Chapter 3
Revascularization for Coronary Artery Disease: Principle and Challenges

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Abstract Coronary revascularization is the most important strategy for coronary artery disease. This review summarizes the current most prevalent approaches for coronary revascularization and discusses the evidence on the mechanisms, indications, techniques, and outcomes of these approaches. Targeting coronary thrombus, fibrinolysis is indicated for patients with diagnosed myocardial infarction and without high risk of severe hemorrhage. The development of fibrinolytic agents has improved the outcomes of ST-elevation myocardial infarction. Percutaneous coronary intervention has become the most frequently performed procedure for coronary artery disease. The evolution of stents plays an important role in the result of the procedure. Coronary artery bypass grafting is the most effective revascularization approach for stenotic coronary arteries. The choice of conduits and surgical techniques are important determinants of patient outcomes. Multidisciplinary decision-making should analyze current evidence, considering the clinical condition of patients, and determine the safety and necessity for coronary revascularization with either PCI or CABG. For coronary artery disease with more complex lesions like left main disease and multivessel disease, CABG results in more complete revascularization than PCI. Furthermore, comorbidities, such as heart failure and diabetes, are always correlated with adverse clinical events, and a routine invasive strategy should be recommended. For patients under revascularization, secondary prevention therapies are also of important value for the prevention of subsequent adverse events.

Keywords Coronary artery disease · Revascularization · Percutaneous coronary intervention · Coronary artery bypass grafting

Since the pathophysiology of coronary artery disease (CAD) was first established in the 1870s that impaired blood supply and caused the myocardial infarction

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(Diodato and Chedrawy 2014), cardiologists had always been striving for approaches for reconstructing coronary blood supply, which was later known as coronary revascularization, to radically resolve the problem.

In 1964, the first coronary artery bypass grafting (CABG) was performed, and 13 years later, percutaneous coronary intervention (PCI) was first available for myocardial revascularization. After decades of continuous advances, both procedures have become conventional therapies for CAD, with over 310,000 CABGs and 1.4 million catheterizations were performed in the United States in 2001 (Riley et al. 2011). In this article, we will introduce the approaches for revascularization and future challenges.

3.1 Evidence and Recommendations for Revascularization

Current guidelines have given recommendations on indications for myocardial revascularization. For patients with stable CAD (SCAD), optimal medical treatment was recommended before revascularization. SCAD with flow-limiting coronary stenosis is indicated to either PCI or CABG to reduce myocardial ischemia and terminate the adverse pathological process. Patients with persist symptoms despite optimal medical treatment and/or improved prognosis will more effectively benefit from revascularization. Revascularization by PCI or CABG is the most effective therapy for angina relief, and improvement of quality of life. These indications was based on randomized control trials (RCTs), in which patients that received revascularizations got better long-term survival benefits (Velazquez et al. 2011; Hlatky et al. 2009; Yusuf et al. 1994).

Revascularization is also recommended for patients with non-ST-segment elevation acute coronary syndromes (NSTEMI) for symptom relief and improvement of prognosis. In a meta-analysis of seven trials, invasive strategy significantly reduced the risk for all-cause mortality (RR = 0.75; 95% CI 0.63–0.90; $P < 0.001$) and myocardial infarction (RR = 0.83; 95% CI 0.72–0.96; $P = 0.012$), as compared with conservative therapy (Bavry et al. 2006).

Current evidence supported early invasive strategy for the NSTEMI, with most pronounced benefits in high-risk patients, but still emphasized risk stratification. Growing evidence suggested that early invasive strategy reduced the risk of recurrent syndrome by 41% for patients with NSTEMI. Intervention within 72 h after diagnosis was especially recommended for patients with higher risk (i.e., diabetes, renal insufficiency, reduced left ventricular function, recent revascularization, et al.) (Katritsis et al. 2011; Navarese et al. 2013).

For patients with onset of symptom with elevated ST-segment or new left bundle branch block on electrocardiography in less than 12 h, reperfusion therapy within the first 2–3 h is definitely recommended to save myocardium and improve prognosis. Reducing the time between symptom onset and provision of reperfusion therapy was the most important factor to improve medical quality and patient's prognosis. With an experienced team, PCI is the primarily recommended reperfusion strategy over

fibrinolysis. PCI was also recommended in patients with onset of symptom more than 12 h and the presence of continuing ischemia, life-threatening arrhythmias, pain, and electrocardiography changes. In patients with severe acute heart failure or cardiogenic shock, PCI is indicated no matter time delay.

3.2 Fibrinolysis

Thrombus in coronary arteries occludes the vessel, arrests blood flow, causes ischemic in myocardium, and provokes acute coronary syndrome. Targeting offending thrombus, thrombolytic therapy is an extensively used therapy for patient with acute ST-elevation (Q wave) myocardial infarction (STEMI), especially for those patients unavailable to PCI in 120 min.

Intravenous infusion of fibrinolytic drugs, commonly plasminogen activators, is utilized to activate the blood fibrinolytic system (Chapin and Hajjar 2015). These agents are highly specific to their substrate plasminogen, which was converted to active enzyme plasmin (Collen and Lijnen 2005). Free plasmin in the blood is very rapidly inactivated by α^2-antiplasmin, but plasmin generated at the fibrin surface is partially protected from inactivation (Collen et al. 1538).

3.2.1 Indications and Contraindications for Fibrinolytic Therapy

Patients with the following criteria are eligible for fibrinolytic therapy: (1) diagnosed of new developed myocardial infarction with confirmed symptoms and evidences; (2) cannot timely receive PCI for revascularization. Fibrinolytic therapy reduces the risk of mortality in patients with acute STEMI by 15–30%, as compared with placebo group and thus should be considered for all eligible patients, especially when PCI is not timely available. Early fibrinolytic therapy is recommended, better in 3 h after the outbreak of chest pain (Kolh and Windecker 2014).

Diseases with high risk of severe hemorrhage are absolute contraindications to fibrinolytic therapy that include previous intracranial hemorrhage (ICH), known structural cerebral vascular lesion, known malignant intracranial neoplasm, ischemic stroke within three months, suspected aortic dissection, active bleeding or bleeding diathesis, significant closed-head or facial trauma within three months, and major trauma or surgery or prolonged cardiopulmonary (>10 min) in less than 2 weeks.

Important relative contraindications include: hypertension with systolic blood pressure over 180 mmHg (Gore et al. 1995; Aylward et al. 1996); ischemic stroke in more than three months previously (Tanne et al. 1998); internal bleeding in the last 2 weeks; noncompressible vascular puncture; anaphylactic reactions to fibrinolytic

agents; prolonged cardiopulmonary (>10 min) in less than 3 weeks; pregnancy; active peptic ulcer; and current use of anticoagulant.

3.2.2 *Fibrinolytic Agents*

After decades of development, the index list of fibrinolytic agents has increased significantly and tends to reduce the risk of adverse events and increase the safety. Streptokinase is the first generation of fibrinolytic agent. Randomized trials have demonstrated that streptokinase reduced in-hospital and short-term mortality (Franzosi et al. 1998; Baigent et al. 1998). However, this early used agent was found to be associated with several adverse effects. Streptokinase is produced by beta-hemolytic streptococcus (Anderson and Willerson 1993; Marder and Sherry 1988) and is actually an antigenic that causes allergic reactions, especially under repeated administrations. Other events include hypotension and bleeding at puncture site. Risk of stroke is much lower but can cause catastrophic outcomes (GUSTO investigators 1993). Fibrinokinase is the other type of fibrinolytic agents (Astrup and Permin 1947), including tissue-type plasminogen activator (t-PA) (Rijken et al. 1979, 1980) and single-chain urokinase-type plasminogen activator (scu-PA or pro-urokinase). In the multisites randomized streptokinase-controlled GUSTO trial enrolling 41,021 patients with myocardial infarction, t-PA reduced 14% (95% confidence interval, 5.9–21.3%) of mortality (Investigators 1993). To date, t-PA is used worldwide in about 300,000 AMI patients every year, and has become a lifesaving drug for the treatment of evolving acute myocardial infarction and other thromboembolic diseases (Collen et al. 1538). Scu-PA is another agent for thrombolysis, which contributed to higher patency rate and reduced risk of complications (Meyer 1989; Spiecker et al. 1999; Bar et al. 1997; Tebbe et al. 1995; Zarich et al. 1995; del Zoppo et al. 1998; Furlan and Abou-Chebl 2002).

The third-generation fibrinolytic agents include recombinant plasminogen activator (r-PA), which is a nonglycosylated deletion mutant of wild-type recombinant tissue-type plasminogen activator (t-PA) (Wu et al. 1990). Early trials have demonstrated that r-PA has a higher rate of TIMI grade III flow at 60 and 90 min compared with t-PA. It was also associated with a reduced need for additional coronary interventions early after thrombolytic procedures. However, r-PA was not shown to get more benefit in either 35-day mortality or the overall incidence of TIMI grade III flow in these early trials (Bode et al. 1996; Smalling et al. 1995). Trials with much higher statistics power were conducted to compare the safety and effect of r-PA with other fibrinolytic agents.

GUSTO III trial compared r-PA with t-PA in 15,059 patients and showed no significant difference between the two drugs in the rate of mortality and stroke. There was no significant difference between r-PA and t-PA in mortality at one year (11.2 vs. 11.1%) (Topol et al. 2000). In INJECT trial, r-PA was compared with streptokinase in the treatment of acute MI (Wilcox 1995), and was shown to be equivalent to standard streptokinase in 35-day mortality, recurrent MI, in-hospital stroke rates, and major

bleeding events. T-PA was also associated with reduced risk of cardiogenic shock or hypotension and heart failure.

3.2.3 Complications

Bleeding and hemorrhagic stroke are two primary complications of all fibrinolytic agents, which raise concerns about risk of harm overwhelming benefits.

3.2.3.1 Bleeding

In GUSTO-I trial, 11.4% of the patients treated by streptokinase and t-PA had moderate bleeding, defined by the need for transfusion without influencing hemodynamic status or a need for interventions, while 1.8% had severe bleeding, defined by substantial hemodynamic compromise that required intervention or treatment (Berkowitz et al. 1997). Risk factors for bleeding include increased age, lighter weight, female sex, African ancestry, and experiencing invasive procedures. Bleeding also increases the risk of nonhemorrhagic adverse events, and accordingly is associated with increased length of hospital stay and mortality (Berkowitz et al. 1997).

3.2.3.2 Stroke

Stroke and intracranial hemorrhage (ICH) are severe complications of fibrinolytic therapy. In FASTRAK II project, stroke and intracranial hemorrhage (ICH) occurred in 1.2 and 0.7% of the patients with fibrinolytic therapy, respectively (Huynh et al. 2004). In patients who developed strokes after fibrinolysis, mortality rate increased to 41% and morbidity rate to 31% (Gore et al. 1995). Similar findings were noted in the (United States) National Registry of Myocardial Infarction-2 registry. Elderly age, female sex, prior history of stroke or transient ischemic attack, hypertension, weight $\leq$65 kg for women or $\leq$80 kg for men, international normalized ratio >4, or prothrombin time >24 s were independently associated stroke and ICH.

3.3 Percutaneous Coronary Intervention

Percutaneous coronary intervention (PCI) has become the most frequently performed therapeutic procedure in medicine. Balloon angioplasty provided a nonsurgical revascularization alternative to CABG, but was limited by acute arterial recoil, dissections, and restenosis. Coronary stents were developed to prevent abrupt artery closure following balloon angioplasty. Bare metal stents (BMS) improved procedural safety and

efficacy, however, was associated with arterial injury and elicited neointimal hyperplasia, leading to restenosis and adverse consequences. Drug-eluting stent (DES) was designed to decrease neointimal hyperplasia and reduced the rate of restenosis. In DES, metallic stent is coated with polymer and antiproliferative agents. The controlled local release of agents has reduced the local proliferative healing response and consistently reduced the risk of restenosis. Randomized trials and large registry studies have reported that DES significantly reduced the risk of repeat revascularization. In a meta-analysis involving 38 trials and 18,000 patients, early generation of DES significantly decreased the rate of repeat revascularization. In a large randomized trial, DES reduced the risk of stent thrombosis, repeat revascularization, and myocardial infarction. As a result, stenting has become the standard of care for PCIs, and DES is placed in most patients.

3.3.1 Type of Drug-Eluting Stents

Currently DESs have the same general components, which include stent platform, polymer, and antiproliferative agents. The difference mainly exists in the biologic characteristics and antiproliferative effects of coating agents.

The first commercially available DESs include the sirolimus-eluting stent and paclitaxel-eluting stent, and are now mostly replaced by second-generation DES with advanced stent platforms and polymer biocompatibility.

The "second-generation" DES, including zotarolimus-eluting stent and the everolimus-eluting stent, has undergone further modification. The stent platform is made of cobalt- or platinum-chromium alloy and is thinner and more deliverable than the first-generation DES. The new-generation DESs have polymer with better pharmacokinetics and are more biocompatible, generating less inflammatory response and more rapid vessel endothelialization, which may be associated with lower rates of myocardial infarction and stent thrombosis. In a meta-analysis of four randomized trials, DES reduced the risk of all-cause death (RR = 0.8, 95% CI 0.59–1.07), myocardial infarction (RR = 0.56, 95% CI 0.43–0.72), stent thrombosis (RR = 0.32, 95% CI 0.20–0.51), and repeat revascularization (RR = 0.57, 95% CI 0.46–0.71).

3.3.2 Indications for Use of Drug-Eluting Stents

DESs provide effective and relatively safe alternatives to CABG for patients with coronary artery disease. In FAME-2 trial, DESs significantly reduced the need for urgent revascularization as compared with medical therapy in patients with stable coronary artery disease (1.6% vs. 11.1%, $P < 0.001$). According to the 2014 guidelines of European Society of Cardiology for myocardial revascularization, use of DES has a class IA recommendation for patients with stable coronary artery disease.

Use of DES in patients with multivessel disease, unprotected left main disease, and diabetes is still a matter of debate.

Stent implantation has become standard reperfusion approach for patients with acute myocardial infarction. Several trials have shown that DES reduced the risk of repeat revascularization in patients with acute myocardial infarction as compared with BMS, but was associated with very late stent thrombosis. In the EXAMINATION study, everolimus-eluting stents reduced the risk of repeat revascularization and stent thrombosis as well. Larger studies with long-term outcomes will provide more detailed evidence on the use of DES for infarction. DES has a class IA recommendation for patients with acute infarction and do not have contradictions for dual antiplatelet therapy.

3.3.3 Periprocedural Complications

Improvements in devices, the use of stents, and aggressive antiplatelet therapy have significantly reduced the incidence of major periprocedural complications of PCI over the past 15–20 years. However, percutaneous and intracoronary procedure also have potential risk of coronary artery complications. The use of guidewires, catheters into the diseased artery, may lead to vessel injuries and consequent major complications.

3.3.3.1 Dissection and Abrupt Closure

Coronary arterial dissection and acute closure were once mostly occurred after percutaneous transluminal coronary angioplasty, without intentional stenting. This complication is commonly due to arterial dissection. Vigorous attempts by guidewire and the following catheters, and the "controlled injury" induced by inflation of the dilation catheter are the main cause of arterial dissection. Dissections occurred in up to 50% of patients who received coronary angioplasty, but were much less frequent since stents are generally used in most percutaneous coronary procedures.

Acute closure was mostly associated with large dissections (Huber et al. 1991; Ellis et al. 1988) and occurs in 4–9% of angioplasty cases. Dissection with reduced flow or total occlusion increases the risk mortality and nonfatal myocardial infarction by 10 times. Most occlusion (90%) can be reversed by stent implantation, but some patients still require bypass surgery to deal with persistent occlusion and ischemia.

3.3.3.2 Intramural Hematoma

Intramural hematoma is often caused by vessel injury after intracoronary procedure. Blood accumulated in the medial space between the internal elastic membrane and

the external elastic membrane. This complication occurs more commonly in coronary angioplasty than in stenting.

3.3.3.3 Perforation

Perforation and rupture of coronary arteries are serious complications that result from guidewire attempts, atherectomy devices, and balloons dilation. Coronary artery perforations occur in 0.2–0.6% of patients undergoing angioplasty and are 0.84% (Stankovic et al. 2004). After stent implantation. but are potentially catastrophic. Significant adverse events occurred in 35% (29 of 84) patients with a perforation, including 7 death (8.3%).

3.3.3.4 Failure of Stent Deployment

The risk of inability to deliver the stent to or expand it within the target lesion is higher for lesions in the left circumflex artery and other longer and complex stenosis. In patients with unsuccessful stent deployment, as much as 43% had major cardiac event in 30 days, as compared with 4% in those with successful deployment (Schuhlen et al. 1998). The risk of stent deployment is much lower for new generations of stents, which ranged from 0.4 to 2% (Bolte et al. 2001).

3.3.3.5 Stent Thrombosis

Stent thrombosis is an uncommon but catastrophic complication which significantly increases the risk of major cardiac events like death and myocardial infarction. The foremost and important risk factor of stent thrombosis is the absence of dual antiplatelet therapy. Acute stent thrombosis (within 24 h) and subacute thrombosis (within 30 days) is also potentially due to angiographic complications, such as residual dissection or slow flow. Late stent thrombosis (after one year) mostly occurs in DES and are related to delayed neointimal coverage and lasting vessel inflammation (Joner et al. 2006).

3.4 Coronary Artery Bypass Grafting

Coronary artery bypass grafting (CABG) is the most commonly performed cardiac surgery and most effective for the revascularization for stenotic coronary arteries. In patients with coronary artery disease caused by partially or completely obstructed atherosclerotic coronary arteries, CABG is used to relieve myocardial ischemia by constructing grafts to bypass culprit lesions and complement blood supply to distal coronary branches.

CABG is very effective in improving the patients prognosis after coronary artery disease, and selecting the eligible patients is a critical precondition for good outcomes. The evaluation of patients for CABG is based on the characteristics and comorbidity of the patient, the coronary anatomy, and, extent of coronary artery disease. CABG is performed primarily for patients with complex stable CAD including over 50% stenosis in left main disease with SYNTAX score over 33, and/or three-vessel disease ($\geq$50%) with SYNTAX score over 23. Patients with two-vessel CAD involving LAD artery and a SYNTAX score $\geq$23 is also recommended to undergo CABG. Patients with impaired left ventricular ejection fraction ($\leq$45%), diabetes, and ischemic mitral regurgitation are getting more survival benefit from CABG.

3.4.1 The Choice of Conduits

After a half-century development, the technique of CABG has undergone extraordinary evolutions. The choice of conduit for collateral blood supply was one of the most important issues associated with patients prognosis.

Left internal thoracic artery (LIMA) and the greater saphenous vein are the most commonly used bypass conduits. LIMA is preferable for grafting for lesions of the anterior descending coronary artery whenever indicated and technically feasible. LIMA was associated with lower mortality rate and much higher ten-year patency rate (Loop et al. 1986) with less progression of atherosclerotic plaque, fibrosis, and calcification within the proximal left anterior descending. The anatomic and histological structure of IMA has made it a favorable conduit for myocardial revascularization and quality indicator in CABG. Bilateral IMA has also been proposed to reduce myocardial infarction, reoperation and PCI after CABG. However, concerns have raised about technical difficulty and increased risk of delayed wound healing caused by postoperative reduction in sternal perfusion. Skeletonization of the IMA has also been suggested for added extra length, although without long-term benefits. Long-term data is still required for further confirmed evidence.

Saphenous vein is the most easily accessible graft for CABG. Besides arterial grafts, most patients who undergo CABG receive at least one saphenous vein graft (SVG). However, about 25% vein grafts failed in the first 12–18 month, and SVGs do not parallel with IMA grafts in their survival benefits, even with aggressive lipid lowering therapies.

Grafts from other arteries, such as the radial artery, the right internal thoracic artery, and the gastroepiploic artery, have been investigated and generally have been shown to have better patency than saphenous-vein grafts but are not routinely used (Suma et al. 2007; Desai et al. 2004). In a review on the choice of conduits in coronary artery bypass surgery, the authors provided opinions on the selection of conduits in accordance with technical accessibility, anatomic feature, angiographic factors, and patients characteristics. Patients with no major risk factors were eligible for bilateral IMA, and RA was indicated for severe target vessel stenosis (>70%),

GEA could be considered for revascularization for inferior wall. However, the author still emphasized that more evidence is needed.

3.4.2 Periprocedural Complications

3.4.2.1 Perioperative Myocardial Infarction

The risk of perioperative myocardial infarction with new Q wave on ECG after CABG ranges from 0 to 10% in different cardiac centers, and is higher in patients with cardiomegaly, long time cardiopulmonary bypass, repeat CABG, and combined cardiac surgery (Chaitman et al. 1983; Yokoyama et al. 2000; Stephan et al. 1996). A new Q wave myocardial infarction indicates poor myocardial perfusion distal to grafts anastomosis. The diagnosis of perioperative myocardial infarction, however, may be difficult, for the CABG-induced postoperative myocardial injury and inflammation also lead to ECG changes and cardiac enzyme elevation. The currently used diagnosis for MI was according to Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Health Federation Task Force definition, which requires increases of biomarkers greater than five times the 99th percentile of the upper reference limit plus either new pathologic Q waves or new left bundle branch block, angiographically documented new graft, native coronary artery occlusion, or imaging evidence of new loss of viable myocardium (Thygesen et al. 2007).

Perioperative myocardial infarction increases the risk of postoperative adverse events. The Coronary Artery Surgery Study (CASS) reported a in-hospital mortality of 9.7% in patients with perioperative new Q wave MI, as compared with 1.0% in those without MI.

3.4.2.2 Early Graft Occlusion

Graft occlusion within the first 30 days after surgery are generally due to suboptimal anastomosis technique and injured graft during harvesting, and occurs in 5–10% of saphenous vein grafts (Dauerman et al. 1996). Antiplatelet therapy, as important secondary preventive strategy, would reduce the risk of postoperative occlusion, and advanced surgical techniques like no-touch approach might also have potential benefits.

3.4.2.3 Low Cardiac Output

Low cardiac output is a relative frequent early postoperative complication. The incidence of low output syndrome is 6% in patients with preoperative left ventricular ejection fraction >40, 12% in those with LVEF between 20–40, and 23% in those

with LVEF <20% (Yau et al. 1999). The incidence of low cardiac output can result from perioperative factors including cardioplegic arrest and ischemic injury, reduced preload, excessive afterload, and perioperative complications like arrhythmias and MI (McKenney et al. 1994; Roberts et al. 1977), and often transient and response to fluid therapy and/or inotropic support. However, persistent low cardiac output for which pharmacologic therapy is ineffective, mechanical support is necessary.

3.4.2.4 Arrhythmias

Arrhythmias are common complications after CABG, and most often are tachyarrhythmias. Atrial fibrillation is one of the most important postoperative events, occurs in 15–40% of CABG cases. Atrial fibrillation after CABG is usually self-limited but is associated with increased risk of adverse outcomes including stroke, in-hospital and long-term mortality (Villareal et al. 2004; Bramer et al. 2010; Mariscalco et al. 2008). Perioperative beta blocker is considered the most effective therapy for the prevention of postoperative atrial fibrillation, and the current guideline recommended continued perioperative beta blocker therapy for patient without contradictions.

3.5 Decision-Making for Revascularization

3.5.1 Heart Team

The concept of Heart Team was first introduced in 2000s through randomized trials (Head et al. 2013). A Heart Team is made up of clinical or noninvasive cardiologists, cardiac surgeons and interventional cardiologists, provides a balanced, multidisciplinary decision-making process. The main job of Heart Team is to review the patient's medical condition and assess anatomy of coronary disease together, to develop the best revascularization options that combines local therapeutic capability and patient preferences. The 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery give a Class I (Level of Evidence: C) recommendations for Heart Team approach to revascularization in patients with unprotected left main or complex CAD (Hillis et al. 2011). Correspondingly, a Class I recommendation was made in 2014 ESC/EACTS Guidelines on myocardial revascularization (Kolh and Windecker 2014).

However, Heart Team has not yet been widely implemented for the novelty of concept, lack of experience and proven benefit, logistical issues, and doctors passive opinions. Moreover, the absence of reliable criteria or guidelines for Heart Team organization and involvement has made the formation and validation of Heart Team more difficult. The process of multidisciplinary decision-making by Heart Team also raised concerns on prolonged time delay before treatment and increasing expense. Therefore, it is crucial to design appropriate organizations and logistics to enlarge the

effect of Heart Team. A coordinator is helpful for acquiring all necessary information for decision making during Heart Team discussion. Leadership, but not dominance, is important for efficient team work, active participation, and innovation. Ad hoc meetings after coronary angiogram may be the best opportunity for Heart Team to collaborate and develop optimal strategy. The process of decision-making has three key points: sufficient information transfer, among physicians, from physicians to patients and patients to physicians; adequate discussion; and consensus.

We believe that a balanced multidisciplinary Heart Team has a promising future for interpret the available diagnostics, implement guideline directed therapy, consider local expertise and through shared decision-making take into account patient preferences, to provide a more objective and uniform decision-making process (Head et al. 2013). However, evidence on the benefit of Heart Team still requires updating. As a paucity of observational and randomized data, further study is still needed to provide insight to the Heart Team approach.

3.5.2 Left Main Disease

Significant left main coronary artery disease (LMCAD defined as a greater than 50% angiographic narrowing) is found in 4–6% of all patients who undergo coronary arteriography (Ragosta et al. 2006) and is associated with high morbidity and mortality owing to the large amount of myocardium at risk (at least 75% of the left ventricle) (Serruys et al. 2009). The optimal management of patients with left main coronary artery disease has been the subject of intense investigation for decades, both CABG and PCI along with best selected preventive therapies was recommended in the newest guidelines on myocardial revascularization for left main coronary artery disease in selective patients, and coronary artery bypass graft surgery (CABG) with best selected preventive therapies is recommended for all patients with significant left main coronary artery disease due to significantly improved survival.

CABG has a long track record of safety and efficacy in patients with LMCAD and is associated with significantly better cardiovascular outcomes, including mortality. In the 1970s, Veterans Administration Cooperative Study compared a strategy of initial CABG versus deferred CABG, substantial survival advantages were observed in patients underwent initial CABG at 2 years and 11 years, and also greater benefit was found in high-risk patients with more than 75% left main stenosis and/or left ventricular dysfunction, compared with patients with 50–75% stenosis and normal left ventricular function. The CASS Registry contained data from 1,484 patients with more than 50% left main CAD initially treated surgically or nonsurgically, median survival duration was 13.3 years in the surgical group, 6.6 years in the medical group (Caracciolo et al. 1995). With the development of surgical technology, Thirty-day mortality of CABG is now under 2% in some United States institutions, and in Fuwai hospital, this rate is lower than 1%.

The LMCAD once was a forbidden territory for percutaneous coronary intervention (PCI), however, the accumulation of experience, coupled with improved

technology and pharmacology, has led to this approach being rapidly evolved and broadly adopted in stenosis (Park et al. 2015), and also for cautiously selected patients with LMCAD. The NOBLE trial (Nordic-Baltic-British Left Main Revascularization) and EXCEL trial (Evaluation of XIENCE vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) were the latest published studies focus on the comparison of CABG with PCI for left main CAD. The NOBLE study, 1201 patients were randomly assigned, reported that CABG might provide a better clinical outcome for treatment of left main coronary artery disease than PCI, regard to the primary endpoint of major adverse cardiac and cerebrovascular events, with 46% excess hazard with PCI over CABG at 5 years ($P = 0.01$). However, the EXCEL trial, in which 1905 participants were enrolled, showed that the primary composite endpoint event of death, stroke, or MI at 3 years occurred in 15.4% of the patients in the PCI group and in 14.7% of the patients in the CABG group ($P = 0.02$ for noninferiority), leading to the conclusion that in patients with left main coronary artery disease and low or intermediate SYNTAX scores, PCI with everolimus-eluting stents was noninferior to CABG. In a 2016 meta-analysis examined the results of PCI versus CABG for unprotected left main coronary artery stenosis, the pooled data were numerically leveraged by EXCEL and varied in their definition of periprocedural MI, leading to a neutral result for the primary endpoint of all-cause death, MI, or stroke (odds ratio, 0.97; 95% confidence interval, 0.79–1.17; $P = 0.73$) (Nerlekar et al. 2016). Taken together, EXCEL and NOBLE confirmed that CABG is the most robust and durable therapy for coronary revascularization in the presence of LMCAD, and also, for the treatment of patients with left main coronary artery disease and low or intermediate SYNTAX scores, PCI with everolimus-eluting stents can be considered as another choice. Meanwhile, a professional Heart Team should also be involved, helps to balance the risks and benefits associated with each procedure in conjunction with the baseline risk profile and patient preferences, and finally make the best choice of the optimum revascularization strategy for an individual patient.

3.5.3 Multivessel Disease

Based on the basic CAD secondary prevention strategies including therapeutic lifestyle changes (TLCs) such as increased physical activity, dietary modification/weight loss, smoking cessation, and adjunctive drug therapies such as the routinely consumption of aspirin and statins, beta blockers and angiotensin converting enzyme inhibitors or angiotensin receptor blockers, patients with stable coronary artery disease involving 2 or 3 vessels should be assessed periodically to determine whether medical therapy or medical therapy with revascularization is a more appropriate strategy for effective relief of angina and improvement in long-term survival.

The choice between coronary artery bypass graft surgery (CABG) versus percutaneous coronary intervention (PCI) in patients with multivessel disease is dependent upon a number of factors, including the number of vessels involved,

the anatomic complexity of the lesions requiring revascularization, likelihood of complete revascularization, patient comorbidities such as diabetes, and patient preference.

The 2009 published SYNTAX trial (The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) enrolled 1800 patients with three-vessel or left main coronary artery disease to undergo CABG or PCI, after 1 years' follow-up, major adverse cardiac or cerebrovascular events (MACCE) were significantly higher in the PCI group (17.8%, vs. 12.4% for CABG; $P = 0.002$), and the rates of death and myocardial infarction were similar between the two groups, but stroke was significantly more likely to occur with CABG (2.2%, vs. 0.6% with PCI; $P = 0.003$), leading to the conclusion that CABG remains the standard of care for patients with three-vessel or left main coronary artery disease. Meanwhile, according to the SYNTAX score, a semi-quantitative tool based on the results of coronary angiography, the sub-group analysis showed that among patients with low (0–22) and intermediate (23–32) SYNTAX scores, the clinical outcomes were comparable with PCI and CABG (13.6 vs. 14.7 and 16.7 vs. 12.0, respectively), whereas in those with a high score (≥33), outcomes were better with CABG (23.4 vs. 10.9%, respectively) at 12 months (Serruys et al. 2009). Five years later, the SYNTAX trial five-year outcomes were reported, which showed that estimates of MACCE were 26.9% in the CABG group and 37.3% in the PCI group ($p < 0.0001$), estimates of myocardial infarction (3.8% in the CABG group vs. 9.7% in the PCI group; $p < 0.0001$) and repeat revascularization (13.7% vs. 25.9%; $p < 0.0001$) were significantly increased with PCI versus CABG, and all-cause death (11.4% in the CABG group vs. 13.9% in the PCI group; $p = 0.10$) and stroke (3.7% vs. 2.4%; $p = 0.09$) were not significantly different between groups. In addition, consistent results were observed in patients with different SYNTAX score risk stratification. Thus, the authors interpret that CABG should remain the standard of care for patients with complex lesions (high or intermediate SYNTAX scores), and for patients with less complex disease (low SYNTAX scores), PCI is an acceptable alternative. The author also suggested that all patients with complex multivessel coronary artery disease should be reviewed and discussed by both a cardiac surgeon and interventional cardiologist to reach consensus on optimum treatment (Mohr et al. 2013).

As noted in the studies above, for many patients with multivessel coronary artery disease, relatively well-preserved left ventricular systolic function, low complexity coronary anatomy, and no diabetes, or say, in a low or intermediate SYNTAX scores (≤32), CABG and PCI may have the same outcomes; for these patients with complex anatomy or diabetes and high SYNTAX scores (≥33), however, CABG is strongly recommended.

Hybrid coronary revascularization (HCR) has been defined as the combination of minimally invasive direct coronary artery bypass surgery and percutaneous coronary intervention (PCI) in selected patients with multivessel coronary artery disease, which is thought to bring together the excellent patency rates and survival benefits associated with the durable left internal mammary artery graft to the left anterior descending artery with the good patency rates of drug-eluting stents, and aims to reduce surgical trauma while preserving long-term survival and minimizing adverse

cardiovascular events. While it has achieved some measure of popularity, HCR has not been evaluated in reliable large-scale randomized trials comparing it with PCI or CABG. The largest observational study to date, published on JACC in 2016, compared 200 patients who underwent HCR and 98 patients who underwent multivessel PCI, and reported that the rate of primary outcome of major adverse cardiac and cerebrovascular events (i.e., death, stroke, MI, and repeat revascularization) within 12 months of the procedure was similar between the two groups after adjustment for baseline risk (0.142 vs. 0.119%, respectively; hazard ratio 1.063; $p = 0.80$) (Puskas et al. 2016). Until evidence from more well-designed randomized trials supporting its use is available, we believe HCR is a reasonable choice at centers with expertise.

3.5.4 CAD with Comorbidities

3.5.4.1 Heart Failure

Heart failure (HF) is a common clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood, and coronary artery disease or ischemic cardiomyopathy is a dominant cause of HF in developed countries. Thus, revascularization with CABG or PCI is indicated for symptomatic relief of angina pectoris in patients with heart failure. The Surgical Treatment for Ischemic Heart Failure (STICH) study (Velazquez et al. 2016) was designed to test the hypothesis that CABG plus guideline-directed medical therapy for coronary artery disease, heart failure, and left ventricular dysfunction would improve survival over that with medical therapy alone in a sample of 1212 patients with CAD and LV dysfunction (EF $\leq$ 35%). After 10 years' follow-up, the authors reported that the primary outcome event (death from any cause) occurred in 359 patients (58.9%) in the CABG group and in 398 patients (66.1%) in the medical therapy group (hazard ratio with CABG vs. medical therapy, 0.84; 95% confidence interval (Tanne et al. 1998), 0.73–0.97; $P = 0.02$ by log-rank test), and the median survival was 1.44 years longer in the CABG group (7.73 years among patients in the CABG group and 6.29 years among patients in the medical therapy group). Based on these results, the STICH supports a significant benefit of CABG plus medical therapy over medical therapy alone with respect to the rate of death from any cause among patients with ischemic cardiomyopathy. Meanwhile, since most studies refer to the revascularization strategies for patients suffering from coronary artery disease and set LV dysfunction as an exclusive criterion, the available data is insufficient to evaluate the efficacy of PCI and compare PCI with CABG in patients with LV dysfunction. A recent propensity score matching study compared PCI with everolimus-eluting stents versus CABG and concluded that in patients with multivessel disease and severe LV systolic dysfunction, PCI with an EES resulted in survival similar to that of CABG (Bangalore et al. 2016). However, we highly recommend that the choice between CABG and PCI should be made by the Heart Team after careful evaluation of the patient's clinical status and coronary anatomy, including SYNTAX score,

comorbidities, and expected completeness of revascularizations, and a specialist in heart failure should also be consulted.

3.5.4.2 Diabetes

Patients with diabetes comprise as many as 25–30% of those who undergo revascularization, and the short- and long-term results of revascularization with percutaneous coronary intervention or coronary artery bypass graft surgery are often worse in diabetic patients (Malmberg et al. 2000), emphasized by a higher risk of cardiovascular events and death than those without diabetes. The approach to revascularization in diabetic patients with left main or lesser degrees of coronary disease is similar to the broad population of patients; however, the optimal revascularization strategy for patients with diabetes and multivessel coronary artery disease remains to be deliberated.

BARI 2D trial (Group et al. 2009) (The Bypass Angioplasty Revascularization Investigation 2 Diabetes) was designed to address the effects of therapy on the rate of myocardial ischemia, a major cause of death in patients with diabetes, and of insulin resistance, the fundamental mechanism underlying diabetes with profound cardiovascular consequences. Overall, 2368 patients with type 2 diabetes mellitus and stable ischemic heart disease were enrolled, at 5 years, the primary endpoints of the rates of survival or freedom from major cardiovascular event death, myocardial infarction (Wu et al. 1990, or stroke) did not differ significantly between the revascularization group and the IMT alone group (88.3 vs. 87.8% and 77.2 vs. 75.9%, respectively). However, in sub-group analysis, the rate of freedom from major cardiovascular events was significantly higher in the CABG plus IMT stratum compared to the corresponding IMT stratum (77.6 vs. 69.5%), predominantly attributable to a reduction in nonfatal MI.

The FREEDOM trial (Farkouh et al. 2012) (Future Revascularization Evaluation in Patients with Diabetes Mellitus) compares CABG against PCI with the use of early-generation DES (94%) in diabetic patients undergoing elective revascularization for multivessel disease without left main coronary stenosis. A total of 1900 patients were enrolled at 140 international centers from 2005 through 2010 and were followed for a minimum of 2 years (median among survivors, 3.8 years). A more frequent primary outcome occurrence (a composite of death from any cause, nonfatal myocardial infarction, and nonfatal stroke) was observed in the PCI group ($P = 0.005$), with 5-year rates of 26.6% in the PCI group and 18.7% in the CABG group, driven by a borderline reduction of all-cause mortality ($P = 0.049$) and by a markedly lower rate of myocardial infarction in the CABG group ($P < 0.001$), leading to the authors' conclusion that for patients with diabetes and advanced coronary artery disease, CABG was superior to PCI in that it significantly reduced rates of death and myocardial infarction.

In the CARDia trial (Kapur et al. 2010) (Coronary Artery Revascularization in Diabetes), 510 diabetic patients with multivessel or complex single-vessel CAD at 24 sites were enrolled and randomly assigned to either CABG or PCI with the use of

either BMS or DES and routine use of abciximab. There were no differences between CABG and PCI for the primary endpoint of 1-year composite of death, myocardial infarction, or stroke (12.4% in the CABG and 11.6% in the PCI group), whereas repeat revascularization was more common among patients assigned to PCI, and also a higher rate of stroke in patients underwent CABG.

Hence, taking currently available evidence into consideration, for diabetic patients with multivessel CAD, CABG is the best revascularization choice; however, among diabetic patients with multivessel disease and low SYNTAX score, PCI can be considered as a treatment alternative.

3.5.5 Unstable Angina and Non-ST-Segment Elevation Acute Coronary Syndromes

Unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI) are part of the continuum of acute coronary syndrome (ACS), and the primary difference between UA and NSTEMI mainly lies in whether the ischemia is severe enough to cause sufficient myocardial damage to release detectable quantities of a marker of myocardial injury. After early risk assessment (TIMI risk score, GRAC 2E risk score, etc.) soon after the diagnosis is made to identify patients at high immediate- and long-term risk for death and cardiovascular events, whether and when coronary angiography and revascularization be performed should be determined. The invasive strategy of angiography followed by revascularization (PCI or CABG) is aimed at relieving symptom and improving long-term prognosis, and which approach to choose is based on comprehensive consideration regards to overall quality of life, length of hospital stays, and potential risk associated with invasive and pharmacological treatments.

The issue of whether patients should undergo early invasive or conservative strategy has long been studied. In general, unstable patients are referred for immediate angiography, high-risk patients are assigned to an invasive strategy, and low-risk patients are assigned to a conservative strategy. A meta-analysis of seven trials that compared early invasive against conservative approach showed a significant reduction in risk for all-cause mortality (early invasive vs. conservative approach, RR = 0.75; 95% CI 0.63–0.90; $P < 0.001$) and myocardial infarction (early invasive vs. conservative approach, RR = 0.83; 95% CI 0.72–0.96; $P = 0.012$) at 2 years without excess of death and myocardial infarction at 1 month (Bavry et al. 2006). A further meta-analysis of eight RCTs showed a significant lower incidence of death, myocardial infarction, or rehospitalization for ACS (OR = 0.78; 95% CI 0.61–0.98) for the invasive strategy at 1 year (O'Donoghue et al. 2008), and mainly attributed to improved outcomes in biomarker-positive (high-risk) patients. The results of these studies demonstrate that age, diabetes, previous myocardial infarction, ST-segment depression, hypertension, body mass index (<25 kg/m^2 or >35 kg/m^2), and treatment strategy were independent predictors of death and myocardial infarction during follow-up. Hence, a routine invasive strategy should be recommended but the

importance of risk stratification in the decision-making process management should be equally valued. For patients who are eligible for invasive strategy, the timing of angiography and revascularization should be based on patient risk profile. The 2014 ESC/EACTS guidelines on myocardial revascularization recommended that patients at very high risk (as defined above) should be considered for urgent coronary angiography (in less than 2 h) (Kolh and Windecker 2014). In patients at high risk, with at least one primary high-risk criterion, an early invasive strategy within 24 h appears to be the reasonable timescale. In lower-risk subsets, with a GRACE risk score of <140 but with at least one secondary high-risk criterion, the invasive evaluation can be delayed without increased risk but should be performed during the same hospital stay, preferably within 72 h of admission. In other low-risk patients without recurrent symptoms, a noninvasive assessment of inducible ischemia should be performed before hospital discharge (Kolh and Windecker 2014).

In stabilized patients, the choice of revascularization modality can be made in analogy to patients with SCAD. In approximately one-third of patients, angiography will reveal single-vessel disease, allowing ad hoc PCI in most cases. However, in patients found to have multivessel disease (including the culprit lesion) after coronary angiography, there are three major options for revascularization: culprit lesion/vessel PCI only, multivessel PCI (including the culprit lesion), or CABG. For patients whom multivessel revascularization is deemed necessary, the revascularization strategy should be determined early by the Heart Team and based on the patient's clinical status, as well as the severity and distribution of the CAD and the characteristics of the lesion. CABG is often preferred over PCI for the treatment of patients with left main or left main equivalent disease, or three-vessel disease involving the left anterior descending artery in patients with a reduced left ventricular ejection fraction or treated diabetes.

The AWESOME (Morrison et al. 2001) and ERACI II (Rodriguez et al. 2001) trials compared CABG with PCI in patients who are angiographically eligible for either approach. These studies came to similar conclusions: long-term mortality was comparable with both strategies but revascularization rates were higher with PCI as the primary strategy. A limitation to both trials is that they were performed before the availability of drug-eluting stents, which markedly reduce the rate of revascularization. The ACUITY trial (Ben-Gal et al. 2010) also compared CABG with PCI in a propensity-matched analysis among patients with multivessel disease. PCI-treated patients had lower rates of stroke, myocardial infarction, bleeding, and renal injury, similar 1-month and 1-year mortality, but significantly higher rates of unplanned revascularization at both 1 month and 1 year. However, only 43% of CABG patients could be matched and there was a strong trend for a higher rate of major adverse cardiac events (MACE) at 1 year with PCI, compared with CABG (25.0% vs. 19.5%, respectively; P 1/4 0.05).

In non-ST-elevation ACS (NSTEACS) patients with multivessel disease for whom PCI is chosen as the revascularization strategy, the operator must decide between culprit only or multivessel PCI. Culprit-lesion PCI does not necessarily require a case-by-case review by the Heart Team when, on clinical or angiographic grounds, the procedure needs to be performed ad hoc after angiography, such as continuing or

recurrent ischemia, hemodynamic instability, pulmonary edema, recurrent ventricular arrhythmias, or total occlusion of the culprit coronary artery requiring urgent revascularization. After culprit-lesion PCI, patients with scores in the two higher terciles of the SYNTAX score should be discussed by the Heart Team, in the context of functional evaluation of the remaining lesions and assessment of patients' comorbidities and individual characteristics (Kolh and Windecker 2014). A retrospective study of 1240 patients with NSTEMI investigated the safety and efficacy of multivessel stenting versus culprit-only stenting with bare metal stents. Multivessel stenting was associated with a significant reduction in the composite endpoint of death, MI, or revascularization during a mean follow-up of 2.3 years (hazard ratio 0.80, 95% CI 0.64–0.99). However, the difference was entirely attributable to a lower revascularization rate. Safety endpoints did not differ between the two groups. Since there have been no randomized trials directly comparing complete to incomplete revascularization (ICR) in NSTEACS patients with multivessel disease, we recommend the assessment of clinical status and disease severity to guide clinical practice until further studies inform decision making between culprit lesion only or multivessel PCI be conducted.

3.5.6 ST-Segment Elevation Myocardial Infarction

ST-elevation myocardial infarction (STEMI) is a clinical syndrome defined by characteristic symptoms of myocardial ischemia in association with persistent electrocardiographic (ECG) ST-elevation and subsequent release of biomarkers of myocardial necrosis (O'Gara et al. 2013). For patients with STEMI, prompt restoration of myocardial blood flow is essential to optimize myocardial salvage and to reduce mortality, and the decision must be made as soon as possible as to whether reperfusion will be achieved with fibrinolytic agents, primary (direct) PCI, or bypass surgery. Here we will mainly address the reperfusion strategy, including primary and secondary PCI and CABG.

Primary PCI is defined as percutaneous catheter intervention in the setting of STEMI, without previous fibrinolysis. It has replaced fibrinolysis as the preferred reperfusion strategy in patients with STEMI, provided it can be performed in a timely manner in high-volume PCI centers with experienced operators and 24-h, 7-day catheterization laboratory activation (Kolh and Windecker 2014). Compared with fibrinolytic therapy, primary PCI produces higher rates of infarct artery patency, TIMI 3 flow, and access site bleeding and lower rates of recurrent ischemia, reinfarction, emergency repeat revascularization procedures, intracranial hemorrhage (ICH), and death (Keeley et al. 2003). Earlier, successful PCI also greatly decreases the complications of STEMI that result from longer ischemic times or unsuccessful fibrinolytic therapy, allowing earlier hospital discharge and resumption of daily activities. Primary PCI has its greatest survival benefit in high-risk patients (Tebbe et al. 1995). For patients undergoing primary PCI, stenting should be preferred over

balloon angioplasty in the setting of primary PCI as it reduces the risk of abrupt closure, re-infarction, and repeat revascularization. Meanwhile, thrombus aspiration has been proposed as an adjunct during primary PCI, to further improve epicardial and myocardial reperfusion by prevention of distal embolization of thrombotic material and plaque debris.

Early, routine, post-thrombolysis angiography with subsequent PCI (if required) has been proven to reduce the rates of re-infarction and recurrent ischemia, which is referred as secondary PCI, compared with a strategy of "watchful waiting" (in this situation, angiography and revascularization were indicated only in patients with spontaneous or induced severe ischemia or LV dysfunction). In cases of failed fibrinolysis, or if there is evidence of re-occlusion or re-infarction with recurrence of ST-segment elevation, the patient should undergo immediate coronary angiography and rescue PCI (Gershlick et al. 2005).

CABG has a limited role in the acute phase of STEMI other than for cardiogenic shock, but it may be indicated for failed PCI, for coronary anatomy not amenable to PCI, and at the time of surgical repair of a mechanical defect, such as ventricular septal, papillary muscle, or free-wall rupture (O'Gara et al. 2013). The implementation of standard operative approach, such as on-pump beating-heart surgery, off-pump techniques, or adjunctive temporary mechanical circulatory support devices has led to improved survival rates after CABG in the acute hospital phase, but the timing of urgent CABG in patients with STEMI should be cautiously considered, and also an alternative antiplatelet strategy in patients with STEMI who may require urgent CABG during their index hospitalization (Hillis et al. 2011).

3.6 Secondary Prevention

Patients with established cardiovascular disease (CVD) have a high risk of subsequent cardiovascular events, including myocardial infarction (MI), stroke, and death; thus, we recommend that all patients with established coronary heart disease should receive interventions to prevent a subsequent CVD event. These are termed secondary prevention, including therapeutic lifestyle changes (TLCs) and adjunctive drug therapies, which can be briefly referred to as *ABCDE plan*; A for Aspirin and Anti-angina therapy, B for Beta-blockers and Blood pressure control, C for Cholesterol lowing and Cigarette quitting, D for Diet control and Diabetes treatment, E for Exercise and Education. The reduction of mortality and improvement of life quality due to effective secondary prevention has been determined by clinical studies and recommended by clinical guidelines (Smith et al. 2006). For patients at high risk (those with a prior CVD event as well as those whose 10-year risk is >10%), older adults, accompanied with diabetes mellitus, chronic kidney disease, interventions to prevent CVD events should be more emphasized and intensified.

3.6.1 Medical Therapy

Medical therapy focuses on comprehensive risk factor modification, including beta-blockers, antiplatelet agents, statins, and so on. Multiple clinical trials have shown that beta-blocker therapy can reduce recurrent MI, sudden cardiac death, and mortality in patients after MI, even in those who are normotensive; and the AHA has recommended that a beta-blocker regimen be initiated and maintained indefinitely for the secondary prevention of CAD in all patients after having an MI, unless contraindicated (Kulik et al. 2015). Antiplatelet agents are also recommended in all patients for the secondary prevention of CAD for peruse of net clinical benefits and reduction in ischemic events. Oral antiplatelet agents for secondary prevention include the cyclo-oxygenase-1 inhibitor aspirin, the ADP-dependent P2Y12 inhibitors clopidogrel, prasugrel and ticagrelor, and aspirin represents the cornerstone in secondary prevention of patients with stable CAD or ACS. The evidence is also well studied that reducing cholesterol levels decreases the risk of recurrent coronary events, and evidence-based cholesterol-lowering guidelines have been established, that statins should be the initial medication accompanied by beta-blockers and other medications for secondary prevention.

3.6.2 Exercise

Regular physical activity (PA) independently decreases the risk of cardiovascular disease (CVD) while also having a positive, dose-related impact on other cardiovascular risk factors. It has increasingly become a focus of CVD primary and secondary prevention (Varghese et al. 2016). Exercise-based cardiac rehabilitation (CR) is the cornerstone for secondary prevention of CVD. Indications include stable angina pectoris, myocardial infarction, undergone cardiac surgery (CABG, valve replacement and so on) and PCI. After pre-exercise screening is completed to identify those in whom exercise should be delayed or prohibited, the general recommendation for patients is 30–60 min daily of moderate-intensity PA for at least 5 days of the week and performed at an intensity of 40–80% of the peak heart rate (Fletcher et al. 2013). To note, some studies also suggest that extreme exercise may evoke acute elevations in troponin I and B-type natriuretic peptide and evidence of transient myocardial dysfunction, which means excessive exercise, may have some acute and/or chronic adverse effects (Trivax et al. 2010). It's more likely a J-curve or U-curve pattern regarding the exercise volume and clinical outcomes, where it is preferable to be in the middle of the distribution.

References

Anderson HV, Willerson JT (1993) Thrombolysis in acute myocardial infarction. N Engl J Med 329(10):703–709

Astrup T, Permin PM (1947) Fibrinolysis in the animal organism. Nature 159(4046):681

Aylward PE, Wilcox RG, Horgan JH et al (1996) Relation of increased arterial blood pressure to mortality and stroke in the context of contemporary thrombolytic therapy for acute myocardial infarction. a randomized trial. GUSTO-I investigators. Ann Intern Med 125(11):891–900

Baigent C, Collins R, Appleby P, Parish S, Sleight P, Peto R (1998) ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. the ISIS-2 (Second international study of infarct survival) collaborative group. BMJ 316(7141):1337–43

Bangalore S, Guo Y, Samadashvili Z, Blecker S, Hannan EL (2016) Revascularization in patients with multivessel coronary artery disease and severe left ventricular systolic dysfunction: everolimus-eluting stents versus coronary artery bypass graft surgery. Circulation 133(22):2132–2140

Bar FW, Meyer J, Vermeer F et al (1997) Comparison of saruplase and alteplase in acute myocardial infarction. SESAM study group. the study in Europe with saruplase and alteplase in myocardial infarction. Am J Cardiol 79(6):727–732

Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT (2006) Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. J Am Coll Cardiol 48(7):1319–1325

Ben-Gal Y, Moses JW, Mehran R et al (2010) Surgical versus percutaneous revascularization for multivessel disease in patients with acute coronary syndromes: analysis from the ACUITY (acute catheterization and urgent intervention triage strategy) trial. JACC Cardiovasc Interv 3(10):1059–1067

Berkowitz SD, Granger CB, Pieper KS et al (1997) Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. the global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO) I investigators. Circulation 95(11):2508–2516

Bode C, Smalling RW, Berg G et al (1996) Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. The RAPID II Investigators. Circulation 94(5):891–898

Bolte J, Neumann U, Pfafferott C et al (2001) Incidence, management, and outcome of stent loss during intracoronary stenting. Am J Cardiol 88(5):565–567

Bramer S, van Straten AH, Soliman Hamad MA, Berreklouw E, Martens EJ, Maessen JG (2010) The impact of new-onset postoperative atrial fibrillation on mortality after coronary artery bypass grafting. Ann Thorac Surg 90(2):443–449

Caracciolo EA, Davis KB, Sopko G et al (1995) Comparison of surgical and medical group survival in patients with left main coronary artery disease. long-term CASS experience. Circulation 91(9):2325–2334

Chaitman BR, Alderman EL, Sheffield LT et al (1983) Use of survival analysis to determine the clinical significance of new Q waves after coronary bypass surgery. Circulation 67(2):302–309

Chapin JC, Hajjar KA (2015) Fibrinolysis and the control of blood coagulation. Blood Rev 29(1):17–24

Collen D, Lijnen HR (2005) Thrombolytic agents. Thromb Haemost 93(4):627–630

Collen D, Lijnen HR. Tissue-type plasminogen activator: a historical perspective and personal account (1538–7933 (Print))

Dauerman HL, Cutlip DE, Sellke FW (1996) Intracoronary thrombolysis in the treatment of graft closure immediately after CABG. Ann Thorac Surg 62(1):280–283

del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M (1998) PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle

cerebral artery stroke. PROACT investigators. prolyse in acute cerebral thromboembolism. Stroke 29(1):4–11
Desai ND, Cohen EA, Naylor CD, Fremes SE (2004) Radial artery patency study I. a randomized comparison of radial-artery and saphenous-vein coronary bypass grafts. N Engl J Med 351(22):2302–9
Diodato M, Chedrawy EG (2014) Coronary artery bypass graft surgery: the past, present, and future of myocardial revascularisation. Surg Res Pract 2014:726158
Ellis SG, Roubin GS, King SB 3rd et al (1988) Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. Circulation 77(2):372–379
Farkouh ME, Domanski M, Sleeper LA et al (2012) Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 367(25):2375–2384
Fletcher GF, Ades PA, Kligfield P et al (2013) Exercise standards for testing and training: a scientific statement from the American heart association. Circulation 128(8):873–934
Franzosi MG, Santoro E, De Vita C et al (1998) Ten-year follow-up of the first megatrial testing thrombolytic therapy in patients with acute myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-1 study. GISSI Investig Circ 98(24):2659–2665
Furlan AJ, Abou-Chebl A (2002) The role of recombinant pro-urokinase (r-pro-UK) and intra-arterial thrombolysis in acute ischaemic stroke: the PROACT trials. prolyse in acute cerebral thromboembolism. Curr Med Res Opin 18 Suppl 2:s44–s47
Gershlick AH, Stephens-Lloyd A, Hughes S et al (2005) Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. N Engl J Med 353(26):2758–2768
Gore JM, Granger CB, Simoons ML et al (1995) Stroke after thrombolysis. mortality and functional outcomes in the GUSTO-I trial. global use of strategies to open occluded coronary arteries. Circulation 92(10):2811–8
Group BDS, Frye RL, August P et al (2009) A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 360(24):2503–2515
GUSTO Investigators (1993) An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 329(10):673–682
Head SJ, Kaul S, Mack MJ et al (2013) The rationale for heart team decision-making for patients with stable, complex coronary artery disease. Eur Heart J 34(32):2510–2518
Hillis LD, Smith PK, Anderson JL et al (2011) ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. Circulation 124(23):e652–e735
Hlatky MA, Boothroyd DB, Bravata DM et al (2009) Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet 373(9670):1190–1197
Huber MS, Mooney JF, Madison J, Mooney MR (1991) Use of a morphologic classification to predict clinical outcome after dissection from coronary angioplasty. Am J Cardiol 68(5):467–471
Huynh T, Cox JL, Massel D et al (2004) Predictors of intracranial hemorrhage with fibrinolytic therapy in unselected community patients: a report from the FASTRAK II project. Am Heart J 148(1):86–91
Joner M, Finn AV, Farb A et al (2006) Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 48(1):193–202
Kapur A, Hall RJ, Malik IS et al (2010) Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. J Am Coll Cardiol 55(5):432–440
Katritsis DG, Siontis GC, Kastrati A et al (2011) Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes. Eur Heart J 32(1):32–40
Keeley EC, Boura JA, Grines CL (2003) Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 361(9351):13–20
Kolh P, Windecker S (2014) ESC/EACTS myocardial revascularization guidelines 2014. Eur Heart J 35(46):3235–3236

Kulik A, Ruel M, Jneid H et al (2015) Secondary prevention after coronary artery bypass graft surgery: a scientific statement from the American heart association. Circulation 131(10):927–964

Loop FD, Lytle BW, Cosgrove DM et al (1986) Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. N Engl J Med 314(1):1–6

Malmberg K, Yusuf S, Gerstein HC et al (2000) Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to assess strategies for ischemic syndromes) Registry. Circulation 102(9):1014–1019

Marder VJ, Sherry S (1988) Thrombolytic therapy: current status (1). N Engl J Med 318(23):1512–1520

Mariscalco G, Klersy C, Zanobini M et al (2008) Atrial fibrillation after isolated coronary surgery affects late survival. Circulation 118(16):1612–1618

McKenney PA, Apstein CS, Mendes LA et al (1994) Increased left ventricular diastolic chamber stiffness immediately after coronary artery bypass surgery. J Am Coll Cardiol 24(5):1189–1194

Meyer J (1989) Randomised double-blind trial of recombinant pro-urokinase against streptokinase in acute myocardial infarction. PRIMI trial study group. Lancet 1(8643):863–868

Mohr FW, Morice MC, Kappetein AP et al (2013) Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 381(9867):629–638

Morrison DA, Sethi G, Sacks J et al (2001) Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. investigators of the Department of Veterans affairs cooperative study #385, the Angina with extremely serious operative mortality evaluation (AWESOME). J Am Coll Cardiol 38(1):143–9

Navarese EP, Gurbel PA, Andreotti F et al (2013) Optimal timing of coronary invasive strategy in non-ST-segment elevation acute coronary syndromes: a systematic review and meta-analysis. Ann Intern Med 158(4):261–270

Nerlekar N, Ha FJ, Verma KP et al (2016) Percutaneous coronary intervention using drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary artery stenosis: a meta-analysis of randomized trials. Circ Cardiovasc Interv 9(12)

O'Donoghue M, Boden WE, Braunwald E et al (2008) Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. JAMA 300(1):71–80

O'Gara PT, Kushner FG, Ascheim DD et al (2013) 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. Circulation 127(4):e362–e425

Park SJ, Ahn JM, Kim YH et al (2015) Temporal trends in revascularization strategy and outcomes in left main coronary artery stenosis: data from the ASAN medical center-left MAIN revascularization registry. Circ Cardiovasc Interv 8(3):e001846

Puskas JD, Halkos ME, DeRose JJ et al (2016) Hybrid coronary revascularization for the treatment of multivessel coronary artery disease: a multicenter observational study. J Am Coll Cardiol 68(4):356–365

Ragosta M, Dee S, Sarembock IJ, Lipson LC, Gimple LW, Powers ER (2006) Prevalence of unfavorable angiographic characteristics for percutaneous intervention in patients with unprotected left main coronary artery disease. Catheter Cardiovasc Interv 68(3):357–362

Rijken DC, Wijngaards G, Zaal-de Jong M, Welbergen J (1979) Purification and partial characterization of plasminogen activator from human uterine tissue. Biochim Biophys Acta 580(1):140–153

Rijken DC, Wijngaards G, Welbergen J (1980) Relationship between tissue plasminogen activator and the activators in blood and vascular wall (0049–3848 (Print))

Riley RF, Don CW, Powell W, Maynard C, Dean LS (2011) Trends in coronary revascularization in the United States from 2001 to 2009: recent declines in percutaneous coronary intervention volumes. Circ Cardiovasc Qual Outcomes 4(2):193–197

Roberts AJ, Niarchos AP, Subramanian VA et al (1977) Systemic hypertension associated with coronary artery bypass surgery. Predisposing factors, hemodynamic characteristics, humoral profile, and treatment. J Thorac Cardiovasc Surg 74(6):846–859

Rodriguez A, Bernardi V, Navia J et al (2001) Argentine randomized study: coronary angioplasty with stenting versus Coronary Bypass surgery in patients with multiple-vessel disease (ERACI II): 30-day and one-year follow-up results. ERACI II investigators. J Am Coll Cardiol 37(1):51–58

Schuhlen H, Kastrati A, Dirschinger J et al (1998) Intracoronary stenting and risk for major adverse cardiac events during the first month. Circulation 98(2):104–111

Serruys PW, Morice MC, Kappetein AP et al (2009) Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 360(10):961–972

Smalling RW, Bode C, Kalbfleisch J et al (1995) More rapid, complete, and stable coronary thrombolysis with bolus administration of reteplase compared with alteplase infusion in acute myocardial infarction. RAPID Investig Circ 91(11):2725–2732

Smith SC Jr, Allen J, Blair SN et al (2006) AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and blood institute. Circulation 113(19):2363–2372

Spiecker M, Windeler J, Vermeer F et al (1999) Thrombolysis with saruplase versus streptokinase in acute myocardial infarction: five-year results of the PRIMI trial. Am Heart J 138(3 Pt 1):518–524

Stankovic G, Orlic D, Corvaja N et al (2004) Incidence, predictors, in-hospital, and late outcomes of coronary artery perforations. Am J Cardiol 93(2):213–216

Stephan WJ, O'Keefe JH Jr, Piehler JM et al (1996) Coronary angioplasty versus repeat coronary artery bypass grafting for patients with previous bypass surgery. J Am Coll Cardiol 28(5):1140–1146

Suma H, Tanabe H, Takahashi A et al (2007) Twenty years experience with the gastroepiploic artery graft for CABG. Circulation 116(11 Suppl):I188–I191

Tanne D, Gottlieb S, Caspi A et al (1998) Treatment and outcome of patients with acute myocardial infarction and prior cerebrovascular events in the thrombolytic era: the Israeli Thrombolytic National Survey. Arch Intern Med 158(6):601–606

Tebbe U, Windeler J, Boesl I et al (1995) Thrombolysis with recombinant unglycosylated single-chain urokinase-type plasminogen activator (saruplase) in acute myocardial infarction: influence of heparin on early patency rate (LIMITS study). liquemin in myocardial infarction during thrombolysis with saruplase. J Am Coll Cardiol 26(2):365–73

Thygesen K, Alpert JS, White HD (2007) Joint ESCAAHAWHFTFftRoMI. Universal definition of myocardial infarction. Eur Heart J 28(20):2525–2538

Topol EJ, Ohman EM, Armstrong PW et al (2000) Survival outcomes 1 year after reperfusion therapy with either alteplase or reteplase for acute myocardial infarction. Circulation 102:1761–1765

Trivax JE, Franklin BA, Goldstein JA et al (2010) Acute cardiac effects of marathon running. J Appl Physiol (1985) 108(5):1148–53

Varghese T, Schultz WM, McCue AA et al (2016) Physical activity in the prevention of coronary heart disease: implications for the clinician. Heart 102(12):904–909

Velazquez EJ, Lee KL, Deja MA et al (2011) Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med 364(17):1607–1616

Velazquez EJ, Lee KL, Jones RH et al (2016) Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med 374(16):1511–1520

Villareal RP, Hariharan R, Liu BC et al (2004) Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. J Am Coll Cardiol 43(5):742–748

Wilcox RG (1995) Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. international joint efficacy comparison of thrombolytics. Lancet 346(8971):329–336

Wu Z, Van de Werf F, Stassen T, Mattsson C, Pohl G, Collen D (1990) Pharmacokinetics and coronary thrombolytic properties of two human tissue-type plasminogen activator variants lacking

the finger-like, growth factor-like, and first kringle domains (amino acids 6–173) in a canine model. J Cardiovasc Pharmacol 16(2):197–203

Yau TM, Fedak PW, Weisel RD, Teng C, Ivanov J (1999) Predictors of operative risk for coronary bypass operations in patients with left ventricular dysfunction. J Thorac Cardiovasc Surg 118(6):1006–1013

Yokoyama Y, Chaitman BR, Hardison RM et al (2000) Association between new electrocardiographic abnormalities after coronary revascularization and five-year cardiac mortality in BARI randomized and registry patients. Am J Cardiol 86(8):819–824

Yusuf S, Zucker D, Peduzzi P et al (1994) Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. Lancet 344(8922):563–570

Zarich SW, Kowalchuk GJ, Weaver WD et al (1995) Sequential combination thrombolytic therapy for acute myocardial infarction: results of the Pro-Urokinase and t-PA enhancement of thrombolysis (PATENT) trial. J Am Coll Cardiol 26(2):374–379