The journey to zero deep-vein thrombosis in critically ill patients

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Prevention of deep-vein thrombosis (DVT) among critically ill patients has been considered a high priority for patient safety initiatives.[1] Recently, the Saudi Critical Care Trials Group published the results of the Pneumatic Compression for Preventing Venous Thromboembolism (PREVENT) trial in the *New England Journal of Medicine*.[2] The trial examined whether the addition of pneumatic compression to pharmacological thromboprophylaxis reduced the incidence of DVT in critically ill patients.[2-4] In this commentary, we review the lessons learned and implications of the PREVENT trial on clinical practice.

Venous thromboembolism (VTE), including DVT and pulmonary embolism (PE), is a common complication of critical illness.[5] In prospective studies that performed screening, DVT was documented in 13%–31% of patients who were not receiving thromboprophylaxis during their intensive care unit (ICU) stay.[6-8] However, DVT has also been documented in 5%–20% of patients who are receiving pharmacologic thromboprophylaxis.[5,9] DVT is associated with increased duration of mechanical ventilation, duration of ICU stay, duration of hospital stay, and hospital mortality.[10] Untreated PE is associated with a mortality of at least 25%.[5] Furthermore, VTE remains clinically unsuspected in a large number of patients and is often diagnosed postmortem.[11,12] In a large study of 6833 autopsies, fatal PE was recorded as the cause of death in 5.2% of adult autopsies, 80% among patients who were older than 60 years, and 80% among medical patients.[12]

With the premise of improved DVT prevention, pneumatic compression is widely used in combination with pharmacologic thromboprophylaxis in critically ill patients. However, there has been limited data regarding this practice. The PREVENT trial examined whether the addition of pneumatic compression to pharmacological thromboprophylaxis reduced the incidence of DVT in critically ill patients.[2-4] The study was conducted in twenty ICUs from Saudi Arabia, Canada, Australia, and India, and was sponsored by King Abdulaziz City for Science and Technology and King Abdullah International Medical Research Center, Riyadh, Saudi Arabia.

In this trial, adult critically ill patients were randomly assigned within 48 h of ICU admission to receive either intermittent pneumatic compression for at least 18 h a day in addition to pharmacologic thromboprophylaxis (pneumatic compression group) or to pharmacologic thromboprophylaxis only (control group). The primary outcome was incident proximal lower-limb DVT as detected after the 3rd calendar day of randomization on twice-weekly screening ultrasound studies through ICU discharge, death, attainment of full mobility, or day 28 (whichever occurred first). DVT detected on days 1–3 was considered prevalent.

A total of 2003 patients were randomized. Most participants were medical patients; one half were admitted from emergency departments. Two-thirds of the patients were mechanically ventilated, and one-third were on vasopressors. Approximately

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58% of the patients were receiving unfractionated heparin at randomization, and the rest were receiving low-molecular-weight heparin. Pneumatic compression was applied for a median of 22 h (interquartile range [IQR], 21–23) per day for a median of 7 days (IQR, 4–13) in the pneumatic compression group. Ultrasounds were performed as scheduled, averaging one ultrasound per 3.5 days in the pneumatic compression group and per 3.8 days in the control group. The primary outcome of incident proximal DVT was not different between the two groups: 3.9% in the pneumatic compression group and 4.2% in the control group (relative risk [RR], 0.93; 95% confidence interval [CI], 0.60–1.44). All lower-limb DVT events (proximal, distal, prevalent, and incident) were not different between the two groups (9.6% in the pneumatic compression group compared to 8.4% in the control group; RR, 1.14; 95% CI, 0.86, 1.51). Similarly, all VTE events were not different (10.4% in the pneumatic compression group and 9.4% in the control group [RR, 1.11; 95% CI, 0.85, 1.44]). Mortality was not different between the two groups. The PREVENT trial demonstrated that pneumatic compression was not associated with reduction in proximal lower-limb DVT rates compared with pharmacologic thromboprophylaxis alone.

Several lessons are learned from the PREVENT trial. The PREVENT study showed that the widely used practice of adjunctive pneumatic compression with pharmacologic thromboprophylaxis is not supported by objective evidence. As such, the PREVENT study is likely to influence this practice.

Second, the PREVENT trial highlights the importance of examining questions related to the effectiveness of therapeutic interventions in randomized controlled trials. This is particularly true for devices that are often introduced to the market with limited data regarding effectiveness on patient-centered outcomes. An accompanying editorial highlighted the need for adequately testing devices before wide implementation.[13]

Third, because the PREVENT trial enrolled patients who could receive pharmacologic thromboprophylaxis early within 48 h of ICU admission, the study cohort consisted largely of medical patients. Trauma patients constituted a small proportion of the whole cohort, and further studies in this group may be warranted.

Finally, the journey for DVT prophylaxis dates back to more than five decades ago; a randomized controlled trial published in 1972 demonstrated that subcutaneous heparin in postoperative patients reduced DVT compared to controls.[14] As this journey to zero DVT continued, other approaches for DVT prevention were tested. The Prophylaxis for Thromboembolism in Critical Care Trial demonstrated that the low-molecular-weight heparin (dalteparin) was of similar effect to unfractionated heparin in critically ill patients, although it was associated with reduction in the occurrence of PE.[15] A systematic review of heparin (unfractionated and low-molecular-weight heparin) versus placebo showed that heparin reduces DVT by around 50% and PE by 50%.[16] These data not only document the benefit of heparin in DVT prevention, but also demonstrate a substantial residual risk even when heparin is administered. To address this residual risk, mechanical thromboprophylaxis methods are often used. Unfortunately, graduated compression stockings were found to be of unclear benefit in DVT prophylaxis.[9] The PREVENT trial demonstrates that adding pneumatic compression to pharmacologic thromboprophylaxis does not confer benefit. In fact, DVT occurred in almost 10% of patients in the PREVENT trial, confirming again that DVT is a common occurrence even in patients receiving pharmacologic thromboprophylaxis. The PREVENT trial highlights the need to explore innovative approaches for DVT prevention, perhaps beyond the existing traditional methods.

While the PREVENT trial showed that the adjunctive use of pneumatic compression with pharmacologic thromboprophylaxis is not effective in reducing incident DVT, pneumatic compression should probably be used in critically ill patients who cannot receive pharmacologic thromboprophylaxis, such as patients with active bleeding or those at high risk for bleeding. Finally, the effectiveness of pneumatic compression in reducing DVT risk in patients with coagulopathy (e.g., patients with a platelet count of $<50 \times 10^9$/L) remains unclear and requires further study.

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Conflicts of interest

There are no conflicts of interest.

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