

## ORIGINAL ARTICLE

# Adjunctive Intermittent Pneumatic Compression for Venous Thromboprophylaxis

Y.M. Arabi, F. Al-Hameed, K.E.A. Burns, S. Mehta, S.J. Alsolamy, M.S. Alshahrani, Y. Mandourah, G.A. Almekhlafi, M. Almaani, A. Al Bshabshe, S. Finfer, Z. Arshad, I. Khalid, Y. Mehta, A. Gaur, H. Hawa, H. Buscher, H. Lababidi, A. Al Aithan, S.A.I. Abdukahil, J. Jose, L.Y. Afesh, and A. Al-Dawood, for the Saudi Critical Care Trials Group\*

## ABSTRACT

**BACKGROUND**

Whether adjunctive intermittent pneumatic compression in critically ill patients receiving pharmacologic thromboprophylaxis would result in a lower incidence of deep-vein thrombosis than pharmacologic thromboprophylaxis alone is uncertain.

**METHODS**

We randomly assigned patients who were considered adults according to the local standards at the participating sites ( $\geq 14$ ,  $\geq 16$ , or  $\geq 18$  years of age) within 48 hours after admission to an intensive care unit (ICU) to receive either intermittent pneumatic compression for at least 18 hours each day in addition to pharmacologic thromboprophylaxis with unfractionated or low-molecular-weight heparin (pneumatic compression group) or pharmacologic thromboprophylaxis alone (control group). The primary outcome was incident (i.e., new) proximal lower-limb deep-vein thrombosis, as detected on twice-weekly lower-limb ultrasonography after the third calendar day since randomization until ICU discharge, death, attainment of full mobility, or trial day 28, whichever occurred first.

**RESULTS**

A total of 2003 patients underwent randomization — 991 were assigned to the pneumatic compression group and 1012 to the control group. Intermittent pneumatic compression was applied for a median of 22 hours (interquartile range, 21 to 23) daily for a median of 7 days (interquartile range, 4 to 13). The primary outcome occurred in 37 of 957 patients (3.9%) in the pneumatic compression group and in 41 of 985 patients (4.2%) in the control group (relative risk, 0.93; 95% confidence interval [CI], 0.60 to 1.44;  $P=0.74$ ). Venous thromboembolism (pulmonary embolism or any lower-limb deep-vein thrombosis) occurred in 103 of 991 patients (10.4%) in the pneumatic compression group and in 95 of 1012 patients (9.4%) in the control group (relative risk, 1.11; 95% CI, 0.85 to 1.44), and death from any cause at 90 days occurred in 258 of 990 patients (26.1%) and 270 of 1011 patients (26.7%), respectively (relative risk, 0.98; 95% CI, 0.84 to 1.13).

**CONCLUSIONS**

Among critically ill patients who were receiving pharmacologic thromboprophylaxis, adjunctive intermittent pneumatic compression did not result in a significantly lower incidence of proximal lower-limb deep-vein thrombosis than pharmacologic thromboprophylaxis alone. (Funded by King Abdulaziz City for Science and Technology and King Abdullah International Medical Research Center; PREVENT ClinicalTrials.gov number, NCT02040103; Current Controlled Trials number, ISRCTN44653506.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Arabi at the Intensive Care Department, Ministry of National Guard Health Affairs, ICU 1425, P.O. Box 22490, Riyadh 11426, Saudi Arabia, or at [arabi@ngha.med.sa](mailto:arabi@ngha.med.sa).

\*A complete list of the members of the Saudi Critical Care Trials Group is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

This article was published on February 18, 2019, at [NEJM.org](http://NEJM.org).

DOI: [10.1056/NEJMoa1816150](https://doi.org/10.1056/NEJMoa1816150)

Copyright © 2019 Massachusetts Medical Society.

**V**ENOUS THROMBOEMBOLISM, INCLUDING both deep-vein thrombosis and pulmonary embolism, is a complication of critical illness.<sup>1,2</sup> In randomized trials, the incidence of deep-vein thrombosis was estimated to be 50% lower with pharmacologic thromboprophylaxis with unfractionated or low-molecular-weight heparin than with no thromboprophylaxis, and guidelines recommend pharmacologic thromboprophylaxis in all critically ill patients.<sup>3</sup> However, deep-vein thrombosis develops in 5 to 20% of critically ill patients despite pharmacologic thromboprophylaxis.<sup>1,4-6</sup>

The incidence of deep-vein thrombosis was reported to be lower with mechanical thromboprophylaxis with intermittent pneumatic compression than with no thromboprophylaxis, but the efficacy of intermittent pneumatic compression may be lower than that of pharmacologic thromboprophylaxis.<sup>7-9</sup> A randomized trial involving hospitalized patients with stroke, among whom 24% had been receiving thrombolysis or prophylactic or therapeutic anticoagulation, showed that the incidence of deep-vein thrombosis was approximately 30% lower with intermittent pneumatic compression than without it.<sup>10</sup> Intermittent pneumatic compression is recommended for patients with a contraindication to pharmacologic thromboprophylaxis,<sup>7,8</sup> but whether the addition of intermittent pneumatic compression to pharmacologic thromboprophylaxis further reduces the risk of venous thromboembolism is uncertain. Previous studies have been limited by nonrandomized designs, confounding from adjunctive use of graduated compression stockings, or suboptimal pharmacologic thromboprophylaxis regimens.<sup>11,12</sup> Moreover, data from trials of intermittent pneumatic compression involving critically ill patients are lacking. Although intermittent pneumatic compression is noninvasive and easy to use, its use is associated with additional cost and may be associated with discomfort, skin injury, and reduced patient mobility.

The dearth of strong evidence regarding mechanical thromboprophylaxis has resulted in inconsistent recommendations in clinical practice guidelines,<sup>7,8,13</sup> and practice variation in the use of adjunctive intermittent pneumatic compression.<sup>14,15</sup> The Pneumatic Compression for Preventing Venous Thromboembolism (PREVENT) trial was an investigator-initiated, pragmatic, international,

multicenter, randomized, controlled trial that evaluated whether adjunctive intermittent pneumatic compression in critically ill patients receiving pharmacologic thromboprophylaxis with unfractionated heparin or low-molecular-weight heparin would result in a lower incidence of proximal lower-limb deep-vein thrombosis than pharmacologic thromboprophylaxis alone.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

We conducted the trial at 20 sites in Saudi Arabia, Canada, Australia, and India.<sup>16</sup> One additional site was terminated by the trial sponsor because some patients had been enrolled without full adherence to the approved informed-consent process, and all data from this site were excluded from the analyses.

The trial protocol, available with the full text of this article at NEJM.org, was designed by the management committee and approved by the institutional review boards at all participating sites. Data monitoring and quality checks were conducted by the management committee and the monitoring unit of King Abdullah International Medical Research Center. The management committee (made up of six of the authors) vouches for the accuracy and completeness of the data and statistical analyses and for the fidelity of the trial to the protocol. The manuscript was written by the writing committee and was approved for submission for publication by all authors. The members of the management and writing committees are listed in the Supplementary Appendix, available at NEJM.org.

The trial was funded by King Abdulaziz City for Science and Technology and King Abdullah International Medical Research Center. The funding agencies had no role in the design or conduct of the trial, the collection and analysis of the data, or the writing of the manuscript. One trial site used study devices provided by Compression Solutions (Table S1 in the Supplementary Appendix), which had no other role in the trial.

### PATIENTS

Medical, surgical, or trauma patients were eligible for inclusion in the trial if they were considered adults according to the local standard at the participating sites ( $\geq 14$ ,  $\geq 16$ , or  $\geq 18$  years of age), weighed at least 45 kg, were expected to stay in

the intensive care unit (ICU) for at least 72 hours, and had no contraindications to pharmacologic thromboprophylaxis with either unfractionated heparin or low-molecular-weight heparin. Patients were enrolled within 48 hours after ICU admission. Exclusion criteria are listed in Table S2 in the Supplementary Appendix. Written informed consent was obtained from all the patients or their surrogate decision makers.

#### RANDOMIZATION AND TRIAL INTERVENTION

The patients were randomly assigned, in a 1:1 ratio, to receive either intermittent pneumatic compression in addition to pharmacologic thromboprophylaxis (pneumatic compression group) or pharmacologic thromboprophylaxis alone (control group). We used a centralized computer-generated randomization system with variable block size. Randomization was stratified according to trial site and type of heparin used.

The devices used for intermittent pneumatic compression in the trial are listed in Table S1 in the Supplementary Appendix. The devices were prioritized in the protocol; when available, sequential compression devices (multichamber cuffs) and thigh-length sleeves were preferred, but nonsequential devices (single-chamber cuffs) and knee-length sleeves were permitted. Foot pumps could be used in addition to thigh-length or knee-length sleeves. Intermittent pneumatic compression was applied to both lower limbs for at least 18 hours per day, with the sleeves removed for skin inspection and care every 8 hours. The procedure was performed and the cuff size selected according to the manufacturers' recommendations and local policies. Intermittent pneumatic compression was discontinued when deep-vein thrombosis or pulmonary embolism was suspected or confirmed or when a leg ulcer or ischemia was diagnosed. It was also discontinued when the goals of care were transitioned to palliation, at attainment of full mobility, or at ICU discharge or trial day 28.

In the control group, intermittent pneumatic compression was permitted only during interruption of pharmacologic thromboprophylaxis. Graduated compression stockings were not permitted in either trial group. The treating team assumed responsibility for patient care, including postrandomization prescriptions of systemic anticoagulation (for reasons other than venous thromboembolism) and antiplatelet agents.

#### MEASUREMENTS

Certified ultrasonographers performed proximal venous ultrasonography of both lower limbs within 48 hours after randomization and then twice weekly and on clinical suspicion of deep-vein thrombosis. Ultrasonographers assessed the venous system for compressibility at 1-cm intervals at the common femoral vein and at proximal, middle, and distal points of the femoral vein, the popliteal vein, and the venous trifurcation. Findings from ultrasonography were interpreted by radiologists who were unaware of the trial-group assignments. We defined proximal deep-vein thrombosis as partial or complete incompressibility of a venous segment at any site. Examination of the distal leg veins (peroneal, posterior tibial, anterior tibial, and muscular veins) was performed according to local hospital practices. Investigations for pulmonary embolism or non-lower-limb venous thrombosis were performed at the discretion of the treating team.

#### TRIAL OUTCOMES

The primary outcome was incident (i.e., new) proximal lower-limb deep-vein thrombosis, as detected on twice-weekly lower-limb ultrasonography after the third calendar day since randomization until ICU discharge, death, attainment of full mobility, or trial day 28, whichever occurred first. Deep-vein thromboses that were detected on trial days 1 to 3 were considered to be prevalent (i.e., preexisting) and were not included in the primary outcome analysis.

Key secondary outcomes included the percentage of patients who had prevalent proximal deep-vein thromboses, the occurrence of any lower-limb deep-vein thromboses (proximal, distal, prevalent, or incident), the occurrence of pulmonary embolism, a composite outcome of venous thromboembolism that included pulmonary embolism or all prevalent and incident lower-limb deep-vein thromboses, a composite outcome of venous thromboembolism or death from any cause at 28 days, and safety outcomes. A full list of secondary and exploratory outcomes is provided in the Supplementary Appendix.

#### STATISTICAL ANALYSIS

After accounting for a 5% loss to follow-up and estimating that 5% of the patients would have prevalent deep-vein thrombosis, we projected that a sample of 2000 patients would provide the trial

with 80% power to detect an absolute difference of 3% in the incidence of proximal lower-limb deep-vein thrombosis with adjunctive intermittent pneumatic compression from an assumed incidence of 7% with pharmacologic thromboprophylaxis alone, at an alpha level of 5%. The independent data monitoring committee reviewed the data after 667 patients (33%) and 1334 patients (66%) had completed follow-up. We used the O'Brien–Fleming method to account for alpha spending and considered a P value of less than 0.048 to indicate statistical significance in the final analysis.

The modified intention-to-treat population comprised all the patients who underwent randomization with the exception of those who withdrew consent for both the intervention and the collection of data and those who were identified as ineligible after randomization. The per-protocol population comprised all the patients who received the assigned intervention and had at least one ultrasonographic study performed.

We used a chi-square test to compare the primary outcome between groups in the modified intention-to-treat population and reported the result as a relative risk with a 95% confidence interval. Secondary analyses of the primary outcome were also performed. We used a generalized linear mixed model to estimate the adjusted relative risk after incorporating trial site as a random effect. We also used an unadjusted Cox proportional-hazards model to examine the primary outcome; we censored data for patients at the time a pulmonary embolism developed, at the time of ICU discharge, at the time of death, or at trial day 28, whichever occurred first, and reported the result as a hazard ratio with a 95% confidence interval. We used Kaplan–Meier curves to compare time-to-event distributions. We also used Cox proportional-hazards models that adjusted for the type of heparin used (unfractionated vs. low-molecular-weight heparin), location before ICU admission (hospital ward vs. other locations), type of admission (trauma vs. other types), use of femoral central venous catheters (yes vs. no), and heart failure (present vs. absent); incorporated trial site as a random effect; and accounted for the competing risk of death. We carried out similar analyses in the per-protocol cohort.

We conducted analyses of the secondary and exploratory outcomes, subgroup analyses, and sensitivity analyses according to the previously pub-

lished trial protocol and statistical analysis plan.<sup>16,17</sup> We did not adjust for multiple comparisons, and we did not impute for missing values. In one sensitivity analysis that addressed the issue of missing baseline ultrasonographic studies, we performed analyses using multiple imputations and worst-case and best-case scenarios. The 95% confidence intervals have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible. All analyses were two-sided and were conducted with the use of SAS software, version 9.4 (SAS Institute).

## RESULTS

### PATIENTS

From July 2014 through August 2018, a total of 16,053 patients were assessed for eligibility. Of these, 2003 patients underwent randomization and were included in the modified intention-to-treat analysis — 991 patients were assigned to the pneumatic compression group and 1012 to the control group (Fig. S1 in the Supplementary Appendix). The characteristics of the patients at baseline did not differ significantly between the two trial groups (Table 1, and Table S3 in the Supplementary Appendix). Prevalent deep-vein thromboses were detected in 34 patients in the pneumatic compression group and in 27 patients in the control group during trial days 1 to 3, and these patients were excluded from the analysis of the primary outcome. The baseline characteristics of the patients who were included in the primary outcome analysis are provided in Table S4 in the Supplementary Appendix.

### INTERVENTION

In the modified intention-to-treat population, intermittent pneumatic compression was used in 972 patients (98.1%) for a median of 22 hours (interquartile range, 21 to 23) per day in the pneumatic compression group and in 103 patients (10.2%) for a median of 0 hours (interquartile range, 0 to 0) per day in the control group (Table 2). Among the 991 patients in the pneumatic compression group, knee-length sleeves were most commonly used (787 patients [79.4%]), and thigh-length sleeves (185 [18.7%]) and foot pumps (121 [12.2%]) were used less often. Further details regarding the use of intermittent pneumatic compression are provided in Table S5 in the Supplementary Appendix.

**Table 1. Baseline Characteristics of the Patients in the Modified Intention-to-Treat Population.\***

Characteristic	Pneumatic Compression Group (N=991)	Control Group (N=1012)
Age — yr	57.6±20.0	58.7±20.5
Male sex — no. (%)	579 (58.4)	569 (56.2)
Body-mass index†	29.0±8.5	28.6±8.0
Location before ICU admission — no. (%)		
Emergency department	497 (50.2)	516 (51.0)
Hospital ward	310 (31.3)	305 (30.1)
Operating room	100 (10.1)	92 (9.1)
Other hospital ICU or ward	76 (7.7)	95 (9.4)
Other location	8 (0.8)	4 (0.4)
APACHE II score‡	20.1±7.8	20.2±7.7
Type of admission — no. (%)		
Medical	787 (79.4)	779 (77.0)
Surgical	135 (13.6)	147 (14.5)
Trauma	69 (7.0)	86 (8.5)
Organ support — no. (%)		
Mechanical ventilation	654 (66.0)	667 (65.9)
Vasopressors	352 (35.5)	364 (36.0)
Pharmacologic thromboprophylaxis at the time of randomization — no. (%)		
Unfractionated heparin	579 (58.4)	583 (57.6)
Low-molecular-weight heparin	412 (41.6)	429 (42.4)
Femoral central venous catheter — no. (%)	147 (14.8)	164 (16.2)
Median no. of days from ICU admission to randomization (IQR)	1.0 (0.0–1.0)	1.0 (0.0–1.0)
Receipt of intermittent pneumatic compression before randomization — no. (%)	129 (13.0)	107 (10.6)

\* Plus–minus values are means ±SD. The patients were randomly assigned to receive intermittent pneumatic compression for at least 18 hours each day in addition to pharmacologic thromboprophylaxis with unfractionated or low-molecular-weight heparin (pneumatic compression group) or pharmacologic thromboprophylaxis alone (control group). The modified intention-to-treat population comprised all the patients who underwent randomization with the exception of those who withdrew consent for both the intervention and the collection of data and those who were identified as ineligible after randomization. Continuous variables were compared between the two trial groups with the use of an independent Student's t-test or Mann–Whitney test, and categorical variables were compared with the use of a chi-square test or Fisher's exact test. None of the baseline characteristics differed significantly between the two trial groups. Additional details on baseline characteristics are provided in Tables S3 and S4 in the Supplementary Appendix. Percentages may not total 100 because of rounding. ICU denotes intensive care unit, and IQR interquartile range.

† The body-mass index is the weight in kilograms divided by the square of the height in meters. Six patients in the pneumatic compression group and two patients in the control group had missing data for body-mass index.

‡ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating more severe disease and higher risk of death.

Protocol deviations occurred in 72 patients in the pneumatic compression group and in 87 patients in the control group, and protocol violations occurred in 28 patients in each group (Table S6 in the Supplementary Appendix). The median duration of the intervention was 7 days (interquartile range, 4 to 13) in the pneumatic compression

group and 7 days (interquartile range, 4 to 14) in the control group.

#### COINTERVENTIONS

The use of pharmacologic thromboprophylaxis (unfractionated heparin vs. low-molecular-weight heparin) did not differ significantly between the

**Table 2. Interventions and Cointerventions in the Modified Intention-to-Treat Population during the Trial Period.\***

Variable	Pneumatic Compression Group (N=991)	Control Group (N=1012)
Median no. of days of the trial intervention (IQR)	7 (4–13)	7 (4–14)
Use of intermittent pneumatic compression during the trial period†		
Patients receiving intermittent pneumatic compression — no. (%)	972 (98.1)	103 (10.2)
Median no. of hours per day of intermittent pneumatic compression applied to both limbs (IQR)	22 (21–23)	0 (0–0)
Type of sleeves used — no. (%)		
Knee-length	787 (79.4)	96 (9.5)
Thigh-length	185 (18.7)	7 (0.7)
Use of foot pumps — no. (%)	121 (12.2)	11 (1.1)
Use of other cointerventions during the trial period		
Graduated compression stockings — no. (%)	10 (1.0)	8 (0.8)
Median no. of days of stocking use (IQR)‡	2 (1–4)	1 (1–2)
Therapeutic anticoagulation for reasons other than venous thromboembolism — no. (%)	58 (5.9)	71 (7.0)
Median no. of days of therapeutic anticoagulation for reasons other than venous thromboembolism (IQR)§	4 (2–9)	4 (2–11)
Antiplatelet therapy — no. (%)		
Aspirin	301 (30.4)	296 (29.2)
Clopidogrel	120 (12.1)	111 (11.0)

\* Additional details on the interventions and cointerventions are provided in Table S7 in the Supplementary Appendix.

† Some patients in the control group received intermittent pneumatic compression, mainly during periods of interruption of pharmacologic thromboprophylaxis (Table S5 in the Supplementary Appendix).

‡ The duration of graduated compression stocking use was calculated only for patients who received graduated compression stockings.

§ The duration of therapeutic anticoagulation for reasons other than venous thromboembolism was calculated only for patients who received therapeutic anticoagulation for reasons other than venous thromboembolism.

two groups at the time of randomization and during the trial, with approximately 58% receiving unfractionated heparin at the time of randomization (Table 1, and Table S7 in the Supplementary Appendix). Graduated compression stockings were used in 10 of 991 patients (1.0%) in the pneumatic compression group and 8 of 1012 patients (0.8%) in the control group (Table 2). The use of therapeutic anticoagulation (for indications other than venous thromboembolism), antiplatelet therapy, mechanical ventilation, renal-replacement therapy, and other cointerventions did not differ between the trial groups.

At least one lower-limb ultrasonographic study was performed in 970 of 991 patients (97.9%) in the pneumatic compression group and 987 of 1012 patients (97.5%) in the control group within a me-

dian of 0 days (interquartile range, 0 to 1) after randomization. On average, one ultrasonographic study per 3.5 days was performed in the pneumatic compression group, and one ultrasonographic study per 3.8 days was performed in the control group (Tables S7 and S8 in the Supplementary Appendix).

#### PRIMARY OUTCOME

Incident proximal deep-vein thrombosis occurred in 37 of 957 patients (3.9%) in the pneumatic compression group and in 41 of 985 patients (4.2%) in the control group (relative risk, 0.93; 95% confidence interval [CI], 0.60 to 1.44;  $P=0.74$ ). Findings from the secondary analyses of the primary outcome in the modified intention-to-treat and per-protocol populations were consistent with

**Table 3. Primary Outcome of Incident Proximal Lower-Limb Deep-Vein Thrombosis in the Modified Intention-to-Treat and Per-Protocol Populations.\***

Variable	Modified Intention-to-Treat Population		Per-Protocol Population	
	Pneumatic Compression Group (N=991)	Control Group (N=1012)	Pneumatic Compression Group (N=959)	Control Group (N=984)
Incident proximal lower-limb deep-vein thrombosis — no./total no. (%)†	37/957 (3.9)	41/985 (4.2)	35/929 (3.8)	41/957 (4.3)
Relative risk (95% CI)	0.93 (0.60–1.44)‡	Reference	0.88 (0.57–1.37)	Reference
Adjusted relative risk (95% CI)§	0.93 (0.61–1.41)	Reference	0.89 (0.58–1.36)	Reference
Median no. of days to the primary outcome event (IQR)	9 (5–15)	8 (5–12)	8 (5–15)	8 (5–12)
Unadjusted hazard ratio (95% CI)	0.95 (0.61–1.48)	Reference	0.90 (0.57–1.41)	Reference
Adjusted hazard ratio (95% CI)				
After incorporating trial site as a random effect¶	1.03 (0.66–1.62)	Reference	1.00 (0.64–1.58)	Reference
After accounting for the competing risk of death	0.97 (0.62–1.51)	Reference	0.93 (0.59–1.46)	Reference

\* Incident (i.e., new) lower-limb deep-vein thromboses were those that were detected on twice-weekly lower-limb ultrasonography after the third calendar day since randomization until ICU discharge, death, attainment of full mobility, or trial day 28, whichever occurred first. Deep-vein thromboses that were detected on trial days 1 to 3 were considered to be prevalent (i.e., preexisting) and were not included in the primary outcome analysis. The per-protocol population comprised all the patients who received the assigned intervention and had at least one ultrasonographic study performed. The 95% confidence intervals (CIs) have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible.

† The denominators represent the number of patients who were evaluated for incident proximal lower-limb deep-vein thrombosis.

‡ P=0.74.

§ A generalized linear mixed model was used to estimate the adjusted relative risk after trial site was incorporated as a random effect. For the modified intention-to-treat population, the least-squares means ( $\pm$ SE) were  $-3.92\pm 0.35$  for the pneumatic compression group and  $-3.84\pm 0.35$  for the control group, with an estimate of the variance of the random center intercept of  $1.03\pm 0.57$ .

¶ The Cox proportional-hazards model was used to estimate the adjusted hazard ratio after trial site was incorporated as a random effect and adjustment was made for the type of heparin used (unfractionated vs. low-molecular-weight heparin), location before ICU admission (hospital ward vs. other location), type of admission (trauma vs. other type), use of femoral central venous catheter (yes vs. no), and heart failure (present vs. absent).

|| The Cox proportional-hazards model was used to estimate the adjusted hazard ratio after the competing risk of death was accounted for and adjustment was made for the type of heparin used, location before ICU admission, type of admission, use of femoral central venous catheter, and heart failure.

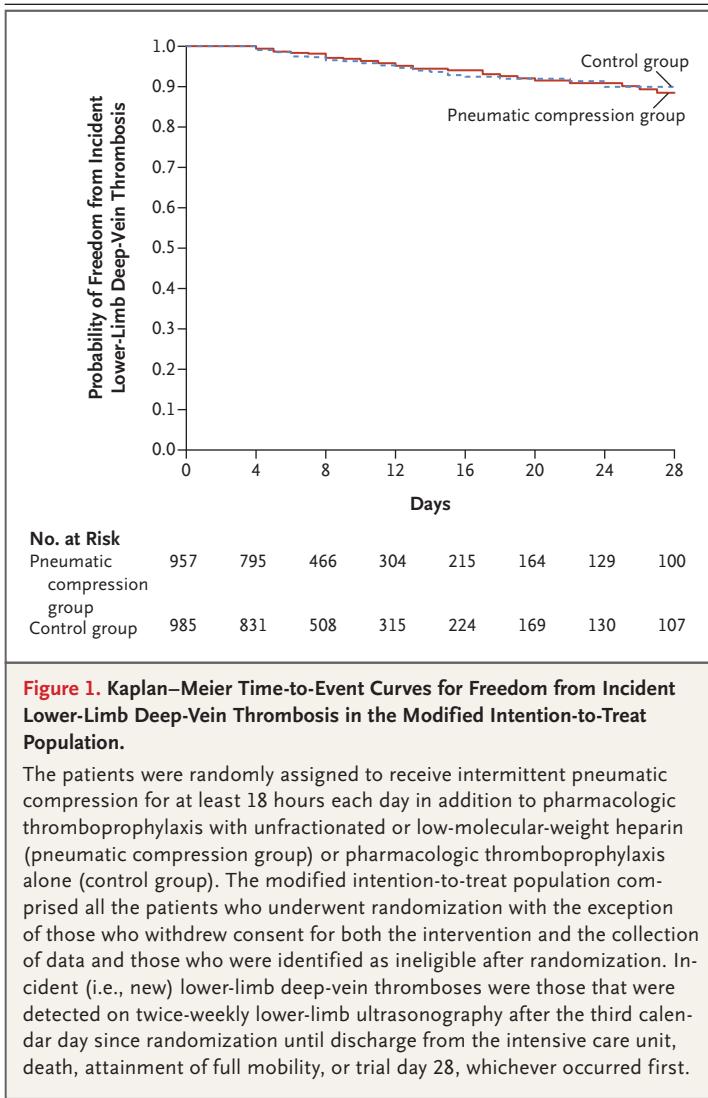
those from the primary outcome analysis (Table 3 and Fig. 1, and Fig. S2 in the Supplementary Appendix). There was no evidence of heterogeneity in the treatment effect with respect to the primary outcome across subgroups (Fig. S3 in the Supplementary Appendix).

## SECONDARY OUTCOMES

Secondary and exploratory outcomes did not differ significantly between the trial groups (Table 4, and Table S9 and Fig. S4 in the Supplementary Appendix). The percentage of patients who had prevalent proximal deep-vein thromboses did not differ significantly between the pneumatic compression group and the control group (3.4% [34 of 991 patients] vs. 2.7% [27 of 1012 patients]; rela-

tive risk, 1.29; 95% CI, 0.78 to 2.12). The percentage of patients who had any lower-limb deep-vein thromboses also did not differ significantly between the pneumatic compression group and the control group (9.6% [95 of 991 patients] vs. 8.4% [85 of 1012 patients]; relative risk, 1.14; 95% CI, 0.86 to 1.51).

Pulmonary embolism occurred in 8 of 991 patients (0.8%) in the pneumatic compression group and in 10 of 1012 patients (1.0%) in the control group (relative risk, 0.82; 95% CI, 0.32 to 2.06). A composite outcome of venous thromboembolism that included pulmonary embolism or all prevalent and incident lower-limb deep-vein thromboses occurred in 103 of 991 patients (10.4%) in the pneumatic compression group and in 95



of 1012 patients (9.4%) in the control group (relative risk, 1.11; 95% CI, 0.85 to 1.44).

The rates of death from any cause (assessed at ICU discharge, 28 days, hospital discharge, and 90 days) did not differ significantly between the two trial groups. The composite outcome of lower-limb deep-vein thrombosis, pulmonary embolism, or death from any cause at 28 days occurred in 231 of 990 patients (23.3%) in the pneumatic compression group and in 243 of 1011 patients (24.0%) in the control group (relative risk, 0.97; 95% CI, 0.83 to 1.14).

The percentages of patients who had lower-limb skin injury or ischemia did not differ significantly between the pneumatic compression group and the control group (Table 4). There were

no reports of serious adverse events (Table S10 in the Supplementary Appendix). Intermittent pneumatic compression was withheld at the request of the patient or family in 63 of 991 patients (6.4%) in the pneumatic compression group, accounting for 225 of 7717 total days of the trial intervention (2.9%) (Table S5 in the Supplementary Appendix).

#### SENSITIVITY ANALYSES

The incidence of proximal lower-limb deep-vein thrombosis did not differ significantly between the pneumatic compression group and the control group in various sensitivity analyses. The sensitivity analyses were conducted to address different cutoff 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 (Table S11 in the Supplementary Appendix).

#### DISCUSSION

In the PREVENT trial, adjunctive intermittent pneumatic compression had no effect on the incidence of proximal deep-vein thrombosis among critically ill patients who were receiving pharmacologic thromboprophylaxis. The lack of effect was observed in the modified intention-to-treat and per-protocol analyses and across all subgroup and sensitivity analyses. The addition of intermittent pneumatic compression to pharmacologic thromboprophylaxis did not result in a lower incidence of pulmonary embolism or a composite outcome of venous thromboembolism or death from any cause at 28 days than pharmacologic thromboprophylaxis alone.

The lack of effect of intermittent pneumatic compression in our trial is unlikely to represent underexposure, as reflected by the data on device use. The use of intermittent pneumatic compression in the control group was minimal and largely per protocol. The use of graduated compression stockings was limited, thereby reducing the risk of contamination of the effect of intermittent pneumatic compression. Our trial therefore does not support the adjunctive use of intermittent pneumatic compression to lower the incidence of proximal lower-limb deep-vein thrombosis among critically ill patients receiving pharmacologic thromboprophylaxis.

**Table 4. Secondary Outcomes in the Modified Intention-to-Treat Population.\***

Outcome	Pneumatic Compression Group (N=991)*	Control Group (N=1012)*	Relative Risk (95% CI)
Venous thromboembolism secondary outcomes — no./total no. (%)			
Incident proximal or distal deep-vein thromboses†	49/957 (5.1)	55/985 (5.6)	0.92 (0.63–1.33)
Prevalent proximal deep-vein thromboses	34/991 (3.4)	27/1012 (2.7)	1.29 (0.78–2.12)
Proximal, distal, incident, or prevalent lower-limb deep-vein thromboses	95/991 (9.6)	85/1012 (8.4)	1.14 (0.86–1.51)
Pulmonary embolism	8/991 (0.8)	10/1012 (1.0)	0.82 (0.32–2.06)
Venous thromboembolism: lower-limb deep-vein thrombosis or pulmonary embolism	103/991 (10.4)	95/1012 (9.4)	1.11 (0.85–1.44)
Non–lower-limb thrombosis	13/991 (1.3)	11/1012 (1.1)	1.21 (0.54–2.68)
Safety outcomes			
Lower-limb skin injury — no./total no. (%)‡			
Stage I: nonblanchable erythema	25/991 (2.5)	22/1012 (2.2)	1.16 (0.66–2.04)
Stage II: partial-thickness ulceration	4/991 (0.4)	6/1012 (0.6)	0.68 (0.19–2.41)
Stage III or IV: full-thickness skin or tissue loss	0/991	0/1012	NA
Limb ischemia — no./total no. (%)			
Toes	5/991 (0.5)	10/1012 (1.0)	0.51 (0.18–1.49)
Up to foot	3/991 (0.3)	3/1012 (0.3)	1.02 (0.21–5.05)
Up to leg	0/991	1/1012 (0.1)	NA
Serious adverse events — no./total no. (%)§	0/991	0/1012	NA
Median no. of days free from mechanical ventilation (IQR)¶	24 (11–28)	23 (8–28)	NA
Median no. of days free from vasopressors (IQR)¶	28 (23–28)	28 (23–28)	NA
Median no. of days outside the ICU (IQR)¶	19 (0–23)	18 (0–23)	NA
Death from any cause — no./total no. (%)			
During ICU stay	151/989 (15.3)	155/1012 (15.3)	1.00 (0.81–1.23)
At 28 days**	145/990 (14.6)	167/1011 (16.5)	0.89 (0.72–1.09)
During hospital stay	248/985 (25.2)	262/1010 (25.9)	0.97 (0.84–1.13)
At 90 days**	258/990 (26.1)	270/1011 (26.7)	0.98 (0.84–1.13)
Composite outcome of lower-limb deep-vein thrombosis, pulmonary embolism, or death from any cause at 28 days — no./total no. (%)	231/990 (23.3)	243/1011 (24.0)	0.97 (0.83–1.14)

\* The 95% confidence intervals have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible. NA denotes not applicable.

† The denominators represent the numbers of patients who were evaluated for incident proximal lower-limb deep-vein thrombosis.

‡ Skin ulceration was staged according to the National Pressure Ulcer Advisory Panel classification, and the highest stage during the trial period was reported.<sup>13</sup>

§ Serious adverse events were defined as skin pressure ulcers of stage 3 or 4 (according to the National Pressure Ulcer Advisory Panel classification<sup>18</sup>) or ischemia due to intermittent pneumatic compression.

¶ Calculations of days free from mechanical ventilation, days free from vasopressors, and days outside the ICU were based on 28 days of observation. There were no missing values for days free of mechanical ventilation and days free from vasopressors, and the median values were calculated for all patients, including those never receiving mechanical ventilation or vasopressors.

|| Data regarding death during ICU stay and days outside the ICU were not available for two patients because they remained in the ICU, and data regarding death during hospital stay were not available for eight patients because they remained in the hospital ward.

\*\* Data regarding death from any cause at 28 days and at 90 days were not available for two patients in the trial cohort who were discharged from the hospital before day 28 and were lost to follow-up.

Intermittent pneumatic compression has been reported to cause skin injury. The Clots in Legs or Stockings after Stroke (CLOTS) 3 trial involving hospitalized patients with stroke reported that skin injuries occurred in 3.1% of the patients who received intermittent pneumatic compression and in 1.4% of the patients who did not.<sup>10</sup> In contrast, we observed no between-group difference in the percentage of patients who had skin injuries. This may be related, at least in part, to the younger age of the patients in the PREVENT trial, who were approximately 20 years younger and might have had less skin fragility and more mobility than the patients in the CLOTS 3 trial.

The main limitation in our trial was the fact that the incidence of the primary outcome in the control group was lower than expected, which reduced the power of the trial; consequently, our results do not rule out the possibility of a clinically important treatment effect (a benefit of as much as 40% or a harm of as much as 44%). We were not able to perform the trial in a blinded manner; patients, caregivers, and ultrasonographers were aware of the trial-group assignment owing to the nature of the intervention. Although adherence to the trial protocol was very good, some patients did not have a baseline ultrasonographic study, and some follow-up ultrasonographic studies were not performed because of the unavailability of ultrasonographers, primarily on weekends. Nevertheless, the frequency of ul-

trasonography was close to the planned schedule. In addition, findings from sensitivity analyses in which multiple imputation and worst-case and best-case scenarios were used were consistent with those from the primary outcome analysis. Because of the pragmatic nature of the trial, participating sites used different intermittent pneumatic compression devices, both knee-length and thigh-length sleeves, and foot pumps in some patients. Our trial does not address the isolated effect of each component.

In conclusion, among critically ill patients who were receiving pharmacologic thromboprophylaxis, we found no benefit of adjunctive intermittent pneumatic compression in the prevention of incident proximal lower-limb deep-vein thrombosis.

Supported by a grant from King Abdulaziz City for Science and Technology (AT 34-65) and a grant from King Abdullah International Medical Research Center (RC12/045/R).

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the chair and members of the data monitoring committee (Dr. Kathryn Rowan [chair], Director of Scientific and Strategic Development and Clinical Trials Unit, Director, Intensive Care National Audit and Research Centre, and the Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London; Dr. Lehana Thabane, the Department of Health Research Methods, Evidence, and Impact and Departments of Anesthesia and Pediatrics, McMaster University, Biostatistics Unit, St. Joseph's Healthcare Hamilton, and Population Health Research Institute, Hamilton Health Sciences, Hamilton, ON, Canada; and Dr. David Garcia, the Department of Medicine, Division of Hematology, University of Washington, Seattle) and the staff at Compression Solutions for providing in-kind devices and supplies to one of the sites.

#### APPENDIX

The authors' full names and academic degrees are as follows: Yaseen M. Arabi, M.D., Fahad Al-Hameed, M.D., Karen E.A. Burns, M.D., Sangeeta Mehta, M.D., Sami J. Alsolamy, M.D., M.P.H., Mohammed S. Alshahrani, M.D., Yasser Mandourah, M.D., Ghaleb A. Almekhlafi, M.D., Mohammed Almaani, M.D., Ali Al Bshabshe, M.D., Simon Finfer, M.D., Zia Arshad, M.D., M.B., B.S., Imran Khalid, M.D., Yatin Mehta, M.D., Atul Gaur, M.D., Hassan Hawa, M.B., Ch.B., Hergen Buscher, M.D., Hani Lababidi, M.D., Abdulsalam Al Aithan, M.D., Sheryl A.I. Abdulkahil, R.N., Jesna Jose, M.Sc., Lara Y. Afesh, M.S.N., and Abdulaziz Al-Dawood, M.D.

The authors' affiliations are as follows: the College of Medicine, King Saud Bin Abdulaziz University for Health Sciences (Y.M.A., S.J.A., S.A.I.A., A.A.-D.), the Departments of Intensive Care (Y.M.A., S.J.A., S.A.I.A., A.A.-D.) and Emergency Medicine, (S.J.A.), Ministry of National Guard Health Affairs, Military Medical Services, Ministry of Defense (Y. Mandourah), the Department of Intensive Care Services, Prince Sultan Military Medical City (G.A.A.), the Department of Pulmonary and Critical Care Medicine, King Fahad Medical City (M.A., H.L.), Critical Care Medicine Department, King Faisal Specialist Hospital and Research Center (H.H.), and the Department of Biostatistics and Bioinformatics (J.J.) and Research Office (L.Y.A.), King Abdullah International Medical Research Center (Y.M.A., S.J.A., S.A.I.A., A.A.-D.), Riyadh, College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, and the Intensive Care Department, Ministry of National Guard Health Affairs (F.A.-H.), and Critical Care Section, Department of Medicine, King Faisal Specialist Hospital and Research Center (I.K.), Jeddah, the Department of Emergency and Critical Care Medicine, College of Medicine, King Fahd Hospital of the University, Imam Abdulrahman Bin Faisal University (M.S.A.), Dammam, the Department of Critical Care Medicine, King Khalid University, Asir Central Hospital (A.A.B.), Abha, and King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, and the Intensive Care Division, Department of Medicine, King Abdulaziz Hospital (A.A.A.), Al Ahsa — all in Saudi Arabia; St. Michael's Hospital, Li Ka Shing Knowledge Institute (K.E.A.B.), the Department of Medicine, Sinai Health System (S.M.), and Interdepartmental Division of Critical Care Medicine, University of Toronto (K.E.A.B., S. M.) — all in Toronto; the George Institute for Global Health (S.F.), the Department of Intensive Care Medicine, Centre for Applied Medical Research, St. Vincent's Hospital (H.B.), and the University of New South Wales, Sydney (S.F., H.B.), and Intensive Care Department, Gosford Hospital, Gosford, NSW (A.G.) — all in Australia; and the Department of Anesthesiology and Critical Care, King George's Medical University, Lucknow (Z.A.), and Institute of Critical Care and Anesthesiology, Medanta—The Medicity, Gurgaon (Y. Mehta) — both in India.

## REFERENCES

1. Cook DJ, Crowther MA. Thromboprophylaxis in the intensive care unit: focus on medical-surgical patients. *Crit Care Med* 2010;38:Suppl:S76-S82.
2. Attia J, Ray JG, Cook DJ, Douketis J, Ginsberg JS, Geerts WH. Deep vein thrombosis and its prevention in critically ill adults. *Arch Intern Med* 2001;161:1268-79.
3. Alhazzani W, Lim W, Jaeschke RZ, Murad MH, Cade J, Cook DJ. Heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care Med* 2013;41:2088-98.
4. Arabi YM, Khedr M, Dara SI, et al. Use of intermittent pneumatic compression and not graduated compression stockings is associated with lower incident VTE in critically ill patients: a multiple propensity scores adjusted analysis. *Chest* 2013;144:152-9.
5. Ibrahim EH, Iregui M, Prentice D, Sherman G, Kollef MH, Shannon W. Deep vein thrombosis during prolonged mechanical ventilation despite prophylaxis. *Crit Care Med* 2002;30:771-4.
6. Kaplan D, Casper TC, Elliott CG, et al. VTE incidence and risk factors in patients with severe sepsis and septic shock. *Chest* 2015;148:1224-30.
7. Qaseem A, Chou R, Humphrey LL, Starkey M, Shekelle P. Venous thromboembolism prophylaxis in hospitalized patients: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2011;155:625-32.
8. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:Suppl:e195s-e226s.
9. Kakkos SK, Caprini JA, Geroulakos G, et al. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism. *Cochrane Database Syst Rev* 2016;9:CD005258.
10. CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration. 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.
11. Limpus A, Chaboyer W, McDonald E, Thalib L. Mechanical thromboprophylaxis in critically ill patients: a systematic review and meta-analysis. *Am J Crit Care* 2006;15:402-10.
12. Lauvrak V, Hafstad E, Fure B. Intermittent pneumatic compression to prevent venous thromboembolism in hospitalized patients: systematic scoping review. Oslo: Knowledge Center for the Health Services at the Norwegian Institute of Public Health, 2016.
13. Afshari A, Fenger-Eriksen C, Monreal M, Verhamme P. European guidelines on perioperative venous thromboembolism prophylaxis: mechanical prophylaxis. *Eur J Anaesthesiol* 2018;35:112-5.
14. Cook D, Laporta D, Skrobik Y, et al. Prevention of venous thromboembolism in critically ill surgery patients: a cross-sectional study. *J Crit Care* 2001;16:161-6.
15. Lacherade JC, Cook D, Heyland D, Chrusch C, Brochard L, Brun-Buisson C. Prevention of venous thromboembolism in critically ill medical patients: a Franco-Canadian cross-sectional study. *J Crit Care* 2003;18:228-37.
16. Arabi YM, Alsolamy S, Al-Dawood A, et al. Thromboprophylaxis using combined intermittent pneumatic compression and pharmacologic prophylaxis versus pharmacologic prophylaxis alone in critically ill patients: study protocol for a randomized controlled trial. *Trials* 2016;17:390.
17. Arabi Y, Al-Hameed F, Burns KEA, et al. Statistical analysis plan for the Pneumatic CompREssion for PreVENTing Venous Thromboembolism (PREVENT) trial: a study protocol for a randomized controlled trial. *Trials* 2018;19:182.
18. Black J, Baharestani MM, Cuddigan J, et al. National Pressure Ulcer Advisory Panel's updated pressure ulcer staging system. *Adv Skin Wound Care* 2007;20:269-74.

Copyright © 2019 Massachusetts Medical Society.