



# Venous Thromboembolism Prevention in Spontaneous Intracerebral Hemorrhage

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**Abstract:** Venous thromboembolism (VTE), encompassing for deep vein thrombosis (DVT) and pulmonary embolism (PE), represents the most feared complication in patients suffering from spontaneous intracerebral hemorrhage (ICH). The balance between VTE risk and the risk of hematoma expansion and/or re-bleeding is the cornerstone of prophylaxis which is based on non-pharmacological and pharmacological strategies. In the latest years results of three randomized clinical trials on non-pharmacological prophylaxis in ischemic and hemorrhagic stroke have been published. Intermittent pneumatic compression has shown to be effective in ICH compared to placebo, whereas graduated compression stockings failed to show their superiority over placebo. Few and low quality studies reported on pharmacological prophylaxis in ICH. Overall, these studies showed that pharmacological prophylaxis could be safe, but whether it is more effective than other non-pharmacological methods remains unclear. A meta-analysis of four randomized controlled studies showed that pharmacological prophylaxis significantly reduces the rate of pulmonary embolism. Consequently, recommendations from Scientific Societies for VTE prevention in ICH are based on weak literature evidence. In the present article, the Authors provide a review on VTE prevention in ICH and propose a practical algorithm for clinical management of this topic.

**Keywords:** Venous Thromboembolism, Prophylaxis, Intracerebral Hemorrhage

## 1. Background

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), represents the most feared complications occurring in patients suffering from ICH (1).

Incidence of VTE in acute phase of ICH ranges from 2 % (0.7% PE, 1.3% DVT) in large studies to 15% for symptomatic VTE events to 75 % for asymptomatic DVT events in smaller case series (2-4). Much recently, the randomized controlled CLOTS (Clots in Legs Or sTockings after Stroke) III trial showed a 30-day 17% cumulative incidence of symptomatic and asymptomatic VTE in the arm of hemorrhagic stroke patients that were not receiving VTE prevention (5).

Timing of VTE events in patients suffering from cerebrovascular events such as ischemic and hemorrhagic stroke has been much recently described. In fact, in 5632 patients enrolled in the CLOTS I and CLOTS II trials, symptomatic and/or asymptomatic VTE events occurred in 11.4% of patients between the seventh and tenth day and 3.1% of patients between twenty-sixth and thirtieth day from stroke onset, respectively (6).

Risk factors for VTE in patients with ICH are represented by older age, female gender, obesity, prolonged bed-rest, legs paralysis, ICH lobar location, large hematoma volume, National Institute of Health Stroke Scale (NIHSS) score  $\geq 12$ , withdrawal of antithrombotic treatment in antithrombotic-related ICH, pro-hemostatic agents such as activated or non-activated prothrombin complex concentrates

or recombinant activated factor VII used for prompt reversal in anticoagulants-related ICH (7-9).

Acute treatment of VTE events involves the use of anticoagulant therapy in full doses. Since the administration of full dose anticoagulant drugs is contraindicated in the acute phase of ICH due to the risk of hematoma expansion, pulmonary embolectomy and/or vena cava filters placement could be the alternative choices. However these procedures are invasive and not always free from serious complications. Therefore the risk of mortality in patients with ICH who develop a VTE event will increase considerably. In fact, VTE represents the second cause of mortality in patients with ICH after ICH its-self, encompassing for 5 % of all-cause mortality (10-13).

Due to this background, VTE prevention represents a cornerstone in the practical management of acute and sub-acute phase of ICH. The purpose of this article is to review on literature evidence on VTE prevention in ICH.

## 2. VTE Prevention in ICH

The balance between VTE risk and the risk of hematoma enlargement and/or re-bleeding is of utmost importance for making decision on which is the optimal strategy for VTE prevention.

Hematoma enlargement occurs in around 38% of the cases in the first 24 hours from ICH onset (14, 15). Of this, 26% of patients develop a hematoma enlargement within 1 hour from symptoms onset, while the remaining 12% occurs in the remaining 20 hours. Re-bleeding is relatively uncommon. Much recently, in the INTERACT II trial re-bleeding occurred in 0.3% of patients (16). So, it is evident that, in the majority of ICH patients, the first 24-48 hours are crucial in terms of mortality and neurological deterioration.

Strategies to prevent VTE in ICH patients are represented by non-pharmacological and pharmacological agents (1, 17).

Non-pharmacological agents are represented by mechanical strategies such as graduated compression stockings (GCS), intermittent pneumatic compression (IPC) and the plantar venous pump (PVP), which represents a subtype of IPC, vena cava filters placement and early mobilization (18).

The evidence of literature relating to mechanical prophylaxis in patients with ICH results from four randomized controlled trials.

The VICTORIAH study, which randomized 141 patients, compared the combination of IPC with GCS versus GCS alone. The combination of the two strategies was significantly superior in reducing the risk of VTE compared with GCS alone [4.7% vs 15.9%, RR 0.29 (95 % CI 0.08-1.0), RRA 11.2%, RRR 71%, NNT 9] (19).

Further evidence for the mechanical prophylaxis derived from the CLOTS trials that were aimed at evaluating the role of mechanical prophylaxis in the population of patients with acute stroke, despite population was mainly represented by patients with ischemic stroke (5, 20, and 21). CLOTS I and II trials did not provide separate results for patients with ischemic and hemorrhagic stroke, so it is unclear whether the

subgroup of patients with hemorrhagic stroke had different results from those with ischemic stroke. In summary, the CLOTS I trial showed that GCS did not provide significant prevention compared to placebo, significantly increasing the risk of skin lesions, while the CLOTS II trial showed that the GCS positioned to the root of the thighs were significantly superior to the GCS positioned below the knees for VTE prevention (20, 21).

In the CLOTS III trial IPC was tested against placebo for VTE prevention (5). Separate results for ischemic and hemorrhagic stroke were displayed. In this trial 163 patients with hemorrhagic stroke undergone to IPC were compared with 159 patients undergone to placebo. VTE prophylaxis with IPC was associated with a significant reduction in the risk of VTE [6.7 % vs 17% (OR 0.36; 95% CI: 0.17 to 0.75), RRA 10.3%, RRR 64%, NNT 10] (5). Of note, the CLOTS III showed that patients undergone to IPC presented a significant reduction in all-cause mortality in follow-up compared to patients undergone to placebo, despite this, results are not available for the subgroup of ICH patients alone (5).

Other possible strategies of non-pharmacological prophylaxis in ICH are represented by the vena cava filters placement and early mobilization. To now, the main indication for vena cava filters placement is represented by the absolute contraindication to anticoagulant therapy (22). Therefore, in this context the main role of vena cava filters should be reserved to patients with ICH who suffer from acute VTE events. Instead, concern exists for the prophylactic role of vena cava filters in ICH patients. There are no studies that have evaluated the role of prophylactic vena cava filters as a strategy for prevention of VTE in the acute phase of ICH. For this purpose, it is reasonable to reserve vena cava filters for patients with ICH who are at very high risk of VTE, such as patients with a history of recent (within 3 months) VTE episode or severe thrombophilia (23, 24). It is important to remark that once time the absolute contraindication ceases, vena cava filters should be removed. However, the removal rate is low, as it was shown by recent reports in the literature (25).

The role of early mobilization as a possible strategy for the prevention of VTE in ICH patients has not been previously investigated.

Randomized controlled clinical trials have clearly demonstrated the efficacy of pharmacological prophylaxis with unfractionated heparin (UFH) and low molecular weight heparins (LMWHs) or fondaparinux in reducing VTE in non-surgical patient with a good safety profile (26). However, these trials excluded patients with recent ICH. Therefore, it is impossible to extrapolate recommendations for ICH patients from this literature evidence. Literature evidence shows that pharmacological VTE prevention in ICH patients is underused. Prabhakaran et al. showed that only 16.5% of 32.690 patients with spontaneous ICH received any VTE prophylaxis, 71.5% and 27.5% of it being by UFH and enoxaparin, respectively (27).

Much recently, a systematic review of literature on studies was aimed to evaluate the efficacy in terms of prevention of VTE and safety in terms of hematoma expansion or

re-bleeding of the pharmacological prophylaxis in ICH patients, found nine studies for around 1750 patients enrolled (1, 28-36). 981 patients received pharmacological prophylaxis, starting at 48 hours in 66.6 % of cases and within a week in 97.6 % of cases. Three studies were randomized and controlled, but one of these was the continuation of one of the previous two. Six studies were retrospective. In three studies, pharmacological prophylaxis was performed by using unfractionated heparin (UFH); in four studies low molecular weight heparins (LMWHs) were used; in two studies both UFH and LMWHs were tested. Two studies compared the pharmacological prophylaxis with mechanical prophylaxis by using GCS, two studies compared the efficacy and safety of UFH starting from different days (second, fourth and tenth day after the ICH event), one study evaluated the efficacy and safety of LMWHs in combination with IPC in patients with ICH with or without ventricular bleeding; in the other studies the pharmacological prophylaxis was compared to placebo. The presence of VTE was systematically detected in three studies, whereas in other three studies VTE was detected only in patients who showed clinical signs of VTE. In one study VTE was defined as fatal PE or death in the presence of clinical or electrocardiographic signs suggestive for PE

detected after the analysis of medical data records. Overall, the overview of these nine studies showed that the pharmacological prophylaxis starting within 48-72 hours from ICH could be effective and safe, even in patients with the ventricular extension bleeding. However, the two studies in which the pharmacological prophylaxis was compared with mechanical agents showed no significant differences in VTE rate between methods (1).

Four of the above mentioned studies, containing a control group, were meta-analyzed (37). The meta-analysis showed that in patients with ICH, pharmacological prophylaxis with UFH or LMWHs significantly reduces the risk of symptomatic and asymptomatic pulmonary embolism [RR 0.37 (95 % CI: 0.17 to 0.80), RRR 63%], not significantly reduced the risk of symptomatic and asymptomatic DVT [RR 0.77 (95 % CI: 0.44 to 1.34 ), RRR 23%] and all-cause mortality [RR 0.76 (95% CI: 0.57-1.03), RRR 24%] without increasing the risk of hematoma expansion [RR 1.42 (95 % CI: 0.57-3.53), RRI 42%] (37).

In the latest years some scientific organizations produced their recommendations (38-44) (Table 1). The strength of the recommendations is weak, especially for pharmacological prevention.

**Table 1.** Summary of recommendations on VTE prophylaxis in ICH.

Year of relapse	Organization	Ref.	Recommended regimen for VTE prophylaxis	Level of evidence and grade of recommendation
2011	American College of Physicians (ACP)	38	Pharmacologic prophylaxis with UFH or LMWHs or a related drug is indicated unless the assessed risk for bleeding outweighs the likely benefits. ACP recommends against the use of mechanical GCS	IB
2012	American college of Chest Physicians (ACCP)	39	Pharmacological prophylaxis with LMWH or UFH started between days 2 or 4 or mechanical prophylaxis with IPC are indicated. Prophylaxis with LMWH should be preferred over UFH. ACCP recommends against mechanical prophylaxis with GCS. Patients at high risk of bleeding such as those with ICH should not be offered pharmacological prophylaxis. Alternative options such as mechanical prophylaxis (IPC, GCS or both) or vena cava filters should be considered if they are at high VTE risk. Pharmacological method should be introduced only when the bleeding risk is resolved.	IIC IB IB
2012	Asian VTE guidelines	40		GPP
2013	International Consensus Statement under the auspices of the Cardiovascular Disease Educational and Research Trust, European Venous Forum, North American Thrombosis Forum, International Union of Angiology and Union Internationale du Phlebologie.	41	IPC combined with GCS is recommended	moderate
2013	Sociedad Española de Neurología Study Group for Cerebrovascular Diseases	42	IPC combined with GCS is recommended in the first 24 hours After 24 hours LMWH could be administered GCS are not recommended, IPC is recommended	IB IIbB
2014	European Stroke Organization (ESO)	43	Insufficient evidence for making strong recommendation on how, when and for pharmacological prophylaxis should be given Pharmacological prophylaxis is NOT recommended to prevent	Moderate/strong Low/weak
2015	National Institute for Clinical Excellence (NICE)	44	DVT/PE in hemorrhagic stroke patients Do not offer GCS for VTE prophylaxis; Consider offering IPC	GPP
2015	American Heart Association/American Stroke Association (AHA/ASA)	45	IPC as soon as possible GCS are not beneficial UFH/LMWH after demonstration of bleeding cessation after 1-4 days from ICH onset	IA IIIA IIbB

Legend: IPC=Intermittent pneumatic compression, GCS=Graduated compression stockings, UFH=Ufractionated heparin, LMWH=Low molecular weight heparin

Based on literature evidence and recommendations, we propose a possible flow chart for VTE prevention in ICH (Figure 1).

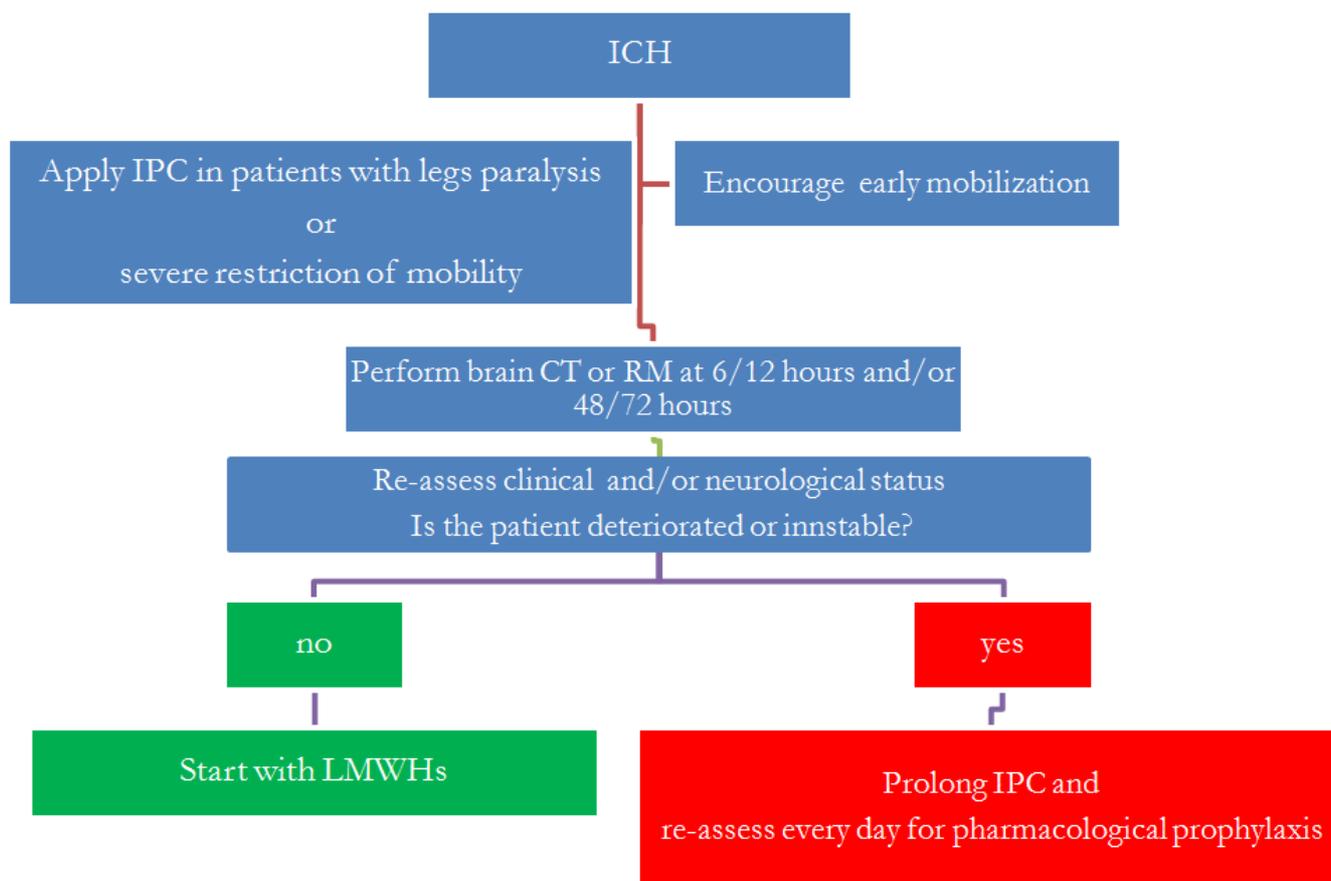


Figure 1. Proposed flow-chart for VTE prevention in ICH.

### 3. Conclusion

VTE is one of the most feared complications of spontaneous ICH, burdened by high mortality and morbidity. Therefore VTE prevention is of utmost importance. Literature lacks on suggesting the best practice for this purpose. IPC has shown to be effective and safe and therefore it should represent the first choice of treatment at least for the first 48-72 hours from symptoms onset. GCS is not recommended because it has shown to be ineffective. Evidence for pharmacological prophylaxis is weak. Prospective studies are warranted and necessary.

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