Association of Baseline Hyperglycaemia with Outcomes of Diabetic and Non-diabetic Acute Ischaemic Stroke Patients treated with Intravenous Thrombolysis: a Propensity Score Matched Analysis from the SITS-ISTR registry

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Abstract

Available data from observational studies on the association of admission hyperglycaemia (aHG) with outcomes of acute ischaemic stroke (AIS) patients treated with intravenous thrombolysis (IVT) are contradictory especially when stratified by diabetes mellitus (DM) history. We assessed the association of aHG (≥144 mg/dl) with outcomes stratified by DM history using propensity score matched (PSM) data from the SITS-ISTR. The primary safety outcome was symptomatic intracranial haemorrhage (SICH); three-month functional independence (FI;mRS scores 0-2) represented the primary efficacy outcome. Patients with and without aHG did not differ in baseline characteristics both in the non-diabetic (n=12,318) and diabetic (n=6,572) PSM subgroups. In the non-DM group, patients with aHG had lower 3-month FI (53.3% vs. 57.9%,p<0.001) rates, higher 3-month mortality rates (19.2% vs. 16.0%,p<0.001) and similar SICH rates (1.7% vs. 1.8%,p=0.563) compared to patients without aHG. Similarly, in the DM group, patients with aHG had lower rates of 3-month favourable functional outcome (mRS scores 0-1, 34.1% vs. 39.3%,p<0.001) and FI (48.2% vs. 52.5%,p<0.001), higher 3-month mortality rates (23.7% vs. 19.9%,p<0.001) and similar SICH rates (2.2% vs. 2.7%,p=0.224) compared to patients without aHG. In conclusion, aHG was associated with unfavorable 3 month clinical outcomes in both diabetic and non-diabetic AIS patients treated with IVT.

Text

Introduction

More than a third of acute ischaemic stroke (AIS) patients present with increased plasma glucose on hospital admission (1, 2). Hyperglycaemia after AIS has been acknowledged as an independent predictor of poor outcome for more than 20 years (3), and more recently several observational studies suggested that increased plasma glucose on presentation is also an independent predictor for symptomatic intracerebral haemorrhage (SICH) and unfavourable clinical outcomes in AIS patients treated with intravenous thrombolysis (IVT) (4-7). Interestingly, this association of hyperglycaemia with poor clinical outcomes has also been reported in patients with successful recanalization following IVT (8).

However, when stratified by the history of diabetes mellitus (DM) data from observational studies on the association of hyperglycaemia with IVT outcomes yields contradictory findings. In the Canadian Alteplase for Stroke Effectiveness Study (CASES) admission hyperglycaemia (>144 mg/dl) was independently associated with poor outcomes following IVT administration in both diabetic and non-diabetic patients (9), while in the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Register (SITS-ISTR) admission hyperglycaemia was only associated with a higher risk of SICH and mortality in patients without a history of diabetes mellitus, but not in diabetic patients (10).

In view of these discrepant findings we sought to assess the association of hyperglycaemia with early outcomes of AIS patients treated with IVT, stratified by the history of DM, using propensity score matched (PSM) data from the SITS-ISTR registry.

Methods

We analyzed prospectively collected data from the SITS-ISTR registry from participating centers treating AIS patients with IVT using the IVT register platform, as previously described (11). We included all IVT-treated AIS patients registered in the SITS-ISTR standard dataset between January 2010 and December 2017 if they had available data regarding: 1. the history of diabetes mellitus, 2. baseline plasma glucose values, 3. disability prior to stroke onset [modified Rankin Scale (mRS) scores more than 1], 4. three-month functional outcome assessment using the mRS-score. Patients who have had endovascular treatment, alone or following administration of tissue plasminongen activator (tPA), were excluded from the present analysis. We also excluded patients enrolled in the SITS-ISTR register before January 2010, since data of these patients have been included in a previous studies investigating the association of admission hyperglycaemia with outcomes in AIS patients treated with IVT (10).

The primary safety outcome was the difference in SICH rates according to the SITS-MOST definition (local or remote parenchymal haemorrhage type 2 on 22–36 hours post-IVT imaging scans combined with NIHSS-score increase ≥4 points or leading to death within 24 hours) (12), while the primary efficacy outcome was the difference in functional independence (FI) rates at 3 months (defined as mRS scores 0-2) between patients with and without hyperglycaemia on hospital admission. Secondary outcome events of interest included: 1. mortality rates at 3 months, 2. favourable functional outcome (FFO) rates at 3 months (defined as mRS scores of 0 or 1), 3. SICH rates according to the ECASS II definition (any intracranial bleed with ≥4 points worsening on the NIHSS score) (13), 4. rates of any parenchymal haemorrhage (PH), 5. the distribution of the 3-month mRS scores (functional improvement) between patients with and without hyperglycaemia on hospital admission. All outcomes were evaluated separately for diabetic and non-diabetic patients, and all analyses were performed in both the unmatched and PSM populations.

Statistical analyses

After dichotomization according to the history of diabetes mellitus and the presence of admission hyperglycaemia (≥144 mg/dl) prior to tissue plasminogen activator (tPA) bolus (14), patients in the active group (presence of admission hyperglycaemia) were matched to control group patients (absence of admission hyperglycaemia) using a structured, iterative propensity score model with the primary objective to maximize the balance in the distribution of possible confounders between the two aforementioned groups. The PSM was performed separately for diabetic and non-diabetic patients. In the PSM algorithm we included all baseline characteristics except for the history of diabetes mellitus and admission hyperglycaemia. The corresponding propensity score of the admission hyperglycaemia variable was then calculated for each subject and a nearest neighbor matching algorithm was then used to match patients with admission hyperglycaemia to patients in the control group (patients without admission hyperglycaemia) on a 1:1 ratio (with no replacement) within 0.2*SD of the logit of the propensity score. The process of PSM has been described in detail in similar analyses of SITS registry (15). To determine whether PSM achieved balance in all potential confounders, we compared all baseline characteristics of patients with admission hyperglycaemia to their PSM counterparts.

Statistical comparisons were performed between the aforementioned PSM groups using the $\chi 2$-test (or the Fisher's exact test) and the unpaired t-test (or Mann-Whitney U-test), where appropriate. The distributions of the mRS-scores at three months between the PSM groups was compared using the Cochran Mantel-Haenszel test. The associations of admission hyperglycaemia and diabetes mellitus history with the outcomes of interest were also evaluated using univariable and multivariable binary logistic or ordinal logistic regression models. In univariable models of all baseline characteristics a threshold of $p<0.1$ was used to identify candidate variables for inclusion in the multivariate regression models that tested statistical significance hypothesis at a significance level of 0.05.

All statistical analyses were performed with RStudio: A Language and Environment for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria) (16), with the use of the "MatchIt" package (Matching software for causal inference) for matching patients across the two groups (17), and the Stata Statistical Software Release 13 (College Station, TX, StataCorp LP).

Results

Out of a total 109,324 consecutive AIS patients treated with IVT between January 1, 2010 and December 30, 2017 we identified 54,206 eligible patients (Figure 1). In the unmatched cohort, non-diabetic patients with admission hyperglycaemia were older ($p<0.001$), more likely to be female ($p<0.001$), with greater neurological severity on admission ($p<0.001$), a higher prevalence of hypertension ($p<0.001$), hyperlipidemia ($p=0.012$), atrial fibrillation ($p<0.001$) and congestive heart failure ($p<0.001$), a lower prevalence of current smoking ($p<0.001$) and previous stroke ($p<0.001$), higher rates of disability prior to the index event ($p=0.006$), higher systolic blood pressure on admission and longer onset-to-treatment times ($p<0.001$) compared to non-diabetic patients without admission hyperglycaemia. Non-diabetic patients with admission hyperglycaemia had lower rates of 3-month FFO (39.3% vs. 46.9%, $p<0.001$) and FI (51.9% vs. 61.3%, $p<0.001$), higher rates of any PH (5.6% vs. 4.5%, $p<0.001$) and SICH according to the ECASS II definition (5.5% vs. 3.8%, $p<0.001$), higher 3-month mortality rates (2.1% vs. 1.4%, $p<0.001$) and higher mRS scores at 3-months [2 (1-5) vs. 2 (0-4), $p<0.001$] compared to non-diabetic patients without admission hyperglycaemia. No difference in the SITS-MOST SICH rates was detected between the two groups (1.9% vs. 1.6%, $p=0.083$; eTable 1, appendix).

In the unmatched cohort of diabetic patients, individuals with admission hyperglycaemia were younger ($p<0.001$), with a lower prevalence of hyperlipidaemia ($p<0.001$) and higher systolic and diastolic blood pressure on admission ($p<0.001$) compared to diabetic patients without admission hyperglycaemia (eTable 1, appendix). Diabetic patients with admission hyperglycaemia had lower rates of 3-month FFO (32.7% vs. 37.7%, $p<0.001$) and FI (46.3% vs. 50.6%, $p<0.001$), higher rates of any PH (7.5% vs. 6.1%, $p=0.008$) and SICH according to the ECASS II definition (7.3% vs. 6.2%, $p=0.039$), higher 3-month mortality rates (2.6% vs. 2.1%, $p<0.001$) and higher mRS scores at 3-months [3 (1-6) vs. 2 (1-5), $p<0.001$]. There was no difference in the SITS-MOST SICH rates (2.8% vs. 2.3%, $p=0.130$) between the two groups (diabetic patients with and without admission hyperglycaemia).

PSM in non-diabetic patients resulted in two groups of 6,159 patients each (Figure 1), balanced for all baseline characteristics (Table 1). Distributions of propensity scores before and after matching are presented in eFigure 1, appendix. Non-diabetic patients with admission hyperglycaemia (68% treated within 3 hours from symptom onset) had lower rates of 3-month FFO (40.6% vs. 44.2%, p<0.001), lower rates of 3-month FI (53.3% vs. 57.9%, p<0.001) and higher rates of 3-month mortality (19.2% vs. 16.0%, p<0.001), as compared to non-diabetic patients without admission hyperglycemia. (Figure 2A). We detected no difference in the rates of any PH (5.1% vs. 4.6%, p=0.176) and SICH between the two groups according to SITS MOST (1.7% vs. 1.8%, p=0.563) and ECASS II definitions (5.0% vs. 4.6%, p=0.307).

Likewise, PSM in diabetic patients resulted in two groups of 3,286 patients each (Figure 1), balanced for all baseline characteristics (Table 2). Distributions of propensity scores before and after matching are presented in eFigure 2, appendix. Diabetic patients with admission hyperglycaemia (65% treated within 3 hours from symptom onset) had lower rates of 3-month FFO (34.1% vs. 39.3%, p<0.001), lower rates of 3-month FI (48.2% vs. 52.5%, p<0.001) and higher rates of 3-month mortality (23.7% vs. 19.9%, p<0.001), as compared to diabetic patients without admission hyperglycemia. (Figure 2B). There was no difference in the rates of any PH (6.4% vs. 6.1%, p=0.551) and SICH according to SITS-MOST (2.2% vs. 2.7%, p=0.224) and ECASS II definitions (6.9% vs. 5.8%, p=0.084) between the two groups.

Both history of diabetes mellitus and admission hyperglycaemia were independently (p<0.05) associated with a lower likelihood of 3-month FFO and 3-month FI, higher risk of 3-month mortality and worse 3-month functional outcomes (shift analysis) on multivariable logistic regression analyses of the unmatched cohort after adjustment for potential confounders (Table 2 & eTables 2-6, appendix). The risk of SICH was associated with a history of diabetes mellitus (OR=1.41, 95%CI: 1.16-1.72, p=0.001) but not with admission hyperglycaemia (OR=1.10, 95%CI: 0.92-1.32, p=0.292) in unmatched AIS patients treated with IVT (Table 2 & eTable 2, appendix). There was no interaction (p>0.1) of the history of diabetes mellitus on the association of admission hyperglycaemia with SICH according to the SITS MOST definition, 3-month FI, 3-month mortality and 3-month functional improvement in the unmatched cohort of AIS patients treated with IVT (eFigure 3, appendix). We detected a significant interaction (p=0.032) of the history of diabetes mellitus on the association of admission hyperglycaemia with 3-month FFO (eFigure 3, appendix). More specifically, admission hyperglycaemia had a more pronounced adverse impact on FFO in diabetic (OR=0.72, 95%CI: 0.65-0.82) than in non-diabetic (OR=0.84, 95%CI: 0.79-0.90) patients.

Finally, increasing admission plasma glucose levels were linearly associated with lower odds of 3-month FI (unadjusted analyses, Figure 3A) and of 3-month FFO (unadjusted analyses, eFigure 4, appendix) both in diabetic and non-diabetic patients. We also documented a linear relationship of increasing admission plasma glucose levels with higher likelihood of 3-month mortality both in diabetic and non-diabetic patients (Figure 3B). The associations of admission plasma glucose levels with outcomes of interest on multivariable logistic regression analyses of the unmatched cohort after adjustment for potential confounders are presented in eTable 7. Increasing admission plasma glucose levels were associated with higher adjusted odds of 3-month mortality, while they were negatively related to the likelihood of 3-month FFO, FI and functional improvement. No independent association of admission plasma glucose with SICH according to the SITS MOST definition was found.

Discussion

Our study showed that admission hyperglycaemia is associated with unfavourable clinical outcomes, including 3-month FFO, FI and functional improvement, in both diabetic and non-diabetic AIS patients. These associations were documented both in the unmatched cohort following adjustment for potential confounders and in the PSM cohorts of diabetics and non-diabetics AIS patients. We documented no relationship of admission hyperglycaemia with the risk of SICH in either diabetic or non-diabetic AIS patients.

Our results are in agreement with the findings of the CASES study (9), confirming hyperglycaemia as an independent risk factor for unfavourable outcomes in AIS patients receiving IVT treatment, while they are not in accordance to the findings of the previous SITS report (10) suggesting potential disparities in the association of admission hyperglycaemia with early functional outcomes according to the history of diabetes mellitus. However, it should be noted that the difference in findings may be attributed to differences in sample sizes (16.049

AIS patients in the previous study (10) vs. 54.206 AIS patients in the current report) and statistical analysis plan (PSM vs. multivariable analyses adjusting for confounders). Despite the strong association of hyperglycaemia in AIS outcomes, also evident in cases of large vessel occlusion treated with mechanical thrombectomy (18, 19), there is currently evidence of improved outcomes in AIS with hyperglycaemia and tight glycaemic control in the acute phase, in patients treated conservatively (20, 21) or with IVT (22). Moreover, the recently presented results from a multicenter, phase III randomized,-controlled clinical trial [The Stroke Hyperglycemia Insulin Network Effort (SHINE) Trial] suggest that intensive glucose control (between 80mg/dL and 130 mg/dL) with IV insulin administration in AIS not only fails to improve functional outcomes but is on the contrary associated with a substantially higher risk for hypoglycaemia (23). In accordance to the aforementioned findings, both guidelines from the European Stroke Organization (ESO) and American Heart Association/ American Stroke Association (AHA/ASA) recommend against the tight treatment of hyperglycaemia in AIS and suggest moderate glycemic control in the range of 140-180 mg/dl (24, 25). In the latest guideline of the American Diabetes Association for inhospital management for critically ill patients it is advised that iv or sc insulin should be used to manage persistent hyperglycemia starting at a cut-off point of 180 mg/dL (10.0 mmol/L). The recommended target glucose range for the majority of critically ill patients should be 140–180 mg/dL (7.8–10.0 mmol/L) (26).

Hyperglycaemia during the acute phase of stroke may indicate patients with abnormal glucose metabolism, who are known to have an increased risk for adverse cardiovascular outcomes (27). Hyperglycaemia is also known to enhance glucose and energy delivery to the ischaemic tissue at the cost of exacerbation of cell injury through multiple mechanisms, including lactic acidosis and oxidative stress (28). Experimental models suggest that hyperglycaemia following ischaemia results in blood-brain barrier dysfunction through an increase in oxidative stress and matrix metalloproteinase-9 activity (29). Post-ischaemic hyperglycaemia has also been associated with exacerbation of ischaemic neuronal damage mediated by transporter signalling (30, 31), in both normal animals and animals with metabolic syndrome (32), and with ineffective collateral circulation due to impaired cerebrovascular reactivity (33). Interestingly, in a small cohort increased blood glucose was associated with greater acute-subacute lactate production and reduced salvage of brain tissue only in AIS patients with perfusion-diffusion mismatch, and not in AIS patients without evidence of viable penumbra on neuroimaging (34).

Baseline plasma glucose prior to IVT administration has been incorporated in the available prediction scores for post-IVT SICH, namely the SITS SICH score (35), the haemorrhage after thrombolysis (HAT) score (36), the SEDAN score (37) and the STARTING-SICH score (38). However, in a retrospective cohort study of 1,112 IVT-treated consecutive AIS patients not only baseline plasma glucose, but also glycated hemoglobin (HbA1c) was highlighted as an important predictor of SICH risk following IVT administration, suggesting that the association between increased plasma glucose and sICH risk may be a consequence of long-term vascular injury attributed to diabetes mellitus rather than the sole result of acute hyperglycaemia (39).

Compared to previous reports our study included significantly higher numbers of both diabetic and non-diabetic patients, incorporating also AIS patients more than 80 years of age and with IVT administration beyond 3 hours. Additionally, we are the first to provide PSM analyses on the association of baseline plasma glucose with outcomes separately for diabetic and non-diabetic patients. Despite these strengths, some limitations of the current report also need to be acknowledged. First, selection and reporting biases cannot be excluded in this retrospective analysis of prospectively collected data from a multinational registry with self-reported safety and effectiveness outcomes and no central adjudication of imaging and clinical outcomes. It should also be noted that the history of diabetes mellitus was recorded according to the relevant information provided in the registry, while glycated hemoglobin (HbA1c) values were not available. Therefore, the possibility that some patients with either undiagnosed diabetes or with unrecorded (in the charts) history of diabetes being falsely allocated to the group of non-diabetic subjects cannot be excluded. Secondly, although PSM groups were balanced for all available baseline characteristics potential imbalances in unmeasured confounders cannot be excluded. More specifically, in diabetic patients we were not able to assess potential drug-class effects of antidiabetic medications on stroke outcomes following IVT (40-42). Additionally, information on antidiabetic treatment duration, adherence and long-term control of diabetes were not available. Likewise, information on the causes of death events is unavailable and thus the relative risk of SICH-related mortality between the two groups cannot be assessed. However, it should be noted that cerebral edema represents a substantial cause of 3-month mortality in SITS registry ranging from 18% to 65% according to cerebral edema type (43). Third, it should be noted that the cut-off value of 144 mg/dl (8 mmol/L) in admission glucose for the definition of hyperglycemia was used for comparability to other studies (3, 8, 9, 14). Thus, the optimal threshold for the definition of clinically relevant hypeglycemia in AIS patients eligible for IVT treatment remains unknown. Finally, missing three month follow-up in a third of total patients and unavailable outcomes of interest in nearly half of the whole patient population included in the present registry (Figure 1) may have introduced additional bias on the reported associations.

In conclusion, our findings indicate that admission hyperglycaemia is associated with unfavourable clinical outcomes in both diabetic and non-diabetic tPA-treated AIS patients in adjusted and PSM analyses. We found no significant increase in the risk of SICH in hyperglycaemic AIS patients treated with IVT. Future randomized-controlled clinical trials on the potential utility of moderate glycaemic control in the population of AIS patients treated with IVT that present with hyperglycaemia before tPA-bolus appear to be warranted.

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PS: performed critical revision of the manuscript, MC: performed critical revision of the manuscript, MN: performed critical revision of the manuscript, DT: performed critical revision of the manuscript, NA: performed critical revision of the manuscript, supervised the study. Dr. Georgios Tsivgoulis is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data and Resource Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Table 1. Baseline characteristics and outcomes of matched groups

Variable	No Diabetes Mellitus history (n=12,318)			Diabetes Mellitus history (n=6,572)		
	HG+ (n=6,159)	HG- (n=6,159)	p-value	HG+ (n=3,286)	HG- (n=3,286)	p-value
Age (mean±SD), years	71.5±13.0	71.3±13.2	0.396	72.4±10.3	72.9±10.3	0.097
Males (%)	51.8	52.6	0.387	57.0	56.9	0.980
Admission NIHSS (median, IQR)	11 (6-17)	11 (6-17)	0.937	10 (6-16)	10 (6-16)	0.193
Hypertension (%)	67.9	68.5	0.486	85.0	85.5	0.531
Hyperlipidemia (%)	26.5	26.4	0.935	48.3	50.0	0.175
Current smoking (%)	14.8	15.3	0.421	13.0	13.1	0.826
Atrial fibrillation (%)	21.4	21.7	0.661	22.3	22.0	0.744
Congestive heart failure (%)	8.3	8.3	0.974	13.2	13.4	0.856
History of previous stroke* (%)	9.9	9.6	0.585	15.7	15.9	0.787
Pre-stroke disability (mRS>1, %)	12.3	11.8	0.423	17.4	18.2	0.439
Statin pretreatment (%)	24.8	24.8	0.983	47.0	46.8	0.863
Antiplatelet pretreatment (%)	34.6	34.4	0.865	52.9	53.1	0.902
Anticoagulant pretreatment (%)	3.8	4.0	0.578	5.2	4.8	0.461
Admission SBP baseline (mean±SD), mmHg	153.2±24.3	152.8±23.7	0.364	157.2±24.2	156.3±24.1	0.115
Admission DBP (mean±SD), mmHg	83.0±14.9	83.1±14.8	0.853	82.9±14.8	82.4±14.5	0.212
Admission plasma glucose (mean±SD), mg/dL	180.5±40.4	107.9±17.3	<0.001	211.7±62.1	111.9±19.5	<0.001
Onset-to-treatment time (mean±SD), min	163.7±65.0	163.3±65.8	0.750	165.6±64.1	166.1±64.8	0.735
SICH (%) – SITS MOST	1.7	1.8	0.563	2.2	2.7	0.224
SICH – ECASS II (%)	5.0	4.6	0.307	6.9	5.8	0.084
Any PH	5.1	4.6	0.176	6.4	6.1	0.551

FFO (%)	40.6	44.2	<0.001	34.1	39.3	<0.001
FI (%)	53.3	57.9	<0.001	48.2	52.5	<0.001
Mortality at 3-months (%)	19.2	16.0	<0.001	23.7	19.9	<0.001
3-month mRS (median, IQR)	2 (1-4)	2 (1-4)	<0.001	3 (1-5)	2 (1-5)	<0.001

HG: hyperglycaemia, SD: standard deviation, NIHSS: National Institutes of Health Stroke Scale, IQR: interquartile range, mRS: modified Rankin Scale, SBP: systolic blood pressure, DBP: diastolic blood pressure, SICH: symptomatic intracranial haemorrhage, FFO: favorable functional outcome, FI: functional independence, PH: parenchymal hemorrhage

Table 2. Overview of the adjusted analyses on the association of admission hyperglycaemia and diabetes mellitus history with outcomes of interest in the unmatched cohort.

	Admission hyperglycaemia		**Diabetes Mellitus**	
Outcome	**OR/cOR (95%CI)**	**p-value**	**OR/cOR (95%CI)**	**p-value**
SICH (SITS-MOST)	1.10 (0.92, 1.32)	0.292	1.41 (1.16, 1.72)	0.001
3-month FFO	0.82 (0.77, 0.86)	<0.001	0.73 (0.68, 0.78)	<0.001
3-month FI	0.79 (0.74, 0.83)	<0.001	0.71 (0.66, 0.75)	<0.001
3-month mortality	1.36 (1.27, 1.46)	<0.001	1.52 (1.41, 1.64)	<0.001
3-month functional improvement	0.82 (0.79, 0.85)	<0.001	0.71 (0.68, 0.75)	<0.001

OR: odds ratio, cOR: common OR, SICH: symptomatic intracranial haemorrhage, FFO: favorable functional outcome, FI: functional independence

FIGURES

Figure 1. Flowchart presenting the selection of eligible and propensity score matched patients.

Figure 2. Distribution of the modified Rankin Scale scores at three months between (A) non-diabetic and (B) diabetic acute ischaemic stroke patients with and without hyperglycaemia prior to the administration of intravenous thrombolysis.

Figure 3. Modeled probability of (A) functional independence and (B) mortality at 3-months following intravenous thrombolysis treatment by admission blood glucose (unadjusted analyses).

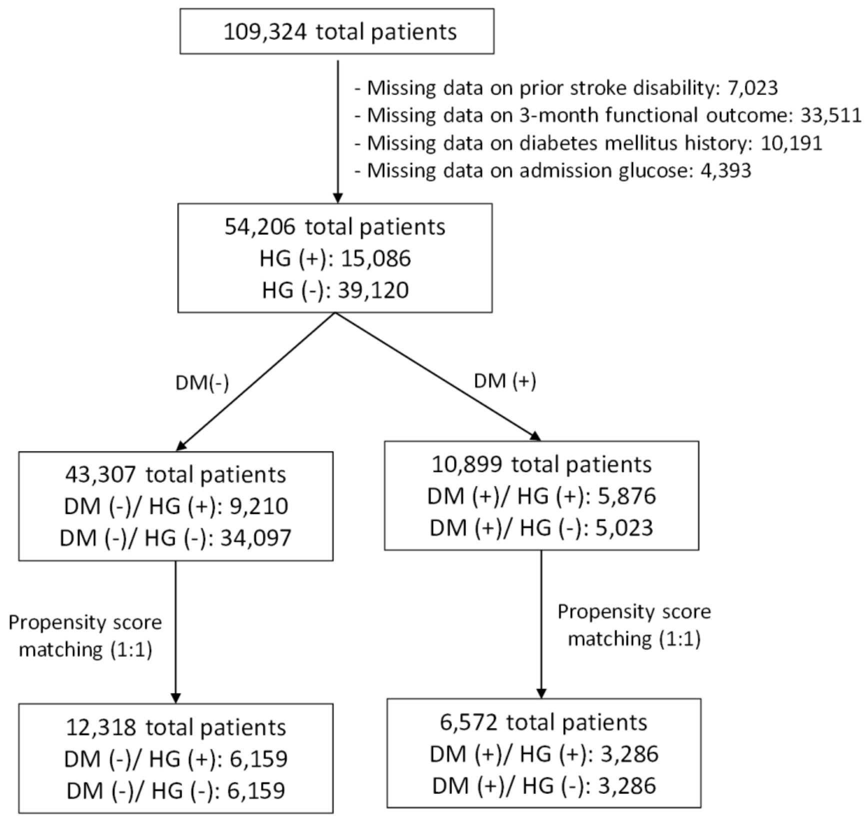

Figure 1. Flowchart presenting the selection of eligible and propensity score matched patients.

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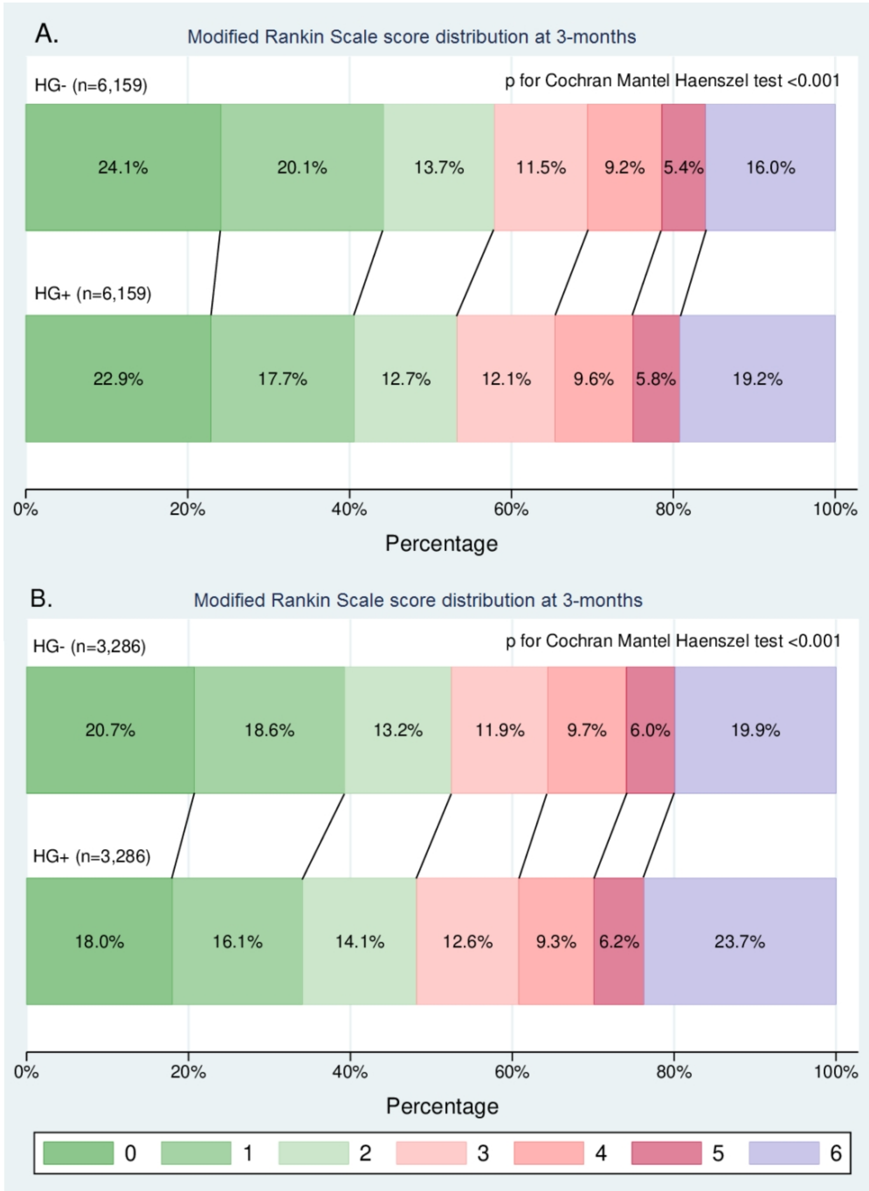

Figure 2. Distribution of the modified Rankin Scale scores at three months between (A) non-diabetic and (B) diabetic acute ischaemic stroke patients with and without hyperglycaemia prior to the administration of intravenous thrombolysis.

291x397mm (96 x 96 DPI)

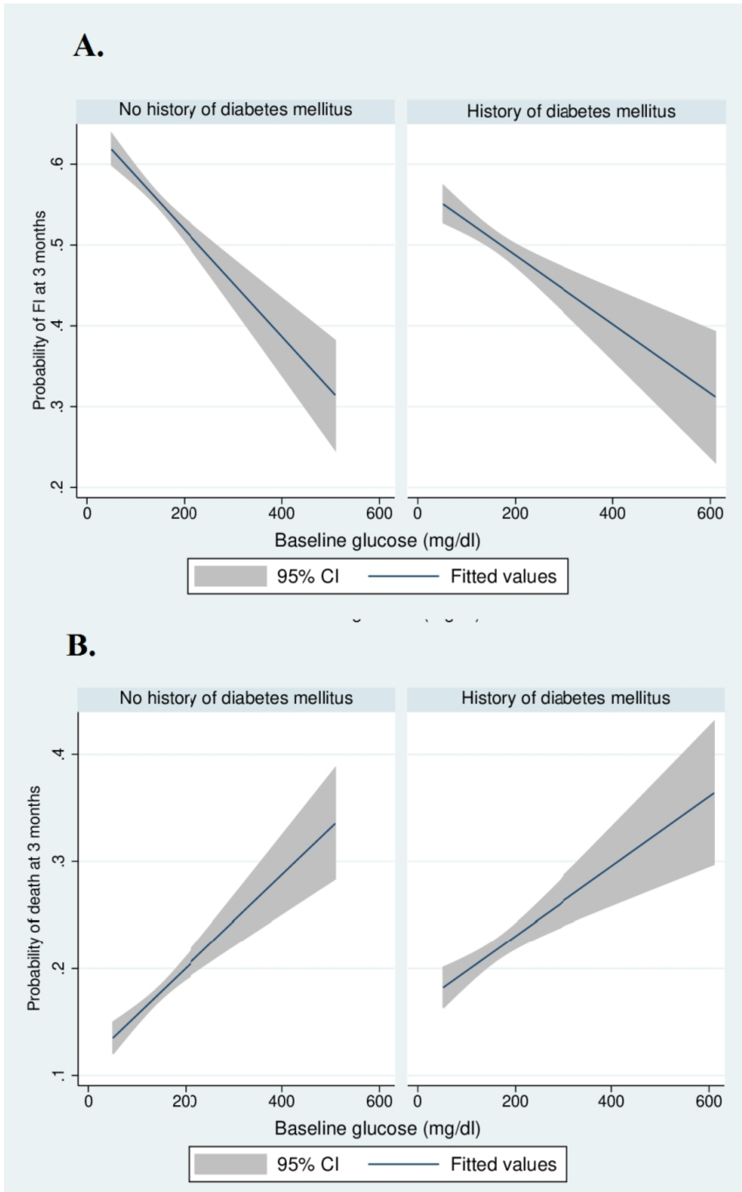

Figure 3. Modeled probability of (A) functional independence and (B) mortality at 3-months following intravenous thrombolysis treatment by admission blood glucose (unadjusted analyses).

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Online Supplemental Materials

eTable 1. Baseline characteristics and outcomes of unmatched groups

Variable	**No Diabetes Mellitus history (n=43,307)**			**Diabetes Mellitus history (n=10,899)**		
	HG+ (n=9,210)	HG- (n=34,097)	p-value	HG+ (n=5,876)	HG- (n=5,023)	p-value
Baseline Characteristics						
Age (mean±SD), years	71.3±12.8	69.1±14.0	<0.001	72.02±10.4	72.8±10.3	<0.001
Males (%)	51.8	54.7	<0.001	57.0	56.2	0.398
Admission NIHSS (median, IQR)	11 (6-17)	10 (6-16)	<0.001	10 (6-17)	10 (6-17)	0.374
Hypertension (%)	68.0	62.2	<0.001	86.0	85.7	0.728
Hyperlipidemia (%)	27.0	25.7	0.012	47.7	51.2	<0.001
Current smoking (%)	15.6	18.6	<0.001	13.6	13.9	0.622
Atrial fibrillation (%)	22.3	19.8	<0.001	23.2	22.8	0.581
Congestive heart failure (%)	8.2	7.7	<0.001	13.3	13.5	0.771
History of previous stroke* (%)	10.5	11.7	<0.001	15.5	16.5	0.170
Pre-stroke disability (mRS>1, %)	12.2	11.2	0.006	17.3	18.3	0.169
Statin pretreatment (%)	24.8	24.7	0.867	46.0	46.3	0.742
Antiplatelet pretreatment (%)	35.2	35.3	0.834	51.4	53.2	0.062
Anticoagulant pretreatment (%)	3.9	3.6	0.216	5.6	4.9	0.106
Admission SBP baseline (mean±SD), mmHg	153.2±24.0	152.0±23.7	<0.001	158.3±25.1	156.3±24.3	<0.001
Admission DBP (mean±SD), mmHg	83.2±14.7	83.0±14.3	0.344	83.6±15.1	82.4±14.5	<0.001
Admission plasma glucose (mean±SD), mg/dL	180.1±41.1	107.7±17.3	<0.001	213.0±63.7	111.8±19.6	<0.001
Onset-to-treatment time (mean±SD), min	162.7±64.9	158.5±63.2	<0.001	164.8±66.1	163.6±64.8	0.348
Outcomes						

SICH-SITS MOST (%)	1.9	1.6	0.083	2.8	2.3	0.130
SICH-ECASS II (%)	5.5	3.8	<0.001	7.5	6.1	0.008
Any PH	5.6	4.5	<0.001	7.3	6.2	0.039
FFO (%)	39.3	46.9	<0.001	32.7	37.7	<0.001
FI (%)	51.9	61.3	<0.001	46.3	50.6	<0.001
Mortality at 3-months (%)	2.1	1.4	<0.001	2.6	2.1	<0.001
3-month mRS (median, IQR)	2 (1-5)	2 (0-4)	<0.001	3 (1-6)	2 (1-5)	<0.001

HG: hyperglycaemia, SD: standard deviation, NIHSS: National Institutes of Health Stroke Scale, IQR: interquartile range, mRS: modified Rankin Scale, SBP: systolic blood pressure, DBP: diastolic blood pressure, SICH: symptomatic intracranial haemorrhage, FFO: favorable functional outcome, FI: functional independence, PH: parenchymal hemorrhage

eTable 2. Univariable and multivariable logistic regression analyses on the probability of symptomatic intracranial haemorrhage according to the SITS MOST definition.

Baseline characteristic	Univariable analysis		Multivariable analysis	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Age	1.04 (1.03, 1.04)	<0.001	1.03 (1.02, 1.04)	<0.001
Males	1.12 (0.98, 1.29)	0.103	-	-
Admission NIHSS	1.04 (1.03, 1.05)	<0.001	1.04 (1.03, 1.05)	<0.001
Hypertension	1.63 (1.39, 1.91)	<0.001	0.98 (0.80, 1.21)	0.881
Diabetes mellitus	1.56 (1.34, 1.82)	<0.001	1.41 (1.16, 1.72)	0.001
Hyperlipidemia	1.20 (1.04, 1.38)	0.014	0.84 (0.68, 1.05)	0.123
Current smoking	0.52 (0.41, 0.65)	<0.001	0.78 (0.58, 1.05)	0.105
Atrial fibrillation	2.25 (2.14, 2.37)	<0.001	1.20 (0.98, 1.46)	0.073
Congestive heart failure	1.33 (1.07, 1.67)	<0.001	0.86 (0.65, 1.14)	0.292
History of previous stroke	1.54 (1.29, 1.85)	<0.001	1.20 (0.95, 1.51)	0.132
Pre-stroke disability	1.23 (1.01, 1.49)	0.035	0.80 (0.62, 1.00)	0.053
Statin pretreatment	1.42 (1.23, 1.66)	<0.001	1.27 (1.02, 1.58)	0.032
Antiplatelet pretreatment	1.89 (1.65, 2.17)	<0.001	1.38 (1.15, 1.67)	0.001
Anticoagulant pretreatment	1.33 (0.95, 1.85)	0.098	1.18 (0.79, 1.76)	0.418
Admission SBP baseline	1.11 (1.08, 1.14)	<0.001	1.07 (1.02, 1.11)	0.002
Admission DBP	1.08 (1.03, 1.13)	0.002	1.04 (0.97, 1.11)	0.248
Hypeglycaemia on admission*	1.33 (1.15, 1.53)	<0.001	1.10 (0.92, 1.32)	0.292
Onset-to-treatment time	1.02 (1.01, 1.03)	<0.001	1.02 (1.00, 1.03)	0.008

OR: odds ratio, 95%CI: 95% confidence intervals, NIHSS: National Institutes of Health Stroke Scale, SBP: systolic blood pressure, DBP: diastolic blood pressure

*≥144 mg/dl vs. <144mg/dl

eTable 3. Univariable and multivariable logistic regression analyses on the probability of 3-month favorable functional outcome (mRS-scores of 0-1)

Baseline characteristic	Univariable analysis		Multivariable analysis	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Age	0.96 (0.96, 0.96)	<0.001	0.97 (0.97, 0.97)	<0.001
Males	1.32 (1.28, 1.37)	<0.001	1.01 (0.96, 1.07)	0.601
Admission NIHSS	0.85 (0.84, 0.85)	<0.001	0.85 (0.84, 0.85)	<0.001
Hypertension	0.63 (0.61, 0.66)	<0.001	0.91 (0.86, 0.96)	0.001
Diabetes mellitus	0.65 (0.62, 0.68)	<0.001	0.73 (0.68, 0.78)	<0.001
Hyperlipidemia	0.96 (0.93, 1.00)	0.059	1.19 (1.11, 1.27)	<0.001
Current smoking	1.47 (1.41, 1.54)	<0.001	0.88 (0.82, 0.94)	<0.001
Atrial fibrillation	0.49 (0.47, 0.52)	<0.001	0.86 (0.80, 0.92)	<0.001
Congestive heart failure	0.49 (0.46, 0.53)	<0.001	0.85 (0.77, 0.94)	0.001
History of previous stroke	0.66 (0.62, 0.69)	<0.001	0.80 (0.73, 0.86)	<0.001
Pre-stroke disability	0.15 (0.14, 0.16)	<0.001	0.19 (0.18, 0.22)	<0.001
Statin pretreatment	0.87 (0.83, 0.90)	<0.001	1.01 (0.94, 1.09)	0.735
Antiplatelet pretreatment	0.70 (0.68, 0.73)	<0.001	1.08 (1.02, 1.14)	0.015
Anticoagulant pretreatment	0.58 (0.52, 0.64)	<0.001	0.98 (0.85, 1.13)	0.799
Admission SBP baseline	0.96 (0.96, 0.97)	<0.001	0.96 (0.95, 0.97)	<0.001
Admission DBP	1.01 (1.00, 1.03)	<0.001	0.97 (0.96, 0.99)	0.022
Hypeglycaemia on admission*	0.69 (0.66, 0.71)	<0.001	0.82 (0.77, 0.86)	<0.001
Onset-to-treatment time	0.99 (0.99, 0.99)	<0.001	0.98 (0.98, 0.99)	<0.001

OR: odds ratio, 95%CI: 95% confidence intervals, NIHSS: National Institutes of Health Stroke Scale, SBP: systolic blood pressure, DBP: diastolic blood pressure

*≥144 mg/dl vs. <144mg/dl

eTable 4. Univariable and multivariable logistic regression analyses on the probability of 3-month functional independence (mRS-scores of 0-2)

Baseline characteristic	**Univariable analysis**		**Multivariable analysis**	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Age	0.95 (0.95, 0.95)	<0.001	0.96 (0.96, 0.97)	<0.001
Males	1.39 (1.34, 1.44)	<0.001	1.03 (0.98, 1.09)	0.229
Admission NIHSS	0.84 (0.84, 0.84)	<0.001	0.84 (0.84, 0.85)	<0.001
Hypertension	0.62 (0.60, 0.64)	<0.001	0.95 (0.90, 1.01)	0.091
Diabetes mellitus	0.64 (0.61, 0.67)	<0.001	0.71 (0.66, 0.75)	<0.001
Hyperlipidemia	0.98 (0.95, 1.02)	0.406	-	-
Current smoking	1.67 (1.59, 1.75)	<0.001	0.95 (0.88, 1.02)	0.155
Atrial fibrillation	0.48 (0.46, 0.50)	<0.001	0.90 (0.84, 0.96)	0.001
Congestive heart failure	0.47 (0.45, 0.51)	<0.001	0.82 (0.75, 0.90)	<0.001
History of previous stroke	0.73 (0.69, 0.77)	<0.001	0.90 (0.83, 0.97)	0.010
Pre-stroke disability	0.22 (0.21, 0.23)	<0.001	0.31 (0.28, 0.33)	<0.001
Statin pretreatment	0.89 (0.86, 0.93)	<0.001	1.16 (1.10, 1.24)	<0.001
Antiplatelet pretreatment	0.69 (0.67, 0.71)	<0.001	1.05 (0.99, 1.11)	0.121
Anticoagulant pretreatment	0.59 (0.54, 0.65)	<0.001	0.98 (0.85, 1.12)	0.750
Admission SBP baseline	0.97 (0.96, 0.97)	<0.001	0.97 (0.96, 0.97)	<0.001
Admission DBP	1.01 (1.01, 1.01)	<0.001	0.99 (0.99, 0.99)	0.027
Hypeglycaemia on admission*	0.66 (0.64, 0.69)	<0.001	0.79 (0.74, 0.83)	<0.001
Onset-to-treatment time	1.00 (0.99, 1.01)	0.202	-	-

OR: odds ratio, 95%CI: 95% confidence intervals, NIHSS: National Institutes of Health Stroke Scale, SBP: systolic blood pressure, DBP: diastolic blood pressure

*≥144 mg/dl vs. <144mg/dl

eTable 5. Univariable and multivariable logistic regression analyses on the probability of 3-month mortality.

Baseline characteristic	**Univariable analysis**		**Multivariable analysis**	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Age	1.07 (1.06, 1.07)	<0.001	1.05 (1.05, 1.06)	<0.001
Males	0.79 (0.76, 0.82)	<0.001	1.25 (1.17, 1.34)	<0.001
Admission NIHSS	1.16 (1.15, 1.16)	<0.001	1.14 (1.14, 1.15)	<0.001
Hypertension	1.72 (1.63, 1.81)	<0.001	1.06 (0.98, 1.14)	0.145
Diabetes mellitus	1.68 (1.60, 1.77)	<0.001	1.52 (1.41, 1.64)	<0.001
Hyperlipidemia	0.99 (0.94, 1.04)	0.717	-	-
Current smoking	0.47 (0.44, 0.51)	<0.001	0.95 (0.85, 1.06)	0.365
Atrial fibrillation	2.25 (2.14, 2.37)	<0.001	1.18 (1.09, 1.27)	<0.001
Congestive heart failure	2.54 (2.38, 2.72)	<0.001	1.54 (1.39, 1.69)	<0.001
History of previous stroke	1.31 (1.23, 1.40)	<0.001	1.03 (0.94, 1.14)	0.520
Pre-stroke disability	3.09 (2.92, 3.26)	<0.001	1.62 (1.49, 1.76)	<0.001
Statin pretreatment	1.11 (1.05, 1.16)	<0.001	0.86 (0.80, 0.93)	<0.001
Antiplatelet pretreatment	1.54 (1.47, 1.61)	<0.001	1.01 (0.94, 1.09)	0.758
Anticoagulant pretreatment	1.96 (1.77, 2.18)	<0.001	1.25 (1.08, 1.45)	0.003
Admission SBP	1.02 (1.02, 1.04)	<0.001	1.01 (1.00, 1.03)	0.049
Admission DBP	1.00 (0.98, 1.01)	0.421	-	-
Hypeglycaemia on admission*	1.68 (1.60, 1.76)	<0.001	1.36 (1.27, 1.46)	<0.001
Onset-to-treatment time	1.00 (0.99, 1.01)	0.386	-	-

OR: odds ratio, 95%CI: 95% confidence intervals, NIHSS: National Institutes of Health Stroke Scale, SBP: systolic blood pressure, DBP: diastolic blood pressure

*≥144 mg/dl vs. <144mg/dl

eTable 6. Univariable and multivariable ordinal regression analyses on the probability of 3-month functional improvement defined as 1-point decrease in 3-month mRS-scores over the entire range of score groupings (shift analysis).

Baseline characteristic	**Univariable analysis**		**Multivariable analysis**	
	cOR (95%CI)	p-value	cOR (95%CI)	p-value
Age	0.95 (0.95, 0.96)	<0.001	0.97 (0.97, 0.97)	<0.001
Males	1.32 (1.28, 1.35)	<0.001	0.96 (0.92, 0.99)	0.038
Admission NIHSS	0.85 (0.85, 0.85)	<0.001	0.85 (0.85, 0.86)	<0.001
Hypertension	0.62 (0.60, 0.64)	<0.001	0.93 (0.90, 0.98)	0.003
Diabetes mellitus	0.63 (0.61, 0.66)	<0.001	0.71 (0.68, 0.75)	<0.001
Hyperlipidemia	0.96 (0.93, 0.99)	0.014	1.13 (1.07, 1.19)	<0.001
Current smoking	1.56 (1.49, 1.61)	<0.001	0.91 (0.86, 0.96)	<0.001
Atrial fibrillation	0.47 (0.45, 0.49)	<0.001	0.86 (0.82, 0.91)	<0.001
Congestive heart failure	0.44 (0.42, 0.47)	<0.001	0.76 (0.70, 0.81)	<0.001
History of previous stroke	0.69 (0.66, 0.72)	<0.001	0.83 (0.78, 0.88)	<0.001
Pre-stroke disability	0.26 (0.25, 0.27)	<0.001	0.39 (0.37, 0.41)	<0.001
Statin pretreatment	0.87 (0.84, 0.90)	<0.001	1.04 (0.99, 1.10)	0.117
Antiplatelet pretreatment	0.68 (0.66, 0.70)	<0.001	1.04 (1.00, 1.10)	0.066
Anticoagulant pretreatment	0.55 (0.51, 0.60)	<0.001	0.93 (0.84, 1.03)	0.184
Admission SBP	0.97 (0.96, 0.97)	<0.001	0.98 (0.97, 0.99)	<0.001
Admission DBP	1.02 (1.01, 1.03)	<0.001	0.97 (0.95, 0.98)	<0.001
Hypeglycaemia on admission*	0.66 (0.64, 0.68)	<0.001	0.82 (0.79, 0.85)	<0.001
Onset-to-treatment time	1.00 (1.00, 1.01)	0.052	0.99 (0.98, 0.99)	<0.001

cOR: common odds ratio, 95%CI: 95% confidence intervals, NIHSS: National Institutes of Health Stroke Scale, SBP: systolic blood pressure, DBP: diastolic blood pressure

*≥144 mg/dl vs. <144mg/dl

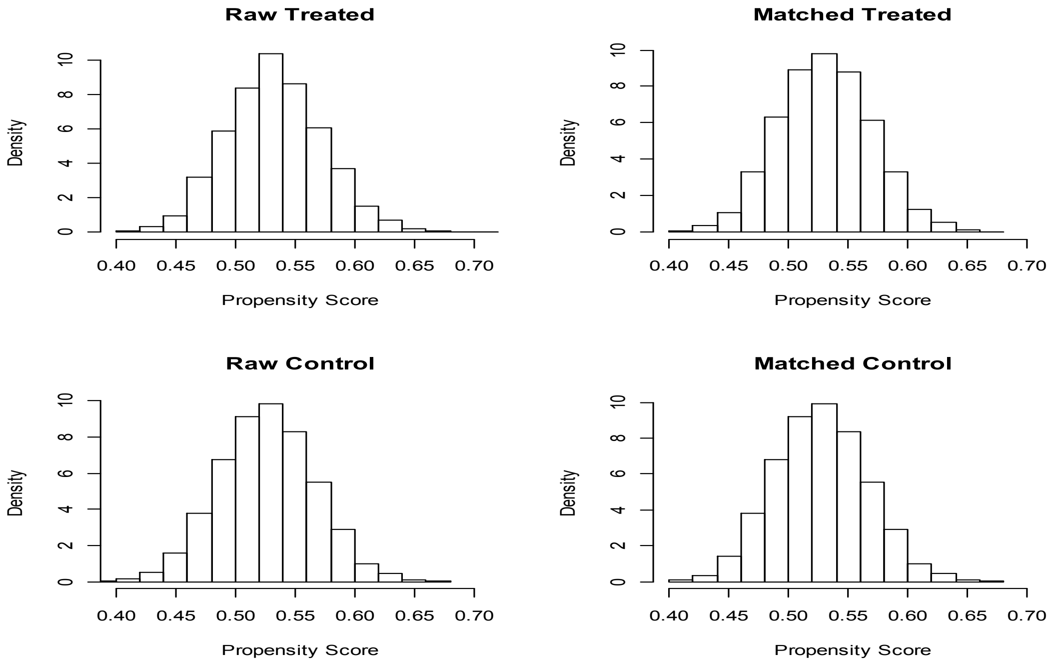
eTable 7. Overview of the adjusted analyses on the association of admission plasma glucose levels and diabetes mellitus history with outcomes of interest in the unmatched cohort.

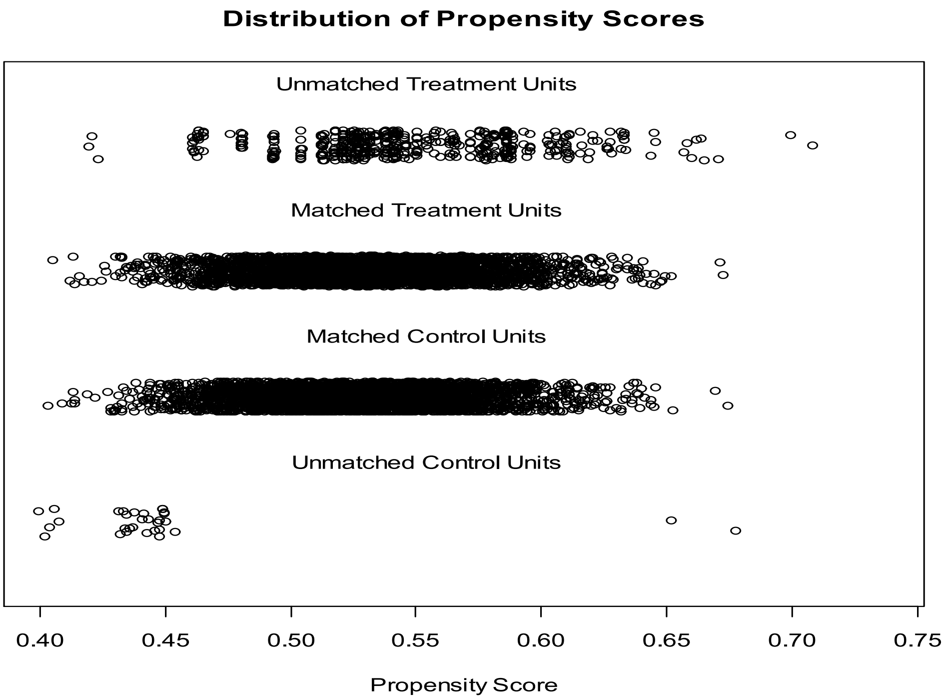
	Admission plasma glucose*		**Diabetes Mellitus**	
Outcome	**OR/cOR (95%CI)**	**p-value**	**OR/cOR (95%CI)**	**p-value**
SICH (SITS-MOST)	1.01 (0.99, 1.03)	0.065	1.37 (1.12, 1.67)	0.002
3-month FFO	0.97 (0.96, 0.98)	<0.001	0.77 (0.72, 0.82)	<0.001
3-month FI	0.97 (0.96, 0.98)	<0.001	0.75 (0.70, 0.80)	<0.001
3-month mortality	1.03 (1.02, 1.04)	<0.001	1.46 (1.35, 1.58)	<0.001
3-month functional improvement	0.97 (0.96, 0.98)	<0.001	0.81 (0.75, 0.88)	<0.001

*per 10mg/dl increase

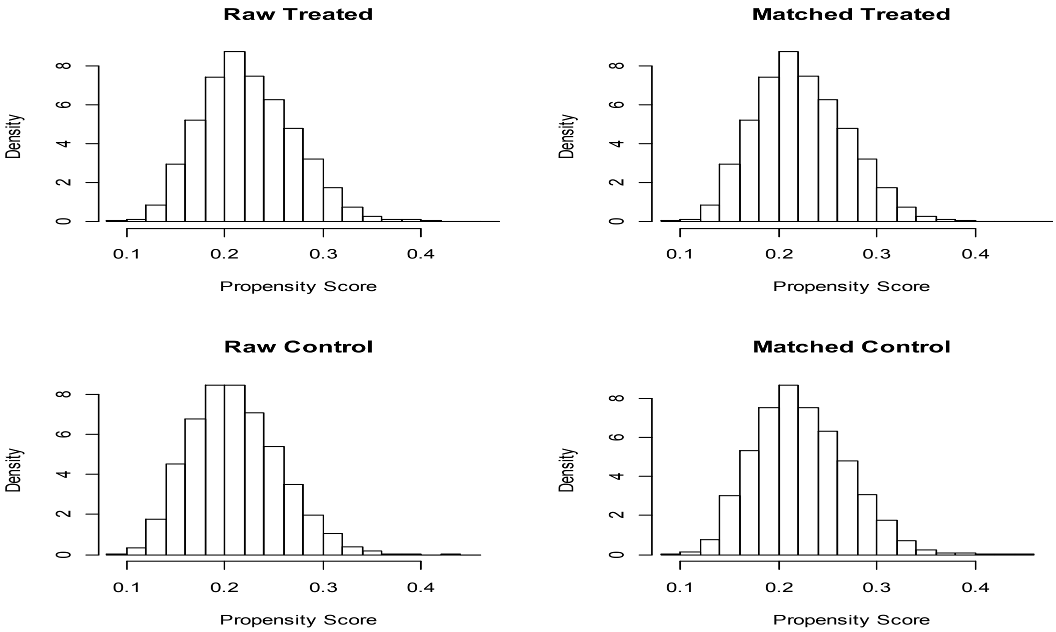
OR: odds ratio, cOR: common OR, SICH: symptomatic intracranial haemorrhage, FFO: favorable functional outcome, FI: functional independence

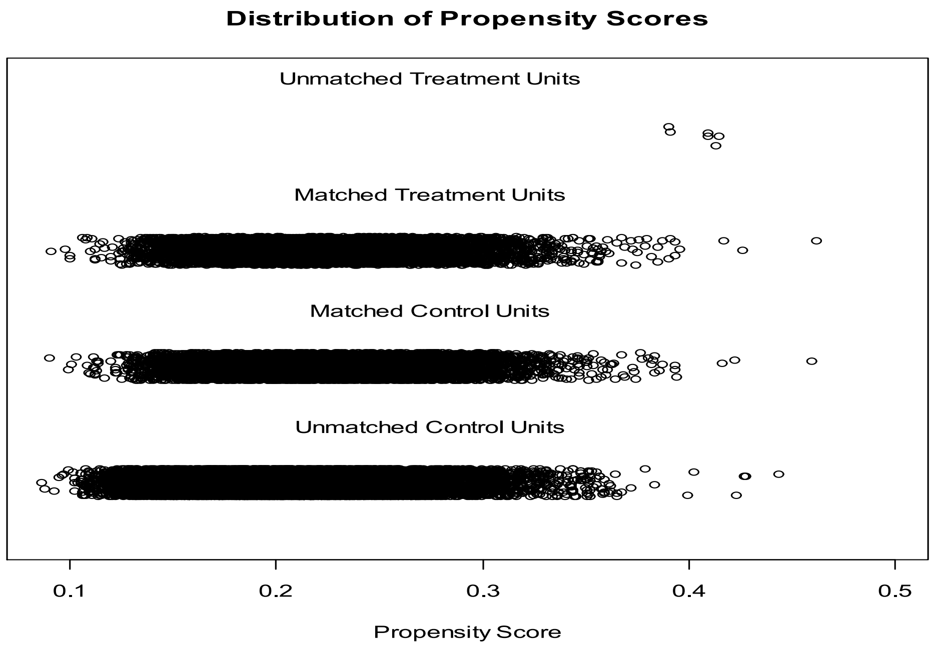
eFigure 1. Distribution of propensity scores for diabetic patients before and after propensity score matching.



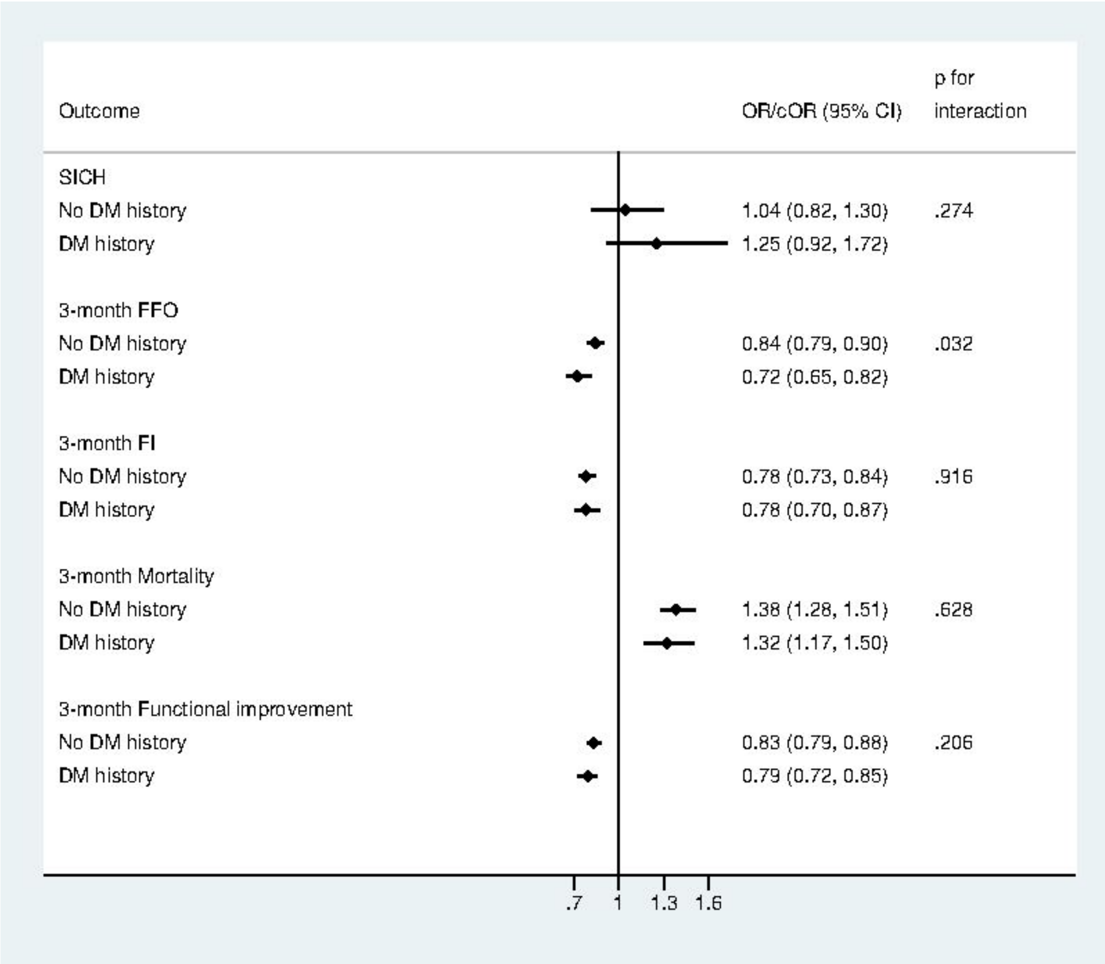


eFigure 2. Distribution of propensity scores for non-diabetic patients before and after propensity score matching.





eFigure 3. Interaction testing between admission hyperglycaemia and history of diabetes mellitus on the outcomes of interest.



eFigure 4. Modeled probability of favorable functional outcome at 3-months following intravenous thrombolysis treatment by admission blood glucose (unadjusted analyses).