Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 57, No. 14, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.10.047

Predictors of New-Onset Diabetes in Patients Treated With Atorvastatin

Results From 3 Large Randomized Clinical Trials

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Objectives We sought to examine the incidence and clinical predictors of new-onset type 2 diabetes mellitus (T2DM) within 3 large randomized trials with atorvastatin.

Background Statin therapy might modestly increase the risk of new-onset T2DM.

Methods We used a standard definition of diabetes and excluded patients with prevalent diabetes at baseline. We identified baseline predictors of new-onset T2DM and compared the event rates in patients with and without new-onset T2DM.

Results In the TNT (Treating to New Targets) trial, 351 of 3,798 patients randomized to 80 mg of atorvastatin and 308 of 3,797 randomized to 10 mg developed new-onset T2DM (9.24% vs. 8.11%, adjusted hazard ratio [HR]: 1.10, 95% confidence interval [CI]: 0.94 to 1.29, p = 0.226). In the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial, 239 of 3,737 patients randomized to atorvastatin 80 mg/day and 208 of 3,724 patients randomized to simvastatin 20 mg/day developed new-onset T2DM (6.40% vs. 5.59%, adjusted HR: 1.19, 95% CI: 0.98 to 1.43, p = 0.072). In the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial, new-onset T2DM developed in 166 of 1,905 patients randomized to atorvastatin 80 mg/day and in 115 of 1,898 patients in the placebo group (8.71% vs. 6.06%, adjusted HR: 1.37, 95% CI: 1.08 to 1.75, p = 0.011). In each of the 3 trials, baseline fasting blood glucose, body mass index, hypertension, and fasting triglycerides were independent predictors of new-onset T2DM. Across the 3 trials, major cardiovascular events occurred in 11.3% of patients with and 10.8% of patients without new-onset T2DM (adjusted HR: 1.02, 95% CI: 0.77 to 1.35, p = 0.69).

Conclusions High-dose atorvastatin treatment compared with placebo in the SPARCL trial is associated with a slightly increased risk of new-onset T2DM. Baseline fasting glucose level and features of the metabolic syndrome are predictive of new-onset T2DM across the 3 trials. (J Am Coll Cardiol 2011;57:1535–45) © 2011 by the American College of Cardiology Foundation

An increased risk of new-onset type 2 diabetes mellitus (T2DM) has been described with a wide variety of drugs, including thiazide diuretics (1,2), beta-blockers (1–3), glucocorticoids (4), niacin (5), and protease inhibitors (6). In a recently published meta-analysis (7) of 13 statin trials with 91,140 participants, statin therapy was associated with a slightly higher incidence of new-onset T2DM (hazard ratio [HR]: 1.09, 95% confidence interval [CI]: 1.02 to 1.17).

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Manuscript received July 28, 2010; revised manuscript received October 4, 2010, accepted October 11, 2010.

Abbreviations and Acronyms

BMI = body mass index
CI = confidence interval
HDL = high-density lipoprotein
HR = hazard ratio
LDL = low-density lipoprotein
MI = myocardial infarction
T2DM = type 2 diabetes mellitus

Little heterogeneity was found between trials, and meta-regression showed that the risk of developing diabetes with statins was highest in trials with older participants but that neither baseline body mass index (BMI) nor change in low-density lipoprotein (LDL) cholesterol concentrations accounted for residual variation in risk. However, other clinical predictors were not examined, and only 1 of the 13 trials in this analysis involved atorvastatin, compared with 6 with pravastatin and 3 with rosuvastatin.

The purpose of this report is to describe the incidence of new-onset T2DM in 3 additional large randomized trials: the TNT (Treating to New Targets) trial (8), in which 80 mg and 10 mg/day of atorvastatin were compared in patients with stable coronary disease; the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial (9), in which atorvastatin 80 mg was compared with simvastatin 20 mg/day in post-myocardial infarction (MI) patients; and the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial (10), in which 80 mg/day of atorvastatin was compared with placebo in patients with a recent stroke or transient ischemic attack. Within each trial, we examined baseline clinical predictors of incident diabetes. In addition, we compared the subsequent event rate after the development of new-onset T2DM with the event rate for patients who did not develop this complication.

Methods

The study design and main findings of the 3 trials have been published (8–10). Eligibility criteria for the TNT trial included an age range of 35 to 75 years, documented coronary disease, and an LDL cholesterol off therapy between 3.4 and 6.5 mmol/l (130 to 250 mg/dl), decreasing to <3.4 mmol/l (130 mg/dl) after an 8-week run-in period on atorvastatin 10 mg/day. Patients were randomized to 10 mg or 80 mg/day of atorvastatin and followed for a median of 4.9 years. Patients were eligible for the IDEAL trial if they were 80 years of age or less, had experienced a definite MI, and qualified for statin therapy according to their national guidelines at the time of recruitment. The IDEAL patients were randomized to atorvastatin 80 mg or simvastatin 20 mg/day and were followed for a median of 4.8 years. Eligibility criteria for the SPARCL trial included a stroke or transient ischemic attack 1 to 6 months before study entry, no known coronary disease, and an LDL cholesterol of 2.6 to 4.9 mmol/l (100 to 190 mg/dl). Patients were randomized to placebo or atorvastatin 80 mg/day and followed for a median of 4.9 years.

Individual patient level data were available from each of the 3 trials and included baseline age; sex; baseline smoking status; history of hypertension and diabetes; history of coronary events and coronary interventions; medications; measurements of heart rate, blood pressure, and BMI; and baseline laboratory values including fasting plasma glucose, white blood cell count, and lipid levels.

New-onset T2DM was defined prospectively with the criteria of the West of Scotland investigators; specifically, ≥2 post-baseline fasting glucose measurements ≥7.0 mmol/l (126 mg/dl) and at least 1 post-baseline glucose >2 mmol/l (36 mg/dl) above baseline (11). We also included patients for whom new-onset T2DM was identified through adverse event reporting. Patients were excluded if they were known to have diabetes at baseline, if baseline fasting glucose was ≥7.0 mmol/l, if <2 post-baseline measurements were available, or if the baseline fasting glucose measurement was missing.

In the TNT trial, 1,771 patients were eliminated from analysis because of known diabetes or a fasting blood glucose ≥7.0 mmol/l at baseline; an additional 635 were excluded because they had missing baseline measurements (n = 3) or <2 post-randomization measurements (n = 632). Thus, of the original TNT cohort, 7,595 (75.9%) of 10,001 were included in this analysis. In the IDEAL trial, 1,427 patients were excluded for known diabetes or a fasting blood glucose ≥7.0 mmol/l at baseline, leaving 7,461 (83.9%) of the original 8,888 patients available for this analysis. In the SPARCL trial, 928 patients were excluded for known diabetes or a fasting blood glucose ≥7.0 mmol/l at baseline, leaving 3,803 (80.4%) of the 4,731 randomized patients available for this analysis.

Statistical analyses. Similar statistical analyses were performed for each trial. Comparisons between patient groups were based on a 2-sample *t* test for continuous variables and Fisher exact test for categorical variables. Variables that were not normally distributed, such as white blood cell count and triglycerides, were log transformed. The HRs and 95% CIs for the development of new-onset T2DM were calculated on the basis of Cox proportional hazard analysis. Multivariate analyses included a full model with the 17 variables listed in Tables 1, 2, 3, 4, 5, and 6, a reduced model with backward elimination of nonsignificant variables at a $p > 0.05$ except for treatment group, and exploratory models with use of beta-blockers and treatment group, with and without other variables. For each trial, the risk of new-onset T2DM was calculated for quintiles of baseline fasting glucose level. A risk score for the development of new-onset T2DM was calculated by allocating a point to each of the following 4 risk factors: baseline fasting glucose >5.6 mmol/l (100 mg/dl), fasting triglycerides >1.7 mmol/l (150 mg/dl), BMI >30 kg/m^2, and a history of hypertension.

Major cardiovascular events in patients with and without new-onset T2DM were assessed with an extensive time-dependent Cox proportional hazard analysis including new-

Table 1 Baseline Characteristics by New-Onset T2DM Status During Follow-Up in the TNT Trial

Baseline Characteristics	Subjects With New-Onset T2DM (n = 659)	Subjects Without New-Onset T2DM (n = 6,936)	Total (n = 7,595)	p Value*
Age, yrs	60.1 ± 8.6	60.7 ± 8.9	60.6 ± 8.9	0.098
Sex, male	538 (81.6%)	5,739 (82.7%)	6,277 (82.7%)	0.484
Current smokers	99 (15.0%)	927 (13.4%)	1,026 (13.5%)	0.233
Hypertension	408 (61.9%)	3,434 (49.5%)	3,840 (50.6%)	<0.0001
Fasting glucose, mg/dl	108.0 ± 10.9	96.4 ± 10.1	97.4 ± 10.7	<0.0001
BMI, kg/m^2	30.65 ± 4.75	27.86 ± 4.11	28.10 ± 4.24	<0.0001
WBC, 10^3/mm^3	6.39 ± 1.53	6.00 ± 1.55	6.03 ± 1.55	<0.0001
SBP, mm Hg	132.6 ± 17.2	129.4 ± 16.2	129.7 ± 16.3	<0.0001
DBP, mm Hg	79.7 ± 9.5	77.9 ± 9.3	78.1 ± 9.3	<0.0001
Total cholesterol, mg/dl	178.2 ± 24.0	174.2 ± 23.6	174.5 ± 23.6	<0.0001
LDL cholesterol, mg/dl	98.6 ± 17.6	97.5 ± 17.3	97.6 ± 17.4	0.108
HDL cholesterol, mg/dl	45.2 ± 10.4	48.2 ± 11.1	48.0 ± 11.1	<0.0001
Total/HDL cholesterol ratio	4.10 ± 0.91	3.75 ± 0.83	3.78 ± 0.84	<0.0001
Triglycerides, mg/dl	158.3 ± 78.9	130.5 ± 61.7	132.7 ± 63.7	<0.0001
Use of statins during screening	417 (63.3%)	4,318 (62.3%)	4,735 (62.3%)	0.614
Use of beta-blockers (before or at baseline)	393 (59.6%)	3,705 (53.4%)	4,098 (54.0%)	0.0025
Treatment with atorvastatin 80 mg	351 (53.3%)	3,447 (49.7%)	3,798 (50.0%)	0.087

Values are mean ± SD or n (%). For white blood cell (WBC) and triglyceride: geometric mean was calculated as the exponential of mean value on natural log scale. Geometric SD is calculated according to Taylor's theorem (Let X = WBC or triglyceride, Y = ln(X). Geometric SD = exp (ln [mean of Y]) · (exp[variance of Y] − 1). *The p values are based on 2-sample *t* test for continuous variables and Fisher exact test for categorical variables.

BMI = body mass index; DBP = diastolic blood pressure; HDL = high-density lipoprotein; HR = hazard ratio; LDL = low-density lipoprotein; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus; TNT = Treating to New Targets trial.

onset T2DM as a time-dependent covariate in the model for univariate analysis and adjusting for treatment group, age, sex, smoking status, baseline fasting glucose and lipid levels, BMI, blood pressure, use of statins before baseline, and use of beta-blocker during screening. All time-dependent covariate Cox proportional hazard analyses were based on a time interval of 6 months.

Results

Baseline features. During follow-up, new-onset T2DM was diagnosed in 659 (8.68%) of 7,595 patients in the TNT trial, 447 (5.99%) of 7,461 patients in the IDEAL trial, and 281 (7.39%) of 3,803 patients in the SPARCL trial. The clinical characteristics at baseline of the patients with and

Table 2 Baseline Characteristics by New-Onset T2DM Status During Follow-Up in the IDEAL Trial

Baseline Characteristics	Subjects With New-Onset T2DM (n = 447)	Subjects Without New-Onset T2DM (n = 7,014)	Total (n = 7,461)	p Value*
Age, yrs	60.5 ± 8.9	61.6 ± 9.6	61.5 ± 9.5	0.012
Sex, male	372 (83.2%)	5,681 (81.0%)	6,053 (81.1%)	0.262
Current smokers	95 (21.3%)	1,495 (21.3%)	1,590 (21.3%)	1.000
Hypertension	179 (40.0%)	2,078 (29.6%)	2,257 (30.3%)	<0.0001
Fasting glucose, mg/dl	107.8 ± 10.8	97.5 ± 9.8	98.1 ± 10.1	<0.0001
BMI, kg/m^2	28.92 ± 4.33	26.82 ± 3.55	26.95 ± 3.64	<0.0001
WBC, 10^3/mm^3	6.81 ± 1.82	6.55 ± 1.85	6.57 ± 1.85	0.0028
SBP, mm Hg	138.8 ± 19.6	136.0 ± 20.0	136.2 ± 20.0	0.0053
DBP, mm Hg	81.8 ± 10.2	80.2 ± 10.2	80.3 ± 10.2	0.0014
Total cholesterol, mg/dl	194.9 ± 38.5	196.9 ± 39.0	196.8 ± 39.0	0.281
LDL cholesterol, mg/dl	118.8 ± 37.7	122.5 ± 34.7	122.3 ± 34.6	0.031
HDL cholesterol, mg/dl	42.8 ± 11.0	46.9 ± 12.1	46.6 ± 12.1	<0.0001
Total/HDL cholesterol ratio	4.83 ± 1.62	4.47 ± 1.40	4.47 ± 1.42	<0.0001
Triglycerides, mg/dl	152.2 ± 85.7	128.7 ± 64.0	130.0 ± 65.5	<0.0001
Use of statins during screening	347 (77.6%)	5,309 (75.7%)	5,656 (75.8%)	0.393
Use of beta-blockers (before or at baseline)	354 (79.2%)	5,221 (74.4%)	5,575 (74.7%)	0.025
Treatment with atorvastatin 80 mg	239 (53.5%)	3,498 (49.9%)	3,737 (50.1%)	0.144

Values are mean ± SD or n (%). For WBC and triglyceride: geometric mean was calculated as the exponential of mean value on natural log scale. Geometric SD is calculated according to Taylor's theorem (Let X = WBC or triglyceride, Y = ln(X). Geometric SD = exp (ln [mean of Y]) · (exp[variance of Y] − 1). *The p values are based on 2-sample *t* test for continuous variables and Fisher exact test for categorical variables.

IDEAL = Incremental Decrease in End Points Through Aggressive Lipid Lowering trial; other abbreviations as in Table 1.

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Table 3 Baseline Characteristics by New-Onset T2DM Status During Follow-Up in the SPARCL Trial

Baseline Characteristics	Subjects With New-Onset T2DM (n = 281)	Subjects Without New-Onset T2DM (n = 3,522)	Total (n = 3,803)	p Value*
Age, yrs	62.7 ± 10.7	62.5 ± 11.7	62.5 ± 11.6	0.725
Sex, male	176 (62.6%)	2,069 (58.8%)	2,245 (59.0%)	0.208
Current smokers	51 (18.2%)	694 (19.7%)	745 (19.6%)	0.585
Hypertension	203 (72.2%)	2,019 (57.3%)	2,222 (58.4%)	<0.0001
Fasting glucose, mg/dl	103.5 ± 11.9	95.2 ± 10.2	95.8 ± 10.5	<0.0001
BMI, kg/m^2	29.30 ± 4.75	26.98 ± 4.33	27.15 ± 4.40	<0.0001
WBC, 10^3/mm^3	6.31 ± 1.65	6.04 ± 1.74	6.06 ± 1.74	0.0093
SBP, mm Hg	141.5 ± 19.3	137.7 ± 19.4	137.9 ± 19.5	0.0013
DBP, mm Hg	84.1 ± 11.1	81.5 ± 10.7	81.7 ± 10.7	<0.0001
Total cholesterol, mg/dl	212.7 ± 27.4	212.6 ± 29.3	212.6 ± 29.1	0.981
LDL cholesterol, mg/dl	132.2 ± 22.3	133.9 ± 24.0	133.7 ± 23.8	0.267
HDL cholesterol, mg/dl	46.9 ± 12.5	51.4 ± 14.1	51.0 ± 14.0	<0.0001
Total/HDL cholesterol ratio	4.78 ± 1.17	4.39 ± 1.19	4.42 ± 1.12	<0.0001
Triglycerides, mg/dl	155.6 ± 78.8	124.9 ± 60.4	126.9 ± 62.3	<0.0001
Use of statins during screening	7 (2.5%)	86 (2.4%)	93 (2.5%)	0.843
Use of beta-blockers (before or at baseline)	72 (25.6%)	602 (17.1%)	674 (17.7%)	0.0006
Treatment with atorvastatin 80 mg	166 (59.1%)	1,739 (49.4%)	1,905 (50.1%)	0.0019

Values are mean ± SD or n (%). For WBC and triglyceride: geometric mean was calculated as the exponential of mean value on natural log scale. Geometric SD is calculated according to Taylor's theorem (Let X = WBC or triglyceride, Y = ln (X). Geometric SD = exp (ln [mean of Y]) · (exp[variance of Y] − 1). *The p values are based on 2-sample *t* test for continuous variables and Fisher exact test for categorical variables.

SPARCL = Stroke Prevention by Aggressive Reduction in Cholesterol Levels; other abbreviations as in Table 1.

without new-onset T2DM are compared in Table 1 for the TNT trial, Table 2 for the IDEAL trial, and Table 3 for the SPARCL trial. A larger proportion of the patients were women in the SPARCL trial compared with the other 2 trials—41% compared with <20%. Hypertension at baseline was reported less commonly in the IDEAL trial, in 30% of the patients compared with 50% in the TNT trial, and 58% in the SPARCL trial, although blood pressure at baseline was as high in the IDEAL trial as in the SPARCL trial, with measurements in the TNT trial being lower. Baseline lipid levels among the 3 trials are not directly comparable, because of differences in prior statin usage; for example, at baseline all the TNT patients had been taking atorvastatin 10 mg/day during an 8-week run-in period. Only 2 patients included in this analysis from the 3 trials were taking diabetes medication at baseline.

Table 4 Univariate and Multivariate Analyses of Predictors of New-Onset T2DM in the TNT Trial

	Univariate Analysis		Multivariate Analysis: Full Model		Multivariate Analysis: Reduced Model	
Baseline Characteristics	HR (95% CI)*	p Value*	HR (95% CI)*	p Value*	HR (95% CI)*	p Value*
Age, yrs per 5-yr increase	0.97 (0.93–1.01)	0.144	0.98 (0.93–1.03)	0.3804	—	—
Fasting glucose per 10-mg/dl increase	2.76 (2.56–2.97)	<0.0001	2.53 (2.34–2.73)	<0.0001	2.53 (2.34–2.73)	<0.0001
BMI per 3-kg/m^2 increase	1.28 (1.25–1.32)	<0.0001	1.20 (1.15–1.25)	<0.0001	1.21 (1.16–1.26)	<0.0001
Natural log [WBC] per 0.25-log (10^3/mm^3) increase	1.27 (1.18–1.38)	<0.0001	1.16 (1.06–1.26)	0.0011	1.15 (1.06–1.24)	0.0012
SBP per 20-mm Hg increase	1.24 (1.13–1.36)	<0.0001	1.072 (0.951–1.210)	0.254	—	—
DBP per 10-mm Hg increase	1.21 (1.11–1.31)	<0.0001	1.024 (0.92–1.14)	0.655	—	—
Total cholesterol per 20-mg/dl increase	1.14 (1.07–1.21)	<0.0001	—	—	—	—
LDL cholesterol per 10-mg/dl increase	1.032 (0.988–1.078)	0.162	—	—	—	—
HDL cholesterol per 10-mg/dl increase	0.76 (0.70–0.82)	<0.0001	—	—	—	—
Total/HDL cholesterol ratio per 1-U increase	1.51 (1.40–1.63)	<0.0001	1.076 (0.96–1.21)	0.228	—	—
Natural log [triglyceride] per 1.0-log (mg/dl) increase	2.78 (2.33–3.32)	<0.0001	1.67 (1.30–2.16)	0.0001	1.85 (1.53–2.22)	<0.0001
Sex, male	0.94 (0.77–1.15)	0.545	1.028 (0.82–1.28)	0.809	—	—
Current smokers	1.14 (0.92–1.41)	0.225	0.83 (0.623–1.10)	0.194	—	—
Hypertension	1.64 (1.40–1.92)	<0.0001	1.21 (1.02–1.43)	0.029	1.24 (1.05–1.46)	0.0098
Use of statins during at screening	1.065 (0.91–1.25)	0.436	1.013 (0.86–1.19)	0.874	—	—
Use of beta-blockers (before or at baseline)	1.28 (1.10–1.50)	0.0018	1.022 (0.87–1.20)	0.789	—	—
Treatment with atorvastatin 80 mg	1.15 (0.98–1.34)	0.082	1.10 (0.94–1.29)	0.221	1.10 (0.94–1.29)	0.226

*The hazard ratio (HR) along with its corresponding 95% confidence interval (CI) and p values are based on Cox proportional hazard analysis.

Abbreviations as in Table 1.

Table 5 Univariate and Multivariate Analyses of Predictors of New-Onset T2DM in the IDEAL Trial

	Univariate Analysis		Multivariate Analysis: Full Model		Multivariate Analysis: Reduced Model	
Baseline Characteristics	HR (95% CI)*	p Value*	HR (95% CI)*	p Value*	HR (95% CI)*	p Value*
Age, yrs per 5-yr increase	0.96 (0.92–1.01)	0.107	0.97 (0.92–1.03)	0.298	—	—
Fasting glucose per 10-mg/dl increase	2.63 (2.40–2.88)	<0.0001	2.49 (2.26–2.75)	<0.0001	2.49 (2.26–2.74)	<0.0001
BMI per 3-kg/m^2 increase	1.45 (1.37–1.55)	<0.0001	1.28 (1.20–1.37)	<0.0001	1.29 (1.20–1.38)	<0.0001
Natural log [WBC] per 0.25-log (10^3/mm^3) increase	1.14 (1.05–1.24)	0.0015	1.07 (0.97–1.18)	0.179	—	—
SBP per 20-mm Hg increase	1.14 (1.04–1.24)	0.0062	1.03 (0.90–1.17)	0.697	—	—
DBP per 10-mm Hg increase	1.14 (1.04–1.25)	0.0038	0.97 (0.86–1.10)	0.669	—	—
Total cholesterol per 20-mg/dl increase	0.98 (0.93–1.02)	0.300	—	—	—	—
LDL cholesterol per 10-mg/dl increase	0.97 (0.94–0.998)	0.035	—	—	—	—
HDL cholesterol per 10-mg/dl increase	0.74 (0.67–0.80)	<0.0001	—	—	—	—
Total/HDL cholesterol ratio per 1-U increase	1.15 (1.10–1.20)	<0.0001	1.03 (0.95–1.12)	0.417	—	—
Natural log [triglyceride] per 1.0-log (mg/dl) increase	2.24 (1.84–2.74)	<0.0001	1.31 (0.996–1.73)	0.054	1.48 (1.19–1.83)	0.0004
Sex, male	1.15 (0.90–1.48)	0.257	1.04 (0.80–1.35)	0.800	—	—
Current smokers vs. never smokers	0.99 (0.79–1.25)	0.956	1.07 (0.77–1.50)	0.677	—	—
Past smokers vs. never smokers	1.20 (0.988–1.45)	0.066	1.07 (0.82–1.40)	0.604	—	—
Hypertension	1.60 (1.32–1.93)	<0.0001	1.35 (1.09–1.67)	0.0057	1.32 (1.09–1.60)	0.005
Use of statins during screening	1.08 (0.87–1.35)	0.497	1.06 (0.83–1.35)	0.650	—	—
Use of beta-blockers (before or at baseline)	1.28 (1.02–1.61)	0.032	1.06 (0.84–1.33)	0.650	—	—
Treatment with atorvastatin	1.16 (0.96–1.40)	0.120	1.19 (0.99–1.44)	0.072	1.19 (0.98–1.43)	0.075

*The HR along with its corresponding 95% CI and p values are based on Cox proportional hazard analysis.
Abbreviations as in Tables 1, 2, and 4.

Predictors of new-onset T2DM. In each of the 3 trials, patients who developed new-onset T2DM were more likely to have hypertension at baseline; to be taking beta-blockers; and to have higher fasting glucose, BMI, white blood cell count, systolic and diastolic blood pressure, total cholesterol/high-density lipoprotein (HDL) cholesterol ratio, triglycerides, and lower HDL cholesterol, as shown in Tables 1 to 3. New-onset T2DM patients were younger in the IDEAL trial ($p = 0.012$), but no age differences were observed in the TNT or SPARCL trials. Sex and current smoking were not associated with new-onset T2DM.

Predictors of new-onset T2DM are listed in Table 4 for the TNT trial, Table 5 for the IDEAL trial, and Table 6 for the SPARCL trial. Fasting glucose, BMI, fasting triglycer-

Table 6 Univariate and Multivariate Analyses of Predictors of New-Onset T2DM in the SPARCL Trial

	Univariate Analysis		Multivariate Analysis: Full Model		Multivariate Analysis: Reduced Model	
Baseline Characteristics	HR (95% CI)*	p Value*	HR (95% CI)*	p Value*	HR (95% CI)*	p Value*
Age, yrs per 5-yr increase	1.02 (0.97–1.07)	0.528	1.04 (0.97–1.11)	0.264	—	—
Fasting glucose per 10-mg/dl increase	2.13 (1.90–2.38)	<0.0001	1.92 (1.71–2.16)	<0.0001	1.96 (1.74–2.20)	<0.0001
BMI per 3-kg/m^2 increase	1.30 (1.22–1.38)	<0.0001	1.19 (1.11–1.28)	<0.0001	1.19 (1.11–1.27)	<0.0001
Natural log [WBC] per 0.25-log (10^3/mm^3) increase	1.18 (1.06–1.31)	0.0031	1.06 (0.94–1.19)	0.364	—	—
SBP per 20-mm Hg increase	1.20 (1.07–1.34)	0.0019	0.93 (0.78–1.10)	0.380	—	—
DBP per 10-mm Hg increase	1.20 (1.09–1.33)	0.0002	1.13 (0.97–1.31)	0.117	—	—
Total cholesterol per 20-mg/dl increase	1.004 (0.93–1.09)	0.920	—	—	—	—
LDL cholesterol per 10-mg/dl increase	0.97 (0.92–1.02)	0.273	—	—	—	—
HDL cholesterol per 10-mg/dl increase	0.76 (0.69–0.84)	<0.0001	—	—	—	—
Total/HDL cholesterol ratio per 1-U increase	1.21 (1.14–1.29)	<0.0001	0.97 (0.86–1.10)	0.671	—	—
Natural log [triglyceride] per 1.0-log (mg/dl) increase	2.99 (2.34–3.81)	<0.0001	2.64 (1.83–3.81)	<0.0001	2.51 (1.92–3.29)	<0.0001
Sex, male	1.13 (0.89–1.44)	0.327	1.10 (0.83–1.45)	0.530	—	—
Current smokers vs. never smokers	0.97 (0.72–1.32)	0.853	0.995 (0.68–1.46)	0.980	—	—
Past smokers vs. never smokers	1.26 (0.996–1.59)	0.054	1.09 (0.82–1.46)	0.563	—	—
Hypertension	1.91 (1.47–2.48)	<0.0001	1.34 (0.997–1.79)	0.052	1.42 (1.08–1.86)	0.012
Use of statins during screening	0.96 (0.45–2.03)	0.913	0.70 (0.33–1.48)	0.346	—	—
Use of beta-blockers (before or at baseline)	1.62 (1.24–2.11)	0.0004	1.14 (0.85–1.52)	0.392	—	—
Treatment with atorvastatin	1.44 (1.14–1.83)	0.0024	1.34 (1.05–1.71)	0.018	1.37 (1.08–1.75)	0.011

*The HR along with its corresponding 95% CI and p values are based on Cox proportional hazard analysis.
Abbreviations as in Tables 1, 3, and 4.

ides, and hypertension were strong predictors by multivariate analysis in all 3 trials. Use of beta-blockers before or at baseline was a predictor by univariate analysis but not by multivariate analysis in any model that included baseline fasting glucose. Baseline blood pressure and HDL cholesterol measurements were strong predictors in univariate but not in multivariate analyses.

Effect of high-dose atorvastatin on new-onset T2DM. In the TNT trial, a trend toward an increase in new-onset T2DM for the atorvastatin 80 mg group was observed (HR: 1.15, 95% CI: 0.98 to 1.34, p = 0.082; and HR: 1.10, 95% CI: 0.94 to 1.29, p = 0.22, for univariate and multivariate analyses, respectively). Similarly, in the IDEAL trial a trend toward an increase in new-onset T2DM was observed in the atorvastatin 80 mg group (HR: 1.16, 95% CI: 0.96 to 1.40, p = 0.12; and HR: 1.19, 95% CI: 0.99 to 1.44, p = 0.072, for univariate and multivariate analyses, respectively). The comparator treatment groups in these trials were atorvastatin 10 mg in the TNT trial and simvastatin 20 mg in the IDEAL trial. In the SPARCL trial, where the comparator group was placebo, the incidence of new-onset T2DM was higher in the atorvastatin 80 mg group (HR: 1.44, 95% CI: 1.14 to 1.83, p = 0.0024; and HR: 1.34, 95% CI: 1.05 to 1.71, p = 0.018, for univariate and multivariate analyses, respectively).

The absolute rates of new-onset T2DM were 9.24% and 8.11% in the TNT trial in the 80 and 10 mg groups, respectively; 6.40% and 5.59% in the IDEAL trial in the atorvastatin and simvastatin groups, respectively; and 8.71% and 6.06% in the SPARCL trial in the atorvastatin 80 mg and placebo groups, respectively.

Effect of baseline fasting glucose on new-onset T2DM. The strongest predictor of new-onset T2DM in all 3 trials was fasting glucose at baseline. As shown in Table 7, higher quintiles of baseline fasting glucose in each trial were associated with higher HRs for developing new-onset T2DM. The glucose ranges in the quintile where the risk first became statistically significant were remarkably consistent across the trials: 5.3 to 5.6 mmol/l (95 to 100 mg/dl) in the TNT trial, 5.3 to 5.6 mmol/l (95 to 100 mg/dl) in the IDEAL trial, and 5.4 to 5.8 mmol/l (98 to 105 mg/dl) in the SPARCL trial.

High-risk subgroups for the development of new-onset T2DM. As shown in Figure 1, the presence of a baseline fasting glucose >5.6 mmol/l (100 mg/dl), fasting triglycerides >1.7 mmol/l (150 mg/dl), BMI >30 kg/m^2, and a history of hypertension were each associated with a much higher risk of new-onset T2DM in each of the 3 trials. The HRs were remarkably consistent across the trials, ranging from 3.49 to 5.78 for fasting glucose, 1.88 to 2.37 for fasting triglycerides, 2.36 to 2.73 for BMI, and 1.60 to 1.91 for hypertension (p < 0.0001 for all).

Patients were assigned 1 point for each of these 4 risk factors. As shown in Table 8, in each of the 3 trials the risk of developing new-onset T2DM increased with an increasing number of risk factors: in the TNT trial, from 1.46% with 0 factors to 30.0% with all 4 factors; in the IDEAL trial, from 1.55% to 24.8%; and in the SPARCL trial, from 2.06% to 34.3%.

As depicted in Figure 2, in each trial not only were patients with none or 1 of the risk factors at low risk for new-onset T2DM but the risk was not increased in the more aggressive statin treatment group. However, in the small number of patients with 3 or all 4 of the risk factors, the incidence was not only high but was increased by more aggressive statin therapy.

Prognosis of patients with new-onset T2DM. Major cardiovascular events (cardiovascular death, MI, stroke, or resuscitated cardiac arrest) occurred in the 3 trials in 157 of 1,387 new-onset T2DM patients (11.3%) and in 1,884 of 17,472 patients who did not develop this complication (10.8%). The HRs for these events in new-onset T2DM patients were 1.03 (95% CI: 0.78 to 1.35, p = 0.83) and 1.02 (95% CI: 0.77 to 1.35, p = 0.69) by univariate and multivariate analyses, respectively. Among patients in the atorvastatin 80 mg groups of the 3 trials, major cardiovascular events occurred in 76 of 756 new-onset T2DM patients (10.1%) and in 867 of 8,684 patients who did not develop new-onset T2DM (10.0%). The HRs for these events in new-onset T2DM patients were 0.90 (95% CI:

Table 7 Risk of New-Onset T2DM According to Quintile of Baseline Fasting Blood Glucose in the 3 Trials

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
TNT					
Range (mg/dl)	<89	≥89–<95	≥95–<100	≥100–<107	≥107
HR (95% CI) (vs. Q1)	—	1.14 (0.73–1.79)	2.10 (1.39–3.18)	3.68 (2.51–5.40)	13.2 (9.3–18.9)
p value (vs. Q1)	—	0.57	0.0004	<0.0001	<0.0001
IDEAL					
Range (mg/dl)	<90	≥90–<95	≥95–<100	≥100–<106	≥106
HR (95% CI) (vs. Q1)	—	1.33 (0.77–2.29)	2.18 (1.34–3.54)	3.79 (2.36–6.08)	10.4 (6.70–16.0)
p value (vs. Q1)	—	0.30	0.0018	<0.0001	<0.0001
SPARCL					
Range (mg/dl)	<88	≥88–<94	≥94–<98	≥98–<105	≥105
HR (95% CI) (vs. Q1)	—	1.15 (0.69–1.90)	1.22 (0.71–2.09)	1.96 (1.23–3.13)	5.89 (3.88–8.96)
p value (vs. Q1)	—	0.59	0.47	0.005	<0.0001

Abbreviations as in Tables 1, 2, 3, and 4.

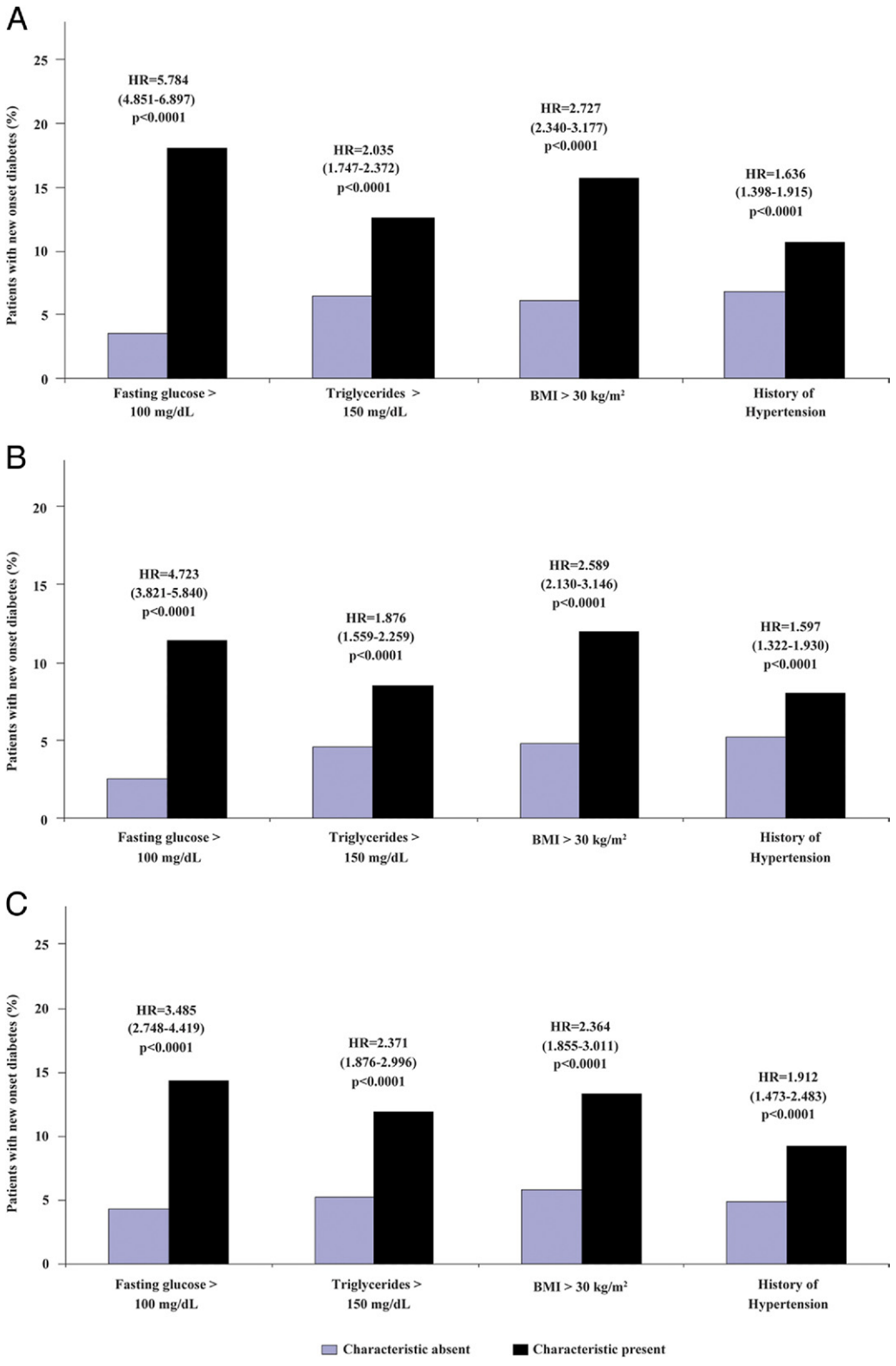

Figure 1 **Incident Diabetes According to Baseline Clinical Predictors**

Incident diabetes in **(A)** the TNT (Treating to New Targets) trial, **(B)** the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial, and **(C)** the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial according to baseline clinical predictors. BMI = body mass index; HR = hazard ratio.

Table 8 Risk of New-Onset T2DM According to Number of Risk Factors at Baseline

Number of Risk Factors	TNT Trial (n = 7,595)			IDEAL Trial (n = 7,595)			SPARCL Trial (n = 3,803)		
	Incidence n/N (%)	HR (95% CI)	p Value	Incidence n/N (%)	HR (95% CI)	p Value	Incidence n/N (%)	HR (95% CI)	p Value
0	22/1,505 (1.46%)	1.00		31/1,996 (1.55%)	1.00		16/776 (2.06%)	1.00	
1	117/2,576 (4.54%)	3.19 (2.02–5.02)	<0.0001	120/2,748 (4.37%)	2.89 (1.95–4.29)	<0.0001	61/1,354 (4.51%)	2.23 (1.31–3.95)	0.0034
2	206/2,082 (9.89%)	7.15 (4.60–11.09)	<0.0001	146/1,802 (8.10%)	5.48 (3.72–8.08)	<0.0001	91/1,085 (8.39%)	4.28 (2.52–7.28)	<0.0001
3	218/1,112 (19.6%)	14.91 (9.62–23.10)	<0.0001	116/778 (14.9%)	10.54 (7.09–15.70)	<0.0001	76/480 (15.8%)	8.58 (5.00–14.71)	<0.0001
4	96/320 (30.0%)	25.40 (16.0–40.4)	<0.0001	34/137 (24.8%)	18.78 (11.5–30.6)	<0.0001	37/108 (34.3%)	20.16 (11.2–36.3)	<0.0001
Total	659/7,595 (8.68%)			447/7,461 (5.99%)			281/3,803 (7.39%)		

Risk of new-onset T2DM according to number of risk factors at baseline (baseline fasting glucose >5.6 mmol/l (100 mg/dl), fasting triglycerides >1.7 mmol/l (150 mg/dl), BMI >30 kg/m^2, and a history of hypertension). Abbreviations as in Tables 1, 2, 3, and 4.

0.60 to 1.34, p = 0.59) and 0.87 (95% CI: 0.58 to 1.30, p = 0.49) by univariate and multivariate analyses, respectively.

Among patients excluded from this study due to the presence of diabetes at baseline, major cardiovascular events occurred in 832 of 4,761 patients overall (17.5%) and in 358 of 2,359 patients (15.2%) in the atorvastatin 80 mg groups.

Discussion

The main findings of this study are 2-fold. First, the 80-mg dose of atorvastatin was associated with an increased risk of new-onset T2DM compared with placebo in the SPARCL trial. The absolute difference between the treatment groups was 2.65% (8.71% vs. 6.06%), and the adjusted HR was 1.34 (95% CI: 1.05 to 1.71). This is slightly higher but still overlaps with the HR of 1.09 (95% CI: 1.02 to 1.17) reported in the meta-analysis of 13 placebo-controlled statin trials (7). In the TNT and IDEAL trials, where the comparator treatment was a lower dose statin, the trends toward an increase in new-onset T2DM in the 80-mg atorvastatin group were not statistically significant.

The second main finding in our study is that the development of new-onset T2DM can be predicted by baseline fasting glucose level and components of the metabolic syndrome—specifically higher triglycerides, higher BMI, and hypertension. These predictors were consistent across all 3 trials, and combining them into a score allowed stratification of the risk of new-onset T2DM. Patients with a score of 0 had a risk of 2% or less in each trial, and those with 1 risk factor had a risk of 4% to 5% (Table 7). Only with 3 or 4 of the risk factors did the risk of new-onset T2DM exceed 10%. With 3 or 4 risk factors, risk also increased in the atorvastatin 80 mg group versus the comparator treatment group (Fig. 2).

Low HDL cholesterol levels were predictive of new-onset T2DM by univariate but not multivariate analysis. White blood cell count, a rough marker of inflammation, was a univariate predictor in all 3 trials but a multivariate predictor only in the TNT trial. Age, sex, and smoking were not consistently predictive of new-onset T2DM.

Previous studies. The baseline variables that predicted new-onset T2DM in these trials were also predictive of spontaneous (12,13) or drug-related (1,3,5,14) new-onset T2DM in previous studies. Fasting glucose, blood pressure, BMI, and triglycerides have been associated with spontaneous new-onset T2DM in patients with hypertension and in those with newly acquired impaired fasting glucose (12,13). In hypertension trials, fasting glucose and BMI have been the strongest predictors of new-onset T2DM (1,3,14). The metabolic syndrome has been shown to be a strong predictor of new-onset T2DM both in clinical trials and in the general population (15–17). These associations are not surprising, because hyperinsulinemia is both a precursor of diabetes and an important underlying cause of the metabolic syndrome.

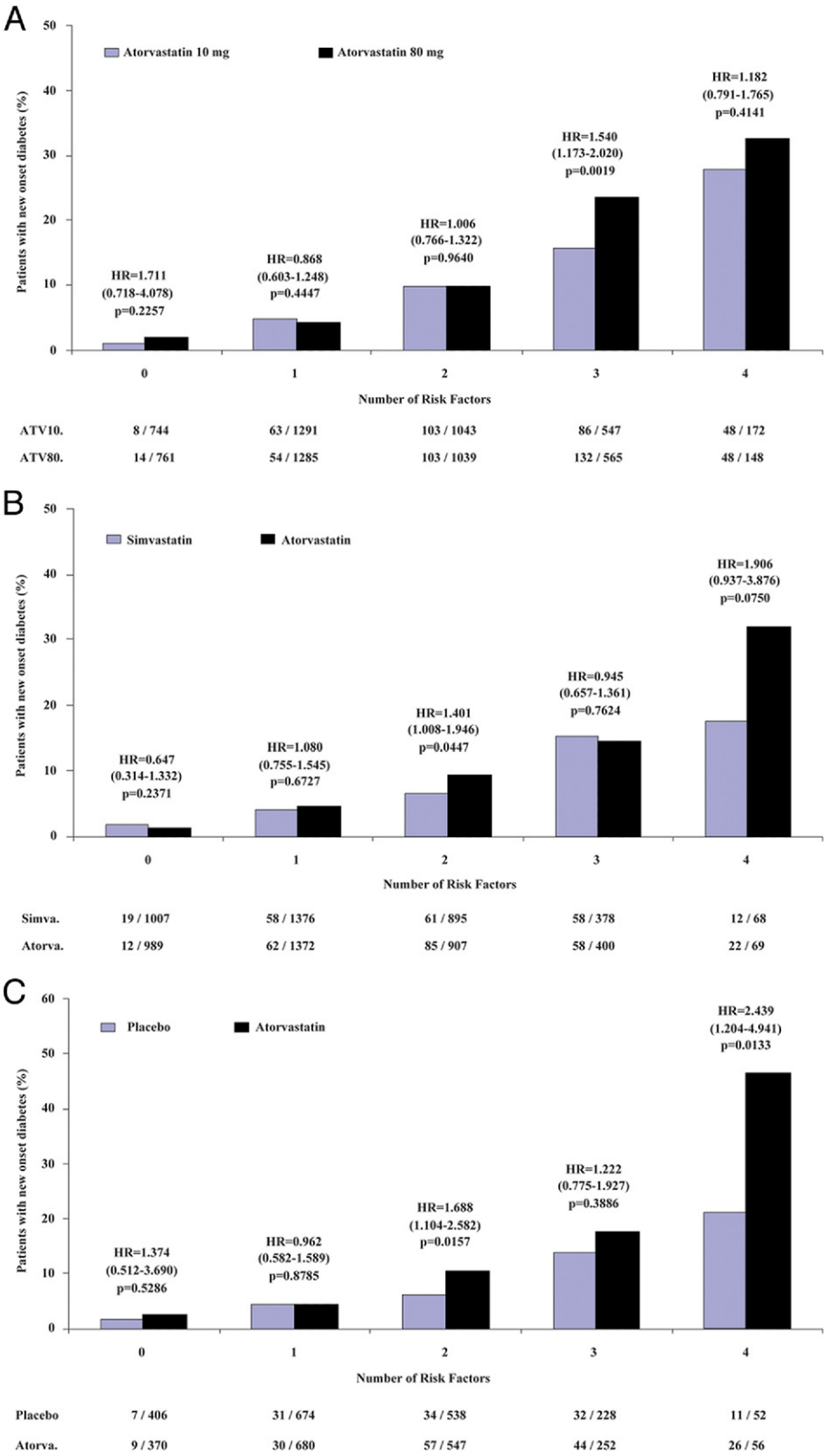

Figure 2 Incident Diabetes According to Number of Risk Factors

Incident diabetes in **(A)** the TNT trial, **(B)** the IDEAL trial, and **(C)** the SPARCL trial according to number of risk factors and treatment group. Atorva. = atorvastatin; ATV10 = atorvastatin 10 mg; ATV80 = atorvastatin 80 mg; Simva. = simvastatin; other abbreviations as in Figure 1.

In small studies, atorvastatin has been reported to worsen glycemic control in Japanese patients (18,19) but not in Europeans (20,21). At the end of 3.9 years of follow-up in the CARDS (Collaborative Atorvastatin Diabetes Study) of 2,838 patients with T2DM (22), adjusted mean glycosylated hemoglobin levels were slightly higher, by 0.105%, in patients randomized to atorvastatin 10 mg/day compared with placebo ($p = 0.03$).

The mechanism underlying the small increase in new-onset T2DM in patients treated with statins is unknown. An increase in cholesterol content of pancreatic beta islet cells has been reported to decrease insulin secretion (23); however, statin treatment would be expected to decrease or have no effect on the cholesterol content of these cells. It is possible that statins decrease insulin sensitivity in liver or muscle, but there is no direct experimental evidence to support this.

Risk/benefit ratio of statins. Cardiovascular risk is assumed to increase with the development of new-onset T2DM, because patients with diabetes have a higher event rate than patients without diabetes. For example, in these 3 trials, a major cardiovascular event occurred in 17.5% of the 4,761 patients with diabetes at baseline compared with 10.8% of the 18,859 patients included in this study without diabetes at baseline. However, the event rate in patients with new-onset T2DM was much lower than that of patients with diabetes at baseline and was not appreciably higher than that of patients without new-onset T2DM (adjusted HR: 1.02, 95% CI: 0.77 to 1.35).

Although these results do not exclude an increased risk of up to 35% and an increased risk might become apparent after longer follow-up, our results suggest that the risk accompanying statin-associated diabetes might not be equivalent to the usual risk of diabetes. Patients who developed thiazide-induced new-onset T2DM in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) were also not at increased risk of a cardiovascular event (24).

The risk factors for new-onset T2DM shown in this study are also risk factors for cardiovascular events. Patients with the metabolic syndrome but without diabetes were at increased risk in the TNT trial (25), and hypertriglyceridemia was a strong predictor of events in the TNT and IDEAL trials (26). By contrast, patients with these risk factors also obtained considerable benefit from high-dose atorvastatin: TNT patients with the metabolic syndrome without diabetes had an event rate of 11.6% in the 10 mg group and 8.2% in the 80 mg group (HR: 0.70, 95% CI: 0.57 to 0.84, $p < 0.0001$) (25).

The authors of the recent meta-analysis calculated that treating 255 patients with a statin for 4 years would induce 1 case of new-onset T2DM but would prevent 5.4 coronary deaths or MIs for each mmol/l reduction in LDL cholesterol (7). This benefit would be greater if strokes and coronary revascularizations were included (7). The benefits of statin treatment thus far outweigh the risks, particularly because it is uncertain as to whether new-onset T2DM itself increases risk.

Study limitations. The overwhelming majority of patients enrolled in these 3 trials were Caucasian, and whether the results are applicable to other populations is unknown. Some evidence suggests that the risk of statin-associated new-onset T2DM might be higher in Japanese patients (18,19). Only 1 of the 3 trials, the SPARCL trial, had a placebo control group, and in that study the 80-mg/day dose of atorvastatin was clearly associated with an increased risk of new-onset T2DM. The trend toward an increased risk in the atorvastatin 80 mg groups in the TNT and IDEAL trials, although not statistically significant, suggests that the incidence might be slightly higher with higher doses or more potent statins.

The definition of new-onset T2DM used here was the same definition used in the WOSCOPS (West of Scotland Coronary Prevention Study) (11) and might be too restrictive, because it requires at least 2 elevated post-baseline fasting glucose measurements. Thus, the absolute incidence of new-onset T2DM might have been underestimated with this definition; however, the improved specificity obtained with stricter criteria for diabetes minimizes bias of the risk estimate due to misclassification.

Conclusions

The use of high-dose atorvastatin seems to be associated with a slight increase in the risk of new-onset T2DM, although the strongest predictors of new-onset T2DM remain baseline fasting glucose and other features of the metabolic syndrome. Although any potential increased risk of new-onset T2DM with atorvastatin might warrant careful monitoring, the benefits of atorvastatin clearly outweigh the risks in patients with coronary or cerebrovascular disease.

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Key Words: diabetes ■ low-density lipoprotein (LDL) cholesterol ■ statin.