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Cardiovascular Event Reduction Versus New-Onset Diabetes During Atorvastatin Therapy:

Effect of Baseline Risk Factors for Diabetes

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Objectives The purpose of this study was to compare the incidence of new-onset diabetes (NOD) with cardiovascular (CV) event reduction at different levels of NOD risk.

Background Statins reduce the number of CV events but increase the incidence of NOD. We previously reported that 4 factors independently predicted NOD: fasting blood glucose >100 mg/dl, fasting triglycerides >150 mg/dl, body mass index >30 kg/m^2, and history of hypertension.

Methods We compared NOD incidence with CV event reduction among 15,056 patients with coronary disease but without diabetes at baseline in the TNT (Treating to New Targets) (n = 7,595) and IDEAL (Incremental Decrease in Endpoints Through Aggressive Lipid Lowering) (n = 7,461) trials. CV events included coronary heart disease death, myocardial infarction, stroke, and resuscitated cardiac arrest.

Results Among 8,825 patients with 0 to 1 of the aforementioned NOD risk factors at baseline, NOD developed in 142 of 4,407 patients in the atorvastatin 80 mg group and in 148 of 4,418 in the atorvastatin 10 mg and simvastatin 20 to 40 mg groups (3.22% vs. 3.35%; hazard ratio [HR]: 0.97; 95% confidence intervals [CI]: 0.77 to 1.22). Among the remaining 6,231 patients with 2 to 4 NOD risk factors, NOD developed in 448 of 3,128 in the atorvastatin 80 mg group and in 368 of 3,103 in the lower-dose groups (14.3% vs. 11.9%; HR: 1.24; 95% CI: 1.08 to 1.42; p = 0.0027). The number of CV events was significantly reduced with atorvastatin 80 mg in both NOD risk groups.

Conclusions Compared with lower-dose statin therapy, atorvastatin 80 mg/day did not increase the incidence of NOD in patients with 0 to 1 NOD risk factors but did, by 24%, among patients with 2 to 4 NOD risk factors. The number of CV events was significantly reduced with atorvastatin 80 mg in both NOD risk groups. (J Am Coll Cardiol 2013; xx:xxx) © 2013 by the American College of Cardiology Foundation

Statin therapy reduces the risk of coronary and cerebrovascular events across a broad spectrum of patients (1), and more intensive treatment provides substantial additional event reduction (2). However, meta-analyses have shown that statin therapy is associated with a 9% increase in the risk of new-onset diabetes (NOD) compared with placebo (3) and that intensive therapy is associated with an additional 12% increase (4). Risk factors for NOD during statin therapy are fasting blood glucose (FBG) >100 mg/dl and features of the metabolic syndrome (5). These predictors

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Abbreviations and Acronyms

CHD = coronary heart disease

CV = cardiovascular

FBG = fasting blood glucose

MI = myocardial infarction

NOD = new-onset diabetes

were found to be similar across 3 atorvastatin trials (5) and are similar to the predictors of incident diabetes not related to statins (6–8).

Despite these considerations, the risk of NOD versus cardiovascular (CV) event reduction has not been evaluated at different levels of diabetes risk. The purpose of this study was to examine, according to baseline risk factors for diabetes, the incidence of NOD and CV events within 2 large secondary prevention trials with atorvastatin.

Methods

The study design and main findings of the TNT (Treating to New Targets) and IDEAL (Incremental Decrease in Endpoints Through Aggressive Lipid Lowering) trials have been published (9–11). In the TNT study, patients ranged in age from 35 to 75 years, had documented stable coronary disease, and had an off-therapy low-density lipoprotein–cholesterol 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. A total of 10,001 patients were randomized to atorvastatin 10 or 80 mg per day and followed for a median of 4.9 years. In the IDEAL study, patients were ≤80 years of age, had experienced a definite myocardial infarction (MI), and qualified for statin therapy according to their national guidelines at the time of enrollment. A total of 8,888 patients were randomized to simvastatin 20 to 40 mg per day or atorvastatin 80 mg per day and followed for a median of 4.8 years.

FBG was measured at each 6-month visit in both TNT and IDEAL trials. NOD was defined prospectively as at least 2 post-baseline FBG measurements ≥7.0 mmol/l (126 mg/dl) and at least 1 post-baseline glucose >2 mmol/l (36 mg/dl) above baseline (12). We also included patients for whom NOD was identified through adverse event reporting. The primary endpoint of the TNT study was a composite of coronary heart disease (CHD) death, nonfatal MI, resuscitated cardiac arrest, and fatal or nonfatal stroke; for the IDEAL trial, the endpoint was a composite of the first 3 of those for TNT (not including stroke). Each of these 4 endpoint events are reported in this analysis; total events as well as patients with events were counted because many patients had multiple events contributing to the burden of disease (13).

In the TNT trial, 1,771 patients were excluded because they were known to have diabetes at baseline or had a baseline FBG ≥7.0 mmol/l; an additional 635 were excluded because <2 post-baseline measurements were available (n = 632) or because the baseline FBG measurement was missing (n = 3). Thus, of the original TNT cohort of 10,001 patients, 7,595 were included in this analysis. In IDEAL, 1,427 patients were excluded for known diabetes or a baseline FBG ≥7.0 mmol/l, leaving 7,461 of the original 8,888 patients available for this analysis.

Statistical analyses. Comparisons of baseline characteristics between patient groups were based on a 2-sample *t* test for continuous variables and Fisher's exact test for categorical variables. Variables that were not normally distributed, specifically white blood cell count and triglyceride levels, were log transformed. The hazard ratios (HRs) and 95% confidence intervals (CIs) for the comparisons of the development of NOD between patient groups were calculated on the basis of Cox proportional hazard analysis. The models contained study (TNT or IDEAL) and treatment group. Similar analyses were used for major CV events.

Results

The baseline characteristics of patients with and without NOD during the TNT and IDEAL trials are listed in Table 1. Patients who developed diabetes had higher FBG, triglyceride levels, body mass index, and systolic and diastolic blood pressure and lower high-density lipoprotein–cholesterol levels at baseline.

The 4 previously defined risk factors for NOD in the TNT and IDEAL cohorts were FBG >100 mg/dl, history of hypertension, body mass index >30 kg/m^2, and fasting triglycerides >150 mg/dl (5). Figure 1 displays the risk of NOD (top) and the risk of a major CV endpoint (bottom) for patients with 0, 1, 2, 3, and 4 of the risk factors for NOD. As the number of risk factors for NOD increased, the CV event rate increased, from 8.5% to 10.1% in the atorvastatin 80 mg group and from 9.0% to 15.0% in the lower-dose group.

Patients at low risk for diabetes. A total of 8,825 patients had 0 to 1 of these risk factors at baseline, 4,081 from TNT and 4,744 from IDEAL, comprising 53.7% of the TNT and 63.6% of the IDEAL cohorts. NOD developed during follow-up in 142 of 4,407 (3.22%) of these patients randomized to atorvastatin 80 mg/day and in 148 of 4,418 (3.35%) randomized to atorvastatin 10 mg/day or simvastatin (HR: 0.97; 95% CI: 0.77 to 1.22). Among these patients at low risk for diabetes, 375 of 4,407 patients had at least 1 CV endpoint event in the atorvastatin 80 mg group and 433 of 4,418 patients had at least 1 event in the atorvastatin 10 mg and simvastatin groups (8.51% vs. 9.80%; HR: 0.87; 95% CI: 0.755 to 0.995; p = 0.042).

Patients at high risk for diabetes. A total of 6,231 patients had 2 to 4 risk factors for diabetes at baseline, 3,514 from TNT and 2,717 from IDEAL, comprising 46.2% of the TNT and 36.4% of the IDEAL cohorts. NOD developed during follow-up in 448 of 3,128 (14.32%) of these patients in the atorvastatin 80 mg group and in 368 of 3,103 (11.86%) patients in the lower-dose groups (HR: 1.24; 95% CI: 1.08 to 1.42; p = 0.0027). The test for interaction between treatment and risk factor group was not statistically significant (p = 0.072). Among these patients at high risk

Table 1 Baseline Characteristics in Patients With and Without Incident Diabetes During Follow-up in the TNT and IDEAL Trials

Variable	Incident Diabetes (n = 1,106)	No Incident Diabetes (n = 13,950)	Total (N = 15,056)	p Value
Age, yrs	60.2 ± 8.7	61.1 ± 9.23	61.1 ± 9.2	0.001
Male sex	910 (82.3)	11,420 (81.9)	12,330 (81.9)	0.776
Current smoker	194 (17.5)	2,422 (17.4)	2,616 (17.4)	0.869
Hypertension	587 (53.1)	5,510 (39.5)	6,097 (40.5)	<0.0001
Fasting blood glucose, mg/dl	107.9 ± 10.9	97.0 ± 10.0	97.8 ± 10.4	<0.0001
Body mass index, kg/m^2	30.0 ± 4.7	27.3 ± 3.9	27.5 ± 4.0	<0.0001
White blood cell count, × 10^3/mm^3	6.56 ± 1.66	6.27 ± 1.73	6.29 ± 1.72	<0.0001
Systolic blood pressure, mm Hg	135.0 ± 18.4	132.7 ± 18.5	132.9 ± 18.5	0.0001
Diastolic blood pressure, mm Hg	80.5 ± 9.8	79.1 ± 9.8	79.2 ± 9.8	<0.0001
Total cholesterol, mg/dl	184.9 ± 31.8	185.6 ± 34.2	185.5 ± 34.1	0.514
LDL-cholesterol, mg/dl	106.6 ± 27.1	110.0 ± 30.1	109.7 ± 29.9	0.0001
HDL-cholesterol, mg/dl	44.3 ± 10.7	47.5 ± 11.6	47.3 ± 11.6	<0.0001
Total cholesterol/HDL-cholesterol ratio	4.39 ± 1.30	4.10 ± 1.20	4.12 ± 1.21	<0.0001
Triglycerides, mg/dl	155.8 ± 81.3	129.6 ± 62.9	131.4 ± 64.6	<0.0001
Use of statin during screening	764 (69.1)	9,627 (69.0)	10,391 (69.0)	0.973
Beta-blockers before or at baseline	747 (67.5)	8,926 (64.0)	9,673 (64.3)	0.017
Treatment = atorvastatin 80 mg	590 (53.4)	6,945 (49.8)	7,535 (50.1)	0.025

Values are mean ± SD or n (%). Geometric mean and SD are presented for white blood cell count and triglycerides. p Values are based on 2-sample Student *t* test for continuous variables and Fisher's exact test for categorical variables.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

for NOD, 315 of 3,128 patients in the atorvastatin 80 mg group and 373 of 3,103 in the lower-dose group had at least 1 CV endpoint event (10.07% vs. 12.02%; HR: 0.82; 95% CI: 0.71 to 0.96; p = 0.011). The HRs for diabetes and CV events in the high- and lower-dose treatment groups according to diabetes risk category are shown in Figure 1.

Multiple endpoint events. A total of 690 of 7,535 patients (9.16%) in the high-dose group and 806 of 7,521 in the lower-dose group (10.72%) experienced at least 1 primary endpoint during follow-up (HR: 0.85; 95% CI: 0.77 to 0.94; p = 0.015). However, the 690 patients with events in the high-dose group experienced a total of 874 endpoint

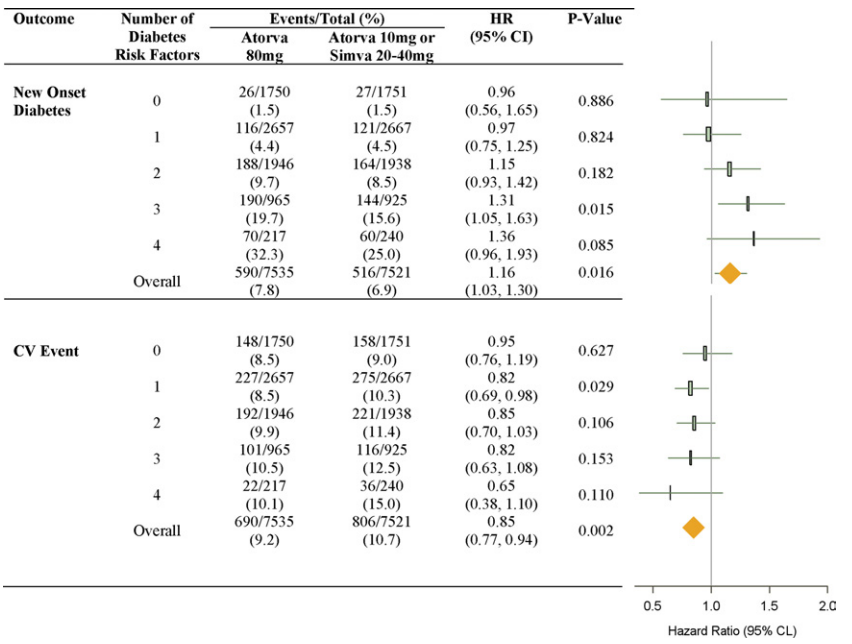

Figure 1 Risk of Developing NOD (top) and CV Events (bottom) According to Number of NOD Risk Factors at Baseline

The new-onset diabetes (NOD) risk factors are fasting blood glucose >100 mg/dl, fasting triglycerides >150 mg/dl, body mass index >30 kg/m^2, and history of hypertension. Atorva = atorvastatin; CI = confidence intervals; CV = cardiovascular; HR = hazard ratio; Simva = simvastatin.

events and the 806 patients with events in the low-dose group experienced 1,038 events. Among the 1,496 patients with events, 1,207 had 1 event, 211 had 2, and 78 had 3 or more. High-dose treatment was associated with a nonsignificant reduction in the number of second and subsequent events (HR: 0.88; 95% CI: 0.69 to 1.11; p = 0.25). The event distribution consisted of 355 CHD deaths, 1,003 nonfatal MIs, 48 resuscitated cardiac arrests, and 48 fatal and 458 nonfatal strokes.

Discussion

The results of this analysis indicated that high-dose, compared with lower-dose, statin increased the risk of NOD among patients with 2 to 4 diabetes risk factors. No increased risk of NOD was seen with high-dose statin treatment in patients with 0 to 1 risk factors for diabetes. Slightly more than half of TNT patients and nearly two-thirds of IDEAL patients were in the low-risk group for diabetes. Compared with low-dose statin, atorvastatin 80 mg reduced the number of CV events both in patients at low and high risk for diabetes.

These results should reassure physicians treating patients at low risk for diabetes. Such patients do not appear to incur an increased risk of diabetes with high-dose atorvastatin and derive benefit in terms of CV event reduction. Among the 6,231 patients in the TNT and IDEAL trials at high risk for NOD, treatment with atorvastatin 80 mg compared with a lower statin dose was associated with 80 more cases of NOD and the prevention of 94 major CV events in 58 patients.

In the 1,501 TNT patients with established diabetes at baseline (14), who were excluded from this analysis, the event rate for the primary endpoint was 13.8% in the atorvastatin 80 mg group compared with 17.9% in the 10 mg group (HR: 0.75; 95% CI: 0.58 to 0.97; p = 0.026). In the Cholesterol Treatment Trialists' meta-analysis of 18,686 patients with diabetes in 14 randomized statin trials, a 1-mmol/l reduction in low-density lipoprotein–cholesterol was associated with a 21% reduction in the number of major vascular events (15), a relative risk reduction nearly identical to that reported in all patients in statin trials (1). In TNT patients with metabolic syndrome at baseline (and thus at high risk for developing diabetes), the number of primary endpoint events was 44% higher than in TNT patients without metabolic syndrome (16), and the primary endpoint reduction in the 80 mg compared with the 10 mg group was 29% (p < 0.0001).

A patient with coronary disease who develops diabetes faces new blood glucose monitoring requirements, increased dietary restrictions, and usually additional chronic drug therapy. These limitations to quality of life are accompanied by the long-term threats of the macrovascular and microvascular complications of diabetes. However, the impact of NOD is relatively minor compared with the CV events included in this analysis: CHD death, MI, resuscitated cardiac arrest, and fatal or nonfatal stroke. Nearly 20% of the patients (286 of 1,496) with these CV events had more than one. Furthermore, other CV events that are prevented by statin treatment such as coronary revascularization, new-onset angina, and transient ischemic attack were not included in this analysis. In considering the balance between NOD and CV event prevention, it is worth noting that the microvascular and macrovascular complications of diabetes occur relatively uncommonly during the first decade after diagnosis (17). Many patients with established vascular disease, such as those in this study, will die from an atherosclerotic event before they develop complications from diabetes.

Similar findings to our study were recently reported from the JUPITER (Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study, in which rosuvastatin was associated with an increased risk for NOD in patients with, but not without, risk factors for diabetes (18). In both groups, the number of CV events was reduced with rosuvastatin, and benefit exceeded risk in patients with diabetes risk factors. In a population-based study from Taiwan, patients prescribed statins had a higher rate of NOD during a median follow-up of 7.2 years, 2.4% versus 2.1%, but a reduced rate of MI, stroke and in-hospital mortality (19).

The mechanism in which statins increase the risk of NOD has been the subject of speculation but is currently unknown. Atorvastatin has been shown to inhibit adipose cell maturation in cell culture and to increase insulin resistance in type 2 diabetic mice (20). Atorvastatin and rosuvastatin have been reported to increase insulin resistance during coronary bypass surgery in patients without diabetes (21). The findings of our study point to the possibility that the mechanism may only be operative in patients with multiple risk factors for diabetes or may be amplified under such conditions.

Study limitations. Diabetes was not a predefined endpoint in either the TNT or IDEAL trial, and the definition that we adopted from Freeman et al. (12) may underestimate the incidence of NOD because it requires 2 elevated FBG measurements post-baseline. Glycosylated hemoglobin was not measured routinely in either trial. Nearly all of patients in these trials were white, and whether the results are applicable to other populations is unknown. Some evidence suggests that the risk of statin-associated NOD might be higher in Japanese patients (22,23).

Conclusions

The risk of NOD did not appear to be increased with atorvastatin 80 mg compared with moderate-dose statin therapy during the 5-year follow-up period of the TNT and IDEAL studies among patients with 0 to 1 of the 4 risk factors for NOD. However, among patients with 2 to 4 risk factors for NOD, atorvastatin 80 mg increased the risk of NOD by 24% compared with standard therapy. In both

groups, high-dose therapy significantly reduced the number of major CV events.

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