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MINIREVIEWS

# Effects of glucose-lowering agents on ischemic stroke

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## Abstract

Diabetes mellitus (DM) is a major risk factor for cardiovascular events, including ischemic stroke. Moreover, ischemic stroke appears to be more severe in these patients and to be associated with less favorable outcomes. However, strict glycemic control does not appear to reduce the risk of ischemic stroke. On the other hand, newer glucose-lowering agents (glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter 2 inhibitors) reduced the risk of cardiovascular events in recent randomized, placebo-controlled trials. Semaglutide also reduced the risk of ischemic stroke. These benefits are independent of glucose lowering and might be due to the favorable effects of these agents on body weight and blood pressure. Pioglitazone also reduced the risk of recurrent stroke in patients with insulin resistance or type 2 DM but the unfavorable safety profile limits its use. In contrast, sulfonylureas and dipeptidyl peptidase 4 inhibitors have a neutral effect on cardiovascular morbidity and might be less attractive options in this high-risk population.

**Key words:** Antidiabetic treatment; Ischemic stroke; Cardiovascular events; Glucose regulation; Neuroprotection



**Core tip:** Diabetes mellitus is a major risk factor for ischemic stroke. However, strict glycemic control does not appear to reduce the risk of ischemic stroke. On the other hand, glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter 2 inhibitors reduce the risk of cardiovascular events. These benefits are independent of glucose lowering and might be due to favorable effects on weight and blood pressure. Pioglitazone also reduced the risk of recurrent stroke but the unfavorable safety profile limits its use. Finally, sulfonylureas and dipeptidyl-peptidase-4 inhibitors have neutral effects on cardiovascular morbidity and might be less attractive options.

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## INTRODUCTION

Diabetes mellitus (DM) is a major risk factor for cardiovascular events, including ischemic stroke[1,2]. Even pre-diabetes, defined as impaired glucose tolerance or impaired fasting glucose, is associated with increased risk for ischemic stroke[3]. In a case-control study in 32 countries[4], DM accounted for approximately 16% of the population attributable risk for ischemic stroke. Interestingly, among patients with DM, women have higher risk for stroke than men[5].

Type 2 diabetes mellitus (T2DM) is usually initially managed with metformin monotherapy and, if not controlled adequately, a variety of other glucose-lowering agents can be added[6,7]. In the present review, we summarize the existing evidence on the effects of antidiabetic agents on the incidence of ischemic stroke.

## EFFECTS OF AGGRESSIVE GLUCOSE LOWERING ON THE RISK OF STROKE

In the United Kingdom Prospective Diabetes Study (UKPDS), metformin reduced the risk of DM-related and all cause mortality in overweight patients with newly diagnosed T2DM[8]. In contrast, in the same study, treatment with sulphonylureas or insulin had no effect on cardiovascular morbidity[9]. Moreover, in patients with long-standing T2DM, 2 large randomized controlled trials (RCT), the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial and the Veterans Affairs Diabetes Trial, showed that more *vs* less aggressive glycemic control had no effect on the incidence of cardiovascular events, including nonfatal stroke[10,11]. Moreover, in the Action to Control Cardiovascular Risk in Diabetes trial ($n$ = 10251 patients with T2DM and established cardiovascular disease (CVD) or additional cardiovascular risk factors)[12], intensive glucose lowering reduced the risk of myocardial infarction (MI) by 20% compared with conventional treatment (95%CI: 0.67-0.96; $P$ = 0.015) but all-cause mortality was higher in the former group by 22% (95%CI: 1.01-1.46; $P$ = 0.04) and the incidence of the primary endpoint, including the risk of ischemic stroke, did not differ between the 2 groups. In contrast, multifactorial treatment, *i.e.*, management of blood pressure and dyslipidemia in addition to glucose lowering, reduced cardiovascular morbidity and mortality in patients with long-standing T2DM in the Steno-2 study[13]. However, another study showed that multifactorial treatment may not lower the incidence of cardiovascular events in patients with newly diagnosed T2DM[14].

A meta-analysis of 28 trials ($n$ = 34912 patients with T2DM) showed that intensive *vs* conventional glycemic control reduces the risk of non-fatal MI by 13% (95%CI: 0.77-0.98; $P$ = 0.02) but has no effect on non-fatal stroke[15]. Another meta-analysis of 5 RCTs ($n$ = 33040 patients with T2DM) showed that intensive glucose lowering resulted in a 17% reduction in non-fatal MI (95%CI: 0.75-0.93) but did not affect the incidence of stroke[16]. Therefore, aggressive glucose lowering treatment does not appear to affect the risk of ischemic stroke.

## GLUCOSE-LOWERING AGENTS: EFFICACY AND SAFETY

### *Metformin*

Metformin lowers $HBA_{1c}$ levels by approximately 1.0%-1.5% and is generally well-tolerated[6,7]. The most frequent side effects are from the gastrointestinal system whereas the most severe adverse event, lactic acidosis, is extremely rare[6]. Interestingly, metformin reduced the risk of new-onset T2DM in obese patients[17] (Table 1).

### *Sulfonylureas*

Sulfonylureas are also potent glucose-lowering agents and are inexpensive but have low rates of adherence[18] and carry substantial risks of hypoglycemia[6,19] and weight gain[6]. In addition, when added to metformin, glimepiride was less effective than exenatide and liraglutide[19,20].

### *Thiazolidinediones*

Thiazolidinediones have similar potency with metformin and sulfonylureas[6]. In obese patients with prediabetes, rosiglitazone reduced the incidence of T2DM[21,22]. However, the safety profile of these agents is suboptimal. Rosiglitazone appears to increase the risk of MI[23-25], although in a reevaluation of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes trial, the risk for first fatal and nonfatal MI was similar during treatment with rosiglitazone and sulfonylurea/metformin [hazard ratio (HR) = 1.13, 95%CI: 0.80-1.59][26]. Both rosiglitazone and pioglitazone are also associated with weight gain, edema, heart failure, bone fractures and urinary bladder cancer[27-31], although another systematic review showed no difference in side effects between pioglitazone and placebo[32].

### *Dipeptidyl peptidase 4 inhibitors*

Dipeptidyl peptidase 4 (DPP-4) inhibitors have moderate glucose-lowering efficacy and relatively high cost but do not increase the risk for hypoglycemia and do not affect weight[6]. In RCTs and in meta-analyses, sitagliptin, vildagliptin and alogliptin had a neutral effect on cardiovascular events[33-36]. In contrast, saxagliptin increased the risk of hospitalization for heart failure but did not affect the incidence of other cardiovascular events[37-39]. Saxagliptin was also evaluated in elderly

**Table 1 Effects of antidiabetic agents on glucose levels, other cardiovascular risk factors and ischemic stroke**

| Agent | Glucose-lowering efficacy | Other favorable effects | Effect on ischemic stroke |
|---|---|---|---|
| Metformin | High | Weight loss | Decrease |
| Sulfonylureas | High | (-) | No effect |
| Thiazolidinediones | High | Reduction in | Might reduce |
| Pioglitazone | | triglyceride levels | the risk of recurrent stroke |
| DPP-4 inhibitors | Moderate | None | No effect |
| (1) Alogliptin, saxagliptin, sitagliptin | | | Reduction (?) |
| (2) Linagliptin | | | |
| GLP-1 agonists | High | Weight loss and blood pressure reduction | No effect |
| (1) Liraglutide, lixisenatide | | | Reduction |
| (2) Semaglutide | | | |
| SGLT-2 inhibitors | Moderate | Weight loss and blood pressure reduction | No effect |
| Empagliflozin | | | |

DPP: Dipeptidyl peptidase; GLP: Glucagon-like peptide; SGLT: Sodium-glucose cotransporter.

patients and was found to have similar safety compared with younger patients[37]. Similar findings were reported for linagliptin[40]. Trelagliptin, a once-weekly DPP-4 inhibitor, was shown to have similar efficacy with daily alogliptin in Japanese patients with T2DM[41]. SYR-472, another once-weekly DPP-4 inhibitor, also appeared to be safe and effective in a phase 2 trial[42].

### *Glucagon-like peptide 1 receptor agonists*

Glucagon-like peptide 1 (GLP-1) receptor agonists are potent glucose-lowering agents, reduce body weight and blood pressure but are expensive and have frequent gastrointestinal side effects[6]. In patients inadequately controlled with metformin monotherapy, adding liraglutide was more effective than adding sitagliptin[43]. More recently, once-weekly preparations of GLP-1 receptor agonists have been developed. Once-weekly exenatide lowered $HbA_{1c}$ levels more than twice-daily exenatide[44] and more than pioglitazone or sitagliptin[45]. However, once-weekly exenatide was less effective than liraglutide[46]. Liraglutide was also more potent than once-weekly albiglutide[47]. On the other hand, once-weekly dulaglutide had similar efficacy with liraglutide[48]. Interestingly, treatment with semaglutide increased the risk of retinopathy (HR = 1.76, 95%CI: 1.11-2.78; $P$ = 0.02)[49].

### *Sodium-glucose cotransporter 2 inhibitors*

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are a relatively new class of glucose-lowering agents with moderate glucose lowering efficacy[6,7]. They appear to be as effective as sulfonylureas but do not increase the risk of hypoglycemia and induce weight loss and reduce blood pressure[50-53]. However, they are associated with genitourinary infections and diabetic ketoacidosis[50-54]. In a recent RCT, empagliflozin delayed the progression of chronic kidney disease[53]. Empaglifozin also reduced the risk of heart failure[54] and cardiovascular mortality[55].

### *α-glucosidase inhibitors*

α-glucosidase inhibitors are rarely used in the management of patients with T2DM due to moderate efficacy and poor tolerability because of gastrointestinal side effects[6]. On the other hand, voglibose reduced the incidence of T2DM in Japanese patients with impaired glucose tolerance[56].

### *Insulin*

Insulin is the most potent glucose-lowering agent[6]. However, its high cost, risk of hypoglycemia and weight gain represent substantial barriers to its use[57,58].

## EFFECTS OF GLUCOSE-LOWERING AGENTS ON ISCHEMIC STROKE

### *Metformin*

In UKPDS, administration of metformin to overweight patients with newly diagnosed T2DM reduced the risk of ischemic stroke more than treatment with sulfonylureas (chlorpropamide or glibenclamide) or insulin ($P$ = 0.032)[8].

### *Sulfonylureas*

In the UKPDS, treatment with chlorpropamide or glibenclamide had no effect on the risk of ischemic stroke. Of note, the relative risk (RR) for non-fatal and fatal stroke in patients who received these agents *vs* conventional treatment was 1.07 (95%CI: 0.68-1.69) and 1.17 (95%CI: 0.54-2.54), respectively, indicating a negative trend for the effects of sulfonylureas[9]. More recently, in a small, multicenter, randomized, double-blind study in 304 Chinese patients with T2DM and established coronary heart disease, metformin reduced the combined endpoint (nonfatal MI, nonfatal stroke, revascularization, cardiovascular and all-cause death) more than glipizide after a median follow-up of 5 years (HR = 0.54, 95%CI: 0.30-0.90; $P$ = 0.026)[59]. Moreover, glimepiride had a less favorable effect than pioglitazone on carotid intima media thickness[60], a marker of subclinical atherosclerosis and a risk factor for ischemic stroke[60]. A systematic review which compared the impact of sulfonylureas on mortality[61], showed that gliclazide and glimepiride were associated with lower rates of cardiovascular and all cause mortality than other members of the class.

### *Insulin*

In the UKPDS, treatment with insulin had no effect on the risk of ischemic stroke[9]. There is no other RCT that evaluated the effects of insulin on the risk of ischemic stroke in patients with T2DM.

### *Thiazolidinediones*

In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE), 5238 patients with T2DM and established CVD were assigned to receive pioglitazone or placebo for 34.5 mo[62]. The incidence of the primary endpoint (all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle) did not differ between the 2 groups but the rates of the main secondary endpoint (all-cause mortality, non-fatal MI, stroke) were 16% lower in the pioglitazone arm (95%CI: 0.72-0.98; *P* = 0.027)[62]. Pioglitazone did not reduce the risk of ischemic stroke in the total study population[62] but reduced the risk of recurrent stroke by 47% in the small subgroup of patients (*n* = 984) with a history of ischemic stroke or transient ischemic attack (TIA)[63].

Recently, pioglitazone was also shown to lower the risk of cardiovascular events in patients with insulin resistance and a history of ischemic stroke or TIA. In the Insulin Resistance Intervention after Stroke (IRIS) trial, 3876 patients were randomized to receive pioglitazone or placebo. After a mean follow-up of 4.8 years, the primary outcome (stroke or MI) occurred in 9.0% of patients in the pioglitazone group and in 11.8% of patients in the placebo group (HR = 0.76, 95%CI: 0.62-0.93; *P* = 0.007)[31]. However, the risk of ischemic stroke did not differ between the 2 groups[31].

In a meta-analysis of 19 trials (*n* = 16390), death, MI or stroke occurred in 4.4% of patients receiving pioglitazone and 5.7% receiving control therapy (HR 0.82, 95%CI: 0.72-0.94; *P* = 0.005). Individual components of the primary end point, including stroke, were all reduced to a similar magnitude with pioglitazone treatment, with HRs ranging from 0.80 to 0.92[29]. In another metanalysis of 3 studies in patients with a history of stroke or TIA, pioglitazone reduced the risk of recurrent stroke by 48% (95%CI: 0.34-0.80)[32].

Aleglitazar is a dual agonist of peroxisome proliferator-activated receptors with insulin-sensitizing and glucose-lowering actions and favorable effects on the lipid profile but showed no effect on cardiovascular morbidity in patients with T2DM and a recent acute coronary syndrome and also increased the risk for gastrointestinal hemorrhage and renal dysfunction[64].

### *DPP-4 inhibitors*

In 3 recently published RCTs, the Examination of Cardiovascular Outcomes with Alogliptin *vs* Standard of Care (EXAMINE) study, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus - Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) trial and the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), alogliptin, saxagliptin and sitagliptin had no effect on the incidence of ischemic stroke compared with placebo in patients with T2DM and established CVD or additional cardiovascular risk factors[33,35,38]. Moreover, the difference in $HbA_{1c}$ between patients treated with DPP-4 inhibitors and the placebo group were very small (0.20-0.36)[33,35,38]. Another DPP-4 inhibitor, linagliptin, reduced the incidence of cardiovascular events compared with glimepiride in a RCT. This result was mainly attributed to a lower number of non-fatal strokes in patients treated with linagliptin compared with those who received glimepiride (RR = 0.27, 95%CI: 0.08-0.97; *P* = 0.0315)[65]. Of note, a study in mice showed that linagliptin-mediated neuroprotection is glucose-independent and likely involves GLP-1 activation[66].

### *GLP-1 receptor agonists*

In the recently published Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, 9340 patients with T2DM and established CVD, chronic heart failure, chronic kidney disease or additional cardiovascular risk factors were randomized to receive liraglutide or placebo. After a median follow-up of 3.8 years, liraglutide reduced the incidence of the primary composite outcome (death from cardiovascular causes, nonfatal MI or stroke) by 13% compared with placebo (95%CI: 0.78-0.97)[67]. However, the risk of ischemic stroke did not differ between the 2 groups[67]. In another recent study, the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with type 2 diabetes (SUSTAIN-6), 3297 patients with similar characteristics with the LEADER trial were randomized to receive the once-weekly GLP-1 receptor agonist semaglutide or placebo for 104 wk[49]. Semaglutide reduced the risk of the primary endpoint (death from cardiovascular causes, nonfatal MI or stroke) by 26% compared with placebo (95%CI: 0.58-0.95)[49]. In addition, the risk of ischemic stroke was decreased by 39% in patients who received semaglutide (95%CI: 0.38-0.99; *P* = 0.04)[49]. Notably, in both the LEADER and SUSTAIN-6 trials, the difference in $HbA_{1c}$ levels between the GLP-1 and placebo groups was small and the reduction in cardiovascular event rates appeared to be mostly due to the reduction in body weight and blood pressure in the former group[49,67]. In contrast, another daily GLP-1 receptor agonist, lixisenatide, had no effect on cardiovascular morbidity, including ischemic stroke, in another recent placebo-controlled, randomized trial, the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial (*n* = 6068 patients with T2DM and a recent acute coronary syndrome)[68]. It is unclear whether this negative effect was due to the different study population (*i.e.*, patients with acute coronary syndrome in ELIXA *vs* patients with stable CVD in LEADER and SUSTAIN-6) or whether it suggests that lixisenatide is less effective than liraglutide and semaglutide in preventing cardiovascular events. In a meta-analysis of 9 trials (*n* = 5107), albiglutide also had no effect on cardiovascular events compared with placebo or active treatment (glimepiride, insulin glargine, insulin lispro, liraglutide, pioglitazone, or

sitagliptin) but very few events occurred ($n$ = 116)[69].

### *SGLT-2 inhibitors*

In the recently published *EMPA-REG* OUTCOME trial, 7020 patients with T2DM were randomly assigned to receive 10 mg or 25 mg of empagliflozin or placebo[55]. After a median follow-up period of 3.1 years, the primary composite outcome (death from cardiovascular causes, nonfatal MI, nonfatal stroke) occurred in 10.5% in the pooled empagliflozin group and in 12.1% in the placebo group (HR = 0.86, 95%CI: 0.74-0.99; $P$ = 0.04)[55]. However, rates of ischemic stroke were numerically higher in patients treated with empagliflozin, although TIAs were numerically lower and fatal and recurrent strokes were not increased[55]. Similar to the studies with GLP-1 receptor agonists, the difference in $HbA_{1c}$ levels between empagliflozin and placebo was small, especially after 94 wk (0.24%-0.36%). On the contrary, reductions during first 12 wk were greater (0.54%-0.60%). The reduction in cardiovascular death rates appeared to be mostly due to the reduction in body weight, blood pressure and possibly a diuretic effect of empagliflozin in patients with heart failure[55] suggesting that the effects on ischemic stroke were independent of glucose lowering.

## GLUCOSE-LOWERING AGENTS AND NEUROPROTECTION

T2DM is associated with more severe stroke and less favorable outcome[70-72]. Preliminary data suggest that glucose-lowering treatment might alleviate the severity of stroke at admission to the hospital and might improve the functional outcome of these patients[73]. In an early retrospective study, patients who were treated with sulfonylureas prior to stroke and continued to receive them during hospitalization had more favorable functional outcome at discharge[74]. In a prospective study, patients who were on sulfonylureas, metformin or insulin prior to stroke had less severe stroke at admission than those who were not on glucose-lowering treatment[75]. Stroke severity and outcome did not differ between these 3 classes of antidiabetic agents[75]. A small retrospective study also suggested that pioglitazone enhances functional recovery in patients with stroke[76]. Finally, it was also recently reported that treatment with DPP-4 inhibitors prior to ischemic stroke improves the functional outcome at discharge and reduces in-hospital mortality[77]. Linagliptin, a DPP-4 inhibitor, might exert neuroprotective actions[67] and its effect on cognition is currently being investigated in the CAROLINA and CARMELINA trials[78,79].

## CONCLUSION

Even though T2DM is a major risk factor for ischemic stroke, strict glycemic control does not appear to reduce cardiovascular morbidity and mortality in these patients compared with conventional treatment. On the other hand, newer glucose-lowering agents, particularly GLP-1 receptor agonists (liraglutide and semaglutide) and empaglifozin, a SGLT-2 inhibitor, appear to reduce the risk of cardiovascular events. Moreover, semaglutide is the only agent that reduced the risk of ischemic stroke in a placebo-controlled trial, although it increased the retinopathy risk. Empaglifozin, on the contrary, might increase the incidence of stroke. It is unclear whether these benefits represent a class effect or are compound-specific. Pioglitazone also appears to reduce the risk of recurrent stroke in patients with prediabetes and established T2DM. On the other hand, sulfonylureas and DPP-4 inhibitors have a neutral effect on ischemic stroke. Basic research showed encouraging results regarding the effects of linagliptin, a DPP-4 inhibitor, on stroke risk, and RCTs evaluating its role in patients with T2DM are ongoing.

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