Diabesity Digest

Diabesity Digest summarises recent key papers published in the area of coexistent diabetes and obesity – diabesity. To compile the digest a PubMed search was performed for the 3 months ending September 2012 using a range of search terms relating to type 2 diabetes, obesity and diabesity. Articles have been chosen on the basis of their potential interest to healthcare professionals involved in the care of people with diabesity. The articles were rated according to readability, applicability to practice, and originality.

The withdrawal of sibutramine: What have we learned since SCOUT?

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Clinicians find their actions to be under the auspices of politicians or authorising bodies. Naturally, as they don't see patients, politicians and authorising bodies can sometimes be wrong, which I argue was the case with the withdrawal of sibutramine, a drug used successfully for a decade to reduce weight and improve global risk factors in obese and overweight individuals.

The Sibutramine Cardiovascular Outcomes Trial (SCOUT; James et al 2010) was a post-licensing obligation regarding cardiovascular safety. The study included high-risk patients – elderly, with cardiovascular disease and diabetes who were contraindicated from taking the drug in normal clinical practice – who stayed on the medication for up to five times longer than the licence would have permitted, regardless of whether they responded. In this case, the harm done was minor: a possible 16% increase in non-fatal cardiovascular events. The two papers discussed here (summarised following this commentary) examine data from SCOUT, and Caterson et al (2012) in particular demonstrate a remarkable conclusion.

Andersson et al (2012) address raised HbA_{1c} as a risk marker, and risk factor, advising that the "relationship between HbA_{1c} levels and outcomes may be more complex than previously recognised." This analysis found "a beneficial effect associated with decreasing HbA_{1c} levels on the all-cause mortality endpoint among those experiencing weight loss, but no effect associated with lowered HbA_{1c} levels among those not experiencing weight loss," subtley adding to our understanding of the complexities of BMI and HbA_{1c}. Caterson et al (2012) provide further post hoc analysis of SCOUT, looking at what outcomes would have been, had sibutramine been used in high-risk patients, but as per the guidelines as they existed for the general population. The study concluded that the outcome would have been a reduction in mortality: "Modest weight loss over the short-term (6 weeks) and longer-term (6 to 12 months) is associated with reduction in subsequent cardiovascular mortality for the following 4 to 5 years, even in those with pre-existing cardiovascular disease." This outcome has now become apparent long after the withdrawal of this agent. The paper compares the importance of the result with that of the UK Prospective Diabetes Study "legacy" effect: "Even the modest degree of weight loss achieved during the first 6 weeks of the SCOUT trial was associated with benefit irrespective of further drug therapy or weight change. This early weight loss of just over 2 kg reduced the incidence of cardiovascular events and mortality over the subsequent 5 years. A similar 'memory' effect has been shown in diabetes treatment and prevention trials. This provides strong confirmatory evidence that interventional weight loss has long term benefit." ■

James W et al (2010) Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med* **363**: 905–17

Diabetologia

Link between HbA_{1c} and CV adverse outcomes/mortality in high risk individuals with T2D in SCOUT

Readability	✓✓
Applicability to practice	✓✓
Originality	✓✓✓

1. This post hoc analysis of SCOUT studied the optimum HbA_{1c} concentration for the prevention of macrovascular complications and deaths in obese cardiovascular high-risk patients with T2D.
2. SCOUT was a randomised, double-blind, placebo-controlled, multicentre study that aimed to compare the effect of sibutramine and lifestyle modification with placebo and lifestyle modification on cardiovascular outcomes in overweight and obese cardiovascular high-risk patients.
3. In this post hoc analysis of SCOUT, hazard ratios for meeting the primary endpoint (non-fatal myocardial infarction, non-fatal stroke, resuscitated cardiac arrest or cardiovascular death) and all-cause mortality were analysed using Cox regression models.
4. Of 8252 patients with T2D included in SCOUT, 7479 had HbA_{1c} measurements available at baseline.
5. The analysis found a beneficial effect associated with decreasing HbA_{1c} levels on the all-cause mortality endpoint among those experiencing weight loss, but no effect associated with lowered HbA_{1c} levels among those not experiencing weight loss.
6. Increasing HbA_{1c} concentrations were associated with increasing risks of cardiovascular adverse outcomes and all-cause mortality in this study of overweight, cardiovascular high-risk subjects with T2D.

Andersson et al (2012). Relationship between HbA(1c) levels and risk of cardiovascular adverse outcomes and all-cause mortality in overweight and obese cardiovascular high-risk women and men with type 2 diabetes. *Diabetologia* **55**: 2348–55

Diabetes, Obesity and Metabolism

Maintained intentional weight loss and CV outcomes in SCOUT

Readability ✓✓✓
Applicability to practice ✓
Originality ✓✓✓

1. SCOUT demonstrated that sibutramine produced greater mean weight loss than placebo but that cardiovascular morbidity was increased.
2. This analysis explored the relationship between weight change during the first year of treatment and its effect on cardiovascular outcomes in the overall population and in the two randomised treatment groups (placebo and sibutramine).
3. During a 6-week lead in period prior to randomisation, subjects received a 10-mg sibutramine dose (plus weight management) prior to being randomised to receive either sibutramine or placebo. This was a safety measure to withdraw subjects with early increases in blood pressure and/or pulse.
4. Participants were overweight or obese, and aged ≥55 years with cardiovascular disease and/or T2D.
5. The primary endpoint was the time from randomisation to the first occurrence of non-fatal myocardial infarction, non-fatal stroke, resuscitated cardiac arrest or cardiovascular death.
6. Mean weight change during the 6-week lead-in period was –2.54 kg. At 12 months, this was –4.18 kg in the sibutramine group and –1.87 kg in the placebo group, meaning there was a total mean weight gain over the year in the placebo group.
7. Degree of weight loss during the lead-in period or to month 12 was associated with a progressive reduction in risk for the total population in primary outcome events and cardiovascular mortality over the 5-year assessment.
8. More adverse events occurred in the sibutramine group, although this appeared to be offset by the modest weight loss during lead-in.
9. Moderate weight loss (3–10 kg) reduced cardiovascular deaths in those with severe, moderate or mild cardiovascular disease.

Caterson ID et al (2012) Maintained intentional weight loss reduces cardiovascular outcomes: results from the Sibutramine Cardiovascular OUTcomes (SCOUT) trial. *Diabetes Obes Metab.* **14**: 523–30

New England Journal of Medicine

Bariatric surgery in the prevention of type 2 diabetes in obese people

Readability ✓✓✓
Applicability to practice ✓
Originality ✓✓✓

1. This study examined data from the ongoing SOS (Swedish Obese Subjects) study. Participants had been followed for up to 15 years at the time of analysis.
2. The effect of bariatric surgery versus usual care on T2D was examined.
3. Although some baseline characteristics varied between the two groups, bariatric surgery appeared markedly more effective than usual care in the prevention of T2D in obese individuals.

Carlsson et al (2012) Bariatric surgery and prevention of type 2 diabetes in Swedish Obese Subjects. *N Engl J Med* **367**: 695–704

Lancet

CV benefits and diabetes risks of statins in primary prevention

Readability ✓✓✓
Applicability to practice ✓✓
Originality ✓✓✓

1. This analysis of the JUPITER (Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study evaluated the balance of vascular benefits and diabetes hazard of statin use.
2. In JUPITER participants were randomised to receive rosuvastatin or placebo with a 5-year follow up.
3. Individuals receiving rosuvastatin with at least one major diabetes risk factor had an increased risk of diabetes but a reduction in the primary endpoint (myocardial infarction, stroke, hospitalisation for unstable angina, arterial revascularisation,or cardiovascular [CV] death); CV and mortality benefits of statins exceeded the diabetes hazard, including in those at high risk of developing diabetes.

Ridker (2012) Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet* **380**: 565–71

Diabetologia

Comparison of a low-carbohydrate diet and a low-fat diet in improving glycaemic control in individuals with type 2 diabetes

Readability ✓✓
Applicability to practice ✓✓✓
Originality ✓✓✓

1. The aim of the study was to compare the effects of a low-fat diet with the effects of a low-carbohydrate diet over a 2-year period.
2. This prospective, randomised, non-blinded parallel trial in Sweden involved 61 adults in primary care with T2D.
3. Primary outcome measures were weight and HbA_{1c}. Interventions were based on four 60-minute meetings during the first year. No meetings were held during the second year.
4. The mean body mass index and HbA_{1c} of the participants at baseline were 32.7 kg/m^2 and 57.0 mmol/mol (7.4 %), respectively. No patients were lost to follow-up.
5. Weight loss was highest at 6 months but did not differ between the two groups over the 2-year study period.
6. After 6 months, insulin doses in the low-carbohydrate group were reduced compared with the low-fat group (p=0.046).
7. At 6 months, high-density lipoprotein cholesterol had increased in the low- carbohydrate diet. Low-density-lipoprotein cholesterol did not differ between the groups.
8. In conclusion, when compliance was good, the findings supported the use of a low-carbohydrate diet as an alternative to a low-fat diet if the primary aim is to improve glycaemic control. Compliance was reduced after 6 months as judged by bodyweight and food records.

Guldbrand H et al (2012) In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. *Diabetologia*. **55**: 2118–27

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