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 November 2013 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 SCOUT study: A soap opera ...the story so far

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Findings from STORM were published in 2000 amongst widespread optimism that the number of effective weight-loss agents would be doubled, orlistat being the only competitor at the time. An odd study, STORM started all participants on the active drug sibutramine, and only those who lost adequate weight were randomised to continue sibutramine or change to placebo, giving, therefore, an indication of successful weight maintenance on medication. Successfully launched and popular, sibutramine induced significant weight loss and was beneficial in lowering HbA_{1c}. However, there was a licensing obligation with sibutramine to perform a cardiovascular outcomes study, because of an observed increase in blood pressure and pulse.

The SCOUT trial recruited those individuals naturally contraindicated to the drug – elderly high-risk participants, mostly with diabetes and cardiovascular disease (CVD) – and continued administering the drug for five times longer than the clinical licence allowed, even if no weight loss was observed. A possible 16% increase in non-fatal cardiovascular events was observed, and sibutramine was withdrawn on the grounds that any obese person could have latent CVD, a decision that displays astounding lack of scientific nous and common sense by the licensing authorities.

Not to lie down, a sub-analysis (Caterson et al, 2012) proved that, had the licence been followed, even in these high-risk individuals, those who lost weight and stayed on the drug would have benefitted from reduced mortality with an added legacy effect similar to UKPDS.

In this latest episode of the soap, another strange paper has been published, by Ali Ghotbi et al (summarised alongside): the team seem to be trying to suggest that the glucose-lowering ("antiglycaemic") agents used by people with diabetes in the study may have impacted on the adverse outcomes in the first publication. Even though the end result answers few questions conclusively, SCOUT is now listed among studies, such as VADT, ADVANCE, ACCORD, etc., that recruited a large number of people with diabetes, did something to them and reported results.

In the paper by Ali Ghotbi et al, the use of insulin monotherapy was considered, slightly disturbingly (in view of ACCORD), neutral in terms of CVD risk, sulphonylureas conferred an increased risk, and metformin a decreased risk. The consistent message is that diet alone or regimens including metformin induced significant reduction in CV events. Unfortunately, hypoglycaemia was not recorded, and an obvious assumption is that diabetes was less "severe" or of shorter duration in those for whom diet alone or metformin sufficed. However, an interesting finding is that CVD risk is lower with triple therapy of metformin, insulin and sulphonylureas than dual therapy with insulin and sulphonylureas, despite the fact that a person on triple therapy would be expected to be further along the disease pathway than someone on dual therapy. Another black eye for sulphonylureas; a feather in the cap for metformin. Sadly, sibutramine remains withdrawn. ■

Caterson ID, Finer N, Coutinho W et al (2012) Maintained intentional weight loss reduces cardiovascular outcomes. *Diabetes Obes Metab* **14**: 523–30

Diabetes Care

Hypoglycaemic agents on cardiovascular outcomes for people with T2D

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

1. A post-hoc, sub-study of the SCOUT trial, was carried out to assess the effect of hypoglycaemic agents on cardiovascular adverse events among overweight and obese people with T2D and at high-risk of cardiovascular disease (CVD).
2. In total, data from 8192 participants were used. They were grouped in terms of hypoglycaemic treatment at baseline of the SCOUT trial. These included: diet alone (n=1394); metformin monotherapy (n=1631); insulin monotherapy (n=1116); sulphonylurea monotherapy (n=1083); metformin plus sulphonylurea (n=1565) and metformin plus insulin (n=1000).
3. The primary end point was the first occurrence of non-fatal myocardial infarction, non-fatal stroke, resuscitation after cardiac arrest, or cardiovascular death. Models were used to assess the impact of the hypoglycaemic treatment at baseline on the primary end point and all-cause mortality.
4. A total of 905 people experienced a primary outcome event (POE) and 708 died. Metformin monotherapy and diet alone were associated with a lower risk of a POE compared to insulin monotherapy (hazard ratio [HR] 0.74; 95% confidence interval [CI], 0.57–0.95; P=0.02) and (HR 0.65; 95% CI, 0.48–0.87; P=0.004) respectively. When adjusted for other variables, metformin monotherapy was associated with reduced mortality compared to insulin monotherapy (adjusted HR 0.73; 95% CI, 0.54–1.00; P<0.005).

Ghotbi AA, Køber L, Finer N et al (2013) Association of hypoglycemic treatment regimens with cardiovascular outcomes in overweight and obese subjects with type 2 diabetes: a substudy of the SCOUT trial. *Diabetes Care* **36**: 3746–53

Metabolism

High fat versus high carbohydrate diets in obese subjects

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

1. Obese subjects (29–44.6 kg/m^2) were randomised to receive a hypocaloric high fat, low carbohydrate (HFLC) diet or a low fat, high carbohydrate (LFHC) diet for 12 weeks.
2. Both diets had an identical calorie deficit of 500 kcal, targeted to induce 0.5–1 lb (0.23–0.45 kg) weight loss per week.
3. As a percentage of daily calorie intake, the HFLC group consumed 33.5% protein, 56.0% fat and 9.6% carbohydrate. The LFHC diet consumed 22.0% protein, 25.0% fat and 55.7% carbohydrate.
4. Of the 55 participants who were randomised to each diet group, 40% withdrew and did not complete the intervention (11 withdrew from each group).
5. The change in percent body weight, lean and fat mass, blood pressure, hip:waist ratio, HbA_{1c}, fasting insulin and glucose, and glucose and insulin response to a 2 h oral glucose tolerance test did not differ (P>0.05) between diets after 12 weeks.
6. The HFLC group had greater mean decreases in serum triglyceride (P=0.07) and greater mean increases in HDL cholesterol (P=0.004). There was also reduced serum inflammation relative to the LFHC after 12 weeks.
7. The HFLC group had greater improvements in blood lipids and systemic inflammation, and were more likely to achieve the recommended 5–10% body weight loss.
8. This study may suggest that HFLC diets may be more beneficial to cardiovascular health and inflammation in obese adults compared with LFHC diets.

Ruth MR, Port AM, Shah M et al (2013) Consuming a hypocaloric high fat low carbohydrate diet for 12 weeks lowers C-reactive protein, and raises serum adiponectin and high density lipoprotein-cholesterol in obese subjects. *Metabolism* **62**: 1779–87

The Lancet

BMI mediators that affect coronary heart disease and stroke risk

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

1. The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration investigated the influence of BMI mediated through blood pressure (BP), cholesterol and glucose on coronary heart disease (CHD) and stroke.
2. Data from 97 prospective cohort studies were pooled, which included 1.8 million participants between 1948 and 2005. From this cohort, there were 57 161 CHD and 31 093 stroke events.
3. The authors estimated the hazard ratio (HR) of BMI on CHD and stroke with and without adjustments for all combinations of BP, cholesterol and glucose.
4. For each 5 kg/m^2 increase in BMI, the HR for CHD and stroke was 1.27 (95% confidence intervals [CI], 1.23–1.31) and 1.18 (95% CI, 1.14–1.22) respectively.
5. BP was the most important mediator, accounting for 31% of the excess risk of CHD and 65% of the excess risk of stroke.
6. The second most important mediator was glucose, adjustment for which lowered HRs to 1.23 (95% CI, 1.19–1.27) for CHD and 1.13 (95% CI, 1.09–1.18) for stroke.
7. The authors estimated that nearly half of the excess risk for CHD and three-quarters of the excess risk for stroke is due to high BMI mediated through BP, cholesterol and glucose. The remaining excess risk is due to other independent factors.

The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (2013) Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke. *Lancet* 21 Nov [Epub ahead of print]

Endocrine Practice

Adding liraglutide treatment for obese people with T1D

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

1. Using data collected from 27 obese people with T1D being treated with insulin and liraglutide, this retrospective study investigated the effect of liraglutide on plasma glucose concentrations, HbA_{1c}, blood pressure (BP) and weight.
2. Liraglutide doses started at 0.6 mg daily, and then increased to 1.2 mg and 1.8 mg in week 2 and 3 respectively. Clinical measures were taken prior and 180 ± 14 days after liraglutide treatment.
3. Mean glucose concentrations, HbA_{1c}, mean body weight, mean systolic BP and total and bolus insulin doses all significantly decreased by 6 months after treatment.

Kuhadiya ND, Malik R, Bellini NJ et al (2013) Liraglutide as additional treatment to insulin in obese patients with type 1 diabetes mellitus. *Endocr Pract* **19**: 963–7

Diabetes Obes Metab

"Obesity paradox" in people with newly diagnosed T2D: Weight and CVD risk

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

1. In a large retrospective study from the UK General Practice Research Database, the authors evaluated the cardiovascular disease (CVD) and mortality risk of normal weight, overweight and obese people recently diagnosed with T2D.
2. The population was split into two cohorts: those with and without prior CVDs (n=10 237 and n=37 272 respectively). Median follow-up was 5 years.
3. Adults with normal weight at diagnosis of T2D had significantly higher mortality risk compared to those who were obese, regardless of whether there was previous history of CVDs.

Thomas G, Khunti K, Curcin V et al (2013) Obesity paradox in people newly diagnosed with type 2 diabetes with and without prior cardiovascular disease. *Diabetes Obes Metab* 29 Oct [Epub ahead of print]

"Addition of liraglutide to insulin treatment improved glycaemic control among people with T1D."

Study acronyms

ACCORD: Action to Control Cardiovascular Risk in Diabetes
ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
SCOUT: Sibutramine Cardiovascular Outcomes
STORM: Sibutramine Trial of Obesity Reduction and Maintenance
UKPDS: United Kingdom Prospective Diabetes Study
VADT: Veterans Affairs Diabetes Trial