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A Mobile Compression Device for Thrombosis Prevention in Hip and Knee Arthroplasty

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Investigation performed at the Scripps Clinic, La Jolla, California; Cleveland Clinic, Cleveland, Ohio; Twin Cities Orthopaedics, Edina, Minnesota; VA Palo Alto Health Care System, Palo Alto, California; Anderson Orthopaedic Clinic, Alexandria, Virginia; Washington University School of Medicine, St. Louis, Missouri; The Center, Orthopedic & Neurosurgical Care & Research, Bend, Oregon; Rubin Institute for Advanced Orthopedics, Baltimore, Maryland; Hospital for Special Surgery, New York, NY; and Arkansas Specialty Orthopaedics, Little Rock, Arkansas

Background: Venous thromboembolic events, either deep venous thrombosis or pulmonary embolism, are important complications in patients undergoing knee or hip arthroplasty. The purpose of this study was to evaluate the effectiveness of a mobile compression device (ActiveCare+S.F.T.) with or without aspirin compared with current pharmacological protocols for prophylaxis against venous thromboembolism in patients undergoing elective primary unilateral arthroplasty of a lower-extremity joint.

Methods: A multicenter registry was established to capture the rate of symptomatic venous thromboembolic events following primary knee arthroplasty (1551 patients) or hip arthroplasty (1509 patients) from ten sites. All patients were eighteen years of age or older with no known history of venous thromboembolism, coagulation disorder, or solid tumor. Use of the compression device began perioperatively and continued for a minimum of ten days. Patients with symptoms of deep venous thrombosis or pulmonary embolism underwent duplex ultrasonography and/or spiral computed tomography. All patients were evaluated at three months postoperatively to document any evidence of deep venous thrombosis or pulmonary embolism.

Results: Of 3060 patients, twenty-eight (0.92%) had venous thromboembolism (twenty distal deep venous thrombi, three proximal deep venous thrombi, and five pulmonary emboli). One death occurred, with no autopsy performed. Symptomatic venous thromboembolic rates observed in patients who had an arthroplasty of a lower-extremity joint using the mobile compression device were noninferior (not worse than), at a margin of 1.0%, to the rates reported for pharmacological prophylaxis, including warfarin, enoxaparin, rivaroxaban, and dabigatran, except in the knee arthroplasty group, in which the mobile compression device fell short of the rate reported for rivaroxaban by 0.06%.

Conclusions: Use of the mobile compression device with or without aspirin for patients undergoing arthroplasty of a lower-extremity joint provides a noninferior risk for the development of venous thromboembolism compared with current pharmacological protocols.

Level of Evidence: Therapeutic Level II. See Instructions for Authors for a complete description of levels of evidence.

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A commentary by Piers Yates, MBBS(Hons), BSc(Hons), MRCS(Eng), FRCS(Tr&Orth), FRACS(Ortho), FAOrthA, is linked to the online version of this article at jbjs.org.

Deep venous thrombosis and pulmonary embolism continue to be important complications after orthopaedic surgical procedures on the lower extremity. Several different modalities have been implicated as responsible for the decreased prevalence of thromboembolic events after surgery, including decreased surgical time and early mobilization. Two broad groups of prophylactic modalities are routinely used: pharmacological agents (anticoagulant and antiplatelet) and mechanical compression devices. Both are effective for the prevention of venous thromboembolism[1-5]; however, each carries its own advantages and disadvantages. The pharmacological agents have the risk of bleeding complications[1,3], which are especially high during the most vulnerable period for venous thromboembolism formation. The mechanical methods have the potential risk of being less efficacious, possibly related to variability in patient compliance, and often are not used following discharge to home. Many studies utilizing compression devices have been published[2,4,5], but all have relied on the use of compression devices while the patient is hospitalized or in a rehabilitation facility. The present study evaluated the efficacy of a mobile compression device (ActiveCare+S.F.T; Medical Compression Systems, Or Akiva, Israel) that is small and portable enough to send the patient home with the device. The use of this compression device for prophylaxis against venous thromboembolism could be recommended if adequate efficacy could be established and if it afforded a reduction in the risk of bleeding complications associated with pharmacological agents.

Previously, a randomized prospective study was powered to evaluate major bleeding events after hip arthroplasties with the pharmacological agent most utilized worldwide (Lovenox; enoxaparin) compared with the mobile compression device[6]. The device was found to be associated with significantly less major bleeding ($p = 0.0004$). Although the venous thromboembolism rate was equal in each arm of this randomized study, the study was not powered sufficiently to determine efficacy[6]. We are aware of no large-scale studies or registries that have evaluated the use of any mobile compression device with or without aspirin to prevent venous thromboembolism after lower-extremity joint arthroplasty.

In order to evaluate the efficacy of this mobile compression device, a registry was established at ten high-volume joint arthroplasty sites across the United States. The trial was designed as a noninferiority trial, which aimed to demonstrate that the mobile compression device was not worse than the comparator pharmacological agents by more than a small, prespecified amount (1.0%). The purpose of the registry was to evaluate the effectiveness of the mobile compression device with or without aspirin in lowering the potential risk of venous thromboembolism during and after hip or knee arthroplasty with the clinical end point of symptomatic deep venous thrombosis and/or pulmonary embolism within three months postoperatively. We compared these rates with the most commonly used pharmacological agents and protocols for noninferiority in preventing venous thromboembolism after arthroplasty of a lower-extremity joint.

Materials and Methods

Orthopaedic surgeons at ten sites in the United States participated in a registry to collect data on postoperative venous thromboembolism in patients who had an arthroplasty of a lower-extremity joint using the mobile compression device. Data were collected from April 1, 2011, to September 30, 2011, on consecutive patients. Data collection was at one designated site that maintained and analyzed the entire registry. Deidentified data from each of the other nine sites were sent to the data collection site. Institutional review board approval was obtained at each site. The trial was registered at ClinicalTrials.gov (NCT01984190). One patient returned for a follow-up evaluation at four weeks postoperatively and had no signs or symptoms of venous thromboembolism, but did not return at the three-month time point and was considered lost to follow-up. Another patient died in the hospital on postoperative day 3. The patient's family declined an autopsy, and therefore venous thromboembolic status could not be determined.

Inclusion and exclusion criteria were the same as those used in a prior study on safety[6] and in other randomized controlled studies of prophylaxis against venous thromboembolism[7-13]. Patients included in the registry were eighteen years of age or older and underwent primary unilateral hip arthroplasty (including hip resurfacing) or primary unilateral knee arthroplasty (including unicondylar knee arthroplasty) using only the mobile compression device with or without aspirin for the prevention of venous thromboembolism. Patients were excluded if they were scheduled for a revision surgery or had a history of venous thromboembolism, a coagulation disorder, a solid malignant tumor, or a major surgical procedure in the three months prior to the arthroplasty. The mobile compression device was applied to all patients perioperatively. The devices were applied to the contralateral leg during the surgical procedures for both knee and hip arthroplasties, and the device was applied to the operatively treated leg at the completion of the procedure before transferring the patient to the postanesthesia care unit. The device was used for a minimum of ten days with or without aspirin. The decision to use aspirin and the aspirin dosage were at the discretion of each surgeon participating in the registry.

This registry collected data on the occurrence of postoperative venous thromboembolism in patients who had an arthroplasty of a lower-extremity joint using this device for prophylaxis against venous thromboembolism. In addition to portability, this device has a liquid crystal display to allow the patient and medical personnel to monitor compliance. Another potential benefit of this mobile compression device is the synchronized flow technology. This technology synchronizes external compressions of the device to the patient's venous phasic flow such that compression occurs in synchronization with the natural venous phasic flow, allowing for a 66% increase in the peak venous velocity as measured at the common femoral vein[14].

If patients presented with symptoms consistent with a deep venous thrombosis or pulmonary embolism at any time before three months postoperatively, they were appropriately studied. At three months, patients completed a questionnaire or were asked routine questions describing any diagnosed deep venous thrombosis or pulmonary embolism event and were examined by the site clinician for swelling, redness, tenderness, and excessive warmth of the extremities. Symptomatic patients were studied by duplex ultrasound for deep venous thrombosis and spiral computed tomography (CT)-angiography for pulmonary embolism at the time of their symptoms within the three-month interval. Deep venous thrombosis was defined as proximal if the thrombus occurred in the popliteal vein or more proximally in the leg. Additional data collected included type of surgery (hip or knee arthroplasty), patient demographics (age, sex, height, and weight), and aspirin use (yes or no). Aspirin usage was assessed dichotomously because the sites that used aspirin had varying protocols for dose and duration of use. The frequency of anesthesia type (percent regional, general, or combined) was collected from each of the sites. Patient characteristics are presented in the Appendix.

Statistical Analysis

The prevalence of venous thromboembolism with so-called standard pharmacological prophylaxis is quite low; hence, establishing that the compression device would be superior to these other regimens would be difficult. Taking

TABLE I Rate of Symptomatic Venous Thromboembolic Events in Patients Using a Mobile Compression Device with or without Aspirin

Event	Total Joint Arthroplasty (N = 3060)	Total Hip Arthroplasty (N = 1509)	Total Knee Arthroplasty (N = 1551)
Venous thromboembolism *(no. [%])*	28 (0.92)	8 (0.53)	20 (1.29)
Deep venous thrombosis *(no. [%])*	23 (0.75)	5 (0.33)	18 (1.16)
Proximal deep venous thrombosis *(no. [%])*	3 (0.10)	1 (0.07)	2 (0.13)
Pulmonary embolism *(no. [%])*	5 (0.16)	3 (0.20)	2 (0.13)

this into consideration, we hypothesized that the mobile compression device would have approximately the same efficacy as pharmacological prophylaxis without the risk of major bleeding. We thus designed a noninferiority study of the mobile compression device versus the standard pharmacological prophylaxis, including warfarin, enoxaparin, rivaroxaban, and dabigatran, with symptomatic end points and similar patient demographics.

Formally, a noninferiority study aims to demonstrate that a treatment is not worse than the comparator (the control) by more than a prespecified, small amount, commonly known as the noninferiority margin. The choice of the noninferiority margin is somewhat subjective; we adopted a 1.0% margin in the present study, with the belief that a 1.0% difference in venous thromboembolism rates between the mobile compression device registry cohort and the pharmacological comparators would not constitute a clinically meaningful difference (e.g., a difference of such magnitude that a physician might choose one or the other regimen). Our margin of 1.0% is more rigorous than the 1.5% margin used in most drug studies. The U.S. Food and Drug Administration published guidelines for the design and conduct of noninferiority trials[15], and these trials have been widely adopted by the pharmaceutical industry.

The noninferiority margin was based on absolute event rate differences. We accepted that the mobile compression device was noninferior if the upper bound of the one-sided 97.5% confidence interval (97.5% CI) around the estimated difference in event rates was below the noninferiority margin. The sample size calculation was based on symptomatic venous thromboembolism rates in patients using warfarin[16-19], enoxaparin[8,11-13], rivaroxaban[8,11-13], and dabigatran[9,10,20] from previously published clinical trial data. We calculated a number of power comparisons prior to initiating the study. We found that sample sizes of 1500 in the device group and any drug group would be sufficient to achieve power in excess of 90% to detect a noninferiority margin difference between the venous thromboembolism proportions in the two groups of 1.0%. In these calculations, we considered venous thromboembolism rates in the drug groups to be between 0.5% and 1.0% and the venous thromboembolism rate in the device group was taken to be the drug group rate + 1.0% under the null hypothesis of inferiority. Power was calculated for the case when the actual venous thromboembolism rate for the device was identical to that for the drug comparator. The test statistic used was the one-sided score test, with the significance level set at 0.025.

SPSS software (version 13.0; SPSS, Chicago, Illinois) and NCSS software (version 7.1.21; NCSS, Kaysville, Utah) were used for sample size calculations and analysis of the registry data. Means were calculated to describe continuous variables (age, height, and weight), and frequencies were calculated to describe categorical variables (surgery type, aspirin use, and the occurrence of symptomatic venous thromboembolism). Upper bound 97.5% CIs were calculated around the observed difference in the rate of venous thromboembolism between the mobile compression device and each drug comparator.

Source of Funding

The funding for this registry was provided by Medical Compression Systems (Or Akiva, Israel). Beyond funding the registry, Medical Compression Systems did not participate in, nor did any of the authors receive compensation for, the registry conduct, analysis, or manuscript preparation.

Results

Overall, symptomatic venous thromboembolism occurred in 0.92% (twenty-eight) of 3060 patients who had an arthroplasty of a lower-extremity joint. Twenty-three patients who had a joint arthroplasty (0.75%) experienced deep venous thrombosis (three proximal and twenty distal thrombi), and five patients (0.2%) had a pulmonary embolism (Table I). The

TABLE II Rates of Symptomatic Venous Thromboembolism and Pulmonary Embolism in the Present Registry Study and in Previous Studies with Similar Demographics

Prophylaxis	Total Joint Arthroplasty*		Hip Arthroplasty*		Knee Arthroplasty*	
	Venous Thromboembolism	Pulmonary Embolism	Venous Thromboembolism	Pulmonary Embolism	Venous Thromboembolism	Pulmonary Embolism
Mobile compression device in the present study	28/3060 (0.92)	5/3060 (0.16)	8/1509 (0.53)	3/1509 (0.20)	20/1551 (1.29)	2/1551 (0.13)
Warfarin[7-10]	45/2012 (2.24)	9/1816 (0.50)	15/534 (2.81)	0/338 (0.0)	30/1478 (2.03)	9/1478 (0.60)
Enoxaparin[11-14]	68/6138 (1.11)	14/3932 (0.35)	26/3413 (0.76)	2/1207 (0.17)	42/2725 (1.54)	12/2725 (0.44)
Rivaroxaban[11-14]	39/6132 (0.64)	1/6132 (0.02)	12/3405 (0.35)	1/3405 (0.03)	27/2727 (0.99)	0/2707 (0.0)
Dabigatran[15-17]	69/5918 (1.17)	10/5918 (0.17)	28/3294 (0.85)	7/3294 (0.21%)	41/2624 (1.56)	3/2624 (0.11)

*The values are given as the number of patients affected divided by the total number in the study, with the percentage in parentheses. Symptomatic deep venous thrombosis location (proximal versus distal) was not specified in published results for the pharmacological agents. The 97.5% confidence intervals are presented in Figures 1-A, 1-B, and 1-C.

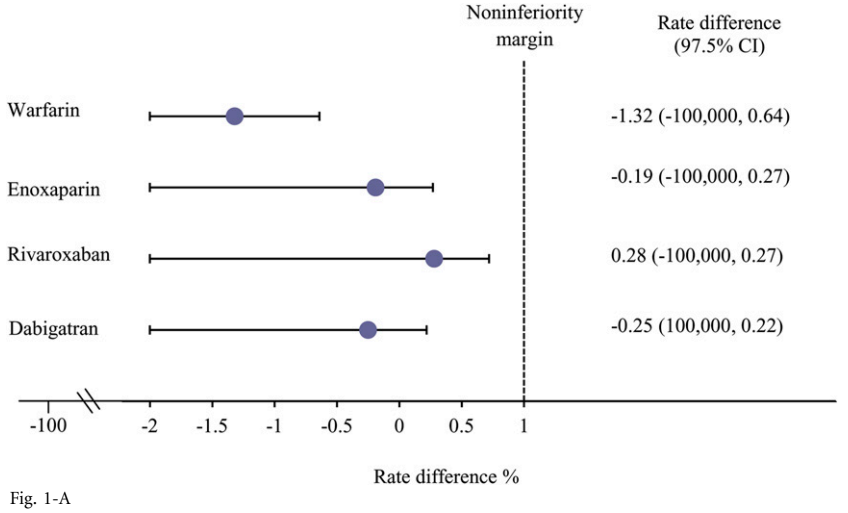

Fig. 1-A

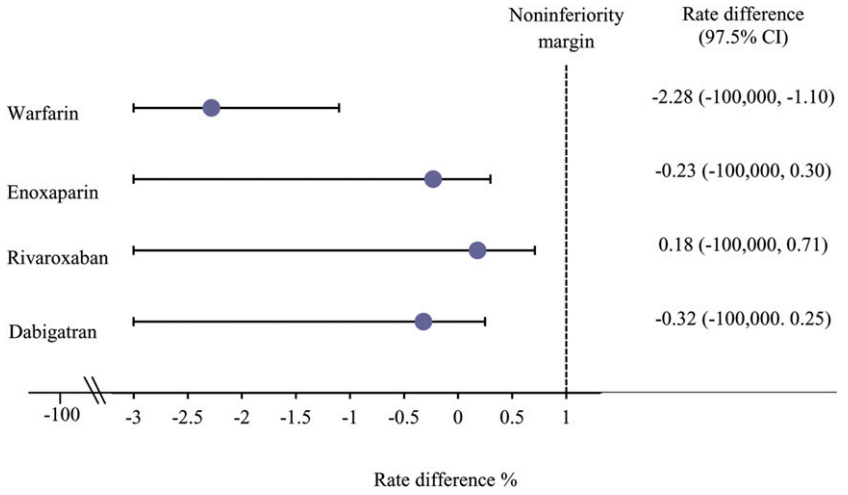

Fig. 1-B

Fig. 1-A Observed rate differences for venous thromboembolism (venous thromboembolism rate with the mobile compression device minus the venous thromboembolism rate with the pharmacological comparator, which is represented by the circular markers) and the 97.5% confidence intervals between the mobile compression device and the current pharmacological comparators in patients who had an arthroplasty of a lower-extremity joint. **Fig. 1-B** Observed rate differences for venous thromboembolism (venous thromboembolism rate with the mobile compression device minus venous thromboembolism rate with the pharmacological comparator, which is represented by the circular markers) and the 97.5% confidence intervals between the mobile compression device and the current pharmacological comparators in patients who had a hip arthroplasty.

1509 patients managed with a hip arthroplasty had eight venous thromboembolic events (a rate of 0.5%), with five deep venous thrombi (one proximal and four distal thrombi) and three pulmonary emboli. The rate of venous thromboembolism in the 1551 patients who had a knee arthroplasty was 1.3% (twenty patients), with eighteen deep venous thrombi (two proximal and sixteen distal thrombi) and two pulmonary emboli (Table I). No fatal pulmonary emboli were reported. One death of a patient with a long-standing history of cardiac disease and previous cardiac stent placement was reported. "Coronary failure" was listed as the cause of death, and the family was unwilling to allow an autopsy, so pulmonary embolism could not be ruled out. The association between aspirin use and the occurrence of venous thromboembolism could not be assessed; among the twenty-eight patients who experienced venous thromboembolism, thirteen (46.4%) were using aspirin and fifteen (53.6%) were not.

The rate of symptomatic venous thromboembolism was reported as 2.2% for warfarin[16-19], as 1.1% for enoxaparin[8,11-13], as 0.64% for rivaroxaban[8,11-13], and as 1.2% for dabigatran[9,10,20] after arthroplasty of a lower-extremity joint (Table II). The rates of symptomatic venous thromboembolism observed in patients who had an arthroplasty of a lower-extremity joint using the mobile compression device were noninferior at a margin of 1.0% to the rates reported for pharmacological prophylaxis, including warfarin, enoxaparin, rivaroxaban, and dabigatran (Figs. 1-A, 1-B, and 1-C). In the knee arthroplasty group, the mobile compression device fell short of the noninferior 1.0% margin to rivaroxaban by 0.06%, but it was noninferior at the 1.0% margin for all other knee and hip arthroplasty groups.

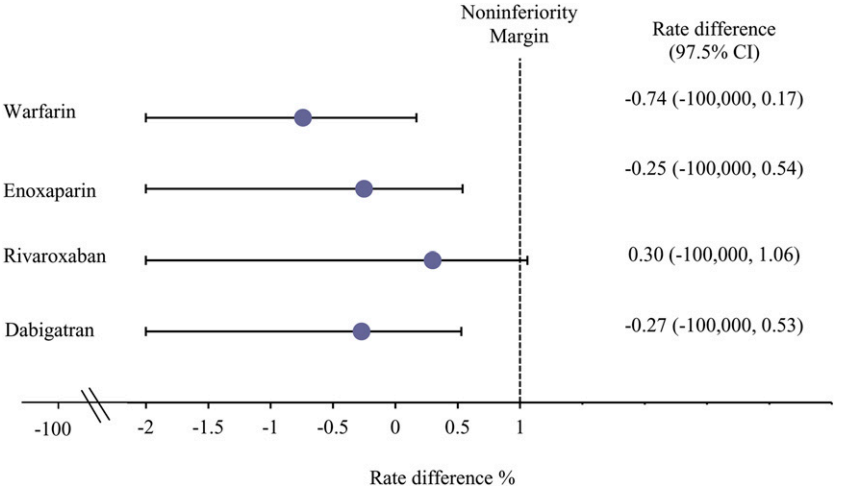

Fig. 1-C

Observed rate differences for venous thromboembolism (venous thromboembolism rate with the mobile compression device minus venous thromboembolism rate with the pharmacological comparator represented by the circular markers) and the 97.5% confidence intervals between the mobile compression device and the current pharmacological comparators in patients who had a knee arthroplasty.

Discussion

We evaluated whether the rates of symptomatic venous thromboembolism associated with the mobile compression device with or without aspirin were noninferior compared with those for warfarin[16-19], enoxaparin[8,11-13], rivaroxaban[8,11-13], and dabigatran[9,10,20] in patients who had hip arthroplasty, patients who had knee arthroplasty, and combined groups of patients who had a hip or knee arthroplasty. These reports compared favorably with the finding in our study of a rate of 0.92% for symptomatic venous thromboembolism after arthroplasty of a lower-extremity joint. Anticoagulants, however, carry an increased risk of major and minor bleeding events. This has been well-documented for enoxaparin[21,22], as well as in a previous study comparing this specific device with enoxaparin[6]. The bleeding risk profiles of warfarin and dabigatran are generally similar to enoxaparin, which is most commonly utilized as the control group in the clinical trials for these newer anticoagulants[23,24]. Rivaroxaban, on the other hand, has a higher risk of bleeding compared with enoxaparin, but is more efficacious at preventing symptomatic venous thromboembolism[23]. This is important information for the orthopaedic surgeon providing an alternative to pharmacological methodology without the risk of major bleeding and with similar efficacy. A cost analysis for the prevention of major bleeding events has been previously published[25]. Because of variations in cost by region and by facility, no comparison with other compression devices could reasonably be conducted. Although we know of no studies on the prevention of venous thromboembolism with the use of inpatient compression systems as monotherapy with symptomatic end points during hospitalization and follow-up after discharge, Froimson et al. compared this mobile compression device with the standard nonmobile compression device commonly used in acute care settings following lower-extremity arthroplasty[26]. The mobile compression device showed a 70% reduction in venous thromboembolic events compared with the nonmobile compression device (when both arms were used as adjunctive therapy to enoxaparin).

A series of guidelines have been developed and published by the American College of Chest Physicians (ACCP)[27] and by the American Academy of Orthopaedic Surgeons (AAOS)[28]. These guidelines utilized a systematic review of the current literature to determine an ideal or best methodology and duration for prophylaxis against venous thromboembolism. Both guidelines use symptomatic end points with duplex ultrasound documentation for deep venous thrombosis and imaging studies for confirmation of pulmonary embolism.

The limitations of our study are those of any registry that lacks a randomized control group. Selection bias is a concern with patient registries. We designed the mobile compression device registry to utilize the same inclusion and exclusion criteria that were used in randomized clinical trials assessing the efficacy of pharmacological agents for prophylaxis against venous thromboembolism. The patients enrolled consecutively in this registry had similar demographics to those reported in the clinical trials of the pharmacological agents. A surgeon at one or more sites could have possibly deviated from the inclusion and exclusion criteria when deciding which of his or her patients should receive the device, potentially resulting in a higher or lower-risk cohort of patients enrolled at that site. The rate of venous thromboembolism at each of the ten sites was similar, leading to the conclusion that the registry protocol was followed cohesively. A selection bias could have also resulted if not all patients who received the device were included in the registry. However, we had only one patient lost to follow-up, who had no signs or symptoms of venous thromboembolism at one month postoperatively.

The registry had a limited data set, and neither bleeding rates nor compliance were documented. These limitations were offset by a previous study of the device[6], which showed a 0% rate of major bleeding events. There is no reason that the bleeding rate would have been greater than in the previous study[6] or with

any other compression device study[29,30]. Compliance, which increases the effectiveness of compression devices[31], was not documented in the registry. If the participants in this study used the device less than the ten days and twenty hours per day reported in the previous study[6], the venous thromboembolism rates would only improve with greater use. The study was not powered to establish any conclusions with respect to the use or nonuse of aspirin in addition to the mobile compression device. Of the twenty-eight patients who had a venous thromboembolic event, 46% were on the aspirin protocol. Similarly, the study was not powered to assess the relationship between anesthesia type and the occurrence of venous thromboembolism. The anesthesia protocols for hip and knee arthroplasty differed from site to site, and we were able to present frequencies only (see Appendix). Another potential study weakness is that each institution reported its duplex ultrasound data and spiral CT data with no adjudication committee to evaluate these studies. However, if any of the positive diagnostic studies had been disallowed by an adjudication committee, a lower rate of deep venous thrombi and pulmonary emboli would have been observed.

To our knowledge, this is the first large multicenter study utilizing an external mobile compression device in an inpatient or outpatient setting for ten days or greater. The results demonstrated noninferior efficacy in the prevention of venous thromboembolism compared with the most commonly used pharmacological protocols, except for rivaroxaban in knee arthroplasty, which lacked noninferiority by 0.06% at the 1.0% margin. On the basis of this study, we recommend that surgeons consider the use of this mobile compression device with or without aspirin for prophylaxis as an alternative to pharmacological prophylaxis in patients treated with arthroplasty of a lower-extremity joint.

Appendix

eA A table showing patient demographic data is available with the online version of this article as a data supplement at jbjs.org. ■

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