Substantial evidence has now supported vigorous lipid intervention in primary and secondary prevention of coronary heart disease (CHD) (1,2), and the evidence supporting intensive lipid intervention with high-dose statins to produce clinical event reduction is especially powerful in the setting of acute coronary syndrome (ACS) (3–5), including the setting of percutaneous coronary intervention (PCI) (6), and acute cerebrovascular disease (7). Guidelines from the National Cholesterol Education Program (8), the American Heart Association/American College of Cardiology (9), and the American Heart Association/American Stroke Association (10) all support recommendations to lower low-density lipoprotein cholesterol (LDL-C) to at least under 100 mg/dl, with recommendations to lower LDL-C <70 mg/dl as a “therapeutic option.” Data to support LDL-C <70 mg/dl are especially applicable in patients following ACS (3–5).

Following PCI, a recent substudy (6) of 2,868 patients randomized to atorvastatin 80 mg or pravastatin 40 mg in PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial demonstrated a 22% reduction (p = 0.002) in the composite end point of major cardiovascular events as well as significant reductions in both target vessel revascularization (TVR) (~39%, p = 0.001) and non–TVR (~42%, p = 0.017) in those treated with high-dose atorvastatin. After adjustment for on-treatment LDL-C and C-reactive protein levels, the odds of reducing TVR with atorvastatin remained significant, suggesting that the reduction in TVR may be in part mediated by pleiotropic effects not accounted for by reductions in LDL-C and systemic inflammation (6,11).

Following PCI, an increase in cardiac biomarkers has been shown to occur in 5% to 30% of patients (12,13), and this elevation of cardiac enzyme is indicative of cell death and a high risk of periprocedural mortality (14). In fact, we recently demonstrated that even borderline increases in troponin following elective PCI predicted a higher mortality (14). Compelling data suggest that the statins may reduce the rate of periprocedural myocardial infarction (MI) (12,13,15).

Briguori (13) assessed the value of a single 80 mg loading dose of atorvastatin the day before elective PCI in 668 statin-naïve patients. They reported a 44% reduction (p = 0.01) in periprocedural MI in the atorvastatin–treated patients, with significant reductions also in the median creatine kinase-myocardial band isoenzyme (p = 0.01) and the frequency of cardiac troponin I elevation >3× the upper limit of normal. In an accompanying editorial, Tsimikas (15) reviewed 6 studies, including 2 in ACS (16,17), of over 2,000 PCI patients (4 studies with atorvastatin [3 using 80 mg and 1 using 40 mg] (13,17–19), 1 with rosuvastatin 40 mg (16), and the other using various statins), demonstrating statistically significant reductions in periprocedural MI using statin therapy. Tsimikas suggested that high doses of a potent statin should be given similar priority as aspirin and clopidogrel prior to patients undergoing PCI.

In this issue of JACC: Cardiovascular Interventions, Kim et al. (20) assessed the efficacy of high-dose atorvastatin (80 mg) versus low-dose atorvastatin (10 mg) in 171 ACS patients with ST-segment elevation MI. This was similar to the regimen used in the large-scale TNT (Treatment to New Targets) trial (21), which demonstrated the efficacy of high–dose (80 mg) atorvastatin versus low–dose (10 mg) atorvastatin in mostly stable patients with established CHD. Although the lipid arms in these 2 trials were similar, the recent PCI in ST-segment elevation MI trial was relatively small with only 30-day follow-up, whereas TNT randomized over 10,000 patients followed for 5 years. Unfortunately, despite the fact that 80 mg atorvastatin was associated with a 46% reduction in the primary end point (death, nonfatal MI, and TVR), the study was not nearly powered enough to assess this end point, because these events occurred in only 9 patients in the low–dose atorvastatin group (compared with 5 events in the high–dose group, p = 0.26). Also, as the investigators mentioned, serial measurement of cardiac enzymes were not available for all patients, and they were unable to calculate enzymatic infarct size using creatine kinase-myocardial band. Nevertheless, immediate high–dose statin loading before PCI showed beneficial effects on myocardial perfusion, including significant reduc-
tions in the corrected Thrombolysis In Myocardial Infarction (TIMI) flow grade count \((p = 0.01)\), as well as increases in myocardial blush grade \((p = 0.02)\) and ST-segment resolution at 90 min after PCI \((p = 0.01)\), all suggesting an improvement in microvascular myocardial perfusion with high-dose \((80 \text{ mg})\) versus low-dose \((10 \text{ mg})\) atorvastatin in ST-segment elevation MI.

With the current level of knowledge, how should clinicians treat patients with CHD, including those undergoing PCI electively or in the setting of ACS? In our opinion, all patients should be treated with a high dose of a potent statin, which should be started as outpatients or, in the setting of ACS, as soon as possible on hospital arrival and certainly before PCI. High-dose \((80 \text{ mg})\) simvastatin showed some benefit during 2-year follow-up compared with low-dose \((20 \text{ mg})\) simvastatin following ACS \((5)\), but as we have recently reviewed elsewhere \((1,2,22)\), although lower doses of simvastatin are generally well-tolerated this high dose of simvastatin \((80 \text{ mg})\) has perhaps the most drug-to-drug interactions and the greatest propensity among the statins for myopathy/rhabdomyolysis, and we believe that this dose \((80 \text{ mg})\) should be used with considerable caution. Rosuvastatin \(40 \text{ mg}\), which is probably the most potent statin, was recently associated with a \(40\%\) to \(50\%\) reduction in periprocedural MI in 445 patients with PCI in ACS \((16)\), and rosuvastatin \(20 \text{ mg}\) recently produced dramatic benefits in primary CHD prevention \((22)\). At present, however, \(80 \text{ mg}\) atorvastatin is the dose with proven efficacy and safety in 2 large-scale ACS trials \((3,4)\), as well as the large PCI substudy \((6)\), 2 large secondary CHD trials \((21,23)\), a large acute cerebrovascular trial \((7)\), and in at least 4 trials before PCI \((12,17,18,20)\), including in the report by Kim et al. \((20)\) in the present issue. Therefore, atorvastatin \(80 \text{ mg}\) probably has the most compelling evidence, with established efficacy and safety in ACS, before and following PCI, as well as in stable CHD. Further trials will likely determine if rosuvastatin’s greater potency translates to additional clinical benefits in ACS as well as in other high-risk patients.

Future studies are needed to determine if doses of statins even higher than standard lipid-lowering doses will result in additional benefit. As suggested by Tsimikas \((15)\), we agree that based on the current data, a rationale for further testing of higher anti-inflammatory doses in well-designed studies is present, as well as doses with other potentially important pleiotropic effects, as suggested by the recent PROVE IT TIMI 22 substudy \((6)\). Finally, there is evidence that high levels of triglycerides and non-high-density lipoprotein cholesterol predicts prognosis following ACS \((24)\). Therefore, as in stable CHD, studies of lipid agents with greater effects on the triglycerides/high-density lipoprotein axis are needed following ACS and in the PCI patient \((25,26)\).

**REFERENCES**


Key Words: acute coronary syndrome • coronary heart disease • low-density lipoprotein cholesterol • myocardial infarction • percutaneous coronary intervention • target vessel revascularization.