Stable Ischemic Heart Disease

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Abstract

Ischemic heart disease (IHD) results from an inadequate supply of blood flow and oxygen to an area of myocardium, typically resulting from a mismatch of myocardial oxygen demand and supply. IHD may have either acute or chronic presentations, and most commonly results from a significant stenosis of greater than 70 % in one or more of the major epicardial coronary arteries secondary to an atherosclerotic plaque which, in acute disease expressions, may rupture or fissure, while in more chronic expressions, typically results from a slowly advancing constrictive process that compromises the arterial lumen. Increasingly, attention is being directed to IHD that may occur in the absence of epicardial coronary artery narrowing such as is observed in patients (most often women) who may exhibit so-called microvascular angina due to involvement of the arteriolar resistance vessels that results in impaired coronary vasodilator reserve. Other non-atherosclerotic causes of IHD include congenital anomalies of the coronary vessels, myocardial bridging, coronary arteritis in association with the systemic vasculitides, and radiation-induced coronary disease. Furthermore, IHD may also occur in the absence of obstructive coronary artery disease (CAD), as in the case of uncontrolled hypertension, aortic valve disease, hypertrophic cardiomyopathy, and idiopathic dilated cardiomyopathy. Moreover, CAD may coexist with these other forms of heart disease.

The term IHD encompasses a spectrum of manifestations that vary from asymptomatic/silent myocardial ischemia to stable (chronic) angina pectoris, as well as more acute manifestations that include Prinzmetal (variant) angina, unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). In addition, individuals with IHD may initially present with signs and symptoms of heart failure, arrhythmias, and potentially sudden cardiac death.

Glossary of Terms

Angina Chest pain, pressure, or tightness caused by decreased blood supply to the heart.

Cardiac catheterization A minimally invasive procedure to diagnose coronary artery disease where a catheter is inserted in to an artery in the arm or leg, followed by injection of contrast dye. The dye fills up the coronary arteries and heart cavity, and X-ray pictures are taken.

Coronary artery bypass grafting A surgical procedure where the diseased coronary arteries are bypassed using venous or arterial grafts, to enhance blood supply to the heart muscle.

Coronary artery disease A gradual accumulation of the lipid-laden material (plaque) in the wall of the coronary artery leading to the narrowing of the lumen of the artery.

Ischemic heart disease Heart disease caused by inadequate supply of oxygenated blood to the heart muscle due to narrowing of the coronary arteries.

Myocardial infarction Permanent damage of the heart muscle due to inadequate blood supply for a prolonged period of time.

Percutaneous coronary intervention A procedure performed during cardiac catheterization where a stent is deployed at the site of significant obstruction or narrowing in the coronary artery to improve blood supply to the heart muscle.

Abbreviations

ACS	Acute coronary syndromes
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CCS	Canadian Cardiovascular Society
ECG	Electrocardiography
IHD	Ischemic heart disease
LV	Left ventricle
MI	Myocardial infarction
NSTEMI	Non-ST-segment elevation myocardial infarction
NYHA	New York Heart Association
OMT	Optimal medical therapy
PCI	Percutaneous coronary intervention
PTCA	Percutaneous transluminal coronary angioplasty
SIHD	Stable ischemic heart disease
STEMI	ST-segment elevation myocardial infarction
UA	Unstable angina

Magnitude and Economic Burden of the Problem

IHD is the leading cause of morbidity and mortality worldwide. In 2009, coronary heart disease caused approximately 400,000 deaths and was the single-most frequent cause of death, resulting in approximately one in six deaths in the United States (Go et al. 2013). In 2010, an estimated prevalence of CAD in the United States was 15.4 million subjects, of whom 7.8 million exhibited angina pectoris and 7.6 million had myocardial infarction (MI). The incidence of stable angina pectoris in age group $\geq$45 years is about 500,000 cases/year (Go et al. 2013). The lifetime risk of developing coronary heart disease after 40 years of age is 49 % for men and 32 % for women. Despite a steady decline in age-specific mortality from CAD over the past several decades, coronary heart disease still remains the leading cause of death worldwide, and it is expected that by 2030, the prevalence of CAD will increase to approximately 20 % from 2013 estimates (Go et al. 2013). Contributory factors include aging of the population, the sustained and growing rise in the worldwide prevalence of obesity, continued cigarette smoking (particularly in less developed countries), the rising prevalence of type 2 diabetes mellitus, as well as untreated (or undertreated) dyslipidemia and hypertension. Moreover, the overall rise in cardiovascular risk factors in younger people at earlier ages will all dramatically increase the incidence and prevalence of IHD in the future.

In addition to the mortality associated with IHD, there are significant quality of life impacts and economic impacts of IHD. Between 2010 and

2030, total direct medical costs spent in the United States for cardiovascular diseases are projected to triple from $273 billion to $818 billion (Heidenreich et al. 2011). In addition to the need for hospitalization, chronic chest pain syndromes also result in significant increases in indirect costs to society at large, due to inability to work or loss of employment, decreased productivity in the workplace, and reduced quality of life. For example, among men aged ≤60 years in the RITA (Randomized Intervention Treatment of Angina) trial, 2 years after coronary revascularization, 22 % and 26 % of patients who underwent coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA), respectively, were unemployed secondary to cardiac reasons (Pocock et al. 1996). Furthermore, patients with angina performed significantly worse in all aspects of quality of life (energy, pain, emotional reactions, sleep, social isolation, and mobility) compared to patients without angina, even if they had only mild angina defined as Canadian Cardiovascular Society angina grade 1 (Pocock et al. 1996). In the BARI (Bypass Angioplasty Revascularization Investigation) study, even after coronary revascularization, about 30 % of the patients did not return to work, and 15–20 % of patients rated their own health as "fair" or "poor" (Hlatky et al. 1997). In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study, 34 % of patients who received percutaneous coronary intervention (PCI) still had angina 1 year later (Boden et al. 2007). In a recent study, regardless of angiographic findings of normal coronary arteries, diffuse nonobstructive CAD, or obstructive CAD, patients with anginal symptoms had three times higher probability of disability pension and 1.5 times higher probability of premature exit from the workforce compared to patients without angina (Jespersen et al. 2013). These data confirm the widespread belief that chronic angina continues to be associated with considerable patient morbidity and impaired functional status which, in turn, argues for a more aggressive approach to management that focuses on both alleviation of anginal symptoms and improvements in clinical outcomes.

Pathobiology of Atherogenesis

During the past few decades, there has been a remarkable evolution in understanding of the pathogenesis of atherosclerosis. Once considered as a lipid storage disease, it is now evident that inflammation plays a pivotal role in all stages of atherogenesis from the initial foam cell pathology to plaque formation to plaque rupture, leading to thrombosis and acute coronary syndromes (ACS) (Libby 2013). The process of atherogenesis begins early during teenage years as demonstrated in the PDAY trial (Strong et al. 1999) and is characterized by accumulation of cholesterol-rich lipids and accompanying inflammatory response in the intimal layer of the arteriolar wall. During the initial stages of atherogenesis, as the plaque burden increases, the atheroma tends to extend outward as a compensatory mechanism to maintain the arterial lumen, known as the Glagov effect, or positive remodeling. Further increase in plaque burden results in encroachment of the atheroma into the lumen resulting in decrease in the diameter of the coronary artery. When the diameter of the epicardial coronary artery is reduced by >70 %, myocardial ischemia results from minimal exertion or at rest, due to myocardial oxygen supply/demand imbalance. The typical progression of coronary atherosclerosis is depicted in Fig. 1 (Abrams 2005).

Types of Lesions

Two types of coronary lesions with different pathobiology have been described in IHD patients as shown in Fig. 2 (Libby and Theroux 2005). Stenotic lesions (severe fibrotic plaques) have thick fibrous caps, smaller lipid cores, more fibrosis, and calcification, and less compensatory enlargement (positive remodeling). These lesions typically produce ischemia secondary to severe obstruction and should be appropriately managed by optimal medical therapy and revascularization reserved for patients with refractory symptoms despite an initial trial of optimal medical therapy and risk factor modification. Nonstenotic lesions

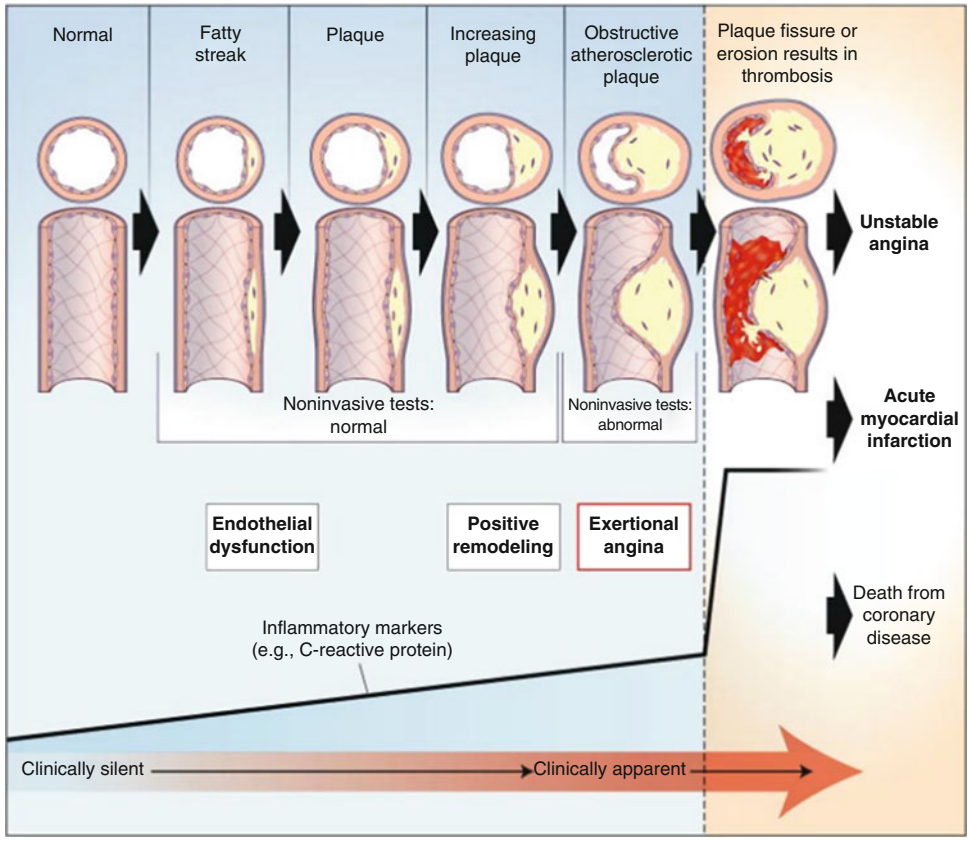


Fig. 1 Typical progression of coronary atherosclerosis (Reproduced with permission from Abrams. N Engl J Med. 2005; Copyright Massachusetts Medical Society)

or vulnerable plaques usually outnumber stenotic plaques and have a large lipid core with thin fibrous caps, susceptible to rupture and thrombosis. These lesions are commonly referred to as thin-capped fibroatheromas (TCFAs). TCFAs often undergo substantial compensatory enlargement (positive remodeling) that leads to underestimation of lesion severity of stenosis by angiography. TCFAs are usually asymptomatic for many years but when disrupted can provoke an episode of acute MI, unstable angina, or sudden death. Management of TCFAs should include lifestyle modification and pharmacotherapy in high-risk individuals. Both types of lesions can coexist in a given individual, and thereby the optimal management of such patients requires both intensive pharmacologic therapy for both types of lesions and revascularization when indicated.

The Pathophysiology of SIHD

As noted above, angina pectoris results from myocardial ischemia, caused by an imbalance between myocardial oxygen requirements and myocardial oxygen supply.

Demand Angina Versus Supply Angina

Angina caused by increased myocardial oxygen requirements, sometimes termed "demand angina," occurs in the setting of elevated heart rate, increase in contractility, and augmentation of left ventricular wall tension. These physiologic responses are triggered and mediated by norepinephrine release in response to exertion

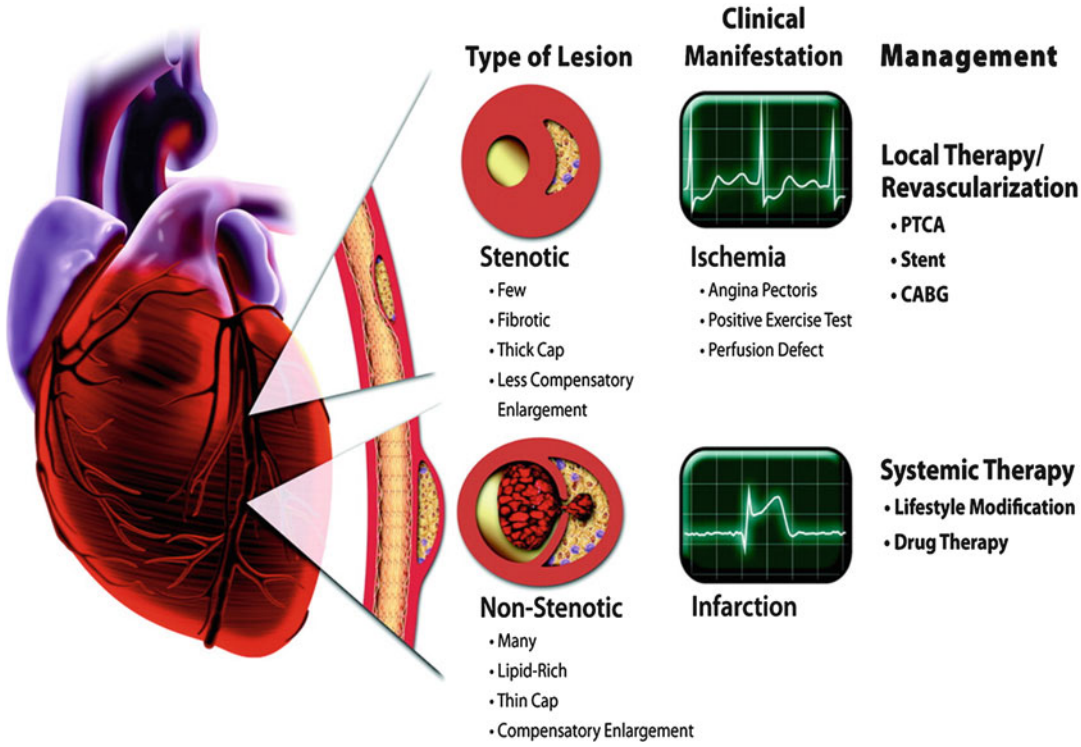


Fig. 2 Simplified schema of diversity of lesions in human coronary atherosclerosis. This schematic depicts two morphological extremes of coronary atherosclerotic plaques – stenotic lesions and nonstenotic lesions. Enlarged segments of schematic show longitudinal section (*left*) and cross section (*right*). *PTCA* percutaneous transluminal coronary angioplasty, *CABG* coronary artery bypass graft (The figure has been adapted from Libby (2005), with permission)

(e.g., increased physical activity), emotion (e.g., anger, sexual activity), or mental stress (e.g., anxiety). Other precipitants of demand angina include physical exertion after a heavy meal or the excessive metabolic demands imposed by hyperthermia, hyperthyroidism, hypertension, tachycardia, cocaine use, and hypoglycemia.

Angina caused by transiently decreased oxygen supply, similar to unstable angina, can occur in patients with chronic stable angina as a consequence of coronary vasoconstriction that results in dynamic transient stenosis and is sometimes referred as "supply angina." In the presence of fixed epicardial coronary stenoses, platelets and leukocytes can elaborate vasoconstrictor substances such as serotonin and thromboxane A2, which along with the decreased production of vasodilators, such as nitric oxide from the damaged endothelium due to coronary atherosclerosis, may lead to abnormal vasoconstrictor response to exercise and other stimuli.

Angina can also result from a decrease in the oxygen-carrying capacity of the blood as seen in severe anemia, in the presence of carboxyhemoglobin, or decreased arterial oxygen content as seen in hypoxemia from pulmonary disorders, by itself or by lowering the threshold for ischemia in patients with moderate coronary obstruction. Anemia may likewise cause demand angina due to reflex tachycardia associated with decreased stroke volume.

In some cases, severe dynamic obstruction alone, in the absence of epicardial coronary stenoses, can cause myocardial ischemia and result in angina at rest, as seen in Prinzmetal (variant) angina.

Fixed-Threshold Angina Versus Variable-Threshold Angina

Angina caused by increased oxygen demands with few if any dynamic (vasoconstrictor) components is referred as fixed-threshold angina. In this entity, the level of physical activity required to precipitate angina is relatively constant. As a result, these patients can often predict the amount of physical activity that will precipitate angina – for example, walking up exactly two flights of stairs at a customary pace, or climbing an incline of known distance. When tested on a treadmill or bicycle, the pressure-rate product (the so-called double product, a correlate of the myocardial oxygen requirement) that elicits angina and/or electrocardiographic evidence of ischemia is relatively constant.

Angina caused by dynamic obstruction from coronary vasoconstriction in the setting of fixed atherosclerotic arterial narrowing is referred as variable-threshold angina. In this entity, coronary vasoconstriction, but not increased myocardial oxygen demand, plays an important role in causing myocardial ischemia. These patients typically have "good" days, when they are capable of substantial physical activity, as well as "bad" days, when even minimal activity can cause clinical and/or electrocardiographic evidence of myocardial ischemia or angina at rest. They often complain of a circadian variation in angina that is more common in the morning. Angina on exertion and sometimes even at rest may be precipitated by cold temperature, emotion, and mental stress.

Mixed Angina

The term mixed angina is used to describe the patients who fall between the two extremes of fixed threshold and variable threshold. In this context, some degree of coronary vasoconstriction due to vasospasm is superimposed on some degree of fixed obstructive coronary disease (typically may be non-flow-limiting stenoses) such that the contribution of a reversible vasospastic component on top of some degree of fixed luminal narrowing results in a supply/demand imbalance, which may be variable relative to a given degree of physical activity. In other words, "mixed angina" represents a combination of "variable-threshold" and "fixed-threshold" angina.

The knowledge of various kinds of angina and their pathophysiology may have important clinical implications for the selection of anti-ischemic agents as well as for their timing of initiation. In patients with demand, or fixed-threshold angina, the beta-blocking agents are likely to be more effective, whereas nitrates and calcium channel blocking agents, at least hypothetically, are likely to be especially effective in patients with supply or variable-threshold angina. To the extent that non-dihydropyridine calcium channel blockers such as verapamil or diltiazem likewise reduce heart rate, they may be effective in both fixed- and variable-threshold angina.

Signs and Symptoms

Angina, derived from the Latin words *angor animi*, essentially translates into symptoms that can best be described as a choking sensation, a feeling of suffocation, anxiety, fear, or terror. William Heberden's initial description of angina in 1768 as conveying a sense of "strangling and anxiety" ("as if life were to be extinguished from the breast. . .") still holds true (Heberden 1772). Angina is the initial presentation in approximately half of CAD patients (Go et al. 2013).

Cardinal features of typical angina pectoris include chest discomfort triggered commonly by increased activity (exercise, sexual intercourse) or emotional stress (anger, fright, stress). Adjectives often used to describe the distress include tightness, heaviness, pressure, constricting, suffocating, crushing, and squeezing. Chest discomfort is usually retrosternal, but radiation is common and usually occurs down the ulnar surface of the left arm, neck, jaw, right arm, or shoulders. Sometimes patients place clenched fist over the

precordium to describe chest pain, referred as a positive Levine's sign. The typical episode of angina pectoris usually begins gradually and reaches its maximum intensity over a period of minutes before dissipating and is relieved within minutes by rest or the use of nitroglycerin. A delay of more than 5–10 min in relief of symptoms by nitroglycerin suggests that the symptoms are either not caused by ischemia or are caused by severe ischemia, as with acute MI or unstable angina. Epigastric discomfort alone or in association with chest pressure may occur. Anginal equivalents (i.e., symptoms of myocardial ischemia other than angina), such as dyspnea, fatigue, syncope, and eructations, are common, particularly in older patients. Chest discomfort while walking in the cold or uphill is also suggestive of angina. Of note, features of angina may be more atypical, and this may be especially so in women. For example, women are far more likely than men to exhibit symptoms of sharp chest discomfort, often with more epigastric radiation, as well as symptoms of fatigue and dyspnea. This often complicates an accurate diagnosis of IHD in women.

In contrast, acute MI is usually associated with prolonged severe pain occurring at rest and unstable angina is characterized by an accelerated pattern and/or occurrence at rest.

Features suggesting the absence of angina pectoris include pain worse with deep breathing (pleuritic), pain localized to the tip of one finger, pain reproduced by movement or palpation of the chest wall or arms, and constant pain lasting many hours or, alternatively, very brief episodes of pain lasting seconds.

Grading the Severity of Angina

The most commonly used system proposed in 1976 by Campeau for grading angina pectoris is the Canadian Cardiovascular Society (CCS) classification (Table 1). In the Appropriateness of Coronary Revascularization (ACRE) study, a higher CCS class was linearly associated with higher number of diseased epicardial vessels discovered at angiography, the presence of impaired left ventricular (LV) function, and subsequent rates of percutaneous coronary intervention (PCI) or bypass surgery (Hemingway et al. 2004). Other scales used are the Specific Activity Scale developed by Goldman and colleagues (Goldman et al. 1981) based on the number of metabolic equivalents achieved and the anginal score by Califf and associates which integrates the clinical features and tempo of angina with electrocardiographic (ECG) changes and offers an independent prognostic information beyond that provided by age, gender, ventricular function, and coronary anatomy (Califf et al. 1988). Any of the above functional classifications are subject to variability in activity tolerance as perceived by patients, and hence the reproducibility is variable. Functional estimates based on the CCS scale or the Specific Activity Scale were 73 % reproducible, but the latter seemed to correlate better with objective measures by treadmill exercise (Goldman et al. 1981).

Table 1 The Canadian Cardiovascular Society **g**rading of **a**ngina **p**ectoris

Grade	Description
Grade I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
Grade II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
Grade III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
Grade IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

Campeau (1976)
Available on the Canadian Cardiovascular Society Website at www.ccs.ca

Types of Angina

Chronic Stable Angina

Chronic stable angina is generally due to a significant obstructive lesion (single or multiple) in one or more coronary arteries, defined as ≥50 % stenosis of the left main coronary artery or ≥70 % stenosis of one or more major epicardial coronary artery. Typically, patients experience predictable and reproducible angina after physical activity, emotional stress, or both, and there is generally complete reversibility of the symptoms with rest or using short-acting nitroglycerin.

Decubitus Angina

Angina in the decubitus position occurs from myocardial ischemia that results from an increase in end-diastolic volume, and myocardial wall stress during recumbency, resulting in increase in oxygen demand. This expression of angina typically occurs shortly after a patient with CAD reclines and assumes a supine or prone position, resulting in a redistribution of blood volume.

Nocturnal Angina

Characteristically, this type of angina awakens the patient, often after going to sleep for several hours, and is likely due to respiratory pattern changes resulting in hypoxemia, episodic tachycardia, or recumbency. Nocturnal angina is a classic feature of unstable angina or Prinzmetal (variant) angina, which typically occurs in the early morning hours before awakening. Nocturnal angina should also raise the suspicion of sleep apnea.

Postprandial Angina

Such anginal episodes are presumably caused by redistribution (or shunting) of coronary blood flow away from the territory supplied by severely stenosed vessels to the epigastric arterial blood supply, causing a "coronary steal" phenomenon.

Refractory Angina

Angina is termed refractory when symptoms are persistent despite optimal medical therapy and myocardial revascularization (percutaneous coronary intervention or coronary artery bypass surgery).

Unstable or Crescendo Angina

Unstable angina is defined as recent-onset CCS class III severity angina, and/or angina occurring at rest (CCS class IV) and lasting >20 min, and/or worsening (crescendo) angina which is more frequent, longer in duration, lower in threshold, or less responsive to nitroglycerin.

Prinzmetal (Variant) Angina or Vasospastic Angina

First described in 1959 by Myron Prinzmetal, this variant form of angina typically occurs at rest, or with minimal exertion, and is caused by focal vasospasm of an epicardial coronary artery. Variant angina can occur both in normal epicardial coronary arteries and in coronary arteries with some degree of atherosclerotic narrowing – either flow limiting or non-flow limiting (Prinzmetal 1959a, b). Prinzmetal angina is characterized by transient ST-segment elevation, rather than ST-segment depression on the electrocardiogram, although either may occur. It is more common in men and in smokers (Sugiishi and Takatsu 1993). Abnormal coronary vasomotor tone or smooth muscle contraction, withdrawal of vagal activity, change in sympathetic activity, endothelial dysfunction, decreased nitric oxide release, and enhanced phospholipase C activity have all been hypothesized in the pathophysiology of vasospastic angina (Stern and Bayes 2009). Prolonged vasospasm can result in myocardial ischemia and infarction.

Patients might also experience life-threatening ventricular arrhythmias and sudden cardiac death. Despite the abovementioned complications, the prognosis of patients with variant angina is generally more favorable than patients with angina secondary to obstructive CAD. In a prospective Coronary Artery Spasm in Patients With Acute Coronary Syndrome (CASPAR) Study, among all patients with suspected ACS who underwent coronary angiography, 28 % of the patients had no culprit lesion. About half of these patients demonstrated coronary vasospasm with reproduction of anginal symptoms on intracoronary provocation with acetylcholine (Ong et al. 2008). During a 3-year follow-up, ACS patients without culprit lesions and proof of coronary spasm had excellent survival with no reported cardiac death or nonfatal myocardial infarction compared to ACS patients with culprit lesions. However, patients with vasospasm continued to have persistent angina requiring repeated angiography in a minority of cases (Ong et al. 2011). In patients with Prinzmetal angina, coronary microvascular spasm in addition to epicardial vasospasm can also contribute to myocardial ischemia. This is particularly more common in women who tend to also have relatively long-lasting anginal symptoms (Sun et al. 2002).

The Anginal Syndrome with Normal Coronary Angiograms (Often Referred to as Syndrome X)

Patients with typical anginal symptoms, objective evidence of myocardial ischemia despite normal coronary angiograms, and no evidence of large epicardial vessel spasm, even after an acetylcholine challenge, are grouped under the anginal syndrome with normal coronary angiograms (or syndrome X) (Cannon and Epstein 1988; Cannon 2009). These patients have electrocardiographic abnormalities (ST-segment depression and/or T-wave inversions) at rest or during the stress test, as well as evidence of reversible stress-induced myocardial perfusion defects on nuclear imaging. The CASS (Coronary Artery Surgery Study) (Kemp et al. 1986) and the WISE (Women's Ischemia Syndrome Evaluation) studies (Sharaf et al. 2001) have reported that up to one-half of patients undergoing coronary angiography are found to have normal or nonobstructed epicardial coronary arteries. The exact pathophysiologic mechanism of this entity is still unknown, but recent evidence is mounting that many such patients may have microvascular angina with associated ischemia due to disease of the coronary arteriolar resistance vessels resulting in impaired coronary flow reserve (Egashira et al. 1993; Hasdai et al. 1997; Bugiardini and Bairey 2005). Other mechanisms including altered autonomic tone (Rosano et al. 1994; Frobert et al. 1995), higher levels of inflammatory markers (intercellular adhesion molecule-1, vasoconstrictor endothelin-1, high-sensitivity C-reactive protein) (Kaski et al. 1995; Lanza et al. 1999), insulin resistance (Chauhan et al. 1994; Swan et al. 1994), abnormal pain perception (sensitive heart syndrome) (Valeriani et al. 2005; Sestito et al. 2008), and estrogen deficiency (Rosano et al. 1995; Kaski 2006) have also been implicated. Up to two-thirds of patients with chest pain and normal coronary arteries have been observed to have psychiatric disorders. Syndrome X is more prevalent in women than in men, and the majority of women are peri- or postmenopausal. Chest pain is frequently atypical and may be severe and disabling with syndrome X. Noncardiac causes of chest pain like esophageal disorders are commonly accompanied in these patients and thus should be excluded. Although reassurance helps many patients, most continue to have recurrent episodes of chest pain resulting in emergency room evaluations, hospitalizations, and repeat cardiac catheterizations, with adverse effects on quality of life, employment, and health-care costs. Despite these factors, the long-term survival of these patients is generally excellent compared to patients with obstructive CAD. In the CASS registry, the 7-year survival rate for patients with chest pain, ejection fraction greater than 50 %, and normal coronary angiograms was 96 % versus 92 % for patients with mild CAD (50 % luminal stenosis) (Kemp et al. 1986).

Certain clinical indicators may predict worse outcomes in these patient populations. In the WISE study, persistent chest pain for more than 1 year in women without obstructive CAD was associated with a twofold increase risk of composite cardiovascular outcomes (Johnson et al. 2006), suggesting that such patient populations would benefit from additional evaluation and aggressive risk factor modification therapy. Studies evaluating anti-ischemic therapy with beta-blockers, calcium channel blockers, and nitrates have produced conflicting results (Bugiardini and Bairey 2005). Studies of estrogen replacement in postmenopausal women with syndrome X have shown improvement in symptoms and/or exercise performance; however, the role of exogenous estrogen in the treatment of this group remains in question. Studies aimed at modulating the abnormal nociceptive cardiac inputs in patients with syndrome X have shown that imipramine (50 mg) and/or spinal cord stimulation in patients with refractory symptoms has beneficial effects on anginal symptoms (Bugiardini and Bairey 2005; Sestito et al. 2008).

Atypical Angina

Patients with some but not all the features of classic angina are often grouped under atypical angina. Patients might complain of pain that is sharp, knifelike, lancinating, or constricting, with highly variable patterns of radiation. Pain might last for seconds, minutes, hours, or entire day with variable response to nitroglycerin. Pain can be pleuritic, positional, or associated with chest wall tenderness. Other atypical symptoms such as nausea, vomiting, and midepigastric discomfort can also occur. Atypical presentations are more frequent in women, elderly, and diabetics, displaying variable pain intensity or thresholds, timing, and characteristics. In the WISE (Women's Ischemic Syndrome Evaluation) study, 65 % of women with ischemia presented with atypical symptoms (Johnson et al. 2006).

Anginal Equivalents

In some patients, particularly diabetics and the elderly, myocardial ischemia may cause symptoms other than classic anginal discomfort. These include dyspnea, diaphoresis, lightheadedness, nausea, emesis, fatigue, weakness, altered sensorium, and fainting (syncope).

Silent (Asymptomatic) Myocardial Ischemia

Silent myocardial ischemia is defined as objective evidence of ischemia in the absence of symptoms related to the ischemia. These patients remain asymptomatic despite ischemic changes (ST depressions or T-wave inversions) on resting ECG, ambulatory electrocardiogram (AECG) monitoring or stress ECG during exercise treadmill testing, and/or reversible wall motion abnormalities or perfusion defects on pharmacological stress imaging studies. In one study, asymptomatic ischemic ST-segment depressions during AECG monitoring were more frequent than symptomatic ischemia in patients with stable CAD (Schang and Pepine 1977). Silent myocardial ischemia occurred in nearly half of the patients with stable CAD during AECG monitoring in the Asymptomatic Cardiac Ischemia Pilot (ACIP) study (Pepine et al. 1994b) and nearly half of the patients admitted with unstable angina during continuous ECG monitoring (Gottlieb et al. 1986). Silent ischemia has also been documented in patients with hypertension (Stramba-Badiale et al. 1998), diabetes mellitus (MiSAD study group 1997), and healthy subjects in the absence of known CAD (Fleg et al. 1992). The exact mechanism of silent ischemia is still controversial, although changes in myocardial oxygen demand or supply have been implicated as the underlying cause. Some studies have demonstrated increased myocardial demand in the genesis of myocardial ischemia by showing an increase in heart rate (Panza et al. 1992) and blood pressure (Deedwania and Nelson 1990) just prior to the silent ischemic events. This mechanism seems plausible, as the increase in the pressure-rate

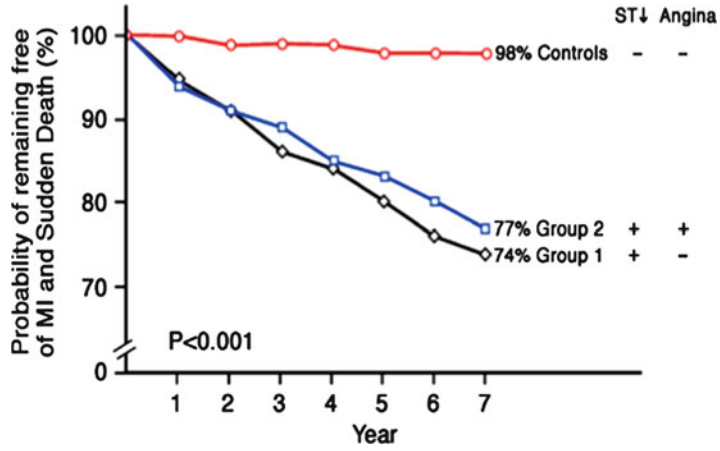


Fig. 3 Prognosis of patients with exercise ischemia with or without symptoms. Probability of remaining free of myocardial infarction and sudden death in control subjects who had no known history of coronary artery disease (*CAD*) and in patients with medically treated CAD and ST-segment depression during exercise with (group #2) or without (group #1) angina (Reprinted with permission, from Weiner et al. (1988))

(double) product has been shown to cause angina in patients with CAD. However, other studies have demonstrated silent ischemic episodes during usual daily activities and were evident at heart rates and activity levels well below the heart rates at which ST-segment depression was noted during exercise stress testing (Schang and Pepine 1977; Deanfield et al. 1983). This raises the possibility of combined increased demand and altered supply secondary to abnormal microvascular and endothelial dysfunction as a likely cause of silent myocardial ischemia (Conti et al. 2012). Studies have also shown a role of physiologic effects of the circadian rhythm, mental stress, and abnormal pain perception in genesis of silent ischemia (Rosen et al. 1996; Sidhu and Boden 2013). Autonomic neuropathy has been implicated in some cases for reduced sensation of pain during the ischemic events (Marchant et al. 1993), especially in patients with diabetes, and is associated with increase morbidity and mortality (Maser et al. 2003).

There are robust data to support that the episodes of myocardial ischemia, regardless of whether they are symptomatic or asymptomatic, are associated with unfavorable outcomes in patients with or without CAD (Conti 2012; Sajadieh et al. 2005; Fleg et al. 1992). In the Coronary Artery Surgery Study (CASS), including patients with mild to moderate CAD treated medically, the likelihood of death or MI during 7-year follow-up was similar between patients with asymptomatic ST-segment depression with exercise and those with symptomatic ST-segment depression with exercise, as shown in Fig. 3 (Weiner et al. 1988).

The pathophysiology of silent myocardial ischemia is likely similar to symptomatic ischemia – i.e., myocardial demand/supply imbalance along with the role of endothelial dysfunction and arterial vasomotor response. Therefore, the cornerstones of optimal medical therapy employed in patients with stable CAD – namely, beta-blockers, calcium channel blockers, long-acting nitrates, and newer antianginal agents, such as ranolazine – can also be employed in treatment of silent ischemia. In the Angina and Silent Ischemia Study (ASIS), patients with stable angina and a high frequency of asymptomatic ischemic episodes on AECG were randomized to propranolol-LA (mean daily dose of 293 mg), diltiazem-SR (mean daily dose of 350 mg), or nifedipine (mean daily dose of 79 mg), with each compared to matching placebo (Stone et al. 1990). In this study, 94 % of all episodes of ambulatory ischemia were asymptomatic, supporting the earlier data regarding the prevalence of asymptomatic ischemia in a stable angina population. Compared with placebo, only

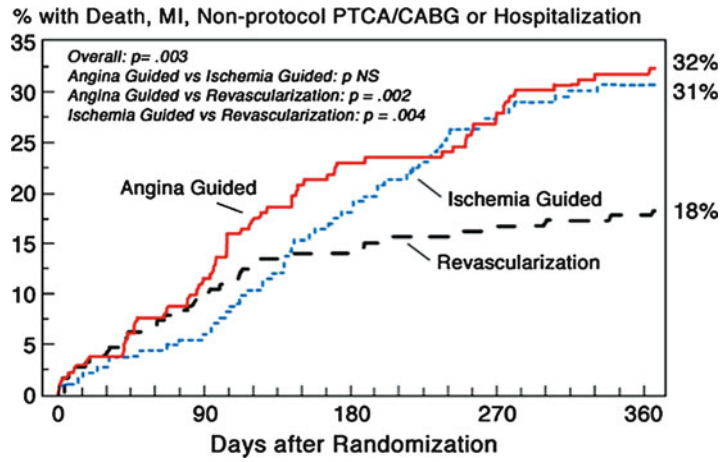


Fig. 4 1-year cumulative rates of death, MI, or cardiac hospitalization in ACIP. Event rates were significantly different between the revascularization group and both the angina guided and ischemia guided. Event rates were not different between either of the medical therapy groups (Reprinted, with Rogers et al. (1995). *ACIP* asymptomatic cardiac ischemia pilot study, *CABG* coronary artery bypass graft, *MI* myocardial infarction, *PTCA* percutaneous transluminal coronary angioplasty)

propranolol was associated with a marked reduction in all manifestations of asymptomatic ischemia during AECG (2.3 vs. 1.0 ischemic episodes/24 h, mean duration of ischemia per 24 h was 43.6 vs. 5.7 min with $P < 0.0001$ for both), while there was an intermediate response to diltiazem. The reduction of frequency in anginal episodes with diltiazem (2.3 vs. 1.9 episodes/24 h) was associated with a strong trend for clinical benefit ($P = 0.08$) in the protocol-completed analysis, while there was a significant reduction ($P = 0.03$) in the intention to treat analysis. Nifedipine had no significant effect on either measured variable for ambulatory ischemia. Frequency of angina was significantly decreased by both propranolol and diltiazem (Stone et al. 1990). Similarly in the Atenolol Silent Ischemia Study Trial (ASIST), 4 weeks of atenolol therapy (100 mg/day) decreased the number of ischemic episodes detected on AECG from 3.6 to 1.7, $P < 0.001$, and also the average duration from 30 to 16.4 min/48 h, $P < 0.001$ (Pepine et al. 1994a).

Coronary revascularization is also effective in reducing the rate of angina and ambulatory ischemia. The Asymptomatic Cardiac Ischemia Pilot (ACIP) study randomized patients with asymptomatic ischemia to medical therapy (atenolol plus nifedipine, if needed, vs. diltiazem plus isosorbide dinitrate, if needed) versus revascularization [percutaneous transluminal balloon angioplasty (PTCA) or coronary artery bypass graft (CABG)] (Knatterud et al. 1994). Medical therapy was further divided into an "angina-guided" strategy to eliminate symptoms and an "ischemia-guided" strategy to eliminate silent ischemia on AECG monitoring. Of note, this study predated the use of coronary stents. The primary outcome of the absence of ischemic episodes on AECG at 12 weeks was significantly reduced in the revascularization (PTCA or CABG) arm compared to the ischemia-guided group and angina-guided group (55 % vs. 41 % vs. 39 %, respectively) (Knatterud et al. 1994). After 1 year, revascularization was superior to both the angina-guided and ischemia-guided medical strategies in suppressing asymptomatic ischemia and was associated with better outcomes as shown in Fig. 4 (Rogers et al. 1995).

Coronary revascularization in the ACS population was evaluated in the Swiss Interventional Study on Silent Ischemia Type II (SWISSI-II) trial. Among 201 patients with silent myocardial ischemia who were recovering from acute MI (>2 months), PCI was associated with a significant reduction in late (up to 10-year) mortality as compared with medical therapy (Erne et al. 2007). It should be noted that the medical therapy as used

in the ACIP and the SWISS-II trial was not as aggressive as the contemporary optimal medical therapy used in trials published after year 2000, COURAGE, STICH, BARI-2D, or FREEDOM trials, thus making the results of this fairly small study somewhat difficult to interpret in the modern era of aggressive medical therapy.

A post hoc analysis of the COURAGE trial evaluated the clinical outcomes in patients with silent myocardial ischemia ($n = 283$, 12 %) as compared to those with symptomatic ischemia ($n = 1997$, 88 %) during a 5-year follow-up (Gosselin et al. 2012). Compared to symptomatic patients, those with silent ischemia had fewer subsequent revascularizations (16 % vs. 27 %, $P < 0.001$) regardless of treatment assignment and fewer hospitalizations for ACS (7 % vs. 12 %, $P < 0.04$). No significant differences in outcomes were observed between the two treatment groups, although there was a trend toward fewer deaths in the PCI group ($n = 7$, or 5 %) compared to the optimal medical therapy (OMT) group ($n = 16$, or 11 %, $p = 0.12$).

The prognostic significance of anginal symptoms was evaluated in a recent post hoc analysis of the BARI-2D trial (Dagenais et al. 2013). Of 2,364 patients with type 2 diabetes and documented CAD: 1,434 (61 %) patients had typical angina symptoms; 506 (21 %) patients had anginal equivalent of dyspnea, fatigue, or diaphoresis on exertion; and 424 (18 %) patients had asymptomatic ischemia. Patients were randomly assigned to a treatment strategy of prompt coronary revascularization (PCI or CABG) with OMT or OMT alone. At the 5-year follow-up, compared to patients with angina or anginal equivalents, those with asymptomatic ischemia had fewer subsequent revascularizations (PCI or CABG) (35 % vs. 32 % vs. 25 %, respectively, $P < 0.001$) regardless of treatment assignment. There were no significant differences in all-cause mortality or composite cardiovascular end points among all three groups, irrespective of the treatment groups assigned. The all-cause mortality in asymptomatic patients ($n = 424$) randomized to OMT was 12 % (31/235) compared to 8 % (20/189) in revascularization group. This shows that that asymptomatic patients with type 2 diabetes, stable CAD, and documented ischemia are at as high risk as similar patients with anginal symptoms and that all of these patients should be managed similarly in terms of risk stratification and preventive therapies. In contrast to the ACIP and SWISS-II trials, the COURAGE and BARI-2D studies did not show any potential benefit of revascularization strategies in silent ischemic patients over optimal medical therapy. This is, in part, due to contemporary aggressive medical therapy used in the later two trials. Furthermore, reduction of silent ischemic episodes has also been documented with aspirin (Mahony 1989), statins (Van Boven et al. 1996), and ACE inhibitors (Tzivoni et al. 1992). This underscores the importance of OMT in the management of silent ischemia patients.

Differential Diagnosis of Chest Pain

In patients with chest pain not consistent with typical angina, other alternative diagnoses should be considered as shown in Table 2.

Physical Examination

The single best clue to the diagnosis of angina in patients with stable CAD is obtaining meticulous clinical history, as the examination in these patients is often normal or nonspecific. Nonetheless, diligent examination may reveal signs of myocardial ischemia due to brief episodes of angina including an S3 gallop and pulmonary rales (transient systolic dysfunction), an S4 gallop (transient diastolic dysfunction), and apical systolic murmurs (transient papillary muscle dysfunction leading to mitral regurgitation). Elevated blood pressure (BP), xanthomas, corneal arcus, acanthosis nigricans, neuropathy, and retinal exudates point to the presence of IHD risk factors. Examination could also reveal related conditions such as heart failure, valvular heart disease, or hypertrophic cardiomyopathy. An audible rub suggests pericardial or pleural disease. Evidence of peripheral vascular disease like carotid or renal artery bruits, a diminished pedal

Table 2 Alternative diagnoses to angina for patients with chest pain

Nonischemic cardiovascular	Pulmonary	Gastrointestinal	Chest wall	Psychiatric
Aortic dissection	Pulmonary embolism	Esophageal	Costochondritis	Anxiety disorders
		Esophagitis	Fibrositis	Hyperventilation
		Spasm	Rib fracture	Panic disorder
		Reflux	Sternoclavicular arthritis	Primary anxiety
Pericarditis	Pneumothorax	Biliary	Herpes zoster (before the rash)	Affective disorders (i.e., depression)
	Pneumonia	Colic		Somatoform disorders
	Pleuritis	Cholecystitis		Thought disorders (i.e., fixed delusions)
		Choledocholithiasis		
		Cholangitis		
		Peptic ulcer		
		Pancreatitis		

Reproduced from Gibbons et al. (2003)

pulse, or a palpable abdominal aneurysm is strongly associated with CAD. Pain reproduced by pressure on the chest wall suggests a musculoskeletal etiology but does not eliminate the possibility of angina due to IHD.

Evaluation and Management

Noninvasive Testing

Biochemical Tests

In patients with stable IHD, initial biochemical evaluation should include blood testing to detect metabolic abnormalities that are risk factors for the development of CAD. These abnormalities include a fasting lipid profile [total cholesterol, triglycerides, low-density lipoproteins (LDL) cholesterol, high-density lipoproteins (HDL) cholesterol, non-HDL cholesterol] and hemoglobin A1c levels to screen for dyslipidemias and diabetes mellitus. A basic metabolic profile and spot urine albumin-to-creatinine ratio should also be performed to screen for chronic kidney disease as it strongly associated with the development and progression of atherosclerotic vascular disease (Brosius et al. 2006).

Other biochemical markers that have been shown to be associated with increased atherogenicity but not recommended by current guidelines for routine risk assessment include lipoprotein (a), apoprotein B, small dense LDLs, and lipoprotein-associated phospholipase A2 (Brunzell et al. 2008; O'Donoghue et al. 2006). These markers add prognostic information to the measurement of total cholesterol and LDL and may be considered as a secondary target for therapy in patients who have achieved therapeutic targets for LDL (Brunzell et al. 2008). In addition, elevated homocysteine levels have also been linked to atherogenesis and increased risk of CAD. Although routine population-wide screening of homocysteine levels are not recommended, it may be useful in patients with premature or accelerated CAD (Malinow et al. 1999).

Compelling evidence for the role of inflammation in atherogenesis has fueled investigation into several novel risk factors for CAD. A number of inflammatory markers have been proposed, including proinflammatory cytokines (interleukin-6, interleukin-1RA, tumor necrosis factor-α), adhesion molecules (intracellular adhesion molecule-1, vascular adhesion molecule-1), and markers of cell activation. Although all are of scientific interest, the clinical use of these markers is limited by their high cost, low availability, and unfavorable biological profile (Biasucci 2004). The marker that has shown a consistent relationship to the risk of incident cardiovascular events is the serum concentration of high-sensitivity C-reactive protein (hsCRP). The prognostic value of hsCRP is additive to traditional risk

factors, including lipids (Buckley et al. 2009); however, the incremental clinical value for screening continues to be debated.

Cardiac biomarkers are typically used to differentiate patients with ACS from those with SIHD. However, recent studies have demonstrated detectable levels of high-sensitivity cardiac troponin T (hs-TnT) (Omland et al. 2009) and high-sensitivity troponin I (hs-TnI) (Omland et al. 2013) in patients with clinically stable IHD were strongly associated with the incidence of cardiovascular death and heart failure independent of conventional risk factors. Moreover, hs-TnI and not hs-TnT was significantly associated with the risk for acute MI. Although such evidence may lead to new applications of troponin in patients with SIHD, clinical use in this population is currently not recommended (Morrow and Antman 2009).

B-type natriuretic peptide (BNP) and its inactive N-terminal fragment (NT-pro-BNP) have been shown to be strong predictors of morbidity and mortality in patients with heart failure and ACS. Recent studies from Denmark (Kragelund et al. 2005) and Norway (Omland et al. 2007) showed that in patients with chronic stable angina, higher quartile of NT-pro-BNP level correlated strongly with decreased survival after adjusting for conventional risk factors. Another prospective study from Germany showed close correlation between the extent of CAD and ischemia in patients with stable CAD to levels of NT-pro-BNP (Weber et al. 2004). These data, taken together, suggest that BNP and NT-pro-BNP offer additional prognostic information in patients with SIHD. However, the clinical utility of such testing remains uncertain in SIHD population.

Resting ECG

The resting ECG is normal in approximately half of the patients with SIHD and in some patients with severe CAD. The most common ECG findings in SIHD include nonspecific ST–T-wave changes with or without abnormal Q waves. Q waves are relatively specific but not sensitive indicators for previous myocardial infarction. In patients with known CAD, the occurrence of ST–T-wave abnormalities on the resting ECG can correlate with the severity of the underlying heart disease, and a normal resting ECG correlates to a favorable long-term prognosis. In patients with SIHD, various conduction disturbances may occur, most frequently left bundle branch block and left anterior fascicular block, and are often associated with impairment of LV function and reflect multivessel CAD and previous myocardial damage. Hence, such conduction disturbances are an indicator of a relatively poor prognosis. Left ventricular hypertrophy on the ECG is also an indicator of worse prognosis in these patients and suggests the presence of underlying hypertension, aortic stenosis, hypertrophic cardiomyopathy, or prior MI with remodeling and warrants further evaluation with echocardiography. During an anginal episode, ECG becomes abnormal in about half of the patients with normal baseline ECG.

Noninvasive Stress Testing

Various diagnostic tests are available for the diagnosing and assessing the prognosis of SIHD patients (Table 3). Functional or stress testing to detect reversible ischemia is the most common noninvasive test to diagnose SIHD. Anatomic testing with multi-slice coronary computed tomographic angiography (CCTA) has recently gained popularity, especially in low-risk population. Appropriate application of these noninvasive tests requires consideration of Bayesian principles, which state that the reliability and predictive accuracy of any test are defined not only by its sensitivity and specificity but also by the prevalence of disease (or pretest probability) in the population under study.

Estimating the Pretest Probability of IHD

Physicians should be able to estimate the pretest probability of IHD following a comprehensive clinical evaluation of the patient. If the pretest probability of IHD is low, further testing is usually not warranted because the likelihood of a false-positive test (i.e., positive test in the absence of obstructive CAD) is higher than that of a true positive. Similarly, in a patient with a very high pretest probability of IHD on the basis of the clinical evaluation, if a stress test is negative, there is a high likelihood that the result is false

Table 3 Noninvasive diagnostic tests for evaluation of stable ischemic heart disease patients

Test	Prerequisites/protocol	Diagnostic end point	Comments	Estimated sensitivity (%)	Estimated specificity (%)
Exercise electrocardiography (Treadmill or bicycle)	Ability to achieve adequate workload	Horizontal or downsloping ST-segment depressions ≥1 mm or ≥2 mm in the presence of baseline ST-segment depression, 80 ms after the J point in three consecutive beats	***High-risk findings***	68 % Sensitivity lower in women	77 %
	Normal resting ECG or minimal resting ST–T-wave abnormalities (<0.5 mm)		Failure to increase SBP >120 mmHg, exaggerated increase or fall in SBP during exercise		
	Discontinue beta-blockers, calcium antagonists, and nitrates 24–48 h prior to the procedure		ST-segment depression ≥2 mm, involving ≥5 leads, persisting ≥5 min into recovery		
	Bruce or modified Bruce protocol		Functional capacity <5 METs		
			Angina at low exercise workloads		
			Abnormal heart rate recovery		
			Exercise-induced ST-segment elevation (aVR excluded)		
			Exercise-induced sustained (>30 s) or symptomatic ventricular tachycardia		
			Duke treadmill score of minus 11 or less		
Exercise stress echocardiography (treadmill or supine/ upright bicycle)	Ability to achieve adequate workload	New or worsening wall motion abnormalities (hypokinesis, akinesis, or dyskinesis)	Additional information regarding structural heart disease, chamber dimensions, and valve function can be obtained	85 %	81 %
	Normal or abnormal resting ECG (except LBBB or paced rhythm)	Changes in global left ventricular function	***High-risk findings***		
	High-quality echocardiographic images are essential	Left ventricular cavity dilation	Same exercise parameters as mentioned in exercise ECG		
	Intravenous contrast agents can improve endocardial border delineation and can result in improved diagnostic accuracy		Wall motion abnormality extending beyond 2 segments or 2 coronary beds		
			Global hypokinesis		
			Left ventricular cavity dilation		

(*continued*)

Table 3 (continued)

Test	Prerequisites/protocol	Diagnostic end point	Comments	Estimated sensitivity (%)	Estimated specificity (%)
Dobutamine stress echocardiography	Inability to achieve adequate workload	New or worsening wall motion abnormalities (hypokinesis, akinesis, or dyskinesis)	Provides similar information as exercise echocardiography	81 %	79 %
	Normal or abnormal resting ECG	Changes in global left ventricular function	***High-risk findings***		
	Incremental dobutamine infusion ± atropine injection	Left ventricular cavity dilation	Wall motion abnormality extending beyond 2 segments or 2 coronary beds		
	High-quality echocardiographic images are essential		Wall motion abnormality developing at low dose of dobutamine (≤10 mcg/kg/min) or at low heart rate (<120 beats/min)		
			Global hypokinesis		
			Left ventricular cavity dilation		
Exercise myocardial perfusion single-photon emission computed tomography (SPECT)	Ability to achieve adequate workload	Inducible single or multiple perfusion abnormalities	Also can provide information on left ventricular function and wall motion	88 %	72 %
	Normal or uninterpretable resting ECG precluding assessment of ischemia (e.g., nonspecific ST–T changes as seen in LVH, LBBB, and patients receiving digitalis)	Left ventricular dilation	***High-risk findings***		
			Markedly abnormal ECG		
			Extensive stress-induced wall motion abnormalities or perfusion defects		
	Can be used in patients with LBBB or electronic pacemaker		Reduced post-stress LVEF ≥5 %		
			Global LVEF (rest or post-stress) <45 %		
			Transient ischemic left ventricular dilatation		
			Increased right ventricular or lung uptake		

Pharmacologic myocardial perfusion SPECT (adenosine, dipyridamole, or regadenoson)	Inability to achieve adequate workload	Inducible single or multiple perfusion abnormalities	Provides similar information as exercise SPECT	90 %	82 %
	Normal or abnormal resting ECG	Left ventricular dilation			
Myocardial perfusion positron-emission tomography (PET) (adenosine or dipyridamole)	Inability to achieve adequate workload	Inducible single or multiple perfusion abnormalities	Provides similar information as pharmacologic SPECT, but has higher spatial resolution, is more accurate, less radiation exposure, and higher cost	90 %	88 %
	Normal or abnormal resting ECG	Left ventricular dilation	***High-risk findings***	Sensitivity higher in women and obese patients compared to SPECT	
	82Rubidium or 13N-ammonia used as myocardial blood flow tracers		Abnormal coronary flow reserve		
Cardiac computed tomographic angiography (CCTA)	No contraindications to contrast agents	Enables direct visualization of coronary lumen	Very high negative predictive value for obstructive CAD	93–97 %	80–90 %
	No renal insufficiency	Degree of stenosis correlates favorably with invasive coronary angiography	In high-risk asymptomatic individuals, coronary calcium score can be estimated which closely correlates with extent of coronary atherosclerosis		
	Able to take beta-blockers (to achieve heart rate <65 bpm) and nitroglycerin (to enhance coronary vasodilation)	Estimating the severity of coronary stenosis is hindered by the presence of dense calcification	***High-risk findings***		
			Multivessel obstructive CAD (≥70 % stenosis) or left main stenosis (≥50 % stenosis)		
	Able to follow breath-hold commands		Coronary artery calcium (CAC) score >400 Agatston units		

(*continued*)

Table 3 (continued)

Test	Prerequisites/protocol	Diagnostic end point	Comments	Estimated sensitivity (%)	Estimated specificity (%)
Pharmacologic stress cardiovascular magnetic resonance (CMR)	Inability to achieve adequate workload	**For cine CMR with dobutamine stress**	Additional information using late gadolinium enhancement (LGE) imaging delineates the extent and severity of scarred myocardium	Dobutamine stress	
	Normal or abnormal resting ECG	New wall motion abnormality		83 %	86 %
		For cine CMR with vasodilator stress	No ionizing radiation	Vasodilator stress	
		New perfusion abnormality	In patients with poor echocardiographic windows, CMR is an option	91 %	81 %

High-risk findings: >3 %/year risk of death or myocardial infarction
Sensitivity and specificity data obtained from Braunwald's textbook, chapter 57. Myocardial PET sensitivity and specificity data obtained from pooled meta-analysis by McArdle et al. (2012)
ECG electrocardiography, *SBP* systolic blood pressure, *METs* metabolic equivalents, *LBBB* left bundle branch block, *LVH* left ventricular hypertrophy, *LVEF* left ventricular ejection fraction, *CAD* coronary artery disease

negative (i.e., negative in the presence of obstructive CAD). Thus, the value of noninvasive stress testing is greatest when the pretest likelihood is intermediate (i.e., between 20 % and 70 %) because the test result is likely to have the greatest effect on the posttest probability of CAD and, hence, on clinical decision making.

A reasonable estimate of pretest probability of IHD can be predicted using the Duke database predictive model (Fihn et al. 2012). The advantage of this model over the one proposed by Diamond and Forrester (Diamond and Forrester 1979) is that it also incorporates ECG findings (ST–T changes or Q waves) and information about risk factors (smoking, diabetes mellitus, and hyperlipidemia) in addition to the age, sex, and type of pain (Table 4).

Basic Principles of Stress Testing

Functional tests are designed to provoke ischemia by using exercise (treadmill or bicycle) or by pharmacological stress agents (beta-agonists such as dobutamine or vasodilators such as adenosine, dipyridamole, or regadenoson) through myocardial demand/supply imbalance or vasodilation-elicited heterogeneity in coronary flow. These tests rely on the principles embodied within the ischemic cascade (Fig. 5), in which graded ischemia of increasing severity and duration produces sequential changes in perfusion, relaxation and contraction, wall motion, repolarization/ECG changes, and, ultimately, symptoms, all of which can be detected by an array of cardiovascular testing modalities (Shaw et al. 2009; Fihn et al. 2012).

Table 4 Comparing pretest likelihood of CAD in low-risk symptomatic patients with high-risk symptomatic patients (Duke database)

	Nonanginal chest pain		Atypical angina		Typical angina	
Age, year	Men	Women	Men	Women	Men	Women
35	3–35	1–19	8–59	2–39	30–88	10–78
45	9–47	2–22	21–70	5–43	51–92	20–79
55	23–59	4–21	45–79	10–47	80–95	38–82
65	49–69	9–29	71–86	20–51	93–97	56–84

Each value represents the percentage with significant CAD. The first is the percentage for a low-risk, mid-decade patient without diabetes mellitus, smoking, or hyperlipidemia. The second is that of a patient of the same age with diabetes mellitus, smoking, and hyperlipidemia. Both high- and low-risk patients have normal resting ECGs. If ST–T-wave changes or Q waves had been present, the likelihood of CAD would be higher in each entry of the table *CAD* indicates coronary artery disease, and *ECG* electrocardiogram (Adapted from Fihn et al. (2012))

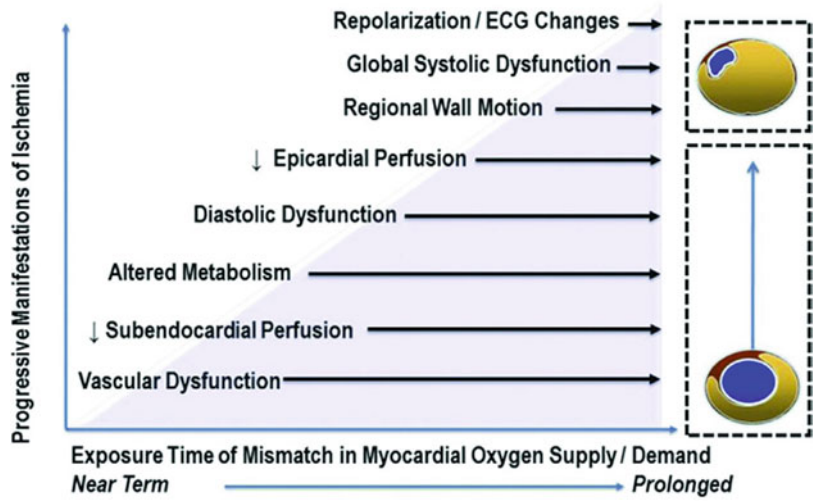


Fig. 5 The Ischemic Cascade. Adapted from Fihn et al. (2012)

Regional or global ventricular function abnormalities occur late in the ischemic cascade and, therefore, are more likely to indicate severe stenosis. Thus, when wall motion abnormalities are seen on stress echocardiography, it demonstrates a higher diagnostic specificity than do perfusion defects, such as those seen on nuclear myocardial perfusion imaging (MPI). On the contrary, isolated perfusion defects can result from stenoses of borderline significance, raising the sensitivity of nuclear MPI for underlying CAD but lowering the specificity for more severe stenosis.

Anatomic noninvasive testing with multi-slice CCTA is more sensitive in detecting obstructive CAD than nuclear MPI, especially when the coronary diameter stenosis is $\leq$70 %, as this degree of stenosis is unlikely to cause a perfusion defect (Shaw and Berman 2009).

Hybrid Imaging

Currently, single modality imaging is largely in use, but combined or hybrid applications are increasingly available, which includes SPECT/CT, PET/CT, and PET/CMR thereby providing an opportunity for combined anatomic (extent of CAD) and functional (ischemia burden) testing in a single setting (Kaufmann and Di Carli 2009; Fihn et al. 2012). Furthermore, novel techniques allow noninvasive assessment of ischemia-causing stenoses using fractional flow reserve (FFR) from CCTA (Koo et al. 2011; Min et al. 2011, 2012). The advantage of hybrid imaging is that, by providing anatomic data, it overcomes technical limitations of myocardial perfusion SPECT or PET and improves interpretative accuracy and, by providing functional information, it adds to an anatomic technique like CCTA or magnetic resonance angiography; however, radiation dose is increased.

Diagnostic Invasive Coronary Angiography

Invasive coronary angiography remains the "gold standard" for the definitive diagnosis of CAD, despite the remarkable evolution of newer noninvasive imaging modalities. In patients with stable ischemic heart disease, the 2012 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (Fihn et al. 2012) and the 2013 European Society of Cardiology (ESC) guidelines (Montalescot et al. 2013) recommend diagnostic evaluation with coronary angiography for further risk stratification in patients with high-risk features on noninvasive testing, in patients with signs and symptoms of heart failure, and in patients with refractory and/or worsening symptoms despite optimal medical therapy. Diagnostic coronary angiography by delineating the extent and severity of obstructive CAD helps in assessing the patient's risk of death and future cardiovascular events (Table 5). It also provides information about the feasibility of

Table 5 CAD prognostic index

Extent of CAD	Prognostic weight (0–100)	5-year survival rate (%)[a]
1-vessel disease, 75 %	23	93
1-vessel disease, 50–74 %	23	93
1-vessel disease, $\geq$95 %	32	91
2-vessel disease	37	88
2-vessel disease, both $\geq$95 %	42	86
1-vessel disease, $\geq$95 % proximal LAD artery	48	83
2-vessel disease, $\geq$95 % LAD artery	48	83
2-vessel disease, $\geq$95 % proximal LAD artery	56	79
3-vessel disease	56	79
3-vessel disease, $\geq$95 % in $\geq$1 vessel	63	73
3-vessel disease, 75 % proximal LAD artery	67	67
3-vessel disease, $\geq$95 % proximal LAD artery	74	59

[a]Assuming medical treatment only. *CAD* indicates coronary artery disease, *LAD* left anterior descending
Reproduced from Califf et al. (1988)

percutaneous or surgical revascularization. The extent of angiographic CAD is defined as 1-vessel, 2-vessel, 3-vessel, or left main disease. The obstruction is considered significant when the visual estimation of stenosis is $\geq$70 % diameter reduction of one or more epicardial coronary arteries or $\geq$50 % diameter reduction of the left main coronary artery. Despite being the "gold standard" test for four decades, coronary angiography has had certain technical limitations. These include interobserver variability in visual estimation of stenosis, inability to distinguish between a stable plaque and a vulnerable plaque, and inability to identify ischemia-causing lesions. Moreover, angiography provides a two-dimensional silhouette of the coronary arterial lumen, thus failing to detect the "positive or expansive remodeling" in the vascular wall which is a characteristic finding in early stages of atherogenesis, thereby underestimating the extent and severity of coronary atherosclerosis. However, remarkable technologic advances have eliminated some of these deficiencies. The use of advanced imaging techniques like intravascular ultrasonography (IVUS) and intravascular optical coherence tomography (OCT) during angiography provides high-resolution cross-sectional images of the coronary arterial walls, which has substantially enhanced the detection and quantification of coronary atheroma even in the presence of normal coronary angiograms (Mintz et al. 1995; McCabe and Croce 2012). IVUS and OCT have also shown a great deal of promise in identifying thin-cap fibroatheromas, which are considered as vulnerable plaques (Nicholls et al. 2006; Raffel et al. 2008; Stone et al. 2011). Similarly, different invasive modalities such as intravascular magnetic resonance imaging, coronary angioscopy, coronary thermography, near-infrared spectroscopy, and palpography are evolving as additional tools for imaging vulnerable plaques (Ohtani et al. 2006; Hamdan et al. 2007; Fujii et al. 2013). The use of a pressure wire to measure the fractional flow reserve (FFR) – an index of physiological significance of a coronary stenosis during angiography – is useful for delineating an intermediate lesion and guiding the PCI based on an abnormal FFR ($<$0.8) and has overcome some of the limitations of coronary angiography (Pijls and Sels 2012).

Guidelines for the Management of Stable Ischemic Heart Disease Patients

Recently published guidelines by ACC/AHA and the ESC strongly recommend an initial management strategy of intensive lifestyle intervention combined with aggressive pharmacologic therapy for all patients with SIHD (i.e., guideline-directed medical therapy) (Fihn et al. 2012; Montalescot et al. 2013). The dual goals of these recommendations are to reduce cardiovascular morbidity and mortality (improve "quantity" of life) as well as the burden of symptoms and ischemia in these patients (improve "quality" of life) as shown in Table 6.

Treatment of Associated Conditions

Conditions such as anemia, fever, infections, occult thyrotoxicosis, tachycardia, drugs that activate sympathetic system like cocaine, heart failure, etc. can precipitate or worsen angina by causing a myocardial oxygen demand/supply imbalance. Prompt recognition and treatment of these conditions will reduce myocardial oxygen demand and improve oxygen delivery, thus alleviating anginal symptoms.

Lifestyle Modifications

Current guidelines strongly emphasize that lifestyle changes should include cigarette smoking cessation, maintaining a healthy weight (body mass index between 18.5 and 24.9 kg/m^2), engaging in regular physical activity (30–60 min of moderate-intensity aerobic activity, at least 5 days and preferably 7 days/week), and adopting a healthy diet (a diet low in saturated fat, cholesterol, and trans fat; high in fresh fruits, whole

Table 6 Guideline recommended dual goals in the management of stable ischemic heart disease patients

Improving "quality" of life		Improving "quantity" of life
Objectives: reduction of ischemic symptoms, improve exercise tolerance and functional capacity		**Objectives:** reduction of recurrent ischemic events, reduction of morbidity and mortality
Anti-ischemic therapy		**Optimal medical therapy**
• Beta-blockers		• Aspirin
• Calcium channel blockers		• Thienopyridines and/or cyclopentyltriazolopyrimidines
• Nitrates		• Statins
• Ranolazine		• ACE inhibitors and/or ARB
• Ivabradine	Approved in Europe	• Aldosterone inhibitors
• Nicorandil		• Anti-ischemic therapy
• Trimetazidine		
Exercise training/cardiac rehabilitation		**Aggressive risk factor modification**
Revascularization		
• PCI		• Smoking cessation
• CABG		• Maintenance of ideal weight
		• Healthy diet
		• Regular physical activity
		• Hypertension (BP <140/90)
		• Hyperlipidemia
		• Diabetes mellitus (HbA1c <7 %)
		Revascularization
		• CABG
		• PCI

ACE angiotensin-converting enzyme, *ARB* aldosterone receptor blockers, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *BP* blood pressure, *LDL* low-density lipoprotein, *HbA1c* glycosylated hemoglobin

grains, and vegetables; and reduced sodium intake) (Fihn et al. 2012).

Smoking Cessation

Cigarette smoking is one of the powerful risk factors for the development of CAD in all age groups. Smoking increases sympathetic tone leading to coronary vasospasm and thus precipitating or worsening angina from myocardial oxygen demand/supply imbalance. Additionally, it has been shown to cause progression of atherosclerosis. Among patients with documented CAD, smokers have a higher 5-year risk of sudden death, MI, and all-cause mortality than those who have quit smoking. Hence, smoking cessation is one of the most powerful and cost-effective approaches in the prevention of CAD progression.

Exercise

Regular aerobic exercise training in patients with CAD has shown to improve functional capacity and myocardial perfusion, retard coronary artery disease progression, and reduce the overall cardiac event rate (Schuler et al. 1992; Haskell et al. 1994; Niebauer et al. 1997; Ornish et al. 1998; Ghatak et al. 2013). A small randomized study in patients with stable CAD demonstrated that 12-month exercise training was associated with higher event-free survival when

compared to percutaneous coronary intervention with stenting (Hambrecht et al. 2004), although this was a small study of only approximately 100 subjects. A systematic review and meta-analysis of 48 randomized controlled trials examining the effectiveness of exercise interventions in a total of 8,940 patients with CAD showed that exercise training was associated with 20 % reduction in all-cause mortality, a 26 % reduction in cardiac mortality, and a favorable but nonsignificant trend in nonfatal MI, CABG, and PCI procedures (Taylor et al. 2004). Exercise capacity measured in metabolic equivalents has shown to be a powerful, independent inverse predictor of cardiovascular events in patients with baseline cardiovascular risk factors or established CAD, despite presence of significant perfusion defects (Podrid et al. 1981; Morris et al. 1991; Bourque et al. 2009; Lee et al. 2011; Padala et al. 2014a). The benefits of exercise in mortality reduction can be explained partially by modification of traditional CAD risk factors. Patients who participate in exercise programs are also more likely to be health conscious, pay attention to diet and weight, and discontinue cigarette smoking. For all these reasons, patients should be urged to participate in regular exercise programs, usually walking, in conjunction with their drug therapy (Wenger 2008).

Obesity

Obesity is an important risk factor for CAD and is often associated with traditional cardiovascular risk factors, including hypertension, hyperlipidemia, and diabetes mellitus (Poirier et al. 2006). Obesity also has been shown to increase sympathetic tone and induce a hypercoagulable state and is associated with markers of inflammation (Pi-Sunyer 2002; Rodríguez-Hernández et al. 2013). In a meta-analysis of 21 cohort studies including more than 300,000 healthy persons, overweight (BMI 25.0–29.9 kg/m2) and obese (BMI $\geq$30 kg/m2) patients had 32 % and 81 % higher risk for cardiovascular events, respectively, compared to those with normal weight, after adjustment for age, sex, physical activity, and smoking (Bogers et al. 2007). The risk of cardiovascular disease is increased particularly in patients with increased waist circumference or waist-to-hip ratio as well as indicators of central obesity, which can be identified by a waist circumference $>$102 cm (40 in.) in men or $>$88 cm (35 in.) in women (Thompson et al. 1991; Hsieh and Yoshinaga 1995; Rimm et al. 1995; Canoy 2010), and in those with extreme obesity, defined as a BMI $\geq$40 kg/m2 (McTigue et al. 2006).

Aggressive Risk Factor Modification

Hypertension

Hypertension is a major independent risk factor for CAD. High blood pressure predisposes to vascular injury, accelerated atherosclerosis, increases myocardial oxygen demand, and intensifies ischemia in patients with preexisting obstructive coronary artery disease. In a collaborative meta-analysis including one million adults with no previous vascular disease, the risk of IHD or stroke doubled for every 20-mmHg increase in systolic blood pressure (range 115–185 mmHg) or 10-mmHg increase in diastolic blood pressure (range 75–115 mmHg) (Lewington et al. 2002). The optimal blood pressure goal in patients with SIHD remains controversial. Although previous professional society guidelines recommends aggressive blood pressure lowering with a target BP of $<$130/80 mmHg in individuals with diabetes mellitus, chronic renal disease, patients with Framingham risk score of $\geq$10 %, CAD and CAD risk equivalents (Rosendorff et al. 2007); the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial targeting a systolic blood pressure below 120 mmHg and the African-American Study of Kidney Diseases and Hypertension (AASK) targeting a systolic blood pressure below 130 mmHg did not show any significant clinical benefit in reducing cardiovascular events with more intensive BP lowering (Cushman et al. 2010; Appel et al. 2010). Accordingly, the recently published Eighth Joint National Committee (JNC 8) guidelines for the management of high blood pressure in adults have raised the blood pressure threshold to initiate antihypertensive therapy in many patients (James et al. 2013). In hypertensive patients aged 60 years or older, the guidelines recommend initiation of

pharmacologic therapy when the systolic blood pressure is ≥150 mmHg or diastolic blood pressure is ≥90 mmHg, with a goal to achieve blood pressure below these cutoffs. For hypertensive patients aged <60 years and for those with diabetes mellitus or chronic kidney disease regardless of age, the guidelines recommend initiation of pharmacologic therapy to target a blood pressure goal of <140/90 mmHg (James et al. 2013).

Hyperlipidemia

Lowering LDL Cholesterol (LDL-C)

Several large randomized clinical trials of lipid lowering therapy have demonstrated a significant reduction in adverse cardiovascular events in patients with SIHD (Cannon et al. 2004; De Lemos et al. 2004; LaRosa et al. 2005; Pedersen et al. 2005). A recently published large prospective meta-analysis by the Cholesterol Treatment Trialist Collaborators included 170,000 individuals from 26 randomized trials of statin therapy (5 trials comparing more vs. less intensive statin therapy and 21 trials comparing statin therapy vs. control) (Baigent et al. 2010). Compared with less intensive regimens, more intensive regimens were associated with significant 13 % reduction in coronary death or nonfatal MI, a 19 % reduction in coronary revascularization, and a 16 % reduction in ischemic stroke. Across all 26 trials, each 40-mg/dL reduction in LDL cholesterol was associated with a 10 % reduction in all-cause mortality and a 20 % reduction in coronary mortality, with corresponding reductions in nonfatal MI, need for coronary revascularization, and first nonfatal ischemic stroke (Baigent et al. 2010). Based on these data, the Adult Treatment Panel III of National Cholesterol Education Program (ATP-III NCEP) updated lipid guidelines in 2004 and recommended that in patients with established CAD, aggressive reduction of LDL cholesterol levels to less than 70 mg/dL (Grundy et al. 2004 Circulation). ATP III also introduced a new secondary target of lipid therapy, namely, non-HDL-C, in patients with elevated triglycerides (≥200 mg/dL). The goal for non-HDL-C is 30 mg/dL higher than the LDL-C goal. However, the recently published, much anticipated, and controversial 2013 ACC/AHA cholesterol treatment guidelines in adults have eliminated LDL cholesterol and non-HDL cholesterol risk-stratified treatment thresholds and targets and have now defined patient eligibility for treatment of dyslipidemia with a statin based solely on projected risk for an atherosclerotic disease-related cardiovascular event (Stone et al. 2013). The guidelines now recommend moderate- or high-intensity statin therapy in patients with clinical atherosclerotic cardiovascular disease irrespective of the LDL or non-HDL cholesterol levels (Stone et al. 2013).

HDL Cholesterol (HDL-C)

Observational data in patients with established CAD have shown that low levels of HDL-C is associated with an incremental risk for adverse coronary events, despite low levels of LDL cholesterol (Barter et al. 2007; Acharjee et al. 2013). The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) Study Group (Rubins et al. 1999) randomized 2,531 men with CAD and HDL-C levels (40 mg/dL or lower) and LDL-C levels (140 mg/dL or lower) to gemfibrozil therapy versus placebo. There was 6 % increase in HDL-C and a 31 % reduction in triglyceride levels in the patients randomized to gemfibrozil 1,200 mg daily during an average 5.1-year follow-up, with no significant difference in LDL-C levels between the groups. Importantly, these changes were associated with a 24 % reduction in the combined outcome of cardiac death, nonfatal MI, and stroke (Rubins et al. 1999). Despite the above data, two recent large randomized studies did not shown any incremental benefit of raising HDL cholesterol among patients with stable IHD who were randomized to extended-release niacin on top of a background of optimal LDL-C treatment with statins, with or without ezetimibe. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) trial enrolled 3,414 high-risk patients receiving statin therapy (mean baseline LDL-C levels were 74 mg/dL and HDL-C levels were 34.5 mg/dL) and randomly assigned them to

high-dose, extended-release niacin (1,500–2,000 mg daily) versus placebo. The trial was stopped prematurely after a mean follow-up period of 3 years, as there was no incremental clinical benefit from the addition of niacin to statin therapy, despite significant improvements in on-treatment LDL-C, HDL-C, and triglyceride levels (Boden et al. 2011). The Second Heart Protection Study, Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial enrolled 25,673 patients with established CAD on statin therapy (mean baseline LDL-C of 63 mg/dL and HDL-C of 44 mg/dl) and randomly assigned them to extended-release (ER) niacin/laropiprant (2,000 mg daily) versus placebo. After 4.5 years of follow-up, there was no significant clinical benefit of ER niacin/laropiprant on the composite primary outcome of major vascular events (cardiac death/nonfatal MI/revascularization or stroke) when added to effective statin-based LDL-lowering therapy (HPS2-THRIVE Collaborative Group 2013; 2014). There was also a significant, but unexpected, increase in serious adverse events in the ER niacin/laropiprant group such as new-onset diabetes, diabetic complications, infection, bleeding, myopathy especially in the Chinese subpopulation, as well as the expected skin and gastrointestinal side effects.

Other therapies aimed at raising the concentration of HDL-C levels have likewise not been convincing to date in achieving clinical event reduction. In a large randomized trial enrolling patients with CAD (mean baseline LDL-C of 83 mg/dL and HDL-C of 46 mg/dL), torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, significantly increased HDL-C by 61 % and further reduced LDL-C by 20 %, but did not decrease progression of coronary atherosclerosis by intravascular ultrasonography (Nissen et al. 2007) and was associated with an increase in ischemic events, including a 60 % increase in mortality. These worse outcomes may be explained, in part, by off-target effects of torcetrapib that increased the renin–angiotensin–aldosterone axis resulting in an increase in blood pressure (Tall 2007). The lack of efficacy may be related to the mechanism of action of this drug class or to molecule-specific adverse effects. A more recent study (Dal-OUTCOMES Trial) undertaken in 15,260 patients with recent ACS (mean baseline LDL-C of 76 mg/dL and HDL-C of 42 mg/dL) were randomized to dalcetrapib, another CETP inhibitor, versus placebo in patients treated with statin therapy. Despite a significant increase in on-treatment HDL-C levels of 31–40 % (with no change in LDL-C levels), there was no difference in the cardiovascular outcomes or mortality (Schwartz et al. 2012).

Diabetes Mellitus

Diabetes is a major cardiovascular disease risk factor and is considered a CAD equivalent. Patients with diabetes have accelerated atherosclerosis and significantly higher incidence of MI, heart failure, and cardiac death when compared to their nondiabetic counterparts (Hammoud et al. 2000). Diabetic patients often have other modifiable risk factors such as obesity, hypertension, and hyperlipidemia. A target-driven, intensified, multifactorial intervention aimed at multiple risk factors in diabetic patients has shown to reduce the risk of cardiovascular disease and microvascular complications by 50 % (Gaede et al. 2003). However, the target HbA1c in patients with diabetes mellitus has not been established definitively by clinical trials. Three studies in patients with type 2 diabetes mellitus targeting intensive blood glucose lowering with a goal HbA1c of $\leq$6.5 % demonstrated significant reduction in microvascular complications, but had no effect on cardiovascular outcomes (Patel et al. 2008; Gerstein et al. 2008; Duckworth et al. 2009). Two of these three trials in fact showed increased mortality in intensive therapy group (Gerstein et al. 2008; Duckworth et al. 2009; Skyler et al. 2009). Based on these trial results, the American Diabetes Association (ADA)/ACC/AHA recommend goal HbA1c of $<$7 % to be reasonable for many younger patients with short duration of diabetes mellitus and a long life expectancy. On the other hand, a HbA1c goal between 7 % and 9 % is reasonable for patients with advanced age/frailty, history of hypoglycemia, long duration of diabetes mellitus with presence of advanced microvascular or macrovascular

complications, or presence of coexisting medical conditions.

Guideline-Directed Medical Therapy (GDMT)

The ACC/AHA/ESC guidelines recommend aggressive pharmacotherapy in patients with SIHD, which can be classified into "disease-modifying" therapies and "antianginal or anti-ischemic" therapies. Three drug classes are classified as being "disease modifying," as they have been shown to reduce mortality and morbidity in patients with SIHD and preserved LV function: antiplatelets, angiotensin-converting enzyme (ACE) inhibitors, and Hydroxy-methyl-glutaryl Co-A reductase (HMGCR) inhibitors. "Antianginal or anti-ischemic" therapies include β-blockers, nitrates, calcium antagonists, and inhibitors of late sodium channel as they have been shown to improve angina and exercise tolerance and reduce ischemia, but have not been proved to reduce mortality in patients with SIHD.

Disease-Modifying Pharmacotherapy for Secondary Prevention

Antiplatelet Therapy

Aspirin

ACC/AHA 2012 guidelines recommend treatment with aspirin in doses of 75–162 mg daily for an indefinite period in the absence of contraindications in all patients with SIHD (class IA). Aspirin inhibits platelet aggregation by irreversibly inhibiting cyclooxygenase 1 and 2 enzymes and thus blocking the production of thromboxane A2. A large meta-analysis of 287 randomized studies including 135,000 high-risk patients showed significant benefit of aspirin for secondary prevention in men and women with stable angina pectoris, previous/acute MI, heart failure, stroke, post CABG, and other high-risk conditions (Antithrombotic Trialists' Collaboration 2002). In a small randomized trial of 333 SIHD patients in the Physicians' Health Study, alternate day aspirin 325 mg for primary prevention showed 87 % risk reduction for first MI (Ridker et al. 1991). Similarly, aspirin 75 mg for primary prevention in 2035 SIHD patients in the Swedish Angina Pectoris Aspirin Trial (SAPAT) resulted in 34 % reduction in acute MI and sudden death compared to placebo (Juul-Moller et al. 1992). Studies examining the appropriate dose of aspirin for secondary prevention have shown that 75–162 mg daily is as effective as 325 mg and is associated with a lower risk of bleeding in both SIHD and ACS patients (Antithrombotic Trialists' Collaboration 2002; Peters et al. 2003; CURRENT-OASIS 7 2010). Dose of aspirin less than 75 mg is not beneficial (Antithrombotic Trialists' Collaboration 2002). Therefore, administration of aspirin daily is advisable for all patients with SIHD without contraindications to this drug (Fihn et al. 2012).

Clopidogrel

ACC/AHA 2012 guidelines recommend treatment with clopidogrel 75 mg as a reasonable option when aspirin is contraindicated in patients with SIHD (class IB). Clopidogrel, a thienopyridine derivative, is a prodrug and requires in vivo conversion to active metabolite that irreversibly binds to the adenosine diphosphate P2Y12 receptor and inhibits platelet aggregation. There are robust data to suggest that the combination therapy with clopidogrel and aspirin significantly reduces cardiovascular events in patients with unstable angina, non-ST-segment elevation MI, and ST-segment elevation MI and those undergoing PCI procedure with or without prior fibrinolytic therapy (Yusuf et al. 2001; Steinhubl et al. 2002; Sabatine et al. 2005; Chen et al. 2005). However, similar benefit has not been demonstrated in clinical trials of SIHD populations so far. In patients with established atherosclerotic vascular disease, the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, treatment with clopidogrel resulted in a modest 8.7 % relative reduction in the risk of vascular death, ischemic stroke, or MI (5.32 % vs. 5.83 %, respectively, $P = 0.043$)

over 2 years (CAPRIE Steering Committee 1996). The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance (CHARISMA) trial randomized patients with clinically evident cardiovascular disease or multiple risk factors to clopidogrel plus aspirin versus aspirin plus placebo and showed no difference in the primary efficacy end point of cardiovascular death, MI, or stroke over a median of 28 months (6.8 % vs. 7.3 %; $P = 0.22$) (Bhatt et al. 2006). Prasugrel and ticagrelor are newer antiplatelet agents approved for use in patients with ACS and in those who undergo PCI procedures, but have not yet been studied in the management of patients with SIHD. Therefore, the role of dual antiplatelet therapy in SIHD patients as standard secondary prevention is currently not recommended and thus requires further research.

Angiotensin-Converting Enzyme (ACE) Inhibitors or Aldosterone Receptor Blockers (ARBs)

The ACC/AHA 2012 guidelines recommend treatment with ACE inhibitors in all patients with SIHD who have hypertension, diabetes mellitus, left ventricular ejection fraction $\leq$40 %, or chronic kidney disease, unless contraindicated (class IA). In patients intolerant to ACE inhibitors, ARBs are recommended (class IA). In patients with left ventricular systolic dysfunction, independent of etiology, analysis from the Studies Of Left Ventricular Dysfunction (SOLVD) and the Survival And Ventricular Enlargement (SAVE) trials showed that in addition to significant reductions in death and heart failure, ACE inhibitor therapy may also reduce acute ischemic cardiovascular events by 20 % (Pfeffer et al. 1992; SOLVD study 1992). Subsequently, two trials of ACE inhibitors in patients with SIHD with normal left ventricular function extended the beneficial effects to this subgroup. The Heart Outcomes Prevention Evaluation (HOPE) study showed that, in 9,297 high-risk patients with atherosclerotic vascular disease or diabetes plus one additional IHD risk factor with no evidence of left ventricular dysfunction, ramipril significantly decreased the primary composite end point of cardiovascular death, MI, and stroke by 22 %, compared with placebo (Yusuf et al. 2000). The European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) trial provided further support to the HOPE trial results and was tested in low-risk 12,218 patients with SIHD and no clinical evidence of heart failure. During a mean of 4.2 years, patients in perindopril group had a 20 % relative risk reduction in the primary composite end point of cardiovascular death, nonfatal MI, or cardiac arrest compared with placebo (Fox et al. 2003). In contradistinction to the HOPE and EUROPA trials, the Prevention of Events with Angiotensin-Converting Enzyme Inhibitor (PEACE) trial, which randomized 8,290 patients with SIHD and normal or near-normal left ventricular function to trandolapril versus placebo, showed no significant difference in the primary end point of cardiovascular death, MI, or need for coronary revascularization (Braunwald et al. 2004). Similarly, in the Quinapril Ischemic Event Trial (QUIET), 1750 SIHD patients with preserved left ventricular function randomized to quinapril versus placebo, there was no significant difference in the reduction of ischemic events and angiographic progression of CAD during a mean follow-up of 27 months, although this finding was attributed to study design limitations (Pitt et al. 2001). However, in a meta-analysis of four randomized trials including HOPE, EUROPA, PEACE, and QUIET trials enrolling 31,555 patients, ACE inhibitor therapy was associated with a 14 % reduction in all-cause mortality and MI (both $P = 0.0004$), a 23 % relative risk reduction in stroke ($P = 0.0004$), and a 7 % reduction in revascularization procedures ($P = 0.025$) compared with placebo (Al-Mallah et al. 2006).

ARBs bind selectively and in a competitive manner to the type 1 angiotensin II receptor and block the vasoconstrictor and aldosterone-secreting effects of angiotensin II. A meta-regression analysis of 26 trials examined the effects of ACE inhibitors and ARBs on major

vascular events by blood pressure effects in 146,838 individuals (Blood Pressure Lowering Treatment Trialists' Collaboration 2007). For each 5-mm Hg reduction in blood pressure with ACE inhibitors, there was a 19 % reduction in the risk for stroke, a 16 % reduction in IHD, and a 27 % reduction in heart failure risk; corresponding figures for the reduction in risk for ARBs were 26 %, 17 %, and 12 %, respectively. There were no significant differences between ARB- and ACE inhibitor-based regimens in the risk of stroke, IHD, and heart failure for each 5-mm Hg reduction in BP. Guidelines therefore recommended that ARBs be substituted in patients with SIHD and hypertension who are intolerant of ACE inhibitors (Fihn et al. 2012).

These beneficial effects of ACE inhibitors and ARBs are mediated by a reduction in left ventricular mass, left ventricular preload and afterload, sympathetic stimulation, vascular hypertrophy, atherosclerosis progression, and protection from plaque rupture and thrombosis and restoring the balance between myocardial oxygen supply and demand. ACE inhibition has also been shown to enhance coronary endothelial vasomotor function and reduce inflammatory changes in animal models of atherosclerosis (Lonn et al. 1994; Prasad et al. 1999; Tummala et al. 1999).

Hydroxy-methyl-glutaryl Co-A Reductase (HMGCR) Inhibitors- Statins

Current ACC/AHA 2012 SIHD guidelines recommend, in addition to lifestyle modifications and dietary therapy, all patients with SIHD should be treated with moderate or high dose of statin therapy with a goal LDL $<$70 mg/dL, unless contraindicated (class IA). For patients who do not tolerate statin therapy, LDL-C-lowering therapy with bile acid sequestrants, niacin, or both is reasonable (class IIa B). However, the recently published 2013 ACC/AHA lipid guidelines recommend moderate- or high-intensity statin therapy in all patients with established atherosclerotic cardiovascular disease irrespective of LDL-C and non-HDL-C levels (Stone et al. 2013). Studies showing beneficial effects of statin therapy have been described previously (see above).

Anti-ischemic/Antianginal Therapy

Beta-Adrenergic Blocking Drugs (Beta-Blockers)

ACC/AHA 2012 guidelines recommend beta-blocker therapy in all patients with normal left ventricular function after ACS (class IA), and in all patients with left ventricular systolic dysfunction (ejection fraction $\leq$40 %) with heart failure or prior MI (class IA). Beta-blockers are recommended as initial agents for relief of angina in patients with SIHD (class IB).

Beta-blockers constitute a cornerstone of anti-ischemic therapy and are the agents of initial choice in patients with SIHD, and especially in those who exhibit "demand angina." Beta-blockers prevent the binding of circulating catecholamines to the beta-adrenergic receptors and reduce myocardial oxygen demand by lowering the heart rate, afterload, rate-pressure product, and contractility and improve myocardial oxygen supply by increasing diastolic filling time and thus coronary perfusion, leading to alleviation of ischemia or anginal symptoms. Long-term use is associated with reduction in left ventricular wall tension and attenuation of cardiac remodeling. Beta-blockers have been studied extensively in patients with ACS and congestive heart failure and are shown to reduce the mortality rates, sudden cardiac deaths, arrhythmias, recurrent MIs, and hospitalizations (Hjalmarson et al. 1983; MIAMI trial research group 1985; Chadda et al. 1986; Packer et al. 1996; Reiter and Reiffel 1998; MERIT-HF 1999; CIBIS-II 1999; Kernis et al. 2004; Halkin et al. 2004). However, there are no large clinical trials evaluating the effects of beta-blockers on mortality or cardiovascular outcomes in SIHD population.

In SIHD patients, beta-blockers effectively reduce the frequency of anginal episodes and raise the threshold of angina when given alone or in combination with other antianginal agents. Beta-blockers have been shown to be more effective than calcium channel blockers in the relief of angina, the reduction of cardiovascular events, and the need for revascularization (Rehnqvist et al. 1995; von Arnim 1995;

Savonitto et al. 1996). Beta-blockers, when combined with dihydropyridine calcium channel blockers, can counteract the dihydropyridine-induced tachycardia and have shown to increase exercise time and a trend toward a lower rate of cardiovascular outcomes (von Arnim 1995; Savonitto et al. 1996). However, one should be prudent when a beta-blocker is combined with non-dihydropyridine calcium channel blockers such as verapamil or diltiazem because of the potential for development of severe bradycardia, AV block, or excessive fatigue. Studies have also shown that the combination of beta-blockers with nitrates is more effective in alleviating anginal symptoms than either monotherapy alone (Waysbort et al. 1991; Krepp 1991). Beta-blockers can counteract nitrate-induced reflex tachycardia, and similarly, nitrates can counteract the increased left ventricular wall tension associated with decreased heart rate from beta-blockers, thus providing a synergistic combination. All beta-blockers are equally effective in SIHD patients (Table 7). The dose of beta-blockers should be titrated to a target resting heart rate of 50–60 beats per minute as tolerated by the patient.

Calcium Channel Blockers

The ACC/AHA 2012 guidelines recommend the use of calcium channel blockers for the relief of symptoms when beta-blockers are contraindicated or cause unacceptable side effects in patients with SIHD (class IB*)*. Calcium channel blockers should be used in combination with beta-blockers for relief of symptoms, when initial treatment with beta-blockers is unsuccessful in patients with SIHD (class IB*)*. Three classes of calcium channel blockers are available: the dihydropyridines (such as nifedipine, amlodipine), the phenylalkylamines (verapamil), and the benzothiazepines (diltiazem) (Table 8). These agents limit the influx of the calcium ions by noncompetitively blocking voltage-sensitive L-type calcium channels resulting in vascular smooth muscle relaxation and negative inotropic, chronotropic, and dromotropic effects. All calcium channel blockers improve myocardial oxygen supply by coronary vasodilation and decrease myocardial oxygen demand by reducing afterload, arterial pressure, and myocardial contractility. In addition, verapamil and diltiazem also possess negative dromotropic effects slowing conduction by depressing intrinsic cardiac pacemaker activity. Calcium channels blockers in patients with SIHD are shown to be effective in reducing the frequency of anginal episodes, ST-segment depression on Holter monitoring, and nitroglycerin consumption and improving exercise duration (Deanfield et al. 1994; Ezekowitz et al. 1995; Boman et al. 1995; Brogden and Benfield 1996). Calcium channel blockers, alone or in combination with nitrates, are also drugs of choice in patients with Prinzmetal (variant) angina as they prevent coronary vasospasm (Antman et al. 1980; Pepine et al. 1981; Johnson et al. 1981). The choice of calcium channel blockers should be individualized based on whether blood pressure (dihydropyridines) or heart rate control (verapamil or diltiazem) is required in addition to control of anginal symptoms. Despite being effective anti-ischemic agents, calcium channel blockers have not been shown to reduce death or MI in randomized trials of patients with SIHD. Therefore, these agents should be used in patients who cannot tolerate beta-blockers or who require additional pharmacotherapy to control their anginal symptoms. However, when diltiazem or verapamil is used in combination with beta-blockers, care must be taken to avoid symptomatic bradycardia. Furthermore, calcium channel blockers are not recommended for routine use in patients with current or prior heart failure symptoms and reduced left ventricular ejection fraction (Fihn et al. 2012).

Nitrates

The ACC/AHA 2012 guidelines recommend the use of long-acting nitrates for relief of symptoms when beta-blockers are contraindicated or cause unacceptable side effects or in combination with beta-blockers for relief of symptoms, when initial treatment with beta-blockers is unsuccessful in patients with SIHD (class IB*)*. Sublingual nitroglycerin or nitroglycerin spray is recommended for immediate relief of angina in patients with

Table 7 Pharmacology, indications, and side effects of commonly used beta-blockers

Drugs and receptor activity	Dose	Elimination	Half-life (h)	Intrinsic sympathomimetic activity	Membrane stabilizing effect	FDA approved indications	Side-effects
β_1 selective							
Acebutolol	200–600 mg bid	Hepatic	3–4	+	+	Hypertension	Severe sinus bradycardia
Atenolol	50–200 mg/day	Renal	6–9	–	–	Hypertension	Sinus arrest
						Angina	Atrioventricular block
						Post-MI	Negative inotropy- CHF
Bisoprolol	5–20 mg/day	50 % renal	9–12	–	–	Hypertension	Gastrointestinal upset
		50 % hepatic					
Betaxolol	5–20 mg/day	Hepatic	12–22	–	–	Hypertension	Depression
Esmolol	Bolus 500 μg/kg, 50–200 μg/kg/min IV	Esterases in red blood cells	4.5 min	–	–	Hypertension	Fatigue
						Post-MI	Lethargy
						Supra-ventricular tachycardia	Weakness
Metoprolol	50–200 mg bid	Hepatic	3–7	–	–	Hypertension	Nightmares
						Angina	Sexual dysfunction
						Post-MI	Cutaneous reactions
						Heart failure	Angina / MI / ventricular arrhythmia on abrupt withdrawal
Metoprolol long acting	100–400 mg	Hepatic	14–25	–	–	Hypertension	
						Angina	
						Heart failure	
β_1 and β_2							
Propranolol	20–80 mg bid-tid	Hepatic	1–6	–	++	Hypertension	Same as **β_1 Selective** *plus*
						Angina	
						Post-MI	Bronchospasm
Propranolol long acting	80–360 mg/day	Hepatic	8–11	–	++	Hypertension	Raynaud phenomenon
						Angina	Intensification of insulin-induced hypoglycemia
Pindolol	2.5–7.5 mg tid	Renal	3–4	+	+	Hypertension	Intensification of vasoconstriction in peripheral vascular disease patients

Nadolol	40–80 mg/day	Renal	40–80	–	–	Hypertension	
						Angina	
Sotalol	40–160 mg bid	Renal	7–18	–	–	Ventricular tachyarrhythmia's	
						Atrial fibrillation/ atrial flutter prevention	
Timolol	10–15 mg bid	Hepatic-renal	4–5	–	–	Hypertension	
						Post-MI	
β_1, β_2, α_2							
Labetalol	200–600 mg bid	Hepatic	6	+	–	Hypertension	All of the above *plus*
						Hypertensive emergency	Hypotension
Carvedilol	3.125–50 mg bid	Hepatic	6–10	–	+	Hypertension	
						Post-MI	
						Heart failure	

FDA U.S Food and Drug Administration, *MI* myocardial infarction, *CHF* congestive heart failure

Table 8 Pharmacology, indications, and side effects of commonly used calcium channel blockers

Drug class and drugs	Dose	Elimination	Half-life (h)	Heart rate	Peripheral vascular resistance	FDA approved indications	Side-effects
Dihydropyridines							
Amlodipine	2.5–10 mg/day	Hepatic	30–50	–	↓↓↓	Hypertension	Hypotension
						Angina	Dizziness
						Coronary spasm	Palpitations
Isradipine	2.5–10 mg bid	Hepatic	8	–	↓↓↓	Hypertension	Headache
Nisoldipine	10–40 mg/day	Hepatic	7–12	–	↓↓↓	Hypertension	Flushing
						Angina	Leg edema Gastrointestinal upset
Nifedipine	10–30 mg tid	Hepatic	2	↑↑	↓↓↓	Angina	
						Coronary spasm	
Nifedipine long acting	90 mg/day	Hepatic	7	↑↑	↓↓	Hypertension	
						Angina	
						Coronary spasm	
Felodipine	2.5–10 mg/day	Hepatic	11–16	↑	↓↓↓	Hypertension	
Nicardipine	20–40 mg tid	Hepatic	2–4	↑	↓↓↓	Hypertension	
						Angina	
Nicardipine long acting	30–60 mg bid	Hepatic	8–10	↑	↓↓	Hypertension	
						Angina	
Non-dihydropyridines							
Diltiazem	30–90 mg tid	60 % hepatic	3–4.5	↓	↓	Angina	Same as above *plus*
		40 % renal				Coronary spasm	Sinus bradycardia
						AF, AFL, PSVT treatment	Atrioventricular block
Diltiazem long acting	120–480 mg/day	60 % hepatic	5–7	↓	↓	Angina	Negative inotropy- CHF (Verapamil >>Diltiazem)
		40 % renal				Coronary spasm	Gastrointestinal upset
Verapamil	80–120 mg tid	85 % hepatic	3–8	↓	↓↓	Hypertension	Gingival hyperplasia (Verapamil)
						Angina	
						Coronary spasm	
						AF, AFL, PSVT treatment	
Verapamil long acting	180–480 mg/day	85 % hepatic	4.5–12	↓	↓↓	Hypertension	

FDA U.S Food and Drug Administration, *AF* atrial fibrillation, *AFL* atrial flutter, *PSVT* paroxysmal supraventricular tachycardia, *CHF* congestive heart failure

Table 9 Pharmacology, indications, and side effects of nitrates

Drug	Route of administration	Dose	Onset of action (min)	Duration of action	Indications	Side effects
Short acting nitrates						
Nitroglycerin	Sublingual	0.3–0.6 mg, up to 1.2 mg as needed	2–5	10–30 min	Acute anginal attack	Headache
					Angina prophylaxis	Hypotension
	Spray/aerosol/mist	0.4 mg, up to 3 doses 5 min apart	2–5	10–30 min	Acute anginal attack	Palpitations
					Angina prophylaxis	Dizziness
Isosorbide dinitrate	Sublingual	2.5–5 mg, up to three doses 5 min apart	5–10	45–120 min	Angina prophylaxis	Syncope
						Tachyphylaxis
Long acting nitrates						
Nitroglycerin	Buccal	1–3 mg thrice daily or as needed	2–5	30–300 min	Angina prophylaxis	Same as above
	Ointment 2 %	7.5–40 mg daily (6 × 6 in.)	20–60	3–8 h	Angina prophylaxis	
	Transdermal patch	0.2–0.8 mg/h, 12 h/day	60–120	8–12 h	Angina prophylaxis	
	Intravenous	5–400 μg/h	Immediately	15–20 min	Recurrent chest pain, systemic hypertension, left-sided heart failure	
Isosorbide dinitrate	Oral	5–80 mg, 2–3 times/daily	30–60	8 h	Angina prophylaxis	
Isosorbide mononitrate	Oral	20 mg twice daily, 7 h apart	30–60	12–14 h	Angina prophylaxis	
Isosorbide mononitrate long acting	Oral	120–240 mg once daily	30–60	12 h	Angina prophylaxis	

SIHD (class IB). Mechanistically, nitrates act by releasing reactive nitric oxide that activates soluble guanylyl cyclase resulting in vascular smooth muscle relaxation. These effects are predominantly seen in venous capacitance vessels, leading to venodilation, a decrease in preload, which in turn reduces left ventricular wall tension, end-diastolic pressure, and myocardial oxygen requirements. Vasodilation of systemic arterial circulation leads to decreased afterload and of epicardial coronary arteries leads to increased coronary perfusion pressure and thus augments myocardial oxygen supply. Furthermore, nitrates cause coronary blood flow redistribution by augmenting collateral blood flow from areas of normal perfusion to ischemic zones (Bøttcher et al. 2002); however, nitrates are unlikely to induce a coronary steal syndrome. Nitrates have also shown to exhibit antiplatelet and antithrombotic effects (Lacoste et al. 1994; Münzel et al. 2002). In patients with SIHD, nitrates are shown to be effective in reducing anginal episodes and increasing exercise capacity and time to the onset of ST-segment depression during exercise treadmill testing (DeMots and Glasser 1989; Parker et al. 1995; Glasser 1997).

Nitrates can be either short acting or long acting (Table 9). Short-acting nitrates are available as

sublingual tablet, capsule, spray, ointment, or patch. They are commonly used for acute relief of anginal pain and prophylactically administered prior to exercise in order to improve exercise tolerance and prevent the onset of exercise-induced anginal symptoms or ischemia (Kimchi et al. 1983; Marmor et al. 1988). Commonly used long-acting nitrates include both isosorbide dinitrate and isosorbide-5-mononitrate. They are often used either as monotherapy or in combination with beta-blockers or calcium channel blockers, to prevent or reduce the frequency of angina episodes in patients with SIHD (Thadani 2006; Boden et al. 2012).

Nitroglycerin Tablets

Sublingual nitroglycerin tablets remain the treatment of choice for relief of acute anginal episodes and for prophylaxis of angina episodes. Tablets need to be stored in dark containers as they lose potency on exposure to light. Patients should be instructed not to chew or swallow the tablet, but to let the tablet dissolve under the tongue. Since sublingual administration avoids first-pass hepatic metabolism, it rapidly appears in the circulation with an onset of action of approximately 1–3 min. The half-life of nitroglycerin is short and within 30–60 min is converted to inactive metabolites by hepatic breakdown minimizing the hemodynamic and clinical effects. The usual dose is 0.3–0.6-mg tablet, which can be repeated every 5 min for relief of angina, but no more than 1.2 mg should be used within a 15-min period due to risk of hypotension. Sublingual nitroglycerin, when taken prophylactically prior to physical activities, can prevent angina for up to 40 min. Tolerance is unlikely to occur with the sublingual tablets due to short duration of action and intermittent use.

Nitroglycerin Spray

An oral nitroglycerin spray dispenses metered, aerosolized doses of 0.4 mg and can be repeated up to a maximum of three sprays for acute relief of anginal discomfort. Onset of action is also approximately 1–3 min, and the effect typically lasts for 30–60 min. It is usually sprayed onto or under the tongue, and therefore, in patients with dry mucosal membranes, the spray may be better absorbed than the sublingual form. For angina prophylaxis, the spray should be used 5–10 min prior to activities that typically provoke angina. Tolerance is unlikely to occur with spray due to short duration of action and intermittent use.

Nitroglycerin Ointment

Nitroglycerin ointment is applied to a clean, dry, and hair-free area, most commonly to the chest in 0.5–2.0-inch. strips with each inch of paste containing approximately 15 mg nitroglycerin. Onset of action is approximately 30 min and the effects last for 4–6 h. If necessary, repeat application of paste can be performed 6 h later. Nitrate-free interval of 10–12 h is recommended to avoid tolerance. Skin absorption of the ointment can be enhanced with increased hydration, rotating the application sites, and by covering the paste with plastic. Ointment preparations are most useful in the settings of severe angina, unstable angina, or nocturnal angina.

Nitroglycerin Transdermal Patches

Nitroglycerin transdermal patches have the drug impregnated into a polymer matrix or suspended in a silicone gel, which results in a constant delivery of the drug across the skin over a 24–48-h period. Transdermal patches should be applied to a clean, dry, and hair-free area. The release rate of the nitroglycerin varies from 0.1 to 0.8 mg/h. Onset of action is 30 min. Transdermal patch applied for 12 h/day has not only been shown to improve exercise duration but also has sustained antianginal effects for 12 h after patch application throughout 30 days of therapy, without significant nitrate tolerance or rebound phenomena.

Nitroglycerin Intravenous

Intravenous nitroglycerin is commonly used in acute settings like ACS, recurrent chest pain, acute decompensated heart failure, acute pulmonary edema, and hypertensive emergencies. Intravenous nitroglycerin is contraindicated in patients with hypotension (SBP <90 mmHg or ≥30 mmHg below baseline), bradycardia (<50 bpm), tachycardia (>100 bpm) in the absence of heart failure, and/or right ventricular infarction. The usual starting dose is 5 mcg/min, which is gradually titrated up by 5 mcg every 3–5 min to 20 mcg/min. If no response is observed at 20 mcg/min, then the dose is increased by 10–20 mcg/min to a maximum dose of 400 mcg/min. Onset of action is immediate and the effect lasts for 3–5 min.

Isosorbide Dinitrate

Isosorbide dinitrate is available as tablets for sublingual, chewable for oral use, and in a capsule for sustained-release forms. Sublingual form of isosorbide dinitrate can be used for relief of an acute anginal attack, but has a slower onset of action (peak effect 5–10 min) than sublingual nitroglycerin tablet or spray and hence is not the preferred agent. Upon oral administration, it undergoes rapid high first-pass hepatic metabolism, and the bioavailability is highly variable (10–90 %) as there is substantial intersubject variability in the pharmacokinetic properties. It has two active metabolites of isosorbide-5-mononitrate ($t_{1/2}$ 5–6 h) and isosorbide-2-mononitrate ($t_{1/2}$ 2 h), which are cleared less rapidly than the parent drug ($t_{1/2}$ 1 h) and are excreted unchanged in the urine. Onset of action is approximately 60 min and the effect lasts for about 8 h. Upon administering doses of isosorbide dinitrate at 30 mg either three or four times daily, partial or complete nitrate tolerance may develop. To prevent nitrate tolerance, eccentric dosage regimens are often employed (Silber et al. 1987). Twice daily regimens should be administered at 8 AM and 1 PM, and thrice daily regimens should be administered at 8 AM, 1 PM, and 6 PM to provide a 10–12-h nitrate-free interval.

Isosorbide-5-Mononitrate

Isosorbide-5-mononitrate is the active metabolite of isosorbide dinitrate, which does not undergo first-pass hepatic metabolism. Bioavailability is 100 % and has low intersubject variability in terms of the plasma concentrations and pharmacokinetic properties. Onset of action is 30–60 min and the effect lasts for about 6–8 h for immediate release and 12–24 h for sustained-release preparations. The sustained-release form is given once daily in a dosage of 30–240 mg. Nitrate tolerance has not been demonstrated with once daily or eccentric dosing regimens but can be seen with twice daily dosing at 12-h intervals.

Nitrate Tolerance

A commonly encountered clinical challenge with the use of nitrates is the development of nitrate tolerance or tachyphylaxis, which can occur with any of the nitrate preparations, if administered continuously. This is seen more often in patients with chronic angina on long-acting nitrates compared to those who present with ACS requiring short-acting nitrates. The exact mechanism of tolerance remains unclear, but one hypothesis is that early counter-regulatory response to nitrates results in neurohormonal activation of vasoconstrictor signals and intravascular volume expansion (pseudotolerance) and long-term treatment results in a loss of nitroglycerine-induced vasodilator responsiveness (vascular tolerance) due to increased vascular superoxide production and potential hypersensitivity to vasoconstrictors (Münzel et al. 2005). Dose escalation of nitrates has not been shown to overcome this effect of tolerance. The primary strategy to prevent nitrate tolerance is to provide a nitrate-free interval, which usually restores responsiveness to nitrates. The optimal duration is unknown, but with nitroglycerin patches and ointment or preparations of isosorbide dinitrate or isosorbide-5-mononitrate, a 10–12-h off period is often recommended.

Nitrate Rebound or Withdrawal

This phenomenon is observed in patients on abrupt discontinuation of long-acting nitrates and manifests as worsening of angina symptomatology. Patients may also have heightened sensitivity to constrictor stimuli upon abrupt cessation of long-acting nitrates. Adjusting the dose and timing of the nitrates in addition to the use of other antianginal drugs can potentially counteract these reactions to cessation.

Inhibitor of Late Sodium Channel-Ranolazine

The ACC/AHA 2012 guidelines recommend the use of ranolazine for relief of symptoms as a substitute when beta-blockers are contraindicated or cause unacceptable side effects (class IIa B) or in combination with beta-blockers for relief of symptoms, when initial treatment with beta-blockers is unsuccessful in patients with SIHD (class IIa A). Ranolazine unlike other antianginal medications exerts its effects without any (minimal if any) change in the hemodynamic parameters (heart rate or blood pressure), making it an attractive option in patients with either bradycardia or hypotension. At therapeutic doses, ranolazine inhibits the late sodium channel influx (late I_{Na}) during cardiac repolarization in ischemic myocytes, thereby reducing intracellular sodium concentrations and subsequently reducing calcium influx via Na^{+}–Ca^{+2} exchange. Reduced intracellular calcium leads to an improvement in ventricular diastolic tension. Thereby, acting as a positive lusitropic drug, ranolazine prevents the left ventricular diastolic dysfunction, which is one of the earliest manifestations in the "ischemia cascade" and thus reduces myocardial oxygen consumption of ischemic cells and ultimately improves angina (Boden 2010). It also inhibits the rapid delayed rectifier potassium current (I_{Kr}) in a dose-dependent manner thus prolonging the ventricular action potential duration and QT_C interval. However, the mean increase in QT_C interval at maximally recommended dosing was only 6 ms, and there was no increase in proarrhythmia or death in 3,162 ACS patients (Scirica et al. 2007). Ranolazine in multiple randomized controls trials such as the MARISA (Monotherapy Assessment of Ranolazine in Stable Angina) (Chaitman et al. 2004b), the CARISA (Combination Assessment of Ranolazine in Stable Angina) (Chaitman et al. 2004a), the ERICA (Efficacy of Ranolazine In Chronic Angina) (Stone et al. 2006), and the TERISA (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina) (Kosiborod et al. 2013) trials has shown to significantly reduce the frequency of angina, need for nitroglycerine use, improved exercise duration and delayed the time to exercise-induced angina and/or ST-segment depression. In the MERLIN (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST elevation acute coronary syndrome) TIMI-36 trial, enrolling 6,560 patients with non-ST elevation MI, the addition of ranolazine to standard treatment did not reduce the incidence of MI or death, but did reduce recurrent ischemia in the postinfarction period (Morrow et al. 2007). Furthermore, ranolazine has demonstrated additional beneficial effects such as significant reductions in HbA1c in patients with diabetes mellitus (Timmis et al. 2006; Morrow et al. 2009) and prevention of supraventricular and ventricular arrhythmias in ACS patients (Scirica et al. 2007; Verrier et al. 2013) and potential role in patients with systolic and diastolic heart failure (Sossalla and Maier 2012).

Antianginal Agents Currently Not Approved in the United States

Nicorandil

Nicorandil is a nicotinamide ester approved as a second-line agent for angina prevention in Europe (Montalescot et al. 2013). It is an adenosine triphosphate (ATP)-sensitive potassium (K^{+}) channel agonist resulting in coronary and peripheral vasodilation which also possesses a nitrate moiety that promotes systemic coronary and venous vasodilation (Simpson and Wellington 2004). As a result of these dual actions, it reduces preload and afterload and increases coronary perfusion and blood flow. Additionally, the K^{+} ATP channel is thought to be involved in ischemic preconditioning suggesting that nicorandil may

have cardioprotective actions (Patel et al. 1999; Markham et al. 2000). In double-blind randomized studies, nicorandil has been shown to have a comparable antianginal efficacy, as measured by exercise tolerance testing, to beta-blockers, calcium channel blockers, and nitrates (Markham et al. 2000). In a prospective, randomized IONA (Impact Of Nicorandil in Angina) trial, nicorandil when added to standard antianginal therapy compared with placebo over a mean period of 1.6 years in 5,126 patients resulted in a 17 % relative risk reduction in the composite of cardiac death, MI, or hospital admission for angina (IONA study group 2002). Furthermore, long-term use of nicorandil has shown to stabilize coronary plaque in SIHD patients (Izumiya et al. 2011). Side effects of nicorandil include headache, flushing, palpitations, nausea, vomiting, and ulcerations of the gastrointestinal tract.

Ivabradine

Ivabradine is a specific and selective inhibitor of the I*f* current in the sinoatrial node, thereby lowering the heart rate without any effects on inotropy or the blood pressure (Montalescot et al. 2013). Lowering the heart rate increases diastolic filling time and thus improves coronary perfusion. Ivabradine is approved as a second-line agent for angina prevention in Europe in patients with normal sinus rhythm with heart rate >60 bpm and with a contraindication or intolerance to beta-blockers (Montalescot et al. 2013). In patients with chronic stable angina, ivabradine reduced peak heart rate during exercise, improved exercise tolerance, and increased the time to onset of activity-limiting angina compared with placebo (Borer et al. 2003). It has also been shown to be non-inferior to atenolol and amlodipine with respect to reducing the number of anginal attacks and frequency of nitroglycerin use as well as improving exercise performance and delaying time to activity-limiting angina and time to ST-segment depression (Tardif et al. 2005; Ruzyllo et al. 2007). In a large randomized trial of 10,917 patients with CAD and reduced left ventricular function, ivabradine did not reduce the primary composite end point of cardiovascular death, hospitalization for MI, or hospitalization for new or worsening heart failure (Fox et al. 2008). However, a post hoc analysis in 1,507 patients with a history of limiting angina showed that ivabradine reduced the primary composite end point by 24 % and rates of hospitalization for MI by 42 % (Fox et al. 2009). Side effects include bradycardia, heart block, dizziness, and transient visual disturbances such as phosphenes (luminous visual field disturbances) as well as blurred vision (Deedwania 2013).

Trimetazidine

Trimetazidine is a metabolic agent that optimizes cardiac metabolism by inhibiting 3-ketoacyl-CoA thiolase, thereby switching the energy substrate from fatty acid oxidation to glucose oxidation which requires less oxygen and thus lowering myocardial oxygen demand requirements without altering the heart rate, blood pressure, or myocardial contractility (Kantor et al. 2000). Trimetazidine is approved as a second-line agent for angina prevention in Europe (Montalescot et al. 2013). In a meta-analysis of randomized studies in patients with chronic stable angina, trimetazidine used as monotherapy or in combination with other antianginal medications was shown to reduce the number of weekly angina episodes and weekly frequency of nitroglycerin use and delay in time to ST-segment depression and had comparable efficacy compared to conventional antianginal therapies such as beta-blockers, calcium channel blockers, and nitrates (Marzilli and Klein 2003; Ciapponi et al. 2005). However, there is paucity of data on the effect of trimetazidine on cardiovascular end points, mortality, or quality of life. Side effects include gastrointestinal symptoms, but the incidence is low.

Non-pharmacological Therapies for Refractory Angina

Enhanced External Counterpulsation

The ACC/AHA 2012 guidelines on SIHD recommend that enhanced external counterpulsation (EECP) may be considered for refractory angina

in patients with SIHD (class IIb, LOE B). EECP therapy consists of electrocardiogram-gated rapid, sequential compression of the lower extremities using inflatable cuffs during diastole, followed by simultaneous decompression during systole. These actions result in diastolic augmentation, increase in coronary perfusion pressure, and decrease in left ventricular afterload; hemodynamic effects similar to those of an intra-aortic balloon pump, but unlike an intra-aortic balloon pump, EECP therapy is external or noninvasive and also increases venous return (Manchanda and Soran 2007). EECP typically consists of 35-h-long treatment sessions administered 5 days a week over a period of 7 weeks. EECP is contraindicated in patients with severe aortic regurgitation, severe peripheral arterial disease, and decompensated heart failure. The various mechanisms implicated in improvement of anginal symptoms and decrease in the long-term morbidity with EECP therapy include improvement in endothelial function, left ventricular diastolic filling time, oxygen consumption, recruitment of collaterals, regression of atherosclerosis, and peripheral training effects similar to exercise (Shechter et al. 2003; Akhtar et al. 2006; Manchanda and Soran 2007). In a meta-analysis of 13 prospective studies incorporating 949 patients who underwent EECP, angina class was reduced by at least one CCS score in 86 % of the patients (95 % confidence interval 82–90 %, Q statistic $P = 0.008$) (Shah et al. 2010). In a study of 363 patients with refractory angina and severe left ventricular dysfunction with an ejection fraction less than 35 % who had been treated with EECP, over a 2-year follow-up period, quality of life improved significantly. Of note, 72 % of patients reported improvement in severity of angina from severe angina to mild or no angina, 52 % discontinued nitroglycerin use, and half of these patients continued to have decreased angina frequency at 2 years of follow-up (Soran et al. 2006). In the randomized MUST-EECP (Multicenter Study of Enhanced External Counterpulsation) trial, 139 patients with angina, documented CAD, and evidence of ischemia on exercise testing, it was found that both the time to $\geq$1 mm ST-segment depression increased and number of anginal episodes decreased significantly in patients treated with active counterpulsation compared with inactive counterpulsation (Arora et al. 1999). One study reported significant improvement in stress-induced myocardial ischemia using radionuclide perfusion treadmill stress test in 175 patients undergoing EECP (Stys et al. 2002). Based on these data, EECP seems to be a reasonable option for patients with refractory angina despite conventional therapies.

Transmyocardial Revascularization

The ACC/AHA 2012 guidelines recommend that transmyocardial revascularization (TMR) may be considered for treatment of refractory angina in patients with SIHD (class IIb B). TMR is a laser-based therapy performed as either a percutaneous catheter-based procedure or a surgical procedure using carbon dioxide XeCl excimer and holmium:YAG lasers in patients with refractory angina (Guleserian et al. 2003; van der Sloot et al. 2004). TMR can be done as a standalone procedure or preferably as an adjunct to CABG surgery. During TMR, numerous transmyocardial channels are created in the left ventricle (Kim et al. 2002). The exact mechanism by which TMR might be efficacious is still debated and remains unclear. Various proposed mechanisms include the stimulation of microcirculation, the creation of myocardial scarring, and denervation of ischemic myocardium (Oesterle et al. 2000; Bridges et al. 2004). In a prospective, randomized study, the percutaneous TMR approach demonstrated no therapeutic benefit in 141 patients presenting with refractory angina (Stone et al. 2002). Randomized trials comparing TMR with medical therapy for refractory angina have demonstrated significant angina relief, increased exercise tolerance, and improved patient's perception of quality of life with TMR but no survival benefit (Burkhoff et al. 1999; Schofield et al. 1999). A meta-analysis of 7 randomized trials involving 1,053 patients with

refractory angina demonstrated that at 1 year of follow-up, TMR when used as the sole procedural intervention compared with medical therapy alone significantly improved angina class, but there was no improvement in mortality (Liao et al. 2005). However, one randomized, multicenter, prospective trial including 212 patients with refractory angina showed a survival benefit as well as significant angina relief at 5 years in the TMR group compared to the medical therapy group (Allen et al. 2004). The role of TMR in patients with refractory angina needs further well-designed randomized trials to better define its role in therapy of stable ischemic heart disease.

Spinal Cord Stimulation

In patients with refractory angina despite optimal medical therapy and/or coronary revascularization, spinal cord stimulation with electrodes inserted into the epidural space using neuromodulation to reduce painful stimulus is an option, although exact mechanism is unclear. The ACC/AHA 2012 guidelines recommend that spinal cord stimulation may be considered for refractory angina in patients with SIHD (class IIb LOE C). In a meta-analysis of 7 randomized studies including 270 patients with refractory angina, spinal cord stimulation was associated with significant improvement in exercise capacity, health-related quality of life, and a nonsignificant trend toward lowering ischemia burden, as well as a decrease nitroglycerin use (Taylor et al. 2009). Adverse events were rare and included infections and lead migration or breakage (Taylor et al. 2009). Similarly, in a prospective, multicenter registry of refractory angina over a follow-up period of 12 months, 121 patients who underwent spinal cord stimulation reported significant reduction in number of angina attacks and frequency of nitrate consumption and improved CCS class and quality of life as assessed by the Short Form 36 and the Seattle Angina Questionnaire (Andréll et al. 2010). However, more randomized trials are still needed, and spinal cord stimulation should be reserved only when all other treatment options have been attempted.

Coronary Artery Disease Revascularization in SIHD Patients

The goals of CAD revascularization with either PCI or CABG in patients with SIHD are to both improve survival and relieve symptoms. The initial treatment strategy for all patients with SIHD should be stringent lifestyle modifications and aggressive GDMT. In SIHD patients with refractory and/or worsening symptoms, despite GDMT (i.e., "failed medical therapy"), or those with high-risk criteria on noninvasive testing, such as inducible ischemia involving a moderate to severe territory of myocardium, and suitable coronary anatomy, revascularization with PCI or CABG may be beneficial (Fihn et al. 2012). Choosing an appropriate revascularization procedure depends on a number of factors including extent and severity of coronary disease, location and type of lesions (i.e., bifurcation lesion, chronic total occlusion, left main coronary artery involvement, etc.), extent of myocardial ischemia, presence of left ventricular dysfunction, and other comorbidities that influence the risks associated with either percutaneous or surgical revascularization.

The ACC/AHA 2012 guidelines recommend a class I indication for revascularization with CABG surgery to improve survival in the following settings: patients with significant ($\geq$50 % diameter) unprotected left main coronary artery stenosis, patients with significant ($>$70 % diameter) 3-vessel disease with or without involvement of the proximal left anterior descending (LAD) artery, and patients with significant ($>$70 % diameter) 2-vessel disease with proximal LAD disease. Therefore, there is no class I indication for PCI to improve survival in SIHD patients. However, PCI has shown to improve angina and quality of life only in selected SIHD patients who remain symptomatic despite GDMT.

Percutaneous Coronary Intervention Versus Medical Therapy in SIHD Patients

During the past four decades, PCI technique has had a remarkable technologic evolution with the advent of bare-metal and drug-eluting stents, continued refinement of stent delivery platforms, development of effective adjunctive antiplatelet therapy, improved operator experience, and quality improvement initiatives which have led to a decline in periprocedural complication rates and an improvement in procedural success rates (Wu et al. 2006). Similar profound advancements in both our understanding of the pathophysiology of CAD and newer therapeutic agents have led to the development of an effective "disease-modifying" pharmacologic therapy with proven survival benefits. Studies comparing PCI with medical therapy prior to the development of coronary stents or disease-modifying pharmacotherapy are of uncertain clinical significance in the modern era. Eleven such studies were evaluated in a meta-analysis comparing PCI with medical therapy in 2,950 SIHD patients and showed no significant differences between the two treatment strategies with regard to mortality, cardiac death, MI, PCI, or CABG during follow-up (Katritsis and Ioannidis 2005). Subsequently, multiple meta-analyses of randomized control trials have failed to show any incremental benefit of an initial PCI strategy over an initial medical therapy strategy in SIHD patients (Cecil et al. 2008; Stergiopoulos and Brown 2012; Thomas et al. 2013; Stergiopoulos et al. 2013). Furthermore, a meta-analysis of 14 studies including 7,818 SIHD patients showed that an initial PCI strategy was associated with overall greater freedom from angina compared with medical therapy (Wijeysundera et al. 2010). However, when the trials were stratified by the year of enrollment, 9 trials prior to 1999 showed significant freedom from angina in the PCI strategy compared to medical therapy, but the 5 trials after the year 2000 demonstrated no difference in angina relief between PCI and medical therapy groups, a finding largely attributable to the robust use of evidence-based medical therapy in mitigating the effect of PCI on angina (Wijeysundera et al. 2010).

Four randomized studies utilizing advanced PCI techniques and enhanced adjunctive pharmacotherapy have been recently published including the Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation (COURAGE) trial (Boden et al. 2007), the Bypass Angioplasty Revascularization Intervention-2 Diabetes (BARI-2D) trial (Frye et al. 2009), the Japanese Stable Angina Pectoris (JSAP) trial (Nishigaki et al. 2008), and the Fractional Flow Reserve versus Angiography for Multivessel Evaluation-2 (FAME 2) trial (De Bruyne et al. 2012) that have evaluated an initial strategy of PCI combined with medical therapy compared with an initial strategy of medical therapy alone in SIHD patients. In the aggregate, none of these studies have shown any significant reduction in hard clinical end points with initial PCI compared to medical therapy (Padala et al. 2014b).

The COURAGE trial (Boden et al. 2007) randomized 2,287 patients with SIHD to an initial strategy of PCI plus optimal medical therapy (OMT) versus OMT alone. Patients were included in the study if they had $\geq$70 % stenosis of coronary artery disease plus objective evidence of ischemia on stress testing or $\geq$80 % stenosis of coronary artery plus classic anginal symptoms. The baseline characteristics of the population enrolled in the COURAGE study reveal the study group was at least intermediate risk as 67 % were hypertensive, 34 % had diabetes mellitus, 71 % were dyslipidemic, 29 % were active tobacco smokers, 39 % had prior MI, and 26 % had undergone previous revascularization with either PCI or CABG. Of the entire study population, 88 % had angina at baseline (30 % CCS class I, 58 % CCS class II–III), and 12 % had silent myocardial ischemia. The average number of angina episodes was 6 per week, and the mean duration of angina was 26 months. Noninvasive testing was positive for ischemia in 85 % of patients. Of the 71 % of patients who underwent stress myocardial perfusion imaging, two-thirds had multiple reversible perfusion defects, and 69 % of patients had multivessel CAD at angiography, while the left anterior descending coronary

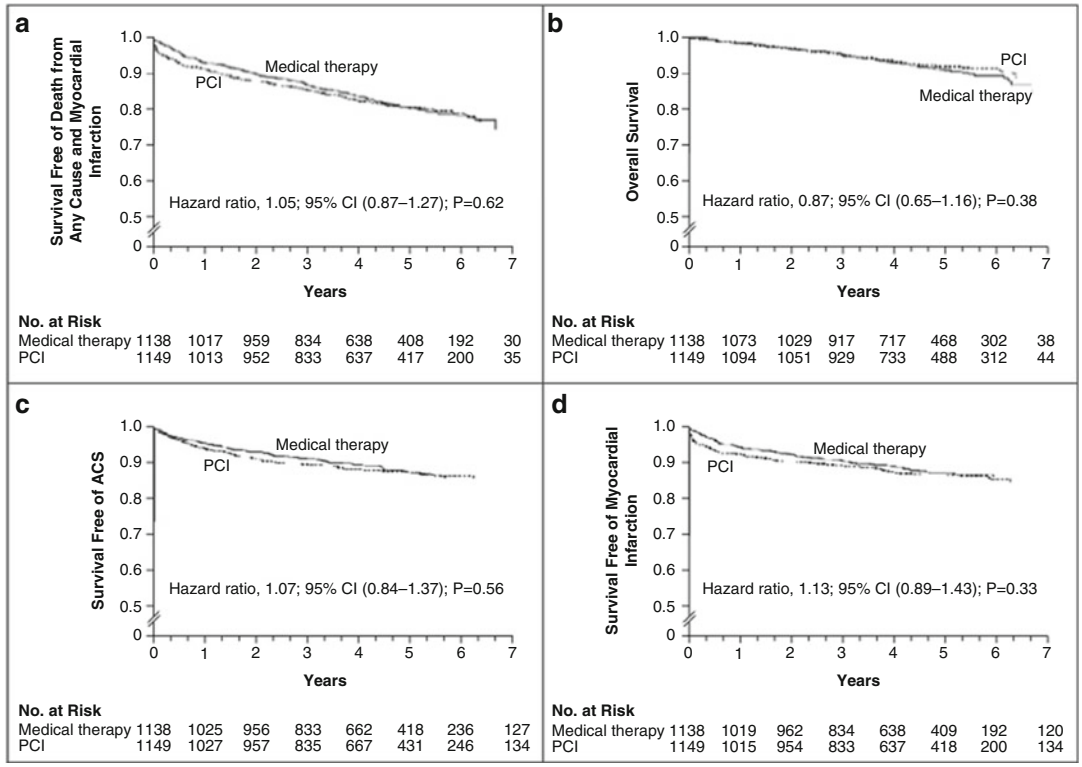


Fig. 6 Kaplan–Meier survival curves. In panel (**a**), the estimated 4.6-year rate of the composite primary outcome of death from any cause and nonfatal myocardial infarction was 19.0 % in the PCI group and 18.5 % in the medical therapy group. In panel (**b**), the estimated 4.6-year rate of death from any cause was 7.6 % in the PCI group and 8.3 % in the medical therapy group. In panel (**c**), the estimated 4.6-year rate of hospitalization for acute coronary syndrome (ACS) was 12.4 % in the PCI group and 11.8 % in the medical therapy group. In panel (**d**), the estimated 4.6-year rate of acute myocardial infarction was 13.2 % in the PCI group and 12.3 % in the medical therapy group. (Reproduced with permission from Boden et al. N Engl J Med. 2007; Copyright Massachusetts Medical Society)

artery was involved in 67 % of patients. During a median follow-up of 4.6 years, the primary end point of all-cause mortality or nonfatal MI occurred in 211 patients in the PCI plus OMT group and 202 patients in the OMT group (19 % vs. 18.5 %; $P = 0.62$) (Fig. 6). There were no significant differences between the groups in the prespecified secondary end point of composite of death, MI, and stroke and hospitalization for unstable angina. In terms of symptom relief, PCI plus OMT resulted in a more rapid symptomatic relief from angina; however, after 4.6 years of follow-up, the reported angina symptoms were no longer statistically different (Maron et al. 2009). Overall, these findings support the hypothesis that there was no clear benefit of initial PCI strategy over initial OMT alone in terms of mortality, nonfatal MI, or cumulative major cardiovascular events in SIHD patients and no long-term difference in angina relief, which has often been touted as the rationale for defaulting to an initial PCI strategy in SIHD patients.

The BARI-2D trial (Frye et al. 2009) randomized 2,368 patients with type-2 diabetes mellitus and SIHD to an initial revascularization group ($n = 1{,}176$), either in the form of PCI ($n = 798$) or CABG ($n = 378$), in combination with OMT versus initial strategy of OMT alone ($n = 1192$). Patients with type 2 diabetes and evidence of significant coronary artery stenosis on coronary angiography with ischemia on stress imaging or classic angina were included. Over a mean follow-up of 5.3 years, the primary end point of all-cause mortality was not statistically significantly

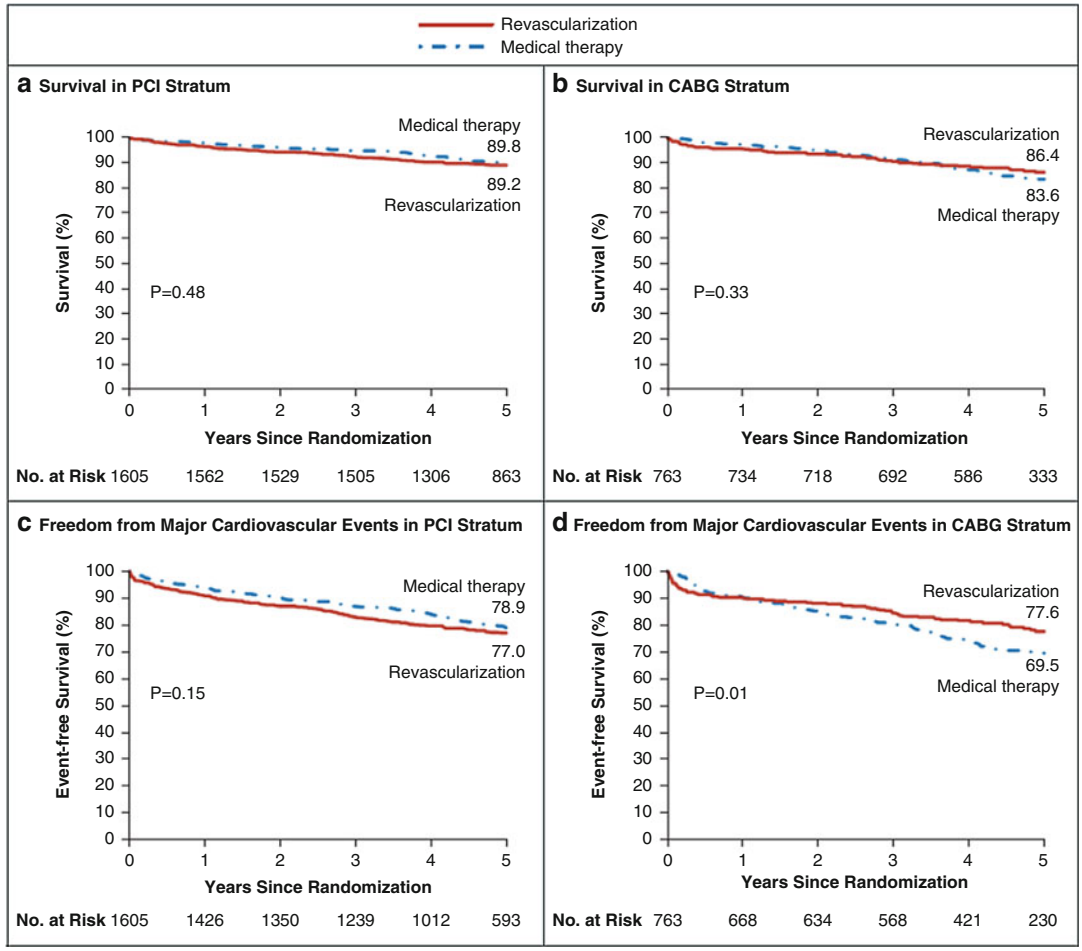


Fig. 7 Rates of Survival and Freedom from Major Cardiovascular Events, According to PCI and CABG Strata. There was no significant difference in rates of survival between the revascularization group and the medical-therapy group among patients who were selected for the percutaneous coronary intervention (PCI) stratum (Panel A) or among those who were selected for the coronary artery bypass grafting (CABG) stratum (Panel B). The rates of freedom from major cardiovascular events (death, myocardial infarction, or stroke) also did not differ significantly between the revascularization group and the medical-therapy group among patients in the PCI stratum (Panel C), but the rates were significantly better among patients in the revascularization group than in the medical-therapy group within the CABG stratum (Panel D). Reproduced with permission from BARI 2D study group et al. N Engl J Med. 2009; Copyright Massachusetts Medical Society.

different, with a 5-year survival of 88.3 % in the revascularization arm versus 87.8 % in the OMT arm ($P = 0.97$) (Fig. 7a). The secondary end point of composite of death, MI, or stroke (major cardiovascular events) was also not statistically different between revascularization and OMT groups (22.8 % vs. 24.1 %; $P = 0.70$) (Fig. 7a). When analyzed separately based on the type of revascularization, patients who underwent PCI plus OMT showed no significant difference versus OMT alone in terms of all-cause mortality (10.8 % vs. 10.2 %; $P = 0.48$) and major cardiovascular events (23 % vs. 21.1 %; $P = 0.15$) (Fig. 7b) which is also consistent with the findings of the COURAGE trial. However, in the CABG subgroup of BARI-2D, all-cause mortality was similar to OMT (13.6 % vs. 16.4 %; $P = 0.33$), but the CABG group had significantly fewer cardiovascular events (22.4 % vs. 30.5 %; $P = 0.01$) (Fig. 7c). These findings were primarily driven

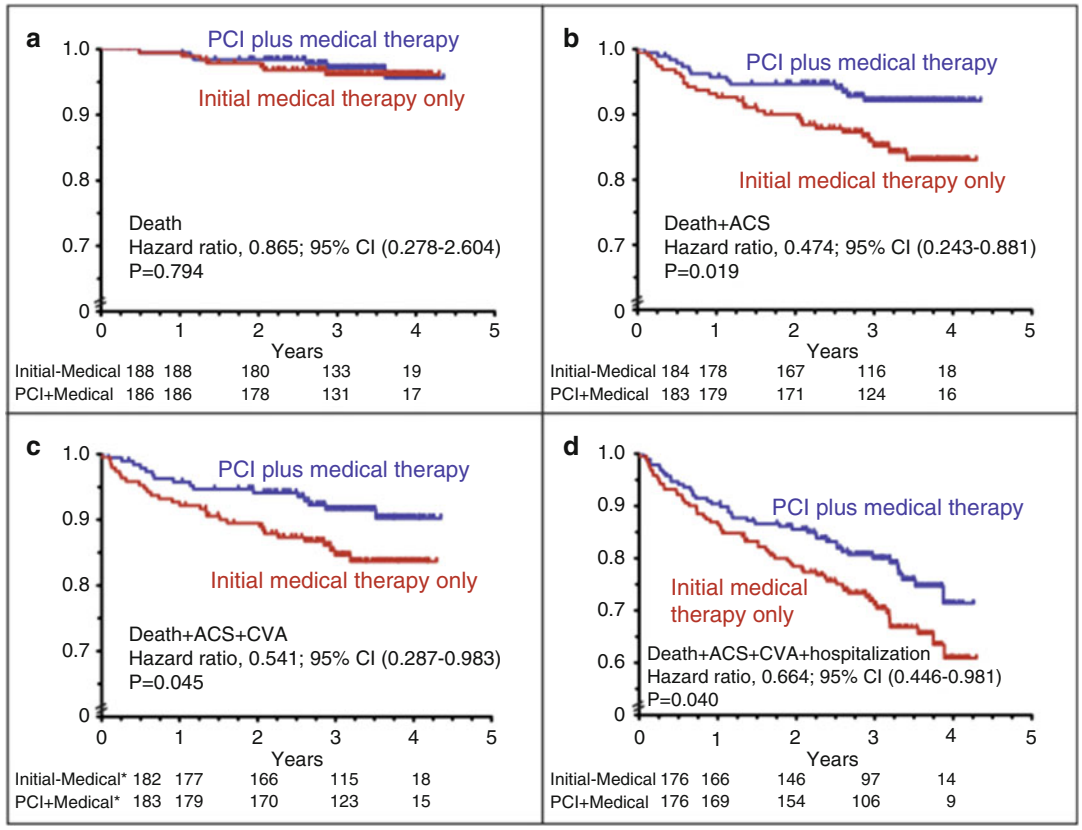


Fig. 8 Kaplan–Meier survival curves for the primary end point. Note that the survival free of all cause of death (death) + acute coronary syndrome (ACS), death + ACS + cerebrovascular accident (CVA), and death + ACS + CVA + hospitalization (emergency hospitalization) in the PCI plus medical therapy group was shifted significantly upward to that in the initial medical therapy only group, although death was similar in the 2 groups. *The number patients in each of the PCI plus medical therapy and initial medical therapy only groups. (Adapted from Nishigaki et al. (2008))

by the reduction in number of nonfatal MIs in the CABG arm. Overall, these findings demonstrate that in diabetic patients with SIHD, an initial strategy of PCI in combination with OMT did not offer any additional, or incremental, benefits compared with OMT alone in terms of all-cause mortality or the composite major cardiovascular events. However, CABG appears to reduce the rate of nonfatal MI when compared with OMT alone in diabetic patients who exhibited more extensive CAD, generally those with 3-vessel CAD. Therefore, a strategy of CABG for revascularization may be beneficial for diabetic patients with more extensive CAD.

The JSAP study (Nishigaki et al. 2008) randomized 384 low-risk SIHD patients to an initial PCI plus OMT versus an initial strategy of OMT alone. Patients with evidence of documented coronary stenosis in 1 or 2 vessels on coronary angiography (excluding the proximal left anterior descending artery) as well as with a positive stress test or exertional angina were included. Over a mean follow-up of 3.3 years, the primary end point of cumulative death rate was not significantly different in the initial PCI plus OMT group compared with the initial OMT group (2.9 % vs. 3.9 %, $P = 0.794$) (Fig. 8). However, ACS occurred significantly less frequently in the initial PCI plus OMT group compared with the initial OMT alone group (5 % vs. 11.7 %, $P = 0.012$), driven primarily by the significantly lower rates of unstable angina and not nonfatal MI

in the initial PCI plus OMT group. Similarly, the rates of emergency hospitalization (20.6 % vs. 31.6 %, $P = 0.042$) and elective repeat revascularization (21.4 % vs. 36.5 %; $P = 0.0011$) were significantly lower in the initial PCI plus OMT group than the initial OMT group. The severity of anginal symptoms was reduced in both groups; however, the severity of angina was significantly lower ($P < 0.05$) in the initial PCI plus OMT group than the initial OMT group at the 1-month, 6-month, 1-year, 2-year, and 3-year follow-up. In summary, the findings of the JSAP study demonstrate that in low-risk patients with SIHD, an initial strategy with PCI in combination with OMT does not offer additional benefits to OMT alone in terms of all-cause mortality or nonfatal MI. However, initial PCI plus OMT resulted in lower rates of unstable angina, emergency hospitalization, and elective repeat revascularization. Furthermore, an initial strategy for PCI appeared to provide more symptomatic angina relief at 3.3 years of follow-up compared with an initial strategy of OMT alone. However, compared to contemporary randomized trials such as the COURAGE and the BARI-2D, it is important to recognize that the JSAP included minimally symptomatic, low-risk CAD patients, who were treated with less intensive routine medical therapy in both groups at baseline and over a shorter follow-up period.

The efficacy of fractional flow reserve (FFR)-guided PCI was evaluated in the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial, which randomized 1,005 patients with multivessel CAD to conventional angiographic-guided PCI or FFR-guided PCI (PCI performed only if FFR was $\leq$0.80). At the end of 1 and 2 years, the composite of death, nonfatal MI, and repeat revascularization was significantly lower in the FFR-guided PCI group (Tonino et al. 2009; Pijls et al. 2010). Unlike the COURAGE, BARI 2D, and JSAP trials, the original FAME trial did not have a medical therapy comparator arm. Although the study results added to the body of literature on utility of FFR to guide PCI, it did not address the key scientific issue of which initial strategy, either OMT or FFR-guided PCI, was optimal in the management of SIHD patients.

Therefore, the FAME 2 trial (De Bruyne et al. 2012) was undertaken in order to address this lack of an OMT comparator in the original FAME trial and included 888 patients with SIHD randomized to an initial strategy of FFR-guided PCI plus OMT versus an initial strategy of OMT alone. Patients who had evidence of coronary artery stenosis on coronary angiography with an FFR $\leq$0.80 were included, while those with an FFR $>$0.80 were treated medically and followed in a registry. After a mean follow-up of merely 7 months, the Data and Safety Monitoring Board halted the recruitment prematurely owing to significant differences in the primary end points between the two groups. The primary end point of composite of all-cause mortality, nonfatal MI, or unplanned hospitalization leading to urgent revascularization was significantly lower in the FFR-guided PCI group as compared with the initial OMT alone group (4.3 % vs. 12.7 %, $P < 0.001$), a difference driven primarily by significantly lower rates of urgent revascularization (1.6 % vs. 11.1 %, $P < 0.001$) (Fig. 9a–d). There were no significant differences between the FFR-guided PCI arm and the initial OMT arm in the prespecified secondary end point of death (0.2 % vs. 0.7 %, $P = 0.31$) or nonfatal MI (3.4 % vs. 3.2 %, $P = 0.89$). The proportion of patients with angina class II to IV was reduced during follow-up in both groups, but the reduction was greater among FFR-guided PCI group. The results of the FAME 2 study were comparable to the JSAP study in that the initial strategy of PCI plus OMT did not reduce the rates of death or nonfatal MI in SIHD patients, but seemed to provide more symptomatic anginal relief over a short follow-up period.

However, certain limitations of the FAME 2 warrant comment (Boden 2012). The demonstrated benefit of PCI over OMT in this study was limited to a statistically significant difference only in the "soft" end point of urgent revascularization, but not to the more meaningful "hard" end points (i.e., cardiovascular mortality or nonfatal MI). Overall, there were very few "hard" events in either arm with only 4 total deaths and 29 myocardial infarctions, suggesting a very low-risk population. The FAME 2 trial was designed to enroll

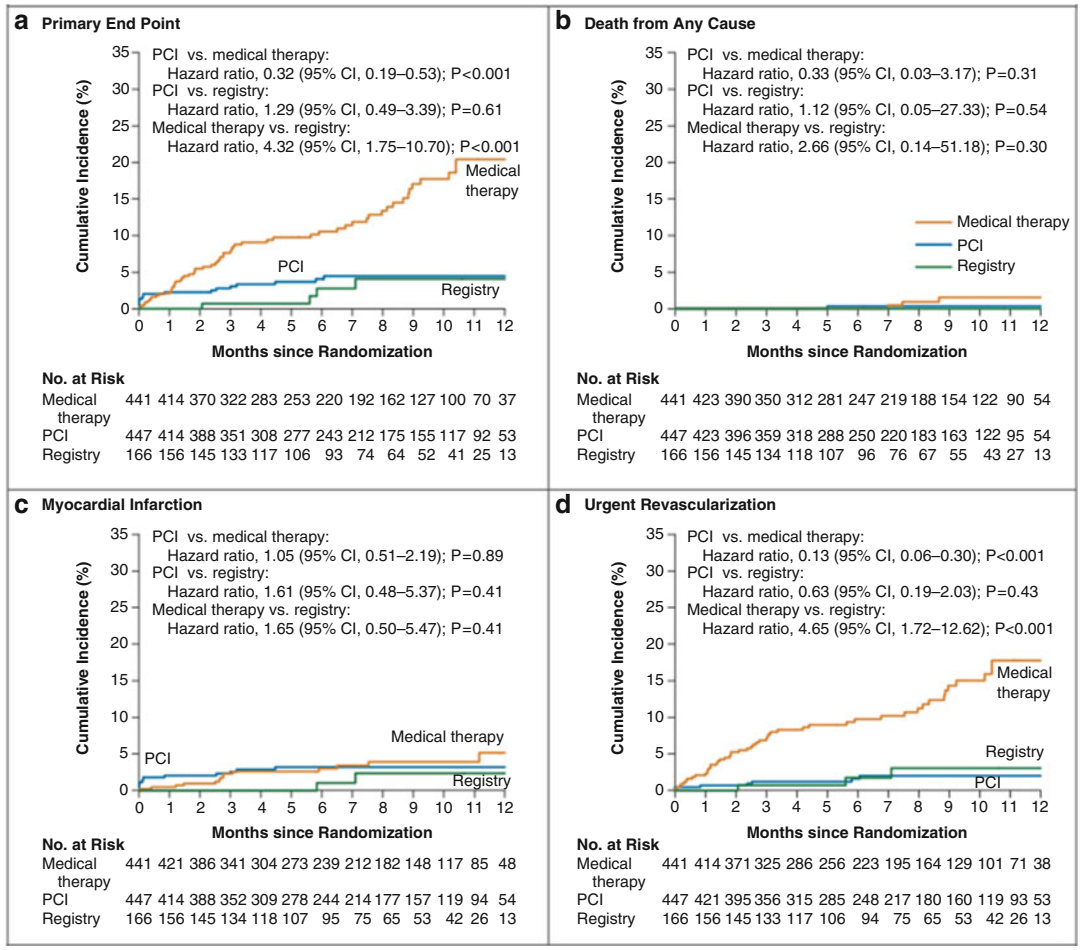


Fig. 9 Cumulative incidence of the primary end point and its components. Kaplan–Meier curves are shown for the cumulative incidence of the primary end point of death, myocardial infarction, or urgent revascularization (panel **a**) and the individual components of the primary end point (panels **b**, **c**, and **d**) in the group that was randomly assigned to PCI and the best available medical therapy (PCI), the group that was randomly assigned to the best available medical therapy alone (medical therapy), and the group that did not undergo randomization and was enrolled in a registry. After 12 months, a total of two primary end point events occurred in the PCI group, none in the medical therapy group, and one in the registry cohort. No deaths occurred after 12 months in any of the groups. Two patients in the medical therapy group, and one in the registry cohort had a myocardial infarction after 12 months. One patient in the registry cohort, and none in the other two groups, had an urgent revascularization performed after 12 months. Reproduced with permission from De Bruyne et al. N Engl J Med. 2012; Copyright Massachusetts Medical Society

1,632 patients, with a projected 2 year follow-up period; however, it was terminated at a mean follow-up of 7 months after enrolling only 54 % of planned participants because of a highly significant treatment difference, a finding driven solely by a difference in the end point of urgent revascularization. More than half of the unplanned revascularizations (52 %) were performed solely on the basis of reported clinical symptoms without supporting evidence of positive cardiac biomarkers or electrocardiographic evidence of ischemia. In the context of a non-blinded trial, there is clearly a concern that decisions regarding interventions during follow-up may have been biased by the knowledge of the previous treatment assignment. Biologically, the follow-up period

was also far too short (average 7 months) for coronary restenosis to emerge, and a longer follow-up may have narrowed the difference in the rates of unplanned revascularization between the groups. Furthermore, the study population in FAME 2, when compared to COURAGE, did not appear to be at particularly high risk (as evidenced by multivessel disease 24 % vs. 69 %, respectively). Finally, while fewer than 80 patients had 12 months of follow-up, the benefit of PCI in improving class II to IV angina symptoms was not significant beyond 6 months. In summary, while FAME 2 demonstrated that an FFR-guided PCI strategy resulted in a lower rate of unplanned revascularizations as compared with medical therapy alone, the notable limitations of the trial as highlighted above make it difficult to justify or generalize the more widespread use of an FFR-guided revascularization approach in the management of SIHD patients.

Based on the data from these multiple randomized trials, an initial strategy of optimal medical therapy combined with intensive lifestyle intervention should be advocated for the majority of patients with SIHD and CCS class I or II anginal symptoms. In SIHD patients with refractory and/or worsening symptoms, despite optimal medical therapy or those with high-risk criteria on noninvasive testing, an initial revascularization strategy with PCI or CABG could be considered appropriate until further data from the ongoing NHLBI/NIH-funded ISCHEMIA trial informs our clinical practice of how best to treat these patients with moderate to severe ischemia and SIHD.

Future Directions

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA Trial, ClinicaTrials.gov, NCT 01471522), funded by the US National Institutes of Health, is currently underway. ISCHEMIA is designed and powered to evaluate the long-term superiority of revascularization of choice combined with OMT versus strategy with OMT alone with respect to cardiovascular death or MI (combined primary end point) in patients with stable CAD and moderate to severe myocardial ischemia as assessed by means of noninvasive stress imaging studies (myocardial perfusion imaging, stress echocardiography, or magnetic resonance imaging). The ISCHEMIA trial is projected to enroll 8,000 patients from among 400 enrolling sites worldwide, with a planned average follow-up period of 4 years.

Coronary Artery Bypass Grafting Versus Medical Therapy in SIHD Patients

Randomized control studies in the late twentieth century have favored CABG over contemporaneous medical therapy (consisting primarily of beta-blockers and nitrates) in regard to angina relief and survival benefit in patients with stable angina (Veterans Affairs Cooperative Study 1984; Passamani et al. 1985; Varnauskas 1988). A meta-analysis published in 1994 of 7 randomized trials incorporating 2,649 SIHD patients demonstrated significant reductions in mortality of 39 % at 5 years, 32 % at 7 years, and 17 % at 10 years in patients undergoing CABG compared to medical therapy (Yusuf et al. 1994). A strategy of initial CABG was more effective than medical therapy with delayed surgery especially for patients with left main CAD, 3-vessel CAD, and multivessel CAD with impaired left ventricular function (Yusuf et al. 1994). However, substantial evolution and progress have occurred in both the surgical techniques and the extent of medical therapy with disease-modifying pharmacologic interventions since that time. Subsequently, the MASS II (Medicine, Angioplasty, or Surgery Study II) trial enrolled 611 patients with stable multivessel CAD and preserved left ventricular fraction and randomized them to medical therapy (consisting of aspirin, beta-blockers, ACEI, statins, and nitrates), PCI, or CABG groups. There was no difference in overall mortality among the three therapeutic regimens over a follow-up period of 5 years and 10 years (Hueb et al. 2007, 2010). However, over a long-term follow-up of 10 years, compared with CABG, medical therapy was associated with a significantly higher incidence of

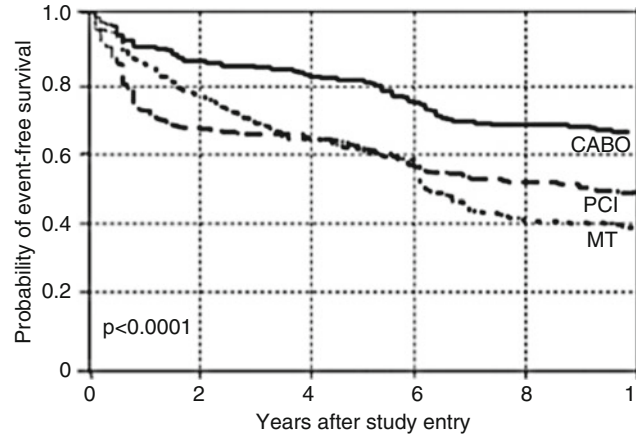
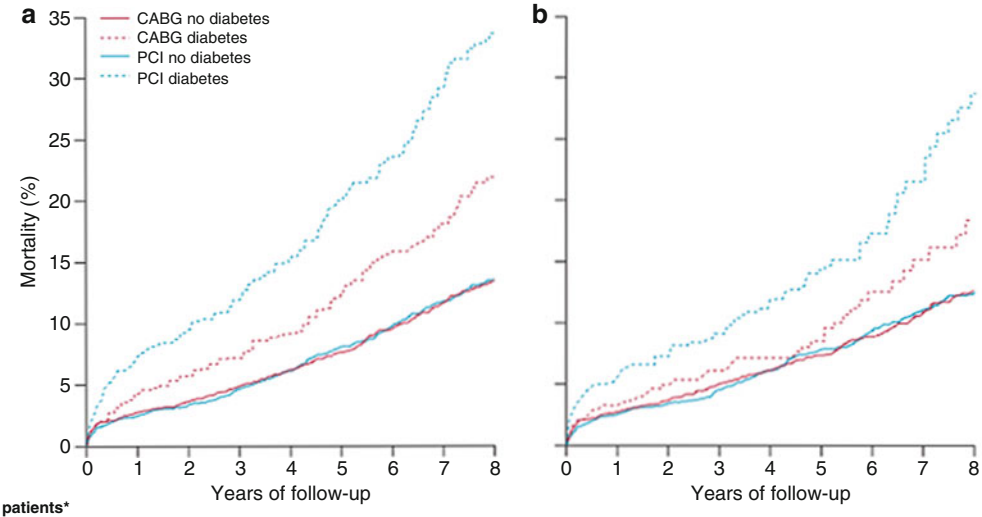


Fig. 10 Probability of event-free survival (free of overall mortality, unstable angina that required revascularization, or Q-wave MI) among patients in the MT, CABG, and PCI treatment groups (Adapted from Hueb et al. (2010))

Patients at risk

Treatment Group	Initial	3 Year	6 Year	10 Year
CABG	203	175	155	150
PCI	205	147	130	108
MT	203	140	121	93



Number of patients*

CABG no diabetes	3263	3169	3089	2877	2677	2267	1592	1380	1274	2529	2457	2382	2179	1992	1598	940	747	655
CABG diabetes	615	587	575	532	498	421	257	225	200	435	420	410	371	344	278	120	91	73
PCI no diabetes	3298	3217	3148	2918	2725	2281	1608	1393	1288	2556	2493	2432	2215	2031	1606	946	750	655
PCI diabetes	618	574	555	508	475	373	218	179	160	445	421	408	369	344	258	110	81	66

Fig. 11 Mortality in patients assigned to coronary artery bypass graft or percutaneous coronary by diabetes status. *CABG* coronary artery bypass graft, *PCI* percutaneous coronary intervention. *Number of patients available for follow-up. Data show overall unadjusted mortality rates for patients with diabetes with diabetes. Panel (**a**) includes from all ten trials. Panel (**b**) excludes patients from the Bypass Angioplasty Revascularization Investigation trial (Adapted from Hlatky et al. (2009))

subsequent MI, need for additional revascularization, and a higher incidence of cardiac death (Fig. 10; Hueb et al. 2010). Similarly, as noted previously, in the CABG subgroup of BARI 2D, overall mortality was similar to optimal medical therapy (13.6 % vs. 16.4 %; $P = 0.33$), but the CABG group had significantly fewer cardiovascular events (22.4 % vs. 30.5 %; $P = 0.01$).

Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in SIHD Patients

A systematic review of the 22 randomized control trials comparing CABG with PCI [balloon angioplasty or bare-metal stenting (BMS)] in patients with 1-vessel CAD of the proximal left anterior coronary artery (8 trials) or multivessel CAD (14 trials) showed that the overall survival was similar in both the groups at 10 years. However, compared with PCI, CABG was more effective in relieving angina and led to fewer repeated revascularizations despite having a higher risk for periprocedural cerebrovascular events (Bravata et al. 2007). One major limitation of this systematic review was that subgroup analyses could not be performed with respect to clinical characteristics, extent of CAD, or ejection fraction. In a collaborative analysis of data from 10 randomized trials comparing CABG and PCI with balloon angioplasty (6 trials) or with BMS implantation (4 trials) in patients with multivessel CAD, similar results were seen as in the prior systematic review by Bravata et al. in terms of mortality, need for repeat revascularization, and angina relief between the groups (Hlatky et al. 2009). In addition, CABG was associated with better outcomes in patients with diabetes mellitus and in those aged >65 years as shown in Figs. 11 and 12 (Hlatky et al. 2009).

In a meta-analysis of 9 nonrandomized, observational studies including 24,268 patients with multivessel CAD who underwent CABG (n = 10,728) or PCI with drug-eluting stents (DES) (n = 13,450) over a mean follow-up of 20 months, there was no difference between the two groups with regard to the composite of death, acute MI, and cerebrovascular events (Benedetto et al. 2009). However, the rates of repeat revascularization were four times higher in patients undergoing PCI compared to CABG, despite the use of DES (Benedetto et al. 2009).

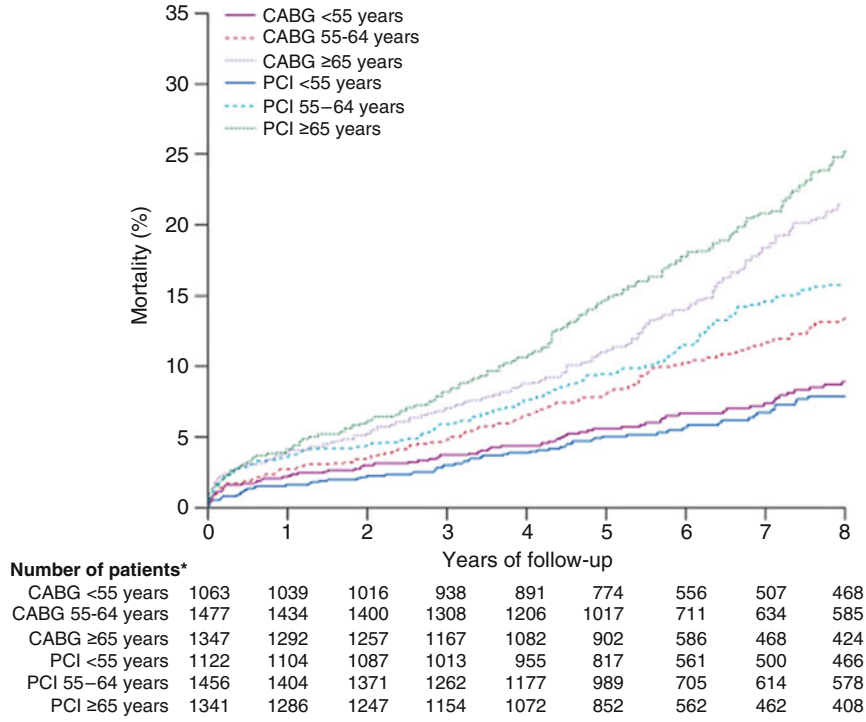


Fig. 12 Mortality in patients assigned to coronary artery bypass graft or percutaneous coronary intervention by age. *CABG* coronary artery bypass graft, *PCI* percutaneous coronary intervention. *Number of patients available for follow-up. Data show overall unadjusted mortality rates for patients aged less than 55 years, 55–64 years, and 65 years or older (Adapted from Hlatky et al. (2009))

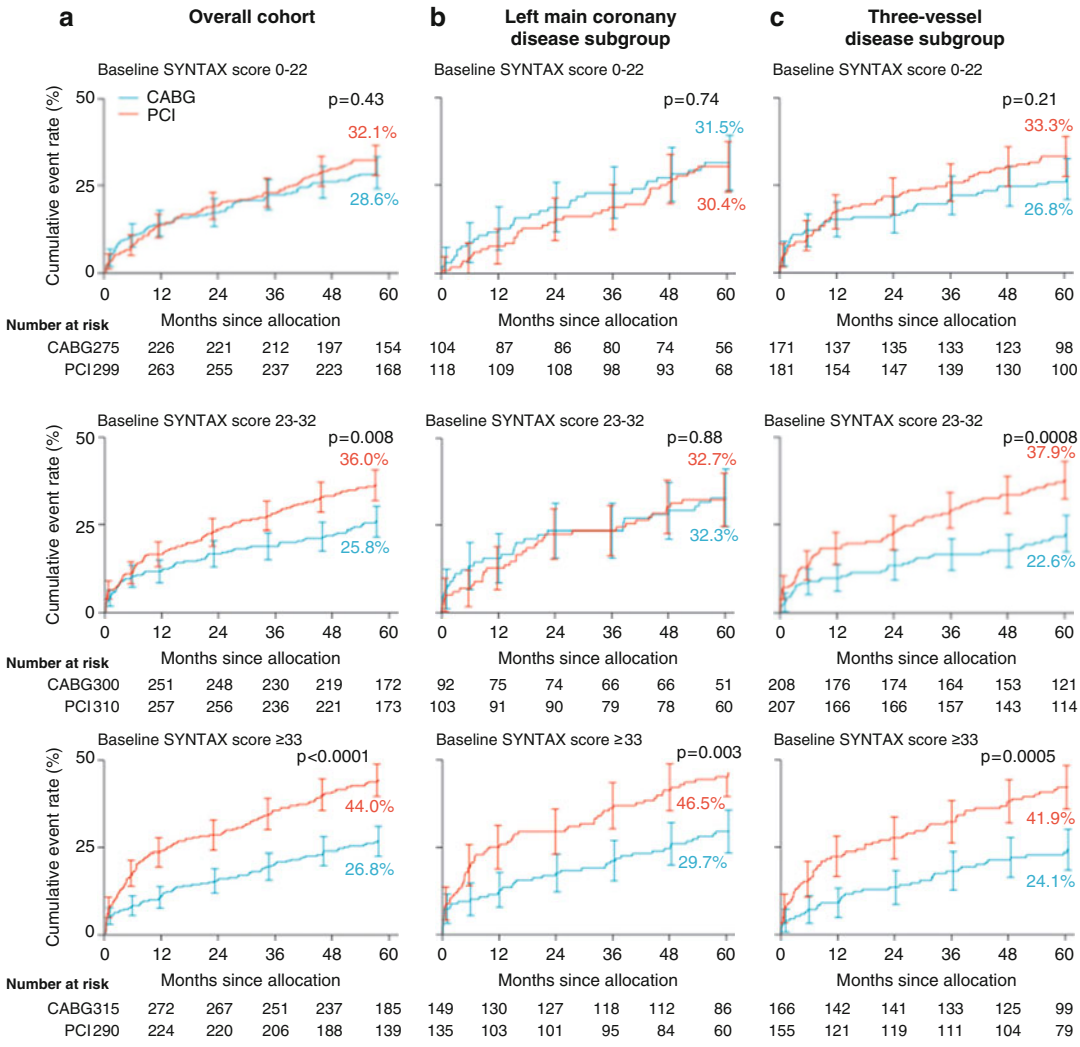


Fig. 13 Kaplan–Meier cumulative event curves for MACCE by baseline SYNTAX score tercile. (**a**) Overall cohort; (**b**) left main coronary disease subgroup; and (**c**) three-vessel disease subgroup (Adapted from Mohr et al. (2013))

Two large randomized trials comparing CABG with DES in patients with multivessel or left main disease have further studied these populations (Serruys et al. 2009; Farkouh et al. 2012). The SYNTAX (the SYNergy Between Percutaneous Coronary Intervention with TAXus and Cardiac Surgery) trial randomly assigned 1,800 patients to undergo CABG or PCI with paclitaxel DES (Serruys et al. 2009). The primary composite end point of a major adverse cardiac or cerebrovascular event (MACCE); i.e., death from any cause, stroke, myocardial infarction, or repeat revascularization was significantly higher in the PCI group compared to the CABG group at 1 year (17.8 % vs. 12.4 %; $P = 0.002$) (Serruys et al. 2009) and at 5 years (37.3 % vs. 26.9 %; $P < 0.0001$) (Mohr et al. 2013). At the end of 5 years, in patients undergoing CABG versus PCI with DES, the rates of all-cause mortality (11.4 % vs. 13.9 %; $P = 0.10$) and stroke (3.7 % vs. 2.4 %; $P = 0.09$) were similar; however, MI (3.8 % vs. 9.7 %; $P < 0.0001$) and repeat revascularization (13.7 % vs. 25.9 %; $P < 0.0001$) were more likely to occur with DES implantation (Mohr et al. 2013).

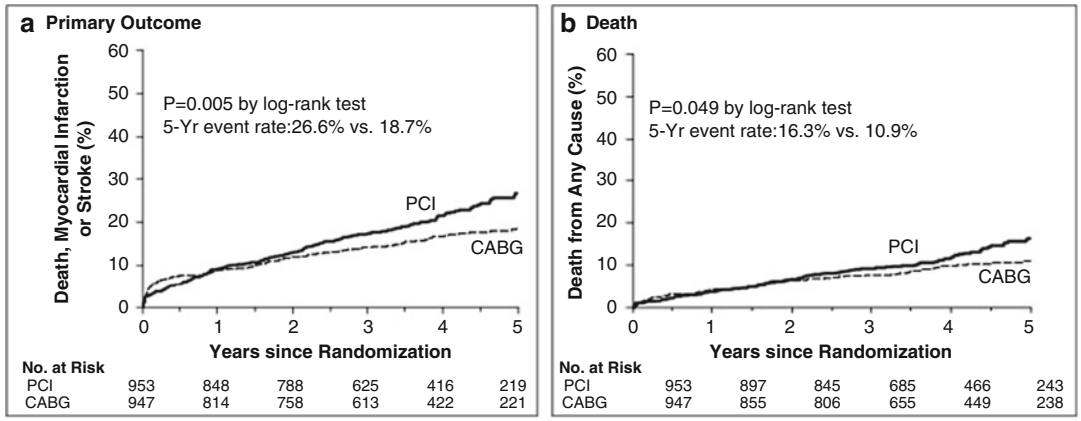


Fig. 14 Kaplan–Meier estimates of the composite primary outcome and death. Shown are rates of the composite primary outcome of death, myocardial infarction, or stroke (panel **a**) and death from any cause (panel **b**) truncated at 5 years after randomization. The P value was calculated by means of the log-rank test on the basis of all follow-up data. Reproduced with permission from Farkouh et al. N Engl J Med. 2012; Copyright Massachusetts Medical Society

In this trial, based on the location, severity, and extent of coronary stenoses, the SYNTAX score was calculated to determine the extent of CAD. A low score was defined as $\leq$22, intermediate 23–32, and high $\geq$33. In patients with low SYNTAX scores, MACCE in those undergoing CABG versus PCI was similar (2.6 % vs. 32.1 %; $P = 0.43$); however, in patients with intermediate or high SYNTAX scores, MACCE was significantly higher in the PCI group compared to CABG (intermediate score, 25.8 % vs. 36.0 %; $P = 0.008$; high score, 26.8 % vs. 44.0 %; $P < 0.0001$) as shown in Fig. 13 (Mohr et al. 2013). These results suggest that CABG should remain the standard of care for patients with complex lesions (intermediate or high SYNTAX scores) and PCI is an acceptable alternative in patients with less complex disease (low SYNTAX scores) or left main coronary disease (low or intermediate SYNTAX scores).

In the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial, 1,900 patients with diabetes and multivessel CAD were randomized to either CABG or PCI with DES (Farkouh et al. 2012). Over a follow-up period of 5 years, the primary composite end point of death from any cause, nonfatal myocardial infarction, or nonfatal stroke occurred more frequently in the PCI group compared to the CABG group as shown in Fig. 14 (26.6 % vs. 18.7 %; $P = 0.005$). The benefit of CABG was primarily driven by differences in rates of both myocardial infarction ($P < 0.001$) and death from any cause ($P = 0.049$) (Fig. 14). However, stroke was more frequent in the CABG group compared to the PCI group (5.2 % vs. 2.4 %; $P = 0.03$) (Farkouh et al. 2012). These results suggest that for diabetes patients with advanced CAD, CABG was superior to PCI in that it significantly reduced rates of death and myocardial infarction, albeit with a higher rate of stroke.

In summary, patients who remain symptomatic despite aggressive medical treatment, or who have more than mild to moderate ischemia or extensive coronary artery disease, revascularization with either PCI or CABG should be considered, depending on the anatomic complexity of disease. CABG surgery is clearly superior to PCI in symptomatic patients with three-vessel or left main coronary artery disease and in diabetic patients with stable ischemic heart disease. In lower-risk patients or in those with one- or two-vessel disease, although PCI may provide equivalent survival outcomes, repeat procedures are more often needed and the long-term procedural durability remains unclear.

Summary

In summary, patients who remain symptomatic despite aggressive medical treatment, or who have more than mild to moderate ischemia or extensive coronary artery disease, revascularization with either PCI or CABG should be considered, depending on the anatomic complexity of disease. CABG surgery is clearly superior to PCI in symptomatic patients with three-vessel or left main coronary artery disease and in diabetic patients with stable ischemic heart disease. In lower-risk patients or in those with one- or two-vessel disease, although PCI may provide equivalent survival outcomes, repeat procedures are more often needed and the long-term procedural durability remains unclear.

Cross-References

- Atherothrombosis
- Antiplatelet Drugs in the Management of Cardiovascular Indications
- Cardiac Syndrome X and Microvascular Angina
- Complications of Percutaneous Coronary Intervention
- Complications of Coronary Artery Bypass Grafting Surgery
- Coronary Artery Spasm: Basic Aspect
- Coronary Artery Spasm: Clinical Aspect
- Coronary Microcirculation: A Clinical Perspective
- Diagnostic Coronary Angiography
- Drugs in the Primary and Secondary Prevention of Coronary Artery Disease
- Gender and Cardiovascular Disease
- Indications of Coronary Artery Bypass Surgery
- Interventional Management of Coronary Artery Disease: Acute Coronary Syndromes
- Left Main Stem Disease
- Lifestyle Interventions for Primary and Secondary Prevention of Cardiovascular Disease
- Lipid Lowering Drugs
- Medical Management of Coronary Artery Disease
- Native Coronary Artery and Bypass Graft Atherosclerosis
- Prevention of Cardiovascular Disease in Older Adults
- Principles of Primary and Secondary Prevention of Cardiovascular Disease

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Further Reading

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