High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction

The IDEAL Study: A Randomized Controlled Trial

Terje R. Pedersen, MD, PhD
Ole Faergeman, MD, DMSc
John J. P. Kastelein, MD, PhD
Anders G. Olsson, MD, PhD
Matti J. Tikkanen, MD, PhD
Ingar Holme, PhD
Mogens Lytken Larsen, MD, DMSc
Fredrik S. Bendiksen, MD
Christina Lindahl, MD
Michael Szarek, MS
John Tsai, MD
for the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group

Context Evidence suggests that more intensive lowering of low-density lipoprotein cholesterol (LDL-C) than is commonly applied clinically will provide further benefit in stable coronary artery disease.

Objective To compare the effects of 2 strategies of lipid lowering on the risk of cardiovascular disease among patients with a previous myocardial infarction (MI).

Design, Setting, and Participants The IDEAL study, a prospective, randomized, open-label, blinded end-point evaluation trial conducted at 190 ambulatory cardiology care and specialist practices in northern Europe between March 1999 and March 2005 with a median follow-up of 4.8 years, which enrolled 8888 patients aged 80 years or younger with a history of acute MI.

Interventions Patients were randomly assigned to receive a high dose of atorvastatin (80 mg/d; n=4439), or usual-dose simvastatin (20 mg/d; n=4449).

Main Outcome Measure Occurrence of a major coronary event, defined as coronary death, confirmed nonfatal acute MI, or cardiac arrest with resuscitation.

Results During treatment, mean LDL-C levels were 104 (SE, 0.3) mg/dL in the simvastatin group and 81 (SE, 0.3) mg/dL in the atorvastatin group. A major coronary event occurred in 463 simvastatin patients (10.4%) and in 411 atorvastatin patients (9.3%) (hazard ratio [HR], 0.89; 95% CI, 0.78-1.01; $P=.07$). Nonfatal acute MI occurred in 321 (7.2%) and 267 (6.0%) in the 2 groups (HR, 0.83; 95% CI, 0.71-0.98; $P=.02$), but no differences were seen in the 2 other components of the primary end point. Major cardiovascular events occurred in 608 and 533 in the 2 groups, respectively (HR, 0.87; 95% CI, 0.77-0.98; $P=.02$). Occurrence of any coronary event was reported in 1059 simvastatin and 898 atorvastatin patients (HR, 0.84; 95% CI, 0.76-0.91; $P<.001$). Noncardiovascular death occurred in 156 (3.5%) and 143 (3.2%) in the 2 groups (HR, 0.92; 95% CI, 0.73-1.15; $P=.47$). Death from any cause occurred in 374 (8.4%) in the simvastatin group and 366 (8.2%) in the atorvastatin group (HR, 0.98; 95% CI, 0.85-1.13; $P=.81$). Patients in the atorvastatin group had higher rates of drug discontinuation due to nonserious adverse events; transaminase elevation resulted in 43 (1.0%) vs 5 (0.1%) withdrawals ($P<.001$). Serious myopathy and rhabdomyolysis were rare in both groups.

Conclusions In this study of patients with previous MI, intensive lowering of LDL-C did not result in a significant reduction in the primary outcome of major coronary events, but did reduce the risk of other composite secondary end points and nonfatal acute MI. There were no differences in cardiovascular or all-cause mortality. Patients with MI may benefit from intensive lowering of LDL-C without an increase in noncardiovascular mortality or other serious adverse reactions.

Trial Registration ClinicalTrials.gov Identifier: NCT00159835.

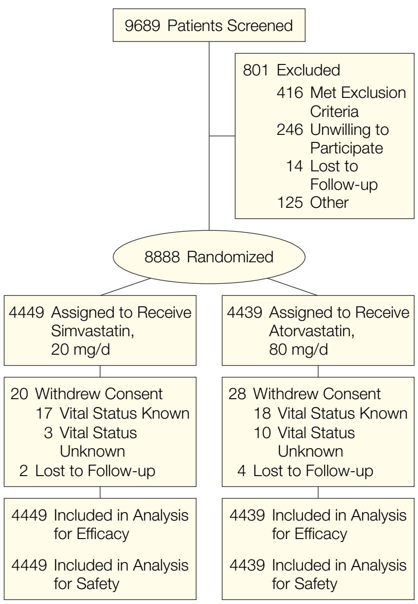
JAMA. 2005;294:2437-2445 www.jama.com

LOWERING OF LOW-DENSITY LIPOprotein cholesterol (LDL-C) with statins has in the last decade become part of the standard treatment regimen in patients with established coronary heart disease (CHD). Following the publication of the results of the Scandinavian Simvastatin Survival Study (4S) in 1994,[1] the most common treatment regimen for such patients in northern Europe has been simvastatin, 20 to 40 mg/d. In a recent trial among patients with acute coronary syndromes, incremental benefit was demonstrated with more intensive lowering of LDL-C to well below 100 mg/dL.[2] In the Treating to New Targets (TNT) study comparing high and low doses of atorvastatin in stable nonacute CHD, a significant improve-

For editorial comment see p 2492.

Author Affiliations and a complete list of the members of the IDEAL Study Group appear at the end of this article.
Corresponding Author: Terje R. Pedersen, MD, PhD, Centre for Preventive Medicine, Ullevål University Hospital, Kirkeveien 166, Bldg 19, N-0407 Oslo, Norway (t.r.pedersen@medisin.uio.no).

Figure 1. Flow of Participants Through the Trial



ment in prognosis with respect to cardiovascular disease was demonstrated.[3] In that study, however, the benefit of reduced cardiovascular mortality appeared to have been offset by a higher number of deaths due to noncardiovascular causes. Although this difference did not reach statistical significance and could well be due to the play of chance, it led to a call for further safety information on the use of atorvastatin at a dose of 80 mg/d.[4]

The Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice[5] in 2003 recommended an LDL-C target level of less than 100 mg/dL (2.5 mmol/L) for CHD patients. The Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel recently introduced a new target of less than 70 mg/dL (1.8 mmol/L) for patients at very high risk.[6] The main hypothesis of the current study, the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study, was that intensive lowering of LDL-C with atorvastatin at the highest recommended dose would yield incremental benefit compared with the moderate, most widely used dose of simvastatin.

METHODS

Study Design and Participants

The IDEAL study was a multicenter, prospective, randomized, open-label, blinded end-point classification trial (the so-called PROBE design[7]) carried out at 190 ambulatory cardiology and private specialist centers in Denmark, Finland, Iceland, the Netherlands, Norway, and Sweden. A detailed description of the study design and baseline characteristics of the patients has been published elsewhere.[8] In brief, recruitment and randomization took place from March 1999 to March 2001 and patients were followed up until March 2005. Records of patients previously treated at the centers were screened for the main eligibility criteria. Potentially eligible patients were invited for a screening visit. Written informed consent was obtained from all patients, and the study was approved by the national or regional review board in all countries and by governmental reimbursing institutions in countries where the main sponsor did not cover all costs.

Men and women aged 80 years or younger with a history of a definite myocardial infarction and who qualified for statin therapy according to national guidelines at the time of recruitment were eligible. The main exclusion criteria were any known contraindications to statin therapy, previous intolerance to statins in low or high doses, liver enzyme levels more than 2 times the upper limit of normal, pregnancy or breastfeeding, nephrotic syndrome, uncontrolled diabetes mellitus, uncontrolled hypothyroidism, plasma triglyceride levels higher than 600 mg/dL (6.8 mmol/L), congestive heart failure (New York Heart Association classification IIIb or IV), hemodynamically important valvular heart disease, gastrointestinal conditions affecting absorption of drugs, treatment with other drugs that seriously affect the pharmacokinetics of statins, and treatment with other lipid-lowering drugs. Patients previously treated with statins qualified if they had not already had titration to a dose higher than the equivalent of 20 mg/d of simvastatin.

After dietary counseling, patients fulfilling the eligibility criteria were randomized to receive simvastatin, 20 mg/d, or atorvastatin, 80 mg/d (FIGURE 1). Study medication was assigned via a central interactive voice response system (ClinPhone, Nottingham, England). Allocation numbers were given out in blocks of 24. Allocation was balanced by center; no other stratification was used. There was no run-in or washout period. Study medication was provided by prescription except in Finland, where it was dispensed at the expense of the sponsor.

Patients were followed up at the centers after 12 and 24 weeks and every 6 months thereafter. If, at 24 weeks, plasma total cholesterol level was higher than 190 mg/dL (5.0 mmol/L), the dose of simvastatin could be increased to 40 mg/d. The dose of atorvastatin could be decreased to 40 mg/d for adverse events. If LDL-C decreased to less than 39 mg/dL (1.0 mmol/L), an investigator would be notified and could consider reducing the statin dose.

All lipid and lipoprotein levels were measured from fasting blood samples. Such measurements, along with liver enzymes and other laboratory measurements, were made at baseline, at 12 and 24 weeks, at 1 year, and yearly thereafter. All measurements were made at a central laboratory. The results of lipid and lipoprotein measurements were not revealed to study personnel during the study except in cases of titration of simvastatin at 24 weeks.

Study Outcomes

The primary clinical outcome was time to first occurrence of a major coronary event, defined as coronary death, hospitalization for nonfatal acute myocardial infarction, or cardiac arrest with resuscitation. Potential myocardial infarction cases were adjudicated according to current guidelines of the Joint European Society of Cardiology/American College of Cardiology. There were 3 prespecified composite secondary outcomes: (1) major cardiovascular events (any primary event plus stroke; the diagnosis of stroke required evidence of a neurological deficit, usually localized, lasting ≥24 hours or until death, usually confirmed by diagnostic imaging); (2) any CHD event (any primary event, any coronary revascularization procedure, or hospitalization for unstable angina); (3) any cardiovascular events (any of the former plus hospitalization with a primary diagnosis of congestive heart failure and peripheral arterial disease, defined as new clinical diagnosis or hospitalization for such disease). In addition, individual components of the composite end points were also prespecified as secondary outcomes, as was all-cause mortality.

In addition to per-protocol reporting by investigators, monitors reviewed patient records at regular intervals to search for potential end points. An end-point classification committee blindly reviewed reports on potential end points and adjudicated outcomes at regular meetings. All reports were first screened by an independent center (Inveresk, Raleigh, NC) for blinding of treatment allocation.

Statistical Analysis

Based on previous experience, it was projected that simvastatin therapy would produce a mean 35% reduction in LDL-C from untreated levels, while the reduction with atorvastatin, 80 mg/d, would be at least 55%, creating a difference in plasma levels of about 40 mg/dL (1 mmol/L). The trial was designed to have 90% power to detect an anticipated 21% relative risk reduction (from 10% to 7.9%) in the primary outcome variable with atorvastatin over 5 years using a 2-tailed α level of .05. Because the risk of the patients first recruited was recalculated to be lower than first anticipated, the originally planned sample size of 7700 patients was increased to 8888. A data and safety monitoring board performed interim analyses when approximately 50% and 75% of the predetermined final number of 774 patients had experienced a primary end point.

The study was initiated by the investigators and scientifically led by a steering committee consisting of independent researchers and investigators and 3 members employed by the sponsor. Monitoring of data collection was provided by the sponsor. A contract research organization (Covance, Horsham, England) reviewed the data for errors and inconsistencies and sent queries to the investigators for clarification. This organization provided the interim reports for the data and safety monitoring board. The final statistical analysis was performed by the sponsor. An independent academic statistician of the steering committee (I.H.) had full access to all of the data at the completion of data collection and verified the analyses of the results.

Kaplan-Meier hazard rates were used to examine incidence over time and the log-rank test was used to assess group differences. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).[9] Statistical analysis was performed using SAS, version 8.2 (SAS Institute Inc, Cary, NC). All analyses in this report are based on the intention-to-treat principle including all randomized patients. Two-sided *P* values of <.05 were regarded as statistically significant.

Table 1. Baseline Participant Characteristics*

Characteristics	Simvastatin (n = 4449)	Atorvastatin (n = 4439)
Age, mean (SD), y	61.6 (9.5)	61.8 (9.5)
Male sex	3597 (80.8)	3590 (80.9)
Blood pressure, mean (SD), mm Hg		
Systolic	137.0 (19.9)	136.7 (20.2)
Diastolic	80.6 (10.2)	80.1 (10.3)
Body mass index, mean (SD)†	27.3 (3.8)	27.3 (3.9)
Cardiovascular history		
>1 Previous MIs	756 (17.0)	738 (16.6)
≤2 mo Since last MI	506 (11.4)	493 (11.1)
Coronary angioplasty only	877 (19.7)	885 (19.9)
CABG surgery only	747 (16.8)	732 (16.5)
Both angioplasty and CABG surgery	163 (3.7)	127 (2.9)
Cerebrovascular disease	376 (8.5)	353 (8.0)
Peripheral vascular disease	195 (4.4)	182 (4.1)
Congestive heart failure	244 (5.5)	293 (6.6)
Atrial fibrillation or flutter	336 (7.6)	347 (7.8)
Risk factors		
Current smoker	943 (21.2)	892 (20.1)
Former smoker	2614 (58.8)	2577 (58.1)
Systemic hypertension	1469 (33.0)	1461 (32.9)
History of diabetes mellitus	537 (12.1)	532 (12.0)
Prerandomization statin therapy		
Simvastatin	2230 (50.1)	2233 (50.3)
Atorvastatin	512 (11.5)	499 (11.2)
Pravastatin	431 (9.7)	419 (9.4)
Other statins	202 (4.5)	187 (4.2)
Concomitant therapy		
Aspirin	3536 (79.5)	3494 (78.7)
Warfarin or dicoumarol	559 (12.6)	558 (12.6)
β-Blockers	3281 (73.7)	3377 (76.1)
Calcium antagonists	840 (18.9)	882 (19.9)
ACE inhibitors	1367 (30.7)	1296 (29.2)
Angiotensin II blockers	270 (6.1)	263 (5.9)

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; MI, myocardial infarction.
*Data are expressed as No. (%) unless otherwise noted.
†Body mass index was calculated as weight in kilograms divided by the square of height in meters.

RESULTS

After screening of patients' records, 9689 potentially eligible patients were called in for a screening visit. Of these, 8888 met the eligibility criteria and were randomized (Figure 1). The main reasons for exclusion were patients' use of higher statin doses than the equivalent of 20 mg/d of simvastatin, unwillingness to participate, and previous adverse experience with statins.

The median follow-up time was 4.8 years (range of surviving participants, 4.0-5.9 years). Six patients were lost to follow-up and 48 patients withdrew consent prior to study close, but vital status was known for 35 of these at the close of the study. Data for these patients have been included in the analysis for the period prior to loss or withdrawal. Vital status at the end of the trial is thus unknown for 19 patients.

Baseline characteristics were well balanced between the 2 treatment groups (TABLE 1). The median time since last myocardial infarction was 22 months in the simvastatin group and 21 months in the atorvastatin group.

At 24 weeks of follow-up, 900 patients (21%) in the simvastatin group had their dosage increased to 40 mg/d. At the end of the study, 1034 (23%) were prescribed simvastatin, 40 mg/d. In patients allocated to receive atorvastatin, 80 mg/d, 250 (6%) had their dosage reduced to 40 mg/d by 24 weeks; in 587 patients(13%), the final dose was 40 mg. Overall adherence, defined as total study medication exposure as a percentage of total follow-up time, was 89% in the atorvastatin group and 95% in the simvastatin group. By the end of the study, 14% of the atorvastatin-allocated and 7% of the simvastatin-allocated patients had permanently discontinued study medication. Most patients who stopped taking the study drug switched to a different statin. In the simvastatin group, 360 patients took a different statin at some point; in 123 (2.8%), it was atorvastatin. In the atorvastatin group, 645 patients took a different statin; in 364 (8.2%), it was simvastatin.

Since the majority of patients allocated to receive simvastatin therapy were already taking simvastatin, 20 mg/d, or another statin at an equivalent dose at the time of randomization, the changes in lipid and lipoprotein levels for the group as a whole were small (TABLE 2). Patients in the simvastatin group who were not taking a statin at the time of randomization had, on average, a reduction in LDL-C of 33% after 12 weeks. In the group allocated to atorvastatin, 80 mg/d, statin-naive patients had a mean reduction in LDL-C of 49%. During treatment, mean (SE) LDL-C levels were 104 (0.3) mg/dL (2.7 [0.008] mmol/L) in the simvastatin group and 81 (0.3) mg/dL (2.1 [0.008] mmol/L) in the atorvastatin group. Total cholesterol and triglyceride levels were also significantly lower in the atorvastatin group compared with the simvastatin group, whereas high-density lipoprotein cholesterol (HDL-C) levels were slightly but significantly higher in the simvastatin group. Apolipoprotein levels changed correspondingly (Table 2).

In December 2004, reports of 702 patients with a confirmed primary end

Table 2. Baseline and Follow-up Levels of Lipids and Lipoproteins*

Lipids and Lipoproteins	Concentration, Mean (SE)							Absolute Effect at 1 y, Mean (95% CI)
	Baseline	12 Weeks	1 Year	2 Years	3 Years	4 Years	5 Years	
No. of patients								
Simvastatin	4438	4373	4290	4168	4033	3930	775	
Atorvastatin	4425	4335	4200	4099	3984	3861	759	
LDL-C, mg/dL								
Simvastatin	121.4 (0.5)	104.7 (0.4)	102.0 (0.4)	103.6 (0.4)	106.4 (0.4)	103.8 (0.4)	99.8 (0.9)	−22.9 (−23.9 to −21.8)
Atorvastatin	121.6 (0.5)	77.7 (0.4)	79.1 (0.4)	82.1 (0.4)	85.8 (0.4)	83.6 (0.4)	80.0 (1.0)	
Total cholesterol, mg/dL								
Simvastatin	195.9 (0.6)	179.3 (0.5)	175.9 (0.5)	176.9 (0.5)	180.2 (0.5)	180.4 (0.5)	176.8 (1.0)	−28.7 (−29.9 to −27.4)
Atorvastatin	196.8 (0.6)	145.5 (0.5)	147.4 (0.5)	150.3 (0.5)	154.4 (0.5)	154.7 (0.6)	153.4 (1.3)	
HDL-C, mg/dL								
Simvastatin	46.1 (0.2)	47.3 (0.2)	47.1 (0.2)	47.2 (0.2)	47.6 (0.2)	50.2 (0.2)	50.6 (0.5)	−1.3 (−1.6 to −1.0)
Atorvastatin	46.0 (0.2)	45.4 (0.2)	45.7 (0.2)	46.0 (0.2)	46.4 (0.2)	48.6 (0.2)	50.1 (0.5)	
Triglycerides, mg/dL								
Simvastatin	146.6 (1.1)	141.8 (1.3)	139.5 (1.3)	136.4 (1.3)	136.4 (1.4)	136.9 (1.3)	137.2 (2.7)	−25.8 (−28.3 to −23.3)
Atorvastatin	151.1 (1.2)	115.5 (0.9)	116.3 (1.0)	114.1 (1.1)	114.8 (1.2)	115.6 (1.1)	118.5 (2.7)	
Apolipoprotein A1, g/L								
Simvastatin	1.39 (0.01)	1.42 (0.01)	1.44 (0.01)	1.47 (0.01)	1.49 (0.01)	1.50 (0.01)	1.52 (0.01)	−0.06 (−0.07 to −0.06)
Atorvastatin	1.39 (0.01)	1.35 (0.01)	1.38 (0.01)	1.41 (0.01)	1.43 (0.01)	1.44 (0.01)	1.48 (0.01)	
Apolipoprotein B, g/L								
Simvastatin	1.19 (0.01)	1.05 (0.01)	1.07 (0.01)	1.03 (0.01)	1.06 (0.01)	1.09 (0.01)	1.08 (0.01)	−0.23 (−0.24 to −0.22)
Atorvastatin	1.19 (0.01)	0.80 (0.01)	0.84 (0.01)	0.82 (0.01)	0.86 (0.01)	0.90 (0.01)	0.91 (0.01)	

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
SI conversion factors: To convert HDL-C, LDL-C, and total cholesterol to mmol/L, multiply by 0.0259. To convert triglycerides to mmol/L, multiply by 0.0113.
*Absolute effect means and 95% CIs were derived from analysis of covariance with terms for treatment and baseline values; *P* values for absolute effect were <.001 for all between-group comparisons.

point had arrived at the coordinating centers. Based on this information, the steering committee decided that the study close-out procedures should be concluded by April 2005, when it was anticipated that the protocol-specified target of 774 patients with a primary end point would have occurred. When all study close-out visits had been performed, a total of 874 patients had actually experienced a primary end point.

The primary end point of coronary death, acute myocardial infarction, or cardiac arrest with resuscitation occurred in 463 patients (10.4%) in the simvastatin group and in 411 (9.3%) in the atorvastatin group (TABLE 3). This corresponds to a relative risk reduction of 11% with atorvastatin, 80 mg/d (HR, 0.89; 95% CI, 0.78-1.01; *P*=.07) (FIGURE 2). A post hoc Cox regression analysis of the primary end point with adjustment for sex, age, statin use at randomization, duration since last myocardial infarction, total cholesterol, and HDL-C resulted in an HR of 0.87 (95% CI, 0.76-0.99; *P*=.04). A preliminary analysis of prespecified subgroups defined by sex and age did not reveal any statistically significant treatment group interactions.

There were 178 coronary deaths (4.0%) in the simvastatin group vs 175 (3.9%) in the atorvastatin group (HR, 0.99; 95% CI, 0.80-1.22; *P*=.90). Nonfatal myocardial infarction occurred in 321 patients (7.2%) in the simvastatin group and in 267 (6.0%) in the atorvastatin group (HR, 0.83; 95% CI, 0.71-0.98; *P*=.02). The composite secondary end point of a major cardiovascular event including stroke was reduced in the atorvastatin group (HR, 0.87; 95% CI, 0.78-0.98; *P*=.02). Similarly, there were reductions in the risk of nonfatal myocardial infarction, any CHD event, and any cardiovascular event. Hemorrhagic strokes occurred in 6 patients in each treatment group. Kaplan-Meier hazard rates for selected components of the secondary end points are shown in FIGURE 3.

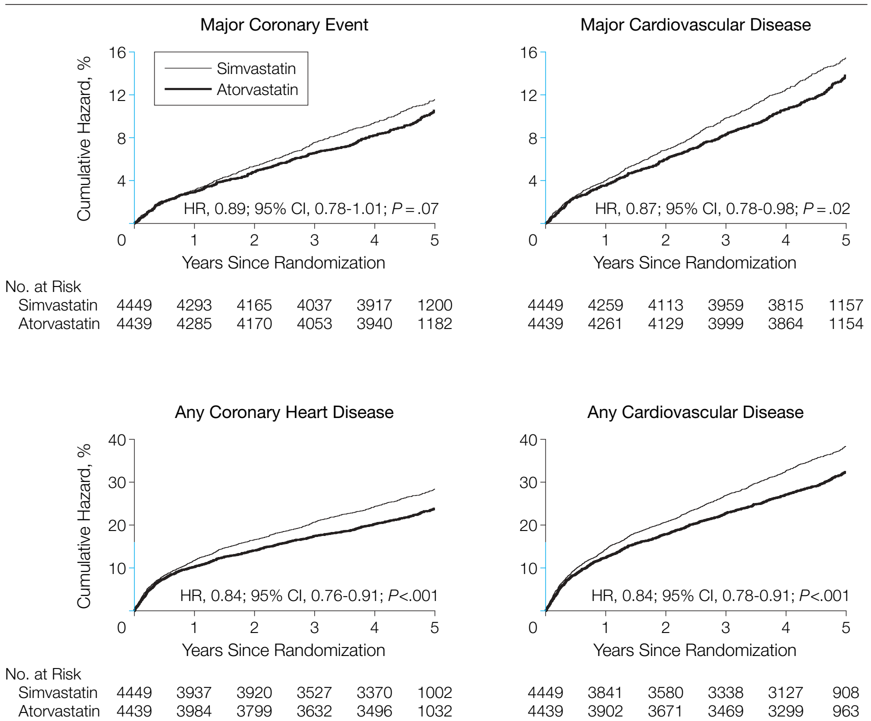
The risk of death from any cause was similar in both study groups (HR, 0.98;

Table 3. Incidence of and Hazard Ratios for Primary and Secondary Efficacy Outcomes

Outcome Measures	Simvastatin, No. (%) (n = 4449)	Atorvastatin, No. (%) (n = 4439)	Hazard Ratio (95% CI)	*P* Value
Major coronary event (primary outcome)	463 (10.4)	411 (9.3)	0.89 (0.78-1.01)	.07
CHD death	178 (4.0)	175 (3.9)	0.99 (0.80-1.22)	.90
Nonfatal myocardial infarction	321 (7.2)	267 (6.0)	0.83 (0.71-0.98)	.02
Cardiac arrest with resuscitation	7 (0.2)	10 (0.2)		
Any CHD event	1059 (23.8)	898 (20.2)	0.84 (0.76-0.91)	<.001
Coronary revascularization	743 (16.7)	579 (13.0)	0.77 (0.69-0.86)	<.001
Hospitalization for unstable angina	235 (5.3)	196 (4.4)	0.83 (0.69-1.01)	.06
Fatal or nonfatal stroke	174 (3.9)	151 (3.4)	0.87 (0.70-1.08)	.20
Major cardiovascular event*	608 (13.7)	533 (12.0)	0.87 (0.78-0.98)	.02
Hospitalization for nonfatal CHF	123 (2.8)	99 (2.2)	0.81 (0.62-1.05)	.11
Peripheral arterial disease†	167 (3.8)	127 (2.9)	0.76 (0.61-0.96)	.02
Any cardiovascular event	1370 (30.8)	1176 (26.5)	0.84 (0.78-0.91)	<.001
All-cause mortality	374 (8.4)	366 (8.2)	0.98 (0.85-1.13)	.81
Cardiovascular	218 (4.9)	223 (5.0)	1.03 (0.85-1.24)	.78
Noncardiovascular	156 (3.5)	143 (3.2)	0.92 (0.73-1.15)	.47
Malignant disease	112 (2.5)	99 (2.2)	0.89 (0.68-1.16)	.38
Suicide/violence/accidental death	9 (0.2)	5 (0.1)	. . .	. . .
Other	30 (0.7)	32 (0.7)	. . .	. . .
Unclassified	5 (0.1)	7 (0.2)	. . .	. . .

Abbreviations: CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval. Ellipses indicate analysis not done because of too few events.
*Major coronary events and stroke.
†Any newly diagnosed peripheral arterial disease or that which has led to hospitalization.

Figure 2. Cumulative Hazard of Cardiovascular Disease

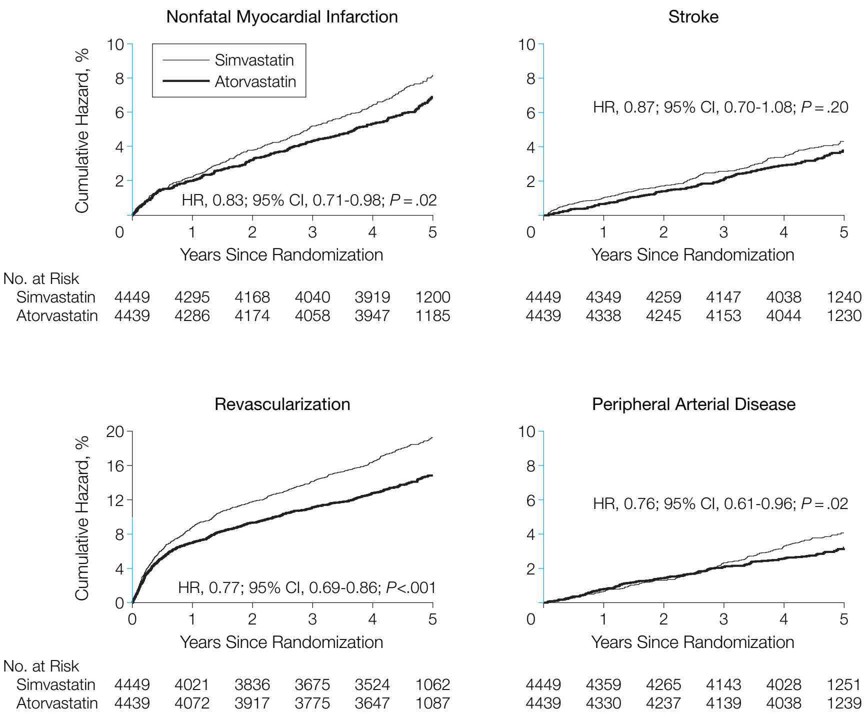


Major coronary event (MCE) was defined as death from coronary disease, nonfatal myocardial infarction, or cardiac arrest with resuscitation. Major cardiovascular disease indicates MCE plus stroke. Any coronary heart disease indicates MCE plus hospitalization for unstable angina pectoris and coronary revascularization procedures. Any cardiovascular disease indicates any of the above plus peripheral vascular disease and hospitalization for nonfatal congestive heart failure. HR indicates hazard ratio; CI, confidence interval.

95% CI, 0.85-1.13; $P=.80$) (Table 3). There were no significant differences in noncardiovascular deaths between the treatment groups. In particular, mortality due to cancer was similar in the 2 groups, at 112 (2.5%) in the simvastatin group and 99 (2.2%) in the atorvastatin group. There were no significant differences in cancer mortality for any particular body system.

There were no significant differences in the frequency of serious clinical adverse experiences between the 2 groups. There were, however, more patients in the atorvastatin group who discontinued study medication because of investigator-reported adverse effects (TABLE 4). Elevation of liver enzyme levels occurred more frequently in the atorvastatin group, but this was not related to any increased incidence of clinical liver disease. Myalgias occurred more frequently in the atorvastatin group, but myopathy rates were exceedingly low in both the atorvastatin and simvastatin groups.

Figure 3. Cumulative Hazard of Nonfatal Myocardial Infarction, Stroke, Coronary Revascularization, and Peripheral Artery Disease



HR indicates hazard ratio; CI, confidence interval.

Table 4. Frequency of Adverse Events and Most Relevant Liver Enzyme Elevations

	Simvastatin, No. (%) (n = 4449)	Atorvastatin, No. (%) (n = 4439)	*P* Value*
Any adverse event	4202 (94.4)	4204 (94.7)	.62
Any serious adverse event	2108 (47.4)	2064 (46.5)	.42
Any adverse event resulting in permanent discontinuation of study drug	186 (4.2)	426 (9.6)	<.001
Adverse events resulting in permanent discontinuation of study drug with incidence ≥0.5% in either treatment group			
Myalgia	51 (1.1)	97 (2.2)	<.001
Diarrhea	9 (0.2)	38 (0.9)	<.001
Abdominal pain	10 (0.2)	37 (0.8)	<.001
Nausea	6 (0.1)	22 (0.5)	.004
Investigator-reported myopathy	11 (0.25)	6 (0.14)	.33
Investigator-reported rhabdomyolysis (subset of coded myopathy)	3 (0.07)	2 (0.05)	>.99
AST >3 × ULN at 2 consecutive measurements	2 (0.04)	18 (0.41)	<.001
ALT >3 × ULN at 2 consecutive measurements	5 (0.11)	43 (0.97)	<.001
Myopathy defined as CPK >10 × ULN at 2 consecutive measurements with muscle symptoms	0	0	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; ULN, upper limit of normal.
*P values were calculated by 2-sided χ^2 test.

COMMENT

The majority of trials on statin therapy in the last decade have examined the effect of lowering LDL-C by 25% to 40%. In the 4S study, the mean LDL-C reduction was 35%.[1] The IDEAL study intended to explore whether a strategy of reducing LDL-C even further would yield incremental benefit. The prespecified primary end point did not achieve statistical significance ($P=.07$), but there were significant reductions in nonfatal acute myocardial infarction and in the secondary composite end points of any CHD event and major or any cardiovascular events. There was no difference in all-cause or cardiovascular mortality. Thus, although the reductions were more modest than expected and although the primary end point was not met, these results indicate that more intensive lowering of LDL-C than usual in patients with previous myocardial infarction might prevent 68 first cardiovascular events (95% CI, 39-97) per 1000 patients over 5 years.

There are several possible reasons why statistical significance was not reached for the primary end point. One explanation might be insufficient difference in levels of LDL-C between the groups since the observed difference was slightly smaller than projected. The initial LDL-C reduction of 49% in statin-naive patients taking atorvastatin, 80 mg/d, was less than expected, and although adherence with this therapy was excellent, it was not as good as in the simvastatin group.

A second possible explanation was that the follow-up duration was only a median of 4.8 years even though the study protocol anticipated the prespecified number of primary end points to be reached after a median of 5.5 years. A third possibility is that the effect of simvastatin on HDL-C would attenuate the difference produced by the improved effect of atorvastatin on LDL-C. However, the impact of statins on HDL-C has not yet been shown to influence patient outcomes.

Design and Adherence

The IDEAL study was carried out with the PROBE design and, thus, did not have the advantages of a double-blind trial. However, the end-point classification was conducted by a blinded clinical end-points committee with the idea of minimizing bias. The open-label design with prescription of study medication had the advantage of being more like a "real-world" setting, but the possibility of bias for some of the physician-initiated end points, such as coronary revascularization and hospitalization for unstable angina, cannot be excluded. The fact that most patients had to pay part of the cost of the study drug apparently did not affect prescription rates, because the cost for the patients of the 2 study drugs was identical.

The apparent adherence to atorvastatin was high and better than that in other comparable trials. The adherence in the simvastatin group was, however, exceptional (95%). The higher adherence to study medication in the simvastatin group than in the atorvastatin group may be explained by the fact that 51% of the patients had been taking simvastatin prior to randomization and were probably comfortable with it, while in an open-label design a high dose of atorvastatin might have led to hesitation by some patients and investigators, especially early in the trial. This also makes it difficult to make reliable comparisons of reported adverse experiences between the 2 treatment regimens.

Comparison With Other Trials

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study compared pravastatin, 40 mg/d, with atorvastatin, 80 mg/d, in patients with recent acute coronary syndromes.[2] In that study, the difference in LDL-C levels between the treatment groups averaged 33 mg/dL (0.86 mmol/L), which produced a 16% relative reduction in the HR of the primary composite end point, which included death, myocardial infarction, unstable angina, coronary revascularization, and stroke. Thus, in that study the patient population was different, since only 11% of the IDEAL population had a recent myocardial infarction (<2 months); in addition, the difference in LDL-C between the treatment groups was larger and the definition of the primary end point was different.

In the TNT study, the primary end point included stroke.[3] When comparing the primary end point of the TNT trial with the same end point in the IDEAL study, the difference between treatment groups was smaller in IDEAL (HR, 0.78 vs 0.87), but the 95% CIs for the HRs overlap. Comparison of the broader end point of any cardiovascular events, however, reveals more similar HRs of 0.81 and 0.84 in the 2 trials, respectively.

A recent prospective meta-analysis of 14 cholesterol-lowering statin trials with more than 90 000 patients found a 23% proportional reduction in the incidence of major coronary events and a 21% proportional reduction in the incidence of major cardiovascular events per 1 mmol/L of LDL-C reduction (corresponding to a 5.5% and 5% reduction in incidences per 10 mg/dL reduction in LDL-C, respectively).[10] Our results are consistent with these findings and are also in accordance with other meta-analyses and epidemiological data on the relationship of cholesterol levels and CHD risk[10-14] and by findings from internal subgroup analyses of results of previous trials.[15,16] Recent findings in trials of other comparative drugs[3,17] and in different clinical settings[2,18] have provided evidence of the same relationship.

The IDEAL trial was not powered to detect a significant difference in all-cause mortality. In the 4S study, the comparator was placebo, and in the placebo group 74% of the deaths were coronary.[1] In IDEAL, only 48% of the deaths in the simvastatin group had a coronary cause, which is considerably lower than the 61% of deaths having a coronary cause in the simvastatin group in 4S. This decline in coronary mortality may well reflect improvements in coronary prevention and care during the last decade. While this improvement must be welcomed, it has made it more difficult for trialists to demonstrate further benefit in survival.

Safety

In the IDEAL study, there was a small and nonsignificant excess of 13 more noncardiovascular deaths in the simvastatin group than in the atorvastatin group. In contrast, atorvastatin, 80 mg/d, was associated with a small and nonsignificant increase in noncardiovascular deaths compared with atorvastatin, 10 mg/d, in the TNT study. Such small differences are likely to have occurred by chance. There was no difference between the groups in the frequency of adverse events that were rated as serious. There were, however, more nonserious adverse events resulting in drug discontinuation in the atorvastatin group. This difference may reflect real nontolerance to a high dose of atorvastatin, but the possibility of reporting bias is present given the open-label design of the trial.

The proportion of patients developing liver enzyme elevation with atorvastatin, 80 mg/d, was low and is comparable with results of other similar trials. The proportion of patients in the simvastatin group who developed liver enzyme elevations was exceptionally small and was significantly lower than in the atorvastatin group. This reporting was not subject to bias, since it was performed by the central laboratory that transferred the results directly to the study database. The low frequency is readily explained by the fact that half of the patients had received simvastatin prior to randomization and were selected as "simvastatin-tolerant."

In summary, when comparing standard and intensive LDL-C–lowering therapies in patients with previous myocardial infarction, there was no statistically significant reduction in the primary end point of major coronary events, but there was reduced risk of other composite secondary end points and nonfatal acute myocardial infarction. There were no differences in cardiovascular and all-cause mortality. The results indicate that patients with myocardial infarction may benefit from intensive lowering of LDL-C without increase in noncardiovascular mortality or other serious adverse reactions.

Author Affiliations: Centre for Preventive Medicine, Ullevål University Hospital, Oslo, Norway (Drs Pedersen and Holme); Department of Medicine–Cardiology A, Århus University Hospital, Århus, Denmark (Drs Faergeman and Larsen); Academic Hospital Amsterdam, Amsterdam, the Netherlands (Dr Kastelein); Department of Internal Medicine, University Hospital, Linköping, Sweden (Dr Olsson); Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland (Dr Tikkanen); Pfizer Sweden, Täby, Sweden (Dr Lindahl); and Pfizer Inc, New York, NY (Mr Szarek and Dr Tsai). Dr Bendiksen is in private practice in Hamar, Norway.

Author Contributions: Dr Pedersen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Pedersen, Faergeman, Tikkanen, Holme, Larsen, Bendiksen, Lindahl.

Acquisition of data: Pedersen, Faergeman, Kastelein, Larsen, Szarek, Tsai.

Analysis and interpretation of data: Pedersen, Faergeman, Kastelein, Olsson, Tikkanen, Holme, Larsen, Lindahl, Szarek, Tsai.

Drafting of the manuscript: Pedersen, Faergeman, Tikkanen, Holme, Lindahl, Szarek.

Critical revision of the manuscript for important intellectual content: Faergeman, Kastelein, Olsson, Tikkanen, Holme, Larsen, Bendiksen, Szarek, Tsai.

Statistical analysis: Pedersen, Faergeman, Holme, Szarek.

Obtained funding: Pedersen, Bendiksen.

Administrative, technical, or material support: Pedersen, Kastelein, Larsen, Lindahl, Tsai.

Study supervision: Pedersen, Faergeman, Olsson, Tikkanen, Larsen.

Financial Disclosures: Dr Pedersen has received consultation fees and speaker's honoraria from Pfizer, Merck, Merck AG, and AstraZeneca and research grants and steering committee fees from Pfizer and Merck. Dr Kastelein has received research grants from Pfizer. Drs Olsson and Holme have received honoraria from Pfizer as steering committee members. Dr Bendiksen was previously employed by Pfizer Norway and has received honoraria from Pfizer as a steering committee member. No other disclosures were reported.

Independent Statistical Analysis: Dr Holme is a statistician at the Ullevål University Hospital, Oslo, Norway, and performed an independent statistical analysis of the raw data set. That analysis confirmed all results reported in this article.

Funding/Support: This study was sponsored by Pfizer Inc.

Role of the Sponsor: Members of the steering committee employed by Pfizer contributed to the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript.

The IDEAL Study Group: *Denmark (1987 patients enrolled)*: S. Abildstrøm, København; E. Agner, Helsingør; B. Alsbjerg, Skive; F. Andersen, Silkeborg; L. Andersen, Nykøbing; L. Andersen, Randers; M. Andersen, Fredericia; N. Andersen, Slagelse; U. Andersen, Slagelse; M. Bay, København; J. Böttzauw, Odder; B. Brendorp, København; H. Brockstedt, Silkeborg; J. Brønnum-Schou, København; J. Buhl, Silkeborg; L. Bune, København; L. Buttenschøn, Holbæk; T. Clausen, København; P. Clemmensen, København; P. Corell, Frederiksberg; J. Dahlin, København; C. Dahlstrøm, Slagelse; M. Dalsgaard, København; D. Damgaard, Århus; H. Dominguez, København; K. Egstrup, Svendborg; P. Eliasen, Holbæk; O. Færgeman, Århus; N. Falstie-Jensen, Hjørring; L. Fog, Hjørring; F. Frandsen, Fredericia; B. Fredenhardt, Holbæk; M. Frederiksen, København; P. Fruergaard, Roskilde; G. Gislason, København; B. Glintborg, Kalundborg; T. Glud, Middelfart; L. Gøtzsche, Randers; P. Grande, København; P. Gustavsen, Næstved; H. Halgreen, Køge; D. Hansen, Holbæk; J. Hansen, København; F. Henriksen, Fredericia; T. Hermann, København; P. Hildebrandt, Frederiksberg; E. Høgh, Odder; L. Holmvang, København; M. Husic, Svendborg; N. Ihlemann, København; T. Jakobsen, Frederiksberg; J. Jaque, Holbæk; B. Jastrup, Odder; G. Jensen, Roskilde; H. Jensen, Hjørring; J. Jensen, Odder; P. Jensen, Holstebro; T. Jensen, Fredericia; T. Jensen, Randers; H. Julsgaard, København; B. Jurlander, København; J. Kanters, Helsingør; V. Kirk, København; T. Kjeld, København; K. Klarlund, Køge; L. Køber, København; C. Kragelund, Frederiksberg; N. Kriegbaum, København; K. Kristensen, Holbæk; M. Kyhn, Næstved; C. Lange, København; C. Larsen, København; J. Larsen, Næstved; M. Larsen, Århus; M. Lessing, Kalundborg; K. Lindvig, København; P. Lomholt, Randers; H. Madsen, Kalundborg; L. Madsen, Frederiksberg; L. Madsen, Holstebro; A. Major-Pedersen, København; J. Markenvard, Fredericia; A. McNair, Frederikssund; T. Melchior, Roskilde; M. Misiorna-Böhme, Svendborg; N. Møller, Svendborg; B. Nielsen, Silkeborg; H. Nielsen, København; I. Nielsen, Roskilde; T. Nielsen, Esbjerg; W. Nielsen, Hvidovre; C. Nøjgaard, Holbæk; O. Nyvad, Holstebro; J. Olsen, Holbæk; E. Olsen, Roskilde; M. Olsen, Frederikssund; M. Ottesen, København; S. Pedersen, Odder; E. Petersen, Hjørring; J. Petersen, Hjørring; J. Poulsen, Middelfart; M. Præstholm, Randers; N. Ralfkiær, Helsingør; H. Rasmussen, København; S. Rasmussen, Hvidovre; V. Rasmussen, Hvidovre; C. Ravens, Fredericia; S. Ravn, Kalundborg; H. Rickers, Grenå; F. Rømer, Silkeborg; N. Roseva-Nielsen, Holbæk; P. Schnohr, København; K. Schultz, Holbæk; M. Schultz, Frederiksberg; B. Sigurd, København; E. Søndergaard, Svendborg; F. Steffensen, Randers; S. Stentebjerg, Skive; T. Svendsen, Holbæk; R. Sykulski, Næstved; A. Teisner, København; C. Terkelsen, Silkeborg; P. Thaning, København; K. Thomsen, Esbjerg; N. Thorball, Roskilde; J. Thorsen, Næstved; C. Torp-Pedersen, København; H. Ulriksen, Skive; M. Vaage-Nilsen, Frederikssund; N. Valeur, København; L. Vigh, Grenå; *Finland (506 patients enrolled)*: M. Äärynen, Siaraalamäki; J. Alanko, Tampere; H. Gylling, Helsinki; R. Heikkilä, Lohja; E. Hussi, Heinola; R. Hyttinen, Jyväskylä; E. Jukka, Rauma; A. Ketomäki, Helsinki; M. Ketonen, Joensuu; R. Kettunen, Mikkeli; L. Koivunen, Lohja; A. Koponen, Lappeenranta; P. Korhonen, Rauma; M. Laakso, Kuopio; M. Lampinen, Salo; S. Lehto, Kuopio; C. Lindström, Tammisaari; K. Luotola, Lappeenranta; J. Melin, Jyväskylä; T. Miettinen, Helsinki; J. Nurminen, Joensuu; H. Oksa, Tampere; T. Olli, Jyväskylä; T. Pekkarinen, Vantaa; O. Penttilä, Lahti; M. Puhakka, Kuopio; R. Radhakrishnan, Helsinki; M. Rajamäki, Lahti; H. Relas, Helsinki; J. Rinne, Tammisaari; A. Strandberg, Kerava; T. Strandberg, Helsinki; R. Sulosaari, Kerava; H. Vanhanen, Helsinki; *Iceland (82 patients enrolled)*: J. Högnason, Reykjavik; G. Oddsson, Reykjavik; G. Sigurdsson, Reykjavik; G. Thorgeirsson, Reykjavik; G. Thorgeirsson, Reykjavik; *the Netherlands (1351 patients enrolled)*: W. Aarnoudse, Eindhoven; E. Badings, Deventer; G. Bartels, Groningen; D. Basart, Hoorn; M. Baselier, Breda; G. Bech, Eindhoven; D. Beelen, Delft; P. Bernink, Groningen; E. Birkhoff-Pieters, Rotterdam; L. Bouwens, Deventer; A. Bredero, Utrecht; P. Bruggink-André de la Porte, Deventer; E. Bruijns, Goes; M. Buijs, Rotterdam; T. Cherpanath, Breda; J. Chin, Weert; P. Chin A Fo, Delft; R. Claessens, 's-Hertogenbosch; A. Constantinescu, Breda; J. De Boo, Goes; I. de Bruin, Capelle aan den IJSSEL; M. de Groot, Eindhoven; S. de la Fuente, Eindhoven; M. de Leeuw, Assen; E. de Melker, Amsterdam; W. de Voogt, Amsterdam; F. Den Hartog, Ede; J. DeWarrimont-Henquet, Heerlen; H. Dohmen, 's-Hertogenbosch; P. Dunselman, Breda; R. Entjes, Eindhoven; M. Faverey, Breda; R. Feld, Heerlen; Y. Foolen, Eindhoven; M. Galjee, Enschede; H. Groeneveld, Deventer; D. Groot, Eindhoven; R. Groutars, Amsterdam; J. Hartog, Utrecht; H. Heijmen, Eindhoven; J. Henneman, Alkmaar; W. Hermans, Tilburg; F. Hersbach, Eindhoven; D. Hertzberger, Nijmegen; A. Herweijer, Zwijndrecht; N. Holwerda, Tilburg; J. Hoorntje, Zwolle; P. Huinink, Eindhoven; C. Janus, Hoorn; H. Klomps, Weert; A. Kloppenberg-Oey, Groningen; M. Kofflard, Zwijndrecht; J. Kooistra-Huizer, Delft; H. Koornstra-Wortel, Oss; J. Kragten, Heerlen; K. Krasznai, Eindhoven; P. Kuijer, Oss; K. Kűleksi, Eindhoven; J. Levert, Delft; A. Liem, Goes; D. Lok, Deventer; J. Louwerenburg, Enschede; P. Melman, Tilburg; H. Michels, Eindhoven; W. Muijs van de Moer, Capelle aan den IJSSEL; P. Nierop, Rotterdam; F. Nijland, Amsterdam; S. Nio, Capelle aan den IJSSEL; A. Oude Ophuis, Nijmegen; J. Peels, Alkmaar; H. Penn, Weert; J. Posma, Groningen; R. Pruijsten, Capelle aan den IJSSEL; P. Rademaker, Eindhoven; A. Ramdat Misier, Zwolle; S. Roeffel, Eindhoven; H. Roeters Van Lennep, Goes; B. Schölzel, Breda; H. Schaafsma, Ede; J. Schroeder-Tanka, Amsterdam; A. Sewnaik-Asarfi, Capelle aan den IJSSEL; F. Smeets, Eindhoven; A. Stammen, Breda; H. Suryapranata, Zwolle; L. Takens, Groningen; T. Tan, Amsterdam; F. Tietge, Deventer; P. Tilon, Hoorn; W. Tonino, Eindhoven; M. Trip, Amsterdam; Y. Tuininga, Deventer; V. Umans, Alkmaar; G. Uytdehaag, Breda; P. Van Bergen, Hoorn; B. Van den Berg, Capelle aan den IJSSEL; B. Van den Branden, Breda; M. Van Der Schaaf, Hoorn; I. Van Eede, Assen; A. Van Es, Enschede; P. Van Kalmthout, Ede; T. Van Loenhout, Ede; R. Van Rijswijk, Tilburg; R. Van Roosmalen, Assen; M. Van Schoot, Enschede; J. Van Wijngaarden, Deventer; L. Van Woerkens, Zwijndrecht; M. Veerhoek, Rotterdam; J. Visser, Amsterdam; A. Weevers, Eindhoven; R. Weidgraaf, Enschede; R. Weijers, Eindhoven; A. Willems, Amsterdam; A. Withagen, Delft; P. Zwart, Oss; *Norway (2453 patients enrolled)*: C. Aase, Haugesund; W. Aasebø, Lørenskog; E. Aaser, Rud; K. Åkre, Stord; S. Andresen, Mysen; P. Antonsen, Bodø; K. Arnesen, Lørenskog; K. Aronsen, Hammerfest; O. Aronsen, Karasjok; I. Asmussen, Førde; I. Axelsson, Notodden; M. Bækkevar, Tønsberg; T. Baisa, Notodden; H. Bjørnstad, Bergen; K. Bjørnstad, Trondheim; H. Dalen, Levanger; R. Dalen, Hammerfest; A. Dimmen, Kristiansund; S. Dyb, Prsgrunn; K.

Dyrkorn, Kragerø; F. Erchinger, Odda; H. Fadnes, Stord; S. Fredwall, Mysen; Ø. Furnes, Hammerfest; K. Gisholt, Nesttun; S. Gravdal, Bergen; T. Graven, Levanger; S. Gudnason, Bergen; H. Haaland, Ålesund; O. Haanæs, Tynset; O. Hagen, Moss; B. Halvorsen, Moss; P. Hamre, Stavanger; V. Hansteen, Oslo; S. Hareide, Volda; E. Hauge, Bergen; T. Haugnes, Mosjøen; M. Heese, Odda; K. Helander, Mo i Rana; A. Hervold, Stavanger; A. Herzog, Oslo; A. Heskestad, Molde; S. Hewitt, Oslo; V. Høeg, Tynset; A. Hognestad, Rikshospitalet, Oslo; L. Holst-Larsen, Haugesund; M. Hosseini, Bergen; A. Hovland, Bodø; U. Hurtig, Tynset; K. Jacobsen, Ålesund; H. Janniche, Tynset; K. Johnsen, Karasjok; O. Jordal, Bergen; R. Karlsen, Stavanger; A. Kask, Bergen; J. Kjekshus, Oslo; J. Kleinau, Levanger; B. Klykken, Levanger; F. Kontny, Oslo; S. Kornstad, Sandvika; A. Koss, Jessheim; B. Kulseng, Trondheim; K. Langaker, Oslo; D. Langvoll, Hammerfest; K. Larsby, Hammerfest; T. Le, Lørenskog; N. Lid, Notodden; A. Lied, Molde; F. Lindberg, Oslo; I. Løfsnes, Rud; M. Mastroianni, Lørenskog; T. Meling, Stavanger; G. Mo, Mosjøen; O. Mortensen, Tønsberg; I. Mujic, Kristiansund; L. Mundal, Førde; P. Munk, Stavanger; S. Nabizadeh, Moss; S. Nadirpour, Haugesund; P. Nesje, Mo i Rana; S. Nitter-Hauge, Oslo; E. Øfjord, Paradis; J. Øvermo, Hammerfest; M. Øwre, Oslo; T. Omland, Flekkefjord; A. Oppdal, Bergen; T. Pedersen, Oslo; Z. Radunovic, Bergen; N. Ringdal, Molde; K. Risberg, Skedsmokorset; G. Schneider, Bodø; H. Selsås, Ålesund; A. Semb, Oslo; P. Sirnes, Hobøl; A. Skag, Paradis; G. Skjelvan, Trondheim; J. Solli, Kristiansand; L. Sommervoll, Tønsberg; J. Sparby, Kongsvinger; T. Steen, Oslo; T. Sund, Lillestrøm; A. Svilaas, Kongsberg; K. Thon, Moss; R. Thorshaug, Bergen; H. Tjønndal, Larvik; S. Toft, Bergen; S. Tonstad, Oslo; T. Torjussen, Kristiansand; T. Torjussen, Mysen; H. Torsvik, Rud; D. Torvik, Prsgrunn; A. Totland, Haugesund; K. Valnes, Oslo; J. Vegsundvåg, Ålesund; C. Von Brandis, Stavanger; B. Von Hoff, Kristiansund; F. Wandel, Odda; M. Wolff, Stavanger; A. Zalmai, Oslo; *Sweden (2509 patients enrolled)*: L. Ahlberg, Finspång; P. Ahlström, Motala; B. Åkerström, Mariestad; H. Åkesson, Karlskoga; S. Akravi, Fagersta; M. Alam, Stockholm; J. Alfredsson, Norrköping; M. Ali, Jönköping; B. Andersson, Göteborg; L. Andersson, Borås; K. Ångman, Hudiksvall; Å. Appelqvist, Uddevalla; B. Atmer, Stockholm; I. Axelsson, Stockholm; J. Bäck, Köping; J. Bäckman, Karlskoga; H. Bastani, Stockholm; A. Berglund, Malmö; S. Berglund, Falun; P. Bhiladvala, Malmö; S. Bhuiyan, Uddevalla; E-B. Billberg, Sala; Ö. Bjuhr, Mölndal; A. Bjurman, Lycksele; K. Boman, Skellefteå; P-Å. Boström, Malmö; H. Brodersson, Gävle; J. Carlsäter, Sala; R. Carlsson, Karlstad; T. Carlsson, Vargberg; C. Dahlén, Falun Lasarett, Falun; G. Dahlén, Grästorp; A. Dahlqvist, Gävle; D. Dalima, Uddevalla; C. Digerfeldt, Norrköping; R. Dziamski, Malmö; E. Eizyk, Ängelholm; L. Ekholm, Ljungby; J. Ellström, Sandviken; P-O. Enander, Lidköping; L. Engqvist, Värnamo; B-O. Ericsson, Fagersta; U-B. Ericsson, Malmö; H. Fahlhammar, Sala; L. Falk, Mölndal; G. Finnas, Katrineholm; B. Frederiksson, Borås; J-E. Frisell, Ludvika; G. Frithz, Eskilstuna; A-M. Fröderberg, Finspång; F. Frogner, Ängelholm; G. Gustafsson, Gävle; P-E. Gustafsson, Gävle; E. Hammarström, Stockholm; O. Hansen, Malmö; S. Hansen, Eksjö; P. Hårdhammar, Halmstad; L. Härdig, Mölndal; M. Hartford, Göteborg; R. Hässler, Finspång; B. Hedbäck, Linköping; M. Henning, Uddevalla; J. Herlitz, Göteborg; P-O. Hermansson, Gävle; O. Herterich, Köping; L-G. Hjerne, Södertälje; C. Höglund, Stockholm; H. Holmberg, Mölndal; C. Ingmar, Karlstad; J-H. Jansson, Skellefteå; J. Jabro, Norrköping; I. Jamil, Karlskoga; D. Javid, Uddevalla; S. Jensen, Karlshamn; T. Jernberg, Stockholm; H. Joborn, Västervik; A. Johansson, Luleå; G. Johansson, Lidköping; L. Johansson, Skellefteå; T. Johansson, Alingsås; T. Jonson, Borås; H. Jul-Nielsen, Grästorp; P. Kalén, Ängelholm; A. Kallryd, Skövde; L. Kareld, Skene; B. Karlson, Göteborg; A-C. Karlsson, Halmstad; B. Karlsson, Kristinehamn; J-E. Karlsson, Jönköping; C. Kihlström, Motala; J. Kjellberg, Alingsås; L. Klintberg, Mölndal; L-E. Larsson, Västervik; L. Lidberg, Finspång; K. Lindberg, Södertälje; B. Linde, Falun; M. Lindgren, Halmstad; B. Lindström, Karlskrona; J. Lindström, Karlstad; M. Lindström, Jönköping; P. Lindström, Bålsta; T. Lindström, Mölndal; H. Lindvall, Karlskoga; P. Löfdahl, Helsingborg; L. Lundkvist, Hudiksvall; B. Malmros, Köping; A. Månsson, Kalmar; B. Moberg, Kristinehamn; D. Mohaupt, Gävle; P-Å. Moström, Mölndal; A. Moum-Nordlund, Uddevalla; P. Nicol, Köping; H. Nilsson, Fagersta; J. Nilsson, Luleå; O. Nilsson, Norrköping; H. Nordström, Alingsås; A. Norrby, Göteborg; P. Nyman, Helsingborg; K. Olsson, Strömstad; W. Osika, Karlskoga; A-M. Ottosson, Norrköping; K. Pedersen, Helsingborg; B. Persson, Mölndal; J. Persson, Malmö; M. Peterson, Lidköping; B. Pettersson, Strömstad; A. Pischel, Uddevalla; B. Polhem, Grästorp; F. Randers, Mölndal; P. Reinius, Kalmar; G. Renklint, Lycksele; A. Richter, Linköping; P. Rindevall, Ludvika; A. Rindner, Skene; M. Risenfors, Mölndal; U. Rosenqvist, Motala; G. Rüter, Helsingborg; V. Salagean, Finspång; K. Saldeen-Niléhn, Göteborg; S. Salovaara, Katrineholm; R. Samo-Ayou, Skövde; S. Sandgren, Borås; A. Sandström, Lycksele; L. Sandström, Stockholm; X. Shatri, Finspång; B. Sinnerstad, Västervik; A. Sjögren, Värnamo; S. Sjögren, Falköping; E. Skarfors, Halmstad; M. Stagmo, Malmö; H. Stakeberg, Vänersborg; G. Stehn, Hässleholm; H. Strömblad, Karlshamn; L. Svennberg, Gävle; K-A. Svensson, Ljungby; O. Svensson, Jönköping; A. Tholén, Strömstad; S. Thorsén, Värnamo; I. Timberg, Hässleholm; H. Tygesen, Borås; G. Ulvenstam, Göteborg; C. Valladares, Norrköping; K. Viidas, Uddevalla; F. Wagner, Helsingborg; S. Wåhlin, Bålsta; N. Wallén, Mariestad; I. Westbom, Karlstad; C. Wettervik, Borås; E. Winger, Sala; P. Wodlin, Motala; R. Zlatewa-Cuenca, Stockholm; *Steering Committee*: T. R. Pedersen (chair), O. Faergeman, J. J. P. Kastelein, A. G. Olsson, M. J. Tikkanen, I. Holme, M. Lytken Larsen, F. S. Bendiksen, C. Lindahl, S. Maehlum, J. Tsai; *Data and Safety Monitoring Board*: D. G. Julian (chair), C. Ballantyne, K. Rasmussen, H. Wedel; *End Point Committee*: C. Thygesen (chair), B. Johannesen, P. Lund Johansen; *Data Analysis*: S. Auster, T. Karam, R. Chan, M. Szarek; *Study Management and Monitoring Offices (Pfizer Inc)*: J. Tsai, N. Cater, B. Suri, C. Elliott, T. Thomas (United States), B. Nicolaisen, I. Stenersen (Norway), J. Versteden (the Netherlands), B. Steenberg (Denmark), P. Kindblom (Sweden), P. Eloranta (Finland); *Central Laboratory*: Medilab, Stockholm, Sweden; *Data Management*: Covance, Horsham, England; *End-Point Blinding and Management*: Inveresk, Raleigh, NC.

REFERENCES

1. Scandinavian Simvastatin Survival Study (4S) Group. Randomized trial of cholesterol-lowering in 4444 patients with coronary-heart-disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389.

2. Cannon CP, Braunwald E, Mccabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495-1504.

3. Larosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425-1435.

4. 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;352:1483-1484.

5. 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;24:1601-1610.

6. Grundy SM, Cleeman JI, Merz CN, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines [published correction appears in *Circulation*. 2004;110:763]. *Circulation*. 2004;110:227-239.

7. Hansson L, Hedner T, Dahlöf B. Prospective Randomized Open Blinded End-point (PROBE) study: a novel design for intervention trials. *Blood Press*. 1992;1:113-119.

8. Pedersen TR, Faergeman O, Kastelein JJP, et al. Design and baseline characteristics of the Incremental Decrease in End Points Through Aggressive Lipid Lowering study. *Am J Cardiol*. 2004;94:720-724.

9. Cox DR. Regression models and life-tables. *J R Stat Soc B Stat Methodol*. 1972;34:187.

10. Cholesterol Treatment Trialists' (CTT) 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;366:1267-1278.

11. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum-cholesterol concentration lower risk of ischemic heart disease? *BMJ*. 1994;308:367-373.

12. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937-952.

13. Holme I. Cholesterol reduction and its impact on coronary artery disease and total mortality. *Am J Cardiol*. 1995;76:10C-17C.

14. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. *Circulation*. 1998;97:946-952.

15. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial Results, II: the relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA*. 1984;251:365-374.

16. Pedersen TR, Olsson AG, Faergeman O, et al. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study. *Circulation*. 1998;97:1453-1460.

17. 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;44:1772-1779.

18. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2004;291:1071-1080.

That approach leaves several critical issues unresolved. First, federal policy actively discourages high-quality research by making access to marijuana by researchers exceedingly difficult. Even when access to marijuana is finally granted, there is substantial variability in the purity and content of the product. Second, researchers need to test the assumption noted by Das that THC is the active ingredient responsible for the perceived beneficial effects. Although that assumption is reasonable, there remains the possibility that marijuana, not THC in isolation, achieves the desirable effects. Third, researchers should test the most efficient delivery system. There may be some added value in smoking that needs to be evaluated.

If research concludes that THC is the beneficial ingredient and that delivery by tablet is safest and most effective, then there is justification for approval of that method only. A synthetic THC oral medication (dronabinol) is already available for prescription with US Food and Drug Administration-approved indications for anorexia associated with weight loss in patients with AIDS and for nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Regulation of the use of marijuana for medical purposes is feasible and socially desirable, but it will require a different way of thinking about the problem. It requires viewing marijuana as a potential medication subject to carefully controlled research, rather than as a drug of strict prohibition.

Lawrence O. Gostin, JD, LLD (Hon)
gostin@law.georgetown.edu
Georgetown Law Center
Washington, DC

Financial Disclosures: None reported.

CORRECTIONS

Author Contribution Omissions: In the Original Contribution entitled "High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction: The IDEAL Study: A Randomized Controlled Trial" published in the November 16, 2005, issue of *JAMA* (2005;294:2437-2445), several contributions were omitted for the author Anders G. Olsson, MD, PhD. In addition to his contributions listed in the article, Dr Olsson contributed to the study concept and design, acquisition of data, drafting of the manuscript, and statistical analysis for the IDEAL trial.

Duplicated Text: In the Original Contribution entitled "Neurologic Adverse Events Associated With Smallpox Vaccination in the United States, 2002-2004" published in the December 7, 2005, issue of *JAMA* (2005;294:2744-2750), a section of text was duplicated. The first 4½ lines on the top of page 2747 should be deleted. Thus, the last sentence on the bottom of page 2746 and continuing onto 2747 should read: "Of the remaining 3 cases, one man had probable encephalitis defined by altered mental status, pleocytosis, and multifocal demyelinating lesions on brain MRI 10 days after primary vaccination."

Incorrect Wording and Data: In the Original Contribution entitled "Combined Tetanus, Diphtheria, and 5-Component Pertussis Vaccine for Use in Adolescents and Adults" published in the June 22/29, 2005, issue of *JAMA* (2005;293:3003-3011), incorrect wording appeared at the end of the Results section. On page 3009, lines 15-16 of the fourth paragraph, " . . . the complaint resolved within 1 day" should read "the patient was hospitalized for 1 day and the complaint subsequently resolved without sequelae." In addition, in Table 4, for the entry "Axillary node swelling," in column 2 (Tdap Adolescents) 676 should be 67.

Incorrect Data: In the Original Contribution entitled "Adverse Events Reported Following Live, Cold-Adapted, Intranasal Influenza Vaccine," published in the December 7, 2005, issue of *JAMA* (2005;294:2720-2725), there were incorrect data in the first full paragraph on page 2724. The corrected paragraph is reprinted below:

Among 11 reports concerning individuals with a prior history of chronic cardiovascular disease, 1 serious case involved a 42-year-old man with a history of uncontrolled hyperlipidemia who was hospitalized with a myocardial infarction 2 days after vaccination. He underwent cardiac catheterization. Among 10 reports from individuals with preexisting metabolic conditions (including 8 with thyroid disease), 1 (a 30-year-old man hospitalized with pneumonia 7 days after vaccination) was serious. There were no other hospitalizations. Among the remaining 15 individuals, 13 had chronic conditions (3 with chronic neurological conditions, 4 with chronic respiratory diseases, 2 with pernicious anemia, 2 with sarcoidosis, 1 with fibromyalgia, and 1 with lupus) and 2 were pregnant; none resulted in hospitalization. One report, in a 48-year-old woman who had a prior history of Bell palsy, was classified as serious.

