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PREvention of VENous Thromboembolism in Hemorrhagic Stroke Patients – PREVENTIHS Study: A Randomized Controlled Trial and a Systematic Review and Meta-Analysis

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Keywords
Intracerebral hemorrhage · Venous thromboembolism · Prevention

Abstract
Background: In this randomized trial, currently utilized standard treatments were compared with enoxaparin for the prevention of venous thromboembolism (VTE) in patients with intracerebral hemorrhage (ICH). ***Methods:*** Enoxaparin (0.4 mg daily for 10 days) was started after 72 h from the onset of ICH. The primary outcome was symptomatic or asymptomatic deep venous thrombosis as assessed by ultrasound at the end of study treatment. The safety of enoxaparin was also assessed. We included the results of this study in a meta-analysis of all relevant studies comparing anticoagulants with standard treatments or placebo. ***Results:*** PREVENTIHS was prematurely stopped after the randomization of 73 patients, due to the low recruitment rate. The prevalence of any VTE at 10 days was 15.8% in the enoxaparin group and 20.0% in the control group (RR 0.79 [95% CI 0.29–2.12]); 2.6% of enoxaparin and 8.6% of standard therapy patients had severe bleedings (RR 0.31 [95% CI 0.03–2.82]). When these results were meta-analyzed with the results of the selected studies (4,609 patients; 194 from randomized trials), anticoagulants were associated with a nonsignificant reduction in

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any VTE (OR 0.81; 95% CI 0.43–1.51), in pulmonary embolism (OR 0.53; 95% CI, 0.17–1.60), and in mortality (OR 0.85; 95% CI 0.64–1.12) without increase in hematoma enlargement (OR 0.97; 95% CI, 0.31–3.04). ***Conclusions:*** In patients with acute ICH, the use of anticoagulants to prevent VTE was safe but the overall level of evidence was low due to the low number of patients included in randomized clinical trials.

Introduction

Venous thromboembolism (VTE) is a common life-threatening complication in patients with stroke. In these patients, an average incidence of asymptomatic deep vein thrombosis (DVT) of 40% has been reported [1]. Additionally, pulmonary embolism (PE) was reported to occur in 2% of patients with stroke [2], and 5% of early deaths after stroke was reported to be due to PE [3]. Graduated compression stockings alone are ineffective in preventing DVT in patients with ischemic or hemorrhagic stroke [4]. The CLOTS 3 study found intermittent pneumatic compression (IPC) to be an effective method of reducing the risk of DVT and possibly improving survival in a wide variety of patients who are immobile after stroke [5]. Prospective trials have also shown that both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are effective in reducing VTE and PE in ischemic stroke patients [6]. The role of anticoagulants for the prevention of VTE in acute hemorrhagic stroke is uncertain [7]. In the CLOTS 3 trial, only 13% of the patients included had an intracerebral hemorrhage (ICH).

A meta-analysis indicated that in patients with hemorrhagic stroke, early anticoagulation is associated with a significant reduction in PE and a nonsignificant reduction in mortality, with the trade-off of a nonsignificant increase in hematoma enlargement [8]. However, these meta-analysis results cannot be reliably applied to clinical practice due to the low quality of the studies included. Anticoagulant agents have not gained wide acceptance because of concern about possible increases in hematoma enlargement.

Objectives

In this multicenter, randomized trial, the use of currently utilized standard treatment alone (IPC and/or early mobilization) was compared with the use of standard treatment plus the administration of a LMWH (enoxaparin) for the prevention of VTE in patients with acute hemorrhagic stroke. Specifically, enoxaparin was started after 72 h from stroke onset and was continued for 10 days. The principal study outcome measures were symptomatic, objectively confirmed VTE or asymptomatic DVT (proximal and/or distal) as assessed by ultrasound examination at 10 days. Patients with symptoms suggestive of DVT had ultrasound during the first 90 days after acute hemorrhagic stroke. Because the use of anticoagulants in patients with hemorrhagic stroke could have been associated with a high risk of rebleeding, the safety of enoxaparin in this clinical setting was also assessed.

Methods

Study Population

The study was designed as a multicentre, prospective, randomized, open, blinded end point clinical trial. Consecutive bedridden patients (with a score of 3 or 4 per item 6 of the NIHSS or the impossibility to maintain an upright position such as in the case of ataxia in patients with hemorrhagic cerebellar stroke), 18 years of age or older with spontaneous ICH on CT scan or patients with intracranial hemorrhage during treatment with oral anticoagulants (after reversal), were assessed for eligibility.

Exclusion criteria were intracranial hemorrhage due to vascular malformation, subarachnoid hemorrhage, subdural hematoma, bleeding disorders (defined by a prothrombin time >30% longer than the control value or a platelet count of <100,000 per mm^3), renal failure defined as a clearance of Cr <30, severe hepatic failure, known neoplastic disease, pregnancy, necessity of therapeutic anticoagulant or antiplatelet agents for concomitant disease, participation in other ongoing clinical trials, or patient refusal to consent.

Study Design and Interventions

Patients were randomized 72 h after the onset of symptoms after having undergone a brain CT scan which, for the study purposes, was considered the baseline examination. This CT must exclude a rebleeding (hematoma expansion), compared to the CT at admission. In case of rebleeding, patients were excluded from randomization. Rebleeding was defined as an increase of 10% in the basal volume measured by standardized and validated criteria [9].

Patients were centrally randomized over the phone using a random list of numbers (even numbers – treatment A; odd numbers – treatment B) closed in an envelope to receive enoxaparin 0.4 mL die plus standard therapy (group A) or standard therapy alone (group B). Treatment with enoxaparin was scheduled to last 10 ± 1 day. A venous eco-color-Doppler examination with a compression test was performed bilaterally on the lower limbs 10 ± 1 day following the start of treatment. This exam evaluated the following 3 points: the common femoral vein at the groin, superficial femoral vein at the mid-thigh, and the popliteal vein at the popliteal fossa up until the trifurcation.

Included patients were visited on a daily basis during their hospital stay in order to monitor any complications as well as to check for symptoms and signs of VTE. An ultrasound exam of the lower limbs was performed in any patient presenting with clinical signs

of suspected deep venous thrombosis. When this exam resulted negative, the patient underwent a second ultrasound exam in accordance with the timetable set out in the protocol. An ultrasound exam of the lower limbs and a CT thoracic angiography was performed in any patient having clinical signs of PE. When these exams resulted negative, the patient underwent a second ultrasound exam in accordance with the timetable set out in the protocol. A positive result from either the CT thoracic angiography or an ultrasound exam necessitated a treatment with heparin (UFH or at a LMWH), warfarin, or vena cava filter according to clinical need. Brain CT scan was performed 10 ± 1 day from the start of treatment or whenever there was a worsening of the clinical condition defined as an increase of 4 points or more on the NIHSS score. Treatment with heparin was suspended whenever CT showed an increase of at least 10% in the volume of cerebral hemorrhage, notwithstanding clinical condition. Lesion volume was centrally measured with the methodology elaborated by Broderick et al. [9]. Antithrombotic treatment different from that which was planned by the protocol during the treatment period was forbidden, except in the case of clinical need (i.e., diagnosis of VTE). Follow-ups at 90 days after cerebral hemorrhage were performed in order to monitor for any clinical signs of VTE or rebleeding. All deaths were recorded. Whenever a symptomatic VTE occurred during follow-up, patients were requested to report any related documentation during the face-to-face visit. The final follow-up, at 90 days, was carried out by an independent physician blinded to the treatment received. After the treatment period outlined in the protocol (10 ± 1 day), additional treatment was left at discretion of the attending physician.

Neuroradiological exams, as well as pulmonary angio-CTs were evaluated by the study coordinating center (University of Perugia) blinded to both the clinical condition of the patients and the arm of randomization.

Venous thromboembolic and intra- and extracranial hemorrhagic events were judged blindly on the type of treatment received by the following physicians from Perugia: G.A., A.A., C.B., V.C., F.G., and M.V.

Risks of Treatments and Procedures

Risks included intra- and extracranial hemorrhagic complications associated with heparin use and/or complications such as ulcers and subcutaneous hematomas due to the use of elastic stockings or IPC. There were no anticipated risks due to diagnostic procedures, given that all of the exams outlined in the protocol had been regularly performed in clinical practice.

End Points

The primary end points of this study were made up of either (1) symptomatic VTE objectively documented as proximal/distal DVT or PE or (2) asymptomatic proximal/distal DVT documented by ultrasound at 10 days. The diagnostic criteria used had already been validated previously were utilized [10]. Secondary end points were any VTE at 90 days, the number of symptomatic and asymptomatic intracranial bleedings as described above in the Methods (an increase of 10% in the basal volume), the number of major extracranial bleedings, and the combined end point of disability (modified Rankin Scale ≥3) and mortality for any cause at 90 days and mortality alone at 90 days.

Major bleedings were defined as (1) the presence in critical organ sites including the retroperitoneal and intraocular spaces, (2) a reduction of 2 or more gr/dL of hemoglobin or the need to carry out a transfusion of 2 or more units of concentrate red blood cells, or (3) fatal bleeding. Medical intervention, including any interruption of study treatment, was considered clinically relevant, but not a major bleeding, for all the events that did not satisfy the above described criteria. All other bleedings were considered minor. For each end point event, centers were required to submit adequate documentation which was evaluated by the adjudication committee.

Statistical Analysis

The primary and secondary end points were evaluated with an intention-to-treat (ITT) analysis that included all the randomized patients in both groups who were treated or not depending on the randomized group. Differences between the 2 groups were calculated using the χ^2 test. The relative risks (RR) were calculated with confidence intervals (CIs). All predefined end points were assessed without adjusting for confounding factors. Post hoc analysis (logistic regression) was planned, in the face of any possible unmatching between the 2 groups, by adjusting for age and sex. The same statistical analyses were planned on the per protocol population; that is, those patients that had been randomized and assessed for type of treatment actually administered.

Sample size was calculated on the basis of an expected incidence of TVE equal to ~20% of non-treated patients, and ~10% of enoxaparin-treated patients. Both groups needed approximately 203 patients each, in order to evidence a statistical difference of 50% with an alpha value equal to 0.05 and a beta value of 0.20. The study was multicentered with 10 Italian centers participating over a 3-year enrollment period.

Systematic Review

Types of Studies and Interventions

We included the results of the PREVENTIHS study in a meta-analysis of all relevant published studies (randomized or not) comparing anticoagulants started within 7 days, with other treatments (IPC and/or elastic stockings or placebo) for prevention of VTE. The following anticoagulant regimens were to be included: subcutaneous UFH, subcutaneous LMWHs, and subcutaneous heparinoids.

Type of Outcome Measures

The primary outcome was any VTE at the end of scheduled follow-up period. Secondary outcomes were PE, growth of ICH, major extracerebral bleeding, and death at the end of scheduled follow-up period. For the outcomes any VTE, PE, growth of ICH, and death, further analyses including only randomized control trials were also performed.

Search Methods for Identification of Studies

We searched electronic databases (MEDLINE and EMBASE) from January 1980 to March 2020 and the Cochrane Library (2020) using the terms stroke, hemorrhagic stroke, intracerebral hemorrhage, heparin, heparinoids, low-molecular-weight heparin, anticoagulants, randomized controlled trial, controlled clinical trial, prevention, deep venous thrombosis, pulmonary embolism, venous thrombosis, and outcome. Bibliographies of journal articles were manually searched to locate additional studies, and abstracts from major international meetings were reviewed to locate any unpublished studies. The relevance of the studies was assessed us-

Table 1. Clinical characteristics of the randomized patients in the PREVENTIHS study

	Enoxaparin group (n = 38)	Controls (n = 35)	p value
Age, mean, years	70.4±13.7	71.5±11.6	0.7
NIHSS on admission, mean	13.8±6.4	13.4±6.9	0.8
Male, *n* (%)	22 (57.9)	18 (51.4)	0.6
IPC, *n* (%)	12 (31.6)	10 (28.6)	0.8
Stockings, *n* (%)	8 (21.0)	5 (14.3)	0.5
Hypertension, *n* (%)	23 (60.5)	25 (71.4)	0.4
Diabetes mellitus, *n* (%)	5 (13.1)	7 (20.0)	0.5
Hyperlipidemia, *n* (%)	6 (15.8)	4 (11.4)	0.7
Smoking, *n* (%)	4 (10.5)	3 (8.6)	1.0
Obesity, *n* (%)	3 (7.9)	3 (8.6)	1.0
Hystory DVT/PE, *n* (%)	2 (5.3)	0	0.5
Aspirin before admission, *n* (%)	9 (23.7)	8 (22.8)	1.0
OA before admission, *n* (%)	4 (10.5)	2 (5.7)	0.7
Deep hemorrhage, *n* (%)	29 (76.3)	20 (57.1)	0.1
Volume of lesion, mean, cm^3	22.2±25.6	24.3±26.2	0.7

IPC, intermittent pneumatic compression; OA, oral anticoagulant; DVT, deep venous thrombosis; PE, pulmonary embolism.

ing a hierarchical approach based on title, abstract, and the full manuscript. If any of these data were not available in the publications, further information was sought by correspondence with the authors. Two investigators (M.P. and V.C.) independently extracted data on study design and study quality.

The data abstracted for each trial were confirmed by a third investigator (M.V.) and any disagreements were resolved by consensus. We recorded the selection process and completed a PRISMA flow diagram.

Assessment of Risk of Bias in Included Studies

The risk of bias was assessed using the validated criteria [11]. We assessed randomization (random sequence generation), allocation concealment, blinding of participants and personnel, blinding of outcome assessment, attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other potential biases from each study and summarized our findings in evidence profile tables.

Measures of Treatment Effect and Assessment of Heterogeneity

Given the presence of possible statistical heterogeneity resulting from the clinical diversity of the selected studies, we used a random-effects model based on the Peto odds ratio method [12] for combining results from the individual studies. We calculated odds ratio (ORs) and 95% CIs, with a random-effects model, for all outcomes. We calculated I^2 statistics, and heterogeneity was classified as moderate (I^2 30–50%), substantial (I^2 50–75%), or considerable (I^2 75–100%). If the results were heterogeneous, we planned to use sensitivity analysis to investigate how the results differed when we excluded studies that were found to have a high risk of bias. All statistical calculations were performed using ProMeta version 2 software (Internovi, Cesena, Italy).

Results

The study was prematurely stopped after the randomization of 73 patients due to the low recruitment rate and the consequent inability to close the study in the anticipated time frame. The study was carried out between May 1, 2016, and March 30, 2020: thirty-eight patients were randomized in the enoxaparin group and 35 in the control group. In Table 1 the characteristics of the randomized patients are summarized. The outcome events are summarized in Tables 2 and 3.

The primary end point, any VTE at 10 days, was 15.8% (6/38 patients) in the enoxaparin group and 20.0% (7/35 patients) in the control group (ITT: adjusted RR 0.97 [95% CI 0.26–3.57]). The secondary end point, the prevalence of DVT (proximal and distal) and PE at 90 days was 18.4% (7/38 patients) in the enoxaparin group and 25.7% (9/35 patients) in the control group (ITT: RR 0.72 [95% CI 0.30–1.72]). Overall, 1/38 of the enoxaparin (2.6%) and 3/35 of the standard therapy (8.6%) patients had severe bleedings (ITT: RR 0.31 [95% CI 0.03–2.82]). Thirteen patients died during the 90-day study period: 7 in the enoxaparin group (18.4%) and 6 in the standard therapy group (17.1%) (ITT: RR 1.07 [95% CI 0.40–2.89]).

Meta-Analysis

Bibliographic search identified 465 potentially eligible citations (see online suppl. Fig. 1; for all online suppl. mate-

Table 2. End point events in the PREVENTIHS study

	Enoxaparin group (n = 38)	Controls (n = 35)	p value
Total DVT/PE at 10 days, n (%)	6 (15.8)	7 (20.0)	0.7
Proximal DVT/PE at 10 days, n (%)	3 (7.9)	1 (2.9)	0.3
Total DVT/PE at 90 days, n (%)	7 (18.4)	9 (25.7)	0.7
PE at 90 days, n (%)	0	2 (5.3)	0.1
Cerebral rebleeding, n (%)	0	3 (8.6)	0.1
Severe extracerebral bleeding, n (%)	1 (2.6)	0	0.3
mRS 0–2 at 90 days, n (%)	11 (28.9)	5 (14.3)	0.1
Mortality at 90 days, n (%)	7 (18.4)	6 (17.1)	1.0

DVT, deep venous thrombosis; PE, pulmonary embolism; mRS, modified Rankin Scale.

rial, see www.karger.com/doi/10.1159/000511574); the selection process and the PRISMA flow diagram are reported. After scanning titles and abstracts, 444 citations were excluded and 21 were retained for further evaluation. From these, 11 studies were excluded for the following reasons: 9 studies did not have a control group [3–21]; one study used vitamin K antagonists [22]; and in one study treatment was given during rehabilitation after 7 days from stroke onset [23]. One further randomized study [24] was excluded because the results of this trial had been included in the results of the study reported by Boeer et al. [25]. The results of the study by Dickman were included in the analyses limited to only randomized trials. The designs of the 9 studies [25–33] as well as the design of the PREVENTIHS study included in this meta-analysis are summarized in online suppl. Table 1.

When the results of PREVENTIHS study were meta-analyzed with the results of these studies (in total 4,609 patients), anticoagulants were associated with a nonsignificant reduction in any VTE (OR 0.81; 95% CI 0.43–1.51, I^2 62.30%), in PE (OR 0.53; 95% CI 0.17–1.60, I^2 52.06%), in mortality (OR 0.85; 95% CI 0.64–1.12, I^2 15.84%) without increasing hematoma enlargement (OR 0.97; 95% CI 0.31–3.04, I^2 54.55%), compared with other treatments. Data on the outcomes and publication bias analyses are presented in online suppl. Table 2, Figure 1, and online suppl. Fig. 2, 3.

When the results of the PREVENTIHS study were meta-analyzed with the results of randomized trials (in total 194 patients), compared with other treatments, anticoagulants were associated with a nonsignificant reduction in PE (OR 0.38; 95% CI 0.14–1.05; I^2 0.00%), and a nonsignificant reduction in any VTE (OR 0.77; 95% CI 0.38–1.57, I^2 0.00%). No differences in any hematoma enlargement and mortality between the 2 groups were observed (OR 0.63; 95% CI 0.03–12.51, I^2 80.05% and OR 1.17; 95% CI 0.47–2.94, I^2 0.00%, respectively). Data on the outcomes and publication bias analyses are presented in Figure 2 and online suppl. Fig. 4, 5.

Table 3. RR of different end points (enoxaparin vs. standard therapy) in the PREVENTIHS study

Total DVT/PE at 10 days (primary end point)	
Intention-to-treat analysis (RR)	
0.79 (95% CI 0.29–2.12)	Unadjusted
0.97 (95% CI 0.26–3.57)	Adjusted for age and sex
Efficacy analysis (RR)	
0.90 (95% CI 0.30–2.70)	Unadjusted
0.97 (95% CI 0.24–4.21)	Adjusted for age and sex
Total DVT/PE at 90 days (secondary end point)	
Intention-to-treat analysis (RR)	
0.72 (95% CI 0.30–1.72)	Unadjusted
0.54 (95% CI 0.04–6.67)	Adjusted for age and sex
Intracerebral and severe extracerebral bleeding	
Intention-to-treat analysis (RR)	
0.31 (95% CI 0.03–2.82)	Unadjusted[a]
Mortality at 90 days	
Intention-to-treat analysis (RR)	
1.26 (95% CI 0.46–3.41)	Unadjusted
1.18 (95% CI 0.30–4.54)	Adjusted for age and sex

RR, relative risk. [a] The adjusted analysis was not performed because of only 4 events.

Study Quality and Assessment of Risk of Bias in Included Studies

The graphic of the risk of bias is reported in online suppl. Fig. 6.

Randomized treatment allocation sequences were not reported in the study carried out by Boeer (Dickmann) et

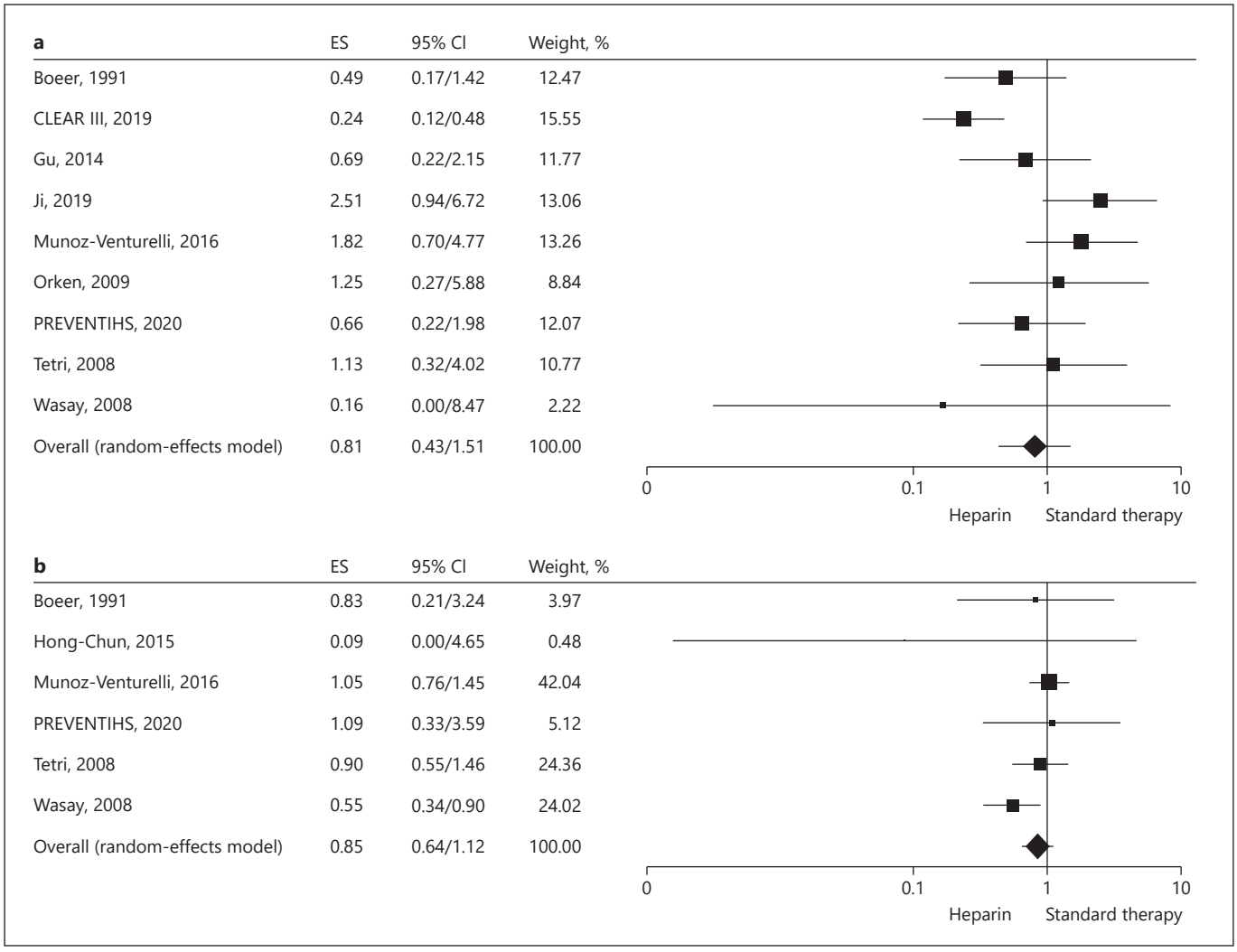

Fig. 1. Any VTE (**a**) and death (**b**) at the end of scheduled follow-up period comparing heparin and no heparin treatments. VTE, venous thromboembolism; CI, confidence interval.

al. [24, 25] and the order of hospital admission dates was not reported in the study carried out by Orken et al. [26]. Investigators were blinded to treatment allocation in 2 of the 3 randomized trials. The studies reported by Wasay, Munoz-Venturelli, Hong-chun, Gu, Tetri, Ji, and CLEAR III trials investigators were not randomized [27–33]. No patients were lost to follow-up in any of the studies. The duration of follow-up was not reported in the study carried out by Wasay et al. [27].

Sensitivity Analyses

Heterogeneity was substantial for the following outcomes: any VTE and PE at the end of scheduled follow-up period and any hematoma enlargement. When the studies reported by the CLEAR trial investigators and Ji [32, 33] were removed from the analysis for the outcome any VTE, the reduction in risk observed with heparin remained statistically nonsignificant without heterogeneity (OR 0.89; 95% CI 0.56–1.41, I^2 0.00%). When the study reported by Munoz-Venturelli et al. [30] was removed from the analysis for the outcome PE, the reduction of the risk became statistically significant without heterogeneity (OR 0.29; 95% CI 0.12–0.71, I^2 0.00%). When the PREVENTIHS study and the study reported by Boeer et al. [25] were alternatively removed from the analysis for the outcome any hematoma enlargement, the increase in risk observed with heparin remained nonsignificant

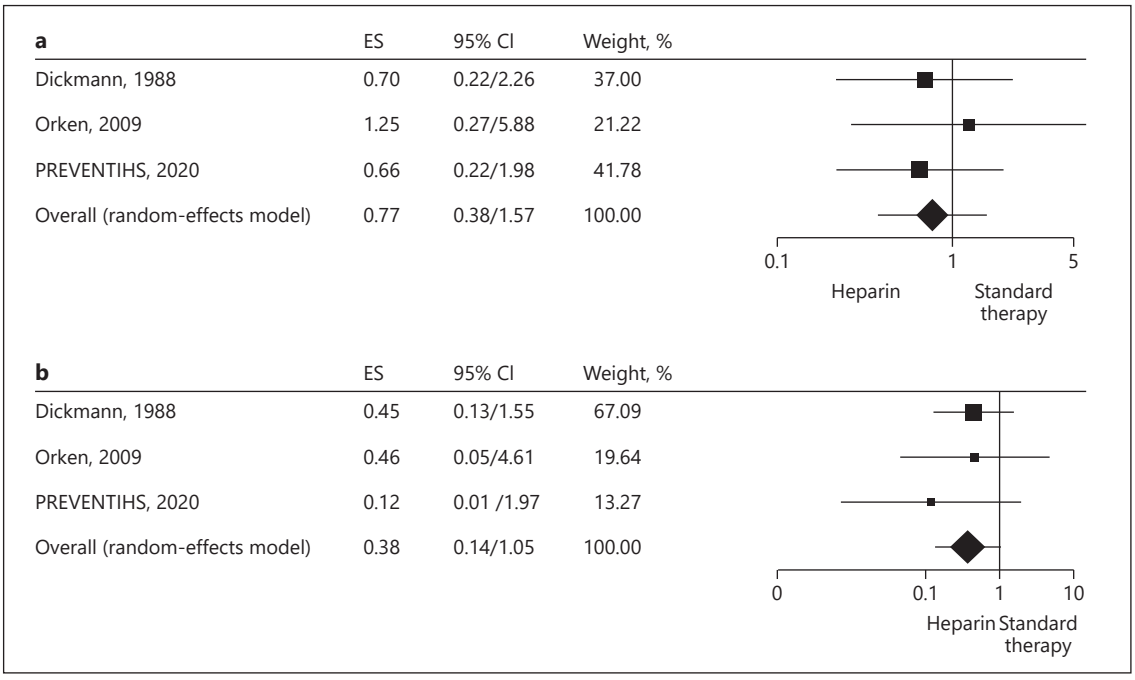

Fig. 2. Any VTE (**a**) and PE (**b**) at the end of scheduled follow-up period comparing heparin and no heparin treatments in randomized control trials. VTE, venous thromboembolism; PE, pulmonary embolism; CI, confidence interval.

with moderate heterogeneity (OR 1.41; 95% CI 0.52–3.83, I^2 34.49% and OR 1.43; 95% CI 0.53–3.50, I^2 35.96%, respectively).

Discussion

Currently, there is no consensus in clinical practice regarding the use of low-dose heparin in patients with cerebral hemorrhage for the prophylaxis of VTE due to the concerns for serious and potentially life-threatening complications, including the risk of hematoma enlargement. Our analysis shows that in patients with hemorrhagic stroke, early heparin prophylaxis for VTE is associated with a nonsignificant reduction in death for any cause and a nonsignificant increase in hematoma enlargement. If we consider the analysis derived from randomized clinical trials, a trend in favor of heparin compared to standard therapy in the reduction of PE was observed.

The CLOTS 3 trial found IPC to be an effective method of reducing the risk of VTE and possibly improving survival in a wide variety of patients who are immobile after stroke, but only 13% of the patients included in the study had an ICH [5]. In the 322 included patients with hemorrhagic stroke, the relative risk of primary outcome (DVT in the proximal veins detected on a screening Doppler ultrasound or any symptomatic DVT in the proximal veins, confirmed on imaging, within 30 days of randomization) was reduced by 64% in the IPC group compared to the no-IPC group (6.7 versus 17% respectively; OR 0.36 [95% CI 0.17–0.75]) [5]. In clinical practice it is sometimes difficult to treat patients with IPC, as the procedure is contraindicated in the presence of severe congestive heart failure, severe skin problems on legs, or severe peripheral vascular disease. IPCs are hard to keep on patients and in fact, adherence issues were noted in the trial. Perfect adherence (IPC use for the entire intended duration) occurred in less than a third of patients. Outside a trial, IPC adherence might be even worse, leading to less benefit. Future studies will need to explore methods that could improve device compliance and that could use technology able to continually monitor IPC use.

Our findings indicate that in patients with acute hemorrhagic stroke, early anticoagulation is relatively safe and this encourages the design of randomized clinical trials aimed at assessing the efficacy and safety of early heparin administration in patients with ICH. However, the

premature interruption of the PREVENTIHS trial highlights the difficulties in randomizing patients in this setting using an anticoagulant, possibly leading to an inappropriate exclusion of eligible patients: even in the 73 patients randomized in the enoxaparin group, no hematoma enlargement was observed during the study period. Another issue is the sample size indeed: excluding PREVENTIHS, where the rate of any VTE was about 18%, in the other studies included in the meta-analysis, the rate of any DVT was low (about 4%), compared to the rate reported and expected in patients with stroke without prophylaxis (15–50%) [1, 34].

Also the optimal timing, type, and dose of treatment remain unclear. In the studies included in this meta-analysis, heparin was started within a range of 24 h to 7 days from stroke onset. No difference was observed in terms of hematoma enlargement and rate of thromboembolic events.

For the definition of hematoma enlargement, we use a proportional cutoff of 10%. This cutoff was lower than the cutoff used in most previous studies (26 or 33%). We adopted this more restricted value given the patients included in the study were more prone to bleeding.

In addition to the limitations shared by all meta-analyses, our analysis has some further limitations. Unfortunately, not all of the included studies were randomized, different heparins were used, there was a lack of homogeneity regarding the definition of the outcome events (symptomatic and/or asymptomatic DVT), and the sample sizes were reduced in some of the studies especially in those that were randomized.

In conclusion, after documentation of cessation of bleeding, low-dose subcutaneous LMWH appears to be safe in patients with ICH and it may be considered on an individual basis for patients with ICH and hemiplegia. Due to the low overall level of the evidence, high-quality randomized control trials with adequate sample sizes are needed.

Acknowledgements

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Statement of Ethics

The study protocol was approved by the local Ethics Committees of the participating hospitals. Clinical Trial Registration: NCT01573169.

Conflict of Interest Statement

Maurizio Paciaroni received honoraria as a member of the speaker bureau of Sanofi-Aventis, Boehringer Ingelheim, Bayer, Bristol Meyer Squibb, Daiichi Sankyo, and Pfizer. Giancarlo Agnelli received honoraria as a member of the speaker bureau of Boehringer Ingelheim and Bayer. Cecilia Becattini received honoraria as a member of the speaker bureau of Bristol Meyer Squibb and Bayer. Valeria Caso received honoraria as a member of the speaker bureau and as consultant or advisory board of Boehringer Ingelheim. Walter Ageno has received speaker's honoraria from, and participated in scientific advisory boards for, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb/Pfizer, and Daiichi Sankyo, and has received research support from Bayer and Boehringer Ingelheim. The other authors have nothing to disclose.

Author Contributions

Maurizio Paciaroni researched the literature, conceived the study, was responsible for data analysis and wrote the first draft of the manuscript. Giancarlo Agnelli was involved to the conception and design of the work, interpretation of data, drafting the work or revising it critically for important intellectual content; he approved the final version to be published. Andrea Alberti was involved in protocol development, gaining ethical approval, and patient recruitment. He reviewed and edited the manuscript and approved the final version of the manuscript. Cecilia Becattini was involved in protocol development, gaining ethical approval, and patient recruitment. She reviewed and edited the manuscript and approved the final version of the manuscript. Francesco Guercini was involved in protocol development, gaining ethical approval, and patient recruitment. He reviewed and edited the manuscript and approved the final version of the manuscript. Giuseppe Martini was involved in protocol development, gaining ethical approval, and patient recruitment. He reviewed and edited the manuscript and approved the final version of the manuscript. Rossana Tassi was involved in protocol development, gaining ethical approval, and patient recruitment. She reviewed and edited the manuscript and approved the final version of the manuscript. Giovanna Marotta was involved in gaining ethical approval and patient recruitment. She reviewed and edited the manuscript and approved the final version of the manuscript. Michele Venti was involved in protocol development, gaining ethical approval, and patient recruitment. He reviewed and edited the manuscript and approved the final version of the manuscript. Monica Acciarresi was involved in protocol development, gaining ethical approval, and patient recruitment. She reviewed and edited the manuscript and approved the final version of the manuscript. Maria Giulia Mosconi was involved in protocol development, gaining ethical approval, and patient recruitment. She reviewed and edited the manuscript and approved the final version of the manuscript. Simona Marcheselli was involved in gaining ethical approval and patient recruitment. She reviewed and edited the manuscript and approved the final version of the manuscript. Lara Fratticci was involved in gaining ethical approval and patient recruitment. She reviewed and edited the manuscript and approved the final version of the manuscript. Cataldo D'Amore was involved in protocol development, gaining ethical approval, and patient recruitment. He reviewed and edited the manuscript and approved the final version of the

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