



## Non-pharmacological Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients

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### Authors' contributions

*This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.*

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### ABSTRACT

Venous thromboembolism (VTE) represents one of the leading causes of mortality and morbidity in acutely ill medical patients. VTE prophylaxis can be assured by pharmacological strategies and, when contraindicated, by non pharmacological measures, such as early mobilization, graduated compression stockings (GCS), intermittent pneumatic compression (IPC) or inferior vena caval filters. Literature evidence on non pharmacological VTE prophylaxis lacks and guidelines are not standardized for hospitalized ill medical patients. Much recently randomized clinical trials in patients with stroke and other medical diseases, seem to increase doubts and reduce certainties in this context. In this review we provide information about non pharmacological thromboprophylaxis in acutely hospitalized ill medical patients.

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## 1. INTRODUCTION

Venous thromboembolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE), is one of the leading causes of mortality and morbidity and it is the one of the most preventable disease in non surgical hospitalized patients [1,2]. In this context, the overall rate of VTE in the absence of thromboprophylaxis is around 10-20%, reaching the rate of 40-50% in some subgroups of medical diseases such as stroke [3]. The burden of VTE in acutely ill medical patient is so severe that to now around 75% of the diagnoses of VTE in hospitalized patients is referred to medical patients and 75% of VTE-related deaths occur in this kind of subjects [1-5]. As abovementioned, the main medical conditions that are associated with risk of VTE are represented by stroke, heart failure, cancer, chronic obstructive pulmonary disease (COPD) associated to respiratory failure (especially when requiring mechanical ventilation), acute myocardial infarction, sepsis, rheumatic and chronic inflammatory bowel diseases. The risk increases significantly when these conditions occur in elderly subjects aged >75 years, in patients with impaired mobility, those with a history of previous VTE and those with inherited or acquired thrombophilia such as antithrombin (AT), protein C or S defects, activated protein C resistance, Factor V Leiden mutation, Factor II mutation, increased Factor VIII, antiphospholipid syndrome [2-6]. Many clinical scores to predict the risk of VTE in ill medical patients were proposed; the latest Edition of American College of Chest Physicians guidelines promoting the Padua score [7] (Table 1).

**Table 1. The Padua score**

<b>Risk factors</b>	<b>Score</b>
Active cancer	3
Previous VTE	3
Bedridden	3
Thrombophilia*	3
Recent (≤1 month) traumatic event or surgery	2
Age ≥70 years	1
NYHA III/IV heart failure or respiratory failure	1
Acute myocardial infarction or stroke	1
Sepsis and/or rheumatic disease	1
Obesity (BMI≥30)	1
Ongoing hormonal treatment	1

\*Antithrombin (AT), protein C or S defects, Factor V Leiden mutation, G20210A mutation, antiphospholipid syndrome

Pharmacological venous thromboprophylaxis recommended if Padua score ≥ 4

## 2. THROMBOPROPHYLAXIS IN ILL HOSPITALIZED MEDICAL PATIENTS

Strategies aimed to prevent VTE are based on pharmacological and non-pharmacological aids, the last represented by early mobilization and/or mechanical methods [3]. These strategies can be combined in patients at high risk of VTE [3].

Randomized controlled trials (RCTs) have clearly demonstrated the efficacy and safety of pharmacological prophylaxis in medical patient [2]. In the previous decade, three mega

RCTs found a relative risk reduction (RRR) of VTE versus placebo ranging from 47% to 63% when administered during hospitalization [8-10]. Unfortunately the abovementioned mega trials excluded patients with acute stroke for whom, however, a meta-analysis of available clinical studies showed that pharmacological prophylaxis significantly reduces the risk of symptomatic DVT, but not the risk of PE and deaths balanced by a non-significant increase in the risk of intracranial and extracranial bleedings [11]. In ischemic stroke patients, the PREVAIL RCT showed the superiority of enoxaparin at dose 40 mg once/daily compared with unfractionated heparin 5000 IU twice/daily (RRR 43%) [12]. Other clinical studies have demonstrated the efficacy and safety of pharmacological prophylaxis in subgroups of acutely ill medical patients, such as COPD exacerbation, heart failure, cancer receiving chemotherapy and elderly [13-16]. Finally, a meta-analysis of literature evidences demonstrated that VTE pharmacological prophylaxis in ill-medical patients significantly reduces the incidence of DVT, non-fatal and fatal PE during hospital stay without increasing the risk of major bleeding, but any advantage on overall mortality was not found [17].

Nevertheless its efficacy, extending VTE prophylaxis to four weeks after hospital discharge seems unsafe both by using parenteral and new oral anticoagulants [18-21], therefore the most recent guidelines suggest to avoid prolonged pharmacological thromboprophylaxis in ill medical patients beyond two weeks [7].

Despite solid literature evidence, pharmacological VTE prophylaxis is still dramatically underused in ill medical patient [22-25].

## 2.1 Non-pharmacological Prophylaxis

The role of early mobilization as a possible strategy for the VTE prevention has been evaluated in stroke patients but solid literature evidence lacks. Since restriction of mobility is a leading risk factor for VTE, early mobilization should always be encouraged, especially in patients with contraindications to the use of pharmacological prophylaxis. However, it's very difficult to standardize this strategy in clinical practice and hence it finds little space in the available guidelines. Literature evidence on early mobilization is poor and unconvincing. In 2009, a Cochrane's revision considered only a single study, carried out on 71 patients in Australia, named AVERT study. This study found a non-significant reduction of mortality and disability in early mobilized patients, which means within 24 hours of stroke symptom onset (OR 0.67, 95% CI: 0.25-1.79) [26,27]. Up to now, another study is also available, named VERITAS study, carried out in the UK on 32 patients in whom early mobilization was initiated within 36 hours of stroke onset [28]. The combination of the two studies showed that no patient who underwent early mobilization (within 24-36 from stroke event) versus 1 patient in 49 (4.2%) who underwent standard treatment developed VTE episodes [29]. However both studies did not report whether patients received pharmacological or mechanical prophylaxis in addition to early mobilization [29]. So, early mobilization, although to be encouraged, has little practical evidence such as non-pharmacological method for VTE prophylaxis in patient with stroke. None study is available in non stroke acutely ill medical patients.

Mechanical methods represent another possibility to perform thromboprophylaxis, adjunctive or alternative to drugs [3]. These are represented by graduated compression stockings (GCS), intermittent pneumatic compression (IPC) and foot venous pump (FVP), the last one ascribed to a particular form of IPC [3,30]. The rationale for mechanical prophylaxis derives from the classical Virchow's triad on thrombosis' development and represented by: stasis, endothelial damage, hypercoagulability [30]. The stillness determines a veno-dilatation that produces venous stasis with induction of possible damage to the endothelial wall and

phenomena of hypercoagulability [30]. It becomes therefore intuitive that the fundamental objective of the mechanical prophylaxis is to avoid the veno-dilation and stasis and to favor the venous return in a centripetal direction.

GCS is the most common and economic form of mechanical prophylaxis. The increase of pressure, made differently and depending on the degree of compression, allows reducing the cross-sectional area of the lower limbs resulting in a more rapid return of venous blood from the periphery to the heart with a speed proportional to the pressure exercised. It has been proven that values of pressure of 18 mmHg at the ankle, 14 mmHg at the level of the calf and 8 mmHg at the level of the thigh are those ideal for a better venous return [30].

The instruments capable of offering an IPC are generally characterized by sleeves which envelop the legs or feet (FVP) which are inflated with air intermittently causing a sort of "squeezing" of the venous blood to the heart. The pressure that is supplied is variable (35-55 mmHg) as well as vary the compression cycles (10-35 seconds) generally followed by periods of 1 minute of deflation [30].

Mechanical prophylaxis has been shown to be effective in surgical patients in the post-operative setting as a measure of VTE prophylaxis [31,32]. Cochrane reviews show that mechanical prophylaxis with GCS alone halves the absolute risk of VTE in patients after surgery [13% in patients with GCS vs 26% in patients without GCS (OR 0.35, 95% CI: 0.26-0.47,  $p < 0.00001$ )] and helps to reduce the absolute risk of VTE by 11% in patients in whom the GCS are associated with another prophylactic method [(4% in patients with GCS in combination with another prophylactic method versus 16% in patients with GCS alone (OR 0.25, 95% CI: 0.17-0.36,  $p < 0.00001$ )] [31,32].

Although literature evidence in hospitalized medical patient lacks, the use of mechanical prophylaxis is not negligible in this context, especially in the U.S., where it was being practiced in 46.2% of patients who performed prophylaxis in the IMPROVE study (23). The ENDORSE survey demonstrated that mechanical prophylaxis is generally used in 8.2% of hospitalized medical patients [25]; in Italy, the GEMINI study showed that mechanical prophylaxis is used only in 1-4% of patients despite 8% of patients presenting with contraindications to pharmacological prophylaxis [24]. For many years, in fact, guidelines agreed on recommendation of mechanical prophylaxis in patients with contraindications to pharmacological prophylaxis, especially in patients with bleeding or high risk of bleeding (ACCP VIII Edition 2008, recommendation IA) [3,33,34].

Among the possible strategies for the prevention of VTE in ill medical patients it should be mentioned the role of vena cava filters. They are indicated in patients with VTE demonstration and absolute contraindications to pharmacological prophylaxis (i.e. active bleeding or hemorrhagic complications of pharmacological prophylaxis). Vena cava filters are disposable in different types: permanent, temporary and removable. The latter, more and more widespread in the latest years, help to prevent episodes of PE in high-risk patients (i.e. in patients with VTE or history of VTE taking antithrombotic prophylaxis and severe inherited or acquired thrombophilia) and can be removed, even after a few months, after cessation of the underlying risk factor or the end of absolute contraindication for which they were placed [35].

### 3. ASSESSMENT OF BLEEDING RISK

The balance between thrombotic and bleeding risk is of utmost importance in the choice of the most appropriate VTE prophylaxis. Few studies have evaluated the risk of bleeding during pharmacological prophylaxis of VTE in acutely hospitalized medical patient. Much recent findings, related to bleeding events recorded in the IMPROVE study, have been published [23]. Out of 11,000 hospitalized medical patients enrolled in this study, the cumulative incidence of major and clinically relevant bleedings and non major bleedings occurring within 14 days of hospital admission, was of 3.2%, with a rate of bleeding linearly related to length of hospital stay [36]. Based on the results of the IMPROVE study, the Authors derived the IMPROVE Bleeding Score (Table 2). Applying this score, the Authors showed that patients with a score  $\geq 7.0$  points had an overall rate of major and clinically relevant non major bleedings of 7.9% and 4.1% against 1.5% and 0.4% respectively of patients with score  $<7.0$  (36). Incidence of bleedings was significantly higher in patients undergoing pharmacological prophylaxis compared with patients not receiving pharmacological prophylaxis (OR 1.57, 95% CI: 1.21-2.05) and in those receiving mechanical prophylaxis compared to patients not undergoing to mechanical prophylaxis (OR 2.45; 95% CI: 1.75-3.43) [36].

**Table 2. The improve bleeding score**

<b>Risk Factors</b>	<b>Score</b>
Moderate renal failure (Creatine Clearance 30-50 ml/min)	1
Male sex	1
Age 40-84 years	1.5
Active cancer	2
Rheumatic diseases	2
Central venous catheters	2
Admission in Intensive Care	2.5
Severe renal failure (Cratinine Clearance $< 30$ ml/min)	2.5
Liver insufficiency (INR $> 1.5$ )	2.5
Age $\geq 85$	3.5
Thrombocytopenia ( $<50 \times 10^9$ cell/L)	4
Recent (three months) bleeding	4
Active gastro-intestinal ulcer	4.5
High bleeding risk when total score $\geq 7$	

Despite the score has not been validated outside of the IMPROVE study population, the IMPROVE Bleeding Risk could represent the first attempt to quantify the risk of bleeding in hospitalized medical patients and has been included in the latest ACCP guidelines (IX Edition, 2012) (7). A score  $\geq 7.0$  in the IMPROVE Bleeding Risk should address toward the optimal prophylactic choice, i.e. avoiding pharmacological prophylaxis [7,36].

### 4. EVIDENCE BASED NON PHARMACOLOGICAL PROPHYLAXIS IN ILL MEDICAL PATIENTS

In previous guidelines of ACCP (VIII Edition, 2008) mechanical prophylaxis was also recommended in patients at high risk of VTE in combination with pharmacological prophylaxis (recommendation, IIA) [3].

The latest evidence of the literature related to clinical trials, have led to a revision of the indications for the use of mechanical prophylaxis that will be described in the next paragraphs.

The main indication for the use of mechanical VTE prophylaxis in ill medical patients has always been considered the absolute contraindication to the use of pharmacological prophylaxis as resulting from the presence of active bleeding or high risk of bleeding [3]. Within ill medical patients, the first hours of ischemic and hemorrhagic stroke are the prototype of contraindication for pharmacological prophylaxis due to high risk clinical deterioration associated to possibility of hemorrhagic transformation in ischemic stroke or hematoma expansion or re-bleeding in hemorrhagic stroke. Therefore, although the majority of the latest available guidelines [37-39], sustains to start pharmacological prophylaxis as soon as possible after the clinical and radiological evidence of stability, for many years guidelines have suggested to perform mechanical prophylaxis in these subjects [40]. In the recent past, however, a RCT, named CLOTS I, aimed to evaluate the effectiveness of GCS versus placebo in patients with stroke (41), failed to demonstrate the effectiveness of GCS (symptomatic DVT 2.9% vs. 3.4%, OR 0.84, 95% CI: 0.53-1.31; asymptomatic DVT 7.2% vs. 7.1%, OR 1.01, 95% CI: 0.4-1.36) and it has even shown that GCS significantly increase skin lesions induced by compression (5.1% vs. 1.3%, OR 4.18, 95% CI: 2,40-7.27) [41]. However, the CLOTS I study showed the superiority of GCS over placebo in preventing distal DVT, PE and 30-day mortality [41]. After CLOTS I, CLOTS II study, aimed to compare the effectiveness of GCS positioned to the root of the thigh against those located below knee [42], showed the superiority of the first over the second (proximal DVT incidence of 6.3% in the complete GCS against 8.8% in the below-knee group, OR 0.69, 95% CI: 0.53-0.91) without, however demonstrate superiority of complete GCS against the below-knee GCS in terms of a significant reduction of distal DVT, PE and 30-day mortality [42].

Finally the CLOTS III study showed a significant reduction of DVT in patients affected by stroke treated with IPC vs placebo in 2876 stroke patients, with a median age of 76 years, . The primary outcome (proximal DVT) occurred in 8.5% (n=122/1438) of patients allocated IPC and in 12.1% (n=174/1438) patients allocated no IPC with an absolute reduction in risk of 3.6% (95% CI: 1.4-5.8%) [43]. Table 3 summarizes the main findings of CLOTS trials.

**Table 3. 30-days symptomatic venous thromboembolism rate in CLOTS trials**

Trial	Incidence				P value	ARR	RRR
	GCS root of the thigh	GCS below knee	IPC	placebo			
CLOTS I	10.0%			10.5%	ns	0.5%	-2%
CLOTS II	6.3%	8.8%			0.008	2.5%	-31%
CLOTS III			8.5%	12.1%	0.001	3.6%	-35%

*Legend: GCS=graduated compression stockings; IPC= intermittent pneumatic compression; ARR=absolute risk reduction; RRR=relative risk reduction*

For many years hemorrhagic stroke has been considered a medical condition with an absolute contraindication to VTE pharmacological prophylaxis and this is still true for a lot of Scientific Societies [44]. In the last 30 years, less than ten clinical studies aimed to analyze

efficacy and safety of pharmacological prophylaxis in this context have been published [44]. Many of these studies enrolled little sample sizes and were not randomized neither controlled. Despite some Scientific Societies [39,47-49] now recommend to start the pharmacological prophylaxis at the time of demonstration of bleeding cessation, it should be remarked that these recommendations are based upon two or three of the mentioned studies, overall enrolling less than 150 patients.

Mechanical prophylaxis is still suggested as a first choice prophylaxis in these patients by all the Scientific Societies that have faced the problem and this strategy should be started at the time of hospitalization and associated or not to pharmacological prophylaxis [44,45-52]. CLOTS I and II studies have included a lot of patients with hemorrhagic stroke, but it is not yet known whether this group of patients presented different results to those with ischemic stroke and therefore at present the only possible claim is that even in the hemorrhagic stroke GCS alone is not effective in the prophylaxis of VTE [41,42]. Subgroups analysis of CLOTS III showed that IPC was particularly effective in reducing VTE in hemorrhagic stroke. In this study, the 163 hemorrhagic stroke patients treated with IPC, the rate of VTE was 6.7% while it was 17% in the 159 patients not undergone to IPC [OR 0.36, 95% CI: 0.17-0.75, absolute risk reduction (ARR) 10.3%, RRR 64%] [43]. It should be emphasized that these findings are consistent with a previous study (named VICTORIAh) in which the combination of IPC plus GCS resulted significantly more effective in reducing the incidence of VTE compared with GCS alone (15.9% vs. 4.7%,  $p < 0.05$ ) [53].

The findings of the literature on mechanical prophylaxis of VTE in patients with ischemic stroke and hemorrhagic stroke have recently been subjected to a Cochrane systematic review [54]. This Cochrane review, which also considers the CLOTS I study, concludes for the lack of efficacy of mechanical devices in reducing DVT events and total mortality compared to placebo. In particular the abovementioned revision shows that while this assertion is absolutely true for GCS, with regard to the IPC exists a trend toward a reduction of the events of DVT to the limits of statistical significance (OR 0.45, 95% CI: 0.19-1.10) but not towards a reduction in mortality [54].

Much recently findings from the LIFENOX study have been published in which the efficacy in terms of reduction in all causes of mortality and safety in terms of bleeding events association was tested between enoxaparin 40 mg/day plus GCS against GCS alone [55]. The study, conducted in seven countries (China, India, Korea, Malaysia, Mexico, Philippines, Tunisia), did not show any statistically significant differences between the two regimens compared during follow-up at 14 (2.9 vs. 2.9%, RR 1.0, 95% CI: 0.8-1.3,  $p = 0.95$ ), 30 (4.9 vs. 4.8%, RR 1.0, 95% CI: 0.8-1.2,  $p = 0.81$ ) and 90 days (8.4 vs. 8.6%, RR 1.0, 95% CI: 0.8-1.1,  $p = 0.71$ ) [55]. The study showed no significant differences either in relation to mortality rate due to cardiopulmonary sudden deaths or deaths from PE and major bleeding, while the rate of minor bleedings was significantly higher in the enoxaparin-GCS group (1.8% vs. 1.1%, RR 1.5, 95% CI: 1.1-2.2,  $p = 0.02$ ) (54). However, it should be remarked that is not possible to extrapolate the rate of non-fatal VTE (DVT and non fatal PE) from published data and therefore if there were significant differences in these endpoints using the two strategies. Despite the surprising findings from the LIFENOX study, the Authors raise important possible limitations that should give pause before the extrapolation of data from this study in clinical practice. Firstly, the Authors emphasize the possibility of statistical limits since than the expected mortality was higher than that observed (7% vs. 4.8%), thus entailing a possible underestimation of the protective effect of pharmacological prophylaxis in reducing mortality. Secondly, it is pointed out by the Authors the ethnic difference of study population, as already mentioned non-Caucasian, which may result in differences in the incidence of

VTE and response to prophylactic strategies used in this study compared to previous trials conducted in Caucasians [8-10]. Moreover, the Authors of the LIFENOX study recognize that the study population had an average age younger of around 10 years, an averaged Body Mass Index lower than 2 points and a representation of lower of around 10 percent of patients with previous episodes of VTE compared to that of previous trials such as the MEDENOX [8]. Additionally in the LIFENOX study data on mobility were not reported [55]. Advanced age, obesity, previous VTE and reduced mobility are in fact among the main VTE risk factors; the absence or, at least, the reduced distribution in the study population of these factors could mean much in terms of lack of efficacy of pharmacological prophylaxis. Sub-analysis of large trials on pharmacological prophylaxis in the medical settings has shown that in the abovementioned subgroups the use of LMWH or fondaparinux have advantages [8-10]. Finally, the Authors emphasize that the aim of the LIFENOX study was the search for fatal VTE events and therefore they may have lost asymptomatic and symptomatic non-fatal VTE events, on which the pharmacological prophylaxis has amply demonstrated its efficacy [8-10].

## **5. NON PHARMACOLOGICAL VTE PROPHYLAXIS IN ILL MEDICAL PATIENTS: GUIDELINES**

Based on the available evidence, mainly from clinical studies conducted in patients with stroke in the acute phase and based on data from literature surveyed until April 2011, the American College of Physicians (ACP) in the latest published guidelines suggest to not use GCS for VTE prophylaxis in hospitalized ill medical patients, both suffering from ischemic or hemorrhagic stroke and affected by other non cerebrovascular diseases, with a strong recommendation of moderate quality [48]. In patients at high risk of bleeding, when pharmacological prophylaxis is contraindicated, the ACP guidelines recommend the use of VTE mechanical prophylaxis by IPC based on evidence from studies of surgical patients but underlining the lack of clinical trials in medical patients [48].

In February 2012 ninth revision of the ACCP guidelines was published. The Authors suggest to make the earliest possible VTE prophylaxis with pharmacological strategies (LMWH as the first choice, UFH as second choice) or using IPC in patients with ischemic stroke who have mobility restrictions [49]. In some individuals at highest risk of VTE, combination of IPC and pharmacological prophylaxis may be indicated [49]. The same Authors declare themselves against (recommendation IIB) the use of GCS [49]. In patients with cerebral hemorrhage and restriction of mobility, IX Edition ACCP guidelines recommend (recommendation IIC) to perform prophylactic pharmacological strategies (LMWH or UFH, the first to prefer) to start between the second and fourth day or with the use of the IPC [49]. Again, we underline that IX Edition ACCP guidelines base their recommendations on three studies respectively published in 1988, 1991 and 2009 [56-58]. The first two studies analyzed together 68 patients treated with UFH started in the second, fourth and tenth day. The last study compared 39 patients treated with enoxaparin 40 mg/day started on the third day with 36 patients treated with GCS. This study found no re-bleeding within the brain or expanding hematoma in both groups, 3 DVT and 1 asymptomatic PE in the enoxaparin group vs 1 asymptomatic DVT and 1 symptomatic PE in the GCS group [58]. Even in hemorrhagic stroke, IX Edition ACCP is against (recommendation IIB) the use of GCS. In selected highest risk hemorrhagic stroke patients the combination of pharmacological prophylaxis and IPC is recommended [49]. Table 4 summarizes the latest guidelines on VTE prophylaxis in hemorrhagic stroke patients.



**Table 4. Summary of latest guidelines on VTE prophylaxis in hemorrhagic stroke patients**

<b>Organization (reference)</b>	<b>Year</b>	<b>Recommended regimen for DVT/PE prophylaxis</b>	<b>Level of evidence</b>
NICE [45,46]	2008 (Stroke) 2010 (VTE)	Pharmacological prophylaxis is NOT recommended to prevent DVT/PE in hemorrhagic stroke patients. Do not offer anti-embolism stockings for VTE prophylaxis; consider offering a foot impulse or intermittent pneumatic compression device.	GPP
AHA/ASA [47]	2010	IPC /GCS as soon as possible UFH/LMWH after demonstration of bleeding cessation	I B IIbB
ACP [48]	2011	Pharmacologic prophylaxis with heparin 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
ACCP [49]	2012	Pharmacological prophylaxis with LMWH or UFH started between days 2 or 4 or mechanical prophylaxis with IPC is indicated. Prophylaxis with LMWH should be preferred over UFH. ACCP recommends against mechanical prophylaxis with GCS.	IIC IB IB
Asian VTE guidelines [50]	2012	Patients at high risk of bleeding such as those with intracerebral hemorrhage 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.	GPP
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 [51]	2013	IPC combined with GCS is recommended	Moderate
Sociedad Española de Neurología Study Group for Cerebrovascular Diseases [52]	2013	2 IPC combined with GCS is recommended in the first 24 hours After 24 hours LMWH could be administered	IB IIbB

In non cerebrovascular patients at high risk of VTE without active bleeding or bleeding risk, the IX Edition ACCP guidelines recommend the use of pharmacological strategies (IB

recommendation) [49], whereas in low risk patient these guidelines are against prophylactic strategies [7]. In patients with active bleeding or high bleeding risk, IX Edition ACCP guidelines recommend against the use of pharmacological prophylaxis (IB recommendation) and suggest the use of mechanical prophylaxis with GCS or IPC (recommendation IIC), pointing to switch toward pharmacological prophylaxis when bleeding stops or the risk of bleeding reduces (Recommendation IIB) [7]. The same type and grade of recommendation is extended to the critical care patient [7].

## **6. CONCLUSION**

Non pharmacological VTE prophylaxis represents a not negligible option for hospitalized ill medical patients since than many patients could have contraindications to pharmacological prophylaxis, but literature lacks in evidence and guidelines are not standardized. Many questions are unresolved. Early mobilizations should be always encouraged but its standardization in clinical practice seems difficult to extend. Vein cava filters are a possible choice in a little percentage of patients and their use could be associated to many potentially fatal complications. Mechanical prophylaxis is a real possibility, but results of clinical trials in non surgical patients disagree. GCS seem clearly to be ineffective in stroke patients but seem to be a real possibility in non cerebrovascular patients with active bleeding or at high risk of bleeding. IPC could be the most effective mechanical strategy but studies on medical patients lack and its widespread in medical setting is limited in many countries. Concerns also exist when to start and for how much time to extend mechanical prophylaxis, especially after hospital discharge and whether combination of subtypes of mechanical prophylaxis with pharmacological strategies effectively reduce the risk of VTE compared with single strategies. Therefore studies on hospitalized medical patients seem warranted in this context.

## **CONSENT**

Consent is not required for this study.

## **ETHICAL APPROVAL**

Ethical approval is not required for this study.

## **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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