Risk of Incident Diabetes With Intensive-Dose Compared With Moderate-Dose Statin Therapy: A Meta-analysis

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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 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 statin therapy.

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 Unpublished data were obtained from investigators.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 I² 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% CI, 1.04-1.22; I²=0%) for new-onset diabetes and 0.84 (95% CI, 0.75-0.94; I²=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.

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statin therapy have suggested an excess risk of incident diabetes among those treated with intensive statin regimens.\textsuperscript{5,6} However, 2 of these trials used nonstandard diagnostic criteria previously used to define incident diabetes.\textsuperscript{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,\textsuperscript{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\textsubscript{1c} levels compared with those receiving the lowest dose or placebo,\textsuperscript{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,\textsuperscript{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.\textsuperscript{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 published and unpublished data from relevant clinical trials.

\section*{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 \textit{statin} and \textit{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 (\textbf{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,\textsuperscript{10-14} and 5 trials were included in the analysis: the Treating to New Targets (TNT) trial,\textsuperscript{15} the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial,\textsuperscript{16} the Aggrastat to Zocor (A to Z) trial,\textsuperscript{17} the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (PROVE IT–TIMI 22) trial,\textsuperscript{18} and the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH).\textsuperscript{3}

\section*{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-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Flow_Diagram.pdf}
\caption{Flow Diagram of the Literature Search}
\end{figure}

CVD indicates cardiovascular disease; RCTs, randomized controlled trials.
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 prereandomization 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 χ² (or Cochran Q statistic) and I² statistics, with P > .10 considered statistically nonsignificant. The I² statistic is derived from the Q statistic [(I–df/Q) × 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 (χ² for heterogeneity = 2.59; P = .60; I² = 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 ($\chi^2$ 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/16408 patients receiving intensive therapy vs 1360 cases/16342 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

<table>
<thead>
<tr>
<th>Source</th>
<th>No Diabetes/All Patients, No. (%)</th>
<th>Trial Population</th>
<th>Intensive/Moderate Regimen</th>
<th>Received Intensive/Received Moderate, No.</th>
<th>Follow-up, y</th>
<th>Methods of Diagnosing Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannon et al (PROVE IT–TIMI 22), 2004</td>
<td>3395/4162 (82)</td>
<td>Recent ACS</td>
<td>Atorvastatin 80 mg/ pravastatin 40 mg</td>
<td>1707/1688</td>
<td>2.0 (0.6)</td>
<td>(1) AE report, (2) DM medication, (3) FPG ≥126 mg/dL twice</td>
</tr>
<tr>
<td>de Lemos et al (A to Z), 2004</td>
<td>3504/4497 (78)</td>
<td>Recent ACS</td>
<td>Simvastatin 40 mg, simvastatin 80 mg/ placebo, simvastatin 20 mg</td>
<td>1768/1736</td>
<td>2.0 (1.5-2.0)</td>
<td>(1) AE report, (2) DM medication</td>
</tr>
<tr>
<td>de Lemos et al (TNT), 2005</td>
<td>7595/10001 (76)</td>
<td>Stable CHD</td>
<td>Atorvastatin 80 mg/ atorvastatin 10 mg</td>
<td>3798/3797</td>
<td>5.0 (0.5)</td>
<td>(1) AE report, (2) DM medication</td>
</tr>
<tr>
<td>Pedersen et al (IDEAL), 2005</td>
<td>7461/8888 (84)</td>
<td>Previous MI</td>
<td>Atorvastatin 80 mg/ simvastatin 20 mg or 40 mg</td>
<td>3737/3724</td>
<td>4.8 (4.4-5.0)</td>
<td>(1) AE report, (2) DM medication, (3) FPG ≥126 mg/dL twice</td>
</tr>
<tr>
<td>Armitage et al (SEARCH), 2010</td>
<td>10797/12064 (89)</td>
<td>Previous MI</td>
<td>Simvastatin 80 mg/ simvastatin 20 mg</td>
<td>5398/3399</td>
<td>6.7 (1.4)</td>
<td>(1) AE report</td>
</tr>
</tbody>
</table>

Total 32752/39612 (83) 16408/16344 4.9 (1.9)1

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.

1SI conversion factor: To convert glucose to mmol/L, multiply by 0.0555.

2No diabetes indicates patients who did not have known diabetes mellitus at baseline.

3Follow-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.

4Excluded patients with known diabetes, FPG level of 126 mg/dL or greater, or both at baseline.

5Total follow-up values are pooled mean (pooled SD).

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

<table>
<thead>
<tr>
<th>Source</th>
<th>BMI, Mean (SD)a</th>
<th>Age, Mean (SD), y</th>
<th>HDL, Mean (SD), mg/dL</th>
<th>LDL, Mean (SD), mg/dL</th>
<th>LDL Reduction, Relative %b</th>
<th>ln Triglycerides, Mean (SD), mg/dL</th>
<th>FPG, Mean (SD), mg/dL</th>
<th>FPG Measured After Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannon et al (PROVE IT–TIMI 22), 2004</td>
<td>28 (4)</td>
<td>64 (9)</td>
<td>43 (16)b</td>
<td>98 (23)b</td>
<td>12</td>
<td>4.97 (0.54)b</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>de Lemos et al (A to Z), 2004</td>
<td>28 (4)</td>
<td>64 (9)</td>
<td>43 (16)</td>
<td>98 (23)</td>
<td>12</td>
<td>4.97 (0.54)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>de Lemos et al (TNT), 2005</td>
<td>28 (4)</td>
<td>64 (9)</td>
<td>43 (16)</td>
<td>98 (23)</td>
<td>12</td>
<td>4.97 (0.54)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pedersen et al (IDEAL), 2005</td>
<td>28 (4)</td>
<td>64 (9)</td>
<td>43 (16)</td>
<td>98 (23)</td>
<td>12</td>
<td>4.97 (0.54)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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.

1SI conversion factor: 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.

A.bCalculated as weight in kilograms divided by height in meters squared.

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

The content is a detailed comparison of cardiovascular benefits and baseline data from five trials comparing intensive-dose to moderate-dose statin therapy. The data are presented in tables, with key findings highlighted. The text provides a summary of the results, emphasizing the benefits and limitations of intensive-dose therapy compared to moderate-dose therapy.
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 ($\chi^2$ for heterogeneity = 7.06; $P = .13$; $I^2 = 43\%$ [95% CI, 0%-79%]) or for noncardiovascular death ($\chi^2$ 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) that studied simvastatin 80 mg and 16% to 22% in the 3 trials (n=18,451) 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...
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; \(I^2=14\%\); 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 \((n=25853)^{5,15,16}\) and 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) \((P < .001\) for interaction). Three trials were conducted in patients with 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 580 events/3424 patients; and OR, 0.83; 95% CI, 0.70-0.98; 2607 events/12,933 patients vs 2961/12,920 patients, respectively) \((P < .001\) for interaction). Three trials were conducted in patients with stable coronary heart disease \((n=25853)^{5,15,16}\) and 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) \((P < .001\) for interaction). Three trials were conducted in patients with 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 580 events/3424 patients; and OR, 0.83; 95% CI, 0.70-0.98; 2607 events/12,933 patients vs 2961/12,920 patients, respectively) \((P < .001\) for interaction). Three trials were conducted in patients with 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 580 events/3424 patients; and OR, 0.83; 95% CI, 0.70-0.98; 2607 events/12,933 patients vs 2961/12,920 patients, respectively) \((P < .001\) for interaction). Three trials were conducted in patients with 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 580 events/3424 patients; and OR, 0.83; 95% CI, 0.70-0.98; 2607 events/12,933 patients vs 2961/12,920 patients, respectively) \((P < .001\) for interaction). Three trials were conducted in patients with 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 580 events/3424 patients; and OR, 0.83; 95% CI, 0.70-0.98; 2607 events/12,933 patients vs 2961/12,920 patients, respectively) \((P < .001\) for interaction).

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 (eFigure 4). There was no significant heterogeneity for these outcomes by study cohort.

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**

<table>
<thead>
<tr>
<th>Incident Diabetes</th>
<th>Developed Diabetes/No Diabetes at Baseline, Pooled No.</th>
<th>Intensive Dose</th>
<th>Moderate Dose</th>
<th>OR (95% CI)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Above median / Below median</td>
<td>657/8103</td>
<td>604/8030</td>
<td>1.09 (0.97-1.22)</td>
<td>.39</td>
</tr>
<tr>
<td>BMI</td>
<td>Above median / Below median</td>
<td>792/8300</td>
<td>696/8313</td>
<td>1.16 (1.04-1.30)</td>
<td>.37</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>Above median / Below median</td>
<td>980/7176</td>
<td>865/7102</td>
<td>1.15 (1.03-1.28)</td>
<td>.55</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>Above median / Below median</td>
<td>400/7363</td>
<td>381/7395</td>
<td>1.06 (0.92-1.22)</td>
<td>.51</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Above median / Below median</td>
<td>574/8874</td>
<td>526/8817</td>
<td>1.15 (1.01-1.31)</td>
<td>.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incident CVD</th>
<th>Developed Diabetes/No Diabetes at Baseline, Pooled No.</th>
<th>Intensive Dose</th>
<th>Moderate Dose</th>
<th>OR (95% CI)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Above median / Below median</td>
<td>1688/8103</td>
<td>1853/8030</td>
<td>0.87 (0.77-0.98)</td>
<td>.49</td>
</tr>
<tr>
<td>BMI</td>
<td>Above median / Below median</td>
<td>1444/8300</td>
<td>1697/8313</td>
<td>0.82 (0.73-0.92)</td>
<td>.83</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>Above median / Below median</td>
<td>1399/7176</td>
<td>1599/7102</td>
<td>0.83 (0.73-0.95)</td>
<td>.65</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>Above median / Below median</td>
<td>1504/7363</td>
<td>1690/7385</td>
<td>0.85 (0.73-0.99)</td>
<td>.93</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Above median / Below median</td>
<td>753/8874</td>
<td>918/8817</td>
<td>0.76 (0.68-0.85)</td>
<td>.91</td>
</tr>
</tbody>
</table>

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 following 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.5

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.

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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 Preiss, Seshasai, Welsh, and Welsh are joint senior authors. Additional Contributions: unpublished data for these analyses were provided to the corresponding author by the SEARCH Collaborative Group.

REFERENCES

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)