

## EDITORIAL



## A Device on Trial — Intermittent Pneumatic Compression in Critical Care

François Lauzier, M.D., James D. Douketis, M.D., and Deborah J. Cook, M.D.

The intensive care unit (ICU) is replete with devices used for monitoring, prevention, diagnosis, treatment, and rehabilitation in critically ill patients. The approval process for high-risk medical devices in the United States is intended to give reasonable assurance of their safety and effectiveness. For approval of noninvasive and non-life-sustaining moderate-risk devices such as those used for intermittent pneumatic compression, the Food and Drug Administration requirements are less stringent and instead focus on showing “substantial equivalence” to devices already on the market.<sup>1</sup> In addition, the post-marketing monitoring of medical devices aims primarily to confirm safety rather than show effectiveness. Consequently, apparently safe technologies can be widely incorporated into practice without proof of clinical benefit. To address this knowledge gap, investigator-initiated, publicly funded randomized trials are crucial to assess which devices have no effect and which do more good than harm and vice versa. As compared with industry-initiated trials, investigator-initiated trials led by collaborative research consortia are more likely to test existing (rather than new) drugs and devices and to examine clinically important and patient-centered outcomes (rather than only mechanisms, physical properties, or other surrogate outcomes).

The premise that mechanical thromboprophylaxis confers added benefit to pharmacologic thromboprophylaxis is based on the multicausal pathogenesis of venous thrombosis. Whereas anticoagulants prevent thrombosis through inhibition of coagulation factor function, mechanical thromboprophylaxis decreases lower-limb venous stasis by displacing blood from the superficial to the deep venous system and may enhance

endogenous anticoagulant activity.<sup>2</sup> Combined thromboprophylaxis that uses both mechanical and pharmacologic interventions has been investigated in high-risk surgical patients and in patients after major trauma and stroke, but data from dedicated trials involving critically ill patients are lacking.<sup>3</sup> Despite sparse support, combined thromboprophylaxis continues to be used in these patients on the basis of indirect evidence.<sup>4</sup>

In the Pneumatic Compression for Preventing Venous Thromboembolism (PREVENT) trial, reported in this issue of the *Journal*, Arabi and colleagues<sup>5</sup> showed that among 2003 medical, surgical, and trauma ICU patients, combined thromboprophylaxis was safe but did not result in a significantly lower incidence of proximal lower-limb deep-vein thrombosis, pulmonary embolism, or other clinical outcomes than pharmacologic thromboprophylaxis alone. The PREVENT trial was conducted at 20 trial sites in four countries, and the patients in the pneumatic compression group received treatment with 1 of 10 different pneumatic compression devices (knee-length sleeves were used in 79% and thigh-length sleeves in 19%); at baseline, 66% of the patients were receiving mechanical ventilation and 36% were vasopressor dependent. Thus, the results of this trial are relevant to a heterogeneous spectrum of ICU patients. Although this pragmatically designed and conducted trial was not performed in a blinded manner, the risk of bias was low, given the randomized design with concealed treatment assignments, high adherence (median duration of the intervention was 22 hours per day for 7 days), few crossovers (0.6% of patients in the control group received the combined intervention), negligible cointerventions (0.9% of patients also used graduated compression stockings),

and minimal loss to follow-up (the primary outcome was assessed in 97% of the patients).

The lack of benefit of the addition of pneumatic compression to pharmacologic thromboprophylaxis with unfractionated or low-molecular-weight heparin in the PREVENT trial may reflect an effect size that was lower than anticipated (relative risk reduction of 43%) and an incidence of the primary outcome with pharmacologic thromboprophylaxis alone that was lower than expected (4% observed vs. 7% expected). It may also signal that we have entered an era in which scaling back the intensity of combined thromboprophylaxis might be considered to avoid the added cost of low-value interventions. However, some uncertainty remains about whether adjunctive pneumatic compression leads to a lower risk of thromboembolism among critically ill trauma patients, who represented only 8% of the trial population and whose baseline risk of proximal deep-vein thrombosis may be higher (17% among patients with traumatic brain injury<sup>6</sup> vs. 4% among the patients in the PREVENT trial).

These findings raise questions about the effect of mechanical thromboprophylaxis alone in ICU patients who have a contraindication to heparin, including those who are bleeding or at risk for bleeding — populations not included in the PREVENT trial. A randomized trial involving 407 critically ill patients at high risk for bleeding, in whom pharmacologic thromboprophylaxis was withheld for 1 week, did not show any benefit of pneumatic compression.<sup>7</sup> By contrast, the Clots in Legs or Stockings after Stroke (CLOTS) 3 trial showed that among 2876 patients with stroke, of whom approximately 30% received prophylactic or therapeutic anticoagulation, the occurrence of proximal lower-limb deep-vein thrombosis was significantly lower among those who received pneumatic compression than among those who did not (8.5% vs. 12.1%).<sup>8</sup> Consequently, the 2016 Surviving Sepsis Campaign Guidelines, based on a low level of evidence, issued a weak recommendation for pneumatic compression in patients who are not receiving pharmacologic thromboprophylaxis,<sup>9</sup> and the 2018 American Society of Hematology guidelines issued a similar conditional recommendation with moderate certainty,<sup>3</sup> leaving the door ajar for further investigation.

The research world of the 21st century grows smaller as global collaboration in critical care

continues to be a welcome opportunity and increasingly a necessity.<sup>10</sup> The PREVENT trial marks a milestone for the Saudi Critical Care Trials Group, leading an investigative team that is diverse in terms of perspectives, professions, gender, and geographic region to address the logistic, legal, and regulatory challenges that inevitably arise during international trials. Such academic alliances enhance the scope and capacity of clinical research, so that questions posed by independent scientists, enabled by peer-reviewed funding, remain paramount for putting medical devices on trial.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Population Health and Optimal Health Practices Research Unit, Centre de Recherche du Centre Hospitalier Universitaire de Québec—Université Laval, and the Departments of Medicine and Anesthesiology and Critical Care Medicine, Université Laval, Québec, QC (F.L.), and the Departments of Medicine (J.D.D., D.J.C.) and Health Research Methods, Evidence, and Impact (D.J.C.), McMaster University, and the Department of Medicine (J.D.D., D.J.C.) and the Division of Critical Care (D.J.C.), St. Joseph's Healthcare, Hamilton, ON — all in Canada.

- Center for Devices and Radiological Health. The 510(k) program: evaluating substantial equivalence in premarket notifications [510(k)]. Guidance for industry and Food and Drug Administration staff. July 28, 2014 (<https://www.fda.gov/downloads/MedicalDevices/.../UCM284443.pdf>).
- Chen AH, Frangos SG, Kilaru S, Sumpio BE. Intermittent pneumatic compression devices — physiological mechanisms of action. *Eur J Vasc Endovasc Surg* 2001;21:383-92.
- Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv* 2018;2:3198-225.
- Lauzier F, Muscedere J, Deland E, et al. Thromboprophylaxis patterns and determinants in critically ill patients: a multicenter audit. *Crit Care* 2014;18:R82.
- Arabi YM, Al-Hameed F, Burns KEA, et al. Adjunctive intermittent pneumatic compression for venous thromboprophylaxis. *N Engl J Med* 2019;380:1305-15.
- Nichol A, French C, Little L, et al. Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. *Lancet* 2015;386:2499-506.
- Vignon P, Dequin PF, Renault A, et al. Intermittent pneumatic compression to prevent venous thromboembolism in patients with high risk of bleeding hospitalized in intensive care units: the CIREA1 randomized trial. *Intensive Care Med* 2013;39:872-80.
- Dennis M, Sandercock P, Reid J, Graham C, Forbes J, Murray G. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. *Lancet* 2013;382:516-24.
- Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017;43:304-77.
- Marshall JC. Global collaboration in acute care clinical research: opportunities, challenges, and needs. *Crit Care Med* 2017;45:311-20.

DOI: 10.1056/NEJMe1902334

Copyright © 2019 Massachusetts Medical Society.