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Review

Dipeptidyl peptidase-4 inhibitors and protection against stroke: A systematic review and meta-analysis

F. Barkas , M. Elisaf , V. Tsimihodimos , H. Milionis *

Department of Internal Medicine, School of Medicine, University of Ioannina, Ioannina, Greece

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Abstract

Background. – Type 2 diabetes mellitus (T2DM) is associated with an increased risk of stroke and an unfavourable outcome following stroke. Apart from pioglitazone, glucose-lowering modalities have not been shown to protect against stroke. Nevertheless, there is evidence from experimental studies of potential neuroprotective effects with dipeptidyl peptidase (DPP)-4 inhibitors, especially if treatment starts before stroke.

Objective. – To perform a meta-analysis of available evidence regarding the risk of stroke in individuals taking DPP-4 inhibitors.

Methods. – All available data from prospective randomized placebo-controlled trials involving DPP-4 inhibitors in T2DM patients published up to December 2015 were considered. The included trials reported data on the incidence of stroke with a recruitment rate of at least 100 diabetes patients and a follow-up of at least 12 weeks.

Results. – A total of 19 small randomized clinical trials (RCTs) evaluating the efficacy and safety of gliptins ($n = 9278$), along with three multicentre prospective double-blind placebo-controlled RCTs assessing cardiovascular outcomes as the primary endpoint and involving 36,395 T2DM patients, were included in the analysis. Pooled analysis of the small RCTs showed a non-significant trend towards benefit with DPP-4 inhibitors against stroke [odds ratio (OR): 0.639, 95% confidence interval (CI): 0.336–1.212; $P = 0.170$]. In contrast, in the analysis of RCTs reporting on cardiovascular safety, there was no difference in the risk of stroke with gliptin treatment compared with a placebo (OR: 0.996, 95% CI: 0.850–1.166; $P = 0.958$).

Conclusion. – The promising data from experimental studies regarding cardioprotective gliptin-associated effects against stroke were not supported by available data from trials specifically looking at cardiovascular safety.

Keywords: Cerebrovascular; Diabetes; Dipeptidyl peptidase-4 inhibitors; Gliptins; Randomized trial; Stroke

1. Introduction

Type 2 diabetes mellitus (T2DM) is among the leading global and regional causes of mortality, and has an accelerating prevalence [1,2]. T2DM is undoubtedly associated with an increased risk of microvascular complications, such as retinopathy, nephropathy and neuropathy [3]. However, macrovascular complications are the primary cause of death in such patients, with acute ischaemic myocardial infarction and stroke accounting for 80% of deaths in diabetic individuals [4]. Despite the development of insulin as well as other agents to improve glycaemic control in diabetes patients, there is considerable debate over whether these treatment modalities can lower the risk of major cardiovascular disease (CVD) outcomes, including stroke [5–8]. Thus far, only pioglitazone, a thiazolidinedione used in the PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) and IRIS (Insulin Resistance Intervention After Stroke) trial, has been shown to reduce the risk of recurrent stroke in high-risk individuals with diabetes and with insulin resistance with prior stroke, respectively [9,10].

The glucagon-like peptide (GLP)-1 receptor (GLP-1R) is a G-protein-coupled receptor expressed in a wide range of tissues, including the pancreas, heart and brain. GLP-1R is activated by GLP-1, a small peptide hormone released by intestinal L cells, which also exerts numerous pleiotropic effects on various

* Corresponding author. Department of Internal Medicine, School of Medicine, University of Ioannina, 45110 Ioannina, Greece.
Tel.: +30 265 100 7516; fax: +30 265 100 7016.
E-mail address: hmilioni@uoi.gr (H. Milionis).

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tissues. The best-characterized property of GLP-1 is its incretin effect by enhancing meal-stimulated insulin secretion from pancreatic β-cells in a glucose-dependent manner, while decreasing glucagon secretion from the pancreas. Endogenous GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase (DPP)-4, which is inhibited by gliptins (DPP-4 inhibitors) [11,12]. There is also intriguing evidence from experimental and clinical studies that the newer DPP-4 enzyme inhibitor drugs have neuroprotective properties and, therefore, may be of benefit in preventing strokes and improving post-stroke outcomes [13].

In the light of such evidence, a meta-analysis was performed of the available data regarding the risk of stroke in diabetic individuals taking DPP-4 inhibitors.

2. Methods

2.1. Data sources and searches

Studies were identified by a systematic review of the English literature published up to 31 December 2015 in MEDLINE (source PubMed) and Embase. Search terms were 'diabetes', 'stroke', 'cerebrovascular', 'dipeptidyl peptidase-4 inhibitors' and 'randomized trial'. Manual checking was also performed of the references listed in the retrieved articles. Unpublished data were sought by scrutinizing the largest clinical trials registry site, ClinicalTrials.gov, using the search terms 'alogliptin', 'linagliptin', 'saxagliptin', 'sitagliptin' and 'vildagliptin'.

2.2. Outcomes and study eligibility

The outcome of interest was the incidence of stroke in diabetic subjects. Studies were considered eligible if:

- they were double-blind randomized controlled trials (RCTs) comparing DPP-4 inhibitors with a placebo and prescribed as either monotherapy or in combination with various common background therapies;
- the duration of treatment was ≥ 12 weeks;
- at least 100 subjects had been recruited;
- they reported data on cerebrovascular disease as either an adverse cardiovascular event or a component of the primary composite cardiovascular outcome of interest.

2.3. Extraction of data

To extract data on stroke incidence from adjudicated trials, data were drawn from tables included in either the trial reports or on the ClinicalTrials.gov website. Data reporting stroke mortality were not included in the present analysis.

Stroke was recorded with the following terms: 'stroke'; 'cerebrovascular accident'; 'ischemic stroke'; 'cerebral infarction'; 'cerebral ischemia'; and 'transient ischemic attack'. Any data reporting cerebral haemorrhage were not included in our analysis.

In cases of multiple treatment arms, the presence of gliptin denoted the gliptin-treated group. On the other hand, when trials had treatment groups of both placebo and a comparator drug, the comparator drug-treated group was excluded, with comparisons performed only between gliptin and placebo-treated groups. In cases of variable doses of a DPP-4 inhibitor, these were all lumped together. Data from extension trials were used in preference to the shorter initial trial only if the study participants remained blinded, whereas open-label extension trials were excluded from the present analysis.

Finally, two separate analyses were performed: the first involved only the small prospective studies reporting on stroke as an adverse cardiovascular event; and the second included the large trials looking at the cardiovascular safety of DPP-4 inhibitors.

The literature search, selection of studies, and extraction and presentation of data were performed independently by two reviewers (F.B., H.M.). Any disagreements between them were resolved by consensus after discussion with the other authors (V.T., M.E.). H.M. performed all the statistical analyses.

2.4. Data synthesis and analysis

For our meta-analyses, fixed-effects and random-effects models of the selected studies were applied on the basis of within-study comparisons, thereby avoiding any biases caused by methodological differences between studies. Cochran's Q-test and the I-square (I^2) statistical method were used to determine heterogeneity between studies [14,15]. These indices were used to assess the percentage of variability across studies, which is due to heterogeneity rather than chance. Heterogeneity was considered significant with a $P < 0.10$ for the Q-test or an $I^2 > 50\%$. All statistical analyses were conducted using Comprehensive Meta-Analysis software, version 2.2.064 (Biostat, Englewood, NJ, USA).

3. Results

Our literature search identified 134 studies matching our criteria (Fig. 1). Of these studies, 51 were excluded because they were not placebo-controlled, and 61 because they reported no relevant outcomes. Ultimately, 22 studies were included in our meta-analysis. Two different analyses were performed, comprising:

- 19 small prospective studies involving data for 9278 subjects and having glycated haemoglobin (HbA_{1c}) as the primary outcome of interest [16–32];
- three recent large-scale RCTs evaluating the effect of gliptins on cardiovascular outcomes and reporting on stroke as their primary composite endpoint ($n = 36{,}395$) [33–35].

Characteristics of all the included trials are summarized in Table 1. The number of subjects ranged from 130 to 16,492, whereas the range of intervention time was 12 weeks to 3 years. Study participants had been diagnosed with T2DM when enrolled into these studies, but either received no hypoglycaemic treatment or had inadequate glycaemic control despite the use