[a]
	Unstable angina[a]
	Severe valvular disease
	Significant arrhythmia
	Uncontrolled CHF
Respiratory	Unable to up a flight of stairs without shortness of breath
	FEV1 < 1 L
	PO_2 < 8 Kpa
	PCO_2 > 6.5 Kpa
Renal	Serum Cr > 200 μmol/L

Adapted from Brown et al. [9], with permission from Elsevier
For criteria with "[a]", intervention is not recommended

However there was a difference in the aneurysm related mortality of 3.6 deaths per 100 person years in the EVAR group and 7.3 deaths per 100 person years in the no-intervention group (P = 0.02). Over the 8 year study period 158 graft related complications occurred in 97 patients with 66 reinterventions in 55 patients. During the study period the mean cost of aneurysm related procedures was $22,687 for the EVAR group and $7,821 in the no-intervention group [4]. There was no difference in QOL between the two groups observed in the midterm analysis [5].

Though this is a randomized clinical trial, a number of aspects of the study's design and analysis introduce bias and reduce the quality of the evidence. First, the intervention arm of the group was compared to a group with no intervention. With no standard therapy for the non-EVAR group, there is risk of bias in the intention to treat design of this study. Indeed, in the no intervention arm [4], there was significant crossover with 33.8 % of patients undergoing aneurysm repair; 12 patients undergoing open repair and 35 patients undergoing EVAR. Second, the 7.3 % perioperative mortality exceeds that of other studies evaluating EVAR in the elective setting. This may be in part due to the 18 patients randomized to EVAR that did not undergo an intervention [4]. Additionally, in the EVAR arm, 4 patients underwent open aneurysm repair, 2 for a ruptured aneurysm. Finally, there were no strict inclusion or exclusion criteria beyond recommended guidelines and the treating physician decided suitability for enrollment [5, 10].

The failure of this study to demonstrate EVAR to be protective against aneurysm related mortality could relate to an underpowered study, high incidence of aneurysm repair in the no treatment arm and, potentially, the use of older endograft technology. Their conclusion of EVAR not being effective in patients deemed unfit for open surgery may not be justified because of these confounding factors [4].

De Martino et al.

In a retrospective review using the Vascular Study Group of New England (VSGNE) database, De Martino et al. stratified patients undergoing EVAR for intact AAAs <6.5 cm into those patients deemed fit and unfit for open surgery. As with EVAR-2, the treating physician made the decision regarding fitness for open surgery. The cohort consisted of EVAR performed in 1344 patients fit for open surgery and 309 unfit for open surgery due to physiologic high-risk. Patients in the unfit group were older and had more heart disease, chronic obstructive pulmonary disease and larger aneurysms than the fit group. They observed a statistically significant difference in all cause perioperative morbidity with rates of 3.7 % in the fit for open surgery group and 12.5 % in the unfit group. They also observed statistically higher rates of cardiovascular complications, respiratory complications, need for vasopressors and intestinal ischemia in the unfit group. Though there was a slight statistically significant increase in number of ICU days for the unfit patients, they did not report an increased total length of stay. Despite having more complications in the unfit group, they do not appear to have affected the overall hospital course. The perioperative morality rate of 0.3 % in the fit for surgery group and 0.7 % in the unfit group was not statistically significant [3].

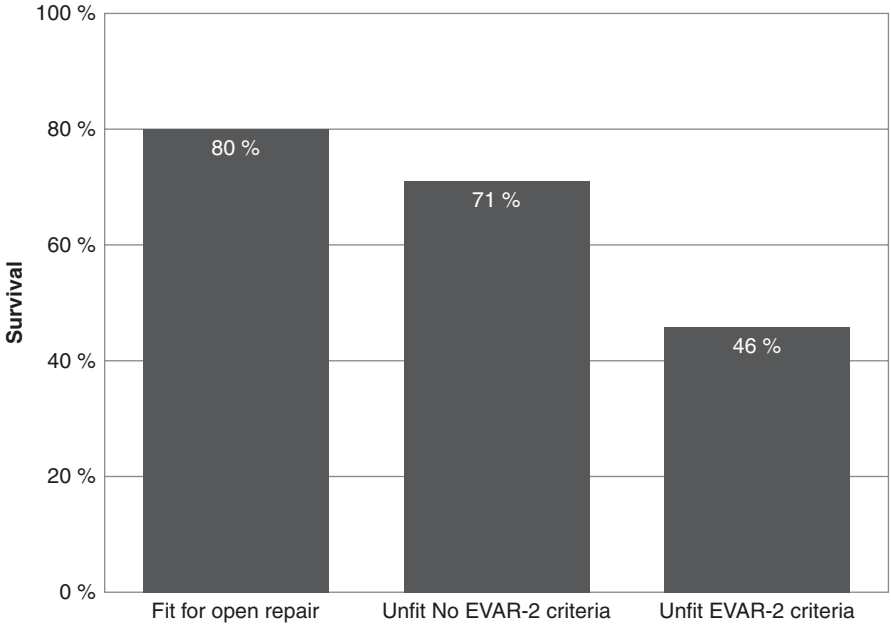

Fig. 8.1 Survival at 4 years in the VSGNE cohort when stratified to fit, unfit with no EVAR-2 criteria and unfit meeting at least 1 EVAR-2 criteria (Based on data from Ref. [3])

The long-term results from the VSGNE cohort showed that patients undergoing EVAR deemed unfit for open surgery did worse than those who were fit for open surgery, as one would expect. At 1, 3 and 5 years, patients fit for open surgery had a survival of 96 %, 89 % and 80 % respectively, compared to survivals of 93 %, 73 % and 61 % for those deemed unfit. As part of their analysis, they divided the unfit patients into patients meeting any criteria in the suggested guidelines for inclusion in EVAR-2 (Table 8.3) and those without any criteria for EVAR-2. The patients in the VSGNE cohort meeting the EVAR-2 guidelines had an even worse 5 year survival rate at 46 % compared to the fit patients at 80 % and those without any EVAR-2 criteria at 71 % (Fig. 8.1) [3]. Because it only evaluated patients undergoing intervention, this study was not able to determine the relative benefit of EVAR compared to no intervention. However, this study does demonstrate that, for patients undergoing EVAR, survival is worse in those with significant medical comorbidities.

Hynes et al.

In another nonrandomized trial, Hynes et al. did not observe the same results seen in EVAR-2. In this study of high-risk patients with AAA, they prospectively followed 66 patients undergoing EVAR and 44 treated with medical therapy at a single institution. Patients were administered treatment based on the clinical setting as determined by

the treating physician. Their observed survival at 4 years was 78.8 % for EVAR compared to 27.9 % in the medical therapy group. In this study, survival without aneurysm related mortality was 97.7 % in the EVAR group compared to 66.8 % in the medical therapy group. Only advanced age and aneurysm size were risks factors for aneurysm related mortality. The EVAR patients had significantly higher QOL when compared to the medical treatment group at 4 years. The QOL metric they used also included a length of life component, so the increased mortality in the medical treatment group largely accounts for the observed difference. Only 5.5 % of the EVAR group required reintervention at 4 years, a much lower rate than was seen in EVAR-2. Patients assigned to treatment based on clinical judgment rather than explicit patient factors introduces a large potential for bias [6]. While the study cohorts likely differed in severity of both physiologic and anatomic risk, it does demonstrate that survival and quality of life is worse in aneurysm patients that do not undergo EVAR. Additionally, the surgeons participating in this study were generally able to identify those highest risk patients and avoid subjecting them to a potentially unnecessary procedure.

Egorova et al.

To determine properly which patients are unfit for surgery, it is necessary to establish a universal definition of fitness. Egorova et al. used a scoring model built using the Medicare Inpatient Standard Analytical file to identify patients that are high-risk for perioperative mortality after elective EVAR. In this study, they identified renal failure requiring hemodialysis (HD), renal failure without HD, clinically significant lower extremity ischemia, increasing age, heart failure, chronic liver disease, female gender, neurological disorders, chronic pulmonary disease, surgeon experience of EVAR <3 procedures, and hospital annual volume of EVAR <7 procedures as risk factors for increased perioperative mortality. Each comorbidity was assigned a weighted score ranging from 1 to 7 based on the odds ratio of increased mortality. They assigned renal failure requiring HD the highest score, as it was the greatest contributor to perioperative mortality. In the Medicare population, 96.6 % of patients had a score of 9 or less with a perioperative mortality rate of <5 %. Only 3.4 % of the Medicare cohort had a score of 13 or higher. A score of 13 correlates to a perioperative mortality rate of 10.6 % with each additional increase in score corresponding to an exponentially increasing perioperative mortality rate (Fig. 8.2) [7]. If validated, this model could become a helpful aid to clinicians in determining a patient's physiologic fitness for EVAR.

Schanzer et al.

To identify risks for aneurysm enlargement after EVAR, Schanzer et al. reviewed pre- and post- EVAR computed tomography (CT) scans in 10,228 patients. By reviewing the baseline CT characteristics, the authors were able to identify patients with anatomic high-risk defined as anatomy outside the indications for use (IFU) for the implanted device. The study used a composite definition of the IFU for clinically

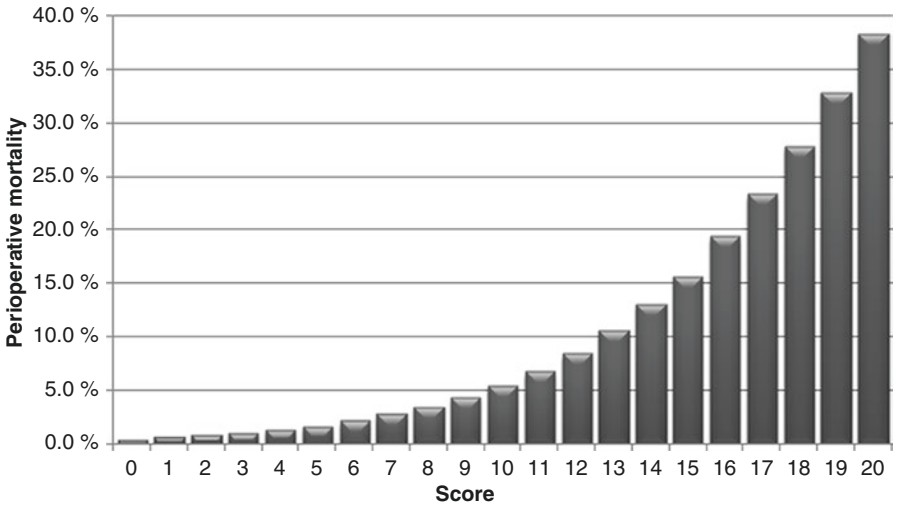

Fig. 8.2 Predicted perioperative mortality based on risk scoring system (Adapted from Egorova et al. [6], with permission from Elsevier)

available EVAR devices to establish the IFU definition used in the study. The primary endpoint for the study was aneurysm enlargement of over 5 mm from the preoperative study. Only 42% of patients had anatomic criteria that fulfilled the most conservative IFU definition, while 69% met a more liberal definition of the IFU. Therefore, 31–58% of this cohort had high-risk anatomy and underwent EVAR. For the entire cohort, 41% had sac enlargement at 5 years. The incidence of sac enlargement was significantly higher in patients treated outside the IFU. The investigators did not have access to specific procedure details including the timing of the EVAR, thus the resulting sac expansion seen on the first postoperative CT could be secondary to expansion prior to EVAR. This could over estimate the incidence of sac enlargement. This study demonstrates a low rate of adherence to device IFU and concludes that non-adherence is correlated with a high rate of post-procedure aneurysm enlargement and continued risk of aneurysm-related mortality [8]. In contrast to other studies in this review, Schanzer, et al. uniquely evaluates the importance of anatomic high-risk in the evaluation of fitness for EVAR.

Lin et al.

Soon after the development of EVAR, interest in treating patients with concurrent AAA and malignancy began. Lin et al. reviewed 108 patients with concurrent AAA and colorectal cancer (CRC) at a single institution. Forty-six patients underwent colectomy for a symptomatic cancer followed by open aneurysm repair in 35 patients and EVAR in 11 patients. Thirty-eight patients underwent aneurysm repair, 26 by open repair and 12 by EVAR, followed by a staged colectomy. Eight patients underwent a

combined open aneurysm repair and colectomy. There were no combined EVAR and colectomies performed. The preoperative morality rate of 13 % in the open repair group was significantly higher than the 0 % seen in the EVAR group. There was also a significant difference in 4-year survival rates between the staged open repairs vs. staged EVARs, being 44 % and 58 % respectively. There was a significant delay in colectomy after open aneurysm repair compared to EVAR (115 days vs. 12 days). They conclude that EVAR is the preferred method to treat patients with synchronous AAA and CRC because it allows for early cancer therapy and better long-term survival [9].

Recommendations Based on the Data

The literature is of low quality, but there appears to be a poorly defined subset of high-risk patients that do not receive a long-term benefit from EVAR. The Medicare cohort used by Egorova et al., identified a group of physiologic high-risk patients with a perioperative mortality rate of >10 % [7]. Other retrospective studies evaluating EVAR in different physiologic high-risk patients have observed a lower perioperative mortality ranging from 0.5 to 9 % [3, 4, 5, 7, 11, 12]. When the EVAR-2 guidelines are applied to patients in the VSGNE cohort, a subgroup of decreased long-term survival emerges [3]. EVAR-2, the only randomized control trial, did demonstrate a benefit for aneurysm related mortality for patients undergoing EVAR, but there was no impact on all cause mortality [4]. This along with the low incidence of aneurysm related mortality in patients treated with EVAR, suggests that the comorbidities that make these patients poor operative risks are the cause of the late mortality [3, 4, 7, 12]. Hynes et al. showed good long-term results for EVAR in their high-risk cohort, though the comparison group consisted of patients they felt would not benefit from the risk associated with EVAR or open surgery [6]. This suggests that physicians are able to select patients that have a poor long-term prognosis from multiple comorbidities and not offer them an intervention. Though these decisions can be made in the clinical environment, the lack of a standardized definition of what constitutes a high-risk patient make it difficult to produce the high quality of research needed to give a strong recommendation regarding the utility of EVAR in this patient population.

The grade of literature as it pertains to quality of life is similarly low. In physiologic high-risk patients, the expected quality of life after EVAR is a critical contributor to making the decision to proceed with a prophylactic intervention. The quality of data regarding QOL after EVAR in high-risk patients is very limited. EVAR-2 did not show a significant difference between the patients in their cohort, but the confounding seen in the study makes it difficult to interpret this finding [5]. Hynes et al. observed higher QOL in their EVAR group, but because of the metric they used, this was largely related to the increased mortality associated with medical management [6]. Need for reintervention associated with EVAR is a potential cause for decreased QOL [13]. In standard risk patients, long-term QOL after EVAR is lower than in patients undergoing open repair [14]. As device technology advances and the need for reintervention decreases, QOL is likely improved.

Several observational studies have shown an initial decrease in QOL that returns to baseline at 6 months after EVAR [15]. Older patients have a slower return to their baseline QOL than younger patient undergoing EVAR. Early intervention has been shown to improve QOL compared to surveillance [16]; this is presumably related to the knowledge of having an untreated aneurysm. We cannot make a recommendation regarding the impact of EVAR on QOL in high-risk patients because of the limited amount of available data.

The literature regarding anatomic high-risk for EVAR raises concerns about the use of commercially available devices outside the IFU. The Schanzer et al. study demonstrates an increased incidence of aneurysm expansion when AAAs are treated outside of the IFU [8]. This could place the patient at a higher risk of aneurysm related mortality. Though other studies have shown no difference in mortality for patients with anatomic high-risk. A higher incidence of graft-related adverse events in high risk anatomy has been repeatedly demonstrated [17–21] and the negative effect on quality of life has been shown [13]. As device technology advances, it is likely that more patients with challenging anatomy will be appropriate for EVAR. Until that time, there is insufficient evidence to support this practice.

The quality of data evaluating the utility of EVAR in the setting of concurrent malignancy is low. The Lin et al. group shows a clear benefit of EVAR over open aneurysm repair for both perioperative and long-term outcomes for patients that present with synchronous AAA and CRC [9]. It is difficult to generalize the treatment of patients with CRC to patients with other types of cancer. Though in smaller numbers, similar results have been shown in patients with other malignancies [22]. EVAR is an attractive option over open surgery because it allows the patient to proceed to cancer treatment earlier over open surgery. The main limitation of a long-term benefit from EVAR in this group of patients is the life expectancy from the underlying malignancy. Therefore, for patients with suitable anatomy for EVAR and a reasonable long-term prognosis from their malignancy, EVAR should be considered. A close collaboration with the patient and the patient's oncologist is critical before proceeding with EVAR, particularly related to the patient's *realistic* malignancy-related mortality risk.

Recommendations

- In patients that are physiologic high-risk in the absence of anatomic high-risk, EVAR could be considered to reduce aneurysm related mortality and improve quality of life. (**Quality of evidence: Low; recommendation moderate**).
- In patients that are physiologic high-risk *and* anatomic high-risk, EVAR should not be considered (**Quality of evidence: Low; recommendation moderate**).
- In patients with a diagnosed malignancy, suitable anatomy for EVAR, and a reasonable long-term prognosis; EVAR should be considered (**Quality of evidence: Low; recommendation moderate**).

A Personal View of the Data

The lack of a standard definition of what constitutes "high-risk" limits the published data on EVAR in this patient population. Studies looking at high-risk patients undergoing EVAR and comparing them to standard risk patients undergoing EVAR are instructive, but it is not surprising that high-risk patients do worse than the standard risk patients post-operatively. The most useful information regarding the utility of treating high-risk patients with EVAR would involve a prospective study using a standardized definition of high-risk patients. The optimal outcome for using EVAR in these patients would be minimized aneurysm related mortality and low all-cause mortality. The EVAR-2 trial attempted to do this, but multiple confounding factors limit its application. Unfortunately, this study is unlikely to be repeated. The guidelines used in EVAR-2 and the model proposed by Egorova et al. are good starting points to define this patient population [5, 7].

Importantly, most studies evaluate patient that are physiologic high-risk (i.e. significant comorbidities) as the primary criteria for high-risk status. However, as Schanzer, et al. point out, evaluation of anatomy and determining anatomic high-risk is extremely important in evaluating patients for EVAR. Therefore, comprehensive understanding of post-EVAR outcomes in high-risk patients need to account for both physiologic and anatomic high-risk.

Not discussed in any of the studies reviewed here is the need for patient engagement in the decision-making process regarding intervention. This is particularly relevant in the group of moderately high-risk patients for whom the existing data is largely equivocal. We often frame a portion of our discussion with these patients around their desires for intervention should their aneurysm rupture. While a high quality discussion on this topic can be difficult and time consuming, it does bring in the patient perspective and help define two key groups of patients: those that would want emergency EVAR, and those that would not. Because it is apparent that high-risk patients will fare worse in the emergency setting than they would in the elective setting, we feel that patients that would pursue emergency surgery should be considered for elective EVAR and those that would not desire emergency surgery should never undergo aneurysm surgery. While this represents a simplistic strategy, we believe that patient engagement is a critically underutilized component of determining which high-risk patients will benefit from EVAR. Concurrent with a broader understanding of fixed outcomes like morbidity and mortality, we feel that shared decision-making tools will bring about improved global outcomes in the treatment of high-risk AAA patients with EVAR.

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Chapter 9
In Patients with Type 2 Endoleaks Does Intervention Reduce Aneurysm Related Morbidity and Mortality Compared to Observation?

Lisa Kang and Brian Funaki

Abstract Type II endoleaks are the most common complication of endovascular aneurysm repair (EVAR) of abdominal aortic aneurysms (AAA). These endoleaks are the result of retrograde blood flow in arteries arising from the excluded portion of the aneurysm sac. The natural history of untreated type II endoleaks is not fully understood. This is confounded by the fact that imaging classification of type II endoleaks is not always accurate. However, it is clear that a subset of type II endoleaks are associated with aneurysm growth and rupture. Familiarity with the risk factors, prophylactic measures for prevention and imaging methods to identify type II endoleaks is essential for optimal management of this complication.

Keywords Type II endoleak • type 2 endoleak • Abdominal aortic aneurysm • Endovascular aneurysm repair • EVAR • Intervention

Introduction

Endovascular aneurysm repair (EVAR) of abdominal aortic aneurysms (AAA) was first performed by Parodi in 1991 [1]. As a minimally invasive option, EVAR has become the treatment of choice for many with infrarenal AAAs [2]. EVAR has advantages of lower peri-operative morbidity and mortality [3–5]. and comparable long-term survival rates [6]. However, data suggest that EVAR is best performed in patients who are younger than 70 years of age and likely to be compliant with the

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necessary follow-up. This is contrary to a common assumption that EVAR would be best for frail and elderly patients unfit for surgery. In these medically unfit patients, optimization of medical management appears to be the best approach [6, 7].

Endoleaks are characterized by persistent blood flow into the excluded portion of the aneurysm sac after EVAR [8, 9]. They complicate 3–44 % of EVAR for AAAs [9–14] and are categorized into 5 types. Type II endoleaks are the most common type [2, 9, 15] and result from retrograde blood flow in arteries which arise from the aneurysm sac. Most commonly, type II endoleaks occur via the inferior mesenteric artery (IMA) and lumbar arteries [2, 12, 14–16]. The internal iliac, sacral, gonadal and accessory renal arteries area less common culprits [17].

Recommendations for management of type II endoleaks have varied widely, ranging from an aggressive approach with intervention on all [16, 18] to labeling these endoleaks "benign" as a group and warranting no intervention [19]. Currently, the consensus is that type II endoleaks are a heterogeneous and exist along a spectrum of clinical significance [20–22].

Search Strategy

A search of the English literature was used to identify published data on type II endoleaks after EVAR of AAAs in human subjects using the PICO outline (Table 9.1). Pubmed and Cochrane Evidence Based Medicine databases were queried. Terms used in this search were "type 2 endoleak" OR "type II endoleak" AND "abdominal aortic aneurysm" Articles were excluded if they did not specifically address type 2 endoleaks after EVAR of AAAs. Furthermore, these articles were analyzed only if their main subject matter consisted of outcome measures related to strategies for prophylaxis of type II endoleaks or management of type II endoleaks. In regards to prophylaxis of type II endoleaks, 8 cohort studies, 2 case control studies, 11 case series and 1 review article were identified for analysis. 10 cohort studies, 2 case control studies, 15 case series, 4 case reports, 3 meta-analyses and 1 review article pertaining to management of type II endoleaks diagnosed after EVAR were included. The search for literature addressing treatment of type II endoleaks also yielded several cohort studies and numerous case reports, although these were not analyzed in depth. Upon review of the references of the included articles identified via the search, an additional 8 cohorts, 2 case control studies, 6

Table 9.1 PICO table for intervention for type II endoleak

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with abdominal aortic aneurysms status post EVAR with type II endoleaks	Elimination of collateral blood flow supplying aneurysm sacs (ex. embolization)	Imaging surveillance only	Morbidity and mortality without and with intervention

case series and 2 reviews were identified and included. Data were classified using the GRADE system. Additional articles cited were for historic and background information.

Results

Clinical Relevance of Type II Endoleaks After EVAR

Published data describe variable outcomes in patients with type II endoleaks, and the natural history remains uncertain [23]. Spontaneous resolution is seen in many type II endoleaks by 6 months after EVAR, with reported resolution rates ranging from 33 to 80 % [11, 21, 24–27]. and most reports show resolution rates >60 %. These endoleaks are considered transient type II endoleaks. Persistent endoleaks, defined as those which remain after 6 months, are much less likely to resolve spontaneously, with reported incidence of predominantly <10 % [21, 25, 28]. Persistent type II endoleaks are associated with increased morbidity including conversion to open repair but not with increased mortality [21]. Earlier reports failed to demonstrate significant association between type II endoleaks and aneurysm rupture [19, 29, 30], probably due to viewing all type II endoleaks as a uniform group. However, the risk for aneurysm sac expansion and rupture is now well documented [21, 22, 26, 30–37]. When all type II endoleaks are considered, sac expansion occurs in 4–35 % [26, 28, 38, 39] and the risk of aneurysm rupture is 1 % or less [40, 41]. When only persistent endoleaks are considered, the risks are greater, with sac expansion occurring in 14–41 % [27, 36, 38, 42, 43] and aneurysm rupture occurring in up to 24 % [44].

Risk and Prevention Strategies

Various clinical factors have been associated with type II endoleaks, some of which are also associated with failure of aneurysm sac regression. These include increased age, hypertension and antithrombotic therapy [45–47]. Smoking and decreased ankle-brachial index are negatively associated with type II endoleak [48].

Morphologic risk factors predictive of type II endoleak include the presence of patent arteries arising from the aneurysm [12, 17, 26, 37, 49–53], a relative lack of mural thrombus within the aneurysm [26, 52, 54–57], and longer aneurysm neck length [58]. Fan et al. showed that 0–3 patent lumbar arteries was associated with a 13 % type II endoleak rate while ≥6 patent lumbar arteries was associated with a 50 % type II endoleak rate [12]. More recently, Brountzos et al. showed that the risk of persistent type II endoleak was increased by a factor of 12 in the presence of a patent IMA and further increased about four to six times by each additional patent branch arising from the aneurysm sac. A minority have shown no correlation between patency of branch vessels and development of type II endoleak [37].

During EVAR, vessels arising from the aneurysm sac and the sac itself may be embolized in attempt to prevent the type II endoleaks from occurring. Prophylactic embolization of the IMA and lumbar arteries is technically feasible with short-term success rates ranging from 83 to 100 % [42, 59–61]. However, the efficacy of these procedures is debated. Alerci et al. reported a significant decreased incidence of type II endoleak in patients who underwent collateral artery occlusion (3.6 %) during EVAR compared to those who did not (47.8 %) in a long-term study [62]. Gould et al. reported no change in the incidence of type II endoleak with prophylactic embolization of AAA branches [43]. However, not all branches were embolized in this study and aneurysm sac enlargement was observed only in the nonembolized group.

An alternative approach to endoleak prophylaxis is to induce thrombosis of the excluded aneurysm sac at the time of EVAR. Early attempts of direct sac embolization successfully prevented type II endoleaks at the expense of increased morbidity and mortality [63]. Subsequently, safe and effective methods of direct sac embolization have been demonstrated [64–67]. Zanchetta et al. reported a low incidence of type II endoleak and a high percentage of stable or decreasing aneurysm size (97 %) following injection of thrombin into the excluded sac at the time of EVAR [64]. Additionally, sac embolization may reduce health care costs relative to EVAR alone [65].

Identification

Multiphase CT with unenhanced, arterial phase contrast-enhanced and delayed images is the primary imaging test used to evaluate for endoleaks after EVAR [11, 20, 38, 68]. Although follow-up protocols vary, CT is frequently performed in the immediate postoperative period, at 6 months, at 12 months and then annually after EVAR [11, 21, 24, 29, 41]. Imaging surveillance is generally lifelong as new endoleaks may develop over time and late sac expansion and rupture can occur [6, 69–72].

Although multiphase CT is the current standard for diagnosis and evaluation of endoleaks, it is not immune to error. In one series, 36 % of type I and type III endoleaks were misclassified as type II endoleaks on CT with recognition on diagnostic angiography or follow-up CT after IMA embolization [73]. In another series, concomitant type I or type III endoleaks which were not identified on CT were observed in 21 % of patients undergoing angiographic evaluation of type II endoleaks [74]. It is important to recognize that all of these misclassifications occurred in patients with aneurysm growth. Therefore, it is clear that a subset of type II endoleaks which are purportedly associated with aneurysm growth actually represent misclassified type I or III endoleaks.

Some advocate using sonography as the first line imaging modality for EVAR follow-up, reserving CT for instances when sonography is equivocal or demonstrates aneurysm growth [28, 41, 74–76]. Gray et al. have adopted a protocol using duplex sonography performed following 6 h of fasting and supplemented by radiography to evaluate for structural abnormalities of the endograft [77]. This group reports sensitivity of 100 % and specificity of 85 % of duplex sonography for detection of endoleaks.

Contrast enhanced ultrasound and contrast enhanced MR angiography appear to have equivalent if not increased sensitivity relative to traditional CT for detection

of endoleaks [78–80]. Gadofoveset, an intravascular gadolinium based contrast agent which binds to serum albumin *in vivo*, may have special utility in evaluation of endoleaks, allowing detection of low-flow type II endoleaks which are below the detection threshold of CTA and may account for some endoleaks classified as type V [79].

Further characterization of endoleaks may be the key in optimizing treatment. Several novel imaging techniques have shown potential utility in evaluating endoleaks. Measurement of endoleak cavity volume (ECV), the enhancing portion of the excluded aneurysm sac, is possible with post-processing of CT images. Increased ECV on delayed CT images is associated with aneurysm enlargement [81]. Four-dimensional dynamic volumetric CT angiography involves rapid axial imaging of a volume of tissue using a modern scanner with a high number of detector rows. Multiple images are obtained over a short interval following contrast injection, producing three-dimensional angiographic images and better demonstrating the anatomy and physiology of the endoleak [82].

Management: Imaging Surveillance Versus Intervention

When a type II endoleak is identified within the first 6 months after EVAR, conservative management is generally indicated as the majority will be transient [11, 20, 83]. Additionally, the vast majority of asymptomatic type II endoleaks with stable or regressing aneurysm sacs do not result in aneurysm rupture. These patients are also generally managed conservatively with ongoing imaging surveillance [20, 27, 69].

Regardless of when a type II endoleak is diagnosed, most agree intervention is warranted if the aneurysm is symptomatic or if there is growth of the excluded sac [17, 48, 83]. Published criteria for significant aneurysm growth vary, with 5 mm used most commonly and proposed threshold size changes ranging from 5 to 10 mm [6, 9, 14, 21, 26, 48, 83–86]. Smaller apparent changes in sac size may reflect the imprecision of CT (and especially ultrasound) measurements rather than true growth [87]. Other triggers for intervention on type II endoleaks include total sac diameter >5.5 cm >6 months after EVAR [22], the presence of persistent endoleak at 6–12 months [17], and sac pressures >20 % of systolic pressure [17]. Some investigators have proposed using measurements of the endoleak cavity, defined as the enhancing portion of the excluded aneurysm sac on CT, to guide the decision to intervene. However, this is not yet widely used in clinical practice.

Interventions

The two primary approaches in the treatment of type II endoleaks are transarterial embolization and translumbar puncture and embolization of the aneurysm sac [9, 21]. Other less common minimally invasive approaches have been described [88–90] and laparoscopic and open surgical techniques are employed by some [91, 92].

Minimally invasive treatment of type II endoleaks is safe, with most published series reporting mortality of <1 % [22, 71, 73, 74]. However, meticulous technique is required as there is potential for significant morbidity, most frequently due to non-target embolization which may result in ischemic lumbar or sciatic neuropathy, colonic necrosis and pulmonary embolus [6, 93–96]. When the transarterial approach is used, the branch artery which is the site of endoleak should be embolized at its origin from the sac to minimize the risk of ischemic complications [17, 41].

Published rates of success, defined as a post-procedural decrease in aneurysm size, vary widely for the transarterial approach and less so for the translumbar approach ranging from 9 to 100 % and 67 to 100 %, respectively [10, 26, 36, 41, 49, 97–100]. Variability in success of transarterial endoleak embolization appears to be largely due to endoleak recurrence and may also relate to technical difficulty of the procedure as all patent side branches may need to be embolized to achieve success [17, 101, 102]. Notably, up to 80 % of cases which initially appear to be technically successful are complicated by recurrent endoleak [10, 49, 80, 98]. Better results with transarterial embolization have been documented when the type II endoleak originates from the IMA compared to lumbar artery endoleaks [26]. As a sole means of management, the transarterial approach often fails to yield satisfactory results [16, 68].

Data showing inadequacy of the transarterial approach alone have resulted in some considering translumbar sac embolization to be superior. Baum et al. describe the excluded aneurysm sac as being analagous to the nidus of an arteriovenous malformation, dynamically recruiting collateral arteries in communication with the excluded aneurysm sac [98]. Therefore, direct translumbar sac puncture and embolization was this group's therapy of choice. However, despite better overall results with the translumbar approach, transarterial embolization of branch arteries may still be beneficial as a measure to prevent non-target embolization when treating the sac with a liquid embolization medium [103].

It is worth noting that the clinical significance of recurrent endoleak is not fully understood and that technical failure (i.e. recurrence of endoleak) may coexist with clinical success (i.e. stabilization or decrease in size of the sac) [40, 73]. Additionally, regression of the sac size may not be required for technical success with some series reporting a decreased rate of rupture following intervention despite a lack of decrease in aneurysm size [40, 58].

Currently, a combination strategy employing embolization of patent arteries arising from the sac and direct embolization of the excluded aneurysm sac appears to be the best approach [6, 68, 73]. As more information becomes available regarding the natural history of type II endoleaks without and with intervention, this treatment approach may be modified.

Successful treatment of a type II endoleak does not obviate the need for continued imaging surveillance, as success rates appear to diminish over time [6, 72]. One series reported that within 5 years of a successful embolization 20 % of patients required another procedure, 38 % exhibited aneurysm sac growth and 8 % required explant and open repair [6]. Delayed endoleaks, detected >1 year after EVAR, were

the most frequent type observed during a longitudinal study with a mean follow-up period of 53 months. Despite initial aneurysm sac shrinkage after EVAR, these delayed endoleaks were associated with subsequent aneurysm sac enlargement [72].

Recommendations

Most type II endoleaks do not need to be treated but should undergo careful surveillance using CTA. Conventional angiography with possible embolization should be performed for sac enlargement or if there is suspicion of pinhole type III endoleak.

A Personal View of the Data

Although published data suggest prophylactic embolization of the excluded aneurysm sac and side branches are reasonable in the prevention of type II endoleaks, these practices are not routinely performed at our institution.

After EVAR, imaging surveillance is necessary. We perform multiphase CT at 1 month, 6 months and 12 months after EVAR. In the absence of evidence of complication, patients are imaged annually thereafter. An increasing trend toward color duplex sonography for EVAR surveillance is recognized. However, sonography is highly operator dependent, limiting routine utilization as the first line imaging modality.

Most type II endoleaks detected within the first 6 months after EVAR resolve spontaneously. No intervention is recommended during this interval in the absence of symptoms or significant sac expansion.

At our institution, we do not intervene upon type II endoleaks which are asymptomatic and are not associated with sac expansion, regardless of persistence. However, if an endoleak is symptomatic or associated with sac expansion (i.e. an increase of >5 mm from pre-EVAR measurements or >5 mm over an interval of 6 months following an initial decrease in aneurysm size) intervention is warranted.

When intervention is indicated based on CT findings, we use a staged approach. Diagnostic angiography is performed initially. Transarterial coil embolization of the IMA is performed if this vessel is shown to a patent and a contributor to the endoleak. Triple phase CT imaging is then repeated in 1 month. If persistent sac perfusion is identified and a type II endoleak is excluded, transarterial embolization of communicating arteries, including the lumbar arteries or accessory renal arteries, is performed. Coils and/or liquid embolic agents are used. If negative, CT guided translumbar sac embolization with a liquid embolic is performed. After another month, diagnostic imaging is again performed. If continued perfusion of the sac is identified, translumbar sac embolization with a liquid embolic is performed. This approach has resulted in a 100 % clinical success rate [73] with a mean follow-up of 27.5 months.

We continue imaging surveillance on a lifelong basis in EVAR patients who have undergone successful endoleak management to detect late recurrence and sac expansion.

Recommendations

- Intervention in patients with type II endoleaks and growing sacs appears to reduce morbidity and mortality compared to observation
- In type II endoleaks with stable aneurysm sacs, we support use of imaging surveillance. No intervention is recommended in this group. (**evidence quality moderate; strong recommendation**)
- Intervention is recommended in patient diagnosed with type II endoleaks with growing aneurysm sacs. (**evidence quality moderate; strong recommendation**)
  - We consider significant aneurysm growth as >5 mm in diameter from the pre-EVAR diameter or >5 mm over an interval of 6 months following an initial decrease in aneurysm size.
  - It is critical to exclude a pinhole Type III endoleak which may be indistinguishable from a Type II endoleak on CT and difficult to visualize on angiography
- For unstable type II endoleaks, a staged approach in treatment is advocated (**evidence quality low; moderate recommendation**)
- Success of intervention should be measured by clinical success (i.e. aneurysm sac shrinkage or stabilization) rather than technical success (absence of endoleak).

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Chapter 10
Ruptured Abdominal Aortic Aneurysm Treated with Endovascular Repair; Does Decompressive Laparotomy Result in Improved Clinical Outcomes?

Chandler A. Long, Veer Chahwala, and Ravi K. Veeraswamy

Abstract There is distinct lack of high grade evidence for guiding surgeons in the management of abdominal compartment syndrome (ACS) following endovascular repair (EVAR) for ruptured abdominal aortic aneurysms (rAAA). Patients who developed ACS after EVAR for a rAAA demonstrate a high morbidity and mortality. Conversely, performing a decompressive laparotomy is not without inherent risks. We therefore sought to evaluate the clinical outcomes of decompressive laparotomy in the treatment of ruptured abdominal aortic aneurysms to answer the question: in patients with a ruptured AAA treated with EVAR, does decompressive laparotomy improve clinical outcomes? Knowledge of the physiologic and clinical risk factors for the development of ACS is important for the management of this complication.

Keywords Abdominal Compartment Syndrome • Laparotomy for ACS • Ruptured Abdominal Aortic Aneurysm • Open Abdominal Treatment (OAT) • Vacuum-assisted Closure (VAC)

Introduction

Endovascular repair of ruptured abdominal aortic aneruysm (rAAA) has become a common modality of repair in those patients with appropriate anatomy [1–5] and a few retrospective studies have demonstrated the incidence of abdominal compartment syndrome (ACS) after EVAR to be 17–20 % [6, 7]. The chapter will review the relevant and pertinent data on decompression laparotomy after endovascular repair

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of rAAA, in order to provide evidence-based treatment recommendations in this complex clinical condition.

Compartment Syndrome is condition in which increased tissue pressure, in a confined anatomic space, results in decreased end-organ perfusion causing ischemia and organ dysfunction. This general condition can be seen in many different locations in the body, depending on the pathology and can be triggered or exacerbated in a number of ways. For example, Intra-abdominal hypertension (IAH), which itself can result from a spectrum of impaired physiologic conditions, may progress to ACS when intra-abdominal pressure (IAP) exceed 20 mmHg in the presences of organ dysfunction [8–10]. The WSACS – the Abdominal Compartment Society segregate IAH into grades; grade I- IAP 12–15 mmHg, grade II – IAP 15–20 mmHg, grade III – 21–25 mmHg, grade IV – >25 mmHg [10]. End organ dysfunction in ACS can manifest through inadequate visceral perfusion, decreased cardiac output, respiratory failure, renal failure and decrease spinal cord perfusion [8, 11]. The development of ACS is usually multifactorial and is exacerbated by the degree of shock. Massive fluid resuscitation increases the intra-abdominal and retroperitoneal volumes that are already compromised by the rupture itself. The subsequent inflammatory response, capillary leak, release of oxygen free radicals and cytokines only further exacerbate the condition.

Search Strategy

A literature search of English language publications from 1984 to 2016 was used to identity published data on abdominal compartment syndrome and intra-abdominal hypertension following repair of abdominal aortic aneurysms and demonstrated in Table 10.1. The PubMed database was searched using the terms "abdominal compartment syndrome," AND/OR "ruptured abdominal aortic aneurysm," OR "pathophysiology," OR "factors associated with," OR "complications," AND "intraoperative" AND/OR "perioperative complications". In total, 15 cohort studies (Table 10.2), 4 review articles and 1 guideline article were included in our analysis. The data and our ultimate recommendations were classified using the GRADE system.

Results

No prospective randomized trial exists examining the efficacy of decompressive laparotomy after endovascular repair for rAAA. The pathophysiology and morbid outcomes of ACS, following aortic surgery, without intervention are well understood [8, 12, 13]. Thus, the crucial question is when or at what threshold do you

Table 10.1 PICO table for treatment of ruptured abdominal aortic aneurysms

P (patients)	I (intervention)	C (comparator)	O (outcome)
Patients with ruptured AAA treated with EVAR	Decompressive Laparotomy	No Laparotomy	Mortality

Table 10.2 Studies performed for abdominal compartment syndrome in patients with rAAA

Author	Year	Number of patients	ACS-outcomes	Quality of evidence
Kron-cohort	1984	7	ACS with higher mortality	Very low
Ohki	2000	25	N/A	N/A
Greenberg	2000	3	N/A	N/A
Rasmussen	2002	45	Initial Mesh Closure reduces ACS and mortality as result of multiple organ failure (MOF)	Very low
Loftus-review	2003	N/A	N/A	N/A
Papavassiliou	2003	75	ACS with higher mortality	low
Veith	2003	35	N/A	N/A
Mehta	2005	30	ACS with higher mortality	Very Low
Djavani	2006	27	Improved survival with IAP monitoring and early decompression	Very low
Greco-state dataset	2006	N/A	N/A	N/A
Mehta	2006	40	ACS with higher mortality	Very low
Acosta	2007	162	ACS with higher mortality	low
Djavani	2009	52	ACS with higher incidence of colon ischemia	Very low
Mayer	2009	102	ACS with higher mortality	Very Low
Makar	2009	30	No difference in mortality of open vs evar	Very low
Starnes	2010	128	ACS with higher mortality	Very low
Mehta-review	2010	N/A	N/A	N/A
Djavani Gidlund	2011	32	N/A	Very low
Kirkpatrick-review	2013	N/A	N/A	N/A
Steuer- review	2016	N/A	N/A	N/A

surgically intervene, given the associated risk of ACS? Due to the inconsistency in diagnosis, and relatively infrequent incidence of the condition, there are only a handful of small and medium sized cohort studies shedding light on this issue.

Abdominal Compartment Syndrome as a Risk Factor for Mortality

An early study by Mehta et al. evaluated 30 patients who were treated with an endovascular repair for rAAA from January 2002 to December 2004 [6]. The researchers found that 6 of the 30 patients (20%) developed ACS necessitating abdominal decompression based on an IAP ≥25 mmHg in conjunction with new onset end-organ dysfunction. Their investigation showed that there were no differences in the preoperative demographics and chronic comorbidities (age, coronary artery disease, hypertension, diabetes, renal insufficiency, smoking status, etc). However, the study did reveal: that the patients that developed ACS: (a) required increased perioperative

volume resuscitation; (b) had significantly greater need of blood transfusion (8 ± 2.5 units vs. 2 ± 1.7 units, P = 0.08); (c) required increased use of an aortic occlusion balloon (67 % vs. 12 %, P = 0.01); (d) demonstrated markedly longer activated partial thromboplastin time (128 ± 84 s vs. 49 ± 31 s, P = 0.013); and (e) had a higher incidence of conversion to aorto uni-iliac devices. The overall mortality for this cohort was 23 % [6]. However, when stratified by the presence of ACS, the mortality for those patients with ACS was significantly higher (67 %) compared to (13 %) those without ACS (P = 0.01). The two surviving patients with ACS experienced considerable morbidity in their post-operative course. One patient developed permanent renal failure requiring dialysis and underwent multiple operations for definitive abdominal wall closure while the other developed bowel ischemia requiring resection and prolonged ventilator support with a tracheostomy. The 21 survivors that did not develop ACS had a more benign post-operative course, with only one occurrence of renal failure and one incidence of myocardial infarction. In addition, two patients in this cohort dealt with a prolonged ileus while another patient developed colonic ischemia necessitating resection. This study by Mehta et al. was significant because it was one of the early studies the demonstrated a lower incidence of ACS following EVAR compared to that previously reported following open aortic repair. It is estimated that ACS occurs in approximately 30 % of patients undergoing open repair for a rupture abdominal aortic aneurysm (rAAA) [14, 15]. However the mortality of patients with ACS in Mehta et al' cohort (67 %) is not much different than the associated mortality (as high as 70 %) in this open surgical cohort with ACS [14, 15].

Physiologic Parameters to Guide Laparotomy for ACS

Building on this foundation, Mayer et al. subsequently published the largest cohort study focusing on ACS after EVAR. This retrospective cohort analysis examined the 10-year experience of 102 patients who underwent emergent endovascular repair for rAAA. The suggested threshold in this study for surgical decompression differed from that of Mehta et al work with broadened characteristics utilized to diagnose ACS. In the Mayer et al. study, surgical decompression was based on IAP >20 mmHg *or* an abdominal perfusion pressure <50–60 mmHg *and* new development of organ dysfunction *or* the presence certain predisposing risk factors of abdominal compartment syndrome. Those factors included deep shock (SBP < 70 mmHg), intra operative fluid resuscitation >5 L, transfusion >6 units of packed red blood cells, hypothermia (<35 °C), vast retroperitoneal hematoma, and/or massive bowel edema [16]. The utilization of broader indications for surgical intervention led to improved mortality rates but a higher incidence compared to previous literature [17–19]. The researchers found that the overall 30-day mortality for emergent EVAR was 13 % (13 of 102 patients) and the stratified mortality for patients without ACS was 8 % (7 of 82 patients) compared to 30 % (6 of 20 patients) for patients with ACS. Decompression was required in 20 patients (20 %), 14 of which were

completed at the time of aneurysm repair and 6 later on while in the intensive care unit [16]. There were similar mortality rates between the two groups whether the decompression was done at the time of repair or in the post-operative period [20].

Another study, done from the United Kingdom (Makar et al.), prospectively evaluated a small cohort of 30 patients presenting with rAAA that were treated with an EVAR or conventional open repair, to assess incidence of ACS and subsequent outcomes associated with each treatment modality [21]. They measured intra-abdominal pressures post operatively at 2 and 6 h, and then daily for 5 days to all patients. A variety of scoring systems (ex: Hardman and MODS scores) were utilized to assess perioperative risk of organ dysfunction and mortality. Their results demonstrated that at the majority of measured time points, IAP was significantly higher in the conventional open repair groups compared to the endovascular group. In addition, the development of SIRS was identified in 14 of the 16 patients that underwent open surgery as compared to only one (of 14) in the endovascular group. One patient in the EVAR group developed ACS and required a decompressive laparotomy. This patient represented one of the two 30-day mortalities in this EVAR group. Despite demonstrating greater risk of organ dysfunction, greater need for blood transfusion and intravenous resuscitation, and increased intra-operative blood loss in the open intervention group, there was no significant difference in mortality, with 2 patients in each group [21]. Due to the small number in their cohort, the study was not sufficiently robust to compare the difference in mortality exhibited in previous studies. However their study did illustrate a correlation between IAP and MODS score, SIRS score, lung injury score, blood loss and transfusion, platelet transfusion, and volume of intravenous fluids at different time points [21].

Lastly, a Swedish analysis touched on the treatment of abnormally elevated IAP before patients reached a threshold for the diagnosis of ACS, an aspect for the topic that is sometimes ignored. The Swedish researchers prospectively collected data on patients from 2004 to 2010 to investigate the frequency of intra-abdominal hypertension (IAH) after EVAR for rAAA. They advocated early conservative treatment with diuretics, pain relief, colloids infusion and neuromuscular blockade for patients with IAH grades I and II (intra-abdominal pressure 12–20 mmHg) [9]. Post-operatively 10 of the 29 (34 %) patients treated with EVAR had IAP >15 mmHg and 6 (21 %) patients had IAP >20 mmHg. Three of the 29 (10 %) patients developed abdominal compartment syndrome and 2 underwent decompressive laparotomy. Interestingly, five of the 6 (83 %) patients with IAP >20 mmHg presented with pre-operative shock compared to only 25 % of the entire cohort and all the patients except for one who presented with preoperative shock, developed some degree of IAH (IAP >12 mmHg) [9]. This supports the notion that the degree of shock influences the risk of developing ACS. The 30-day mortality for patients who underwent EVAR for rAAA in their study was 13 % (4/32).

Djavani Gidlund et al. utilized aggressive post-operative monitoring of EVAR patients after rAAA for IAH. The threshold for treatment of abdominal compartment syndrome begins, for many surgeons, when IAP exceeds 20 mmHg. However, Djavani Gidlund et al. advocated medical treatment of IAH grades I and II (IAP 12–20 mmHg) to prevent progression of the condition and avoid the need for surgical

intervention. Mayer et al. added defined, predisposing risk factors into the criteria for the indications of surgery. Their mortality rates in the ACS population following endovascular repair for rAAA was lower than previously described in other studies. This is probably due to the fact that the liberalization of their indications for surgery raises the sensitivity of the diagnosis of ACS and allows for earlier intervention. Regardless of the degree to which one uses routine post-operative monitoring of IAH or what threshold is used to validate surgery, a consistent algorithm must be used by the surgeon or institution to maximize the efficacy of treatment.

Closure of Laparotomy for ACS

With regard to manner of closure of the abdomen after laparotomy, many methods have proven appropriate, and the level of familiarity and preference of the surgeon or institution should be considered. Rasmussen et al. evaluated the role of mesh closure in patients with rAAA treated with open repair. This study identified that severe anemia (hemaglobin < 10), prolonged shock (>18 min of systolic blood pressure <90 mmHg), preoperative cardiac arrest, massive resuscitation (>3.5 L/h), profound hypothermia (T < 33 C), and severe acidosis (base deficit < 13) as factors indicating the need for mesh based abdominal closure [15]. In their study, patients who underwent (early) mesh closure at the initial operation had lower multiple organ failure (MOF) scores, a lower mortality rate (51 % versus 70 %), and were less likely to die from MOF (11 % versus 70 %;) than patients who underwent (late) mesh closure after a second operation in the postoperative period for abdominal compartment syndrome [15]. No patients in the early mesh closure group had intra-abdominal hypertension or abdominal compartment syndrome develop [15]. Although this study evaluated patients with ACS after open repair, it supports the initial use of mesh closure to minimize the development of abdominal compartment syndrome and reduce the rate of mortality as the result of MOF.

Another study described the technique of open abdominal treatment (OAT) and vacuum-assisted closure (VAC) following endovascular repair of rAAA [20]. Clinical findings in the abdomen led to two possible pathways: (1) temporary closure with a plastic bag silo closure and conventional secondary dressing, or (2) a VAC system. Important indicators for this decision included the volume of the intra-abdominal organs protruding from the abdomen due to massive swelling and suspicion of impending bowel necrosis due to prolonged ischemia from hypotension, compression, and elevated IVP [20]. The abdomen was temporarily closed with a simple, large, sterile plastic drape or bag if the above factors were present. Conversely, OAT was initially done with a VAC device if none of the above factors were present. Ultimately, four patients required antibiotic therapy for abdominal infection, and all infections resolved. Abdominal wall closure (direct closure, 11; closure with polypropylene mesh, 3; bilateral anterior rectus abdominis sheath turnover flap, 1) was achieved in a delayed fashion after a median of 6 days.

A Personal View of the Data

The inferential value of the evidence gleaned from the available literature is low to very low since the evidence is based on observational cohort studies, most of which are small in size. Given the paucity of data, our methodology favors a more aggressive approach to the diagnosis and treatment of this condition because of the high mortality rate if appropriate treatment is not administered promptly. We feel that early treatment of Grade I and II intra-abdominal hypertension is warranted due to the low risk and high potential reward if successful. In addition, we would advocate for surgical decompression for IAP >20 mmHg (*or* an abdominal perfusion pressure <50–60 mmHg) in the setting of new organ dysfunction. In a situation of high IAP and/or low to marginal abdominal perfusion pressures but without organ dysfunction, the presence of predisposing risk factors of abdominal compartment syndrome, we feel, supports the decision for decompressive laparotomy. We do not make any recommendations in regard to the manor of closure. Our sentiment is that the crucial component to this aspect is not the method, but timing of the intervention that affects outcomes.

Recommendations

- We recommend measuring IAP in post-operative rAAA patients treated with EVAR who exhibit any known risk factors of ACS (**Quality of evidence low, Strong recommendation**)
- We recommend a protocolized approach to the monitoring and management of intra-abdominal hypertension (**Quality of evidence low, Strong recommendation**)
- We recommend early treatment with medical therapy of Grade I and II intra-abdominal hypertension, pending there are no contraindication to desired treatment. (**Quality of evidence low, weak recommendation**)
- We recommend surgical decompression of the abdomen if (1) IAP >20 mmHg *or* an abdominal perfusion pressure <50–60 mmHg *AND* (2) new development of organ dysfunction *or* the presence certain predisposing risk factors of abdominal compartment syndrome discussed above. (**Quality of evidence low, weak recommendation**)

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Chapter 11
In a Patient with Blunt Traumatic Aortic Injury, Does TEVAR Improve Survival Compared to Open Repair or Expectant Management?

Gerald R. Fortuna Jr. and Ali Azizzadeh

Abstract Aortic injury remains a top cause of mortality in patients involved in traumatic mechanisms, especially following blunt trauma, where it is the second-most common cause of death. A significant number of these deaths occur prior to arriving at medical facilities. In addition, of those who reach a hospital, the diagnosis and treatment of aortic injury can pose significant clinical dilemmas. Blunt traumatic aortic injury (BTAI) is frequently associated with other injuries that may or may not pose a more urgent need for intervention. Improved diagnosis, based on high-fidelity computed tomography (CT) imaging, aggressive medical therapy with blood pressure control, minimally invasive treatment options using advanced devices, and streamlined treatment algorithms have improved the care of patients with BTAI. These significant developments have transitioned the treatment of patients with BTAI into a predominantly endovascular approach when repair is required. Surgeons have a much better evidence-based approach as to whether observation, open repair (OR), or an endovascular approach is the most appropriate form of treatment for a patient with BTAI. Even with these advancements, however, level I data remain sparse in the literature and single-center series still make up the predominant form of support for intervention options. This chapter examines the available evidence and shows that in patients with BTAI, TEVAR improves survival compared to OR or expectant management.

Keywords Traumatic aortic injury • Blunt aortic injury • Aortic transection • Thoracic endovascular aortic repair • Non-operative management of thoracic aortic injuries • Open thoracic aorta repair

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Introduction

According to the National Trauma Data Bank, the incidence of blunt traumatic aortic injury (BTAI) is 0.3 % in the United States [1]. Modern autopsy studies report that aortic rupture is present in 1/3 of patients who die from blunt trauma [2]. Of patients who make it to a hospital, challenges in diagnosing BTAI and concomitant polytrauma injury patterns have posed difficult diagnostic and treatment decisions for physicians. One study reported that up to 66 % of patients arriving at hospitals with BTAI were unable to receive treatment, with a nonoperative mortality rate of 68 % [1]. However, the last two decades have seen significant changes in both the detection of BTAI and its treatment. Major advances in imaging techniques with high-fidelity, multi-slice CT imaging and improvements in minimally invasive endovascular repair have ushered in an evolution in the care of patients with BTAI. The traditionally accepted open approach strategy to BTAI has rapidly been complimented, and for most injury patterns replaced, with thoracic endovascular aortic repair (TEVAR) as the first-line treatment for anatomically suitable injuries. Over the last two decades, the morbidity and mortality associated with BTAI has been reported to be significantly reduced in an increasing number of reports in the literature because of the introduction of these advances in imaging and the increased use of endovascular techniques in patients with BTAI [2–12]. However, despite this trend in the literature of improved outcomes with TEVAR, there is a relative paucity of true level I data to support its overwhelming use as a first-line treatment. In fact, in the first and only study in the literature not sponsored by industry, Demetriades and colleagues, as part of the American Association for the Surgery of Trauma (AAST) Blunt Traumatic Aorta Injury study group, raised concerns over the widespread use of TEVAR for BTAI [3]. These concerns were mostly due to increased complication rates associated with the devices and their access sites [3].

Since Demetriades' 2008 AAST multicenter study, however, TEVAR devices and techniques have undergone significant advances that have specifically addressed many of the concerns published in that study. Advancements in actual stent graft design and construction have produced more compliant and conformable devices that have resulted in significantly improved overall device safety and efficacy profiles. In addition, today's devices have lower profiles, reducing access site sheath sizes and, in most high-volume centers, this advancement in device technology has seen percutaneous placement of endovascular stents surpass traditional bilateral groin cut-downs. A wider variety of sizes and lengths available to surgeons has also broadened the proportion of patients with BTAI who are amenable to endovascular repair. In addition, the Society of Vascular Surgery (SVS) made unprecedented strides in advancing TEVAR as a front-line treatment for BTAI when it widely supported the use of TEVAR, despite lacking an "on label" FDA indication for use in its 2012 Clinical Practice Guidelines [13]. These recommendations were supported largely by improved outcomes of TEVAR compared to traditional OR in single-center studies. It is important to note, however, that despite this increased trend in the use of TEVAR for BTAI, there remains only a small

number of non-industry based multicenter data that is available to examine patient outcome in this endovascular-centric era of treating aortic injury. Further, it is important to note that there is very limited data on the long-term outcome, durability, and reintervention rates of patients with BTAI who have undergone TEVAR.

Search Strategy

A literature search of English language publications from 2000-2014 was used to identity published data on BTAI using the PICO outline (Table 11.1). Databases searched were PubMed, Embase, Science Citation Index/Social sciences Citation Index and Cochrane Evidence Based Medicine. Terms used in the search were "blunt aortic injury," "blunt traumatic aortic injury," "traumatic aortic injury," "aortic transection," "thoracic aortic injury," "thoracic aortic injury," "thoracic endovascular aortic repair," "nonoperative management of thoracic aortic injuries," and "open thoracic aorta repair."

Classification of Blunt Traumatic Aortic Injuries

There is no debate that CT imaging has undergone significant advancements in both image quality and image acquisition speed over the last two decades. This has resulted in CT imaging techniques and "pan scanning" becoming an essential part of the overwhelming majority of patients' with blunt traumatic injuries initial evaluations. This increased fidelity of images and ubiquitous nature of CT in emergency departments has made identifying BTAI much easier. BTAI represents a spectrum of lesions that range from intimal tear to aortic rupture. Naturally, the treatment for all injuries is not the same. In 2009, we proposed a classification system based on the extent of injury to the anatomic layers of the aortic wall: intimal tears (Grade 1), intramural hematomas (Grade II), pseudoaneurysms (Grade III), and ruptures (Grade IV) (Fig. 11.1).

The SVS adopted this classification system in 2011 as part of its clinical practice guidelines for the treatment of BTAI [13]. While widely accepted as part of the SVS BTAI treatment guidelines, it is important to note that other grading scales have also been developed that take into account additional CT imaging findings, such as hemothorax and aortic dimensions, in the area of injury as well as to physiologic

Table 11.1 PICO table for operative approach to patients with blunt traumatic aortic injury

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with blunt traumatic aortic injury	TEVAR	Open operation and medical management	Survival

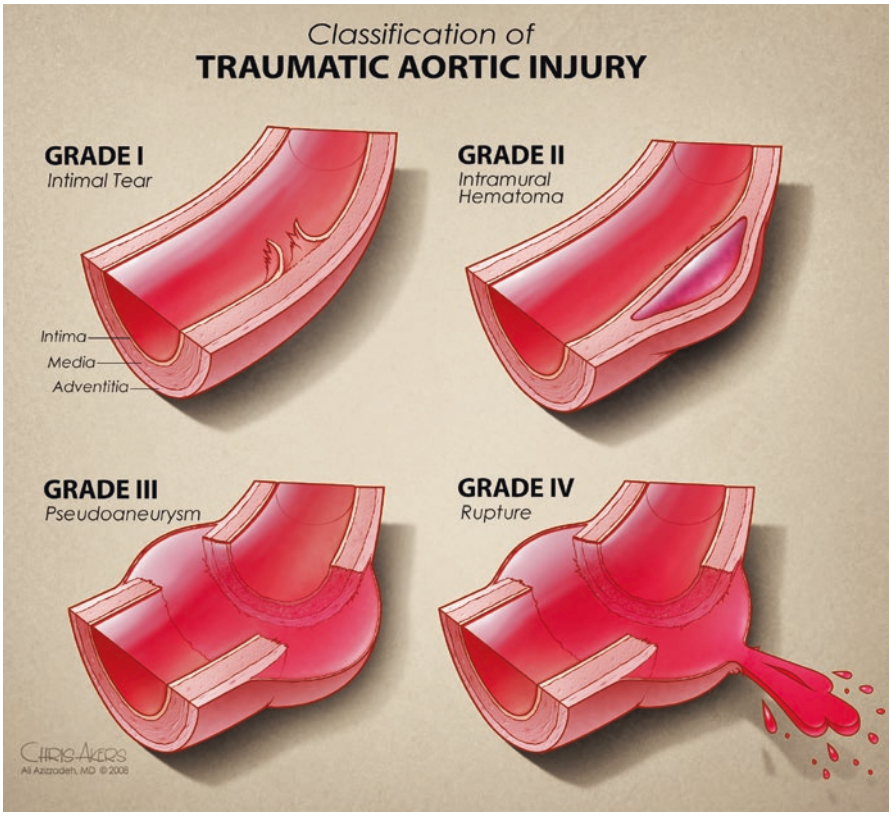

Fig. 11.1 SVS BAI Grading Scale "Classification of traumatic aortic injury (Adapted with permission from the Azizzadeh A, et al. [14], Copyright Society for Vascular Surgery, 2009)

parameters at the time of ED presentation [15–18]. Due to lack of prospective trials evaluating treatment outcomes implementing these grading scales, only low-grade evidence is available in the literature supporting one scale over the other. Despite superiority of a single grading scale, it is imperative that some form of grading scale be systematically used when addressing treatment algorithms. Using the available treatment options appropriately is critical to optimizing successful outcomes in patients with BTAI.

BAI Treatment Options

As stated earlier, in 2011 the SVS tasked an expert panel to develop clinical practice guidelines for the treatment of BTAI [13]. After a systematic review and meta-analysis of the literature, the committee reached a consensus based on expert

opinion. More definitive recommendations could not be reached due to the overwhelming "low-grade" evidence based primarily from single-center studies available for review [14]. The systematic review included 7,768 patients from 139 studies. The study revealed a significantly lower mortality rate in patients who underwent TEVAR, compared to OR, and nonoperative management (9 %, 19 %, and 46 %, respectively, P < .01). Based on this, the SVS Clinical Practice Guidelines suggest urgent endovascular repair for Grade II-IV injuries with suitable aortic anatomy once other injuries have been stabilized [13]. These recommendations are supported by the results of the only non-industry sponsored Level II data available in the literature from the AAST Aortic Injury Study Group reported in 2008 [3]. These results supported improved outcomes with initial blood pressure optimization, followed by delayed intervention after 24 hours, as compared to patients who underwent emergent repair within 24 hours of presentation [3]. What needs further refinement within the literature is to determine the exact optimal timing for aortic repairs based on grade and the natural course of aortic injuries if left untreated, especially in patients with lower grade BTAI. A more refined description of patient risk factors for early rupture after BTAI would also help define optimal timing for repair, as this complication almost invariably leads to mortality. Some centers have reported nonoperative management with anti-impulse therapy for Grade I and select Grade II injuries [15–18, 20]. The inclusion of Grade II injuries into nonoperative management directly conflicts with SVS guidelines but has been supported in a number of single-institution studies [15–18, 20]. The Achilles heel of nonoperative management in patients with BTAI is the notoriously poor compliance of this patient cohort with medical therapy and follow-up imaging protocols.

Literature Summary

At present, the most impactful series in the literature on contemporary management of BTAI comes from two studies. The AAST prospective multicenter trial by Demetriades et al. and the Aortic Trauma Foundation (ATF) retrospective multicenter study, which was in press at the time of this writing [3, 21]. Both studies report similar trends and outcomes in regard to the use of TEVAR, mortality, and paraplegia rates. In the AAST study, 64.8 % of patients were treated with an endovascular approach and 35.2 % were treated with OR, with an overall mortality rate of 13.5 % [3]. Mortality with OR was 23.5 % compared to 7.2 % with endovascular repair (p value < 0.001) [3]. In regard to postoperative paraplegia, patients repaired with an open approach had an incidence of 2.9 %, all associated with bypass procedures, while an incidence of 0.8 % was found in patients repaired with an endovascular approach [3]. The solo paraplegia complication in the endovascular group was due to stent graft collapse and thrombosis [3]. The most striking finding in the AAST report was the significant number of device-related complications. In the group of patients repaired with an endovascular approach, 20 % experienced device-related complications [3]. Most of these complications were related to endoleaks (14.4 %), with the remaining complications related to access sites [3].

The 2014 Aortic Foundation multicenter study reported results from 382 patients from 9 American College of Surgeons (ACS) verified trauma centers [19]. The SVS grading scale was used with patients in the following distribution: 94 Grade 1 injuries, 68 Grade II injuries, 192 Grade III injuries, and 28 Grade IV injuries [21]. Nonoperative management was used as the initial method of treatment in 32.2 % of the patients with only two failures [21]. Both patients, one Grade II injury and one Grade IV, were subsequently repaired with TEVAR without complication [19]. The overall mortality rate for patients managed nonoperatively was 34.4 % with an aortic mortality rate of 9.8 % [19]. They represented a significantly older group of the cohort and predominantly consisted of Grade 1 injuries [19]. Of the patients repaired operatively, OR was selected in 16 % with a mortality rate of 8.6 % and an aortic-related mortality of 2.5 % [19]. The interesting finding in this group is that median time from admission to OR was 36.4 hours, with half of the patients being repaired within 6 hours of admission [19]. This is important to note as it could indicate the need for operative repair more urgently than endovascular resources could be mobilized. An endovascular approach with TEVAR was chosen in 52 % of the cohort with a hospital mortality rate of 8.6 % with an aortic-related mortality of 2.5 % [19]. The study reported 2 deaths during the operative placement of TEVAR, neither of which were due to the procedure itself [19]. The study also reported 6 TEVAR failures, with salvage coming in the form of 2 repeat TEVARS and 4 conversions to open approaches [19]. TEVAR complications consisted of 6 malpositioned endografts (3.0 %), 5 endoleaks (2.5 %), 1 incidence of paralysis (0.5 %), and 2 strokes (1.0 %) [19]. Coverage of the left subclavian artery was required in 41.4 % of the patients treated with TEVAR [19].

When the operative groups were compared directly, the results revealed that patients who were treated with OR had higher ISS scores, more likely to have mediastinal hematomas with associated compression, faster time to repair from admission and higher transfusion rates [21]. Overall complication rates were similar between operative approaches. When all treatment modalities were compared, the overall in-hospital mortality for all patients with BAI was 18.8 %, with 34.4 % in patients managed nonoperatively, 19.7 % for patients repaired with open techniques, and 8.6 % for those repaired with TEVAR ($p = 0.021$) [21]. Mortality as related to BAI Grading was 0 % in Grade I, 2.9 % in Grade II, 5.2 % in Grade 3, and 46.4 % in Grade 4 [21]. Most aortic-related deaths reported in this series occurred prior to patients having an opportunity for surgical intervention of any type (18/25 deaths) [21]. Of the patient deaths following operative intervention, all had an ISS > 25 [21]. Three of these seven deaths had a GCS of 3 upon arrival with head AIS scores >3, two required massive transfusions, three required emergent laparotomies and five dying within 24 hours of admission [21]. These findings represent the poly-trauma nature of these patients and the significant amount of force transferred as a result of deceleration injury mechanisms.

The study reported that the independent predictors of all-cause mortality were higher ISS scores, higher SVS BAI grades, low admission GCS, need for blood transfusion in the first 24 hours and nonoperative management [21]. When direct aortic-related mortality was analyzed, higher ISS, SVS grade of injury and chest

AIS scores were predictive [21]. Ultimately, in this study cohort, intervention with TEVAR proved to be protective against aortic-related mortality.

While these landmark studies set the most recent benchmark for care of patients with BTAI, Karmy-Jones et al. provided a comprehensive review of the BTAI literature up until 2010. This report reviewed 62 retrospective reviews and six meta-analysis [16]. At that time, 25 papers were available comparing TEVAR to OR [16]. Using the key phrases in the above stated search strategy, eight additional studies were identified for review. All studies available in the literature comparing TEVAR to OR are available for review in Table 11.2.

In summary, 1,721 patients were repaired using TEVAR vs. 3,499 patients repaired with OR. TEVAR mortality rates ranged 0–25 % while OR ranged from 0 to 50 %. Stroke rates were 0–13 % for TEVAR and 0–20 % for OR. Finally, paralysis rates ranged from 0 to 10 % for TEVAR and 0–13 % for OR. Only five of the studies evaluated within this table show a mortality benefit from TEVAR to repair BTAI at a p value ≤ 0.05, with the findings from the ATF being the most definitive and complete analysis performed as of this writing. These findings highlight the overall lack of high-grade evidence present in the surgical literature today.

While it is clear that endovascular repair is a safe and effective way to treat patients with BTAI, there is tremendous opportunity for investigators to study and report new data in well-designed study protocols. With that said, TEVAR has established itself as an intervention that has low mortality rates, low complication rates, and exceptional outcomes. These results make it unlikely that a prospective, randomized controlled trial is likely to be performed by future investigators. Future studies will likely continue to come from single-center studies. However, multi-institutional trials centered on durability, reintervention rates, long-term outcomes, and robust registries have the potential to advance our understanding of BTAI the furthest.

A Personal View of the Data

Blunt aortic injury remains a major cause of fatality in people injured traumatically. Over the last two decades, significant advancements have been made in imaging quality and device manufacturing that has paved the road for innovative treatment approaches to patients with blunt aortic injury. Multicenter trials have allowed researchers to categorize and grade blunt aortic injury patterns, which has allowed for higher volume centers to analyze results of different treatment options. These data have shown us that nonoperative management with tight blood pressure control with beta-blockers, calcium channel blockers and nitrates is safe and effective in patients with lower grade injuries. It has proven to be a useful adjunct in patients who are older or too frail for operative intervention, although complications and mortality rates are increased in this subset of patients.

Advances in the device industry have led to covered stent grafts in a wider range of “off the shelf” sizes, with lower profile access sheaths, more conformable and

Table 11.2 TEVAR vs. open repair and clinical outcomes

	TEVAR						Open repair				
Author (year)	N	Mortality (%)	CVA (%)	Para-plegia (%)	Endo-leak	LSCA Coverage (%)	N	Mortality (%)	CVA (%)	Para-plegia (%)	Study type (quality of evidence)
DuBose (2014)	198	8.6	1	0.5	2.5	41	61	19.7	0	0	Retrospective multicenter cohort (low)
DiEusanio (2013)	44	2.3	2.3	0	NR	NR	31	0	0	0	Single-center retrospective cohort (low)
Estrera (2013)	69	4	3	0	NR	NR	106	14	3	10	Retrospective single-center cohort (low)
Watson (2013)	11	7	7	0	NR	NR	26	42	9	6	Retrospective single-center cohort (low)
Karmy-Jones (2013)											Review (low)
Riesenman (2012)	26	12	8	0	0	NR	49	37	6	6	Single-center retrospective (low)
Xenos (2011)	121										
Canaud (2011)	40	0	0	0	2.5	NR	35	11.4	0	0	Single-center retrospective cohort (low)
Hong (2011)	558	11	1.9	1.8	NR	NR	1351	12	0.7	0.8	NIS database (low)
Durham (2010)	13	9.1	NR	0	NR	NR	22	0	NR	7.7	Single-center retrospective (low)
Estrera (2010)	32	0	3	0	NR	NR	113	21	0.8	2.6	Single-center retrospective (low)
Jonker (2010)	71	6	2.9	0	NR	NR	261	17	2.3	0.8	Single-center retrospective (low)

Lang (2010)	10	0	0	0	NR	NR	30	7	0	3.3	Single-center retrospective (low)
Tong (2010)	15	7.2	NR	0	7.4	NR	7	22.5	NR	28.5	Single-center retrospective (low)
Arthurs (2009)	95	18	0	1.6	NR	NR	665	19	0.6	2	NTD review (low)
Azizzadeh (2009)	27	0	3.7	0	NR	NR	15	0	0	0	Single-center retrospective (low)
Feezor (2009)	22	0	0	0	14	95	14	50	NR	NR	Single-center prospective (low)
Geisbusch (2009)	14	14	7	0	NR	NR	14	36	0	0	Single-center retrospective (low)
Kauver (2009)	8	13	13	0	NR	NR	5	0	0	0	Multicenter retrospective (low)
Demetriades (2008)	125	7.2	1.6	0.8	14.4	NR	68	23.5	0	2.9	Prospective, multicenter cohort (low)
Buz (2008)	39	7.7	2.5	0	NR	NR	35	20	0	0	Single-center retrospective (low)
Botta (2008)	27	0	3.7	0	NR	NR	4	0	0	0	Single-center retrospective (low)
Moainnie (2008)	26	15	0	0	NR	NR	26	15	0	0	Single-center retrospective (low)
Yamane (2008)	14	7	0	0	NR	NR	12	8	0	0	Single-center prospective (low)
Riesenman (2007)	14	14	7	0	NR	NR	48	40	2	0	Single-center retrospective (low)
Midgley (2007)	12	0	0	0	NR	NR	16	3	0	6	Single-center retrospective (low)

(continued)

Table 11.2 (continued)

	TEVAR						Open repair				
Author (year)	N	Mortality (%)	CVA (%)	Para-plegia (%)	Endo-leak	LSCA Coverage (%)	N	Mortality (%)	CVA (%)	Para-plegia (%)	Study type (quality of evidence)
McPhee (2007)	8	25	0	0	NR	NR	5	20	20	0	Single-center retrospective (low)
Akowuah (2007)	7	0	0	0	NR	NR	8	13	0	13	Single-center retrospective (low)
Kokotsakis (2007)	22	10	0	10	NR	NR	10	4.5	0	0	Single-center retrospective (low)
Andrassy (2006)	14	14	0	0	NR	NR	16	19	0	13	Single-center retrospective (low)
Broux (2006)	13	15	0	0	NR	NR	17	23	0	5.8	Single-center retrospective case control study (low)
Cook (2006)	19	21	0	0	NR	NR	23	26	0	4	Single-center prospective database retrospective review (low)
Lebl (2006)	7	14	0	0	NR	NR	10	20	0	0	Single-center retrospective (low)

compliant devices, and overall improved safety profiles. The last two decades have seen endovascular approaches go from augmenting OR approaches to blunt aortic injuries to becoming the treatment modality of choice. While OR techniques will remain an alternative option in the approach to the management of these injury patterns, modern data is showing very low complication rates with endoleaks, stent migration and access sites while at the same time improved mortality results and an overall protective effective from aortic related deaths with the use of TEVAR. Admittedly, there remains a lack of strong Grade I evidence in the literature on this topic. However, significant efforts are currently in process to develop a national aortic registry that hopes to bring the ability to pool information from high and low volume centers alike to help answer some of the questions still plaguing this injury pattern. The goals of the ATF are aimed at continuing to answer questions as to the natural course of low grade aortic injuries that are managed nonoperatively, the optimal timing for operative intervention, high-risk factors for early aortic rupture, and long-term durability and need for reintervention rates of patients treated with endovascular devices. It is difficult to argue that an age of endovascular repair of blunt aortic injuries is here or that the results are favorable. Devices continue to evolve, as do the techniques to place these devices. There remained much work to be done in this area and collaborative efforts will be a driving force in finding answers.

For now, these authors strongly advocate that TEVAR is the best first-line treatment option for patients with Grade II-IV BTAI who have suitable aortic anatomy for repair. Figure 11.2a, b demonstrates a Grade IV BTAI who was successfully treated with TEVAR. For those who do not, OR remains a tried-and-true means of treatment with nonoperative blood pressure management being an integral part of the treatment algorithm for all patients.

The next section outlines the most salient points when deciding to proceed with TEVAR. These points are sure to evolve as we progress in our research of BTAI, but represent a safe and effective way to approach these injuries at the present time.

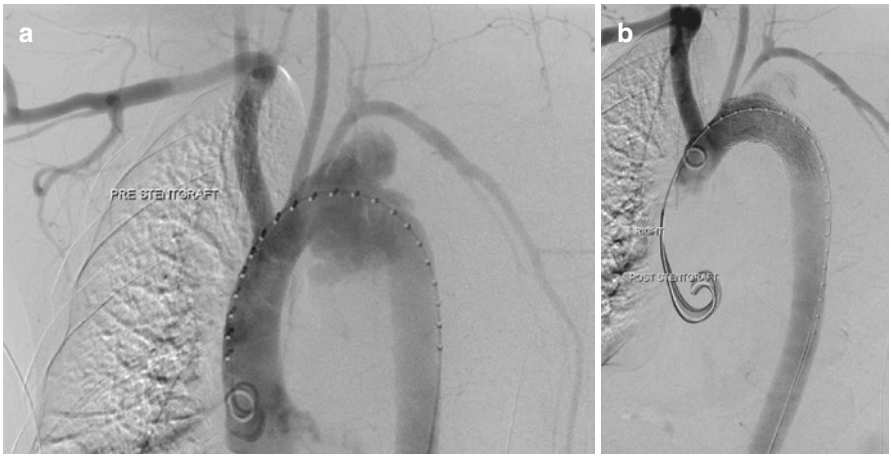

Fig. 11.2 (**a**) Grade IV BTAI pre-stent graft repair. (**b**) Grade IV BTAI post-stent graft repair

Recommendations

- CT angiography is the mainstay imaging modality for screening and diagnosing BTAI **(Quality of evidence low; strong recommendation).**
- Tight blood pressure control should be utilized in all patients diagnosed with BTAI prior to operative repair, unless contraindicated by other injuries **(Quality of evidence low; strong recommendation).**
- Medical management with anti-impulse blood pressure control is recommended for patients with Grade I injury **(Quality of evidence low; strong recommendation).**
- TEVAR is the treatment of choice for all patients with Grade II-IV BTAI who have suitable anatomy **(Quality of evidence low; strong recommendation).**
- OR is an alternative approach for patients who are not suitable candidates for TEVAR **(Quality of evidence low; moderate recommendation).**

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Part II
Lower Extremity Arterial Disease

Chapter 12
In Patients with Aortoiliac Occlusive Disease, Does Endovascular Repair Improve Outcomes When Compared to Open Repair?

Michael S. Hong and William C. Pevec

Abstract Aortobifemoral bypass (ABF) has long been the gold standard for treatment of aortoiliac occlusive disease, proving to be a durable procedure with a 10 year patency rate of 80–90 % in more recent reports. Peri-operative mortality of 1–3 % can be achieved.

Endovascular treatment of aortoiliac lesions has evolved rapidly over the past two decades. Long segment stenosis and occlusion are now increasingly being treated with endovascular therapy, reflecting significant changes in practice patterns since the publication of the Trans-Atlantic Inter-Society Consensus Group (TASC) Guidelines in 2007.

Contemporary results demonstrate that compared to ABF, endovascular therapy has a lower primary patency rate, but similar secondary patency and limb salvage up to 5, and perhaps even 10, years after the index procedure.

Keywords Aortobifemoral bypass • Aortoiliac occlusive disease • Iliac stent • Iliac angioplasty • Endovascular therapy

Introduction

Aortobifemoral bypass (ABF) has long been the gold standard for aortoiliac occlusive disease (AIOD), proving to be a durable procedure with a 10 year patency rate of 80–90 % in more recent reports [1–3]. Peri-operative mortality of 1–3 % can be achieved [1, 2, 4, 5]. However, endovascular therapy is gaining an increasingly prominent role as a less invasive option in the treatment of aortoiliac occlusive lesions. Endovascular therapy offers revascularization of aortoiliac lesions while

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avoiding the morbidity of a laparotomy, arterial clamping and unclamping, general anesthesia, and large fluid shifts in the post-operative period.

In response to the early enthusiasm for endovascular therapy, the Trans-Atlantic Inter-Society Consensus Group (TASC) guidelines were published in 2000, in attempt to balance the appeal of minimally invasive therapies with their durability. The guidelines were subsequently amended in 2007, and recommended open bypass for TASC C and D lesions [6]. Since the latest update, results of endovascular therapies for TASC C and D lesions have been reported, with varying results based on indication, use of selective versus primary stenting, and concomitant procedures.

This chapter is intended to guide an evidence-based discussion on the contemporary treatment of patients with aortoiliac occlusive disease, by comparing aortobifemoral bypass with endovascular therapy in regards to patency, morbidity, mortality, and quality of life. It also serves to address patient-specific and intraoperative factors, with particular attention to endovascular treatments.

Search Strategy

A literature search of English language publications published between 2000 and 2014 was performed using the PICO outline (Table 12.1). The PubMed and PubMed Central database was used to identify articles. Suggested related articles, referred studies in retrieved articles, reviews, and referenced articles were also evaluated. Search terms were “aortoiliac disease”, “aortoiliac occlusive disease”, “aortofemoral”, “aortobifemoral bypass”, “iliac stent”, “iliac angioplasty”, “TASC”, “endovascular therapy”, “endovascular treatment”, “hybrid”, “quality of life” and combinations thereof.

Results

Aortobifemoral Bypass

According to the TASC guidelines, patients with diffuse stenosis or occlusions, comprising TASC D lesions, are best suited to open surgical bypass. This procedure however requires general anesthesia, a laparotomy, and aortic cross clamping. Due to the extent of physiological insult with these maneuvers, mortality and systemic morbidity rates are substantial.

Table 12.1 PICO table

Patients	Intervention	Comparator group	Outcomes
Patients with aortoiliac occlusive disease	Endovascular therapy	Aortobifemoral bypass	Primary patency, primary-assisted patency, secondary patency, limb salvage, LOS, complication rate, quality of life

The weighted average of 30-day mortality was 2.4 % for ABF in studies published since 2000. A recent meta-analysis by Chiu, which spans four decades of data, reports 4 % mortality, 16 % systemic complications, and 6 % local complications in 5738 cases [7]. Dimick reported ABF procedures from the 1997 Nationwide Inpatient Sample, which is a 20 % sampling of 483 U.S. hospitals of various sizes and types. In-hospital mortality in this report was 3.3 % [8]. This number is the same as de Vrie's reported mortality rate of 3.3 % in "recent" (post-1975) ABF results [9].

It may be tempting to assume that with improved pre-operative optimization, patient selection, and critical care, operative mortality has significantly improved with ABF in the new millennium. However, this assumption has been refuted by published reports, and the reasons are multifactorial. First, as Back demonstrated, ABF is now utilized for patients with increasingly complex anatomy, often requiring suprarenal or supraceliac clamping, and visceral revascularization [10]. Second, fewer ABF are being performed, and Dimick's previously referenced work demonstrated mortality rate of 3.7 % for low-volume hospitals (<25 ABF/year) compared to 2.2 % for high-volume hospitals (>25 ABF/year) [8]. Third, as endovascular therapy further matures, newer vascular surgeons will have had less open training compared to their more senior counterparts, which will further exacerbate challenges with ABF. It is predicted that by 2015, vascular trainees will complete fellowship having performed only 10 open aortic repairs, and by 2020, only 5 [11].

Morbidity from ABF is generally categorized into systemic (e.g. MI, pneumonia, sepsis, stroke) versus local (e.g. hematoma, lymphocutaneous fistula, surgical site infection). A large proportion of systemic complications are pulmonary. A meta-analysis by de Vries reported a systemic morbidity of 12 % and local morbidity of 7 % in ABF results spanning four decades, whereas Chiu reported 16 % and 6 % respectively over a similar timeframe [7, 9] (Table 12.2).

Table 12.2 Aortobifemoral bypass outcomes

Author	Year	N	Mortality	Morbidity	Primary patency 1 year	Primary patency 5 years	Secondary patency 5 years
Faries	2001	370	0	18[a]		93	
Back	2003	107	4	34			
Reed	2003	281	1	32		85	92
Dimick	2003	3073	3.3				
Hertzer	2007	255	1.2	26	96	88	
Kashyap	2008	86	7	14[a]			
Chiesa	2009	822	0.1	8[a]			
Burke	2010	118	0.8	51[a]		89	
Sachwani	2013	101	4	40[a]			
Weighted Avg		5213	2.4	30	96	89	92

[a]Represents sum of all complications, no overall morbidity was given, not included in weight averages

Aortoiliac Angioplasty and Stenting

Endovascular therapy for aortoiliac arterial occlusive disease (AIOD) is an appealing alternative to ABF. It can be performed percutaneously or with open femoral arterial exposure, without general anesthesia, and can be combined with adjunctive procedures without taking on significantly more risk.

Although endovascular therapy is often provided to those with prohibitive cardiopulmonary risk for open surgery, mortality is still less than 1 %, based on a weighted average extracted from a recent systematic review of 1711 patients [12]. However, it is important to note that these are high-risk patients undergoing a low-to-medium risk procedure, and mortality in high volume single institution retrospective studies can sometimes be as high as 4 %. Therefore, caution is advised even for endovascular therapy.

In contrast to ABF, morbidity resulting from endovascular treatment of AIOD consists predominantly of local or arterial complications. Hematoma, pseudoaneurysm, retro-peritoneal hemorrhage, arterial dissection, arterial perforation, and distal emboli have been described [13]. Systemic complications are less common, but MI, renal injury, pulmonary edema, stroke, and others, as a whole, occur at a range of about 3–4 % [14]. Combined, the morbidity rate is about 13 % when a weighted average is calculated from Jongkind's systemic review. A smaller meta-analysis of 323 TASC C/D cases reported a morbidity rate of 15 %, of which three quarters were local complications [14] (Table 12.3).

Comparison of Endovascular vs Open Bypass

The results of endovascular therapy are difficult to directly compare with the results of aortobifemoral bypass. Most studies are retrospective single institution studies, and often, endovascular therapy is favored in patients with advanced cardiopulmonary disease that preclude an open operation, and aortobifemoral artery bypass is often limited to patients with more extensive arterial occlusive disease [15]. With this caveat in mind, ABF has a mortality rate of 3–4 %, compared to about 1 % for endovascular therapy. Morbidity is generally higher with ABF, with far more systemic complications, whereas endovascular treatment usually has local complications that are more easily managed, or arterial complications that can often be managed with endovascular techniques.

Compared with the gold standard of aortobifemoral bypass, endovascular treatment of aortoiliac lesions has inferior primary patency, but acceptable primary assisted and secondary patency. According to several meta-analyses, aortobifemoral bypass primary patency rates are 80–86 % at 5 years, and 72–79 % at 10 years, whereas primary patency rates with endovascular therapy are 60–86 % at 5 years. Primary assisted and secondary patency however are comparable between the two interventions, with similar 5 year secondary patency for each procedure type ranging from 80 to 98 %. Limb salvage rates closely track those of secondary patency.

Table 12.3 Endovascular outcomes

Author	Year	N	Mortality	Morbidity	Primary patency 1 year	Primary patency 5 years	Secondary patency 5 years
Schurmann	2002	110		8.2		66	79
Galaria	2005	394	1.8	7		53	79
Kudo	2005	151	0	0.7	76	49	99
Balzer	2006	89	0	14.6	95		
Leville	2006	89	3.4	12.3			
AbuRahma	2007	151	0	8.6	75		
Kashyap	2008	83	4	15[a]	90		
Chang	2008	171	2.3	22		60	98
Sixt	2008	438	0	0.9	86		
Koizumi	2009	466	0	3		82	
Burke	2010	174	1.1	22[a]		85	
Ozkan	2010	127	1	24		63	93
Pulli	2011	223	0	0		80	93
Ichihashi	2011	413	0	4.8	90	83	98
Chen	2011	121	1	8.9	86		
Ye	2011	787	2.9	15.3	89	64	83[b]
Danczyk	2012	788	0.1	7.8			
Sachwani	2013	103	0	19[a]			
Humphries	2014	254	0	1.6	90		
Weight Avg		5132	0.8	7.1	87	71	91

[a]Represents sum of all complications, no overall morbidity was given, not included in weight averages

[b]Only 91 pts included in this analysis

Given the disparity between primary and primary-assisted and secondary patency, the question arises: "How many patients treated with endovascular therapy require additional procedures to maintain patency?" Fortunately, it appears that the majority have durable results, and only about 15 % require re-intervention at 5.7 years. Re-interventions after endovascular treatment tend to be endovascular, and therefore the minimally invasive advantages are maintained [16]. Though open surgery has higher primary patency rates, open operations are also susceptible to anastomotic stenosis, graft occlusion, and pseudoaneurysm, with a re-intervention rate as high as 18 % in a high-volume series [2].

The few studies available unanimously conclude that quality of life is increased after either aortobifemoral bypass or endovascular treatment, though none compared outcomes by type of intervention. Functional outcome with open bypass was improved at 2 year follow up as measured by the SF-36 score in one study, and 80 % sustained a "satisfactory" outcome at 4.5 years [17, 18]. The Dutch Iliac Stent Trial is one of the few studies reporting quality of life after endovascular intervention, and reported sustained Rand-36 score improvement among physical and functional parameters at 5 years [19].

Endovascular Considerations

Endovascular treatments continue to evolve. As such, there is still substantial uncertainty regarding evidence based endovascular management of aortoiliac lesions. A few of these matters are discussed.

TASC Classification

Although endovascular therapy has traditionally been limited to TASC A and B lesions, many institutions have reported favorable results after treating more extensive C and D lesions in the aortoiliac segment. Studies that compared their results by TASC level have found no statistically significant difference with regards to primary or secondary patency at up to 10 years [20–22]. In one study, there was also no difference in the rate of secondary interventions those who had isolated common or external iliac disease compared with those with diffuse iliac disease [13].

Several authors provide indirect explanations for the comparable success even in advanced lesions. Pulli noted that occlusive lesions were treated with more than double the length of stents than stenotic lesions, while Piazza and Ichihashi used more stents for TASC C/D lesions compared to A/B lesions [21, 23, 24]. Danczyk evaluated patients who had CIA-or-EIA versus CIA-and-EIA stents (one versus two segment disease), and noted no difference in need for secondary interventions at 7 years (16.8 % vs 14.2 %). Furthermore, Danczyk noted that of the 95 patients requiring additional endovascular interventions, only 49 were due to in-stent stenosis, which suggests that primary patency is significantly affected by progression of atherosclerosis in untreated arterial segments [13]. In summary, advanced aortoiliac lesions, whether classified as occlusive or TASC C/D, do not necessarily fare worse than more limited stenotic or TASC A/B lesions.

Technical Success

In treating aortoiliac occlusion, one consideration is the ability to cross the lesion. Ye's meta-analysis of mostly older studies reports technical success of 93.7 % and 90.1 % for TASC C and D lesions, respectively, with no significant difference. Contemporary technical success rates may be even higher with newer re-entry devices available. Indeed, many authors report 99–100 % technical success with iliac occlusions [14, 15, 23, 24].

One notable complication more frequently seen in C/D lesions is iliac perforation. This complication is presumably due to over-dilation of an area with significant atherosclerotic plaque. The majority of these iliac ruptures were successfully treated endovascularly with either temporary balloon occlusion or an insertion of a covered stent.

Primary Versus Selective Stenting

Generally speaking, TASC A/B lesions can be treated with selective stenting, whereas C/D lesions seem to benefit from primary stenting [25]. The Dutch Iliac Stent trial (randomized, controlled trial) compared selective and primary stenting and demonstrated no significant differences in primary patency, ABI, or rate of re-interventions at up to 8 years, though this patient cohort presented predominantly with claudication, and fewer than 10 % had iliac occlusion [19]. In contrast, a meta-analysis demonstrated that for TASC C and D lesions, there was a statistically significant higher primary patency rate with primary stenting compared to selective stenting at years 2 and 3, with no significant difference at 1 and 5 years [14]. A single center retrospective trial with 10 year follow up demonstrated higher patency rates with primary stenting in TASC C and D lesions, but no difference for primary versus selective stenting in TASC A and B lesions [26].

Covered Versus Bare Metal Stents

The COBEST trial evaluated common and external iliac arteries treated with balloon expandable covered or bare metal stents, and found higher primary patency with covered stents [27]. However additional studies report conflicting results, some showing improved patency with covered stents, and some with bare metal stents [28, 29]. The Dutch Iliac Stent Trial (DISCOVER) is currently enrolling patients in a multicenter, double-blind, randomized, controlled trial to further clarify the role of covered versus bare metal stents in the common iliac artery for advanced disease [30].

Special Considerations

Vascular specialists have generally advocated conservative management for claudication in infrainguinal disease. The Comparing Exercise Therapy with Angioplasty for Claudication (CETAC) trial included patients with claudication and either aortoiliac or femoral-popliteal disease. In this intent-to-treat analysis, half of the supervised exercise group crossed over during the 7 years of follow up. However, the authors note two main findings to support a conservative approach to claudication. First, half of the exercise group were able to avoid procedures altogether, and had significantly improved treadmill performance and quality of life compared to baseline after 7 years. Second, among those who eventually crossed over, these patients still had half the number of procedures overall than the angioplasty first group, since 27 % of the angioplasty group required secondary procedures [31].

The iliac arteries are larger with higher volume flow than the infrainguinal arteries, and endovascular procedures in the iliac arteries have favorable durability compared to femoral-popliteal interventions. For this reason, an endovascular-first approach for claudication due to aortoiliac disease is appealing. CLEVER, a multicenter, randomized, controlled trial for patients with claudication and aortoiliac disease, demonstrated greater improvement in the Peak Walking Time with supervised exercise compared to endovascular therapy at 6 months, with no difference in the Claudication Onset Time. Despite improved treadmill performance, disease-specific questionnaires (Walking Impairment Questionnaire and Peripheral Artery Questionnaire) suggest statistically better quality of life with endovascular therapy. Long term results from this trial are still in process [32].

Aside from the risk factors of cardiopulmonary disease and other comorbid conditions, other patient-specific considerations are relevant in choosing treatment. Younger patients (less than 50 years) in particular have been shown to have less durable results after either aortobifemoral bypass or endovascular therapy. Reed reported ABF results at 5 years, and primary and secondary patency rates were only 66 and 79 % for those younger than 50, compared to 96 and 98 % for the 60+ age group [4]. Schurmann reported that, in a group with a mean age of 57, primary and secondary patency rates of iliac stenting were 66 and 79 % at 5 years, and 46 and 55 % at 10 years [33]. In young patients, though they often have favorable cardiopulmonary status, an endovascular-first approach may be preferred due to poor durability of either intervention.

Older patients tend to have more durable results than younger patients with open bypass but with higher morbidity and mortality [2, 4, 8]. In addition, the advantage of the better durability of aortobifemoral artery bypass must be balanced against the upfront risks of mortality and systemic morbidity in elderly patients with limited life expectancy (Table 12.4).

Patients with previous laparotomy, and even previous aortobifemoral bypass, are not automatically excluded from subsequent open surgery. Scali and others recently reported outcomes of 19 redo-aortobifemoral bypass grafts and compared them to a case-control cohort of carefully selected patients with similar operative indications and co-morbidities undergoing primary ABF. Most of the redo-ABF patients underwent a trans-peritoneal ABF as their first procedure, and were subsequently treated with a retroperitoneal approach during their redo operation. Though there was greater blood loss and longer procedure times, there was no difference in major complication rates, length of hospital stay, or long term survival. There were no in-hospital or 30-day deaths [34].

Table 12.4 Mortality and durability by age

Author	Age	Mortality	1 year patency	5 year patency
Reed	<50	0		66
	50–60	1.0		87
	>60	2.1		97

Recommendations

Patients with aortoiliac disease presenting with claudication should primarily be managed medically, with risk factor modification and an exercise program. Such conservative management has been shown to have similar improvements in functional outcome without the peri-operative morbidity of intervention. However, failure of conservative management, with lifestyle limiting symptoms, is an appropriate indication for endovascular intervention.

Whereas TASC II recommended endovascular therapy in A and B lesions, data consistently demonstrate that good results can be obtained with TASC C and D lesions, with similar technical success and patency rates, particularly when these advanced lesions are managed with primary stenting. The data on covered versus bare metal stents are still evolving and a current randomized, controlled trial will help guide management in the future.

Endovascular therapy, even for advanced lesions, has similar primary-assisted and secondary patency, as well as limb salvage, compared to aortobifemoral bypass. Moreover, the majority of patients undergoing endovascular therapy do not require re-intervention. Although aortobifemoral artery bypass is typically avoided in patients with severe cardiopulmonary disease, endovascular intervention can typically be offered to these patients with low risk of mortality. In younger patients, the durability of open bypass is poor, and a less invasive treatment may be warranted, accepting the need for re-interventions. In older patients, while durability is good, there is higher peri-operative morbidity and mortality. Taken together, endovascular therapy should be considered as a first-line option for most patients with advanced aortoiliac occlusive disease.

Personal View of the Data

Management of claudication should primarily be conservative, with appropriate risk factor modification and an exercise program. Though endovascular interventions are safe, they are not without risk. Endovascular therapy for claudication should be reserved for those who fail conservative management with symptoms that are lifestyle-limiting.

In critical limb ischemia due to aortoiliac occlusive disease, we favor an endovascular-first approach.

The aortoiliac segment is large with high volume flow, making it an ideal anatomic region for endovascular intervention. Recent studies have provided consistent evidence that endovascular therapy is a reasonable first-line therapy not only for TASC A/B disease, but also more extensive C/D lesions. Though primary patency is lower with endovascular therapy, with adequate surveillance and re-intervention when indicated, secondary patency and limb salvage are nearly as good as aortobifemoral bypass. As with open bypass, ensuring adequacy of outflow with adjunctive procedures such as femoral endarterectomy and profundaplasty will likely yield better outcomes.

Recommendations

- Patients presenting with claudication due to aortoiliac arterial occlusive disease can achieve similar functional outcome with an exercise program compared to endovascular therapy, with fewer interventions over a similar period. Endovascular intervention can be offered for failure of conservative management (**evidence quality high; strong recommendation**).
- An endovascular-first approach is appropriate for aortoiliac intervention, regardless of TASC classification or the presence of occlusion. Endovascular therapy is particularly indicated in patients with prohibitive cardiopulmonary risk factors, short life expectancy, or previous laparotomy (**evidence quality medium; moderate recommendation**).
- Primary stenting should be considered for TASC C and D lesions (**evidence quality medium; moderate recommendation**).
- There are inadequate data to recommend a covered stent over a bare metal stent.
- Aortobifemoral bypass can be considered for patients with adequate cardiopulmonary reserve and anatomically extensive disease, and for those who fail endovascular therapy (**evidence quality low; weak recommendation**).

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Chapter 13
In Patients with Aortoiliac Occlusive Disease, Does Extra-anatomic Bypass Improve Quality of Life and Limb Salvage?

George E. Havelka and William H. Pearce

Abstract Aortoiliac occlusive disease (AIOD) often manifests as claudication or, in its advanced forms, as critical limb ischemia (CLI), both of which can worsen a patient's quality of life and increase the likelihood of limb loss. Surgical correction usually requires either an anatomic, invasive surgery (aortobifemoral bypass) or a less invasive, extra-anatomic approach (femorofemoral bypass, axillofemoral bypass). A patient's co-morbidities and ability to withstand an invasive surgery often dictate which revascularization technique will be used. Understanding the ability of an extra-anatomic bypass to prolong limb survival and improve a patient's quality of life compared to anatomic revascularization is crucial to accurately anticipate a patient's outcome.

Keywords Aortoiliac occlusive disease • Femorofemoral bypass • Axillofemoral bypass • Peripheral vascular disease quality of life • Limb salvage • Amputation free survival

Introduction

Aortoiliac occlusive disease (AIOD) most often develops due to progression of atherosclerosis present at the aortic bifurcation. Claudication is the most common symptom that patients experience. Critical limb ischemia (CLI) characterized by

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rest pain and tissue loss likely develops when patients exhibit multilevel disease, with atherosclerotic involvement of their femoral, popliteal, and infrageniculate arterial system. Patients with disease localized to only their aortoiliac segments are often younger, smoke, and have high cholesterol. Their AIOD becomes mitigated by the existence of collateral circulation pathways, which allow enough blood flow to the lower extremities to stave off CLI. Patients with multilevel disease and tissue loss are more likely to be older, have co-morbidities such as diabetes mellitus (DM) and hypertension (HTN), and have concomitant atherosclerotic disease in additional, remote arterial beds such as in the coronary and cerebrovascular circulation.

Patients with claudication derived from AIOD will often complain of intermittent claudication affecting the lower legs, thighs, hips and/or buttocks. Up to 30 % of males may complain of erectile dysfunction (ED). Leriche syndrome encompasses the classic constellation of symptoms of patients with AIOD claudication: lower extremity proximal claudication, ED, diminished femoral pulses, and muscle atrophy in the legs. Claudication is a relative indication for surgery as the majority of these patients are at a low risk of limb loss (2–3 % annually) [1]. The development of collateral circulation helps offset the potential for worsening limb ischemia and these patients may show improvement without surgery, especially if they modify their lifestyle in accordance with physician recommendations. Surgery should be offered to claudicants whose disease has a significant detrimental impact on their life. A young patient whose livelihood involves ambulation (a mail carrier) would be disproportionately affected by short distance claudication compared to an elderly patient who is minimally ambulatory at baseline. In the former, surgery becomes an important treatment option.

Surgery should always be considered in patients presenting with CLI. Patients whose disease has progressed to rest pain and tissue loss are at a much higher risk for limb loss than their claudication-only counterparts. An important consideration in these patients is how extensive their lower extremity disease may be. Patients with CLI are more likely to have multilevel disease, requiring correction of the AIOD as well as a distal procedure (either simultaneous or staged) to address the out-flow component of their peripheral arterial disease (PAD).

Surgical intervention for AIOD may involve open, endovascular, or a hybrid approach. Many patients are now candidates for endovascular reconstruction of their aortoiliac segment. Open anatomic bypass, such as an aortobifemoral bypass (AFB), is an excellent option with unsurpassed long-term patency rates for AIOD. Many patients, however, are not candidates for either endovascular or anatomic bypass surgery. These patients become candidates for an extra-anatomic bypass (EAB). EAB vessels are defined as those that course through the body in a manner distinct and physically removed from the native circulation that they are designed to bypass. Axillobifemoral bypass (AxBF), axillounifemoral bypass (AxUF), and femorofemoral bypasses (FF) are examples of EAB that are used to treat high-risk patients in need of aortoiliac reconstruction. EABs have been shown to have inferior long-term patency rates compared to anatomic bypasses. However, the morbidity and mortality associated with an EAB are superior to open anatomic

repair for AIOD. Candidates for an EAB, therefore, are those believed to be at too high a risk to undergo an ABF but with anatomy not conducive to an endovascular approach. Such patients often suffer from advanced, numerous co-morbidities (coronary artery disease, chronic obstructive pulmonary disease), may have hostile abdomens (intra-abdominal infections or adhesions, stomas), or may have previously placed grafts that have since become infected. EAB may not be an option on the rare occasion when the patient's condition makes surgery prohibitive under any circumstance.

There are many surgical options to consider when contemplating reconstruction for AIOD. Not all bypasses, however, are created equal. Studies have shown that anatomic revascularization has long-term patency rates that an EAB does not approach. Other markers of surgical success, however, may be just as or even more important than patency rate. Primary goals of revascularization are avoiding amputations and improving a patient's quality of life (QOL). This chapter seeks to answer the question of whether extra-anatomic bypasses for aortoiliac occlusive disease contribute to significant prolongation of amputation-free survival rate and improvements in patients' quality of life.

Search Strategy

A literature search of English language publications produced between 1996 and 2014 pertaining to extra-anatomic bypass for aortoiliac occlusive disease and the subsequent effect on limb salvage and quality of life was conducted. The PICO formula for postulating a question was used to help guide our search (Table 13.1). PubMed, Embase, and Cochrane Evidence Based Medicine were the databases searched. Search terms included "aortoiliac occlusive disease," "aortoiliac disease AND femorofemoral bypass," "aortoiliac disease AND axillofemoral bypass," "aortoiliac disease AND quality of life," "femorofemoral bypass AND quality of life," "axillofemoral bypass AND quality of life," and "aortoiliac disease AND extra-anatomic bypass". Articles were excluded from consideration if they focused only on anatomic (aortobifemoral, iliofemoral) bypasses or endovascular reconstruction. Thirteen retrospective studies, two prospective studies, and one randomized control trial were identified. Each article was classified according to the GRADE system (Table 13.2).

Table 13.1 PICO table for limb salvage rates and quality of life associated with extra-anatomic bypass for aortoiliac occlusive disease

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients experiencing claudication or critical limb ischemia from aortoiliac occlusive disease	Extra-anatomic bypass	Anatomic bypass	Effect on limb salvage rates and quality of life

Table 13.2 Literature published between 1996 and 2014 with associated GRADE score for limb salvage and quality of life endpoints

Author	Year	Design	Limb salvage GRADE	Quality of life GRADE
Berce	1996	Retrospective	Low	Very low
Passman	1996	Retrospective	Moderate	Low
Mii	1998	Retrospective	Low	Very low
Martin	2000	Retrospective	Low	Very low
Mingoli	2000	Retrospective	Low	Very low
Nackman	2001	Prospective	Low	Low
Mingoli	2001	Retrospective	Moderate	Very low
Pai	2003	Retrospective	Very low	Moderate
Mii	2005	Retrospective	Moderate	Very low
Pursell	2005	Retrospective	Low	Low
Ricco	2005	Randomized	Moderate	Low
Frankini	2007	Retrospective	Low	Low
Hertzer	2007	Retrospective	Moderate	Very low
Thuijls	2008	Retrospective	Very low	Low
Leidenbaum	2009	Retrospective	Low	Very low
Kumar	2011	Prospective	Low	Low

Results

Clinical Relevance of Amputation-Free Survival and Improvement in Quality of Life

Critical limb ischemia carries a significant risk of limb loss. Within 1 year of presentation, up to 40 % of patients require a major amputation and up to 20 % have died. The overall 30-day mortality of a major amputation, defined here as either a below-the-knee (BKA) or above-the-knee (AKA) amputation, is 8 % with a 30-day overall complication rate of 30 %. Nelson et al. demonstrated 30-day mortality rates for BKA and AKA of 6.5 % and 12.8 %, respectively [2]. Aulivola et al. arrived at similar conclusions with 30-day mortality rates for BKA and AKA of 5.7 % and 16.5 % respectively [3]. In addition, they found 1-year survival rates to be 74.5 % after a BKA and 50.6 % after an AKA. Astonishingly, 1/2 of all patients requiring an AKA had died within 1 year of surgery. Fortunately, revascularization has a profound positive impact on limb salvage rates for patients with critical limb ischemia. Hallett et al. were able to show a 50 % reduction in major amputation rates for patients undergoing either surgical or endovascular reconstruction [4]. Limb salvage, therefore, becomes a critical endpoint when determining the benefit of limb revascularization to the patient and the ultimate success of an operation.

Claudication carries a minimal risk of limb loss, approaching 5 % at 5 years [5]. Operative intervention to correct claudication is performed with the hope of improving the patient's QOL. Dumville et al. published data supporting an improvement in

QOL following bypass surgery using the Medical Outcomes Study Short Form-36 Health Survey (SF-36) [6]. QOL also becomes important in patients with CLI. Patients are at risk of losing their mobility and independence after undergoing a major amputation. Only 80 % of patients receiving a BKA are able to ambulate vs. 50 % of patients with an AKA. In addition, amputees are more prone to depression as they struggle to come to terms with the loss of their limb. Revascularization for lifestyle-limiting claudication and CLI, therefore, becomes an important means by which to increase the patient's QOL.

Extra-anatomic Bypass for Aortoiliac Occlusive Disease

Most studies relating to extra-anatomic bypasses for AIOD focus on one type of bypass (either axillofemoral or femorofemoral) to the exclusion of the other. Additionally, most do not include aortobifemoral direct anatomic bypass in their analysis. Overall, this limits the interpretation of the data in regard to limb salvage and quality of life. However, limb salvage is an outcome in most of the studies included herein. Quality of life is rarely measured directly but graft patency, ankle-brachial indices, and symptom-free survival may be considered surrogates for this elusive outcome.

Berce et al. performed a retrospective analysis of their personal experience with Femorofemoral bypass (FFB) surgery for AIOD [7]. Their goal was to demonstrate that FFB was safer than performing anatomic aortoiliac surgery. Limb salvage was one outcome they considered. This study involved 211 patients, all of whom underwent surgery for claudication. None had surgery for CLI. No other types of extra-anatomic bypasses were performed. Limb salvage at 1, 5, and 10 years was 99 %, 97 %, and 97 %, respectively (Table 13.3). Limb patency appeared to be excellent, but only claudicants were included in the study. Quality of life was not directly measured. Graft patency, however, was measured (Table 13.4). Graft patency at 1, 5, and 10 years was 96 %, 72 %, and 64 %, respectively. Overall, the GRADE of this study in regard to limb salvage is deemed *low quality*. The reason the study was assigned a grade of low quality was because the study was retrospective in design and did not directly compare limb salvage rates to direct anatomic revascularization. In addition, the study enrolled only patients suffering from claudication and not CLI. The GRADE of this study for quality of life is deemed *very low*. A higher grade could not be assigned as quality of life was not a directly measured outcome. Only an indirect assumption about EAB impact on quality of life could be gained based on patency rates.

Mingoli et al. retrospectively reviewed 228 patients undergoing FFB [8]. One hundred eighty eight patients underwent surgery for CLI, while 40 suffered from intermittent claudication. This study had relatively long-term follow-up with patient outcomes recorded out to 10 years. Limb salvage rates were 85.5 % at 5 years and 80.1 % at 10 years. Again, quality of life was not directly measured. Primary patency was used in its place with outcomes of 70.2 % at 5 years and 48.1 % at 10 years.

Table 13.3 Limb salvage for extra-anatomic and anatomic bypasses with follow-up through 10 years

Author	N	ABF	EAB	Limb salvage					
				6 months	1 year	2 years	3 years	5 years	10 year
Berce	211	–	211	–	99 %	–	–	97 %	97 %
Passman	247	139	108	–	–	–	–	89 % EAB 79 % ABF	–
Mii	115	–	115	–	–	–	–	100 % EAB 78 % ABF	–
Martin	61	–	61	–	95 %	–	–	–	–
Mingoli	228	–	228	–	–	–	–	85.5 %	80 %
Nackman	125	74	51	–	–	98 %	–	–	–
Mingoli	76	–	76	–	–	–	–	78 % EAB 87 % ABF	–
Mii	164	65	99	–	100 %	–	–	93 % EAB 100 % ABF	–
Pursell	144	–	144	–	91 % CLI 100 % C	–	79 % CLI 99 % C	79 % CLI 97 % C	–
Ricco	143	69	74	–	–	–	–	98 % EAB 98 % ABF	–
Frankini	75	–	75	–	–	–	–	67 %	–
Hertzer	536	355	181	–	–	–	–	91 % EAB 95 % ABF	–
Thuijls	95	–	95	–	–	–	–	94 %	–
Liedenbaum	45	–	45	–	83 %	–	–	83 %	–
Kumar	38	32	6	83 %	–	–	–	–	–

Note: All percentages are for extra-anatomic bypass limb salvage unless otherwise specified
EAB extra-anatomic bypass, *ABF* aortobifemoral bypass, *C* claudication, *CLI* critical limb ischemia

The GRADE for limb salvage was considered to be *low,* primarily because there was no anatomic revascularization comparison group. The GRADE for QOL was indirectly inferred from patency rates at 5 and 10 years, and, therefore, was assigned a value of *very low*.

Table 13.4 Primary patency rates of extra-anatomic bypasses for aortoiliac occlusive disease with follow-up through 10 years

Author	N	ABF	EAB	Primary patency rate				
				1 year	2 years	3 years	5 years	10 year
Berce	211	–	211	96 %	–	–	72 %	64 %
Passman	247	139	108	–	–	–	74 % EAB 80 % ABF	–
Mii	115	–	115	89 %	–	81 %	73 %	70 %
Martin	61	–	61	86 %	–	72 %	63 %	–
Mingoli	228	–	228	–	–	–	70 %	48
Mingoli	76	–	76	–	–	–	71 % EAB 83 % ABF	–
Pai	161	–	161	71 %	–	–	–	–
Mii	164	65	99	–	93 % EAB 95 % ABF	–	83 % EAB 93 % ABF	65 % EAB 90 % ABF
Ricco	143	–	74	71 % EAB 92 % ABF	–	–	55 % EAB 83 % ABF	–
Frankini	75	–	75	–	–	–	70 %	–
Hertzer	536	355	181	–	–	–	80 % EAB 90 % ABF	–
Thuijls	95	–	95	82 %	–	–	57 %	–
Leidenbaum	45	–	45	69 %	–	51 %	51	–

Note: All percentages are for extra-anatomic bypass limb salvage unless otherwise specified
EAB extra-anatomic bypass, *ABF* aortobifemoral bypass

A subsequent study published by Mingoli et al. the following year investigated limb salvage and patency rates in femorofemoral bypasses compared to aortobifemoral bypasses at 5 years [9]. The limb salvage rates for EAB and anatomic reconstruction were not significantly different (78 % and 87 % at 5 years, respectively). Again, patency rates were used as a surrogate for quality of life. Patency rates were found to be worse for EAB than for anatomic bypasses (71 % and 83 % at 5 years, respectively). The GRADE for the limb salvage data was considered *moderate*, even though only one type of EAB was included, because there was a direct anatomic surgery comparison group. The GRADE for QOL was *very low* since patency rates were used for QOL estimates.

Mii et al. retrospectively studied limb salvage and patency rates in 99 patients having undergone FFB compared to 65 who underwent ABF bypass [10]. Of the 99

patients undergoing EAB, 95 had femorofemoral bypasses and 4 had iliofemoral bypasses. Limb salvage data was available for only 32 patients. Overall, the limb salvage rates were excellent with no significant difference between the two groups. At 5 years, limb salvage for the FFB cohort was 93 % and the ABF cohort was 100 %. Data for primary patency rates were compiled at years 2, 5, and 10. For the FFB patients, primary patency was 93 %, 83 %, and 65 %. Primary patency rates were better for the ABF patients with measures of 95 %, 93 %, and 90 %. Although direct comparisons were being made between patients with EAB and anatomic revascularization, we considered the quality of data to be *low*. This GRADE classification can be justified since there was a small number of patients out of the total starting number who were followed for limb salvage and only one type of EAB, the FFB, was studied. Again, since primary patency was used as a marker for QOL, the quality of this data was deemed *very low*.

Pursell et al. retrospectively looked at 144 patients, all of whom underwent FFB for AIOD [11]. Ninety-three patients had surgery for claudication with a mean ambulating distance of 50 ft. Twenty-six patients were bypassed for rest pain and 25 received surgery for various degrees of tissue loss. This study did not seek to compare EAB with anatomic revascularization, but sought to compare outcomes, specifically limb salvage and relief of symptoms, between those suffering initially from intermittent claudication versus CLI. Limb salvage rates were significantly better in the claudicants at 1, 3, and 5 years (100 %, 99 %, and 97 %, respectively) than in the patients with CLI (91 %, 79 %, and 79 %, respectively). FFB for claudication conferred significantly greater relief of symptoms at 1, 3, and 5 years (87 %, 83 % and 71 %, respectively) than did FFB for CLI (64 %, 54 %, and 43 %, respectively). The GRADE score for limb salvage is considered *low*. There is no direct comparison with an anatomic bypass group and only FFB bypasses were included in the study. The GRADE score for QOL was considered *low* as well. Even though there was no direct comparison to an anatomic bypass group, this article was able to show that EAB did confer an improvement in symptoms in patients treated for both claudication and CLI (although the claudicants benefitted more). An improvement in symptoms is considered to be a better indirect measurement of QOL than primary patency rates.

Thuijls et al. published a retrospective study of 95 patients who underwent FFB for AIOD (45 for claudication and 50 for tissue loss) [12]. Limb salvage rate was reported as 94.7 % for the study, whose duration approached 5 years. The article was unclear, however, on exactly the length of the follow-up period during which these amputations took place. Primary patency was found to be 88.2 % at 1 year and 57.3 % at 5 years. The authors also determined the Rutherford clinical status for the limb in question and were able to assess whether there was a change in status subsequent to bypass. In fact, they found an improvement in the Rutherford class in 59 patients (89 %) and a deterioration in only 7 (11 %). Data on limb clinical status was available for only 66 patients. The limb salvage GRADE was considered *very low*. There was no anatomic revascularization comparison group, the period of follow-up was vague, and there was no subgroup analysis based on patients suffering from claudication vs. CLI. The data on quality of life, inferred from primary patency rates

and Rutherford classification, was deemed *low* quality. Only indirect conclusions could be drawn in regards to QOL.

Mii et al. performed a retrospective studied that followed limb salvage and primary patency in 81 patients undergoing either axillobifemoral or axillounifemoral bypass for AIOD [13]. Fifty-two patients presented with claudication while 27 patients (and a total of 36 limbs) were considered to have CLI. The limb salvage rate at the end of the study, carried out to 7 years, was 100 %. No patient underwent a major amputation, regardless of whether they suffered initially from claudication or CLI. Primary patency at 1, 3, 5, and 7 years was found to be 89 %, 81 %, 73 %, and 70 %, respectively. The GRADE for limb salvage data is considered to be *low*. Despite expanding the study to include two different types of EAB for AIOD, their analysis did not differentiate between the bypass types. Also, there was no ABF group for comparison. The GRADE for QOL is *very low* as primary patency is being used as a QOL marker.

Martin et al. also sought comparisons between axillobi- and axillounifemoral bypass for AIOD [14]. This was another retrospective study that enrolled 60 patients who subsequently underwent 61 EAB (53 axillobifemoral bypasses and 8 axillounifemoral bypasses). Thirteen patients suffered from intermittent claudication while 47 patients presented with CLI (30 with rest pain and 17 with tissue loss). Over a follow-up period averaging 13 months, only 1 major amputation was reported. The amputation occurred in a patient who received an axillounifemoral bypass. No data was presented relating to the amputation-free period of patients having undergone axillobifemoral bypass. The primary patency rates at 1, 3, and 5 years were 86 %, 72 %, and 63 %, respectively. The GRADE for limb salvage is deemed to be *low* as there is no direct comparison to an ABF group and there is no subgroup analysis between the two types of EAB included in this study. The GRADE for QOL is *very low* as only primary patency rates can be used to infer what effect EAB may have on QOL.

Frankini et al. looked retrospectively at their experience performing EAB for AIOD over a 15-year period, composed of 75 patients undergoing 79 EAB [15]. They included a large variety of EAB types in their analysis (iliofemoral crossover 41.8 %; femorofemoral crossover 24 %; axillobifemoral 21.5 %; axillounifemoral 7.6 %; axillounipopliteal 1.3 %; axillobipopliteal 1.3 %). Patients with CLI (86 %) were more common than those with claudication only (8.9 %). Infection was an indication for operation in 5.1 % of the study population. Limb salvage was determined to be 67.6 % at 5 years while primary patency rates were found to be 70 % at 5 years. The GRADE for limb salvage is *low*. There is no ABF comparison group and they did not compare limb salvage and patency rates between the different EAB types. The GRADE for QOL is *very low*. Primary patency was the only data reflecting indirectly on QOL.

Liedenbaum et al. performed a retrospective analysis of 45 patients undergoing EAB for AIOD [16]. They included patients undergoing either axillobifemoral (27 patients) or axillounifemoral (18 patients) bypass. Patients who may have undergone FFB were not included. Limb salvage rates at 1 year (84 %) and 5 years (84 %) were tabulated. Primary patency at 1, 3, and 5 years was 69 %, 51 %, and 51 %,

respectively. The GRADE for limb salvage is *low* as there is no ABF comparison group and no subgroup analysis between the different types of EAB included in the study. In addition, there was a high number of patients lost to follow-up (51 %) at the end of 5 years. The GRADE for QOL is *very low* since only primary patency rates are reported.

Passman et al. performed a retrospective study looking at EAB in comparison to ABF surgeries in regard to limb salvage and patency [17]. A total of 247 patients were enrolled; 108 received axillofemoral bypasses (99 were axillobifemoral and 9 were axillounifemoral bypasses) and 139 received ABF bypasses. CLI was the diagnosis for the majority of those undergoing EAB bypass (80 % vs. 42 % of ABF patients). Claudication was the most common complaint in those patients undergoing ABF surgery (58 % vs. 20 % of EAB patients). Limb salvage rates at 5 years were not significantly different between the groups undergoing EAB bypass (89 %) and ABF (78 %). Primary patency rates were also not significantly different (74 % at 5 years for EAB; 80 % at 5 years for ABF). The GRADE for limb salvage in this study is *moderate* mainly because there is a direct comparison between anatomic and extra-anatomic bypass outcomes. The study, however, is retrospective, and there is neither blinding nor allocation concealment. The primary patency rate is a surrogate for QOL and, therefore, is considered of *very low* value.

Nackman et al. published a prospective study looking at the limb salvage rates and quality of life in patients undergoing EAB and ABF for AIOD [18]. The authors enrolled 125 patients who received either EAB or ABF. The choice of surgery was made by the surgeon on a patient-to-patient basis and was not randomized. CLI was the chief complaint of 45 % of patients and 55 % complained of intermittent claudication. Limb salvage was determined to be 100 % at 2-year follow-up, but no differentiation was made between those patients undergoing EAB vs. ABF bypass. Quality of life was measured pre- and post-operatively by using the SF-36 survey, specifically designed to measure QOL. Ninety percent of all enrolled patients agreed to participate. All QOL parameters significantly improved after surgery for AIOD, regardless of whether the patient underwent an EAB or ABF bypass. QOL was found to be most closely linked to the patients' underlying co-morbidities, and not to the bypass surgery itself. The GRADE for limb salvage was considered to be *low* in quality. The authors did not distinguish between limb salvage outcomes for those undergoing EAB vs. AFB, however, the limb salvage rate was excellent, determined to be 100 % at 2 years. Unfortunately, we do not know how many or what types of EAB the patients received compared to those having AFB. The QOL data is considered *low* as well. Despite using a standardized survey to quantify QOL, there is no analysis of the results based on whether the patient underwent an EAB or AFB bypass. In general, everyone's QOL was shown to improve and co-morbidities were found to be more closely linked than surgery type to QOL. One may infer that QOL in patients undergoing EAB is likely reported as worse than those undergoing AFB since the reason a patient is offered an EAB is usually due to the severity of their co-morbidities in the first place.

Ricco et al. was the only randomized control trial that compared EAB to ABF [19]. The authors enrolled 143 patients, 74 of whom were randomized to the group

receiving FFB while 69 were randomized into the AFB group. Limb salvage, primary patency, arterial-brachial indices, and ED data were compiled. The limb salvage rates were not significantly different, with a rate of 98.6 % for the EAB group and 98.5 % for the AFB group. Primary patency rates, however, were significantly worse for those undergoing EAB bypass, in agreement with other studies. The primary patency rates at 5 and 10 years for the EAB and AFB groups were 71.8 % and 55.6 % vs. 92.7 % and 82.9 %, respectively. Although the ABI increased for both groups post-operatively, there were no significant differences in the degree of change between groups. ED was improved in both groups. Pre-operatively, 8.6.% in the AFB group complained of ED compared to 3.4 % post-op while 8.9 % in the EAB group complained of ED pre-operatively compared to 4.5 % post-op. The GRADE initially for this study was high, but was ultimately reduced to *moderate*. The exclusion criteria for the study led to the enrollment of relatively healthy subjects, different from most patient populations who undergo EAB. Patients were offered only FFB, they had only unilateral iliac artery disease and were excluded if they had CLI, and they were healthier overall than the typical patient undergoing EAB. The GRADE score for QOL is considered to be *low*. Patency rates, ABIs and ED can all be used to draw conclusions on a patient's QOL. However, primary patency rates and ABIs have been shown to be unreliable markers when trying to predict a patient's subjective QOL. In this study, the number of patients experiencing ED pre- and post-op were too few to allow any real generalization about the effects of AFB and EAB to QOL in this regard.

Hertzer et al. conducted a retrospective study of 536 patients, 355 of whom underwent AFB and 181 who underwent EAB, comparing rates of primary patency and limb salvage [20]. Of the 181 who underwent EAB, 90 received FFB, 15 had axillounifemoral bypasses, and 76 had axillobifemoral bypasses. Overall, 50 % received surgery for claudication and 50 % for CLI. Limb salvage rates were not significantly different between EAB and AFB at 5 years (91.2 % and 95.5 %, respectively). Primary patency agreed with previous studies in showing a worse patency rate of EAB vs. AFB at 5 years (80 % vs. 90 %, respectively). The limb salvage GRADE is considered *moderate* because several different types of EAB bypass were included in the study and there was an AFB group for comparison. There was not a subgroup analysis of limb salvage based on EAB type, however. The study was also retrospective, not a randomized control trial, with no blinding or allocation concealment. The GRADE for QOL is *very low*, since only primary patency rates were reported.

Kumar et al. prospectively looked at a cohort of 38 patients who underwent revascularization for AIOD [21]. All patients presented with CLI. The majority of these patients underwent AFB. Only 6 patients in this study received an EAB (3 with FFB, 1 with axillofemoral bypass, 1 with axillopopliteal bypass). The limb salvage rate at 6 months for the EAB group was 83 %. This study attempted to quantify QOL by utilizing the Rand-36 Item Health Survey 1.0 form. This showed a significant improvement in QOL at both 1-month and 6-month follow-up appointments. The GRADE for limb salvage is considered *low*, primarily because the follow-up period was so short (6 months) and the number in the EAB group was so low

(6 patients). The GRADE for the QOL data is *low*. Despite demonstrating an improvement in QOL with the Rand-36 form, there is no comparison of QOL improvement between the AFB and EAB groups.

Pai et al. published a retrospective study encompassing 161 patients looking at effect of EAB on ABIs as well as improvement in symptoms post-operatively [22]. Sixty-six patients underwent FFB for claudication while 95 underwent FFB for CLI. At 1 year, there was a significant improvement in ABI from 0.31 to 0.65. In addition, 100 out of 117 patients following up endorsed an improvement in their symptoms; 50 of these had CLI pre-operatively. Eleven patients' symptoms were unchanged while 6 had worsening of symptoms. This study did not look at limb salvage as an endpoint. The GRADE for QOL is moderate with the majority of patients stating their symptoms were improved after surgery. ABIs also improved, but there was no correlation made between a patient's post-operative ABI and their post-operative symptoms. One drawback was that this was a retrospective study that did not use a standardized QOL survey to quantify their patients' QOL pre- and post-operatively.

Recommendation

Advanced aortoiliac occlusive disease contributes to worsening quality of life and confers a risk of limb loss as the disease progresses. Anatomic, aortobifemoral bypass has been shown to have an unsurpassed, long-term patency rate, thus contributing to limb salvage and, theoretically, improvement in quality of life. ABF is not an option in a number of patients, who may require a less-invasive, extra-anatomic bypass due to the severity of their co-morbidities, the presence of infection, or the hostile condition of their abdomen. There is little data comparing limb salvage in patients undergoing an EAB and their post-operative quality of life vs. that seen after AFB. The data that does exist, often retrospective studies evaluating only one type of EAB, supports a high rate of limb salvage. Several studies comparing limb salvage rates between EAB and AFB directly show equality in limb salvage rates with the reported differences not reaching statistical significance. *Therefore, we **conditionally** recommend extra-anatomic bypass for aortoiliac disease to achieve limb salvage rates comparable to aortobifemoral bypass, knowing that high quality randomized control studies exploring this comparison are lacking*. Extracting data pertinent to quality of life was difficult in most of the studies examined. Often, only indirect surrogate markers for quality of life, such as primary patency rates, were reported. Variables such as primary patency and post-operative ABI have not consistently been shown to correspond to a patient's stated quality of life. In addition, the studies that did employ standardized QOL questionnaires had flaws that made their applicability to EAB difficult, at best. *Therefore, we recommend using extra-anatomic bypass **judiciously** when attempting to improve a patient's quality of life, until such time as well designed studies specifically evaluating a patient's quality of life after an EAB are published.*

Recommendations

- In patients who are not candidates for an aortobifemoral bypass we recommend extra-anatomic bypass for aortoiliac disease to achieve limb salvage rates comparable to aortobifemoral bypass, (**Quality of evidence low; Recommendation strong**)
- In patients who are not candidates for an aortobifemoral bypass we recommend extra-anatomic judiciously when attempting to improve a patient's quality of life. (**Quality of evidence low; Recommendation strong**)

Personal View of Data

The literature supports lower extremity revascularization for critical limb ischemia and for patients with severe, lifestyle limiting claudication. For those who can tolerate the procedure, aortobifemoral bypass has excellent long-term patency and limb salvage rates. Extra-anatomic bypass has excellent limb salvage rates as well, which may approach or equal those seen with in-line anatomic repair. Long-term patency rates, however, consistently have been shown to be superior with ABF surgery. For that reason, ABF should be performed, especially for CLI, when patient condition and co-morbidities allow. If the patient is not considered a candidate for the more invasive ABF surgery, then an EAB should be offered with the acceptance of lower primary patency rates. Quality of life improvement has not been reliably established in the literature in regard to EAB for AIOD. That being said, some improvement in quality of life should be expected in a patient with CLI or severe claudication who is undergoing revascularization, be it anatomic or extra-anatomic. Surgery should proceed with the expectation of QOL improvement, despite the absence of good data in the literature to support that outcome.

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Chapter 14
In Patients with Critical Limb Ischemia Does Bypass Improve Limb Salvage and Quality of Life When Compared to Endovascular Revascularization?

Jeffrey J. Siracuse and Alik Farber

Abstract Lower extremity critical limb ischemia (CLI) is a morbid condition that is marked by intractable foot or ankle pain at rest and/or the presence of ischemic ulcerations or necrotic tissue. It is associated with limb amputation, diminution of quality of life, and mortality. Although CLI is treated with limb revascularization it is unclear whether patients benefit more from open surgical repair or endovascular intervention. Although a number of studies have compared outcomes between open and endovascular approaches to treat CLI most have been hampered by retrospective design, lack of controls, lack of standardization of treatment modalities, sponsor and operator bias, inclusion of claudicants, and short or incomplete follow-up. One randomized trial (BASIL) demonstrated no difference in the quality of life associated with these two interventions, although, amputation free survival was higher with bypass in patients who survived 2 years after randomization. Further randomized trials are needed to compare the role of endovascular therapy and surgical bypass in CLI.

Keywords Rest pain tissue loss • Bypass • Endovascular • Limb salvage • Quality of life

Introduction

Lower extremity critical limb ischemia (CLI) is a debilitating condition that is associated with extended hospitalizations, readmissions, infectious complications, limb loss, and an overall poor quality of life [1–4]. Treatment primarily involves revascularization to improve limb perfusion distal to the zone of arterial stenosis or

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occlusion, often with concurrent management of underlying tissue loss and associated infectious complications. Revascularization modalities include open surgery, which consists of endarterectomy and bypass, and endovascular therapy, which includes balloon angioplasty, stenting, and atherectomy. Although both revascularization strategies are commonly practiced, patterns of use vary widely and there exists much controversy and debate about which revascularization option is optimal for any given patient [5–7].

Two endpoints of particular interest, when comparing revascularization strategies, include quality of life (QOL) and limb salvage. Quality of life is a broad concept and in different studies has different methods of evaluation and definitions [4, 8–10]. In general, this assessment involves the evaluation of both patient physical ability and psychosocial state. This can be objectively assessed by examining both functional ability and social support as well as subjectively assessing the patient's perception through standardized surveys. Factors that contribute to QOL include peri-procedural and long-term functional status, limb preservation, infectious complications, prolonged hospitalizations, and frequent hospital admissions. Limb preservation not only contributes to QOL, but is also an important independent primary outcome. Several studies have compared different revascularization options and the effect of these on limb salvage, freedom from reintervention, QOL, and survival. However, many of these are retrospective analyses where the lesion characteristics and severity of disease are not always analyzed [4, 10–18].

Assessment of which intervention is best for a specific patient is important as the number of patients with CLI rises and, given healthcare reform, physicians must most effectively use their resources to achieve best results and outcomes [1]. This chapter addresses outcomes of open surgical and endovascular interventions as they relate to limb salvage and QOL.

Search Strategy

A literature search of English language publications from 2009 to 2014 was used to identity published data on amputation rates and QOL after bypass and endovascular interventions for CLI using the PICO outline (Table 14.1). Databases searched included PubMed, Google scholar, and Cochrane Evidence Based Medicine. Terms used in the search were ("bypass" OR "endovascular" OR "angioplasty") AND ("critical limb ischemia," OR "limb ischemia") OR "amputation"; and ("critical limb ischemia" OR "angioplasty" OR "limb" OR amputation) AND "quality of

Table 14.1 PICO table for quality of life and limb salvage after surgical bypass and endovascular interventions

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with critical limb ischemia	Endovascular interventions	Surgical bypass	Quality of life and limb salvage

life". Articles were excluded if they did not address either QOL aspects or amputation rates, had the majority of their patients as claudicants, or contained only one treatment arm. One randomized control trial and six single center retrospective cohort studies were included in our analysis. The data was classified using the GRADE system.

Results

Limb Salvage

The only randomized clinical trial comparing open bypass to endovascular interventions for CLI is the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial [9, 11, 14]. This was a prospective multicenter study sponsored by United Kingdom National Institute of Health Research Technology Assessment Program and included patients with severe limb ischemia which is a less stringent definition of ischemia that does not include ankle or toe pressure thresholds. To be enrolled in BASIL, patients had to be suitable for either open surgery or endovascular intervention and were randomized to a bypass surgery first or balloon angioplasty first strategy. Primary endpoints were amputation free survival (AFS), overall survival, heath-related QOL, and cost-effective use of hospital resources. In the initial year, surgery was associated with lower rate of early failure and reintervention, while having similar perioperative mortality, and higher perioperative morbidity [11]. Initial analysis of this trial showed that there was no significant difference in AFS at 1 and 3 years (68 % and 57 % for surgery and 71 % and 52 % for angioplasty first) [11]. Surgery was associated with significantly more morbidity and perioperative complications (57 % vs. 41 %, difference 15.5 %, 95 % CI 5.8–24.8). Most of these events were infections, wound complications, and cardiovascular events. Post-hoc survival curve analysis showed a reduced hazard in amputation-free survival (HR 0.37, 95 % CI 0.17–0.77, p = 0.008) and all-cause mortality (0.34, 95 % CI 0.17–0.71, p = 0.004) for surgery compared to angioplasty among patients who survived more than 2 years [11].

Long term follow up revealed that the surgery first strategy was associated with a lower hazard for amputation free survival (HR 0.85; 95 % CI 0.50–1.07; p = 0.108) and improved overall survival (HR 0.61; 95 % CI 0.50–0.75; p = 0.009) [14]. Furthermore, patients who underwent bypass surgery after an initial failed angioplasty had significantly worse outcomes than those who underwent bypass as the initial therapy, highlighting the potential negative implications of an endovascular-first approach. Surgical patients treated with vein bypass had significantly higher amputation free survival compared to those treated with prosthetic grafts [14, 15]. Soga et al. performed a retrospective review of CLI patients over a 6 year period at 14 centers in Japan [12]. These authors compared initial treatment using bypass versus endovascular therapy. Amputation free survival, limb salvage, overall survival and major adverse cardiac events were not different between the two groups,

overall and when adjusted for covariates. Freedom from major adverse limb events (HR, 0.66; 95 % CI: 0.47–0.92, P = 0.01) and major adverse cardiovascular and limb events (HR, 0.75; 95 % CI: 0.58–0.97, P = 0.02) were lower in the endovascular therapy group. Trans-Atlantic Intersociety Consensus (TASC) II classification, lesion length and percent stenosis were all recorded in this study. However multivariate analysis was based on comorbidities alone and did not include anatomical characteristics. Bypass was used to treat significantly more TASC II D lesions as well as longer, more stenotic, and more chronic total occlusions than endovascular therapy, thus potentially skewing results.

Dosluoglu et al. performed a retrospective single center analysis of patients undergoing infrainguinal revascularization for CLI to assess patient characteristics and outcomes. Patients in the endovascular group were older, had more diabetes, tissue loss, and renal insufficiency. The open group had a higher level of infrapopliteal revascularization. The 30 day mortality was higher in the open group (6 % vs. 2.8 %), however this did not reach statistical significance (P = .079). There was no difference in AFS, overall survival, or primary patency. Secondary patency and primary assisted patency were higher with endovascular interventions. However, in this study the endovascular patients had less extensive disease therefore a side by side comparison cannot be accurately assessed. The open group had 99 % TASC II D lesions and the endovascular group has 52 % TASC II D lesions. TASC II classification was not adjusted for in multivariate analysis.

Korhonen and colleagues performed a single center retrospective study comparing AFS between endovascular interventions and bypass [17]. Patients undergoing endovascular therapy had lower AFS (42 % vs. 53.7 %, p = .003) and freedom from surgical re-intervention (86.2 % and 94.3 %, P</001). Propensity score analysis showed that leg salvage and freedom from surgical re-intervention were worse after endovascular therapy than after bypass (among the 241 propensity score-matched pairs, 74.3 % vs. 88.2 %, p = 0.031, and 86.1 % vs. 89.8 %, p = 0.025, respectively). Differences in survival, AFS and freedom from any re-intervention were not observed. The same group then published their data in octogenarians. The propensity match scored two cohorts based on comorbidities, indications, and vessel involvement for patient greater than 80 years old with CLI [16]. The endovascular cohort at 2 years had a higher AFS (53 % vs. 44.9 %, P = .005) and bypass surgery was an independent factor in decreased AFS (RR 1.55, 95 % CI 1.24–1.93). However propensity scoring did not take into account the extent of disease, occlusive vs. stenotic lesions, lesion length, and TASC II making direct comparison difficult.

Quality of Life

Healthcare QOL was assessed using the Vascular Quality of Life Questionnaire (VascuQol) that specifically assesses pain, symptoms, activities, social, and emotional wellbeing. The generic Short Form 36 (SF-36) health survey and utility scores from the EuroQoL 5-D (EQ-5D) were also used. The BASIL trial did not find

significant differences in the QOL between the two treatment strategies [9]. The methodology of the BASIL trial has been criticized on numerous fronts [16]. First, the trial limited allowable procedures in their endovascular cohort to angioplasty alone, which does not represent current management strategy. Exclusion of tools in the armamentarium of the endovascular specialist, such as stents, both biases the trial results and severely limits their generalizability. Second, AFS is significantly flawed as a primary endpoint to compare revascularization strategies as it both overemphasizes non-treatment-related mortality and underemphasizes limb-related events specifically attributable to treatment modality. Third, the study did not address the influence of anatomic patterns of disease on outcome. Fourth, the trial did not include any assessment of the hemodynamic success or failure of the treatment arms, a significant omission given the importance of objectively measuring treatment-related changes in perfusion in patients with CLI [9, 11, 14, 15].

Vogel and colleagues looked at changes in functional status in elderly patients treated with bypass and endovascular interventions by linking Medicare inpatient claims with nursing home assessment data [10]. A functional impairment score, based on need for assistance with activities of daily living, was calculated pre-procedurally, post-procedurally and at 6 months. Both patient groups demonstrated a decrease in their functional status, corresponding to the severity of their disease, in the immediate post-operative period. The less invasive endovascular procedure did not result in less impairment of functional status. Other factors that impaired long-term functional status post-procedure were female gender and poor baseline cognitive and functional ability. Recovery rates at 6 months were higher in the bypass than in the endovascular group. This is an analysis comparing large administrative databases and has limitations. Although the pre-operative functional status was similar, the severity of disease and details of the reconstruction were unclear. Furthermore, patients who were readmitted and those who had concurrent amputations were excluded.

When looking at QOL broken down into different categories, a retrospective survey sent out to patients after open and endovascular interventions revealed no difference between endovascular and open surgery post-procedure in patients [4]. However, compared to age and gender matched cohorts, patients undergoing open vascular surgery overall scored considerably lower for every variable. The largest differences seen in mobility, breathing, sleeping, discomfort, vitality, and sexual activity. Surgical patients were also less likely to have social support, more likely to have walking limitations, worse Geriatric Depression and Life Satisfaction scores, and a poorer perception of health.

A Personal View of the Data

Data reviewed herein suggest that those patients with CLI who are expected to live more than 2 years may benefit from open revascularization over endovascular therapy. In addition open vascular revascularization is associated with higher

Table 14.2 Data comparing open vs. endovascular treatment of critical limb ischemia

Author (year)	N endo	N bypass	Limb salvage	Quality of life	Disease extent compared?	Type (quality of evidence)
Bradbury (2010) [14]	224	228	Favors open surgery	No difference	No	Randomized, prospective, multicenter (moderate)
Remes (2010) [4]	131	100	N/A	No difference	No	Retrospective, single center (low)
Arvela (2011) [16]	277	307	Favors endovascular	N/A	No	Retrospective, single center (low)
Korhonen (2011) [17]	517	341	Favors open surgery	N/A	No	Retrospective, single center (low)
Dosluoglu (2012) [13]	363	151	No difference	N/A	No	Retrospective, single center (low)
Soga (2013) [12]	223	237	No difference	N/A	No	Multicenter, retrospective (low)
Vogel (2014) [10]	350	352	N/A	Favors open surgery	No	Medicare database (low)

post-procedural morbidity than endovascular therapy. Little else can be definitively concluded from these data (Table 14.2).

There are few areas of medicine that have as little consensus to support treatment strategy as does the management of CLI. The decision to recommend surgical or endovascular revascularization varies significantly among providers and is based on a range of factors, including disease pattern, availability of autogenous conduit, training, surgical and endovascular skill sets, access to an appropriate procedural environment, and perhaps most importantly, disparate treatment biases. There is general agreement that some patients considered poor candidates for surgery are well served by endovascular revascularization. What is presently not known is which therapy is more suitably offered to patients who are candidates for both open and endovascular treatment. This lack of clarity in current treatment algorithms for CLI has led to a blurring of the standard of care, inevitable misapplication of technology, and likely increased health care expenditure.

Persistent clinical equipoise in combination with a paucity of comparative effectiveness data to guide treatment of CLI has led to a multidisciplinary effort to organize the BEST-CLI Trial, a prospective, randomized, multicenter, controlled trial to compare Best Endovascular versus Best Surgical Therapy in patients with Critical Limb Ischemia. This trial is funded by the National Lung Heart and Blood Institute (NHLBI) of the National Institutes of Health and aims to enroll 2,100 patients with CLI at 120 sites in North America over the course of 4 years. The aim of BEST-CLI is to compare treatment efficacy, functional outcomes and cost in patients with CLI undergoing best open surgical or best endovascular revascularization [19]. The BEST-CLI trial started enrollment in

September of 2014 and promises to comprehensively answer many questions that remain unanswered with regard to the management of patients with CLI and infrainguinal PAD. Its multidisciplinary structure is specifically designed to welcomes all stakeholders across the United States and Canada. This effort aims to define practice in the field.

Recommendations

- We recommend for patients with a high likelihood of long-term survival that they should undergo bypass surgery for critical limb ischemia (**evidence moderate, recommendation weak**).
- We recommend for patients with poor long-term survival should that they should undergo endovascular intervention (**evidence moderate, recommendation weak**).

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Chapter 15
In Patients with Limb-Threatening Ischemia Who Are Not Candidates for Revascularization Do Non-operative Options Improve Outcomes Compared to Amputation?

Craig Weinkauf and Joseph L. Mills Sr.

Abstract Patients with critical limb ischemia (CLI) or limb-threatening ischemia comprise a heterogenous population with varying co-morbidities that strongly influence outcomes after therapeutic intervention. Broadly, there are three treatment strategies for patients with limb-threatening ischemia: direct revascularization (open or endovascular), amputation and medical treatment with local wound care. Although many affected patients do well with surgical revascularization, disease recurrence brings many patients back with ever-diminishing surgical options. This review discusses clinical decision-making, and particularly evaluates options for patient care when arterial anatomy or patient co-morbidities do not support surgical revascularization. This topic is an increasingly important one as data indicate direct intervention is not always a reasonable clinical option and as definitions for therapeutic success progress beyond graft/stent patency and limb salvage and non-surgical options to promote wound healing improve.

Keywords Limb threatening ischemia • Critical limb ischemia • Peripheral arterial disease • Peripheral vascular disease • Wound healing

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Search Strategy

A literature search of English language publications for the past 5 years was used to identify published data on critical limb ischemia. Databases searched were PubMed and Cochrane Evidence Based Medicine. Terms used in the search were "critical limb ischemia," "peripheral vascular disease," "peripheral arterial disease," "treatment for critical limb ischemia." Searches were limited to clinical trials or meta-analyses. Over 100 separate articles were retrieved that met inclusion criteria. All abstracts were reviewed and relevant manuscripts were read in detail and included in this review. Each subdivision title within this review was then further searched for that subtitle AND "PAD," "peripheral arterial disease," "critical limb ischemia" and "peripheral vascular disease." Select literature reviews and referenced manuscripts on critical limb ischemia were also evaluated. Data and recommendations were classified using the GRADE system.

Introduction

The primary objective of this chapter is to raise awareness that there are increasingly more tools to not only evaluate but also to treat a patient with CLI. We evaluate the literature that predicts outcomes for surgical CLI patients because these data help guide our clinical judgment and define patients who might better be treated with non-surgical management. Finally, as the key focus of the chapter, we review relevant and contemporary literature for management of patients with CLI who have no possibility of revascularization (Table 15.1). These topics range from medical therapy that vascular physicians could implement tomorrow to experimental treatments that would require referral to centers conducting experiments for these therapies.

Critical Limb Ischemia

The term critical limb ischemia is actually a misnomer because it implies a specific hemodynamic cut-off and a critical situation; i.e., without urgent intervention, limb loss will inevitably result. Although that may be true for a subset of CLI patients, for many it is not. Paramount to addressing concerns for treatment options is to

Table 15.1 PICO table for non-operative medical therapies for the treatment of limb threatening ischemia

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with limb-threatening ischmia	Non-operative medical therapies	Amputation	Graft patency, major limb amputation, quality of life, and death

understand the natural history of the disease [1, 2]. What happens when patients with CLI are not revascularized or have their limb amputated? In the Biancari meta-analysis of 83,000 patients, 20 % of patients were treated without surgery [1]. Of those patients, 1-year survival was 75.4 % and amputation-free survival was 51.4 %. In the BASIL trial, which included patients with "severe PAD" but who did not meet stringent criteria for CLI, at 5 years 37 % had died [3].

In the placebo arm of the Circulase trial, which enrolled patients with hemodynamic and clinical criteria for CLI, the amputation rate at 6 months was only 13 % [4]. With wound care alone in 149 patients with CLI, Marston and colleagues reported a 52 % wound healing rate with a 23 % major limb amputation rate at 12 months [5]. A more recent study from Sweden evaluated over six-hundred patients with diabetic foot ulcers who had either a systolic TP < 45 mmHg or an AP < 80 mmHg and who did not undergo endovascular or surgical revascularization. They reported that 50 % healed primarily with standard wound care or after minor amputation; 17 % healed a major amputation; and 33 % died with limbs intact but with unhealed wounds [6]. These considerations strongly suggest that care for patients with severe PAD and wounds must be individualized and that the term CLI may imply a false sense of doom for many patients. For these and many other reasons, we prefer the terms threatened limb and limb-threatening ischemia.

Surgical Intervention in Limb-Threatening Ischemia: Predictors of Surgical Failure and How to Define Successful Outcomes

Limb-threatening ischemia is a disease spectrum and patients suffering from it comprise a heterogeneous group. Determining treatment for any given patient should be individualized and based on their associated comorbidities and overall goal for mobility. Below, we discuss relevant studies that help define the probability of successful treatment for such patients and associated algorithms. The majority of studies evaluated and discussed here regularly define primary success as a composite of mortality and limb loss ± vessel/bypass patency. Unless otherwise noted, these studies are retrospective analyses with multivariate Cox models to estimate hazards ratios.

Demographic and Patient Risk Factors

In our analysis, 9 relevant studies were included in this section. Overall, the predictors for worse outcome (graft failure, major amputation, poor quality of life, death) were dialysis dependent renal failure, functional dependence, tissue loss and age >80 years. These factors had the highest predictive value and were the most commonly reported factors that contribute to poor outcomes. Other key factors included low serum albumin, current smoking, atrial fibrillation, prior amputation, emergency operation,

CHF, CAD, no statin usage, and need for multiple vein segments for bypass. Specific to patients with diabetes and PAD, the prospective EURODIALE trial, which was published prior to our 5-year search window, found that wound size, degree of PAD, ESRD and age were predictive of wound healing in diabetic patients [7].

Multiple groups have developed models to predict surgical outcomes based on a variety of combinations of these characteristics and risk factors. Meltzer et al. evaluated NSQIP data and developed a composite index called a "CRAB" (Comprehensive Risk Assessment for Bypass) score to predict 30-day perioperative mortality and major morbidity (sepsis, MI, stroke, pneumonia, PE, renal failure, graft failure, major wound infection) in patients with PAD undergoing revascularization surgery. This index is based on age, tissue loss, dialysis dependence, functional status, emergency operation and prior amputation status. The calculated scores categorize patients into low-, medium- and high-risk patient groups, which have correspondingly 5, 14 and 25 % risks of 30-day mortality and major morbidity [8]. Another risk assessment tool, the PIII CLI risk score, predicts amputation-free survival (AFS) in patients undergoing infrainguinal bypass [9]. In decreasing order of importance, this system categorizes patients according to dialysis dependence, tissue loss, age and CAD. With these four characteristics patients were determined to be high, moderate and low risk, stratifications, respectively associated with AFS rates of 45 %, 64 % and 88 %. *The looming question raised by these data is whether surgery* (*endovascular or open*) *would or should be denied to some selected surgical candidates based only on their predicted failure risk*.

Wound and Anatomic Risk Factors

Specific anatomic risk factors are also predictive of poor surgical outcomes. As discussed, the EURODIALE trial found baseline ulcer size to be a key outcome predictor in patients with diabetes [6]. More recently, Lida and colleagues retrospectively evaluated 1057 limbs in 884 patients that had endovascular procedures (stent or angioplasty) between 2004 and 2010 with 2-year follow-up. They found that calcified lesions, target vessels <3.0 mm, lesions >30 cm in length and no below-knee run-off were all associated with worse outcomes. High risk-patients by their model had a 70 % chance (about 2X increased probability) of major amputation or reintervention compared to their low-risk group [10].

Non-surgical Treatment Options for Limb Threatening Ischemia

Risk Factor Optimization and Pharmaceutical Treatments

There are many excellent reviews and large randomized controlled trials that define beneficial pharmaceutical practices for treating patients with PAD. In summary,

anti-platelet agents, statin therapy, blood pressure control, diabetes control and smoking cessation all have high-quality data that support their efficacy. However, studies that address whether pharmaceutical intervention specifically influences outcomes, particularly wound healing and AFS in "CLI" patients are much more limited.

Statins

Statin therapy was evaluated in a retrospective non-randomized manner in Japan. Tomoi et al. reviewed 812 patients with CLI treated by angioplasty and then discharged on a statin (169) or without (643). Survival, freedom from re-intervention and freedom from amputation were significantly higher in those treated with statins [13].

Cilostazol

A retrospective analysis evaluated 63 patients with CLI 3 months after revascularization with infrapopliteal angioplasty. In the 32 treated with cilostazol (compared to no cilostazol), re-occlusion was significantly lower (20.5 % vs 43.6 %, $p = 0.015$) [14]. In another small study, Cilostazol was found to significantly increase skin perfusion pressure in patients with CLI [15].

Propionyl-L-Carnitine

Propionyl-L-Carnitine is an over-the-counter anti-oxidant thought to improve endothelial function and microcirculation. One study evaluated 48 patients randomized to placebo vs treatment [16]. They found a significant increase in endothelium responsiveness and reduction in pain in treated versus the control group.

Steroids

The hypothesis that steroids are effective in the treatment has long been shown to be incorrect. A recent meta-analysis included 3 placebo-controlled trials with 109 total patients. They found no benefit for testosterone over placebo [17].

Prostanoids

Prostanoids are a class of bioactive molecules comprised of prostacyclins, prostaglandins and thromboxanes. They signal through autocrine and paracrine pathways to help regulate very diverse pathways including labor and delivery, bronchoconstriction, vasoconstriction, vasodilation, pain and segments of immune and inflammatory pathways including platelet activation and inhibition. Formulations of PGE1 and PGI2 are the two key molecules that have been used and studied the most for

treatment of CLI and PAD. PGE1 is a vasodilator that is used to treat erectile dysfunction, maintain patent ductus arteriosus and promote peripheral vascular vasodilation. PGI2 inhibits platelet activation and has vasodilatory effects. Enthusiasm in many parts of the world for the use of prostanoids in CLI has been great, but the supporting data are limited. Ruffolo and colleagues published a recent meta-analysis that included 20 RCTs and found moderately favorable results for ulcer healing (RR 1.54) and pain relief (RR 1.32) [18]. A more recent meta-analysis evaluated prostanoids in PAD and included 2773 patients from 18 RCTs [19]. They concluded that data were poor in quality, and although some studies showed moderate benefit, side-effects (headaches, nausea, pain, diarrhea) led to patient withdrawal, and no definitive evidence supported using prostanoids in patients with PAD. The Scottish-Finnish trial, the most recently published placebo-controlled RCT, was felt to be adequately powered with 111 patients, but could not detect a difference between ulcer healing or amputation rate at 6 months between the treatment arm receiving taprostene (PGI2) versus placebo [20]. These data echoed the earlier Circulase trial, which found no benefit for lipo-ecraprost (PGE1); the latter study was terminated after 383 patients had been enrolled because interim analysis showed no benefit [4].

Wound Care

As previously discussed, patients with critical limb ischemia are not all critical. In addition, the term was never intended to be applied to patients with diabetes, who now constitute the largest group of patients presenting with threatened limbs due to the global epidemic of diabetes. Local wound care alone (albeit with significant effort and at a facility that can provide a high level of care) results in approximately a 50 % wound-healing rate at 1 year and a major amputation rate of only 25 %. These data are reinforced in retrospective reviews as well as the placebo arms of various studies cited above. These numbers may seem surprisingly positive, but are difficult to generalize because patient populations and severity of CLI within these and other studies are not uniform. The SVS WIfI (Wound, Ischemia, foot Infection) lower extremity threatened limb classification should help better stratify amputation risk and allow more meaningful inter-study comparisons through a better patient classification system [21]. The underlying premise of SVS WIfI classification is that amputation risk increases as the disease burden or limb stage presentation progresses from stage 1 (very low risk) to stage 4 (high-risk). Ischemia is one component of this system, along with wound size and complexity, and the presence and severity of infection.

Cell Therapy

Cell therapy for patients with CLI is a promising field for clinical and basic science research. The treatment strategy is to harvest autologous stem cells and deliver them back to patients; the goal of the therapy is the development of improved and new

blood vessels in addition to wound healing in diseased limbs. We reviewed 22 studies published in the past 5 years and reference the largest 5 studies with 50–100 patients per study [5, 22–25]. All 22 studies had encouraging results, although the data from these studies are highly heterogeneous. Various cell types are used in the treatment; multiple mechanisms for harvesting cells are employed; delivery back to the patient is intravenous, intramuscular or intra-arterial. Because of this heterogeneity, the current meta-analyses on the topic are limited and add little more than the cumulative picture of the overall positive results in several independent small studies.

After evaluating 22 new trials combined with published meta-analyses, we believe these data and the various modalities employed in cellular treatment strategies are the most promising area of novel treatments for patients with limb-threatening ischemia and no surgical options (and should likely expand to those with surgical options). Important questions remain to be answered: Which bone marrow cell type and which harvesting and delivering modality are most beneficial? A key impediment to answering these questions and, more importantly, expanding the use of cell therapy is the availability of technology and expertise.

Gene Therapy

Gene therapy has used various strategies to deliver genetic material that can be translated into pro-angiogenic gene-products (VEGF, FGF, HGF, Del-1, HIF-1). There are two recent relevant meta-analyses. Hammer and colleagues evaluated 1494 patients from 12 RCTs [26]. They found no benefit or harm for gene therapy for all-cause mortality, amputations or wound healing. Another meta-analysis with slightly different criteria included 543 patients from 6 RCTs found no benefit for amputation rate, but found an increased rate of non-serious adverse events (edema, hypotension and proteinuria) [27]. These data did show however, that serious adverse events such as mortality, malignancy and retinopathy did not increase in treated patients compared to placebo-controlled patients. Similar to evaluating data from cell therapy studies, each study had slightly different delivery strategies (viral, plasmid, naked DNA) and different angiogenic factors, greatly undermineing the validity of the meta-analyses. Six additional studies were completed in the past 5 years that are small in number and add no more conclusive evidence.

Early studies in this field of research found limited benefit and significant side effects for these pro-angiogenic gene therapies, which has mitigated enthusiasm for pursuing this avenue of research. However, there are ongoing trials pursuing different targets with similar treatment strategies. The majority of new studies are focusing on delivery of HGF or FGF via plasmid-based systems. All have very small numbers of patients and show mildly encouraging to equivocal results. The logic of genetically promoting blood vessel development is enticing and sensible. However, these data indicate that our basic science knowledge of how to achieve that end is either inadequate or is not being employed.

Spinal Cord Stimulation

Spinal cord stimulation (SCS) consists of an implantable device that delivers pulsed electrical signals to the spine via probes inserted into the epidural space. A recent meta-analysis included 450 patients from 6 trials evaluating spinal cord stimulation (SCS) for CLI patients. Limb salvage after 12 months was significantly higher, decrease in Fontaine score significantly better and pain was significantly reduced in the intervention arm. However, re-implantion was required in 15 % of patients secondary to complications and infection occurred in 3 % [28].

These data are not randomized or controlled. As such, even the moderate benefits seen garner little support to recommend SCS. Compared to the risks, SCS implantation is not supported.

Hyperbaric Oxygen

The theoretical benefit of hyperbaric oxygen therapy (HBOT) is that under increased pressure and with a higher concentration of oxygen in the air, more oxygen should be delivered to blood-deprived tissue. The evidence for the effect of HBOT on PAD or CLI is of low quality and inconsistent. Kranke et al. published a meta-analysis in 2012 and were able to combine 118 patients from 3 RCTs [29]. They found HBOT significantly prevented major amputations at 1 year (RR 0.31, CI .13–.71), but had insufficient data regarding wound healing. A more recent meta-analysis of two adequate RCTs evaluating HBOT in patients with ischemic diabetic foot ulcers reported a non-significant improved ulcer healing at 1 year but no difference in amputation [30]. A recent RCT that included 75 patients with diabetic foot ulcers showed the beneficial effect of HBOT diminished with worsening ABI, toe pressure and $TcPO_2$ [31]. Those with $TcPO_2 < 25$ mmHg on the dorsum of foot had no benefit. These data could explain the conflicting data from multiple previous trials; as the patient populations had increasingly severe PAD, outcomes were worse.

There are limited, but positive data for the use of HOBT in diabetic foot ulcers. However, when patients also have PAD, data are generally mixed. As such, in patients with limb threatening ischemia, there are no data to support the use of HBOT in patients with diabetes, particularly given its significant expense. A Netherlands-based RCT that plans to enroll 275 patients with diabetic foot ulcers and ischemia may provide key answers.

Hypertensive Extracorporeal Limb Perfusion

A group in Australia has published small but encouraging studies in sheep [32] and humans [32, 33]. In the larger human study, 20 patients with CLI (leg or arm) and no options other than amputation were treated with blood pressures 200–300 % of the patient's MAP (maximal pressure 300 mmHg). To do this, the ischemic limb's

circulation was isolated via an endoluminal balloon catheter or occlusive cuff, and hypertensive flow was provided by extracorporeal pump. Each patient had 1–3 sessions, several days apart, for a total of 20–80 h of on-pump time. Technical success and safety were achieved. At 22 months 8/20 patients had avoided the planned amputation and 4 more had delayed the amputation by several months. Mean ABIs in those who kept limbs increased from 0.04 ± 0.07 to 0.63 ± 0.39 ($p < 0.05$). While these data are encouraging, their applicability and further investigation will likely be slowed by technology and system requirements.

Deep Vein Arterialization

Mutirangura and colleagues performed an arterial bypass with distal anastomosis at the paramalleolar posterior tibial vein using synthetic conduit in 26 patients with CLI and no other options for surgical revascularization [32]. Valves were destroyed as needed. At 6 months, 19/26 had complete resolution of pain and ulcer. At 24 months, survival was 87.5%, limb salvage was 76% and graft patency was 49.2%. This is a novel approach with positive results. A key benefit to this intervention is the relative ease to translate into one's own practice. It is not clear whether deep or superficial vein reflux or ongoing venous congestion would be a contraindication to the procedure.

ArtAssist

Louridas and colleagues reported their pilot study in 33 legs (25 patients) with non-operative CLI treated with ArtAssist [34]. At 3 months 42% of legs were amputated and toe pressures of the salvaged limbs showed significant improvement. The largest study to date was published by Tawfick and colleagues who treated 175 patients with CLI and no surgical options for revascularization from 2005 to 2012 [35]. At 1 year, toe pressures increased from 19.9 to 35.4 mmHg ($p < 0.0001$); limb salvage was 95% at 5 years. They also found that ArtAssist was significantly cheaper than a below-the-knee amputation in comparable patients. One can presume a limb salvage rate of 95% is better than what would have been expected with intense wound care alone, but the only other study has a much lower limb salvage rate of 58%. This treatment is safe and non-invasive so its use is likely to expand, but no randomized trials to evaluate efficacy have been done.

Recommendations

In this chapter, we have tried to evaluate relevant data from the past 5 years that help define alternative treatment plans for every limb-threatening ischemia patient. However, the key focus has been on how to treat such a patient who has no revascularization options and has mobility/life expectancy supportive of attempts at limb

salvage. The summary of recommendations that follows is based on the GRADE system, which makes two key judgments: quality of evidence and level of recommendation [36–38]. Quality of evidence is based on relevance of clinical outcome and clinical trial design/execution. Strong vs Weak recommendation is based on: 1) the balance of benefit and harm; 2) quality of evidence; 3) cost effectiveness.

No Recommendation (Insufficient Data)

- **Gene therapy** has very mixed results for the treatment of limb-threatening ischemia. These data are difficult to interpret because each gene of interest is unique. Early trials showed some positive results, but also significant side effects; other trials have shown no benefit. VEGF-based strategies would not be recommended, but FGF- or HGF-based strategies are not unreasonable for experimental treatment in patients who understand the risks and potential benefits. **Quality of Evidence = Low. Recommendation = none**
- **Propionyl-L-Carnitine** is an over-the-counter medicine with very weak data to support its use. **Quality of Evidence = Low. Recommendation = none**

Negative Recommendations

- **Hyperbaric oxygen therapy is not recommended**. It has mild benefit in diabetic patients, but does not thus far seem to benefit patients with CLI. The benefit is low and treatment is expensive and time-consuming. However, if a patient wants the treatment and can afford it, there are limited unwanted side effects. **Quality of Evidence = Low. Recommendation = weak**.
- **Spinal cord stimulation is not recommended**. The benefit is minimal and risks and costs are high. **Quality of evidence = moderate. Recommendation = strong**.
- **Prostanoid therapy is not recommended**. Data are mixed but the largest RCTs show no benefit. **Quality of evidence = moderate. Recommendation = weak**.
- **Steroid therapy is not recommended**. There is no evidence of benefit and side effects are significant. **Quality of evidence = low. Recommendation = strong**.

Positive Recommendations

- **ArtAssist is recommended**. Data are limited, but available data are congruent and positive. Negative side effects are minimal. **Quality of Data = low. Recommendation = weak**.

- **Deep vein arterialization is recommended** as an experimental treatment. The data are positive, but the total treatment number is very small. **Quality of Evidence = very low. Recommendation = weak**.
- **Hypertensive extracorporeal limb perfusion is recommended** as an experimental treatment. The data are positive, but the total treatment number is very small. **Quality of evidence = very low. Recommendation = weak**.
- **Cell therapy is recommended** as an experimental treatment. There are a significant number of small trials (many RCTs) and the majority of the data are congruent. Treatment may be expensive, but treatment is well tolerated. Similar therapies are used in numerous fields, most often in the form of a clinical trial that limits expenses to the patient. **Quality of evidence = moderate. Recommendation = strong**.
- **Cilostazol is recommended**. The drug is poorly studied for in the specific setting of CLI, but what data are available are positive and the drug is better studied in PAD. **Quality of evidence = low. Recommendation = weak**.
- **Statin therapy is recommended**. Data specific for evaluating effects in those with limb-threatening ischemia are limited, but available data for treatment of cardiac disease and PAD are strong. **Quality of evidence = very weak. Recommendation = strong**.

A Personal View of the Data

The recent review written by Conte at al addresses the controversy over endovascular versus open surgical intervention and touches on key factors needed to assess patients and plan therapy [12]. Some current data suggest revascularization is performed in 90–95 % of patients with "CLI." These data reflect the expanded role of endovascular options (tibial angioplasty) in the past 5 years. The duration of these more aggressive below-the-knee interventions in a population of vascular patients who increasingly suffer from diabetes is unclear, but no good long-term data are available for how frequently and how soon those patients return requiring amputations or non-surgical management of their CLI. Most sources suggest that 10–30 % of CLI patients have no revascularization options.

To appropriately guide therapies for patients with limb-threatening ischemia, vascular specialists must have reliable means of evaluating outcomes. Historically, graft patency, major limb amputation, and death have been the most frequently used endpoints for judging therapeutic success. These are useful events for clinical research because they are more easily defined and reportable. However, quality of life and functional status, although more difficult to measure and track, are likely more meaningful metrics by which to judge success. Nordanstig and colleagues have streamlined the 25-question Vascular Quality of Life Questionnaire (VascuQoL-25) to increase ease of use. This questionnaire achieves high precision and discriminative properties with only 6 questions, and is validated to evaluate vascular patients' quality of life [11].

Based on our literature review, we suggest that when revascularization is not an option for your patients, amputation is not always necessary. Every CLI patient is not equal, but we have been surprised and encouraged by the successes reported with meticulous wound care alone in selected high risk patients. In addition, there are adjunctive procedures/treatments that we have discussed above which may be appropriate for specific individuals. Judging which treatment is most appropriate for any given patient is the difficult job of a surgeon, but we are focused on evaluating a patient's functional status and matching treatments with long-term functional goals.

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Chapter 16
In the Patient with Profunda Artery Disease, Is Open Revascularization Superior to Endovascular Repair for Improving Rest Pain?

Jordan R. Stern and Victor M. Bernhard

Abstract The profunda femoris artery is the major collateral source of blood supply to the lower leg in patients with atherosclerotic obstruction of the superficial femoral artery. Open revascularization of the profunda is beneficial for patients with chronic limb ischemia, as technical success rates are high and durable patency has been demonstrated in a number of studies. However, there are strong advocates for increased use of endovascular techniques in the common femoral and profunda segments, reserving open surgery for patients who have failed catheter-based treatment. From currently available data, which consists almost entirely of retrospective analyses with the exception of one relatively small prospective randomized trial, we recommend that patients who are able to tolerate open surgery, do not have a hostile groin due to current or past infection or imbedded prosthetic material, and are not morbidly obese should preferably undergo open common femoral endarterectomy/profundaplasty as indicated. Endovascular therapy is a suitable option in those unable to tolerate open surgery, or in those with the aforementioned mitigating factors.

Keywords Femoral artery • Profunda femoris • Profundaplasty • Endovascular repair • Femoral endarterectomy • Femoral angioplasty • Rest pain • Critical limb • Ischemia

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Introduction

The profunda femoris artery (PFA) is the major collateral source of blood supply to the lower leg in patients with atherosclerotic obstruction of the superficial femoral artery (SFA). Atherosclerotic involvement of the PFA is usually limited to its ostium and proximal segment, and is almost invariably associated with extension of plaque into the common femoral artery (CFA) [1, 2]. Severe stenosis or occlusion of the CFA alone without extension into the PFA is less common, but in essence represents a functional obstruction to flow through the PFA. It has long been recognized that PFA revascularization can be beneficial in limb salvage for critical limb ischemia (CLI) and claudication [2–4]. However, technical considerations such as scarred groins and the presence of autogenous or prosthetic grafts originating near the femoral bifurcation can make the classic open profundaplasty a difficult and arduous procedure with increased potential for surgical site infection (SSI) [5]. Additionally, patients with severe peripheral arterial disease may have co-morbidities that increase the risk of open surgical repair.

With the widespread adoption of endovascular procedures for lower extremity arterial disease, there are strong advocates for increased use of these techniques in the common femoral and profunda segments, reserving open surgery for patients who have failed catheter-based treatment. Generally speaking, the PFA is well suited to endovascular revascularization, since the diseased portion is generally limited to the ostial segment and the adjacent CFA. However, this approach is not without its own set of challenges. A heavily calcified and stenotic femoral bifurcation can make selective catheterization of the PFA quite difficult. If the common femoral artery is occluded, the PFA may not be accessible by the standard approach from the contralateral leg or an arm. Furthermore, obstructions at the femoral bifurcation generally present with additional lesions involving the aorto-iliac inflow and/or the superficial femoral-popliteal outflow and tibial/pedal run-off. In these situations, management of the PFA may be dictated largely by the choice of technique to manage the other sites of disease [6].

For all of these reasons, the debate continues regarding the optimal management strategy for the profunda. Should endovascular profundaplasty be the first-line procedure for these patients and open profundaplasty be relegated to a historical footnote, playing only a limited role when endovascular procedures fail or are not feasible? Herein we aim to review the relevant literature, and make recommendations with regard to the appropriate use of both endovascular and open PFA revascularization techniques.

Search Strategy

In order to identify the pertinent data, PubMed, Medline and Google Scholar were queried for studies examining open and endovascular repair of occlusive disease of the common femoral and profunda femoris arteries according to the PICO outline (Table 16.1). All relevant studies examining open common femoral endarterectomy

Table 16.1 PICO table – endovascular vs. open intervention on the profunda femoris artery

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with limb ischemia secondary to diseased profunda femoris or common femoral artery	Endovascular therapy	Open common femoral endarterectomy and/or profundaplasty	Technical success, primary patency, limb salvage

with or without profundaplasty were included without restriction on publication date since there has been no significant change in technique from the time of initial reports. With regard to endovascular interventions, however, only studies published after 2000 were included in order to more accurately reflect outcomes relating to current therapy in an era of rapidly advancing endovascular technology. Only two studies were identified that directly compared the two techniques [7, 8], one of which provided the only prospectively randomized, controlled data set [7]. The included studies were evaluated using the GRADE system [9, 10].

Results

A critical review of the literature did not provide data for either technique that clearly separated results for patients with rest pain from those with claudication, ulcer or tissue loss. In order to determine the most appropriate procedure for patients with rest pain alone, we have assessed the available published data regarding technical success, safety, immediate hemodynamic and clinical improvement, durability, the need for re-intervention, and limb salvage and with this information attempt to infer the best approach for varying patient circumstances.

Open Surgery: The Gold Standard

The first profundaplasty was performed in 1953 by Norman Freeman, but was not reported until 1961 [11]. Since then, open common femoral endarterectomy with or without profundaplasty has become a well-established approach for restoring the collateral function of the PFA to relieve claudication and limb-threatening ischemia, and to improve the healing potential for a below the knee amputation when limb salvage is not feasible. Success is dependent upon iliac inflow and tibial/pedal run-off as well as the quality of arterial collaterals across the knee. The latter can be estimated by calculating the profunda-popliteal collateral index (PPCI) derived from pre-operative segmental limb pressure measurements using the formula: $PPCI = ((AK\ Pressure - BK\ Pressure)/AK\ Pressure)$ [12]. An index greater than 0.5 predicts high resistance due to poor collaterals and is a strong indicator of failure, whereas an index of less than 0.25 has been associated with a 67 % success rate [12].

The outcomes for PFA/CFA endarterectomy are presented in Table 16.2. Data from the early 1970s showed that profundaplasty could be performed safely and with good results [2–4]. Towne et al. [4] presented a series of 237 profundaplasties in 209 patients, 69 (29 %) performed as an isolated procedure and 169 (71 %) in combination with some form of inflow augmentation. Operative mortality was 2 % and immediate technical success was achieved in 99 % of claudicants and 89 % of CLI. The patency rate for claudicants was 77 % at 5 years but only 23 % for CLI, with only an insignificantly lower success for isolated repairs versus those with associated inflow procedures. However, since patency was not assessed by direct visualization in many of the patients, failure may have been the result of progression of disease in the tibial/pedal run off bed rather than the profundaplasty itself. Amputation was required in 43 limbs, all but one in the limb salvage group. All 24 with below-knee amputations had patent profunda repairs whereas the profunda was occluded in 17 of 19 requiring above-knee amputation. Lawson et al. [3] demonstrated a 100 % technical success rate with no perioperative mortality for profundaplasty as a limb salvage procedure. Limb salvage was 87 % and 77 % and patency was 80 % and 60 % at 1- and 2.5-years, respectively. In 1987, Fugger et al. [13] described their experience with profundaplasty as a standalone procedure from a prospectively maintained database of 168 patients treated for SFA occlusion. 68 % of patients had clinical improvement, more commonly in those with better tibial runoff and without ischemic ulceration. The limb salvage rate was 68 %, and of those amputated only 41 % were above-knee. More contemporary data has consistently shown good outcomes as well. In 2001 Cardon et al. [18] published their experience with 110 limbs undergoing endarterectomy of the femoral bifurcation for claudication or CLI. Although only 84 % of procedures were technically successful, perioperative mortality was 1 %. Local morbidity was 22 %, but complications were mostly of a minor nature not requiring re-operation. Patency at 3- and 5-years was 95 % and 88 %. Clinical improvement was sustained in 80 % and 71 % of patients over the same intervals. Kang et al. (2008) [21] retrospectively reviewed 58 patients (65 limbs) from their prospectively maintained database who underwent common femoral endarterectomy (CFE). Two-thirds of these patients were claudicants and one-third had CLI. All cases were technically successful. 1-year and 5-year patency was 93 % and 91 % respectively, and there were no amputations. Concomitant endovascular inflow and outflow (hybrid) procedures were performed in 37 (57 %) limbs. Recurrent stenosis occurred in the CFA in only 1 of 28 isolated CFEs but in 4 of 37 of the hybrid procedures. In the same year, Kechagias et al. [23] published a similar retrospective series of CFE, with 15-year follow-up data. Endarterectomy extended into the proximal PFA in 39 % of these patients. Freedom from ipsilateral re-intervention was 68 %, 51 % and 42 % over 5-, 10- and 15-year intervals. However, only one re-intervention was required at the original endarterectomy site. Limb salvage was 94 % at 5 and 10 years, and 85 % at 15 years. Independent predictors of major amputation were current smoking status and critical limb ischemia. Al-Koury et al. [24], Ballotta et al. [26] and Desai et al. [27] have recorded similar results. Each of these studies achieved 100 % technical success with CFE, and primary patency rates of greater than 90 % at up to 7 years [26]. Limb salvage rates were high, 87 % in the Desai study and 100 % in both the Al-Koury and Ballotta series.

Table 16.2 Open common femoral and/or profunda femoris revascularization series

Author (year)	N (limbs)	Indication (%CLI) [a]	Technical success (%)	Primary patency	Limb savage	Peri-op mortality (%)	Complication rate
Towne (1981) [4]	209 (239)	60 %	100	77 % claudication, 23 % CLI (5 years)	80 % IP, 36 % PA (6 years)	2	17 %
Lawson (1983) [3]	11 (15)	100 %	100	80 % (1 year)	87 %	0	–
Fugger (1987) [13]	163	SFA occlusion	100	96 % (1 month)	68 % (Fontaine III,IV)	8.6	–
Mukherjee (1989) [14]	29	41 %	100	100 %	100 %	0	0 %
Springhorn (1991) [15]	22 (29)	69 %	96	96 %	–	0	31 %
Jacobs (1995) [16]	51 (68)	69 %	100	81 % (1 year), 54 % (4 years)	96 %	0	29 %
Hoch (1999) [17]	51 (53)	79 %	100	95 % (1 year), 88 % (3 years)	90 %	3.9	31 %
Cardon (2001) [18]	101 (110)	52 %	84	95 % (3 years), 88 % (5 years)	93 %	1	2.7 %
Nelson (2002) [19]	34	59 %	100	85 % (1 year)	100 %	0	15 %
Salvolainen (2007) [20]	97 (106)	47 %	100	–	96 %	3.6	9 %
Kang (2008) [21]	58 (65)	32 %	100	93 % (1 year), 91 % (5 years)	100 %	0	9 % (5 % major)
Chang (2008) [22]	171 (193)	54 %	98	97 %	95 %	2.3	22 %
Kechagias (2008) [23]	90 (111)	31 %	100	–	93 %	1.8	17.1 %
Al-Koury (2009) [24]	95 (105)	35 %	100	100 % (11 month)	95 %	1	7.6 %
Derksen (2009) [25]	140	25 %	–	–	–	0.7	14.3 %
Ballotta (2010) [26]	117 (121)	40 %	100	100 % (1 year), 96 % (7 years)	100 %	0	6.6 %
Desai (2010) [27]	81 (87)	48 %	100	93 % (3 years)	87 %	1	5 %

[a] *CLI* ischemic rest pain and/or tissue loss, Fontaine III-IV/Rutherford 4–6; *IP* inflow and profundaplasty; *PA* profundaplasty alone; dash (–) denotes no information available

Open surgery to address occlusive disease of the femoral bifurcation has stood the test of time and is both safe and durable. However, less invasive endovascular therapies are being applied with increasing frequency based on concerns regarding tolerance for open surgery in high risk patients, technical difficulties with re-operative groins, operating time, length of hospital stay and local wound complications. In an investigation centered on surgical site infections (SSI) following CFE, Derksen et al. [25] noted a 14 % SSI rate with 75 % of those requiring re-operation. Independent risk factors for development of SSI were re-operative groins and placement of drains at the initial procedure. Although similar incidences of SSI have been reported in other studies, most have been minor problems responding to non-operative therapy [21, 23, 24, 26].

Endovascular Intervention: The Alternative

Angioplasty of the PFA has been performed since the 1970s [28]. The results of this early data noted both clinical and hemodynamic improvement as well as limb salvage in the majority of patients with femoral-popliteal obstruction. Endovascular surgery has advanced significantly since that time, and has become the favored modality for many complex lesions of the lower extremity on the basis of low morbidity, shorter hospital stay and faster recovery [5]. Since outcomes will presumably improve along with rapidly advancing technology, only recent data (since 2000) is included in this review. The relevant studies are summarized in Table 16.3.

Both Silva et al. [29] and Dick et al. [32] reviewed patients treated by isolated balloon angioplasty of the PFA. 62 % of 32 limbs evaluated in the Silva study and all of the 55 in the Dick study had SFA occlusions. In the Silva study, technical success was achieved in 94 %, and procedural success (defined as technical success plus an ABI increase > 0.1) was 91 %. Freedom from amputation at 34 months was 94 % and ipsilateral freedom from re-intervention was 90 %. Those patients who underwent profundaplasty alone (31 %) demonstrated a significant improvement in ABI from 0.4 to 0.72 and none required major amputation. The data from Dick et al. is somewhat less convincing. Technical success was 85 % and there was no significant increase in ABI. Primary patency was 61 % and 48 % at 1 and 3 years respectively, leading the authors to conclude that there is only modest sustained benefit from this approach and it should be reserved for limb salvage in patients without a surgical alternative.

To specifically address the role of endovascular surgery in complex patients, Donas et al. (2009) [6] retrospectively reviewed a small group of 15 patients with critical limb ischemia (i.e. Rutherford class 4–6) at high risk for surgery and 2 or more prior groin procedures. These patients showed significant hemodynamic improvement with an average ABI increase from 0.3 at baseline to 0.66 at 30 days, 0.7 at18 months and 0.6 at 3 years. Rest pain was relieved and ischemic ulcers resolved within one month in all patients. Primary patency at 3

Table 16.3 Endovascular CFA/profunda interventions (published series since 2000)

Author (Year)	N (limbs)	Location	Indication (%CLI)[a]	Technical success (%)	Primary patency	Limb savage	Peri-op mortality (%)	Complication rate
Silva (2001) [29]	31 (32)	PFA	59	94	90 % (34 months)	94 % (34 months)	3	9 %
Stricker (2004) [30]	27 (33)	CFA/PFA	18	100	87 % (1 year)	96 % (30 month)	0	0 %
Silva (2004) [31]	20 (21)	CFA	43	100	90 % (1 year)	90 % (1 year)	5	0 %
Dick (2006) [32]	55	PFA	31	85	61 % (1 year), 48 % (3 years)	100 % (3 years)	0	1.8 %
Donas (2009) [6]	15	PFA	100	100	80 % (3 years) (2^{o} patency 86 % 3 years)	93 % (3 years)	0	0 %
Azema (2011) [33]	36 (40)	CFA	30	100	95 % (1 year)	97 % (1 year)	0	5.5 %
Bauman (2011) [34]	98 (104)	CFA	19	98	27 % CLI, 32 % claud (2 years)	94 % CLI 100 % claud (1 year)	0	2 %
Bonvini (2011) [35]	321 (360)	CFA/PFA	22	93	81 (1 year)	99 %	1.2	6.4 % (1.4 % major)
Paris (2011) [36]	26	CFA	39	96	88 % (14 months)	96 % (14 months)	0	–
Ahn (2012) [37]	61 (69)	CFA	45	81	67 % (1 year)	–	0	1.4 %
Bonvini (2013) [38]	94 (97)	CFA	20	91	86 % (1 year)	100 %	1	7.2 %
Datillo (2013) [39]	30 (31)	CFA	40	90	88 % (1 year)	96 % (1 year)	0	13 % (7 % major)

(continued)

Table 16.3 (continued)

Author (Year)	N (limbs)	Location	Indication (%CLI)[a]	Technical success (%)	Primary patency	Limb savage	Peri-op mortality (%)	Complication rate
Davies (2013) [40]	42 (44)	PFA +/– Fem-pop segment	73	94	81 % (1 year)	78 % (1 year)	0	2.3 %
Davies (2013) [41]	115 (121)	CFA	62	90	77 % (1 year)	84 % (1 year)	2.5	6 %
Yamawaki (2013) [42]	87 (104)	CFA	45	100	52 % (1 year)	95 % (1 year)	3.4	1 %
Mehta (2014) [43]	167	CFA	45	–	83 % (17 months)	95 % (17 months) All in CLI pts	0.6	2.4 %

[a]*CLI* ischemic rest pain and/or tissue loss, Fontaine III-IV/Rutherford 4–6; dash (–) denotes no information available

years was 80 %, secondary patency was 86 %. There was one amputation, a conversion from below-knee to above-knee, yielding an overall limb salvage rate of 94 % at 3 years.

Davies et al. [40] compared those patients undergoing balloon angioplasty on the PFA alone to those undergoing both PFA and femoral-popliteal (FP) segment interventions. Technical success (defined as post-procedural stenosis < 30 %) was achieved in 94 % of PFA alone and 85 % of PFA + FP cases. There was no significant difference in limb salvage (72 PFA vs. 78 % PFA + FP) and freedom from re-intervention (81 PFA vs. 96 % PFA + FP) between the two groups, and the authors concluded that endovascular PFA revascularization alone is a reasonable option even if the FP segment cannot be addressed.

Additional studies addressing endovascular interventions on the CFA and PFA are outlined in Table 16.3. Results have been relatively consistent over the reference time period, with high technical success rates of 81–100 %. For those studies reporting this metric, limb salvage rates of greater than 90 % were routinely seen at follow-up intervals of 1–3 years. Primary patency has been somewhat more variable, with reported rates varying from 52 to 95 %.

For those patients unsuitable for open repair and facing amputation, an endovascular approach may be the only option for limb salvage. Taylor et al. [44] specifically addressed this population in a retrospective review of 314 patients with CLI who had significant functional limitations or medical co-morbidities that prohibited open revascularization. Of these, 131 (42 %) patients underwent PTA and 183 patients (58 %) underwent major limb amputation. Perioperative mortality was not significantly different but was relatively high overall (4.4 % for amputees and 3.8 % for PTA), consistent with the high-risk nature of these patients. At 2 years, however, there was a significant survival advantage for amputees (48 % vs. 29 %). On life-table analysis there was unsurprisingly an ambulation difference favoring PTA in the short-term, but this difference became non-significant by 12 months. Maintenance of independent living status was also short-lived, with the advantage for the PTA group lasting only 3 months. This study included all lower extremity lesions and no subgroup analysis was performed on CFA and/or PFA lesions, but the suggestion is that PTA may not impart any significant benefit over primary amputation for these very debilitated patients.

Head to Head Comparison

The study by Diehm et al. [8] presented a retrospective review of 21 limbs with CFA/PFA obstruction and occluded femoral-popliteal segments with critical limb ischemia (57 % ischemic rest pain, 43 % ulceration and tissue loss). Patients underwent either PFA balloon angioplasty with or without stenting (67 %), or open profundaplasty (33 %). Both groups had 100 % technical success and in-hospital limb salvage, however there were 2 perioperative deaths (29 %) in the group of 7 patients subjected to endarterectomy. The results of these two cohorts together demonstrated a 55 %

mortality rate, 36% need for major amputation, and 49% ipsilateral re-intervention rate at 12 months. Ischemic rest pain resolved in 67% while ulcerations healed in only 11%, which is consistent with the findings of others that CFE/profundaplasty is significantly more likely to relieve rest pain than heal ischemic ulcers. A direct comparison of safety and efficacy between groups was not possible due to small sample size.

Linni et al. published the only prospective, randomized, controlled study in 2014 [7]. Of the 116 consecutive patients with atherosclerotic disease of the CFA, 80 met criteria for inclusion and analysis on an intent-to-treat basis. Patients were randomized to CFA balloon angioplasty and placement of a bio-absorbable stent or open endarterectomy. Interventions were technically successful in 97.5% of the endovascular patients and 100% of the open patients. There were 7 surgical site infections in the open group that were minor (not requiring intervention), and none in the endo group. Elevated body mass index appeared to be a promoting factor for SSI, consistent with the findings of others. Both operating time (68 vs.113 min) and length of hospital stay (1.6 vs. 6.8 days) were significantly longer in the open group. Six of the stent patients had early failures (5 of which were re-occlusions), versus none in the open group. At 1 year, primary patency was 80% for endo and 100% for open, and secondary patency was 84% vs. 100%. There was no significant difference between groups in post-operative rates of clinical improvement, ABI or limb salvage. Of the 6 stent failures, 5 required target lesion re-intervention whereas none were required in the open surgical group ($p = .023$). It is noteworthy that 57.5% of the endovascular treated limbs and 47.5% those managed by open endarterectomy had concomitant inflow and or infra-inguinal outflow procedures. The investigators did not stratify their results based on the presence or absence of adjunctive maneuvers or clinical presentation, probably because the number of patients in each group was insufficient for statistical analysis. Based on their demonstration of lower patency and the need for more interventions in the stent patients, despite the lower risk of surgical site infection, the investigators concluded that open CFA endarterectomy is superior to CFA stenting.

Recommendations

Open revascularization of the profunda has been shown to be beneficial for patients with critical limb ischemia. Technical success rates are high, and durable patency has been demonstrated in a number of studies [4, 21, 23, 24, 26] (evidence quality strong). For those with occluded femoral-popliteal segments, profundaplasty can provide limb salvage and clinical improvement in a majority of patients, or permit a lower level of amputation to below the knee when further revascularization is not feasible. This is especially true for patients with better tibial runoff and no ischemic tissue loss (evidence quality moderate). With regard to endovascular surgery, PTA of the femoral bifurcation appears to be a feasible and safe operation with high technical success rates (evidence quality strong). Operative mortality rates appear to be slightly lower for endovascular procedures although most recent studies demonstrate equivalence [21, 23, 24]. Immediate and long-term patency of endovascular repair generally appears to be less than that for

open surgery, which is confirmed by the limited amount of randomized data. However, in view of less frequent local wound complications, and shorter operating times and hospital stays it is difficult to establish a clear advantage for either approach. The addition of endovascular inflow and/or outflow procedures concurrent with the profunda/common femoral intervention appear to be readily accomplished regardless of the technique employed for relief of common femoral/profunda obstruction.

Recommendations

- For patients who are able to tolerate open surgery, do not have a hostile groin, and are not morbidly obese should preferably undergo common femoral endarterectomy and/or profundaplasty. (**evidence quality moderate, strong recommendation**).
- For those patients unsuitable for open repair and facing amputation, an endovascular approach may be the only option for limb salvage. (**evidence quality low, weak recommendation**).

A Personal View of the Data

There is no clear evidence to prefer the open surgical rather than the endovascular approach for rest pain versus the other Rutherford classes of ischemic severity. Comparison of outcomes is confounded by the retrospective nature of all but one report, the relatively small number of cases in most studies and the addition of varied ancillary maneuvers that may be the primary factor relating to immediate and long term outcomes. It is obvious that strong recommendations for the appropriate application of PTA/stent versus endarterectomy of the common femoral/profunda segment to maximize profunda collateral function will require a large multicenter, prospective study, preferably randomized.

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Chapter 17
In Patients with Limb-Threatening Vascular Injuries, Is There a Role of Prophylactic Fasciotomy to Reduce Ischemic Injury?

Melanie Hoehn, Megan Brenner, and Todd E. Rasmussen

Abstract Patients with unrecognized or untreated extremity compartment syndrome are at high risk of amputation and the rates following major extremity vascular injury are high. Despite this, no clear evidence exists supporting the use of prophylactic fasciotomy. The procedure itself is associated with significant morbidity. Risk factors such as ischemia time, location of injury, concurrent injuries, and hypotension should be used to stratify which patients are most likely to benefit.

Keywords Fasciotomy • Compartment syndrome • Ttrauma • Ischemia

Introduction

Compartment syndrome is a feared clinical sequelae of lower extremity injury-induced ischemia and it is associated with significant morbidity and mortality [1]. While it is generally agreed that the diagnosis of extremity *compartment* syndrome mandates immediate fasciotomies, the debate as to the ideal timing of the intervention continues. Advocates of early prophylactic fasciotomies cite that fasciotomies reduce the risk of compartment syndrome and therefore its highly morbid consequences. Opponents argue that fasciotomies have morbidity as well, and that their use prophylactically is unnecessary.

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There are two mechanisms by which vascular injury can lead to compartment syndrome. In cases of arterial injury and limb ischemia, the ischemia-reperfusion phenomenon is thought to play a major role. As ischemic times lengthen, microvascular permeability increases resulting in an increasing amount of interstitial edema. When reperfusion occurs free radicals further increase the permeability leading to increasing amounts of edema. This results in increased pressure within a fixed fascial compartment, mechanical injury to muscle and nerve, reversible ischemia, and eventually, irreversible necrosis [2].

Venous injuries can also lead to compartment syndrome of the extremity if ligation or transection of a major vein occurs. The venous outflow obstruction leads to venous hypertension, which reduces capillary perfusion. This results in ischemic tissue injury which further increases the edema, eventually resulting in necrosis as above.

Added to this biochemical event is the direct traumatic injury to the bone and soft tissue. Frequently these patients suffer significant bony and soft tissue injuries and develop hematoma, which all exacerbate the tissue injury and resulting edema. Occultly injured soft tissue, muscle beds, lymphatics, large vessels, and microvasculature may also play a role.

Technique

Lower extremity fasciotomy was first described by Horn and Hughes in the 1940s, initially being performed by a single incision with fibular excision to release all 4 compartments: anterior, lateral, superficial and deep posterior [3, 4]. Decades later, this evolved into a single lateral incision without fibulectomy. Today, the gold standard approach is a 2 incision, 4-compartment release. In this technique, longitudinal incisions are made on the medial and lateral aspects of the lower leg. Laterally the intermuscular septum is localized and the anterior and lateral compartments are sharply incised on each side. Medially the fascia is open to release the superficial posterior, and the soleus is taken down off the fibula to release the deep posterior compartment (Figs. 17.1, 17.2, and 17.3).

Many techniques exist for primary and secondary closure, including simple interrupted sutures, shoe lace technique, vacuum dressing, wet to dry dressings, and

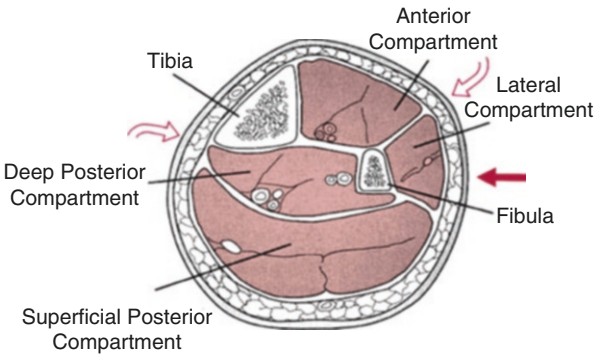

Fig. 17.1 Cross-section of calf illustrating the four compartments. *Open arrows* show sites of double-incision fasciotomy, *closed arrow* shows site of single-incision fasciotomy (This article was published in *Current Surgical Therapy*, 5th Edition. John L. Cameron, *Compartment Syndrome*, pg. 850, Copyright Elsevier ©1995)

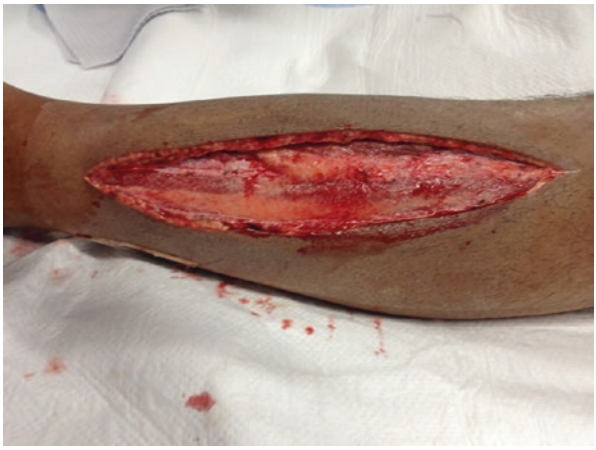

Fig. 17.2 Demonstration of the medial incision for a four compartment fasciotomy

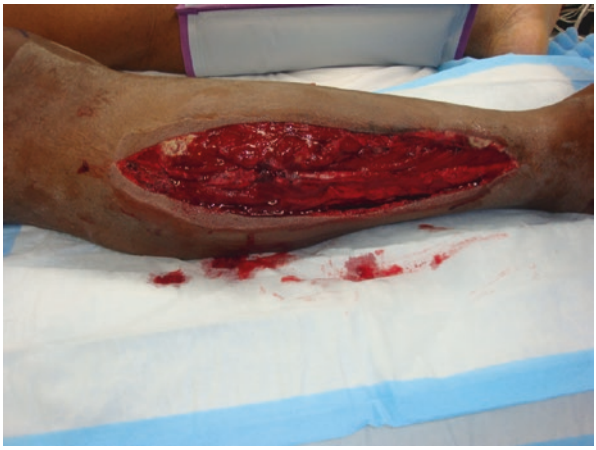

Fig. 17.3 Demonstration of the lateral incision for a four compartment fasciotomy

Table 17.1 PICO table

	I (intervention)	C (comparator)	O (outcomes)
Patients with limb threatening vascular injuries	Early fasciotomy	Ischemic injury	Limb salvage

skin grafting. There is also newer technology, such as the DermClose. It is a dynamic dermatotraction mechanical device which serves as an external tissue expander and has been used with some success [5].

Search Strategy

A literature search of English language publications from 1978 to 2013 was used to identity published data on prophylactic fasciotomy after lower extremity trauma. Databases searched were PubMed. Terms used in the search were “fasciotomy”, “lower extremity trauma”, “compartment syndrome”, and “ischemia” (Table 17.1).

Results

Time Course of Compartment Syndrome

Nerves are the structure most sensitive to the effects of compartment syndrome. Animal models have delineated the time course of irreversible damage to the nerves. Regardless of peak compartment pressures, if release of pressure occurred within 4 h, nerve conduction returned to baseline. After 12 h complete irreversible ischemia occurred. Between 4 and 12 h the peak compartment pressure is significant. With exceptionally high pressures irreversible necrosis occurs at 4 h. This data suggests there is a small window for reversal of the process [6, 7].

One translational study recently investigated functional outcomes in a swine model of hemorrhagic shock, hind limb ischemia, and reperfusion with prophylactic fasciotomy at 1, 3, and 6 h of ischemia. Increasing ischemic intervals resulted in incremental increases in compartment pressure without reaching >30 mmHg. While trends were observed in sensory improvement between the 3- and 6 h groups, this was not statistically significant, nor did it translate to a notable difference in functional outcomes. While this demonstrates that the use of prophylactic fasciotomies in this particular swine model of hemorrhagic shock does not improve functional outcome, all ischemic times were 6 h or less. This suggests in short ischemic times prophylactic fasciotomies may not be beneficial [8].

Risk Factors

There are several clinical features that are associated with an increase need for fasciotomies and presumably compartment syndrome. In a single large series, mechanism of injury is not independently associated with need for fasciotomy [9]. Arterial ligation and combined arterial-venous injuries both have increased risk of compartment syndrome. The level of the injury also plays a significant role. Popliteal injuries have a significant increase in the need for fasciotomies (61 %) vs injuries above the knee (19 %) [10]. Prolonged ischemia time of >4–6 h is also associated with an increased risk. Lastly, prolonged hypotension is associated with both the need for fasciotomies and limb loss [9, 11].

Complications of Prophylactic Fasciotomy

Fasciotomy, while inherently performed for limb salvage, can result in significant complications including amputation. The most feared complication is incomplete compartment release or delayed fasciotomy, resulting in a high rate of morbidity and mortality [12]. The most commonly missed compartments were the anterior and posterior deep compartments containing the main neurovascular bundles of the

leg. Patients who underwent delayed fasciotomy had a 3-fold increase in mortality and twice the rate of amputation. Chronic venous insufficiency may be a result of loss of the muscle pump and deterioration of venous hemodynamics.[13]. Nerve damage and neuropathic pain have been documented in patients after fasciotomy resulting in decreased plantar flexion, dorsal extension, sensory deficits in 53–70 %, and pain in 15–26 % which increased with exertion. Approximately 7 % rate of superficial peroneal nerve injury occurs with fasciotomy [14], leading to inability to evert the foot, and loss of sensation over the dorsum of the foot. Minor but potentially lifestyle limiting complications also occur such as pain, disfiguring wounds, infection, skin changes, and recurrent ulcerations [15, 16].

Prevention Strategies: Prophylactic Fasciotomy

Advocates of prophylactic fasciotomies stress that early fasciotomy can reduce the high morbidity associated with compartment syndrome. The largest review of prophylactic fasciotomies in patients with vascular injury is a retrospective review of the National Trauma Databank (NTDB) from 2002 to 2006. [17]. The NTDB is the largest trauma database in the US, and is comprised of voluntarily-reported patient information. Inclusion criteria were patients greater than 18 with lower extremity arterial injury, arterial repair, and fasciotomy. Patients were divided into 2 groups relative to the timing of fasciotomy – the late group had a fasciotomy performed less than 18 h after the vascular repair, while the early group was decompressed within 12 h. Outcomes were in-hospital mortality, amputation rates, complications, and length of hospital and ICU stays.

Six hundred and twelve patients underwent arterial repair and fasciotomies for lower extremity arterial injury. Most patients underwent early fasciotomies (n = 543), while a minority were performed late (n = 69). After adjusting for mechanism of injury and injury severity score, early fasciotomy was associated with a fourfold lower risk of amputation, which was maintained across subgroups defined by vessel injured, mechanism of injury (MOI), procedure performed, and presence of venous or bony injury. Multivariate analysis adjusting for gender, injury location, MOI, ISS, fracture, nerve and venous injury demonstrated a 23 % shorter length of hospital stay for the early fasciotomy group. Even after excluding the iliac artery injuries (an inherently more injured group), major lower limb amputation was significantly higher in the late fasciotomy group, and total length of hospital stay was significantly shorter in the early fasciotomy group.

Recommandations (Table 17.2)

In the setting of vascular injury, we recommend prophylactic fasciotomy for the following circumstances:

- Combined arterial/venous injuries (**Low quality, strong recommendation**)
- Ligation of major vessel (**Low quality, strong recommendation**)

Table 17.2 Studies used for early fasciotomy

	Number of patients	Major vascular injury (%)	Early fasciotomy (%)	Amputation rate (early) (%)	Mortality (early) (%)	Delayed fasciotomy (%)	Amputation (delayed) (%)	Mortality (delayed) (%)	Quality of evidence
Ritenour et al.	336	32	88	15	6	22	31	20	Low
Williams et al.	88	34	69	3.3	1.6	31	7.4	7.4	Low
Farber et al.	612	100	89	8.5	3.9	11	24.6	2.9	Low
Finkelstein et al.	5					100	100	20	Very low

- Popliteal injuries at or below the knee (**Low quality, strong recommendation**)
- Greater than 6 h of ischemic time (**Low quality, strong recommendation**)
- Associated significant bony and/or soft tissue injury (**Low quality, strong recommendation**)
- Equivocal indications and inability to perform physical exam (**Low quality, strong recommendation**)

A Personal View of the Data

Unfortunately, no randomized controlled trials exist to assess the use of prophylactic fasciotomies; however, in the setting of major vascular injury we strongly recommend the use of prophylactic fasciotomy in the majority of cases. Practically speaking an ischemic time of less than 6 h is difficult to achieve in routine practice. Additionally, significant associated injuries and inability to monitor exam are common place in trauma patients. The frequent development of compartment syndrome in vascular injury as well as the high consequence of a missed diagnosis drive this recommendation.

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Chapter 18
In Patients with Popliteal Entrapment Syndrome, Does Surgery Improve Quality of Life?

Rachel E. Heneghan and Niten Singh

Abstract Popliteal entrapment syndrome (PES) is a rare disorder characterized by popliteal artery compression and symptoms of lower extremity ischemia. It is divided into two main subgroups – anatomic and functional popliteal entrapment. Anatomic popliteal entrapment was first described in the 1870s and is caused by abnormal anatomic development of the popliteal artery and/or gastrocnemius muscle. Functional PES is caused by hypertrophy of the gastrocnemius/soleus complex in anatomically normal subjects. Patients typically present in the second to third decades of life, are physically active and may be professional athletes, and have no other cardiovascular risk factors for the development of vascular disease. Surgical intervention via myotomy of the medial head of the gastrocnemius or myotomy plus interposition vein or prosthetic graft for more advanced disease remains the cornerstone of therapy for these patients; however long-term quality of life data is limited to retrospective reviews.

Keywords Popliteal artery • Entrapment • Revascularization • Interposition graft • Myotomy

Introduction

Popliteal entrapment syndrome, or PES, is a rare condition. In post-mortem examination of limbs, it was seen in 3.5–4.3 % of patients by Gibson [1]. However, not all cases are symptomatic and thus the clinical incidence has been found to be much lower, approximately 0.17 % in a large screening study of Greek military men [2]. Approximately 90 % of reported cases are in men, more than half of patients are symptomatic before 30 years of age, and the defect is bilateral in 20 % of patients [3]. It is characterized by sudden onset calf pain during exertion or a history of

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progressive claudication over months to years, and patients often have abnormal or absent pedal pulses on examination during active plantar flexion and passive dorsiflexion [4]. Symptoms are those commonly seen in patients with an atherosclerotic etiology for claudication but none of the risk factors.

Anatomic PES was first described by Stuart in 1879 in Edinburgh, England. He was a medical student at the time and dissected a gangrenous, amputated leg, noting his findings of an aneurysmal popliteal artery running medial to the medial head of gastrocnemius [5]. Obviously the limb had progressed far past intervention and was amputated for ischemia. PES was first successfully [2] treated by Hamming in 1959 – he transected the medial head of the gastrocnemius muscle and performed a thromboembolectomy in a 12-year-old boy complaining of claudication. In 1965, Love and Whelan coined the current name "popliteal entrapment syndrome" and the late 1960s to 1970s were rich in publications describing presentation, diagnostic techniques, and operative intervention for these patients.

Anatomic PES is a result of abnormal embryological development of the popliteal artery and gastrocnemius muscle. In the lower extremity, the fetal sciatic artery gives rise to the popliteal and tibial vessels below the knee, while the femoral artery, which develops later, contributes to the popliteal artery above the knee (Fig. 18.1). The proximal sciatic artery regresses as the femoral artery matures, and at the same time, the gastrocnemius muscle migrates cephalad, dividing into a lateral and medial head, and attaching to the femoral epicondyles. During the division of the gastrocnemius muscle, the popliteal artery is forming from the sciatic and femoral

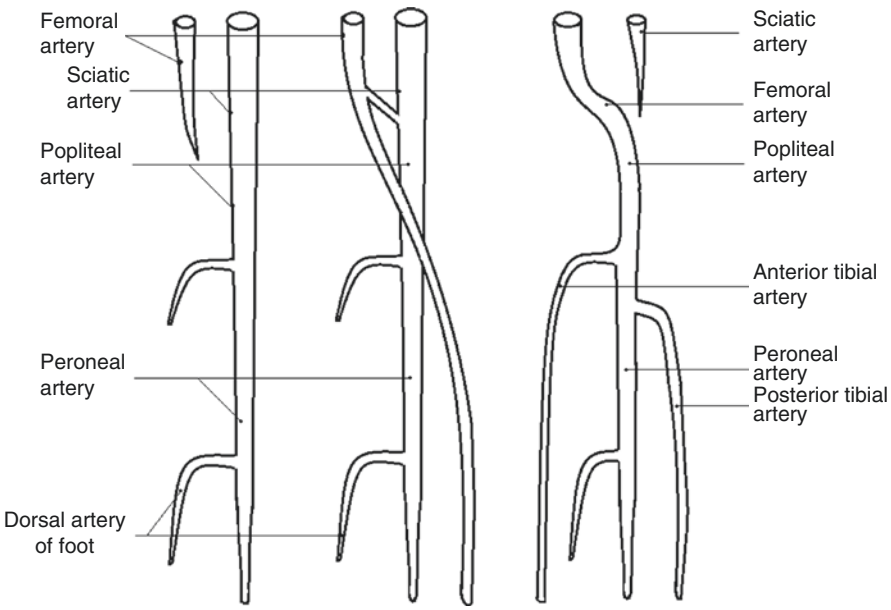

Fig. 18.1 Stages of embryological development of the lower limb arterial system (Adapted from McMurrich's [23])

arteries. Anomalies in the formation of the adult popliteal artery or migration and attachment of the medial head of the gastrocnemius muscle leads to PES [3].

PES is classified into six types based on the embryologic origin with type VI now considered functional PES. Type I occurs most commonly, in approximately 50 % of cases, and involves deviation of the popliteal artery medially to the medial head of gastrocnemius. The adult artery either forms later or the medial head of the gastrocnemius migrates early to its normal position on the medial femoral epicondyle. Type I accounts for approximately 50 % of cases of PES. Type II PES occurs when the medial head of gastrocnemius abnormally migrates to a lateral position, compressing the popliteal artery and it accounts for 25 % of all cases of PES. Type III PES involves an accessory slip of gastrocnemius muscle that compresses a normally situated popliteal artery. This likely represents embryologic remnants that mature from the migrating muscle and accounts for 6 % of cases. Type IV PES represents persistence of the fetal axial artery and lies below the popliteus muscle, causing compression of the artery. Type V includes any of type I-IV in addition to the popliteal vein (Fig. 18.2) [3].

The 6th type of PES is also known as functional popliteal entrapment, was first described by Rignault, et al. in 1985 [6]. Arterial occlusion occurs when the popliteal artery runs in its proper anatomic course, as does the medial head of the gastrocnemius, but the artery is compressed between the heads of a hypertrophied gastrocnemius/soleus muscle complex, especially during exercise. This type is commonly seen in professional athletes and military personnel.

The clinical classification of PES is based on symptoms. Class 0 are patients with anatomic PES diagnosed incidentally who are asymptomatic. Class 1 patients

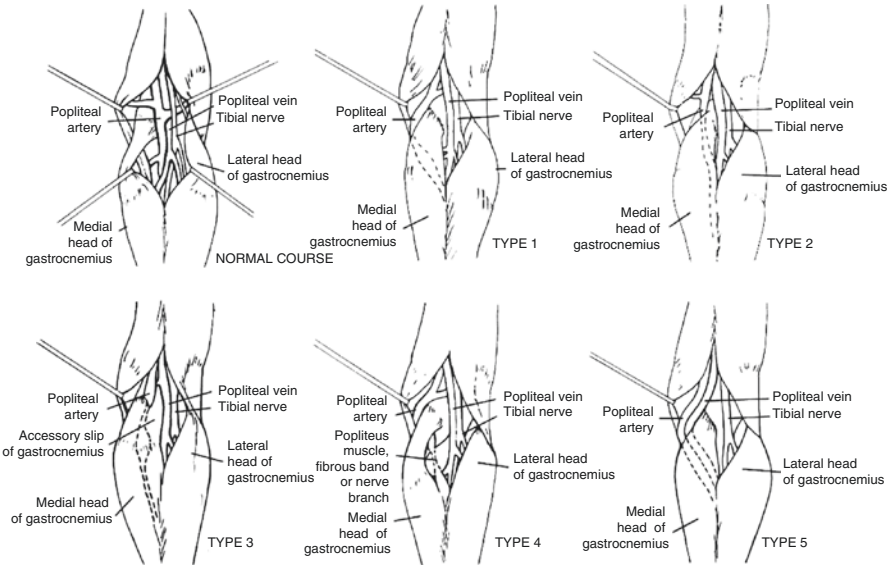

Fig. 18.2 Diagram of the types of popliteal artery entrapment (Reprinted from Rich et al. [24]. With permission from American Medical Association)

complain of pain, paresthesia, and cold feet after physical training or vigorous physical labor. Class 2 patients experience claudication while walking more than 100 m, and class 3 patients experience claudication in less than 100 m. Class 4 patients have rest pain, and class 5 patients have evidence of pedal necrosis [2].

Search Strategy

A literature search of English language publications from 2000 to 2013 was used to identify published data on popliteal entrapment syndrome using the PICO outline (Table 18.1). Databases searched were PubMed, Science Direct, Ovid, Medline, and Cochrane. Terms used in the search were "popliteal entrapment," "functional popliteal entrapment," "popliteal entrapment syndrome." Articles were excluded if they were single case studies. The data was classified using the GRADE system.

Results

As with any rare clinical entity, prospective data regarding management and outcomes of popliteal entrapment syndrome are sparse. Since the original clinical description and treatment in 1959, the published body of work consists of retrospective single-institution series detailing patient presenting symptoms, operative management, and surgical outcomes. There is limited information on improved patient quality of life; however there are a multitude of studies that address long-term follow up and patency. One must infer from the long-term data regarding return to activity and rates of re-intervention some idea of impact on quality of life. Here we will review the literature, including diagnosis, surgical management and outcomes, as well as what has been stated regarding follow-up satisfaction in these patients.

Presentation and Diagnosis

The most common presenting symptom as seen in Table 18.2 was intermittent claudication [14–22]. Eight patients in were asymptomatic at the time of diagnosis. In a systematic review of 30 studies on PES by Sinha, et al. in 2012, 22 of the 30 papers reported

Table 18.1 PICO table for surgical intervention for popliteal entrapment syndrome

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with popliteal entrapment syndrome	Surgical intervention (myotomy, interposition graft)	No surgical correction	Quality of life, follow-up symptoms, complications, re-interventions, return to prior level of activity

Table 18.2 Presenting symptoms, diagnosis, treatment, and outcomes of PES

Author (year)	N	Study type	Symptoms	Diagnostic methods	Diagnosis	Operation performed	Outcome	Mean follow up	Recurrence
Zayed (2014) [14]	30	RS	IC	CTA provocation, ABI	Functional PES	MTS	100 % resolution at 9 months	9 months	20 %, 53 % returned to competition level
Liu (2014) [8]	27	RS	IC (100 %) Ischemia (69 %) Paresthesia (38 %)	DUS, CTA MRI, DSA for FPES	Anatomic and functional PES	MT (27) ± vein patch (13) MT+ long bypass (2), MT + IP graft (6)	22/24 patients had complete resolution.	26 months	DUS surveillance, none
Igari (2014) [15]	29	RS	IC (22) Rest pain (2) Foot ulcer (1) Asymptomatic (4)	ABI, DUS, CT, MRI	PAES (NOS)	MT (4) MT + IP graft (24) MT + bypass (1)	No early complications, ABI normalized. No mention of symptoms.	68 months	3 re-operative – stenosis or occlusion of interposition graft
Radowsky (2013) [16]	5	RS	IC	ABI (5) DUS (1) MRA + CTA (3) CTA (2) DSA (2)	Type 1 Type II Type III Type IV Functional	MT + IP graft (2) MT (2) MTS (1)	Wound seroma (1) Calf numbness (1)	0–3 years	Normal ABI, symptom free (4) Not reported (1)
Kim (2012) [17]	22	RS	IC (18) Rest pain (3), Necrosis (1)	DUS + CTA, MRI, or DSA	PAES NOS	MT + IP graft (14) Fem-pop bypass (5) Fem-PT bypass (1) Pop-PT bypass (2)	81 % patency at 1 year, 6 total occluded. 1 common peroneal nerve palsy	74 months	No mention of resolution of symptoms

(continued)

Table 18.2 (continued)

Author (year)	N	Study type	Symptoms	Diagnostic methods	Diagnosis	Operation performed	Outcome	Mean follow up	Recurrence
Lane (2012) [10]	55	PS	IC (100%)	ABI, DUS provocation, DSA	FPES	MT + posterior fasciotomy	8/44 with symptoms 7/44 with re-intervention	Not reported	4 abnormal DUS post-op without symptoms.
Turnipseed (2009) [12]	57	RS	IC (50) Ischemia (6) Calf swelling (2) Paresthesia (19)	MRI provocation	FPES (43) PAES (14)	MT	Infection/seroma, develop CRECS complaints (38%), no reoperation required, no recurrence	46 months	Not reported
Bustabad (2006) [18]	12	RS	IC (5) Ischemia (3) Asymptomatic (4)	ABI, DUS, MRA, DSA	7 PAES 1 PVES 3 FPES	Pop-pop IP graft (7), Fem-pop (1) Pop-TP truck (1), Angioplasty/patch (1)	8/11 asymptomatic 3/11 with IC 1/11 with IC during exercise.	3.6 years	Anti-platelet agents indicated
Turnipseed (2002) [19]	37	RS	IC (33) Paresthesia (14) Calf swelling (3) Ischemia (3)	ABI, duplex, (all) DSA or MRA (all)	FPES (30) PAES (7)	MTS (30) MT + bypass (7)	Compartment syndrome (1) Popliteal lymph fistula (1) Hematoma (2) Saphenous neuritis (1) Tibial periostitis (1)	18 months for PAES, 65 months for FPES	No recurrent symptoms. 24 of 27 athletic FPES returned to full activity. 3 retired.
Ohara (2001) [20]	11	RS	IC (9) Foot coldness (2)	ABI, DUS, CTA, DSA	PAES NOS	MT + IP graft (7) MT + vein patch (3) MT (1)	10/11 asymptomatic	10.9 years	1 occlusion, no reoperation

Levien (1999) [21]	88	RS	IC (70) Ischemia (18)	ABI + DUS, DSA	FPES PAES	MT (66) MT + vein bypass (16) Non op (6)	14/15 return to sports. 1 amputation	3.9 years	None reported
Di Marzo (1997) [22]	30	RS	IC (29) Necrosis (1)	Provocative DUS + DSA	PAES	MT (20) MT + IP graft (5) MT + fem-PT bypass (3) Pop-TP trunk (1) Fem-TP trunk bypass (1)	Patency of myotomy better than reconstructed. 3/30 in-hospital thrombosis 5/30 wound complications	95 months	1 patient, bilateral recurrence. 1 MT thrombosis 2 bypass thromboses.

N number, *RS* retrospective, *PS* prospective, *IC* intermittent claudication, *PES* popliteal entrapment syndrome, *FPES* functional PES, *CTA* computed tomography angiography, *MRI* magnetic resonance imaging, *MRA* magnetic resonance angiography, *DUS* duplex ultrasound, *ABI* ankle brachial index, *DSA* digital subtraction angiography, *MTS* musculotendinous section/debridement of gastrocnemius/soleus muscle complex, *MT* myotomy. *IP* interposition, *NOS* not otherwise specified, *Fem-pop* femoral to popliteal artery bypass, *Fem-PT* femoral to posterior tibial artery bypass, *Pop-PT* popliteal to posterior tibial artery bypass, *Pop-pop* popliteal to popliteal artery interposition graft, *Pop-TP trunk* popliteal to tibioperoneal trunk bypass, *Fem-TP trunk* femoral to tibioperoneal trunk bypass

IC as the most common presenting symptom, acute ischemia was reported in a median of 11 % of patients, and approximately 18 % of patients diagnosed were asymptomatic [7]. Twenty-four of 30 studies had a median prevalence of 24 % of patients who presented with popliteal artery occlusion, and 15 of 30 studies had a median 13.5 % prevalence of post-stenotic dilatation or aneurysm formation of the popliteal artery at the time of presentation. In 3 studies, the duration of symptoms was described, and was anywhere from 4 h to 10 years, with a median of 12 months, however there was no correlation between symptom duration and degree of arterial damage [7].

Detailed physical examination is prudent in the evaluation of patients who present with symptoms of PES. A thorough extremity exam for color or temperature differences and pedal pulse examination are mandatory. Ankle-brachial index (ABI) may be useful in popliteal occlusion, however in cases of functional or non-occlusive PES, ABI are not reliable for diagnosis and are often normal. However, baseline and follow up ABI's are useful to assess patency after surgical intervention [8, 9]. Doppler and duplex ultrasonography (DUS) during provocative maneuvers of passive and active plantar and dorsiflexion have also been widely applied. In a retrospective review by Lane, et al., in 2012, they report that if during DUS patients demonstrated a reduction in diameter of the popliteal artery (from 50 to 75 % or more) where the two heads of the gastrocnemii meet, a relative change in velocities in the popliteal fossa with plantar flexion, and distal waveform reduction, or show signs of reactive hyperemic response, as shown by an increase in the velocities, PES should then be verified by MRI/MRA or CT angiography [10]. Imaging in functional entrapment is not routine prior to operative intervention. It is the experience of the authors that surgical exploration can be the next step if patients present with clinical symptoms and ultrasound findings of PES.

The range of tests performed in the studies reviewed is shown in Table 18.2. All papers incorporated some form of provocative imaging, whether it was DUS/ABI, or arteriography (CT, MR, or DSA). This was similarly seen in Sinha's systematic review, which found a median number of 3 tests performed on patients with suspected PES [7]. Arteriography, both at rest and with provocative maneuvers, was performed in 28 of 30 studies, followed by treadmill DUS/ABPI in 18 of 30, and either CT or MR in 12/30 studies [7]. Provocation angiography had a mean sensitivity 97 % (range 85–100 %), provocation duplex U/S mean sensitivity 83 % (50–100), provocation Doppler/ABPI mean 90 % sensitivity (50–100), MR provocation mean 94 % sensitivity, (76.5–100), CT provocation demonstrated 100 % sensitivity. We have reported on our early experience with intravascular ultrasound (IVUS) during the diagnostic arteriogram to examine the artery for any intimal changes and confirm compression during provocative maneuvers [6]. Our initial results have been very promising, adding another potential confirmatory tool as well assisting in operative management.

Surgical Intervention

The majority of literature about popliteal artery entrapment discusses diagnosis and surgical management. Non-operative management of this entity is not commonly

practiced as the vast majority of patients are young, healthy, and present with lifestyle limiting claudication that is surgically treatable. In addition, repetitive trauma of the artery may lead to aneurysmal dilation and potential occlusion over a prolonged period. Of the papers considered in this review, all but 6 patients underwent surgical intervention, for a total of 397 patients. In Sinha's systematic review, they did identify 17 patients managed without surgery, with patient refusal as the most common reason in 9 of 17 cases, and other reasons not specified. Non-operative results ranged from complete resolution after cessation of extreme physical activity in functional PES in 4 patients to amputation in 1 patient with hypercoagulability after unsuccessful thrombolysis in anatomic PES [7].

When faced with Types I-V PES and acute limb ischemia in an otherwise healthy individual, surgical intervention is mandated due to potential loss of limb. In asymptomatic anatomic PES, some authors argue for early intervention with myotomy to prevent potential sequelae, as interposition grafts in the case of advanced disease have been shown to have a higher complication rate, including thrombosis and wound dehiscence [8, 11]. There were eight asymptomatic patients reported in the literature and included in this review, all of whom underwent operative management, with no post-operative complications reported.

In cases of delayed PES presentation, the decision to operate requires more thorough evaluation as to the true limitation posed by the process and should be limited to symptomatic patients who experience a decrease in their function or inability to participate in sporting activities, as well as those patients that have evidence of intimal damage or post-stenotic aneurysmal changes [8, 11, 12].

The current described surgical options include musculotendinous resection for functional entrapment and myomectomy of the medial head of the gastrocnemius in anatomic cases to release the entrapment. Both a medial and posterior approach to the popliteal artery have been described and advocated by different authors. Our group believes in the case of patients with a patent popliteal artery a posterior approach is warranted as it affords the best exposure of the artery as well as the surrounding musculature. In patients with an occluded popliteal artery, a medial approach may be beneficial if the distal anastomosis is to be made at the tibioperoneal trunk or a tibial vessel. As mentioned above, we have reported on the use of intraoperative duplex ultrasound to assess the vessel for intimal damage as well as complete release of anatomic compression when treating patients with functional PES. As the muscle mass in these patients can be quite hypertrophied, our goal is to resect only the offending region and not the complete medial gastrocnemius muscle as this can be debilitating for young athletes or military personnel. After resecting the visible muscle compressing the popliteal artery, we perform an intraoperative DUS to ensure no residual compression remains. If popliteal arterial damage is observed, such as long-segment stenosis, popliteal occlusion, or aneurysmal degeneration, then a number of arterial reconstructive options are available. Most studies describe use of saphenous vein bypass using an interposition graft. It is well known in the vascular literature that vein grafts have much higher 5 year-patency than prosthetic grafts below the knee, and should be used whenever possible. Endovascular techniques do not address the underlying anatomic or functional abnormality and can result in stent occlusion and critical limb ischemia, requiring emergent operative intervention [13].

Outcomes and Follow-up

Fifty-nine patients (14.6 %) experienced a post-operative complication or recurrence, as seen in table 18.2. The number of patients who returned to their prior level of activity with complete resolution and no recurrence of their symptoms was nearly 100 %, and can also be seen in table 18.2. Sinha reported a median failure rate of 27.5 % but the reporting was too heterogeneous to analyze further [7]. ABI's and duplex ultrasound studies were the most common surveillance modalities chosen, however this is not well reported. In addition, quality of life results are not reported but can be inferred by return to prior functional status. A caveat in this patient population is the majority are young and often not in the same area for long-term follow-up. As opposed to those that undergo a venous interposition graft and have routine graft surveillance, many of these patients are not seen in a long-term fashion.

A Personal View of the Data

A large number of single institution experience retrospective reviews have been published regarding the diagnosis and surgical management of popliteal entrapment syndrome, but without prospective data, strong guidelines regarding treatment of this entity remain elusive. In addition, these patients are not typical patients seen by vascular surgeons. Many present to their primary care physician and because of the youth and lack of comorbidities are managed conservatively or referred to orthopedics for a potential musculoskeletal cause. It is often when the patient's symptoms worsen and they have complications such as occlusion or aneurysmal dilation with embolization that we are consulted. The majority of the literature consists of treatment of high performance athletes or military personnel whose career is threatened by what many would deem claudication with more extreme activity than in the normal population that could be resolved simply by changing their lifestyle and limiting their activity. The authors feel that symptomatic PES I-V warrants operative management after a thorough preoperative work-up confirms the diagnosis with myotomy and in cases where the artery is damaged, venous interposition graft. Type VI or functional popliteal arterial entrapment should also be managed surgically in patients who are unwilling to decrease their level of physical activity, and we believe completion intraoperative duplex assists in the extent of muscular resection. In the above scenarios, provocative maneuvers during evaluation are critical to accurately diagnose and treat this process. We recommend baseline ABI's, stress Doppler and duplex ultrasound, and either MR or CT arteriography, although MR may be better at imaging the soft tissue structures in cases of functional PES. In addition we believe that IVUS during the diagnostic arteriogram offers another promising confirmatory adjunct as well as assessment of any intimal damage to the artery.

Recommendations

- For patients with symptomatic PES I-V diagnosed with either vascular lab studies, axial imaging, or diagnostic arteriography, we recommend surgical intervention with either myotomy or myotomy plus interposition vein graft or bypass depending on the degree of popliteal damage (**evidence quality low; weak recommendation**).
- For patients with symptomatic Type VI PES diagnosed with the above-mentioned modalities, we recommend surgical intervention with myotomy and popliteal artery evaluation with possible reconstruction if damaged (**evidence quality low; weak recommendation**).
- For patients with asymptomatic anatomic PES diagnosed with axial imaging, we cannot recommend surgical intervention with myotomy (**evidence quality low; weak recommendation**). However these patients should be followed with periodic physical examination and non-invasive studies for any potential arterial damage that can occur.

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Part III
Mesenteric Disease

Chapter 19
In Patients with Acute Mesenteric Ischemia Does an Endovascular or Hybrid Approach Improve Morbidity and Mortality Compared to Open Revascularization?

Mark Wyers and Fahad Shuja

Abstract Acute mesenteric ischemia (AMI) covers a broad range of vascular pathologies ranging from acute arterial embolism or thrombosis, to the eventual manifestation of untreated chronic mesenteric ischemia. In recent decades, with improved anticoagulation management, the incidence of SMA embolism has declined. Currently, the most common presentation is an acute exacerbation of chronic atherosclerotic mesenteric vessel occlusion. The clinical manifestations and time course of this are much more variable and difficult to stratify. Regardless of the cause, in the absence of timely restoration of blood flow, there will be progression to bowel ischemia, peritonitis and death. The entity was first described in 1895, however it was not until the 1950s that techniques for restoration of mesenteric blood flow were described. Initial operative strategies included SMA embolectomy, SMA thromboendarterectomy and aorto-mesenteric bypass. Angiography was used primarily for diagnostic purposes but early reports of intra-arterial thrombolysis using heparin and streptokinase were published in the 1970s. With further advancements in endovascular techniques, percutaneous revascularization has become the preferred modality for treating patients with chronic mesenteric ischemia. However, the standard of care for AMI remains unclear and mortality rates remain quite high. Traditionalists would argue that there is no substitute for an open abdominal exploration and assessment of bowel viability. They are skeptical of recent publications citing favorable outcomes with purely percutaneous treatments for AMI, maintaining that it does not allow for assessment of bowel viability, requires advanced technical skills and is more time consuming compared to open approach. Alternatively, a combined open and endovascular, or "hybrid" approach can be viewed as a compromise that still honors traditional surgical principles to evaluate bowel viability. Milner et al. were the first to publish a case report on a "hybrid" approach to

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AMI. They combined open and endovascular strategies to establish mesenteric blood flow. Briefly, the SMA is exposed at the base of the transverse mesocolon. A patch angioplasty is then performed at the site of intended arterial puncture site, through which, an SMA stent is deployed via retrograde cannulation. Proponents of this technique assert that it allows for assessment of bowel viability, and offers direct access to SMA revascularization rather than the long and sometimes challenging transbrachial or transfemoral approach. Since the first description of this technique in 2004, several groups have published their experience with this approach. In this chapter, we aim to summarize the literature on endovascular techniques (including hybrid approach) for treating acute mesenteric ischemia, and how they compare to the traditional open revascularization strategies.

Keywords Mesenteric ischemia • Mesenteric stent • ROMS • Mesenteric bypass • Reterograde mesenteric stent • CT diagnosis mesenteric ischemia • Bowel ischemia • SMA embolectomy • SMA stent • SMA bypass

Introduction

Acute mesenteric ischemia (AMI) covers a broad range of vascular pathologies ranging from acute arterial embolism or thrombosis, to the eventual manifestation of untreated chronic mesenteric ischemia. In recent decades, with improved anticoagulation management, the incidence of SMA embolism has declined. Currently, the most common presentation is an acute exacerbation of chronic atherosclerotic mesenteric vessel occlusion. The clinical manifestations and time course of this are much more variable and difficult to stratify. Regardless of the cause, in the absence of timely restoration of blood flow, there will be progression to bowel ischemia, peritonitis and death. The entity was first described in 1895 [1], however it was not until the 1950s that techniques for restoration of mesenteric blood flow were described. Initial operative strategies included SMA embolectomy [2], SMA thromboendarterectomy [3] and aorto-mesenteric bypass [4]. Angiography was used primarily for diagnostic purposes but early reports of intra-arterial thrombolysis using heparin and streptokinase were published in the 1970s [5]. With further advancements in endovascular techniques, percutaneous revascularization has become the preferred modality for treating patients with chronic mesenteric ischemia [6]. However, the standard of care for AMI remains unclear and mortality rates remain quite high. Traditionalists would argue that there is no substitute for an open abdominal exploration and assessment of bowel viability. They are skeptical of recent publications citing favorable outcomes with purely percutaneous treatments for AMI [7–10], maintaining that it does not allow for assessment of bowel viability, requires advanced technical skills and is more time consuming compared to open approach. Alternatively, a combined open and endovascular, or "hybrid" approach can be viewed as a compromise that still honors traditional surgical principles to evaluate bowel viability. Milner et al. were the first to publish a case report on a "hybrid"

approach to AMI [11]. They combined open and endovascular strategies to establish mesenteric blood flow. Briefly, the SMA is exposed at the base of the transverse mesocolon. A patch angioplasty is then performed at the site of intended arterial puncture site, through which, an SMA stent is deployed via retrograde cannulation [12]. Proponents of this technique assert that it allows for assessment of bowel viability, and offers direct access to SMA revascularization rather than the long and sometimes challenging transbrachial or transfemoral approach. Since the first description of this technique in 2004, several groups have published their experience with this approach [12–20]. In this chapter, we aim to summarize the literature on endovascular techniques (including hybrid approach) for treating acute mesenteric ischemia, and how they compare to the traditional open revascularization strategies.

Search Strategy

A literature search of English language publications from 1990 to 2014 was used to identity published data on endovascular or open approaches to AMI using the PICO outline (Table 19.1). Databases searched were PubMed, Medline, and Cochrane Evidence Based Medicine. Terms used in the search were "mesenteric ischemia treatment", "mesenteric ischemia endovascular", "acute mesenteric ischemia revascularization", acute mesenteric ischemia AND endovascular approach", and "mesenteric ischemia stenting". Articles were excluded if they limited their analysis to chronic mesenteric ischemia. We did not find any prospective, randomized controlled trials on this subject. Eight case series, three reviews, one consensus paper and two case reports were included in our analysis. The data was classified using the GRADE system.

Results

Incidence and Risk Factors for AMI

Contemporary population-based studies on the epidemiology of this disease entity are lacking. According to a Swedish study based on autopsy and operating room data, the incidence of AMI in the city of Malmo was 12.9/100,000 person-years.

Table 19.1 PICO table for interventions on acute mesenteric ischemia

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Patients with acute mesenteric ischemia	Endovascular revascularization	Open revascularization	Mortality, morbidity, bowel resection

More than two third of the cases had thromboembolic etiology, while the remainder was venous occlusions or non-occlusive mesenteric ischemia [21]. Clinical risk factors include atrial fibrillation, recent myocardial infarction, congestive heart failure and peripheral arterial emboli [22]. Up to 40 % of patient with acute mesenteric ischemia have a history of post-prandial abdominal pain in the past, suggesting an acute-on-chronic process [23].

Presentation and Diagnosis of AMI

Common manifestations of AMI include abdominal pain, nausea and vomiting. Unless transmural bowel involvement is present, there may be minimal tenderness to palpation upon initial presentation. Unfortunately, these symptoms overlap with several other intra-abdominal pathologies and commonly lead to a delay in diagnosis or misdiagnosis. This diagnostic challenge is one of the main reasons why mortality from acute mesenteric ischemia has remained 50–70 % over the years [19, 21, 24]. Therefore, physicians need to maintain a high index of suspicion. Once suspected, a multi-detector row computed tomography angiography (MDCTA) forms the cornerstone of the diagnostic algorithm [25–28]. It provides excellent visualization of the celiac artery and the SMA and aids in excluding other causes of abdominal pain. Furthermore, it allows for assessment of bowel wall thickness, pneumatosis, mucosal, and bowel wall enhancement pattern that support the diagnosis of AMI. There is no single radiographic finding that is perfectly sensitive or specific, but using a combination of CT criteria achieves a positive and negative predictive value of 100 % and 96 % respectively [29].

Treatment of AMI

Once suspected, treatment is divided into three aspects; appropriate resuscitation, prompt restoration of blood flow and resection of non-viable bowel. Resuscitation usually involves isotonic crystalloid fluids. Various clinical parameters are used as objective evidence of adequate resuscitation, including mentation, heart rate, blood pressure, urine output and degree of metabolic acidosis. AMI is a surgical problem, however and resuscitation should not delay revascularization and abdominal exploration, if needed. Based on the pre-operative CT and clinical exam, it can be determined whether the patient has peritonitis or not, and whether the occlusion is embolic or thrombotic in nature. Presence of peritonitis necessitates laparotomy to assess bowel viability and need for resection. Grossly necrotic bowel is resected. The bowel ends may be stapled off and anastomosis or stoma formation performed at a second-look laparotomy.

Mesenteric revascularization in the acute setting is typically focused on the SMA only and precedes bowel resection in order to minimize the length of intestine

removed. Revascularization may take one of three forms depending on the etiology of the occlusion, suspicion for bowel infarction and available resources:

Open – SMA embolectomy, mesenteric bypass, endarterectomy
Endovascular – aspiration embolectomy, rheolytic thrombectomy, catheter-directed thrombolysis, angioplasty and stent
Hybrid – retrograde open mesenteric stent

Endovascular Therapeutic Options

The SMA can be approached percutaneously via femoral or brachial artery. Brachial approach is preferred if there is a sharp downward angle between the SMA and the aorta. If percutaneous access fails, the SMA can be accessed in an open, retrograde fashion by exposing it at the base of the mesocolon. Once access is established, there are different endovascular options to treat an SMA occlusion:

Aspiration Embolectomy

This is a viable option in patients without any need for bowel resection. Briefly, over a stiff 0.035-in. wire, a 7-Fr sheath with a removable hub is placed proximal to the embolus. A hydrophilic 0.035-in. guidewire is then passed through the embolus. Over this wire, the tip of a 6-Fr guiding catheter is passed through the embolus. After removing the guidewire, a 20-ml syringe aspiration is applied manually to the guiding catheter accompanied with catheter withdrawal. Several passes are usually required. A small series out of Sweden reported 9 cases of percutaneous aspiration embolectomy of the SMA [7]. Technical success (defined as restoration of SMA blood flow) was achieved in all 7, however all patients had residual embolus in at least one branch of SMA upon completion. There was one case of SMA dissection, treated with stent. One patient went on to require bowel resection. In-hospital mortality was 10 %. Another small series from Germany reported 6 cases of percutaneous aspiration embolectomy [8]. SMA blood flow was restored to normal in 5, while 1 patient had diminished blood flow upon completion due to a dissection. In-hospital mortality was 33 %.

Catheter-Directed Thrombolysis

In cases of incomplete aspiration embolectomy or distal embolization, percutaneous SMA thrombolysis is an option in patients without peritonitis or high risk of bleeding. With the sheath placed in proximal SMA, a multiple side-hole infusion catheter or a microcatheter is advanced in the embolus and a thrombolytic agent infused, with repeat angiography at 12–24 h interval. A paper from the Swedvasc registry

reported cases of percutaneous thrombolysis for acute SMA occlusions [9]. Between 1987 and 2009, 34 patients underwent this intervention. No one had peritonitis. Notably, 47 % of patients underwent an adjunctive endovascular procedure at the time of thrombolysis (aspiration embolectomy, angioplasty/stenting, mechanical thrombectomy, papaverine infusion). Complete or partial lysis was achieved in 30 patients (88 %). Six bleeding complications were noted, which were all self-limiting. In-hospital mortality was 26 %. Successful thrombolysis was associated with decreased mortality.

Antegrade Angioplasty and Stenting

This allows treatment of underlying stenotic or occlusive lesions primarily or after thrombolysis. For ostial or heavily calcified lesions, balloon-expandable stents are preferred over self-expanding ones owing to their superior radial force. A completion angiography is performed after stent placement, as well as pressure measurement. If the residual pressure gradients across the lesion/stent exceeds 10 mmHg, additional angioplasty and/or stenting is performed.

Retrograde Recanalization and Stenting of the Superior Mesenteric Artery

This "hybrid" approach was first described by Milner et al. in 2004 and has since been described by various groups in North America and Europe [11–20]. Variations in the technique have been described but in general, the SMA is punctured anteriorly with a micropuncture needle and 0.018" wire. The inner cannula of the micropuncture set can be used instead of a sheath. Lateral fluoroscopy is used to advance the wire to the level of the obstruction. Retrograde arteriography is performed. A torque device and minimal shaping of the wire is the default, trying to maintain luminal position of the wire. A guiding catheter may also provide some necessary support and steerablity. Once the lesion is crossed and aortic access is obtained, the arteriotomy is made to include the wire, with the wire left in place. The arteriotomy should be kept as proximal on the SMA as possible. The artery is carefully inspected. Occasionally there is thrombus in the proximal SMA that can be retrieved with a clamp. A limited endarterectomy is performed and a patch angioplasty is performed with either vein or bovine pericardium. Prior to completion of the patch a 6 or 7 Fr sheath is advanced over the wire in through the side of the arteriotomy. The sutures are secured with a rubber shod while the artery is stented. Usually a 3–4 mm predilation is performed with repeat retrograde contrast injection to identify the SMA origin. If visualization of the SMA origin or aorta remains poor, a femoral puncture can be used to place a flush catheter in the aorta for imaging purposes. Most often a 6 or 7 mm balloon expandable stent or stentgraft is required. This approach allows the surgeon to evaluate the bowel and intervene on the vasculature at the same time.

Furthermore, in case of bowel perforation, it avoids the use of a prosthetic bypass in a contaminated operative field. The largest case series on retrograde open mesenteric stenting comes from a Dutch group, published in 2014 [20]. They analyzed 68 patients with AMI presenting between 2007 and 2011. In this report, percutaneous mesenteric artery stenting was the preferred treatment in patients without peritonitis, while retrograde open mesenteric stenting (ROMS) was reserved for cases of percutaneous technical failure. Technical difficulty, including the inability to cross the lesion with a wire, was the most common reason for failure of percutaneous revascularization. Fifty of these patients were able to undergo percutaneous mesenteric artery stenting, while 15 required retrograde stenting. Technical success (defined as successful completion of the procedure and <30 % residual stenosis) was achieved in 14 of 15 patients despite the preceding percutaneous failure. One patient underwent bowel resection despite successful revascularization. Two patients had progression of bowel ischemia and required a second laparotomy and bowel resection. The mortality rate in ROMS group at 30 days was 20 % and primary stent patency (defined as uninterrupted patency) was 91 %. At 12 months, mortality rate for ROMS patients was still 20 %, while primary stent patency was 83 %. Primary assisted patency (defined as revision of the revascularization method to prevent impending occlusion) was 91 % while secondary patency (defined as restored patency after occlusion by thrombectomy or angioplasty) was 100 %. Unfortunately, patient outcomes in the percutaneous stenting group were not reported in this study.

Open Versus Endovascular Revascularization for AMI

To date, there is no randomized clinical trial for comparison of open versus endovascular mesenteric revascularization for acute ischemia. Available data is limited to single center studies [12, 30] and nationwide reports [6, 29] (Table 19.2). Block et al. published the national trends in Sweden for revascularization for AMI [29] and

Table 19.2 Results of endovascular or hybrid repair for acute mesenteric ischemia

Study	Patients	Outcome classification	Typical risk for endovascular technique	Relative risk for open technique	Quality of evidence
Arthurs et al. [30]	Endo = 56 Open = 14	Mortality	36 %	50 %	Low
Wyers et al. [12]	Endo = 8 ROMS = 6 Open = 5	Mortality	100 % endo 17 % ROMS	80 %	Low
Ryer et al. [18]	Endo = 49 Open = 17	Mortality	15 %	23 %	Low
Block et al. [29]	Endo = 42 Open = 121	Mortality	28 %	42 %	Low
Blauw et al. [20]	Endo = 50 ROMS = 15	Mortality	Endo not reported 20 % ROMS	NA	Low

ROMS retrograde open mesenteric stenting, *NA* not applicable

demonstrated an increasing trend towards endovascular strategies. In 2009, endovascular treatment surpassed open surgery (29 versus 24 cases respectively). A similar analysis of the National Inpatient Sample (NIS) database from 2000 to 2006 also showed a significant increase of endovascular treatments for AMI but still more open procedures. In that 6-year period 64.5 % of patients with AMI underwent open surgery compared to 35.5 % who underwent endovascular revascularization [6]. In Swedvasc [29], there was no difference in 30-day mortality between open and endovascular surgery for embolic occlusions (37 versus 33 %). However, for thrombotic occlusions, mortality rate was significantly higher after open than endovascular treatment (56 versus 23 %). Similar trends were reported in the North American study by Schermerhorn et al. [6], where endovascular interventions had a 16 % in-hospital mortality compared to 39 % mortality after open surgical repair. Notably, those undergoing percutaneous revascularization had significantly higher rates of medical co-morbidities but a lower rate of bowel resection. The difficulty in these large database reviews and retrospective AMI studies resides in the ability to stratify patients between truly acute and subacute presentations and to overcome the selection bias between the two treatments.

Block et al. published their analysis of all SMA revascularization procedures performed for acute mesenteric ischemia between 1999 and 2006 as recorded in the Swedvasc registry [29]. Their experience appears to mirror other modern reports of the treatment of AMI with a transition to more endovascular treatments over the study period. A total of 163 patients were analyzed (121 open, 42 endovascular). Treatment strategies differed significantly depending on the type of occlusion with 85 of 99 embolic occlusions undergoing surgical embolectomy. In contrast, patients with thrombotic occlusion were treated more often treated with percutaneous endovascular procedures in 20 of 54 patients; an additional 4 were treated with retrograde open mesenteric stenting (ROMS); the remaining 21 patients underwent bypass or thromboendarterectomy. The time from symptom onset to treatment was shorter in open treatment arm, a statistic heavily influenced by the number of embolic presentations in that group. Bowel resection and incidence of short bowel syndrome were higher in patients undergoing open surgery. Thirty-day mortality rates were 42 % vs 28 % ($p = 0.03$) for open and endovascular surgery. The two groups however are likely very different in terms of their disease severity at presentation. Patients in the endovascular group had greater delays to treatment yet had a lower incidence of bowel resection and better survival, suggesting a more subacute or acute on chronic presentation. Technical failure was 21 % in the endovascular group and 14 % in the open group. In both subgroups, revascularization failure was a harbinger of very poor outcome with 30-day mortalities of 56 % and 87 % in the endovascular and open cohorts respectively. This discrepancy also highlights the selection bias between the open and endovascular groups.

In a small case series of 13 AMI patients, Wyers et al. [12] noted that the intervention with the lowest mortality (17 %) was retrograde mesenteric stenting, compared to 80 % mortality for open bypass. Despite the small sample size of the study, it established ROMS as a viable revascularization method. ROMS technical success

was 100 % including 4 patients that had failed a previous antegrade percutaneous approach.

Arthurs et al. reviewed the Cleveland Clinic experience of 70 AMI patients over a 9 year period [30]. They report a very aggressive endovascular approach in 81 % of the total, using prolonged lytic therapy, mechanical thrombectomy and primary stenting.. As in the Swedvasc registry, endovascular procedures were applied more commonly to thrombotic (72 %) than to embolic occlusions (28 %). Technical failure in endovascular therapy group was 13 % overall and did not differ significantly between thrombotic (11 %) and embolic (15 %) disease. Patients undergoing open revascularization also had significantly longer segments of bowel resection, and were almost twice as likely to develop pulmonary or renal failure post-operatively. The mortality difference between the two treatment arms, 39 % for endovascular and 50 % for open treatment, did not reach statistical significance. Only when endovascular failures were excluded, however, did this difference reach statistical significance (36 % versus 50 %, respectively $p<0.05$). Such exclusion however is not sound when comparing two treatment strategies and the former intention to treat analysis is more appropriate. There were no revascularization failures in the open revascularization group.

When reviewing literature on the subject, it is critical to distinguish between acute and sub-acute ischemia, and the time to intervention. The selection bias in the available retrospective analyses is evident but difficult to control for. The outcomes of interventions are highly likely to be dependent on these patient variables rather than the treatment they received. It is evident that patients with embolic occlusions, who are more likely to have more acute and critical symptoms, are treated more often with traditional open thrombectomy. Treatment delay with prolonged thrombolyitics and a higher endovascular treatment failure rate, as demonstrated in the Cleveland Clinic experience, is not well tolerated in this group. Patients with thrombotic occlusions of the SMA tended to have a more insidious presentation [29] this built-in delay in diagnosis and presentation selects out a more heterogeneous patient group that may tolerate the occlusion better and therefore have more ability to undergo less invasive endovascular procedures and still have a lower rate of abdominal exploration and bowel resection [29]. Similarly, patients treated with endovascular means had a median duration of symptoms of 62 hours, compared to 26 hours for open surgery. Yet, traditional therapy group had a 3 fold longer segment of bowel resection than endovascular arm (160 cm versus 52 cm, $p<0.05$) [30]. Sixty hours of ischemia without death and shorter length of bowel gangrene would again indicate a sub-acute presentation and favorably, but incorrectly, biases the outcomes of endovascular therapy. The Swedvasc registry data showed similar findings [29], where 24 % of patients receiving endovascular therapy had a history of abdominal angina, and therefore, an indication that there was an element of sub-acute or acute-on-chronic presentation. Such pitfalls are inevitable in retrospective case series and can only be addressed by a well-designed prospective, randomized clinical trial. Due to the low incidence of AMI and emergent presentations, such a trial is unlikely to take place.

Recommendations

Because endovascular revascularizations can be technically challenging, time consuming and have a technical failure rate of 13–20 %, they are best reserved for patients with sub-acute presentations without suspicion of bowel infarction. In patients without peritonitis, endovascular revascularization is associated with lower morbidity and mortality (GRADE; Moderate). Furthermore, patients undergoing successful endovascular revascularization have a better survival than open surgery (GRADE; Low). These observations however, more likely reflect a selection bias rather than the superiority of the percutaneous endovascular approach broadly applied to AMI patients. Survival in patients with failed endovascular intervention is not statistically different than open surgery (GRADE; Low). Most importantly, prolonged attempts at percutaneous intervention should not be allowed to delay laparotomy and bowel assessment/resection.

Once the need for bowel assessment has been established, the decision between a traditional bypass and hybrid retrograde stenting of the SMA are both good options. In patients with severe AMI presenting with peritoneal signs, immediate laparotomy and assessment of bowel viability is imperative. From a technical viewpoint, there are likely some advantages that favor a hybrid approach to the treatment of acute mesenteric ischemia. In these cases, a hybrid procedure with retrograde SMA revascularization has some potential advantages over open revascularization. This technique has a high rate of technical success, and allows prompt attention to the bowel. In the setting of peritoneal sepsis, the use of a prosthetic graft and the time and complexity of saphenous vein harvest can also be avoided. While not conclusive, the small series of carefully selected patients treated with ROMS may suggest a survival advantage. More widespread experience with this technique and further comparison is necessary. (GRADE; Moderate).

A Personal View of the Data

The data published on the topic of acute mesenteric ischemia is insufficient to be able to make a firm treatment recommendation in the treatment of acute mesenteric ischemia. Both reporting bias and patient selection bias are evident. All of the reports are relatively small retrospective case series from single centers. Patient acuity at the time of presentation is highly variable and likely represents the single largest effect on the outcome rather than the mode of treatment. Patients that present with an acute SMA embolus may have a more acute presentation and may develop bowel ischemia more rapidly. On average, there may be more of a need for bowel exploration in this group. Also in this group, surgical embolectomy likely confers a more expedient revascularization than endovascular mechanical or pharmacomechanical treatments that can be time consuming and have a higher rate of technical failure. Therefore a traditional surgical approach is favored for acute embolic presentations.

Patient acuity and the incidence of bowel ischemia are most variable in patients that present with acute on chronic or thrombotic mesenteric ischemia. It is this variability, combined with patient selection bias and such small numbers that makes it impossible to make any strong recommendations between treatment modalities for this acute on chronic group that presents with terminal mesenteric thrombosis.

Patient selection bias is most notable in reports of percutaneous endovascular interventions. Early detection and treatment before the onset of irreversible bowel ischemia is the key to patient survival. Ironically, at the opposite end of the spectrum, the patients in this group that present in the most delayed fashion, may also have improved outcomes. Because they have well developed collaterals, given the same degree of mesenteric vascular occlusion, they may have fewer symptoms and a lower incidence of bowel necrosis. Certainly the morbidity and mortality from AMI is associated with extent of bowel ischemia. Although difficult to assess based on exam, vessel involvement and laboratory tests (which tend to be non-specific), if there is low suspicion of non-viable bowel, low enough that abdominal exploration is not necessary, then and endovascular approach seems reasonable.

Recommendations

- Endovascular therapy for the treatment of AMI is not broadly applicable. (**Evidence quality: low; weak recommendation**)
- Because of the rapid degree of progression with embolic presentations of AMI a traditional operative approach with embolectomy is likely the safer approach. (**Evidence quality: low; moderate recommendation**)
- For acute on chronic presentations were there is little concern for bowel ischemia, an initial percutaneous endovascular approach is reasonable. (**Evidence quality: moderate; moderate recommendation**)
- If there is any concern about bowel viability, enough to warrant abdominal exploration then an operative bypass or hybrid ROMS procedure is the better revascularization choice. (**Evidence quality moderate; recommendation strong**)

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Chapter 20
Chronic Mesenteric Arterial Disease: Does an Endovascular/Hybrid Approach Improve Morbidity and Mortality as Compared to Open Revascularization?

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Abstract The evaluation of a patient with chronic mesenteric ischemia (CMI) can be challenging because symptoms are often unspecific and patients have advanced age and multiple comorbidities. Decision on type of intervene is based on a thorough and careful review of clinical risk, presentation and anatomical features. Advances in diagnostic imaging, medical therapy, surgical and endovascular techniques resulted in improved outcomes. During the last decade, mesenteric angioplasty and stenting gained widespread acceptance and became the most frequently utilized treatment for CMI, relegating open surgery to patients who fail endovascular therapy or have complex lesions unsuitable to it. The aim of this chapter is to review current evidence to determine if endovascular/hybrid approaches improve morbidity and mortality as compared to open revascularization for chronic mesenteric ischemia.

Keywords Mesenteric arterial occlusive disease • Mesenteric artery stents • Mesenteric artery duplex ultrasound • Chronic mesenteric disease • Superior mesenteric artery stenosis • Celiac artery stenosis

Search Strategy

A Pubmed search was performed between 1980 and 2014 using the key terms of "Chronic mesenteric" OR "Visceral" AND "ischemia", "endovascular" and "open". The comparison of published reports is difficult due to inconsistent reporting

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Table 20.1 Difficulty in Comparing Retrospective Reports of Open versus Endovascular Treatment of Chronic Mesenteric Ischemia

Small patient cohorts	Limited follow up
Variability in definition of technical success	Variable clinical presentation (acute vs chronic)
Variable patient comorbidities	Physician's treatment preference
Mixture of open revascularization (i.e. antegrade, retrograde)	Mixture of endovascular techniques (i.e. angioplasty alone vs stenting)
Different etiologies (i.e. arteritis, median arcuate, atherosclerosis)	Lack of time-dependent outcomes (i.e. patency rates, symptom recurrence, restenosis and re-intervention)

Table 20.2 PICO outline used for Pubmed search

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Patients with chronic mesenteric ischemia	Angioplasty Stenting	Open surgical revascularization	Morbidity and mortality

standards (Table 20.1). Eleven open and 21 endovascular cohort studies were identified. The data was classified using the GRADE system (Table 20.2).

Results

Clinical Presentation

The natural history of patients with symptoms of CMI is not well understood because revascularization is typically recommended. There are no cohort studies with a control or medical treatment arm, and it is generally accepted that once a patient develops symptoms of chronic ischemia revascularization is indicated, as there is considerable risk of progression to cachexia or bowel gangrene.

The most common cause of CMI is atherosclerotic disease, accounting for over 90% of cases in most series. Other non-atherosclerotic lesions such as vasculitis, dissection, fibromuscular dysplasia, radiation arteritis, mesenteric venous stenosis or occlusion, drug-induced arteriopathy, and mid-aortic syndrome can present with symptoms of mesenteric ischemia. The typical patient is female with median age of 65 years old (range 40–90 years old) [1–3]. Classic symptoms include abdominal pain, weight loss, and 'food fear', and the pain is often mid abdominal, crampy, dull, post-prandial and begins within a few minutes to 30 min after meals, persisting for as long as 5–6 h. Avoidance of certain foods, unintentional weight loss with associated malnutrition and cachexia can be common. The clinical presentation can be less specific in some patients with more vague abdominal pain, nausea, vomiting or change in bowel habits without the classic post prandial component. Previous history of smoking and the diagnoses of hypertension and hyperlipidemia are documented in

over 60–70 % with other clinical sequelae of atherosclerotic disease including coronary artery, cerebrovascular and peripheral arterial disease [2, 4, 5].

Diagnostic Imaging

Catheter-based arteriography is still considered the "gold-standard" diagnostic study for CMI, but its role has diminished over the last decade as a confirmatory and planning test [6]. Mesenteric duplex ultrasound is the most frequently utilized screening study. A negative duplex ultrasound study essentially excludes the diagnosis of mesenteric artery disease [7–12].

Cross-sectional imaging with either computed tomography angiography (CTA) or magnetic resonance angiography (MRA) is indicated in most patients to provide anatomical detail and to help exclude other causes of abdominal pain and weight loss. Although the choice of CTA or MRA is somewhat related to individual expertise at the institution, but most centers use CTA. Anatomical detail about the number of vessels affected and lesion characteristics (diameter, length, presence of occlusion, calcification, thrombus or tandem lesions) are key factors that affect selection of type of revascularization.

Indications for Revascularization

There is no role for a non-operative approach in patients with symptomatic disease. Excessive delays in proceeding with definitive revascularization or use of parenteral nutrition alone have been associated with clinical deterioration, bowel infarction and risk of sepsis from catheter-related complications [13, 14]. The indication of prophylactic revascularization in patients with asymptomatic disease remains controversial. Based on the report by Thomas et al., there may be a role for prophylactic revascularization in patients with severe three-vessel disease, particularly for those with difficult access to medical care who live in remote or underserved areas [15]. Revascularization has been advised in asymptomatic patients with severe three-vessel disease undergoing aortic reconstructions for other indications.

Choice of Open Versus Endovascular Revascularization

Treatment goals are to relieve symptoms, restore normal weight and prevent bowel infarction. The number of mesenteric revascularizations has increased 10-fold in the United States in the last decade, largely because of improved diagnosis and

decreased morbidity of endovascular therapy. Treatment selection has evolved in most centers with angioplasty and stenting surpassing open bypass as the first option in over 80 % of the patients treated for CMI [1, 2, 16]. There are no prospective randomized comparisons between the two techniques, but retrospective reviews show decreased morbidity, length of stay and convalescence time with endovascular revascularization compared to open repair [2, 17]. Mesenteric bypass offers improved patency, lower rates of re-interventions and better freedom from recurrent symptoms [1, 2, 5, 17–27].

Endovascular Revascularization

In most centers, mesenteric angioplasty and stenting is the first choice of treatment in patients with CMI who have suitable lesions, independent of their clinical risk. The ideal lesion for angioplasty and stenting is a short, focal stenosis or occlusion with minimal to moderate calcification or thrombus. The technical difficulty of endovascular procedures is increased by presence of severe eccentric calcification, flush occlusion, and in patients with longer lesions, small vessels and tandem lesions affecting branches. Although these anatomical features are not contraindications to an endovascular approach, technical result is often not optimal with higher rates of arterial complications and restenosis [28, 29].

The primary goal of percutaneous treatment is to restore antegrade flow to at least one of the three mesenteric arteries, preferentially the SMA. Although there are no prospective comparisons between angioplasty alone and primary stenting, most agree that routine stenting is indicated based on experience with renal ostial lesions, elastic recoil and higher rates of restenosis with angioplasty alone [25, 30–39]. Additionally, there are no randomized comparisons between SMA and celiac stent placement. Two retrospective studies have shown a non-significant trend towards lower recurrence rates with two-vessel stenting [40, 41], but recent reports have not shown difference in outcomes [42, 43]. Two-vessel mesenteric intervention may be indicated in patients with severe gastric ischemia who do not have good collateral network between the CA and SMA.

CA stenting should not be performed if there is active compression by the median arcuate ligament because there is risk of stent fracture and compression. However, CA stenting may be considered in higher risk patient who fail attempted recanalization of the SMA, or in those where an SMA intervention is felt to have a low yield for success due to excessive calcification or long segment occlusion. In these patients, celiac stenting may be considered a ‘bridge’ to open bypass or retrograde SMA stenting [44]. Angioplasty of the IMA in our experience carries a higher risk of rupture, dissection or embolization, and is not advised with rare exceptions.

Endovascular mesenteric revascularization carries definitive risk. The average 30-day mortality in a recent systematic review was 6 % (0–21 %), surpassing the mortality reported for other types of endovascular interventions, including aortic, renal and carotid procedures. The most common causes of death after mesenteric

stenting are cardiac events, gastrointestinal bleeding and bowel ischemia. Distal embolization occurs in 8 % of patients treated by SMA stents without embolic protection, with higher rates among patients with sub-acute symptoms, occlusion, long lesions (>30 mm) and severe calcification [45]. Therefore, selective use of embolic protection in these patients should be considered. The most commonly reported complications are access-related problems in 2–15 %, renal insufficiency in 5–12 %, acute bowel ischemia in 1–5 %, gastrointestinal bleeding in 1–4 %, cardiac events in 1–3 %, and respiratory complications in 3 %.

Open Revascularization

Mesenteric bypass has also been increasingly performed in patients who have failed a percutaneous intervention because of flush occlusion, occluded stent, or in patients with recurrent in-stent stenosis who failed multiple re-interventions. Our preference in a lower risk group has been to offer open revascularization if the anatomy is unfavorable for angioplasty and stenting or for patients with non-atherosclerotic lesions [45–48].

Contemporary reports from large volume centers have shown that mesenteric bypass can be performed with mortality rates of <3 % [2, 19, 49]. Improvements in the outcomes of mesenteric reconstructions can be attributed to several factors, including technical refinements, better patient selection and advances in medical, anesthetic and critical care management. In the first two Mayo Clinic reports from 1981 to 1992, over 50 % of the patients had three-vessel revascularization and concomitant aortic reconstruction was performed in 20–30 % of patients [50, 51]. The operative mortality was 10 % in both reports.

Reconstruction of the CA and the SMA using a bifurcated polyester graft originating from the supra-celiac aorta compromises over 80 % of open mesenteric reconstructions [2, 16, 49]. This approach is selected in lower risk patients who are not ideal candidates for endovascular treatment and have multi-vessel disease without evidence of significant supra-celiac aortic calcification or debris. Supra-celiac-origin grafts are not ideal in patients with compromised cardiac or pulmonary function or those with extensive atherosclerosis or circumferential calcification of the supra-celiac aorta. Other sources of inflow such as the infra-renal aorta or the iliac arteries are preferred in these higher risk patients [52]. Aortic reconstruction is reserved for the rare patient who needs it for an inflow source, or in whom aortic pathology necessitates repair [2]. Trans-aortic endarterectomy is rarely indicated, but may be considered in patients who failed or are not candidates for endovascular therapy and have bacterial contamination or perforated bowel, previous abdominal irradiation, extensive abdominal wall hernias, or other hostile conditions [53].

A hybrid approach using a midline laparotomy to expose the SMA and endovascular technique to place a retrograde SMA stent avoids the need for extensive dissection, vein harvesting and use of a prosthetic graft, and may be selected in patients with extensive aortoiliac disease and no good source of inflow or in those with acute

mesenteric ischemia, bowel gangrene and contamination [54–56]. This hybrid option provides one of the most expeditious methods of revascularization in patients with difficult occlusions.

Complications rates after open mesenteric revascularization average 20–40 % [1, 3, 6, 52, 57–60]. Most common problems were pulmonary (15 %), gastrointestinal (14 %), cardiac (10 %) and renal complications (4 %). Patients with severe malnutrition require perioperative nutritional support; prolonged ileus occurs in 8 % of the patients, often requiring parenteral nutrition [2]. Meticulous wound closure is important, particularly in the patient with malnutrition, due to risk of wound related complications (4–8 %). In a few patients, compartment syndrome requires abdominal decompression [2, 61]. Early graft thrombosis is uncommon (<2 %) and indicates technical problems, poor run-off or hyper-coagulable state [2]. Technical imperfections may be a cause of early graft failure after mesenteric revascularization. We have routinely performed intra-operative DUS in all patients who undergo open mesenteric and found the patients who left the operating room with a normal study had remarkably low early thrombosis (<1 %) and late re-intervention (3 %) rates [62].

Comparative Results of Open and Endovascular Revascularization

Morbidity, Mortality and Survival

Based on review of single-center reports and a systematic review, endovascular revascularization has been associated with decreased morbidity, length of stay and convalescence time [17]. Morbidity and length of stay averages 11 % and 3 days with endovascular, compared to 33 % and 14 days with open surgery [17]. Mortality rates are similar based in a recent systematic review, which indicates average 30-day mortality of 6 % (0–15 %) for open and 5 % (0–21 %) for endovascular revascularization [17]. Open surgical bypass can be performed with low mortality in good risk patients operated on institutions with large experience in these types of reconstructions [1, 23]. A recent review of 229 patients treated for CMI using clinical risk stratification showed similar mortality for open (2.7 %) and endovascular (2.4 %) revascularization [2]. Mortality was 1 % for low-risk and 6.7 % for high-risk patients treated by open bypass, with the highest mortality rate (8.9 %) in those patients who had concomitant aortic reconstructions. Nonetheless, despite the excellent results reported in large volume centers, these operations carry high mortality in the community, reaching 20 % in the State of New York and 13 % in the United States [1, 23].

Poor prognostic indicators for long-term patient survival after mesenteric revascularization include advanced age and presence of severe cardiac, pulmonary or renal disease [2, 63]. The type of revascularization has not been shown to affect survival, but comparative analysis is limited by selection bias favoring open bypass for good risk and endovascular revascularization for higher risk patients. Tallarita et al. reported long-term survival in a cohort of 343 patients treated for CMI, and

showed nearly identical 5-year survival rates using propensity matched scores for patients treated by open (57 %) or endovascular (60 %) revascularization [63]. Five-year patient survival averaged 71 % for low-risk, 49 % for intermediate-risk, and 38 % for high-risk patients. Freedom from mesenteric-related death was 91 % after open and 93 % after endovascular revascularization at 5 years. Independent predictors of any cause mortality were age >80 years, chronic kidney disease stage IV or V, diabetes and home oxygen therapy. Chronic kidney disease stage stage IV or V and diabetes were independently associated with mesenteric related death. The most common causes of late death were cardiac events, followed by cancer, respiratory complications and mesenteric-related complications. The combined rate of early and late mesenteric-related death was 8 % for patients treated by open and 6 % for those who had endovascular revascularization.

Symptom Relief

Both methods of revascularization are highly effective with average symptom improvement in 88 % of patients treated by endovascular and 93 % of those treated by open revascularization [17]. A pooled review of the literature suggests that angioplasty alone may be associated with lower rates of technical success (78 %) compared to stenting (94 and 93 %) [23]. Symptom improvement is noted immediately after revascularization, but it is not uncommon for patients to complain of modest bloating and worsening diarrhea. The presence of persistent abdominal pain suggests other diagnosis (e.g. motility disorder, irritable bowel syndrome) or inadequate revascularization.

Restenosis and Re-interventions

Most single-center reports and a systematic review indicate that open reconstructions are more durable. Bypass is associated with lower rates of restenosis, better patency, and higher freedom from recurrent symptoms or re-interventions compared to mesenteric angioplasty and stenting. Primary patency of open bypass averaged 89 % at 5 years in a recent review of the pooled literature (57–92 %) with freedom from re-interventions of 93 % [23]. A recent contemporary report by Ryer et al. indicated that open bypass has been increasingly performed in patients with more comorbidities and worse anatomy, but maintained excellent primary patency of 76 % at 5 years [6]. In the systematic review of van Petersen et al. [17], endovascular treatment was associated with increased restenosis (37 % versus 15 %), symptom recurrences (30 % versus 13 %) and re-interventions (20 % versus 9 %) when compared to open revascularization. Primary patency was lower for mesenteric stenting (51 % versus 86 %), with similar secondary patency rates (83 % versus 87 %), respectively.

Overall, endovascular treatment has been plagued by higher rates of restenosis when compared to patency rates reported for open reconstructions (Tables 20.3 and 20.4) [2, 5, 19, 20, 26, 27, 40, 41, 64–71]. There are currently no reporting standards or consensus on the definition of in-stent restenosis, which is largely based on surveillance duplex ultrasound imaging [72–74]. Most reports have included a large number of patients treated by angioplasty alone and had inconsistent reporting standards. Review of large clinical experiences have shown that primary stenting is associated with less restenosis and re-interventions [29]. The average 3-year primary patency rate for bare metal stents is 52 % (range, 30–81 %) calculated from pooled literature [23]. Clinical data on re-interventions for in-stent restenosis remains scarce. Options include balloon angioplasty with cutting or cryoplasty balloons, redo stenting with bare metal, drug-eluting or covered stents and atherectomy [75, 76].

Contemporary reports show modest improvement in primary patency at 1-year ranging from 76 to 90 % [2, 40, 41, 66]. The secondary patency rate is better than 90 %, as evidenced by reports of mesenteric re-interventions [23, 29]. Oderich et al. recently reported a nonrandomized comparison of covered versus bare metal stents in 225 patients treated for CMI [77]. Covered stents had 92 % primary and 100 % secondary patency rates at 3-years, rivaling the results of open bypass. Covered stents outperformed bare metal stents, with less restenosis, symptomatic recurrences, re-interventions, and better patency rates. These observations held fast both in primary interventions for native artery lesions, and in re-interventions for in-stent or native artery restenosis after endovascular procedures. Independent predictors of restenosis were use of bare metal stents, cigarette smoking, advanced age and female gender [77].

Recurrent symptoms of mesenteric ischemia affect approximately 10 % of patients who undergo open mesenteric reconstruction, usually from stenosis or thrombosis of one or more graft limbs [2, 19]. In these patients, a minimally invasive approach is appealing. Reoperations are technically more challenging because of scar, distal involvement and risk of damage to important collaterals. Giswold et al. reported operative mortality of 6 % and primary patency at 4 years of 62 % among 22 patients who underwent redo mesenteric revascularization [78]. Kanamori et al. showed interventions for failing mesenteric bypass grafts carried similar outcomes whether the reintervention was done endovascular or open. The entire patient cohort survival at 5 years was 60 % [79].

A Personal View of the Data

Despite the widespread acceptance of angioplasty and stenting as first line therapy for the treatment of CMI, we have maintained an individualized approach to each patient. We proceed in this manner because of the high rate of restenosis. In good risk patients, with a reasonable survival, we will offer open revascularization for the treatment of CMI. In those patients where open revascularization is not an option or have a shorter term survival, we will offer endovascular repair. We prefer the use of

Table 20.3 Endovascular outcomes of bare metal versus covered stents for mesenteric arterial occlusive disease

Author (year)	N	Vessels	Stented vessels %	Technical success	Mortality	Morbidity	Recurrence	Re-intervention	Primary patency	Follow-up Months
Bare metal stents										
Kasirajan (2001)	28	32	82	100	11	18	34	–	73 at 3 years	24
Matsumoto (2002)	33	47	32	88	0	13	15	15	–	20
van Wanroij (2004)	27	33	94	93	0	11	–	19	81 at 19 months	19
Landis (2005)	29	63	27	97	7	10	45	37	70	28
Silva (2006)	59	79	100	96	2	–	17	17	71	38
Biebl (2007)	23	40	96	–	0	4	26	22	–	10
Atkins (2007)	31	42	87	100	3.2	13	23	16	58	15
Sarac (2008)	65	87	100	–	8	31	–	31	65	12
Lee (2008)	31	41	–	98	14	6	44	10	69 at 7 years	32
Dias (2009)	43	49	100	98	0	23	12	33	–	43
Oderich (2009)	83	105	72	95	2.4	18	31	31	41 at 5 years	36
Fioole (2009)	51	60	100	93	0	4	25	22	86	25
Peck (2010)	49	66	89	100	2	16	29	29	64 at 3 years	37
Schoch (2011)	107	116	78	100	0	–	42	42	67	16
Turba (2012)	166	221	74	92	3	10	17	19	67	34

(continued)

Table 20.3 (continued)

Author (year)	N	Vessels	Stented vessels %	Technical success	Mortality	Morbidity	Recurrence	Re-intervention	Primary patency	Follow-up Months
AbuRahma (2013)	83	105	100	97	2	2	35	30	19	31
Ahanci (2013)	121	140	100	100	0.8	14	34.8	34.8	63 at 1 year	12
Oderich (2013)	156	173	80	–	6.4	–	21	21	–	64
Grilli (2014)	47	47	87	87	14.6	–	17	17	78 at 2 years	24
Covered stents										
Schoch (2011)	14	14	100	100	0	–	–	0	100	16
Oderich (2012)	42	42	100	98	0	12	10	10	92 at 3 years	19
Total	1288	1602	85	96	3.6	12.8	26.5	22.7		26.4

Table 20.4 Open surgical outcomes for mesenteric arterial occlusive disease

Author (year)	n	Vessels	Mortality %	Morbidity	Recurrence	Re-intervention	Primary Patency	Follow-up Months
Leke (2002)	17	25	6	41	0	0	100 at 34 months	34
Cho (2002)	25	41	4	–	32	20	57 at 5 years	64
Brown (2005)	33	51	9	30	9	7	100 at 6 months	34
Sivamurthy (2006)	46	66	15	46	32	12	83 at 6 months	9
Biebl (2007)	26	48	8	42	11	8	–	25
Kruger (2007)	39	67	2.5	12	5	3	92 at 5 years	39
Atkins (2007)	49	88	2	4	22	22	90	42
Mell (2008)	80	120	3.8	26	11	11	90	46
Oderich (2009)	146	265	2.7	36	6	5	88 at 5 years	36
Low risk	101	–	0.9	37	6	6	94 at 5 years	–
High risk	45	–	6.7	38	11	11	90 at 5 years	–
Concomitant aortic reconstruction	23	–	8.4	–	–	–	–	–
Rawat (2010)	52	75	13	32	15	13	81	41
Ryer (2012)	116	203	2.5	50	14	16	86 at 5 years	43
Total	629	1049	6.3	32	14	11	–	38

covered stents over bare metal stents because of the reduction in restenosis, recurrences and reinterventions. A significant weakness in this area is the fact that there is no prospective study comparing open and endovascular mesenteric revascularization techniques.

Summary of Recommendations

1. Both open and endovascular interventions are highly effective at alleviating symptoms. (**Evidence quality moderate; strong recommendation**)
2. For higher risk patients endovascular mesenteric revascularization has become a first line therapy, with excellent technical success and low perioperative morbidity and mortality, but higher rates of reintervention with bare-metal stents. (**Evidence quality moderate; strong recommendation**)
3. In good risk patients, open mesenteric revascularization is more durable, has lower rates of reintervention, but has higher perioperative morbidity and mortality. (**Evidence quality moderate; strong recommendation**)
4. In patients undergoing an endovascular approach, the use of covered stents has shown primary and secondary patency rates rivaling the results of open mesenteric bypasses. (**Evidence quality weak; moderate recommendation**)

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Chapter 21
In Patients with Mesenteric Ischemia Is Single Vessel Reconstruction Equivalent to Multiple Vessel Revascularization?

Omar C. Morcos and Tina R. Desai

Abstract Chronic mesenteric ischemia is an uncommon, but life threatening diagnosis that can be treated with open surgical or endovascular techniques. The literature examining mesenteric ischemia is comprised primarily of retrospective reviews and case series and very rarely directly addresses the issue of whether revascularization of one of the three mesenteric arteries is sufficient, or whether multivessel revascularization is required. Retrospective series in the literature support both single and multivessel revascularization when open surgery is undertaken, but most experts recommend multivessel revascularization when possible. These recommendations are based on studies showing improved symptom free survival, the serious consequences of graft failure when only one vessel is revascularized, and the desire to avoid reoperative mesenteric revascularization, which may be associated with increased morbidity. Endovascular revascularization, on the other hand, is most commonly performed to address a single vessel. These procedures are associated with less morbidity even if repeat procedures are necessary and recurrent disease can often be addressed endovascularly with relative ease compared to redo open surgery. Furthermore the morbidity of endovascular procedures is often highest when complex multivessel procedures involve extensive disease or recanalization of occlusions. Therefore addressing a single vessel, preferably the superior mesenteric artery, is preferred with these procedures.

Keywords Chronic mesenteric ischemia • Mesenteric ischemia • Surgery • Vascular surgery • Endovascular • Mesenteric bypass • Revascularization

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Introduction

Although a significant number of elderly people may have hemodynamically significant mesenteric stenosis (17.5 % based on a duplex study of 553 healthy adults), the clinical syndrome of mesenteric ischemia remains rare [1]. Based on autopsy studies, the "Mikkelsen rule" supports the concept that at least two of the three mesenteric vessels (celiac, superior mesenteric artery, and inferior mesenteric artery) must be involved to result in clinical symptoms [2]. Even when multiple mesenteric vessels are affected, the presence of symptoms depends on the collateral blood supply between the main mesenteric arteries and from additional vessels such as the hypogastric arteries.

Search Strategy

The databases searched included PubMed and the clinicaltrials.gov registry. A literature search of articles published between 1980 and 2014 was undertaken in order to identify reported data on treatment of chronic mesenteric ischemia. Search terms included in the search were "chronic" AND "mesenteric ischemia", AND/OR "revascularization", AND/OR "intervention", AND/OR "endovascular", AND/OR "surgical", OR "surgical mesenteric revascularization", OR "endovascular mesenteric revascularization". Articles were excluded if they did not address the issue of single versus multiple vessel revascularization. Twenty-two retrospective review articles and one meta-analysis were included in this review. No relevant clinical trials were identified in the clinicaltrials.gov registry.

The resulting literature examining mesenteric ischemia is comprised primarily of individual case reports, case series, and retrospective reviews, most of which include <100 patients and encompass long periods of time. There are no prospective randomized studies available but there is at least one meta-analysis, which attempts to compile more substantial patient numbers to attempt to allow conclusions regarding variables that influence outcomes. Patency data and follow up are limited and true graft failure is underestimated as many studies lack routine imaging follow up in asymptomatic patients. Data exploring endovascular repair are available over only the past two decades, and outcomes in these studies are most frequently reported in terms of technical success or short to intermediate term freedom from clinical recurrence, with very limited patency data. All the studies are inconsistent in terms of reporting of presenting clinical syndromes (acute vs. chronic mesenteric ischemia), inclusion of various pathologies (atherosclerosis vs. compression syndromes vs. vasculitis vs. aneurysmal disease), and types of operations included (bypass vs. endarterectomy vs. angioplasty vs. stenting, inflow source of bypass, configuration of bypass, and combined aortic procedures), making comparisons difficult. Furthermore, some (early) studies discuss "complete revascularization" of all affected vessels, while later studies address two vessel versus single vessel bypass.

Table 21.1 PICO table

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with chronic mesenteric ischemia	Single-vessel repair	Multi-vessel repair	Freedom from symptoms; long-term freedom from restenosis; long-term freedom from recurrence of symptoms

The current chapter will explore the literature with a focus on single versus multiple vessel revascularization for chronic mesenteric ischemia, based on all of the above literature (Table 21.1). Pathology such as aneurysmal disease, vasculitis, and arcuate ligament compression syndrome, are not included in these recommendations. Open surgical revascularization and endovascular treatment of chronic mesenteric ischemia will be considered separately.

Results

Open Revascularization

Multivessel revascularization is generally recommended for patients who are undergoing open surgical revascularization for symptomatic chronic mesenteric ischemia (Table 21.2). This can be accomplished via antegrade bypass originating from the supraceliac aorta to the celiac and superior mesenteric arteries, retrograde bypass to multiple mesenteric vessels originating from the infrarenal aorta or iliac artery, or transaortic endarterectomy.

Improved patency and freedom from recurrent symptoms with multivessel revascularization has been demonstrated directly and indirectly in several nonrandomized case series. Early experience from the Mayo Clinic was described by Hollier et al. who reported a 20 year experience with operation for chronic mesenteric ischemia [3]. They noted a 50 % recurrence rate when one of the three mesenteric arteries was reconstructed, compared to an 11 % recurrence rate if all diseased vessels were reconstructed. Recurrence correlated inversely with number of visceral arteries that were revascularized. A subsequent study described a later experience from the same institution and confirmed these findings. This study included antegrade bypasses (of which there were none in the Hollier study) and found improved graft patency and patient survival in those undergoing three vessel repair compared to those who had two or one vessel repair (patency, 94 % vs. 54 % vs. 0 % for three, two, and one vessel revascularization; survival, 73 % vs. 57 % vs. 0 %) [4]. This study, like the earlier Mayo Clinic experience, defined symptomatic graft failure as the endpoint, so the true patency data are not known.

Another study of 85 patients with open mesenteric revascularization from Cleveland Clinic also confirmed improved outcomes with "complete" revascularization

Table 21.2 Summary of open surgical interventions for chronic mesenteric ischemia

Reference	Intervention	Comparison	Endpoint	Result	Recommendation
Hollier et al. [3]	Three vessel reconstruction	Single vessel reconstruction	Symptomatic graft failure	11 % vs. 50 %	Multivessel revascularization
McAfee et al. [4]	Three vessel reconstruction	Single vessel reconstruction	Symptomatic graft failure	94 % vs. 0 %	Multivessel revascularization
Mateo et al. [5]	All affected vessels	"Incomplete" reconstruction	Death from mesenteric ischemia	All patients who died from mesenteric ischemia had "incomplete" reconstruction	Multivessel revascularization
Schneider et al. [6]	Nonrecurrent	Recurrent mesenteric ischemia	Number of vessels revascularized at original operation	1.9 vs. 1.5 (# vessels reconstructed at initial operation less for recurrent group)	Multivessel revascularization
Parmeshwarappa et al. [7]	Single vessel reconstruction		Restenosis	33.3 %	Single vessel Revascularization
Oderich et al. [8, 9] (metaanalysis)	Multivessel reconstruction	Single vessel reconstruction	Recurrent symptom Restenosis	5 % vs. 14 % 5 % vs. 8 %	No recommendation
Park et al. [10]	Multivessel reconstruction	Single vessel reconstruction	Graft patency Recurrent symptom	NS NS	Single vessel Revascularization
Oderich et al. [8, 9]	Multivessel reconstruction	Single vessel reconstruction	patency	NS	Multivessel revascularization
Gentile et al. [11]	Single vessel reconstruction	None	Graft patency Survival	89 % (4 years) 82 % (4 years)	Single vessel revascularization
Foley et al. [12]	Single vessel reconstruction	None	Graft patency Survival	79 % (9 years) 61 % (5 years)	Single vessel revascularization

compared to "incomplete" [5]. In this review, 25 % of patient had all affected mesenteric vessels treated while 75 % had "incomplete" revascularization. This study attempted to evaluate recurrence in terms of both symptoms as well as objective evaluation of patency by Duplex ultrasound, CT angiography, or intra arterial angiography with 64 % of their patients having at least one of these studies in the postoperative period. They noted that all patients who died from mesenteric ischemia in the follow up period had "incomplete" revascularization and more patients with "incomplete" revascularization had recurrent symptoms at 5 years and had a lower overall survival rate. However, this improvement in freedom from symptoms and survival came at an expense of increased perioperative complications.

In a study of redo mesenteric bypass, Schneider noted that significantly fewer vessels were revascularized at the original operation in patients who were undergoing reoperation for recurrent mesenteric ischemia compared to a nonrecurrent group [6]. A small recent study reporting single vessel revascularization noted that three of nine patients developed restenosis or graft stenosis in the follow up period [7]. And finally, Oderich attempted a meta-analysis of combined data available in the literature and found a 14 % symptom recurrence rate with single vessel reconstruction compared to 5 % when multiple vessels were reconstructed [8]. This type of analysis is clearly limited by the differences in patient population, operation types, and endpoints reported in the various included studies.

Several additional studies have examined whether multivessel revascularization results in better patency and freedom from symptoms without finding a clear difference in outcomes. Park and colleagues reevaluated the Mayo Clinic experience in 2002 [10], and found no difference in patency or symptom free survival based on number of vessels revascularized. However, their series included a minority of single vessel revascularizations (19/98 patients). They continued to recommend multivessel revascularization based on equivalent results, to achieve a "margin of safety" in these challenging patients. Kruger also found no difference in patency between single and multivessel revascularization, but continued to recommend multivessel reconstruction based on the nature of outcomes when single vessel grafts occluded [13].

Several authors, including two series from the Oregon group, continue to support single vessel mesenteric revascularization. An earlier study by Gentile et al. demonstrated 89 % graft patency and 82 % survival rates at 4 years with single vessel reconstruction [11]. Foley and colleagues reported a later experience from the same group, continuing to support single vessel revascularization with a 9 year primary assisted patency rate of 79 % and 5 year patient survival rate of 61 % [12]. However, almost half of the patients included in this series had acute mesenteric ischemia, which represents a different circumstance than a chronic presentation.

Additional indirect data supporting multivessel revascularization can be extrapolated from studies examining open surgical versus endovascular procedures for chronic mesenteric ischemia. Kougias and colleagues examined surgical and endovascular mesenteric revascularization. They found significantly better freedom from recurrent symptoms in the surgical revascularization group, 64 % of which had two vessel reconstruction, compared to the endovascular group, 21 % of which had two vessel reconstruction. They attributed the improved outcomes of the surgical group

to higher incidence of two vessel revascularization [14]. Oderich noted better patency with open revascularization (77 % of whom had multiple vessels treated) compared to an endovascular approach (75 % of whom had a single vessel treated) [9]. However, when they examined single versus two vessel revascularization separately in the open and endovascular groups, they were not able to find a significant difference, potentially due to the limited number of patients in the groups. Kasirajan found similar patency but greater recurrence of symptoms in patients treated via an endovascular approach compared to open surgery [15]. Again, the patients in the endovascular group had fewer vessels treated per patient compared to the open surgical group (1.1/patient vs. 1.5/patient), indirectly supporting multivessel reconstruction.

Another rationale supporting multivessel reconstruction is the idea that the consequences of graft occlusion of one of multiple revascularized vessels may not be as severe as if a single graft occludes in patients who typically have multivessel disease. Based on the principle that at least two mesenteric vessels must be diseased to result in symptoms, maintaining patency of one of two reconstructed vessels may be sufficient and provide a "margin of safety" as Park and colleagues have advocated [10]. They noted that symptoms only occurred if both limbs of a bifurcated graft became stenotic or occluded or if a single graft to the SMA developed recurrent disease. In 7 patients with stenosis in one of multiple vessels revascularized, no symptoms occurred. Kruger also noted that patients with multivessel reconstruction in whom only one vessel developed recurrent disease did not manifest symptoms, whether this occurred in the acute postoperative setting or in long term follow up [13].

The type of symptom presentation with recurrent disease may also differ depending on whether single or multiple vessel revascularization is utilized. Occlusion or stenosis of a single revascularized vessel in the setting of typical multivessel disease may be more likely to result in acute symptoms, which are commonly fatal. In the original Oregon experience, two of three patients with late graft failure after a single vessel revascularization died [11]. Similarly, in Mateo's series from the Cleveland Clinic, all patients who died from mesenteric ischemia were ones who had undergone "incomplete" revascularization [5]. Giswold reports another series of patients with recurrent mesenteric ischemia after an original single vessel mesenteric bypass of which almost half presented with acute symptoms [16]. Certainly, recurrence of disease in the absence of mesenteric ischemia symptoms, or at the least, avoidance of acute mesenteric ischemia presents a more manageable situation than acute symptomatic recurrence, and in this situation, redo procedures may not be necessary at all, or can be attempted minimally invasively.

Initial multivessel revascularization may help to avoid subsequent redo mesenteric bypass by improving patency or preventing symptoms in the setting of recurrent disease. While some of the patients with recurrence may be able to be managed minimally invasively with an endovascular approach, many patients with recurrence will require reoperation due to the location and severity of the disease. Reoperation for mesenteric ischemia is a more difficult operation that is associated with significant morbidity and mortality. While several studies of reoperation for mesenteric ischemia have been unable to find a significant difference in morbidity and mortality compared to initial operation, these series had very limited numbers (under

50 patients). Most of them failed to take into account the group of one third to one half of the patients who presented with acute symptoms, which was almost universally fatal [6, 16, 17].

The evaluation of multivessel versus single vessel operative revascularization is further limited by confounding technical variables. Variable sources of inflow are included in all of the studies reported in the literature. Although inflow source has not been shown to be important in determining patency, most antegrade bypasses tend to include two vessels (celiac and SMA) rather than single vessel retrograde SMA bypass from the infrarenal aorta or iliac artery. Similarly, transaortic endarterectomy better lends itself to multivessel revascularization. These variations in anatomic approach may be important in the determination of outcomes in addition to simply whether one or two vessels are reconstructed.

There are specific circumstances in which single vessel reconstruction is advocated. Reoperation for chronic mesenteric ischemia is a technically more difficult procedure involving previously dissected mesenteric vessels and the need for additional exposure with potential for increased morbidity. Giswold has advocated single vessel bypass in this situation to limit operative time and bleeding [16]. It is important to confirm the adequacy of collateral flow to mesenteric vessels which are not revascularized if single vessel reconstruction is being considered. Although not within the scope of this chapter, most authors recommend single vessel revascularization of the SMA in the treatment of acute mesenteric ischemia where rapid revascularization and limitation of operative time are crucial in the treatment of critically ill patients.

Endovascular Revascularization

Historically, the mainstay of treatment of chronic mesenteric ischemia has been via open surgical techniques. However, recent experience with endovascular interventions has led to a change in treatment paradigm. Endovascular treatment of mesenteric ischemia was first described in 1980 [18] and has allowed treatment of patients deemed to be too high risk for surgical revascularization. Over the last decade there has been a threefold increase in the treatment of CMI, largely due to endovascular interventions [19]. Early data with endovascular treatment are difficult to interpret because the patients initially selected for this type of intervention were limited to high risk patients who could not undergo open surgery, contributing to the modest results initially noted. Over time, relatively healthier patients have undergone first line treatment with endovascular stenting attributable to reasonable treatment outcomes [20–22] and reduced morbidity and mortality [19]. By 2005, endovascular treatment for CMI exceeded the number of open surgical revascularizations [19].

Even with recent growth of the endovascular experience in mesenteric ischemia, evaluation of single versus multivessel endovascular revascularization is difficult, with very limited retrospective studies and with relatively short follow up, varying definition of outcomes, and no consistent objective evaluation of patency using

noninvasive or invasive imaging techniques. Single vessel revascularization is more commonly utilized with endovascular procedures. The importance of the superior mesenteric artery in the mesenteric circulation is well established and success rates (usually defined as resolution of symptoms) with isolated endovascular revascularization are very high with relatively low morbidity [23]. There is, furthermore, no conclusive level I evidence available to date to suggest that single vessel revascularization of the superior mesenteric artery is inferior to revascularization of two mesenteric arteries [24, 25]. Most data (Table 21.3) consists of single institution retrospective reviews showing that periprocedural morbidity is low (0–18 %) and patency of 30–90 % at 2 years has been reported [21, 22, 25]. In the study by the Matsumoto group, the primary assisted long term clinical success rate was 97 %. However, this group did not treat total occlusions, instead focusing on stenosis alone. There was no difference in clinical success rates between patients who had more than one vessel treated when compared with patients who only had one vessel treated. The Steinmetz group stented less than half of the target lesions and primarily used angioplasty alone, likely accounting for their lower long term patency. Several additional retrospective studies have shown no difference in patency with stenting of one versus two mesenteric vessels [9, 23, 26]. Oderich et al. demonstrated identical freedom from symptoms at three years (57 %) between patients with one vessel versus two vessel revascularization. Fioole's group had over 90 % initial success rate and 60 % primary patency rate at 2 years. Aburahma's group reported freedom from recurrent symptoms at 5 years of 65 %.

Other retrospective data have supported two vessel endovascular intervention, with improved freedom from recurrent symptoms or reintervention [27]. The cohort was small, however, and only 35 % of patients in this study (17 patients) had two vessels treated simultaneously. Unfortunately, many of the studies addressing one versus two vessel interventions have numerous confounding factors such as use of angioplasty versus stenting, use of covered versus uncovered stents, and recanalization of occluded versus stenotic vessels, that make conclusions regarding the benefit of one versus two vessel revascularization very difficult.

The overall limited morbidity and relatively low surgical stress of endovascular interventions on patients renders repeat interventions more hospitable than with open surgical repair. Limiting the time and extent of a procedure in such a sick patient population may help contribute to improved outcomes with interventions being performed on additional vessels as needed at a later date. Additionally studies, such as Oderich's experience, have shown good outcomes even in patients who develop restenosis after single vessel endovascular revascularization, with all patients experiencing a resolution of symptoms and with no mortalities after a repeat intervention [9]. While repeat access of the circulation is relatively straightforward from an endovascular approach, multivessel endovascular procedures may present significant technical challenges such as attempting to cross an occlusion or intervening on an inferior mesenteric artery, which is prone to dissection of the vessel wall. Limiting procedures to the most important vessel and/or most straightforward revascularization may be able to limit morbidity while improving symptoms. This rationale supports the recommendation for single vessel stenting as a subsequent

Table 21.3 Summary of endovascular interventions for chronic mesenteric ischemia

Reference	Intervention	Comparison	Endpoint	Result	Recommendation
Aburahma et al. [23]	One or two vessel stenting	Historical open revascularization	Patency or symptom recurrence	83 % freedom from symptoms at 1 year	Single vessel revascularization (equivalent outcomes)
Fioole et al. [26]	One or two vessel stenting	None, retrospective review	Patency or symptom recurrence	86 % primary patency at 1 year	Single vessel revascularization
Matsumoto et al. [21]	One or two vessel angioplasty or stenting	None	Patency or symptom recurrence	83 % at 20 months	No recommendation
Oderich et al. [8, 9]	One vessel revascularization	Multivessel revascularization	Patency or symptom recurrence	5 % vs. 14 %	No recommendation
Peck et al. [27]	One or two vessel revascularization	None	Patency	61 % at 36 months	No recommendation
Rose et al. (1995)	One or two vessel revascularization	none	Patency	67 % at 9 months	No recommendation
Sarac et al. (2008)	Occluded vessel	Stenotic vessel	Patency or symptom recurrence	65 % at 1 year	No recommendation (but no difference in outcomes between one or multivessel)
Sharafuddin et al. [22]	One or two vessel revascularization	none	Patency	92 % at 6 months	No recommendation

procedure (either on another mesenteric vessel or a repeat intervention on the same vessel), if necessary, can be accomplished with relatively low morbidity.

Recommendations

In conclusion, the literature examining single vessel versus multivessel revascularization via open and endovascular techniques is limited to retrospective studies with differing endpoints, and numerous confounding variables. Two vessel revascularization (including the superior mesenteric artery) is recommended for chronic mesenteric ischemia with multivessel involvement in patients undergoing open surgical repair. With endovascular interventions, repeat procedures are not associated with the same increased morbidity, and technical aspects of recanalization of occlusions or extensive stenosis may be difficult, supporting single vessel intervention first. Additional or recurrent lesions can be addressed at a future time if necessary.

Recommendations

- Two vessel repair (including the superior mesenteric artery) is recommended for patients with multivessel involvement undergoing open surgical repair (**Evidence quality poor; Strength of recommendation: weak**).
- Single vessel revascularization is preferred for patients undergoing operation for acute mesenteric ischemia or redo operations. (**Evidence quality poor; Strength of recommendation: moderate**)
- Single vessel repair is recommended for patients undergoing endovascular repair. Repeat procedures, if needed, can be addressed at a future time (**Evidence quality poor; strength of recommendation: weak**).

A Personal View of the Data

The literature examining single versus multiple vessel revascularization for mesenteric ischemia is limited to case reports, case series, and retrospective reviews. There are no randomized prospective trials. The studies examining open revascularization are somewhat more robust than those evaluating endovascular procedures. Overall, the literature is divided in its recommendations, and authors report acceptable results with both types of reconstruction. This results in recommendations which are largely based on personal experience and indirect rationale.

Like most vascular surgeons, presentation with chronic mesenteric ischemia is infrequent in our practice. We generally choose multivessel revascularization for open revascularization because of equivalent results, and the desire to avoid redo operations or consequences of bypass graft failure of a single graft. On the other hand, endovascular interventions may be associated with increasing complications

when multiple or occluded vessels are addressed. Since repeat endovascular procedures are more approachable, the strategy of addressing one mesenteric is generally employed with endovascular interventions.

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Chapter 22
In Patients with Celiac Artery Compression Syndrome, Does Surgery Improve Quality of Life?

Grace Zee Mak

Abstract Symptomatic celiac artery compression is a controversial diagnosis that should be considered in patients with chronic abdominal pain of unknown etiology despite an extensive medical evaluation. Once suspected, patients should undergo screening mesenteric duplex. Diagnosis is confirmed with the findings of elevated celiac artery velocities which normalize with respiration followed by CT angiogram showing the typical "J-hook" conformation of the celiac artery. Patients should then undergo evaluation by a multi-disciplinary team to appropriately select patients for surgical treatment. Surgical options include release of the median arcuate ligament, with or without neurolysis of the celiac nerve plexus, and with or without concomitant revascularization procedures. Approaches can be open, laparoscopic, robotic, or retroperitoneal. Surgical treatment has an overall success rate with 70–80 % patients reporting improved abdominal pain and quality of life. Post-operatively, patients can have persistent or recurrent abdominal pain and should undergo re-evaluation for possible need for revascularization procedure for stenosis of the celiac artery or celiac plexus block if the celiac artery is normalized. Additionally, some of these patients will have persistent pain consistent with a functional gastrointestinal disorder that will then require medical management.

Keywords Celiac artery compression • Median arcuate ligament syndrome • Surgical release of median arcuate ligament

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Introduction

Celiac artery compression has been the source of much controversy since Lipshutz originally described the anatomic anomaly in 1917 followed by description of the association with digestive symptoms by Harjola (1963) and Dunbar (1965) [1, 2]. Classically, it has been described as compression at the origin by the diaphragmatic crus, or median arcuate ligament, most pronounced during expiration. This arterial compression is thought to lead to a "steal phenomenon" and foregut ischemia causing abdominal pain [1, 3, 4]. The periaortic ganglia and celiac plexus are also thought to be overstimulated leading to splanchnic vasoconstriction and ischemia further worsening the symptoms. Some postulate disruption of neuro-enteric pain pathways affecting visceral hypersensitivity mediated through the celiac ganglia [1, 3]. The classic presenting symptoms consist of post-prandial epigastric pain, nausea, and weight loss as well as the presence of an epigastric bruit increased with expiration [5]. There have also been reports of severe abdominal pain and diarrhea following exercise in well-trained athletes [3, 6, 7].

Significant controversy exists as to the true existence of this syndrome. Proponents of the syndrome attribute the symptoms to both ischemia from celiac artery compression as well as hypertrophy of the celiac nerve plexus and associated neuropathy. Histologic changes (intimal hyperplasia, elastic fiber proliferation, and disorganization of the adventitia) in the arterial wall of the celiac artery have been described in patients with celiac artery compression as well [8]. Classically, it was believed that gastrointestinal ischemia only occurred when two of the three major intestinal vessels were involved; however, many no longer support this notion and now believe that gastrointestinal ischemia is multifactorial in nature including a neurologic component [1, 4, 9]. However, opponents of the syndrome cite the incidental findings of elevated velocities and celiac artery compression with no associated symptoms as well as previous reports of inconsistent symptom improvement following surgical release [1, 4, 9].

Given this controversy, symptomatic celiac artery compression is generally considered to be a diagnosis of exclusion. Mesenteric duplex findings consist of elevated velocities of the celiac artery with normalization during deep inspiration as the ligament moves more inferiorly releasing the compression. Angiography and CT angiogram images demonstrate the classic "J-hook" conformation at the origin normalized during inspiration. With the advent of more minimally invasive, rapid, high definition, and accurate imaging modalities, this diagnosis is being made with increasing frequency [3].

Given the poorly understood pathophysiology, there has been debate regarding whether surgical treatment is indicated at all and also the exact surgery to be performed. Surgical options consist of [1] division of the ligament releasing the compression of the celiac artery at its origin [2]; with or without neurolysis of the celiac plexus, and [3] revascularization of the celiac artery either using endovascular or bypass techniques during the original procedure or at a later date. Current surgical therapy consists of open, laparoscopic, and robotic techniques. Regardless of the approach utilized, the general surgical principles are unchanged.

Many retrospective reviews have been published describing the surgical techniques and their safety, but no prospective randomized controlled studies have been performed. Thus, we can only evaluate the outcomes following surgical release of the compression and its effect on abdominal pain and overall quality of life.

Search Strategy

Literature search of English language publications was performed extending from 2006 to 2014 to identify published data on the surgical treatment of celiac artery compression in both adults and children utilizing the PICO outline shown in Table 22.1. The following databases were searched: PubMed, SUM search, and Cochrane Evidence Based Medicine.

Search words included "celiac artery compression", "celiac artery compression syndrome", "celiac artery compression surgery", "celiac artery compression syndrome surgery", "median arcuate ligament", "median arcuate ligament syndrome", "median arcuate ligament surgery", and "median arcuate ligament syndrome surgery", "Dunbar syndrome", "Dunbar syndrome surgery", and "celiac band compression".

Articles not specifically addressing the surgical treatment of celiac artery compression as well as case reports of only one or two patients were excluded. There were no studies comparing operative to non-operative management in celiac artery compression, and no randomized control trials were found. Fifteen retrospective reviews and five review articles were included in the analysis. The data was classified using the GRADE system.

Results

Pre-operative Predictors of Surgical Outcome

Given the findings of asymptomatic celiac artery compression and the multitude of causes for abdominal pain, it is crucial that patients are evaluated for all possible etiologies of abdominal pain prior to being diagnosed with celiac artery compression. There has currently been very little published with specific protocols for diagnosis. Mak et al. reported the use of a specific diagnostic protocol. Complete medical evaluation should include blood work (CBC, chemistry panel, liver function tests, amylase, lipase,

Table 22.1 PICO table for surgical treatment of celiac artery compression

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with symptomatic celiac artery compression	Surgical therapy	Patients with persistent symptoms	Relief of pain and other symptoms, Improved quality of life

erythrocyte sedimentation rate, C-reactive protein, prealbumin, thyroid function tests), upper GI, small bowel follow-through, abdominal ultrasound, upper endoscopy with biopsy, and evaluation for inflammatory bowel disease and celiac disease. Patients are then screened with mesenteric duplex. Positive findings consist of peak systolic velocities (PSV) in the celiac artery greater than 200 cm/s and an end diastolic velocity (EDV) greater than 55 cm/s. Further demonstration of a decrease in PSV with deep inspiration is suggestive of celiac artery compression. El-Hayek et al. utilized similar diagnostic criteria of PSV >200 cm/s in both inspiratory and expiratory phases [8]. Sultan et al. used these criteria as well as retrograde flow within the hepatic artery (100% predictive of severe celiac stenosis or occlusion) [1]. Patients then undergo CT angiogram to evaluate the conformation of the celiac artery in both inspiratory and expiratory phases [3].

Once the diagnosis is confirmed, it is crucial that patients are evaluated for proper patient selection for surgical intervention. Patient characteristics reported to be predictive of successful outcomes following surgery include post-prandial pain, age from 40 to 60 years, and weight loss of 10 kg or greater. Factors predictive of persistence of symptoms following surgery include atypical pain, periods of remission, age over 60 years, history of psychiatric or alcohol abuse, and weight loss of less than 10 kg [3, 6, 8, 10, 11].

Additionally, Mak et al. reported incorporating psychiatric and chronic pain service in the pre-operative and post-operative evaluations given the correlation between chronic physical pain and psychological pain. Pre-operatively, all patients are evaluated by a multi-disciplinary team consisting of general and vascular surgery, psychiatry, and pain service. This team then discusses each patient, and surgery is not considered until the patient has been unanimously cleared by the entire team [3].

Mensink described the "gastric exercise test" to detect gastrointestinal ischemia. Before, during, and after 10 min of exercise, gastric tonometry was performed measuring gastric and arterial PCO_2. Positive results were defined as gastric-arterial PCO_2 gradient >0.8 kPa after exercise, increase in gastric PCO_2 from baseline to peak exercise, and an arterial lactate level <8 mmol/L. Following surgical release of the celiac artery compression, repeat tonometry was performed at 3 and 6 months. All patients who were symptom-free post-operatively had normalized tonometry results while only 25% of patients with persistent symptoms showed normalized results. While this is not a single test that can predict success, it is an additional test to add to one's armamentarium during the evaluation for surgical candidacy [5, 8, 12].

Surgical Technique

Published techniques for the surgical release of celiac artery compression consist of open, laparoscopic, and robotic procedures (all of which have been shown to be safe and effective). The general principles and goals of the procedures are similar – division of the median arcuate ligament including overlying lymphatics and soft tissue to release the celiac artery with or without division of the celiac nerve plexus. Some use intra-operative duplex to verify adequate release while others determine

adequate release by conformational change of the celiac artery. While there is debate regarding performance of celiac artery revascularization procedures concomitantly with the release or at a later date if symptoms recur, there is a general consensus not to perform endovascular stenting of the celiac artery pre-operatively as these stents generally fail due to external compression from the median arcuate ligament [1, 4, 5, 13]. One novel approach was described by van Petersen in which retroperitoneal endoscopic lysis of the median arcuate ligament was performed with similar safety and success rates [14].

Surgical Outcomes

The data that currently exists regarding the efficacy of surgery is quite limited with relatively short follow-up. The literature mostly consists of retrospective reviews consisting of relatively small case numbers [1–5, 7, 8, 11, 13–20]. Overall, reviews have found generally good outcomes following surgical treatment including release of the ligament (laparoscopic and open), neurolysis, and celiac artery revascularization with the majority of studies showing improved post-operative abdominal pain. Average success rate of being symptom-free following surgical intervention is reported to be 70–80 % [15, 16]. Table 22.2 summarizes the findings of retrospective reviews evaluating the efficacy of surgical treatment for celiac artery compression [1–5, 7, 8, 11, 13, 14, 17–20].

One of the few larger published series by Mak et al. consists of 46 pediatric cases treated by laparoscopic release of the median arcuate ligament. The success rate was reported to be 83 % with improved abdominal pain and quality of life. Post-operatively, a total of six patients required additional procedures due to persistent abdominal pain and nausea (two celiac plexus nerve blocks, two angiographies with angioplasties, one open aortoceliac bypass, and one local block at previous umbilical port incision). Of these six patients, four still reported no improvement in abdominal pain. One of the limitations of this study was the poor compliance in completing the post-operative quality of life surveys. This improved later in the study but led to poor long-term follow-up data for the initial patients [3]. The second large published series by van Petersen consisted of 46 patients who underwent retroperitoneal endoscopic release of the median arcuate ligament. They reported a success rate of 89 % with 30 patients reporting no symptoms at follow-up and 11 patients reporting clear improvement of symptoms [14].

Post-operative morbidity was minimal and self-limited in the literature. Morbidity is listed in Table 22.2 [1–5, 7, 8, 11, 13, 14, 17–20]. Some patients did have self-limiting diarrhea immediately post-operatively due to the celiac sympathectomy [1].

For those patients with recurrent or persistent abdominal pain, they are re-evaluated for possible restenosis of the celiac artery either due to formation of an intravascular web or the inherent conformation of the celiac artery. These patients often require revascularization procedures either via endovascular or open approaches. Additionally, there are some patients that will have normalization of their velocities, thus indicating,

Table 22.2 Comparison of studies of operative treatment for symptomatic celiac artery compression

Study	Pts	Operative procedure performed	Post-operative results							Quality of evidence
			Pts lost to follow-up	Complete resolution of abdominal pain	Partial resolution of abdominal pain	Overall satisfaction	Quality of life	Follow-up	Overall morbidity	
El-Hayek et al. [8]	15	Laparoscopic/ robotic release (2 pt underwent re-vascularization)	3	9/12 (75 %)	2/12 (17 %)	100 %	–	15.4 months (mean)	–	Retrospective review (low)
Sultan et al. [1]	11	Open release with celiac sympathectomy (3 pt underwent re-vascularization)	0	8	1	–	–	60 months (mean)	1 (30 day) acute renal failure, chest infection	Retrospective review (low)
Cienfuegos et al. [5]	7	Laparoscopic release	–	2/3	1/3	–	–	6 months–8 years	–	Retrospective review (low)
Mak et al. [3]	46	Laparoscopic release (3 pt underwent re-vascularization)	15	31/46 (67 %)		–	Overall improved (15/18 pt)	1.5–34.7 months	4 (fullness in chest requiring esophageal dilation in 2, pancreatitis in 1, pain at umbilical port site in 1)	Retrospective review (low)
Tulloch et al. [17]	14	Laparoscopic/open release with celiac sympathectomy (3 pt underwent re-vascularization)	0	13		–	–	2–65 months	1 with splenic infarction from embolization	Retrospective review (low)

Roseborough et al. [4]	15	Laparoscopic/open release with celiac sympathectomy (6 pt underwent re-vascularization)	0	9	5	–	–	–	1 with gastroparesis requiring Jtube, 1 with chronic pancreatitis	Retrospective review (low)
Kohn et al. [7]	6	Laparoscopic/open release with celiac sympathectomy	0	5 (83 %)	1 (16.7 %)	100 %	–	48.6 months (mean)	0	Retrospective review (low)
Baccari et al. [13]	16	Laparoscopic/open release with celiac sympathectomy (2 pt underwent re-vascularization)	0	16	0	–	–	28.3 months (mean)	–	Retrospective review (low)
Berard et al. [2]	11	Laparoscopic/open release with celiac sympathectomy (1 pt underwent re-vascularization)	0	8	1	–	–	34 months (mean)	–	Retrospective review (low)
Nguyen et al. [18]	5	Laparoscopic release	0	5	0	–	–	1–56 months	–	Retrospective review (low)

(continued)

Table 22.2 (continued)

Study	Pts	Operative procedure performed	Post-operative results							Quality of evidence
			Pts lost to follow-up	Complete resolution of abdominal pain	Partial resolution of abdominal pain	Overall satisfaction	Quality of life	Follow-up	Overall morbidity	
Grotemeyer et al. [19]	18	Open release (11 pt underwent re-vascularization)	3	11 (73.33 %)		–	–	40.68 months (mean)	Redo laparotomy in 3 pt, 2 pt with neurologic symptoms, 1 pt with pancreatitis	Retrospective review (low)
Joyce et al. [11]	6	Laparoscopic release	0	–	–	–	6	13 months (mean)	none	Retrospective review (low)
Do et al. [20]	16	Laparoscopic/ robotic release with celiac sympathectomy	0	10	1	–	–	1–85 months	–	Retrospective review (low)
van Petersen et al. [14]	46	Retroperitoneal endoscopic/open release (6 pt underwent re-vascularization)	0	30 (65 %)	11	–	–	2–42 months	–	Retrospective review (low)

that they have chronic functional abdominal pain. Mak et al. published a protocol for those patients with persistent symptoms. Repeat duplex ultrasound is first performed. Patients with significantly elevated velocities as well as continued respiratory variation then undergo angiography with possible angioplasty. In those patients with normalized celiac artery velocities, repeat CT angiogram is performed to evaluate for intra-abdominal pathology following surgery. If the CT is normal, patients are offered celiac plexus nerve block by anesthesia and are counseled that they may have functional abdominal pain [3]. Similar treatment algorithm was published by Duffy et al. in 2009 [21].

All the reviewed studies reported high patient satisfaction following surgical release. Though there are some patients in each study that reported no change in post-operative abdominal pain, the great majority reported at least some resolution of abdominal pain symptoms as well as overall patient satisfaction of the procedure. Even some patients who did not have complete symptomatic relief reported that they would undergo the surgery again [8].

Recommendations

Given the small case numbers and lack of randomized controlled trials, it is impossible to determine any true guidelines for diagnosis, selection of appropriate surgical candidates, or the best surgical approach. We can only develop recommendations based on the known literature.

Patients should first undergo complete medical evaluation prior to being diagnosed with celiac artery compression. Once all other diagnoses have been excluded, patients should undergo mesenteric duplex screening. If the celiac artery PSV is greater than 200 cm/s and normalizes with deep inspiration, patients should then undergo CT angiogram to evaluate the conformation of the celiac origin. Patients should then undergo evaluation by the multi-disciplinary team including general surgery, vascular surgery, psychiatry, and pain service to determine their suitability/eligibility for surgery. Patients should only undergo surgical release if they are unanimously cleared for surgery by this multi-disciplinary team. The appropriate patient selection to undergo this surgery is absolutely crucial.

Surgery should then be performed by an experienced team to ensure that the surgery is safe, adequate, and effective. The exact surgery performed can be release of the median arcuate ligament alone, combined with neurolysis, or combined with revascularization procedure. The celiac artery velocities should normalize with no respiratory variation seen on intra-operative duplex. Most patients will experience an improvement in their abdominal pain as well as overall quality of life. However, there will be a small group of patients that either do not improve or develop recurrent pain following surgery.

Initially, these patients should be re-evaluated with repeat mesenteric duplex. If the celiac velocities are elevated, they should undergo angiogram with possible angioplasty. Some patients may require multiple balloon angioplasties or even bypass reconstruction due to the formation of webs within the vessel or stenosis of

the vessel due to remodeling of the vessel from chronic compression. Those with normal celiac artery velocities should first undergo CT abdomen and pelvis to ensure the pain is not due to post-operative complications. If this is negative, they are referred to anesthesia for celiac nerve plexus blocks and may have functional GI disorder requiring medical management.

It is imperative that an algorithm be followed for not only initial evaluation of these patients but also the surgical procedure and post-operative management particularly for the later management of recurrent abdominal pain. The multidisciplinary approach and management is extremely important throughout the entire clinical course from initial consultation to the post-operative management.

A Personal View of the Data

In patients with chronic abdominal pain of unclear etiology despite an extensive evaluation, the diagnosis of celiac artery compression syndrome should be considered. Diagnosis requires both elevated celiac artery velocities and normalization with inspiration on mesenteric duplex as well as "j-hook" conformational change seen on CT angiogram. Once diagnosed, patients should be evaluated by a multidisciplinary team. Selecting the appropriate patients to undergo surgical treatment is absolutely crucial. Developing a plan as a multi-disciplinary team entails not only the decision to proceed with surgery but also the pre-operative preparation, immediate post-operative care, and long-term follow-up. Of critical importance is appropriately managing patient and family expectations. There should be complete candor that surgical release has been reported to be successful in 65–80 % patients with improved abdominal pain and quality of life, and that there is a possibility of persistent post-operative pain.

Adequate surgical treatment requires meticulous technique to ensure complete release of the ligament so that the end result is not only a normal appearing conformation of the celiac artery from the ostia to the bifurcation but also a normalization of celiac artery velocities with no respiratory variation as well as an adequate neurolysis dividing the celiac nerve plexus. It is imperative that the surgical team has adequate general surgery and vascular expertise. The combination of minimally invasive surgical expertise as well as the vascular surgery expertise allows for a safe, effective procedure. Intra-operative duplex capabilities have allowed our group to more effectively ensure adequate lysis.

Long-term follow-up is extremely important as patients can have recurrent pain. When this occurs, it is also crucial to have a treatment algorithm including repeat mesenteric duplex, CT angiogram, angiogram with angioplasty, and bypass reconstruction. Pain that persists without increased celiac artery velocities should be treated with celiac plexus block and further treatment for functional gastro-intestinal disorders.

Randomized controlled studies of patients diagnosed with celiac artery compression comparing non-operative management to surgery or placebo surgery to surgery would be beneficial to better delineate the effectiveness of surgery; however, there are

ethical issues in the design of such trials. Additionally, our experience has been that patients seen in our clinic request surgery as they are desperate for any possible solution due to the chronic pain. Another possible study would be a randomized control trial comparing surgery alone to celiac plexus block alone to surgery with celiac plexus block. There is much opportunity to study the most effective management of these complex patients. It would also be useful to look at the patient characteristics or pre-operative evaluation that may predict success after surgical treatment as well as follow these patients for an extended period of time for long-term follow-up.

Given the small numbers of patients diagnosed with symptomatic celiac artery compression, it has been difficult to perform analysis of a large volume of patients. Thus, large multi-center studies would be necessary to perform adequate studies.

Recommendations

- In patients with celiac artery compression and chronic abdominal pain, surgeons should consider operative release of the ligament to improve pain. The success of surgical treatment for celiac artery compression is predicated on appropriate patient selection, release of the median arcuate ligament with normalization of celiac artery velocities as well as neurolysis of the celiac plexus, and appropriate post-operative follow-up with evaluation for possible need for further surgical intervention particularly in the case of recurrent abdominal pain (**evidence quality low; moderate recommendation**).
- Surgical treatment for celiac artery compression should be done only after thorough medical evaluation. The diagnosis should be confirmed by mesenteric duplex showing elevated velocities and normalization with inspiration as well as CT angiogram showing "J-hook" conformational change of the celiac artery at the origin. Additionally, there should be a multidisciplinary pre-operative evaluation including psychiatry and pain service. There should be a frank discussion with the patient and family that this diagnosis as the cause of abdominal pain is a diagnosis of exclusion and thus the surgical treatment is a last resort. It is also imperative to manage patient expectations with the knowledge that the pain may persist following surgery (**evidence quality low; strong recommendation**).
- Patients that do not have unanimous clearance from the entire multidisciplinary team should not undergo surgery (**evidence quality low; strong recommendation**).

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Chapter 23
In Patients with Superior Mesenteric Artery Syndrome, Is Enteric Bypass Superior to Duodenal Mobilization?

Monika A. Krezalek and John C. Alverdy

Abstract Superior mesenteric artery syndrome is an infrequent cause of duodenal obstruction within the narrowed aortomesenteric angle. The condition is characterized by vague and elusive symptomatology thus often making it difficult to diagnose. In addition, the etiology remains poorly defined and standard diagnostic criteria are lacking. Following a trial of supportive medical management, the surgical treatment options include traditional open or minimally invasive duodenojejunostomy, division of the ligament of Treitz (Strong's procedure), or gastrojejunostomy. Duodenojejunostomy has been the favored surgical technique historically and most described in the literature. Due to the rarity of the syndrome and overall inconsistencies in diagnosis and treatment, there is a paucity of evidence in the literature to strongly recommend one technique over the other. Available case series and case reports lack appropriate follow-up. Based on the existing data and our personal experience, our preference is to perform a laparoscopic duodenojejunostomy for the treatment of medically refractory SMA syndrome. However, larger and more rigorous studies will be needed to make more evidence-based recommendations.

Keywords Superior Mesenteric Artery Syndrome • Wilkie's Syndrome • Cast Syndrome • Aortomesenteric Obstruction • Chronic Duodenal Obstruction • Duodenojejunostomy • Strong's Procedure

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Introduction

Superior mesenteric artery (SMA) syndrome is an uncommon cause of duodenal outlet obstruction and is often difficult to diagnose due to its vague and elusive symptomatology. Clinically it is characterized by postprandial epigastric abdominal pain, nausea, bilious vomiting and weight loss. Pain is classically relieved by assuming a prone, knee-to-chest or lateral decubitus position [1, 2]. SMA syndrome affects predominantly young women between 10 and 39 years of age and thin, asthenic build [1, 3, 4]. While it is a very rare disease with an exact prevalence that is unknown, it is estimated to have an incidence of 0.013–0.3 % based on upper gastrointestinal barium studies [4, 5]. Yet because there is no gold standard imaging test to confirm the diagnosis, its incidence is likely overrepresented [2, 6]. SMA syndrome was originally described in 1861 by Carl von Rokitansky based on his post-mortem observations of young asthenic females. He described acute gastric and duodenal dilation as a result of compression of the duodenum by the root of mesentery [7, 8]. The first large series consisting of 75 patients was published in 1921 by D. P. D. Wilkie, in which he described treatment options that are used today and still remain effective [1]. Along this historical context, the entity is still often referred to as Wilkie's Syndrome. The condition has been given many names over the years; chronic duodenal ileus, Cast syndrome (pernicious vomiting that resulted from the application of body cast [9, 10]), arteriomesenteric duodenal compression [11], aorto-mesenteric artery compression syndrome [12]. Wilkie proposed that congenital alteration in the relationship of the vessels to the duodenum, aggravated by an acute insult, leads to symptom onset and worsening [1]. Guthrie proposed that the disease is the result of man's upright posture acquired late in evolution [8].

The superior mesenteric artery originates at an acute angle off the aorta behind the neck of the pancreas at the level of first lumbar vertebrae. The aortomesenteric angle contains retroperitoneal fat, lymphatics, the uncinate process of the pancreas, and the left renal vein as it crosses over the aorta [13] (Fig. 23.1). The interposed adipose tissue within the aortomesenteric window is thought to displace the SMA anteriorly to a degree sufficient to allow for the duodenum to cross through the window without extrinsic compression. When this is no longer the situation, the etiology of SMA syndrome is believed to be due to vascular compression of the third portion of the duodenum as a result of a narrowed aortomesenteric angle. Classically explained, significant weight loss leading to critical loss of the fat pad within this angle is the proposed etiopathogenesis of SMA syndrome [6, 14, 15]. Congenital or acquired anatomic variations, such as short and high insertion of the ligament of Treitz, low origin of superior mesenteric artery, lumbar lordosis, or malrotation may also predispose to the syndrome [4, 6, 14, 16]. Symptom onset is reported to be precipitated by acute insults that lead to rapid weight loss and depletion of the abdominal adipose tissue (malabsorption, cancer, trauma, burns, neurological disorders, eating disorders, bariatric surgery), external compression (cast), intra-abdominal compression (dissecting aortic aneurysm), or mesenteric tension due to surgical alterations (proctocolectomy with ileoanal pouch anastomosis,

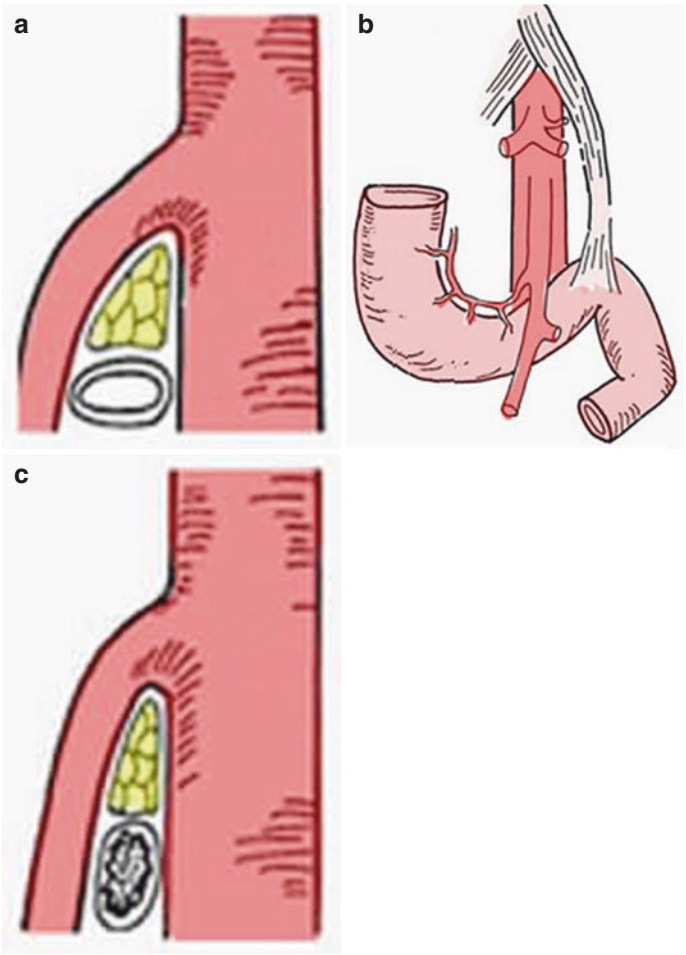

Fig. 23.1 Superior mesenteric artery and the aorta form an acute aorto-mesenteric angle (**a**). In superior mesenteric artery syndrome, the angle is markedly narrowed resulting in compression of the third portion of the duodenum (**b**, **c**)

corrective spinal surgery) [6, 8, 17–21]. The extent to which these disorders are also associated with an acquired gastric and duodenal motility disorder contemporaneous with a diagnosis of SMA, and the extent to which each contributes to the symptoms, is unstudied and therefore unknown.

Although patient demographics and presenting symptoms are similar between superior mesenteric artery syndrome and megaduodenum, the former is postulated to be a mechanical obstruction without underlying myopathy ruled out by duodenal biopsies whereas the latter is a hereditary motility disorder [4, 6, 14]. SMA syndrome often remains an ambiguous diagnosis as it can be overshadowed by

co-exisitingmedical conditions involving severe malnutrition, psychosocial eating- related disorders and substance abuse [14, 22]. Surgeons tend to be consulted for SMA syndrome when medical therapy and conservative management fail and generally focus on the mechanical plausibility of the diagnosis based on imaging. The indications for surgery remain a challenge since the diagnosis of SMA syndrome is typically made clinically since there is much variation in the interpretation and significance of imaging studies. It should be noted that imaging studies do not rule in the diagnosis of SMA syndrome, most often they rule it out. For these reasons, the diagnosis of SMA syndrome often remains ambiguous at best with the diagnosis confirmed when patients symptoms improve following surgery. Results of surgical outcomes are by and large incomplete and thus should be viewed with caution.

In general the diagnosis of SMA syndrome is suspected when patients can no longer maintain their weight without exogenous nutritional support, display symptoms suggestive of duodenal obstruction, and have had all other potential causes ruled out. It is good practice to first have patients screened in an eating disorders clinic by a specialist including a dietician. Once the possibility of an eating disorder is ruled out, the diagnosis is considered when an upper gastrointestinal contrast study and CT angiogram are together suggestive of SMA syndrome. Median arcuate ligament syndrome, which can cause symptoms similar to SMA syndrome, should also be ruled out, as well as any endoluminal or extrinsic obstructive cause of duodenal obstruction.

The radiologic criteria for the diagnosis of SMA syndrome can be highly subjective and a comprehensive review of the literature is beyond the scope of this review. In general, upper barium study should be performed by an experienced radiologist who is familiar with the diagnosis. Additionally a CT angiogram should confirm that there is narrowing of the aortomesenteric window. Surgeons considering intervention should realize that there is much variability in the measurement of the aortomesenteric window from one radiologist to another and much subjectivity in the interpretation of the upper barium study. While the degree of angulation at the aortomesenteric site is used as criteria with specific numerical cutoffs, there is no consensus among radiologists as to how the angle is measured. Consideration of surgery should involve clear communication between the radiologist and surgeon as to the findings on imaging.

Once conservative measures have failed and the patient can no longer maintain their weight within a healthy range, surgery should be considered. Surgical options include enteric bypass (side-to-side duodenojejunostomy or gastrojejunostomy) or mobilization of the duodenum at the ligament of Treitz (Strong's procedure).

Search Strategy

A literature search of English language publications from 1921 to 2014 was used to identity published data on surgical treatment of superior mesenteric artery syndrome. Databases searched were PubMed, Ovid, and GoogleScholar. Terms used in

the search were "Superior Mesenteric Artery Syndrome", "Wilkie's Syndrome", "Cast Syndrome", "Duodenal Ileus", "Aortomesenteric Compression Syndrome", "Duodenojejunostomy" AND ("Open" OR "Laparoscopic"), "Gastrojejunostomy" AND ("Open" OR "Laparoscopic"), "Strong's Procedure" AND ("Open" OR "Laparoscopic"), and "Duodenal Mobilization" AND("Open" OR "Laparoscopic"). Reference lists of the retrieved publications were manually reviewed for additional publications. We noted that majority of large, comprehensive series dated back to 1960–1980s, while most recently only small case series and case reports are available. The data was classified using the GRADE system (Table 23.1).

Results

Clinical Results of Duodenojejunostomy

Duodenojejunostomy was first described by Bloodgood in 1907 and performed by Stavely in 1908 (Fig. 23.2). It was shown to be a successful treatment option for SMA syndrome by Wilkie in 1921 [1]. Since, it has been the most frequently utilized operative procedure for treatment of this condition, having a published success rate of around 80 % [23–25]. In 1978 Lee and Mangla published a review of 146 patients surgically treated for SMA syndrome, concluding that duodenojejunostomy had superior outcomes to both Strong's procedure and gastrojejunostomy [26]. Their quoted success rate was 90 % in terms of symptomatic relief. In 1984, Gustafsson et al. published a 100 % success rate in ten patients treated with duodenojejunostomy [3]. In 1989, a case series of 16 operative patients showed the opposite results; only one patient achieved complete symptom resolution, while the only significant improvement was decreased frequency of vomiting in the others [4]. The first successful laparoscopic duodenojejunostomy was described in 1998 by Gersin and Heniford [27]. More recently in 2009, Merrett et al. described eight patients treated with duodenojejunostomy with duodenal division, reporting 100 % success rate demonstrating no evidence of obstruction on imaging and weight gain in all eight patients post-operatively; however, the details of post-operative assessments and symptom resolution were omitted [14]. In 2010, Munene et al. published a literature review of nine case reports of patients with SMA syndrome treated with laparoscopic duodenojejunostomy reporting a 100 % success rate for the operation in ten patients. However, follow-up data was lacking and the criteria used for determination of operative success was missing [28]. In 2012, Lee at al. published a

Table 23.1 PICO table

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Patients with superior mesenteric artery syndrome	Duodenojejunostomy	Duodenal mobilization (Strong's procedure)	Symptom resolution

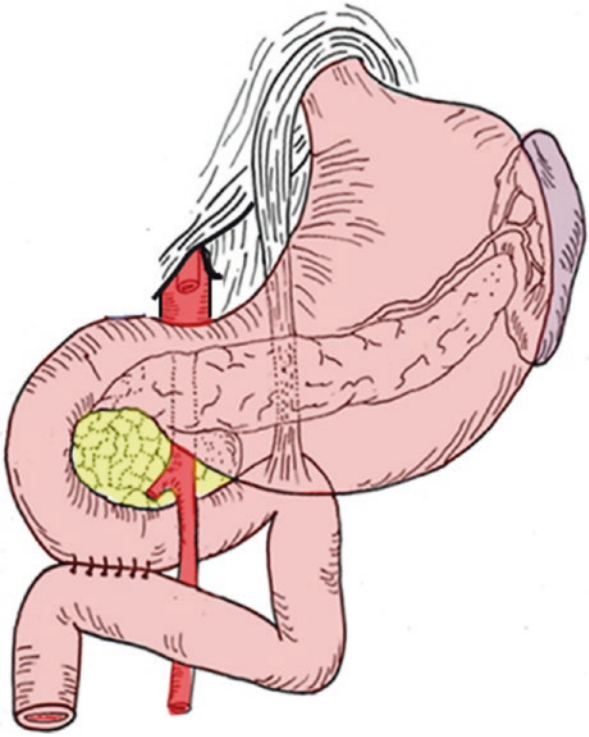

Fig. 23.2 Duodenojejunostomy

100 % success rate for eight patients who underwent laparoscopic duodenojejunostomy and a 100 % success rate for two patients who underwent open duodenojejunostomy [22]. Retrospective review by Pottorf et al. of 12 cases of SMA treated with laparoscopic duodenojejunostomy report 92 % success in symptom improvement [29]. Most published studies suffer from a very small sample size, short follow-up, and lack of information regarding the criteria used to determine long term success (Table 23.2). Other small case reports consisting of one or two patients, revealed similar conclusions and suffer from the same lack of objective preoperative assessment tools compared to blinded postoperative assessment in the long term [30, 31, 35].

Clinical Results of Gastrojejunostomy

Gastrojejunostomy allows for gastric decompression; however, inadequate relief of duodenal obstruction may lead to failure of symptom resolution and complications such as blind loop syndrome, bile reflux and ulcers [14, 26] (Fig. 23.3). Even back

Table 23.2 Quality of follow up data in more recently published studies

Reference	Number of patients	Intervention	6 month outcome reported	Details of follow up	Quality of follow up (0–3 points)
Gustafsson et al. [3]	10	Open duodeno-jejunostomy	Yes – successful in 10/10	Minimal	1
Ylinen et al. [4]	16	Open duodeno-jejunostomy	Yes – successful in 3/16 only	Detailed	3
Gersin et al. [27]	1	Laparoscopic duodeno-jejunostomy	No	Lacking	0
Richardson et al. [29]	2	Laparoscopic duodeno-jejunostomy	No	Lacking	0
Kim et al. [30]	2	Laparoscopic duodeno-jejunostomy	Yes – successful in 2/2	Minimal	1
Merett et al. [14]	8	Open duodeno-jejunostomy	Yes - successful in 8/8	Minimal	1
Singaporewalla et al. [31]	1	Laparoscopic duodeno-jejunostomy	No	Lacking	0
Munene et al. [28]	1	Laparoscopic duodeno-jejunostomy	No	Lacking	0
Lee et al. [22]	8	Laparoscopic duodeno-jejunostomy	Yes – successful in 8/8	Minimal	1
	4	Open duodeno-jejunostomy	Yes – successful in 4/4	Minimal	1
	2	Open gastro-jejunostomy	Yes – successful in 1/2	Minimal	1
Pottorf et al. [29]	12	Laparoscopic duodeno-jejunostomy	No	Lacking	0
Massoud [32]	4	Laparoscopic duodenal mobilization	Yes – successful in 3/4	Detailed	2
Villalba et al. [33]	1	Open duodenal mobilization	Yes – not successful	Detailed	2
Ha et al. [34]	19	Open duodenal derotatation	Yes – successful in 18/19	Detailed	2
Welsch et al. [6]	1	Open duodenal mobilization	Yes – successful in 1/1	Minimal	0

Quality of follow up is determined by following grading system: strategy for follow up and patient outcomes described (1 point), follow-up performed at or after 6 months from surgery (1 point), questionnaire used for post-operative symptom assessment (1 point). Scoring: 0 – Follow up absent, 1 – Poor, 2 – Fair, 3 – Good

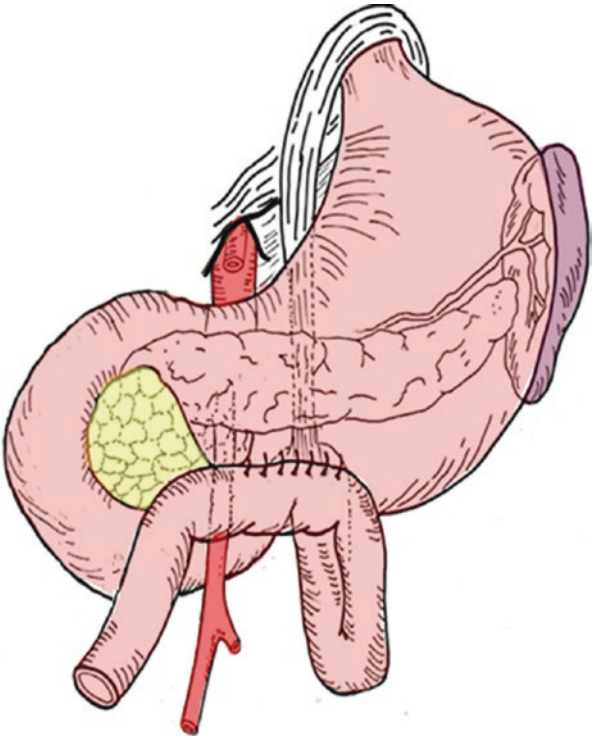

Fig. 23.3 Gastrojejunostomy

in 1921, Wilkie described treatment of SMA syndrome by gastrojejunostomy as a "mistake" due to "post-operative troubles" [1]. It has been largely abandoned as a treatment of SMA syndrome, but remains an option in cases where the other two procedures are deemed unsafe due to duodenal scarring or ulceration.

Clinical Results of Mobilization of the Duodenum

In 1958, Strong introduced lysis of the ligament of Treitz and lowering the duodenojejunal flexure away from the narrow aortomesenteric axis as a surgical option claiming the added benefits of a shorter duration of the procedure and avoidance of a bowel anastomosis [36] (Fig. 23.4). Over the next decade, the procedure was repeated infrequently [37, 38]. The disadvantage of this operation is its potential inadequate caudal displacement of the duodenum due to short inferior pancreaticoduodenal artery or adhesions leading to failure of symptom resolution and scar formation leading to symptom recurrence and potential increased difficulty at reoperation [24]. There is limited published data available for this procedure. In

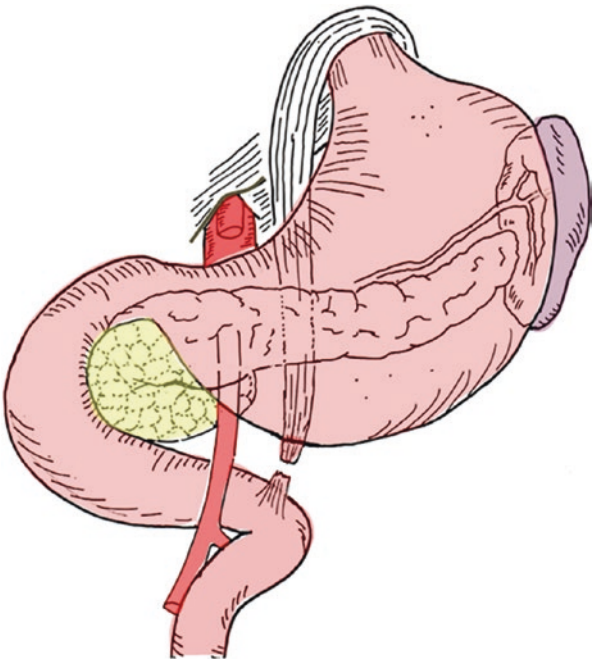

Fig. 23.4 Strong's procedure (mobilization of the ligament of Treitz)

1995 Massoud reported a case series of four patients treated with laparoscopic release of ligament of Treitz with 75 % success rate [32]. The largest recent retrospective review published by Ha et al. describes a modification to the procedure with mobilization of the right colon, terminal ileum and their respective mesenteries (duodenal derotation) in order to facilitate access to the third portion of the duodenum and to reduce the angular torque on the duodenum. They report nineteen adolescent patients who underwent the above procedure and quote a success rate of 95 % in terms of symptom relief [34]. This is one of the largest and more complete retrospective reviews of the topic; however the utility of the additional steps of the operation remains questionable.

Recommendations Based on the Data

Due to the rarity of the superior mesenteric artery syndrome, randomized controlled studies are unavailable. By the late 1980s, most of the comprehensive literature on the topic had been published. Since then, the more current available literature includes mostly small case series and individual case reports.

The available limited results and their incomplete interpretation and analysis does not provide sufficient statistical power to allow for evidence based recommendations for one particular operation versus the other. Historically, duodenojejunostomy has been the preferred operation due to reports published in the early history of the disease. However, it is difficult, if not outright impossible, to determine the actual results of these studies, as most lack the appropriate criteria for follow up and tracking of symptom resolution in patients afflicted by SMA syndrome. An optimal study would require the following study elements: (1) objective pre-operative symptoms assessment via a comprehensive questionnaire- based assessment tool performed by a non-treating clinician, (2) a standardized consensus based diagnosis of SMA syndrome involving surgeon, radiologist, and gastroenterologist, standardization of the surgical procedure and (3) long term objective follow-up assessment using a multi-element assessment tool performed by a non-treating clinician. This long term assessment would include post-operative symptom resolution, discontinuation of prior medical treatments, significant weight gain, and re-imaging showing complete resolution of the obstruction and lack of any pre-SMA angle duodenal dilatation previously observed on imaging. Unfortunately, in general, most studies we reviewed fail to outline the criteria used to determine surgical success including the degree of symptom resolution.

Regarding SMA syndrome, laparoscopic duodenojejunostomy has been shown to be an effective and safe operation when performed by an experienced surgeon. It is the preferred method by many, including our group. It should be considered in patients with chronic symptomatology who have failed other approaches. Minimally invasive application of the Strong's procedure is a viable alternative in younger patients with acute onset of disease.

A Personal View of the Data

We recommend laparoscopic duodenojejunostomy for the surgical treatment of the SMA syndrome. In experienced hands, it is safe, simple and potentially curative. We believe it is the most direct and logical way to alleviate obstruction at the SMA angle and therefore it should theoretically have the lowest rate of recurrence since the actual obstructing lesion is completely bypassed. We recommend caution in diagnosing SMA syndrome and vigilance to avoid misinterpretation of the results of previously reported case studies.

Given the incomplete assessments of the long term results of one operation versus the other and the lack of accounting for the placebo effect of general anesthesia and surgery and the confounding variables of postoperative pain management and continuous medical management, we recommend a team approach to surgical treatment of patients with SMA syndrome.

Recommendations

- **Recommendation for a thorough psychiatric assessment, especially eating disorders, prior to surgical intervention.** Grade of recommendation 1C (**evidence quality low; strong recommendation**)
- **Recommendation against performing a gastrojejunostomy for the treatment of SMA Syndrome, unless other approaches are not safe due to duodenal scarring or ulceration.** Grade of recommendation 1C (**evidence quality low; strong recommendation**)
- **Cannot recommend for or against laparoscopic duodenojejunostomy over duodenal mobilization for the treatment of SMA Syndrome.** Grade of recommendation 2C (**evidence quality low; weak recommendation**)
- **Recommend consideration of laparoscopic duodenojejunostomy in patients with chronic symptomatology who have failed other approaches.** Grade of recommendation 2C (**evidence quality low; weak recommendation**)

Recommend consideration of laparoscopic duodenal mobilization procedure in younger patients with acute onset of disease. Grade of recommendation 2C (evidence quality low; weak recommendation)

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Chapter 24
In Patients with Renovascular Hypertension Is There a Role for Open or Endovascular Revascularization Compared to Medical Management?

Joie C. Dunn, Sung Wan Ham, and Fred A. Weaver

Abstract Renovascular hypertension occurs when an existing renal artery stenosis (RAS) leads to hypoperfusion of the juxtaglomerular apparatus of the kidney resulting in an increase in renin production with subsequent up regulation of the renin-angiotensin-aldosterone system. The most common pathology of RAS is atherosclerosis. Non-atherosclerotic etiologies of RAS include fibromuscular dysplasia (FMD), dissection, trauma, congenital hypoplastic syndromes and arteritis. Both medical management, and endovascular (angioplasty/stenting) or open revascularization strategies have been used to treat the hypertensive diathesis, however comparative data of the competing strategies is limited.

Recent randomized trials have demonstrated that medical management should be the first line therapy for patients with atherosclerotic RAS with revascularization, by either endovascular or open surgical technique, being reserved for patients with resistant hypertension (blood pressure greater than 140/90 despite maximum tolerated doses of three antihypertensive with one being a diuretic), non-cardiac flash pulmonary edema, or bilateral severe RAS (>90 %) associated with renal dysfunction (ischemic nephropathy).

Our recommended initial treatment strategy for atherosclerotic RAS mediated renovascular hypertension is optimal medical management. Renal artery angioplasty/stenting is safe with high degree of technical success, and should be considered as the first line of revascularization therapy. Open surgical revascularization is reserved for patients with renal artery anatomy not amenable to endovascular revascularization such as a renal artery occlusion and renal artery

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disease associated with extensive aortic occlusive or aneurysm disease requiring open repair.

Keywords Renovascular hypertension • Renal artery stenosis • Endovascular • Stenting

Introduction

Renovascular hypertension occurs when an existing RAS leads to hypoperfusion of the juxtaglomerular apparatus of the kidney resulting in an increase in renin production with subsequent up regulation of the renin-angiotensin-aldosterone system. Atherosclerosis accounts for more than 90 % of RAS and, affects approximately 6.8 % of elderly patients [1]. Other less common causes of RAS include FMD, arteritis, dissection, trauma, and congenital hypoplastic syndromes [2–4].

Renovascular hypertension exists in 1–5 % of hypertensive patients [5]. Historical features of patients with renovascular hypertension include one or more of the following: onset of hypertension in patients younger than 30 and older than 55, an abrupt increase in existing hypertension which was previously mild and well controlled, hypertension resistant to multi-drug therapy, unexplained episodes of "flash" pulmonary edema, unexplained deterioration in renal function in a non-diabetic patient [1]. Physical findings are few beyond a cuff blood pressure greater than 140/90. An epigastric bruit is found in a minority of patients and patients with atherosclerotic RAS may have associated extremity pulse deficits or bruits. The optimal treatment strategy is an area of controversy, particularly the comparative roles of best medical therapy versus revascularization by renal artery angioplasty/stenting. General goals of revascularization include the improvement in blood pressure control, the lowering of doses and number of antihypertensive medications, the preservation of renal function, and the prevention of cardiovascular events [6].

Search Strategy

A literature search of English language publications from 1990 to 2014 was used to identify published data on renovascular hypertension, RAS and treatment strategies. Primary database search was performed through PubMed. Terms used in the search were "renovascular hypertension" "atherosclerotic renal artery stenosis" "non-atherosclerotic renal artery stenosis" "Takaysu/renal artery stenosis" AND "interventions" "open surgery" "endovascular therapy" "medical management" "CORAL trial" "ASTRAL trial." Six randomized controlled trials, ten cohort studies, one meta-analysis, one consensus statement, and 12 review articles were identified. The data was classified using the GRADE system (See Table 24.1).

Table 24.1 Results

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Patients with renovascular hypertension secondary to atherosclerotic stenosis Or Patients with renovascular hypertension secondary to non-atherosclerotic stenosis	Angioplasty Stenting Open surgical revascularization	Optimal medical management	Mortality from cardiovascular or renal cause, myocardial infarction, stroke, hospitalization for heart failure, progressive renal insufficiency, need for permanent renal-replacement therapy, preservation of renal function, Improvement in blood pressure, or antihypertensive medication reduction

Atherosclerotic Renal Artery Stenosis

Atherosclerotic RAS is more common than typically appreciated, and has a higher incidence in individuals with concomitant coronary artery (15–23 %), aortoiliac (28–38 %), and peripheral vascular disease (45–59 %). Atherosclerotic lesions typically involve the ostia and proximal renal artery [1]. Despite the prevalence of angiographic as well as hemodynamically significant RAS, the relative role of optimal medical therapy versus revascularization, particularly renal artery angioplasty/stenting is controversial.

Optimal Medical Therapy Versus Angioplasty/Stenting Plus Optimal Medical Therapy

Initial studies comparing medical versus endovascular management began with renal artery angioplasty alone. Three separate randomized trials (SNRASCG, EMMA, DRASTIC) all failed to demonstrate significant improvement in blood pressure or renal function with angioplasty alone when compared to optimal medical therapy [7–9]. The inadequacy of angioplasty alone for atherosclerotic RAS was first documented by van de Ven. He demonstrated that primary patency at 6 months was significantly better (75 % vs. 29 %) and restenosis rates were lower (14 % vs. 48 %) in patients subjected to angioplasty plus stenting when compared to angioplasty alone [10].

Based on these earlier studies, randomized trials were performed comparing optimal medical therapy with optimal medical therapy plus renal artery angioplasty/stenting. The STAR trial (Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery) and ASTRAL trial (Angioplasty and Stent for Renal Artery Lesions) were designed to determine whether optimal medical therapy plus renal artery angioplasty/stenting reduced adverse cardiovascular or renal events

when compared to optimal medical therapy alone [11–13]. Both studies failed to demonstrate that renal artery angioplasty/stenting and optimal medical management were better than optimal medical management alone in reducing cardiovascular and renal events [12–14].

However both trials had serious design limitations. The STAR trial was criticized for being underpowered with only 140 patients and included many patients who may have had clinically insignificant RAS. While ASTRAL had a larger enrollment, 806 patients, only 59 % of patients randomized to angioplasty/stenting had angiographic evidence of RAS >70 %. In addition, the design of the trial excluded patients with RAS who in the opinion of the investigators would definitely benefit from renal artery angioplasty/stenting. This biased the results in general against angioplasty/stenting. Finally, there was concern over operator experience due to the low rate of technical success (78.6 %) of the angioplasty/stenting procedure [15, 16].

The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study was a multicenter, randomized, controlled trial that compared optimal medical therapy with optimal medical therapy plus renal artery angioplasty/stenting in patients with atherosclerotic RAS. Inclusion criteria included patients with hypertension (SBP >155 mmHg or higher on ≥2 antihypertensive medications) and angiographic renal artery stenosis of at least 80–99 % or RAS greater than 60 % but less than 80 % with a systolic pressure gradient of at least 20 mmHg. The primary endpoint was the composite end point of death from cardiovascular or renal cause, myocardial infarction, stroke, hospitalization for heart failure, progressive renal insufficiency or need for permanent renal-replacement therapy. No significant difference in the primary composite endpoint was found between the medical and stenting/angioplasty groups (35.8 % and 35.1 %, P = 0.58). In addition, similar results were seen for the individual components of the composite endpoint [17].

CORAL as designed required that after randomization, patients were prohibited from crossing over to the competing arm for the duration of the study. By limiting crossovers, many patients with severe bilateral renal artery disease may have been treated outside the trial by renal artery angioplasty/stenting rather than subjecting them to the possibility of medical therapy only. This biased the study group towards patients with less severe renal artery disease and potentially excluded the subset of patients who may have received the most benefit from a renal artery intervention (i.e. severe bilateral renal artery stenosis associated with heart failure/flash pulmonary edema, malignant refractory hypertension or renal dysfunction) [18].

A recent meta-analysis of the six major randomized control trials (SNRASCG, EMMA, DRASTIC, STAR, ASTRAL, CORAL), concluded that renal artery angioplasty with or without stenting for atherosclerotic RAS was no better than optimal medical therapy alone in achieving blood pressure control or preserving renal function. However, it is important to note that in the angioplasty/stenting group a trend toward a lower rate of major events, including acute heart decompensation, renal dysfunction, stroke, and mortality was demonstrated [19].

Given the shortcomings of the available literature, particularly for patients who might truly benefit from renal artery angioplasty/stenting, a consensus document was produced in 2014 by the Society for Cardiovascular Angiography and

Interventions (SCAI). The consensus is based on the major randomized trials, cohort studies, and the multi-societal guidelines recommendations from ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease.

The Consensus recommendations were divided into three categories based on varying levels of appropriateness for renal artery angioplasty/stenting: (1) Renal artery angioplasty/stenting represents appropriate care, (2) Renal artery angioplasty/stenting may represent appropriate care, and (3) Renal artery angioplasty/stenting rarely represents appropriate care. Patients deemed appropriate for renal artery angioplasty/stenting included those with cardiac disturbance syndrome or "flash" pulmonary edema, severe (>90 %) bilateral renal artery stenosis or stenosis to a solitary kidney, accelerated or resistant hypertension, or global renal ischemia associated with renal dysfunction. Patients in whom renal artery angioplasty/stenting may represent appropriate care include those with unilateral severe (90 %) renal artery stenosis, hypertension and prior episodes of unexplained congestive heart failure or patients at high risk for progressive ischemic nephropathy who could benefit from revascularization for stabilization of renal function. Finally, patients in whom renal artery angioplasty/stenting is rarely appropriate are those who have RAS with controlled blood pressure and normal renal function, mild to moderate renal artery stenosis, ischemic nephropathy already requiring hemodialysis greater than 3 months, and chronic total occlusions of the renal arteries [20]. Although not specifically addressed in this consensus statement, it is also important to emphasize that the "prophylactic" or "drive-by" renal artery angioplasty/stenting of clinically occult atherosclerotic RAS is rarely if ever appropriate [12–14].

Open Surgical Intervention

Surgical revascularization is considered for patients with anatomically challenging or high-risk atherosclerotic RAS not amenable to endovascular intervention. Blood pressure response rates in selected patients undergoing open surgical revascularization have been favorable, with up to 85 % being cured or showing significant improvement in the hypertensive diathesis [21]. Open surgical repair of atherosclerotic RAS is durable, with patency rates in one series as high as 97 % at a mean follow-up of 3 years [21]. In a large case series by Darling, 687 open renal artery reconstructions were performed over a 23-year period. The majority of procedures were performed in conjunction with aortic reconstruction (531/687), with an overall morbidity of 15.5 % and mortality of 5.5 %. In the subgroup of patients who underwent an isolated renal artery procedure, the morbidity was 14.1 % and mortality was 3.2 %. Primary graft patency at 5 years was 95 % [22].

Given the current use of renal artery angioplasty/stenting as the first line revascularization strategy for atherosclerotic RAS, the use of open renal artery revascularization for an isolated RAS is rare. However, a role for open surgery remains for patients with an occluded renal artery or arteries with early bifurcation, small diameter (<3 cm), or severe concentric calcification; or patients with other abdominal aortic pathology (i.e. aortoiliac occlusive disease, aneurysmal disease) that

require concomitant open repair; or in selected patients who fail renal artery stenting or develop restenosis following intervention [20, 21].

Non-atherosclerotic Renal Artery Stenosis

Non-atherosclerotic RAS, primarily FMD, accounts for a significant portion of patients with renovascular hypertension [23]. Other non-atherosclerotic pathologies include renal artery dissection, aneurysm, arteritis, congenital hypoplastic syndromes and trauma. No randomized clinical trials for non-atherosclerotic RAS comparing optimal medical management to renal artery angioplasty/stenting exist, but the principles of medical and, endovascular or open revascularization are the same as for patients with atherosclerotic RAS. Optimal treatment is predicated on a variety of considerations including lesion pathology, patient age, severity of hypertension and associated renal dysfunction.

Optimal Medical Therapy Versus Angioplasty and Stenting (Non-atherosclerotic Renal Artery Stenosis)

The primary indication for renal revascularization in a patient with non-atherosclerotic renal artery disease is resistant hypertension [24]. When required in patients with FMD, renal angioplasty alone has been shown to be effective for most lesions isolated to the main renal artery. Three recent case series of renal angioplasty for FMD have documented reasonable results. Hypertension improvement was seen in 21–76 % of patients with a primary patency of the renal intervention being 50–71 % at 5 years [25–27]. Davies demonstrated that 71 % of patients maintained improvement or cure in hypertension at 5 years [28]. Stent placement is rarely if ever required for FMD and should be reserved for residual stenosis >30 % or a flow limiting dissection [26]. Other non-atherosclerotic renal artery pathologies are managed on a case-by-case basis, since depending on the anatomy and lesion, open or endovascular revascularization may be preferred.

Open Surgical Intervention (Non-atherosclerotic Renal Artery Stenosis)

Open surgical revascularization for FMD is uncommon and is reserved for patients with extension of FMD into secondary renal artery branches or associated with a renal artery aneurysm, or in patients who fail endovascular intervention. Overall cure and improvement rates in hypertension for open revascularization are 33 % to 63 % and 24 % to 57 % respectively. Five year primary graft patency ranges from 75 to 85 % [29–32]. In a recent series of 43 patients with non-atherosclerotic renal artery disease primary graft patency was 80 % at 5 years, and survival 78 % at 10 years. Open revascularization was associated with an improvement in blood pressure, less antihypertensive medication and improvement in renal function [33]. For

patients with arteritis, and specifically Takayasu's arteritis, open surgical revascularization is the primary revascularization strategy. Primary patency has been demonstrated as high as 79 % at 5 years, with a statistically significant reduction of anti-hypertensive medication requirements [34].

Recommendations

The management of renovascular hypertension is stratified by the RAS pathology: atherosclerotic and non-atherosclerotic.

For atherosclerotic RAS, optimal medical therapy is the appropriate first line therapy for most patients. Renal artery angioplasty/stenting should be considered for patients with significant RAS (>60 %) associated with "flash" pulmonary edema, resistant hypertension, or in selected patients with renal insufficiency and either severe (>90 %) bilateral renal artery stenosis or severe stenosis to a solitary functioning kidney. Open revascularization should be considered in patients who are reasonable surgical candidates who have unfavorable renal artery anatomy for angioplasty/stenting (i.e. early bifurcation, small diameter vessels (<3 cm); vessels with severe concentric calcification, renal artery occlusion) or those with associated renal artery aneurysms, complex aortic disease or concomitant aortic disease that requires open repair; or in selected patients with severe bilateral renal artery disease or a solitary kidney, especially if associated with renal dysfunction.

The optimal management of non-atherosclerotic renovascular hypertension varies and is largely dependent on RAS pathology. For patients with hypertension easily controlled with one or two antihypertensives, medical therapy is preferred. However, for patients with resistant hypertension revascularization should be considered. Balloon angioplasty alone is preferred for FMD confined to the main renal artery with open surgical revascularization employed for FMD associated renal artery aneurysms or branch vessel involvement; or patients who have failed endovascular management. Open surgical revascularization is also the primary therapy for selected non-FMD lesions, specifically renal artery stenosis secondary to Takayasu's arteritis.

A Personal View of the Data

The prospective randomized trials to date have consistently failed to show any beneficial effect of renal artery angioplasty/stenting over optimal medical therapy alone for the treatment of renovascular hypertension due to atherosclerotic RAS. However, these trials by design excluded many patients who would have benefited the most from endovascular intervention. While ample evidence has demonstrated the safety and the high technical proficiency of renal artery angioplasty/stenting, the benefits in blood pressure control and preservation or improvement in renal function have been difficult to validate. Despite dissonance in the published data, we continue to be of

the opinion that renal artery angioplasty/stenting has a beneficial role in a select subset of patients of with atherosclerotic RAS mediated renovascular hypertension.

Comparative data regarding non-atherosclerotic RAS is lacking. However, for FMD, simple angioplasty is safe and relatively effective. Unfortunately, the role of endovascular revascularization in non-FMD lesions is less certain. Data from our own institution indicates open revascularization is preferred for Takayasu's arteritis and may be the optimal choice for most non atherosclerotic RAS. However, a comparator population is lacking for most non-FMD management leaving it up to physician judgment and experience to decide the appropriate treatment for the individual patient.

Recommendations

- **Renovascular Hypertension due to Atherosclerotic RAS**
  - We recommend optimal medical therapy as first line treatment (**evidence quality high; strong recommendation**).
  - For patients with cardiac disturbance syndrome or "flash" pulmonary edema, severe (>90 %) bilateral renal artery stenosis or stenosis to a solitary kidney, accelerated or resistant hypertension (failure of >3 maximally tolerated medications including the use of a diuretic), or ischemic nephropathy, we recommend renal artery angioplasty/stenting (**evidence quality moderate; strong recommendation**).
  - For patients with unilateral severe (90 %) renal artery stenosis and resistant hypertension or prior episodes of congestive heart failure without a primary cardiac etiology or patients with progressive ischemic nephropathy who could benefit from revascularization for preservation of renal function, we recommend renal artery angioplasty/stenting as this group of patients may benefit (**evidence quality moderate; moderate recommendation**).
  - For patients with controlled blood pressure and normal renal function, mild to moderate RAS, chronic ischemic nephropathy already requiring hemodialysis greater than 3 months and chronic total occlusions of the renal arteries, we do not recommend renal artery angioplasty/stenting, and especially "prophylactic" or "drive-by" interventions on clinically occult atherosclerotic RAS (**evidence quality high; strong recommendation**).
  - Open surgical revascularization should be considered for those that meet criteria for revascularization but have lesion characteristics not amenable to endovascular management or have concomitant abdominal aortic pathology that requires open surgical repair (**evidence quality strong; strong recommendation**).
- **Renovascular Hypertension due to Non-atherosclerotic RAS**: The optimal treatment for renovascular hypertension due to non-atherosclerotic RAS varies widely and largely depends on the pathology of the renal artery stenosis. Patients with resistant hypertension and FMD confined to the main renal artery are best managed initially by renal artery angioplasty. Other pathologies are managed on a case by case basis.

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Chapter 25
Does Endovascular Repair Reduce the Risk of Rupture Compared to Open Repair in Splanchnic Artery Aneurysms?

Benjamin J. Pearce

Abstract Aneurysms of the splanchnic circulation (VAA-visceral artery aneurysm) carry an especially high mortality with rupture. Repair of VAA requires a precise understanding of the collateral circulation and determination of whether maintenance of patency is required to prevent end organ ischemia. In elective cases of VAA repair, both open and endovascular techniques confer excellent results with limited mortality; the latter being mostly employed for ablative therapies. The main determinants of modality will be the need to maintain perfusion of the end organ and the complicating factors to surgical exposure. In cases where ablative aneurysm treatment is planned regardless of modality, endovascular repair is an appropriate first step. In cases requiring maintenance of in-line flow to the parent artery or when persistent aneurysm flow would result in ongoing bleeding, open surgery remains the most appropriate option.

Keywords Visceral • Splanchnic • Artery • Aneurysm • Endovascular • Ligation • Bypass • Embolization

Introduction

Decision making in visceral artery aneurysms (VAA) is complicated by lack of consensus in nomenclature, limited disease prevalence, wide range of native arteries involved, and absence of prospective comparison and meta-analysis of treatment strategies. The majority of contemporary series [1–3] use the term VAA in reporting true and false aneurysms of the splanchnic arteries (Celiac-CA, Superior Mesenteric-SMA, Inferior Mesenteric-IMA) and their branches and exclude the

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renal arteries. Others [4–6] use the term VAA to encompass aneurysms of the renal arteries. To avoid confusion, this chapter will focus on the specific decision making in splanchnic artery aneurysms as the indications for treatment and mechanism of repair of renal artery aneurysms are more nuanced. Further, although the etiology of true and false aneurysms of the splanchnic arteries is different, the surgical approach and peri-operative considerations between open surgical repair (OSR) and endovascular splanchnic artery repair (ESAR) in both of these entities are similar and appropriate for this analysis. To avoid confusion with splenic artery aneurysms (SAA) specifically, the abbreviation VAA (visceral artery aneurysms) will be used in this chapter to indicate aneurysms of the splanchnic circulation not including the renal arteries.

The overall incidence of VAA is estimated between 0.1 and 2 % [7–10]. A review of more than 3,600 aortograms demonstrated a presence of splenic artery aneurysm at 0.78 % [11]. However, widespread use of intra-abdominal imaging has increased the referrals for incidentally found VAA in contemporary vascular practice [2]. The distribution of VAA is as follows [12]:

Splenic(60 %) → Hepatic(20 %) → SMA(5.5 %) → CA(4 %) → Gastric/Gastroepiploic(4 %) → Jejunal(3 %) → Pancreaticoduodenal(2 %) → Gastroduodenal(1.5 %) → IMA

The male:female distribution vary between the various types of VAA as do the reported risks of rupture and indications for repair. Unfortunately, this combination has made evaluation in a prospective fashion difficult and the treatment options so varied that meta-analysis is not possible. In general, the most common VAA—splenic and hepatic—behave similar to other intra-abdominal aneurysms and can be followed by size with treatment threshold at 2 cm. However, mortality with rupture is exceedingly high in the celiac, pancreatic branches, gastric branches, and IMA and any aneurysm in these locales warrant treatment.

Given the wide variety of aneurysms encompassed in VAA, approach to repair is broad as well. The single factor governing surgical approach is the rich collateral network seen in the splanchnic arterial bed. The need to maintain in-line vascular flow is the critical determinant to choice of repair regardless of open or endovascular approach. Other factors include hostile abdomen, recent sepsis, patient fitness, pancreatitis, need for liver transplantation, etc. The focus of this analysis will be to evaluate the efficacy of endovascular vs. open repair of VAA and determine the approach most suited to the clinical scenario.

Search Strategy

A literature search of English language publications from 1995 to 2014 was used to identity published data on visceral artery aneurysms and VAA (Table 25.1). Databases searched were PubMed, Embase, Google Scholar, and Cochrane Evidence Based Medicine. Terms used in the search were “visceral artery,” “visceral artery aneurysm,” “splanchnic artery,” “splanchnic artery aneurysm,” “digestive artery,”

Table 25.1 PICO table for choice of intervention in splanchnic artery aneurysms

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with VAA or VAPA regardless of symptom status	Open or Endovascular repair of VAA by any means	Natural History studies of VAA	1. Mortality and morbidity associated with intervention stratified by operative strategy and indication 2. Need for aneurysm related re-intervention

VAA Visceral Artery Aneursysms excluding those in the renal vasculature, *VAPA* Visceral Artery Pseudoaneurysms excluding those in the renal vasculature

"digestive artery aneurysm," AND ("treatment," "repair," "surgery," "open surgery," "endovascular," "endovascular surgery," "intervention"). Articles were excluded if they were limited to renal artery aneurysms only. Twelve cohort studies and two review articles were included in the analysis. No randomized control trials and no Cochrane Reviews were found on VAA repair, open or endovascular. Cohorts included for analysis were those with more than 10 patients total or with a very narrow focus which adds to the evaluation. The data were classified using the GRADE system.

Results

Clinical Relevance of Splanchnic Artery Aneurysms

The indication to repair all VAA is the prevention of rupture, bleeding into viscus, or existing rupture. As the arterial cascade of the splanchnic vasculature consists of either direct branches off the aorta (Celiac, SMA, IMA) or intraperitoneal location of the branches (Gastroepiploic, Gastric, Ilio-jejunal), fatality with rupture is exceedingly high. Mortality rates in the setting of rupture range from 20 % for hepatic artery aneurysms to 100 % for Celiac [13]. Even in contemporary series of patients who undergo intervention, mortality can reach 29 % in the post-operative period [14].

Pregnancy is a well known risk factor for development of VAA and precipitating factor in rupture. This is an especially harrowing circumstance as mortality is extending to both the patient and the fetus. Maternal mortality is estimated at 75 % and fetal mortality exceeding 90 % in the setting of ruptured VAA [15, 16]. In the setting of VAA identified in a pregnant patient, or a woman of child bearing age, consideration of repair should be given regardless of size [12, 14]. Likewise, the hormonal milieu and change in portal pressure associated with cirrhosis has led to a higher incidence of SAA in patients being evaluated for liver transplantation. This has resulted in an increase in mortality and morbidity in the patient population and is an indication for repair [14, 17].

While the mortality of ruptured VAA is unacceptably high, the actual incidence of rupture outside of pregnancy is relatively low. In fact, several cohorts have demonstrated a benign rate of growth in asymptomatic VAA and low incidence of rupture. Abbas et al. [18] identified 168 splenic artery aneurysms followed without intervention at the Mayo Clinic over a 20 year period. The incidence of rupture was 0 % and only 17(10 %) patients required surgical intervention due to increase in size. In the overall cohort, annual rate of growth was <1 mm/year and aneurysm related mortality was 0 %. The same group showed similar results when following small hepatic artery aneurysms (HAA) in 22 patients over 5 years with none requiring surgery or suffering rupture [19].

The natural history of other VAA are not as precisely understood and the mortality with rupture remains high [12]. As stated, Celiac, SMA, IMA, Gastric/Gastroepiploic, Pancreatic, and Gastroduodenal artery aneurysms have mortality rates with rupture of 30–100 % [20]. Owing to their low prevalence and small size of the native arteries in these beds, no size criteria are predictive of rupture and the presence of aneurysm, regardless of symptom status, is indication for repair [12]. Likewise, visceral artery pseudoaneurysms (VAPA) are especially dangerous. The most common etiologies of VAPA are iatrogenic, traumatic or mycotic. Unlike degenerative aneurysms, VAPA are symptomatic in 90 % of cases manifest as rupture, gastro-intestinal hemorrhage, abdominal pain, and fever [3]. In series which evaluate intervention in both VAA and VAPA [2, 3], the indication for repair was VAPA in more than half of the cases and the mere presence of VAPA warrants intervention.

Treatment Strategies

Given the benign natural history of asymptomatic degenerative VAA, operative mortality must be exceptionally low to warrant repair in splenic or hepatic artery aneurysms at size <2 cm [14]. In the setting of any asymptomatic VAA, appropriate time for surgical planning should be taken and consideration of all options—OSR or ESAR—is necessary. Conversely, symptomatic VAA or VAPA often require urgent intervention, and yet the hemodynamic instability or presence of adverse factors for direct access to the aneurysm, e.g. acute pancreatitis/phlegmon, may influence choice of surgical approach. The existing cohorts of intervention for both ruptured and intact VAA treated by both OSR and ESAR are summarized in Tables 25.2, 25.3, 25.4, 25.5, and 25.6.

Regardless of urgency or indication, the single most determining factor in selection of modality for treatment is the collateral circulation around the area of the aneurysm. This will dictate whether ablative techniques—suture ligation, splenectomy, endoaneurysmorrhaphy, aneurysmectomy, coiling, glue—are adequate for treatment or whether in-line flow must be maintained to an end organ. OSR with bypass, primary repair, patch angioplasty, or extra-anatomic bypass to preserve organ perfusion is well understood; however, endovascular techniques such as stent

Table 25.2 Results with Open Surgical Repair(OSR): ruptured aneurysms at presentation

Author	No.	Location	Mortality	Morbidity	Reinterventions
Wagner et al. (1997) [21]	9	Mixed	11.1 %	33 % splenectomy	NR
Abbas et al. (2002) [18]	10	Splenic	20 %	100 % splenectomy 50 % distal pancreatectomy	0
Carr et al. (2001) [22]	7	Mixed	29 %	57 %	1
Sessa et al. (2004) [23]	12	Mixed	28 %	46 %	0
Pulli et al. (2008) [4]	1	Pancreaticoduodenal	0 %	0 %	NR
Ghariani et al. (2013) [24]	1	Splenic	0 %	NR	NR

NR not reported

Table 25.3 Results with Open Surgical Repair (OSR): intact aneurysms at presentation

Author	No.	Location	Mortality	Morbidity	Reinterventions
Abbas et al. (2002) [18]	36	Splenic	5.1 %	28.2 % splenectomy 10.3 % distal pancreatectomy	0
Carr et al. (2001) [22]	8	Mixed	0 %	25 %%	NR
Sessa et al. (2004) [23]	8	Mixed	0	12 %	0
Pulli et al. (2008) [4]	50	Mixed[a]	2 %	10 % splenectomy	0
Ghariani et al. (2013) [24]	77	Mixed	1.7 %	49 %	5 early post op, 1 late for VAA

Early post-op reoperations for surgical complication(ischemic colitis, abscess, hernia) not VAA
[a]Excluded 9 Renal artery aneurysms from manuscript

Table 25.4 Results with Endovascular Splanchnic Artery Repair (ESAR): ruptured aneurysms at presentation

Author	Number	Location	Mortality	Morbidity	Reinterventions
Carr et al. (2001) [22]	4	Mixed	0 %	25 %	1
Sessa et al. (2004) [23]	2	Mixed	0 %	50 %	NR
Tulsyan et al. (2007) [3]	22	Mixed	18.18 %	13.6 % access site related	2
Fankhauser et al. (2011) [2]	24	Mixed	NR	NR	NR

NR not reported

Table 25.5 Results with Endovascular Splanchnic Artery Repair (ESAR): intact aneurysms at presentation

Author	Number	Location	Mortality	Morbidity	Reinterventions
Sessa et al. (2004) [23]	11	Mixed	0 %	18 % end organ infarction	1
Tulsyan et al. (2007) [3]	26	Mixed	0 %	34.6 %	1
Fankhauser et al. (2011) [2]	161	Mixed	6.3 % (all cases of bleeding)	14.1 % infarcts 6.8 % access	5 aneurysm 1 bile duct

Table 25.6 Cohorts with BOTH OSR and ESAR

Author	Modality of treatment	Number treated	Mortality	Morbidity	Reinterventions
Sessa et al. (2004) [23]					
	OSR	29 (13 Rupture)	10.3 %	24.1 %	2
	ESAR	13 (2 Rupture)	0 %	46.2 %	3 (1 persistent flow)
Sachdev et al. (2006) [25]					
	OSR	24 (4 Rupture)	4.2 %	33.3 %	4 (1 for VAPA at graft anastomosis)
	ESAR	35 (10 Rupture)	2.8 %	25.7 %	7 (4 for persistent aneurysm)
Marone et al. (2011) [6][a]					
	OSR	74 (7 Rupture)	1.3 %	9.4 % (5 splenectomies)	
	ESAR	20 (0 Rupture)	0 %	10 %	4 conversions
Ferrero et al. (2011) [1]					
	OSR	23 (4 Rupture)	4.2 %	34.2 %	
	ESAR	9 (2 Rupture)	22.2 %	22.2 %	1 immediate conversion
Mazzaccaro et al. (2015) [26]					
	OSR	13	7.6 %	5.2 %	NR
	ESAR	19	0 %	15.3 %	NR

OSR open surgical repair, *ESAR* endovascular splanchnic artery repair, *NR* not reported

[a]Included 18 Renal Artery aneurysm

graft placement or multi-layered stent placement may be limited by tortuosity of target vessels, inadequate size of target vessel, or inability to attain seal without sacrificing important collaterals. It is generally well accepted that splenic perfusion is maintained with ablation of the proximal and mid-splenic arteries as is hepatic circulation with common hepatic ligation in the setting of a patent GDA and adequate evaluation for replaced hepatic anatomy [14, 27]. The short course and proximal location of CA aneurysms to the aortic circulation makes covered stenting difficult although many patients will tolerate loss of celiac patency without compromise of visceral perfusion [4, 24]. Similarly, the rich connections within the pancreatico-duodenal and epiploic arcades make ablative therapy of vessels within these areas straightforward [6, 27].

As expected, the most significant mortality occurs in patients presenting with rupture. As demonstrated in Table 25.2, the mortality with ruptured VAA undergoing OSR is between 10 and 30 % in series with more than one patient [8, 18, 21, 23]. By comparison, those undergoing elective OSR at the same institutions have favorable mortality of 0–5.1 % [4, 8, 18, 23, 24] (Table 25.3). In the only large series reporting endovascular treatment of ruptures, the mortality in these cases was similar at 18.8 % [3] (Table 25.4). Fankhauser et al. [2] is the largest series of ESAR but they did not report mortality related to presentation. However, their overall mortality was 6.3 % and all of those were reported as cases of bleeding at presentation. If these cases were all in the rupture category, the mortality in this cohort would approach 50 %.

The applicability of ESAR limits the possibility of randomized comparison. Exclusion of VAA with maintenance of in-line perfusion continues to be the most significant barrier to ESAR in all presentations. The tortuosity of the parent vessels, combined with the short landing zones for seal make covered stent grafting as sole therapy unattractive, especially in the urgent setting. Initial success with multilayer flow modulating stents that theoretically maintain branch vessel patency but encourage aneurysm thrombosis may change the paradigm for treatment of lesions in the CA, SMA and hepatic circulations [1]. Ferrero et al. [1], utilized 4 such stents in hepatic arteries with 100 % procedural success. One patient died post operatively and one stent thrombosed on follow up for a success rate of 50 % in utilizing these stents. Even in the largest series of attempted endovascular repair of VAA, Tulsyan et al. [3] exclusively utilized ablative techniques for VAA treatment and Fankhauser et al. [2] only attempted vessel preserving therapy in 10 of 185 aneurysms for a combined rate of attempted stenting of only 4.3 % in the most experienced hands.

Operative morbidity appears similarly equivalent between the two groups. The most common morbidity in both OSR and ESAR relates to splenic function. While splenectomy is known to have adverse long term affect on infectious risk, it is generally well tolerated. The majority of the morbidity in the OSR groups are listed as need for concurrent splenectomy [4, 18, 21]. As ablative techniques(embolization or ligation) are the most prevalent modalities of therapy in both OSR and ESAR, other ischemic complications are reported at equal rates. These include hepatic ischemia, biliary ischemic stricture, subsequent cholecystectomy, and bowel ischemia

[2, 4, 23, 24]. The need for colon resection appears to be related more to the hypotension and fluid shifts associated with rupture and open therapy in hemodynamically unstable patients [24]. Conversely, the majority of ischemic complications from ESAR appear to be self limited post-splenic infarct syndrome although splenic sepsis has been reported [2, 3, 23, 25].

Ultimately, in addition to limiting mortality, the goal of therapy is prevention of rupture. In the OSR experience, only one patient required subsequent intervention for persistent or procedurally related VAA [25]. One additional patient was reported to have recanalization of a ligated aneurysm after OSR [24]. All other reported VAA associated death in OSR patients are due to untreated metachronous intra-abdominal aneurysm rupture [4, 22]. Conversely, each series evaluating ESAR have documented incomplete ablation of aneurysm in the acute phase and late persistent aneurysm flow in treated vessels [1–3, 6, 23, 26]. Treatment of these lesions requires repeat ESAR or open conversion. Fortunately, open conversion appears to be well tolerated, but incomplete sealing of ruptured aneurysms theoretically increases patient risk [6]. The data make drawing absolute conclusions on the risk of incomplete treatment difficult as the cohort studies do not report an intention to treat analysis. Further, surgical conversion may be complicated when the decision to pursue ESAR was due to hostile anatomic features in the first place.

Recommendations

While the overall incidence of VAA is low, the mortality associated with rupture is exceedingly high. In elective cases, the operative mortality and morbidity is excellent for both OSR and ESAR. Due to the infrequency of this condition, the majority of the studies encompass experience over decades. Endovascular techniques have evolved in vascular disease during this time and newer devices have been available only in the latter portion of these studies. A bias exists in the literature to treat the more complicated or ruptured cases with OSR, thus drawing direct comparison between modalities impossible. No randomized trials have been performed and none of the existing cohorts have utilized patient satisfaction or quality of life metrics to document preference for ESAR. However, review of the existing literature elucidates two important points. First, ESAR is limited mainly to lesions amenable to ablative therapy. Second, persistent aneurysm flow or late aneurysm permeability is a complication primarily of ESAR. In elective cases where ablation is the goal regardless of technique, ESAR should be the first line of treatment due to ease of the procedure on both the operator and patient. In cases where avoidance of end organ ischemia is paramount, OSR remains the gold standard. And in regard to the question posed in the title of this chapter, ESAR cannot be stated to improve rupture prevention in VAA. Clearly, OSR results in less continued perfusion of the aneurysm and less need to re-intervene to treat the index VAA.

A Personal View of the Data

Despite the paucity of high GRADE evidence, some very clear guidance can be gained from the existing cohorts. While bias exists to treat the highest risk cases of VAA—ruptured and bleeding—with OSR, it may, in fact, be these patients who ultimately benefit from less invasive surgery as seen with ruptured abdominal aneurysms. The most sophisticated operators reporting on ESAR [2, 3] demonstrate excellent results in unstable patients. As more centers develop endovascular programs and gain facility with balloon occlusion control of the aorta for exsanguinating hemorrhage, the applicability of ESAR in unstable patients should improve. Further, ESAR can extend life saving therapy to patients with intraparenchymal VAA or with hostile abdominal pathology. Vigilant surveillance of these patients is necessary to prevent late rupture. However, in cases requiring maintenance of patency, especially CA, SMA, and proper HA, OSR should remain the technique of choice. Overall, intervention is very successful in preventing mortality, especially in the elective setting. Prompt attention to incidentally recognized VAA is critical and will allow for appropriate planning regardless of technique.

Recommendations

- For elective cases with ablative technique planned to treat VAA, ESAR is the first modality of choice (**evidence quality low; weak recommendation**).
- In cases requiring maintenance of patency to prevent organ ischemia, OSR is the optimum treatment strategy (**evidence quality moderate; strong recommendation**).
- ESAR does NOT confer a decrease in rupture for VAA over OSR and continued follow up imaging is warranted when utilizing these techniques (**evidence quality moderate; strong recommendation**).

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Part IV
Cerebrovascular Disease

Chapter 26
In Patients with Asymptomatic Carotid Artery Stenosis Does Current Best Medical Management Reduce the Risk of Stroke Compared to Intervention (Endarterectomy or Stent)?

James R. Brorson

Abstract Cervical carotid artery stenosis is amenable to correction by surgical endarterectomy or by endovascular angioplasty and stenting, with low rates of periprocedural complications. Yet in asymptomatic patients treated medically, rates of stroke associated with medically-treated carotid stenosis are low, limiting the potential benefits of these interventions. Randomized prospective trials including the Asymptomatic Carotid Atherosclerosis Study (ACAS), the Veterans Affairs (VA) study, and the Asymptomatic Carotid Surgery Trial 1 (ACST-1), all demonstrated some benefit of endarterectomy over medical therapy for asymptomatic stenosis. However there is uncertainty whether the benefit persists with respect to modern medical therapy, which has advanced since the time of these trials. For carotid angioplasty and stenting for asymptomatic carotid stenosis, benefits can only be indirectly inferred, based on results found to be comparable to those with endarterectomy in prospective trials. Based on current evidence, medical therapy, including control of risk factors, antiplatelet and statin therapy, and blood pressure treatment, are recommended for all patients with atherosclerotic carotid plaque. Endarterectomy for asymptomatic carotid stenosis can be recommended conditionally, in patients with severe stenosis. Carotid angioplasty and stenting for asymptomatic patients can only be recommended in selected cases where patient factors preclude safe endarterectomy. Stratification of risk based on plaque characteristics or detection of microemboli from asymptomatic carotid plaque may contribute to decision making in favor of intervention over medical management. Comparison of endarterectomy

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or angioplasty and stenting to modern medical therapy in a randomized, prospective fashion, such as is proposed in the CREST-2 trial, is needed to provide better guidance in these management decisions.

Keywords Carotid stenosis • Asymptomatic • Endarterectomy • Angioplasty • Stenting • Plaque • Antiplatelet therapy • Statin therapy

Introduction

The carotid bifurcation is easily observable by non-invasive methods, readily approached surgically through soft tissues, and, in skilled hands, quite amendable to operative or endovascular correction of stenosis. These features make stenosis of the cervical carotid artery an attractive target for the vascular or endovascular surgeon. Yet the management of asymptomatic carotid stenosis has been the focus of substantial controversy, for several reasons. First, the risk of stroke linked to asymptomatic carotid disease has generally been found to be rather low. In carotid disease, the best-established and weightiest factor determining risk of subsequent stroke is a recent prior history of associated ischemic symptoms (TIA or stroke). Thus, in one observational study, asymptomatic carotid stenosis of any degree of narrowing was associated with lesser risk of stroke than was even mild stenosis (<50 %) when accompanied by symptoms [1]. Furthermore, 45 % of the strokes occurring in those with asymptomatic carotid stenosis were attributable to lacunes or cardioembolism, and presumably not preventable by removal of the carotid plaque. The small risk of subsequent stroke attributable to asymptomatic stenosis limits the potential benefit from intervention, leaving little margin for benefit from an active intervention with any associated peri-procedural risks.

The second reason for controversy has been a dearth of data. While several randomized prospective studies of carotid endarterectomy in asymptomatic carotid disease have been undertaken, as reviewed below, each of the studies has methodological limitations. No data exist that compare carotid angioplasty and stenting to medical therapy in asymptomatic carotid disease; comparisons have only been made to endarterectomy. Finally, since the era that the randomized prospective studies of carotid endarterectomy in asymptomatic carotid stenosis were performed, medical therapy for stroke prevention has advanced, raising questions as to whether the benefits measured in these older studies would still persist. In particular, statin therapy was not generally available at the time the older trials were performed, and evidence suggests that it has a major impact on risks of stroke in atherosclerotic carotid disease. These factors have led to widespread uncertainty regarding the basis for recommending intervention over medical therapy for asymptomatic carotid stenosis. Does current best medical therapy reduce the risk of stroke for patients with asymptomatic carotid stenosis just as well as do endarterectomy or angioplasty and stenting?

Table 26.1 PICO table for Treatment of asymptomatic carotid artery stenosis

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with asymptomatic carotid artery stenosis	Carotid Endarterectomy, Carotid stent with embolic protection.	Conventional Medical management	Stroke and death

Search Strategy

A literature search of English language publications from 1984 to 2015 was used to identity published randomized controlled trial data on treatment strategies for asymptomatic carotid stenosis using the PICO outline (Table 26.1). PubMed and Cochrane Evidence Based Medicine databases were queried. Terms used in the search were "asymptomatic carotid stenosis," AND "carotid endarterectomy" AND "medical management" or "asymptomatic carotid stenosis," AND "carotid stent" AND "medical management". Articles were excluded if they did not specifically address treatment of asymptomatic carotid stenosis, if they were single-center studies, or if they selected only for high-risk endarterectomy candidates. Five randomized-controlled trials and four meta-analyses were included comparing endarterectomy or angioplasty and stenting with medical therapy alone or with each other. The data were classified using the GRADE system. Selected articles describing natural history of asymptomatic carotid stenosis patients were also reviewed.

Results

Carotid Endarterectomy Compared to Medical Therapy

Randomized studies of the effectiveness of CEA for asymptomatic carotid disease have consisted of the Veteran's Affairs (VA) study [2], the Asymptomatic Carotid Artery Surgery (ACAS) study [3], and the Asymptomatic Carotid Surgery Trial 1 (ACST-1) [4].

The first published major randomized study of asymptomatic carotid stenosis was the VA study [2]. In this trial, conducted at 11 VA medical centers between 1983 and 1991, 444 male veterans with 50–99 % carotid stenosis, without symptoms, were randomized between endarterectomy and medical therapy. Stenosis was confirmed by angiogram in all patients, and was defined by strict criteria like those established for the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [5], comparing the minimal diameter to the distal diameter where the

walls are parallel. Medical therapy, applied to both medical and surgical groups, consisted of aspirin 650 mg twice daily without definition of other medical interventions. Statin use is not mentioned; it would have been minimal in this era. Endarterectomy was accomplished with a low surgical 30 day mortality rate of 1.9 %, and nonfatal stroke rate of 2.4 %. Three additional nonfatal strokes occurred as a result of arteriography, for a combined stroke and death rate of 4.7 %. Follow-up continued over a mean period of 4 years. In terms of the primary endpoint, the combined incidence of transient ischemic attack (TIA), transient monocular blindness, and stroke, cumulative event rates were reduced to 12.8 % in the surgical group versus 24.5 % in the medical group ($p < 0.001$). In terms of ipsilateral stroke only, excluding TIA, rates were 9.4 % in the medical group, and 4.7 % in the surgical group, not quite reaching statistical significance. When combined outcomes of death and stroke, including peri-operative events, were analyzed, there was no significant difference between treatment groups. Thus there was a signal of benefit for CEA, but it was limited by angiographic and surgical complication rates, and it depended in part on prevention of TIAs, events of less morbidity than strokes. Further, the VA study provided no information about carotid disease management in women.

Soon after the VA study was published, results of ACAS appeared [3]. ACAS compared endarterectomy to medical therapy in 1662 patients found to have asymptomatic carotid stenosis of 60 % or greater, over the years 1988–1993. Patients were aged 40–79 years. Carotid stenosis was measured as diameter reduction by catheter angiography and NASCET-like criteria in all surgical patients, whereas patients in the medical group were not required to have angiography, with definition of stenosis by ultrasound-determined velocity criteria considered sufficient. Medical treatment consisted of aspirin 325 mg daily in all patients, as well as review of stroke risk factors. Statin therapy was not mentioned and would have been rare in this era. In this trial, surgical patients had a rate of perioperative stroke or death of 2.3 % (19 patients); 5 of 19 complications were cerebral infarctions directly following arteriography.

ACAS applied as the primary endpoint any stroke or death in the perioperative period, or ipsilateral cerebral infarction in the follow-up period, which was a median of 2.7 years. Rates of this endpoint were projected to 5 years to be 5.1 % in patients assigned to surgery, compared to 11.0 % in those in the medical group. This was a significant difference favoring the benefits of surgery, in an analysis focused on ipsilateral strokes as the primary target for prevention.

The Asymptomatic Carotid Surgery Trial-1 (ACST-1) [4] followed patients for a 10 year period from 1993 to 2003, following randomization to CEA or medical therapy. These patients were deemed to have “severe” unilateral or bilateral carotid stenosis, determined by carotid duplex ultrasound. Severe stenosis was defined by local criteria; it reportedly generally consisted of carotid artery diameter reduction of at least 60 %, but without a fixed minimum percentage. Medical therapy was “appropriate medical care”, and this was not further prescribed by the trial. Notably,

medical therapies applied increased substantially during the trial, with lipid-lowering drug use increasing from <10 % to more than 80 %, and anti- hypertensive medication use also increasing, from 51 to 55 % at the start of the trial to 87–89 % at the conclusion of the trial. Deferred CEA was performed in 26 % of patients in the medical group over 10 years.

The perioperative risk of stroke or death was 3.0 %. The trial's primary endpoint was the risk of perioperative stroke or death, or any stroke during follow-up. These outcomes were reduced to 6.9 % in surgically-treated patients versus 10.9 % in medically –treated patients over 5 years, and 13.4 % versus 17.9 % over 10 years. Interestingly, contralateral strokes were reduced in the surgical group, as well as the ipsilateral strokes. Net benefits were significant both for men and for women up to 75 years at entry; benefits for patients older than 75 were not established.

With the marked increase in use of lipid-lowering drugs over the course of the study period, it was particularly interesting to note that the benefits of endarterectomy were significant both for patients on lipid-lowering therapy as well as those not. However, absolute risks of stroke were less in patients on lipid-lowering therapy, so that risk reductions by surgery were cut nearly in half in these patients, with absolute risk reductions of 2.1 % at 5 years, and 5.0 % at 10 years. Thus, while ASCT-1 gives further documentation of the benefit of carotid endarterectomy for asymptomatic carotid disease, it also confirms the beneficial effects of statin therapy and the increasingly narrow window for producing benefit by intervention with advancement of medical therapy.

The benefits of surgery over medical therapy in these trials, when considered in terms of absolute risk reduction for stroke, have been modest, because of the low underlying risk of stroke in medically treated patients. Moreover, the advancement of medical therapy for stroke prevention since the era in which these trials were conducted has included introduction of widespread use of statin therapy, additional options for antihypertensive medications, and new antiplatelet agents in addition to aspirin. Indeed, a recent small prospective study suggested a substantially lower annualized risk of stroke or TIA in ACS patients with asymptomatic carotid stenosis >50 %, treated medically [6], compared to the annualized risks above 2 % in medical groups in most of these trials (Table 26.2). These considerations have led to a growing impression among some physicians that medical treatment alone might be the appropriate best management for most patients with asymptomatic carotid stenosis. On the other hand, an important fraction of the strokes ascribed to the surgical arms of two of these studies occurred due to cerebral angiography, a procedure that is no longer widely used prior to endarterectomy today. Other surgical techniques are likely to have advanced as well. The evidence from ACST-1 can be cited as evidence that even in patients on lipid-lowering therapy, carotid endarterectomy has measurable benefit for secondary stroke prevention. Thus advocates of both medical and surgical management can claim that results would be better in their study arms now.

Table 26.2 Annualized stroke rates in prospective clinical studies of asymptomatic carotid disease patients

Study (years run)	Patient group (% asymptomatic)	Carotid stenosis severity	Medical therapy used	Peri-procedure risk (any stroke[a] or death)	Annualized stroke risk (medical group)	Annualized stroke risk (surgical group)
VA study (1983–1987)	444 male veterans (100 %)	50–99 % (by angiogram)	Aspirin 650 mg BID	4.7 % (3 of 8 strokes due to angio)	2.4 % (9.4 % over 4 years)	1.2 % (4.7 % over 4 years)
ACAS (1988–1993)	1662 (100 %)	>60 % (angiogram in surgical patients only)	Aspirin 325 mg daily	2.3 % (5 of 19 strokes due to angio)	2.2 % (11.0 % projected to 5 years)	1.0 % (5.1 % projected to 5 years)
ACST-1 (1993–2003)	3120 (100 %)	"Severe" by Doppler; (generally >60 % but no fixed minimum)	Variable; increasing statin use over the study period	3.0 %	2.2 % (10.9 % over 5 years)[a]	1.4 % (6.9 % over 5 years)[a]
CREST (2000–2008):		>60 % by angiography or >70 % by ultrasound	"current standard of care" after perioperative period	Rates over all patients:		
CEA group	47.3 % of 1240 patients			2.3 %	–	0.7 % (2.7 % over 4 years)[a,b]
CAS group	47.1 % of 1262 patients			4.4 %	–	1.1 % (4.5 % over 4 years)[a,b]
ACES (1999–2007):		>70 % by ultrasound	Not defined			
(−) micro-embolic signal	84 % of 482 patients			–	0.7 %	–
(+) micro-embolic signal	16 % of 482 patients			–	3.6 %	–

Procedural annualized rates reported include peri-operative period stroke and death risks

VA veterans affairs, *ACAS* asymptomatic carotid atherosclerosis study, *ACST-1* the asymptomatic carotid surgery trial 1, *CREST* carotid revascularization endarterectomy vs. stenting trial, *ACES* asymptomatic carotid emboli study, *CEA* carotid endarterectomy, *CAS* carotid angioplasty and stenting

[a]Includes contralateral stroke events

[b]Includes death events

Management Guidelines

With this evidence base, how should the patient with asymptomatic carotid stenosis be managed today? Interest in answering this question has propelled planning for a new major randomized trial comparing contemporary medical therapy against intervention with either endarterectomy or angioplasty and stenting, resulting in initiation of the CREST-2 trial, currently in early stages of patient enrollment.

Expert opinion, as codified in national guidelines such as those published by the American Heart Association or the American Academy of Neurology, has been noncommittal regarding recommendations for patients with asymptomatic carotid stenosis. The joint American Stroke Association-endorsed guideline of 2011 [7] concluded with a recommendation that "it is reasonable to perform CEA in asymptomatic patients who have more than 70 % stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low", and stated conditions under which "it is reasonable" to choose either CEA or CAS when revascularization is indicated. For those asymptomatic patients with less severe stenosis of 60 % by angiography or 70 % by validated Doppler ultrasound, a recommendation was made that CAS might be considered, "but its effectiveness compared with medical therapy alone … is not well established." These guidelines wisely leave room for individualized patient decisions.

However, in the same year, an editorial in the American Academy of Neurology's journal, *Neurology*, offered a strong opinion that "there is increasing evidence that best medical treatment alone might be the appropriate management for patients with asymptomatic carotid stenosis" [8]. The same issue contained papers describing approaches attempting to stratify asymptomatic carotid plaques between those at low risk for subsequent embolization and clinical events, and those at higher risk, with evidence that these methods of risk stratification could separate the small group of asymptomatic carotids stenosis patients with a high risk of stroke in follow-up from the majority of patients with low risk. Both groups used as one feature the detection by transcranial Doppler (TCD) monitoring of high intensity transient signals suggestive of microemboli. Detection of any microemboli in either of 2 one hour TCD monitoring sessions had been previously described in the Asymptomatic Carotid Emboli Study (ACES), in a prospective fashion, as indicating a fivefold higher risk of ipsilateral ischemic stroke over a 2 year period [9]. In the 2011 publication, the patients from this study database who had both detection of microemboli and carotid artery plaque graded as echolucent on duplex ultrasonography were found to have an 8 % annual risk of ipsilateral stroke over 2 years of monitoring, a risk increased by more than 10 fold over those patients without both of these features, who had annual risks under 1 % [10]. Another study used three dimensional ultrasound to identify plaque ulcerations, and found that the combination of at least 3 plaque ulceration with detection of microemboli by TCD monitoring also predicted a group with markedly elevated stroke risk, in a 3 year monitoring period, over those without these features [11]. Patients without these markers of risk again had a very low rate of stroke, with a combined stroke and death rate of 2 % over 3 years. Both studies, like the ACES study, identify a minority of patients with elevated risk, and find that when

these patients are separated out, the remaining majority of asymptomatic carotid stenosis patients have risks that compare favorably with those in surgically-treated cohorts (Table 26.2). Reviewing these results, the editorialists noted the promise of these approaches to risk stratification, but also the need to confirm these results in more "adequately powered" studies", and they concluded that for patients with asymptomatic carotid stenosis, "it seems necessary and prudent to argue for intensified medical management rather than revascularization procedures", casting doubt on the appropriateness of intervention for asymptomatic carotid disease in general [8].

Applying structured grading of the quality of evidence [12] to this question, it can be observed that while the quality was fairly strong of the original randomized studies such as ACAS and ACST-1 that demonstrated benefit of CEA over medical therapy, the magnitude of the benefit to absolute stroke rate was modest, at best. The advancement in therapy since the time of these trials were performed confers significant variability to the recommendation. The overall recommendation in favor of carotid endarterectomy for patients with severe asymptomatic stenosis is thus conditional. The decision must depend on patient factors and preference. For carotid angioplasty and stenosis, there is only indirect evidence for benefit, as CAS has only been directly compared to CEA in prospective randomized trials. Thus the modest benefit over medical therapy is only indirectly inferred, with concerns that the higher peri-procedural stroke rate found for CAS over CEA in the CREST trial [13] may eliminate the benefit over medical therapy. The recommendation for CAS must be conditionally against the procedure for routine use for asymptomatic stenosis, reserving consideration of it for young patient with severe stenosis and factors precluding endarterectomy.

Recommendations

- Asymptomatic carotid plaque lacking complex features and producing only a mild to moderate degree of stenosis is best managed medically. Medical treatment should include aggressive targeting of risk factors, especially smoking, hypertension and diabetes, treatment with high-intensity statin therapy, and long-term treatment with antiplatelet monotherapy with clopidogrel or aspirin (**Evidence quality moderate; strong recommendation**).
- In patients with severe asymptomatic carotid stenosis, >70 % by NASCET-like criteria, determined by non-invasive methods, CEA can be recommended conditionally in appropriate patients, in centers with peri-procedural risks of stroke and death under 3 % (**Evidence quality moderate; strong recommendation**).
- Additional features of the plaque morphology, echogenicity, and activity in producing TCD-detectable microemboli may contribute to assessment of risk and to decision-making (**Evidence quality weak; moderate recommendation**).
- Routine use of endovascular angioplasty and stenting for asymptomatic carotid stenosis is not recommended. In young patients with severe asymptomatic stenosis, with plaque features suggesting high risk, and with factors limiting the appropriateness of endarterectomy, carotid angioplasty and stenting may be considered as an alternative to medical therapy (**Evidence quality weak; strong recommendation**).

A Personal View of the Data

In all cases, it is appropriate to counsel patients that the absolute benefits of surgical revascularization are probably lessened compared to those reported in the older trials, due to advancements in medical therapy. For many patients, risk reduction by medical therapy may be similar to that achieved by surgical or endovascular revascularization. Periodic monitoring of asymptomatic plaque with non-invasive duplex ultrasound imaging is reasonable. If significant plaque progression from a moderate to more severe degree of stenosis occurs, carotid revascularization is reasonable in low-risk patients.

Features of microemboli detection, plaque echolucency, or plaque ulceration may be used as predictors of stroke risk in asymptomatic carotid stenosis patients, although outcomes-based trials of risk-stratifying strategies are lacking. It is reasonable to suppose that such features that significantly elevate the natural history risk under medical treatment, would substantially tip the balance between risks and benefits in favor of recommending endarterectomy for asymptomatic carotid disease.

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Chapter 27
In Patients with Symptomatic Carotid Artery Stenosis Is Endarterectomy Safer Than Carotid Stenting?

Benjamin Colvard and Wei Zhou

Abstract Stroke is a leading cause of morbidity, mortality, and health care expenditure in the United States. Carotid disease accounts for a significant number of ischemic strokes and debate continues as to the most appropriate management for symptomatic carotid stenosis. The importance of surgical intervention, i.e. carotid endarterectomy (CEA), for symptomatic carotid stenosis has been widely accepted based on multiple well-constructed trials published in the early 1990s. Carotid artery stenting (CAS) was initially approved by the FDA in 2004, and has gained momentum as an alternative to CEA. A number of multicenter trials have demonstrated the safety of CAS in both asymptomatic and symptomatic patients; however questions remain as to the long-term durability, as well as the proper patient selection for CAS. In this chapter, we review the current methods of treatment of symptomatic carotid stenosis, and discuss factors that influence the decision to perform CEA or CAS. In general, if the surgeons risk of stroke is acceptably low, CEA should be performed for patients with a >50 % symptomatic carotid stenosis. CAS should only be considered as an alternative for those with prohibitive medical comorbidities, and those with hostile anatomy.

Keywords Carotid endarterectomy • Carotid stenting • Carotid stenosis • Stroke care • Safety

Introduction

Stroke is the fourth leading cause of death in the United States, and is a leading cause of disability and healthcare expenditure. In fact, almost 800,000 Americans experience a new or recurrent stroke each year, which resulted in direct and indirect

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costs of $36.5 billion in 2010. It is estimated that 87 % of strokes are ischemic, with an estimated 20–30 % thought to be the result of atherosclerotic carotid artery disease [1, 2]. Given these data, the prevention of stroke and TIA due to extra-cranial carotid occlusive disease is an important health care goal, which has been the topic of large amounts of research, and controversy remains regarding the optimal management of this disease.

Multiple clinical trials have demonstrated the superiority of CEA over medical management in patients with symptomatic carotid disease [3–5]. Over the past two decades however, the management of symptomatic carotid disease has evolved with the increased use of carotid artery stenting and improved medical therapy. While CEA remains the most frequently performed operation for stroke prevention, the rate of CAS has increased dramatically. Dumont and colleagues queried the Nationwide Inpatient Sample (NIS) between 1998 and 2008 and found that the number of CEAs performed remained fairly stable, at about 21,000 per year. As the NIS database represents roughly one fifth of patients treated in the US, the number of CEAs performed per year is estimated at 105,000. During this same period, the rate of CAS increased from 2.8 to 12.6 % of all carotid revascularization procedures. The total number of CAS performed in the US was estimated at 3235 in 1998, and 15,655 in 2008 [6]. For symptomatic carotid disease, the current Society for Vascular Surgery (SVS) guidelines recommend CEA as the first-line therapy for patients with a greater than 50 % stenosis, with CAS being reserved for those with unfavorable anatomy (prior surgery, radiation, high lesions), or prohibitive medical comorbidities (severe CAD, COPD, or CHF) [7]. In addition, a multi-specialty consensus statement broadly recommends CAS as an alternative to CEA in symptomatic patients with greater than 50 % ICA stenosis if the expected periprocedural stroke or mortality rate is less than 6 % [8]. This chapter addresses reported safety of CAS versus CEA for symptomatic carotid stenosis.

Search Strategy

A computer-assisted literature search of English language publications from 1991 to 2014 was used to identity published data on the safety of CAS and CEA in symptomatic carotid stenosis, using the PICO outline (Table 27.1). Databases searched were Medline, and Cochrane Evidence Based Medicine. Terms used in the search were “symptomatic carotid stenosis, AND endarterectomy, AND stent”, “carotid endarterectomy AND carotid stenting AND outcomes”, “carotid endarterectomy versus carotid stenting”, and “CEA versus CAS”. Electronic links to related articles and reference lists of selected articles were hand-searched to retrieve more studies. Articles were excluded if they specifically addressed asymptomatic carotid stenosis. The data was classified using the GRADE system.

Table 27.1 PICO table for safety of CEA over CAS for symptomatic carotid artery stenosis

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with symptomatic carotid stenosis	CEA or CAS	Best medical management, CAS, or CEA	Myocardial infarction, stroke, death

Results

Major Trials

The current SVS guidelines for treatment of symptomatic carotid disease recommend surgical intervention for patients with symptomatic carotid stenosis of 50 % or greater [7]. The benefit of carotid endarterectomy for symptomatic carotid stenosis is widely accepted. Multiple randomized, multicenter trials have demonstrated this benefit [3–5]. The NASCET trial was one of the first such studies, and included over 600 symptomatic patients across 50 centers in the US and Canada. In this study, symptomatic patients with ≥70 % stenosis of the internal carotid artery (ICA) based on carotid duplex criteria, were randomized to either medical management alone (antiplatelet agent, antihypertensive agents, antilipid therapy, and antidiabetic therapy), or medical management in addition to CEA. Randomization was terminated early in February of 1991 due to strong evidence of benefit for CEA over medical management alone in patients with high-grade stenosis. They demonstrated an absolute risk reduction (ARR) of 17 % for ipsilateral stroke at 2 years. This was in the context of perioperative risk of stroke or death of 2.1 %. Months after this paper was published, the smaller, VA cooperative study was released and further illustrated the benefit of CEA in symptomatic male patients. This trial randomized 193 men with symptomatic carotid stenosis of ≥50 % to either CEA with medical management, or medical management alone. They demonstrated an ARR of 11.7 % for CEA vs. medical management. In patients with >70 % stenosis, this benefit was even more profound with an ARR of 17.7 %. The risk of stroke in patients undergoing CEA was 7.7 % over 11.9 months, compared with 19.4 % in nonsurgical patients. The perioperative stroke or death rate was 5.5 % in this study (2.2 % stroke, 3.3 % mortality) (VA coop study). The European Carotid Surgery Trial (ECST) was published 7 years later, and showed benefit of CEA in symptomatic patients with greater than 80 % stenosis. They randomized 3024 symptomatic patients across 97 centers in Europe and Australia. The risk of major stroke or death in the perioperative period was 7 %. They were only able to show benefit for CEA in patients with 80 % stenosis, and this benefit was gained at 3 years from surgery, with an ARR of 11.6 %. Their analysis also demonstrated higher perioperative risk in women, leading to their recommendation to operate on symptomatic carotid stenosis of 90 % or greater in women. However, the criteria on degree of stenosis were significantly different between NASCET and ECST. For example, 80 % stenosis based on ECST criteria is

equivalent to roughly 70 % stenosis by NASCET criteria. In 2002, the ECST group published long-term data that demonstrated a 4.5 % risk of ipsilateral stroke at 10 years, suggesting that CEA is a durable treatment for symptomatic carotid stenosis [9]. Finally, in 2011, Rerkasem and Rothwell published a review comparing the results of the NASCET, VACSP, and ECST trials. They highlighted the fact that one of the major differences in the trials was in the measurement of carotid stenosis on angiograms, resulting in higher levels of stenosis in the ECST trial compared to both NASCET and VASCP. The authors obtained the patient data from all three trials and merged them into a single composite database. The ECST angiograms were reviewed and stenosis recalculated based on the methods used in NASCET and VASCP to achieve uniformity between the three studies. They found no significant difference in operative stroke or death rate, which was 7 %, and higher in women. Their analysis showed that the benefit of CEA increases with increasing degree of stenosis. The number needed to treat to prevent one event at 5 years was six for ipsilateral stroke and operative stroke or death. In a comparison between ECST and NASCET, the NNT (number needed to treat to prevent one event) at 5 years for patients with 50–99 % stenosis was nine for men, and 36 for women. Age also had an effect, with a NNT of five for age ≥75, and 18 for age <65. Thus, they showed a benefit for CEA in women with ≥70 % stenosis, and men with stenosis ≥50 % [10].

These landmark studies were instrumental in designating CEA as the gold standard in the treatment of symptomatic carotid stenosis. CAS was first performed in 1994, and was approved by the FDA in 2004. The safety of CAS has been evaluated in multiple studies (Table 27.2). The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was one of the first studies to investigate endovascular treatment as a therapy for carotid occlusive disease [11]. This study enrolled both symptomatic and asymptomatic patients, and randomized them to either CEA or endovascular treatment (angioplasty and/or stent). Of a total of 504 randomized patients, they had a 10 % stroke or death rate in the endovascular arm, and a 9.9 % rate in the CEA arm. The rate of cranial nerve injury was 8.7 % in the surgery arm, and none were reported in the endovascular arm. This study was the first to suggest that CAS was at least as safe as CEA in treating carotid stenosis. However the study is criticized for having an unacceptably high stroke or death rate for CEA. The durability of CAS was also called in to question based on their finding of significantly increased rate of ipsilateral high-grade stenosis in the CAS group at 1 year. Nonetheless, technical advances in CAS have resulted in the more widespread use of embolic protection devices, as well as stenting, rather than angioplasty alone.

The first major trial to evaluate CAS was the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial. This trial enrolled symptomatic and asymptomatic patients who had at least one high-risk criterion. 334 patients were randomized to CEA or CAS with embolic protection. Cranial nerve palsy was observed in 4.9 % of CEA patients, and again, none for CAS patients. The 30-day stroke, MI, or death rate was 4.4 % in the CAS arm, and 9.9 % in the CEA arm (P = 0.06). This outcome was similar in the subgroup analysis for symptomatic patients. They concluded that CAS was not inferior to CEA in high risk patients with symptomatic and asymptomatic carotid stenosis. In fact, the

Table 27.2 Major trials comparing CAS and CEA in symptomatic patients with carotid stenosis

Trial	Symptomatic patients/total patients	30-day outcome (%) (CAS/CEA)	≥1 year outcome (%) (CAS/CEA)	Cranial nerve injury (%) (CAS/CEA)
CAVATAS	488/504	Stroke or death 10/10 (Includes 16 asymptomatic patients)	Disabling stroke, death 14.3/14.2 (3 years)	0/8.7
SAPPHIRE	96/334	Stroke, death, or MI 2.1/9.3 (p=0.18)	Stroke, death, or MI 16.8/16.5 (p=0.95) (1 year)	0/4.9
CREST	1321/2502	Stroke, death, or MI 6.7/5.4 (HR 1.26)	No symptomatic subgroup analysis	0.3/4.7
SPACE	1214/1240	Ipsilateral stroke or death 6.8/5.5 (RR 1.24) (excluding major protocol violations)	Ipsilateral ischemic stroke or vascular death 10.3/9.4 (HR 1.18) (2 years)	Not given
EVA-3S	527/527	Stroke or death 9.6/3.9 (RR 2.5)	Non-procedural ipsilateral stroke 1.5/1.5 (4 years)	Not given
ICSS	1710/1710	Stroke, death, or MI 7.4/4 (p=0.003)	Fatal or disabling stroke 3.4/4.3 (p=0.03)	0.1/5.4

CAS carotid artery stent, *CEA* carotid endarterectomy, *MI* myocardial infarction, *HR*: hazard ratio, *RR* relative risk, *CAVATAS* the carotid and vertebral artery transluminal angioplasty study, *SAPPHIRE* stenting and angioplasty with protection in patients at high risk for endarterectomy, *CREST* carotid revascularization endarterectomy versus stenting trial, *SPACE* stent-protected angioplasty versus carotid endarterectomy, *EVA-3S* endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis, *ICSS* international carotid stenting study

primary endpoint incidence (30-day death, stroke, or MI, plus 1-year ipsilateral stroke or death from neurologic causes) was significantly lower in the CAS arm. This study would eventually lead to the approval of CAS for symptomatic, high-risk patients. Furthermore, 3-year outcomes of the SAPPHIRE study participants continued to show non-inferiority of CAS, with no significant difference in risk of target vessel revascularization, stroke, or other major adverse event at 3 years [12]. Critics of the SAPPHIRE trial cite potential bias based on commercial funding, and the participation of the inventor of the protection device as an investigator [13]. In addition, the high rate of stroke in the CEA arm is thought to be unacceptably high and non-applicable to most centers of excellence.

There are three more contemporary trials (SPACE, EVA-3S, and ICSS) comparing CEA and CAS for symptomatic patients. The Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial was published in 2008, and randomized 1214 symptomatic patients to either CAS or CEA. [14] 60 patients were excluded for major protocol violations, resulting in a per protocol cumulative incidence of stroke or death within 30 days of 6.81 % for CAS, and 5.51 % for CEA. The rate of ipsilateral stroke between 30 days and 2 years was 2.2 % for CAS, and 1.9 % for

CEA. Again, recurrent stenosis was significantly more common in the CAS group than the CEA group (11.1 % vs. 4.6 %, P = 0.0009). This study also demonstrated an age-related benefit. Patients <68 years old had significantly less periprocedural risk with CAS than CEA, while CEA was significantly less risky in those over 68 years of age. The authors concluded that CEA had better outcomes in the periprocedural time in symptomatic patients compared to CAS, however at 2 years there was no difference in the prevention of recurrent neurologic events. This study was limited by lack of power to detect differences in CAS and CEA beyond the periprocedural time frame, as well as a significant dropout rate which may have skewed their results.

In 2008, 4 year results of the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial were published [15]. This study randomized 527 symptomatic patients with >60 % stenosis to either CEA or CAS (with embolic protection). They found that 6.2 % of CEA patients suffered either ipsilateral stroke or death within 30 days of their procedure, compared to 11.1 % of CAS patients (a hazard ratio of 1.97). In addition, they again showed increased risk of CAS in patients over 70 years of age. They found that the 4 year cumulative risk of stroke or death was higher for CAS, and that this risk was primarily during the periprocedural period. They concluded that CAS is effective at preventing medium term ipsilateral stroke, but that the procedure should be improved in order to be accepted as an alternative to CEA in symptomatic patients.

Short-term results of the International Carotid Stenting Study (ICSS) were published in 2010. This was an international, multicenter, randomized, controlled trial comparing CEA to CAS in patients with recently symptomatic carotid stenosis. It is the largest trial to date comparing stenting to endarterectomy in symptomatic patients. They randomized a total of 1713 patients to either CEA or CAS, and had 821 patients in the per protocol CEA arm, and 828 in the per protocol CAS arm. Embolic protection was used in 72 % of CAS cases. They demonstrated a 30-day procedural risk of stroke, death, or MI that was higher in the CAS arm (7.4 % vs. 4 %). The rate of cranial nerve injury for CEA was 5.4 % (with only 1 event resulting in disability), and hematoma requiring intervention or extended hospital stay was 0.9 % in the CAS arm, and 3.4 % in the CEA arm ($p = 0.0007$). The authors concluded that CEA was safer than CAS for patients with symptomatic carotid stenosis, with CAS having an almost doubled risk of stroke, death, or MI. The trial is criticized for lack of consistent usage of embolic protection device and heterogeneous experience of stent operators. In 2014, long-term results of the study were published. The 5-year cumulative risk of fatal or disabling stroke was not significantly different between the two groups (6.4 % for CAS, 6.5 % for CEA). CEA had a lower risk of procedural stroke or death, and ipsilateral stroke during follow up, than CAS (7.2 % vs. 11.8 % cumulative 5-year risk). This difference was mainly due to more non-disabling strokes in the CAS group. The authors therefore concluded that stenting was as effective as endarterectomy in preventing fatal or disabling stroke up to 10 years after treatment [16, 17].

Most recently, the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) was published in 2010 and was a landmark multicenter prospective randomized study that enrolled both symptomatic and asymptomatic patients [18]. A

total of 2502 patients were randomized to either CEA, or CAS. There was no significant difference in the primary endpoint of periprocedural (within 30 days) stroke, MI, or death, between the two groups (7.2 % for CAS, 6.8 % for CEA). They did observe a significantly higher rate of periprocedural stroke in the CAS group (4.1 % vs. 2.3 %, P = 0.012), and a higher rate of MI in the CEA group (2.3 % vs. 1.1 %, P = 0.032). At 4 years, there was no significant difference in ipsilateral stroke. The risk of cranial nerve palsy for CEA was 4.7 %. They also showed that patients >70 years had better outcomes with CEA, while patients <70 were better served by CAS, which was also shown in the SPACE trial. Importantly, in symptomatic patients, CAS had a significantly higher stroke and death rate than CEA (6 % vs. 3.2 %). Critics of this study cite the inclusion of periprocedural MI as a primary end-point, especially given their inclusion criteria for MI which were quite mild and included minor myocardial infarctions that would be unlikely to cause significant effect on a patient's long-term health. CAS was again shown to have higher stroke and death rates in symptomatic patients, females, and older patients, which raised the question whether CAS and CEA are actually equivalent for symptomatic patients [19].

Local Complications

When considering the safety of CEA versus CAS, the risk of stroke and death are the major outcomes that are typically evaluated. Local complications should be considered as well given their potential to cause long-term morbidity, and secondary interventions. Cunningham et al. reviewed data from the ECST trial to estimate the risk of motor cranial nerve (CN) injury during CEA. 6.2 % of patients in the ECST trial suffered one or more cranial nerve palsies (including motor and sensory deficits). At four month follow up, 8 % of these injuries were persistent, and all of these persisted out to the 2 year follow up [20]. Schauber and colleagues prospectively reviewed 183 CEA procedures with thorough neurologic evaluations pre- and post-operatively. They reported an incidence of CN injury of 14.2 %, with 1.1 % being permanent [21]. CN injury is generally a minor, transient complication of CEA, however it can be permanent and given the essentially negligible risk associated with CAS, it should be considered when choosing one procedure over the other. This consideration is especially important in the re-operative patient or post-radiation patient, as well as those with a previous contralateral CN injury.

Personal View of the Data

Symptomatic carotid stenosis is frequently encountered in the clinical practice of vascular surgeons. The recommendation to intervene on symptomatic carotid stenosis is based on sound evidence (NASCET, ECST, and VASCP), however the choice of endarterectomy or stenting is less clear. It is reasonable to consider CEA in

symptomatic patients with ipsilateral carotid stenosis of ≥50 %, if the operative risk of stroke is <6 %. Patients should be expected to have reasonable functional status following the neurologic event that prompts surgical evaluation. In addition, data from CREST, and SPACE would suggest that in patients >70 years of age, CEA is safer than CAS. In patients with comorbidities prohibitive of general anesthesia, CAS is a reasonable alternative. Patients should be well informed of the risk of local complications, including cranial nerve injury, which is not negligible. Given the higher rate of cranial nerve injuries in certain groups of patients (prior ipsilateral operation, irradiation, stomas), CAS is also considered a reasonable alternative. Based on multiple large prospective randomized trials, CEA is a better option than CAS with lower periprocedural stroke and death rates. Long-term outcomes, excluding peri-operative events, appear to be similar between the two approaches. Information on how best medical therapy shapes the treatment decision and outcome is still lacking.

Recommendations

- In patients with symptomatic carotid stenosis intervention is recommended. (**Evidence quality is strong; recommendation is strong**).
- It is reasonable to consider CEA in symptomatic patients with ipsilateral carotid stenosis of ≥50 % (**Evidence quality is strong; recommendation is strong**),
- In patients with prohibitive comorbidities, CAS is a reasonable alternative (**Evidence quality is strong; recommendation is strong**).

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Chapter 28
In Patients Undergoing Carotid Endarterectomy, Is the Eversion Technique Superior to a Patch Technique to Reduce Restenosis?

Lewis B. Schwartz

Abstract Carotid endarterectomy (CEA) is the treatment of choice for symptomatic carotid stenosis and selected asymptomatic lesions. CEA is most often performed via a longitudinal anterior arteriotomy in the common carotid artery (CCA) extending through the carotid bulb and into the internal carotid artery (ICA). Many surgeons feel that this so-called "standard" technique (sCEA) allows for optimal visualization and excision of the plaque, and maximally facilitates arterial reconstruction. An alternative technique, known as "eversion endarterectomy" (eCEA) has also been popularized. eCEA is performed by transecting the carotid bulb just below the bifurcation and removing the plaque by everting the media/adventitia using the plaque as a mandrill over which to establish a cleavage plane. The purpose of this chapter is to describe, review and compare these methods of CEA, and make recommendations as to the optimal technique of the operation.

Keywords Carotid • Endarterectomy • Carotid endarterectomy • Eversion technique • Stroke

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Introduction

Standard Carotid Endarterectomy (sCEA)

The hallmark of the standard technique of CEA (sCEA) is longitudinal carotid arteriotomy. It was originally performed by Michael DeBakey in 1953 in a patient with stroke and carotid occlusion [1], and first described by Felix Eastcott and Charles Rob in 1954 who explored and then resected the diseased carotid bifurcation of a woman who was found to have critical stenosis after sustaining 33 separate transient ischemic attacks [2].

In the modern era, sCEA is performed via a cervical skin incision parallel and anterior to the sternocleidomastoid muscle. Following incision, the platysma muscle is divided, the internal jugular vein retracted laterally and the facial vein ligated. The carotid sheath is incised and the common carotid (CCA), external carotid (ECA), internal carotid (ICA) and superior thyroid arteries identified and controlled. In order to expose the proximal ICA, the descending branch of the ansa cervicalis is divided facilitating superomedial retraction of the hypoglossal nerve. The patient is systemically anticoagulated and the internal, common and external carotid arteries sequentially clamped. A longitudinal arteriotomy is made in the CCA extending onto the ICA, and a cleavage plane developed within the arterial media to extract the plaque under direct vision (Fig. 28.1). The endarterectomy proceeds in the proximal-to-distal (caudal-to-cranial) direction. When the ECA is reached, it is endarterectomized via eversion by temporarily releasing its clamp. Finally, the distal portion of the plaque lining the proximal ICA is excised under direct vision, with care to make its endpoint smooth and free of residual stenosis.

The sCEA technique is ubiquitous, being utilized in the majority of the more than 100,000 CEA procedures performed annually [4]. It was the primary technique employed by investigators demonstrating the efficacy of the procedure in multicenter randomized trials [5, 6]. The contemporary clinical results of CEA are, perhaps, best illustrated by the *Carotid Revascularization Endarterectomy vs. Stenting Trial* (CREST) trial which randomized 2502 patients with carotid stenosis to undergo either CEA or carotid artery stenting in 117 North American centers [7]. Although the use of the sCEA wasn't mandatory, the fact that 62 % of patients underwent patch angioplasty suggests that it was the dominant technique. For the 1240 patients undergoing CEA in the trial, the overall risks of death, major ipsilateral stroke and any stroke were 0.3 %, 0.3 % and 2.3 %, respectively. It's instructive to note that the overall incidence of periprocedural stroke in patients undergoing primary CEA (2.3 %) was statistically significantly lower than in patients undergoing primary stenting (4.1 %; $p = 0.01$).

Proponents of the sCEA technique point to its proven clinical utility and the fundamental surgical advantage of direct visualization of the distal extent of the plaque. Other potential benefits include the relative ease of intraluminal shunt insertion, the option to provide enhanced luminal size through the use of patch angioplasty, the avoidance of circumferential dissection with minimal disturbance of the

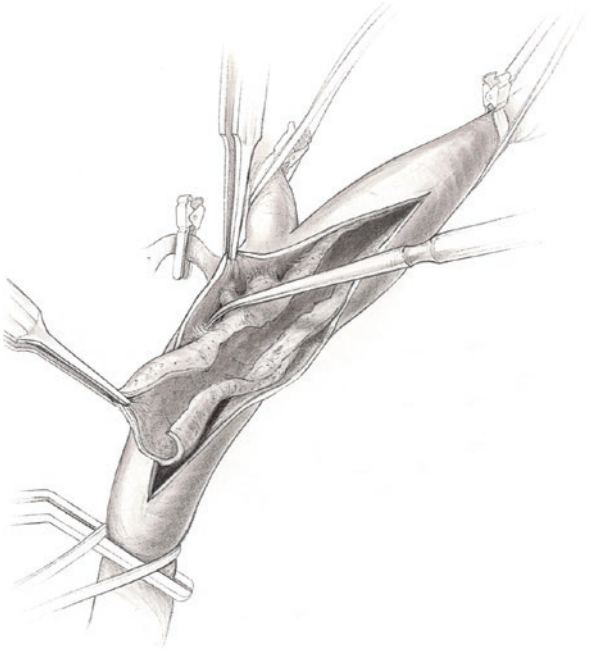

Fig. 28.1 Standard carotid endarterectomy (Adapted from Zarins and Gewertz [3]. With permission from Elsevier)

carotid baroreceptors, and the efficiency with which the procedure can be taught to surgical trainees.

The technical success of sCEA technique depends, in some measure, upon successful eversion endarterectomy of the ECA. Indeed, the ease of ECA eversion was likely the stimulus for the rise in popularity of the alternative technique: eversion CEA (eCEA).

Eversion Carotid Endarterectomy (eCEA)

ECEA was originally described by Michael DeBakey in his classic clinical review of extracardiac vascular surgery published in 1959 [8–10]. It is performed via a similar incision as sCEA, although some would argue that eCEA requires only a limited operative field and can be performed through a smaller incision. Surgical exposure of the carotid bifurcation proceeds identically to sCEA, except that the arteries should be freed from the surrounding tissues circumferentially, and division of the superior thyroid artery should be performed as a matter of routine.

Once the arteries have been exposed and clamped, the CCA is transected just proximal to the bifurcation. Figure 28.2 depicts a CCA that is transected transversely, although many authors recommend oblique transection as a means to facilitate visualization and closure. Following division of the CCA, endarterectomy of the ICA and ECA is performed by developing a cleavage plane within the arterial

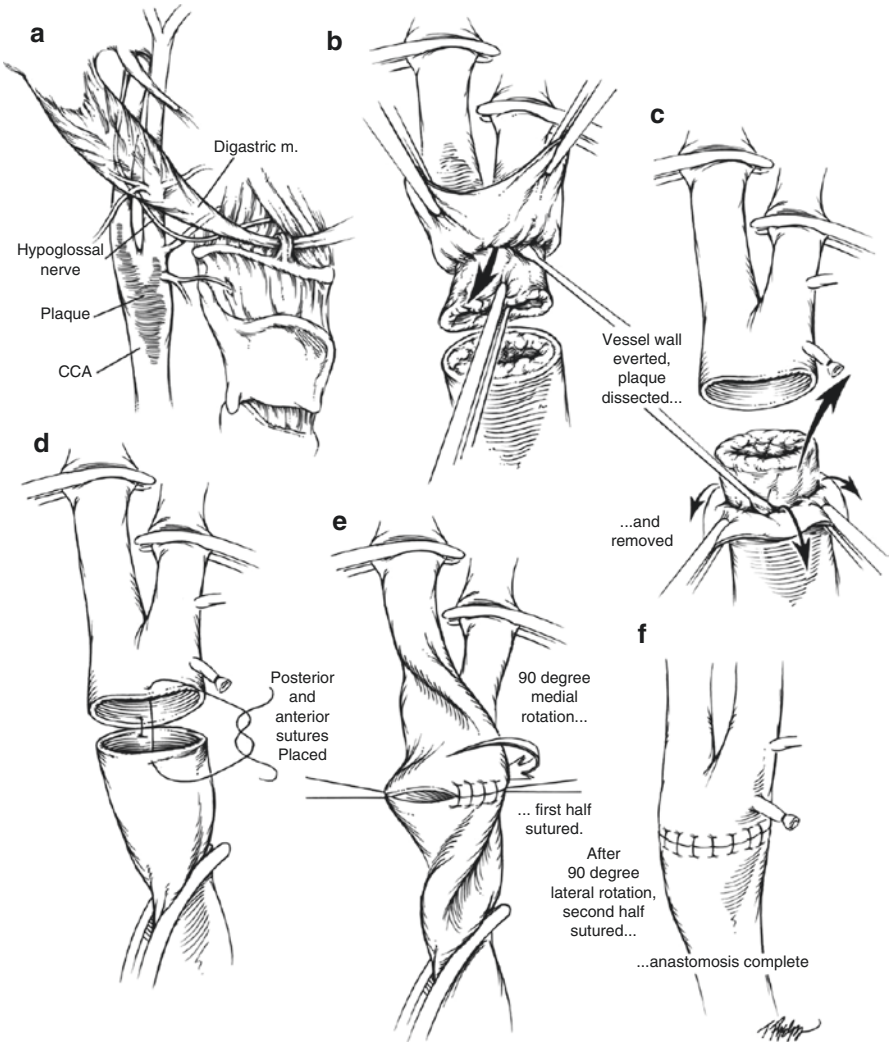

Fig. 28.2 Eversion carotid endarterectomy (Adapted from Black et al. [11]. With permission from Elsevier)

media and everting it over the plaque (Fig. 28.2b). The plaque acts as a natural mandrill over which to fold the artery; it is gently retracted caudad to facilitate the dissection. Eversion CEA of the ECA is performed in an identical fashion as in sCEA. Because primary carotid plaques are localized to the bulb and proximal ICA, downward retraction and careful blunt withdrawal of the plaque will cause it to "pop" out of the ICA once it reaches its natural endpoint. The result is complete excision of the plaque from the both the ECA and ICA with achievement of a smooth residual lumens that contain no suture lines (Fig. 28.2c).

Attention is then turned toward the CCA which is everted in a similar fashion through, theoretically, the same cleavage plane. There's rarely a natural proximal endpoint of the plaque within the CCA so it's transected sharply after a distance of approximately 2 cm. If the ICA is redundant, a rim of CCA can be resected to accomplish its straightening. End-to-end anastomosis of the two ends of the transected CCA is facilitated by rotating the "freely floating" artery within the field (Fig. 28.2e). The completed reconstruction bears no suture line within the ICA (Fig. 28.2f). In the 1990s, several surgeons described modifications to the above technique, most notably Vanmaele et al. who proposed transection, eversion and reimplantation of the ICA at its origin [12], and Reigner et al. who described oblique transaction of the ICA distal to the lesion followed by eCEA through longitudinal incision of the CCA and ECA [13].

Proponents of the eCEA technique point to the more limited dissection it requires, the rapidity in which it can be performed, the ease to which arterial redundancy can be addressed, the advantages of placing sutures in the widest part of the bifurcation, the avoidance of patches leading to better fluid dynamics [14], the fact that the reconstruction is accomplished without tacking stitches or suture lines in the ICA [15, 16] and, potentially, reduced restenosis [17]. Some even advocate the procedure for recurrent stenoses [18, 19].

Search Strategy

A search of the University of Chicago *Articles Plus* + database was conducted for the years 1997–2015 to identify published data regarding open surgical approaches to treat carotid artery disease using the PICO outline (Table 28.1). The University of Chicago *Articles Plus* + is a database and search tool that allows simultaneous searching of a broad range of articles, books, and other collections. An *Articles Plus* + search includes hundreds of the Library's article databases, including MEDLINE, Science Direct and Academic Search Premier, over 40,000 journals and periodicals, the University of Chicago library catalog, and digitized collections of documents and images from a variety of organizations.

Eight comparative trials, and four single arm studies, were included in the analysis (see Tables 28.2 and 28.3).

Table 28.1 PICO table for technical approach to CEA

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients undergoing carotid endarterectomy	Standard carotid endarterectomy	Eversion carotid endarterectomy	Restenosis Stroke Death

Table 28.2 Large single-arm series of eCEA

Author and Reference	Year	n (CEAs)	Sympto-matic (%)	Shunt use (%)	Mean cross-clamp time (min)	Cranial/ cervical nerve injury (%)	Reexploration for hemorrhage (%)	Peri-operative stroke/death (%)	Median follow-up (years)	Restenosis (%)	Late ipsilateral stroke (%)
Ballotta et al. [20]	2014	1773	72 %	16 %	NR	4.5 %	4.3 %	0.4 %	11.2	0.5 %	0.5 %
Ballotta and Giau [21]	2003	624	64 %	7 %	NR	0.5 %	0.0 %	0.6 %	4.3	0.0 %	0.0 %
Black et al. [11]	2011	534	44 %	0 %	18	0.9 %	0.6 %	3.8 %	8.9	4.1 %	NR
Radak et al. [22]	2012	9897	98 %	0 %	12	0.8 %	1.7 %	NR	NR	4.3 %	NR
Weighted Average			**90 %**	**2.6 %**		**1.3 %**	**1.9 %**	**1.1 %**		**3.6 %**	**0.3 %**

Table 28.3 Large comparative series of sCEA and eCEA

Author and reference	Year	n (CEAs)		Symptomatic (%)		Shunt use (%)		Mean cross-clamp time (min)		Cranial/ cervical nerve injury (%)		Reexploration for hemorrhage (%)		Peri-operative stroke/death (%)		Median follow-up (years)	Restenosis (%)		Late ipsilateral stroke (%)	
		sCEA	eCEA	sCEA	eCEA	sCEA	eCEA	sCEA	eCEA	sCEA	eCEA	sCEA	eCEA	sCEA	eCEA		sCEA	eCEA	sCEA	eCEA
Brothers [23]	2005	100	100	40 %	37 %	59 %	87 %	NR	NR	NR	NR	NR	NR	3.0 %	2.0 %	2.4	38.0 %	6.0 %	NR	NR
Cao et al. [24]	1997	240	274	45 %	51 %	28 %	2 %	28	26	NR	NR	NR	NR	1.2 %	0.7 %	2.3	6.1 %	1.9 %	NR	NR
Cao et al. [25, 26]	1998	675	678	60 %	57 %	16 %	11 %	35	32	3.7 %	3.8 %	2.5 %	3.5 %	1.3 %	1.3 %	2.8	5.5 %	2.8 %	11.4 %	9.4 %
Crawford et al. [27]	2007	155	135	30 %	31 %	14 %	0 %	NR	NR	0.0 %	0.8 %	0.0 %	0.0 %	1.9 %	0.0 %	1.0	4.5 %	5.2 %	1.1 %	0.0 %
Demirel et al. [28]	2012	310	206	100 %	100 %	65 %	17 %	NR	NR	8.1 %	8.2 %	5.0 %	8.0 %	0.3 %	4.0 %	2.0	3.2 %	2.4 %	2.9 %	0.0 %
Green et al. [15]	2000	167	107	NR	NR	25 %	8 %	NR	NR	NR	NR	NR	NR	3.0 %	0.9 %	NR	4.7 %	4.6 %	NR	NR
Shah et al. [16]	1998	474	1934	44 %	34 %	6 %	4 %	NR	15	1.1 %	0.3 %	1.1 %	1.2 %	7.3 %	3.1 %	1.5	1.1 %	0.3 %	NR	NR
Yasa et al. [29]	2014	202	178	44 %	40 %	12 %	3 %	13	10	1.5 %	1.1 %	1.5 %	1.1 %	1.6 %	1.6 %	2.2	3.0 %	2.2 %	4.0 %	0.6 %
Weighted Average		2323	3612	55.9 %	43.9 %	23.7 %	8.0 %			3.2 %	1.6 %	2.4 %	2.2 %	2.6 %	2.3 %		5.4 %	1.6 %	7.1 %	5.4 %

Single-Arm Studies of eCEA

The clinical results of several large, single-arm series of eCEA are shown in Table 28.2; they demonstrate that excellent results have been achieved by surgeons devoted to this technique. Including over 12,000 eCEA procedures, the (weighted) averages of reported cranial/cervical nerve injury, reoperation for hemorrhage and peri-operative stroke/death were 1.3 %, 1.9 % and 1.1 %, respectively. After long-term follow-up (4–12 years), the risk of late ipsilateral stroke was only 0.3 %. The majority of patients in this analysis were culled from the experience of Radak, et al. whose series of 9,897 eCEAs in the Republic of Serbia represents the largest series reported to date [22].

Comparative Studies

The results of several prospective and retrospective studies directly comparing sCEA to eCEA are shown in Table 28.3. The studies encompass over 5,000 procedures in a variety of geographies and institutions. About half of all patients were symptomatic. The preference for performing eCEA without shunting is evident in the data as shunts were utilized in only 8 % of eCEA procedures compared to 24 % of sCEA procedures. Cross-clamp time was generally shorter for eCEA procedures, although only by a few minutes. Accepting that methods of reporting varied fairly widely among these studies, there appeared to be little discernable differences in short-term outcome measures including cranial/cervical nerve injury, the need to re-explore for hemorrhage and peri-operative stroke/death (weighted average 2.6 % for sCEA and 2.3 % for eCEA). Interestingly, some studies and meta-analyses conclude that peri-operative stroke/death is significantly lower after eCEA [16, 17], while others draw an opposite, but no less convincing, conclusion [28]. In the aggregate, these data appear to demonstrate clinical equipoise between sCEA and eCEA.

Long-term anatomic and clinical results are also shown in Table 28.3. After median follow-up intervals ranging from 1 to 2.8 years, the incidences of restenosis for sCEA and eCEA were 5.4 % and 1.6 %, respectively. However, one study reported the rate of >50 % restenosis of sCEA as 38 % which should probably be considered an outlier [23]. If this study is excluded from the analysis, the difference in the rates of restenosis is small, if present at all. Similarly, although not every study reported numeric rates for patients sustaining an ipsilateral stroke in the follow-up period; those that did generally found the risks to be comparable for the two procedures.

Interestingly, several authors have suggested that eCEA induces more post-operative hemodynamic liability than sCEA, the purported mechanism being that circumferential dissection of the blub denervates the terminal afferent fibers of the Nerve of Hering within the carotid sinus [28, 30–33]. Although some studies have shown that post-operative blood pressure control is more problematic after eCEA compared to sCEA, no differences in clinical outcome have been conclusively demonstrated to date.

Recommendation
Carotid endarterectomy can be safely and reliably performed using either standard or eversion techniques (**Quality of Evidence, strong; level of recommendation, strong**).

Personal View of the Data

Carotid endarterectomy (CEA) is the treatment of choice for symptomatic carotid stenosis and selected asymptomatic lesions. It can be safely and reliably performed using either standard or eversion techniques. Although the differences in these techniques have been exhaustively studied over the past decade, this author agrees with the overall conclusion reached by Piergiorgio Cao in 2002 after his comprehensive review of this same subject: "Until data are available, the choice of the surgical technique for CEA should depend on the experience and preference of the operating surgeon" [19].

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Chapter 29
In Patients with a Stroke Attributable to a Carotid Artery Stenosis, Does Waiting to Operate Reduce the Risk of Complications?

David A. Nation and Benjamin M. Jackson

Abstract Stroke is a significant cause of death and morbidity in the United States, with many patients affected by stroke originating from embolization of carotid artery plaque. Large multicenter randomized controlled trials have demonstrated the efficacy of carotid endarterectomy (CEA) and carotid stenting at minimizing stroke risk in select patient populations. The optimal timing of intervention should optimize stroke prevention while minimizing the risk of complications. Pooled data from the large randomized controlled trials demonstrated that endarterectomy is best performed within 2 weeks of symptom onset, after which time the benefit of carotid endarterectomy for stroke prevention declines. Data is mixed regarding the risk/benefit profile of very early endarterectomy performed within the first 48 h. For patients with stroke in evolution or crescendo transient ischemic attacks, urgent carotid endarterectomy may be of benefit in highly selected patients but the data do not clearly support either urgent intervention or medical management.

Keywords Carotid artery stenosis • Stroke • TIA • Complications • Timing of surgery • Endarterectomy

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Table 29.1 PICO table for timing of intervention after stroke

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with a stroke attributable to a carotid artery stenosis	Carotid endarterectomy, Carotid stent with embolic protection	Timing of intervention	Stroke and death

Introduction

Thromboembolic stroke is a leading cause of death in the United States and a major source of morbidity [1]. Carotid artery atherosclerosis is a significant contributor to this problem, with 10–16 % of strokes attributable to an ipsilateral carotid plaque [2]. It is generally accepted that patients with hemorrhagic stroke or large hemispheric stroke are not candidates for carotid intervention, but many patients with mild to moderate stroke or transient ischemic attack (TIA) may benefit from revascularization. Multiple large randomized controlled trials have documented the benefit of surgery for carotid artery stenosis [3–5], but there has been controversy regarding the optimal timing of intervention.

Search Strategy

A literature search of English language publications was conducted from the years 1980–2014 to identify published date regarding timing of operative intervention for carotid artery disease following stroke using the PICO outline (Table 29.1). Databases searched included Pubmed, Medline, Embase, and Cochrane Evidence Based Medicine. Terms used in the search were "timing of carotid endarterectomy after stroke", "benefit delayed carotid endarterectomy", "timing of carotid endarterectomy post stroke", and "carotid endarterectomy". Reference lists of identified studies were also examined for additional sources. Articles were excluded if they did not include analysis of symptomatic patients or did not report the timing of intervention after stroke or transient ischemic attack (TIA).

Three randomized controlled trials, six systematic reviews, 17 retrospective studies, five subgroup analyses from prior randomized controlled trials, one prospective randomized trial, five prospective non-randomized trials, and eight reviews/editorials were included in the analysis. See Table 29.2. The data was classified using the GRADE system.

Results

Historical Background for Timing of Carotid Endarterectomy

The optimal timing of surgery following a stroke or transient ischemic attack (TIA) must balance the risks of the procedure against the benefit of preventing a recurrent stroke. In the past the preferred approach was to allow a waiting period of at least

Table 29.2 Summary of studies identified in literature review

Authors	Study type	Date	Number of patients
Paty et al.	Retrospective	1997	200
Hoffman and Robbs	Retrospective	1999	232
Paty et al.	Retrospective	2004	228
Rantner et al.	Retrospective	2005	104
Rockman et al.	Retrospective	2006	1046
Suzue et al.	Retrospective	2007	72
Ehsan et al.	Retrospective	2008	49
Gladstone et al.	Retrospective	2009	105
Lin et al.	Retrospective	2009	224
Ois et al.	Retrospective	2009	163
Crozier et al.	Retrospective	2011	10
Rantner et al.	Retrospective	2011	468
Annambhotla et al.	Retrospective	2012	312
Leseche et al.	Retrospective	2012	27
Stromberg et al.	Retrospective	2012	2596
Mono et al.	Retrospective	2013	94
Villwock et al.	Retrospective	2014	72,797
Bond et al.	Systematic Review	2003	–
Giles and Rothwell	Systematic Review	2007	10,126
Patterson et al.	Systematic Review	2009	–
Rerkasem and Rothwell	Systematic Review	2009	–
Karkos et al.	Systematic Review	2009	915
Rerkasem and Rothwell	Systematic Review	2011	6092
Baron et al.	Review/Editorial	2006	–
Gasecki and Eliasziw	Review/Editorial	1998	–
Baron and Baty	Review/Editorial	2008	–
Naylor et al.	Review/Editorial	2008	–
Naylor et al.	Review/Editorial	2008	–
Rothwell	Review/Editorial	2008	–
Keldahl and Eskandari	Review/Editorial	2010	–
Kennedy and Brown	Review/Editorial	2012	–
Mayberg et al. (VA trial)	Randomized controlled trial	1991	189
ECST Study	Randomized controlled trial	1998	3024
Barnett et al. (NASCET)	Randomized controlled trial	1998	2267
Rothwell et al.	RCT subgroup analysis	2003	6092
Eliasziw et al.	RCT subgroup analysis	2004	1129
Rothwell et al.	RCT subgroup analysis	2004	5893
Rothwell et al.	RCT subgroup analysis	2004	5893
Rantner et al.	RCT subgroup analysis	2006	226
Ballotta et al.	Prospective randomized	2002	86
Ballotta et al.	Prospective nonrandomized	2008	102
Bartoli et al.	Prospective nonrandomized	2009	12

(continued)

Table 29.2 (continued)

Authors	Study type	Date	Number of patients
Salem et al.	Prospective nonrandomized	2011	109
Capoccia et al.	Prospective nonrandomized	2011	62
Capoccia et al.	Prospective nonrandomized	2012	48

VA veterans affairs, *ECST* the european carotid surgery trial, *NASCET* north american symptomatic carotid endarterectomy trial, *RCT* randomized controlled trial

2–6 weeks after symptom onset prior to considering operative intervention, based on concerns of higher perioperative complications and risk of hemorrhagic conversion [6]. This concern was prompted by multiple early studies which showed higher risks with early operation [7–9], and was highlighted by Giordano et al. in 1985, who noted an 18.5 % postoperative stroke rate in patients having surgery at less than 5 weeks and therefore recommended a 5 week waiting period [10]. These recommendations were based on studies during a time when the availability of CT and MRI imaging was limited and intensive care with aggressive blood pressure control was less common.

More contemporary studies have not supported these prior concerns. Numerous recent series have demonstrated equivalent or improved outcomes with earlier intervention for symptomatic carotid disease when compared to delayed repair [11–18]. Furthermore, it is now recognized that there is a significant risk of recurrent stroke without intervention, which ranges from 5 to 10 % at 7 days and 15–20 % at 30 days [19–21]. This has led to multiple guidelines recommending surgical treatment of symptomatic carotid stenosis within 14 days [22–25]. However, there remains controversy concerning the optimal time for intervention, especially in particular subsets of patients.

Although there are many studies evaluating the broad question of optimal timing for carotid intervention after stroke, the degree of heterogeneity and inconsistency between studies often makes comparison difficult. Definitions of early surgery, hyperacute surgery, degree of stroke, and methods of patient assessment sometimes differ widely between studies. In addition many of these studies were conducted – at least in part – before the availability of what we would now consider optimal medical management.

Evidence for Surgery at Less Than Two Weeks for TIA and Mild Stroke

The large randomized multicenter trials North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST) provided the most robust patient cohort of symptomatic patients undergoing CEA [3, 5]. These studies demonstrated benefit for intervention in symptomatic patients with significant associated carotid stenosis and defined the important role of endarterectomy in management of these patients [3, 5]. Of note, these studies excluded patients with severe stroke and carotid occlusion, and the results are applicable only to

patients with non-disabling stroke. A pooled analysis of data from these studies was conducted by Rothwell et al. in 2004 to evaluate the impact of timing on patient outcomes [18]. This study found that the greatest benefit to surgery was in patients who were randomized within two weeks of their ischemic event. The number needed to treat to prevent one stroke in 5 years increased from 5 patients in the <2 week group to 125 patients in the >12 week group. Absolute risk reduction from surgery in 5 year cumulative risk (ipsilateral stroke at 5 years and any stroke or death within 30 days of surgery) dropped from 18.5 % at <2 weeks to 9.8 % at 2–4 weeks, 5.5 % at 4–12 weeks, and 0.8 % at >12 weeks when considering symptomatic patients with >50 % carotid stenosis. This declining risk reduction with operative delay was even more significant when only patients with >70 % stenosis were considered, with drop from 30.2–17.6 % to 11.4–8.9 % at these same time intervals, respectively. For patients with 50–69 % stenosis the benefit of endarterectomy was erased after the 12 week mark. A separate NASCET and ECST subset analysis noted that women may have an even more striking decline in benefit from CEA with increasing time from symptom onset [26]. Based on these data, multiple consensus guidelines recommend intervention within the 2 week window following symptom onset [23, 27].

Risk of Recurrent Stroke

The goal of carotid surgery is to decrease the risk of stroke. Risk of recurrent stroke is highest in the first 7–14 days after the index neurologic event [20], and the risk of recurrent stroke while on medical therapy falls significantly over the following year [3, 5]. As such, moves toward earlier intervention should maximize benefit from stroke reduction, assuming that perioperative event rates are equivalent. Indeed, there is evidence that waiting longer after symptom onset may lead to additional strokes that could have been prevented with endarterectomy [28–30]. Rantner et al. noted that 11.8 % of patients waiting for a delayed CEA had a secondary stroke or carotid occlusion during the 4 week waiting period, with most occurring at the 3–4 week mark [28]. Analysis of the medical arm of the NASCET trial demonstrated a 90 day risk of recurrent neurologic event in 20.1 % of patients that presented with TIA, and 2.3 % of patients that presented with hemispheric stroke [29]. This study also noted a 5.5 % risk in the first 2 days alone for the TIA group. Ois et al. reported even higher risk of early stroke or TIA recurrence, with 27.6 % of patients presenting with mild stroke or TIA having recurrent neurological event, and 20.9 % occurring in the first 72 h [30]. Both NASCET and ECST subgroup analyses demonstrated the greatest benefit in regards to recurrent stroke in patients who underwent surgery within 7 days of the neurologic event [18, 31].

Perioperative Risk

The concerns for increased perioperative risk in the early period after stroke or TIA must also be considered to evaluate the risk/benefit profile with early intervention in symptomatic carotid disease. Pooled analysis of the NASCET and ECST data

demonstrated a 30 day stroke and death rate of 7 %[26], and published guidelines cite benefit to CEA when a surgeon's perioperative risk is <6 % [32]. Numerous recent studies have evaluated this and generally shown similar risk profiles at different times of intervention [12, 13, 15, 17, 33, 34]. Rerkasem and Rothwell performed a systematic review in 2009 to evaluate operative risk based on the timing of surgery, and found no significant difference between early or later endarterectomy in patients with stable neurologic status after a non-disabling stroke or TIA [17]. Concerns about causing hemorrhagic conversion also appear to be largely unfounded in patients with mild stroke or TIA, with a Cochrane review demonstrating a 0.2 % incidence of intracranial hemorrhage in this patient subset [33]. On the other hand, patients with major stroke or stroke in evolution appear to be at substantially higher risk [17]. Ballotta et al. performed a prospective randomized study comparing early to late endarterectomy, which demonstrated no difference in perioperative stroke, survival, or stroke-free survival at 3 years [13]. Paty et al. [15] retrospectively looked at perioperative stroke risk at 1 week time intervals after CEA, and found no significant differences. Permanent deficit developing perioperatively occurred in 2.8 % of patients operated on at <1 week, 3.4 % at 1–2 weeks, 3.4 % at 2–3 weeks, and 2.6 % at 3–4 weeks. The only factor that was associated with post-operative permanent neurologic deficit was the size of the lesion on preoperative imaging. Annambhotla et al. [34] performed a retrospective analysis and found no difference between early (<30 days) versus late (>30 days) endarterectomy in regards to 30 day mortality, stroke, or MI. Ballotta et al. [12] performed a prospective study evaluating 102 patients who had CEA within 2 weeks of minor stroke or TIA. They did not have any perioperative deaths, strokes, or episodes of cerebral bleeding in their series, although 2.9 % of their patients did suffer transient neurologic deficits perioperatively. Cerebral infarcts on preoperative imaging studies did not affect the risk of subsequent neurologic impairment.

Surgery in the "Hyperacute" Period

Large metanalyses demonstrating the early risk of recurrent stroke or TIA [20, 35] after the initial neurologic event led to more investigation into even earlier intervention. Several studies have examined whether intervention within the very early period after the neurologic event is safe. Rantner et al. [16] did a small retrospective study which included 7 patients that underwent surgery within 6 hours of the event, with none of these patients experiencing a perioperative complication. Stromberg [36] et al. performed a prospective study including 2596 patients to determine if the timing of surgery had impact on stroke and mortality rates at 30 days. They found that patients undergoing CEA within 2 days of an ischemic event did worse than the delayed CEA group, with 11.5 % stroke and mortality rates compared to 3.6 % for the 3–7 day group, 4 % for the 8–14 day group, and 5.4 % for the 15–180 day group. Time to intervention was the strongest determinate of stroke or death, with an odds ratio of 4.24 (CI 2.07–8.70, $p < 0.001$) when the early group was compared to the 3–7 day group. Rockman et al. [37] noted higher rates of perioperative stroke in

patients that underwent endarterectomy within 48 hours after TIA or stroke, with a 5.1 % risk in the early group compared to 1.6 % in the delayed group. Interestingly, they also noted increased risk for early intervention in subgroup analysis of TIA patients. As this was a 10-year review, many of these patients underwent treatment before the era of improved imaging and intensive care.

There is a reasonable argument to be made that the higher perioperative risk is justified by the stroke prevention benefit [22]. Capoccia et al. suggested that there may be benefit to earlier intervention, and noted that early operative intervention may improve neurologic outcomes as well as reduce recurrent stroke in patients with mild to moderate neurologic events, as documented by improvement in NIHSS scores [38]. Mono et al. in a recent retrospective review [39] noted similar procedure-related stroke risk in intervention within 48 h (4.5 %) and after 48 % (4.1 %). They also noted that all recurrent strokes prior to surgery occurred within the first 72 hours [39].

There is data to suggest that certain patient subsets (high ASA class, more severe neurologic deficits) are at higher risk for early intervention, and that risk stratification may help determine the best candidates for early surgery [40]. Further data is needed to clarify the risk in this hyperacute time period, and at least one study protocol has been proposed with this intent [41].

Differences Based on Severity of Stroke/TIA

Data to guide treatment of patients with severe stroke is more limited than those with mild stroke or TIA, as this patient subset was excluded from the large randomized trials ECST and NASCET. It has long been accepted that patients with severe stroke with significant functional deficits and large territory infarcts do poorly with CEA [9], but there remains interest in whether select patients with moderate deficits can still benefit from early intervention. Capoccia et al. [38] looked at patients with moderate stroke who underwent CEA for symptomatic carotid lesions >50 % and had National Institutes of Health Stroke Scale (NIHSS) scores ≥4 (mean score was 7.05 ± 3.41). Patients had a wide range of time to surgery (2–280 hours), but all patients in this study had stable or improved NIHSS scores at the time of discharge, and there were no worsening NIHSS scores or recurrent strokes noted in this series. The authors concluded that high NIHSS scores do not contraindicate early surgery and may lead to improved neurologic outcome. It should be noted that patients with NIHSS scores in the severe range (>22) were excluded from this analysis.

Management of Crescendo TIA/Stroke in Evolution

Patients with unstable symptoms such as crescendo TIA or stroke in evolution must be considered separately from those patients with stable mild to moderate deficits. Operating on this patient subset has higher risk, as shown by Rerkasem and Rothwell

in a review that noted a 20.2 % risk of stroke or death after urgent CEA for patients with stroke in evolution and 11.4 % risk in patients with crescendo TIA [17]. The more recent studies included in the review had no better outcomes than the older ones. Other reviews have also shown higher risk for postoperative death and stroke in patients presenting with unstable symptoms [42–44], with one review demonstrating an odds ratio of 4.9 (95 % confidence interval 3.4–7.1) when compared to patients with stable symptoms [42]. It has been pointed out that most of the patients included in these reviews were from small retrospective studies over long time periods [45], and it is possible that carefully selected patients in specialized centers may do well with urgent CEA today. Indeed, despite the apparent poor results of surgery in this patient subset overall, some studies have demonstrated that surgery can be effective in carefully selected patient groups [45, 46]. Capoccia et al. performed a prospective single center study to determine whether some patients with unstable symptoms may benefit from urgent CEA [46]. This study evaluated 46 patients with stroke in evolution or crescendo TIA, and found a significant improvement in NIHSS score in the stroke in evolution group after surgery when compared to preoperative score. This study included patients with mild to moderate deficits and <1/3 of middle cerebral artery territory infarct on preoperative imaging. They argued that the benefit of urgent CEA is to eliminate the embolic focus and protect the additional viable brain tissue at risk [46]. Leseche et al. [45] did a retrospective review of patients undergoing CEA for stroke in evolution, and did not have any stroke or death in their series of 27 patients at 3 month follow-up. Patients in this study underwent CEA at a mean of 6 days after symptom onset however, as compared to <24 h in all patients from the Capoccia et al. study. The good success rate in these selected studies when compared to poor results in larger reviews highlights the need for randomized controlled trials to determine the benefit of CEA in patients with unstable symptoms. Acceptable results have also been reported in patients undergoing an initial period of anticoagulation followed by delayed CEA [47], and there remains some degree of individual surgeon bias in regards to whether urgent endarterectomy or initial anticoagulation is the best course of action [6].

Management Following Thrombolysis for Acute Stroke

Intravenous and intra-arterial thrombolysis are well accepted treatment modalities in certain patient subgroups with acute stroke [48]. There has been interest in determining whether early CEA in patients that underwent thrombolysis is safe and whether it can prevent recurrent stroke, although the data remain limited. Bartoli et al. [49] performed a prospective nonrandomized trial to evaluate this question, and in 12 neurologically stable patients that underwent CEA at a median of 6 days after thrombolysis, noted an 8.3 % risk of stroke or death at 30 days (1 patient, nonfatal hemorrhagic stroke). Crozier et al. [50] in a retrospective database review identified 10 patients that underwent CEA within 23 days after intravenous thrombolysis. These patients did well with no postoperative stroke or death, but there were two

mild bleeding complications noted. It is also unclear what the exact criteria were for operative intervention, given the retrospective nature of the study.

Carotid Stenting

There have been few studies looking at timing of intervention for carotid stent placement. Lin et al. [51] performed a retrospective review comparing symptomatic patients with intervention within 4 weeks versus after 4 weeks, and found similar stroke rates between each group at 30 days (3.45 % for early group and 5.95 % in late group, p = 0.5). There was no statistical difference for either stroke risk or their composite outcome of stroke, MI, intracranial hemorrhage, and death, although it was noted that octogenarians has worse outcomes overall.

Summary

Patients with mild to moderate stroke or TIA who have stable neurologic symptoms, carotid stenosis >50 % by NASCET criteria, and acceptable operative risk should undergo carotid endarterectomy within 2 weeks of onset of symptoms. This is in concurrence with published national and international recommendations [23, 32, 52]. To maximize risk reduction for recurrent stroke, surgery should be performed early in that 2 week period, with the caveat that surgery performed in the first 48 h may be associated with a higher risk profile [36, 53]. Women should also be considered for early intervention, as the benefit of CEA may taper off more rapidly with increased time from symptom onset when compared to male patients.

In general, patients with mild to moderate symptoms benefit from endarterectomy. There is no significant evidence that intervention is beneficial to patients with severe deficits on presentation.

Urgent endarterectomy may be compelling in carefully-selected patients with crescendo TIA or stroke in evolution, although it is unclear if this is beneficial overall when compared to initial medical management. Randomized trials are needed to determine if surgery can decrease the overall risk to the patient despite elevated perioperative risk when compared to patients with stable symptoms.

A Personal View of the Data

The data from the large prospective randomized controlled trials, although they were not designed specifically to evaluate optimal timing of intervention, are very compelling in their suggestion that CEA is best performed during the initial 2-week window. Based on this data, extended wait times after symptom onset create diminishing

returns in regards to stroke prevention, which of course is the primary impetus behind surgery for carotid occlusive disease. Despite numerous small retrospective studies and several large reviews, there remains a relative paucity of data regarding the exact patient subsets that are likely to benefit the most from early intervention. Investigation into risk stratification methods may help elucidate this question [54], which has important implications at the population level, where limited resources may prevent many patients from undergoing early endarterectomy [55]. In addition it is important to note that advances in cerebrovascular imaging and medical treatment for stroke care continue to evolve and improve, which will require ongoing re-evaluation of the optimal timing of surgical therapy in these patients.

Recommendations

- For patients with TIA or mild stroke and stable neurologic status, carotid endarterectomy should be performed within the first 2 weeks after symptom onset in order to maximize stroke prevention (**evidence quality moderate; strong recommendation**)
- Decision to operate within 48 h of symptom onset may provide a benefit in stroke reduction at the cost of increased peri-operative risk, and may be considered in select patients (**evidence quality low, weak recommendation**)
- Surgery should be performed within 3 months of symptom onset: Delay of surgery greater than 3 months after symptom onset appears to negate the stroke reduction benefit of endarterectomy in patients with 50–69 % carotid stenosis, and decreases the benefit in patients with 70–99 % stenosis (**evidence quality moderate, strong recommendation**)
- There is insufficient evidence to support urgent endarterectomy for patients with unstable symptoms such as crescendo TIA or stroke in evolution, as compared to initial medical management with anticoagulation (**evidence quality low, weak recommendation**).
- Endarterectomy may be performed after thrombolysis for acute stroke with acceptable outcomes in highly selected patients (**evidence quality very low, weak recommendation**)

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Chapter 30
In Patients with a Peri-procedural Cerebral Thromboembolism, Does Neurovascular Rescue Improve Clinical Outcome?

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Keywords Neurovascular rescue • Peri-procedural embolism • Peri-procedural stroke

Introduction

Stroke is the third leading cause of morbidity and mortality in the US, following cardiac diseases and lung cancer. Stroke from cranio-cervical vascular intervention is a devastating complication and is one of most important risk factors for determining post-intervention quality of life. To enumerate, the risk of stroke from percutaneous coronary interventions (PCI) has been well documented with procedure related stroke rates ranging from 0.1 to 0.4 % [3, 5, 15]. However, this very low incidence could be the 'tip of the iceberg' since coronary intervention related stroke is only suspected when the patient becomes symptomatic [30]. Similarly, thromboembolic events are seen not infrequently after neuro-interventional procedures such as aneurysm coiling and head and neck embolization. Recent successful completion of multiple acute ischemic stroke trials showed firm benefits of performing mechanical thrombectomy for acute ischemic stroke patients [7, 13]. Thus, given the increasing use of percutaneous techniques, we seek to determine if neurovascular rescue (emergency neuro-interventional procedure) in patients with peri-procedural embolic complication improves patients' clinical outcome.

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Search Strategy

We conducted a Pubmed search of the English literature for acute endovascular treatment of procedural thromboembolic complications using the PICO outline (Table 30.1). We selected all studies that described details of method (procedural or medication intervention) used for thrombolysis and subsequent outcome of this endeavor (especially related to recanalization, stroke, hemorrhage and final patient outcome). The search period was restricted to the last 17 years (1998 to 2015) in order to limit outdated practices of management of intracranial thromboembolic complication affecting our observation and inference. Search terms included "neurovascular rescue", AND/OR "cerebral embolization during percutaneous coronary interventions", AND/OR "stroke after cardiac surgery", AND/OR "cerebral embolization", AND/OR "thrombo-embolic complications from neuro-intervention", AND "carotid stenting and embolization" AND/OR "peri-procedural embolization". The selected studies were carefully examined for details pertaining to incidence of thrombo-embolic complications, their treatment and both radiological and neurological outcomes. Individual case reports, letters to the editors, commentaries or summaries, case series with less than three patients and literature reviews without associated cases were excluded. All related references of selected articles were also analyzed so as to not miss any other case series that didn't show up in the initial search results. The data was classified using the GRADE system.

Results

Symptomatic neurologic thrombo-embolic events during percutaneous procedures including coronary, cervicocerebral, intracranial and aortic intervention are variable but reasonably rare. Transcranial Doppler examination performed during PCIs show significant increased rates of high-intensity transient signals (HITS) but the patient shows no signs and symptoms of stroke [18, 36]. One of the reasons for this disparity could be that occult micro-emboli developed during coronary procedures may not be symptomatic, although the long-term effects of such events to the brain are unknown. On the other hand, thrombo-embolic complication risk of neuro-endovascular interventions appears to be higher than expected. Approximately one-third of patients undergoing a neuro-intervention reported having procedure related thrombo-embolic

Table 30.1 PICO table for neurovascular rescue in patients with peri-procerural cerebral thromboembolism

P (patients)	I (intervention)	C (comparator group)	O (outcomes measured)
Patients with peri-procedural cerebral thromboembolism	Neurovascular rescue	No intervention	Clinical and radiographic stroke, and mortality

events in earlier reports [26, 31]. However, the thrombo-embolic complication risks nowadays are around 1 % with the use of heparinized solution for irrigation and better implant technology [12].

Evidence for Prevention

Embolic Protection Devices

The majority of data related to cerebral thromboembolism prevention is obtained from the carotid stenting literature and the use of embolic protection devices. Initially, significant differences in the peri-procedural stroke rate between carotid artery stenting (CAS) and carotid endarterectomy (CEA) was attributed to thrombo-embolic complications arising from endovascular intervention [21]. Expectedly, distal embolic protection devices were shown to reduce the occurence of cerebral embolism and were routinely used for patient care [22]. Subsequently, proximal embolic protection devices with flow reversal has gained traction with MR imaging studies showing further reduction in the number of embolic stroke when proximal balloon occlusion is employed for thromboembolism protection [2]. Stabile et al. in their meta-analysis of 8 studies that included close to 400 patients show significant reduction in cerebral embolism with proximal balloon protection when compared to distal filter protection [33]. It is notable that the above study was based on MR diffusion weighted imaging, while peri-procedural and long-term outcomes between these same groups has not shown any difference in other trials [6].

Antiplatelet Therapy

Another aspect of cerebral thromboembolism prevention during endovascular procedures involves modulation of patient rheology. Anti-platelet medications have been shown to reduce formation of thrombus at the lesion site, especially when a vascular stent is employed. In a retrospective study of 449 patients undergoing CAS who had documentation of aspirin administration and P2Y12 assays at the time of stenting, patients with a P2Y12 reaction units (PRU) < 198 had an associated lower incidence of ischemic neurologic sequela and death post CAS [32]. There is moderate to strong evidence supporting the use of dual anti-platelet treatment in CAS. McKevitt and colleagues performed a prospective, randomized, unblinded trial comparing the safety of aspirin and clopidogrel to 24 hours of heparin and aspirin. The trial was stopped early due to an unacceptably high level of complications in the heparin arm. There was not a significant difference in bleeding, however, the neurologic complication rate in the 24 hour heparin group was 25 % compared to 0 % ($p = 0.02$) in the clopidogrel group. This led the authors to conclude that dual anti-platelet regimen has a significant impact on reducing adverse neurological

outcomes [23]. Frequently, patients who are scheduled to undergo a CAS placement are treated with daily aspirin and clopidogrel for five days prior to the anticipated procedure. Emergent utilization of carotid or intracranial stent is associated with significant risk of thromboembolism and is prevented by administering a loading dose of aspirin and clopidogrel.

Evidence for Use of Neurovascular Rescue

Acute stroke or neurologic deficit during a procedure is a devastating complication and can be caused by emboli or thrombosis. Neurovascular rescue is the endovascular approach to remove the inciting blockage. Techniques include retrieval devices, aspiration catheters, wire or balloon fragmentation and local intra-arterial infusion of agents to induce thrombolysis. We found 465 cases of thromboembolic complications in 22 case series consisting of about 13,164 and 41,665 patients who had neuro angiography and coronary angiography, respectively (Table 30.2). Neuro-endovascular interventions showed a thrombo-embolic rate of 3.3 % (429 out of 13,164) while coronary angiography procedures were lower at 0.09 %. The most common neuro-endovascular intervention complicated by thromboembolic events was coil embolization of intracranial aneurysms. Interestingly, both ruptured and un-ruptured aneurysm treatment carried similar thromboembolic risk. Thrombus formation at the coil-parent artery interface was more frequent than distal embolic complications. IIB/IIIA inhibitor administration (abciximab®, tirofiban® and eftifibatide®) was the most common rescue method employed for intra-procedural thrombolysis [9, 19]. Mechanical thrombectomy was used relatively infrequently and often as adjunct with IIB/IIIA inhibitor administration in these circumstances.

The angiographic result of rescue treatment, categorized according to Thrombolysis in Myocardial Infarction (TIMI) grading system, was available for 396 patients [4]. Complete recanalization (TIMI grade 3) was seen in 196 patients (49.5 %), while 147 (37.1 %) patients had partial recanalization (TIMI grade 2). Recanalization efforts were unsuccessful in 53 patients (13.4 %), who were categorized TIMI grade 0 with no distal flow. No clear association between recanalization and incidence of stroke or long-term clinical outcome has been reported and represents a need for further investigation. However, the data demonstrated a trend of reducing stroke incidence and improvement in neurological outcomes better when complete recanalization had been achieved. Some series reported better recanalization (more grade 3 and grade 2 TIMI) with earlier initiation of active intervention [11, 24, 25]. Complete recanalization is more likely related to shorter ‘symptom (occlusion) to treatment’ time interval, as corroborated by multiple studies [5, 11, 24, 25]. In addition, achieving better recanalization degree might result in better clinical outcomes. Zaidat et al. reported that the degree of flow restoration was associated with that of clinical outcome and lesser complications, though statistical significance was only achieved when clot dissolution was complete [40].

Table 30.2 Compilation of case series reporting of treatment of cerebral thromboembolism

Study	Cohort size	Thromboembolic complications (%)	Recanalization technique	TIMI 0	TIMI 1/2	TIMI 3	Hemorrhages	Strokes	Outcome good/bad	Death
Aggour et al. [1]	390	39 (10)	Abciximab	2	8	13		11	17/6	
Bruening et al. [8]	225	16 (7.1)	Tirofiban	1	1	14			8/6	2
Cho et al. [9]	372	39 (10.4)	Tirofiban	2	3	34	2			
Cronqvist et al. [10]	352	20 (5.6)	Mechanical, Fibrinolytics	1	9	10	3	3	14/3	2
Duncan and Fourie [11]	207	6 (2.9)	Abciximab	1	1	4		2		
Fiorella et al. [12]	1102	13 (1.2)	Abciximab		6	7	1	5	10/3	
Jeon et al., [16]	64	10 (15.6)	Tirofiban		2	8		6	8	
Jones et al. [17]	609	38 (6.2)	Abciximab	14	24				30/8	
Kang et al. [19]	228	24 (10.5)	Tirofiban		21	4				
Linfante et al. [20]	184	19 (10.3)	Abciximab							
Arnold et al. [5]	34187	12 (0.03)	Abciximab, Mechanical		6	6	2	10	9/3	
Workman et al. [38]	210	14 (6.7)	Heparin ± Abciximab	2	5	2				
Mounayer et al. [24]	227	13 (5.7)	Abciximab			12		1		1
Al-Mubarak et al. [3]	12857	9 (0.07)	Mechanical, Fibrinolytics	1	7		1	5	6	2
Park et al. [25]	606	32 (5.2)	Abciximab		15	17	3	4		
Ries et al. [28]	515	48 (9.3)	Abciximab					16	34/14	
Song et al. [31]	100	7 (7)	Abciximab	1	2	4	1	3		
Hähnel et al. [14]	723	9 (1.2)	Mechanical, Fibrinolytics		2	2			4/3	2

(continued)

Table 30.2 (continued)

Study	Cohort size	Thromboembolic complications (%)	Recanalization technique	TIMI 0	TIMI 1/2	TIMI 3	Hemorrhages	Strokes	Outcome good/bad	Death
Velat et al. [35]	1373	29 (2.1)	Abciximab, Mechanical Thrombectomy	4	6	19	3		24/3	2
Yi et al. [39]	298	7 (2.3)	Eptifitabide				2			
Zaidat et al. [40]		21	Mechanical, Fibrinolytics	7	7	5	3	3	10/7	4
Ramakrishnana et al. [27]		40	Eptifitabide	1	8	31	6	14		
Total	54829	425		37	133	192	27	83	174/57	15

All available case series (subject size >3) were selected and pertinent information regarding the original procedure, thromboembolic event, rescue treatment rendered, complications and outcome were collected. There was no standard outcome measure tool used across the board, for the purpose of our study independence, Modified Rankin Scale (MRS) <3 and Glasgow Outcome Scale (GOS) >4 were considered good outcome. GOS 5, good recovery; GOS 4, moderate disability; GOS 3, severe disability; GOS 2, persistent vegetative state; GOS 1, death; (Only available data is included the table and hence addition of all individual columns will not be equal to total)

Carotid Artery Stenting

The CREST (Carotid Revascularization Endarterectomy and Stenting Trial) study which compared carotid endarterectomy (CEA) and carotid artery stenting (CAS) showed similar composite outcomes in both modalities though there was a higher incidence in peri-operative myocardial infarction in the CEA group (1.1 % vs 2.3 %, p = 0.03) and increased risk of all stroke in the CAS group (4.1 % vs. 2.3 %, p = 0.01) [21]. Also, the same study did not show any difference between the CEA and CAS group in terms of procedure related mortality (<1 %). As such, much of the data is derived from trials in patients suffering from acute ischemic stroke not related to CAS.

Active intervention including intravenous t-PA infusion and endovascular thrombectomy of acute cerebral thromboembolism causing large vessel occlusion has demonstrated its clinical benefits in selected cases. In particular, recently completed randomized clinical trials have demonstrated that combining endovascular mechanical thrombectomy in acute ischemic stroke results in a better clinical outcome than intravenous t-PA infusion alone [7, 13]. The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) is a randomized control phase 3, multicenter clinical trial in patients presenting with acute stroke and randomized to intra-arterial therapy(intra-arterial thrombolysis, mechanical treatment or both) plus usual care (which could include intravenous administration of alteplase) or usual care alone (control group). Five hundred patients were entered and the data demonstrated an absolute difference of 13.5 % (95 % CI, 5.9–21.1) in the rate of functional independence (based on modified Rankin score, 0–2) in favor of the intra-arterial intervention (32.6 % bd. 19.1 %) [7]. There was no significant difference in mortality or intracerebral hemorrhage. Similarly the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) ESCAPE trial was stopped early because of a demonstration that the primary outcome favored intervention. The rate of functional independence (demonstrated by the 90-day modified Rankin scale (MRS) of 0–2) was increased in the intervention group (53.0 % vs. 29.3 % in the control group; p < 0.001) [13]. These studies support the approach that aggressive invasive therapy in the setting of acute stroke results in improvement in functional outcomes; however, these studies are not directly applicable to the peri-procedural group.

In a retrospective study of 477 patients with cerebral aneurysms undergoing endovascular embolization, usage of the IIB/IIIA inhibitor (abciximab) therapy (both intra-arterial and intra venous) for the rescue treatment in cases of thrombus formation was shown to be safe. This was in combination with peri-procedural anticoagulation(heparin) and platelet inhibition therapy (ASA and clopidogrel) [28]. Despite the safety demonstration, clinical efficacy was not addressed; however, because this was demonstrated to be safe, abciximab became a common first line therapy for neurovascular rescue in other procedures outside of aneurysm coiling. Unfortunately, there are no good clinical trials for neurovascular rescue in patients undergoing CAS.

Neurovascular Rescue During Cardiac Procedures

With the advent of trans-catheter aortic valve implantation, there has been an increased interest in the risk of peri-coronary procedural cerebral embolism [18, 36]. The usage of embolic protection devices during trans-catheter aortic valve implantation has been advocated considering the cognitive impact of multiple emboli in the face of otherwise asymptomatic patient [37]. Recent increase in the volume of endovascular cardiac interventions has raised awareness of the risk of peri-procedural cerebral thrombo-embolism and the role of neuro-endovascular rescue procedures. The risk of acute stroke was reported as 3.6 % in about 400 patients who underwent Transcatheter Aortic Valve Implantation (TAVI) in which almost nearly 75 % of these occurred on the first postoperative day [34]. Salinas et al. report such a case of neuro-endovascular rescue where post TAVI, the patient developed hemiparesis due to a large middle cerebral artery thrombus, which was retrieved with complete revascularization and neurological recovery [29].

Complications of Neurovascular Rescue

Hemorrhagic complications are a common concern when using pharmacologic thrombolysis. This is even more worrisome in cases of ruptured cerebral aneurysms, because of the worse clinical outcomes when compared to unruptured aneurysms. Based on our pooled data, there were 27 among 466 patients (5.8 %) instances of hemorrhagic events after pharmacologic thrombolysis, which is higher than what has been reported in literature. Though de novo bleeding episodes occurred, other causes of bleeding included were re-bleeding episodes of ruptured aneurysms, and interventional procedure related bleeding (e.g. ventriculostomy related hemorrhage) [27, 39]. The risk of hemorrhagic complications might have been increased with the use of IIB/IIIA inhibitors and heparin; nevertheless the rate of spontaneous bleeding due to these agents still appears to be relatively low.

A Personal View of the Data

Pre and post procedural precise neurological examination are essential for timely detection and managements of acute thromboembolic events. When possible, intra procedural regular interval neurological examinations are recommended to identify any new deficits at the earliest possible time. Patients under general anesthesia present a significant limitation to prompt and timely detection of those events. Therefore, intra-procedural neurophysiological monitoring in the form of Electroencephalography (EEG) and/or Somato-sensory Evoked Potentials (SSEP) can be helpful adjuncts to pick up on subtle changes during the procedure, when the patient is not awake. Any suspicion of acute ischemic stroke due

to thromboembolic events needs immediate evaluation by specialty team, for example stroke team, for prompt diagnosis and application of appropriate management. In case of thromboembolic complication during percutaneous procedures, prompt intervention including pharmacologic thrombolysis and mechanical thrombectomy should be applied which have shown better clinical outcome.

Recommendations
Cerebral thromboembolism during or after percutaneous procedures including coronary, cervicocerebral, intracranial and aortic intervention is not an uncommon event, thus a high index of suspicion is essential for early detection and diagnosis.

- The best strategy for procedure related cerebral thromboembolism would be prevention which can be achieved with adherence to good technique, continuous irrigation through arterial access sheath and use of heparin if not contra-indicated (**evidence quality low, strong recommendation**).
- Patients undergoing carotid artery stenting should be receiving both aspirin and clopidogrel before the start of the procedure (**evidence quality low, strong recommendation**).
- Carotid artery stenting should be performed with an embolic protection device to prevent thromboembolic complications (**evidence quality moderate, strong recommendation**).
- Early detection and appropriate application of neurovascular rescue including usage of anti-platelet agents such as IIB/IIIA inhibitors and mechanical thrombectomy greatly reduces neurologic morbidity of such a complication (**evidence of quality low, strong recommendation**).

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Chapter 31
In Patients with Extra-cranial Carotid Artery Aneurysms, Does an Endovascular Approach Improve Clinical Outcomes Compared to Open Repair?

Marguerite Hoyler and Nicholas J. Morrissey

Abstract Extracranial carotid artery aneurysms (ECAAs) are rare but potentially devastating clinical entities, with notable risk of rupture and thromboembolism. ECAA management strategies include open surgery (ligation, clipping, bypass, and resection) as well as endovascular techniques. There are no formal clinical guidelines regarding optimal management of carotid artery aneurysms. However, a review of recent literature suggests that endovascular intervention may be preferable to open surgery, particularly in patients with high-lying aneurysms or a history of ipsilateral surgery or radiation of the neck. More research is needed regarding this important topic.

Keywords Carotid aneurysm • Extracranial • Surgery • Endovascular • Stent-graft

Introduction

Accounting for approximately 1% of all peripheral aneurysms [1, 2], extracranial carotid artery aneurysms (ECAAs) are rare but potentially devastating clinical entities. These lesions may develop secondary to atherosclerosis, connective tissue diseases, and radiation of the head and neck; pseudoaneurysms may arise following blunt or penetrating trauma or prior carotid artery surgery. Risk factors include hypertension, hyperlipidemia and the presence of other peripheral artery aneurysms [3]. Although patients may experience aneurysm rupture, thromboembolic stroke (CVA), transient ischemic attack (TIA), or cranial nerve compression syndromes, many are asymptomatic at the time of diagnosis.

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The first repair of a carotid artery aneurysm was performed in 1805, via carotid ligation [4]. Today, aneurysm resection and reconstruction is considered standard of care, though surgical strategies also include ligation, bypass and clipping [5]. Endovascular techniques include bare and covered stents and embolization coils. This recent proliferation of treatment options presents clinicians with a notable challenge in clinical decision-making: most centers perform less than one carotid aneurysm repair each year, and there are currently no professional guidelines or consensus statements regarding optimal management of carotid aneurysms. [6] In this chapter, we review and comment upon the literature regarding surgical and endovascular repair of extracranial carotid artery aneurysms.

Search Strategy

We conducted a literature search of English language publications in the PubMed, Embase, SCOPUS and CINAHL dabatases. Search terms included "carotid aneurysm," "extracranial," "vascular," AND "stent-graft," "endovascular" OR "surgery" OR "surgical."

Articles published before 1995 were excluded, as were case reports, opinion pieces, and papers addressing non-carotid aneurysms or carotid aneurysms in pediatric patients. The quality of the articles was rated using the GRADE system.

Outcomes of interest included perioperative and long-term cranial nerve injury, TIA, ispilateral stroke, and mortality attributed to the carotid artery aneurysm or intervention (Table 31.1). When described in the literature, mortality secondary to other causes was also recorded.

Results

Fifteen articles were selected for inclusion in this chapter, including one systematic literature review and 14 retrospective reviews. Four articles described open surgical and endovascular interventions, 8 described open surgery only, and three focused exclusively on endovascular methods.

Table 31.1 PICO table for management of carotid artery aneurysms

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with extracranial carotid artery aneurysms	Endovascular intervention	Open surgery	Perioperative and long-term cranial nerve injury, TIA, ispilateral stroke, mortality, other procedure-related complications

Surgical v. Endovascular Intervention

Studies describing both surgical and endovascular interventions are summarized in Table 31.2.

In a retrospective review of 25 patients, Angiletta and colleagues reported the results of 23 surgical repairs and 3 endovascular repairs of carotid aneurysms [5]. With a mean follow-up period of 33 months for the endovascular group, no mortality or aneurysm-related morbidity was reported among patients in the endovascular group. The surgical cohort, followed an average of 7.5 years, included two patients with transient post-operative cranial nerve injuries and one with a stroke of the facial nerve. A further surgical patient developed a neck hematoma requiring reoperation, and a final two patients suffered myocardial infarctions.

Fankhauser and colleagues presented a retrospective review of 25 true aneurysms and 116 pseudoaneurysm managed medically (75), surgically (48), or with an endovascular approach (18) [2]. Among the patients treated with open surgery, one suffered a perioperative stroke attributed to a thrombosed graft, and another required reoperation for bleeding on post-operative day two. None of the patients managed with endovascular approaches experienced perioperative or long-term complications.

Szopinski and colleagues described 15 patients who presented with carotid artery aneurysms, nine of whom underwent surgical reconstruction and three of whom underwent endovascular repair [7]. No intra- or peri-operative deaths occurred in either group, but three post-operative deaths were reported in the surgical cohort: one patient died 43 days post-op due to a stroke sustained during aneurysm resection; another died 3 years post-op from a CVA; a final patient died from a myocardial infarction (MI) 10 years after his aneurysm repair. The surgical cohort also included one patient requiring re-operation for hematoma, one patient with TIA, and a final patient with transient cranial nerve injuries. In the 2-year follow-up period for endovascular patients, no aneurysm- or treatment-related morbidity or mortality was reported. Three patients received medical management; one of these had previously undergone two failed attempts at endovascular treatment (guidewire unable to pass aneurysm). One medically-managed patient died of stroke 9 months after initial presentation.

Zhou and colleagues published a review of all carotid artery aneurysm repairs performed at their institution between 1984 and 2004, and compared the outcomes of procedures performed before and after the introduction of endovascular treatment methods [8]. Prior to 1995, 100 % of the 20 carotid aneurysm patients managed by this group underwent open surgery; subsequently, 14 of 20 patients (70 %) underwent endovascular repair instead. The authors did not compare outcomes between surgical and endovascular repairs. However, they did note that patients in the more recent cohort were less likely to suffer cranial nerve injury (14 % v. 5 %, $p<0.04$) or wound complications (9 % v. 0 %, $p<0.05$), and had a significantly shorter in-hospital stay (3.5 ± 1.2 days v. 9.4 ± 3.5 days, $p<0.01$). Procedure-related mortality and 30-day stroke rate were similar across groups, though the combined perioperative death rate and 30-day stroke rate were higher in patients treated before the introduction of endovascular methods (14 % v. 5 %, $p<0.04$).

Table 31.2 Studies describing open surgery and endovascular interventions

		Surgical							Endovascular								
Author (year)	N (Ans/ Pts)	N (Ans)	Etiology	Technique	30-day Morb.	30-day Mort.	Late Morb.	Late Mort	N (Ans)	Etiology	Technique	30-day Morb.	30-day Mort.	Late Morb.	Late Mort.	Follow up (mean, range)	Study type and quality of evidence
Angiletta (2014) [5]	26/25	23	AA (18); infection (1); trauma (4)	Aneurysmorraphy and vein graft (2) Prosthetic graft (1) REE (15) Vein graft (5)	CVA (1) Hematoma (1) MI (2) TCNI (2)	0	CVA (2)	Cardiac disease (4); lung cancer (2)	3	Arteritis (3)	Covered stent (3)	0	0	0	0	7.5 years (3.0–18.0)	Retrospective Very low
Fankhauser (2015) [2]	141/132 75 managed medically	48	FMD (15); CTD (6); CEA (17); trauma (3): other (5);	Aneurysmorraphy (1) Prosthetic graft (3) REE (7) Vein graft (4)	CVA (1); reoperation due to bleeding (1)	0	0	0	18	CEA (4); trauma (3); other (11)	carotid sacrifice/ embolization (3); bare stent with coil (11); covered stent (4);	0	0	0	0	33.9 months (0–167 months)	Retrospective Low
Szopinski (2005) [7]	15 3 managed medically, including 1 awaiting surgery	9	AA (3); CEA (1); trauma (3); other (2)	Aneurysmorraphy (1) Aneurysmorraphy and prosthetic graft (1) Prosthetic graft (1) REE (2) Vein graft (1) Other (3)	Hematoma (1) TIA (2)	Intraoperative CVA (1)	0	CVA (1); MI (1)	3	Trauma (1); CEA (1); AA (1)	Covered stent (3)	0	0	0	0	NR	Retrospective Very low

Table 31.2 (continued)

		Surgical							Endovascular								
Author (year)	N (Ans/ Pts)	N (Ans)	Etio-logy	Technique	30-day Morb.	30-day Mort.	Late Morb.	Late Mort	N (Ans)	Etio-logy	Technique	30-day Morb.	30-day Mort.	Late Morb.	Late Mort.	Follow up (mean, range)	Study type and quality of evidence
Zhou (2006) [8]	42/42	28	1985–1994: AA (12); PsA (8); trauma (2) 1995–2004: AA (10); PsA (7); trauma (3)	1985–1994: carotid ligation (4); resection and graft (12); resection and patch angio-plasty (6) 1995–2004: carotid ligation (1); resection and graft (5)	CNI (3); CVA (1)	2 (9%)	0	1 (5%)	14	NR	1995–2004: balloon exclusion (1) Stent graft (7) Stent graft with coil (6)	NR	NR	NR	NR	4.6 years (24 days – 20 years)	Retro-spective Low

AA atherosclerotic aneurysm, *Ans* aneurysms, *CNI* cranial nerve injury, *CTD* connective tissue disorder, *FMD* fibromuscular dysplasia, *Morb.* morbidity, *Mort.* mortality, *NR* not reported, *PsA* pseudoaneurysm, *Pts* patients, *REE* resection and end-to-end anastomosis, *TA* true aneurysm, *TCNI* transient CN injury
One patient died of CVA 9 months after presentation

Surgical Management Only

Studies describing surgical management are summarized in Table 31.3. All were retrospective reviews of institutional or national data. Attigah and colleagues (2009) presented a retrospective review of 64 carotid reconstructions in 57 patients between 1980 and 2004 [9]. They reported a perioperative stroke rate of 1.6 % (1/64 patients), and TIA rate of 6.3 % (4 patients). The authors also presented a novel system for classifying carotid artery aneurysms according to location and morphology.

In 2009, Donas and colleagues reported 55 patients with 61 ECAAs treated with open surgery between 1986 and 2007 [10]. Complications included 3 perioperative graft thromboses (4.9 %), four cerebral strokes (6.5 %), and one MI. Overall mortality was 3.6 %: one patient died of stroke and one of cardiac decompensation. The authors compared patients with degenerative aneurysms and aneurysms secondary to prior carotid endarterectomy, and found no significant differences in post-operative morbidity, mortality or complication rates.

El-Sabrout and colleagues (2000) reported the results of 29 aneurysms and 38 pseudoaneurysms managed surgically between 1960 and 1995 [6]. Overall, three fatal strokes, two non-fatal strokes and one MI were directly attributed to aneurysm repair (mortality/major stroke incidence 9 %; minor stroke incidence 1.5 %). Four patients suffered cranial nerve injury (5.9 %). With a mean follow-up of 5.9 years, a further 19 patients died of non-aneurysm-related causes. Of note, all three fatal strokes occurred between 1960 and 1966, and an unspecified number of patient outcomes were self-reported via mail-in survey.

In 1996, Faggioli and colleagues reported 24 ECAAs in 20 patients treated operatively between 1974 and 1995 [1]. Elective surgery was performed in 22 cases, with no perioperative mortality, a 4.5 % perioperative stroke rate, and a 20.8 % rate of cranial nerve injury. Long-term complications included one late TIA and one recurrent aneurysm, both in patients with vein grafts. Emergency surgery was performed in two cases of ruptured aneurysms; one of these patients died.

Garg and colleagues (2012) reported a series of 16 carotid aneurysms managed between 2005 and 2010: 14 were treated surgically and two medically [11]. Among patients who underwent surgery, no stroke or aneurysm-related mortality was documented in the 30-day post-operative period, nor in the follow-up period averaging 22 months. One patient died 10 months post-operatively of unrelated causes. One patient developed a transient cranial nerve palsy, and another patient required reoperation at 4 months for graft stenosis. (Although the authors indicated that outcomes for the medically-managed group included development of symptoms and changes in aneurysm characteristics on imaging, none of these outcomes were included.)

In a review of prospectively-collected national data, Nordanstig and colleagues (2014) reported a 33 % perioperative complication rate among 48 patients who underwent surgical repair of extracranial carotid artery aneurysms between January, 1997 and December, 2011 [12]. They reported 2 non-fatal perioperative strokes, 2 fatal perioperative strokes (1 contralateral), and 6 permanent cranial nerve injuries. Of note, the authors only collected data from follow-up appointments conducted 1-month and 1-year post-operatively. No additional longitudinal data was included.

Table 31.3 Studies describing open surgery

Author (year)	N (aneurysms/ patients)	Etiology	Technique	30-day morbidity	30-day mortality	Late morbidity	Late mortality	Mean follow up (range) OR (±SD)	Study type and quality of evidence
Attigah (2008)	64/57	AA (47) CTD (1) FMD (3) Infection (1) Prior surgery (8) Other (4)	Carotid ligation (1) Direct suture (6) Patch (6)[a] REE (14) Synthetic graft (20) Vein graft (16)	CVA (1; 1.6 %) MI (1) Reoperation due to bleeding/ hematoma (2) Transient CN injury (13; 20.3 %) Transient hemiplegia (4; 6.3 %)	0	Permanent CN injury (6.3 %)	Fatal CVA (2)	13.5 years (0.3–25)	Retro-spective Low
Donas (2009) [10]	61/55	AA (32); prior surgery (29)	Synthetic graft (27); synthetic patch (22); vein graft (12);	CVA (4) thrombosis (3) Permanent recurrent laryngeal nerve injury (3) Transient recurrent laryngeal nerve injury (3) Other transient CN injury (3) Other permanent CN injury (6)	CVA (1); cardiac causes (1)	NR	NR	42.7 months (± 22.0 months)	Retro-spective Low

(continued)

Table 31.3 (continued)

Author (year)	N (aneurysms/ patients)	Etiology	Technique	30-day morbidity	30-day mortality	Late morbidity	Late mortality	Mean follow up (range) OR (±SD)	Study type and quality of evidence
El-Sabrout (2000) [6]	67/65	CEA (38); trauma (6); AA (23)	Clipping (2) Ligation (1) Plication, patch (1) Primary anastomosis (10) Resection and repair (3) Synthetic graft (7) Synthetic patch (35) Vein graft (2) Vein patch (4) Other (2)	Non-fatal CVA (2); CN injury (4)	MI (1); CVA (3)	Infection requiring reoperation (6); restenosis requiring reoperation (1); hematoma requiring reoperation (2)	MI (11); other (8)	5.9 years (1.5 months – 30 years)	Retro-spective Low
Faggioli (1996) [1]	24/20	FMD (12); AA (9); CEA (2); trauma (1)	Aneurysmectomy (2); aneurysmectomy and vein patch (2); aneurysmectomy and synthetic patch (1); synthetic graft (3); transposition (9); vein graft (7)	CVA (1; 4.5 %); transient CN injury (5; 20.8 %)	Aneurysm rupture (1)	Recurrent aneurysm requiring reoperation (2); TIA (1)	NR	96.7 ± 88.15 months	Retro-spective Very low
Garg (2012) [11]	16/15 2 managed medically	AA (4); CEA (5); trauma (5)	Aneurysmectomy with primary anastomosis (5) Bypass (1) Plication and patch angioplasty (1) Synthetic graft (3) Vein graft (4)	Transient CN Injury (1)	0	Graft stenosis requiring reoperation (1)	MI (1)	22 months (1–58 months)	Retro-spective Very low

Table 31.3 (continued)

Author (year)	N (aneurysms/ patients)	Etiology	Technique	30-day morbidity	30-day mortality	Late morbidity	Late mortality	Mean follow up (range) OR (±SD)	Study type and quality of evidence
Nordanstig (2014) [12]	48	AA (34); infection (2); PsA (12)	Direct suture (3) Ligation (2) Resection and end-to-end anastomosis (16) Synthetic graft (11) Synthetic patch (1) Vein graft (14) Vein patch (1)	MI (2); non-fatal CVAs (2); perioperative bleeding requiring re-operation (2);	Fatal CVA (1 ipsilateral, 1 contralateral); other (1)	Permanent CN injury (6)	NR	1 year	Retro-spective Low
Rosset (2000) [13]	25	AA (9); dysplasia (12); trauma (3); other (1)	Patch repair (1); vein graft (24);	CVA (1) Permanent CN injury (1) TIA (2) Transient CN injury (10)	0	Focal epileptic seizure (1); TIA (1)	MI (2)	66 months (12–150 months)	Retro-spective Very low
Srivasta (2009)	19	AA (7); mycotic pseudo-anuerysms (7); vein patch aneurysms (5)	Aneurysmectomy with end-to-end anastomosis (1); patch repair (6); prosthetic graft (3) Vein graft (9);	CVA (2); TIA (1); transient CN injury (1)	0	Symptomatic stenosis (1); Asymptomatic occlusion (1)	0	48 months	Retro-spective Very low

AA atherosclerotic aneurysm, *Ans* aneurysms, *CEA* carotid endarterectomy, *CN* cranial nerve, *CTD* connective tissue disorder, *CVA* stroke, *FMD* fibromuscular dysplasia, *MI* myocardial infarction, *NR* not reported, *PsA* pseudoaneurysm, *Pts* patients, *REE* resection and end-to-end anastomosis, *TA* true aneurysm, *TCNI* transient CN injury, *TIA* transient ischemic attack

[a]These numbers did not add up to 64

Rosset and colleagues (2000) reported the surgical management of 25 patients with internal carotid artery aneurysm (22) or pseudoanuerysm (3) managed between 1980 and 1997 [13]. They reported one perioperative stroke and two TIAs. Eleven cranial nerve palsies were observed, ten of which resolved. One patient subsequently developed occlusion of his vein graft, but remained asymptomatic at 14-month follow-up.

Finally, Srivasta and colleagues (2009) reported 19 patients who underwent surgical repair of carotid aneurysms between 1998 and 2008 [3]. The authors reported two perioperative embolic strokes (10.5 %) and one TIA, as well as one asymptomatic stenosis 5 years post-operatively.

Endovascular Management

Studies describing endovascular management are summarized in Table 31.4. In 2004, Bergeron and colleagues reported five ECAAs managed with an endovascular approach, with a mean follow-up of 3.6 years (±1.3 years) [14]. The authors reported one TIA in the perioperative period, and one access site hematoma requiring re-operation. One patient developed an asymptomatic endoleak, requiring extension of the covered stent graft. All patients otherwise remained asymptomatic and no mortality was reported.

Li and colleagues (2011) presented a systematic review of English-language literature regarding endovascular stenting of extracranial carotid artery aneurysms between 1995 and 2010 [15]. Across 113 studies involving 224 patients, they reported an overall in-hospital endoleak rate of 8.1 %, in-hospital stroke rate of 1.8 % and in-hospital mortality rates of 4.1 %, without any procedure-related deaths. Cranial nerve injury occurred in 0.5 % of patients. Over half (50.9 %) of aneurysms were post-traumatic; atherosclerosis and connective tissue diseases accounted for 4.5 and 3.1 % of all aneurysms, and were significantly more common among true aneurysms relative to pseudoaneurysms. Emergent surgical conversion was required in 0.4 % of all patients, and in 7.7 % of patients with true aneurysms ($p < 0.05$). In this study, indications for endovascular repair included prior neck irradiation or surgery (20 patients; 8.8 %), high position of the aneurysm (40 patients; 17.9 %), poor health (7; 3.1 %), and neck infection/inflammation (6; 2.7 %). Patients who received bare metal stents were significantly more likely to require re-intervention (22.9 % v. 0 %, $p < 0.0001$), to develop in-stent graft stenosis (5.9 % v. 0 %, $p = 0.038$), and to experience late complications (23.5 % v. 8.3 %, $p = 0.031$). Bare metal stent patients were also significantly less likely to demonstrate post-operative thrombosis of the aneurysm sac (70.6 % v. 95.8 %, $p = 0.0002$).

More recently, Seward and colleagues reported stent-graft repair of 14 extracranial carotid pseudoaneurysms in 12 patients [16]. In a median follow-up time of 6.25 months (range 0–50 months), they reported no perioperative neurologic complications. One patient developed an asymptomatic carotid dissection that resolved on follow-up imaging; another patient developed a femoral access site hematoma and deep vein thrombosis. One patient with bilateral aneurysms was lost to follow up; the others either remained asymptomatic or experienced improvement of aneurysm-related symptoms.

Table 31.4 Studies describing endovascular interventions

Author (year)	N(aneurysms/ patients)	Etiology	Technique	30-day morbidity	30-day mortality	Late morbidity	Late mortality	Follow up	Study type and quality of evidence
Bergeron (2004) [14]	5/4	NR	Covered stent graft (5)	Hematoma requiring reoperation (1); TIA (1)	0	Endoleak requiring reoperation (1)	0	3.6 years (±1.3 years)	Retrospective Very low
Li (2011)	224 patients	AA (10) CEA (25) CTD (7) Dissection (15) Iatrogenic injury (11) Infection (5) Surgery and/ or radiation (25) Trauma (114) Other (12)	Bare stent graft (31.6 %); covered stent graft (68.4 %)	CVA (1.8 %); endoleak (8.1 %);	4.1 %; 0 procedure-related deaths	CVA (0.5)	2.6 %; 0 procedure-related deaths	15.4 months (±15.3 months)	Systematic literature review Moderate
Seward (2014)	14/12	FMD (4); trauma (6); other (4)	Stent graft (12) Stent graft and coils (2)	Access site hematoma (1); asymptomatic dissection, no re-operation (1)	0	0	0	6.25 months (0–50 months)	Retrospective Very low

AA atherosclerotic aneurysm, *CEA* carotid endarterectomy, *CTD* connective tissue disorder, *CVA* stroke, *FMD* fibromuscular dysplasia, *NR* not reported, *TIA* transient ischemic attack

Medical Management

Several studies included patients who received medical therapy, as opposed to surgical management. Rosset and colleagues summarized four studies, published between 1926 and 1989, in which patients received conservative management with anticoagulation [13]. This approach was associated with a combined death and stroke rate of up to 71 % (of 42 patients) in the 1920s, and 50 % (of 18 patients) managed in the 1980s. In the former study, "cure or improvement" was noted only in 12 % of non-surgical patients [4].

In their study, Szopinski and colleagues described three patients who refused invasive treatment, including one who had undergone two prior attempts at endovascular repair 2 years earlier [7]. One patient died of stroke 9 months after presentation; the other two remained asymptomatic 2 and 6 years after initial treatment attempts and presentation, respectively [7].

More recent data may be more encouraging regarding the outcomes of medical management. Fankhauser and colleagues reported 75 patients with carotid artery aneurysm or pseudoaneurysm (10 and 65 patients, respectively) who were managed non-operatively with aspirin, anticoagulation and/or serial imaging [2]. In a mean follow-up period of 33.9 months, no patients experienced death or major morbidity related to their aneurysms. However, the patients in this cohort were more likely to be asymptomatic on presentation than were patients who underwent surgical or endovascular intervention.

Summary

There are currently no formal guidelines regarding management of extracranial carotid artery aneurysms. The literature indicates that these lesions can be successfully managed via open surgery or endovascular repair, with acceptable stroke and mortality rates. However, the literature lacks randomized controlled trials comparing these management strategies, and retrospective studies comparing theses treatment modalities frequently have shorter follow-up periods for endovascular cases. Furthermore, the retrospective reviews published to date tend not to directly compare the outcomes of different management strategies. This likely reflects the small sample size, and inability to power statistically significant comparisons. Nonetheless, the data included in this review suggest that endovascular repair may be associated with lower stroke and mortality rates, peri-operatively and long-term.

A Personal View of the Data

The literature lacks a randomized-controlled trial comparing medical, surgical and endovascular management strategies. Nonetheless, due to an apparently diminished risk of peri-operative and long-term complications, the endovascular approach seems likely to become the favored choice in years to come.

In the meantime, more research and data are needed to determine which patients are best-suited to surgical versus endovascular management for carotid artery aneurysms. Researchers publishing data on this subject would do well to stratify all results according to both aneurysm etiology and intervention type, which thus far has not often been done. Standardized classifications of aneurysms according to anatomic location, such as the schema proposed by Attigah and colleagues [9], should be broadly utilized. Whenever possible, clinical justification for open or endovascular intervention should be specified (e.g. aneurysm location, patient comorbidities, etc.), as well as the use of intraluminal shunts and distal protection devices (for open surgery), and covered or bare metal stent grafts (for endovascular interventions).

Just as importantly, more information is needed regarding the natural history of carotid artery aneurysms [12], as well as indications and outcomes of medical management of these lesions. There is compelling evidence that carotid aneurysms and pseudoaneurysms can be safely managed with anticoagulation and serial monitoring [2]. Furthermore, different aneurysm morphologies may have different risks for enlargement and possibly rupture [17]. ECAAs secondary to a range of etiologies may also present differential risks of thrombotic and/or embolic events. This has obvious bearing on the need for surgical or endovascular –as opposed to medical – management.

Finally, due to the rarity of this disease entity, we propose that carotid artery aneurysms would be best managed in centralized referral centers. Such centralization would also facilitate prospective, randomized-controlled trials comparing surgical, endovascular and medical management.

Recommendations

- In patients with ECAAs we recommend endovascular management, particularly in patients in whom open surgery would be especially challenging (e.g. those with a history of ipsilateral neck radiation or surgery, or whose aneurysms are high-lying). (**evidence quality weak; moderate recommendation**)
- In endovascular interventions, covered stents should be used instead of bare metal stents. (**evidence quality weak; strong recommendation**)
- When pursuing an endovascular option, clinicians should be prepared to convert to open surgery if necessary; this may be more likely in patients with true aneurysms, as opposed to pseudoaneurysms. (**evidence quality weak; strong recommendation**)

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Chapter 32
In Patients with Carotid Artery Dissection, Is Stenting Superior to Open Repair to Improve Clinical Outcomes?

Reshma Brahmbhatt and Ravi R. Rajani

Abstract Carotid artery dissection is a rare but potentially devastating entity. Clinical sequale can include stroke, cranial nerve dysfunction, carotid stenosis, and pseudoaneurym formation. Anticoagulation is the mainstay of treatment, but in patients who fail anticoagulation or have contraindications to anticoagulation, surgical therapy is often considered. Open surgical repair had historically been the traditional therapy of choice, but percutaneous therapy with stent placement has become increasingly commonplace. No randomized trials exist regarding optimal surgical management of carotid artery dissection. Current literature supports both open and endovascular treatment as safe and effective for carotid artery dissection.

Keywords Carotid • Dissection • Endovascular • Surgery • Stent

Introduction

Arterial dissection is defined as a disruption or tear in the intimal layer, which allows blood to create false flow lumens within the layers of the arterial wall. The resultant intramural hematoma propagates distally, causing stenosis and possible occlusion of the true flow lumen. Additionally, the weakening of the arterial wall can lead to aneurysmal changes with a potential to become a thromboembolic source. Dissection of the carotid artery can potentially lead to significant complications such as stroke, cranial nerve dysfunction, and aneurysm formation. Carotid

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Table 32.1 PICO table for operative approach to carotid artery dissection

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Patients with Carotid artery dissection and failed medical management	Endovascular stenting	Open surgery	Stroke, death, cranial nerve injury, patency

dissection is estimated to be the contributing etiology in 2 % of patients who have suffered an index stroke. This is particularly true in younger patients with stroke, where a dissection is identified in as many as 22 % of cases [1–3].

Medical management is the mainstay for uncomplicated carotid dissection. A 2003 Cochrane Database Review found no randomized trials evaluating antiplatelet vs. anticoagulant therapy or either intervention vs. controls [4]. A more recent meta-analysis also noted the lack of randomized data regarding antiplatelet and anticoagulant treatment in carotid artery dissection. However, their results suggested antiplatelet therapy should be given precedence over antcoagulation [5]. The Cervical Artery Dissection in Stroke Study trial (CADISS) is a currently ongoing randomized trial comparing antiplatelet therapy to anticoagulation in cervical artery dissection. Recent publication of their non-randomized arm revealed no difference in 3 month outcomes (stroke, transient ischemic attack, major bleeding, or death) between the two treatment modalities [6]. Despite controversy on whether antiplatelet treatment or anticogulation is ideal, medical management remains the mainstay of treatment for carotid artery dissection. Surgical treatment is reserved only for patients who have a contraindication to anticoagulation (active bleeding, other injuries requiring surgical management, etc.) or for those who fail medical management. Failure of medical management can be described as fluctuating or worsening neurologic symptoms while on medical therapy, severely compromised blood flow, aneurysmal degeneration, and symptomatic aneurysm (including cranial nerve deficit). With the emergence of endovascular techniques for carotid interventions, it is unclear if endovascular approaches improve clinical outcomes when compared to traditional open surgical management (Table 32.1).

Search Strategy

A literature search of English language publications in PubMed, Embase, and Cochrane Evidence Based Medicine databases from inception-2014 was used to identify literature on surgical management of carotid artery dissection. Terms used in the query were “carotid artery dissection”, “cerebrovascular injury”, “cerebrovascular dissection”, “carotid injury” AND “stent”, and “surgery”. Articles were then individually examined and excluded if they did not include a surgical approach to management, did not pertain to the extracranial carotid artery, described thrombolysis only, or were not available online or at a medical library. A total of 65 eligible papers were identified: 45 describing endovascular management, 13 describing open

surgical management, and 7 systematic reviews on overall management. There were no randomized trials. Of the 45 articles on endovascular management, there were 11 retrospective reviews, 5 results of prospective cohorts, and 29 case series. Additionally, there were five general review articles regarding the management of carotid artery dissection and appropriate recommendations. The data was subsequently classified based on the GRADE level of recommendation.

Results

Outcomes After Open Repair

Thirteen articles were identified describing results after open surgical therapy – three retrospective reviews and ten case reports (Table 32.2). Overall, 87 patients are included. The majority of the currently selected articles were published before 1999 [7–19]. While there are a variety of specialties that have reported on this subject, vascular surgery and neurosurgery are most represented. The etiology of dissection was primarily spontaneous or traumatic, though there is one reported iatrogenic injury [8]. Medical management was initially attempted in only 5 of the 13 articles [7, 9, 10, 12, 19]. The most commonly used repair technique was saphenous vein interposition graft, though other techniques such as bypass, endarterectomy, and ligation are also described. Most patients clinically improved following revascularization. While follow-up information is limited, most interposition and bypass grafts appear to have been patent at the time of publication. The largest single series is a retrospective review of 50 patients with symptomatic carotid dissection published in 2000 by Muller et.al. 40 patients underwent saphenous vein interposition grafting, five underwent ligation of the internal carotid artery, three underwent endarterectomy, and two underwent gradual dilation with patch angioplasty. There was one death and 4 strokes (2 from occluded grafts) in the population. There was also a 38 % incidence of cranial nerve injury [19].

Overall, open surgical reconstruction for carotid artery dissection appears to be safe in selected patients based on small case series. There is insufficient evidence to compare standard medical therapy with open surgical reconstruction.

Outcomes After Endovascular Repair

In contrast to the data on open surgical repair of carotid dissection, the majority of data published on carotid stenting for dissection has been published after 2000. Again, there are no randomized trials. The 45 identified manuscripts represent 29 case reports/series, followed by 11 retrospective reviews and 5 reports of prospective cohorts (Table 32.3) [20–64]. Overall, 390 patients are included. Vascular surgery, neurosurgery, and neurointerventional radiology represent the most common

Table 32.2 Open surgical repair of carotid dissection

Study	Patients (n)	Mechanism	Medical management	Intervention	Type of study (grade of evidence)
Aspalter et al. (2013) [14]	2	Traumatic	Not attempted	Interposition vein graft	Case report (low)
Takeuchi et al. (2012) [15]	1	Traumatic	Not attempted	Double-bypass with proximal cervical ICA ligation	Case report (low)
Geraldes, et al. (2012) [16]	1	Spontaneous	Aspirin	CCA interposition graft with synthetic	Case report (low)
Cuff and Thomas (2005) [17]	1	Traumatic	Not attempted	Interposition vein graft	Case report (low)
Findlay et al. (2002) [18]	2	Spontaneous	Not attempted	Embolectomy	Case report (low)
Muller et al. (2000) [19]	50	Spontaneous, traumatic	Failed or not attempted	40 interposition vein graft; 5 carotid ligation; 3 endarterectomy; 2 gradual dilation with patch angioplasty	Retrospective series (low)
Alimi et al. (1998) [7]	8	Traumatic	Failed or not attempted	Interposition vein graft	Retrospective series (low)
Koennecke et al. (1998) [8]	1	Iatrogenic	Not attempted	Interposition vein graft	Case report (low)
Vishteh et al. (1998) [9]	16	Traumatic	Failed or not attempted	Interposition vein graft	Retrospective series (low)
Humphrey et al. (1993) [10]	1	Spontaneous	Failed	Interposition vein graft	Case report (low)
Waespe et al. (1988) [11]	1	Traumatic	Not attempted	EC-IC bypass, occlusion of L ICA aneurysm by detachable balloon	Case report (low)
Miyamoto et al. (1984) [12]	1	Spontaneous	Failed	Superficial temporal to MCA bypass	Case report (low)
Dragon et al. (1981) [13]	2	Traumatic	Not attempted	1 intimal tacking; 1 Interposition vein graft	Case report (low)

ICA internal carotid artery, *CCA* common carotid artery, *MCA* middle cerebral artery, *EC-IC* extracranial-intracranial

Table 32.3 Endovascular stent placement in carotid dissection

Study	Patients (n)	Mechanism	Medical management	Type of study (grade of evidence)
Schulte et al. (2008) [37]	7	Traumatic, iatrogenic	Failed or contraindicated	Prospective cohort (low)
Cohen et al. (2005) [48]	12	Traumatic	Failed or contraindicated	Prospective cohort (low)
Cohen et al. (2005) [49]	10	Traumatic	Failed or contraindicated	Prospective cohort (low)
Cothren et al. (2005) [47]	46	Traumatic	Failed or contraindicated	Prospective cohort (low)
Bassi et al. (2003) [55]	7	Traumatic, spontaneous	Failed	Prospective cohort (low)
Asif et al. (2014)	22	Traumatic, spontaneous	Failed (aspirin and plavix)	Retrospective series (low)
Seth et al. (2013) [23]	47	Traumatic	Failed or contraindicated	Retrospective series (low)
Ahlhelm et al. (2013) [26]	7	Traumatic, spontaneous, iatrogenic	Failed or contraindicated	Retrospective series (low)
Yin et al. (2011) [28]	33	Traumatic, spontaneous	Failed or contraindicated	Retrospective series (low)
Edgell et al. (2005) [46]	7	Spontaneous	Failed or contraindicated	Retrospective series (low)
Kansagra et al. (2014) [64]	2	Traumatic, iatrogenic	Unknown	Retrospective series (low)
Cohen et al. (2012) [27]	23	Traumatic	Failed or contraindicated	Retrospective series (low)
DiCocco et al. (2011) [32]	50	Traumatic	Failed or contraindicated	Retrospective series (low)
Ohta et al. (2011) [30]	43	Traumatic, spontaneous	Failed or not attempted	Retrospective series (low)
Chandra et al. (2007) [42]	1	Spontaneous	Failed	Retrospective series (low)
Edwards et al. (2007) [41]	4	Traumatic	Failed	Retrospective series (low)

specialties represented in the selected literature. The procedures were performed for traumatic, spontaneous, and iatrogenic dissections. Most descriptions report symptomatic improvement with a low periprocedural complication rate. While follow-up data is limited, most series report a low incidence of early stent thrombosis.

The indications for stent placement continue to be poorly defined. Thirty-one of the selected series report failure or contraindication to medical management as the primary reason for endovascular management. However, the type and duration of attempted medical therapy remain unclear in most reports. Twelve studies did not attempt medical management at all prior to intervention. It remains undefined what truly constitutes failure of medical therapy.

Several large series have demonstrated that stenting appears to be a safe procedure for selected cases of carotid dissection. A large retrospective review in 2013 evaluated the outcome of 53 self-expanding stents placed for symptomatic traumatic carotid dissection. The authors found that 6.4 % of patients had transient postoperative symptoms, 2.1 % had luminal narrowing or a new aneurysm on follow up, and 2 % had asymptomatic stent occlusion on follow up. In all, 4.3 % of patients required some form of reintervention. Overall, they concluded that carotid stenting for traumatic cervical carotid dissection was safe and effective [23]. Similarly, a large single-center experience with stenting for traumatic carotid dissection in 2012 concluded that stenting appeared to be safe in selected patients. Twenty-three patients underwent stenting; 70 % had improved symptoms after the procedure and 26 % had stable symptoms. There was one death in their study from unrelated traumatic injuries. All stents were patent at follow up [27]. A 2011 retrospective review examining stents placed for both traumatic and spontaneous carotid dissection reported no postoperative stenosis or major cardiovascular events in their 33 patients. One patient did have a recurrent TIA after the procedure, but there was no permanent neurologic deficit. The authors' conclusion was that stenting is a safe treatment option in selected cases of carotid dissection [28].

While there are no studies that compare open repair to endovascular repair, there are some retrospective studies that evaluate anticoagulation alone versus endovascular management. Unfortunately, many of the studies have a limited number of patients, making drawing conclusions difficult. For example, a 2007 single-center experience with spontaneous carotid dissection included 12 patients, only one of which underwent revascularization. That patient underwent bilateral carotid stent placement, but unfortunately suffered postoperative intracranial hemorrhage. The authors concluded that anticoagulation was safer than stent placement as none of the patients who were anticoagulated suffered any complications [42]. A 2005 study evaluated 46 patients with blunt cerebrovascular injury, 23 of whom underwent stent placement. Of the 23 stent patients, 4 had postoperative strokes and 1 developed a subclavian artery dissection. Eight patients with available follow-up had post-stent occlusion (45 % compared to 5 % carotid occlusion in the anticoagulation group). The authors concluded that the risks of carotid artery stenting in this setting outweigh the benefits [47]. Finally, a large series analyzing 222 trauma patients with blunt cerebrovascular injury included 50 patients treated with carotid stenting. At follow up, the authors saw no difference in complications or patency between the anticoagulation and stent group, claiming stents were safe but no better than anticoagulation [32].

There have been two systematic reviews published regarding the role of endovascular management in carotid artery dissection. A 2008 systematic review which evaluated 13 studies and 63 stents found no mortalities, 100 % patency and 11 % stroke rate at a 16 month mean follow up period [65]. In 2013, a systematic review which included 23 studies and 201 patients tabulated a 4 % rate of perioperative cardiovascular adverse events, as well as a 2.1 % rate of recurrent TIA. The authors concluded stents are safe for use in carotid dissection [66].

Multiple review articles and management guidelines have also been published regarding the appropriate management of traumatic carotid dissection and role for

endovascular management (Table 32.4). The consensus of all of these articles is that anticoagulation should remain as first line therapy. If patients fail anticoagulation or are not candidates for anticoagulation, endovascular management remains a safe therapy. It remains undecided what constitutes a true failure of medical therapy [67–71].

Recommendations

Carotid artery dissection is an uncommon, but potentially serious condition that can lead to significant morbidity and mortality. They can occur spontaneously, or as the result of trauma or iatrogenic injury. The first line treatment for carotid artery dissection remains anticoagulation. However, in patients with continued symptoms or those in whom anticoagulation is contraindicated, revascularization may be warranted. Both open surgical repair and endovascular stent placement have been described. Both techniques have been reported to have good outcomes (evidence quality weak). Modern publications have focused mainly on endovascular

Table 32.4 Review articles regarding the management of carotid artery dissection

Study	Title	Recommendation	Type of study (grade of evidence)
Fusco and Harrigan (2011) [69]	Cerebrovascular dissections: a review. Part II: blunt cerebrovascular injury	Anticoagulation as primary treatment, endovascular therapy for refractory patients. Surgery only for patients who are not candidates for endovascular therapy	Review article based on low grade evidence
Bromberg et al. (2010) [67]	Blunt cerebrovascular injury practice management guidelines: the Eastern Association for the Surgery of Trauma	Grade I and II injuries should be anticoagulated. Grade III and higher, or symptomatic patients should be considered for an intervention	Review article based on low grade evidence
Moulakakis et al. (2010) [70]	An update of the role of endovascular repair in blunt carotid artery trauma	Anticoagulation as primary treatment, endovascular therapy for refractory patients. Surgery only for patients who are not candidates for endovascular therapy	Review article based on low grade evidence
DuBose et al. (2008) [68]	Endovascular stenting for the treatment of traumatic internal carotid injuries	Early results on endovascular therapies are encouraging, but data is limited	Review article based on low grade evidence
Redekop (2008) [71]	Extracranial carotid and vertebral artery dissection: a review	Anticoagulation as primary treatment, consider stent placement in symptomatic patients or acute hemodynamic instability	Review article based on low grade evidence

techniques, which have been shown to have minimal postoperative complications and good patency rates at follow up (evidence quality weak). Based on the available data, we make a weak recommendation for endovascular carotid stent placement in symptomatic carotid artery dissection following failure of attempted medical therapy.

Personal View of the Data

There is ample data supporting anticoagulation as first-line therapy in patients with carotid artery dissection, but no clear consensus duration of treatment or what constitutes failure. Open repair has become increasingly rare. There are no randomized trials and all of the data for either open surgical or endovascular management is of weak quality. However, data supports both types of surgical intervention as safe and effective in appropriately selected patients. Due to the relatively rare incidence of carotid artery dissection and good reported outcomes with both techniques, there is unlikely to be a head-to-head trial between open repair and endovascular stent placement. Future endeavors should continue to define what constitutes true failure of medical therapy, as well as identifying patients who may be considered for prophylactic stenting while still asymptomatic.

Recommendations

- Anticoagulation remains the first-line therapy for carotid artery dissection (**evidence quality moderate, strong recommendation**)
- For patients who fail or are not candidates for anticoagulation, both open surgical repair and endovascular stent placement represent equally safe and effective management (**evidence quality low, weak recommendation**)

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Chapter 33
In Patients with Cervico-Thoracic Vascular Injuries Is Endovascular Repair Superior in Long-Term Durability When Compared to Open Repair?

Shahriar Alizadegan and Peter J. Rossi

Abstract Trauma to the great vessels, descending thoracic aorta, and the cervical carotid and vertebral arteries is uncommon but management can be very challenging. Endovascular therapy has changed surgeons' approach to these injuries. While short term results have been promising, especially in the treatment of subclavian artery injuries, long term results are lacking; long-term outcomes are of paramount importance in a group of relatively young patients that would be expected to have a long life expectancy after recovery from their trauma. We will review current data regarding short- and long-term outcomes after endovascular management of blunt and penetrating injuries to the cervicothoracic vessels, provide examples of successful treatment, and make recommendations for current management strategies and areas of future research.

Keywords Vascular trauma • Endovascular management • Carotid artery injury • Subclavian artery injury • Thoracic aortic injury

Introduction

Trauma to the great vessels, descending thoracic aorta, and the cervical carotid and vertebral arteries is uncommon but management can be very challenging. Over the last several years, paralleling the development of these techniques in other arenas, there has been an explosion in reports of treatment of both blunt and penetrating

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Table 33.1 PICO table

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with cervicothoracic vascular injury	Endovascular repair	Open repair	Technical success, durability

arterial injuries in these distributions by endovascular means. While short term results have been promising, especially in the treatment of subclavian artery injuries, long term results are lacking; long-term outcomes are of paramount importance in a group of relatively young patients that would be expected to have a long life expectancy after recovery from their trauma.

Selecting which injuries may be appropriate for endovascular management is a particular challenge. A perception exists among many surgeons that patients with acute arterial injuries, especially hemodynamically unstable patients with ongoing hemorrhage, are inappropriate for endovascular management, despite data showing improved outcomes in unstable patients with ruptured aortic aneurysms managed with an "endo-first" approach. An increasing percentage of both blunt and penetrating vascular injuries in the US are being managed by vascular surgeons with endovascular techniques [1–3] and it is of significant importance that all surgeons have an understanding of the situations in which endovascular therapy may be a viable and readily applied alternative to major open vascular reconstruction in severely injured patients. We will review current data regarding short- and long-term outcomes after endovascular management of blunt and penetrating injuries to the cervicothoracic vessels, provide examples of successful treatment, and make recommendations for current management strategies and areas of future research. Given the large volume of data available on endovascular repair of the thoracic aorta for trauma, we will examine this separately from other cervicothoracic vascular injuries.

Search Strategy

We reviewed the English-language literature from the OVID and PubMed databases from 2005 to 2015 to identify published data on surgical approaches to patients with cerviothoracic vascular injury (PICO Table 33.1). We elected to include only literature starting in 2005 in an attempt to only include patients treated with modern endovascular devices and techniques. Search terms used were "trauma", AND("verterbral" OR "carotid" OR "subclavian" OR "innominate"), AND "endovascular repair"; Case reports and small case series were excluded from analysis, as they contained only descriptions of procedures but no information regarding intermediate- and long-term outcomes. No randomized trial data were found. Relevant studies meeting our inclusion criteria are included in Table 33.2.

Table 33.2 Summary of literature review

Study	Patients (#)	Follow-up duration (median)	Vessels involved	Procedures	Outcomes	Quality
Desai et al. (2014) [9]	10	13 months	Common carotid (1) Internal carotid (2) Subclavian (7)	Stent graft	Patent grafts at follow-up; no complications reported	Low
Maughan et al. (2013) [4]	17	22.2 months	Vertebral (iatrogenic)	Observation, stenting or coil embolization	76 % no change in neurological status 2 patients with neurological decline	Low
Seth et al. (2013) [10]	47 (53 injuries, 47 blunt, 6 penetrating)	Up to 7 years	Cervical internal carotid	Stent graft, coil emoblization	Technical success 100 % 1 stent occlusion, 1 stent-related false aneurysm, 3 transient ischemic attacks	Moderate
Rocha et al. (2013) [11]	8	17 months	Subclavian/axillary (5) Carotid (3)	Stent graft	2 subclavian grafts occluded within one year; no other complications	Low
Dubose et al. (2012) [15]	160 (literature review)	Up to 70 months	Axillary/subclavian	Stent graft	84.4 % durable patency 6.3 % repeat intervention 3.1 % open conversion	Moderate

(continued)

Table 33.2 (continued)

Study	Patients (#)	Follow-up duration (median)	Vessels involved	Procedures	Outcomes	Quality
Shalhub et al. (2011) [17]	34 (16 open, 12 endo, 3 converted to open)	235 days (open) 411 days (endo)	Innominate (11) Subclavian (16) Axillary (7)	Stent graft	3 immediate conversions 100 % patent at 1 year follow-up both open and endo Endo times and blood loss significantly less than open	Low
duTroit et al. (2008) [16]	57	48 months	Subclavian/axillary (penetrating)	Stent graft	3/57 early graft occlusion 2 died within 30 days 5 short-term stenosis	Moderate
DuBose et al. (2008) [12]	113	2 weeks-2 years	Internal carotid	Unclear (literature review)	9.7 % occlusion rate, 94 % alive with no neurologic sequelae at follow-up	Low
Maras et al. (2006) [13]	20	Up to 2 years	Internal carotid (20)	Stent graft or bare-metal stents	3 long-term occlusions Study performed prior to availability of current endografts	Low
Cothren et al. (2005) [14]	46 (23 stented, 23 medical management)	2–35 months	Internal carotid (23)	Bare-metal stent	21 % complication rate, 45 % occlusion rate for stenting; 5 % complication rate for medical management	Moderate

Results

While increasing numbers of endovascular repairs are being performed for vascular trauma [1, 2] no randomized trials were identified comparing endovascular to open repair. Similarly, very few data were available regarding long-term outcomes of endovascular repair.

Vertebral Artery

Maughan and colleagues [4] examined vertebral artery injuries occurring in the setting of neck surgery, providing some of the only available data regarding endovascular treatment of these lesions for trauma. Seventeen vertebral artery injuries were identified out of 8213 patients undergoing neck or skull-base surgery over a 15 year period. Nine of the 17 patients underwent endovascular repair of their injuries with either coil embolization or endovascular stenting, and at a median follow-up of 22 months, none of the treated patients had significant neurological sequelae. However, numerous authors [5–8] have noted that management of vertebral artery injuries is controversial, with medical management (antiplatelet agents and/or anticoagulation) often superior to surgical or endovascular management. Anticoagulation and antiplatelet therapies have not been compared head-to-head for medical management purposes. No clear conclusions can be drawn from the literature to recommend routine endovascular management of vertebral artery injuries, regardless of grade, in the absence of ongoing hemorrhage or neurological deterioration.

Carotid Artery

More data exist with regard to endovascular management of carotid artery injuries. Desai and coworkers [9] recently reviewed the charts of 28 patients with arterial injuries in Houston. Of these injuries, only 10 were to the carotid (7) and subclavian (3) arteries. All endovascular repairs were completed with covered endografts. While all repairs were patent at a median follow-up of 13 months, longer-term outcomes were not assessed. No complications were reported during the follow-up period in the ten relevant patients. Similarly, Seth and colleagues [10] retrospectively reviewed 50 cervical internal carotid interventions in 47 patients that were treated with endovascular stenting, coil embolization, or both; only one patient suffered stent occlusion, and three patients suffered transient ischemic attacks. Outcomes at up to 7 years were excellent. While similar results have been reported by other authors [11–13], there was an initial negative experience with carotid stenting for trauma reported by Cothren and coworkers in 2005; they demonstrated a stent occlusion rate of 45 % in 23 patients treated for trauma [14]. However, more recent experience has demonstrated safety, excellent technical success, and good

short-term outcomes for these procedures in carotid trauma. Long-term outcomes are lacking, and multi-center prospective trials are needed. At this time, moderate-quality evidence exists to support endovascular repair of carotid artery injuries with ongoing bleeding, neurological changes or false aneurysms; we recommend endovascular repair for patients that are hemodynamically unstable, and that have difficult to access injuries (i.e. distal internal carotid artery, proximal common carotid artery, strength of recommendation: weak).

Subclavian and Innominate Arteries

Subclavian and innominate artery injuries can be notoriously difficult to control, and are often well situated for endovascular repair. DuBose and coworkers [15] reviewed the English-language literature regarding endovascular management of subclavian/axillary artery trauma. A total of 160 injuries (150 subclavian, 10 axillary) were well-described, culled from 31 separate reports. 84.4 % were patent for duration of follow-up, with 18 patients requiring delayed repeat intervention. duToit and coworkers [16] published the largest single series reviewing endovascular management of these injuries, including 57 patients. There were four short-term complications (one femoral artery injury, three acute endograft occlusions), and five patients required repeat intervention for stenosis. Technical success for the initial endovascular repair was 100 %. Similar results were reported by Shalhub and colleagues [17], examining innominate, subclavian and axillary artery injuries. Long-term results of prospective studies do not exist for these procedures, and again multicenter trials are needed. Subclavian/innominate injuries should be managed endovascular means when feasible (grade of evidence: moderate, strength of recommendation: strong).

A Personal View of the Data

There is a common misperception that endovascular repair of arterial injuries should not be employed in patients with hemodynamic instability. We have taken the converse approach; patients with hemodynamic instability are often very well suited to endovascular repair by a vascular surgeon, who has the unique ability to quickly convert between open, endovascular, and hybrid techniques in the appropriate settings with a high-quality hybrid endovascular suite. As an example, Fig. 33.1 demonstrates a patient that sustained a trans-cervical gunshot wound, with one wound at the angle of the mandible on each side of the neck, and exsanguinating hemorrhage from the left neck on arrival. Successful endovascular treatment of the internal carotid artery with a covered endograft was achieved. Figure 33.2 demonstrates an example of successful treatment of a subclavian injury.

Our institution was a participant in the RESCUE trial [18], and we have consistently adopted an “endo-first” approach to all descending thoracic aortic injuries. Every descending thoracic aortic injury is immediately evaluated by our multidisciplinary

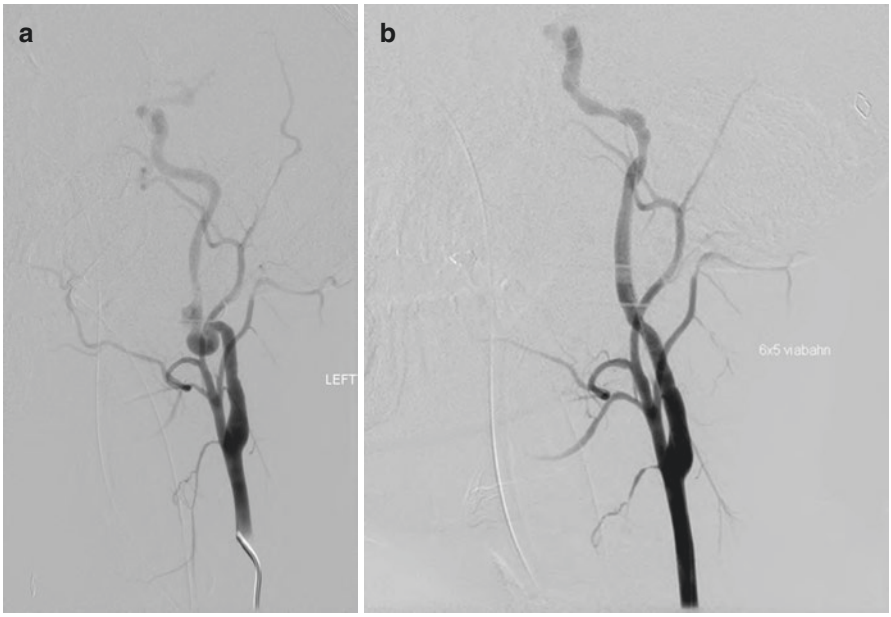

Fig. 33.1 (**a**) Transcervical gunshot wound, internal carotid artery injury, initial arteriogram, showing distal internal carotid artery false aneurysm. (**b**) Final arteriogram showing successful exclusion of false aneurysm with endograft (Gore Viabahn, Flagstaff, AZ)

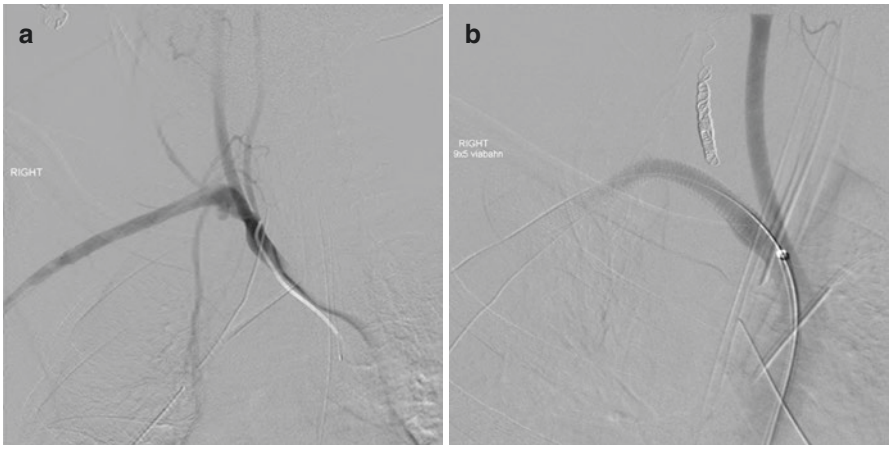

Fig. 33.2 (**a**) Proximal right subclavian artery disruption. (**b**) Completion arteriogram, after vertebral embolization and placement of endograft (Gore Viabahn, Flagastaff, AZ)

team of cardiothoracic surgeons, vascular surgeons, and interventional radiologists; all services are immediately activated for every injury, with endovascular repairs being performed by a collaborative team from vascular surgery and interventional radiology. We have not had as much success adopting the endo-first approach with peripheral and cervico-thoracic injuries as we have with thoracic aortic injuries. This has been due to

resistance from other providers, who believe that an endovascular approach to these injuries is slower than open surgical treatment despite data to the contrary.

We propose that endovascular treatment and open surgical treatment of cervicothoracic arterial injuries are complementary approaches, and that sometimes a hybrid approach is the best; this can be done only by vascular surgeons in a well-equipped hybrid endovascular surgical suite, with the ability to switch between modalities based on the clinical situation. Ongoing research will need to center on both the optimal initial approach to these injuries, as well as the long-term outcomes in this relatively young group of patients.

Recommendations

1. Vertebral artery injuries should be managed medically in the absence of active hemorrhage or neurological deterioration (**grade of evidence: poor, strength of recommendation: weak**).
2. Carotid artery injuries should be managed by endovascular techniques for difficult-to-access injuries (distal internal carotid, proximal common carotid), active hemorrhage, and false aneurysms (**grade of evidence: low quality, strength of recommendation: weak**).
3. Subclavian/innominate artery injuries should be managed by endovascular techniques when anatomically suitable (**grade of evidence: moderate, strength of recommendation: strong**).
4. There are no data to support routine endovascular therapy of aortic arch/great vessel origin injuries, and these should be considered open surgical cases until new data are available (**grade of evidence: weak, strength of recommendation: strong**).

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Part V
Venous and Arteriovenous Disease

Chapter 34
In Patients with Iliofemoral Deep Vein Thrombosis Does Clot Removal Improve Functional Outcome When Compared to Traditional Anticoagulation?

Mikin V. Patel and Brian Funaki

Abstract Iliofemoral deep vein thrombosis is a common clinical condition which often results in post-thrombotic syndrome, a cause of long-term morbidity due to diminished function. The mainstays of treatment for deep vein thrombosis include anticoagulation and compression therapy but these only prevent propagation of the venous clot. Therapeutic options which actively remove clot decrease the risk of post-thrombotic syndrome when compared to conventional anticoagulation alone, an effect attributed to alleviated obstruction and decreased damage to venous valves. Removal of venous clot with catheter-directed thrombolysis is a safe, effective treatment option which can improve functional outcomes in iliofemoral deep vein thrombosis. In patients with contraindication to thrombolytic therapy, surgical thrombectomy is an alternative which also improves functional outcomes in iliofemoral deep vein thrombosis.

Keywords Iliofemoral DVT • Post-thrombotic syndrome • Catheter directed thrombolysis • Surgical thrombectomy

Introduction

Deep vein thrombosis (DVT) is a very common disorder with an estimated lifetime incidence of 2.5–5 % [1]. One out of every two to three patients with DVT develop post-thrombotic syndrome (PTS) which manifests as chronic pain, intractable edema, or leg ulceration and results in significant morbidity [2–6]. PTS has been

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shown to carry considerable negative socioeconomic consequences to both individual patients and the healthcare system [7–9]. Proximal venous thromboses are associated with poorer functional outcomes [6], so optimal treatment of iliofemoral DVT is imperative.

Current clinical guidelines strongly recommend treatment of DVT with anticoagulation to prevent propagation of clot and decrease the risk of acute complications such as pulmonary embolus or recurrent DVT [10, 11]. Studies have evaluated compression stockings to reduce the incidence of PTS and guidelines strongly support their use, yet PTS still affects nearly 25 % of patients despite anticoagulation and compression stocking therapy [3, 11, 12]. Additionally, more recent placebo-controlled studies have suggested that compression stockings may actually have no effect on the incidence of PTS [13].

PTS is generally accepted to be a consequence of sustained venous hypertension from obstruction and insufficient venous valves which are damaged by the inflammatory reaction in the presence of acute thrombus. Therefore, prevailing theory supports the prompt removal of venous clot to prevent development of PTS. Multiple interventions have been developed to remove venous clot including catheter-directed pharmacologic or pharmacomechanical thrombolysis (CDT), percutaneous aspiration thrombectomy (PAT), and surgical thrombectomy [14, 15].

Measuring the efficacy of interventions for DVT can be somewhat challenging but often begins with biomarkers and venous patency on imaging. Ultimately, the goal of clot removal is to prevent PTS and improve functional outcome so a number of scoring systems, including the commonly used Villalta score, have been developed to incorporate both patient symptoms and clinical signs [16]. This chapter reviews the evidence to identify whether clot removal strategies lead to better functional outcomes than conventional anticoagulation for patients with iliofemoral DVT.

Search Strategy

A literature search of English language publications from 1995 to 2015 was used to identity published data on treatment of iliofemoral DVT with clot removal or conventional anticoagulation using the PICO outline (Table 34.1). PubMed, Cochrane Evidence Based Medicine, and Embase databases were queried. Terms used in the search were “iliofemoral/thrombectomy,” “iliofemoral/thrombolysis,” “deep vein thrombosis/thrombolysis/anticoagulation,” and “deep vein thrombosis/thrombectomy/anticoagulation.” Articles were excluded if they did not specifically address iliofemoral DVTs. Five randomized-controlled trials, seven cohort studies, and two meta-analyses were included and compared thrombolysis or thrombectomy treatment with conventional anticoagulation therapy alone. The data was classified using the GRADE system. Additional studies and articles were cited and, although they did not directly compare thrombus removal with conventional anticoagulation, provided historical and background information.

Table 34.1 PICO table for clot removal of iliofemoral DVT

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Patients with iliofemoral deep vein thrombosis	Thrombus removal strategies (pharmacologic or pharmacomechanical catheter directed thrombolysis, percutaneous aspiration thrombectomy, or surgical thrombectomy)	Conventional anticoagulation and compression stockings	Development of post-thrombotic syndrome and functional outcomes

Results

Catheter Directed Thrombolysis

Background

Catheter-directed thrombolysis for iliofemoral DVT, first described in 1991, involves placement of a catheter into the venous thrombus and infusing thrombolytic agents directly into the clot so the drug can be given in high local concentrations and is protected from neutralization by circulating inhibitors [17]. CDT has been well established as an effective means of thrombus removal in acute iliofemoral DVT with multiple cohort and observational studies demonstrating an approximately 90 % success rate for restoring venous patency with a rate of significant bleeding at less than 10 % [18–22]. The largest of these studies, a multicenter prospective registry study which included 221 patients with iliofemoral DVT, found an 83 % rate of successful (>50 %) lysis of the clot with a primary patency rate of 60 % at 1 year [23]. The major complication of CDT is bleeding which was reported to occur in 11 % of patients in this study, 39 % of which represented hematoma at the venous insertion site. This study is somewhat limited by inclusion of femoropopliteal DVTs which may confound results of CDT for iliofemoral DVTs.

The safety and efficacy of CDT for iliofemoral DVT is generalizable to diverse patient populations. Smaller series and case studies have demonstrated efficacy and safety in cancer patients [24], pregnant patients [25], those with congenital venous anomalies [26, 27]. Current guidelines support CDT as a secondary treatment option for acute proximal DVT but limits this recommendation to patients with iliofemoral DVT, symptoms for <14 days, good functional status, life expectancy over 1 year, and low risk of bleeding [11, 28]. Ultimately, the body of literature supports CDT as an effective, safe treatment option for iliofemoral DVT and guidelines have been established to improve treatment quality [29].

Choice of Pharmacologic Agent for Thrombolysis

The choice of pharmacologic agent for thrombolysis in each study varies by availability and institutional preference. Historically, Urokinase (Abbokinase, Abbott

Laboratories, Chicago, IL) was the dominant thrombolytic agent for treatment of venous occlusion. After it was removed from the market in 1999, recombinant plasminogen activators including tissue plasminogen activator (tPA) (Activase, Genentech, San Francisco, CA) and reteplase (rPA) (Retavase, Centocor, Malvern, PA) became the prevailing thrombolytic agents for use in CDT. Fortunately, studies have investigated the difference between the various agents and have found no significant difference in terms of efficacy or safety [21, 22, 30]. Therefore, the thrombolytic agents will be considered equivalent for the purposes of this review.

Pharmacomechanical Thrombolysis

Traditional pharmacologic CDT offers potential benefits to conventional anticoagulation but also involves greater risk of bleeding and incurs costs including longer hospital stays. The use of pharmacomechanical thrombectomy devices are thought to augment venous clot removal and allow for shorter treatment duration. A variety of these devices are available on the market including the Amplatz thrombectomy device (Microvena, White Bear Lake, MN), AngioJet thrombectomy device (Possis Medical, Minneapolis, MN), Trellis infusion system (Covidien, Minneapolis, MN), and EkoSonic endovascular system (EKOS Corporation, Bothell, WA). Each one of these devices aims to mechanically fragment and extract venous clot by using rotational, rheolytic, or ultrasound-assisted mechanisms [31].

Several studies have compared pharmacomechanical thrombectomy devices to standard CDT with infusion catheters and the results suggest that they can decrease length of hospital stay and overall cost while maintaining similar rates of safety and efficacy [32, 33]. Current guidelines advocate the use of pharmacomechanical thrombectomy when expertise is available [28], however no study directly compares the development of PTS or functional outcomes between patients receiving treatment with pharmacologic CDT and those receiving pharmacomechanical CDT. Many of the cohort studies evaluating CDT did not stratify results based on the use of pharmacomechanical thrombolysis so, for the purposes of this review, "CDT" will refer to both pharmacologic and pharmacomechanical catheter directed thrombolysis unless specified.

Functional Outcomes with CDT Versus Conventional Treatment Only

A number of studies directly compare functional outcomes when CDT is added to conventional anticoagulation and compression stocking therapy versus conventional therapy only for iliofemoral DVT. These studies vary widely in terms of the patient populations, thrombolytic agent used, use of pharmacomechanical thrombolysis, and outcomes measured. Nevertheless, a meta-analysis including five studies found that, compared to anticoagulation, CDT was associated with a statistically significant reduction in risk of PTS (RR 0.19; 95 % CI 0.07–0.48) with follow-up periods ranging from 16 to 90 months [34]. A second meta-analysis

including four studies which reported incidence of PTS at 6 to 24 months also found a significant risk reduction in patients receiving thrombolysis (RR 0.64; 95 % CI 0.52–0.79) [35]. These meta-analyses included a number of cohort studies and small randomized control trials which, overall, support CDT in addition to conventional anticoagulation therapy to reduce the incidence of PTS and improve functional outcomes [36–40].

The largest randomized controlled trial evaluating the use of CDT in treatment of iliofemoral DVT to date is the Catheter-directed Venous Thrombolysis (CaVenT) study. This multicenter study evaluated adult patients with first-time iliofemoral DVT presenting within 21 days of symptom onset and randomized 209 patients with 108 receiving only conventional anticoagulation therapy and 101 receiving CDT in addition. The CDT treatment group was given pharmacologic CDT with tPA for up to 4 days followed by the guideline-recommended dose of oral anticoagulation and compression stocking therapy. 90 % of patients completed 24 month follow up. The rate of iliofemoral patency as measured by ultrasonography and air plethysmography was higher in the CDT group at 6 months (65.9 % vs. 47.4 %, $p = 0.012$) and only 5 (4.9 %) clinically relevant bleeding complications were reported [41]. Moreover, the rate of PTS as measured by the Villalta scoring system was 41.1 % in the CDT group compared with 55.6 % in the control group ($p = 0.047$). Further subgroup analysis, however, found that quality of life (QOL) as reported by patients through the generic EQ-5D and the 26-item disease-specific VEINES-QOL/Sym questionnaires did not differ between CDT and control groups at 24 months [42]. The CaVenT study found a somewhat weakly significant difference in PTS between CDT and control groups with follow up analysis of patient-reported QOL showing no different between treatment groups. One potential explanation for the lack of a more robust effect may, in part, be due to only approximately half of the randomized patients having thrombus extending to the iliac level [43].

The ATTRACT trial is an ongoing randomized controlled clinical trial which has enrolled approximately 692 patients and will be comparing the effect of pharmacomechanical CDT in addition to conventional therapy versus conventional therapy alone on risk of PTS and QOL measures at 2 years [44]. This study excludes patients with active cancer diagnoses or pregnancy, but stratifies the patient population by exact venous segment involved and allows treating physicians the discretion to use mechanical thrombectomy devices. The results from this study should provide high-quality evidence about functional outcomes in iliofemoral DVT when CDT is added to conventional treatment.

Percutaneous Aspiration Thrombectomy

Despite the popularity of and support for CDT in treatment of iliofemoral DVT, it is associated with an increase in risk of bleeding. Potential disadvantages of CDT include relatively long durations of treatment, cost of devices, and potential damage to the venous valves [45, 46]. In response, PAT has been proposed as an alternative

treatment strategy to consider as an alternative adjunct therapy to conventional anticoagulation.

A single randomized controlled trial including 42 patients found a significant improvement in a 6-point clinical symptom score used to evaluate patients at 12 month follow up (0.81 for PAT group vs. 2.43 for control group, $p < 0.001$) [47]. This study was limited, however, and did not evaluate development of PTS as follow-up data were available only to 12 months post-treatment.

Surgical Thrombectomy

Surgical thrombectomy was developed before the advent of CDT and, while early studies reported relatively poor results, contemporary technique (including operative fluoroscopy, correction of underlying venous lesions, creation of an adjunctive arteriovenous fistula, and use of anticoagulation to avoid re-thrombosis) has likely improved the safety and efficacy of surgical thrombectomy [14]. Nevertheless, the procedure is more invasive than CDT and requires general anesthesia so guidelines reserve surgical thrombectomy only for patients who may benefit from clot removal but have contraindications to thrombolytic therapy [11, 28].

Data supporting surgical thrombectomy is somewhat limited due to indirect comparison with conventional CDT and discordant time intervals during which the studies were performed. A meta-analysis including 10 studies, one of which was a randomized controlled trial, did find that surgical thrombectomy was associated with a statistically significant reduction in risk of developing PTS (RR 0.67; 95% CI 0.52–0.87) [34]. The randomized controlled trial evaluated 30 patients and found that, at 10-year follow-up, there was a trend towards higher rate of symptom-free survival and decreased rates of leg swelling, varicose veins, venous claudication, and leg ulcers in patients who had undergone surgical thrombectomy versus those who had received only anticoagulation therapy [48].

Recommendations

Patients with iliofemoral DVT benefit from venous clot removal, specifically by a reduction in rates of PTS. Prompt removal of clot resolves venous obstruction and reduces the damage to venous valves from the acute inflammatory reaction. Moderate-grade evidence supports CDT in reducing the risk of PTS and improving function outcomes, findings that have been demonstrated by multiple randomized controlled trials and large cohort studies. Although risk of PTS was decreased by the use of CDT in the CaVenT trial, subgroup analysis did not show any difference in terms of surveyed QOL. The results of the ATTRACT trial will augment the evidence in the current literature and may strengthen the quality of evidence supporting CDT. The addition of CDT to standard anticoagulation is therefore currently

recommended for patients with iliofemoral DVT as long as they have no specific contraindication to thrombolytic therapy.

Moderate-grade evidence supports the use of surgical thrombectomy to improve functional outcomes in iliofemoral DVT. Despite the potential surgical complications and more invasive nature of the procedure, surgical thrombectomy is a viable treatment option and can be considered as long as the benefit of avoiding the morbidity associated with PTS outweighs the risks of surgery. Specifically, surgical thrombectomy should be considered in patients with good baseline functional capacity and life expectancy with contraindications to CDT.

Low-grade evidence supports the use of percutaneous aspiration thrombectomy for clot removal in improving functional outcomes. Only one limited, small study evaluated outcomes in patients receiving PAT in addition to anticoagulation. Until further evidence is available, no specific recommendation can be made regarding PAT for treatment of iliofemoral DVT.

Recommendations

- Catheter directed thrombolysis, whether pharmacologic or pharmacomechanical, is recommended to improve functional outcomes in patients with iliofemoral DVT and without contraindication to thrombolytic therapy (**evidence quality moderate; strong recommendation**).
- For patients with contraindication to thrombolysis, surgical thrombectomy should be offered as a treatment option to patients for whom the benefit in terms of functional outcome outweighs the risk of surgery (**evidence quality moderate; strong recommendation**).

A Personal View of the Data

Iliofemoral DVT is a common problem which commonly results in significant morbidity as PTS manifests long-term. Our experience supports the use of CDT for patients with acute iliofemoral DVT and good baseline functional status and life expectancy. Additionally, we believe that the use of pharmacomechanical CDT can decrease length of hospital stay while offering similar safety and technical efficacy rates to standard pharmacologic CDT. However, we await the results of the ATTRACT trial before making formal recommendations about the use of these devices for effect on functional outcomes. Surgical thrombectomy is a relatively rare procedure and is typically only considered in unusual clinical scenarios. We also believe that the aforementioned clot removal options are used to augment the medical anticoagulation and compression stocking therapies which are still staples in treatment of all patients with iliofemoral DVT. While we encourage clot removal to improve long term functional outcomes, each patient's individual risk and potential benefit must be considered carefully and with astute clinical judgment.

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Chapter 35
In Morbidly Obese Patients Undergoing Major Abdominal Operative Procedures, Does Inferior Vena Cava Filter Placement Prevent Massive PE?

Thuong G. Van Ha

Abstract Morbidly obese patients undergoing major abdominal surgery are at increased risk for development of venous thromboembolism. Prophylactic measures are taken to prevent the two manifestations of venous thromboembolism, deep vein thrombosis and pulmonary embolism in the peri-operative period. Despite use of mechanical compression devices and pharmacologic agents such as low-molecular weight heparin, some patients still develop venous thromboembolism. The use of prophylactic inferior vena cava filters in the morbidly obese patient population is increasing though not without additional risk. It is important to evaluate for the safety and efficacy of these devices in the prevention of massive pulmonary embolism.

Keywords IVC filter • Prophylactic IVC filter • Morbidly obese surgical patients • Venous thromboembolism • Deep venous thrombosis • Pulmonary embolism

Introduction

Venous thromboembolism (VTE) manifests as deep vein thrombosis (DVT) or pulmonary embolism (PE). Inferior vena cava (IVC) filters are routinely placed for prevention of (PE) in patients with DVT or history of PE who cannot receive standard medical therapy. However, concerns about their long-term safety have led to the introduction of retrievable IVC filters. Many retrievable filters have been approved for permanent use with option for retrieval.

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For patients undergoing surgery, the Caprini Model and the Caprini Scores are commonly used for risk assessment for baseline VTE [1]. In this model, patients are stratified into very low risk, low risk, moderate risk, and high risk groups. Very low risk patients have a VTE baseline risk of less than 0.5 % without prophylaxis. For the low risk group, the VTE baseline risk is 1.5 %, and for the moderate risk group, it is about 3 %. For the high risk group, the baseline risk increases to 6 %. This group includes patients who undergo colorectal surgery, cancer surgery, hip or knee arthroplasty, and trauma surgery. Factors that elevate baseline risk in surgical patients include obesity, cancer, advanced age, history of VTE, and medical co-morbidities.

Obese patients undergoing major abdominal surgery are at increased risk for VTE [2, 3]. This includes bariatric surgery patients, who are considered to have moderate to high baseline risk for VTE. In the super-obese patients, with body mass index (BMI) > 50 kg/m^2, who are considered high risk, perioperative management for the prevention of VTE is particularly challenging due to high incidence of major comorbidities associated with this population, including sleep apnea, congestive heart failure, pulmonary hypertension, and venous stasis. In addition, the dose and agent of anticoagulation is not well-defined [4]. The incidence of PE in this population can be as high as 17 % [5]. Mechanical compression and chemical prophylaxes are standard prophylactic therapies, though the agent, dose, and duration of chemical prophylaxis are yet to be elucidated. IVC filter use in this population has been on the rise, though the evidence for its prophylactic use is unclear. In 2003, Sappala et al. analyzed 12 deaths from PE among 5,554 gastric bypass operations for morbid obesity. They assessed risk factors and concluded that prophylactic IVC filters are highly recommended in patients with severe venous stasis, BMI > 60 kg/m^2, history of VTE, and hypercoagulable state [6]. We aim to examine the literature regarding the effectiveness of IVC filter in preventing massive PE in morbidly obese patients undergoing major abdominal surgery.

Search Strategy

A literature search of English language publications was performed in the time period of 2004–2014 using the PICO outline (Table 35.1). Publications were identified on the subject of IVC filter use in obese patients undergoing major open abdominal surgery. When it was evident that the available literature focus for morbidly obese patients and major abdominal surgery was on the bariatric population, the word bariatric was included in the searches. Terms used: “Obese Patients”, “Bariatric

Table 35.1 PICO table for IVC filters in morbidly obese patients undergoing abdominal surgery

P = Patients morbidly obese undergoing abdominal surgery
I = Placement of an IVC filter
C = No IVC filter
O = Pulmonary embolism

P patients, *I* intervention, *C* comparator group, *O* outcomes measured

Surgery", "Abdominal Surgery" AND "IVC filters" OR "Pulmonary Embolism"; "Bariatric IVC filter"; "Morbidly Obese Surgery Filter". Databases used were PubMed and Embase. Cross references were made with bibliography of studies obtained through searches.

Articles were excluded if they addressed surgical patients and IVC filter without mention of obesity. Studies of obese patients without mention of IVC filter were also excluded.

Results

Studies Favoring the Use of IVC Filters

No randomized control trials (RTC) were identified comparing patients with IVC filter and no IVC filter in the population of interest. There were numerous observational studies in the bariatric patient population, both retrospective and prospective [7–22]; (Table 35.2). Most studies are observational and involve small number of patients. These studies include several comparing cohorts with IVC filter to controlled cohorts without. Most studies are either advocating IVC filter use in morbidly obese patients, or neutral about filter use, citing benefit in the prevention of PE, or lack of major complications regarding its use. Gargiulo et al., in a study of 58 patients with IVC filter who underwent gastric bypass surgery, out of a total of 571 morbidly obese patients, showed that 56 patients remained free of VTE, while only one developed a DVT that resolved with treatment [9]. The only mortality was in a patient who required multiple operations from bypass complications and who could not be treated with intravenous heparin, progressed to IVC thrombosis and phlegmasia cerulea dolens requiring bilateral above knee amputations; the patient subsequently died. They concluded that use of IVC filter is benign with maximal benefit in term of PE prevention. Piano et al. reported a prospective observational study of 59 consecutive high risk patients undergoing laparoscopic gastric bypass or duodenal switch [13]. Patients were considered high risk if they met any of these criteria: BMI > 55 kg/m^2, hypercoagulable state, severe immobility, venous stasis, or previous history of VTE. The mean BMI was 61 ± 10 kg/m^2. One patient developed PE with filter in place while not on post-operative anti-coagulation and there was no death. The primary retrieval rate was 90 % and 3 patients underwent another attempt and all had successful retrievals. There were no complications with filter placement or retrieval. The authors concluded that use of filters in high risk bariatric patients is safe and offer potential clinical benefit.

Studies Against the Use of IVC Filters

A few studies question the efficacy and safety of IVC filter in what is considered high risk patient groups. Li et al. used the Bariatric Longitudinal Database (BOLD), comprised of patients undergoing Roux-en-Y gastric bypass and adjustable gastric

Table 35.2 Studies of IVC filter use in morbidly obese patients

Year	Study authors	# of subjects receiving filter	Mean BMI kg/m^2	Breakthrough PE %	DVT %	Conclusion on IVC filter use
2013	Birkemyer et al.	1077	58	0.84	1.2	No benefit with significant risk. Use should be discouraged
2012	Li et al.	322	45.3 ± 7.0	0.31	0.92	Unable to establish outcome benefit
2011	Vaziri et al.	44	58 ± 9.4	0	5.0	No PE but high incidence of DVT. Recommend timely filter retrieval
2010	Gargiulo et al.	58	62 ± 4	0	3.4	Benign with max benefit
2010	Birkmeyer et al.	542		3.45 with history of VTE		No reduction in PE and may cause additional complications. Use should be limited
2009	Varizi et al.	30	40	0	13.3	Recommend use in conjunction with standard VTE prophylaxis
2009	Overby et al.	160	51.4	0	3.13	Trend toward reduced PE rate
2007	Kardys et al.	27	70 ± 3	3.7 %	0	Efficacy of IVUS guided filter placement in preventing PE
2007	Halmi et al.	27	48.7 ± 4.2	0	0	Safe measure for PE prophylaxis
2007	Piano et al.	59	61 ± 10	1	0	Safe with potential clinical benefit
2007	Schuster et al.	24	57 ± 7.5	0 but 1 PE after retrieval	21	Recommend in select high risk patients
2007	Obeid et al.	248	60.0	4.4	1.2	Reduced PE in high risk group to comparable low risk group
2006	Trigilio-Black et al	41	64.2 ± 12	0	0	Associated with no PE
2006	Gargiulo et al.	58	51	0		Significant reduction in perioperative PE
2006	Frezza and Wachtel	15	46.93	0	0	High risk patient should receive IV heparin or IVC filter
2005	Keeling et al.	14	56.5 ± 4.45	0	0	Recommend in high risk patients

IVUS intravascular ultrasound, *BMI* body mass index, *PE* pulmonary embolism, *DVT* deep venous thrombosis, *IV* intravenous

banding surgeries [21]. They identified 332 patients (out of 97,218) who had concurrent prophylactic IVC filter placement. For this small group of patients, they had more co-morbidity, including sleep apnea, history of VTE, pulmonary hypertension, and obesity hypoventilation syndrome. This group also had longer length of operative duration and hospital stay, and was associated with higher incidence of DVT and higher mortality from PE and indeterminate causes. The authors summarized their findings as concurrent use of IVC filters was associated with increased health resource utilization and a higher mortality in patients undergoing bariatric operations, and concluded that they were unable to establish an outcome benefit for concurrent IVC filter use.

Birkmeyer et al. looked at a cohort of 1,077 patients with IVC filters and compared them to 1,077 matched control patients out of a database of 35,477 bariatric surgery patients [22]. From this database, they found 95 % of patients in the low-risk group, 4 % in the medium-risk group and 1 % in the high-risk group. In the matched study cohorts the breakdown was 69, 22, and 9 % for high-risk, medium-risk, and low-risk group respectively. They found that compared to their matched cohort using propensity scores, IVC filter patients had higher rates of VTE, higher but not statistically significant rate of PE, and higher rates of surgery related complications. The authors acknowledge limitations of their study including outcomes of interest being a rare event affecting the statistical power, a lack of data on hypercoagulable states in the registry, multitude of IVC filter available with difference in efficacy and safety profile, and the 30-day after surgery endpoint. The authors concluded that, based on their study, IVC filters do not reduce the risk of PE in high-risk bariatric patients and use of IVC filters should be discouraged.

Review Studies

Five review studies were identified (Table 35.3). Rajasekhar and Crowther reviewed the literature and included 11 prospective or retrospective cohort observational studies [23]. They noted the extreme heterogeneity in the studies, both in techniques

Table 35.3 Review articles on IVC filter use in high risk bariatric patients

Year	Authors	Studies reviewed	Comparative studies	Conclusion on IVC filters
2010	Rajasekhar and Crowther	11	4	Cannot recommend routine use
2012	Shamian and Chamberlain	12	4	Best evidence supports use in high risk patients
2013	Brotman et al.	13	5	No evidence to support use
2014	Rowland et al.	18	5	Should only be considered in high risk patients

Compartive studies refer to studies where controlled cohorts are compared to patients with IVC filter cohorts

and results. Risk factors were not uniformly defined (such as cutoff BMIs) or listed. Despite some studies showing benefit of IVC filters in preventing PE, the authors caution against routine IVC filter use due to complications, device cost, and interestingly, possible delay in pharmacologic prophylaxis in their presence. In another review, Shamian and Chamberlain reviewed 12 studies with overlapping studies from the previously mentioned review [24]. They assert that though there is no consensus in the literature, these studies showed filters are associated with low complication rate and may reduce post-operative PE in high risk patients and that best evidence supports consideration of IVC filter use in patients with BMI > 50 kg/m^2, a history of VTE, prolonged immobility, a hypercoagulable state, pulmonary insufficiency and hypertension, and chronic venous stasis. In addition they advocate removing filters within 3 months if possible due to higher success rate. Rowland et al. pooled 497 patients from 12 case series and reported a DVT rate of 0–20.8 % and PE rate 0–6.4 % [25]. Though they concluded that the data suggest that patients who have IVC placement might be at higher risk of developing PE and DVT, and a small cohort of patients with multiple risk factors for VTE benefited from reduced PE related mortality after IVC filter insertion. Brotman et al.'s review of all types of prophylaxis, included five studies that had comparison between IVC filter group and non-IVC filter group, did not find sufficient evidence to support use of IVC filter and found low level of evidence that IVC filter use was associated with increase rate of DVT and higher rate of mortality [26]. The fifth review, by Kaw et al. included six studies; all of them compared an IVC filter group to a non-IVC filter group. They concluded that IVC filter use was associated with increase in DVT but not PE and overall mortality was not significantly increased [27]. Of note, these reviews had overlap of available studies, and yet the recommendations were as heterogeneous as the available data.

Recommendations

There is a lack of consensus in the use of IVC filters prophylactically. Different guidelines have different recommendations. From the various studies and reviews cited above, the data is not sufficient to recommend for or against the use of IVC filter in morbidly obese patients undergoing major abdominal surgery.

The ASMBS Statement

The American Society for Metabolic and Bariatric Surgery (ASMBS) [4], in their position statement, considers patients undergoing bariatric surgery to be at moderate to high risk for having thrombotic complications and VTE prophylaxis should be used, including early ambulation, and a combination of mechanical and chemoprophylaxis. The recommendation regarding IVC filters is that their use should be

in selected high risk patient in whom the risks of VTE are deemed to be greater than the risks of filter-related complications. In addition, IVC filters should be used in combination with mechanical and chemical prophylaxis.

Other Recommendations

The ACCP guidelines 9th edition do not recommend use of prophylactic filters defined as placement of filters in patients without current venous thromboembolic disease [28]. However, other guidelines, such as those from the Society of Interventional Radiology [29] and the Eastern Association for the Surgery of Trauma [30], indicate a role for this particular use. The SIR guidelines, in particular include in the indication for prophylactic use in surgical procedure in patients at high risk of VTE. Given the differences in guidelines recommendations, it is not surprising that compliance with guidelines has been suboptimal [31].

A Personal View of the Data

For high risk morbidly obese patients undergoing major abdominal surgery, there appears to be mixed results with the use of prophylactic IVC filter with more recent observational studies recommending against the use of filter for this indication. The data is further complicated by many different types of filters available, route of insertion, and though not mentioned in the study, level of expertise in placing and retrieving filters. However, each patient must be assessed individually. For patients with multiple risk factors, especially if they have a hypercoagulable disorder and if they fall into super-obese group, if the risk of IVC filter insertion and indwelling is lower than that of PE, one might want to consider using filter prophylactically. Overall morbidity from IVC filter placement is low. To minimize filter complications, retrieval should be performed as soon as possible. There is an evolution in the types of retrievable IVC filter and practicing physicians must identify those with the best safety profile. There might be an advantage to placing filter in separate setting under conscious sedation, if possible, to minimize overall OR and anesthesia time.

From the available data, patients who receive IVC filter prior to surgery tend to be sicker with higher operative risk as well as higher VTE risk, as demonstrated by the study by Birkmeyer et al. where it was shown that patients who received IVC filters required longer duration of operation, more repeat operations, and more complications [22]. This is unlikely to be attributable to the indwelling IVC filters alone and more likely to be a reflection of the patients' high risk to undergo surgery. Randomized controlled trials are needed to address the question of prophylactic IVC filter use in morbidly obese patient undergoing major abdominal surgery.

Recommendations
For morbidly obese patients undergoing major abdominal surgery should have VTE prophylaxis (**evidence quality low; strong recommendation**)

- Standard VTE prophylaxis should be administered if no contraindications
  - Mechanical compression
  - Pharmacologic
- IVC filter placement should be assessed on an individual basis (**evidence quality low; weak recommendation**)
  - Use is probably justified in high risks patients with multiple predisposing risk factors for VTE including hypercoagulable state, superobese status, history of VTE, and medical comorbidities
  - IVC filter should be removed as soon as possible to negate the effect of indwelling filter complications
  - Types of filter should be a consideration in terms of safety and efficacy

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Chapter 36
In Patients with Chronic Venous Stenosis, Does Placement of a Stent Improve Patency Compared to Recurrent Angioplasty?

Jeffrey Y. Wang and Arthur C. Lee

Abstract The endovascular treatment of chronic venous stenosis or occlusion in both the upper and lower extremities are increasing in frequency. Chronic venous stenoses in the upper extremity are primarily related to dialysis access, indwelling catheters, and pacemakers. In the lower extremity, they are primarily related to chronic deep vein thrombosis, surgical complications, and iliac vein compression syndrome. Many resources are expended to maintain appropriate dialysis access in the end-stage renal failure population. Treating patients with post thrombotic syndrome secondary to venous stenoses in the femoroiliocaval segments can alleviate debilitating symptoms, improve quality of life, and help heal ulcerations. In treating the upper central veins in a patient with end-stage renal disease on dialysis it seems that stenting does not convey an advantage in patency or longevity of the dialysis access over multiple angioplasties. In treating the lower central veins angioplasty followed by primary stenting seems to be the overwhelming modality of choice, combining the benefits of a low complication rate and high long-term patency rates.

Keywords Chronic venous stenosis • Angioplasty • Stent • Dialysis

Introduction

Percutaneous endovascular procedures have emerged over the last decade as the preferred method of treatment for venous diseases. The low rates of morbidity and mortality associated with endovenous procedures are likely to have influenced their popularity. In the upper extremities most chronic venous stenoses or occlusions are related to

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Table 36.1 PICO table for treatment of chronic venous stenosis

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Patients with upper and lower extremity chronic venous stenosis	Endovascular treatment with angioplasty alone	Angioplasty with placement of stent	Patency

dialysis access, long-term central venous access, or pacemaker/defibrillator placement [1–3]. In the lower extremities chronic venous occlusions are more commonly related to iliac vein compression syndrome, history of deep vein thrombosis, or injury to the vein [4, 5]. There are two primary areas of concern for the vascular specialist. The first is the treatment of chronic venous stenosis in the dialysis access patient. The other is the treatment of chronic venous stenosis in the femoroiliocaval segment.

The dialysis population survival is dependent on their ability to obtain dialysis. Their ability to obtain dialysis is dependent on the patency of the dialysis access which in turn is greatly affected by the patency and the obstructive status of the central veins [1, 6]. The patency of the central veins affects both patients with fistulas and grafts as well as patients who are reliant on central catheters. In this subset of patients central venous stenosis and occlusions are common conditions which reduce long-term patency of upper extremity arteriovenous access as they are a common cause for acute thrombosis or obstruction [6, 7]. While it is reasonable to employ angioplasty and or stenting to relieve the stenosis to maintain patency. It is still undecided whether multiple balloon angioplasties or primary stenting is more appropriate in the treatment of central venous stenosis.

Post thrombotic syndrome affects a large number of patients in the United States where there are 6–7 million patients who have venous stasis changes and 500,000 patients with leg ulcers yearly. 47 % of patients with femoroiliocaval DVT and thrombosis will go on to develop post thrombotic syndrome and 33 % with post thrombotic syndrome will go on to develop ulceration [8, 9]. May Thurner's also affects a large number of patients, although the exact number is unknown. Reports range from 18 to 59 % of patients who have left lower extremity deep vein thrombosis can be attributed to May Thurner's [10]. Proper evaluation and endovascular treatment of chronic venous stenosis in the femoroiliocaval segment can lead to the reduction in post thrombotic syndrome symptoms [11]. Although in the literature reviewed there was not a direct head-to-head comparison of angioplasty versus stenting when treating femoroiliocaval obstructions. There was a strong tendency towards stenting in the femoroiliocaval venous segment when there was a symptomatic stenosis or occlusion.

Search Strategy

A literature search of English language publications was used to identity published data on endovascular treatment of chronic venous stenosis using the PICO outline (Table 36.1). The Google Scholar and MEDLINE databases were searched as well as the Cochrane Central Register of Controlled Trials using the following search

terms: “Chronic venous stenosis” AND/OR “Angioplasty”, “Stent”, “Pacemaker”, “May Thurner”, “Iliac compression syndrome”, “dialysis”, “indwelling catheter”, “balloon dilation”, and “recurrent angioplasty versus stent placement”.

Articles were excluded if they were related to: Multiple Sclerosis; chronic cerebrospinal venous insufficiency; thrombecomy; Malignancy; Kidney, liver, lung or heart transplant; Pulmonary vein stenosis; Saphenous vein bypass in either periphery or cardiac; foreign language articles, or articles were case reports involving less than ten patients. No restrictions were made on date or type of publication.

Results

There were 46 articles included in the analysis. The articles were required to include data on either angioplasty or stenting of chronic venous stenosis to be included in the analysis. There were two small prospective randomized controlled study comparing PTA to stent in dialysis patients (Table 36.2) and none in the femoroiliocaval group (Table 36.3). The remainder were retrospective studies In the femoroiliocaval vein group there were no articles with greater than ten patients that were treated with balloon angioplasty as a single modality.

Venous Stenosis in Dialysis Patients

Endovascular percutaneous transluminal angioplasty (PTA) is an accepted alternative to surgical revision for hemodialysis related stenoses or occlusions [31]. However, PTA alone is complicated by restenosis or occlusion. For this reason, it has been proposed that PTA with concomitant stent placement will increase patency. In the treatment of venous stenosis in dialysis patients, Quinn reported one small prospective randomized trial which included 87 consecutive patients who had venous stenosis and were undergoing hemodialysis; 47 patients were randomized to percutaneous angioplasty (PTA) alone and 40 were randomized to PTA and stent placement. Ninety-nine percent of the patients (n = 86) had polytetrafluoroethylene (PTFE) access grafts while one percent (n = 1) had an arteriovenous fistula. The locations of the stenosis (n = 85) and occlusions were both peripheral (n = 59), central (n = 20), or both (n = 8). Peripheral sites included axillary, basilic, cephalic, and saphenous veins and venous anastomoses. Central locations included the subclavian, brachiocephalic, and iliac veins. Anticoagulation was not given after the procedure. Outcomes were primary and secondary patency at 60, 180 and 360 days post intervention and determined by venography. A stenosis or restenosis of 60 % or greater was classified as hemodynamically significant. For peripheral sites, the primary patency rates were 55 %, 31 %, and 10 %, respectively, and for stents were 36 %, 27 %, and 11 %, respectively (P = .6528). The secondary patency rates for PTA were 94 %, 80 %, and 71 %, respectively, and for PTA and stents were 73 %, 64 %, and 64 %, respectively (P = .1677). For central sites, the primary patency rates for PTA were 81 %, 23 %, and 12 %, respectively, and for stents were 67 %, 11 %, and 11 %, respectively (P = .4595).

Table 36.2 Studies performed for Venous stenosis in dialysis patients

Author	Year	Number of patients	Location	Angioplsty or Stent better	Quality of evidence
Quinn -RCT	1995	87-Dialysis patients	Central and peripheral	No difference	Moderate
Hoffer-RCT	1997	34-Dialysis patients	Peripheral venous	No difference	Moderate
Bakken		24 Dialysis patients	Central	No difference	Very low
Lumsden- retrospective review of central stent	1992	25 –central venous stenosis treated with stent	Central	N/A	Very low
Beathard	1992	285 patients-vascular access stenosis treated with angioplasty	Central and peripheral	N/A	Very low
Vorwek	1995	65 Dialysis patients-vascular access stenosis treated with angioplasty and stent	Central and peripheral	N/A	Very low
Mickley	1997	14 Dialysis patients-vascular access stenosis treated with angioplasty and stent	Central	N/A	Very low
Turmel-Rodrigues	1993	59 Dialysis patients- vascular access stenosis treated with angioplasty	Central and peripheral	N/A	Very low
Aytekin	2004	14 Dialysis patients- vascular access stenosis treated with angioplasty and stent	Central	N/A	Very low
Gray	1995	52 Dialysis patients- vascular access stenosis treated with angioplasty and stent	Central and peripheral	N/A	Very low
Jones	2011	52 Dialysis patients- vascular access stenosis treated with angioplasty and covered stent	Central	N/A	Very low
Vesely	1997	20 Dialysis patients- vascular access stenosis treated with angioplasty and covered stent	Central	N/A	Very low

RCT randomized control trial, *RRT* retrospective review trial

The secondary patency rates for PTA were 100 % at each interval, and for stents were 100 %, 89 %, and 78 %, respectively (P = .5408) [32]. They concluded at one year there was no difference and primary secondary patency between dialysis patients who have been treated with PTA or PTA and stent placement.

In a similar prospective randomized study by Hoffer and reported in 1997, 37 grafts in 34 patients were treated with either PTA alone (n = 20) or PTA with stent (n = 17). Inclusion criteria for this study were: (1) that the access was a dysfunctional upper extremity PTFE loop graft, (2) the stenosis was in a vein peripheral to the subclavian, (3) the lesion had recurred within 6 months of a previous angioplasty. Patients differed somewhat in that the stent group had more prior interventions. The 30, 60, 180, and 360 day primary and secondary patency for the different groups did not differ significantly, but the adjunctive stent placement increased the cost of the procedure by 90 % [33].

Bakken reported in 2007 in a retrospective fashion the only other head to head comparison of angioplasty versus stenting to treat upper central venous stenosis in the dialysis patient. Primary stenting (PTS) was used to treat 26 patients (35 % male; average age, 57 ± 15 years) with 26 central venous stenoses, and primary angioplasty (PTA) was used to treat 47 patients (45 % male; average age, 57 ± 18 years) with 49 central venous stenoses. Primary and primary assisted patency were one of the endpoints. Primary patency was equivalent between groups, with 30-day rates of 76 % for both groups and 12-month rates of 29 % for PTA and 21 % for PTS (P = .48). Assisted primary patency was also equivalent (P = .08), with a 30-day patency rate of 81 % and 12-month rate of 73 % for the PTA group, vs PTS assisted patency rates of 84 % at 30 days, and 46 % at 12 months. Ipsilateral hemodialysis access survival was equivalent between groups. The PTS group underwent 71 percutaneous interventions per stenosis (average, 2.7 ± 2.4 interventions), and the PTA group underwent 98 interventions per stenosis (average, 2.0 ± 1.6 interventions). The PTS group hemodialysis access site was an average of 1.0 ± 1.3 years old at the time of the initial intervention, and the hemodialysis access in the PTA group was an average of 1.1 ± 1.2 years old [1]. The authors concluded that endovascular therapy with PTA or PTS for central venous stenosis is safe; however, neither offers durable outcomes and PTS does not improve on the patency rates versus angioplasty and does not add longevity to the hemodialysis access site.

Multiple other retrospective and a few prospective studies have reported similar results to the prior studies [34–40]. Although some studies report higher patency rates early on for stenting, patency past one year is similar to the previous reports [41, 42]. The other studies however do not directly compare balloon angioplasty to primary stenting. It is clear that there is a lack of substantial randomized controlled trials in this area. Furthermore, the studies presented have inherent biases including selection bias and attrition bias which weakens the evidence.

Symptomatic Femoroiliocaval Venous Stenosis

Lower extremity venous outflow obstruction plays an important role in the pathophysiology of chronic venous insufficiency [17, 43]. Etiologies include post-thrombotic occlusion or stenosis [44], and the presence of external iliac vein compression and

Table 36.3 Studies performed for venous stenosis or occlusion in the femoroiliocaval veins

Author	Year	Number of patients	Primary patency	Primary assisted	Secondary patency	Quality of evidence
Neglén [12]	2000	137	52 %		90 %	Very low
O'Sullivan [13]	2000	39	79 % (1 year)			Very low
Abu Rahma [14]	2001	18	83 %, 69 %, 69 % (1, 3, and 5 years)			Very low
Hurst [15]	2001	18	89, 79 % (6, 12 months)			Very low
Lamont [16]	2002	15	93, 87 % (6, 16 months)	100 % (6,16 months)		Very low
Raju [11]	2002	38	49 % (2 years)	62 % (2 years)	76 % (2 years)	
Neglen [17]	2003	429	92.8 % (13 months)	95.1 % (13 months)		Very low
Neglen [18]	2004	316	75 % (3 years)	92 % (3 years)	93 % (3 years)	Very low
Neglen [5]	2007	870	67 % 72 (months)	89 % (72 months)	93 % (72 months)	Low
Neglen [19]	2008	177 Limbs with stents crossing inguinal ligament	52 % (42 months)	80 % (42 months)	86 % (42 months)	Very Low
Hartung [20]	2009	89	83 % (38 months)	89 % (38 months)	93 % (38 months)	Very low
Kölbel [21]	2009	59	67 %	75 %	79 % (25 months)	Very low
Raju [22]	2009	131	32 %	58 %	66 %	Very low
Rosales [23]	2010	34	67 % (2 years)	76 % (2 years)	90 % (2 years)	Very low
Ye [24]	2012	205	98.7 (4 years)	100 % (4 years)	N/A	Very low
Raju [25]	2014	217 limbs	69 % (24 months)	93 % (24 months)	N/A	Very low
Sang [26]	2014	67	70.7 % (36 months)	N/A	82.8 % (36 months)	Very low
Blanch Alerany [27]	2014	36	74 % (33 months)	87 % (33 months)	89 % (33 months)	Very low
Catarinella [28]	2015	153	65 % (24 months)	78 % (24 months)	89 % (24 months)	Very low
Liu [29]	2014	48	93 % (12 months)	N/A	N/A	Very low
Ye [30]	2014	110	70 %	90 %	94 %	Very low

N/A not applicable

intraluminal webs [45]. Despite clinical success of the fem-femoral bypass (Palma procedure) [46], percutaneous intervention has replaced bypass surgery as the primary treatment in part to the studies listed below. In patients who have symptomatic chronic femoroiliocaval stenosis the largest experience have been reported by Raju and Neglen. In 2000 they reported their experience of 139 consecutive lower extremities with chronic iliac venous obstruction (61 limbs with primary disease and 78 with post-thrombotic disease) that were treated by balloon dilation and stenting. Overall, the results were very promising with no mortality and primary, primary-assisted and secondary cumulative patency rates of the stented area at 2 years were 52%, 88% and 90%, respectively, in the post-thrombotic group 60%, 100% and 100% in the May-Thurner syndrome group. Clinical improvement in pain and swelling and ulceration were demonstrated in both groups [12]. They concluded that chronic iliac vein obstruction that appears to be a symptomatic lesion can be treated safely and effectively by endovascular surgery regardless of etiology, and that stenting after balloon dilation is advised in all venoplasties. They went on to report several increasingly larger studies including a report on 304 limbs in 2001 with a demonstration of actuarial primary and secondary stent patency rates at 24 months of 71 and 90% [11]; of and an even larger series of 938 limbs in 2006 [6]. They also demonstrated excellent secondary patency rates in stent placed across the inguinal crease [19]. In multiple small series patency rates ranged from 32 to 98.7% for primary patency and 66 to 100% for secondary patency for femoroiliocaval stents [5, 11–30] (Table 36.3).

Recommendations

Upper extremity venous stenosis in dialysis patients

1. For the treatment of venous stenosis in dialysis patients, endovenous treatment may be performed with patency outcomes of percutaneous angioplasty equivalent to angioplasty and stent for both peripheral and central stenoses. (**Quality of evidence: Moderate; Recommendation: Moderate**)
2. If there is a residual obstructive lesion after angioplasty stenting should be performed (**Quality of evidence: Low; Recommendation: Moderate**)
3. If there is no residual obstruction after angioplasty, primary stenting does not provide benefit in terms of long-term patency nor does it increase the longevity of the hemodialysis access (**Quality of evidence: Low; Recommendation: Moderate**)

Femoroiliocaval Venous stenosis/occlusion

1. When the diagnosis of iliac vein compression syndrome has been made primary stenting is recommended (**Quality of evidence: Very Low; Recommendation: Strong**)
2. Stenting below the inguinal ligament should be done with caution (**Quality of evidence: Very Low; Recommendation: Moderate**)
3. When the diagnosis of ileo-caval occlusion or stenosis has been made primary stenting is recommended (**Quality of evidence: Very Low; Recommendation: Strong**)

Personal View of the Data

Overall, the data for treatment venous stenoses/occlusion in both the upper and lower extremity is weak data with studies that are biased by: selection, detection, and reporting. There is a significant lack of randomized controlled trials in the treatment of these lesions. In the upper extremity, there were some very small randomized controlled trials early on; however, in the femoroileocaval venous obstruction/occlusion group there was no significant data on primary balloon angioplasty. My suspicion is that at the time of procedure there were a large number of lesions that had significant recoil after angioplasty or had significant flow limitations after angioplasty which then subsequently required stenting. Also in the case of iliac vein compression syndrome the pathophysiology dictates that to alleviate the compression, stenting will be required. Stenting below the inguinal ligament subjects the stents to the same forces that any stent placed across the hip joint would encounter. That being said there was a significant patency difference in favor of the ileo-caval group for patency of the primarily placed stents over that of the dialysis access group. In the dialysis group there was no benefit in terms of patency or longevity of the dialysis access when comparing multiple balloon angioplasties versus primary stenting. In the studies that were reviewed, stenting of the central vein was performed if balloon angioplasty yielded a suboptimal result. Stenting across the clavicular first rib junction subjected the stent to the force of the clavicle compressing the subclavian vein on the first rib. In a comparison of dialysis access catheters placed in the internal jugular vein as compared to the subclavian vein it was noted that there was a much higher incidence of subclavian stenosis as compared to the internal jugular vein stenosis [15, 17, 47].

In conclusion for patients with femoroileocaval venous obstruction, primary stenting after angioplasty seems to be the accepted strategy for treatment of these lesions. Recommendations have also been made for the liberal use of IVUS when treating these types of lesions. Stenting into the inferior vena cava does not seem to have significant consequences in terms of patency. However stenting below the inguinal ligament does seem to impact patency rates of stents. For patients with upper central vein stenosis secondary to dialysis access, there seems to be little to no difference between recurrent angioplasty versus primary stenting. However most studies did include the use of bailout stenting.

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Chapter 37
In Patients with Chronic Venous Ulcer Is the Unna Boot Still the Best Approach to Wound Care

Ann M. Zmuda

Abstract Of the four most common causes of lower extremity ulcerations (including arterial insufficiency, neuropathy, pressure and ischemia, and venous insufficiency), venous insufficiency is the most frequent, accounting for nearly 80 % of all lower leg ulcers. That number correlates to approximately one million people of the seven million that have venous insufficiency in the United States [1]. These lesions appear to be more common in women than men and are most frequently seen in patients between the ages of 60–80. However, according to Nelzen et al. [2] in their survey of the epidemiology of venous ulcerations, 22 % of individuals have their first ulcer before the age of 40. The Unna's Boot Compression System, first developed by the German dermatologist Paul Gerson Unna, has been considered the standard of treatment for venous leg ulcerations since its inception in 1986 [3]. While compression therapy is still the key to healing venous leg ulcerations, there is evidence to suggest that multi-layered elastic bandages versus the rigid, inelastic Unna's boot bandages, have become the current mainstay of therapy.

Keywords Unna's boot • Venous ulcerations • Venous insufficiency • Compression therapy • Multilayered elastic bandages • Rigid inelastic bandages

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Introduction

Of the four most common causes of lower extremity ulcerations (including arterial insufficiency, neuropathy, pressure and ischemia, and venous insufficiency), venous insufficiency is the most frequent, accounting for nearly 80 % of all lower leg ulcers. That number correlates to approximately one million people of the seven million that have venous insufficiency in the United States [1]. These lesions appear to be more common in women than men and are most frequently seen in patients between the ages of 60–80. However, according to Nelzen et al. [2] in their survey of the epidemiology of venous ulcerations, 22 % of individuals have their first ulcer before the age of 40. In a study performed by Franks et al. [4], it was found that venous ulcer patients experienced increases in stress, pain from the lesions, and difficulty in coping in day to day life all leading to a negative impact on the quality of life of these patients. There are increased medical costs as well as days of work lost.

The objectives of the management of chronic venous ulcerations include controlling edema, healing the ulcer, and preventing recurrence. Studies have shown that compression therapy has increased ulcer healing versus no compression [5]. Compression therapy counteracts venous hypertension by facilitating venous return toward the heart, improving venous pump function and lymphatic drainage. It also reduces edema [6]. Venous ulcerations, unlike their counterparts, are found in the lower extremities, usually located at or above the level of the medial ankle joint. The area that extends medially between the mid-calf and the medial malleolus, frequently referred to as the "gaiter area", is also a commonly affected region. They develop due to venous hypertension, although the exact link between venous hypertension and venous ulceration is unknown. The ulcerations are typically irregular in shape, shallow in depth, and produce large amounts of serous drainage. The base of these ulcers may start out initially as fibrinous with a yellow gel-like slough, but they eventually evolve to a granular bed with debridement and treatment (Fig. 37.1). Very rarely are they necrotic unless there is an underlying arterial insufficiency, infection, or trauma. The surrounding skin is hyper-pigmented due to hemosiderin deposits in the tissue and the lower extremity is typically edematous with varicosities present.

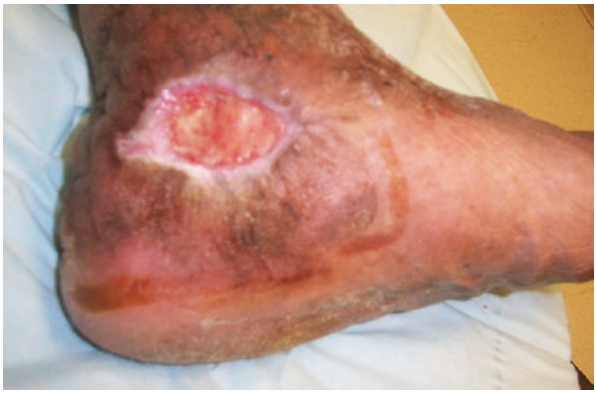

Fig. 37.1 Venous ulceration. This is a typical chronic venous ulceration with shallow, irregular edges, granulation tissue and fibrin base, serous exudate, and hyperpigmentation

Table 37.1 PICO table for Chronic Venous Ulcer

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Patients with lower extremity chronic venous ulceration	Treatment of the ulceration with the Unna Boot (Rigid in-elastic compression)	Multi-layered elastic compression or no compression	Time to healing of the chronic venous ulceration

Eczematous changes of the skin, referred to as venous stasis dermatitis, may also be seen as erythematous, scaling, and pruritic. Atrophie blanche – smooth, ivory-white atrophic plaques of sclerosis speckled with telangiectasia-has been described in up to one third of patients with chronic venous insufficiency [7]. Lipodermatosclerosis may also be seen, especially in long-standing venous disease; this process occurs due to the chronic fibrosing of the dermis and subcutaneous tissue seen in venous insufficiency resulting in the skin becoming very firm and indurated. Eventually the leg will take on the appearance of an inverted bottle – proximal leg swells, distal leg constricts secondary to the fibrosis and loss of subcutaneous fat.

Search Strategy

A literature search of English language publications from 1988 to 2013 was utilized to identify published data on various forms of compression therapy for the treatment of chronic venous ulcerations using the PICO outline (Table 37.1). Databases searched included PubMed, Cochrane Evidence Based Medicine, and Medline. Terms used in the search included: "venous leg ulcerations" AND "compression therapy" OR "Unna boot", OR, "elastic compression bandages", OR "inelastic compression bandages", AND/OR "chronic venous ulcer therapy". Data were classified using the GRADE system.

Results

Compression Therapy for Chronic Venous Ulceration Healing

The cornerstone of venous ulcer treatment is graduated compression therapy, assuming there is no arterial insufficiency or congestive heart failure. It is thought to assist ulcer healing by reducing distension in the leg veins and accelerating venous blood flow [8]. Compression therapy reverses venous hypertension by improving the venous pump and lymphatic drainage. It reduces edema and prevents the leaking of fluids and molecules from the capillaries, improving cutaneous blood flow [9]. There are two types of compression bandages: inelastic and elastic bandages. The most commonly known inelastic or rigid bandage is the Unna's Boot. It was first developed by the German dermatologist Paul Gerson Unna, and has been considered the

standard of treatment for venous leg ulcerations since its inception in 1986 [3]. The Unna boot is a moist zinc oxide and calamine lotion-impregnated paste bandage that works by creating high pressure with muscle contracture, however, it provides very little pressure at rest. Unna's boots require the patient be ambulatory for the calf muscle to press against the bandage in order to achieve compression [10]. It also has the disadvantage in that the boot does not accommodate for changes in the volume of the leg as edema decreases and it has limited absorptive capacity so needs frequent reapplication. Elastic compression wraps provide constant pressures. These bandages accommodate volume changes, conform to the leg better, and provide both resting and working pressure. The main disadvantage to these systems is their difficulty in application. Elastic bandages can either be a single- or a multilayer system. Multiple studies have found that multilayer elastic compression bandages seem to be superior to single-layer, inelastic compression bandages [8, 11, 12].

Fletcher et al. reviewed 24 randomised controlled trials to estimate the clinical effectiveness of compression systems for treating venous leg ulcers [11]. Six of the trials they reviewed looked at compression versus no compression; three of these compared Unna's boot dressings to wound dressings alone and three compared multilayered compression to no compression. What they found was a higher proportion of healed venous ulcerations when compression was used. Then they looked at six trials where elastic multilayer high compression bandages were used versus inelastic compression. In three of those studies, three-layer elastic high compression bandages versus low compression were compared. Here they found an overall significant increase in the odds of healing at 3 months with the high compression bandages. In the other three small studies they looked at, they found no difference between a four-layer high compression bandage versus an Unna's boot with a short stretch bandage however they did find higher healing rates with four-layer and short stretch bandages versus an Unna's boot plus outer support. Finally, they looked at multilayer high compression systems versus single layer systems. Pooling the four trials the review show that multilayer high compression bandages were associated with a higher rate of complete venous ulcer healing when compared to single layer bandages.

The most comprehensive systematic review and meta-analysis of randomised controlled trials evaluating the effects on venous ulcer healing with compression bandages and stockings came from O'Meara et al. [12]. The study included 48 randomised controlled trials with a total of 4,321 participants. O'Meara and her group found, like Fletcher, that compression increases ulcer healing rates compared with no compression. They also found in their analysis that multilayer systems containing an elastic bandage appeared to be more effective than their rigid inelastic counterparts. In further review they also saw that single-component compression bandage systems are less effective than multi-component compression and in the pooling of two studies significantly more participants and ulcers were completely healed by 3–4 months when the compression system incorporated an elastic rather than inelastic bandage.

In another study by O'Meara, the four-layered bandage was compared with the short stretch bandage for venous leg ulcers. In this review, patient level data was reviewed for 5 trials consisting of 797 patients [8]. The four-layered bandage was

associated with a significantly shorter time to healing (95 % confidence interval) than the short stretch bandage, increasing the chance of healing by around 30 %.

Type of Wound Dressing

Wound dressings are also often used in the treatment of venous leg ulcerations, underneath the compression wraps. These are used to facilitate quicker wound healing as well as prevent adherence of the bandage to the ulceration [13]. Numerous wound dressings are available including calcium alginate, foams, hydrocolloids, and hydrogels. A systematic review and meta-analysis was done looking at the effectiveness of dressings applied to venous leg ulcers [14]. The authors looked at 42 randomised clinical trials comparing hydrocolloid, low adherent, foam, alginate, and hydrogel dressings. They concluded that there was no significant difference in clinical effectiveness to justify the use of one dressing over another. Therefore the choice of dressings to be used underneath compression bandages should be chosen based on cost as well as patient and physician preference and ease of application [14].

Negative Pressure Wound Therapy

Negative pressure wound therapy (NPWT) is a device based approach that has been promoted for the use in complex wounds [15]. There is very little data supporting the use of NPWT for the treatment of chronic venous ulceration. In a prospective trial by Vuerstaek et al. [16], of 60 patients with chronic leg ulcers (chronic venous, combined arterial and venous, or microangiopathic), patients were included if they had undergone at least 6 months of ambulatory conservative treatment. Those with venous or combined arterial/venous leg ulceration were treated with multi-layer, short, stretch bandages. The study compared NPWT with standard care in the treatment of these challenging ulcers. Wounds randomized to NPWT were treated until 100 % granulation had occurred. All patients received a punch skin-graft transplant. The primary outcome was time to wound healing. The median time in the NPWT cohort was 28 days (95 % CI 25.5–32.5) compared to 45 days (95 % CI 36.2–53.8). Overall, the results are limited by the study design (venous ulceration was sub-group analysis), total number of patients and inclusion of multiple etiologies for ulceration.

Personal View of the Data

There is strong evidence to support the use of compression for the treatment of chronic venous ulceration and has been supported over no compression therapy in the Society for Vascular Surgery and American Venous Forum Clinical Practice

guidelines [17]. For this reason, our mainstay therapy for patients with complex lower extremity venous ulcerations is the four layered bandage system. This is combined with topical agents that maintain the moist environment, but wick away wound exudate. Follow up for the patient is frequent and combined with debridement as necessary. We have found that the four layered compression bandage system is better than the Unna Boot at healing these challenging wounds.

Recommendations

- Compression therapy is the key to healing venous ulcerations. (**evidence high quality; strong recommendation**)
- The rigid, inelastic Unna's Boot is not the best approach to wound care in treating the venous ulceration. (**evidence quality moderate; strong recommendation**)
- Multi-layered elastic compression bandages are more effective than single-layered systems. (**evidence quality moderate; strong recommendation**)
- Four layered bandage systems heal wounds faster than multi-layered systems with a short stretch bandage. (**evidence quality moderate; strong recommendation**)
- There is no evidence to support one type of dressing to be used on the ulceration underneath the compression bandage versus another and the choice of dressing should be based on cost as well as patient and physician preference. (**evidence quality moderate; strong recommendation**)
- Negative pressure wound therapy should not be used for chronic venous ulceration. (**evidence quality weak; strong recommendation**)

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Chapter 38
In Patients with Threatened or Occluded Dialysis Access Grafts, Is It Better to Salvage the Graft, or Create a New Site?

Mona G. Flores and Eugene S. Lee

Abstract Threatened or occluded access grafts are a frequent complication in patients undergoing hemodialysis and are associated with increased length of stay, morbidity, mortality, and hospital costs. An ideal access is one that can be reliably developed, delivers an optimal dialysis dose, and is resistant to thrombosis, infection, and the need for re-intervention. Access grafts generally have a greater likelihood to initial successful use and greater success for access salvage, but are prone to frequent failure and shorter long term patency. Arteriovenous fistula, however, are associated with lower likelihood to initial successful use, but have longer patency rates with fewer long term complications. When faced with a threatened graft and a secondary arteriovenous fistula is feasible, the best management approach may be an intervention to initially save the threatened graft but plans should be in place to perform a secondary arteriovenous fistula. If a secondary arteriovenous fistula is not performed prior to the third intervention to save the threatened graft, likelihood of a successful conversion to a secondary arteriovenous fistula decreases.

Keywords Dialysis access • Thrombosis • Stenosis • Treatment of vascular access complications • Arteriovenous fistula maturation • Arteriovenous graft • Arteriovenous shunt • Clinical trial

Introduction

Over the past several years, the incidence of patients requiring hemodialysis has risen in accordance to the aging population and the incidence of diabetes. Since 2000, the adjusted ESRD incident rate in those aged 75 years and older has increased by 11 %, to 1744 patients per million individuals [1]. Moreover, survival of the very elderly patients who remain on hemodialysis more than 90 consecutive days is

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about 3 years [2]. A major challenge to maintain patients on hemodialysis is the construction and maintenance of the hemodialysis access site so that ongoing hemodialysis can continue until the end of the patient's life.

The ideal vascular access for dialysis is one that allows dialysis for the longest period of time with fewest interventions, complications, and lowest costs. The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) and the Fistula First Breakthrough Initiative (FFBI) have implemented clinical practice guidelines in an effort to maximize hemodialysis access longevity. A major goal of the FFBI was to have AV fistula prevalence of 66 % by 2009. By 2011, the US prevalent AVF rate was 57.9 % [3]. Unfortunately, in attempting to achieve the FFBI goals, there was an increase in AVF non-maturation rates of 20–50 % [4].

Presently, the NKF-KDOQI guidelines recommend an AV fistula in the wrist, followed by an elbow primary fistula [Recommendation 2.1] [5]. However, with the placement of a brachiocephalic or brachiobasilic arteriovenous fistula, the forearm is abandoned as an access site. Allon et al. propose the possible placement of a forearm AV loop graft with the cephalic or basilic vein as the outflow vein [6]. Hence a distal graft is placed in preference over a proximal (elbow) AV fistula. This approach decreases catheter days until a long term access is used and preserves the more distal anatomic site for access. This chapter addresses the decision analysis of treating patients with threatened or occluded access grafts with ongoing salvage techniques or constructing a new arteriovenous fistula site if one is available.

Search Strategy

A literature search of human subjects, English language publications published from 2008 to 2014 was used to identify published data on the treatment of threatened or occluded access grafts. Comprehensive databases searched were PubMed, Embase, and Cochrane Evidence Based Medicine. Terms used in the search alone or in combination included "dialysis access," "thrombosis," "stenosis," "treatment of vascular access complications," "arteriovenous fistula maturation," "arteriovenous graft," "arteriovenous shunt," **AND** "clinical trial." Articles were excluded if they did not specifically address dialysis access. All randomized control trials, cohort studies, guidelines, systematic reviews, and review articles pertaining to the treatment of threatened or occluded grafts were included in our analysis. We also used references from the articles we retrieved through our above query. The data was classified using the GRADE system (Table 38.1).

Table 38.1 Studies on access patency rates in patients on hemodialysis

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients with occluded or threatened Dialysis access grafts	Graft Salvage	Create a new vascular access at a new site	Primary patency, secondary patency, morbidity, cost

Results

Society for Vascular Surgery Clinical Practice Guidelines

After the publication of the NFK-KDOQI Clinical Practice Guidelines, followed by the Fistula First Breakthrough Initiative (FFBI), Sidawy et al., published the Society for Vascular Surgery's (SVS) clinical practice guidelines for the surgical placement and maintenance of arteriovenous hemodialysis access [7]. Within the SVS clinical practice guidelines, two recommendations deal specifically with threatened or occluded access grafts. "A plan and protocol for eventual conversion of forearm prosthetic access to a secondary autogenous AV access should be put in place at the presence of any sign of failing forearm prosthetic AV access, or after the first failure" (GRADE 2, very low-quality evidence) [8]. The rationale for this is to convert the prosthetic access mature outflow vein to an arteriovenous fistula, or to identify a new, remote site for arteriovenous fistula construction in a patient where the prosthetic access outflow vein is not deemed suitable. No high-quality evidence was found to support a strategy of converting prosthetic accesses with impending failure to secondary autogenous accesses, and these recommendations were based on very low-quality evidence consisting of unsystematic observations and the consensus of experts [8]. With respect to the management of a non-functional or failed arteriovenous access, the SVS guidelines recommend open surgery, endovascular therapy, or a combination of both to maintain or restore patency in AV access (GRADE 2, very low-quality evidence). Both open and endovascular interventions may add an average of 12 months of functionality with low morbidity and mortality while preserving future sites of access [8].

Arteriovenous Fistula Compared with Arteriovenous Graft

In our literature search, we attempted to find new evidence published after the 2008 SVS guidelines [7], that would address the specific question: In patients with threatened or occluded access grafts, is it better to salvage the graft, or create a new site? To date, no clinical trials have been performed to address such a specific question. However, there are a few studies that compared the patency of arteriovenous fistulas and grafts (Table 38.2), which we considered while developing our treatment recommendations.

In the right patient, aggressive efforts result in a functioning AVF, which provides adequate dialysis with relatively few interventions required to maintain its long-term patency for dialysis. In the wrong patient, aggressive efforts to achieve a mature AVF may result in numerous failed surgical and percutaneous procedures and prolonged catheter dependence, with all its associated complications [4]. In 2008, Schild et al., published a retrospective study of 1700 dialysis access cases (58.7 % fistulae, 41.3 % grafts), with the goal of determining if too many fistulae were being performed without attention to specific patient profiles. Their results showed a median patency of 10 months, with no statistically significant difference between access types: upper arm (70.1 %), lower arm (24.5 %) and thigh (5.4 %)

Table 38.2 Studies evaluating patency in arteriovenous fistulas (AVF) and arteriovenous grafts (AVG)

Study	Number of patients	Type of dialysis access	Primary patency	Secondary patency	Cumulative patency	Dialysis catheter use	Quality of evidence
Schild et al. (2008) [9]	1700	AVF vs. AVG	AVF: 10 % median patency AVG:10 % median patency				Moderate
Slayden et al. (2008) [10]	Group 1 (40) Group 2 (108)	SAVF with protocol VS. SAVF with no protocol	Group 1: 82.5 % at 12 months, and 60.0 % at 24 months Group 2: 55.5 % at 12 months, and 50.5 % at 24 months	N/A	Group 1: 92.5 % at 12 months, and 87.5 % at 24 months Group 2: 94.4 % at 12 months, and 91.6 % at 24 months	Group 1: 22/40 (55 %) Group 2: data not available	Low
Salman et al. (2009) [11]	62	SAVF type I VS. SAVF type II	SAVF type I: 87 % at 6 months, 14 % at 12 months SAVF type II: 71 % at 6 months, 11 % at 12 months	SAVF type I: 100 % at 12 months, 100 % at 24 months, and 83 % at 36 months SAVF type II: 92 % at 12 months, 88 % at 24 months, and 83 % at 36 months	N/A	SAVF type I: 21/35 (50 %) SAVF type II: 27/27 (100 %)	Low
Woo et al. (2009) [12]	tAVF (190) AVG(168)	tAVF vs. AVG	tAVF: 48 % at 5 years AVG: 14 % at 45 years	tAVF: 57 % at 5 years AVG: 19 % at 45 years			Low
Morosetti et al. (2011) [13]	57	BBAVF (30) VS. AVG (27)	BBAVF: 86, 61 and 60 % at 6, 12 and 24 months AVG: 55, 32 and 21 % at 6, 12 and 24 months	BBAVF: 86, 76 and 66 % at 6, 12 and 24 months AVG: 72, 52 and 34 % at 6, 12 and 24 months	N/A	N/A	Low

(continued)

Study	Number of patients	Type of dialysis access	Primary patency	Secondary patency	Cumulative patency	Dialysis catheter use	Quality of evidence
Disbrow et al. (2012) [14]	AVF (89) AVG(59)	AVF vs. AVG		AVF: 71, 62 % at 6 and 24 months AVG: 72, 57 % at 6 and 24 months		AVF: 81 days (median) AVG: 38 days (median)	Low
Davoudi et al. (2013) [15]	60	BVT vs. AVG	BVT: 23.3 % at 1 year AVG: 30 % at 1 year				Moderate
Lok et al. (2013) [16]	AVF(1140) AVG(128)	AVF vs. AVG			AVF: 7.4 months AVG:15 months (for first access)		Moderate

SAVF secondary arteriovenous fistula, *tAVF* transposed arteriovenous Fistulas, *BBAVF* autogenous brachial-basilic arteriovenous fistula, *BVF* basilic vein transposition fistula

arteriovenous fistulas or grafts. Graft infection rate was 9.5 % and fistula infection rate was 0.9 % ($p < 0.001$). The overall infection rate was 4.5 %. An infection significantly decreased patency (4 vs. 11 months). Thrombosis occurred in 24.7 % of grafts and 9.0 % of fistulae. Their conclusion was that grafts had equivalent long-term patency to fistulas and that an AVG graft should be placed in patients who are not candidates for an AV fistula [17].

In 2009, Woo et al., retrospectively compared the outcomes of upper arm transposed arteriovenous fistulas (tAVF) to upper arm prosthetic grafts. A total of 190 patients with an upper arm tAVF were compared with 168 patients with AVG chosen from a pool of 476 concurrently performed AVG procedures. Primary patency for tAVF was higher than for AVG: 48 % vs. 14 % at 5 years ($P < .0001$). Secondary patency rate for tAVF was also higher than for AVG: 57 % vs. 19 % at 5 years ($P < .0001$). Nine percent of tAVF compared with 53 % of AVG required one or more surgical and/or percutaneous revisions to maintain secondary patency ($P < .0001$). Multivariate analysis revealed that utilization of a tAVF was associated with a reduced risk of primary (Hazard Ratio [HR] 0.47, 95 % Confidence Interval [CI] 0.35–0.64, $P < .0001$) and secondary failure (HR 0.59, 95 % CI 0.42–0.81, $P = .0001$). Woo et al. concluded that as long as a patient is a candidate for a tAVF based on anatomic criteria, a tAVF should be placed before an AVG [18].

In 2011, Morosetti et al., published a comparison of autogenous brachial-basilic AVF (BBAVF) and AVG in 57 patients, 27 randomized to undergo AVG placement and 30 randomized to BBAVF. Primary and secondary patency rates were higher for BBAVF than for AVG, but not statistically significant. They concluded that a BBAVF should be the first choice in patients with a good life expectancy and who can rely on an available temporary vascular access, and that an AVG could be an alternative in patients with compromised clinical conditions and in whom a temporary vascular access is not reliable, considering that the long-term outcome may be considered beneficial [19].

In 2012, Disbrow et al. published outcomes for 89 AVF patients and 59 AVG patients with equivalent vascular anatomy who were on dialysis via a catheter at the time of vascular access placement. Similar secondary patency was achieved by AVG and AVF at 12 (72 % vs. 71 %) and 24 months (57 % vs. 62 %), respectively ($p = 0.96$). The number of interventions required to maintain patency for AVF ($n = 1$; range 0–10) and AVG ($n = 1$; range 0–11) were not different ($p = 0.36$). However, the number of catheter days to first access use was more than doubled in the AVF group (median 81 days) compared with the AVG group (median 38 days; $p < 0.001$). They concluded that for patients who are receiving dialysis via catheter at the time of access placement, the maturation time, risk of non-maturation, and interventions required to achieve a functional AVF can negate its benefits over AVG, and that a fistula first approach might not always apply to patients who are already on dialysis when referred for chronic access placement [14].

In 2013, Davoudi et al., published the study results of 60 randomized patients to either a basilic vein transpositions (BVT) or AVG. After at least 1 year of follow-up, the access failure rate in the BVT and AVG groups was 23.3 % and 30 %, respectively. In addition, the mean primary patency time in the BVT and AVG groups was 244.13 ± 103.65 and 264.97 ± 149.28, respectively and there was no statistically significant difference between the two groups studied ($P = .5$). Since their results showed similar patency and complication rates to AVG and BVT, they

deemed AVG the preferred hemodialysis access when there are no suitable forearm veins to create arteriovenous fistulas [15].

In 2013, Lok et al. published cumulative patency (time from access creation to permanent failure) of 1140 hemodialysis patients with fistulas (1012) or grafts (128). The primary failure rate was 40 % for fistulas versus 19 % for grafts (P < 0.001). Cumulative patency did not differ between fistulas (7.4 months) and grafts (15.0 months) for the patients' first access [HR, 0.99; 95 % CI, 0.79–1.23; P = 0.85]). Compared with functioning fistulas, grafts necessitated twice as many angioplasties (1.4 versus 3.2/1000 days, respectively; P < 0.001) and significantly more thrombolysis interventions (0.06 versus 0.98/1000 days; P < 0.001) to maintain patency once matured and successfully used for dialysis. They concluded that even though cumulative patency did not differ between fistulas and grafts, grafts needed more interventions to maintain functional patency [20].

Arteriovenous Grafts and Secondary Arteriovenous Fistulas

Similarly, Slayden et al. reviewed their experience and outcomes converting AVGs to secondary arteriovenous fistulas (SAVF), utilizing the mature outflow vein of the AVG when possible, otherwise creating a new AVF at a remote site. Group 1 had a SAVF protocol in place during the study period with specific criteria for timing SAVF construction, while group 2 did not have a specific protocol to convert a graft into a SAVF. Indications for creating a SAVF were AVG thrombosis, dysfunction, erosion, bleeding, or steal syndrome involving the existing AVG. SAVFs were classified according to location and the potential for utilizing the existing mature AVG outflow vein. Group 1, which had 40 patients, underwent SAVF surgery prior to loss of the AVG, minimizing catheter use. Cumulative patency was 92.5 % at 1 year and 87.5 % at 2 years. Of the 102 patients in group 2, only 19.3 % were referred for SAVF surgery prior to loss of the AVG or outflow vein. Cumulative patency was 94.4 % at 1 year and 91.6 % at 2 years. They concluded that failure, dysfunction, or complications of AVGs may be resolved by conversion to a SAVF, and that this is best served by having a plan be in place to transition the AVG patient to an AVF when the AVG is threatened [10].

Salman et al. also studied SAVFs in a prospective trial, where they divided SAVFs into 2 types: SAVF type I, where the outflow vein of a dysfunctional arteriovenous dialysis access is used to create the fistula, and SAVF type II, where an arteriovenous fistula is created in the ipsilateral or contralateral extremity when an outflow vein is absent. Overall 62 (type I, n = 35; type II, n = 27) SAVFs were created over a 5 year period. The primary patency rates for types I and II SAVF at 6 and 12 months were 87 % and 14 % (type I) and 71 % and 11 % (type II), respectively. The secondary patency rates for type I at 12, 24, and 36 months were 100 %, 100 %, 83 %, respectively, and for type II were 92 %, 88 %, 83 %, respectively. The primary and secondary patency rates between the groups were not statistically significant. The cumulative patency rates for type I at 12, 24, and 36 months were 100 %, 100 %, and 94 %, respectively, and for type II were 96 %, 96 %, and 91 %, respectively. Type I required 1.4 procedures/year, and type II needed 1.5 procedures/year. Tunneled dialysis catheters were required in 21 patients with type I and 27 patients with type II SAVF. They concluded that both types of fistulas had excellent secondary and cumulative patency rates [11].

A Personal View of the Data and Recommendations

Arteriovenous fistulas have shown been consistently to perform better long term once constructed and deemed usable. However, all of the studies are head to head comparisons of a fistula or a graft. The reality of hemodialysis access rests upon distal long term access sites moving proximally and the hopes of minimal interventions to maintain dialysis during the lifetime of a renal failure patient. When a forearm AV fistula is not possible, we recommend a "catheter last" policy. In violation of the NKF-DOQI guidelines, if a forearm AV fistula is not possible, we recommend the construction of a forearm AV loop graft with the outflow vein to be the cephalic or basilic vein, this is in preference to a primary arteriovenous fistula originating at the elbow [DOQI guideline]. When the forearm AV graft is threatened or occluded, we recommend a one-time salvage procedure, either open or endovascular. Upon the second occasion of a threatened or occluded graft, we recommend converting to a secondary arteriovenous fistula without an attempt at salvage of the graft. If the outflow vein is the cephalic vein, direct access can be performed. If the outflow vein is the basilic or brachial vein, then transposition can occur and a temporary catheter can be placed for 2 weeks until the transposed vein is incorporated for safe access. These recommendations are based on weak evidence, as there is one retrospective study and one prospective trial, with some early positive results. However, a prospective long term trial should be considered in evaluating the overall lifetime total interventions, complications, and overall survival of these patients with an overall approach of catheter last as opposed to fistula first.

Recommendations

- For patients requiring dialysis, construct a forearm AV fistula first and a catheter until the fistula is mature (**very low quality of evidence; moderate recommendation**).
- For patients where a forearm AV fistula is not feasible, construct a forearm AV loop graft where the outflow vein is the cephalic vein, antecubital vein, or the basilic vein (**very low quality of evidence; moderate recommendation**).
- Upon the first occasion of a threatened or occluded graft, perform a salvage procedure for the initial procedure; the patient will need to be tracked so that further subsequent salvage procedures are not performed. Further interventions at salvage risk the feasibility of conversion to a secondary AV fistula (**low quality of evidence; strong recommendation**).
- Upon the second occasion of a threatened or occluded graft, perform a secondary AV fistula: brachiocephalic fistula, which is ready for use immediately after surgery, or a brachiobasilic/brachiobrachial transposition with the intervening use of an indwelling catheter for 2 weeks until the transposition can be safely accessed (**low quality of evidence; moderate recommendation**).

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Chapter 39
In Patients with New Arteriovenous Fistulas, Are There Effective Strategies to Enhance AVF Maturation and Durability Beyond Waiting?

Syed Ali Rizvi and Anil P. Hingorani

Abstract Autogenous arteriovenous fistulas are optimal conduits for hemodialysis due to their excellent long-term patency, low rates of infections and lower mortality rates. Yet, they are associated with a higher rate of failure to mature. As such, patient factors should be identified and modified, if possible, along with patient-centered surgical planning that includes the choice of vessels and techniques to yield the best possible outcomes for maturation. Furthermore, the postoperative period often requires a multidisciplinary team approach as arteriovenous fistula durability and maturation can be improved with appropriately timed endovascular or surgical interventions.

Keywords Arteriovenous fistula maturation • Creation • Durability • BAM • Neointimal hyperplasia • Anastomosis

Introduction

Autogenous arteriovenous fistulas (AVFs) are optimal conduits for hemodialysis. They have excellent long-term patency, low infection rates, less incidence of steal syndrome, stenosis, and lower mortality. Therefore, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI), Society for Vascular Surgery (SVS), and Fistula First Breakthrough Initiative (FFBI) recommend an AVF should be placed at least six months prior to the anticipated need for hemodialysis (HD) [1–5]. Clear documentation exists discussing the deleterious effects of tunneled dialysis catheters (TDC) and recommending early placement of AVF [1–4]. The 2003 guidelines of FFBI had set a prevalence goal of 66% AVF, to be met by

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2009, for those undergoing dialysis [5]. However, despite our increased prevalence of AVF creation, we have not met the goal. The U.S. Renal Data System Annual Data Report for 2013 (USRDS) reports an 81 % prevalence of TDC at initiation of therapy and 58.9 % AVF creation at initiation of hemodialysis [4]. The incidence of functional AVF at the first outpatient dialysis treatment is only slightly improved from 35.5 % in 2007 to 37 % in 2011 [4].

Subsequently, once a new autogenous AVF is created, the time to maturation can be lengthy and as many as 20–60 % fail to mature [3, 4, 6–23]. This adds the need for more procedures and a tunneled dialysis access catheter. Thus, vascular access dysfunction has now become a major contributor to cost, hospitalization and the overall morbidity and mortality [4, 24]. Many studies have attempted to elucidate the cause of access dysfunction by examining preoperative, intraoperative, or postoperative issues along with some adjuvant therapies that attempt to improve maturation and durability of these fistulae.

Search Strategy

A literature search of English language publications from January 2000 to October 2014 was used to identify published data on effective strategies to enhance maturation and durability of new AVF using the PICO outline (Table 39.1). The PubMed database was utilized and the search terms included "creation of arteriovenous fistulas", "maturation of arteriovenous fistulas", "patency of arteriovenous fistulas", "durability of arteriovenous fistulas", and "end stage renal disease AND fistulas." Articles were excluded if they specifically addressed grafts, only addressed specific complications such as steal phenomena, pediatric population, lower extremity fistulas, or involved discussion of fistulas in non-human models. Abstracts of the relevant titles were subsequently obtained and evaluated for eligibility. Further, review of the full article was then completed to include or exclude each article as appropriate. We then adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scheme to classify the data. We also utilized the guidelines, opinions and data discussed in FFBI, NKF-KDOQI, SVS as well as the Annual Report of the USRDS to complete this chapter.

Table 39.1 PICO table for effective strategies to enhance AVF maturation and durability beyond waiting in patients with new arteriovenous fistulas

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Patients with ESRD requiring arteriovenous fistulae	Preoperative, intraoperative, and postoperative measures	Waiting for maturation or failure	Enhance maturation and durability of new arteriovenous fistulas

Results

Definition of AVF Maturation

The definition of AVF maturation is as defined by KDOQI. It is the "rule of 6's." This entails that a fistula must be 6 mm in diameter with a tourniquet, less than 6 mm deep, have blood flow >600 ml/min, and should be evaluated for non-maturation within 6 weeks after creation [1, 2].

Preoperative Factors for AVF Failure (Table 39.2)

The USRDS states that of the patients who received greater than or equal to 1 year pre-ESRD nephrology care, 30 % had a maturing a fistula and 50 % had a functional fistula at initiation of dialysis. This is approximately five times greater as compared to patients who were not referred to a nephrologist [4, 27, 38]. Thus, suggesting that earlier referral to a nephrologist may be of significant benefit [29].

Selecting appropriate access sites is critical for AVF maturation and preoperative duplex ultrasound may play an important role. One randomized trial, by Nursal et al. compared physical exam findings to duplex ultrasound preoperatively for site selection and showed no difference in AVF maturation or function [39]. Two other randomized trials supported the use of preoperative duplex ultrasound over physical examination for AVF maturation rate, but these studies had significant shortcomings in follow-up and the reported definition of patency [32, 38]. A similar topic was also discussed by Patel et al. They found an increase in creation of AVF due to duplex use but possibly worse rates of AVF maturation [31]. Indeed, a prospective trial with significant power to measure differences in maturation rates between ultrasound and physical exam findings is required to investigate the true role of preoperative duplex.

Vessel diameters have also been addressed to document their effect on AVF maturation. Wong et al. reported a higher rate of fistula failure with smaller arteries, <1.6 mm in diameter [15]. A literature review by Glass et al. showed that radial artery diameter (RAD) determined patency as RAD < 2 mm vs. RAD >2 mm yielded 40 % vs. 59 % AVF maturation, respectively [35]. Kheda et al. showed that small artery elasticity (2.25 ml/mmHg vs 3.71 ml/mmHg × 100 p = 0.02) was more predictive for AVF maturation than arterial diameters [20]. Shinstock et al. further demonstrated that a one mm increase in arterial diameter was associated with 30 % decrease of AVF abandonment with a median follow-up of 379 days [24]. Current guidelines suggest a minimum arterial diameter of 2 mm for successful AVF creation at the wrist, but guidelines for other locations is lacking [3, 24, 30, 38, 40].

Similarly, studies have also addressed vein diameters. A meta-analysis by Glass et al. revealed that duplex derived cephalic vein diameters <2 mm and >2 mm resulted in 29 % vs 71 % of AVF maturation, respectively [35]. Application of tourniquets during use of duplex to assess vein diameters was addressed in studies by Lockhart et al.

Table 39.2 Studies discussing preoperative reasons for failure and ways to improve maturation and durability

Author	Discussion	Study type (quality of evidence)
Dageforde et al. [26]	N = 158 Outcome: Greater than 2/3 of AVF with < 2.7 mm minimum vein diameter (MVD) on preop duplex failed to mature in 6 months Increased MVD on preoperative duplex mapping is associated with decreased risk of failure of maturation and improved long-term patency (P = 0.005 and P = 0.001, respectively)	Retrospective (low quality)
Allon et al. [25]	N = 145 Outcome: Postoperative AVF stenosis equal in those with preexisting venous intimal hyperplasia and does that do not (46 % vs 53 % P = 0.49) Postop non-maturation 30 % of those with postop stenosis vs 7 % in those without postop stenosis (P = 0.001) More interventions needed to maintain patency in those with postoperative stenosis than those without stenosis (P = 0.008)	Prospective (low quality)
Mortaz et al. [26]	N = 130 Outcome: Diabetes does not have a negative impact on the AVF rate of patency and its duration to maturation	Retrospective (low quality)
Hanko et al. [27]	N = 508 Outcome: Pre-dialysis AVF creation rates were 79 % of those who chose and started hemodialysis (HD), 39 % of those who chose peritoneal dialysis but started HD and 50 % of those in the undecided group who commenced HD	Retrospective (low quality)
Renaud et al. [28]	N = 280 Outcome: One and 2 year primary (P = 0.547) and secondary (P = 0.990) patency rates comparable for those age <65 years vs. age ≥ 65 years	Retrospective (low quality)
Ishaque et al. [8]	N = 249 Outcome: African American (AA) males may have smaller median basilic and cephalic vein diameters. AA males more likely to have AV graft vs. non AA males (17.9 % vs. 7.1 % P = 0.009)	Retrospective (low quality)
Oliver et al. [29]	N = 1929 Outcome: 40 % had their first fistula creation 3–12 months prior to starting dialysis, 30 % AVF created > 1 year prior to dialysis, 30 % within 90 days of starting dialysis	Retrospective (low quality)

Table 39.2 (continued)

Author	Discussion	Study type (quality of evidence)
Schinstock et al. [24]	N = 293 Outcome: Risk of reduced primary patency increased with diabetes (HR = 1.54) Risk of reduced PP and SP was decreased with larger arteries (HR = 0.83, HR = 0.69) One mm increase in arterial diameter was associated with 30 % decrease of AVF abandonment with a median follow-up of 379 days	Retrospective (low quality)
Allon et al. [9]	N = 50 Outcome: Preop arterial diameter was associated with upper arm AVF maturation (p = 0.007) Medial fibrosis was similar in nonmaturing and mature AVF (60 % vs 66 % P = 0.2)	Prospective (low quality)
Lockhart et al. [30]	N = 73 Outcome: Sonography used for Radiocephalic arteriovenous fistula (RCAVF) to separate patients into group 1 (pre-tourniquet vein diameter ≥ 2.5 cm) and group 2 (pre-tournique < 2.5 cm and after application of tourniquet increased to ≥ 2.5 cm) Fistula success rate similar in both groups (39 % vs. 33 % P = 0.624) Tourniquet application increased the total number of usable forearm fistula	Retrospective (low quality)
Patel et al. [31]	N = 202 Outcome: AVF creation rate increased from 61 % to 73 %, but functional maturation rates decreased from 73 % to 57 % (P < 0.05) after implementation of preoperative imaging and aggressive vein use	Retrospective (low quality)
Wong et al. [32]	N = 402 Outcome: Improved trend of patients who underwent ultrasound preoperatively vs. clinical exam alone, started using their AVF (81 % vs. 69 % P = 0.11)	Literature review (low quality)
Kheda et al. [20]	N = 32 Outcome: Average small artery elasticity index was lower in failed than in matured fistulas (P = 0.02)	Prospective (Low Quality)

(continued)

Table 39.2 (continued)

Author	Discussion	Study type (quality of evidence)
Lauvao et al. [33]	N = 298 Outcome: AVF location (P = 0.032) and vein size (P = 0.002) significantly affected maturation in univariate analysis Only vein diameter was independent predictor of AVF functional maturation (P = 0.002)	Retrospective (low quality)
Kosoy et al. (2009)	N = 100 Outcome: Mean duration of operation was shorter in Brachiocephalic arteriovenous fistula (BCAVF) vs. Brachiobasilic arteriovenous fistula (BBAVF) (P < 0.001), but no significant differences in postop complications or morbidity or mortality. Primary patency was similar at one and 3 year follow-up (P = 0.8)	Prospective (low quality)
Lok et al. [21]	N = 422 Outcome: Internally validated risk equation found age ≥ 65 years, peripheral vascular disease (PVD), coronary artery disease, non-white rate to be predictive of failure to mature	Retrospective (low quality)
Lazarides et al. [34]	N = 1841 (13 studies) Outcome: Higher rates of RCAVF failure in elderly at 12 months and 24 months (OR = 1.525, P = 0.001 and OR 1.357, P = 0.019 Secondary analysis showed effect in favor or elbow BCAVF vs. RCAVF in elderly (P = 0.004)	Literature review (moderate quality)
Glass et al. [35]	N = 433 for RAD and 386 for CVD, 20 studies Outcome: Mean radial artery diameter (RAD) yielding fistula success for (RAD) > 2.0 mm and RAD < 2.0 mm, 59 % vs. 40 %, respectively Fistula success rate between cephalic vein diameter (CVD) > 2.0 mm and CVD < 2.0 mm was 71 % vs 29 %, respectively	Literature review (low quality)
Monroy-Cuadros et al. [36]	N = 831 Outcome: Incidence of primary failure = 10 % Age > 65 years (P = 0.001), history of diabetes (P = 0.007), history of smoking (P < 0.001), presence of forearm fistula (P < 0.001), and low initial intra-access blood flow < 500 ml/min (P < 0.001) were independently associated with loss of primary patency	Retrospective review (low quality)

Author	Discussion	Study type (quality of evidence)
Hingorani et al. [37]	N = 41 Outcome: Venodilatation as a percentage increase after application of tourniquet compared with native state was 37 % for distal cephalic vein, 31 % for midcephalic vein, and 32 % for midbasilic vein Venodilatation as a percentage increase after placement of regional anesthesia nerve block compared with after tourniquet application was 42 % for distal cephalic, 19 % for midcephalic, 26 % for midbasilic veins Venodilatation is augmented with regional anesthesia and tourniquet compared with using a tourniquet alone and may allow more options for access creation	Retrospective (low quality)
Wayne et al. [23]	N = 73 Outcome: Absence of PVD, aspirin use, and absence of previous permanent dialysis access were associated with higher primary patency rates Higher mean arterial pressure (MAP) during maturation relative to preoperative MAP associated with lower patency Maturation period hemodynamics pay play important role in dialysis access patency	Retrospective (low quality)

and Hingorani et al. These studies suggested a role for the use of tourniquets during the duplex exam before the placement of AVF [30, 37]. Thus, NKF-DOQI recommends a minimum vein diameter of 2.5 mm for creation of AVF [1, 2, 33].

Specific Populations

In 1966, Cimino and Brescia described their novel technique for fistula creation with an 11 % failure to maturation rate. The patients' median age was 43 years with almost all having glomerulonephritis as the cause of their end stage renal disease. Today, the failure rate is fivefold as high and the age group requiring dialysis with the fastest growth is >85 years old [4, 21]. The meta-analysis by Lazarides et al. showed that in the elderly (range varying among studies from >50 to >70 years), radio-cephalic AVF (RCAVF) was significantly more likely to fail than in the non-elderly at 12 months (OR = 1.525, p = 0.001) and 24 months (OR = 1.357, p = 0.012) [34]. However, many other studies have shown conflicting data [8, 21, 23, 26, 28].

Other factors and their effects on AVF maturation have also been examined. Although the major cause of AVF failure to maturation is venous intimal hyperplasia (VIH) [41], studies have shown that AVF in those with preexisting VIH, calcifications, or stenosis were equally likely to mature than in those without these lesions [21, 25]. Studies documenting the effects of BMI have been largely inconclusive [20, 38] and studies on the effects of gender have not shown significant differences in maturation [38]. Finally, diabetes has been associated with worse primary patency [38, 42].

Intraoperative Factors Affecting AVF Failure, Maturation and Durability (Table 39.3)

Studies addressing intraoperative measures to assess maturation of AVF have largely focused on intraoperative volume flow, blood pressure (BP), tissue handling, vessel distension, and anastomosis techniques. Saucy et al. discussed intraoperative blood flow in RCAVF after completion of anastomosis using a transit time ultrasonic flowmeter as well as follow-up post op using color flow ultrasound to estimate blood flow. They found that intraoperative blood flow volume with a cutoff of 120 ml/min had 67 % sensitivity, 75 % specificity, and 91 % positive predictive value to predict early failure [12]. Others have demonstrated an association between low mean arterial pressure (MAP) on the day of fistula placement and lower maturation rate. Higher diastolic BP during maturation relative to preoperative diastolic BP has also been associated with lower maturation rate. These studies demonstrate the significance of hemodynamics in fistula maturation [23, 38].

Tissue handling has been a possible implication in "swing point" or juxta-anastomosis stenosis, thus, minimal tissue handling is advocated [18, 22, 43–45]. In a prospective randomized trial, Lin et al. discussed interrupted technique using nitinol clips to create anastomosis versus sutures. They demonstrated promising AVF

Table 39.3 Studies discussing intraoperative reasons for failure and ways to improve maturation and durability

Author	Discussion	Study type (quality of evidence)
Kotoda et al. [40]	N = 1 Outcome: Case-report of balloon-assisted creation and maturation of small caliber cephalic vein and small caliber radial artery for AVF creation	Case report (low quality)
Kanko et al. [43]	N = 67 Outcome: 89 % patency rate in 6 months using the "diamond-shape anastomosis" technique	Retrospective (low quality)
Manson et al. [44]	N = 10 Outcome: Technical feasibility (n = 10/10, 100 %), safety and clinical success of the Optiflow implant for AVF creation was addressed. One hundred percent patients had diameters > 6 mm at Day 42, but more studies needed	Retrospective (low quality)
Bharat et al. [45]	N = 125 Outcome: Decreased juxta-anastomotic stenosis in piggyback Straight Line Onlay Technique (pSLOT) patients (P = 0.04) pSLOT revealed decreased overall AVF failure rate of 16.7 %, compared with side to side technique rate of 33.3 %, and end to side rate if 40.3 %, (P = 0.01)	Retrospective (low quality)
Dukkipati et al. [46]	N = 6 studies evaluating patency rates for BBAVF N = 10 studies comparing BBAVF vs. BCAVF vs. AVGraft N = 2 studies comparing BBAVF vs. BBrAVF vs. AVG N = 3 studies comparing One-stage vs. Two-stage BBAVF Outcome: Rate of BBAVF primary failure is approx. 15–20 % (range = 0–40 %) Mean 1-year patency rate is approx. 72 % (range = 23–90 %) Mean 2-year patency rate is approx. 62 % (range = 11 –86 %) Limited evidence supports Two-stage BBAVF with increased primary patency at 15 months compared to One-stage	Literature review (low quality)
Robertson et al. [47]	N = 73 Outcome: No significant difference in functional patency rates at 6 weeks between one stage vs. two stage brachiobasilic fistula creation (76 % vs. 84 % P = 0.545). No difference observed in long-term patency (P = 0.431)	Retrospective (low quality)
Bonforte et al. [11]	N = 459 Outcome: Middle arm fistula (MAF) primary patency at 4 years from creation was 79 % Higher risk of MAF failure was found in women (P = 0.19), underweight patients (P = 0.010), and MAF implantation after starting hemodialysis (P < 0.001)	Retrospective (low quality)
Bhalodia et al. [19]	N = 58 Outcome: Primary failure was lower for proximal Radiocephalic AVF (pRCF) than distal RCF (dRCF) (32 % vs. 59 % P = 0.05) Cumulative survival similar between pRCF and dRCF (92 % vs. 86 % at 1-year and 74 % vs 76 % at 2 years P = 0.56)	Retrospective (low quality)

(continued)

Table 39.3 (continued)

Author	Discussion	Study type (quality of evidence)
Saucy et al. [12]	N = 58 Outcome: Intra-operative blood flow in functioning radiocephalic AVF was significantly higher compared to non-functioning radiocephalic AVF (230 ml/min vs 98 ml/min P = 0.007) 1-week and 4-week blood flow measurements were also higher in functioning AVF vs. non functioning (753 ml/min vs. 228 ml/min P = 0.0008 and 915 ml/min vs. 245 ml/min P < 0.0001) Intra-op blood flow of 120 ml/min revealed a sensitivity of 67 %, specificity of 75 % and positive predictive value of 91 % for functioning RCAVF	Retrospective (low quality)
Lin et al. [48]	N = 132 Outcome: Nitinol surgical clips used to compare outcomes against sutured anastomosis in forearm and upper arm fistulae Clipped forearm AVF (FAVF) had improved maturation at 6-weeks vs. sutured anastomosis (86 % vs. 69 %, P < 0.05) Clipped forearm AVF also had improved patency at 12, 24, and 36 months (P < 0.05) No difference was measured in clipped vs. sutured upper arm AVF maturation or patency	Prospective (low quality)
Fila et al. [68]	N = 93 Outcome: Significant impact and failure to mature was due to increased body-mass index (P = 0.041), artery diameter (P < 0.001), vein diameter (P = 0.004), and vein diameter after dilation using serially increasing diameter dilators (P = 0.002) Those patients with vein diameters < 2 mm, only vein diameter after dilatation significantly affected function (P = 0.004)	Retrospective (low quality)

maturation rates, 86 % at 6 weeks using clips versus 69 % with sutures (p < 0.05). However, no difference in patency was noted [48]. These data have not been replicated and the significant cost of these devices has limited their use.

Suture techniques have also been examined. There are devices that allow for sutureless anastomosis. However, minimal success was exhibited in one pilot study in humans [44]. Inconclusive reports are present on four quadrant sutures vs. continuous vs. interrupted techniques [38, 43]. Anastomosis creation in an end (vein) to side (artery) manner has become widely accepted since the report by Wedgwood et al. demonstrated a decrease in incidence of VIH [38] compared to end to end or side to side manner. Still, there are other techniques such as on-lay and posterior straight on-lay that offer similar patency; however, these were in small case series [45].

Studies discussing location of new arteriovenous fistulae are abundant. Some have discussed that distal RCAVF carry less potential for maturation compared with proximal RCAVF. Two retrospective analyses have shown equal if not better patency with proximal or middle arm RCAVF [11, 19]. However, in reality, physical limita-

tions including quality and caliber of the available artery and vein are more likely to determine the site of AVF placement.

Retrospective analyses of single-stage versus two-stage brachio-basilic AVF (BBAVF) have documented improved patency at 1-year and 2-year with two-stage procedures [46, 47]. Koksoy et al. [67] reported from a randomized prospective study the patency of single-stage BBAVF vs brachio-cephalic AVF (BCAVF). These data only included patients with prior failed RCAVF with patent upper arm veins. Their study showed that, although BCAVF creation required shorter duration of procedures, primary patency remained the same [49]. Furthermore, Ascher et al. reported similar AVF maturation rates of 91 % vs. 87 % ($p = 0.3$) for BCAVF vs. BBAVF, respectively [50].

Postoperative Factors Affecting AVF Failure, Maturation and Durability (Table 39.4)

As recommended by FFBI, every new AVF should be evaluated for maturation at 4 weeks [5]. If the access is not maturing at 4 weeks, or flow remains low (<500 ml/min), or cannulation of the AVF is not feasible, a fistulogram is recommended for evaluation [3, 54].

The four most useful surveillance methods for dysfunction, as described by NKF-DOQI, are serial access flow measurements, measurement of static venous pressure, pre-pump arterial pressure, and duplex ultrasound scanning [38]. If access surveillance is abnormal, a fistulogram can be performed [1, 2, 38]. A meta-analysis completed by Casey et al. found 12 studies addressing surveillance versus clinical monitoring [59]. Only three of these studies showed that vascular intervention after abnormal surveillance led to a significant reduction in risk of access thrombosis (RR 0.53 95 % CI 0.36–0.76) and a non-significant risk of AVF access abandonment [3]. Other studies have documented that clinical monitoring of AVF has 96 % sensitivity and 93 % negative predictive value [63]. Thus, clinical monitoring may be equal to surveillance. This, however, is not very likely to be applicable in our communities where thorough physical exams are resource intensive and rare, and surveillance may be advocated [3, 10, 59]. Indeed, if clinical exam is equivocal, duplex ultrasound can be beneficial.

Specific treatment options for non-maturing AVF rest with the physician. Ascher et al. noted that simple and extended salvage procedures may extend the lifespan of the AVF [58]. Certainly, debate exists between open surgical techniques and endovascular PTA techniques. In a retrospective analysis by Tindi and Roy-Chaudhry, it was shown that open surgical treatment may be superior to endovascular treatment. In a nonrandomized study of male Veterans' Affairs hospital patients, AVF maturation rates between endovascular or open surgical techniques were compared to the controls that did not undergo either procedure. The open surgical arm and no treatment requirement arm had similar maturation rates of 83 % vs 86 %, while only 40 % of the PTA arm AVF matured [53]. Other studies have cited secondary patency

Table 39.4 Studies discussing postoperative reasons for failure and ways to improve maturation and durability

Author	Discussion	Study type (quality of evidence)
Lynch et al. [6]	Keywords: QI Coordination Teams Increased Follow-Up But Not Maturation N = 198 Outcome: Institutional quality-improvement (QI) program developed well-defined office follow-up schedule after AVF creation Compliance within first-30 days post AVF creation increased from Pre-QI to QI group (48 % vs. 65 % P = 0.015) No difference in failure to mature rate for the pre-QI and QI group (22 % vs 21 % P = 0.816)	Retrospective (low quality)
Gorin et al. [7]	N = 30 patients, 31 AVF created Outcome: Office-based ultrasound guided angioplasty of AVF performed n = 48 for failing to mature and remaining 7 interventions performed for stenosis 90-day patency = 93 % 85 % AVF treated for FTM achieved functional status Four perifistular hematomas; three resulted in AVF thrombosis. No patients required hospitalization. Office setting valuable tool in management of dialysis access	Retrospective (low quality)
Usta et al. [69]	N = 80 Outcome: Factors influencing AVF function were radial artery diameter (P = 0.02), intraoperative flow (P = 0.01), intraoperative pulsatility index (P = 0.01), and postoperative flow (P = 0.01) Intraoperative ultrasound and postop DUS can help identify AVFs that are unlikely to function and may need early intervention	Retrospective (low quality)
Lee et al. [41]	N = 12 Outcome: Vein samples obtained from AV anastomosis at time of AVF creation showed neointimal hyperplasia in 10 of 12 specimens	Retrospective (low quality)
Tan et al. [10]	N = 44 Outcome: Patients on HD who received endovascular interventions for access problems were analyzed. No periop complications 100 % technical success rate Median time for first endovascular intervention was 13 months for AVF and 8 months for AVG Median time for restenosis or failure was 11 months for AVF and 5 months for AVG	Retrospective (low quality)
De Marco Garcia et al. [51]	N = 62 Outcome: Intraoperative balloon angioplasty utilized to upgrade small caliber veins during AVF creation 85 % remained patent and subsequently underwent Balloon assisted maturation (BAM) with a resulting functional AVF	Retrospective (low quality)

Table 39.4 (continued)

Author	Discussion	Study type (quality of evidence)
Raynaud et al. [13]	N = 25 Outcome: Percutaneous transluminal angioplasty (PTA) performed at forearm artery lesions for failing distal access maturation In 91 % of patients after PTA, accessed used for hemodialysis without difficulty Primary patency rates were 83 % (range = 60–93 %) at 1-year and 74 % (range = 47–89 %) at 2-years	Retrospective (low quality)
Rayner et al. [52]	N = 3674 Outcome: Observational data at hemodialysis, hemofiltration, or hemodiafiltration facilities in Europe and U.S. Significant differences in clinical practice currently exist between countries regarding AVF creation and timing of first cannulation Cannulation ≤ 14 days after creation was associated with 2.1 fold higher likelihood of subsequent AVF failure compared to AVF cannulated > 14 days (P = 0.006)	Prospective (high quality)
DerDerian et al. [17]	N = 30 patients, 143 Balloon-assisted maturation Outcome: Balloon-assisted maturation is a controversial method for developing AVF Average BAM per patient was 4.8 (range = 1–7 procedures) 74 developed post procedural hematoma, 76 showed increase in volume flow measurement, but no correlation (P = 0.87) Hematomas most frequently during 2nd BAM procedure (24.3 % of all hematomas) 8 mm balloon group, statistical difference was noted in percent increase in volume flow measurement (VFM) with presence of a hematoma and percent increase in VFM without presence of a hematoma (P = 0.027) Suggest a more aggressive approach to BAM with use of larger balloons to create hematoma formation and minimizing excessive dilation procedures, may have a significant effect in maturation based on VFM	Retrospective (low quality)
Lee et al. [53]	N = 89 Outcome: 46 of 89 (52 %) patients required intervention to achieve maturation. Thirty-one patients had surgical revision, 15 patients had endovascular interventions Cumulative survival longer in AVF receiving surgical interventions compared with angioplasty to promote AVF maturation (P = 0.05) One-year cumulative survival was 86 % vs. 83 % vs. 40 % for no intervention vs. surgery vs. angioplasty, respectively	Retrospective (low quality)

(continued)

Table 39.4 (continued)

Author	Discussion	Study type (quality of evidence)
Robin et al. [54]	N = 69 Outcome: Ultrasound measurements at 2–4 months post AVF creation are highly predictive of fistula maturation and adequacy for dialysis	Retrospective (low quality)
Swinnen et al. [22]	N = 68 Outcome: 33 AVF received Juxta-anastomosis Stenting (JXAS) for failure to mature, 35 received JXAS for inadequate dialysis Technical success in placement of nitinol stent was 97 %. 75 % of those that were failing to mature were brought to maturity after JXAS	Retrospective (low quality)
Geogiadis et al. [42]	N = 72 Outcome: ESRD diabetics with radial artery Monckeberg calcifications receiving Radiocephalic arteriovenous fistula (RCAVF) had worse late clinical outcomes compared with ESRD diabetics with healthy arm vessels. Long-term benefits may be lost in diabetics with extensively calcified vessels for distal RCAVF fistulae	Prospective (low quality)
Bountouris et al. [55]	N = 159 Outcome: 50 % of primary percutaneous transluminal angioplasty (PTA) required no further intervention. Fifty percent required at least one reintervention Primary assisted patency was 89 % at 6 months and 85 % at 12 months	Literature review (low quality)
Miller et al. [56]	N = 122 Outcome: Successful AVF maturation in 118/122 patients Follow-up of 109 of 118 patients was achieved (mean = 24 months, range = 0.25–60 months)	Retrospective (low quality)
Miller et al. [57]	N = 140 Outcome: Thrombosed fistulae that were never used for hemodialysis underwent endovascular salvage procedures, such as thrombectomy, BAM, elimination of competing branching veins, etc. Cost analysis revealed percutaneous procedures costs $4,881 to $14,998 less than access abandonment and new access creation	Retrospective (low quality)
Hingorani et al. [58]	N = 46 patients, 75 revisions Outcome: Simple and extended salvage procedures may allow maturation and add to the life span of AVFs for hemodialysis Suggest an advantage to open techniques as compared with percutaneous techniques but only in terms of requiring fewer subsequent procedures	Retrospective (low quality)

Table 39.4 (continued)

Author	Discussion	Study type (quality of evidence)
Casey et al. [59]	N = 1363 patients Outcome: Surveillance followed by intervention led to a non-significant reduction of risk of access thrombosis (RR, 0.82; 95 % CI, 0.58–1.16), and access abandonment (RR, 0.80; 95 % CI, 0.51–1.25) Vascular intervention after abnormal access surveillance led to significant risk reduction of access thrombosis (RR, 0.53; 95 % CI, 0.36–0.76) Potential benefit of AV access surveillance followed by interventions to restore patency is based on low quality evidence	Literature review (moderate quality)
Marks et al. [60]	N = 20 Outcome: 20 AVF underwent office guided duplex balloon angioplasties 18 of 20 were for failing AVF Excellent duplex imaging quality and technical advances in endovascular tools allowed performance of AVF balloon angioplasties in office with technical success	Retrospective (low quality)
Ascher et al. [61]	N = 25 patients, 32 angioplasties Outcome: No systemic complications. One patient developed arm hematoma One patient had focal intraluminal dissection not obstructing the flow Increase from mean volume flow from preoperative to postoperative (350 ± 180 lm/min to 933 ± 332 ml/min, P < 0.001)	Retrospective (low quality)
Gallagher et al. [62]	N = 45 patients, 185 duplex guided BAM Outcome: 99.5 % successfully dilated-one required surgical exploration due to large AVF rupture AVF failed to mature in 7 of remaining 44 patients (16 %) because of proximal vein stenosis All of the 7 subsequently matured after successful balloon angioplasty of the venous outflow	Retrospective (low quality)
Dember et al. [14]	N = 877 Outcome: Enrollment stopped after 877 participants, based on intervention efficacy. Fistula thrombosis occurred in 12.2 % assigned to Clopidogrel vs 19.5 % assigned to placebo (P = 0.018) Failure to attain suitability for dialysis did not differ between placebo and Clopidogrel.	Multicenter, prospective RCT (high quality)

with endovascular salvaging techniques to be up to 77 %, 61 % and 32 % at 12 months, 24 months, and 36 months, respectively [56]. Literature review by Bountouris et al. showed that results of PTA vs. open surgery are similar for salvaging failing fistulas and mirror the SVS guidelines that local expertise should guide therapy [3, 55]. Very limited quality of data exists due to mostly retrospective analysis to recommend firm guidelines.

Studies documenting endovascular interventions to enhance AVF maturation remain controversial [13]. Some studies describe balloon assisted maturation (BAM) as a technique that can promote VIH and cellular proliferation, leading to stenosis due to increase in luminal pressure, medial hypertrophy, or abnormal wall shear [16, 17, 64]. Other authors speculate that BAM heals into a large fibrous conduit as seen on fistulograms post BAM and contributes to increased AVF patency [17, 51]. These studies have suggested using a combination of limited interventions with large caliber balloons to achieve maturation [17, 57]. De Marco Garcia et al. achieved 85 % maturation of new AVFs after performing primary balloon angioplasty during the index procedure for creation in small caliber (<3 mm) veins and subsequent BAM within 2 months of creation [51]. Indeed, many studies have documented the safety of performing these procedures at outpatient centers [7, 56, 57, 60–62].

Other techniques of endovascular AVF maturation or salvage have shown varying results using a combination of cutting or non-cutting balloons [18, 56]. Juxta-anastomotic stenting using non-covered nitinol stents to treat VIH [22], angioplasty to treat stenosis, thrombectomy or thrombolysis as appropriate to treat access thrombosis, and embolization of collateral side branches as needed to ensure adequate fistula flow have all shown promising results [18, 56].

Furthermore, open AVF management strategies are based on treating the underlying cause of nonfunctioning of AVF. In an access that is too deep causing an AVF to become nonfunctional, but free of significant stenosis, transposition and re-tunneling with or without moving the site of anastomosis can improve functionality. Open ligation of patent side branches may be attempted if large patent branches, usually greater than 2 mm, are found to be shunting blood away from AVF and preventing adequate maturation [3].

Arterial inflow problems represent about 3–5 % of all stenoses in HD access. The site of stenosis may be anywhere in the inflow arteries. PTA with or without stenting is the preferred option for stenosis involving >50 % of arterial diameter causing insufficient inflow [3].

Poor venous outflow is another major problem for AVF maturation. After access creation, aggressive surveillance may be undertaken. Diagnosis of early venous stenosis (<7 days after creation) is usually a technical error and should be revised with open technique. Late diagnosis of these stenoses can be treated using balloon angioplasty.

Thrombosis of fistula can be divided as early or late. Early thrombosis (<30 days from creation) is usually due to technical error and a thorough evaluation of the fistula should be performed to assess the worth of re-exploration versus assessment of a new site. Management of thrombosed access begins with thrombectomy, then identifying, and treating the stenotic lesion. Shorter lesions respond well to patch angioplasty of lesions with either venous or prosthetic materials. Longer lesions require bypass of the diseased segment [3]. Endovascular options with thrombectomy and treating underlying lesions can be performed as a standard technique.

Finally, timing of first AVF cannulation may also correlate with the likelihood of failure. Rayner et al. have described time of cannulation with <14 days after creation resulting in 2.1 fold likelihood of AVF failure ($p = 0.006$) compared to AVF cannulation >14 days post creation [52].

Adjuvant Therapies

Smoking has long been recognized as a factor for vascular disease. Studies have shown early and late AVF failure among cigarette smokers [3, 36]. Osborn et al. conducted a Cochrane review of medical treatment as adjuvant therapy for improving AVF maturation. Their analysis of trials starting from 1970s to the present, including antiplatelet agents such as aspirin, clopidogrel, ticlodipine, dipyridimole, documented marginal success of these therapies. One trial comparing low dose of warfarin with placebo was stopped early due to increased bleeding in the treatment group. A trial using clopidogrel was also stopped early due to significantly decreased risk of early AVF thrombosis compared to placebo, but no difference was found in maturation [14]. A single trial of fish oil, 4 g daily, showed favorable outcomes. Yet, the quality of data from these single studies has remained insufficient to recommend use [65].

Recommendations

The systematic review of literature demonstrates the scarcity of evidence-based data available, lack of randomized controlled trials, with recommendations mostly based on retrospective analysis or observational studies in this field. Indeed, based on the data analyzed, the new autogenous AVF is prone to multitude of problems, yet remains as the best option we have for hemodialysis. Strategies to enhance AVF patency and durability extend to time well before and after the placement of a fistula.

Preoperatively, the following are recommended:

1. Smoking cessation
2. Timely referral for nephrology care and vascular access placement
3. Ultrasound imaging to ensure adequate arterial diameters of at least 2.0 mm radial artery and 2.5 mm cephalic vein at the wrist (preferably performed by the surgeon himself or herself) .

Intraoperatively, the following are recommended

1. Non-dominant, upper extremity distal fistulas recommended to preserve other sites for future access
2. End to side anastomosis is preferred
3. Intraoperative blood flow measurement, if available, of at least 120 ml/min after creation and search for cause of poor volume flow if present

Postoperatively, the following are recommended

1. Follow-up with access surgeon at 4 weeks to examine the fistula
2. No cannulation prior to 14 days
3. "Rule of 6's" to evaluate for maturation
4. If AVF does not meet the criteria for maturation, or displays signs of early failure, referral for duplex ultrasound and/or fistulogram is needed
5. BAM may have a role to improve maturation
6. Endovascular approach, including angioplasty, stenting, thrombectomy, thrombolysis, venous branch ligation may be utilized as appropriate
7. Open techniques such as fistula superficialization, interposition vein grafts, transposition or even ligation of branches may be needed for specific problems

A Personal View of the Data

AVF dysfunction is a major burden to our patients and society. Identifying patients that may require closer surveillance postoperatively is critical. Taking care of these patients requires aggressive preoperative, intraoperative and postoperative assessment to understand features that may help us improve maturation rates and durability. While there is ample data from retrospective studies, case reports, and observational prospective cohorts, there is limited to no data assessing results in randomized clinical trials to truly achieve the best outcomes. Hence, our knowledge is limited to the current published research, presentations at major meetings, as well as peer-reviewed guidelines. Nevertheless, understanding the pathophysiology of failure to mature AVFs and utilizing appropriate strategies that propose timely referral, selection of vessels for creation of AVF, followed by aggressive monitoring utilizing endovascular options first, may improve our patients' outcomes.

Recommendations

- Smoking cessation (**strong recommendation, low quality evidence**)
- Timely referral for care and access (**strong recommendation, very low quality evidence**)
- Preoperative ultrasound imaging (**strong recommendation, very low quality evidence**)
- Use arteries with diameter >2 mm (**strong recommendation, very low quality evidence**)
- Use veins with diameter >2.5 mm (**strong recommendation, very low quality evidence**)
- Distal site of non-dominant upper extremity as first access choice (**strong recommendation, very low quality evidence**)

- Surgeon follow-up within 4 weeks (**strong recommendation, very low quality evidence**)
- End to side anastomosis (moderate recommendation, very low quality data)
- Reassess AVF if intraoperative blood flow <120 ml/min (**moderate recommendation, very low quality data**)
- AVF surveillance (**moderate recommendation, very low quality evidence**)
- Endovascular or open treatment (**moderate recommendation, very low quality evidence**)
- BAM to enhance maturation (**moderate recommendation, very low quality evidence**)

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Part VI
Perio-operative Management

Chapter 40
In Patients with Cardiovascular Disease, Do Statins Alone, or in Combination with Other Medications Improve Mortality?

Bjoern D. Suckow and Philip P. Goodney

Abstract Patients with peripheral arterial disease are at increased risk of cardiovascular morbidity and mortality and dyslipidemia is a key factor in the formation of peripheral arterial disease. Statin therapy not only effectively lowers serum cholesterol, but also exhibits pleiotropic effects that reduce vascular inflammation and results in plaque stabilization, halting and potentially reversing the progression of peripheral arterial disease. Many hypothesize that satin therapy can improve survival in patients who undergo vascular surgery. While a definitive pathway remains elusive, several studies demonstrate a clear association between statin therapy and improved survival among these patients. Several data suggest that the addition of anti-platelet therapy to statin therapy may confer additional survival benefit. It is less clear, however, whether other medical therapy, such as angiotensin-converting enzyme inhibitors, calcium channel blockers or fenobibrate provides any additive survival benefit in addition to statins.

Keywords Statin • Peripheral arterial disease • Mortality • Vascular surgery • Combination therapy

Introduction

Atherogenic dyslipidemia, characterized by elevated LDL cholesterol, low HDL cholesterol and high triglyceride levels, is a major risk factor for cardiovascular disease and is responsible for more than 50 % of population-attributable vascular risk [1]. Resultantly, patients with peripheral arterial disease (PAD) who undergo revascularization procedures face higher comorbid event rates and have an elevated mortality risk than those without dyslipidemia. Hydroxymethylglutaryl-CoA reductase inhibitors (statins) lower primarily LDL cholesterol levels by inhibiting de-novo

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cholesterol synthesis. In addition to lowering serum cholesterol levels, statin therapy has been shown to improve endothelial function, reduce systemic vascular inflammation, stabilize atherosclerotic plaque and reduce thrombogenic response [2]. Therefore, statins appear to be associated with a significant reduction in cardiovascular morbidity and mortality [3–5].

However, a meta-analysis of 14 randomized studies on statin therapy in patients with cardiovascular disease found that even those treated with statins retain a significant 14 % risk of experiencing a major vascular event (myocardial infarction – MI, stroke or coronary death) over 5 years [3]. This finding was corroborated by several other investigations, which noted that, depending on the cardiovascular risk profile, patients who effectively lower their cholesterol with statins still have a 10–29 % risk of suffering a major cardiovascular event [5–7]. Therefore, the question arises whether concomitant medical therapy in combination with statin therapy may confer additional survival benefit in patients with cardiovascular disease who require vascular surgery. Anti-platelet therapy, anticoagulants, anti-hypertensive therapy and other cholesterol-lowering agents, such as fenofibrate, alone have a beneficial effect on cardiovascular health. This chapter will summarize the positive associations between statin therapy and survival in vascular surgery patients while also addressing the potential benefit of additional medical therapy to statin therapy on major cardiovascular event rates.

Search Strategy

A literature search of English language publications from 2000 to 2014 was used to identify published data on the association between statin therapy alone, or in combination with additional medical therapy, and mortality in patients with peripheral arterial disease, specifically those who require vascular surgery. This was done using the PICO outline delineated in Table 40.1. The databases searched were PubMed, the Library of Congress, LISTA, Web of Science Core Collection, and Cochrane Evidence Based Medicine. Search terms included “statin”, “statin therapy”, “mortality”, “death”, “survival”, “vascular disease”, “vascular surgery”, “cardiovascular disease”, “carotid disease/stenosis”, “abdominal aortic aneurysm”, “peripheral vascular disease”, “anti-platelet”, “anti-hypertensive”, “anticoagulant”, “cholesterol lowering”, “fibrate”, “combination medical therapy”, and “optimal medical management”. Articles were excluded if they addressed patients who underwent non-vascular surgery. The data were assessed using the GRADE system.

Table 40.1 PICO table for statin and medical therapy in peripheral artery disease patients

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Patients with peripheral arterial disease who require vascular surgery	Statin therapy plus additional medical therapy	Statin therapy alone	Mortality

Table 40.2 Overview of key studies on the impact of statin therapy alone on survival in vascular surgery patients

Type of vascular surgery or intervention	Study	Main finding of statin therapy	Limitation
Carotid disease	Wallaert et al.	Better 5-year survival	Observational
	Larsen et al.	50 % reduction in risk of death	Varied follow-up
	Brott et al.	CREST-2 currently accruing patients	Awaiting results
Abdominal aortic aneurysm	Stoner et al.	Better survival, fewer costs	Single center
	Twine et al.	Meta analysis: better survival with statins; effect on AAA expansion less clear	Heterogeneity between studies
Peripheral arterial disease	Conte et al.	30 % reduction in mortality	Narrow population
	Suckow et al.	30 % reduction in mortality	Observational
	Ward et al.	50 % reduction in 5-year mortality	Retrospective
	Farber/Menard et al.	BEST currently accruing patients	Awaiting results

Results

Statin Therapy Alone

There do not exist any trials in which patients who undergo major vascular surgery are randomized to statin therapy versus no statin therapy. However, ample evidence exists from randomized trials that show a protective benefit from statin therapy in patients with cardiovascular disease. The JUPITER trial [8] and the Heart Protection Study [9] among others have clearly delineated a survival benefit in patients with coronary disease. Given the similar pathophysiologic role of atherosclerosis in coronary disease and PAD, modern vascular surgery treatment guidelines have adopted a recommendation for vascular surgery patients to be taking statin therapy.

At the time of NASCET, ACAS and ECST for carotid stenosis, the best medical therapy arms did not include statin therapy [10–12]. Since then, no randomized trial on carotid disease has vetted best medical therapy including statins versus surgical treatment. Multiple observational cohort and database studies, however, suggest that statin use has a protective effect on mortality in patients with carotid stenosis (Table 40.2). For example, the Vascular Study Group of New England noted that statin use was clearly associated with improved 5-year survival in patients who underwent carotid endarterectomy for asymptomatic carotid stenosis [13]. A series by Larsen et al. followed 230 patients with carotid stenosis who did not undergo repair over an average of 13 years. They noted that those on statin therapy had a 50 % relative risk reduction of death compared to those not on statins [14]. The

CREST-2 trial is designed to provide clearer randomized data on the association between statin therapy, additional medical therapy and survival in patients with carotid disease.

In patients with abdominal aortic aneurysm (AAA), similar survival trends are noted. For example, Stoner et al. found that in a series of 401 patients who underwent open or endovascular aneurysm repair, statin use was significantly linked with improved survival and afforded a direct cost savings of about $3,500 per patient [15]. A meta-analysis of 6 studies found that in patients with AAA, statin use was not associated with improved 30-day mortality (OR 0.22, $p=0.25$). However, long-term mortality was significantly less in those AAA patients on statins at 1 year (OR 0.44, $p=0.003$), 2 years (OR 0.43, $p=0.002$), and 5 years after repair (OR 0.57, $p<0.001$) [16]. For patients under surveillance for small AAAs, the data on statin therapy is less clear. One meta-analysis from 2010 reviewing five studies suggests that AAA sac expansion rates are slower for patients on statin therapy than those who are not [17]. However, a more recent meta-analysis from 2014 found that between eight studies, statin use was not associated with AAA sac expansion [18]. No direct data exist on the impact of statin therapy on mortality in AAA patients under surveillance for small aneurysms.

The PREVENT III trial is one of the few randomized studies on patients with PAD and critical limb ischemia [19]. While the use of statin therapy was not randomized in this cohort, a post-hoc analysis demonstrated statin use as an independent predictor of 1-year survival associated with a 30% risk reduction in mortality [20]. This finding is mirrored in our own work, where we found that prolonged post-operative statin use was associated with a reduction in mortality (HR 0.7, $p=0.03$) as far as 5 years after lower extremity bypass surgery for critical limb ischemia [21]. Notably, in both the PREVENT III cohort and our patient cohort from New England, statin therapy was not linked to a change in bypass graft patency or major limb amputation. A retrospective review by Ward et al. similarly described statin use as an independent predictor of improved survival 5 years after lower extremity bypass surgery (OR 0.5, $p=0.004$) [22]. Other series by Aiello et al. and Dosluoglu et al. describe a significant association between statin therapy and improved 2- or 5-year survival in patients who underwent lower extremity revascularization procedures [23, 24]. The BEST-CLI trial is just beginning to enroll and may be able to offer further insight into the impact of statin therapy on patient and graft-specific outcomes in those who undergo revascularization for critical limb ischemia. As with CREST-2, this national trial will help to define new practice patterns when these exciting data have been captured and reported back to cardiovascular physicians worldwide.

Statin Therapy in Combination with Other Medical Therapy

No randomized data exists that investigates the impact of statin therapy in combination with other medical therapy on survival in patients who undergo vascular surgery. One study of a large prospectively collected quality improvement database in

Table 40.3 Overview of studies investigating combination therapy of statin plus other medications

Medication in addition to statin	Study	Main finding of combination therapy	Notes about the effect
Antiplatelet agents	DeMartino et al.	25 % reduction in mortality	Dose–response evident with multiple agents
Antiplatelet agents and ACE inhibitors	Creager et al.	35 % reduction in mortality	Need at least two of three agents (statin, ACE inhibitor, antiplatelet) to see effect
ACE inhibitors	Koh et al.	18 % reduction in CRP	No effect of either agent alone
	Athyros et al.	35 % reduction in MACE	Post-hoc analysis of secondary endpoint

CRP C-reactive protein, *MACE* major adverse cardiac event (myocardial infarction or cardiovascular death)

patients undergoing vascular surgery compared the use of statins and anti-platelet therapy [25]. Among a cohort of nearly 15,000 patients who underwent peripheral revascularization, abdominal aortic aneurysm repair or carotid revascularization, the use of both statin and antiplatelet therapy was significantly associated with the best 5-year survival (79 %). Patients only on a statin or only on an anti-platelet agent had lower 5-year survival (74 % and 72 %, respectively) compared to only 61 % survival for patients on neither agent (log rank p-value < 0.001). In multivariable analysis, the only predictor for improved survival was the use of both statin and anti-platelet agent (OR 0.75, p = 0.009, Table 40.3). Creager et al. analyzed 5 years of data from the National Health and Nutrition Examination Survey on 7,458 patients with PAD as defined by an ankle-brachial index less than 0.9. They assessed the patients for use of statins, anti-platelet therapy and angiotensin-converting enzyme inhibitors (ACEI). In multivariable analysis, they found that patients with PAD did not demonstrate a statistically significant mortality benefit unless they were taking two or more of these medical therapies (HR 0.35, p = 0.02).

A few studies have examined the additional benefit of various medical treatments to statins in patients with cardiovascular disease in general. Koh and colleagues have suggested through their work that statins and ACEI may have a synergistic effect. In their analyses of patients with cardiovascular disease, they noted that both agents together reduce serum CRP levels by 18 % while either agent alone had no effect on CRP levels [26]. Further, in combination, the two agents had a greater reduction in measured tissue factor than either alone [27].

In real-world application, however, the synergistic effect of statins and ACEI may be less pronounced. The GREACE trial was a randomized prospective study investigating the effect of atorvastatin on coronary heart disease. In one post-hoc analysis, the investigators compared the synergistic effect of statins and ACEI. Among the 1,600 patients followed for 3 years, the authors found a nearly statistically significant 34 % relative risk reduction (p = 0.08) in the combined endpoint of cardiovascular death and MI for those on both statins and ACEI compared

to those on statins alone [28]. The JCAD study is a Japanese cohort of patients with cardiovascular disease identified on angiography that has been followed prospectively [29]. One post-hoc analysis of this 13,812 patient cohort compared statin and ACEI use among them. Assessing for a broad outcome of all-cause mortality, MI or stroke, they found a significant reduction in outcome at 3 years for patients on both statin and ACEI compared to neither (HR 0.78, p = 0.03). However, there was no significant difference in outcome when comparing patients on a statin with those on a statin and ACEI (overall event rate 7.5 % versus 8 %, p = NS) [30]. The SCAT trial was a prospective, randomized Canadian trial in which 460 patients with coronary disease were treated with either statin, ACEI, neither or both. Mortality rates for those on a statin only were similar to those on both agents (5 % vs. 6 %, p = NS) [31].

Other therapeutics that have been compared with statin use include calcium channel blockers (CCB) and fenofibrate. Kohro et al. performed a propensity-matched analysis of patients on CCB or statins on the JCAD cohort mentioned above. They found no difference in mortality or cardiovascular event rates between patients on a statin or on both a statin and a CCB [32]. A meta-analysis investigating the use of atorvastatin and fenofibrate across 14 studies postulates that these agents may in synergy have a greater lipid-reducing ability and therefore may decrease cardiovascular event rates from 22 to 5 % over 10 years [2]. However, no data regarding mortality is presented. Larger comparative series and randomized studies are necessary to assess the additive benefit of anti-platelet, ACEI, CCB and fenofibrate to statin therapy in vascular surgery patients. In combination, these will ideally define what is best optimal medical therapy for patients with cardiovascular disease who require operative intervention for PAD.

Recommendations

Atherosclerotic disease is a major risk factor for cardiovascular mortality in patients who undergo vascular surgery while statin therapy has direct and pleiotropic effects that reduce the risk of mortality, even in this high-risk patient cohort. In multiple studies, across multiple procedures and settings, high-quality data demonstrates a survival benefit associated with statin use in patients with cardiovascular disease. Further high and moderate quality data shows that in patients with cardiovascular disease who undergo vascular surgery, statin use is associated with improved long-term survival.

We believe this current body of evidence supports that all patients with cardiovascular disease who undergo major vascular surgery should be on statin therapy. Moderate quality data suggests that the addition of anti-platelet therapy to statin therapy may provide additional survival benefit. Our recommendation regarding the addition of anti-platelet therapy to statin therapy for the purpose of improving survival alone is somewhat less enthusiastic, not because the hypothesis for a benefit of survival is not plausible, but rather because the quality of evidence is moderate at

best. Finally there is low quality data regarding the use of ACEI and only very low quality data regarding the use of CCB or fenofibrate in combination with statins in cardiovascular patients. Therefore, based on this weak foundation of evidence, we cannot recommend using these medications in addition to statins specifically for the purpose of achieving a survival benefit.

A Personal View of the Data

Patients in need of major vascular surgery are among the highest-risk candidates due to a multiplicity of factors, including age, comorbid conditions and the nature of the operations required. Given the ubiquitous underlying pathologic process of atherosclerosis, these patients have several linked and competing causes of cardiovascular morbidity and mortality, such as stroke, MI, and PAD. We feel that statin therapy reduces vascular inflammation, stabilizes atherosclerotic plaque and therefore directly lowers the mortality risk that derives from these heterogeneous conditions. Unless there exists a direct contra-indication, we recommend that all patients with PAD should be on statin therapy. Similarly, the data on anti-platelet therapy in preventing cardiovascular mortality is sound. While it has not been investigated in depth as an adjunct to statins, we feel that the data on anti-platelet therapy alone is of good quality and therefore recommend that all patients with cardiovascular disease take anti-platelet therapy unless contra-indicated. Other adjunctive medical therapies and their protective effects on cardiovascular death in addition to statin therapy will require further investigative efforts.

Recommendations

- For patients with cardiovascular disease who require major vascular surgery, we recommend the routine use of statin therapy (**evidence quality high; strong recommendation**).
- We recommend the additional use of anti-platelet therapy in combination with statin therapy (**evidence quality moderate; weak recommendation**).
- ACE-inhibitors, calcium channel blockers or fenofibrate may confer an additive protective effect on survival in addition to statin therapy (**evidence quality very low; weak recommendation**).

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Chapter 41
In Patients Who Have Undergone a Lower Extremity Bypass for PAD, Does Dual Anti-platelet Therapy Improve Outcomes?

William Bevilacqua and Christopher L. Skelly

Abstract Failure of lower extremity bypass for patients with lower extremity peripheral arterial disease in the first 30 days is felt to be a technical complication and results in occlusion of the bypass. Thrombosis can result in devastating complications such as limb loss. In order to prevent these complications, surgeons will frequently treat patients with dual anti-platelet therapy in the perioperative period. The evidence behind such a strategy of dual-antiplatelet therapy in the post-operative period has yet to define what the best practices are. Very few head to head randomized controlled trials comparing dual anti-platelet therapy to monotherapy exist. However, data can be gathered from these and other reliable sources to begin to create a paradigm for optimal anti-platelet therapy following lower extremity bypass. The use of antiplatelet monotherapy with aspirin for lower extremity vein bypasses is the most widely accepted strategy at present. Based on current literature, there is not enough evidence to support routine use of dual anti-platelet therapy for lower extremity vein bypass. Dual anti-platelet therapy should be considered for prosthetic lower extremity bypass based on current data. Dual anti-platelet therapy post-operatively is safe and does not result in an increased risk of bleeding. Optimizing lower extremity bypass patency rates can be challenging but ideal post-operative anti-platelet strategies have emerged.

Keywords Dual anti-platelet therapy • Lower extremity bypass • Aspirin • Clopidogrel • Medical therapy

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Introduction

Peripheral arterial disease affects approximately 8.5 million Americans, with a higher prevalence in the elderly, non-Hispanic blacks, and women [1]. This disease process often leads to severe limb ischemia, defined as presence of tissue loss and/or rest pain in 50–100 per 100,000 [2]. Morbidity, mortality and consumption of a great deal of social and health care resources are attributed to this disease process annually. A combination of an aging population, continued tobacco consumption, and diabetes has resulted in a need for treatment of critical limb ischemia. Lower extremity arterial bypass using vein or prosthetic graft like PTFE are used commonly in the treatment of severe limb ischemia. Ten to fifteen percentage of patients diagnosed with peripheral arterial disease will go on to receive bypass grafting. Despite rigorous surviellance, upto 40% of peripheral bypasses will fail at 1 year [3].

Improving patency rates of lower extremity bypass would lead to decreased rates of complications and re-intervention. Dual anti-platelet therapy (DAPT) to improve patency, has been reported in the coronary literature, but is not as well reported in the PAD literature. Furthermore, the antiplatelet prescribing practices of vascular surgeons after lower extremity procedures are highly variable [4, 5]. In this chapter we review the relavent literature to answer the question: in patients who have undergone a lower extremity bypass for PAD, does dual anti-platelet therapy improve outcomes?

Search Strategy

A search of the English literature was used to identify published data on antiplatelet therapy after lower extremity peripheral vascular intervention using the PICO outline (Table 41.1) was performed. Pubmed and Cochrane Evidence Based Medicine databases were queried and limited to 2000–2015. Terms used in this search were "Antiplatelet" OR "Antiplatelet Therapy" AND "peripheral vascular" or "peripheral vascular procedures". Articles were excluded if they did not specifically address surgical intervention. One prospective randomized placebo controlled study [6] and two meta-analysis [7, 8] pertaining to the management of post procedure anti-platelet management were included (Table 41.2). The meta-analyses included many of the original studies from the 1980s and 1990s. Data were classified using the GRADE system. Additional articles cited were for historic and background information.

Table 41.1 PICO table for intervention for antiplatelet therapy in patients undergoing lower extremity bypass

P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)
Patients who have undergone lower extremity bypass	Single agent Anti-thrombotic pharmacotherapy	Dual agent anti-thrombotic pharmacotherapy	Amputation Free Survival

Table 41.2 Summary of publications for dual anti-platelet therapy in lower extremity bypass

	P (Patients)	I (Intervention)	C (Comparator)	O (Outcomes)	
Author (year)	Patients who have undergone lower extremity bypass	Single agent Anti-thrombotic pharmacotherapy	Dual agent anti-thrombotic pharmacotherapy	Graft patency	Quality of evidence
Belch [6] (CASPAR, 2011)	851	ASA + placebo 426	ASA+ clopidogrel 425	No difference	Strong
Collins [7] Meta-analysis (2004)	2690	Antiplatelet	None or placebo	Favors antiplatelet	Meta-analysis (moderate)
Bedenis [8] (2015)	5683	ASA, or ASA/ dipyridamole	Nothing or placebo (6 studies) Pentoxifylline (2 studies) Indobufen (1 study) Prostaglandin E1 (1 study) (1 study) Naftidrofuryl (1 study) Clopidogrel and ASA (1 study)	Could not be evaluated	Meta-analysis (moderate)

Results

Secondary interventions for graft failures have continued to plague patients undergoing lower extremity bypass surgery. Bypass grafts can undergo early or late thrombosis, with early graft thrombosis being defined as less than 30 days and late thrombosis as failures that occur after this point. Most authors point to technical failure as the root cause of early graft thrombosis and that prevention of this failure is based on proper surgical technique and not pharmacological intervention as the key to avoidance of early graft failure. To highlight the need for increasing the focus on maintaining patency and improve failure rate beyond technique, we briefly describe two high quality trials. Primary patency rate in the Project of Ex-Vivo vein graft Engineering via Transfection III (PREVENT III) was a randomized, double blinded, multicenter trial attempting to evaluate the prevention of graft failure pharmacologically with novel agent edofiligide. Primary patency rate in the PREVENT III trial was approximately 60% at 1 year for all patients [3]. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) study was also a multicenter,

randomized control trial attempting to ascertain whether an endovascular approach or surgical approach would yield better results. Amputation-free survival was 68 % at 1 year and at a re-intervention rate of only 18 % for those randomized to surgical bypass for lower extremity revascularization [2]. These studies highlight the fact that despite technical success surgical revascularization continues to require intervention to prevent graft failure. There remains a significant need to determine strategies to reduce lower extremity bypass failure. In this chapter we will focus on the adjunctive use of anti-platelet therapy for both autologous and prosthetic bypass grafting.

Antiplatelet Agents

Several pharmacologic agents have been used to help increase lower extremity arterial reconstruction patency. Antithrombotic therapy can be defined as any form of antithrombotic treatment including antiplatelet or anticoagulant, with the focus on antiplatelet therapy. Anticoagulant therapy was not in the scope of this article. A recent meta-analysis demonstrated that anti-platelet agent use results in improved autologous and prosthetic graft patency at both 1 and 2 years [7]. Acetylsalicylic acid (ASA) is the most commonly used anti-platelet agent in the world due to its safety profile and low cost. Aspirin inhibits platelet cyclooxygenase-1 in an irreversible manner. This subsequently blocks the production of thromboxane A2 and prevents further platelet recruitment and activation. In higher doses, aspirin can inhibit COX 2 as well. Patients with vascular disease benefit from aspirin with a 25 % reduction in risk for cardiovascular death, stroke, or myocardial infarction [9, 10]. Low dose aspirin (75–150 mg) is proven to be as effective as higher doses with lower risk of side effects. Gastric ulcer disease is the most common side effect and is dose dependent. Major bleeding risk for patients taking aspirin is 1–3 % annually. ASA allergy causing bronchospasm has been reported in up to 0.3 % of patients and should be avoided in this population. There is both a clinical and biochemical phenomenon known as aspirin resistance but the clinical applications are not useful as testing for the biochemical condition is not standardized. ASA may be continued up until the time of surgery in patients who are at high risk for cardiovascular events as are most patients requiring vascular surgery [10].

Clopidogrel is the most commonly used of the P2Y12 antagonists that selectively block an ADP receptor on platelets. This blocks the effect of platelet recruitment and activation that aspirin produces but through a different mechanism. This group also includes, ticlopidine, and prasurgel and are known collectively as thienopyridines. The effect of thienopyridines on blocking the P2Y12 receptor is also irreversible and lasts for the life of the platelet. These medications are metabolized in the liver by cytochrome p450 enzyme system. As these drugs require metabolic activation, drug-drug interactions and loss of these enzymes may delay or reduce drug activation and reduce the effect of the drug. Prasurgel is converted to active form most efficiently and therefore has the most rapid onset of action. Ticagrelor inhibits P2Y12 but does not require metabolic activation, giving it a more rapid onset of

action and is reversible meaning that the effect is lost more rapidly as well. Clopidogrel has been shown to be marginally more effective than aspirin in terms of reducing ischemic cardiovascular events [10]. The delay in onset of action means that loading doses must be given for the thienopyridines. Bleeding comprises the major side effect of clopidogrel, prasurgel, and ticagrelor, which can also cause mild dyspnea and asymptomatic bradycardia. Resistance to clopidogrel is more common and more significant clinically than aspirin resistance. Up to a third of patients may exhibit some form of clopidogrel resistance through loss of CYP2C19 alleles. Proton pump inhibitors, specifically omeprazole may also lead to a decreased effectiveness of clopidogrel in terms of preventing ADP induced platelet aggregation. Patients undergoing surgery should stop clopidogrel or prasurgel 7–10 days prior to surgery and ticagrelor 5 days prior to surgery due to higher risk of bleeding than with aspirin. Elective surgery should be delayed if recent coronary stenting prevents clopidogrel from being discontinued [10].

Dipyridamole has been used in combination with aspirin (aggrenox) due to its relatively weak antiplatelet effect as an independent medication. It is used mostly for patients who are being treated for transient ischemic attacks. Dipyridamole blocks phosphodiesterase which then prevents breakdown of cyclic AMP which reduces platelet activation. Side effects include vasodilatation which can be deleterious in patients with pre-existing cardiac disease. Aggrenox produced similar rates of stroke reduction as clopidogrel but had increased rates of bleeding complication. Onset of action is rapid and half life is short for dipyrimadole alone but aspirin component means that platelet inhibition will last for approximately 7–10 days [10].

Clinical Trials

The use of antiplatelet therapy in the treatment of patients who have undergone bypass has not been standardized as demonstrated in two large prospective trials. The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial reported results of an angioplasty or surgery first strategy. Of all patients randomized to the bypass first strategy, 62 % were receiving an antiplatelet agent. The data for this study was accrued in the United Kingdom from 1999 to 2004 [2]. Amputation free survival without secondary intervention at 12 months follow up for the surgery first group was noted to be 56 % during the course of the trial. The study was not designed to test whether anti-platelet therapy alone had an impact on graft patency. The PREVENT III trial was a randomized, double blinded study designed to examine whether the novel agent edifoligide would prevent vein graft failure in patients undergoing infra-inguinal bypass. The study randomized 1404 patients in North America from 2001 to 2003. Sixty seven percent of all patients were noted to be on anti-platelet therapy at the time of the lower extremity bypass (50 % on ASA and 17 % on thienopyridine). At time of discharge, the number of patients on anti-platelet therapy had increased to 80 %. The effect this had on patency is unclear from the trial data. Patients treated in the university hospital setting, those with CAD, and

those with hyperlipidemia were more likely to have received anti-platelet therapy at time of discharge [2]. Antiplatelet agent use in patients with peripheral arterial disease continues to increase even prior to lower extremity bypass. Simons, et al. demonstrated that approximately 82–84 % of patients undergoing lower extremity bypass in New England from 2003 to 2009 were on antiplatelet agent at the time of surgery [11].

A meta-analysis by Collins in 2004 encompasses a significant body of literature from the 1980s and 1990s. In this review, aspirin and dipyridamole (separately or combined) were the most common agents used [7]. There was a demonstration of beneficial effects of antiplatelet treatment with an overall risk of graft occlusion in the treated group of half that of the placebo or control group (odds ratio [OR] = 0.46, 95 % confidence interval [CI]:0.32–0.67). In the saphenous groups, the odds of occlusion were slightly higher (OR = 0.55; 95 % CI: 0.41–0.73). In the prosthetic grafts the odds of occlusion in the treatment group was 0.25 suggesting the importance of antiplatelet therapy in this cohort. There was an overall reduction in all-cause mortality with the use of antiplatelet therapy (OR = 0.7; 95 % CI: 0.51–0.95) following bypass operation. These data demonstrated the benefit of antiplatelet therapy to both graft patency as well as overall subject mortality. There was a trend towards a reduction in lower extremity amputation, but there were limited studies including this as an endpoint [7]. This data corroborated The Antiplatelet Trialists' Collaboration which demonstrated a 43 % ±8 % reduction in occlusion of grafts or native vessels in patients receiving antiplatelet therapy versus control [12].

Despite this demonstration of improved patency using antiplatelet therapy, lower extremity bypass graft failure rate remains high and a target for improved outcomes. The Clopidogrel and Acetylsalicylic acid (ASA) in Bypass Surgery for Peripheral Arterial Disease (CASPAR) trial sought to determine if dual antiplatelet therapy was superior to ASA alone in patients undergoing below-knee bypass grafting [6]. The study was designed as a prospective, multicenter, randomized, double-blind, placebo-controlled trial. Eight hundred fifty one patients in Europe and Australia between ages 40–80 were randomized 2–4 days post-operatively to either (1) continue baseline ASA (75–100 mg daily) alone or (2) start clopidogrel (75 mg daily) (DAPT) as well post-operatively if unilateral bypasses with distal anastomosis below the knee were patent. Exclusion criteria included other simultaneous bypass grafting, high risk for peri-operative bleeding, and current or anticipated need for warfarin. Patients were allowed to be included with short duration of NSAID use and LMWH use as needed at prophylactic dose as indicated for DVT chemoprophylaxis. Follow up was to be no less than 6 months and no greater than 24 months. The study participants were stratified according to graft type, all synthetic and all vein grafts. Primary endpoints were the first occurrence of: occlusion of the bypass graft; or any surgical or endovascular procedure on the bypass graft; or amputation above the ankle; or death. The primary safety endpoint was severe bleeding defined according to the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded Coronary arteries (GUSTO) classification [13]. Follow up was performed at 1 month and then every 6 months until 24 months of follow-up had been completed. This was accomplished with physical exam, duplex scanning, ankle-brachial

indices, and angiography as indicated. Patient compliance was assessed at each subsequent follow up visit.

The CASPAR study provided strong evidence which demonstrated no difference in primary endpoints of occlusion, revascularization, amputation or death for patients when evaluated as whole for those patients on DAPT compared to ASA alone [6]. The authors included results of prospectively planned subgroup analysis that again demonstrated no difference in adverse event rates for those undergoing lower extremity bypass graft with autologous conduit that were randomized to ASA alone or to clopidogrel and ASA. However, the authors did find a significant reduction in graft occlusions and amputations for those patients with prosthetic grafts on DAPT as opposed to those on ASA alone. Forty seven percent of patients on ASA alone suffered graft occlusions whereas only 32 % in the dual antiplatelet group had the same complication at 12 months. The number of patients who underwent amputation above the ankle was 19.2 % in patients with synthetic graft who received ASA alone compared to 9.4 % in those who received clopidogrel + ASA. There was no difference in mortality rates between patients who on ASA alone and those on dual antiplatelet therapies that underwent lower extremity bypass with synthetic grafts. Safety endpoints were defined as rates of post-operative bleeding. Almost 5 % of patients in the dual therapy group had to discontinue the medication due to bleeding compared to less than 1 % in the ASA only group [6]. For patients undergoing autologous venous bypass, mild and moderate bleeding was noted to be significantly higher in the ASA + clopidogrel patients than those in the ASA alone group. This difference was not seen in patients undergoing prosthetic lower extremity bypass grafting. The authors conclude that DAPT may allow prosthetic infra-inguinal arterial bypass to achieve equivalence to that of lower extremity bypass with venous conduit.

In a commentary to the CASPAR results, it was pointed out that the study does not contain the data to support this conclusion [14]. The more logical conclusion to reach would be that dual antiplatelet therapy may be of benefit and should be considered for patients undergoing below knee arterial bypass with synthetic conduit where it would not be indicated for those patients undergoing similar bypasses with venous conduits. The safety data demonstrated in the CASPAR trial would also support this conclusion to be safe as well. Clopidogrel whether combined with ASA or alone has been shown to be safe to continue peri-operatively for peripheral arterial surgery [4, 15]. The CASPAR trial was not designed specifically to examine whether or not dual antiplatelet therapy would be of benefit for patients undergoing prosthetic bypass grafting as this was a secondary analysis. Further randomized trials would be needed to duplicate these results in order to obtain strong evidence recommending dual antiplatelet is of clinical benefit for these patients. Other criticisms of the CASPAR data include the fact that a significantly lower proportion of bypasses with tibial or pedal targets as compared to the North American PREVENT III trial demonstrating that this data may not be as applicable in a North American clinical practice [14]. Also less than half of the patients enrolled in the CASPAR trial were on a statin therapy at the time of lower extremity bypass.

Finally, we reviewed a recent Cochrane meta-analysis that was the update of older data analysis and included 16 studies of 5683 patients [8]. There were nine

different treatment groups evaluated with the most robust conclusions based on ASA or ASA and dipyridamole versus placebo or nothing. The data continued to demonstrate improved graft patency in the ASA or ASA and dipyridamole treatment groups (OR = 0.42; 95 % CI 0.22–0.83; P = 0.01; 952 participants). There was no difference in side effects, including bleeding, gastrointestinal, and wound or graft infection. Contrary to the analysis performed by Collins [7], this meta-analysis did not demonstrate the all-cause mortality benefit to anti-platelet therapy. The difference in mortality outcome may be representing a selection bias in the articles reviewed by each. Data pertaining to clopidogrel was reflective of the single CASPAR study [6]. Finally, data comparing asprin to prostaglandin E1, naftidrofuryl, or pentoxifylline did not include enough data to draw meaningful conclusions.

A Personal View of the Data

Recommendations

- For patients undergoing infra-inguinal bypass surgery, recommend the use of anti-platelet agent to improve patency (either ASA or ASA and dipyridamole) (**Evidence quality moderate; Strength of recommendation: strong**)
- For patients undergoing infra-inguinal bypass surgery with prosthetic graft, recommend dual-antiplatelet(ASA and dipyridamole or clopidogrel) (**Evidence quality moderate; Strength of recommendation: strong**)

These recommendations summarize the available literature in a very concise and effective way. The literature to date has not shown dual anti-platelet therapy to be more advantageous for patients who have undergone lower extremity arterial bypass except in the case of synthetic conduits that have a distal target vessel below the knee. The available evidence has shown both single and dual anti-platelet therapy to be safe in the peripheral arterial disease population in terms of major bleeding risk.

In practice we approach each patient on an individualized basis realizing that benefits of the operation can be lessened by an increased risk of post-operative outcomes. In patients who are to undergo an infra-inguinal bypass with autologous vein, we will continue aspirin for these patients. Frequently we are forced to intervene on patients who have had a recent coronary intervention and require DAPT. In these cases we have found no significant increase in significant bleeding [4, 15, 16]. In patients who are to undergo a prosthetic bypass, we will typically discharge the patient on DAPT regiment of aspirin and clopidogrel unless the patient has had a bleeding complication. We do not use dipyridamole because the majority of our patients are on multiple medications and older than 65. Dipyridamole can cause orthostatic hypotension in the elderly [17] and aspirin was effective alone as well [8]. The topic of anticoagulant therapy was not in the scope of this chapter. However, in patients who are on anticoagulation who require lower extremity bypass we will

typically hold the anticoagulation in the peri-operative period and ensure that the patient is on a single anti-platelet agent specifically aspirin. On discharge we would resume the anticoagulation and continue the aspirin. We try to avoid the combination of DAPT and anticoagulation.

There is also mounting evidence that continuing these anti-platelet agents through the peri-operative period for patients undergoing peripheral arterial surgery is also safe [4, 11, 15, 18]. Although dual anti-platelet therapy is not indicated for the majority of infra-inguinal bypass surgery, ensuring lower extremity bypass patients adhere to a strict regimen of an anti-platelet agent and a statin seems to be the most effective course for effective outcomes in PAD patients [19]. Major studies examining the medical therapy and outcomes for patients undergoing lower extremity bypass have yet to achieve this strict adherence to aspirin and statin therapy. Therefore, future studies must endeavor to achieve this in order to allow a more effective review of the current therapy for patients with peripheral arterial disease undergoing bypass surgery.

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Chapter 42
In Patients Undergoing Vascular Surgery, Does Preoperative Coronary Revascularization Reduce the Risk of Myocardial Infarction and Death?

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Abstract Tens of millions of surgical procedures are performed annually in the United States and the world over. A significant proportion of these procedures are associated with perioperative adverse cardiac events and these in turn, increase cardiovascular morbidity and mortality. Perioperative myocardial infarction, variably defined in the historical literature, may in fact occur in greater than 1 in 10 post-surgical patients by current definitions. Preoperative risk assessment may be carried out using a variety of validated risk prognostication models. While guideline-driven medical therapies form the foundation of risk reduction in patients undergoing non-cardiac surgery, high-risk findings on non-invasive assessment may necessitate coronary angiography. Whereas coronary revascularization is widely accepted as the standard of care in preoperative patients with acute coronary syndromes or acute myocardial infarction, the practice of routine preoperative coronary revascularization for the purpose of cardiac risk reduction, is neither supported by the available trial data nor endorsed by the U.S. and European clinical practice guidelines, even in patients undergoing high risk noncardiac surgeries. Despite this, contemporary registry data bears out the wide usage of preoperative coronary revascularization. Small European studies have hinted at benefit associated with a strategy of routine coronary angiography and when necessary, percutaneous revascularization, in high-risk patients pending vascular operations. However these reports have yet to be confirmed in large-scale, randomized, multicenter trials. Unanswered questions remain regarding the optimal duration of dual antiplatelet therapy and timing of surgery in patients who have had prior percutaneous coronary revascularization.

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Introduction

The rate of major cardiac complications associated with noncardiac surgery ranges from <1 to 4 % in the older published literature, and primarily comprises myocardial ischemia/infarction (MI) with an incidence of 2–4 % and the risk of cardiac death ranging from 0.5 to 1.5 % [1–4]. With the routine use of high sensitivity cardiac biomarkers and shifting patterns of postoperative cardiac surveillance however, recent investigations have suggested that the incidence of cardiac ischemic events, many asymptomatic, may be substantially higher. The Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators studied 15,133 patients, >45 years of age and undergoing noncardiac surgery requiring overnight admission; an elevated (fourth-generation) troponin T value of >0.02 ng/mL within 3 days of surgery, was found in 11.6 % of patients. Importantly, the observed 30-day mortality rate of 1.9 % in this group was substantially higher than in the comparator group with normal troponin T values with stratified increases in mortality seen with troponin levels of ≤0.01, 0.02, 0.03–0.29 and ≥0.30, respectively [5]. The risk of postoperative cardiac events is dependent on numerous clinical factors including inflammation, anemia, coagulopathy, sympathetic nervous system stimulation, preexisting cardiac disease and the magnitude and duration of hemodynamic stress incurred during the perioperative period [6–8]. The type and extent of the surgery being performed are also well-recognized as important determinants of cardiac risk, with vascular surgery patients having among the highest rates of perioperative complications due to common risk factors contributing to both cardiac and vascular disease in general and the presence of concurrent, and often silent, coronary artery disease, specifically [1, 4, 9–11]. Preoperative cardiac risk assessment is vital in evaluating patient risk prior to non-emergent, noncardiac surgery, with the fundamental goal of identifying those patients with underlying structural cardiac disease and/or obstructive coronary artery disease who are likely to be at the highest risk of myocardial infarction and death. Identification of patients at high risk of perioperative cardiac complications may thus allow care providers to modify cardiac risk via pharmacologic optimization and/or coronary revascularization, delay or alteration of the surgical plan or some combination of these strategies [1, 6, 9]. To this end, several prediction models have been developed to prognosticate the risk of major adverse cardiac events (MACE) and provide recommendations for evaluations to further characterize and mitigate this risk. This may involve non-invasive quantification of cardiac structure and performance as well as estimation of ischemic burden, invasive assessment of coronary anatomy and potentially, performance of percutaneous or surgical revascularization prior to the surgery. Over the last three decades, numerous studies have undertaken the challenging task of defining the role of coronary revascularization prior to noncardiac surgery within the larger cardiac

Table 42.1 PICO table of search strategy terms

P (Patients)	I (Intervention)	C (Comparator group)	O (Outcomes measured)
Patients undergoing noncardiac surgery	Preoperative risk assessment to identify those with CAD with coronary angiography and coronary revascularization	No preoperative angiography/coronary revascularization	Perioperative cardiovascular morbidity and mortality

risk reduction strategy. The literature accrued over this period and its application to contemporary practice is discussed below.

Search Strategy

A search of the English language literature was used to identify published data on the perioperative cardiac risk associated with noncardiac surgery and the impact of preoperative coronary angiography and coronary revascularization on cardiac risk, as outlined in PICO format in Table 42.1. Pubmed and Google Scholar databases were queried from 1984 to 2016 using terms "preoperative/perioperative risk assessment," OR "coronary revascularization," AND "noncardiac surgery" or "vascular surgery." Articles were excluded if they did not address pre or perioperative cardiac risk assessment.

Results

Preoperative Risk Stratification

Risk stratification involves identifying patient risk factors in the context of the specific surgical intervention being proposed. Combination of the patient risk factors along with the surgical risks determines the likely risk of cardiac complications in the perioperative period. Initial history and physical exam should focus of identification of conventional cardiac risk factors. These include recent myocardial infarction, unstable angina, decompensated heart failure, and severe symptomatic valvular dysfunction. Additionally, conditions such as diabetes, prior stroke or transient ischemic attack and renal insufficiency should be identified, as they increase the risk of myocardial infarction. The type of surgery determines in part, the surgical risk. In the 2014 European Society of Cardiology/European Society of Anaesthesiology guidelines on non-cardiac surgery, high risk surgeries are those broadly estimated to confer a >5 % risk of 30-day cardiovascular death and MI, including aortic and major vascular surgery, many intra-peritoneal and

intra-abdominal surgeries, pneumonectomy, total cystectomy, lung or liver transplant [9]. Intermediate risk procedures are those associated with a 1–5 %, 30-day risk of cardiovascular death and MI and include such operations as endarterectomy or stenting for symptomatic carotid disease, endovascular aneurysm repair, percutaneous peripheral arterial revascularization, head and neck surgery and renal transplant. The 2014 Perioperative Clinical Practice Guidelines put forth by the American College of Cardiology and the American Heart Association use the more parsimonious designations of "low risk" versus "elevated risk" where the combined surgical and patient characteristics predict perioperative MACE rates of <1 % or ≥1 %, respectively [1].

Numerous schema for assessment of patient risk are available, including the Revised Cardiac Risk Index (RCRI), the myocardial infarction/cardiac arrest (MICA) risk calculator by Gupta et al. and the Vascular Study Group of New England Cardiac Risk Index (VSG-CRI) [12, 13], with RCRI remaining the most commonly used. The RCRI, also referred to as the Lee index, was validated in a study of over 2800 patients published in 1999 and has since been shown to be robust in identifying patients with low versus high cardiac risk [13, 14]. The newer MICA score, derived using the National Surgical Quality Improvement Program (NSQIP) database inclusive of 211,410 patients, has been shown to better predict perioperative cardiac risk compared to the RCRI (C statistic 0.874 versus 0.747) however has yet to be confirmed via broad external validation [12]. One of the acknowledged weaknesses of the widely-used RCRI score is its ability to accurately predict the cardiac risk in patients undergoing vascular surgery. The VSG-CRI score was developed specifically for this patient population and has been demonstrated to be superior in predicting risk of adverse cardiac events in patients undergoing vascular surgery compared to RCRI [15].

Invasive Cardiac Assessment and Revascularization

Once a patient at high perioperative MACE risk has been identified through a combination history, physical examination and aforementioned risk prediction models, the next decisions often relate to proceeding with invasive cardiac diagnostics and coronary revascularization prior to surgery. The role of routine coronary angiography prior to surgery has long been an area of debate with conflicting results in the published literature. Hertzer et al. found that in a prospective cohort of 1000 patients undergoing routine coronary angiography in the context of planned elective vascular surgery, preoperative revascularization with coronary artery bypass grafting (CABG) in patients with severe coronary artery disease (CAD) improved 5-year mortality as compared to those with severe CAD who were not revascularized prior to surgery [16]. A decade later, Eagle et al. published a larger study using medically managed and surgically revascularized

patients from the Coronary Artery Surgery Study registry who subsequently underwent noncardiac surgery [17]. In a total of 1961 patients undergoing higher-risk (abdominal, vascular, thoracic, and head and neck) surgery, prior CABG was associated with fewer postoperative deaths (1.7 % versus 3.3 %, P = .03) and MIs (0.8 % versus 2.7 %, P = .002) compared with the cohort of patients with medically managed CAD. In the same analysis it was also noted that patients undergoing low risk surgeries (urologic, orthopedic, breast) had low mortality irrespective of revascularization history [17]. These trials thus indicated that surgical coronary revascularization may be beneficial in patients with severe multivessel coronary artery disease undergoing high risk noncardiac procedures; however, these trials also drew criticism given their retrospective and non-randomized nature and also because of the implicit risk associated with the revascularization itself.

Since then, several randomized controlled trials have been conducted to understand the role of preoperative revascularization (inclusive of percutaneous and surgical revascularization) in patients undergoing high risk surgery. The CARP trial screened 5859 patients from 18 Veterans Affairs medical centers, of which 510 patients (9 %) were randomized to either coronary revascularization or medical management prior to elective vascular procedures (peripheral arterial revascularization or abdominal aortic aneurysm surgery) [18]. Eligibility was determined by a preoperative coronary angiogram that demonstrated ≥70 % stenosis in ≥1 coronary artery, amenable to revascularization. The majority of exclusions were either due to low cardiac risk, need for urgent vascular surgery, or due to history of revascularization with CABG or percutaneous coronary intervention (PCI) without evidence of ischemia. In this pivotal trial, prophylactic revascularization, either with PCI (59 %) or CABG (41 %), did not reduce 30-day MI rates compared to optimal medical management (12 % vs. 14 %). Additionally, there was no difference in mortality at 2.7-year follow-up (22 % vs 23 %) [18]. Limitations of the study included the fact that patients with obstructive left main coronary artery disease and left ventricular ejection fraction <20 % were excluded, and that the majority of the patients either had 1 or 2 vessel disease with preserved left ventricular function, potentially biasing the study towards a lower risk population and therefore fewer potentially preventable events. Indeed, only 32 % of the study population had triple vessel coronary disease and only about 40 % of study patients were reportedly symptomatic. Nevertheless, the topline results of the study left little room to support routine revascularization in stable coronary artery disease patients prior to elective vascular surgery. A separate analysis of patients who were screened and randomized (n = 462) as well as registry patients not randomized (n = 586, some because of high-risk coronary anatomy), lent some insight to the fate of patient cohorts omitted from or under-represented in the original CARP analysis [19]. Garcia et al. found that preoperative revascularization of unprotected left main coronary artery disease (discovered in 4.6 % of patients undergoing coronary angiography before vascular surgery) was associated with improved survival (0.84

vs 0.52, p <0.01). Survival was not improved however, in patients with 2-vessel (0.80 vs 0.79, p = 0.83) or 3-vessel coronary artery disease (0.79 vs 0.71, p = 0.15) undergoing revascularization [19].

In a similar timeframe, the DECREASE-V study also examined this issue by screening 1880 preoperative vascular surgery patients and further stratifying those with ≥3 risk factors (n = 430) using either dobutamine stress echocardiography or stress nuclear imaging [20]. Patients found to have extensive stress-induced ischemia on the non-invasive test (n = 101) were then randomized to revascularization (n = 49) or no revascularization (n = 52). In this relatively small but admittedly high-risk cohort of patients with inducible ischemia, there was no difference in non-fatal MI or overall survival rate at 30 days, 1 year and 2.8 years of follow-up, once again questioning the value of prophylactic revascularization prior to surgery [20, 21].

Another prospective, randomized study published in 2009 by Monaco et al., assigned 208 patients with an RCRI score ≥2 undergoing high risk vascular surgery, to either a "selective" angiography strategy where coronary angiography was performed only on the basis of a positive noninvasive stress test or to a "systematic" angiography strategy where coronary angiography was performed in all patients [22]. Not surprisingly, the rate of revascularization was higher in the "systematic angiography group" (58.1 % vs. 40.1 %; p = 0.01) and while there was a numerical reduction in MACE at 30 days in the systematic strategy, this did not reach statistical significance (4.8 % vs. 11.7 %, p = 0.1). At long term follow-up the "systematic angiography" strategy was associated with statistically significant reduction in cardiac events, including mortality at 4 years (69.6 % vs. 86.6 %, p = 0.003). The results were both provocative and impressive given that both groups were medically optimized with aggressive beta-blockade to HR <60 beats per minute. Important differences exist between the previously detailed CARP and DECREASE trials and the study by Monaco et al. Less severe coronary artery disease was encountered in CARP versus in this study (44 % of patients with 3-vessel CAD) potentially reducing the benefits of revascularization in the former. It should also be noted that both DECREASE-V and CARP required a demonstration of ischemia on noninvasive stress testing prior to revascularization. A number of limitations to this study have also been pointed out including its small size, and unblinded design [23–25]. In a similar study, Illuminati et al. randomized 426 patients pending carotid endarterectomy, with no evidence of CAD on history, ECG or echocardiogram to coronary angiography with selective revascularization versus carotid endarterectomy without prior coronary angiography. The authors concluded that routine ("systematic") use of angiography significantly reduced the incidence of late MI and improved long-term survival, even after adjustment for covariates although lack of blinding was cited as an important limitation of this study as well [26]. Still other investigators have evaluated the utility of coronary angiography in other high risk cohorts such as patients undergoing surgery for type A aortic dissection, and have found no difference in mortality or MACE between those who underwent coronary angiography and those that did not [27].

In deference to the totality of observational and trial literature, the current ACC/AHA and ESC/ESA clinical practice guidelines are in general agreement as to the matter of prophylactic revascularization in stable or low-intermediate risk patients with CAD, for the purpose of reducing perioperative cardiac events: In both guideline statements, prophylactic revascularization garners a Class III designation (not recommended), Level of Evidence B and the stipulation in the ACC/AHA guidelines that there is "no benefit" [1, 9]. Both documents do however, endorse the performance of coronary revascularization before noncardiac surgery for accepted clinical indications (ACC/AHA guidelines: "when indicated by existing clinical practice guidelines", ESC/ESA guidelines: "according to the applicable guidelines for management in stable coronary artery disease", Class of recommendation: 1 (both), Level of evidence: C (ACC/AHA), B (ESC/ESA) [1, 9]. The European recommendations are further nuanced, stating that "late revascularization after successful non-cardiac surgery should be considered, in accordance with ESC Guidelines on stable coronary artery disease" (Class 1, Level of evidence C) and that "prophylactic myocardial revascularization before high-risk surgery may be considered, depending on the extent of a stress-induced perfusion defect" (Class IIb, Level of evidence B) [1, 9].

There is also general agreement with respect to revascularization in patients presenting with non-ST- elevation acute coronary syndromes (NSTE-ACS) and ST-elevation myocardial infarction (STEMI) in the setting of a pending elective noncardiac surgery even in the absence of any prospective trial to date addressing this clinical scenario. Both U.S and European recommendations support revascularization in accordance with the relevant clinical practice guidelines. Similarly, in patients requiring urgent or emergency surgery (without unstable cardiac disease) clinical risk stratification, guideline-directed medical therapy (if time and clinical condition permit) and proceeding with surgery without angiography/revascularization, is recommended [1, 6, 9].

When percutaneous revascularization is being considered for any of the aforementioned indications, the complex interplay between the completeness and durability of the revascularization, the anticipated duration of dual antiplatelet therapy, the type of stent(s) used and the urgency of the noncardiac surgery, must be taken into careful consideration.

Current Practice and Remaining Areas of Uncertainty

As detailed, the preponderance of clinical investigations have found little or no value for routine angiography and revascularization in stable preoperative patients, even when high risk noncardiac surgery is being considered. A small handful of studies have provided some tantalizing glimpses of benefit but still require confirmation in large-scale, randomized, blinded investigations. The relative homogeneity of trial findings and guideline recommendations notwithstanding however, clinical practice is often influenced considerably by individual clinician experience and judgment

and also by local practice standards. The largest and most contemporary snapshot of U.S. practice was provided by Schulman-Marcus et al. who performed a retrospective analysis using the National Cardiovascular Data Registry (NCDR) CathPCI Registry [28]. A total of 194,444 patients undergoing coronary angiography prior to noncardiac surgery, were studied in a descriptive fashion. The majority of those studied (117,821, 60.6 %) were reportedly asymptomatic, with obstructive CAD found in 48.1 % of patients and revascularization (PCI or CABG) recommended in nearly one quarter of the overall cohort. Drug-eluting stents were used in 40.8 % and bare-metal stents in 48.8 % of PCI patients, delaying the planned surgery for a variable, and often extended, period of time [28]. Despite several acknowledged limitations of this study including lack of information regarding the type of surgery being planned or post-surgical outcomes, an accompanying editorial calls attention to the enormity of the rift between guideline-recommended care and contemporary US practice [28, 29]. Furthermore, the procedural complications reported in this study (including procedural mortality of 0.05 %) and more benign phenomena such as avoidable treatment delays incurred by unnecessary medical testing, as highlighted by Sharma et al. highlight the fact that clinicians often deliver suboptimal care to the preoperative patient, despite their best intentions and judgment [29, 30].

A number of important issues relevant to this population remain unstudied, understudied or studied but without consensus opinion as of yet. As noted previously, there have been no randomized studies of prophylactic revascularization versus medical optimization in preoperative patients with acute coronary syndromes. Given the powerful clinical biases that deter the performance of non-emergent surgery on a patient perceived to be suffering from an unstable ischemic syndrome, it seems unlikely that much data will be forthcoming in this population. The importance of complete percutaneous revascularization (versus culprit lesion-only revascularization) in patients found to have multivessel CAD at the time of primary PCI for STEMI, has been underscored by recent randomized studies such as the Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) trial and the Complete versus Lesion-only Primary PCI (CvLPRIT) trial [31, 32]. While these studies do not directly address the preoperative population, it bears recognition that many patients undergoing culprit-only STEMI PCI in some timeframe preceding surgical candidacy will unwittingly enter the “gray-zone” of revascularization considerations for residual obstructive (non-culprit) CAD. Finally, the optimal timing of surgery and management of oral antiplatelet therapy in patients undergoing noncardiac surgery following recent percutaneous revascularization with stenting is another important, if contentious, issue [6]. While it is beyond the scope of this chapter to do more than introduce this issue, it merits recognition that both U.S. and European preoperative cardiovascular evaluation guidelines, several individual studies and the recently published 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease, have all lent clarity to this important issue [33–36]. The patient with coronary artery disease, either prior or active, who is being prepared for noncardiac surgery, deserves

consideration of these key issues in order to insure the highest likelihood of an uneventful perioperative course and recovery.

Recommendations

- Routine preoperative coronary angiography is not recommended in patients with stable cardiac disease or cardiac risk factors (**evidence quality high; strong recommendation**).
- Preoperative revascularization for the purpose of reducing perioperative cardiac events in patients with stable cardiac disease/symptoms, is not recommended (**evidence quality high; strong recommendation**).
- Preoperative coronary angiography and revascularization is reserved for a subset of patients deemed high risk on the basis of clinical history and risk of the planned surgery and with abnormal noninvasive testing with high risk clinical features suggestive of ischemia (**evidence quality moderate; moderate recommendation**).
- Revascularization may be considered in patients found to have obstructive left main coronary artery disease and in whom the risk of proceeding without revascularization outweighs the risk of delaying surgery (**evidence quality low; moderate recommendation**).

A Personal View of the Data

It has been estimated that nearly one million adverse cardiac events occur each year following noncardiac operations in the United States [37, 38]. The challenge of meticulous but evidence-based risk stratification and risk mitigation in patients undergoing noncardiac surgery may be summarized by the popular idiom, “The devil is in the details”. While clinical experience and local practice standards may favor a “more is more” approach, several decades worth of clinical data have yet to find any consistent benefit with routine preoperative coronary revascularization. That noted, the decision to defer invasive risk stratification and possible revascularization must take into consideration numerous patient-specific variables such as urgency of the surgery, functional capacity, degree and extent of ischemia on noninvasive cardiac evaluation and left ventricular performance. Patients with a definite or likely diagnosis of an unstable ischemic syndrome should undergo coronary angiography and revascularization as dictated by the coronary anatomy and clinical practice guidelines. The optimal therapeutic approach in preoperative patients with stable but progressive (“crescendo”) angina or in stable patients with left main or extensive coronary artery disease have not yet been clearly defined by the available data however reluctance to proceed with non-urgent surgery without invasive assessment and revascularization, is understandable. Finally, coronary

artery disease and ischemic syndromes are by their very nature, dynamic and progressive processes. Even the clinical manifestations of stable CAD could vary greatly on the basis of hemodynamic status, physiologic stresses and rheologic milieu. Thus, reconsideration of the original perioperative risk reduction strategy is prudent if serial assessments of the at-risk patient suggest a cardiac risk profile in transition.

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