Research Article

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Rivaroxaban versus low-molecular-weight heparins for short- and long-term prognosis in patients with deep vein thrombosis after spontaneous intracranial hemorrhage

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Aim: Anticoagulation is the cornerstone of deep vein thrombosis (DVT) treatment, but in patients with intracerebral hemorrhage, it requires a delicate balance between preventing thrombosis and minimizing the risk of rebleeding. To assess the effects of rivaroxaban on short- and long-term clinical prognosis in patients with DVT who have suffered spontaneous intracranial hemorrhage (sICH). **Materials & methods:** The study retrospectively enrolled 327 sICH patients with DVT from 11 October 2019 to 18 September 2023. The primary outcomes were defined as recurrent sICH, bleeding-related events and mortality within 90 days and 1 year. Multivariate logistic regression was conducted to evaluate the association between rivaroxaban and clinical outcomes based on inverse probability of treatment weighting. **Results:** Of the included patients, 230 received low-molecular-weight heparins (LMWH) and 97 received rivaroxaban. The reoccurrence rate of sICH was 1.30 and 2.06% in the LMWH and rivaroxaban groups, respectively. Bleeding rates were 8.70% in the LMWH group and 5.15% in the rivaroxaban group. The mortality was less frequent in patients received rivaroxaban than LMWH, following up 90 days (8.25 vs 15.65%, p = 0.07) and 1 year (10.42 vs 25.22%, p = 0.003). Multivariate and inverse probability of treatment weighting-adjusted analyses confirmed the association of rivaroxaban with reduced 1-year mortality and better functional recovery. **Conclusion:** Rivaroxaban use in DVT patients after sICH was associated with lower long-term mortality and better functional independence, without significantly increasing the risk of sICH recurrence or bleeding complications. These findings should be interpreted with caution and require confirmation through prospective randomized trials.

Plain language summary: Rivaroxaban or low-molecular-weight heparin, which is safer for patients with intracerebral hemorrhage?

What is this article about? Patients who survive a sudden brain bleed (spontaneous intracerebral hemorrhage) often develop blood clots in the legs (deep vein thrombosis) due to limited mobility. This study compared the safety and effectiveness of two blood thinners – an oral medication (rivaroxaban) and an injectable medication (low-molecular-weight heparins, LMWH) – in these high-risk patients.

What were the results? We analyzed data from 327 patients and found: Patients taking rivaroxaban had a lower 1-year death rate (10.4 vs 25.2%) and were more likely to regain daily independence (56.7 vs 33.5%) compared with those using LMWH. Both medications showed similar safety: the risk of another brain bleed (1.3–2.1%) or serious bleeding (5–8%) was not significantly different between the two groups.

Why is this important? Doctors often hesitate to prescribe blood thinners after a brain bleed due to fears of triggering more bleeding. This study is the first to show that rivaroxaban not only safely prevents leg clots but may also save lives and improve recovery by reducing deadly complications like lung clots. These findings provide strong evidence for choosing rivaroxaban, especially for patients who cannot easily receive daily injections. It could help more survivors return to normal life with fewer risks.

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Keywords: mortality • rivaroxaban • spontaneous intracranial hemorrhage • venous thromboembolism

Spontaneous intracerebral hemorrhage (sICH), a devastating subtype of stroke, accounts for 10–15% of all stroke cases, and effective interventions remain limited [1]. The mortality rate of sICH is nearly 50%, and approximately 76% of survivors are left with permanent disabilities [1–3]. Deep vein thrombosis (DVT) is a common complication in patients with sICH because of limb paralysis and increased prothrombotic activity [4,5]. Patients with sICH have a two- to fourfold higher risk of developing DVT compared with those with acute ischemic stroke, and the incidence can reach 20–40% when assessed by ultrasonography during hospitalization [6–8]. In patients with sICH, the occurrence of DVT is not only frequent but also associated with serious complications. Pulmonary embolism (PE), a potentially life-threatening early complication of DVT, occurs in approximately 10% of cases. Post-thrombotic syndrome, the predominant long-term sequela, affects up to 30% of patients and is associated with chronic pain, limb swelling and venous skin ulceration [9]. Moreover, DVT is linked to increased long-term mortality, with 1- and 5-year rates reaching 22% and 39%, respectively [10]. Anticoagulants are the primary treatment for DVT [11]. However, in patients with intracerebral hemorrhage (ICH), formulating an anticoagulation regimen requires careful consideration of the trade-off between preventing thrombotic progression and avoiding the risk of recurrent bleeding.

Pooled data supporting anticoagulant therapy have not shown an increased risk of major bleeding events in patients with sICH [12,13]. Low-molecular-weight heparins (LMWH), recommended by the American Heart Association/American Stroke Association (AHA/ASA) guidelines, are widely used and represent the standard prophylactic anticoagulant for patients at risk of DVT [14]. Multiple clinical trials and meta-analyses have consistently shown that LMWH significantly reduces the incidence of venous thromboembolic events (such as DVT and PE) in patients with ICH, without increasing the risk of hematoma expansion [15]. Recently, the number of sICH patients receiving oral anticoagulant therapy has been increasing [16]. Rivaroxaban, an oral anticoagulant that acts directly on factor Xa, has been approved for the prevention of DVT in postoperative patients [17,18]. Numerous randomized trials show that rivaroxaban is noninferior to LMWH for preventing DVT and with no significant differences in major bleeding rate [19,20]. These findings suggest that rivaroxaban may serve as an effective alternative for the treatment of DVT after ICH, with the potential clinical advantages of oral administration and no need for routine monitoring. However, a meta-analysis indicates that rivaroxaban might increase the risk of bleeding [21]. The efficacy and safety of rivaroxaban for DVT have not been assessed in patients with sICH. The effects of anticoagulant treatment on short- and long-term clinical prognosis are still unclear.

Therefore, our study aims to evaluate the rates of sICH recurrence and bleeding in patients who received anticoagulants. We also sought to investigate whether patients with DVT suffering from sICH can get short- and long-term benefits from rivaroxaban therapy.

Materials & methods

Study participants

The study was a retrospective cohort study of patients diagnosed with sICH and DVT from 1 August 2019 to 18 September 2023. Detailed information for patients was obtained from the electronic medical record system. Patients were eligible for entry if they were aged 18 years or older, diagnosed with sICH by radiology, diagnosed with DVT via lower extremity Doppler ultrasonography or CT venography and treated with rivaroxaban or LMWH. The procedures followed in this study were in accordance with the ethical standards established by the local ethics committee (Approval No. 2024010).

DVT, rivaroxaban & LMWH administration

DVT in patients following sICH was defined based on electronic medical records during inpatient hospitalization. DVT was diagnosed via lower extremity Doppler ultrasonography or CT venography. Rivaroxaban was administered orally at a dose of 15 mg twice daily with food for 21 days, followed by 20 mg once daily to maintain the treatment. LMWH (Clexane, 4000–6000 IU and Nadroparin, 3075–6150 IU) was administered subcutaneously twice daily for a period of 5–7 days until the DVT was resolved. The dosage of anticoagulants was determined by the physician according to the patient's condition.

Study treatments & interventions

Our study collected data for patients that were extracted from the electronic medical record system, including age, gender, medical history, admission systolic blood pressure, clinical symptoms, the location of sICH, the volume of sICH, admission The National Institutes of Health Stroke Scale (NIHSS) score, admission Glasgow Coma Scale (GCS) score and history of recent surgery.

Outcomes measures

The primary outcomes were recurrent sICH, bleeding-related events during hospitalization and mortality within 90 days and 1 year. Recurrent sICH and bleeding-related events occurred during intake of the first dose of anticoagulants and 2 days after the last dose. Bleeding-related events included gastrointestinal bleeding, subcutaneous ecchymosis, requiring an infusion of hemoglobin 2U or more, or a decrease in the hemoglobin level of 2 g/dl. The other outcomes included the proportion of patients with favorable outcome, functional independence and excellent outcome at 90 days and 1 year. Favorable outcome was defined as a Modified Rankin Scale (mRS) ranging from 0 to 3, functional independence as an mRS ranging from 0 to 2 and excellent outcome as an mRS ranging from 0 to 1.

Statistical analysis

Categorical variables were presented as percentages and compared using the Chi-square test or Fisher exact test, appropriately. Continuous variables were shown using the median (interquartile range, IQR) and Mann–Whitney U test to analyze the difference between the rivaroxaban and heparin group. Additionally, we performed inverse probability of treatment weighting (IPTW) to reduce differences in baseline characteristics between two groups, assigning a weight of mean of propensity scores (PS)/PS for the rivaroxaban and (1-mean of PS)/1-PS for heparin group. To evaluate the balance of variables, we utilized the standardized mean difference (SMD). After applying the weighting, all variables achieved excellent balance, with SMD values less than 0.1. Briefly, we performed multiple logistic regression to build a propensity score, which took rivaroxaban versus heparin as a binary result. And, the value of the weighted SMD, which was used to evaluate the balance between treatment groups, of low 20% was considered appropriate.

Furthermore, we assessed the association between anticoagulants and clinical outcomes using multivariate logistic regression analysis adjusting sex, age, baseline NIHSS, baseline GCS and surgery. Logistic regression analysis was also conducted to examine the association between rivaroxaban and clinical prognostics based on the IPTW model. The Kaplan–Meier survival curve was plotted to describe the survival status of patients treated with rivaroxaban or heparin.

Subgroup analyses

Subgroup analyses were performed to assess the heterogeneity of associations between mortality within 1 year and anticoagulants. Clinically relevant subgroups of interest included age, sex, sICH location and surgical procedure. Multivariate logistic regression adjusting for sex, age, baseline NIHSS, baseline GCS and surgery was applied. Additionally, binary logistic regression based on the IPTW model was conducted.

Statistical analysis was performed with the IBM SPSS Statistics, Version 26.0 program. Armonk, NY: IBM Corp. RStudio software (version 1.4.1106) was applied to build a forest plot and Kaplan–Meier survival curve. Statistical significance was defined as $p < 0.05$ (2-tailed).

Results

Baseline characteristic

A total of 395 patients were diagnosed with sICH and DVT between 11 October 2019 and 11 October 2023. Detailed exclusion criteria of our study were presented in Figure 1. Finally, 327 patients were enrolled in the present analyses, including 230 patients treated with LMWH and 97 patients with rivaroxaban. Among all participants, 176 (53.82%) were male, and the median age was 64 (IQR, 58–71) years. The proportion of males (63.92 vs 49.57%, $p = 0.02$) and patients with a history of smoking (19.59 vs 6.09%, $p < 0.001$) was higher in the rivaroxaban group than in the LMWH group (Table 1). In addition, significant differences in clinical symptoms and surgical procedures were observed between the LMWH and rivaroxaban groups.

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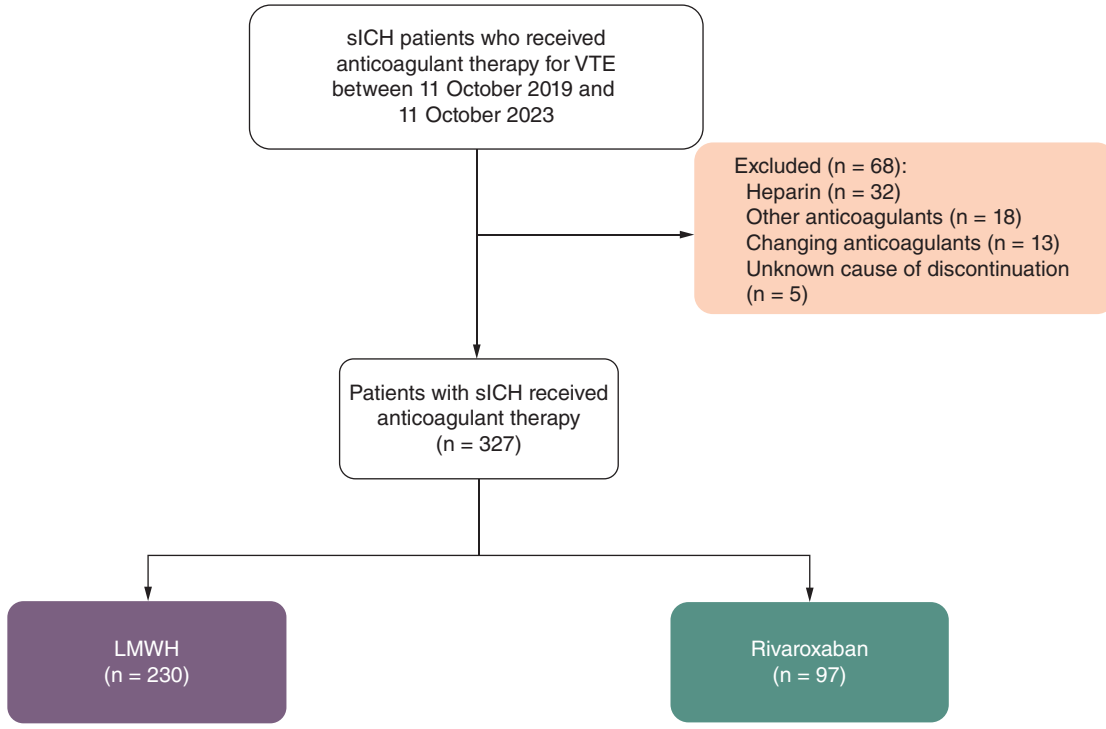

Figure 1. Flow of patients in the study.

Clinical outcomes

Of these groups, three patients (1.30%) and two patients (2.06%) reoccurred sICH events in the LMWH and rivaroxaban groups, respectively. Further, the proportion of bleeding-related events was 8.70% in LMWH cohorts and 5.15% in rivaroxaban cohorts. Compared with LMWH, our finding observed that patients could get benefits from rivaroxaban in favorable outcome (64.95 vs 50.87%, p = 0.02) and functional independence (32.99 vs 18.26%, p = 0.004) as following-up at 90 days (Table 2 & Figure 2). The likelihood of mortality within 90 days was more frequent in LMWH than in rivaroxaban (15.65 vs 8.25%, p = 0.07), although the difference did not arrive at a significant level. Additionally, patients receiving LMWH had a low proportion of excellent outcome (16.96 vs 27.84%, p = 0.03), functional independence (33.48 vs 56.70%, p < 0.001), favorable outcome (61.30 vs 81.44%, p < 0.001) and high rates of mortality (25.22 vs 10.42, p = 0.003) within 1 year compared with the rivaroxaban group (Table 2). The Kaplan–Meier survival curve also indicated that patients with rivaroxaban had less frequent mortality (Figure 3).

Rivaroxaban was associated with functional independence (adjusted odds ratio, aOR: 2.31, 95% CI: 1.24–4.28, p = 0.01) at 90 days after adjusting for covariates. Particularly, the association between rivaroxaban and favorable outcome at 1 year was identified based on IPTW (OR: 1.45, 95% CI: 1.02–2.05, p = 0.04) and multivariate (OR: 3.00, 95% CI: 1.54–5.86, p < 0.001) logistic regression analyses (Table 3). In addition, rivaroxaban treatment was associated with reduced 1-year mortality (multivariate analysis, aOR: 0.32, 95% CI: 0.14–0.69, p = 0.004; IPTW analysis, OR: 0.38, 95% CI: 0.24–0.61, p < 0.001).

Subgroup analyses

Additional analyses stratified by patient characteristics showed that the association between rivaroxaban and reduced mortality within 1 year was more pronounced in those who were older than 65 years, those with basal ganglia sICH events, and those undergoing minimally invasive surgery (Figure 4). IPTW analyses supported the finding that the mortality at 1-year follow-up in the rivaroxaban group was lower in patients with basal ganglia sICH and those undergoing minimally invasive surgery than in the LMWH group.

Discussion

In our study of 327 patients with DVT, we observed that recurrent sICH occurred in 1.30 and 2.06% of patients treated with LMWH and rivaroxaban, respectively. The rate of bleeding-related events was 8.70% in the LMWH

Table 1. Baseline characteristics of intracranial hemorrhage patients with venous thromboembolism in low-molecular-weight heparins and rivaroxaban.

Variable	Unmatched			IPTW		
	LMWH (n = 230)	Rivaroxaban (n = 97)	p-value	LMWH (n = 326.8)	Rivaroxaban (n = 283)	p-value
Age, years, median (IQR)	65 (58–71)	63 (56–71)	0.29	65.00 (58.00–71.00)	64.00 (57.46–70.00)	0.96
			0.37			0.86
18–65	125 (54.35)	58 (59.79)		181.45 (55.52)	161.50 (57.07)	
>65	105 (45.65)	39 (40.21)		145.35 (44.48)	121.50 (42.93)	
Male, n (%)	114 (49.57)	62 (63.92)	0.02	175.20 (53.60)	155.10 (54.80)	0.89
Hypertension, n (%)	151 (65.65)	72 (74.23)	0.13	222.51 (68.10)	202.06 (71.40)	0.69
Diabetes mellitus, n (%)	18 (7.83)	4 (4.12)	0.22	28.18 (8.62)	13.26 (4.69)	0.42
Pre-stroke	63 (27.39)	21 (21.65)	0.28	80.26 (24.56)	55.47 (19.60)	0.41
Smoking, n (%)	14 (6.09)	19 (19.59)	<0.001	27.97 (8.56)	34.74 (12.28)	0.37
Drinking, n (%)	5 (2.17)	3 (3.09)	0.62	6.96 (2.13)	3.07 (1.08)	0.36
Baseline NIHSS, median (IQR)	22 (14–32)	22 (15–32)	0.46	21.20 (14.00–32.00)	22.55 (18.00–32.00)	0.35
Baseline GCS, median (IQR)	11 (8–13)	11 (8–13)	0.73	11.00 (8.00–13.00)	10.00 (7.00–12.00)	0.16
SBP	167 (150–188)	160 (143–181)	0.09	165.00 (147.18–183.94)	161.67 (142.00–182.62)	0.82
DBP	95 (83–107)	91 (82–98)	0.12	94 (82–105)	92 (83–101.51)	0.85
ICH Location			0.35			0.84
Lobar	42 (18.26)	11 (11.34)		54.76 (16.76)	35.80 (12.65)	
Basal ganglia	115 (50.00)	60 (61.86)		181.36 (55.50)	182.35 (64.44)	
Thalamus	39 (16.96)	17 (17.53)		52.55 (16.08)	42.81 (15.13)	
Cerebellum	15 (6.52)	4 (4.12)		17.00 (5.20)	11.25 (3.98)	
Brainstem	7 (3.04)	2 (2.06)		7.99 (2.44)	4.59 (1.62)	
Other	12 (5.22)	3 (3.09)		13.11 (4.01)	6.16 (2.18)	
ICH volume (cm^3) at admission, median (IQR)	27 (14–46)	29 (17–39)	0.85	26 (14–46)	29 (20–36)	0.66
Encephalocele	18 (7.83)	8 (8.25)	0.90	19.97 (6.11)	20.50 (7.25)	0.70
Clinical symptom, (n)%						
Headache	5 (2.17)	10 (10.31)	0.003	12.14 (3.72)	14.06 (4.97)	0.62
Epilepsy	0	2 (2.06)	0.09	0 (0)	2.14 (0.76)	0.15
Paralyzed	227 (98.70)	91 (93.81)	0.04	320.09 (97.96)	273.93 (96.80)	0.56
Aphasia	15 (6.52)	18 (18.56)	0.001	41.46 (12.69)	38.05 (13.44)	0.89
Coma	201 (87.39)	45 (46.39)	<0.001	243.23 (74.44)	198.65 (70.20)	0.55
Hospital days	38 (28–60)	38 (28–57)	0.54	36 (26–56.69)	38 (30–56)	0.30
Surgery producer			0.002			0.72
Minimally invasive	36 (15.65)	19 (19.59)		165.79 (50.74)	159.62 (56.41)	
Craniotomy	62 (26.96)	9 (9.28)		53.37 (16.33)	49.06 (17.34)	
Craniectomy	19 (8.26)	16 (16.49)		68.89 (21.08)	40.17 (14.20)	
No	113 (49.13)	53 (54.64)		38.72 (11.85)	34.1 (12.06)	

DBP: Diastolic blood pressure; GCS: Glasgow Coma Scale; ICH: Intracranial hemorrhage; IPTW: Inverse probability of treatment weighting; IQR: Interquartile range; LMWH: Low-molecular-weight heparins; NIHSS: The National Institutes of Health Stroke Scale; SBP: Systolic blood pressure; VTE: Venous thromboembolism.

group and 5.15% in the rivaroxaban group. Rivaroxaban use was associated with significantly reduced risk of all-cause mortality and an increased likelihood of a favorable outcome at 1 year.

Nielsen *et al.* [12] reported that the rates of recurrent ICH were 8.6 per 100 person-years for patients receiving anticoagulants versus 8.0 per 100 person-years for those receiving no antithrombotic treatment (adjusted HR: 0.91; 95% CI: 0.56–1.49) in patients following sICH, based on 1 year of follow-up. Among ICH patients, the rate of major extracranial bleeding was 1.5% in patients treated with anticoagulant therapy [12]. A meta-analysis investigating the safety of anticoagulants in sICH patients suggested that there was no significant difference between anticoagulant and nonanticoagulant cohorts (8.0 vs 4.0%, relative risk: 1.42; 95% CI: 0.57–3.53; p = 0.45) [13]. Based on these data, anticoagulation treatment for DVT in ICH patients appeared to be safe and effective [22].

Table 2. Comparing the clinical outcomes of spontaneous intracranial hemorrhage patients with venous thromboembolism in heparin and rivaroxaban.

Outcome	Unmatched			IPTW		
	LMWH	Rivaroxaban	p-value	LMWH	Rivaroxaban	p-value
Recurrent sICH	3 (1.30)	2 (2.06)	0.64	3.64 (1.11)	2.54 (0.90)	0.82
Bleeding-related events	20 (8.70)	5 (5.15)	0.27	23.35 (7.15)	11.00 (3.89)	0.27
mRS at 90 days	3 (3–4)	3 (2–4)	0.01	3 (3–5)	3 (3–4)	0.65
0–1	8 (3.48)	7 (7.22)	0.24	11.66 (3.57)	9.11 (3.22)	0.86
0–2	42 (18.26)	32 (32.99)	0.004	62.69 (19.19)	61.87 (21.86)	0.63
0–3	117 (50.87)	63 (64.95)	0.02	181.97 (55.69)	147.79 (52.23)	0.69
Mortality within 90 days	36 (15.65)	8 (8.25)	0.07	45.42 (13.90)	19.41 (6.86)	0.11
mRS at 1 year	3 (2–3)	2 (1–3)	0.004	3 (2–5)	3 (2–3)	0.15
0–1	39 (16.96)	27 (27.84)	0.03	54.12 (16.56)	55.53 (19.62)	0.56
0–2	77 (33.48)	55 (56.70)	<0.001	121.40 (37.15)	113.51 (40.11)	0.70
0–3	141 (61.30)	79 (81.44)	<0.001	214.11 (65.52)	207.58 (73.36)	0.37
Mortality within 1 year	58 (25.22)	10 (10.42)	0.003	73.98 (22.64)	27.63 (9.76)	0.02

IPTW: Inverse probability of treatment weighting; LMWH: Low-molecular-weight heparins; mRS: Modified Rankin Scale; sICH: Spontaneous intracranial hemorrhage; VTE: Venous thromboembolism.

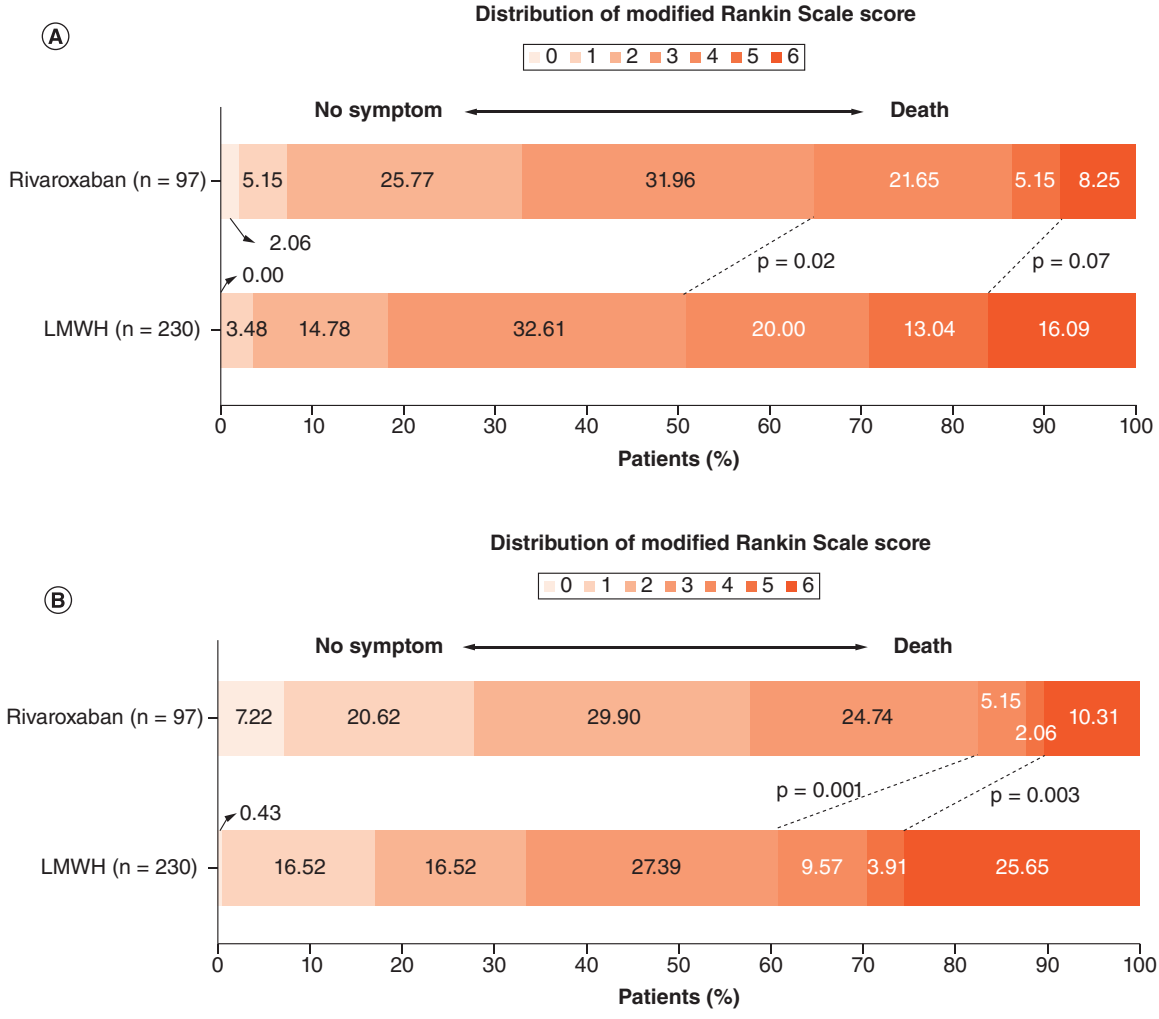

Figure 2. Distribution of the Modified Rankin Scale scores. (A) The mRS distribution in the following 90 days, and **(B)** the mRS distribution in the following 1 year.
mRS: Modified Rankin Scale.

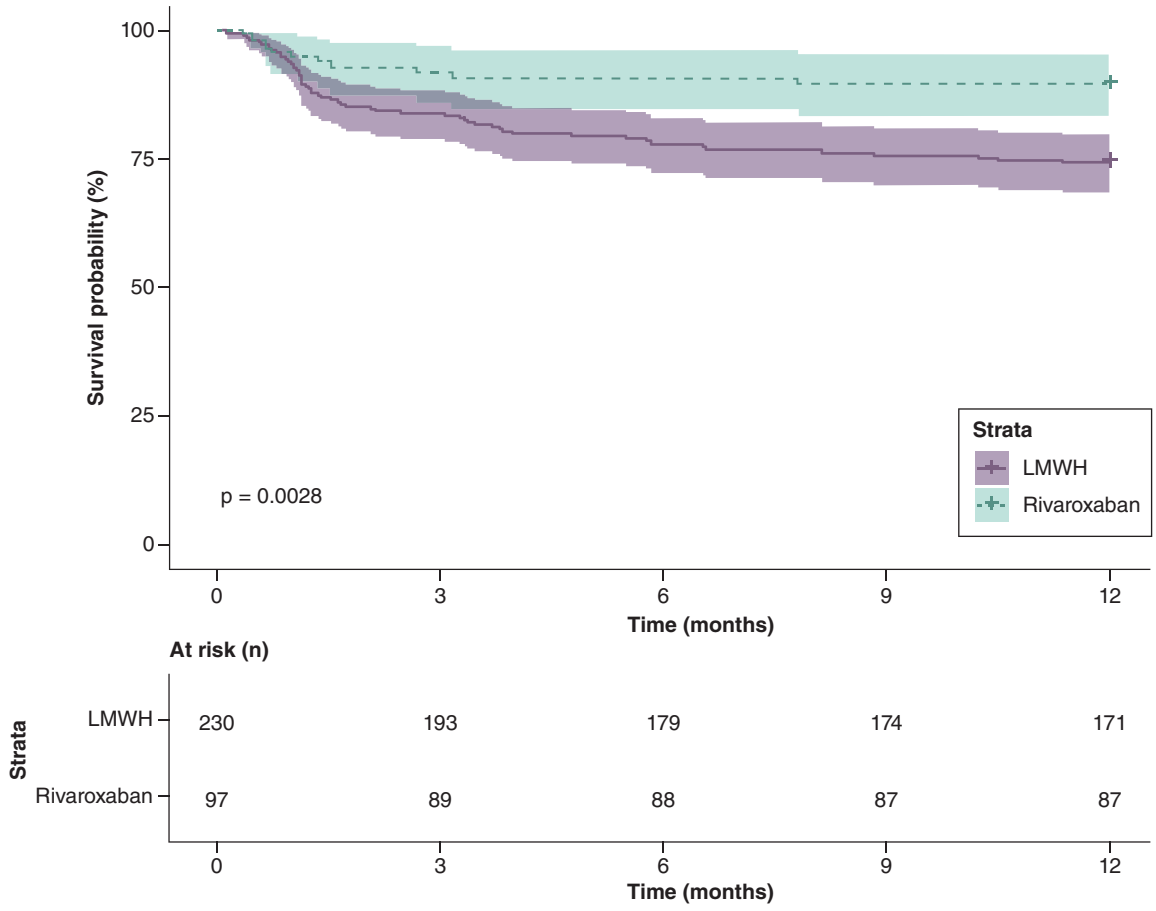

Figure 3. Kaplan–Meier survival plot. Kaplan–Meier survival estimate of cumulative mortality during the 1-year follow-up period in rivaroxaban and LMWH cohorts.
LMWH: Low-molecular-weight heparin.

Table 3. The association of rivaroxaban and short- and long-term clinical outcomes.

	Adjusted OR (95% CI)	p-value	IPTW OR (95% CI)	p-value
mRS 90 days	2.03 (1.29–3.18)	0.002	1.14 (0.86–1.52)	0.35
mRS 0–1	2.20 (0.73–6.66)	0.16	0.90 (0.37–2.17)	0.81
mRS 0–2	2.31 (1.24–4.28)	0.01	1.18 (0.80–1.75)	0.41
mRS 0–3	1.64 (0.93–2.89)	0.09	0.87 (0.63–1.20)	0.39
Mortality	0.49 (0.21–1.15)	0.10	0.46 (0.26–0.80)	0.01
mRS 1 year	2.40 (1.53–3.76)	<0.001	1.29 (0.97–1.71)	0.08
mRS 0–1	1.80 (0.96–3.37)	0.07	1.07 (0.70–1.64)	0.75
mRS 0–2	2.39 (1.34–4.25)	0.003	1.04 (0.75–1.44)	0.82
mRS 0–3	3.00 (1.54–5.86)	0.001	1.45 (1.02–2.05)	0.04
Mortality	0.32 (0.14–0.69)	0.004	0.38 (0.24–0.61)	<0.001

CI: Confidence interval; GCS: Glasgow Coma Scale; IPTW: Inverse probability of treatment weighting; mRS: Modified Rankin Scale; NIHSS: The National Institutes of Health Stroke Scale; OR: Odds ratio;
Adjusting for sex, age, baseline NIHSS, baseline GCS and surgery producer.

A meta-analysis, analyzing 9 studies and 4055 patients with sICH noted that anticoagulant therapy was not associated with a significantly increased risk of hematoma expansion (6.6 vs 3.2%, p = 0.14) in comparison with no-anticoagulant cohorts [23]. Our findings observed low rates of recurrence of sICH and bleeding-related events, which indicated that anticoagulant treatment for patients with DVT after sICH was safe.

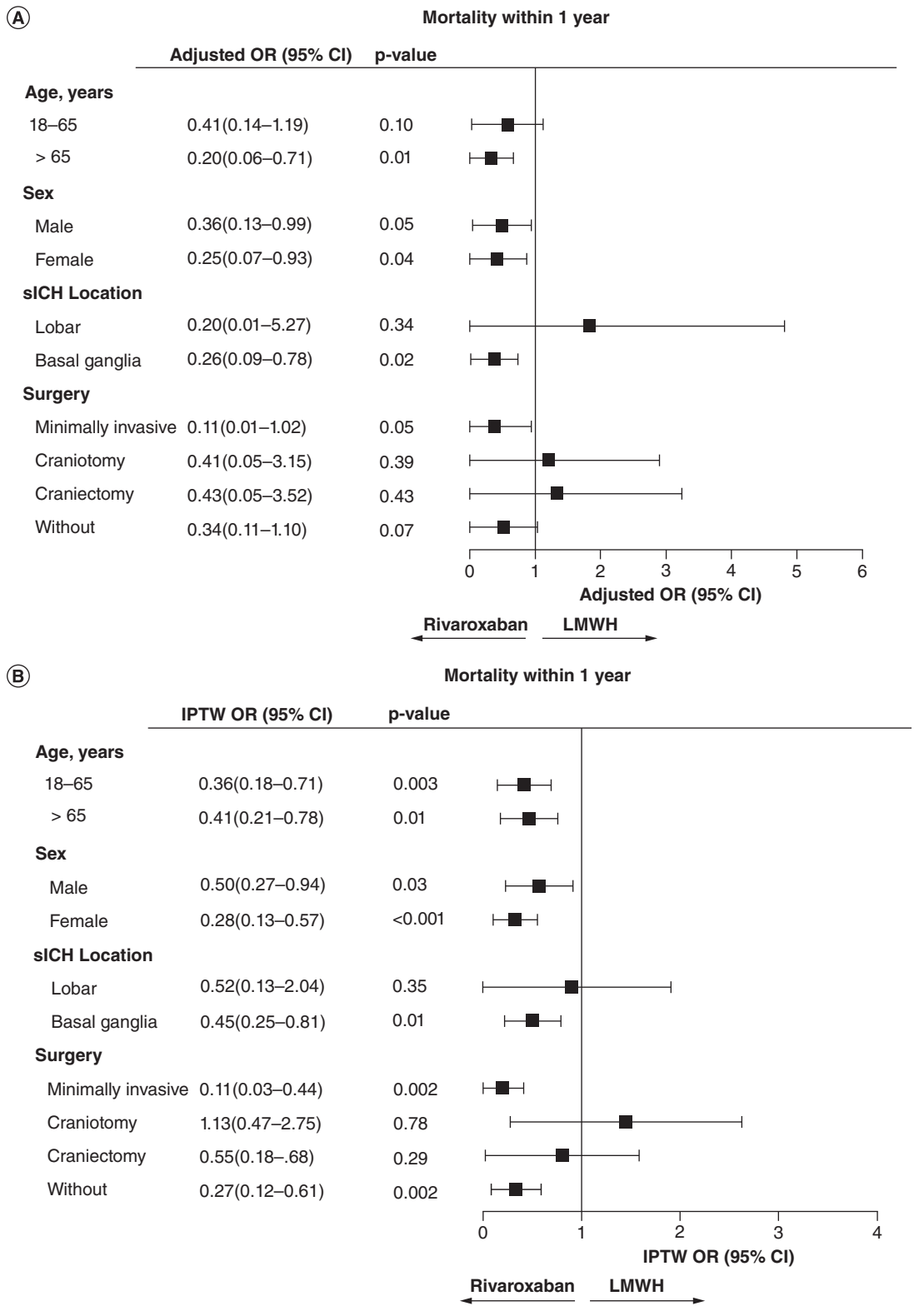

Figure 4. Analysis of mortality within 1 year in subgroups. The forest plot shows the effects of rivaroxaban on mortality within 1 year across four subgroups based on multivariate logistic regression analysis adjusting sex, age, baseline NIHSS, baseline GCS and surgery **(A)** and binary logistic regression analysis in the IPTW model **(B)** LMWH. GCS: Glasgow Coma Scale; IPTW: Inverse probability of treatment weighting; LMWH: Low-molecular-weight heparins; NIHSS: The National Institutes of Health Stroke Scale.

DVT is a common complication in patients with sICH [24]. In-hospital DVT was associated with a high risk of poor outcomes in patients with sICH [25]. Chu *et al.* [22] noted that patients with ICH may benefit from oral anticoagulant therapy, which was associated with decreased mortality during hospitalization (17.86 vs 53.85%), 28-day (21.43 vs 61.54%), 3-month (32.14 vs 69.23%) and 1-year (42.86 vs 76.92%). Furthermore, Sembill *et al.* [26] revealed that initiating anticoagulant therapy after ICH was associated with a more favorable functional outcome (76.5 vs 33.3%, $p = 0.01$) and decreased mortality (26.1 vs 60.4%, $p < 0.01$) compared with patients who did not receive anticoagulant therapy at 12-month follow-up. Therefore, it is reasonable to suggest that anticoagulant therapy may help improve functional independence in patients after sICH [27]. Our finding supported that rivaroxaban was associated with a long-term favorable outcome and reduced risk of mortality. This may be explained by less frequent recurrent DVT of rivaroxaban therapy. LMWH inhibits factor Xa, thereby blocking the conversion of prothrombin to thrombin [28,29]. Rivaroxaban binds directly to factor Xa and inhibits its activity, with approximately 10,000-fold selectivity over other related serine proteases.. Rivaroxaban also inhibits prothrombinase activity [30]. Indeed, SELECT-D trial [31] indicated that patients treated with rivaroxaban had a lower incidence of DVT, observed in 4% versus 11% of patients [32]. Furthermore, the study also evaluated the organ bleeding of rivaroxaban, which implied rivaroxaban was associated with a reduced risk of organ bleeding events versus heparins at 3, 6 and 12 months [33]. Regretfully, our study did not collect information on organ bleeding events during the follow-up.

Based on multivariate and IPTW logistic regression, subgroup analysis results indicated that patients received rivaroxaban with basal ganglia sICH were observed with uncommon mortality within 1 year. A meta-analysis identified the efficacy of anticoagulant therapy in patients after ICH regardless of ICH location [32]. In our study, the age of the rivaroxaban group was younger (median age, 59 vs 64) in patients with basal ganglia sICH than in heparin cohorts. Several studies reported that the oldest have a higher mortality than the younger [34,35]. Additionally, the rates of without suffering surgery (45 vs 40%) and minimally invasive (21.67 vs 14.78%) were more common in patients treated with rivaroxaban. Clinical data demonstrated that minimally invasive surgery could facilitate the reduction of hematoma volume and decrease the morbidity of craniectomy [36], which could reduce the opportunity of mortality.

Multiple limitations need to be considered while interpreting our results. First, the retrospective design of our study, along with the lack of randomization in anticoagulant therapy, inevitably introduced selection bias. Although baseline disease severity was comparable between groups (GCS median [IQR]: 11 [8–13], $p = 0.73$), significantly more patients received LMWH than rivaroxaban (230 vs 97). This discrepancy likely reflects differences in the route of administration: rivaroxaban is taken orally, whereas LMWH is administered via subcutaneous injection. In hospitalized ICH patients with severe conditions, clinicians may prefer injectable therapies due to their greater controllability, ease of use and lower reliance on patient compliance, which may have introduced treatment allocation bias. To reduce this bias, IPTW was applied to balance observed covariates between groups. However, IPTW cannot fully account for unmeasured confounders such as physician preference or practical considerations in drug administration. In addition, the inherent limitations of retrospective studies – such as incomplete documentation, missing data and potential recall bias – may also have impacted the accuracy and completeness of the collected information. Specifically, the coagulation parameters before and after anticoagulant therapy were incomplete, such as prothrombin time, activated partial thromboplastin time and thrombin time. Second, our sample size of sICH patients with DVT was small, and we could not adjust more confounding factors by performing multivariate logistic regression. Third, the details of organ bleeding events and recurrent thromboembolism were not recorded during follow-up. Moreover, to the best of our knowledge, studies directly comparing the efficacy and safety of rivaroxaban and LMWH in the treatment and prevention of venous thromboembolism following sICH remain limited. The lack of relevant external studies for comparison limits the generalizability of our findings; therefore, the conclusions of this study should be interpreted with caution. Considering these limitations, further validation through randomized controlled trials is required to confirm our findings.

Conclusions

In conclusion, our study revealed the safety of rivaroxaban in the management of DVT in patients with sICH. Notably, rivaroxaban was associated with a long-term favorable outcome and reduced risk of all-cause mortality in patients with DVT after sICH. Future large-scale studies are necessary to confirm the benefits of rivaroxaban for patients with DVT.

Summary points

- During hospitalization, 20–40% of spontaneous intracranial hemorrhage (sICH) patients develop deep vein thrombosis. Anticoagulation must balance thromboprophylaxis and rebleeding risks.
- Retrospective comparison of rivaroxaban (oral) versus low-molecular-weight heparins (LMWH) (injectable) in 327 sICH patients with deep vein thrombosis (LMWH: 230; rivaroxaban: 97), adjusted via inverse probability of treatment weighting.
- No significant differences in sICH recurrence (LMWH: 1.30% vs rivaroxaban: 2.06%) or bleeding events (LMWH: 8.70% vs rivaroxaban: 5.15%).
- Rivaroxaban reduced 1-year mortality (10.42 vs 25.22%, $p = 0.003$) and improved functional independence (mRS 0–2: 56.70% vs 33.48%, $p < 0.001$).
- Mortality reduction with rivaroxaban was pronounced in basal ganglia hemorrhage (aOR: 0.32, $p = 0.004$). Benefits in minimally invasive surgery cohorts were noted but lacked explicit statistical details.
- Potential advantages of rivaroxaban include oral administration and sustained anticoagulation.
- Rivaroxaban is a safe alternative to LMWH post-sICH, offering survival and functional benefits, particularly for long-term use. Prospective trials are needed.

Author contributions

Conceptualization, J Li; Data curation, Q Song and G Zhang; Formal analysis, J Li and Q Song; Investigation, G Zhang, G Tong and C Bian; Methodology, J Li, Q Song, H Zhang and Y Wang; Software, G Tong and H Zheng; Supervision, H Zheng; Validation, J Li; Writing – original draft, J Li; Writing – review & editing, Y Wang.

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Writing disclosure

No funded writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by Ethics Committee of the First Hospital of Yulin approval: number 2024010. As this was a retrospective trial, written informed consent from participants was not required in accordance with local guidelines.

Data availability statement

The data that support the findings of this study are not publicly available but are available from the corresponding author or data sharing committee upon reasonable request.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Hemphill JC, Greenberg SM, Anderson CS *et al.* Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 46(7), 2032–2060 (2015).
2. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet* 373(9675), 1632–1644 (2009).
3. Fang MC, Go AS, Chang Y *et al.* Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am. J. Med.* 120(8), 700–705 (2007).

4. Ji R, Li G, Zhang R *et al.* Higher risk of deep vein thrombosis after hemorrhagic stroke than after acute ischemic stroke. *J. Vasc. Nurs.* 37(1), 18–27 (2019).
5. Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. *Lancet* 388(10063), 3060–3073 (2016).
6. Skaf E, Stein PD, Beemath A *et al.* Venous thromboembolism in patients with ischemic and hemorrhagic stroke. *Am. J. Cardiol.* 96(12), 1731–1733 (2005).

• **Venous thromboembolism (VTE) rates in hospitalized stroke patients were 1.17% for ischemic stroke and 1.93% for hemorrhagic stroke.**

7. Kawase K, Okazaki S, Toyoda K *et al.* Sex difference in the prevalence of deep-vein thrombosis in Japanese patients with acute intracerebral hemorrhage. *Cerebrovasc. Dis.* 27(4), 313–319 (2009).
8. Ogata T, Yasaka M, Wakugawa Y *et al.* Deep venous thrombosis after acute intracerebral hemorrhage. *J. Neurol. Sci.* 272(1–2), 83–86 (2008).

• **Intracerebral hemorrhage patients with severe neurological deficit and high D-dimer value are at increased risk of developing deep vein thrombosis.**

9. Min SK, Kim YH, Joh JH *et al.* Diagnosis and treatment of lower extremity deep vein thrombosis: Korean Practice Guidelines. *Vasc. Specialist Int.* 32(3), 77–104 (2016).
10. Naess IA, Christiansen SC, Romundstad P *et al.* Incidence and mortality of venous thrombosis: a population-based study. *J. Thromb. Haemost.* 5(4), 692–629 (2007).
11. Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. *Lancet* 388(10063), 3060–3073 (2016).
12. Nielsen PB, Larsen TB, Skjøth F *et al.* Restarting anticoagulant treatment after intracranial hemorrhage in patients with atrial fibrillation and the impact on recurrent stroke, mortality, and bleeding: a nationwide cohort study [published correction appears in *Circulation* 135(7), e48 (2017)]. *Circulation* 132(6), 517–525 (2015).

•• **Oral anticoagulant treatment significantly reduced ischemic stroke/all-cause mortality, supporting its reintroduction after intracranial hemorrhage.**

13. Paciaroni M, Agnelli G, Venti M, Alberti A, Acciarresi M, Caso V. Efficacy and safety of anticoagulants in the prevention of venous thromboembolism in patients with acute cerebral hemorrhage: a meta-analysis of controlled studies. *J. Thromb. Haemost.* 9(5), 893–898 (2011).

• **In hemorrhagic stroke patients, early anticoagulation significantly reduces pulmonary embolism and slightly increases hematoma enlargement, with a nonsignificant reduction in mortality.**

14. Greenberg SM, Ziai WC, Cordonnier C *et al.* 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke* 53(7), e282–e361 (2022).
15. Zhou Y, Wang G, Xue C *et al.* Effect of heparin for the prevention of venous thromboembolism in patients with spontaneous intracranial cerebral hemorrhage: a meta-analysis. *Ther. Adv. Drug Saf.* 15, 20420986241253469 (2024).

• **In patients with spontaneous intracranial hemorrhage, prophylactic use of heparin may be beneficial because it reduces the incidence of VTE and mortality without increasing the risk of additional bleeding.**

16. Pennlert J, Asplund K, Carlberg B *et al.* Antithrombotic treatment following intracerebral hemorrhage in patients with and without atrial fibrillation. *Stroke* 46(8), 2094–2099 (2015).
17. Perzborn E, Roehrig S, Straub A, Kubitza D, Mueck W, Laux V. Rivaroxaban: a new oral factor Xa inhibitor. *Arterioscler. Thromb. Vasc. Biol.* 30(3), 376–381 (2010).

•• **Rivaroxaban reduced venous thromboembolism rates after hip or knee arthroplasty compared to enoxaparin, with no significant difference in major bleeding, indicating a favorable benefit-to-risk profile.**

18. Lassen MR, Ageno W, Borris LC *et al.* Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N. Engl. J. Med.* 358(26), 2776–2786 (2008).
19. Eriksson BI, Borris LC, Friedman RJ *et al.* Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N. Engl. J. Med.* 358(26), 2765–2775 (2008).
20. EINSTEIN Investigators, Bauersachs R, Berkowitz SD *et al.* Oral rivaroxaban for symptomatic venous thromboembolism. *N. Engl. J. Med.* 363(26), 2499–2510 (2010).
21. Gómez-Outes A, Terleira-Fernández AI, Suárez-Gea ML, Vargas-Castrillón E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. *BMJ* 344, e3675 (2012).
22. Chu Q, Liao L, Wei W *et al.* Venous thromboembolism in ICU patients with intracerebral hemorrhage: risk factors and the prognosis after anticoagulation therapy. *Int. J. Gen. Med.* 14, 5397–5404 (2021).
23. Pan X, Li J, Xu L, Deng S, Wang Z. Safety of prophylactic heparin in the prevention of venous thromboembolism after spontaneous intracerebral hemorrhage: a meta-analysis. *J. Neurol. Surg. A Cent. Eur. Neurosurg.* 81(3), 253–260 (2020).
24. Otite FO, Khandelwal P, Malik AM, Chaturvedi S, Sacco RL, Romano JG. Ten-year temporal trends in medical complications after acute intracerebral hemorrhage in the United States. *Stroke* 48(3), 596–603 (2017).

25. Li J, Wang D, Wang W *et al.* In-hospital venous thromboembolism is associated with poor outcome in patients with spontaneous intracerebral hemorrhage: a multicenter, prospective study. *J. Stroke Cerebrovasc. Dis.* 29(8), 104958 (2020).
26. Sembill JA, Wieser CY, Sprügel MI *et al.* Initiating anticoagulant therapy after ICH is associated with patient characteristics and treatment recommendations. *J. Neurol.* 265(10), 2404–2414 (2018).

•• **Oral anticoagulant were more frequently recommended and started in younger patients with better functional recovery independent from intracranial complications.**

27. Kuramatsu JB, Huttner HB. Management of oral anticoagulation after intracerebral hemorrhage. *Int. J. Stroke* 14(3), 238–246 (2019).
28. Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI. Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) [published correction appears in *Chest* 134(2), 473 (2008)]. *Chest* 133(Suppl. 6), S141–S159 (2008).
29. Meng J, Liu W, Xiao Y, Tang H, Wu Y, Gao S. The role of aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis after total knee arthroplasty: a meta-analysis of randomized controlled trials. *Int. J. Surg.* 109(11), 3648–3655 (2023).
30. Samuelson BT, Cuker A, Siegal DM, Crowther M, Garcia DA. Laboratory assessment of the anticoagulant activity of direct oral anticoagulants: a systematic review. *Chest* 151(1), 127–138 (2017).
31. Young AM, Marshall A, Thirlwall J *et al.* Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J. Clin. Oncol.* 36(20), 2017–2023 (2018).
32. Biffi A, Kuramatsu JB, Leasure A *et al.* Oral anticoagulation and functional outcome after intracerebral hemorrhage. *Ann. Neurol.* 82(5), 755–765 (2017).
33. Coleman CI, Caroti KS, Abdelgawwad K *et al.* Effectiveness and safety of rivaroxaban and low molecular weight heparin in cancer-associated venous thromboembolism. *JACC Cardio. Oncol.* 5(2), 189–200 (2023).
34. Forti P, Maioli F, Domenico Spampinato M *et al.* The effect of age on characteristics and mortality of intracerebral hemorrhage in the oldest-old. *Cerebrovasc. Dis.* 42(5–6), 485–492 (2016).
35. James ML, Cox M, Xian Y *et al.* Sex and age interactions and differences in outcomes after intracerebral hemorrhage. *J. Womens Health (Larchmt)* 26(4), 380–388 (2017).
36. Vitt JR, Sun CH, Le Roux PD. Hemphill JC 3rd. Minimally invasive surgery for intracerebral hemorrhage. *Curr. Opin. Crit. Care* 26(2), 129–136 (2020).