Have a statin, but not cake too

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Analyses of clinical trial data have linked statin treatment to an increased risk of diabetes in a dose-dependent manner, albeit modestly so (Sattar et al, 2010; Preiss et al, 2011). While this risk of diabetes seems surprising and has been widely reported, some commentators, including myself, have been careful to remind clinicians that the risk–benefit ratio remains strongly in favour of statins in those with existing cardiovascular disease (CVD) and those at risk of CVD (Byrne and Wild, 2011; Preiss and Sattar, 2012). However, a more recent observational study based on an analysis of the Women's Health Initiative (Culver et al, 2012; summarised alongside), suggests a significantly greater diabetes risk in statin recipients. It should be remembered, however, that observational data can never fully overcome confounding and thus this study must be treated with caution. Data from randomised placebo-controlled trials are more likely to reflect genuine drug effects.

Even so, are there any implications of the modest statin–diabetes association for clinical practice and any credible mechanisms for such an effect? The answer to the latter question remains unclear but could include statin-mediated alterations in insulin resistance (though evidence for this is currently conflicting) or effects on insulin secretion, or other indirect mechanisms; ongoing work will probably establish relevant pathways in the near future. Also, it remains unclear if all statins have the same effect, although, as noted above, more intensive statin therapy increases diabetes risk to a greater extent (Preiss et al, 2011). Nevertheless, the consistency of recent reports has led the Food and Drug Administration (2012) to add diabetes risk to the statin label.

In terms of clinical management, statins remain indicated in people with diabetes given the strong evidence of CVD risk reduction (Cholesterol Treatment Trialists' Collaborators, 2008). Interestingly, however, results from a recent placebo-controlled trial, which included atorvastatin therapy in one of the arms, suggested an increase in HbA_{1c} level of around 0.3% with statin therapy compared with placebo (Holman et al, 2009), a finding which deserves further investigation.

What about statin prescription to individuals without diabetes? A recent editorial in the *New England Journal of Medicine* has correctly concluded that "clinicians should monitor glucose or glycated hemoglobin in patients with multiple risk factors for diabetes who take statins, but they should continue to prescribe statins when indicated as part of a multifactorial approach to managing cardiovascular risk" (Goldfine, 2012). In addition, at the time of new statin prescription, patients should now be warned about the slightly higher risk of diabetes and, as a result, be reminded that they need to take lifestyle changes more, not less, seriously to offset potential diabetes risk. In short, the recent findings of the statin-related increased risk of diabetes, while modest in strength, remind us that there is no such thing as a free lunch.

Byrne CD, Wild SH (2011) Increased risk of glucose intolerance and type 2 diabetes with statins. *BMJ* **343**:d5004

Cholesterol Treatment Trialists' Collaborators (2008) Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* **371**:117-25

Food and Drug Administration (2012) *FDA Expands Advice on Statin Risks*. Available at: http://1.usa.gov/x3VO6H (accessed 23.05.12)

Goldfine AB (2012) Statins: is it really time to reassess benefits and risks? *N Engl J Med* **366**: 1752–5

Holman RR, Paul S, Farmer A et al (2009) Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes (AFORRD): a randomised controlled trial. *Diabetologia* **52**: 50–9

Preiss 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

Preiss D, Sattar N (2012) Pharmacotherapy: Statins and new-onset diabetes – the important questions. *Nat Rev Cardiol* **9**: 190–2

Sattar N, Preiss D, Murray HM et al (2010) Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* **375**: 735–42

ARCH INTERN MED

New-onset diabetes in women on statins

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

1 The authors investigated whether new-onset diabetes is associated with statin use among postmenopausal women participating in the Women's Health Initiative.

2 Postmenopausal women aged 50–79 years in the USA were recruited between 1993 and 1998; the current analysis included data up to 2005. Statin use was captured at enrolment and year 3 and incident diabetes was determined annually from enrolment.

3 Cox proportional hazards models were used to estimate the risk of diabetes by statin use, with adjustments for confounders. Subgroup analyses by race, obesity status, and age group were conducted.

4 Women without diabetes and with no missing data at baseline (n=153 840) were studied. At baseline, 7.04% were taking statins. There were 10 242 incident cases of self-reported diabetes over 1 004 466 person-years of follow-up.

5 Statin use at baseline was associated with an increased risk of diabetes (hazard ratio [HR], 1.71; 95% CI, 1.61–1.83). This association remained after adjusting for other potential confounders (multivariate-adjusted HR, 1.48; 95% CI, 1.38–1.59) and was observed for all types of statins. Subset analyses evaluating the association of self-reported diabetes with statin use in 125 575 women confirmed these findings.

6 It was concluded that statin medication use in postmenopausal women is associated with an increased risk for new-onset diabetes and this may be a medication class effect.

Culver AL, Ockene IS, Balasubramanian R et al (2012) Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Arch Intern Med* **172**: 144–52

"There was a continual increase in body weight in people with T2D, and considerable differences in the impact on weight using alternative treatment regimens."

DIABETOLOGIA

What works for NAFLD

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

1 The authors performed a meta-analysis of 78 randomised trials to examine the evidence for managing liver disease and cardiometabolic risk in non-alcoholic fatty liver disease (NAFLD).

2 Lifestyle-induced weight loss was safe and improved cardiometabolic risk profile; a weight loss ≥7% improved histological NAFLD activity, but was achieved by under half of participants.

3 Thiazolidinediones improved NAFLD activity, glucose, lipid and inflammatory variables and delayed fibrosis progression; pioglitazone also improved blood pressure.

4 The authors concluded that when lifestyle intervention for NAFLD fails, pioglitazone may be useful.

Musso G, Cassader M, Rosina F, Gambino R (2012) Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. *Diabetologia* **55**: 885–904

DIABETES OBESITY AND METABOLISM

Therapy type affects weight increase

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

1 This study aimed to describe the pattern of weight change in people with T2D over time and when using various antidiabetes treatment regimens.

2 The weight trend was determined from 1995 to 2010 for both prevalent and incident cases, using the UK General Practice Research Database.

3 Mean standardised weight in prevalent cases increased from 83.4 to 92.1 kg for men and from 73.5 to 79.9 kg for women ($P<0.0001$). For incident cases, the figures were 86.7 to 93.6 kg for men and 76.0 to 80.7 kg for women ($P<0.001$).

4 The largest weight increase (median 4.1 kg) over 12 months was for those using thiazolidinedione plus insulin, while the largest decrease (median –7.0 kg) was for metformin plus exenatide (both $P<0.001$).

5 It was concluded that there was a continual increase in body weight in people with T2D, and considerable differences in the impact on weight using various antidiabetes agents.

Morgan CL, Jenkins-Jones S, Evans M et al (2012) Weight change in people with type 2 diabetes: secular trends and the impact of alternative anti-hyperglycaemic drugs. *Diabetes Obes Metab* **14**: 424–32

DIABETES RES CLIN PRACT

Diabetes increases in rural areas of low-income countries

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

1 The authors performed a systematic review of studies reporting diabetes prevalence in rural parts of low- and middle-income countries (LMICs).

2 Rural prevalence of diabetes in LMICs was 5.6% (95% confidence interval, 4.6–6.6), and similar between men and women. This estimate remained robust in separate analyses accounting for study quality, level of heterogeneity, age and sex. Diabetes prevalence increased over time, from 1.8% in 1985–1989 to 5.2% in 1995–1999 to 6.4% in 2000–2004 and to 8.6% in 2005–2010.

3 The authors concluded that the prevalence of diabetes in rural parts of LMICs has risen dramatically. As 55% of LMIC populations live in rural areas, this trend has enormous implications for the global burden of diabetes.

Hwang CK, Han PV, Zabetian A et al (2012) Rural diabetes prevalence quintuples over twenty-five years in low- and middle-income countries: a systematic review and meta-analysis. *Diabetes Res Clin Pract* Jan 17 [Epub ahead of print]

DIABETOLOGIA

Sedentary time is associated with metabolic factors

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

1 The authors investigated whether objectively measured sedentary time and interruptions in sedentary time are associated with metabolic factors in people with T2D.

2 People aged 30–80 years with newly diagnosed T2D ($n=528$) participated in a diet and physical activity programme. Waist circumference (WC), fasting HDL-cholesterol, insulin and blood glucose levels, insulin resistance (IR) and physical activity (accelerometer) were measured.

3 Each hour of sedentary time was associated with larger WC (unstandardised regression coefficient, 1.89 cm [95% confidence interval {CI}, 0.94–2.83]; $P<0.001$), higher insulin (8.22 pmol/L [95% CI, 2.80– 3.65]; $P=0.003$) and IR (0.42 [95% CI, 0.14– 0.70]; $P=0.004$), and lower HDL-cholesterol (–0.04 mmol/L [95% CI, –0.06 to –0.01]; $P=0.005$). Adjustment for WC attenuated all associations.

4 Amount of sedentary time at baseline predicted HDL-cholesterol (–0.05 mmol/L [95% CI, –0.08 to –0.01]; $P= 0.007$), insulin levels (8.14 pmol/L [95% CI, 1.51–14.78]; $P=0.016$) and IR (0.49 [95% CI, 0.08–0.90]; $P=0.020$) at 6 months, though not WC.

5 Baseline breaks in sedentary time (BST) did not substantially predict any metabolic variables at follow-up. No change was seen in sedentary time or BST between baseline and 6 months' follow-up.

6 The authors concluded that increased periods of sedentary time is associated with a poorer metabolic profile in T2D.

Cooper AR, Sebire S, Montgomery AA et al (2012) Sedentary time, breaks in sedentary time and metabolic variables in people with newly diagnosed type 2 diabetes. *Diabetologia* **55**: 589–99

DIABETES CARE

HbA_{1c} no substitute for oral glucose test in pregnant women

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

1 The authors compared associations of maternal glucose and HbA_{1c} with adverse outcomes in the multinational Hyperglycemia and Adverse Pregnancy Outcome Study and aimed to determine if HbA_{1c} measurement can provide an alternative to an oral glucose tolerance test (OGTT) in pregnant women.

2 Eligible pregnant women underwent a 75-g OGTT at 24–32 weeks' gestation. A sample for HbA_{1c} was also collected. Neonatal anthropometrics and cord serum C-peptide were measured. Associations with outcomes were assessed using multiple logistic regression with adjustment for potential confounders.

3 Among 23316 participants, 21064 had a nonvariant HbA_{1c} result. Associations were significantly stronger with glucose measures than with HbA_{1c} for birth weight, sum of skinfolds, and body fat >90th percentile and for fasting and 1-hour glucose for cord C-peptide (all $P<0.01$). Odds ratios (ORs) for birth weight >90th percentile for each measure higher by 1 standard deviation were 1.39, 1.45 and 1.38, respectively, for fasting, 1-h and 2-h plasma glucose and 1.15 for HbA_{1c}. ORs for cord C-peptide >90th percentile were 1.56, 1.45 and 1.35 for glucose, respectively, and 1.32 for HbA_{1c}. ORs were similar for glucose and HbA_{1c} for primary caesarean section, pre-eclampsia, and preterm delivery.

4 On the basis of associations with adverse outcomes, the researchers concluded that HbA_{1c} measurement is not a useful alternative to OGTT in pregnant women.

Lowe LP, Metzger BE, Dyer AR et al (2012) Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations of maternal A1C and glucose with pregnancy outcomes. *Diabetes Care* **35**: 574–80

DIABETES CARE

No geographical gap in glycaemia and glucose relationship

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

1 Researchers analysed baseline HbA_{1c} and fasting plasma glucose (FPG) to determine the effect of oral antidiabetes drugs (OAD), and identify geographic and ethnic differences.

2 Analysis was performed of 12527 participants with dysglycaemia or early T2D recruited in from several countries and ethnic groups.

3 A strong relationship between FPG 5.6–9.0 mmol/L and the corresponding HbA_{1c} was seen across geographic regions and ethnic groups.

4 It was concluded that the strong relationship between HbA_{1c} and FPG in moderate dysglycemia is not significantly affected by ethnic or geographic differences. Use of an OAD alters the relationship and should be considered when interpreting HbA_{1c}.

Ramachandran A, Riddle MC, Kabali C et al (2012) Relationship between A1C and fasting plasma glucose in dysglycemia or type 2 diabetes: an analysis of baseline data from the ORIGIN trial. *Diabetes Care* **35**: 749–53

DIABETES RES CLIN PRACT

Global diabetes epidemic grows

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

1 In order to estimate global diabetes prevalence, researchers at the International Diabetes Federation (IDF) used data from 110 countries.

2 In 2011, there were 366 million people with diabetes worldwide, a figure expected to rise to 552 million by 2030.

3 Most people with diabetes live in low and middle-income countries, and these countries will also see the greatest increase in diabetes over the next 19 years.

4 The highest regional diabetes prevalence is in the Middle East and north Africa, followed by North America, the Caribbean, and the western Pacific. Africa is expected to have the largest proportional increase in the number of adults with diabetes by 2030.

5 The authors concluded that these data build on previous IDF estimates and show that the global diabetes burden continues to grow.

Whiting DR, Guariguata L, Weil C, Shaw J (2011) IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* **94**: 311–21

DIABETOLOGIA

Evidence against glargine–cancer link

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

1 The authors investigated whether the risk of cancer in insulin glargine users is higher than in human insulin users in people with T2D.

2 Exposure rates varied from 2273 and 614 person-years for incident exclusive users of insulin glargine or human insulin, respectively, to 3125 and 2341 person-years for all participants predominantly using insulin glargine or human insulin, respectively.

3 Cancer risk was higher among those exposed to insulin or sulphonylureas. Adjusted hazard ratios for death or cancer associated with insulin glargine compared with human insulin ranged from 0.58 (95% confidence interval [CI], 0.32–1.06) to 0.56 (95% CI, 0.36–0.87).

4 It was concluded that there was no excess risk of cancer in people with T2D on insulin glargine alone compared with those on human insulin alone.

Blin P, Lassalle R, Dureau-Pournin C et al (2012) Insulin glargine and risk of cancer: a cohort study in the French National Healthcare Insurance Database. *Diabetologia* **55**: 644–53

"In 2011, there were 366 million people with diabetes worldwide, a figure expected to rise to 552 million by 2030."