

# Mechanical Compression Versus Subcutaneous Heparin Therapy in Postoperative and Posttrauma Patients: A Systematic Review and Meta-Analysis

Robert W. Eppsteiner · Jennifer J. Shin ·  
Jonas Johnson · Rob M. van Dam

Published online: 29 November 2009  
© Société Internationale de Chirurgie 2009

## Abstract

**Background** The risk of postoperative venous thromboembolic disease is as high as 30%, with an associated fatality risk of 1%. Therefore, prophylaxis is essential, but the optimal regimen remains controversial. This study was designed to systematically review and quantitatively summarize the impact of mechanical compression versus subcutaneous heparin on venous thromboembolic disease and posttreatment bleeding in postsurgical and posttrauma patients.

**Methods** Computerized searches of the MEDLINE and EMBASE databases through November 2008 were

performed and supplemented with manual searches. We included studies that had: (1) a patient population undergoing surgery or admitted immediately posttrauma, (2) a randomized comparison of prophylaxis with mechanical compression versus subcutaneous heparin, (3) outcome measured in terms of deep vein thrombosis (DVT), pulmonary embolism (PE), or bleeding.

**Results** Two reviewers independently extracted data from the original articles, which represented 16 studies, including a total of 3,887 subjects. Meta-analysis was performed using a random effects model. The pooled relative risk for mechanical compression compared with subcutaneous heparin was 1.07 (95% confidence interval [CI] 0.72, 1.61) for DVT and 1.03 (95% CI 0.48, 2.22) for PE. Mechanical compression was associated with a significantly reduced risk of postoperative bleeding compared with subcutaneous heparin (risk ratio 0.47; 95% CI 0.31, 0.70). Subgroup analyses by heparin type suggested that low molecular weight heparin may reduce risk of DVT compared with compression (relative risk 1.80; 95% CI 1.16, 2.79) but remains similarly associated with an increased risk of bleeding.

**Conclusions** These results suggest that the overall bleeding risk profile favors the use of compression over heparin, with the benefits in term of venous thromboembolic disease prophylaxis being similar between groups. Subgroup analyses suggest that low molecular weight heparin may have a differential effect; this observation should be further evaluated in future studies.

---

Drs. Eppsteiner and Shin are first co-authors and contributed equally to the work.

---

**Electronic supplementary material** The online version of this article (doi:10.1007/s00268-009-0284-z) contains supplementary material, which is available to authorized users.

---

R. W. Eppsteiner  
Department of Otolaryngology-Head and Neck Surgery,  
University of Iowa, 200 Hawkins Drive, Iowa, IA 52242-1078,  
USA  
e-mail: robert-eppsteiner@uiowa.edu

J. J. Shin (✉)  
Harvard Medical School, Massachusetts Eye and Ear Infirmary,  
243 Charles Street, Boston, MA 02114, USA  
e-mail: jennifer\_shin@meei.harvard.edu

J. Johnson  
Department of Otolaryngology, University of Pittsburgh School  
of Medicine, 203 Lothrop Street, Pittsburgh, PA 15213, USA

R. M. van Dam  
Harvard School of Public Health, 665 Huntington Avenue,  
Boston, MA 02115, USA

## Introduction

Venous thromboembolic disease (VTE) is a significant and potentially fatal problem; the incidence of death resulting

from pulmonary embolus (PE) is estimated to be 250,000 per year in the United States alone [1]. The risk of VTE is increased during the perioperative period, because both intraoperative and postoperative immobility, as well as potential causes for surgical intervention (i.e., malignancy, trauma), increase the risk for deep vein thrombosis (DVT) [2–4]. In general surgical patients without prophylaxis against VTE, the incidence of DVT has been reported to be as high as 30%, with an associated fatality risk of 1% [1]. Given the potential for significant respiratory distress from pulmonary infarction, as well as the potential for sudden death, preventative measures against VTE become essential for most patients.

The primary prophylactic modalities are mechanical and pharmacologic methods. Mechanical methods include pneumatic compression boots, foot pumps, and graduated compression stockings. Multiple mechanical methods remain in use, according to the discretion of the surgeons and the intrinsic requirements of the surgical site, especially because some data support that there is no difference in the effectiveness of the various compression types [5]. Benefits of mechanical prophylaxis include lack of interference with the clotting cascade, the ability to start and stop the intervention with ease, and constant visible evidence of compliance. Risks associated with mechanical prophylaxis include skin irritation, periods of noncompliance, and device malfunction. The other main prophylactic option is pharmacologic, which primarily includes heparin (unfractionated or fractionated), with some practitioners utilizing warfarin and aspirin as secondary modalities [6]. Benefits of heparin include ease of administration, improved patient compliance, and a lower risk of patient self-discontinuation. Risks include injection site reaction, drug interaction, dosing errors, and heparin-induced thrombocytopenia.

There is no clearly established consensus for the choice of prophylaxis modality, even within subspecialties, according to recent surveys of surgeons [7, 8]. Data are mixed, and it is difficult to establish clear conclusions across studies, which vary according to intervention and surgical type. Furthermore, much data is field-specific, focusing on only orthopedic, general surgical, or trauma patients, which makes it difficult for surgeons outside those disciplines to draw conclusions that encompass data from all of the most relevant disciplines. Given the uneven nature of the data as a whole, as well as multiple studies for which the statistical power may not have been adequate to detect clinically relevant effects, we performed a systematic review and meta-analysis to evaluate effects on VTE and bleeding of mechanical compression versus subcutaneous heparin therapy in postoperative and posttrauma patients.

## Methods

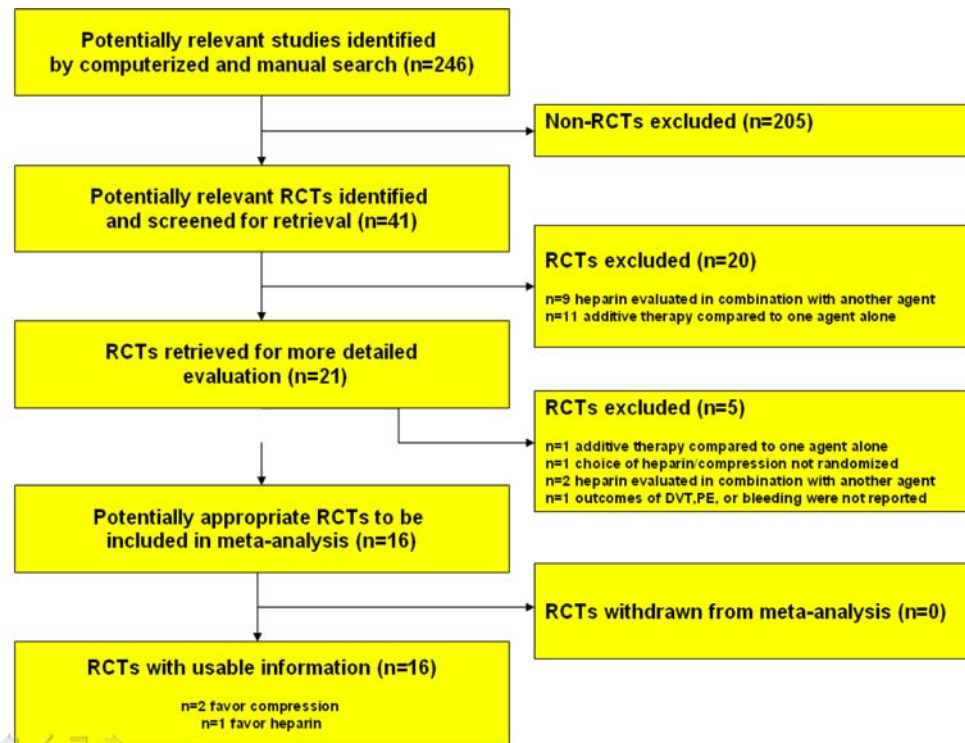
### Search strategy

A combination of computerized and manual searches was performed to identify all relevant data. A computerized PubMed search of MEDLINE 1966 to November 2008 was performed. The medical subject headings “heparin” or “low-molecular weight heparin” were exploded and the articles were collected into a first group. Next, articles obtained by exploding the medical subject heading “intermittent pneumatic compression devices” and those that mapped to text words “boots” or “compression” were collected into a second group. Next, the medical subject headings “pulmonary embolism” and “venous thrombosis” were exploded, and the resulting articles were collected into a third group. Finally, the three groups were cross-referenced. This search yielded 226 studies. A similar search was performed in EMBASE through November 2008, cross-referencing the exploded Emtree terms “deep vein thrombosis” or “pulmonary embolism” with “compression garment” or “intermittent pneumatic compression,” which yielded 20 additional references. The abstracts for all of the publications identified by these PubMed and EMBASE searches were evaluated according to the inclusion/exclusion criteria described below. Reference lists for relevant narrative reviews and criteria-meeting publications and were searched manually for additional studies. In addition, topic experts were contacted to determine if any additional studies or unpublished data could be identified. Titles and abstracts for all identified studies were reviewed, and ultimately 41 full articles were evaluated in detail (Fig. 1).

### Inclusion/exclusion criteria

The articles identified by the computerized and manual search strategy described above were evaluated to identify those that met the following inclusion criteria: (1) patient population undergoing surgery or admitted immediately posttrauma; (2) prophylaxis with mechanical compression versus subcutaneous heparin; (3) outcome measured in terms of deep vein thrombosis (DVT), pulmonary embolism (PE), or bleeding; (4) randomized, controlled trials (RCTs). Articles were excluded if: (a) randomization occurred but the choice of compression versus heparin was not randomized; (b) heparin was evaluated not alone but only in combination with other agents (such as dihydroergotamine); (c) additive therapy with heparin and compression was examined in comparison to one agent alone. This process yielded 16 RCTs that met our inclusion criteria [9–24].

**Fig. 1** Flow diagram showing the stages of the identification of studies for the meta-analysis



#### Data extraction

Data extraction was focused on items relevant to the study results, potential sources of heterogeneity among those results, and study identification (author, year of publication, full reference citation). Extracted data included: (1) the number/percent of patients who developed DVT, PE, or bleeding (major, minor, transfusion-requiring) during the postoperative or posttrauma follow-up period; (2) the *p* value, confidence interval, or standard error of the mean, as reported; (3) the number of subjects in each group; and (4) the follow-up time. Data collection also included multiple potential sources of heterogeneity among studies: (a) the type and regimen of compression used (pneumatic calf/thigh pump, foot pump, graduated compression stocking); (b) the type of heparin (unfractionated, low molecular weight) and its method of administration; (c) the screening regimen used to identify thromboembolic disease; (d) whether blinding was used in those measuring outcomes; (e) compliance; (f) criteria for withdrawal from the study; (g) age of subjects; (h) whether an intention-to-treat analysis was performed. Two reviewers extracted data independently using standardized tables.

#### Quantitative data synthesis

The primary outcome measure was risk of DVT with compression versus heparin therapy. The secondary outcomes were PE risk and bleeding risk. Data analysis was

performed in Stata version 10. Outcomes were evaluated as binary variables, with standard errors calculated according to the probability functions of the binomial distribution. *A priori*, it was determined that random effects analyses would be performed [25, 26]. This approach incorporates the heterogeneity of effects in the analysis of the overall treatment efficacy and obtains conservative pooled estimates that allow for between-study heterogeneity in addition to sampling error. Heterogeneity among studies was evaluated using the  $I^2$  statistic, which describes the percentage of total variation across studies that is due to differences among studies, rather than chance [27]. Subgroup analyses were performed in two ways: (1) a stratified analysis using the “metan” command, focusing on the *a priori* chosen variables (type of compressive device, type of heparin, type of bleeding reported, and type of patient/surgery); (2) meta-regression was performed using the “metareg” command and was used to evaluate whether there was an impact of the type of compressive device (pneumatic calf/thigh boot, foot pump, graduated compression stocking, or dual-modality compression), heparin type (unfractionated or low molecular weight), bleeding type (major, minor, or transfusion requirement), and patient type (trauma, orthopedic, gynecologic, general surgery, or urology). Publication bias was assessed with Egger’s and Begg’s statistical tests and the funnel plot [28, 29]. Sensitivity analyses were performed using the “metainf” command calculating pooled estimates while excluding one study at

a time to ensure that the summary results were not unduly influenced by any single study.

## Results

### Study characteristics

The 16 eligible RCTs of mechanical compression versus heparin included a total of 3,887 participants [9–24]. Study characteristics are described in Table 1. Fourteen of the studies used a single modality for compression: pneumatic calf/thigh compression, foot pump, or graduated compression stockings. Two studies used dual-modality compression devices: one used both pneumatic calf compression and graduated compression stockings [23], and the other used both foot pump and graduated compression stockings [24]. Heparin therapy was administered subcutaneously in the unfractionated or low molecular weight form. In six studies, the radiologists who interpreted the DVT screening imaging were blinded to the treatment group of the patient. Thromboembolic outcomes were most commonly reported as the percent of patients who developed DVT or PE. Occasionally it was reported as the percent of limbs identified with thrombus. Bleeding outcomes were described as percent with major or minor bleeding, hematoma formation, transfusion requirement, oozing, or ecchymosis at the wound. The risk of DVT/PE could be affected by many potential confounders, including age, body habitus, duration of procedure, presence of malignancy, lower extremity and pelvic surgery/injuries, estrogen supplementation, and comorbid conditions (especially those interfering with ambulation). In addition, the use of nonsteroidal anti-inflammatory agents or warfarin therapy for concomitant medical disease could potentially influence results regarding both thromboemboli and bleeding. All of the criteria-meeting RCTs confirmed that their randomization process resulted in similar levels of potential confounders in nearly all categories in both groups.

### Effect on risk of deep vein thrombosis

The primary outcome measure was the proportion of participants who developed DVT. Outcomes were compared in subjects receiving mechanical compression versus subcutaneous heparin during the postoperative or posttraumatic period. The pooled estimate of the risk ratio was 1.07 (95% CI 0.72, 1.61), indicating that there was no difference in the risk of DVT between mechanical compression and subcutaneous heparin (Fig. 2). However, heterogeneity among studies was relatively

high, with an  $I^2$  statistic of 62.4% (95% CI 35, 78), indicating that 62.4% of the variation in study results was due to study heterogeneity rather than sample variation. We therefore evaluated whether effects differed by type of mechanical compression, type of heparin, type of patient, or blinding using stratified and meta-regression analysis (Table 2).

The subgroup analysis according to the type of heparin suggested a difference in effects on DVT of unfractionated and low molecular weight heparin. Among the studies that used unfractionated heparin, there was a nonsignificant trend toward a lower risk of DVT with heparin compared with compression therapy (risk ratio 0.71; 95% CI 0.42, 1.19). In contrast, in studies that used low molecular weight heparin, there was a significantly higher risk of DVT with compression (risk ratio 1.80; 95% CI 1.16, 2.79) compared with heparin. Meta-regression corroborated this difference in effects by type of heparin used ( $p = 0.03$ ).

We did not observe significant effect modification by type of mechanical compression therapy (pneumatic calf/thigh compression, foot pump, or graduated compression stockings; Table 2). However, when compression type and heparin type were modeled simultaneously in meta-regression analysis, the difference between graduated compression stockings and pneumatic compression became marginally statistically significant ( $p = 0.045$ ). This suggests that the relative risk of DVT for graduated compression stockings versus heparin may be higher than for pneumatic compression versus heparin.

The stratified analysis suggested that there was a higher risk of DVT with compression versus heparin in studies with blinding but not in studies without blinding (Table 2). The  $p$  value for effect modification by blinding was 0.08. There was, however, a significant association between which studies were blinded and which used low molecular weight heparin ( $p = 0.007$ ). When adjusted for the type of heparin, no appreciable effect modification by blinding was observed ( $p = 0.70$ ). In addition, there was no indication of effect modification by patient type (orthopedic, trauma, gynecologic, general, or urologic surgery; Table 2).

### Effects on risk of pulmonary embolus

The first secondary outcome measure was the proportion of subjects who developed PE in patients treated with compression versus heparin in 3,677 subjects in 15 studies. The pooled estimate of this risk ratio was 1.03 (95% CI 0.48, 2.22), suggesting no difference in effects on PE between the therapies. Heterogeneity among studies appeared low with an  $I^2$  statistic of 0% (95% CI 0, 62). Given the lack of heterogeneity, we did not conduct subgroup analyses for this endpoint.

**Table 1** Study characteristics for the included randomized, controlled trials of the effects of compression versus heparin on venous thromboembolic disease and bleeding in postsurgical and posttrauma patients

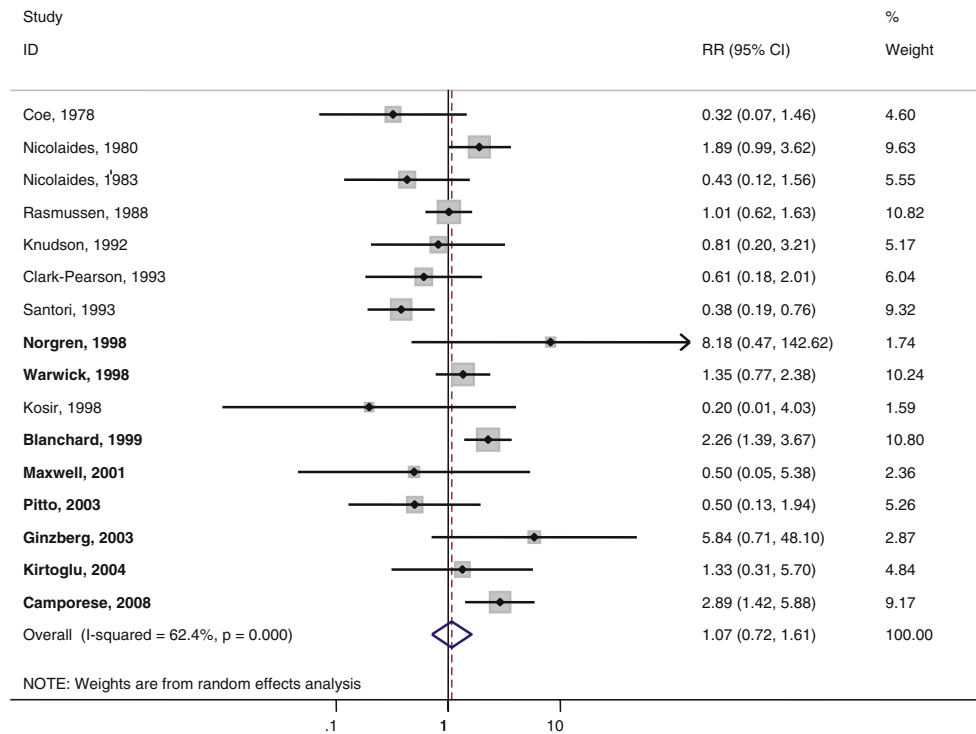
Study (year)	Sample size <sup>a</sup>	Patient characteristics	Follow-up	Blinding of radiologist	Compression device	Heparin type	%DVT	%PE	%Bleeding <sup>b</sup>
Camporese (2008)	1761 (2043)	42 yo (mean) Knee arthroscopy	91 days	Yes	Graduated compression stockings	LMW	Compression 4.4 Heparin 1.5	0.3 0.3	3.3 4.4
Ginzburg (2003)	398 (442)	42 yo Trauma	30 days	No	Pneumatic compression	LMW	Compression 2.7 Heparin 0.5	0.5 0.5	3.6 6
Warwick (1998)	274 (290)	69 yo (mean) Total hip replacement	3 months	Yes	Foot pump	LMW	Compression 18 Heparin 13	0.7 0	11.7 50
Nicolaides (1980)	251 (271)	Age NR General and urologic surgery	7 days	No	Pneumatic compression	UF	Compression 22.2 Heparin 11.7	0.6 0.6	NR NR
Rasmussen (1988)	248 (248)	41–87 yo Major abdominal surgery	5 days	No	Graduated compression stockings	UF	Compression 29.7 Heparin 29.4	0 0	NR NR
Clarke-Pearson (1993)	208 (218)	22–89 yo Gynecologic surgery	30 days	No	Pneumatic calf	UF	Compression 4 Heparin 6.5	0 0	16.8 31.8
Maxwell (2001)	211 (211)	35–87 yo Gynecologic oncology	30 days	Yes	Pneumatic compression	LMW	Compression 0.9 Heparin 1.9	0 0	0 1
Pitto (2003)	200 (216)	18–80 yo Hip arthroplasty	45 days	Yes	Foot pump	LMW	Compression 3 Heparin 6	0 0	3 3
Kosir (1998)	136 (160)	62.5 yo (mean) General surgery	30 days	No (DVT)	Pneumatic compression	UF	Compression 0 Heparin 3	1.5 1.5	NR NR
Santori (1994)	132 (132)	71 yo (mean) Total hip replacement	6 weeks	No	Foot pump	UF	Compression 13.4 Heparin 35.4	0 3.1	0 13.8
Blanchard (1999)	130 (130)	>40 yo Total knee arthroplasty	12 days	Yes	Foot pump	LMW	Compression 54 Heparin 23.9	0 0	0 1.5
Kurtoglu (2004)	120 (120)	18–76 yo Head/spine trauma	7 days	No	Pneumatic calf compression	LMW	Compression 6.6 Heparin 5.0	3.3 6.6	1.7 1.7
Knudson (1992)	113 (113)	17–93 yo Trauma	21 days	No	Pneumatic compression and graduated compression stockings	UF	Compression 6.6 Heparin 8.1	7.9 2.7	NR 2.7
Nicolaides (1983)	100 (100)	58 yo (mean) Major abdominal surgery	20 days	No	Pneumatic compression	UF	Compression 6 Heparin 14	NR NR	NR NR
Coe (1978)	81 (83)	59 yo (mean) Open urologic surgery	30 days	No	Pneumatic calf	UF	Compression 6.8 Heparin 21.4	0 0	31 50
Norgren (1998)	40 (51)	49–87 yo Knee replacement	17 days	Yes	Graduated compression stockings and foot pump	LMW	Compression 19 Heparin 0	4.8 0	NR NR

DVT deep vein thrombosis, PE pulmonary embolism, TED thromboembolic deterrent, UF unfractionated heparin, LMW low molecular weight heparin, NR not reported

<sup>a</sup> Data are those who completed the study with those who were initially recruited in parentheses

<sup>b</sup> Bleeding outcomes are reported as all bleeding types combined

**Fig. 2** Pooled estimate of deep vein thrombosis risk with mechanical compression versus subcutaneous heparin. A risk ratio >1 suggests an increased risk with compression, whereas a risk ratio <1 suggests an increased risk with heparin. The point estimate for the risk ratio for each study is shown by the central circle. The weight assigned to each study is represented by the surrounding box. The horizontal line through each box shows the 95% confidence interval for the risk ratio for each individual study. The pooled treatment effect is shown as the center of the diamond whose left and right extremes represent the associated confidence interval



**Table 2** Subgroup analyses for the effects of compression versus heparin on deep vein thrombosis according to subtypes of compression, heparin, surgery, and blinding

	No. of studies	Stratified analyses		Meta-regression
		Pooled RR (95% CI)	I-squared (95% CI)	p value for difference between strata
All compression vs. all heparin	16	1.07 (0.72, 1.61)	62 (35, 78)	–
<i>Compression types<sup>a</sup></i>				
Pneumatic compression	9	1.07 (0.62, 1.85)	69 (38, 85)	Reference
Foot pump	5	1.16 (0.59, 2.29)	55 (0, 83)	0.88
Graduated compression stocking	4	1.75 (0.74, 4.14)	60 (0, 87)	0.21
<i>Heparin types</i>				
Unfractionated	8	0.71 (0.42, 1.19)	55 (0, 80)	Reference
Low molecular weight heparin	8	1.80 (1.16, 2.79)	33 (0, 70)	0.03
<i>Patient/Surgery types</i>				
General or urologic surgery	5	1.08 (0.59, 1.96)	66 (20, 86)	Reference
Orthopedic surgery	6	1.14 (0.46, 2.85)	80 (53, 92)	0.88
Trauma	3	1.47 (0.53, 4.07)	19 (0, 92)	0.57
Gynecologic surgery	2	0.58 (0.20, 1.70)	0 (0, 99)	0.51
<i>Blinding of radiologist diagnosing DVT</i>				
Not blinded	10	0.81 (0.49, 1.33)	53 (3, 77)	Reference
Blinded	6	1.73 (1.04, 2.86)	45 (0, 78)	0.08

RR relative risk, CI confidence interval

p values for the regression analyses represent the potential significance of the impact of the row variable as an effect modifier of the DVT outcome for compression versus heparin

<sup>a</sup> Total number of studies in the compression types subgroups exceeds 16 because 2 of the studies used two types of these devices simultaneously

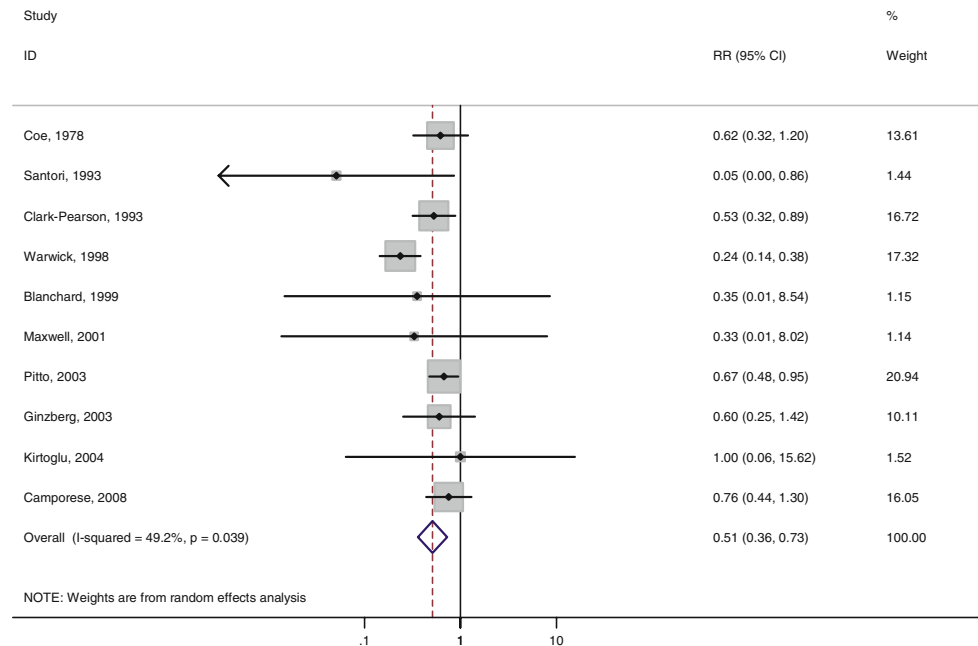
Compression stratified subgroups show comparative results for each type of compression versus all heparin

Heparin stratified subgroups show comparative results for all compression versus each type of heparin

Patient/surgery and blinding stratified subgroups show comparative results for all compression versus all heparin



**Fig. 3** Pooled estimate of all types of bleeding risk with mechanical compression versus subcutaneous heparin. A risk ratio  $<1$  suggests increased risk with heparin, whereas a risk ratio  $>1$  suggests an increased risk with compression therapy. The point estimate for the risk ratio for each study is shown by the central *circle*. The weight assigned to each study is represented by the surrounding *box*. The *horizontal line* through each *box* shows the 95% confidence interval for the risk ratio for each individual study. The pooled treatment effect is shown as the center of the diamond whose left and right extremes represent the associated confidence interval



### Effects on risk of bleeding

The other secondary endpoint was the proportion of subjects who developed bleeding complications while on compression versus heparin. Comparative bleeding outcomes were reported in 10 of the 16 trials. Meta-analysis revealed that subcutaneous heparin was associated with a significantly increased risk of postoperative bleeding for all bleeding outcomes combined (Fig. 3), with a risk ratio of 0.46 (95% CI 0.31, 0.70) for compression relative to heparin. The  $I^2$  statistic was 41.8% (95% CI 0, 72). The absolute risk of any type of bleeding ranged from 0–50% (median 5.9%) within study populations, with a 0–13.9% risk of major bleeding (median 1.5%).

We also evaluated the types of bleeding that were reported in the trials separately. Major bleeding (risk ratio 0.43; 95% CI 0.19, 0.98), minor bleeding (risk ratio 0.51; 95% CI 0.26, 0.98), and the risk of undergoing transfusion (risk ratio 0.73; 95% CI 0.56, 0.95) were all lower for compression compared with heparin.

In addition, a subgroup analysis was performed based on the type of heparin used in the study: unfractionated or low molecular weight. There was less bleeding with compression compared with heparin regardless of the type of heparin used (unfractionated heparin: risk ratio 0.47; 95% CI 0.32, 0.70; low molecular weight heparin: risk ratio 0.51; 95% CI 0.40, 0.64). Meta-regression confirmed that the type of heparin did not modify the effect on bleeding risk ( $p = 0.93$ ). Similarly, the risk of bleeding was substantially lower for compression compared with heparin regardless of the patient type (orthopedic: risk ratio 0.44; 95% CI 0.21, 0.89; gynecologic: risk ratio 0.52, 95% CI

0.32, 0.87; trauma: risk ratio 0.63, 95% CI 0.28, 1.43; general and urologic surgery: risk ratio 0.61, 95% CI 0.32, 1.15). Meta-regression showed no significant effect modification by type of patient (orthopedic  $p = 0.66$ , gynecologic  $p = 0.86$ , trauma  $p = 0.94$ , with general surgical and urologic as the reference).

### Sensitivity analysis and assessment of publication bias

A sensitivity analysis was performed to ensure that no single study influenced the overall results unduly. No omission of single studies substantially changed the pooled estimates for compression therapy versus heparin for DVT risk (risk ratio range 0.98 [95% CI 0.65, 1.47] to 1.24 [0.86, 1.79]) or bleeding risk (risk ratio range 0.50 [95% CI 0.34, 0.74] to 0.63 [0.51, 0.79]).

There was no evidence of publication bias for the primary outcome of DVT risk as assessed by Begg's test ( $p = 0.685$ ), Egger's test ( $p = 0.322$ ), or the funnel plot (Supplementary Fig. A). Likewise, there was no evidence of significant publication bias for the secondary outcome of bleeding risk as assessed by Begg's ( $p = 0.245$ ), Egger's test ( $p = 0.659$ ), or the funnel plot (Supplementary Fig. B).

### Discussion

In our meta-analysis of 16 RCTs of mechanical compression versus subcutaneous heparin, there was no significant difference in thromboembolic outcomes (DVT, PE) for postsurgical and posttrauma patients. In contrast, the risk of bleeding was substantially lower for mechanical

compression compared with heparin therapy. Overall DVT, PE, and bleeding risks were low in individual studies, and many of the individual trials seemed underpowered to detect clinically significant differences between heparin and compression therapy. This meta-analysis provided a combined sample size of 3,887 subjects with results applicable to the primary DVT outcome; such a sample size provides a well-powered analysis, with greater ability to demonstrate a difference that may not be uncovered by the smaller individual studies.

The relatively large sample size of our study also may have helped uncover an increased bleeding risk that was not consistently demonstrated in individual trials (only two of these trials showed a significant bleeding effect). The results of this meta-analysis show that heparin was associated with a substantially higher risk of minor bleeding, major bleeding, and blood transfusion compared with mechanical compression. In a subgroup analysis, both unfractionated and low molecular weight heparin appeared to increase the risk of bleeding compared with compression.

There were differences in the thromboembolic outcomes in subgroup analyses. In a stratified analysis according to type of heparin, low molecular weight heparin, but not unfractionated heparin, was associated with a lower risk of DVT compared with compression. This finding must be considered with some caution, because subgroup analyses are prone to chance findings and require confirmation in additional studies. The question of whether low molecular weight heparin may have more favorable effects on DVT than unfractionated heparin has been addressed in meta-analyses of patients undergoing homogenous surgical interventions. Some of these meta-analyses data suggest that there is only a trend toward less DVT with low molecular weight heparin [30], whereas other data suggest that low molecular weight heparin results in superior prophylaxis [31–33]. These results are consistent with the results of our meta-analysis. However, these analyses were specific to orthopedic and general surgery patients, and therefore, it remains unclear whether the results are generalizable to patients undergoing surgery in other disciplines.

Our results also suggested that the type of compression therapy may be relevant with potentially a less favorable effect of graduated compression stockings on DVT. This finding was marginally significant after taking the effect of heparin type into account and also requires confirmation in further studies. Another compression-associated factor that must be considered is the potential for noncompliance, which may often occur, particularly in trauma patients [34]; outside of the rigor of RCTs, compliance may be decreased. Blinded studies appeared to be more likely to report higher risk of DVT with compression, compared with heparin, than unblinded studies. However, the use of

blinding was significantly associated with the use of low molecular weight heparin in these studies, and the differences associated with blinding disappeared when both heparin and blinding were simultaneously considered in a regression model. There was no suggestion of effect modification by the type of patient. Although no difference was demonstrated in this stratified analysis, it is very important to consider this level of analysis, especially because trauma patients are so distinct from elective surgical patients. In trauma patients, the inflammatory cascade is more activated, causing coagulation pathways to be affected in different ways. This result was consistent with previously published trauma-specific results, which compared the results of prophylaxis with different types of heparin versus mechanical compression, also showing no difference between these two groups [35].

There are several limitations to our meta-analysis. First, studies that were included had a variety of study designs (differing surgical types, compression types, and heparin types) with significant heterogeneity in study results for the DVT and bleeding analyses. We have addressed this heterogeneity by using DerSimonian and Laird random effects analysis [25, 26]. In addition, we conducted stratified and meta-regression analyses to evaluate the impact of individual study characteristics on the overall results. A second limitation was that our study includes data that were collected without blinding in the primary studies. Only six of the studies blinded the radiologist reading the DVT diagnostic studies, and the bleeding outcomes were typically not evaluated in a blinded fashion. Furthermore, patients and caregivers cannot be blinded because of the obvious differences between compression and heparin prophylaxis. Thus, there is an element of expectation bias that may not be surmountable in this analysis. Furthermore, with regard to bleeding outcomes, the results of the subgroup analysis are in the direction that expectation bias would be expected to lead. Such expectation may have created a tendency toward a reporting bias, although there appears to be no significant publication bias as assessed by Begg's and Egger's test. We have been able to partially address this potential for bias by performing subgroup analyses of the blinded studies, although this analysis is limited by the association between blinded studies and those that used low molecular weight heparin. A third limitation is that our analysis was limited to studies published in English and those identified through contact with English-speaking experts in the field. A fourth limitation is that our study was meant to address the issues of thromboembolic disease and bleeding in only the postsurgical or posttraumatic setting. As defined by the inclusion and exclusion criteria, our study was not meant to determine the impact of compression versus heparin in the nonoperative settings in which patients are at risk for thromboembolic disease, such as



malignancy or generalized immobility. Thus, it is not clear whether these results can be generalized to other types of patients.

The overall results of these analyses suggest that when compression and subcutaneous heparin are compared, the benefits (thromboembolic disease prevention) are similar but the risks (bleeding) are increased with subcutaneous heparin. Further studies are needed to confirm our subgroup finding that low molecular weight heparin, but not unfractionated heparin, may decrease the risk of DVT compared with compression therapy. Potential benefits of heparin should be carefully weighed against the increased risk of bleeding in the decision to use heparin rather than mechanical compression in postsurgical and posttrauma patients. There may, however, be situations where additional heparin-associated benefits are anticipated, such as when compression is not a viable option, or in patients with microvascular anastomoses or ischemic wounds or those at especially increased risk for thromboembolic disease. These situations may create situations in which the potential additional benefits of heparin could outweigh the higher risk of bleeding.

**Acknowledgments** Jennifer J. Shin thanks Mr. Thomas Y. Lin for his assistance during the preparation of this manuscript.

## References

- Qadan M, Tyson M, McCafferty MH, Hohmann SF, Polk HC Jr (2008) Venous thromboembolism in elective operations: balancing the choices. *Surgery* 144:654–661
- Hitos K, Cannon M, Cannon S, Garth S, Fletcher JP (2007) Effect of leg exercises on popliteal venous blood flow during prolonged immobility of seated subjects: implications for prevention of travel-related deep vein thrombosis. *J Thromb Haemost* 5:1890–1895
- Bajzar L, Chan AK, Massicotte MP, Mitchell LG (2006) Thrombosis in children with malignancy. *Curr Opin Pediatr* 18:1–9
- Barrett J, Hamilton W (2006) Malignancy and deep vein thrombosis. *Br J Gen Pract* 56:886
- Spain DA, Bergamini TM, Hoffmann JF, Carrillo EH, Richardson JD (1998) Comparison of sequential compression devices and foot pumps for prophylaxis of deep venous thrombosis in high-risk trauma patients. *Am Surg* 64:522–526
- Freedman KB, Brookenthal KR, Fitzgerald RH Jr, Williams S, Lonner JH (2000) A meta-analysis of thromboembolic prophylaxis following elective total hip arthroplasty. *J Bone Joint Surg Am* 82-A:929–938
- Cook D, McMullin J, Hodder R, Heule M, Pinilla J, Dodek P, Stewart T (2001) Prevention and diagnosis of venous thromboembolism in critically ill patients: a Canadian survey. *Crit Care* 5:336–342
- Wu EC, Barba CA (2000) Current practices in the prophylaxis of venous thromboembolism in bariatric surgery. *Obes Surg* 10:7–14
- Kurtoglu M, Yanar H, Bilsel Y, Guloglu R, Kizilirmak S, Buyukkurt D, Granit V (2004) Venous thromboembolism prophylaxis after head and spinal trauma: intermittent pneumatic compression devices versus low molecular weight heparin. *World J Surg* 28:807–811
- Ginzburg E, Cohn SM, Lopez J, Jackowski J, Brown M, Hameed SM (2003) Randomized clinical trial of intermittent pneumatic compression and low molecular weight heparin in trauma. *Br J Surg* 90:1338–1344
- Warwick D, Harrison J, Glew D, Mitchelmore A, Peters TJ, Donovan J (1998) Comparison of the use of a foot pump with the use of low-molecular-weight heparin for the prevention of deep-vein thrombosis after total hip replacement. A prospective, randomized trial. *J Bone Joint Surg Am* 80:1158–1166
- Nicolaides AN, Fernandes e Fernandes J, Pollock AV (1980) Intermittent sequential pneumatic compression of the legs in the prevention of venous stasis and postoperative deep venous thrombosis. *Surgery* 87:69–76
- Nicolaides AN, Miles C, Hoare M, Jury P, Helms E, Venniker R (1983) Intermittent sequential pneumatic compression of the legs and thromboembolism-deterrent stockings in the prevention of postoperative deep venous thrombosis. *Surgery* 94:21–25
- Maxwell GL, Synan I, Dodge R, Carroll B, Clarke-Pearson DL (2001) Pneumatic compression versus low molecular weight heparin in gynecologic oncology surgery: a randomized trial. *Obstet Gynecol* 98:989–995
- Clarke-Pearson DL, Synan IS, Dodge R, Soper JT, Berchuck A, Coleman RE (1993) A randomized trial of low-dose heparin and intermittent pneumatic calf compression for the prevention of deep venous thrombosis after gynecologic oncology surgery. *Am J Obstet Gynecol* 168:1146–1154
- Pitto RP, Hamer H, Heiss-Dunlop W, Kuehle J (2004) Mechanical prophylaxis of deep-vein thrombosis after total hip replacement: a randomised clinical trial. *J Bone Joint Surg Br* 86:639–642
- Kosir MA, Schmittinger L, Barno-Winarski L, Duddella P, Pone M, Perales A, Lange P, Brish LK, McGee K, Beleski K, Pawlak J, Mammen E, Sajahan NP, Kozol RA (1998) Prospective double-arm study of fibrinolysis in surgical patients. *J Surg Res* 74:96–101
- Rasmussen A, Hansen PT, Lindholt J, Poulsen TD, Toftdahl DB, Gram J, Toftgaard C, Jespersen J (1988) Venous thrombosis after abdominal surgery: A comparison between subcutaneous heparin and antithrombotic stockings, or both. *J Med* 19(3–4):193–201
- Blanchard J, Meuwly JY, Leyvraz PF, Miron MJ, Bounameaux H, Hoffmeyer P, Didier D, Schneider PA (1999) Prevention of deep-vein thrombosis after total knee replacement. Randomised comparison between a low-molecular-weight heparin (nadroparin) and mechanical prophylaxis with a foot-pump system. *J Bone Joint Surg Br* 81:654–659
- Coe NP, Collins RE, Klein LA, Bettmann MA, Skillman JJ, Shapiro RM, Salzman EW (1978) Prevention of deep vein thrombosis in urological patients: a controlled, randomized trial of low-dose heparin and external pneumatic compression boots. *Surgery* 83:230–234
- Santori FS, Vitullo A, Stopponi M, Santori N, Ghera S (1994) Prophylaxis against deep-vein thrombosis in total hip replacement. Comparison of heparin and foot impulse pump. *J Bone Joint Surg Br* 76:579–583
- Camporese G, Bernardi E, Prandoni P, Noventa F, Verlato F, Simioni P, Ntita K, Salmistraro G, Frangos C, Rossi F, Cordova R, Franz F, Zucchetto P, Kontothanassis D, Andreozzi GM (2008) Low-molecular-weight heparin versus compression stockings for thromboprophylaxis after knee arthroscopy: a randomized trial. *Ann Intern Med* 149:73–82
- Knudson MM, Collins JA, Goodman SB, McCrory DW (1992) Thromboembolism following multiple trauma. *J Trauma* 32:2–11
- Norgren L, Toksvig-Larsen S, Magyar G, Lindstrand A, Albrechtsson U (1998) Prevention of deep vein thrombosis in knee

- arthroplasty. Preliminary results from a randomized controlled study of low molecular weight heparin vs. foot pump compression. *Int Angiol* 17:93–96
25. DerSimonian R, Kacker R (2007) Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials* 28:105–114
  26. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. *Control Clin Trials* 7:177–188
  27. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. *BMJ* 327(7414):557–560
  28. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. *Biometrics* 50:1088–1101
  29. Sterne JA, Gavaghan D, Egger M (2000) Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol* 53:1119–1129
  30. Koch A, Bouges S, Ziegler S, Dinkel H, Daures JP, Victor N (1997) Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses. *Br J Surg* 84:750–759
  31. Howard AW, Aaron SD (1998) Low molecular weight heparin decreases proximal and distal deep venous thrombosis following total knee arthroplasty. A meta-analysis of randomized trials. *Thromb Haemost* 79:902–906
  32. Nurmohamed MT, Rosendaal FR, Buller HR, Dekker E, Hommes DW, Vandenbroucke JP, Briet E (1992) Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. *Lancet* 340(8812):152–156
  33. Handoll HH, Farrar MJ, McBirnie J, Tytherleigh-Strong G, Milne AA, Gillespie WJ (2002) Heparin, low molecular weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures. *Cochrane Database Syst Rev* 4:CD000305
  34. Cornwell EE III, Chang D, Velmahos G, Jindal A, Baker D, Phillips J, Bonar J, Campbell K (2002) Compliance with sequential compression device prophylaxis in at-risk trauma patients: a prospective analysis. *Am Surg* 68:470–473
  35. Velmahos GC, Kern J, Chan LS, Oder D, Murray JA, Shekelle P (2000) Prevention of venous thromboembolism after injury: an evidence-based report—part I: analysis of risk factors and evaluation of the role of vena caval filters. *J Trauma* 49:132–139