Direct Comparison of the A to Z and PROVE IT Trials
A Second Chance to Gain a First Impression

B. Greg Brown, MD, PhD

Two similar clinical trials in patients presenting with acute coronary syndromes (ACS), the Aggrastat to Zocor (A to Z) and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)–TIMI 22 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. 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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First, it should be noted that the between-trial comparisons of the overall benefits of intensive therapy, though tending to favor PROVE IT, were not statistically significant in 2 of the 3 between-trial endpoint comparisons (\( P=0.52, 0.03, \) and 0.55). The PROVE IT trial’s intensive-therapy benefits were significantly greater than those of the A to Z trial (\( P=0.03 \)) only for the PROVE IT primary end point, which included revascularization >30 days after enrollment. This weakened my first impression. Second, during the final 20 months of treatment, there were compelling between-trial similarities in relative treatment effects in favor of intensive therapy. During the initial 4 months, however, the between-trial outcome differences clearly favored PROVE IT. The authors identify differences in design and execution between the 2 trials that could explain these early differences (intensity of therapy, timing and magnitude of the low-density lipoprotein cholesterol [LDL-C] and high-sensitivity C-reactive protein [hsCRP] reduction, differences in index event revascularization, or the play of chance). As noted earlier, the play-of-chance explanation appears credible but is certainly not the whole story.

Although the authors’ conclusions are well considered and consistent with their data, some deserve greater emphasis, and there are other possible interpretations. Their most striking finding appears in the data in Table 3 of their article, as plotted for visual impact in the Figure, which demonstrates a substantial overall difference in intensive- versus moderate-treatment benefits among patients enrolled in the United States compared with those enrolled outside the United States. Enrollment outside the United States accounted for 79% of all A to Z patients; 60% were from Europe, 19% were from South America, Australia/New Zealand/Asia, and Africa, and none were from Canada. Only 29% of PROVE IT patients were enrolled outside the United States, principally in Canada and western Australia.

Viewed from this perspective, the 924 US A to Z patients derived an overall benefit from intensive therapy (18% to 33% risk reduction) that was virtually identical to if not somewhat greater than that of the 2948 US PROVE IT patients. Indeed, the US A to Z intensive-treatment effect approached significance for all end points (\( P=0.10, 0.16, \) and 0.08) despite being only one third the size of the US PROVE IT sample. Conversely, the 3572 outside-US A to Z and 1214 outside-US PROVE IT patients derived virtually identical, diminishingly small, and uniformly nonsignificant benefit from intensive treatment. Given this data presentation, the obvious explanation for the “disparity” between trials is that A to Z enrolled 79% of its patients outside the United States, whereas PROVE IT enrolled only 29% of non-US subjects. Risk reductions with intensive therapy do not differ between the 2 studies when they are compared on level playing fields (US versus non-US locations) by common predefined primary end points.

Why is this so? Because it is unlikely that the drugs differed in their effects or that the investigators differed in their protocol execution at different enrollment locations, other differences in trial design or clinical practice appear to have interacted with the imbalance in patient distribution at US sites (A to Z, 29%; PROVE IT, 71%) to create the apparent difference in trial outcomes. In other words, a factor that decreases the effectiveness of statin therapy will diminish the relative benefit of intensive treatment most greatly in the trial with the highest prevalence of that factor. The authors

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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 ACS 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 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, ie, 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), 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 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 \( \approx 63 \text{mg/dL} \) 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 endpoint 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 $\approx$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 $\text{HDL}_{1,2,4}$, 11% $\geq$60% of treated patients progress to the same event expected without lipid-lowering therapy. The next genuine advances will be found not in a marginally more powerful (and toxic?) statin/dosage but in combinations of statins with therapies that treat other forms of dyslipidemia (high-density lipoprotein, triglycerides, and particle size)$^{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.

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Circulation. 2006;113:1382-1384
doi: 10.1161/CIRCULATIONAHA.106.612374
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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