

Early Prophylactic Anticoagulation in Patients with Severe Spontaneous Intracerebral Hemorrhage: A Target Trial Emulation Study

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Research Article

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Abstract

Background and objectives: For patients with severe spontaneous intracerebral hemorrhage (ICH), venous thromboembolism (VTE) prophylaxis must balance thrombotic risk against the risk of hematoma expansion. Observational studies are particularly vulnerable to immortal time bias. We therefore used a target trial emulation (TTE) framework to assess the effectiveness and safety of early prophylactic anticoagulation in severe ICH.

Methods: We conducted a retrospective cohort study using the MIMIC-IV database and emulated a target trial. Admission to the intensive care unit (ICU) marked time zero, followed by a 48-hour treatment-assignment window. Patients were classified according to whether prophylactic anticoagulation began within 48 hours. Inverse probability of treatment weighting (IPTW) balanced baseline covariates. The primary outcomes were 28-day VTE (effectiveness) and major rebleeding (safety). Fine-Gray models treated all-cause death as a competing event, whereas Cox proportional-hazards models assessed 28-day all-cause mortality.

Results: Of 2,097 eligible patients with severe ICH, 904 (43%) received early prophylactic anticoagulation. Baseline characteristics were well balanced after IPTW, with all standardized mean differences below 0.1. Early prophylactic anticoagulation was not associated with a significant change in major rebleeding risk (subdistribution hazard ratio [sHR], 1.019; 95% confidence interval [CI], 0.750–1.385; $P = 0.903$) or 28-day VTE risk (sHR, 1.191; 95% CI, 0.823–1.723; $P = 0.355$) compared with no anticoagulation. It was associated with lower 28-day all-cause mortality (hazard ratio [HR], 0.708; 95% CI, 0.582–0.861; $P < 0.001$). No significant interaction was observed across subgroups defined by age, sex, baseline Glasgow Coma Scale score, ICH score, body mass index, or Charlson Comorbidity Index.

Conclusions: Among patients with severe ICH, prophylactic anticoagulation initiated within 48 hours of ICU admission was not associated with increased major rebleeding or a significant change in 28-day VTE risk. The treatment was associated with lower 28-day all-cause mortality. These associations require confirmation in prospective studies.

1. Introduction

Spontaneous intracerebral hemorrhage (ICH) is one of the most lethal stroke subtypes, with an estimated global annual incidence of 24.6 per 100,000 people and a 30-day case-fatality rate of 35–52%^[1]. The 2021 Global Burden of Disease study reported that ICH accounted for 28.8% of incident strokes but 45.6% of stroke deaths^[2]. Patients with severe ICH commonly have limb paralysis, prolonged immobilization, and disturbances of coagulation and fibrinolysis, all of which increase the risk of venous thromboembolism (VTE), which may be two- to fourfold higher than in patients with ischaemic stroke^[3]. The incidence of deep-vein thrombosis (DVT) within the first week of admission may reach 35.7% in neurocritical-care populations^[4]. VTE and related complications may affect the clinical course and are associated with short-term mortality and functional impairment. Conversely, prophylactic

anticoagulation may increase the risk of hematoma expansion or rebleeding. Balancing thromboprophylaxis against secondary bleeding remains a clinical challenge in the management of severe ICH.

The 2022 guideline from the American Heart Association/American Stroke Association (AHA/ASA) states that, in non-ambulatory patients with spontaneous ICH, initiating low-dose unfractionated heparin or low-molecular-weight heparin (LMWH) 24–48 hours after ICH onset may be reasonable, because the potential benefit of preventing thrombosis may outweigh the risk of ICH^[5]. Nevertheless, concern about rebleeding has limited the use of pharmacological VTE prophylaxis to approximately 16.5% of patients with ICH in routine practice^[6]. Recent meta-analyses suggest that early LMWH reduces DVT incidence (3.6% versus 17.5%; RR, 0.25; 95% CI, 0.18–0.35) without increasing hematoma expansion^[6, 7]. However, the available evidence is limited by small sample sizes, unclear definitions of anticoagulation timing, and infrequent use of rigorous causal-inference methods to address biases inherent to observational studies. In particular, immortal time bias can arise because patients who die or rebleed early cannot receive anticoagulation, whereas patients who survive long enough are more likely to enter the anticoagulated group, potentially leading to systematic overestimation of treatment benefit^[8].

Target trial emulation (TTE) has increasingly been used to strengthen causal inference from observational data. Hernán and Robins^[9] proposed that investigators should prespecify the target randomized controlled trial (RCT) to be emulated and align eligibility, treatment assignment, and follow-up at time zero, thereby reducing immortal time bias. Fu et al.^[10] emphasized that TTE depends on explicit time anchors, consistent eligibility criteria, and clearly defined exposure groups that approximate the design of an RCT. Combining TTE with propensity-score inverse probability of treatment weighting (IPTW) and a Fine-Gray competing-risk model can further address baseline confounding and competing events. Although this approach has been applied in cardiovascular and renal research, its use to evaluate early prophylactic anticoagulation in patients with severe ICH remains limited.

We used the MIMIC-IV database to conduct a retrospective cohort study. The prespecified aims were to determine whether prophylactic anticoagulation initiated within 48 hours of ICU admission affected 28-day VTE risk in patients with severe ICH and whether it increased 28-day intracranial rebleeding risk. Twenty-eight-day all-cause mortality was analysed as a secondary outcome. The analysis combined a TTE framework with IPTW and a Fine-Gray competing-risk model to support clinical interpretation of these observational data.

2. Materials and Methods

2.1 Study design and data source

This retrospective cohort study used the MIMIC-IV database and a target trial emulation (TTE) framework^[11] for causal inference. MIMIC-IV contains de-identified clinical data from patients admitted to the intensive care units (ICUs) of Beth Israel Deaconess Medical Center (BIDMC) in Boston^[12].

Database access was authorized, and the institutional review board (IRB) waived the requirement for informed consent.

2.2 Target trial emulation framework and time definition

We defined ICU admission as time zero (T0) and the subsequent 48 hours as the treatment-assignment window (grace period), thereby aligning the baseline state and temporal sequence with a randomized controlled trial. Follow-up began when this window ended (T0 + 48 h) and continued for a maximum of 28 days.

2.3 Definition of the intervention and comparator

We classified exposure from electronic prescription records during the 48-hour treatment-assignment window. The intervention group comprised patients who received subcutaneous prophylactic-dose LMWH (for example, enoxaparin ≤ 40 mg/day) or unfractionated heparin ($\leq 5,000$ U) between T0 and T0 + 48 h. The comparator group comprised patients who received no anticoagulant during the same window or only very-low-dose heparin ($< 1,000$ U) for catheter locking.

2.4 Definition and ascertainment of outcomes

We extracted the effectiveness and safety outcomes, VTE and rebleeding, from radiology reports using natural-language processing (NLP). Twenty-eight-day all-cause mortality was obtained directly from the database survival records.

2.5 Extraction and definition of baseline covariates

Baseline covariates that could influence treatment assignment and clinical outcomes were extracted around T0. Variables were selected on the basis of epidemiological evidence and the causal-inference framework. Age, sex and body mass index (BMI) are associated with VTE risk and survival outcomes^[13]. The Glasgow Coma Scale (GCS) and modified ICH score were used to reflect initial neurological impairment and disease severity^[14], whereas the Charlson Comorbidity Index (CCI) summarized comorbidity burden using a published algorithm^[15]. These variables were selected to control the principal confounders while limiting the risk of overfitting and inflated weighting variance in the propensity-score model^[16].

2.6 Eligibility criteria

We initially identified 2,382 adults (≥ 18 years of age) with a first diagnosis of spontaneous ICH who were admitted to an ICU. To reduce immortal time bias and maintain baseline comparability, we excluded patients who experienced an early competing event (death, VTE or rebleeding) or were discharged early during the 48-hour assignment window ($n = 203$), those who received therapeutic-dose anticoagulation ($n = 79$), and those lacking core variables required for propensity-score estimation, such as GCS or BMI ($n = 3$). The final cohort comprised 2,097 patients who completed the assignment window and met all eligibility criteria.

2.7 Statistical analysis

To reduce confounding in this observational study, we first applied propensity-score inverse probability of treatment weighting (IPTW) to balance baseline covariates between groups and assessed balance using standardized mean differences (SMDs), with $SMD < 0.1$ prespecified as acceptable. Because all-cause death was a competing event, weighted Fine-Gray models were used to estimate subdistribution hazard ratios (sHRs) and 95% confidence intervals (CIs) for VTE and rebleeding. Weighted Cox proportional-hazards models were used to estimate hazard ratios (HRs) for all-cause mortality. Individual-level cluster-robust standard errors were used to account for within-person dependence introduced by weighting. Prespecified subgroup analyses were conducted using core baseline variables, and interaction terms were used to evaluate effect heterogeneity. Sensitivity analyses included unweighted multivariable adjustment, conventional survival models that ignored competing risks, and E-value analyses. Data extraction and NLP processing were performed in Python 3.10, and statistical analyses were conducted in R 4.1.3. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

3. Results

3.1 Study Population and Baseline Characteristics

The study utilized a 48-hour grace period following ICU admission (T0) to assign treatment strategies. Patients who experienced early competing events (death, VTE, or rebleeding), early discharge, or received therapeutic-dose anticoagulation within this 48-hour window were excluded to prevent immortal time bias. Abbreviations: LMWH, low-molecular-weight heparin; T0, time zero; UFH, unfractionated heparin.

The final cohort comprised 2,097 patients with severe spontaneous ICH who completed the 48-hour treatment-assignment window and met the TTE criteria (baseline characteristics are shown in Table 1). Of these, 904 (43%) received prophylactic anticoagulation within 48 hours (intervention group), whereas 1,193 (57%) did not (comparator group). The median age was 70 years (interquartile range [IQR], 58–80 years), and 984 patients (47%) were women.

Table 1

Baseline clinical and demographic characteristics of the overall cohort stratified by venous thromboembolism and major bleeding events within 28 days after severe intracerebral hemorrhage

Characteristic	All Patients	Confirmed VTE	No Confirmed VTE	Major Bleeding	No Major Bleeding
	N = 2097	N = 121	N = 1976	N = 169	N = 1928
Demographics					
Age, Median (Q1-Q3)	70 (58–80)	69 (56–80)	70 (58–81)	66 (53–75)	70 (58–81)
Sex, n (%)					
Female	984 (47)	61 (50)	923 (47)	81 (48)	903 (47)
Male	1113 (53)	60 (50)	1053 (53)	88 (52)	1025 (53)
BMI, n (%)					
< 30	1819 (87)	91 (75)	1728 (87)	129 (76)	1690 (88)
≥ 30	278 (13)	30 (25)	248 (13)	40 (24)	238 (12)
Comorbidities, n (%)					
Diabetes mellitus	536 (26)	31 (26)	505 (26)	37 (22)	499 (26)
Hypertension	1316 (63)	76 (63)	1240 (63)	110 (65)	1206 (63)
COPD	267 (13)	20 (17)	247 (13)	23 (14)	244 (13)
Congestive heart failure	310 (15)	23 (19)	287 (15)	24 (14)	286 (15)
Liver disease	123 (5.9)	4 (3.3)	119 (6.0)	16 (9.5)	107 (5.5)
Chronic kidney disease	273 (13)	12 (9.9)	261 (13)	19 (11)	254 (13)
Active cancer	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Disease severity					
CCI, Median (Q1-Q3)	5 (4–7)	5 (3–7)	5 (4–7)	5 (3–7)	5 (4–7)
GCS, Median (Q1-Q3)	9 (6–14)	7 (3–12)	10 (6–14)	7 (4–12)	10 (6–14)
Notes: Continuous variables are presented as median (interquartile range). CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, Intraventricular hemorrhage; VTE, venous thromboembolism.					

Characteristic	All Patients	Confirmed VTE	No Confirmed VTE	Major Bleeding	No Major Bleeding
	N = 2097	N = 121	N = 1976	N = 169	N = 1928
Demographics					
Initial hematoma volume, mL, Median (Q1-Q3)	22 (9–41)	21 (14–27)	22 (9–47)	35 (17–47)	18 (9–40)
IVH, n (%)	379 (18)	33 (27)	346 (18)	73 (43)	306 (16)
ICH score, n (%)					
0	540 (26)	23 (19)	517 (26)	22 (13)	518 (27)
1	767 (37)	36 (30)	731 (37)	55 (33)	712 (37)
2	590 (28)	41 (34)	549 (28)	62 (37)	528 (27)
3	182 (8.7)	20 (17)	162 (8.2)	25 (15)	157 (8.1)
4	18 (0.9)	1 (0.8)	17 (0.9)	5 (3.0)	13 (0.7)
Treatment, n (%)					
Invasive mechanical ventilation	724 (35)	67 (55)	657 (33)	102 (60)	622 (32)
Therapeutic anticoagulation within 48 h					
Anticoagulated	904 (43)	58 (48)	846 (43)	74 (44)	830 (43)
Not Anticoagulated	1193 (57)	63 (52)	1130 (57)	95 (56)	1098 (57)
Notes: Continuous variables are presented as median (interquartile range). Categorical variables are shown as count (percentage). CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, Intraventricular hemorrhage; VTE, venous thromboembolism.					

3.2 Incidence and timing of 28-day adverse events

During the 28-day follow-up, adverse events are summarized in Table 2. Overall mortality was 36.9% (773/2,097). Confirmed VTE occurred in 121 patients (5.8%), including 82 cases of DVT (3.9%) and 51 cases of pulmonary embolism (PE; 2.4%); 45 patients with VTE died, corresponding to an event-specific mortality of 37.2%. Major bleeding (rebleeding) occurred in 169 patients (8.1%), of whom 75 died, corresponding to an event-specific mortality of 44.4%. In the event-combination analysis, 1,177 patients (56.0%) experienced none of the prespecified adverse events. Single events included death alone (31.6%), rebleeding alone (3.4%), and VTE alone (2.6%); 66 patients (3.1%) experienced both rebleeding and death. Rebleeding occurred earliest, with a median time of 2.4 days (IQR, 0.8–6.6 days), whereas the

median times to all-cause death and VTE were 5.1 days (IQR, 2.0–11.4 days) and 5.6 days (IQR, 2.9–12.0 days), respectively. Event combinations and temporal distributions are shown in Fig. 2.

Table 2
Adverse event incidence and event-specific mortality (in 28 days) in the overall cohort of severe intracerebral hemorrhage patients

Event	Patients, n (%) (N = 2097)	Mortality among patients with the event: Deaths/Events, n (%)
Confirmed VTE	121 (5.8)	45/121 (37.2)
Deep vein thrombosis (DVT)	82 (3.9)	32/82 (39.0)
Pulmonary embolism (PE)	51 (2.4)	16/51 (31.4)
Major Bleeding Events	169 (8.1)	75/169 (44.4)
All-cause Mortality (Overall cohort)	773 (36.9)	
Notes: Event incidence was calculated relative to the total study population (N = 2097). Event-specific mortality was defined as the proportion of all-cause mortality among patients who developed each corresponding adverse event. DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.		

Notes: (A) Distribution of combined 28-day clinical event profiles (rebleeding, venous thromboembolism, and all-cause mortality), presented as absolute patient numbers in the overall cohort. (B) Temporal distribution of major clinical events within 28 days after the 48-hour landmark, showing the median, interquartile range, and overall range of event days for all-cause mortality, major rebleeding, and venous thromboembolism. Abbreviations: VTE, venous thromboembolism

3.3 Baseline covariate balance after IPTW

Before IPTW, the two groups showed modest differences. After weighting, age, sex, BMI, GCS score, CCI and modified ICH score were well balanced (Table 3). Supplementary Figure S1 shows the absolute SMDs before and after weighting; all post-weighting SMDs were < 0.1, meeting the prespecified balance criterion.

Table 3

Baseline covariate balance before and after inverse probability of treatment weighting in patients with severe intracerebral hemorrhage

Characteristic	Pre-IPW		Post-IPW	
	Anticoagulated	Not Anticoagulated	Anticoagulated	Not Anticoagulated
	N = 904	N = 1,193	N = 2,097	N = 2,097
Age, Median (Q1-Q3)	70 (58–80)	69 (57–81)	70 (58–80)	70 (57–81)
Sex, n (%)				
Female	423 (47)	561 (47)	(47)	(47)
Male	481 (53)	632 (53)	(53)	(53)
BMI, n (%)				
< 30	794 (88)	1,025 (86)	(87)	(87)
≥ 30	110 (12)	168 (14)	(13)	(13)
GCS, Median (Q1-Q3)	10.0 (6.0–14.0)	9.0 (6.0–14.0)	9.0 (6.0–13.0)	9.0 (6.0–14.0)
CCI, Median (Q1-Q3)	5.00 (4.00–7.00)	5.00 (4.00–7.00)	5.00 (4.00–7.00)	5.00 (4.00–7.00)
ICH score, n (%)				
0	245 (27)	295 (25)	(25)	(26)
1	347 (38)	420 (35)	(37)	(36)
2	251 (28)	339 (28)	(30)	(27)
3	55 (6.1)	127 (11)	(7.2)	(9.5)
4	6 (0.7)	12 (1.0)	(0.9)	(0.9)
Notes: Continuous variables are presented as median (interquartile range). Categorical variables are shown as percentage. Pre-IPW cohorts included unmatched anticoagulated and non-anticoagulated groups. Post-IPW cohorts represented balanced study populations after inverse probability of treatment weighting. CCI, Charlson Comorbidity Index; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IPW, inverse probability weighting.				

3.4 Association between prophylactic anticoagulation and 28-day clinical outcomes

For the primary analysis, we applied a Fine-Gray model to the IPTW-weighted cohort and treated all-cause death as a competing event. Compared with no anticoagulation, prophylactic anticoagulation

initiated within 48 hours was not associated with a significant change in VTE risk (sHR = 1.191, 95% CI, 0.823–1.723; P = 0.355) or major rebleeding risk (sHR = 1.019, 95% CI, 0.750–1.385; P = 0.903). It was associated with lower 28-day all-cause mortality (HR = 0.708, 95% CI, 0.582–0.861; P < 0.001) (Fig. 3). Weighted cumulative-incidence-function (CIF) curves for VTE and rebleeding, together with the weighted Kaplan–Meier curve for all-cause mortality, are shown in Fig. 4.

Across subgroups defined by age, sex, baseline GCS score, modified ICH score, BMI and CCI, no significant interaction was observed for VTE or rebleeding outcomes (all interaction P values > 0.05). Sensitivity analyses are shown in Fig. 3, and the E-value analysis is shown in Supplementary Figure S2. In unweighted multivariable competing-risk and Cox models, anticoagulation was not significantly associated with VTE (sHR = 1.225, 95% CI, 0.846–1.774; P = 0.283) or rebleeding (sHR = 1.031, 95% CI, 0.758–1.401; P = 0.847), but was associated with lower all-cause mortality (HR = 0.674, 95% CI, 0.550–0.826; P < 0.001). In IPTW-weighted Cox models that ignored competing risks, no significant difference was observed for VTE (HR = 1.107; P = 0.588) or rebleeding (HR = 0.962; P = 0.802). The unweighted multivariable Cox models yielded similar findings. The E-values for the point estimate and the lower bound of the 95% CI for all-cause mortality were 1.86 and 1.46, respectively.

Notes: Weighted analyses evaluated 28-day clinical outcomes. CIF were plotted for VTE and rebleeding, treating all-cause death as a competing event. Weighted Kaplan-Meier curves were utilized for 28-day all-cause mortality. Shaded areas indicate 95% confidence intervals. Abbreviations: CIF, cumulative incidence function; IPTW, inverse probability of treatment weighting; VTE, venous thromboembolism.

Discussion

We analysed 2,097 patients with severe ICH from the MIMIC-IV database using a TTE framework and competing-risk models to evaluate prophylactic anticoagulation initiated within 48 hours of ICU admission. Early prophylactic anticoagulation was not associated with a significant change in major intracranial rebleeding risk (sHR = 1.019, 95% CI, 0.750–1.385) or 28-day VTE risk (sHR = 1.191, 95% CI, 0.823–1.723), but was associated with lower 28-day all-cause mortality (HR = 0.708, 95% CI, 0.582–0.861; P < 0.001). The mortality association was more apparent among patients with a GCS score of 3–8 or an ICH score of 3–5. These findings suggest that prophylactic anticoagulation within 48 hours did not increase major rebleeding risk in this study population, although prospective studies are needed.

Early anticoagulation was not associated with an increased risk of major rebleeding (8.1%; weighted sHR = 1.019). This finding is consistent with the 2022 AHA/ASA recommendation that pharmacological VTE prophylaxis may be considered 24–48 hours after ICH onset^[5] and with recent meta-analyses indicating that LMWH does not increase bleeding risk^[6, 7]. We did not observe a significant reduction in VTE. The relatively low incidence of confirmed VTE in this cohort (5.8%, 121/2,097) limited statistical power, and the opportunity to undergo imaging-based screening may have influenced VTE detection. Because VTE ascertainment depended on clinical diagnosis and imaging evidence, some asymptomatic or unscreened events may have been missed. In addition, patients who were clinically stable and

expected to survive longer may have been more likely to receive anticoagulation, indicating potential residual confounding [8]. The TTE design excluded early events within 48 hours, and the Fine-Gray model treated all-cause death as a competing event, thereby reducing related bias^[10].

An important finding was the association between prophylactic anticoagulation within 48 hours and lower 28-day all-cause mortality (HR = 0.708, 95% CI, 0.582–0.861; $P < 0.001$). Because complete information on DVT and PE burden was unavailable, we cannot determine whether this association was mediated by VTE prevention. Previous studies suggest that heparin may have anti-inflammatory and neuroprotective effects in addition to anticoagulant activity, including effects on neutrophil extracellular trap formation and leukocyte infiltration^[17, 18]; these mechanisms were not directly measured in the present study. No significant interaction was observed for VTE or rebleeding outcomes (all interaction P values > 0.05). The greater mortality association observed among patients with a GCS score of 3–8 or an ICH score of 3–5 should be considered exploratory. A meta-analysis by Zhou et al.^[19] also reported lower mortality (OR = 0.70; $P = 0.006$), whereas the meta-analysis by Li et al.^[6] and the Cochrane review^[20] did not identify a significant difference. These discrepancies may reflect differences in study populations and baseline risk.

The main methodological feature of this study was the use of a TTE framework with an explicit time zero and a 48-hour treatment-assignment window. Aligning eligibility, treatment assignment and follow-up in time can reduce immortal time bias^[9, 10]. IPTW and cluster-robust standard errors were used to adjust for baseline characteristics, including age, GCS, CCI and ICH score; all post-weighting SMDs were < 0.1 . The E-value for the point estimate of the all-cause mortality association was 1.86, and that for the lower bound of the 95% CI was 1.46. These values quantify the strength of an unmeasured confounder that would be required to fully explain the observed association, but they do not exclude residual confounding.

Several limitations should be considered. First, a retrospective observational design cannot eliminate unmeasured confounding, even when combined with TTE and IPTW. Information on hematoma stability, the specific anticoagulant and dose, and adherence to mechanical prophylaxis may have been incomplete. Second, MIMIC-IV is a single-centre US database, and differences in patient mix and clinical practice may limit generalizability. Third, VTE was identified mainly through clinical diagnosis rather than systematic screening, so asymptomatic DVT may have been underestimated. Finally, the 28-day follow-up covered only the acute phase and did not capture long-term functional outcomes. These findings require further evaluation in multicentre prospective studies.

Among 2,097 patients with severe ICH, prophylactic anticoagulation initiated within 48 hours of ICU admission was not associated with increased intracranial rebleeding and was associated with lower 28-day all-cause mortality; VTE risk did not differ significantly. Because this retrospective observational study was subject to possible residual confounding, outcome under-ascertainment and limited generalizability, the findings should not be interpreted as definitive evidence of a causal effect.

Multicentre prospective studies, and randomized trials where feasible, are needed to evaluate the benefits and risks of early prophylactic anticoagulation.

Declarations

Confirmation of Original Submission

This manuscript has not been published in whole or in part elsewhere, and is not currently under consideration by any other journal. No portion of the data or text has been previously published or submitted concurrently to another publication. A single study has not been split into multiple parts for submission to multiple journals.

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Ethical Approval and Informed Consent

This study was conducted in accordance with the ethical standards of the Institutional Review Board (IRB) of Zhengzhou Central Hospital affiliated to Zhengzhou University and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was reviewed and approved by the IRB of Zhengzhou Central Hospital affiliated to Zhengzhou University (ZXYY2024161).

This is a retrospective observational study utilizing de-identified electronic health record data. For this type of study, formal consent is not required. The requirement for individual written informed consent was waived by the IRB owing to the retrospective nature of the study and the use of de-identified data. No identifiable patient information (names, dates of birth, hospital numbers, or other confidential health care information) is disclosed in this manuscript.

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Author contributions

Tingting An and Qiong Wu contributed equally to this work and should be regarded as joint first authors. Tingting An: Conceptualization, Data curation, Formal analysis, Writing – original draft. Qiong

Wu: Conceptualization, Data curation, Writing – original draft, Investigation. Jing Xu: Resources, Data validation, Methodology. Yanhui Wang: Visualization, Formal analysis, Investigation. Yifei Liang: Statistical methodology, Software, Formal analysis validation. Chengjian Li: Data curation, Investigation. Tao Song: Resources, Supervision. Huihui Ding: Visualization, Writing – review & editing. Yifan Ma: Data curation, Investigation. Lanjuan Xu*: Conceptualization, Project administration, Supervision, Writing – review & editing, Funding acquisition

Disclosure of Potential Conflicts of Interest

The authors declare that they have no conflicts of interest. All authors have no financial or non-financial relationships or interests that could influence or bias the work described in this manuscript.

Artificial Intelligence (AI)–Assisted Technology Statement

During the preparation of this manuscript, AI-assisted language editing tools were used solely for English language polishing and reference format standardization. No AI tool was used for study design, data collection, data analysis, result interpretation, or generation of substantive scientific content. AI was not used for creating tables, figures, graphs, or images, nor for literature search, classification, or bibliographic analysis.

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Confirmation of Reporting Checklist Use

This study is a retrospective observational cohort study implemented using target trial emulation methodology. The study was conducted and the manuscript was prepared in strict accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The completed STROBE checklist has been uploaded as a supplementary file with this submission

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Figures

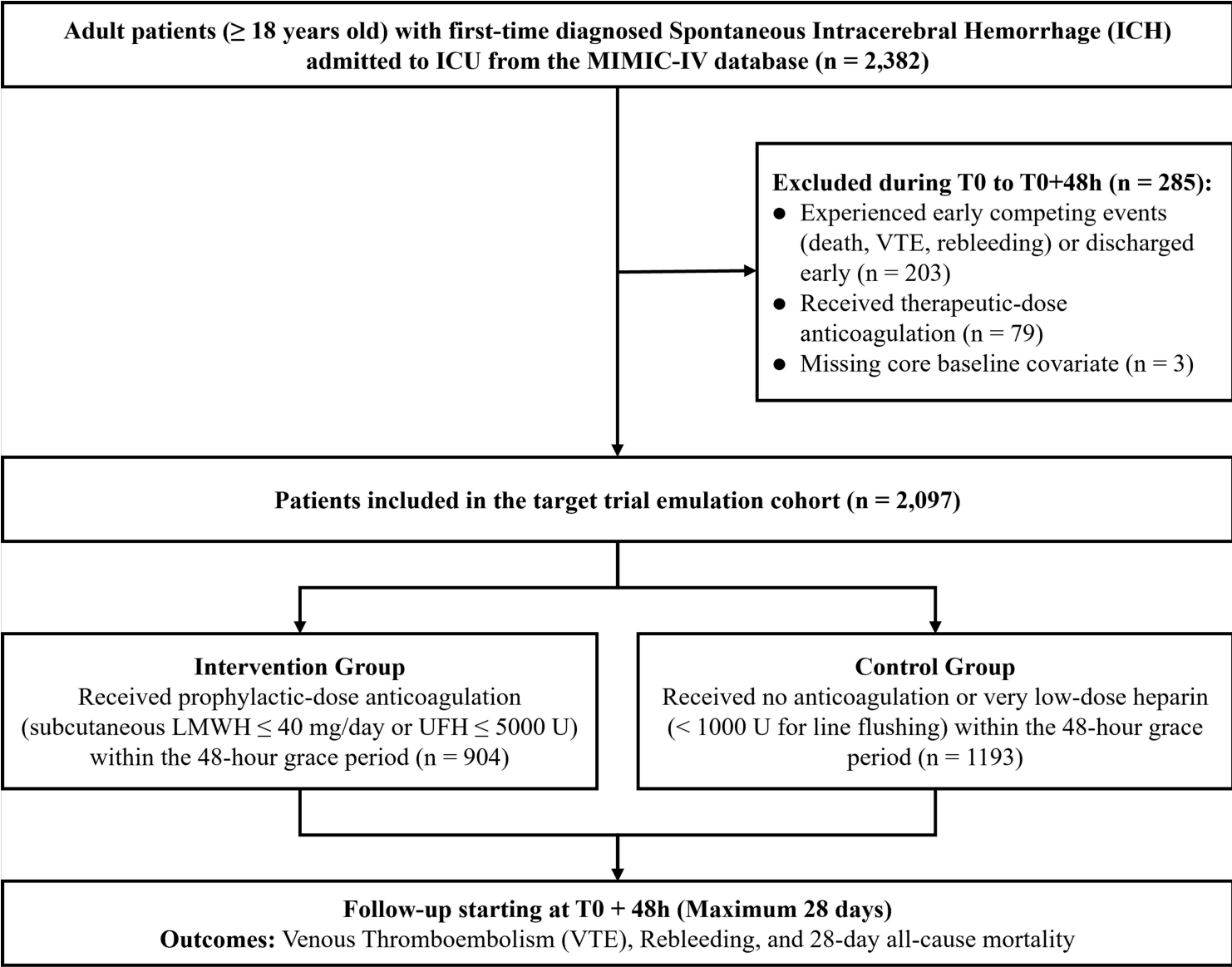


Figure 1

Patient selection flowchart for the target trial emulation of prophylactic anticoagulation in patients with ICH

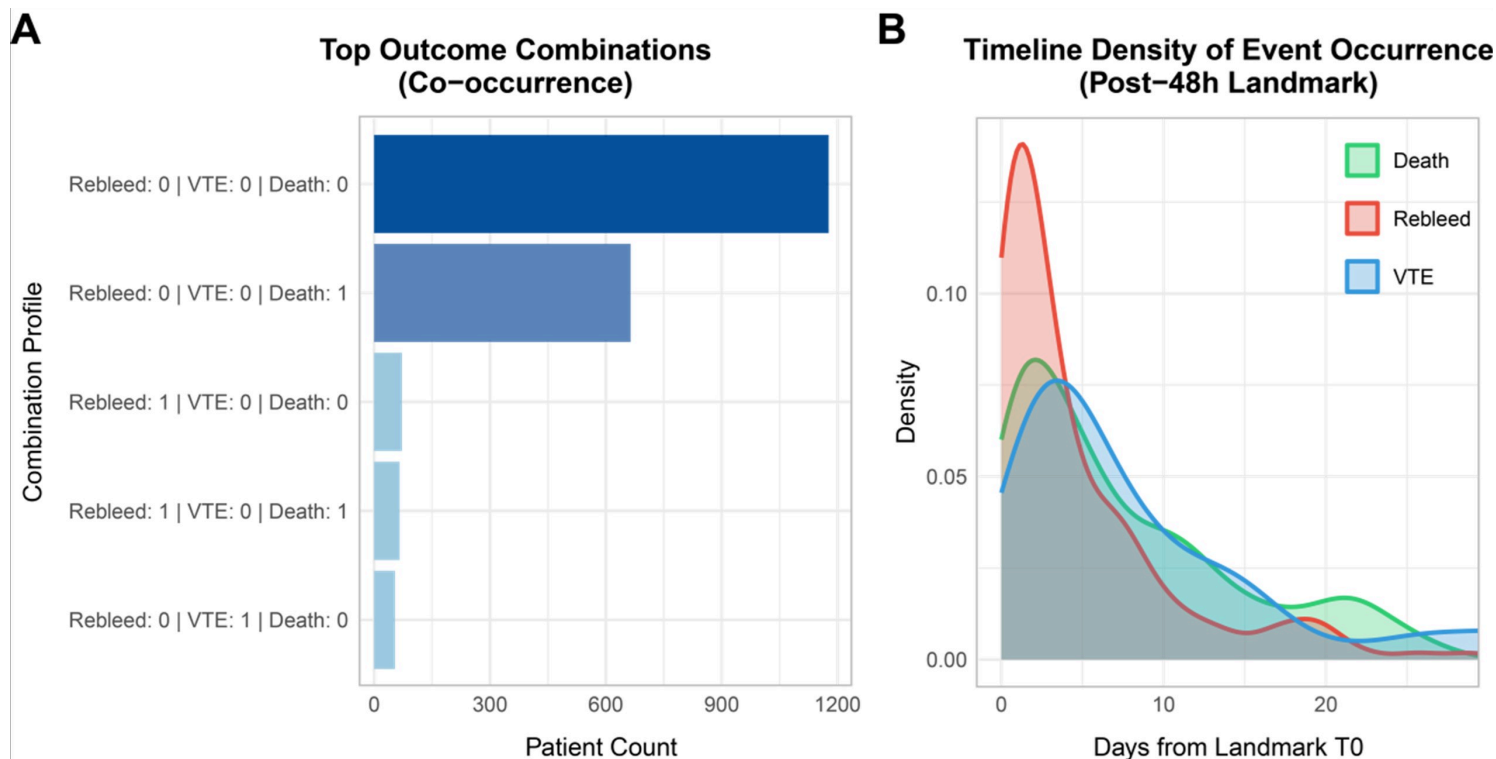


Figure 2

Outcome combination distribution and temporal characteristics of clinical events in the overall cohort of patients with severe intracerebral hemorrhage

Notes: (A) Distribution of combined 28-day clinical event profiles (rebleeding, venous thromboembolism, and all-cause mortality), presented as absolute patient numbers in the overall cohort. (B) Temporal distribution of major clinical events within 28 days after the 48-hour landmark, showing the median, interquartile range, and overall range of event days for all-cause mortality, major rebleeding, and venous thromboembolism. Abbreviations: VTE, venous thromboembolism

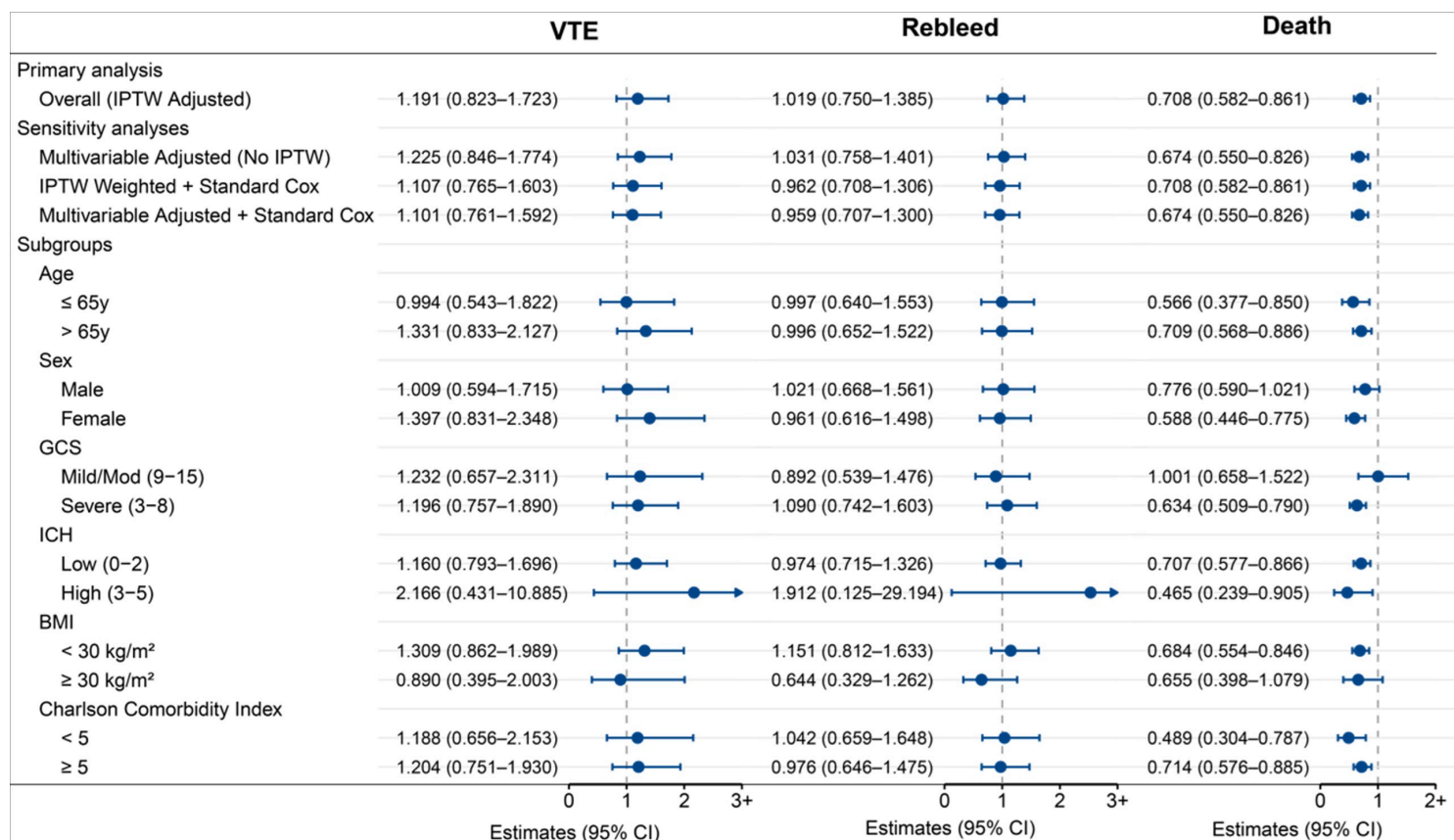


Figure 3

Clinical outcomes according to 48-hour prophylactic anticoagulation: primary IPTW analysis, sensitivity analyses and prespecified subgroup analyses

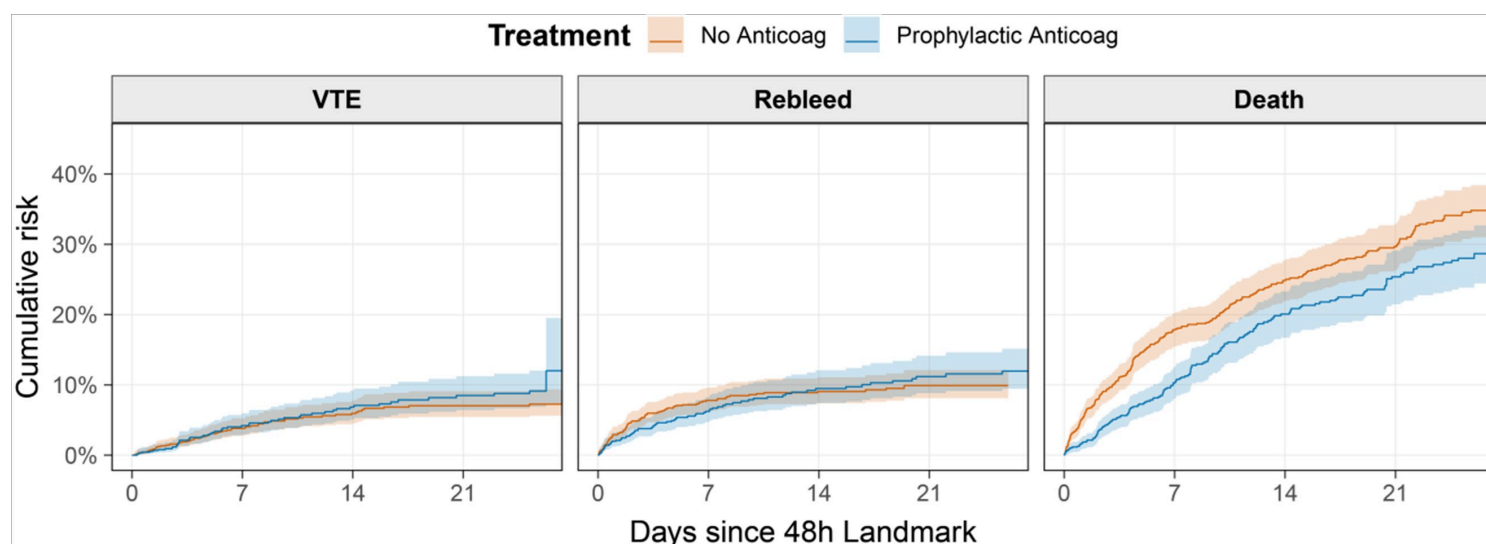


Figure 4

Cumulative incidence and survival outcomes by 48-hour prophylactic anticoagulation status after IPTW

Notes: Weighted analyses evaluated 28-day clinical outcomes. CIF were plotted for VTE and rebleeding, treating all-cause death as a competing event. Weighted Kaplan-Meier curves were utilized for 28-day all-cause mortality. Shaded areas indicate 95% confidence intervals. Abbreviations: CIF, cumulative incidence function; IPTW, inverse probability of treatment weighting; VTE, venous thromboembolism.

Supplementary Files

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