Direct Comparison of the A to Z and PROVE IT Trials

A Second Chance to Gain a First Impression

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Two similar clinical trials in patients presenting with acute coronary syndromes (ACS), the Aggrastat to Zocor (A to Z)\(^1\) and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)–TIMI 22\(^2\) trials, each compared intensive versus moderate statin therapies for 2 years. PROVE IT demonstrated a significant benefit from intensive therapy (16% reduction, \(P=0.005\) in its primary end point), whereas A to Z found only a favorable trend (11% reduction, \(P=0.14\) in its somewhat different primary end point). Like many clinicians reading these 2 reports, my first impression was that these data demonstrated the superiority of 80 mg of atorvastatin over 80 mg of simvastatin. Market share shifts soon reflected this perception. Wiviott et al\(^3\) have compared these studies in detail to ask whether the observed differences were explained by true differences in drug efficacy or, alternatively, by differences in trial design or practice differences among the 2 studies’ clinical sites (factors that, in this analysis, may be linked to different practice patterns inside or outside the United States). Event rates in the “early” 4-month phase and the “late” 20-month phase were examined separately. This is a well-written and well-reasoned post hoc comparison between 2 “similar” trials that nevertheless have certain important hypothesis-generating differences.

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identify certain factors that most plausibly contribute to this interaction, as follows.

**PCI Frequency at Index ACS Presentation**

In both studies, the index PCI frequency was 79% in US centers, but outside the United States it was 34% in A to Z and 44% in PROVE IT. Could the low frequency of index event percutaneous coronary intervention (PCI) at centers outside the United States have selectively disadvantaged simvastatin and thus, diminished its effect size in A to Z? The higher event rate in the first 5 to 10 months after ACSs is attributed to increased thrombogenesis in the fresh, active, atherothrombotic “culprit lesion,” usually a severe stenosis, and is associated with striking elevations of hsCRP. Current use of drug-eluting stents and concomitant use of antithrombotic agents uniformly diminish this component mechanism of coronary events in ACS. If the culprit lesion is not stabilized early by PCI, early atherothrombotic events, typically not prevented by statins, will occur in both treatment groups and dilute any potential benefit of intensive statin therapy.

Multivariate models entering significant univariate correlates of the end points have been published online and have consistently shown highly significant, independent, expected associations of these end points with age, diabetes, smoking, and prior myocardial infarction (MI). By contrast, intensive therapy, index event PCI, site of enrollment, and trial did not consistently contribute to the models at $P<0.05$. This analysis is used to infer that these predictive variables, especially US enrollment, were less important determinants of outcome. However, the inclusion of 3 highly related covariates, namely, index PCI, enrollment site, and trial, appears to violate the fundamental requirement of multivariate analysis, i.e., that entered variables must be statistically independent. If enrollment site were dropped from the models, as it should, it seems likely that index PCI would emerge as a consistent and highly significant predictor of favorable outcomes.

**Intensity of Therapy in the First 4 Months**

During the first 4 months of A to Z, there was absolutely no reduction in the primary end point with early/intensive simvastatin. By contrast, in PROVE IT, there was a significant 22% relative risk reduction from intensive therapy (80 mg atorvastatin) based on the same A to Z end point and a 26% reduction in death/MI. It may be possible but seems unlikely that the moderate therapy, delayed for 4 months in A to Z, would explain the lack of event divergence during that period when compared with a proven effective simvastatin dosage (40/80 mg). Because Kaplan-Meier curves diverged at 1 to 2 months in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) and PROVE IT trials but not for 6 to 8 months in A to Z and Lescol Intervention Prevention Study (LIPS) (20 mg fluvastatin versus placebo in ACS), one cannot exclude a time-selective pleiotropic effect of atorvastatin that is inoperative in simvastatin or fluvastatin. Alternatively, findings from the first 4 months of A to Z may be explained in part by the adverse interaction of residual culprit lesion instability with infrequent index event PCI in A to Z, as discussed earlier.

The inflammatory marker hsCRP fell to lower levels in the first 4 months, and there was a greater intensive-moderate differential in PROVE IT than in A to Z. This also provides a plausible explanation for early event differences for those who believe CRP to be a mediator of risk. Alternatively, persistent hsCRP elevation in A to Z may be a reflection of persistent inflammatory activity in the disrupted culprit plaque, more pronounced in those not receiving index event PCI. Although many of these questions remain unresolved, these early-event data present an excellent opportunity to further study the interplay of presenting diagnosis, early PCI, statin type, dose, and lipid response as determinants of hsCRP time course and its relation to event frequency.

**Intensity of Therapy in the ‘Chronic’ Final 20 Months**

Between-trial differences in LDL-C lowering plausibly contributed to the overall differences in outcome. In the late phase, LDL-C averaged ~63 mg/dL with intensive therapy in both studies (Figure 2A in the article by Wiviott et al), 75 mg/dL with 20 mg simvastatin in A to Z, and 95 mg/dL with 40 mg pravastatin in PROVE IT. On the basis of results from a recent meta-analysis and with the assumption that it can be applied to a 20-month follow-up, the 12-mg/dL LDL-C differential in A to Z would predict a major coronary event reduction, relative to moderate therapy, of 7%; the 32-mg/dL differential in PROVE IT would similarly predict a reduction of 18%. Thus, A to Z was in theory substantially disadvantaged in this comparison owing to the much lower LDL-C levels achieved with its moderate-dose simvastatin control.
Revascularization as a Component of the Primary End Point

Another issue that deserves greater emphasis is that the defined PROVE IT primary end point was typically 10% to 13% more frequent than the A to Z end point in each of the 2 studies (see Figure). The 4 components of the A to Z end point (cardiovascular death, nonfatal MI, ACS rehospitalization, and stroke) were similar in definition to 4 of the 5 PROVE IT components. However, a fifth PROVE IT end-point component, revascularization performed >30 days after randomization, added substantially to PROVE IT event frequency. Such increased event frequency might increase statistical power. However, revascularization as a trial end point has been debated because it is not always performed for clearcut progressive ischemia. If performed arbitrarily, it simply introduces “noise” and may diminish power. It can also introduce bias. In this comparison, the PROVE IT end point consistently outperformed the A to Z end point, or death/MI, in demonstrating the apparent superiority of 80 mg of atorvastatin. Although this seems to exclude the concern over introduced noise, it raises the alternative concern that patients randomized to moderate therapy will more likely be revascularized because the LDL-C is “not low enough.” Indeed, it is curious that the frequency of hospitalization for confirmed ischemia was ~5% in both trials but that there was a roughly 12% to 14% revascularization frequency in PROVE IT that does not appear associated with ischemic instability. Thus, statin efficacy conclusions based on the PROVE IT composite end point seems less compelling.

This excellent comparative analysis has changed my first impression of the lessons from these 2 studies; it permits 3 conclusions that deserve emphasis. First, simvastatin and atorvastatin at 80 mg are equivalent in their superiority over moderate therapy in reducing risk by 20% to 25% when compared on the level playing field of US enrollment, a rough surrogate for frequent index event PCI with its associated antithrombotic therapies. Simply stated, PCI deals first with the residual instability of the culprit lesion and appears to eliminate a component of risk not responsive to lipid-lowering therapy, thereby unmasking the known risk-reducing potential of intensive LDL-C lowering. Conversely, absent an initial PCI, the residual unstable plaque triggers early events in both intensive- and moderate-treatment groups.

Second, unqualified revascularization should be eliminated as a component of the primary-event composite. Procedures increase event frequency, but their relation to progressive ischemic instability is uncertain, and their use is subject to bias by the primary care physician, who may recommend revascularization if the LDL-C is not low enough.

Finally, I believe we have reached a point of diminishing returns in pursuit of more aggressive statin use. Despite on-treatment LDL-C levels reaching nearly 60 mg/dL,1,2,4,11,12 >60% of treated patients progress to the same event expected without lipid-lowering therapy. The next genuine advances will be found not in a marginally more powerful (and toxic?) statin/dosage but in combinations of statins with therapies that treat other forms of dyslipidemia (high-density lipoprotein, triglycerides, and particle size)13,14 and other mechanisms of plaque instability.

Disclosures
Dr Brown has served on advisory boards for Pfizer and Merck and has received a grant from Bristol Myers-Squibb.

References
6. The T3A Investigators. Early effects of tissue plasminogen activator, added to conventional therapy, on the culprit coronary lesion in patients presenting with ischemic cardiac pain at rest. Circulation. 1993;87:38–52.

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