

ORIGINAL ARTICLE

Adjunctive Intermittent Pneumatic Compression for Venous Thromboprophylaxis

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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 (≥ 14 , ≥ 16 , or ≥ 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.)

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VENOUS THROMBOEMBOLISM, INCLUDING both deep-vein thrombosis and pulmonary embolism, is a complication of critical illness.^{1,2} 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.³ However, deep-vein thrombosis develops in 5 to 20% of critically ill patients despite pharmacologic thromboprophylaxis.^{1,4-6}

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.^{7,9} 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.¹⁰ Intermittent pneumatic compression is recommended for patients with a contraindication to pharmacologic thromboprophylaxis,^{7,8} 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.^{11,12} 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,^{7,8,13} and practice variation in the use of adjunctive intermittent pneumatic compression.^{14,15} 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.¹⁶ 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 (≥ 14 , ≥ 16 , or ≥ 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.^{16,17} 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 ± 0.35 for the pneumatic compression group and -3.84 ± 0.35 for the control group, with an estimate of the variance of the random center intercept of 1.03 ± 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

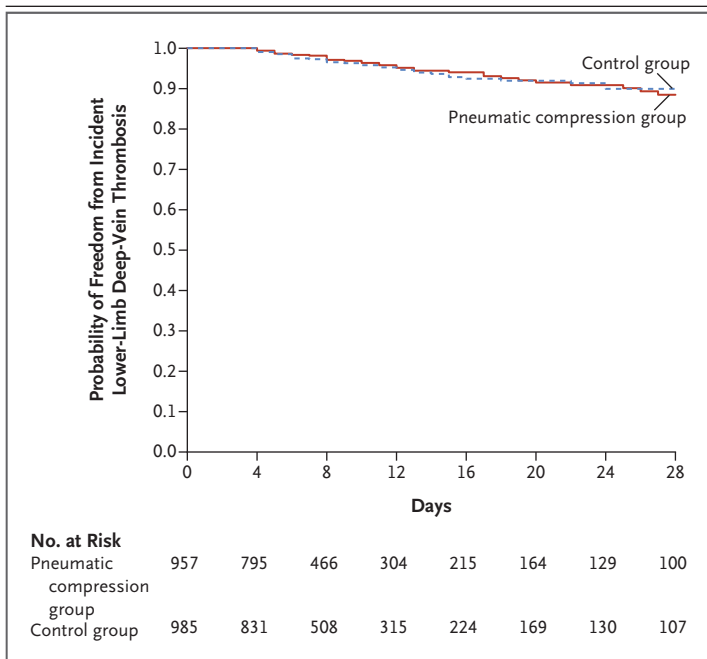


Figure 1. Kaplan–Meier Time-to-Event Curves for Freedom from Incident Lower-Limb Deep-Vein Thrombosis in the Modified Intention-to-Treat Population.

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. 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 discharge from the intensive care unit, death, attainment of full mobility, or trial day 28, whichever occurred first.

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.¹⁸

§ Serious adverse events were defined as skin pressure ulcers of stage 3 or 4 (according to the National Pressure Ulcer Advisory Panel classification¹⁸) 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.¹⁰ 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.

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

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APPENDIX

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Does this recent randomised controlled trial of intermittent pneumatic compression devices really indicate that they are ineffective in critical care patients?

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Provenance: This is an invited article by the Section Editor Xue-Zhong Xing [National Cancer Center (NCC)/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, China].

Comment on: Arabi YM, Al-Hameed F, Burns KEA, *et al.* Adjunctive intermittent pneumatic compression for venous thromboprophylaxis. *N Engl J Med* 2019;380:1305-15.

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Arabi *et al.* (1) reported the results of their multicentre, international randomised controlled trial (RCT) (ISRCTN44653506) of adjunctive Intermittent Pneumatic Compression (IPC) for Venous Thromboprophylaxis in *N Engl J Med* in Feb 2019.

Their purpose was to reliably establish whether IPC in critically ill patients receiving pharmacologic thromboprophylaxis [heparin/low molecular weight heparins (LMWH)] would result in a lower incidence of deep vein thrombosis (DVT) than heparin/LMWH alone.

Within 48 hours of admission to a critical care unit they randomly assigned adult patients to heparin/LMWH plus IPC for ≥ 18 hours each day (intervention) or heparin/LMWH alone (control). The primary outcome was a new proximal DVT, detected on compression Duplex ultrasound (CDU) of the deep veins of the legs, carried out twice a week, starting on day three after randomization until discharge from critical care, death, recovery of mobility, or four weeks after randomisation, whichever occurred first.

They randomised 2,003 patients, 991 were randomised to the intervention (IPC) arm and 1,012 to the control arm. Adherence was reasonable, IPC was worn for a median of 22 hours per day for a median of 7 days. A proximal DVT was identified in 37 of 957 (3.9%) in the IPC arm and in 41 of 985 (4.2%) in the control arm [risk ratio (RR) = 0.93; 95% confidence interval (CI), 0.60 to 1.44; $P=0.74$]. Pulmonary embolism (PE) or any DVT was detected in 103 of 991

(10.4%) in the IPC arm and in 95 of 1,012 (9.4%) in the control arm (RR = 1.11; 95% CI, 0.85 to 1.44), and death from any cause at 90 days occurred in 258 of 990 (26.1%) in the IPC arm and 270 of 1,011 (26.7%), in the control arm (RR = 0.98; 95% CI, 0.84 to 1.13).

The authors concluded that in patients in critical care who were receiving heparin/LMWH, the use of IPC did not significantly reduce the risk of venous thromboembolism or death compared with heparin/LMWH alone.

As the lead for the CLOTS trials collaboration, I was personally surprised by this result. In 2013, we reported the results of the CLOTS3 trial (ISRCTN93529999) (2). We aimed to determine if IPC reduced the risk of DVT, PE and death in immobile stroke patients admitted to hospital in the UK. The background to the CLOTS3 trial was that DVT, PE and related deaths were regarded as important complications in patients hospitalised with severe stroke (3,4). However, previous trials, including a trial of almost 20,000 patients had shown that whilst prophylactic heparin might reduce the risk of DVT and PE, it increased the risk of bleeding, and had no net benefit (5,6). Subsequent individual patient data meta-analyses could not identify any specific subgroup of stroke patients who might benefit from prophylactic heparin (7). Also, trials had demonstrated that graduated compression stockings did not reduce the incidence of DVT in immobile stroke patients (8). A systematic review of RCTs in patients undergoing surgery

had suggested that IPC reduced the risk of DVT (9). The CLOTS3 trial was a multicentre parallel group RCT assessing IPC in immobile patients with acute stroke. We recruited patients from day 0 to day 3 of admission and randomised them to receive IPC or no IPC on a background of normal care. A technician who was masked to treatment allocation performed a CDU 7 to 10 days and, wherever practical, 25 to 30 days after randomisation. Patients were followed for 6 months to detect later symptomatic VTE and deaths. The primary outcome was proximal DVT on a screening CDU or any symptomatic DVT in the proximal veins, confirmed on imaging, within 30 days of randomisation. Patients were analysed according to their treatment allocation. We enrolled 2,876 immobile stroke patients in 94 centres in the UK. A proximal DVT was detected in 122 (8.5%) of 1,438 in the IPC arm and 174 of 1,438 (12.1%) in the no IPC arm; an absolute reduction in risk of 3.6% (95% CI, 1.4 to 5.8) [adjusted risk ratio 0.69 (95% CI, 0.55 to 0.86); $P=0.001$]. Survival to 6 months was significantly better in the IPC arm [hazard ratio 0.86 (95% CI, 0.74 to 0.99), $P=0.042$]. We concluded that IPC was effective in reducing the incidence of DVT and possibly improving survival in patients who are unable to walk independently after stroke.

There are no definite explanations for these apparently divergent results. Both trials were methodologically similar and quite robust. However, compared with CLOTS3, Arabi *et al.* did not attempt to mask those carrying out the CDUs which could have led to some expectation bias. However, this would generally be expected to lead to an over estimate of treatment effect. Also, their follow up protocol, although intensive with frequent scanning, was dependent on patients' length of stay in critical care. Ideally, in RCTs follow up is to a fixed time point after randomisation, and will therefore be similar in the two arms. However, there was little difference in the actual duration of follow up between the two arms.

There are other differences between the trials. This trial included a far more heterogeneous group of patients in terms of their underlying condition—most were admitted with medical problems—few were post-surgical or had stroke.

In critical care prophylaxis with heparin/LMWH is recommended for those judged to be at low bleeding risk. In ischaemic stroke, prophylaxis with heparin/LMWH is far more controversial. Previous meta-analyses of trials of heparins/LMWH in medical patients, including those with stroke ($n=36,122$) have shown significant reductions

in pulmonary emboli (three in 1,000, 95% CI, 1 to 3), but only non-significant reduction in deaths (six in 1,000, 95% CI, 0 to 11), perhaps partly because any reduction in major VTE was offset by a significant increase in major bleeds (four in 1,000, 95% CI, 1 to 7) (10,11). Interestingly, studies in critical care mirror these data (12). In this trial heparin/LMWH was given to all of the patients whereas in CLOTS3 only 21.5% received anticoagulation or alteplase—this might contribute to the lower rate of proximal DVT (3.9%) and VTE (9.9%) within 28 days compared with the CLOTS3 trial (10.3%, 19.9% respectively within 30 days).

The sample size of this trial was based on an expected absolute risk reduction of 3% from an expected proximal DVT rate of 7% in the control arm to 4%, but the actual risk was 3.9% across the arms. Therefore, the trial had much less power than predicted. The 95% CI of their result (95% CI, 0.60 to 1.44), includes the point estimate from the CLOTS 3 trial (0.69), so they may simply have been underpowered and unlucky, and failed to identify an effect similar to that seen in CLOTS3.

A subgroup analysis of CLOTS3 based on the baseline use of alteplase or anticoagulants showed no significant interaction with the effect of IPC, however this subgroup analysis was underpowered. Given that anticoagulation and IPC are presumed to be working on two different sides of Virchow's triad, I find it difficult to imagine that the presence of anticoagulation would negate the effectiveness of IPC. However, because of the reduced incidence of VTE with anticoagulation, this would make the effect more difficult to demonstrate in a randomised trial because the event rates would be lower.

Both trials used IPC, but in CLOTS3 all patients had thigh-length compression delivered by a single device (Covidien SCD Express system) which delivered, sequential, circumferential compression at a frequency determined by the rate of venous refill. Arabi *et al.* took a more pragmatic approach and did not specify the type of IPC. Only 18.7% delivered thigh-length compression, with the remainder providing either calf only or foot compression. A range of devices will have provided different types of compression. There have been no reliable trials to indicate whether the type of compression (thigh *vs.* calf *vs.* foot; single or sequential, circumferential or other, fast or slow, fixed or variable frequency) impacts on the effectiveness in reducing the risk of VTE, but different manufacturers justify their approaches on the basis venous flow rates.

In conclusion, the neutral result presented by this trial is

unexpected. Given the strong evidence that IPC is effective in peri operative patients and those with stroke I wonder whether lack of sufficient statistical power and perhaps the type of IPC used might explain their result. I think it would be justified to carry out a larger RCT, testing thigh-length, sequential IPC in a broad range of high-risk critical care patients with and without pharmacological prophylaxis before concluding that IPC is ineffective.

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Footnote

Conflicts of Interest: M Dennis received departmental funding from the National Institute for Health Research Health Technology Assessment Boards to run the CLOTS 3 trial. Covidien provided compression equipment to the sites participating in the trial. M Dennis has no personal interest in Covidien and has never accepted any funding, grants or speakers fees from them.

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