

# The Treatment of Diabetes after an Acute Ischaemic Stroke

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## Abstract

People with diabetes are at increased risk of ischaemic stroke and outcome after stroke is worse. This paper reviews the treatment of patients with diabetes after ischaemic stroke. First, management of hyperglycaemia in the acute stage will be addressed. We will make the point that, despite the fact that admission hyperglycaemia is a common risk factor for poor outcome after ischaemic stroke, there is still much uncertainty about whether intensive glucose-lowering therapy after stroke benefits clinical outcome. Secondary prevention of further cardiovascular events after stroke is the other main topic of this review. We will show that there are important opportunities for the reduction of stroke risk in diabetes, through a rigorous evaluation and treatment of associated risk factors.

## Keywords

Diabetes, ischaemic stroke, prevention, treatment, outcome

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Diabetes and ischaemic stroke are common conditions that often co-occur. The relationship between diabetes and stroke is bidirectional. On the one hand, people with diabetes have a more than two-fold increased risk of ischaemic stroke compared to people without diabetes.<sup>1</sup> On the other hand, acute stroke can give rise to abnormalities in glucose metabolism, which in turn may affect outcome.<sup>2</sup> In the current review, which is based on a recent paper from our group in the *Lancet Neurology*,<sup>3</sup> we describe the management of diabetes both in the acute stage of stroke and in the longer term, with regard to secondary prevention.

## Diabetes and the Risk of Stroke

A recent meta-analysis of prospective studies including 530,083 participants reported a hazard ratio for ischaemic stroke of 2.3 (95 % confidence interval [CI] 2.0–2.7) in people with versus people without diabetes.<sup>1</sup> Considering that the estimated world-wide prevalence of diabetes in adults is around 10 %, this implies that one in eight to nine cases of stroke is attributable to diabetes.

Diabetes is associated with different aetiological subtypes of ischaemic stroke, including lacunar and athero- and cardioembolic strokes.<sup>4–6</sup> Moreover, the risk of atrial fibrillation, the major cause of thromboembolic stroke, is increased by 40 % in diabetes.<sup>7</sup> Diabetes-associated risk factors for stroke include diabetes-specific factors (e.g. hyperglycaemia) and vascular risk factors (e.g. hypertension, dyslipidaemia), but also genetic, demographic, and lifestyle factors. The contribution of these factors, many of which are strongly interrelated, is likely to differ according to diabetes type and age.

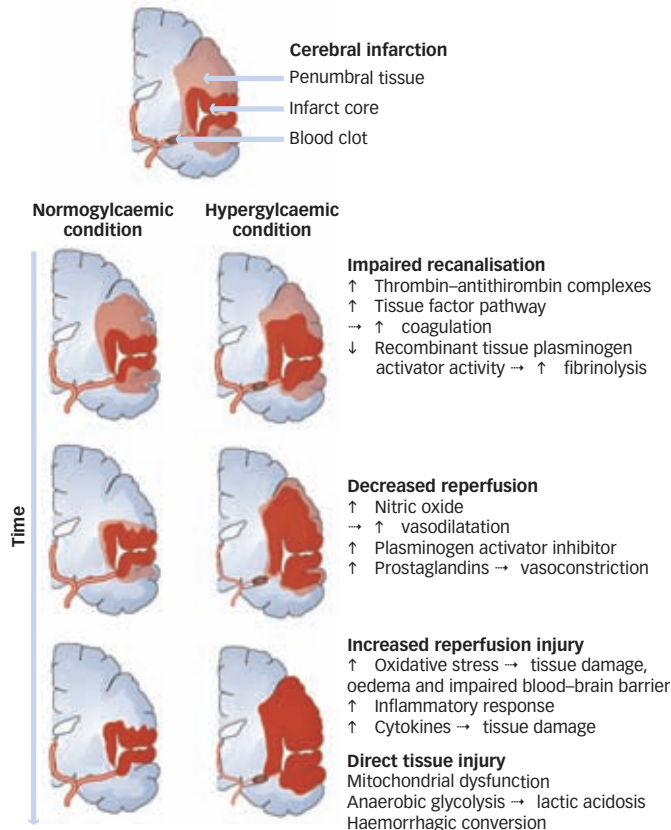
## Hyperglycaemia and Stroke Outcome

Hyperglycaemia occurs in 30–40 % of patients with an acute ischaemic stroke.<sup>2,8</sup> The majority of these patients does not have a known history of diabetes.<sup>2</sup> In a proportion of patients hyperglycaemia reflects pre-existing but unrecognised diabetes, but more often it is due to an acute stress response, commonly named ‘stress hyperglycaemia’. Stress hyperglycaemia is defined as a fasting glucose >6.9 mmol/l or a random glucose >11.1 mmol/l during hospital stay that spontaneously reverts to normal range after discharge.<sup>9</sup> Hence, glucose levels at admission generally do not distinguish between stress hyperglycaemia and diabetes. In this setting, elevated glycated haemoglobin (HbA<sub>1c</sub>) levels (≥6.5 %) can help to identify previously undiagnosed diabetes.<sup>9,10</sup>

Patients with ischaemic stroke who are hyperglycaemic at admission are at increased risk of poor outcome. Compared to normoglycaemic patients, patients with hyperglycaemia and a known history of diabetes have an elevated relative risk of in-hospital or 30-day mortality (unadjusted relative risk 2.0 [95 % CI 0.04–90.1]).<sup>2</sup> In those without a history of diabetes this risk is 3.3 (95 % CI 2.3–4.7).<sup>2</sup> The association between hyperglycaemia and poor outcome primarily involves patients with large-vessel infarction.<sup>11</sup> In small-vessel ‘lacunar’ stroke, moderate hyperglycaemia has even been associated with improved outcome.<sup>8</sup>

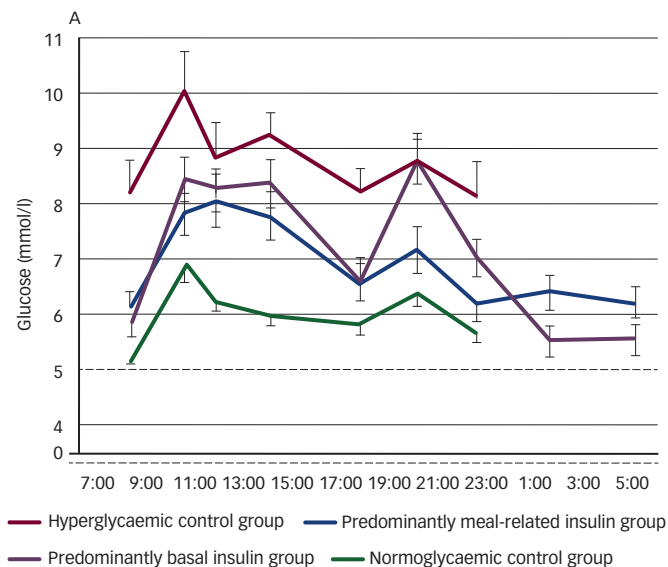
There is still uncertainty whether the association between hyperglycaemia and poor stroke outcome reflects a causal relation. The acute stress response of the body after stroke is a key factor in the development of post-stroke hyperglycaemia and as such it could be argued that hyperglycaemia is just an epiphenomenon, indirectly reflecting stroke severity and the condition of the patient.

**Figure 1: Hyperglycaemia and Infarct Evolution**



Schematic representation of infarct evolution over time. Hyperglycaemia can have deleterious effects on various physiological processes associated with infarct evolution in patients with acute ischaemic stroke. Source: Reproduced with permission from Nature publishing group, Kruyt et al., 2010.<sup>11</sup>

**Figure 2: Glucose-lowering Therapy After Ischaemic Stroke**



Data are from a randomised controlled trial on insulin treatment of post-stroke hyperglycaemia. Note the fluctuations in glucose levels over the day in the insulin treated groups. Source: Reproduced with permission from Vriesendorp et al., 2009.<sup>18</sup>

Nevertheless, the link between hyperglycaemia and poor outcome appears to be largely independent of other (confounding) factors.<sup>2</sup> Moreover, experimental and clinical studies have identified several mechanisms through which hyperglycaemia could aggravate cerebral damage in ischaemic stroke, including impaired recanalisation and

reperfusion injury. Figure 1 summarises these mechanisms. For a more detailed discussion, please see Kruyt et al., 2010.<sup>11</sup>

## Management of Diabetes and Hyperglycaemia in Acute Ischaemic Stroke

Plasma glucose levels should be measured on admission in all patients suspected of acute ischaemic stroke, regardless of history of diabetes, because glucose levels can direct diagnosis and treatment. There is no reason to exclude patients with a known history of diabetes from receiving thrombolytic therapy. The odds of improvement after thrombolysis are similar in people with or without a history of diabetes (odds ratio [OR] 1.5, 95 % CI 1.3–1.6; OR 1.53, 95 % CI 1.4–1.6), respectively).<sup>12</sup> It is less clear if thrombolysis is safe and effective in people with severe hyperglycaemia at admission. Trials on intravenous thrombolysis have excluded patients with glucose levels above 22.2 mmol/l. Observational data indicate that hyperglycaemia may affect the efficacy of thrombolysis. Transcranial Doppler imaging studies, for example, have demonstrated that hyperglycaemia is associated with persistent arterial occlusion after thrombolytic treatment. Others observed that the risk of haemorrhage after thrombolysis is increased for patients with admission glucose levels above 10 mmol/l.<sup>13</sup>

The observed relationship between hyperglycaemia and poor outcome in patients with ischaemic stroke raises the question whether outcome can be improved by glucose-lowering treatment. Experience in conditions other than stroke, in particular medical or surgical patients at an intensive care unit (ICU), or patients undergoing coronary artery bypass grafting, suggests that glucose-lowering treatment might indeed improve clinical outcome.<sup>14–16</sup> However, the positive results from these studies have been somewhat tempered by later studies that could not confirm the results. A recent systematic review concluded that there is no consistent evidence that intensive insulin therapy improves health outcomes in hospitalised patients, whereas it is clear that such treatment increases the risk of severe hypoglycaemia.<sup>17</sup>

Several studies specifically evaluated the feasibility and safety of glucose-lowering therapy in patients with acute stroke. Although glucose levels can be lowered through various insulin treatment regimens, it can be difficult to achieve stable normoglycaemia in the first few days after stroke onset, probably because oral food intake causes fluctuating glucose levels (see Figure 2).<sup>18</sup> A possible solution to this problem was reported in a study that used continuous tube feeding in combination with intravenous insulin administration.<sup>19</sup> There also remain important safety issues regarding glucose-lowering treatment, as even with intensive monitoring a substantial number of patients may experience one or more episodes of hypoglycaemia.<sup>11,18</sup> Introduction of continuous glucose monitoring devices and computer-guided treatment algorithms may help to improve the treatment protocols and enhance safety.

Current American Heart Association (AHA) and European Stroke Organisation (ESO) guidelines on ischaemic stroke management advise that glucose levels exceeding 11.1 and 10.0 mmol/l, respectively, should trigger insulin therapy (see Box 1).<sup>20,21</sup> It should be noted, however, that there is as yet no definite evidence that glucose-lowering therapy improves clinical outcome in patients with acute ischaemic stroke. Randomised controlled trials specifically targeting patient with stroke have failed to show beneficial effects. A meta-analysis including 1,296

patients with acute stroke from seven trials observed no benefit of intensive insulin therapy over regular care on outcome (OR 1.0, 95 % CI 0.8–1.3). The risk of symptomatic hypoglycaemia was significantly higher in the intensively treated group insulin (OR 25.9, 95 % CI 9.2–72.7).<sup>22</sup> Importantly, the results of this systematic review were mainly determined by the 926 participants of, the Glucose Insulin in Stroke (GIST-UK) trial.<sup>23</sup> Although this was a landmark trial in this field, it did have some limitations. Patients were treated for only 24 hours, during which mean plasma glucose levels were only 0.57 mmol/l lower in the intensively treated than the saline treated group. Currently, a new large randomised controlled trial is being initiated that will randomise 1,400 patients to standard care (aiming at glucose levels <10 mmol/l) or intravenous insulin treatment (aiming at glucose levels between 4.4 to 7.2 mmol/l) for 72 hours after stroke (Johnston et al., SHINE, NCT01369069). The study will use an insulin infusion protocol that has been proven safe and feasible in a pilot study.<sup>24</sup>

## Secondary Prevention

Several risk factors for stroke in patients with diabetes are potentially modifiable, in particular life style factors, glucose levels, blood pressure and dyslipidaemia (see *Box 2*). These risk factors have been targeted in several large randomised controlled trials. Neurologists often distinguish between primary prevention (e.g. prevention of first stroke) and secondary prevention (e.g. prevention after transient ischaemic attack (TIA) or ischaemic stroke). Although this review is written from the perspective of secondary prevention, it should be acknowledged that the literature on prevention of cardiovascular events in people with diabetes does not always allow to make this distinction.

Lifestyle probably has the largest impact on the risk of stroke. Therefore, smoking, obesity, inactivity, excessive alcohol intake and unhealthy diets should be strongly discouraged in patients with diabetes, even more so after the occurrence of a TIA or stroke. Lifestyle modification in patients with diabetes is associated with a substantial decline in stroke incidence (hazard ratio [HR] 0.62, 95 % CI 0.39–0.98).<sup>25</sup> Moreover, modest weight loss (5–10 % of body weight) in patients with type 2 diabetes has been associated with a significant improvement of cardiovascular risk factors and glycaemic control.<sup>26,27</sup>

## Glucose-lowering Therapy

Three large long-term trials have compared the effects of intensive versus standard glycaemic control on cardiovascular outcomes in relatively high-risk participants with longstanding type 2 diabetes. Two of these trials showed no difference with intensive glycaemic control.<sup>28,29</sup> The Action to Control Cardiovascular Risk in Diabetes Study (ACCORD) study terminated its glycaemic control study after 3.7 years due to an increased mortality in the intensive treatment group (target HbA<sub>1c</sub> < 42 mmol/mol, 6 %).<sup>30</sup> Participants assigned to the intensive therapy group were subsequently switched to the standard control group (target HbA<sub>1c</sub> between 53 and 64 mmol/mol, 7–7.9 %) and followed for on average 1.2 years. Both before and after the transition the risk for non-fatal stroke was similar. Reasons for the higher mortality in the intensive therapy group remained unclear.<sup>31</sup> In a meta-analysis including 34,533 patients with type 2 diabetes no beneficial effects of tight glycaemic control versus standard glycaemic control could be demonstrated on stroke rates during a mean treatment period of five years (HR 0.96, 95 % CI 0.8–1.1).<sup>32</sup>

## Box 1: Management Of Hyperglycaemia In Ischaemic Stroke

- Treat hyperglycaemia (recommended cut off points: 10.0 mmol/l or 11.1 mmol/l),<sup>20,21</sup> consider that:
  - benefit on clinical outcome is not established; and
  - Phase II studies show that glucose regulation is feasible, but fluctuations in glucose levels and risk of hypoglycaemia are a concern.<sup>11,18</sup>
- Differentiate between stress hyperglycaemia and newly diagnosed diabetes.<sup>9</sup>

Source: Based on Luitse et al., 2012.<sup>3</sup>

## Box 2: Stroke Prevention In Diabetes

- Lower blood pressure below 130/80 mmHg. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are recommended as first line treatment.<sup>10,35</sup>
- Prescribe statins.<sup>10</sup>
- Discourage smoking, inactivity, excessive alcohol intake and obesity.
- Prescribe platelet aggregation inhibitors for secondary prevention in patients with sinus rhythm.<sup>38</sup>
- Apply the CHA<sub>2</sub>DS<sub>2</sub>-VASC score and prescribe warfarin in patients with clinically manifest vascular disease and with atrial fibrillation.<sup>10,41</sup>
- Perform carotid surgery in patients with symptomatic high grade carotid stenosis.<sup>46</sup>

Source: Based on Luitse et al., 2012.<sup>3</sup>

The Diabetes Control and Complications Trial (DCCT) showed that 1,422 patients with type 1 diabetes, who were treated with intensive control of glucose levels during six and a half years, had a reduced risk of cardiovascular events over a mean follow up of 17 years of 57 % (95 % CI 12–79 %) as compared to patients receiving conventional treatment.<sup>33</sup> However, strokes were rare, with only one event in the intensive treatment group and five in the conventional treatment group.<sup>33</sup>

Taken together, the results of available studies do not provide sufficient evidence that stroke prevention will be improved by intensive glucose-lowering therapy either in type 1 or in type 2 diabetes. Clinicians should balance the risk of (recurrent) hypoglycaemia against the advantages of a lower HbA<sub>1c</sub> level, taking into account patient's age, the duration of diabetes and patient's co-morbidities.

## Vascular Risk Factors

In patients with type 2 diabetes lowering of blood pressure has a large impact on the risk of future stroke. A recent meta-analysis of patients with type 2 diabetes or impaired glucose tolerance evaluated the results of 37,736 patients from 13 trials that aimed to compare control of blood pressure ≤135 mmHg with ≤140 mmHg.<sup>34</sup> More intensive control of blood pressure was associated with a 10 % reduction in all-cause mortality (OR 0.90, 95 % CI 0.83–0.98) and a 17 % reduction in strokes (OR 0.83, 95 % CI 0.73–0.95) as compared with standard treatment. This difference was mainly driven by the trials that aimed at a systolic pressure between 130

and 135 mmHg. Control of blood pressure below 130 mm Hg was associated with a greater reduction in stroke, but there was a 40 % increase in serious adverse events with no benefit for cardiac, renal and retinal outcomes.<sup>34</sup> Most guidelines recommend a blood pressure below 130/80 mmHg for patients with diabetes.<sup>10</sup> The choice of antihypertensive drugs is probably less important than the target levels. Currently, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are often recommended as the first line medication.<sup>10,35</sup>

The Heart Protection Study demonstrated in a *post hoc* analysis that a daily dose of 40 mg simvastatin administered to 5,963 patients with type 2 diabetes, of whom half did not have any evidence of arterial occlusive disease, was associated with a 28 % (95 % CI 8–44 %) reduction in ischaemic stroke, independent of the baseline lipid levels.<sup>36</sup> In 9,795 patients with type 2 diabetes, of whom 7,664 patients had no history of cardiovascular disease, micronised fenofibrate 200 mg once daily as compared with placebo reduced the risk of cardiovascular events (HR 0.89, 95 % CI 0.80–0.99), including ischaemic stroke (HR 0.91, 95 % CI 0.73–1.1).<sup>37</sup> Based on this evidence statins are recommended for secondary prevention in all patients with type 2 diabetes and in most patients also for primary prevention, depending on their 10-year cardiovascular risk.<sup>10</sup> There is no consensus about the choice of statins.

### Antithrombotic Treatment

No major trial has studied the effectiveness of antithrombotic medication for the secondary prevention of stroke specifically in a diabetic population. A meta-analysis that investigated the efficacy of antithrombotic agents in more than 5,000 patients with diabetes concluded that these drugs reduced both coronary events and ischaemic stroke to a similar degree as in patients without diabetes.<sup>38</sup> Hence, current policy for prescription of antithrombotic drugs for secondary prevention is similar in patients with or without diabetes. A meta-analysis on the use of aspirin for primary prevention in

patients with diabetes demonstrated no benefits with respect to the reduction of serious vascular events, including stroke.<sup>39</sup> Although the impact of antithrombotic treatment on the prevention of future cardiovascular events is relatively low as compared to rigorous control of risk factors, it should be considered in each patient with diabetes at risk for future vascular complications.

Diabetes is a risk factor for atrial fibrillation.<sup>40</sup> In addition, diabetes increases the risk of embolic complications in patients with atrial fibrillation as is reflected in the CHA<sub>2</sub>DS<sub>2</sub>-VASC score.<sup>41</sup> Therefore, patients with diabetes and atrial fibrillation should receive platelet aggregation inhibitors if they have none of the other risk factors included in the CHA<sub>2</sub>DS<sub>2</sub>-VASC<sup>41</sup> and anticoagulants in all other cases.<sup>42</sup> Recently, dabigatran, rivaroxaban and apixaban have been proven to protect patients with atrial fibrillation as good, or even better than warfarin, but the definite role of these new antithrombotic agents in patients with a recent TIA or minor ischaemic stroke remains to be established.<sup>43</sup>

### Carotid Surgery

Carotid endarterectomy for secondary stroke prevention in patients with high-grade stenosis of the carotid artery is effective, but has not been specifically investigated in diabetic patients. Both the peri-procedural and long-term risks are higher in patients with diabetes than in non-diabetic patients,<sup>44,45</sup> but this should not be a reason to withhold the surgery in this patient group.

### Conclusion

Diabetes is a key factor in the risk of ischaemic stroke and in stroke outcome. Evaluation of diabetes status and blood glucose levels is therefore an essential component of the diagnostic work-up after stroke. Optimal glucose management in the acute stage of stroke is still an area of uncertainty that warrants further investigations. Rigorous management of vascular risk factors can prevent strokes in people with diabetes. ■

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