Hyperglycaemia in acute intracerebral haemorrhage

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A thesis submitted in fulfilment of the requirements for the degree of

Master of Philosophy

Sydney School of Public Health
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August 2016

Declaration

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Signature:

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Dr Anubhav Saxena

Date: October 2016

Author's contribution

The work presented in this thesis was carried out by the author under supervision of Professor Craig Anderson and Professor Hisatomi Arima at The George Institute for Global Health. The data in this thesis is from a multi-centre randomised control trial (INTERACT2) which was designed and implemented by Professor Craig Anderson. I wrote the first and subsequent drafts of the manuscripts (all Chapters). Further detailed information about co-author contributions have been documented at the beginning of Chapter 2 and 3.

Chapter 3 of this thesis is published as: Saxena A, Anderson CS, Wang X, Sato S, Arima H, Chan E, Muñoz-Venturelli P, Delcourt C, Robinson T, Stapf C, Lavados PM, Wang J, Neal B, Chalmers J, Heeley E. Prognostic significance of hyperglycemia in acute intracerebral hemorrhage: the INTERACT2 study. Stroke 2016;47:682-8.

Authorship attribution statement attestation
As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

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Professor Craig Anderson

Date: 26 October 2016

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Bibliography

INSULINFARCT: Intensive versus Subcutaneous Insulin in Patients with Hyperacute Cerebral Infarction

INTERACT: The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial

NEMESIS: North East Melbourne Stroke Incidence Study

SHINE: The Stroke Hyperglycemia Insulin Network Effort

THIS: Treatment of hyperglycemia in ischemic stroke

Publications/Presentations

Publications

Saxena A, Anderson CS, Wang X, Sato S, Arima H, Chan E, Muñoz-Venturelli P, Delcourt C, Robinson T, Stapf C, Lavados PM, Wang J, Neal B, Chalmers J, Heeley E. Prognostic Significance of Hyperglycemia in Acute Intracerebral Hemorrhage: The INTERACT2 Study. Stroke 2016;47:682-8.

Presentations

Saxena A, Anderson CS, Wang X, Arima H, Heeley E, Delcourt C. Significance of hyperglycaemia in acute intracerebral haemorrhage: INTERACT2 results. International Journal of Stroke; 9, S1: Special Issue: Abstracts of the 25th Annual Scientific Meeting of the Stroke Society of Australasia, 30 July-1 August 2014, Hamilton Island, Queensland, Australia.

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Abstract

Background and rationale

Acute intracerebral haemorrhage (ICH) results from rupture of cerebral vasculature leading to bleeding into the cerebral parenchyma. ICH represents 10-50% of stroke, depending on the population studied, is associated with significant morbidity and mortality, and has limited treatment options. The INTERACT2 trial was designed to assess the role of blood pressure lowering therapy in intracerebral haemorrhage. Guideline therapy (target systolic blood pressure [SBP] <180 mmHg) was compared against intensive lowering (SBP <140 mmHg). The outcomes assessed in this trial were death or major disability (according to the modified Rankin scale at 90 days) following ICH. Hyperglycaemia has been widely studied in acute illnesses as myocardial infarction, ischaemic stroke, traumatic brain injury and ICH, and is associated with adverse outcomes. The incidence of hyperglycaemia in the acute phase is due to a combination of factors: diabetic pathophysiology and stress hyperglycaemia. Animal models have specifically examined hyperglycaemia in ICH and have found association with haematoma volume, expansion and perihaematomal oedema. Accordingly, I performed secondary analyses in the INTERACT2 dataset to determine the association between hyperglycaemia and outcomes. The aim was also to understand the underlying mechanism and assess the potential role of hyperglycaemic management in ICH.

Methods

The INTERACT2 cohort was divided into two groups: normoglycaemia (blood glucose level <6.5) and hyperglycaemia (blood glucose level >6.5). Baseline characteristics were summarised as mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables, and as number (%) for categorical variables. Collinearity and interactions between variables were checked. Independent associations between baseline characteristics and level of blood glucose (normoglycaemia and hyperglycaemia) and history of diabetes mellitus, were examined in multivariable logistic regression models. Adjustment was made for all significant baseline variables to determine independent predictors of hyperglycaemia. 90-day clinical outcomes studied were: death alone, major disability lone and death or major disability.

Multivariable logistic regression models adjusted by all the significant and clinically important baseline variables as well as significant interactions were used to determine associations of baseline level of blood glucose, both as continuous and categorical (fourths) variables, and clinical outcomes, as well as the association between a history of diabetes mellitus and clinical outcomes. Blood glucose data was also categorised based on diagnostics thresholds (<6.1, 6.1–7.0, >7.0 mmol/L) and sensitivity analyses were performed to further examine associations with primary outcomes. Univariate analysis was also performed to determine associations with 24 hour neurological deterioration, non-fatal adverse events and causes of death. The associations of hyperglycaemia on absolute increase in haematoma and perihaematomal oedema volumes over 24 hours were assessed by an analysis of covariance (ANCOVA) including the same adjusted variables above.

Results

Of the 2829 ICH patients, 176 were excluded because of missing baseline blood glucose measurements. Of the remaining 2653 patients, 1348 (51%) presented with hyperglycaemia (>6.5 mmol/L) and 292 (11%) had a history of diabetes mellitus. Baseline characteristics of INTERACT2 patients were compared between normoglycaemic and hyperglycaemic patients. All characteristics with significant difference on univariate analysis were included in the multivariate model. On multivariate analyses, the independent predictors of hyperglycaemia at admission were: female gender, patients outside of China, stroke severity (by National Institutes of Health stroke scale (NIHSS) score), systolic blood pressure (SBP), history of diabetes, cortical location of the haematoma, intraventricular haemorrhage (IVH) extension, and haematoma volume (ICH only). In non-diabetic patients, independent predictors were female sex, recruitment outside of China, high NIHSS score (an indicator of more severe neurological impairment), cortical location of ICH, large volume haematoma, and IVH extension. Primary and secondary outcomes were compared by admission blood glucose. There was a strong and near continuous relationship between baseline blood glucose level and death or major disability (odds ratio [OR] 1.29, 95% confidence interval [CI] 1.19-1.40; P<0.0001) and death (OR 1.23, 95%CI 1.12-1.37; P<0.0001) at 90 days, and these variables remained significant when adjusted for other confounders and significant interactions: adjusted odds ratio [aOR] 1.11, 95%CI 1.00-1.24; P<0.0001, aOR 1.16 95% CI (1.01-1.33); P=0.043 for death or major disability and death,

respectively. Quartile analysis of admission blood glucose showed significant association with poorer outcomes in the highest quartile (aOR 1.35, 95%CI 1.01-1.80, P=0.015). For secondary outcomes: early neurological deterioration, non-fatal serious adverse events and fatal serious adverse events were all significantly greater in hyperglycaemic patients. Hyperglycaemic patients had significantly higher baseline haematoma volumes, with (14.6 vs 11.6 mL, *P* <0.0001) and without intraventricular haemorrhage (11.6 vs 10.2 ml, *P* <0.01), and less deep (78.8% vs. 86.5%, *P* <0.001) and more cerebellar (5.9% vs. 1.1%, *P* <0.01) haematomas. Diabetic patients had significantly lower haematoma volume in comparison with non-diabetics (DM 9.2 mL vs. NDM 11.2 mL; p < 0.01) whilst there was no association with haematoma location or IVH extension. Hyperglycaemic patients had no difference in haematoma growth (mean adjusted, 5.1% vs 6.8%, *P* =0.13) and perihaematomal oedema (mean adjusted 86.0% vs 94.1%, *P* =0.46) in the first 24 hours.

Discussion and conclusions

Admission hyperglycaemia and history of diabetes mellitus was shown to be an independent predictor of poor outcome in patients with predominantly mild to moderate severity of ICH (INTERACT2 cohort). Significantly greater adverse events (fatal and non-fatal) and early neurological deterioration was also found in the hyperglycaemic patients. The underlying mechanism of the hyperglycaemia may be a combination of diabetic pathophysiology and the physiological stress response. This was reflected in the determinants of hyperglycaemia which included history of diabetes mellitus, haematoma characteristics (ICH volume, superficial haematoma location, IVH extension), ICH severity by NIHSS score and demographic factors (females, recruitment outside China). Interestingly, diabetic patients presented with significantly lower haematoma volumes and no association with haematoma location or IVH extension, suggesting distinct pathophysiology between diabetic hyperglycaemic and non-diabetic hyperglycaemic patients.

Whilst animal models suggest that hyperglycaemia exacerbates haematoma expansion and perihaematomal oedema, these associations were not observed in INTERACT2 analyses. However, hyperglycaemic patients did present with significantly greater IVH extension, baseline haematoma volumes, and of cerebellar and cortical location of the haematomas. More detailed

haematoma location analysis is required to determine if specific cerebral regions responsible for glucose homeostasis are affected in hyperglycaemic patients as this will reveal more about the underlying cause for hyperglycaemia. Significantly higher baseline SBP was found in hyperglycaemic patients and further analyses is required to identify the benefit of intensive blood pressure lowering in patients presenting with admission hyperglycaemia.

There are limited data and guidelines regarding the management of hyperglycaemia in ICH. Intensive insulin therapy creates the risk of hypoglycaemic events which threatens to worsen outcome. However, the results of this investigation illustrate significant association between hyperglycaemia and adverse outcomes. Based on these findings, there is justification in proceeding with a clinical trial to evaluate benefits and harms of therapy to control hyperglycaemia in ICH.

Acknowledgements

First and foremost I would like to thank my primary supervisor, Professor Craig Anderson, at The George Institute for Global Health. I met him during my first year of medical school when I embarked on this Master's degree and throughout this journey he has been a constant support. He has provided guidance, direction and motivation at every step. He has always encouraged me in my endeavours and supported my decisions over the course of this degree.

I would also like to sincerely thank my co-supervisors, Professor Hisatomi Arima and Dr Emma Heeley, who assisted me in the early stages of my research in formulating my research questions. Since then they have provided critiques and comments on all my work which has allowed me to complete this thesis.

I must also thank Dr Xia Wang who has been an immense support throughout this thesis. She has been integral in assisting with my statistical analyses. She has always been patient and available to answer my questions whilst also providing comments on how I can improve my work.

Chapter 1: Introduction

Intracerebral Haemorrhage: Burden and Aetiology

Burden of Stroke

Stroke is the second highest cause of death and the leading cause of disability and costing $2.14 billion to Australians annually. Each year there are predicted to be 60000 new and recurrent strokes. Intracerebral haemorrhage (ICH) is characterised by bleeding within the parenchyma of the brain and accounts for 10-50% of strokes and is associated with significant mortality. Globally, from 1990 to 2010, the incidence of ICH decreased in high-income countries (12%, 95% CI 6-17), whilst increased (12%, 95% CI -3 to 22) in low and middle-income countries who have a significant burden of stroke through high incidence, prevalence, mortality, disability-adjusted life years (DALYs) lost[1]. Specifically, examining stroke in high-income countries from 2000-2008, the mortality following ICH was 41.0% in comparison with ischaemic stroke (14.3%) and subarachnoid haemorrhage (SAH) (30.0%). In contrast, stroke mortality for low income countries for ICH, SAH and ischaemic stroke, was 38.7%, 43.9% and 16.7%, respectively.

A systematic review and meta-analyses by Van Asch et al.[2] assessed 36 eligible studies of the incidence, mortality and functional outcome for ICH during 1980-2008. 1-month mortality of 40.4% was reported, however, few data pertained to outcomes beyond 3-months. Functional outcomes were available for 6 of the 36 included trials, thereby requiring further data.

The specific costs of stroke subsets in the Australian population were investigated in NEMESIS study[3] and found that ICH accounted for 26% of stroke costs ($334.5 million) compared to $936.8 million (72%) attributed to ischaemic stroke. Anterior circulation ischaemic stroke were responsible for the greatest hospitalisation costs followed by ICH, however, average lifetime costs were greater in ICH and were 1.6-2 fold greater than ischaemic stroke. Similar findings were presented in a German population study[4] where the economic burden and management strategies were followed for one year post-ICH. Compared with ischaemic stroke, ICH had greater hospital and rehabilitation costs, hospitalisation periods and admission rates to intensive

care units (ICU). Gender differences have also been reported in the literature, with females associated with poorer outcomes and greater mortality[5,6] in studies with multivariate modelling.

Functional outcomes were also assessed and revealed reduced problem solving ability (47.9%), memory storage and retrieval capacity (50.9%), vision impairment (29.4%) and decreased speech comprehension (29.2%)[4]. Another investigation showed a potential association with dementia and cognitive impairment following ICH[7] with domains of executive function, episodic memory and psychomotor speed being affected. The wide range of neuropsychological and cognitive impairments associated post-ICH may contribute to the significant societal and individual burden of this disease process.

Causes of Intracerebral Haemorrhage

ICH refers to the extravasation of blood outside the cerebral vasculature into brain parenchyma. A number of risk factors and causes for ICH have been identified. The most important is hypertension. Others relate to various vasculopathies, abnormal coagulation, specific genetic markers, cerebral aneurysms, and arteriovenous malformations (AVMs). Use of specific medications, in particular anticoagulants and antiplatelet agents, also cause ICH, whilst the role of common chronic diseases such as diabetes mellitus has also been proposed yet remains debated. Age remains the most significant non-modifiable risk factor.

Hypertension

Hypertension has been established as a significant aetiological factor associated with ICH with a number of proposed mechanisms, such as oxidative stress that disrupts the cerebral circulation. Activation of the renin-angiotensin system (RAS) in hypertension leads to increased superoxide production. Animal models have shown that elevated superoxide levels were associated with greater incidence and volumes of ICH[8]. Didion et al.[9] explored the role of copper zinc superoxide dismutase in protecting against endothelial dysfunction and superoxide induced damage, whilst also reporting a concentration dependent effect of angiotensin II in causing increased superoxide levels. However, experimental models testing clinical relevance of oxidative stress in ICH found injections of superoxide dismutase yielded no reduction in neurological injury[10].

Another proposed mechanism links the pathology of hypertensive ICH through the reactive hyperplasia within the vascular smooth muscle leading to collagen type IV deposits in the endothelial wall[11]. This fibrinoid necrosis within the vasculature may alter its contractility and distribution of these pathological vessels in high-pressure regions (diencephalon, basal ganglia) may represent the association with ICH[12].

Vasculopathy

Cerebral amyloid angiopathy (CAA) is a vasculopathy where amyloid (Aβ) protein accumulates within the endothelium of cerebral vasculature specifically in cortical vessels. These proteins aggregate within the tunica media and adventitia and disease progression results in degeneration of the vessel wall. β-amyloid deposition activates matrix metalloproteinases which may further contribute to the deterioration of cerebral vasculature.[13] This fragility in cerebral blood vessels leads to microaneurysm formation and is reported to be responsible for 12-15% of lobar located ICH. Early investigations reported this vasculopathy induced ICH,[14] whilst Wagle et al.[15] through a radiographic case series, underlined CAA as a cause of ICH. More recently differences between CAA and hypertensive pathology were investigated.[16] With differing patterns of involved vasculature, the surgical management is also distinct in CAA-induced ICH.

Genetic causes of ICH and CAA

Genetic factors related to both hypertension and CAA may also contribute to the aetiology of ICH. The apolipoprotein gene APOE-ε4 has an established role in the pathology of Alzheimer's disease[17,18], however, a strong positive correlation has also been reported with CAA.[19]

The role of apolipoprotein E is to maintain cerebrovascular function, however, the APOE4 isoform results in blood-brain barrier disruption, susceptibility to uptake of neurotoxic proteins and overall neurodegeneration. Greenberg et al.[20] found that the ApoE-ε4 genotype has an independent effect, distinct from Alzheimer's disease, upon CAA as well CAA-associated ICH. This gene was further linked with 5 years earlier onset of lobar ICH in comparison with controls. The genetic correlation with CAA-induced lobar ICH has been extensively investigated and it has been proposed that ApoE-ε2 increases the incidence of vascular rupture and this effect is independent of Alzheimer's pathology. In contrast, ApoE-ε4 is associated with greater amyloid deposition in the vessel wall, atherosclerotic changes and is correlated with Alzheimer's Disease.[21]

The ApoE ε4 was also found to be independently associated with lobar ICH.[22] A Chinese population study of ICH patients found higher frequency of patients with ε3/ε4 allele compared to controls,[23] whilst the presence of either ε2 or ε4 resulted in a 28% recurrence rate in comparison to 10% for normal controls[24]. In addition, recent investigation[25] demonstrated that the ε2 genotype was also associated with haematoma expansion as observed in patients with lobar ICH. This expansion was even greater in patients with CAA indicating there may be a common mechanism between these aetiological factors.

Vascular changes and defects

The formation of aneurysms and presence of AVM are also considered significant risk factors for ICH. Although aneurysmal rupture is most commonly associated with subarachnoid haemorrhage, ICH from intracavernous carotid artery[26] and anterior ethmoidal artery[27] aneurysms have been reported. AVM are embryonic vascular malformations caused by direct anastomoses between cerebral arterial and venous vasculature. AVM increase the risk of ICH, are associated with poorer outcomes and there is a greater incidence of rupture post-ICH[28].

Haematological and coagulation disorders

Haematological disorders such as haemophilia, vitamin K deficiency, coagulation defects and von Wildebrand factor deficiency, increase bleeding risk and are therefore linked with more severe ICH. For both Haemophilia A and B spontaneous ICH is frequently reported with the neonatal risk being 40-80 times greater than the normal population[29]. Vitamin K deficiency in ICH was investigated in the Turkish population and reported 33% case mortality.[30] Specifically, coagulopathies have been linked with lobar ICH[31] and short-term mortality (1-month) was found to be significantly higher in patients with elevated bleeding profiles (International Normalised Ratio, INR). Liver dysfunction is another proposed aetiological factor of ICH possibly through effects upon platelet function and coagulation. Fujii et al.[32] examined this association and found significantly greater mortality and haematoma volumes in patients with liver dysfunction.

Diabetes mellitus

Diabetes mellitus is a metabolic disease with multi-system complications. It is a known risk factor for coronary artery disease, myocardial infarction, and ischaemic stroke, and is associated with poor outcome. However, the association with ICH is not robust. Epidemiological analyses reveal the relative risk of ICH in diabetics as 1.6 in comparison with non-diabetics[33], however,

population studies in Iran contrast these findings and show no association between ICH and diabetes mellitus.[34]

The association of diabetes mellitus with adverse outcomes following ICH has also been investigated with conflicting results. Earlier studies found significantly higher mortality rates in diabetics (54.5%) in comparison with non-diabetics (26.3%),[35] and at 7 and 30-days[36]. In contrast, prospective analysis of 1438 Chinese patients found no association with adverse outcomes.[37] Therefore, conflicting evidence exists regarding this association with further analysis required for a more comprehensive understanding.

Potential mechanisms underlying diabetes-induced ICH involve diabetic ketoacidosis (DKA) and microvascular complications. The diabetic hyperglycaemic state increases oxidative stress thereby disrupting endothelial cells and damaging microvasculature. Associated systemic inflammation also contributes to various signalling pathways which disrupt endothelial function and exacerbate neurological injury.[38] Another mechanism by which diabetes may predispose individuals to ICH is through the formation of atherosclerotic plaques in the vascular endothelium. The hyperglycaemic state results in non-enzymatic glycosylation of lipids and proteins, thereby accelerating atheroma formation.[39] With existing uncertainty in the role of diabetes mellitus in ICH, further investigation is required to explore this association and understand potential mechanisms involved.

This thesis examines the incidence of stress hyperglycaemia and its independent predictors in ICH patients (Chapter 2). It analyses outcomes of early neurological deterioration and longer term outcomes of 3-month major disability and death (Chapter 3). Comparisons of haematoma volumes, intraventricular extension and haematoma location are also explored in patients with normal and elevated admission blood glucose levels (Chapter 4). We hypothesised that patients with admission hyperglycaemia would have significantly higher incidence of early neurological deterioration and poorer longer term outcomes (death or major disability) at 3 months. Other hypotheses were that patients with admission hyperglycaemia would have more severe haematoma characteristics such as larger haematoma volume, higher rates of intraventricular extension, haematoma growth and perihaematomal oedema.

Chapter 2 - Stress hyperglycaemia and its determinants

2.1 Presentation Details

Oral Presentation at Stroke Society of Australasia (SSA) annual scientific meeting in 2016 (Brisbane)

2.2 Abstract

Determinants of hyperglycaemic response in intracerebral haemorrhage: INTERACT2 results

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Background and Purpose: Hyperglycaemia is common after acute intracerebral haemorrhage (ICH) and is associated with adverse outcomes. We aimed to identify the determinants of hyperglycaemic response among participants of the INTERACT2 study.

Methods: INTERACT2 was an international, multicentre, prospective, open, blinded endpoint, randomised controlled trial of 2839 ICH patients (<6hr) with elevated systolic blood pressure (SBP) assigned to intensive (target SBP <140mmHg) or guideline-based (SBP <180mmHg) BP management. Determinants of baseline hyperglycaemia were identified in multivariable logistic regression models.

Results: Available baseline data on blood glucose in 2653 (93%) patients showed. significant predictors of hyperglycaemia were female sex, recruitment outside China, high SBP, high NIHSS score, history of diabetes mellitus, cortical location of ICH, large haematoma volume, and intraventricular extension (all P<0.001). Independent predictors of hyperglycaemia in non-diabetic patients (n = 2361) were female sex, high SBP, recruitment outside of China, high NIHSS score, cortical location of ICH, large volume haematoma and intraventricular extension.

Conclusions: Hyperglycaemic reaction in acute ICH reflects a combination of physiological stress related to the severity of underlying disease and associated dysglycaemia from associated diabetes mellitus.

2.3 Hyperglycaemia in acute medical conditions and association with adverse outcomes

Hyperglycaemia refers to the elevation in plasma glucose and is a clinical finding that is linked with many emergency scenarios such as ICH, acute myocardial infarction (AMI), trauma and ischaemic stroke. The incidence of hyperglycaemia has further been found to be specifically associated with adverse functional outcomes and increased rates of mortality. Increased hospital mortality has been reported with increments in blood glucose and adverse outcomes seen with admission hyperglycaemia.[40] This raises the question of the mechanism and whether the stress hyperglycaemia or an underlying diabetic pathophysiology needs to be considered.

Admission hyperglycaemia has also been linked with adverse outcomes in other neurological disease processes such as traumatic brain injury where there is an association with infectious morbidity[41], severe disability and mortality[42] and acute ischaemic stroke where admission hyperglycaemia is correlated with haemorrhagic transformation[43] and adverse outcomes at 3-months[44].

The presentation of hyperglycaemia has been considered independent of diabetes as non-diabetic patients presenting to cardiac and neurosurgical units reported significantly increased mortality.[45] In critical illness, hyperglycaemia has been observed in 38% of patients, of which a significant proportion are non-diabetic. Non-diabetic hyperglycaemic patients are at greater risk of adverse outcomes with 16% mortality in comparison with 3% mortality reported in diabetic hyperglycaemic patients.[46]

In terms of functional outcomes hyperglycaemic patients also had longer hospital admission periods and were more frequently admitted into rehabilitation or extended care facilities. The adverse outcomes linked with hyperglycaemia may be related to the increased risk of infectious complications in critical illness[47,48] or the oxidative stress due to generation of oxygen free radicals.[49]

Acute myocardial infarction and cardiac surgery

Acute myocardial infarction generates a physiological stress and the resulting hyperglycaemia has been widely reported. Significantly higher in-hospital mortality has been reported in myocardial infarction patients presenting with hyperglycaemia (16%) in comparison with normoglycaemia (6%).[50] However, when dividing the hyperglycaemic group into diabetics and non-diabetics there was no significant difference in mortality. These findings were affirmed by Capes et al.[51] who demonstrated a 3.9 times greater risk of mortality in non-diabetic hyperglycaemic patients in comparison with normoglycaemic controls. This suggests that the association between hyperglycaemia and poorer outcomes is separate from diabetic pathophysiology. In myocardial infarction, potential pathways in the acute setting include activation of inflammatory cascades with increased levels of circulating interleukins, activation of T-cell differentiation and elevated inflammatory markers (C-reactive protein.[52]

The hyperglycaemia may also exacerbate the myocardial necrosis due to oxidative stress and the p66Shc protein plays an integral role in regulating the oxidative equilibrium and causing cardiac mitochondrial dysfunction.[49] This protein contributes to the production of hydrogen peroxide thereby stimulating mitochondrial apoptosis.[53] The elevated blood glucose was also correlated to increased levels of myocardial necrotic factors such as Troponin I and creatine kinase MB.[54] This suggests that the hyperglycaemia is related to the physiological stress following infarction.

Adverse outcome have been reported following cardiac surgery and infectious complications (sternal wound infections) and longer hospitalisation is reported.[55] These markers of poor outcome must also be assessed in ICH.

Direct clinical application may suggest that tighter glycaemic control would be advantageous, however, intensive insulin regimens have failed to show significant clinical benefit and resulting hypoglycaemic events must be weighed against the theoretical benefit.[56-58]

Neurological conditions

Hyperglycaemia has also been recorded in brain-related emergencies such as traumatic brain injury (TBI), acute ischaemic stroke and, most relevantly, ICH and these are linked with adverse outcomes based on morbidity and mortality.[59] Jeremitsky et al.[60] monitored blood glucose over 5 days in TBI patients and found that early hyperglycaemia was linked with poorer functional outcomes (GCS) and mortality. Independent risk factors for patients requiring neurosurgical intervention (craniotomy) for management of TBI were hyperglycaemia, age, GCS <9 and severity of TBI.[61] In this study the hyperglycaemic group had higher in-hospital mortality in comparison with normoglycaemic controls (31% vs 20%, $p < 0.02$). Paediatric TBI is another critical condition where the incidence of hyperglycaemia is associated with poor outcomes.[62,63]

Ischaemic stroke

In the context of ischaemic stroke, hyperglycaemia is observed in 20-50% of patients.[64] Specifically, higher mortality rates were reported at 30 days, 1 year and 6 years ($p <0.01$ for all).[65] These findings have been confirmed in subsequent investigations reporting worsened clinical outcomes[66] and significantly increased 28-day mortality[67]. An earlier study found no significant difference in survival or functional outcome between hyperglycaemia and normoglycaemic patients at 3 months[68], however, this had a smaller cohort encompassing all stroke subtypes (lacunar infarcts, cerebral infarcts and ICH).

ICH

A number of investigations have demonstrated the presence of hyperglycaemia in ICH.[69-71] Stress hyperglycaemia was reported in 27.3% (n=109) of patients with 45% mortality in the hyperglycaemic group in comparison with 5% mortality in normoglycaemic patients.[71] Other investigations found hyperglycaemia in 59.3% of patients at admission, with less than half of these (44%) experiencing prolonged hyperglycaemia at 72-hours. The association of hyperglycaemia and survival also shows significantly greater in-hospital and 3-month mortality.[72]

Numerous mechanisms involving oxidative stress, haematoma expansion and cerebral oedema have been discussed with respect to hyperglycaemia and ICH. Hyperglycaemic animal models have illustrated increased haematoma expansion following ICH and the proposed mechanism is via plasma kallikrein (PK). Binding of PK with collagen inhibits platelet aggregation, especially in diabetic rats. Haematoma expansion in the subarachnoid space and haematoma volume were significantly greater in diabetic rats in comparison with non-diabetic controls perhaps indicating that hyperglycaemic conditions relate with haemorrhagic expansion.[73] Further animal models have underlined the role of hyperglycaemia in causing vasogenic and cytotoxic cerebral oedema as well as perihaematomal cell death. TNF-α and possible interleukins have been suggested (IL-1β).[74] These findings of haematoma expansion were supported by Kimura et al.[70] who reported increased brain oedema in hyperglycaemic patients which may further contribute to the poor outcomes and neurological deterioration.

The clinical significance of examining hyperglycaemia in ICH is to determine whether targeting blood glucose level may be advantageous in restricting haematoma growth, perihaematomal oedema and provide more favourable outcomes. This has been investigated in animal models where intensive blood glucose lowering therapy resulted in significantly lower intracranial pressure and decreased incidence of cerebral hypoxia. Neurochemistry markers such as pyruvate, lactate and glutamate were also significantly lower in the intensive insulin management group.[75] This may lead to the decreased formation of oxidation free radicals thereby ameliorating oxidative stress upon neurons. The role of superoxide production and oxidative stress was underlined through rat models where correlation with blood-brain barrier disruption was observed.[76] The BBB disruption may lead to calcium influx, anaerobic glycolysis and cerebral parenchymal acidosis representing a possible mechanism for exacerbated neurological injury. Neurological complications following ICH may also occur as hyperglycaemia is associated with haemorrhagic transformation of ischaemic infarcts within the parenchyma of the brain.[77]

2.4 The role of insulin resistance in hyperglycaemia

Insulin is a key regulator of glucose uptake and metabolism with its actions taking effect upon muscle and adipose tissue. The role of insulin in carbohydrate metabolism is to accelerate glycolysis and induce glycogen synthesis.[78] Insulin resistance is a pathological condition where

tissue sensitivity to insulin is impaired leading to dysfunctional glucose metabolism and elevated serum glucose levels. Potential mechanisms of insulin resistance are thought to involve defects in insulin signalling involving GLUT4, PIP-3 kinase and insulin responsive substrate (IRS) proteins.[79] In the context of intracerebral haemorrhage the associations of insulin resistance with age and hypertension must be addressed.

Early investigations explored the potential role of ageing in insulin resistance by comparing young and old subjects.[80] Fink et al. compared insulin binding by examining adipose tissue biopsies in young and old patients and found no difference in binding. Insulin resistance was assessed using oral glucose tolerance testing with older subjects having higher levels of serum insulin and glucose. Based on these results, Fink et al. postulated that impaired insulin resistance may be related to the ageing process due to post-receptor defects. There were multiple limitations in this early study, with only limited baseline characteristics available to compare the young and old group and the small sample size restricting the statistical power. More recent studies suggest that insulin resistance in older patients is related to higher levels of obesity and visceral adiposity.[81]

Metabolic syndrome and its components must also be considered, specifically the relationship between insulin resistance and hypertension. Metabolic syndrome refers to inter-related conditions of insulin resistance, hypertension, dyslipidaemia and obesity all of which are significant risk factors for cardiovascular and cerebrovascular disease.[82] The relationship between hypertension and insulin resistance has been studied extensively through animal models, genetic studies and clinical investigations. Studies of glucose metabolism in the hypertensive rat model display impairment in insulin mediated glucose transport when compared with controls.[83] Genome wide scanning has also revealed potentially common loci for diabetes and hypertension.[84]

Therefore, when studying the role of acute hyperglycaemia in intracerebral haemorrhage the interplay with existing insulin resistance must be considered. History of diabetes mellitus represents insulin resistance, however, does not account for undiagnosed diabetes mellitus, impaired fasting glucose and impaired glucose tolerance. In the INTERACT2 study population

the history of hypertension is relatively high (72.8%) and the median age is 63.3 years (see Table 1) with these factors potentially contributing to insulin resistance. History of diabetes (11.0%) is also recorded and adjusted for in the analyses as will be described later, however, undiagnosed diabetes and impaired insulin resistance is difficult to account for. Whilst acute hyperglycaemia may reflect the physiological stress response to the neuronal injury of ICH, mechanisms of insulin resistance driven by ageing, obesity and hypertension may also be critical in the elevated glucose levels recorded.

The relationship of insulin resistance in ischaemic stroke has been well-established; however, current evidence is conflicting in intracerebral haemorrhage. In ischaemic stroke insulin resistance is now being considered as a therapeutic target as part of secondary prevention (IRIS trial).[85] This trial assessed the potential to treat insulin resistance with pioglitazone to reduce recurrence of vascular events. Patients with insulin resistance and a history of stroke or TIA in the preceding 6 months were included and pioglitazone therapy was shown to reduce recurrent stroke and major vascular events.[86] Whilst the association of insulin resistance with intracerebral haemorrhage is still controversial, further investigation into this association is warranted.

2.5 Hyperglycaemia and post-ICH outcome

Recent studies have reported that hyperglycaemia is an independent predictor of mortality[59,70] and adverse functional recovery based on the modified Rankin scale (mRS).[87] The functional status was characterised into favourable (mRS <3) and poor outcome (mRS ≥3). Elevated blood glucose was associated with poor functional recovery in non-diabetic patients, whilst increased mortality was found in both diabetic and non-diabetic patients. Tertile and quartile analysis of admission blood glucose further reveals increased risk of mild, moderate and severe handicap.[88]

Therefore, current literature provides contrasting evidence with regards to the incidence, outcomes and management of hyperglycaemia in ICH. INTERACT2 with its significant cohort size, data on admission blood glucose and record of death and major disability over 3-months allows these questions to be adequately addressed.

Determinants of hyperglycaemia in INTERACT2

The incidence of hyperglycaemia and association with poor outcomes in acute illness has been extensively described above. However, the mechanisms involved are not clearly understood. Specifically in ICH the relationship of hyperglycaemia with demographic, biochemical and clinical factors needs to be explored. Determinants of hyperglycaemia have been investigated in myocardial infarction, cardiac surgery and hepatic steatosis with the associated physiological stress resulting in elevated blood glucose levels. The uncertainty is whether hyperglycaemia is due to physiological stress or due to pre-existing glucose intolerance and undiagnosed DM.

Ladeira et al.[54] examined the predictors of hyperglycaemia in myocardial infarction with multivariate models showing myocardial necrosis, history of diabetes mellitus and glucose metabolism (HbA1c, insulin levels) to be significantly associated with hyperglycaemia. To effectively assess whether diabetic pathophysiology or stress hyperglycaemia is the key mechanism markers of glucose metabolism were studied in patients without diabetes mellitus. Stratifying these patients into HbA1c (<5.7, 5.-6.4, >6.4) it was found the admission blood glucose was significantly greater with higher HbA1c groups. This suggests that undiagnosed diabetes mellitus and glucose intolerance may be the driving mechanism in hyperglycaemia. Further, diabetes mellitus was the strongest determinant of hyperglycaemia in this investigation (odds ratio [OR] 27, 95 confidence interval [CI] 3.7-195.7;, P=0.001). On the other hand, the significant association with myocardial necrosis (measured through CK-MB and troponins) reported (OR 21.9, 95%CI 1.3-360.9; P=0.03) supports the stress mechanism where the more critical condition induces a greater glycaemic response.

The hyperglycaemic mechanism has also been explored in patients undergoing cardiac catheterisation.[89] Four groups of analysis were: patients without diabetes mellitus or acute coronary syndromes (ACS), diabetes mellitus and ACS, diabetes mellitus only, and ACS only. Again the strongest association with hyperglycaemia was seen in the diabetes mellitus group (OR 9.4, 95%CI 3.9-22.4; P<0.001) whilst ACS was also independently associated with hyperglycaemia (OR 4.6, 95%CI 2.3-9.0; P<0.001). Whilst Ladeira et al.[54] excluded diabetic patients from their study, this investigation excluded patients with HbA1c $\geq$ 6.5% to assess the minimise interaction from patients with chronic hyperglycaemia and poor diabetic control.

Retrospective analysis of cardiac surgery patients also examined predictors of hyperglycaemia.[90] More comprehensive exclusion criteria was applied, excluding patients with HbA1c ≥6.5%, known diabetes mellitus, pre-operative random BSL ≥200 mg/dL and patients taking diabetic medications. Continuous BSL was monitored 4 hourly for a 72-hour period rather than baseline BSL used in other investigations. Results from this study showed multiple determinants of hyperglycaemia including: age, gender, body mass index, clinical parameters such as left ventricular ejection fraction and previous cardiac surgery. Pre-operative cardiogenic shock was another independent predictor of hyperglycaemia which supports the stress mechanism where activation of shock-related stress hormones may play a role in the elevated BSL. Other reported predictors of hyperglycaemia in cardiac surgery include ACE inhibitors[91] and pre-existing metabolic syndrome[92].

Determinants of hyperglycaemia in acute stroke (ischaemic and ICH) include stroke severity, infarct size whilst there is conflicting evidence regarding the role of neuroendocrine hormones. Early studies divided patients into normoglycaemia, known diabetes, newly diagnosed diabetes and non-diabetic hyperglycaemia.[93] Whilst no association was found with lesion site and stroke severity (Toronto stroke scale) was significantly greater in non-diabetic hyperglycaemic patients. Significant association between infarct size and hyperglycaemia has also been reported in ischaemic stroke.[93,94] Previous investigations have also discussed the role of the neuroendocrine hormones in the stress hyperglycaemic response. O'Neill et al.[95] found that insulin, glucagon, cortisol but not catecholamines (epinephrine, norepinephrine) were significantly associated with BSL, however, this was on univariate analysis with a small cohort (n=23) and part of a single-centre study.

The INTERACT2 study allows a similar assessment to be conducted for ICH. Whilst severity of AMI was linked with markers of myocardial necrosis (CKMB), in ICH haematoma characteristics such as volume and IVH extension represent the severity. As history of diabetes was recorded at admission this association can also be explored in the INTERACT2 cohort.

Methods

The INTERACT2 trial included 2839 patients assigned to intensive or guideline-recommended antihypertensive therapy. Demographic and clinical characteristics recorded at the time of enrolment included a history of diabetes mellitus and level of blood glucose. Stroke severity was

measured using the GCS and National Institutes of Health stroke scale (NIHSS) at baseline, 24 hours, and at Day 7 (or upon discharge from hospital if this occurred earlier). History recorded at baseline also included: past medical history (hypertension, heart disease, prior ICH, prior undifferentiated stroke) and current medications (insulin or glucose lowering therapy, aspirin or antiplatelet agents, warfarin or anticoagulation, antihypertensive therapy). Clinical measurements of systolic and diastolic BP, GCS score and demographic details of age, gender and recruitment centre were also recorded. Using CT analysis haematoma characteristics of haematoma volume, location and IVH extension were assessed.

Baseline characteristics were summarized as mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables, and as number (%) for categorical variables. Collinearity and interactions between variables were checked. Independent associations between baseline characteristics and level of blood glucose, defined as normoglycaemia (<6.5 mmol/L) or hyperglycaemia (≥6.5 mmol/L), and with a history of diabetes mellitus, were examined in multivariable logistic regression models with all significant baseline variables. These multivariable analyses were performed for the entire cohort (n = 2839) and in non-diabetic patients (n = 2361).

Results

Of the 2829 ICH patients, 176 were excluded because of missing baseline blood glucose measurements. Table 1 shows the baseline characteristics of the remaining 2653 patients, which included 1348 (51%) with hyperglycaemia (>6.5 mmol/L) and 292 (11%) with diabetes mellitus. On univariate analysis hyperglycaemic patients were significantly more often female, from outside of China, had greater cortical haematomas, diabetes mellitus, higher SBP, greater clinical severity of stroke, and larger haematomas with IVH extension. No collinearity was found between the baseline variables. All significant interactions (age x NIHSS ≥15, China x IVH extension, baseline haematoma volume x deep location of haematoma, and deep location of haematoma x IVH extension) were included in the multivariable analyses. This showed that female gender, patients outside of China, stroke severity (by NIHSS), SBP, history of diabetes, cortical location of haematomas, IVH extension and haematoma volume (ICH only) were significant independent predictors of hyperglycaemia (Table 1). In non-diabetic patients

independent predictors were female sex, recruitment outside of China, high NIHSS score, SBP, cortical location of ICH, large volume haematoma and IVH extension (Table 2).

Discussion

Our multivariate analysis identified the determinants of hyperglycaemia in the INTERACT2 cohort. Key demographic predictors were females and patients recruited from outside China, whilst age was only significant in univariate analyses. The two important clinical parameters were stroke severity and baseline SBP. Univariate associations of hyperglycaemia with history of hypertension and heart disease did not remain after multivariate adjustment, whilst DM is found to be the strongest independent predictor of baseline hyperglycaemia. The critical haematoma characteristics that are also significant predictors are haematoma location (cortical), IVH extension and ICH volume.

These results confirm previous investigation by Passero et al.[96] (n=764) who identified haematoma volume, IVH extension and initial mean arterial pressure (MAP) as well as GCS (only in univariate INTERACT2 analyses) as independent predictors of hyperglycaemia in univariate analysis only without adjustment for diabetes mellitus. Fogelholm et al.[97] found hyperglycaemia in non-diabetic patients was predicted by haematoma volume, midline shift of cerebral structures and high MAP. Our study showed significant association between hyperglycaemia and SBP in non-diabetic patients, confirming these earlier findings.

IVH was also examined in INTERACT2 and aligns with previous investigation by Appelboom et al.[72]. This study specifically examined the relationship between IVH and hyperglycaemia with IVH categorised based on the IVH score[98], a popular rating scale of clinical severity and prognosis in ICH. Determinants of hyperglycaemia in this study (n=104) were diabetes mellitus and IVH score with a linear relationship reported between admission blood glucose levels and the IVH score (multivariate analyses). Accordingly, greater IVH severity is associated with a more severe hyperglycaemic state. This may support the stress hyperglycaemia hypothesis whereby the driver of the glucose levels is the severity of the neurological injury. Other haematoma characteristics such as haematoma volume and location were not determinants of hyperglycaemia in multivariate analyses unlike INTERACT2 findings. Our much larger, multi-centre investigation suggests that a number of haematoma characteristics (volume, location, IVH

extension) are all significantly associated with admission hyperglycaemia and need to be individually examined to understand the mechanism and the impact upon survival outcomes.

Table 2.1: Baseline characteristics by admission blood glucose in INTERACT2 cohort; multivariate analyses

	All (N=2653)	Glucose<6.5 (N =1305)	Glucose≥6.5(N=1348)	*P value*	*Adjusted OR*	*P value*
Age, median(IQR)*	63.3(54.4-73.8)	62.1(53.8-72.3)	64.5(54.9-75.1)	<0.0001		
Male sex*	1655(62.4)	863(66.1)	792(58.8)	<0.0001	0.74(0.62-0.88)	0.0006
Recruited from China*	1764(66.5)	943(72.3)	821(60.9)	<0.0001	0.74(0.61-0.88)	0.0009
GCS, median (IQR)	14(13-15)	14(13-15)	14(12-15)	<0.0001		
Time to randomisation, hours	3.7(2.8-4.7)	3.7(2.8-4.6)	3.7(2.8-4.8)	0.54		
NIHSS, median (IQR)*	11(6-16)	9(5-14)	12(7-16)	<0.0001	1.03(1.01-1.04)	0.0004
Systolic BP, mmHg, mean(SD)*	179.0(17.0)	177.2(16.9)	180.0(16.8)	<0.0001	1.01(1.01-1.02)	0.0001
Diastolic BP, mmHg, mean±SD	100.9±14.6	101.2±14.1	100.6±15.2	0.27		
History of hypertension*	1928(72.8)	922(70.7)	1006(74.7)	0.0197		
Current use of antihypertensive therapy	1209(45.6)	556(42.6)	653(48.5)	0.0024		
Heart disease*	287(10.8)	115(8.8)	172(12.8)	0.0011		
Prior intracerebral haemorrhage	217(8.2)	105(8.1)	112(8.3)	0.80		
Prior ischaemic or undifferentiated stroke	302(11.4)	145(11.1)	157(11.7)	0.66		
History of diabetes*	292(11.0)	46(3.5)	246(18.3)	<0.0001	5.91(4.21-8.31)	<0.0001
Use of warfarin anticoagulation	77(2.9)	31(2.4)	46(3.4)	0.11		
Use of aspirin or other antiplatelet agent*	260(9.8)	95(7.3)	165(12.3)	<0.0001		
Insulin therapy or glucose lowering treatment	179(6.8)	31(2.4)	148(11.0)	<0.0001		
Deep location of haematoma§*	2036(83.0)	1052(86.8)	984(79.4)	<0.0001	0.51(0.40-0.65)	<0.0001
IVH Extension*	685(27.9)	264(21.8)	421(34.0)	<0.0001	1.77(1.46-2.14)	<0.0001
Haematoma volume at baseline, mL, median (IQR)						
ICH*	10.9(5.7-19.5)	10.2(5.4-17.0)	11.6(6.2-21.9)	<0.0001	1.01(1.00-1.02)	0.0068
Combined (ICH+IVH)	13.1(6.4-23.8)	11.6(5.9-20.0)	14.6(7.0-28.0)	<0.0001		

Data are n(%), mean (SD), or median (IQR)
§ Deep location refers to location in the basal ganglia or thalamus.
P values are based on chi-squared, t-test or Wilcoxon rank sum test.
*****all significant univariate variables were put into the multivariable model. We reduced the full model by successively removing the nonsignificant covariates until all the remaining predictors remained statistically significant (P<0.05).

Table 2.2: Baseline characteristics by admission blood glucose in Non-diabetic Patients

	Glucose<6.5 (N =1259)	Glucose≥6.5(N=1102)	*P value*	*Adjusted OR*	*P value*
Age, mean(SD)	62.4(12.6)	64.3(13.2)	0.0007		
Male sex	833(66.2)	634(57.5)	<0.0001	0.71(0.60-0.86)	0.0003
Recruited from China	920(73.1)	702(63.7)	<0.0001	0.71(0.59-0.86)	0.0004
GCS, median (IQR)	14(13-15)	14(12-15)	<0.0001		
Time to randomization, hours	3.7(2.8-4.6)	3.7(2.8-4.8)	0.35		
NIHSS, median (IQR)	9(5-14)	12(7-17)	<0.0001	1.03(1.02-1.05)	<0.0001
Systolic BP, mmHg, mean(SD)	177.2(16.9)	180.0(16.8)	<0.0001	1.01(1.01-1.02)	0.0001
Diastolic BP, mmHg, mean(SD)	101.5(14.0)	101.2(15.3)	0.0038		
History of hypertension	884(70.3)	793(72.1)	0.33		
Current use of antihypertensive therapy	523(41.6)	490(44.6)	0.15		
Heart disease	109(8.7)	118(10.7)	0.092		
Prior intracerebral haemorrhage	100(8.0)	89(8.1)	0.90		
Prior ischaemic or undifferentiated stroke	137(10.9)	116(10.6)	0.79		
Use of warfarin anticoagulation	29(2.3)	31(2.8)	0.43		
Use of aspirin or other antiplatelet agent	89(7.1)	106(9.6)	0.0243		
Insulin therapy or glucose lowering treatment	6(0.5)	5(0.5)	0.94		
Deep location of haematoma§	1015(87.0)	790(78.1)	<0.0001	0.47(0.37-0.60)	<0.0001
IVH Extension	253(21.7)	345(34.1)	<0.0001	1.81(1.48-2.20)	<0.0001
Haematoma volume at baseline, mL, median (IQR)	10.2(5.5-17.1)	12.2(6.5-23.5)	<0.0001	1.01(1.00-1.02)	0.0093

Data are n(%), mean (SD), or median (IQR)
§ Deep location refers to location in the basal ganglia or thalamus.
P values are based on chi-squared, t-test or Wilcoxon rank sum test.
*****all significant univariate variables were put into the multivariable model. We reduced the full model by successively removing the nonsignificant covariates until all the remaining predictors remained statistically significant (P<0.05).

Chapter 3: Prognostic significance of hyperglycaemia in acute intracerebral haemorrhage

3.1 Publication Details

Saxena A, Anderson CS, Wang X, Sato S, Arima H, Chan E, Muñoz-Venturelli P, Delcourt C, Robinson T, Stapf C, Lavados PM, Wang J, Neal B, Chalmers J, Heeley E. Prognostic Significance of Hyperglycaemia in Acute Intracerebral Haemorrhage: The INTERACT2 Study. Stroke; a journal of cerebral circulation 2016;47:682-8.

3.2 Author contributions

AS contributed to data analysis, wrote the first draft of the manuscript, drafted the response to reviewers' comments and prepared the final draft of the manuscript for publication. XW performed statistical analyses and contributed to statistical design of the study. CSA supervised the analyses, contributed to the concept and rationale of the study, assisted in reviewer responses and preparing the final draft. SS, HA, EC, PMV, CD, TR, PML, JW, BN, JC and EH provided comments on data interpretation and the manuscript.

3.3 Abstract

Background and Purpose: We aimed to determine associations of baseline blood glucose and diabetes mellitus with clinical outcomes in participants of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2).

Methods: INTERACT2 was an international prospective, open, blinded endpoint, randomised controlled trial of 2839 patients with spontaneous ICH (<6 hr) and elevated systolic blood pressure (SBP) randomly assigned to intensive (target SBP <140 mmHg) or guideline-based (SBP <180 mmHg) BP management. Associations of hyperglycaemia at presentation (>6.5 mmol/L) and combined and separate poor outcomes of death and major disability (scores of 3-6, 3-5, and 6, respectively, on the modified Rankin scale) at 90 days were determined in logistic regression models.

Results: In 2653 patients with available data, there were 1348 (61%) with hyperglycaemia and 292 (11%) with diabetes mellitus. Associations of baseline blood glucose and poor outcome

were strong and near continuous. After adjustment for baseline variables, the highest fourth (7.9-25.0 mmol/L) of blood glucose was significantly associated with combined poor outcome (adjusted odds ratio [aOR] 1.35, 95% confidence interval [CI] 1.01-1.80; P trend 0.015). Diabetes mellitus also predicted poor outcome (aOR 1.46, 95% CI 1.05-2.02; P = 0.023) though more important for residual disability than death on separate analysis.

Conclusions: Hyperglycaemia and diabetes mellitus are independent predictors of poor outcome in patients with predominantly mild to moderate severity of ICH. These data support guideline recommendations for good glycaemic control in patients with ICH.

Clinical Trial Registration - URL: http://clinicaltrials.gov. Unique Identifier: NCT00716079

3.3 Manuscript

Introduction

Acute ICH is the most serious and least treatable form of acute stroke[99] for which established prognostic factors include clinical severity and location and volume of haematoma at presentation.[100] While stress hyperglycaemia is associated with adverse outcomes in many medical conditions, including acute ischaemic stroke,[101,102] traumatic brain injury[63] and acute myocardial infarction,[50] evidence specifically related to the critical condition of ICH is varied and conflicting due to previous studies being limited to small single centre series[72,88] with short duration of follow-up.[103] Animal models have shown that elevated BP exacerbates cerebral injury following ICH[104] and have explored associations between hyperglycaemia and cerebral oedema. There may be a supra-additive effect of hyperglycaemia and the hypertensive response in ICH on outcome. The purpose of this study was to quantify risk associations of hyperglycaemia and diabetes mellitus among participants of the INTERACT2.[105] Our hypothesis was that hyperglycaemia is associated with poor outcome in ICH.

Materials and Methods

INTERACT2 was an international, multicentre, prospective, open-label, assessor-blinded end-point, randomised controlled trial, the details of which are described elsewhere.[105] In brief, 2839 patients with CT-confirmed spontaneous ICH within 6 hours of onset and elevated systolic BP (SBP, 150-220 mmHg) were randomly assigned to receive intensive (target SBP <140 mmHg within 1 hour) or guideline-recommended (target SBP <180 mmHg) BP lowering therapy using

locally available agents according to standardised protocols. The study protocol was approved by the appropriate ethics committee at each participating site, and written informed consent was obtained from the patient or an appropriate surrogate.

Demographic and clinical characteristics recorded at the time of enrolment included a history of diabetes mellitus and level of blood glucose. Stroke severity was measured using the Glasgow coma scale (GCS) and National Institutes of Health stroke scale (NIHSS) at baseline, 24 hours, and at Day 7 (or upon discharge from hospital if this occurred earlier). For each CT scan, uncompressed digital images were sent to a central analysis laboratory in DICOM format on a CD-ROM identified only with the patient's unique study number. Haematoma volumes with and without inclusion of any IVH component were calculated independently by trained scientists who were blind to clinical data, treatment, and date and sequence of scan. This calculation was done with computer-assisted multi-slice planimetric and voxel threshold techniques in MIStar software (version 3.2) (Apollo Medical Imaging Technology, Melbourne, Australia). Inter-reader reliability was checked by periodic re-analysis of the scans (15%) throughout the study to avoid drift (intraclass correlation coefficients 0.92).

The primary clinical outcome was death or major disability, defined by scores 3-6 on the modified Rankin scale (mRS) at 90 days.[106] Secondary outcomes were separately those of death and major disability (mRS score of 6 and 3-5, respectively), and serious adverse events including early neurological deterioration (defined as an increase of ≥4 on the NIHSS or a decline of ≥2 on the GCS from baseline to 24 hours post-randomisation). Primary causes of death were classified into 3 categories: (i) direct effects of initial ICH, defined as any death after the onset of the randomised ICH event in a patient who had progressive neurological deterioration and either the baseline or follow-up brain scan showed haematoma with mass effect, midline shift, or significant extension of initial haematoma in the absence of a clear extra-cranial cause for the death; (ii) recurrent cardiovascular event, defined by clear clinical evidence of a recurrent stroke, coronary vascular event, or sudden death, according to standard definitions; (iii) other causes, defined by clear evidence of death due to a non-neurological cause that included pneumonia, sepsis, or injury.

Baseline characteristics were summarized as mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables, and as number (%) for categorical variables.

Collinearity and interactions between variables were checked. Independent associations between baseline characteristics and level of blood glucose, defined as normoglycaemia (<6.5 mmol/L) or hyperglycaemia (≥6.5 mmol/L), and with a history of diabetes mellitus, were examined in multivariable logistic regression models with all significant baseline variables. Curves of predicted 90-day outcomes according to baseline glucose level were constructed using predicted values and 95% confidence intervals (CI) from the univariate logistic regression models. Multivariable logistic regression models adjusted by all the significant and clinically important baseline variables as well as significant interactions were also used to determine associations of baseline level of blood glucose, both as continuous and categorical (fourths) variables, and clinical outcomes, as well as the association between a history of diabetes and clinical outcomes. Sensitivity analyses were conducted to examine clinical outcomes based on diagnostic thresholds of blood glucose for normoglycaemia, pre-diabetes, and diabetes mellitus (<6.1, 6.1–7.0, >7.0 mmol/L, respectively). Cox proportional hazard modelling was used to measure survival over 90-days post-ICH. The associations of hyperglycaemia on absolute increase in haematoma and perihaematomal oedema volumes over 24 hours were assessed by an analysis of covariance (ANCOVA) including the same adjusted variables above. Data are presented with odds ratios (OR) and 95%CI. A two sided P value <0.05 was set as the level for statistical significance. All statistical analyses were performed using SAS version 9.3 (SAS institute, Cary, NC, USA).

Results

Of the 2829 ICH patients, 176 were excluded because of missing baseline blood glucose measurements (Figure 1). Table 1 shows the baseline characteristics of the remaining 2653 patients, which included 1348 (51%) with hyperglycaemia (>6.5 mmol/L) and 292 (11%) with diabetes mellitus. After adjusting for confounding factors, hyperglyacemic patients were significantly more often female, from outside of China, had greater cortical haematomas, diabetes mellitus, higher SBP, greater clinical severity of stroke, and larger haematomas with intraventricular haemorrhage (IVH) extension. Whereas patients who presented with a history of diabetes mellitus tended to be older, more often from outside China, had lower diastolic BP, greater history of hypertension, heart disease, and use of antihypertensive, antiplatelet and warfarin anticoagulation therapies, and with lower haematoma volume than those patients without diabetes mellitus (Table 2).

No collinearity was found between the baseline variables. All significant interactions (age x NIHSS ≥15, China x IVH extension, baseline haematoma volume x deep location of haematoma, and deep location of haematoma x IVH extension) were included in the multivariable analyses. There was a strong and near continuous relationship between baseline blood glucose level and death or major disability (OR 1.29, 95%CI 1.19-1.40; P<0.0001) and death (OR 1.23, 95%CI 1.12-1.37; P<0.0001) at 90 days and they were still significant after adjusted by confounders and significant interactions: adjusted odds ratio [aOR] 1.11, 95%CI 1.00-1.24; P<0.0001, aOR 1.16 95% CI (1.01-1.33); P=0.043 for death or major disability and death, respectively (Figure 2). Table 3 shows that the combined poor outcome of death or major disability was significantly greatest for the highest fourth of baseline blood glucose (aOR 1.35, 95% CI 1.01-1.80; P trend 0.015). Similar trends were evident for death (P trend 0.062) and major disability (P trend 0.041). The trends are also similar after removing the variable of randomised lowering treatment from the multivariate model (Table 4). A history of diabetes mellitus (Table 5) was significantly associated with death or major disability (aOR 1.46, 95% CI 1.05-2.02; P = 0.023) and major disability (aOR 1.51, 95% CI 1.08-2.12; P = 0.017), but not for death alone (aOR 0.96, 95% CI 0.62-1.51; P = 0.87). For diagnostic thresholds of blood glucose, significant trend was found for death or major disability (P = 0.01) and major disability (P = 0.031). In patients with admission blood glucose >7.0 mmol/L, there was significantly greater association with poor outcome (aOR 1.36, 95% CI 1.08-1.71) (Table 6). Adjusted Cox regression models indicate increasing risks of death by increasing (fourths) levels of baseline blood glucose (Figure 3a), although this association did not appear independent of diabetes mellitus (Figure 3b). In regard to reported serious adverse events (Table 7), hyperglycaemic patients had significantly greater frequency of early neurological deterioration (16.5% vs. 13.1%; P = 0.014), death (14.4% vs. 8.9%; P <0.0001) and non-fatal adverse events (25.5% vs. 20.6%; P = 0.003) in comparison with normoglycaemic patients. However, there was no apparent difference in the frequencies of fatal and non-fatal ischaemic, cardiovascular or infectious events between the two groups of patients, but these numbers were small. Patients with a history of diabetes mellitus experienced significantly more non-fatal serious adverse events, particular of major cardiovascular events, during follow-up, but the frequency of early neurological deterioration or deaths from the initial ICH was similar to those without diabetes mellitus (Table 8). There was a trend toward higher glucose levels among patients with higher baseline haematoma and perihaematomal oedema

volumes (Table 9 and 10, respectively). However, there was no significant difference of increase in either hematoma and perihaematomal oedema volumes between patients with admission glucose <6.5 or ≥6.5 mmol/L. These relationships are further explored in Chapter 4.

Discussion

This study shows that elevated blood glucose levels and diabetes mellitus both predict serious outcomes in patients with predominantly mild to moderate severity of acute ICH. Hyperglycaemia appears to influence prognosis of the acute event, increasing the risks of early neurological deterioration and death directly from the ICH, but without any apparent effect on growth in either haematoma or perihaematomal oedema over 24 hours (Chapter 4). Further, a near continuous association was evident between the level of blood glucose at presentation and the separate and combined outcomes of death and major disability over the subsequent 90 days. Moreover, the association was not affected by randomised BP lowering treatment. While diabetes mellitus was also associated with poor outcome, this appears to relate more to effects on residual disability and increased risks of future cardiovascular events rather than through a direct effect on the initial event.

Our findings extend previous reports of elevated blood glucose being a predictor of adverse outcomes in ICH.[70,88,97,103] In particular, the finding of a trend towards greater mortality from hyperglycaemia that was observed in Korean multi-centre study[103] of 1387 ICH patients, but not with that seen in a smaller Finnish study.[97] Sensitivity analysis of outcomes based on diagnostic thresholds (reference group <6.1 mmol/L) of blood glucose rather than fourths (reference group of 2.6–5.6 mmol/L) potentially allowed more clinically relevant glucose levels to be assessed. Specifically, the patient groups with admission glucose levels <6.1 and 6.1–7.0 mmol/L had less adverse outcomes than those with admission levels >7.0 mmol/L.

In contrast to previous studies that have defined critical prognostic thresholds of hyperglycaemia, such 8[107] or 10 mmol/L,[72] we have shown no threshold but rather a strong continuous relationship between admission blood glucose and poor outcome in the INTERACT2 dataset. The multivariable analyses indicate that these associations are specific to hyperglycaemia rather than that of the pathophysiology of diabetes mellitus. In contrast to previous studies showing that diabetes mellitus is an independent predictor of mortality after acute ischaemic stroke,[108] and

for in-hospital[35] and 1[36] and 3 months[69,96,109] time points after ICH, we did not find that diabetes mellitus predicted death after ICH.

The exact pathophysiological mechanisms underlying the adverse effects of hyperglycaemia in ICH are yet to be elucidated. Hyperglycaemia has been shown to induce neuronal apoptosis in experimental ICH in adult Sprague-Dawley male rats,[110] but other reactions from inflammatory (interleukin-1β and tissue necrosis factor alpha)[111,112] and toxic (cerebral lactate and lactate/pyruvate ratios)[113] effects of oxygen free radical generation[114] may also be important. Elevated white blood cells have been found to be positively correlated with glucose levels in ICH and are also an independent predictor of poor outcome.[115] The leucocytosis may represent an inflammatory response caused by the hyperglycaemia and may exacerbate further neurological injury.

Recent studies have also shown increased superoxide production, disruption of the blood-brain barrier,[76,116] and enhanced cerebral oedema[74] in hyperglycaemic rat models. Moreover, the study of Parsons et al.[117] in patients with ischaemic stroke has shown an association of hyperglycaemia and brain lactate and penumbral damage, quantified by magnetic resonance imaging with spectroscopy, which suggests there could be a similar mechanistic pathway in ICH.

Whatever the mechanism, our data lend support guideline recommendations for good glycaemic control in ICH[118] and suggest that a blood glucose level of <7.0 mmol/L may be an optimal therapeutic target despite the absence of randomised evidence. In the United Kingdom Glucose Insulin in Stroke Trial (GIST-UK),[119] there was no effect of glucose-potassium-insulin compared to saline over the initial 24 hours on mortality in 933 patients with stroke (including 114 with ICH) when the trial was stopped early because of slow enrollment. Moreover, a meta-analysis of randomised controlled trials comparing glycemic control by insulin with usual care in patients with ischaemic stroke also showed no benefit regarding mortality or functional outcome and increased risk of hypoglycaemic events, suggesting the potential harmful effects of intensive glycaemic control to vulnerable ischaemic penumbra.[120] However, there are still significant uncertainties regarding optimal glucose levels and glycaemic control methods in acute stroke, especially in ICH which distinct pathophysiological mechanisms from ischaemic stroke.

Strengths of our study include the large and heterogeneous patient population which had rigorous prospective and systematic evaluations early after the onset of acute ICH. However, as these

analyses were not pre-specified, they are open to chance or biased associations, and therefore the findings require further validation. Another limitation is that they are based on single measurements of blood glucose and thus prone to regression dilution bias as well as some misclassification bias with respect to diabetes mellitus status since this was based only on a history of the condition at presentation. Although our study had a much lower frequency of diabetes mellitus (11%) than has been reported in other studies (14-23%),[72,88,96] many of the participants were from China where the frequency of obesity and diabetes mellitus is lower than in the west. Finally, as the INTERACT studies excluded patients with a high likelihood of early death and planned surgical evacuation of haematoma, these findings may not be applicable to patients with severe ICH.

In summary, our study has shown that hyperglycaemia has strong and continuous associations with poor outcomes from predominantly mild to moderate severity of ICH. Hyperglycaemia appears to have a direct deleterious effect on the initial ICH, whereas diabetes mellitus reduces the potential for recovery and increases the risk of subsequent cardiovascular events. In the absence of randomised evidence, these findings support current guidelines recommending treatment of hyperglycaemia in ICH.[121]

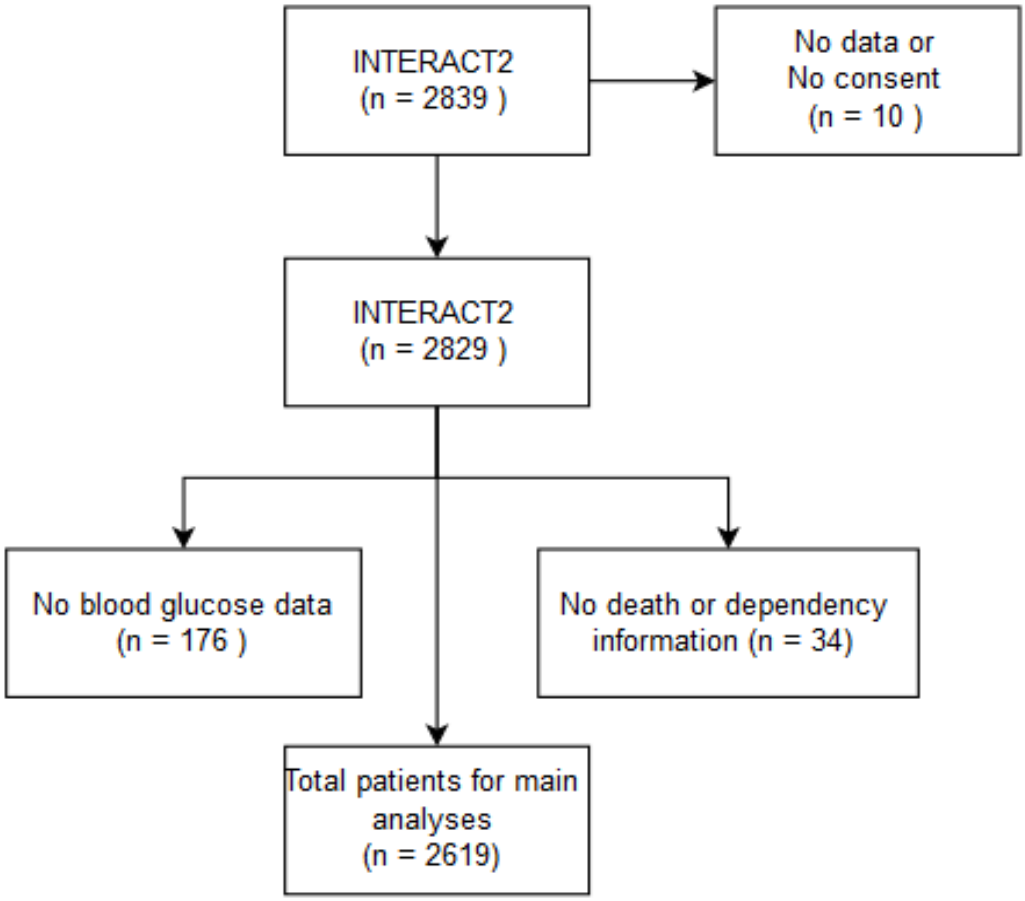

Figure 1: Patient flow in INTERACT2 study and admission blood glucose analysis

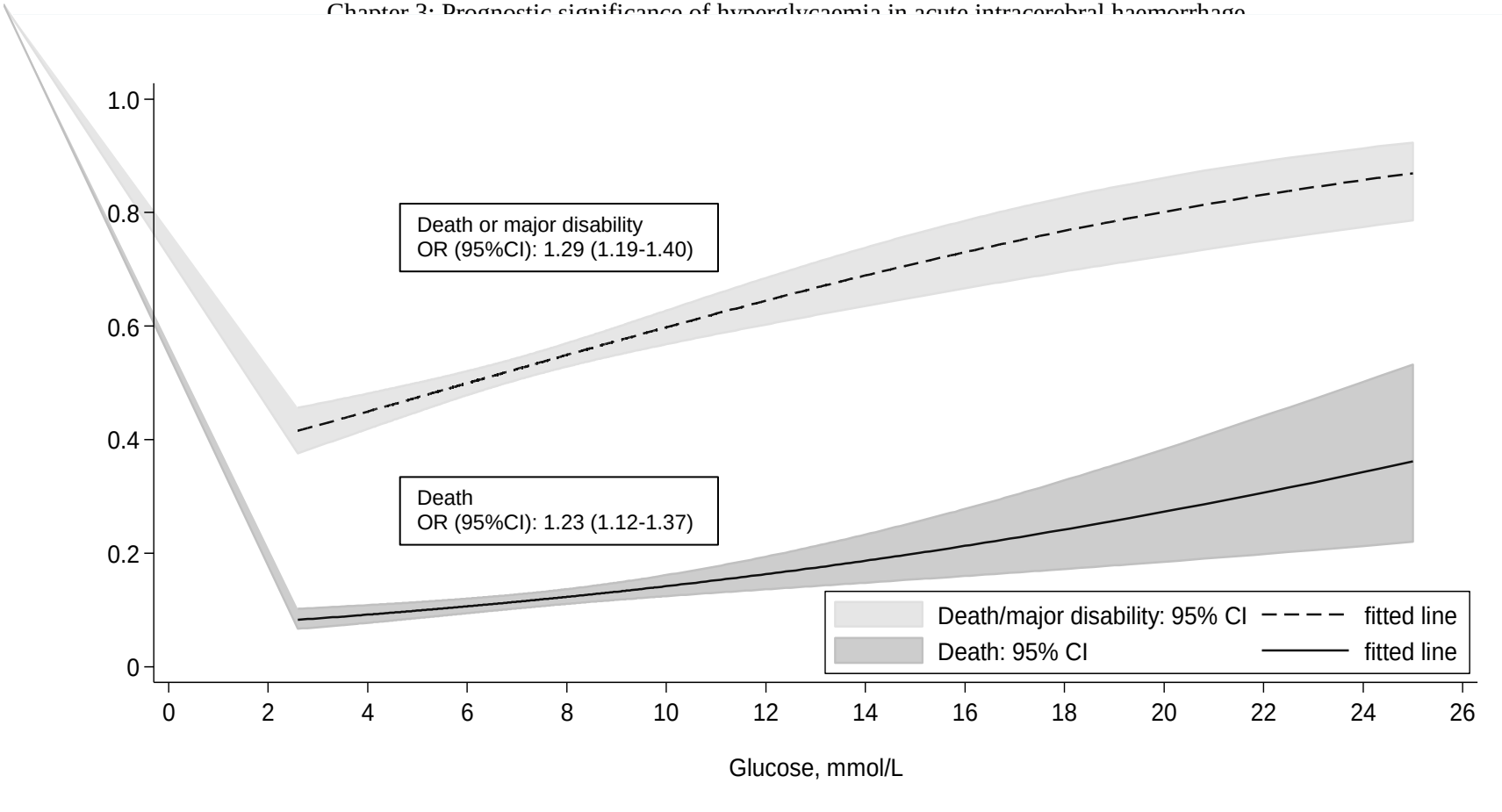

Figure 2: Predicted probabilities of outcome by baseline blood glucose level

OR represents odds ratio for outcome; 95% CI represents 95% confidence interval; AOR represents adjusted odds ratio of outcome.

Multivariate model adjusted for age, geographical region, gender, history of heart disease, history of hypertension, history of diabetes mellitus, use of aspirin or warfarin, baseline haematoma volume and location, intraventricular extension, baseline systolic blood pressure, admission National Institutes of Health stroke scale (score ≥15), randomised treatment, age x NIHSS≥15, china x intraventricular extension, baseline haematoma volume x deep location of haematoma, and deep location of haematoma x intraventricular extension.

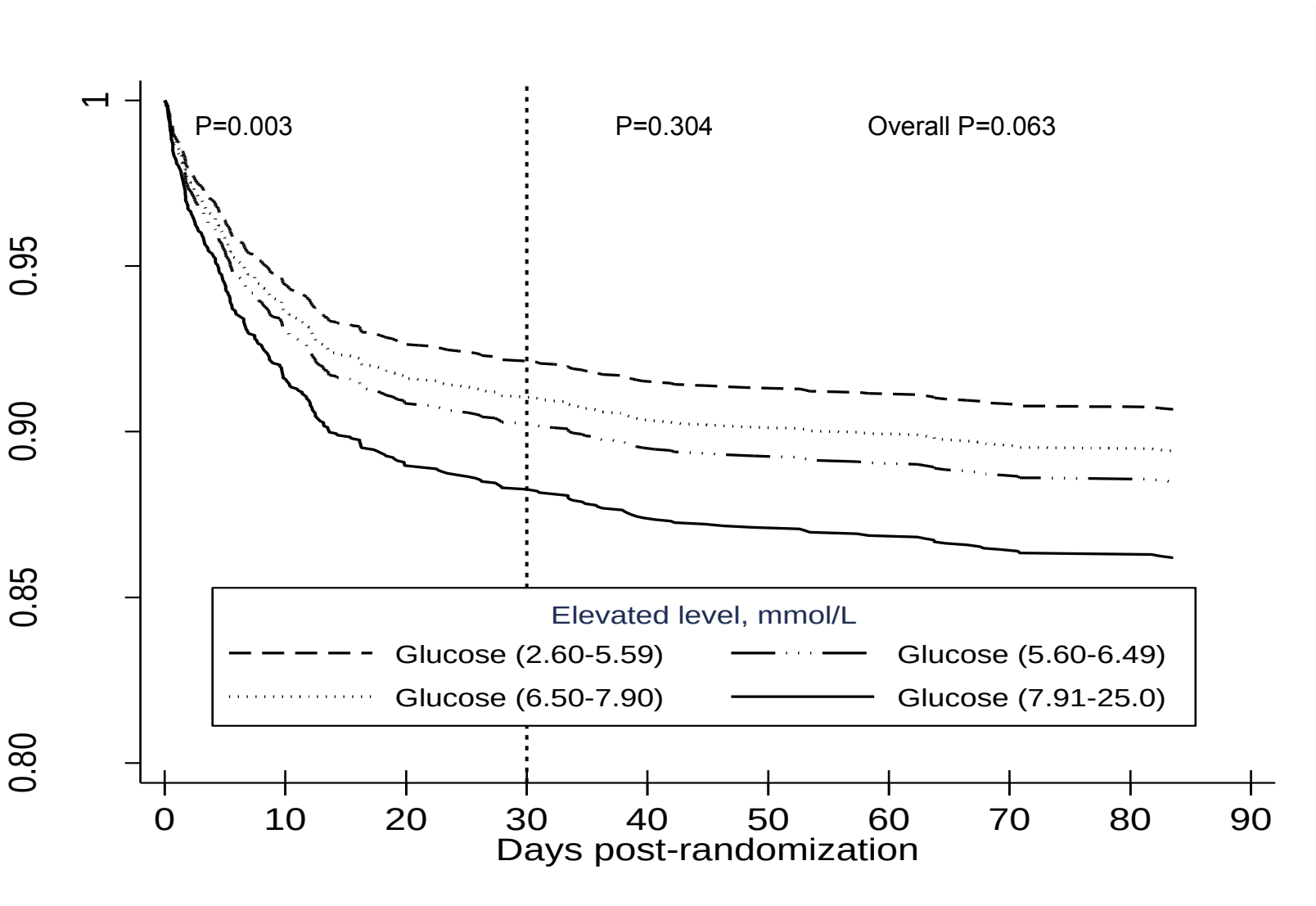

Figure 3a: Cox proportional hazards regression curves for fourths of baseline blood glucose and death

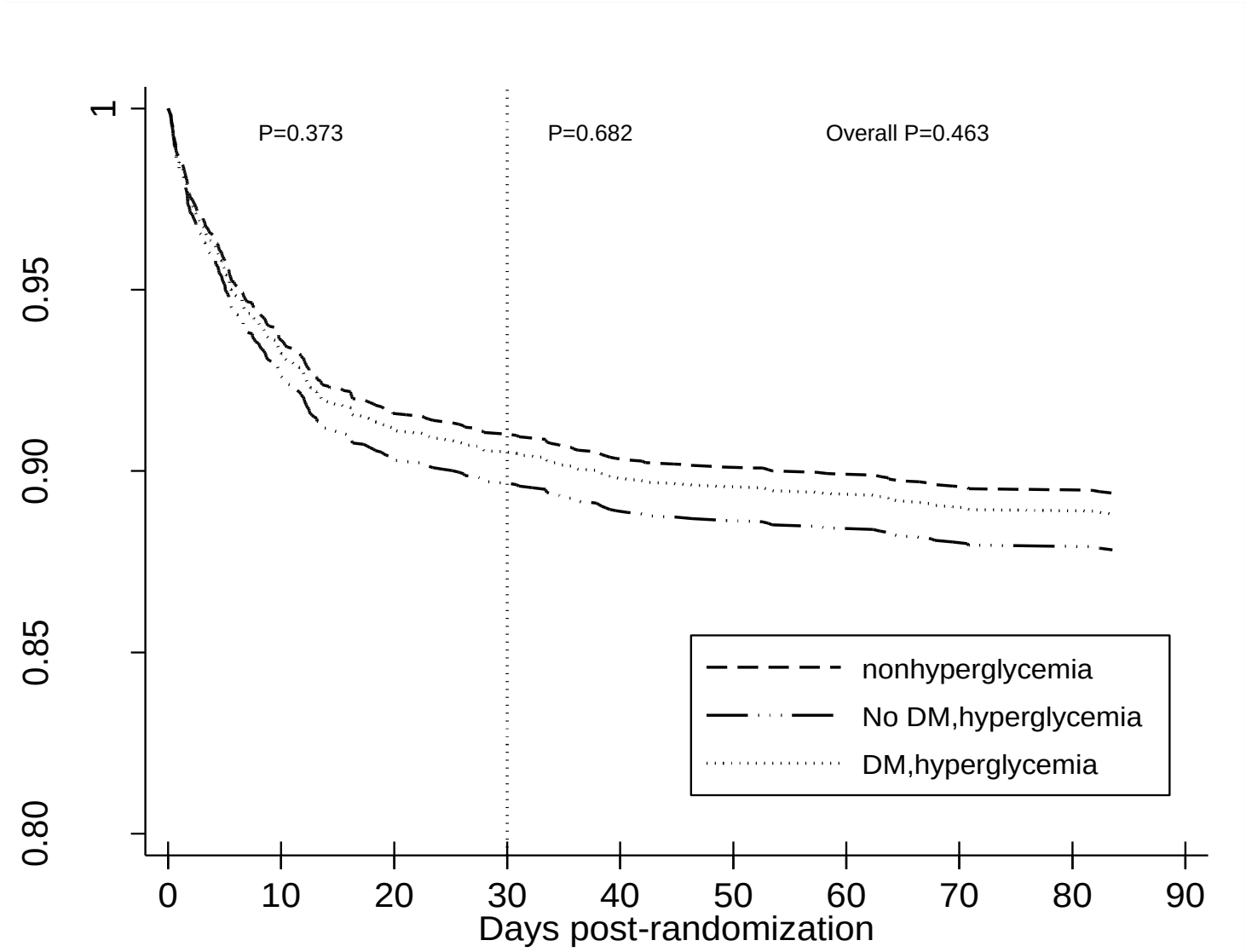

Figure 3b: Cox proportional hazards regression curves for death according to level of presence of hyperglycaemia (>6.5 mmol/L) and history of diabetes mellitus (DM)

Table 3.1: Patients characteristics according to baseline blood glucose level

	Baseline glucose level, mmol/L				
Variable	2.60-5.59 (N=644)	5.60-6.49 (N=661)	6.50-7.90 (N=693)	7.91-25.0 (N=655)	P value
Age, yr	62 (12)	63 (13)	65 (13)	65 (13)	<0.001
Male	436 (68)	427 (65)	411 (59)	381 (58)	0.001
Recruited from China	487 (76)	456 (69)	422 (61)	399 (61)	<0.001
Time to randomization, hr	3.8 (2.8-4.7)	3.7 (2.9-4.6)	3.7 (2.8-4.8)	3.7 (2.8-4.7)	0.94
Level of consciousness, GCS score	15 (13-15)	14 (13-15)	14 (12-15)	14 (12-15)	<0.001
Neurological impairment, NIHSS score	8 (4-13)	10 (6-15)	12 (7-16)	12 (7-17)	<0.001
Systolic BP, mmHg	177 (17)	177 (17)	180 (17)	182 (17)	<0.001
Diastolic BP, mmHg	102 (14)	101 (14)	100 (15.3)	100 (15)	0.49
History of hypertension	454 (71)	468 (71)	494 (71.4)	512 (78)	0.004
Use of antihypertensive therapy	277 (43)	279 (42)	309 (44.7)	344 (53)	0.001
Heart disease	58 (9)	57 (9)	72 (10.4)	100 (15)	<0.001
Prior ICH	52 (8)	53 (8)	56 (8.1)	56 (9)	0.98
Prior ischaemic / undifferentiated stroke	76 (12)	69 (10)	82 (11.9)	75 (12)	0.84
History of diabetes mellitus*	22 (3)	24 (4)	52 (7.5)	194 (30)	<0.001
Insulin or glucose lowering treatment*	13 (2)	18 (3)	28 (4.1)	120 (18)	<0.001
Use of warfarin anticoagulation	10 (2)	21 (3)	19 (2.8)	27 (4)	0.049
Use of aspirin or other antiplatelet agent	46 (7)	49 (7)	77 (11.1)	88 (14)	<0.001
Deep location of haematoma†	514 (85)	538 (88)	524 (81.0)	460 (78)	<0.001
IVH extension	120 (20)	144 (24)	209 (32.3)	212 (36)	<0.001
Haematoma volume, mL					
ICH	9.0 (4.6-16.1)	11.4 (6.2-18.7)	11.5 (6.4-20.8)	11.9 (6.0-22.8)	<0.001
Combined ICH + IVH	10.2 (5.1-18.0)	13.3 (7.1-21.8)	14.2 (7.2-27.0)	15.3 (7.0-29.1)	<0.001

Data are n (%), mean (±SD), or median (IQR). aOR, denotes adjusted odds ratio; BP, blood pressure; NIHSS, National Institutes of Health stroke scale; GCS, Glasgow coma scale; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage.

P values based on chi-squared, t-test or Wilcoxon rank sum test.

*As there was a strong collinearity between history of diabetes mellitus and insulin or glucose lowering treatment, only diabetes mellitus was included in the multivariable analyses

†Deep location refers to location in the basal ganglia or thalamus.

Table 3.2: Baseline characteristics for ICH patients according to the presence of diabetes mellitus

	All (N=2826)	No diabetes mellitus (N=2521)	Diabetes mellitus (N=305)	P value
Age	63 (54-74)	63 (54-73)	67 (60-76)	<0.001
Male	1777 (63)	1579 (63)	107 (65)	0.44
Recruited from China	1917 (68)	1764 (70)	153 (50)	<0.001
Time to CT scan, hr	1.8 (1.2-2.7)	1.8 (1.2-2.7)	1.8 (1.3-2.9)	0.16
NIHSS score	11 (6-15)	10 (6-15)	12 (7-16)	0.12
Systolic BP, mmHg	179 (17)	179 (17)	180 (17)	0.32
Diastolic BP, mmHg	101 (15)	102 (15)	97 (14)	<0.001
Heart rate, beats/min	76 (68-86)	76 (68-86)	78 (70-87)	0.057
History of hypertension	2048 (73)	1786 (71)	262 (86)	<0.001
Antihypertensive therapy	1274 (45)	1069 (42)	205 (67)	<0.001
Beta-blocker	227 (8)	178 (78)	49 (16)	<0.001
Calcium-channel blocker	393 (14)	319 (13)	74 (24)	<0.001
History of heart disease	299 (11)	238 (9)	61 (20)	<0.001
Prior intracerebral haemorrhage	229 (8)	201 (8)	28 (9)	0.47
Prior ischaemic or undifferentiated stroke	323 (11)	273 (11)	50 (16)	0.004
Use of warfarin anticoagulation	81 (3)	63 (3)	18 (6)	0.001
Use of aspirin or other antiplatelet agent	265 (9)	198 (8)	67 (22)	<0.001
Insulin therapy or glucose lowering treatment	183 (7)	12 (1)	171 (56)	
Deep location of haematoma*	2180 (84)	1940 (83)	240 (84)	0.84
Left hemisphere site of haematoma	1312 (50)	1170 (50)	142 (50)	0.83
Intraventricular extension	739 (28)	647 (28)	92 (32)	0.12
Haematoma volume, mL				
Haematoma alone	10.9 (5.8-19.5)	11.2 (5.9-19.7)	9.2 (4.7-16.7)	0.002
Combined with intraventricular haemorrhage	13.1 (6.5-23.8)	13.3 (6.6-23.9)	11.4 (5.6-22.8)	0.035

Data are n (%), mean (SD), or median (IQR). aOR indicates adjusted odds ratio; BP, blood pressure; CT, computed tomography; NIHSS, National Institutes of Health Stroke Scale; and ICH, intracerebral haemorrhage. P values based on chi-squared, t-test or Wilcoxon rank sum test.

*Deep location refers to location in the basal ganglia or thalamus.

Table 3.3: Fourths of baseline blood glucose and 3-month outcomes after acute intracerebral haemorrhage

Outcome	Fourths of glucose		Events	OR (95%CI)	P trend	Multivariate	
	Category	N	n (%)			aOR (95% CI)	P trend
Death or major disability	<5.6	637	268 (42)	1.0	<0.001	1.0	0.015
	5.6-6.5	650	319 (49)	1.33 (1.07-1.65)		1.07 (0.82-1.39)	
	6.5-7.9	685	395 (58)	1.88 (1.51-2.33)		1.31 (1.01-1.71)	
	>7.9	647	399 (62)	2.22 (1.77-2.77)		1.35 (1.01-1.80)	
Death	<5.6	637	45 (7)	1.0	<0.01	1.0	
	5.6-6.5	650	70 (11)	1.59 (1.07-2.35)		1.37 (0.88-2.12)	0.062
	6.5-7.9	685	86 (13)	1.89 (1.29-2.76)		1.16 (0.76-1.79)	
	>7.9	647	107 (17)	2.61 (1.81-3.76)		1.63 (1.06-2.51)	
Major disability	<5.6	592	223 (38)	1.0	<0.001	1.0	0.041
	5.6-6.5	580	249 (43)	1.25 (0.99-1.57)		1.04 (0.79-1.37)	
	6.5-7.9	599	309 (52)	1.76 (1.40-2.22)		1.32 (1.00-1.74)	
	>7.9	540	292 (54)	1.95 (1.54-2.47)		1.27 (0.94-1.72)	

OR denotes odds ratio; aOR, adjusted odds ratio; CI, confidence interval

*adjusted for age, geographical region, gender, history of heart disease, history of hypertension, history of aspirin or warfarin use, history of diabetes mellitus, baseline haematoma volume and location, intraventricular extension, baseline systolic blood pressure, National Institute of Health stroke scale (NIHSS) score (≥15), randomised treatment, and age x NIHSS≥15, China x intraventricular extension, baseline haematoma volume x deep location of haematoma, and deep location of haematoma x intraventricular extension

Table 3.4: Quartiles of baseline blood glucose and 90-day outcomes after acute intracerebral haemorrhage (not adjusted by randomised BP lowering treatment)

Outcomes	Glucose (mmol/L)		Events	Multivariable	
	Category	N	n (%)	aOR (95% CI)	P trend
Death or major disability	<5.6	637	268 (42)	1.0	0.016
	5.6-6.5	650	319 (49)	1.06 (0.81-1.38)	
	6.5-7.9	685	395 (58)	1.31 (1.01-1.70)	
	>7.9	647	399 (62)	1.35 (1.01-1.80)	
Death	<5.6	637	45 (7)	1.0	
	5.6-6.5	650	70 (11)	1.37 (0.88-2.12)	0.062
	6.5-7.9	685	86 (13)	1.16 (0.76-1.79)	
	>7.9	647	107 (17)	1.63 (1.06-2.51)	
Major disability	<5.6	592	223 (38)	1.0	0.043
	5.6-6.5	580	249 (43)	1.03 (0.78-1.36)	
	6.5-7.9	599	309 (52)	1.32 (1.00-1.73)	
	>7.9	540	292 (54)	1.27 (0.94-1.72)	

OR indicates odds ratio; aOR, adjusted odds ratio; and CI, confidence interval.
*Adjusted for age, geographical region, sex, history of hypertension, heart disease, and diabetes, use of aspirin and/or warfarin use, baseline haematoma volume and location, intraventricular extension, baseline systolic blood pressure, National Institute of Health Stroke Scale (NIHSS) score (≥15), and age*NIHSS≥15, China*intraventricular extension, baseline haematoma volume*deep location of haematoma, and deep location of haematoma*intraventricular extension.

Table 3.5: Outcomes from intracerebral haemorrhage, by diabetes mellitus status

Outcomes		n (%)	OR	P value	aOR	P value
Death or major disability						
No	2329	1192 (51)	1.0		1.0	
Yes	287	186 (65)	1.76 (1.36-2.27)	<0.001	1.43 (1.03-2.00)	0.035
Death						
No	2329	267 (12)	1.0		1.0	
Yes	287	39 (14)	1.22 (0.85-1.74)	0.29	0.93 (0.59-1.46)	0.74
Major disability						
No	2062	925 (45)	1.0		1.0	
Yes	248	147 (59)	1.79 (1.37-2.34)	<0.001	1.49 (1.06-2.10)	0.023

OR indicates odds ratio; aOR, adjusted odds ratio.

Models were adjusted for age, geographical region, sex, history of hypertension, diabetes, and heart disease, use of aspirin and/or warfarin, baseline haematoma volume and location, intraventricular extension, baseline systolic blood pressure, National Institute of Health stroke scale (NIHSS) score (≥15), randomised treatment, and age*NIHSS ≥15, China*intraventricular extension, baseline haematoma volume*deep location of haematoma, and deep location of haematoma*intraventricular extension.

Table 3.6: Baseline blood glucose (mmol/L) by diagnostic thresholds for diabetes mellitus and 90-day outcomes after acute ICH

	Glucose (mmol/L)		Events	Crude		Multivariable adjusted*	
Outcomes	Category	N	n (%)	OR (95% CI)	P trend	aOR (95% CI)	P trend
Death or major disability	<6.1	996	443 (45)	1	<0.001	1	0.010
	6.1-7.0	655	349 (53)	1.42 (1.17-1.74)		1.13 (0.88-1.43)	
	>7.0	968	589 (61)	1.94 (1.62-1.74)		1.36 (1.08-1.71)	
Death	<6.1	996	85 (9)	1	<0.001	1	0.081
	6.1-7.0	655	70 (11)	1.28 (0.92-1.79)		0.93 (0.63-1.36)	
	>7.0	968	153 (16)	2.01 (1.52-2.67)		1.34 (0.95-1.89)	
Major disability	<6.1	911	358 (39)	1	<0.001	1	0.031
	6.1-7.0	585	279 (48)	1.41 (1.14-1.74)		1.11 (0.87-1.43)	
	>7.0	815	436 (54)	1.78 (1.47-2.15)		1.30 (1.02-1.65)	

OR indicates odds ratio; aOR, adjusted odds ratio; CI, confidence interval; ICH, intracerebral haemorrhage

*Adjusted for age, geographical region, sex, history of hypertension, diabetes, and heart disease, use of aspirin and/or warfarin, baseline haematoma volume and location, intraventricular extension, baseline systolic blood pressure, National Institute of Health Stroke Scale (NIHSS) score (≥15), randomised treatment, and age*NIHSS ≥15, China*intraventricular extension, baseline haematoma volume*deep location of haematoma, and deep location of haematoma*intraventricular extension.

Table 3.7. Serious adverse events, by baseline blood glucose level

	Glucose level		
	<6.5 mmol/L (N=1305)	≥6.5 mmol/L (N=1348)	P value
Early neurological deterioration	168/1282 (13.1)	217/1313 (16.5)	0.014
Non-fatal serious adverse events	269/1305 (20.6)	344/1348 (25.5)	0.003
Initial ICH	26/1305 (2.0)	36/1348 (2.7)	
Cardiovascular disease	27/1305 (2.1)	37/1348 (2.7)	
Recurrent ICH	6/1305 (0.5)	2/1348 (0.1)	
Ischaemic/undifferentiated stroke	3/1305 (0.2)	7/1348 (0.5)	
Acute coronary event	3/1305 (0.2)	5/1348 (0.4)	
Other cardiovascular disease	15/1305 (1.1)	23/1348 (1.7)	
Non-cardiovascular disease	101/1305 (7.7)	137/1348 (10.2)	
Severe hypotension	4/1305 (0.3)	7/1348(0.5)	
Fatal serious adverse events	115/1297 (8.9)	193/1343 (14.4)	<0.001
Initial ICH	66/1297 (5.1)	124/1343 (9.2)	<0.001
Cardiovascular disease	12/1297 (0.9)	16/1343 (1.2)	
ICH	1/1297 (0.1)	1/1343 (0.1)	
Ischaemic/undifferentiated stroke	1/1297 (0.1)	0/1343	
Acute coronary event	2/1297 (0.2)	2/1343 (0.1)	
Other vascular disease	1/1297 (0.1)	3/1343(0.2)	
Other cardiac disease	7/1297 (0.5)	10/1343 (0.7)	
Non-cardiovascular disease	37/1297 (2.9)	53/1343 (4.0)	
Renal failure	1/1297 (0.1)	3/1343 (0.2)	
Respiratory infections	12/1297 (0.9)	14/1343 (1.0)	
Sepsis (includes other infections)	6/1297 (0.5)	4/1343 (0.3)	
Non-vascular medical	18/1297 (1.4)	32/1343(2.4)	

ICH denotes intracerebral haemorrhage

Table 3.8: Safety outcomes during 90-day follow-up after intracerebral haemorrhage, stratified by diabetes mellitus status at baseline

	No diabetes mellitus (N=2358)	Diabetes mellitus (N=295)	P value
Early neurological deterioration	345/2308 (15.0)	40/285 (14.0)	0.68
Non-fatal serious adverse events	509/2358 (21.6)	101/285 (34.6)	<0.001
Any neurological deterioration from intracerebral haemorrhage	81/2358 (3.4)	7/285 (2.5)	
Cardiovascular disease	56/2358 (2.4)	19/285 (6.7)	<0.001
Recurrent intracerebral haemorrhage	7/2358 (0.3)	1/285 (0.4)	
Ischaemic or undifferentiated stroke	10/2358 (0.4)	4/285 (1.4)	
Acute coronary event	9/2358 (0.4)	1/285 (0.4)	
Other cardiovascular disease	33/2358 (1.4)	14/285 (4.9)	
Non-cardiovascular disease	242/2358 (10.3)	41/285 (14.4)	<0.001
Severe hypotension	9/2358 (0.4)	5/285 (1.8)	
Cause of death	267/2358 (11.3)	39/285 (13.4)	0.24
Direct effects of primary intracerebral haemorrhage event	165/2358 (7.0)	23/285 (7.9)	0.51
Cardiovascular disease	21/2358 (0.9)	7/285 (2.4)	
intracerebral haemorrhage	Feb-58	0	
Ischaemic/undifferentiated stroke	Jan-58	0	
Acute myocardial infarction/coronary event/other	4/2358 (0.2)	0	
Other vascular disease	4/2358 (0.2)	0	
Other cardiac disease	10/2358 (0.4)	7/285 (2.4)	
Non-cardiovascular disease	81/2358 (3.4)	9/285 (3.1)	
Renal failure	3/2358 (0.1)	1/285 (0.3)	
Respiratory infections	23/2358 (1.0)	3/285 (1.0)	
Sepsis (includes other infections)	9/2358 (0.4)	1/285 (0.3)	
Non-vascular medical	46/2358 (2.0)	4/285 (1.4)	

Table 3.9: Haematoma growth over 24 hours post-randomisation by glucose levels

	Glucose <6.5 mmol/L(n=422)		Glucose ≥6.5 mmol/L(n=489)		P value
	Baseline	24 hours	Baseline	24 hours	
Haematoma volume (mL), mean±SD	13.4±13.3	17.7±22.9	16.9±16.6	20.4±21.1	
Haematoma growth					
Absolute growth volume (mL), crude mean (95% CI)	4.3 (2.8-5.9)		3.4 (2.0-4.9)		0.40
Absolute growth volume (mL), adjusted mean* (95% CI)	6.9 (3.9-9.9)		5.4 (2.8-8.0)		0.19

SD indicates standard deviation; and CI, confidence interval.
*Adjusted for age, geographical region, sex, history of hypertension, diabetes, and heart disease , use of aspirin and/or warfarin, baseline haematoma volume and location, intraventricular extension, baseline systolic blood pressure, randomised treatment, China*intraventricular extension, baseline haematoma volume*deep location of haematoma, and haematoma location*intraventricular extension.

Table 3.10: Growth of perihaematomal oedema over 24 hours post randomisation by glucose levels

	Glucose <6.5 mmol/L (n=376)		Glucose ≥6.5 mmol/L (n=413)		P Value
	Baseline	24 hours	Baseline	24 hours	
Perihaematomal oedema volume (mL), mean±SD	2.8±3.6	5.5±7.8	3.5±4.8	6.1±8.2	
Growth of perihaematomal oedema					
Absolute growth volume (mL), crude mean (95% CI)	2.7 (2.1-3.3)		2.6 (2.0-3.1)		0.81
Absolute growth volume (mL), adjusted mean* (95% CI)	3.0 (1.9-4.1)		2.6 (1.6-3.5)		0.29

SD indicates standard deviation; and CI, confidence interval.
*Adjusted for age, geographical region, sex, history of hypertension, diabetes, and heart disease, use of aspirin and/or warfarin, baseline haematoma volume and location, intraventricular extension, baseline systolic blood pressure, randomised treatment, China*intraventricular extension, baseline haematoma volume*deep location of haematoma, and haematoma location*intraventricular extension

Chapter 4: Hyperglycaemia and haematoma parameters in intracerebral haemorrhage

4.1 Presentation details

Oral presentation at European Stroke Conference 2015 (Glasgow, United Kingdom)

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4.2 Abstract

Background and Purpose: Uncertain pathophysiological mechanisms underlie the adverse outcomes associated with hyperglycaemia in intracerebral haemorrhage (ICH). We aimed to determine the relation of hyperglycaemia to haematoma characteristics among participants of the INTERACT2 study.

Methods: INTERACT2 was an international, multicentre, prospective, open, blinded endpoint, randomised controlled trial involving 2839 patients with ICH (<6 hr) and elevated systolic blood pressure (SBP) randomly assigned to intensive (target SBP <140 mmHg) or guideline-based (SBP <180 mmHg) BP management during 2008-2012. Associations of hyperglycaemia (≥6.5 mmol/l) and haematoma volumes at baseline (in all) and 24 hours (in 963 patients) and perihaematomal oedema volumes (in 789 patients) were determined in ANOVA models.

Results: Baseline blood glucose was recorded in 2653 (93%) patients. Hyperglycaemic patients had significantly higher baseline haematoma volumes, with (14.6 vs 11.6 ml, *P* <0.0001) and without intraventricular haemorrhage (11.6 vs 10.2 ml, *P* <0.01), and less deep

(78.8% vs. 86.5%, *P* <0.001) and more cerebellar (5.9% vs. 1.1%, *P* <0.01) haematomas. Hyperglycaemic patients had no difference in haematoma expansion (mean adjusted, 5.1% vs 6.8%, *P* =0.13) and perihaematomal oedema (mean adjusted 86.0% vs 94.1%, *P* =0.46) in the first 24 hours.

Conclusions: Hyperglycaemia is associated with bleeding location and greater severity of initial haematoma volumes in acute ICH patients, but has no clear effect on either haematoma expansion or early cerebral oedema.

4.3 Manuscript

Introduction

Intracerebral haemorrhage refers to bleeding within the brain parenchyma. Significant morbidity and mortality has been reported following ICH with a 1-month case fatality of 40.4% and functional independence of 12 to 39%[2]. The INTERACT2 analyses examined independent predictors of both death and major disability at 3 months. This showed a significant association between admission blood glucose and adverse outcomes (death and major disability) independent of diabetes mellitus (DM). Whilst DM was significantly associated with major disability, no association was reported with mortality alone. The hyperglycaemic group also experienced significantly greater neurological deterioration over the first 24 hours post-admission. Uncertainty exists over the mechanism underlying this association between hyperglycaemia, adverse outcomes and neurological deterioration.

Specific haematoma characteristics such as haematoma volume, location, intraventricular haemorrhage (IVH) and cerebral oedema are associated with adverse outcomes. Haematoma expansion 24 hours post-ICH has been reported in a number of studies[122-125] and occurs in 14.3%[123] to 38%[125] of ICH and is independently associated with increased mortality and morbidity[126]. Animal models suggest that hyperglycaemia induces haematoma expansion; however, there is limited human data to confirm this effect[127,128].

Restricting haematoma growth is essential in limiting neuronal damage and perihaematomal oedema which is critical in the acute management of ICH. Protecting the potential 'penumbra' in ICH is also a consideration; however, controversy exists regarding its existence. The role of the penumbra has been tested in animal models where haematoma was

induced through injection of autologous blood into deep white matter and measurement of regional cerebral blood flow (rCBF). The evidence is conflicting with earlier studies showing reduced rCBF[129] and other investigations reporting no difference in rCBF pre- and post-haematoma.[130] Imaging studies using PET[131] and MRI[132] found regions of cerebral hypoperfusion, however, no evidence of ischaemia in the perihaematomal zone. Therefore, whilst limiting haematoma volume may be important there is still ongoing controversy regarding whether there is a salvageable penumbra in ICH. Animal models have been used to analyse the effects of hyperglycaemia upon the ischaemic territory by measuring lactate levels and hydrogen ion concentration. In these models of ischaemic stroke, hyperglycaemia was associated with higher levels of lactate in the ischaemic territories.[133] There is uncertainty regarding these associations in intracerebral haemorrhage with the role of hyperglycaemia requiring further assessment. This current study aimed to investigate the relationship of admission hyperglycaemia with haematoma growth, IVH and cerebral oedema to identify a potential role of tighter glycemic control in management.

Methods

Trial Design

The present study is a prospective, randomised, open-label, assessor-blinded end-point (PROBE), multicentre, international clinical trial (INTERACT2). From 2008 to 2012 data was obtained from over 140 international centres with 2826 patients being included in this study. Patient inclusion depended on age ≥ 18 years, blood pressure measurement between 150 and 220 mmHg (2 systolic measurements) and CT or MRI confirmed ICH diagnosis. Exclusion criteria included: GCS score of 3-5, surgical intervention, structural abnormality causing ICH or large volume ICH. Haematoma enlargement was measured in a specific cohort of 963 patients with 911 having admission blood glucose data available.

Baseline demographics (age, gender, ethnicity), medical history of diabetes mellitus, hypertension, heart disease, previous strokes and current medications (insulin, antihypertensives, calcium and beta blockers) were noted. We also recorded blood glucose, blood pressure (systolic, diastolic) and biochemical markers at admission. Admission GCS was used to assess level of consciousness and severity of ICH was graded using NIHSS score at 24 hours.

CT and MRI Analyses

CT and MRI scans were performed at baseline. Radiological analysis was performed to calculate ICH volume and the presence and volume of intraventricular haemorrhage extension. Location of the primary ICH, presence of hydrocephalus, midline shift of cerebral structures was also recorded. In a selected subset of patients, both ICH and IVH volume was measured at 24 ± 3 hours. These radiological scans were analysed using MIStar version 3.2 to calculate haematoma volume, intraventricular extension, subdural haemorrhage and other parameters.

Statistical Analyses

Patients were categorized into two groups based on admission blood glucose: normoglycaemia (0-6.5 mM) and hyperglycaemia (> 6.5 mM). The effects of admission blood glucose on relative and absolute changes in haematoma volume were assessed by means of an analysis of covariance. The relative change in haematoma volume was log-transformed to remove skewness after the addition of the value 1.1 to eliminate negative values. Baseline haematoma volume, IVH presence and volume was compared between groups. Admission blood glucose tertiles and quartiles in relation to haematoma volume were also studied and the p-trend was determined.

Haematoma growth was calculated as absolute (mL) and proportional (%). Our multivariate model adjusted for age, geographical region, sex, history of stroke, treatment, baseline haematoma volume, baseline systolic blood pressure, admission NIHSS score≥15, use of aspirin, use of warfarin or other anti-platelet drugs, and history of diabetes. The association between history of diabetes mellitus and haematoma growth was also modelled and adjusted for the aforementioned covariates (excluding history of DM).

All statistical analyses were performed using SAS version 9.3 (SAS institute, Cary, NC, USA). A two sided P value <0.05 was set as the level for statistical significance.

Results

Table 1 illustrates baseline differences in haematoma characteristics between normoglycaemic and hyperglycaemic patients. Stroke characteristics were more severe in the hyperglycaemic group with greater haematoma volume (11.6 mL normoglycaemia vs. 14.6 mL hyperglycaemia, p<0.01) and incidence of intraventricular extension (21.8% normoglycaemia vs. 34.0% hyperglycaemia, p<0.01). Cerebellar haemorrhage was significantly more frequent in hyperglycaemic patients (1.1% normoglycaemia vs. 5.9%

hyperglycaemia, p<0.01) whilst deep ICH was significantly less frequent (86.8% normoglycaemia vs. 79.4% hyperglycaemia, p<0.01). Increasing quartiles of admission blood glucose correspond with greater combined haematoma volumes with significant p-trend (Table 2).

Diabetic patients had significantly lower haematoma volume in comparison with non-diabetics (DM 9.2 mL vs. NDM 11.2 mL; p < 0.01) whilst there was no association with haematoma location or IVH extension (Table 3).

Of the 2653 patients in the INTERACT2 study, haematoma growth was analysed in a cohort of 963 patients (Table 4). 52 patients without admission blood glucose measurements were excluded. There was no difference in haematoma growth within the hyperglycaemic group. In hyperglycaemic patients: adjusted haematoma growth (normoglycaemic 6.8 ml (95%CI 4.3-9.2) vs. hyperglycaemic 5.1 ml (95%CI 3.0-7.2); p = 0.46) and mean adjusted ICH+IVH growth [normoglycaemic 9.2 ml (95%CI 5.5-12.8) vs. hyperglycaemic 6.9 ml (95%CI 3.8-10.0); p = 0.17] showed no difference.

Similarly, there was no difference in perihaematomal oedema expansion over 24 hours between hyperglycaemic and normoglycaemic patients [hyperglycaemic group: 2.8 ml (95%CI 2.0-3.5), normoglycaemic group: 3.3 ml (95%CI 2.4-4.2); p = 0.19)] (Table 6). There was also no difference found between diabetic and non-diabetic patients [DM 6.2 ml (95%CI 2.5-9.9) vs. NDM 5.7 ml (95%CI 3.3-8.1); p = 0.79] (Table 5).

Discussion

The present study examined radiological analyses following ICH and considered the effect of admission hyperglycaemia and diabetes mellitus. Baseline radiological characteristics illustrated that patients with elevated blood glucose at admission had significantly higher haematoma volume and IVH volume. In contrast, multivariate analyses showed diabetic patients had significantly lower haematoma volume. Haematoma growth and cerebral oedema growth at 24 hours were hypothesised as mechanisms for the previously reported neurological deterioration, however, no association was found with admission hyperglycaemia or history of diabetes mellitus.

This study found that admission hyperglycaemia is correlated with more severe ICH characteristics, such as haematoma volume and IVH extension, in line with existing literature[69,97]. Quartiles of admission blood glucose displayed a significant p-trend with

respect to haematoma volume and admission blood glucose >6.5mM was significantly associated with incidence of IVH extension. Haematoma expansion and cerebral oedema have also been previously linked with hyperglycaemia with future potential to examine this relationship in the INTERACT2 cohort[73,127,128].

Cerebellar haemorrhages were significantly more frequent in hyperglycaemic patients whilst deep haematomas (thalamus and basal ganglia) were less frequent. Previous data has shown that cerebellar haemorrhage in hyperglycaemic patients is associated with increased severity with more frequent intraventricular extension, brainstem compression, hydrocephalus and larger haematoma diameter[59]. These parameters are all predictors of adverse outcomes following cerebellar haemorrhage[134]. Associations with diabetes mellitus were also explored to assess if diabetic patients were predisposed to haematoma in specific locations. However, no specific regions were identified (Table 4.3). ICH location analysis performed by Zhang et al.[135], examined deep and lobar ICH and the admission blood glucose levels for these specific ICH sub-types. When comparing the sub-types no significant difference in admission blood glucose was reported, unlike our findings where patients with deep ICH were less likely to present with hyperglycaemia.

With hyperglycaemic patients more likely to have cerebellar haemorrhage, specific complications must be considered. The risk of brainstem herniation is increased in cerebellar haemorrhage with data showing significantly greater one-week mortality in such cases[136]. Whilst this analysis was not performed in INTERACT2, the association with hyperglycaemia would assist in understanding the linking mechanisms. Potentially, cerebellar injury would disrupt neuronal processing and coordination of inputs which may explain the clinical deterioration observed over 24 hours and longer term adverse outcomes at 3 months.

I noted that patients in the hyperglycaemic group had more severe ICH characteristics such as haematoma volume and IVH extension in line with existing literature[69,97]. Quartiles of admission blood glucose (Table 2) displayed a significant p-trend with respect to haematoma volume. This is in line with previous findings where significantly higher ICH volume has been reported in patients with admission hyperglycaemia[69,137].

Admission hyperglycaemia was also significantly associated with incidence of IVH extension and significantly greater IVH volume at admission. This relationship between admission blood glucose and IVH score was investigated by Appelboom et al.[69]. As previously

discussed, the linear correlation supports the stress hyperglycaemia hypothesis whereby more severe neurological injury results in greater hyperglycaemic response.

Currently there is limited evidence regarding the relationship between haematoma expansion and admission hyperglycaemia. Kazui et al.[128] reported that the interaction of systolic blood pressure (>200 mmHg) with both fasting plasma glucose and HbA1c were independent predictors of haematoma enlargement. Whilst this was a much smaller study (n=186) it questioned the potential role of hypertension and DM in inducing ICH growth. HbA1c was used as a parameter for DM, whilst elevated fasting plasma glucose was studied to indicate stress hyperglycaemia. Another study recorded blood glucose levels 5 times over 3 days following admission and categorised patients into increasing and declining levels[99]. In patients with increasing blood glucose association was found with haematoma expansion and perihaematomal oedema expansion.

My hypothesis that hyperglycaemic patients would have significantly greater haematoma growth was also extrapolated from studies involving ischaemic stroke which demonstrated that hyperglycaemia was significantly associated with haemorrhagic transformation in the cat model[138], rats[139,140] and humans[43]. However, unlike these proposed mechanisms and previous findings the current study displayed that admission hyperglycaemia and DM held no association with haematoma growth.

Animal models illustrated profound cerebral oedema with hyperglycaemia following ICH[74]. However, these experimental findings do not translate to the current investigation where no association was found between admission blood glucose and cerebral oedema at 24 hours. My results for perihaematomal oedema and haematoma expansion are in line with the smaller study by Feng et al.[141] where no association was reported with hyperglycaemia. This earlier investigation used mean glucose levels over 72-hours which illustrate the effect of prolonged elevation in BSL upon neuronal injury.

The findings in the current study are in direct contrast with the investigation by Liu et al.[73] where DM was modelled in rats using streptozotocin. In this experimental model, plasma kallikrein was identified as a central mediator in increasing haematoma growth and was therefore used to induce expansion. This animal model tested whether DM or hyperglycaemia was the underlying factor in haematoma expansion and found that normalizing blood glucose with insulin prior to ICH resulted in significantly lower haematoma expansion. Furthermore inducing hyperglycaemia in NDM rats resulted in

increased haematoma growth. Hyperglycaemia amplified the action of kallikrein in inhibiting platelet aggregation thereby facilitating greater haematoma expansion. The increased plasma osmolality caused by increased blood glucose further contributed to haematoma growth. These findings indicated the potential use of insulin therapy to maintain tight glucose control in the acute management of ICH.

Broderick et al.[127] studied determinants of haematoma enlargement (n=353) and also found that serum blood glucose was significantly associated with greater ICH growth (p=0.02) and ICH+IVH growth (p=0.0306). Although statistically significant, this study could not demonstrate whether admission blood glucose was a causative factor or a marker of haematoma growth.

A number of mechanisms have been reported involving hyperglycaemia, haematoma expansion and neuronal damage. Badjatia et al.[142] studied subarachnoid haemorrhage (SAH) patients and found a positive association between mean blood glucose and the incidence of vasospasm. Patients who experienced vasospasm after SAH presented with significantly higher admission blood glucose. Vasospasm may exacerbate bleeding and has been proposed as part of the pathophysiology linking hyperglycaemia and haematoma expansion.

Animal models have illustrated that hyperglycaemia promotes superoxide generation and blood-brain barrier disruption leading to exacerbation of haemorrhage and increased haematoma volume[76]. An experimental Sprague-Dawley rat model has also established the role of aquaporin-4 (AQP-4) in exacerbating ICH[116] with downregulation noted in hyperglycaemic rats. Further, hyperglycaemia was positively associated with severe BBB disruption, as well as increased brain water content[74] and vasogenic oedema[116]. Whilst these mechanisms may contribute to the significantly greater baseline ICH volume in hyperglycaemic patients, the link with haematoma growth was not confirmed in the present study.

The current investigation illustrates the complete opposite as hyperglycaemic patients had lower median haematoma growth in terms of absolute (mL) and proportional growth (%). This was seen for ICH and ICH+IVH. The INTERACT2 analyses is the first large scale (911 patients) human study analysing the relationship between hyperglycaemia and haematoma expansion. However, the results of the present study do not align with experimental animal models.

Previous human studies have evaluated the pro-thrombotic effect of hyperglycaemia and these factors may be involved in ICH. Specifically, hyperglycaemia accelerates the rate of thrombus formation and coagulation via the collagen and thrombin pathway[143,144]. Intravenous endotoxin administration has also been used to simulate the inflammatory state[145] and in hyperglycaemic patients (12 mM) coagulation was significantly higher. Similarly hyperglycaemia and platelet function have been studied in the context of acute coronary syndrome[144]. Hyperglycaemic patients had significantly higher formation of thrombin-antithrombin complexes in comparison with normoglycaemic patients whilst platelet activation markers were also significantly elevated. These studies suggest that hyperglycaemia in acute medical conditions is associated with increased platelet function and coagulation. In the context of ICH this may result in coagulation of haematoma thereby limiting haematoma growth by decreasing bleeding over 24 hours.

My findings illustrate the positive association between hyperglycaemia and baseline haematoma volume, however, patients with DM showed an unexpected association. Baseline haematoma volume was significantly lower in diabetic patients. This is in direct contrast to the significantly greater haematoma volumes seen in hyperglycaemic patients. Further, in diabetic patients haematoma growth was higher in the DM group with marginal significance ($p=0.11$). Therefore, we report directly contrasting associations of baseline haematoma volume with DM and admission blood glucose. This suggests distinct pathophysiological pathways in stress hyperglycaemia and diabetes mellitus.

However, both DM and admission hyperglycaemia hold no association with haematoma growth. Existing literature has established that DM is responsible for a hypercoagulable state[146-148]. Specifically, diabetic patients present with increased concentration of clotting factors and von Wildebrand factor, increased platelet aggregation and impaired fibrinolysis. The lack of association between DM and haematoma growth may also be related to levels of plasminogen activator inhibitor 1 (PAI-1). Elevated PAI-1 has been found in DM[149-152] and although this increases the risk of macrovascular complications (acute ischaemic stroke, acute myocardial infarction) it may also play a role in limiting continued bleeding following ICH thereby restricting haematoma growth.

This investigation represents one of the largest cohorts of ICH patients analysed for haematoma volume, location and IVH (2653 patients) as well as haematoma growth (963 patients). However, certain limitations need to be addressed. Although blood glucose was

only measured upon admission, continuous measurement to calculate persistent hyperglycaemia may have been more effective in elucidating the mechanism with haematoma growth. Undiagnosed diabetic patients were not included. Other studies have also examined brain oedema and total brain water content to elicit the effect of hyperglycaemia upon perihaematomal regions. This may be an area that could be further analysed. The limitations of secondary analysis are also present in our investigation.

Conclusions

In conclusion, my secondary analysis revealed that patients with admission hyperglycaemia had more severe characteristics relating to their ICH. This included significantly higher haematoma volume and IVH extension. However, haematoma growth and cerebral oedema were not associated with admission hyperglycaemia or history of diabetes mellitus. Whilst further investigation is required, at this stage our study indicates that tight blood glucose control is not required to limit haematoma expansion.

Results

Table 4.1: Haematoma Characteristics in Normoglycaemic and Hyperglycaemic patients

	All (N=2653)	**Glucose<6.5 (N =1305)**	**Glucose≥6.5 (N=1348)**	**P value**
Haematoma Location				
Lobar	251(10.2)	112(9.2)	139(11.2)	0.11
Deep	2025(82.6)	1048(86.5)	977(78.8)	<0.01
Cerebellar	86(3.5)	13(1.1)	73(5.9)	<0.01
Ventricular	11(0.5)	4(0.3)	7(0.6)	
Brainstem	77(3.1)	35(2.9)	42(3.4)	0.48
Deep location of haematoma§– no./total no. (%)	2036(83.0)	1052(86.8)	984(79.4)	<0.01
Left hemisphere site of haematoma- no./total no. (%)	1223(49.9)	590(48.7)	633(51.1)	0.24
IVH Extension - no./total no. (%)	685(27.9)	264(21.8)	421(34.0)	<0.01
Haematoma volume at baseline, mL, median (IQR)				
ICH	10.9(5.7-19.5)	10.2(5.4-17.0)	11.6(6.2-21.9)	0.01
IVH	0.0(0.0-0.8)	0.0(0.0-0.0)	0.0(0.0-2.4)	
Combined	13.1(6.4-23.8)	11.6(5.9-20.0)	14.6(7.0-28.0)	<0.01

§ Deep location refers to location in the basal ganglia or thalamus.
P values are based on chi-squared, t-test or Kruskal-Wallis test

Table 4.2: Baseline haematoma volume stratified by glucose (quartiles)

	Q1	Q2	Q3	*Q4*
Haematoma volume at baseline, mL, median (IQR)				
ICH	9.0(4.6-16.1)	11.4(6.2-18.7)	11.5(6.4-20.8)	11.9(6.0-22.8)
Combined(ICH+IVH)	10.2(5.0-18.0)	13.3(7.1-21.8)	14.2(7.2-27.0)	15.3(7.0-29.1)

Table 4.3: Haematoma Characteristics in DM and NDM

	All (N=2826)	Non-Diabetes Mellitus (N =2521)	Diabetes Mellitus (N=305)	*P*	Adjusted OR (95% CI)	*P*
Location– no (%)						
Lobar	260(10.0)	228(9.8)	32(11.2)			
Deep	2168(83.0)	1930(83.0)	238(83.2)			
Cerebellar	89(3.4)	80(3.4)	9(3.2)			
Ventricular	12(0.5)	10(0.4)	2(0.7)			
Brainstem	80(3.1)	75(3.2)	5(1.8)			
Deep location of haematoma§– no./total no. (%)	2180(83.5)	1940(83.4)	240(83.9)	*0.84*		
Left hemisphere site of haematoma - no./total no. (%)	1312(50.3)	1170(50.3)	142(49.7)	*0.84*		
IVH Extension - no./total no. (%)	739(28.3)	647(27.8)	92(32.2)	*0.12*		
Haematoma volume at baseline, mL, median (IQR)						
ICH	10.9(5.8-19.5)	11.2(5.9-19.7)	9.2(4.7-16.7)	*0.03*	1.01(1.0-1.02)	*0.01*
IVH	0(0-0.8)	0(0-0.6)	0(0-1.9)			
Combined	13.1(6.5-23.8)	13.3(6.6-23.9)	11.4(5.6-22.8)	*0.06*		

Table 4.4: Haematoma Growth parameters at 24 hours post randomisation, by admission blood glucose

	All (N=911)		Glucose<6.5(N=422)		Glucose≥6.5 (N =489)		Absolute (mls) / proportional (%) less in patients with glucose≥6.5 (95% CI)	P Value
Haematoma volumes, baseline to 24 hours	Baseline	24 hours	Baseline	24 hours	Baseline	24 hours		
Haematoma (ml), mean unadjusted (SD)	15.3±15.3	19.2±22.0	13.4±13.3	17.7±22.9	16.9±16.6	20.4±21.1		
Haematoma + IVH (ml), mean unadjusted (SD)	17.7±16.9	23.2±29.5	14.9±14.6	21.1±33.3	20.1±18.4	25.0±25.7		
Haematoma growth								
Growth (ml), mean unadjusted (95%CI)			4.3(2.8-5.9)		3.4(2.0-4.9)		0.9(-1.2-3.0)	0.40
Growth (ml), mean adjusted* (95% CI)			6.8(4.3-9.2)		5.1(3.0-7.2)		1.7(-0.5-3.9)	0.13
Growth (%), median unadjusted (95% CI)			19.6%(13.6-25.8%)		17.3%(11.8-23.0%)		2.2%(-6.5-10.8%)	0.59
Growth (%), median adjusted (95% CI)			29.2%(19.2-40.0%)		25.7%(17.3-34.6%)		3.6%(-5.6-12.7)	0.46
Haematoma + IVH growth								
Growth (ml), mean unadjusted (95%CI)			6.2(3.9-8.5)		4.9(2.8-7.0)		1.2(-1.9-4.4)	0.43
Growth (ml), mean adjusted* (95% CI)			9.2(5.5-12.8)		6.9(3.8-10.0)		2.3(-1.0-5.6)	0.17
Growth (%), median unadjusted (95% CI)			22.1%(15.8-28.7%)		19.1%(13.4-25.1%)		2.8%(-6.1-11.7%)	0.51
Growth (%), median adjusted (95% CI)			34.9%(24.1-46.6%)		29.5%(20.6-39.1%)		5.4%(-4.4-15.1%)	0.29

Table 4.5: Haematoma Growth parameters at 24 hours post randomisation, by diabetes mellitus status

	All (N=963)		Non-Diabetes Mellitus (N =833)		Diabetes Mellitus (N =130)		Absolute (mls) / proportional (%) less in patients with IVH(95% CI)	P Value
Haematoma volumes, baseline to 24 hours	Baseline	24 hours	Baseline	24 hours	Baseline	24 hours		
Haematoma (ml), mean unadjusted (SD)	15.4±15.3	19.4±22.2	15.6 ±15.4	19.4 ± 22.5	14.2±14.9	19.0±20.3		
Haematoma + IVH (ml), mean unadjusted (SD)	17.8±17.0	23.5±29.9	17.9±16.9	23.5±30.3	17.1±17.4	24.0±26.8		
Haematoma growth			24 hours minus baseline		24 hours minus baseline			
Growth (ml), mean unadjusted (95%CI)			3.8(2.7-4.9)		4.8(2.0-7.6)		-0.9(-3.9-2.1)	0.54
Growth (ml), mean adjusted* (95% CI)			5.7(3.3-8.1)		6.2(2.5-9.9)		-0.5(-3.8-2.9)	0.79
Growth (%), mean unadjusted (95% CI)			17.0%(12.8-21.3%)		26.7%(15.5-38.8%)		-10.4(-25.6-4.8)	0.11
Growth (%), median adjusted (95% CI)			24.9%(15.4-35.2%)		29.5%(14.8-46.0%)			0.52

Table 4.6: Cerebral oedema parameters at 24 hours post randomisation

	Glucose<6.5(N=376)		Glucose≥6.5 (N =413)		P Value
Cerebral oedema volume, baseline to 24 hours	Baseline	24 hours	Baseline	24 hours	
Cerebral oedema (ml), median unadjusted (IQR)	1.7(0.8-3.5)	3.3(1.5-6.2)	2.0(1.0-3.9)	3.7(1.8-7.1)	
Absolute Growth (ml), mean unadjusted (95%CI)	2.7(2.1-3.3)		2.6(2.0-3.1)		0.81
Growth (ml), mean adjusted* (95% CI)	3.3(2.4-4.2)		2.8(2.0-3.5)		0.19
Relative Growth (%), mean unadjusted (95% CI)	85.2(71.1-100.3)		74.3(61.7-87.9)		0.28
Growth (%), mean adjusted (95% CI)	94.1(71.6-119.5)		86.0(67.0-107.1)		0.46

Multivariate Model adjusted for age, geographical region, sex, history of stroke, history of hypertension, treatment, baseline haematoma volume, IVH extension, baseline systolic blood pressure, and history of diabetes.

Chapter 5: Discussion and concluding remarks

Conclusions from Analyses

My investigation examined admission hyperglycaemia in ICH specifically determining incidence, independent predictors, associations with outcome (primary and secondary) and haematoma parameters, relationship with diabetes mellitus and potential underlying mechanisms.

From baseline data I analysed demographic factors, clinical parameters and haematoma characteristics (volume, location, IVH extension) that were independent predictors of admission hyperglycaemia. In multivariate analysis (n=2653) after adjusting for all significant variables of univariate analysis and clinically significant interactions, the strongest independent predictor for hyperglycaemia was diabetes mellitus (aOR 5.91 95%CI 4.21-8.31, P<0.0001) (Table 2.1). To minimise the confounding effect of diabetes mellitus, independent predictors of hyperglycaemia in the non-diabetic patients (n=2361) were also determined (Table 2.2).

Demographics such as gender (females) and patients recruited outside of China were determinants of hyperglycaemia in the complete and non-diabetic analyses. Significant association was also present between hyperglycaemia and ICH severity as determined by the NIHSS score. Severity is also reflected through haematoma parameters with haematoma volume and IVH extension being significant predictors of hyperglycaemia. This analysis in non-diabetic patients illustrates the potential stress hyperglycaemic mechanisms involved outside of the diabetic effect. Hyperglycaemic patients were also found to have significantly fewer deep haematomas when compared to normoglycaemic patients. This baseline analysis of haematoma characteristics directed my research into a more extensive examination of ICH parameters (Chapter 4).

In the hyperglycaemic group, haematoma volume was significantly greater at baseline. To further examine if there was an incremental trend, I separated the cohort into quartiles by admission blood glucose. Increasing quartiles of blood glucose were associated with greater median ICH and combined (ICH + IVH) volume (Table 4.2).

The significance of haematoma location with potential mechanisms and suggestions for future studies

Baseline analysis showed association between hyperglycaemia with superficial territory of ICH. I performed further location analysis to investigate the mechanism of hyperglycaemia. If certain haematoma territories, responsible for glucose metabolism, were more commonly affected in the hyperglycaemic group this would potentially suggest the underlying mechanism. I examined associations with lobar, cerebellar and deep haematomas. Hyperglycaemic patients were more likely to have cerebellar (5.9% hyperglycaemic group vs. 1.1% normoglycaemic group) and superficial/cortical haematomas whilst deep and thalamic haematomas were significantly less frequent.

Cerebellar haemorrhage is associated with poorer outcomes and significant long-term morbidity and mortality. Due to anatomical location, cerebellar haemorrhage can lead to ventricular and brainstem compression. Involvement of the fourth ventricle can accelerate elevation in intracranial pressure thereby limiting cerebral perfusion and exacerbating neuronal injury. Cerebellar haemorrhage can also cause brainstem compression with the potential for trans-tentorial herniation with a smaller study (n=42) showing 60% of patients exhibiting radiological signs of brainstem compression and herniation.[153] Determinants of outcome in cerebellar haemorrhage include haematoma volume, diameter and initial GCS score. Poor functional recovery and significant mortality at 6 months has been previously reported.[154,155] Data assessing hyperglycaemia in cerebellar haemorrhage has been limited; however, the investigation by Wu et al.[59] determined independent predictors of outcome. They reported haematoma diameter and admission hyperglycaemia (> 7.8 mmol/L) to be predictive of mortality at discharge. In the 86 patients with cerebellar haemorrhage in INTERACT2 cohort, 84.9% presented with admission hyperglycaemia (n=73). Further investigation of hyperglycaemia specifically in cerebellar haemorrhage can be performed to examine associations with haematoma parameters (volume and diameter) and complications (brainstem compression, trans-tentorial herniation). This may also reveal potential mechanism for poorer outcomes in hyperglycaemic ICH patients.

A limitation of my approach was that the categorisation of location was too general. More specific categorisation would underline potential critical neuroanatomical regions affected by ICH and involved in dysfunction of glucose metabolism. Determining the involvement of regions such as the hypothalamus may provide further understanding for the cause of elevated blood glucose levels. The hypothalamus regulates glycaemic control with

specialised glucose sensing neurons involved in insulin regulation at the pancreatic islet cells as seen in animal models.[156] Glucose kinase activity in the hypothalamus mediates processing of glucose and initiates the insulin response via the neural-islet axis. Chronic down-regulation of these hypothalamic insulin receptors lead to glucose intolerance and pancreatic islet cell impairment reflecting their role in glucose metabolism in the rat model.[157] Distinct glucose-sensitive regions in the hypothalamus that have been identified include the ventromedial[158], lateral and arcuate nucleus[159]. The dorsal vagal complex in the brainstem also contains glucose sensitive neurons involved in glucose homeostasis[160] with recent studies reporting the role of the nucleus of solitary tract in detecting circulating glucose. Analysing the specific location of ICH in patients with hyperglycaemia may indicate if these glucose-critical regions are damaged and thereby responsible for the hyperglycaemic state rather than a generalised physiological stress response.

Blood glucose level is also affected by autonomic activation and neurohormonal signalling. The release of adrenocorticotropic hormone (ACTH) from the anterior pituitary induces cortisol release via the hypothalamic-pituitary-adrenal axis (HPA axis). The net effect is a hyperglycaemia through increased hepatic gluconeogenesis and decreased peripheral uptake of glucose. Sympathetic activation will also cause hyperglycaemia through increased serum adrenaline and noradrenaline. Damage to structures involved in autonomic pathways and the HPA axis may also explain the hyperglycaemic response. Whilst this could not be determined in the present study, more specific location analysis may allow this. In the INTERACT2 analyses, cortisol and catecholamine levels were not recorded. An earlier study by van Kooten et al. measured catecholamine levels as a surrogate marker for physiological stress and found no association with blood glucose and suggested that hyperglycaemia was not a result of the stress response[161]. A limitation of this analysis is that plasma catecholamine levels are not an accurate marker of sympathetic nervous system activation. The plasma concentration of catecholamines only represents a proportion of total neurotransmitter released and plasma levels are also affected by local neuronal uptake.[162] Catecholamine levels are also determined by physiological stimuli such as breathing, emotional stimuli and body positions (standing, squatting). These factors may have contributed to the lack of association found in this observational study. The statistical significance of this study was also limited by its small cohort size (n=91). Further investigation is required in determining the association of stress hormones (catecholamines, cortisol) with blood glucose levels as this will highlight the magnitude of the stress component in hyperglycaemia.

Mechanism driving hyperglycaemia: stress response or diabetic pathophysiology

The primary question in terms of the mechanism is whether the driver of hyperglycaemia is the severity of the ICH (by volume, location, IVH extension) or if an inherent dysglycaemic state caused by diabetes (diagnosed or undiagnosed). I also aimed to determine if hyperglycaemia acts as a marker of this physiological stress and diabetic pathophysiology or whether it exacerbates neuronal injury. From the baseline characteristics and determinants of hyperglycaemia, a significant association was observed with history of diabetes (n=292). Undoubtedly diabetic patients would be more prone to hyperglycaemia due to impaired glucose homeostasis mechanisms and accordingly 84.2% of diabetics in our study presented with admission hyperglycaemia. However, there were still 1102 non-diabetic hyperglycaemic patients in our analyses. Within this group there would be a proportion of undiagnosed diabetics and patients with pre-diabetes (impaired fasting glucose and impaired glucose tolerance) which must be accounted for. The determinants of the hyperglycaemia in the non-diabetics were parameters of ICH severity (haematoma volume and location, IVH extension, NIHSS score) as well as demographic differences. Therefore, there are multiple mechanisms at play in the presentation of hyperglycaemia. There is the contribution of diabetic pathophysiology and potentially undiagnosed diabetes. However, outside of this effect the severity of the haematoma is the other significant driver highlighting the role of the stress response.

The role of BP lowering in hyperglycaemic and diabetic patients: a potential treatment effect

The INTERACT2 study compared intensive and guideline based BP lowering therapy in acute ICH in terms of long-term outcome (3-month death or major disability). The main paper[105] examined primary (death or major disability) and secondary outcomes (mRS score, health-related quality of life, fatal and non-fatal adverse events). It also compared the treatment effect across 8 subgroups: age, region (from or outside China), time to randomisation, baseline SBP, history of hypertension, baseline NIHSS score, baseline haematoma volume and location. Across all subgroups there was no significant difference in primary or secondary outcomes.

In this analysis, the treatment effect with admission blood glucose and history of diabetes mellitus was not studied. However, there is the potential to revisit these earlier models and assess the potential treatment effect in the hyperglycaemic group. This would involve comparing hyperglycaemic patients treated with guideline and intensive therapy and

reviewing whether there are differences in primary and secondary outcomes. More recent INTERACT2 analyses explored the efficacy of BP reduction of SBP in hypertensive patients by comparing minimal (<10 mm Hg), moderate (10-20 mm Hg) and large (≥ 20 mm Hg) changes in SBP and determining association with poor outcomes (death or major disability).[163] This showed that large reductions in SBP during the first hour and maintained over 7 days were less associated with poor outcome in comparison with minimal reductions (<10 mm Hg). There is also the potential to assess how hyperglycaemic patients respond to different degrees of BP reduction.

At baseline, the hyperglycaemic patients presented with significantly greater SBP (P=0.0001). It is critical to evaluate the differences between guideline and intensive therapy and to determine how aggressively blood pressure should be lowered in this important subset of ICH patients. The treatment effect must also be explored in the diabetic patients. The microvascular complications of diabetes are well documented and the overlap between diabetes and hypertension is known. Both are significant cardiovascular and cerebrovascular risk factors and accelerate atherosclerosis. Therefore, exploring potential treatment effects in both hyperglycaemic and diabetic patients will provide valuable data regarding the therapeutic approach to these patient subsets and whether a distinct BP lowering strategy is required when treating ICH patients presenting with diabetes or admission hyperglycaemia.

Association between admission hyperglycaemia and outcomes

After establishing baseline characteristics and determinants of hyperglycaemia, I investigated the associations with primary and secondary outcomes. Primary outcomes were death or major disability, death alone, and major disability alone, at 90 days whilst secondary outcomes were neurological deterioration over the first 24 hours, and fatal and non-fatal adverse events.

Existing data on hyperglycaemia in ICH and associations with outcomes is represented in Table 1 and 2. The majority of data evaluates outcomes either at discharge or in the first month post ICH with limited data on longer term follow-up. However, the majority of these studies report significant association with poorer survival in the hyperglycaemic patients. Our findings at 3-months build upon the existing literature with the advantage of INTERACT2 analyses being the significantly larger cohort size, multi-centre data and comprehensive study design.

Our multivariate model adjusted for all significant baseline variables and clinically significant interactions and patients were divided based on admission blood glucose (quartile analysis). There was a significant association with death or major disability (P trend=0.015), specifically in the two highest quartiles of admission blood glucose (Q3 aOR 1.31 95%CI 1.01-1.71; Q4 aOR 1.35 95%CI 1.01-1.80). When admission blood glucose was examined as a continuous variable the significant association with poor outcome was also noted (aOR 1.11, 95%CI 1.00-1.24; P<0.0001). Therefore, our analyses confirm that admission hyperglycaemia is an independent predictor of poor outcome, independent of diabetes mellitus, haematoma volume, IVH extension and other significant interactions.

When comparing INTERACT2 results with existing literature, the baseline characteristics of other studies must be considered. Specifically, the proportion of patients presenting with hyperglycaemia varies across different trials (Table 5.1). This is also affected by differing definitions of hyperglycaemia applied in different investigations. I selected 6.5 mmol/L as this was the median level of admission blood glucose and allowed effective categorisation of patients for quartile analysis. Given that the majority of our patients were from China, the proportion of diabetes in the study (11%) was surprisingly lower than other trials. However, these 292 patients were enough to provide significant statistical power for outcome analyses. The primary outcomes also varied across the ICH trials conducted to date with in-hospital, 30-day and 3-month mortality and morbidity being investigated. Long-term outcomes (3-months) were limited by smaller cohort sizes, univariate analysis and conflicting results. My analyses of the INTERACT2 cohort overcame limitations of cohort size and multivariate analysis showed significant association with poor outcome (death or major disability) at 3-months.

Safety outcomes, adverse events and early neurological deterioration in INTERACT2 analyses

Analysis of secondary outcomes also provided further information regarding the underlying mechanisms in admission hyperglycaemia. Hyperglycaemic patients experienced greater fatal adverse events (Table 3.3) primarily caused by the initial haematoma itself. Complications in hyperglycaemic ICH patients was earlier explored by Passero et al.[96] who found greater cerebral and infectious complications. My analyses showed that there were significantly greater deaths due to the initial ICH (P<0.001) and significantly greater early neurological deterioration (P=0.014) in the hyperglycaemic patients. However, there were no significant differences in rates of sepsis and respiratory infections between hyperglycaemic and

normoglycaemic patients. Early neurological deterioration was measured as decreases in GCS (≥ 2 points) or increased ICH severity (≥ 4 points NIHSS score)[105]. These clinical measures of neurological deterioration could be due to evolution of symptoms from the initial ICH or attributed to progression of the initial haematoma. As a result, I compared haematoma characteristics (haematoma growth and perihaematomal oedema) over the first 24 hours as causes of worsening neurological status and as potential mechanisms for the poorer long term outcomes in hyperglycaemic patients.

Safety outcomes were also assessed in the diabetic and non-diabetic patients. In contrast to analyses for hyperglycaemia and normoglycaemia, the data on those with diabetes mellitus showed significantly greater cardiovascular adverse events (non-fatal) with no associations with early neurological deterioration. There were no significant differences in causes of death between those with and without diabetes mellitus is in keeping with multivariate model finding showing no significant association of diabetes with mortality. Comparing the differences in safety outcomes between diabetes and hyperglycaemia reveals that there may be distinct mechanisms involved in these two patient groups. The association of diabetes with cardiovascular events reflects microvascular and macrovascular complications of the disease. To better understand these mechanisms, I explored associations of haematoma growth and perihaematomal oedema with admission blood glucose and also history of DM (Chapter 4).

To elucidate the mechanism underlying adverse outcomes in hyperglycaemia, I examined haematoma characteristics based on previous investigations and animal models. Induced hyperglycaemia in animal models showed haematoma expansion and exacerbation of perihaematomal oedema. However, there has been limited data in clinical trials of ICH assessing these parameters. Therefore, in sub-study analysis of the INTERACT2 cohort, I explored potential mechanisms explaining the significant neurological deterioration seen in the hyperglycaemic group. I hypothesised that hyperglycaemic patients would experience greater haematoma growth and perihaematomal oedema 24 hours post-ICH aligning with early neurological deterioration reported in hyperglycaemic patients. Surprisingly, there was no difference in haematoma growth or perihaematomal oedema in patients with hyperglycaemia. These results suggest that hyperglycaemia may play a role in initial haematoma growth, with significantly greater baseline haematoma volume but with limited change in volume over 24 hours. Haematoma characteristics that were not examined in my analyses included hydrocephalus and brainstem compression due to lack of specific data collected, which could be explored in future studies.

Whilst increased IVH volume is associated with poor outcomes[164], this was adjusted for in multivariate analyses and associations between hyperglycaemia and IVH have been previously reported[72]. Appelboom et al.[72] reported linear relationship between IVH severity score and the admission blood glucose level. Further, IVH was found to be an independent predictor of critical hyperglycaemia which has been confirmed in the INTERACT2 analyses. Hyperglycaemia may exacerbate neuronal injury through blood brain barrier disruption, oxidative damage and inflammatory activation thereby causing extension into the ventricular system. Therefore, hyperglycaemia is associated with specific severe haematoma characteristics and these may contribute to the associated neurological deterioration, mortality and major disability.

Associations of diabetes mellitus and outcome

Earlier studies have investigated associations between diabetes mellitus and ICH, specifically focusing on complications, determinants and outcomes. Arboix et al.[35] in univariate analyses found significantly greater mortality in diabetic patients and in multivariate models reported significant association with previous ICH, haematoma affecting multiple locations and cranial nerve palsy. INTERACT2 analyses also found that diabetics were significantly more like to have experienced previous stroke (ischaemic or undifferentiated), however, found no associations with specific ICH location. Baseline differences in diabetic patients reflected the shared pathophysiology with cardiovascular disease with significantly greater history of hypertension, heart disease and specific medications (beta-blocker, calcium channel blocker, anti-hypertensive, insulin therapy) (Table 3S1).

Interestingly at baseline, diabetic patients had significantly smaller ICH (diabetes 9.2 ml vs. non-diabetes 11.2 ml, P=0.002) and combined haematoma volumes (diabetes 11.4 ml vs. non-diabetes 13.3 ml, P=0.035) (Table 3S1). There was also no association seen with IVH extension or location of haematoma. These baseline characteristics starkly contrast the comparison between hyperglycaemic and normoglycaemic patients where hyperglycaemia was significantly associated with greater haematoma volumes, IVH extension and specific haematoma locations (cerebellar and cortical). These differences between diabetic and hyperglycaemic patients indicate distinct mechanisms involved in these patient groups. The non-diabetic hyperglycaemic patients are affected by the stress response to the acute haematoma with poorer outcomes potentially exacerbated by elevated blood glucose levels. In diabetic patients the hyperglycaemia may result from multiple mechanisms including the

impaired glucose homeostasis from the disease along with physiological stress response to the acute ICH.

In terms of outcomes, diabetic patients had significantly greater death or major disability (aOR 1.43 95%CI 1.03-2.00, P=0.035) and major disability alone (aOR 1.49 95%CI 1.06-2.10, P=0.023), however, no association with death alone (P=0.743) (see Table 3S3). This confirms recent Chinese population study (n=1438) who also reported DM was not a significant predictor of mortality.[37]

Clinical application, Insulin Therapy and Potential for RCT

My investigation of hyperglycaemia and diabetes mellitus in spontaneous ICH raises the question of whether there is a role of targeted insulin therapy for specific blood glucose levels. Whilst my data showed no critical threshold of blood glucose, a significant trend was observed with increasing levels at admission associated with poorer outcomes. Current guidelines are far from comprehensive regarding the approach to hyperglycaemia in ICH.

Older studies investigating the role of intensive insulin therapy in Intensive Care Units provided positive evidence for this approach. A 'landmark' trial by van den Berghe et al.[165] is frequently cited. This prospective, randomised controlled trial (n=1548) compared conventional (target blood glucose: 10.0-11.1 mmol/L) to intensive therapy (target blood glucose: 4.4-6.1 mmol/L). 4% of these patients were admitted in ICU for neurologic disease with the majority being post-cardiac surgery. Benefits reported from this trial included reduced ICU admission length, decreased rates of septicaemia, less prolonged requirement for ventilation and most importantly reduced mortality. These findings were supported in a later Chinese study[166].

However, subsequent trials have yielded mixed results in terms of the benefits of intensive insulin therapy (IIT) in critically ill patients. Meta-analysis of these patients (n = 8432) showed no significant difference with in-hospital mortality.[167] Adverse event analysis showed significantly greater hypoglycaemic events but also showed significantly lower incidence of septicaemia in the IIT group. It should be noted that inclusion criteria was for ICU patients and represented a wide range of patient types (cardiac surgery, acute cerebrovascular events, trauma, acute coronary syndrome, sepsis). Further systematic reviews[168-170] found no survival benefit and significantly greater IIT-induced hypoglycaemic events. Arabi et al. investigated the clinical significance of this hypoglycaemia and reported no significant difference in mortality when compared with controls.[171] In patients with critical

hypoglycaemia (BSL < 1.2 mmol/L) a trend towards poorer outcomes was noted but this was not statistically significant in multivariate analyses.

Whilst aforementioned studies focused on medical and surgical ICU patients, more recent trials have been conducted in stroke with the majority of literature examining on acute ischaemic stroke. An early pilot study tested the safety and tolerability in controlling BSL between 5-8 mmol/L and found that insulin requirements decreased within 48-hours suggesting a role for early aggressive therapy to control glycemic control.[172] The randomised pilot study (THIS)[173] explored the differences in clinical outcomes at 3 months by looking at mRS scores ≤2, Stroke-Specific Quality of Life, modified Barthel Index and NIHSS. Hypoglycaemic events were experienced in the IIT group, however, these were mostly asymptomatic and easily resolved. Whilst clinical outcomes were more favourable in the IIT patients these results were not statistically significant. This study has been extended upon with the SHINE trial which is currently underway.[174] This investigation will compare standard vs. intensive insulin management in hyperglycaemic stroke patients with targeted cohort of 1400 patients. The primary end-point will be 90-day clinical outcome using modified Rankin scale.

The INSULININFARCT trial examined the effect of IIT upon infarct growth using MRI imaging. Although more optimum glycaemic control was achieved with IIT, this therapy was also significantly associated with larger infarct growth. However at 90-days there was no difference in mortality or serious adverse events.[175] Further analysis of a sub-group of this trial (n=99) examined the effect of insulin therapy upon the penumbral region. Hyperglycaemic patients experienced worsened ischaemic damage; however, the insulin therapy had no effect upon severity of ischemia.

In ICH there is limited literature regarding the role of IIT. Godoy et al.[176] studied the effect of insulin therapy. Whilst mild hypoglycaemia was reported it was associated with no significant adverse outcomes. There was no change in mortality in patients treated with insulin for tight glycemic control.

At this stage there is not enough evidence regarding the potential of IIT in ICH. From INTERACT2 analyses, where significant associations were observed with hyperglycaemic patients and early neurological deterioration and later clinical outcomes (3-months), there is a definite need for further investigation into the effect of tight glycaemic control upon outcome. Although our sub-study analysis showed no association with haematoma growth and

perihaematomal oedema, further confirmatory investigation is required and other haematoma characteristics such as hydrocephalus and brainstem herniation must be examined. The majority of patients in INTERACT2 were of mild-moderate severity (based on NIHSS score). Assessing the role of hyperglycaemia in different severity ICH would also be useful.

I recommend the undertaking of a randomised pilot trial to examine the safety and tolerability of IIT in ICH, before proceeding to a large scale clinical endpoint trial. Specifically, I would examine in-hospital mortality, hypoglycaemic events, infectious and cerebral complications during hospital admission. Three-month clinical outcomes would also be assessed (death or major disability). We would also want to determine differences in haematoma growth, perihaematomal oedema following tighter glycaemic control. With the difference in hyperglycaemia based on location reported, it may also be interesting to investigate if deep vs. cortical haematomas are more responsive to aggressive insulin therapy.

However, before proceeding to a large-scale clinical trial it is essential to directly examine the relationship between glycaemic control and intracerebral haematoma growth. A proof-of-concept (PoC) trial would allow the signal between tight glycaemic control and haematoma growth to be assessed and may also provide preliminary insights into the efficacy of this therapy. Specifically, it would assist in examining the association between tight glycaemic control and increases in haematoma volume, intraventricular extension and perihaematomal oedema.

The advantages of PoC studies are in their simplified study design and small-scale approach which limits funding requirements and overcome issues of timing related with large clinical trials. Examining adverse events such as rates of hypoglycaemia will also provide integral information regarding the safety of tighter glycaemic control in intracerebral haemorrhage patients. These studies may also suggest an optimum therapeutic window for glycaemic control. Results from such trials will assist in determining the need and benefit for further larger-scale investigation.

Limitations of PoC trials must also be considered. Statistical power will be reduced by smaller sample sizes and potential confounding variables such as age, gender, medical history (hypertension, coronary artery disease), medications (anti-coagulation, anti-platelet therapy, anti-hypertensives) must be considered and adjusted for. The time required for recruitment of suitable patients is another factor that could reduce efficiency of the trial.

A number of recent trials have investigated outcomes associated with intensive insulin therapy in neurocritical care and acute ischaemic stroke with varying results. Poorer outcomes with significantly higher hypoglycaemic events and higher mortality have been reported[177] with 71% incidence of hypoglycaemia found in ischaemic stroke patients.[178] The INSULINFARCT trial[179] also studied insulin therapy in ischaemic stroke and whilst hyperglycaemia exacerbated neuronal ischaemia, there was no improvement in infarct volumes in patients receiving intensive insulin therapy. Therefore the ethical considerations of performing PoC studies must be taken into account as aggressive insulin therapy may subject patients to potentially significant harm. Before commencement these risks must be examined, however, a PoC trial with small sample size may provide a vital starting point in understanding the role of insulin therapy in intracerebral haemorrhage.

Overall, my investigation has provided a comprehensive overview on the role of hyperglycaemia in ICH with the recommendation for a proof-of-concept study comparing intensive and standard glycaemic control in ICH.

Table 5.1: Overview of studies assessing association hyperglycaemia and outcomes at 1-month and 3-month

Study	Cohort Size	% Hyperglycaemia	% Diabetes	Hyperglycaemia definition	Outcome	Critical Level	AOR	P value
Early Outcome								
Appelboom	104		23.20%	10mM	Discharge Mortality	10mM	4.381(1.186–16.174)	0.03
Franke	157	50.30%	N/A	≥8 mmol/L	2-Day Mortality	>8mM	5.5	0.01
Samiullah	399	27.30%		≥7 mmol/L (fasting) or ≥8.6 mmol/L	In-Hospital Mortality		10.9(4.72-25.32)	<0.001
Tetri	379	33.80%	17.94%	>8.0mM	2 day Mortality	-	1.04 (0.95–1.13)	Not Significant
Kimura	100		Not Reported	>150 mg/dl	14-Day Mortality	>150 mg/dl	37.34(1.40-992.73)	0.031
Outcome at 1-month								
Fogelholm	290		11.90%	9.1 mM	28 day Mortality		1.22(1.07-1.40)	0.004
Bejot	465			≥8.6 mmol/L	1-Month Mortality	≥8.6 mmol/L	2.51(1.23-2.43)	0.002
Lee	1387		11.60%	-	<30 day Mortality	-	1.10(1.01-1.19)	0.03
Lee	1119		NDM	-	Non-DM, <30 day	-	1.11(0.999-1.22)	0.053
Passero	637	43.20%	17%	≥130 mg/dl	30 day Mortality	≥130 mg/dl	1.099(0.947-1.275)**	
Godoy	295		50.17%	≥7.22 mmol/l or 130 mg/dl	30-Day Mortality	9.08 mmol/l	1.51(1.23–1.85)	<0.0001
Tapia-Perez	116		31.90%	>140 mg/dL	30-Day Mortality	>140 mg/dL	2.65(1.15–6.12)	0.02
Tan	3756	39.60%	N/A	≥7.5mM	In-hospital to 1-month Mortality	-	3.46(1.66-7.20)	0.0009
Outcome at 3-months								
Passero	637	43.20%		≥130 mg/dl	3-Month Mortality	≥130 mg/dl	1.086(0.941-1.253)**	
Appelboom	104			10mM	3-month Mortality	10mM	10.85(1.886–62.41)	0.02
Tetri	379			>8.0mM	3 Month Mortality	-	1.04 (0.99–1.10)	Not Significant
INTERACT2	2653	61%	11%	>6.5mM	3-Month Death or Major Disability	-	1.11 (1.00-1.24)	P<0.0001
INTERACT2	2653	61%	11%	>6.5mM	3-Month Mortality	-	1.16 (1.01-1.33)	P=0.043

Table 5.2: Other studies investigating associations between hyperglycaemia and poor outcomes in ICH

Study	Cohort Size	% Hyperglycaemia	% Diabetes	Hyperglycaemia definition	Outcome	Critical Level	AOR	P value
Sun	149		23.50%	≥140 mg/dl	Late Neurological Deterioration	140 mg/dl	2.614 (1.146–5.965)	0.022
Zhang	54	-	DM group	-	Poor Outcome, mRs >2	-	1.109(0.704–1.394)	0.078
Zhang	234	-	NDM group	-	Poor Outcome, mRs >2	-	0.995(0.763–1.26)	0.105
Qureshi	60	42%	N/A	-	modified Rankin Score 4-6	114 mg/dl	2.64(1.03-6.75)	
Stead	237	19.80%		140 mg/dl				0.0037
Feng	135	33.30%	19.26%	≥150 mg/dl	modified Rankin Score ≥3	≥150 mg/dl		
Lee	1387		11.60%	-	> 30 day Mortality	-	1.05(0.98-1.11)	0.15
Lee	1119		NDM	-	Post-ICH Mortality	-	1.10(1.03-1.17)	
Lee			NDM	-	Non-DM, >30 day	-	1.07(0.99-1.16)	0.09
Wu	62	N/A	27.40%	≥140 mg/dl	Poor Outcome, Glasgow Outcome Scale	≥140 mg/dl	25.217	0.008
Bejot	465			≥8.6 mmol/L	Function Handicap	≥8.6 mmol/L	2.51(1.43-4.40)	0.01

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