Cholesterol Metabolism and Statin Effectiveness in Hemodialysis Patients*

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Blood cholesterol concentration is determined both by endogenous cholesterol from hepatic and extrahepatic synthesis and by exogenous cholesterol derived from intestinal absorption of dietary and biliary cholesterol (1). Serum concentrations of plant sterols (campesterol, sitosterol, and avenasterol) and noncholesterol sterols, such as cholestanol, are markers of intestinal cholesterol absorption efficiency (2).

HMG-CoA reductase inhibitors (statins) work by inhibiting hepatic cholesterol synthesis and do not directly affect intestinal absorption. It has been suggested that patients with a high cholestanol-to-cholesterol ratio (CR) (i.e., “cholesterol absorbers”) may be relatively resistant to statin therapy. This hypothesis was tested among 868 Finnish patients within the 4S trial (Scandinavian Simvastatin Survival Study) of simvastatin 20 to 40 mg daily versus placebo. There was a trend towards smaller effects of simvastatin on coronary events among those with a higher CR (rate ratios [RR]: 0.623, 95% confidence interval [CI]: 0.395 to 0.982 in the first quartile [Q1]; 0.657, 0.426 to 0.998 in Q2; 0.753, 0.502 to 1.13 in Q3; and 1.166, 0.791 to 1.72 in Q4) (3). The proportional reductions in total cholesterol were significantly smaller in Q1 versus Q4 (25.6 ± 0.9% vs. 29.4 ± 0.9%; p = 0.003). Although the absolute reductions were not reported, because the baseline total cholesterol was similar (5.87 to 5.99 mmol/l) among quartiles it may be estimated that the absolute reduction was around 0.3 mmol/l smaller in Q1 versus Q4 (4). Meta-analyses conducted by the CTT (Cholesterol Treatment Trials) Collaboration (5,6) have shown that the absolute reduction in low-density lipoprotein (LDL) cholesterol correlates strongly with the relative reduction in major coronary events: each 1 mmol/l (39 mg/dl) lower LDL cholesterol corresponds to a one-quarter reduction in risk of major coronary events. A difference of 0.3 mmol/l in the absolute reductions in serum total cholesterol between quartiles might, therefore, result in a difference of about 8% in relative risk reductions—too little to explain the 4S trial trend.

This hypothesis has now been revisited among patients undergoing hemodialysis. In this issue of the Journal, investigators report results of the 4D (Die Deutsche Diabetes Dialyse) trial of atorvastatin, 20 mg daily, versus placebo among 1,255 diabetic hemodialysis patients (7). Allocation to atorvastatin did not significantly reduce the incidence of the composite outcome of cardiac death, nonfatal myocardial infarction, and fatal or nonfatal stroke (RR: 0.92; 95% CI: 0.77 to 1.10). It has previously been demonstrated that patients undergoing hemodialysis tend to be relative cholesterol absorbers (8). In the present study, analysis of the effects of atorvastatin among tertiles of CR showed that the hazard ratios (HR) for the primary endpoint in the lowest, middle, and highest tertiles were 0.72 (95% CI: 0.52 to 1.00; p = 0.049), 0.79 (95% CI: 0.53 to 1.16; p = 0.225), and 1.21 (95% CI: 0.85 to 1.74; p = 0.287), respectively. Silbernagel et al. (7) conclude that CR may be useful to distinguish hemodialysis patients who are “cholesterol synthesizers” (and may respond to statins) from those who are cholesterol absorbers (who might benefit from treatments that inhibit intestinal cholesterol absorption).

Before considering the observed results’ plausibility, it is important to appreciate that, based on the

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observed result (189 vs. 204 events for an RR of 0.89), about 13% (~1 in 8) of randomly generated subdivisions into tertiles would be expected to generate at least 1 statistically significant (p < 0.05) tertile simply by chance. The findings in this study are therefore not as unlikely as they appear based on the p value of 0.049.

If the mechanism for this observed effect is a relative lack of LDL-lowering efficacy among cholesterol absorbers, then this theory might gain support if there was evidence that variation in cholesterol absorption influenced the magnitude of the LDL cholesterol reductions achieved by atorvastatin 20 mg daily. Specifically, it would be helpful to know whether the absolute reductions in LDL (or total) cholesterol were consistent with the observed trend towards less benefit among cholesterol absorbers. Unfortunately, information about changes in lipid profile in CR tertiles was not provided, so we cannot answer this question directly. In a previous study of 113 hemodialysis patients, however, patients with CR above the median had lower LDL cholesterol concentration than those below the median (162 ± 35 mg/dl vs. 195 ± 40 mg/dl; p < 0.001) (9), so it is plausible that the absolute reduction in LDL cholesterol is negatively correlated with CR.

The authors of the present study suggest that inhibition of intestinal absorption of cholesterol by ezetimibe might have been an important reason why, in contrast to the negative findings of their 4D trial (7) and the AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) trial of rosvastatin in hemodialysis patients (10), the SHARP (Study of Heart and Renal Protection) trial showed that simvastatin 20 mg plus ezetimibe 10 mg daily reduced the risk of major atherosclerotic events in patients with chronic kidney disease (CKD) (11). There were, however, major design differences (other than treatment regimen) among these trials. One that may have had a critical bearing on the trial findings was that the primary outcomes of the 4D and AURORA trials included substantial numbers of events that were nonatherosclerotic (and hence could not have been prevented by lowering cholesterol), whereas the key outcome of the SHARP trial included only atherosclerotic events (11,12).

The rationale for using the combination of simvastatin 20 mg daily plus ezetimibe 10 mg daily in the SHARP trial was to achieve the largest possible LDL cholesterol reduction without a high-dose statin. In the recently reported results of the IMPROVE-IT trial (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial), the relative reduction in major vascular events resulting from the LDL cholesterol reduction achieved by ezetimibe was equivalent to that predicted for the same LDL cholesterol reduction achieved by a statin (13). In the SHARP trial, the mean absolute reduction in LDL cholesterol was lower at the trial midpoint among dialysis patients (23 mg/dl) than among nondialysis patients (37 mg/dl), and—as predicted by the CTT meta-analysis—the relative risk reduction in major atherosclerotic events was smaller in dialysis patients than among nondialysis patients (RR: 0.90; 95% CI: 0.75 to 1.08 vs. RR: 0.78; 95% CI: 0.67 to 0.91). The relative risk reductions after adjusting for differences in achieved LDL cholesterol reductions, however, were similar (p = 0.65) in dialysis patients (RR: 0.84; 95% CI: 0.62 to 1.13, per 1 mmol/l [39 mg/dl] reduction in LDL cholesterol) and in nondialysis patients (RR: 0.78; 95% CI: 0.66 to 0.91, per 1 mmol/l [39 mg/dl] reduction in LDL cholesterol) (11), consistent with benefit in both patient groups.

The relevant conclusion, therefore, is that larger benefits in patients with CKD would be likely if LDL cholesterol is reduced more intensively than in the SHARP trial, for example, with the combination of ezetimibe 10 mg daily and atorvastatin 20 mg or rosvastatin 10 mg daily. Irrespective of the physiological importance of cholesterol absorption in patients with moderate-to-severe CKD, which remains unclear even after the present study, the trial evidence in this high-risk group of patients is consistent with a goal of reducing LDL cholesterol by as much as can be achieved safely.

REFERENCES


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