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Extended thromboprophylaxis with low-molecular weight heparin (LMWH) following abdominopelvic cancer surgery

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ABSTRACT

Background: Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Certain abdominopelvic cancer surgeries are associated with a six to 14-fold increased risk of DVT versus surgeries for benign disease, and extended thromboprophylaxis using perioperative LMWHs may further reduce VTE rates over standard duration administration. This review assesses the value of extended low molecular weight heparin (LMWH) thromboprophylaxis as a recommended strategy after abdominopelvic cancer surgery.
Data sources: Six eligible randomized controlled trials (RCTs), seven meta-analyses (MAs), and five non-randomized cohort studies were identified evaluating extended versus standard thromboprophylaxis following abdominopelvic cancer surgery.
Findings and conclusions: Available evidence showed significantly reduced rates of VTE for extended versus standard LMWH thromboprophylaxis following abdominopelvic cancer surgery, with some studies showing trends toward reduced rates of symptomatic VTE events. Many of these studies showed significantly reduced rates of proximal DVT and some showed trends toward reduced PE, suggesting potentially important clinical benefits.

Introduction

Venous thromboembolism (VTE) is a global health care problem resulting in substantial mortality, morbidity, and increased cost of medical care. VTE includes deep vein thrombosis (DVT; asymptomatic or symptomatic, proximal or distal) and pulmonary embolism (PE), a complication of potentially life-threatening consequence. The yearly age adjusted annual incidence rate of VTE is reported to be from 110 among women and 130 for men per 100,000, representing the third most common circulatory disorder in the West,[1] with reported incidence rates of DVT alone (without PE) and PE (with or without DVT) ranging from 45 to 117 and 29 to 78 per 100,000 person years, respectively.[1,2]

Risk factors for VTE include venous stasis, vascular injury, and the induction of hypercoagulable states (Virchow's triad), and patients undergoing major abdominopelvic surgery are exposed to all

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three of these factors.[3] VTE events are 10–100 times more frequent in surgical than medical inpatients,[4] with asymptomatic DVT rates associated with major abdominopelvic surgery reported to be 15%–40% and fatal PE rates of 0.2%–0.9% in the absence of VTE prophylaxis.[1,5–8] Cancer is also associated with a hypercoagulable state leading to increased VTE risk,[9] and the risk of VTE in patients with cancer has been reported to be seven-fold higher than in individuals without malignancy, which can contribute to increased mortality and interfere with cancer therapy.[10,11] Studies have also shown a significant nearly six and 14-fold increased risk of DVT and PE, respectively, in patients receiving gynecologic surgery for cancer compared with those undergoing similar surgeries for benign disease.[12,13] The Caprini score sums individual VTE risk factors for patients undergoing surgery and is one of the most commonly used metrics for defining higher risk patients (score ≥5), which include those ≥41 years old undergoing surgery for either cancer (score ≥5) or for benign disease with additional risk factors (score ≥3).[14] Given the increased VTE risk in these patients, particularly for those undergoing abdominopelvic cancer surgeries, optimal thromboprophylaxis is a subject of great clinical concern.

Standard medical thromboprophylaxis typically consists of unfractionated heparin or low molecular weight heparins (LMWHs) administered during the post-operative period for up to 10 days. This practice is common in patients undergoing abdominopelvic surgery who have VTE risk factors and are not at increased risk for major bleeding complications. VTE risk factors include longer duration of surgery[15] and an increased period of immobilization,[16] as well as increased age, and obesity, among others.[17–22] Standard thromboprophylaxis has been shown to significantly reduce rates of clinical VTE (71%), risk of DVT (72%), and clinical PE (75%) compared with no thromboprophylaxis.[6] Despite this, two major meta-analyses (MA), show residual VTE rates of 5.6% and 14.3% in patients following standard approaches[3,23] and there is some indication that a hypercoagulable state may persist for up to a month[24] with many VTE events (40%) occurring more than 21 days from surgery.[25] These data suggest the need for more prolonged prophylaxis.

Extended thromboprophylaxis is typically defined as LMWH use for up to one month following surgery. Evidence from MAs or randomized controlled trials (RCTs) demonstrating significantly improved outcomes for a new therapy compared with standard of care is usually required to support a change in clinical practice.[26] Although emerging evidence on extended thromboprophylaxis suggests that this approach is safe and can further reduce VTE rates,[3,11,23] this practice has not been widely adopted.[27] The purpose of this review is to assess the risks and benefits of extended LMWH thromboprophylaxis for reducing rates of VTE events following abdominopelvic cancer surgery.

Materials and methods

MAs, RCTs and prospective or retrospective cohort trials evaluating the efficacy and/or safety of extended thromboprophylaxis with LMWH for at least four weeks (28–30 days) compared with standard thromboprophylaxis (six to ten days) after abdominopelvic cancer surgery as the primary outcome/endpoint were reviewed. Pubmed, Medline, EMBASE, the Cochrane Central Register of Controlled Trials (all time to July 2017), in addition to the American Society of Hematology, the International and the North American Societies on Thrombosis and Haemostasis, and the Mediterranean League against Thrombosis conference databases (July 2015 to July 2017) were searched using the terms surgery, cancer, thromboprophylaxis and clinical study (or respective aliases) while following Cochrane Intervention Review methodological standards.[28] A supplemental bibliographic search of recent review articles and directed searches for updated reports of specific studies was also conducted to identify further published or unpublished studies. Studies were reviewed at abstract and full text levels for key eligibility criteria, and only clinical trials (no case reports) investigating extended thromboprophylaxis as outlined above were deemed eligible (Fig. 1; Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] Diagram). VTE was defined as a DVT (symptomatic or asymptomatic, proximal or distal) with or without a PE event, and data on rates of VTE, DVT and PE, as well as incidence of bleeding were extracted and summarized.

Results

Nine hundred and seven records yielded six RCTs, seven MAs, and five non-randomized cohort trials evaluating the efficacy and/or safety of extended compared with standard thromboprophylaxis using LMWH after abdominopelvic cancer surgery as the primary outcome/endpoint (PRISMA, Fig. 1). Vazquez et al. (2015) was excluded as the study focused on adherence to extended thromboprophylaxis following an educational initiative rather than efficacy.[29]

A total of six RCTs were identified, with primary end-points and screening methods summarized in Table 1. The primary end-point of most studies was VTE, defined as either asymptomatic or symptomatic DVT verified by venogram or ultrasonography or PE verified most commonly by ventilation/perfusion lung scintigraphy. Two open, blinded RCTs evaluated extended versus standard thromboprophylaxis in patients undergoing major abdominal and/or non-cardiac thoracic surgery for both cancer and benign disease.[30,31] Lausen et al. (1998) evaluated extended versus standard thromboprophylaxis with tinzaparin in 118 patients, 69% of which had cancer.[30] Overall, rates of VTE were not reported for this trial, although a non-significant reduction in late asymptomatic and symptomatic DVT rates were observed for extended versus standard thromboprophylaxis (5.2% vs. 10%, $P = 0.49$, Table 2). No proximal DVT or confirmed PE events were seen in either arm, and bleeding events were similar (2 vs. 3 events). However, this study had 67% follow-up and was terminated early due to lack of funding. The FAME trial by Rasmussen et al. (2006) assessed extended dalteparin in 343 patients (58% had cancer).[31] Significantly reduced rates of VTE seven to 28 days after surgery (7.3% vs. 16.3%, relative risk reduction [RRR] 55%, 95% confidence interval (CI) 15%–76%, $P = 0.012$), asymptomatic and symptomatic DVT (7.3% vs. 14.9%, $P = 0.027$), and proximal DVT (1.8% vs. 8.0%, $P = 0.009$) were seen for extended versus standard thromboprophylaxis, but not for distal DVT (5.5% vs. 7.4%, $P = 0.28$). Major bleeding events (1 vs. 4) were similar, and no deaths were reported in either arm. An unpublished double-blind RCT by Jorgensen et al., 2002 in 108 abdominal cancer surgery patients indicated a non-significant reduction in rates of asymptomatic and symptomatic DVT (8% vs. 23%, 95% CI -29% to 0) and proximal DVT (2% vs. 9%, 95% CI -16% to 2%) for extended (5 weeks) versus standard (1 week) tinzaparin32.

Three larger RCTs evaluated extended versus standard LMWH thromboprophylaxis following abdominopelvic surgery for cancer (Table 2).[33–35] The double-blind, placebo-controlled ENOXACAN II trial by Bergqvist et al. (2002) showed significant reductions in the primary endpoint of verified VTE rates between one to four weeks with extended versus standard enoxaparin in 332 patients (4.8% vs. 12.0%, $P = 0.02$), which persisted at three months (5.5% vs. 13.8%, $P = 0.01$).[33] Trends in reduced rates of proximal DVT at 1–4 weeks (0.6% vs. 1.8%) and at 3 months (1.2% vs. 2.4%) as well as rates of distal DVT at 1–4 weeks (4.2% vs. 10.2%) and at 3 months (4.2% vs. 10.2%) were also seen. Symptomatic DVT occurred in six patients (not broken down by arm), and there were no documented PEs at

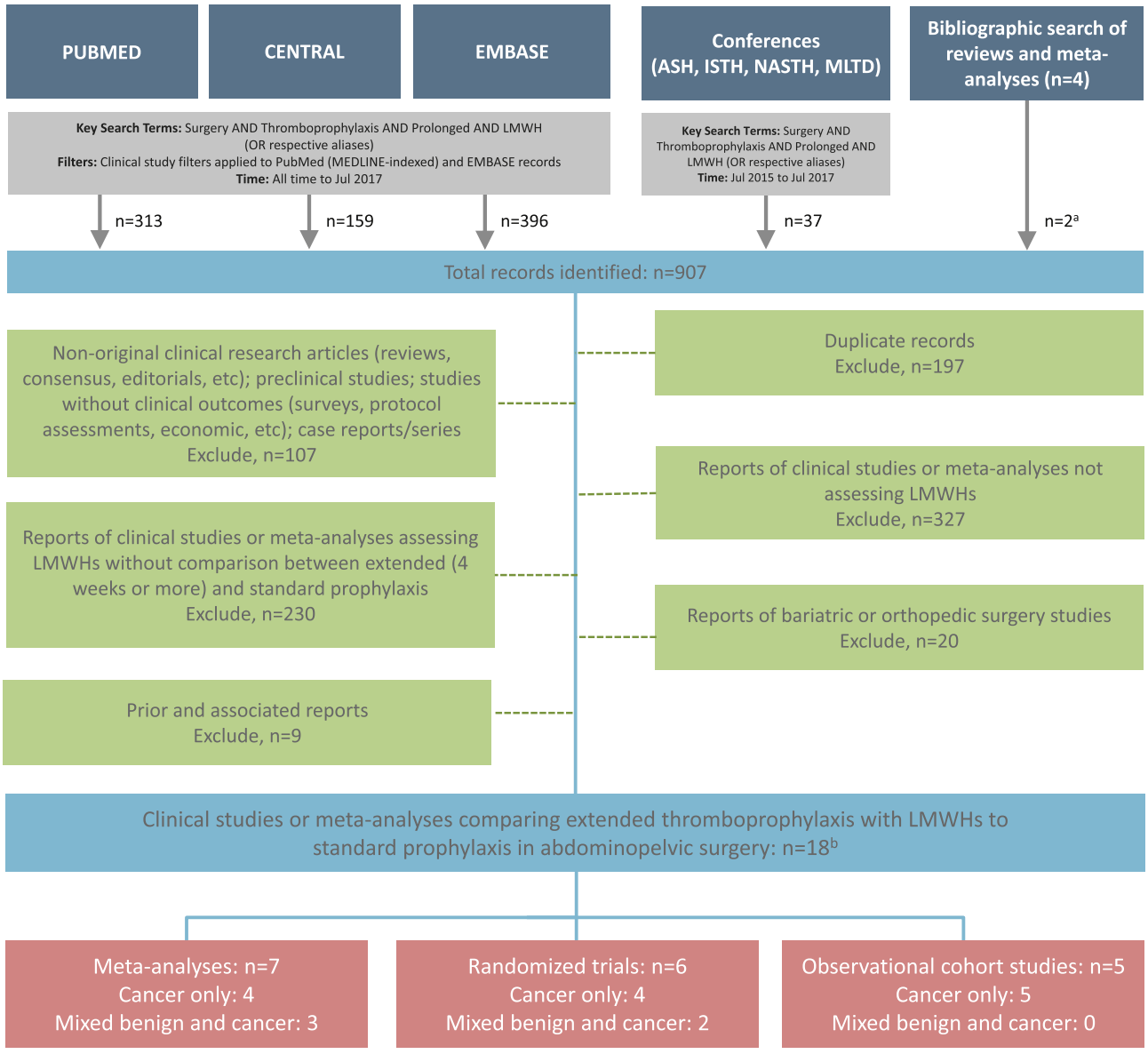

Fig. 1. PRISMA diagram. Publication and conference databases were searched, supplemented by a bibliographic search of recent review articles and directed searches for updated reports of specific studies. Studies were reviewed at abstract and full text levels for key eligibility criteria, and only clinical trials (no case reports) evaluating the efficacy and/or safety of extended thromboprophylaxis with LMWH for at least four weeks compared with standard thromboprophylaxis from six to ten days were deemed eligible. [a] Primary reports of eligible studies that were not identified through database. [b] Corresponding to a total of 17 reports since 2 studies were reported in a single conference abstract. Abbreviations: ASH, American Society of Hematology; ISTH, International Society on Thrombosis and Haemostasis; LMWH, Low molecular weight heparin; MLTD, Mediterranean League against Thrombotic Diseases; NASTH, North American Society on Thrombosis and Haemostasis.

any time point in the extended enoxaparin group as compared with one patient (0.6%) at one to four weeks and 2 patients (1.2%) at three months in the standard thromboprophylaxis arm. There were no significant differences in bleeding or other complications during the double-blind or follow-up periods. Nine patients died within three months after surgery, three in the extended enoxaparin group and six in the control group.

The double-blind, placebo-controlled CANBESURE trial by Kakkar et al. (2010) did not show significantly reduced rates in the primary endpoint of VTE or all-cause mortality at 4 weeks (double-blind period) among 488 abdominopelvic cancer surgery patients who received extended versus standard bemiparin (10.1% vs. 13.3%, $P = 0.26$),[34] although significantly reduced rates were seen when restricted to proximal DVT, symptomatic non-fatal PE and VTE-related deaths (major VTE, 0.8% vs. 4.6%, RRR 82.4%, 95% CI 21.5%–96.1%, $P = 0.01$). A trend toward reduced rates of asymptomatic and symptomatic DVT for extended versus standard bemiparin (7.7% vs. 12.1%, $P = 0.10$) became significant when restricted to proximal DVT (0.4% vs. 3.3%, RRR 87.9%, 95% CI 4.0%–98.5%, $P = 0.02$), but not distal DVT (7.3% vs. 8.8%, RRR 17.1%, 95% CI -51.8% to 54.7%, $P = 0.54$). Similar results were also observed for the double-blind plus follow-up periods (74–90 days after randomization). One symptomatic DVT occurred in each group, with none during the three month follow-up period, and no non-fatal PE events occurred. Among 625 patients in the safety analysis, bleeding events were low and similar between arms (0.3%–0.6%), as were deaths by any cause (2.4% vs. 1.3%).

The open, unblinded, randomized PRO-LAPS I trial by Vedovati et al. (2014) assessed extended versus standard thromboprophylaxis using multiple LMWHs in 225 patients receiving laparoscopic

Table 1
VTE end-points, and screening methods for randomized trials of extended LMWH thromboprophylaxis in abdominopelvic cancer surgery. VTE end-points and screening methods listed for randomized controlled trials assessing extended thromboprophylaxis with LMWH in abdominopelvic surgery for cancer ordered by size of trial.

Trial	Primary VTE End-point[a]	VTE Detection and Review Methods
Bergqvist et al. (2002) ENOXACAN II Double-blind, placebo-controlled	Asymptomatic and symptomatic DVT or PE	Confirmatory and scheduled imaging procedures • DVT verified by venograms • Symptomatic PE confirmed by ventilation–perfusion lung scanning or pulmonary angiography, or both • Venography between days 25 and 31 Imaging review • Evaluated by the venography reading committee (consisting of three radiologists)
Kakkar et al. (2010) CANBESURE NCT00219973 Double-blind, placebo-controlled	Asymptomatic and symptomatic DVT or non-fatal PE or death	Confirmatory and scheduled imaging procedures • Symptomatic DVT confirmed by unilateral venography or Doppler-ultrasound • Non-fatal PE was verified by perfusion/ventilation lung scintigraphy, pulmonary arteriography or spiral computed tomography • Bilateral ascending venography on day 18–22 Imaging review • Centrally evaluated by an independent committee of five experts on vascular radiology
Rasmussen et al. (2006) FAME Open-label, assessor-blinded	Asymptomatic and symptomatic DVT or PE	Confirmatory and scheduled imaging procedures • Symptomatic DVT confirmed by unilateral venography • Symptomatic PE verified by ventilation/perfusion lung scintigraphy • DVT or PE verified by autopsy • Bilateral venography on day 28 Imaging review • Individually evaluated, at a single center, by two blinded radiologists with a specific interest in venography
Vedovati et al. (2014) PROLAPS I NCT01589146 Unblinded, open	Asymptomatic and symptomatic DVT or PE	Confirmatory and scheduled imaging procedures • Objective testing was required whenever VTE was suspected • Symptomatic PE verified by computed tomography or pulmonary angiography or ventilation/perfusion lung scanning • Complete compression ultrasonography of the lower limbs on day 28 ± 2 after surgery Imaging review • Study outcome events were locally adjudicated by a blinded study investigator
Lausen et al., 1998 Open-label, assessor-blinded	Asymptomatic and symptomatic DVT	Confirmatory and scheduled imaging procedures • Symptomatic DVT verified by ascending venogram • PE diagnosed by combined perfusion/ventilation lung scintigraphy[b] • Bilateral venography on day 28 Imaging review • All venograms were evaluated by two blinded radiologists with a specific interest in angiology and DVT
Jorgensen et al. (2002) Study B, unpublished Double-blind, placebo-controlled	Asymptomatic and symptomatic DVT	Confirmatory and scheduled imaging procedures • Confirmatory imaging procedures not reported • Bilateral venography performed after 28–35 days Imaging review • Imaging review protocol not reported

DVT, deep vein thrombosis; LMWH, low molecular weight heparins; PE, pulmonary embolism; VTE, venous thromboembolic event.
[a] The authors report that: "pulmonary embolism was suspected in two, but not verified in any of our patients".

surgery for colorectal cancer; 84 patients (37%) received enoxaparin, 41 (18%) received dalteparin, and 100 (45%) received nadroparin35. Extended LMWHs showed significantly reduced rates in the primary endpoint of VTE at four weeks (0% vs. 9.7%, $P = 0.001$) and at three months (0.9% vs. 9.7%, $P = 0.005$). Trends for reduced rates of symptomatic or proximal DVT at four weeks (0% vs. 1.8%) and three months (0.9% vs. 1.8%) were also seen for extended thromboprophylaxis. At four weeks and three months, no PE events occurred and rates of bleeding and death were low and similar between arms (from 0% to 0.9%).

Seven MAs assessed extended versus standard thromboprophylaxis in patients undergoing abdominopelvic surgery (Table 3).[3,11,23,32,36–38] Rasmussen et al. (2009) assessed extended thromboprophylaxis using a variety of LMWHs in 901 patients receiving major abdominopelvic surgery for malignant (80%) and benign (20%) disease.[23] This MA included both of the major RCTs available at the time: FAME (Rasmussen et al.[31]), ENOXACAN II (Bergqvist et al.[33]) as well as two smaller RCTs, Lausen et al.,[30] and Jorgensen et al.[32] Accepted imaging techniques for diagnoses were required, and no significant heterogeneity between the included trials was detected. Analysis of the pooled RCT data in 901 patients showed significantly reduced rates in the co-primary outcome of VTE (6.1% vs. 14.3%, Peto odds ratio [OR] 0.41, 95% CI 0.26 to 0.63, $P < 0.0005$, number needed to treat (NNT) = 13; $I^2 = 0.0\%$), asymptomatic and symptomatic DVT (Peto OR 0.43, 95% CI 0.27 to 0.66, $P < 0.0005$, NNT = 14; $I^2 = 0.0\%$) proximal DVT (Peto OR 0.27, 95% CI 0.13 to 0.57, $P < 0.001$; NNT = 26; $I^2 = 0.0\%$) and symptomatic VTE (Peto OR 0.22, 95% CI 0.06 to 0.80, $P = 0.022$, NNT = 66; $I^2 = 0.0\%$) with extended versus standard thromboprophylaxis.[23] No difference in rates of bleeding (both major and minor) among 1242 patients (4.1% vs. 3.7%, Peto OR 1.11, 95% CI 0.62 to 1.97, $P = 0.73$, NNH = 250; $I^2 = 0.0\%$) or death rates within 3 months (co-primary outcome) among 1021 patients (5.8% vs. 5.35%, Peto OR 1.12, 95% CI 0.65 to 1.93, $P = 0.68$, NNH = 250; $I^2 = 13\%$) were observed with extended versus standard thromboprophylaxis.

Fagarasanu et al. (2016), a more recent and larger MA, included the two most recent RCTs (CANBESURE, Kakkar et al.[34] and PROLAPS I, Vedovati et al.[35]), as well as the ENOXACAN II RCT[33] and four observational studies (Schmeler et al. 2013[39]; Samama et al. 2014[40]; Ibrahim et al. 2014[41] and Kukreja et al. 2015[42]).[3] A total of 4807 patients were included in the analysis. Objective VTE diagnoses using accepted imaging techniques were required, and heterogeneity was low reflecting minor differences between studies. Among all studies, significantly reduced rates of VTE were seen with extended versus standard thromboprophylaxis (2.6% vs. 5.6%, risk ratio [RR] 0.44, 95% CI 0.28 to 0.70, $P = 0.0005$, NNT = 39;

Table 2
Randomized controlled trials assessing efficacy and safety of extended thromboprophylaxis with LMWH in abdominopelvic surgery for cancer. Studies are ordered by patient numbers included in the trials.

Trial	Type of surgery	Risk Class Risk Factors	Regimen(s)	n	VTE (%) [95% CI]	DVT (%) [95% CI]	PE (%) [95% CI]	Bleeding Events (n)	Treatment-related deaths (n)
Bergqvist et al. (2002) ENOXACAN II Double-blind, placebo-controlled	Elective, open surgery for abdominopelvic cancer	NA Surgery for cancer	Extended thromboprophylaxis40 mg of En once daily for 6–10 days (open label) followed by En for 19–21 days	253	n = 165 VTE @ 1–4 wk[a,b]: 4.8% RRR 60% [10% −82%] (P = 0.02) VTE 3 mo: 5.5% (P = 0.01)	n = 165 Proximal DVT @ 1 −4 wk: 0.6% Proximal DVT @ 3 mo: 1.2% Distal DVT @ 1–4 wk: 4.2% Distal DVT @ 3 mo: 4.2%	n = 165 PE @ 1 −4 wk: 0% PE @ 3 mo: 0%	Major@ 1–4 wk: 1 (P > 0.99) Minor@ 1–4 wk: 12 (P = 0.66) Total @ 1–4 wk[a]: 13 (P = 0.51) Major@ 3 mo: 3 (P = 0.62) Minor@ 3 mo: 12 (P = 0.66) Total @ 3 mo: 18 (P = 0.20)	@ 1–4 wk: 0 @ 3 mo: 0
			Standard thromboprophylaxis 40 mg of En once daily for 6–10 days (open label) followed by placebo once daily for 19–21 days	248	n = 167 VTE @ 1–4 wk[a,b]: 12% VTE 3 mo[a]: 13.8%	n = 167 Proximal DVT @ 1 −4 wk: 1.8% Proximal DVT @ 3 mo: 2.4% Distal DVT @ 1–4 wk: 10.2% Distal DVT @ 3 mo: 10.2%	n = 167 PE @ 1 −4 wk: 0.6% PE @ 3 mo: 1.2%	Major@ 1–4 wk: 0 Minor@ 1–4 wk: 9 Total @ 1–4 wk: 9 Major@ 3 mo: 1 Minor@ 3 mo: 9 Total @ 3 mo: 11	@ 1–4 wk: 0 @ 3 mo: 1
Kakkar et al. (2010) CANBESURE NCT00219973 Double-blind, placebo-controlled	Abdominopelvic surgery for cancer	NA Surgery for cancer	Extended thromboprophylaxis once daily sc injections of Bm 3500 IU (0.2 mL) for 28 ± 2 days, the first dose starting 6 h after surgical wound closure	248	VTE + Death @ 4 wk[a,c]: 10.1% RRR 24.4% [-23.7% −53.8%] (P = 0.26)	Any DVT @ 4 wk: 7.7% RRR 36.6 [-10.0% −63.4%] (P = 0.10) Proximal DVT @ 4 wk: 0.4% RRR 87.9 [4.0% −98.5%] (P = 0.02) Distal DVT @ 4 wk: 7.3 RRR 17.1 [-51.8% −54.7%] (P = 0.54)	Non-fatal PE @ 4 wk: 0%	Major@ 4 wk[a]: 2 Minor@ 4 wk: 1	0
			Standard thromboprophylaxis once daily sc injections of Bm 3500 IU (0.2 mL) for 8 ± 2 days, the first dose starting 6 h after surgical wound closure followed by Placebo for 20 ± 2 additional days	240	VTE + Death @ 4 wk[a,c]: 13.3%	Any DVT @ 4 wk: 12.1% Proximal DVT @ 4 wk: 3.3% Distal DVT @ 4 wk: 8.8%	Non-fatal PE @ 4 wk: 0%	Major@ 4 wk[a]: 1 Minor@ 4 wk: 1	0
Rasmussen et al. (2006) FAME Open-label, assessor-blinded	Major abdominal surgery	NA	Extended thromboprophylaxis once-daily sc Dl, 5000 IU, and graduated compression stockings for 7 days followed by Dl for a further 21 days	165	VTE @ 1–4 wk[a]: 7.3% RRR 55% [15% −76%] (P = 0.012) Symptomatic VTE: 0	Any DVT @ 1–4 wk: 7.3% RRR 51% [6% −74%] (P = 0.027) Proximal DVT @ 1 −4 wk: 1.8% RRR 77% [22%–93%] (P = 0.009) Distal DVT @ 1–4 wk: 5.5% RRR 25% [-30% −67%] (P = 0.28)	NR	Major@ 1–4 wk[a]: 1 Minor@ 1–4 wk[a]: 3	0
			Standard thromboprophylaxis with once-daily sc Dl, 5000 IU, and graduated compression stockings for 7 days	178	VTE @ 1–4 wk[a]: 16.3% Symptomatic VTE: 1.7%	Any DVT @ 1–4 wk: 14.9% Proximal DVT @ 1 −4 wk: 8.0%	NR	Major@ 1–4 wk[a]: 4 Minor@ 1–4 wk[a]: 2	0

(*continued on next page*)

Table 2 (*continued*)

Trial	Type of surgery	Risk Class Risk Factors	Regimen(s)	n	VTE (%) [95% CI]	DVT (%) [95% CI]	PE (%) [95% CI]	Bleeding Events (n)	Treatment-related deaths (n)
						Distal DVT @ 1–4 wk: 7.4%			
Vedovati et al. (2014) PRO-LAPS I NCT01589146 Unblinded, open	Laparoscopic surgery for colorectal cancer	NA Surgery for cancer	Extended thromboprophylaxis with LMWH for 28 ± 2 days starting on the evening before surgery	112	VTE @ 4 wk[a]: 0% [0%–3.3%] (P = 0.001) VTE @ 3 mo: 0.9% [0.2%–4.9%] (P = 0.005)	Symptomatic or Proximal DVT @ 4 wk: 0% Symptomatic or Proximal DVT @ 3 mo: 0.9%	@ 4 wk: 0 @ 3 mo: 0	Major@ 4 wk[a]: 1 Major@ 3 mo: 1	@ 4 wk: 0 @ 3 mo: 0
			Standard thromboprophylaxis with LMWH for 8 ± 2 days starting on the evening before surgery	113	VTE @ 4 wk[a]: 9.7% [5.5%–16.6%] VTE @ 3 mo: 9.7% [5.5%–16.6%]	Symptomatic or Proximal @ 4 wk: 1.8% Symptomatic or Proximal @ 3 mo: 1.8%	@ 4 wk: 0 @ 3 mo: 0	Major@ 4 wk[a]: 1 Major@ 3 mo: 1	@ 4 wk: 0 @ 3 mo: 0
Lausen et al., 1998 Open-label, assessor-blinded	Major abdominal or non-cardiac thoracic surgery	NA	Extended thromboprophylaxis with Tz 3500 IU sc once daily, and the wearing of thigh-length graded compression stockings during the first 7 days followed by 3 weeks of Tz	58	NR	Any DVT @ 4 wk[a]: 5.2% [1%–14%] (P = 0.49) Proximal DVT@ 4 wk: 0%	NR	2	NR
			Standard thromboprophylaxis with Tz 3500 IU sc once daily, and the wearing of thigh-length graded compression stockings during the first 7 days	60	NR	Any DVT @ 4 wk[a]: 10% [4%–21%] Proximal DVT@ 4 wk: 0%	NR	3	NR
Jorgensen et al. (2002) Study B, unpublished Double-blind, placebo-controlled	Surgery for abdominal malignancy	NA Surgery for cancer	Extended thromboprophylaxis with Tz during hospitalization followed by Tz for additional 28 days	NR	NR	Any DVT: 8% Delta = −15% [-29% −0%] (P = NS) Proximal DVT: 2% Delta = −7% [-16% −2%] (P = NS)	NR	NR	NR
			Standard thromboprophylaxis with Tz during hospitalization followed by placebo	NR	NR	Any DVT: 23% Proximal DVT: 9%	NR	NR	NR

Bm, bemiparin; CI, confidence interval; Dl, dalteparin; DVT, deep vein thrombosis; En, enoxaparin; h, hours; IU, international units; LMWH, low molecular weight heparin; mo, months; n, number; NA, not applicable; NR, not reported; NS, not significant; PE, pulmonary embolism; RRR, relative risk reduction; sc, sub-cutaneous; Tz, tinzaparin; VTE, venous thromboembolic event; wk, weeks.

[a] Primary endpoint, efficacy or safety.

[b] All patients received En for 6–10 days, and venography screening was performed between days 25 and 31 or sooner if symptoms of venous thromboembolism occurred.

[c] Venography screening was performed on day 18–22, 2 days before the last injection.

Table 3
Meta-analyses assessing efficacy and safety of extended thromboprophylaxis with LMWH in abdominopelvic surgery for cancer. Studies are ordered by total patient numbers when available or by number of trials included in the analysis otherwise.

Study	Type of surgery	Risk Class Risk Factors	Regimen(s)	n	VTE (%) [95% CI]	DVT (%) [95% CI]	PE (%) [95% CI]	Bleeding Events (n)	Treatment-related deaths (n)
Fagarasanu et al. (2016) MA of randomized and non-randomized, prospective controlled clinical trials	Abdominopelvic cancer surgery	NA Surgery for cancer	Extended thromboprophylaxis with LMWH for approximately 4 wk	4807 RCTs, n = 3 Obs, n = 4	n = 2292 VTE: 2.6% RR 0.44 [0.28–0.70] (P = 0.0005)	n = 966 Proximal DVT: 1.4% RR 0.46 [0.23–0.91] (P = 0.03) n = 413 Distal DVT: 6.0% RR 0.63 [0.32–1.22] (P = 0.17)	n = 966 PE: 0.8% RR 0.56 [0.23–1.40] (P = 0.22)	n = 787 Major @ 3 mo: 14 (P = 0.71) n = 933 Major @ 1 mo: 3	n = 720 All-cause @ 3 mo: 4.2% RR 0.79 [0.47–1.33] (P = 0.37)
			Standard thromboprophylaxis with LMWH for ≤2 wk		n = 2209 VTE: 5.6%	n = 862 Proximal DVT: 2.8% n = 407 Distal DVT: 9.3%	n = 862 PE: 1.3%	n = 713 Major @ 3 mo: 7 n = 671 Major @ 1 mo: 2	n = 643 All-cause @ 3 mo: 3.6%
Guo et al. (2017) MA of randomized clinical trials and prospective or observational studies	Abdominopelvic cancer surgery	NA Surgery for cancer	Extended thromboprophylaxis with LMWH for a period of 4 wk	2085 RCTs, n = 3 Obs, n = 3	NR	n = 979 Any DVT: 4.3% RR 0.57 [0.39–0.83] P = 0.003	n = 979 0.9% RR 0.66 [0.29–1.52] P = 0.33	n = 538 4.1% RR 1.48 [0.78–2.80] P = 0.23	n = NR VTE-related death: 1
			Standard thromboprophylaxis with LMWH for <2 wk	**Median Follow-up:** 3 mo	NR	n = 969 Any DVT: 7.1%	n = 969 1.3%	n = 627 All: 2.4%	n = NR
Bottaro et al. (2008) MA of randomized, controlled clinical trials	Major abdominopelvic surgery	NA Surgery for cancer in 70.6% of patients	Extended thromboprophylaxis with LMWH for 3–4 wk	1104 RCTs, n = 3	VTE: 5.93% RR 0.44 [0.28–0.7] (P = sig)	Any DVT: 5.93% RR 0.46 [0.29–0.74] (P = sig) Proximal DVT: 1% RR 0.24 [0.09–0.67] (P = sig)	NR	21 3.85% RR 1.12 [0.61–2.06] (P = NS)	NA
			Standard thronboprophylaxis with LMWH		VTE: 13.6%	Any DVT: 12.9% Proximal DVT: 4.72%	NR	19 3.48%	NA
Rasmussen et al. (2009) MA of randomized and non-randomized, controlled clinical trials	Abdominopelvic surgery for cancer or benign disease	NA	Extended thromboprophylaxis with LMWH for at least 1 mo	901 RCTs, n = 4	n = 446 VTE: 6.1% OR 0.41 [0.26–0.63] (P < 0.0005) Symptomatic VTE: 0.2% Peto OR 0.22 [0.06–0.80] (P = 0.02)	n = 446 Any DVT: 6.1% OR 0.43 [0.27–0.66] (P = 0.00013) Proximal DVT: 1.1% OR 0.27 [0.13–0.57] (P = 0.00066)	NR	n = 614 All: 25 4.1% OR 1.11 [0.62–1.97] (P = 0.73)	n = 498 All-cause: 29 5.8% OR 1.12 [0.65–1.93]
			Standard thromboprophylaxis with or without placebo		n = 455 VTE: 14.3% Symptomatic VTE: 1.7%	n = 455 Any DVT: 13.6% Proximal DVT: 5.1%	NR	n = 628 All: 23 3.7%	n = 523 All-cause: 28 5.4%
Akl et al. (2008) MA of randomized, controlled clinical trials	Abdominopelvic surgery for cancer	NA Surgery for cancer	Extended thromboprophylaxis with LMWH for up to 41 days Standard thromboprophylaxis with LMWH	NR RCTs, n = 3	NR	Any DVT @ 4 wk: RR = 0.21 [0.05–0.94] (P = sig)	NR	Major @ 4 wk: RR = 2.94 [0.12–71.85] (P = NS) Major @ 3 mo: RR = 2.94 [0.31–28.08] (P = NS) Minor @ 4 wk and 3 mo: RR = 1.31 [0.56–3.05] (P = NS)	All-cause @ 3 mo: RR = 0.49 [0.12–1.94] (P = NS) All-cause @ 12 mo: RR = 1.23 [0.70–2.15] (P = NS)

(*continued on next page*)

Table 3 (*continued*)

Study	Type of surgery	Risk Class Risk Factors	Regimen(s)	n	VTE (%) [95% CI]	DVT (%) [95% CI]	PE (%) [95% CI]	Bleeding Events (n)	Treatment-related deaths (n)
Rasmussen et al. (2003) MA of randomized controlled clinical trials	Major abdominal surgery for cancer	NA Surgery for cancer	Extended thromboprophylaxis with LMWH for 4 wk	219 RCTs, n = 2	NR	Any DVT: NR (P = 0.005) Proximal DVT: Peto OR 0.18 [0.06–0.53] (P = 0.002)	NR	NR	NR
			Standard thromboprophylaxis with LMWH for 1 wk	230 RCTs, n = 2				NR	NR
Jorgensen et al. (2002) Individual patient data MA of randomized, controlled clinical trials	Major general surgery or surgery for abdominal malignancy	NA	Extended thromboprophylaxis with Tz during hospitalization plus additional 28 days	NR RCTs, n = 2	NR	Any DVT: 7% OR 0.38 [0.16 –0.91] (P < 0.05) Proximal DVT: 1% OR 0.21 [0.05–0.96] (P < 0.05)	NR	NR P = NS	NR P = NS
			Standard Tz thromboprophylaxis during hospitalization with or without placebo for additional 28 days		NR	Any DVT: 15% Proximal DVT: 6%	NR	NA	NA

CI, confidence interval; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; MA, meta-analysis; mo, months; n, number; NA, not applicable; NR, not reported; NS, not significant; Obs, observational trials; (Peto) OR, (Peto et al.) odds ratio; PE, pulmonary embolism; RCTs, randomized clinical trials; RR, risk ratio; sig, significant; Tz, tinzaparin; VTE, venous thromboembolic event; wk, weeks.

$I^2 = 47\%$), with similar results when restricted only to RCTs (n = 1,045, RR 0.43, 95% CI 0.21 to 0.88, P = 0.02; $I^2 = 50\%$).[3] Among all RCTs and two observational studies,[39,42] the rate of proximal DVT was also significantly lower with extended versus standard thromboprophylaxis (1.4% vs. 2.8%, RR 0.46, 95% CI 0.23 to 0.91, P = 0.03, NNT = 71; $I^2 = 0.0\%$). Proximal DVT benefit was more pronounced although not quite significant when the analysis was restricted to RCTs (RR 0.33, 95% CI 0.10 to 1.03, P = 0.06; $I^2 = 0.0\%$). No significant differences in the rates of distal DVT (2 RCTs, RR 0.63, 95% CI 0.32 to 1.22, NNT = 30), symptomatic PE (all RCTs, 2 observational, 0.8% vs. 1.3%, RR 0.56, 95% CI 0.23 to 1.40, NNT = 200) or major bleeding (all RCTs, 1 observational, 1.8% vs. 1.0%; RR 1.19, 95% CI 0.47 to 2.97, NNH = 125; $I^2 = 0.0\%$ overall; RCTs only, RR 1.20, 95% CI 0.31 to 4.58; $I^2 = 0.0\%$) were observed for extended versus standard thromboprophylaxis.

Although methodologies varied, findings from five other published MAs evaluating extended versus standard thromboprophylaxis are outlined in Table 3. These MAs support findings from Rasmussen et al. [21] and Fagarasanu et al. [3], and all report significantly reduced rates of VTE and/or asymptomatic and symptomatic DVT,[11,32,36–38] with three showing significantly reduced rates of proximal DVT for extended versus standard thromboprophylaxis.[32,37,38] There were also no reported significant differences in the rates of bleeding or mortality.[11,36,37]

Three prospective observational studies[39,40,42] and two retrospective studies[41,43] were also identified (Table 4). Trends toward rates of VTE with extended thromboprophylaxis were seen in four studies[39,41–43] which were significant in two.[39,43] Another study showed that thromboprophylaxis duration (<4 weeks) significantly predicted VTE on multivariate analysis (RR 7.85, 95% CI 3.03 to 20.30, P < 0.0001).[40]

Discussion

Among the seven MAs and six RCTs,[3,11,23,30–38] many showed statistically significant reduced rates of VTE (asymptomatic and symptomatic) with extended compared with standard LMWH thromboprophylaxis following abdominopelvic cancer surgery.

Does extended thromboprophylaxis with LMWH reduce rates of VTE following abdominopelvic cancer surgery?

Four of six RCTs evaluated rates of VTE, defined as asymptomatic DVT, symptomatic DVT, or PE as their primary endpoint, and all four showed reduced rates of VTE for extended versus standard thromboprophylaxis (ENAXOCAN II, CANBESURE, FAME, and PRO-LAPS I).[31,33–35] Improvements were significant in three[31,33,35] and non-significant in one.[34] Authors suggest that lack of benefit in the latter may be due to limitations in study design,[44] underpowering of the study which included all-cause mortality in the primary end-point, or perhaps differences in agent effectiveness. Four of six RCTs reported rates of asymptomatic and symptomatic DVT rates, which was the primary outcome in two trials, All four showed trends toward reduced rates of DVT with extended compared with standard thromboprophylaxis,[30–32,34] and in one trial (FAME) this difference was statistically significant.[31] The other three (CANBESURE, Lausen et al. and Jorgenssen et al.) showed non-significant trends toward reduced rates of asymptomatic and symptomatic DVT,[30,32,34] although Lausen et al. and Jorgenssen et al. were likely too small to establish significance.[30,32]

Meta-analyses use statistical methods to combine results from multiple studies resulting in increased power and more accurate effect size estimates[45,46,47,48] Three of the seven MAs reporting VTE showed significantly reduced rates for extended versus standard thromboprophylaxis,[3,23,37] with little or no heterogeneity between trials. The largest MA by Fagarasanu et al.[3] analyzed three RCTs and included the most recent (CANBESURE and PRO-LAPS 1)[34,35] and Rasmussen et al., 2009 included the greatest number of RCTs.[4,23] Both showed similar effect sizes, with an RR of 0.44 reported in Fagarasanu et al.[3] and an RR of 0.45 in Rasmussen et al. (estimated from an OR of 0.41[49]). Statistical heterogeneity between studies assessing VTE included in these MAs was either low (Rasmussen et al. $I^2 = 0.0\%$) or moderate (Fagarasanu et al. $I^2 = 47\%$). It should be noted that the Rasmussen et al. MA was published prior to the most recent RCTs and included patients with benign disease.[23] The Fagarasanu et al. MA also focused only on cancer patients[3] and included the recent negative CANBESURE trial.[34] Six MAs reported DVT,[11,23,32,36–38] with all reporting significantly reduced rates of asymptomatic and symptomatic DVT for extended

Table 4
Prospective, observational or retrospective studies assessing efficacy and safety of extended thromboprophylaxis with LMWH in abdominopelvic surgery for cancer. Studies are ordered by study category then by patient numbers analyzed.

Trial	Type of surgery	Risk Class Risk Factors	Regimen(s)	n	VTE (%) [95% CI]	DVT (%) [95% CI]	PE (%) [95% CI]	Bleeding Events (n)	Treatment-related deaths (n)
Prospective, observational studies									
Samama et al. (2014) PRéOBS Real-world, prospective, observational study	Abdominopelvic surgery for cancer	NA Surgery for cancer	Extended thromboprophylaxis, consisting mainly of LMWH duration ≥4[4–6] wk	1366	VTE: NR RR 7.85 [3.03–20.30] (P < 0.0001)[a]	NR	NR	Fatal bleeding: 0.1% Bleeding in a critical organ: 0.3% Bleeding necessitating re-intervention: 1.7%	1.5%
			Standard thromboprophylaxis, consisting mainly of LMWH of duration <4 wk	1013	VTE: NR	NR	NR		
Schmeler et al. (2013) Prospective cohort study	Laparotomy for gynecologic cancer	NA Surgery for cancer	Extended thromboprophylaxis with En 40 mg sc every 24 h for a total of 28 days postoperatively	334	VTE within 30 days: 0.6% 78% reduction (P = 0.040) VTE within 90 days: 3.0% (P = 0.619) Median time between surgery and VTE diagnosis: 57 days (P = 0.012)	NR	NR	NR	1
Schmeler et al. (2013) Prospective cohort study	Laparotomy for gynecologic cancer	NA Surgery for cancer	Historic cohort of patients who underwent surgery prior to implementation of extended thromboprophylaxis protocol	300	VTE within 30 days: 2.7% VTE within 90 days: 3.7% Median time between surgery and VTE diagnosis: 12 days	NR	NR	NR	1
			Extended thromboprophylaxis with En 40 mg sc every 24 h for a total of 28 days postoperatively	334	VTE within 30 days: 0.6% 78% reduction (P = 0.040) VTE within 90 days: 3.0% (P = 0.619) Median time between surgery and VTE diagnosis: 57 days (P = 0.012)	NR	NR	NR	1
Kukreja et al. (2015) Prospective cohort study	Major surgery for urologic cancer	High Risk (Caprini) Surgery for cancer	Per protocol extended thromboprophylaxis	107	VTE: 7%	Any DVT: 5%	PE: 3%	Prophylaxis complications: 9 (8%)	All-cause: 18 (17%) Fatal PE: 0 (0%)
			Per protocol standard thromboprophylaxis	42	VTE: 17%	Any DVT: 14%	PE: 5%	Prophylaxis complications: 7 (17%)	All-cause: 10 (24%) Fatal PE: 1 (2%)
			Not per protocol extended thromboprophylaxis	83	VTE: 17%	Any DVT: 12%	PE: 7%	Prophylaxis complications: 6 (7%)	All-cause: 16 (19%) Fatal PE: 1 (1%)
			Not per protocol standard thromboprophylaxis	100	VTE: 21%	Any DVT: 15%	PE: 7%	Prophylaxis complications: 12 (12%)	All-cause: 22 (22%) Fatal PE: 2 (2%)
Retrospective studies									
Pariser et al. (2017) Retrospective institutional database review	Radical cystectomy for cancer	NA	En daily for extended thromboprophylaxis continued until 28 days after discharge	168	VTE: 5% (P = 0.024) Multivariate Analysis of VTE: OR 0.33 [0.14–0.76] (P = 0.009)[a]	NR	NR	NR	NR
			sc heparin before induction and then every 8 h until discharge home	234	VTE: 12%	NR	NR	NR	NR
Ibrahim et al. (2014) Retrospective institutional database review	Gynecologic cancer surgery	NA Surgery for cancer	Tz extended thromboprophylaxis for 4 wk post-surgery	157	VTE: 4.09% (P = NS)	NR	NR	NR	NR
			Tz standard thromboprophylaxis	179	VTE: 7.25%	NR	NR	NR	NR

CI, confidence interval; DVT, deep vein thrombosis; En, enoxaparin; LMWH, low molecular weight heparin; n, number; NA, not applicable; NR, not reported; NS, not significant; OR, odds ratio; PE, pulmonary embolism; RR, risk ratio; sc, sub-cutaneous; Tz, tinzaparin; VTE, venous thromboembolic event; wk, weeks.
[a] Result of multivariate analysis assessing risk factors associated with VTE.

thromboprophylaxis, and low trial heterogeneity for this endpoint reported by Rasmussen et al. ($I^2 = 0.0\%$). Data from observational trials also support these findings, suggesting reduced rates of VTE or DVT with extended thromboprophylaxis (Table 4).

Are reductions in rates of VTE/DVT clinically important?

Despite demonstrated reductions in rates of VTE and asymptomatic and symptomatic DVT with extended thromboprophylaxis,

Table 5
Major North-American, European and International guidelines on the use of extended thromboprophylaxis for abdominal and/or pelvic surgery.

Association/Group	Year	Type of Surgery	Patient Population(risk of VTE)	Extended prophylaxis (Yes/No) [duration]	Type of Prophylaxis	Strength of Recommendation (weak, medium, strong)
Oncologic surgery						
National Comprehensive Cancer Network (NCCN)	2017	Abdominopelvic surgery for cancer	High-risk (GI malignancy, previous history of VTE, anesthesia time greater than 2 h, bed rest >4 days, advanced-stage disease, >60 years)	Yes, 4 weeks post surgery	LMWH (Dl, En); Fondaparinux; UFH; Aspirin; Warfarin	medium (2A - uniform consensus based on lower level of evidence)
Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	2017	Laparoscopic for cancer	NR	Yes, 4 weeks post surgery	LMWH	weak
American Society of Clinical Oncology (ASCO)	2013	Cancer surgery	High-risk (Restricted mobility, obesity, history of VTE or with additional risk factors as listed in Table 3 [see source])	Yes, 4 weeks post surgery	LMWH	NA
Enhanced Recovery After Surgery Society (ERAS)	2016	Gynecologic/oncology surgery	NR	Yes, 4 weeks post surgery	NA	strong
	2013	Pancreaticoduodenectomy	NR	Yes, 4 weeks post surgery	LMWH	strong
	2013	Elective rectal/pelvic surgery	High-risk (colorectal cancer or other patients with increased risk of VTE)	Yes, 4 weeks post surgery	LMWH	strong
	2013	Colonic Surgery	High-risk (patients with cancer)	Yes, 4 weeks post surgery	LMWH	strong
	2013	Radical cystectomy for bladder cancer	NR	Yes, 4 weeks post surgery	LMWH	strong
	2012	Abdominopelvic surgery for cancer	High-risk (See Tables 5 and 6 at source)	Yes, 4 weeks post surgery	LMWH	strong(1B)
American College of Chest Physicians (ACCP)	2012	Abdominopelvic surgery for cancer	High-risk (See Tables 5 and 6 at source)	Yes, 4 weeks post surgery	LMWH	strong(1B)
American College of Obstetricians and Gynecologists (ACOG)	2007	Gynecologic surgery	Highest-risk (Major surgery in patients >60 years plus prior venous thromboembolism, cancer, or hypercoagulable state)	Yes, 4 weeks post surgery	LMWH	weak
National Institute for Health and Care Excellence (NICE)	2015	Abdominopelvic surgery for cancer	NR	Yes, 4 weeks post surgery	Pharmacological prophylaxis	NA
European Association of Urology (EAU)	2017	Urological cancer (Multiple procedures)	Medium-High (Also dependent on type of surgery)	Yes, 4 weeks post surgery	Pharmacological prophylaxis(LMWH; UFH - no sufficient data to warrant on-label use for post-surgery thromboprophylaxis.)	weak-strong
European Society for Medical Oncology (ESMO)	2011	Abdominopelvic surgery for cancer	NR	Yes, 4 weeks post surgery	LMWH	strong(1A)
International Initiative on Thrombosis and Cancer (ITAC-CME)	2017	Surgery for cancer	High-risk (See panel 4 at source for list of risk factors and risk prediction models)	Yes, 4 weeks post surgery	LMWH	strong(1B)
UpToDate (premier evidence-based clinical decision support and reference service)	2017	Abdominal and/or pelvic surgery for cancer	High-risk (General and abdominal-pelvic surgery with a Caprini score of 5 or more, or plastic and reconstructive surgery with a Caprini score of 7–8)	Yes 3–4 weeks (abdominal/ pelvic cancer surgery)	LMWH	weak (2A)
International Consensus Statement - Cardiovascular Disease Educational and Research Trust, European Venous Forum, North American Thrombosis Forum, International Union of Angiology and Union Internationale du Phlebologie	2013	Patients with cancer	High-risk	Yes, 4 weeks post surgery	LMWH	low
The Australia & New Zealand Working Party on the Management and Prevention of Venous Thromboembolism	2007	Curative surgery for cancer	NR	Yes, 4–5 weeks post surgery	Pharmacological prophylaxis	weak

Dl, dalteparin; DVT, deep vein thrombosis; En, enoxaparin; GI, gastrointestinal; LMWH, low molecular weight heparin; NA, not applicable; NR, not reported; UFH, unfractionated heparin; VTE, venous thromboembolic event.
Note: A search for relevant guidelines addressing the use of prolonged thromboprophylaxis with LMWH was also performed, using PubMed and a general web search engine using the keywords "Surgery AND Thromboprophylaxis AND Guideline OR respective ALIASES". This was complemented with a bibliographic search of five clinical reviews identified in the original database search.

Table 6
Level of support for extended LMWH thromboprophylaxis by site of cancer-specific surgery.

Surgical site(s)	MAs			RCTs		Prospective or retrospective cohort studies	Guidelines recommending extended thromborophylaxis
Abdominopelvic	Fagarasanu 2016 N = 4807	Guo 2017 n = 2085	Akl 2008 n = NR	Bergqvist 2002 n = 332	Kakkar2010 n = 488	Samama 2014 n = 2379	ASCO, ERAS, NCCN, ACCP, NICE, ESMO, UpToDate
Evidence	Overall VTE, Proximal DVT	Overall DVT	Overall DVT	Overall VTE	Proximal DVT	Overall VTE	
Abdominal	0			Vedovati 2014 n = 225		0	ASCO, ERAS, NCCN, ACCP, ESMO, UpToDate
Evidence	NA			Overall VTE		NA	
Pelvic	0			0		Pariser 2017 n = 402	ASCO, ERAS, NCCN, ACCP, ESMO, EAU, Aus/NZ Working Party
Evidence	NA			NA		Overall VTE	
Gynecologic Cancer	0			0		Schmeler 2013 n = 634	ACCP, ERAS, ACOG, International Consensus, Aus/NZ Consensus
Evidence	NA			NA		Overall VTE within 30 days	

ACCP, American College of Chest Physicians; ACOG, American College of Obstetricians and Gynecologists; Aus/NZ, Australia & New Zealand; DVT, deep vein thrombosis; EAU, European Association of Urology; ERAS, Enhanced Recovery after Surgery; ESMO, European Society for Medical Oncology; LMWH, low molecular weight heparin; MA, meta-analysis; n, number; NA, not applicable; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; NR, not reported; NS, not significant; RCTs, randomized clinical trials; VTE, venous thromboembolic event.
Note: Table lists studies showing a statistically significant benefit for use of extended LMWH thromboprophylaxis as well guidelines supporting use by type of cancer surgery. Studies are ordered by level of support/endorsement by type of surgery.

widespread adoption of this approach has been slow. This may due to a perceived lack of clinical importance of VTE as an endpoint, as many of these events are asymptomatic. We therefore also assessed more rare and relevant outcomes including symptomatic VTE (including symptomatic PE) and proximal DVT. Interestingly, symptomatic VTE was not assessed in most trials. However, both the Rasmussen et al. MA[23] and the FAME RCT[31] showed reduced rates of symptomatic VTE for extended versus standard thromboprophylaxis. FAME showed three cases of symptomatic VTE, all non-fatal PE, in the standard thromboprophylaxis group (1.7%) compared with none for extended thromboprophylaxis. Pooled outcomes from the Rasmussen et al. MA showed statistically significant reductions in symptomatic VTE with low heterogeneity between trial observations (Peto OR 0.22, $P = 0.022$, $I^2 = 0.0\%$), although specific symptomatic VTE events were not specified.[23] Numerical reductions in symptomatic DVT were also seen in two RCTs.[33,35]

All six RCTs, however, assessed rates of proximal DVT,[30–35] with significant benefit evident in two,[31,34] a trend favoring extended thromboprophylaxis in three,[32,33,35] and no proximal DVT events in either arm reported in one.[30] All five MAs assessing rates of proximal DVT showed significant reductions with extended thromboprophylaxis.[3,23,32,37,38] The degree of risk reduction for proximal DVT was greater in the Cochrane analysis by Rasmussen et al. compared with the Fagarasanu et al. MA (OR 0.27 vs. RR 0.46),[3,23] likely due to methodological differences. Three RCTs and two MAs evaluated PE as an endpoint.[33–35] A trend toward reduced rates of PE was seen in the largest RCT by Bergqvist et al.,[33] with no PE events reported in the other two RCTs.[34,35] Trends toward reduced PE were also seen with extended thromboprophylaxis in the two MAs, although rates across all arms were relatively low (0.8%–1.3%).[3,11] The number of patients needed to treat to detect one event, however, is much higher for the more rare clinically relevant events such as symptomatic VTE (NNT = 66, Rasmussen et al.) and PE (NNT = 200, Fagarasanu et al.) compared with VTE (NNT = 13 and 39 for Rasmussen et al. and Fagarasanu et al. respectively) or asymptomatic and symptomatic DVT (NNT = 14, Rasmussen et al.), making it more difficult to confirm benefit for these less frequent VTE events. Furthermore, although reduced rates of VTE and DVT appear clinically important, it should be noted that up to one third of patients in larger RCTs[31,33,34] were censored from these analyses, primarily due to venography noncompliance. As asymptomatic patients are more likely to be noncompliant, exclusion of these patients may have resulted in an over-representation of symptomatic patients, and study outcomes may therefore overestimate event rates compared to general clinical populations. However, asymptomatic VTE does not necessarily mean a benign course of disease and since regular screening was performed on compliant patients in these studies, symptomatic events may have also been prevented compared with the general population potentially offsetting this effect. Regardless of these unfortunate limitations in study design, data from a number of studies in higher risk cancer surgery patients who are not at higher risk for bleeding events showed significantly reduced rates of proximal DVT, with trends toward reduced rates of PE and symptomatic VTE with extended versus standard thromboprophylaxis, which was significant in one MA.[23] This approach is now recommended by major thromboprophylaxis guidelines for abdominopelvic cancer surgery (Table 5). New studies to confirm reduced rates of VTE with extended thromboprophylaxis in the context of improved surgical techniques and post-operative care are warranted.

Do the benefits for extended thromboprophylaxis extend to all abdominopelvic sites for cancer surgery?

Two RCTs[33,34] assessed extended thromboprophylaxis following general abdominopelvic cancer surgery involving the gastrointestinal tract (excluding esophagus), genitourinary tract, or gynecologic sites, showing significantly reduced rates of VTE in one[33] (Tables 2 and 6), numerically improved asymptomatic and symptomatic DVT rates,[33,34] and/or significantly improved rates of proximal DVT.[34] Two RCTs looked at abdominal-specific cancer surgery; one showed significantly reduced rates of VTE in patients receiving laparoscopic surgery for colorectal cancer,[35] and the other demonstrated approximate 3–4-fold non-significantly reduced rates of asymptomatic and symptomatic DVT and proximal DVT for extended versus standard thromboprophylaxis in patients receiving surgery for abdominal malignancies.[32] No RCTs focused specifically on pelvic-only surgery for cancer, although prospective and retrospective cohort studies showed reduced VTE events with extended versus standard thromboprophylaxis specifically in patients undergoing general urologic,[42] bladder-specific,[43] or gynecologic major cancer surgeries[39,41] (Table 4). Clinical benefit for extended thromboprophylaxis was assessed in a broad range of sites across multiple studies, and MAs indicated low to no heterogeneity among these studies,[3,11,23] suggesting that all abdominopelvic cancer surgery sites may benefit from extended thromboprophylaxis.

Do patients receiving laparoscopic abdominopelvic cancer surgery benefit from extended thromboprophylaxis?

Many laparoscopic cancer surgeries are of the same duration or longer than open surgery (more than 45 min) and patients undergoing these procedures are likely to have a similar VTE risk (Caprini score ≥5), suggesting a potential benefit for extended thromboprophylaxis in these patients. A single RCT (PRO-LAPS I) assessed benefits of this approach in 225 patients undergoing laparoscopic surgery for colorectal cancer, demonstrating significantly reduced rates of VTE at four weeks and three months.[35] Moreover, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guideline suggest use of extended thromboprophylaxis in higher risk patients receiving laparoscopic colorectal cancer surgery based on the outcomes of this study.[50] However, given the lack of comparative data demonstrating benefit in other abdominopelvic sites, with some case series indicating little or no benefit in patients undergoing minimally invasive laparoscopic procedures for gynecologic malignancies,[51–55] consideration of extended thromboprophylaxis should currently be limited to patients undergoing laparoscopic colorectal surgery for cancer.

What is the risk of bleeding or treatment-related deaths associated with extended versus standard thromboprophylaxis?

A primary concern assessed in most included RCTs and MAs is that extended thromboprophylaxis could increase major, clinically relevant non-major (CRNM), and/or minor bleeding events.[3,11,23,30–37] The International Society on Thrombosis and Haemostasis (ISTH) defines major bleeding as: bleeding leading to death, leading to reduced hemoglobin (≥2 g/dL) or requiring ≥2 units of blood, involving a critical area or organ such as retroperitoneal, intracranial, and/or intraocular, being serious or life threatening, requiring surgical/medical intervention to stop/control the hemorrhage, or if it is unexpected and prolonged and/or causes hemodynamic instability.[56] Although only established in 2005, the largest RCTs follow similar definitions,[31,33–35] with slight variations including clinically overt bleeding warranting treatment cessation.[34] No significant increases in major, minor, or CRNM bleeding, or treatment-related deaths were observed for extended thromboprophylaxis in any RCTs or MAs.[3,11,23,30–37] Available evidence therefore suggests that extended thromboprophylaxis using LMWHs is safe.

Does the length of surgery or duration of hospital stay affect outcomes?

Longer surgery defined as >45 min by the Caprini scale are at a substantial risk for VTE events.[14] As most cancer surgeries exceed this limit, they are generally considered higher risk. Shorter hospital stays on the other hand are generally associated with lowered VTE risk,[57,58] as they often involve reduced periods of immobilization. However, it is unclear whether this translates to reduced rates of VTE, as shorter stays may also involve shorter courses of standard thromboprophylaxis. As none of the eligible studies reported endpoints by length of surgery or hospital stay, it is unclear how these factors affect outcomes. As practice patterns evolve, individual risk profiles should be considered to optimize thromboprophylaxis duration for patients with shorter surgeries or hospital stays.

What are the relative benefits of individual LMWH agents?

Clinical practice guidelines generally consider LMWHs equally effective and safe in terms of management and standard thromboprophylaxis.[19,59] Levels of support for the extended use of specific LMWHs vary, however, with greater level of evidence for enoxaparin and dalteparin. The ENOXACAN II reported significantly reduced rates of VTE for enoxaparin, the FAME study reported significantly reduced rates of VTE/DVT and proximal DVT for dalteparin31, and the PRO-LAPS 1 trial showed benefit for both agents.[35] The level of evidence for bemiparin and tinzaparin is lower, although indication of benefit is apparent. Although the CANBESURE study did not show significantly reduced rates of VTE or DVT (asymptomatic and symptomatic) with bemiparin, significant improvements in proximal DVT rates were reported.[34] Two smaller trials failed to show benefit for tinzaparin30,32; however a pooled MA of these studies showed some benefit.[32] The National Comprehensive Cancer Network (NCCN) 2017 guidelines indicate a preference for dalteparin or enoxaparin based on the United States Food and Drug Administration approval, cost, ease of administration, monitoring, and ability to reverse anticoagulation.[60] Among the LMWH agents currently approved for use in Canada (enoxaparin, dalteparin, nadroparin and tinzaparin) the benefit of extended thromboprophylaxis likely applies to all agents.[61]

What are the barriers to adoption and how can compliance be improved?

Despite data from numerous randomized studies and MAs showing significantly reduced rates of VTE and DVT (asymptomatic and symptomatic) for extended LMWH prophylaxis, widespread adoption of this approach has been slow.[62] A number of barriers to adoption persist in many countries, including extra cost, a lack of access due to limited reimbursement, and challenges associated with coordinating parenteral administration after discharge from hospital. Ultimately these barriers may be secondary to a widespread perception that reduced of overall rates of VTE are not clinically relevant. In the setting of abdominopelvic surgery, however, thromboprophylaxis using at least standard duration LMWH is standard practice, and our assessment also shows significantly reduced rates of clinically relevant end-points such as proximal DVT[3,23,31,32,34,37,38] and symptomatic VTE[23] for extended versus standard LMWH thromboprophylaxis, in addition to trends toward reduced rates of symptomatic VTE or DVT[31,33,35] and PE.[3,11,33] Further research evaluating the benefits of extended prophylaxis on symptomatic events is warranted, in addition to efforts to identify and remove barriers to adoption at the patient, surgeon and industry level.[63–65]

Conclusions

Published and unpublished evidence indicates significantly reduced rates of VTE and of asymptomatic and symptomatic DVT, significant and clinically relevant reductions in the rates of proximal DVT, and trends toward reduced rates of symptomatic VTE and PE with no increased bleeding or treatment-related deaths for extended compared with standard LMWH thromboprophylaxis following abdominopelvic cancer surgery. Individual risk factors should guide thromboprophylactic duration in patients with lower risk features or shorter hospital stays.

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