Editorial Commentary

Efficacy and safety profiles of mechanical and pharmacological thromboprophylaxis

Mario Ganau[1], Gianfranco K. I. Ligarotti[2], Marco Meloni[3], Salvatore Chibbaro[4]

[1]Department of Neurosurgery, Oxford University Hospitals, Oxford, UK; [2]Institute of Aerospace Medicine, Milan, Italy; [3]Department of Neurosurgery, Milano-Bicocca University, Milan, Italy; [4]Department of Neurosurgery, University of Strasbourg, Strasbourg, France

Correspondence to: Salvatore Chibbaro, MD, PhD, FEBNS. Department of Neurosurgery, University of Strasbourg, 1 Avenue Molière, F-67098 Strasbourg, France. Email: schibbaro@hotmail.com.

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Venous thromboembolism (VT) has always attracted the attention of the scientific community as one of the most common causes of acquired morbidity and mortality in hospitalized patients. The objective of VT prophylaxis protocols is mostly aimed at preventing deep vein thrombosis (DVT) and pulmonary embolisms (PE). Their incidence may in fact be as high as 20% to 40% in high-risk populations, such as polytraumatized and critically ill patients (1). Although low-dose subcutaneous unfractionated heparin (UFH) or low molecular-weight heparin (LMWH) are estimated to reduce VT incidence by 50% (2), several studies (3-5) have demonstrated that mechanical prophylaxis with elastic compression and intermittent pneumatic compression (IPC) can further reduce the incidence of DVT/PE, and are widely advocated in at risk patients.

Recently, the investigators of the PREVENT trial (6), a multicenter, randomized trials (ClinicalTrials.gov number: NCT02040103) conducted in Saudi Arabia, Canada, Australia and India concluded that adjunctive IPC in critically ill patients receiving pharmacological thromboprophylaxis with UFH or LMWH did not result in a lower incidence of proximal lower limb DVT than pharmacologic thromboprophylaxis alone. Actually, the incidence of VT resulted inferior in the control group receiving pharmacological prophylaxis alone (9.4% versus 10.4%), indicating that patients receiving IPC and pharmacological prophylaxis had a higher relative risk of DVT and PE (6). To prevent, in our opinion, the misunderstanding that blindly accepting the results of the PREVENT trial could create in the medical community it is worth highlighting some criticalities in terms of design and data analysis.

The PREVENT trial certainly took into account the fact that the majority of VT develop within the first week after hospitalization, and that a linear correlation exists between bed immobilization during hospitalization and DVT occurrence, hence the investigators considered DVT diagnosed within the first 3 days of enrolment as prevalent (i.e., pre-existing), and focused solely on incident (i.e., new) proximal DVT as primary outcome. Secondary outcomes considered were a composite outcome measure of VT (any sort of DVT including proximal, distal, prevalent, or incident, +/– the occurrence of PE) and death from any cause at 28 days. Nonetheless, being a pragmatic trial, a wide variety in the pharmacological thromboprophylaxis, and more importantly in the IPC models used, exists: in fact, depending on the enrolling centre IPC could be either sequential or non-sequential devices (i.e., multichamber or single-chamber cuffs), with varying length extending to the thigh or the knee, with or without foot pumps. Of note, the use of graduated compression stockings, which is advocated by many national and international organizations (7,8) as one of the first line prevention measures for VT, were not

permitted in either trial group.

Three relevant aspects, in our opinion, that severely affect the internal and external validity of the PREVENT study should be highlighted. First, the authors did not explore whether patients included in the study had different baseline risk of VT. The hypercoagulative state of patients admitted to intensive care unit (ICU) is highly dependent from the reason for admission (i.e., post-surgical patients, recent history of stroke, myocardial infarct, traumas, sepsis, etc.), hence it must be considered a multifactorial event (9). This cascade is sustained by the immediate and prolonged release of cytokines (and other inflammatory mediators), the post-ictal pick in thrombin levels, the deposition of fibrin on endothelial surfaces and finally the diffuse platelet aggregation. As such, the approach to our patients should be tailored to their individual needs and this aspect was not taken into account in the PREVENT study protocol.

Second, a significant deviation from the study protocol was due to the fact that ultrasonographic investigations (UI) required to identify the presence of proximal or distal DVT were not homogeneously used across the entire study population. Although the authors admit that patients in the IPC group were monitored more strictly, not all patients included in the study underwent a baseline UI and some follow ups were not performed because of unavailability of ultrasonographers, especially on weekends.

Third, one major limitation of the trial is that it focused on composite measures of VT without trying to address the isolated effect of each IPC device on the incidence of proximal versus distal DVT. While the optimization of medical and surgical management has increased the survival rate of patients, even for those with high APACHE score on admission to hospital, the prevalence of co-morbidities (i.e., in the elderly population) along with incidence of complication (i.e., multiorgan involvement) may significantly affect the interpretation of composite measures such as incidence of any type of DVT and PE or death for any cause. As a result of the impossibility to conduct subgroup analysis, which might help make sense of the unexpected conclusions reached by this trial, we should be careful drawing any conclusion at all.

In addition, the limitations highlighted above should be put into context. In fact, it should be noted that the PREVENT study was designed as a superiority trial and the investigators calculated the power and sample groups around this hypothesis; unfortunately, though, the flawed design might explain why in this interventional study a subset of participants did not conform to the protocol and crossover from one group to the other. The authors decided to address those protocol violations by considering an intention-to-treat (ITT) analysis hence dealing with effectiveness of the intervention rather than its efficacy. The principle of ITT analysis is that all participants should be analyzed in the group to which they had been randomized (i.e., as if they had received the intervention which they were supposed to receive), irrespective of the treatment actually received, this is the recommended method in superiority trials to avoid any bias (10). Per-protocol (PP) analysis is a comparison of treatment groups that includes only those patients who completed the treatment originally allocated; if done alone, this analysis leads to bias mostly related to the imbalanced study groups. A null superiority trial should not be easily converted in a noninferiority one, where both ITT and PP analysis are recommended, and both approaches should support noninferiority (11). In the PREVENT trial results from the two type of statistical analysis are slightly divergent, hence they cannot rule out that the results observed are due to chance, absence of patients' stratification, or missing data. The strategy considered to mitigate these aspects implied the use of various sensitivity analyses; those were conducted to address different cut-off points for defining the primary outcome, missing baseline ultrasonographic studies, absence of follow up ultrasonographic studies and the effect of short stay in the ICU as a competing outcome (6). Of note, the sensitivity analysis revealed that the incidence of proximal lower limb DVT did not differ significantly between the two groups hence making the study null. This should be the only take-home message regarding the PREVENT trial: it failed, for various reasons, to address its research question; therefore, while it can serve to help researcher designing in the future more structured research trial, its results should not be considered, as they are, in our clinical practice.

When such a study fails both scientists and the wider medical community are left disappointed due to the lack of clarity. Hopefully, we have already a series of answers from previous studies that can guide our daily hospital routine. In terms of the VT pathophysiology we know that during any period of limited mobility the deep veins of the lower limbs, and less commonly of the upper limbs, are subject to formation of thrombi, and both can contribute to PE, hence explaining why IPC alone is not enough to reduce the mortality associated with DVT (12). We also know that trauma patients or those requiring surgical intervention are rather more challenging because pharmacological prophylaxis of thromboembolism might

be contraindicated due to the risk of postoperative bleeding and thrombocytopenia. For this reason, it is important to stratify patients according to their baseline risk of DVT. Higher-risk subgroups for developing DVT may be identified according to the presence in the anamnesis of one or more of the following criteria: preoperative bed rest, obesity, oral contraceptives, previous episode of DVT and/or PE, severe neurological deficits such dense hemiparesis or hemiplegia. Those with genetic hypercoagulopathic syndromes, including factor V Leiden mutation, elevated antiphospholipid antibodies, deficiencies of antithrombin, protein C, and protein S, are also uniquely susceptible to new-onset and/or recurrent DVT and PE after surgical procedures (13,14).

Furthermore, we should remember that beside Doppler Ultrasounds other more sophisticated investigations can be considered for patients with suspected DVT, they include: fibrinogen labelled with iodine 125 (I^{125}), venography, and D-Dimer testing (15-17). According to this classification moderate risk patients present an expected incidence of calf (distal) and proximal DVT of 10–40% and 2–8%, respectively, whereas their incidence of symptomatic and fatal PE is roughly 1–8% and 0.1–0.4%, respectively. Those values are almost doubled in high risk patients: expected incidence of distal DVT of 40–80%, proximal DVT of 10–20%, symptomatic PE of 5–10% and fatal PE of 1–5%. On the contrary, patients at low risk, present an expected incidence of distal DVT and PE of 1.3% and 0.6%, respectively (18). Although anticoagulation is paramount in the prevention of VT, this approach has also some strict contraindication. For instance, despite the general reluctance over the years to use anticoagulant prophylaxis for trauma patients, especially for those with head injury who have suffered intracranial bleeding or for whom intracranial surgery might be needed, or who may require orthopedic intervention, the use of mechanical and pharmacological thromboprophylaxis should be considered and their use tailored in agreement to the most recent guidelines (7).

In conclusion, the investigators of the PREVENT trial should be commended for their attempt to shade light on the use of IPC devices in an ICU setting, nonetheless the design of their study was affected by a number of criticalities/biais and the only relevant result seems to be that, in contrast to previous studies (19,20), it did not detect any, between-group, difference in the incidence of skin injuries. Concerns regarding discomfort, skin injuries and reduced mobility of patients have always been the most relevant ones preventing a widespread adoption of this mechanical thromboprophylaxis. This aspect of the PREVENT trial should hence be considered as a further indication that IPC are not only an effective and inexpensive method of reducing the risk of DVT and improving survival in immobile patients, as demonstrated by previous randomized trials (20,21), but also very safe for our patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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