regular exercise, along with the application of pharmacotherapies, if necessary.

Emerging Risk Factors for Atherosclerotic Vascular Disease: A Critical Review of the Evidence

Hackam DG, Anand SS.
JAMA. 2003;290:932-940.

This careful review of emerging or novel cardiac risk factors found that, after distilling the literature since 1990 (373 papers), 4 conventional risk factors had consistent relationships with cardiovascular disease. However, few data were available regarding the additive yield of screening for novel factors (high-sensitivity C-reactive protein [hs-CRP], fibrinogen, lipoprotein(a), homocysteine). Furthermore, randomized trials of individuals specifically treating these novel factors with available therapies are lacking. The authors concluded that the explanatory power of the conventional cardiovascular risk factors has been systematically underestimated—creating an artificial or exaggerated case for novel risk factors. The other major challenge is that each novel risk factor poses a validation dilemma. For example, lipoprotein(a) and fibrinogen do not have proven reduction therapies available. Homocysteine is typically only modestly elevated in a subset of the general population but markedly elevated in those with renal dysfunction, an independent risk state in its own right.[1] Lastly, hs-CRP is fraught with problems as an independent risk factor because it is heavily confounded by conventional risk factors such as obesity, sedentary lifestyle, and dyslipidemia. To make matters worse, interventions that have been proven to reduce cardiovascular risk such as aspirin, exercise, weight reduction, and lipid-lowering therapy all reduce levels of hs-CRP. So the critical issue with this risk factor, as measured in populations, is that those with low hs-CRP values have low cardiovascular event rates, probably due to their risk reducing strategies (particularly aspirin and statin use).[2] Because epidemiological studies of hs-CRP have not taken these factors into account, the relationship between hs-CRP and CHD may be entirely due to confounding and effect modification—much like the previously observed relationship between estrogens and CHD.

Collectively, these studies discount the traditional notion that 50% of cardiac events occur in patients with no cardiovascular risk factors. In fact, virtually all patients with cardiac events have modifiable or reversible risk factors. These risk factors largely have their origins in excess body fat and a sedentary lifestyle. Efforts to modify or reverse conventional risk factors should take priority over attempts to identify novel risk factors at this time. ■

References
1. McCullough PA. Why is chronic kidney disease the "spoiler" for cardiovascular outcomes? *J Am Coll Cardiol.* 2003;41(5):725-728.
2. McCullough PA. The antiinflammatory effects of statins. *N Engl J Med.* 2001;345(16):1209.

Angina Pectoris

Ranolazine: A New Drug and a New Paradigm for Management of Myocardial Ischemia and Angina

Reviewed by Prediman K. Shah, MD, FACC, FACP, FCCP
Division of Cardiology and Atherosclerosis Research Center, Cedars-Sinai Medical Center, Los Angeles, CA
[*Rev Cardiovasc Med.* 2004;5(3):186-188]

Recurrent symptomatic myocardial ischemia (angina pectoris) resulting from reduced coronary blood flow relative to myocardial oxygen requirements is a common manifestation of ischemic heart disease. Angina is frequently treated with interventions that reduce myocardial workload and/or improve myocardial blood flow, such as drugs (nitrates, ß-blockers, calcium channel blockers), risk-factor modification, and invasive revascularization with percutaneous coronary interventions or bypass surgery. A number of patients with ischemic heart disease continue to suffer from recurrent angina despite maximally tolerated medical therapy, and a certain proportion of them are unsuitable for invasive revascularization because of coronary anatomic considerations (eg, diffuse disease, small-caliber vessels, chronic total occlusions not amenable to or with failed attempts to revascularize) or very high-risk status. These patients, estimated to number approximately 26 million in the United States, have impaired quality of life and few viable options. Although a number of alternative approaches, such as

A new paradigm for treating myocardial ischemia has been introduced: the use of novel compounds to improve the metabolic efficiency of myocardium.

transmyocardial laser revascularization, angiogenic drug and gene therapy, enhanced external counterpulsation, and spinal cord electrical stimulation, have been introduced and tested, all of these options have produced inconsistent results in clinical trials. In recent years, a new paradigm for treating myocardial ischemia has been introduced: the use of novel compounds to improve the metabolic efficiency of myocardium without a direct effect on myocardial workload or perfusion. One such compound is ranolazine. Ranolazine is thought to partially inhibit myocardial fatty acid oxidation, leading to a reciprocal increase in glucose utilization; this results in greater adenosine triphosphate generation per mole of oxygen used, thereby delaying the development of myocardial ischemia.[1,2] In a monotherapy dose-escalating trial, ranolazine was shown to improve exercise tolerance and anginal frequency in a dose-dependent fashion; however, efficacy relative to standard antianginal therapy had not been demonstrated.[3]

Effects of Ranolazine with Atenolol, Amlodipine, or Diltiazem on Exercise Tolerance and Angina Frequency in Patients with Severe Chronic Angina: A Randomized Controlled Trial

Chaitman BR, Pepine CJ, Parker JO, et al.
JAMA. 2004:291:309–316.

In the most recent double-blind, placebo-controlled trial, CARISA (Combination Assessment of Ranolazine in Stable Angina), a group of investigators evaluated the efficacy of 2 different doses of sustained-release once daily ranolazine (750 mg and 1000 mg) in 823 patients with known coronary artery disease, recurrent stable angina, and reproducible exercise-induced ischemia 3–9 minutes into a standard electrocardiogram (ECG) stress test protocol. Patients received either placebo or 1 of the 2 ranolazine dosages for 12 weeks, and exercise testing was performed at 2 and 12 weeks after randomization. Eighty-six patients dropped out (32 before the 2-week evaluation and 54 before the 12-week evaluation), leaving 258 placebo-treated patients and 533 ranolazine-treated patients (272 taking the 750-mg dose and 261 the 1000-mg dose). All patients were receiving background therapy of atenolol 50 mg/day, amlodipine 5 mg/day, or diltiazem 180 mg/day.

Trial results are shown in Table 1. Compared with patients receiving placebo, ranolazine patients experienced a statistically significant increase in exercise duration and time to onset of angina, and a statistically nonsignificant increase in time to onset of ECG signs of ischemia. These effects were accompanied by a significant reduction in weekly anginal episodes and nitroglycerine consumption. There was no clear-cut dose response with ranolazine, and there was no adverse effect on mortality. The most frequent adverse effects with ranolazine included constipation, fatigue, and nausea. A modest increase in QTc interval was noted with ranolazine, but no ventricular arrhythmias were noted. However, 5 patients in the ranolazine group had unexplained syncope, with 4 of these patients taking concurrent diltiazem and all 5 taking angiotensin-converting enzyme (ACE) inhibitors.

Table 1
Effects of Ranolazine on Anginal and Exercise Parameters and Angina Frequency in Chronic Stable Angina Patients

	Placebo	Ranolazine 750 mg	Ranolazine 1000 mg
Change in exercise duration (s)	91.7	115.4	115.8
Difference from placebo		23.7	24
P value (vs placebo)		.03	.03
Change in time to angina onset (s)	114.3	144	140.3
Difference from placebo		29.7	26
P value (vs placebo)		.01	.03
Change in time to ECG ischemia (s)	125.1	145.1	146.2
Difference from placebo		19.9	21.1
P value (vs placebo)		.10	.09
Weekly anginal episodes	3.3	2.5	2.1
P value (vs placebo)		.006	<.001

Exercise test was performed 12 hours after dose (presumed trough of blood levels of ranolazine). Exercise was also performed 4 hours after dose (presumed peak drug levels after dose) and showed similar results that were marginally better than those observed 12 hours after the dose. ECG, electrocardiogram. Adapted from Chaitman et al.

Comment

Although this study provides important new information regarding a novel form of pharmacotherapy for management of recurrent angina, the overall magnitude of effect on markers of efficacy compared with placebo is relatively modest. In clinical practice, most patients with difficult-to-treat angina tend to be taking combination antianginal drugs (ß-blockers, calcium channel blockers, nitrates), which are then titrated to maximal tolerated doses. In the CARISA trial, the investigators used fixed doses of a ß-blocker or calcium channel blocker as background therapy. This creates uncertainty as to how effective ranolazine would have been against a background of maximally tolerated standard combination antianginal therapy. Although the drug seemed to be generally well tolerated, with no adverse impact on mortality, the relatively high frequency of syncope observed with ranolazine

indicates a potential problem that will require careful surveillance. Syncope might have resulted from hypotensive actions unmasked at high doses and in the presence of other vasodilating drugs (diltiazem, ACE inhibitors). Although the authors did not note any ventricular arrhythmias, and QTc prolongations were generally short, caution might be warranted regarding the potential for arrhythmogenesis. Not withstanding these limitations, ranolazine might emerge as a useful adjunct in the management of patients with symptomatic myocardial ischemia, especially when standard antianginal measures are ineffective or poorly tolerated. If the U.S. Food and Drug Administration approves this novel agent for clinical use, postmarketing surveillance for adverse effects would be strongly advised in view of the occurrence of the above-mentioned syncope. ■

References

1. McCormick JG, Barr RL, Wolff AA, Lopaschuk GD. Ranolazine stimulates glucose oxidation in normoxic, ischemic and reperfused ischemic rat hearts. *Circulation*. 1996;93:135–142.
2. Wolff AA, Rotmensch HH, Stanley WC, Ferrari R. Metabolic approaches to the treatment of ischemic heart disease: the clinician's perspective. *Heart Fail Rev*. 2002;7:187–203.
3. Chaitman BR, Skettino SL, Parker JO, for the Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) investigators. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with severe angina. *J Am Coll Cardiol*. In press.