# Clinical reviews

Our panel of GPs review recent research papers in their specialist areas that may influence the way you practise

**Reviewers**

**Addiction**
**Dr Jez Thompson**
GPwSI Substance Misuse, Leeds

**Cardiovascular disease**
**Dr Peter Savill**
GP Watercress Medical, Medstead
GPwSI Cardiology, Southampton

**Diabetes**
**Dr Matthew Lockyer**
GP with an interest in diabetes, Suffolk

**Dr Peter Savill**
GP Watercress Medical, Medstead
GPwSI Cardiology, Southampton

**Mental health**
**Dr Phillip Bland**
Former GP with an interest in mental health, Dalton-in-Furness

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GP with an interest in respiratory disease, Wrexham and Associate GP Dean for North Wales

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**Dr Richard Ma**
GP with an interest in sexual health and NIHR Research Fellow, Imperial College, London

**Smoking cessation**
**Dr Jez Thompson**
GPwSI Substance Misuse, Leeds

**Urology**
**Dr Jonathan Rees**
GPwSI Urology, Bristol

## Diabetes

# Sulphonylureas and the risk of adverse cardiovascular outcomes

The use of sulphonylureas as a second-line substitution for metformin in type 2 diabetes is associated with increased rates of myocardial infarction (MI), all cause death and severe hypoglycaemia, a population-based cohort study has found.

The study used data from the UK Clinical Practice Research Datalink (CPRD) to analyse a cohort of type 2 diabetes patients retrospectively. The CPRD contains medical records from more than 14 million patients registered at more than 680 general practices.

From the population of type 2 patients available a base cohort was created from patients newly treated with metformin monotherapy between 1998 and 2013. Patients were followed up until the end of March 2014. The date of entry to the base cohort was the first prescription of metformin as monotherapy. Patients under 40 years of age, those with less than a year of medical history in the CPRD, women with any previous diagnosis of polycystic ovary disease, and any patient with previous use of hypoglycaemic drugs prior to entry to the cohort were excluded from the study.

The base cohort included 77,138 patients with a first prescription of metformin during the study period. Once a patient was prescribed sulphonylurea therapy as add on, or alternative, therapy they were matched with a control patient from the base cohort who was continuing on metformin monotherapy.

The participants resembled those commonly seen in clinical practice. Their average age was 64 years, 44% were women, and 53% had an $HbA_{1c}$ level > 8% (63.9 mmol/mol).

For the overall mortality data, patients where no close control match could be made were excluded.

A total of 25,699 patients added, or switched to, sulphonylureas during follow-up. During a mean follow-up of 1.1 years, the use of sulphonylureas compared with metformin was associated with an increased risk of:

- MI: hazard ratio (HR) 1.26 (95% CI: 1.01-1.56)
- All-cause mortality: HR 1.28 (95% CI: 1.15-1.44)
- Severe hypoglycaemia: HR 7.6 (95% CI: 4.64-12.44)

There were trends to increased cardiovascular death and ischaemic stroke. The effects were greater if sulphonylurea therapy was substituted as monotherapy rather than added as dual therapy.

The authors of an accompanying editorial in the *BMJ* comment:[1]

'It is hard to define clinical practice based on an observational study, as patients using different treatments may differ in ways that are unmeasured.

'This study, however, is well designed and the relations appear strong and consistent when examining several important macrovascular clinical outcomes. The results were also robust to sensitivity analyses, which varied the definitions of the patient's exposure and tested the sensitivity to unmeasured confounders.'

This study adds weight to the evidence that, although sulphonylureas reduce $HbA_{1c}$ this is a surrogate marker, and outcome studies suggest they are associated with increased rates of circulatory disease and premature death. They are known to cause significant hypoglycaemia, and this study confirms this. Despite these problems, they are still included in national guidance as second-line agents and remain widely prescribed.

The study authors conclude: 'Our study showed an increased risk of MI, all cause mortality, and severe hypoglycaemia associated with the use of second-line sulphonylureas compared with remaining on metformin monotherapy

'The associations with MI and all cause mortality were driven by the switching to sulphonylureas and not the addition of sulphonylureas. Thus, in line with current recommendations on the treatment of type 2 diabetes, continuing metformin when introducing sulphonylureas is safer than switching.'

**DR MATTHEW LOCKYER**

**Douros A, Dell'Aniello S, Yu OHY et al. Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study. *BMJ* 2018;362:k2693**

**REFERENCE**

**1** D'Agostino McGowan L, Roumie CL. Sulfonylureas as second line treatment for type 2 diabetes. *BMJ* 2018;362:k3041

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