

Switching to certain antidiabetic drugs linked to increased risk of major complications

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For people with type 2 diabetes, switching to sulfonylurea drugs to control blood sugar levels is associated with an increased risk of complications compared with staying on the drug metformin, finds a

study in *The BMJ* today.

As such, the researchers say that continuing metformin when introducing sulfonylureas is safer than switching.

Metformin is a "first-line" therapy (the first drug that will be tried) for patients with type 2 diabetes. But sulfonylureas are the most commonly prescribed "second line" treatment, and often used in combination with metformin.

The safety of sulfonylureas has been studied extensively. However, little is known about the specific risk of adding or switching to sulfonylureas compared with staying on metformin treatment alone.

So a research team, led by Professor Samy Suissa at McGill University in Canada, set out to assess whether adding or switching to sulfonylureas is associated with an increased risk of serious complications, compared with remaining on metformin alone in patients with type 2 diabetes.

They analysed data from the UK Clinical Practice Research Datalink for over 77,000 patients (average age 64 years) with type 2 diabetes who started metformin treatment between 1998 and 2013.

Patients who subsequently added or switched to a sulfonylurea were identified and matched to a similar patient who continued metformin alone.

Hospital records were then used to monitor admissions for [heart attack](#) (myocardial infarction) and ischaemic stroke, [cardiovascular death](#), death from any cause ("all cause mortality"), and dangerously low [blood sugar levels](#) (severe hypoglycemia).

During an average follow-up period of just over a year, sulfonylurea use

(switching and adding combined) was associated with an increased risk of heart attack (7.8 v 6.2 per 1000 person years), all cause mortality (27.3 v 21.5), and severe hypoglycaemia (5.5 v 0.7), compared with continuing metformin alone.

There was also a trend towards increased risks of ischaemic stroke (6.7 v 5.5 per 1000 person years) and cardiovascular death (9.4 v 8.1) with sulfonylurea use.

Compared with adding sulfonylureas to metformin treatment, switching to sulfonylureas was associated with a greater risk of heart attack and all cause mortality, but no differences were found for ischaemic stroke, cardiovascular death, or severe hypoglycaemia.

Findings remained similar after further analyses to test the strength of the results.

This is an observational study, so cannot establish cause and effect, and the researchers say they cannot rule out the possibility that some of the observed risk may be due to other unmeasured (confounding) factors. Nevertheless, they say their results are highly generalisable and the large sample size allowed the calculation of precise estimates.

As such, they conclude that sulfonylureas as second line drugs "are associated with an increased risk of myocardial infarction, all cause mortality, and severe hypoglycaemia, compared with remaining on metformin monotherapy."

Importantly, the associations with [myocardial infarction](#) and all cause mortality "were driven by switching to sulfonylureas and not the addition of sulfonylureas," they add. "Thus, in line with current recommendations on the treatment of type 2 diabetes, continuing [metformin](#) when introducing sulfonylureas is safer than switching."

In a linked editorial, US researchers Lucy D'Agostino McGowan and Christianne Roumie, say this new evidence helps to individualise [treatment](#) decisions and minimise harm.

They point out that it is hard to define [clinical practice](#) based on an observational study, as [patients](#) using different therapies may differ in ways that are unmeasured. However, they say this study "is well designed and the relationships appear strong and consistent."

More information: Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study, The *BMJ*, www.bmj.com/content/362/bmj.k2693

Editorial: Sulfonylureas as second line treatment for type 2 diabetes, The *BMJ*, www.bmj.com/content/362/bmj.k3041

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