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Prophylactic heparin in acute intracerebral hemorrhage: a propensity score-matched analysis of the INTERACT2 study

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Abstract

Background: Indication and timing of pharmacological venous thromboembolism prophylaxis in intracerebral hemorrhage patients is controversial.

Aims: To determine whether use of subcutaneous heparin during the first 7 days after spontaneous intracerebral hemorrhage increases risks of death and disability.

Methods: Data are from the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) study. Patients with acute intracerebral hemorrhage (<6 hours) and elevated systolic blood pressure were included; patients received subcutaneous heparin following local best practice standards of care. Multivariable logistic regression and propensity score matched analysis were used to determine associations of heparin use on death and disability (modified Rankin scale) at 90 days.

Results: In 2525 patients with available data, there were 465 (22.5%) who received subcutaneous heparin. They had higher death or major disability at 90 days in crude (odds ratio 2.29, 95% confidence interval 1.85–2.84; $p < 0.001$), adjusted (odds ratio 1.62, 95% confidence interval 1.26–2.09; $p < 0.001$) and propensity score matched (odds ratio 2.06, 95% confidence interval 1.53–2.77; $p < 0.001$) analyses. In propensity score matched analysis, heparin-treated patients had significant lower mortality (odds ratio 0.55, 95% CI 0.35–0.87; $p = 0.01$) but greater major disability (odds ratio 1.68, 95% confidence interval 1.25–2.28; $p < 0.001$) at 90 days. However, no mortality difference was found in analysis restricted to 48-hour survivors.

Conclusions: Use of subcutaneous heparin is associated with poor outcome in acute intracerebral hemorrhage, driven by increased residual disability. Despite the limitations of this study, and no clear relation of heparin with bleeding risk, we recommend careful consideration of the need for venous thromboembolism prophylaxis with heparin in intracerebral hemorrhage patients.

Trial registration: http://www.clinicaltrials.gov NCT00716079.

Keywords

Cerebral hemorrhage, intracranial hemorrhage, heparin, outcome, clinical trial, venous thromboembolism, prophylaxis

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Introduction

Venous thromboembolism (VTE) is one of the leading preventable causes of in-hospital death and morbidity.[1,2] Stroke patients are at particularly high risk of VTE, due mainly to their restricted mobility, with reported frequencies as high as 40%.[3] Patients with acute intracerebral hemorrhage (ICH) have a 2.5- to 4-fold greater risk as compared to those with acute ischemic stroke.[4,5] The indications for, and timing of, pharmacological VTE prophylaxis with subcutaneous low-dose heparin in ICH patients is controversial due largely to clinician concerns over the harms of bleeding, in particular extension of the hematoma of ICH and of recurrent ICH,[6] offsetting any potential benefits of the treatment.[7] Guidelines addressing this issue have generally recommended use of heparin in persistently immobile ICH patients on the basis of the considerable evidence in favor of heparin prophylaxis together with small studies indicating its safety in this setting.[8–11] Recently, intermittent pneumatic compression of the legs for immobile stroke patients has been shown to reduce VTE and improve survival, and guidelines recommendations have been revised accordingly.[11–13] However, intermittent pneumatic compression is not widely used in many health care systems for various reasons.[7] The present analysis aimed to determine whether subcutaneous heparin use was associated with poor clinical outcome among patients with acute ICH who participated in the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2).

Methods

Study design and patients

INTERACT2 was an international, multicenter, open, blinded endpoint assessed, randomized controlled trial, the details of which are outlined elsewhere.[14,15] Briefly, 2839 patients with spontaneous ICH (<6 hours) and elevated systolic blood pressure (SBP, 150–220 mmHg) were included from 144 hospitals in 21 countries between October 2008 and August 2012. Excluded were patients with a definite indication for, or contraindication to, intensive BP-lowering treatment; a structural cerebral cause for the ICH; deep coma (scores 3–5 on the Glasgow coma scale [GCS[16]]); massive hematoma with a poor prognosis; or if early surgery to evacuate the hematoma was planned. The ethics committees for each site approved the study and informed consent was obtained from all patients or relevant surrogates. The study is registered with ClinicalTrials.gov (NCT00716079).

Procedures

During the first seven days after ICH, any use of subcutaneous unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) was prospectively recorded. Patients received such treatment following local best practice guidelines and the treating physician's preference. Participants were randomly allocated to BP-lowering treatment; in intensive BP-lowering arm, intravenous treatment and oral agent(s) were commenced at admission, with the goal of achieving a systolic BP level <140 mmHg over the next 7 days; for the guideline group, patients may receive BP treatment if their SBP was >180 mmHg.[15]

Outcome measures

Demographic and clinical characteristics were recorded at the time of enrolment, with clinical severity measured with the GCS and National Institutes of Health stroke scale (NIHSS)[17] at baseline, 24 hours, and at day 7 (or earlier upon discharge from hospital). Functional outcome was assessed by an assessor blinded to all aspects of the treatment. The primary clinical outcome was a 'poor outcome' defined by either death or major disability, according to scores 3 to 6 on the modified Rankin scale (mRS)[18] at 90 days post-randomization. Secondary outcomes were mortality, major disability (mRS 3–5), and unfavorable shift in distribution of mRS, all at 90 days.

Statistical analysis

As patients were not randomized to receive heparin, we anticipated that those with and without heparin would differ with respect to their baseline characteristics; this was first compared to make adjusted comparisons. Predictors of heparin use and the primary outcome among baseline characteristics of participants were determined by Chi square test for binary measures, t-test for approximately normally distributed variables, and Wilcoxon log-rank test for skewed continuous variables. A multivariable logistic regression model, including all univariate significant predictors of heparin treatment and the primary outcome, and other clinically important factors (gender and randomization to intensive BP lowering treatment), was constructed to produce estimates of the treatment effect of heparin (Online Supplementary eTables 1 and 2).[19–21] Based on the coefficients from this model, a propensity score (PS) was generated for each patient. Only patients with complete data were included in the analysis to maximize balancing in the PS analysis with the largest number of variables, and to avoid the pitfalls of

imputing data. Heparin and non-heparin-treated patients were matched 1:1 without replacement, using a caliper width equal to 0.2 of the standard deviation (SD) of the logit of the PS (0.19). Logistic regression models using generalized estimating equation methods were used to test the effect of heparin use on primary and secondary outcomes in overall, adjusted, and PS-matched population.

A multivariable logistic regression was performed with the overall population by heparin use to detect variables independently associated with poor outcome at 90 days. Additionally, a sensitivity analysis was performed to account for potential selection bias, considering only patients who survived the first 48 hours after the ICH. Similarly, subgroup analysis by clinical severity using the NIHSS score (<15 vs. ≥15) at 24 hours after ICH was undertaken to test the consistency of the results. Causes of death at 90 days by subcutaneous heparin use were compared in overall population and in those who survived the first 48 hours using Chi square test.

Data were reported as odds ratio (OR) and 95% confidence intervals (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

Among 2525 patients with complete baseline and outcome data, 465 (22.5%) received subcutaneous heparin within the first week post-randomization. Table 1 outlines the characteristics of included patients. In heparin-treated patients, 322/465 (69%) had a poor outcome (death or major disability) at 90 days, whereas in those who did not receive heparin, 1021/2060 (50%) had a poor outcome (OR 2.29, 95% CI 1.85–2.84; $p < 0.001$). Likewise, adjusted analysis indicates that heparin-treated patients had a significantly worse outcome (OR 1.62, 95% CI 1.26–2.09; $p < 0.001$). A similar difference was observed in PS-matched analysis (n = 372 per group), where death or major disability was more frequent, 246/372 (66%), in heparin-treated patients compared to 181/372 (49%) in non-heparin patients (OR 2.06, 95% CI 1.53–2.77; $p < 0.001$) (Figure 1). Within the baseline characteristics, age, NIHSS score ≥15, intraventricular extension, and hematoma volume were independently associated with poor outcome in patients who received heparin. These same variables plus baseline SBP and deep location of hematoma were associated with poor outcome in the non-heparin group (Supplementary eTable 3). For heparin and non-heparin patients, admission NIHSS score ≥15 was the strongest predictor of poor outcome for those factors included in the multivariate analysis (Supplementary eTable 3).

The risk of major disability (mRS score 3–5) at 90 days was significantly higher in patients treated with heparin (271/414 [66%] vs. 804/1843 [44%], respectively, OR 2.45, 95% CI 1.96–3.06; $p < 0.001$). Similar results were seen in PS-matched analysis, with increased major disability in heparin-treated patients (200/327 [61%] vs. 158/327 [48%] OR 1.68, 95%CI 1.25–2.28; $p < 0.001$) (Figure 1). There was a significantly higher unfavorable shift on the mRS at 90 days in the heparin-treated patients in both the crude analysis (OR 1.87, 95% CI 1.57–2.24; $p < 0.001$) and the PS-matched analysis (OR 1.72, 95% CI 1.34–2.21; $p < 0.001$; Figure 1).

No difference in mortality was found between heparin-treated patients (51/465, 11%) compared to non-heparin patients (217/2060, 11%) in crude analysis. However, adjusted analysis showed significant lower mortality in the heparin group (OR 0.60, 95% CI 0.41–0.87; $p = 0.01$) and PS-matched analysis revealed a significant lower risk of death of 33/372 (9%) in heparin-treated patients compared to 56/372 (15%) in non-heparin-treated patients (OR 0.55, 95% CI 0.35–0.87; $p = 0.01$) (Figure 2).

Since mortality during the first 48 hours after ICH was higher in the non-heparin group (41/2060 [2%] vs. 1/464 [0.2%]; most events caused by index ICH [Table 2]), a sensitivity analysis was performed to account for potential selection bias in the use of heparin. Censuring of the dataset for survivors at first 48 hours after admission revealed no difference in the risk of death at 90 days (Figure 2), and a higher risk of the combined poor outcome at 90 days in heparin-treated patients (Supplementary eTable 4). Neither in the overall population nor in 48-hour survivors was there any difference regarding cause-specific mortality between the heparin and non-heparin groups (Table 2). There were only five episodes of deep venous thrombosis (three events in heparin and two in non-heparin group) and 12 of pulmonary embolism (eight events in heparin and four in non-heparin group) reported during follow-up.

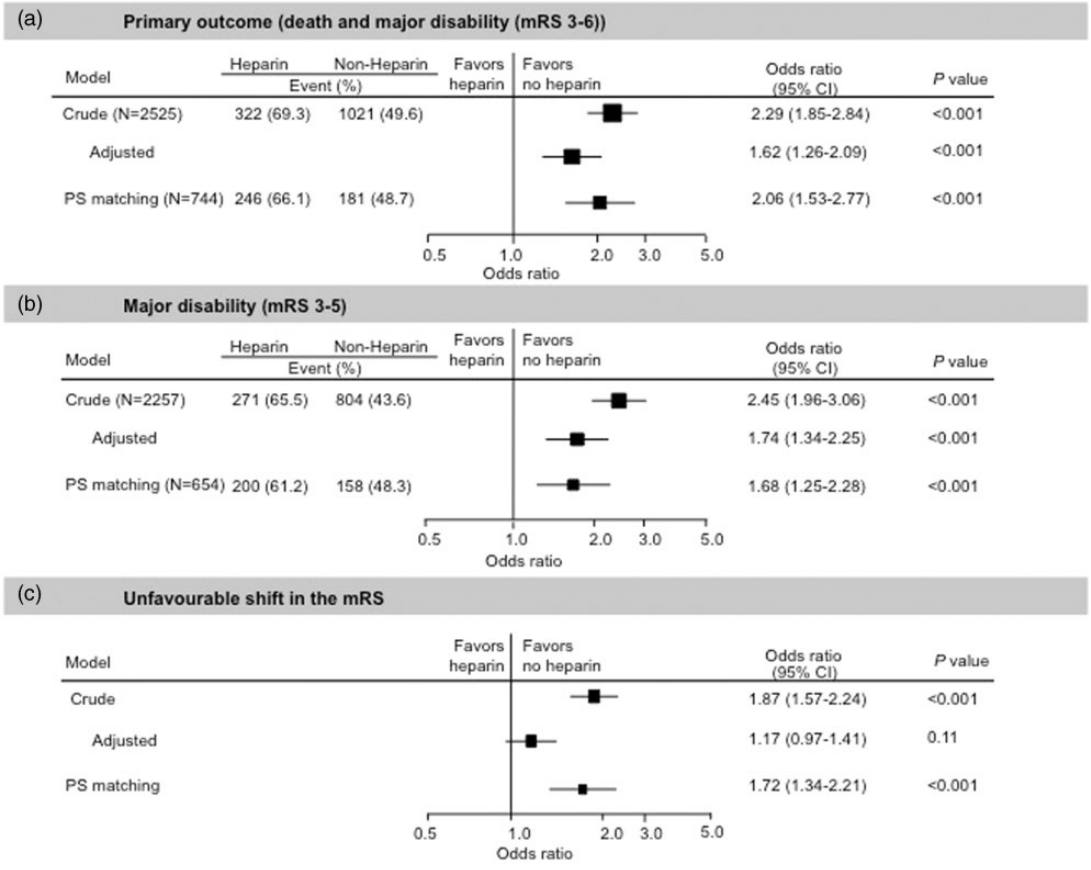
Stratification for stroke severity by NIHSS score at 24 hours showed that patients with mild to moderate neurological impairment (NIHSS score<15) had worse functional outcome in association with heparin use in the crude, adjusted, and PS-matched analysis (Supplementary eTable 5). Furthermore, when a separated outcome analysis was performed in patients with NIHSS scores <15, heparin use was associated with a higher risk of major disability at 90 days but conversely there was no difference in mortality at this time (Supplementary eTable 5). No significant difference was found on the risks of any outcome in analysis restricted to initially more severely impaired patients defined by NIHSS score ≥15 at 24 hours.

Table 1. Covariate distribution by treatment group in overall population and in propensity score (PS) matched sub-population

	Overall			PS-matched		
Baseline characteristics	No heparin (n = 2060)	Heparin (n = 465)	*p* Value	No heparin (n = 372)	Heparin (n = 372)	*p* Value
Demographic						
Age, mean (SD), years	62.8 (12.6)	67.8 (13.2)	<0.001	65.3 (12.0)	65.8 (13.3)	0.53
Male	1275 (61.9)	288 (61.9)	0.99	228 (61.3)	233 (62.6)	0.71
Medical history						
Acute coronary and other cardiac disease	194 (9.4)	80 (17.2)	<0.001	37 (10.0)	48 (12.9)	0.20
Diabetes mellitus	201 (9.8)	73 (15.7)	<0.001	40 (10.8)	46 (12.4)	0.49
Prior intracerebral haemorrhage	174 (8.5)	25 (5.4)	0.03	17 (4.6)	22 (5.9)	0.41
Prior ischemic/undifferentiated stroke	253 (12.3)	33 (7.1)	0.001	21 (5.7)	31 (8.3)	0.15
Medications						
Antihypertensive therapy	896 (43.5)	241 (51.8)	0.001	155 (41.7)	170 (45.7)	0.27
Oral anticoagulant or antiplatelet therapy	177 (8.6)	131 (28.2)	<0.001	48 (12.9)	60 (16.1)	0.21
Lipid lowering therapy	102 (5.0)	83 (17.9)	<0.001	18 (4.9)	43 (11.6)	<0.001
Clinic features						
Time from onset to randomization, median (IQR), hours	3.8 (2.8–4.8)	3.5 (2.6–4.6)	<0.001	3.8 (2.9–4.8)	3.5 (2.7–4.7)	0.18
Systolic BP, mean (SD), mmHg	178.9 (17.0)	179.0 (16.5)	0.85	178.2 (16.4)	178.8 (16.6)	0.66
NIHSS score ≥15[a]	533 (25.9)	185 (39.8)	<0.001	120 (32.3)	135 (36.3)	0.25
CT findings						
Hematoma volume at baseline, median (IQR), mL	10.7 (5.8–18.7)	11.4 (5.6–21.5)	0.11	10.9 (5.8–18.2)	11.3 (5.5–20.6)	0.45
Left hemisphere site of hematoma	1037 (50.3)	234 (50.3)	0.99	188 (50.5)	182 (48.9)	0.66
Deep location of hematoma[b]	1735 (84.2)	383 (82.4)	0.33	311 (83.6)	310 (83.3)	0.92
Intraventricular extension	567 (27.5)	136 (29.3)	0.45	103 (27.7)	105 (28.2)	0.87
Randomized to intensive BP lowering	1022 (49.6)	236 (50.8)	0.66	179 (48.1)	193 (51.9)	0.30

BP: blood pressure; NIHSS: National Institutes of Health Stroke Scale; CT: computed tomography; PS: propensity score.
Data are presented in numbers (%) unless otherwise stated.
[a]NIHSS scores can range from 0 (normal, no neurological deficit) to 42 (coma with quadriplegia).
[b]Deep location refers to location in the basal ganglia or thalamus.

Figure 1. Estimated treatment effects of heparin on different outcomes, according to different sets of analysis: crude data, adjusted analysis (adjusted by age, gender, prior intracerebral hemorrhage (ICH), prior ischemic or undifferentiated stroke, prior coronary artery disease, diabetes mellitus, antihypertensive treatment, aspirin or warfarin use, statin or other lipid lower agents, time from ICH to randomization, National Institutes of Health stroke scale (NIHSS) score, baseline systolic blood pressure, intraventricular extension, randomized blood pressure lowering treatment, and location, side and volume of hematoma) and propensity score (PS) matched analyses. Panel A shows the effect of heparin in the primary outcome (death and major disability according to the modified Rankin scale [mRS] scores 3–6) at 90 days; Panel B shows the effects of heparin on major disability (mRS 3–5) at 90 days; Panel C shows the effects of heparin on the unfavorable shift in the mRS at 90 days.



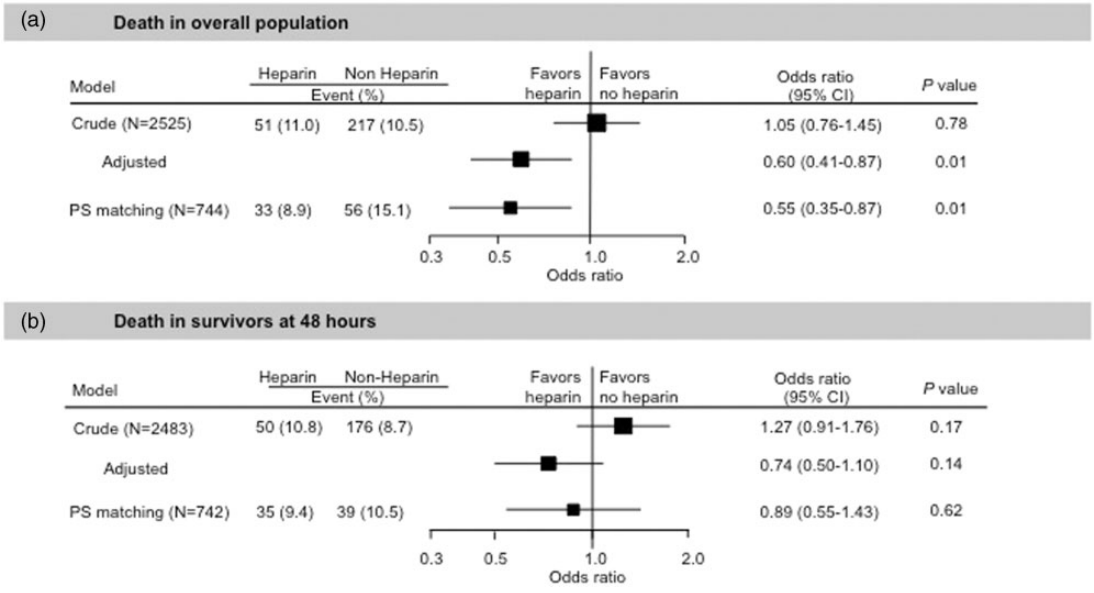
Discussion

In this post-hoc analysis of the INTERACT2 study, use of heparin within the first 7 days of ICH was significantly associated with an increased risk of poor outcome, driven largely by greater residual disability rather than by increased mortality in patients. The risk of death from any cause, including direct effects of the initial ICH or recurrent stroke, was not significantly different between heparin and non-heparin patients after accounting for certain baseline imbalances.

The finding of higher disability in patients treated with heparin was not explained by there being greater rebleeding or hematoma expansion from this treatment in this patient group. Although we did not have data regarding hematoma size after heparin use in this study, previous prospective studies indicate that any such risks are low in acute ICH patients receiving LMWH or low-dose of UFH.[22–26] Because of the robustness of the statistical analysis in reducing the influence of confounders and imbalances in baseline prognostic factors, we can consider the association of heparin use and poor functional outcome to be real, and particularly given that greater residual disability was observed in the mild-to-moderate impaired group of ICH patients (baseline NIHSS score <15). Hence, we consider that special care should be given to considering the use of heparin in ICH patients.

The limited impact of heparin use on mortality in ICH patients has been described elsewhere.

Figure 2. Estimated treatment effects of heparin on death at 90 days, according to different sets of analysis: crude data, adjusted analysis (adjusted as per Figure 1) and propensity score (PS) matched analyses. Panel A shows the effect of heparin on death at 90 days in overall population; Panel B shows the effects of heparin on death at 90 days in survivors at 48 hours.



A meta-analysis showed that early anticoagulation was associated with significant reduction in pulmonary embolism but with a non-significant reduction in mortality.[25] Higher mortality rate during the first 48 hours after ICH in patients without heparin may be related to the stroke severity rather than of increased thromboembolic complications. However, our sensitivity analysis appears to exclude any potential treatment bias whereby treating clinicians may have avoided use of VTE prophylaxis in patients with very severe ICH patients.

The observed low rates of heparin use and mortality seen in the INTERACT2 population most likely relates to the inclusion of predominantly milder severity of ICH patients and who received active management as part of a clinical trial. This likely translated into a low rate of VTE recorded in this cohort, although we recognize that deep venous thrombosis and pulmonary embolism are significantly underestimated in research and clinical practice without systematic screening.

This is the largest reported prospective cohort study of heparin use in ICH, and efforts were made to address potential confounding from baseline imbalances in patient characteristics according to heparin use. PS matching is a reliable statistical technique to reduce such bias,[19–21] and the consistency of the results across additional adjusted and stratified analysis provides strength to the conclusions that can be drawn from these data. Moreover, as patients were recruited from a diverse range of hospitals and health care settings, and assessed according to a standardised protocol and objective measurements, the results are likely to be both internally and externally valid for acute ICH patients who fulfilled criteria for participation in a clinical trial, that is patients with predominantly mild-moderate severity of ICH who presented with a hypertensive response. Another strength of our study is the assessment of the effects of heparin on disability, a crucial outcome for ICH patients that has not been included in previous reports.

The study has several limitations. First, the post-hoc approach and lack of randomization to heparin/no heparin in a clinical trial population means that these analyses are prone to chance associations and selection bias. Multivariate analysis and PS matching may reduce but not eliminate such bias, particularly as residual confounding may still exist from unmeasured factors that influenced treatment selection.[27] Another issue is that our study was still underpowered to allow precise estimates for modest degrees of association, and we did not include data on the timing and type of heparin use. We can only assume that such treatment was likely to have been started 48 hours after ICH onset in line with the recommendations of clinical guidelines and best standards of care.[28,29] Finally, the study lacked routine follow-up investigations to allow detection of later ICH extension, pulmonary embolism, and deep venous thrombosis.

In conclusion, use of subcutaneous heparin during the first seven days after spontaneous ICH was associated with worse clinical outcome at 90 days, although there was no clear effect on mortality. Despite the

Table 2. Comparison of causes of death at 90 days for overall population and in survivors at 48 hours

	Overall population (N = 2525)			Survivors to 48 h (N = 2483)		
	Heparin use			Heparin use		
	No (n = 2060)	Yes (n = 465)	*p* Value	No (n = 2019)	Yes (n = 464)	*p* Value
Dead patients at 90 days	217 (10.5)	51 (11.0)	0.78	176 (8.7)	50 (10.8)	0.17
Cause of death						
Direct from index ICH	133 (6.5)	22 (4.7)	0.16	93 (4.6)	21 (4.5)	0.94
Cardiovascular disease	19 (0.9)	8 (1.7)		19 (0.9)	8 (1.7)	
Recurrent ICH	0 (0)	2 (0.4)		0 (0)	2 (0.4)	
Ischemic/undifferentiated stroke	2 (0.1)	0 (0)		2 (0.1)	0 (0.0)	
Acute coronary or other cardiac event	3 (0.1)	1 (0.2)		3 (0.1)	1 (0.2)	
Other cardiovascular disease	14 (0.7)	5 (1.1)		14 (0.7)	5 (1.1)	
Non-cardiovascular disease	65 (3.2)	21 (4.5)	0.14	64 (3.2)	21 (4.5)	0.15
Renal failure	3 (0.1)	1 (0.2)		3 (0.1)	1 (0.2)	
Respiratory infections	24 (1.2)	5 (1.1)		24 (1.2)	5 (1.1)	
Sepsis (includes other infections)	3 (0.1)	6 (1.3)		3 (0.1)	6 (1.3)	
Non-vascular medical	35 (1.7)	9 (1.9)		34 (1.7)	9 (1.9)	

ICH: intracerebral haemorrhage.
Data are presented in numbers (%).

limitations of this study, and no clear relation of heparin with bleeding risk, we recommend careful consideration of the need for VTE prophylaxis with heparin in ICH patients.

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Declaration of Conflicting Interests

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Authors' contributions

PMV, CA: conception and design, acquisition, and interpretation of data for the work, drafting of the work, final approval of the version to be published.
XW: analysis and interpretation of data, critical revision of the manuscript, final approval of the version to be published.
PL, CS, TR, EH, CD, RL, JC: substantial contributions to conception and acquisition of data, interpretation of data and critical review for important intellectual content, final approval of the version to be published.

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