Randomized Trials of Treatment for Chronic Stable Angina

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"A major problem . . . is the lack of sufficient data comparing antianginal and placebo treatment."[1] I would certainly agree with this statement, which was made five years ago, regarding the pharmacologic therapy of chronic stable angina pectoris. In the current era, in which we worship at the altar of "evidence-based medicine," it is somewhat sobering to note the relative lack of randomized control trials underpinning therapies for the common condition of chronic stable angina.

The cornerstones of anti-ischemic pharmacologic therapy in patients with chronic stable angina pectoris are the nitrates, β-blockers, and, as a second line therapy or in patients with contraindications to β-blockers, the calcium channel blockers. In addition, the angiotensin-converting-enzyme inhibitors and "statins" plus other aspects of risk-factor reduction play a key role, and it is possible that both classes of agents have additional anti-ischemic properties. Aspirin is strongly indicated in patients without contraindications.

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Nitrates

The efficacy of nitroglycerin in relieving symptoms is undisputed. The addition of long-acting nitrates is frequently utilized, but the objective is again symptomatic relief, and there is no evidence from randomized control trials that clinical outcomes are affected. No trials have been performed, nor are they being planned.

Beta-Blockers

Few would challenge the place of β-blockers in the therapeutic armamentarium of effort angina, and their pharmacologic actions make sense in this setting. The only placebo-controlled trial is the Atenolol Silent Ischemia Study (ASIST) trial, which demonstrated a benefit for atenolol over placebo in patients with mild effort angina or silent ischemia.[2] I agree with Opie that "the closer the patient is to an acute myocardial infarction, the stronger are the data for the safety of β-blockers and also for their efficacy."[3]

Combination Beta-Blocker and Calcium Channel Blocker Therapy

Combining these two agents provides the greatest antianginal efficacy in comparison with either drug alone, as shown in the International Multicenter Angina Exercise (IMAGE), Total Ischemic Burden Bisoprolol Study (TIBBS), and Circadian Anti-Ischemia Program in Europe (CAPE) trials, and the combination is safest in the case of the dihydropyridines.[4–6] A recent meta-analysis of 59 trials demonstrated no difference in cardiac death and myocardial infarction between β-blockers and calcium channel blockers, but the former were less likely to be discontinued because of adverse side effects, particularly so in the case of nifedipine.[7] Despite the lack of randomized, controlled trials on the role of nitrates and β-blockers in effort angina, their use together with the calcium channel blockers in selected patients is widely accepted on the basis of their pharmacologic profile and efficacy in reducing symptoms.

Given this current state of affairs and the plethora of trials of antiplatelet and antithrombotic agents in acute coronary syndromes, two randomized controlled trials of patients with effort angina that were presented at the recent American Heart Association meetings generated, not surprisingly, a great deal of interest.

The Impact of Nicorandil in Angina Study

Nicorandil is an antianginal drug currently licensed in the United Kingdom, Japan, and some other countries but not in the United States. It acts through several mechanisms, including nitric oxide formation and as a potassium channel opener, with consequent beneficial effects on ischemic preconditioning, and as an antiadrenergic agent during experimental ischemia.[8]

Design

The Impact of Nicorandil in Angina (IONA) study, presented by Dr. H. Dargie, was a randomized placebo-controlled trial conducted exclusively in the United Kingdom.[9,10] Nicorandil was initiated at a dose of 10 mg two times a day and increased to 20 mg two times a day after two weeks. Patients with stable angina (85% New York Heart Association Class I or II) but with other high-risk features, eg, ejection fraction of less than 45%, age above 65 years, prior coronary revascularization, diabetes, and hypertension, were included. Apparently, the usual therapy with β-blockers, aspirin, and statins were maintained during the 1.6-year follow-up period.

Results

A total of 5126 patients were recruited. The primary endpoint of coronary heart disease, death, myocardial infarction, or admission for chest pain occurred in 13.1% of treated patients versus 15.5% among placebo controls (P = .01). In regard to the secondary endpoint of coronary heart disease, death, and myocardial infarction, there was a strong trend toward a benefit (4.2% vs 5.2%, P = .68) and in regard to *all* cardiovascular events, benefit was shown as 14.7% among treated patients versus 17% in placebo controls (P = .025). Moreover, the Kaplan-Meier Curves showed a rapid separation from the very beginning, suggesting an early

Main Points

- The Atenolol Silent Ischemia Study trial demonstrated a benefit for atenolol over placebo in patients with mild effort angina or silent ischemia.
- Three recent trials have demonstrated that combining β-blocker and calcium channel blocker therapy provides the greatest antianginal efficacy in comparison with either drug alone; the combination is safest in the case of the dihydropyridines.
- A recent meta-analysis demonstrated no difference in cardiac death and myocardial infarction between β-blockers and calcium channel blockers, but the former were less likely to be discontinued because of adverse side effects, particularly with nifedipine.
- Nicorandil acts through several mechanisms, including nitric oxide formation and as a potassium channel opener, with beneficial effects on ischemic preconditioning.
- The Impact of Nicorandil in Angina (IONA) study showed a strong trend toward benefit in coronary heart disease, death, and myocardial infarction.
- The Combination Assessment of Ranolazine for Stable Angina multinational trial, though too short at 12 weeks to assess death and myocardial infarction, suggests that ranolazine may be effective and safe for patients who are remain symptomatic despite standard antianginal therapy.

benefit from this drug.

This is a very positive trial, and among currently utilized antianginal therapies for stable or chronic effort angina, nicorandil can lay claim to being the *only* drug subjected to a large, placebo-controlled trial with "hard" clinical outcomes as an endpoint.

The Combination Assessment of Ranolazine for Stable Angina Trial

The Combination Assessment of Ranolazine for Stable Angina (CARISA) multinational trial was presented by Dr. B. Chaitman of St. Louis University.[9,10] Ranolazine belongs to a class of compounds that act as fatty acid oxidase inhibitors and that presumably have a beneficial metabolic effect on the ischemic myocardium. Normally, the myocardium metabolizes fatty acids for the generation of adenosine triphosphate, but this is an aerobic process requiring oxygen. In the setting of ischemia, free fatty acids increase. One mechanism whereby agents such as the fatty acid oxidase inhibitors may be metabolically effective is by shifting myocardial metabolism away from free fatty acids to a glucose, which is a more efficient fuel.

Design

CARISA is a phase III, multinational, randomized, double-blind, placebo-controlled trial of 823 patients with stable angina. Patients were randomized to either 12 weeks of two different courses of ranolazine (750 mg two times a day or 1000 mg two times a day) or placebo. In this trial all patients received standard antianginal therapy with atenolol, diltiazem, or amlodipine.

The primary endpoint was exercise duration on the treadmill at 12 weeks (12 hours postdose corresponding to trough levels). Secondary endpoints included exercise duration at peak drug levels (4 hours postdose), time to the onset of angina, ST-segment depression at both peak and trough levels, and the frequency of angina.

Results

The results from the two ranolazine groups were combined. For 12 weeks the symptom-limited exercise duration at trough levels increased by a mean of 116 seconds in the treatment group versus 92 seconds in the placebo group ($P \leq .03$).

In regard to the frequency of angina, this was reduced by an average of 1.3 and 1.7 episodes per week in the two ranolazine groups, compared to a reduction by 0.6 attacks (compared to baseline) per week in the placebo arm ($P \leq .01$). Ranolazine also increased the duration of exercise prior to electrocardiographic evidence of ischemia.

Minor side effects included nausea, dizziness, and constipation, when noted, in 8% of patients, and serious adverse events were no different from placebo. There was mild prolongation of the QTC interval to 4.5 and 7.7 milliseconds in the two ranolazine groups ($P \leq .001$ vs placebo).

Conclusions

This trial was not powered to address "hard outcomes," for example, death and myocardial infarction, and in any event, the duration of follow-up was too short, namely, 12 weeks. Nonetheless, it is a very useful study suggesting that ranolazine may be an effective and safe drug for use in patients who remain symptomatic on standard antianginal therapy, particularly in the face of contraindications or technical issues limiting the use of coronary revascularization. A U.S. Food and Drug Administration application for release of this drug is expected to be made during the current year.

Summary

The last decade has witnessed a veritable barrage of trials of agents used in the acute coronary syndromes (both ST-segment elevation and non-ST-segment elevation) and of coronary revascularization technique. Nonetheless, many patients with ischemic heart disease have symptomatic, limiting, chronic, stable angina and for many reasons may not be candidates for coronary revascularization. These two trials provide us with welcome, objective evidence that new and effective antianginal therapies are on the horizon and may soon enter the arena of routine clinical practice. ■

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