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Prevention of venous thromboembolism in acute spontaneous intracerebral haemorrhage: A survey of opinion

Rom Mendel^{a,b}, Nadir Abdelhameed^c, Rustam Al-Shahi Salman^d, Hannah Cohen^e, Dar Dowlatshahi^f, Nicholas Freemantle^g, Maurizio Paciaroni^h, Adrian Parry-Jonesⁱ, Christopher Price^j, Nikola Sprigg^k, David J. Werring^{a,*}

^a Stroke Research Centre, UCL Queen Square Institute of Neurology, London, UK

^b Department of Neurology, Assuta Ashdod Medical Center, Israel

^c Stroke department, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, UK

^d Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

^e Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK

^f Department of Medicine (Neurology), University of Ottawa Brain and Mind Institute and Ottawa Hospital Research Institute, Ottawa, ON, Canada

^g Institute of Clinical Trials and Methodology UCL, UK

^h Stroke Unit and Division of Cardiovascular Medicine, University of Perugia, Perugia, Italy

ⁱ Geoffrey Jefferson Brain Research Centre, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, M13 9PR, UK

^j Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne NE2 4HH, UK

^k Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, City Hospital Campus, Nottingham, UK

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ABSTRACT

Introduction: People immobilized following acute spontaneous intracerebral haemorrhage (ICH) are at risk of venous thromboembolism (VTE) but the role of short-term prophylactic anticoagulation remains uncertain. We surveyed UK clinical practice and opinion regarding preventing VTE after ICH.

Patients and methods: An online survey was sent to stroke healthcare professionals within the United Kingdom and Ireland via a professional society (British and Irish Association of Stroke Physicians (BIASP)).

Results: One hundred and twenty-three staff members responded to the survey, of whom 80% were consultant stroke physicians. All responders except one considered the issue to be important or extremely important, but only 5 (4%) were “extremely certain” and 51 (41%) “fairly certain” regarding the optimal treatment approach. Intermittent pneumatic compression (IPC) devices alone were the most used method (in 60%) followed by IPC devices and switching to low molecular weight heparin (LMWH) (in 30%). We identified high levels of uncertainty regarding the role of anticoagulation, and its optimal timing; uncertainty was greater in lobar compared to deep ICH. Most respondents (93%) consider a randomised controlled trial investigating the role of pharmacological VTE prophylaxis after acute ICH as important and would consider participation.

Discussion and conclusion: The optimal method for the prevention of VTE in non-traumatic ICH patients remains an area of clinical uncertainty. Clinical trials assessing short-term anticoagulation in patients after acute ICH would be beneficial in providing evidence to resolve this clinical dilemma.

1. Introduction

Acute spontaneous (non-traumatic) intracerebral haemorrhage (ICH) accounts for 8–15% of all strokes in Western countries, affecting approximately three million people worldwide each year [1,2]. It remains the least treatable form of stroke with a mortality of 40% in the first month and 55% in 1 year [3]. Survivors frequently have a severe

residual disability, a high risk of recurrent ICH, and other serious vascular events [4,5].

Venous thromboembolism (VTE) including leg deep vein thrombosis (DVT) and pulmonary embolism (PE) are common and serious concerns in people who are immobile soon after having a stroke. The risk of DVT is about 4 times higher after ICH than in patients with acute ischemic stroke [6]. The in-hospital incidence of VTE in patients with ICH is

* Corresponding author at: Stroke Research Centre, UCL Institute of Neurology, First Floor, Russell Square House, 10-12 Russell Square, London, WC1B 5EH, UK.
E-mail address: d.werring@ucl.ac.uk (D.J. Werring).

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approximately 3–7% (risk of PE ~1–2% and of DVT 1–4%) [7]; most occur within the first 7 days, suggesting that early preventative measures are likely to be most effective in reducing its incidence [8]. Current VTE prophylaxis measures include intermittent pneumatic compression (IPC) devices and anticoagulation with unfractionated heparin (UFH) or low molecular weight heparins (LMWH).

IPC devices reduce the rate of radiologically and clinically detected VTE and are the current standard of care, although the randomised controlled trials (RCTs) included only a small proportion of patients with ICH [9–11]. IPC devices are recommended by the current American guidelines (2022) for non-ambulatory patients with spontaneous ICH, starting on the day of diagnosis [12]. However, IPC devices are not always well tolerated, are not suitable for all patients, and availability remains challenging within some stroke services [10]. Moreover, in the largest trial (CLOTS 3) [9] only 45% of patients were randomised on day 0–1.

Short-term prophylactic anticoagulation is an alternative approach for VTE prevention. A meta-analysis of 4 studies (of which 2 were randomised) suggested that UFH or LMWH started at 48–96 h after ICH may reduce the risk of PE (1.7% vs. 2.9%; RR, 0.37; 95% CI, 0.17–0.80) without a significant increase in hematoma enlargement [13]. A recent systematic review of the RCT evidence for starting versus avoiding short-term prophylactic dose anticoagulation after ICH found that the evidence is very uncertain about the effect on death, venous thromboembolism, ICH, and independent functional status [14]. A network meta-analysis of RCTs of prophylactic anticoagulation versus pneumatic devices to prevent VTE after ICH found insufficient data to make meaningful comparisons between prophylactic dose anticoagulation and the current clinical standard of care with IPC devices [10].

Guideline recommendations for pharmacological VTE prophylaxis after ICH, summarized in Table 1, vary and are based on expert opinion because of the limited evidence for safety and efficacy [13,15–22]. American guidelines made a weak recommendation suggesting that low-dose UFH or LMWH to reduce the risk for VTE in non-ambulatory patients 24–48 h after spontaneous ICH may be reasonable [12], while the European Stroke Initiative Council (2006) recommended that anticoagulation with UFH or LMWH should be considered as soon as 24 h after ICH, especially in high-risk patients [23]. By contrast, the ESO guideline did not make any recommendation due to low quality and weak strength of evidence [24].

VTE prophylaxis in ICH patients, therefore, appears to be a persisting area of clinical uncertainty. The role, optimal timing, and preferred agent for prophylactic anticoagulation all remain unclear. We did a survey that aimed to evaluate stroke clinicians' opinions and current practice within the United Kingdom and Ireland, and views regarding a future randomised controlled trial to inform clinical practice and guidelines.

2. Materials and methods

A survey was created online using www.onlinesurveys.ac.uk. An online format was used to maximize response return and ease of dissemination. Questions aimed to assess what medical staff does in practice, rather than knowledge of guidelines. The survey consisted of 18 questions (see online Supplemental Data). The first question addressed the professional role in caring for people with stroke. The next three questions explored the clinical importance of the issue in the responders' view, whether they were uncertain regarding the optimal

Table 1

Summary of currently available guidelines regarding the use of anticoagulants for VTE prophylaxis in patients with acute intracerebral haemorrhage.

Guideline	Method of prophylaxis	Timing	Recommendation	Grade of Recommendation
American Heart Association/ American Stroke Association 2022 Guideline for the management of patients with spontaneous ICH [12]	low-dose UFH or LMWH	24 to 48 h from ICH onset	In non-ambulatory patients with spontaneous ICH low-dose UFH or LMWH can be useful to reduce the risk of PE. Initiating prophylaxis at 24 to 48 h from ICH onset may be reasonable to optimize the benefits of preventing thrombosis relative to the risk of hematoma expansion	COR: 2a/2b (moderate/ weak) LOE: C-LD (limited data)
Canadian stroke best practice recommendations: Management of Spontaneous Intracerebral Haemorrhage, 7th Edition Update 2020 [28]	LMWH	48 h and documentation of hematoma stabilization	Chemoprophylaxis (LMWH) can be initiated after 48 h and documentation of hematoma stabilization on neuroimaging (Documenting hematoma stabilization requires an additional scan that is separated by at least 24 h from the baseline scan)	Evidence Level B (Desirable effects outweigh or are closely balanced with undesirable effects or vice versa)
Venous thromboembolism in over 16 s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism London: National Institute for Health and Care Excellence (NICE); 2019 Aug 13 [29]			Do not offer pharmacological VTE prophylaxis to people with ruptured cranial vascular malformations or people with intracranial haemorrhage (spontaneous or traumatic) until the lesion has been secured or the condition has stabilized	
Prophylaxis of Venous Thrombosis in Neurocritical Care Patients: An Evidence- Based Guideline: A Statement for Healthcare Professionals from the Neurocritical Care Society 2016 [30]	prophylactic doses of subcutaneous UFH or LMWH	48 h of hospital admission	We suggest using prophylactic doses of subcutaneous UFH or LMWH to prevent VTE in patients with stable hematomas and no ongoing coagulopathy beginning within 48 h of hospital admission	Weak recommendation Low-quality evidence
European Stroke Organization (ESO) 2014 Guidelines for the management of spontaneous intracerebral haemorrhage [24]			There is insufficient evidence from RCTs to make strong recommendations about how, when, and for whom anticoagulation should be given to prevent DVT or improve outcome after intracerebral haemorrhage	Quality of evidence: Low Strength: Weak
The European Stroke Initiative Writing Committee and the Writing Committee for the EUSI Executive Committee 2006 Recommendations for the management of intracranial haemorrhage - part I: spontaneous intracerebral haemorrhage [23]	Low-dose subcutaneous heparin or LMWH	24 h	Low-dose subcutaneous heparin or LMWH should be considered after 24 h, especially in patients who are at high risk of thromboembolism	Class IV evidence (Evidence from uncontrolled studies, case series, case reports, or expert opinion)

VTE = venous thromboembolism; ICH = intracerebral haemorrhage; LMWH = low molecular weight heparin; RCT = randomised controlled trial; DVT = deep vein thrombosis; UFH = unfractionated heparin; PE = pulmonary embolism; COR = class of recommendation; LOE = level of evidence.

treatment approach, and the current standard practice they use. Further questions explored the use of IPC devices, and the current standard of care, including: whether IPC devices are well tolerated by all patients; whether they are convenient for ward staff; how certain staff is about the current criteria for offering IPC devices; and the optimal duration of use in practice. Further questions explored responders' views on the role of short-term prophylactic anticoagulation, including whether they would offer LMWH or DOACs (direct oral anticoagulants), and the optimal timing. The survey included four clinical vignettes of exemplar patients with ICH including in a lobar or non-lobar location (see online Supplemental Data). In each scenario, respondents were asked to give their views on whether and when they would use anticoagulation. Finally, the survey explored responders' opinions about the importance of an RCT investigating the role of short-term prophylactic anticoagulation after ICH, the optimal design of such a trial, and whether they would participate. The survey was drafted, piloted, reviewed, amended, and then circulated to members of the British and Irish Association of Stroke Physicians (BIASP) along with a cover letter detailing the background of the project. We distributed invitations via email with a hyperlink allowing access to the online survey. Responders were provided 7 weeks to complete the survey, with reminders sent prior to the closing date. We used simple descriptive statistics to report the responses.

3. Results

The survey was sent to all members (approximate number 650) of the British and Irish Association of Stroke Physicians (BIASP) in June 2022. A total of 123 members and associate members completed the survey. Among the respondents, 80% ($n = 98$) were consultant stroke physicians, 14.5% ($n = 18$) were stroke trainees, 1.5% ($n = 2$) were nurses and the remaining 4% ($n = 5$) were other physicians involved in stroke care. 74% ($n = 91$) of the responders considered VTE prophylaxis after acute ICH to be extremely important, 25% ($n = 31$) considered it important,

and only one respondent found the issue fairly unimportant (Fig. 1a). However, only 46% ($n = 56$) of responders were certain to some extent regarding the optimal treatment approach; 5 were extremely certain, and 51 were fairly certain.

The current practice of survey respondents for VTE prophylaxis after ICH is shown in Fig. 1b. IPC devices from admission to hospital discharge or until mobile was the most common standard practice, followed by IPC and switching to LMWH, being used by 60% ($n = 74$) and 30% ($n = 37$) of responders, respectively. Only one responder used a combination of IPC devices and LMWH initially, and another used LMWH alone. 8% ($n = 10$) of responders use different methods, including: TED stockings after 30 days of IPC if the patient is still immobile; LMWH alone only for patients with small volume ICH and high VTE risk; and LMWH alone if the patient is unlikely to tolerate IPC devices.

The opinions about convenience and tolerability of IPC devices for patients and staff are shown in Fig. 1c and Fig. 1d, respectively. 53% ($n = 63$) of responders felt that IPC devices are well tolerated by all or most patients, while 6.5% ($n = 8$) considered them not tolerated by most patients. However, when responders were asked regarding their view on convenience and tolerability of IPC devices for staff, 65% ($n = 80$) of responders felt that IPC devices are always or mostly convenient, while 35% ($n = 43$) felt IPC devices are always or mostly inconvenient to some extent for ward staff.

Views on certainty about the use of IPC devices and anticoagulation for VTE prevention after ICH are shown in Fig. 2. Only 20% ($n = 24$) of responders were extremely certain, and 60% ($n = 74$) fairly certain, about the current criteria for using IPC devices (Fig. 2a). 50% ($n = 62$) of responders were extremely or fairly certain about the duration for which IPC devices should be offered (Fig. 2b). Most responders 59% ($n = 72$) would use anticoagulation in some patients with acute ICH depending on the risk of VTE and of further intracranial haemorrhage, followed by 28% ($n = 34$) who were uncertain about the role of anticoagulants in

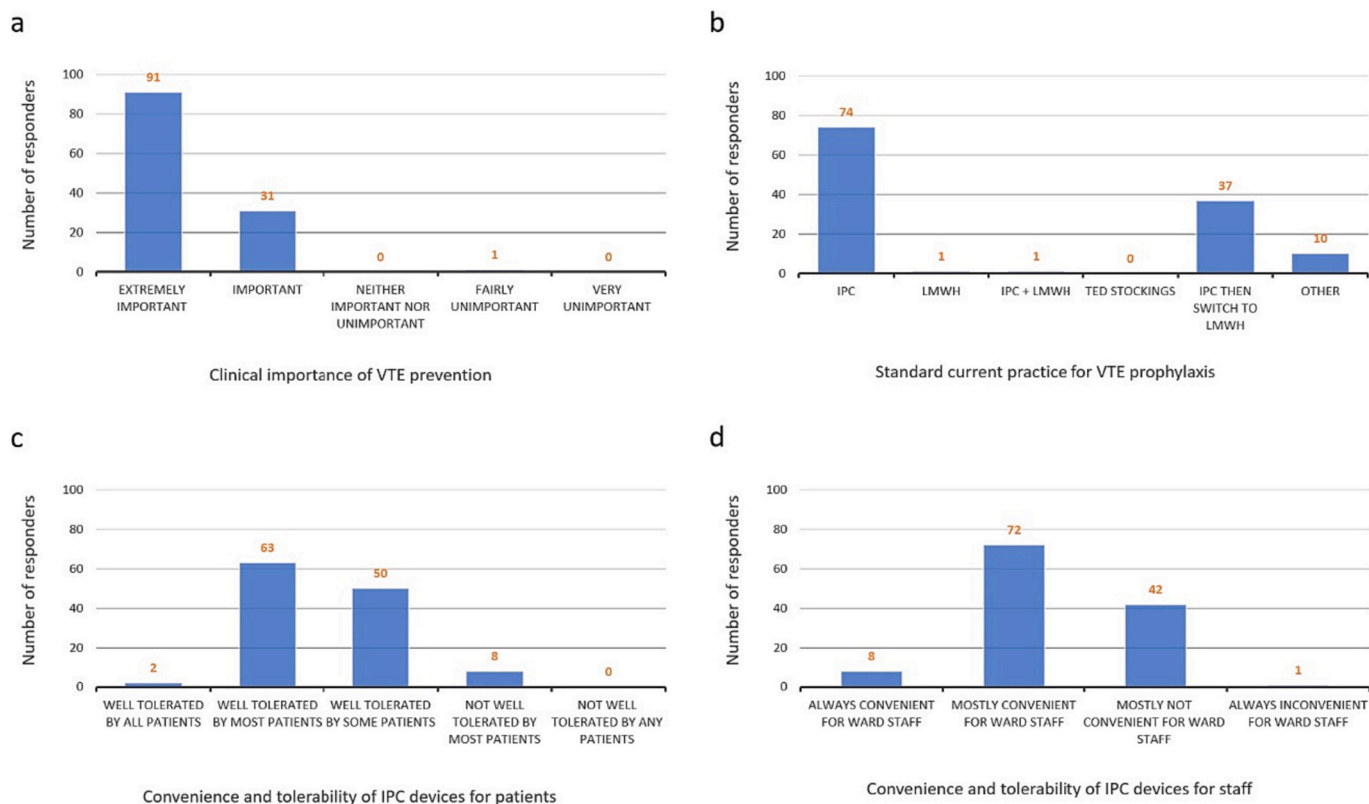


Fig. 1. (a) Clinical importance of VTE prevention; (b) standard current practice for VTE prophylaxis; (c) convenience and tolerability of IPC devices for patients; (d) convenience and tolerability of IPC devices for staff.

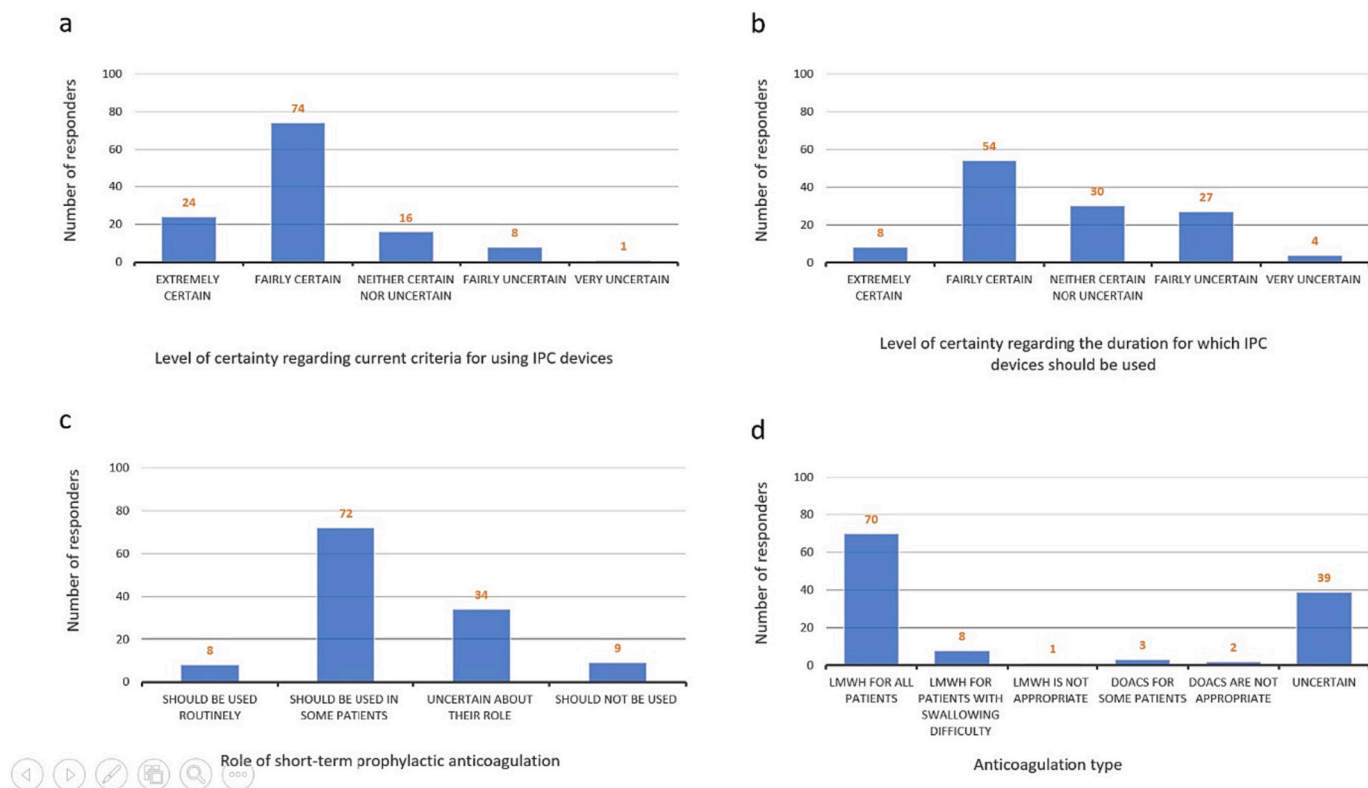


Fig. 2. (a) Level of certainty regarding current criteria for using IPC devices; (b) level of certainty regarding the duration for which IPC devices should be used; (c) role of short-term prophylactic anticoagulation; (d) views on the type of anticoagulation that might be used for VTE prevention.

these patients. Only 6.5% ($n = 8$) felt that anticoagulants should currently be used routinely, while 7% ($n = 9$) would not use anticoagulants routinely under any circumstances (Fig. 2c). There was less uncertainty regarding the preferred anticoagulant to use: most responders (57% ($n = 70$)) consider LMWH an appropriate choice for all patients without contraindications, and 6.5% ($n = 8$) only for patients who cannot swallow oral medications. Only 2.4% ($n = 3$) considered DOACs appropriate for some patients (Fig. 2d).

When asked about the timing of using anticoagulants, for any ICH regardless of location (Fig. 3a), 41% ($n = 50$) of the participants would consider anticoagulants after 72 h if repeat head computerized tomography (CT) shows no increase in ICH volume, followed by 28% ($n = 34$) who do not think there is any role for anticoagulation, and 15% ($n = 18$) who would consider giving anticoagulant after 72 h without repeating the brain scan. When treating a patient with deep ICH (Fig. 3b), the responders' answers were similar to the overall responses. 43% ($n = 53$) of them would consider anticoagulants after 72 h if repeat CT does not show ICH extension, 27% ($n = 33$) do not think there is any role for anticoagulation in these patients, and 12% ($n = 15$) would use anticoagulant after 72 h without repeating imaging. However, when facing a patient with lobar ICH (Fig. 3c), 38% ($n = 47$) of responders felt there is no role for anticoagulation, followed by responders that would consider anticoagulation after 72 h with (34%) or without (13%) repeated imaging. In patients who cannot have IPC devices for any reason (Fig. 3d), trends were similar to the deep ICH scenario: 42% ($n = 52$) would consider anticoagulants after 72 h and additional imaging, 14% ($n = 17$) after 72 h without imaging, and 12% ($n = 15$) would not use anticoagulants at all. Interestingly, in this scenario, 10.5% ($n = 13$) and 8% ($n = 10$) of responders would consider anticoagulants after 48 h and 24 h, respectively, after imaging.

Participants' views on a randomised controlled trial (RCT) are shown in Fig. 4. The vast majority (93%) of respondents consider randomised controlled trials (RCT) investigating the role of pharmacological VTE prophylaxis after acute ICH as extremely important (61%) or important

(32%). 93% of respondents would definitely participate or consider participating contingent on adequate funding. There was a range of views on the preferred intervention for an RCT of VTE prophylaxis after acute ICH: 29% ($n = 36$) of responders felt anticoagulation with LMWH plus IPC devices should be the preferred intervention, followed by 23% ($n = 28$) that felt anticoagulation with LMWH alone, and 23% ($n = 28$) who were not sure what the intervention should be. Only 16% ($n = 20$) thought the intervention should be anticoagulation with DOACs alone or LMWH for those unable to swallow, and 9% ($n = 11$) thought the intervention should be IPC devices plus DOACs or LMWH for those unable to swallow. The preferred comparator was IPC devices alone in the majority (84.5% ($n = 104$)) of responders. 7% ($n = 9$) thought the comparator should be no VTE prophylaxis, while 8% ($n = 10$) were not sure what the comparator should be.

4. Discussion

This UK online survey, completed mainly by consultant stroke physicians, clearly shows a lack of consensus regarding the optimal treatment approach for VTE prophylaxis after acute ICH. We also found that the current standard of care, IPC devices, were not considered tolerated by patients or considered convenient by staff by a substantial proportion of respondents. Our findings indicate that an RCT evaluating the role of short-term pharmacological VTE prophylaxis after ICH is supported by the great majority of stroke clinicians surveyed.

The uncertainty regarding using short-term prophylactic anticoagulation in patients with ICH probably results from the lack of large-scale high-quality evidence for its safety and efficacy; the limited data from randomised studies is summarized in Table 2. An early randomised study (1988) [15] found that prophylactic dose UFH given at 4 days compared with 10 days after ICH did not increase the risk of rebleeding, but did not reduce VTE, possibly because the earlier treatment time was too late to reduce the incidence of VTE which peaks between days 2 and 7 of hospitalization [18]. An extension phase of this study (1991) [16]

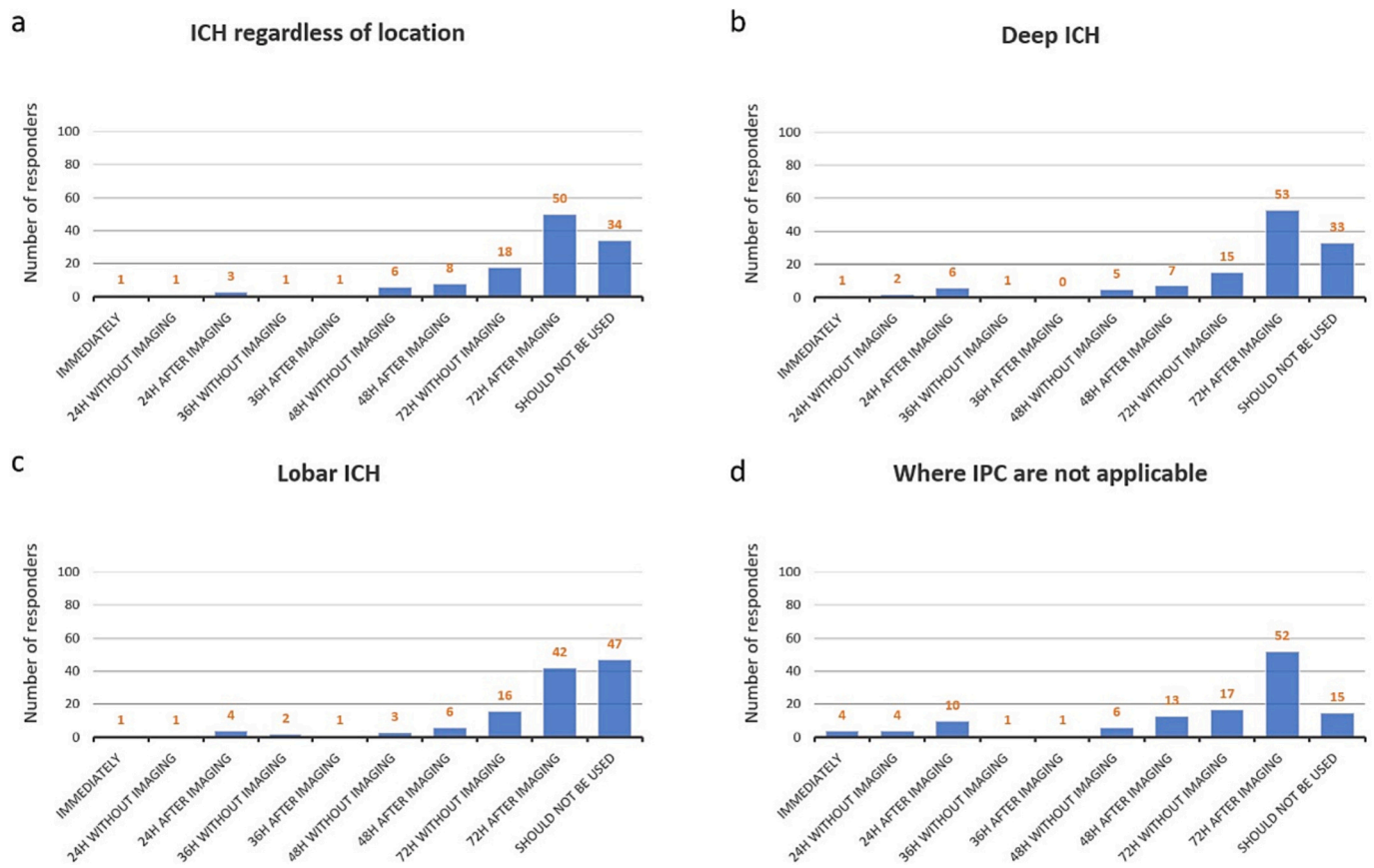


Fig. 3. Views on the timing of prophylactic anticoagulation to prevent VTE after: (a) ICH regardless of location; (b) deep ICH; (c) lobar ICH; (d) in patients in whom IPC devices are not applicable.

suggested that low-dose heparin given at 48 h after ICH was safe and significantly reduced the risk of PE, but combined observational data with the previous RCT findings. A subsequent single-center trial study [22] which randomly allocated 75 patients with ICH to LMWH 40 mg versus compression stockings 48 h after stroke onset found that LMWH was not associated with increased hematoma growth or systemic bleeding. A more recent multicenter randomised trial [25] - which was prematurely stopped after the randomisation of 73 patients due to low recruitment rate - found that early (≤ 72 h) treatment with heparin plus standard therapy compared to standard therapy alone was associated with a non-significant reduction in death of any cause and a non-significant increase in hematoma enlargement. A recent Cochrane review [14] synthesized data from the four published randomised trials of starting versus avoiding short-term prophylactic dose parenteral anticoagulation after ICH. This did not show clear evidence for benefit or harm, but there was considerable qualitative heterogeneity between interventions, comparators, and timing of assessments and some included trials were at high or uncertain risk of bias. No RCT reported on all major adverse cardiovascular events (MACE). The authors found that the evidence is very uncertain about the effect of starting short-term prophylactic dose anticoagulation on death (RR 1.00, 95% CI 0.59 to 1.70, $P = 1.00$; 3 RCTs; very low certainty evidence), venous thromboembolism (RR 0.84, 95% CI 0.51 to 1.37, $P = 0.49$; 4 RCTs; very low-certainty evidence), ICH (RR 0.24, 95% CI 0.04 to 1.38, $P = 0.11$; 2 RCTs; very low-certainty evidence), or independent functional status (RR 2.03, 95% CI 0.78 to 5.25, $P = 0.15$; 1 RCT; very low-certainty evidence) over 90 days. There was no evidence of an increased risk of recurrent ICH.

We also noted uncertainty regarding the potential timing of prophylactic anticoagulation. A systematic review and meta-analysis demonstrated the logarithmic nature of hematoma expansion with a

major drop (the rate of decline was steepest at 0.5–3 h) in the proportion of cases as time passed from symptom onset [26]. In a randomised trial of the timing of anticoagulation initiation [27] 139 patients were randomly allocated to either enoxaparin 20 mg twice daily at 24 h or 72 h after ICH and found no difference in haematoma enlargement. Therefore, initiating heparin treatment as soon as 24–48 h after ICH onset, as suggested by the American guidelines, might be reasonable [12]. Nevertheless, the results of this survey demonstrated that clinicians were more likely to start anticoagulation in most ICH patients only 72 h after repeat imaging, and this should be considered when designing an RCT.

The data from the randomised studies discussed above are clearly limited with regard to the overall effects of short-term prophylactic anticoagulation and furthermore lack evidence regarding subgroups including those defined by haematoma location, volume, intraventricular extension, or previous antithrombotic therapy. The sample sizes are small, limiting precision. Haematoma location may be of clinical relevance for decision-making according to our survey findings; avoiding anticoagulation in cases of lobar ICH probably reflects the fear of further bleeding in patients with suspected cerebral amyloid angiopathy (CAA). The lack of reliable methods to predict the risk of haematoma expansion likely contributes to clinicians' hesitancy in recommending early anticoagulation. Although multivariable prediction models for intracerebral haemorrhage growth have been developed (including brain imaging findings such as the black hole, blend, island, and swirl signs, all probably related to turbulent blood flow) there are currently no models that are sufficiently accurate, simple, or validated for routine clinical use. In any case, an important aspect of treatment prior to commencing any form of anticoagulation after ICH is to mitigate any modifiable risk factors for bleeding (such as haemodynamic instability, very high blood pressure, hyperglycemia, or infection).

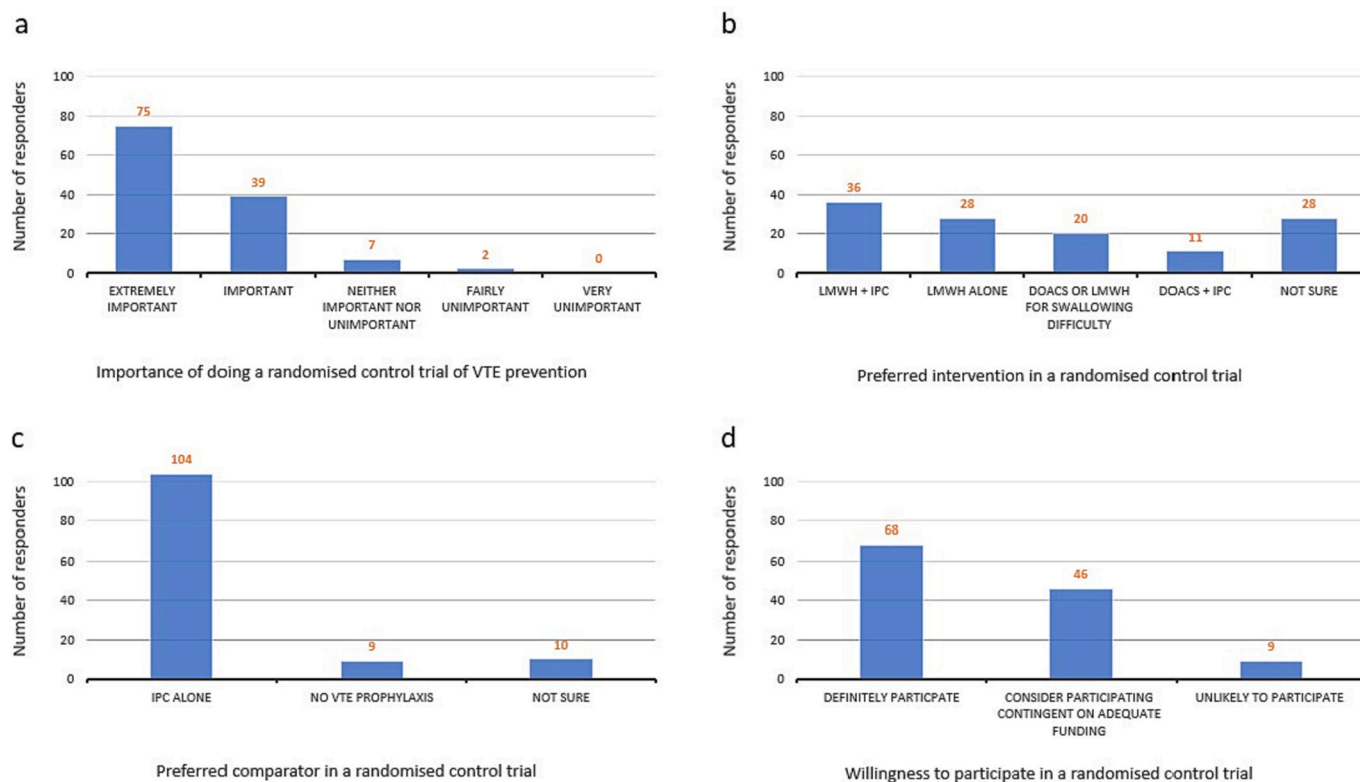


Fig. 4. Views on: (a) the importance of a randomised controlled trial of VTE prevention after ICH; (b) preferred intervention in a randomised controlled trial; (c) preferred comparator in a randomised controlled trial; (d) willingness to participate in a randomised controlled trial.

Finally, although our survey indicates that LMWH is a preferred agent for short-term anticoagulation there are currently no available data regarding the safety and efficacy of DOACs soon after ICH. DOACs are becoming more available and widely used, as they offer convenience, potentially lower risk of bleeding, and a growing experience with reversal agents. Moreover, whenever possible patients' convenience and preference should clearly be considered when choosing between oral administration, subcutaneous injection, and IPC devices.

Strengths of our survey include an acceptable return rate (123 of approximately 650 BIASP members (18.9%)) making the findings likely to reflect current practice and opinion in the UK and Ireland. This survey was distributed online and used case scenarios which we carefully developed to reflect real-life decision-making and be simple to complete. The design of this survey was anonymized to try to reduce bias.

This survey had several limitations. Medical staff with a clinical or research interest in the topic were perhaps more likely to answer, creating a risk for selection bias. There is also a risk of social desirability bias, i.e., where responders answer in a way they thought they should answer rather than what they would actually do. Respondents' practices and views, like other surveys of large physician organizations, reflect different regions and medical centers and may vary according to the place of care and timing in which patients are being cared for. Patients' experiences and preferences were not explored, and respondents' view on the optimal LMWH dosage was not sought. Furthermore, to keep the survey simple and of manageable length we were not able to include the many potentially relevant clinical or laboratory factors that may influence bleeding risk (e.g., haemodynamic instability, very high blood pressure, hyperglycemia, or infection). This was a survey evaluating medical staff views within the UK and Ireland, so results may not represent other European and non-European countries.

5. Conclusion

This online survey of UK medical staff treating patients after ICH showed persisting uncertainty regarding the optimal treatment approach for VTE prophylaxis. Large clinical randomised trials evaluating the safety and efficacy of short-term prophylactic anticoagulation after acute ICH using mechanical and pharmacological interventions (either alone, or in combination) are needed.

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Ethical approval

Not applicable.

Informed consent

Not applicable.

Guarantor

DJW.

Contributorship

DJW obtained funding and supervised the project. NA, RASS, HC, DD, NF, MP, APJ, CP, NS, and DJW conceived and designed the survey. Ms. Amy Gent collected and analyzed the responses. RM and DJW performed the literature search and drafted the initial article. All authors provided a critical revision of the article for important intellectual

Table 2

Summary of randomised studies evaluating the use of short-term anticoagulants for VTE prophylaxis in patients with acute intracerebral haemorrhage.

Study	Design	Number of patients	Intervention	Outcome
Qian et al. [27] 2021	Multicenter, prospective, randomised trial	139	LMWH (enoxaparin) 20 mg twice a day 24 h compared with 72 h after haemorrhage	Early enoxaparin treatment was not associated with enlargement of the hematoma, increased amount of poor outcome or increased death rate Only 3 patients developed VTE, 2 in the early and one in the late group No patients developed PE Enoxaparin was associated with a non-significant increase in hematoma enlargement and a non-significant reduction in death for any cause
Paciaroni et al. [25] 2020	Multicenter, prospective, randomised trial (stopped)	73	Enoxaparin 0.4 mL (40 mg) daily for 10 days 72 h after haemorrhage compared with standard therapy alone	Enoxaparin was not associated with increased hematoma growth or any other systemic bleeding Asymptomatic DVT was non-significantly more common in the enoxaparin group
Orken et al. [22] 2009	Single-center randomised controlled trial	75	Enoxaparin 40 mg daily compared to compression stockings 48 h after stroke onset	Asymptomatic DVT was non-significantly more common in the enoxaparin group
Dickmann et al. [15] 1988	Single-center randomised controlled trial	46	UFH 5000 units 8 hourly four days compared with ten days after haemorrhage	Early heparin treatment did not increase the risk of rebleeding

VTE = venous thromboembolism; LMWH = low molecular weight heparin; IPC = intermittent pneumatic compression; DVT = deep vein thrombosis; PE = pulmonary embolism; UFH = unfractionated heparin.

content and approved the final version.

Declaration of Competing Interest

None of the authors have any financial disclosures or conflicts of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jns.2023.120855>.

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