Prognostic Significance of Hyperglycemia in Acute Intracerebral Hemorrhage
The INTERACT2 Study

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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 Hemorrhage Trial (INTERACT2).

Methods—INTERACT2 was an international prospective, open, blinded end point, randomized controlled trial of 2839 patients with spontaneous intracerebral hemorrhage (<6 hours) and elevated systolic blood pressure randomly assigned to intensive (target systolic blood pressure <140 mm Hg) or guideline-based (systolic blood pressure <180 mm Hg) BP management. Associations of hyperglycemia 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 hyperglycemia 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 1.35, 95% confidence interval 1.01–1.80; *P* trend 0.015). Diabetes mellitus also predicted poor outcome (adjusted odds ratio 1.46, 95% confidence interval 1.05–2.02; *P*=0.023), though more important for residual disability than death on separate analysis.

Conclusions—Hyperglycemia and diabetes mellitus are independent predictors of poor outcome in patients with predominantly mild to moderate severity of intracerebral hemorrhage. These data support guideline recommendations for good glycemic control in patients with intracerebral hemorrhage.

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Key Words: clinical trial ■ death ■ diabetes mellitus ■ disability ■ hyperglycemia ■ outcome ■ prognosis

Acute intracerebral hemorrhage (ICH) is the most serious and least treatable form of acute stroke[1] for which established prognostic factors include clinical severity and location and volume of hematoma at presentation.[2] Although stress hyperglycemia is associated with adverse outcomes in many medical conditions, including acute ischemic stroke,[3,4] traumatic brain injury,[5] and acute myocardial infarction,[6] evidence specifically related to the critical condition of ICH is varied and conflicting because of previous studies being limited to small single-center series[7,8] with short duration of follow-up.[9] Animal models have shown that elevated blood pressure (BP) exacerbates cerebral injury after ICH[10] and of an association between hyperglycemia and cerebral edema. There may be a supra-additive effect of hyperglycemia and

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the hypertensive response in ICH on outcome. The purpose of this study was to quantify risk associations of hyperglycemia and diabetes mellitus among participants of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2).[11] Our hypothesis was that hyperglycemia is associated with poor outcome in ICH.

Materials and Methods

INTERACT2 was an international, multicenter, prospective, open-label, assessor-blinded end point, randomized controlled trial, the details of which are described elsewhere.[11] In brief, 2839 patients with computed tomography–confirmed spontaneous ICH within 6 hours of onset and elevated systolic BP (150–220 mm Hg) were randomly assigned to receive intensive (target systolic BP <140 mm Hg within 1 hour) or guideline-recommended (target systolic BP <180 mm Hg) BP-lowering therapy using locally available agents according to standardized 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 enrollment included a history of diabetes mellitus and level of blood glucose. Stroke severity was measured using the Glasgow coma scale and National Institutes of Health stroke scale at baseline, 24 hours, and at Day 7 (or on discharge from hospital if this occurred earlier). For each computed tomography 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. Hematoma volumes with and without inclusion of any intraventricular hemorrhage 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 multislice planimetric and voxel threshold techniques in MIStar software (version 3.2; Apollo Medical Imaging Technology, Melbourne, Australia). Inter-reader reliability was checked by periodic reanalysis 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 to 6 on the modified Rankin scale[12] at 90 days. Secondary outcomes were separately those of death and major disability (modified Rankin scale score of 6 and 3–5, respectively) and serious adverse events, including early neurological deterioration (defined as an increase of ≥4 on the National Institutes of Health stroke scale or a decline of ≥2 on the Glasgow coma scale from baseline to 24 hours postrandomization). Primary causes of death were classified into 3 categories: (1) direct effects of initial ICH, defined as any death after the onset of the randomized ICH event in a patient who had progressive neurological deterioration, and either the baseline or follow-up brain scan showed hematoma with mass effect, midline shift, or significant extension of initial hematoma in the absence of a clear extracranial cause for the death; (2) recurrent cardiovascular event, defined by clear clinical evidence of a recurrent stroke, coronary vascular event, or sudden death, according to standard definitions; (3) other causes, defined by clear evidence of death because of a non-neurological cause that included pneumonia, sepsis, or injury.

Baseline characteristics were summarized as mean (standard deviation) or median (interquartile range) 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 normoglycemia (<6.5 mmol/L) or hyperglycemia (≥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 mellitus and clinical outcomes. Sensitivity analyses were conducted to examine clinical outcomes based on diagnostic thresholds of blood glucose for normoglycemia, pre-diabetes mellitus, and diabetes mellitus (<6.1, 6.1–7.0, >7.0 mmol/L, respectively). Cox proportional hazard modeling was used to measure survival over 90 days post ICH. The associations of hypergycemia on absolute increase in hematoma and perihematoma edema volumes over 24 hours were assessed by an analysis of covariance, including the same adjusted variables above. Data are presented with odds ratios (OR) and 95% CI. A 2-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).

Results

Of the 2829 ICH patients, 176 were excluded because of missing baseline blood glucose measurements (Figure in the online-only Data Supplement). Table 1 shows the baseline characteristics of the remaining 2653 patients, which included 1348 (51%) with hyperglycemia (>6.5 mmol/L) and 292 (11%) with diabetes mellitus. After adjusting for confounding factors, hyperglycemic patients were significantly more often female, from outside of China, had greater cortical hematomas, diabetes mellitus, higher systolic BP, greater clinical severity of stroke, and larger hematomas with intraventricular hemorrhage 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 hematoma volume than those patients without diabetes mellitus (Table I in the online-only Data Supplement).

No collinearity was found between the baseline variables. All significant interactions (age×National Institutes of Health stroke scale ≥15, China×intraventricular hemorrhage extension, baseline hematoma volume×deep location of hematoma, and deep location of hematoma×intraventricular hemorrhage 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 OR [aOR] 1.11, 95% CI 1.00 to 1.24; *P*<0.0001 and aOR 1.16, 95% CI 1.01–1.33; *P*=0.043 for death or major disability and death, respectively (Figure 1). Table 2 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 randomized lowering treatment from the multivariate model (Table II in the online-only Data Supplement). A history of diabetes mellitus (Table III in the online-only Data Supplement) 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*=0.871). 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

Table 1. Patients Characteristics According to Baseline Blood Glucose Level

Variable	Baseline Glucose Level, mmol/L				*P* Value
	2.60–5.59 (N=644)	5.60–6.49 (N=661)	6.50–7.90 (N=693)	7.91–25.0 (N=655)	
Age, y	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, h	3.8 (2.8–4.7)	3.7 (2.9–4.6)	3.7 (2.8–4.8)	3.7 (2.8–4.7)	0.936
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, mm Hg	177 (17)	177 (17)	180 (17)	182 (17)	<0.001
Diastolic BP, mm Hg	102 (14)	101 (14)	100 (15.3)	100 (15)	0.486
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)	0.983
Prior ischemic/undifferentiated stroke	76 (12)	69 (10)	82 (11.9)	75 (12)	0.835
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 hematoma†	514 (85)	538 (88)	524 (81.0)	460 (78)	<0.001
IVH extension	120 (20)	144 (24)	209 (32.3)	212 (36)	<0.001
Hematoma 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). *P* values based on chi-squared, *t* test, or Wilcoxon rank-sum test. BP indicates blood pressure; GCS, Glasgow coma scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; and NIHSS, National Institutes of Health stroke scale.

*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.

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 IV in the online-only Data Supplement). Adjusted Cox regression models indicate increasing risks of death by increasing (fourths) levels of baseline blood glucose (Figure 2A), although this association did not appear independent of diabetes mellitus (Figure 2B). In regard to reported serious adverse events (Table 3), hyperglycemic patients had significantly greater frequency of early neurological deterioration (16.5% versus 13.1%; P=0.014), death (14.4% versus 8.9%; P<0.0001), and nonfatal adverse events (25.5% versus 20.6%; P=0.003) in comparison with normoglycemic patients. However, there was no apparent difference in the frequencies of fatal and nonfatal ischemic, cardiovascular, or infectious events between the 2 groups of patients, but these numbers were small. Patients with a history of diabetes mellitus experienced significantly more nonfatal 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 V in the online-only Data Supplement).

There was a trend toward higher glucose levels among patients with higher baseline hematoma and perihematomal edema volumes (Tables VI and VII, respectively, in the online-only Data Supplement). However, there was no significant difference of increase in either hematoma or perihematomal edema volumes between patients with admission glucose <6.5 or ≥6.5 mmol/L.

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. Hyperglycemia seems 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 hematoma or perihematomal edema over 24 hours. 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 randomized BP lowering treatment. Although diabetes mellitus was also associated with poor outcome, this seems 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.

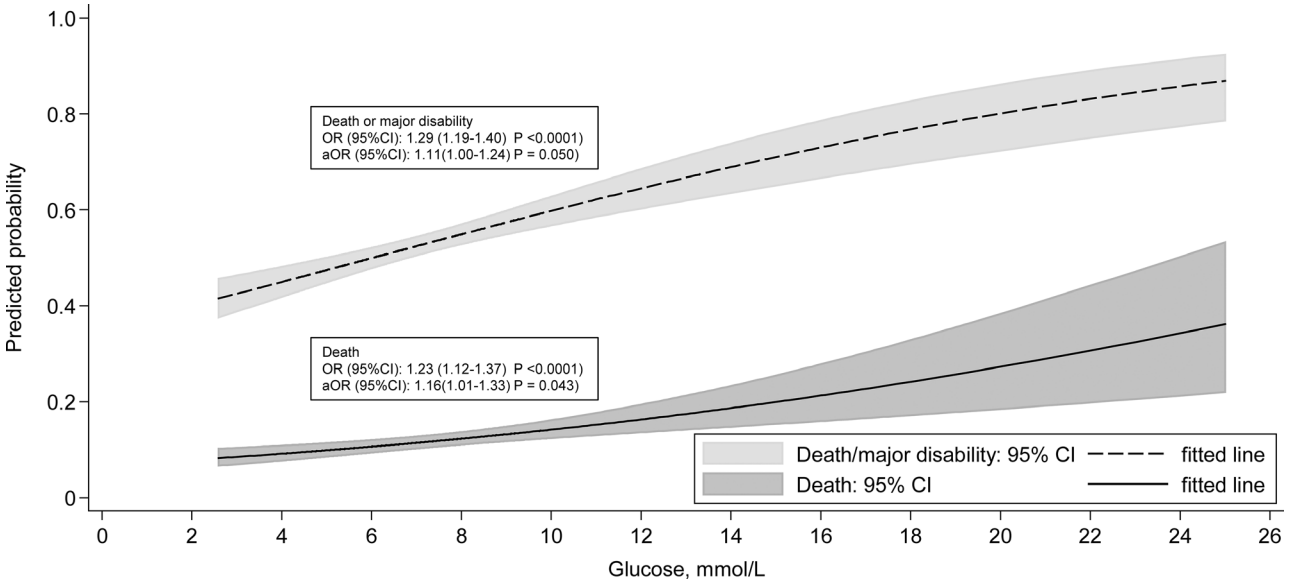

Figure 1. Predicted probabilities of outcome by baseline blood glucose level. Multivariate model adjusted for age, geographical region, sex, history of heart disease, history of hypertension, history of diabetes mellitus, use of aspirin or warfarin, baseline hematoma volume and location, intraventricular extension, baseline systolic blood pressure, admission National Institutes of Health stroke scale (score ≥15), randomized treatment, age×NIHSS ≥15, china×intraventricular extension, baseline hematoma volume×deep location of hematoma, and deep location of hematoma×intraventricular extension. aOR indicates adjusted odds ratio of outcome; 95% CI, 95% confidence interval; NIHSS, National Institutes of Health stroke scale; and OR, odds ratio for outcome.

Our findings extend previous reports of elevated blood glucose being a predictor of adverse outcomes in ICH[8,9,13,14]; in particular, the finding of a trend toward greater mortality from hyperglycemia that was observed in Korean multicenter study[9] of 1387 ICH patients, but not with that seen in a smaller Finnish study.[13] 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 to 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 hyperglycemia, such as 8[15] or 10 mmol/L,[7] for mortality, we have shown no threshold but rather a strong continuous relationship between this exposure and poor outcome in the INTERACT2 data set. The multivariable analyses indicate that these associations are specific to hyperglycemia rather than that of the pathophysiology of diabetes mellitus. In contrast to previous studies showing that diabetes mellitus is an independent

Table 2. Fourths of Baseline Blood Glucose and 3-Month Outcomes After Acute Intracerebral Hemorrhage

	Fourths of Glucose, mmol/L					Multivariate*	
Outcome	Category	n	Events, n (%)	OR (95% CI)	*P* Trend	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)	

aOR indicates adjusted odds ratio; CI, confidence interval; and OR, odds ratio.

*Adjusted for age, geographical region, sex, history of heart disease, history of hypertension, history of aspirin or warfarin use, history of diabetes mellitus, baseline hematoma volume and location, intraventricular extension, baseline systolic blood pressure, National Institute of Health stroke scale (NIHSS) score (≥15), randomized treatment, and age×NIHSS≥15, China×intraventricular extension, baseline hematoma volume×deep location of hematoma, and deep location of hematoma×intraventricular extension.

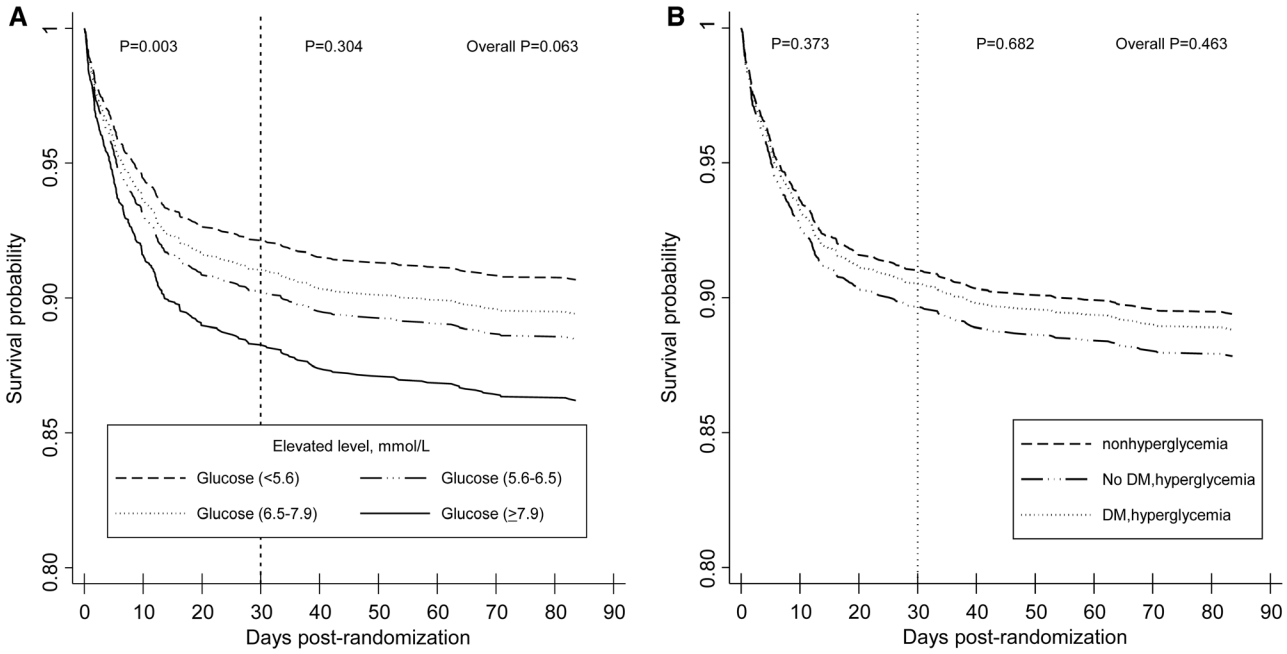

Figure 2. A, Cox proportional hazards regression curves for fourths of baseline blood glucose and death. **B**, Cox proportional hazards regression curves for death according to level of presence of hyperglycemia (>6.5 mmol/L) and history of diabetes mellitus (DM).

predictor of mortality after acute ischemic stroke,[16] and for in-hospital[17] and 1[18] and 3 months[19–21] time points after ICH, we did not find that diabetes mellitus predicted death after ICH.

The exact pathophysiological mechanisms underlying the adverse effects of hyperglycemia in ICH are yet to be elucidated. Hyperglycemia has been shown to induce neuronal

Table 3. 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
Nonfatal 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)	
Ischemic/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)	
Noncardiovascular 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)	
Ischemic/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)	
Noncardiovascular 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)	
Nonvascular medical	18/1297 (1.4)	32/1343 (2.4)	

ICH denotes intracerebral hemorrhage.

apoptosis in experimental ICH in adult Sprague–Dawley male rats,[22] but other reactions from inflammatory (interleukin-1β and tissue necrosis factor alpha)[23,24] and toxic (cerebral lactate and lactate/pyruvate ratios)[25] effects of oxygen-free radical generation[26] may also be important. Recent studies have also shown increased superoxide production, disruption of the blood–brain barrier,[27,28] and enhanced cerebral edema[29] in hyperglycemic rat models. Moreover, the study of Parsons et al[30] in patients with ischemic stroke has shown an association of hyperglycemia 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 glycemic control in ICH[31] and suggest that a blood glucose level of <7.0 mmol/L may be an optimal therapeutic target, despite the absence of randomized evidence. In the United Kingdom Glucose Insulin in Stroke Trial (GIST-UK),[32] there was no effect ofglucose–potassium–insulin compared with 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 randomized controlled trials comparing glycemic control by insulin with usual care in patients with ischemic stroke also showed no benefit regarding mortality or functional outcome and increased risk of hypoglycemic events, suggesting the potential harmful effects of intensive glycemic control to vulnerable ischemic penumbra.[33] However, there are still significant uncertainties regarding optimal glucose levels and glycemic control methods in acute stroke, especially in ICH which has different pathophysiological mechanisms from ischemic 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 prespecified, 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 because 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% to 23%),[7,8,20] many of the participants were from China where the frequency of obesity and diabetes mellitus is lower than in the west. Finally, because the INTERACT studies excluded patients with a high likelihood of early death and planned surgical evacuation of hematoma, these findings may not be applicable to patients with severe ICH.

In summary, our study has shown that hyperglycemia has strong and continuous associations with poor outcomes from predominantly mild to moderate severity of ICH. Hyperglycemia seems 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 randomized evidence, these findings support current guidelines recommending treatment of hyperglycemia in ICH.[34]

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Disclosures

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