Editorial Commentary

Interpretation of the PREVENT study findings on the adjunctive role of intermittent pneumatic compression to prevent venous thromboembolism

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Intermittent pneumatic compression (IPC) is an established, effective and safe mechanical—physical method of thromboprophylaxis, used for decades in a wide range of patients at risk for hospital-acquired venous thromboembolism (VTE) (1-3).

Being a physical method, IPC lacks the bleeding side-effects of pharmacological prophylaxis (4). This makes IPC the method of choice in patients with bleeding, such as those with trauma or gastrointestinal bleeding, or at a high risk for bleeding, such as those undergoing neurosurgical operations or having hypocoagulability.

Unfortunately, there is no perfect method of thromboprophylaxis, with the residual risk being relatively high, around 30% of the baseline frequency of VTE observed without any preventive measure (3). In an effort to improve the effectiveness of the existing methods, combined (pharmacological and mechanical) modalities are widely practiced following publication of controlled and randomized controlled trials showing superior efficacy compared with single modalities. The results of these trials on combined modalities (intermittent compression and pharmacological prophylaxis) are summarized in a 2016 Cochrane review, written by the authors of this article and collaborators (4). This study analyzed a 22 trials on 9,137 participants; 15 trials were randomized and included 7,762 patients. Symptomatic PE occurred equally frequent with IPC and combined modalities. Deep vein thrombosis (DVT) occurred in 4.1% in patients using IPC and 2.19% in patients using combined modalities, which corresponded to a reduced frequency of DVT in favor of combined IPC and pharmacological prophylaxis (OR 0.52). The use of an anticoagulant with an IPC, though, increased the risk of any bleeding compared to use of IPC alone (0.66% *vs.* 4.0% with combined modalities OR 5.04). Findings for major bleeding were similar (OR 6.81). There was no difference in the incidence of DVT between subgroups such as orthopedic *vs.* non-orthopedic patients (P=0.16). Combined modalities reduced the incidence of symptomatic PE (1.20% *vs.* 2.92% for pharmacological prophylaxis alone, OR 0.39) based on 10 studies in 3,544 patients. The incidence of DVT with pharmacological prophylaxis *vs.* combined modalities was statistically non-significant. When IPC was added to anticoagulation, hemorrhage rates were the same. The systematic review concluded that the results agree with what has been suggested by the guidelines, which support the utilization of combined IPC and pharmacological prophylaxis in hospitalized patients at risk of developing VTE (limited to those with trauma or undergoing surgery) and that additional studies on the role of combined modalities in VTE prevention are required.

Very similar results regarding graduated compression stockings (GCS) have been reported by several randomized

controlled trials (RCTs) and a Cochrane review (5). The latter showed that GCS are useful in reducing DVT in hospitalized patients who have undergone general and orthopedic surgery, supported by evidence of high-quality. The effectiveness of GCSs was clinically and statistically significant when GCS were used alone or in combination with other methods of thromboprophylaxis. The authors reported that GCS probably reduce the frequency of proximal DVT, and that GCS may reduce the risk of PE. This is supported by moderate-quality and low-quality evidence, respectively. Surprisingly, they noted a lack of evidence for effectiveness of GCS in medical patients.

The mode of action of mechanical methods (IPC and GCS) is known for decades. Primarily reducing venous stasis by increasing venous flow velocity (6), they have additional beneficial effects on hypercoagulability and venous endothelial injury (7-9). Since there is no perfect method for VTE prevention and their combination is indeed better than single modalities, it is plausible to explain the effect of combined modalities as a result of synergism, taking into account that pharmacological methods do not reduce perioperative venous stasis. Of note, IPC and GCS are not interchangeable modalities and it is suggested that they should be used in combination, to tackle more completely venous stasis during the period the IPC device is not functional, for example during patient transfer outside the ward to have a diagnostic test performed. Battery powered IPC devices do have an advantage by maintaining compression around the clock (6), but combining IPC with GCS is still recommended as a full shield against venous stasis.

The need for further evidence supporting the use of combined modalities was highlighted in the two Cochrane reviews described above investigating GCS and IPC (4,5). This kind of evidence was sought by the prospective RCT PREVENT published recently in the *NEJM* (10).

In PREVENT, critically ill patients within 48 hours after admission to an intensive care unit (ICU) were randomly assigned to use either IPC in addition to pharmacologic thromboprophylaxis (unfractionated or low-molecular-weight heparin) or pharmacologic thromboprophylaxis alone (control group) (10). The trial was conducted at 20 sites in Saudi Arabia, Canada, Australia, and India. The primary outcome measure was any new proximal DVT of the legs, on ultrasound performed twice-weekly after the third day since randomization until ICU discharge, death, attainment of full mobility, or trial day 28, whichever occurred first. The PREVENT investigators randomized 2003 patients into the two groups, 991 of them to the IPC group and the remaining 1,012 patients to the control group. DVT was observed in 3.9% in the IPC group and in 4.2% in the control group (relative risk, 0.93; P=0.74). VTE and all cause death at 90 days were similar in the two groups. The authors concluded that among critically ill patients who were receiving pharmacologic thromboprophylaxis, additional us of IPC did not significantly reduce the incidence of ultrasound detected proximal DVT than pharmacologic thromboprophylaxis alone.

The PREVENT investigators should be commended for this large trial where IPC was applied for a median of 22 h daily for a median of 7 days. Compliance was obviously excellent in this study because of the type of patients included. However, the negative results of PREVENT, which contrast similar studies, should be carefully appraised.

Unlike other studies using clinically proven IPC devices, such as the sequential compression device (SCD) compression system in the CLOT3 trial in stroke patients, where DVT and death were reduced with SCD (6,11), in PREVENT the protocol allowed use of a number of IPC devices, most of them not clinically proven to prevent VTE. The heterogeneity in device selection was evident with devices using non-sequential and/or calf sleeves being allowed. Furthermore, the study was clearly contaminated with the use of IPC in about 10% of the control group, where pharmacological prophylaxis was temporarily stopped. Without use of an IPC, VTE may have been higher to allow a meaningful difference. Therefore, the trial design was essentially IPC + pharmacological prophylaxis versus pharmacological prophylaxis with optional IPC use, making the two groups not exactly similar for the background intervention.

PREVENT had a low general risk of bias. Selection bias (random sequence generation and allocation concealment) was low due to use of a centralized computer-generated randomization system with variable block size. Furthermore, randomization was stratified according to trial site and type of heparin used. However, performance and detection bias were both high because patients, caregivers, and ultrasonographers were aware of the trial group assignment. Potentially this could have affected the reported results, for example selectively withholding anticoagulation or IPC in one of the two treatment groups. The multicenter design of the trial however and the data provided on daily IPC usage but also for pharmacologic prophylaxis in more than 50% of the intervention period (over 90% in both groups) indicate a rather effective protocol implementation. Sonographers

could be expected to overreport DVT detection in the control group, which was not the case. Nevertheless, attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias are all judged to be low.

A major area of concern that may have affected the results is the timing the primary outcome measure was recorded. In PREVENT, baseline ultrasound was performed to detect and exclude patients with prevalent DVT diagnosed within the first three calendar days of inclusion. Prevalent DVT, presumably proximal and distal DVT, was diagnosed in 34 patients in the IPC group and in 27 patients in the control group; these patients were excluded from the analysis of the primary outcome. Incident (defined as new) lower-limb proximal DVTs were defined as those diagnosed on twice-weekly lower-limb ultrasonography after the third calendar day since randomization. Incident DVT was detected in 37 patients in the IPC group and in 41 patients in the control group. The large number of DVT cases occurring during the run-in phase compared to the main study that spanned up to day 28, is indicative of a long pre-existing hospitalization period, so that that PREVENT was essentially a trial where IPC was tested for its efficacy in preventing delayed onset DVT. It is likely that patients at high risk for DVT developed DVT well before IPC was started, leaving no room for further improvement. Indeed, randomization was performed within two days of ICU admission, while about 23% of patients had a prior hospitalization in the past 3 months. Furthermore, no details on the length of hospital stay before ICU admission were provided for patients transferred from another ward or hospital. This group comprised 40% of all patients. We believe that the investigators placed IPC sleeves on patient legs immediately after randomization, although this is not explicitly stated in their protocol and trial report (10,12). Based on the above observations on delayed application of IPC, someone may suggest that the study should be repeated in surgical and/or trauma patients, with randomization and IPC application occurring preoperatively. The efficacy of IPC as an adjunct to pharmacological prophylaxis in orthopedic and cardiothoracic patients is well established (4), and it remains to be tested in large studies in other patient types.

DVT type mostly diagnosed was proximal DVT. Detection of distal DVT was left at the discretion of the sonographers. Unfortunately, the exact number of patients having their distal veins visualized was not provided, and so was the number of those who developed incident distal DVT the results of whom were reported in aggregate with prevalent distal DVT. It is therefore obvious that some patients with distal DVT were left untreated and received trial interventions instead. The fact that ultrasound was performed twice weekly may have altered the clinical expression of DVT, since asymptomatic DVT received treatment attention. The PREVENT authors are planning to compare their results received with surveillance against outcomes of critically ill patients not receiving surveillance for DVT (13). This study may shed some light into the foggy terrain of thromboprophylaxis in ICU patients.

Medical patients comprised nearly 80% of all patients in PREVENT. Taking into account the delayed onset of IPC use, PREVENT was essentially a trial of delayed thromboprophylaxis in mostly medical patients, where pharmacological prophylaxis with rivaroxaban in the MARINER trial has been recently shown to be totally ineffective (14). Concurrent use of an antiplatelet in about 40% of trial patients in PREVENT may have had an effect on the results by reducing the power of the study.

Generalization of trials is of paramount importance. In PREVENT, 16,053 patients were assessed for eligibility, with only 2003 (about 12%) of them undergoing randomization. This is a limitation not acknowledged by the trial authors. Future work in the form of high quality and appropriately powered RCTs should investigate the role of combined modalities in patient groups not represented in our Cochrane review on combined modalities and also in those with borderline significance likely to represent a type II error due to their small sample size. Cost-effectiveness analyses should supplement these original studies and their meta-analyses.

In conclusion, the authors have tried to solve the uncertainty brought by the PREVENT trial by critically reviewing the results provided by its investigators. Most likely, the delayed application of IPC in a predominantly medical cohort of patients admitted to an ICU explains the lack of effectiveness, without ignoring the fact that IPC use was also allowed in the control group. Use of a variety of IPC devices of variable proof of clinical effectiveness may have reduced further the true effect size of IPC.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at http://dx.doi.org/10.21037/atm.2020.01.68). Dr. JAC reports personal fees from Recovery force, personal fees from Sanofi, personal fees from BMS, personal fees from Pfizer, personal fees from Alexion Pharmaceutics, outside the submitted work. The other 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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