

**Editorial Comment**

**Combination Therapy for Angina Pectoris**

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In recent years a variety of new agents have become available for the therapy of angina pectoris. Among the most prominent of these are the calcium entry blocking agents, which currently occupy a key role in the treatment of both acute and chronic ischemic heart disease. Both beta-adrenergic antagonists and the calcium entry blockers have been utilized as monotherapy for angina pectoris, but there has not been good objective evidence to demonstrate the clinical superiority of one class of agent over the other. Thus, the choice must currently be made on the basis of the side effect profile as well as, in some instances, on economic considerations.

Considerable evidence suggests that combination therapy utilizing both classes of agents may be more effective than monotherapy, particularly in patients whose condition is refractory to one type of agent or who are unable to tolerate higher doses of one class. Typically, a calcium entry blocker has been added to a beta-adrenergic antagonist. The current study of Humen et al. (1) has extended a prior study by the same group (2) in which it was concluded that propranolol and diltiazem should be considered the combination of choice because of their low incidence of adverse clinical effects. The current study of Humen et al. (1) demonstrates the superiority of the combination of high dose (360 mg/day) diltiazem with propranolol in doses that produced “full beta blockade,” defined as a maximal heart rate of less than 120 beats/min during stress testing and a propranolol dose of at least 160 mg/day. Although one may question the definition of “full beta blockade,” the evidence is impressive, both subjectively and objectively, that high dose diltiazem therapy in combination with propranolol produced better relief of ischemic heart disease than did propranolol alone or propranolol in combination with diltiazem at a dose of 240 mg/day.

Limitations of study. The study demonstrates one lesson of such investigations—the variability of angina pectoris. Thus, even with the requirement for entry into the study that angina must be present in the face of beta blockade, 25% of the patients were no longer limited by angina during the course of the investigation, despite receiving identical therapy during the double-blind phase.

A design flaw of the current report is that no placebo measurements were made, although these were included in the previous study by the same group (2). Furthermore, by not testing high dose diltiazem (360 mg/day) alone, the current study does not show that combination therapy is superior to monotherapy with high dose diltiazem. This issue was addressed by Hung et al. (3), who noted that diltiazem alone, 90 mg four times/day, was as effective as either moderate dose propranolol (60 mg four times/day) or the combination of diltiazem and propranolol in improving exercise tolerance, reducing myocardial ischemia and increasing left ventricular function in patients with stable angina. Diltiazem at a dose of 360 mg/day is effective monotherapy (4–7) and as much as 480 mg/day in divided doses is well tolerated and highly effective in some patients who do not respond to other treatment. Thus, the study would have been more useful had the design included a comparison of propranolol and high dose diltiazem therapy with high dose diltiazem treatment alone.

Rationale and combined advantages of combined therapy. Nevertheless, there are good reasons for the use of combination therapy. Thus, Pfisterer et al. (8) demonstrated in humans a regional anti-ischemic effect of sublingual nitroglycerin and intravenous nifedipine and metoprolol, as evidenced by improved regional left ventricular function. They concluded that despite the similar anti-ischemic effects of all three drugs, the underlying hemodynamic mechanisms were quite different, thus providing a rationale for combined forms of therapy. More recently, Matsuzaki et al. (9) demonstrated in a single vessel chronic coronary stenosis model in the conscious dog that the combination of atenolol and diltiazem was significantly better than either drug alone in reducing ischemia. They hypothesized that atenolol substantially reduced myocardial oxygen consumption of the left ventricle while the vasodilator action of diltiazem increased perfusion to the ischemic zone, either directly or through an increase of blood flow in coronary collateral vessels supplying that zone. A combination of reduced myocardial oxygen demand and augmentation of absolute blood flow to the ischemic zone thus improved distribution within that region in this animal model.

Possible danger of congestive heart failure. Finally, the dangers of congestive heart failure produced by combination therapy must be considered. Although both verapamil and nifedipine in combination with beta-adrenergic
blockers have been reported to induce congestive heart failure in susceptible patients, the combination of diltiazem and propranolol has not been adequately studied. Diltiazem alone has been used with beneficial effects in severe congestive heart failure (10), and in the normal conscious dog, the combination of intravenous diltiazem and propranolol does not adversely affect left ventricular performance (11). Strauss et al. (12) recently reported on a patient who tolerated propranolol therapy without difficulty for many years and had an excellent response with high dose diltiazem monotherapy; however, the combination of diltiazem and propranolol resulted in the development of congestive heart failure. Although none of the patients studied by Humen et al. (1) had reduced left ventricular performance, one still must be exceedingly cautious when using the combination of a beta-adrenergic antagonist with a calcium entry blocking agent such as diltiazem in the presence of overt or suspected congestive heart failure.

References