Early thrombosis prophylaxis with enoxaparin is not associated with hematoma expansion in patients with spontaneous intracerebral hemorrhage

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Abstract

Background: Early pharmacological deep vein thrombosis (DVT) prophylaxis is recommended by guidelines, but rarely started within 48 hours. We aimed to analyze the effect of early (within 48h) versus late (>48h) DVT prophylaxis on hematoma expansion (HE) and outcome in patients with spontaneous intracerebral hemorrhage (ICH).

Methods: We analyzed 134 consecutive patients admitted to a tertiary neuro-intensive care unit with diagnosed spontaneous ICH, obtained informed consent and without previous anticoagulation, a severe coagulopathy, hematoma evacuation, early withdrawal of therapy or ineligibility for DVT prophylaxis according to our institutional protocol. Significant late HE was defined as ≥6mL increase of hematoma volume between neuroimaging within 48h and day 3-6. Multivariate analysis was performed to identify risk factors for late HE, poor 3-month outcome (mRS≥4) and mortality.

Results: Patients had a median Glasgow Coma Scale Score of 14 (IQR 10-15), ICH volume of 11mL (IQR 5-24) and were 71 years old (IQR 61-76). 56% (N=76) received early DVT prophylaxis, 37% (N=50) late DVT prophylaxis and 8 (6%) had unknown bleeding onset. Patients with early DVT prophylaxis had smaller ICH volume (9.5mL, IQR 4-18.5; versus 17.5mL, IQR 8-29; p=0.038) and more often were comatose (26% versus 10%, p=0.025). Significant late HE (N=5/134, 3.7%) was associated with larger initial ICH volume (p=0.02) and lower thrombocyte count (p=0.03) but not with early DVT prophylaxis (p=0.36). Early DVT prophylaxis was not associated with worse outcome.

Conclusion: Significant late HE is uncommon and DVT prophylaxis within 48h of symptom onset may be safe in selected ICH patients.

Introduction

Intracerebral hemorrhage (ICH) is a devastating disease with high morbidity and mortality [1] and prognosticated incidence increase, due to higher life expectancy.[2] One potentially modifiable contributor to poor outcome is hematoma expansion (HE)[3], which is associated with admission hypertension, hyperglycemia, hemorrhagic diathesis and radiological characteristics such as the initial hematoma volume, shape or density, intraventricular extension (IVH), and black hole, island [4], blend [5] or spot sign on admission CT-scan.[6] Protracted HE may occur in up to half of patients with anticoagulant treatment or coagulopathies.[3,6-8] Deep venous thrombosis (DVT) prophylaxis is recommended for bed-ridden ICH-patients to prevent DVT and pulmonary embolism (PE),[9] however its influence on HE and optimal timing remain unclear.[10] Whereas HE usually occurs early, [11,12] thrombotic events peak between the 2nd and 7th day after ictus.[10] Due to the absence of large randomized controlled trials and paucity of high-quality data, guideline recommendations are divergent. The American Stroke Association (ASA) recommends using low molecular weight heparin (LMWH) or unfractionated heparin (UFH) for DVT-prevention in bed-ridden ICH-patients within 1-4 days from onset, after documenting cessation of bleeding, [13] whereas the Neurocritical Care Society (NCS) [14] recommends DVT-prophylaxis within 48h of hospital admission (weak recommendations with low-quality evidence). The European Stroke Organization (ESO) found insufficient evidence to advise how, when and for whom anticoagulation should be given to prevent unfavorable outcome or reduce risk of DVT.[15]

Large discrepancies between guidelines and clinical practice exist, with <20% of ICH patients receiving DVT prophylaxis and of those just 50% being treated within the first 2 days.[10] This may show reluctance to follow guidelines which are not supported by strong evidence but are rather based heavily on expert opinion.

Our institutional protocol aims to provide DVT-prophylaxis after spontaneous-ICH as soon as safety criteria have been fulfilled. These refer to patients with stable neurological examination, without significant progression of hematoma or suspected untreated vascular defects in the neuroimaging, who are not candidates for neurosurgery, were not previously anticoagulated, had no coagulopathy, underlying malignancy or general contraindications for LMWH such as advanced renal (creatinine clearance under 15mL/h) or hepatic (Child-Pugh class C) failure, history of heparin induced thrombocytopenia or heparin allergy and received full ICU therapy (i.e. no withholding or withdrawal of care).

We aimed to study the safety of such a protocol and compared patients who received "early" (<48h) DVT-prophylaxis with the ones who received enoxaparin ≥48h after ictus ("late"), analyzing ICH volume-dynamic, hematoma expansion and 3-month outcome.

Materials and Methods

Four-hundred-and-seven consecutive ICH-patients admitted to the neuro-intensive care unit (NICU) at a tertiary hospital (Medical University of Innsbruck, Austria, 2012-2017) were screened. All patients were primarily admitted to the NICU. A small number of patients with small hematomas were admitted to the Stroke-Unit if admission capacity to the NICU was limited. Inclusion criteria were spontaneous-ICH diagnosed on CT-scan and consent for the prospective data collection according to local regulations.

Patient's baseline characteristics, admission variables, hospital complications and outcome data were prospectively collected in our institutional ICH-database, approved by the local ethics committee (Medical University Innsbruck, AN4088292/4.3). Hospital complications were prospectively recorded and assessed in weekly meetings by the clinical team. Standard of care conformed to current ASA and ESO guidelines.[13,15]

DVT-prophylaxis with enoxaparin (20mg/2000 IU or 40mg/4000 IU of Lovenox, Sanofi-Aventis GmbH, Vienna) was administered subcutaneously. *Early and late-DVT prophylaxis* were defined as LMWH given within 48-hours of symptom onset or ≥48-hours.

Repeated head-CT was performed based on the clinical necessity. The *first*-CT was the admission CT-scan. The *second*-CT was the CT that showed the largest hematoma volume within 48h of admission, before enoxaparin administration. The *third*-CT was deemed to be recorded between day 3 and 6.

Sufficient repeated CT-scans corresponding to these criteria were available in 108 (80.5%) patients for volumetric hematoma assessment.

Significant-HE was defined as >6ml increase in volume. We defined the *initial*-HE as progression of ICH volume between second and first CT-scan and a *late*-HE as the volume-difference between the third and second CT-scan.

The volumetric hematoma measurement was performed primarily using the ABC method [16] (IMPAX EE R20 software, Agfa Healthcare N.V., Mortsel Belgium). As we expected some inaccuracy, especially in irregular shaped ICH, we employed a secondary screening method using a planimetric semi-automated volume analysis (syngo®, Siemens Healthcare GmbH, Erlangen, Germany), centered on a manually defined region of interest around the ICH and a radiodensity between 44-100 Hounsfield-units (HU).[17,18] ICH volumes were calculated using 4-mm thick transverse sections. Measurements were repeated by 2 independent observers in all patients with significant hematoma expansion and averaged in case of discrepant results.

Risk factors screened for association with late HE were age, APACHE-II score, ICH-score, admission GCS, initial ICH volume, initial HE, admission within 6 hours of symptom onset, mild thrombocytopenia (100.000-150.000/mm^3), admission INR >1.4 or aPTT over 37seconds (reference value for local laboratory), early DVT-prophylaxis, dose of enoxaparin, history of hypertension, antiplatelet-medication before admission, intraventricular extension and “black hole sign”[19], “island sign” [4], “blend sign”[5], heterogeneous density and irregular shape of hematoma on the second CT-scan. [6]

Outcome was assessed at 3 months by a research assistant blinded to imaging data and clinical course, using the modified Ranking Scale (mRS).[20] Unfavorable outcome was defined for mRS≥4.

Statistical analysis:

Statistical analysis was performed using IBM SPSS Statistics (v.24 64-bit) and R studio (v.1.0.153). Differences between binary variables were analyzed using the Chi-square test. Continuous or ordinal variables were compared using the *t-test* or the *Mann-Whitney U* test, according to distribution. The significance of change in hematoma volumes between repeated CT’s was calculated using the *Wilcoxon signed rank test*. The univariate analysis for risk factors was realized independently for each factor using binary logistic regression. The multivariate analysis for factors associated with late hematoma expansion and functional outcome at 3-months was performed using generalized linear

models with binary outcome response with Logit as link function and a type III analysis. The contributors to the 90 days mortality were described through a *Cox regression* analysis. A p-value <0.05 was set as the statistically significant threshold. The graphical rendering was done using R studio version 1.0.153 and GraphPad Prism 7.

Results

Patient selection

We excluded patients who underwent hematoma evacuation (N=83), were orally anticoagulated (N=58), had severe coagulopathy (N=6) or other causes for the ICH (i.e. cerebral venous sinus thrombosis, trauma, malignancy, aneurysmal subarachnoid hemorrhage with intra-parenchymal bleeding, N=19). Furthermore, we excluded patients for whom treatment was withheld or withdrawn within the first 72 hours (N=39), who did not receive LMWH during ICU stay (N=61 with general contraindications for LMWH, early hematoma progression, severe coagulopathy, early triage to another ward, or a combination of these), were admitted >48 hours after ictus (N=5) or had data with insufficient quality in the registry or medical records (N=2) leaving 134 ICH patients eligible for analysis. (**Figure 1**).

Symptom onset time was precisely documented in 97/134 (72.4%) or estimated (based on anamnesis "around noon" -12:00, "during breakfast" 08:00) in 29/134(21.6%) cases. 12 patients with enoxaparin given first after the third CT-scan and 8 patients with underminable symptom onset (however admitted within 48h) were excluded from analysis of late hematoma expansion, but included in the outcome analysis. One of the 8 patients with undeterminable symptom onset had early HE and none developed late HE, having received LMWH at 25h [IQR 23-48] after admission.

Patient characteristics and clinical course

Median age at admission was 71 [IQR 61-76] years, the ICH-score was 1 [IQR 0-2] and 19% were comatose on admission (**Table 1**). Median time from ICH onset to diagnosis was 2.2 hours [IQR 1.4 h - 4.8 h] and to NICU admission 3.4 hours [IQR 2.1-6.9 hours]. Repeated head-CT scans were performed at 14.6 hours [IQR 9.1-23.4] ("second") and 4.2 days [IQR of 2.9-6.6 days] ("third") after ictus and screened for HE.

Two patients developed thrombotic complications - DVT and PE (day 5 and 15 after admission). One of these patients had a history of DVT and have received 20 mg enoxaparin daily and the other was diagnosed with de-novo atrial fibrillation and developed PE while receiving 40mg of enoxaparin daily. Gastrointestinal (GI) bleeding occurred in 3 patients (upper GI bleeding, N=2; rectal bleeding, N=1), and resolved by red-blood cell transfusions without impacting outcome. Heparin induced thrombocytopenia was not diagnosed in any ICH-patient.

Early and late DVT prophylaxis and hematoma expansion

DVT prophylaxis was given 32 hours [IQR 25-49] after NICU admission at a dose of 40mg (N=97, 72.3 %) or 20 mg (N=37, 27.6%). Most patients received LMWH within 48 hours after symptom onset (N=76, 56%) or NICU admission (N=96, 72%) (**Figure 2**).

Patients with early DVT-prophylaxis (60%) had significantly smaller initial hematoma volume (p=0.038) and were more often comatose on admission (p=0.025), but did not differ in other demographic, clinical or radiographic variables when compared to patients receiving late (>48h) DVT prophylaxis (**Table 2**).

Absolute hematoma volume between the second and the third cerebral CT-scan in the early prophylaxis group slightly decreased by -0.45 ml (±5.2; P=0.017) and showed no significant change in the late prophylaxis group (P=0.15). However, the difference in hematoma dynamic between the early and delayed DVT prophylaxis groups was non-significant (P>0.4).

Factors associated with late hematoma expansion

Twenty-five patients had significant initial (18.6%) and 5 patients had late HE (3.7%). The characteristics of patients with late HE are presented in **Supplementary Table 1.**

All patients with late HE were admitted within 6-hours [median 2.4 (IQR 1.8-4h)] after ictus and 4/5 received early prophylaxis (4 with 40mg Enoxaparin and 1 with 20mg Enoxaparin). Two patients had significant initial HE (15 and 21 ml). In univariate analysis, risk factors for late HE were mild thrombocytopenia (OR 8.15, CI 1.26-52.7, P=0.029), initial ICH volume (per-ml↑) (OR 1.098, CI 1.031-1.170, P=0.004) and significant initial HE (OR 8.3, CI 1.277-53.95, P=0.027), but not APACHE II score, enoxaparin dose, ICH Score, admission GCS, age, abnormal admission INR or aPTT, history of hypertension, antiplatelet medication, intra-ventricular extension and early-LMWH application (P>0.05, respectively). Of the screened radiological signs we have found a significant association

between late HE and blend sign (OR 35, CI 4.53-273, p=0.001), island sign (OR 14.4, CI 1.53-136,p=0.02) **(Table 3-A)**. In the multivariate analysis, only initial hematoma volume and mild thrombocytopenia were associated with late HE, while early DVT prophylaxis was not (**Table 3-B**).

LMWH administration and outcome

In-hospital and 3-month mortality were low (3% and 13% respectively) as poor-grade ICH patients were excluded. 3-month outcome is presented in **Figure 3**. Two of the four patients who died during hospitalization had significant HE (one initial and one late). In univariate analysis factors associated with in-hospital mortality were ICH-Score (per 1-point↑) (OR 7.069, CI 1.665-30.01, P= 0.008) and APACHE II score (per 1-point↑) (OR 1.19, CI 1.03-1.39, P= 0.016). In the multivariate model, factors associated with 3-month mortality were ICH-score (per 1-point↑) (OR 2.17, CI 1.27-3.71, P=0.005) and initial HE (OR 4.69, CI 1.24-17.75, P=0.023). Neither early DVT-prophylaxis nor late HE was significantly associated with 3-months mortality. In the multivariate analysis factors associated with unfavorable outcome were admission ICH score, initial HE (N=25, 18.6%), need for nasogastric feeding (N=46, 34%) but not early DVT-prophylaxis (p=0.061) or late HE (**Table 3-C**).

Discussion

Our main finding is that early pharmacological DVT prophylaxis (<48h from ICH onset) is safe in selected ICH patients with stable hematoma volume and was not associated with late hematoma expansion, increased hospital mortality or poor functional outcome at 3 months. We also found that late HE occurs rarely in this selected patient population and may occur more frequently in patients with large hematomas, coagulation derangements such as thrombocytopenia and might be predicted by radiological signs (blend or island sign). Our results are consistent with previous studies and

support the ASA and NCS recommendations. [13,14,21,22] This finding is important as delayed or lack of DVT prophylaxis may be associated with higher mortality.[23] Patient selection for early DVT prophylaxis seems important as shown in two previous trials excluding patients with hemorrhagic diathesis and secondary causes of ICH.[24,25]

Despite recent recommendations for using intermittent pneumatic compression devices, pharmacological prophylaxis with LMWH remains important due to higher costs, low adherence rates as well as improved efficacy using devices together with LMWH.[26,27]

A analysis of the Premier Hospital database(15% of annual hospital discharges in the USA), [10] showed that only 11.1% of ICH patients received DVT-prophylaxis within 4 days as recommended by the ASA since 2007,[28] and 7.4% receive LMWH within 48-hours as recommended by the NCS guidelines[14].

We calculated the time of DVT-prophylaxis from ictus and not from the time of NICU admission, which is important as time to admission may largely differ based on local infrastructure. In our cohort these times were low with a median 2.2-hours to diagnosis and 3.4-hours to NICU admission. We strongly recommend that time from ICH-onset should be integrated in the prescription of LMWH for DVT prophylaxis and data should be provided when analyzing HE, which is time-dependent, and was not reported in previous studies.[22,24,25,29]

We used uniform DVT prophylaxis with enoxaparin compared to previous studies which used different LMWHs and/or UFH [21,22,29], which are heterogenous compounds with distinct pharmacological and biochemical proprieties that should not be used interchangeably, according to the Federal Drug Administration, World Health Organization, American Heart Association and American College of Cardiology.[30]

Significant early and late HE occurred in 18.6% and 3.7% of patients, consistent with previous studies reporting a cumulative incidence of 13-32%[3].The highest risk of HE is highest within 3-hours of onset (1/3 of ICH patients) and decreases to 11% in the time periods 3-6h and 6h-24h post ICH. [31,32] Late HE occurred seldom consistent with previous reports [11,12] with just 2 patients having HE after 24h.

There were some deviations from the institutional protocol, which suggests that some factors associated with late HE might be preventable. Three patients with late HE had a mild coagulation derangement (mild thrombocytopenia), a known risk factor[33], and in one patient the cessation of

bleed was not documented before the start of DVT prophylaxis. The fifth patient had a very large initial ICH volume (99mL).

Although significant HE is not defined by general agreement (with various studies using 3mL, 6mL, 12.5 mL and/or percentage increase), we used 6mL as the threshold, which has a reported specificity of 88% and sensitivity of 35% for poor outcome (mRS 4-6) [3], previously used to validate the CTA spot-sign.[32]

Although, in our cohort, the 6 mL threshold for initial HE correlates with poor outcome and survival in the multivariate models, the same threshold did not reach statistical significance for late HE. This could be due to the low number of patients with late HE and confounders such as large initial hematoma size. However, of these, one died during hospitalization, three had a poor functional outcome and only one had a good functional outcome (mRS=2). There is, at the time, little data in the literature that explore the association between later HE and clinical outcome.

Limitations

Although the analysis was done retrospectively, our data were prospectively recorded and reflect daily clinical practice in our institution where DVT prophylaxis is aimed to be prescribed promptly after fulfilling the safety criteria but also left to the neuro-intensivist's decision who integrates clinical information, severity of illness and results of repeated neuroimaging. DVT-prophylaxis was prescribed later in patient with larger size hematomas. The decision to withhold therapy led to the exclusion of patients with poor prognosis. Furthermore, ICH-patients with abnormal coagulation status or who underwent neurosurgery were excluded, limiting the generalizability of our results. Still we included patients with diverse clinical and radiographic characteristics: ICH volume (range 1-102mL), ICH-Score (range 0-4 points), APACHE II (range 0-31 points) and age groups (range 29-92-years). Moreover, the sample size, especially since late HE was a rare occurrence, although larger than previous studies on LMWH safety and HE, might have been too small, and thus responsible for some negative results.

The repeated cerebral imaging was not always performed at predefined time points. An investigator blinded to the time of DVT prophylaxis used two ICH volume assessment methods (the conventional ABC and a software-based semiautomatic method) to identify all patients with HE, and in case of discrepancy, 2 independent reviewers recalculated the volume. Although the software-based method is more reliable compared to the ABC/2, [34,35] this was technically available in just 68.5%

of CT-scans analyzed. The software-based method identified just one extra patient with a HE bordering our chosen threshold. We did identify considerable differences in individual patients between methods, especially when the hematoma was irregular or separated, which would make the method preferable especially in patients with oral anticoagulants or hemorrhagic diathesis. [34]

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Disclosures

None

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Figure Legends

Figure 1 – Patient selection

Legend:

Abbreviation: ICH: intracerebral hemorrhage

Figure 2- Time of deep venous thrombosis prophylaxis with enoxaparin from admission time (A) and from time of onset (B).

Figure 3 – Three-month outcome in patients who received early (within 48 hours of symptom onset) or late (>48h) deep venous thrombosis prophylaxis.

Legend:

Abbreviation: mRS: modified Rankin scale

The number in each category is the absolute number of patients.

Reference:

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Table Legends

Table 1 legend:
Abbreviation: ICH, intracerebral hemorrhage. DVT, deep venous thrombosis. GCS, Glasgow Coma Scale. APACHE, acute physiology and chronic health evaluation. NICU, neurointensive care unit. mRS, modified Rankin scale.
*: Aspirin 100 mg or Clopidogrel 75mg
†: Pneumonia: as radiologic infiltrate and elevated white blood cell (WBC) count or fever;
‡: Urinary tract infection: ≥5 WBC/mm^3 and positive nitrite or bacterial culture;
§: Software based volumetric analysis was available for 88 patients (65.6%)
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Table 2 legend:

Abbreviation: ICH, intracerebral hemorrhage. GCS, Glasgow Coma Scale. APACHE, acute physiology and chronic health evaluation. EVD, external ventricular drain

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Table 3 legend:

Abbreviations: INR: international normalized ratio; aPTT: activated Partial Thromboplastin Time; ICH: intracerebral hemorrhage, DVT: deep vein thrombosis

*: measured in admission-CT

**: Mild thrombocytopenia:100.000-150.000 thrombocytes/mm^3

†: ICH volume difference between CT2 (largest hematoma volume within 48h of admission, before enoxaparin administration) and CT1 (admission);

††: ICH volume difference between CT3 (day 3 - 6) and CT2.

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3. Li Q et al. Black Hole Sign: Novel Imaging Marker That Predicts Hematoma Growth in Patients With Intracerebral Hemorrhage.*Stroke*.2016;**47**:1777-81.

Tables

Table 1. Characteristics of the cohort

Demographic s Characteristics	**ICH Cases , N =134 (%)**
Age,years, Median (IQR)	71 (61-76)
Female	68 (50.7)
Medical history	
Diabetes Mellitus	18 (13.4)
Hypertension	77 (57.4)
Antiplatelet medication *	37(27.6)
Previous ICH	7 (5.2)
Clinical characteristics	
Admission GCS (NICU), Median (IQR)	14 (10-15)
GCS<9	26 (19.4)
APACHE II, Median (IQR)[1]	11 (8-15.5)
Admission Systolic Blood Pressure (mmHg), Median (IQR)	156 (137-178)

ICH Score	0 points 1 point 2 points	34 (25%) 47 (35%) 28 (21%)	3 points 4 points 6 points	16 (11.9%) 7 (5%) 0
Hospital course				
Initial hematoma expansion (before DVT prophylaxis)			25 (18.6)	
Intubation for more than 48h			32 (23.9)	
Hydrocephalus requiring external ventricular drain			18 (13)	
Days of NICU Stay, Median (IQR)			7 (4-16)	
Radiological characteristics				
Hematoma volume on admission, Median (IQR)			11 (5-24)	
Lobar hemorrhage			41 (30.5)	
Deep brain hemorrhage			82 (61.2)	
Cerebellum hemorrhage			7 (5.2)	
Brainstem hemorrhage			4 (3)	
Concomitant intraventricular hemorrhage			59 (44)	
Suspected etiology				
Hypertension			81 (60.4)	
Probable amyloid angiopathy (modified Boston criteria) [2]			14 (10.4)	
Possible amyloid angiopathy (modified Boston criteria) [2]			7 (5.2)	
Arteriovenous malformation			6 (4.5)	
Other/idiopathic			26 (19.4)	

Table 2. Characteristics of ICH patients based on time of LMWH administration

	Enoxaparin before 48 hours from ICH (before) N = 76	**Enoxaparin after 48 hours from ICH (after) N = 50**	**Significance (p)**
Hours to prophylaxis from ictus; Median (IQR)	32 (27-36)	59 (52-82)	

Sex	Male	36 (47%)	27 (54%)	0.466
	Female	40 (52%)	23 (46%)	
Age, median (IQR)		68 (60-75)	73 (63-78)	0.557
ICH Volume, median (IQR)		9.5 (4-18.5)	17.5 (8-29)	**0.038**
Initial hematoma expansion		11 (14.5%)	13 (26%)	0.165
Infratentorial location		7 (9.2 %)	4 (8%)	0.542
ICH Score < 3 points		61 (80.2%)	43 (86%)	0.478
ICH Score	0 points	20 (26%)	13 (26%)	0.605
	1 point	25 (32%)	19 (38%)	
	2 points	16 (21%)	11 (22%)	
	3 points	10 (13%)	6 (12%)	
	4 points	5 (6.5%)	1 (2%)	
	5 points	0	0	
GCS Median, IQR		13 (8-15)	14 (13-15)	0.062
GCS<9		20 (26%)	5 (10%)	**0.038**
Intraventricular extension		36 (47%)	21 (43%)	0.554
APACHE II Score [1]		10 (8-17)	11 (7-16)	0.56
Hydrocephalus requiring EVD		10 (13%)	6 (12%)	0.562
Intubation during hospital stay		24 (31%)	12 (24%)	0.42
Lost to follow-up (3-month)		6 (8%)	5 (10%)	0.752

Table 3. Factors associated with late hematoma expansion and unfavorable outcome

(A) Radiological signs associated with late hematoma expansion (based on second CT) -univariate

Factor	Odds Ratio	Significance	95% Confidence Interval

Island sign[1]	14.4	0.02	1.53-136
Blend sign[2]	35	0.001	4.53-273
Black-hole sign[3]	4.5	0.21	0.42-48
Heterogenous density	8.89	0.022	1.361-58
Irregular shape of hematoma	1.367	0.78	0.143-13.089

(B) Factors associated with late hematoma expansion -multivariate

Factor	Odds Ratio	Significance	95% Confidence Interval
Initial* hematoma volume (1mL increase)	1.089	0.019	1.014-1.17
Mild thrombocytopenia**	42.3	0.042	1.155-1549
Enoxaparin in the first 48 hours after ictus	9.18	0.238	0.232-363
Blend sign or island sign on second CT	25.2	0.084	0.65-975

(C) Factors associated with unfavorable outcome (modified Rankin scale≥4 at 3-months)

Factor	Odds Ratio	Significance	95% Confidence Interval
ICH Score (1-point increase)	1.760	0.033	1.046-2.961
Need for nasogastric tube	9.916	0,000305	2.854-34.445
Initial† hematoma expansion (>6mL)	4.079	0.039	1.076-15.462
Early enoxaparin (<48h) for DVT prophylaxis	0.393	0.061	0.148- 1.046
Late††: hematoma expansion (>6mL)	1.353	0.817	0.057-9.505

Supplementary Table 1. Characteristics of patients with late hematoma expansion

Patient no./ Characteristic	**P1**	**P2**	**P3**	**P4**	**P5**
Age	54	67	73	46	70
ICH type	Lobar hemorrhage	Lobar hemorrhage	Basal ganglia hemorrhage	Basal ganglia hemorrhage	Lobar hemorrhage
Initial ICH volume (ml)	99	28	60	25	32
Time to enoxaparin (h)*	44	36	31	36	55
Enoxoparin dosis (mg/day)	40	40	20	40	40
Interval in which late†† hematoma expansion occurred (h)	26-95	15-80	8-120	9-48	25-70
Late hematoma expansion (ml)	10	7	15	9	6
Initial hematoma expansion† (>6ml)	No	No	No	Yes (15ml)	Yes (21ml)
Thrombocytopenia	No	Yes	Yes	No	Yes
Blend Sign[1] on CT 2	No	Yes	No	Yes	Yes
Island Sign[2] on CT 2	No	Yes	Yes	Yes	Yes
Heterogenous density on CT2	Yes	No	Yes	Yes	No

Supplementary table 1 legend:

Abbreviation: ICH, intracerebral hemorrhage

*: from ictus

†: ICH volume difference between CT2 (largest hematoma volume within 48h of admission, before enoxaparin administration) and CT1 (admission);

††: ICH volume difference between CT3 and CT2

References:

1. Li Q, Zhang G, Huang Y et al. Blend Sign on Computed Tomography: Novel and Reliable Predictor for Early Hematoma Growth in Patients With Intracerebral Hemorrhage. *Stroke*. 2015;**46**:2119-23

2. Li Q, Liu QJ, Yang WS et al. Island Sign: An Imaging Predictor for Early Hematoma Expansion and Poor Outcome in Patients With Intracerebral Hemorrhage. *Stroke*. 2017;**48**:3019-3025