Managing Patients With Chronic Angina: Emerging Therapeutic Options for Improving Clinical Efficacy and Outcomes

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Coronary heart disease (CHD) remains the leading cause of death among American men and women. However, advances in the treatment of acute coronary syndrome and an increasing number of therapies to reduce recurrent cardiac events have led to more patients surviving with chronic CHD. The primary symptom of chronic CHD is angina (chest pain on exertion or under mental or emotional stress).

More than 6.5 million Americans suffer from angina, and the prevalence will continue to grow as patients live longer with CHD and as the population ages. Angina can severely limit patients’ functional status and diminish their quality of life. Patients with angina are less satisfied with their care. Moreover, angina is predictive of subsequent acute coronary syndrome and death among CHD outpatients. Given its prevalence and impact on health, chronic angina should not be treated as a benign condition and deserves increased attention from health care practitioners.

While angina is treatable through a range of pharmacologic treatments as well as coronary revascularization, it is often inadequately treated in clinical practice. For example, outpatients with chronic angina report a median frequency of 2 episodes/week, and the majority of these patients perceive their health as “fair” or “poor.” There is also a misperception that angina is largely obviated in an era of coronary stenting and early invasive therapy for acute coronary syndrome. Yet, more than one quarter of patients have some angina 1 month after discharge for acute myocardial infarction, and one third of patients report daily to weekly angina 7 months after admission to the hospital for treatment of acute coronary syndrome. Ultimately, many CHD patients are left with varying degrees of residual angina despite treatment. This has provided the impetus to develop new pharmacologic therapies to better manage chronic angina.

The first article in this supplement describes the epidemiology, pathogenesis, and treatment of chronic angina, including the use of vasculoprotective and antianginal drug therapies and coronary revascularization procedures. The approved uses, pharmacology, pharmacodynamics, pharmacokinetics, efficacy, safety, and place in therapy of ranolazine—the first new antianginal drug therapy introduced in more than 20 years for the treatment of chronic angina—are addressed in detail in the second article. In the third article, the economic burden of chronic angina in the United States is quantified, and recent trends in the use of coronary revascularization are characterized. The clinical outcomes from and long-term costs of percutaneous coronary intervention, coronary artery bypass grafting, and medical management are compared in patients with chronic angina.

DISCLOSURES
This article is based on a presentation given by the author at a symposium titled “Emerging Therapies for Management of Patients with Stable Angina.”
Focus on Clinical Efficacy and Outcomes at the Academy of Managed Care Pharmacy's 18th Annual Meeting and Showcase in Seattle, Washington, on April 5, 2006. The symposium was supported through an educational grant from CV Therapeutics, Inc. The author received an honorarium from CV Therapeutics, Inc. for participation in the symposium. He is a consultant for CV Therapeutics, Inc.

REFERENCES


Stable Angina: Current State of Disease Management

PAUL P. DOBESH, PharmD, FCCP, BCPS

ABSTRACT

OBJECTIVE: To describe the epidemiology, impact, pathogenesis, patient presentation, and treatment of stable angina, including the use of vasculoprotective and antianginal drug therapies and coronary revascularization procedures.

SUMMARY: Stable angina is an age-related condition that typically affects men at an earlier age than women, adversely affects quality of life, and increases mortality. Stable angina is the result of an increase in myocardial oxygen demand in the setting of coronary arteries chronically narrowed by large, stable atherosclerotic plaques and a diminished myocardial oxygen supply. The characteristics of the chest pain or discomfort contribute to the clinical presentation. Treatment guidelines call for efforts to modify CHD risk, antianginal drug therapy, and patient education. Angiotensin-converting enzyme inhibitors and low-dose aspirin or clopidogrel may be used to reduce the risk of myocardial infarction and death. A beta-blocker or a nondihydropyridine calcium channel blocker may be used as initial antianginal drug therapy, and a long-acting nitrate or diltiazem may be added. The choice among antianginal drug therapies often hinges on patient characteristics, contraindications, and adverse effects. Revascularization with percutaneous coronary intervention or coronary artery bypass graft surgery is an option for ischemia refractory to maximum tolerated dosages of antianginal therapy.

CONCLUSION: Various drug therapies may be used to manage stable angina, with coronary revascularization as an option in patients who are refractory to drug therapy. However, antianginal drug therapies may prove inadequate for managing anginal episodes for a variety of reasons, and revascularization is not always effective.

KEYWORDS: Burden of disease, Pharmacotherapy, Stable angina, Treatment guidelines, Revascularization

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Stable angina is one of several possible manifestations of coronary artery disease (CAD), a common, deadly, and costly disease in the United States (see the Introduction to this supplement). CAD and other cardiovascular diseases are age-related conditions (Figure 1). While CAD is the leading cause of death for both women and men, women usually develop CAD about 10 years later than men, and they experience myocardial infarction (MI), sudden death, and other serious sequellae roughly 20 years after men. The initial manifestation of CAD usually is angina in women and MI in men.

Among patients with CAD, the total number of patients with chronic stable angina is difficult to determine. Chronic stable angina is the initial manifestation of ischemic heart disease in approximately half of patients. Using these numbers, along with estimates based on patients surviving MI, it is predicted that between 6 and 12 million Americans have chronic stable angina. The risk of mortality is greatest for white men, followed by white women, black men, and black women.

Impact

Angina has a substantial impact on mortality and quality of life. Angina episodes typically are triggered by exertion or emotional stress, so the physical activities of patients with stable angina are limited. In a prospective study of 8,908 Veterans Affairs outpatients with CAD who were followed for an average of 2 years, the risk of death increased progressively with the self-reported degree of physical limitation due to angina. The average age of participants was 67 years, 98% were male, 66% were white, and 25% had diabetes mellitus (DM). There were 896 deaths. A high degree of physical limitation increased the risk of death 2.5 times compared with little or no physical limitation, a difference that is significant. The degree of physical limitation may reflect the extent of atherosclerosis, which narrows the coronary arteries and reduces the blood and oxygen supply to the myocardium.

The patient characteristics, frequency of angina attacks, and impact of angina on perceived well-being were assessed in 5,125 outpatients with chronic stable angina living in a variety of geographic areas. The average patient age was 69 years, 53% of patients were women, 70% had more than 1 associated illness, and 64% received more than 1 cardiovascular drug. The median frequency of angina was approximately twice weekly. Ninety percent of patients experienced angina during activity, and 47% also had angina at rest. The frequency of angina was significantly correlated with patients’ perception of their overall well-being, with poorer health associated with higher frequencies of angina.

Pathogenesis

Angina is the result of myocardial ischemia, which is due to an imbalance between myocardial oxygen supply and demand. In a healthy person, the myocardial blood flow and oxygen supply

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increase in response to increases in oxygen demand during physical exertion through various humoral, neural, and metabolic mechanisms that regulate vascular resistance and coronary blood flow.6

Angina episodes in patients with chronic stable angina are typically precipitated by an increase in myocardial oxygen demand (MVO$_2$) in the setting of a fixed decrease in supply. The major determinants of MVO$_2$ include heart rate, myocardial contractility, and intramyocardial wall tension. Intramyocardial wall tension is the leading contributor to increased MVO$_2$ and is directly related to the radius or size of the ventricular cavity and blood pressure, but indirectly related to the ventricular muscle mass. The rate of increase of MVO$_2$ can be as important as the total amount of MVO$_2$. The rate-pressure product, or double product, is a common non-invasive measure of MVO$_2$, which is the product of the heart rate and systolic blood pressure (SBP). However, any change in contractility or volume loading of the left ventricle (LV) is not considered by the double product.

The etiology of the fixed decrease in supply is long-standing, well-developed atherosclerotic plaques. Coronary plaques that contribute to exertional angina symptoms usually obstruct ≥70% of the epicardial coronary vessel lumen.7 The reduction in supply is a result of obstruction of coronary blood flow by a large plaque compared with a ruptured plaque as in an acute coronary syndrome. The plaques in chronic stable angina patients are more stable, have a reduced lipid pool, and rupture infrequently. Since their geometry does not typically change acutely, they provide a relatively fixed decrease in myocardial oxygen supply.

The plaques provide a resistance to coronary blood flow in the epicardial vessels that generally do not offer any resistance to flow in patients without disease. Increases in MVO$_2$ are met by vasodilation of endocardial vessels that feed the myocytes. In patients with a fixed coronary lesion in the epicardial vessels, the endocardial vessels must dilate to provide adequate oxygen and blood supply to the myocytes at rest. During periods of increased MVO$_2$ in these patients, the endocardial vessels are already maximally vasodilated and, therefore, can provide no additional myocardial oxygen supply. The increased MVO$_2$ can come from increased physical activity or emotional stress. Since the increased MVO$_2$ demand cannot be satisfied due to the fixed reduction in supply, and maximal endocardial vasodilation at rest, angina is precipitated.

### Patient Presentation

The diagnosis of stable angina involves a detailed history to characterize the nature, timing, and location of chest discomfort; precipitating factors; and the response to palliative measures (i.e., nitroglycerin or rest).8 The PQRST mnemonic (Precipitating factors and Palliative measures, Quality of pain, Region and Radiation of pain, Severity of pain, Temporal factors) often is used by clinicians to evaluate chest pain and help rule in or out a cardiac cause. Other elements of a diagnostic work-up for a patient with suspected angina and CAD should include a physical examination, history of risk factors for CAD (cigarette smoking, dyslipidemia, hypertension, DM, and family history of premature CAD), electrocardiography, chest X-ray, and possibly an echocardiography, radionuclide imaging studies, and/or coronary angiography.9

The typical complaints of a patient with chronic stable angina includes chest pain that is precipitated by exertion, such as walking, gardening, house cleaning, or sexual activity. Upon exertion, MVO$_2$ has exceeded what can be provided by the fixed decrease in supply from the occlusive atherosclerotic plaque. The chest pain is typically relieved by rest or sublingual nitroglycerin (SL NTG). The quality of angina chest pain is often described as squeezing, crushing, a heaviness, or tightness in the chest. It can also be more vague and described as a numbness or burning in the chest. Chest pain that is described as sharp in origin, pain that increases with inspiration or expiration, or a reproducible pain with palpation is usually not cardiac pain. The region of the pain is substernal and may radiate to the right or left shoulder, right or left arm (left more commonly than right), neck, back, or abdomen. The severity of cardiac chest pain can be difficult to quantify since pain is a subjective measure, but the pain is usually considered severe and ranked a 5 or higher on a 10-point scale. It is important to remember that women and the elderly may present with atypical chest pain, and patients with DM may have a decreased sensation of pain due to complications of neuropathy. By definition, the timing or duration of the chest pain in patients with chronic stable angina is less than 20 minutes, but is usually around 5 to 10 minutes. A variety of noncardiac causes of chest pain must also be considered, such as gastroesophageal reflux, esophageal motility disorders, biliary colic, costosternal syndrome, or musculoskeletal disorders.9,10

The most recent guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA) for
Low-dose aspirin (81 mg/day) is recommended, with *↓* ↓↓ *Antianginal Drug Therapy* *↓* ↓

Prevention of MI and death is another Clearly the major contributing factor to successful utilization are greatly reduced. *↑* ↓↓

Regardless of whether the patient is utilizing medical management, revascularization, or a combination of approaches, patients need treatment for acute attacks of angina. About 75% of all exertional angina episodes will be relieved with the first SL NTG dose with another 10% to 15% of patients achieving relief with the next 2 doses. *↓* The tablets also may be used prophylactically before situations likely to provoke angina such as exercise. *↔*

Clearly the major contributing factor to successful use of SL NTG is appropriate patient education from the pharmacist. If patients do not receive appropriate patient counseling on the use and storage of this agent, the opportunities for successful utilization are greatly reduced. *↓* ↓↓

Beta-blockers are commonly used in the management of patients with chronic stable angina. By reducing heart rate, myocardial contractility, and intramyocardial wall tension (Table 1), beta-blockers impact all of the major contributing factors of MVO₂. Heart-rate reduction may also improve myocardial oxygen delivery by prolonging diastole and increasing the time for myocardial perfusion. Beta-selectivity does not impact the efficacy of beta-blockers in the treatment of chronic stable angina, and all agents appear equally effective. Beta 1-selective agents would be preferred in patients with chronic obstructive pulmonary disease (COPD), peripheral vascular disease, DM, dyslipidemias, and sexual dysfunction.*↑* ↓↓

Calcium channel blockers (CCBs) are also effective in reducing angina episodes in patients with chronic stable angina. Like beta-blockers, nondihydropyridine (NDHP) CCBs reduce all of the components of MVO₂ (Table 1). The similarity in pharmacodynamic effects of beta-blockers and NDHP CCBs suggests that either drug class might be used as initial antianginal therapy in patients with stable angina. All dihydropyridine (DHP) CCBs provide blood pressure reduction and, therefore, a reduction in intramyocardial wall tension. However, there is variation between the DHP CCBs in their impact on contractility and development of reflex tachycardia. Both DHP and NDHP CCBs provide some increase in myocardial blood flow. This increase in flow is due to the ability of the CCBs to decrease the cellular uptake of calcium and dilate epicardial coronary arteries. Most studies comparing beta-blockers and CCBs in patients with stable angina focused on the impact on the number and duration of angina episodes or the increase in exercise time to 1-mm ST segment depression.*↑* Few studies have compared the impact of these drug therapies on cardiovascular outcomes or mortality in patients with stable angina.

Calcium channel blockers and beta-blockers are equivalent in efficacy for relieving angina and increasing exercise time, although

**TABLE 1 Impact of Antianginal Drug Therapies on Myocardial Oxygen Demand**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Oxygen Demand</th>
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<tbody>
<tr>
<td></td>
<td>Heart Rate</td>
<td>Contractility</td>
<td>Intramyocardial Wall Tension</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Nondihydropyridine calcium channel blockers (i.e., diltiazem and verapamil)</td>
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<td></td>
</tr>
<tr>
<td>Dihydropyridine calcium channel blockers*</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td></td>
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<tr>
<td>Long-acting nitrates</td>
<td>↑</td>
<td>↔</td>
<td>↓</td>
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</tbody>
</table>

* Dihydropyridine calcium channel blockers include amiodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, and nisoldipine.*

**Antianginal Drug Therapy**

The antiangina drug therapies used in patients with stable angina provide their benefit by mainly reducing the different components of MVO₂ (Table 1). Some agents may also provide some coronary vasodilation and increased myocardial oxygen supply, but this is not the primary method of benefit, and results are not consistent between agents. Aspirin, clopidogrel, and angiotensin-converting enzyme (ACE) inhibitors are vasculoprotective therapies that reduce the risk of MI and death in patients with stable angina.*

All patients with chronic stable angina should have access to SL NTG tablets or spray as recommended in the ACC/AHA guidelines. *↓* Regardless of whether the patient is utilizing medical management, revascularization, or a combination of approaches, patients need treatment for acute attacks of angina. About 75% of all exertional angina episodes will be relieved with the first SL NTG dose with another 10% to 15% of patients achieving relief with the next 2 doses. *↓* The tablets also may be used prophylactically before situations likely to provoke angina such as exercise. *↓* Clearly the major contributing factor to successful use of SL NTG is appropriate patient education from the pharmacist. If patients do not receive appropriate patient counseling on the use and storage of this agent, the opportunities for successful utilization are greatly reduced. *↓*

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managing patients with chronic stable angina were released in 2002.* Important advances have been made since then, but the guidelines remain relevant. According to the ACC/AHA guidelines, the goal of treatment in most patients with stable angina is the complete or nearly complete elimination of chest pain and a return to normal activities with minimal adverse effects, although the goal for an individual depends on his or her clinical characteristics and preferences.* Prevention of MI and death is another therapeutic objective in this patient population. A 3-pronged approach to treatment is outlined in the guidelines, including modification of CAD risk, antianginal therapy, and patient education about the risk factors, pathophysiology, complications, and treatment of CAD.*

Despite the fact that the patient with chronic stable angina has already developed CAD, risk-factor reduction and management are important to prevent progression of atherosclerotic disease. Smoking cessation and lifestyle modification (i.e., diet, exercise, weight reduction if overweight) for patients with dyslipidemia or hypertension also are recommended to reduce CAD risk. Antilipemic and antihypertensive drug therapy in accordance with guidelines of the National Cholesterol Education Program’s Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults and the Joint National Committee for Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, respectively, may be required. *↑* ↓↓ Management of DM through lifestyle modification and, if needed, antidiabetic drug therapy, is advised because DM is considered a CAD risk equivalent. *↑* Low-dose aspirin (81 mg/day) is recommended, with clopidogrel as an alternative for patients with contraindications to aspirin.* The antithrombotic effect of aspirin and clopidogrel reduces the risk of MI and death.*
some studies suggest that beta-blockers are more effective than DHP CCBs. In a randomized double-blind, parallel-group study of 330 patients with chronic stable angina, both the beta-blocker bisoprolol and the DHP CCB nifedipine reduced the number of angina episodes and duration of angina episodes. While both groups demonstrated a significant benefit over baseline, bisoprolol was significantly more effective than nifedipine for both outcomes. In a randomized, double-blind, placebo-controlled study of 280 patients with stable angina, the beta-blocker metoprolol and nifedipine both increased exercise time (66 seconds metoprolol and 43 seconds for nifedipine; P < 0.01 for both compared with baseline), although metoprolol was more effective than nifedipine (P < 0.05). These findings suggest that an NDHP may be a better choice than a DHP for patients with stable angina if a CCB is chosen.

In a randomized, double-blind, parallel-group study of the beta-blocker atenolol, the DHP CCB nifedipine, and a combination of these 2 drugs in 682 patients with chronic stable angina, there was a nonsignificant trend toward a lower incidence of cardiac death, nonfatal MI, and unstable angina with combination therapy compared with monotherapy (12.8% atenolol, 11.2% nifedipine, and 8.5% combination therapy; P = 0.14), and there was no significant difference between atenolol and nifedipine. In 809 patients with chronic stable angina, there were no significant differences between metoprolol and the NDHP CCB verapamil in mortality (5.4% metoprolol vs. 6.2% verapamil; P = NS [not significant]) or quality of life. These findings suggest that cardiovascular outcomes and mortality are similar regardless of whether a beta-blocker or CCB is used as initial antianginal therapy in patients with stable angina.

According to ACC/AHA guidelines, a beta-blocker should be used as initial antianginal drug therapy in patients with stable angina in the absence of contraindications to beta-blocker use. The guidelines call for the addition or substitution of an NDHP CCB if beta-blockers are contraindicated, cause unacceptable adverse effects, or are ineffective in controlling angina episodes. The ACC/AHA recommendation for use of beta-blockers as initial antianginal therapy in patients with stable angina is based largely on robust evidence of a survival benefit from beta-blocker therapy in other patient populations that often develop stable angina (e.g., patients with a recent MI or hypertension). The choice between a beta-blocker and CCB for an individual with stable angina probably will hinge on patient characteristics and the contraindications and adverse effects associated with the drugs (Table 2). For example, a beta-blocker is appropriate for a patient with a recent MI, but an NDHP CCB may be preferred for a patient with COPD and no history of MI.

The choice of add-on therapy for a patient with inadequate control of angina episodes from a beta-blocker may depend on whether the patient has continued hypertension. A long-acting nitrate may be added if hypertension is absent, or a DHP CCB could be added if hypertension is present. Tachycardia associated with nitrates or DHP CCBs is attenuated by beta-blockers and NDHP CCBs.

Long-acting nitrates (e.g., nitroglycerin ointment and transdermal patches, isosorbide dinitrate, and isosorbide mononitrate extended-release tablets) dilate coronary arteries, which increase myocardial oxygen supply, and they decrease intramyocardial wall tension and MVO₂, although they may cause reflex tachycardia. Long-acting nitrates increase exercise tolerance and prevent or delay the onset of angina.

Long-acting nitrates should not be used as monotherapy in patients with stable angina because a 10- to 14-hour nitrate-free interval is needed on a daily basis to prevent the development of tolerance, which limits the efficacy of such therapy. The use of another antianginal agent in combination with the long-acting nitrate is needed to provide protection from ischemia during this nitrate-free interval. Ideally, a long-acting nitrate is added to a beta-blocker or NDHP CCB in a patient whose heart rate is at or near the goal of 55 to 60 beats per minute at rest. Long-acting nitrates also are beneficial for patients with heart failure.

### Table 2: Contraindications to Use of and Adverse Effects From Antianginal Drugs

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Contraindications</th>
<th>Adverse Effects</th>
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</thead>
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<tr>
<td>Beta-blockers</td>
<td>Bradycardia</td>
<td>Bradycardia</td>
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<tr>
<td></td>
<td>Hypotension</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Severe peripheral vascular disease</td>
<td>AV block</td>
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<tr>
<td></td>
<td>Signs of peripheral hyperfusion</td>
<td>Prolonged PR interval on the ECG</td>
</tr>
<tr>
<td></td>
<td>Prolonged PR interval on the ECG</td>
<td>Second- or third-degree AV block</td>
</tr>
<tr>
<td></td>
<td>Severe COPD</td>
<td>Severe COPD</td>
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<tr>
<td></td>
<td>History of asthma</td>
<td>History of asthma</td>
</tr>
<tr>
<td></td>
<td>Difficult-to-control insulin-dependent diabetes mellitus</td>
<td>Bradycardia</td>
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<tr>
<td>Calcium channel blockers</td>
<td>Moderate or severe LV failure</td>
<td>Hypotension</td>
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<tr>
<td></td>
<td>Second- or third-degree AV block</td>
<td>Pulmonary congestion</td>
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<td>Unstable angina and acute MI</td>
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<td>Hypotension</td>
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<td>Fluishing</td>
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<td></td>
<td>Reflex tachycardia</td>
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<tr>
<td></td>
<td></td>
<td>Contact dermatitis</td>
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<td>(from topical dosage forms)</td>
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AV = atrioventricular; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; LV = left ventricular; MI = myocardial infarction; RV = right ventricular.
Inflation of the balloon compresses the role of ACE inhibitors

Patients utilizing off-pump bypass with sternotomy can undergo multivessel bypass, but data on patients with left main disease and impaired LV function are limited. By reducing the need for cardiopulmonary bypass and preventing the need for clamping of the aorta, there is a significant reduction in adverse neurologic events, length of hospitalization, and cost.\textsuperscript{19}

Revascularization does not always eliminate angina episodes or the need for antianginal medications. In 1,205 patients with multivessel disease who underwent PCI or CABG in the hope of achieving angina relief, approximately 10\% to 20\% continued to experience angina and roughly 60\% to 80\% required antianginal medication 1 year after the procedure.\textsuperscript{20} In another group of 1,755 patients who underwent PCI for angina symptoms or acute MI, angina persisted 1 year after the intervention in 26\% of patients.\textsuperscript{21}

Role of ACE Inhibitors

ACE inhibitors have no effect on angina, but they may reduce the risk of MI and death in patients with stable angina.\textsuperscript{9} The results of studies of the use of ACE inhibitors in patients with CAD are somewhat controversial. Several, but not all, studies demonstrated a reduction in morbidity and mortality, especially in patients with heart failure, DM, or a previous MI.\textsuperscript{9, 21-24} Therefore, ACE inhibitors have a role in the management of stable angina despite their lack of an impact on angina episodes. However, the use of ACE inhibitors may be limited by hypotension from antianginal drug therapies or may limit the ability to use certain antianginal drug therapies for the same reason.

Conclusion

Patients with chronic stable angina make up a significant portion of patients with CAD. The goals of therapy in these patients consist of reducing angina symptoms and prolonging life. Current medical therapy with the use of beta-blockers, CCBs, and nitrates has been shown to improve angina symptoms, but not reduce mortality. Proper patient evaluation and screening will aid in appropriate antianginal medication selection for each individual. When used in appropriate situations, revascularization can improve angina control compared with medical therapy alone. Regardless if a medical and/or revascularization approach is utilized, patients require aggressive risk-factor reduction against smoking, hypertension, and hyperlipidemia. The pharmacist must play a key role in not only recommending and monitoring the prescribed therapy but also in educating patients.

DISCLOSURES

This article is based on a presentation given by the author at a symposium titled “Emerging Therapies for Management of Patients with Stable Angina: Focus on Clinical Efficacy and Outcomes” at the Academy of Managed Care Pharmacy’s 18th Annual Meeting and Showcase in Seattle, Washington, on April 5, 2006. The symposium was supported through an educational grant from CV Therapeutics, Inc. The author received an honorarium from CV Therapeutics, Inc. for participation in the symposium. He discloses no potential bias or conflict of interest relating to this article.

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Stable Angina: Current State of Disease Management


Advances in the Management of Stable Angina

TOBY C. TRUJILLO, PharmD, BCPS

ABSTRACT

OBJECTIVE: To describe the approved uses, pharmacology, pharmacodynamics, pharmacokinetics, efficacy, safety, and place in therapy of ranolazine, the first new antianginal drug therapy introduced in more than 20 years for the treatment of chronic angina.

SUMMARY: The mechanism of action of ranolazine is unknown, but it may involve inhibition of the late sodium current in the myocardium, thereby preventing sodium-induced intracellular calcium overload during ischemia. This mechanism differs from that of other antianginal agents, which primarily affect myocardial oxygen supply or demand through hemodynamic effects. Ranolazine undergoes extensive metabolism, primarily by cytochrome P-450 (CYP) 3A4, so interactions with drugs that are moderate to potent inhibitors of CYP3A4 need to be considered. Ranolazine is also a P-glycoprotein (P-gp) substrate and inhibitor, and it may interact with other P-gp substrates and inhibitors. In patients with an inadequate response to other antianginal agents, the addition of ranolazine to existing antianginal therapy increases exercise duration and the time to angina on an exercise treadmill test, and it decreases the frequency of angina attacks and nitroglycerin use. The drug produces antianginal effects without significantly affecting either heart rate or blood pressure. Ranolazine prolongs the QT interval on the electrocardiogram, but the overall electrophysiologic effects of the drug suggest that it is not expected to cause torsades de pointes.

CONCLUSION: Ranolazine has a unique mechanism of action that may be complementary to that of conventional antianginal agents in the treatment of chronic angina. An understanding of the potential for drug interactions, disease interactions, and contraindications is needed to ensure safe and effective use of the drug.

KEYWORDS: Drug interactions, Electrophysiologic effects, Pharmacotherapy, Ranolazine, Stable angina

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Despite documented efficacy in reducing the burden of angina, conventional antianginal agents (i.e., beta-blockers, calcium channel blockers, long-acting nitrates) are limited by contraindications (e.g., beta-blockers in asthma), as well as intolerance because of side effects or adverse hemodynamic manifestations. While revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) effectively reduces the number of anginal attacks, not all patients will receive complete relief. In addition, many patients are not candidates for revascularization therapy even when they experience continued anginal attacks while on aggressive medical therapy with conventional antianginal agents. Given the limitations with current treatment options for angina, there is a clear need for new therapies, particularly therapies without the limitations of conventional antianginal medications. Ranolazine, the first new antianginal drug introduced in more than 20 years, appears to be such an agent.

Ranolazine was approved by the U.S. Food and Drug Administration (FDA) in January 2006 for the treatment of chronic angina in combination with amiodipine, beta-blockers, or nitrates.1 Ranolazine is not indicated for monotherapy at this time and should be reserved for patients with an inadequate response to other antianginal drugs.2 Ranolazine, available as 500 mg extended-release tablets, should be initiated at a dose of 500 mg twice daily and may be titrated up to 1,000 mg twice daily as needed based on clinical symptoms.3

Pharmacology

Conventional antianginal agents reduce myocardial oxygen demand, usually by decreasing heart rate and blood pressure or by increasing myocardial oxygen supply as a result of coronary vasodilation (see the preceding article by Dobesh in this supplement). Unlike most other antianginal agents, the antianginal effect of ranolazine does not depend on a reduction in heart rate or blood pressure.1,2

While it is established that ranolazine does not significantly affect hemodynamics, recent work has potentially identified its mechanism of action. In the past, ranolazine was thought to maintain myocardial function during ischemia by inhibiting fatty acid oxidation and shifting myocardial energy production from fatty acid oxidation to glucose oxidation, which produces a higher amount of adenosine triphosphate per oxygen molecule consumed.1,4 However, these effects are observed only at plasma concentrations that far exceed those achieved with doses used clinically. Therefore, at this time, metabolic modulation does not appear to play a significant role in the relief of angina by ranolazine.5,6 More recent clinical evidence indicates that the antianginal effect of ranolazine may involve an electrophysiologic mechanism. Depolarization of myocardial cell membranes is initiated by the rapid influx of sodium ions into the myocardial cell through

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sodium channel openings.\(^1\) Within milliseconds of this rapid influx of sodium into the cell, sodium channels are rapidly inactivated through a gating mechanism. However, under normal conditions, a certain percentage of sodium channels fail to inactivate, resulting in a small but detectable late sodium current during the plateau phase of the action potential. Recent investigations indicate that this late sodium current is augmented in pathologic conditions such as ischemia or heart failure. This increase in intracellular sodium ultimately results in an increase in intracellular calcium, likely through the reverse mode of the sodium-calcium exchanger. Elevated intracellular calcium results in myocardial dysfunction, as well as increased left ventricular diastolic wall stiffness (i.e., increased myocardial oxygen demand). Additionally, elevated wall tension causes extravascular compression of coronary vessels, which may decrease oxygen supply to the myocardium. These effects may create a cycle of progressively worsening ischemia.\(^1,3\)

Recent animal studies have identified that, at clinically relevant plasma concentrations, ranolazine selectively inhibits late sodium entry into the cell without significantly affecting the rapid upstroke of sodium at the onset of the action potential.\(^2,5\) Consequently, ranolazine would be expected to prevent consequences of ischemia, such as myocardial dysfunction, elevated wall tension, and reduced oxygen supply. In fact, based on this proposed mechanism, ranolazine would be expected to produce greater clinical benefit in patients with more severe or frequent angina. It is important to note that conventional antianginal agents work to prevent myocardial ischemia from developing through restoration of the balance between myocardial oxygen supply and demand.\(^6\) Because ranolazine would be expected to prevent the consequences of ischemia once it develops, the drug should be an effective complement to conventional antianginal agents in treating patients with chronic stable angina.

### Pharmacokinetics

Ranolazine is rapidly and extensively metabolized in the intestine and liver, and its absorption is variable.\(^1\) Peak plasma concentrations of ranolazine are reached 2 to 5 hours after oral administration of the extended-release formulation.\(^1\) The bioavailability of extended-release tablets is 76% compared with oral ranolazine solution.\(^1\) Food does not have a clinically important effect on the peak plasma concentration or area under the plasma concentration-time curve (AUC) of ranolazine.\(^1\) Therefore, the drug may be taken with or without meals.

The apparent terminal half-life of ranolazine is 7 hours.\(^1,7\) Steady-state ranolazine plasma concentrations are achieved within 3 days of twice-daily dosing with the extended-release preparation.\(^1\) The peak-to-trough ranolazine plasma concentration ratio is 1.6 to 3.0, suggesting that the drug will produce relatively consistent therapeutic effects throughout the dosing interval.\(^1\) At steady-state and therapeutic dosages, the relationship between dosage and both peak plasma concentration and AUC is nearly linear, but these pharmacokinetic measures increase slightly more than proportionally to the dosage.\(^1\) Ranolazine is approximately 62% bound to plasma proteins (primarily \(\alpha\)-acid glycoprotein) at therapeutic plasma concentrations.\(^1,7\)

Ranolazine undergoes extensive metabolism in the liver and intestine, with less than 5% of an oral dose excreted unchanged in the urine and feces.\(^1\) After a single oral dose of ranolazine oral solution, approximately 75% of the dose was excreted in the urine and 25% was excreted in the feces.\(^1\) Ranolazine is metabolized primarily by cytochrome P-450 (CYP) 3A4 and to a lesser extent (10% to 15% of a given dose) by CYP2D6.\(^1,2,7,8\) It is unknown whether the metabolites of ranolazine are pharmacologically active.\(^1\)

### Clinical Trials

Initial studies with ranolazine utilized an immediate-release formulation dosed 3 times a day. While these studies did produce favorable results for ranolazine in terms of increasing exercise tolerance at peak concentrations, the peak-to-trough ratio was unfavorable. Subsequently, the efficacy of the extended-release formulation of ranolazine in the treatment of patients with chronic stable angina was demonstrated in 3 pivotal phase 3 clinical trials. Participants in these studies were primarily white, mostly male, with an average age between 60 and 65 years. As would be expected of patients with chronic stable angina, many patients had a history of diabetes mellitus, heart failure, hypertension, myocardial infarction (MI), and PCI or CABG.\(^1,2,9,10,12\)

### Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) Study

The MARISA study was a randomized, double-blind, placebo-controlled, 4-period crossover study of 191 adults with coronary artery disease (CAD) and angina.\(^9\) Patients were eligible for the study if they had at least a 3-month history of stable angina that responded to either beta-blockers, calcium channel blockers, or long-acting nitrates. Upon discontinuation of their current antianginal medications, patients were enrolled if they developed exercise-limiting angina or electrocardiogram (ECG) changes indicative of ischemia on 2 exercise treadmill tests. Patients were randomly assigned to receive extended-release ranolazine 500 mg, 1,000 mg, 1,500 mg, or placebo orally twice daily for 1 week (ranolazine monotherapy is not approved by the FDA, but it was used in this study). Overall, the study had 4 treatment periods, with each patient crossing over to each treatment arm in a random fashion. At the end of each week of treatment, exercise treadmill testing was performed at 4 hours and 12 hours after drug administration, times that correspond to peak and trough ranolazine plasma concentrations.

The average patient was aged 64 years, 73% of the patients were male, and 91% of patients were white.\(^9\) The primary efficacy analysis included 175 patients who completed 3 of the 4 treatment periods. At both times corresponding to trough and peak plasma ranolazine concentrations, all 3 ranolazine dosages
The CARISA study was a randomized, double-blind, placebo-controlled, parallel-group trial of 823 adults with symptomatic chronic angina despite treatment with conventional antianginal drug therapy. Eligibility and enrollment criteria were similar to the MARISA study except that patients in the CARISA study were allowed to continue on monotherapy with fixed doses of atenolol 50 mg/day, amlodipine 5 mg/day, or extended-release diltiazem 180 mg/day. Patients were randomly assigned to receive extended-release ranolazine 750 mg or 1,000 mg or placebo orally twice daily as add-on therapy for 12 weeks. Sublingual nitroglycerin was allowed. Exercise treadmill testing was performed 4 hours after drug administration after 2 weeks and 12 weeks of treatment, and 12 hours after drug administration after 2 weeks, 6 weeks, and 12 weeks of treatment.

The average patient was aged 64 years, and roughly 3 out of 4 patients were male. After 2 weeks of treatment, the exercise duration and time to angina were significantly increased by both ranolazine dosages compared with placebo at the times corresponding to both peak and trough plasma drug concentrations. The time to 1 mm ST-segment depression on the ECG was significantly increased by both ranolazine dosages compared with placebo only at the time of peak plasma drug concentration (Table 2). All improvements were sustained over the 12 weeks of therapy.

At the time of trough plasma ranolazine concentrations, the average exercise duration was 24 seconds longer with both ranolazine dosages than with placebo, and the average time to angina was 26 to 30 seconds longer with ranolazine than with placebo. The magnitude of increase in exercise duration or time to angina is comparable with those observed in studies of conventional antianginal agents, although studies directly comparing ranolazine with conventional agents are needed.

Ranolazine also demonstrated benefits in other clinical end points. At baseline, the average number of angina attacks per week was 4.5. After 12 weeks of treatment, the frequency of angina was reduced to a significantly greater extent by both ranolazine dosages than by placebo. The average number of attacks per week was 3.3 in the placebo group, 2.5 in the ranolazine 750 mg twice-daily group, and 2.1 in the ranolazine 1,000 mg twice-daily group after 12 weeks of treatment. The average number of sublingual nitroglycerin doses used per week after 12 weeks of treatment also was significantly lower in both ranolazine groups (2.1 with 750 mg twice daily and 1.8 with 1,000 mg twice daily) compared with the placebo group (3.1).
Ranolazine demonstrated minimal effects on blood pressure and heart rate. Dose-related adverse effects from ranolazine were similar to those reported in the MARISA study. Tolerance to ranolazine did not develop during the 12 weeks of treatment. Long-term survival rates in patients continuing ranolazine in an open-label extension of the CARISA study were similar to those reported in the open-label extension of the MARISA study. The survival rate was 98.4% in 480 patients who continued taking ranolazine for 1 year and 95.9% in 173 patients who continued the drug for 2 years.

Efficacy of Ranolazine in Chronic Angina (ERICA) Study

The multicenter, randomized, placebo-controlled, parallel-group ERICA study involved 565 patients with chronic angina. After a 2-week qualifying phase in which an oral placebo was given twice daily along with amlodipine 10 mg/day (the maximum recommended dosage for treating angina), patients with 3 or more anginal attacks per week were randomly assigned to receive extended-release ranolazine 500 mg or placebo orally twice daily for 1 week, followed by titration to ranolazine 1,000 mg or placebo twice daily as tolerated over the subsequent 6-week double-blind treatment phase. Patients randomized to placebo for the first week received placebo for the subsequent 6 weeks (i.e., there was no crossover between treatments). Amlodipine was continued throughout the study in both treatment groups. Sublingual nitroglycerin was used as needed to treat angina episodes. Long-acting nitrates were used in conjunction with amlodipine in 43% of patients randomized to placebo, and 46% of patients randomized to ranolazine therapy.

The characteristics of the 2 treatment groups (ranolazine and placebo) were similar at baseline. The mean age was 62 years, 72% of patients were male, and 99% were white. Most patients (89%) had hypertension, 80% had a history of MI, 51% had congestive heart failure, 23% were current smokers, and 19% had diabetes mellitus. The average frequency of angina attacks (5.6 attacks per week) and nitroglycerin consumption (4.6 times per week) were similar in the 2 groups despite the use of amlodipine in all patients and long-acting nitrates in nearly half of patients.

At the end of the 6-week treatment phase, the average weekly number of angina attacks had decreased to a significantly greater extent in the ranolazine group (to 2.88) than in the placebo group (to 3.31). A significantly greater decrease in the average number of times weekly that nitroglycerin was used also was observed in the ranolazine group (to 2.03) than in the placebo group (to 2.68). These effects appeared consistent regardless of patient age (less than 65 years versus 65 years or older) and use of long-acting nitrates. Stratification of the angina frequency and nitroglycerin use data by baseline angina severity revealed that ranolazine had a greater impact in patients with more angina attacks at baseline.

Similar to previous trial experience, ranolazine was well tolerated in the ERICA study, with most adverse effects classified as mild or moderate in severity. The most common increase in adverse effects with ranolazine compared with placebo were constipation (8.9% versus 1.8%), dizziness (3.9% versus 2.5%), nausea (2.8% versus 0.7%), and headache (2.8% versus 2.5%). There were no significant changes from baseline in supine or standing systolic or diastolic blood pressure or heart rate measurements in either treatment group.

Safety

More than 3,300 patients received ranolazine in clinical trials, including nearly 1,200 patients who received the drug in the 3 pivotal phase 3 clinical trials, for a total of 2,710 patient-years of exposure to the drug. In open-label study extensions, 639 patients were exposed to ranolazine for more than 1 year, 578 patients were exposed to the drug for more than 2 years, and 372 patients were exposed for more than 3 years.

While the effect of ranolazine on long-term mortality is not known and is the focus of ongoing studies, currently available information does not demonstrate an adverse effect on mortality from the drug. In the CARISA study, the longest of the 3 pivotal phase 3 studies, 3 (1%) of 269 placebo-treated patients, 2 (0.7%) of 279 patients in the ranolazine 750 mg twice-daily group, and 1 (0.4%) of 275 patients in the ranolazine 1,000 mg twice-daily group died during the study. Previously reported survival data from the open-label portions of the MARISA and CARISA studies also suggest that ranolazine does not have an adverse effect on survival. In controlled studies, the rate of discontinuation of the study drug because of adverse effects was 6% with ranolazine and 3% with placebo.

Disease and Drug Interactions

Ranolazine interactions with various diseases and drugs are well characterized. Mild, moderate, and severe hepatic impairment (Child-Pugh classes A, B, and C) are contraindications to the use of extended-release ranolazine. The plasma concentrations of ranolazine were increased 1.3- and 1.6-fold in patients with mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment, respectively, compared with healthy volunteers.

Renal impairment is not a contraindication to the use of extended-release ranolazine. Nevertheless, the drug should be used with caution in this patient population, especially patients with severe renal impairment. The pharmacokinetics of extended-release ranolazine (an 875 mg loading dose followed by four 500 mg doses every 12 hours) were evaluated in 8 healthy subjects and 21 subjects with mild-to-severe renal impairment. At steady state, the ranolazine AUC for the 12-hour period after drug administration was increased by 72%, 80%, and 97% in subjects with mild, moderate, and severe renal impairment, respectively, compared with the healthy subjects. Since plasma concentrations of ranolazine may increase by 50% in patients with varying degrees of renal impairment, careful assessment of patient response and tolerability should take place prior to dose titration, and 500 mg twice daily may represent the maximum dose that...
Ranolazine has been shown to increase plasma concentrations of simvastatin 80 mg/day when used concurrently. Coadministration of extended-release ranolazine 1,000 mg twice daily and simvastatin 80 mg/day was used concomitantly.

Steady-state ranolazine plasma concentrations were increased 1.2-fold when 20 mg/day of paroxetine, a potent CYP2D6 inhibitor, and extended-release ranolazine 1,000 mg twice daily were used simultaneously. However, no adjustment in extended-release ranolazine dosage is required when the drug is used with paroxetine or other CYP2D6 inhibitors because CYP2D6 plays a limited role in ranolazine metabolism. However, ranolazine may inhibit the activity of CYP2D6 and the metabolism of certain other drugs (e.g., tricyclic antidepressants, some antipsychotic agents) by this isoenzyme. Although ranolazine can also inhibit CYP3A4, ranolazine and its most abundant metabolites are not known to inhibit the metabolism of substrates for CYP1A2, 2C9, 2C19, or 2E1.

### QT Interval Prolongation

Ranolazine is contraindicated in patients receiving drugs that prolong the QT interval on the ECG, including class Ia antiarrhythmic agents (e.g., quinidine), class III antiarrhythmic agents (dofetilide, sotalol), erythromycin, and certain antipsychotic agents (e.g., thioridazine, ziprasidone), and in patients with preexisting QT interval prolongation. Ranolazine has been shown to prolong the QT interval corrected for heart rate (QTc) in a dose- and plasma-concentration-related manner. Several agents that cause QT prolongation have been associated with proarrhythmia, specifically torsades de pointes, and sudden cardiac death. The relationship between QT prolongation and proarrhythmia has not been studied in patients receiving ranolazine, but the possibility of additive prolongation of the QT interval and a higher incidence of proarrhythmia should be considered when ranolazine is used in a patient who has preexisting QT interval prolongation, is receiving another drug that prolongs the QT interval, or has an elevated risk for torsades de pointes (e.g., uncorrected hypokalemia or hypomagnesemia).
A baseline ECG should be obtained before initiating ranolazine.

The relationship between change in QTc interval and ranolazine plasma concentration is well established. At ranolazine plasma concentrations up to 4 times higher than those associated with the maximum recommended dosage, the relationship is linear with a slope of about 2.6 msec per 1,000 ng/mL. The slope is steeper in patients with hepatic impairment, with 3-fold greater increases in QTc interval prolongation for each increment in plasma concentration compared with patients without hepatic impairment. In patients without hepatic impairment, the average QTc interval prolongation is 6 msec at the maximum recommended dosage, although a prolongation of at least 15 msec has been observed in the 5% of the population with the highest plasma concentrations.

Drugs that produce QT prolongation immediately raise concern in clinicians that the risk of proarrhythmia may be increased. However, it is well established that not every agent that produces QT prolongation is associated with an elevated risk for proarrhythmia. Although torsades de pointes is associated with some drugs that prolong the QT interval (e.g., dofetilide), the incidence of torsades de pointes is low in patients treated with other drugs that cause QT interval prolongation (e.g., amiodarone). Thus, a better surrogate measure of the proarrhythmic potential of drug therapies is needed.

Recent work indicates that prolongation of repolarization (as observed by an increased QT interval) alone is not sufficient to increase the risk of proarrhythmia, specifically in this case torsades de pointes. However, risk for torsades is increased when QT prolongation is accompanied by an increase in early after-depolarizations (EADs) and increased dispersion of repolarization (Figure 1). The risk of EADs increases as the action potential duration increases. EADs can produce ectopic beats and extrasystoles, serving as the trigger to initiate and then perpetuate torsades de pointes. Dispersion of repolarization refers to the spatial variability among different parts of the ventricular wall (i.e., the endocardium, midmyocardium, and epicardium) in the time to repolarization (i.e., refactoriness). The dispersion is the difference between the longest action potential duration and the shortest action potential duration in different areas. An increase in the dispersion of repolarization can be viewed at the necessary substrate for proarrhythmia, setting the stage for reentry (i.e., abnormal cardiac impulse conduction). Certain class III antiarrhythmic agents associated with an increased incidence of torsades de pointes increase the action potential duration in all parts of the ventricular wall, but they increase it to a much greater extent in the midmyocardium, thereby increasing the dispersion of repolarization. Since QT prolongation must be accompanied by an increase in EADs, as well as an increase in the dispersion of repolarization throughout the myocardium, a more thorough assessment of the electrophysiologic effects of ranolazine is needed to predict the risk of proarrhythmia.

Animal work has demonstrated that ranolazine prolongs the action potential duration and the QT interval, but it suppresses EADs and reduces dispersion of repolarization. In addition, it was noted that ranolazine suppresses the proarrhythmic effects of some drugs that prolong the QT interval (e.g., d-sotalol). Overall, it appears that the electrophysiologic effects of ranolazine are similar to those of amiodarone, which is associated with a very low incidence of proarrhythmia and torsades de pointes. Because the cellular electrophysiology underlying the effect of ranolazine on the QT interval is fundamentally different from that of drugs known to cause torsades de pointes, ranolazine is not expected to cause torsades de pointes. To date, no cases have been reported in clinical trials with ranolazine. However, adequate post-marketing surveillance will likely be necessary to adequately define the proarrhythmic potential of the agent.

### Place in Therapy

Ranolazine therapy appears to be useful as add-on therapy in patients with extensive CAD and angina that is not controlled with conventional antianginal agents. Ranolazine may be particularly beneficial for the subset of patients who are not candidates for revascularization and remain symptomatic despite the use of maximum dosages of multiple antianginal agents, or have hemodynamic limitations that preclude initiation or titration to optimal dosages of conventional antianginal agents. As with all drug therapies, the risks associated with ranolazine use (e.g., potential for drug interactions) need to be considered before initiating therapy.

Additional clinical experience will help clarify the place in therapy for ranolazine. The long-term efficacy and safety of ranolazine treatment for up to 12 months will be evaluated in approximately 5,500 patients with non-ST elevation acute coronary syndromes treated with standard therapy in the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes study (also referred to as MERLIN-TIMI 36). This phase 3, international, randomized, double-blind, placebo-controlled, parallel-group study began in October 2004. The primary end point is the time to first occurrence of any element of the composite of cardiovascular death, MI, or recurrent ischemia. Additional end points include exercise tolerance test performance, quality of life, and pharmacoeconomic benefit.

### Conclusion

Ranolazine has a unique mechanism of action that may be complementary to that of conventional antianginal agents. Ranolazine, when added to conventional antianginal therapy, is effective for the treatment of chronic angina. Ongoing studies will better define the effect of ranolazine on hard outcomes such as mortality, as well as its place in therapy in the treatment of patients throughout the spectrum of CAD. Despite the drug’s proven benefit, providers will need to be familiar with the potential for drug interactions, disease interactions, and defined contraindia-
tions in order to use the medication in the safest manner possible. Although ranolazine can prolong the QT interval, it is not expected to cause proarrhythmia because of its overall electrophysiologic effects.

DISCLOSURES
This article is based on a presentation given by the author at a symposium entitled “Emerging Therapies for Management of Patients with Stable Angina: Focus on Clinical Efficacy and Outcomes” at the Academy of Managed Care Pharmacy’s 18th Annual Meeting and Showcase in Seattle, Washington, on April 5, 2006. The symposium was supported through an educational grant from CV Therapeutics, Inc. The author received an honorarium from CV Therapeutics, Inc. for participation in the symposium. He has served as a consultant for CV Therapeutics, Inc.

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Chronic stable angina limits daily activities and has an adverse impact on quality of life despite the availability of a variety of therapeutic modalities. One in 3 previously employed patients is unable to return to work within 1 year after revascularization.

Stable angina has a staggering societal and economic impact. In the United States, the annual direct and indirect costs of angina, including lost productivity and work days, are measured in tens of billions of dollars.

The direct costs of chronic stable angina from a societal perspective in the year 2000 were estimated by developing a cost-of-illness model based on medical utilization data from National Center for Health Statistics databases, national average Medicare reimbursement rates, International Classification of Diseases, Ninth Revision (ICD-9) codes, and databases of medications valued at average wholesale revenues. Because angina is a manifestation of coronary artery disease (CAD) and estimates based on the ICD-9 code for CAD might overestimate costs but estimates based on the ICD-9 code for narrowly defined chronic angina (NCA) might underestimate costs, a range of estimates was calculated. The lower end of this range was based on the ICD-9 code for NCA, and the upper end of the range was based on the ICD-9 code for CAD. The true cost of chronic angina is thought to lie between the lower and upper ends of this range. Because chronic angina is not always the primary diagnosis and limiting the analysis to primary diagnoses might underestimate costs, separate estimates were made for NCA and CAD when they were listed as any diagnosis as well as when they were the primary diagnosis. Medicare reimbursement rates were used because they are readily available, most patients with angina and CAD are elderly, and Medicare is the primary payer for this age group.

The total direct cost of illness was conservatively estimated at $1.8 million for NCA as a primary diagnosis, with $8.9 million for NCA as any diagnosis. Less conservative estimates of $33 million and $75 million were made for the total direct cost of illness when CAD was the primary diagnosis and CAD was listed as any diagnosis, respectively. The largest components of the direct costs of NCA as the primary diagnosis were outpatient visits (38%), hospitalizations (16%), and prescription medications (15%). By contrast, the largest components of the direct costs of CAD as the primary diagnosis were hospitalizations (74%), nursing home stays (22%), and outpatient visits (10%). Hospitalizations contributed a much larger portion to the direct costs of CAD as a primary diagnosis than NCA as a primary diagnosis (74% versus 16%) largely because of the expense of revascularization and treatment of acute myocardial infarction (MI). The average cost of hospitalization per utilization ranged from $3,744 for NCA as a primary diagnosis to $12,024 for CAD as a primary diagnosis.
Estimates by the Health Care Financing Administration (now the Centers for Medicare & Medicaid Services) of the total health care expenditures for CAD ranged from $54 billion to $105 billion (adjusted for 2000 dollars). Another estimate of the total direct expenditures for heart disease in the United States was $71 billion (adjusted for 2000 dollars). The cost of hospitalization was the largest component, accounting for roughly 60% to 75% of these totals. It includes medications and all other therapies provided during a hospital stay.

Revascularization

The use of coronary revascularization (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) has increased markedly in recent years. In 2003, an estimated 664,000 PCI procedures and 467,000 CABG surgeries were performed in the United States at a mean charge of $38,203 and $83,919, respectively. Extrapolation of these figures suggests a total direct cost for revascularization in excess of $64 billion in 2003. The number of PCI procedures increased 326% between 1987 and 2003. PCI is now more commonly performed than CABG. In 2003, 84% of patients undergoing coronary angioplasty received a stent, and the rate of coronary stent insertion increased 147% between 1996 and 2000.

Single-Vessel Disease

In a 2004 review of several studies of the costs of revascularization published between 2000 and 2004, Nagle and Smith expressed the costs in 2003 dollars, which allows comparisons. In one study, the median cost of the initial hospitalization for PCI with planned stent insertion for coronary heart disease involving a single vessel was $10,452 in 2003 dollars. Another study compared the costs of routine stent implantation (i.e., primary stenting) with those of provisional stenting (i.e., the insertion of stents during balloon angioplasty only if the results of angioplasty were less than optimal) in patients with single-vessel disease. The mean cost of the initial hospitalization was higher ($11,694) for primary stenting than for provisional stenting ($10,681). However, the mean total cost after 6 months was lower ($12,925) for primary stenting than for provisional stenting ($13,285). The investigators concluded that primary stenting improved clinical outcomes at a cost comparable to or slightly less than that of provisional stenting in patients with single-vessel disease.

Multivessel Disease

The 2004 review by Nagle and Smith also compared the costs of PCI and CABG in 3 studies of patients with multivessel disease, in 2003 dollars. The costs of multivessel stenting in 100 patients and CABG in 200 patients who were followed for a median of 2.8 years were compared in a retrospective, matched cohort study. The mean initial hospitalization cost was significantly lower ($20,088 vs. $27,669), despite a significantly higher need for at least one repeat revascularization procedure in the multivessel stenting group.

Two other longer studies comparing the costs of PCI and CABG in patients with multivessel disease suggest that the cost gap between PCI and CABG narrows over time because of the need for repeat revascularization after PCI. In a randomized, controlled study, the mean initial hospitalization cost was $6,627 lower in patients undergoing PCI than in patients undergoing CABG. The difference between PCI and CABG in the mean total cost was $5,153 after 3 years, and it decreased to $2,605 after 8 years. In 2003 dollars, the mean total 8-year cost was $56,343 in the PCI group and $58,948 in the CABG group, a difference that is not significant.

The total lifetime costs for initial angioplasty with primary stenting, initial angioplasty with provisional stenting, CABG with primary stenting, CABG with provisional stenting, and CABG without stenting in patients with multivessel disease were modeled using data from a substudy of the Bypass Angioplasty Revascularization Investigation. The total lifetime costs were similar, ranging from $154,018 to $163,587 in 2003 dollars.

Drug-Eluting Stents

The initial treatment costs, follow-up costs, and total 1-year costs were compared in 1,058 patients with complex stenoses in a single coronary vessel who planned to undergo PCI and were randomly assigned to implantation of a drug-eluting stent or a bare-metal stent after PCI. The initial treatment cost was $2,856 per patient higher in the drug-eluting stent group compared with the bare-metal stent group, a difference that is significant. The economic impact, from a hospital perspective, over a 5-year period of a proposed change in Medicare reimbursement policy for drug-eluting stents and converting from bare-metal stents to drug-eluting stents was simulated by a computer model. An annual patient volume of 3,112 and the use of drug-eluting stents in 85% of stent implants during the first year were assumed in the model. In 2003 dollars, the model predicted a shift from a $2.01 million annual profit to a $5.41 million loss in the first year and a $6.38 million annual loss in subsequent years. Thus, more than $28 million in revenue would be diverted from the hospital over a 5-year period under the conditions of the model (i.e., adoption of the Medicare reimbursement policy for drug-eluting stents). The potential for loss of revenue may, in part, explain lower rates of use of drug-eluting stents in some hospitals than in others.
Justifying the Costs

In summary, both PCI and CABG are costly procedures. The costs of PCI for single-vessel disease are less than the costs of PCI for multivessel disease. In patients with multivessel disease, the initial costs of PCI with or without stenting are lower than the initial costs of CABG, but the long-term costs of PCI and CABG are similar. Drug-eluting stents have the potential to greatly affect the economics of revascularization, but additional data are needed to quantify the impact.

The long-term benefits of PCI and CABG are unclear and controversial. Although short-term improvements in anginal symptoms and quality of life have been demonstrated with revascularization, these improvements may subside over time. Twenty-three percent of patients undergoing PCI or CABG report their health as poor or fair 5 years after the procedure.

Comparison with Medical Management

Evidence suggests that revascularization often is considered before medical therapy has been given an adequate trial. Guidelines of the American College of Cardiology and American Heart Association for the treatment of chronic stable angina call for the use of medical therapy unless contraindicated before considering revascularization (see the article by Trujillo in this supplement).

Meta-Analysis

A meta-analysis of 11 randomized trials comparing PCI with conservative medical treatment in a total of 2,950 patients with stable CAD found no significant difference between the 2 groups in mortality (n = 95 vs. n = 101, respectively), a composite of cardiac death or MI (n = 126 vs. n = 109, respectively), nonfatal MI (n = 87 vs. n = 66, respectively), the need for CABG (n = 109 vs. n = 106, respectively), or the need for PCI during follow-up (n = 219 vs. n = 243, respectively). There was an increase in relative risk of nonfatal MI by approximately 30% in the PCI group compared with the conservative medical treatment group, largely related to the PCI procedure. The difference between the 2 groups was not significant. A possible survival benefit was seen for PCI in trials of patients with a recent MI. Thus, in the absence of a recent MI, PCI did not offer any benefit in terms of reduced risk of death, MI, or need for repeat revascularization compared with conservative medical treatment.

Randomized Intervention Treatment of Angina (RITA-2)

The costs of PCI and medical management were compared in several studies. In the second, the RITA-2 trial, 1,018 patients with stable CAD were randomly assigned to undergo PCI or receive continued medical management. Health service resource use data were collected prospectively over a 3-year follow-up period.

At the end of the 3 years, the incidence of the composite end point of death or MI was significantly higher (P=0.025) in the PCI group (7.3%) than in the medical management group (4.1%), largely due to procedure-related nonfatal MI. The incidence of grade 2 or worse angina was significantly lower (P <0.001) in the PCI group (17%) than in the medical management group (27%) after 1 year of follow up, but there was no significant difference (P=0.43) between the 2 groups in this end point after 3 years of follow up (20% versus 22%, respectively).

After the initial treatment strategy in the RITA-2 study, the number of subsequent PCI procedures was higher in the medical management group than in the PCI group (118 PCI procedures in 102 patients in the medical management group versus 73 PCI procedures in 62 patients in the PCI group), but the number of coronary angiograms was higher in the PCI group than in the medical management group (171 coronary angiogram procedures in 131 patients in the PCI group versus 110 coronary angiogram procedures in 93 patients in the medical management group). The number of CABG procedures was similar in the 2 groups (37 CABG procedures in 37 patients in the medical management group and 38 CABG procedures in 37 patients in the PCI group). As expected, the use of antianginal medications (beta-blockers, calcium channel blockers, and long-acting nitrates) was higher in the medical management group than in the PCI group. The use of community-based resources (general practitioner visits, district nurse visits, and trial research assistants) was similar in the 2 groups.

The average hospital unit cost, which includes medical and nursing staff, standard procedure-related drugs and anesthetics, equipment, consumables, and overhead, was nearly twice as high in the PCI group as in the medical management group. The
difference between the total costs of the 2 therapeutic approaches did not diminish over time (Figure 1). The cost of PCI as an initial strategy exceeded the cost of medical management as an initial strategy by 74% over 3 years.

Medical, Angioplasty, or Surgery Study (MASS-II)
The clinical outcomes and effective costs of medical management, PCI with stenting, and CABG were compared after 1 year in the MASS-II, a randomized study of 611 patients with multivessel CAD and preserved left ventricular function.23 The baseline characteristics of the 3 treatment groups were similar, except for a higher incidence of previous acute MI in the PCI plus stenting group than in the other 2 groups and a higher incidence of class III or IV angina pectoris in the CABG group than in the other 2 groups.

The incidence of death during 1 year of follow-up was similar in the 3 groups: 1.9% with medical management, 4.4% with PCI plus stenting, and 3.9% with CABG.24 However, significantly larger percentages (P < 0.0001) of patients in the PCI plus stenting group (79%) and CABG group (88%) remained angina-free after 1 year than patients in the medical management group (49%). The need for angioplasty was significantly higher (P = 0.0003) in the PCI plus stenting group (8.3%) than in the medical management group (3.5%) and the CABG group (0.5%). The average time to first event (acute MI, need for revascularization procedure, or death) was similar in the 3 groups: 4.6 months in the medical management group and PCI plus stenting group and 3.7 months in the CABG group.

The analysis of effective costs was performed taking into consideration clinical outcomes as well as the costs of treatment over a 1-year period.25 Expected costs, costs per event-free year of life gained from treatment, and costs per angina- and event-free year of life gained from treatment were determined for all 3 interventions. The expected costs were lowest for medical management, higher for PCI plus stenting, and highest for CABG. The event-free cost of 1 year of life gained with medical management, PCI plus stenting, and CABG was $2,454, $10,348, and $12,404, respectively. The cost per angina- and event-free year of life gained from medical management, PCI plus stenting, and CABG was $5,006, $13,099, and $14,095, respectively. Thus, medical management presented the lowest cost but at the greatest increment increase. The effective costs of PCI plus stenting and CABG were similar when clinical outcomes were considered in the cost analysis. The most stable costs were presented by the CABG group.

Trial of Invasive Versus Medical Therapy in Elderly Patients With Chronic Angina (TIME) Study

In the TIME study, the costs and benefits of using either PCI or CABG were compared with those of medical therapy over a 1-year period in 188 elderly patients (aged 75 years or older) with chronic CAD and angina.26 The primary end point was quality of life and freedom from major adverse clinical events (death, nonfatal MI, or hospitalization for uncontrolled symptoms or acute coronary syndrome, with or without the need for revascularization).

The incidence of major adverse clinical events over the 1-year TIME study period was significantly lower (P < 0.0001) in the invasive therapy group (0.38 events per patient) than in the medical therapy group (1.0 event per patient).26 Angina severity decreased and quality of life improved from baseline in both treatment groups, with no significant differences between the 2 groups after 1 year.

The average cost was significantly higher (P < 0.0002) with invasive therapy than with medical therapy during the first 30 days, but the cost in the subsequent 11 months was significantly higher (P = 0.004) with medical therapy than with invasive therapy.26 The total cost over the 1-year study period was slightly lower in the medical therapy group compared with the invasive therapy group, but the difference was not significant (P = 0.08).

Analysis of the incremental cost to prevent a major adverse clinical event favors the use of invasive therapy instead of medical therapy in this patient population.26 However, little improvement in quality of life is associated with substitution of medical therapy with invasive therapy.

Conclusion

Chronic stable angina is associated with large direct and indirect costs, with a large share of the costs associated with hospitalization and revascularization. Revascularization is sometimes used without an adequate trial of medical management, despite higher costs and a lack of clear evidence of long-term clinical benefits.

DISCLOSURES

This article is based on a presentation given by the author at a symposium entitled “Emerging Therapies for Management of Patients with Stable Angina: Focus on Clinical Efficacy and Outcomes” at the Academy of Managed Care Pharmacy’s 18th Annual Meeting and Showcase in Seattle, Washington, on April 5, 2006. The symposium was supported through an educational grant from CV Therapeutics, Inc. The author received an honorarium from CV Therapeutics, Inc. for participation in the symposium. She discloses no potential bias or conflict of interest relating to this article.

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Managing Patients With Chronic Angina: Emerging Therapeutic Options for Improving Clinical Efficacy and Outcomes

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Posttest Worksheet: Managing Patients With Chronic Angina: Emerging Therapeutic Options for Improving Clinical Efficacy and Outcomes

1. Which of the following play a key role in the pathogenesis of stable angina?
   a. Large, unstable atherosclerotic plaques that decrease contractility and increase myocardial oxygen demand
   b. Large, stable atherosclerotic plaques that narrow coronary arteries and decrease myocardial oxygen supply
   c. Small, unstable atherosclerotic plaques that are prone to rupture, resulting in thrombosis
   d. Small, stable atherosclerotic plaques that increase intramyocardial wall tension and myocardial oxygen demand

2. Which of the following patient presentations is consistent with stable angina?
   a. Stabbing chest pain that is localized over the left lateral chest wall and lasts for several seconds
   b. Crushing chest pain that radiates to the forehead and lasts for several minutes
   c. Sharp chest pain that radiates to the back and lasts for several hours
   d. Chest pressure that radiates to the left shoulder and arm and lasts for several minutes

3. Which of the following is part of the PQRST mnemonic for assessment of chest pain in a patient with suspected stable angina and coronary heart disease?
   a. Frequency of pain
   b. Palliative measures
   c. Prolongation of the QT interval
   d. Time to ST segment depression

4. Which of the following drug therapies should be considered as an alternative to beta-blockers for initial antianginal drug therapy in patients with stable angina?
   a. Long-acting nitrates
   b. Dihydropyridine calcium channel blockers
   c. Nondihydropyridine calcium channel blockers
   d. Angiotensin-converting enzyme (ACE) inhibitors

5. Which of the following drug therapies should be added in a patient with stable angina and inadequate control of anginal episodes from a beta-blocker but no hypertension?
   a. A long-acting nitrate
   b. A dihydropyridine
   c. A nondihydropyridine
   d. An ACE inhibitor
6. Which of the following precludes the use of long-acting nitrates as monotherapy in patients with stable angina?
   a. The risk of reflex tachycardia
   b. The need for a daily nitrate-free interval
   c. The risk of atrioventricular block
   d. The risk of bronchospasm

7. The mechanism of action of ranolazine differs from that of other antianginal agents because ranolazine acts by
   a. inhibiting fatty acid oxidation.
   b. reducing heart rate and blood pressure.
   c. increasing early after-depolarizations (EADs).
   d. preventing sodium-induced calcium overload during ischemia.

8. The metabolism of ranolazine primarily involves
   a. cytochrome P-450 (CYP) 3A4.
   b. CYP2D6.
   c. CYP1A2.
   d. P-glycoprotein.

9. Which of the following was demonstrated with ranolazine treatment in the Efficacy of Ranolazine in Chronic Angina (ERICA) study?
   a. Decreases in exercise duration and time to angina
   b. Decreases in the frequency of angina attacks and nitroglycerin use
   c. Decreases in the time to angina and 1 mm ST segment depression
   d. Decreases in the frequency of angina attacks and beta-blocker use.

10. Which of the following drugs is contraindicated in patients receiving ranolazine because of the risk of an interaction?
   a. Cimetidine
   b. Theophylline
   c. Verapamil
   d. Warfarin

11. Which of the following disease states is a contraindication to the use of ranolazine?
   a. Renal impairment only if it is severe and requires hemodialysis
   b. Mild, moderate, and severe renal impairment
   c. Hepatic impairment only if it is severe (Child-Pugh class C)
   d. Mild, moderate, and severe hepatic impairment (Child-Pugh classes A, B, and C)

12. A drug-induced increase in dispersion of repolarization is important primarily because it can lead to
   a. thrombosis.
   b. tolerance to the therapeutic effect of the drug.
   c. torsades de pointes.
   d. intracellular calcium overload.

13. Ranolazine is not expected to cause torsades de pointes because
   a. it suppresses EADs and increases dispersion of repolarization.
   b. it suppresses EADs and decreases dispersion of repolarization.
   c. it increases EADs and decreases dispersion of repolarization.
   d. it does not prolong the action potential or QT interval.

14. Which of the following ranges corresponds to the direct costs of chronic stable angina from a societal perspective in the year 2000 estimated conservatively using a cost-of-illness model and ICD-9 codes for narrowly defined chronic angina as a primary diagnosis (lower end of the range) and as any diagnosis (upper end of the range)?
   a. $1.8 million to $8.9 million
   b. $33 million to $75 million
   c. $1.8 billion to $8.9 billion
   d. $33 billion to $75 billion

15. Which of the following is the largest component of the direct cost of coronary artery disease (CAD) when it is listed as the primary diagnosis?
   a. Hospitalizations
   b. Nursing home stays
   c. Outpatient visits
   d. Prescription medications

16. Which of the following trends in the use of coronary revascularization has been observed in the United States in recent years?
   a. The number of coronary artery bypass grafting (CABG) procedures has decreased dramatically, although CABG is still more commonly performed than percutaneous coronary intervention (PCI).
   b. The number of PCI procedures has increased dramatically, although CABG is still more commonly performed than PCI.
   c. The number of CABG procedures has increased dramatically, and CABG is now more commonly performed than PCI.
   d. The number of PCI procedures has increased dramatically, and PCI is now more commonly performed than CABG.
17. Which of the following statements about the initial treatment costs and follow-up costs of bare-metal stents and drug-eluting stents in patients with complex stenoses in a single coronary vessel is correct?
   a. The initial treatment cost and follow-up costs are lower with drug-eluting stents than with bare-metal stents because of volume discounts.
   b. The initial treatment cost is lower with drug-eluting stents than with bare-metal stents because of a lower rate of procedure-related nonfatal myocardial infarction (MI), but the follow-up cost is similar with drug-eluting and bare-metal stents.
   c. The initial treatment cost is higher with drug-eluting stents than with bare-metal stents, but the follow-up cost is lower with drug-eluting stents than bare-metal stents because of a lower need for repeat revascularization.
   d. The initial treatment cost and follow-up costs are higher with drug-eluting stents than with bare-metal stents because of patent protection for drug-eluting stents.

18. Which of the following statements about the comparative initial and long-term costs of PCI and CABG in patients with stable angina is correct?
   a. The initial costs for PCI are lower than those for CABG, but the long-term costs of PCI are higher than those for CABG.
   b. The initial costs for PCI are higher than those for CABG, but the long-term costs of PCI are lower than those for CABG.
   c. The initial costs for PCI are higher than those for CABG, but the long-term costs of PCI are similar to those for CABG.
   d. The initial costs for PCI are lower than those for CABG, but the long-term costs of PCI are similar to those for CABG.

19. Which of the following statements best summarizes the findings from the meta-analysis of 11 randomized trials comparing PCI with conservative medical treatment in patients with stable CAD?
   a. In the absence of a recent MI, PCI did not offer any benefit in terms of reduced risk of death, MI, or need for repeat revascularization compared with conservative medical treatment.
   b. In all patients, PCI significantly reduced the risk of death, MI, and need for repeat revascularization compared with conservative medical treatment.
   c. In the absence of a recent MI, PCI significantly reduced the risk of death, MI, and need for repeat revascularization compared with conservative medical treatment.
   d. In patients with a recent MI, PCI significantly increased the risk of death, MI, and need for repeat revascularization compared with conservative medical treatment.

20. Which of the following statements best summarizes the findings of the RITA-2 study comparing the costs of PCI and medical management over a 3-year period in patients with stable CAD?
   a. The initial costs were nearly twice as high with PCI as with medical management, but the cost gap narrowed over the 3-year period.
   b. The initial costs were nearly twice as high with medical management as with PCI, but the cost gap narrowed over the 3-year period.
   c. The initial costs were nearly twice as high with PCI as with medical management, and the cost gap did not diminish over the 3-year period.
   d. The initial costs were nearly twice as high with medical management as with PCI, and the cost gap did not diminish over the 3-year period.

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