

# Chronic Stable Angina

Robert J. DiDomenico and Larisa H. Cavallari

## INTRODUCTION

Ischemic heart disease (IHD), also called coronary heart disease or coronary artery disease, is an imbalance between myocardial oxygen demand and supply. The majority of patients with IHD (nearly 60%) suffer from angina pectoris, or simply angina.<sup>1</sup> Angina, defined as discomfort in the chest or adjacent areas resulting from compromised blood supply to the myocardium, is the most common symptom of ischemia.<sup>2</sup> Chronic stable angina is the predictable occurrence of ischemic symptoms with physical activity or other conditions that increase oxygen demand. Another manifestation of IHD is acute coronary syndrome (ACS), which includes unstable angina and myocardial infarction (MI). It is discussed in more detail in Chapter 7 (Acute Coronary Syndrome).

Ischemic heart disease affects approximately 16,800,000 American adults; more than half of them suffer from chronic stable angina. Women generally develop IHD 10 years later than men, following menopause. Ischemic heart disease is the leading cause of death in the United States, contributing to one in every five deaths in 2005. The rate of death from IHD has decreased in recent decades, largely as a result of improved therapies, increased revascularization procedures, and risk factor modification. The estimated cost associated with IHD for 2009 is over \$165 billion.<sup>1</sup> A summary of the epidemiological data can be seen in **Table 6-1**.

**Table 6-1:** Epidemiology of ischemic heart disease—2009

Prevalence (age 20+)	Incidence	Mortality (2005)	Hospital Discharges (2006)	Cost (2009)
16,800,000	935,000 (MI)	445,700	1,760,000	\$165.4 billion

MI = myocardial infarction

Adapted from reference 1.

## PATHOPHYSIOLOGY

Ischemic heart disease is caused by the narrowing of one or more of the major coronary arteries. The hallmark feature of chronic stable angina is an established atherosclerotic plaque that impedes coronary blood flow. The pathophysiology of atherosclerosis is depicted in **Figure 6-1**.

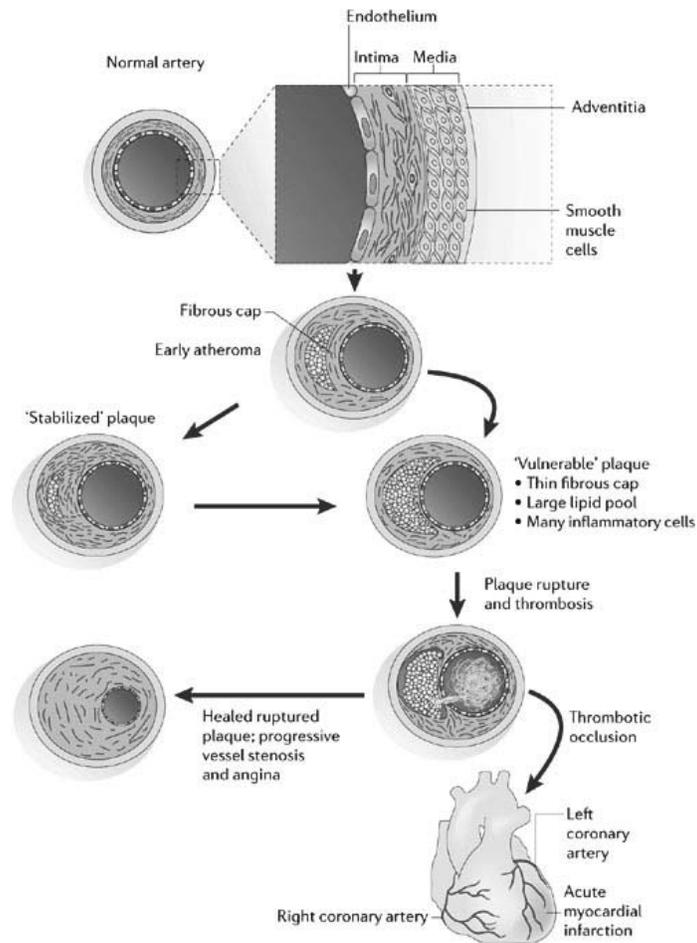
Atherosclerotic plaques develop as lipids [e.g., low density lipoprotein (LDL) cholesterol] from the bloodstream and penetrate and deposit in the intimal layer of the coronary arteries. In response to lipid deposition, inflammatory mediators are released, causing endothelial dysfunction, promoting migration and proliferation of smooth muscle cells to “stabilize” the growing plaque by forming a thick fibrous cap, and producing a prothrombotic environment.<sup>3</sup> Atherosclerotic plaques, particularly “vulnerable” plaques characterized by a large lipid core and thin fibrous cap, are prone to rupture, triggering platelet activation and aggregation, stimulation of the clotting cascade, and release of more inflammatory mediators. In response to plaque rupture, a thrombus may form at the site of injury, acutely impeding blood flow and precipitating acute ischemia, and perhaps infarction. Alternatively, the inflammatory response to plaque rupture may “heal” the plaque by promoting progressive stenosis progresses. As the atheroma grows in size, the lumen of the coronary artery begins to narrow, decreasing coronary blood flow. The development of IHD is strongly influenced by the presence of several risk factors shown in **Table 6-2**.

**Table 6-2: Major risk factors for ischemic heart disease**

Modifiable	Non-Modifiable
Hypertension	Age
Dyslipidemia	<ul style="list-style-type: none"> <li>• Men: &gt;45 years of age</li> <li>• Women: &gt;55 years of age</li> </ul>
<ul style="list-style-type: none"> <li>• Elevated LDL cholesterol</li> <li>• Elevated non-HDL cholesterol</li> <li>• Elevated triglycerides</li> <li>• Low HDL cholesterol</li> </ul>	Gender
Diabetes mellitus	<ul style="list-style-type: none"> <li>• Men</li> <li>• Post-menopausal women</li> </ul>
Cigarette smoking	Family history of premature cardiovascular disease in first-degree relative (e.g., parent or sibling) younger than:
Physical inactivity	<ul style="list-style-type: none"> <li>• 55 years of age (male family member)</li> <li>• 65 years of age (female family member)</li> </ul>
Obesity	

LDL = low density lipoprotein; HDL = high density lipoprotein

*Adapted from reference 2.*



**Figure 6-1:** Pathophysiology of coronary atherosclerosis  
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The plaque characteristic of chronic stable angina generally consists of a small lipid-laden core surrounded by a thick fibrous cap. In general, when the plaque occludes 70% or more of the coronary artery, myocardial oxygen supply cannot meet increases in oxygen demand, ischemia may develop, and the patient may experience angina during periods of exertion or emotional distress.<sup>2,4</sup> Vasospasm can also occur at the site of an atherosclerotic plaque or occasionally in the absence of significant atherosclerosis (variant or Prinzmetal's angina), impairing coronary blood flow, inducing ischemia, and precipitating angina. If ischemia persists for sufficient duration, it may lead to MI. Other complications associated with IHD include heart failure, arrhythmias, and death.

### CLINICAL PRESENTATION, DIAGNOSIS, AND DISEASE CLASSIFICATION

Patients with symptomatic IHD generally present with symptoms of angina. The hallmark symptom of angina is chest discomfort described in **Table 6-3**. Angina symptoms may also be associated with dyspnea and diaphoresis or present with atypical symptoms such as indigestion; epigastric burning; isolated jaw, neck, or back pain; nausea; and vomiting. Atypical presentations are more common in women, patients with diabetes, and the elderly.<sup>4</sup>

**Table 6-3:** Classical symptoms associated with angina pectoris

<b>Quality</b>	<b>Location</b>
Pressure or heaviness	Over or very near the sternum
Burning sensation	Anywhere between epigastrium and pharynx
Tightness or squeezing	Occasionally limited to left shoulder or arm
Shortness of breath	Rarely limited to right arm
Feeling of constriction of larynx and/or trachea	Limited to lower jaw
Visceral quality (deep, heavy, squeezing, aching)	Lower cervical or upper thoracic spine
Gradual increase/decrease in intensity	Left interscapular or suprascapular area
<b>Precipitating Factors</b>	<b>Radiation</b>
Exercise or physical exertion	Medial aspect of left arm
Effort that involves use of arms above head	Left shoulder
Cold environment	Jaw
Walking against wind	Occasionally right arm
Walking after a large meal	
Emotional factors involved with exercise	
Fright or anger	
Sexual intercourse	

**Table 6-3:** Classical symptoms associated with angina pectoris (cont'd)

Duration	Relieving Factors
30 seconds–30 minutes	Nitroglycerin (within 5 minutes) Rest

*Adapted from references 2 and 4.*

A thorough history and physical examination are important when making the diagnosis of chronic stable angina (Table 6-4). Not only will they aid in differentiating between cardiac and noncardiac etiologies (Table 6-5), but they will also help to determine the presence and severity of symptoms, identify precipitating causes (e.g., cocaine use), detect possible complications of chronic stable angina (e.g., heart failure signs and symptoms), and perhaps detect the presence of atherosclerotic vascular disease elsewhere (e.g., cerebrovascular disease).

**Table 6-4:** Clinical classification of chest pain

Type of Chest Pain	Characteristics
Typical angina	1. Substernal chest discomfort with characteristic quality and duration 2. Provoked by exertion or emotional distress 3. Relieved by rest or nitroglycerin
Atypical angina	Meets two of the criteria above
Noncardiac chest pain	Meets one or none of the criteria above

*Adapted from reference 2.*

**Table 6-5:** Selected nonischemic etiologies of chest pain

Cardiac	Pulmonary	Gastrointestinal	Musculoskeletal	Psychiatric
Aortic dissection	Pulmonary embolism	Esophagitis	Costochondritis	Panic/anxiety attack

**Table 6-5:** Selected nonischemic etiologies of chest pain (cont'd)

Cardiac	Pulmonary	Gastrointestinal	Musculoskeletal	Psychiatric
Pericarditis	Pneumothorax	Esophageal reflux	Rib fracture	Depression
	Pneumonia	Cholecystitis	Sternoclavicular arthritis	Delusions
	Pleuritis	Peptic ulcer		
		Pancreatitis		

*Adapted from reference 2.*

Several tests may be performed to make the diagnosis of chronic stable angina, including stress testing and coronary angiography. Critical elements included in the diagnostic work-up of patients with chronic stable angina are listed in **Table 6-6**. For additional information related to the diagnostic tools used in these patients, please refer to Chapter 1 (Cardiovascular Testing).

**Table 6-6:** Key elements of the diagnostic work-up of patients with ischemic heart disease

Traditional Diagnostic Modalities	Purpose
History	Assess for IHD risk factors, presence and severity of symptoms, IHD complications, precipitating factors
Physical examination	Assess for IHD complications, presence of other atherosclerotic vascular disease, presence of other cardiovascular disease
Rest 12-lead electrocardiogram	Evaluate for ST-segment changes and other electrocardiographic evidence of IHD at rest
Treadmill or bicycle electrocardiogram	Evaluate for ST-segment changes and other electrocardiographic under stress indicative of IHD
Noninvasive stress imaging (includes exercise or pharmacologic stress echocardiogram (e.g., dobutamine),	Echocardiography-based imaging studies evaluate for left ventricular wall motion abnormalities and/or dilatation indicative of

exercise or pharmacologic stress, radionuclide (technetium-99m sestamibi or thallium-201) myocardial perfusion scan]	IHD; radionuclide imaging studies evaluate myocardial perfusion defects and viability indicative of IHD
Coronary angiography	Detects the location and extent of coronary atherosclerosis and provides access for percutaneous coronary intervention, if necessary
<b>Evolving Diagnostic Modalities</b>	<b>Purpose</b>
Coronary artery calcium scoring by computed tomography	Detects calcium deposits in the coronary arteries indicative of atherosclerosis; coronary artery calcium score is calculated and risk of IHD-related adverse events is estimated
Computed tomography angiography	Noninvasive, 3-dimensional assessment of coronary atherosclerosis
Magnetic resonance angiography	Noninvasive, 3-dimensional assessment of coronary atherosclerosis

Once the diagnosis of chronic stable angina has been made, it is important to classify the severity of illness and evaluate the presence of unstable angina. Two classification systems for angina are shown in **Table 6-7**. Patients with unstable angina should be referred to a hospital for emergent evaluation and treatment (see Chapter 7, Acute Coronary Syndromes).

**Table 6-7: Classification systems for angina pectoris**

<b>Canadian Cardiovascular Society Classification (CCSC) System for Angina Pectoris</b>	<b>Typical Presentations of Unstable Angina</b>
<i>Class I</i> Angina does not occur with ordinary physical activity (e.g., walking) but does occur with strenuous, rapid, or prolonged exertion	<i>New Onset Angina</i> Angina of at least CCSC Class III severity first occurring within 2 months
<i>Class II</i> Slight limitation of ordinary physical activity (e.g., walking >2 blocks; climbing >1 flight of stairs; walking uphill, in the cold, or in the wind; under emotional stress; or shortly after awakening from sleep)	<i>Increasing Angina</i> Previously diagnosed angina that is more frequent, longer in duration, and lower in threshold

**Table 6-7:** Classification systems for angina pectoris (cont'd)

<b>Canadian Cardiovascular Society Classification (CCSC) System for Angina Pectoris</b>	<b>Typical Presentations of Unstable Angina</b>
<i>Class III</i> Marked limitation with ordinary physical activity (e.g., walking <2 blocks, climbing 1 flight of stairs)	<i>Rest Angina</i> Angina at rest and occurring >20 minutes duration within 1 week
<i>Class IV</i> Angina with any physical activity and/or at rest	

*Adapted from references 2 and 5.*

## TREATMENT PRINCIPLES

The primary goals for treatment of patients with chronic stable angina are to reduce the risk of death and MI and then alleviate and prevent symptoms of angina.<sup>2</sup> With regard to symptom control, the American Heart Association (AHA)/American College of Cardiology (ACC) state the goal “should be the complete, or nearly complete, elimination of angina chest pain and the return to normal activities” consistent with the Canadian Cardiovascular Society (CCS) class I angina.<sup>2</sup> Secondary goals include controlling modifiable risk factors and avoiding or minimizing adverse events related to therapy.

Several drug therapies have been proven to reduce major adverse cardiac events in patients with IHD. Similarly, both pharmacologic and interventional (e.g., PCI, CABG) therapies are effective at controlling angina symptoms. Finally, non-pharmacologic lifestyle modifications are often necessary in combination with drug and interventional therapies to control modifiable IHD risk factors.

### *Non-pharmacologic treatments*

#### **Control of risk factors**

Several non-pharmacologic therapies are recommended in patients with chronic stable angina. Lifestyle modifications reduce IHD risk factors, slow disease progression, and decrease the risk for IHD-related complications.<sup>6-11</sup> Specific modifications are listed in **Table 6-8**.

**Table 6-8:** Selected guideline recommendations for the non-pharmacological treatment (lifestyle modifications) of chronic stable angina

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**American College of Cardiology/American Heart Association**

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***Smoking cessation and avoidance of environmental tobacco smoke exposure***

- Follow-up, referral to smoking cessation programs, and/or pharmacotherapy is recommended (Class I, Level of Evidence: B).

***Dietary modifications***

- For all patients, dietary therapy should include reduced intake of saturated fats (to <7% of total calories), trans-fatty acids, and cholesterol (to <200 mg/day) (Class I, Level of Evidence: B).
- Adding 2 g/day of plant stanol/sterols and/or > 10 g/day of viscous fiber is reasonable to lower LDL cholesterol (Class IIa, Levels of Evidence: A).
- For all patients, it may be reasonable to encourage consumption of omega-3 fatty acids in the form of fish or a capsule (1 g/day) (Class IIb, Level of Evidence: B).

***Physical activity***

- All patients should be encouraged to engage in 30 to 60 minutes of moderate-intensity aerobic activity (e.g. brisk walking) on most, preferably all, days of the week (Class I, Level of Evidence: B).
- Medically supervised programs (cardiac rehabilitation) are recommended for at-risk patients (e.g., recent acute coronary syndrome or revascularization, heart failure) (Class I, Level of Evidence: B).

***Weight management***

- When indicated, it is useful to encourage weight maintenance/reduction through an appropriate balance of physical activity, caloric restriction, and formal behavioral programs at each clinic visit with the goal of achieving and maintaining a BMI between 18.5 and 24.9 kg/m<sup>2</sup> (Class I, Level of Evidence: B).
  - The initial goal of weight loss therapy should be to gradually reduce body weight by approximately 10% from baseline. Further weight loss can be attempted if indicated through further assessment (Class I, Level of Evidence: B).
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*Adapted from references 11 and 13.*

Cigarette smoking is the single most preventable cause of IHD and IHD-related death. In patients with IHD, smoking cessation has been associated with lower mortality risk.<sup>6</sup> Therefore, behavioral and/or pharmacologic therapies (e.g., nicotine replacement, bupropion, and varenicline) aimed at smoking cessation

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should be recommended in all active smokers with chronic stable angina. Weight loss should be encouraged for patients whose body mass index exceeds 25 kg/m<sup>2</sup>.<sup>12,14</sup> All patients with newly diagnosed angina should receive dietary counseling, regardless of weight. The AHA recommends a diet that includes a variety of fruits and vegetables (at least 5 servings per day), grains (at least 6 servings per day), low-fat or non-fat dairy products (at least 2 servings per day), fish (at least 2 servings per week), legumes, poultry, and lean meats while limiting the intake of salt (<6 grams per day), cholesterol (<300 mg per day), and alcohol (≤1 drink per day for women, ≤2 drinks per day for men). In particular, fatty fish such as salmon and herring, which are high in omega-3 fatty acids, are recommended.<sup>13</sup> Regular exercise facilitates weight loss and blood pressure reduction. The most recent guidelines recommend moderate-intensity exercise, ideally 30 to 60 minutes every day.<sup>12,13</sup>

### Symptomatic relief of angina

Interventional approaches to restore coronary blood flow, relieve symptoms, and prevent cardiac events include percutaneous coronary intervention (PCI), which may include percutaneous transluminal coronary angioplasty (PTCA), intracoronary stent placement and/or rotational atherectomy, and coronary artery bypass graft (CABG) surgery. Candidates for PCI are typically patients with mild angina symptoms (e.g., CCS Class I or II) but with evidence of high-risk features from noninvasive testing or those with more marked symptoms of angina (e.g., CCS Class III or IV). Additionally, PCI candidates also must have one or more critical (>70%) coronary artery occlusions with anatomy amenable to PCI and a significant area of viable myocardium.<sup>2,15</sup> In most patients, either a bare metal stent (BMS) or drug-eluting stent (DES) is deployed within the coronary artery at the site of the occlusion to maintain patency of the vessel. Drug-eluting stents are impregnated with an antiproliferative drug (paclitaxel, sirolimus, or everolimus), which is released over a period of weeks, in an effort to inhibit restenosis.<sup>16</sup> See Chapter 1 (Cardiovascular Testing) for more discussion regarding cardiac catheterization and PCI.

Coronary artery bypass grafting may be indicated for patients with extensive coronary atherosclerosis, generally considered as greater than 70% occlusion of three or more coronary arteries, particularly if left ventricular dysfunction is also present, or greater than 50% occlusion of the left main coronary artery.<sup>2</sup> When used for these indications, CABG surgery has been shown to reduce mortality from IHD compared to standard medical therapy.<sup>17</sup> During CABG, a form of open-heart surgery, vascular conduits are “harvested” from other areas of the body (generally a saphenous vein from the leg and/or an internal mam-

mary artery detached from the chest wall) and engrafted to the affected coronary arteries distal to the atherosclerotic plaque, restoring coronary blood flow.<sup>18</sup>

## PHARMACOTHERAPY

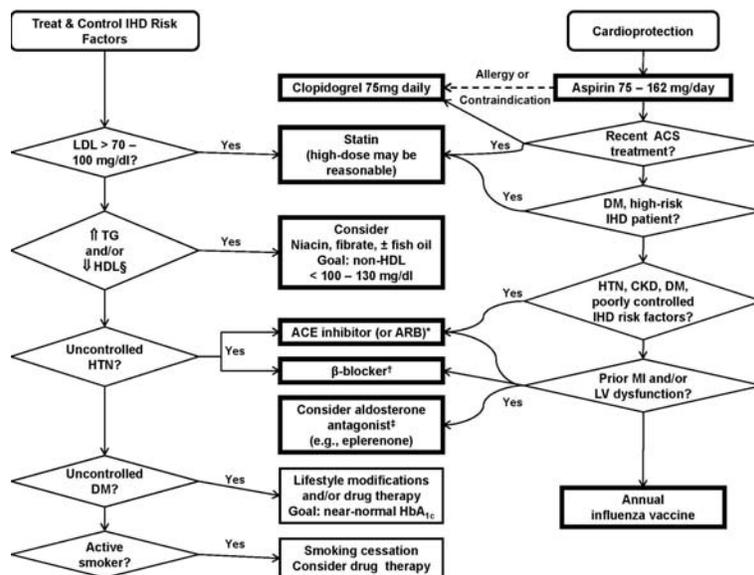
An algorithmic approach to the treatment of patients with chronic stable angina is shown in **Figures 6-2** and **6-3** and the recommendations of the AHA, ACC, and other organizations are summarized in **Tables 6-9** and **6-10**. To address the primary goals for the treatment of chronic stable angina (reduce the risk of death and MI, treatment and prophylaxis of angina symptoms), the therapies used to accomplish both of these goals can be loosely categorized as “cardioprotective” and anti-anginal.

### *Control of risk factors; primary and secondary prevention*

Several drug classes have been shown to reduce the risk of major adverse cardiac events (MACE), typically death and MI. Aspirin, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (commonly known as statins) have all been shown to reduce MACE in patients with or at high risk for developing IHD.

Aggressive control of IHD risk factors is an important treatment principle. Nicotine replacement therapy, bupropion, and varenicline have been studied as pharmacologic aids for smoking cessation in patients with IHD and appear to be safe and effective. Unless contraindicated, all patients with chronic stable angina should be treated with aspirin as it has been shown to reduce the risk of MACE in this population. If contraindications are present, then clopidogrel should be substituted for aspirin.<sup>2</sup> Following hospitalization for acute coronary syndrome (ACS, unstable angina or MI), the combination of aspirin and clopidogrel has been shown to be superior to aspirin alone and should be considered in chronic stable angina patients recently hospitalized for ACS.<sup>19-21</sup> Because of their ability to reduce MACE in various settings, ACE inhibitors or ARBs and beta-blockers are recommended in patients with chronic stable angina who have had an MI as well as those with the following comorbidities: hypertension, left ventricular dysfunction (e.g., heart failure), chronic kidney disease (ACE inhibitors and ARBs, not beta-blockers), and those with poorly controlled risk factors (ACE inhibitors and ARBs, not beta-blockers).<sup>11,22,23</sup> Similarly, statins are recommended in patients with chronic stable angina because of their effectiveness at primary and secondary prevention of MACE in patients with or at high risk for IHD.<sup>12,24,25</sup>

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**Figure 6-2:** Treatment algorithm for control of risk factors and primary/secondary prevention in patients with IHD

\* Unless otherwise contraindicated, angiotensin converting enzyme inhibitors should be considered in patients with ischemic heart disease with prior myocardial infarction, left ventricular dysfunction, hypertension, chronic kidney disease, and diabetes mellitus and in most patients with established coronary artery disease.

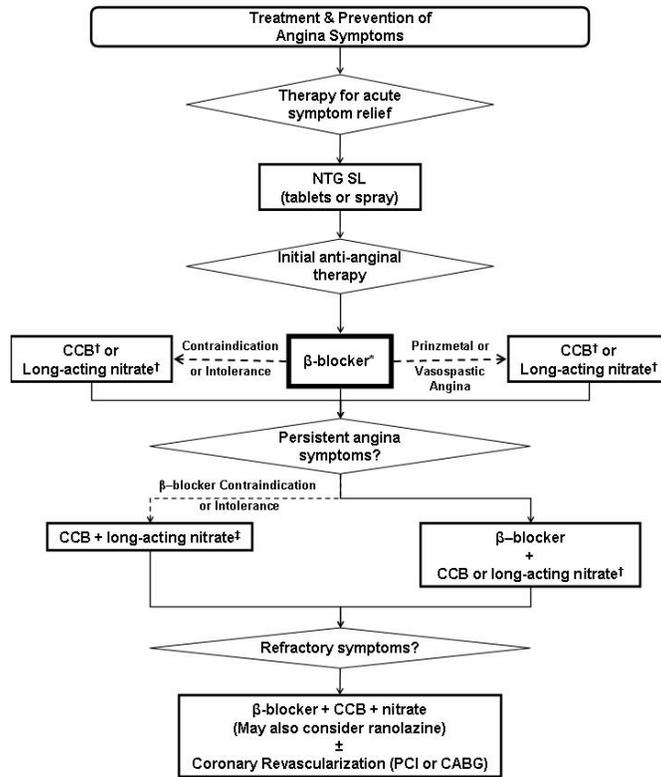
† Unless otherwise contraindicated, beta-blockers should be considered in patients with ischemic heart disease with prior myocardial infarction, left ventricular dysfunction, and hypertension and as initial therapy for the prevention and treatment of angina symptoms.

‡ Aldosterone antagonists are recommended for post-myocardial infarction patients with left ventricular dysfunction and either diabetes mellitus or heart failure in the absence of significant renal dysfunction or hyperkalemia who are being treated with therapeutic doses of angiotensin converting enzyme inhibitors and beta-blockers.

§ Elevated triglycerides defined as >150 mg/dL; low high-density lipoprotein cholesterol defined as <40 mg/dL.

IHD = ischemic heart disease; MI = myocardial infarction; DM = diabetes mellitus; HbA<sub>1c</sub> = glycosylated hemoglobin; HTN = hypertension; CKD = chronic kidney disease; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; LV = left ventricular; TG = triglyceride; HDL = high density lipoprotein; ACS = acute coronary syndrome; LDL = low density lipoprotein

*Adapted from references 2 and 12.*



**Figure 6-3:** Treatment algorithm to treat and prevent angina symptoms

\* Unless otherwise contraindicated, beta-blockers should be the initial drug used for the prevention of angina symptoms in patients with and without a history of myocardial infarction

† For patients with contraindications or intolerance to beta-blockers, calcium channel blockers or long-acting nitrates should be the initial therapy used for the prevention of angina symptoms. When selecting one of these agents, the clinician should consider the patient’s blood pressure, left ventricular function, and heart rate.

‡ For patients with contraindications or intolerance to beta-blockers requiring combination therapy with a calcium channel blocker and long-acting nitrate, the clinician should consider the patient’s left ventricular function and heart rate when deciding on the type of calcium channel blocker to use (dihydropyridine vs nondihydropyridine).

NTG = nitroglycerin; SL = sublingual; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft surgery

*Adapted from references 2 and 12.*

**Table 6-9:** Selected guideline recommendations for pharmacotherapy to control risk factors and reduce major adverse cardiac events in chronic stable angina

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**Therapies to Reduce Risk of Death and Myocardial Infarction**

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***Antiplatelet and anticoagulant therapy***

- Aspirin should be started at 75–162 mg daily and continued indefinitely in all patients unless contraindicated (Class I, Level of Evidence: A).
- Clopidogrel should be considered and continued indefinitely when aspirin is absolutely contraindicated (Class IIa, Level of Evidence: B).
- Clopidogrel should be given following percutaneous coronary intervention for at least 12 months following implantation of a drug-eluting stent (Class I, Level of Evidence: B).
- Clopidogrel should be given following percutaneous coronary intervention for at least 1 month and, ideally, up to 12 months following implantation of a bare metal stent (Class I, Level of Evidence: B).
- Low-intensity anticoagulation [target international normalized ratio (INR): 1.5] with warfarin in addition to aspirin (Class IIb, Level of Evidence: B).
- Use of warfarin in combination with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely (Class I, Level of Evidence: B).
- Use of dipyridamole should be avoided in patients with chronic stable angina (Class III, Level of Evidence: B).

***Beta-blockers***

- Beta-blockers should be started and continued indefinitely in all patients with previous myocardial infarction (MI), acute coronary syndrome, or left ventricular dysfunction with or without symptoms of heart failure, unless contraindicated (Class I, Level of Evidence: A).
- Beta-blockers should be considered as initial therapy in asymptomatic ischemic heart disease (IHD) patients without prior history of MI unless contraindicated (Class IIa, Level of Evidence: C).

***Renin-angiotensin-aldosterone system blockade***

- Angiotensin converting enzyme (ACE) inhibitors should be started and continued indefinitely in all patients with left ventricular ejection fraction (LVEF) less than or equal to 40% and in those with hypertension, diabetes, or chronic kidney disease unless contraindicated (Class I, Level of Evidence: A).
- ACE inhibitors should be started and continued indefinitely in patients who are not lower risk\*, unless otherwise contraindicated (Class I, Level of Evidence: B).
- The use of ACE inhibitors in low-risk\* patients is reasonable, unless contraindicated (Class IIa, Level of Evidence: B).

**Table 6-9: Selected guideline recommendations for pharmacotherapy to control risk factors and reduce major adverse cardiac events in chronic stable angina (cont'd)**

- Angiotensin receptor blockers (ARBs) are recommended for patients with hypertension, indications for but intolerant to ACE inhibitors, heart failure, history of MI with LVEF  $\leq$ 40% (Class I, Level of Evidence: A).
- ARBs may be considered in combination with ACE inhibitors for heart failure due to left ventricular dysfunction (Class IIb, Level of Evidence: B).
- Aldosterone antagonists are recommended in combination with ACE inhibitors and beta-blockers in post-MI patients with LVEF  $<$ 40% and in patients with diabetes or heart failure in the absence of significant renal impairment, hyperkalemia, or other contraindication (Class I, Level of Evidence: A).

***Lipid-lowering therapy***

- In patients with IHD, reducing LDL cholesterol to  $<$ 70 mg/dL with high-dose statin therapy is reasonable (Class IIa, Level of Evidence: A).
- In patients with diabetes, statin therapy is indicated, regardless of baseline LDL cholesterol if cardiovascular disease is present or the patient has one or more risk factors for IHD (Level of Evidence: A).<sup>46</sup>

***Immunizations***

- An influenza vaccine is recommended for patients with cardiovascular disease (Class I, Level of Evidence: B).

**Control of Ischemic Heart Disease Risk Factors**

***Hypertension***

- In patients with established IHD with hypertension, beta-blockers and/or ACE inhibitors should be used initially to control blood pressure (Class I, Level of Evidence: C).
- Blood pressure goal in all patients with IHD is  $<$ 130/80<sup>22</sup> (Class IIa, Level of Evidence: B).

***Diabetes mellitus***

- Lifestyle modifications and pharmacotherapy should be utilized to achieve near-normal glycosylated hemoglobin (HbA<sub>1c</sub>  $\sim$ 7.0 g/dL) (Class I, Level of Evidence: B).

***Dyslipidemia***

- In patients with IHD, low density lipoprotein (LDL) cholesterol should be  $<$ 100 mg/dL (Class I, Level of Evidence: A).
- In patients with IHD with baseline LDL cholesterol  $\geq$ 100 mg/dL at moderate to high risk being treated with lipid-lowering therapy, a reduction in LDL cholesterol of at least 30–40% is recommended (Class I, Level of Evidence: A).

**Table 6-9: Selected guideline recommendations for pharmacotherapy to control risk factors and reduce major adverse cardiac events in chronic stable angina (cont'd)**

- In patients with IHD being treated with lipid-lowering therapy, if LDL cholesterol is  $\geq 100$  mg/dL, LDL-lowering therapy should be intensified (Class I, Level of Evidence: A).
- In patients with IHD and baseline LDL cholesterol between 70–100 mg/dL, it is reasonable to treat with lipid-lowering drugs to achieve LDL cholesterol  $< 70$  mg/dL (Class IIa, Level of Evidence: B).
- If a goal LDL cholesterol  $< 70$  mg/dL has been targeted but is not achievable due to high baseline LDL cholesterol, statins alone or in combination with other drugs should be used to achieve LDL cholesterol reductions of  $\geq 50\%$  (Class IIa, Level of Evidence: C).
- In patients with triglycerides (TG)  $> 200$  mg/dL, either niacin or fibrate therapy should be considered to reduce non-high density lipoprotein (HDL) cholesterol to  $< 130$  mg/dL (Class I, Level of Evidence: B).
  - For patients with TG  $\geq 500$  mg/dL, niacin or fibrate therapy should be initiated before LDL-lowering drugs (Class I, Level of Evidence: C).

\* Lower risk is defined as normal LVEF in patients who have cardiovascular risk factors that are well controlled and in whom revascularization has been performed.

*Adapted from references 2, 12, and 21–27.*

### *Symptomatic relief of angina*

Four primary classes of drugs are used to control symptoms in patients with chronic stable angina: beta-blockers, calcium channel blockers (CCBs), nitrates, and ranolazine. Although their specific mechanisms of action differ, these drugs generally work by reducing oxygen demand in the setting of decreased oxygen demand (e.g., partially occlusive atherosclerotic plaque). Anti-anginal drugs reduce oxygen demand in many ways that may include one or more of the following pharmacodynamic effects—reduced blood pressure, reduced heart rate, decreased myocardial wall tension, improved coronary blood flow, and/or decreased contractility. Calcium channel blockers and nitrates, by way of coronary artery vasodilation, improve coronary blood flow, increasing oxygen supply.<sup>2,4</sup>

Several factors must be considered when selecting appropriate anti-anginal therapy. As discussed above, beta-blockers reduce the risk of death and MI in patients who have had a prior MI.<sup>28</sup> Because beta-blockers also improve mortality in patients with hypertension and heart failure due to left ventricular dysfunction, they are recommended as initial anti-anginal therapy in all patients

unless otherwise contraindicated.<sup>2</sup> Both beta-blockers and CCBs lower blood pressure because they are useful in patients with anginal symptoms and concomitant hypertension. To reduce oxygen demand, it is common to target a resting heart rate of 55–60 beats/minute (perhaps as low as 50 beats/minute in more symptomatic patients) in patients with chronic stable angina.<sup>2</sup> Therefore, since both beta-blockers and nondihydropyridine CCBs (e.g., diltiazem, verapamil) decrease heart rate, they are often used to achieve the target heart rate and prevent symptoms of angina. CCBs and nitrates cause vasodilation of the coronary arteries because they are useful when treating patients in whom vasospasm contributes to their pathogenesis (e.g., Prinzmetal's angina).<sup>2</sup> Oral nitrates and ranolazine do not have appreciable effects on blood pressure. Therefore, they may be beneficial for patients with angina symptoms and low or normal blood pressure.

Ranolazine is metabolized primarily by the cytochrome P450 3A4 (CYP3A4) enzyme and to a lesser extent by CYP2D6; it also weakly inhibits the activity of these two enzymes.<sup>29</sup> Therefore, several drug–drug combinations interact with ranolazine, and ranolazine is contraindicated in patients also treated with strong CYP3A4 inhibitors (e.g., diltiazem).<sup>30</sup> Because ranolazine can prolong the QT interval (see Clinical Controversies), it is also contraindicated in patients with pre-existing QT prolongation and in patients taking drugs known to prolong the QT interval.<sup>30</sup> Ranolazine is not indicated as monotherapy, and its role in the treatment of chronic stable angina is evolving.

As discussed above, an interventional approach to treating patients with chronic stable angina is PCI, most often involving the use of either BMS or DES. Intracoronary stents are thrombogenic, requiring combination antiplatelet therapy with aspirin and clopidogrel. In patients with BMS, aspirin and clopidogrel combination should be continued for at least 1 month and, ideally, up to 1 year, followed by aspirin indefinitely.<sup>15,19,21,26,31</sup> In patients having DES placed, the duration of combination antiplatelet therapy is longer and the risk of acute stent thrombosis and MACE increases significantly if combination therapy is discontinued prematurely. In December 2006, the Food and Drug Administration recommended that the duration of dual antiplatelet therapy in patients with DES be a minimum of 12 months (indefinite dual therapy may be considered if the risk of bleeding is low). The ACC, AHA, American College of Chest Physicians (ACCP), and the Society of Cardiovascular Angiography and Interventions recently endorsed this recommendation and incorporated it into updated practice guidelines.<sup>15,19-21,26,31</sup> A recent study comparing optimal medical therapy plus PCI to optimal medical therapy alone in patients with stable IHD found no difference in clinical outcomes (see Clinical Controversies).<sup>32</sup>

**Table 6-10:** Guideline recommendations for pharmacotherapy to relieve and prevent symptoms of angina

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**American College of Cardiology/American Heart Association**

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***Beta-blockers***

- Beta-blockers should be considered as initial therapy in all patients with angina symptoms unless contraindicated [Class 1, Level of Evidence: A (patients with prior myocardial infarction), Level of Evidence: B (patients without history of myocardial infarction)].

***Calcium channel blockers (CCBs)***

- CCBs may be considered as initial therapy in patients with anginal symptoms with contraindications or intolerance to beta-blockers [Class I, Level of Evidence: B (when beta-blockers contraindicated), Level of Evidence: C (intolerance to beta-blockers)].

***Nitrates***

- All patients with chronic stable angina should be prescribed sublingual nitroglycerin tablets or spray for the immediate relief of acute symptoms of angina (Class I, Level of Evidence: B).
- Long-acting nitrates may be considered as initial therapy in patients with anginal symptoms and contraindications or intolerance to beta-blockers [Class I, Level of Evidence: B (when beta-blockers contraindicated), Level of Evidence: C (intolerance to beta-blockers)].

***Combination therapy***

- Combination therapy with beta-blockers and either CCBs or long-acting nitrates are recommended when monotherapy with beta-blockers is ineffective (Class I, Level of Evidence: B).

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*Adapted from reference 2.*

## **MONITORING**

Desired therapeutic outcomes for patients with chronic stable angina are to alleviate acute symptoms of myocardial ischemia, prevent recurrent symptoms, reduce the risk of MACE, and avoid or minimize adverse drug effects.<sup>2</sup> Assessment of the safety and effectiveness of chronic stable angina therapy must be performed at each follow-up visit and includes several key elements listed in **Table 6-11**.

**Table 6-11:** Elements to determine at follow-up visits of patients with IHD

- 
- Blood pressure
  - Heart rate and rhythm
  - History of dizziness, presyncope, syncope
  - Frequency and intensity of symptoms of angina
  - Adverse events to pharmacotherapy
  - Adherence to pharmacotherapeutic regimen
  - IHD-related complications such as heart failure
  - Presence of new co-morbidities
  - Existing risk factors and presence of new risk factors
- 

The effectiveness of anti-anginal therapy may be assessed by questioning patients regarding the frequency and intensity of angina symptoms. In particular, patients should be questioned regarding sublingual nitroglycerin use. More frequent use or an increase in the number of doses necessary for symptom relief would suggest worsening disease and the need for therapy adjustment and further diagnostic evaluation. Adherence to both lifestyle modifications and pharmacotherapeutic regimens should also be assessed and appropriate education provided at each patient visit. Assessment of blood pressure and heart rate are important as elevations in both can increase oxygen demand and precipitate angina symptoms. If blood pressure is elevated (e.g., >130/80 mmHg, including those with diabetes or chronic kidney disease) and/or resting heart rate is not at goal (55–60 beats/minute), pharmacotherapy should be adjusted in an effort to achieve these goals and prevent symptoms of angina. Additional evaluation and therapy adjustment may also be necessary for patients presenting with signs or symptoms of new comorbidities or risk factors for IHD.

Drug safety is largely assessed through monitoring hemodynamic parameters (assessing for bradycardia, tachycardia, and hypotension) and questioning patients about the development of adverse effects. Monitoring parameters for specific drugs for chronic stable angina are listed in Appendix X. Frequent blood pressure monitoring is necessary when initiating or increasing the dose of beta-blockers with alpha-blocking effects (e.g., labetalol and carvedilol), which may cause pronounced blood pressure reduction. Heart rate should be closely moni-

tored with drugs that have negative chronotropic effects (e.g., beta-blockers, verapamil, or diltiazem) or the potential to cause reflex tachycardia (e.g., nitrates or dihydropyridine CCBs). Patients should also be assessed for the presence of signs and symptoms of heart failure (see Chapter 8, Chronic Heart Failure) because this may reflect a complication of IHD as well as an adverse effect of negative inotropic drugs (e.g., beta-blockers, verapamil, or diltiazem) used to treat chronic stable angina.

## CLINICAL CONTROVERSIES

***Is PCI superior to medical therapy for chronic stable angina?*** Over the last few decades, the use of PCI as a primary treatment modality in patients with chronic stable angina has increased in frequency. Recently, the COURAGE study investigated whether PCI with optimal medical management was superior to optimal medical therapy alone.<sup>32</sup> Optimal medical therapy consisted of standard anti-anginal therapy plus an ACE inhibitor or ARB plus aggressive dyslipidemia therapy (goals: LDL cholesterol 60–85 mg/dL, HDL cholesterol >40 mg/dL, and triglycerides <150 mg/dL). No differences in the incidence of death or nonfatal MI were observed between the groups over a median of 4.6 years of follow-up. Therefore, in patients with chronic stable angina, optimal medical therapy is recommended and PCI should be reserved for patients with refractory or unstable symptoms.

***Are thiazolidinediones (TZDs) safe to use in patients with IHD?*** TZDs are very effective agents for the treatment of diabetes mellitus and are commonly prescribed. However, two meta-analyses recently raised concern that rosiglitazone, a TZD, increases the risk of death and MI in patients with diabetes.<sup>33,34</sup> In contrast, a meta-analysis evaluating the same events associated with pioglitazone, another TZD, demonstrated significantly fewer MACE in patients receiving the drug.<sup>35</sup> Similar results were also observed in a posthoc analysis of patients with previous MI from the PROactive study.<sup>36</sup> Therefore, data regarding the risk of IHD-related adverse events is inconsistent and may be drug specific rather than a class effect. An increased risk of heart failure is consistent across the trials.<sup>34–36</sup> As a result, TZDs should be used with caution in patients with IHD and concomitant heart failure.

***Can beta-blockers be used to treat chronic stable angina in patients who use cocaine?*** Cocaine blocks the reuptake of norepinephrine and dopamine, resulting in an accumulation of these catecholamines and a heightened sympathetic state, increasing blood pressure and heart rate. The use of beta-blockers in these patients is controversial. Although they can block the  $\alpha$ -1-receptor-mediated

effects on the heart, beta-blockade may lead to unopposed  $\alpha$ -1-receptor-mediated vasoconstriction, resulting in coronary vasoconstriction and hypertension. This phenomenon has been poorly studied in humans, but has been demonstrated in several experimental models. Recently, the AHA released a scientific statement advising against the use of beta-blockers in patients presenting to the hospital with chest pain.<sup>37</sup> Further, the use of beta-blockers in patients who use cocaine should be considered on an individual basis and likely reserved for those with compelling indications (MI, left ventricular dysfunction, ventricular arrhythmias).<sup>37</sup>

***Is dual antiplatelet therapy with aspirin and clopidogrel superior to aspirin alone in stable IHD?*** Combination antiplatelet therapy with aspirin and clopidogrel is commonly prescribed for patients with IHD following PCI with either BMS or DES and following hospitalization for ACS. Since combination therapy reduces MACE in the above scenarios, the CHARISMA study evaluated the effect of long-term aspirin and clopidogrel therapy in patients with or at high risk for IHD.<sup>38</sup> Unlike previous trials in PCI and ACS, combination therapy offered no benefit over monotherapy with aspirin, increased the risk of moderate bleeding complications, and was associated with an increase in ischemic events in asymptomatic patients. Subgroup analyses revealed a marginal benefit in patients with “symptomatic” cardiovascular disease as well as those who had prior cardiovascular events (e.g., MI, stroke, symptomatic peripheral arterial disease).<sup>38,39</sup> For this reason, the ACCP suggests the combination of low-dose aspirin and clopidogrel in patients with symptomatic IHD (Class 2B recommendation).<sup>21</sup> However, given the marginal benefit observed in subgroup analyses, the limitations of subgroup analyses, and potential bleeding risk, one must weigh the risks and benefits of combination antiplatelet therapy in patients with IHD in the absence of ACS or PCI with stent placement.

***Is rosuvastatin “cardioprotective” in patients with elevated C-reactive protein levels?*** Elevated C-reactive protein (CRP), an inflammatory marker, has been identified as a moderate predictor of IHD.<sup>40</sup> Recently, nearly 18,000 healthy patients without evidence of IHD but with elevated high-sensitivity CRP were randomized to receive either rosuvastatin 20 mg daily or placebo.<sup>41</sup> The trial was stopped early following a median follow-up duration of nearly 2 years because rosuvastatin was found to lower the risk of MACE by nearly 50% in these healthy patients. Not surprisingly, patients treated with rosuvastatin also had significantly lower LDL cholesterol (50% lower) and triglycerides (17% lower) than those in the placebo arm. Therefore, the use of statins, in general, and rosuvastatin, in particular, may play a role in cardioprotection for otherwise healthy patients with elevated high-sensitivity CRP.

**To what extent does ranolazine prolong QT interval?** Early studies with ranolazine revealed a significant dose-related increase in QT interval (mean increase 5–14 milliseconds) compared to placebo following 12 weeks of therapy in patients with chronic stable angina, raising safety concerns regarding the potential to induce torsades de pointes, a potentially lethal ventricular tachyarrhythmia.<sup>42,43</sup> An open-label extension of these earlier studies (ROLE program) followed more than 700 patients for an average of 2.8 years to better characterize the long-term safety and tolerability of ranolazine.<sup>44</sup> The mean QT prolongation observed in these patients was 2.4 milliseconds, although 1.2% of patients experienced excessive QT prolongation (QT interval >500 milliseconds). Importantly, no cases of torsades de pointes were reported and nobody discontinued therapy as a result of QT prolongation. Therefore, the clinical significance of ranolazine-induced QT prolongation is questionable. Nevertheless, it remains contraindicated in patients with pre-existing QT prolongation and in those taking other drugs known to prolong QT interval.<sup>30</sup>

## FUTURE TREATMENTS

Because IHD is the largest killer among adults in the United States, many experimental therapies for the treatment and prevention of it are either in development or currently being investigated. One experimental approach being investigated is angiogenesis as a way to promote neovascularization, or new blood vessels, in patients with IHD. Angiogenesis involves the local administration (e.g., during coronary angiography and/or PCI) of vascular growth factors, typically a vascular endothelial growth factor (VEGF) or fibroblast growth factor (FGF), perhaps along with endothelial progenitor cells or stem cells in an effort to promote angiogenesis.<sup>45</sup> Although this experimental therapy holds promise, the safety and efficacy remain unknown.

Experimental antithrombotic drugs are potential additions to the treatment arsenal for IHD.<sup>46</sup> Presently, two classes of experimental drugs appear to hold the most promise for patients with IHD: adenosine diphosphate (ADP) antagonists and oral factor Xa inhibitors. Two oral ADP antagonists are currently in Phase III development. Prasugrel is a thienopyridine that is a more potent inhibitor of platelet aggregation than clopidogrel. AZD6140 is a competitive inhibitor of P2Y<sub>12</sub> with rapid inhibition of platelet aggregation. Both drugs are being studied for chronic use in combination with aspirin in patients following hospitalization for ACS. Two oral factor Xa inhibitors, apixaban and rivaroxaban, are currently in Phase II development for secondary prevention of cardiac events in patients following ACS. If these therapies prove safe and effective for secondary prevention following ACS, their role in patients with chronic stable angina may also expand.

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