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ORIGINAL ARTICLE – HEALTHCARE POLICY AND OUTCOMES

Role of Extended Thromboprophylaxis After Abdominal and Pelvic Surgery in Cancer Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

Background. Abdominopelvic cancer surgery increases the risk of postoperative venous thromboembolism (VTE). Low-molecular-weight heparin (LMWH) thromboprophylaxis is recommended, and the role of extended thromboprophylaxis (ETP) is controversial. We performed a systematic review to determine the effect of ETP on deep vein thrombosis (DVT), pulmonary embolism (PE), major bleeding, and all-cause mortality after abdominal or pelvic cancer surgery.

Methods. A search of the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials was undertaken, and studies were included if they compared extended duration (2–6 weeks) with conventional duration of thromboprophylaxis (2 weeks or less) after cancer surgery. Pooled relative risk (RR) was estimated using a random effects model.

Results. Seven randomized and prospective studies were included, comprising 4807 adult patients. ETP was associated with a significantly reduced incidence of all VTEs [2.6 vs. 5.6 %; RR 0.44, 95 % confidence interval (CI) 0.28–0.70, number needed to treat (NNT) = 39] and proximal DVT (1.4 vs. 2.8 %; RR 0.46, 95 % CI 0.23–0.91, NNT = 71). There was no statistically significant difference in the incidence of symptomatic PE (0.8 vs. 1.3 %; RR 0.56, 95 % CI 0.23–1.40), major bleeding (1.8 vs. 1.0 %; RR 1.19, 95 % CI 0.47–2.97), and all-cause mortality (4.2 vs. 3.6 %; RR 0.79, 95 % CI 0.47–1.33). None of the outcomes differed if randomized trials were analyzed independently.

Conclusions. ETP after abdominal or pelvic surgery for cancer significantly decreased the incidence of all VTEs and proximal DVTs, but had no impact on symptomatic PE, major bleeding, or 3-month mortality. ETP should be routinely considered in the setting of abdominal and pelvic surgery for cancer patients.

Venous thromboembolism (VTE), comprised of deep vein thrombosis (DVT) and pulmonary embolism (PE), is promoted by venous stasis, vascular injury and hypercoagulable states, known historically as Virchow's triad. Cancer patients undergoing major abdominal or pelvic surgery are exposed to these three insults and consequently have a substantial thrombotic risk.

Patients with an active neoplastic disease undergoing major surgery have at least twice the risk of postoperative DVT and nonfatal PE, and more than three times the risk of fatal PE compared with patients undergoing surgery for non-inflammatory benign conditions.[1,2] In patients with active cancer, the most common risk factor for developing DVT is recent surgery.[3,4]

Postoperative activation of the coagulation system persists beyond the first 7–10 days following surgery, with the VTE incidence remaining as high as 25 % even after 4–6 weeks following the surgical intervention.[5–8] The @RISTOS study,[9] a prospective observational study of

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more than 2300 patients undergoing general, urologic, or gynecologic surgery for cancer, reported VTE as the most common cause of death at 30 days after surgery, with VTE representing the cause of death in 46.3 % of all reported fatalities (overall death rate was 1.72 %). Furthermore, 40 % of VTE events occurred later than 21 days after surgery, when most patients had the thromboprophylaxis interrupted.[9] These initial observations laid the logical foundation for studies on extended VTE prophylaxis in this setting. Multiple studies have compared the safety and efficacy of extended-duration VTE prophylaxis, i.e. for 3–4 weeks after surgery compared with in-hospital prophylaxis only in abdominal surgery.[3,10,11] The results favored extended-duration prophylaxis in terms of reducing the incidence of symptomatic and asymptomatic DVTs, but were inconclusive regarding differences in safety outcomes such as major bleeding and death.[12] However, cancer is a major risk factor for bleeding and this could impact the safety of employing extended VTE prophylaxis routinely in patients undergoing major surgery for cancer.[12,13] In keeping with this concern, the current guidelines regarding VTE prophylaxis from the American College of Chest Physicians (ACCP) recommend that "high-risk VTE patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk of major bleeding complications" receive pharmacologic prophylaxis with low-molecular-weight heparin (LMWH) for 4 weeks postoperatively.[12] However, there is no reference to a VTE risk or bleeding scoring systems to be used to risk stratify patients. The only systematic review on this topic was published in 2008[10] and included one cancer-specific trial along with several cancer subgroups from other trials. Since then, several cancer-specific trials have been published.

We hypothesized that extended thromboprophylaxis (ETP) after major abdominal or pelvic cancer surgery is safe and effective. We performed a systematic review to compare the efficacy and safety of ETP (i.e. between 2 and 6 weeks) versus conventional thromboprophylaxis [CTP] (i.e. $\leq$2 weeks) after abdominal or pelvic surgery in cancer patients.

METHODS

We performed a systematic review of randomized controlled trials (RCTs) and observational cohort studies that included adult patients ($\geq$18 years of age) who received thromboprophylaxis with LMWH after abdominal or pelvic cancer surgery. This study is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[14,15] A priori protocol was registered at PROSPERO (CRD42014014465).

Search Strategy

Databases searched included the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE, from inception through May 2015. The search strategy identified all relevant publications in any language. We used the Medical Subject Heading (MeSH) terms 'abdominal surgery', 'pelvic surgery', and 'thromboprophylaxis'. This search was supplemented by additionally screening abstracts from annual major hematology and oncology conferences [American Society of Hematology, European Hematology Association, and American Society of Clinical Oncology (ASCO)], screening health technology assessments and clinical trials registries, and contacting authors and manufacturers of anticoagulants for additional studies and unpublished data. Finally, a manual search of the reference lists of retrieved studies was performed to identify any further studies.

Study Selection

To be eligible, studies had to meet the following criteria. (i) Randomized clinical trials or prospective observational cohort comparing ETP with CTP in patients undergoing major abdominal or pelvic surgery for cancer. CTP was defined as anticoagulant prophylaxis of no more than 2 weeks after surgery, whereas ETP was defined as thromboprophylaxis for a period of 2–6 weeks after surgery. (ii) Use of thromboprophylaxis with LMWH after surgery. (iii) All VTE outcomes had to be objectively diagnosed using accepted imaging modalities [compression ultrasound for DVT and computed tomography (CT) pulmonary angiography (CTPA) or ventilation–perfusion (VQ) scan for PE]. Asymptomatic DVT detected on mandatory screening or symptomatically diagnosed DVT and/or PE were included. (iv) The study reported at least one of the following outcomes of interest: DVT (symptomatic or screened), PE, mortality, major bleeding (as defined by the International Society on Thrombosis and Haemostasis [ISTH],[16] or as defined by the investigators). Duplicate publications were excluded.

Two reviewers (AF, GA) screened each citation. Studies considered relevant by one or both reviewers were retrieved, and the full text was independently assessed by two reviewers. Disagreements were resolved by discussion. A bibliographic electronic tool was used to download all references and ensure the absence of reference duplication.

Data Extraction

Two reviewers independently abstracted the data describing baseline characteristics (including age, sex, type of surgery, duration and type of thromboprophylaxis, and

follow-up duration), and outcomes. Discrepancies were solved by discussion. We contacted authors of the respective publications to obtain missing information, and results of intention-to-treat analyses were collected if reported. Both efficacy and safety outcomes were extracted. The efficacy outcomes were objectively confirmed VTE (PE, DVT, or both); proximal DVT (pDVT; i.e. involving the popliteal vein or more proximal venous segments); distal DVT (dDVT; i.e. involving infra-popliteal deep leg veins); and PE. The safety outcomes were major bleeding and all-cause mortality.

Quality Assessment

We used the Newcastle–Ottawa Scale for the assessment of cohort studies.[17] This is an eight-item instrument that uses a star system to assess methodological quality across three categories: the methods of selecting the study groups, the comparability between groups, and the ascertainment of the outcome of interest. Scores range from 0 to 9 stars (electronic supplementary Table 1). Two reviewers independently scored each study and disagreements were resolved by discussion.

Statistical Methods

The Cochrane Collaboration-recommended program, Review Manager V 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen; 2014), was used to analyze the data. Overall estimated effect size and variation were expressed as relative risk (RR) with a 95 % confidence interval (CI). The DerSimonian and Laird random effects model assumption was used to adjust for within- and between-study heterogeneity,[18] and the I^2 statistic was calculated to quantify heterogeneity.[19] Forest plots were used to illustrate the individual studies, their final pooled effect size, and each individual study's weight (based on the inverse of variance plus heterogeneity).

RESULTS

Study Selection and Characteristics

Overall, 2763 unique records were identified and screened based on the prespecified inclusion criteria. A total of 32 studies were selected for full-text review, among which only seven were eligible for the quantitative data synthesis and meta-analysis (Fig. 1).[2,20–25] Characteristics of these studies are included in Table 1; three studies were RCTs[2,20,25] and four were observational studies.[21–24] The mean age of participants was 63 years (range 20–90). For abdominal and non-gynecologic pelvic cancer surgery, women represented 46 % of the study population. The type of cancers, surgeries, and thromboprophylaxis regimens included are outlined in Table 1. The three RCTs employed mandatory screening for asymptomatic DVT at 4 weeks after surgery, using either bilateral venography[20,24] or bilateral compression ultrasonography.[25] Screening imaging for PE was not performed in any of the studies. The proportion of patients who completed screening assessments was 66 % in the study by Bergqvist et al.,[20] 78 % in the study by Kakkar et al.,[2] and 100 % in the study by Vedovati et al.[25] Symptomatic DVTs in all studies were investigated with unilateral venography or compression ultrasound, and all PEs were diagnosed after symptomatic events using either CTPA or VQ scanning.

Quality Assessment and Risk of Bias

Most of the studies scored more than six stars in the Newcastle–Ottawa scale,[26] indicating moderate to high quality and low risk of bias (electronic supplementary Table 1). The three RCTs had high quality scores (eight stars). The study by Ibrahim et al. was published as an abstract, and was therefore excluded from the quality assessment.[21] All studies had fewer than 5 % of patients who were lost to follow-up.

Efficacy Outcomes

All Venous Thromboembolisms The ETP regimen significantly reduced the incidence of all VTEs compared with the CTP regimen [2.6 % (59/2292) vs. 5.6 % (124/2209); RR 0.44, 95 % CI 0.28–0.70, number needed to treat (NNT) = 39] [Fig. 2].

Proximal Deep Vein Thrombosis (DVT) The incidence of pDVT was extracted from all three RCTs and two observational studies. Overall, the incidence of pDVTs was significantly lower in the ETP group compared with the CTP group [1.4 % (14/966) vs. 2.8 % (24/862); RR 0.46, 95 % CI 0.23–0.91, NNT = 71] (Fig. 3). All events in one RCT and both observational studies were symptomatic. The other two RCTs did not specify whether events were symptomatic or asymptomatic.

Distal DVT dDVT was only reported in two of the RCTs.[2,20] Twenty-five episodes of dDVT were diagnosed in the ETP group compared with 38 episodes in the CTP group; However, the results did not reach a statistically significant level (RR 0.63, 95 % CI 0.32–1.22, NNT = 30) (electronic supplementary Fig. 1). All but one of the dDVTs were asymptomatic and found on the mandatory day 28 screening.

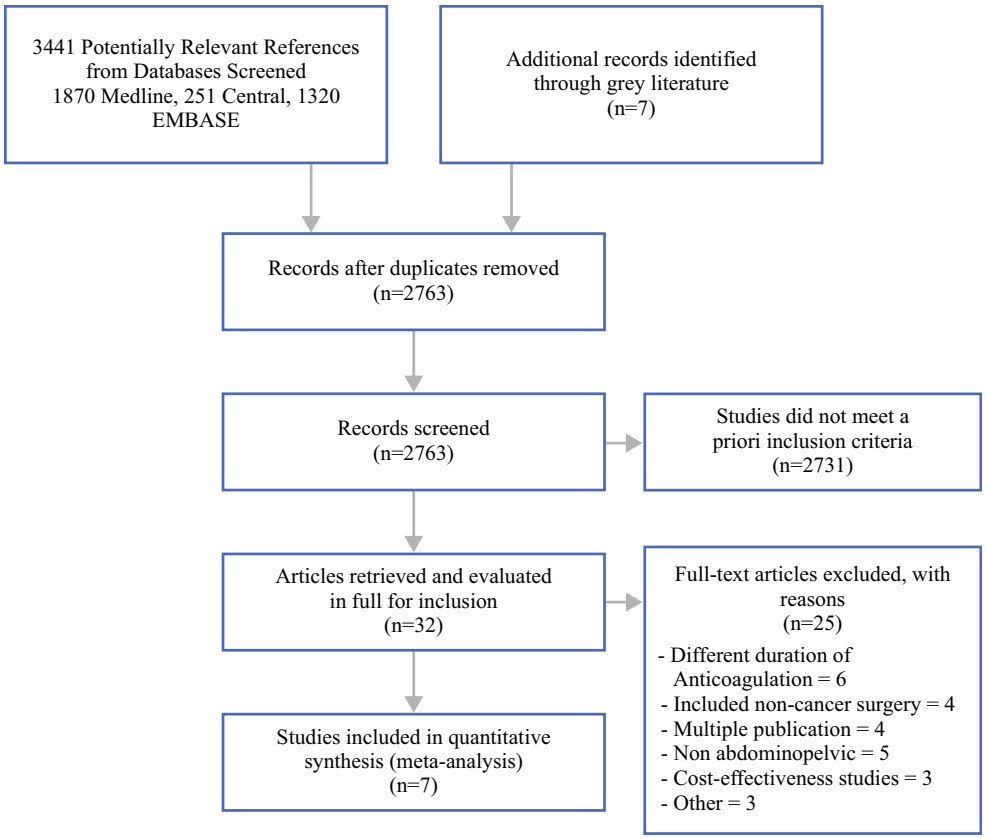

FIG. 1 Study selection process

Pulmonary Embolism The incidence of PE was low. Nineteen PEs were reported, with eight occurring in the ETP group and 11 in the CTP group. Overall, there was no statistically significant difference in the incidence of PE between the two groups [0.8 % (8/966) vs. 1.3 % (11/862); RR 0.56, 95 % CI 0.23–1.40, NNT = 200] (electronic supplementary Fig. 2).

Safety Outcomes

Major Bleeding Events The total incidence of major bleeding events at 3 months was 1.4 %. All RCTs reported data for the incidence of major bleeding, whereas only one observational study reported this safety outcome.[22] There was no statistically significant difference in the incidence of major bleeding between the two groups: 1.8 % (14/787) in the ETP group versus 1.0 % (7/713) in the CTP group (RR 1.19, 95 % CI 0.47–2.97, NNT = 125) (Fig. 4). At 1 month, the incidence of major bleeding events reported for the ETP and CTP arms was very low: 0.3 % (3/933) and 0.3 % (2/671), respectively.[2,20,25]

All-Cause Mortality Overall mortality during the first 3 months after surgery was similar in both groups [ETP 4.2 % (30/720) vs. CTP 3.6 % (23/643); RR 0.79, 95 % CI 0.47–1.33, NNT = 167] (electronic supplementary Fig. 3). During the first month, the RCTs reported a total mortality of 1 % (6/613) in the ETP group versus 0.5 % (3/601) in the CTP group, with all these fatal events occurring in only one of the studies.[2] Causes of death were available in two of the RCTs.[20,25] Only one fatal PE was reported in these studies. Major bleeding was not reported as being the cause of any death in the three RCTs.[2,20,25]

Sensitivity Analysis None of the outcomes differed if observational studies were analyzed separately from RCTs. A comparison between the RR of ETP versus CTP and between RCT analysis and observational study analysis is shown in electronic supplementary Table 2.

DISCUSSION

We performed a systematic review and meta-analysis to assess the efficacy and safety of ETP using LMWH after abdomen and pelvic cancer surgery. Compared with CTP, ETP was associated with a significant reduction in the incidence of all VTEs and pDVTs. No significant difference was observed in the incidence of PE but it should be noted that the rate of PE was very low in all studies. In addition, no difference in the risk of major bleeding events

TABLE 1 Characteristics of the included studies

Studies included	Design	Arms	Duration of TP	*N*	Median age (years)	Male sex (%)	Indication for TP		Prophylaxis treatment	Screening method used	Follow-up
							Type of surgery	Type of cancer			
Bergqvist et al.[20]	RCT	E	28 ± 3 days	253	65	62	Open	GI, GU, gyne	Enoxaparin	Veno	3 months
		C	8 ± 2 days	248	66	58					
Kakkar et al.[2]	RCT	E	28 ± 2 days	315	65	46	Open	GI, GU, gyne	Bemiparin	Veno	3 months
		C	8 ± 2 days	310	64	50					
Vedovati et al.[25]	RCT	E	29 ± 2 days	112	66	58	Lap	Colorectal	Enoxaparin or dalteparin	US	3 months
		C	7 ± 2 days	113	65	55					
Schmeler et al.[24]	OBS	E	~4 weeks	334	58	0	Open	Gyne	Enoxaparin	None	3 months
		C	<2 weeks	300	57	0					
Samama et al.[23]	OBS	E	>4 weeks	1169	NA	NA	Open or lap	GI, GU, gyne	LMWH, unspecified	None	9 ± 3 weeks
		C	~1 week	1168	NA	NA					
Ibrahim et al.[21]	OBS	E	~4 weeks	157	NA	0	Open	Gyne	Tinzaparin	None	3 months
		C	1–2 weeks	179	NA	0					
Kukreja et al.[22]	OBS	E	~28 days	107	NA	NA	Open or lap	GU	Enoxaparin or dalteparin	None	1 year
		C	~1 week	42	NA	NA					

RCT randomized controlled trial, *OBS* observational study, *E* extended duration thromboprophylaxis, *C* conventional thromboprophylaxis, *TP* thromboprophylaxis, *lap* laparoscopic, *GI* gastrointestinal, *GU* genitourinary, *gyne* gynecological, *LMWH* low-molecular-weight heparin, *veno* bilateral lower limb venogram, *US* bilateral lower limb compression ultrasound, *NA* not available

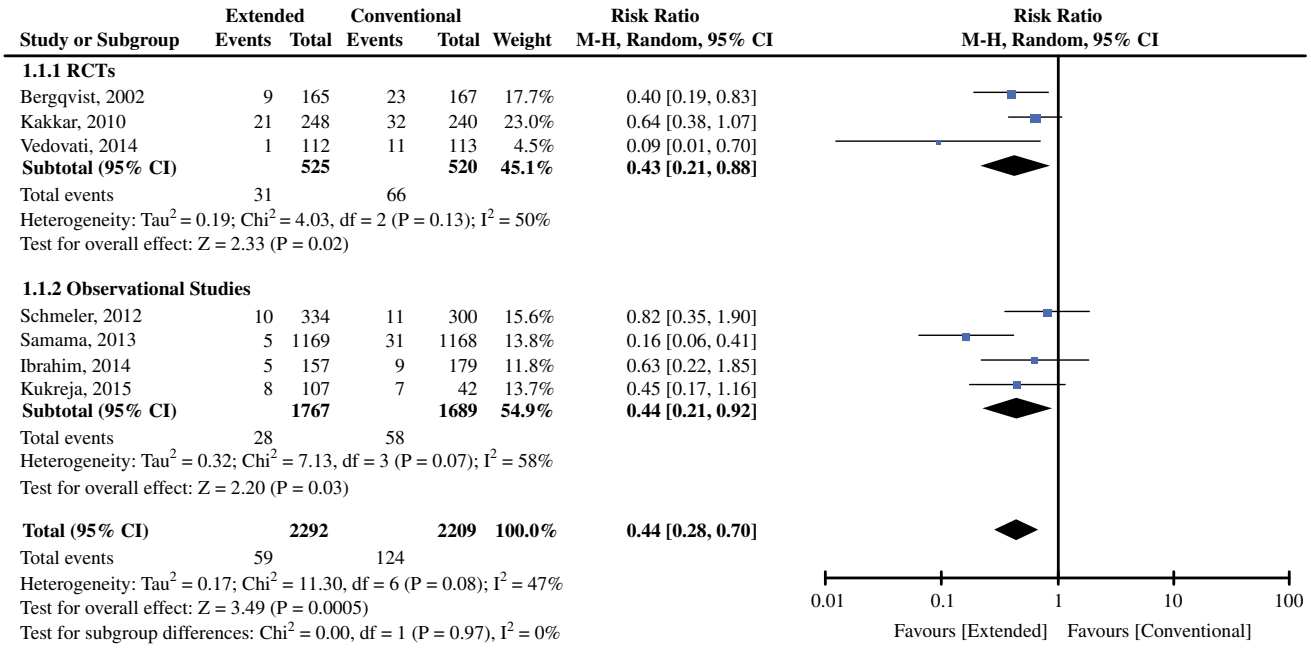

FIG. 2 Comparison of extended versus conventional thromboprophylaxis. Meta-analysis of all venous thromboembolic events. *M–H* Mantel–Haenszel, *CI* confidence interval, *RCTs* randomized controlled trials, *df* degrees of freedom

or 3-month all-cause mortality was noted. This suggests a favorable risk-to-benefit ratio for ETP in the prevention of postoperative VTE in this setting. Therefore, our data strongly support a wider implementation and utilization of ETP in the setting of abdominal and pelvic surgery for cancer patients.

It is important to note that the DVT endpoints of the included RCTs were driven by asymptomatic events detected by mandatory bilateral venography or compression ultrasonography. Very few events were symptomatic DVT: 3/30 and 3/11 in the studies by Bergqvist et al.,[20] and Vedovati et al.,[25] respectively, which are the only RCTs

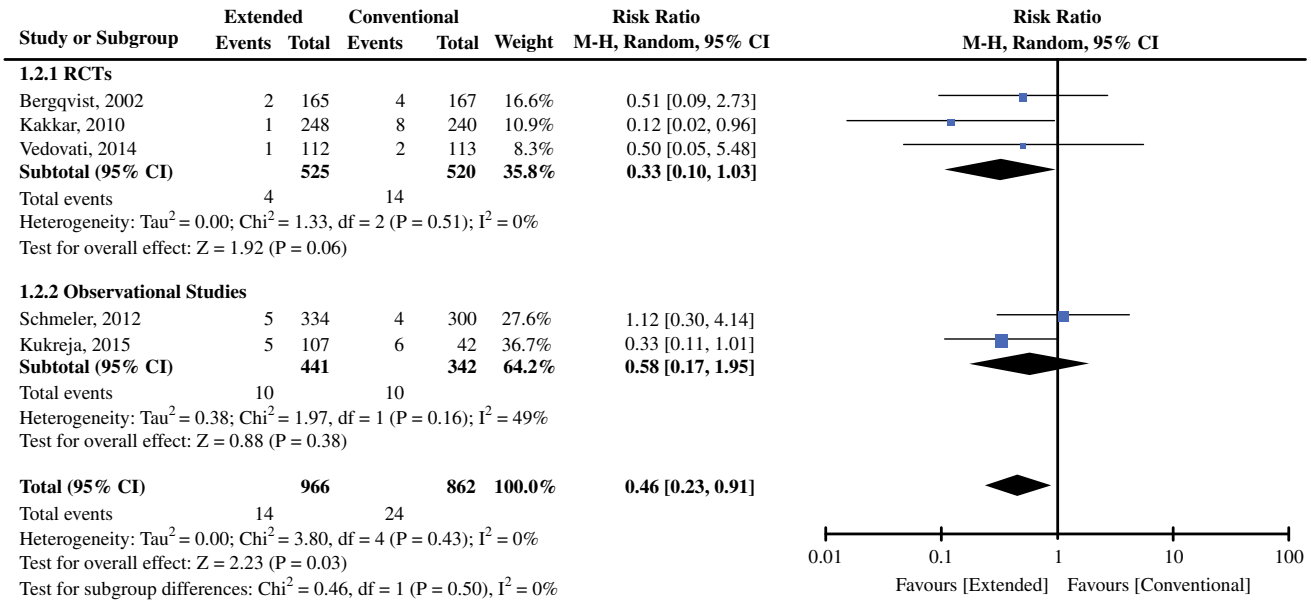

FIG. 3 Comparison of extended versus conventional thromboprophylaxis. Meta-analysis of the proximal deep venous thrombosis events. *M–H* Mantel–Haenszel, *CI* confidence interval, *RCTs* randomized controlled trials, *df* degrees of freedom

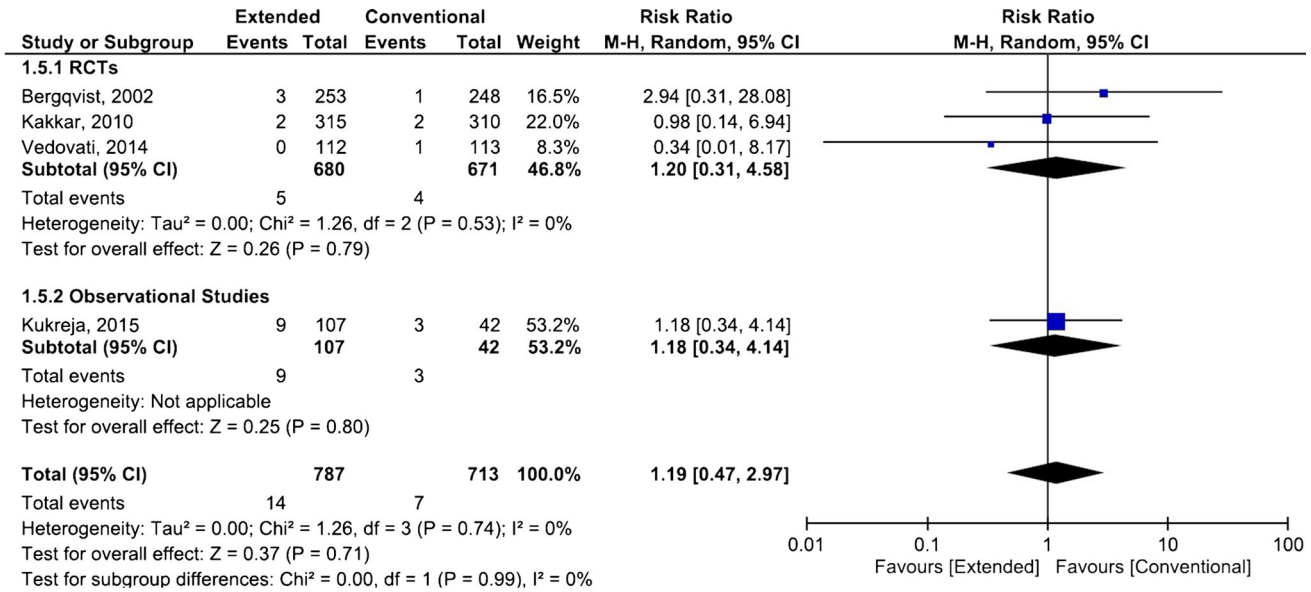

FIG. 4 Comparison of extended versus conventional thromboprophylaxis. Meta-analysis of major bleeding events. The definition of major bleeding varied slightly between the studies. In all studies, major bleeding included intracranial bleeding, clinically overt bleeding associated with a fall in hemoglobin level of 20 g/L or more, clinically overt bleeding leading to transfusion of two or more units of packed cells, and clinically overt bleeding warranting anticoagulant cessation and/or specific medical or surgical intervention to stop the bleeding. In addition, in a subset of studies the definition of major bleeding included intraocular bleeding,[20,25] retroperitoneal bleeding,[2,20,25] epidural hematoma,[22,25] and pericardial bleeding, bleeding in a non-operated joint, or intramuscular bleeding with compartment syndrome, assessed in consultation with the surgeon.[25] *M–H* Mantel–Haenszel, *CI* confidence interval, *RCTs* randomized controlled trials, *df* degrees of freedom

that reported the number of symptomatic events separately. In keeping with this, in the observational studies, where all DVT events were symptomatically diagnosed, the overall incidence of VTE was found to be much lower than that found in the RCTs (2.5 vs. 9.3 %, respectively). In addition, the total incidence of symptomatic DVT is lower in the studies using screening imaging tests [Bergqvist et al. 0.6 % (3/501) and Vedovati et al. 1.3 % (3/225)]. This is not unexpected as the proportion of patients on anticoagulation increases after positive screening tests.

Even though these two studies reported a very small number of symptomatic DVTs, ETP was associated with fewer cases of symptomatic DVT than CTP (one vs. two at 3 months, in each of these studies). Similarly, the first meta-analysis of extended versus conventional VTE prophylaxis in abdominopelvic surgery,[11] which included both cancer and non-cancer patients, reported a statistically significant reduction of symptomatic VTE in the extended arm. Three of four trials included in this review are not included in our study as they are not cancer-specific trials. Each individual trial had wide CIs that crossed the line of unity, but the overall meta-analysis favored ETP.[11]

The clinical significance of asymptomatic DVTs is debatable. On the one hand, screening for DVT is not employed in general clinical practice. Most events picked up on screening tests are dDVTs,[11] and only 25 % of untreated calf DVTs are expected to extend proximally.[27] This systematic review and meta-analysis also demonstrated no difference in PE or mortality between the CTP and ETP groups, which suggests that many of the asymptomatic DVT events are not clinically relevant. On the other hand, the postoperative state, particularly on the background of cancer, is highly thrombogenic. It is plausible that asymptomatic and/or distal DVT may have a larger potential to progress and embolize in these conditions compared with the general population. Other high VTE risk situations have previously been studied, including post major orthopedic surgery, where a correlation between venography results and the incidence of late symptomatic VTE was found,[28] and a reduction of asymptomatic DVT translated into a corresponding decrease of symptomatic DVT and post-thrombotic syndrome.[29,30] Additionally, a significant relationship was previously reported between the presence of asymptomatic DVT and 3-month mortality in medical patients.[31] Finally, large autopsy series have shown that fatal PE is seldom preceded by clinically recognized DVT.[32] Asymptomatic DVT and dDVT are part of the same spectrum of disease as symptomatic DVT, pDVT, and PE. It is unknown which characteristics of the patient, the cancer, the surgery, and the postoperative course, if any, would predict situations where asymptomatic and dDVT are more likely to progress. While overall bleeding rates were similar, anticoagulation can be associated with major bleeding, and finding an appropriate balance is important to more effectively select and target thromboprophylaxis strategies. Thrombotic potential in the postoperative setting can be decreased by additional strategies, including early ambulation, use of epidural rather than general anesthesia, when feasible, and opting for less invasive procedures requiring shorter length of in-hospital stay.

Current practice guidelines on thromboprophylaxis differ in the recommendations on cancer patients in the postoperative setting (electronic supplementary Table 3). In regard to the role of ETP, the European Society for Medical Oncology (ESMO)[33] guidelines recommend ETP for all patients undergoing major abdominal or pelvic surgery. In comparison, the ASCO[34] and National Comprehensive Cancer Network (NCCN)[35] guidelines each recommend extended VTE prophylaxis in this setting only for patients with high VTE risk features (electronic supplementary Table 3). The ACCP guidelines[12] also address the need for ETP after abdominal or pelvic surgery for cancer, but recommend both VTE and bleeding risk to be assessed before such strategy is implemented (electronic supplementary Table 3). Unfortunately there are no validated tools on assessing thrombotic or hemorrhagic risk in this setting. As such, practical application of these guidelines still pose a challenge.

Our systematic review and meta-analysis has limitations. First, only three RCTs were identified that compared the two thromboprophylaxis strategies. Second, there were insufficient data on specific cancer types and stages, and thus individualized recommendations cannot be derived from our data. Third, heterogeneity may have been introduced by having a mix of different types of surgeries as two studies allowed the inclusion of laparoscopic interventions and one excluded open surgeries altogether. Laparoscopic interventions are associated with activation of the coagulation cascade, but the faster recovery and shorter period of immobility might decrease the overall VTE risk for this patient subgroup and introduce some heterogeneity. Fourth, with the exception of two studies,[2,20] all other trials included in our analysis used an open-label design, which may introduce bias regarding physician clinical suspicion for VTE and patient symptom reporting. Last, the LMWH differed between studies and we cannot comment on whether one particular LMWH was more effective or safer than another.

The strengths of this study include the comprehensive search and the inclusion of all major prospective studies to date assessing ETP after major abdominal and pelvic cancer surgery. Outcomes between studies were reasonably similar and all VTEs were objectively diagnosed. Despite minor difference between studies, statistical heterogeneity was low.

CONCLUSIONS

Administration of LMWH for extended duration thromboprophylaxis after abdominal or pelvic surgery for cancer significantly reduces the incidence of VTE and pDVT, without increasing the risk of major bleeding. ETP should be routinely considered in the setting of abdominal and pelvic surgery for cancer patients. Tailoring the VTE prophylactic treatment to individual patient risk factors and

cancer characteristics remains very important for an optimal outcome.

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