Blood glucose, antidiabetic drugs, and risk of stroke

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ABSTRACT

Diabetes mellitus is a well-established risk factor for stroke. Among people without baseline diabetes or cardiovascular disease, a low fasting glucose level of <70 mg/dL is associated with an increased risk of stroke. Individuals with pre-diabetes based on impaired glucose tolerance have an independent risk of stroke that is 20% greater than those with normal glycemia. Pre-diabetes based on a more recent guideline recommended definition of impaired fasting glucose (100 to 125 mg/dL) is not linked to future stroke risk, while fasting glucose 110 to 125 mg/dL is linked to an increased stroke risk. Despite the relationship between elevated blood glucose and stroke risk, lowering blood glucose with oral antidiabetic drugs is usually not associated with reduced cardiovascular events. Yet, among high cardiovascular risk patients on background metformin therapy, subcutaneous semaglutide/dulaglutide reduces future stroke risk; and among ischemic stroke patients with insulin resistance, prediabetes, and diabetes mellitus, pioglitazone lowers risks of recurrent stroke and major vascular events. Pending the conduct of definitive randomized controlled trials, a combination of metformin, pioglitazone and an sodium-glucose co-transporter 2 inhibitor or a combination of metformin, pioglitazone and subcutaneous semaglutide/dulaglutide might be reasonable therapeutic strategies for reducing secondary stroke risk in diabetic patients.

Keywords: Blood glucose; Hypoglycemic agents; Stroke

INTRODUCTION

Diabetes mellitus is an established risk factor for both incident and recurrent stroke [1,2]. However, intensive glycemic control does not prevent risk of stroke in diabetic patients [3]. Many large randomized controlled trials of antidiabetic drugs have been published recently, but since occurrence of stroke was not a prespecified primary endpoint, the effect of individual antidiabetic drug on the risk of stroke might be overlooked. In this article, we review the evidence currently available for the relation between blood glucose levels and risk of stroke, and clarify the effect of individual antidiabetic drugs on stroke prevention. We then propose potential therapeutic strategies to combine antidiabetic drugs to maximize cardiovascular benefits, and mitigate side effects in ischemic stroke patients with type 2 diabetes.

BLOOD GLUCOSE AND RISK OF STROKE

Diabetes mellitus and risk of stroke

A meta-analyses including data for over 530,000 people from 102 prospective studies suggested that comparing people with diabetes versus those without, future risks were higher for ischemic stroke (hazard ratio [HR], 2.27; 95% confidence interval [CI], 1.95 to 2.65), hemorrhagic stroke (HR, 1.56; 95% CI, 1.19 to 2.05), and unclassified stroke (HR, 1.84; 95% CI, 1.59 to 2.13) after adjustment for age, sex, smoking status, body mass index, and systolic blood pressure [4]. For people with diabetes mellitus, future risks for ischemic stroke were especially higher in women, in people with a higher body mass index, and in people aged between 40 and 59 years [4].

Prediabetes and risk of stroke

The growing obesity epidemic in the United States of America has been linked with a surge in rates of prediabetes [5]. People with prediabetes harbor the same vascular risk factors (hypertension, dyslipidemia, obesity, physical inactivity, insulin resistance, and inflammation) that place people with diabetes mellitus at a high risk of major cardiovascular events [6]. In eight studies with information about fasting glucose 100 to 125 mg/dL, the pooled estimate did not show increased risk of stroke after adjustment for established cardiovascular risk factors (relative risk [RR], 1.08; 95% CI, 0.94 to 1.23) [7]. In five studies with information about fasting glucose 110 to 125 mg/dL, the pooled estimate showed an increased risk of stroke after adjustment for established cardiovascular risk factors (RR, 1.21; 95% CI, 1.02 to 1.44) [7]. In eight studies with information about impaired glucose tolerance or combination of impaired fasting glucose and impaired glucose tolerance, the pooled estimate showed an increased risk of stroke after adjustment for established cardiovascular risk factors (RR, 1.26; 95% CI, 1.10 to 1.43) [7]. In three studies that provided information on participants with fasting glucose of 100 to 109 mg/dL, the pooled estimate did not show an increased risk of stroke (RR, 0.94; 95% CI, 0.73 to 1.20) [7].

Low fasting glucose and risk of stroke

Since glucose is a necessary body nutrient, and blood glucose concentration is regulated by various hormones within a narrow range in the body [8], it is conceivable that fasting blood glucose lower than a certain threshold may be associated with harmful effects among people without baseline diabetes mellitus and cardiovascular disease. A meta-analysis
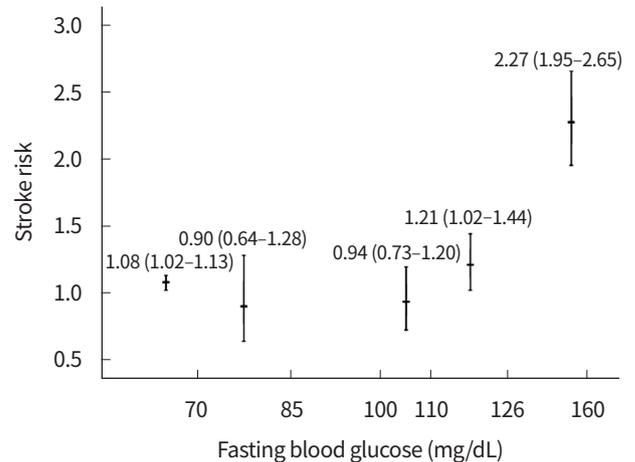

Fig. 1. The relationship between fasting blood glucose levels and stroke risk. Adapted from Emerging Risk Factors Collaboration et al. [4], Lee et al. [7], and Liao et al. [9].

found that in studies using fasting glucose <85 mg/dL as cutoff, the pooled estimate did not show an increased risk of total stroke (HR, 0.90; 95% CI, 0.64 to 1.28), ischemic stroke (HR, 1.03; 95% CI, 0.94 to 1.12), or hemorrhagic stroke (HR, 0.98; 95% CI, 0.88 to 1.09) [9]. However, approximately 5% of people without diabetes and cardiovascular disease at baseline have fasting blood glucose levels <70 mg/dL and these individuals harbor greater hazards of future total stroke (HR, 1.08; 95% CI, 1.02 to 1.13) and ischemic stroke (HR, 1.06; 95% CI, 1.01 to 1.10), as compared to individuals with a normal blood glucose level [9].

The relationship between fasting blood glucose levels and stroke risk is presented in the Fig. 1.

ANTIDIABETIC DRUGS FOR STROKE PREVENTION

Metformin for stroke prevention

In the UK Prospective Diabetes Study (UKPDS), a secondary analysis compared the 342 patients allocated metformin with 951 patients allocated intensive blood-glucose control with chlorpropamide, glibenclamide, or insulin and found metformin showed a greater effect than chlorpropamide, glibenclamide, or insulin for reducing stroke risk (RR, 0.59 vs. 1.14, P=0.03) among diabetic patients who were overweight [10]. However, a 10-year follow-up of UKPDS did not show a significant risk reduction for stroke in people assigned to metformin group [11]. Also, all of the metformin-treated subjects were overweight or obese, and the number receiving this treatment (n=342) would be considered relatively small for a cardiovascular outcomes study by today's standards. Fi-

nally, a Cochrane review suggested no clear evidence about whether metformin monotherapy compared with behavior change, no intervention, or other glucose-lowering drugs influences patient-important outcomes, including nonfatal stroke [12].

Sulfonylureas for stroke prevention

In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, gliclazide use compared with placebo had no effect on non-fatal stroke [13]. A Cochrane review suggested inconclusive evidence about whether metformin plus sulfonylurea compared with metformin plus another glucose-lowering intervention showed benefit or harm for most patient-important outcomes, including nonfatal stroke [14]. On the other hand, in a Bayesian meta-analysis of both randomized controlled trials and cohort studies, the risk of stroke was significantly higher in sulfonylurea users than users taking other anti-diabetic agents [15].

Glinides for stroke prevention

The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial showed that among people with prediabetes, one or more cardiovascular risk factors, or known cardiovascular disease, nateglinide compared with placebo neither decreased or increased the risk of nonfatal or fatal stroke (HR, 0.89; 95% CI, 0.69 to 1.15) [16].

Pioglitazone for stroke prevention

In a subgroup analysis of diabetic patients with prior stroke in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), pioglitazone compared with placebo was associated with a lower risk of fatal or nonfatal stroke (HR, 0.53; 95% CI, 0.34 to 0.85) [17]. In the Insulin Resistance Intervention after Stroke (IRIS) trial involving patients without diabetes but with insulin resistance along with a recent history of ischemic stroke or transient ischemic attack, pioglitazone compared with placebo reduced the risk of stroke or myocardial infarction (HR, 0.76; 95% CI, 0.62 to 0.93) [18]. A meta-analysis including three randomized controlled trials with 4,980 participants suggested that pioglitazone use in stroke patients with insulin resistance, prediabetes, and diabetes mellitus was associated with lower risks of recurrent stroke (HR, 0.68; 95% CI, 0.50 to 0.92) and future major cardiovascular events (HR, 0.75; 95% CI, 0.64 to 0.87) [19].

Dipeptidyl peptidase-4 inhibitors for stroke prevention

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study showed that among patients with type 2 diabetes and established cardiovascular disease, adding sitagliptin to usual care did not decrease or increase the risk of stroke (HR, 0.97; 95% CI, 0.79 to 1.19) [20]. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 trial showed that among patients with type 2 diabetes who had a history, or at risk for, cardiovascular disease, adding saxagliptin did not decrease or increase the risk of ischemic stroke (HR, 1.11; 95% CI, 0.88 to 1.39) [21]. The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) trial showed that among adults with type 2 diabetes and high cardiovascular and renal risk, linagliptin compared with placebo did not decrease or increase the risk of nonfatal or fatal stroke (HR, 0.91; 95% CI, 0.67 to 1.23) [22]. A meta-analysis of 36 randomized trials suggested there was no significant difference in stroke risk (RR, 1.02; 95% CI, 0.88 to 1.17) with the use of dipeptidyl peptidase-4 inhibitors, compared with placebo [23].

Sodium-glucose co-transporter 2 inhibitors for stroke prevention

The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patients (EMPA-REG OUTCOME) trial showed that among type 2 diabetic patients at high risk for cardiovascular events, empagliflozin compared with placebo did not significantly decrease or increase the risk of nonfatal or fatal stroke (HR, 1.18; 95% CI, 0.89 to 1.56) [24]. The numeric difference in stroke between empagliflozin and placebo in the modified intent-to-treat analysis was primarily due to 18 patients in the empagliflozin group (vs. 3 on placebo) with a first event > 90 days after last taking of study drug. In a sensitivity analysis based on events during treatment or ≤ 90 days after last dose of drug, the HR for stroke with empagliflozin versus placebo was 1.08 (95% CI, 0.81 to 1.45) [25]. The Canagliflozin Cardiovascular Assessment Study (CANVAS) Program showed that among patients with type 2 diabetes and an elevated risk of cardiovascular disease, canagliflozin compared with placebo did not decrease or increase the risk of fatal or nonfatal stroke (HR, 0.87; 95% CI, 0.69 to 1.09) [26]. The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) trial showed that among patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease, dapagliflozin did not decrease or increase the risk of stroke

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(HR, 1.01; 95% CI, 0.84 to 1.21) [27]. A meta-analysis of these 3 large randomized controlled trials suggested sodium-glucose co-transporter 2 (SGLT-2) inhibitors compared with placebo had no effect on stroke (HR, 0.97; 95% CI, 0.86 to 1.10) [28].

Glucagon-like peptide-1 receptor agonists for stroke prevention

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial showed that among patients with type 2 diabetes and high cardiovascular risk, use of liraglutide compared with placebo did not significantly reduce the risk of stroke (HR, 0.86; 95% CI, 0.71 to 1.06) [29]. The preapproval Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) showed that among type 2 diabetic patients at high risk for cardiovascular events, subcutaneous semaglutide once weekly, compared with placebo, reduced the rate of nonfatal stroke (HR, 0.61; 95% CI, 0.38 to 0.99) [30]. The Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial showed that among type 2 diabetes with either previous cardiovascular disease or cardiovascular risk factors, subcutaneous dulaglutide once weekly, compared with placebo, reduced the rate of ischemic stroke (HR, 0.75; 95% CI, 0.59 to 0.94) and similar effects for dulaglutide on stroke were observed in people with or without a history of stroke or transient ischemic attack [31]. The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial showed that among type 2 diabetic patients with or without previous cardiovascular disease, subcutaneous injections of once-weekly exenatide compared with placebo did not significantly reduce the risk of nonfatal stroke (HR, 0.85; 95% CI, 0.70 to 1.03) [32]. The Peptide Innovation for Early Diabetes Treatment (PIONEER) 6 trial showed that among diabetic patients at high cardiovascular risk, once-daily oral semaglutide compared with placebo did not significantly reduce the risk of nonfatal stroke (HR, 0.74; 95%

CI, 0.35 to 1.57) [33]. A network meta-analysis evaluating all antidiabetic drugs suggested the risks of stroke were lower with use of subcutaneous semaglutide and dulaglutide in patients at increased cardiovascular risk who received metformin-based background treatment [34].

Acarbose for stroke prevention

The Acarbose Cardiovascular Evaluation (ACE) trial showed that among Chinese patients with coronary heart disease and impaired glucose tolerance, use of acarbose compared with placebo did not reduce the risk of fatal or nonfatal stroke (HR, 0.97; 95% CI, 0.70 to 1.33) [35]. In a Taiwan nationwide cohort study, acarbose was associated with a borderline higher risk of ischemic stroke (HR, 1.05; 95% CI, 1.00 to 1.10) than metformin and therefore did not support the notion that acarbose should be a first-line antidiabetic agent [36].

Insulin for stroke prevention

In the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, which involved people 50 years of age or older with impaired fasting glucose, impaired glucose tolerance, or early type 2 diabetes in addition to other cardiovascular risk factors, insulin glargine compared with standard care did not decrease or increase the risk of total stroke (HR, 1.03; 95% CI, 0.89 to 1.21) [37].

Antidiabetic drugs that may reduce future stroke risk are presented in the Table 1.

COMBINATION OF ANTIDIABETIC DRUGS FOR SECONDARY STROKE PREVENTION

Since pioglitazone use might be associated with reduced recurrent stroke risk in ischemic stroke patients with insulin resistance, prediabetes, and diabetes mellitus [19], the Taiwan Society of Cardiology and the Diabetes Association of Republic of China (Taiwan) recommend metformin plus pioglitazone for dual therapy in diabetic patients with a history of

Table 1. Antidiabetic drugs that may reduce future stroke risk

Variable	Population	Route of drug administration	Hazard ratio of stroke (active vs. placebo)
Pioglitazone	Stroke patients with insulin resistance, prediabetes, or type 2 diabetes	Oral once daily	0.68 (0.50–0.92)
Semaglutide	Type 2 diabetic patients at high risk for cardiovascular events	Subcutaneous injection once weekly	0.61 (0.38–0.99)
Dulaglutide	Type 2 diabetes with either previous cardiovascular disease or cardiovascular risk factors	Subcutaneous injection once weekly	0.75 (0.59–0.94)

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ischemic stroke [38]. However, a meta-analysis of randomized controlled trials shows that the risks of heart failure, edema and weight gain are higher in patents taking pioglitazone [39]. As shown in a randomized controlled trial, the potential risk of heart failure can be mitigated, even eliminated, by excluding patients with a history of heart failure and using safety algorithms that trigger dose reduction of pioglitazone for excessive weight gain or edema [18]. Still, mild weight gain or edema seems inevitable once pioglitazone is used [18]. It would be helpful if adding another antidiabetic drug to metformin and pioglitazone could mitigate the side effects of pioglitazone and/or potentially maximize cardiovascular protection, without an increase in the risk of hypoglycemia.

Metformin + pioglitazone + SGLT-2 inhibitor

A meta-analysis of four randomized controlled trials suggested that compared to pioglitazone alone, an SGLT-2 inhibitor plus pioglitazone improved glycemic control, reduced body weight and lowered blood pressure, without an increased risk of hypoglycemia [40]. Furthermore, SGLT-2 inhibitor use can reduce incident risks of heart failure, cardiovascular death, end stage renal disease, albuminuria, and atrial fibrillation [24,26,27,41-44]. Although SGLT-2 inhibitor use is not associated with reduced risk of stroke, its potential to mitigate the side effects of pioglitazone and its cardio-renal protective effect make it an optimal antidiabetic drug to be added to metformin and pioglitazone in ischemic stroke patients with type 2 diabetes.

Metformin + pioglitazone + subcutaneous dulaglutide or semaglutide

The Assessment of Weekly AdministRation of LY2189265 (du-laglutide) in Diabetes-1 (AWARD-1) trial showed that among patients treated with metformin and pioglitazone, once-weekly subcutaneously injection of dulaglutide compared with placebo resulted in significantly larger improvements in glycosylated hemoglobin (HbA1c), and percentages of patients achieving target HbA1c goals, as well as significant weight reduction, and no dulaglutide-treated patients reported severe hypoglycemia [45]. Since use of subcutaneous dulaglutide or semaglutide is associated with reduced risk of stroke and major cardiovascular events [30,31,46], and adding subcutaneous dulaglutide or semaglutide to metformin and pioglitazone mitigates the side effects of pioglitazone, improves blood glucose control, but is less likely to increase risk of hypoglycemia, such a combination could be a reasonable therapeutic regimen to be used in ischemic stroke patients with type 2 diabetes.

Suggested strategy for combination of antidiabetic drugs in ischemic stroke patients with type 2 diabetes is presented in Table 2.

CONCLUSION

The risk of stroke is increased among people with diabetes, people without diabetes but with impaired glucose tolerance, people with fasting glucose between 110 and 125 mg/dL, and those with fasting glucose <70 mg/dL. Among stroke patients with insulin resistance, prediabetes, or diabetes mellitus, pioglitazone use might be associated with a reduced risk of recurrent stroke and major cardiovascular events. Among diabetic patients with increased cardiovascular risk, once-weekly subcutaneous injection of semaglutide or dulaglutide reduces future stroke risk. The combination of

Table 2. Suggested strategy for combination of antidiabetic drugs in ischemic stroke patients with type 2 diabetes

	Metformin + pioglitazone + SGLT-2 inhibitor	Metformin + pioglitazone + subcutaneous dulaglutide or semaglutide
Advantage	1. High potency of blood glucose lowering	1. High potency of blood glucose lowering
	2. Low risk of hypoglycemia	2. Low risk of hypoglycemia
	3. Mitigate side effects (e.g., weight gain) of pioglitazone	3. Mitigate side effects (e.g., weight gain) of pioglitazone
	4. Antiatherosclerotic effects (e.g., reduce stroke and major cardiovascular events) and insulin resistance reduction through pioglitazone use	4. Antiatherosclerotic effects (e.g., reduce stroke and major cardiovascular events) and insulin resistance reduction through pioglitazone use
	5. Cardio-renal protective effects (e.g., reduce heart failure, cardiovascular death, atrial fibrillation, ESRD, albuminuria) through SGLT-2 inhibitor use	5. Antiatherosclerotic effects (e.g., reduce stroke and major cardiovascular events) and renal protective effects (e.g., reduce albuminuria) through subcutaneous dulaglutide/semaglutide use

SGLT-2, sodium-glucose co-transporter 2; ESRD, end stage renal disease.

metformin, pioglitazone and SGLT-2 inhibitor or combination of metformin, pioglitazone and subcutaneous semaglutide/dulaglutide could be considered as reasonable therapeutic strategies for optimally effective and safe secondary stroke prevention in ischemic patients with type 2 diabetes, pending robust evidence from randomized controlled trials.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: ML, BO.
Acquisition, analysis, or interpretation of data: ML, BO.
Drafting the work or revising: ML, BO.
Final approval of the manuscript: ML, BO.

REFERENCES

1. Spencer EA, Pirie KL, Stevens RJ, Beral V, Brown A, Liu B, et al. Diabetes and modifiable risk factors for cardiovascular disease: the prospective Million Women Study. Eur J Epidemiol 2008;23:793-9.
2. Callahan A, Amarenco P, Goldstein LB, Sillesen H, Messig M, Samsa GP, et al. Risk of stroke and cardiovascular events after ischemic stroke or transient ischemic attack in patients with type 2 diabetes or metabolic syndrome: secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Arch Neurol 2011;68:1245-51.
3. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, et al. 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;373:1765-72.
4. 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;375:2215-22.
5. Garber AJ, Handelsman Y, Einhorn D, Bergman DA, Bloomgarden ZT, Fonseca V, et al. Diagnosis and management of prediabetes in the continuum of hyperglycemia: when do the risks of diabetes begin? A consensus statement from the American College of Endocrinology and the American Association of Clinical Endocrinologists. Endocr Pract 2008;14:933-46.
6. DeFronzo RA, Abdul-Ghani M. Assessment and treatment of cardiovascular risk in prediabetes: impaired glucose tolerance and impaired fasting glucose. Am J Cardiol 2011;108(3 Suppl):3B-24B.
7. 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.
8. Shrayyef MZ, Gerich JE. Normal glucose homeostasis. In: Poretsky L, editor. Principle of diabetes mellitus. 2nd ed. New York (NY): Springer; 2010. p. 19-35.
9. Liao HW, Saver J, Yeh HC, Chen CS, Wu YL, Lee M, et al. Low fasting glucose and future risks of major adverse outcomes in people without baseline diabetes or cardiovascular disease: a systematic review and meta-analysis. BMJ Open 2019;9:e026010.
10. 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). Lancet 1998;352:854-65.
11. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.
12. Gnesin F, Thuesen AC, Kahler LK, Madsbad S, Hemmingsen B. Metformin monotherapy for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev 2020;6:CD012906.
13. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72.
14. Madsen KS, Kahler P, Kahler LK, Madsbad S, Gnesin F, Metzendorf MI, et al. Metformin and second- or third-gen-

eration sulphonylurea combination therapy for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev 2019;4:CD012368.

15. Bain S, Druyts E, Balijepalli C, Baxter CA, Currie CJ, Das R, et al. Cardiovascular events and all-cause mortality associated with sulphonylureas compared with other antihyperglycaemic drugs: a Bayesian meta-analysis of survival data. Diabetes Obes Metab 2017;19:329-35.

16. NAVIGATOR Study Group, Holman RR, Haffner SM, McMurray JJ, Bethel MA, Holzhauer B, et al. Effect of nateglinide on the incidence of diabetes and cardiovascular events. N Engl J Med 2010;362:1463-76.

17. Wilcox R, Bousser MG, Betteridge DJ, Schernthaner 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;38:865-73.

18. 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;374:1321-31.

19. Lee M, Saver JL, Liao HW, Lin CH, Ovbiagele B. Pioglitazone for secondary stroke prevention: a systematic review and meta-analysis. Stroke 2017;48:388-93.

20. 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;373:232-42.

21. 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;369:1317-26.

22. 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.

23. Rehman MB, Tudrej BV, Soustre J, Buisson M, Archambault P, Pouchain D, et al. Efficacy and safety of DPP-4 inhibitors in patients with type 2 diabetes: meta-analysis of placebo-controlled randomized clinical trials. Diabetes Metab 2017;43:48-58.

24. 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;373:2117-28.

25. Zinman B, Inzucchi SE, Lachin JM, Wanner C, Fitchett D, Kohler S, et al. Empagliflozin and cerebrovascular events in patients with type 2 diabetes mellitus at high cardiovascular risk. Stroke 2017;48:1218-25.

26. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.

27. 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;380:347-57.

28. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31-9.

29. 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;375:311-22.

30. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834-44.

31. Gerstein HC, Hart R, Colhoun HM, Diaz R, Lakshmanan M, Botros FT, et al. The effect of dulaglutide on stroke: an exploratory analysis of the REWIND trial. Lancet Diabetes Endocrinol 2020;8:106-14.

32. 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;377:1228-39.

33. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381:841-51.

34. Tsapas A, Avgerinos I, Karagiannis T, Malandris K, Manolopoulos A, Andreadis P, et al. Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: a systematic review and network meta-analysis. Ann Intern Med 2020;173:278-86.

35. Holman RR, Coleman RL, Chan JC, Chiasson JL, Feng H, Ge J, et al. Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2017;5:877-86.

36. Chang CH, Chang YC, Lin JW, Chen ST, Chuang LM, Lai MS. Cardiovascular risk associated with acarbose versus

metformin as the first-line treatment in patients with type 2 diabetes: a nationwide cohort study. J Clin Endocrinol Metab 2015;100:1121-9.

37. ORIGIN Trial Investigators, Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319-28.

38. Chiang CE, Lin SY, Lin TH, Wang TD, Yeh HI, Chen JF, et al. 2018 Consensus of the Taiwan Society of Cardiology and the Diabetes Association of Republic of China (Taiwan) on the pharmacological management of patients with type 2 diabetes and cardiovascular diseases. J Chin Med Assoc 2018;81:189-222.

39. Liao HW, Saver JL, Wu YL, Chen TH, Lee M, Ovbiagele B. Pioglitazone and cardiovascular outcomes in patients with insulin resistance, pre-diabetes and type 2 diabetes: a systematic review and meta-analysis. BMJ Open 2017;7: e013927.

40. Liao HW, Wu YL, Sue YM, Lee M, Ovbiagele B. Sodium-glucose cotransporter 2 inhibitor plus pioglitazone vs pioglitazone alone in patients with diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Endocrinol Diabetes Metab 2018;2:e00050.

41. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019; 380:2295-306.

42. Heerspink HJ, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-46.

43. McMurray JJ, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008.

44. Okunrintemi V, Mishriky BM, Powell JR, Cummings DM. Sodium-glucose co-transporter-2 inhibitors and atrial fibrillation in the cardiovascular and renal outcome trials. Diabetes Obes Metab 2021;23:276-80.

45. Wysham C, Blevins T, Arakaki R, Colon G, Garcia P, Atisso C, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care 2014;37:2159-67.

46. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomized placebo-controlled trial. Lancet 2019;394:121-30.