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Commentary

Prevention of venous thromboembolism in critically ill patients: current state and future perspectives

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Venous thromboembolic disease (VTE) is a major complication of intensive care, responsible for significant morbidity and mortality. It remains a constant challenge for clinicians because of the conflicting risks of thrombosis and hemorrhage [1–3]. Identifying thromboembolic events is often complicated by sedation, mechanical ventilation, or the severity of illness. Some thromboses, especially subclinical ones or those linked to intravascular devices, may be underdiagnosed [4]. In this context, implementing appropriate thromboprophylaxis is essential. Proposed strategies have been the subject of repeated recommendations from national and international societies, but these recommendations often diverge and frequently rely on low-level evidence [5–7].

In the first place, it should be underlined the imbalance between the number of available Clinical Practice Guidelines (CPGs) and the small number of underlying Randomized Controlled Trials (RCTs). The prevention of VTE in intensive care constitutes a particularly sensitive domain, taking into account the severity of patients and the coexistence of a high thrombotic and hemorrhagic risk. The limited Evidence-Based Medicine often obliges to group data in order to gain statistical power, at the cost of methodological compromises: joint inclusion of surgical and medical patients although the mechanisms differ, grouping together of all low-molecular-weight heparins (LMWHs) and of all dosages (fixed or adjusted), maintenance of studies of limited quality exposing to bias. These methodological choices lead to heterogeneous and poorly reproducible interpretations, even if the technique of meta-analysis is itself robust. Moreover, regional susceptibility and specificity limit the universal applicability of CPGs emanating from the major international reference societies of the field (ASH, ACCP, NICE). Finally, the elaboration of reliable CPGs in this field requires professionalism, expertise, and considerable means for the synthesis and interpretation of data, explaining the superior quality of the guidelines produced by established societies such as the ACCP, NICE, or ASH, compared with others evaluated by the AGREE II and RIGHT tools.

In this context, the study by Wei et al. brings an important contribution by evaluating in a systematic way the quality of the available CPGs and by carrying out a network meta-analysis of RCTs comparing different pharmacological and mechanical approaches of prevention of VTE in critically ill patients [8]. The authors show that the methodological quality of the CPGs is heterogeneous, with poor scores for the implication of stakeholders and for applicability, joining the observations already formulated by other critical evaluations of tools such as AGREE II and RIGHT [9,10]. Only four CPGs (NICE 2019, ACCP 2012, ASH 2018 and 2019) reach a practical value considered high, while most of them consider LMWH as a homogeneous class, without differentiation of molecule nor of dosage [11–14]. This absence of distinction is astonishing, considering the notable differences between LMWH in terms of molecular weight, anti-Xa/anti-IIa ratio and, consequently, pharmacodynamic profile. As an example, enoxaparin presents a ratio of 3.6:1, against 8:1 for bemiparin [6]. These differences are recognized by the regulatory agencies who do not consider LMWH as interchangeable. The absence of distinction in the CPGs thus limits their practical scope and their capacity to orient an individualized therapeutic choice.

The network meta-analysis performed by Wei et al. on 7636 patients

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from 12 RCTs (Fig. 1) does not show any statistically significant difference between the different LMWH, nor between LMWH and unfractionated heparin (UFH), for the prevention of DVT, pulmonary embolism (PE), or composite VTE events [15–26]. A significant reduction in DVT risk is however observed when LMWH are pooled and compared with UFH, with an odds ratio of 0.71 (95 %CI 0.42–0.99), confirming results already suggested by the meta-analyses of Fernando et al. and Eck et al., which also concluded to a relative superiority of LMWH over UFH for DVT in hospitalized or critically ill patients [27,28]. These results corroborate the landmark trial by Fraisse et al., which had shown the efficacy of nadroparin compared with placebo in medical ICU patients [15], but contrast with the XPRESS trial where enoxaparin 40 mg/day had not demonstrated a significant reduction of VTE in septic patients [16]. The great heterogeneity of individual trial results probably reflects problems of dosage and exposure.

Indeed, several recent pharmacokinetic works have shown that the standard LMWH doses often used in intensive care lead to suboptimal anti-Xa levels in a significant proportion of patients [29–32]. The pathophysiological alterations specific to the critical state — capillary leak, subcutaneous edema, hyperinflammation, hypermetabolism — modify absorption and clearance, altering the dose–exposure–effect relationship otherwise well characterized in stable patients [30]. Many authors have thus suggested that a dosage adjustment based on pharmacokinetics could limit these variations and optimize prophylaxis. However, the main obstacle is the absence of any validated target value for anti-Xa activity: there exists no recognized reference threshold, which explains why the CPGs have not integrated this type of approach.

The analysis of Wei et al. also brings to light the structural limits of the available literature. The number of trials remains very low with regard to the diversity of the strategies evaluated. These studies present an often-insufficient power, a marked heterogeneity of the included populations (surgical versus medical), and, in many cases, a methodological quality that is not optimal. In this context, to draw robust conclusions for a given molecule or a given dosage is extremely difficult. The grouping of LMWH within a same therapeutic class seems to constitute the most cautious approach, in the image of the NICE and ASH recommendations, whereas to associate heterogeneous dosing regimens (fixed doses versus adjusted) exposes to major methodological biases. Indeed, the MEDENOX trial had shown that fixed dosages could turn out to be insufficient in certain populations [33], while the meta-analysis of Grange et al. underlined the potential interest of adjusted regimens in comparison with standard doses in the context of trauma [34].

The question of mechanical alternatives is also addressed by the analysis of Wei et al., which does not find a clear superiority of intermittent pneumatic compression (IPC) in comparison with anticoagulants or with placebo. However, IPC appears as a pertinent option in patients at high hemorrhagic risk, as had shown the CIREA1 trial demonstrating a reduction of DVT with IPC in this specific context [26]. There again, the current recommendations often are content to indicate IPC as an alternative without specifying the modalities of use, the optimal duration, nor the patient profiles the most likely to benefit from it [11,35–37].

The analysis of Wei et al. also brings to light the great fragility of the available safety data. The suggestion of a lower hemorrhagic risk with high-dose UFH relies on a single small-size trial [17], and must therefore be interpreted with caution. In practice, clinicians know that the hemorrhagic risk in intensive care does not reduce itself to the choice of molecule but depends on a multitude of dynamic factors, ranging from coagulopathies induced by inflammation to repeated invasive procedures [3].

Thus, the contribution of this work is multiple: it confirms the relative superiority of LMWH compared with UFH on the criterion of DVT, which justifies their privileged place in intensive care. When refining the analysis, no significant difference could be demonstrated between the different LMWH, whether enoxaparin, nadroparin, dalteparin, or bemiparin. If the latter appeared better ranked in certain ranking analyses and showed a signal of superiority in sensitivity analyses, this result relied on a single monocentric trial of small scale [24], and must be interpreted with caution. In practice, LMWH therefore constitute the first option in the absence of contraindication, UFH remains an alternative in patients with severe renal failure, and IPC imposes itself in case of major hemorrhagic risk, but these choices reflect more clinical compromises than genuine scientific evidence.

Future research should be oriented along several axes. The realization of pragmatic multicenter randomized trials — with all the difficulties of conducting such trials in intensive care — remains essential in

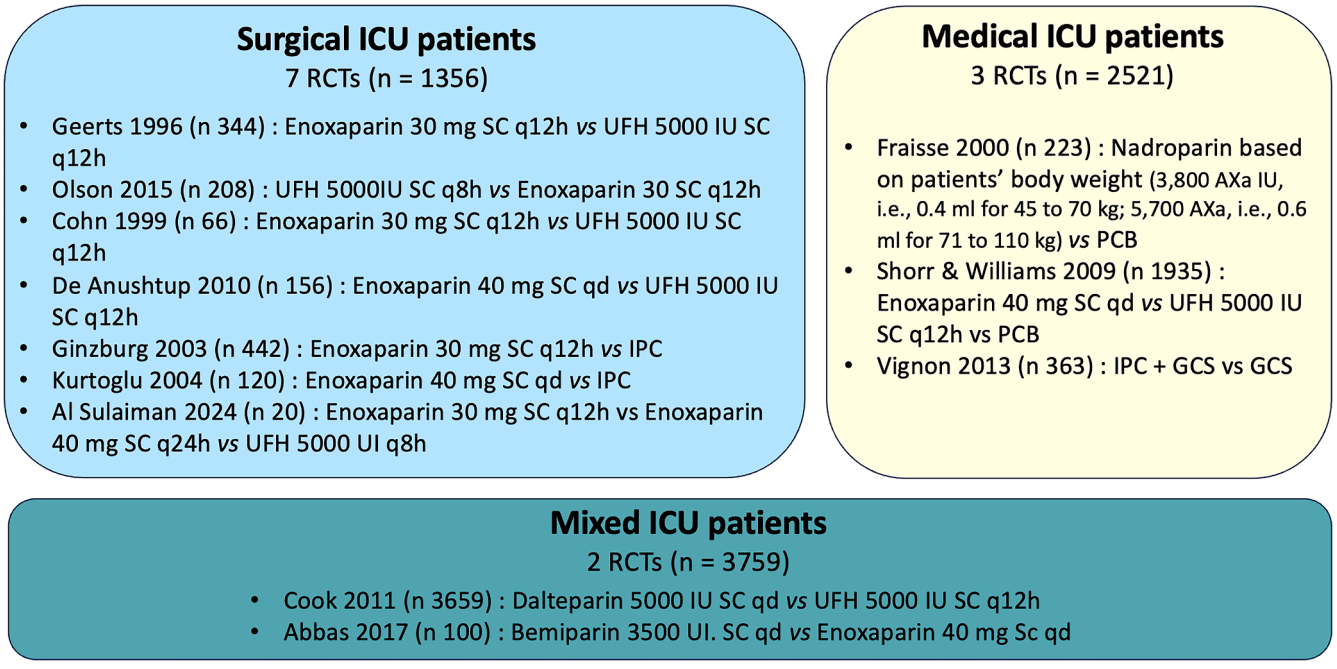

Fig. 1. Included RCTs (Wei et al., EJIM 2025) — ICU VTE prophylaxis.
PCB: placebo, IPC: intermittent pneumatic compression, GCS: graduated compression stockings, UFH: unfractionated heparin.

order to refine optimal prophylactic strategies. The evaluation of individualized protocols, integrating the characteristics specific to each patient (weight, body mass index, inflammatory state, renal function), represents a particularly promising approach [29–32]. Modeling could contribute to identifying a target range in terms of hemorrhagic and thromboembolic risk for anti-Xa activities, and thus propose an individualized dosing adjustment scheme taking into account patient-specific characteristics.

It now seems essential to make a finer distinction between patients in medical intensive care and those in surgical intensive care, as their pathophysiological profiles and risk patterns differ significantly. Moreover, the potential value of combined strategies associating pharmacological and mechanical prophylaxis deserves to be confirmed by randomized controlled trials with sufficient statistical power.

In this perspective, several clinical trials are currently ongoing (NCT05487066, NCT00493896, NCT06958588, NCT02396732).

Finally, the emergence of new classes of anticoagulants targeting factor XI opens new perspectives. By potentially dissociating physiological hemostasis from pathological thrombosis, these therapeutic agents could redefine thromboembolic prevention strategies in this population. Indeed, they have demonstrated in phase II and III trials an efficacy comparable to, or even superior to, conventional anticoagulants, while being associated with a significantly reduced risk of bleeding. The potential of these new factor XI–targeting agents, however, will need to be clarified through dedicated clinical trials in this population [38].

In summary, Wei et al. remind that the prevention of venous thromboembolism in critically ill patients remains a complex and still poorly defined issue, due to the lack of dedicated trials, the methodological variability of existing studies, and the absence of solid data to guide practice. This uncertainty fully justifies the implementation of multicenter and pragmatic trials, able to specify the most effective strategies and to translate them into truly operational recommendations at the patient's bedside.

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