Effect of Lowering LDL Cholesterol Substantially Below Currently Recommended Levels in Patients With Coronary Heart Disease and Diabetes

The Treating to New Targets (TNT) study

JAMES SHEPHERD, MD[1]
PHILIP BARTER, MD, PHD[2]
RAFAEL CARMENA, MD[3]
PRAKASH DEEDWANIA, MD[4]
JEAN-CHARLES FRUCHART, PHARMD, PHD[5]
STEVEN HAFFNER, MD[6]
JUDITH HSIA, MD[7]
ANDREI BREAZNA, PHD[8]
JOHN LAROSA, MD[9]
SCOTT GRUNDY, MD, PHD[10]
DAVID WATERS, MD[11]
FOR THE TREATING TO NEW TARGETS INVESTIGATORS

OBJECTIVE — The Treating to New Targets study showed that intensive lipid-lowering therapy with atorvastatin 80 mg/day provides significant clinical benefit beyond that afforded by atorvastatin 10 mg/day in patients with stable coronary heart disease (CHD). The objective of our study was to investigate whether similar benefits of high-dose intensive atorvastatin therapy can be achieved in patients with CHD and diabetes.

RESEARCH DESIGN AND METHODS — A total of 1,501 patients with diabetes and CHD, with LDL cholesterol levels of <130 mg/dl, were randomized to double-blind therapy with either atorvastatin 10 (n = 753) or 80 (n = 748) mg/day. Patients were followed for a median of 4.9 years. The primary end point was the time to first major cardiovascular event, defined as death from CHD, nonfatal non–procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke.

RESULTS — End-of-treatment mean LDL cholesterol levels were 98.6 mg/dl with atorvastatin 10 mg and 77.0 mg/dl with atorvastatin 80 mg. A primary event occurred in 135 patients (17.9%) receiving atorvastatin 10 mg, compared with 103 patients (13.8%) receiving atorvastatin 80 mg (hazard ratio 0.75 [95% CI 0.58–0.97], P = 0.026). Significant differences between the groups in favor of atorvastatin 80 mg were also observed for time to cerebrovascular event (0.69 [0.48–0.98], P = 0.037) and any cardiovascular event (0.85 [0.73–1.00], P = 0.044). There were no significant differences between the treatment groups in the rates of treatment-related adverse events and persistent elevations in liver enzymes.

CONCLUSIONS — Among patients with clinically evident CHD and diabetes, intensive therapy with atorvastatin 80 mg significantly reduced the rate of major cardiovascular events by 25% compared with atorvastatin 10 mg.

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Patients with type 2 diabetes are at high risk of coronary heart disease (CHD) (1,2). Furthermore, patients with diabetes who experience a myocardial infarction have a poorer prognosis and a higher CHD mortality rate either immediately or in the long term than nondiabetic patients with a prior myocardial infarction (3,4).

Dyslipidemia is a major contributor to the increased CHD risk in patients with type 2 diabetes (5,6) and is characterized by elevated levels of triglycerides and low levels of HDL cholesterol. LDL cholesterol is similar to that in the general population, although the LDL particles are smaller, denser, and more atherogenic. Lowering elevated LDL cholesterol levels with statins has demonstrated significant reductions in cardiovascular events in patients with diabetes and CHD (7–10). Due to the high cardiovascular risk conferred by type 2 diabetes, current treatment recommendations consider patients with diabetes to be CHD risk equivalents (11–13) and have established an LDL cholesterol goal of <100 mg/dl (2.6 mmol/l) in these patients. Recent cardiovascular outcomes trials have raised the issue of lower optimal treatment targets for patients with CHD (14,15). While the American Diabetes Association (ADA)-recommended goal of therapy remains at an LDL cholesterol <100 mg/dl, the potential for a more aggressive LDL cholesterol goal of <70 mg/dl (1.8 mmol/l) has been proposed as a treatment option in patients with

From the [1]Department of Vascular Biochemistry, University of Glasgow, Glasgow, U.K.; [2]The Heart Research Institute, Department of Medicine, University of Sydney, Sydney, Australia; the [3]Endocrinology Department, Clinic University Hospital, University of Valencia, Valencia, Spain; the [4]Cardiology Division, Veterans Affairs Central California Health Care, University of California San Francisco School of Medicine, San Francisco, California; the [5]Lipoprotein and Atherosclerosis Research Unit, Institut National de la Santé et de la Recherche Médicale, Pasteur Institute, Lille, France; the [6]Department of Medicine, University of Texas Health Science Center, San Antonio, Texas; the [7]Division of Cardiology, George Washington University Medical Center, Washington, DC; the [8]Biometrics Department, Pfizer, New York, New York; the [9]State University of New York Downstate Medical Center, State University of New York Health Science Center, Brooklyn, New York; the [10]Center for Human Nutrition, Departments of Clinical Nutrition and Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas; and the [11]Division of Cardiology, School of Medicine, San Francisco General Hospital, University of California San Francisco School of Medicine, San Francisco, California.

Address correspondence and reprint requests to James Shepherd, Biochemistry, Royal Infirmary, Glasgow, G4 OSF, U.K. E-mail: jshepherd@gri-biochem.org.uk.

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Abbreviations: ADA, American Diabetes Association; CHD, coronary heart disease; TNT, Treating to New Targets.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Baseline characteristics of patients with diabetes*

Baseline characteristic (at randomization)	Atorvastatin 10 mg	Atorvastatin 80 mg
n	753	748
Men	544 (72.2)	550 (73.5)
Age (years)	62.8 ± 8.0	63.2 ± 7.9
Race		
White	670 (89.0)	670 (89.6)
Black	48 (6.4)	39 (5.2)
Other	35 (4.6)	39 (5.2)
Systolic blood pressure (mmHg)	134.7 ± 17.3	134.3 ± 17.6
Diastolic blood pressure (mmHg)	76.8 ± 9.5	77.1 ± 9.9
BMI (kg/m^2)	30.7 ± 5.6	30.1 ± 5.0
Diabetes duration (years)	8.3 ± 8.5	8.8 ± 8.8
Diabetes control		
Oral hypoglycemic drug only	324 (43.0)	326 (43.6)
Insulin only	101 (13.4)	94 (12.6)
Insulin + oral hypoglycemic drug	157 (20.8)	146 (19.5)
No diabetes medications*	171 (22.7)	182 (24.3)
Fasting plasma glucose (mg/dl)	153.9 ± 49.3	154.0 ± 49.9
Plasma creatinine (mg/dl)	1.19 ± 0.23	1.19 ± 0.25
A1C (%)	7.4 ± 1.3	7.4 ± 1.2
Cardiovascular history		
Angina	606 (80.5)	632 (84.5)
Hypertension	536 (71.2)	525 (70.2)
Former smoker	484 (64.3)	446 (59.6)
Myocardial infarction	414 (55.0)	442 (59.1)
Coronary artery bypass graft	420 (55.8)	403 (53.9)
Coronary angioplasty	370 (49.1)	402 (53.7)
Peripheral arterial disease	151 (20.1)	168 (22.5)
Congestive heart failure	105 (13.9)	108 (14.4)
Current smoker	72 (9.6)	86 (11.5)
Cerebrovascular accident	67 (8.9)	68 (9.1)
Lipids		
LDL cholesterol		
mg/dl	96.7 ± 17.8	95.6 ± 18.4
mmol/l	2.50 ± 0.46	2.47 ± 0.48
Total cholesterol		
mg/dl	174.9 ± 24.5	174.7 ± 24.6
mmol/l	4.52 ± 0.63	4.52 ± 0.64
Triglycerides		
mg/dl	169.2 ± 78.9	171.3 ± 80.9
mmol/l	1.91 ± 0.89	1.93 ± 0.91
HDL cholesterol		
mg/dl	44.6 ± 9.2	45.2 ± 11.1
mmol/l	1.15 ± 0.24	1.17 ± 0.29
Apolipoprotein B	113.6 ± 20.0	112.5 ± 19.5

Data are means ± SD or *n* (%). *Patients who were not recorded as taking oral hypoglycemic agents or insulin at study entry.

type 2 diabetes and overt cardiovascular disease (12).

The Treating to New Targets (TNT) study (16) was designed to provide more information on the optimal level of LDL cholesterol for cardiovascular risk reduction in patients with established CHD. Reduction to a mean LDL cholesterol level of 77 mg/dl (2.0 mmol/l) with atorvastatin 80 mg/day was associated with a 22% relative risk reduction in cardiovascular events compared with reduction to a mean LDL cholesterol of 101 mg/dl (2.6 mmol/l) with atorvastatin 10 mg/day (16). The current subanalysis of the TNT study investigates whether similar benefits of lowering lipids to levels beyond current recommendations with high-dose intensive statin therapy can be achieved in patients with CHD and diabetes.

RESEARCH DESIGN AND METHODS

— The design of the TNT study has been described in detail previously (16,17). Patients eligible for inclusion were men and women aged 35–75 years with clinically evident CHD, defined as previous myocardial infarction, previous or present angina with objective evidence of atherosclerotic CHD, or previous coronary revascularization procedure. Patients were included in the current analysis if they had prior history of diabetes noted on their prescreening form (fasting glucose levels at screening were not used). Major exclusion criteria included statin hypersensitivity, current liver disease, nephrosis, pregnancy or uncontrolled CHD risk factors, CHD event or revascularization within less than a month, congestive heart failure, unexplained creatine phosphokinase levels more than six times the upper limit of normal, life-threatening malignancy, or immunosuppressive or lipid-lowering drug treatment.

Any previously prescribed lipid-regulating drugs were discontinued at screening, and all patients required a wash-out period of 1–8 weeks (8 weeks for those who had and 1 week for those who had not previously received lipid-regulating drugs). To ensure that all patients at baseline achieved LDL cholesterol levels consistent with the current guidelines for the treatment of stable CHD, patients with LDL cholesterol between 130 and 250 mg/dl (3.4–6.5 mmol/l) and triglycerides ≤600 mg/dl (6.8 mmol/l) entered an 8-week open-label period with atorvastatin 10 mg/day. At the end of the run-in phase (week 0), those patients with a mean LDL cholesterol <130 mg/dl (3.4 mmol/l) (determined at weeks −4 and −2) were randomized to double-blind therapy with either atorvastatin 10 or 80 mg/day. During the double-blind period, follow-up visits occurred at week 12 and at months 6, 9, and 12 in the 1st year and every 6 months thereafter. At each visit, vital signs, clinical end points, adverse events, and concurrent medication information were collected. In addition, on alternating visits (i.e., annually), physical examinations and electrocardiograms were performed and laboratory specimens collected.

Efficacy outcome measures

The primary efficacy outcome measure was the time to first occurrence of a major cardiovascular event, defined as CHD

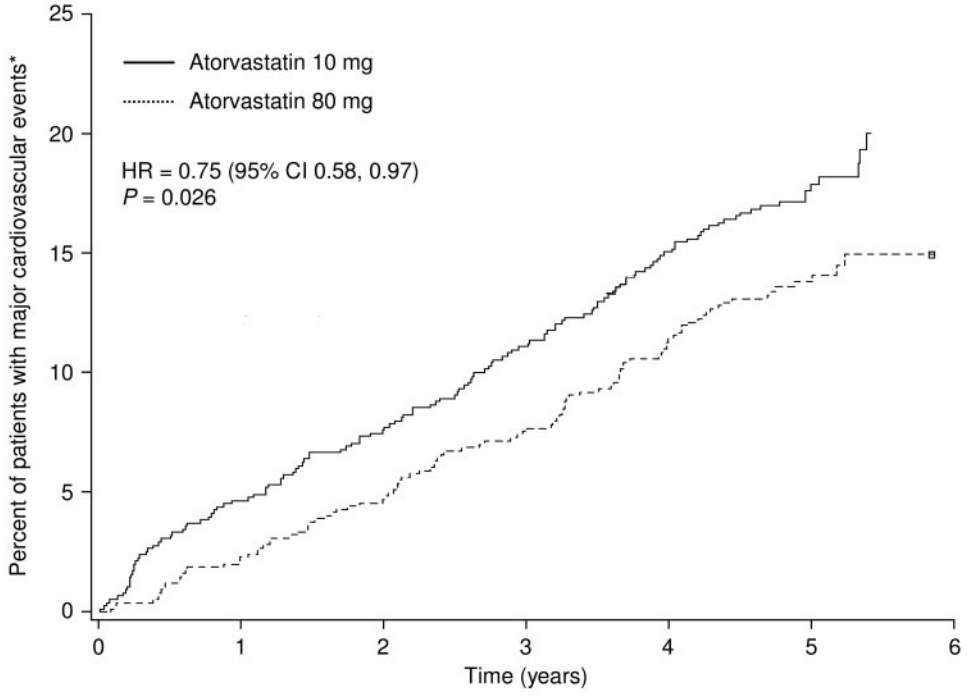

Figure 1—*Kaplan-Meier estimates of the incidence of major cardiovascular events in patients with diabetes. *Composite of CHD death, nonfatal non–procedure-related myocardial infarction, resuscitated cardiac arrest, and fatal or nonfatal stroke.*

death, nonfatal non–procedure-related myocardial infarction, resuscitated cardiac arrest, and fatal or nonfatal stroke. Secondary efficacy outcome measures included any cardiovascular event, major coronary event (CHD death, nonfatal non–procedure-related myocardial infarction, or resuscitated cardiac arrest), any coronary event, cerebrovascular event, peripheral arterial disease, documented angina, hospitalization for congestive heart failure, and all-cause mortality.

Statistical analysis

Cholesterol inclusion/exclusion criteria were selected to achieve an average level of 100 mg/dl (2.6 mmol/l) in the atorvastatin 10 mg/day treatment arm. To reach an average LDL cholesterol level in the comparator group of ~75 mg/dl (1.9 mmol/l), atorvastatin 80 mg/day was chosen. Differences between the atorvastatin 80- and 10-mg treatment groups were based on log-rank analyses of the first occurrence of a major cardiovascular event during the 5-year follow-up period in each group. Relative risks and hazard ratios (HRs) and their 95% CIs were calculated using the Cox regression model. Two-sided P values <0.05 were regarded as significant. Tests for heterogeneity were used to determine whether the treatment effects observed in patients with diabetes differed from those in patients without diabetes.

RESULTS — Of a total of 10,001 patients randomized, 1,501 (15%) had diabetes, of whom 753 received atorvastatin 10 mg and 748 received atorvastatin 80 mg. Patients with diabetes were generally slightly older (63 vs. 61 years), more overweight (BMI 30.4 vs. 28.5 kg/m^2), and included more women (27 vs. 19%) than the overall population. Hypertension (71 vs. 54%), coronary bypass (55 vs. 47%), peripheral arterial disease (21 vs. 12%), and cerebrovascular accident (9 vs. 5%) were more prevalent in the diabetes subgroup than in the overall population. Baseline characteristics of patients with diabetes were similar between the two treatment groups, as were baseline LDL cholesterol, total cholesterol, triglycerides, HDL cholesterol, and apolipoprotein B. The proportion of patients managing their diabetes with oral hypoglycemic agents, insulin, or a combination thereof was similar between treatment groups (Table 1).

Changes in lipids

During the open-label period, atorvastatin 10 mg reduced LDL cholesterol from a mean of 160.3 mg/dl (4.1 mmol/l) to 96.2 mg/dl (2.5 mmol/l) for all patients with diabetes. End-of-treatment LDL cholesterol levels increased by 3% to a mean of 98.6 mg/dl (2.5 mmol/l) in patients with diabetes who continued atorvastatin 10 mg, while a further reduction of 19% to a mean of 77.0 mg/dl (2.0 mmol/l) was observed in patients with diabetes who were assigned to atorvastatin 80 mg ($P < 0.0001$). Similar treatment effects were observed for total cholesterol and triglycerides. At the end of treatment, total cholesterol increased from baseline by 2% to a mean of 177.9 mg/dl (4.6 mmol/l) with atorvastatin 10 mg and was further reduced by 13% to a mean of 150.6 mg/dl (3.9 mmol/l) with atorvastatin 80 mg. Triglycerides increased from baseline by 11% to 178.3 mg/dl (2.0 mmol/l) with atorvastatin 10 mg, while atorvastatin 80 mg resulted in an additional reduction of 10% to 145.3 mg/dl (1.6 mmol/l). There was little change in HDL cholesterol in either treatment group over the course of the study.

Efficacy outcomes

Over the 5 years of double-blind treatment, a primary event was experienced by 103 patients with diabetes (13.8%) receiving atorvastatin 80 mg and 135 patients (17.9%) receiving atorvastatin 10 mg. This represented a 25% reduction in the risk of major cardiovascular events in favor of the high-dose group (HR 0.75 [95% CI 0.58–0.97], $P = 0.026$) (Fig. 1). Consistent with the significant findings in the overall population, trends toward a benefit in favor of atorvastatin 80 mg were observed for the time to the primary end point components nonfatal non–procedure-related myocardial infarction (0.79 [0.55–1.14], $P = 0.202$), fatal/

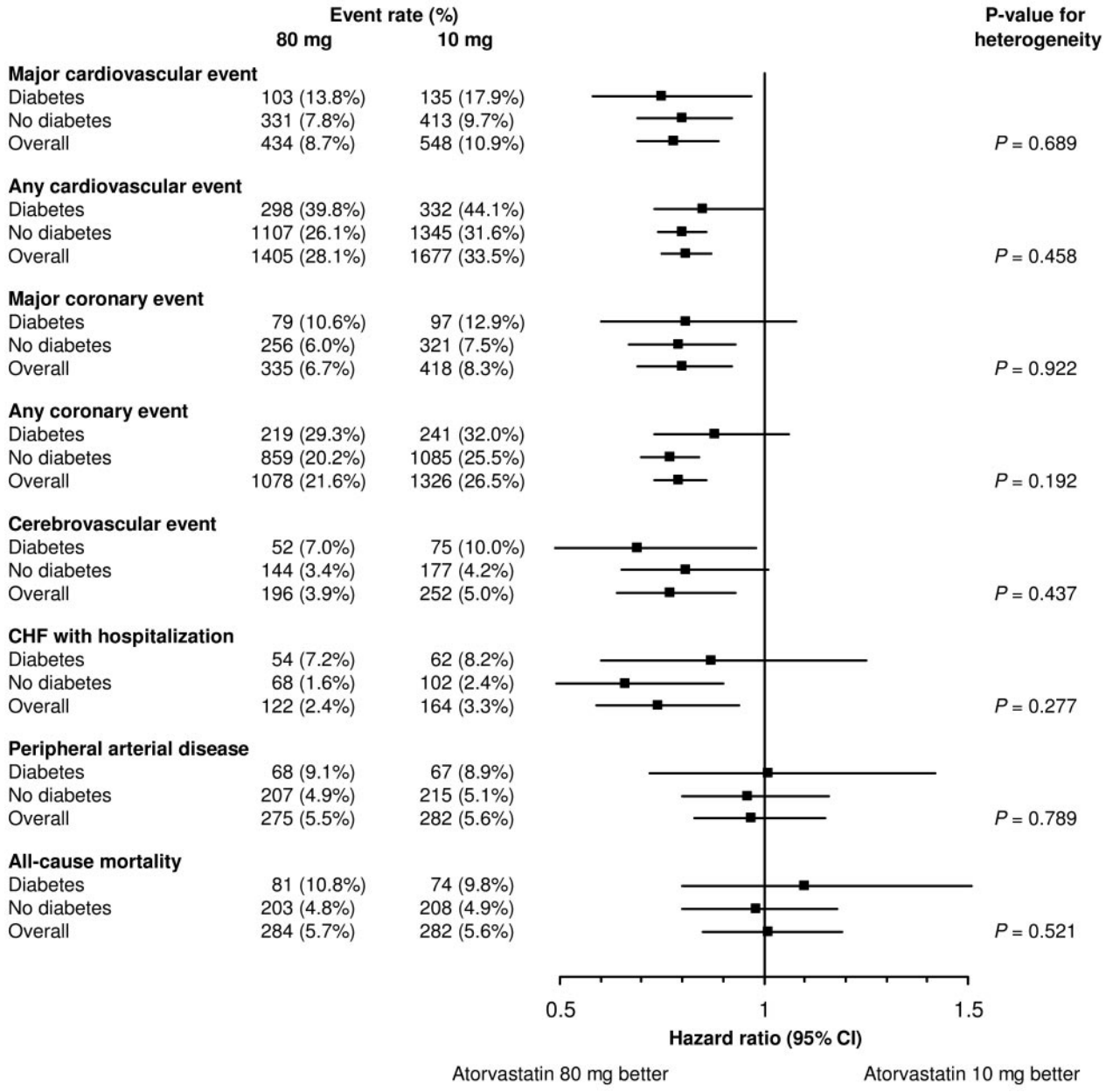

Figure 2—*HRs and heterogeneity tests for primary and secondary outcomes in patients with and without diabetes. Composite end points include major cardiovascular events (CHD death, nonfatal non–procedure-related myocardial infarction, resuscitated cardiac arrest, and fatal or nonfatal stroke), any cardiovascular event (cerebrovascular event, congestive heart failure [CHF]with hospitalization, CHD death, myocardial infarction, resuscitated cardiac arrest, coronary revascularization, and documented angina), major coronary events (CHD death, nonfatal non–procedure-related myocardial infarction, and resuscitated cardiac arrest), any coronary event (major coronary event, coronary revascularization, procedure-related myocardial infarction, and documented angina), and cerebrovascular events (fatal and nonfatal stroke and transient ischemic attack).*

nonfatal stroke (0.67 [0.43–1.04], P = 0.075), and CHD death (0.74 [0.47–1.18], P = 0.203), although there were insufficient events in the subgroup of patients with diabetes to reach significance. Significant differences between the groups in favor of atorvastatin 80 mg were observed for the secondary outcomes of time to cerebrovascular event (0.69 [0.48–0.98], P = 0.037) and time to cardiovascular event (0.85 [0.73–1.00], P = 0.044; Fig. 2). Consistent with the overall population, there was no significant difference between the treatments for all-cause mortality (Fig. 2). There was a reduction in cardiovascular mortality with atorvastatin 80 mg (5.2%) compared with atorvastatin 10 mg (6.5%), while noncardiovascular mortality was higher in the atorvastatin 80-mg group (5.6%) than in the atorvastatin 10-mg group (3.3%). However, the study was not powered to detect a significant difference between the treatment groups for mortality.

For all primary and secondary efficacy outcomes, there was a higher incidence of events in the subgroup of patients with diabetes than in the overall group, and there was no significant heterogeneity of treatment effect between patients with and without diabetes (Fig. 2). A decreased incidence of primary event rates was observed in the atorvastatin 80-

Table 2—*Major cardiovascular event rate in patients with diabetes by A1C, age, screening LDL cholesterol, and duration of diabetes*

	Atorvastatin 10 mg (n = 753)		Atorvastatin 80 mg (n = 748)		P value for heterogeneity
	Event rate (%)	n	Event rate (%)	n	
A1C ≤7	16.2	290	9.2	261	
A1C >7	20.6	359	15.9	359	0.30
Quintiles of baseline age (years)					
≤52.9	16.3	147	9.0	155	
>52.9–59.1	11.6	146	11.2	142	
>59.1–64.5	20.4	167	17.2	134	
>64.5–69.4	19.0	158	14.8	142	
>69.4	22.2	135	17.0	165	0.24
Quintiles of screening LDL cholesterol (mg/dl)					
≤142	17.9	134	11.9	143	
>142–154	18.5	151	13.0	154	
>154–166	16.9	160	13.2	144	
>166–184	21.4	154	14.6	157	
>184	15.1	152	16.0	150	0.78
Quintiles of duration of diabetes (years)					
≤2	15.0	147	12.3	138	
>2–4	19.3	109	13.8	116	
>4–8	15.8	184	12.3	162	
>8–14	18.5	130	13.3	150	
>14	24.2	161	15.4	162	0.99
A1C ≤7	16.2	290	9.2	261	
A1C >7	20.6	359	15.9	359	0.30

compared with the 10-mg group across all quintiles of patient age and duration of diabetes and in patients with HbA_{1c} (A1C) ≤7% and A1C >7% (Table 2).

Additional benefit from atorvastatin 80 vs. 10 mg was observed early in the disease process of diabetes, with patients across all quintiles of diabetes duration in the atorvastatin 80-mg group experiencing a reduced incidence of first stroke compared with those in the atorvastatin 10-mg group. Moreover, patients with and without good glycemic control randomized to atorvastatin 80 mg experienced a lower incidence of first major cardiovascular event, coronary event, stroke, nonfatal non–procedure-related myocardial infarction, and CHD death than patients randomized to atorvastatin 10 mg, with a significant reduction in risk for major cardiovascular events in patients with A1C ≤7%.

Safety and tolerability

In the diabetic population, treatment-related adverse events were experienced by 41 patients (5.4%) receiving atorvastatin 10 mg and 52 patients (7.0%) receiving atorvastatin 80 mg. These rates are similar to those observed in the overall TNT population (5.8% for atorvastatin 10 mg and 8.1% for atorvastatin 80 mg). Treatment-related myalgia was reported in 27 patients (3.6%) receiving atorvastatin 10 mg and 18 patients (2.4%) receiving atorvastatin 80 mg. Persistent elevations more than three times the upper limit of normal (occurring twice within 4–10 days) in alanine aminotransferase and/or aspartate aminotransferase were observed in three patients (0.4%) receiving atorvastatin 10 mg and seven patients (0.9%) receiving atorvastatin 80 mg. There were no significant differences between the treatment groups in the rate of treatment-related adverse events, including myalgia, or persistent elevations in liver enzymes. No incidents of rhabdomyolysis were reported in either treatment group with diabetes.

Of 8,500 patients without diabetes at screening, 865 (10.2%) developed diabetes during the course of the study, 425 in the atorvastatin 10-mg group and 440 in the atorvastatin 80-mg group (odds ratio 1.04, P = 0.59).

CONCLUSIONS — The TNT study confirmed and extended the growing body of evidence indicating that lowering LDL cholesterol to values well below currently recommended levels with more intensive statin therapy is associated with additional cardiovascular benefit (14–16,18,19). The current subanalysis of the TNT study indicates that these benefits are consistent in patients with diabetes and CHD. Among patients with clinically evident CHD and diabetes, intensive therapy with atorvastatin 80 mg significantly reduced the rate of major cardiovascular events by 25% compared with a more moderate regimen of atorvastatin 10 mg (P = 0.026).

For secondary outcomes, intensive therapy with atorvastatin 80 mg significantly reduced the rate of all cardiovascular events and cerebrovascular events compared with atorvastatin 10 mg. For major coronary events, all coronary events, congestive heart failure with hospitalization, peripheral arterial disease, and all-cause mortality, HRs and CIs were consistent with the overall study population, and there was no significant heterogeneity of treatment effect between patients with and without diabetes, indicating that the significant results of the main study hold true for patients with diabetes.

An increased event rate was observed for the subgroup of patients with diabetes compared with the overall TNT study group across all primary and secondary efficacy outcomes, providing a clear indi-

cation of the extremely high cardiovascular risk of these patients with CHD and diabetes. That said, the statin treatment effect did not differ significantly across other cardiovascular risk factors, such as increasing patient age, screening LDL cholesterol, duration of diabetes, and A1C. Event rates in the diabetic patients in both the atorvastatin 10- and 80-mg arms of the TNT study were lower than those observed in diabetic patients in the treatment arms of other statin secondary prevention trials (7–10), and the lower event rate observed across the full range of age, diabetes duration, and glycemic control in the high-dose atorvastatin group further demonstrates that patients with CHD and diabetes receive benefit from intensive versus more moderate statin treatment.

Data from this TNT subanalysis demonstrated that lowering LDL cholesterol with intensive atorvastatin therapy to levels <100 mg/dl (2.6 mmol/l) presents no additional safety concerns in patients with diabetes compared with the overall population or compared with more moderate lowering of LDL cholesterol with atorvastatin 10 mg. Despite no significant difference between the treatment groups for mortality, the rate was low in both treatment arms. Of further note in this population at significant risk of cardiovascular death, the atorvastatin 80-mg arm is the first cohort from secondary prevention studies (14,20,21) for which the incidence of cardiovascular deaths did not exceed noncardiovascular deaths.

This is a subanalysis of patients with diabetes in TNT and thus a post hoc analysis. The potential cardiovascular benefits observed are consistent with trends in previous studies in patients with diabetes and CHD (7–10). Furthermore, the prospective design of the TNT study in reducing LDL cholesterol from a baseline mean of <130 mg/dl (3.4 mmol/l), following earlier treatment with atorvastatin 10 mg, to either a target of 100 mg/dl (2.6 mmol/l) or 75 mg/dl (1.9 mmol/l), allows some insight into the benefits of lowering beyond current recommended targets in patients with diabetes and CHD.

In 2005, the ADA updated its clinical practice recommendations for patients with diabetes and cardiovascular disease, noting that these individuals are at very high risk for subsequent clinical events (12). On the basis of randomized trials of moderate versus intensive lipid lowering in very-high-risk (albeit nondiabetic) populations (15,19), the ADA advised that use of high-dose statin to achieve an LDL cholesterol level of <70 mg/dl was a therapeutic option in diabetic patients with cardiovascular disease. The analysis of patients with diabetes in the TNT study strengthens the evidence for this recommendation by *1*) confirming the high cardiovascular event rate in CHD patients who also have diabetes, *2*) providing direct evidence of cardiovascular risk reduction with high-dose statin therapy in this population, and *3*) demonstrating that this risk reduction is independent of baseline LDL cholesterol. Pending a definitive trial, these data suggest that the use of high-dose statin to achieve an LDL cholesterol level considerably <100 mg/dl (12) may be appropriate for patients with diabetes and CHD, irrespective of their initial LDL cholesterol level, age, duration of diabetes, or glycemic control.

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