

Prevalence of diabetes and its effects on stroke outcomes: A meta-analysis and literature review

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ABSTRACT

Aims/Introduction: Diabetes mellitus is an established risk factor for stroke and maybe associated with poorer outcomes after stroke. The aims of the present literature review were to determine: (i) the prevalence of diabetes in acute stroke patients through a meta-analysis; (ii) the association between diabetes and outcomes after ischemic and hemorrhagic stroke; and (iii) to review the value of glycosylated hemoglobin and admission glucose-based tests in predicting stroke outcomes.

Materials and Methods: Ovid MEDLINE and EMBASE searches were carried out to find studies relating to diabetes and inpatient stroke populations published between January 2004 and April 2017. A meta-analysis of the prevalence of diabetes from included studies was undertaken. A narrative review on the associations of diabetes and different diagnostic methods on stroke outcomes was carried out.

Results: A total of 66 eligible articles met inclusion criteria. A meta-analysis of 39 studies ($n = 359,783$) estimated the prevalence of diabetes to be 28% (95% confidence interval 26–31). The rate was higher in ischemic (33%, 95% confidence interval 28–38) compared with hemorrhagic stroke (26%, 95% confidence interval 19–33) inpatients. Most, but not all, studies found that acute hyperglycemia and diabetes were associated with poorer outcomes after ischemic or hemorrhagic strokes: including higher mortality, poorer neurological and functional outcomes, longer hospital stay, higher readmission rates, and stroke recurrence. Diagnostic methods for establishing diagnosis were heterogeneous between the reviewed studies.

Conclusions: Approximately one-third of all stroke patients have diabetes. Uniform methods to screen for diabetes after stroke are required to identify individuals with diabetes to design interventions aimed at reducing poor outcomes in this high-risk population.

INTRODUCTION

Diabetes mellitus is a highly prevalent and growing chronic disease affecting an estimated 415 million people globally in 2015, and is predicted to affect 642 million people by 2040¹. Given that diabetes is a well-recognized risk factor for neurovascular disease^{2–4}, it is postulated that a significant proportion of stroke inpatients will have comorbid diabetes mellitus. A large, international, multi-center case–control study across 32 countries ($n = 26,919$)

showed that diabetes, defined using a threshold of glycosylated hemoglobin (HbA1c) of $\geq 6.5\%$ (48 mmol/mol), was found in 26% of acute stroke inpatients compared with 22% of non-stroke controls. Those with diabetes had higher odds (odds ratio [OR] 1.33, 95% confidence interval [CI] 1.18–1.5) of ischemic stroke compared to those with hemorrhagic stroke (OR 0.72, 95% CI 0.6–0.87)³. Additionally, studies have estimated that approximately 20–33% of acute stroke inpatients may have diabetes^{3,5,6}. A problem in the literature remains the lack of consistency in the definition of the diagnosis of diabetes.

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A number of studies have shown an association between comorbid diabetes and increased mortality^{7,8}, length of hospital stay, readmission rates, and poorer functional and rehabilitation outcomes after stroke^{9–12}. In contrast, other studies have reported no significant differences in post-stroke outcomes between people with or without diabetes^{13,14}.

Table 1 | Relationship between diabetes status and neurological function and rehabilitation outcome in stroke inpatients

| Study | Sample size | Diabetes diagnosis | Patient population | Outcome measure | Poorer outcomes observed in patients with: | | |
|---|-------------|---|----------------------------|--|--|---------------------------|----------|
| | | | | | No diabetes | No significant difference | Diabetes |
| Tuttolomondo <i>et al.</i> ¹⁴ | 306 | Known diabetes treated by diet, oral hypoglycemic agents or insulin | AIS | mRS Scandinavian stroke scale | ✓ | ✓ | |
| Tanaka <i>et al.</i> ²⁶ | 242 | OGTT or HbA1c ≥6.5% or random BGL ≥11.1 mmol/L | AIS | mRS NIHSS (increased in ≥2 points in first 14 days) | | | ✓ ✓ |
| Roquer <i>et al.</i> ⁵⁵ | 1,088 | Previous diagnosis or HbA1c ≥6.5% | AIS | mRS | | | ✓ |
| Lei <i>et al.</i> ⁸ | 1,877 | History or FBG or random BGL | AIS | mRS | | ✓ | |
| Tang <i>et al.</i> ⁵⁶ | 419 | FBG or OGTT or HbA1c | AIS (Thrombolysis only) | NIHSS and mRS | | | ✓ |
| Wang <i>et al.</i> ³⁸ | 1,438 | FBG or 2-h post glucose | AHS | mRS | | ✓ | |
| Saxena <i>et al.</i> ⁵⁷ | 2,653 | Medical history | AHS | mRS | | | ✓ |
| Ripley <i>et al.</i> ¹³ | 367 | Medical history | Both | FIM | | ✓ | |
| Koennecke <i>et al.</i> ⁵⁰ | 16,518 | Random FBG level or a history of diabetes | Both | mRS | | | ✓ |
| Piernik-Yoder <i>et al.</i> ¹² | 35,243 | ICD-9 coding | Both | FIM FIM gain | | | ✓ ✓ |

Studies are ordered in priority of stroke type and year of study. AHS, acute hemorrhagic stroke; AIS, acute ischemic stroke; BGL, blood glucose level; FBG, fasting blood glucose; FIM, Functional Independence Measure; HbA1c, glycated hemoglobin; mRS, modified Rankin Score; NIHSS, National Institute of Health Stroke Scale; OGTT, oral glucose tolerance test.

Table 2 | Relationship between diabetes status and length of stay, readmission rates or stroke recurrence in stroke inpatients

| Study | Sample size | Diabetes diagnosis | Patient population | Outcome of interest | Poorer outcomes observed in: | | |
|---|-------------|--------------------|--------------------|---|------------------------------|---------------------------|----------|
| | | | | | No diabetes | No significant difference | Diabetes |
| Sun <i>et al.</i> ³⁹ | 9,766 | History or FBG | AIS AHS | Stroke recurrence (1 year) | | | ✓ |
| Tseng <i>et al.</i> ⁴² | 468 | ICD-9-CM coding | Both | Stroke recurrence (1 year) | | ✓ | |
| Li <i>et al.</i> ¹¹ | 1,194 | ICD-9-CM coding | AIS | Readmission (1 year) | | ✓ | |
| | | | | Readmission (1 month) | | ✓ | |
| | | | | Readmission (6 months) | | | ✓ |
| | | | | Readmission (1 year) | | | ✓ |
| Wu <i>et al.</i> ⁵⁸ | 2,186 | Medical history | AIS | Stroke recurrence (3 months and 1 year) | | ✓ | |
| Sun <i>et al.</i> ³⁹ | 9,766 | History or FBG | AIS AHS | Length of stay | | | ✓ |
| Delbari <i>et al.</i> ⁵⁴ | 953 | History or FBG | AIS | Length of stay | | ✓ | |
| Piernik-Yoder <i>et al.</i> ¹² | 35,243 | ICD-9 coding | Both | Length of stay | | | ✓ |
| Nakagawa <i>et al.</i> ⁴⁷ | 740 | Unspecified | AIS | Length of stay | | | ✓ |

Studies were arranged in order of stroke type and year of publication. AHS, acute hemorrhagic stroke; AIS, acute ischemic stroke; FBG, fasting blood glucose; ICD-9-CM, International Classification of Diseases Ninth Revision Clinical Modification.

Table 3 | Relationship between diabetes status and mortality in stroke inpatients

| Study | Sample size | Diabetes diagnosis | Patient population | Outcome of interest | Poorer outcomes observed in: | | |
|---------------------------------------|-------------|---|--------------------|--|------------------------------|---------------------------|----------|
| | | | | | No diabetes | No significant difference | Diabetes |
| Kamalesh <i>et al.</i> ⁴⁵ | 48,733 | Medical records | AIS | Mortality (60 days and 1 year post-discharge) | | ✓ | |
| Lei <i>et al.</i> ⁸ | 1,877 | Medication use or FBG ≥ 7.0 mmol/L or random blood glucose ≥ 11.0 mmol/L or self-reported | AIS | Mortality (3 months and 1 year post-discharge) | | | ✓ |
| Saxena <i>et al.</i> ⁵⁷ | 2,653 | Medical records | AHS | Death and major disability (mRS 3–6) | | | ✓ |
| Wang <i>et al.</i> ³⁸ | 1,438 | FBG or 2-h post glucose | AHS | Mortality (≥ 1 month) | ✓ | | |
| Sun <i>et al.</i> ³⁹ | 9,766 | ICD-9CM codes | Both | In-hospital mortality | ✓ | | |
| Koennecke <i>et al.</i> ⁵⁰ | 16,518 | FBG ≥ 7 mmol/L or a history of diabetes | Both | In-hospital mortality | ✓ | | |
| Eriksson <i>et al.</i> ⁷ | 12,375 | Medical records | Both | Median survival | | | ✓ |
| Braun <i>et al.</i> ⁵¹ | 537 | History or prescribed anti-diabetic treatment or blood glucose ≥ 11.1 mmol/L | Both | In-hospital mortality | ✓ | | |

Studies were arranged in order of stroke type and year of publication. AHS, acute hemorrhagic stroke; AIS, acute ischemic stroke.

Table 4 | Glycated hemoglobin as a continuous measure and its relationship to post-stroke outcomes

| Study | Sample size | Patient population | Outcome of interest | HbA1c association with outcome of interest |
|---|-------------|----------------------------|-----------------------------------|--|
| Wu <i>et al.</i> ⁵⁸ | 1,540 | AIS | Stroke recurrence (1 year) | Positive association |
| Lei <i>et al.</i> ⁸ | 1,877 | AIS | Mortality | Positive association |
| Hjalmarsson <i>et al.</i> ¹⁷ | 501 | AIS | Mortality (30 days and 12 months) | Positive association |
| Masrur <i>et al.</i> ⁷¹ | 58,265 | AIS (thrombolysis only) | Stroke severity (NIHSS ≥ 7) | Positive association |
| Xu <i>et al.</i> ⁵⁹ | 2,137 | General medical inpatients | Mortality | Positive association |
| | | | Cardiovascular mortality | U-shaped association |

Studies were arranged in order of stroke type and year of publication. AIS, acute ischemic stroke; NIHSS, National Institute of Health Stroke Scale.

The best measure of dysglycemia that predicts adverse stroke outcomes is unknown. Some researchers argue that it is the acute or 'stress' hyperglycemia; that is, peaks of blood glucose levels during an acute stroke admission, which confers poorer outcomes,^{15,16} whereas others propose that it is chronic dysglycemia that drives the pathological processes in stroke patients^{8,17}. The uncertainty in the literature offers an opportunity for further research to inform best clinical practice.

Compared with fasting blood glucose (FBG), testing of HbA1c has the advantage of providing an average measure of glycaemia over the past 120 days, thereby reducing the potential for misdiagnosis as a result of stress hyperglycemia¹⁸. Testing requires only one blood draw and does not require the patient to be fasted, and as such, has the potential to be utilized in the hospital setting for routine screening of diabetes mellitus¹⁹. A limitation of the use of HbA1c relates to conditions that affect red blood cell count and the survival time of red blood cells, such as anemia or other

hemoglobinopathies¹⁸. Previous studies have shown that HbA1c can predict the risk of incident stroke²⁰. With the increasing burden of diabetes, there might be a role for routine HbA1c testing in all people admitted with stroke²¹ in order to identify and improve glycemic management^{22,23}.

The aims of the present literature review were: (i) to estimate the prevalence of recognized and unrecognized diabetes in stroke populations from the included studies through a meta-analysis; (ii) to examine the associations of acute hyperglycemia and diabetes and outcomes after ischemic or hemorrhagic stroke; and (iii) to review the value of HbA1c compared with admission serum glucose-based tests in predicting stroke outcomes.

METHODS

Two reviewers carried out a literature search using both Ovid Medline and Ovid Embase databases to include articles published in English between 1 January 2004 and 1 April 2017. The

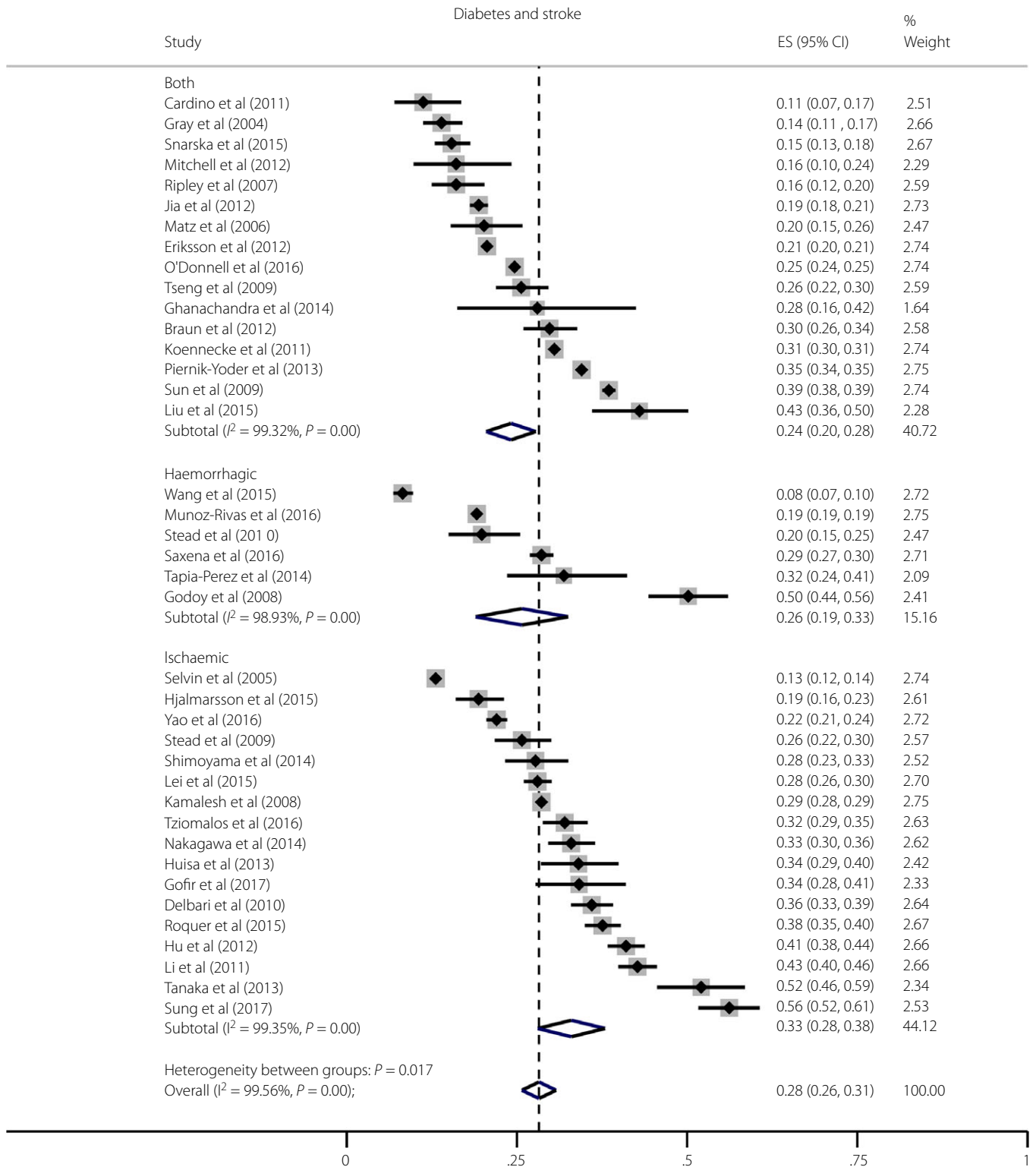


Figure 1 | Meta-analysis of the prevalence of diabetes in studies of ischemic and/or hemorrhagic stroke patients. A total of 39 studies in total were meta-analyzed: 17 studies included only ischemic stroke, six studies included only hemorrhagic stroke, and 16 studies included both ischemic and hemorrhagic stroke. Heterogeneity testing (I^2) was carried out. Only full articulated studies with a clear definition of diagnosis for diabetes based on either history or antidiabetic medications including insulin or biochemical diagnostic measures were included. Thrombolysis studies were excluded. CI, confidence interval; ES, effect size.

following medical subject headings (MeSH) were combined: 'stroke,' 'stroke, lacunar,' 'cerebral hemorrhage,' 'cerebral infarction,' 'cerebrovascular accident,' 'diabetes mellitus,' 'hyperglycemia,' 'stress, physiological,' 'length of stay,' 'readmission,' 'patient readmission,' 'hemoglobin A, glycosylated,' 'morbidity,' 'mortality' and 'prevalence' and their variants. Articles published in English that described the prevalence of diabetes mellitus or acute hyperglycemia in a stroke population and/or its effects on mortality, neurological recovery, rehabilitation outcomes, inpatient length of stay, readmission rates and stroke recurrence were included in the present review. Additional articles were obtained by manually reviewing the reference lists of included studies.

A meta-analysis of the prevalence of diabetes in stroke cohorts was carried out of 39 studies that included a clear definition of diagnosis for diabetes based on either patient history, use of antidiabetic medications or biochemical diagnostic methods. Thrombolysis studies were excluded in the meta-analysis of diabetes prevalence in stroke patients, as these studies would have selected for a subgroup of ischemic stroke patients receiving thrombolysis, but were included in the outcome analysis. Given that stress hyperglycemia might overestimate the prevalence of diabetes in studies using glucose-based criteria to diagnose diabetes, a further meta-analysis of diabetes prevalence was carried out on studies using HbA1c as diagnostic criteria for diabetes. Variables included in the analysis were the number

of participants, type of stroke and the prevalence of study participants with known diabetes. The meta-analysis was carried out in Stata 12.1 using the metaprop procedure (StataCorp, College Station, TX, USA; <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4373114>). No ethics approval was required for this literature review.

RESULTS

A total of 2,242 articles were identified during the literature search. After excluding duplicates and reviewing titles and abstracts to meet our inclusion criteria, a total of 66 articles containing data from 522,645 patients were included. Details regarding type and year of study, number of participants, study setting, diagnostic criteria for diabetes, type of stroke and outcomes measured are displayed in Tables 1–4.

Prevalence of diabetes

The present meta-analysis of 39 studies totaling 359,783 patients estimated that the prevalence of diabetes in all stroke inpatients was 28% (95% CI 26–31), with significant heterogeneity in the proportion of diabetes between the studies (Figure 1; $P = 0.017$). The prevalence of diabetes was higher in people with ischemic stroke (33%, 95% CI 28–38) compared with hemorrhagic stroke (26%, 95% CI 19–33) and in studies that included both stroke types (24%, 95% CI 20–28).

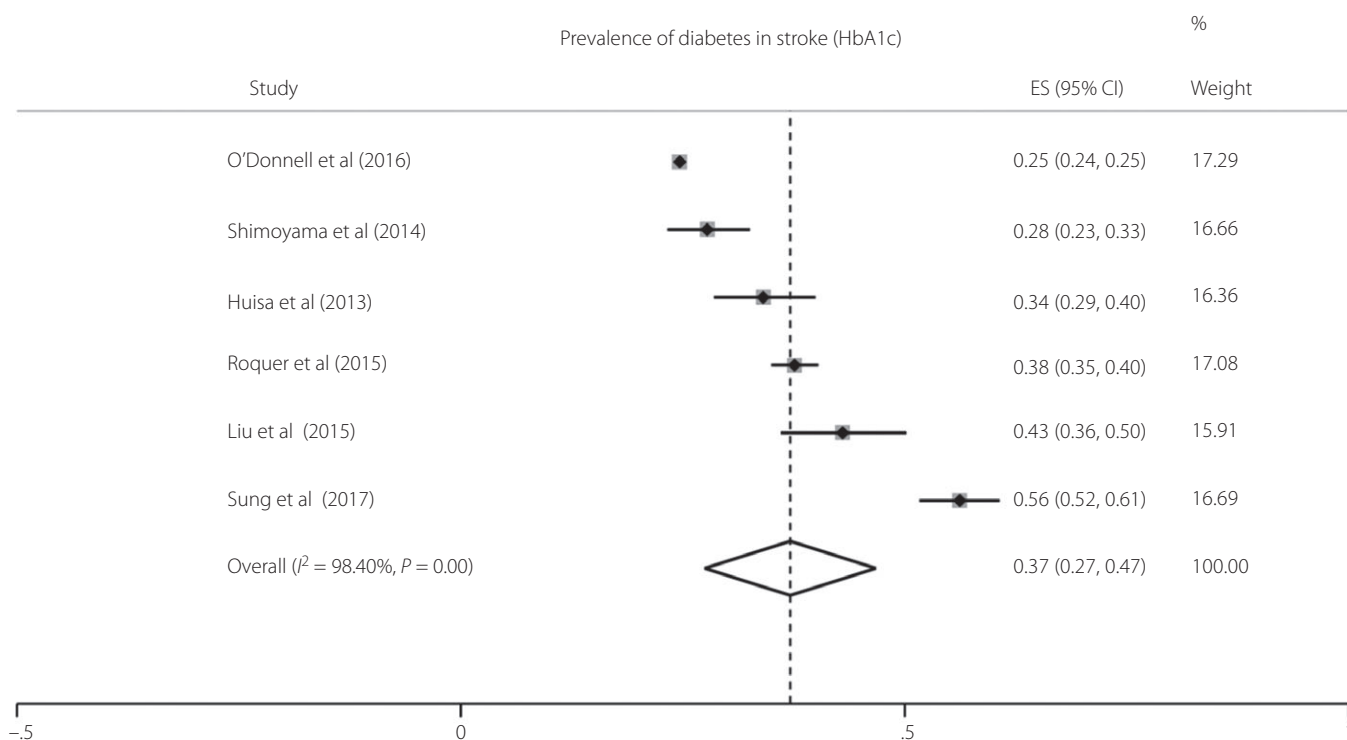


Figure 2 | Meta-analysis of the prevalence of diabetes in studies of ischemic and/or hemorrhagic stroke patients using glycated hemoglobin (HbA1c) alone as the diagnostic criteria for diabetes mellitus. A total of six studies were meta-analyzed: four studies included only ischemic stroke, and two studies included both ischemic and hemorrhagic stroke. Heterogeneity testing (I^2) was carried out. Thrombolysis studies were excluded. CI, confidence interval; ES, effect size.

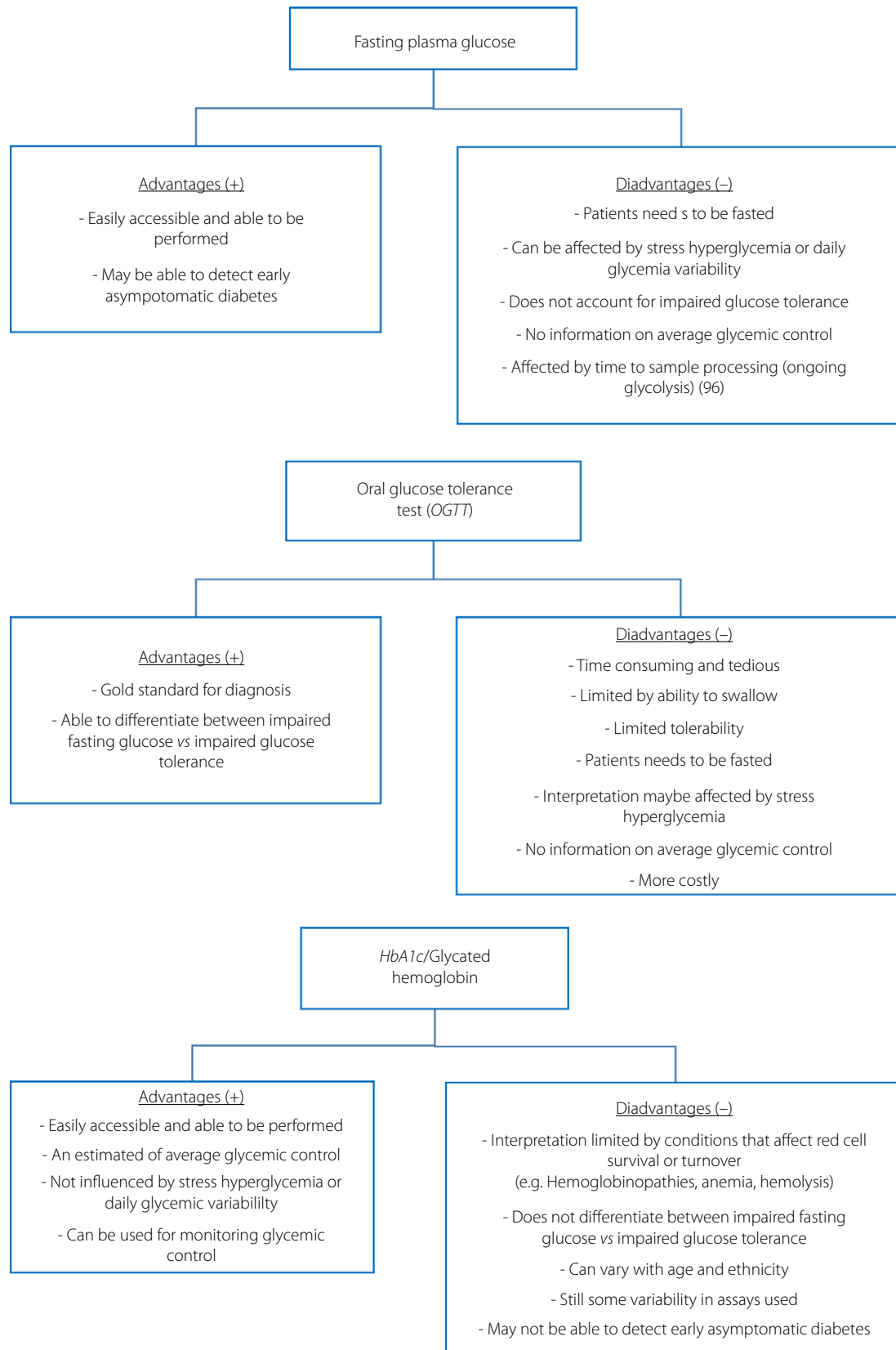


Figure 3 | This figure outlines the clinical advantages and disadvantages of glucose-based diagnostic methods vs glycated hemoglobin.

A meta-analysis of studies using HbA1c alone to diagnose diabetes estimated the prevalence of diabetes in all stroke types to be 37% (95% CI 27–47; Figure 2).

The general prevalence of known diabetes in the included studies ranged between 8.2 and 56.2%, and the prevalence of previously unrecognized diabetes mellitus ranged between 5 and 33% (Table S1)^{5,6,21,24–33}. After excluding studies that used glucose-based criteria to diagnose diabetes, the prevalence of known diabetes ranged between 16 and 56.2%, and undiagnosed diabetes between 5 and 30.9%. In studies using HbA1c and a history of diabetes as a diagnostic criteria, an estimated 24.7–56.2% of stroke patients had known diabetes.

There were five studies^{34–38} that included purely hemorrhagic stroke, with a prevalence of diabetes ranging between 8.2 and 50.2%.

Geographically, the mean prevalence of diabetes in stroke inpatients was highest in Southeast Asian (Singapore³⁹, India³², Indonesia⁴⁰) and East Asian countries (China^{8,29,38,41}, Japan^{16,26}, Taiwan^{11,42–44}), which were 33.5 and 32.3%, respectively, and mostly in Taiwan^{11,43,44}. The mean prevalence in studies from North America^{12,13,20,21,30,37,45–47} and Europe^{5,7,17,34–36,48–53} was 27.5 and 26.4%, respectively. Only one study in the Middle East estimated a prevalence of 36%⁵⁴. There have been no studies in Australasia examining the effect of acute hyperglycemia or diabetes on post-stroke outcomes in our defined search period.

Diabetes and outcomes after stroke

The relationship between diabetes and neurological outcome is summarized in Table 1. Six studies^{12,26,50,55–57} showed an association between diabetes and poorer neurological outcome, whereas four studies^{8,13,14,38} did not show a difference. Between these studies, the outcome measures used were the modified Rankin scale (mRS)^{8,14,26,38,50,55–57}, Functional Independence Measure^{12,13} and the Scandinavian stroke scale¹⁴. The diagnosis of diabetes differed between the studies, with some using medical history alone or medical coding^{12–14,57}, whereas others carried out either FBG^{8,38,50}, HbA1c⁵⁵ or both^{26,56}.

Most studies^{12,39,47} showed an association between diabetes and a longer in-hospital length of stay among stroke inpatients (Table 2)⁵⁴. In three studies^{11,39,58}, diabetes was associated with increased hospital readmission and stroke recurrence at 3 months⁵⁸, 6 months¹¹ and 1 year^{11,39} after index stroke in people who had ischemic stroke, but not hemorrhagic stroke (Table 2)^{39,42}. Two out of seven studies showed that diabetes was associated with increased mortality post-discharge⁸ and reduced median survival⁷ compared with people without diabetes (Table 3). In all studies that analyzed HbA1c as a continuous measure, increasing HbA1c was associated with worse stroke outcomes; increased stroke severity, mortality rates and stroke recurrence^{8,17,58,59} (Table 4).

Differences in diagnostic methods for diabetes

All studies utilized various methods of diagnosing diabetes: 32 used medical history or International Classification of Diseases

Ninth Revision coding alone, 15 studies carried out glucose-based methods (i.e., random or FBG, or the oral glucose tolerance test [OGTT]), 11 studies used HbA1c alone, and six studies combined HbA1c and glucose-based methods. Just two studies used all three methods. Given the variability in the use of different diagnostic criteria, Figure 3 outlines the clinical advantages and disadvantages of HbA1c compared with traditional glucose-based testing (i.e., FBG and OGTT).

DISCUSSION

By undertaking a meta-analysis, we showed that the combined mean prevalence of diabetes in ischemic and/or hemorrhagic stroke studies was 28%. The present review showed that the presence of acute hyperglycemia and diabetes was associated with poorer stroke outcomes. We also showed that significant heterogeneity exists in the diagnostic methods for diabetes within the current literature.

The present meta-analysis showed that the mean prevalence of diabetes was higher in stroke patients compared with the general inpatient population, which ranges between 20 and 33%^{60–63}, and higher in ischemic compared with hemorrhagic stroke patients. The higher prevalence of diabetes in ischemic compared with hemorrhagic stroke is consistent with the findings of a recent systematic review and meta-analysis of risk factors between ischemic and hemorrhagic stroke⁶⁴.

An important observation in the present review of the literature is the heterogeneity in the method of diagnosing diabetes. The phenomenon of stress hyperglycemia⁶⁵ is a significant confounder that might overestimate the prevalence of diabetes in studies using glucose-based testing (i.e., FBG or OGTT). Despite this, studies using HbA1c alone still estimated the prevalence of known and undiagnosed diabetes to range between 16–56.2% and 5–30.9%, respectively.

Stress hyperglycemia is a well-recognized phenomenon that occurs after any acute illness, and is usually detected during a hospital admission. It is defined as 'hyperglycemia resolving spontaneously after dissipation of an acute illness,' which can also occur in people with pre-existing diabetes⁶⁶. Three prospective observational studies^{33,67,68} showed that 50–70% of people with hyperglycemia on admission had a normal OGTT at 3 or 6 months post-stroke, suggesting that stress hyperglycemia might be transient in many acute stroke inpatients. Post-stroke hyperglycemia, defined as an elevated random or FBG, in people with and without diabetes, is common within hours of stroke^{49,65}, and has been independently associated with poorer outcomes after stroke, particularly in those without known diabetes. Identification and correct classification of post-stroke hyperglycemia are clearly required to better clarify the pathophysiological relationships between glycemic control and stroke. Although FBG remains a commonly measured glycemic parameter to diagnose pre-diabetes and diabetes⁶⁹, its accuracy in acute stroke might be affected by stress hyperglycemia^{49,67,68}. In a majority of the studies included in the present review, an admission random

glucose or a FBG was carried out and included in the analysis of the outcomes.

Stress hyperglycemia has been associated with poorer functional outcomes^{15,17,40,70} and mortality⁷¹, irrespective of diabetes status after an acute ischemic stroke. However, more studies have found that stress hyperglycemia has been associated with infarct volume growth, early neurological deterioration (increase of ≥ 4 points on National Institute of Health Stroke Scale)¹⁶, poorer functional outcome^{12,40,41,71,72}, higher mortality^{32,43,46,53,73} and longer hospital stay⁴⁰ in people without a history of diabetes, including patients who underwent thrombolysis^{71,74–76} and mechanical thrombectomy⁷⁷. This association remained even after adjusting for stroke severity and stroke subtype. The definition of diabetes in these studies was, however, heterogeneous.

In contrast, two prospective observational studies^{52,78} did not find a direct relationship between stress hyperglycemia and poorer stroke outcomes, but found that stress hyperglycemia was associated with more severe stroke and rather the severity of the stroke that led to poorer outcomes.

On a physiological and radiological level, stress hyperglycemia has been associated with a larger infarct volume on presentation^{32,79}, and might contribute to poorer stroke recovery through impairment of the fibrinolytic process^{80,81} and delayed reperfusion of the ischemic penumbra⁸². In animal studies, stress hyperglycemia appears to induce further cerebral damage by inducing a pro-inflammatory response⁸³, exacerbating brain edema surrounding intracranial hemorrhage⁸⁴, disrupting the blood–brain barrier⁷⁹ and increasing the risk of hemorrhagic transformation^{85,86}.

In acute hemorrhagic stroke, stress hyperglycemia has also been found to be associated with early mortality^{36,57,87} and worse functional outcome^{34,36,37,48,57}, irrespective of prior diabetes status³⁴ and after adjusting for stroke severity and subtype^{34,36,57,87}. In a study that included all stroke patients, Snarska *et al.* observed that hyperglycemia as a continuous variable on admission was associated with increased in-hospital mortality, with a higher BGL threshold in those with diabetes (≥ 12.2 mmol/L) compared with those without diabetes (≥ 6.3 mmol/L). This risk is likely to be an underestimate, given that diabetic status was recorded from medical records, therefore people with unrecognized diabetes were included in the 'non-diabetic' group⁴⁸. A separate study³⁴ also found that every increase in 1.0 mmol/L in admission plasma glucose > 5.0 mmol/L was associated with a 33% increased likelihood of 30-day mortality in people with hemorrhagic stroke, after adjusting for diabetic status.

Overall, these studies highlight the importance of detecting hyperglycemia post-stroke and recognizing the potential for poorer outcomes. However, the variability in the findings of stress hyperglycemia and stroke outcomes between people with and without diabetes raises the question of whether chronic dysglycemia (i.e., existing diabetes) carries some degree of neuroprotection in the setting of post-stroke stress hyperglycemia.

The mechanisms are not clearly understood and warrant further research.

Diabetes has been associated with an increased all-cause in-hospital mortality in general hospital inpatients, with a higher contribution from a cerebrovascular cause^{4,10,88–90}. Diabetes is associated with atherothrombotic strokes, whereas cardioembolic strokes are more common in patients without diabetes^{8,14,26,46}.

Although there is some conflicting evidence in studies of people with ischemic^{13,14,51} and hemorrhagic stroke³⁸, diabetes is typically associated with poorer functional outcome^{8,12,26,27,50,55}, especially in poorly controlled diabetes (HbA1c $> 7\%$)⁹¹. Diabetes has also been associated with worse neurological deterioration (decrease of National Institute of Health Stroke Scale points < 4 at 24 h, or < 8 at day 7), poorer recovery (mRS > 1 at 3 months) and increased risk of hemorrhagic development⁷² in people treated with thrombolysis for ischemic stroke⁵⁶. An explanation for this might be incomplete recanalization after thrombolysis, as suggested in one study⁹². Diabetes has been associated with a reduced amount of recovery after rehabilitation¹², higher risk of mortality in some^{7,8,71} but not all studies^{45,51,93} and a risk factor for recurrent ischemic stroke^{11,39,58}. The effect of diabetes on length of hospital stay has been inconsistent^{12,39,47,54}. The relationship between diabetes and poorer stroke outcomes still remained after adjusting for stroke severity and subtypes.

A larger study by Kamalesh *et al.*⁴⁵ who followed 48,733 people from Veteran Hospitals after an acute ischemic stroke found no significant difference in mortality between those with and without diabetes at 60 days and at 1 year. A major limitation of that study was the confounding effect of having a strong male bias (98% men), limiting its generalizability, as women with diabetes might have a higher risk of cardiovascular mortality compared with men^{94,95}. Furthermore, the diagnosis of diabetes was based solely on discharge reports.

Overall, diabetes has been associated with poorer clinical outcomes, except for mortality, after ischemic stroke, and there appears to be a relationship between increasing HbA1c and poorer clinical outcomes after stroke. The lack of a strong association between diabetes and increased mortality after stroke is an interesting point, and would warrant further larger, prospective studies using a combination of HbA1c as a measure of chronic glycemia and glucose-based testing to evaluate this association. The exact mechanism to explain the difference between the effects of acute vs chronic dysglycemia on poorer stroke outcomes remains unclear and could have implications in its management.

Only a few studies have examined a hemorrhagic-stroke-only population, raising the question of the importance of diabetes and its management in hemorrhagic strokes.

In the limited number of small retrospective studies that recruited only people with hemorrhagic stroke, acute hyperglycemia^{36,57,87} and a history of diabetes^{48,57} were both independent predictors of poor outcomes at 14 days (National Institute

of Health Stroke Scale >15)³⁶ and 3 months (mRS 3–6)⁵⁷, and increased mortality^{36,57,87} in people with intracerebral hemorrhage. This might be explained by larger initial intracerebral hematomas in people who present with acute hyperglycemia⁵⁷.

In a study of 237 people who presented to the emergency department with hemorrhagic stroke³⁷, admission hyperglycemia (random plasma glucose >7.8 mmol/L) predicted early mortality (death within 7 days) and poor functional outcome at discharge (mRS \geq 3) only in the non-diabetic subgroup, again suggesting a difference in pathophysiological effects of acute and chronic hyperglycemia.

Other studies also did not find an association between diabetes and increased in-hospital mortality^{35,38} or hospital length of stay³⁹ in hemorrhagic stroke patients after adjusting for common cardiovascular risk factors including age, hypertension, atrial fibrillation and other comorbidities.

In the present review, the evidence between diabetes and stroke outcomes in hemorrhagic stroke was heterogeneous. The fact that acute hyperglycemia was more strongly associated with poorer stroke outcomes compared with existing diabetes probably reflects the higher severity of stroke in patients with hyperglycemia rather than the effects chronic dysglycemia.

The studies in the present review varied in both the method and timing of diagnosing diabetes. Studies using the OGTT might underestimate the prevalence of diabetes due to the inability to complete the test, but might also overestimate the prevalence of diabetes as a result of stress hyperglycemia.

Two studies that used a combination of FBG, OGTT or HbA1c estimated the prevalence of undiagnosed diabetes in stroke inpatients to be between 27 and 32.7%^{28,31}. Despite heterogeneous study methods, the consistently high proportion of people with undiagnosed diabetes suggests an urgent need for wider diabetes screening of people in the acute stroke setting.

Studies that compared three glycemic measures – FBG vs random admission glucose vs HbA1c – consistently found that elevated FBG (\geq 7 mmol/L)⁹⁶, random admission glucose or blood glucose 2-h post OGTT (\geq 11.1 mmol/L)^{44,53,96} were independent predictors of poor neurological outcome^{44,96}, higher rates of mortality^{53,96} and stroke recurrence⁹⁶ post-stroke compared with a single HbA1c \geq 6.5%. Receiver operating characteristic analysis⁴⁴ showed a different threshold of FBG in individuals with diabetes (FBG >7.8 mmol/L) compared with individuals without diabetes (FBG >6.05 mmol/L). In one study⁹⁶, an elevated random glucose \geq 11.1 mmol/L was a poor prognostic marker in non-diabetics or individuals with diabetes with good control (HbA1c <6.5%). Nevertheless, an elevated HbA1c has been shown to be associated with poorer stroke outcomes^{8,17,91} and stroke recurrence⁵⁸, even after accounting for mean plasma glucose and stroke severity. HbA1c >6.5% has also been found to be a predictor of symptomatic intracerebral hemorrhage after thrombolysis for ischemic stroke⁷².

Interestingly, a Chinese study carried out by Xu *et al.*⁵⁹ that followed 2,137 people with diabetes aged >65 for 10 years

showed a U-shaped relationship between HbA1c and stroke mortality, with a HbA1c inflection point of 6.5%. The significance and reason for this finding are uncertain.

Given these studies show the utility of both traditional glucose-based criteria and HbA1c in both the diagnosis of diabetes and predictors of stroke outcome, there might be a role in the combined use of these diagnostic tools as a screen for diabetes and a predictor for stroke outcomes. More prospective studies incorporating all three glycemic measures would be useful in confirming its utility.

The present review incorporated a large number of studies over the past 10 years, giving a current overview and understanding of the association between diabetes and stroke outcomes. It is important to note that clinical factors, such as age, sex, body mass index, antihyperglycemic medication and the presence of diabetes complications, could confound the effects of diabetes and stroke outcomes, and might not have been accounted for in some of the studies given their retrospective nature. Hypoglycemia is associated with increased morbidity and mortality^{97,98}; however, only one study³⁴ recorded hypoglycemia as a covariable to assess its effects on morbidity or mortality in stroke patients.

As the burden of diabetes rises, stroke as a major complication of diabetes is expected to rise. More efficient and accurate ways of screening for diabetes are required to minimize the progressive burden this will have on the global healthcare system. Whether tight control of diabetes or acute hyperglycemia after stroke is beneficial is not within the scope of the present review and remains an important question.

Currently, the literature examining the relationship between diabetes and stroke outcomes has been inconsistent and variable, raising the need for larger prospective studies, with consistent definitions of diabetes and stroke outcome measures. The use of HbA1c as a diagnostic tool for diabetes, and implementation of new recommendations for functional outcome measurement in stroke research⁹⁹ would provide consistency in future studies to develop clinically robust evidence to guide management.

In conclusion, diabetes is a highly prevalent comorbidity in acute stroke patients, and is associated with poorer stroke outcomes compared with people without diabetes. Acute hyperglycemia is strongly associated with poorer stroke outcomes in people with or without diabetes. Until now, there is significant heterogeneity in the diagnostic methods of diabetes in studies examining the association between diabetes and post-stroke outcomes. A combination of HbA1c with glucose-based testing might serve as a solution to this.

DISCLOSURE

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Prevalence of previously unrecognized diabetes, known diabetes and pre-diabetes in stroke inpatients.