

Risk of Incident Diabetes With Intensive-Dose Compared With Moderate-Dose Statin Therapy

A Meta-analysis

David Preiss, MRCP

Sreenivasa Rao Kondapally
Seshasai, MD

Paul Welsh, PhD

Sabina A. Murphy, MPH

Jennifer E. Ho, MD

David D. Waters, MD

David A. DeMicco, DPharm

Philip Barter, MD, PhD

Christopher P. Cannon, MD

Marc S. Sabatine, MD, MPH

Eugene Braunwald, MD

John J. P. Kastelein, MD, PhD

James A. de Lemos, MD

Michael A. Blazing, MD

Terje R. Pedersen, MD, PhD

Matti J. Tikkanen, MD, PhD

Naveed Sattar, MD, PhD

Kausik K. Ray, MD

STATIN THERAPY SIGNIFICANTLY reduces cardiovascular events among individuals with and without a history of diabetes mellitus compared with placebo.^{1,2} Intensive-dose statin therapy has also been shown to further reduce cardiovascular events compared with moderate-dose statin therapy.^{1,3} A recent meta-analysis of 13 randomized placebo and standard care controlled trials

See also Patient Page.



CME available online at
www.jamaarchivescme.com
and questions on p 2584.

Context A recent meta-analysis demonstrated that statin therapy is associated with excess risk of developing diabetes mellitus.

Objective To investigate whether intensive-dose statin therapy is associated with increased risk of new-onset diabetes compared with moderate-dose statin therapy.

Data Sources We identified relevant trials in a literature search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (January 1, 1996, through March 31, 2011). Unpublished data were obtained from investigators.

Study Selection We included randomized controlled end-point trials that compared intensive-dose statin therapy with moderate-dose statin therapy and included more than 1000 participants who were followed up for more than 1 year.

Data Extraction Tabular data provided for each trial described baseline characteristics and numbers of participants developing diabetes and experiencing major cardiovascular events (cardiovascular death, nonfatal myocardial infarction or stroke, coronary revascularization). We calculated trial-specific odds ratios (ORs) for new-onset diabetes and major cardiovascular events and combined these using random-effects model meta-analysis. Between-study heterogeneity was assessed using the I^2 statistic.

Results In 5 statin trials with 32 752 participants without diabetes at baseline, 2749 developed diabetes (1449 assigned intensive-dose therapy, 1300 assigned moderate-dose therapy, representing 2.0 additional cases in the intensive-dose group per 1000 patient-years) and 6684 experienced cardiovascular events (3134 and 3550, respectively, representing 6.5 fewer cases in the intensive-dose group per 1000 patient-years) over a weighted mean (SD) follow-up of 4.9 (1.9) years. Odds ratios were 1.12 (95% confidence interval [CI], 1.04-1.22; $P=0\%$) for new-onset diabetes and 0.84 (95% CI, 0.75-0.94; $I^2=74\%$) for cardiovascular events for participants receiving intensive therapy compared with moderate-dose therapy. As compared with moderate-dose statin therapy, the number needed to harm per year for intensive-dose statin therapy was 498 for new-onset diabetes while the number needed to treat per year for intensive-dose statin therapy was 155 for cardiovascular events.

Conclusion In a pooled analysis of data from 5 statin trials, intensive-dose statin therapy was associated with an increased risk of new-onset diabetes compared with moderate-dose statin therapy.

JAMA. 2011;305(24):2556-2564

www.jama.com

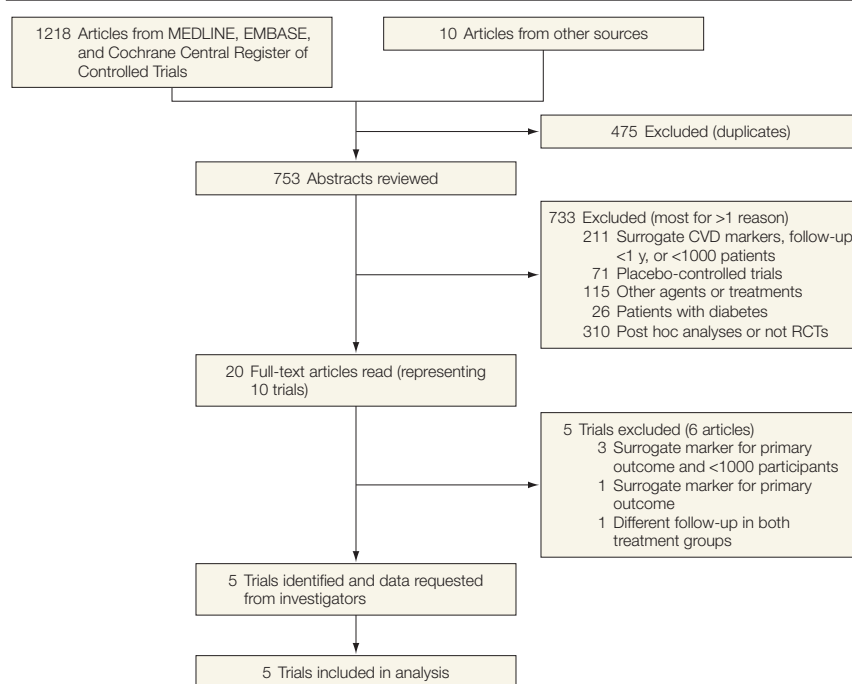
involving 91 140 individuals reported that among patients treated with statins, the risk of developing diabetes was 9% higher (95% confidence interval [CI], 2%-17%) over a 4-year period compared with patients randomized to placebo or standard care.⁴ Recently, findings of 3 large end-point trials comparing intensive- to moderate-dose

Author Affiliations are listed at the end of this article.
Corresponding Authors: David Preiss, MRCP, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, 126 University Pl, Glasgow G12 8TA, Scotland (david.preiss@glasgow.ac.uk); and Kausik K. Ray, MD, Division of Cardiac and Vascular Sciences, St George's University of London, Cranmer Terrace, London SW17 0RE, England (kray@sgul.ac.uk).
Clinical Review Section Editor: Mary McGrae McDermott, MD, Contributing Editor. We encourage authors to submit papers for consideration as a Clinical Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

statin therapy have suggested an excess risk of incident diabetes among those treated with intensive statin regimens.^{5,6} However, 2 of these trials used nonstandard diagnostic criteria previously used to define incident diabetes.⁷ Additionally, published data from a fourth large clinical trial suggested the possibility of a deterioration in glucose control in patients receiving intensive statin therapy,⁸ and a recent report of 220 patients with hypercholesterolemia treated with placebo or different doses of atorvastatin and followed up for only 2 months found that those receiving the highest dose developed greater insulin resistance, higher insulin levels, and higher hemoglobin A_{1c} levels compared with those receiving the lowest dose or placebo,⁹ suggesting a potential dose effect. Although no significant relationship was observed between the extent of decreasing low-density lipoprotein (LDL) cholesterol values and new-onset diabetes in the meta-analysis of placebo and standard care controlled trials,⁴ most of those trials used modest-intensity statins and trial populations also differed greatly, which may have obscured any meaningful association.

Confidence in the observed association between statin therapy and the development of diabetes would be enhanced by providing further large-scale evidence of a dose-dependent association.⁴ Given the cardiovascular benefits of statins and the likely increasing use of intensive statin regimens, it is important to quantify any potential long-term risks to enable physicians and patients to make informed choices. Furthermore, it would be of value to investigate whether any specific group of patients is at higher risk of diabetes when receiving intensive statin therapy than others. We therefore examined the associations of intensive-dose statin therapy vs moderate-dose therapy with the development of diabetes and the occurrence of major cardiovascular events, respectively, by conducting a collaborative meta-analysis of pub-

Figure 1. Flow Diagram of the Literature Search



CVD indicates cardiovascular disease; RCTs, randomized controlled trials.

lished and unpublished data from relevant clinical trials.

METHODS

We gathered data from large randomized end-point statin trials primarily designed to assess the effect of intensive-dose statin treatment compared with moderate-dose therapy on cardiovascular outcomes. Inclusion criteria included trials of 1000 or more participants exposed to statin therapy with a minimum mean follow-up of 1 year. Length of follow-up in both treatment groups was required to be identical to avoid bias in ascertainment of new-onset diabetes. We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials with the terms *statin* and *HMG CoA reductase inhibitor* and names of individual statins as title words and keywords and combined these with a search for the keywords *intensive* or *aggressive* to identify trials performed in adult patients (initial search date, January 8, 2010; updated April 4, 2011) and published in English from January 1, 1996, until

March 31, 2011 (FIGURE 1). Abstracts and manuscripts were reviewed independently by 2 readers (D.P. and P.W.). A third reviewer (N.S.) settled discrepancies. After the full articles were reviewed, 5 trials were excluded,¹⁰⁻¹⁴ and 5 trials were included in the analysis: the Treating to New Targets (TNT) trial,¹⁵ the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial,¹⁶ the Aggrastat to Zocor (A to Z) trial,¹⁷ the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (PROVE IT–TIMI 22) trial,¹⁸ and the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH).⁵

Data Sources

Investigators from all 5 trials provided data for incident diabetes and major cardiovascular events according to a standard data query sheet (eFigure 1, available at <http://www.jama.com>). To ascertain whether any specific patient subgroups were at greater risk of de-

veloping diabetes while receiving intensive statin therapy, we collected data on the key end points among those with data for body mass index (BMI), high-density lipoprotein (HDL) cholesterol, triglycerides, age, and fasting plasma glucose (FPG) (where available) above and below the trial medians, as these factors are associated with diabetes risk. A PRISMA checklist was provided at the time of manuscript submission.¹⁹

Quality Assessment

Two authors (D.P. and P.W.) used an established tool²⁰ to independently evaluate the quality of each trial. Nine characteristics were assessed: randomization; concealment of treatment allocation; similarity of groups at baseline; eligibility criteria; whether outcome assessors, participants, and care providers, respectively, were blinded to treatment allocation; availability of point estimates; and intention-to-treat analysis, thereby allowing each trial to be awarded a Delphi score of 0 to 9. Disagreement was resolved through consensus and discussion.

End Points

A patient was considered to have developed diabetes if (1) there was an adverse event report of newly diagnosed diabetes during the trial, (2) he or she commenced glucose-lowering medication during the trial, or (3) he or she had 2 FPG values of 126 mg/dL or greater during the trial. (To convert glucose to mmol/L, multiply by 0.0555.) For the 2 trials with data published using nonstandard diabetes criteria (as in the third criterion but also requiring a ≥ 36 -mg/dL increase in FPG from baseline),⁶ we performed a reanalysis of the data using the standard diagnostic criteria but also included a sensitivity analysis using the nonstandard criteria previously used in the West of Scotland Coronary Prevention Study.⁷ We also collected data on a composite cardiovascular end point consisting of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary artery bypass surgery, and percutaneous coronary intervention as well

as data for specific cardiovascular events and all-cause mortality. For trials that recruited patients shortly after an acute coronary syndrome (ACS), we used the prespecified trial definitions that included only those revascularization procedures not linked to the prerandomization index event. These consisted of procedures performed more than 30 days after randomization in the PROVE IT-TIMI 22 study and only ischemia-driven procedures in the A to Z study.

Statistical Analysis

To identify potential associations of intensive-dose vs moderate-dose statin therapy with incident diabetes and cardiovascular events, we calculated odds ratios (ORs) and 95% CIs from the available data for the number of patients who did not have diabetes at baseline and those who developed diabetes and cardiovascular events during follow-up. Study-specific ORs were pooled using a random-effects model meta-analysis to account for between-study heterogeneity that may have been introduced by the differing methods for diagnosing diabetes available in the trials and different trial populations. Statistical heterogeneity across studies was quantified using the χ^2 (or Cochran Q statistic) and I^2 statistics, with $P > .10$ considered statistically nonsignificant. The I^2 statistic is derived from the Q statistic ($[Q - df/Q] \times 100$) and provides a measure of the proportion of the overall variation attributable to between-study heterogeneity.²¹ Although we used both published and unpublished information in our meta-analysis, we nevertheless assessed the potential for publication bias through formal tests, namely the funnel plot and Egger test. To evaluate the effect of statins across clinically relevant subgroups, we calculated stratum-specific ORs for incident diabetes and major cardiovascular events and combined them using random-effects meta-analysis. In exploratory analyses, we compared results in patients with recent ACS with those with stable coronary heart disease and also compared results for trials in which simvastatin

80 mg and atorvastatin 80 mg were the respective intensive regimens. All P values were 2-sided and $P < .05$ was considered statistically significant. Analyses were conducted using Stata version 10.1 (StataCorp, College Station, Texas).

RESULTS

Five randomized clinical trials provided data on 32 752 nondiabetic participants over a weighted mean (SD) follow-up of 4.9 (1.9) years. During follow-up, 2749 participants (8.4%) developed diabetes (1449 of whom were assigned intensive-dose therapy, 1300 assigned moderate-dose therapy), and 6684 (20.4%) experienced a major cardiovascular event (3134 assigned intensive-dose therapy, 3550 assigned moderate-dose therapy) (TABLE 1, TABLE 2, and FIGURE 2). Of the 2749 diagnoses of diabetes, 2059 (75%) were identified by nonbiochemical methods (ie, commencement of glucose-lowering medication or adverse event reporting), 219 (8%) by elevated FPG values in the trial, and 471 (17%) by more than 1 method. Trials were of high quality with a median Delphi score of 9 (range, 6-9).

New-Onset Diabetes

In the combined data set, there were 149 more cases of incident diabetes in participants assigned to intensive statin treatment than in those receiving moderate therapy (OR, 1.12; 95% CI, 1.04-1.22) (Figure 2). In absolute terms, there were 2.0 additional cases of diabetes per 1000 patient-years among those receiving intensive-dose therapy (mean [SD] 18.9 [5.2] cases per 1000 patient-years with high-dose statin treatment vs 16.9 [5.5] cases per 1000 patient-years with moderate-dose therapy), corresponding to a number needed to harm of 498 per year. There was no significant heterogeneity between trials for new-onset diabetes (χ^2 for heterogeneity = 2.59; $P = .60$; $I^2 = 0\%$ [95% CI, 0%-79%]). Likewise, there was no evidence of publication bias ($P = .54$) (eFigure 2).

Cardiovascular Benefit

In the combined data set, there were 416 fewer patients with cardiovascular events who received intensive-dose therapy (OR, 0.84; 95% CI, 0.75-0.94) (Figure 2). In absolute terms, there were 6.5 fewer first major cardiovascular events per 1000 patient-years among those receiving intensive statin therapy (mean [SD] 44.5 [20.4] cases per 1000 patient-years with high-dose treatment and 51.0 [23.6] cases per

1000 patient-years with moderate-dose therapy), corresponding to a number needed to treat of 155 to prevent 1 cardiovascular event per year. There was significant heterogeneity between trials for major cardiovascular events (χ^2 for heterogeneity = 15.04; $P = .004$; $I^2 = 74%$ [95% CI, 36%-90%]). However, there was no evidence of publication bias ($P = .70$) (eFigure 2). Odds ratios for specific components of the composite cardiovascular end point are

provided in TABLE 3, showing similar associations between intensive statin therapy and each cardiovascular end point component. Intensive-dose therapy was not associated with lower all-cause mortality compared with moderate-dose statin therapy (OR, 0.93; 95% CI, 0.81-1.05; 1318 cases/16 408 patients receiving intensive therapy vs 1360 cases/16 342 patients receiving moderate doses). Intensive statin therapy was not associated with lower

Table 1. Descriptions of the 5 Included Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy

Source	No Diabetes/ All Patients, No. (%) ^a	Trial Population	Intensive/ Moderate Regimen	Received Intensive/ Moderate, No.	Follow-up, y ^b	Methods of Diagnosing Diabetes
Cannon et al (PROVE IT-TIMI 22), ¹⁸ 2004	3395/4162 (82)	Recent ACS	Atorvastatin 80 mg/ pravastatin 40 mg	1707/1688	2.0 (0.6)	(1) AE report, (2) DM medication, (3) FPG \geq 126 mg/dL twice
de Lemos et al (A to Z), ¹⁷ 2004	3504/4497 (78)	Recent ACS	Simvastatin 40 mg, simvastatin 80 mg/ placebo, simvastatin 20 mg	1768/1736	2.0 (1.5-2.0)	(1) AE report, (2) DM medication
LaRosa et al (TNT), ¹⁵ 2005 ^c	7595/10 001 (76)	Stable CHD	Atorvastatin 80 mg/ atorvastatin 10 mg	3798/3797	5.0 (0.5)	(1) AE report, (2) DM medication, (3) FPG \geq 126 mg/dL twice
Pedersen et al (IDEAL), ¹⁶ 2005 ^c	7461/8888 (84)	Previous MI	Atorvastatin 80 mg/ simvastatin 20 mg or 40 mg	3737/3724	4.8 (4.4-5.0)	(1) AE report, (2) DM medication, (3) FPG \geq 126 mg/dL twice
Armitage et al (SEARCH), ⁵ 2010	10 797/12 064 (89)	Previous MI	Simvastatin 80 mg/ simvastatin 20 mg	5398/5399	6.7 (1.4)	(1) AE report
Total	32 752/39 612 (83)			16 408/16 344	4.9 (1.9)^d	

Abbreviations: ACS, acute coronary syndrome; AE, adverse event; A to Z, Aggrastat to Zocor trial; DM, diabetes mellitus; CHD, coronary heart disease; FPG, fasting plasma glucose; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering study; MI, myocardial infarction; PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction study; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; TNT, Treating to New Targets study.

SI conversion factor: To convert glucose to mmol/L, multiply by 0.0555.

^aNo diabetes indicates patients who did not have known diabetes mellitus at baseline.

^bFollow-up values are mean (SD) for the TNT, SEARCH, and PROVE IT-TIMI 22 studies and median (interquartile range) for the A to Z and IDEAL studies.

^cExcluded patients with known diabetes, FPG level of 126 mg/dL or greater, or both at baseline.

^dTotal follow-up values are pooled mean (pooled SD).

Table 2. Baseline Data From Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy

Source	BMI, Mean (SD) ^a	Age, Mean (SD), y	HDL, Mean (SD), mg/dL	LDL, Mean (SD), mg/dL	LDL Reduction, Relative % ^b	In Triglycerides, Mean (SD), mg/dL	FPG, Mean (SD), mg/dL	FPG Measured After Baseline
Cannon et al (PROVE IT-TIMI 22), ¹⁸ 2004	29 (5)	58 (11)	39 (12)	109 (31)	22	5.05 (0.44)	104 (11) ^c	Not specified ^c
de Lemos et al (A to Z), ¹⁷ 2004	NA	60 (11)	39 (12)	113 (27)	15	5.00 (0.39)	NA	NA
LaRosa et al (TNT), ¹⁵ 2005 ^d	28 (4)	61 (9)	47 (12)	98 (20)	22	4.89 (0.42)	97 (11)	Annually
Pedersen et al (IDEAL), ¹⁶ 2005 ^d	27 (4)	62 (10)	47 (12)	125 (35)	16	4.87 (0.44)	99 (11)	Final visit
Armitage et al (SEARCH), ⁵ 2010	28 (4)	64 (9)	43 (16) ^e	98 (23) ^e	12	4.97 (0.54) ^e	NA	NA

Abbreviations: A to Z, Aggrastat to Zocor trial; FPG, fasting plasma glucose; HDL, high-density lipoprotein cholesterol; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering study; LDL, low-density lipoprotein cholesterol; NA, not available; PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction study; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; TNT, Treating to New Targets study.

SI conversion factors: To convert HDL and LDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; glucose to mmol/L, multiply by 0.0555.

^aCalculated as weight in kilograms divided by height in meters squared.

^bCalculated as [LDL(intensive-dose group) - LDL(moderate-dose group)]/LDL(baseline).

^cFor baseline FPG level, there were 315 results from the PROVE IT-TIMI 22 participants, which were similarly distributed between treatment groups.

^dExcluded patients with known diabetes, FPG level of 126 mg/dL or greater, or both at baseline.

^eNonfasting.

rates of noncardiovascular death as compared with moderate-dose statin therapy (OR, 0.98; 95% CI, 0.87-1.10; 559 cases/16 408 patients receiving intensive therapy vs 571 cases/16 342 patients receiving moderate doses). There was no significant heterogeneity between trials for all-cause mortality (χ^2 for heterogeneity = 7.06; $P = .13$; $I^2 = 43%$ [95% CI, 0%-79%]) or for noncardiovascular death (χ^2 for heterogeneity = 3.41; $P = .49$; $I^2 = 0%$ [95% CI, 0%-79%]).

Subgroup Analyses

Cardiovascular benefit was consistent across all subgroups of participants, including those defined by age, HDL cholesterol level, triglyceride concentration, BMI (assessed in 4 trials^{5,15,16,18}; n = 29 036; 6192 events), and

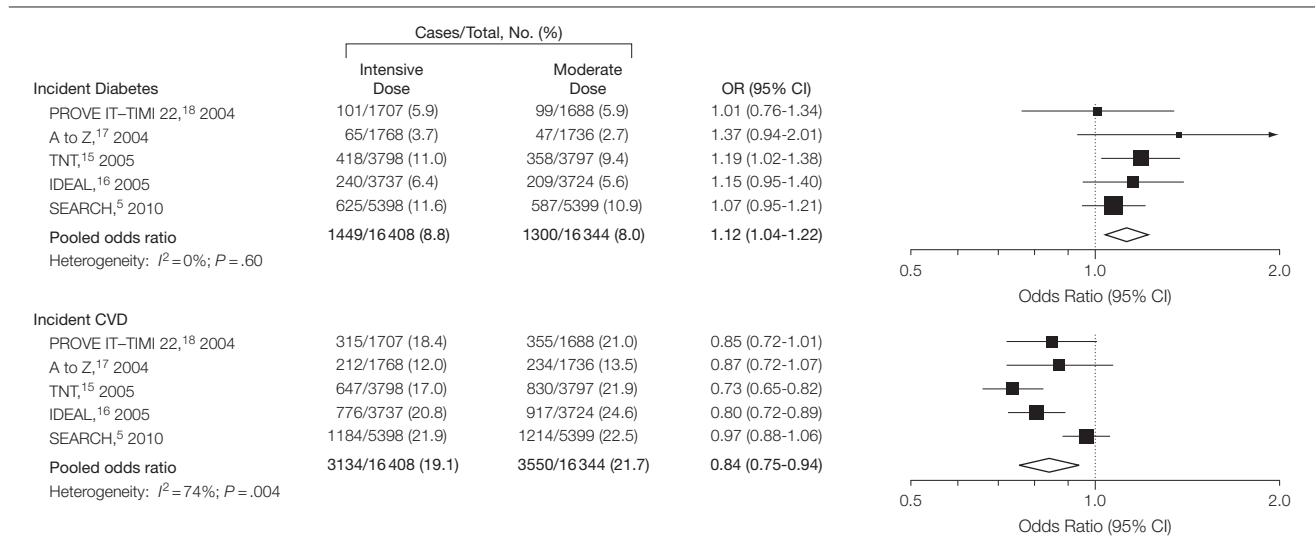
FPG level (assessed in 3 trials^{15,16,18}; n = 16 352; 3436 events) above and below the trial medians at baseline (FIGURE 3). The odds of developing diabetes among participants receiving intensive compared with moderate statin therapy was also similar for patients differing by age, HDL cholesterol level, BMI (2626 events), and FPG level (1302 events) at baseline but was higher in those with triglyceride concentrations below the median compared with those with higher triglyceride levels. The trial-specific medians of these variables are provided in the eTable.

Statin Type and Trial Population

The difference in relative LDL cholesterol reduction between the more- and less-intensive statin groups was 12% to 15% in the 2

trials (n = 14 301)^{5,17} that studied simvastatin 80 mg and 16% to 22% in the 3 trials (n = 18 451)^{15,16,18} that studied atorvastatin 80 mg. The odds of developing diabetes was comparable with simvastatin 80 mg (OR, 1.13; 95% CI, 0.93-1.38; $I^2 = 0%$; 690 cases/7166 patients receiving simvastatin 80 mg vs 634 cases/7135 patients with moderate-dose statins) and atorvastatin 80 mg (OR, 1.15; 95% CI, 1.03-1.28; $I^2 = 0%$; 759 cases/9242 patients with atorvastatin 80 mg vs 666 cases/9209 patients with moderate-dose statin) ($P = .56$ for interaction) (eFigure 3). In contrast, there was no significant cardiovascular benefit over moderate-dose therapy in the trials of simvastatin 80 mg (OR, 0.95; 95% CI, 0.88-1.03; $I^2 = 0%$; 1396 events/7166 patients with simvastatin

Figure 2. Meta-analysis of New-Onset Diabetes and First Major Cardiovascular Events in 5 Large Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy



Data marker size indicates relative weight of the studies; OR, odds ratio; and CI, confidence interval.

Table 3. Pooled Event Rates and Odds Ratios for Individual Components of the Composite Cardiovascular End Point

End Point	Event Rate (SD) [Events/Patients, No.] ^a		OR (95% CI)	I^2 (95% CI), %	Annual NNT
	Intensive-Dose Regimen	Moderate-Dose Regimen			
Cardiovascular death	9.12 (4.78) [759/16408]	10.04 (5.85) [789/16342]	0.94 (0.83-1.07)	15 (0-82)	1087
Nonfatal myocardial infarction	13.74 (8.45) [912/16408]	15.47 (8.54) [1041/16342]	0.87 (0.79-0.95)	0 (0-79)	578
Nonfatal stroke ^b	4.74 (1.43) [394/16407]	5.39 (1.36) [436/16342]	0.90 (0.78-1.03)	0 (0-79)	1538
Coronary revascularization	27.92 (18.86) [1906/16407]	33.78 (21.45) [2326/16343]	0.80 (0.71-0.90)	63 (3-86)	171

Abbreviations: CI, confidence interval; NNT, number needed to treat; OR, odds ratio.

^aEvent rate is the number of events per 1000 patient-years.

^bIncludes fatal and nonfatal strokes from the IDEAL study.¹⁶

80 mg vs 1448 cases/7135 patients with moderate-dose statin therapy), whereas there was a significant benefit for atorvastatin 80 mg (OR, 0.78; 95% CI, 0.73-0.85; $P=14\%$; 1738 events/9242 patients with atorvastatin 80 mg vs 2102 events/9209 patients with moderate-dose statin therapy) ($P<.001$ for interaction). Three trials were conducted in patients with stable coronary heart disease ($n=25\,853$)^{5,15,16} and 2 in patients following recent ACS ($n=6899$).^{17,18} Intensive statin therapy was associated with higher odds of incident diabetes following ACS (OR, 1.15; 95% CI, 0.85-1.54; 166 cases/3475 patients with intensive therapy vs 146 cases/3424 patients with moderate-dose therapy) and in stable coronary heart disease (OR, 1.12; 95% CI, 1.03-1.22; 1283 cases/12 933 patients with

intensive therapy vs 1154 cases/12 920 patients with moderate-dose therapy), while cardiovascular events were lower in both conditions (OR, 0.86; 95% CI, 0.76-0.98; 527 events/3475 patients vs 589 events/3424 patients; and OR, 0.83; 95% CI, 0.70-0.98; 2607 events/12 933 patients vs 2961/12 920 patients, respectively) (eFigure 4); there was no significant heterogeneity for these outcomes by study cohort.

Sensitivity Analyses

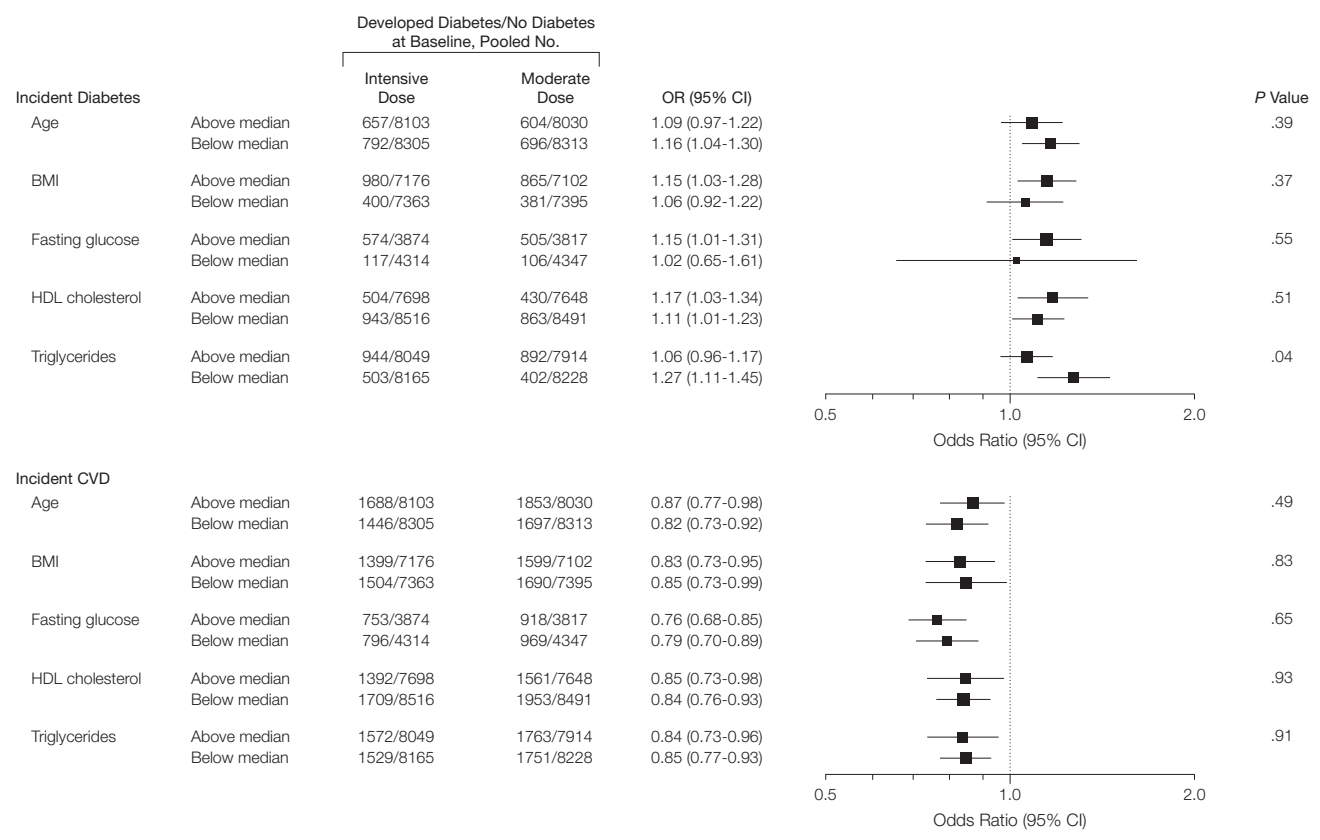
In sensitivity analyses, the overall risk of developing diabetes (assessed in 3 trials^{5,15,16}) and the reduction in cardiovascular events (assessed in 5 trials), calculated by combining trial-specific hazard ratios, produced similar results to the primary analysis (eFig-

ure 5). The risk of developing diabetes for patients receiving intensive statin therapy using nonstandard diagnostic criteria in 2 trials, namely TNT¹⁵ and IDEAL,¹⁶ was also qualitatively similar to the primary analysis in which standard diagnostic criteria were used (OR, 1.11; 95% CI, 1.03-1.21) (eFigure 6). Fixed-effects model meta-analysis produced similar results to random-effects model meta-analysis for new-onset diabetes when pooling data from the 5 trials.

COMMENT

This study demonstrates that use of intensive-dose statin therapy compared with moderate-dose statin therapy was associated with a higher incidence of new-onset diabetes (OR, 1.12). However, intensive statin

Figure 3. Subgroup Analyses for New-Onset Diabetes and First Major Cardiovascular Events



Data were available for age, high-density lipoprotein (HDL) cholesterol levels, and triglyceride concentrations in all trials; for body mass index (BMI) in 4 trials; and for fasting plasma glucose levels in 3 trials. The medians of the variables are per-trial medians, which are provided in the eTable. P values apply to heterogeneity between groups. Data marker size indicates relative weight of the studies; OR, odds ratio; and CI, confidence interval.

therapy was associated with fewer major cardiovascular events (OR, 0.84). In this combined trial population, although the risk of new-onset diabetes and the benefit of cardiovascular event reduction for patients receiving intensive therapy were similar in relative terms, when expressed in absolute terms there was 1 additional case of diabetes for every 498 patients treated for 1 year compared with 1 fewer patient experiencing a cardiovascular event for every 155 patients treated for 1 year. The cardiovascular benefit described here may be a conservative estimate because 3 trials have demonstrated that intensive statin therapy also reduces multiple cardiovascular events if intensive statin therapy is continued.²²⁻²⁴ These findings complement the recent observation of excess risk of developing diabetes among patients treated with statins compared with those receiving placebo.⁴

The benefits of statin therapy were consistent across all subgroups and for each component of the primary efficacy end point, including cardiovascular death. Analyses of all-cause mortality were consistent with observations for cardiovascular death, although the generalizability of these findings to other populations is less clear because these depend on the relative contributions of cardiovascular death (modified by statins) and noncardiovascular death (nonmodifiable by statins) in those populations. For new-onset diabetes, however, there was some evidence that the odds of new-onset diabetes was higher among individuals with triglyceride concentrations below the median level of distribution with intensive statin treatment, which, in the absence of a biologically plausible mechanism, may be a chance finding given the modest statistical significance in the context of multiple statistical tests. The higher incidence of new-onset diabetes and lower incidence of cardiovascular events were similar in patients fol-

lowing recent ACS and those with stable coronary disease. In the trials we studied whose control groups were different but comparable, the relative LDL-cholesterol reduction was greater in those that used atorvastatin 80 mg than in those that used simvastatin 80 mg.²⁵ Whereas the odds of developing diabetes was similar on both, there was a significantly lower odds of cardiovascular events in the trials with high-dose atorvastatin but not with high-dose simvastatin.¹

Important questions remain. First, a potential mechanism to explain the findings of a higher incidence of diabetes with statin therapy compared with placebo, and intensive-dose therapy compared with moderate-dose therapy, has not been identified. Possibilities include a direct and off-target effect. For example, statins may influence muscle or liver insulin action directly, resulting in higher diabetes risk. Data from an animal model suggest that statin-induced myopathy is associated with the development of muscle insulin resistance, providing a potential mechanism.²⁶ Second, it remains unclear whether statin therapy is associated with a generalized tendency for an increase in diabetes risk in many who take statins or whether there is a specific group of individuals at particular risk. Analysis of data from subgroups did not provide conclusive data. Third, although statin therapy is associated with a higher incidence of diabetes, to what extent this may carry with it the important associated long-term risks of developing microvascular disease is unknown. To date, no large clinical studies have examined the associations of statin therapy with microvascular disease. In contrast, fibrate therapy is associated with lower rates of microvascular complications.^{27,28} We hypothesize that given that cardiovascular risk from diabetes is modest in the first decade after diagnosis,²⁹ and as the benefit of statin therapy increases over time and in

absolute terms with increasing age,³⁰ net cardiovascular benefit in high-risk individuals will still strongly favor statin therapy. Finally, it would be of interest to investigate the impact of intensive statin therapy on glycemic control and treatment requirements in patients with established diabetes. One consideration to help quantify potential concerns is the establishment of a registry to examine these issues of long-term risk. Our findings suggest that clinicians should be vigilant for the development of diabetes in patients receiving intensive statin therapy.

Strengths of this meta-analysis include the following: first, we were able to include data from all the relevant clinical trials and thereby provide adequate power to detect potentially modest effects. Second, access to trial data allowed relevant subgroup analyses. And third, it was possible to provide a comparison of the potential risk of new-onset diabetes with cardiovascular benefit, thereby providing clinically useful information. Potential weaknesses include the following: first, different methods for diagnosing diabetes were available for the 5 trials, and the trials were not designed to assess new-onset diabetes. However, the low heterogeneity in new-onset diabetes as well as the very similar sensitivity analysis using the nonstandard criteria in 2 trials provides confidence in the results obtained. Second, analyses of incident diabetes were not prespecified in the trial designs and only 1 trial (TNT¹⁵) included regular measurement of FPG as a consequence. Because undiagnosed diabetes is relatively common,³¹ it is possible that we may have somewhat underestimated the risk of incident diabetes in the trial participants. Third, because all 5 trials specifically included participants with established coronary disease at high risk of future cardiovascular events rather than diabetes, our findings may not necessarily be generalizable to populations at higher

risk of incident diabetes. Fourth, analyses were conducted without access to individual participant data. Fifth, we cannot exclude the possibility that intensive statin therapy may have caused more adverse effects and therefore led to differences in routine clinical care between those treated with intensive- and moderate-dose regimens, resulting in detection bias.

In conclusion, this meta-analysis extends earlier findings of an increased incidence of diabetes with statin therapy by providing evidence of a dose-dependent association.

Author Affiliations: BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (Drs Preiss, Welsh, and Sattar); Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom (Dr Seshasai); TIMI Study Group, Cardiovascular Division, Harvard Medical School, Boston, Massachusetts (Ms Murphy and Drs Cannon, Sabatine, and Braunwald); Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Boston (Dr Ho); Department of Medicine, University of California, San Francisco (Dr Waters); Global Pharmaceuticals, Pfizer, New York, New York (Dr DeMicco); Heart Research Institute, Sydney, Australia (Dr Barter); Department of Vascular Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands (Dr Kastelein); Division of Cardiology, University of Texas Southwestern Medical Center, Dallas (Dr de Lemos); Duke Clinical Research Institute, Durham, North Carolina (Dr Blazing); University of Oslo and Centre for Preventative Medicine, Oslo University Hospital, Ullevål, Oslo, Norway (Dr Pedersen); University of Helsinki and Division of Cardiology, Helsinki University Hospital, and Folkhälsan Research Center, Helsinki, Finland (Dr Tikkanen); and Division of Cardiac and Vascular Sciences, St George's University of London, London, United Kingdom (Dr Ray).

Author Contributions: Dr Ray 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. Drs Preiss and Seshasai are joint first authors, and Drs Sattar and Ray are joint senior authors.

Study concept and design: Preiss, Seshasai, Welsh, Sattar, Ray.

Acquisition of data: Murphy, Waters, DeMicco, Barter, Cannon, Braunwald, Lemos, Blazing, Pedersen, Tikkanen, Ray.

Analysis and interpretation of data: Preiss, Seshasai, Welsh, Murphy, Ho, Waters, Cannon, Sabatine, Kastelein, Pedersen, Tikkanen, Sattar, Ray.

Drafting of the manuscript: Preiss, Seshasai, Welsh, Sattar, Ray.

Critical revision of the manuscript for important intellectual content: Preiss, Seshasai, Murphy, Ho, Waters, DeMicco, Barter, Cannon, Sabatine, Braunwald, Kastelein, Lemos, Blazing, Pedersen, Tikkanen, Sattar, Ray.

Statistical analysis: Seshasai, Preiss, Murphy, Ray.
Administrative, technical, or material support: DeMicco, Braunwald, Kastelein, Blazing, Tikkanen.
Study supervision: Welsh, Cannon, Kastelein, Sattar, Ray.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure

of Potential Conflicts of Interest. Ms Murphy reported receiving research grant support through the TIMI Study Group from Bristol-Myers Squibb and Merck. Dr Ho reported receiving consulting fees from Pfizer. Dr Waters reported receiving honoraria for lectures from Bristol-Myers Squibb and Pfizer and consulting for Merck Schering Plough and Pfizer for participation in clinical trial committees. Dr DeMicco reported being an employee of Pfizer. Dr Barter reported acting as member on advisory boards for AstraZeneca, CSL, Merck, Novartis, Pfizer, and Roche; receiving honoraria from Abbott, AstraZeneca, Merck, Novartis, Pfizer, and Roche; and participating in clinical trials sponsored by AstraZeneca, Merck, Pfizer, and Roche. Dr Cannon reported receiving research grants or support from Accumetrics, AstraZeneca, GlaxoSmithKline, Intekrin Therapeutics, Merck, and Takeda; acting on advisory boards (funds donated to charity) for Alnylam, Bristol-Myers Squibb/sanofi, and Novartis; receiving honoraria for independent educational symposia from AstraZeneca and Pfizer; and acting as a clinical advisor with equity for Automedics Medical Systems. Dr Sabatine reported receiving research grant support through Brigham and Women's Hospital from AstraZeneca, Bristol-Myers Squibb/sanofi-aventis, Schering Plough, and Amgen; consulting for AstraZeneca and Bristol-Myers Squibb/sanofi-aventis; and lecturing for Bristol-Myers Squibb/sanofi-aventis. Dr Braunwald reported receiving research support for the TIMI Study Group from Merck, AstraZeneca, and Pfizer. Dr Kastelein reported having participated in clinical trials sponsored by Pfizer, AstraZeneca, Merck, Eli Lilly, sanofi-aventis, Roche, Novartis, Boehringer Ingelheim, Isis, and Genzyme and receiving lecturing and consulting fees from Pfizer, AstraZeneca, Merck, Eli Lilly, sanofi-aventis, Roche, Novartis, Isis, Genzyme, and Kowa. Dr de Lemos reported consulting for AstraZeneca and receiving honoraria from Merck/Schering and Pfizer for lectures (>2 years ago). Dr Blazing reported receiving speaking or consulting fees from Merck and being the principal investigator on a research grant from Schering-Plough administered through the Duke Clinical Research Institute. Dr Pedersen reported receiving speakers' honoraria from and consulting for Pfizer and Merck-Schering Plough and receiving speakers' honoraria from AstraZeneca. Dr Tikkanen reported participating in clinical trials sponsored by Pfizer and Takeda, acting as member of a steering committee for a trial sponsored by Pfizer, and being a member of an advisory board of MSD Finland. Dr Sattar reported consulting for and receiving lecture fees from Merck, Pfizer, and AstraZeneca and having received research grant support from Pfizer. Dr Ray reported consulting/lecturing at symposia funded by Novo Nordisk, Roche, Pfizer, Merck, sanofi-aventis, and AstraZeneca. No other disclosures were reported.

Online-Only Material: The eTable and eFigures 1 through 6 are available at <http://www.jama.com>.

Additional Contributions: Unpublished data for these analyses were provided to the corresponding authors by the SEARCH Collaborative Group.

REFERENCES

- Baigent C, Blackwell L, Emberson J, et al; Cholesterol Treatment Trialists' (CCT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681.
- Kearney PM, Blackwell L, Collins R, et al; Cholesterol Treatment Trialists' (CCT) Collaborators. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet*. 2008;371(9607):117-125.
- Cannon CP, Steinberg BA, Murphy SA, Mega JL,

Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol*. 2006;48(3):438-445.

4. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375(9716):735-742.

5. Armitage J, Bowman L, Wallendszus K, et al; Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet*. 2010;376(9753):1658-1669.

6. Waters DD, Ho JE, DeMicco DA, et al. Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials. *J Am Coll Cardiol*. 2011;57(14):1535-1545.

7. Freeman DJ, Norrie J, Sattar N, et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation*. 2001;103(3):357-362.

8. Sabatine MS, Wiviott SD, Morrow DA, McCabe CH, Cannon CP. High-dose atorvastatin associated with worse glycemic control: a PROVE-IT TIMI 22 substudy. *Circulation*. 2004;110(suppl III):834.

9. Koh KK, Quon MJ, Han SH, Lee Y, Kim SJ, Shin EK. Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients. *J Am Coll Cardiol*. 2010;55(12):1209-1216.

10. Koren MJ, Hunninghake DB; ALLIANCE Investigators. 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(9):1772-1779.

11. Deedwania P, Stone PH, Bairey Merz CN, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). *Circulation*. 2007;115(6):700-707.

12. Nissen SE, Tuzcu EM, Schoenhagen P, et al; REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2004;291(9):1071-1080.

13. Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous vein coronary artery bypass grafts. *N Engl J Med*. 1997;336(3):153-162.

14. Crouse JR III, Raichlen JS, Riley WA, et al; METEOR Study Group. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. *JAMA*. 2007;297(12):1344-1353.

15. LaRosa JC, Grundy SM, Waters DD, et al; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352(14):1425-1435.

16. Pedersen TR, Faergeman O, Kastelein JJ, et al; Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA*. 2005;294(19):2437-2445.

17. de Lemos JA, Blazing MA, Wiviott SD, et al; A to Z Investigators. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA*. 2004;292(11):1307-1316.

18. Cannon CP, Braunwald E, McCabe CH, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350(15):1495-1504.
19. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
20. Verhagen AP, de Vet HCW, de Bie RA, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol*. 1998;51(12):1235-1241.
21. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
22. Murphy SA, Cannon CP, Wiviott SD, McCabe CH, Braunwald E. Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compared with moderate lipid-lowering statin therapy after acute coronary syndromes from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis In Myocardial Infarction 22) trial. *J Am Coll Cardiol*. 2009;54(25):2358-2362.
23. LaRosa JC, Deedwania PC, Shepherd J, et al; TNT Investigators. Comparison of 80 versus 10 mg of atorvastatin on occurrence of cardiovascular events after the first event (from the Treating to New Targets [TNT] trial). *Am J Cardiol*. 2010;105(3):283-287.
24. Tikkanen MJ, Szarek M, Fayyad R, et al; IDEAL Investigators. Total cardiovascular disease burden: comparing intensive with moderate statin therapy insights from the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial. *J Am Coll Cardiol*. 2009;54(25):2353-2357.
25. Jones PH, Davidson MH, Stein EA, et al; STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol*. 2003;92(2):152-160.
26. Mallinson JE, Constantin-Teodosiu D, Sidaway J, Westwood FR, Greenhaff PL. Blunted Akt/FOXO signalling and activation of genes controlling atrophy and fuel use in statin myopathy. *J Physiol*. 2009;587(pt 1):219-230.
27. Chew EY, Ambrosius WT, Davis MD, et al; ACCORD Study Group; ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med*. 2010;363(3):233-244.
28. Keech AC, Mitchell P, Summanen PA, et al; FIELD Study Investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet*. 2007;370(9600):1687-1697.
29. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men: influence of age at onset, diabetes duration, and established and novel risk factors. *Arch Intern Med*. 2011;171(5):404-410.
30. Baigent C, Keech A, Kearney PM, et al; 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(9493):1267-1278.
31. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and pre-diabetes in the US population in 1988-1994 and 2005-2006. *Diabetes Care*. 2009;32(2):287-294.

We feel safe, huddled within human institutions—churches, banks, madrigal groups—but these connections melt away at the basic moment. The self's responsibility, then, is to achieve rapport if not rapture with the giant, cosmic other: to appreciate, let's say, the walk back from the mailbox.

—John Updike (1932-2009)