Risk-benefit analysis of use of statins for primary prevention of cardiovascular disease in subjects without diabetes

Diabetes, prediabetes and metabolic syndrome are associated with a two- to threefold increased risk for cardiovascular disease and all-cause mortality[1,2]. In a meta-analysis of the Cholesterol Treatment Trialists Collaboration involving 169,138 individuals from 26 randomized studies which recruited at least 1,000 patients with at least 2 years' treatment duration, the authors concluded that for every 1 mmol/L reduction in low-density lipoprotein cholesterol (LDL-C), there was a 22% reduction in all vascular events and 10% in all-cause mortality, mainly as a result of coronary heart disease and other cardiac causes. These clinical benefits remained consistent in all subgroup analyses stratified by age, sex, obesity, presence and types of diabetes, concomitant cardiovascular risk factors, and history of prior cardiovascular or renal events[3].

The latest Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial (JUPITER) study[4] recruited subjects without diabetes and LDL-C <3.3 mmol/L with no prior history of cardiovascular disease, but high levels of high-sensitivity C-reactive protein > 2.0 mmol/L. After 1.9 years, the trial was stopped prematurely because of a 44% reduction in the primary cardiovascular end-point in the rosuvastatin group compared with the placebo group, although there was a higher incidence of physician-reported diabetes in the rosuvastatin group. In a subsequent analysis involving 13 statin trials (which included JUPITER) with 91,140 participants, of whom 4,278 developed diabetes during a mean of 4 years, statin therapy was associated with a 9% increased risk for incident diabetes, which was not influenced by the degree of LDL-C lowering or types of statin. Treatment of 255 patients with statins for 4 years resulted in one extra case of diabetes.

One of the main objectives of preventing diabetes is to reduce the risk of cardiovascular disease. In a recent meta-analysis of 10 randomized clinical trials involving 23,152 patients followed up for 3.75 years, diabetes was delayed or prevented by 17% (48% for non-drug approaches vs 30% for drug approaches). There was a non-significant trend towards a reduction in myocardial infarction by 41% and stroke by 30% with no effect on death rates[5]. Despite these encouraging, albeit inconclusive, results on clinical outcomes, as well as challenges in implementing a large-scale lifestyle modification program in non-trial settings, some experts advocated the use of 'polypills' containing multiple drugs including statins, aspirin and angiotensin-converting enzyme inhibitors to prevent cardiovascular disease. However, these concepts are often met with skepticism because of a lack of definitive evidence[6]. The latest 'diabetogenic' effects of statins have thus raised another concern regarding this drug-based approach to prevent diabetes and cardiovascular disease.

In the latest analysis of the JUPITER trial[7], the incidence of diabetes in subjects with at least one risk factor (metabolic syndrome, impaired fasting glucose, body mass index (BMI) ≥30 kg/m^2 or glycated hemoglobin ≥ 6%) was 1.88 per 100 person-years compared with 0.18 per 100 person-years in subjects without risk factors. The average time to diagnosis was 84 weeks in the rosuvastatin group and 90 weeks in the placebo group. In these high-risk subjects, the primary cardiovascular end-point and death rate was reduced by 39 and 17%, respectively, with a 28% increase in the diabetes rate. For subjects without risk factors for diabetes, rosuvastatin reduced the primary end-point by 52% and the death rate by 22%, with no increase in diabetes (Figure 1). Amongst those who developed diabetes, statin reduced the risk of cardiovascular disease by 37%, which was similar to the 44% reduction in the entire cohort. These findings have raised two important questions: (i) what are the mechanisms for the diabetogenic effects of statin? and (ii) what is the place of therapy of statin in primary prevention of cardiovascular disease in non-diabetic subjects, who often harbor risk factors for diabetes?

For the first question, it has been proposed that inhibition of the intracellular 3-hydroxy-3-methylglutaryl-coenzyme A pathway might lead to reduced intracellular cholesterol content with increased intracellular uptake of plasma cholesterol in the β-cells. The latter could have negative effects on the machinery implicated in insulin secretion and insulin sensing. These included inhibition of glucose transporters, delayed adenosine triphosphate production, pro-inflammatory and oxidative stress, inhibition of calcium channel-dependent insulin secretion, and apoptosis of the β-cells. In short-term clinical studies, an increase in fasting plasma glucose, glycated hemoglobin and homeostatic model assessment (HOMA) index of insulin resistance have been reported with some, but not all statins[8].

For the second issue, the latest analysis of the JUPITER study[7] has provided important insights. First, in low-risk

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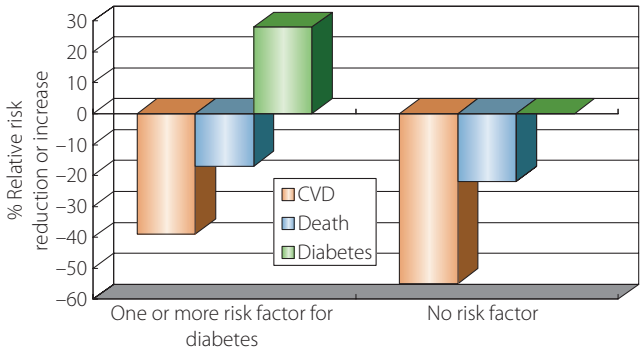

Figure 1 | Diabetes risk and cardiovascular disease (CVD) benefits of statin therapy in subjects with or without risk factors for diabetes. Adapted from Ridker *et al.*[7]

patients without diabetes and no prior history of cardiovascular disease, statin reduced the risk of cardiovascular disease by 44%, with a rate of 0.77 per 100 person-years in the rosuvastatin group and 1.36 per 100-person-years in the placebo group. Second, 99% of subjects who subsequently developed diabetes could be identified using simple clinical and biochemical measures, such as BMI, fasting plasma glucose, glycated hemoglobin and metabolic syndrome. Third, in these subjects, statin treatment prevented 134 vascular events or deaths for every 54 new cases of diabetes diagnosed. This was compared with avoidance of 86 vascular events or deaths with no new cases of diabetes diagnosed in subjects without risk factors.

These latest results are reassuring and support a risk–benefit ratio in favor of statins, even in patients with low event rates. However, chronic hyperglycemia is associated with an increased risk of vascular, cancer, non-vascular and non-cancer events[1]. As such, a 9–12% increased risk of diabetes associated with the use of statins might have long-term significance. This might be particularly relevant to subjects with a family history and/or genetic risk who are at risk of having early onset of diabetes with long disease duration. In Asians, who tend to have a low risk for coronary heart disease, but a high risk for diabetes often accompanied by reduced β-cell response to metabolic stress, visceral obesity, insulin resistance and a dyslipidemic pattern of high triglyceride and low HDL-C, the benefit–risk ratio of statins might be attenuated[9]. Although the effectiveness of statins in preventing cardiovascular[10] and renal disease[11] in Asian type 2 diabetic patients has been shown in observational cohorts, the efficacy of statins in the prevention of cardiovascular disease and its long-term metabolic consequences in Asian non-diabetic populations has yet to be proven.

During the past two decades, lifestyle modification and non-statin drugs, such as metformin, α-glucosidase inhibitors, peroxisome proliferator-activated receptor-γ agonists and renin angiotensin system inhibitors, have been shown to reduce the risk of diabetes in subjects with impaired glucose tolerance[12]. Falling short of its effects on macrovascular complications, lifestyle modification has recently been shown to reduce microvascular complications, such as retinopathy, on long-term follow up[13].

Against this background, there is a need to carry out long-term studies to evaluate the effects of statins, non-statin drugs and lifestyle modification on the incidence of diabetes and cardiovascular disease in high-risk subjects, such as those with prediabetes and metabolic syndrome. In Japan, there is an ongoing open label, randomized, controlled, parallel-group comparative study to evaluate the effect of pitavastatin versus lifestyle modification on the risk of diabetes in 1,269 subjects with impaired glucose tolerance to be followed up for 5 years. The study is expected to complete by 2015[14].

Without doubt, these studies will motivate researchers to carry out epidemiological, clinical and experimental studies that will provide new insights into the effects of statins on diabetes and cardiovascular disease, and other clinical outcomes. Meanwhile, there is a growing consensus to adopt an integrated approach comprising of using a composite risk score including clinical (e.g., age, sex, family history, obesity, blood pressure) and laboratory measures (e.g., fasting/random plasma glucose, lipids, glycated hemoglobin) to detect high-risk subjects[15]. This should be followed by a global risk assessment, periodic monitoring and structured lifestyle modification, with an emphasis on weight reduction, control of blood pressure and early drug treatment to normalize blood glucose for prevention and control of these disease burdens[1].

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