

ORIGINAL ARTICLE

# Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease

John C. LaRosa, M.D., Scott M. Grundy, M.D., Ph.D.,  
David D. Waters, M.D., Charles Shear, Ph.D., Philip Barter, M.D., Ph.D.,  
Jean-Charles Fruchart, Pharm.D., Ph.D., Antonio M. Gotto, M.D., D.Phil.,  
Heiner Greten, M.D., John J.P. Kastelein, M.D., James Shepherd, M.D.,  
and Nanette K. Wenger, M.D., for the Treating to New Targets (TNT) Investigators\*

## ABSTRACT

### BACKGROUND

Previous trials have demonstrated that lowering low-density lipoprotein (LDL) cholesterol levels below currently recommended levels is beneficial in patients with acute coronary syndromes. We prospectively assessed the efficacy and safety of lowering LDL cholesterol levels below 100 mg per deciliter (2.6 mmol per liter) in patients with stable coronary heart disease (CHD).

### METHODS

A total of 10,001 patients with clinically evident CHD and LDL cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) were randomly assigned to double-blind therapy and received either 10 mg or 80 mg of atorvastatin per day. Patients were followed for a median of 4.9 years. The primary end point was the occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal non–procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke.

### RESULTS

The mean LDL cholesterol levels were 77 mg per deciliter (2.0 mmol per liter) during treatment with 80 mg of atorvastatin and 101 mg per deciliter (2.6 mmol per liter) during treatment with 10 mg of atorvastatin. The incidence of persistent elevations in liver aminotransferase levels was 0.2 percent in the group given 10 mg of atorvastatin and 1.2 percent in the group given 80 mg of atorvastatin ( $P < 0.001$ ). A primary event occurred in 434 patients (8.7 percent) receiving 80 mg of atorvastatin, as compared with 548 patients (10.9 percent) receiving 10 mg of atorvastatin, representing an absolute reduction in the rate of major cardiovascular events of 2.2 percent and a 22 percent relative reduction in risk (hazard ratio, 0.78; 95 percent confidence interval, 0.69 to 0.89;  $P < 0.001$ ). There was no difference between the two treatment groups in overall mortality.

### CONCLUSIONS

Intensive lipid-lowering therapy with 80 mg of atorvastatin per day in patients with stable CHD provides significant clinical benefit beyond that afforded by treatment with 10 mg of atorvastatin per day. This occurred with a greater incidence of elevated aminotransferase levels.

From the State University of New York Health Science Center, Brooklyn (J.C.L.); the University of Texas Southwestern Medical Center, Dallas (S.M.G.); San Francisco General Hospital, San Francisco (D.D.W.); Pfizer, Groton, Conn. (C.S.); the Heart Research Institute, Sydney (P.B.); Institut Pasteur, Lille, France (J.-C.F.); Weill Medical College of Cornell University, New York (A.M.G.); Universitätsklinikum Eppendorf, Hamburg, Germany (H.G.); Academic Medical Center, University of Amsterdam, Amsterdam (J.J.P.K.); the University of Glasgow, Glasgow, United Kingdom (J.S.); and Emory University School of Medicine, Atlanta (N.K.W.). Address reprint requests to Dr. LaRosa at the State University of New York Health Science Center, 450 Clarkson Ave., Brooklyn, NY 11203, or at [jlclarosa@downstate.edu](mailto:jlclarosa@downstate.edu).

\*Participants in the TNT Study are listed in the Appendix.

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**T**HE VALUE OF LOWERING LOW-DENSITY lipoprotein (LDL) cholesterol levels in preventing major cardiovascular events and stroke has been well documented. Recent studies have raised the issue of optimal treatment targets for patients with coronary heart disease (CHD).<sup>1-4</sup> The value of reducing LDL cholesterol levels substantially below 100 mg per deciliter (2.6 mmol per liter) in patients with CHD, particularly those with stable nonacute disease, has not been clearly demonstrated.

The Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel<sup>5</sup> and the most recent guidelines of the Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice<sup>6</sup> have recommended an LDL cholesterol level of less than 100 mg per deciliter as the goal of therapy for patients at high risk for CHD. On the basis of data from the Heart Protection Study (HPS)<sup>1</sup> and the Pravastatin or Atorvastatin Evaluation and Infection Trial (PROVE IT),<sup>2</sup> the NCEP in conjunction with the American Heart Association and the American College of Cardiology subsequently introduced a more aggressive, but optional, LDL cholesterol goal of less than 70 mg per deciliter (1.8 mmol per liter) for patients at very high risk for CHD, even if baseline LDL cholesterol levels were below 100 mg per deciliter.<sup>7</sup> However, PROVE IT was conducted in a population of patients with acute coronary syndromes who were at very high risk for cardiovascular disease, and although many patients in the HPS who began with an LDL cholesterol level of less than 100 mg per deciliter benefited from statin therapy, this benefit was in comparison with placebo. Thus, there is no definitive evidence that intensive statin therapy, with a goal of reducing LDL cholesterol levels to approximately 70 mg per deciliter, is associated with better outcomes than moderate statin therapy, with a goal of reducing LDL cholesterol levels to about 100 mg per deciliter in patients with stable CHD. Data from the Treating to New Targets (TNT) Study make it possible to test this hypothesis.

#### METHODS

The design of the TNT Study has been described in detail previously.<sup>8</sup> All patients gave written informed consent, and the study was approved by the local research ethics committee or institutional review board at each center.

#### PRIMARY HYPOTHESIS

The primary hypothesis of the study was that reducing LDL cholesterol levels to well below 100 mg per deciliter in patients with stable CHD and slightly elevated LDL cholesterol levels (despite previous therapy with low-dose atorvastatin) could yield an incremental clinical benefit. This hypothesis was tested in a double-blind, parallel-group design. The occurrence of major cardiovascular outcomes was compared in two groups of patients: one group received 10 mg of atorvastatin daily with the goal of an average LDL cholesterol level of 100 mg per deciliter, and the other group received 80 mg of atorvastatin daily with the goal of an average LDL cholesterol level of 75 mg per deciliter (1.9 mmol per liter).

#### PATIENT POPULATION

Eligible patients were men and women 35 to 75 years of age who had clinically evident CHD, defined by one or more of the following: previous myocardial infarction, previous or current angina with objective evidence of atherosclerotic CHD, and a history of coronary revascularization. The exclusion criteria have been described in detail previously.<sup>8</sup> Randomization occurred between July 1998 and December 1999.

#### STUDY PROTOCOL

Any previously prescribed lipid-regulating drugs were discontinued at screening, and all patients completed a washout period of one to eight weeks. To ensure that, at baseline, all patients had LDL cholesterol levels consistent with then-current guidelines for the treatment of stable CHD, patients with LDL cholesterol levels between 130 and 250 mg per deciliter (3.4 and 6.5 mmol per liter, respectively) and triglyceride levels of 600 mg per deciliter (6.8 mmol per liter) or less entered an eight-week run-in period of open-label treatment with 10 mg of atorvastatin per day. At the end of the run-in phase (week 0), patients with a mean LDL cholesterol level of less than 130 mg per deciliter (3.4 mmol per liter) (determined four weeks and two weeks before randomization) were randomly assigned to double-blind therapy with either 10 mg or 80 mg of atorvastatin per day. During the double-blind period, follow-up visits occurred at week 12 and at months 6, 9, and 12 in the first year and every 6 months thereafter.

**EFFICACY OUTCOMES**

The primary efficacy outcome was the occurrence of a major cardiovascular event, defined as death from CHD, nonfatal non–procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke. Secondary outcomes included a major coronary event (defined as death from CHD, nonfatal non–procedure-related myocardial infarction, or resuscitation after cardiac arrest), a cerebrovascular event, hospitalization for congestive heart failure, peripheral-artery disease, death from any cause, any cardiovascular event, and any coronary event.

**STATISTICAL ANALYSIS**

Epidemiologic data suggested that the treatment-related difference in LDL cholesterol levels between the two groups would translate into 20 to 30 percent fewer recurrent coronary events at five years in the group given 80 mg of atorvastatin than in the group given 10 mg of atorvastatin. The study's original target enrollment was approximately 8600 patients on the basis of a projected number of 750 major coronary events during an average follow-up of 5.5 years. However, the recruitment rate was higher than expected, and 10,003 patients underwent randomization, all but 2 of whom received the study drug.

In February 2003, the steering committee added stroke (fatal or nonfatal) to the primary efficacy outcome. This change was made before any data were reviewed and preceded the first interim analysis by the independent data and safety monitoring board. At the time, evidence was accumulating of the beneficial role of statins in reducing the risk of stroke. The change in the primary end point was made to clarify this role. This modification led to an increase in the projected number of primary events to 950 (750 coronary events plus 200 strokes) during the trial, providing the study with a statistical power of 85 percent to detect an absolute reduction of 17 percent in the five-year cumulative rate of the primary efficacy outcome in the group given 80 mg of atorvastatin, as compared with the group given 10 mg of atorvastatin, with the use of a two-sided test at an alpha level of 0.05.

All analyses were performed on an intention-to-treat basis. All randomized patients who were dispensed one dose of the study drug were included in the analyses. The primary and secondary composite end points were analyzed from the time of the first dose of study drug to the first event, ac-

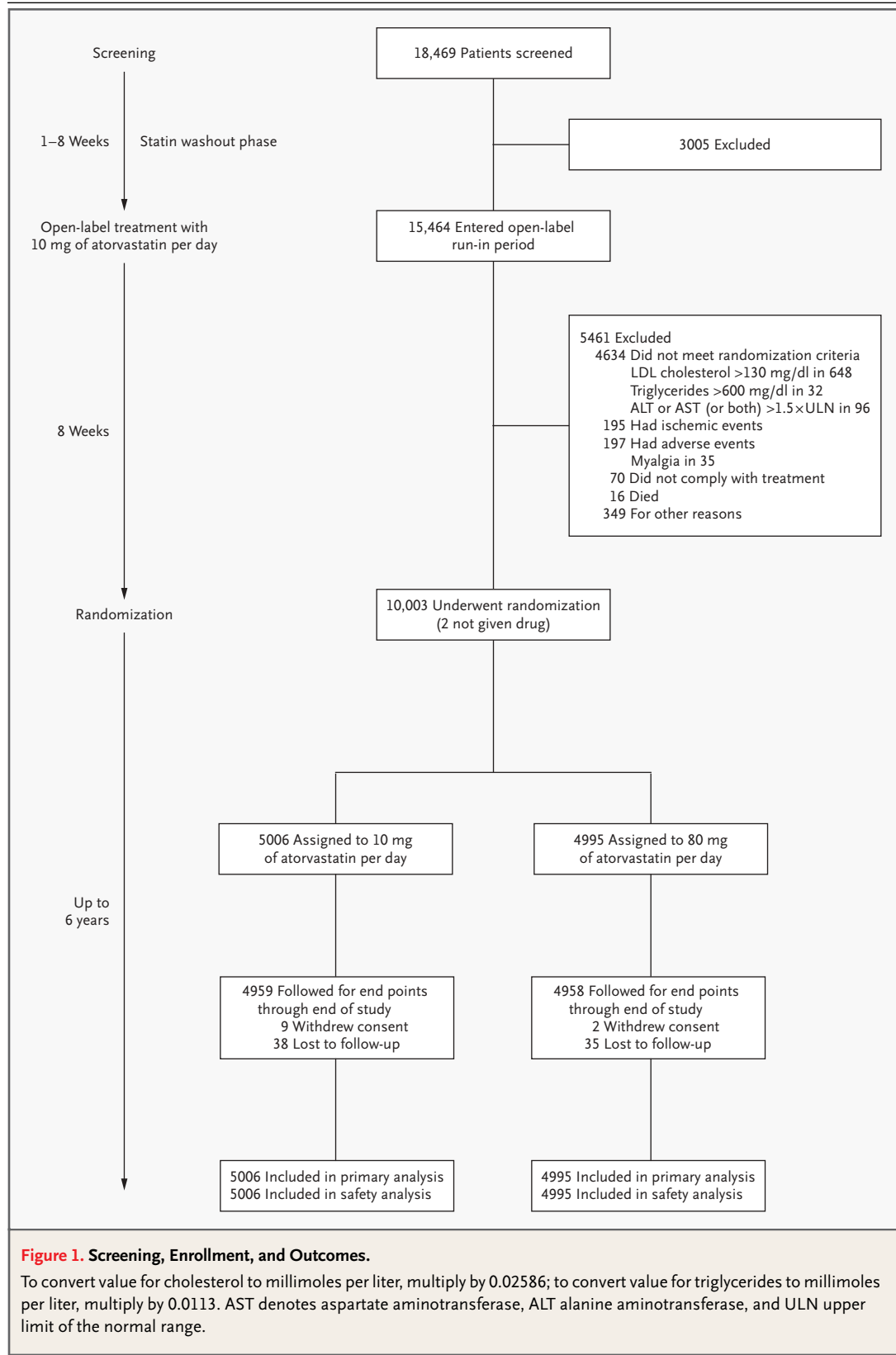
ording to the Kaplan–Meier method. The study had a statistical power of only 40 percent to detect a 10 percent reduction in the risk of death from any cause with the use of a two-sided test at an alpha level of 0.05.

Two interim efficacy analyses were performed and were based on a two-sided Peto type of monitoring boundary. For the final primary analysis, an adjusted P value of 0.049 was considered to indicate statistical significance, given a type I error rate of 0.05. For all secondary outcomes, a P value of 0.05 was considered to indicate statistical significance, and all tests were two-sided.

The sponsor initiated the study. The steering committee developed the protocol in collaboration with the sponsor and took responsibility for the final version. ICON Clinical Research (North Wales, Pennsylvania) managed all data. ICON and Pfizer provided site monitoring throughout the study. An independent end-points committee adjudicated all potential end points in a blinded fashion. An independent data and safety monitoring board with its independent statistical-support group from the University of Wisconsin performed interim monitoring and analyses of efficacy, safety, and data quality. The data were analyzed by the sponsor according to the statistical-analysis plan approved by the steering committee. The steering committee had unrestricted, request-based access to the study data, which were retained by the sponsor, and wrote the article without constraints from the sponsor. The steering committee assumes overall responsibility for the integrity of the data, for the accuracy of the data analyses, and for the completeness of the material reported. The data reported were those available to the steering committee as of January 29, 2005.

**RESULTS****PATIENT POPULATION**

A total of 18,469 patients were screened at 256 sites in 14 countries (Fig. 1). Of these, 15,464 patients (83.7 percent) were deemed eligible to enter the open-label run-in period. A further 5461 patients were excluded after the open-label run-in phase. Most of these excluded patients (4634, or 84.9 percent) did not meet randomization criteria. Other reasons included adverse events in 197 (3.6 percent), death or an ischemic event in 211 (3.9 percent), and lack of compliance in 70 (1.3 percent).



A total of 10,001 patients underwent randomization and received double-blind treatment with either 10 mg or 80 mg of atorvastatin. The time of randomization was taken as the baseline for the study. Patients were followed for a median of 4.9 years.

The two groups were well matched at baseline (Table 1), and the pattern of use of concomitant medications was similar in the two groups. Blood pressure was controlled for the duration of the study in both groups.

#### CHANGE IN LABORATORY VALUES

During the open-label period, the LDL cholesterol level was reduced by 35 percent in the overall pa-

tient population, from a mean of 152 mg per deciliter (3.9 mmol per liter) to a mean of 98 mg per deciliter (2.6 mmol per liter). Figure 2 summarizes post-randomization lipid values in the two groups. Mean LDL cholesterol levels during the study were 77 mg per deciliter (2.0 mmol per liter) among patients receiving 80 mg of atorvastatin and 101 mg per deciliter (2.6 mmol per liter) among those receiving 10 mg of atorvastatin (Fig. 2A).

Total cholesterol levels (Fig. 2B) and triglyceride levels (Fig. 2C) decreased significantly from baseline to week 12 in the group given 80 mg of atorvastatin ( $P < 0.001$  for both comparisons), and the levels remained stable during the treatment period. Both doses of atorvastatin produced nonsig-

**Table 1. Baseline Characteristics of the Patients.\***

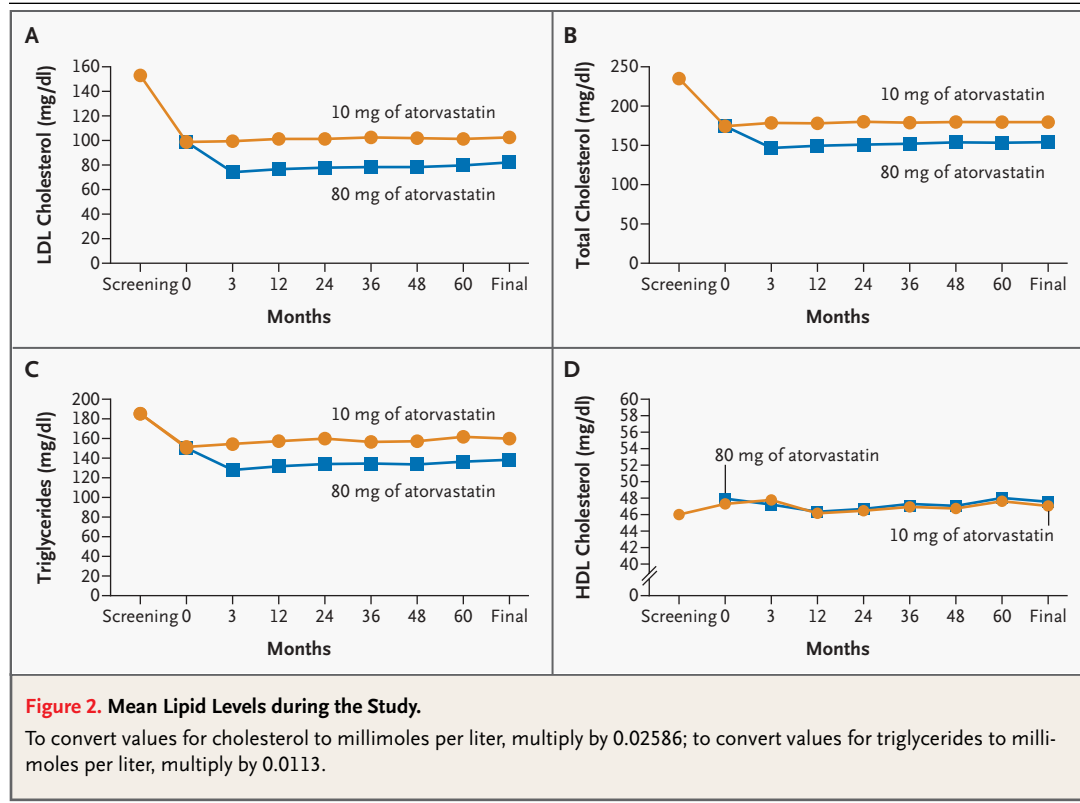
Characteristic	10 mg of Atorvastatin (N=5006)	80 mg of Atorvastatin (N=4995)
Age — yr	60.9±8.8	61.2±8.8
Male sex — no. (%)	4045 (80.8)	4054 (81.2)
White race — no. (%)†	4711 (94.1)	4699 (94.1)
Systolic blood pressure — mm Hg	131±17	131±17
Diastolic blood pressure — mm Hg	78±10	78±10
Body-mass index‡	28.6±4.7	28.4±4.5
Cardiovascular history — no. (%)		
Current smoker	672 (13.4)	669 (13.4)
Former smoker	3167 (63.3)	3155 (63.2)
Systemic hypertension	2721 (54.4)	2692 (53.9)
History of diabetes mellitus	753 (15.0)	748 (15.0)
Myocardial infarction	2888 (57.7)	2945 (59.0)
Angina	4067 (81.2)	4084 (81.8)
Cerebrovascular accident	263 (5.3)	255 (5.1)
Peripheral-artery disease	570 (11.4)	603 (12.1)
Congestive heart failure	404 (8.1)	377 (7.6)
Arrhythmia	927 (18.5)	907 (18.2)
Coronary revascularization		
Angioplasty	2719 (54.3)	2688 (53.8)
Bypass	2338 (46.7)	2317 (46.4)
Lipids — mg/dl§		
LDL cholesterol	98±18	97±18
Total cholesterol	175±24	175±24
Triglycerides	151±72	151±70
HDL cholesterol	47±11	47±11

\* Plus-minus values are means ±SD.

† Race was self-designated.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

§ To convert values for cholesterol to millimoles per liter, multiply by 0.02586; to convert values for triglycerides to millimoles per liter, multiply by 0.0113. LDL denotes low-density lipoprotein, and HDL high-density lipoprotein.



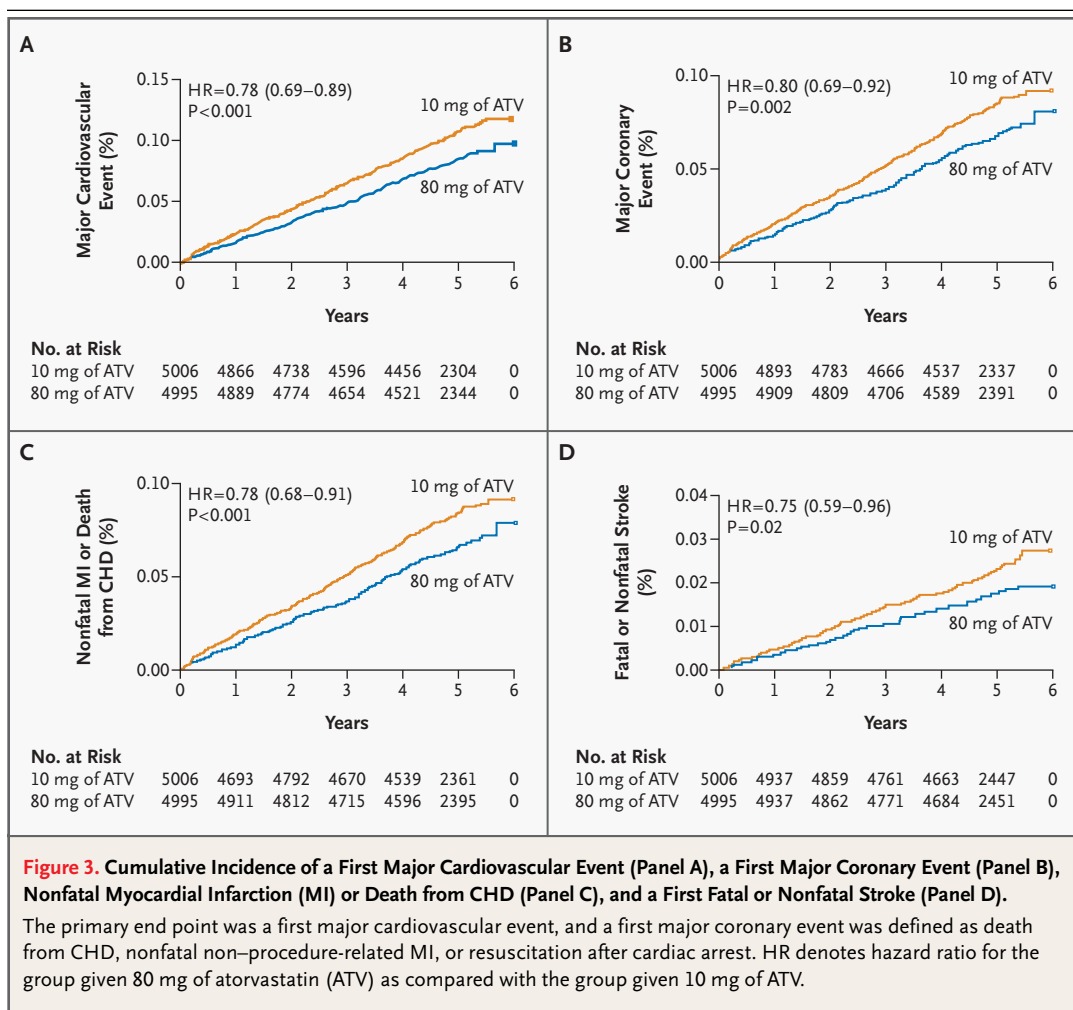
nificant increases over baseline in high-density lipoprotein (HDL) cholesterol levels, with no significant difference between the groups during the course of the study (Fig. 2D).

**EFFICACY OUTCOMES**

A total of 434 patients in the group given 80 mg of atorvastatin and 548 patients in the group given 10 mg of atorvastatin had a primary event during the study, representing an event rate of 8.7 percent and 10.9 percent, respectively. This rate was equivalent to an absolute reduction of 2.2 percent in the group given 80 mg of atorvastatin. As compared with the group given 10 mg of atorvastatin, the group given 80 mg had a 22 percent relative reduction in the primary composite efficacy outcome of death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke (hazard ratio, 0.78; 95 percent confidence interval, 0.69 to 0.89;  $P < 0.001$ ) (Fig. 3). There were 545 major cardiovascular events (as a first or subsequent event) in the group given 80 mg of atorvastatin and 715 events in the group given 10 mg of atorvastatin (Table 2 shows only first events).

Outcomes for individual components of the primary end point are shown in Table 2. Relative reductions in the risk of death from CHD, nonfatal non-procedure-related myocardial infarction, and fatal or nonfatal stroke with treatment with 80 mg of atorvastatin, as compared with 10 mg of atorvastatin, were all consistent with the reduction observed for the primary composite outcome. There was no statistical interaction for age or sex in the primary outcome measure.

As compared with patients given 10 mg of atorvastatin, patients given 80 mg of atorvastatin also had significant reductions in the risk of a major coronary event (hazard ratio, 0.80; 95 percent confidence interval, 0.69 to 0.92;  $P = 0.002$ ), any coronary event (hazard ratio, 0.79; 95 percent confidence interval, 0.73 to 0.86;  $P < 0.001$ ), a cerebrovascular event (hazard ratio, 0.77; 95 percent confidence interval, 0.64 to 0.93;  $P = 0.007$ ), hospitalization with a primary diagnosis of congestive heart failure (hazard ratio, 0.74; 95 percent confidence interval, 0.59 to 0.94;  $P = 0.01$ ), and any cardiovascular event (hazard ratio, 0.81; 95 percent confidence interval, 0.75 to 0.87;  $P < 0.001$ ) (Table 2). The effect



of 80 mg of atorvastatin on the risk of peripheral-artery disease did not differ significantly from that of 10 mg of atorvastatin (hazard ratio, 0.97; 95 percent confidence interval, 0.83 to 1.15; P=0.76).

The risk of death from any cause also did not differ significantly between the two drug regimens (hazard ratio, 1.01; 95 percent confidence interval, 0.85 to 1.19; P=0.92). There were 155 deaths from cardiovascular causes in the group given 10 mg of atorvastatin (3.1 percent) and 126 in the group given 80 mg of atorvastatin (2.5 percent; hazard ratio, 0.80; 95 percent confidence interval, 0.64 to 1.08; P=0.08). There were 127 deaths from noncardiovascular causes in the group given 10 mg of atorvastatin (2.5 percent) and 158 in the group given 80 mg of atorvastatin (3.2 percent; hazard ratio, 1.25; 95 percent confidence interval, 0.99 to 1.57; P=0.06).

Cancer accounted for more than half the deaths from noncardiovascular causes in both groups — 75 in the group given 10 mg of atorvastatin (1.5 percent) and 85 in the group given 80 mg of atorvastatin (1.7 percent; hazard ratio, 1.13; 95 percent confidence interval, 0.83 to 1.55; P=0.42) — and there were 43 deaths (0.9 percent) and 58 deaths (1.2 percent), respectively, from nontraumatic causes other than cancer (hazard ratio, 1.35; 95 percent confidence interval, 0.91 to 2.00; P=0.13). There were 16 hemorrhagic strokes in the group given 80 mg of atorvastatin and 17 in the group given 10 mg of atorvastatin. Deaths from hemorrhagic stroke or trauma (including accidental death, suicide, and homicide) were infrequent, and the rates did not differ significantly between the two groups.

No significant increase in adverse events of any type was identified among patients who had very

**Table 2.** Estimated Hazard Ratio for Individual Components of the Primary and Secondary Efficacy Outcomes.\*

Outcome	10 mg of Atorvastatin (N=5006)	80 mg of Atorvastatin (N=4995)	Hazard Ratio (95% CI)	P Value
	<i>no. with first event (%)</i>			
<b>Primary outcome</b>				
Total major cardiovascular events	548 (10.9)	434 (8.7)	0.78 (0.69–0.89)	<0.001
Death from CHD	127 (2.5)	101 (2.0)	0.80 (0.61–1.03)	0.09
Nonfatal, non–procedure-related myocardial infarction	308 (6.2)	243 (4.9)	0.78 (0.66–0.93)	0.004
Resuscitation after cardiac arrest	26 (0.5)	25 (0.5)	0.96 (0.56–1.67)	0.89
Fatal or nonfatal stroke	155 (3.1)	117 (2.3)	0.75 (0.59–0.96)	0.02
<b>Secondary outcomes</b>				
Major coronary event†	418 (8.3)	334 (6.7)	0.80 (0.69–0.92)	0.002
Cerebrovascular event‡	250 (5.0)	196 (3.9)	0.77 (0.64–0.93)	0.007
Hospitalization for congestive heart failure	164 (3.3)	122 (2.4)	0.74 (0.59–0.94)	0.01
Peripheral-artery disease§	282 (5.6)	275 (5.5)	0.97 (0.83–1.15)	0.76
Death from any cause	282 (5.6)	284 (5.7)	1.01 (0.85–1.19)	0.92
Any cardiovascular event	1677 (33.5)	1405 (28.1)	0.81 (0.75–0.87)	<0.001
Any coronary event¶	1326 (26.5)	1078 (21.6)	0.79 (0.73–0.86)	<0.001

\* In each row, only the first event for each patient is counted. CI denotes confidence interval.

† This was the original primary outcome (death from CHD, nonfatal non–procedure-related myocardial infarction, or resuscitation after cardiac arrest).

‡ A cerebrovascular event was defined as fatal or nonfatal stroke or transient ischemic attack.

§ Peripheral-artery disease was defined as any new diagnosis of peripheral-artery disease, any admission related to its treatment, or any incidental discovery of plaques or stenosis.

¶ Any coronary event was defined as a major coronary event, revascularization procedure, procedure-related myocardial infarction, or documented angina.

low levels of LDL cholesterol (less than 70 mg per deciliter [1.8 mmol per liter]), as compared with those with higher levels.

#### SAFETY

Adverse events related to treatment occurred in 406 patients in the group given 80 mg of atorvastatin, as compared with 289 patients in the group given 10 mg of atorvastatin (8.1 percent vs. 5.8 percent,  $P<0.001$ ). The respective rates of discontinuation due to treatment-related adverse events were 7.2 percent and 5.3 percent ( $P<0.001$ ). Treatment-related myalgia was reported by 241 patients in the group given 80 mg of atorvastatin and by 234 patients in the group given 10 mg of atorvastatin (4.8 percent and 4.7 percent, respectively;  $P=0.72$ ). A total of 60 patients receiving 80 mg of atorvastatin had a persistent elevation in alanine aminotransferase, aspartate aminotransferase, or both (defined as two consecutive measurements obtained 4 to 10 days apart that were more than three times the upper lim-

it of the normal range), as compared with 9 patients receiving 10 mg of atorvastatin (1.2 percent vs. 0.2 percent,  $P<0.001$ ). There were no persistent elevations in creatine kinase (defined as two consecutive measurements obtained 4 to 10 days apart that were more than 10 times the upper limit of the normal range). Five cases of rhabdomyolysis were reported (two in the group given 80 mg of atorvastatin and three in the group given 10 mg of atorvastatin); relevant clinical information about these cases is presented in Table 3.

#### DISCUSSION

This trial provides evidence that the use of intensive atorvastatin therapy to reduce LDL cholesterol levels below 100 mg per deciliter is associated with substantial clinical benefit in patients with stable CHD. Both atorvastatin groups had low rates of CHD events. The rate in the group given 10 mg of atorvastatin was lower than rates reported with

**Table 3. Characteristics of Five Patients with Rhabdomyolysis.\***

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Clinical presentation	Congestive heart failure, MI, respiratory failure, pneumothorax	Accidental fall	Pneumonia and sepsis	Weakness with concomitant ingestion of alcohol and cetirizine	Postoperative thromboembolic disease; occluded arterial supply to right arm and left leg
Atorvastatin group	80 mg	10 mg	10 mg	10 mg	80 mg
Muscle symptoms	No	Yes	No	Yes	No
Creatine kinase (U/liter)					
Peak	4228	611	4913	7265	Not available
Normal range	25–195	55–170	Not available	<180	Not available
Creatine kinase >10×ULN	Yes	No	Yes	Yes	Not available
Creatinine elevation (or urinary abnormalities)	Undetermined	Yes (marginal increase in creatinine)	Not available	Undetermined	Renal failure

\* The criteria of the American College of Cardiology, American Heart Association, and National Heart, Lung, and Blood Institute for rhabdomyolysis are muscle symptoms plus a creatine kinase level that is more than 10 times the upper limit of the normal range (>10×ULN) plus an elevation in creatinine or urinary abnormalities (e.g., myoglobinuria).<sup>9</sup> Cases were identified by the investigator with direct responsibility for the patient; none of the cases were believed to be related to the study drug. MI denotes myocardial infarction.

statin treatment in placebo-controlled, secondary-prevention trials of populations with a baseline risk similar to that of our patients.<sup>1,10,11</sup>

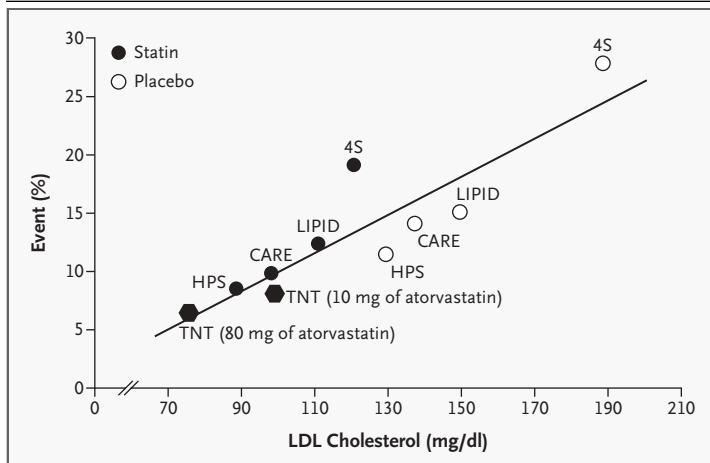
The relative reduction in the risk of the primary composite end point of death from CHD, nonfatal non–procedure-related myocardial infarction, resuscitation after cardiac arrest, and fatal or nonfatal stroke was 22 percent in the group given 80 mg of atorvastatin, as compared with the group given 10 mg of atorvastatin. Our findings indicate that the quantitative relationship between reduced LDL cholesterol levels and reduced CHD risk demonstrated in prior secondary-prevention trials of statins holds true even at very low levels of LDL cholesterol (Fig. 4). If these results were extrapolated to clinical practice, the use of an 80-mg dose of atorvastatin to reduce LDL cholesterol levels from a baseline of 101 mg per deciliter to 77 mg per deciliter in 1000 patients with stable CHD would prevent 34 major cardiovascular events over a period of five years; in other words, approximately 30 patients would need to be treated to prevent one event.

Evaluation of individual components of the primary and secondary end points shows that treatment with 80 mg of atorvastatin had a consistent and significant beneficial effect on most measures of CHD-related morbidity and mortality. The clinical benefit of reducing LDL cholesterol levels sub-

stantially below 100 mg per deciliter extended beyond the CHD-related vasculature. As compared with the 10-mg dose of atorvastatin, intensive therapy with high-dose atorvastatin reduced the risk of cerebrovascular events by 23 percent. There was no significant difference between groups in the numbers of hemorrhagic strokes as a first event.

The study was not adequately powered to detect changes in the risk of death from any cause. There were no significant differences between the two atorvastatin groups in the risk of death from cardiovascular or noncardiovascular causes. The rates of death from coronary causes in both groups were very low as compared with those in previous secondary-prevention trials of statins, accounting for only about one third of all deaths. As a consequence, the 20 percent reduction in the risk of death from CHD in the group given 80 mg of atorvastatin as compared with the group given 10 mg of atorvastatin was not large enough to have a significant effect on the risk of death from any cause.

In both groups, cancer (mainly lung and gastrointestinal) was the leading noncardiovascular cause of death; other causes included respiratory diseases, infection, degenerative diseases, and metabolic abnormalities. Although for most of these noncardiovascular causes, the number of deaths was slightly higher in the group given 80 mg of atorvastatin than in the group given 10 mg of atorva-



**Figure 4. Event Rates Plotted against LDL Cholesterol Levels during Statin Therapy in Secondary-Prevention Studies.**

HPS denotes Heart Protection Study,<sup>1</sup> CARE Cholesterol and Recurrent Events Trial,<sup>10</sup> LIPID Long-term Intervention with Pravastatin in Ischaemic Disease,<sup>11</sup> and 4S Scandinavian Simvastatin Survival Study.<sup>12</sup> Event rates for HPS, CARE, and LIPID are for death from CHD and nonfatal myocardial infarction. Event rates for 4S and the TNT Study also include resuscitation after cardiac arrest. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

statin, no single cause (according to body system or pathologic process) and no single type of cancer accounted for the nonsignificant difference in deaths from any cause between the groups.

The findings regarding drug safety are consistent with the adverse-event profiles of these two doses of atorvastatin reported in other large-scale trials of atorvastatin.<sup>2,3</sup> The exclusion of 131 patients because of abnormal liver-function tests or myalgia during the run-in phase is unlikely to account for the low incidence of persistent elevations in liver aminotransferase levels and the low

rate of muscle-related adverse events during the study.

In summary, our findings demonstrate that the use of an 80-mg dose of atorvastatin to reduce LDL cholesterol levels to 77 mg per deciliter provides additional clinical benefit in patients with stable CHD that is perceived to be well controlled at an LDL level of approximately 100 mg per deciliter. These data confirm and extend the growing body of evidence indicating that lowering LDL cholesterol levels well below currently recommended levels can have clinical benefit.

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#### APPENDIX

The following persons participated in the TNT Study: **Steering Committee:** J. LaRosa (chair), New York; P. Barter, Sydney; J.-C. Fruchart, Lille, France; A. Gotto, New York; H. Greten, Hamburg, Germany; S. Grundy, Dallas; D. Hunninghake, Minneapolis; J. Kastelein, Amsterdam; J. Shepherd, Glasgow; D. Waters, San Francisco; N. Wenger, Atlanta; **End-Points Committee:** L. Cohen (chair), New Haven, Conn.; J.-M. LaBlanche, Lille, France; H. Levine, Boston; U. Sechtem, Stuttgart, Germany; F. Wely, Boston; **Data and Safety Monitoring Board:** C. Hennekens (chair), Miami; V. Brown, Atlanta; R. Carmena, Valencia, Spain; R. D'Agostino, Boston; S. Haffner, San Antonio, Tex.; E. Leitersdorf, Jerusalem; **Investigators (numbers of randomized patients in parentheses):** *Australia (608 patients):* C. Aroney, P. Barter, J. Bradley, D. Colquhoun, A. Dart, M. d'Emden, J. Lefkowitz, R. Minson, G. Nelson, R. O'Brien, P. Roberts-Thomson, A. Thomson, D. Sullivan, P. Thompson; *Austria (29 patients):* H. Drexel, H. Sinzinger, F. Stockenhuber; *Belgium (300 patients):* P. Chenu, G. Heyndrickx, J. Van Cleemput, A. Van Dorpe, W. Van Mieghem, P. Vermeersch; *Canada (1052 patients):* M. Arnold, R. Baigrie, J. Bergeron, C. Gagné, J. Davignon, J. Ducas, J. Genest, L. Higginson, G. Hoag, J. Bonet, A. Ignaszewski, L. Leiter, S. LePage, P. Ma, M. McQueen, D. Mymin, B. O'Neill, B. Sussex, P. Theroux, G. Tremblay, W. Tymchak, J. Warnica; *France (207 patients):* P. Attali, J. Bonnet, L. Caster, R. Constans, J. Demarcq, I. Giron, J. Leymarie, J. Mansourati, J. Ollivier, F. Paillard, J. Ponsonnaille; *Germany (144 patients):* U. Beil, H. Fritz, D. Hüwel, W. Huppertz, W. Liebscher, K. Schussmann, E. Steinhagen-Thiessen; *Ireland (53 patients):* B. Buckley, P. Crean; *Italy (75 patients):* A. Branzi, P. Fioretti, G. Gensini, N. Mininni, G. Pinelli, E. Uslenghi; *the Netherlands (788 patients):* R. Anthonio, J. Bonnier, H. Crijns, H. Dohmen, P. Dunselman, M. Galjee, B. Hamer, J. Hoortjé,

J. Jukema, A. Oude-Ophuis, H. Plokker, J. Posma, J. Ruiter, M. Trip, A. van Boven; *South Africa* (523 patients): A. Dalby, L. Disler, A. Doubell, J. King, E. Lloyd, J. Marx, P. Roux; *Spain* (525 patients): M. Anguita, C. Brotons, C. Calvo, J. Cruz-Fernandez, F. Fernandez-Aviles, A. Fernandez-Cruz, I. Ferreira, E. Gonzalez, E. Lage, P. Mata, J. Mostaza, R. Muñoz-Aguilera, E. Lopez de Sa, G. Pedro, G. Permanyer, A. Pozuelo, R. Querejeta, J. Ribera, E. Ros-Rahola, M. Vela; *Switzerland* (91 patients): W. Angehrn, L. Kappenberger, T. Moccetti, H. Saner; *United Kingdom* (299 patients): D. Brydie, A. Chauhan, R. Greenbaum, H. Kadr, C. Kaski, R. Mattu, W. McCrea, J. McMurray, D. Mikhailidis, A. Salmasi, N. Samani, M. Shiu, A. Timmis, S. Turley, J. Wictome; *United States* (5309 patients): R. Abadier, S. Alexander, B. Asbill, J. Bagdade, B. Beard, J. Becker, V. Bittner, R. Blumenthal, M. Bolton, W. Bremner, D. Brewer, C. Brown, K. Browne, J. Carstens, W. Cefalu, J. Chambers, J. Cohen, M. Collins, S. Crespin, M. Cressman, R. Curry, M. Davidson, G. De Gent, J. de Lemos, P. Deedwania, D. Dixon, J. Duncan, C. East, D. Edmundowicz, B. Efron, M. Elam, M. Ettinger, R. Feldman, D. Fiske, J. Forrester, G. Fraser, Z. Freedman, S. Freeman, V. Fonseca, D. Frid, K. Friday, J. Geohas, H. Ginsberg, A. Goldberg, E. Goldenberg, D. Goldner, D. Goldscher, B. Gordon, S. Gottlieb, M. Grayson, R. Guthrie, J. Guyton, J. Haas, F. Handel, R. Hartman, J. Henry, M. Hepp, R. Heuser, D. Herrington, M. Hibbard, C. Hjelm Dahl-Monsen, G. Hopkins, V. Howard, J. Hsia, D. Hunninghake, S. Jafri, P. Jones, P. Kakavas, J. Kane, L. Keilson, E. Kerut, R. Kloner, R. Knopp, J. Kostis, L. Kozlowski, R. Krasuski, A. Kugelmass, K. LaBresh, J. Larry, C. Lavie, B. Lewis, S. Lewis, M. Linton, P. Linz, R. Lloret, V. Lucarella, J. Maciejko, D. McElroy, J. McGhee, M. McGowan, W. McGuinn, M. Melucci, J. Merillat, M. Michalski, D. Miller, L. Miller, M. Miller, M. Mirro, V. Miscia, J. Mossberg, B. Musa, S. Nash, R. Nesto, M. Neustel, T. Noonan, J. O'Keefe, B. Olafsson, S. Oparil, T. Pearson, C. Pepine, G. Peterson, G. Pogson, K. Powers, D. Rader, R. Reeves, J. Reusch, G. Revtyak, D. Robertson, J. Robinson, W. Robinson, M. Rocco, J. Robinson, J. Rodgers, R. Rosenson, E. Roth, S. Sadanandan, K. Salisbury, D. Sato, J. Saucedo, E. Schaefer, H. Schrott, L. Seman, G. Schectman, C. Schmalfuss, D. Schneider, B. Sobel, R. Schneider, S. Schwartz, P. Seigel, M. Seyal, S. Sharp, D. Shindler, D. Smith, D. Sprecher, L. Solberg, E. Sontz, J. Stamper, E. Stein, V. Subbarao, A. Susmano, A. Talle, P. Thompson, J. Torelli, F. Torres, D. Triffon, G. Vetrovec, N. Vijay, W. Wickermeier, K. Wool, M. Zakrzewski, S. Zarich, J. Zavoral, F. Zieve.

## REFERENCES

- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
- Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-504.
- Sever PS, Dahlof B, Poulter NR, et al. 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.
- Koren MJ, Hunninghake DB. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the ALLIANCE study. *J Am Coll Cardiol* 2004;44:1772-9.
- 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.
- De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J* 2003;24:1601-10.
- Grundey 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. [Erratum, *Circulation* 2004;110:763.]
- Waters DD, Guyton JR, Herrington DM, et al. Treating to New Targets (TNT) Study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? *Am J Cardiol* 2004;93:154-8.
- Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Circulation* 2002;106:1024-8.
- Sacks FM, Pfeffer MA, Moyé LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001-9.
- The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-57.
- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.

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