Getting With the ACC/AHA Guidelines for the Treatment of Chronic Angina as a Disease State

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The primary objective of treatment in patients with chronic coronary artery disease (CAD) and stable angina is relief of symptoms and improvement of clinical outcome. The American College of Cardiology/American Heart Association guidelines have emphasized the role of evidence-based therapies. There have been regular updates of the guidelines, with an effort to include the latest data in the recommendations. Since the 2002 guidelines were published, there have been several pivotal studies that have provided strong support for the role of aggressive and optimal medical therapy in improving clinical outcomes in patients with chronic CAD. Recent data from 2 landmark studies have emphasized that optimal medical therapy is as effective as myocardial revascularization with percutaneous coronary intervention or coronary artery bypass grafting in reducing risk of adverse clinical outcomes. The 2009-2010 guidelines will likely incorporate the findings of these studies and accordingly modify the recommendations for treatment of patients with chronic CAD and stable angina.
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Coronary heart disease (CHD) remains a prevalent and complex health problem in the United States. The clinical gamut of CHD includes asymptomatic individuals with nonobstructive coronary artery disease (CAD), patients with chronic CAD and stable angina pectoris, and patients who have previously experienced an acute coronary event or an acute coronary syndrome (ACS), such as unstable angina or acute myocardial infarction (MI).[1] CAD is associated with the presence of clinical risk factors (eg, hypertension,

dyslipidemia, smoking, diabetes mellitus). The risk of developing CAD and associated coronary events appears to increase with the presence of additional risk factors in a given person.[2] Cardiovascular (CV) events that occur in patients with CAD include death and MI, as well as the development of heart failure.

Although it is not feasible to precisely identify the individual who might develop CV events associated with CHD, risk factors and other risk markers can be used to estimate a person's risk of developing major clinical events associated with CAD. Furthermore, targeting certain risk factors for intervention might result in a decrease in the risk of CV events and a decrease in mortality.

The American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for the management of patients with stable angina apply predominantly to symptomatic individuals with chronic or suspected CAD.[3] However, the management suggestions generally will also apply to asymptomatic patients with risk factors, who appear to be at high risk for developing CAD and its complications. These guidelines have been regularly updated, with the last update in 2007.[4] As there has been a considerable number of newer studies and the approval of ranolazine, a new class of drug for angina, it is likely that the new guidelines will incorporate substantial changes. As we await the release of the new guidelines, it will be useful for cardiologists to become aware of the possible changes that might be relevant to the management of their patients with chronic stable angina. In the following section, we will review the current guidelines-based approaches in the management of patients with chronic angina, with an emphasis on projected changes that might be recommended in the new 2009-2010 guidelines for the management of this disorder.

Table 1
General Actions of Antianginal Drugs

Class	Heart Rate	Arterial Pressure	Venous Return	Myocardial Contractility	Coronary Flow
β-Blockers	↓	↓	↔	↓	↔
DHP CCB	↑*	↓	↔	↓	↑
Non–DHP CCB	↓	↓	↔	↓	↑
Long-Acting Nitrates	↑/↔	↓	↓	↔	↑
Ranolazine (Na-CI)	↔	↔	↔	↔	↔

↔ indicates no effect; ↑ indicates increase; ↓ indicates decrease.
*Except amlodipine.
CCB, calcium channel blocker; DHP, dihydropyridine.

The goals of treatment in patients with stable angina and chronic CAD are to reduce symptoms, thereby improving quality of life, reducing myocardial ischemia and, more importantly, preventing death and MI.[3] The 2007 guidelines update further emphasized that an important goal of treatment in chronic stable angina is complete or nearly complete relief of anginal symptoms.[4] To achieve this goal, there are several available pharmacologic antianginal drugs, as well as various revascularization modalities for relief of symptoms. It is, however, important to emphasize that in addition to therapy directed toward symptom relief, concomitant aggressive risk factor modification is essential because it is what really reduces risk of coronary events and death.

Antianginal Therapies: Pharmacologic Approach

Treatment of patients with stable angina and chronic CAD with conventional pharmacologic antianginal drugs includes the use of nitrates, β-blockers, and calcium channel blockers (CCBs). These drugs exert their antianginal effect by modulating parameters of cardiac workload, such as heart rate, blood pressure, and myocardial contractility. The recently approved antianginal drug ranolazine, however, works by a unique mechanism and does not affect heart rate, blood pressure, or myocardial contractility (Table 1). The following discussion highlights some of the current recommendations from the guidelines.

β-Blockers

β-Blockers have been recommended as the mainstay of therapy for most patients with chronic angina, especially those with prior or recent history of MI.[3] β-blockers exert their antianginal effect through a reduction of hemodynamic parameters of cardiac work, such as heart rate, blood pressure, and myocardial contractility. Although the ischemic threshold is not increased by β-blocker therapy, the time to achieve this ischemic threshold is prolonged, thereby allowing the patient to engage in longer-lasting physical activities in daily life before angina occurs.

The 2007 guidelines update recommended β-blockers as class 1A (strongest recommendation).[4] Despite this recommendation, it is

important to note that there is a paucity of data available from randomized controlled trials that have systematically assessed the role of β-blocker therapy in improving long-term outcome in patients with chronic, stable CAD. This is in contrast to the vast amount of available data from studies that have evaluated the clinical benefit of β-blocker therapy in patients who have experienced an acute MI. Treatment with a β-blocker has been associated with reduction in mortality rates in patients recovering from an acute MI, although not in patients with stable angina or chronic CAD. Limited data from the Atenolol Silent Ischemia Trial (ASIST) are available evaluating the effects of β-blocker therapy on clinical outcomes.[5] The ASIST study primarily assessed the effects of atenolol on clinical outcomes in patients with evidence of CAD who were mildly symptomatic (Canadian Cardiovascular Society class I-II) or asymptomatic and who demonstrated asymptomatic ischemia during ambulatory electrocardiogram monitoring. During ambulatory monitoring, compared with placebo, treatment with atenolol resulted in a significant reduction in the heart rate, the frequency of ischemic episodes, the average duration of ischemia, and the proportion of patients who experienced ischemia. Evaluation of clinical outcomes revealed that, compared with the placebo group, the atenolol group experienced a significantly lower risk (11.1 vs 25.3%, respectively; $P = .001$) of the primary composite clinical endpoint that included death, resuscitation from ventricular tachycardia or ventricular fibrillation, nonfatal MI, hospitalization for unstable angina, aggravation of angina requiring known antianginal therapy, or need for myocardial revascularization during the follow-up period of 12 months. However, assessment of individual hard clinical endpoints revealed a similar risk of death and nonfatal MI between the groups.

The ASIST study is the only study that compared the effects of treatment with a β-blocker to placebo on clinical outcomes in patients with chronic CAD. Other studies have compared the effects of β-blocker therapy with those of CCBs on clinical outcomes in patients with stable angina.[6,7] Overall, in these studies, treatment with a β-blocker or a calcium channel blocker resulted in similar rates of death, cardiac death, and nonfatal MI.

It is, therefore, important to note that although β-blockers are recommended as class 1A for patients with history of MI and those with congestive heart failure or left ventricular (LV) dysfunction, there are limited data to suggest better outcomes in patients with chronic stable angina without these conditions. Additionally, β-blockers are associated with a high rate of adverse events and have limited utility in patients with resting bradycardia. They are also poorly tolerated by patients with peripheral arterial disease or with chronic obstructive pulmonary disease.

Nitrates

Although nitrates remain one of the most frequently used antianginal drugs in the treatment of stable angina, the ACC/AHA guidelines have recommended long-acting nitrate therapy as class 1B only for patients in whom β-blocker therapy is contraindicated or initial therapy with a β-blocker is not successful in controlling symptoms or not tolerated.[3] Furthermore, nitrates have not undergone evaluation in a prospective trial to determine their effects on hard clinical outcomes, such as death and MI in patients with chronic stable angina. The antianginal effect of nitrates is attributed to vasodilatation, primarily through venodilation, and results in a reduction in chamber dimension and cardiac work. Additionally, because of their coronary artery vasodilatory effect, nitrates are also effective in relieving coronary artery spasm in patients with Prinzmetal's angina. Sublingual nitroglycerin preparations are still considered the most effective antianginal drugs for relief of acute angina and usually result in prompt relief of symptoms. A drawback of prophylactic long-acting nitrate therapy is the tendency for patients to develop tolerance with regular long-term use. The development of tolerance to nitrates can be prevented by observing a nitrate-free period of 10 to 12 hours.

Calcium Channel Blockers

The CCBs are recommended as class 1B only when initial treatment with β-blockers is either contraindicated or not effective in controlling symptoms or produces unacceptable side effects. The 2007 guidelines did not modify recommendations regarding the use of CCBs in patients with stable angina.[4] CCBs exert their antianginal effect through reduction in parameters of cardiac workload (heart rate, blood pressure, and myocardial contractility) (Table 1). Because of their potent vasodilating activity, they are particularly effective for angina associated with coronary artery vasospasm.

There is also a paucity of data from prospective, controlled trials regarding the effects of CCBs on clinical outcomes in patients with stable CAD and angina. A Coronary Disease Trial Investigating Outcome with Nifedipine GITS (ACTION) in patients with stable CAD evaluated the clinical benefit of this treatment.[8] During the study, compared with

placebo, nifedipine gastrointestinal therapeutic system (GITS) produced a small but significant ($P < .0001$) increase in the mean heart rate (1 bpm) during follow-up and a significant mean reduction in the systolic and diastolic blood pressures. In this trial, compared with placebo, treatment with the long-acting nifedipine GITS was associated with similar rates of the primary composite endpoint as well as the individual endpoints of death, MI, and stroke.

Late Sodium Channel Blocker: Ranolazine

Ranolazine, a late sodium channel blocking agent, is the newest drug recently approved for treatment of chronic angina. It is important to note that ranolazine is the first new antianginal drug approved by the Food and Drug Administration in 25 years. Although initially it was only approved for patients who remain symptomatic on standard antianginal therapy, based on the findings from the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36 (MERLIN-TIMI 36) study, ranolazine has now been approved as first-line therapy for patients with chronic stable angina.[9,10] It is likely that the new guidelines will incorporate the use of ranolazine.

As previous guidelines have not included discussion on efficacy of ranolazine, in the following section we will provide some background information regarding the efficacy of ranolazine in management of chronic angina. Although the antianginal mechanism of ranolazine is not fully understood, it is thought to involve the selective inhibition of late cellular sodium influx. The findings from trials that have evaluated ranolazine showed that, compared with conventional antianginal agents such as nitrates, β-blockers, and CCBs, its antianginal effect is accomplished without any reduction in hemodynamic parameters (such as heart rate, blood pressure, preload, and inotropy) (Table 1).[11-13]

Ranolazine has been evaluated extensively in patients with evidence of CAD and stable angina and in patients with non–ST-elevation ACS.[9,10,14-16] Trials in patients with stable angina include the Monotherapy Assessment of Ranolazine In Stable Angina (MARISA),[14] the Combination Assessment of Ranolazine In Stable Angina (CARISA),[15] and the Efficacy of Ranolazine In Chronic Angina (ERICA) trials.[16] The MERLIN-TIMI 36 study[10] evaluated the effect of ranolazine, compared with placebo, over a follow-up of 12 months in a prespecified subgroup (n = 3565) of ACS patients with a pre-ACS history of chronic angina (mean duration of chronic angina was 5.2 years).

The MARISA and CARISA studies evaluated, in a double-blind manner, the effects of ranolazine compared with placebo on exercise duration. The ERICA study examined the frequency of angina episodes.

In the MARISA trial, ranolazine at 500 mg to 1500 mg twice daily was associated with a significant increase in exercise duration during a follow-up of 12 to 24 months.[14] The CARISA study evaluated addition of ranolazine at 750 or 1000 mg twice daily to patients already receiving antianginal drugs.[15] In this study, addition of ranolazine was associated with a significant increase in exercise duration at 3 months as well as during follow-up at 12 to 24 months. The ERICA trial evaluated ranolazine, 1000 mg twice daily, during a relatively shorter follow-up period (6 weeks) in patients who were still experiencing angina on amlodipine given in a maximum dose of 10 mg/d.[16] In this study, compared with placebo, addition of ranolazine significantly reduced the frequency of angina episodes (3.3% vs 2.9%, respectively [$P = .017$]).

Although the primary results of the MERLIN-TIMI 36 study did not reveal any benefit of treatment with ranolazine, it did establish the safety of ranolazine in a large group of high-risk patients with ACS. Further evaluation of the MERLIN-TIMI 36 data in the prespecified group of patients with history of angina before ACS was recently published.[10] In this prespecified subanalysis, the investigators evaluated the effect of ranolazine, compared with placebo, on the composite endpoint of CV death, MI, or recurrent ischemia as well as the efficacy endpoints of need for modification of antianginal therapy and exercise duration on a stress test performed at 8-months follow-up. Compared with placebo, ranolazine was associated with a significantly lower risk of the primary composite endpoint (CV death, MI, or recurrent ischemia) at 30 days (23.3% vs 19.8% [$P = .039$]) and at 12 months (29.4% vs 25.2% [$P = .017$]). However, the primary risk reduction was afforded by a reduction in the rate of recurrent ischemia at 30 days (17.2% vs 13.7%, respectively [$P = .015$]) and at 12 months (21.1% vs 16.5%, respectively [$P = .002$]). At 12 months, ranolazine did not significantly reduce the risk of CV death or MI (12.5% vs 11.9%, respectively).[9,10] The exercise treadmill test findings at the 8-month evaluation revealed significant improvement in total exercise duration, exercise time to ischemia, and time to onset of angina in patients randomized to ranolazine. These data from this prespecified subanalysis of the MERLIN-TIMI 36 study suggest a favorable effect of ranolazine and provide

further support to the data from other trials (discussed earlier) designed primarily for evaluation of angina parameters in patients with chronic stable angina.

The findings from these studies indicate that ranolazine is a safe and well-tolerated antianginal medication. Ranolazine has been shown to be effective in patients who continue to experience angina symptoms despite treatment with conventional antianginal agents. Ranolazine can also be safely used in patients with compromised hemodynamic parameters (eg, those with baseline bradycardia and/or a tendency to develop significant hypotension), a condition that usually limits the use of optimal doses of standard antianginal drugs. Ranolazine can also be safely used in patients with diabetes, heart failure, and chronic obstructive pulmonary disease.

Antianginal Combination Therapy

Although previous ACC/AHA guidelines have not provided specific recommendations regarding the use of combination therapy, it is important to note that patients with stable CAD and angina quite often fail to achieve reasonable control of symptoms during antianginal monotherapy. In such cases, combination therapy is often necessary to improve the frequency or severity of anginal episodes. Generally, combination therapies include a β-blocker and a long-acting nitrate or a calcium channel blocker. Ranolazine has been extensively evaluated and shown efficacious in combination with standard antianginal drugs. Combination therapy with ranolazine is easier to use because it does not have any effect on heart rate and blood pressure (which are often low in patients already on optimal doses of β-blockers, nitrates, or CCBs). Combination therapy should be tailored to each patient based partly on the extent of other associated comorbid conditions. The effect of combination antianginal therapy on hard clinical outcomes has not been evaluated in prospective randomized controlled trials.

Other Pharmacotherapy and Risk Factor Interventions to Prevent MI and Death

The ACC/AHA guidelines have strongly emphasized the critical role of other proven pharmacologic agents and aggressive risk factor modification in all patients with chronic angina. It is critical to note that in contrast to the lack of documentation of improvement in hard events with antianginal drugs, risk-factor modification—especially lipid-lowering therapy with statins and treatment of hypertension in patients with stable CAD—has been convincingly shown to reduce the risk of coronary events and cardiac mortality. In the following sections, we will provide a brief overview of selected important therapies recommended by the guidelines in patients with stable CAD.

Antiplatelet Therapy: Aspirin

Although the previous ACC/AHA guidelines in 2002[3] and the update in 2007[4] have recommended the use of aspirin as class 1A, this is primarily based on the fact that the use of aspirin has been associated with decreased adverse cardiac outcomes in patients recovering from acute MI.[3] Aspirin has not undergone extensive evaluation in patients with stable angina.

The effect of aspirin, 160 mg/d, on clinical outcomes was evaluated in the Swedish Angina Pectoris Aspirin Trial (SAPAT) in patients with stable angina and presumed chronic CAD.[17] In this study, compared with placebo, treatment with aspirin significantly reduced the risk (12.1% vs 8% [$P = .003$]) of the primary composite endpoint (nonfatal MI, fatal MI, or sudden death). In addition, the aspirin group had a significantly lower risk (7.6% vs 4.6% [$P = .003$]) of nonfatal MI. The rates of all-cause mortality, sudden death, and stroke were similar between the groups.

A subanalysis of the Physician's Health Study (PHS) in the group (n = 333) of patients with a history of chronic angina evaluated the effect of aspirin (325 mg given on alternate days) on clinical outcomes.[18] In this analysis, as compared with placebo, treatment with aspirin significantly reduced the risk of MI (12.9% vs 3.9% [$P < .001$]) but, interestingly, also significantly increased the risk of stroke (1.3% vs 6.2% [$P = .02$]). All-cause mortality rates were similar between the groups. Because of the paucity of supporting data in chronic stable angina and recent concerns raised about the interactions between aspirin and angiotensin-converting enzyme (ACE) inhibitors, as well as the concern of increased risk of bleeding in the elderly, it is conceivable that the new guidelines might lower the strength of recommendation for routine use of aspirin in all patients with chronic stable angina.

ACE Inhibitors

The ACC/AHA guidelines have recommended ACE inhibitor therapy as class 1A for patients with stable CAD, especially those with LV dysfunction, hypertension, diabetes mellitus, and chronic kidney disease (CKD).[4] The ACE inhibitors have vasculoprotective effects and as such are attractive treatment options in patients with chronic CAD and stable angina. Two relatively large randomized, controlled studies, the Heart Outcomes Prevention Evaluation

(HOPE) trial,[19] and the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA),[20] evaluated the effect of ACE inhibition in patients with stable CAD.

The HOPE trial showed that, compared with placebo, the ramipril group experienced a significantly lower risk (17.8% vs 14% [$P < .001$]) of the primary clinical composite endpoint (CV death, MI, or stroke).[19] The EUROPA study evaluated the effect of another ACE inhibitor, perindopril, on clinical outcomes in patients with stable CAD and angina. In this study, compared with placebo, the perindopril group experienced a relatively small but significantly lower risk (9.9% vs 8% [$P = .0003$]) of the composite endpoint that included nonfatal MI, CV death, or resuscitated arrest.[20]

Because some patients are unable to tolerate ACE inhibitor therapy (primarily due to cough), the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)[21] evaluated whether treatment with the angiotensin receptor blocker telmisartan was noninferior to ramipril and also if combining the 2 drugs would result in any additional benefit. The results of this large study revealed that treatment with telmisartan was indeed noninferior to ramipril, but there was no benefit of combining the 2.[21] Based on the results of the ONTARGET study, it is conceivable that the new guidelines will recommend treatment with telmisartan as a suitable alternative in patients intolerant to treatment with an ACE inhibitor.

Risk Factor Modification

Lipid-Lowering Interventions and Agents

The 2002 ACC/AHA guidelines had recommended lipid-lowering therapy in all patients with documented or suspected CAD and low-density lipoprotein cholesterol (LDL-C) greater than 130 mg/dL, with a target LDL-C of less than 100 mg/dL.[3] The 2007 update modified this recommendation to include the target LDL-C of less than 70 mg/dL or high-dose statin therapy as a reasonable goal (class IIa [A]).[4] It is likely that the 2009-2010 guidelines will now modify the 2007 recommendation to level IA because several recent trials have documented an additional benefit of lowering LDL-C to less than 70 mg/dL.

The recommendation regarding LDL-C lowering therapy with statins is based on results of several landmark studies (Table 2) that have evaluated the effects of lipid-lowering therapy in patients with evidence of CAD or in patients with CAD–risk equivalent disorders. Statins have also been shown to have anti-ischemic actions. Although the precise mechanism of statins' anti-ischemic effects is not well-defined, it is postulated to be related to improvement in endothelial function as well as to the anti-inflammatory effects demonstrated by these agents.

In addition, there have been several recent large-scale randomized controlled trials[22-24] that have compared the effect of intensive lipid-lowering therapy with a high-dose statin versus moderate lipid-lowering therapy on clinical outcomes in patients with stable CHD. All of these trials have shown that intensive lipid-lowering therapy with statins, with the goal of achieving LDL-C of less than 70 mg/dL, is associated with significantly lower risk of fatal and nonfatal coronary events. Based on the results of these recent trials, it is likely that the 2009-2010 guidelines for patients with chronic CAD and stable angina will make stronger recommendations for intensive lipid-lowering therapy with statins to achieve LDL-C of less than 70 mg/dL in all patients with stable CHD.

Management of Diabetes Mellitus in Patients With Stable CHD

The 2007 ACC/AHA guidelines for management of patients with CHD and angina have recommended (IB) that diabetes management include

Table 2
Lipid Reduction Trials: Secondary Prevention in Established CHD

	Composite Endpoint	Mortality	MI	Stroke
4S[32]	↓	↓	↓	↓
CARE[33]	↓	↔	↓	↓
LIPID[34]	↓	↓	↓	↓
AVERT[22]	↓	↔	↔	↔
HPS[35]	↓	↓	↓	↓
TNT[23]	↓	↔	↓	↓
IDEAL[24]	↔	↔	↓	↔

↔ indicates no effect; ↓ indicates decreased risk.
4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol and Recurrent Events Trial; LIPID, Long-Term Intervention With Pravastatin in Ischaemic Disease; AVERT, Atorvastatin versus Revascularization Treatment; HPS, Heart Protection Study; TNT, Treating to New Targets; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering.

lifestyle and pharmacotherapy measures to achieve a near-normal hemoglobin A_{1c}.[4] The 2009-2010 guidelines will most likely modify these recommendations again because of the recent findings from 3 large randomized controlled trials[25-28] showing no benefit of intensive glycemic control (to near normal hemoglobin A_{1c} of ≤ 6). Instead, there was a significant increased risk of severe hypoglycemia that was associated with increased mortality. Based on these findings, the joint scientific statement from the ACC/AHA/American Diabetes Association has already recommended that a hemoglobin A_{1c} level below 7 is adequate and safe for patients with CHD.[25] Furthermore, this statement also emphasizes that vigorous modification of other risk factors, such as blood pressure and cholesterol, are more beneficial in reducing the risk of future coronary events in patients with CVD.[25] It would therefore be appropriate for the 2009-2010 guidelines to choose similar recommendations for the management of patients with diabetes and CHD.

Myocardial Revascularization

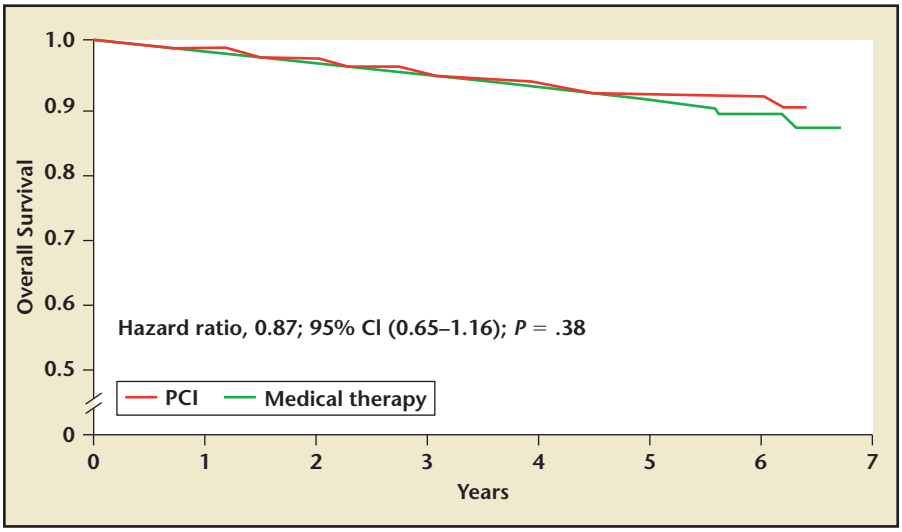
Coronary artery bypass grafting (CABG) surgery and percutaneous coronary intervention (PCI) are established myocardial revascularization modalities in the management of patients with CAD and angina. Both modalities are effective in decreasing the frequency and severity of angina episodes, particularly in patients with progressive angina despite treatment with conventional antianginal drugs.

In most trials, compared with medical treatment, coronary artery revascularization by CABG or PCI in patients with chronic CAD and stable angina has improved symptoms to a greater degree. However, routine coronary revascularization has not reduced the risk of death or the risk of subsequent MI in patients with stable angina. Posthoc analyses of these studies have revealed several clinical profiles derived from angiographic findings that identify patients at risk of adverse outcomes.[29] The high-risk angiographic profiles include patients with left main coronary artery with greater than 75% luminal stenosis, 3-vessel CAD and impaired LV function, and proximal left-anterior descending coronary artery with greater than 75% stenosis as part of 2-vessel CAD.[29]

The 2002 ACC/AHA guidelines had recommended (class IA) CABG for patients with significant left main coronary stenosis, 3-vessel disease, or 2-vessel disease with significant proximal left-anterior descending coronary artery stenosis, with either LV dysfunction or demonstrable ischemia. PCI was recommended (IB) for patients with 2-vessel or 3-vessel stenosis and a significant proximal left-anterior descending coronary artery with suitable anatomy in absence of diabetes.[3] Additionally, PCI or CABG was recommended (IB) for patients with 1-vessel or 2-vessel CAD with a large area of viable myocardium and high-risk criteria on noninvasive testing. The 2007 guidelines update did not modify any of the 2002 recommendations.[4] However, it is quite likely that these recommendations will be modified based on the results of 2 pivotal studies that have recently been published.[30,31]

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial compared the clinical efficacy of PCI plus optimal medical therapy (OMT) versus OMT alone in patients with stable CAD.[30] OMT consisted of not only treatment with a β-blocker and, when needed, diltiazem, but also included aggressive management of risk factors for CAD. During the median follow-up of 55 months, both the OMT as well as the OMT plus PCI groups had similar rates of the primary composite (death and nonfatal MI) outcome (18.5% vs 19.0%, respectively) (Figure 1). As expected, a

Figure 1. *Data from the COURAGE trial. Estimated 4.6-year rate of death from any cause was 7.6% in the PCI group and 8.3% in the optimal medical therapy group. CI, confidence interval; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; PCI, percutaneous coronary intervention. Adapted with permission from Boden WE et al. Optimal medical therapy with or without PCI for stable coronary disease.* N Engl J Med. *2007;356:1503-1516.*[30] *Copyright © 2007 Massachusetts Medical Society. All rights reserved.*



significantly greater proportion of patients in the PCI group were angina-free at 1 year (58% vs 66%, respectively [$P < .001$]) and at 3 years (67% vs 72%, respectively [$P = .02$]). However, this benefit was lost at 5 years (72% vs 74%, respectively).[30]

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial in patients with diabetes, CAD, and classic angina compared the effects of prompt revascularization by discretionary CABG or PCI with medical therapy alone on clinical outcomes.[31] During the 5-year follow-up, there was no difference in the primary outcome of all-cause mortality between the revascularization and medical therapy groups (Figure 2).

The results of these landmark studies clearly emphasize that myocardial revascularization should be recommended primarily for symptom control in most patients with chronic CAD and stable angina. The 2009-2010 guidelines will clearly need to modify the recommendations of the 2002 guidelines to reflect the findings from these studies.

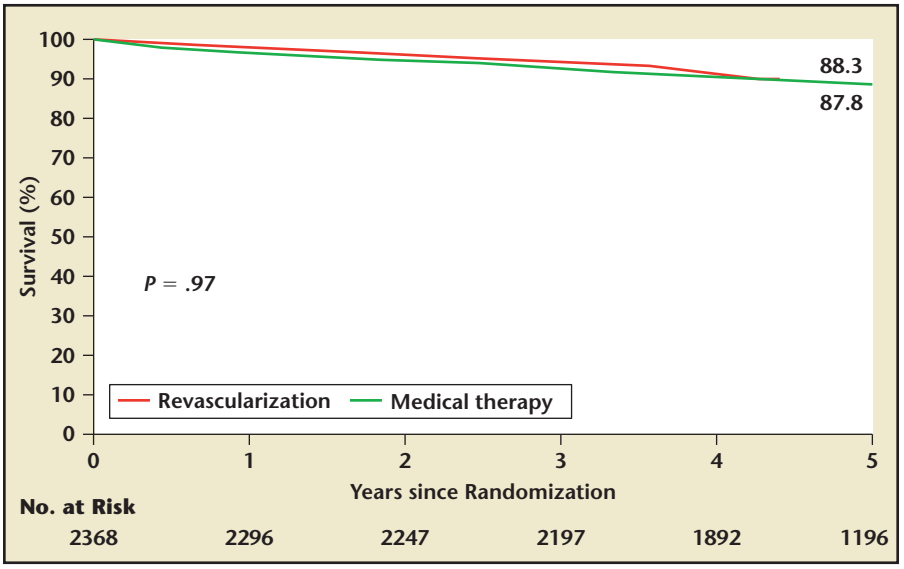


Figure 2. *Data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study. Similar survival rates between the revascularization group and the optimal medical therapy group. Adapted with permission from BARI 2D Study Group et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease.* N Engl J Med. *2009;360:2503-2515.*[31] *Copyright © 2009 Massachusetts Medical Society. All rights reserved.*

Conclusion

The management of patients with chronic CAD and stable angina should consist of evidence-based therapies as recommended by the ACC/AHA guidelines. The goals of therapy should not only include control of symptoms but also consist of aggressive risk factor management to improve clinical outcomes. There have been several pivotal studies conducted in patients with chronic CAD since the 2002 guidelines. The results of these studies have provided strong support for the role of aggressive OMT in improving clinical outcomes in patients with chronic CAD. Furthermore, the results of the

Main Points

- The American College of Cardiology/American Heart Association guidelines for the management of patients with stable angina apply predominantly to symptomatic individuals with chronic or suspected coronary artery disease (CAD). However, the management suggestions generally also apply to asymptomatic patients with risk factors, who appear to be at high risk for developing CAD and its complications.
- Although β-blockers are recommended as class 1A for patients with history of myocardial infarction and those with congestive heart failure or left ventricular dysfunction, there are limited data to suggest better outcomes in patients with chronic stable angina without these conditions.
- Ranolazine, a new late sodium channel blocking agent, has been approved as first-line therapy for patients with chronic stable angina.
- In contrast to the lack of documentation of improvement in hard events with antianginal drugs, risk-factor modification—especially lipid-lowering therapy with statins and treatment of hypertension in patients with stable CAD—has been convincingly shown to reduce the risk of coronary events and cardiac mortality.
- Angiotensin-converting enzyme inhibitors have vasculoprotective effects and as such are attractive treatment options in patients with chronic CAD and stable angina.
- Several recent trials have documented an additional benefit of lowering low-density lipoprotein cholesterol to less than 70 mg/dL, which will likely be reflected in new management guidelines.

COURAGE and BARI 2D studies have demonstrated that OMT is as effective as myocardial revascularization with PCI or CABG in reducing risk of adverse clinical events in patients with chronic CAD. Based on these findings, it will be necessary for the 2009-2010 guidelines to make several important modifications to the recommendations for management of patients with chronic CAD and stable angina. ■

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