**Name of Journal: *World Journal of Diabetes***

**Manuscript NO: 33261**

**Manuscript Type: Minireviews**

**Effects of glucose-lowering agents on ischemic stroke**

Avgerinos K *et al*. Glucose-lowering agents and ischemic stroke

**Konstantinos Avgerinos, Konstantinos Tziomalos**

**Konstantinos Avgerinos, Konstantinos Tziomalos,** First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, 54636 Thessaloniki, Greece

**Author contributions:** Avgerinos K drafted the review; Tziomalos K critically revised the draft.

**Conflict-of-interest statement:** All authors declare no conflict of interest related to this publication.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to: Konstantinos Tziomalos, MD, PhD, Assistant Professor** of Internal Medicine,First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, 1 Stilponos Kyriakidi Street, 54636 Thessaloniki, Greece. ktziomal@auth.gr

**Telephone:** +30-2310-994621

**Fax:** +30-2310-994773

**Received:** January 30, 2017

**Peer-review started:** February 12, 2017

**First decision:** March 28, 2017

**Revised:** April 20, 2017

**Accepted:** May 3, 2017

**Article in press:**

**Published online:**

**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

**© The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

Avgerinos K, Tziomalos K. Effects of glucose-lowering agents on ischemic stroke. *World J Diabetes* 2017; In press

**INTRODUCTION**

Diabetes mellitus (DM) is a major risk factor for cardiovascular events, including ischemic stroke[[1](#_ENREF_1),[2](#_ENREF_2)]. Even pre-diabetes, defined as impaired glucose tolerance or impaired fasting glucose, is associated with increased risk for ischemic stroke[[3](#_ENREF_3)]. In a case-control study in 32 countries[[4](#_ENREF_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](#_ENREF_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](#_ENREF_6),[7](#_ENREF_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 (ADVANCE) trial and the Veterans Affairs Diabetes Trial (VADT), showed that more versus less aggressive glycemic control had no effect on the incidence of cardiovascular events, including nonfatal stroke[[10,11](#_ENREF_8)]. Moreover, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (*n* = 10251 patients with T2DM and established cardiovascular disease (CVD) or additional cardiovascular risk factors)[[12](#_ENREF_14)], intensive glucose lowering reduced the risk of myocardial infarction (MI) by 20% compared with conventional treatment [95% confidence interval (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](#_ENREF_11)]. However, another study showed that multifactorial treatment may not lower the incidence of cardiovascular events in patients with newly diagnosed T2DM[[14](#_ENREF_12)].

A meta-analysis of 28 trials (*n* = 34912 patients with T2DM) showed that intensive versus 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 HBA1c levels by approximately 1.0%-1.5% and is generally well-tolerated[[6](#_ENREF_6),[7](#_ENREF_7)]. The most frequent side effects are from the gastrointestinal system whereas the most severe adverse event, lactic acidosis, is extremely rare[[6](#_ENREF_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](#_ENREF_6),19] and weight gain[[6](#_ENREF_6)]. In addition, when added to metformin, glimepiride was less effective than exenatide and liraglutide[19,2[0](#_ENREF_24)].

***Thiazolidinediones***

Thiazolidinediones have similar potency with metformin and sulfonylureas[6]. In obese patients with prediabetes, rosiglitazone reduced the incidence of T2DM[[21,22](#_ENREF_25)]. 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 (RECORD) 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](#_ENREF_6)]. In RCTs and in meta-analyses, sitagliptin, vildagliptin and alogliptin had a neutral effect on cardiovascular events[[33-36](#_ENREF_35)]. 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 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](#_ENREF_43)]. SYR-472, another once-weekly DPP-4 inhibitor, also appeared to be safe and effective in a phase 2 trial[[42](#_ENREF_44)].

***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](#_ENREF_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 HbA1c 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](#_ENREF_49)]. 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](#_ENREF_6),[7](#_ENREF_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](#_ENREF_51)-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].

***a-glucosidase inhibitors***

-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](#_ENREF_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 (CIMT)[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), 5,238 patients with T2DM and established CVD were assigned to receive pioglitazone or placebo for 34.5 mo[[6](#_ENREF_64)2]. 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](#_ENREF_34)]. 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[6[4](#_ENREF_67)].

***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 HbA1c 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](#_ENREF_69)]. 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 HbA1c 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 lisixenatide 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 HbA1c 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.

**REFERENCES**

1 **Selvin E**, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004; **141**: 421-431 [PMID: 15381515 DOI: 10.7326/0003-4819-141-6-200409210-00007]

2 **Sarwar N**, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; **375**: 2215-2222 [PMID: 20609967 DOI: 10.1016/S0140-6736(10)60484-9]

3 **Lee M**, Saver JL, Hong KS, Song S, Chang KH, Ovbiagele B. Effect of pre-diabetes on future risk of stroke: meta-analysis. *BMJ* 2012; **344**: e3564 [PMID: 22677795 DOI: 10.1136/bmj.e3564]

4 **O'Donnell MJ**, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, Rao-Melacini P, Zhang X, Pais P, Agapay S, Lopez-Jaramillo P, Damasceno A, Langhorne P, McQueen MJ, Rosengren A, Dehghan M, Hankey GJ, Dans AL, Elsayed A, Avezum A, Mondo C, Diener HC, Ryglewicz D, Czlonkowska A, Pogosova N, Weimar C, Iqbal R, Diaz R, Yusoff K, Yusufali A, Oguz A, Wang X, Penaherrera E, Lanas F, Ogah OS, Ogunniyi A, Iversen HK, Malaga G, Rumboldt Z, Oveisgharan S, Al Hussain F, Magazi D, Nilanont Y, Ferguson J, Pare G, Yusuf S. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet* 2016; **388**: 761-775 [PMID: 27431356 DOI: 10.1016/S0140-6736(16)30506-2]

5 **Huxley RR**, Peters SA, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2015; **3**: 198-206 [PMID: 25660575 DOI: 10.1016/S2213-8587(14)70248-7]

6 **Inzucchi SE**, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015; **38**: 140-149 [PMID: 25538310 DOI: 10.2337/dc14-2441]

7 **Palmer SC**, Mavridis D, Nicolucci A, Johnson DW, Tonelli M, Craig JC, Maggo J, Gray V, De Berardis G, Ruospo M, Natale P, Saglimbene V, Badve SV, Cho Y, Nadeau-Fredette AC, Burke M, Faruque L, Lloyd A, Ahmad N, Liu Y, Tiv S, Wiebe N, Strippoli GF. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA* 2016; **316**: 313-324 [PMID: 27434443 DOI: 10.1001/jama.2016.9400]

8 **UK Prospective Diabetes Study (UKPDS) Group**. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352**: 854-865 [PMID: 9742977 DOI: 10.1016/S0140-6736(98)07037-8]

9 **UK Prospective Diabetes Study (UKPDS) Group**. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352**: 837-853 [PMID: 9742976 DOI: 10.1016/S0140-6736(98)07019-6]

10 **Patel A**, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**: 2560-2572 [PMID: 18539916 DOI: 10.1056/NEJMoa0802987]

11 **Duckworth W**, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360**: 129-139 [PMID: 19092145 DOI: 10.1056/NEJMoa0808431]

12 **Gerstein HC**, Miller ME, Byington RP, Goff DC, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545-2559 [PMID: 18539917 DOI: 10.1056/NEJMoa0802743]

13 **Gaede P**, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; **358**: 580-591 [PMID: 18256393 DOI: 10.1056/NEJMoa0706245]

14 **Griffin SJ**, Borch-Johnsen K, Davies MJ, Khunti K, Rutten GE, Sandbæk A, Sharp SJ, Simmons RK, van den Donk M, Wareham NJ, Lauritzen T. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. *Lancet* 2011; **378**: 156-167 [PMID: 21705063 DOI: 10.1016/S0140-6736(11)60698-3]

15 **Hemmingsen B**, Lund SS, Gluud C, Vaag A, Almdal TP, Hemmingsen C, Wetterslev J. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2013; **11**: CD008143 [PMID: 24214280 DOI: 10.1002/14651858.CD008143.pub3]

16 **Ray KK**, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009; **373**: 1765-1772 [PMID: 19465231 DOI: 10.1016/S0140-6736(09)60697-8]

17 **Kahn SE**, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006; **355**: 2427-2443 [PMID: 17145742 DOI: 10.1056/NEJMoa066224]

18 **Rajendran R**, Kerry C, Rayman G. Temporal patterns of hypoglycaemia and burden of sulfonylurea-related hypoglycaemia in UK hospitals: a retrospective multicentre audit of hospitalised patients with diabetes. *BMJ Open* 2014; **4**: e005165 [PMID: 25009134 DOI: 10.1136/bmjopen-2014-005165]

19 **Gallwitz B**, Guzman J, Dotta F, Guerci B, Simó R, Basson BR, Festa A, Kiljański J, Sapin H, Trautmann M, Schernthaner G. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. *Lancet* 2012; **379**: 2270-2278 [PMID: 22683137 DOI: 10.1016/S0140-6736(12)60479-6]

20 **Garber A**, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, Hale PM, Zdravkovic M, Bode B. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 2009; **373**: 473-481 [PMID: 18819705 DOI: 10.1016/S0140-6736(08)61246-5]

21 **Gerstein HC**, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006; **368**: 1096-1105 [PMID: 16997664 DOI: 10.1016/S0140-6736(06)69420-8]

22 **Zinman B**, Harris SB, Neuman J, Gerstein HC, Retnakaran RR, Raboud J, Qi Y, Hanley AJ. Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study. *Lancet* 2010; **376**: 103-111 [PMID: 20605202 DOI: 10.1016/S0140-6736(10)60746-5]

23 **Nissen SE**, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356**: 2457-2471 [PMID: 17517853 DOI: 10.1056/NEJMoa072761]

24 **Singh S**, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007; **298**: 1189-1195 [PMID: 17848653 DOI: 10.1001/jama.298.10.1189]

25 **Nissen SE**, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med* 2010; **170**: 1191-1201 [PMID: 20656674 DOI: 10.1001/archinternmed.2010.207]

26 **Mahaffey KW**, Hafley G, Dickerson S, Burns S, Tourt-Uhlig S, White J, Newby LK, Komajda M, McMurray J, Bigelow R, Home PD, Lopes RD. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. *Am Heart J* 2013; **166**: 240-249.e1 [PMID: 23895806 DOI: 10.1016/j.ahj.2013.05.004]

27 **Lago RM**, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *Lancet* 2007; **370**: 1129-1136 [PMID: 17905165 DOI: 10.1016/S0140-6736(07)61514-1]

28 **Home PD**, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009; **373**: 2125-2135 [PMID: 19501900 DOI: 10.1016/S0140-6736(09)60953-3]

29 **Loke YK**, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 2009; **180**: 32-39 [PMID: 19073651 DOI: 10.1503/cmaj.080486]

30 **Colmers IN**, Bowker SL, Majumdar SR, Johnson JA. Use of thiazolidinediones and the risk of bladder cancer among people with type 2 diabetes: a meta-analysis. *CMAJ* 2012; **184**: E675-E683 [PMID: 22761478 DOI: 10.1503/cmaj.112102]

31 **Kernan WN**, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, Guarino PD, Lovejoy AM, Peduzzi PN, Conwit R, Brass LM, Schwartz GG, Adams HP, Berger L, Carolei A, Clark W, Coull B, Ford GA, Kleindorfer D, O'Leary JR, Parsons MW, Ringleb P, Sen S, Spence JD, Tanne D, Wang D, Winder TR. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. *N Engl J Med* 2016; **374**: 1321-1331 [PMID: 26886418 DOI: 10.1056/NEJMoa1506930]

32 **Liu J**, Wang LN. Peroxisome proliferator-activated receptor gamma agonists for preventing recurrent stroke and other vascular events in patients with stroke or transient ischaemic attack. *Cochrane Database Syst Rev* 2015; **10**: CD010693 [PMID: 26511368 DOI: 10.1002/14651858.CD010693.PUB3]

33 **Green JB**, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2015; **373**: 232-242 [PMID: 26052984 DOI: 10.1056/NEJMoa1501352]

34 **McInnes G**, Evans M, Del Prato S, Stumvoll M, Schweizer A, Lukashevich V, Shao Q, Kothny W. Cardiovascular and heart failure safety profile of vildagliptin: a meta-analysis of 17 000 patients. *Diabetes Obes Metab* 2015; **17**: 1085-1092 [PMID: 26250051 DOI: 10.1111/dom.12548]

35 **White WB**, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013; **369**: 1327-1335 [PMID: 23992602 DOI: 10.1056/NEJMoa1305889]

36 **Papagianni M**, Tziomalos K. Cardiovascular effects of dipeptidyl peptidase-4 inhibitors. *Hippokratia* 2015; **19**: 195-199 [PMID: 27418775]

37 **Leiter LA**, Teoh H, Braunwald E, Mosenzon O, Cahn A, Kumar KM, Smahelova A, Hirshberg B, Stahre C, Frederich R, Bonnici F, Scirica BM, Bhatt DL, Raz I. Efficacy and safety of saxagliptin in older participants in the SAVOR-TIMI 53 trial. *Diabetes Care* 2015; **38**: 1145-1153 [PMID: 25758769 DOI: 10.2337/dc14-2868]

38 **Scirica BM**, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013; **369**: 1317-1326 [PMID: 23992601 DOI: 10.1056/NEJMoa1307684]

39 **Udell JA**, Bhatt DL, Braunwald E, Cavender MA, Mosenzon O, Steg PG, Davidson JA, Nicolau JC, Corbalan R, Hirshberg B, Frederich R, Im K, Umez-Eronini AA, He P, McGuire DK, Leiter LA, Raz I, Scirica BM. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe renal impairment: observations from the SAVOR-TIMI 53 Trial. *Diabetes Care* 2015; **38**: 696-705 [PMID: 25552421 DOI: 10.2337/dc14-1850]

40 **Barnett AH**, Huisman H, Jones R, von Eynatten M, Patel S, Woerle HJ. Linagliptin for patients aged 70 years or older with type 2 diabetes inadequately controlled with common antidiabetes treatments: a randomised, double-blind, placebo-controlled trial. *Lancet* 2013; **382**: 1413-1423 [PMID: 23948125 DOI: 10.1016/S0140-6736(13)61500-7]

41 **Inagaki N**, Onouchi H, Maezawa H, Kuroda S, Kaku K. Once-weekly trelagliptin versus daily alogliptin in Japanese patients with type 2 diabetes: a randomised, double-blind, phase 3, non-inferiority study. *Lancet Diabetes Endocrinol* 2015; **3**: 191-197 [PMID: 25609193 DOI: 10.1016/S2213-8587(14)70251-7]

42 **Inagaki N**, Onouchi H, Sano H, Funao N, Kuroda S, Kaku K. SYR-472, a novel once-weekly dipeptidyl peptidase-4 (DPP-4) inhibitor, in type 2 diabetes mellitus: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2014; **2**: 125-132 [PMID: 24622716 DOI: 10.1016/S2213-8587(13)70149-9]

43 **Pratley RE**, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, Thomsen AB, Søndergaard RE, Davies M. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet* 2010; **375**: 1447-1456 [PMID: 20417856 DOI: 10.1016/S0140-6736(10)60307-8]

44 **Drucker DJ**, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D, Porter L. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet* 2008; **372**: 1240-1250 [PMID: 18782641 DOI: 10.1016/S0140-6736(08)61206-4]

45 **Bergenstal RM**, Wysham C, Macconell L, Malloy J, Walsh B, Yan P, Wilhelm K, Malone J, Porter LE. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet* 2010; **376**: 431-439 [PMID: 20580422 DOI: 10.1016/S0140-6736(10)60590-9]

46 **Buse JB**, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, Hoogwerf BJ, Gao A, Boardman MK, Fineman M, Porter L, Schernthaner G. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet* 2013; **381**: 117-124 [PMID: 23141817 DOI: 10.1016/S0140-6736(12)61267-7]

47 **Pratley RE**, Nauck MA, Barnett AH, Feinglos MN, Ovalle F, Harman-Boehm I, Ye J, Scott R, Johnson S, Stewart M, Rosenstock J. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. *Lancet Diabetes Endocrinol* 2014; **2**: 289-297 [PMID: 24703047 DOI: 10.1016/S2213-8587(13)70214-6]

48 **Dungan KM**, Povedano ST, Forst T, González JG, Atisso C, Sealls W, Fahrbach JL. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet* 2014; **384**: 1349-1357 [PMID: 25018121 DOI: 10.1016/S0140-6736(14)60976-4]

49 **Marso SP**, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016; **375**: 1834-1844 [PMID: 27633186 DOI: 10.1056/NEJMoa1607141]

50 **Cefalu WT**, Leiter LA, Yoon KH, Arias P, Niskanen L, Xie J, Balis DA, Canovatchel W, Meininger G. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet* 2013; **382**: 941-950 [PMID: 23850055 DOI: 10.1016/S0140-6736(13)60683-2]

51 **Barnett AH**, Mithal A, Manassie J, Jones R, Rattunde H, Woerle HJ, Broedl UC. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2014; **2**: 369-384 [PMID: 24795251 DOI: 10.1016/S2213-8587(13)70208-0]

52 **Ridderstråle M**, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. *Lancet Diabetes Endocrinol* 2014; **2**: 691-700 [PMID: 24948511 DOI: 10.1016/S2213-8587(14)70120-2]

53 **Wanner C**, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med* 2016; **375**: 323-334 [PMID: 27299675 DOI: 10.1056/NEJMoa1515920]

54 **Fitchett D**, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. *Eur Heart J* 2016; **37**: 1526-1534 [PMID: 26819227 DOI: 10.1093/eurheartj/ehv728]

55 **Zinman B**, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; **373**: 2117-2128 [PMID: 26378978 DOI: 10.1056/NEJMoa1504720]

56 **Kawamori R**, Tajima N, Iwamoto Y, Kashiwagi A, Shimamoto K, Kaku K. Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. *Lancet* 2009; **373**: 1607-1614 [PMID: 19395079 DOI: 10.1016/S0140-6736(09)60222-1]

57 **Tziomalos K**. Barriers to insulin treatment in patients with type 2 diabetes mellitus. *Expert Opin Pharmacother* 2017; **18**: 233-234 [PMID: 28067057 DOI: 10.1080/14656566.2017.1280462]

58 **Phung OJ**, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA* 2010; **303**: 1410-1418 [PMID: 20388897 DOI: 10.1001/jama.2010.405]

59 **Hong J**, Zhang Y, Lai S, Lv A, Su Q, Dong Y, Zhou Z, Tang W, Zhao J, Cui L, Zou D, Wang D, Li H, Liu C, Wu G, Shen J, Zhu D, Wang W, Shen W, Ning G. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. *Diabetes Care* 2013; **36**: 1304-1311 [PMID: 23230096 DOI: 10.2337/dc12-0719]

60 **Mazzone T**, Meyer PM, Feinstein SB, Davidson MH, Kondos GT, D'Agostino RB, Perez A, Provost JC, Haffner SM. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA* 2006; **296**: 2572-2581 [PMID: 17101640 DOI: 10.1001/jama.296.21.joc60158]

61 **Simpson SH**, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. *Lancet Diabetes Endocrinol* 2015; **3**: 43-51 [PMID: 25466239 DOI: 10.1016/S2213-8587(14)70213-X]

62 **Dormandy JA**, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, Mokán M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; **366**: 1279-1289 [PMID: 16214598 DOI: 10.1016/S0140-6736(05)67528-9]

63 **Turner RC**, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 1999; **281**: 2005-2012 [PMID: 10359389 DOI: 10.1001/jama.281.21.2005]

64 **Lincoff AM**, Tardif JC, Schwartz GG, Nicholls SJ, Rydén L, Neal B, Malmberg K, Wedel H, Buse JB, Henry RR, Weichert A, Cannata R, Svensson A, Volz D, Grobbee DE. Effect of aleglitazar on cardiovascular outcomes after acute coronary syndrome in patients with type 2 diabetes mellitus: the AleCardio randomized clinical trial. *JAMA* 2014; **311**: 1515-1525 [PMID: 24682069 DOI: 10.1001/jama.2014.3321]

65 **Gallwitz B**, Rosenstock J, Rauch T, Bhattacharya S, Patel S, von Eynatten M, Dugi KA, Woerle HJ. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. *Lancet* 2012; **380**: 475-483 [PMID: 22748821 DOI: 10.1016/S0140-6736(12)60691-6]

66 **Darsalia V**, Ortsäter H, Olverling A, Darlöf E, Wolbert P, Nyström T, Klein T, Sjöholm Å, Patrone C. The DPP-4 inhibitor linagliptin counteracts stroke in the normal and diabetic mouse brain: a comparison with glimepiride. *Diabetes* 2013; **62**: 1289-1296 [PMID: 23209191 DOI: 10.2337/db12-0988]

67 **Marso SP**, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016; **375**: 311-322 [PMID: 27295427 DOI: 10.1056/NEJMoa1603827]

68 **Pfeffer MA**, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med* 2015; **373**: 2247-2257 [PMID: 26630143 DOI: 10.1056/NEJMoa1509225]

69 **Fisher M**, Petrie MC, Ambery PD, Donaldson J, Ye J, McMurray JJ. Cardiovascular safety of albiglutide in the Harmony programme: a meta-analysis. *Lancet Diabetes Endocrinol* 2015; **3**: 697-703 [PMID: 26276240 DOI: 10.1016/S2213-8587(15)00233-8]

70 **Reeves MJ**, Vaidya RS, Fonarow GC, Liang L, Smith EE, Matulonis R, Olson DM, Schwamm LH. Quality of care and outcomes in patients with diabetes hospitalized with ischemic stroke: findings from Get With the Guidelines-Stroke. *Stroke* 2010; **41**: e409-e417 [PMID: 20224058 DOI: 10.1161/STROKEAHA.109.572693]

71 **Tziomalos K**, Spanou M, Bouziana SD, Papadopoulou M, Giampatzis V, Kostaki S, Dourliou V, Tsopozidi M, Savopoulos C, Hatzitolios AI. Type 2 diabetes is associated with a worse functional outcome of ischemic stroke. *World J Diabetes* 2014; **5**: 939-944 [PMID: 25512800 DOI: 10.4239/wjd.v5.i6.939]

72 **Hatzitolios AI**, Didangelos TP, Zantidis AT, Tziomalos K, Giannakoulas GA, Karamitsos DT. Diabetes mellitus and cerebrovascular disease: which are the actual data? *J Diabetes Complications* 2009; **23**: 283-296 [PMID: 18358748 DOI: 10.1016/j.jdiacomp.2008.01.004]

73 **Magkou D**, Tziomalos K. Antidiabetic treatment, stroke severity and outcome. *World J Diabetes* 2014; **5**: 84-88 [PMID: 24748923 DOI: 10.4239/wjd.v5.i2.84]

74 **Kunte H**, Schmidt S, Eliasziw M, del Zoppo GJ, Simard JM, Masuhr F, Weih M, Dirnagl U. Sulfonylureas improve outcome in patients with type 2 diabetes and acute ischemic stroke. *Stroke* 2007; **38**: 2526-2530 [PMID: 17673715 DOI: 10.1161/STROKEAHA.107.482216]

75 **Favilla CG**, Mullen MT, Ali M, Higgins P, Kasner SE. Sulfonylurea use before stroke does not influence outcome. *Stroke* 2011; **42**: 710-715 [PMID: 21330623 DOI: 10.1161/STROKEAHA.110.599274]

76 **Lee J**, Reding M. Effects of thiazolidinediones on stroke recovery: a case-matched controlled study. *Neurochem Res* 2007; **32**: 635-638 [PMID: 16960755 DOI: 10.1007/s11064-006-9138-3]

77 **Tziomalos K**, Bouziana SD, Spanou M, Kostaki S, Papadopoulou M, Giampatzis V, Dourliou V, Kostourou DT, Savopoulos C, Hatzitolios AI. Prior treatment with dipeptidyl peptidase 4 inhibitors is associated with better functional outcome and lower in-hospital mortality in patients with type 2 diabetes mellitus admitted with acute ischaemic stroke. *Diab Vasc Dis Res* 2015; **12**: 463-466 [PMID: 26297528 DOI: 10.1177/1479164115597867]

78 **Marx N**, Rosenstock J, Kahn SE, Zinman B, Kastelein JJ, Lachin JM, Espeland MA, Bluhmki E, Mattheus M, Ryckaert B, Patel S, Johansen OE, Woerle HJ. Design and baseline characteristics of the CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA®). *Diab Vasc Dis Res* 2015; **12**: 164-174 [PMID: 25780262 DOI: 10.1177/1479164115570301]

# 79 Boehringer Ingelheim. Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [accessed 2017 Apr 10]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT01897532 NLM Identifier: NCT01897532

**P-Reviewer:** García-Mayor RV, Johansen OE, Lyerly Jr JW, Raghow RS, Tomkin GH **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Specialty type:** Endocrinology and metabolism

**Country of origin:** Greece

**Peer-review report classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): D, D

Grade E (Poor): 0

**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  Pioglitazone | High | Reduction in triglyceride levels | Might reduce the risk of recurrent stroke |
| DPP-4 inhibitors  (1) Alogliptin, saxagliptin, sitagliptin  (2) Linagliptin | Moderate | None | No effect  Reduction (?) |
| GLP-1 agonists  (1) Liraglutide, lixisenatide  (2) Semaglutide | High | Weight loss and blood pressure reduction | No effect  Reduction |
| SGLT-2 inhibitors  Empaglifozin | Moderate | Weight loss and blood pressure reduction | No effect |

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