Review Article
Prevention of venous thromboembolism in gynecological cancer patients undergoing major abdominopelvic surgery: A systematic review and network meta-analysis

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HIGHLIGHTS
• Choice of perioperative VTE prophylactic measures in cancer patients is debatable.
• The effects of these measures in gynecological cancer patients were compared.
• Graduated compression stockings plus LMWH had highest probability to prevent VTE.
• Sequential compression devices (SCD) gave lowest bleeding among active measures.
• SCD plus LMWH seemed to be optimally balanced between risks for VTE and bleeding.

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ABSTRACT
Objective. Although thromboprophylaxis is recommended to reduce death and disability from venous thromboembolism (VTE), it remains underused due to a perceived risk of bleeding, especially in major abdominopelvic surgical patients.

Methods. We conducted a systematic literature review to identify all eligible randomized controlled trials (RCTs), searching MEDLINE and Scopus databases through November 25, 2020. RCTs published in any language were eligible if they studied in gynecological cancer patients undergoing major abdominopelvic surgery and assessed efficacy of mechanical and pharmacological interventions. Studies with insufficient data for pooling or those comparing different doses/schedules of interventions were excluded. Outcomes of interest were composite VTE (ie, deep vein thrombosis or pulmonary embolism) and major bleeding. Relevant data were extracted for direct and network meta-analyses. Risk ratios (RR) and 95% confidence interval (CI) were estimated and the best intervention probability calculated for each outcome. This study was registered with PROSPERO (CRD42019145508).

Results. We identified 1990 studies; 20 RCTs (4970 patients) were eligible. The overall risk of bias was of some concern. In direct meta-analyses, antithrombins were superior to unfractionated heparin in preventing composite VTE (RR 0.69; 95% CI 0.48–0.99), with no difference detected in the rate of major bleeding for any pairwise comparison. In network meta-analyses, graduated compression stockings plus low-molecular-weight heparin (LMWH) was top-ranked for prevention of composite VTE, whereas sequential compression devices (SCD) ranked second, after no treatment, for major bleeding. In a clustered ranking plot, SCD plus LMWH provided optimal balance between efficacy and safety.

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1. Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a serious complication following major abdominopelvic surgery, doubling the risk of morbidity and mortality and is the second leading cause of death in cancer patients [1]. Risk of VTE is 4 to 7 times higher in cancer patients than the general population. In absolute terms, approximately 20% of cancer patients present with VTE [2]. The incidence of VTE varies by cancer type and tumor burden, and is particularly high in patients with mucin-secreting adenocarcinoma of the ovary, pancreas, stomach, and colon, as well as brain tumors [3,4]. Patients with gynecological cancers are at higher risk, not only from the malignancy itself and the consequent abdominopelvic surgery, but also from additional risk factors including advanced age, high body mass index (BMI), comorbidities, immobility, hormonal therapy, venous obstruction, thrombin formation, and treatment modalities (eg, long operative time, chemotherapy, and targeted therapy) [5,6].

A previous study estimated that VTE risk was approximately 14-fold higher in patients with gynecological cancer than those without cancer, reporting DVT and PE incidence ranging from 17% to 40% and 1% to 2.6%, respectively [7–9]. The 28-day case fatality rate was 11% after the first VTE event, with survivors experiencing an impaired quality of life despite treatment [10,11]. As such, VTE prophylaxis should be considered as a high priority in these patients.

The three factors predisposing to venous thrombosis comprise the Virchow's triad of endothelial injury, venous stasis or blood flow turbulence, and hypercoagulable state [12]. Many prophylactic strategies have been developed to mitigate these factors. Two types of VTE prophylaxis are available in surgical patients, ie, mechanical and pharmacological methods. The former (ie, graduated compression stockings [GCS], and sequential compression devices [SCD] or intermittent pneumatic compression [IPC] devices) help reduce venous stasis and may promote endogenous fibrinolysis, while pharmacological intervention (eg, unfractionated heparin [UH] [13], low-molecular-weight heparin [LMWH]), prevent clot formation by impairing the clotting cascade [14].

Prophylactic interventions initiated before gynecological procedures can reduce VTE incidence by 50–70% [8]. Given all cancer patients are classified as high risk, clinical practice guidelines by the American Society of Clinical Oncology (ASCO) [15] and the National Comprehensive Cancer Network (NCCN) [16] recommend that all cancer patients undergoing major surgical intervention should receive pharmacologic thromboprophylaxis with either UH or LMWH unless there is contraindication of high bleeding risk. These measures should begin before surgery and continue for at least 7–10 days, including extending up to 28 days in patients at high-risk [15]. Despite strong recommendations for VTE prophylaxis, many physicians still underuse these agents [17].

To date, only two systematic reviews have evaluated VTE prophylaxis in gynecological cancers; one review in 2007 [8] used direct meta-analysis (DMA) to evaluate the effects of only a few therapeutic methods (ie, UH vs LMWH and UH vs no prophylaxis) on VTE. The other systematic review in 2011 [13] included 9 studies with gynecological cancers, but they failed to apply DMA due to insufficient data. Neither study considered the risk of bleeding. Given the wide range of prophylactic interventions currently available, an updated systematic review and network meta-analysis (NMA) to evaluate all evidence of thromboprophylaxis in gynecological cancer patients undergoing major abdominopelvic surgery would identify the most effective and safest prophylaxis for perioperative and postoperative VTE in these patients.

2. Methods

2.1. Search strategy and selection criteria

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement extension for network meta-analysis and was prospectively registered with PROSPERO (registration number: CRD42019145508) [18].

We identified relevant studies published in any language in MEDLINE via PubMed and Scopus through November 25th, 2020. The search strategy is reported in Supplementary Table S1. Reference lists of articles were also explored for additional relevant studies.

Two reviewers (PI and KV) independently selected studies. Disagreements were resolved through discussion and consensus with a senior author (KT). Titles and abstracts were screened, and full texts
reviewed. Randomized controlled trials (RCTs) published in any language were eligible if they met the following criteria: a) included gynecological cancer patients who underwent major abdominopelvic surgery; b) compared any pair of interventions: GCS, SCD/IPC, UH, LMWH, antithrombins, combined treatment, and no treatment/usual care/placebo; and c) reported any VTE occurrence (ie, DVT, PE, or VTE) or major bleeding events. Studies were excluded if they compared the same drugs with different dosages or formulations. For duplicate publications, the most complete was included in the analysis. Non-English studies were translated by using Google Translate service (https://translate.google.com/).

The interventions of interest were no treatment/usual care/placebo, mechanical methods (ie, GCS and SCD/IPC), pharmacological methods (ie, UH, LMWH, and antithrombins which include dermatan sulfate [DS] and defibrotide [DF]), and combined treatment (ie, GCS plus LMWH, SCD plus LMWH, and UH plus dihydroergotamine [UHDE]).

Two main outcomes were considered: composite VTE occurrence and major bleeding. Composite VTE occurrence comprised either DVT or PE. If RCT reported DVT and PE, but not for VTE, the maximum number of events among these 2 outcomes was used as the number of composite VTE. DVT included both symptomatic and asymptomatic DVT that was confirmed by radiofibrinogen uptake test, venography, duplex (Doppler) ultrasound, computed tomography (CT) scan or impedance plethysmography. PE was confirmed by CT scan (spiral or with contrast), pulmonary angiogram or ventilation/perfusion scan including echocardiography. Major bleeding was defined as the presence of at least one of the following conditions as per the International Society of Thrombosis and Haemostasis: fatal bleeding, symptomatic bleeding (ie, intracranial, intraspinal, pericardial, intraocular, or retroperitoneal), extra-surgical site bleeding causing a fall in hemoglobin level of ≥2 g/dL, or leading to transfusion of ≥2 units of blood, surgical site bleeding that requires a second intervention, or unexpected and prolonged and/or sufficiently large bleeding to cause hemodynamic instability [19].

2.2. Data extraction and checking

Two reviewers (PI and KV) independently extracted data including general data (study design, year of publication), participants’ characteristics (mean age, weight, BMI, underlying disease, cancer type, cancer stage, operative procedure, operative time), treatment (intervention type, dosage, and duration), and outcomes (ie, DVT, PE, VTE, and major bleeding). Potential risk of bias was also assessed independently by the same reviewers using Risk of Bias in randomized trials tool (RoB2) [20]. Disagreements between reviewers were resolved by discussion and consensus with a senior reviewer (KT).

2.3. Statistical analysis

Intention-to-treat analysis was carried out for the entire quantitative synthesis. DMA was performed by pooling risk ratios (RR) if there were at least three studies with similar interventions and outcomes. Cochran’s Q test and Higgins I² statistics were applied to assess heterogeneity. A random-effects model (DerSimonian and Laird) was chosen for pooling RRs if heterogeneity was present (p < 0.1 or I² ≥ 25%). Otherwise, a fixed-effect model using the inverse-variance method was chosen. Sources of heterogeneity (ie, setting, participants, and treatments) were subsequently explored by fitting each factor in a meta-regression; a subgroup analysis was performed accordingly. Publication bias was assessed using Egger’s test and funnel plots.

A network map was constructed to display head-to-head comparisons in all included RCTs. A NMA consistency model was constructed to indirectly compare the treatment effects among all treatment regimens using a two-stage approach. Treatments were then ranked using the surface under the cumulative ranking curve (SUCRA) method. A higher SUCRA value corresponds to a higher level of efficiency and safety indicating better treatments. A clustered ranking plot to illustrate the SUCRAs of composite VTE occurrence and major bleeding was constructed to simultaneously reflect the benefit from lowering VTE and major bleeding. The consistency assumption was checked using a design-by-treatment interaction model [21,22]. Potential for small-study effects, seen as a proxy for publication bias, was assessed using a comparison-adjusted funnel plot.

Kappa statistics were applied to estimate disagreements in study selections and data extractions between reviewers. Stata software package, version 16.1 (StataCorp. 2019. College Station, TX, USA) was used to perform statistical analysis. A p < 0.05 was considered statistically significant for all analyses, except for Cochran’s Q test, which used a p < 0.1.

3. Results

A total of 20 RCTs [23–42], 3 of which [30,32,41] were non-English, met the inclusion criteria from 1990 articles identified (Fig. 1). Agreement for study eligibility between both reviewers was 94.5% (kappa coefficient 0.68). The RCTs published between 1983 and 2015 were mainly conducted in the USA, Italy, and France with sample sizes ranging between 30 and 885, totalling 4970 participants. Characteristics of included studies are summarized in Table 1. Of these, 14 RCTs [24–28,30–32,34,35,38,40–42] included only gynecological cancer patients, whereas the rest [23,29,33,36,37,39] included mixed patients with percentage of cancer patients ranging from 63.9% to 93.8%. Percentage of ovarian cancer patients was reported in only 9 RCTs [23,24,34,35,37,38,40–42], which ranged from 7.5% to 100% with a median of 28%. Mean age ranged from 46.7 to 69.9 years. Seven studies [27,30,31,39–42] reported mean BMI which varied from 22.3 to 27.5 kg/m², 4 of which [30,31,39,40] had mean BMI ≥25 kg/m². Two-thirds of the RCTs included patients who underwent total abdominal hysterectomy without lymphadenectomy. The mean operative time varied from 72.9 to 482.2 with a median of 199 min. VTE was investigated and diagnosed 7 to 42 days after operation with a median of approximately 10 days.

Nine VTE prophylactic methods were evaluated in the 20 RCTs, ie, no treatment (6 RCTs), GCS (2 RCTs), SCD (4 RCTs), UH (14 RCTs), LMWH (7 RCTs), antithrombins (4 RCTs), GCS plus LMWH (1 RCT), SCD plus LMWH (1 RCT), and UHDE (1 RCT). Their regimens, dosages, and treatment schedules are summarized in Supplementary Table S2.

Most of the studies included clinically diagnosed DVT and PE (Table 1). Nineteen RCTs [23,24,26–42] reported DVT, PE, or VTE events with time of diagnosis between seven and 42 days; Ten RCTs [27,28,31,32,34,37,40–42] reported major bleeding, see Supplementary Table S3. Out of 19 VTEs, 12 RCTs provided VTE data, whereas 3 RCTs provided only DVT, and 4 RCTs provided both DVT and PE data. Agreement between reviewers regarding data extraction was 86% (kappa coefficient 0.85).

The risk of bias for individual studies is provided in Supplementary Figs. S1A and S1B. Over 94% (18 RCTs) of included RCTs were of some concerns because they provided no details of randomization. In addition, blinding was not possible in these surgical studies owing to the nature of the interventions. The agreement between both reviewers was 93.8% with a kappa coefficient of 0.84.

3.1. Direct meta-analysis

There were two DMAs among three treatments on each outcome. The results of the DMAs are presented in Supplementary Tables S4 and S5 and Fig. 2. In brief, antithrombins had significantly lower composite VTE occurrence risk compared to UH with pooled RR (95% CI) of 0.69 (0.48, 0.99) with no heterogeneity observed; whereas LMWH and UH were not significantly different. Likewise, none of the treatments showed a significant difference in the major bleeding outcome. Funnel plots indicated no obvious evidence of asymmetry, consistent with the Egger’s test (Supplementary Figs. S2A and S2B).
3.2. Network meta-analysis

Treatment comparisons were mapped for both VTE and bleeding outcomes (Fig. 3). Results of NMAs are as follows:

3.2.1. Venous thromboembolism

Data from 19 RCTs (4692 patients) consisting of direct comparisons between nine treatments were pooled for composite VTE occurrence. Among single agent prophylaxis options, the three most effective treatments in lowering composite VTE occurrence were GCS, antithrombins, and LMWH or UH with pooled RRs (95% CI) of 0.10 (0.00, 2.01), 0.51 (0.18, 1.42), 0.71 (0.35, 1.44), and 0.71 (0.39, 1.30), respectively, relative to no treatment, although none was significant (Table 2). UH, LMWH, and SCD demonstrated 7 to 8 times higher risk of VTE than GCS, but none was significant. Adding LMWH to GCS or SCD lowered the composite VTE occurrence relative to monotherapy with each agent, with pooled RRs of 0.20 (0.01, 4.61) and 0.18 (0.02, 1.54), respectively. The top-ranked treatments in lowering composite VTE occurrence by SUCRA were GCS plus LMWH, SCD plus LMWH, and GCS with the SUCRAs of 91.0%, 76.6%, and 75.4%, respectively (Supplementary Fig. S3).

3.2.2. Major bleeding outcome

Ten RCT (2697 patients) consisting of 6 and 15 direct and indirect comparisons were pooled for the major bleeding outcome. All 5 monotherapy
### Table 1: Characteristics of included studies.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Treatment</th>
<th>Total patients</th>
<th>Center</th>
<th>Mean age (years)</th>
<th>Mean BMI (kg/m²)</th>
<th>%Varicose vein</th>
<th>%Prior VTE</th>
<th>Obesity</th>
<th>%Cancer</th>
<th>Time since surgery to VTE diagnosis (days)</th>
<th>Reported outcomes</th>
<th>Method of VTE diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarke-Pearson D [23]</td>
<td>USA</td>
<td>UH vs No treatment</td>
<td>185</td>
<td>Single</td>
<td>69.9</td>
<td>NR</td>
<td>31.9</td>
<td>5.4</td>
<td>NR</td>
<td>84.3</td>
<td>42</td>
<td>DVT, PE, VTE</td>
<td>Signs/symptoms, I125, venography, plethysmography, V/Q, PA</td>
</tr>
<tr>
<td>Clarke-Pearson D [24]</td>
<td>USA</td>
<td>SCD vs No treatment</td>
<td>194</td>
<td>Single</td>
<td>69.0</td>
<td>NR</td>
<td>30.0</td>
<td>3.0</td>
<td>NR</td>
<td>100.0</td>
<td>42</td>
<td>DVT, PE, VTE</td>
<td>Signs/symptoms, I125, venography, plethysmography, V/Q, PA</td>
</tr>
<tr>
<td>Clarke-Pearson D [25]</td>
<td>USA</td>
<td>UH vs No treatment</td>
<td>182</td>
<td>Single</td>
<td>53.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>100.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turner GM [26]</td>
<td>England</td>
<td>GCS vs No treatment</td>
<td>196</td>
<td>Single</td>
<td>46.7</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>90.0</td>
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<td></td>
</tr>
<tr>
<td>Fricker JP [27]</td>
<td>France</td>
<td>LMWH vs UH</td>
<td>80</td>
<td>Single</td>
<td>57.6</td>
<td>24.8</td>
<td>43.7</td>
<td>13.7</td>
<td>NR</td>
<td>100.0</td>
<td></td>
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<tr>
<td>Samama M [28]</td>
<td>France</td>
<td>LMWH vs UH</td>
<td>885</td>
<td>Multiple</td>
<td>56.7</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>100.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarke-Pearson D [29]</td>
<td>USA</td>
<td>UH vs No treatment</td>
<td>304</td>
<td>Single</td>
<td>60.6</td>
<td>NR</td>
<td>18.1</td>
<td>3.6</td>
<td>NR</td>
<td>86.4</td>
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<tr>
<td>Dindelli M [30]</td>
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<td>Antithrombin vs UH</td>
<td>50</td>
<td>Single</td>
<td>58.7</td>
<td>26.1</td>
<td>NR</td>
<td>NR</td>
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<td>100.0</td>
<td></td>
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<td></td>
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<tr>
<td>Ferrari A [31]</td>
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<td>Antithrombin vs UH</td>
<td>60</td>
<td>Single</td>
<td>57.5</td>
<td>26.1</td>
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<td>100.0</td>
<td></td>
<td></td>
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<tr>
<td>Fontanelli A [32]</td>
<td>Italy</td>
<td>Antithrombin vs UH</td>
<td>81</td>
<td>Single</td>
<td>59.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>100.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarke-Pearson D [33]</td>
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<td>UH vs SCD</td>
<td>208</td>
<td>Single</td>
<td>56.0</td>
<td>NR</td>
<td>17.8</td>
<td>1.9</td>
<td>NR</td>
<td>63.9</td>
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<tr>
<td>Urlep-Sallinovic V [34]</td>
<td>Slovenia</td>
<td>LM + DHE vs UH</td>
<td>225</td>
<td>Single</td>
<td>56.4</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>85.0</td>
<td></td>
<td></td>
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<tr>
<td>Von Tempelhoff GF [35]</td>
<td>Germany</td>
<td>LMWH vs UH</td>
<td>605</td>
<td>Single</td>
<td>58.0</td>
<td>25.0</td>
<td>42.2</td>
<td>4.7</td>
<td>NR</td>
<td>79.6</td>
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<tr>
<td>Ward B [36]</td>
<td>Australia</td>
<td>LMWH vs UH</td>
<td>566</td>
<td>Single</td>
<td>55.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>81.4</td>
<td></td>
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<tr>
<td>Di Carlo V [37]</td>
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<td>Antithrombin vs UH</td>
<td>842</td>
<td>Multiple</td>
<td>63.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>93.7</td>
<td></td>
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<tr>
<td>Baykal C [38]</td>
<td>Turkey</td>
<td>LMWH vs UH</td>
<td>102</td>
<td>Single</td>
<td>57.4</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>10.8%</td>
<td></td>
<td></td>
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<tr>
<td>Maxwell GL [39]</td>
<td>USA</td>
<td>LMWH vs SCD</td>
<td>211</td>
<td>Single</td>
<td>69.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>100.0</td>
<td></td>
<td></td>
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<tr>
<td>Bergqvist D [40]</td>
<td>Europe</td>
<td>LMWH vs No treatment</td>
<td>332</td>
<td>Multiple</td>
<td>63.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>93.7</td>
<td></td>
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<tr>
<td>Zheng H [41]</td>
<td>China</td>
<td>GCS + LMWH vs GCS</td>
<td>247</td>
<td>Single</td>
<td>50.7</td>
<td>NR</td>
<td>24.8</td>
<td>NR</td>
<td>NR</td>
<td>100.0</td>
<td></td>
<td></td>
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<tr>
<td>Nagata C [42]</td>
<td>Japan</td>
<td>SCD + LMWH vs SCD</td>
<td>30</td>
<td>Multiple</td>
<td>57.1</td>
<td>22.3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>20.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation:** BMI, body mass index; DHE, dihydroergotamine; GCS, graduated compression stockings; kg, kilograms; LMWH, low molecular weight heparin; m, meters; NR, not reported; SCD, sequential compression device; UH, unfractionated heparin; VTE, venous thromboembolism; BMI, body mass index; CT scan, computerized tomography scan; CTA, computerized tomography angiography; DHE, dihydroergotamine; DVT, deep vein thrombosis; GCS, graduated compression stockings; I125 Fibrinogen, iodine 125-labeled fibrinogen scanning; kg, kilograms; LND, lymphadenectomy; LMWH, low molecular weight heparin; m, meter; NR, not reported; PA, pulmonary arteriography; PE, pulmonary embolism; SCD, sequential compression device; UH, unfractionated heparin; V/Q, ventilation-perfusion scan; VTE, venous thromboembolism.
options, ie, UHDHE, UH, antithrombins, LMWH, and SCD, had higher risk of major bleeding when compared with no treatment with pooled RRs of 5.04 (0.05, 496.48), 4.72 (0.43, 51.46), 4.16 (0.36, 47.76), 2.93 (0.30, 28.63), and 2.18 (0.14, 33.49) respectively, although none were significant (Table 2). SCD was 0.43 (0.01, 30.71), 0.46 (0.09, 2.45), and 0.52 (0.09, 3.00) times less likely to have major bleeding than UHDHE, UH, and antithrombins, respectively, but none were significant. The top three active treatments in lowering major bleeding were SCD, SCD plus LMWH, and LMWH with SUCRAs of 60.2%, 56.8%, and 54.8%, respectively (Supplementary Fig. S4).

3.2.3. Treatment ranking

Risk of major bleeding and benefit from prevention of composite VTE occurrence were simultaneously considered using cluster plots of SUCRAs of lowering composite VTE occurrence on the y-axis and major bleeding on the x-axis (Fig. 4). Seven treatments with data available for VTE occurrence and major bleeding were considered. The plot was divided into 4 quadrants: the upper right reflected the best treatment and the lower left reflected the worst treatment. The clustering identified only SCD plus LMWH as the best treatment option for lowering VTE occurrence and major bleeding.
Results of network meta-analyses of composite VTE occurrence and major bleeding outcomes for all treatments relative to each other under the consistency model.

<table>
<thead>
<tr>
<th></th>
<th>SCD plus LMWH</th>
<th>No treatment</th>
<th>GCS plus LMWH</th>
<th>LMWH</th>
<th>Antithrombin</th>
<th>SCD plus LMWH plus Antithrombin</th>
<th>UHDHE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>16.0, 0.0</td>
<td>0.10 (0.00, 2.01)</td>
<td>0.88 (0.37, 2.09)</td>
<td>0.71 (0.39, 1.30)</td>
<td>0.71 (0.35, 1.44)</td>
<td>0.51 (0.18, 1.42)</td>
<td>0.02 (0.00, 1.53)</td>
</tr>
<tr>
<td>SCD</td>
<td>10.16 (0.50, 207.46)</td>
<td>75.4, 7.8</td>
<td>8.93 (0.39, 205.81)</td>
<td>7.21 (0.33, 156.35)</td>
<td>7.25 (0.33, 160.62)</td>
<td>5.15 (0.21, 124.88)</td>
<td>0.20 (0.01, 4.61)</td>
</tr>
<tr>
<td>LMWH</td>
<td>1.41 (0.77, 2.58)</td>
<td>0.14 (0.01, 3.01)</td>
<td>1.24 (0.49, 3.14)</td>
<td>1.41 (0.52, 3.82)</td>
<td>53.2 (0.50, 195.20)</td>
<td>0.13 (0.00, 17.99)</td>
<td>492.2 (0.38, 432.42)</td>
</tr>
<tr>
<td>Antithrombin</td>
<td>1.97 (0.70, 5.52)</td>
<td>0.19 (0.01, 4.60)</td>
<td>1.73 (0.49, 6.13)</td>
<td>1.41 (0.53, 3.82)</td>
<td>60.2 (0.24, 243.41)</td>
<td>0.03 (0.00, 2.25)</td>
<td>0.22 (0.02, 2.37)</td>
</tr>
<tr>
<td>SCD plus LMWH</td>
<td>6.50 (0.63, 67.62)</td>
<td>0.64 (0.01, 29.15)</td>
<td>5.71 (0.65, 50.36)</td>
<td>4.61 (0.43, 49.23)</td>
<td>4.64 (0.42, 51.00)</td>
<td>3.30 (0.27, 40.86)</td>
<td>0.13 (0.00, 17.99)</td>
</tr>
<tr>
<td>UHDHE</td>
<td>1.32 (0.41, 4.24)</td>
<td>0.13 (0.01, 3.30)</td>
<td>1.16 (0.30, 4.54)</td>
<td>0.94 (0.35, 2.54)</td>
<td>0.94 (0.30, 2.96)</td>
<td>0.67 (0.18, 2.45)</td>
<td>0.03 (0.00, 2.36)</td>
</tr>
<tr>
<td>LMWH plus Antithrombin</td>
<td>0.34 (0.03, 3.33)</td>
<td></td>
<td>0.52 (0.09, 3.00)</td>
<td>1.14 (0.68, 1.88)</td>
<td>0.70 (0.29, 1.69)</td>
<td>36.4 (1.4)</td>
<td></td>
</tr>
<tr>
<td>SCD plus LMWH plus Antithrombin</td>
<td>0.52 (0.00, 59.43)</td>
<td></td>
<td>1.13 (0.02, 54.43)</td>
<td>2.46 (0.04, 166.60)</td>
<td>1.53 (0.02, 97.28)</td>
<td>2.16 (0.03, 151.19)</td>
<td>56.8 (0.50, 119.43)</td>
</tr>
</tbody>
</table>

**b) Major bleeding: risk ratios (95%CIs)**

- No treatment: 79.1, 45.3
- SCD: 0.46 (0.02, 219.76) 5.04 (0.05, 496.48) 2.18 (0.14, 33.49) 4.72 (0.43, 51.46) 2.93 (0.30, 28.63) 4.16 (0.36, 47.76) 0.46 (0.02, 7.05) 60.2, 8.0
- LMWH: 0.34 (0.03, 3.33) 0.71 (0.26, 1.93) 0.03 (0.00, 2.27) 0.22 (0.02, 2.37) 1.07 (0.34, 3.32) 0.03 (0.00, 2.27) 0.22 (0.02, 2.37) 1.06 (0.34, 3.32)
- Antithrombin: 0.24 (0.02, 2.76) 0.52 (0.09, 3.00) 1.14 (0.68, 1.88) 0.70 (0.29, 1.69) 36.4 (1.4) 36.4 (1.4)
- SCD plus LMWH: 0.52 (0.00, 59.43) 1.13 (0.02, 54.43) 2.46 (0.04, 166.60) 1.53 (0.02, 97.28) 2.16 (0.03, 151.19) 56.8 (0.50, 119.43) 0.43 (0.01, 30.71) 0.94 (0.02, 47.34) 0.58 (0.01, 31.37) 0.83 (0.02, 43.09) 0.38 (0.00, 120.96) 36.7, 14.5
- UHDHE: 0.43 (0.01, 30.71) 0.94 (0.02, 47.34) 0.58 (0.01, 31.37) 0.83 (0.02, 43.09) 0.38 (0.00, 120.96) 36.7, 14.5

Effect of an intervention in row was compared to effect of an intervention in column. Risk ratio (RR) < 1 favors the treatment along top and RR > 1 favors the treatment along left-hand column. Each diagonal cell contains SUCRA; percentage probability of being best treatment (lower composite VTE occurrence and major bleeding) of each treatment.

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### 4. Discussion

We conducted a systematic review, DMA, and NMA to provide a comprehensive assessment of VTE prophylaxis interventions and identify the most effective modality with the least side effects for gynecological cancer patients undergoing major abdominopelvic surgery. Nineteen RCTs (9 interventions, 4692 patients) and 10 RCTs (7 interventions, 2669 patients) were considered in the composite VTE occurrence and the major bleeding networks, respectively. Our NMA findings suggested that a combination of GCS plus LMWH was best at lowering composite VTE occurrence, while SCD was the safest for major bleeding. However, a combination of SCD plus LMWH provided the optimal balance between composite VTE occurrence and major bleeding.

In our DMA, antithrombins, either DS or UFH, were more effective for VTE prevention. DS is a glycosaminoglycan effective on both free and fibrin-bound thrombin which inhibits thrombus formation, while UFH is a drug characterized by its antithrombotic and profibrinolytic activity. Both drugs have proven effective in the prevention of postoperative DVT in general and following orthopedic surgery with a low rate of hemorrhagic complications [43,44]. Unfortunately, the results of DMA were inconsistent with NMA, therefore, this pooling should be further updated when more studies are published.

To our knowledge, only two systematic reviews [8,13] have previously evaluated VTE prophylaxis in gynecological cancer patients. The first review in 2007 [8] considered only effects of pharmacological methods, ie, UH vs LMWH (N = 5) and UH vs no prophylaxis (N = 3). They found that UH could significantly prevent DVT by 42% relative to no prophylaxis, but it was not significantly different from LMWH. The later review in 2011 [13] described evidence from 9 studies in which the overall incidence of clinical VTE prophylaxis in gynecological cancers ranged from 0 to 14.8% and it was as high as 34.6% in non-prophylaxis. Neither VTE prevention nor bleeding between prophylactic methods was compared. Our study represents the most recent and comprehensive synthesis of evidence from 20 RCTs to evaluate not only the efficacy in prevention of VTE, but also safety from bleeding for VTE prophylaxis strategies. This synthesis incorporated more interventions (ie, 9 pharmacological and non-pharmacological methods including no treatment, GCS, SCD, UH, LMWH, antithrombins, GCS plus LMWH, SCD plus LMWH, and UHDHE) than previous reviews. Effects of all currently available interventions on VTE prophylaxis and bleeding following gynecological cancer surgery, but not for non-surgery, were considered in our NMA.

The most recent clinical practice guidelines by the ASCO [15] and the NCCN [16] recommended pharmacologic thromboprophylaxis with either UH or LMWH for all cancer patients undergoing major surgery. These pharmacologic treatments, particularly UH, require prothrombin time monitoring, which is inconvenient and costly. Mechanical methods are also recommended in addition to pharmacologic thromboprophylaxis, but not as monotherapy unless pharmacologic methods are contraindicated. The ASCO guideline does not specify the choice of mechanical thromboprophylaxis, but the NCCN recommends IPC or SCD. However, patient's compliance with SCD varied because it was commonly associated with discomfort, heat, skin bullae, and itching from the compression pad, and lack of mobility. Despite being rare, some serious complications may also include compartment syndrome and skin necrosis [45]. Although SCD was considered as the safest option, this method's efficacy in the reduction of VTE events was not high, as shown by its poor ranking in the composite VTE occurrence outcome. As such, the use of SCD alone as a primary intervention is questionable and does not represent the best option for the prevention of VTE.
SCD plus LMWH was noticeably superior to LMWH alone in terms of efficacy and safety as indicated by clustered ranking analysis placing it fourth in terms of composite VTE occurrence and major bleeding. However, the mechanisms that lead to a lower rate of major bleeding following SCD with LMWH intervention compared to LMWH alone have yet to be fully elucidated. Previous studies have reported higher risk of bleeding with a daily dose of 5000 antiXa IU LMWH but not with a daily dose of 2500 antiXa IU LMWH when compared with 5000 heparin units twice daily [46,47]. The lower LMWH dosage combined with SCD may lead to reduced bleeding complications compared to the higher LMWH dosage (4000 antiXa IU versus 6000 antiXa IU) as recommended in both guidelines.

This NMA confirms the effectiveness of combination interventions that use both mechanical and pharmacological methods for the prevention of VTE. These results highlight the necessity for consideration of both efficacy and safety of pharmacological prophylactic approaches, especially if those with better efficacy for VTE prevention were more likely to increase risk of bleeding. As such, the benefit-risk balance requires careful consideration for clinical prescribing decisions. Nevertheless, this evidence was based on a relatively small number of studies and additional studies to investigate combination interventions including GCS with or SCD with LMWH would provide an opportunity for more robust and meaningful conclusions.

In addition, decision analysis of high-risk gynecological cancer patients also identified the dual prophylaxis strategy combining SCD with LMWH as cost-effective and a reasonable use of healthcare resources [48]. Although the addition of LMWH to SCD offered a marginal improvement in the risk associated with VTE occurrence, the intervention was considered costly, exceeding $50,000 per life-year saved in patients considered high-risk for the development of perioperative and postoperative VTE. In contrast, consideration of long-term disability and costs associated with post-thrombotic syndrome would increase the cost-effectiveness of VTE prophylaxis. Future studies with a full economic evaluation for all available VTE prophylactic methods are needed to verify the most cost-effective option and take account of reduced hospital stay, rehabilitation, mortality, and long-term complications, such as pulmonary hypertension and post-thrombotic syndrome.

Our study had several strengths. Our NMA included the most recent published RCTs and more recently available treatments not considered in previous reviews [8,13]. We also included non-English language searches to retrieve all available relevant evidence because negative results tend to be published in native language journals. This analysis identified no evidence of heterogeneity in all pairwise comparisons and no discrepancy between direct and indirect treatment evidence in NMA, indicating that despite methodological and clinical differences, the main findings were robust. Furthermore, the risk of bias assessed was not high. Although the patients were not blinded in most studies, the measurement bias remained small because all outcomes of interest evaluated were objective.

However, the results of this analysis should be carefully considered. First, many studies were not recent with most published between 1983 and 2000 and only five published post 2000. Patient characteristics, VTE prophylactic methods, and modalities of cancer treatment have changed considerably over this period and evaluation of the efficacy of VTE prevention may have changed. Secondly, only a small number of studies were available for inclusion in both DMA and NMA, and both results were inconsistent and the precision of treatment effects might be questionable. For instance, results of DMA for antithrombins in lowering composite VTE was marginally significant relative to UH, but it was not in the NMA when the sample size of UH group was increased by borrowing data from other comparisons. Likewise, for LMWH vs UH, estimation of treatment effects from both DMA and NMA were still imprecise due to a small number of included studies. In addition, the sample size for each RCT was quite small, which resulted in zero number of bleeding outcome for most studies. Although we could estimate RRs by applying continuity correction, filling the zero cells with a small value, the estimated treatment effects on bleeding were imprecise. Therefore, caution should be exercised when interpreting and applying the results. Thirdly, although the majority of the participants had gynecological cancer who underwent abdominopelvic surgery, the study population also included a minority of patients with other cancers or benign gynecological conditions. Our results should not be applied to those patients who did not have surgery. Fourthly, the included RCTs in our review had insufficient description of risk factors for VTE occurrence: operative procedure (ie, laparotomy or...
laporoscopy), cancer type (ie, ovarian, uterine, cervical, or vulvar cancer), cancer stage (ie, early, advanced, or recurrent), BMI, and anesthesia type (ie, with or without epidural anesthesia). Sub-group analysis could not be performed to identify any specific group of patients such as obesity who might gain more benefit than general patients. Lastly, not all trials reported bleeding complications. Despite this, the agreement between the results for bleeding complications and those for VTE prevention efficacy provided some reassurance for our main conclusion.

In conclusion, this systematic review and NMA provides a comprehensive summary of the current evidence base for VTE prophylactic strategies used for preventing perioperative and postoperative VTE in gynecological cancer patients undergoing major abdominopelvic surgery. The results showed that SCD with LMWH represented the preferred strategy in terms of efficacy and safety. However, not one prophylactic strategy could be considered superior in all aspects. Therefore, larger future studies alongside economic evaluations are still needed to obtain more robust results on the risk-benefit balance and cost-effectiveness of pharmacologic and non-pharmacologic therapies in this clinical setting.

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None.

**Declaration of Competing Interest**

The authors declare no conflict of interest.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgygyno.2021.01.027.

**References**


**Supplementary information**


