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Meta-Analysis of the Role of Intermittent Pneumatic Compression of the Lower Limbs to Prevent Venous Thromboembolism in Critically Ill Patients

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Abstract

Critically ill patients (patients treated in a medical or surgical intensive care unit) are at high risk of venous thromboembolism (VTE) development (deep vein thrombosis [DVT] and/or pulmonary embolism). Multiple thromboprophylaxis strategies have been used for the prevention of VTE in this population with various outcomes. Therefore, we aimed to evaluate the efficacy of intermittent pneumatic compression (IPC) prophylaxis in the lower limb compared with no treatment, anticoagulant use, or their combinations in reducing risk. A comprehensive electronic database search was conducted for all randomized clinical trials (RCTs) comparing the clinical outcomes of IPC versus anticoagulants or no treatment or their combinations for the prevention of VTE for critically ill patients. The primary outcome was VTE. The secondary outcome was DVT. We performed a Bayesian network meta-analysis to calculate odds ratios (ORs) and 95% credible intervals (CrIs). We included 5 RCTs with 3133 total patients, represented by a mean age of 49.61 ± 18 years, while 60.28% were male. There was a significant reduction of the primary outcome (incidence of VTE events) when no treatment was compared with IPC (OR = 0.36; 95% CrI = 0.18-0.71), anticoagulation alone (OR = 0.30; 95% CrI = 0.12-0.68), or anticoagulation with IPC (OR = 0.34; 95% CrI = 0.13-0.81). In addition, there was a significant reduction in DVT when no treatment was compared with IPC (OR = 0.45; 95% CrI = 0.21-0.9), anticoagulation alone (OR = 0.16; 95% CrI = 0.03-0.66), or anticoagulation with IPC (OR = 0.18; 95% CrI = 0.03-0.84). However, there were no significant differences between other comparisons (IPC vs anticoagulation alone, anticoagulation alone vs anticoagulation with IPC, or anticoagulation with IPC vs IPC alone) regarding VTE or DVT incidence. Among critically ill patients, IPC alone, anticoagulation alone, and IPC with anticoagulation were associated with a significant reduction of VTE and DVT incidence compared with no treatment. However, there was no significant difference between these modalities when compared together. Therefore, further larger studies comparing those different thromboprophylaxis modalities and their combinations are needed to provide more robust results for future clinical recommendations.

Keywords

intermittent pneumatic compression, IPC, thromboprophylaxis, VTE, DVT, critical care

Introduction

Critically ill patients (patients treated in a medical or surgical intensive care unit [ICU]) are at high risk of venous thromboembolism (VTE) development (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]), with an estimation of 27% on average for VTE occurrence in this patient population.[1,2]

The recognition of this problem started a couple of decades ago, when this concern was studied in many studies, and solutions started to surface with improved and targeted thromboprophylaxis measures[3-5] (This problem was

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recognized decades before spurring studies and trials. This finding and gap in knowledge led to the emergence of improved and targeted thromboprophylaxis measures.)

Multiple well-studied thromboprophylaxis modalities exist. They are divided into pharmacologic thromboprophylaxis, with unfractionated heparin or low-molecular-weight heparin (LMWH), or mechanical thromboprophylaxis comprising intermittent pneumatic compression (IPC), lower extremities pumps, or compression stockings.[6]

Furthermore, based on a large meta-analysis done by Ho and Tan in 2013, it was found that for hospitalized patients, in general, IPC was effective in reducing VTE, and combining pharmacological thromboprophylaxis with IPC was more effective than using IPC alone, this conclusion does not apply to critically ill patients, especially with conflicting data in the literature.[7,8]

With the emergence of large randomized controlled trials (RCTs),[9] we aim to evaluate the efficacy of IPC compared with other thromboprophylaxis measures and their combinations in critically ill hospitalized patients.

Methods

Data Sources

The study used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) Statement 2015.[10] TH, SD, and YZ performed a comprehensive search of the literature using PubMed, EMBASE, and the Cochrane Collaboration Central Register of Controlled Trials from inception to June 2019. Any disagreements were resolved by consensus. The following search terms were used: intermittent pneumatic compression, critical care, critically ill patients, deep vein thrombosis, venous thromboembolism, thromboprophylaxis, and anticoagulation.

Selection Criteria and Data Extraction

The study inclusion criteria were the following: (1) all studies are RCTs; (2) all studies' primary objectives included thromboprophylaxis; (3) IPC is used for thromboprophylaxis in any study arm as single or add-on therapy; (4) IPC alone or in combination with other thromboprophylaxis modalities is compared with placebo or no treatment or anticoagulation or other combinations of the thromboprophylaxis modalities; (5) all studies include exclusively critically ill patients treated in either a surgical or a medical ICU; and (6) DVT, VTE, or death outcomes are reported. The study exclusion criteria were the following: (1) precious meta-analyses, commentaries, retrospective studies, case-control studies, case reports/series, prospective studies that are not randomized; (2) any subgroup analysis of an RCT or post hoc analysis; (3) when thromboprophylaxis was used in any study, however, none the outcomes of interest were reported; and (4) thromboprophylaxis used for none of the critically ill patients. From each eligible study, 2 authors, TH and HD, extracted the data, and a third author, MSM, resolved any discrepancies.

Outcomes

Our primary outcome was VTE. Secondary outcomes were all-cause mortality, DVT, PE, and bleeding.

Quality Assessment

The risk of bias in the included studies was assessed using the Cochrane Collaboration. Each of the included studies was assessed for risk of bias for random sequence generation, allocation concealment, the blindness of participants and health care personnel, the blindness of outcome assessment, incomplete outcome data, selective reporting, and other biases. Two reviewers (YZ and TH) performed quality assessments independently, and any discrepancy was resolved with a third reviewer (VS).

Statistical Analysis

We performed a network meta-analysis using Markov Chain Monte Carlo simulation with little informative prior distributions to derive the posterior distribution. Convergence was assessed using the Brooks-Gelman-Rubin method, while the random-effects model for consistency was reported as odds ratios (ORs) and Bayesian 95% credible intervals (CrIs). The relative treatment effects were reported as a probability of the best, second best, third best, and so on. Inconsistencies were assessed by comparing the deviance residuals and deviance information criteria statistics to identify any present loops in the treatment network. Data were analyzed using NetMetaXL v1.6.1 and WinBUGS v1.4.3. Pairwise meta-analysis was not completed due to limited direct comparisons between the different treatment arms in the studies.

Results

Study Selection and Trial Characteristics

Figure 1 illustrates the study selection process. We included 5 RCTs with 3133 total patients, mean age of 49.61 years, and a male percentage of 60.28%. Table 1 and Table 2 illustrate the characteristics of the included trials and patient demographics, respectively.[9,11-14]

In the 5 included studies, 2 studies assessed the role of IPC in surgical ICUs, 2 studies assessed the role of IPC in medical ICUs, and 1 assessed IPC's role in both surgical and medical ICUs. Two RCTs compared IPC alone with

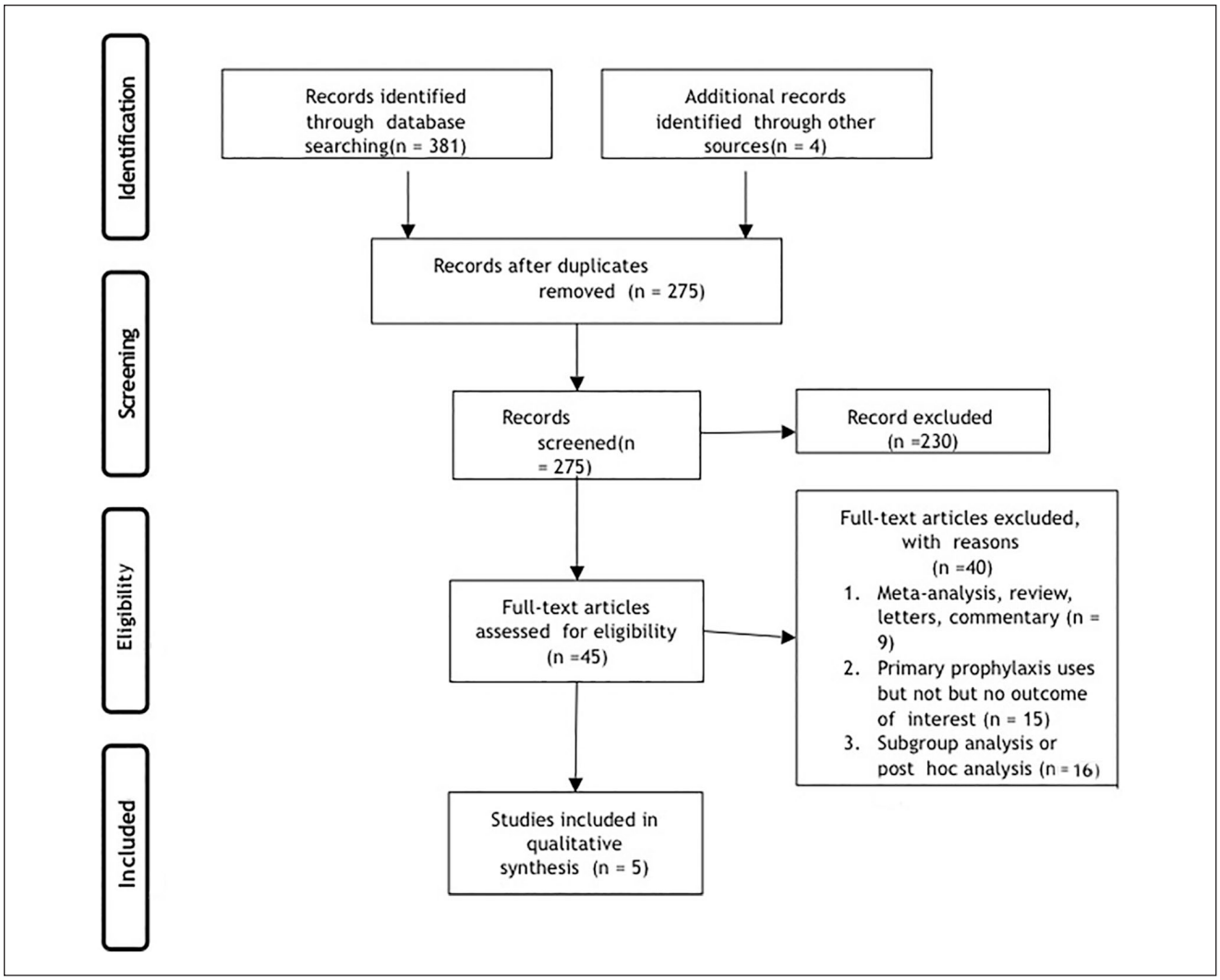

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

anticoagulation, another 2 studies compared IPC alone with no treatment, and, finally, 1 study compared anticoagulation alone to IPC plus anticoagulation. The anticoagulation method used the most was LMWH. Included studies have performance bias as blinding to study participants and personnel was not possible secondary to the nature of interventions. A quality assessment has been summarized in Figure 2.

Primary Outcome

There was a significant reduction of the primary outcome (incidence of VTE events) when no treatment was compared with IPC (OR = 0.36; 95% CrI = 0.18-0.71), anticoagulation alone (OR = 0.30; 95% CrI = 0.12-0.68), or anticoagulation with IPC (OR = 0.34; 95% CrI = 0.13-0.81). However, there were no significant differences between other comparisons (IPC vs anticoagulation alone, anticoagulation alone vs anticoagulation with IPC, or anticoagulation with IPC vs IPC alone) regarding VTE incidence (Figure 3).

Secondary Outcomes

There was a significant reduction in DVT when no treatment was compared with IPC (OR = 0.45; 95% CrI = 0.21-0.9), anticoagulation alone (OR = 0.16; 95% CrI = 0.03-0.66), or anticoagulation with IPC (OR = 0.18; 95% CrI = 0.03-0.84). However, there were no significant differences between other comparisons (IPC vs anticoagulation alone, anticoagulation alone vs anticoagulation with IPC, or anticoagulation with IPC vs IPC alone) regarding DVT incidence (Figure 4).

There were no significant differences between all comparisons regarding mortality reduction (Figure 5).

Table 1. Details of the Randomized Clinical Trials.

Studies	Country/ sites	Total number of patients/subgroups	Study design	Inclusion criteria	Exclusion criteria	Types of interventions	Duration of intervention	Follow-up duration	Primary outcomes	Secondary outcomes	Type of ICU
Ginzburg et al[11]	USA	IPC: 224/LMWH: 218	A prospective randomized trial	Adult; severe injury; ISS >9; 1 arm or leg available for IPC, not needed systemic anticoagulation and had no contraindication to LMWH	<18 years of age; ISS >9; need for systemic anticoagulation; unlikely to survive or remain in hospital >7 days; renal failure (Cr >3.4); pregnancy; BMI >25 kg/m^2, pts unable to undergo bilateral Doppler ultrasonography, contraindication to anticoagulation, such as intracranial bleeding or uncontrolled hemorrhage from other sites for >24 hours after admission, coagulopathy (prothrombin time >3 seconds longer than control or platelet count less than 50000/mm^3)	LMWH: enoxaparin 30 mg SC BID every 12 hours or use an IPC device	From <24 hours after trauma until independent walking or discharge	30 days (patients were followed until discharge from hospital, 30 days from the time of admission or death, which ever occurred first)	Development of DVT and/ or clinically significant PE	Major bleeding and minor bleeding	Trauma and surgical ICU
Kurtoglu et al[12]	Turkey	IPC group: 60/LMWH group: 60	A prospective randomized controlled trial	Patients with severe head/spinal trauma in ICU	Age <14 year; hepatic or renal failure; spinal cord injury; hx of DVT; high bleeding risk (platelets <100 000/μL or INR >1.5); regular use of anticoagulation. Pts with continuing hemorrhage on control scans within 24 hours of admission or who required craniotomy	LMWH: enoxaparin 40 mg SC qd or IPC	From <24 hours after admission for 7 to 10 days	Until 1 week post discharge	Incidence of DVT/PE and mortality	N/A	Trauma ICU

(continued)

Table 1. (continued)

Studies	Country/ sites	Total number of patients/subgroups	Study design	Inclusion criteria	Exclusion criteria	Types of interventions	Duration of intervention	Follow-up duration	Primary outcomes	Secondary outcomes	Type of ICU
Zhang et al[13]	China	IPC group: 79/control: 83	A prospective randomized controlled trial	Patients admitted to ICU	Regular use of anticoagulant	IPC or no measures were taken to prevent VTE in the control group	28 days after ICU admission	28 days	Development of DVT, PE, and noncardiac sudden death	Duration of MV, length of stay in ICU, and ICU mortality rate	Medical ICU
Vignon et al[14]	France	IPC + GCS group: 204/ GCS group: 202	A multicenter open-label, randomized, outcome-blinded trial	Age >18years; high risk of bleeding on ICU admission (symptomatic bleeding, organic lesion likely to bleed; PLT <50 000, aPTT ratio >2, PT <40)	Hx of DVT; ICU stay >36 hourd (admission >36 hours) or likely to be <72 hours; life-support limitation; mechanical heart valve; C/I to mechanical prophylaxis, refusal, logistic reasons	IPC + GCS and no treatment + GCS	6 days after ICU admission	Follow-up on days 6, 30, and 90	Occurrence of a VTE between days 1 and 6	Occurrence of a symptomatic VTE between day 6 and day 90, and death from any cause up to day 30 or day 90	Medical ICU
Arabi et al[9]	20 sites in Saudi Arabia, Canada, Australia, and India	IPC and thromboprophylaxis: 991/ thromboprophylaxis: 1012	A multicenter randomized controlled trial	Adults; weight >45 kg; expected ICU stay >72 hours; no C/I to heparin	IPC >24 hours in current admission; in ICU >48 hours; tx with other thromboprophylaxis; therapeutic dose of heparin, inability to apply IPC; pregnancy; life expectancy ≤7 days or palliative care; limitation of life support, allergy to the sleeve material; IVC filter	IPC + LMWH and LMWH-only group	7 days	90 days	Development of new proximal DVT in lower extremities	Development of any DVT and PE	Medical surgical and trauma ICU

Abbreviations: ICU, intensive care unit; IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin; GCS, graduated compression stockings; ISS, injury severity score; Cr, creatinine; BMI, body mass index; pts, patients; PLT, platelets; aPTT, activated partial thromboplastin time; PT, prothrombin time; C/I, contraindication; DVT, deep vein thrombosis; INR, international normalized ratio; IVC, inferior vena cava; tx, treatment; PE, pulmonary embolism; VTE, venous thromboembolism; qd, once daily; SC, subcutaneous; BID, twice daily; N/A, not applicable; MV, mechanical ventilation.

Table 2. Patients Demographics.

Studies	Age in years	Male sex	BMI (kg/m^2)	Duration of hospitalization in days	Rate of intubation	Time spent in ICU in days	Type of ICU admission (medical, trauma, or surgical)
Ginzburg et al[11]	IPC group: 41 LMWH group: 42	IPC group: 167 Pts (75%) LMWH group: 160 pts (73%)	N/A	IPC group: 20.9 ± 33.4 LMWH group: 15.5 ± 15	N/A	• IPC group: 6.3 (10.7) • LMWH group: 5.0 (7.9)	Trauma and surgical
Kurtoglu et al[12]	IPC group and LMWH group median age: 37.1 years (18-76 years)	47 (39%)	IPC: 16.4 ± 7.5 LMWH: 17.2 ± 8.9	IPC: mean 10.3 ± SD 3.6 days (4-39) LMWH: mean 10.7 ± SD 4.4 days (3-75)	N/A	• IPC: mean 10.3 ± SD 3.6 days (4-39) • LMWH: mean 10.7 ± SD 4.4 days (3-75)	Trauma
Zhang et al[13]	N/A	N/A	N/A	IPC: 9 ± 7 Control: 10 ± 7	N/A	• IPC group: 9 ± 7 • No treatment group: 10 ± 7	Medical
Vignon et al[14]	IPC + GCS group: 56.3 ± 16.5 GCS group: 54.6 ± 17.5	IPC + GCS group: 132 Pts (64.7%) GCS group: 137 pts (67.8%)	IPC + GCS group: 25.6 ± 4.9 GCS group: 25.4 ± 5.5	N/A	IPC + GCS group: 169 (82.8%) GCS group: 167 (82.7%)	N/A	Medical
Arabi et al[9]	IPC + thromboprophylaxis group: 57.6 ± 20.0 Thromboprophylaxis group: 58.7 ± 20.5	IPC + thromboprophylaxis group: 579 pts (58.4%) Thromboprophylaxis group: 569 pts (56.2%)	IPC + thromboprophylaxis group: 29.0 ± 8.5 Thromboprophylaxis group: 28.6 ± 8.0	N/A	IPC + thromboprophylaxis group: 654 (66.0%) Thromboprophylaxis group: 667 (65.9%)	• IPC + thromboprophylaxis group: 8 (4, 15) • Thromboprophylaxis group: 8 (5, 16)	IPC + thromboprophylaxis group: • Medical: (787) 79.4% • Surgical: (135) 13.6% • Trauma: (69) 7% Thromboprophylaxis group: • Medical: (779) 77% • Surgical: (147) 14.5% • Trauma: (86) 8.5%

Abbreviations: BMI, body mass index; ICU, intensive care unit; IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin; pts, patients; N/A, not applicable; SD, standard deviation GCS, graduated compression stockings.

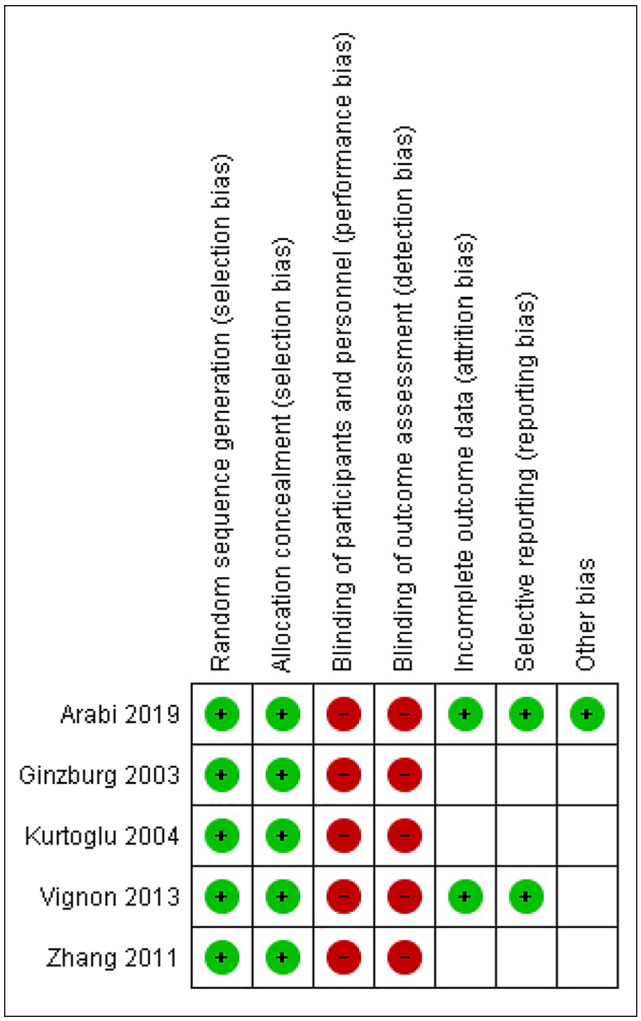

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. Empty blanks indicate an unclear risk of bias.

Due to low reported numbers of PE and bleeding incidences across all RCTs, their analyses were inconclusive.

Table 3 shows all the outcomes data as collected from all 5 RCTs.

Discussion

In this meta-analysis of 5 RCTs, IPCs were equally as effective as anticoagulation for thromboprophylaxis in critically ill patients, both as measures alone and their combination were effective in reducing VTE compared with no treatment. A head-to-head comparison between IPC and anticoagulation did not show a difference based on the data provided in this study.

In 2006, Limpus et al conducted a meta-analysis; however, limited data and evidence showed no difference between the use of compressive and pneumatic devices when compared with no treatment or use of LMWH. However, their uncertainty did not allow for a reliable clinical recommendation.[15]

In an economic evaluation of VTE prophylaxis strategies in critically ill trauma patients at risk of bleeding, a state where anticoagulation is contraindicated, IPCs were considered among other mechanical thromboprophylactic measures as adequate and cost-effective.[16]

Michael et al and Kahn et al concluded that IPC use for thromboprophylaxis in critically ill patients should only come in place when there are contraindications for anticoagulation or when bleeding is a major concern.[17,18]

In 2013, Arabi et al conducted multiple propensities score-adjusted analyses and found that the use of IPC was associated with a significantly lower VTE risk, whereas graduated compression stocking use was not. The association was consistent across all types of prophylactic heparin used and was not affected by trauma or surgical admission.[19]

In 2016, Park et al concluded in their meta-analysis that the efficacy of mechanical thromboprophylaxis in VTE prevention was not as robust as anticoagulation since they had similar bleeding profiles with slightly better prophylaxis with anticoagulation compared with mechanical thromboprophylaxis.[20]

Finally, in a recent Cochrane review article, combining IPC with anticoagulation reduced the incidence of DVT when compared with IPC alone, as well as the incidence of PE when compared with anticoagulation alone. There was no difference between combined and individual modalities in PE incidence when compared with compression alone or in DVT incidence when compared with anticoagulation alone. Compared with IPC alone, adding pharmacological prophylaxis to IPC raised the bleeding risk, a side effect that was not found for IPC when added to pharmacological prophylaxis.[21]

The strengths of our meta-analysis include an extensive search of the available literature. Furthermore, we included only RCTs, which helps eliminate the likelihood of confounding bias from nonrandomized studies. Our study also only focused on IPC as thromboprophylaxis in solely critically ill patients compared with previous studies. However, there are several limitations in the included clinical trials. First, almost all included trials have performance bias as blinding to study participants and personnel was not possible secondary to the nature of interventions. Second, due to various trial designs and protocols, there were differences in the anticoagulation dosing and the different control methods and thromboprophylaxis combinations used. Third, the safety of all measures was not possible due to the small numbers of bleeding events reported in the trials that rendered its analysis inconclusive.

In light of those limitations that prevented our study from drawing more robust conclusions, it shows the importance of more future studies that can try to create better

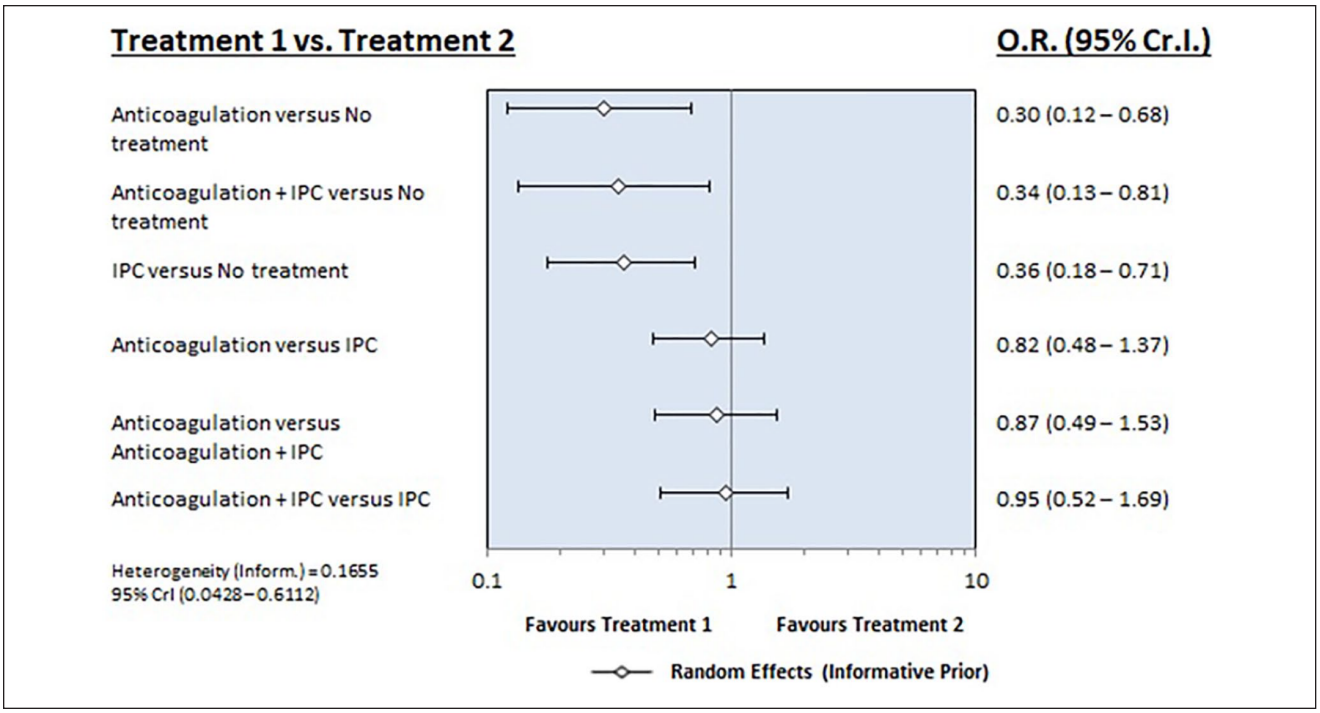

Figure 3. Forest plot of the primary outcome (venous thromboembolism incidence).

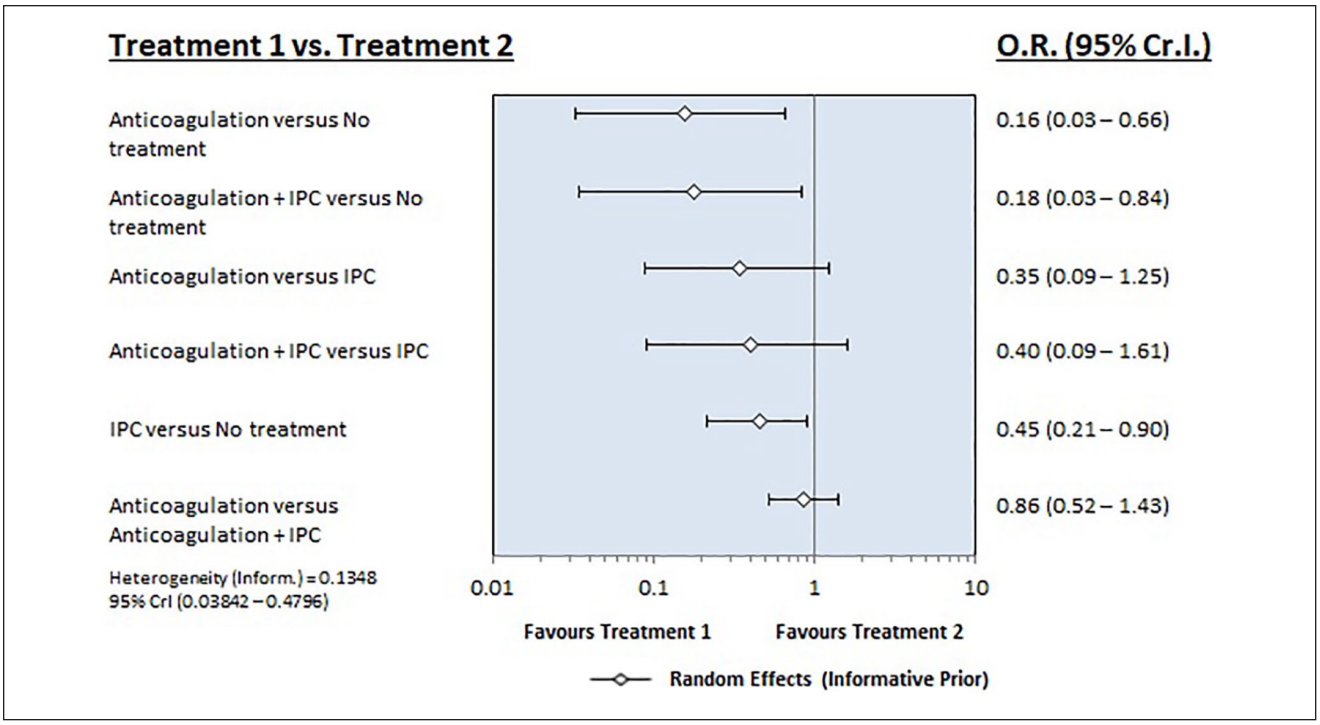

Figure 4. Forest plot of deep vein thrombosis incidence.

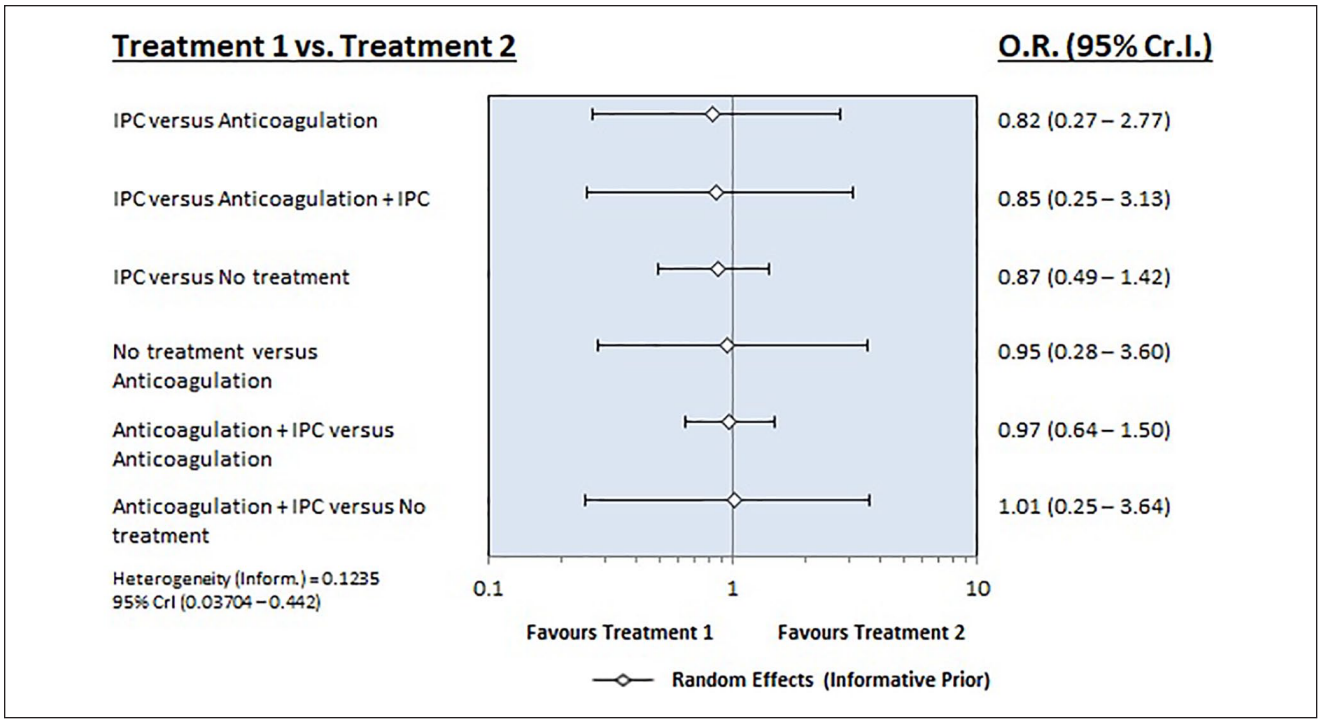

Figure 5. Forest plot of all-cause mortality.

Table 3. Detailed Data of All Reported Primary and Secondary Outcomes.

Studies	Number of patients	DVT	PE	VTE	Death	Bleeding
Ginzburg et al[11]	• IPC group: 224 Pts • LMWH group: 218 Pts	• IPC group: 6 Pts (2.7%) • LMWH group: 1 Pt (0.45%) • $P = .122$	• IPC group: 1 Pt (0.44%) • LMWH group: 1 Pt (0.45%)	• IPC group: 7 Pts (3.14%) • LMWH group: 2 Pts (0.9%) • $P = .176$	• IPC group: 0 Pts • LMWH group: 0 Pts	• IPC group: 8 Pts • LMWH group: 13 Pts
Kurtoglu et al[12]	• IPC group: 60 Pts • LMWH group: 60 Pts	• IPC group: 4 Pts (6.6%) • LMWH group: 3 Pts (5.0%)	• IPC group: 2 Pts (3.3%) • LMWH group: 4 Pts (6.6%)	• IPC group: 6 Pts (9.9%) • LMWH group: 7 Pts (11.6%)	• IPC group: 7 Pts (11.6%) • LMWH group: 8 Pts (13.3%)	• IPC group: 5 Pts (8.2%) • LMWH group: 9 Pts (14.8%)
Zhang et al[13]	• IPC group: 79 Pts • No treatment group: 83 Pts	• IPC group: 3 Pts (3.8%) • No treatment group: 16 Pts (19.28%) • $P < .01$	• IPC group: 0 Pts • No treatment group: 8 Pts (9.64%) • $P < .01$	• IPC group: 3 Pts (3.8%) • No treatment group: 24 Pts • (28.92%)	• IPC group: 1 Pts • (1.26%) • No treatment group: 6 Pts (7.23%) • $P < .01$	N/A
Vignon et al[14]	• IPC + GCS group: 204 Pts • GCS group: 202 Pts	• -IPC + GCS group: 13 Pts • GCS group: 16 Pts	• IPC + GCS group: 1 Pt • GCS group: 1 Pt	• IPC +GCS group: 14 Pts • GCS group: 17 Pts	• IPC + GCS group: 69 Pts • GCS group: 68 Pts	• IPC + GCS group: 17 Pts • GCS group: 20 Pts
Arabi et al[9]	• IPC + thromboprophylaxis group: 991 Pts • Thromboprophylaxis group: 1012 Pts	• IPC + thromboprophylaxis group: 95 Pts • Thromboprophylaxis group: 85 Pts	• IPC + thromboprophylaxis group: 8 Pts • Thromboprophylaxis group: 10 Pts	• IPC + thromboprophylaxis group: 103 Pts • Thromboprophylaxis group: 95 Pts	• IPC + thromboprophylaxis group: 258 Pts • Thromboprophylaxis group: 270 Pts	N/A

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; IPC, intermittent pneumatic compression; Pts, patients; LMWH, low-molecular-weight heparin; N/A, not applicable; GCS, graduated compression stockings.

blinding among study components, have better clarity, and conform to protocols and assess safety better.

Conclusion

Among critically ill patients, IPC alone, anticoagulation alone, or IPC with anticoagulation was associated with a significant reduction of VTE and DVT incidence compared with no treatment. However, there was no significant difference between these modalities when compared together. Therefore, more extensive studies comparing different thromboprophylaxis modalities and their combinations are needed to provide more robust results for future clinical recommendations.

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Declaration of Conflicting Interests

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