Stroke and the person with diabetes

Importance of the condition in relation to diabetes care

- Diabetes is a well-established independent risk factor for both ischaemic and haemorrhagic stroke, but this risk is modifiable.
- Diabetes can cause pathologic changes in blood vessels at numerous locations, but can lead to stroke if cerebral vessels are directly affected. People with diabetes are especially susceptible to the consequences of cerebral small-vessel diseases.
- Hyperglycaemia confers greater risk of stroke occurrence. Mortality is higher and post-stroke outcomes are poorer in individuals with uncontrolled glucose levels.

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There are opportunities in primary care to improve stroke outcomes in individuals with diabetes. It requires prompt and persistent implementation of evidence-based medical therapies, especially for hypertension, as well as routine encouragement and support to implement beneficial lifestyle practices.

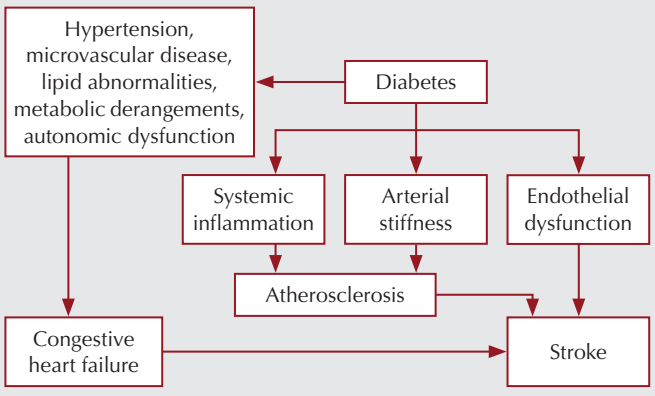
The adjusted hazard ratios (HRs) for stroke for patients with diabetes are:

- 2.27 (95% CI, 1.95–2.65) for ischaemic stroke
- 1.56 (95% CI, 1.19–2.05) for haemorrhagic stroke
- 1.84 (95% CI, 1.59–2.13) for unclassified stroke.[1]

Individuals with type 1 diabetes are more likely to suffer coronary heart disease and peripheral arterial disease. Those with type 2 diabetes are more likely to have obesity, peripheral arterial disease, large-artery atherosclerosis and stroke.[2]

Possible mechanisms that increase the risk of stroke in diabetes include vascular endothelial dysfunction, increased early-age arterial stiffness, systemic inflammation and thickening of the capillary basal membrane (see figure).

Abnormalities in early left-ventricular diastolic filling are commonly seen in type 2 diabetes, with an increased risk of heart failure and embolic stroke, related to microvascular disease, metabolic derangements, interstitial fibrosis, hypertension and autonomic dysfunction.[3]



Possible mechanisms of stroke in individuals with diabetes.[3]

Individuals with diabetes are more likely to have limb weakness and dysarthria as signs of lacunar cerebral infarction than those without diabetes. They also have a higher relative prevalence of subcortical infarction and lower relative prevalence of intracerebral haemorrhage.[4] A study of participants with ischaemic stroke observed higher frequencies of lacunar infarct and hypertension in those with diabetes.[5]

Type 2 diabetes increases risk of atrial fibrillation (a leading risk factor for stroke) by approximately 35%.[6] People with advanced renal complications have substantially higher excess risks (three-fold with stage 5 chronic kidney disease). Among people with type 2 diabetes, those at increased risk (including older people and those with advanced renal complications) should be screened for atrial fibrillation. This is simply achieved by pulse-taking during blood pressure measurements.[6]

Diabetes is a factor used to calculate the CHA_2DS_2VASc score, used to identify individuals with atrial fibrillation at high risk of stroke and who may benefit from anticoagulation treatment (see Javaid, 2021).[7]

Intensive therapy

The Diabetes Control and Complications Trial (DCCT) randomised participants with type 1 diabetes to receive intensive (INT) or conventional (CON) therapy for an average of 6.5 years. Follow-up of the cohort in the Epidemiology of Diabetes Interventions and Complications (EDIC) study 12 years later observed an aggregate reduction of 42% (95% CI, 9–63; P=0.016) in cardiovascular disease (CVD) risk and 57% (95% CI, 12–79; P=0.018) in major adverse cardiovascular events (non-fatal myocardial infarction [MI] or stroke or CVD death) in the INT group compared to the CON group.[8]

Lifestyle change

Lifestyle changes, including controlling weight, minimising total fat intake (especially saturated fat), increasing fibre intake and physical activity, can reduce incidence of diabetes in high-risk individuals. However, intensive lifestyle interventions only aiming at weight reduction do not lead to a corresponding reduction in CVD in overweight or obese individuals with type 2 diabetes. The Look AHEAD (Action for Health in Diabetes) trial reported no significant difference in CV morbidity and mortality between its intensive lifestyle intervention for weight loss and control groups after a median follow-up of 9.6 years.[9] Specifically, the primary outcome (a composite of death from CV causes, non-fatal MI, non-fatal stroke or hospitalisation for angina) occurred in 418 individuals in the control group and in 403 in the intervention group (1.92 and 1.83 events per 100 person-years, respectively; P=0.51). Additionally, there was no difference in stroke occurrence (80 in the control group versus 85 in the intervention group; P=0.78).[9]

Although weight loss itself does not seem to be effective in reducing CV events, intensified multifactorial intervention is. In the Steno-2 study, subjects with type 2 diabetes and persistent microalbuminuria were randomised to either INT or CON therapy. Targets for the INT group included HbA_{1c} of <48 mmol/mol, fasting serum total cholesterol of <4.5 mmol/L, fasting serum triglyceride of <1.7 mmol/L, systolic blood pressure (SBP) of <130 mmHg and diastolic blood pressure (DBP) of <80 mmHg. There were sustained beneficial effects in the INT group with respect to CV events (HR, 0.41 [95% CI, 0.25–0.67; P<0.001]) and deaths from CV causes (HR, 0.43 [95% CI, 0.19–0.94; P=0.04]). During the 13.3 years of follow-up, 6 individuals (6 strokes) in the INT group and 18 individuals (30 strokes) in the CON group suffered strokes.[10]

Key messages (from the ESC/EASD guidelines on diabetes, pre-diabetes and CV diseases)[11]

Lifestyle

- As well as being a core part of type 2 diabetes management, lifestyle changes as part of multifactorial intervention are key to prevent diabetes and its CV complications, including stroke.
- Reduced calorie intake is recommended to lower excessive body weight in people with diabetes.
- A Mediterranean diet supplemented with olive oil and/or nuts reduces the incidence of major CV events.
- Moderate-to-vigorous physical activity of ≥150 min/week is recommended for the prevention and control of diabetes.

Glucose control

- A near-normal HbA_{1c} target (<53 mmol/mol) will decrease microvascular complications in people with diabetes.
- Tighter glucose control initiated early in the course of diabetes in younger individuals reduces CV outcomes over a 20-year timescale.
- Less-rigorous targets should be considered in older people on an individualised basis, and in those with severe comorbidities or advanced CVD.

Blood pressure control

- Target SBP to 130 mmHg in people with diabetes and <130 mmHg if tolerated, but not <120 mmHg. In older people (aged >65 years), the SBP goal is 130–139 mmHg.
- Target DBP to <80 mmHg, but not <70 mmHg.
- Optimal BP control reduces the risk of micro- and macrovascular complications.
- Guidance on lifestyle changes must be provided for patients with diabetes and hypertension.
- Evidence strongly supports the inclusion of an angiotensin-converting enzyme inhibitor (ACEi), or an angiotensin receptor blocker (ARB) in those who are intolerant to ACEis.
- BP control often requires multiple drug therapy with a renin–angiotensin–aldosterone system (RAAS) blocker, and a calcium-channel blocker or diuretic. Dual therapy is recommended as first-line treatment.
- The combination of an ACEi and ARB is not recommended.
- In pre-diabetes, the risk of new-onset diabetes is lower with RAAS blockers than with beta-blockers or diuretics.
- People with diabetes on combined antihypertensive treatments should be encouraged to self-monitor BP.

Statins

- Statins effectively prevent CV events and reduce CV mortality, and their use is associated with a limited number of adverse events. Because of the high-risk profile of people with diabetes, intensive statin treatment should be individualised.

Antidiabetes drugs

- SGLT2 inhibitors
  - Empagliflozin, canagliflozin or dapagliflozin are recommended in people with type 2 diabetes and CVD, or those at very high/high CV risk, to reduce CV events.
  - Empagliflozin is recommended in people with type 2 diabetes and CVD to reduce the risk of death.
- GLP-1 receptor agonists
  - Liraglutide, semaglutide or dulaglutide are recommended in people with type 2 diabetes and CVD, or those at very high/high CV risk, to reduce CV events.
  - Liraglutide is recommended in people with type 2 diabetes and CVD, or at very high/high CV risk, to reduce the risk of death.

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