Statin Therapy and Risk of Developing Type 2 Diabetes: A Meta-Analysis

Swapnil N. Rajpathak, md, drph[1]
Dharam J. Kumbhani, md, sm[2]
Jill Crandall, md[1]

Nir Barzilai, md[1]
Michael Alderman, md[1]
Paul M. Ridker, md[3]

OBJECTIVE — Although statin therapy reduces cardiovascular risk, its relationship with the development of diabetes is controversial. The first study (West of Scotland Coronary Prevention Study [WOSCOPS]) that evaluated this association reported a small protective effect but used nonstandardized criteria for diabetes diagnosis. However, results from subsequent hypothesis-testing trials have been inconsistent. The aim of this meta-analysis is to evaluate the possible effect of statin therapy on incident diabetes.

RESEARCH DESIGN AND METHODS — A systematic literature search for randomized statin trials that reported data on diabetes through February 2009 was conducted using specific search terms. In addition to the hypothesis-generating data from WOSCOPS, hypothesis-testing data were available from the Heart Protection Study (HPS), the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), and the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA), together including 57,593 patients with mean follow-up of 3.9 years during which 2,082 incident diabetes cases accrued. Weighted averages were reported as risk ratios (RRs) with 95% CIs using a random-effects model. Statistical heterogeneity scores were assessed with the Q and I^2 statistic.

RESULTS — In the meta-analysis of the hypothesis-testing trials, we observed a small increase in diabetes risk (RR 1.13 [95% CI 1.03–1.23]) with no evidence of heterogeneity across trials. However, this estimate was attenuated and no longer significant when the hypothesis-generating trial WOSCOPS was included (1.06 [0.93–1.25]) and also resulted in significant heterogeneity (Q 11.8 [5 d.f.], $P = 0.03$, $I^2 = 57.7\%$).

CONCLUSIONS — Although statin therapy greatly lowers vascular risk, including among those with and at risk for diabetes, the relationship of statin therapy to incident diabetes remains uncertain. Future statin trials should be designed to formally address this issue.

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The role of statins in primary and secondary prevention of cardiovascular disease (CVD), including among patients with type 2 diabetes, is well established. However, the relationship of statin therapy to incident type 2 diabetes is controversial. In the first study that evaluated this association using the West of Scotland Coronary Prevention Study (WOSCOPS) published in 2001, prava-statin at 40 mg/day was reported to be associated with a 30% risk reduction for incident diabetes, although the upper bound of the 95% CI for that observation was 0.99 (1). The WOSCOPS, however, required an increase in fasting glucose ≥36 mg/dl above baseline for diagnosis of incident diabetes in addition to the standard diagnostic criteria of fasting glucose ≥126 mg/dl. Subsequent hypothesis-testing analyses from randomized trials of pravastatin, simvastatin, atorvastatin, and rosuvastatin have suggested either no risk or a slight hazard; in one head-to-head comparison, use of atorvastatin 80 mg was slightly more likely than 40 mg pravastatin to result in incident diabetes, data which have suggested to some that this effect may relate to dose or potency (2–6). Further, in the recent Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), statin treatment was associated with a small increase in physician-diagnosed diabetes, although without an increase in glucose levels (relative risk [RR] 1.25 [95% CI 1.05–1.49]). Given these uncertainties, we conducted a meta-analysis of available trials to identify what role, if any, statin therapy might have in the development of type 2 diabetes.

RESEARCH DESIGN AND METHODS

Search strategy, inclusion criteria, and data extraction

We searched the Medical Literature Analysis and Retrieval System Online (MEDLINE) and Cochrane databases for randomized clinical trials (from inception to February 2009) using the following medical subject heading terms diabetes: statins, HMG CoA reductase inhibitor, pravastatin, atorvastatin, lovastatin, simvastatin, cerivastatin, rosuvastatin, and fluvastatin. To increase the sensitivity of our search, eligible studies were cross-referenced using the Science Citation Index (SCI). We also reviewed recently presented data at national and international meetings. Additionally, we looked through Internet-based sources of information (www.cardiosource.com, www.google.com, www.clinicaltrialresults.org, www.theheart.org, and www.tctmd.com). We also corresponded with experts in the field, and in the case of eligible statin trials where diabetes incidence data were not reported in the published article, we contacted the investigators directly for this information.

Our meta-analysis included all randomized placebo-controlled trials that have reported data on incidence of type 2 diabetes during follow-up. To generate

See accompanying editorial, p. 1941.

summary statistics, we included both primary and secondary cardiovascular prevention trials but excluded registries and other nonrandomized analyses as well as studies where patients had preexisting diabetes or where one statin was compared with another. In addition, we excluded studies where other lipid-lowering medications were used either in lieu of or in addition to statins. Studies examining the role of statins on nonclinical outcomes where no data on diabetes was available were excluded, as were studies limited to specialized noncardiovascular populations.

The primary clinical outcome of interest was the incidence of new-onset diabetes. Because this was not uniformly diagnosed, the different definitions in each trial were separately recorded. Physician- or patient-reported new-onset diabetes was permissible.

Two independent reviewers (S.N.R. and D.J.K.) abstracted the following variables in each study: *1*) patient demographics, *2*) number of patients who experienced and who were at risk for the outcome of diabetes, *3*) type and dose of statin used, *4*) criteria used for diagnosis of diabetes, and *5*) duration of follow-up. Discrepancies were resolved through a third reviewer (J.C.).

The methodological quality of the included randomized clinical trials was assessed using criteria suggested by Jadad et al. (7). Because all studies met at least three of the five criteria, they were judged to be of high quality. No formal scoring method was therefore used.

Statistical analyses

On an a priori basis, we elected to perform a hypothesis-testing meta-analysis that excluded the initial observations from WOSCOPS as well as an analysis of all available data including the hypothesis-generating WOSCOPS data. Summary RRs with 95% CIs were computed for each outcome. RRs were defined as the risk of cumulative incidence of diabetes among those who received statins compared with that among those who received placebo. The summary RR and its 95% CI were estimated using the DerSimonian and Laird method for random effects (8). The random-effects model is reported in the text and figures. To assess heterogeneity across studies, we used the Cochran Q statistic based on the pooled RR by Mantel-Haenszel and measured inconsistency (I^2; the percentage of total variance across studies attributable to het-

erogeneity rather than chance) of treatment effects across trials (9). We used Begg and Mazumdar's funnel plot to assess for publication bias (10). All P values were two tailed, and $P < 0.05$ was considered statistically significant. All analyses were performed using STATA software version 10.0 (STATA, College Station, TX) and Comprehensive Meta-Analysis software version 2 (Biostat, Englewood, NJ).

RESULTS — Six trials met inclusion criteria (Figure 1 and Table 1) and included 57,593 randomized patients (*n* for statin intervention = 28,842; *n* for placebo = 28,751). Three studies (WOSCOPS, the Anglo-Scandinavian Cardiac Outcomes Trial [ASCOT], and the JUPITER) were primary cardiovascular prevention trials, whereas three were secondary prevention trials (the Heart Protection Study [HPS], the Long-Term Intervention with Pravastatin in Ischemic Disease [LIPID] Study, and the Controlled Rosuvastatin Multinational Study in Heart Failure [CORONA]). Two of the trials used 40 mg/day pravastatin (WOSCOPS and LIPID), two rosuvastatin (CORONA 10 mg/day and JUPITER 20 mg/day), one 40 mg/day simvastatin (HPS), and one 10 mg/day atorvastatin (ASCOT). Clinical follow-up ranged from

a median 1.9 years (JUPITER) to over 5 years (LIPID), with a weighted mean duration of follow-up of 3.9 years. The primary analysis of data from these trials suggested an 8–44% risk reduction in CVD incidence comparing statin group with placebo group. Because the study populations for each trial differed considerably, we have provided the baseline characteristics of individual trials in Table 2.

Together, the six studies reported a total of 2,082 incident cases of diabetes during follow-up. The criteria for ascertainment of type 2 diabetes varied in these studies (Table 1). Three studies (HPS, CORONA, and JUPITER) relied on physician-reported diagnosis and treatment for diabetes, whereas the other three (WOSCOPS, ASCOT, and LIPID) also incorporated standardized diagnostic criteria based on plasma glucose levels or oral glucose tolerance test. In addition to the standardized fasting glucose criteria ($\geq$126 mg/dl plasma glucose on two occasions), the WOSCOPS trial also required a $\geq$2 mmol/l (or 36 mg/dl) increase in fasting glucose level from baseline for diabetes diagnosis.

Among the individual studies, four of the studies reported a null association between statin use and diabetes risk. One study (WOSCOPS) reported a statistically

568 articles identified from MEDLINE, Cochrane, and Science

526 excluded based on title and abstract since the study design, study population or outcomes of interest were not relevant

42 full-text articles and 1 abstract were retrieved for detailed evaluation

36 excluded since data on incident diabetes was not reported and 1 abstract was excluded due to lack of placebo control group

6 studies included in the meta-analysis

Figure 1—*Flowchart of selection of studies for inclusion in the meta-analysis.*

Table 1—*Randomized controlled trials evaluating the effect of statin use risk of incident type 2 diabetes*

Study	Study population, follow-up time	Median follow-up	Intervention (sample size)	Diagnosis of incident diabetes	Results for primary outcome, RR (95%CI)	Results for diabetes	
						Incident diabetes cases (n in statin group/n in placebo group)	RR (95% CI) for diabetes comparing statin treatment with placebo
WOSCOPS (2001)[1]	Men aged 45–67 years (mean 55.2 years) from West of Scotland with moderately elevated cholesterol	4.9 years	Pravastatin 40 mg (n = 2,999) vs. placebo (n = 2,975)	Fasting glucose ≥126 mg/dl on two occasions, one of which must be ≥36 mg/dl above baseline or use of hypoglycemic agents	Nonfatal MI and cardiovascular death, 0.69 (0.57–0.83)	57/82	0.7 (0.50–0.99)
HPS (2003)[2]	Adults (78% men) aged 40–80 years (mean 62.1 years) with occlusive arterial disease	4.6 years	Simvastatin 40 mg (n = 7,291) vs. placebo (n = 7,282)	Initiation of pharmacotherapy for diabetes or a specific report of diabetes during follow-up	All-cause mortality, 0.87 (0.81–0.94)	335/293	1.14 (0.98–1.33)
ASCOT (2003)[3]	Adults aged 40–79 years (mean 63.2 years) with hypertension and at high-risk for CVD	3.3 years	Atorvastatin 10 mg (n = 3,910) vs. placebo (n = 3,863)	Fasting glucose ≥126 mg/dl or 2-h OGTT glucose level ≥200 mg/dl	Nonfatal MI, cardiovascular death, 0.64 (0.50–0.83)	154/134	1.15 (0.91–1.44)
LIPID (2003)[4]	Adults aged 31–75 years (mean 62 years) with CVD	5 years	Pravastatin 40 mg (n = 3,970) vs. placebo (n = 3,967)	Fasting glucose ≥126 mg/dl or reported use of diabetes medication (oral agents or insulin)	Cardiovascular death, 0.76 (0.65–0.88)	172/181	0.95 (0.77–1.16)
CORONA (2007)[5]	Elderly adults (mean age 73 years) with heart failure	2.7 years	Rosuvastatin 10 mg (n = 1,771) vs. placebo (n = 1,763)	Physician-diagnosed diabetes	Cardiovascular death, nonfatal MI, and nonfatal stroke, 0.92 (0.83–1.02)	Number of incident diabetes cases: 100 in statin group and 88 in placebo group. RR for diabetes comparing statin treatment with placebo: 1.13 (95% CI: 0.86, 1.50)	
JUPITER (2008)[6]	Multicenter trial with a median follow-up of 1.9 years. Apparently healthy men and women (median age 66 years) with LDL cholesterol <130 mg/dl and hsCRP ≥2.0 mg/l	1.9 years	Rosuvastatin, 20 mg (n = 8,901) vs. placebo (n = 8,901)	Physician-diagnosed diabetes	Nonfatal MI and stroke, unstable angina, arterial revascularization, and cardiovascular death, 0.56 (0.46–0.69)	270/216	1.25 1.05–1.49

hsCRP, high-sensitivity C-reactive protein; MI, myocardial infarction; OGTT, oral glucose tolerance test.

Table 2—*Baseline characteristics of study population in the included trials*

	WOSCOPS	HPS	LIPID	ASCOT	CORONA	JUPITER
Age (years)	55.2	63.9	62.0	63.1	73.0	66.0
Men (%)	100.0	75.3	83.0	81.2	76.0	61.8
Caucasian (%)	NA	NA	NA	94.7	NA	71.2
Diabetes at baseline (%)	1.2	29.0	11.9	24.6	29.5	0
BMI (kg/m^2)	26.0	27.6	NA	28.7	27.0	28.4
Prior MI (%)	0	41.0	64.0	0	60.0	0
LDL cholesterol (mg/dl)	192.0	131.5	152.5	132.6	138.5	108.0
HDL cholesterol (mg/dl)	44.0	41.0	36.3	50.7	48.4	49.0
Triglycerides (mg/dl)	163.0	186.0	136.2	146.9	178.0	118.0
FBG (mg/dl)	85.0	NA	101.0	111.7	NA	94.0
A1C (%)	NA	NA	NA	NA	NA	5.7
FBG measurement laboratory	Central	Central	Central	Central	Central	Central
Concomitant medications (%)						
β-Blockers	NA	NA	47	NA	75	NA
Thiazides	NA	NA	NA	NA	13	NA
ACEI/ARB	NA	NA	16	NA	91.5	NA

Data are means for continuous variables, except for JUPITER, where median values were reported. ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; FBG, fasting blood glucose; MI, myocardial infarction; NA, not available.

significant protective effect of statin use on diabetes incidence (RR 0.70 [95% CI 0.50–0.99]; $P = 0.042$), whereas one (JUPITER) reported a significant positive association (1.25 [1.05–1.49]; $P = 0.01$).

In a meta-analysis of the five hypothesis-testing trials, the summary RR for incident diabetes was 1.13 (95% CI 1.03–1.24; $P = 0.007$) (Fig. 2). This corresponded to a risk difference of 0.5% (0.2–0.8). No significant heterogeneity was observed in this latter analysis (Q statistic = 4.06 [4 d.f.], $P = 0.40$, $I^2 = 1.6\%$), and we observed no evidence in these hypothesis-testing analyses of any interaction by specific drug. However, when the hypothesis-generating WOSCOPS was included in the analyses, the summary RR from the random-effects model was 1.06 (95% CI 0.93–1.23; $P = 0.38$) (Fig. 2). This analysis also revealed significant heterogeneity (Q statistic = 11.8 [5 d.f.], $P = 0.03$, $I^2 = 57.7\%$) driven largely by the WOSCOPS data. Further, there was no evidence of publication bias ($P = 0.15$).

CONCLUSIONS — In the first study that evaluated the statin-diabetes association, Freeman et al. (1) reported an inverse association between pravastatin use and diabetes incidence in the WOSCOPS (RR 0.7 [95% CI 0.55–0.99]) but used additional nonstandardized criteria for diabetes diagnosis. Subsequent statin trials did not confirm this protective effect, and in the recent JUPITER a small but significant increase in physician-reported diabetes was reported among statin users compared with those taking placebo, although in the absence of any effect on glucose levels (6). As suggested here, and contrary to the hypothesis-generating data from WOSCOPS, in this meta-analysis of five hypothesis-testing trials a small but statistically significant increase in diabetes incidence may be associated with statin use, which does not appear to be drug or dose specific. This potential effect was attenuated and no longer significant in meta-analysis of all available data including WOSCOPS.

Our data suggest that continued efforts to understand relationships between statin therapy and diabetes are needed, both in future clinical trials and in terms of laboratory exploration. Understanding the potential mechanisms that may explain this effect will require direct experimental effort. One possible explanation is that in addition to CVD protective effects, statin therapy may interfere with normal glucose metabolism (11). In this regard, both in vitro and in vivo data suggest that atorvastatin decreases adipocyte maturation and results in a decline in expression of GLUT4 and upregulation of GLUT1 in cultured preadipocytes and in mice (12). This results in a marked reduction in insulin-mediated cellular glucose uptake caused by decreased insulin sensitivity, which may possibly result in exacerbation of glucose intolerance (13). It is also possible that statin-induced insulin resistance may result from inhibition of isoprenoid biosynthesis, an intermediate product in cholesterol formation, because these effects can be reversed by the isoprenoid precursor mevalonate (12,14). Furthermore, in addition to inducing insulin resistance, statin therapy may also directly affect insulin secretion. From this perspective, the most relevant experimental data in rats have demonstrated that when pancreatic β-cells are incubated with statins, insulin secretion is reduced due to inhibition of glucose-stimulated increase in free cytoplasmic Ca^{2+} and L-type Ca^{2+} channels (15). Similar findings were also reported in another study using a β-cell line, MIN6 cells, where investigators demonstrated that high doses of lipophilic but not hydrophilic statins decrease insulin secretion, either due to hydroxymethylglutaryl-CoA inhibition or cytotoxicity (16). Another possibility is that statins may uncover diabetes in high-risk individuals, which on a population basis could result in modest hazard. For example, within the JUPITER, 77% of those in the intervention arm who developed diabetes in the follow-up had impaired fasting glucose at study entry; this is not surprising because JUPITER, unlike all prior statin trials, enrolled subjects on the basis of elevated high-sensitivity C-reactive protein, an inflammatory biomarker that is associated with increased diabetes risk. Balancing this modest risk to major macrovascular benefits is important because this JUPITER subgroup also was observed to have large and highly significant reductions in myocardial infarction, stroke, and cardiovascular death associated with rosuvastatin allocation.

A few studies have suggested that statin use may result in an increase in A1C levels (2,17), although these effects have been quite small. Human data also raise the possibility that lipophilic and hydrophilic statins may have different effects on glucose (18). In this regard, the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22) trial reported that although treatment with both 80 mg atorvastatin and 40 mg pravastatin were both associated with a small increase in A1C (atorvastatin 0.37% and pravastatin 0.18%), atorvastatin significantly increased risk of developing an A1C >6% compared with pravastatin (RR 1.84 [95% CI 1.52–2.22]; $P < 0.0001$) (19). Similarly, in two Japanese studies among nondiabetic adults, atorvastatin but not pravastatin was asso-

All Studies (n = 6)

	No. Statins / Total (%)	No. Placebo / Total (%)		Study Estimate (95% CI)
WOSCOPS	57/2999 (1.9)	82/2975 (2.8)		0.69 (0.49, 0.96)
HPS	335/7291 (4.6)	293/7252 (4.0)		1.14 (0.98, 1.33)
ASCOT	154/3910 (3.9)	134/3863 (3.5)		1.14 (0.90, 1.43)
LIPID	172/3970 (4.3)	181/3967 (4.6)		0.95 (0.77, 1.16)
CORONA	100/1771 (5.6)	88/1763 (5.0)		1.13 (0.86, 1.49)
JUPITER	270/8901 (3.0)	216/8901 (2.4)		1.25 (1.05, 1.49)
Combined	1088/28842 (3.8)	994/28751 (3.5)		RR = 1.06 (0.93, 1.22) p = 0.38

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Excluding WOSCOPS (n = 5)

	No. Statins / Total (%)	No. Placebo / Total (%)		Study Estimate (95% CI)
HPS	335/7291 (4.6)	293/7252 (4.0)		1.14 (0.98, 1.33)
ASCOT	154/3910 (3.9)	134/3863 (3.5)		1.14 (0.90, 1.43)
LIPID	172/3970 (4.3)	181/3967 (4.6)		0.95 (0.77, 1.16)
CORONA	100/1771 (5.6)	88/1763 (5.0)		1.13 (0.86, 1.49)
JUPITER	270/8901 (3.0)	216/8901 (2.4)		1.25 (1.05, 1.49)
Combined	1031/25843 (4.0)	912/25776 (3.5)		RR = 1.13 (1.03, 1.23) p = 0.008

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Statin Better Statin Worse

Figure 2—*Meta-analysis of clinical trials evaluating the effects of statins on diabetes risk.*

ciated with an increase in A1C levels (12,18).

Certain limitations of our meta-analysis warrant consideration. First, our analysis was restricted to the few clinical trials that reported data on diabetes incidence in statin trials; other statin trials may have data on diabetes available that can augment these analyses. Second, none of these clinical trials were conducted with diabetes as the primary outcome and therefore were not statistically powered to evaluate this outcome. Our data are also limited in that the diagnostic criterion for diabetes varied among the trials and often was based on physician report rather than systematic surveil-lance. Finally, we cannot rule out the possibility that the increased risk of diabetes among statin users may be due to survival bias related to better survival in the intervention group. We conducted meta-analysis both with and without the initial hypothesis-generating WOSCOPS for two important reasons. First, as indicated earlier, WOSCOPS used additional non-standardized criteria for diabetes diagnosis. Second, the practice of conducting summary analysis after excluding the chronologically first (hypothesis-generating) study is commonly used in meta-analysis. In fact, Fleming et al. (20) recently suggested that this approach is important to avoid any regression-to-the-mean effect and to provide the most un-biased estimates of effect. Furthermore, when we additionally conducted a meta–regression analysis of the included trials, both age ($P = 0.029$) and female sex ($P = 0.002$) were significantly associated with an increased risk of statin-induced diabetes. When both age and sex were included together, only sex (elevated risk among women) remained significant ($P = 0.044$). WOSCOPS was the only trial that included only men and hence may be considered as an outlier for this additional reason. Finally, unlike the analysis that excluded WOSCOPS, there was significant heterogeneity between trials when WOSCOPS was included in the analysis.

Nonetheless, we believe the fully inclusive meta-analysis is also meaningful, underscoring the need for future statin trials to formally investigate this issue.

In conclusion, in the hypothesis-testing component of this meta-analysis, we found no evidence for a protective role of statin treatment on incident diabetes but rather observed a small but significant increase in risk. By contrast, this effect was attenuated and no longer significant in a meta-analysis that included all available evidence, including the original hypothesis-generating data. Given this uncertainty, ongoing efforts in clinical and experimental settings should continue to investigate these relationships. In the meantime, the clear benefits of statins on CVD likely outweigh any potential detrimental effects on glucose metabolism and diabetes risk.

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