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PROF-ETEV study: prophylaxis of venous thromboembolic disease in critical care units in Spain

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For the PROF-ETEV study investigators.

The members of the PROF-ETEV study investigators are given in the "Appendix".

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Abstract *Purpose:* Venous thromboembolic disease (VTE) in critically ill patients has a high incidence despite prophylactic measures. This fact could be related to an inappropriate use of these measures due to the absence of specific VTE risk scores. To assess the current situation in Spain, we have performed a cross-sectional study, analyzing if the prophylactic measures were appropriate to the patients' VTE risk. *Methods:* Through an electronic questionnaire, we carried out a single day point prevalence study on the VTE prophylactic measures used in several critical care units in Spain. We performed a risk stratification for VTE in three groups: low, moderate–high, and very high risk. The American College of Chest Physicians guidelines were used to determine if the patients were receiving the recommended prophylaxis. *Results:* A total of 777 patients were included; 62 % medical, 30 % surgical, and 7 % major trauma patients. The median number of the risk factors for VTE was four. According to the proposed VTE risk score, only 2 % of the patients were at low risk, whereas 83 % were at very high risk. Sixty-three percent of patients received pharmacological prophylaxis, 12 % mechanical prophylaxis, 6 % combined prophylaxis, and 19 % did not receive any prophylactic measure. According to criteria suggested by the guidelines, 23 % of medical, 71 % of surgical, and 70 % of major trauma patients received an inappropriate prophylaxis. *Conclusions:* Most critically ill patients are at high or very high risk of VTE, but there is a low rate of appropriate prophylaxis. The efforts to improve the identification of patients at risk, and the implementation of appropriate prevention protocols should be enhanced.

Keywords
Venous thromboembolic disease · Critically ill patients · Antithrombotic therapy · Critical care unit

Introduction

Venous thromboembolic disease (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is currently the main preventable complication in hospitalized patients [1]. Although its incidence has decreased from 30–60 to 5–10 % [2–4] after the introduction of routine VTE prophylactic measures, it remains a common clinical entity in critically ill patients.

For over 20 years, the American College of Chest Physicians (ACCP) has been regularly publishing guidance on VTE prophylaxis [5]. However, the first guidelines including specific recommendations for critically ill patients are relatively recent [6]. In general, these recommendations include the use of pharmacological prophylaxis as the main preventive measure, leaving mechanical prophylaxis for patients at high risk of bleeding.

The appropriate prescription of thromboprophylaxis can improve VTE prevention and has been proposed as a cost-effective strategy [7]. It has also been considered as an indicator of both health care quality and patient safety [8]. However, recent epidemiological studies show a poor implementation of the prophylactic measures proposed in the guidelines [9–12].

Little data regarding compliance with VTE prophylaxis recommendations in critically ill patients are available in Spain. The purpose of this study was to describe the VTE prophylactic measures actually used, as well as to determine if their use was appropriate in accordance with ACCP 2012 guidelines [13, 14].

Methods

The PROF-ETEV study was a multicenter, epidemiological, and cross-sectional study performed in patients admitted to different critical care units in Spain. A coordination committee ("Appendix") was responsible for the selection of the most relevant units in the country, which were sent the study protocol. The subsequent electronic questionnaire (e-CRF) was sent to those who chose to participate. This e-CRF format was considered appropriate to obtain the required data, as it had been previously used in prior epidemiological studies [12, 15].

The patients' anonymity was strictly maintained in e-CRF and in the corresponding database. The Ethical Committee of Clinical Research of Gregorio Marañón University Hospital reviewed and approved the study protocol in June 2013 and waived the need for informed consent. Finally, on 26 June 2013 a single day point prevalence study on actual VTE prophylactic measures was carried out.

Inclusion criteria

Patients over 18 years old admitted to units at 10:00 a.m. on the survey day.

Exclusion criteria

Patients receiving any type of anticoagulation or with a diagnosis of VTE disease.

Collected data

1. Units' data: number of beds, number of patients admitted with systemic anticoagulation or VTE disease, as well as the use of some VTE prophylaxis protocol within the unit.
2. Patients' data: epidemiologic data, reason for admission (medical, surgical, or major trauma pathologies), specific data related to their stay in the unit (disease severity, mechanical ventilation, vasopressor drugs), risk factors for VTE, and risk factors for bleeding [13, 14, 16–23], as well as the VTE prophylactic measures actually used: pharmacological [low dose unfractionated heparin (LDUH), low molecular weight heparin (LMWH) and others]; mechanical [intermittent pneumatic compression (IPC) and graduated compression stocking (GCS)], and combined (pharmacological and mechanical measures simultaneously).

Risk stratification for VTE

In the absence of VTE risk scores for critically ill patients, we performed a risk stratification based on the algorithm proposed by Laport and Mismetti [16], to which the modified risk assessment proposed by Caprini [19, 20] was associated, as it contains a very high risk group (DVT rate 40–80 %), wherein many of the critically ill patients could be included [2]. Thus, three groups of patients were established: low risk, moderate–high risk (receiving the same type according to ACCP 2012 guidelines), and very high risk patients (Table 1).

Risk of bleeding

The patients were considered at high risk of bleeding if they had either multiple risk factors (bleeding risk score >7), or one of the three risk factors most strongly associated with bleeding according to the IMPROVE study [13, 21]: active gastroduodenal ulcer, bleeding within the 3 months prior to admission, or platelet count no greater than 50,000 mm^3.

Table 1 Risk stratification for VTE disease and the ACCP 2012 recommendations

Stable patient[1] 1. Without vasoppresor theraphy 2. Without mechanical ventilation 3. Without acute cardiac pathology 4. Without acute respiratory pathology	**Apply Caprini modified Score**[2]	Medical pathology	Low risk Caprini score < 1	No prophylaxis	1B
			High risk Caprini score ≥ 2	Conventional prophylaxis	2C
		Surgical pathology	Moderate-High risk* Caprini score 2-4	Conventional prophylaxis	1B
			Very high risk Caprini score ≥ 5	Combined prophylaxis	2C
		Major Trauma pathology	Moderate-High risk * Caprini score 2-4	Conventional prophylaxis	1B
			Very high risk Caprini score ≥ 5	Combined prophylaxis	2C
Unstable patient[1] 1 Vasoppresor theraphy 2 Mechanical ventilation 3 Acute cardiac patjology 4 Acute respiratory pathology		Medical pathology	High risk Caprini score ≥ 2	Conventional prophylaxis	2C
		Surgical pathology	Moderate-High risk* Caprini score 2-4	Conventional prophylaxis	1B
			Very high risk Caprini score ≥ 5	Combined prophylaxis	2C
		Major Trauma pathology	Moderate-High risk* Caprini score 2-4	Conventional prophylaxis	1B
			Very high risk Caprini score ≥ 5	Combined prophylaxis	2C
1 Based on algorithm proposed by Laport S. and Mismetti P. [16] 2 Caprini modified score [19, 20] 3 ACCP 2012 recommendations [13,14] Conventional prophylaxis: pharmacologycal or mechanical prophylaxis Combined prophylaxis: pharmacologycal and mechanical prophylaxis together					ACCP 2012[3]

[2] Adaptation of Caprini modified score

1 Point	2 Points	3 Points	5 Points
Age 41-60 years	Age 61-74 years	Age over 75 yeras	Elective arthroplasty
Minor surgery	Major surgery or laparoscopic surgery (> 45 min)	History of VTE	Hip, pelvis, or leg fracture
Prior major surgery (< 1 months)	Arthroscopic surgery	Any Thrombophilia	Acute spinal cord injury
Varicose veins or swollen legs	Malignancy		Stroke
Inflamatory bowel disease	Confined to bed (> 72 h)		Multiple trauma
Swollen legs	Immobilizing plaster cast		
Obesity (BMI>25)	Central venous access		
Acute myocardial infarction			
Congestive heart failure (< 1 months)	**0-1 points ---------- Low risk** **2 points ---------- Moderate risk** **3-4 points ---------- High risk** **≥ 5 points ---------- Very high risk**		
Sepsis (< 1 months)			
Lung disease (< 1 months)			
Abnormal pulmonary function (COPD)			
Medical patient at bed rest	* We have combined the moderate and high-risk groups due to the ACCP guidelines recommended the same type of prophylaxis (conventional prophylaxis)		
Pregnancy, postpartum or recurrent spontaneous abortion			
Oral contraceptives or hormone replacement			

Contraindications to pharmacological prophylaxis

The following clinical situations were considered as contraindications: active gastroduodenal ulcer, bleeding on admission, intracranial hemorrhage, major surgery, major trauma, platelet count no greater than 50,000 mm^3, and severe coagulopathy (aPTT ratio or INR >2).

Contraindications to mechanical prophylaxis

The following clinical situations were considered as contraindications: dermatitis, ulcers, edema, and severe peripheral vascular disease.

Adequate prophylaxis consideration

This was based on ACCP 2012 recommendations [13, 14] (Table 1).

Statistical analysis

As a result of the characteristics of the study only a descriptive analysis was performed. The Kolmogorov–Smirnov test was used to analyze if quantitative variables were adjusted to normal, in which case they were expressed as a mean (standard deviation), and otherwise expressed as a median (interquartile range). Analysis of qualitative variables was expressed as a number and percentage.

IBM® SPSS® Statistics version 21 was used for all statistical analyses.

Results

Seventy-three out of the 83 critical care units initially selected (88 %) participated in the study. Most of the units were medical-surgical (86 %) and belonged to level III hospitals (72 %). Only 35 % (26 units) used a VTE prophylaxis protocol and 11 % (8 units) reported the use of a VTE risk score.

A total of 972 patients were admitted on the survey day (median 12, IQR 6–17). One hundred and ninety-five patients (20 %) were excluded: 174 (17.7 %) were receiving anticoagulation and 23 (2.3 %) had been diagnosed with VTE disease.

Seven hundred and seventy-seven patients were finally included; their characteristics are summarized in Table 2. It should be noted that 62 % of patients (481/777) presented some medical pathology at admission; 23.6 % (183/777) were receiving vasopressor therapy; 43 % (333/777) required invasive mechanical ventilation; and 6.3 % (43/777) required non-invasive mechanical ventilation. Median length of unit stay up to the survey date was 5 days (IQR 2–12).

Risk factors for VTE, before admission and during hospitalisation, are shown in Table 3. Patients exhibited a median of four risk factors for thrombosis (IQR 3–6). According to the VTE risk score proposed, 16 patients (2.1 %) were at low risk, 115 (14.8 %) at moderate–high risk, and 646 (83.1 %) at very high risk, including 362 (46 %) of medical patients (Table 3).

Two hundred patients (26 %) were considered at high risk of bleeding and 214 patients (27.5 %) had pharmacological prophylaxis contraindications, mainly due to recent major surgery, thrombocytopenia, and coagulopathy (see the electronic supplementary material).

Figure 1 summarizes the VTE prophylactic measures actually used. Eighty-one percent of the patients (627/777) were receiving some prophylactic measure: 78.6 % (378/481) of the medical patients, 84.3 % (199/236) of the surgical patients, and 83.3 % (50/60) of the major trauma patients. Time elapsed before the application of any prophylactic measure was 1 day (IQR 0–1), although in 25 % of major trauma patients prophylaxis was delayed until the third day (median 1 day, IQR 1–3).

Pharmacological prophylaxis was the most common prophylactic measure, as it was used in 78.3 % (491/627) of the patients. Overall, pharmacological prophylaxis was administered to 92.5 % (521/563) of the potentially suitable patients. LMWH was almost the only pharmacological agent used (97 %, 477/491). Time taken until pharmacological prophylaxis application was 1 day (IQR 1–3), although in 25 % of patients with major trauma it was delayed until the seventh day (median 3 days, IQR 1–7). Enoxaparin (76.8 %) and bemiparin (18.4 %) were the most common forms of LMWH used.

LMWH dose was adjusted by anti-Xa factor level in only four patients (0.8 %), although a different dose than the usual was administered in 78 patients (15 %), mainly as a result of severe renal failure (6.6 %), high risk of bleeding (2.7 %), obesity (2.9 %), and high risk of VTE (2.9 %). Up to the survey day only six patients with pharmacological prophylaxis had suffered bleeding complications (1.1 %). There was a suspicion of heparin-induced thrombopenia in 15 patients (2.8 %), although it was only confirmed in two cases (0.4 %).

Mechanical prophylaxis was used in 15 % of all patients (94/627), but only in 39 % (82/214) of the potentially suitable patients, as a result of pharmacological prophylaxis contraindications. The most common form of mechanical prophylaxis was IPC, used in 77 % of patients (105/136). Some contraindication for mechanical devices was reported in 4.6 % of the patients (36/777), mainly as a result of severe injury in lower extremities or peripheral vascular disease.

Table 2 Characteristics of the study population related to the reasons for admission

	Patients, *N* (%)	Age	Sex (male), %	APACHE II	SOFA admission	SOFA survey day	Vasopressor therapy, *N* (%)	Mechanical ventilation, *N* (%)
Medical pathology	481 (61.9 %)	62 ± 14	64 %	18 ± 9	6 ± 4	4 ± 4	123 (25.5 %)	215 (45.2 %)
Surgical pathology	236 (30.4 %)	62 ± 15	64 %	16 ± 8	5 ± 4	3 ± 3	50 (21 %)	81 (35.2 %)
Major trauma pathology	60 (7.7 %)	49 ± 19	79 %	15 ± 7	5 ± 3	4 ± 3	16 (24.4 %)	37 (56 %)
Total	777	61 ± 15	65 %	17 ± 8	6 ± 4	4 ± 4	183 (23.6 %)	333 (43 %)

APACHE II Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment

Table 3 Risk factors and risk score for venous thromboembolism

	Medical pathology, *N* (%)	Surgical pathology, *N* (%)	Major trauma pathology, *N* (%)	Total, *N* (%)
Risk factors for venous thromboembolism before admission in the unit[a]				
Immobility	200 (42 %)	69 (30 %)	18 (29 %)	287 (37 %)
Age >70 years	166 (35 %)	85 (37 %)	9 (16 %)	260 (33 %)
Recent surgery	42 (9 %)	107 (46 %)	10 (18 %)	159 (21 %)
Active cancer	57 (12 %)	62 (27 %)	1 (2 %)	120 (15 %)
Obesity (BMI >25)	61 (13 %)	20 (9 %)	2 (4 %)	83 (11 %)
Chronic pulmonary disease	34 (7 %)	15 (6 %)	2 (4 %)	51 (7 %)
Chronic heart failure	39 (8 %)	7 (3 %)	–	46 (6 %)
Previous VTE	11 (2 %)	5 (2 %)	–	16 (2 %)
Risk factors for venous thromboembolism during stay in the unit[b]				
Central venous catheter	348 (73 %)	208 (90 %)	57 (93 %)	613 (79 %)
Immobility >48 h	329 (69 %)	148 (64 %)	44 (72 %)	521 (67 %)
Mechanical ventilation	228 (48 %)	92 (40 %)	39 (62 %)	359 (46 %)
Sedation	181 (38 %)	70 (30 %)	38 (62 %)	289 (37 %)
Vasopressors	133 (28 %)	50 (21 %)	12 (20 %)	195 (25 %)
Sepsis	131 (27 %)	54 (23 %)	–	185 (24 %)
Acute heart failure	115 (14 %)	–	–	115 (14 %)
Stroke	61 (13 %)	24 (10 %)	–	85 (11 %)
Multiple transfusions	43 (9 %)	23 (10 %)	11 (18 %)	77 (10 %)
Paralytic agents	38 (8 %)	11 (5 %)	12 (22 %)	61 (8 %)
Renal replacement therapy	40 (8 %)	15 (6 %)	–	55 (7 %)
Acute respiratory failure	27 (6 %)	–	–	27 (6 %)
VTE risk score[c]				
Low risk				
Stable patient Caprini score ≤1	16 (3.4 %)	–	–	16 (2.1 %)
Moderate–high risk				
Unstable or stable patient Caprini score 2–4	103 (21.4 %)	12 (5 %)	–	115 (14.8 %)
Very high risk				
Unstable or stable patient Caprini score ≥5	362 (75.3 %)	224 (95 %)	60 (100 %)	646 (83.1 %)

[a] Based on [16–19]
[b] Based on [24]
[c] Based on [16, 19, 20]

Combined prophylaxis was used in 6.7 % of patients (42/627), mainly in major trauma patients (14 %) and surgical patients (10 %). The most common combination was an IPC device with an LMWH (80.5 %). In patients at very high risk of VTE only 9.5 % (27/284) received this prophylactic modality, excluding medical patients, as its use in such patients is not currently recommended.

One hundred and fifty patients (19.3 %) did not receive any prophylactic measure. The absence of prophylaxis was more frequent in medical patients (21.4 %) than in surgical (16.7 %) or major trauma (16.7 %) patients. Note that 75 % of patients without prophylaxis (117/150) had pharmacological prophylaxis contraindications.

According to the proposed VTE risk stratification (Table 1) and the ACCP 2012 recommendations, 23.3 % (112/481) of medical patients, 71.3 % (168/236) of surgical patients, and 70 % (42/60) of major trauma patients were being administered an inadequate prophylaxis.

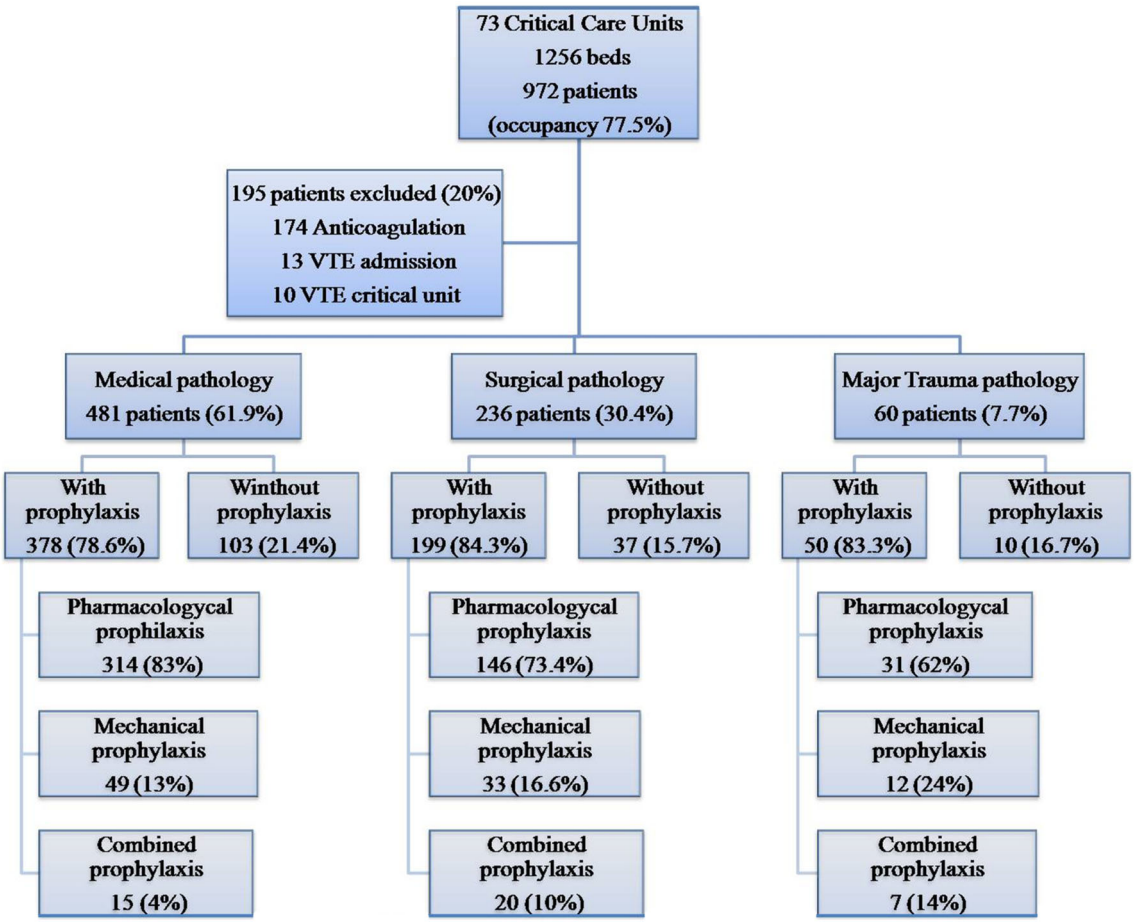

Fig. 1 VTE prophylactic measures actually used in critical care units in Spain

Discussion

The PROF-ETEV study is the first national record of VTE prophylactic measures used in critically ill patients carried out in Spain. It is also an attempt to evaluate the appropriateness of VTE prophylaxis prescriptions according to the guidelines in a wide variety of critical care units.

In agreement with previous studies [9–12] we found a poor guideline adherence. Our data show that VTE prophylactic measures were improperly used in a significant number of patients (42 %). The most serious failure to comply was observed in 19 % of patients that did not receive any prophylactic measure at all. There was a poor use of mechanical prophylaxis, only used in a third of the patients with indication, as well as an infrequent use of combined prophylaxis, used only in 11 % of the patients at very high risk of VTE.

Only 36 % of the units reported the use of some VTE prophylaxis protocol, far from the ACCP recommendations [14, 15] and the compliance of quality indicators proposed by our national scientific society [8]. In the absence of VTE risk scores for critically ill patients we have proposed a risk stratification (Table 1), including risk factors for VTE as well as specific clinical situations in critically ill patients [24], in order to improve the selection of the most suitable prophylactic measure. According to this score, a large number of patients would be at very high risk of VTE.

With reference to our results, we conducted a review of the literature on this topic.

Prophylaxis for VTE in critically ill patients

The ACCP 2012 guidelines suggest the use of prophylaxis in the critical patient (grade 2C). Although there are few clinical trials in critically ill patients, which impedes high levels of evidence and recommendation, it is most unlikely that new clinical trials will be developed in this respect. Instead, systematic reviews and meta-analysis could be a useful way to approach this subject. A study by Alhazzani et al. [25], including 7,226 critically ill patients, showed the benefits of pharmacological

prophylaxis versus the absence of any prophylaxis in DVT (RR 0.51, 95 % CI 0.41–0.63) and PE (RR 0.52, 95 % CI 0.28–0.97). Ho and Tan [26], in a study involving 16,164 patients using mechanical prophylaxis due to pharmacological prophylaxis contraindication, showed a reduction in DVT (RR 0.43, 95 % CI 0.36–0.52) and PE (RR 0.48, 95 % CI 0.33–0.69). Finally, in a record of 175,665 critically ill patients of 134 ICUs in Australia and New Zealand, prophylaxis omission on the first day of admission was associated with a mortality increase (OR 1.22, 95 % CI 1.15–1.30) [27].

Pharmacological prophylaxis in critically ill patients

Following the ACCP recommendations (grade 2C), pharmacological prophylaxis with heparin was the most common prophylactic measure. In Spain, as in other European countries [9, 12], LMWH was almost the only drug used. The variability in the use of different heparins reflects the lack of evidence with regards to a greater benefit in medical patients [3, 14, 28], although there seems to be a greater benefit in using LMWH in very high risk surgical and major trauma patients [15]. In this respect, the meta-analysis published by Alhazzani et al. [25] and Kanaan et al. [29] showed a reduction in VTE disease in patients treated with LMWH versus LDUH.

The LMWH mostly used was enoxaparin. There are no clinical trials showing superiority of an LMWH in particular [30] and, therefore, there are no recommendations to this regard [14, 15]. The standard dose of LMWH was the most widely used. Although adjusted in only four patients according to factor anti-Xa levels, in a significant percentage of patients (15 %) a different dose was used. This was dependent on specific clinical features such as renal failure, obesity, and a high risk of VTE or bleeding. Currently, guidelines do not recommend routine use of factor anti-Xa levels to adjust LMWH dose [14, 15, 31], although controversy still exists [32–34]. However, the administration of repeated doses of enoxaparin in patients with renal function impairment could produce accumulation of the drug, and a decrease in dose would be justified [31]. In our study the LMWH dose was adjusted only in 30 % of patients with renal failure.

Mechanical prophylaxis in critically ill patients

In patients with pharmacological prophylaxis contraindications, the ACCP guidelines suggest (grade 2C) the use of mechanical prophylaxis [14, 15]. A quarter of the patients analyzed had a high risk of bleeding and/or other pharmacological prophylaxis contraindication. However, only a small percentage of these patients received mechanical prophylaxis [35].

In Spain, the most common form of mechanical prophylaxis was the IPC. A recent randomized trial specifically designed to evaluate the potential benefit of GCS or IPC in ICU patients with a high risk of bleeding did not find differences between these mechanical devices [36]. A recently published meta-analysis (RR 0.43, 95 % CI 0.36–0.52) [25] and a prospective cohort study (HR 0.45, 95 % CI 0.22–0.95) [37], have shown the effectiveness of IPC, but not of GCS, to reduce DVT in medical or surgical critically ill patients. Nevertheless, in certain groups of patients, such as surgical and major trauma patients with very high risk of VTE, there seems to be a greater benefit with IPC, which is, therefore, suggested by the guidelines [15]. Lastly, we refer to the CLOTS-3 trial [38], a multicenter, randomized study, whose objective was to assess the efficacy of an IPC device in immobile patients with acute stroke, showing a reduction of DVT and mortality.

Combined prophylaxis in critically ill patients

Guidelines suggest the use of combined prophylaxis in surgical and major trauma critically ill patients at very high risk of VTE (grade 2C) [14]. In the absence of specific clinical trials in this respect, the meta-analyses published by Barrera et al. [39] and Kakkos et al. [40] have shown favorable results to this effect. Results of the CLOTS-3 study [38], where around a third of the patients with IPC had associated pharmacological prophylaxis, lead us to believe that combined prophylaxis could also be effective in certain medical patients at very high risk of VTE. Despite this, in our study only a very small percentage of the patients received combined prophylaxis.

Our results are similar to those from others studies conducted in different countries [9–12]. It seems that, regardless of the local or individual circumstances in each country, improper use of VTE prophylaxis measures in critically ill patients is a widespread problem. We believe this could be partly due to the complexity of the guidelines, caused by the great variety of pathologies present in critically ill patients. We propose a simplified algorithm of VTE prophylaxis (Fig. 2) based on a current literature review, guidelines, and results provided by our study. This may facilitate the implementation of prophylactic measures, thus improving compliance.

Our study has several limitations. Despite the high number of units and patients taking part, the results should not be generalized to all units in the country. The cross-sectional design of the study only allows the assessment of the compliance of prophylactic measures until the survey day. The stratification of the patients' VTE risk, as well as the considerations related to the adequacy of the actual prophylaxis used, based on ACCP 2012 guidelines, derives from the present study's

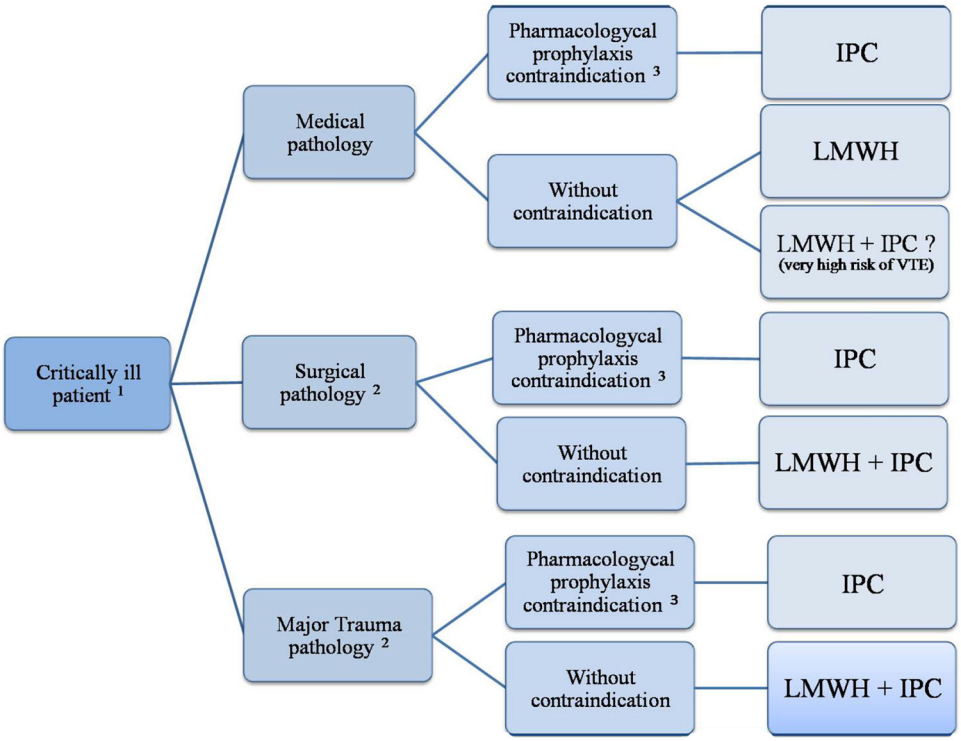

Fig. 2 Simplified algorithm of the VTE prophylaxis in critically ill patients. *IPC* intermittent pneumatic compression, *LMWH* low molecular weight heparin. *1* Every critically ill patient requires prophylaxis. *2* Every surgical or major trauma patient is considered at very high risk of VTE. *3* Daily assessment of the situation to adapt VTE prophylaxis

coordinating committee and is, therefore, subject to discussion.

Conclusions

The PROF-ETEV study emphasizes that most critically ill patients are at high or very high risk of VTE, but there is a low rate of appropriate prophylaxis. The efforts to improve the identification of patients at risk as well as the implementation of appropriate prevention protocols should be enhanced.

Conflicts of interest Pablo Garcia Olivares and Jose Eugenio Guerrero Sanz have participated in several symposiums about venous thromboembolic disease in critically ill patients, organized by Covidien Spain S.L.

Appendix

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