

Simvastatin plus Ezetimibe Improves Cardiovascular Outcomes in Patients with Chronic Kidney Disease

But would a statin alone have produced similar results?

Two previous trials failed to demonstrate the effectiveness of statins for preventing adverse cardiovascular events in patients on dialysis ([JW Cardiol Aug 19 2005](#) and [Mar 30 2009](#)). In SHARP, a randomized trial, investigators compared simvastatin plus ezetimibe with placebo. Of the 9270 patients (age, ≥ 40 ; mean age, 62; 63% men) with chronic kidney disease and no histories of acute myocardial infarction (AMI) or coronary revascularization, about one third were on dialysis. The study was funded by the drug combination's manufacturer, who participated in the study design.

Patients had creatinine levels of at least 1.7 mg/dL in men or 1.5 mg/dL in women. Nonadherent participants were excluded after a 6-week, single-blind, run-in placebo course. The primary endpoint was first major atherosclerotic event. At baseline, mean total cholesterol level was 189 mg/dL, and mean LDL cholesterol level was 108 mg/dL.

At study midpoint, the mean LDL cholesterol level was 33 mg/dL lower in the treatment group than in the placebo group. During a median follow-up of 4.9 years, a primary endpoint occurred in 11.3% of patients in the treatment group and 13.4% of those in the placebo group (relative risk, 0.83; 95% confidence interval, 0.74–0.94; $P=0.002$). Although the rate of nonfatal AMI or death from coronary heart disease did not differ significantly between groups, the rates of nonhemorrhagic stroke and revascularization (coronary, carotid, aortic, or leg) were significantly lower in the treatment group, whereas all-cause mortality was nonsignificantly *higher* (24.6%, vs. 24.1% with placebo). The study was underpowered for comparison by dialysis status; the rate of the primary endpoint in patients on hemodialysis was 15.2% in the treatment group and 15.9% in the placebo group.

Comment: This study is difficult to translate into practice for several reasons. First, it is underpowered to show whether combination therapy improves outcomes in patients on hemodialysis, the group that did not benefit in previous statin studies. Second, the investigators did not compare the drug combination to statin-only therapy, so we cannot determine whether ezetimibe conferred any additional benefit over statin therapy alone. Finally, although the statin and ezetimibe combination was efficacious in this cohort, it primarily affected revascularization — a soft endpoint — rather than death or adverse cardiac events. The bottom line: Our approach to patient care will be the same today as it was before SHARP's publication.

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