

## Does intensified cholesterol lowering provide greater protection from cardiovascular events among patients with stable coronary artery disease?

LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352(14):1425-35.

**Background:** It is unknown whether intensive lowering of low-density lipoprotein (LDL) cholesterol levels to less than 2.6 mmol/L decreases the risk of cardiovascular events among patients with stable coronary artery disease (CAD).

**Design:** This double-blind study randomly assigned 10 001 patients with a history of myocardial infarction, angina or coronary revascularization to treatment with 10 mg atorvastatin per day or 80 mg per day after an 8-week, open-label run-in period. The primary outcome was a composite of death from CAD, nonfatal myocardial infarction, resuscitated cardiac arrest or stroke. All analyses were performed by intention-to-treat according to the first event experienced.

**Results:** The average patient enrolled was 61 years old, male (81%), white (94%), had a history of coronary revascularization (82%) and was at some distance from the qualifying event (mean 1.7 years). Concomitant medications included aspirin in 88% of cases,  $\beta$ -blockers in 55%, angiotensin-converting-enzyme inhibitors in 28% and nitrates in 32%.<sup>1</sup> Comorbidities such as heart failure, cerebrovascular disease and diabetes mellitus were infrequent (all < 15%).

The median follow-up was 4.9 years. Serum LDL levels were reduced from a baseline of 3.9 mmol/L to 2.6 and 2.0 mmol/L among those assigned to atorvastatin 10 mg per day and 80 mg per day respectively. The primary outcome was reduced by 22%

(95% confidence interval [CI] 11–31) in the high-dose group, which corresponded to an absolute risk reduction of 2.2%. Myocardial infarction, stroke and CAD-related death were each reduced by 20%–25%, but total mortality was unaffected (hazard ratio [HR] 1.01, 95% CI 0.85–1.19). Treatment-related adverse events and persistently raised liver enzyme levels were more frequent in the high-dose group (8.1% v. 5.8% and 1.2% v. 0.2% respectively,  $p < 0.001$  for both) with no increase in muscle symptoms or rhabdomyolysis reported.

First, the study protocol specified no fewer than 18 exclusion criteria. In particular, patients over 75 years and those with uncontrolled hypertension or diabetes; significant valvular, gastrointestinal, hepatic or renal disease; or an ejection fraction less than 30% were excluded.<sup>1</sup> Although it is conceivable that these patients may derive a greater absolute benefit because of higher baseline risk, the favourable risk–benefit ratio of this trial cannot be generalized to patients with multiple severe comorbidities, very old patients or those taking other lipid-modifying drugs.

Second, it is noteworthy that the trend toward reduction of cardiovascular death was matched by a nearly significant increase in death from noncardiovascular

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### The trend toward reduction of cardiovascular death was matched by a nearly significant increase in death from noncardiovascular causes, a finding the investigators attributed to chance.

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**Commentary:** Recent evidence involving patients with acute coronary syndromes suggests intensive cholesterol lowering with high-dose statin therapy confers added benefit over a less aggressive, lower dose approach.<sup>2</sup> However, until now, it was unknown whether such benefits could be extended to the broader population of patients with stable CAD. Considered in the light of previous placebo-controlled trials, the results of this study suggest that high-dose atorvastatin reduces the risk of cardiovascular events in this population by 40%–50%. However, there are two caveats.

causes (HR 1.25, 95% CI 0.99–1.57;  $p = 0.07$ ), a finding the investigators attributed to chance.

Other cholesterol-lowering strategies have been shown to be helpful in high-risk patients. For example, use of simvastatin 40 mg per day (compared with placebo) was found to be broadly beneficial among patients with peripheral artery disease, cerebrovascular disease or diabetes.<sup>3</sup> Also, an approach targeting high-density (HDL) cholesterol with fibrates or niacin also seems to confer independent benefit in patients with vascular disease.<sup>4</sup>

**Practice implications:** It is increasingly clear that patients across the spectrum of CAD benefit substantially from aggressive cholesterol lowering to an LDL level as low as 2.0 mmol/L. It remains unclear whether maximal lowering of LDL levels and raising HDL levels should be combined or which patients might best respond to which approach; further trials are now studying these options. Since there is evidence that adverse events due to atorvastatin are somewhat increased at higher doses, patients with stable CAD might

still best be started on a low dose of a statin, with the dosage increased to the maximum recommended among those who tolerate such therapy.

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