Editorial Comment

Is There a Role for Angiotensin-Converting Enzyme Inhibitors in The Treatment of Chronic Myocardial Ischemia?*

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Antianginal agents. The mechanism or mechanisms of action of antianginal drugs are an appropriate area of inquiry for investigators. The three standard agents used in the treatment of chronic effort angina—nitrates, beta-adrenergic blocking agents and calcium channel antagonists—have differing effects on the peripheral vasculature, coronary artery bed and myocardial performance. All of these drugs, however, reduce myocardial work at rest and exercise, usually through a lowering of one or more of the factors that affect left ventricular wall tension. Beta-blockers lower heart rate, particularly during activity, whereas the nitrates and the dihydropyridines (nifedipine) increase heart rate; verapamil and diltiazem have a modest negative chronotropic action. Blood pressure is lowered by all three classes of drugs but nitrate tolerance attenuates their hypotensive actions. Coronary artery vasodilation occurs with nitrate or calcium channel antagonist administration. All three groups of drugs have been shown to enlarge coronary stenosis caliber. Nevertheless, the benefit of antianginal drugs in enhancing coronary blood supply remains an unproved hypothesis as an important mechanism for relief of angina in patients who receive a nitrate or calcium channel blocker, whereas this action cannot be implicated for the beta-blockers.

Potential role of angiotensin-converting enzyme (ACE) inhibitors in angina pectoris. The ACE inhibitors are a remarkable class of drugs that are highly effective in the treatment of hypertension and congestive heart failure. There is an ample hypothetic rationale for the relief of myocardial ischemia with these agents. The ACE inhibitors decrease arterial vascular resistance and systemic blood pressure and reduce myocardial oxygen consumption (1–3). They may have a coronary artery dilating action through inhibition of local and circulating angiotensin II and they increase coronary artery flow in certain circumstances (1,4,5). Thus, it is reasonable to administer ACE inhibitors in an effort to reduce myocardial work during exercise and possibly increase coronary blood supply, actions that should alleviate angina. In addition, it is conceivable that direct myocardial and coronary artery ACE inhibition might be beneficial to patients with coronary artery disease (1,6,7). These drugs have sympatholytic action; there is no reflex tachycardia after ACE inhibitor administration.

Several preliminary studies have sought to employ ACE inhibitors for angina. In hypertensive patients with anginal chest pain, these agents have shown some promise in alleviating determinants of myocardial ischemia (8,9). However, the record of ACE inhibitors in stable angina in the absence of hypertension has been mixed (9–16). Some previous trials (8,11,12), including our own (10), have not shown a benefit. The well designed study by Klein et al. (17) in this issue of the Journal, utilizing the ACE inhibitor benazepril, reaches a comparable conclusion, that there is no efficacy for benazepril in effort angina. Thus, it seems advisable to discontinue the use of ACE inhibitors for the therapy of chronic stable angina in normotensive subjects.

ACE inhibitors in silent myocardial ischemia: the present study. There is a tantalizing suggestion in the study of Klein et al. (17) that the ACE inhibitors may reduce asymptomatic episodes of ischemia, although benazepril had no effect on exercise-induced angina or ST segment depression. There is experimental support for anti-ischemic activity of these agents (3–7,13,14). Blockade of the conversion of angiotensin I to angiotensin II should decrease coronary artery vasoconstriction and improve coronary blood flow, particularly in patients with episodic coronary vasoconstriction or an abnormal vasomotor response to exercise. In addition, the sympatholytic effects of these drugs might decrease coronary vascular tone, possibly preventing or reversing episodes of coronary constriction that could be responsible for some episodes of asymptomatic ischemia. It is possible that drug therapy with ACE inhibitors might prove ineffective when compared with placebo in rigidly controlled exercise test protocols in patients with angina yet reduce the number of episodes of ambulatory silent ischemia, which are typically less intense than induced ischemia and are more likely to be caused by transient decreases in coronary blood supply.

In my judgment, the conclusion of Klein et al. (17) that ACE inhibitor therapy might be effective in silent ischemia is premature. The data for a reduction of silent ischemic attacks by benazepril represent only a trend toward improvement. In addition, ambulatory monitoring was carried

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out for only 24 h, whereas most experts currently recommend ≥48 h for baseline and intervention studies. The day-to-day frequency of silent myocardial ischemia is not known but it may be quite variable (18).

In any case, the likelihood that clinicians will select an ACE inhibitor for treatment of silent ischemia is very low. The currently available conventional antiangiinal agents are effective in reducing ambulatory myocardial ischemia, although they do not appear to completely abolish the episodes. Similarly, there is little current enthusiasm for aggressive treatment of silent ischemia in itself; this attitude seems appropriate given the methodologic difficulties in its accurate detection and quantification and the uncertain benefit of initiating therapy solely for silent episodes of ST segment depression.

**Metoprolol OROS in angina pectoris: the present study.**

The study of Klein et al. (17) is an exemplary investigation in many ways and is an excellent model for studies of angina. It represents classic antiangiinal study design and employs a relatively large group of patients who are carefully categorized. All patients were documented to have not only obstructive coronary artery disease, but also active myocardial ischemia as determined by the presence of four anginal attacks in the preceding month. (It is unclear whether or not this was during therapy.) In addition, the patients were carefully withdrawn from all antiangiinal medications, so that the experimental drugs were evaluated without potential competing or attenuating effects, or both, of other antiischemic agents. Careful treadmill exercise test procedures were utilized.

The long-acting OROS formulation of metoprolol employed in this protocol was very effective. Exercise tests were performed at least 24 h after the drug was given, documenting antiangiinal efficacy over a sustained period. The heart rate and blood pressure data also indicate that beta-adrenergic blockade persisted throughout the 24 h period.

**Conclusions.** This is a well designed, traditional antiangiinal drug study. The results indicate convincingly that metoprolol OROS is a beneficial antiangiinal formulation that has an extraordinarily long duration of action. There is no evidence that ACE inhibition plays a role in relief of stable effort angina pectoris. There is a suggestion that ACE inhibitors may reduce the number of episodes of silent myocardial ischemia, but the data base is small and the results are of uncertain significance. This hypothesis should stimulate further work utilizing ACE inhibitors in investigations of coronary vasomotor tone and silent ischemia. However, the current clinical relevance of this concept appears to be limited.

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**References**