Journal of the American College of Cardiology Vol. 48, No. 3, 2006

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.04.070

Meta-Analysis of Cardiovascular Outcomes Trials Comparing Intensive Versus Moderate Statin Therapy

Christopher P. Cannon, MD, Benjamin A. Steinberg, BA, Sabina A. Murphy, MPH, Jessica L. Mega, MD, Eugene Braunwald, MD

Boston, Massachusetts

OBJECTIVES The purpose of this study was to conduct a meta-analysis that compares the reduction of cardiovascular outcomes with high-dose statin therapy versus standard dosing.

BACKGROUND Debate exists regarding the merit of more intensive lipid lowering with high-dose statin therapy as compared with standard-dose therapy.

METHODS We searched PubMed and article references for randomized controlled trials of intensive versus standard-dose statin therapy enrolling more than 1,000 patients with either stable coronary heart disease or acute coronary syndromes. Four trials were identified: the TNT (Treating to New Targets) and the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid-Lowering) trials involved patients with stable cardiovascular disease, and the PROVE IT–TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction-22) and A-to-Z (Aggrastat-to-Zocor) trials involved patients with acute coronary syndromes. We carried out a meta-analysis of the relative odds on the basis of a fixed-effects model using the Mantel-Haenszel method for the major outcomes of death and cardiovascular events.

RESULTS A total of 27,548 patients were enrolled in the 4 large trials. The combined analysis yielded a significant 16% odds reduction in coronary death or myocardial infarction ($p < 0.00001$), as well as a significant 16% odds reduction of coronary death or any cardiovascular event ($p < 0.00001$). No difference was observed in total or non-cardiovascular mortality, but a trend toward decreased cardiovascular mortality (odds reduction 12%, $p = 0.054$) was observed.

CONCLUSIONS Intensive lipid lowering with high-dose statin therapy provides a significant benefit over standard-dose therapy for preventing predominantly non-fatal cardiovascular events. (J Am Coll Cardiol 2006;48:438–45) © 2006 by the American College of Cardiology Foundation

Numerous large, randomized, controlled trials have documented that cholesterol-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduces the risk of death or cardiovascular events in populations with or without a history of coronary artery disease, and across a wide range of cholesterol levels (1).

Recent trials have demonstrated that high-dose statins (also referred to as intensive statin therapy) appear to be more effective than standard-dose statins at reducing cardiovascular events, as seen in the PROVE IT–TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction-22) and TNT (Treating to New Targets) trials (2,3). However, 2 trials, the A-to-Z (Aggrastat to Zocor) and IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) (4,5), had non-significant trends toward benefit of intensive statin therapy for their pre-specified primary end point, raising questions regarding the reliability of this observation. In order to determine more accurately the clinical utility of intensive statin therapy, we performed a meta-analysis of these 4 trials, which represent more than 100,000 patient-years of observation directly comparing high-dose versus standard-dose statin therapy.

METHODS

We performed a PubMed search for randomized clinical trials comparing intensive statin therapy with standard-dose statin therapy, and carried out a hand search of references from these original articles and related reviews. Study selection criteria were randomized, controlled trials enrolling more than 1,000 patients that reported clinical outcomes as their primary end point. We intended to look at studies that were adequately powered to detect treatment effects on clinical events. Thus, similar to the Cholesterol Treatment Trialists' (CTT) review of placebo-controlled trials (1), the scope of our search was limited to those trials that randomized 1,000 patients or more and were sufficiently powered to detect clinical end points.

Four randomized trials were identified. The PROVE IT–TIMI-22 (n = 4,162) (2), A-to-Z (n = 4,497) (4),

From the Thrombolysis In Myocardial Infarction Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. The PROVE IT–TIMI-22 trial was sponsored by Bristol-Myers Squibb and Sankyo Co. LTD, and the A-to-Z trial was sponsored by Merck. Dr. Cannon currently receives research grant support from Merck, AstraZeneca, and Schering-Plough, and serves on advisory boards and/or is a consultant to AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Schering-Plough, Pfizer, and Sanofi-Aventis. Mr. Steinberg is a research fellow supported by The Stanley J. Sarnoff Endowment for Cardiovascular Science, Inc., Great Falls, Virginia. Dr. Braunwald receives research grant support from Bristol-Myers Squibb, Merck, Pfizer, and Schering-Plough.

Manuscript received January 23, 2006; revised manuscript received March 30, 2006, accepted April 4, 2006.

Abbreviations and Acronyms

A-to-Z	= Aggrastat-to-Zocor trial
ACS	= acute coronary syndrome
CI	= confidence interval
CTT	= Cholesterol Treatment Trialists
IDEAL	= Incremental Decrease in End Points Through Aggressive Lipid-Lowering trial
LDL	= low-density lipoprotein
MI	= myocardial infarction
NCEP	= National Cholesterol Education Program
OR	= odds ratio
PROVE IT–TIMI-22	= Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction-22 trial
TNT	= Treating to New Targets trial

TNT (n = 10,001) (3), and IDEAL (n = 8,888) (5) trials yielded a population of 27,548 patients with either stable coronary heart disease or acute coronary syndromes (ACSs). These patients were randomized to standard-dose or high-dose statin, as determined by the individual trial: pravastatin 40 mg versus atorvastatin 80 mg in the PROVE IT–TIMI-22 trial; 10 mg versus 80 mg atorvastatin in the TNT trial; placebo followed by 20 mg simvastatin versus 40 mg followed by 80 mg simvastatin in the A-to-Z trial; and simvastatin 20 mg titrated to 40 mg versus 80 mg atorvastatin in the IDEAL trial. The following end points were compared across all of the trials: 1) the combined incidence of coronary death or non-fatal myocardial infarction (MI); 2) the combined incidence of coronary death or any cardiovascular event (MI, stroke, hospitalization for unstable angina, or revascularization); and 3) the incidence of stroke; and 4) the incidence of cardiovascular, non-cardiovascular, and all-cause mortality.

Statistical analysis. The absolute event rates through follow-up for mortality are presented for cardiovascular death and any cardiovascular events. Because different trials used varying definitions, subtle differences exist in the end point of coronary death or any adverse cardiovascular event. The IDEAL and TNT trials both included cardiac arrest with resuscitation as a major event. Furthermore, the TNT trial included only non-fatal, non–procedure-related MIs, and the definition of unstable angina varied (unstable angina requiring hospitalization in the PROVE IT–TIMI-22 and IDEAL trials, readmission for ACS in the A-to-Z trial, and documented angina in the TNT trial). In order to more closely mirror the definitions used in the TNT and IDEAL trials, the composite end point of all cardiovascular end points used for the PROVE IT–TIMI-22 and A-to-Z trials differs from that in the original manuscripts to include revascularization at any time and only coronary death. In addition, low-density lipoprotein (LDL) values reported are on-treatment means for the duration of the individual study (not medians, as reported for some trials), based on the intention-to-treat population. Thus, results presented here may appear to differ from those in the trials' primary publications.

A meta-analysis was performed of the relative odds based on a fixed-effects model using the Mantel-Haenszel method. Heterogeneity between individual studies was incorporated into the summary estimate and was influenced by trial sample size and the number of events observed. A random-effects model was also performed as a sensitivity analysis. Results are presented as odds ratios (ORs) with their 95% confidence intervals (CIs) and p values. A p value of <0.05 was considered statistically significant.

RESULTS

Study design and baseline characteristics for each of the 4 qualifying trials are shown in Table 1. The LDL cholesterol levels in each arm of each trial are presented in Figure 1. These values are based on the intention-to-treat populations. The mean on-treatment LDL cholesterol concentrations in the standard therapy arms ranged from 97 mg/dl (2.49 mmol/l) in the PROVE IT–TIMI-22 trial (2) to 104

Table 1. Trial Design and Baseline Characteristics of the Four Trials Included in the Meta-Analysis

	PROVE IT–TIMI-22 (2)	A-to-Z (4)	TNT (3)	IDEAL (5)
n	4,162	4,497	10,001	8,888
Population	Post-ACS	Post-ACS	Stable CAD	Stable CAD
Treatment arms	40 mg pravastatin vs. 80 mg atorvastatin	Placebo (4 months) then 20 mg simvastatin vs. 40 mg simvastatin (1 month) then 80 mg simvastatin	10 mg atorvastatin vs. 80 mg atorvastatin	20 mg simvastatin vs. 80 mg atorvastatin
Duration	24 months (mean)	721 days (median)	4.9 yrs (median)	4.8 yrs (median)
Run-in	None	None	10 mg atorvastatin (8 weeks) per guidelines	None
Primary end point	Death, MI, UA requiring hospitalization, revascularization (>30 days), stroke	CV death, MI, readmission for ACS, stroke	CHD death, Non–procedure-related MI, resuscitation after cardiac arrest, stroke	CHD death, MI, cardiac arrest with resuscitation

A to Z = Aggrastat to Zocor trial; ACS = acute coronary syndrome; CAD = coronary artery disease; CHD = congenital heart disease; CV = cardiovascular; IDEAL = Incremental Decrease in End Points Through Aggressive Lipid-Lowering trial; MI = myocardial infarction; PROVE IT–TIMI-22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction trial; TNT = Treating to New Targets trial; UA = unstable angina.

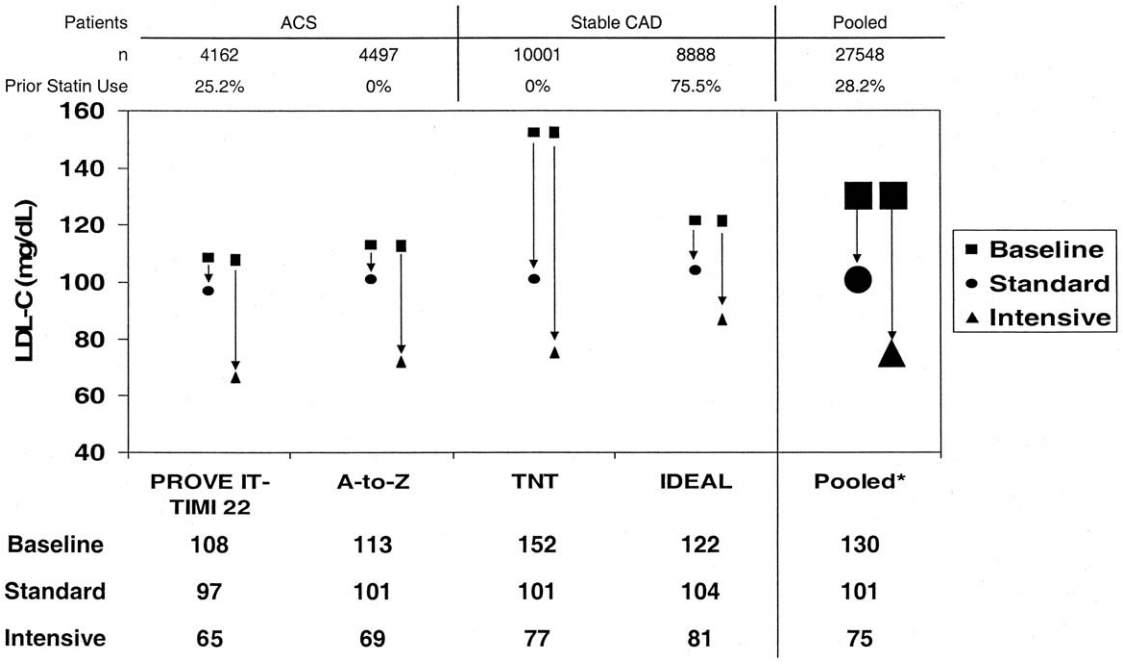

Figure 1. Low-density lipoprotein cholesterol (LDL-C) levels of trials comparing high-dose to standard-dose statin therapy. *Values for trials are estimated means, as not all individual LDL-C measurements were available.

mg/dl (2.67 mmol/l) in IDEAL (5). The differences in LDL between treatment arms within a trial ranged from a low of 23 mg/dl (0.59 mmol/l) in the IDEAL trial (5) to a high of 32 mg/dl (0.82 mmol/l) in the PROVE IT–TIMI-22 and A-to-Z trials (2,4), in part based on differences in the percentage of patients on statin therapy at baseline. The pooled analysis, in which approximately one-fourth of the patients were on prior statin therapy, showed that with standard-dose therapy, LDL cholesterol declined by 22% to a mean of 101 mg/dl (2.59 mmol/l), whereas with high-dose therapy, it declined by 42% to a mean of 75 mg/dl (1.92 mmol/l). This yielded a final difference in LDL of 25.7% (101 vs. 75 mg/dl) between the 2 treatment groups.

Individual and pooled analyses for coronary death or MI are shown in Figure 2. Although each trial individually had lower rates with intensive statin therapy when considered independently, only the TNT trial had a significant difference. The pooled analysis, however, yielded an overall significant odds reduction of 16% for coronary death or MI (9.4% vs. 8.0%, OR 0.84, 95% CI 0.77 to 0.91, $p < 0.00001$).

The risk of coronary death or any adverse cardiovascular events (MI, stroke, hospitalization for unstable angina, or

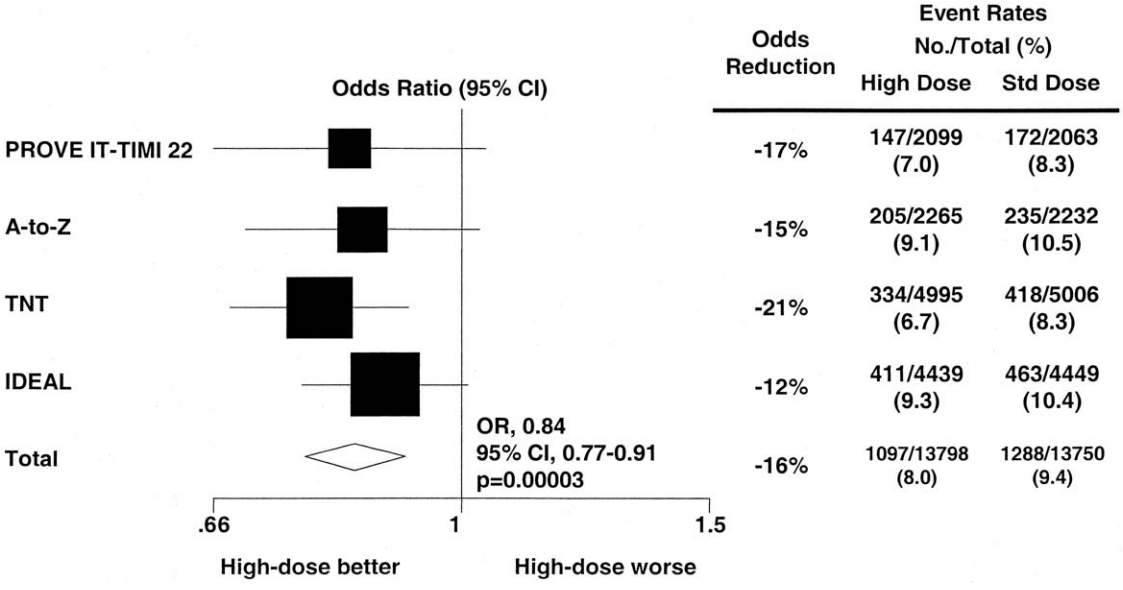

Figure 2. Individual trials and pooled analysis showing a highly significant 16% reduction in the risk of coronary death or myocardial infarction ($p < 0.0001$). CI = confidence interval; OR = odds ratio.

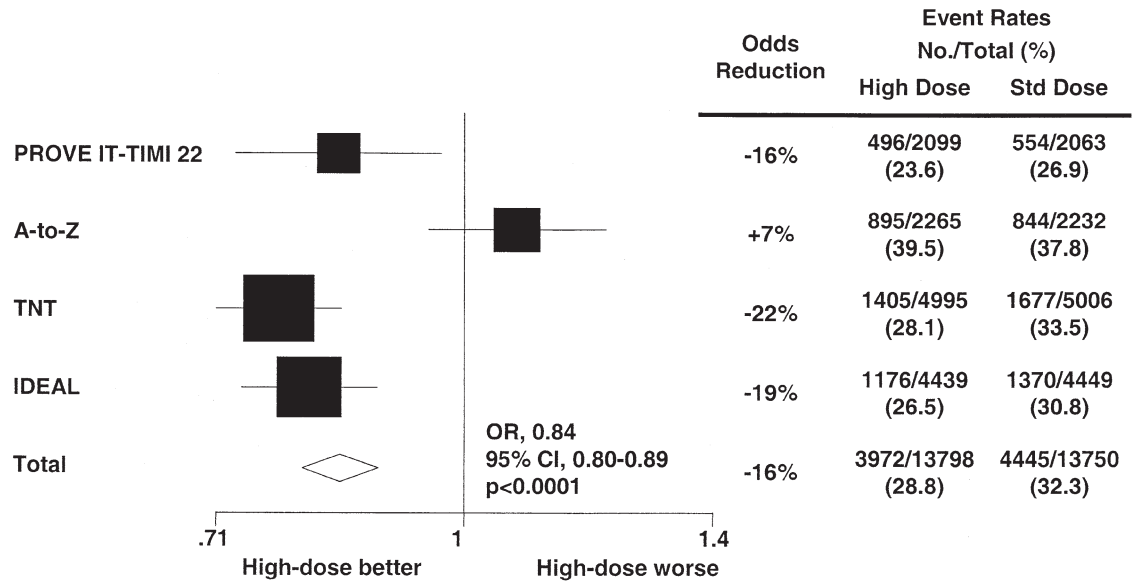

Figure 3. Individual trials and pooled analysis showing a highly significant 16% reduction in the risk of coronary death or any cardiovascular event (myocardial infarction, stroke, hospitalization for unstable angina, or revascularization) ($p < 0.0001$). CI = confidence interval; OR = odds ratio.

any revascularization) was reduced significantly in the intensive statin group in 3 of the 4 trials and neutral in the A-to-Z trial (Fig. 3). The pooled analysis yielded a significant 16% reduction of coronary death or any cardiovascular events (32.3% vs. 28.8%, OR 0.84, 95% CI 0.80 to 0.89, $p < 0.0000001$).

Cardiovascular death tended to be lower in the high-dose groups in 3 trials, and neutral in the IDEAL trial. Pooling the data yielded a trend to reduction in cardiovascular mortality by 12% (3.8% vs. 3.3%, OR 0.88, 95% CI 0.78 to 1.00, $p = 0.054$) (Fig. 4A). Rates for non-cardiovascular death and total mortality were also compared. Although 1 trial (TNT) reported a non-significant increase in non-cardiovascular death in the intensive therapy group (3.2% vs. 2.5%), 1 trial was neutral (A-to-Z) and 2 showed non-significantly lower rates. The pooled rates revealed no significant differences between the 2 groups (2.4% in the standard-dose group vs. 2.5% in the intensive, OR 1.03, 95% CI 0.88 to 1.20, $p = 0.73$) (Fig. 4B). The effects on all-cause mortality demonstrated a trend toward benefit in the PROVE IT–TIMI-22 and A-to-Z trials, but a neutral effect in TNT and IDEAL. In the cumulative experience, there was a non-significant 6% reduction in all-cause mortality (6.2% vs. 5.9%, OR 0.94, 95% CI 0.85 to 1.04, $p = 0.20$) (Fig. 4C). Data for rates of stroke yielded a significant odds reduction of 18% (2.8% vs. 2.3%, OR 0.82, 95% CI 0.71 to 0.96, $p = 0.012$) when pooled across all 4 trials (Fig. 5). Each of the observations was similar when the analysis was performed with a random-effects model. For the end point of coronary heart disease death or MI, the random-effects model yielded an odds reduction of 16.5% (OR 0.835, 95% CI 0.77 to 0.91, $p < 0.0001$).

Severe adverse events, as reported by the trials in their original manuscripts, are listed in Table 2 (6).

DISCUSSION

This analysis, involving more than 100,000 patient-years of observation, found a highly significant 16% reduction of coronary death or MI ($p < 0.00001$) and, similarly, a 16% reduction in coronary death or any cardiovascular events in patients receiving high-dose statin therapy versus those receiving standard-dose therapy ($p < 10^{-12}$). Although there was also a favorable trend in reduction of cardiovascular death with high-dose statins, the predominant benefit was seen in preventing the non-fatal events of MI, stroke, unstable angina, and revascularization. These data underscore the significant clinical benefit of high-dose statin therapy over standard doses in patients with known coronary artery disease, whether treated immediately after an acute coronary event or in the stable secondary prevention setting.

Extrapolating these data indicates that for every million patients with chronic or acute coronary artery disease, such as those entered into these trials, treated for 5 years, intensive rather than standard statin dosing would prevent more than 35,000 cardiovascular events (including more than 14,000 coronary deaths or MIs). On the basis of our analysis, this yields a number needed to treat of just 29 patients (for 2 years following an ACS, or for 5 years in stable patients) to prevent a cardiovascular event. It should be recalled that these benefits are in addition to those achieved by standard statin therapy, which has been shown to be highly effective (1). Placebo-controlled standard-dose statin trials showed a reduction in cardiovascular mortality by 20%, and of major cardiovascular events by 25% (1). Thus, when the present analysis is considered in light of the meta-analysis of placebo-controlled trials, it is possible that the benefit of high-dose statins as compared with placebo

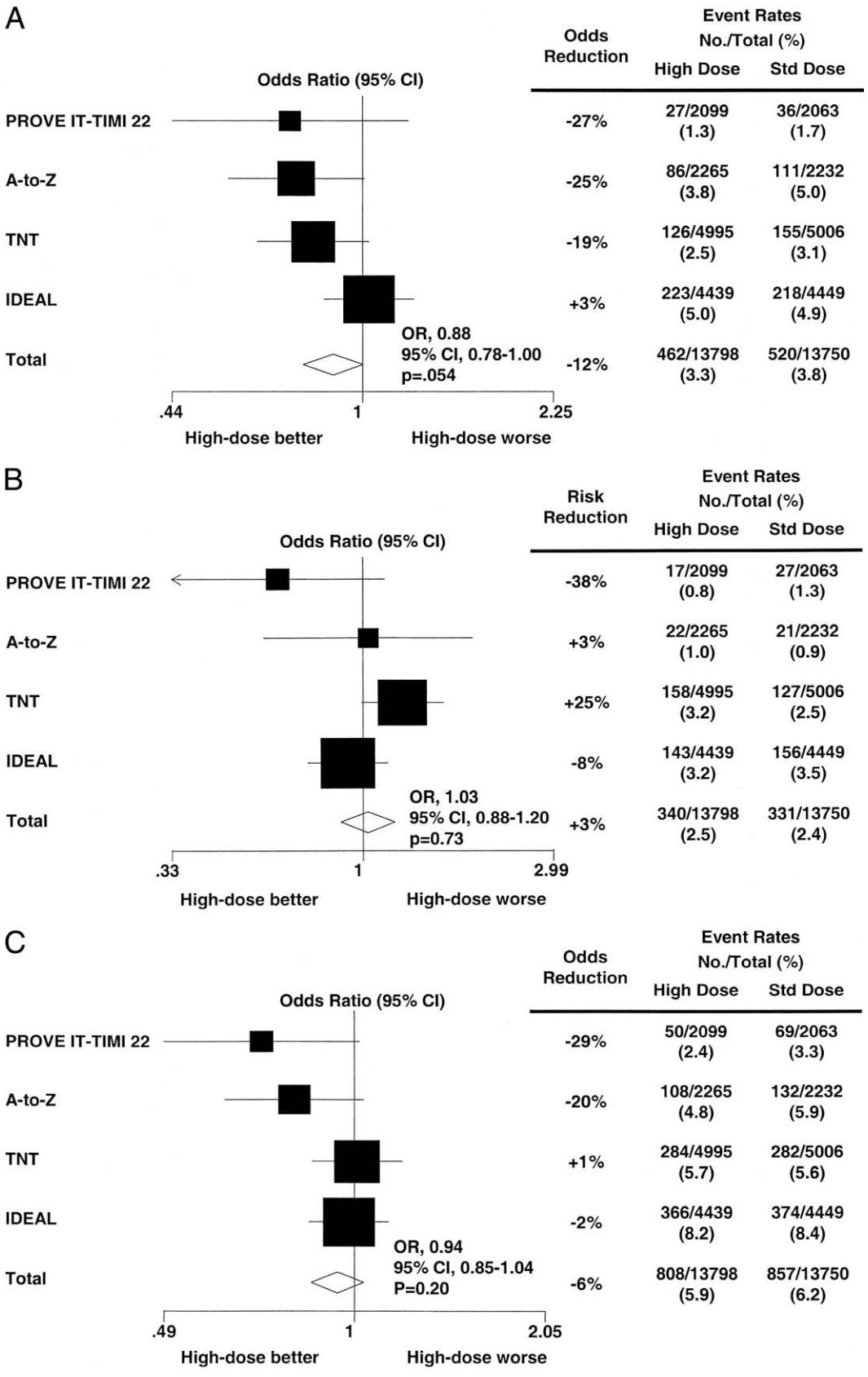

Figure 4. Individual and pooled analyses showing non-significant trend in reduction of cardiovascular death **(A)**, no increased risk of non-cardiovascular mortality **(B)**, and a non-significant trend toward decreased overall mortality with high-dose statins **(C)**. CI = confidence interval; OR = odds ratio.

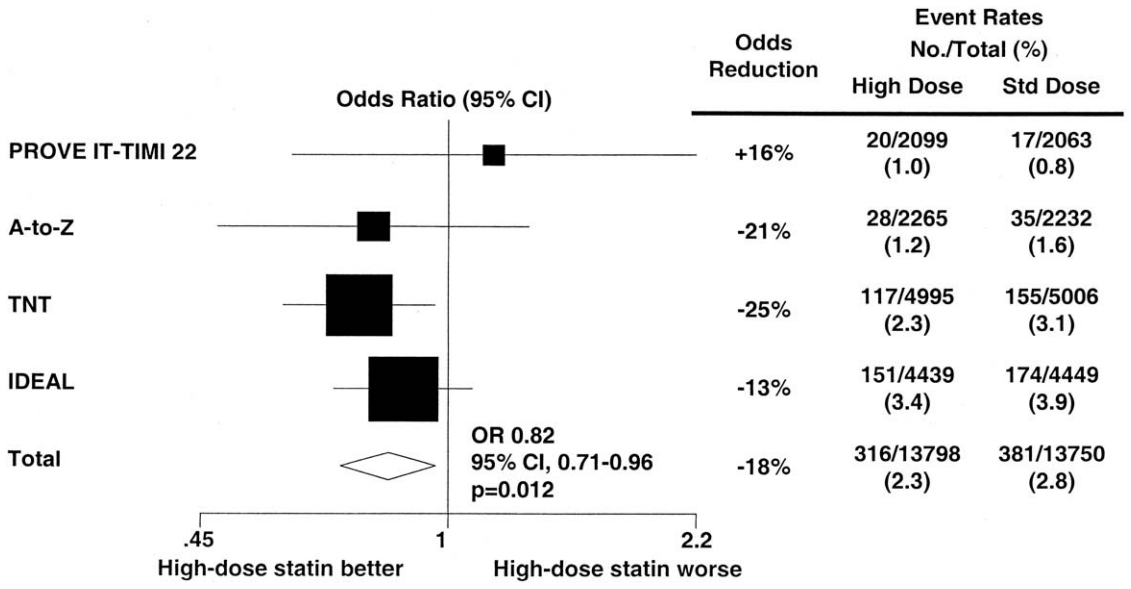

Figure 5. Individual and pooled analyses demonstrating a significant 18% reduction of stroke with intensive statin therapy. CI = confidence interval; OR = odds ratio.

could be a 40% reduction in cardiovascular events for the large number of patients at risk who are not currently on any statin.

Our data expand upon prior analyses of LDL reduction versus clinical event reductions. Although we did not have complete patient-level data to precisely gauge risk reduction per unit LDL reduction, our study is consistent with the previously published rates from the CTT meta-analysis, where roughly 1.8 mg/dl reduction in LDL led to a 1% reduction in cardiovascular events (1). Thus, the 26 mg/dl difference in LDL we observed in this analysis would be expected to lead to approximately a 14% decrease in cardiovascular events, and we observed a 16% reduction in events. However, this analysis is a comparison of LDL lowering using different doses of statins to reduce cardiovascular events. Because we lack patient-level data and because statins have been shown to reduce other markers of cardiovascular disease (such as C-reactive protein) (7), we cannot make any conclusions as to the expected risk reduction through other means of lowering LDL.

In determining current practice patterns of the use of statins, several surveys have shown underutilization of these agents (8–12). In some series, 40% to 50% of patients who have evidence of cardiovascular disease and are eligible for statin therapy by National Cholesterol Education Program (NCEP) III Guidelines do not receive any statin therapy. This was highlighted by the guidelines committee as a major national priority—to expand the use of statins to all eligible patients (13). In addition, studies of "real-world" clinical practice have indicated significant *under-dosing* of statins in high-risk populations (8). In 1 recent report, nearly half of the patients were receiving doses below those tested in clinical trials (e.g., 10 mg of simvastatin or pravastatin), which would be associated with smaller reductions in LDL and which have not been shown to reduce clinical events (8). Conversely, fewer than 5% were taking high-intensity statin therapy (80 mg simvastatin or 80 mg atorvastatin) (8–11). Although some studies have noted improvement in the prescription of high-dose statins in the past year in response to the PROVE IT–TIMI-22 trial (2,9), use remains quite low (5% to 15%) (12). With the substantial benefits of high-dose compared with standard-dose statin therapy seen in this meta-analysis, not only should physicians and health-care systems work to improve

Table 2. Severe Adverse Event Rates for Each Trial

Trial	Rhabdomyolysis (n)*		CK >10 × ULN (n)†		AST and/or ALT >3 × ULN (n)‡	
	Standard Dose	High Dose	Standard Dose	High Dose	Standard Dose	High Dose
PROVE IT–TIMI-22 (2,6) (n = 4,162)	0%	0%	0.10%	0.15%	1.1%	3.3%
A-to-Z (4) (n = 4,497)	0%	0.13%	0.04%	0.4%	0.36%	0.84%
TNT (3) (n = 10,001)	0.06%	0.04%	0%	0%	0.18%	1.2%
IDEAL (5) (n = 8,888)	0.07%	0.05%	0%	0%	0.16%	1.37%

Follow-up periods are 2 years for the PROVE IT–TIMI-22 and A-to-Z trials and 5 years for the TNT and IDEAL trials. Percentages for all events except those in the PROVE IT–TIMI-22 trial were back-calculated from numbers presented in published manuscripts. *Cases were based on the treating physician's diagnosis for the TNT and IDEAL trials, and a definition of CK levels higher than 10,000 U/l for A to Z. †A to Z reported 1 additional patient with an alcohol-related rise in CK without muscle symptoms. ‡The PROVE IT–TIMI-22 trial reported elevations in ALT; IDEAL reported as number of abnormalities.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; ULN = upper limit of normal; other abbreviations as in Table 1.

the percentage of patients on statins, they should ensure that patients receive the appropriate, evidence-based dose.

This meta-analysis also underscores the role of high-dose statins in preventing stroke. Although much attention in prevention of stroke has focused on antithrombotic therapy, few advances in this approach have occurred in recent studies (14). The meta-analysis of all placebo-controlled statin trials showed a relative risk reduction of stroke by 17% (1). Our data indicate that high-dose statins, compared to standard-dose statins, such as were employed in the previously cited meta-analysis (1), could significantly enhance that effect by an additional 18%, to yield an overall reduction of stroke by approximately one-third. This represents an important intervention for patients, most of whom do not have a history of cerebrovascular disease.

Concerns have surfaced about the possibility of an associated increase in non-cardiovascular mortality with high doses compared with standard doses of statins as a result of a trend toward increased non-cardiovascular mortality in the TNT trial (3,15). However, our pooled analyses, which included the TNT trial, found essentially identical rates in the high-dose (2.5%) versus the standard-dose (2.4%) groups ($p = 0.73$). In addition, the recent CTT review of 90,056 patients in 14 placebo-controlled trials found not only no increase in non-vascular mortality, but a significant 12% reduction in all-cause deaths ($p < 0.0001$) (1). Thus, much of the concern for both standard-dose and high-dose statin use and non-cardiovascular death seems to be merely chance observation in an individual trial or anecdotal evidence, but not supported by the totality of the evidence.

Therefore, results of this meta-analysis should have substantial implications for both physicians and their patients. In an effort to provide for maximum reduction of cardiovascular events, intensive statin therapy should be considered in the same realm as other proven therapies such as smoking cessation and aspirin use for secondary prevention (16,17). Accordingly, we believe these data support the NCEP's 2004 amendment to the Adult Treatment Panel III Guidelines (13,18) and should provide the impetus for the guidelines committee to consider upgrading the target of 70 mg/dl from "optional" to "recommended" for high-risk patients (such as those enrolled in these trials), thereby maximizing the opportunity to achieve the benefits of intensive statin therapy demonstrated here.

Study limitations. Although 27,548 patients is the largest analysis of intensive statin therapy to date, it remains underpowered to detect a statistical difference in cardiovascular death and total mortality (19). An additional trial comparing 80 mg of simvastatin to 20 mg of simvastatin, SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) (20), is ongoing—and this trial combined with our meta-analysis should provide further information on these 2 important end points. The duration of treatment and follow-up differed between the trials, but was relatively long-term for each of the respective conditions (2 years for the ACS trials, and 5 years for the trials of stable coronary artery disease). However, similar differences in duration of trials are present in most other meta-analyses, including the overview of prior statin-versus-placebo trials where durations ranged from 3 years (in several trials such as ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial] [21], CARDS [Collaborative Atorvastatin Diabetes Study] [22], and PROSPER [PROspective Study of Pravastatin in the Elderly at Risk] [23]) to 5 years (in others). We did not have individual patient data, and thus could not assess the degree of LDL lowering versus clinical benefit as was done in the CTT analysis, but this latter collaborative group is in the process of collecting the data to carry out such an analysis. We cannot determine from this analysis whether the benefit is seen because high-dose statins were used or because low LDL levels were achieved. Thus, we are not able to say, if a patient achieved an LDL of <70 mg/dl using moderate-dose statin, whether outcomes would be better if a higher-dose statin were used (which would achieve an LDL of even lower). Ongoing trials are addressing whether further reductions can be seen with even higher-intensity LDL lowering. Finally, we did not assess cost-benefit in this analysis; these analyses are ongoing in individual trials and should be useful to determine the cost (or potential savings) associated with the observed clinical benefit of this more intensive secondary prevention strategy.

Conclusions. Intensive lipid lowering with statins provides a significant benefit over standard-dose statin therapy for preventing non-fatal cardiovascular events, including stroke, with a trend toward decreasing cardiovascular mortality as well. These data support a broader use of intensive statin therapy for patients with stable coronary heart disease, as well as those with a recent ACS.

Reprint requests and correspondence: Dr. Christopher P. Cannon, TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: cpcannon@partners.org.

REFERENCES

1. Baigent C, Keech A, Kearney PM, et al., Cholesterol Treatment Trialists' Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78.
2. Cannon CP, Braunwald E, McCabe CH, et al., Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction-22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–504.
3. LaRosa JC, Grundy SM, Waters DD, et al., Treating to New Targets Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425–35.
4. de Lemos JA, Blazing MA, Wiviott SD, et al., A-to-Z Investigators. Early intensive vs. a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A-to-Z trial. JAMA 2004;292:1307–16.
5. Pedersen TR, Faergeman O, Kastelein JJ, et al., Incremental Decrease in End Points Through Aggressive Lipid-Lowering Study Group. High-dose atorvastatin versus usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 2005;294:2437–45.

6. Wiviott SD, de Lemos JA, Cannon CP, et al. A tale of two trials: a comparison of the post-acute coronary syndrome lipid-lowering trials A-to-Z and PROVE IT–TIMI-22. Circulation 2006;113: 1406–14.
7. Albert MA, Danielson E, Rifai N, Ridker PM, PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA 2001;286:64–70.
8. Steinberg BA, Braganza AJM, Eminowicz G, et al. Are statins being underdosed in clinical practice? Data from TACTICS-TIMI 18. Crit Pathways Cardiol 2005;4:169–73.
9. Austin PC, Mamdani MM. Impact of the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22/Reversal of Atherosclerosis with Aggressive Lipid Lowering trials on trends in intensive versus moderate statin therapy in Ontario, Canada. Circulation 2005;112:1296–300.
10. Carroll MD, Lacher DA, Sorlie PD, et al. Trends in serum lipids and lipoproteins of adults, 1960–2002. JAMA 2005;294:1773–81.
11. Fonarow GC, French WJ, Parsons LS, Sun H, Malmgren JA. Use of lipid-lowering medications at discharge in patients with acute myocardial infarction: data from the National Registry of Myocardial Infarction 3. Circulation 2001;103:38–44.
12. Steinberg BA, O'Hagan P, Chadwell P, Turner G, Cannon CP. Statin use and low-density lipoprotein cholesterol goals in 2004: how are we doing applying National Cholesterol Education Program III Guidelines (abstr)? J Am Coll Cardiol 2006;47 Suppl 47:209A.
13. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227–39.
14. Diener HC, Bogousslavsky J, Brass LM, et al., MATCH Investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364:331–7.
15. Pitt B. Low-density lipoprotein cholesterol in patients with stable coronary heart disease—is it time to shift our goals? N Engl J Med 2005;352:1483–4.
16. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. JAMA 2003;290:86–97.
17. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71–86.
18. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
19. Topol EJ. Intensive statin therapy—a sea change in cardiovascular prevention. N Engl J Med 2004;350:1562–4.
20. Clinical Trial Service Unit. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH). Available at: http://www.ctsu.ox.ac.uk/projects/search.shtml. Accessed November 18, 2005.
21. Sever PS, Dahlof B, Poulter NR, et al., ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003;361:1149–58.
22. Colhoun HM, Betteridge DJ, Durrington PN, et al., CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–96.
23. Shepherd J, Blauw GJ, Murphy MB, et al., PROSPER Study Group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623–30.