Stroke & Diabetes Update

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Disclosures:

None

Objectives

Review diabetes pathophysiology

Diabetes and stroke statistics

Novel diabetes medications and relationship to stroke risk

Implications for stroke prevention

Discuss the impact of multidisciplinary care on stroke outcomes

Definition

Diabetes mellitus (DM):

A group of metabolic disorders of carbohydrate metabolism

Glucose is underutilized as energy source and/or over-produced due to inappropriate gluconeogenesis and glycogenolysis

Results in hyperglycemia

- **Type 1 diabetes (T1D)**
  - Pancreatic β-cell destruction with absolute insulin deficiency
  - Usually caused by immunological disorders (this form includes LADA, latent autoimmune diabetes of the adults, with late-onset
- **Type 2 diabetes (T2D)**
  - Broad spectrum of variations
    - Insulin resistance with relative insulin deficit
    - Insulin secretion defect with insulin resistance
- **Gestational diabetes (GD)**
  - Occurrence of diabetes during pregnancy and its resolution at the end of the gestational period
  - Some complications developed in this phase may be irreversible

ADA, 2025

Diagnosis of T1D and T2D

Table 2.1—Criteria for the diagnosis of diabetes in nonpregnant individuals

A1C ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (≥7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (≥11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal results from different tests which may be obtained at the same time (e.g., A1C and FPG), or the same test at two different time points.

ADA, 2025

Hyperglycemia and A1C

- Hyperglycemia = elevated blood glucose
- Glycated hemoglobin (A1C) = measures the percentage of hemoglobin that is attached to glucose. Higher glucose levels lead to a higher percentage of glycated hemoglobin

Glycemic Variability (GV)

- GV = a measure of temporal variations in blood glucose levels
- Found to be associated with mortality and CVD in T2DM and was determined to be of greater prognostic value than hyperglycemia and A1C in AIS patients

CDC National Diabetes Statistics (2021)

- 38.4 million people have diabetes (11.6% of the U.S. population)
- Percentage of adults with diabetes increased with age
  - 29.2% among those aged 65 years or older
- 8.7 million adults aged 18 years or older who met laboratory criteria for diabetes were not aware of or did not report having diabetes

Diabetes and Stroke

- Prevalence: >30 million Americans have diabetes
- 7th leading cause of death in the U.S.
- Adults with DM are twice as likely to have a stroke compared to adults without DM
- Known to be intrinsically related to CVD
- Every 2 minutes an American adult with DM is hospitalized for stroke

Pathophysiology of AIS in PWD

Diabetes-related cerebral microvascular dysfunction affected primarily by:

- Hyperglycemia
- Obesity
- Insulin resistance
- Hypertension
- Increased arterial stiffness
  - Exposes small vessels in the brain to abnormal flow pulsations
  - May also contribute to the pathogenesis of cerebral SVD

Increased oxidative stress and inflammation are believed to contribute to microvascular endothelial dysfunction

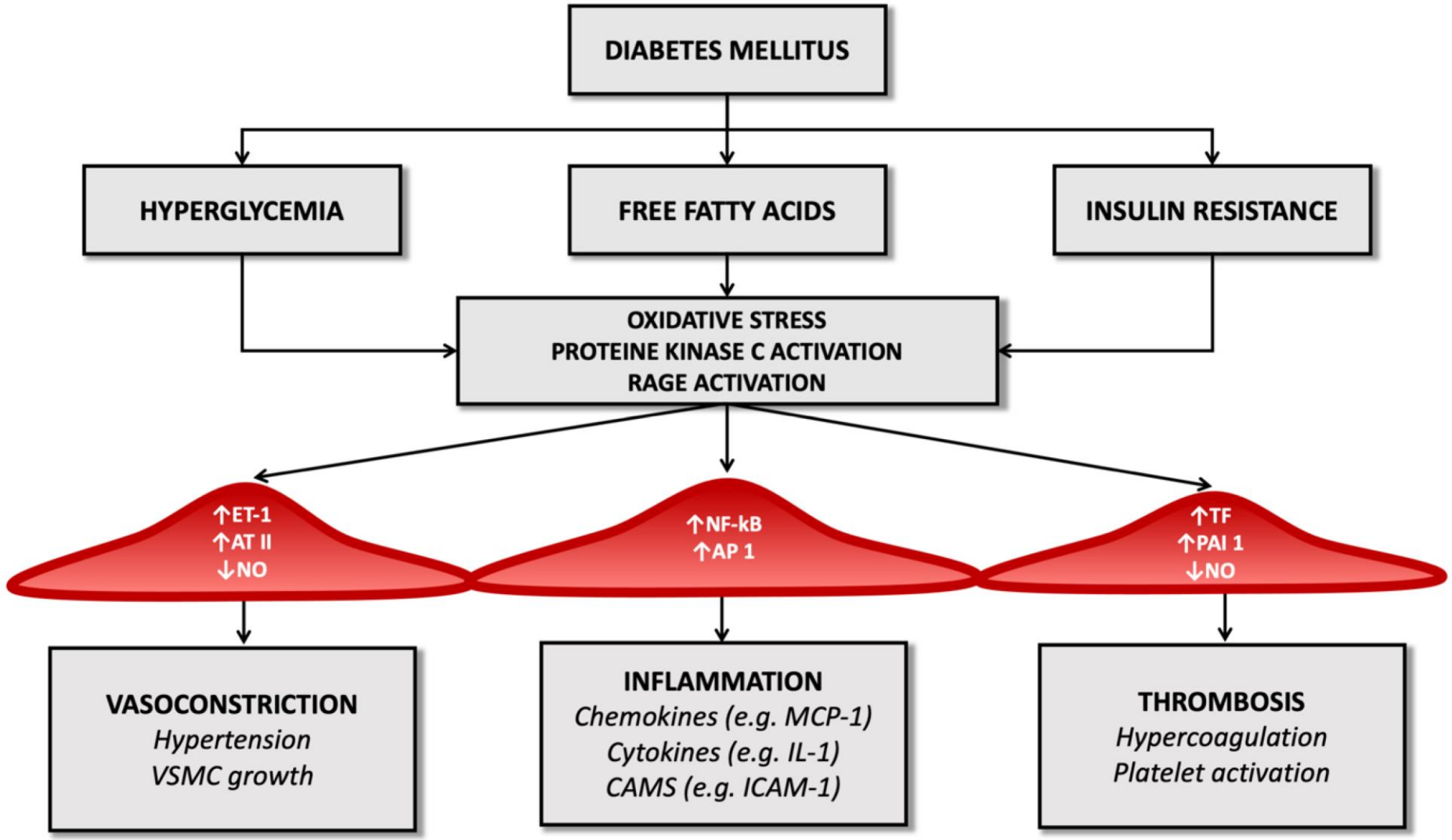
Individuals with T2D have an overall 35% higher risk of atrial fibrillation compared with the general population (3)

Diabetes and Hypertension

Among U.S. adults aged 18 years or older with diagnosed diabetes, crude estimates for 2017–2020:

- 80.6% had a systolic blood pressure of 130 mmHg or higher or diastolic blood pressure of 80 mmHg or higher or were on prescription medication for their high blood pressure
- 70.8% had a systolic blood pressure of 140 mmHg or higher or diastolic blood pressure of 90 mmHg or higher or were on prescription medication for their high blood pressure

CDC, 2025


DIABETES MELLITUS
HYPERGLYCEMIA
FREE FATTY ACIDS
INSULIN RESISTANCE
OXIDATIVE STRESS
PROTEINE KINASE C ACTIVATION
RAGE ACTIVATION
↑ET-1
↑AT II
↓NO
↑NF-kB
↑AP 1
↑TF
↑PAI 1
↓NO
VASOCONSTRICTION
Hypertension
VSMC growth
INFLAMMATION
Chemokines (e.g. MCP-1)
Cytokines (e.g. IL-1)
CAMS (e.g. ICAM-1)
THROMBOSIS
Hypercoagulation
Platelet activation

Maida et al

Diabetes and Stroke

- T2DM is associated with a two- to threefold increase in the risk of stroke, and approximately 10% of newly diagnosed T2DM patients develop stroke within 5 years of diagnosis
- Ischemic stroke with acute hyperglycemia (without history of DM), is at a threefold higher risk of 30-day mortality, in contrast to twofold 30-day mortality in DM patients
- Ischemic stroke: People with Diabetes (PWD) are relatively younger and have more comorbidities than those without diabetes (3,4)

Diabetes and Stroke

- Prevalence of diabetes in people with all types of stroke is 28% (33% ischemic, 26% hemorrhagic)
- Acute hyperglycemia is presumably associated with an increased risk of hemorrhagic transformation after stroke in patients treated with thrombolysis
- Likelihood of stroke recurrence is greater for individuals with diabetes than those without diabetes (3,4)

Factors potentially increasing risk of stroke in PWD

- Endothelial dysfunction
- Vessel stiffness
- Systemic and local inflammation (CRP)
- Atherosclerosis
- Dyslipidemia
- Hyperglycemia
- Insulin resistance
- Atrial fibrillation

Diabetes and Stroke

- A J-shaped relationship has also been reported between ICH and A1c, suggesting that both over and undertreating DM may be associated with increased risk
- Studies have shown T1DM to carry a substantially higher likelihood of long-term mortality after an ICH as compared to T2DM
- Both T1D andT2D are associated with a higher incidence of ICH compared to non-DM (4)

Diabetes and Stroke Risk Factors

Duration of diabetes

- Associated with the risk of ischemic stroke
  - Up to 3 percent each year
  - Triples ≥ 10 years
  - Increased risk of atherosclerotic lesions
  - More severe endothelial dysfunction

Obesity

- May contribute to the development of endothelial dysfunction

Hypertension

- Microvascular disease
- Metabolic derangements
- Vascular fibrosis
- Autonomic dysfunction

Post-stroke Outcomes

- Studies have shown that people with stroke and DM have worse post-stroke outcomes compared with those with stroke but without DM
- Post-discharge mortality rates are higher in individuals with ischemic stroke and DM versus those without DM
- Median survival is lower in people with either type of stroke (i.e., ischemic or hemorrhagic) and DM compared with those without DM
- Stroke severity alone is unlikely to explain the higher mortality and lower survival in people with DM
- In general, the length of in-hospital stay is longer among individuals with stroke who have DM compared with those without DM (2)

Diabetes Medications

Classes of non-insulin glucose-lowering agents

- GLP-1 Ras
- Thiazolidinediones
- Sodium-glucose cotransporter-2 inhibitors (SGLT-2is)
- Dipeptidyl peptidase-4 inhibitors (DPP-4is)
- Sulfonylureas
- Biguanides
- Meglitinides
- Alpha-glucosidase inhibitors

Medication/Drug Class	Action	Trials	Benefit
GLP1 RAs	Mimic glucagon-like peptide, stimulating insulin release, reducing glucagon production, slowing gastric emptying, and increasing satiety	LEADER HARMONY SUSTAIN-6 REWIND	Lower death rates from any cause, CV death, MI, or stroke Reduction in CV events
SGLT2 inhibitors	inhibit the reabsorption of glucose in the kidneys, leads to increased urinary glucose excretion	CREDENCE VERTIS CV CANVAS DECLARE-TIMI EMPA-REG OUTCOME	Neutral/no significant effect on risk of AIS in PWD, 50% reduction in hemorrhagic stroke Significant reduction in HF risk
DPP4 inhibitors	increase the levels of incretin hormones, GLP-1 and GIP, block GLP-1 breakdown, stimulate insulin secretion and reduce glucagon secretion	SAVOR TECOS CARMELINA	Neutral effects Discordant findings Potential increased risk of HF
TZDs	Insulin sensitizers	PROactive IRIS	T2DM and IR patients, TZDs may mitigate the risk of recurrent stroke and related vascular events

Clinical Guidelines for Stroke Prevention

In 2018, the ADA and the European Association for the Study of Diabetes (EASD) published a consensus report in which it was recommended, after metformin, preference for SGLT2is and GLP1-Ra in patients with established cardiovascular disease or chronic kidney disease (7)

Diabetes Medications

- GLP-1 Ras
  - multisystem effects
  - improve pancreatic response to food
  - delayed gastric emptying and increased satiety
  - reduce blood glucose levels
  - Reduce body weight
  - Reduce blood pressure
- Most GLP-1 RAs reduce cardiovascular event risk among those with T2D who are at high cardiovascular risk or with previous ASCVD
  - Reduction in HbA1c, LDL cholesterol, blood pressure, weight, urine albumin/creatinine ratio, and high-sensitivity
  - Intensive glycemic control achieved with agents other than GLP-1 RAs or pioglitazone has not been shown to have any significant effect on stroke events in people with T2D
  - Suggests that the beneficial effect of GLP-1 RAs on stroke is not solely due to glycemic control (5,7)

Diabetes Medications

- SGLT2 inhibitors
  - Multisystem effects
  - Inhibit the reabsorption of glucose and sodium in the kidneys, leads to increased urinary glucose excretion, lower blood sugar levels
  - Have been shown to have cardiovascular protective effects, such as reducing blood pressure and improving heart function
  - Reduction in HbA1c, LDL cholesterol, blood pressure, weight, urine albumin/creatinine ratio, and high-sensitivity
  - Some studies suggest that SGLT2 inhibitors may help protect the kidneys from damage
  - Can also lead to weight loss by reducing appetite and increasing energy expenditure

Diabetes Medications

- Thiazolidinediones
  - Increase insulin sensitivity
  - Alter the transcription of genes influencing carbohydrate and lipid metabolism, resulting in changed amounts of protein synthesis
  - Many potential adverse events, including weight gain, CHF, bone fractures, macular edema, and possibly bladder cancer
  - Option for most insulin-resistant patients—identifiable by an increased waist circumference, low HDL cholesterol level, and fatty liver—may benefit patients with high risk or history of CVD (5,7)

Study of population-based retrospective cohort of people with T2DM

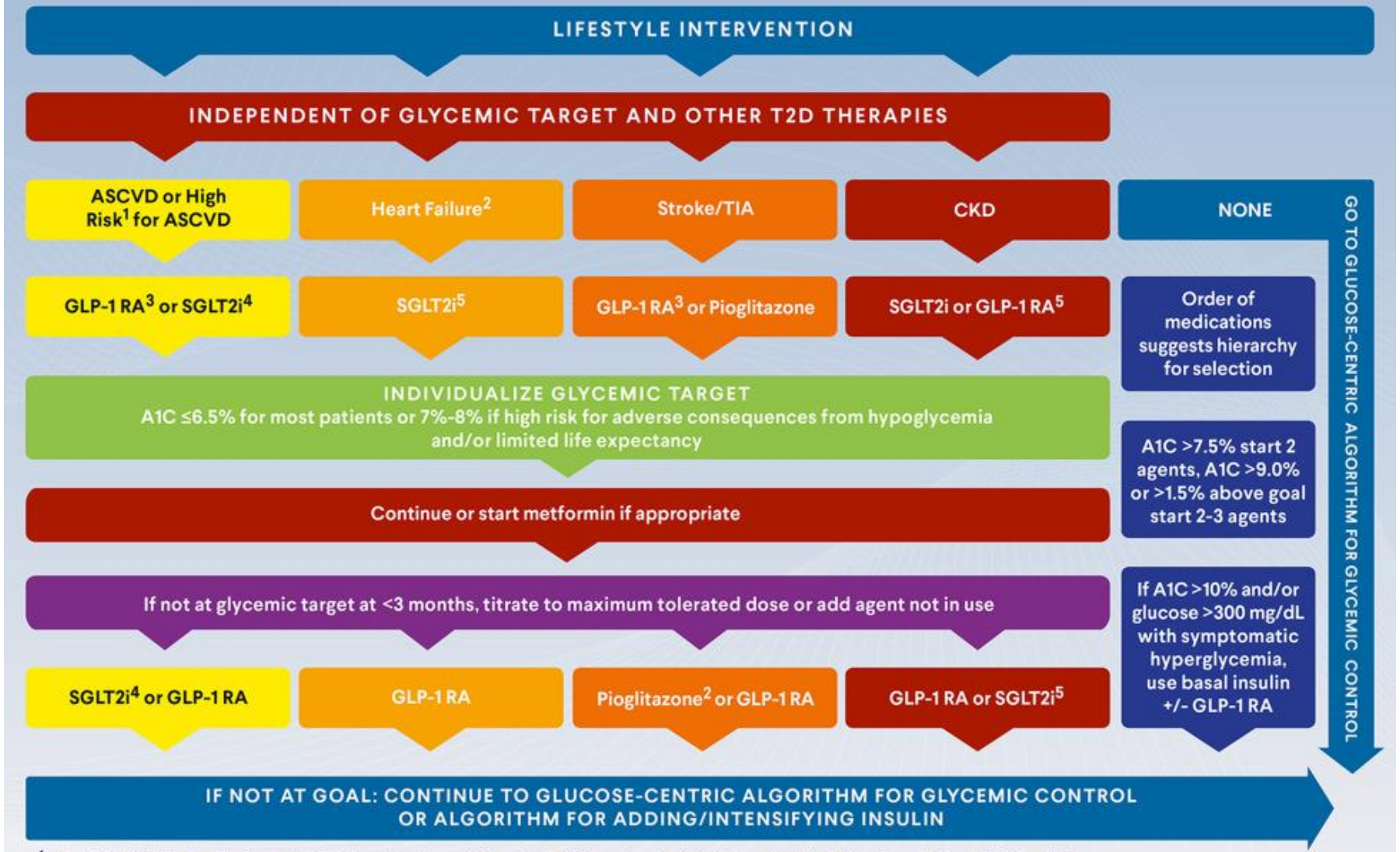
- Patients who received SGLT2i or GLP-1RA matched by propensity score matching
- No significant difference between the SGLT2i and GLP1-Ra groups
- Patients with a history of stroke seemed to benefit more from the use of GLP1-Ra
- Significantly higher risk of ischemic stroke among people on SGLT2is compared with GLP1-Ra users
- Risks of hemorrhagic stroke and cardioembolic stroke were similar for the groups treated with both pharmacological groups (7)

Liu et al, 2023

Implications for Stroke Prevention

- SGLT2is may aid in reducing the incidence of hospitalizations for HF CE composite, and most evidence suggests that the benefit on 3P-MACE may be limited to people with established CVD (7)

COMPLICATIONS-CENTRIC ALGORITHM FOR GLYCEMIC CONTROL



[1]High risk for ASCVD: albuminuria or proteinuria, hypertension and left ventricular (LV) hypertrophy, LV systolic or diastolic dysfunction, ankle-brachial index <0.9.
[2]TZDs are contraindicated in NYHA Class III/IV HF. [3]ASCVD: liraglutide/semaglutide/dulaglutide or Stroke: semaglutide/dulaglutide.
[4]canagliflozin/empagliflozin. [5]Use SGLT2i or GLP-1 RA with proven benefit.

Algorithm Figure 6-Complications-Centric Glycemic Control

For Professionals

American Heart Association.

American Diabetes Association.

Know Diabetes by Heart™

Learn more about treatment guidelines for cardiovascular disease and type 2 diabetes.

Diabetes and Stroke

People living with diabetes are at higher relative risk (2) for stroke

Diabetes medications with proven benefits for stroke reduction

Pioglitazone has been shown to reduce the risk for stroke for those with insulin resistance

GLP-1 RAs, specifically dulaglutide and semaglutide, have been shown to reduce the risk for stroke

Hypertension and dyslipidemia, both common conditions coexisting with type 2 diabetes, also increase risk for stroke.

For hypertension:

<130/80

Target blood pressure

For dyslipidemia:

<70mg/dL

Target LDL-C for primary prevention

<55mg/dL

Target LDL-C for secondary prevention

- Statin therapy is the first-choice for primary and secondary prevention.
- Add-on therapies, including ezetimibe, PCSK9i, inclisiran, and bempedoic acid, if not meeting LDL goal on statins or intolerant to them.
- Fibrates or EPA are recommended to lower triglycerides to <150 mg/dL

EPA: eicosapentaenoic acid
PCSK9i: proprotein convertase subtilisin/kexin type 9 inhibitors
GLP-1 RA: glucagon-like peptide-1 receptor agonist
LDL-C: low-density lipoprotein cholesterol

Learn more at **KnowDiabetesbyHeart.org**

This infographic is based on recommendations from the ADA's Standards of Care in Diabetes – 2024

Summary

- The mechanism by which DM mediates outcomes after stroke is complex
- Patients with DM are at risk of serious complications, including stroke, heart disease, retinopathy, chronic kidney disease, and limb amputation
- Identification and use of appropriate medications for diabetes management can potentially reduce the risk of initial and/or recurrent stroke
- Optimal glucose control using anti-diabetic medications is beneficial in the treatment of T2DM and stroke patients
- The increased risk of stroke in T2DM patients offers diagnostic and therapeutic opportunities towards early risk stratification and optimization of therapies
- DM is associated with poor post-stroke outcomes, including longer long-term disability (>50%) and higher mortality, relative to patients with controlled glucose levels
- Late diagnosis and treatment can exacerbate complications

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QUESTIONS

THANK YOU

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