Reducing Ischemic Stroke in Diabetes: The Role of GLP-1 RAs

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KEY TAKEAWAYS

- Stroke is a significant cause of mortality worldwide, and diabetes is an independent risk factor for ischemic stroke occurrence and recurrence.
- Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) lower the risk of ischemic stroke through beneficial effects on traditional stroke risk factors such as hyperglycemia, hypertension, and dyslipidemia.
- Primary care practitioners (PCPs) can play a substantial role in reducing ischemic stroke; studies have indicated that patients who have a PCP at the time of first stroke have a lower risk of stroke recurrence.
- Clinical practice guidelines recommend treating type 2 diabetes in patients with or at risk for cardiovascular (CV) disease with glucose-lowering agents with proven CV benefit, such as GLP-1 RAs and sodium-glucose cotransporter-2 (SGLT2) inhibitors.
- Based on meta-analyses of CV outcomes trials, GLP-1 RAs have a substantial and statistically significant benefit on ischemic stroke risk reduction, whereas SGLT2 inhibitors have a nonsignificant effect.
- The use of GLP-1 RAs, in addition to nonpharmacologic and pharmacologic management of traditional stroke risk factors, is a key component of complex therapy for ischemic stroke risk reduction.

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INTRODUCTION

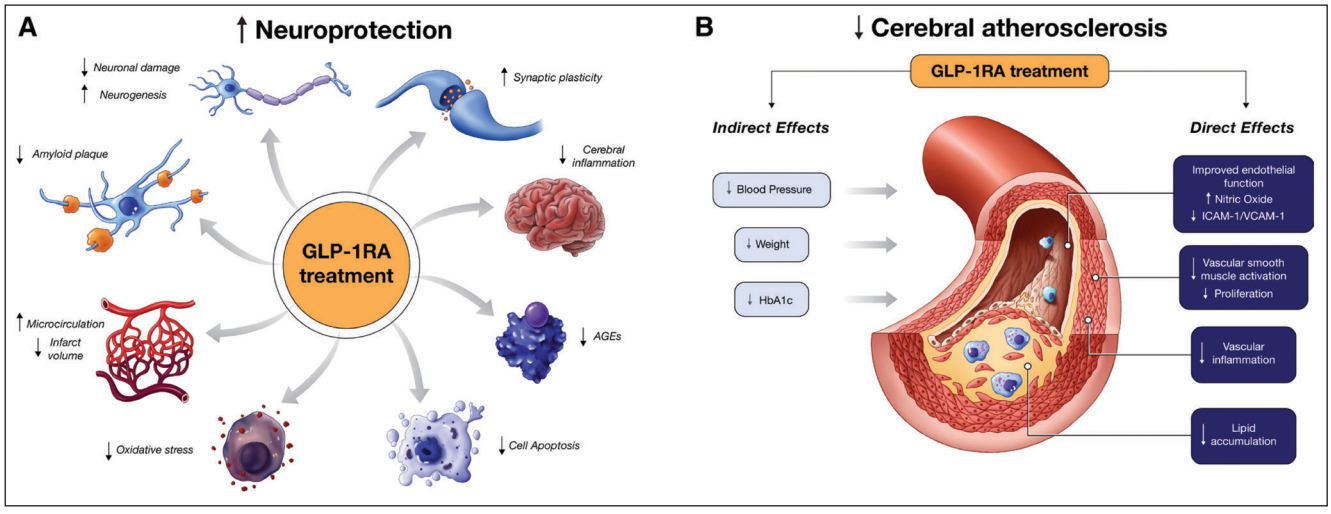
Stroke is a substantial cause of disability and mortality worldwide, with an estimated 80.1 million stroke cases each year.[1,2] In the United States (US), about 1 in 6 deaths from cardiovascular (CV) disease is due to stroke, and about every 3.5 minutes, someone in the US dies from a stroke.[3] Ischemic strokes account for approximately 84% of strokes.[1] Transient ischemic attacks (TIAs) are episodes of cerebral ischemia without resulting permanent infarction; some definitions of TIA assign a time frame that effects must fall within.[4] TIAs are often grouped with ischemic stroke for management recommendations and trial outcomes.[5] Hemorrhagic strokes occur when a weakened blood vessel in the brain ruptures.[6] They are less common than ischemic strokes and have different risk and treatment profiles.[6] The focus of this article is ischemic stroke.

Patients who have experienced a stroke are at high risk of having another stroke, especially within the first 30 days following a first stroke.[7] Additionally, recurrent strokes have a higher chance of disabling or fatal outcomes.[1]

Diabetes is an independent risk factor for ischemic stroke occurrence and recurrence and is a risk factor for neurovascular disease.[1,8] Accordingly, about one-third of individuals who have experienced stroke have diabetes.[9] Although ischemic and hemorrhagic strokes have different risk factor profiles, uncontrolled diabetes raises the risk for both ischemic and hemorrhagic strokes.[10,11] As such, reducing the risk of stroke in patients with diabetes highlights a critical need in clinical practice.

Stroke risk for patients with type 2 diabetes (T2D) can be substantially reduced with targeted intervention. For

FIGURE 1. Possible mechanisms for ischemic stroke risk reduction with GLP-1 RAs



Abbreviations: AGEs, advanced glycation end products; HbA1c, hemoglobin A1c; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular adhesion molecule-1.

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example, the Steno-2 study demonstrated a 69% reduction in the risk of stroke in patients with T2D with implementation of a multifaceted intervention that targeted multiple risk factors of CV disease.[12] Interventions included a low-fat diet, exercise regimen (90–150 minutes of light to moderate physical activity per week), angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker therapy, a daily vitamin-mineral supplement, daily low-dose aspirin, and stepwise therapy for treatment of T2D, hypertension, and dyslipidemia.[13]

Several glucose-lowering medications have demonstrated benefit in reducing risk of major adverse CV events, primarily glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors.[14]

The PCP's role in reducing ischemic stroke risk

Since primary care practitioners (PCPs) manage most patients with T2D and concurrently address other vascular risk factors such as lipids and hypertension across the disease continuum, they are typically aware of patients' stroke risk factors. Studies have demonstrated that patients who have a PCP at the time of first stroke have a lower risk of stroke recurrence.[15]

CASE SCENARIO 1

A 57-year-old man with T2D and dyslipidemia was recently hospitalized for a TIA. He is seeing his PCP for a post-hospitalization follow-up visit. His glycated hemoglobin (A1c) today is 7.4%. The patient's current medications include metformin 1000 mg twice daily, glipizide XL 10 mg daily, atorvastatin 80 mg daily, lisinopril 10 mg daily, and aspirin 81 mg daily.

The patient in case scenario 1 is at risk for ischemic stroke due to his recent TIA, along with T2D and dyslipidemia comorbidities. The PCP should evaluate his medication regimen for adjustments to reduce the risk of recurrent stroke.

POTENTIAL MECHANISMS OF GLP-1–MEDIATED STROKE RISK REDUCTION

Cardiovascular and cerebral effects of GLP-1

Several mechanisms have been proposed for the actions of GLP-1 on cardiac physiology to reduce atherosclerotic CV disease (ASCVD) risk, including stroke (**FIGURE 1**).[16-18] Based on experimental data, GLP-1 receptors are present in various components of the CV and central nervous systems, leading to beneficial effects on stroke prevention due to stimulation of these receptors from GLP-1 RAs.[17] Notably, all GLP-1 RAs cross the blood-brain barrier, enabling them to activate GLP-1 receptors in the brain.[19] Examples of antiatherosclerotic CV and cerebral effects of GLP-1 activation include improved endothelial function, enhanced plaque stability, reduced vascular smooth muscle proliferation, higher nitric oxide levels, decreased cerebral inflammation and cell apoptosis, and reduced oxidative stress.[17,18]

Improvement in traditional stroke risk factors

GLP-1 RAs have beneficial effects on hyperglycemia, dyslipidemia, blood pressure, body weight, and inflammation, which are recognized stroke risk factors.[17] Although the benefit of GLP-1 RAs on some factors is more established than on others, all may contribute to the lower risk of stroke observed with GLP-1 RAs in patients with T2D (**FIGURE 1**).[17,18]

Hyperglycemia is noted to have a causal relationship with increased risk of ischemic stroke, and reductions in A1c in CV outcomes trials (CVOTs) of GLP-1 RAs were associated with lower risk of nonfatal stroke.[17,20,21] Lipid abnormalities and hypertension heighten the risk of ischemic stroke in patients with T2D.[22,23] GLP-1 RAs have demonstrated improvements in lipid levels, specifically through mitigating postprandial increases in triglycerides and apolipoproteins and modulating lipoprotein metabolism.[17] The mechanisms of blood pressure reduction by GLP-1 activation are not yet fully elucidated.[17]

GUIDELINE RECOMMENDATIONS FOR USE OF GLP-1 RECEPTOR AGONISTS TO PREVENT STROKE IN PATIENTS WITH DIABETES

American Diabetes Association (ADA) standards of medical care

To reduce the risk of ASCVD events such as stroke, the 2023 ADA Standards of Medical Care recommend individualizing antihyperglycemic therapy based on comorbidities and risk factors, in addition to optimizing risk reduction through blood pressure and lipid management.[14,24] For patients with diabetes and ASCVD or indicators of high risk, a GLP-1 RA or SGLT2 inhibitor with proven CV benefit is preferred.[24]

AHA/ASA stroke prevention guidelines

The American Heart Association/American Stroke Association (AHA/ASA) Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack also recommends treating T2D with glucose-lowering agents such as GLP-1 RAs, which have proven to reduce the risk of future major adverse CV events.[5]

CLINICAL EVIDENCE FOR GLP-1 RECEPTOR AGONISTS IN STROKE RISK REDUCTION

Starting in 2008, the FDA mandated cardiovascular outcome trials (CVOTs) comparing the drug to placebo for CV safety to be conducted on antihyperglycemic agents submitted for approval in the US.[25] These data form the basis of CV risk assessment for GLP-1 RAs and other T2D medications.

The GLP-1 RAs evaluated in CVOTs include semaglutide, dulaglutide, liraglutide, lixisenatide, and exenatide. A summary of CVOT data can be helpful to compare specific CV outcomes of each agent, including for ischemic stroke, and can inform prescribing decisions (**TABLE 1**). Of note, the only GLP-1 RAs to demonstrate statistically significant benefit for stroke risk reduction in CVOTs are semaglutide injection and dulaglutide. The GLP-1 RAs with indications for reducing major CV events in adults with T2D who have established CV disease are semaglutide injection, dulaglutide, and liraglutide.[32-34]

TABLE 1. CVOTs of GLP-1 RAs in T2D and key outcomes related to ASCVD and stroke

Trial (drug)	Patients (n)	Inclusion criteria	Primary outcome HR (95% CI)[a]	Stroke HR (95% CI)[a]
SUSTAIN-6[26] (semaglutide injection)	3297	T2D and preexisting CV disease, CKD, or HF at ≥50 years of age or CV risk at ≥60 years of age	3-point MACE **0.74 (0.58-0.95)**	**0.61 (0.38-0.99)**
PIONEER-6[27] (semaglutide oral)	3183	T2D and high CV risk (age ≥50 years with established CV disease or CKD, or age ≥60 years with CV risk factors only)	3-point MACE 0.79 (0.57-1.11)	0.74 (0.35-1.57)
REWIND[28] (dulaglutide)	9901	T2D and prior ASCVD event or risk factors for ASCVD	3-point MACE **0.88 (0.79-0.99)**	**0.76 (0.61-0.95)**
LEADER[29] (liraglutide)	9340	T2D and preexisting CV disease, CKD, or HF at ≥50 years of age or CV risk at ≥60 years of age	3-point MACE **0.87 (0.78-0.97)**	**0.86 (0.73-1.00)**
ELIXA[30] (lixisenatide)	6068	T2D and history of ACS (<180 days)	4-point MACE 1.02 (0.89-1.17)	1.12 (0.79-1.58)
EXSCEL[31] (exenatide)	14,752	T2D with or without preexisting CV disease	3-point MACE 0.91 (0.83-1.00)	0.85 (0.70-1.03)

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; MACE, major adverse cardiovascular event; T2D, type 2 diabetes.

[a]Note: Boldface text indicates statistically significant results.

Of note, tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist, did not have a significantly higher or lower risk of stroke based on a meta-analysis of 7 SURPASS phase 3 trials (HR = 0.81, 95% CI, 0.39–1.68).[35]

Meta-analyses of GLP-1 RAs and stroke risk reduction

Several meta-analyses of GLP-1 RAs, including CVOTs, have been conducted to detect class benefit on ASCVD events, including stroke. One analysis of the Taiwan Health Insurance Database from 2011 to 2017 matched 4,460 individuals with T2D taking GLP-1 RAs with 13,380 patients taking dipeptidyl peptidase-4 (DPP-4) inhibitors.[36] Those taking GLP-1 RAs had a lower risk of nonfatal stroke than those taking DPP-4 inhibitors.[36]

Another meta-analysis of 8 trials and 60,080 patients with T2D found that GLP-1 RAs were associated with a statistically significant 17% reduction in fatal or nonfatal stroke compared to placebo.[37] A third meta-analysis of the same 8 trials found that GLP-1 RAs significantly reduced nonfatal stroke by 15% and fatal stroke by 16%.[38] Notably, the ELIXA trial, evaluating lixisenatide, showed a higher risk of stroke in the overall patient population, likely because patients enrolled in ELIXA had recent coronary syndrome.[38] A sensitivity analysis in one of the meta-analyses excluded patients from ELIXA and found marginally increased benefits of GLP-1 RAs.[37] Of note, both of these meta-analyses included ELIXA and PIONEER-6 in the 8 trials, indicating that results may be applicable to lixisenatide and oral semaglutide.

Other T2D medications and stroke risk reduction

SGLT2 inhibitors. One meta-analysis of 4 SGLT2 inhibitor CVOTs found no overall effect on stroke risk.[39] Another meta-analysis evaluated 6 CVOTs of SGLT2 inhibitors and found no statistically significant benefit in several stroke subanalyses.[40] A third meta-analysis of the same 6 SGLT2 inhibitor CVOTs did not find a significant association with lower stroke risk.[38]

Analysis of 19 randomized trials of DPP-4 inhibitors, including a total of 9,278 patients, showed a nonsignificant trend toward benefit for stroke (OR 0.639, 95% CI: 0.336–1.212; P = .170).[41] Pioglitazone has been associated with lower risk of recurrent stroke in patients with insulin resistance or T2D, but its unfavorable CV side effect profile limits use in patients at high CV risk.[42] Sulfonylureas have a neutral effect on stroke risk.[42]

Key message. Meta-analyses of CVOTs for GLP-1 RAs indicate that these therapies demonstrate substantial reduction of ischemic stroke versus placebo in patients with T2D.[5,37,43] In contrast, other T2D medications do not have significant ischemic stroke benefit in patients with T2D, except for pioglitazone, which is limited by CV side effects.[5,40] Therefore, of agents recommended by guidelines to mitigate CV risk in patients with diabetes (GLP-1 RAs and SGLT2 inhibitors), GLP-1 RAs are the preferred therapies for reducing risk of ischemic stroke.

REDUCING STROKE RISK IN PRIMARY CARE—PRACTICAL APPLICATION

As a primary point of care for patients with T2D who have experienced or are at risk of ischemic stroke, PCPs should be familiar with implementing evidence-based complex therapy to reduce stroke risk.

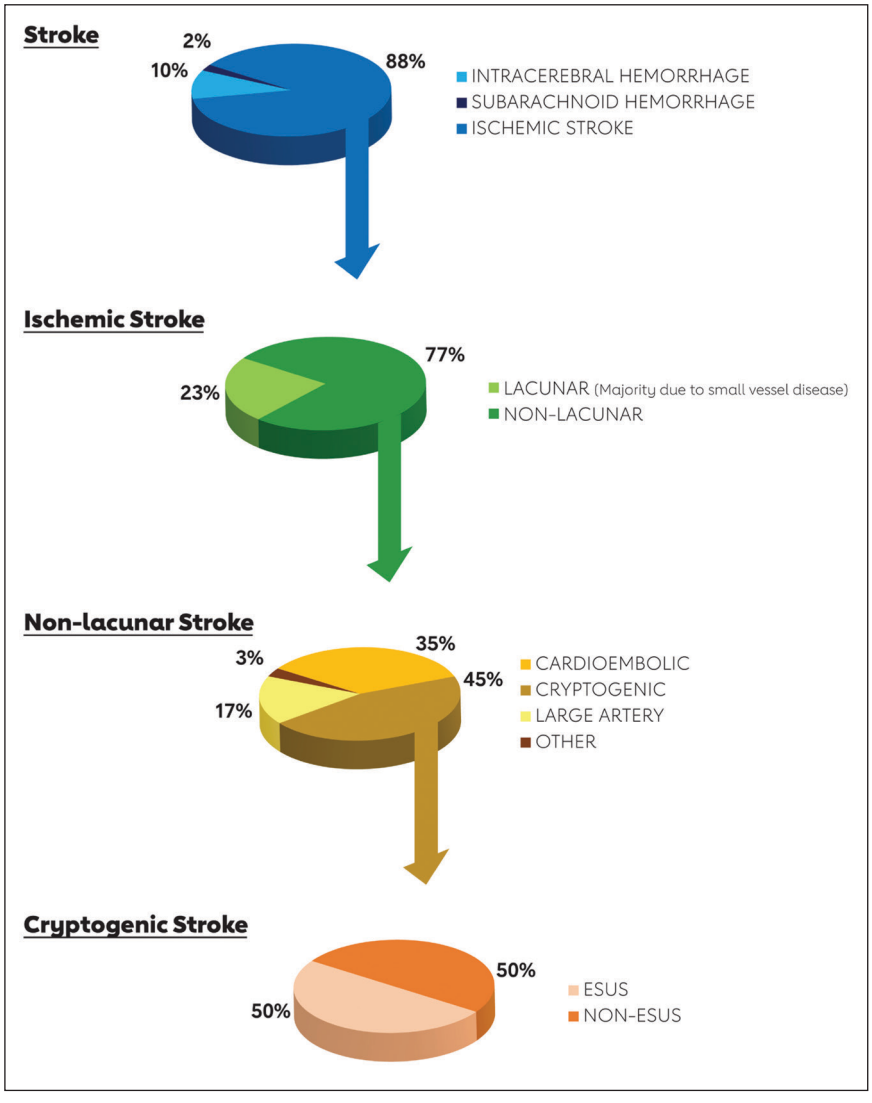
Primary prevention. Highlights of mainly primary-prevention approaches to ASCVD and stroke risk reduction, based on the ADA Standards of Medical Care, are discussed below.

- Antihyperglycemic therapy should be selected based on clinical characteristics such as ASCVD, high CV risk, heart failure, and chronic kidney disease (CKD).[24]
- GLP-1 RAs and SGLT2 inhibitors are recommended for ASCVD or high CV risk, but GLP-1 RAs are noted to have benefit in stroke prevention and SGLT2 inhibitors are not.[24]
- Hypertension is managed by targeting a blood pressure of <130/80 mm Hg, if it can be safely attained, and selection of antihypertensive agent depending on the patient's clinical characteristics.[14]
- Lipid management and primary prevention of ASCVD with moderate-intensity statin therapy is indicated for patients aged 40 to 75 years with diabetes, with high-intensity statins indicated in certain high-risk situations (including patients with ASCVD).[14]
- Lifestyle adjustments to diet and physical activity are suggested for improving and maintaining optimal levels of blood glucose, blood pressure, and lipids.[14,24]

Secondary prevention. Since management strategies for ischemic stroke depend on the subtype, defining ischemic stroke etiology, when possible, can help guide therapy (**FIGURE 2**). Topline recommendations from the AHA/ASA guidelines on secondary stroke prevention include the following[5]:

- Generally, managing vascular factors such as hypertension, diabetes, and lipids is a priority, as well as encouraging smoking cessation and engaging in multidisciplinary management.
- For patients with T2D and ASCVD, including ischemic stroke, GLP-1 RA therapy is recommended, regardless of baseline A1c.
- A healthy diet, specifically a low-sodium or Mediterranean diet, is suggested for stroke risk reduction.
- For nearly all patients who have experienced a stroke,

FIGURE 2. AHA/ASA conceptual representation of ischemic stroke subtypes



Abbreviation: ESUS, embolic stroke of undetermined source.

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barring any contraindications, antithrombotic treatment with antiplatelet or anticoagulant drugs is recommended.

The reader is referred to the full AHA/ASA guideline (https://www.ahajournals.org/doi/10.1161/STR.0000000000000375) for further discussion and detailed therapeutic strategy for secondary ischemic stroke prevention by subtype.

Revisiting case scenario 1, the PCP should consider optimizing the patient's T2D regimen to include an antihyperglycemic agent with additional A1c-lowering effects, as well as ASCVD risk reduction. Specifically, adding a GLP-1 RA would likely improve the patient's A1c and reduce the risk of ischemic stroke.

CASE SCENARIO 2

A 67-year-old female with T2D, atrial fibrillation, and CKD presents to her PCP for her annual visit. She has a family history of stroke but has been stroke free. Her medications include metformin 1000 mg daily, apixaban 2.5 mg twice daily, rosuvastatin 20 mg daily, and irbesartan 300 mg daily. Her A1c is 6.8%. At today's visit, her estimated glomerular filtration rate has declined to 21 mL/min/1.73 m^2, down from 30 mL/min/1.73 m^2 6 months ago.

In case scenario 2, the patient is at risk for ischemic stroke and would benefit from therapies that reduce stroke risk, in addition to further workup of her kidney impairment. Her kidney function has deteriorated to the point where clinicians may consider discontinuing metformin in favor of a safer agent. The degree of kidney impairment also precludes use of SGLT2 inhibitors. Discontinuing metformin and initiating a GLP-1 RA would reduce the patient's risk of ischemic stroke and improve the safety of her medication regimen, given her CV risk factors and decreased kidney function.

SUMMARY

Patients with diabetes are at increased risk for ASCVD events and should receive therapy with beneficial effects on CV outcomes—especially patients with additional CV risk factors. GLP-1 RAs have demonstrated a reduced risk of ischemic stroke in patients with T2D compared to other T2D medications, and several mechanisms have been proposed. PCPs treating patients with T2D who are at risk for occurrence or recurrence of ischemic stroke should consider incorporating GLP-1 RAs as an important component of stroke risk reduction, consistent with current evidence and clinical practice guidelines. ●

REFERENCES

1. Zhang L, Li X, Wolfe CDA, O'Connell MDL, Wang Y. Diabetes as an independent risk factor for stroke recurrence in ischemic stroke patients: an updated meta-analysis. *Neuroepidemiology*. 2021;55(6):427-435. doi:10.1159/000519327
2. Katan M, Luft A. Global burden of stroke. *Semin Neurol*. 2018;38(02):208-211. doi:10.1055/s-0038-1649503
3. Centers for Disease Control and Prevention. Stroke facts. Centers for Disease Control and Prevention. Published October 14, 2022. Accessed March 21, 2023. https://www.cdc.gov/stroke/facts.htm
4. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease: the American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. 2009;40(6):2276-2293. doi:10.1161/STROKEAHA.108.192218
5. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2021;52(7). doi:10.1161/STR.0000000000000375
6. American Stroke Association. Hemorrhagic strokes (bleeds). American Heart Association. Accessed March 21, 2023. https://www.stroke.org/en/about-stroke/types-of-stroke/hemorrhagic-strokes-bleeds
7. Mohan KM, Wolfe CDA, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. *Stroke*. 2011;42(5):1489-1494. doi:10.1161/STROKEAHA.110.602615
8. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet*. 2016;388(10046):761-775. doi:10.1016/S0140-6736(16)30506-2
9. Lau LH, Lew J, Borschmann K, Thijs V, Ekinci EI. Prevalence of diabetes and its effects on stroke outcomes: a meta-analysis and literature review. *J Diabetes Investig*. 2019;10(3):780-792. doi:10.1111/jdi.12932
10. Chen R, Ovbiagele B, Feng W. Diabetes and stroke: epidemiology, pathophysiology, pharmaceuticals and outcomes. *Am J Med Sci*. 2016;351(4):380-386. doi:10.1016/j.amjms.2016.01.011
11. Hägg S, Thorn LM, Forsblom CM, et al. Different risk factor profiles for ischemic and hemorrhagic stroke in type 1 diabetes mellitus. *Stroke*. 2014;45(9):2558-2562. doi:10.1161/STROKEAHA.114.005724
12. Gæde P, Oellgaard J, Kruuse C, Rossing P, Parving HH, Pedersen O. Beneficial impact of intensified multifactorial intervention on risk of stroke: outcome of 21 years of follow-up in the randomised Steno-2 study. *Diabetologia*. 2019;62(9):1575-1580. doi:10.1007/s00125-019-4920-3
13. Gæde P, Vedel P, Larsen N, Jensen GVH, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348(5):383-393. doi:10.1056/NEJMoa021778
14. ElSayed NA, Aleppo G, Aroda VR, et al. 10. Cardiovascular disease and risk management: *Standards of Care in Diabetes—2023*. *Diabetes Care*. 2023;46(Suppl 1):S158-S190. doi:10.2337/dc23-S010
15. Lank RJ, Lisabeth LD, Sánchez BN, et al. Recurrent stroke in midlife is associated with not having a primary care physician. *Neurology*. 2019;92(6):e560-e566. doi:10.1212/WNL.0000000000006878
16. Drucker DJ. The cardiovascular biology of glucagon-like peptide-1. *Cell Metab*. 2016;24(1):15-30. doi:10.1016/j.cmet.2016.06.009
17. Vergès B, Aboyans V, Angoulvant D, et al. Protection against stroke with glucagon-like peptide-1 receptor agonists: a comprehensive review of potential mechanisms. *Cardiovasc Diabetol*. 2022;21(1):242. doi:10.1186/s12933-022-01686-3
18. Goldenberg RM, Cheng AYY, Fitzpatrick T, Gilbert JD, Verma S, Hopyan JJ. Benefits of GLP-1 (glucagon-like peptide 1) receptor agonists for stroke reduction in type 2 diabetes: a call to action for neurologists. *Stroke*. 2022;53(5):1813-1822. doi:10.1161/STROKEAHA.121.038151
19. Cheng D, Yang S, Zhao X, Wang G. The role of glucagon-like peptide-1 receptor agonists (GLP-1 RA) in diabetes-related neurodegenerative diseases. *Drug Des Devel Ther*. 2022;16:665-684. doi:10.2147/DDDT.S348055
20. Maiorino MI, Longo M, Scappaticcio L, et al. Improvement of glycemic control and reduction of major cardiovascular events in 18 cardiovascular outcome trials: an updated meta-regression. *Cardiovasc Diabetol*. 2021;20(1):210. doi:10.1186/s12933-021-01401-8
21. Benn M, Emanuelsson F, Tybjærg-Hansen A, Nordestgaard BG. Impact of high glucose levels and glucose lowering on risk of ischaemic stroke: a Mendelian randomisation study and meta-analysis. *Diabetologia*. 2021;64(7):1492-1503. doi:10.1007/s00125-021-05436-0
22. Yaghi S, Elkind MSV. Lipids and cerebrovascular disease: research and practice. *Stroke*. 2015;46(11):3322-3328. doi:10.1161/STROKEAHA.115.011164
23. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387(10022):957-967. doi:10.1016/S0140-6736(15)01225-8
24. ElSayed NA, Aleppo G, Aroda VR, et al. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes–2023. *Diabetes Care*. 2023;46(Suppl 1):S140-S157. doi:10.2337/dc23-S009
25. Sharma A, Pagidipati NJ, Califf RM, et al. Impact of regulatory guidance on evaluating cardiovascular risk of new glucose-lowering therapies to treat type 2 diabetes mellitus: lessons learned and future directions. *Circulation*. 2020;141(10):843-862. doi:10.1161/CIRCULATIONAHA.119.041022
26. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141
27. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381(9):841-851. doi:10.1056/NEJMoa1901118
28. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394(10193):121-130. doi:10.1016/S0140-6736(19)31149-3
29. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827
30. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373(23):2247-2257. doi:10.1056/NEJMoa1509225
31. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017;377(13):1228-1239. doi:10.1056/NEJMoa1612917
32. Ozempic (semaglutide) injection. Prescribing information. Novo Nordisk A/S; 2022
33. Trulicity (dulaglutide) injection. Prescribing information. Eli Lilly and Company; 2022
34. Victoza (liraglutide) injection. Prescribing information. Novo Nordisk A/S; 2022
35. Sattar N, McGuire DK, Pavo I, et al. Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis. *Nat Med*. 2022;28(3):591-598. doi:10.1038/s41591-022-01707-4
36. Lin DSH, Lee JK, Chen WJ. Major adverse cardiovascular and limb events in patients with diabetes treated with GLP-1 receptor agonists vs DPP-4 inhibitors. *Diabetologia*. 2021;64(9):1949-1962. doi:10.1007/s00125-021-05497-1
37. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol*. 2021;9(10):653-662. doi:10.1016/S2213-8587(21)00203-5
38. Li J, Ji C, Zhang W, Lan L, Ge W. Effect of new glucose-lowering drugs on stroke in patients with type 2 diabetes: a systematic review and meta-analysis. *J Diabetes Complications*. 2023;37(1):108362. doi:10.1016/j.jdiacomp.2022.108362
39. Arnott C, Li Q, Kang A, et al. Sodium-glucose cotransporter 2 inhibition for the prevention of cardiovascular events in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *JAHA*. 2020;9(3):e014908. doi:10.1161/JAHA.119.014908
40. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol*. 2021;6(2):148. doi:10.1001/jamacardio.2020.4511
41. Barkas F, Elisaf M, Tsimihodimos V, Milionis H. Dipeptidyl peptidase-4 inhibitors and protection against stroke: a systematic review and meta-analysis. *Diabetes Metab*. 2017;43(1):1-8. doi:10.1016/j.diabet.2016.10.006
42. Avgerinos K, Tziomalos K. Effects of glucose-lowering agents on ischemic stroke. *World J Diabetes*. 2017;8(6):270-277. doi:10.4239/wjd.v8.i6.270
43. Bellastella G, Maiorino MI, Longo M, et al. Glucagon-like peptide-1 receptor agonists and prevention of stroke systematic review of cardiovascular outcome trials with meta-analysis. *Stroke*. 2020;51(2):666-669. doi:10.1161/STROKEAHA.119.027557