18 Percutaneous Coronary Intervention for Stable Ischemic Heart Disease

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About Us Christiana Care Health System located in Delaware is a two-campus multispecialty hospital system. The Center for Heart and Vascular Health is part of the Christiana campus with a 900-bed hospital.

The heart and vascular center provides patient-centered cardiology solutions ranging from complex coronary interventions to structural heart procedures including but not limited to left atrial appendage occluders and percutaneous aortic valve implants. We also have a robust acute myocardial infraction response program which is in line with all the metrics set by ACC/AHA, including door to balloon time. The center provides patients with services related to cardiothoracic surgery as well. Our invasive volume is quite robust, with over 4700 diagnostic cases and nearly 1600 interventional coronary cases performed in the fiscal year 2015.

Multidisciplinary heart teams which comprise invasive cardiology, noninvasive cardiology, cardiac surgery, and advance heart failure specialists help make the complex patient- centered decisions ranging from valvular heart disease, advanced heart failure and transplantation and ischemic heart disease.

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When it pertains to stable ischemic heart disease (SIHD), we ensure patients are on multiple antianginal medications prior to considering angiography or surgical bypass with strict adherence to appropriate use criteria (AUC) with additional annual internal review of cases with the heart team to verify compliance with those criteria. We also go through the SCAI AUC tool intra-procedurally to chart appropriateness of those cases before percutaneous coronary intervention (PCI) is undertaken.

Introduction

- Coronary angiography and revascularization began in the 1960s and has evolved dramatically into a robust platform for not only diagnosis of coronary disease but also complex percutaneous intervention.
- The phenomenal number of procedures, over a million by the mid-2000s in the United States alone [1], has helped improve operator expertise. This coupled with advances in equipment, specifically in stent technology, has made percutaneous intervention an increasingly preferred modality in various clinical scenarios.
- With this, the world saw ever-increasing revascularization of coronary stenoses in patients ranging from those with asymptomatic lesions to those suffering an acute

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myocardial infarction (MI). However, even though coronary intervention through both PCI and coronary artery bypass grafting (CABG) have greatly improved outcomes in the setting of acute coronary syndrome (ACS), the same has not been systematically true for stable ischemic heart disease (SIHD) [2].

The Early Experience: CABG Versus Medical Therapy

- The first studies that looked at revascularization of SIHD as opposed to medical therapy were the initial CABG trials, including the VA study, CASS trial, and ECSS in Europe [3, 4]. They showed relief from angina symptoms, falling by 50% over 10 years [5]. Nonetheless, the outcomes were suboptimal, highlighting several limitations:
  - First, much of the short-lived benefit was secondary to graft occlusion as internal mammary artery (IMA) grafts were not used as frequently as in contemporary practice [6].
  - Second, medical therapy in both arms was markedly distinct from modern recommendations with a lack of robust lipid lowering, blood pressure control, antianginal medications, antiplatelet medications, and lifestyle modifications—all mainstays of current treatment.
- What these studies were pivotal in highlighting, however, were patient characteristics associated with poorer survival. These included:
  - Low left ventricular ejection fraction (LVEF).
  - Three-vessel coronary disease (>70% stenosis).
  - >50% left main disease.
  - Two- to three-vessel disease which included the proximal left anterior descending (LAD) artery [7].
- Interestingly, what these trials failed to show was a mortality benefit or freedom from subsequent myocardial ischemia for low risk patients. In the CABG Surgery Trialists Collaboration meta-analysis, even though the high-risk patients showed a benefit with CABG, the lowest risk category trended toward increased mortality with CABG and postsurgical complications [8].
- Although these trials are now more of historical interest, they certainly helped us define three crucial clinical considerations that impact outcomes in the SIHD population:
  - The anatomical complexity and burden of coronary artery disease.
  - Severity of left ventricular dysfunction.
  - Degree and extent of comorbid conditions.

Moving Ahead: Percutaneous Coronary Intervention for SIHD

- With the advent of PCI, trials started looking at this modality in SIHD and how it compared to both medical therapy and traditional bypass graft surgery. The initial trials compared balloon angioplasty to medical therapy. Most notable of these trials was RITA 2 [9]. This trial showed no mortality benefit of PCI in SIHD, something that was reinforced in a subsequent meta-analysis looking at optimal medical therapy (OMT) against balloon angioplasty. Furthermore, while balloon angioplasty was initially better at controlling anginal symptoms, this proved at the expense of more frequent repeat revascularizations and periprocedural MIs.
- Many of these early-experience PCI events were related to the high rate of restenosis and acute vessel closure with balloon angioplasty alone. The advent of coronary stents, and in particular drug eluting stents (DES), significantly reduced the incidence of these complications and the transition into our modern practice [10]. With this, the notion that medical therapy was better at preventing adverse outcomes to intervention was challenged once again.
- Nonetheless, in the years preceding the Clinical Outcomes of Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, a routine invasive strategy for SIHD was the default. This was despite guideline

recommendations for a strategy of OMT with intensive antianginal medication utilization, lifestyle modifications, and risk factor reduction [2].

- In 2004, >1 million stent procedures were performed in the US with data showing that 85% of PCIs were performed in patients with SIHD [11]. It was assumed that revascularization of a symptomatic coronary stenosis would lead not only to improvement in angina but also a reduction in hard cardiovascular (CV) endpoints.
- Yet, Katritsis and colleagues published a meta-analysis in 2005 including 11 randomized trials and 2950 patients that failed to demonstrate a significant reduction in death, MI, or need for subsequent revascularization with PCI in this population [12]. What was clearly lacking was a single, large randomized study that compared modern PCI techniques to OMT in the treatment of SIHD.

The Modern Era

- The COURAGE Trial aimed to answer this question [13]. The study randomized 2287 patients with SIHD to a strategy of OMT vs. PCI with OMT and evaluated all-cause mortality and nonfatal MI with a median follow-up of 4.6 years.
- Eighty-five percent of the participants had undergone a stress evaluation with 2/3 of the nuclear studies demonstrating multiple perfusion abnormalities. Nearly 70% of participants had multivessel disease on angiography with >30% having involvement of the proximal LAD. Surprisingly, the study revealed no significant difference in the primary outcome.
- Furthermore, even though the PCI arm had a lower incidence of repeat revascularization in the short-term, over 70% of participants in both arms were free of angina by end-of-study.
- Although it has been said the compliance to OMT in COURAGE would be difficult to replicate in the real world, the overall importance of OMT was highlighted and the role of PCI in SIHD was shown to confer limited long-term symptom benefit with no survival advantage. Indeed, OMT was mandated in both arms of the COURAGE trial and remains the standard of care today, whether revascularization is performed or not.
- Following this, the BARI-2D trial shed further light on the topic. The original BARI trial evaluated CABG vs. PCI and showed no mortality difference in the overall population, but in a subgroup analysis of patients with diabetes, CABG conferred a survival benefit over angioplasty [14].
- The more contemporary BARI-2D trial considered once again a high-risk population with diabetes, and again compared medical therapy alone against prompt revascularization with either CABG or PCI, with OMT in both arms [15]. The trial failed to show a mortality benefit at 5 years with intervention. Of note, when the results were stratified by intended treatment, the CABG arm had significant improvement in major cardiovascular outcomes compared to medical therapy, primarily driven by a nearly 50% reduction in the rate of nonfatal MI (14.6% vs. 7.4%), something that was not seen with PCI.
- The subsequent FREEDOM and BEST trials further supported these findings [16, 17]. These studies compared revascularization with CABG vs. DES-PCI in patients with DM and multivessel CAD. While not specifically comparing revascularization strategies to OMT, these studies showed CABG to be superior to DES-PCI by way of reduction in major adverse cardiovascular events at the expense of an increased rate of stroke.
- The importance of these studies was the use of DES, which in theory would optimize results of PCI revascularization. Of the 1149 patients randomized to PCI in COURAGE, 14% received balloon angioplasty alone, 86% received angioplasty with stent implantation, and 97% of the stents implanted were bare metal stents (BMS); DES, where used, were first generation.
- Yet, despite the widespread use and availability of the best-performing everolimus family

of stents used exclusively in the BEST trial, the dramatic decrease in the need for additional procedures with modern DES PCI still failed to match revascularization achieved by CABG.

Why Does PCI Fail?

Degree of Revascularization

- Perhaps some of the unique benefit seen specifically with CABG over medical therapy was tied to the degree of ischemic reduction. In general, complete revascularization confers a long-term survival benefit when compared to incomplete revascularization, especially in those with a large burden of disease. For example, analyses of the SYNTAX trial (a study which evaluated PCI versus CABG in patients using a quantified anatomy-based risk score) allowed for calculation of a residual SYNTAX score [18, 19]. This score defined the degree of remaining disease burden after PCI. A score of >8 after PCI was associated with higher mortality (35.3% mortality with a score > 8 versus 8.7% with score 0–4 and 11.4% with score 4–8, $p < 0.001$) as reviewed in the post hoc analysis of the ACUITY trial and then validated by the SYNTAX trial at 5-year follow-up [18].
- Second, a meta-analysis of 35 trials with almost 90,000 patients demonstrated that complete revascularization resulted in a lower rate of death and MI in long-term follow-up and was more likely achieved when CABG was the treatment modality [20].
- These data point to the fact that in patients with a greater burden of disease, lowering the degree of ischemia was beneficial and CABG appeared best able to accomplish this. However, this remains true for PCI in SIHD as well.
- In an aging population with significant comorbidities, the rate of surgical turndown cannot be discounted. Therefore, the degree of pre and post ischemia burden after PCI may be an important marker for meaningful success [21].
- The forthcoming ISCHEMIA (clinicaltrials.gov NCT01471522) and SYNTAX II (clinicaltrials.gov NCT02015832) trials will hopefully expand on this subject [22]. The ongoing ISCHEMIA trial is enrolling patients with moderate ischemic burden as seen on noninvasive testing with randomization to OMT vs. revascularization plus OMT. As randomization will take place before an invasive ischemic evaluation, it plans to expand our understanding of even the most complex of ischemic disease including left main stenosis.

Effects of Comorbidities

- It has become clear through studies such as BARI-2D that comorbid conditions such as diabetes and left ventricular dysfunction can significantly modify risk. Furthermore, end-organ manifestations of those comorbidities are predictive of a poor long-term prognosis, with degree of severity conferring differential risk.
- It is with this in mind that risk scores such as ACEF, which incorporates, age, serum creatinine, and LVEF have been created and validated in predicting inpatient mortality after CABG. A step further is the incorporation of the anatomical SYNTAX score with components of ACEF to formulate the SYNTAX II score [22]. This score incorporates both anatomical and clinical variables and will attempt to enhance our choice of medical therapy versus revascularization and selection of revascularization modalities where appropriate.
- As an example, a patient with low comorbid complexity and a low anatomical SYNTAX score will have a low SYNTAX II score and will presumably be preferred for medical therapy alone or possibly with PCI, while a patient with significant comorbidities and high anatomical complexity will have a higher SYNTAX II score and may benefit from revascularization, specifically with CABG. The ongoing SYNTAX II trial plans to validate this concept.

Ischemic Burden as a Predictor of Outcomes

- The fact that SIHD patient with diabetes and multivessel CAD garnered benefit from surgical revascularization points to a high burden of anatomical disease, and by extension, degree of ischemia, as a predictor of incremental benefit from revascularization over medical therapy. As this was not consistent with the findings of COURAGE, this begs the question as to whether assessment of degree of jeopardized myocardium should play a role in patient assessment.
- As such, evidence mounts toward classifying patients with SIHD more objectively using both anatomy and ischemic burden. The nuclear sub-study of the COURAGE trial evaluated outcomes based on the degree of ischemic reduction as measured by rest/stress SPECT myocardial perfusion imaging [23]. Significant ischemia reduction was seen more in the PCI and OMT arm as opposed to OMT alone. Although degree of ischemic reduction did not predict outcomes in the overall population, patients with a moderate to severe ischemia burden to start with AND a decrease of >5% ischemia burden showed a significant trend toward event free survival.
- To better quantify this, trials utilizing fractional flow reserve (FFR) were undertaken. The FAME trial showed that limited intervention to lesions with FFR ≤0.8 was effective and safe (see also Chap. 15) [24]. In fact, at 1-year follow-up the primary endpoint of MI, death, or repeat revascularization was significantly reduced in the FFR arm.
- The subsequent FAME 2 trial sought to build upon the findings of FAME and reconcile them with COURAGE by determining if *FFR-guided* PCI with OMT compared to OMT alone could improve outcomes in patients with SIHD [25]. This trial was terminated early given the significant difference in the primary endpoint. At 1 year, the composite endpoint of death, MI, or urgent revascularization was significantly reduced by FFR-guided PCI with OMT versus OMT alone, primarily driven by an eightfold reduction in urgent revascularization for ACS.
- Of those requiring urgent revascularization, just under half presented with significant evidence of ischemia: 21.5% with troponin positivity and 26.8% with unstable angina and ischemic ECG changes. Of note, inclusion of urgent revascularization as an endpoint has been met with some criticism given the overall rate of MI was unchanged by FFR-guided therapy. It therefore remains questionable, given the weight of evidence, whether revascularization with PCI, even with functional assessment of lesion-specific ischemic impact, results in benefit that warrants procedural risks over proven OMT. Further study is necessary.

Conclusion

- Trials looking at OMT versus intervention such as BARI-2D and COURAGE have reinforced our understanding that SIHD can be treated effectively with medical therapy. Intervention has not been shown to offer a survival benefit, and even symptom relief is transient.
- However, we have also come to realize there is a subset of patients who benefit from revascularization, specifically surgical revascularization, highlighting the need for better tools to stratify patients into categories that would confer this benefit, whether anatomical, ischemia-driven, or both.
- How best to incorporate such tools and to improve patient outcomes awaits further study. Since writing this chapter there has been a huge amount of focus and significant discussion on the results of the ORBITA trial [26]. Although beyond the scope of this manuscript to dissect the trial results further, we would strongly recommend the reader to read further on the topic, including an excellent Editorial on a substudy of ORBITA [27, 28].

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