

Original Paper

Prevalence, Predictors and Prognosis of Post-Stroke Hyperglycaemia in Acute Stroke Trials: Individual Patient Data Pooled Analysis from the Virtual International Stroke Trials Archive (VISTA)

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Key Words

Acute stroke management · Glucose · Hyperglycaemia · Stroke outcome

Abstract

Background: Post-stroke hyperglycaemia (PSH) is associated with higher mortality and dependence, but further data on predictors of PSH and its evolution over time are required. We examined the prevalence, predictors, and prognosis of acute PSH using data from well-characterised clinical trials in the VISTA database. **Methods:** Data were extracted for individual participants enrolled <24 h after stroke with ≥ 1 blood glucose readings documented. PSH was defined as glucose >7.0 mmol/l. Outcome measures were: (1) prevalence of PSH; (2) predictors of PSH by binary logistic regression; (3) mortality, and (4) favourable functional outcome [modified Rankin Scale (mRS) score <2] at day 90. **Results:** For 2,649 subjects treated at a median 5.5 h after admission, PSH was present in 1,126 (42.6%, 95% CI 40.7–44.5) on admission and within the first 48 h in 1,421 (53.7%, 95% CI 51.8–55.6). PSH developed between 24 and 48 h in 19.4% (95% CI

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17.5–21.4) of initially normoglycaemic subjects. Admission and 48-hour PSH were predicted predominantly by a history of diabetes (for admission PSH: OR 7.40, 95% CI 5.60–9.79) and less clearly by stroke severity. Favourable outcome (mRS <2) at day 90 was less likely with PSH within the first 48 h, advanced age, and higher NIHSS score, and more likely with recombinant tissue plasminogen activator treatment. **Conclusions:** Over 40% of ischaemic stroke patients are hyperglycaemic on admission, and 20% of those who are initially normoglycaemic develop hyperglycaemia within 48 h. Diabetes is the strongest predictor of acute hyperglycaemia. Hyperglycaemia within the first 48 h is independently associated with higher mortality and poorer functional outcome, with an absolute increase of 12.9%.

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Introduction

Post-stroke hyperglycaemia (PSH) is recognised as a predictor of poor outcome, and intervention to lower glucose is widely recommended by clinical guidelines. However, there is a paucity of evidence on key issues concerning hyperglycaemia, and recent results of clinical trials raise concerns about the safety of insulin therapy.

In a meta-analysis of observational studies, hyperglycaemia was associated with increased relative risks of both death and of death or dependence in non-diabetic patients after stroke [1], but the studies included in this meta-analysis were predominantly retrospective and heterogeneous, with no consistent definitions of the glucose level that defined hyperglycaemia or timing of blood sampling. Individual studies reached divergent conclusions on outcome [2]. More recent analyses from more homogeneous clinical populations (either in randomised, controlled trials of intravenous thrombolysis or of populations receiving intravenous thrombolysis as routine therapy) confirm an independent adverse prognostic association of early hyperglycaemia, potentially related to an increased risk of symptomatic intracranial haemorrhage [3, 4], attenuation of the benefit of alteplase on infarct growth [5] or recanalisation [4, 6].

The estimated prevalence of hyperglycaemia has varied widely among studies (8–63% [1, 7, 8]), probably as a result of several factors, including varying thresholds for defining hyperglycaemia in different studies, different sampling methods, and different times of blood sampling. The temporal profile of blood or tissue glucose after stroke is complex [4, 9]. Solitary glucose measurements underestimate the incidence of hyperglycaemia, and admission glucose alone does not predict early infarct expansion on brain imaging, or poor 3-month outcome, whereas more frequent, or continuous, measurements of glucose do [9], and glucose levels over the first 48 h after stroke appear to be the most significant predictor of outcome [6].

However, only a minority of patients remain normoglycaemic throughout the first 24 h after stroke (15% in the ECASS-2 cohort), and only a minority of those with sustained hyperglycaemia exhibit hyperglycaemia on admission [4]. Identification of and appropriate selection of patients for glucose-lowering interventions are therefore unclear. Several possible predictors of hyperglycaemia have been proposed by different studies. These often include stroke severity [10–12] (some authors postulating that the association with poor outcome is an artefact, dependent primarily on stroke severity), but also prior dysglycaemia [13, 14]. An association of hyperglycaemia with catecholamine concentrations has been lacking [15], and suggestions of a specific neuroanatomical trigger have not been supported, at least for hyperglycaemia present within the first 3–6 h after stroke onset [16–20].

In addition, insulin treatment in patients with modest hyperglycaemia (median 7.6 mmol/l) starting on average 13 h after stroke in GIST-UK was not beneficial [21], and other trials in stroke [22] and medical intensive care patients [23] highlight potential dangers of aggressive glucose lowering.

More robust additional data on PSH are therefore required, particularly regarding predictors of hyperglycaemia and whether factors such as increasing [24] or sustained [6] elevation of blood glucose are more important markers of risk than a solitary measurement. We sought to establish the prevalence of hyperglycaemia in acute stroke trial populations and to explore the predictors and prognostic value of hyperglycaemia at different times after stroke onset by interrogating individual patient data from VISTA [25].

Methods

Individual patient data were obtained from VISTA [25], which includes individual patient data from placebo groups (and some active treatment groups) of stroke trials. Data are anonymised with respect to individual trial identifiers. Trials which met the following criteria were sought: (1) trials of acute intervention initiated within 24 h of stroke onset, and (2) protocol-defined recording of blood glucose at least on admission.

Anonymised data included age, sex, medical history, blood glucose concentration on admission (and at any other available time point during the initial 72 h of a trial), National Institutes of Health Stroke Scale (NIHSS) score on admission, day-90 modified Rankin Scale (mRS) score and mortality. Onset to randomisation or treatment time was assumed to be a reasonable surrogate for the time of initial blood glucose concentration (designated admission blood glucose) since hypo- or hyperglycaemia was generally an exclusion criterion for trials, and blood results before randomisation therefore would have to be available.

Hyperglycaemia was defined as blood glucose >7 mmol/l (126 mg/dl). The influence of hyperglycaemia on outcome was evaluated both for admission hyperglycaemia and for hyperglycaemia documented at any time within 48 h of trial inclusion. In the population for whom ≥ 2 blood glucose measurements were available, increase in blood glucose from admission was also explored as a predictive factor. Additionally, different thresholds of blood glucose to define hyperglycaemia were tested in exploratory analyses.

Descriptive data were prepared for all subjects for whom admission blood glucose concentration was available. Predictors of hyperglycaemia on admission or at any time within the first 48 h of trial inclusion were identified by a forward stepwise binary logistic regression model. Predictors of death at day 90 and favourable outcome at day 90 (defined as mRS 0–1) were looked for using the same method. This search was conducted for the entire population with ≥ 1 blood glucose readings available and was repeated for the subgroup for whom >1 blood glucose reading was available within the first 72 h after randomisation in order to explore the effect of increase in blood glucose on outcome. Baseline demographic and prognostic indices were compared by *t* tests for normally distributed data, Mann-Whitney *U* tests for non-normally distributed data, and χ^2 tests for discrete categorical variables.

Results

Data were available for 2,898 subjects in trials fulfilling the criteria. Valid admission blood glucose was available for 2,649 subjects, who comprised the study population. Trial time windows ranged from 4.5 to 24 h. Median time from disease onset to treatment was 5.5 h. No information was available on treatment with insulin or oral hypoglycaemic agents during the trials, or on the policies of participating units regarding hyperglycaemia management. Haemoglobin A_{1c} was not documented in any trial.

Table 1. Baseline characteristics of the study population

	Normoglycaemia (≤7.0 mmol/l)	Hyperglycaemia (>7.0 mmol/l)	All	p
Subjects, n	1,522	1,127	2,649	
Age, years	66.9 ± 13.0	69.4 ± 10.5	68.0 ± 12.1	<0.001
Sex				
Male	868 (57.0%)	602 (53.4%)	1,470 (55.5%)	0.069
Female	654 (43.0%)	525 (46.6%)	1,179 (44.5%)	
Onset-to-treatment time, h	5.6 (4.1–9.8)	5.3 (4.0–7.8)	5.5 (4.0–8.8)	0.007
Onset-to-treatment interval				
0–3 h	142 (9.4%)	109 (9.8%)	251 (9.6%)	0.004
3–6 h	907 (60.2%)	732 (65.8%)	1,639 (62.6%)	
6–12 h	294 (19.5%)	189 (17.0%)	483 (18.4%)	
12–24 h	164 (10.9%)	83 (7.5%)	247 (9.4%)	
rtPA treatment	648/1,522 (42.6%)	454/1,127 (40.3%)	1,102/2,649 (41.6%)	0.248
Admission NIHSS score	13 (8–18)	15 (10–20)	14 (9–19)	<0.001
Glucose, mmol/l				
Admission	5.82 ± 0.77	10.14 ± 3.48		<0.001
Highest documented level (24–48 h)	6.59 ± 2.01	9.13 ± 3.69		<0.001
Change from admission	+0.78 ± 2.06	–0.92 ± 3.50		<0.001
Medical history				
Transient ischaemic attack	131/1,315 (10.0%)	99/1,037 (9.5%)	230/2,352 (9.8%)	0.780
Previous stroke	122/698 (17.5%)	100/524 (19.1%)	222/1,222 (18.2%)	0.500
Myocardial infarction	98/1,315 (7.5%)	102/1,037 (9.8%)	200/2,352 (8.5%)	0.044
Hypertension	670/1,315 (51.0%)	616/1,037 (59.4%)	1,286/2,352 (54.7%)	<0.001
Atrial fibrillation	158/936 (16.9%)	127/740 (17.2%)	285/1,676 (17.0%)	0.896
Smokers				
Never	887 (58.4%)	711 (63.1%)	1,598 (60.4%)	0.005
Current	305 (20.1%)	172 (15.3%)	477 (18.0%)	
Ex- or passive	327 (21.5%)	243 (21.6%)	570 (21.6%)	
Diabetes	71/1,519 (4.7%)	300/1,126 (26.6%)	371/2,645 (14.0%)	<0.001

Values are means ± SD or medians with interquartile ranges in parentheses, unless otherwise indicated.

Baseline characteristics of the population as a whole, and divided according to presence or absence of hyperglycaemia >7 mmol/l on admission, are presented in table 1. Data on prior diagnosis of diabetes mellitus were available for 2,645 subjects.

Prevalence

Admission hyperglycaemia was present in 1,126 of 2,645 subjects (42.6%, 95% CI 40.7–44.5) and hyperglycaemia at some point within the first 48 h in 1,421 of 2,645 subjects (53.7%, 95% CI 51.8–55.6). Hyperglycaemia was present on admission in 36.3% of non-diabetics and 80.9% of diabetics, and was documented within 48 h of admission in 48.1% of non-diabetics and 88.1% of diabetics.

Hyperglycaemia was documented between 24 and 48 h after study enrolment in 296 of 1,522 subjects (19.4%, 95% CI 17.5–21.4) who were normoglycaemic on admission. An increase in blood glucose between admission and 48 h was documented in 908 of 1,913 subjects (47.5%, 95% CI 45.2–49.7) for whom data were available, 647 of 1,068 subjects who were initially normoglycaemic (60.6%) and 261 of 845 subjects (30.9%) who were initially hyperglycaemic ($p < 0.001$). An increase in blood glucose from admission was documented in a higher proportion of patients with less severe strokes (53.9% in the lowest vs. 44.7% in the highest quartile of NIHSS scores; $p = 0.0205$, χ^2 test for trend).

Table 2. Predictors of hyperglycaemia >7 mmol/l

a On admission

Factor	OR	95% CI	p
Time window 6–12 vs. 0–3 h	0.49	0.34–0.71	0.0001
Time window 12–24 vs. 0–3 h	0.50	0.33–0.75	0.0009
Admission NIHSS score (per 4 points)	1.14	1.08–1.21	<0.0001
Diabetes mellitus	7.40	5.60–9.79	<0.0001

Non-predictive variables were age, sex, rtPA treatment, history of transient ischemic attack, myocardial infarction, hypertension or smoking status.

b Within the first 48 h

Age (per 10 years)	1.12	1.03–1.21	0.006
Time window 6–12 vs. 0–3 h	0.48	0.33–0.69	0.0001
Time window 12–24 vs. 0–3 h	0.37	0.24–0.56	<0.0001
Admission NIHSS score (per 4 points)	1.15	1.09–1.21	<0.0001
Hypertension	1.27	1.06–1.52	0.0102
Diabetes mellitus	7.91	5.65–11.08	<0.0001

Predictors

Hyperglycaemia on admission was more likely with a history of diabetes and a higher NIHSS score, and was less likely when blood was sampled later after stroke onset (table 2a). Diabetes was associated with an odds ratio (OR) of 7.40 (95% CI 5.60–9.79) for admission hyperglycaemia. The OR of hyperglycaemia in the highest quartile of NIHSS scores (scores ≥ 19) was 1.6 compared to the lowest quartile (scores 0–8). The same factors were associated with hyperglycaemia within the first 48 h, with the addition of a history of hypertension and advanced age (table 2b). Again, diabetes was the strongest predictor (OR 7.91, 95% CI 5.65–11.08).

Prognosis

mRS score at day 90 was documented in 2,392 subjects. Predictors of favourable outcome (mRS 0 or 1) at day 90 are listed in table 3a. Hyperglycaemia within the first 48 h, advanced age, and NIHSS score were associated with a reduced likelihood of favourable outcome, while recombinant tissue plasminogen activator (rtPA) treatment was associated with an increased likelihood of favourable outcome.

Predictors of death at day 90 are listed in table 3b. Hyperglycaemia within the first 48 h, increasing age and stroke severity were associated with a greater likelihood of death, while rtPA treatment was associated with a reduced likelihood of death. Other factors (including admission glucose and admission hyperglycaemia) were not significant. Day-90 mRS categories are shown for normoglycaemic subjects and for subjects with hyperglycaemia within 48 h (fig. 1). The absolute difference in favourable outcome (mRS 0–1) was 12.9% (95% CI 9.2–16.7). Outcome was poorer with hyperglycaemia with or without rtPA treatment (fig. 2a) and at all quartiles of the admission NIHSS score (fig. 2b).

For the subgroup of 1,624 subjects in whom additional blood glucose recordings were available after admission, 761 exhibited an increase of at least 0.01 mol/l, while in 863 blood glucose decreased or remained unchanged after admission. Since numbers were evenly distributed, this may represent regression to the mean. Diabetes was associated with a twofold increase in risk of increasing blood glucose, while higher admission glucose or the presence of admission hyperglycaemia were associated with a reduced risk. In this subgroup, prognos-

Fig. 1. Day-90 outcome on mRS by presence or absence of hyperglycaemia >7 mmol/l within the first 48 h. 0-6 = Categories on the mRS.

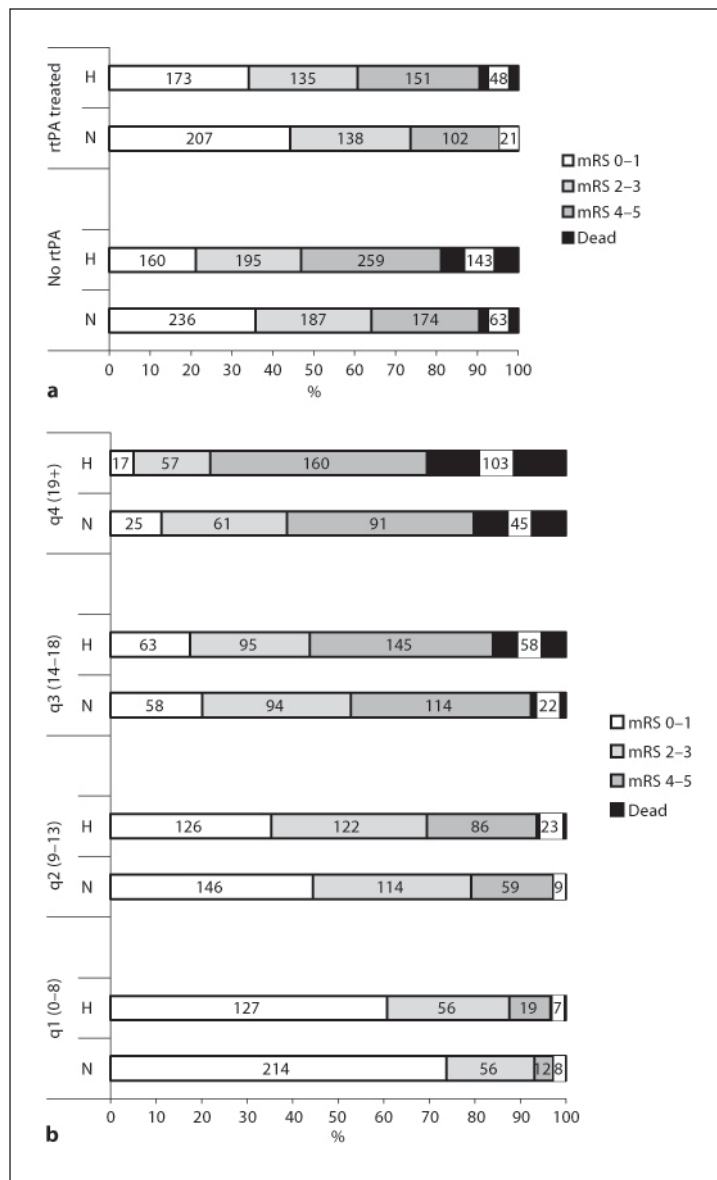
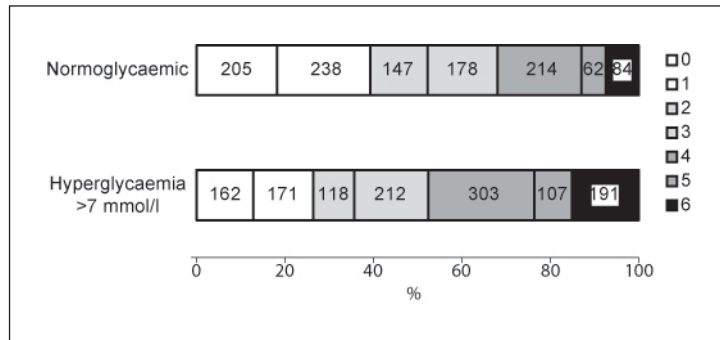


Fig. 2. Day-90 outcome on mRS by presence or absence of hyperglycaemia >7 mmol/l within the first 48 h and intravenous rtPA treatment (a). b Quartiles of admission NIHSS score. H = Hyperglycaemia; N = normoglycaemia.

Table 3. Predictors of a favourable outcome and mortality at day 90 in all subjects, and predictors of a favourable outcome in patients with ≥ 1 blood glucose measurements

a Favourable outcome (mRS 0–1) in all subjects

Factor	OR	95% CI	p
Age, per 10 years	0.86	0.78–0.95	0.002
rtPA treatment	1.35	1.09–1.69	0.007
Admission NIHSS score (per 4 points)	0.44	0.40–0.48	<0.001
Ex- or passive smoker vs. never smoker	1.46	1.11–1.91	0.006
Hyperglycaemia within 48 h	0.70	0.56–0.87	0.002

b Mortality at day 90 in all subjects

Age, per 10 years	1.83	1.55–2.17	<0.001
Male sex	1.36	0.99–1.85	0.052
Current smoker vs. never or ex-smoker	1.68	1.11–2.56	0.015
rtPA treatment	0.49	0.35–0.69	<0.001
Admission NIHSS score (per 4 points)	1.67	1.52–1.83	<0.001
Hyperglycaemia within 48 h	1.66	1.23–2.25	0.001

c Favourable outcome (mRS 0–1) in patients with ≥ 1 blood glucose measurements (n = 1,360)

Age, per 10 years	0.82	0.73–0.91	<0.001
rtPA treatment	1.43	1.11–1.84	0.006
Admission NIHSS score (per 4 points)	0.48	0.43–0.54	<0.001
Hyperglycaemia within 48 h	0.58	0.45–0.75	<0.001
Increase from initial blood glucose	0.73	0.57–0.95	0.017

tic markers were evaluated with a further logistic regression model: data for 1,360 subjects with complete information on all factors could be included in the model, and a favourable outcome was significantly associated with rtPA treatment and less likely with increasing age, NIHSS score, presence of hyperglycaemia within 48 h, and also with increased blood glucose levels from admission (table 3c). Likelihood of death at 3 months was significantly associated with advanced age, rtPA treatment, time window, NIHSS score, smoking status, hyperglycaemia within 48 h and also increase in blood glucose.

Exploratory analyses repeated the logistic regression models with different thresholds of hyperglycaemia (10, 15, and >15 mmol/l). No alternative definition was independently significant when hyperglycaemia >7 mmol/l within the first 48 h was included in the model.

Discussion

Observational studies consistently identify PSH to be associated with increased mortality and reduced likelihood of a good recovery, with a meta-analysis of older observational studies reporting a relative risk of death by 30 days of 3 and a relative risk of death or dependence of 1.41 in non-diabetics with PSH [1] and more recent observational studies in less heterogeneous clinical populations confirming this association [3–6]. Treatment of PSH remains an area of clinical uncertainty [26–28], and insulin treatment was ineffective in the only large randomised controlled trial on stroke, although the trial was underpowered and had a number of other issues that raise questions about its generalisability [21]. Other recent

trials highlight potential for insulin to worsen outcome [29]. If current guidelines to intervene with aggressive glucose lowering were universally implemented, previous data suggest that the proportion of stroke patients requiring insulin infusions would range from 13% if based on acute admission values only (which are of doubtful prognostic value except where thrombolysis is given) to 86% within the first 24 h [4]. Single values have less prognostic value than sustained hyperglycaemia, and hyperglycaemia at any time within 48 h following admission may be more relevant than single recordings [6]. This insight has potentially major implications for stroke management, given the major staffing requirements for insulin infusion management and high incidence of hypoglycaemia in stroke unit settings [30]. In this context, further information on the predictors and natural history of PSH is necessary.

The VISTA database offers a large cohort of participants in acute stroke trials with rigorous source data verification, a median time from stroke onset to admission of <6 h, and a high treatment rate with intravenous thrombolysis. The population is wider than that encountered in thrombolysis trials or registers, although a high proportion in this dataset received such treatment. We confirmed a high prevalence of hyperglycaemia in acute stroke patients, and we also found that diabetes was a far stronger predictor than stroke severity. We moreover confirmed that the presence of elevated blood glucose during the first 48 h after admission for stroke was more strongly associated with a poorer chance of favourable outcome than was a single acute high glucose measurement.

The prevalence of hyperglycaemia (43% on admission, rising to 54% documented within 48 h of stroke) almost certainly underestimates the true prevalence since trial protocols generally exclude patients with very high glucose, and most available trial datasets documented only 1 blood glucose concentration. More frequent blood glucose measurements indicate a profile of increasing blood glucose over the first 24 h after stroke [9].

The odds of hyperglycaemia either on admission or within 48 h were increased sevenfold in those with a diagnosis of diabetes. Diabetes also predicted the likelihood of an increase in blood glucose after admission. In contrast, the contribution of stroke severity was much less. This finding suggests that pre-existing abnormalities of blood glucose levels are the most important predictors of acute hyperglycaemia, which is consistent with acute PSH being probably more suited as a marker of underlying insulin resistance [13] than the concept of ‘stress hyperglycaemia’ related to acute physiological stress [14, 31]. Follow-up of stroke survivors identifies a very high prevalence of insulin resistance phenotypes, present in up to 77% [13, 32]. The association of an increase in blood glucose with less severe stroke is an intriguing finding that suggests that introduction of feeding in this group may add further complexity to the prediction of hyperglycaemia.

The detrimental effect of hyperglycaemia within the first 48 h on 3-month outcome was confirmed, being associated with both higher mortality and a reduced likelihood of good recovery. Furthermore, in the subset of patients in whom >1 blood glucose measurement was documented, increase in blood glucose was also an independent predictor of poor outcome.

The VISTA dataset offers well-validated multisite data and therefore allows clinical questions to be addressed in a large database of acute stroke patients, but it has several limitations. The trials included in VISTA were not designed to study blood glucose, and thus they did not document certain important measures: for example, absence of haemoglobin A_{1c} concentration makes it impossible to distinguish undiagnosed diabetes from ‘stress’ hyperglycaemia. Blood glucose was documented after admission in only around two thirds of patients, and the timing of repeat sampling ranged from 24 to 72 h. We do not know whether blood sampling coincided with trial randomisation or which method was used for blood glucose measurement, although it is reasonable to assume that sampling was performed at acute presentation and that whole blood laboratory glucose measurement was the standard method. Important interventions that may impact on glucose measurement were not reported,

most prominently feeding status, intravenous fluid regimes, and hypoglycaemic medication. While most trial protocols prohibit experimental interventions other than the intervention being tested, it is possible that local investigators may have intervened to control blood glucose according to local interpretation of guidelines, which is known to vary widely [33]. Inevitably, amalgamation of different trial datasets imposes limitations due to differences in recording of medical history variables, and incomplete data restricted the terms that could be used in the regression models. Although our decision to define hyperglycaemia based on a threshold of 7 mmol/l is arbitrary, it is one of several thresholds employed in the previous literature, and no alternative index of hyperglycaemia was superior in regression models when this threshold was included. Consistent with the prospective observational data from the GLIAS study [6], we also found that hyperglycaemia documented at any time within 48 h was a better predictor of outcome than admission values. If the detrimental effect of hyperglycaemia is not confined to the very early time periods when hyperglycaemia might be expected to influence infarct growth or haemorrhagic transformation risk, alternative mechanisms for adverse outcomes should be identified. This observation also implies that short-term insulin treatment regimes (e.g. 24 h in GIST-UK [21]) may be insufficient and is consistent with a retrospective analysis of medical intensive care patients, in whom 72-hour intensive insulin therapy was necessary for benefit [34].

Faced with limited evidence, guidelines offer different recommendations regarding management, and the stroke physicians' behaviour reflects this uncertainty [28, 33]. Recent experience from acute myocardial infarction and intensive care unit trials that failed to replicate initially positive reports of intervention and identified potential hazards due to hypoglycaemia should give pause for thought [35–39]. Despite many potential mechanisms whereby hyperglycaemia might be harmful in the evolution of ischaemic brain damage [40, 41], it remains possible that it is simply a marker for poor prognosis due to unrecognised insulin resistance. With the exception of increased symptomatic intracerebral haemorrhage risk in thrombolysis patients, and a possible attenuation of the beneficial effect of intravenous rtPA on infarct growth, it remains unclear whether the association of hyperglycaemia with poor outcome represents an effect on acute infarct evolution or on later adverse events, since most studies report only 3-month outcomes.

The results of our analysis emphasise the necessity of documenting blood glucose in all acute stroke trials. The detrimental effect of hyperglycaemia within the first 48 h, an absolute reduction in favourable outcome of almost 13%, is greater than the treatment effect of intravenous rtPA, and hyperglycaemia should be included as a stratifying variable in all acute stroke trials.

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Disclosure Statement

No authors have any conflict of interest with respect to this paper.

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