Major journals

Statins: Potential diabetogenic agents?

Marc Evans, Consultant Physician, Llandough Hospital, Cardiff

Hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are commonly prescribed drugs, which convey benefits for people at risk of cardiovascular disease. However, recent data has suggested a potential increased risk of incident diabetes in association with statin therapy (Reiss et al, 2011), in particular simvastatin, atorvastatin and rosuvastatin, in comparison with placebo. By contrast, data from the West of Scotland coronary prevention study (WOSCOPS) suggested that people taking pravastatin faced a 30% lower risk of diabetes compared with placebo. Several meta-analyses have attempted to identify the risk of new onset diabetes associated with statin treatment, but only limited data exist for direct comparisons of individual statins.

The objective of this population-based cohort study (summarised alongside) was to estimate the relation between use of particular statins and incident diabetes. Hazard ratios were calculated to quantify the influence of dose and type of statin on the risk of developing diabetes. Compared with pravastatin (the reference drug in this study), there was an elevated risk of incident diabetes with atorvastatin use (adjusted hazard ratio [HR] 1.22; 95% CI, 1.15–1.29), rosuvastatin use (HR 1.18; 95% CI, 1.10–1.26), and simvastatin use (HR 1.10; 95% CI, 1.04–1.17). No significantly increased risk was detected among people who were prescribed fluvastatin (HR 0.95; 95% CI, 0.81–1.11) or lovastatin (HR 0.99; 95% CI, 0.86–1.14). The absolute risk for incident diabetes was approximately 31 events per 1000 years for atorvastatin and 34 events per 1000-person years for rosuvastatin. A lower absolute risk was observed with simvastatin (26 outcomes per 1000 person-years) compared with pravastatin (23 outcomes per 1000 person-years), with the results being consistent for statin use in both primary and secondary prevention. This study demonstrated a 10–22% increased risk of incident diabetes for some statins, which is consistent with meta-analysis of clinical trial data (Reiss et al, 2011 and Waters at el, 2011), in which a dose-dependent increased risk of incident diabetes has been demonstrated with both simvastatin and atorvastatin. Following adjustment for dose, the risk of incident diabetes in this study became non-significant with rosuvastatin. When interpreting the data from this population-based analysis it is important to recognise the limitations of such a study. Firstly, this study could not account for diabetes risk factors such as previous family history, body weight and ethnicity. Data on HbA_{1c} values, blood lipids, concentration and triglyceride concentrations were not collected, and thus could not be used in risk stratification or diagnosis. In addition, no data on marketing or on physicians' preferences to prescribe particular statins were collected. Despite the fact that the statin groups were well-balanced with regard to demographic and clinical variables, it is impossible to exclude the possibility of residual confounding.

A variety of potential mechanisms may account for the results seen in this study. As a consequence of de novo cholesterol synthesis inhibition, increased plasma derived low-density lipoprotein (LDL) cholesterol production might cause inflammation and oxidation within the beta-cell, consequently impairing insulin secretion (Sampson et al, 2011). Statins might also inhibit calcium-mediated pancreatic insulin release and reduce expression of the beta-cell glucose transporters (GLUT)-2 and GLUT-4. Moreover, statins may also interfere with the synthesis of ubiquinone (CoQ10), which could modify insulin secretion. The extent to which statins are involved in these mechanisms of diabetes onset varies and is in agreement with why particular statins may pose a higher risk compared to others (Sampson et al, 2011). The results of this study further inform the debate around the potential risk of incident diabetes in association with statin therapy and suggest that in people considered at an elevated risk of diabetes, pravastatin may be the preferred drug.

Reiss D, Seshasai SR, Welsh P et al (2011) Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* **305**: 2556–64

Sampson UK, Linton MF, Fazio S (2011) Are statins diabetogenic? *Curr Opin Cardiol* **26**: 342–73

Waters DD, Ho JE, DeMicco DA et al (2011) Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials. *J Am Coll Cardiol* **57**: 1535–45

BMJ

Do statins increase the risk of new onset diabetes?

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Recent evidence suggests that new-onset diabetes could be linked with the use of hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors, which are also known as statins.

2 The authors conducted a retrospective, population-based cohort study to investigate the risk of new-onset diabetes associated with different types of statins in a Canadian population.

3 A total of 471 250 participants aged 66 years or over without diabetes were included in the study. Only those who had been treated with statins for under a year participated.

4 An increased risk of diabetes was found with atorvastatin (adjusted hazard ratio [HR] 1.22; 95% CI, 1.15–1.29) rosuvastatin (HR 1.18; 95% CI, 1.10–1.26), and simvastatin (HR 1.10; 95% CI, 1.04–1.17), when compared with pravastatin. Diabetes risk was not increased with fluvastatin (HR 0.95; 95% CI, 0.81–1.11) or lovastatin (HR 0.99; 95% CI, 0.86–1.14).

5 Pravastatin treatment was associated with the lowest absolute risk for incident diabetes (23 outcomes per 1000 person-years) compared to simvastatin (26 outcomes per 1000 person-years), atorvastatin (31 outcomes per 1000 person-years) and rosuvastatin (34 events per 1000 person-years).

6 The authors concluded that higher potency statins, such as atorvastatin and simvastatin, may be associated with an elevated risk of new onset diabetes when compared with pravastatin.

Carter AA, Gomes T, Camacho X et al (2013) Risk of incident diabetes among patients treated with statins: population based study. *BMJ* **346**: f2610

AM J MED

Intensive lifestyle interventions can reduce CVD risk

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 It is estimated that bariatric surgery is performed on under 1% of eligible people. Therefore, non-surgical alternatives such as lifestyle interventions are urgently needed to treat obese people who require this procedure.

2 The authors aimed to examine if an intensive lifestyle intervention could alter body weight and cardiovascular disease (CVD) risk factors in a cohort of severely obese (BMI ≥40 kg/m^2), overweight (25≤ BMI <30 kg/m^2), class I (30≤ BMI <35 kg/m^2) and class II obese (35≤ BMI <40 kg/m^2) individuals over a period of 4 years.

3 Participants (*n*=5145) aged 45–76 years with T2D and a BMI of 25 kg/m^2 were randomised to receive an intensive lifestyle intervention involving physical exercise and calorie restriction or diabetes support and education.

4 After 4 years, participants receiving the intensive lifestyle intervention displayed significantly greater reductions in body weight compared with those receiving diabetes support and education (*Ps*<0.05).

5 In the intensive lifestyle group, similar changes were observed in triglycerides, low-density-lipoprotein cholesterol, diastolic blood pressure and HbA_{1c} across all weight groups. Severely obese participants, however, had smaller improvements in high-density-lipoprotein cholesterol and systolic blood pressure than less obese individuals (*Ps*<0.05).

6 The authors concluded that intensive lifestyle interventions can be efficacious in reducing CVD risk factors and inducing weight loss in the long-term.

Unick JL, Beavers D, Bond DS et al (2013) The long-term effectiveness of a lifestyle intervention in severely obese individuals. *Am J Med* **126**: 236–42

BMJ

Population weight fluctuations, diabetes and CVD

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The aim of this study was to establish if population-wide weight fluctuations are associated with diabetes and cardiovascular disease (CVD) mortality in a Cuban population over a 30-year interval.

2 The authors conducted four cross-sectional surveys in the city of Cienfuegos, Cuba and carried out a systematic review of existing literature.

3 Population-wide weight loss was observed in the 1990s, which was associated with decreased rates of diabetes and CVD.

4 Population-wide weight gain was observed in 1995, which was associated with a rise in diabetes prevalence (116%) and incidence (140%). Diabetes mortality increased by 49% and the rate of decline of coronary heart disease mortality slowed.

5 The authors concluded that a population-level association between weight fluctuations and mortality from diabetes and CVD could be observed in Cienfuegos between 1980–2010.

Franco M, Bilal U, Orduñez P et al (2013) Population-wide weight loss and regain in relation to diabetes burden and cardiovascular mortality in Cuba 1980–2010. *BMJ* **346**: f1515

AM J MED

SMI prevalence is higher with diabetes

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 The authors sought to determine the prevalence and predictors of silent myocardial infarction (SMI) in people with and without diabetes.

2 In total, 1621 people were included in the derivation cohort and were compared to 338 individuals in the validation cohort.

3 In the derivation cohort, the prevalence of SMI was 28.5% in those with diabetes and 21.5% in people without the condition. Diabetes was found to be an independent predictor for SMI occurrence (odds ratio 1.5; 95% CI, 1.1–1.9; *P*=0.004).

4 The authors concluded that SMI occurs more frequently in people with diabetes compared to those without the condition.

Arenja N, Mueller C, Ehl NF et al (2013) Prevalence, extent, and independent predictors of silent myocardial infarction. *Am J Med* **126**: 515–22

BMJ

QStroke algorithm is efficacious

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The authors set out to prospectively evaluate the efficacy of the QStroke risk algorithm for predicting stroke and ischaemic attack in people with no history of such events.

2 Data from 3 500 000 people aged 25–84 years were included in the derivation cohort and compared to 1 900 000 participants in the validation cohort.

3 QStroke had higher levels of discrimination and calibration compared to the Framingham score. The Qstroke D statistic was 2.3 in men and 2.4 in women.

4 Discrimination levels were reduced in people with atrial fibrillation, but QStroke displayed an improved performance compared to the CHADS2 and CHA2DS2VASc risk algorithms.

5 The authors concluded that QStroke is a valid risk algorithm for measuring absolute stroke risk.

Hippisley-Cox J, Coupland C, Brindle P (2013) Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores. *BMJ* **346**: f2573

"After 4 years, participants receiving the intensive lifestyle intervention displayed significantly greater reductions in body weight compared to those receiving diabetes support and education (Ps<0.05)."