(LDL-C level of 145 mg/dL to 250 mg/dL). Six hundred sixty-eight patients were randomized to 12 weeks of active treatment in one of ten groups: placebo; E; S (10 mg); S (10 mg) + E; S (20 mg); S (20 mg) + E; S (40 mg); S (40 mg) + E; S (80 mg); and S (80 mg) + E.

Ezetimibe monotherapy resulted in an 18% reduction in LDL-C along with an 8% reduction in triglyceride levels and a 5% increase in high-density lipoprotein cholesterol (HDL-C). Coadministration of ezetimibe and simvastatin (pooled doses) was more effective than simvastatin alone (pooled doses) in reducing levels of LDL-C from baseline (49.9% vs 36.1%). Pooled analysis revealed that coadministration was also able to provide a 2.4% increase in HDL-C and 7.5% reduction in triglyceride levels over what was observed with simvastatin alone. Coadministration of 10 mg of ezetimibe plus 10 mg of simvastatin was able to effect a 44% reduction in LDL-C, equal to what was observed with 80 mg of simvastatin alone. A combination of 10 mg ezetimibe with 80 mg of simvastatin was observed to result in a 57% reduction in LDL-C. The coadministration of ezetimibe and simvastatin was well tolerated, with an observed overall safety profile similar to that of monotherapy with simvastatin and that of placebo.

In those patients who are intolerant of statins, ezetimibe provides an alternative monotherapy strategy or one that could be combined with other lipid therapies.

Coadministration of ezetimibe with a low(er)-dose statin provides a well-tolerated treatment option. Combination therapy also provides an opportunity to achieve NCEP ATP III target LDL-C concentrations in patients in whom monotherapy lacks sufficient potency or in patients who have adverse reactions to the higher statin doses. In those patients who are intolerant of statins, ezetimibe provides an alternative monotherapy strategy or one that could be combined with other lipid therapies, including niacin and fibric acid derivatives. ■

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Atherosclerosis

The Calcium Channel Blocker Lacidipine Slows the Progression of Carotid Atherosclerosis

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Calcium Antagonist Lacidipine Slows Down Progression of Asymptomatic Carotid Atherosclerosis: Principal Results of the European Lacidipine Study on Atherosclerosis (ELSA), a Randomized, Double-Blind Long-Term Trial

Zanchetti A, Bond MG, Hennig M, et al.
Circulation. 2002;106:2422–2427.

Hypertension contributes to cardiovascular events, in part by predisposing the patient to atherosclerosis and its progression. Antihypertensive drugs include calcium channel blockers; experimental data have suggested that these agents may also have antiatherogenic effects independent of their antihypertensive effects. The highly lipophilic, long-acting calcium channel blocker lacidipine has been shown to have antioxidant effects and is particularly effective in reducing atherosclerosis in animal models.

In this study, the investigators used B-mode carotid ultrasound to measure carotid intima-media thickness (IMT) as an index of carotid atherosclerosis in order to evaluate and compare the long-term effects of lacidipine and beta-blockers on atherosclerosis in hypertensive patients over a 4-year period. Several studies had previously documented the generally consistent relationship of carotid IMT to cardiovascular events, making it a useful surrogate marker for clinical events.

A total of 2035 hypertensive patients (systolic blood pressure, 150–210 mm Hg; diastolic blood pressure, 95–115 mm Hg) were recruited from 410 European centers and randomized to lacidipine (755 out of 1023 patients completed the trial) or atenolol (764 out of 1012 subjects completed the trial). At the end of the study, among those who completed the study, there was significantly

less progression of carotid IMT in the lacidipine group compared to the atenolol group (mean IMT change, .0359 vs .0579; $P < .009$). Moreover, the annual rate of progression (mm/yr) was slower among patients in the lacidipine group than among those in the atenolol group

At the end of the study, among those who completed the study, there was significantly less progression of carotid IMT in the lacidipine group compared to the atenolol group (mean IMT change, .0359 vs .0579; P < .009).

(.0087 vs .0145; $P = .0073$). These beneficial effects of lacidipine were noted despite the observation that lacidipine reduced blood pressure less than atenolol did.

As far as clinical cardiovascular events were concerned, the overall event rate was quite low, and no significant differences were observed between the lacidipine and atenolol groups, although the trend favored lacidipine. Thus, this long-term study showed that lacidipine slowed the progression of carotid IMT (and, by inference, atherosclerosis) better than atenolol did, even though lacidipine lowered blood pressure less than atenolol did, suggesting that this calcium channel blocker has a blood pressure–independent antiatherogenic effect. Similar results have been reported previously in smaller studies comparing calcium channel blockers to diuretics. ■

Renal Insufficiency

The Prognostic Value of Renal Function in Patients with Congestive Heart Failure and Acute Myocardial Infarction

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This series of articles emphasizes the important role of renal function in the prognosis of patients with chronic congestive heart failure and acute myocardial infarction. The impact on prognosis is related to the metabolic syndrome associated with renal insufficiency, which includes insulin resistance and activation of the renin-angiotensin-aldosterone axis and the sympathetic nervous system. Of possibly equal importance are the less aggressive treatments, such as reperfusion therapies, that patients with renal insufficiency receive.

The Prognostic Value of Estimated Creatinine Clearance Alongside Functional Capacity in Ambulatory Patients with Chronic Congestive Heart Failure

Mahon N, Blackstone E, Francis G, et al.
J Am Coll Cardiol. 2002;40:1106–1113.

Over the last 2 to 3 years, our understanding of the importance of renal dysfunction in cardiovascular mortality and morbidity has become much clearer. Clinical studies by McCullough,[1] Berger,[2] and others as well as our improved understanding of the devastating consequences of contrast nephropathy have underscored the clear, inverse relationship between renal function and cardiovascular mortality. The estimation of creatinine clearance (CrCl) using the Cockcroft-Gault formula seems

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to provide a much better assessment of renal function than does serum creatinine. Using the Cockcroft-Gault formula, CrCl = [(140 − age in years) × weight in kg]/(serum creatinine in mg/dL × 72). For women, this number is multiplied by 0.85.

The study by Mahon and colleagues was designed to determine the prognostic significance of the CrCl calculation compared with a 6-minute walk test in ambulatory patients with chronic congestive heart failure. The authors divided the study patients into quartiles by their estimated CrCl: first quartile, 7.8 to 47.1 mL/min; second quartile, 47.1 to 63.8 mL/min; third quartile, 63.9 to 85.8 mL/min; and fourth quartile, 86.0 to 193.6 mL/min. Relevant patient information is presented in Table 1.

In this trial, despite no difference in ejection fraction across the quartiles of renal function as estimated by CrCl, a clear relationship between CrCl and mortality exists. Of note is that the quartiles where this relationship exists begin at serum creatinine levels in the 1.2- to