REVIEW ARTICLE

# Potentials of incretin-based therapies in dementia and stroke in type 2 diabetes mellitus

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**ABSTRACT**

Patients with type 2 diabetes mellitus are at risk for accelerated cognitive decline and dementia. Furthermore, their risk of stroke is increased and their outcome after stroke is worse than in those without diabetes. Incretin-based therapies are a class of antidiabetic agents that are of interest in relation to these cerebral complications of diabetes. Two classes of incretin-based therapies are currently available: the glucagon-like-peptide-1 agonists and the dipeptidyl peptidase-4 -inhibitors. Independent of their glucose-lowering effects, incretin-based therapies might also have direct or indirect beneficial effects on the brain. In the present review, we discuss the potential of incretin-based therapies in relation to dementia, in particular Alzheimer's disease, and stroke in patients with type 2 diabetes. Experimental studies on Alzheimer's disease have found beneficial effects of incretin-based therapies on cognition, synaptic plasticity and metabolism of amyloid-β and microtubule-associated protein tau. Preclinical studies on incretin-based therapies in stroke have shown an improved functional outcome, a reduction of infarct volume as well as neuroprotective and neurotrophic properties. Both with regard to the treatment of Alzheimer's disease, and with regard to prevention and treatment of stroke, randomized controlled trials in patients with or without diabetes are underway. In conclusion, experimental studies show promising results of incretin-based therapies at improving the outcome of Alzheimer's disease and stroke through glucose-independent pleiotropic effects on the brain. If these findings would indeed be confirmed in large clinical randomized controlled trials, this would have substantial impact.

## INTRODUCTION

The prevalence of diabetes mellitus is increasing, with more than 380 million people being affected throughout the world[1]. Type 2 diabetes mellitus accounts for 90% of these cases[1]. End-organ complications, in particular vascular disease, are a major concern in diabetes care and treatment. Well-known vascular complications of type 2 diabetes mellitus include coronary heart disease, nephropathy, retinopathy and lower-limb amputations[1]. Accelerated cognitive decline is another complication in type 2 diabetes mellitus, potentially resulting in mild cognitive impairment (MCI) or dementia[2]. Also, patients with type 2 diabetes mellitus have an increased risk of stroke, and have a worse stroke outcome compared with patients without type 2 diabetes mellitus[3].

The pathophysiology of type 2 diabetes mellitus is characterized by insulin resistance, relative insulin deficiency and pancreatic β-cell dysfunction[4]. Reduction of insulin resistance and raising of endogenous insulin secretion are important targets of antidiabetic drugs. Many classes of such antidiabetic drugs have been available for decades; for example biguanides, sulfonylurea, thiazolidinediones (TZD), insulin and α-glucosidase inhibitors. Incretin-based therapies are another class of antidiabetic agents that have recently become available for treatment of type 2 diabetes mellitus. These compounds are of possible interest also in relation to dementia and stroke, because besides improving glucose homeostasis, they might have additional direct or indirect beneficial effects on the brain. In the present review, we will discuss the potential of incretin-based therapies in relation to cognitive decline and dementia, in particular Alzheimer's disease (AD), in patients with type 2 diabetes mellitus. We will also discuss incretin-based therapies in relation to stroke risk in patients with type 2 diabetes mellitus, and their potential to improve stroke outcome.

## BRIEF BACKGROUND ON INCRETIN-BASED THERAPIES

Incretin-based therapies in type 2 diabetes mellitus are divided into two categories, the glucagon-like-peptide-1 (GLP-1) agonists and the dipeptidyl peptidase-4 (DPP4)-inhibitors. Currently registered GLP-1 agonists for type 2 diabetes mellitus treatment are exenatide (the synthetic form of exendin-4, a naturally occurring GLP-1 agonist), liraglutide, lixisenatide and dulaglutide. GLP-1 agonists require subcutaneous administration. Examples of currently registered DPP-4 inhibitors are sitagliptin, linagliptin, saxagliptin, vildagliptin and alogliptin. DPP-4 inhibitors are administered orally. Whereas endogenous GLP-1 has a half-life in the order of a few minutes, the half-life of incretin-based compounds is several hours[5,6], thus enabling their application for diabetes treatment. GLP-1 agonists and DPP-4 inhibitors are currently used as second-line therapies in type 2 diabetes mellitus, or in triple therapy regimens, and are also applied for first-line use in the case of intolerance or contraindications to metformin[7]. Incretin-based therapies have a favorable safety profile and a low risk of hypoglycemia[8–10].

## BIOLOGY OF INCRETIN HORMONES IN PERIPHERAL ORGANS AND THE BRAIN

### Biology of Incretins

Incretins are gastrointestinal hormones secreted from the gut into the bloodstream, minutes after oral nutrient intake, that promote insulin secretion from the pancreatic β-cells. The most important incretins in humans are GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Both GLP-1 and GIP have an insulinotropic effect, and together contribute approximately 50–70% of the total insulin secretion after oral glucose ingestion, denoted as "the incretin effect." Oral food ingestion is the primary physiological stimulus for GLP-1 and GIP secretion, from the intestinal endocrine L-cells and K-cells, respectively[11]. After secretion, levels of intact circulating GLP-1 and GIP drop rapidly as a result of enzymatic inactivation by DPP-4 and renal clearance. For that reason, in the circulation the half-life of bioactive GLP-1 is less than 2 min, that of GIP is 7 min[12]. In pancreatic β-cells, GLP-1 and GIP bind to their G-protein coupled receptors, GLP-1 receptor (GLP-1R) and GIP receptor (GIPR)[12]. After GLP-1 and GIP binding to its receptor, 3′, 5′-cyclic monophosphate-protein kinase A is the major signaling pathway[12,13].

Apart from promoting glucose-dependent insulin secretion and insulin synthesis, GLP-1 and GIP have been shown to have growth factor-like properties on the pancreatic β-cells in preclinical models. GLP-1 and GIP promote β-cell proliferation and decrease β-cell apoptosis[11].

GLP-1R and GIPR are also expressed in extrapancreatic organs, and GLP-1 and GIP can thus exert actions on these organs as well (Table 1). These actions include extrapancreatic mechanisms involved in glucose homeostasis (Table 2)[11,14,15]. For example, GLP-1 slows down gastric emptying, thereby reducing increases in meal-associated blood glucose levels[11]. Also, GLP-1 reduces food intake and promotes satiety[16,17].

**Table 1** | Expression of glucagon-like-peptide-1 and glucose-dependent insulinotropic polypeptide receptor in different organs[11,12]

| GLP-1 receptor | GIP receptor |
|---|---|
| Pancreatic β-cells | Pancreatic β-cells |
| Heart | Heart |
| Lung | Lung |
| Stomach, intestine (ileum and colon) | Stomach, duodenum |
| Kidney | Kidney |
| Brain | Brain |
| Autonomic nervous system: nodose ganglion of the vagal nerve | Thyroid |
| Skin | Trachea |
| | Thymus |
| | Spleen |
| | Adrenals |
| | Bone |
| | Adipose tissue |
| | Testis |

GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like-peptide-1.

**Table 2** | Effects of glucagon-like-peptide-1 and glucose-dependent insulinotropic polypeptide on peripheral tissues[11,14,15]

| Action | GLP-1 | GIP |
|---|---|---|
| Endocrine pancreas | Glucose-independent insulin release ↑<br>β-Cell proliferation ↑<br>β-Cell apoptosis ↓<br>Glucose-dependent glucagon ↓ | Glucose-independent insulin release ↑<br>β-Cell proliferation ↑<br>β-Cell apoptosis ↓<br>Glucagon secretion ↑ |
| Food intake and weight | Food intake ↓<br>Promotion of weight loss | |
| Gastrointestinal system | Gastric emptying ↓ | |
| Cardiovascular effects | Blood pressure ↓<br>Endothelial function ↑<br>Cardioprotective | |
| Bone | Bone formation ↑<br>Bone absorption ↓ | Bone absorption ↓ |
| Lipid metabolism | Fatty acid synthesis ↓<br>Fatty acid oxidation ↑ | Lipogenesis ↑ |

GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like-peptide-1.

Studies on the extrapancreatic effects of GIP are relatively scarce, but it is known that GIP is involved in lipogenesis in adipose tissue[12,14].

Incretins also act on the brain; peripherally secreted GLP-1 can cross the blood–brain barrier (BBB) by passive diffusion[18]. Furthermore, within the brain, a small amount of GLP-1 is produced in the nucleus of the solitary tract in the caudal brainstem, thus functioning as a neurotransmitter[19]. Binding

sites for GLP-1Rs in the brain are located in the hypothalamus, hippocampus, striatum, brain stem, substantia nigra and subventricular zone, among other structures[20]. The GIP-R is expressed in the cerebral cortex, hippocampus and the olfactory bulb[12]. It seems that peripherally administered GLP-1 also plays a role in glucose homeostasis, food intake and satiety through brain GLP-1R[12,16].

There is evidence in animals that direct administration of GLP-1 in the brain leading to brain GLP-1R signaling influences peripheral glucose metabolism. Under hyperglycemic conditions, intracerebroventricular (ICV) administration of a GLP-1 agonist through stimulation of brain GLP-1R induces insulin secretion, and activates peripheral pathways inhibiting glucose uptake and promotes glycogen storage in the liver[21]. Another study showed that hindbrain administration of GLP-1 increased glucose-stimulated insulin secretion and reduced hepatic glucose production[22]. Some animal studies have shown that direct administration of a GLP-1-agonist in the brain leading to GLP-1R signaling leads to a decrease in food intake and to induction of satiety or anorexia[16,23].

## Pleiotropic effects of incretins and incretin-based therapies on the brain

Incretins appear to have additional effects on the brain that are not directly related to glucose metabolism. In several neuronal cell line studies, GLP-1 induced neurite outgrowth[24,25]. One study found that ICV infusion of GIP stimulated progenitor cell proliferation in the rat hippocampus[26]. Furthermore, a study of GIPR-knockout mice showed that disruption of the GIP signaling pathways leads to a diminished number of progenitor cells in the dentate gyrus[27]. These findings suggest that incretins have neurotrophic properties in the brain.

In addition to these neurotrophic properties, GLP-1 appears to have neuroprotective properties. Neuronal cell line studies showed that GLP-1 protected against $H_2O_2$-induced toxicity by raising the expression of anti-apoptotic proteins[28,29]. In another cell line study, GLP-1 also protected against oxidative stress-induced neuronal cell apoptosis[30]. Also, GLP-1 protected rat cultured hippocampal cells *in vitro* against glutamate-induced apoptosis[24].

Another interesting observation is that incretins could influence synaptic plasticity; that is, long-term potentiation (LTP) and cognition. LTP is the cellular correlate of memory formation, and is defined as a persisting enhancement in signal transmission between two neurons, resulting from their synchronous activity[19]. In rodent models, ICV injection of GLP-1 or GIP enhanced LTP in the hippocampus[31–33]. In contrast, administration of a GIP-antagonist inhibited induction of LTP[33]. On a behavioral level, ICV administration of a GLP-1 agonist in mice enhanced associative and spatial learning through GLP-1R[34]. Additional evidence for incretin involvement in plasticity and cognition came from studies in GLP-1R or GIP-R knockout mice, in which LTP and cognition were impaired[27,35].

In mice, the GLP-1 agonists exenatide, liraglutide and lixisenatide can all cross the BBB after peripheral administration[36,37]. Some studies have shown that the DPP-4 inhibitors linagliptin and vildagliptin do not pass the BBB[38,39]. However, other studies have suggested that an increased plasma level of GLP-1 or inhibition of DPP-4, enhance transport of GLP-1 across the BBB[18,40]. DPP-4 inhibitors might also influence the brain through vascular effects. This potential mode for modulation was suggested in a study wherein oral linaglipin treatment in type 2 diabetes mellitus rats restored insulin-mediated vasorelaxation of middle cerebral arteries. This result implies that linagliptin acts on the brain through the vasculature[41].

The direct neuronal effects that are reported for the incretins themselves have also been observed for incretin-based therapies. Neuronal cell line studies showed that the GLP-1 agonist exendin-4 promotes cell proliferation, neuronal differentiation and neurite outgrowth[42–45]. Furthermore, a number of rodent studies on peripheral administered GLP agonists found an increased rate of neuronal cell proliferation[46,47] and stimulation of neuroneogenesis[37,48].

Neuronal cell line studies on GLP-agonists showed protection against $H_2O_2$-induced toxicity[43,45]. In a cell line study on human neuroblastoma cells, liraglutide enhanced cell viability and stimulated a range of growth-factor related protective processes, which resulted in a reduced rate of apoptosis[49].

GLP-1 agonists and DPP-4 inhibitors might have beneficial effects on LTP and cognition as well. In one study, ICV injection of liraglutide was effective in LTP[31]. Subcutaneous injections of exendin-4 and liraglutide in obese mice improved disturbances of LTP[50,51]. Peripheral administration of DPP-4 inhibitors (sitagliptin and vildagliptin) in high-fat diet rats led to improvement of cognitive functioning in several studies[52–54].

## TYPE 2 DIABETES MELLITUS, DEMENTIA AND INCRETIN-BASED THERAPIES

Cognitive impairment and dementia are increasingly recognized as important complications of type 2 diabetes mellitus. For instance, patients with type 2 diabetes mellitus perform slightly worse on a range of cognitive tasks, compared with patients without type 2 diabetes mellitus[55]. The rate of cognitive decline in patients with type 2 diabetes mellitus can be up to twofold faster compared with normal aging[2]. Patients with type 2 diabetes mellitus have an increased risk for MCI, compared with patients without type 2 diabetes mellitus[2]. Furthermore, the proportion of patients who convert from MCI to dementia is 1.5–3-fold higher in patients with than in those without type 2 diabetes mellitus[2]. Type 2 diabetes mellitus also increases the risk of dementia. A meta-analysis including more than 30,000 people of whom 16% had type 2 diabetes mellitus showed that the relative risk (RR) for dementia was 1.5 (95% confidence interval [CI] 1.3–1.7)[56]. This increased risk for dementia applies to both AD, with a RR of 1.5 (95% CI 1.4–1.7) and vascular dementia, with a RR of 2.5 (95% CI 2.1–3.0). However, despite the fact that the relative risk of vascular dementia is higher

than that of AD in patients with type 2 diabetes mellitus, AD is the most common type of dementia in type 2 diabetes mellitus patients, because the absolute risk of AD is higher than that of vascular dementia[56].

The question is what causes accelerated cognitive decline and increased dementia risk in patients with type 2 diabetes mellitus. Glycemic control is an obvious candidate, and has been investigated in a substantial number of studies. A systematic review of cross-sectional and longitudinal observational studies in people with type 2 diabetes mellitus reported that measures of glycemia, particularly high glycated hemoglobin concentration and glucose variability, are negatively associated with cognitive function. However, the strength of the association is weak, and glycated hemoglobin generally accounted for less than 10% of the variance in cognition in the included studies[57]. With regard to glucose-lowering treatment, available randomized controlled trials (RCTs) report no consistent beneficial effects of intensified vs standard glucose-lowering treatment on cognitive functioning in patients with type 2 diabetes mellitus[57,58]. A Cochrane systematic review found no evidence for cognitive benefit in relation to types and intensity of glucose-lowering treatments[59]. In concordance, a recent meta-analysis of 24,000 patients with type 2 diabetes mellitus reported that intensive glycemic control was not associated with a slower rate of cognitive decline compared with regular treatment (standardized mean difference 0.02 95% CI –0.03–0.08)[60].

Nevertheless, some glucose-lowering drugs might improve cognitive functioning independent of glucose lowering through other drug class effects[61]. Rodent models have suggested beneficial glycemia-independent effects of biguanides and TZD on AD pathology[61]. However, whereas some clinical studies on AD patients reported beneficial effects of TZD, other studies did not confirm these results[61,62]. In the context of the present review, we focus on possible drug class effects of incretin-based therapies on cognition.

Preclinical studies on the effects of incretin-based therapies on dementia have focused on AD. The core etiological processes in AD are considered to be aberrant amyloid-β (Aβ) processing, leading to formation of toxic Aβ oligomers and aggregation of microtubule-associated protein tau (MAPT)[63]. Aβ oligomers are derived from amyloid precursor protein (APP) by cleavages by two membrane-bound proteases[64]. These Aβ oligomers can cause synaptic dysfunction, inflammation and neuronal cell death[63,64]. Phosphorylation of MAPT induces the formation of neurofibrillary tangles (NFT). Hyperphosphorylation of MAPT leads to a dissociation of NFTs, resulting in neuron damage[65]. Interestingly, disturbances in amyloid or MAPT processing have been linked to brain insulin resistance in AD[66,67].

In rodent models of AD, ICV administered (Val[8])GLP-1, GIP and liraglutide led to improvement of learning and memory[13,68,69]. ICV-infused (Val[8])GLP-1 and geniposide (a GLP-agonist) prevented against Aβ-induced decline of spatial learning[70,71]. Peripherally-administered exenatide and liraglutide

prevented or improved memory performance in various rodent models of AD[72–74], including in one late stage AD model[75], and one diabetes-related AD model[76]. Peripherally-administered DPP-4 inhibitors sitagliptin, vildagliptin and saxagliptin improved memory impairment in AD rodents[77–79]. In addition to these cognitive effects, incretins have beneficial effects on synaptic plasticity in rodent models of AD. ICV-infused (Val[8]) GLP-1 or GIP reversed impairment of LTP induced by Aβ[32,33,70]. ICV-infused liraglutide and peripherally-administered exendin-4 also enhanced LTP in an AD model[31], and in a diabetes-related AD model[80]. One study showed that peripherally-administered D-Ala[2]GIP facilitated synaptic plasticity in mice at an advanced state of AD[81]. Two studies showed that peripherally-administered (Val[8])GLP-1 and D-Ala[2]GIP had beneficial effects on LTP in both AD rodents and wild-type rodents[82,83]. In another study, peripherally-administered liraglutide enhanced LTP in late-stage AD rodents as well as in wild-type rodents[75]. In addition, a number of studies showed prevention of synaptic loss[33,72,75,83].

Several preclinical studies have also explored effects of incretins on the core etiological processes of AD. Neuronal cell line studies showed that exendin-4 reduced the levels of Aβ[80], other neuronal cell line studies found that exendin-4 reduced levels of APP, but had no impact on Aβ levels[42,80]. In rodent models of AD, peripherally-administered geniposide and D-Ala[2]GIP reduced levels of Aβ plaque load[81,83–85]. However, two other studies reported no reduction of both APP and Aβ levels, despite the fact that treatment did have beneficial effects on memory or LTP[82,86]. Peripherally-administered liraglutide reduced both Aβ and APP levels[72], even in a late-stage AD rodent model[75]. Furthermore, peripherally-administered sitagliptin, saxagliptin and vildagliptin lowered the levels of Aβ[77–79]. With regard to tau metabolism, studies in AD rodents showed that centrally-administered (Val[8])GLP-1[68] and geniposide[71], as well as peripherally-administered exendin-4 and liraglutide[74,76], reduced tau phosphorylation[68,71]. Peripherally-administered saxagliptin and vildagliptin reduced tau phosphorylation[78,79], whereas one study reported that sitagliptin was not effective against tau phosphorylation, and instead worsened it[87].

Neuronal cell line studies and AD rodent models showed that GLP-1 and GIP ameliorated oxidative stress-induced injury[76,80,85,86], and protected against cell death induced by Aβ[42,88]. Furthermore, various studies reported that D-Ala[2]GIP reduced the inflammatory response in rodent AD models[81,83,85]. Also, sitagliptin, saxagliptin and vildagliptin showed anti-inflammatory properties[77–79], as well as liraglutide in a late-stage AD rodent model[75]. Moreover, peripherally-administered liraglutide and D-Ala[2]GIP increased neuronal progenitor cell proliferation and neurogenesis in AD rodent models[72,75,83].

The key question is of course whether these promising results in experimental studies also translate into clinically relevant treatment effects in humans. The results of two RCTs in people with MCI or early AD, but without type 2 diabetes mellitus are awaited (Table 3). As patients with type 2 diabetes

**Table 3** | Randomized controlled trials on the effect of incretin-based agents on mild cognitive impairment and Alzheimer's disease

| Study | Agent | Study population | Endpoint |
|---|---|---|---|
| A pilot study of Exendin-4 in Alzheimer's disease (NCT01255163) | Agent: exendin-4 Comparator: placebo | Phase 2 study Period: 2010–2016 Patients aged ≥60 years (without diabetes), with MCI or early AD | Primary end-point: Safety and tolerability of exendin-4 Secondary end-point: Behavorial and cognitive performance measures Changes on structural and functional MRI and MRS Hormonal and metabolic changes and changes in CSF and plasma AD biomarkers Clinical Dementia Rating ADAS – cognitive subscale |
| ELAD study (NCT01843075) | Agent: liraglutide Comparator: placebo | Phase 2 study Period: 2014–2017 Patients aged 50–85 years (without diabetes), with AD | Primary end-point: FDG-PET imaging: change in cerebral glucose metabolic rate FDG-PET imaging: change in cerebral glucose metabolic rate from baseline to follow up in the treatment group compared with the placebo group Secondary end-point: Change in z-scores for the ADAS Executive, MRI changes, CSF markers, and microglial activation |

AD, Alzheimer's disease; ADAS, Alzheimer's Disease Assessment scale; CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose-positron emission tomography; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy.

mellitus are at increased risk for MCI and dementia, possibly through mechanisms that are influenced by incretin-based therapies, there is a particular need for additional RCTs, especially in this group.

## TYPE 2 DIABETES MELLITUS, STROKE AND INCRETIN-BASED THERAPIES

### Type 2 diabetes mellitus and prevention of stroke
Diabetes is a risk factor for stroke, and is linked to worse stroke outcome[3]. In a meta-analysis of prospective studies, the reported hazard ratio (HR) for ischemic stroke in patients with diabetes was 2.3 (95% CI 2.0–2.7)[89]. In the same meta-analysis, the HR for hemorrhagic stroke was 1.6 (95% CI 2.0–2.7). Assuming a population-wide prevalence of diabetes of 10% in adults aged over 50 years, the diabetes-attributable risk of stroke is at 12%[89].

Again, the question is whether glycemia is the causal link between type 2 diabetes mellitus and the increased risk of stroke. Indeed, glycemia has been studied extensively in this context. Two landmark RCTs reported that the risk of stroke was not affected by intensive glycemic control in patients with longstanding type 2 diabetes mellitus[90,91]. A subsequent meta-analysis including 34,533 type 2 diabetes mellitus patients also showed that intensive glycemic control did not reduce stroke risk compared with regular treatment (HR 5-year stroke risk

0.96, 99% CI 0.8–1.1)[92]. A Cochrane meta-analysis including 34,912 type 2 diabetes mellitus patients reported the same finding (RR 1, 95% CI 0.84–1.19)[93].

Apparently, levels of glycemia by itself have no major impact on stroke risk in type 2 diabetes mellitus. However, some glucose-lowering drugs might affect stroke risk independent of glucose lowering. In the context of the present review, we consider such potential class effects for incretin-based therapies in the primary and secondary prevention of stroke. Two RCTs on saxagliptin or alogliptin vs a placebo in patients with type 2 diabetes mellitus and a previous history of cardiovascular events (including stroke) showed a similar incidence of non-fatal ischemic stroke in the treatment and placebo groups (HR 0.91, 95% CI 0.55–1.50 and HR 1.11, 95% CI 0.88–1.39)[94,95]. A subsequent RCT on sitagliptin vs a placebo in patients with type 2 diabetes mellitus and established cardiovascular disease, including ischemic stroke, also showed no difference in incidence of stroke (HR 0.97, 95% CI 0.79–1.19)[96]. In contrast, a recent prospective meta-analysis pooled data of RCTs on the effects of linagliptin vs other therapies (glimepiride, voglibose or placebo) on major cardiovascular events in 5,847 patients with type 2 diabetes mellitus and low prevalence of prior cardiovascular events[97]. The incidence rate of non-fatal stroke was significantly reduced in the linagliptin group compared with the other groups (HR 0.34, 95% CI 0.15–0.75)[97]. The results of six ongo-

ing trials are still awaited (Table 4). In sum, for secondary prevention of stroke, there is currently no evidence for a class effect of DPP-4 inhibitors. However, preliminary data do show that incretin-based therapies might be effective in primary prevention of stroke, and results of further RCTs are awaited.

## Type 2 diabetes mellitus and outcome of stroke

Diabetes is associated with poor functional outcome after ischemic stroke (odds ratio [OR] 1.5, 95% CI 1.1–1.9)[98], and with an increased mortality 1 year after ischemic stroke (HR 1.2, 95% CI 1.1–1.2)[99]. Diabetes also increases the risk of

post-stroke dementia (OR 1.4, 95% CI 1.2–1.7)[100]. Furthermore, hyperglycemia in the acute phase of stroke is associated with poor outcome, also in people without diabetes. Hyperglycemia is present in 30–40% of the patients with acute ischemic stroke[3]. A systematic review found that admission hyperglycemia occurred in 8–63% of non-diabetic stroke patients, and in 39–83% of diabetic patients[101]. A recent systematic review on the association between hyperglycemia at admission and outcome after ischemic stroke showed that hyperglycemia at admission is a predictor of neurological deterioration occurring within 24 h after ischemic stroke[102]. Furthermore, the

**Table 4** | Randomized controlled trials on the effect of incretin-based agents on incidence of stroke

| Study | Agent | Study population | End-point | Results (if applicable) |
|---|---|---|---|---|
| EXAMINE trial (2013)[95] (NCT00968708) | Agent: alogliptin Comparator: placebo | 5,380 T2DM patients with a recent ACS | Primary end-point: a composite of death from CV disease, non-fatal myocardial infarction or non-fatal stroke | Similar incidence in both groups for non-fatal stroke (HR 0.91, 95% CI 0.55–1.50, $P = 0.71$) |
| SAVOR-TIMI 53 (2013)[94] (NCT01107886) | Agent: saxagliptin Comparator: placebo | ≥16,000 T2DM patients with a history of, or were at risk for a CV event | Primary end-point: a composite of CV death, myocardial infarction or ischemic ischemic stroke | Similar incidence in both groups for non-fatal ischemic stroke (HR 1.11, 95% CI 0.88–1.39, $P = 0.38$) |
| TECOS[96] (NCT00790205) | Agent: sitagliptin Comparator: placebo | 14,671 T2DM patients with established CV disease | Primary endpoint: a composite defined as CV-related death, non-fatal MI, non-fatal stroke, or unstable angina requiring hospitalizations | Similar incidence in both groups for fatal or non-fatal stroke (HR 0.97, 95% CI 0.79–1.19, $P = 0.76$) |
| ELIXA (NCT01147250) | Agent: lixisenatide Comparator: placebo | Phase 3 study Period: 2010–2015 6,000 T2DM patients after ACS | Primary end-point: a composite of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina | |
| LEADER (NCT01179048) | Agent: liraglutide Comparator: placebo | Phase 3 study Period: 2010–October 2015 9,340 T2DM patients | Primary end-point: a composite of CV death, non-fatal MI and non-fatal stroke | |
| CAROLINA (NCT01243424) | Agent: linagliptin Comparator: glimepiride | Phase 3 study Period: 2010–2018 6,000 T2DM patients with a high CV risk profile | Primary end-point: a composite of CV death non-fatal myocardial infarction, non-fatal stroke and hospitalization for unstable angina pectoris | |
| REWIND (NCT01394952) | Agent: dulaglutide Comparator: placebo | Phase 3 study Period: 2011–2019 9,622 T2DM patients | Primary end-point: a composite of CV death, non-fatal MI and non-fatal stroke | |
| CARMELINA (NCT01897532) | Agent: linagliptin Comparator: placebo | Phase 4 study Period: 2013–2018 8,300 T2DM patients with a high risk of CV events | Primary end-point: a composite of CV death, non-fatal MI and non-fatal stroke. | |
| EXSCEL (NCT01144338) | Agent exenatide Comparator: placebo | Phase 4 study Period: 2010–2017 14,000 T2DM patients | Primary end-point: a composite of CV death, non-fatal MI and non-fatal stroke. | |

ACS, acute coronary syndrome; CV, cardiovascular; MI, myocardial infarction; T2DM, type 2 diabetes.

unadjusted relative risk of in-hospital or 30-day mortality after an ischemic stroke in patients with hyperglycemia at admission is 3.3 (95% CI 2.3–4.7) in those without known diabetes, and 2.0 (95% CI 0.40–90.1) in patients with diabetes[3]. This elevated risk is independent of other predictors of poor outcome[3]. Often, hyperglycemia at admission is the result of a stress response rather than reflecting pre-existing unrecognized diabetes[103].

The question is of course whether the relationship between hyperglycemia and outcome after stroke is causal, or whether hyperglycemia is mostly an epiphenomenon that reflects stroke severity or other concomitant adverse factors. Several pathophysiological processes have been identified through which hyperglycemia could increase cerebral damage[104]. Furthermore, experimental studies in hyperglycemic rodents found an association between treatment with antidiabetic agents and outcome of ischemic stroke[105–107]. Several RCTs have therefore explored if tight glycemic control in the acute phase of stroke can improve stroke outcome. A Cochrane meta-analysis of 11 of such studies, involving 1,583 patients with stroke and admission hyperglycemia, showed no difference in outcome after stroke between intensively monitored intravenous insulin treatment and usual care (OR 1.0 95% CI 0.8–1.2)[108].

Although the currently available data show that tight glycemic control offers no benefit for stroke outcome, glucose-lowering drugs might affect outcome of stroke through class effects independent of glucose lowering. Rodent studies have suggested beneficial glycemia-independent effects of biguanides, sulfonylureas and TZD on outcome of ischemic stroke[109–111].

Preclinical studies have investigated the effects of incretin-based therapies on outcome of stroke. Pre-stroke treatment with ICV-administered exendin-4 or peripherally-administered alogliptin effectively reduced neurological deficits and infarct volume in normoglycemic rodents[112,113]. Post-stroke treatment with peripherally-administered exendin-4 or liraglutide also showed protection against motor impairment, and led to reduction of infarct volume in normoglycemic rodents[114,115]. Combined pre- and post-stroke treatment with peripherally-administered exendin-4 led to increased spontaneous motor activity in normoglycemic rodents[116].

The effects of incretin-based therapies have also been studied in diabetic rodent models of ischemic stroke. Post-stroke treatment with peripherally-administered exendin-4 in diabetic rodents resulted in a reduction of infarct volume in a dose-dependent manner[117]. Combined pre- and post-treatment with peripherally-administered linagliptin in diabetic rodents showed a trend toward a decrease in infarct volume[118]. In a recent rodent model, post-stroke treatment with peripherally-administered linagliptin improved stroke-induced cognitive impairment, independent of glucose-lowering effects[119].

These apparent beneficial effects of incretin-based therapies on outcome of ischemic stroke could involve several mechanisms. Incretin-based therapies might act on salvage of the penumbra. The penumbra is the part of the ischemic zone that can recover if adequate reperfusion is re-established in the early stage of ischemic stroke[3]. Two studies found increased expression of GLP-1Rs and protein levels in the penumbra after induction of ischemia[116,120].

Inflammation or oxidative stress might also play a role. After stroke, microglial activation, an inflammatory response, induces various neurotoxic free radicals, cytotoxic and pro-inflammatory mediators, and contributes to infarct progression[114,116]. Rodent models showed inhibited microglial activation and microglial migration, thereby suppressing the inflammatory response induced by ischemic stroke[116,117]. In addition, rodent models of ischemic stroke showed that incretin-based therapies might protect against oxidative stress and neuronal cell death[114,115,117].

Incretin-based therapies have shown neurotrophic properties after ischemic stroke by increasing neuroblast formation and neuronal stem cell (NSC) proliferation, thereby not affecting stroke-induced neurogenesis[117]. Pre-treatment of peripherally-administered linagliptin has been shown to enhance NSC proliferation only in diabetic mice, but not in non-diabetic mice. However, linagliptin did not ameliorate NSC in vitro, suggesting that the effect of linagliptin on NSC in diabetic mice is indirect.

RCTs in patients with stroke are required to investigate the clinical effects of incretin-based therapies on stroke outcome. Because possible effects of such therapies do not appear to be primarily mediated through glucose-lowering effects, such trials need not be limited to patients with ischemic stroke and hyperglycemia or type 2 diabetes mellitus. A RCT could involve patients with a stroke regardless of the presence of admission hyperglycemia. Nevertheless, if such trials would show benefit of incretin-based therapies on stroke outcome, this might be particularly relevant for patients with type 2 diabetes mellitus. Patients with type 2 diabetes mellitus already on incretin-based therapy would then be "protected" from the moment of stroke onset onwards, rather than from the moment the first dose of the drug is given after admission for stroke, as would be the case in other patients.

## CONCLUSION

In conclusion, preclinical studies show that incretin-based therapies might hold promise in the treatment of dementia, in particular AD, and stroke. In AD models, incretin-based therapies improve cognition and synaptic plasticity, show anti-inflammatory and anti-oxidative properties, and reduce Aβ levels and tau phosphorylation. RCTs of incretin-based therapies on stroke prevention showed no reduction of stroke risk, although a recent prospective meta-analysis showed promising results. The results of ongoing RCTs on stroke prevention are still awaited. In addition, experimental studies on stroke outcome show beneficial effects on functional outcome, infarct volume, inflammation and oxidative stress.

If the results of the experimental studies are confirmed in RCTs, this would be particularly relevant for patients with

type 2 diabetes mellitus, who are at increased risk of stroke and dementia, and who of course also require a form of glucose-lowering treatment. If class effects of incretin-based therapies in treatment of dementia or stroke would indeed be established, this is likely to have a substantial impact on treatment recommendations. Nevertheless, at this stage, we should be somewhat cautious in our optimism, as both in the field of dementia and in stroke it has proven difficult to translate treatments with great promise in rodents to evidence-based therapies in humans.

## ACKNOWLEDGMENTS

## DISCLOSURE

GJB consults for and receives research support from Boehringer Ingelheim, and consults for Takeda Pharmaceuticals. Compensation for these services is transferred to his employer, the UMC Utrecht. The other authors declare no conflict of interest.

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