Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 51, No. 20, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.12.054

Intensive Lipid-Lowering With Atorvastatin for Secondary Prevention in Patients After Coronary Artery Bypass Surgery

Sanjiv J. Shah, MD,*† David D. Waters, MD,* Philip Barter, MD,‡ John J. P. Kastelein, MD, PHD,§ James Shepherd, MD,‖ Nanette K. Wenger, MD,¶ David A. DeMicco, DPHARM,# Andrei Breazna, PHD,# John C. LaRosa, MD**

San Francisco, California; Chicago, Illinois; Sydney, Australia; Amsterdam, the Netherlands; Glasgow, United Kingdom; Atlanta, Georgia; and New York, New York

Objectives The aim of this post hoc analysis from the TNT (Treating to New Targets) trial is to determine whether patients with previous coronary artery bypass grafting (CABG) surgery achieved clinical benefit from intensive low-density lipoprotein (LDL)-cholesterol lowering.

Background The development and progression of atherosclerosis is accelerated in coronary venous bypass grafts.

Methods A total of 10,001 patients with documented coronary disease, including 4,654 with previous CABG, were randomized to atorvastatin 80 or 10 mg/day and were followed for a median of 4.9 years. The primary end point was the occurrence of a first major cardiovascular event (cardiac death, nonfatal myocardial infarction, resuscitated cardiac arrest, or stroke).

Results A first major cardiovascular event occurred in 11.4% of the patients with prior CABG and 8.5% of those without prior CABG ($p < 0.001$). In CABG patients, mean LDL-cholesterol levels at study end were 79 mg/dl in the 80-mg arm and 101 mg/dl in the 10-mg arm, and the primary event rate was 9.7% in the 80-mg arm and 13.0% in the 10-mg arm (hazard ratio 0.73, 95% confidence interval 0.62 to 0.87, $p = 0.0004$). Repeat revascularization during follow-up, either CABG or percutaneous coronary intervention, was performed in 11.3% of the CABG patients in the 80-mg arm and 15.9% in the 10-mg arm (hazard ratio 0.70, 95% confidence interval 0.60 to 0.82, $p < 0.0001$).

Conclusions Intensive LDL-cholesterol lowering to a mean of 79 mg/dl with atorvastatin 80 mg/day in patients with previous CABG reduces major cardiovascular events by 27% and the need for repeat coronary revascularization by 30%, compared with less intensive cholesterol-lowering to a mean of 101 mg/dl with atorvastatin 10 mg/day. (A Study to Determine the Degree of Additional Reduction in CV Risk in Lowering LDL Below Minimum Target Levels [TNT]; NCT00327691) (J Am Coll Cardiol 2008;51:1938–43) © 2008 by the American College of Cardiology Foundation

Coronary artery bypass graft surgery (CABG) is a major advance in the care of patients with coronary disease (1,2). Over 500,000 patients now undergo CABG in the United States each year, making it the most frequent major operation performed (2). Although CABG improves symptoms and decreases mortality in certain subsets, coronary athero-

From the *Division of Cardiology, San Francisco General Hospital, and the Department of Medicine, University of California, San Francisco, California; †Division of Cardiology, Department of Medicine, Northwestern University, Chicago, Illinois; ‡Heart Research Institute, Sydney, Australia; §Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; ‖University of Glasgow, Glasgow, United Kingdom; ¶Emory University School of Medicine, Atlanta, Georgia; #Pfizer Inc., New York, New York; and the **State University of New York Health Science Center, New York, New York. Funding for the study was provided by Pfizer Inc. Dr. Waters has received investigator-initiated research funding from Merck; consulting fees from Merck, Schering-Plough, and Pfizer; and honoraria for lectures from Pfizer. Dr. Barter has received grant support from Pfizer; consulting fees from AstraZeneca, LifeCycle Pharma, Merck, and Sanofi-Aventis; and honoraria for lectures from AstraZeneca, Fournier-Pharma, Merck, Pfizer, and Sanofi-Aventis. Dr. Kastelein has received grant support, consulting fees, and honoraria for lectures from AstraZeneca, Bristol-Myers Squibb, Merck, Pfizer, Sankyo, and Schering-Plough. Dr. Shepherd has received consulting fees from AstraZeneca, GlaxoSmithKline, Merck, Schering-Plough, and Oxford Biosensors and honoraria for lectures from AstraZeneca, Merck, Pfizer, and Schering-Plough. Dr. Wenger has received grant support from Merck and Pfizer, and consulting fees from Abbott, AstraZeneca, CV Therapeutics, Merck, Pfizer, Schering-Plough, and Sanofi-Aventis. Dr. DeMicco is a Pfizer employee. Dr. Breazna is a Pfizer employee. Dr. LaRosa has received consulting fees from AstraZeneca, Bristol-Myers Squibb, Merck, and Pfizer, and honoraria for lectures from Pfizer.

Manuscript received October 12, 2007; revised manuscript received December 12, 2007, accepted December 17, 2007.

sclerosis continues to progress in native coronary arteries. In fact, atherosclerosis of native coronary and saphenous vein grafts (SVG) is accelerated, and low-density lipoprotein (LDL) cholesterol is an important causative factor (3). The accelerated atherosclerosis in these patients results in recurrent angina in 15% and ischemic events in 10% at 5 years after CABG (1).

On the basis of the findings of several recent studies, including the TNT (Treating to New Targets) study, aggressive lowering of LDL-cholesterol to 70 to 80 mg/dl or lower in coronary patients decreases major cardiovascular events (4–6). However, the role of aggressive lipid-lowering in patients with CABG is less clear. Prior trials (7–10) have found that lipid-lowering after CABG decreases angiographic progression of native coronary and SVG atherosclerosis and might decrease major cardiovascular outcomes. However, in all these randomized trials, LDL cholesterol in the treatment groups was reduced to no lower than 90 to 100 mg/dl.

We hypothesized that aggressive lipid-lowering with atorvastatin 80 mg to achieve LDL cholesterol of 80 mg/dl would reduce major cardiovascular events in CABG patients, compared with conventional lipid-lowering therapy. The TNT study was ideal for testing this hypothesis, because 4,654 patients with prior CABG were randomized to high- or low-dose atorvastatin.

Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
CHD = coronary heart disease
CI = confidence interval
HR = hazard ratio
LDL = low-density lipoprotein
SVG = saphenous vein graft

Methods

Study design and patients. The design of the TNT study has been described in detail previously (4,11). All patients gave written informed consent, and the study was approved by the research ethics committee or institutional review board at each participating center. Eligible participants were men and women ages 35 to 75 years who had clinically evident coronary heart disease (CHD), defined as previous myocardial infarction, previous or current angina with objective evidence of atherosclerotic CHD, or a history of coronary revascularization. A history of CABG was determined by patient self-report. The most important exclusion criteria were hypersensitivity to statins, active liver disease, nephrotic syndrome, uncontrolled diabetes or hypertension, a coronary event or revascularization within 1 month, an ejection fraction <30%, significant valvular disease, and nonskin cancer or another survival-limiting disease.

Eligible patients with LDL cholesterol levels above 130 mg/dl off treatment underwent an 8-week run-in period of open-label treatment with 10 mg of atorvastatin daily. At the end of the run-in phase, participants with LDL <130 mg/dl were randomized in a double-blind fashion to 80 mg or 10 mg of atorvastatin daily. Patients were followed for a median of 4.9 years.

Statistical analyses. The primary outcome was the occurrence of a major cardiovascular event, defined as death from CHD, nonfatal nonprocedure-related myocardial infarction, resuscitated cardiac arrest, or stroke (fatal or nonfatal). Coronary revascularization was a component of a secondary end point.

Differences in baseline characteristics in participants with and without prior CABG were determined with *t* tests for continuous variables and chi-squared tests for dichotomous variables. We used the same tests to compare CABG patients in the 80- and 10-mg groups.

All analyses were performed on an intention-to-treat basis. All randomized patients who were dispensed 1 dose of the study drug were included in the analyses. The primary and secondary composite end points were analyzed from the time of first dose of study drug to the first event, according to the Kaplan-Meier method. We calculated the frequency of the primary and secondary efficacy outcomes and corresponding hazard ratios (HRs) (unadjusted) during our analysis of differences between post-CABG and non-CABG patients. We repeated this analysis in the subset of post-CABG patients, comparing high-dose and low-dose atorvastatin treatment groups.

Table 1 Baseline Characteristics of Patients by History of CABG Surgery

	Prior CABG (n = 4,654)	No Prior CABG (n = 5,347)	p Value
Age, yrs	62.8 ± 8.2	59.5 ± 9.1	<0.0001
Male (%)	3,881 (83.4%)	4,218 (78.9%)	<0.0001
White (%)	4,389 (94.3%)	5,021 (93.9%)	0.394
Body mass index, kg/m^2	28.5 ± 4.6	28.5 ± 4.6	0.822
Cardiovascular risk factors (%)			
Current smoker	426 (9.2%)	915 (17.1%)	<0.0001
Hypertension	2,696 (57.9%)	2,716 (50.8%)	<0.0001
Diabetes mellitus	823 (17.7%)	678 (12.7%)	<0.0001
Cardiovascular history (%)			
Angina	3,924 (84.3%)	4,226 (79.0%)	<0.0001
Myocardial infarction	2,450 (52.6%)	3,383 (63.3%)	<0.0001
Cerebrovascular accident	309 (6.6%)	208 (3.9%)	<0.0001
Peripheral-arterial disease	727 (15.6%)	446 (8.3%)	<0.0001
Percutaneous coronary intervention	1,456 (31.3%)	3,951 (73.9%)	<0.0001
Lipids (mg/dl)*			
LDL cholesterol	98 ± 17	97 ± 18	0.101
Total cholesterol	175 ± 24	174 ± 24	0.183
Triglycerides	154 ± 73	148 ± 69	<0.0001
HDL cholesterol	47 ± 11	48 ± 11	<0.0001

*Lipid values at the end of the 8-week run-in period on atorvastatin 10 mg/day.
CABG = coronary artery bypass grafting surgery; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 2 Baseline Characteristics by Treatment Group Among Patients With CABG

	Atorvastatin 10 mg (n = 2,338)	Atorvastatin 80 mg (n = 2,316)	p Value
Age, yrs	62.8 ± 8.2	62.7 ± 8.2	0.931
Male, n (%)	1,941 (83.0%)	1,940 (83.8%)	0.495
White, n (%)	2,197 (94.0%)	2,192 (94.6%)	0.319
Body mass index, kg/m^2	28.6 ± 4.7	28.5 ± 4.4	0.166
Cardiovascular risk factors, n (%)			
Current smoker	221 (9.5%)	205 (8.9%)	0.477
Hypertension	1,377 (58.9%)	1,319 (57.0%)	0.185
Diabetes mellitus	420 (18.0%)	403 (17.4%)	0.615
Cardiovascular history, n (%)			
Angina	1,969 (84.2%)	1,955 (84.4%)	0.855
Myocardial infarction	1,201 (51.4%)	1,249 (53.9%)	0.080
Cerebrovascular accident	155 (6.6%)	154 (6.6%)	0.975
Peripheral-arterial disease	346 (14.8%)	381 (16.5%)	0.121
Percutaneous coronary intervention	739 (31.6%)	717 (31.0%)	0.633
Lipids (mg/dl)*			
LDL cholesterol	98 ± 18	98 ± 17	0.457
Total cholesterol	175 ± 24	175 ± 24	0.911
Triglycerides	154 ± 73	154 ± 72	0.743
HDL cholesterol	47 ± 11	47 ± 11	0.339

*Lipid values at the end of the 8-week run-in period on atorvastatin 10 mg/day.
Abbreviations as in Table 1.

Results

Patient characteristics. Of the 10,001 total TNT participants, 4,654 (47%) had a history of CABG. Compared with participants without a history of CABG, those with CABG were older, more likely male, and were more likely to have a history of diabetes mellitus, cerebrovascular accident, and peripheral arterial disease, as shown in Table 1.

Of the 4,654 patients with prior CABG, 2,316 were randomized to atorvastatin 80 mg/day and 2,338 were randomized to atorvastatin 10 mg/day. As shown in Table 2, the clinical features of the CABG patients in the 80- and 10-mg groups were similar. The mean interval between CABG and study screening was 3.9 ± 4.3 years in the 80-mg group and 4.0 ± 4.4 years in the 10-mg group.

Changes in lipid levels in CABG patients. In the atorvastatin 80-mg group, LDL-cholesterol was reduced from 163 mg/dl in samples collected before the 8-week run-in period to 79 mg/dl at study end, a 51% reduction. In the 10-mg group, LDL-cholesterol was reduced from 163 mg/dl before treatment to 101 mg/dl at study end, a 38% reduction. Triglyceride levels were reduced by 34% among patients receiving atorvastatin 80 mg and by 23% among patients receiving 10 mg. The high-density lipoprotein cholesterol levels were similar in the 80- and 10-mg groups during treatment.

Events during follow-up. A first major cardiovascular event (CHD death, myocardial infarction, resuscitated cardiac arrest, or stroke) occurred in 529 CABG patients (11.4%) and in 453 patients (8.5%) without prior CABG (HR 1.38, 95% confidence interval [CI] 1.22 to 1.56; p < 0.0001) as depicted in Figure 1. Other end point events were also more common in patients with previous CABG, as shown in Table 3.

Among post-CABG patients, a primary end-point event occurred in 224 patients (9.7%) in the 80-mg atorvastatin group compared with 305 patients (13.0%) in the 10-mg group, a 27% relative risk reduction and a 3.3% absolute risk reduction (HR 0.73, 95% CI 0.62 to 0.87, p = 0.0004). The Kaplan-Meier curves for the primary outcome for the 80- and 10-mg groups of CABG patients are illustrated in Figure 2. During follow-up, 262 patients (11.3%) in the

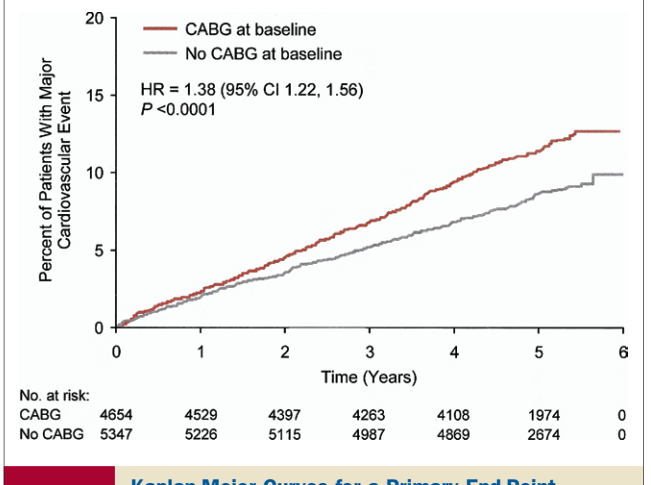

Figure 1 Kaplan-Meier Curves for a Primary End-Point Event in Patients With and Without Prior CABG

Primary end points were cardiac death, myocardial infarction, resuscitated cardiac arrest, and stroke. CABG = coronary artery bypass graft surgery; CI = confidence interval; HR = hazard ratio.

Table 3 Events During Follow-Up in Patients With and Without Prior CABG

Event Type	Prior CABG (n = 4,654)	No Prior CABG (n = 5,347)	Prior/No Prior Hazard Ratio (95% CI)	p Value
Major cardiovascular event	529 (11.4%)	453 (8.5%)	1.38 (1.22–1.56)	<0.0001
Nonfatal MI	281 (6.0%)	270 (5.0%)	1.22 (1.04–1.45)	0.0181
Resuscitated cardiac arrest	30 (0.6%)	21 (0.4%)	1.67 (0.96–2.92)	0.0712
Stroke	153 (3.3%)	119 (2.2%)	1.51 (1.19–1.92)	0.0007
Cardiovascular death	162 (3.5%)	119 (2.2%)	1.59 (1.25–2.01)	0.0001
CHD death	136 (2.9%)	92 (1.7%)	1.72 (1.32–2.24)	0.0001
Noncardiovascular death	147 (3.2%)	138 (2.6%)	1.26 (1.00–1.59)	0.0485
Death	309 (6.6%)	257 (4.8%)	1.41 (1.20–1.67)	<0.0001
Major cardiovascular event or death	651 (14.0%)	585 (10.9%)	1.32 (1.18–1.47)	<0.0001
CHD death or nonfatal MI	391 (8.4%)	344 (6.4%)	1.33 (1.15–1.54)	0.0001
First cardiovascular event	1,500 (32.2%)	1,582 (29.6%)	1.11 (1.04–1.19)	0.0033
First coronary event	1,093 (23.5%)	1,311 (24.5%)	0.95 (0.88–1.03)	0.2510
Major coronary event	404 (8.7%)	345 (6.5%)	1.36 (1.18–1.57)	<0.0001
Heart failure hospital stay	186 (4.0%)	100 (1.9%)	2.19 (1.72–2.79)	<0.0001
Stroke/transient ischemic attack	255 (5.5%)	193 (3.6%)	1.55 (1.29–1.87)	<0.0001
Transient ischemic attack	110 (2.4%)	87 (1.6%)	1.47 (1.11–1.95)	0.0069
Peripheral vascular disease	357 (7.7%)	200 (3.7%)	2.13 (1.79–2.53)	<0.0001

CABG = coronary artery bypass graft surgery; CHD = coronary heart disease; CI = confidence interval; MI = myocardial infarction.

80-mg group and 371 patients (15.9%) in the 10-mg group underwent repeat coronary revascularization, either with CABG or percutaneous coronary intervention, resulting in a 30% relative risk reduction and a 4.6% absolute reduction (HR 0.70, 95% CI 0.60 to 0.82, $p < 0.0001$). The Kaplan-Meier curves for this outcome are shown in Figure 3. The combined end point of a major cardiovascular event or coronary revascularization occurred in 417 patients (18.0%) in the 80-mg group compared with 566 patients (24.2%) in the 10-mg group, a 28% relative risk reduction and a 6.2% absolute reduction (HR 0.72, 95% CI 0.64 to 0.82, $p < 0.0001$), as shown in Figure 4. The number of CABG patients needed to treat with 80 mg compared with 10 mg over the 4.9 years of follow-up to prevent a major cardiovascular event or coronary revascularization is 16. The primary and secondary end-point rates for the 80- and 10-mg groups are listed in Table 4.

Safety. In the cohort with CABG at baseline, discontinuations from therapy due to treatment-related adverse events during the 4.9 years of follow-up occurred in 87 patients (3.8%) in the atorvastatin 80-mg group and in 62 patients (2.7%) in the atorvastatin 10-mg group ($p = 0.04$). Treatment-related myalgias were reported in 1.3% of patients in both groups, and no post-CABG patient experienced an elevation of creatinine phosphokinase >10 × the upper limit of normal on 2 consecutive measurements.

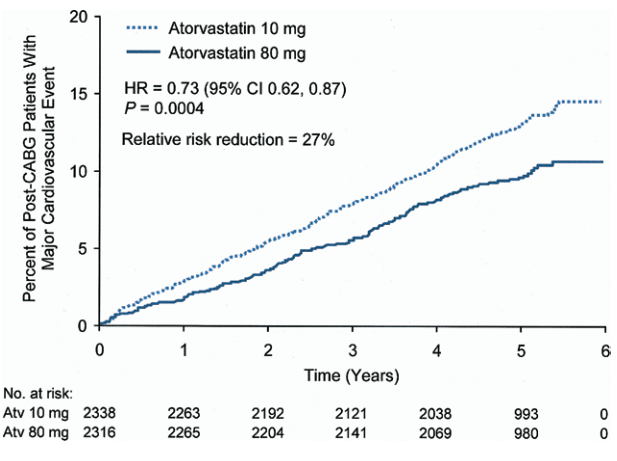

Figure 2 Kaplan-Meier Curves for the Primary End Point Among Patients With Prior CABG

Abbreviations as in Figure 1.

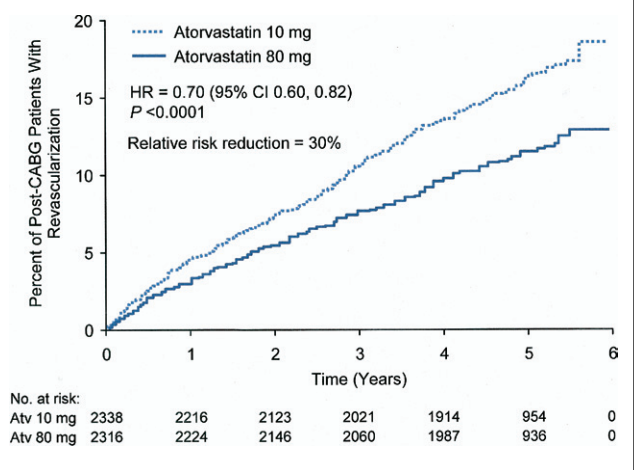

Figure 3 Kaplan-Meier Curves for Coronary Revascularization Among Patients With Prior CABG

Revascularization was either repeat CABG or percutaneous coronary intervention, in the 80- and 10-mg atorvastatin groups among patients with prior CABG at baseline. Abbreviations as in Figure 1.

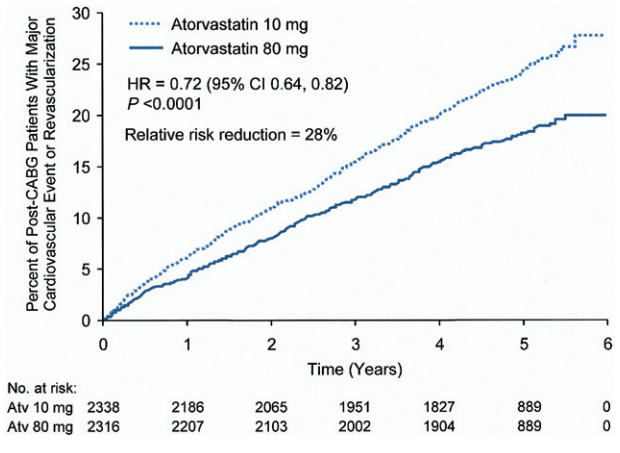

Figure 4 **Kaplan-Meier Curves for a Combination of the Primary End Point or for Coronary Revascularization**

Abbreviations as in Figure 1.

Elevated alanine aminotransferase or aspartate aminotransferase >3 × the upper limit of normal on consecutive measurements occurred in 1.1% of patients in the 80-mg group and 0.3% of those in the 10-mg group (p = 0.0003).

Discussion

Patients with previous CABG who had their LDL-cholesterol lowered to approximately 80 mg/dl with atorvastatin 80 mg had a significantly better outcome than those with LDL-cholesterol lowered to approximately 100 mg/dl with 10 mg of atorvastatin. Compared with the less-aggressively treated patients, those in the atorvastatin 80-mg group experienced a 27% reduction in major cardiovascular events and a 30% reduction in repeat coronary revascularization (either CABG or percutaneous coronary intervention) during a mean follow-up of 4.9 years. The number needed to treat with 80 mg compared with 10 mg to prevent 1 of these events was 16.

Previous studies. The only large randomized trial of statins specifically designed to study patients after CABG was the Post-CABG trial (8,9), which randomized 1,351 patients with patent venous bypass grafts to 40 or 2.5 mg/day of lovastatin, such that LDL-cholesterol levels during follow-up ranged from 93 to 97 mg/dl in the higher-dose group and 132 to 136 mg/dl in the lower-dose group. After 4.3 years, graft deterioration was less common in the aggressively treated group (8), and during subsequent follow-up the event rate was also lower (9).

The results of the Post-CABG trial and the results of the CABG patients in TNT are complementary. Both report that more aggressive LDL-cholesterol–lowering is associated with better outcomes, and TNT extends the benefit to LDL-cholesterol levels in the range of 80 mg/dl. The Post-CABG trial provides anatomic evidence of reduced progression of SVG disease, whereas TNT documents event reduction for most cardiovascular end points.

Study limitations. This study has several limitations. Analysis of CABG patients was not pre-specified in the study protocol. Thus, important prognostic information related to CABG, such as number and type of bypass grafts, number of diseased vessels, preoperative symptoms, and left ventricular function, is not available.

All patients were treated with a statin so that no comparator placebo group is available. However, on the basis of previous studies in different populations, atorvastatin 10 mg reduced events by approximately one-third (12,13). The

Table 4 **Events During Follow-Up in CABG Patients in the 10- and 80-mg Group**

Event Type	Atorvastatin 10 mg (n = 2,338)	Atorvastatin 80 mg (n = 2,316)	Hazard Ratio (95% CI)	p Value
Major cardiovascular event	305 (13.0%)	224 (9.7%)	0.73 (0.62–0.87)	0.0004
Nonfatal MI	167 (7.1%)	114 (4.9%)	0.68 (0.54–0.86)	0.0015
Resuscitated cardiac arrest	16 (0.7%)	14 (0.6%)	0.88 (0.43–1.81)	0.7332
Stroke	84 (3.6%)	69 (3.0%)	0.83 (0.60–1.14)	0.2463
Cardiovascular death	93 (4.0%)	69 (3.0%)	0.75 (0.55–1.02)	0.0667
CHD death	80 (3.4%)	56 (2.4%)	0.70 (0.50–0.99)	0.0436
Noncardiovascular death	62 (2.7%)	85 (3.7%)	1.39 (1.00–1.93)	0.0493
Death	155 (6.6%)	154 (6.6%)	1.00 (0.80–1.25)	0.9771
Major cardiovascular event or death	355 (15.2%)	296 (12.8%)	0.83 (0.71–0.97)	0.0184
CHD death or nonfatal MI	231 (9.9%)	160 (6.9%)	0.69 (0.56–0.84)	0.0003
First cardiovascular event	836 (35.8%)	664 (28.7%)	0.77 (0.69–0.85)	<0.0001
First coronary event	626 (26.8%)	467 (20.2%)	0.73 (0.65–0.82)	<0.0001
Major coronary event	237 (10.1%)	167 (7.2%)	0.70 (0.58–0.86)	0.0005
Heart failure hospital stay	108 (4.6%)	78 (3.4%)	0.72 (0.54–0.97)	0.0289
Stroke/transient ischemic attack	145 (6.2%)	110 (4.7%)	0.76 (0.59–0.98)	0.0308
Peripheral vascular disease	179 (7.7%)	178 (7.7%)	1.00 (0.82–1.24)	0.9677
Transient ischemic attack	66 (2.8%)	44 (1.9%)	0.67 (0.46–0.98)	0.0379
First repeat revascularization during follow-up	371 (15.9%)	262 (11.3%)	0.70 (0.60–0.82)	<0.0001

Abbreviations as in Table 3.

results of this analysis indicate that the 80-mg dose and lowering LDL-cholesterol to approximately 80 mg/dl instead of 100 mg/dl provides substantial additional event reduction.

The TNT patient population was overwhelmingly Caucasian and male, with LDL-cholesterol levels off treatment between 130 and 250 mg/dl. Whether similar benefits would be seen in different types of patients is uncertain.

Safety. Atorvastatin 80 mg was well tolerated in TNT, both in CABG patients and in the overall study population. A total of 18,696 patients have been treated with atorvastatin 80 mg in randomized clinical trials, most for 4 to 5 years (4–6,12–15). Across these trials, the incidence of hepatic enzyme elevation >3 × the upper limit of normal on repeat measurements was 1.43%, and only 4 patients had creatine kinase levels >10 × the upper limit of normal on repeat measurements.

Both in CABG patients and in the entire TNT cohort of 10,001 patients, total mortality did not differ between the 80- and 10-mg groups. This net balance was the result of a decrease in CHD death and an increase in noncardiovascular death in the 80-mg group compared with the 10-mg group, with both differences of borderline statistical significance. The increase in noncardiovascular mortality was not concentrated in any diagnostic category and thus might be a chance finding. Noncardiovascular mortality was identical in the 80-mg atorvastatin arms of TNT and IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering trial) (3.2%); noncardiovascular mortality in the simvastatin arm of IDEAL was 3.5%, a finding that does not substantiate an increased noncardiovascular risk with high-dose atorvastatin (5).

Conclusions

In conclusion, aggressive lipid-lowering with atorvastatin 80 mg decreases major cardiovascular events and the need for repeat revascularization in patients with previous CABG. Because this is an especially high-risk population that tends to be undertreated with lipid-lowering therapy, this treatment should be the new standard of care, with the goal of reducing cardiovascular morbidity and mortality and prolonging bypass graft patency.

Reprint requests and correspondence to: Dr. David D. Waters, Room 5G1, Division of Cardiology, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, California 94110. E-mail: dwaters@medsfgh.ucsf.edu.

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