



Effects of Thiazolidinedione and New Antidiabetic Agents on Stroke

Chang Ho Ahn,^a Soo Lim^{a,b}

^aDepartment of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

^bDepartment of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

Patients with hyperglycemia are at a high risk of cardio- and cerebrovascular diseases. Diabetes patients also have poor outcomes after cerebrovascular disease development. Several classes of drugs are used for diabetes management in clinical practice. Thiazolidinedione (TZD) was introduced in the late 1990s, and new antidiabetic agents have been introduced since 2000. After issues with rosiglitazone in 2007, the U.S. Food and Drug Administration strongly recommended that trials investigating cardiovascular risk associated with new antidiabetic medications should be conducted before drug approval in the United States, to prove the safety of these new drugs and to determine their superiority to previous medications. Currently, results are available from two studies with TZD focusing on cardiovascular diseases, including stroke, and from 12 cardiovascular outcome trials focusing on major adverse cardiovascular events associated with new antidiabetic agents (four with dipeptidyl peptidase-4 inhibitors, three with sodium-glucose cotransporter-2 inhibitors, and five with glucagon-like peptide-1 analogues). These studies showed different results for primary cardiovascular outcomes and stroke prevention. It is important to determine whether prescription of TZD or new antidiabetic medications compared to conventional treatment, such as sulfonylurea or insulin, is better for stroke management. Furthermore, it is unclear whether drugs in the same class show greater safety and efficacy than other drugs for stroke management.

Correspondence: Soo Lim
Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea
Tel: +82-31-787-7035
Fax: +82-31-787-4051
E-mail: limsoo@snu.ac.kr

Received: January 3, 2019
Revised: April 1, 2019
Accepted: April 5, 2019

Keywords Stroke; Diabetes mellitus; Thiazolidinediones; Dipeptidyl-peptidase IV inhibitors; Sodium-glucose transporter 2; Glucagon-like peptide 1

Introduction

Diabetes management requires coordinated efforts to change the patient's lifestyle to include a healthy diet and regular exercise, and to manage multiple risk factors, to prevent or delay complications such as stroke.¹⁻³ Patients with hyperglycemia or diabetes mellitus (DM) are at high risk of cerebrovascular ischemic stroke.^{4,5} DM is also associated with poor outcome in patients with cerebral hemorrhage.⁶ However, it is unclear whether it is better to prescribe intensive glucose-lowering treatment than conventional treatment for stroke manage-

ment, and whether specific antidiabetic agents are safer and more efficacious than other drugs for stroke management.

Here, we discuss the mechanisms underlying the relationship between glucose homeostasis and stroke development, and provide an overview of the efficacy of glucose-lowering treatment in stroke management. We also discuss evidence from recent large clinical trials of thiazolidinedione (TZD) and new antidiabetic medications such as dipeptidyl peptidase-4 (DPP4) inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and glucagon-like peptide-1 (GLP1) analogues, which suggest the potential of these agents in primary and secondary stroke prevention.

Glucose metabolism and stroke

The association between DM and stroke involves the interplay of complex mechanisms, including various hemodynamic and metabolic pathways (Figure 1). DM is characterized by chronic low-grade inflammation, oxidative stress, endothelial dysfunction, hypercoagulability, dyslipidemia, and insulin resistance.⁷ These factors contribute individually and collectively to diabetic macrovascular complications. Three distinct pathways are involved in diabetes-associated increased vasculopathy: increased production of advanced glycosylation end products (AGEs),⁸ increased reactive oxygen species (ROS) production and oxidative damage to vessels,⁹ and activation of the aldose reductase pathway, which is driven by high blood glucose concentration.¹⁰ Activation of protein kinase C (PKC) isozymes is also involved in diabetes-related vascular complications.¹⁰

High circulatory glucose concentrations facilitate the non-enzymatic glycosylation of proteins in the blood vessel walls, resulting in AGE formation. Binding of AGE to its receptors aggravates atherogenicity by accelerating oxidation and uptake

of low density lipoprotein (LDL).⁸ Hyperglycemia stimulates the upregulation of AGEs. Moreover, nuclear factor κ B and activator protein-1 increase proatherogenic gene expression and recruit numerous mediators of atherogenesis, including white blood cells, adhesion molecules, monocyte chemoattractant protein-1, and other inflammatory cytokines.¹¹

Hyperglycemia-induced ROS generation and insulin resistance damage vascular smooth muscle and endothelial cells.¹² Superoxide anions neutralize nitric oxide (NO) by forming peroxynitrite ions, which decrease the bioavailability of endothelium-derived NO.¹³ This inhibits endothelium-mediated vasodilation, stimulates abnormal platelet activation, and increases vascular smooth muscle cell proliferation and migration (Figure 1). ROS also increases LDL oxidation in vessel walls.¹³

Evidence suggests the role of PKC activation in hyperglycemia-induced vascular and endothelial dysfunction.¹⁰ Glucose transported into vascular cells stimulates *de novo* synthesis of diacylglycerol and PKC activation. PKC isoforms activation stimulates proatherosclerotic gene expression and vascular cell proliferation and migration, and impairs NO-mediated vasodilation. PKC acti-

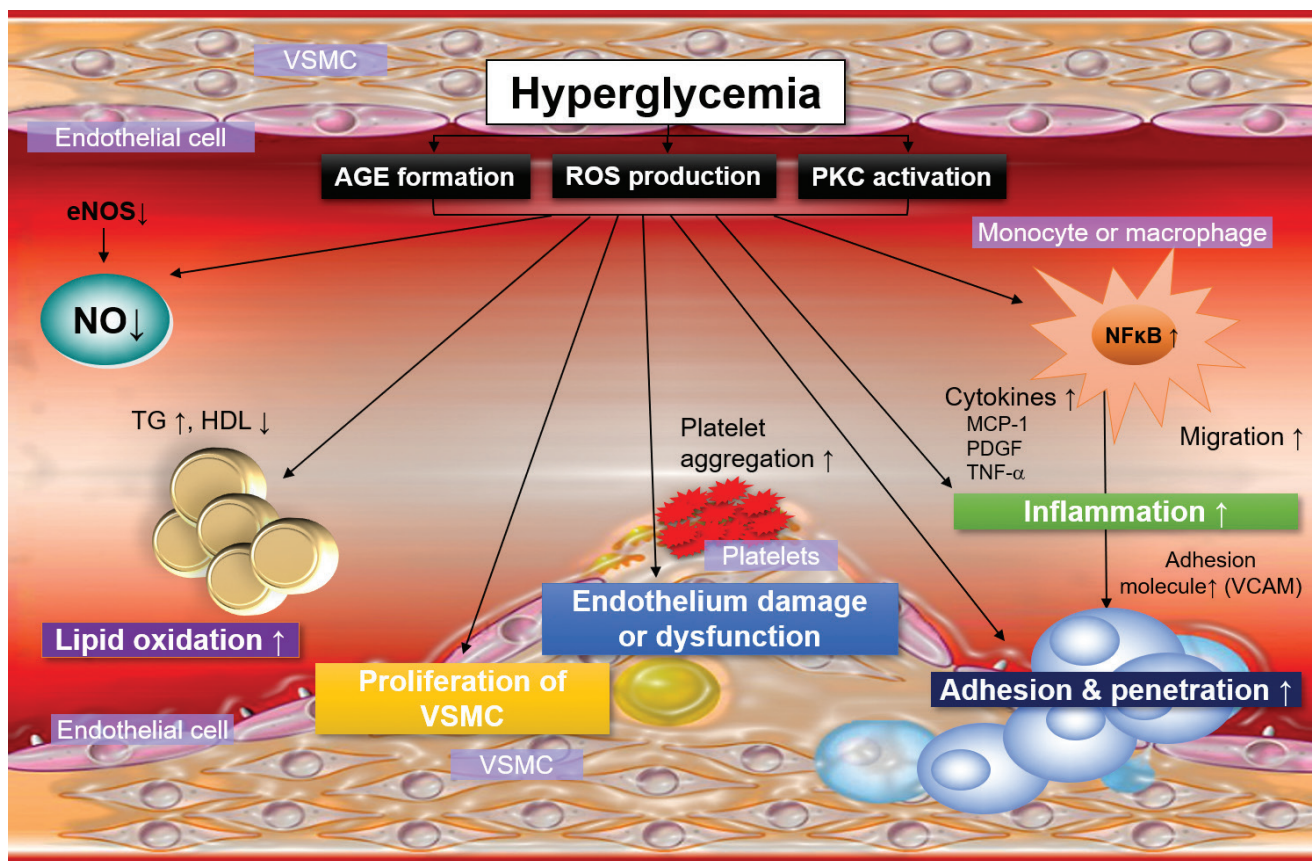


Figure 1. Pathogenic mechanisms for the involvement of hyperglycemia in the development of atherosclerotic cerebrovascular diseases. VSMC, vascular smooth muscle cell; AGE, advanced glycosylation end product; ROS, reactive oxygen species; PKC, protein kinase C; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; TG, triglyceride; HDL, high density lipoprotein; NF κ B, nuclear factor κ B; MCP-1, monocyte chemoattractant protein-1; PDGF, platelet-derived growth factor; TNF- α , tumor necrosis factor- α ; VCAM, vascular cell adhesion molecule.

vation also increases vascular endothelial cell permeability.¹⁴

The relationship between direct clinical risk factors and their roles in stroke development is illustrated in Figure 2. In addition to hyperglycemia and insulin resistance, high blood pressure, dyslipidemia, and smoking are implicated in the pathogenesis of stroke by increasing peripheral resistance and accelerating atherosclerosis. High urinary albumin excretion is another independent predictor of stroke in diabetes patients.¹⁵ These factors aggravate inflammation and increase oxidative stress, leading to endothelial dysfunction, increased thrombotic activity, and accelerated vascular smooth muscle cell proliferation and migration. These processes contribute to thrombus formation and plaque progression, which increase stroke risk.

Diabetic autonomic neuropathy and retinopathy are also risk factors for stroke.^{16,17} Therefore, several clinical factors are involved in increasing stroke risk.

Ideal approach to decreasing the risk of cardiovascular outcomes in diabetes patients

Evidence for the beneficial effects of intensive glycaemic control in preventing cardiovascular diseases is inconclusive. However, intensive glycaemic control as a part of a multifactorial intervention for atherosclerotic risk factors was effective in reducing cardiovascular disease risk and overall mortality in the Steno-2 study^{1,18} and cerebrovascular disease risk in the Japan Diabetes Outcome Intervention Trial 3 (J-DOIT3) study.¹⁹ The Ste-

no-2 trial was the first to investigate the impact of multifactorial interventions in patients with type 2 diabetes (T2D), even though the sample size was small ($n=160$). Investigators treated study participants with multiple pharmacological agents and implemented lifestyle modifications that targeted hyperglycemia, hypertension, dyslipidemia, and microalbuminuria. This multifactorial intervention with intensive glycaemic control (target glycosylated hemoglobin [HbA1c] level $<6.5\%$) reduced the incidence of the composite cardiovascular endpoint (hazard ratio [HR], 0.47; 95% confidence interval [CI], 0.24 to 0.73; $P=0.008$)¹⁸ and overall mortality (HR, 0.54; 95% CI, 0.32 to 0.89; $P=0.02$).¹ Another study involving Japanese patients with diabetes (the J-DOIT3 study) included an intensified intervention with tight glycaemic control (target HbA1c $<6.2\%$). This study observed substantial benefit for cerebrovascular event prevention, including stroke and the need for carotid endarterectomy, percutaneous transluminal cerebral angioplasty, and carotid artery stenting, compared with that associated with conventional therapy (target HbA1c $<6.9\%$) in patients with T2D (HR, 0.42; 95% CI, 0.24 to 0.74; $P=0.002$).¹⁹ The success of multifactorial intervention trials in reducing atherosclerotic vascular disease risk suggests the complex multifactorial nature of atherosclerosis. Therefore, focusing on a single risk factor may not be sufficient to alter its progression.

Mechanistically, severe hypoglycemia may aggravate brain injury²⁰ because the brain uses glucose as its primary fuel. Intensive glucose lowering with antidiabetic medications that do not induce hypoglycemia is helpful in stroke prevention. In addition, hyperglycemia increases stroke risk even in prediabetes patients.²¹ Therefore, controlling hyperglycemia to achieve normal glucose levels may be beneficial to prevent cerebrovascular disease.

TZD and new antidiabetic agents such as DPP4 inhibitors, SGLT2 inhibitors, and GLP1 analogues do not induce hypoglycemia. This may be why an active glucose-lowering approach with these agents was shown to be neutral (DPP4 inhibitors) or beneficial (TZD, SGLT2 inhibitors, and several GLP1 analogues) on cardiovascular outcomes compared with the effects of previous agents such as sulfonylurea and insulin. Optimal glucose control that does not induce hypoglycemia may therefore be the ideal approach to achieve better cerebrovascular outcomes.

Randomized controlled trials with TZD and new agents

The results of stroke in randomized controlled trials (RCTs) with TZD and new antidiabetic agents are summarized in Table 1.

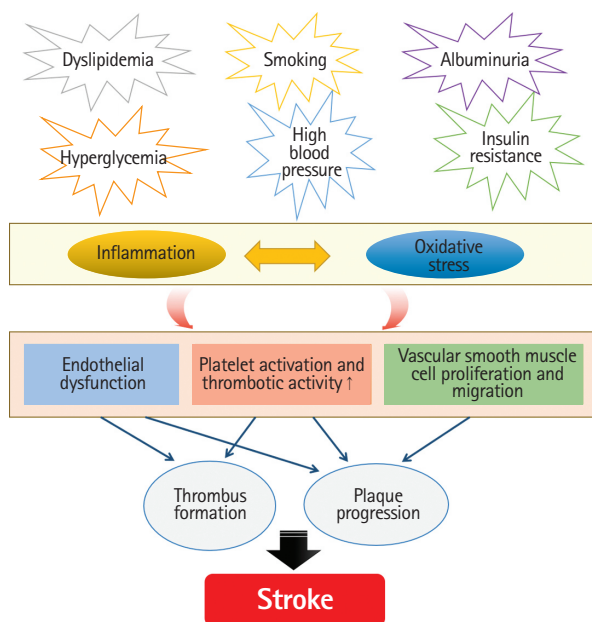


Figure 2. Contributing risk factors and their roles in the development of stroke.

Table 1. Stroke events in recent cardiovascular outcome studies of antidiabetic medications

Drug (study name)	Stroke events	HR (95% CI)
TZD		
Pioglitazone (PROactive) ²⁴	Stroke	0.81 (0.61–1.07)
Pioglitazone (IRIS) ^{26*}	Stroke	0.82 (0.61–1.10)
DPP4 inhibitors		
Saxagliptin (SAVOR-TIMI) ³⁰	Ischemic stroke	1.11 (0.88–1.39)
Alogliptin (EXAMINE) ³¹	Nonfatal stroke	0.91 (0.55–1.50)
Sitagliptin (TECOS) ³²	Fatal or nonfatal stroke	0.97 (0.79–1.19)
Linagliptin (CARMELINA) ³³	Fatal or nonfatal stroke	0.91 (0.67–1.23)
SGLT2 inhibitors		
Empagliflozin (EMPA-REG OUTCOME) ³⁵	Fatal or nonfatal stroke	1.18 (0.89–1.56)
Canagliflozin (CANVAS) ³⁶	Fatal or nonfatal stroke	0.87 (0.69–1.09)
Dapagliflozin (DECLARE-TIMI58) ³⁷	Ischemic stroke	1.01 (0.84–1.21)
GLP1 analogues		
Lixisenatide (ELIXA) ⁴³	Stroke	1.12 (0.79–1.58)
Once weekly exenatide (EXSCEL) ⁴⁴	Fatal or nonfatal stroke	0.85 (0.70–1.03)
Liraglutide (LEADER) ⁴⁰	Fatal or nonfatal stroke, or TIA	0.86 (0.71–1.06)
Semaglutide (SUSTAIN-6) ⁴¹	Nonfatal stroke	0.61 (0.38–0.99)
Albiglutide (HARMONY Outcome) ⁴²	Nonfatal stroke	0.86 (0.66–1.14)

HR, hazard ratio; CI, confidence interval; TZD, thiazolidinedione; PROactive, PROspective pioglitazone Clinical Trial In macroVascular Events; IRIS, Insulin Resistance Intervention after Stroke; DPP4, dipeptidyl peptidase-4; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus; SGLT2, sodium-glucose cotransporter-2; EMPA-REG OUTCOME, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; CANVAS, Canagliflozin Cardiovascular Assessment Study; DECLARE-TIMI58, Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; GLP1, glucagon-like peptide-1; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; TIA, transient ischemic attack; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide 6; HARMONY, albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease.

*IRIS study recruited participants with insulin resistance, but without type 2 diabetes mellitus.

TZDs

The beneficial effects of TZDs have been shown in clinical studies through carotid ultrasonography to measure carotid intima-media thickness (IMT), a surrogate marker of cerebrovascular diseases. Carotid IMT progression was significantly attenuated after treatment with rosiglitazone, a TZD, for 48 weeks compared with that after placebo treatment (−0.012 mm vs. 0.031 mm, respectively; *P*=0.03) in non-diabetes patients.²² In patients with T2D, carotid IMT decreased significantly more after pioglitazone treatment for 24 weeks (−0.054 mm) than after glimepiride treatment (−0.002 mm, *P*<0.005).²³ These changes were accompanied by insulin resistance attenuation. TZDs may therefore act as insulin sensitizers and play a role in preventing or regressing atherosclerosis, particularly in the carotid artery.

The PROspective pioglitazone Clinical Trial In macroVascular Events (PROactive) study is a prospective, double-blind study of 5,238 patients with T2D with a history of macrovascular disease. In this study, pioglitazone did not reduce composite car-

diovascular outcome risk, including death from any cause, nonfatal myocardial infarction, stroke, acute coronary syndrome, leg amputation, coronary revascularization, or leg revascularization (HR, 0.90; event rate: 19.7% [514/2,605] for pioglitazone vs. 21.7% [572/2,633] for placebo; 95% CI, 0.80 to 1.02).²⁴ The rates of stroke did not differ between the two groups (HR, 0.81; event rate: 3.3% [86/2,605] in the pioglitazone group vs. 4.1% [107/2,633] in the placebo group; 95% CI, 0.61 to 1.07) (Figure 3). In a later analysis of patients from the PROactive study with previous stroke, the rate of fatal or nonfatal stroke events was significantly lower in the pioglitazone group than that in the placebo group (HR, 0.53; event rate: 5.6% in the pioglitazone group vs. 10.2% in the placebo group; 95% CI, 0.34 to 0.85).²⁵

The Insulin Resistance Intervention after Stroke (IRIS) study evaluated the efficacy of pioglitazone in 3,876 non-diabetes patients who previously experienced ischemic stroke or transient ischemic attack (TIA).²⁶ Pioglitazone therapy reduced the

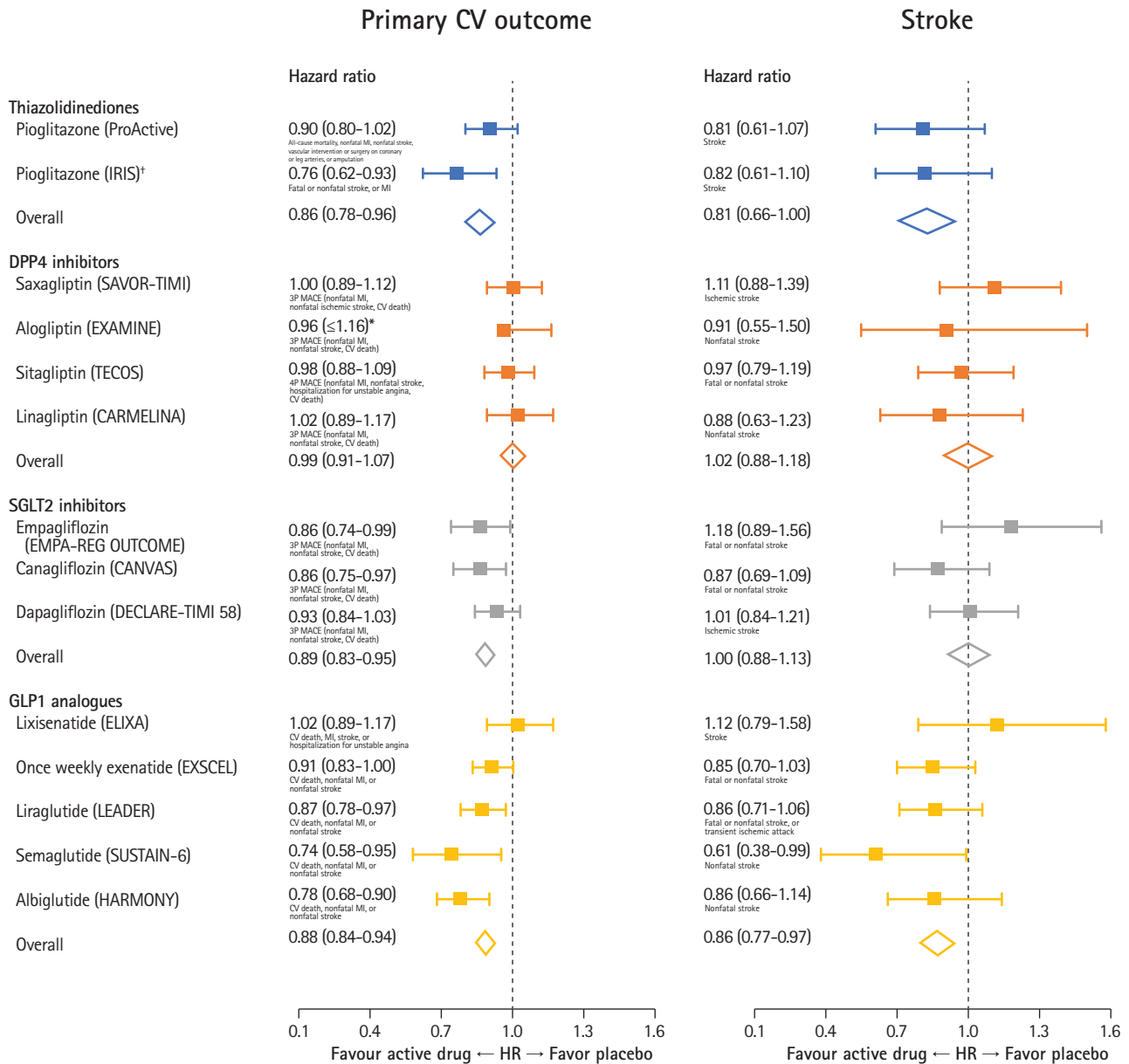


Figure 3. Effect of thiazolidinedione and novel antidiabetic agents on primary cardiovascular outcome and stroke. The hazard ratios (HRs) with 95% confidence intervals (CIs) are provided for the active drug compared with the placebo. Primary cardiovascular outcomes are slightly different in each study. The overall effects were calculated using fixed effects models unless there was a significant heterogeneity among trials. Heterogeneity of the clinical trials was assessed using Cochran's Q test and Higgins and Thompson's I^2 ($P < 0.05$ or $I^2 > 50$ were considered as indicative of significant heterogeneity). Analyses were performed using R version 3.5.1 (R Foundation for Statistical Computing). PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; IRIS, Insulin Resistance Intervention after Stroke; MI, myocardial infarction; DPP4, dipeptidyl peptidase-4; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction; MACE, major adverse cardiovascular event; CV, cardiovascular; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus; SGLT2, sodium-glucose cotransporter-2; EMPA-REG OUTCOME, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; CANVAS, CANagliflozin CardioVascular Assessment Study; DECLARE-TIMI58, Dapagliflozin Effect on CardiovascuLAR Events-Thrombolysis in Myocardial Infarction 58; GLP1, glucagon-like peptide-1; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide 6; HARMONY, albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease. *The parenthetical value is the upper boundary of the one-sided repeated CI, at an α -level of 0.01; [†]IRIS study recruited participants with insulin resistance, but without type 2 diabetes mellitus.

occurrence of stroke and myocardial infarction (event rate: 9.0% in the pioglitazone group vs. 11.8% in the placebo group; HR, 0.76; 95% CI, 0.62 to 0.93) (Figure 3).²⁶ However, the rate of stroke alone did not differ between the pioglitazone and placebo groups (HR, 0.82; 95% CI, 0.61 to 1.10) (Figure 3).

In a review of RCTs that compared TZDs and placebo for the secondary prevention of stroke and related vascular events in people who had experienced stroke or TIA, TZD reduced stroke recurrence (relative risk, 0.52; 95% CI, 0.34 to 0.80).²⁷ Therefore, TZDs may reduce recurrent stroke and related vascular event risk both in patients with T2D and in those with insulin resistance.

DPP4 inhibitors

DPP4 inhibitors are new antidiabetic agents for T2D²⁸ that do not induce hypoglycemia or weight gain. Although these and GLP1 analogues have similar incretin-based activities, their effects on cardiovascular disease risk differ.²⁹ Cardiovascular safety trials of DPP4 inhibitors such as saxagliptin,³⁰ alogliptin,³¹ sitagliptin,³² and linagliptin³³ showed neutral effects on the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. Besides these safety trials,³⁰⁻³² no study has focused on the effects of DPP4 inhibitors on the primary or secondary prevention of stroke alone. HRs for the outcome of ischemic stroke, nonfatal stroke, and fatal or nonfatal stroke were 1.11 (95% CI, 0.88 to 1.39; $P=0.38$), 0.91 (95% CI, 0.55 to 1.50; $P=0.71$), 0.97 (95% CI, 0.79 to 1.19; $P=0.76$), and 1.02 (95% CI, 0.89 to 1.17; $P=0.74$) for saxagliptin, alogliptin, sitagliptin, and linagliptin, respectively (Figure 3).

SGLT2 inhibitors

SGLT2 inhibitors are emerging antidiabetic agents³⁴ that show cardiovascular benefits. Empagliflozin resulted in a beneficial cardiovascular outcome in the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial.³⁵ The primary composite outcome, including death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, occurred in 10.5% of patients in the empagliflozin group and 12.1% of those in the placebo group (HR, 0.86; 95.02% CI, 0.74 to 0.99). Cardiovascular risk was reduced as early as 6 months, suggesting the cardiovascular benefit associated with empagliflozin is unlikely to be induced by its glucose-lowering properties. Furthermore, empagliflozin therapy was associated with an increased but nonsignificant risk of ischemic stroke (HR, 1.24; 95% CI, 0.92 to 1.67; $P=0.16$).

The CANagliptin CardioVascular Assessment Study (CANVAS) program showed that patients treated with canagliflozin had a lower risk of cardiovascular events than those who received the placebo. However, canagliflozin showed no benefit

in preventing stroke, although the point estimate was <1 for fatal or nonfatal stroke compared with the placebo (HR, 0.87; 95% CI, 0.69 to 1.09).³⁶

In the Dapagliflozin Effect on CardiovascuLAR Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI58) study, 40.6% of participants showed established atherosclerotic cardiovascular disease and 59.4% had multiple cardiovascular risk factors. Dapagliflozin therapy was not superior in terms of the original primary cardiovascular outcome (HR, 0.93; 95% CI, 0.84 to 1.03) but showed benefits in reducing the risk of cardiovascular mortality or hospitalization for heart failure (HR, 0.83; 95% CI, 0.73 to 0.95).³⁷ The point estimates for ischemic stroke were similar in the dapagliflozin and placebo arms (HR, 1.01; 95% CI, 0.84 to 1.21) (Figure 3).

A recent population-based observational study showed that SGLT2 inhibitors (dapagliflozin, empagliflozin, or canagliflozin) were associated with reduced cardiovascular mortality compared to other glucose-lowering drugs (HR, 0.53; 95% CI, 0.40 to 0.71; $P<0.05$).³⁸ Furthermore, no difference in nonfatal stroke risk was observed between the groups treated with the SGLT2 inhibitor and placebo (HR, 0.86; 95% CI, 0.72 to 1.04). A meta-analysis of SGLT2 inhibitors and stroke risk also showed the neutral effects of SGLT2 inhibitors on stroke risk compared to that of the placebo.³⁹ Evidence therefore suggests that SGLT2 inhibitor use is associated with reduced rates of cardiovascular events and mortality. However, in cardiovascular outcome trials, SGLT2 inhibitors showed inconsistent or nonsignificant effects on stroke risk.

GLP1 analogues

Among five GLP1 analogues evaluated, liraglutide,⁴⁰ semaglutide,⁴¹ and albiglutide⁴² showed superiority in terms of composite cardiovascular outcome. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)⁴⁰ trial, the HR for fatal or nonfatal stroke was 0.86 (95% CI, 0.71 to 1.06; $P=0.16$) in the liraglutide-treated group. In the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide (SUSTAIN)-6 trial,⁴¹ the HR for nonfatal stroke was 0.61 (95% CI, 0.38 to 0.99; $P=0.04$) in the semaglutide-treated group (Figure 3). The Harmony Outcomes study reported the superiority of albiglutide therapy in terms of the cardiovascular composite outcome (HR, 0.78; 95% CI, 0.68 to 0.90) but not of stroke (HR, 0.86; 95% CI, 0.66 to 1.14).⁴²

In contrast, lixisenatide treatment (Evaluation of Lixisenatide in Acute Coronary Syndrome [ELIXA] study)⁴³ and once-weekly exenatide treatment (Exenatide Study of Cardiovascular Event Lowering [EXSCEL] study)⁴⁴ were not superior in terms of stroke prevention or primary cardiovascular outcome. Therefore, stud-

ies of GLP1 analogues have produced inconsistent results for primary cardiovascular outcome, and their effects on stroke remain unclear.

Effects of individual antidiabetic agents on stroke

TZDs

TZD is an agonist of peroxisome proliferator-activated receptor- γ (PPAR γ), a nuclear receptor that regulates the transcription of genes involved in glucose and lipid metabolism. TZD increases insulin sensitivity in muscle and adipose tissue. However, PPAR γ is expressed ubiquitously in other tissues and TZD exerts various pleiotropic effects. In terms of cerebrovascular diseases, TZD has both neuroprotective and antiatherosclerotic effects.

TZD improves the survival of neurons and glial cells, especially microglia, by reducing neuroinflammation.^{45,46} Accordingly, TZD is protective against both ischemic and excitotoxic neuronal stress.⁴⁷ In mouse models of oxygen/glucose deprivation or glutamate/N-methyl-D-aspartate toxicity, PPAR γ activation reduced neuronal death. However, mice lacking PPAR γ in neurons were more susceptible to ischemic damage caused by focal cerebral ischemia.⁴⁸

TZD also prevents atherosclerosis progression. *In vivo* studies of atherosclerosis have shown the antiatherosclerotic effects of TZDs. Rosiglitazone reduced atherosclerosis development in LDL-receptor-deficient mice.⁴⁹ Lobeglitazone, another TZD, reduced atheroma burden in a balloon-injury model using high-fat and high-fructose diet-fed apolipoprotein E (apoE)-knockout mice.⁵⁰ These antiatherosclerotic effects may be independent of TZD's metabolic effects. Rosiglitazone showed beneficial effects on atherosclerosis independent of its effects on glucose and lipid levels in insulin-insufficient streptozotocin-treated apoE-knockout mice.⁵¹ TZD can act on monocytes, endothelial cells, and vascular smooth muscle cells, which are crucial in the pathogenesis of atherosclerosis. TZD reduces proinflammatory cytokine production in monocytes, reduces adhesion molecule and chemokine expression in endothelial cells, and suppresses vascular smooth muscle cell proliferation and migration.⁵² Collectively, these effects may contribute to TZD's antiatherosclerotic properties.

There are few human mechanistic studies available, but TZD has also been shown to improve endothelial function in humans. In an RCT of patients with impaired glucose tolerance, endothelial function measured by brachial artery flow-mediated dilation improved after treatment with pioglitazone at 30 mg/day for 12 weeks.⁵³

DPP4 inhibitors

DPP4 inhibitors increase circulating active GLP1 levels two-fold, and potential antiatherosclerotic effects of DPP4 inhibitors may occur through GLP1 action. In apoE-knockout mice fed a high-fat diet, sitagliptin treatment decreased atherosclerotic plaque burden.^{54,55} However, in human studies, results were inconsistent. In two RCTs, alogliptin and sitagliptin therapy both attenuated the progression of carotid IMT, as measured via carotid ultrasonography.^{56,57} Conversely, another RCT of sitagliptin showed no effects on carotid IMT.⁵⁸ In animal studies, DPP4 inhibitors also showed direct antistroke effects. In high-fat diet-fed obese diabetic mice, linagliptin reduced brain infarct volume after middle cerebral artery occlusion, whereas glimepiride did not reduce brain ischemic lesions despite the greater attenuation of hyperglycemia.⁵⁹

Several basic cell studies support the antiatherosclerotic effects of DPP4 inhibitors. Direct treatment of human vascular endothelial cells with sitagliptin decreased tumor necrosis factor- α -induced upregulation of adhesion molecules.⁶⁰ Another *in vitro* study showed that sitagliptin decreased the production of ROS and increased endothelial NO synthase expression in endothelial cells.⁶¹ Therefore, the antiatherosclerotic effects of DPP4 inhibitors may be explained by their anti-inflammatory and antioxidant properties.⁶²

GLP1 is not the only substrate of DPP4. DPP4 inactivates various peptide hormones including glucose-dependent insulinotropic polypeptide, B-type natriuretic peptide, stromal cell-derived factor-1 α (SDF1 α), and substance P.⁶³ In a recent study of mice, linagliptin treatment increased active SDF1 α levels in brain tissue, and blockade of the SDF1 α -C-X-C chemokine receptor type 4 (CXCR4) pathway with a specific antagonist abolished the positive effects of linagliptin on functional outcomes after stroke.⁶⁴

SGLT2 inhibitors

SGLT2 inhibitors reduce hyperglycemia by bypassing the action of insulin and inducing glycosuria, and by reducing body weight and blood pressure.⁶⁵ This unique mode of action modulates both hyperinsulinemia and conventional cardiovascular risk factors, including visceral obesity and albuminuria.⁶⁶ We recently showed that the atheromatous plaque area in the aortic arch was significantly smaller after empagliflozin treatment than after sulfonylurea treatment in atherosclerosis-prone mice.⁶⁷ Another study showed that empagliflozin treatment mitigated coronary artery thickening and remodeling and vascular dysfunction in *db/db* mice.⁶⁸ Interestingly, SGLT2 inhibitors induce hyperketonemia, which may provide a "thrifty substrate" and lead to cardioprotective effects.⁶⁹ Increased ketone levels may

also directly affect the risk of stroke. In rodent studies, β -hydroxybutyrate, a ketone body that is increased after SGLT2 inhibitor treatment, could reduce brain infarct size by activating neuroprotective macrophages, and shift glucose metabolism toward reducing oxidative stress.^{70,71} Therefore, the diverse metabolic and hemodynamic effects of SGLT2 inhibitors appear to protect the cardiovascular system,⁷² although it is unclear whether this also applies to the cerebrovascular system.

However, in the EMPA-REG OUTCOME trial, empagliflozin treatment slightly increased stroke risk.³⁵ Dehydration and/or increased hematocrit was a proposed mechanism for this finding. However, studies of two other SGLT2 inhibitors reported inconsistent results: decreased stroke risk was observed in the canagliflozin group in the CANVAS program³⁶ and a neutral effect was observed in the dapagliflozin group in the DECLARE-TIMI58 study.³⁷ So far, it is unclear whether this is a class effect or that of individual drugs. Therefore, mechanistic studies of SGLT inhibitors are warranted.

GLP1 analogues

The cardioprotective effects of GLP1 have been consistently reported in preclinical studies, including endothelial function modulation via macrophage inflammatory response inhibition,⁷³ increased endothelial NO production, reduced vascular adhesion molecule release,⁷⁴ and suppressed vascular cell migration.⁷⁵ In an atherosclerotic mouse model, a 4-week infusion of GLP1(7–36) amide, an active form of GLP1, suppressed atherosclerosis development and macrophage infiltration in the aortic wall.⁷⁶ This effect was blocked by co-infusion with exendin(9–39), a specific GLP1 receptor antagonist, suggesting that GLP1 analogues exert an antiatherosclerotic effect through the GLP1 canonical receptor.

The antiatherosclerotic or vasculoprotective effects of GLP1 and GLP1 analogues have also been observed in rodent stroke models.^{77–79} After cerebral ischemia-reperfusion injury, intraperitoneal or intracerebroventricular administration of liraglutide, a GLP1 analogue, consistently reduced the cerebral infarct volume in rats.⁷⁸ These neuroprotective effects are induced by increasing antioxidant effects, upregulating vascular endothelial growth factor production,⁷⁸ and reducing proinflammatory cyclooxygenase-2 and prostaglandin E2 concentrations.⁷⁹ These findings suggest that GLP1 analogues play a favorable role in the cardiovascular system through gluoregulatory, antiatherosclerotic, anti-inflammatory, and blood pressure-lowering effects, and by improving endothelial function.⁸⁰

Conclusions

So far, evidence suggests that optimal glucose control without inducing hypoglycemia has beneficial effects in the treatment of cardiovascular diseases including stroke. Accordingly, international guidelines for diabetes management recommend achieving a glycemic target goal to prevent or delay both micro- and macrovascular complications.^{81,82}

Several recent large-scale studies of new antidiabetic medications suggest that these agents have beneficial effects in preventing the development of composite cardiovascular outcome and/or related mortality. However, their effects on stroke remain unclear. Empagliflozin treatment in the EMPA-REG OUTCOME trial showed a nonsignificant increase in stroke incidence,³⁵ although this contrasted with the effects of canagliflozin in the CANVAS program (nonsignificant decrease)³⁶ and dapagliflozin in the DECLARE-TIMI58 study (neutral).³⁷

Although the semaglutide trial showed significant beneficial effects on nonfatal stroke, the cardiovascular outcome trials were underpowered for the specific stroke endpoints. More studies using ertugliflozin (SGLT2 inhibitor) and dulaglutide (once-weekly GLP1 analogue) are currently ongoing in the hope of improving vascular outcomes and total mortality in patients with diabetes at high stroke risk.^{83,84} Until the results of these studies are released, multifactorial interventions targeting individual cerebrovascular risk factors are required to improve clinical outcomes in diabetes patients after a stroke or at high risk of stroke. More mechanistic studies focusing on the mechanisms underlying the effects of these agents on stroke risk are needed.

Disclosure

The authors have no financial conflicts of interest.

Acknowledgments

This work was supported by the Korean Diabetes Association and Seoul National University Bundang Hospital.

References

1. 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.
2. Yang Y, Yao JJ, Du JL, Bai R, Sun LP, Sun GH, et al. Primary prevention of macroangiopathy in patients with short-duration type 2 diabetes by intensified multifactorial interven-

- tion: seven-year follow-up of diabetes complications in Chinese. *Diabetes Care* 2013;36:978-984.
3. Griffin SJ, Borch-Johnsen K, Davies MJ, Khunti K, Rutten GE, Sandbæk A, et al. 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.
 4. Stead LG, Gilmore RM, Bellolio MF, Mishra S, Bhagra A, Vaidyanathan L, et al. Hyperglycemia as an independent predictor of worse outcome in non-diabetic patients presenting with acute ischemic stroke. *Neurocrit Care* 2009;10:181-186.
 5. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375:2215-2222.
 6. Saxena A, Anderson CS, Wang X, Sato S, Arima H, Chan E, et al. Prognostic significance of hyperglycemia in acute intracerebral hemorrhage: the INTERACT2 study. *Stroke* 2016; 47:682-688.
 7. Luchsinger JA, Tang MX, Stern Y, Shea S, Mayeux R. Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *Am J Epidemiol* 2001;154: 635-641.
 8. Schmidt AM, Yan SD, Wautier JL, Stern D. Activation of receptor for advanced glycation end products: a mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis. *Circ Res* 1999;84:489-497.
 9. Baynes JW, Thorpe SR. Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. *Diabetes* 1999;48:1-9.
 10. Idris I, Gray S, Donnelly R. Protein kinase C activation: isozyme-specific effects on metabolism and cardiovascular complications in diabetes. *Diabetologia* 2001;44:659-673.
 11. Rösen P, Nawroth PP, King G, Möller W, Tritschler HJ, Packer L. The role of oxidative stress in the onset and progression of diabetes and its complications: a summary of a Congress Series sponsored by UNESCO-MCBN, the American Diabetes Association and the German Diabetes Society. *Diabetes Metab Res Rev* 2001;17:189-212.
 12. Hennes MM, O'Shaughnessy IM, Kelly TM, LaBelle P, Egan BM, Kissebah AH. Insulin-resistant lipolysis in abdominally obese hypertensive individuals. Role of the renin-angiotensin system. *Hypertension* 1996;28:120-126.
 13. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 2002;287:2570-2581.
 14. Ishii H, Jirousek MR, Koya D, Takagi C, Xia P, Clermont A, et al. Amelioration of vascular dysfunctions in diabetic rats by an oral PKC beta inhibitor. *Science* 1996;272:728-731.
 15. Guerrero-Romero F, Rodríguez-Morán M. Proteinuria is an independent risk factor for ischemic stroke in non-insulin-dependent diabetes mellitus. *Stroke* 1999;30:1787-1791.
 16. Töyry JP, Niskanen LK, Länsimies EA, Partanen KP, Uusitupa MI. Autonomic neuropathy predicts the development of stroke in patients with non-insulin-dependent diabetes mellitus. *Stroke* 1996;27:1316-1318.
 17. Cheung N, Rogers S, Couper DJ, Klein R, Sharrett AR, Wong TY. Is diabetic retinopathy an independent risk factor for ischemic stroke? *Stroke* 2007;38:398-401.
 18. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383-393.
 19. Ueki K, Sasako T, Okazaki Y, Kato M, Okahata S, Katsuyama H, et al. Effect of an intensified multifactorial intervention on cardiovascular outcomes and mortality in type 2 diabetes (J-DOIT3): an open-label, randomised controlled trial. *Lancet Diabetes Endocrinol* 2017;5:951-964.
 20. Bree AJ, Puente EC, Daphna-Iken D, Fisher SJ. Diabetes increases brain damage caused by severe hypoglycemia. *Am J Physiol Endocrinol Metab* 2009;297:E194-E201.
 21. 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.
 22. Sidhu JS, Kaposzta Z, Markus HS, Kaski JC. Effect of rosiglitazone on common carotid intima-media thickness progression in coronary artery disease patients without diabetes mellitus. *Arterioscler Thromb Vasc Biol* 2004;24:930-934.
 23. Langenfeld MR, Forst T, Hohberg C, Kann P, Lübber G, Konrad T, et al. Pioglitazone decreases carotid intima-media thickness independently of glycemic control in patients with type 2 diabetes mellitus: results from a controlled randomized study. *Circulation* 2005;111:2525-2531.
 24. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. *Lancet* 2005;366:1279-1289.
 25. Wilcox R, Bousser MG, Betteridge DJ, Scherthaner G, Pirags V, Kupfer S, et al. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke* 2007;38:865-873.
 26. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE,

- Gorman M, et al. Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med* 2016;374:1321-1331.
27. 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.
 28. Yusta B, Baggio LL, Estall JL, Koehler JA, Holland DP, Li H, et al. GLP-1 receptor activation improves beta cell function and survival following induction of endoplasmic reticulum stress. *Cell Metab* 2006;4:391-406.
 29. Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Circulation* 2017;136:849-870.
 30. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317-1326.
 31. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;369:1327-1335.
 32. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;373:232-242.
 33. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA* 2019;321:69-79.
 34. Kalra S. Sodium glucose co-transporter-2 (SGLT2) inhibitors: a review of their basic and clinical pharmacology. *Diabetes Ther* 2014;5:355-366.
 35. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117-2128.
 36. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondou N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644-657.
 37. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;380:347-357.
 38. Birkeland KI, Jørgensen ME, Carstensen B, Persson F, Gulseth HL, Thuresson M, et al. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. *Lancet Diabetes Endocrinol* 2017;5:709-717.
 39. Guo M, Ding J, Li J, Wang J, Zhang T, Liu C, et al. SGLT2 inhibitors and risk of stroke in patients with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2018;20:1977-1982.
 40. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311-322.
 41. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834-1844.
 42. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB Sr, Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 2018;392:1519-1529.
 43. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015;373:2247-2257.
 44. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017;377:1228-1239.
 45. Pérez MJ, Quintanilla RA. Therapeutic actions of the thiazolidinediones in Alzheimer's disease. *PPAR Res* 2015;2015:957248.
 46. Barbier O, Torra IP, Duguay Y, Blanquart C, Fruchart JC, Glinneur C, et al. Pleiotropic actions of peroxisome proliferator-activated receptors in lipid metabolism and atherosclerosis. *Arterioscler Thromb Vasc Biol* 2002;22:717-726.
 47. Shimazu T, Inoue I, Araki N, Asano Y, Sawada M, Furuya D, et al. A peroxisome proliferator-activated receptor-gamma agonist reduces infarct size in transient but not in permanent ischemia. *Stroke* 2005;36:353-359.
 48. Zhao X, Strong R, Zhang J, Sun G, Tsien JZ, Cui Z, et al. Neuronal PPARgamma deficiency increases susceptibility to brain damage after cerebral ischemia. *J Neurosci* 2009;29:6186-6195.
 49. Li AC, Brown KK, Silvestre MJ, Willson TM, Palinski W, Glass CK. Peroxisome proliferator-activated receptor gamma ligands inhibit development of atherosclerosis in LDL receptor-deficient mice. *J Clin Invest* 2000;106:523-531.
 50. Lim S, Lee KS, Lee JE, Park HS, Kim KM, Moon JH, et al. Effect of a new PPAR-gamma agonist, lobeglitazone, on neointimal formation after balloon injury in rats and the development of atherosclerosis. *Atherosclerosis* 2015;243:107-119.

51. Calkin AC, Forbes JM, Smith CM, Lassila M, Cooper ME, Jan-deleit-Dahm KA, et al. Rosiglitazone attenuates atherosclerosis in a model of insulin insufficiency independent of its metabolic effects. *Arterioscler Thromb Vasc Biol* 2005;25:1903-1909.
52. Wang N, Yin R, Liu Y, Mao G, Xi F. Role of peroxisome proliferator-activated receptor- γ in atherosclerosis: an update. *Circ J* 2011;75:528-535.
53. Quinn CE, Lockhart CJ, Hamilton PK, Loughrey CM, McVeigh GE. Effect of pioglitazone on endothelial function in impaired glucose tolerance. *Diabetes Obes Metab* 2010;12:709-715.
54. Zeng Y, Li C, Guan M, Zheng Z, Li J, Xu W, et al. The DPP-4 inhibitor sitagliptin attenuates the progress of atherosclerosis in apolipoprotein-E-knockout mice via AMPK- and MAPK-dependent mechanisms. *Cardiovasc Diabetol* 2014;13:32.
55. Matsubara J, Sugiyama S, Sugamura K, Nakamura T, Fujiwara Y, Akiyama E, et al. A dipeptidyl peptidase-4 inhibitor, des-fluoro-sitagliptin, improves endothelial function and reduces atherosclerotic lesion formation in apolipoprotein E-deficient mice. *J Am Coll Cardiol* 2012;59:265-276.
56. Mita T, Katakami N, Shimomura I, Watada H. Response to comment on Mita et al. Sitagliptin attenuates the progression of carotid intima-media thickening in insulin-treated patients with type 2 diabetes: the sitagliptin preventive study of intima-media thickness evaluation (SPIKE). A randomized controlled trial. *Diabetes Care* 2016;39:455-464. *Diabetes Care* 2016;39:e104-e105.
57. Mita T, Katakami N, Yoshii H, Onuma T, Kaneto H, Osonoi T, et al. Alogliptin, a dipeptidyl peptidase 4 inhibitor, prevents the progression of carotid atherosclerosis in patients with type 2 diabetes: the study of preventive effects of alogliptin on diabetic atherosclerosis (SPEAD-A). *Diabetes Care* 2016;39:139-148.
58. Oyama J, Murohara T, Kitakaze M, Ishizu T, Sato Y, Kitagawa K, et al. The effect of sitagliptin on carotid artery atherosclerosis in type 2 diabetes: the PROLOGUE randomized controlled trial. *PLoS Med* 2016;13:e1002051.
59. Darsalia V, Ortsäter H, Olverling A, Darlöv E, Wolbert P, Nyström T, et al. The DPP-4 inhibitor linagliptin counteracts stroke in the normal and diabetic mouse brain: a comparison with glimepiride. *Diabetes* 2013;62:1289-1296.
60. Hu Y, Liu H, Simpson RW, Dear AE. GLP-1-dependent and independent effects and molecular mechanisms of a dipeptidyl peptidase 4 inhibitor in vascular endothelial cells. *Mol Biol Rep* 2013;40:2273-2279.
61. Ishibashi Y, Matsui T, Takeuchi M, Yamagishi S. Sitagliptin augments protective effects of GLP-1 against advanced glycation end product receptor axis in endothelial cells. *Horm Metab Res* 2011;43:731-734.
62. Zhou Y, Guo Z, Yan W, Wang W. Cardiovascular effects of sitagliptin: an anti-diabetes medicine. *Clin Exp Pharmacol Physiol* 2018;45:628-635.
63. Fadini GP, Avogaro A. Cardiovascular effects of DPP-4 inhibition: beyond GLP-1. *Vascul Pharmacol* 2011;55:10-16.
64. Chiazza F, Tammen H, Pintana H, Lietzau G, Collino M, Nyström T, et al. The effect of DPP-4 inhibition to improve functional outcome after stroke is mediated by the SDF-1 α /CXCR4 pathway. *Cardiovasc Diabetol* 2018;17:60.
65. Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects. *Nat Rev Endocrinol* 2012;8:495-502.
66. Inzucchi SE, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S, et al. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. *Diab Vasc Dis Res* 2015;12:90-100.
67. Han JH, Oh TJ, Lee G, Maeng HJ, Lee DH, Kim KM, et al. The beneficial effects of empagliflozin, an SGLT2 inhibitor, on atherosclerosis in ApoE (-/-) mice fed a western diet. *Diabetologia* 2017;60:364-376.
68. Lin B, Koibuchi N, Hasegawa Y, Sueta D, Toyama K, Uekawa K, et al. Glycemic control with empagliflozin, a novel selective SGLT2 inhibitor, ameliorates cardiovascular injury and cognitive dysfunction in obese and type 2 diabetic mice. *Cardiovasc Diabetol* 2014;13:148.
69. Ferrannini E, Mark M, Mayoux E. CV protection in the EMPA-REG OUTCOME trial: a "thrifty substrate" hypothesis. *Diabetes Care* 2016;39:1108-1114.
70. Rahman M, Muhammad S, Khan MA, Chen H, Ridder DA, Müller-Fielitz H, et al. The β -hydroxybutyrate receptor HCA2 activates a neuroprotective subset of macrophages. *Nat Commun* 2014;5:3944.
71. Bazzigaluppi P, Lake EM, Beckett TL, Koletar MM, Weisspapir I, Heinen S, et al. Imaging the effects of β -hydroxybutyrate on peri-infarct neurovascular function and metabolism. *Stroke* 2018;49:2173-2181.
72. Lim S, Eckel RH, Koh KK. Clinical implications of current cardiovascular outcome trials with sodium glucose cotransporter-2 (SGLT2) inhibitors. *Atherosclerosis* 2018;272:33-40.
73. Arakawa M, Mita T, Azuma K, Ebato C, Goto H, Nomiyama T, et al. Inhibition of monocyte adhesion to endothelial cells and attenuation of atherosclerotic lesion by a glucagon-like peptide-1 receptor agonist, exendin-4. *Diabetes* 2010;59:1030-1037.
74. Gaspari T, Liu H, Welungoda I, Hu Y, Widdop RE, Knudsen LB, et al. A GLP-1 receptor agonist liraglutide inhibits endothelial cell dysfunction and vascular adhesion molecule expression in

- an ApoE^{-/-} mouse model. *Diab Vasc Dis Res* 2011;8:117-124.
75. Lim S, Lee GY, Park HS, Lee DH, Oh TJ, Kim KM, et al. Attenuation of carotid neointimal formation after direct delivery of a recombinant adenovirus expressing glucagon-like peptide-1 in diabetic rats. *Cardiovasc Res* 2017;113:183-194.
 76. Nagashima M, Watanabe T, Terasaki M, Tomoyasu M, Nohtomi K, Kim-Kaneyama J, et al. Native incretins prevent the development of atherosclerotic lesions in apolipoprotein E knockout mice. *Diabetologia* 2011;54:2649-2659.
 77. Li Y, Perry T, Kindy MS, Harvey BK, Tweedie D, Holloway HW, et al. GLP-1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism. *Proc Natl Acad Sci U S A* 2009;106:1285-1290.
 78. Sato K, Kameda M, Yasuhara T, Agari T, Baba T, Wang F, et al. Neuroprotective effects of liraglutide for stroke model of rats. *Int J Mol Sci* 2013;14:21513-21524.
 79. Kim S, Jeong J, Jung HS, Kim B, Kim YE, Lim DS, et al. Anti-inflammatory effect of glucagon like peptide-1 receptor agonist, exendin-4, through modulation of IB1/JIP1 expression and JNK signaling in stroke. *Exp Neurobiol* 2017;26:227-239.
 80. Lim S, Kim KM, Nauck MA. Glucagon-like peptide-1 receptor agonists and cardiovascular events: class effects versus individual patterns. *Trends Endocrinol Metab* 2018;29:238-248.
 81. American Diabetes Association. 6. Glycemic targets. *Diabetes Care* 2017;40(Suppl 1):S48-S56.
 82. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm: 2017 executive summary. *Endocr Pract* 2017;23:207-238.
 83. Franchi F, Rollini F, Aggarwal N, Hu J, Kureti M, Durairaj A, et al. Pharmacodynamic comparison of prasugrel versus ticagrelor in patients with type 2 diabetes mellitus and coronary artery disease: the OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus)-4 Study. *Circulation* 2016;134:780-792.
 84. Kim JB, Joung HJ, Lee JM, Woo JS, Kim WS, Kim KS, et al. Evaluation of the vascular protective effects of new oral anticoagulants in high-risk patients with atrial fibrillation (PREFER-AF): study protocol for a randomized controlled trial. *Trials* 2016;17:422.