Sulphonylurea therapy and cardiovascular risk

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New glucose-lowering therapies are required to demonstrate that in pre-launch studies, there is no sign of increased cardiovascular disease (CVD) risk. There is also a requirement to demonstrate CVD safety by conducting a large prospective study with CVD end-points. Many of these CVD studies on glucose-lowering agents launched in the past 6 years are due to report in the next few years (2014–2016).

Glucose-lowering agents that have been available for many years have not been subjected to these regulations and therefore there is no definitive up-to-date research to determine the presence or extent of CVD risk from sulfonylurea (SU) therapy.

SUs interfere with a myocardial ATP-sensitive potassium channel, impairing the ability of myocardiocytes to adapt to ischaemia (Scognamiglio et al, 2002). In addition, hypoglycaemia, which is a common side effect of SU therapy, is associated with adverse CVD outcomes (Monami et al, summarised alongside). The approved package labels for SU therapies bear a warning for increased CVD risk (Phung et al, 2013, summarised alongside).Two recent meta-analyses looking at the possible CVD risks from SU therapy have recently been e-published ahead of print and are highlighted in this commentary.

The Monami paper reports on 115 selected randomised controlled trials (RCTs) of at least 24 weeks comparing SU with placebo or active comparator. Sixty-two trials recorded the outcome of major cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction, stroke, acute coronary syndromes and/or heart failure reported as serious adverse events. Only 30 of these trials reported at least one adverse event. They conclude that the use of SUs is associated with increased mortality, and higher risk of stroke, whereas the overall incidence of MACE appears to be unaffected. They also state that the results need to be interpreted with caution, mainly because of limitations in trial quality and under-reporting of CVD events and mortality. Their view is that the CVD safety of SUs cannot be considered as established unless it is evaluated in long-term CVD outcomes trials.

The Phung paper looks at 33 papers (covering 1 325 446 people) of both RCTs, observational and cohort studies of SU therapy, which measure CVD outcomes. They report that in all studies, compared with other oral glucose-lowering therapies, SU treatment was associated with a significantly increased risk of CVD death and composite CVD event. They conclude that SU use may elevate the risk of CVD. They state that their meta-analysis expands the pool of studies evaluating CVD mortality compared with prior observations while using adjusted estimates and assessing an additional outcome of a composite cardiovascular event. They feel that their results warrant consideration in clinical practice when other treatment options may be available.

Both of these papers suggest that the CVD safety of SUs cannot be considered as established. In my opinion, the place of SU therapy in glucose-lowering treatment will need to be re-assessed. It will be interesting to see what the updated NICE guideline on T2D says about the place of SU therapy when it is published in 2015.

Scognamiglio R, Avongaro A, Vigili D et al (2002) Effects of treatment with sulfonylurea drugs or insulin on ischaemia-induced myocardial dysfunction in type 2 diabetes. *Diabetes* **51**:808–812

DIABETES, OBESITY AND METABOLISM

SU therapy and mortality risk

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

1 The authors performed a meta-analysis examining outcomes of sulphonylurea (SU) treatment in T2D.

2 SUs were not significantly associated with an increase in major cardiovascular events (MACE) compared to other diabetes treatments (Mantel–Haenszel odds ratio [MH-OR] 1.08; 95% CI, 0.86–1.36; P=0.52). SU use was associated with a significant increase in mortality (MH-OR 1.22; 95% CI, 1.01–1.49; P=0.047) and stroke (MH-OR 1.28; 95% CI, 1.03–1.60; P=0.026).

3 The authors concluded that SU use is associated with a higher risk of stroke and mortality in people with T2D but the incidence of MACE is unaffected.

Monami M, Genovese S, Mannucci E (2013) Cardiovascular safety of sulfonylureas. *Diabetes Obes Metab* 17 Apr [Epub ahead of print]

DIABET MED

T2D: Does sulphonylurea therapy increase cardiovascular risk?

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

1 There is much debate over the possible association between sulphonylurea (SU) use and the risk of cardiovascular disease in people with T2D.

2 The authors conducted a systemic literature review and meta-analysis to investigate the relationship between SU treatment and cardiovascular outcomes in people with T2D.

3 Medline and CENTRAL were searched for clinical and observational studies throughout December 2011. A total of 33 studies with 1 325 446 participants were identified for inclusion into the study.

4 Compared to other oral diabetes treatments, SU use was found to be associated with an elevated risk of cardiovascular death (relative risk 1.27; 95% CI, 1.18–1.34, n=27 comparisons) and an increased risk of composite cardiovascular events such as myocardial infarction, stroke or cardiovascular-related hospitalisation (relative risk 1.10; 95% CI, 1.04–1.16, n=43 comparisons).

5 When compared to metformin, the relative risk for SU use and cardiovascular disease were 1.26 (95% CI, 1.17–1.35, n=17 comparisons) and 1.18 (95% CI, 1.13–1.24, n=16 comparisons).

6 The authors concluded that SU therapy was associated with an enhanced the risk of adverse cardiovascular outcomes in people with T2D, which may warrant careful consideration in clinical practice.

Phung OJ, Schwartzman E, Allen RW et al (2013) Sulphonylureas and risk of cardiovascular disease: Systematic review and meta-analysis. *Diabet Med* 11 May [Epub ahead of print]

DIABETOLOGIA

Variation in the global incidence of T2D in young people

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

1 Several studies have reported an increase in the prevalence of T2D in children and adolescents, which is associated with an elevated risk of morbidity and mortality in later life.

2 The authors systematically searched PubMed, the Cochrane Database of Systematic Reviews, Scopus, EMBASE and Web of Science to identify evidence of T2D incidence and prevalence in children and young people across multiple countries.

3 Thirty-seven population-based studies from 13 countries were identified for inclusion. Age, calendar time, geographical regions and ethnicity were all found to influence the prevalence of T2D in the study population. As a result, a range of 0–300 per 100 000 person-years was established for T2D incidence, and a range of 0–5300 was obtained for T2D prevalence.

4 Significant variation in response rates (60–96%) and ascertainment rates (53–99%) were observed. The authors found methodological differences in T2D detection, with population screening, diagnosis from healthcare provider and administrative database searches being the most commonly used. Guidelines and diagnostic tests also differed across the countries included in the study.

5 The authors concluded that the global incidence and prevalence of T2D in children and adolescents significantly varies between countries, age groups and ethnicities. The authors suggest that this variation can be explained by both methodological and population differences between studies.

Fazeli Farsani S, van der Aa MP, van der Vorst MM et al (2013) Global trends in the incidence and prevalence of type 2 diabetes in children and adolescents: a systematic review and evaluation of methodological approaches. *Diabetologia* **56**: 1471–88

LANCET

Vidagliptin in older people with T2D

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

1 The authors aimed to determine the feasibility of achieving individualised targets for glycaemic control in a cohort of older people aged ≥70 years with T2D (*n*=278).

2 Participants were randomised to receive vildagliptin (*n*=137) or a placebo (*n*=137) for 24 weeks as a part of this double-blind, multinational trial.

3 A total of 72 (52.6%) participants achieved their target when receiving vildagliptin (adjusted odds ratio 3.16; 96.2% CI, 1.81–5.52; *P*<0.0001) compared to 37 (27%) with placebo.

4 HbA_{1c} decreased from baseline 63 mmol/mol [7.9%]) by 9.8 mmol/mol (0.9%) in those that received vildagliptin. A difference of -6.5 mmol/mol (-0.6%) was observed between the groups.

5 The authors concluded that individualised glycaemic targets can be safely and effectively achieved in older people with the use of vildagliptin.

Strain WD, Lukashevich V, Kothny W et al (2013) Individualised treatment targets for elderly patients with type 2 diabetes using vildagliptin add-on or lone therapy (INTERVAL). *Lancet* 22 May [Epub ahead of print]

DIABET MED

Time from diagnosis to therapy initiation

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

1 The authors conducted a population-based study to investigate how the selection and timing of first-line pharmacotherapy has been influenced in older people with T2D, following changes to clinical guidelines which urge more timely treatment initiation.

2 Data from 64 368 Canadian participants revealed that first-line metformin therapy had increased from 20.1% to 79.9% between 1994–2006. Median time from diagnosis to therapy initiation increased from 1.8 years to 4.6 years and glibenclamide use had decreased from 71.1% to 9.8%.

3 The authors concluded that the time from diagnosis to therapy initiation has became longer despite guidelines promoting quicker therapy initiation.

Foster PD, Mamdani MM, Juurlink DN et al (2013) Trends in selection and timing of first-line pharmacotherapy in older patients with Type 2 diabetes diagnosed between 1994 and 2006. *Diabet Med* 16 Apr [Epub ahead of print]

DIABET MED

HbA_{1c} and the risk of hospitalisation in T2D

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

1 There is little evidence examining the relationship between HbA_{1c} and risk of hospitalisation in people with T2D.

2 The 2-year risk of all-cause hospitalisation was analysed in 4704 individuals from 18 general practices in Cambridgeshire.

3 A non-linear relationship was observed between HbA_{1c} and risk of all-cause, diabetes and vascular-related hospital admissions (*P*<0.001 for all) with a threshold HbA_{1c} value of 61 mmol/mol (95% CI, 55–66 mmol/mol [7.7%, 95% CI, 7.2–8.2%]). No significant associations were observed below the threshold.

4 Risk of all-cause hospital admission, diabetes and vascular-related admissions increased by 6.3%, 6.4% and 15.9% respectively, with every 11 mmol/mol (1%) increase in HbA_{1c} above the threshold value (*P*< 0.001).

5 The authors concluded that a non-linear correlation exists between the risk of hospitalisation and HbA_{1c} in people with T2D.

Yu D, Simmons D (2013) Relationship between HbA1c and risk of all-cause hospital admissions among people with Type 2 diabetes. *Diabet Med* 22 May [Epub ahead of print]

> *"The authors concluded that the time from diagnosis to therapy initiation has became longer despite guidelines promoting quicker therapy initiation."*