Stratified Meta-Analysis of Intermittent Pneumatic Compression of the Lower Limbs to Prevent Venous Thromboembolism in Hospitalized Patients

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Background—Optimal thromboprophylaxis for patients at risk of bleeding remains uncertain. This meta-analysis assessed whether intermittent pneumatic compression (IPC) of the lower limbs was effective in reducing venous thromboembolism and whether combining pharmacological thromboprophylaxis with IPC would enhance its effectiveness.

Methods and Results—Two reviewers searched MEDLINE, EMBASE, and the Cochrane controlled trial register (1966—February 2013) for randomized, controlled trials and assessed the outcomes and quality of the trials independently. Trials comparing IPC with pharmacological thromboprophylaxis, thromboembolic deterrent stockings, no prophylaxis, and a combination of IPC and pharmacological thromboprophylaxis were considered. Trials that used IPC <24 hours or compared different types of IPC were excluded. A total of 16 164 hospitalized patients from 70 trials met the inclusion criteria and were subjected to meta-analysis. IPC was more effective than no IPC prophylaxis in reducing deep vein thrombosis (7.3% versus 16.7%; absolute risk reduction, 9.4%; 95% confidence interval [CI], 7.9–10.9; relative risk, 0.43; 95% CI, 0.36–0.52; $P<0.01$; $I^2=34\%$) and pulmonary embolism (1.2% versus 2.8%; absolute risk reduction, 1.6%; 95% CI, 0.9–2.3; relative risk, 0.48; 95% CI, 0.33–0.69; $P<0.01$; $I^2=0\%$). IPC was also more effective than thromboembolic deterrent stockings in reducing deep vein thrombosis and appeared to be as effective as pharmacological thromboprophylaxis but with a reduced risk of bleeding (relative risk, 0.41; 95% CI, 0.25–0.65; $P<0.01$; $I^2=0\%$). Adding pharmacological thromboprophylaxis to IPC further reduced the risk of deep vein thrombosis (relative risk, 0.54; 95% CI, 0.32–0.91; $P=0.02$; $I^2=0\%$) compared with IPC alone.

Conclusions—IPC was effective in reducing venous thromboembolism, and combining pharmacological thromboprophylaxis with IPC was more effective than using IPC alone. **(*Circulation*. 2013;128:1003-1020.)**

Key Words: prevention & control ■ venous thromboembolism

Venous thromboembolism is an important preventable cause of morbidity and mortality in hospitalized patients.[1] The latest data show that venous thromboembolism affects 900 000 individuals in the United States each year, increasing the overall healthcare cost substantially.[2] Evidence suggests that thromboprophylaxis is of pivotal importance in reducing the mortality and morbidity of venous thromboembolism. Although underuse of thromboprophylaxis in many situations has improved with education and automated electronic alert systems, recent studies have shown that many hospitalized patients at risk of venous thromboembolism remained not treated with thromboprophylaxis in a timely fashion.[3,4] Because bleeding from antithrombotic agents is a strong predictor of mortality, many clinicians perceive that the risk of bleeding from pharmacological thromboprophylaxis is more important than the risk of venous thromboembolism, and this contributes to the underuse of early thromboprophylaxis.[5,6]

Clinical Perspective on p 1020

Intermittent pneumatic compression (IPC) of the lower limbs, including the thigh, calf, and foot pumps, have been in use to prevent deep vein thrombosis (DVT) for many decades. According to the latest American College of Chest Physicians evidence-based clinical practice guidelines on antithrombotic therapy and the prevention of thrombosis,[7] IPC or thromboembolic deterrent stockings (TEDS) are recommended as thromboprophylaxis for patients who are at risk of bleeding, and if venous thromboembolism risk persists and risk of bleeding subsides, pharmacological thromboprophylaxis can be substituted for mechanical thromboprophylaxis for patients at low or moderate risk of venous thromboembolism and added to mechanical prophylaxis for patients at high risk of venous thromboembolism. However, these Grade 2C recommendations were based mainly on consensus among experts or weak evidence. Whether IPC is effective in reducing venous

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thromboembolism, in particular pulmonary embolism (PE), compared with no prophylaxis, TEDS, or pharmacological thromboprophylaxis and whether a combination of IPC and pharmacological thromboprophylaxis is more effective than IPC alone remain uncertain.[8]

We hypothesized that IPC of the lower limbs is an effective form of thromboprophylaxis, comparable to pharmacological thromboprophylaxis, but that adding pharmacological thromboprophylaxis to IPC may further improve its effectiveness in reducing venous thromboembolism. In this stratified meta-analysis, we assessed the effect of IPC on risk of venous thromboembolism compared with no IPC prophylaxis, TEDS, pharmacological thromboprophylaxis, and a combination of IPC and pharmacological thromboprophylaxis.

Methods

Data Sources and Study Selection

Two reviewers searched the Cochrane controlled trial register (2012, issue 4) and the EMBASE (January 1988–February 23, 2013) and MEDLINE (1966–February 12, 2013) databases independently. During the electronic database search, the following exploded Medical Subject Heading (MeSH) terms were used: "pneumatic compression," "sequential compression," "external compression," "intermittent compression," or "pumps" with "venous thromboembolism," "deep vein thrombosis," or "pulmonary embolism." The search was limited to clinical trials, letters, editorial reviews, or randomized, controlled trials without any language restrictions. The reference lists of related editorials, reviews, and original articles identified were searched for relevant trials. Finally the Web sites of the International Network of Agencies of Health Technology Assessment in Health Care were searched to ensure that all suitable trials were included.

In this study, only randomized, controlled trials comparing the effect of IPC with no IPC prophylaxis, TEDS, pharmacological thromboprophylaxis, and a combination of IPC and pharmacological thromboprophylaxis on risk of venous thromboembolism in hospitalized patients were included. Trials using pneumatic compression during surgery only or for <24 hours after surgery, trials comparing different compression devices without a placebo group, and trials that did not report venous thromboembolism as an outcome were excluded.

Two reviewers independently examined all identified trials to confirm that they fulfilled the inclusion criteria and recorded the trial characteristics and outcomes using a predesigned data abstraction form. This abstraction form was also used to record information on the quality of the trial such as allocation concealment, randomization method, blinding of treatment, and assessment of outcome, as well as inclusion and exclusion criteria. The grading of allocation was based on the Cochrane approach as adequate, inadequate, or uncertain. When the reported methodology and results of the included trials were unclear, the corresponding authors of the trials were contacted to clarify the data. There was no disagreement between the 2 independent reviewers in the data abstracted.

Statistical Analysis

DVT and PE were the primary outcomes of this study. The other outcomes assessed included the risk of systemic or surgical wound bleeding complications and hospital mortality. During the analyses, studies were stratified into 4 strata: comparing IPC with no IPC prophylaxis, TEDS, pharmacological thromboprophylaxis, and a combination of IPC and pharmacological thromboprophylaxis. If both the IPC group and the comparative group such as unfractionated heparin received the same concomitant background thromboprophylaxis (eg, TEDS) in the trial, this would be considered a comparison of IPC with pharmacological thromboprophylaxis because any protective effect of TEDS on venous thromboembolism should have been balanced between the 2 groups.

Outcomes were reported as absolute risk reduction and relative risk (RR) with 95% confidence interval (CI) using a random-effects model; the presence of heterogeneity between trials was assessed by the χ^2 statistics; and the extent of inconsistency was assessed using I^2 statistics.[9] An I^2>40% was considered significant heterogeneity in this study. Data were analyzed by the Review Manager (version 4.2.6 for Windows; Oxford, UK: The Cochrane Collaboration, 2003) and Comprehensive Meta-analysis (version 2.2.034; Biostat, USA, 2006). A value of P<0.05 was taken as significant in this meta-analysis.

Sensitivity Analyses, Publication Bias, and Meta-Regression

To assess the reasons for any heterogeneity in the results and whether the efficacy of IPC could be different in different situations, a series of sensitivity analyses were conducted. These included a restricted analysis by excluding trials that did not use blinding in the assessment of venous thromboembolism, excluding trials that reported risk of asymptomatic PE, stratifying trials that compared the IPC group against an unfractionated heparin or a low-molecular-weight-heparin/fondaparinux group, and stratifying trials on different subgroups of patients, including only elective orthopedic patients, nonsurgical patients, nonorthopedic surgical patients, or total knee versus hip arthroplasty patients.

Publication bias was assessed by a funnel plot using either DVT or PE as an end point. Meta-regression was used to assess any potential interaction between the effectiveness of IPC and the duration of IPC use.

Results

Characteristics of the Included Studies

Of the 102 trials identified from the literature and assessed in detail, 70 trials from 15 countries involving a total of

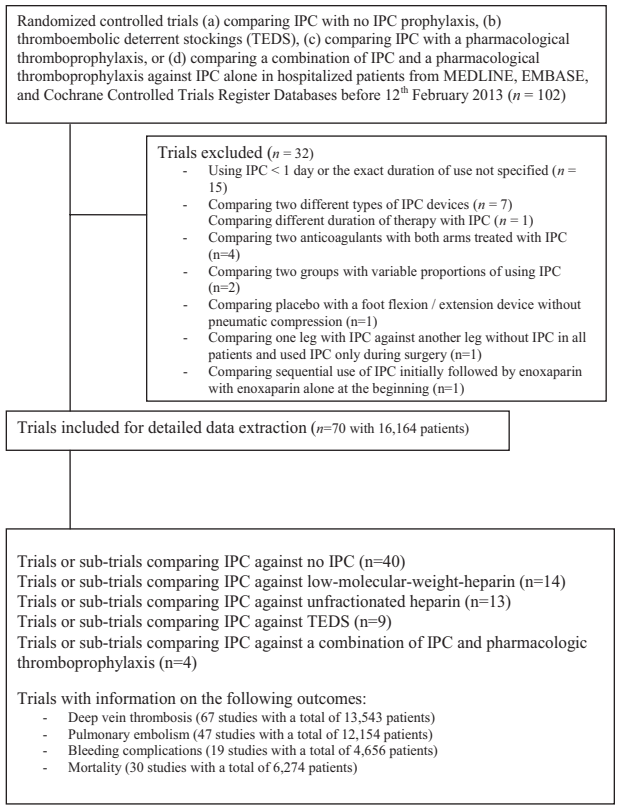

Figure 1. Flow chart showing the inclusion and exclusion of studies of intermittent pneumatic compression (IPC) devices on risk of venous thromboembolism in the meta-analysis. TEDS indicates thromboembolic deterrent stockings.

Table. Characteristics of the Studies of the Effects of IPC of the Lower Limbs on the Risk of VTE

Study: Country of Origin, Year of Publication, Funding Source (Reference)	Inclusion and Exclusion Criteria	Interventions and No. of Patients Analyzed	(1) VTE Diagnostic Criteria and (2) Outcomes Reported	Allocation Concealment, Blinding, Intention to Treat, Lost to Follow-Up
Blanchard et al, Switzerland, 1999, Swiss National Science Foundation, Sanofi-Winthrop Pharma Basel, and Novamedix Andover (10)	Inclusion: total knee arthroplasty+body weight 40-100 kg+>40 y of age Exclusion: history of VTE, contraindications to anticoagulation, and prior total knee joint arthroplasty	Foot pumps (n=67) or LMWH (n=63); either treatment was continued until phlebography	(1) Bilateral phlebography 8–12 d after surgery or compression USS if phlebography was impossible (2) DVT, PE, bleeding complications, and mortality	Allocation concealment adequate, no blinding, analysis by intention to treat, all patients completed the study
Bradley et al, UK, 1993, Novamedix Ltd (11)	Inclusion: total hip arthroplasty+age between 45 and 85 y Exclusion: not described	Foot pumps (n=30) or control (n=44); both groups received TEDS and 5000 U heparin 2 times daily until hospital discharge	(1) Bilateral phlebography 12 d after surgery (2) DVT	Allocation concealment inadequate, single blinded, analysis by intention to treat, all completed the study
Bustson et al, Canada, 1981, Lyne-Nicholson Inc (12)	Inclusion: general abdominal surgery with duration equal to or greater than cholecystectomy+age >20 y Exclusion: emergency surgery	Calf pumps (n=62) or control (n=57), until ambulatory, usually 24–48 h but some up to 4 d after surgery	(1) ^{125}Iodine fibrinogen leg scan for 14 d or hospital discharge, DVT confirmed by phlebography; autopsy results were also used (2) DVT, PE, and mortality	Allocation concealment adequate, no blinding, analysis by intention to treat, all completed the study
Chandhoke et al, US, 1992, no external funding (13)	Inclusion: major open urologic operation with duration >2 h Exclusion: VTE history, prolonged immobility, heart failure, and inherited risk of VTE	Thigh leg and pumps (n=47) until day 5 or fully ambulatory or warfarin (n=53) to achieve prothrombin time >1.5 from baseline until hospital discharge	(1) Doppler USS preoperatively and 1–2 wk after surgery followed by phlebography to confirm DVT (2) DVT, PE, bleeding complications, and mortality	Allocation concealment inadequate, no blinding, analysis by intention to treat, all completed the study
Chin et al, Singapore, 2009, no external funding (14)	Inclusion: total knee arthroplasty Exclusion: VTE history, BMI >30 kg/m^2, use of aspirin or anticoagulant, immobilization, heart failure, stroke within 3 mo, renal and liver impairment, and peripheral vascular disease	4 Groups including no VTE prophylaxis as control (n=110), TEDS (n=110), calf pumps (n=110) after surgery, or LMWH (n=110); VTE prophylaxis was used for 5–7 d or until the diagnosis of VTE was made for all patients	(1) Compression USS for DVT (timing of scan and whether it was performed only on symptomatic patients were not reported) and ventilation-perfusion and CTPA for symptomatic PE (2) DVT, PE, and bleeding complications	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Clark-Pearson et al, US, 1984, no external funding (15)	Inclusion: major surgery for gynecological malignancy Exclusion: treated with anticoagulant within 6 wk or patients with acute VTE	Calf pumps (n=55) for 5 d after surgery or control without VTE prophylaxis (n=52)	(1) ^{125}Iodine fibrinogen scan alternate days after surgery and impedance plethysmography on day 5 after surgery followed by confirmation with phlebography and ventilation-perfusion and CTPA scan for symptomatic PE (2) DVT, PE, and mortality	Allocation concealment unclear, single blinded, analysis by intention to treat, 8% did not complete the study
Clark-Pearson et al, US, 1993, no external funding (16)	Inclusion: major surgery for gynecological malignancy Exclusion: treated with anticoagulant within 6 wk or patients with VTE within 3 mo	Calf pumps (n=101) for 5 d after surgery or heparin 5000 U 3 times daily (n=107) for ≥7 d until full ambulation or hospital discharge	(1) ^{125}Iodine fibrinogen scan and symptoms of DVT/PE reviewed daily after surgery, positive fibrinogen scan was followed by confirmation with phlebography and symptomatic DVT was investigated by impedance plethysmography, USS, or phlebography; ventilation-perfusion and CTPA scan for symptomatic PE (2) DVT, PE and bleeding complications	Allocation concealment adequate, no blinding, analysis by intention to treat, 5% did not complete the study
Edwards et al, US, 2008, Medical Compression ActiveCare DVT (17)	Inclusion: either total hip or knee arthroplasty Exclusion: VTE history and prophylaxis other than LMWH	Calf pumps (n=141) until hospital discharge or control (n=136), both groups also received LMWH for 7–8 d after surgery	(1) Duplex USS before hospital discharge (2) DVT, PE, and mortality	Allocation concealment unclear, no blinding, analysis not by intention to treat, 13.4% did not complete the study

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Table. Continued

Study: Country of Origin, Year of Publication, Funding Source (Reference)	Inclusion and Exclusion Criteria	Interventions and No. of Patients Analyzed	(1) VTE Diagnostic Criteria and (2) Outcomes Reported	Allocation Concealment, Blinding, Intention to Treat, Lost to Follow-Up
Eisele et al, Germany, 2007, Aircast Europe (18)	Inclusion: orthopedic surgery other than those on upper limbs+age 20–86 y Exclusion: existing DVT and surgery on legs	Calf pumps (n=901) until able to walk or control (n=902), both groups received LMWH until hospital discharge	(1) Duplex USS before hospital discharge (2) DVT	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Fisher et al, Canada, 1995, no external funding (19)	Inclusion: pelvic or lower limb fractures that occurred within 24 h before admission Exclusion: coagulation abnormality, malignancy, severe vascular or liver disease	Thigh and calf pumps (n=145) or control (n=159) until ambulating or DVT was diagnosed	(1) Doppler USS between days 3 and 5, then every 5 d until ambulating and ventilation-perfusion scan between days 5 and 10 after surgery, and equivocal or positive tests from these studies were followed by phlebography and pulmonary angiograms, respectively (2) DVT, PE, and mortality	Allocation concealment adequate, single blinded, analysis not by intention to treat, 12% did not complete the study
Fordyce et al, UK, 1992, no external funding (20)	Inclusion: primary total hip arthroplasty Exclusion: past history of VTE	Foot pumps (n=39) until ambulating or control (n=40)	(1) Phlebography between days 6 and 9 after surgery (2) DVT and mortality	Allocation concealment adequate, single blinded, analysis not by intention to treat, 6% did not complete the study
Gallus et al, Australia, 1983, G.A. Middleton (21)	Inclusion: >50 y of age and total hip arthroplasty Exclusion: not described	Calf and foot pumps (n=43) or control (n=47) until day 7 after surgery	(1) Daily ^{125}iodine fibrinogen leg scan, and impedance plethysmography and phlebography on day 7 after surgery (2) DVT	Allocation concealment adequate, single blinded, analysis by intention to treat, all completed the study
Ginzburg et al, US, 2003, Huntleigh Flowtron (22)	Inclusion: trauma patients with injury severity score ≥9 and at least 1 leg and 1 arm available for IPC Exclusion: contraindications to LMWH, age <18 y, renal failure, pregnancy, morbidly obese, and acquired coagulopathy	Calf pumps to both leg or 1 arm and 1 leg (n=224) or LMWH (n=218) until ambulating or hospital discharge	(1) Doppler USS within 24 h of admission and weekly thereafter or when DVT was suspected; symptomatic PE was diagnosed by CTPA or ventilation-perfusion scan (2) DVT, PE, bleeding complications, and mortality	Allocation concealment adequate, no blinding, analysis by intention to treat, all completed the study
Goldhaber et al, US, 1995, Kendall Healthcare Products, Acuson Computed Sonography, and National Institute of Health (23)	Inclusion: coronary artery bypass surgery Exclusion: peripheral vascular disease, history of VTE, heart valve surgery, intra-aortic balloon pump, planned postoperative anticoagulation	Thigh, leg and ankle pumps (n=172) or control (n=172) until USS on day 4; all patients received aspirin and TEDS	(1) Doppler USS on day 4 after surgery or thereafter (2) DVT, PE, and mortality	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Hardwick et al, US, 2011, no external funding (24)	Inclusion: total hip arthroplasty and age >18 y Exclusion: history of VTE, mental deficiency, coagulation disorder, solid malignancy, and peptic ulcer disease	Calf pumps (n=198) or LMWH (n=194) for 10 d; 63% of the calf pump group patients were also given aspirin as DVT prophylaxis	(1) Doppler USS on days 10–12 after surgery, symptomatic PE was investigated by CTPA (2) DVT, PE, and bleeding complication	Allocation concealment adequate, no blinding, analysis not by intention to treat, 0.8% did not complete the study
Hills et al, UK, 1972, Kabi Pharmaceutical, Ministry of Health, Flowtron-Aire Ltd (25)	Inclusion: elective general surgical operation under general anesthesia and >40–60 y of age Exclusion: leg, breast, or thyroid surgery, treated with anticoagulant before surgery, likely to stay in hospital for <5 d	Calf and foot pumps (n=70) or control (n=70) for 24–48 h until the patient was ambulating after surgery	(1) Radioactive fibrinogen leg scan daily for 7 days (2) DVT	Allocation concealment adequate, no blinding, analysis not by intention to treat, 2.9% did not complete the study

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Table. Continued

Study: Country of Origin, Year of Publication, Funding Source (Reference)	Inclusion and Exclusion Criteria	Interventions and No. of Patients Analyzed	(1) VTE Diagnostic Criteria and (2) Outcomes Reported	Allocation Concealment, Blinding, Intention to Treat, Lost to Follow-Up
Hull et al, Canada, 1990, Ontario Ministry of Health and Canadian Heart Foundation (26)	Inclusion: total hip arthroplasty Exclusion: history of VTE, allergic to radiocontrast, aspirin therapy	Thigh and calf pumps (n=152) or control (n=158) for 14 d or until hospital discharge	(1) ^{125}Iodine fibrinogen leg scan daily for 14 d, impedance plethysmography from alternate days from day 5 after surgery, phlebography on day 14, hospital discharge, or earlier if these other scans were positive; symptomatic PE investigated by ventilation-perfusion scan and, if it was not a high probability result, followed by pulmonary angiography (2) DVT, PE, and mortality	Allocation concealment adequate, single blinded, analysis by intention to treat, all completed the study
Hull et al, Canada, 1979, Canadian Heart Foundation, American Hospital Supply Corporation (27)	Inclusion: elective knee surgery, >30 y of age Exclusion: allergic to radiocontrast, severe peripheral vascular disease, skin ulceration	Calf pumps (n=32) or control (n=29) until hospital discharge or day 17 after surgery when all patients were fully ambulating	(1) ^{125}Iodine fibrinogen leg scan at 48 h postoperatively and those with positive scan had phlebography within 24–48 h after the positive fibrinogen scan; all other patients had phlebography on days 14–17 after surgery (2) DVT, PE and mortality	Allocation concealment adequate, single blinded, analysis by intention to treat, all completed the study
Kaempffe et al, US, 1991, no external funding (28)	Inclusion: lower limb total joint arthroplasty Exclusion: not described	Thigh and calf pumps (n=48) or Coumadin (n=52) until phlebography was performed, usually on day 10 after surgery	(1) Phlebography when fully ambulating, usually on day 10 after surgery; nuclear venography, impedance plethysmography, or Doppler USS if allergic to radiocontrast (2) DVT and mortality	Allocation concealment adequate, single blinded, analysis not by intention to treat, 33% did not complete the study
Knudson et al, US, 1992, Kendall Health Care Products (29)	Inclusion: adult trauma patients Exclusion: age <17 y, pregnancy, minor injuries, expected to be discharged within 48 h	Thigh and calf pumps (n=76) or heparin 5000 U twice daily (n=37) until ambulating	(1) USS every 5 d up to 3 wk or discharge; ventilation-perfusion scan and pulmonary angiography for unexplained hypoxemia (2) DVT, PE, and bleeding complications	Allocation concealment inadequate, no blinding, analysis not by intention to treat, all completed the study
Knudson et al, US, 1994, Kendall Health Care Products (30)	Inclusion: adult trauma patients Exclusion: age <18 y, pregnancy, prisoner, DVT on initial imaging	Thigh and calf pumps (n=58) or control (n=130) or heparin 5000 U twice daily (n=63) until ambulating	(1) USS every 5–7 d up to 3 wk or discharge; pulmonary angiography for symptomatic PE (2) DVT, PE, and mortality	Allocation concealment inadequate, no blinding, analysis not by intention to treat, 6% did not complete the study
Knudson et al, US, 1996, Rhone Poulenc Rorer Pharmaceuticals, Inc (31)	Inclusion: adult trauma patients with injury severity score >10, major pelvic fracture, spinal fracture with neurological deficits, Glasgow Coma Scale score <9, fractures of the lower extremity above the ankle, history of DVT, age >50 y Exclusion: age <18 y, pregnancy, prisoner, VTE on admission	Thigh and calf pumps (n=61) or foot pumps if with lower-extremity fractures (n=21) or LMWH (n=120); compliance with study treatment was monitored daily for at least 10 d, but the exact duration of study treatment used was not described	(1) USS every 5–7 d until discharge; pulmonary angiography for symptomatic PE (2) DVT, PE, and bleeding complications	Allocation concealment unclear, double blinded, analysis not by intention to treat, 24% did not complete the study
Kosir et al, US, 1996, VA Medical Research Fund and Wayne State University (32)	Inclusion: general surgical operation >1 h Exclusion: history of VTE, use of intravenous heparin or Coumadin during and after surgery	Thigh and calf pumps (n=25) for 48 h or control (n=45) or heparin 5000 U twice daily (n=38) for 7 d	(1) USS preoperatively and on days 1, 4, and 30 after surgery (2) DVT	Allocation concealment unclear, single blinded, analysis not by intention to treat, 21% did not complete the study

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Table. Continued

Study: Country of Origin, Year of Publication, Funding Source (Reference)	Inclusion and Exclusion Criteria	Interventions and No. of Patients Analyzed	(1) VTE Diagnostic Criteria and (2) Outcomes Reported	Allocation Concealment, Blinding, Intention to Treat, Lost to Follow-Up
Kurtoglu et al, Turkey, 2004, no external funding (33)	Inclusion: severe head or spinal trauma in intensive care unit Exclusion: <14 y of age, spinal cord injury, coagulopathy, history of DVT, hepatic or renal dysfunction	Calf pumps (n=60) for 48 h or LMWH (n=60) until intensive care unit discharge	(1) USS done on intensive care admission, 7 d after admission, 7 d after discharge, and CTPA for all between days 7 and 10 (2) DVT, PE, bleeding complications, and mortality	Allocation concealment inadequate, no blinding, analysis by intention to treat, all completed the study
Lieberman et al, US, 1994, no external funding (34)	Inclusion: total hip arthroplasty under hypotensive epidural anesthesia Exclusion: history of VTE, allergic to aspirin or radiocontrast, lower-extremity ulcers, hypercoagulable, or coagulopathy	Thigh and calf pumps (n=113) or control (n=118); both groups also received aspirin 325 twice daily; study treatment continued until phlebography on days 6–8 after surgery	(1) Phlebography on days 6–8 after surgery (2) DVT, PE, and mortality	Allocation concealment adequate, single blinded, analysis not by intention to treat, 11% did not complete the study
Lacut et al, France, 2005, Agnece Francaise de Securite Sanitaire des Produits de Sante and Tyco Healthcare (35)	Inclusion: traumatic or spontaneous intracranial hemorrhage and >18 y old Exclusion: extradural or subdural hematoma, trauma involving lower extremity, DVT within 3 mo, peripheral vascular disease	Thigh, calf and ankle pumps (n=74) or control (n=77) until day 10 after admission	(1) Compression USS on day 10, symptomatic PE by ventilation-perfusion or CTPA (2) DVT and mortality	Allocation concealment adequate, single blinded, analysis by intention to treat, 12% did not complete the study
Maxwell et al, US, 2001, Pharmacia Corp and Venodyne and ACOG /Ethicon Research Award (36)	Inclusion: age >40 y and major abdominal or pelvic surgery for gynecologic malignancy Exclusion: VTE within 6 mo, contraindications to heparin, coagulopathy	Calf and foot pumps (n=106) or LMWH (n=105) until day 5 after surgery	(1) Doppler USS on days 3–5 after surgery (2) DVT, PE, and bleeding complications	Allocation concealment adequate, single blinded, analysis not by intention to treat, 7.5% did not complete the study
McKenna et al, US, 1980, no external funding (37)	Inclusion: age >40 y and total knee arthroplasty Exclusion: VTE within 6 mo	Thigh and calf pumps (n=10) or control (n=12) or aspirin 325 mg (n=9) or aspirin 1300 mg (n=12) for hospital discharge	(1) ^{125}Iodine fibrinogen leg scan alternative day until ambulating and phlebography 1–2 d before discharge; ventilation-perfusion scan for all positive phlebography studies and, by the end of the study, on all patients (2) DVT, PE, bleeding complications, and mortality	Allocation concealment adequate, no blinding, analysis not by intention to treat, 6.5% did not complete the study
Mellbring et al, Sweden, 1986, Swedish National Association against Heart and Lung Diseases (38)	Inclusion: age >50 y and abdominal surgery Exclusion: treated with anticoagulant, allergic to radiocontrast, ischemic heart and peripheral vascular diseases	Calf pump on either left or right leg (n=54) or heparin (5000 U twice daily) with dihydroergotamine 0.5 mg twice daily (n=54) until fully ambulating	(1) ^{125}Iodine fibrinogen leg scan alternative day until day 9 after surgery or discharge (2) DVT and mortality	Allocation concealment adequate, no blinding, analysis not by intention to treat, 5.3% did not complete the study
Nicolaides et al, UK, 1983, AG Leventis Foundation Research Division of Kendall Corp (39)	Inclusion: age >30 y and major abdominal surgery Exclusion: not described	Thigh and calf pumps (n=50) for a minimum of 72 h and until ambulating or heparin 5000 U twice daily (n=50) until discharge	(1) ^{125}Iodine fibrinogen leg scan alternative day until discharge (2) DVT	Allocation concealment adequate, no blinding, analysis by intention to treat, all completed the study
Ramos et al, US, 1996, no external funding (40)	Inclusion: open heart surgery Exclusion: DVT before surgery, bleeding complication, or intraoperative mortality	Thigh and calf pumps (n=1355) or control (n=1196) and both groups also treated with heparin 5000 U twice daily for 4–5 d or until fully ambulating	(1) Ventilation-perfusion scan for unexplained dyspnea or significant hypoxia with no interval chest x-ray changes, pulmonary angiography for intermediate- or low-probability scan, and autopsy results (2) PE	Allocation concealment adequate, no blinding, analysis not by intention to treat, 8.4% did not complete the study

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Table. Continued

Study: Country of Origin, Year of Publication, Funding Source (Reference)	Inclusion and Exclusion Criteria	Interventions and No. of Patients Analyzed	(1) VTE Diagnostic Criteria and (2) Outcomes Reported	Allocation Concealment, Blinding, Intention to Treat, Lost to Follow-Up
Santori et al, Italy, 1994, no external funding (41)	Inclusion: total hip arthroplasty under general anesthesia Exclusion: history of VTE, varicose vein, malignant neoplasm	Foot pumps (n=67) or heparin 5000 U 3 times daily (n=65) for 7–10 d	(1) Doppler USS and liquid crystal thermography at days 8–10 after surgery and phlebography if USS scan was positive or with clinical signs of DVT (2) DVT, PE, bleeding complications, and mortality	Allocation concealment adequate, no blinding, analysis by intention to treat, all completed the study
Silbersack et al, Germany, 2004, Aircast Europa GmbH (42)	Inclusion: age >18 y and total hip or knee arthroplasty Exclusion: severe heart or renal failure, peripheral vascular disease, active malignant disease, and coagulopathy	Calf pumps (n=68) or LMWH (n=63) until day 10 and then both groups were treated with LMWH until day 30 after surgery	(1) Compression and Doppler USS between 6 and 12 d and on weeks 6 and 12 after surgery, symptomatic PE by CTPA (2) DVT and PE	Allocation concealment unclear, single blinded, analysis not by intention to treat, 5.8% did not complete the study
Stannard et al, US, 1996, no external funding (43)	Inclusion: total hip arthroplasty Exclusion: history of VTE, fracture neck of femur, age <18 y, peripheral vascular disease	Foot pumps (n=25) or foot pumps with heparin (5000 U twice daily for 3 d then aspirin 325 mg twice daily; n=25) or heparin followed by aspirin without foot pumps (n=25) until 2 wk after surgery	(1) Doppler USS on 2 occasions (weeks 1 and 2 after surgery); phlebography for patients with positive USS results (2) DVT, PE, bleeding complications, and mortality	Allocation concealment unclear, single blinded, analysis by intention to treat, all completed the study
Stone et al, UK, 1996, no external funding (44)	Inclusion: total hip arthroplasty Exclusion: aspirin therapy, cancer, history of VTE, and gastric ulcer	Calf pumps (n=25) or LMWH (n=25) for hospital discharge	(1) Doppler USS at 1 and 6 wk after surgery (2) DVT and PE	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Stranks et al, UK, 1992, no external funding (45)	Inclusion: subcapital fracture of femur Exclusion: history of VTE, malignancy, and chronic venous insufficiency	Foot pumps (n=41) or control (n=39) for 7–10 d until ambulating	(1) Doppler USS between 7 and 10 d after surgery (2) DVT and PE	Allocation concealment unclear, no blinding, analysis not by intention to treat, 2.5% did not complete the study
Turpie et al, Canada, 1989, no external funding (46)	Inclusion: age ≥16 y and brain or spinal cord tumors or injury or subarachnoid hemorrhage Exclusion: allergic to radiocontrast, trauma involving the legs, anticoagulation, mild injury not hospitalized for >24 h	Thigh and calf pumps (n=78) or control (n=80) for 14 d or hospital discharge; both groups received TEDS	(1) ^{125}Iodine fibrinogen leg scan daily for 14 d or discharge, impedance plethysmography on days 3, 5, 7, 9, 11, and 14 or day of discharge; phlebography if either of the above scan was positive for DVT (2) DVT, PE, and mortality	Allocation concealment adequate, single blinded, analysis by intention to treat, all completed the study
Turpie et al, Canada, 2007, Sanofi-Synthelabo and GlaxoSmithKline (47)	Inclusion: abdominal surgery >45 min and age >40 y with weight >50 kg Exclusion: peripheral vascular disease requiring vascular surgery, pregnancy, hemorrhagic stroke or neurosurgery within 3 mo, severe renal impairment, thrombocytopenia, active bleeding, or life expectancy <6 mo	Fondaparinux (n=650) or control (n=659) for 5–9 d; both groups received intermittent thigh or calf compression with a median period of 4 d	(1) Phlebography between days 5 and 10 after surgery; symptomatic PE by ventilation-perfusion scan, pulmonary angiography, or CTPA (2) DVT, PE, bleeding complications, and mortality	Allocation concealment adequate, double-blinded, analysis by intention to treat, 33.8% did not complete the efficacy assessment of the study
Turpie et al, Canada, 1979, no external funding (48)	Inclusion: intracranial or spinal disease or injury and age >16 y Exclusion: allergic to radiocontrast, peripheral vascular disease, multiple trauma, mild injury requiring <24 h of hospitalization	Calf pumps (n=103) or control (n=96) until fully ambulating, discharge, or a maximum of 14 d	(1) ^{125}Iodine fibrinogen leg scan and impedance plethysmography on days 3, 5, 7, 10, and 14 after surgery; phlebography to confirm positive results of screening test (2) DVT	Allocation concealment adequate, no blinding, analysis not by intention to treat, 8.7% did not complete the study

(*Continued*)

Table. Continued

Study: Country of Origin, Year of Publication, Funding Source (Reference)	Inclusion and Exclusion Criteria	Interventions and No. of Patients Analyzed	(1) VTE Diagnostic Criteria and (2) Outcomes Reported	Allocation Concealment, Blinding, Intention to Treat, Lost to Follow-Up
Turpie et al, Canada, 1977, no external funding (49)	Inclusion: elective craniotomy or intracranial hemorrhage Exclusion: VTE within 12 mo, peripheral vascular disease	Calf pumps (n=65) or control (n=63) for 5 d	(1) ^{125}Iodine fibrinogen leg scan for 5 d and continued until 14 d if not ambulatory (2) DVT	Allocation concealment adequate, no blinding, analysis not by intention to treat, 20.5% did not complete the study
Vignon et al, France, 2012, French Ministry of Health, Covidien (50)	Inclusion: age >18 y and critically ill at high risk of bleeding as evidenced by active bleeding, anemia, or abnormal coagulation tests Exclusion: VTE within 3 mo, peripheral vascular disease, and mechanical heart valve	Thigh and calf pumps (n=205) or control (n=202) for 6 d	(1) Compression USS on day 6 (2) DVT, PE, and mortality	Allocation concealment adequate, single blinded, analysis not by intention to treat, 10.8% did not complete the study
Weitz et al, US, 1986, National Institute of Health (51)	Inclusion: adult patients who had elective craniotomy Exclusion: not described	Calf pumps (n=5) or control (n=9) for 6 d	(1) ^{125}Iodine fibrinogen leg scan daily until discharge and positive scans were confirmed by phlebography (2) DVT	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Westrich et al, US, 2006, no external funding (52)	Inclusion: unilateral or bilateral total knee arthroplasty Exclusion: history of VTE, allergic to aspirin, peptic ulcer disease, treated with an anticoagulant	Foot pumps (n=61 with 81 arthroplasties) or control (n=61 with 83 arthroplasties); both groups also received aspirin 325 mg twice daily until DVT screening test was done	(1) Phlebography or Doppler USS if allergic to radiocontrast between days 4 and 7 (2) DVT	Allocation concealment inadequate, single blinded, analysis by intention to treat, all completed the study
Wilson et al, UK, 1992, no external funding (53)	Inclusion: total knee arthroplasty Exclusion: not described	Foot pumps (n=28) or control (n=31) for 9 to 10 d	(1) Phlebography on day 9 or 10 after surgery, ventilation-perfusion scan for symptomatic PE (2) DVT and PE	Allocation concealment unclear, single blinded, analysis by intention to treat, all completed the study
Windisch et al, Germany, 2011, no external funding (54)	Inclusion: total knee arthroplasty Exclusion: age <60 y, BMI >40 or <25 kg/m^2, venous insufficiency, newly diagnosed DVT	Foot pumps (n=40) or control (n=40) for 8 d; both groups also treated with LMWH	(1) Doppler USS on day 8 (2) DVT and PE	Allocation concealment unclear, single blinded, analysis by intention to treat, all completed the study
Woolson et al, US, 1991, no external funding (55)	Inclusion: total hip arthroplasty Exclusion: allergic to aspirin or warfarin, bleeding diathesis, recently diagnosed peptic ulcer disease	Thigh and calf pumps alone (n=73), pumps with aspirin 650 mg twice daily (n=70) or pumps with warfarin to achieve prothrombin time at 1.2–1.3 times control (n=69) until phlebography on the day before discharge	(1) Phlebography on the day before discharge, on average 7 d after surgery (2) DVT and PE	Allocation concealment adequate, no blinding, analysis not by intention to treat, 21% did not complete the study
Pambianco et al, US, 1995, US Department of Education (56)	Inclusion: stroke patients who had a paralyzed or severely weakened lower limb Exclusion: anticoagulant treatment, hemorrhagic stroke, >100 wk after stroke, active cancer	Calf pumps (n=117) for 8 h/d, heparin 5000 U 3 times daily (n=120), or control (n=115) for 28 d or discharge	(1) Doppler USS twice per week until either discharge or day 28 (2) DVT	Allocation concealment adequate, no blinding, analysis by intention to treat, 18.4% did not complete the study
Zhang et al, China, 2011, university research grant (57)	Inclusion: age >18 y, critically ill Exclusion: DVT before admission, expected to die within 14 d or to stay in intensive care unit <24 h, treated with an anticoagulant, lower-limb disease	Thigh and calf pumps (n=79) or control (n=83) until day 28	(1) USS on days 3 and 7 and then weekly until day 28 (2) DVT, PE, and mortality	Allocation concealment adequate, no blinding, analysis not by intention to treat, 25.3% did not complete the study

(*Continued*)

Table. Continued

Study: Country of Origin, Year of Publication, Funding Source (Reference)	Inclusion and Exclusion Criteria	Interventions and No. of Patients Analyzed	(1) VTE Diagnostic Criteria and (2) Outcomes Reported	Allocation Concealment, Blinding, Intention to Treat, Lost to Follow-Up
Yang et al, China, 2009, Capital Medical Research Fund (58)	Inclusion: gynecological surgery patients with increased risk of VTE, age >45 y, obesity, malignancy, and previous history of VTE Exclusion: not described	Thigh and calf pumps (n=47) or control (n=48) or LMWH (n=48) until ambulating	(1) Doppler USS on day 5 (2) DVT	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Coe et al, US, 1978, no external funding (59)	Inclusion: adults undergoing open urologic surgery Exclusion: declined to give consent	Calf pumps (n=29) or control (n=24) or heparin 5000 U twice daily (n=28) until hospital discharge	(1) ^{125}Iodine fibrinogen leg scan daily until discharge and positive scans were confirmed by phlebography (2) DVT, PE, and bleeding complications	Allocation concealment adequate, single blinded, analysis not by intention to treat, 2.4% did not complete the study
Skillman et al, US, 1978, no external funding (60)	Inclusion: adults undergoing neurosurgical operation on brain or spine Exclusion: declined to give consent	Calf pumps (n=47) or control (n=48) until ambulating or up to 17 d after surgery	(1) ^{125}Iodine fibrinogen leg scan daily until discharge and positive scans were confirmed by phlebography (2) DVT and PE	Allocation concealment adequate, single blinded, analysis by intention to treat, all completed the study
Ivanic et al, Austria, 2006, no external funding (61)	Inclusion: total hip arthroplasty Exclusion: history of VTE and BMI >33 kg/m^2	Foot pumps (n=20) 2 h/d for 5 d or control (n=21)	(1) Doppler USS on day 6 after surgery (2) DVT and PE	Allocation concealment unclear, single blinded, analysis not by intention to treat, 2.4% did not complete the study
Serin et al, Turkey, 2010, no external funding (62)	Inclusion: trauma and emergency surgical patients requiring mechanical ventilation >7 d Exclusion: age <14 y, coagulopathy, treated with an anticoagulant, liver or kidney dysfunction	Calf pumps (n=94) or LMWH (n=152) until ambulating or up to 17 d after surgery	(1) Doppler USS on days 3 and 7 (2) DVT, PE, bleeding complications, and mortality	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Bachmann et al, US, 1976, US PHS grant HL 14636, and Firma Castle Comp (63)	Inclusion: total hip or knee arthroplasty Exclusion: not described	Thigh and calf pumps (n=28) 2 h/d until ambulating or control (n=26)	(1) ^{125}Iodine fibrinogen leg scan alternative day until ambulating and positive scan confirmed by phlebography (2) DVT and PE	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Caprini et al, US, 1983, Kendall and the Dee and Moody Fund (64)	Inclusion: mainly abdominal or urologic surgical procedures Exclusion: allergic to radiocontrast, treated with an anticoagulant, operation on the breast or leg	Thigh and leg pumps (n=38) or TEDS (n=39) for at least 72 h or ambulating	(1) ^{125}Iodine fibrinogen leg scan alternate days until ambulating, Doppler USS on day 1 and then every third day until ambulating, phlebography if there were clinical signs and symptoms of DVT (2) DVT and PE	Allocation concealment adequate, no blinding, analysis by intention to treat, all completed the study
Wautrecht et al, Belgium, Kendall Healthcare Products, 1996 (65)	Inclusion: neurosurgical patients undergoing surgery for brain tumors Exclusion: allergic to radiocontrast, VTE within 2 y, peripheral vascular disease, neoplasm other than brain tumors, pregnancy, coagulopathy	Thigh and leg pumps (n=25) or control (n=10) for at least 72 h until ambulating or a maximum of 10 d; both groups got TEDS	(1) Phlebography between days 8 and 10, symptomatic PE diagnosed by ventilation-perfusion scan (2) DVT and PE	Allocation concealment adequate, single blinded, analysis not by intention to treat, 8% did not complete the study
Rokito et al, US, 1996, Kendall Healthcare Products (66)	Inclusion: >1-level spinal decompression or fusion Exclusion: history of thrombophlebitis or PE, treated with an anticoagulant, bleeding disorder	Thigh and leg pumps (n=33) or control (n=42) or Coumadin (n=35), until USS study, all patients received TEDS	(1) Doppler USS between days 5 and 7, indeterminate or positive results were evaluated by phlebography (2) DVT, PE, and bleeding complications	Allocation concealment unclear, single blinded, analysis by intention to treat, all completed the study

(*Continued*)

Table. Continued

Study: Country of Origin, Year of Publication, Funding Source (Reference)	Inclusion and Exclusion Criteria	Interventions and No. of Patients Analyzed	(1) VTE Diagnostic Criteria and (2) Outcomes Reported	Allocation Concealment, Blinding, Intention to Treat, Lost to Follow-Up
Sobieraj-Teague et al, Canada, 2012, Golden Horseshoe Biosciences Network and Saringer Incorp (67)	Inclusion: cranial or spinal surgery or intracranial hemorrhage with motor deficits Exclusion: leg ulceration, peripheral neuropathy or arterial disease, severe renal impairment or allergic to radiocontrast	Calf pumps (n=75) or control (n=75) until phlebography or USS assessment or symptomatic of VTE	(1) Phlebography on day 9 or discharge; USS scan was used with contraindications to radiocontrast (2) DVT and PE	Allocation concealment adequate, single blinded, analysis by intention to treat, all completed the study
Siragusa et al, Italy, 1994, no external funding (68)	Inclusion: hip arthroplasty Exclusion: not reported	Calf pumps (n=35) or placebo (n=35), both groups received heparin; duration of calf pumps used not reported	(1) Phlebography on day 10 (2) DVT and PE	Allocation concealment uncertain, no blinding, analysis by intention to treat, all completed the study
Borow et al, US, 1981, no external funding (69)	Inclusion: all types of surgical and orthopedic or vascular patients if the duration of surgery >1 h Exclusion: not reported	Calf pumps (n=79), heparin 5000 U twice daily (n=86), aspirin 600 mg twice daily (n=78), TEDS (n=91), or control (n=89)	(1) ^{125}Iodine fibrinogen scan daily and impedance plethysmography and Doppler USS every 3 or 4 d after surgery (2) DVT and PE	Allocation concealment inadequate, no blinding, analysis by intention to treat, all complicated the study
Hartman et al, US, 1982, no external funding (70)	Inclusion: hip surgery Exclusion: not described	Thigh and calf pumps (n=52) for 5–6 d or control (n=52)	(1) Phlebography, ^{125}iodine fibrinogen scan, and Doppler USS on alternate days after surgery until ambulating (2) DVT and PE	Allocation concealment inadequate, no blinding, analysis not by intention to treat, 1% did not complete the study
Warwick et al, UK, 1998, funding from Novamedix Services and authors declared that they had received benefits from a commercial party related to the subject matter of the study (71)	Inclusion: hip arthroplasty Exclusion: treatment with anticoagulant, active cancer, coagulopathy, gastrointestinal ulceration	Foot pumps (n=136) or LMWH (n=138) for 8 d; both groups also received TEDS	(1) Phlebography on day 6, 7, or 8 after surgery and symptomatic PE by ventilation-perfusion scan (2) DVT and PE	Allocation concealment adequate, single blinded, not by intention to treat, 4.8% did not complete the study
Hansberry et al, US, 1991, no external funding (72)	Inclusion: age >40 y and scheduled for open urologic surgery Exclusion: sensitive to heparin or dihydroergotamine, treated with aspirin, other antiplatelet agents, or anticoagulants	Thigh and calf pumps (n=24) for 48 h, TEDS (n=25), or heparin 5000 U plus dihydroergotamine 2.5 mg twice daily (n=25)	(1) ^{111}In-labeled autologous platelet imaging on days 1, 3 and 6 after surgery or hospital discharge and symptomatic PE by ventilation-perfusion scan (2) DVT, PE, and bleeding complications	Allocation concealment uncertain, no blinding, not by intention to treat, 5.1% did not complete the study
Pitto et al, New Zealand, 2004, authors declared that they had received benefits from a commercial party related to the subject matter of the study (73)	Inclusion: hip arthroplasty Exclusion: age <18 or >80 y, treatment with anticoagulant, active cancer, coagulopathy, gastrointestinal ulceration	Foot pumps (n=100) for 12 d or LMWH (n=100); both groups also received TEDS	(1) Doppler USS on days 3, 10, and 45 (2) DVT, PE, and bleeding complication	Allocation concealment adequate, single blinded, not by intention to treat, 7.4% did not complete the study
Warwick et al, UK, 2002, authors declared that they had received benefits from a commercial party related to the subject matter of the study (74)	Inclusion: knee arthroplasty Exclusion: treated with anticoagulant, coagulopathy, painful joints, or wounds in the feet	Foot pumps (n=117) or LMWH (n=112) until hospital discharge	(1) Phlebography between days 6 and 8 after surgery and symptomatic PE by ventilation-perfusion scan (2) DVT, bleeding complications, and mortality	Allocation concealment adequate, single blinded, intention to treat, all completed the study
Van Arsdalen et al, US, 1983, funding from Kendall Corp (75)	Inclusion: prostatectomy Exclusion: not described	Calf pumps (length not defined; n=16) or TEDS (n=21), duration of use not defined	(1) ^{125}Iodine fibrinogen scan daily until day 10 and phlebography to confirm DVT diagnosis (2) DVT, PE, and mortality	Allocation concealment adequate, no blinding, intention to treat, all completed the study
Bucci et al, US, 1989, funding from JOBST Institute Inc (76)	Inclusion: craniotomy Exclusion: history of VTE, bed rest >48 h, or unable to give consent	Calf pumps (n=32) or TEDS (n=38) until ambulatory	(1) Impedance plethysmography twice within first week after surgery; phlebography and pulmonary angiography to confirm DVT and PE, respectively (2) DVT, PE, and mortality	Allocation concealment unclear, no blinding, intention to treat, all completed the study

(*Continued*)

Table. Continued

Study: Country of Origin, Year of Publication, Funding Source (Reference)	Inclusion and Exclusion Criteria	Interventions and No. of Patients Analyzed	(1) VTE Diagnostic Criteria and (2) Outcomes Reported	Allocation Concealment, Blinding, Intention to Treat, Lost to Follow-Up
Salzman et al, US, 1982, no external funding (77)	Inclusion: unstable angina or myocardial infarction Exclusion: not described	Calf pumps (n=20), TEDS (n=23), or heparin 5000 U twice daily (n=29) until hospital discharge	(1) ^{125}Iodine fibrinogen scan and impedance plethysmography daily, ventilation-perfusion scan to confirm symptomatic PE (2) DVT, PE, and mortality	Allocation concealment unclear, no blinding, intention to treat, all completed the study
Ryan et al, US, 2002, ≥1 authors received grants from Aircast Incorp (78)	Inclusion: total hip arthroplasty Exclusion: history of VTE, peripheral vascular disease, contraindication to MRI scan	Calf pumps (n=50) or TEDS (n=50), both groups also received aspirin 325 mg twice daily for 4–5 d	(1) Magnetic resonance venography on days 3–5 after surgery (2) DVT and PE	Allocation concealment unclear, single blinded, intention to treat, all completed the study
Pedegana et al, US, 1977, no external funding (79)	Inclusion: total hip arthroplasty Exclusion: not described	Calf pumps (n=44) or TEDS (n=56) until day 4 after surgery, then all patients with TEDS until hospital discharge	(1) Doppler USS on days 1, 4, and 7 after surgery, symptoms of DVT or positive USS scan results were investigated further by technetium venography ventilation-perfusion (2) DVT, PE, and mortality	Allocation concealment inadequate, no blinding, intention to treat, all completed the study

BMI indicates body mass index; CT, computed tomography; CTPA, computed tomography pulmonary angiogram; DVT, deep vein thrombosis; IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin; MRI, magnetic resonance imaging; PE, pulmonary embolism; TEDS, thromboembolic deterrent stockings; USS, ultrasound scan; and VTE, venous thromboembolism.

16 164 hospitalized patients met the inclusion criteria and were subjected to meta-analysis (Figure 1).[10–79] The majority of the studies (93%) were reported in English. There were 27 trials on orthopedic surgical patients (39%); 17 trials on general surgical, including urology patients (24%); 11 trials on neurology or neurosurgical patients (16%); 8 trials on critically ill or trauma patients (12%); 4 trials on gynecological surgery patients (6%); and 3 trials on cardiology or cardiac surgical patients (4%). Thirteen trials had >2 comparative arms in the trials.* The overall quality of the trials was modest; 37 trials (53%) had adequate allocation

*References 14, 30, 32, 37,43, 44, 45, 48, 49, 66, 69, 72, 77.

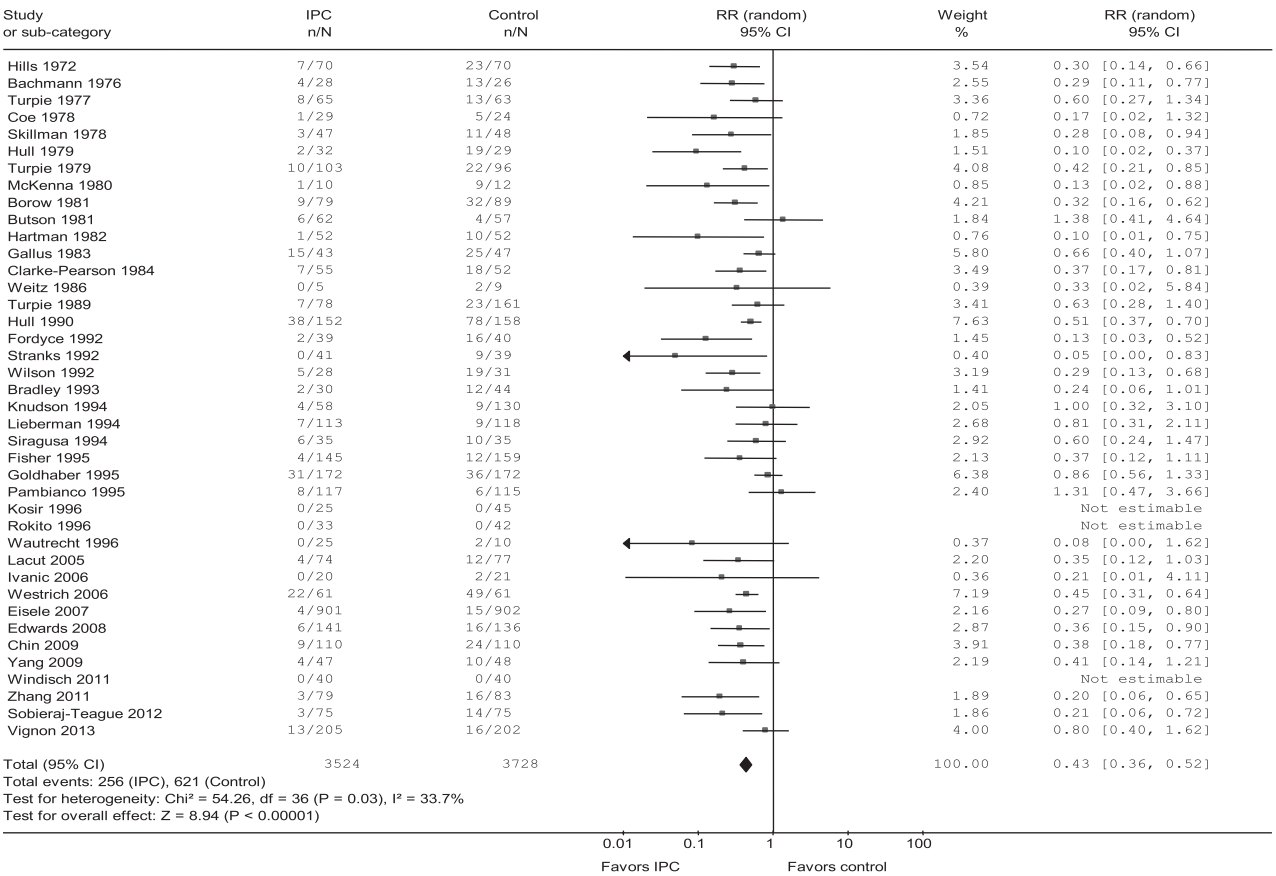

Figure 2. Forest plot showing the effect of intermittent pneumatic compression (IPC) on the risk of deep vein thrombosis compared with placebo. Studies are listed according to the order of their year of publication. CI indicates confidence interval; and RR, relative risk.

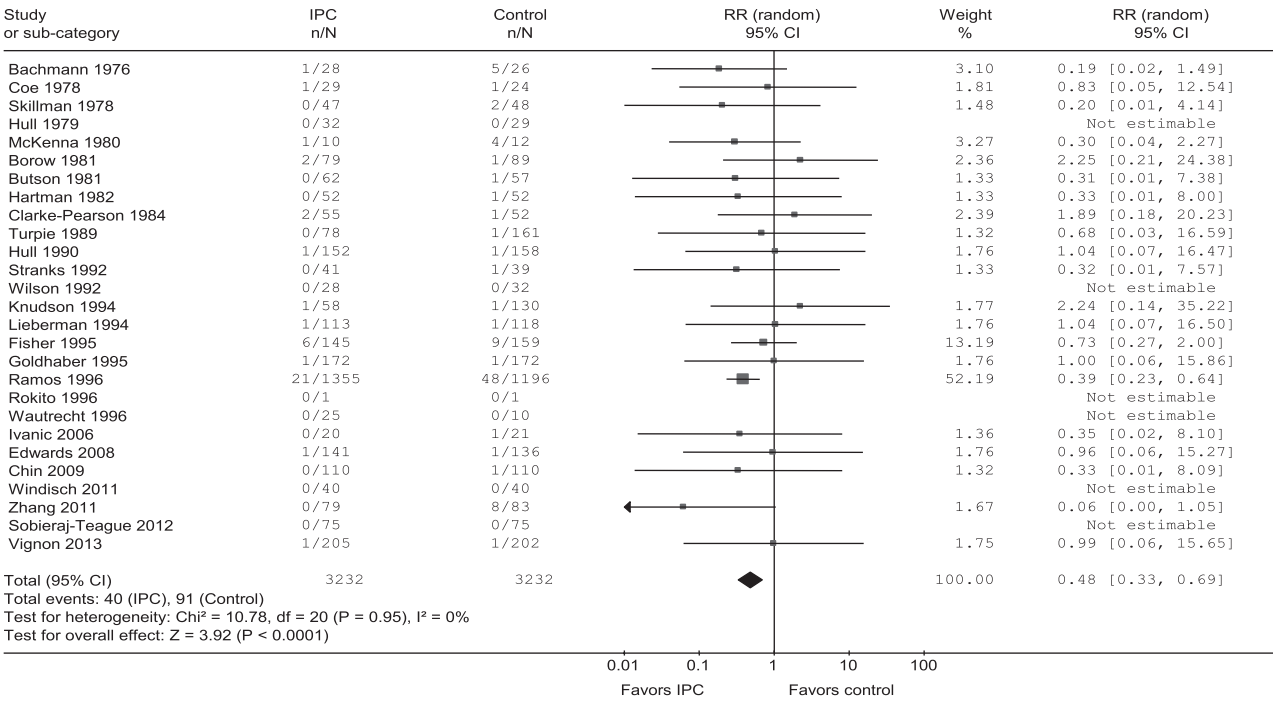

Figure 3. Forest plot showing the effect of intermittent pneumatic compression (IPC) on the risk of pulmonary embolism compared with placebo. Studies are listed according to their year of publication. CI indicates confidence interval; and RR, relative risk.

concealment, and 31 trials (44%) used blinding in assessing the outcomes of venous thromboembolism. The detail characteristics, outcomes, quality, and funding sources of the trials are described in the Table.

Effect of IPC on Risk of DVT, PE, and Mortality Compared With No IPC Prophylaxis or TEDS

IPC was more effective than no IPC prophylaxis in reducing DVT (40 trials: 7.3% versus 16.7%; absolute risk reduction, 9.4%; 95% CI, 7.9–10.9; RR, 0.43; 95% CI, 0.36–0.52; $P<0.01$; $I^2=34\%$) and PE (26 trials: 1.2% versus 2.8%; absolute risk reduction, 1.6%; 95% CI, 0.9–2.3; RR, 0.48; 95% CI, 0.33–0.69; $P<0.01$; $I^2=0\%$; Figures 2 and 3). Mortality, however, was not significantly different between the 2 groups (RR, 0.89; 95% CI, 0.73–1.09; $P=0.27$; $I^2=0\%$).

In 9 trials that directly compared IPC and TEDS alone, IPC was associated with a reduced risk of DVT (RR, 0.61; 95% CI, 0.39–0.93; $P=0.02$; $I^2=0\%$) but not PE (RR, 0.64; 95% CI, 0.21–1.95; $P=0.43$; $I^2=0\%$) compared with TEDS (Figure 4).

Effect of IPC on Risk of DVT, PE, Bleeding Complications, and Mortality Compared With Pharmacological Thromboprophylaxis

IPC appeared to be as effective as pharmacological prophylaxis in reducing PE (RR, 1.19; 95% CI, 0.62–2.29; $P=0.59$; $I^2=0\%$) and was associated with a reduced risk of bleeding (RR, 0.41; 95% CI, 0.25–0.65; $P<0.01$; $I^2=0\%$; Figure 5). However, significant heterogeneity in the risk of DVT between trials existed, and when pooled, IPC appeared to be as effective as pharmacological thromboprophylaxis in reducing DVT (RR, 0.93; 95% CI, 0.69–1.26; $P=0.66$; $I^2=52\%$; Figure 6). Mortality was not significantly different between the 2 groups (RR, 0.92; 95% CI, 0.44–1.90; $P=0.81$; $I^2=0\%$).

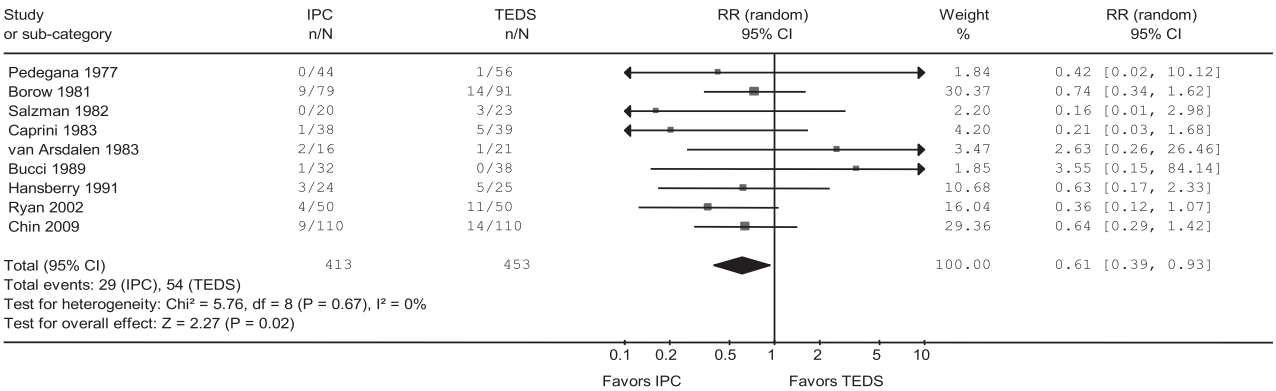

Figure 4. Forest plot showing the effect of intermittent pneumatic compression (IPC) on the risk of deep vein thrombosis compared with thromboembolic deterrent stockings (TEDS). Studies are listed according to their year of publication. CI indicates confidence interval; and RR, relative risk.

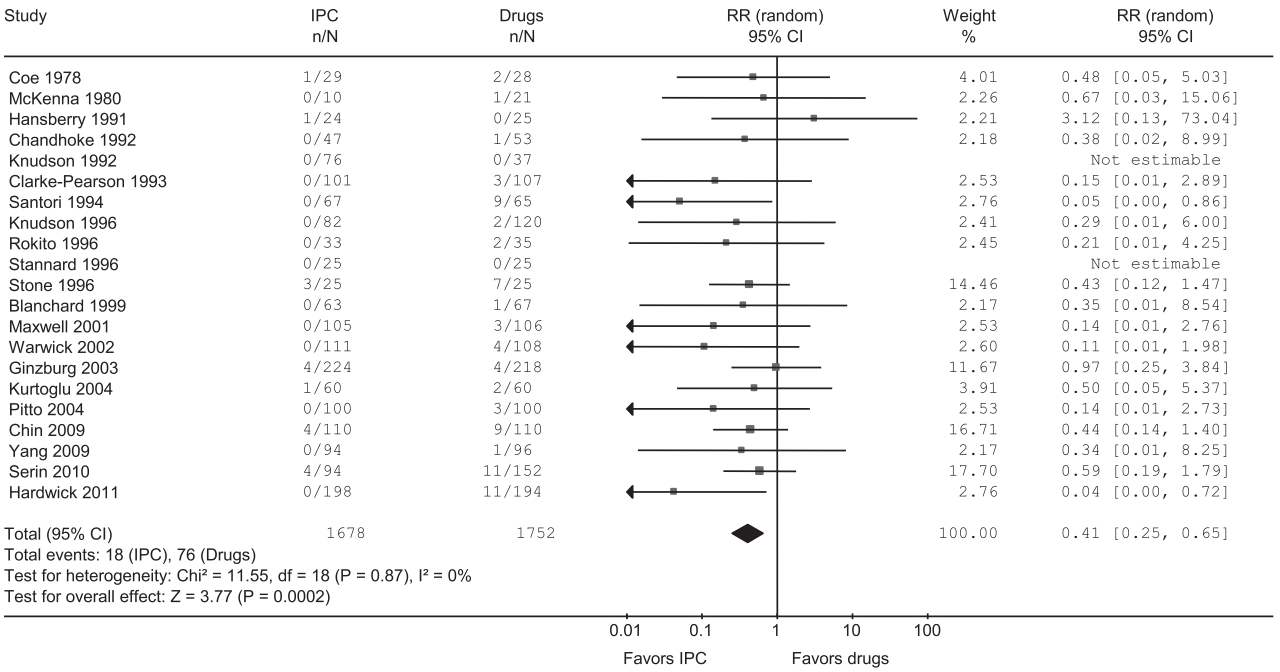

Figure 5. Forest plot showing the effect of intermittent pneumatic compression (IPC) on risk of systemic bleeding or bleeding complications from the wound compared with a pharmacological thromboprophylaxis. Studies are listed according to the order of their year of publication. CI indicates confidence interval; and RR, relative risk.

Effect of IPC on Risk of DVT, PE, and Mortality Compared With a Combination of Pharmacological Thromboprophylaxis and IPC

Adding pharmacological thromboprophylaxis to IPC further reduced the risk of DVT (RR, 0.54; 95% CI, 0.32–0.91; P=0.02; I^2=0%) but not PE (RR, 0.62; 95% CI, 0.13–3.02; I^2=0%) compared with the use of IPC alone. Mortality was not significantly different (RR, 0.61; 95% CI, 0.20–1.86; P=0.38).

Sensitivity Analyses

Heterogeneity in the outcome of DVT remained by comparing IPC with only low-molecular-weight-heparin or unfractionated heparin alone. The risk of DVT (14 trials: RR, 1.26; 95%

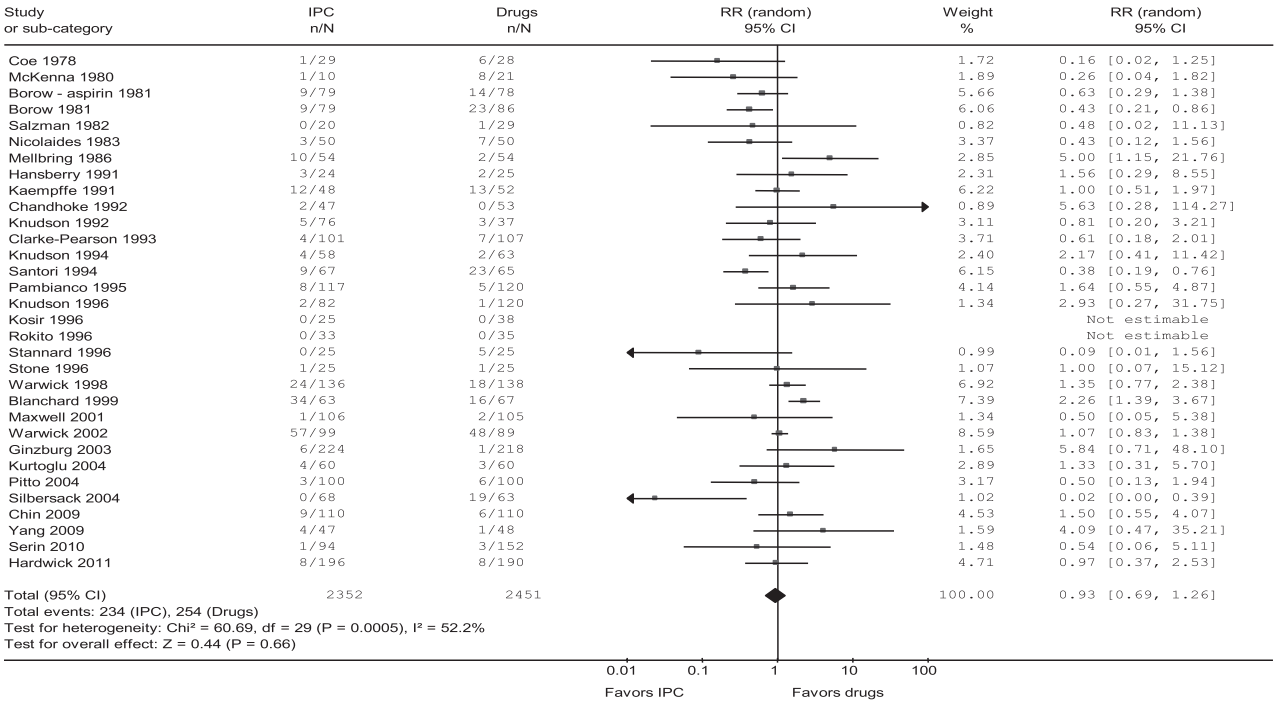

Figure 6. Forest plot showing the effect of intermittent pneumatic compression (IPC) on risk of deep vein thrombosis compared with pharmacological thromboprophylaxis. Studies are listed according to the order of their year of publication. CI indicates confidence interval; and RR, relative risk.

CI, 0.86–1.83; P=0.23; I^2=43%) and PE (10 trials: RR, 0.99; 95% CI, 0.36–2.76; P=0.99; I^2=0) did not appear to be statistically different between the IPC and low-molecular-weight-heparin groups. Similar results were observed by comparing IPC with unfractionated heparin (DVT from 12 trials: RR, 0.73; 95% CI, 0.42–1.26; P=0.26; I^2=53%; PE from 8 trials: RR, 1.24; 95% CI, 0.45–3.39; P=0.68; I^2=0).

After the exclusion of 3 studies that used routine scanning to detect asymptomatic PE,[19,33,37] IPC remained associated with a reduced risk of symptomatic PE compared with no IPC prophylaxis (RR, 0.46; 95% CI, 0.31–0.68; P<0.01; I^2=0%) and was associated with a similar effect on risk of PE compared with pharmacological thromboprophylaxis (RR, 1.40; 95% CI, 0.69–2.83; P=0.35; I^2=0%).

After the analysis was restricted to studies that used blinding in the assessment of outcomes, IPC remained associated with a reduced risk of DVT (RR, 0.41; 95% CI, 0.31–0.52; P<0.01; I^2=37%) but not PE (RR, 0.73; 95% CI, 0.37–1.46; P=0.38; I^2=0%) compared with no IPC prophylaxis, and the risk of DVT (RR, 0.74; 95% CI, 0.42–1.30; P=0.30; I^2=61%) and PE (RR, 1.38; 95% CI, 0.30–6.32; P=0.68; I^2=0%) remained not statistically different between IPC and pharmacological thromboprophylaxis.

After the analysis was restricted to elective orthopedic patients only, the magnitude and direction of the protective effect of IPC on risk of DVT (RR, 0.41; 95% CI, 0.32–0.52; P<0.01; I^2=29%) and PE (RR, 0.42; 95% CI, 0.17–1.07; P=0.07; I^2=0%) compared with no IPC prophylaxis remained unchanged. Similarly, the risk of DVT remained not different between IPC and pharmacological thromboprophylaxis in elective orthopedic patients (RR, 0.86; 95% CI, 0.56–1.31; P=0.48; I^2=66%).

After the analysis was restricted to nonsurgical patients only, the magnitude and direction of the protective effect of IPC on risk of DVT (9 trials: RR, 0.53; 95% CI, 0.35–0.81; P<0.01; I^2=37%) and PE (6 trials: RR, 0.64; 95% CI, 0.29–1.42; P=0.27; I^2=0%) compared with no IPC prophylaxis were similar to the results when all trials were pooled. Similarly, the risk of DVT (7 trials: RR, 1.40; 95% CI, 0.70–2.81; P=0.34; I^2=0%) and PE (6 trials: RR, 1.32; 95% CI, 0.47–3.73; P=0.60; I^2=0%) remained not different between IPC and pharmacological thromboprophylaxis in nonsurgical patients without significant heterogeneity.

After the analysis was restricted to nonorthopedic surgical patients only, the magnitude and direction of the protective effect of IPC on risk of DVT (12 trials: RR, 0.44; 95% CI, 0.30–0.65; P<0.01; I^2=43%) compared with no IPC prophylaxis were similar to the results when all trials were pooled, although the risk of PE (8 trials: RR, 0.95; 95% CI, 0.29–3.15; P=0.93; I^2=0%) was not significantly different between the 2 groups. Similarly, the risk of DVT (7 trials: RR, 0.77; 95% CI, 0.33–1.78; P=0.53; I^2=44%) and PE (6 trials: RR, 1.61; 95% CI, 0.41–6.21; P=0.49; I^2=0%) remained not different between IPC and pharmacological thromboprophylaxis in nonorthopedic surgical patients.

After the analysis was restricted to knee arthroplasty patients only, the magnitude and direction of the protective effect of IPC on risk of DVT (6 trials: RR, 0.31; 95% CI, 0.19–0.51; P<0.01; I^2=44%) compared with no IPC prophylaxis were similar to the results when all trials were pooled, although the risk of PE (5 trials: RR, 0.31; 95% CI, 0.06–1.71; P=0.18; I^2=0%) was not significantly different between the 2 groups. Similarly, the risk of DVT (4 trials: RR, 1.32; 95% CI, 0.73–2.37; P=0.36; I^2=70%) and PE (4 trials: RR, 1.10; 95% CI, 0.19–6.50; P=0.91; I^2=0%) remained not different between IPC and pharmacological thromboprophylaxis in knee arthroplasty patients. After the analysis was restricted to hip arthroplasty patients only, the magnitude and direction of the protective effect of IPC on risk of DVT (8 trials: RR, 0.48; 95% CI, 0.33–0.70; P<0.01; I^2=32%) and PE (4 trials: RR, 0.64; 95% CI, 0.15–2.80; P=0.56; I^2=0%) compared with no IPC prophylaxis were similar to the results of knee arthroplasty patients only. Similarly, the risk of DVT (6 trials: RR, 0.068; 95% CI, 0.35–1.32; P=0.25; I^2=54%) and PE (6 trials: RR, 0.72; 95% CI, 0.19–2.69; P=0.62; I^2=0%) remained not different between IPC and pharmacological thromboprophylaxis in the hip arthroplasty patients.

Publication Bias and Meta-Regression

With either DVT or PE used as an end point, no significant publication bias was observed when IPC was compared with pharmacological thromboprophylaxis or no IPC prophylaxis, respectively (Figure 7A and 7B). Most trials used IPC as a mechanical thromboprophylaxis between 3 and 10 days, and meta-regression did not show a significant association between the duration of use of IPC and its protective effect on risk of DVT (slope=−0.1, 95% CI, −0.03 to 0.02; P=0.61; Figure 8).

Discussion

This stratified meta-analysis showed that IPC of the lower limbs in hospitalized patients was effective in reducing venous thromboembolism compared with no IPC prophylaxis or TEDS, that its protective effect appeared to be comparable to that of pharmacological thromboprophylaxis, and that when combined with pharmacological thromboprophylaxis its protective effect on venous thromboembolism could be further enhanced. These results have clinical significance and require careful consideration.

First, our study has confirmed the results of a previous small meta-analysis of 2270 patients that IPC is effective in reducing venous thromboembolism,[80] in both surgical and nonsurgical patients. Our study supports our traditional belief in the pathogenesis of venous thromboembolism. According to the Virchow triad,[81] venous stasis resulting from immobilization of a patient is 1 of 3 key elements in the pathogenesis of venous thromboembolism. Studies have shown that IPC of the lower limbs may improve venous blood flow in the venous system and increase fibrinolytic activity.[51,82] Thus, it is perhaps not surprising to observe that IPC is more effective than no prophylaxis or TEDS in reducing venous thromboembolism. Using IPC alone, however, may not be completely effective in preventing thromboembolism in high-risk patients,[83] especially those with multiple risk factors for venous thromboembolism, including cancer, obesity, history of thromboembolism, or prolonged immobilization after surgery or trauma. For such patients, a multimodality approach by combining IPC and pharmacological thromboprophylaxis would be most effective in reducing venous thromboembolism because the

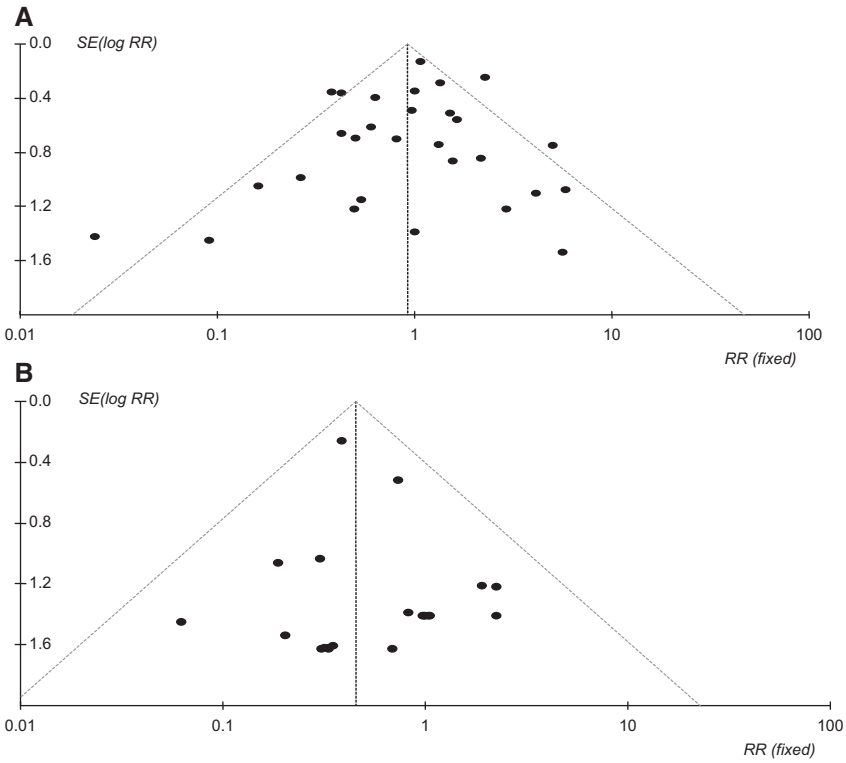

Figure 7. A, Funnel plot showing a lack of apparent publication bias in reporting the risk of deep vein thrombosis when intermittent pneumatic compression (IPC) was compared with pharmacological thromboprophylaxis. **B**, Funnel plot showing a lack of apparent publication bias in reporting risk of pulmonary embolism when IPC was compared with no IPC prophylaxis. RR indicates relative risk.

combined use of IPC and pharmacological thromboprophylaxis can tackle both venous stasis and hypercoagulability simultaneously.

Second, underuse of thromboprophylaxis remains common in many institutions.[3,4] IPC is an attractive option of thromboprophylaxis because it is applicable to almost all hospitalized patients, including those who have active bleeding or an increased risk of bleeding. Our results showed that IPC was superior to TEDS in reducing the risk of DVT; thus, for patients who are at high risk of bleeding, IPC will be a useful bridging measure until the risk of bleeding is deemed to be acceptable for initiation of pharmacological thromboprophylaxis. Although we could not demonstrate a significant mortality difference by using IPC as a thromboprophylaxis compared with no IPC prophylaxis, a reduction in symptomatic PE is still desirable because of its effects on the morbidity of patients and cost to the healthcare system.[84,85] Given that the cost of the disposable component of IPC is relatively low ($180),[86] the estimated cost to reduce 1 symptomatic PE is estimated to be $10 600; this is cost-effective compared with the total costs associated with the treatment of PE and its complications ($20 000).[87,88] Therefore, our data strongly support the American College of Chest Physicians latest clinical practice guidelines on prevention of thrombosis that IPC should be used as early as possible for hospitalized patients who have contraindications to pharmacological thromboprophylaxis and that pharmacological thromboprophylaxis should be added to IPC instead of replacing it when the risk of bleeding subsides for patients who are at high risk of venous thromboembolism.

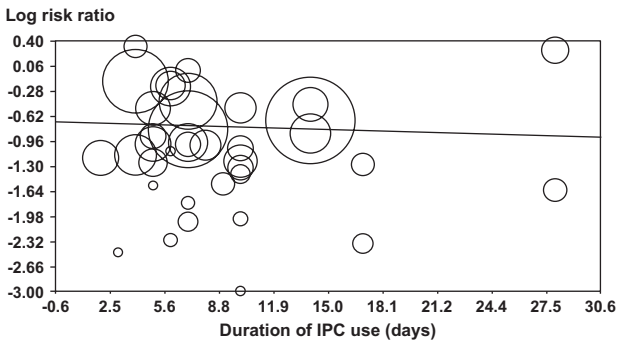

Figure 8. Meta-regression on the relationship between the effectiveness of intermittent pneumatic compression (IPC) on deep vein thrombosis compared with no IPC prophylaxis and duration of use of the IPC. The size of the markers is proportional to the size of the trials.

The last consideration is the limitations of the study. First, previous reviews have shown that TEDS is effective in reducing venous thromboembolism.[89] Although our results showed that IPC was more effective than TEDS in reducing DVT, outcome data on PE were limited. Therefore, whether IPC is superior to TEDS in reducing symptomatic PE remains unproven. Second, there was significant heterogeneity in the outcome on DVT between trials comparing pharmacological thromboprophylaxis with IPC, and this was not related to whether the trials used either low-molecular-weight-heparin or unfractionated heparin. Although IPC appeared to be as effective as pharmacological thromboprophylaxis in reducing PE without significant heterogeneity between the pooled trials, it is possible that some forms of pharmacological thromboprophylaxis will be more effective than IPC in reducing DVT under certain circumstances or for those who are at high risk of venous thromboembolism. Third, IPC was used during the period when the patients were at risk of DVT in the pooled trial. Thus, the negative association between the duration of

IPC use and its effectiveness does not suggest that an extended period of using IPC is not indicated for patients who remain at risk of venous thromboembolism for a prolonged period of time. Finally, although most IPC devices rely on similar mechanisms to improve venous blood flow to reduce venous thromboembolism, the number of trials that directly compared different IPC devices is limited, and whether different types of IPC will have similar efficacy in reducing venous thromboembolism and tolerability by different patient groups remains uncertain.[90,91]

Conclusions

Applying IPC to the lower limbs was effective in reducing venous thromboembolism in hospitalized patients compared with no IPC prophylaxis or TEDS, and when combined with pharmacological thromboprophylaxis, its protective effect on DVT could be further enhanced. IPC as part of a multimodality approach to prevent venous thromboembolism in hospitalized patients is strongly recommended.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The ideal thromboprophylaxis method in patients at risk of bleeding remains uncertain. Devices that apply intermittent pneumatic compression to the lower limbs can improve venous blood flow in the lower limbs and hence reduce the risk of deep vein thrombosis in patients who are immobile. In this stratified meta-analysis, we assessed the effects of intermittent pneumatic compression of lower limbs compared with no compression, thromboembolic deterrent stockings, or pharmacological thromboprophylaxis on risk of venous thromboembolism. We also assessed whether adding pharmacological thromboprophylaxis to pneumatic compression would improve its effectiveness. A total of 16 164 hospitalized patients from 70 trials met the inclusion criteria and were subjected to meta-analysis. Intermittent pneumatic compression was more effective than no compression in reducing deep vein thrombosis and pulmonary embolism. The number needed to treat to prevent 1 deep vein thrombosis and pulmonary embolism was 11 and 63, respectively. Intermittent pneumatic compression was also more effective than thromboembolic deterrent stockings in reducing deep vein thrombosis and appeared to be as effective as pharmacological thromboprophylaxis but with a reduced risk of bleeding. Adding pharmacological thromboprophylaxis to intermittent pneumatic compression further reduced the risk of deep vein thrombosis compared with using pneumatic compression alone. The current evidence suggests that intermittent pneumatic compression of the lower limbs is effective in reducing venous thromboembolism, and when combined with pharmacological thromboprophylaxis, its effectiveness in reducing venous thromboembolism can be further enhanced. Intermittent pneumatic compression of the lower limbs as part of a multimodality approach to prevent venous thromboembolism in hospitalized patients is strongly recommended.

Stratified Meta-Analysis of Intermittent Pneumatic Compression of the Lower Limbs to Prevent Venous Thromboembolism in Hospitalized Patients

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