Chapter 8

Medical and Surgical Management and Outcomes for Coronary Artery Disease

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Additional information is available at the end of the chapter

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Abstract

Coronary artery disease (CAD) is a major cause of death and disability in developed countries. Although coronary artery disease mortality rates worldwide have declined over the past decades, CAD remains responsible for about one third or more of all deaths in individuals over the age of 35 years. Various methods of treatment have been proposed including medical therapy, catheter-based interventions, and lastly, coronary artery bypass grafting. The purpose of this chapter is to outline those treatment regimens and examine the literature detailing their outcomes in hopes of guiding treatment.

Keywords: coronary artery disease, management, outcomes, coronary artery bypass grafting, PCI

1. Introduction: coronary artery disease, an overview and disease burden

Coronary artery disease (CAD) represents a spectrum of clinical syndromes caused by insufficient coronary blood flow to the myocardium. It is almost always due to subintimal atheroma deposition leading to arterial luminal stenosis or occlusion and wall thickening. Coronary atherosclerosis usually involves the proximal portions of larger coronary arteries, especially at or just beyond branching sites. Myocardial ischemia and necrosis occur when coronary blood flow is impaired by atherosclerotic stenosis, resulting in increased oxygen demand. In the setting of symptomatic CAD, compensatory physiologic processes are insufficient to provide adequate myocardial perfusion. The effect is either supply ischemia, responsible for myocardial infarction (MI) and most episodes of unstable angina, or demand ischemia, where coronary blood flow is insufficient during period of increased myocardial demands

from exercise, tachycardia, fever, hypertension, or emotional distress [1]. Because the heart has virtually no stores of oxygen and relies entirely on aerobic metabolism, within seconds of coronary occlusion, its high rate of energy expenditures results in a sudden decline of oxygen tension and left ventricular function impairment. The subendocardium is most vulnerable to myocardial ischemia as its collateral flow is lowest; thus, myocardial necrosis progresses toward the epicardium with continued ischemia.

Coronary artery disease is a major cause of death and disability in developed countries. Although coronary artery disease mortality rates worldwide have declined over the past decades, CAD remains responsible for about one third or more of all deaths in individuals over the age of 35 years. In 2017, the Heart Disease and Stroke Statistics update of the American Heart Association reported that 16.5 million persons aged 20 years or older in the United States have coronary artery disease, with a slight male predominance of 55%. In 2013, The Global Burden of Disease estimated that 17.3 million deaths worldwide were related to cardiovascular disease, a 41% increase since 1990 [2–6]. Significant risk factors include but are not limited to age, male sex, hypertension, hyperlipidemia, diabetes mellitus, obesity, tobacco use, family history, and peripheral vascular disease. As one can see, the incidence and prevalence of coronary artery disease are staggering; thus, managing and treating these patients is of utmost concern.

2. Treatment goals of coronary artery disease

The goal of treatment for coronary artery disease is to decrease the frequency and severity of angina symptoms and to increase the duration of one's functional capacity (duration of angina-free exercise). Furthermore, one hopes to prolong life and reduce the incidence of acute coronary syndromes. Such goals are accomplished by increasing myocardial oxygen supply or decreasing myocardial oxygen consumption or both. The reduction in cardiac mortality and incidents of myocardial infarction is achieved by pharmacotherapy and stabilization of atherosclerotic plaques. Comorbid conditions that are treatable could aggravate

Goal	How to Achieve the Goal
Abolish or reduce anginal episodes	Trial of antianginal drugs Coronary revascularization
Increase angina-free walking or exercise	Antianginal drugs Coronary revascularization
Prolong life and reduce acute coronary events (unstable angina, myocardial infarction, coronary death)	Lifestyle modification Modify or correct risk factors Daily aspirin Pharmacotherapy of dyslipidemia Control of hypertension Beta blockers, ACE inhibitors, and CABG surgery in special situations

Figure 1. Management of chronic stable angina.

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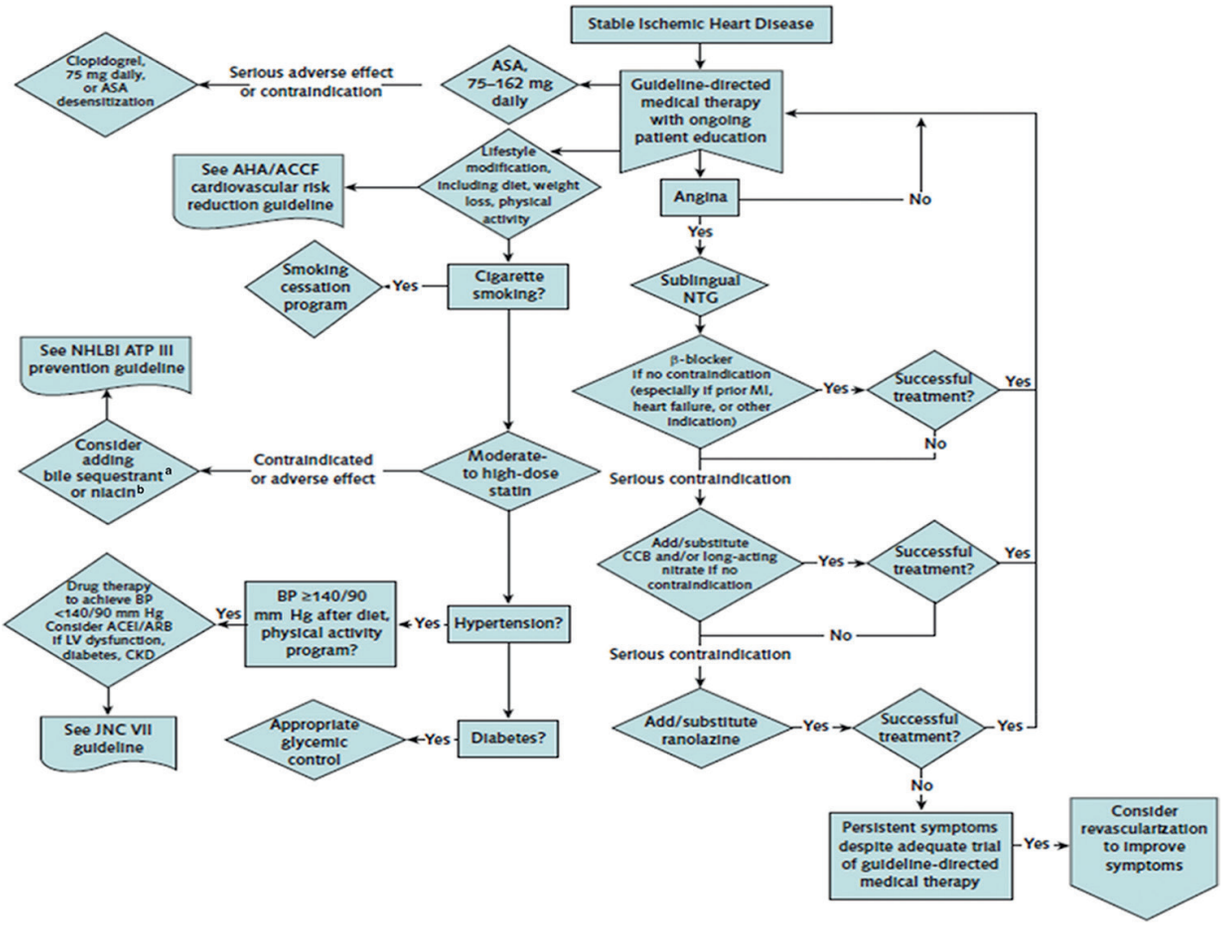

Figure 2. Treatment algorithm for stable ischemic heart disease. *From Ref. [11].

angina, and these conditions must be sought and treated in all patients who have chronic stable angina. There are three options for treatment of stable angina-drug therapy, coronary balloon angioplasty, and coronary artery bypass graft surgery [7–10].

As no two patients are the same, therapy should be individualized and consideration should be given to the risks and benefits of each therapeutic option with regard to symptom relief and longevity. **Figure 1** shows the treatment goals for chronic stable angina and how to achieve them [7–10], and **Figure 2** shows the treatment algorithm for chronic stable angina [11].

3. Medical management of coronary artery disease

From the above treatment algorithm, one can see that there is a large armamentarium at one's disposal for the treatment of coronary artery disease. The uses of these drugs and their mechanisms of action will be outlined below.

Beta blockers have been shown to be very effective in the treatment and management of stable angina. These agents decrease myocardial work and improve exercise tolerance. The primary

mechanism of this benefit is through a competitive blockade of β-adrenergic receptors that reduces heart rate and contractility and therefore myocardial O_2 demand. In addition, beta blockers decrease exercise-induced vasoconstriction and blunt the rise in systolic blood pressure during exercise. Beta blockers also increase coronary perfusion by prolonging diastolic perfusion time. Such drugs should be titrated to a heart rate of 50–60 beats per minute at rest and less than 100 beats per minute with exercise.

Calcium channel blockers act mainly by vasodilatation and reduction of peripheral vascular resistance. The nondihydropyridine agents (verapamil and diltiazem), a T-channel blocker (mibefradil), and bepridil inhibit the sinoatrial and atrioventricular nodes and thus also reduce myocardial oxygen demand. The dihydropyridine agents (e.g., nifedipine, amlodipine, felodipine, and nisoldipine) do not affect the sinoatrial or atrioventricular nodes in humans; their mechanism of action is primarily by dilating the coronary arteries and reducing peripheral vascular resistance (and thus reducing myocardial O_2 demand) and by increasing coronary blood flow. Calcium channel blockers block the entry of calcium into the calcium channels in both smooth muscle and myocardium so that less calcium is available to the contractile apparatus. The net result is vasodilatation and a decrease in myocardial contractility. All calcium channel blockers inhibit L-type calcium current in arterial smooth muscle at low concentration and therefore dilate coronary arteries. A major antianginal effect is coronary vessel dilatation and prevention of exercise-induced vessel constriction. Afterload reduction and, in the case of nondihydropyridine channel blockers, the suppressant effects on the sinoatrial node and myocardium also contribute to antianginal efficacy.

Nitrates are coronary vasodilators, and they are anti-ischemic, although the antianginal effects are more far-reaching. Nitrates produce venodilatation, thereby reducing preload, and high doses of nitrates also reduce afterload through arterial vasodilatation. The reduction of preload is secondary to reduced venous return, which in turn reduces ventricular volume and intracavitary pressure and ventricular wall stress. Nitrates can produce dilatation of the site of stenotic coronary lesions and thus increase perfusion to the ischemic myocardium. Nitrates also increase collateral blood flow to ischemic areas. These drugs have not been shown to have an impact on cardiac death from coronary artery disease; however, they have been shown to reduce the rate of angina frequency and increase time to ischemia ECG findings on stress test.

Ranolazine is a selective inhibitor of late sodium influx into myocytes, reducing myocardial contractility. This drug is usually used in combination with beta blockers significantly reducing the frequency of angina and increases exercise duration and time to onset of angina.

Statins are lipid-lowering drugs that work by inhibiting HMG-CoA Reductase. Improvement of myocardial ischemia during ambulatory monitoring has been shown in several studies; however, it is not known whether these agents improve exercise performance [12]. Lipid-lowering agents are recommended for patients with stable angina who have dyslipidemia because these agents have an important influence on prognosis for these patients. High intensive therapy targets an LDL reduction of greater than 50% in high-risk patients and a reduction of 30–50% in those patients who cannot tolerate a high-intensity treatment regimen.

ACE inhibitors (captopril, enalapril, and lisinopril) work by inhibiting the angiotensin-converting enzyme. These drugs are a class I recommendation for patients with chronic CAD with LV dysfunction LVEF <40% or diabetes and a class II recommendation for CAD patients without these features [13, 14].

Daily use of aspirin has been shown to reduce the incidence of sudden death and acute myocardial infarction in stable angina. In the Swedish Angina Pectoris Aspirin Trial (SAPAT), daily use of aspirin was associated with a 34% reduction in the incidence of sudden death and acute myocardial infarction, with an absolute reduction of 12 sudden deaths for every 1000 patients treated during the 15-month period [15]. The relative reduction in secondary endpoints (vascular events, vascular death, all-cause mortality, and stroke) ranged from 22 to 32%. There was no difference in major bleeding episodes, including hemorrhagic strokes, between the aspirin and placebo groups. On the basis of these data and available data of the usefulness of aspirin in acute myocardial infarction and unstable angina, it is mandatory that aspirin be used in all patients with stable angina, unless they are unable to tolerate the medication because of either an allergic reaction or intolerable gastrointestinal side effects [8, 16].

Clopidogrel works by selectively inhibiting the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Patients who are intolerant to aspirin therapy may be treated with clopidogrel. Long-term treatment with a combination of aspirin plus clopidogrel is not superior to aspirin treatment alone and increases the risk of bleeding [17], and it is not recommended for treatment of patients with stable angina. However, combination of aspirin plus clopidogrel for up to 3–12 months after coronary artery stenting reduces adverse clinical outcomes and is indicated in this group of patients.

4. Percutaneous coronary intervention (PCI)

PCI has become one of the most commonly performed medical procedures in the United States, with more than 600,000 procedures performed annually. Over the past decade, the use of drug-eluting stents (DESs) has supplanted the use of older stents, referred to as bare-metal stents (BMSs). Almost all percutaneous coronary interventions (PCIs) performed currently involve stent placement. Thus, although the term percutaneous coronary intervention refers to any therapeutic coronary intervention, it has become essentially synonymous with coronary stent implantation. PCI is performed for coronary revascularization in patients with stable coronary disease as well as, in the appropriate clinical settings, in those with acute coronary syndromes. In **Figures 3** and **4**, one can see a schematic diagram of a PCI [18].

Indications for PCI include:

1. Moderate-to-severe stable angina with evidence of reversible ischemia
2. High-risk unstable angina or non-ST segment elevation myocardial infarction
3. Acute ST segment elevation myocardial infarction

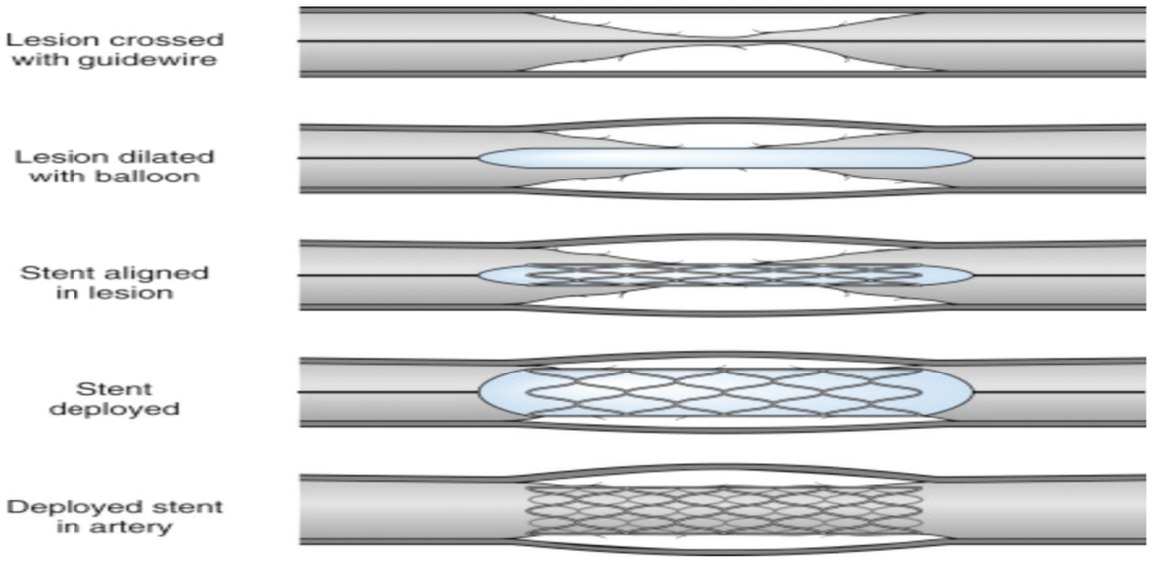

Figure 3. Schematic diagram of a PCI.

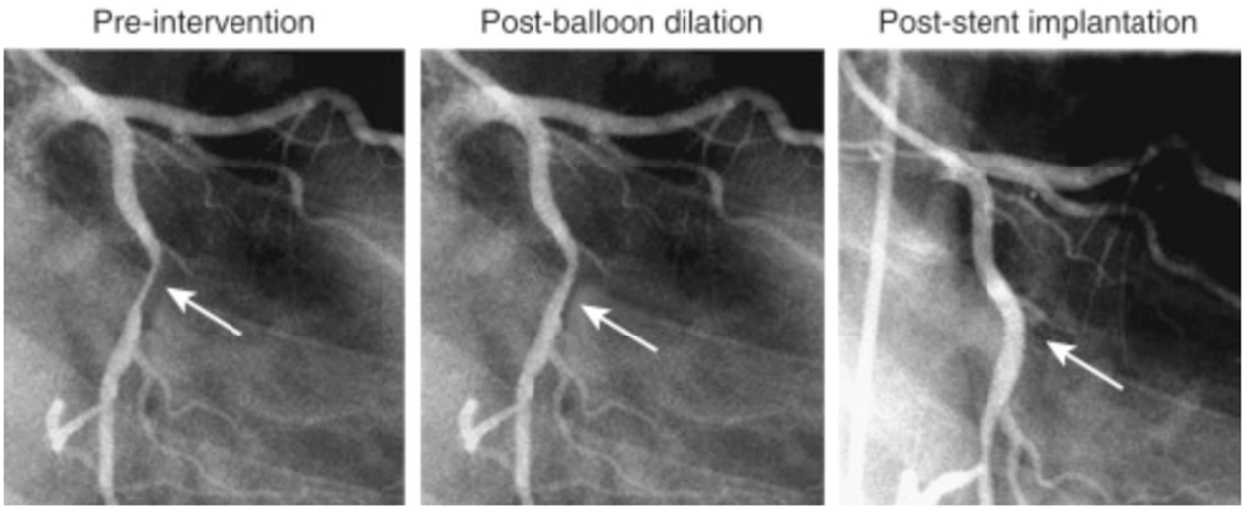

Figure 4. Percutaneous intervention of the circumflex artery seen angiographically [17]. Images from [18].

4. Rescue percutaneous coronary intervention after failed thrombolysis
5. Cardiogenic shock after myocardial infarction
6. Revascularization after successful resuscitation
7. Patients with diabetes mellitus

The only absolute contraindication to PCI is the lack of vascular access or active untreatable severe bleeding, which precludes the use of anticoagulation and antiplatelet agents. Relative contraindications include the following:

- A bleeding diathesis or other conditions that predispose to bleeding during antiplatelet therapy.

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- Severe renal insufficiency unless the patient is on hemodialysis or has severe electrolyte abnormalities.
- Sepsis.
- Poor patient compliance with medications.
- A terminal condition, such as advanced or metastatic malignancy, that indicates a short life expectancy.
- Other indications for open-heart surgery.
- Anatomic features of poor success.
- Failure of previous PCI or not amenable to PCI based on previous angiograms.
- Severe cognitive dysfunction or advanced physical limitations.

Patients generally should not undergo PCI if the following conditions are present:

- Only a very small area of myocardium is at risk.
- There is no objective evidence of ischemia (unless the patient has clear anginal symptoms and has not had a stress test) with either noninvasive or invasive testing (e.g., fractional flow reserve). One should also beware of false-negative stress tests in patients with left-main CAD.
- There is a low likelihood of technical success.
- The patient has left main or multivessel CAD with a high SYNTAX score and is a candidate for coronary artery bypass grafting (CABG).
- There is insignificant stenosis (less than 50% luminal narrowing).
- The patient has end-stage cirrhosis with portal hypertension resulting in encephalopathy or visceral bleeding.

Following PCI, the patient should be placed on antiplatelet therapy. Patients who are already on aspirin therapy should continue with 81 mg of aspirin daily. Those who are not on aspirin should receive 325 mg of non–enteric-coated aspirin preferably 24 hours prior to PCI, after which aspirin should be continued indefinitely at a dose of 81 mg daily. A loading dose of a P2Y12 inhibitor should be given prior to PCI with stent placement. Following a loading dose of a P2Y12 inhibitor, a maintenance dose is continued. The recommendations for dose and duration are as follows:

- In patients undergoing elective BMS implantation, the duration of P2Y12 inhibitor therapy should be a minimum of 1 month.
- For patient undergoing elective DES implantation (with a second-generation DES) for stable ischemic heart disease, the duration of P2Y12 inhibitor therapy should be at least 6 months.
- For patients undergoing stent BMS or DES implantation in the setting of ACS, clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be continued for at least 12 months. In this setting, ticagrelor and prasugrel are preferred over clopidogrel.

- Shorter duration therapy may be reasonable in patients at high risk for bleeding. Conversely, longer duration therapy may be reasonable in those at higher risk for ischemia but not for bleeding.

5. Coronary artery bypass grafting (CABG)

The decision for surgery is made based on the comprehensive evaluation of the patient. Anatomic considerations that favor recommendation for CABG include presence of significant LM or proximal LAD CAD, multivessel CAD, and presence of lesions not amenable to stenting. The presence of diabetes also favors surgical revascularization over stenting in operable patients. Depressed ejection fraction has been recognized as an additional indication for CABG.

Although the coronary anatomy may be suitable for bypass, each patient's comorbidities should be considered in the overall risk-benefit analysis. Preoperative renal insufficiency, peripheral vascular disease, recent myocardial infarction, or recent stroke, as well as emergency operation and cardiogenic shock, has been identified as factors that increase mortality. The decision to offer CABG or PCI should be determined by a multidisciplinary heart team that evaluates the appropriate therapy on a case-by-case basis.

The current American Heart Association Guidelines for coronary artery bypass grafting can be found in **Figure 5**.

6. A review of the literature: which treatment is best?

Three early prospective randomized trials comparing CABG with medical therapy were conducted in the late 1970s and were reported in the early 1980s. The Veterans' Affairs (VA) cooperative trial, European Coronary Surgery Study (ECSS), and Coronary Artery Surgery Study (CASS) showed long-term superiority of surgery over medical therapy in patients with left main (LM) coronary artery disease, significant coronary artery disease involving the LAD artery, and multivessel disease.

The first study was reported in 1982 in the European Coronary Surgery Study [19]. This study randomized 768 men to medical or surgical treatment. In follow-up extending to 8 years, survival was significantly improved by surgery in patients with significant three-vessel disease and in patients with significant stenosis in the proximal LAD coronary artery who had two- or three-vessel disease. Compared with medically treated patients, late mortality was reduced by 53% at 5 years in surgically treated patients, and among those with three-vessel disease, the 5-year mortality rate was lowered by 66%. In the subgroup of patients with significant narrowing of the proximal LAD coronary artery, the 5-year mortality rate was lowered 60% by surgery.

The second study reporting the efficacy of coronary revascularization was the 1984 Veterans Administration study [20]. This study evaluated the long-term survival after CABG in 686 patients with stable angina, and patients were observed for an average of 11.2 years. The 7-year survival curves for the total population of patients showed a statistically significant survival benefit of 77% with surgical therapy compared with 70% survival with medical

AHA/ACC Guidelines for CABG *
Asymptomatic/Mild Angina
Class I 1. Left main stenosis 2. Left main equivalent (proximal LAD and proximal circumflex) 3. Three-vessel disease
Class IIa 1. Proximal LAD stenosis and one- or two-vessel disease
Class IIb 1. One- or two-vessel disease not involving proximal LAD If a large territory at risk on noninvasive studies or LVEF≤50%, IIa and IIb become class I indications
Stable Angina
Class I 1. Left main stenosis 2. Left main equivalent (proximal LAD and proximal circumflex) 3. Three-vessel disease 4. Two-vessel disease with proximal LAD stenosis and EF <50% or demonstrable ischemia 5. One- or two-vessel disease without proximal LAD stenosis but with a large territory at risk and high-risk criteria on noninvasive testing 6. Disabling angina refractory to medical therapy
Class IIa 1. Proximal LAD stenosis with one-vessel disease 2. One- or two-vessel disease without proximal LAD stenosis, but with a moderate territory at risk and demonstrable ischemia
Unstable Angina/Non–ST-Segment Elevation MI (NSTEMI)
Class I 1. Left main
2. Left main equivalent 3. Ongoing ischemia not responsive to maximal nonsurgical therapy
Class IIa 1. Proximal LAD stenosis with one- or two-vessel disease
Class IIb 1. One- or two-vessel disease without proximal LAD stenosis when PCI not possible (becomes class I if high-risk criteria on noninvasive testing)
ST-Segment Elevation (Q wave) MI
Class I 1. Failed PCI with persistent pain or shock and anatomically feasible 2. Persistent or recurrent ischemia refractory to medical treatment with acceptable anatomy who have a significant territory at risk and not a candidate for PCI 3. Requires surgical repair of post-infarct ventricular septal rupture or mitral valve insufficiency 4. Cardiogenic shock in patients <75 years of age who have ST elevation, LBBB, or a posterior MI within 18 hours of onset 5. Life-threatening ventricular arrhythmias in the presence of ≥50% left main stenosis or three-vessel disease
Class IIa 1. Primary reperfusion in patients who have failed fibrinolytics or PCI and are in the early stages (6–12 h) of an evolving STEMI 2. Mortality with CABG is elevated the first 3–7 days after STEMI/NSTEMI. After 7 days, criteria for revascularization in previous sections apply.
Poor LV Function
Class I 1. Left main stenosis 2. Left main equivalent 3. Proximal LAD stenosis and two- to three-vessel disease
Class IIa 1. Significant viable territory and noncontractile myocardium
Life-Threatening Ventricular Arrhythmias
Class I 1. Left main disease 2. Three-vessel disease
Class IIa 1. Bypassable one- or two-vessel disease 2. Proximal LAD disease and one- or two-vessel disease. These become class I indications if arrhythmia is resuscitated cardiac death or sustained ventricular tachycardia.
Failed PCI
Class I 1. Ongoing ischemia with significant territory at risk 2. Shock
Class IIa 1. Foreign body in critical position 2. Shock with coagulopathy and no previous sternotomy
Class IIb 1. Shock with coagulopathy and previous sternotomy
Previous CABG
Class I 1. Disabling angina refractory to medical therapy 2. Nonpatent previous bypass grafts, but with class I indications for native CAD
Class IIa 1. Large territory at risk 2. Vein grafts supplying LAD or large territory are >50% stenosed

Figure 5. AHA/ACC guidelines for CABG.

treatment. This benefit diminished by 11 years of observation, but a survival advantage persisted 11 years in surgical patients with three-vessel disease and impaired left ventricular function and in those at high clinical risk defined by preoperative ST-segment depression, history of myocardial infarction, or hypertension (**Figure 6**).

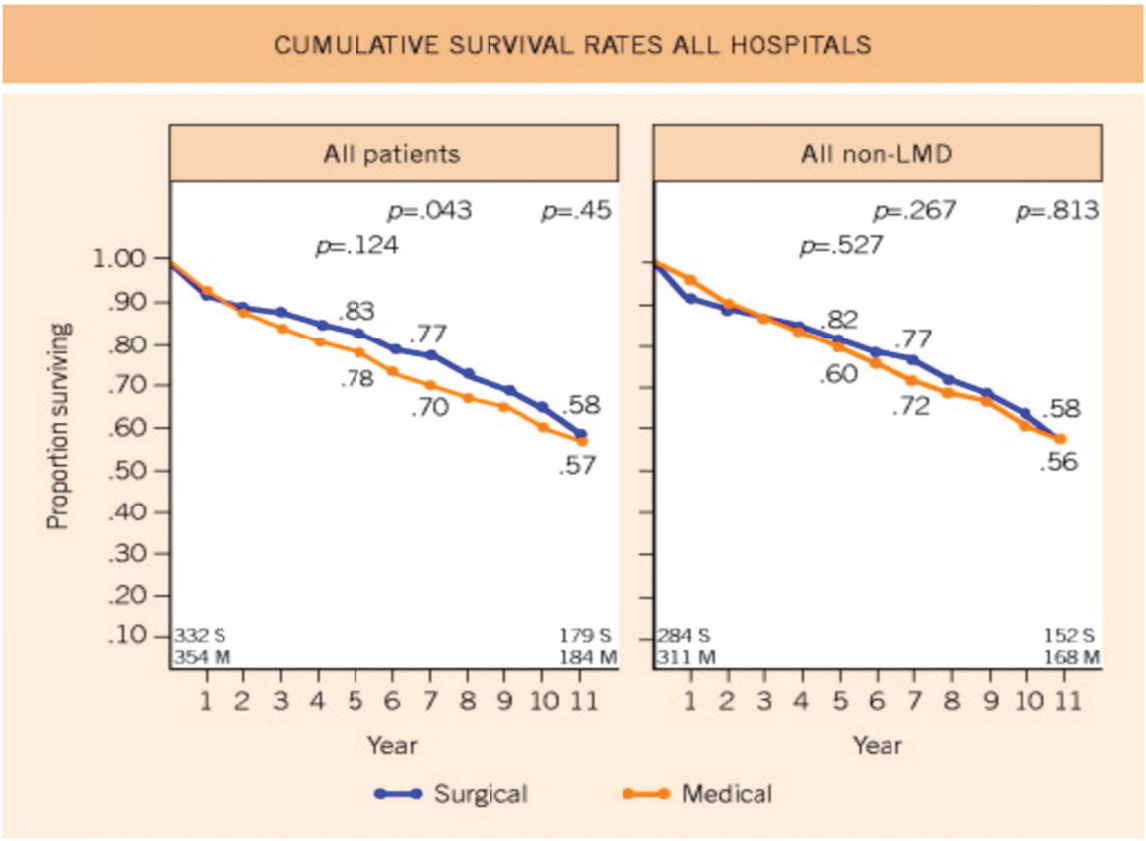

Figure 6. VA study results. Eleven-year cumulative survival for all patients according to treatment assignment. Survival curve for randomized medical (M) and surgical (S) groups in all patients and all patients without left main disease (non-LMD). From Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group [20].

Finally, the Coronary Artery Surgery Study (CASS) [21] reported survival data of 780 patients with stable angina and ejection fractions greater than 35% who were assigned to receive medical or surgical therapy. At 8 years of follow-up, 87% of surgically treated patients were alive compared with 84% of those receiving medical therapy. Although not statistically significant, the trend favored surgical therapy. Of note, the subgroup with three-vessel disease and a reduced ejection fraction of less than 50% but greater than 35% had a significant survival benefit in the surgical group at 7 years of 88% compared with 65% in the medical therapy group (**Figure 7**).

While the above studies showed the impact coronary revascularization has on patient long-term outcomes compared to medical therapy alone, there remained much debate in regard to efficacy and patient survival when comparing coronary artery bypass grafting and percutaneous coronary interventions. Perhaps, the single most important trial comparing the two interventions was the SYNTAX trial. This trial involved 85 treatment centers and 1800 patients with multivessel or left main coronary artery disease. These showed worse outcomes in the PCI group as compared to the CABG group, with increased composite major adverse cardiac and cerebrovascular events (MACCE: death, stroke, MI, or repeat revascularization). Although there was no significant difference in all-cause mortality and stroke at 5 years, MI and repeat revascularization were both increased in the PCI group. Of note, in patients with three-vessel coronary artery disease (CAD), CABG in comparison with PCI was associated with a significantly reduced rate of MI-related death, which was the leading cause of death

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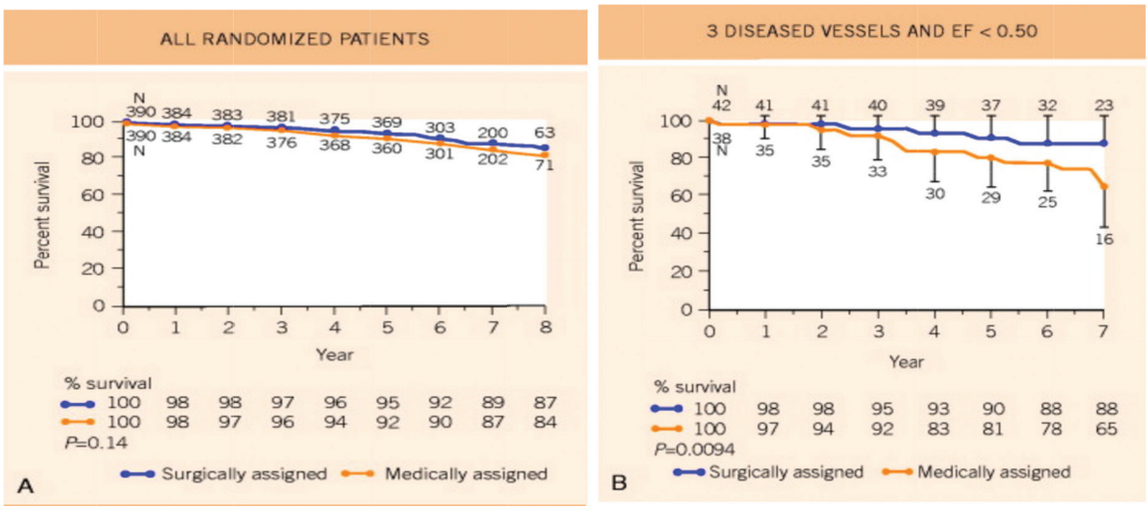

Figure 7. CASS results. Cumulative survival for patients participating in the CASS randomized trial. (A) Survival curve for all patients assigned to medical or surgical therapy and (B) survival curve for patients with three diseased vessels and ejection fractions (EF) less than 0.50 assigned to medical or surgical therapy. From Killip et al. [21].

after PCI. The study concluded that patients with more complex disease (3VD with intermediate-high SYNTAX scores and LM with high SYNTAX score) have an increased risk of a MACCE event with PCI, and CABG is the preferred treatment option.

The syntax score is a scoring system developed by the SYNTAX trial investigators to quantify the extent and complexity of CAD based on findings at cardiac catheterization. Scores are divided into terciles: low (0–22), intermediate (23–32), and high (≥33), with higher scores representing more extensive and complex CAD. The SYNTAX score was found to correlate with PCI risk and outcome but not with CABG risk and outcome. Patients with higher SYNTAX scores generally benefited from a revascularization strategy of CABG in preference to PCI. This is reflected in current guidelines, which state that it is reasonable to choose CABG over PCI as a revascularization strategy in patients with complex three-vessel disease and high SYNTAX score.

It must be noted that for patients with complicated coronary artery disease, coronary artery bypass surgery has been shown to be superior to that of PCI. From the studies above, it can be noted that this difference can be seen after a 5 year follow up period. Thus, for patients with triple vessel disease, diabetes and reduced ejection fraction, coronary artery bypass surgery should be the standard of care.

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