SYSTEMATIC REVIEW

OPEN

Effect of Intermittent Pneumatic Compression in Addition to Pharmacologic Prophylaxis for Thromboprophylaxis in Hospitalized Adult Patients: A Systematic Review and Meta-Analysis

Cécile Duval, PharmD, MBA[1,2]
Caroline Sirois, BPharm, PhD[3,4]
Félix H. Savoie-White, MSc[1,2]
Pier-Alexandre Tardif , MSc[2]
Mélanie Bérubé, RN, PhD[2,5]
Alexis F. Turgeon, MD, MSc[2,6]
Deborah J. Cook, MD, MSc[7,8]
François Lauzier, MD, MSc[2,6]
Lynne Moore, PhD[1,2]

OBJECTIVES: Venous thromboembolic events (VTE) are frequent complications in hospitalized patients and a leading cause of preventable death in hospital. Pharmacologic prophylaxis is a standard of care to prevent VTE in patients at risk, the additional value of intermittent pneumatic compression (IPC) is uncertain. We aimed to evaluate the efficacy of adding IPC to pharmacologic prophylaxis to prevent VTE in hospitalized adults.

DATA SOURCES: We searched the Cochrane Central Register of Controlled Trials, Embase, MEDLINE, Cumulative Index to Nursing and Allied Health Literature, ClinicalTrials.gov, and the International Clinical Trials Registry Platform from inception to July 2022.

STUDY SELECTION: We included randomized controlled trials comparing the use of IPC in addition to pharmacological thromboprophylaxis to pharmacological thromboprophylaxis alone in hospitalized adults.

DATA EXTRACTION: Meta-analyses were performed to calculate risk ratio (RR) of VTE, deep venous thrombosis (DVT), and pulmonary embolism (PE). We assessed the risk of bias using the Cochrane Risk of Bias Tool for Randomized Trials, Version 2 and the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation approach.

DATA SYNTHESIS: We included 17 trials enrolling 8,796 participants. The IPC was mostly applied up to the thigh and pharmacological thromboprophylaxis was primarily low-molecular-weight heparin. Adjunctive IPC was associated with a decreased risk of VTE (15 trials, RR = 0.53; 95% CI [0.35–0.81]) and DVT (14 trials, RR = 0.52; 95% CI [0.33–0.81]) but not PE (seven trials, RR = 0.73; 95% CI [0.32–1.68]). The quality of evidence was graded low, downgraded by risk of bias and inconsistency. Moderate and very low-quality evidence, respectively, suggests that adjunctive IPC is unlikely to change the risk of all-cause mortality or adverse events. Subgroup analyses indicate a more evident apparent benefit in industry-funded trials.

CONCLUSIONS: Results indicate low-quality evidence underpinning the additional use of IPC to pharmacological thromboprophylaxis for prevention of VTE and DVT. Further large high-quality randomized trials are warranted to support its use and to identify patient subgroups for whom it could be beneficial.

KEY WORDS: intermittent pneumatic compression devices; pulmonary embolism; Venous thromboembolic events; venous thrombosis

Venous thromboembolic events (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), are the second most frequent medical complication of hospitalization, the leading cause of preventable

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death in hospital and one of the main drivers of increased length of stay and hospital costs (between $8,870 and $19,130 2021 U.S. dollars per complication) (1–5). Without thromboprophylaxis, hospital-acquired DVT occurs in 10% to 40% of medical or general surgical patients, in 40% to 60% of major orthopedic patients, and in 60% to 80% of spinal cord injury patients (6).

Pharmacological thromboprophylaxis with heparin is a standard of care for hospitalized patients to prevent VTE. If anticoagulants are contraindicated, mechanical prophylaxis (e.g., intermittent pneumatic compression [IPC]) has been recommended (7, 8). However, the value of mechanical thromboprophylaxis is questionable in patients without a contraindication to anticoagulants. Based on very low certainty in the evidence of effect, the most recent American Society of Hematology (ASH) guidelines suggest adding mechanical thromboprophylaxis for patients undergoing major surgery receiving pharmacological thromboprophylaxis (7) but not for medical patients (8). Given that anticoagulation and IPC intervene on two different aspects of Virchow's triad, it seems unlikely that an anticoagulant would negate the effectiveness of IPC (9). However, IPC is noisy, causes patient discomfort, can interfere with sleep or early mobilization and may be a risk factor for delirium (10–13). These factors could result in suboptimal compliance with combined pharmacologic and mechanical thromboprophylaxis (6) and lead to decreased effectiveness of the latter. Furthermore, in addition to equipment costs, IPC increases nursing workload (14) and has significant environmental costs (single-use plastic sleeves). Evidence suggests that the effectiveness of adjunctive IPC may vary among target populations with different baseline risks and risk factors, for example, general and abdominal-pelvic surgery, major trauma, or critically ill patients (15, 16).

Current systematic reviews show inconsistent results on the efficacy of adjunctive IPC in hospitalized patients (17, 18) and additional randomized controlled trials (RCTs) have been conducted since the publication of these reviews and of the most recent ASH guidelines (7, 8, 19–22). A systematic review of the best available evidence is needed to inform future guidelines.

We aimed to evaluate the efficacy of adding IPC to pharmacologic thromboprophylaxis to prevent VTE in patients at risk admitted to hospital.

METHODS

We conducted a systematic review and meta-analysis using methodological approaches outlined in the Cochrane Handbook for Systematic Reviews (23) and reported results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (24). The protocol was registered in Prospero (CRD42021250319) (25).

Design and Search Strategy

Electronic databases including Cochrane Central Register of Controlled Trials, Embase, MEDLINE, Cumulative Index to Nursing and Allied Health Literature, ClinicalTrials.gov, and International Clinical trials registry platform were searched from database inception to July 5, 2022. The search strategy included terms relating to the intervention and the outcome with both high-precision and high-sensitivity validated search filters for retrieving RCTs (26) (**Appendix 1**, http://links.lww.com/CCX/B66). A manual search of references of systematic reviews and each identified article was performed. We used EndNote X9 for reference management.

Study Selection

Two reviewers (C.D., F.H.S.-W.) independently screened trials retrieved for eligibility by titles and abstracts and evaluated the potentially eligible trials for inclusion or exclusion using full-text reports. If trials were reported in multiple papers, we retained results of the largest cohort if the same outcomes were reported. In the case of disagreement, consensus was sought out and a third reviewer (L.M.) was consulted when necessary.

Study Eligibility

RCTs comparing the use of IPC (any type, any duration) in addition to pharmacological thromboprophylaxis (any drug, any dose) to pharmacological thromboprophylaxis alone (any drug, any dose) in hospitalized adults were considered eligible. Trials were included if at least 75% of the cohort sample was at least 18 years old. Eligibility was not restricted by language or date. Only peer-reviewed publications were considered.

Outcomes

Primary outcomes were VTE (which may include all distal and proximal lower-limb DVT, PE, or other thrombotic events reported by authors), proximal and distal lower-limb DVT, and PE according to the authors' definition. Secondary outcomes were all-cause

mortality and adverse events (i.e., treatment-related death, discontinuation of thromboprophylaxis, any other adverse events reported by authors).

Data Extraction

Independently in duplicate, two reviewers (C.D., F.H.S.-W.) abstracted data on study design and setting (randomization method, dates, country, number and type of hospitals, funding), participants (inclusion and exclusion criteria, number of participants randomized and included at the end of trials, mean age, % men, thromboprophylaxis indications, comorbidities), intervention and comparator (drug and dose of anticoagulants, IPC type and duration, elastic compression, other interventions), and outcomes (measure, follow-up and method). For each outcome, we extracted the number of subjects per group and the number of events. The abstraction form was pilot tested iteratively until acceptable agreement was achieved. In the case of missing data, up to three emails were sent to corresponding authors. In the case of disagreement, consensus was sought out and a third reviewer (L.M.) was consulted when necessary.

Risk of Bias (Quality) Assessment

Two reviewers (C.D., F.H.S.-W.) independently assessed risk of bias using the Cochrane Risk of Bias Tool for Randomized Trials, Version 2. The risk of bias on each item was rated as low, high, or unclear. In the case of disagreement, consensus was sought, and a third reviewer (L.M.) was consulted when necessary. Funnel plots were generated with Review Manager Version 5.4.1 (RevMan) to assess publication bias for primary outcomes. Since blinding of the intervention to the participants and healthcare providers was not possible, we did not consider performance bias when assessing overall risk of bias.

Data Synthesis

All statistical analyses were conducted with RevMan. Results were expressed as risk ratios (RRs) with 95% CIs weighted according to the Mantel-Haenszel method (27). Statistical heterogeneity was assessed using the I^2 statistic and considered important if greater than 50%. Meta-analyses were performed using a DerSimonian and Laird random-effects model.

Subgroup and Sensitivity Analyses

We performed prespecified subgroup analyses to evaluate the robustness of the results and explore potential sources of heterogeneity. We examined population (trauma, elective orthopedic surgery, elective nonorthopedic surgery, and medical patients), type of anticoagulant (unfractionated heparin, low-molecular-weight heparin [LMWH], and direct oral anticoagulants), IPC size (only on the foot, up to the calf or up to the thigh), duration of IPC use (< 18 hr/d, ≥ 18 hr/d) (16), and industry funding from IPC manufacturers (yes, no). We also restricted analyses to trials with a low risk of bias. We conducted sensitivity analyses by restricting the DVT outcome to proximal DVTs only.

Effect modification assessment was based on The Cochrane handbook for systematic reviews (23). We considered subgroup effects with a p value of less than 0.10 to be statistically significant. Heterogeneity within subgroups was considered important if I^2 greater than 50% (23).

Quality of Evidence

The quality of evidence for primary outcomes was assessed independently by two reviewers with content expertise (C.D., F.H.S.-W.) using the Grading of Recommendations Assessment, Development and Evaluation approach (28).

A copy of template data collection forms, data extracted from included studies and data used for all analyses in the review are available on request.

RESULTS

Search Results

Overall, we identified 1861 trials, of which 17 (8,796 participants) were retained for quantitative analysis (**Fig. 1**) (19–22, 29–41).

Characteristics of Included Trials

The trials spanned data collected from 1994 to 2019 with 48 to 2,551 participants (**eTable 1**, http://links.lww.com/CCX/B66). Trials were conducted in North America (20, 29–31, 33, 34, 37), Europe (22, 35, 36, 38, 39), and Asia (19–21, 32, 40, 41). Two trials were conducted in multiple countries (20, 34). Populations included patients with elective orthopedic surgery (n = 7) (30, 32, 35, 37, 38, 40, 41), nonorthopedic surgery (n = 5)

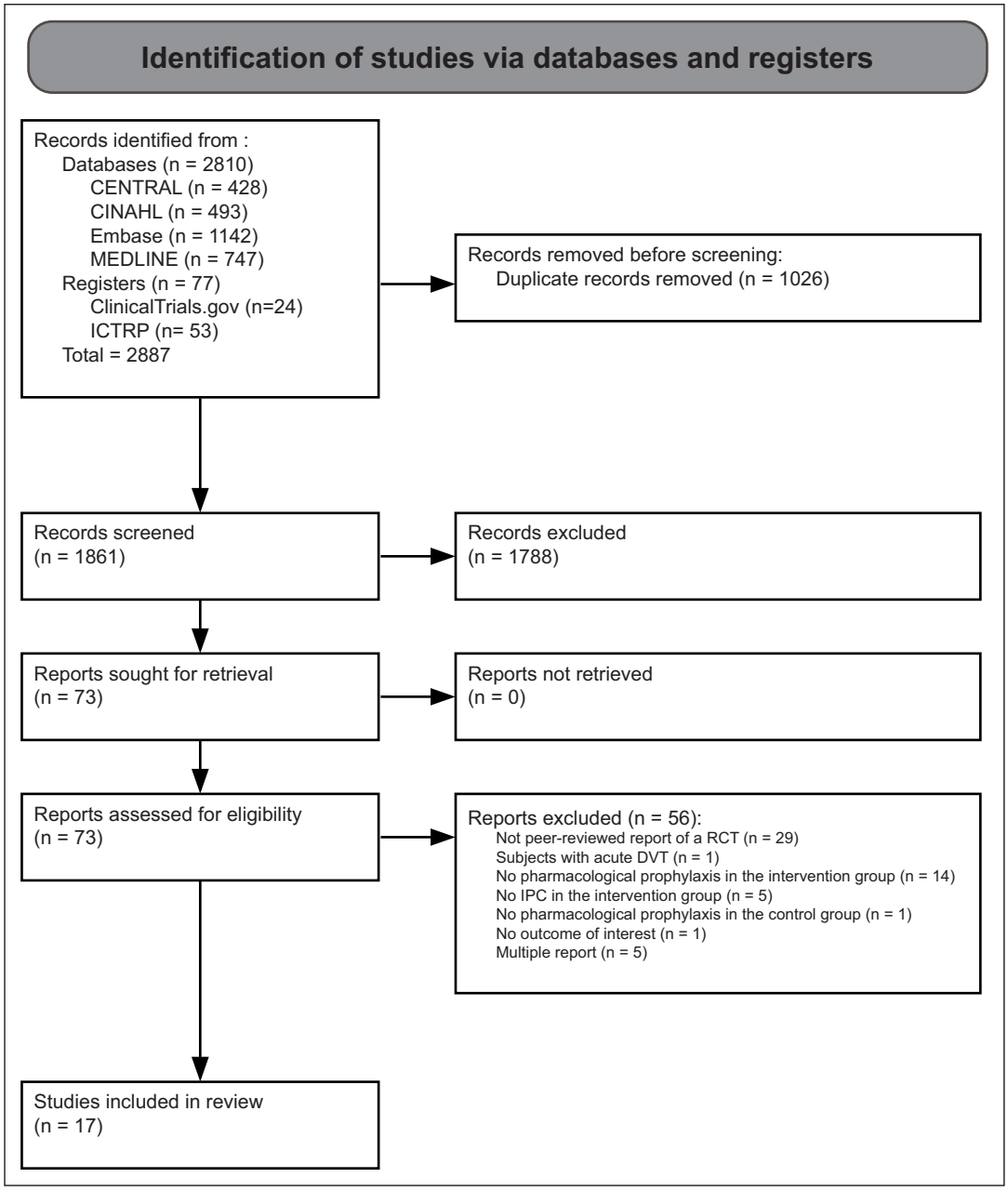

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. CENTRAL = Cochrane Central Register of Controlled Trials, CINAHL = Cumulative Index to Nursing and Allied Health Literature, DVT = deep venous thrombosis, ICTRP = International Clinical Trials Registry Platform, IPC = intermittent pneumatic compression, RCT = randomized controlled trial.

(19, 21, 29, 31, 33), medical conditions (n = 1) (39), trauma (n = 1) (34), or multiple diagnoses (n = 3) (20, 22, 36). The IPC was mostly applied up to the thigh (19, 21, 29, 31, 33, 39, 41) and pharmacological thromboprophylaxis was primarily LMWH (19, 21, 31–33, 35–38).

All trials reported the number of thromboembolic events (DVT or PE or both), 15 trials reported all-cause mortality (19–22, 30–38, 40, 41), and eight trials reported adverse events (19, 20, 22, 31, 34, 38, 40, 41). After exclusion of trials with no events, 15 trials were included in the meta-analysis for VTE, 14 for DVT, seven for PE, four for all-cause mortality, and six for adverse events (**Table 1**, **Figs. 2–4**; and **Appendix 2**, http://links.lww.com/CCX/B66).

Risk of Bias in Included Trials

The risk of performance bias was high for all trials as none employed a sham device in the control group (**eTable 2**, http://links.lww.com/CCX/B66).

The risk of detection bias was rated as unclear in 12 trials for VTE, seven trials for DVT, 10 trials for PE because, even if the outcome was measured objectively by a blinded evaluator, only symptomatic subjects were assessed. As the clinicians who assessed the symptoms were unblinded, we could not exclude a detection bias. The overall risk of bias was rated low for one trial for VTE (39), two trials for DVT (20, 39), and no trials for PE.

Effect of the Intervention

Venous Thromboembolism. The frequency of VTE in the intervention group was half that of the control group (RR = 0.53 [0.35–0.81]) and statistical

TABLE 1.
Summary of Findings and Quality of the Evidence

Outcomes	No. of Trials	Anticipated Absolute Effects[a] (95% CI)		Relative Effect			Quality of the Evidence
		Risk With Pharmacological Prophylaxis Alone	Risk With Both Pharmacological and Mechanical Prophylaxis	Risk Ratio (95% CI)	I^2, %	No. of Participants (Studies)	Grading of Recommendations Assessment, Development and Evaluation Rating
Venous thromboembolic events	15	86 per 1,000	46 per 1,000 (30–70)	0.53 (0.35–0.81)	78	8,684 (15)	Low[b]
Deep venous thrombosis	14	90 per 1,000	47 per 1,000 (30–73)	0.52 (0.33–0.81)	70	6,073 (14)	Low[b]
Pulmonary embolism	7	25 per 1,000	18 per 1,000 (8–42)	0.73 (0.32–1.68)	54	5,708 (7)	Low[b]
All causes mortality	4	20 per 1,000	19 per 1,000 (17–22)	0.96 (0.83–1.10)	0	2,928 (4)	Moderate
Adverse events	7	6 per 1,000	6 per 1,000 (5–8)	1.05 (0.82–1.35)	0	3,483 (7)	Very low[c]

[a]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]The quality of the evidence for venous thromboembolic events, deep venous thrombosis and pulmonary embolism was graded low because of the high risk of bias and the inconsistency.

[c]The quality of the evidence for adverse events was graded very low because of the risk of bias due to blinding, the indirectness (because the definition of adverse events and reporting of this outcome was not uniform across studies) and the imprecision (with only 6/17 studies contributing to the effect estimate, the number of events is small).

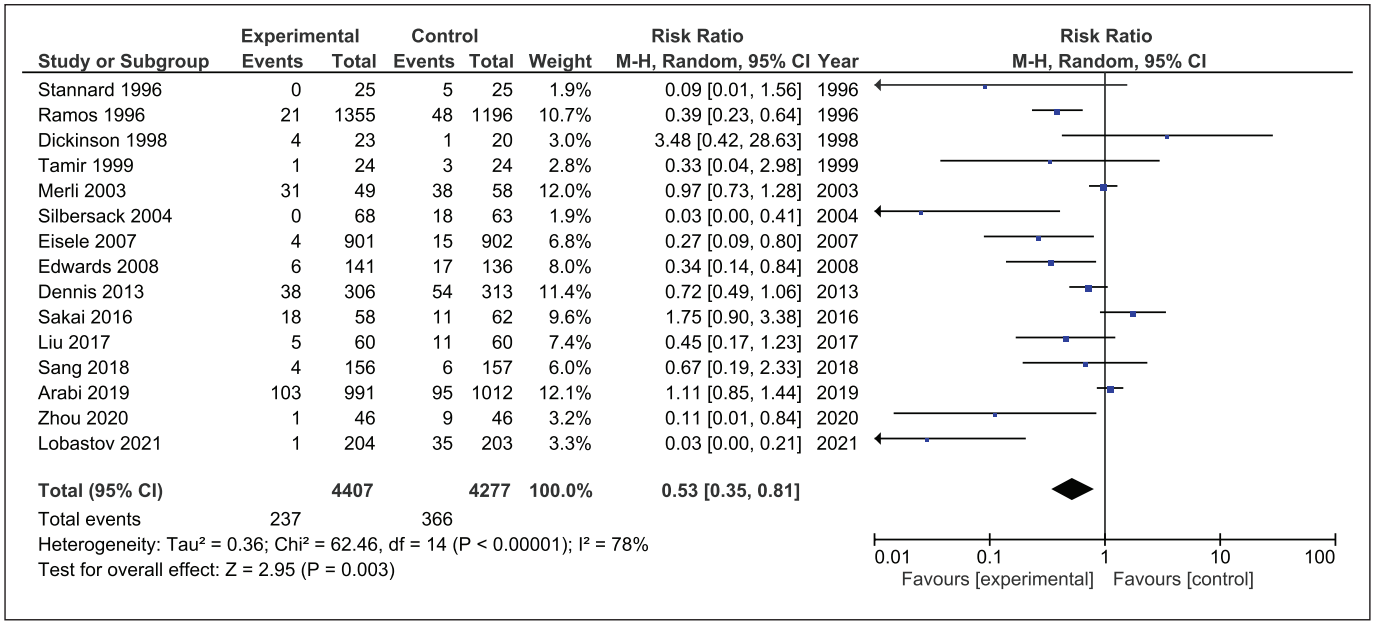

Figure 2. Forest plot for venous thromboembolic events. *df* = degrees of freedom, M-H = Mantel-Haenszel.

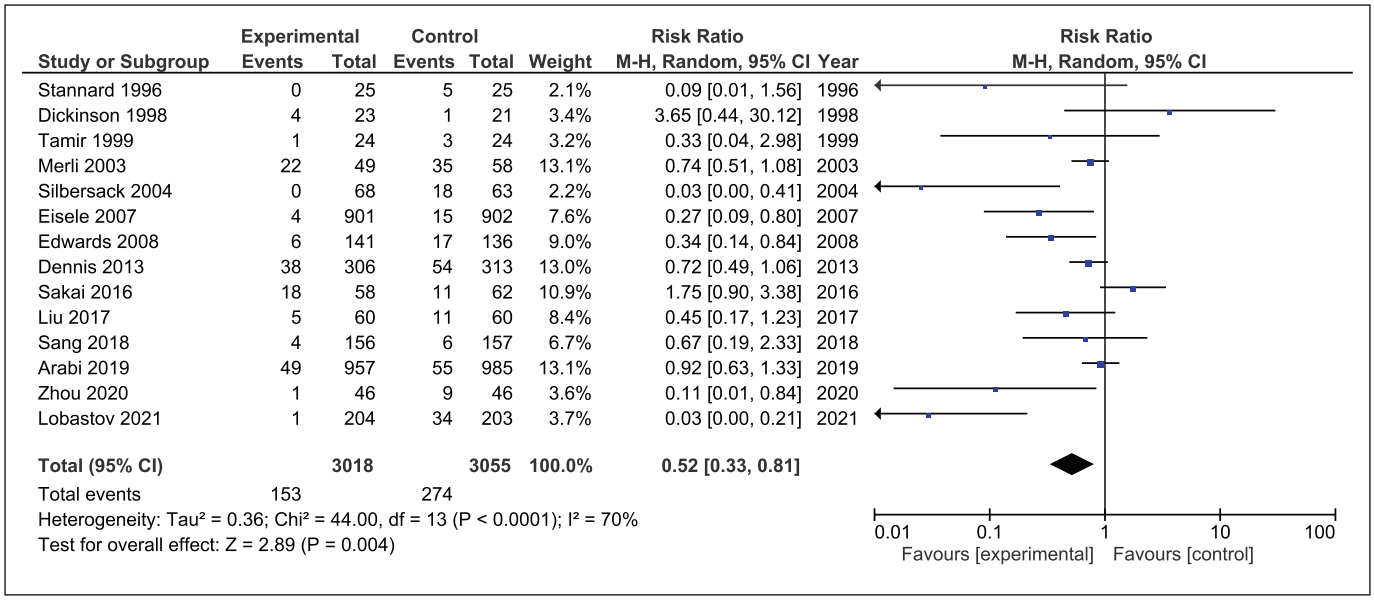

Figure 3. Forest plot for deep venous thromboses. *df* = degrees of freedom, M-H = Mantel-Haenszel.

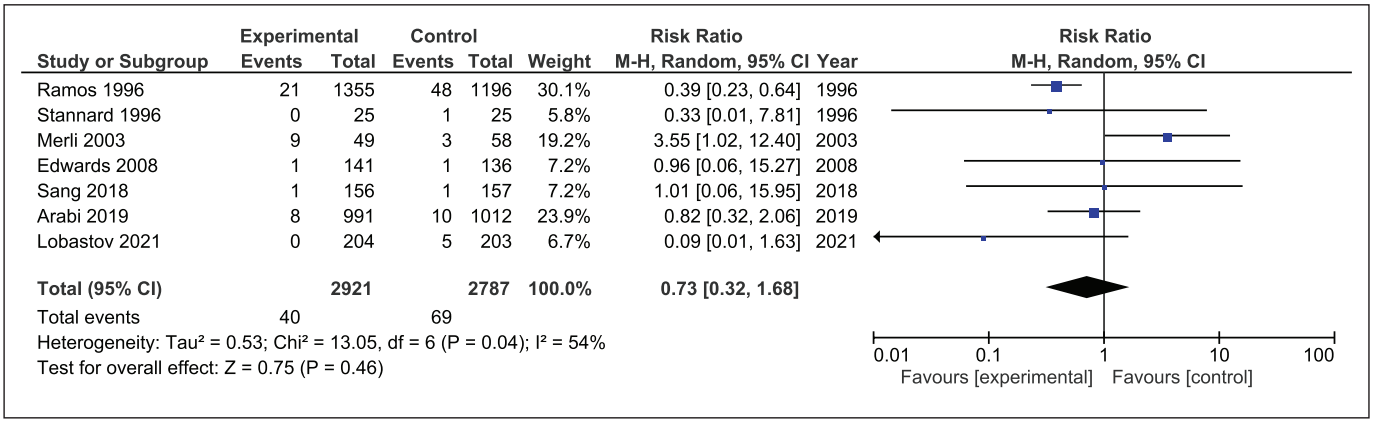

Figure 4. Forest plot for pulmonary embolism. *df* = degrees of freedom, M-H = Mantel-Haenszel.

TABLE 2.
Subgroup Analyses

Subgroup analysis	Venous Thromboembolic Events	Deep Venous Thrombosis	Pulmonary Embolism
Main analyses	RR = 0.53 (0.35–0.81), 15 studies, 8,684 participants, I^2 = 78%	RR = 0.52 (0.33–0.81), 14 studies, 6,073 participants, I^2 = 70%	RR = 0.73 (0.32–1.68), seven studies, 5,708 participants, I^2 = 54%
Type of population			
Trauma	RR = 0.33 (0.07–1.69), four studies, 677 participants, I^2 = 57%	RR = 0.65 (0.37–1.14), four studies, 677 participants, I^2 = 5%	RR = 3.55 (1.02–12.40), one study, 107 participants, I^2 = not applicable
Elective orthopedic surgery	RR = 0.38 (0.15–0.96), seven studies, 2,165 participants, I^2 = 73%	RR = 0.35 (0.13–0.91), seven studies, 1,535 participants, I^2 = 75%	RR = 0.61 (0.08–4.86), two studies, 327 patients, I^2 = 0%
Elective nonorthopedic surgery	RR = 0.35 (0.11–1.06), five studies, 3,376 participants, I^2 = 69%	RR = 0.30 (0.06–1.48), five studies, 940 participants, I^2 = 70%	RR = 0.40 (0.24–0.66), two studies, 2,864 patients, I^2 = 0%
Medical	RR = 0.79 (0.59–1.07), two studies, 2,133 participants, I^2 = 0%	RR = 0.79 (0.59–1.07), two studies, 2,133 participants, I^2 = 0%	Not estimable
Type of drug			
Unfractionated heparin	RR = 0.52 (0.22–1.26), three studies, 3,715 participants, I^2 = 76%	RR = 0.45 (0.05–4.01), two studies, 1,164 participants, I^2 = 62%	RR = 0.38 (0.23–0.63), two studies, 2,601 participants, I^2 = 0%
Low-molecular-weight heparin	RR = 0.31 (0.13–0.71), nine studies, 3,943 participants, I^2 = 64%	RR = 0.31 (0.13–0.71), nine studies, 3,943 participants, I^2 = 63%	RR = 0.31 (0.03–3.60), two studies, 720 participants, I^2 = 0%
Direct oral anticoagulant	RR = 0.90 (0.26–3.09), two studies, 240 participants, I^2 = 76%	RR = 0.94 (0.25–3.53), two studies, 240 participants, I^2 = 80%	Not estimable
Industry funding			
Industry funded/ industry supplied material	RR = 0.20 (0.06–0.65), five studies, 2,618 participants, I^2 = 83%	RR = 0.21 (0.07–0.65), five studies, 3,237 participants, I^2 = 82%	RR = 0.31 (0.03–3.38), two studies, 684 participants, I^2 = 31%
None	RR = 0.96 (0.67–1.35), six studies, 2,755 participants, I^2 = 53%	RR = 0.81 (0.54–1.22), six studies, 2,694 participants, I^2 = 54%	RR = 1.31 (0.55–3.13), three studies, 2,617 participants, I^2 = 21%
IPC size			
Foot	RR = 0.54 (0.08–3.50), three studies, 218 participants, I^2 = 68%	RR = 0.54 (0.08–3.50), three studies, 218 participants, I^2 = 68%	RR = 0.33 (0.01–7.81), one study, 50 participants, I^2 = not applicable
Calf	RR = 0.31 (0.10–1.03), four studies, 2,260 participants, I^2 = 82%	RR = 0.31 (0.10–1.03), four studies, 2,260 participants, I^2 = 82%	RR = 0.96 (0.06–15.27), one study, 277 participants, I^2 = not applicable
Thigh	RR = 0.46 (0.27–0.77), eight studies, 4,202 participants, I^2 = 65%	RR = 0.46 (0.24–0.90), seven studies, 1,651 participants, I^2 = 67%	RR = 0.38 (0.23–0.62), three studies, 3,271 participants, I^2 = 0%
IPC duration			
< 18 hr/d	RR = 0.12 (0.04–0.36), four studies, 2,352 participants, I^2 = 35%	RR = 0.10 (0.03–0.37), four studies, 2,293 participants, I^2 = 46%	RR = 0.16 (0.02–1.38), two studies, 457 participants, I^2 = 0%
≥ 18 hr/d	RR = 0.74 (0.47–1.17), nine studies, 6,046 participants, I^2 = 77%	RR = 0.71 (0.42–1.21), eight studies, 3,461 participants, I^2 = 66%	RR = 0.64 (0.21–1.98), five studies, 5,069 participants, I^2 = 76%
Overall risk of bias = low	RR = 0.72 (0.49–1.06), one study, 619 participants, I^2 = not applicable	RR = 0.81 (0.61–1.09), two studies, 2,561 participants, I^2 = 0%	Not estimable

IPC = intermittent pneumatic compression, RR = risk ratio.

heterogeneity was important (I^2 = 78%). The quality of the evidence was graded as low, downgraded by risk of bias and inconsistency (**Tables 1** and **2**, Fig. 2; and **eTable 3**, http://links.lww.com/CCX/B66).

A statistically significant subgroup effect was only found for industry funding (IPC appears to be more effective in industry-funded trials; p = 0.01) and IPC duration (IPC appears to be more effective if worn less than 18 hr/d; p = 0.003). However, there was important unexplained heterogeneity within subgroups, except in the subgroup of patients who used IPC less than 18 hr/d (I^2 = 35%). Therefore, the validity of the association estimate for each subgroup is uncertain, as individual trial results are inconsistent. With only one trial at low overall risk of bias, we could not conduct meaningful analysis for this factor (Table 2; and Appendix 2, http://links.lww.com/CCX/B66).

The funnel plot (**Appendix 3**, http://links.lww.com/CCX/B66) suggests that most large trials have effects measures close to the null. The asymmetrical appearance of the funnel plot, with a gap at the bottom right corner of the graph, is compatible with the possibility of publication bias (42).

Deep Venous Thrombosis. The frequency of DVT in the intervention group was half that of the control group (RR = 0.52 [0.33–0.81]) and statistical heterogeneity was important (I^2 = 70%). The quality of the evidence was graded as low, downgraded by risk of bias and inconsistency (Tables 1 and 2, Fig. 3; and eTable 3, http://links.lww.com/CCX/B66).

As for VTE, a significant subgroup effect was only found for industry funding (p = 0.03) and IPC duration (p < 0.00001) (Table 2; and Appendix 2, http://links.lww.com/CCX/B66). The funnel plot for DVT (Appendix 3, http://links.lww.com/CCX/B66) is similar to the one for VTE.

When restricted to the two trials at low risk of bias (20, 39), analysis showed a smaller and nonstatistically significant effect (RR = 0.81 [0.61–0.19]). The sensitivity analysis restricted to proximal DVTs showed a smaller and nonstatistically significant effect (RR = 0.70 [0.47–1.03]) and less statistical heterogeneity (I^2 = 24%) than the main analysis (Table 2; and Appendix 2, http://links.lww.com/CCX/B66).

Pulmonary Embolism. The frequency of PE was not different between groups (RR = 0.73 [0.32–1.68]). Statistical heterogeneity was important (I^2 = 54%). The quality of the evidence was graded as low, downgraded by risk of bias and inconsistency (Tables 1 and 2 and Fig. 4).

None of the subgroup analysis for PE suggested a subgroup effect. The only statistically significant interaction was found in the subgroup analysis by type of population (p = 0.006). However, trials were unevenly distributed among the subgroups, either in number of trials or in number of participants. Furthermore, the subgroup effect was no longer statistically significant if we excluded the trauma subgroup, comprising a single trial. The reduction of heterogeneity in the subgroups was mainly from the pooling of effect measure estimates with wide CIs (Table 2; and Appendix 2, http://links.lww.com/CCX/B66).

The funnel plot for PE (Appendix 3, http://links.lww.com/CCX/B66) has an unusual shape that precludes assessment about a potential publication bias, especially since it includes fewer than 10 trials, leading to low power for tests of asymmetry (42).

Secondary Outcomes. No difference was observed for all-cause mortality or adverse events between groups. Reported adverse events were limited to bleeding and skin injury. Heterogeneity was null for both analyses. The quality of the evidence was graded as moderate for all-cause mortality and very low for adverse events (Table 1; and Appendix 2, http://links.lww.com/CCX/B66).

DISCUSSION

In this systematic review, adjunctive IPC was associated with an overall decrease of 50% in the risk of VTE. This effect was also observed for DVT but not for PE. The source of funding and duration of IPC influenced these findings. The quality of evidence for VTE, DVT and PE was graded low due to high risk of bias of included studies and high between-study heterogeneity. No differences in mortality or in adverse events were observed.

Our results differ from previous systematic reviews. We confirmed the reduction of the risk of DVT associated with the addition of IPC to pharmacologic prophylaxis shown in one systematic review (18) but not in another (17). We did not confirm the reduced risk of PE observed in these two reviews. The inclusion in our review of recently published RCTs (19–22, 41), of studies using anticoagulants other than heparin and

the exclusion of observational studies could explain these discrepancies.

The influence of industry funding we observed is consistent with the literature: industry-funded trials often lead to more favorable efficacy results than those funded by other sources (43). The asymmetry of the funnel plot, suggesting publication bias, could be partly explained by unpublished industry-funded studies, as manufacturers only need to demonstrate lack of harm and "substantial equivalence" for the approval noninvasive medical devices (24, 25). However, even if industry funding can lead to an overestimation of the effect, it is a risk factor for bias rather than a bias in itself (44). Confounding factors, such as selection or detection methods, could be involved in the subgroup differences. We conducted subgroup analyses according to industry funding declared by the authors, which may be a poor proxy (45) because methods for reporting, assessing, and handling the influence of industry involvement still need to be developed (43). To better evaluate the benefits of the addition of IPC, it would be important to better evaluate the potential impact of funding sources, or even better, to conduct independent trials.

The effect of the duration of the IPC application observed in our meta-analysis is counterintuitive and inconsistent with previous trials in which increased duration of IPC was associated with a lower frequency of DVT (46, 47). This contradiction could be explained by lower adherence in the group with intended use greater than 18 hours. Differences in compliance could explain the large heterogeneity in the subgroup with longer intended use because each study verifies compliance in different ways, both quantitatively (number of checks) and qualitatively (reliability of checks).

There were insufficient trials to conduct meaningful subgroup analyses for the other factors but they could explain some of the heterogeneity in effects. The type of population is already considered in thromboprophylaxis regimen recommendations, which supports the clinical relevance of this subgroup analysis. The effectiveness of mechanical prophylaxis seems to be proportional to the volume of tissue compressed (48) but IPC devices applied up to the thigh may be more difficult to use, interfering with postoperative dressings (30).

The differences in DVT locations considered across trials may explain heterogeneity; IPC may be less effective in preventing proximal DVTs. The location of DVT is a major issue in its therapeutic management, since while a proximal DVT generally mandates full anticoagulation, whereas a range of practices are used for a distal DVT, including watchful waiting.

The remaining unexplained heterogeneity could be related to the sample size or confounding factors such as sex, age, body mass index, or comorbidities that vary between trials. Lack of information prevented adequate subgroup analyses based on these characteristics. Other IPC characteristics, such as the type of compression (sequential, with multiple inflatable chambers or single), the inflation rate (low or fast), the frequency (fixed or adjusting to the venous refill rate) could also have an impact on their efficacy (9, 39, 48). We noted that some characteristics are shared by the same trials; for example, four out of five industry-funded trials (35–37, 39) were conducted in elective orthopedic surgery, used LMWH, represented almost all trials with compression applied to the calf and most of the industry-funded trials included screening for both proximal and distal DVT in the days following treatment. This could cause an additional confounding bias and makes it difficult to identify unique factors that explain heterogeneity or groups in which IPC may be of benefit. Finally, variability in the effect of the intervention could be attributed to treatment differences other than the addition of compression between the intervention and control groups (19, 39).

Included trials all had a high risk of performance bias due to lack of blinding for the intervention. However, this unlikely to be addressed in future trials because the use of a sham device would not be considered ethical due to the increased risk of DVT, cost, and comfort.

This review involved a comprehensive search of current literature, duplicate trial selection, assessment and abstraction, and adherence to Cochrane methodology. We followed a published protocol and report results according to PRISMA guidelines. However, there are several limitations.

First, VTE events were rare, generating wide confidence limits for some results (23). Second, the unusual shape of funnel plots precluded the exclusion of publication bias, which could lead to an overestimation of the effect. Finally, the results of some registered trials have not yet been published, such as those from the Efficacy of the Association Mechanical Prophylaxis + Anticoagulant Prophylaxis on Venous Thromboembolism Incidence in Intensive Care Unit (ICU) study (49), whereas others have only been presented in conference abstracts and could not be included in this review (50–52).

Along with limitations related to the original trials, these study limitations preclude strong recommendations on the addition of IPC to pharmacological thromboprophylaxis to prevent VTE.

CONCLUSIONS

Implications for Practice

Our results suggest there is low-quality evidence underpinning the addition of IPC to pharmacological thromboprophylaxis for prevention of VTE and DVT. The apparent benefit is more evident in industry-funded trials. We found no evidence of benefits for PE, all-cause mortality or adverse events.

The results of this review may call for new studies to inform an update of guideline recommendations, which support the additional use of IPC in patients undergoing major surgery.

Implications for Research

Results indicate that further large high-quality randomized trials are warranted to support the use of adjunctive IPC and to identify patient subgroups for whom it could be beneficial. Cost-effectiveness data are needed to justify healthcare resources used for IPC treatment. Future research should also strive to evaluate patient-centered adverse events related to IPC use, such as delirium or sleep disorders, which were not evaluated in any of the included trials.

1 *Department of Social and Preventative Medicine, Université Laval, Quebec City, QC, Canada.*

2 *Population Health and Optimal Health Practices Research Unit, Trauma-Emergency-Critical Care Medicine, Centre de Recherche du CHU de Québec-Université Laval (Hôpital de l'Enfant-Jésus), Quebec City, QC, Canada.*

3 *Faculty of Pharmacy, Université Laval, Quebec City, QC, Canada.*

4 *Centre of Excellence on Aging of Quebec, VITAM Research Centre on Sustainable Health, Quebec City, QC, Canada.*

5 *Faculty of Nursing, Université Laval, Quebec City, QC, Canada.*

6 *Department of Anesthesiology and Critical Care Medicine, Faculty of Medicine, Université Laval, Quebec City, QC, Canada.*

7 *Department of Medicine, Division of Critical Care, McMaster University, Hamilton, ON, Canada.*

8 *Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada.*

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For information regarding this article, E-mail: cecile.duval.1@ulaval.ca

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