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Review

# Impact of glucose-lowering therapies on risk of stroke in type 2 diabetes

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ABSTRACT

Patients with type 2 diabetes (T2D) have an increased risk of stroke compared with people without diabetes. However, the effects of glucose-lowering drugs on risk of ischaemic stroke in T2D have been less extensively investigated than in coronary heart disease. Some evidence, including the UKPDS, has suggested a reduced risk of stroke with metformin, although the number of studies is limited. Inhibition of the $K_{ATP}$ channels increases ischaemic brain lesions in animals. This is in agreement with a recent meta-analysis showing an increased risk of stroke with sulphonylureas *vs.* various comparators as both mono- and combination therapy. Pioglitazone can prevent recurrence of stroke in patients with previous stroke, as already shown in PROactive, although results are less clear for first strokes. As for DPP-4 inhibitors, there was a non-significant trend towards benefit for stroke, whereas a possible increased risk of stroke with SGLT2 inhibitors—and in particular, empagliflozin in the EMPA-REG OUTCOME trial—has been suggested and requires clarification. Experimental results support a potential protective effect of GLP-1 receptor agonists against stroke that has, at least in part, been translated to clinical benefits in T2D patients in the LEADER and SUSTAIN-6 trials. Further interventional studies are now warranted to confirm the effects of glucose-lowering agents on risk of stroke in patients with T2D. In summary, the effects of antidiabetic drugs on risk of stroke appear to be heterogeneous, with some therapies (pioglitazone, GLP-1 receptor agonists) conferring possible protection against ischaemic stroke, other classes showing a neutral impact (DPP-4 inhibitors, insulin) and some glucose-lowering agents being associated with an increased risk of stroke (sulphonylureas, possibly SGLT2 inhibitors, high-dose insulin in the presence of insulin resistance).



## Introduction

Patients with type 2 diabetes (T2D) have an increased risk of stroke compared with people without diabetes. In the Swedish National Patient Register, patients with T2D had a 1.5-fold greater risk of stroke compared with the general population [1]. Furthermore, epidemiological studies have shown that diabetes is associated with greater stroke morbidity and lethality [2].

In recent large, prospective, cardiovascular randomized controlled trials (RCTs) such as the Outcome Reduction with Initial Glargine Intervention (ORIGIN) study, the incidence of any stroke during follow-up was similar to those of any myocardial infarction (MI) [3]. Considering the marked increase in incidence of strokes in the diabetic population and heavy burden of this complication, it is of major interest to better investigate the potential impact of each pharmacological glucose-lowering class on incidence of stroke, especially given the controversy over the effects of antidiabetic agents on cardiovascular complications [4]. The relationship between glycaemic control and risk of stroke remains unclear in T2D. Intensive glycaemic control was not associated with any significant reduction in risk of stroke, as summarized in a meta-analysis of all interventional trials comparing the effects of more- and less-intensive glucose control on risk of major cardiovascular events in patients with T2D [5]. Furthermore, the relationship between hypoglycaemia and risk of stroke has not been clearly established. In a nationwide Taiwanese cohort, hypoglycaemia was

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associated with a two-fold increased risk of hospitalization for stroke [6], which suggests that glucose-lowering drugs that induce hypoglycaemia might be increasing the risk of stroke in T2D.

The purpose of the present comprehensive review is therefore to summarize findings on the effects of antidiabetic therapies on the risk of stroke in T2D. It should be mentioned that, in most of the studies cited here, no distinction was made between risk of ischaemic and haemorrhagic stroke with any glucose-lowering drug.

## Metformin

Although some studies have shown its protective effects against cardiovascular risk and related mortality, the evidence for metformin in stroke prevention remains limited and sometimes conflicting [7].

### *Experimental setting*

In experimental studies, metformin, an activator of AMP-activated protein kinase (AMPK), has been shown to exert direct vascular effects by increasing vascular endothelial growth factor (VEGF) expression and improving microvascular density.

The benefits conferred by metformin on cerebral microcirculation appear to be independent of its glucose-lowering effects [8]. Some authors have suggested that metformin administered in the period after stroke attenuates stroke-induced oxidative stress and restores angiogenic signalling in the brains of diabetic rats [9].

### *Clinical studies*

The results of prospective interventional studies of the effects of metformin on the incidence of stroke are sparse. In the UK Prospective Diabetes Study (UKPDS), metformin therapy was associated with a reduced risk of stroke compared with conventional lifestyle therapies (–44%, $P = 0.03$; Table 1) and other intensive treatments (chlorpropamide, glibenclamide, insulin; $P = 0.032$) in a small number of overweight T2D patients [10]. A trend towards fewer stroke events was also reported in patients treated with metformin in the relatively short (1-year) Comparative Outcomes Study of Metformin Intervention Versus Conventional Approach (COSMIC) [11]. However, in A Diabetes Outcome Progression Trial (ADOPT), there was no difference in stroke incidence between metformin, rosiglitazone or glyburide treatment over 5 years [12].

In a meta-analysis of four trials involving more than 10,000 T2D patients, the secondary outcome of 'all strokes' was not significantly reduced by metformin treatment (–24%, $P = 0.18$; Table 1), as was the case for other cardiovascular outcomes [7].

In a retrospective 5-year follow-up observational cohort study of 11,293 Chinese T2D patients, metformin monotherapy together with lifestyle recommendations was associated with a 25% reduction in risk of stroke compared with lifestyle modifications alone in a multivariable Cox proportional-hazards regression model, after adjusting for potential confounders [13]. A recent study based on a large Taiwanese database showed that diabetes patients taking metformin had a reduced risk of incident stroke, which persisted even after adjusting for age, gender, hypertension, atrial fibrillation, hyperlipidaemia, coronary artery disease and medications, including antiplatelet, coumadin and statin therapies (Table 1) [14]. A secondary stratified analysis revealed that metformin was more protective in patients at higher risk of stroke. A population-based case control study using an integrated healthcare delivery system in the US state of Washington also showed that current use of metformin, compared with never use, was associated with a significantly lower risk of stroke in T2D patients using long-acting insulin (Table 1) [15].

One observational study evaluating the effects of metformin on stroke severity and outcomes in T2D patients with acute ischaemic stroke showed that those already treated with metformin prior to stroke onset had a reduced neurological severity compared with those who had not taken metformin [16]. In that study, metformin pretreatment was independently associated with mild neurological symptoms after adjusting for confounding factors. In contrast, there was no benefit with metformin on functional outcomes [16]. In a recent meta-analysis, the incidence of dementia tended to be reduced with metformin [relative risk (RR): 0.79, 95% confidence interval (CI): 0.62–1.01; $P = 0.064$] [17].

As a whole, these findings support not only a possible protective effect of metformin on stroke incidence, but also on neurological outcomes after the stroke period. However, the level of clinical evidence is limited, and further prospective interventional trials are welcome to definitively prove its beneficial impact on brain ischaemia and secondary neurological deficits.

## Sulphonylureas (SUs)

These agents bind to SU receptor (SUR1) subunits, which inhibit $K_{ATP}$ channels and, therefore, stimulate insulin secretion by β cells. $K_{ATP}$ channels are expressed in cardiac myocytes and neuronal cells especially in the hippocampus and cortex [18].

### *Experimental setting*

Findings from animal models *in vitro* and *in vivo* support the notion that inhibition of $K_{ATP}$ channels increases ischaemic brain lesions and that, in contrast, activation of $K_{ATP}$ channels confers neuroprotection during cerebral ischaemia [19]. Activation of $K_{ATP}$ channels has been suggested to exert a brain-protective role during ischaemia. Focal ischaemia leads to more severe neurological defects in Kir6.2 knockout mice [19], and inhibition of the $K_{ATP}$ channels by SU increased the size of the induced infarct.

### *Clinical studies*

In the UKPDS intensive arm of newly diagnosed T2D patients treated with SUs, no difference in stroke incidence was observed with chlorpropamide, although a trend towards higher risk was noted with glibenclamide compared with conventional dietary therapy (+38%, $P = 0.12$; Table 1) [20].

In a meta-analysis published in 2013, pooling the studies reporting on stroke found no statistically significant associations with SU use in stroke, and no differences between RCTs and observational studies (Table 1) [21]. However, a more recent comprehensive meta-analysis of 17 studies, involving a total of 27,705 patients, showed that patients treated with SUs had a higher risk of stroke than those receiving comparator drugs [22]. This increased risk of stroke was consistently noted whether SU was used as monotherapy or in combination (Table 1) [22]. Furthermore, an increased risk of stroke was observed in prospective randomized studies, where the impact of confounding factors is more limited, while direct comparisons revealed an increased risk of stroke with SU *vs.* diet alone, metformin, dipeptidyl peptidase (DPP)-4 inhibitors and insulin [22]. These findings were confirmed by another Bayesian meta-analysis showing an association between SU therapy and higher risk of major cardiovascular disease-related events, including strokes, compared with other glucose-lowering drugs (Table 1) [23]. Thus, these two meta-analyses support the notion that SU therapy can enhance risk of stroke in T2D and therefore suggest avoiding this

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