Cardiovascular drugs that increase the risk of new-onset diabetes

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The prevalence of type 2 diabetes is increasing worldwide, and diabetes is a strong adverse prognostic factor among patients with cardiovascular (CV) disease. Four classes of drugs that are commonly used for CV risk reduction, statins, niacin, thiazide diuretics, and ß-blockers, have been shown to increase the risk of new-onset diabetes (NOD) by 9% to 43% in meta-analyses or large-scale clinical trials. Clinical predictors for drug-related NOD appear to be similar to the predictors that have been described for NOD unrelated to drugs: fasting blood glucose >100 mg/dL and features of the metabolic syndrome such as body mass index >30 kg/m^2, serum triglycerides >150 mg/dL, and elevated blood pressure, among others. The mechanisms whereby these drugs increase the risk of NOD are incompletely understood, although different hypotheses have been suggested. Lifestyle intervention consisting of diet and exercise has been shown in multiple studies to reduce the risk of NOD by approximately 50%, with persistent benefit during long-term follow-up. In patients at high risk for NOD, niacin should be avoided, and for hypertension, an angiotensin-converting enzyme inhibitor or even a ß$_1$-selective blocker might be a better choice than a standard ß-blocker. For thiazide diuretics and particularly statins, benefit in terms of CV event reduction outweighs the risk of NOD. (Am Heart J 2014;167:421-8.)

Worldwide, the prevalence of type 2 diabetes continues to increase rapidly, with more than 371 million cases in the year 2012.[1] Diabetes is thus becoming a more prevalent risk factor for cardiovascular (CV) disease, and a higher proportion of patients with CV disease have diabetes. Among patients with CV disease, diabetes is a strong adverse prognostic factor. Controlling for blood pressure, low-density lipoprotein cholesterol, and glycosylated hemoglobin (HbA_{1C}) levels reduces CV risk in patients with diabetes; however, only a minority of them successfully attains these multiple goals,[2] despite recent increasing use of drug treatment.[3]

Within this context, it is troublesome that some of the drugs used to reduce CV risk have been shown either to increase the risk of new-onset diabetes (NOD) or to interfere with glucose control in patients with established diabetes. The purpose of this article is to review clinical trial data for 4 commonly used classes of drugs, statins, niacin, thiazide diuretics, and ß-blockers. For each drug class, an attempt will be made to quantify the benefit of treatment and potential harm based on clinical trial results and meta-analyses of trials. The data from these sources documenting the increased risk of NOD with these drugs are summarized in Figure 1.

Predictors of NOD

Studies in different populations have consistently identified the same cluster of risk factors for NOD. *Impaired fasting glucose* (IFG; defined as a fasting blood sugar from 100 to 125 mg/dL), a family history of diabetes, and features of the metabolic syndrome are associated with an increased risk of NOD.[4] Lifestyle factors, low body mass index (BMI), diet, nonsmoking, moderate alcohol consumption, and regular physical activity were all associated with a reduced risk of NOD in a large cohort study, with BMI being the most important of these factors.[5]

Algorithms that predict the risk of NOD have been developed.[6] These scores can be used to assess the risk of NOD using self-reported or routinely available clinical data, reserving laboratory testing for subjects at higher risk. Parental diabetes, obesity, and metabolic syndrome traits effectively predicted NOD in the Framingham Offspring Study cohort.[7] The addition of variables that are more difficult to obtain, including a 2-hour post–oral glucose tolerance test glucose level, levels of fasting

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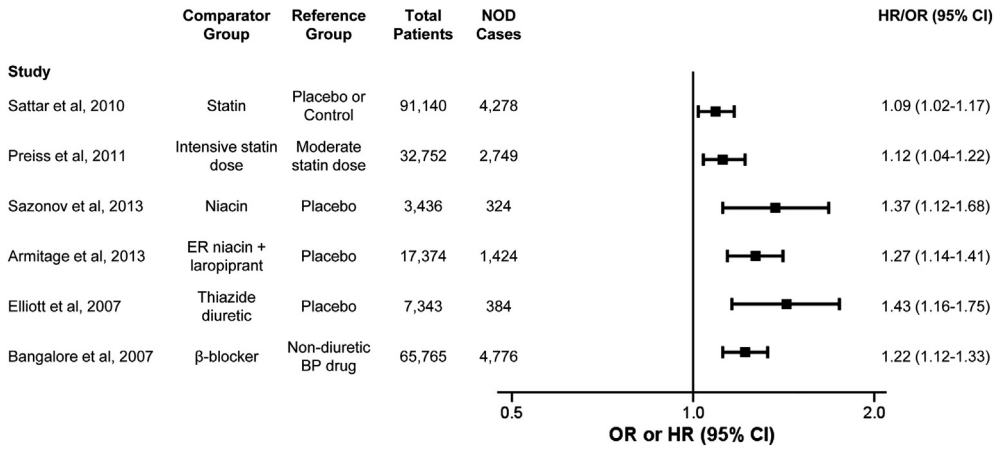
Figure 1



Meta-analyses and clinical trials of CV drugs that increase the risk of NOD. Included are a meta-analysis of statin vs placebo trials, a meta-analysis of intensive vs moderate statin treatment trials, 2 studies of niacin vs placebo, a meta-analysis of thiazide diuretics vs placebo, and a meta-analysis of β-blocker vs other blood pressure drugs.

insulin, and CRP levels, did not improve the discrimination of the clinical model.

Statins and NOD

In a meta-analysis of 13 large randomized placebo-controlled statin trials with 91,140 participants, of whom 4,278 developed diabetes during a mean follow-up of 4 years,[8] statin treatment was associated with a 9% increased risk of diabetes (odds ratio [OR] 1.09, 95% CI 1.02-1.17). It was concluded from this meta-analysis that treatment for 225 patients with a statin for 4 years would result in one extra case of diabetes. The risk appeared to be similar for lipophilic and hydrophilic statins. Pravastatin or lovastatin was used in 7 of the 13 trials in this meta-analysis, and the results may thus underestimate the risk of NOD with higher doses of more potent statins.

The results of the Stroke Reduction by Aggressive Reduction in Cholesterol Levels (SPARCL) trial were not available for this meta-analysis. In that trial, placebo was compared with atorvastatin 80 mg/d in 4,731 patients over a median follow-up of 4.9 years.[9] The risk of NOD was increased in the atorvastatin group (OR 1.34, 95% CI 1.05-1.71). Adding this trial to the previous meta-analysis increases the risk of NOD from 1.09 to 1.12 (95% CI 1.05-1.18).

A subsequent meta-analysis compared the risk of NOD between intensive and moderate-dose statin treatment across 5 trials involving 32,752 participants, of whom 2,749 developed NOD.[10] Compared with moderate-dose therapy, intensive treatment was associated with a 12% increase in the risk of NOD (OR 1.12, 95% CI 1.04-1.22), but a 16% decrease (OR 0.84, 95% CI 0.75-0.94) in the risk of a first major CV event. The risk of NOD was similar for simvastatin 80 mg and atorvastatin 80 mg compared with moderate treatment; however, high-dose atorvastatin significantly reduced CV events (OR 0.78, 95% CI 0.73-0.85) compared with moderate treatment, whereas high-dose simvastatin did not (OR 0.95, 95% CI 0.88-1.03). The authors calculated that one extra case of diabetes per year would occur for every 498 patients treated with an intensive vs a moderate dose, but that one fewer patients would experience a major CV event for every 155 patients treated per year.

In 3 large trials where atorvastatin 80 mg was compared with atorvastatin 10 mg (Treating to New Targets; TNT), simvastatin 10 to 20 mg (Incremental Decrease in Endpoints Through Aggressive Lipid Lowering; IDEAL), or placebo (Stroke Reduction by Aggressive Reduction in Cholesterol Levels; SPARCL), the same 4 clinical factors independently predicted NOD: fasting blood glucose (FBG) >100 mg/dL, triglycerides >150 mg/dL, BMI >30 kg/m^2, and a history of hypertension.[9] These factors are similar to those that predict NOD in people not being treated with a statin, as discussed in the previous section. The risk of developing NOD for 5 years was <2% in each trial for patients with none of the 4 NOD risk factors, but increased to 25% or greater when all 4 were present.

In a subsequent report involving 15,056 participants from 2 of these trials (TNT and IDEAL), the risk of NOD was compared with CV event reduction according to the number of NOD risk factors at baseline.[11] Among 8,825 patients who had 0 or 1 NOD risk factor at baseline, NOD developed during 5 years of follow-up in 3.22% of those randomized to atorvastatin 80 mg and to 3.35% of those randomized to lower dose statin treatment. Among these patients at low risk for NOD, high-dose atorvastatin treatment was associated with a significant reduction in