



Burton, J. K. , Quinn, T. J. and Fisher, M. (2019) Diabetes and stroke. *Practical Diabetes*, 36(4), pp. 126-131.

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This is the peer reviewed version of the following article:

Burton, J. K. , Quinn, T. J. and Fisher, M. (2019) Diabetes and stroke. *Practical Diabetes*, 36(4), pp. 126-131. (doi: [10.1002/pdi.2230](https://doi.org/10.1002/pdi.2230))

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Deposited on: 23 July 2019

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Practical Diabetes

Diabetes and Stroke

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Abstract

The association between diabetes and stroke is well established. Recent large scale, international population studies suggest that diabetes is one of the most important modifiable risk factors for cerebrovascular disease. Despite this, we still have a relative paucity of evidence around the management of diabetes in stroke. The landscape is evolving and recent studies are helping establish best practice and suggesting new therapeutic opportunities. It is possible to develop a practical and clinical synthesis of the evidence around managing diabetes in adult patients with stroke and cerebrovascular disease, based on large trials, systematic reviews and guidelines, and focussing on the scenarios most often encountered in clinical practice. It is also important to recognise that there are common situations where robust evidence is lacking, but practical guidance for clinicians can be suggested.

Key words

Diabetes mellitus, stroke, ischaemic, haemorrhagic, cerebrovascular, risk factors

Key points

- Diabetes is a risk factor for all forms of stroke disease
- Hyperglycaemia in the acute phase after stroke is not all caused by diabetes, but all cases should be investigated for the possibility of underlying diabetes
- Aggressive management of hyperglycaemia in acute stroke is not supported by evidence from randomised trials, and risks causing harm secondary to hypoglycaemia
- In a person living with diabetes and stroke, the management of vascular risk factors, including blood pressure, lipid lowering and appropriate antithrombotic therapy, is just as important as managing glycaemia.

Introduction

Observational epidemiology suggests that diabetes is a risk factor for all stages of the stroke journey, from cerebrovascular disease found incidentally on neuro-imaging, through to incident acute stroke and its longer-term recovery.

For acute stroke, meta-analysis of prospective studies of individuals with diabetes and no history of vascular disease, indicates adjusted hazard ratios (HR) of 2.27 (95%CI 1.95-2.65) for ischaemic stroke and HR 1.84 (95%CI 1.59-2.13) for haemorrhagic stroke.(1) This increased risk is independent of traditional cardiovascular risk factors.(1) International case-control data estimates an Odds Ratio (OR) of 1.16 (95%CI 1.05-1.30) for diabetes and risk of any first stroke event,(2) giving a population attributable risk of 3.9% (95%CI 1.9-7.6).(2) Risks are elevated in all common forms of diabetes and in all stroke subtypes. Large population studies tend to focus on people with type 2 diabetes, but UK Primary Care data identified a HR for stroke of 3.7 in men and 4.8 in women with type 1 diabetes over seven years of follow-up.(3) People with Type 1 diabetes are also at higher risk of developing an intracerebral haemorrhage (RR 1.74 95% CI 1.38-2.21) and of dying as a consequence (RR 1.35 95%CI 1.01-1.70).(4)

Similarly, individuals presenting with acute stroke are more likely to have diabetes. Meta-analysis of 39 studies of inpatients diagnosed with stroke found an estimated prevalence of diabetes of 28% (95%CI 26-31%), although the authors highlight significant heterogeneity in diagnostic approaches.(5)

For those who experience stroke, the presence of diabetes or abnormal glycaemic status is associated with poor outcomes. A new diagnosis of diabetes made at time of presentation with acute stroke has been associated with poorer functional outcomes at one year in both ischaemic (OR 2.58; 95%CI 1.95-3.43)(6) and haemorrhagic stroke (OR 1.93; 95%CI 1.10-3.38).(7) Finnish observational data identified a five-year survival of only 58% in a cohort of people with type 1 diabetes experiencing incident stroke, with mortality associated with worsening renal function.(8)

Mechanistic studies suggest that hyperglycaemia can worsen ischaemic neuronal injury. However, the pathological effect of diabetes on the cerebral vasculature is not limited to clinically overt stroke. Cerebral small vessel disease (cSVD) is increasingly recognised as a risk factor for stroke and vascular dementia, with diabetes considered an important potentially modifiable risk factor.(9) Recent Mendelian randomisation data suggests a causal association between Type 2 diabetes and cSVD.(10) Diabetes may potentiate and/or moderate neurological damage, and diabetes is associated with an elevated risk of undifferentiated dementia, before a stroke event (OR 1.90, 95%CI 1.25-2.88) and afterwards (HR 1.53, 95%CI 1.18-1.98).(11)

Acute Stroke

Hyperglycaemia in acute stroke

A large proportion of stroke events occur in people living with diabetes. Larger still is the proportion of people with an acute stroke that have abnormal glycaemia following a stroke event. Immediate post-stroke hyperglycaemia is estimated to affect 42.6% (95%CI 40.7-44.5%) of admissions, with a further 19.4% developing hyperglycaemia within 48-hours of admission.(12) Not all of these cases have diabetes, although hyperglycaemia in hospitalised patients is a recognised predictor of developing type 2 diabetes. Secondary analysis of data from the Glucose Insulin in Stroke Trial found 42% of those with hyperglycaemia at the time of acute stroke had a normal glucose tolerance at three month follow-up and 21% had diabetes mellitus.(13) Normal plasma glucose at the time of acute stroke does not exclude abnormalities in glucose metabolism, and up to a third of these individuals may have impaired glucose tolerance or abnormal glycosylated haemoglobin levels on formal testing.(14) The presence of admission hyperglycaemia with elevated glycosylated haemoglobin levels provided a positive predictive value of 80% and negative predictive value of 96% for diabetes at three months.(13)

Any form of abnormal glycaemia seems to have an adverse prognostic effect and diabetes status or glucose feature in most acute stroke risk stratification tools.(15) Hyperglycaemia within the first 48 hours increases the risk of a poorer functional outcome by 12.9% (95%CI 9.2-16.7%).(12) Subjects with elevated plasma glucose levels are at a 1.5-fold higher risk of mortality over three years of follow-up.(16) The mechanisms which account for this worsening of outcomes associated with hyperglycaemia have not been fully established.(17)

Glycaemic control in acute stroke

Given that abnormal glycaemia is common and associated with poor outcomes, it would seem intuitive that we should intervene to normalise blood glucose concentrations. The most recent Cochrane Review on intensive glycaemic control identified 11 randomised trials with 1583 participants.(18) Maintaining serum glucose levels within normal range (defined as 4 to 7.5 mmol/L) in the first 24 hours after acute ischaemic stroke was not associated with any differences with respect to death, dependency or neurological deficit.(18) Conversely, trying to achieve normoglycaemia in the acute period is not necessarily a benign intervention. The review reported a number needed to harm of only nine for symptomatic hypoglycaemia.(18)

This lack of evidence to support acute treatment is reflected in guidelines. The European Stroke Organisation Guidance including published data to July 2015, states that current evidence does not demonstrate any significant benefit of tight glycaemic control using intravenous (IV) insulin in acute stroke on functional outcomes or survival.(19) However, the authors highlight that this conclusion is based on low quality evidence with significant heterogeneity in the included trials with respect to selection bias, different target glucose levels and different control interventions.(19) There is discordance between the two UK

guideline bodies on the approach to management of hyperglycaemia in acute stroke. The Scottish Intercollegiate Guidelines Network state:

“routine use of insulin regimens to lower blood glucose in patients with moderate hyperglycaemia after acute stroke is not recommended.....patients with hyperglycaemia should be formally assessed to exclude or confirm a diagnosis of impaired glucose tolerance or diabetes”(20)

Whereas the National Institute for Health and Care Excellence Guidance states:

“People with acute stroke should be treated to maintain a blood glucose concentration between 4 and 11 mmol/litre.”(21)

However, both guidelines emphasise that the management of those with an established diagnosis of diabetes should follow usual management protocols, including administration of essential insulin for people with type 1 diabetes.

The Stroke Hyperglycaemia Insulin Network Effort (SHINE) trial seeks to address the uncertainties in current practice around how best to manage hyperglycaemia in acute stroke.(22) The trial recruited 80% of participants with known type 2 diabetes, and initial results suggest no improvement in functional outcomes ($p=0.55$) when using intensive continuous IV insulin therapy (target blood sugar 80-130mg/dL), compared to an approach described as ‘Standard sliding scale therapy’ but which involved administration of subcutaneous insulin every six hours to a target of <10.0 mmol/L.(23) The early results also found an increased risk of severe hypoglycaemia in the intensive treatment group (2.6% versus 0%).(23)

Thrombolysis and glycaemic control

The association between hyperglycaemia and adverse outcomes has been evaluated among stroke patients receiving thrombolysis treatment using observational datasets. These have identified that both acute hyperglycaemia at hospital admission (>7.8 mmol/l) and chronic hyperglycaemia (plasma glycosylated haemoglobin HbA1c >48 mmol/mol) are associated with increased in-hospital mortality and length of stay.(24) These effects are magnified as admission glucose increases above 11.1 mmol/l and HbA1c increase above 64 mmol/mol.(24) Hyperglycaemia on admission is also associated with early-neurological deterioration in those treated with IV thrombolytic agents (OR 1.17, 95%CI 1.07-1.28 per 1mmol/L increase).(25)

More recent data has focused on identifying those with impaired fasting glucose, rather than hyperglycaemia alone. This identifies that those with impaired fasting glucose are at higher risk of poorer functional outcomes than those with normal fasting glucose, adjusted common OR 2.77 (95%CI 1.54-4.97).(26) Based on observational data, the initial licence for thrombolytic therapy in acute ischaemic stroke discouraged thrombolysis in those with diabetes and previous stroke. With time and experience, it

is now recognised that while this group are at risk of poor outcomes, the risk is greater still if no treatment is given.

At one time there was substantial anxiety about thrombolysis in people living with diabetes. We now recognise that while this group, particularly people with poor glycaemic control, are at higher risk of complications from thrombolytic therapy, they are also at higher risk of poor outcomes from stroke per se. Trial and registry data have consistently shown that overall, people living with diabetes benefit from intravenous thrombolysis given as per licence. Whether the same arguments apply to mechanical thrombectomy procedures or thrombolysis given based on advanced imaging parameters remains to be seen.

Feeding and fluids

There is a lack of high quality evidence to guide fluid replacement in stroke.(27) For all patients, current practice guidance advocates any regime that allows volume replacement while avoiding iatrogenic hypo or hyperglycaemia.(20) This is based on extrapolation of data from the Glucose Insulin in Stroke (GIST-UK) trial which observed a fall in plasma glucose levels in the 24-hours after stroke when IV saline was administered exclusively.(28)

Clinical guidelines have been co-produced by the Joint British Diabetes Societies for Inpatient Care with NHS Diabetes and the Primary Care Diabetes Society to help improve the inpatient management of people with stroke who have diabetes and require enteral feeding.(29) These recommend a target blood sugar of 6-12 mmol/L during enteral feeding; minimising use of IV insulin; establishing a subcutaneous insulin regime or administration of glucose-lowering agents via an NG tube; administering insulin at start of a bolus feed regime; monitoring capillary glucose 4-6 hourly when feed running and hourly if feed is unexpectedly stopped.(29)

Most hospitalised patients with stroke and diabetes will be older and more likely to be frail and at risk of polypharmacy. Where swallow is impaired, there is an increased risk of developing a hyperosmolar hyperglycaemic state (HHS). HHS is a serious, but uncommon complication of stroke in people living with diabetes. There is a lack of empirical data around HHS in acute stroke. Treatment is the same as in other cases of HHS and prevention is key with careful monitoring of fluid balance and electrolytes.

Pragmatic guidance

Clinicians working in stroke should be mindful of the importance of glycaemic state. Blood glucose should be checked in every suspected stroke to exclude neuroglycopenia. It would seem reasonable to also check HbA1C. Where stroke is complicated by hyperglycaemia, aggressive blood glucose should be avoided and intervention may only be needed where blood glucose is very high. For patients with diabetes who have

impaired swallow, establishing early nasogastric feeding and liaison with nutritional teams can prevent harmful fluctuations in glucose.

Primary and secondary prevention of stroke

General considerations

The presence of diabetes is a risk factor for all stroke syndromes, including intracerebral haemorrhage and transient ischaemic attack (TIA). The guidance on primary and secondary prevention generally applies to all types of stroke, unless specified. There are few large RCTs that specifically target diabetes in stroke survivors and so the evidence base is generally extrapolated from stroke subgroups of prevention studies.

Non-pharmacological approaches

Non-pharmacological approaches involving patient education have long been accepted as key components of diabetic care and guidelines,(30) and are likely to be just as important in stroke survivors. Educational approaches which included face-to-face methods, cognitive reframing and exercise content were the most likely to improve glycaemic control from meta-regression of 28 educational interventions.(31) For the many stroke survivors with type 2 diabetes and obesity, engagement in weight management interventions may improve glycaemic control and other vascular risk factors.(32, 33) Bariatric surgery is associated with reduced rates of myocardial infarction (HR 0.56 95%CI 0.34-0.93), but has not demonstrated specific benefits on stroke (HR 0.73 95%CI 0.41-1.30) based on data from Swedish intervention study data.(34) While dietary and exercise interventions are crucial, recommendations may need to be modified based on any physical and cognitive impairments resulting from the stroke.

Medical management of hyperglycaemia

In people with type 1 diabetes the administration of insulin therapy as a continuous subcutaneous infusion delivered *via* an insulin pump device is associated with more favourable HbA1c levels compared to multiple subcutaneous injections.(35) Observational data suggests that, over 6.8 years of follow-up, insulin pump treatment in people with type 1 diabetes is associated with lower risk of fatal cardiovascular disease (coronary heart disease or stroke) HR 0.58 95% CI 0.40-0.85, compared to multiple daily injections.(36)

Analysis of the overweight subgroup of participants included in the UK Prospective Diabetes Study treated with Metformin identified macrovascular benefits from therapy,(37) a finding which continues to influence prescribing practice. The lack of significant reduction in stroke events or stroke mortality would not provide evidence against such treatment and metformin continues to be a first line treatment for many people with type 2 diabetes.

Management algorithms for type 2 diabetes have been updated to reflect the newer agents which are now in routine clinical use.(30) The key antidiabetes drugs are summarised in Table 1. Pooled data from

published meta-analyses are included, summarising the effects of treatment using each agent on risk of stroke. It is noteworthy that many of these do not achieve statistical significance for stroke alone, but pooled primary outcomes or those for cardiovascular events often will.(38-42) One exception is in the meta-analyses of trials of pioglitazone which show statistical significance in stroke and recurrent stroke.(43, 44) These analyses included the PROactive trial (PROspective pioglitAzone Clinical Trial in macroVascular Events 04), which showed a significant reduction in recurrent stroke with pioglitazone treatment, but no treatment effect for first stroke.(45)

The Insulin Resistance Intervention after Stroke (IRIS) trial treated patients without a diagnosis of diabetes (but with evidence of insulin resistance) who had recently experienced a stroke or TIA with pioglitazone or placebo.(46) Pioglitazone treatment was associated with a lower risk of diabetes (HR 0.48 95%CI 0.33-0.69), but higher risk of weight gain >4.5kg (52.2% vs 33.7%, p<0.001) and fracture requiring surgery or hospital admission (5.1% vs 3.2%, p=0.003).(46) Over five years follow-up treatment with pioglitazone was associated with a reduced risk of any stroke (HR 0.75 95%CI 0.60-0.94), with statistically significant effects on reducing ischaemic stroke (HR 0.72 95%CI 0.57-0.91), but not haemorrhagic stroke (HR 1.00 95%CI 0.50-2.00).(47) The implications of IRIS for clinical practice are still debated. Pioglitazone for primary prevention has not entered clinical guidelines and is not routine in practice, as most consider the risk benefit ratio unfavourable. However, if the treatment could be targeted to those most at risk of stroke but at lesser risk of adverse effects then the intervention may achieve greater traction. This is not pure speculation, modelling studies based on IRIS data suggested a targeted approach may have net efficacy.(48, 49)

In addition, data are presented on key Cardiovascular Outcome Trial (CVOT) findings with respect to stroke, available for new agents evaluating drug safety in those at high vascular risk or with established cardiovascular disease. In SUSTAIN-6 semaglutide significantly reduced stroke as a secondary endpoint, and the clinical applicability of this finding is uncertain at this point in time.(50)

Network meta-analysis of new antidiabetic medications found no evidence of increased cardiovascular events.(51) One consideration is whether effects of treatment impact multiple other systems and that by reducing these risks, improvements in outcomes occur. For example, use of linked Scottish routine health data identified that treatment with dapagliflozin was associated with reduced HbA1c, systolic blood pressure (-4.32mmHg 95%CI -4.84 to -3.79) and body weight after three months of exposure.(52)

Management of other risk factors

The evidence with respect to risk factor management and direct effects on stroke risk has been more clearly established. Indeed in the patient with stroke and diabetes, attending to blood pressure and lipids may have greater effect on recurrence than treating glycaemia. Meta-regression analyses demonstrate that

for every 10mmHg reduction in systolic blood pressure, there is a reduced risk of stroke (RR 0.73 95%CI 0.68-0.77).(53) Absolute risk reduction in stroke events among people with type 2 diabetes for blood pressure reduction is 4.06 (95% CI 2.53-5.40).(54) Cholesterol lowering for adults with diabetes is effective in reducing vascular mortality (RR 0.87 95%CI 0.76-1.00) and stroke events (RR 0.79 95%CI 0.67-0.93).(55) Adults with diabetes should have atrial fibrillation managed as it would among those without a diagnosis of diabetes, as a further important component of reducing risk of stroke.(56) Supporting people living with diabetes to reduce their risk factors is vital – those with type 1 diabetes who met no risk factor targets had a HR 12.03 (95% CI 7.66-18.85) for stroke over 10.4 years, compared to an HR 1.17 (95 CI 1.15-2.88) for those achieving all targets.(57)

Pragmatic Guidance

Diabetes often accompanies other recognised cardiovascular risk factors such as hypertension and dyslipidaemia. In many cases, optimal management of the person living with stroke and diabetes looks similar to management of stroke per se, for example in ischaemic stroke antihypertensive and potent statin therapy would routinely be given. However, given the increased risk associated with diabetes in combination with other risk factors, the thresholds for initiating treatment may be lower and the therapeutic targets may be more stringent albeit this is not a formal recommendation in UK stroke guidelines.

Although stroke can occur at any age, it remains a disease predominantly seen in older adults. Guidelines based on evidence from middle aged populations with single diseases may not be applicable to frail, older adults with multimorbidity. This is particularly true in stroke, where frailty or pre-frailty is the norm.(58)

Table 1: Summary of antidiabetes drugs and stroke risk data

Drug class	Drug names	Stroke risk from meta-analyses of randomised controlled trial data	Stroke risk from statistically significant Cardiovascular Outcome Trials (CVOT)
Biguanides	Metformin	Meta-analysis of 13 trials Stroke RR 1.04 (0.73-1.48)(38)	CVOT data not available
Sulphonylureas	Glibenclamide Gliclazide Glimepiride Glipizide Tolbutamide	Meta-analysis of 23 trials Stroke OR 1.16 (0.81-1.66)(39)	CVOT data not available
DPP-4 inhibitors	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Meta-analysis of 19 trials Stroke OR 0.64 (0.34-1.21)(40)	All CVOT data neutral for major adverse cardiovascular events(59)
Thiazolidinediones	Pioglitazone	Meta-analysis of 4 trials Stroke RR 0.81 (0.68-0.96)(43) Meta-analysis of 3 trials Recurrent stroke HR 0.68 (0.50-0.92)(44)	CVOT data not available
SGLT-2 inhibitors	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Meta-analysis of 27 trials Stroke HR 0.84 (0.61-1.16)(41)	EMPA-REG OUTCOME fatal and nonfatal stroke HR 1.18 (0.89-1.56)(60) Sensitivity analysis including only cerebrovascular events on treatment or within 90 days HR 1.08 (0.81-1.45)(60) CANVAS Program nonfatal stroke HR 1.93 (1.46-2.56)(61) DECLARE-TIMI 58 Ischaemic stroke HR 1.01 (0.84-1.21)(62)
GLP-1 receptor agonists	Albiglutide Dulaglutide Exenatide	Meta-analysis of 77 trials Stroke RR 0.88 (0.76-1.02)(42)	Harmony Outcomes fatal and nonfatal stroke HR 0.86 (0.66-1.14)(63)

	Liraglutide Lixisenatide Semaglutide		LEADER fatal and nonfatal stroke HR 0.86 (0.71-1.06)(64) SUSTAIN-6 Nonfatal stroke HR 0.61 (0.38-0.99)(50)
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Glossary

95%CI – 95% confidence interval

CANVAS Program – Canagliflozin Cardiovascular Assessment Study

CI – contraindications

CVOT – cardiovascular outcome trials

DECLARE-TIMI 58 – Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58

DKA – diabetic ketoacidosis

DPP-4 inhibitors – Dipeptidylpeptidase-4 inhibitors

EMPA-REG OUTCOME – Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients

GLP-1 receptor agonists – Glucagon-like peptide-1 receptor agonists

HbA1c – plasma glycosylated haemoglobin

HR – hazard ratio

IV – intravenous

LEADER – Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results

OR – odds ratio

RCT – randomised controlled trial

RR – risk ratio

SGLT-2 inhibitors – Sodium-glucose co-transporter 2 inhibitors

SUSTAIN-6 – Semaglutide in Subjects with Type 2 Diabetes

TIA – transient ischaemic attack

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