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Narrative Review

Antidiabetic drugs and stroke risk. Current evidence

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ABSTRACT

Cardiovascular disease (CVD) is the major cause of morbidity and mortality for individuals with type 2 diabetes (T2D). In particular, the risk for stroke is twice that of patients without diabetes, and diabetes may be responsible for >8% of first ischemic strokes. Therefore, the way to prevent stroke in these patients has become an important issue.

Traditionally, glucose-lowering drugs had not been shown to protect against stroke. Moreover, several antidiabetic drugs (i.e., sulfonylureas, rosiglitazone) have been reported to be associated with increased risks of CVD and stroke. On the contrary, data on the CV risks and benefits associated with new antidiabetic treatment in patients with T2D are emerging - and look promising. Therefore, it could be of great value to find out if any type of these new antidiabetic agents has protective effect against stroke.

We review the available evidence regarding the risk of stroke in individuals taking non-insulin antidiabetic agents.

To date, several antidiabetic agents have shown to have a positive effect on stroke prevention. The accumulated evidence suggests that metformin, pioglitazone and semaglutide reduce stroke risk. These agents do not represent only a way of controlling blood glucose and but also offer the opportunity to reduce stroke risk.

Surely, new data from ongoing and future studies will provide additional information to select the best treatment for decreasing stroke risk in T2D patients.

1. Introduction

Cardiovascular disease (CVD) is the major cause of morbidity and mortality for individuals with diabetes mellitus [1]. The risk for stroke, heart disease, and death from CVD in patients with diabetes is more than double compared with that in age-matched subjects [1], and >70% of patients with type 2 diabetes (T2D) die of CV causes [2].

In particular, diabetes is associated with a substantially increased risk for stroke.

Meta-analysis of prospective studies showed a hazard ratio (HR) of 2.27 for ischemic stroke in diabetics compared to non-diabetics [3], and, on a population level, diabetes may be responsible for >8% of first ischemic strokes [4]. Besides, stroke outcomes are worse among diabetics, resulting in increased mortality and disabilities [4].

Therefore, the way to prevent stroke in these patients has become an important issue. Moreover, it could be of great value to find out if one kind of antidiabetic agent has superior protective effect against stroke over another.

Nevertheless, until recently, no antidiabetic drug has been proven to reduce stroke incidence or recurrence and, besides, glucose lowering has generally been disappointing in terms of CV protection in the context of diabetes [1,2]. However, there is distinct hope that newer antidiabetic agents will have CV benefits independent of glycemic control.

In fact, now things have changed and novel diabetes therapies have been evaluated in CV safety trials. In 2008, following the withdrawal of rosiglitazone from the market because of potential negative impact on CVD outcomes the Food and Drug Administration (FDA) issued guidance on the assessment of CVD risk for all new drugs to treat T2D [5,6]. Likewise, the European Medicines Agency (EMA) issued similar guidelines in 2012 for drug developers to investigate and rule out potentially harmful drug interactions [7]. Following this, a large number of patients with T2D have been enrolled in CV outcome trials.

Currently, eight randomized controlled trials involving around 70,000 participants have been completed and have demonstrated the CV safety of dipeptidyl peptidase-4 inhibitors (saxagliptin, alogliptin and sitagliptin), glucagon-like peptide-1 receptor agonists (lixisenatide, liraglutide and semaglutide) and a sodium-glucose co-transporter-2 inhibitor (empagliflozin, canaglifozin) in patients with T2D. Four of these trials have in fact reported superiority of the study drug over placebo in terms of CV outcomes [8].

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Here, we provide a brief overview of the CV effects of existing and emerging non-insulin antihyperglycemic medications with a particular focus on effects on stroke risk (see Table 1).

2. Conventional antidiabetic agents and stroke

It is necessary to highlight the fact that, until recently, most of the major trials of antidiabetic drugs have focused on establishing glucose-lowering properties, whereas assessment of the effect of these drugs on CV outcomes has been limited [5]. For example, the effects of sulfonylureas (SU) and metformin on CV risk have not been evaluated in long-term trials [5].

In relation to stroke risk, SU drugs have shown both beneficial and detrimental effects in experimental stroke models [9]. Besides, the question of the cerebrovascular safety of SU therapy for patients with T2D has been addressed in several clinical studies of T2D patients hospitalised with acute stroke and preadmission treatment with SU or other antidiabetic drugs [9]. Interestingly, some studies report a potential benefit of SUs [10], whereas others report no benefit [11] or a potential detrimental effect [12].

Nevertheless, SU are ATP-sensitive potassium (K_{ATP}) channel blockers [13]. Activation of K_{ATP} channels plays a neuroprotective role in ischemia; therefore, SU treatment in patients with T2D may inhibit the neuroprotective effects of K_{ATP} channels and increase the risk of stroke [13,14].

A recent meta-analysis including 17 trials and 27,705 subjects indicated that patients with T2D receiving SU treatment have a higher relative risk for stroke morbidity than those receiving comparator drugs (Odds Ratio-OR-1.39; 95% CI 1.16–1.65) [14].

On the contrary, metformin has shown to have potential benefits on stroke.

Metformin, a synthetic dimethyl biguanide is considered today the first-choice drug for the treatment of T2D [15]. In fact, the results released in 1998 from the United Kingdom Prospective Diabetes Study (UKPDS), a 20-year study involving 23 centers, provided evidence that treatment with metformin compared with insulin and SU reduced the vascular complications associated with T2D accelerated the clinical use of metformin [16].

The vascular protective actions of metformin are thought to be secondary to the antihyperglycemic effects of metformin that are mediated

Table 1
Stroke risk in major cardiovascular outcome studies with new antidiabetic drugs.

Drug	Trial	Number of patients	Median follow-up time (years)	Stroke risk	Comment
Dipeptidyl peptidase-4 inhibitors					
Saxagliptin	SAVOR-TIMI 53	16,492	2.1	HR 1.11 (0.88–1.39) p = 0.38 IS	Higher risk of heart failure (HR 1.27; 95% CI, 1.07 to 1.51; p = 0.007)
Alogliptin	EXAMINE	5380	1.6	HR 0.91 (0.55–1.50) p = 0.71 NFS	
Sitagliptin	TECOS	14,671	3	HR 0.97 (0.79–1.19) p = 0.76 FS/NFS	
Linagliptin	CARMELINA	8300	4	NA	Expected completion date: January 2018
Linagliptin (vs. Glimepiride)	CAROLINA	6000	7.6	NA	Expected completion date: September 2018
Glucagon-like peptide-1 agonists					
Lixisenatide	ELIXA	6068	2.1	HR 1.12 (0.79–1.578) p = 0.54 FS/NFS	
Liraglutide	LEADER	9340	3.8	HR 0.86 (0.71–1.06) p = 0.16 FS/NFS	
Semaglutide	SUSTAIN 6	3297	3	HR 0.61;(0.38–0.99) p = 0.04 NFS	Higher risk of retinopathy (HR 1.76, 95% CI 1.11 to 2.78; p = 0.02)
Exenatide	EXSCEL	14,000	3	NA	Expected completion date: April 2018
Dulaglutide	REWIND	9622	6.5	NA	Expected completion date: April 2019
Albiglutide	HARMONY Outcomes	9400	3–5	NA	Expected completion date: May 2019
Sodium-glucose cotransporter-2 inhibitors					
Empagliflozin	EMPA-REG OUTCOME	7020	3.1	HR 1.24 (0.92–1.67) p = 0.16 NFS	
Canagliflozin	CANVAS	4339	6–7	HR 0.87 (0,69–1.09) p = 0.54 NFS	Canagliflozin doubles the risk for lower-limb amputation
Dapagliflozin	DECLARE-TIMI 58	17,150	4–5	NA	Expected completion date: April 2019
Ertugliflozin	VERTIS CV Study	8000	5–7	NA	Expected completion date: June 2020

Clinical Trial names:
CANVAS: CANagliflozin cardioVascular Assessment Study.
CARMELINA: Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus.
CAROLINA: Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes.
DECLARE-TIMI 58: Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events.
ELIXA: Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome during Treatment With AVE0010 (Lixisenatide).
EMPA-REG OUTCOME: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients.
EXSCEL: Exenatide Study of Cardiovascular Event Lowering Trial.
EXAMINE: Cardiovascular Outcomes Study of Alogliptin in Patients With Type 2 Diabetes and Acute Coronary Syndrome.
HARMONY Outcomes, Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects with Type 2 Diabetes Mellitus.
LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long-Term Evaluation.
REWIND: Researching Cardiovascular Events With a Weekly Incretin in Diabetes.
SAVOR-TIMI 53: Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes Medications.
SUSTAIN 6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes.
TECOS: Sitagliptin Cardiovascular Outcomes Study (MK-0431–082).
VERTIS CV Study: Randomized, double-blind, placebo-controlled, parallel-group study to assess cardiovascular outcomes following treatment with Ertugliflozin (MK-8835/PF-04971729) in subjects with Type 2 Diabetes Mellitus and established vascular disease.
IS: Ischemic stroke. FS: Fatal stroke. NFS: Non Fatal Stroke. NA: Non available.

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