Early, aggressive lipid management in the treatment of acute coronary syndromes

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The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study has suggested that very early, aggressive therapy to reduce low-density lipoprotein levels beyond current recommendations (100 mg/dL) reduces cardiovascular morbidity and mortality in patients with acute coronary syndromes. PROVE-IT randomized subjects to either 40 mg of pravastatin or 80 mg of atorvastatin, daily. Atorvastatin therapy reduced the primary outcome (cardiovascular morbidity and mortality) by 16% compared with pravastatin during 2 years of follow-up. The PROVE-IT study adds valuable information to the medical literature in the acute treatment of acute coronary syndromes and suggests that the previous low-density lipoprotein goals for patients with acute coronary heart disease are not appropriate for all patients. The results of the PROVE-IT study were significant enough to lead to modifications of lipid guidelines. However, the PROVE-IT trial and subsequent alterations in guidelines have the potential for misinterpretation and misuse of high-dose statins. Based on the subgroup analysis of the study, acute coronary syndromes patients who have low-density lipoprotein concentrations greater than or equal to 125 mg/dL may benefit from early, high-dose statin therapy more than those with lower baseline low-density lipoprotein levels.

Active, aggressive lipid management has for several years been part of the standard of care for patients with existing coronary heart disease (CHD). Recently, the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study has suggested that very early and more aggressive therapy to reduce low-density lipoprotein (LDL) levels beyond current recommendations (<100 mg/dL) may provide enhanced benefit in reducing cardiovascular morbidity and mortality in patients with acute coronary syndromes (ACSs) [1,2]. In 2001, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study found high-dose atorvastatin therapy (80 mg daily) compared with placebo reduced cardiovascular morbidity when administered shortly after an ACS event after only 16 weeks of therapy [3]. Shortly thereafter, the Heart Protection Study (HPS) suggested regardless of baseline LDL concentrations, even those below what are considered goal levels, statin therapy reduces cardiovascular morbidity and mortality in patients with CHD and other high-risk patients [4]. However, the MIRACL, HPS, and other landmark studies assessing primary or secondary prevention of CHD all compared statin therapy with placebo [5–7]. The PROVE-IT study is the first trial of its kind to actually compare two different statins to obtain different LDL levels in reducing CHD events. It comes on the heels of the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial that showed slower progression of atherosclerosis in patients with CHD using high-dose atorvastatin therapy (80 mg daily) compared with moderate-dose pravastatin therapy (40 mg daily) [8]. The results of the PROVE-IT study, as well as the HPS, were significant enough to alter our perception of LDL goals in certain patients with established heart disease and have led to modifications of key consensus recommendations [9,101].

Methods & results

The PROVE-IT study was an international, randomized, double-blind, comparative trial that included over 4000 patients with ACS. ACS in this study was defined as either an acute myocardial infarction (MI) (with or without ST segment elevation) or high-risk unstable angina. To be included in the study, men or women aged 18 years or older were required to have had an ACS event within the preceding 10 days and to be in a stable condition at the time of enrollment.

Keywords: acute coronary syndrome, atorvastatin, cardiovascular disease, cholesterol, lipids, myocardial infarction, pravastatin, simvastatin, statins, unstable angina

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Total cholesterol (TC) levels were to be 240 mg/dL or less if subjects were not receiving long-term lipid-lowering therapy at the time of screening or 200 mg/dL or less if receiving such. Subjects were excluded if they were already receiving a statin at a dose of 80 mg daily at the time of their ACS event or if niacin or fibrate therapy could not be discontinued prior to randomization. Subjects were randomized to receive either 40 mg once daily of pravastatin (n = 2063) or 80 mg once daily of atorvastatin (n = 2099). If during follow-up on two consecutive screenings subjects in the pravastatin group had LDL concentrations above 125 mg/dL, their dose could be increased to 80 mg daily. No other lipid-lowering agents were allowed during the trial. The primary outcome of the study was the composite outcome of all-cause mortality, MI, unstable angina requiring hospitalization, coronary revascularization, or stroke. Secondary outcomes included the risk of each individual component of the primary outcome and the composite outcome of CHD mortality, nonfatal MI, or revascularization.

Baseline characteristics were similar between the two groups with the exception that more patients in the pravastatin group (6.6%) had peripheral arterial disease compared with the atorvastatin group (5.0%). The average age was 58 years and subjects were primarily male (78%) and white (90%). A total of 34% of subjects had an MI with ST-segment elevation at randomization while the majority of subjects had either unstable angina (29%) or a MI without ST-segment elevation (36%) as their ACS event. During the trial, 93% of subjects received aspirin therapy, 85% β-blockers, and 69% received angiotensin-converting enzyme inhibitor therapy. The median baseline LDL, high-density lipoprotein, and triglyceride levels were 106 mg/dL, 39 mg/dL, and 156 mg/dL respectively. Mean follow-up duration for the study was 24 months (range 18–36). The median LDL level in the pravastatin group at the study's end was 95 mg/dL (an approximately 10% relative reduction from baseline) while in the atorvastatin group the end median LDL level was 62 mg/dL, 41% relative decrease ($p < 0.001$).

The composite primary outcome occurred within 2 years in 26.3% of subjects in the pravastatin group and 22.4% in the atorvastatin group accounting for a 3.9% absolute reduction and a 16% relative risk reduction favoring atorvastatin (hazard ratio 0.84, 95% confidence interval [CI] 0.74–0.95; $p = 0.005$). The composite secondary outcome also favored atorvastatin with a 14% relative reduction ($p = 0.029$). Among the individual components of the primary outcome, only need for revascularization (14% relative reduction, $p = 0.04$) and recurrent unstable angina (28% relative reduction, $p = 0.02$) were found to be significantly altered though there was at least a trend in all outcomes except stroke (neutral effect) favoring the atorvastatin group.

There were no differences between the two groups in the rates of discontinuation for adverse events or patient preference. Elevations in alanine aminotransferase (ALT) levels greater than three times the upper limit of normal occurred more often in the atorvastatin group than the pravastatin group, 3.3 and 1.1%, respectively ($p < 0.001$). No significant differences were noted in the rates of discontinuation for reported myalgias, muscle aches, or elevated creatine kinase levels between the two groups and no cases of rhabdomylolysis were reported in either group. It should be noted that the study was funded by the manufacturer of pravastatin and not atorvastatin.

Discussion & significance

The PROVE-IT study was well designed in size and scope of clinical outcomes assessed. It adds valuable information to the medical literature in the acute treatment of ACSs and suggests that the previous LDL goals for patients with acute CHD are not appropriate for all patients. Quick, aggressive LDL lowering resulted in a significant, although modest, reduction in cardiovascular morbidity, though failed to demonstrate a reduction in all-cause or cardiovascular mortality. The benefits observed in the trial appear to outweigh the risks associated with high-dose statin therapy. In 2 years of therapy with high-dose atorvastatin compared with medium-dose pravastatin, the number needed to treat to prevent the primary composite outcome is 26. The numbers needed to treat to prevent a revascularization procedure or a hospitalization for unstable angina are 40 and 77 respectively. The number needed to harm (by elevated ALT) during the same time period is 45.

Compared with other secondary prevention trials [5,6], the clinical benefit of lipid lowering in the PROVE-IT study was found very early on with a divergence in the primary outcome noted after only 3 months of therapy (albeit not statistically significant until 18 months). This is likely attributable to the acute nature of the subject's condition and their early risk for subsequent events.

Subgroup analysis to detect differences between patient groups was significant only for baseline LDL concentration. Specifically, the subgroup of patients with a baseline LDL greater than or equivalent to 125 mg/dL (n = 1091) showed a significant reduction in the primary outcome while the majority population of the study whose baseline levels were below this cut off (n = 2885) showed no statistical improvement in the outcome though the trend favored atorvastatin. This would suggest that those with higher LDL concentrations are at an overall increased risk for a CHD event compared with those with lower values and benefit from significant LDL reduction. It is likely that those subjects with a baseline LDL concentration below 100 mg/dL did not clinically benefit from the aggressive LDL reduction of high-dose atorvastatin therapy (only a 3% difference in the primary outcome between groups) and the PROVE-IT authors admit that the lower the baseline LDL concentration at baseline, the more attenuated the clinical benefit [10].

It is unknown, and too little data exists to speculate, whether there is some difference between the various statins in clinical benefit beyond their LDL lowering capabilities. The PROVE-IT data should not be misconstrued to suggest atorvastatin is clinically superior to pravastatin in reducing cardiovascular outcomes. There is no way of knowing if maximum daily doses of pravastatin had been used (80 mg daily), would the benefit between groups have been diminished.

Since the publication of PROVE-IT, another trial has emerged assessing different dosing strategies to obtain different LDL reductions in ACS. The A to Z trial employed very different dosing strategies and a different statin than the PROVE-IT study and as such, comparisons are difficult [11]. The A to Z trial found no clinical benefit between treating ACS patients with early, moderate simvastatin doses (40 mg daily for one month followed by 80 mg daily) compared with late, low doses (placebo for 4 months followed by 20 mg daily). The LDL levels obtained were 66 mg/dL and 81 mg/dL in the early, moderate dosing group and the late, low-dosing group respectively. The lack of clinical benefit may have been due to a much smaller difference in LDL levels between the two groups and/or smaller reductions in C-reactive protein levels noted in the trial compared with PROVE-IT [12].

Based on the PROVE-IT results, the updated 2004 American College of Cardiology recommendations have endorsed the lower LDL goal for patients with ST-segment elevated MI (and will likely in the future for subjects with non-ST elevated MI and unstable angina, last updated 2002) [101]. The Adult Treatment Plan has also in kind recommended the lower LDL goal for patients with ACS [9].

Expert opinion & conclusion

The PROVE-IT study is truly a landmark trial in lipid management of CHD, in this case, early treatment of ACS events. The results of the trial and the alterations in consensus recommendations, however, may be prone to misinterpretation and also may result in inappropriate use of high-dose statin therapy. The PROVE-IT data suggests that some patients with a recent ACS event will benefit from more aggressive lipid lowering therapy than what was previously recommended by past guidelines (LDL < 100 mg/dL) and the goal of an LDL concentration less than 70 mg/dL may be warranted in certain ACS patients. Individuals most likely to benefit are those that most closely resemble the subjects assessed in the PROVE-IT study (i.e. patients with a recent, within 10 days, ACS event with moderately elevated TC levels before their ACS event). Based on the subgroup analysis of the study, one could argue that only those who fit those criteria and also have LDL concentrations greater than or equivalent to 125 mg/dL may or will benefit more than those with lower baseline LDL levels. This is a matter for further investigation.

Caution should be used when extrapolating the PROVE-IT study results to other patients. For subjects with a history of an ACS event but well beyond the 10 day inclusion criteria of the PROVE-IT study, simply altering patient's lipid therapy to high-dose atorvastatin or to obtain a target LDL less than 70 mg/dL based on this study may not be appropriate. According to the HPS, however, lipid-lowering therapy regardless of baseline LDL level (high or low) is beneficial even if only approximately a 30% LDL reduction is achieved. The HPS should not be interpreted to suggest that a goal of less than 70 mg/dL is clinically beneficial in CHD patients with significantly elevated LDL (e.g., > 150 mg/dL). A LDL of less than 70 mg/dL, however, may be appropriate in those with baseline LDL levels already at previous guideline goals (i.e., < 100 mg/dL).

Perhaps the biggest controversy in lipid management today is should we be treating to a specific target LDL level or reducing LDL levels by a specific percent in all patients? The current literature is conflicting in this area and more investigation is needed. Future data from the Treating to New Targets (TNT) study may shed some light on the subject [13]. The ongoing TNT is a large statin study involving over 10,000 patients with existing CHD. It is designed to determine whether high doses of atorvastatin (80 mg daily) to obtain LDL levels well below 100 mg/dL will reduce clinical outcomes compared with lower atorvastatin dosing (10 mg daily) to obtain LDL levels near 100 mg/dL. Other trials designed to assess various prespecified percent reductions in LDL (e.g. 30 versus 50%) with statins are warranted.

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