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Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery (Review)

Felder S, Rasmussen MS, King R, Sklow B, Kwaan M, Madoff R, Jensen C

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[Intervention Review]

Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery

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ABSTRACT

Background

This an update of the review first published in 2009.

Major abdominal and pelvic surgery carries a high risk of venous thromboembolism (VTE). The efficacy of thromboprophylaxis with low molecular weight heparin (LMWH) administered during the in-hospital period is well-documented, but the optimal duration of prophylaxis after surgery remains controversial. Some studies suggest that patients undergoing major abdominopelvic surgery benefit from prolongation of the prophylaxis up to 28 days after surgery.

Objectives

To evaluate the efficacy and safety of prolonged thromboprophylaxis with LMWH for at least 14 days after abdominal or pelvic surgery compared with thromboprophylaxis administered during the in-hospital period only in preventing late onset VTE.

Search methods

We performed electronic searches on 28 October 2017 in the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, LILACS and registered trials (Clinicaltrials.gov October 28, 2017 and World Health Organization International Clinical Trials Registry Platform (ICTRP) 28 October 2017). Abstract books from major congresses addressing thromboembolism were handsearched from 1976 to 28 October 2017, as were reference lists from relevant studies.

Selection criteria

We assessed randomized controlled clinical trials (RCTs) comparing prolonged thromboprophylaxis (≥ fourteen days) with any LMWH agent to thromboprophylaxis during the admission period only followed by placebo or no thromoprophylaxis after discharge. The population consisted of persons undergoing abdominal or pelvic surgery for both benign and malignant pathology. The outcome measures included VTE (deep venous thrombosis (DVT) or pulmonary embolism (PE)) as assessed by objective means (venography, ultrasonography, pulmonary ventilation/perfusion scintigraphy, spiral computed tomography (CT) scan or autopsy). We excluded studies exclusively reporting on clinical diagnosis of VTE without objective confirmation.

Data collection and analysis

Review authors identified studies and extracted data. Outcomes were VTE (DVT or PE) assessed by objective means. Safety outcomes were defined as bleeding complications and mortality within three months after surgery. Sensitivity analyses were also performed with unpublished studies excluded, and with study participants limited to those undergoing solely open and not laparoscopic surgery. We used a fixed-effect model for analysis.

Main results

We identified seven RCTs (1728 participants) evaluating prolonged thromboprophylaxis with LMWH compared with in-hospital thromoprophylaxis followed by placebo or no thromboprophylaxis after discharge. The searches resulted in 1632 studies, of which we excluded 1528. One hundred and four abstracts, eligible for inclusion, were assessed of which seven studies met the inclusion criteria.

For the primary outcome, the incidence of overall VTE after major abdominal or pelvic surgery was 13.2% in the control group compared to 5.3% in the patients receiving out-of-hospital LMWH (Mantel Haentzel (M-H) odds ratio (OR) 0.38, 95% confidence interval (CI) 0.26 to 0.54; I^2 = 28%; moderate-quality evidence).

For the secondary outcome of all DVT, seven studies, n = 1728, showed prolonged thromboprophylaxis with LMWH to be associated with a statistically significant reduction in the incidence of all DVT (M-H OR 0.39, 95% CI 0.27 to 0.55; I^2 = 28%; moderate-quality evidence). We found a similar reduction when analysis was limited to incidence in proximal DVT (M-H OR 0.22, 95% CI 0.10 to 0.47; I^2 = 0%; moderate-quality evidence).

The incidence of symptomatic VTE was also reduced from 1.0% in the control group to 0.1% in patients receiving prolonged thromboprophylaxis, which approached significance (M-H OR 0.30, 95% CI 0.08 to 1.11; I^2 = 0%; moderate-quality evidence).

No difference in the incidence of bleeding between the control and LMWH group was found, 2.8% and 3.4%, respectively (M-H OR 1.10, 95% CI 0.67 to 1.81; I^2 = 0%; moderate-quality evidence).

No difference in mortality between the control and LMWH group was found, 3.8% and 3.9%, respectively (M-H OR 1.15, 95% CI 0.72 to 1.84; moderate-quality evidence).

Estimates of heterogeneity ranged between 0% and 28% depending on the analysis, suggesting low or unimportant heterogeneity.

Authors' conclusions

Prolonged thromboprophylaxis with LMWH significantly reduces the risk of VTE compared to thromboprophylaxis during hospital admittance only, without increasing bleeding complications or mortality after major abdominal or pelvic surgery. This finding also holds true for DVT alone, and for both proximal and symptomatic DVT. The quality of the evidence is moderate and provides moderate support for routine use of prolonged thromboprophylaxis. Given the low heterogeneity between studies and the consistent and moderate evidence of a decrease in risk for VTE, our findings suggest that additional studies may help refine the degree of risk reduction but would be unlikely to significantly influence these findings. This updated review provides additional evidence and supports the previous results reported in the 2009 review.

PLAIN LANGUAGE SUMMARY

Do blood thinner injections given after abdominal surgery further reduce blood clots if continued after discharge from the hospital?

Review question

For persons having surgery on the abdomen and pelvis, does continuing blood thinner injections after discharge from a hospital stay decrease the likelihood of developing a blood clot in the lower limbs or lungs when compared to usual treatment in the hospital?

Why is this important?

The complication of developing a blood clot can range from asymptomatic to potentially fatal, depending on the location and severity of the clot. After a postoperative patient is considered safe for discharge from the hospital, evidence suggests an ongoing risk for developing a blood clot in the weeks to months following the operation. Although recommended by some guidelines, not all physicians recommend discharging a postoperative patient home with a prolonged course of blood thinner injections.

What was found?

Seven studies were found that addressed this question, including a total of 1728 patients. Continuing blood thinning injections after hospital discharge decreased the risk of both blood clots in the limbs and in the lungs. This review determined that the overall incidence of having a blood clot is reduced from 13.2%, when no post-discharge blood thinner injections are used, to 5.3% when a blood thinner injection is prescribed for at least 14 days following discharge in 30 days follow-up. Both symptomatic and asymptomatic blood clots decreased with the use of prolonged duration blood thinner injections in postoperative patients. No increase in bleeding complications

or death, common concerns when blood thinners are used, were observed in patients treated with prolonged duration blood thinner injections.

What does this mean?

Continuation of blood thinning injections for at least 14 days after abdominal or pelvic surgery reduces the risk of blood clots.

Summary of findings for the main comparison.

Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery

Patient or population: patients undergoing abdominal or pelvic surgery

Settings: inpatient followed by outpatient, worldwide

Intervention: thromboprophylaxis with low molecular weight heparin for ≥ 14 days

Comparison: thromboprophylaxis during hospitalization only

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Risk with only in-hospital thromboprophylaxis	Risk with thromboprophylaxis ≥14 days			
All VTE Follow-up: 30 days postoperatively	**Study population**		**OR** 0.38, (0.26 to 0.54)	1728 (7 RCTs)	⊕⊕⊕⊖ **moderate**[1]
	132 per 1000	**50 per 1000** (34 to 71)			
All DVT Follow-up: 30 days postoperatively	**Study population**		**OR** 0.39, (0.27 to 0.55)	1728 (7 RCTs)	⊕⊕⊕⊖ **moderate**[1]
	129 per 1000	**50 per 1000** (35 to 71)			
Proximal DVT Follow-up: 30 days postoperatively	**Study population**		**OR** 0.22, (0.10 to 0.47)	1728 (7 RCTs)	⊕⊕⊕⊖ **moderate**[1]
	39 per 1000	**9 per 1000** (4 to 18)			
Symptomatic VTE Follow-up: 30 days postoperatively	**Study population**		**OR** 0,30, (0.08 to 1.11)	1728 (7 RCTs)	⊕⊕⊕⊖ **moderate**[1]
	10 per 1000	**3 per 1000** (1 to 11)			
Bleeding complications Follow-up: 3 months postoperatively	**Study population**		**OR** 1.10, (0.67 to 1.81)	2239 (7 RCTs)	⊕⊕⊕⊖ **moderate**[1]
	28 per 1000	**31 per 1000** (19 to 51)			

Mortality Follow-up: 3 months postoperatively	**Study population**		**OR** 1.15, (0.72 to 1.84)	1881 (7 RCTs)	⊕⊕⊕⊖ **moderate**[1]
	38 per 1000	**43 per 1000** (28 to 68)			

*The **corresponding risk** (and its 95% CI interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds Ratio; **RCT: r**andomized Controlled Trial; **VTE:** venous Thromboembolism; **DVT:** deep venous thrombosis

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level for serious risk of bias (includes at least one study with overall high risk of bias)

Summary of findings 2. Additional summary of findings

Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery

Patient or population: patients undergoing abdominal or pelvic surgery

Settings: inpatient followed by outpatient, worldwide

Intervention: thromboprophylaxis with low molecular weight heparin for ≥ 14 days

Comparison: thromboprophylaxis during hospitalization only

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Risk with only in-hospital thromboprophylaxis	**Risk with thromboprophylaxis ≥14 days**			
All VTE (subgroup analysis open only) Follow-up: 30 days postoperatively	**Study population**		**OR** 0.42, (0.29 to 0.60)	1503 (6 RCTs)	⊕⊕⊕⊖ **moderate**[1]
	138 per 1000	**58 per 1000** (40 to 83)			
All DVT (subgroup analysis open only) Follow-up: 30 days postoperatively	**Study population**		**OR** 0.43, (0.30 to 0.62)	1503 (6 RCTs)	⊕⊕⊕⊖ **moderate**[1]
	134 per 1000	**58 per 1000** (40 to 83)			

All VTE (sensitivity analysis unpublished) Follow-up: 30 days postoperatively	**Study population**		**OR** 0.38, (0.27 to 0.56)	1620 (6 RCTs)	⊕⊕⊕⊖ **moderate**[1]
	128 per 1000	**49 per 1000** (35 to 72)			
All DVT (sensitivity analysis unpublished) Follow-up: 30 days postoperatively	**Study population**		**OR** 0.40, (0.27 to 0.58)	1620 (6 RCTs)	⊕⊕⊕⊖ **moderate**[1]
	124 per 1000	**50 per 1000** (33 to 72)			

*The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds Ratio; **RCT:** randomized Controlled Trial; **VTE:** venous thromboembolism; **DVT:** deep venous thrombosis

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level for serious risk of bias (includes at least one study with overall high risk of bias)

BACKGROUND

Description of the condition

Patients undergoing major abdominal or pelvic surgery are at increased risk of developing postoperative venous thromboembolic (VTE) complications (Najjar 2016; Rasmussen 2009). The incidence of VTE following abdominal surgery in the absence of thromboprophylaxis has been reported to be between 19% to 29% in high-risk patients (Geerts 2001; Geerts 2004; Rasmussen 2009). For this reason, VTE thromboprophylaxis is routinely prescribed for postoperative patients, reducing the risk of VTE by up to 60% (Gross 2014).

Prospective studies have demonstrated the risk for post-discharge VTE remains elevated four to six weeks following surgery, with a cumulative incidence of VTE reaching up to 33.9% (Clarke-Pearson 1984; Merkow 2011; Scurr 1988; Sørensen 1990). Though a large proportion of VTE-related morbidity is attributable to postthrombotic syndrome, pulmonary hypertension, or recurrent thrombosis, VTE has been shown to be the most common cause of 30-day mortality following cancer surgery and increase overall mortality by six-fold (Agnelli 2006; Merkow 2011).

According to the Agency for Healthcare Research and Policy, VTE prevention for at-risk patients presents the most significant opportunity to improve patient safety in hospitals among 79 patient safety practices due to its efficacy, cost-effectiveness, and benefit-risk ratio (Bahl 2010). Despite randomized trial data and clear guideline recommendations supporting post-discharge extended-VTE thromboprophylaxis following abdominal and pelvic cancer surgery (Gould 2012; NCCN 2016), a national sample of Medicare beneficiaries reported only 1.5% of patients receiving and then filling a prescription for its use (Merkow 2011).

Description of the intervention

The increased risk of VTE has been definitively proven to extend beyond the inpatient stay, with up to one third of all VTE events occurring post-discharge (Gross 2014; Merkow 2011). Abdominal surgery creates a hypercoagulable state (Dahl 1995; Galster 2000; Iversen 2002; Rahr 1994), which has been well-measured by thromboelastography (TEG), a more sophisticated coagulation monitoring method that allows evaluation of all stages of the coagulation and fibrinolytic process (Akay 2009; Mahla 2001). A population-based, prospective study from the UK reported the risk of VTE to remain 10 to 50 times higher in weeks seven to 12 following inpatient surgery (Sweetland 2009). Thus, it would seem reasonable to consider extending VTE prophylaxis beyond the time when the patient is usually hospitalized, since the risk persists after hospital discharge.

How the intervention might work

The efficacy of extended duration thromboprophylaxis in patients undergoing major abdominal or pelvic surgery has been studied and supported by data, despite the apparent slow adoption into clinical practice. The Cochrane Review published in 2009 included four eligible studies and demonstrated a statistically significant reduction in the incidence of overall VTE after major abdominal or pelvic surgery in the control group (14.3%) as compared to patients receiving extended duration low molecular weight heparin (LMWH) (6.1%) ($P < 0.0005$) (Rasmussen 2009). Prolonged thromboprophylaxis with LMWH was also associated with a statistically significant reduction in the incidence of symptomatic VTE from 1.7% in the control group to 0.2% in the extended thromboprophylaxis group ($P = 0.02$). In addition, bleeding complications and mortality were not increased with prolonged thromboprophylaxis with LMWH.

Why it is important to do this review

This update is necessary because adoption of extended VTE prophylaxis has been slow, but research has actively continued on this topic. A reassessment of the current evidence may help spur increased adoption of extended VTE prophylaxis.

This update includes three more trials (Kakkar 2010; Sakon 2010; Vedovati 2014), increasing the number of included persons analyzed from 1242 to 1728.

OBJECTIVES

To evaluate the efficacy and safety of prolonged thromboprophylaxis with low molecular weight heparin (LMWH) for at least 14 days after abdominal or pelvic surgery compared with thromboprophylaxis administered during the in-hospital period only in preventing late onset venous thromboembolism (VTE).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized clinical trials (RCTs) comparing prolonged thromboprophylaxis interventions with solely in-hospital prophylaxis followed by placebo or no treatment were included. Objective, systematic assessment of VTE via diagnostic methods (venography, ultrasonography/doppler, ventilation/perfusion lung scintigraphy, computed tomography (CT) and/or autopsy) were mandatory for studies to be eligible for inclusion. Studies using only symptomatic diagnosis of VTE rather than confirmatory objective methods were excluded. Cluster trials were not considered.

Types of participants

Trials that included patients undergoing open or minimally invasive abdominal or pelvic surgery were included. Specific restrictions were not placed on the disease process for which surgery was being performed, so patients with both benign and malignant disease were included.

Types of interventions

Trials reporting the use of LMWH were considered (including varying dosages). Patients allocated to the intervention of prolonged thromboprophylaxis required administration of a LMWH for ≥ 14 days postoperatively to be eligible for study inclusion.

Similar to the initial review, unfractionated heparin, mechanical methods (graded compression stockings, sequential compression devices), and Vitamin K antagonists were excluded since these differing methods of VTE prophylaxis would make comparison difficult. In addition, oral anticoagulants such direct thrombin inhibitors or Factor Xa inhibitors were not considered in this review for the same reason.

Types of outcome measures

Primary outcomes

The primary outcome for the review was:

1. incidence of VTE within 30 days after surgery, including both symptomatic and asymptomatic VTE and PE (verified by objective methods: radiographic diagnosis/confirmation (duplex ultrasonography, CT angiography)).

Secondary outcomes

Secondary outcomes included:

1. incidence of all deep venous thrombosis (DVT);
2. incidence of proximal DVT (defined as thrombi located in and above the popliteal vein);
3. incidence of symptomatic VTE;
4. bleeding complications within three months of surgery, defined as major or minor bleeding according to the definition provided in the individual studies;
5. mortality within three months of surgery.

Search methods for identification of studies

Electronic searches

Electronic searches were conducted with assistance from a medical librarian and Information Specialist trained in performing systematic reviews.
Searches were conducted in the Cochrane Central Register of Controlled Trials (CENTRAL) 2017, issue 9, Embase from 1947, PubMed from 1967, and LILACS from 1967.

Details of the search strategy for each database are given in the Appendices:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 1);
2. Embase 1947 to October 2017 (Appendix 2);
3. PUBMED 1967 to October 2017 (Appendix 3);
4. LILACS 1967 to October 2017 (Appendix 4);
5. Registered Trials: Clinicaltrials.gov (Appendix 5);
6. Registered Trials: WHO ICTRP (Appendix 6).

Searching other resources

The bibliography of each trial report were checked for additional references. The abstract books of the congresses arranged by The International Society on Thrombosis and Haemostasis as well as The Mediterranean League against Thrombosis were handsearched back to 1976.

Data collection and analysis

Selection of studies

All identified reports from electronic and manual searches were reviewed independently by two review authors (SIF and RSK) for consideration for inclusion. Consensus was obtained in cases where the review authors disagreed on the inclusion of the study.

Studies reporting on different types of LMWH were entered into the same analysis if the dose of LMWH was found comparable in anti-Xa units (20 mg enoxaparin equals 2500 anti-Xa units).

Data extraction and management

Two review authors (SIF and RSK) independently extracted data and differences were resolved through discussion. The following data were extracted: type of prophylaxis, duration of thromboprophylaxis, type of VTE end point, total incidence of VTE including specific rates of DVT (total, proximal and distal) and PE (total and fatal) within 30 days after surgery, bleeding events, severity of bleeding and total number of transfusions. Data were entered into Review Manager 5 (RevMan 5.3) by one review author (SIF) and verified by another review author (CCJ) (Figure 1).

Figure 1. Study flow diagram The primary search performed resulted 1698 studies, of which 1528 were excluded by reviewing the title and or removing duplicates, 104 were selected to be evaluated by the abstract, of these seven met the inclusion criteria. We excluded 97 studies by the primary selection because they lacked inclusion of patients undergoing abdominal or pelvic surgery, did not address thromboprophylaxis beyond day 14 after surgery, or were not clinical controlled trials. One trial were excluded as it was a double publication (Rasmussen 2003), and one because it was a review (Rasmussen 2003a). In addition, we found one trial by handsearching and only as an

abstract presentation, and was reported as unpublished data (Jørgensen 2002). One study is actively recruiting patients (Zheng 2017), however, study methodology was not explicity outlined in the trial protocol.

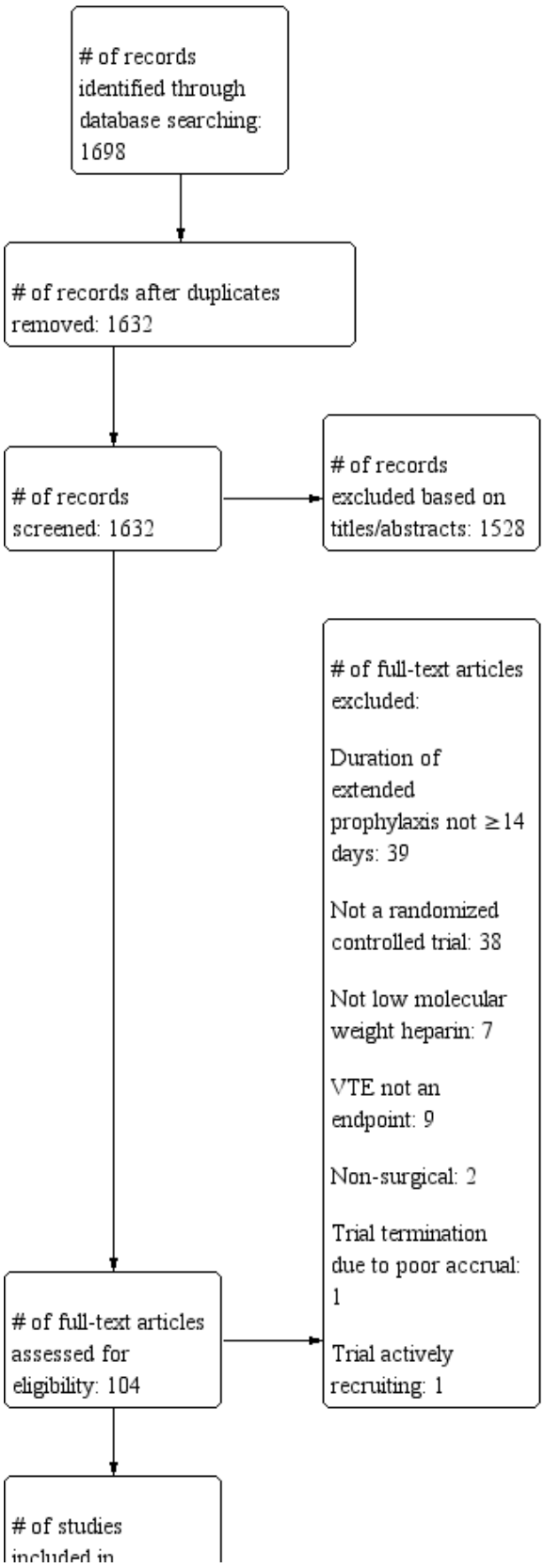
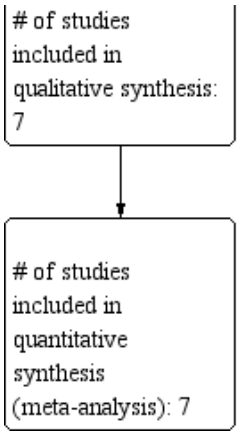


Figure 1. (Continued)



Assessment of risk of bias in included studies

We used Cochrane's tool for assessing risk of bias, described in Table 8.5.d of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two review authors (SIF and CCJ) independently assessed risk of bias for each study and any differences were discussed and consensus reached.

We assessed the risks of bias of the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective reporting bias.

Each domain was judged as low risk, high risk or unclear risk of bias according to predefined criteria described in Cochrane's 'Risk of bias' tool (Higgins 2011).

Measures of treatment effect

No comparisons across different trials between apparently equal groups were made because of the well-documented substantial inter-observer variation regarding the reported end points in various prophylactic trials, which substantially can influence the incidence of VTE (Wille-Jørgensen 1992). Variations in diagnostic objective measures across trials were acceptable as long as the method was uniformly applied within the individual study to all patients.

Outcomes were measured as dichotomous, either present or absent. Treatment effect was estimated using Mantel Haentzel (M-H) odds ratios (OR) with 95% confidence intervals (CIs). As the included studies were relatively clinically homogeneous, we applied a fixed-effect model.

A P value < 0.05 was considered to represent statistical significance.

Unit of analysis issues

The unit of analysis was the individual patient. No trials with an alternate unit of analysis were identified in the search, and thus unit of analysis issues did not apply.

Dealing with missing data

This updated review was conducted with a modified intention-to-treat analysis of patients reaching an evaluable VTE end point. Because objective assessment of VTE/DVT can be invasive or inconvenient, or both, in each study there was a substantial minority of patients who did not reach an evaluable VTE end point.

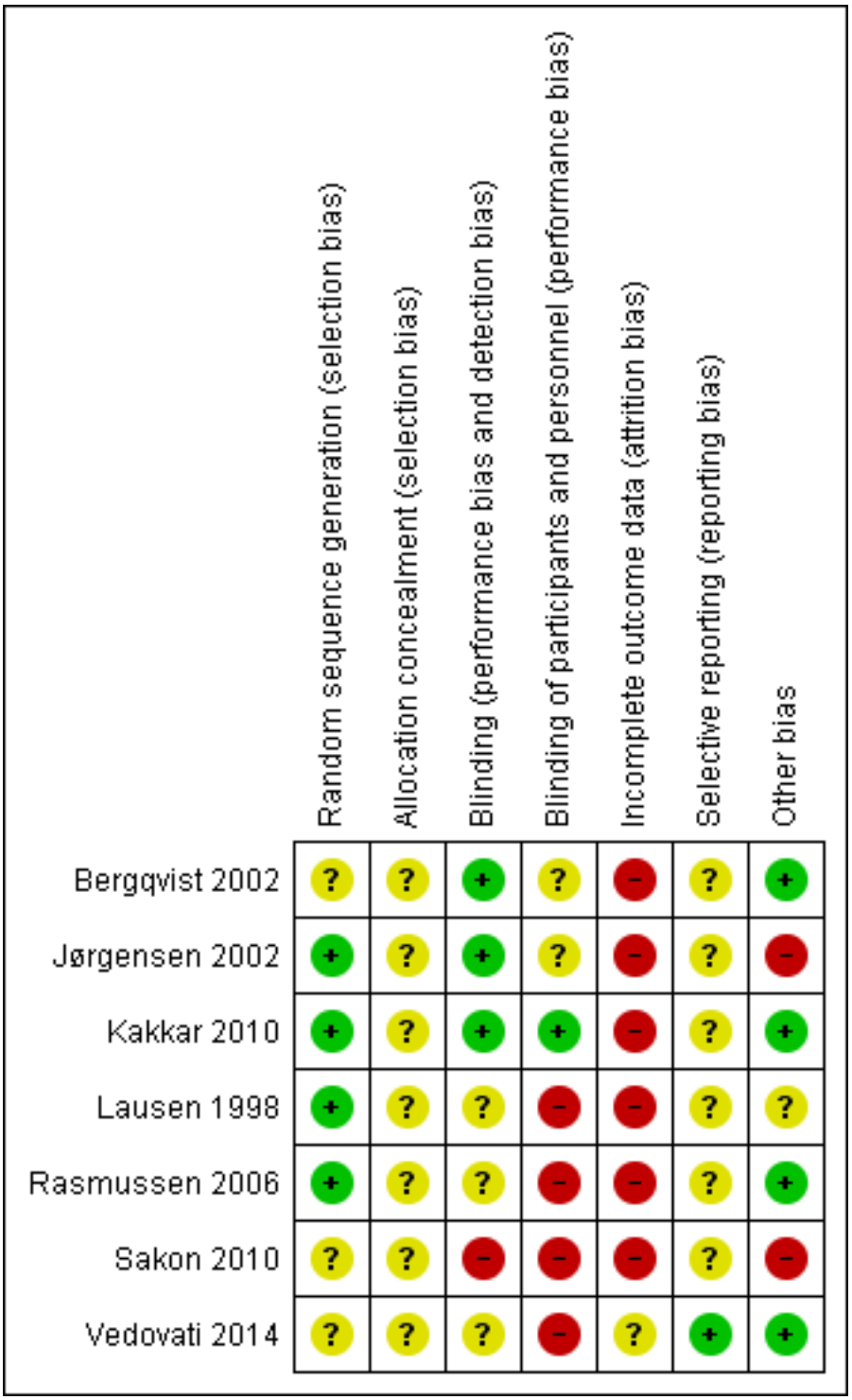
1. Bergqvist 2002: 81 (32.7%) patients in placebo group and 88 (34.8%) patients in the experimental group excluded due to lack of adequate venography
2. Jørgensen 2002: Study terminated prematurely due to lack of funding and high attrition rate (rate not reported)
3. Kakkar 2010: 67 (21.3%) patients in experimental group, 70 (22.6%) patients excluded due to inadequate venography
4. Lausen 1998: Study terminated prematurely due to lack of funding. Of 176 eligible patients (87 in extended prophylaxis group and 89 in control group), 29 (33.3%) excluded in experimental group and 29 (32.6%) in the control group
5. Rasmussen 2006: 44 (19.8%) patients in control group and 40 (19.5%) patients in experimental group excluded
6. Sakon 2010: 26 patients (23.9%) in experimental group and seven patients (18.4%) in control group excluded from total treated population due to inadequate VTE assessment or measurement
7. Vedovati 2014: The study was interrupted after the results of the interim analysis showed a significant reduction in the rate of VTE in patients assigned to extended prophylaxis (P < 0.01)

Because the attrition rate was not reported in the Jørgensen study, we could not perform a best-case/worst-case scenario, however, a sensitivity analysis was performed excluding this study.

Assessment of heterogeneity

Clinical and methodological heterogeneity were assessed by evaluating the risk of bias as detailed in the 'Risk of bias' table (Figure 2) and Characteristics of included studies. We quantified statistical heterogeneity using the I^2 statistic (I^2=((Q-df/Q) x100% where Q was the Chi^2 statistic, and df represented the degrees of freedom). This illustrated the percentage of the variability in effect estimates resulting from heterogeneity rather than sampling error (Higgins 2011).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Cut-off values for the I^2 statistic were:

0% to 40%: might not be important;
30% to 60%: may represent moderate heterogeneity;
50% to 90%: may represent substantial heterogeneity;
75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We did not assess funnel plot asymmetry for outcomes reported, as there were fewer than 10 studies, which is considered unreliable as described in the *Cochrane Handbook for Systematic Reviews of Intervention* (Chapter 10, Sterne 2011).

Data synthesis

Data analysis was performed using the RevMan 5 software (RevMan 2014). Summary ORs and 95% CIs were computed for:

1. all VTE;
2. all DVT;
3. proximal DVT;
4. symptomatic VTE;
5. bleeding complications;
6. mortality.

A fixed-effect model was used since the studies were relatively clinically homogeneous (e.g. comparing the same medication over a minimum time period).

'Summary of findings' Table

We assessed the overall quality of evidence for the main review outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach in Summary of findings for the main comparison). The 'Summary of findings' table highlighted the overall quality of the body of evidence for the main review outcomes, using the GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, indirectness, imprecision and publication bias). Judgements about the quality of the evidence (high, moderate, low or very low) were justified, documented and incorporated into the reporting of results for each outcome.

The GRADE system classifies the quality of evidence into one of four grades.

Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence on the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Subgroup analysis and investigation of heterogeneity

There was concern for clinical heterogeneity given that the Vedovati 2014 study was conducted in laparoscopic patients who may have a different baseline VTE risk. Therefore, a post-hoc subgroup analysis was done for all VTE and all DVT to evaluate whether the results would differ if this study was excluded.

Sensitivity analysis

There was concern as the Jørgensen 2002 study was terminated prematurely due to lack of funding and attrition rate, but the attrition rate was not reported. An additional post-hoc subgroup analysis for all VTE and all DVT was performed with this study excluded.

RESULTS

Description of studies

Results of the search

The primary search revealed 1632 studies, of which 1528 were excluded by reviewing the title and/or removing duplicates. We selected 104 abstracts to be evaluated and of these seven met the inclusion criteria (Figure 1). The 97 studies excluded in the initial selection lacked inclusion of patients undergoing abdominal or pelvic surgery, did not address thromboprophylaxis beyond day 14 following surgery, or were not controlled trials. One trial was excluded as it was a double publication (Rasmussen 2003), and one because it was a review (Rasmussen 2003a) In addition, one trial was included by handsearch as an abstract presentation, and is thus reported as unpublished data (Jørgensen 2002). An ongoing study in China was identified (Zheng 2017), however, the trial protocol did not describe the duration of low molecular weight heparin (LMWH) prophylaxis.

Included studies

The initial version of this review was published in the Cochrane Library in 2009 and included four studies (Rasmussen 2009). This update adds three more studies (Kakkar 2010; Sakon 2010; Vedovati 2014) and increases the number of trial participants from 1242 to 1728. Studies were published between 1998 and 2014.

Six randomized controlled trials (RCTs) published as full-text articles and one RCT published as an abstract met the inclusion criteria of this review and were included in the meta-analysis (Bergqvist 2002; Jørgensen 2002; Kakkar 2010; Lausen 1998; Rasmussen 2006; Sakon 2010; Vedovati 2014). The trials by Bergqvist and Kakkar were double-blinded RCT's, while the trials of Rasmussen, Lausen, and Vedovati were open-label trials with blinded assessment of the venograms or compression ultrasounds. The Sakon trial did not explicity state whether the objective endpoint was assessor blinded. The unpublished double-blinded Jorgensen RCT data were available within a meta-analysis, which also included the data from Lausen 1998. Both of these trials were terminated prematurely due to lack of funding. The data from Lausen 1998 were entered into the present analysis once, thus the data obtained from the Jorgensen study for the present analysis are the unpublished data of the Jorgensen study from that meta-analysis.

Five studies included only cancer patients (Bergqvist 2002; Jørgensen 2002; Kakkar 2010; Sakon 2010; Vedovati 2014). whereas

two trials considered patients undergoing general surgery for both benign and malignant diseases (Lausen 1998; Rasmussen 2006). Only one study (Vedovati 2014) performed minimally invasive (laparoscopic) abdominal surgery, with the remaining studies strictly open surgery. Three trials (Kakkar 2010; Sakon 2010; Vedovati 2014) were added to the current update from the original review done in 2009, analyzing a total of 1728 participants in seven studies for the primary end point of venous thromboembolism.

Excluded studies

Relevant excluded studies and the reasons for exclusion can be found in the Characteristics of excluded studies table.

Risk of bias in included studies

No trial had a low risk of bias across all the categories. All trials had at least one, and up to four, categories with high risk of bias. For the majority of categories, the risk of bias was unclear. Risk of bias is illustrated in Figure 2.

Allocation

All studies were RCTs, but there was variation in the detail provided as to how patients were randomized. In four studies, randomization was by computer-generated allocation and therefore low risk (Jørgensen 2002; Kakkar 2010; Lausen 1998; Rasmussen 2006). In three studies, allocation was apparently random but the method was not described in the manuscript (Bergqvist 2002; Sakon 2010; Vedovati 2014), and therefore judged as an unclear risk of bias.

Blinding

Studies had a range of degree of blinding. In the majority, the outcomes assessors were blinded; however, in one study, neither patients, healthcare providers or outcomes assessors were blinded (Sakon 2010). In other studies, outcomes assessors (e.g. those reading the venograms) were blinded but the patients and healthcare providers were not (Lausen 1998; Rasmussen 2006; Vedovati 2014), and therefore there was some risk for bias. In three studies, patients, healthcare providers and outcomes assessors were all blinded (Bergqvist 2002; Jørgensen 2002; Kakkar 2010). Only four studies specifically reported whether data analysts were blinded, raising the possibility of bias in the other studies where this was not reported. In two of these studies, data analysts were blinded (Bergqvist 2002; Jørgensen 2002), and in two they were not (Lausen 1998; Rasmussen 2006). Thus, in only two studies were all participants, healthcare providers, outcomes assessors and data analysts specifically stated to have been blinded (Bergqvist 2002; Jørgensen 2002).

Incomplete outcome data

In all studies but one (Vedovati 2014), there was high risk of attrition bias due to significant attrition. This significant rate of attrition may be related to the invasiveness of the procedures used to determine DVT/VTE incidence (e.g. venogram) and also technical difficulties with the procedures. Attrition rates varied from 18.4% to 32.7% in the placebo groups and 19.5% to 34.8% in the treatment groups. In one study, the attrition rate was reported to be high and was a cause of the termination of the study, but the exact attrition rate was not reported (Jørgensen 2002).

Selective reporting

In all studies but one (Vedovati 2014), analysis was done on a modified intention-to-treat analysis of patients reaching an evaluable VTE end point (e.g. verification of symptomatic VTE, venogram or ultrasound), and were therefore of unclear risk of bias. Only one study performed an intention-to-treat analysis, and in that study all patients actually reached an evaluable VTE end point (Vedovati 2014).

Other potential sources of bias

In the Jørgensen 2002 study, the venograms were re-evaluated by the same radiologists who assessed the venograms in the study by Lausen and colleagues (Lausen 1998), in order to perform a meta-analysis with the results of the study of Lausen and colleagues, introducing the possibility of bias (Jørgensen 2002).

In Lausen 1998, a prespecified definition of bleeding complication was not used, and rather specific bleeding complications were listed, leaving which complications were considered bleeding complications open to interpretation.

Sakon 2010 was supported by a pharmaceutical manufacturer, which also provided editorial support. The principal investigator reported several relevant conflicts of interest.

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2** Additional summary of findings

The search provided the opportunity to compare extended prophylaxis with LMWH to placebo or no treatment with the following outcome parameters: Overall VTE, all deep venous thrombosis (DVT), proximal DVT, symptomatic VTE and bleeding complications.

The studies evaluated for VTE at o rnear the four-week mark after surgery, as detailed in the Characteristics of included studies table.

Primary outcome

Incidence of venous thromboembolism (all VTE)

The incidence of VTE after major abdominal or pelvic surgery was 13.2% in the control group as compared to 5.3% in the patients receiving out-of-hospital low molecular weight heparin (LMWH) (Mantel Haentzel (M-H) odds ratio (OR) 0.38, 95% confidence interval (CI) 0.26 to 0.54; I^2 = 28%; 7 studies, n= 1728; moderate-quality evidence) (Figure 3). Subgroup analysis of trials including only patients operated with an open technique (i.e. excluding patients operated upon laparoscopically (Vedovati 2014) showed similar findings with an incidence of VTE of 13.8% in the control group and 6.0% in the treatment group (M-H 0.42, 95% CI 0.29 to 0.60; I^2 = 9%; 6 studies, n= 1503; moderate-quality evidence) (Figure 4). Similarly, sensitivity analysis with exclusion of the prematurely terminated trial (Jørgensen 2002) showed a benefit for extended prophylaxis with LMWH, with VTE occurring in 12.8% of the control group and 5.2% of the treatment group (M-H OR 0.38, 95% CI 0.27 to 0.56; I^2 = 38%;6 studies, n= 1620; moderate-quality evidence) (Figure 5).

Figure 3. Forest plot of comparison: 1 LMWH versus placebo, outcome: 1.1 All VTE.

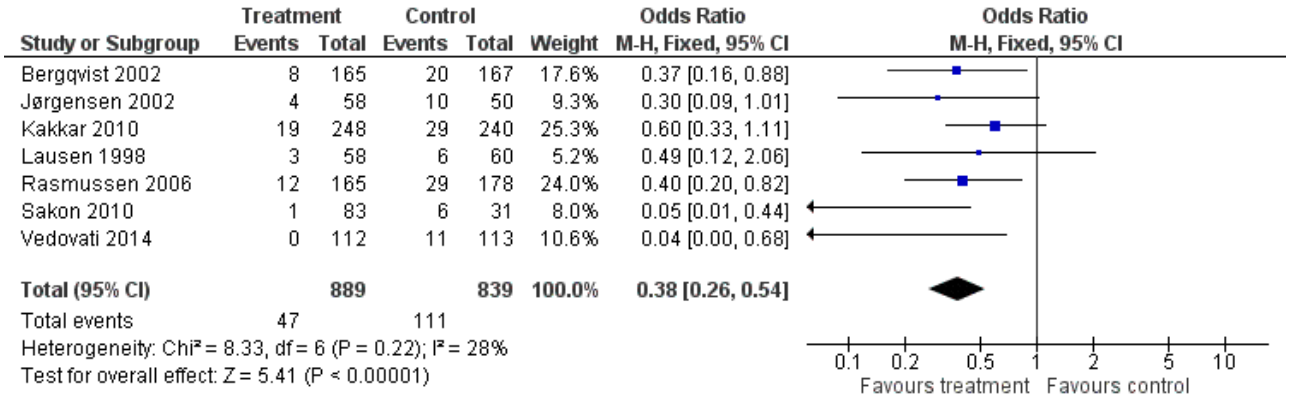


Figure 4. Forest plot of comparison: 1 LMWH versus placebo, outcome: 1.6 All VTE (Subgroup analysis: Open resections only, laparoscopic excluded (Vedovati 2014)).

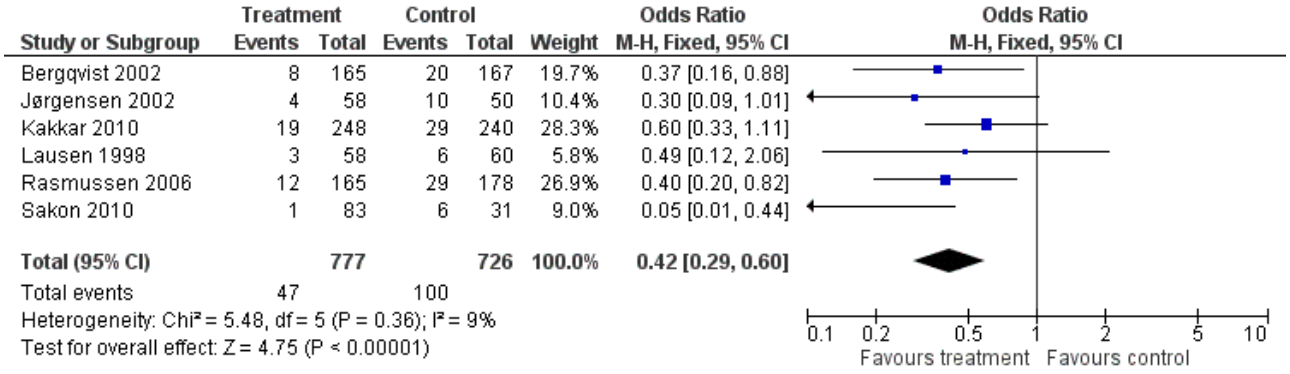
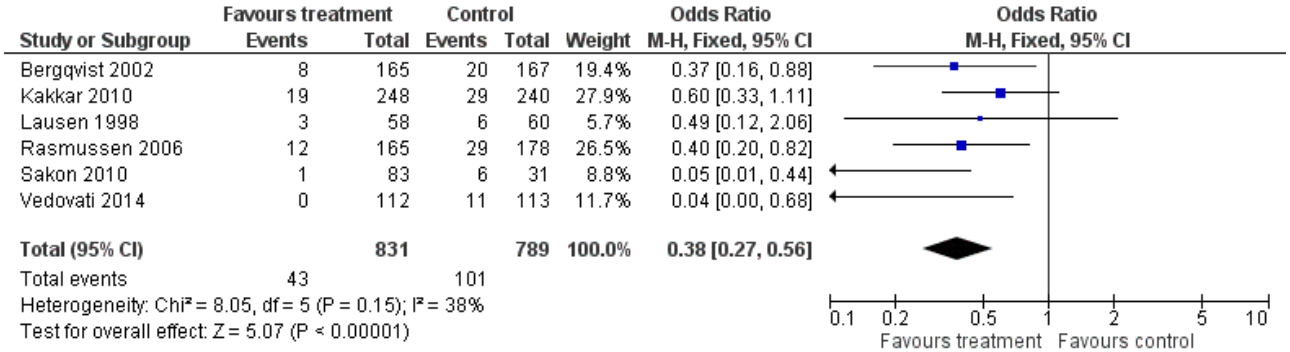


Figure 5. Forest plot of comparison: 1 LMWH versus placebo, outcome: 1.8 All VTE (Sensitivity analysis: Unpublished study excluded (Jørgensen 2002)).



Secondary outcomes

Incidence of deep venous thromboembolism (all DVT)

Prophylaxis with LMWH as compared to control also offered better protection against all DVT (M-H OR 0.39, 95% CI 0.27 to 0.55; I^2 = 28%; 7 studies, n= 1728; moderate-quality evidence). DVT occurred in 12.9% of the control group versus 5.3% of the treatment group (Figure 6). In the subgroup analysis including only open technique, the rate of DVT was 13.3% in controls and 6.4% in the treatment group (M-H OR 0.43, 95% CI 0.30 to 0.62; I^2 = 8%; 6 studies, n= 1503; moderate-quality evidence) (Figure 7). Exclusion of the prematurely terminated trial (Jørgensen 2002) did not affect the results, with DVT occurring in 12.4% of the control group versus 5.2% of the treatment group (M-H OR 0.40, 95% CI 0.27 to 0.58; I^2 = 38%; 6 studies, n= 1620; moderate-quality evidence) (Figure 8).

Figure 6. Forest plot of comparison: 1 LMWH versus placebo, outcome: 1.2 All DVT.

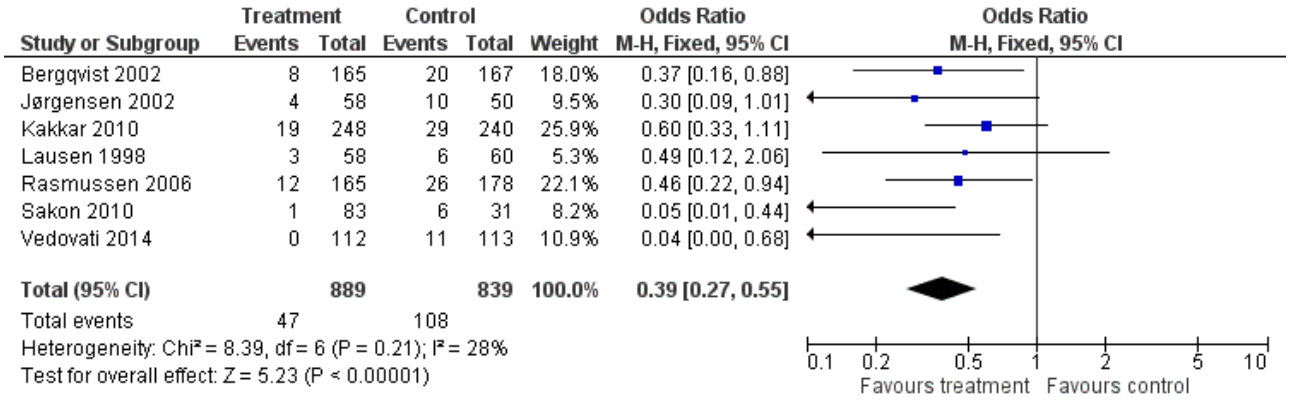


Figure 7. Forest plot of comparison: 1 LMWH versus placebo, outcome: 1.7 All DVT (Subgroup analysis: Open resections only, laparoscopic excluded (Vedovati 2014)).

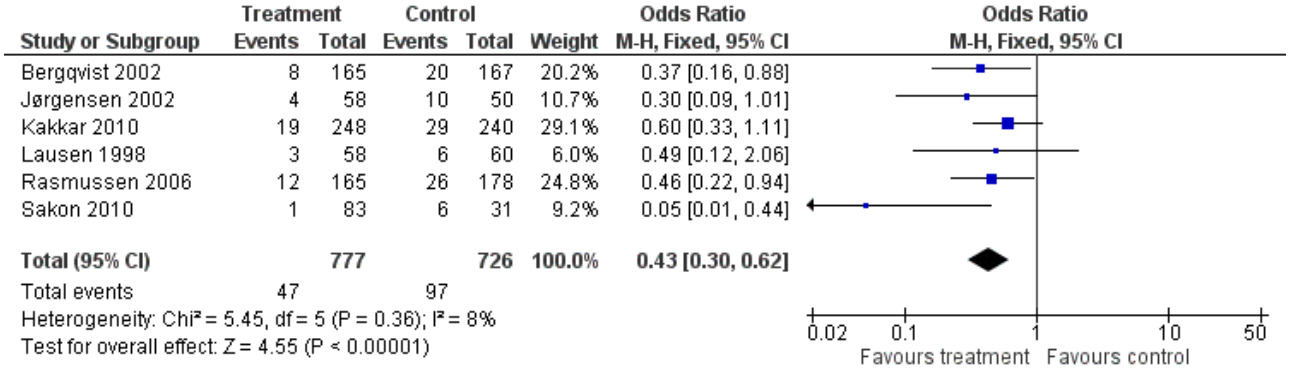
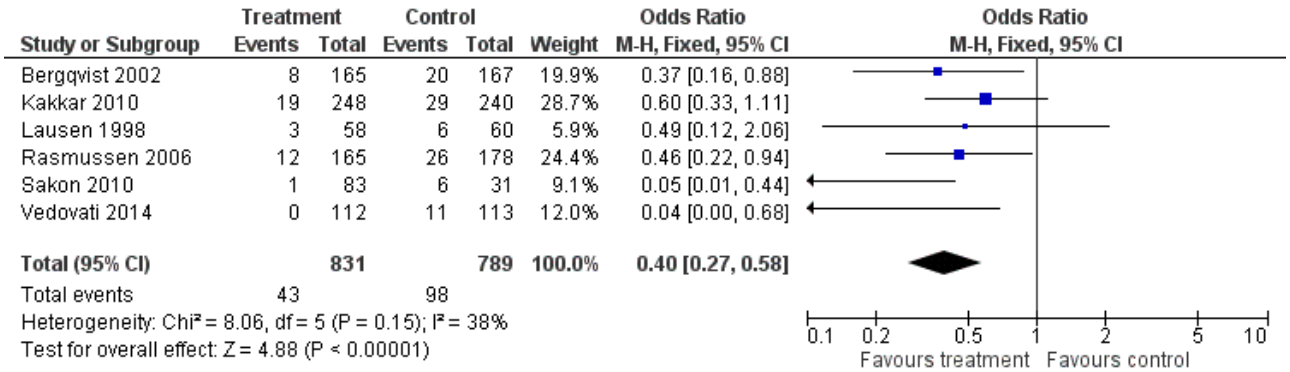


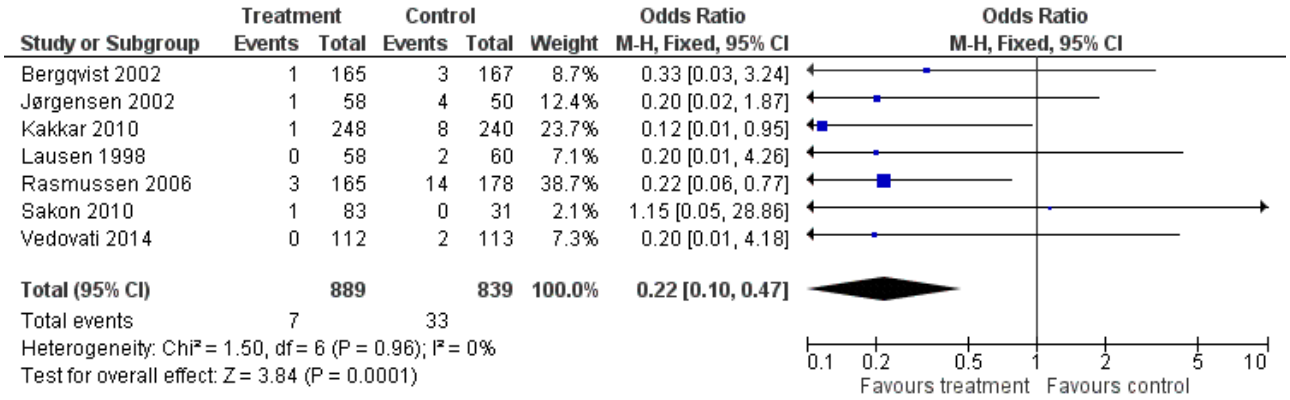
Figure 8. Forest plot of comparison: 1 LMWH versus placebo, outcome: 1.9 All DVT (Sensitivity analysis: Unpublished study excluded (Jørgensen 2002)).



Incidence of proximal deep venous thromboembolism (proximal DVT)

When the outcome was limited to proximal DVT (thus excluding more distal DVT which may not be clinically significant), there was still a reduction in DVT with extended LMWH. Rates of proximal DVT were 3.9% in the control group and 0.8% in the treatment group (M-H OR 0.22, 95% CI 0.10 to 0.47; $I^2 = 0\%$; 7 studies, n= 1728; moderate-quality evidence) (Figure 9).

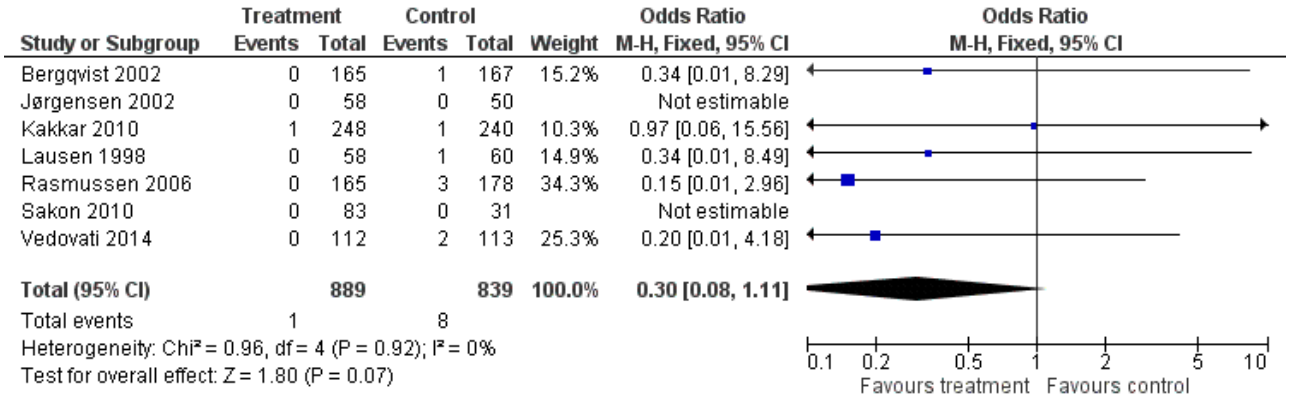
Figure 9. Forest plot of comparison: 1 LMWH versus placebo, outcome: 1.3 Proximal DVT.



Incidence of symptomatic venous thromboembolism (symptomatic VTE)

Prolonged thromboprophylaxis with LMWH was associated with a trend toward a reduction of symptomatic VTE, 1.3% in the control group versus 0.1% in the treatment group (M-H OR 0.30, 95% CI 0.08 to 1.11; $I^2 = 0\%$; 7 studies, n= 1728; moderate-quality evidence). (Figure 10).

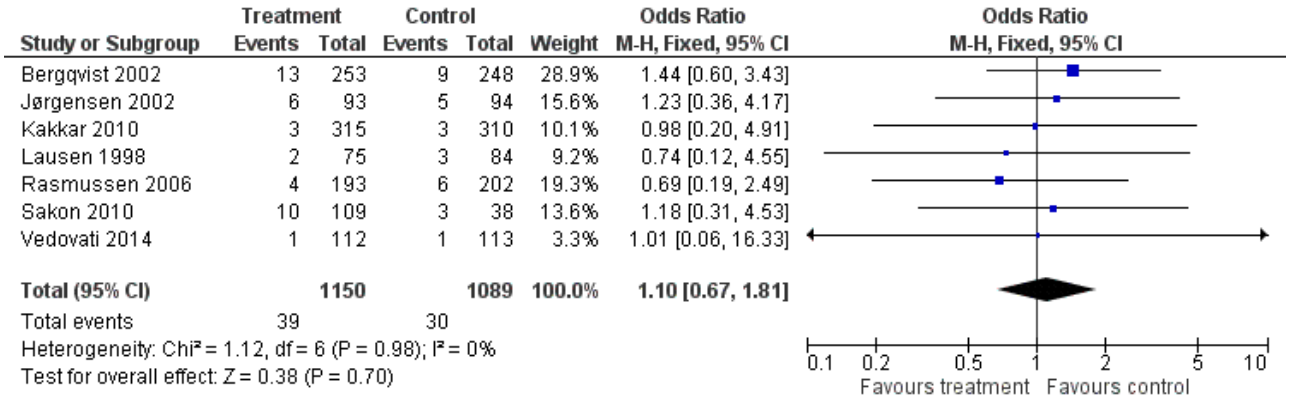
Figure 10. Forest plot of comparison: 1 LMWH versus placebo, outcome: 1.4 Symptomatic VTE.



Bleeding complications

There was no significant difference regarding the incidence of overall (both major and minor) bleeding between the control group (2.8%) and the LMWH group (3.4%), (M-H OR 1.10, 95% CI 0.67 to 1.81; $I^2 = 0\%$; 7 studies, n= 2239; moderate-quality evidence). (Figure 11).

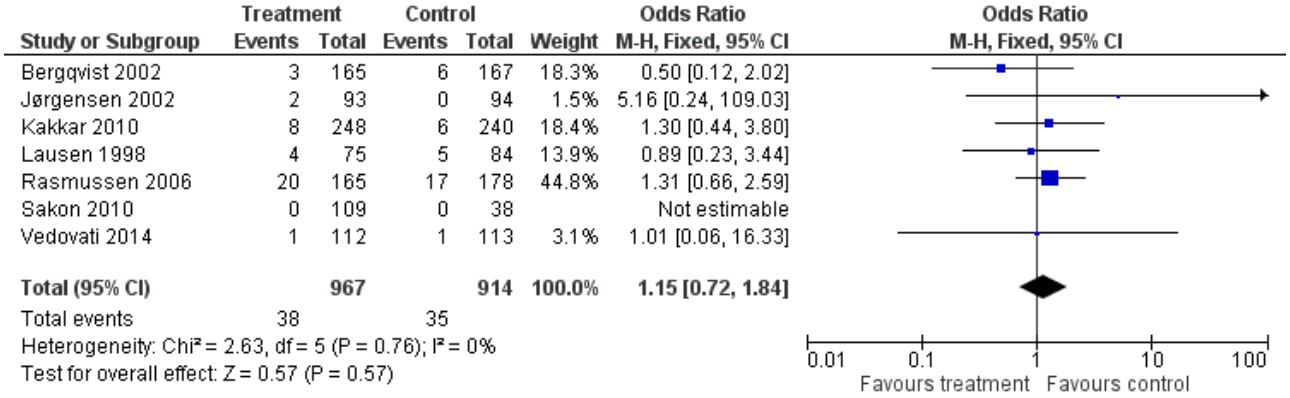
Figure 11. Forest plot of comparison: 1 LMWH versus placebo, outcome: 1.5 Bleeding complications.



Mortality

There was no significant difference regarding the incidence of mortality between the control group (3.8%) and the LMWH group (3.9%), (M-H OR 1.15, 95% CI 0.72 to 1.84; I^2 = 0%; 7 studies, n = 1881; moderate-quality evidence). (Figure 12) The number of patients in the safety population were higher than in the other outcome groups since all patients receiving at least one injection of the treatment and not necessarily reaching the evaluable end point were included for this analysis.

Figure 12. Forest plot of comparison: 1 LMWH versus placebo, outcome: 1.10 Mortality at 90 days.



Thus, extended LMWH demonstrated a reduction in all thrombotic outcomes (all VTE, all DVT, proximal DVT and symptomatic VTE) with no difference in bleeding complications or mortality.

DISCUSSION

Summary of main results

In the first version of this review which included four studies, (Bergqvist 2002; Jørgensen 2002; Lausen 1998; Rasmussen 2006), prolonged thromboprophylaxis with low molecular weight heparin (LMWH) compared with prophylaxis limited to in-hospital treatment only, significantly reduced the risk of major venous thromboembolism (VTE) in patients undergoing major abdominal or pelvic surgery. Three trials (Kakkar 2010; Sakon 2010; Vedovati 2014) were added to the current update, analyzing a total of 1728 participants in seven studies, confirming the initial review's findings.

The incidence of VTE after major abdominal or pelvic surgery was reduced from 13.2% in the control group to 5.3% in the patients receiving out-of-hospital LMWH (Mantel Haentzel (M-H) odds ratio (OR) 0.38, 95% confidence interval (CI) 0.26 to 0.54; I^2 = 28%). Similarly, all deep venous thrombosis (DVT) was also reduced: 12.9% of the controls versus 5.3% of the treatment group (M-H OR 0.39, 95% CI 0.27 to 0.55; I^2 = 28%).

When the analysis was limited to solely proximal DVT or symptomatic VTE, a benefit of extended prophylaxis was still apparent. Rates of proximal DVT were 3.9% in the control group and 0.8% in the treatment group (M-H OR 0.22, 95% CI 0.10 to 0.47; I^2 = 0%) and symptomatic VTE was 1.0% and 0.1%, respectively (M-H OR 0.30, 95% CI 0.08 to 1.11; I^2 = 0%).

Importantly, there was no significant difference regarding the incidence of overall (both major and minor) bleeding between the control group (2.8%) and the LMWH group (3.4%), (M-H OR 1.10, 95% CI 0.67 to 1.81; I^2 = 0%).

No study established mortality as a primary efficacy end point; however, several did report mortality as a secondary outcome. The incidence of objectively confirmed PE was extremely low across the studies, which would typically be considered the embolic event most likely to account for a mortality. However, no study identified a fatal PE with certainty. Causes of mortality among the studies, when described, were secondary to medical and/or surgical complications or progression of disease (for patients with malignancy). A small minority of patients died of a sudden cardiac arrest, however, among these patients, no patient was confirmed to have a PE nor was clinically suspected of experiencing a PE event. There was no difference in overall mortality between the control group (3.8%) and the LMWH group (3.9%), (M-H OR 1.15, 95% CI 0.72 to 1.84; I^2 = 0%).

No study correlated the VTE end point to the anatomic location of pathology (intra-peritoneal versus extra-peritoneal) or type of operation. For this reason, no analysis could be performed stratifying abdominal versus pelvic surgery.

In six of the seven included studies (Bergqvist 2002; Kakkar 2010; Lausen 1998; Rasmussen 2006; Sakon 2010; Vedovati 2014), objective confirmatory evaluation was used only for clinically suspected pulmonary embolism (PE). (Jørgensen 2002 is an unpublished abstract, such that the information of PE assessment was not available). Evaluation for PE was performed by ventilation/perfusion lung scintigraphy, pulmonary angiography, computed tomography (CT) scan, or autopsy. However, the event rate for PE among all trials was nominal, therefore a sensitivity analysis was not performed (Analysis 1.4) Bergqvist 2002 reported one PE occurring in the placebo group and confirmed by objective testing during the trial period, and one patient in the placebo group identified on autopsy during the follow-up period (which was an unsuspected PE). Kakkar 2010 reported no objectively identified PE during the study trial period, nor in the follow-up period. Nine deaths occurred during the double-blind period, five associated with identifiable causal medical reasons, and the remaining four (one in the placebo group, three in the LMWH group) did not undergo confirmatory autopsy or have a positive objective test

identifying PE. Lausen 1998 reported no objectively identified PE events. Eleven patients died during the trial, however, the authors reported these patients to have died under circumstances not clinically suggestive of a PE. Rasmussen 2006 reported three cases of symptomatic, non-fatal cases of PE, with two of these events verified by ventilation/perfusion lung scintigraphy or CT scan, or both (all patients within the control group). Jørgensen 2002, Sakon 2010 and Vedovati 2014 reported no PE events in either group.

Overall completeness and applicability of evidence

The studies included in this analysis were all designed on 'surrogate' end points based on objective diagnosis (venography, ultrasonography, ventilation/perfusion scintigraphy, CT or autopsy) performed at extended time intervals following surgery. The clinical relevance of asymptomatic cases of VTE detected objectively has been questioned, as the majority of these are confined to the lower extremity veins with limited potential for propagation or embolization. However, even asymptomatic postoperative VTE is associated with a 59% relative risk increment of developing late post-thrombotic syndrome (Wille-Jørgensen 2005). Furthermore, a highly significant association between asymptomatic proximal VTE and 90-day mortality has been described in medical patients (Vaitkus 2007). This increased mortality risk supports prior autopsy series reporting symptomatic DVT seldom precede a fatal PE (Huber 1992; Lindblad 1991). Additionally, orthopedic surgery patients receiving extended thromboprophylaxis with LMWH have shown a relative reduction of asymptomatic DVT translating into a corresponding reduction of symptomatic DVT (Arnesen 2003; Eilkelboom 2001; Hull 2001). Based on these observations, asymptomatic VTE does have clinical importance, thus representing more than a 'surrogate' end point.

Although inpatient thromboprophylaxis is considered standard hospital practice and prolonged thromboprophylaxis is both effective and safe under most circumstances, outpatient VTE thromboprophylaxis is infrequently utilized for at-risk patients (Kalka 2009; Merkow 2011). Two of the included studies described a high rate (more than 97% of the patients) of compliance during the study trial, (Lausen 1998; Rasmussen 2006), while compliance was not reported in the remaining five studies (Bergqvist 2002; Jørgensen 2002; Kakkar 2010; Sakon 2010; Vedovati 2014). Despite the strong evidence reported in the initial version of the review (Rasmussen 2009), along with the American Society of Clinical Oncology, (Lyman 2015) National Cancer Center Network (Version 1.2016) ,and the American College of Chest Physician guidelines (Gould 2012), the proportion of patients receiving prolonged thromboprophylaxis is surprisingly low. It remains unclear why these data-driven recommendations have not translated into routine clinical practice, however, a number of financial, social, and provider-level barriers may discourage prolonged VTE thromboprophylaxis (Merkow 2011). In a national study using administrative data, Amin and colleagues found that among patients undergoing major abdominal surgery, approximately 60% received inpatient thromboprophylaxis, yet only 1.6% of patients meeting the American College of Chest Physician guidelines for extended prophylaxis filled an outpatient prescription within 30 days of discharge (Amin 2010). Interestingly, the authors also found that among orthopedic surgery patients analyzed separately within the study, 54.4% filled a prescription for outpatient VTE prophylaxis. Other reports have documented post-discharge VTE thromboprophylaxis in the orthopedic population approaching 90% (Bergqvist 2012). In another study focusing on colorectal surgical patients, only 1.2% of Medicare beneficiaries received guideline-recommended post-discharge thromboprophylaxis (Merkow 2011).

Accurate assessment of a patient's VTE risk is critical to improving compliance with prophylaxis guidelines. Practical methods for VTE risk stratifying surgical inpatients have been developed (Caprini 2001; Rogers 2007), however, these models have been criticized for being cumbersome as well lacking strong external validation (Gould 2012). The weight each risk factor confers to a patient's postoperative VTE relative risk is cumulative. Notably, malignancy is recognized as a moderate risk factor in the Caprini model (but not in the Rogers Risk Score), but inflammatory bowel disease is a minor risk factor, (Bahl 2010, Gross 2014; Merkow 2014). In a NSQIP analysis, the postoperative rate of VTE in IBD patients was found to be significantly greater than the rate of VTE in patients who have colorectal cancer undergoing similar operations, particularly in the post-discharge timeframe (40% occurred post-discharge), emphasizing the deficiencies in currently utilized VTE risk-assessment tools (Gross 2014).

Quality of the evidence

The robustness of the outcome in the primary analysis of overall VTE and of symptomatic VTE was demonstrated by the fact that exclusion of the unpublished data (Jørgensen 2002) and exclusion of the exclusively laparoscopic study (Vedovati 2014) did not alter the conclusions of this analysis. These findings also occur despite a relatively high attrition rate in all trials included. In the Bergqvist study, almost one third of the patients did not undergo venography or had un-interpretable venogram. In the study by Kakkar and colleagues, the proportion of patients in whom inadequate or no venography was obtained (21.5% LMWH group and 22.5% control) was also relatively high. The inability to objectively measure the primary VTE end point for a significant number of trial participants (attrition rates varied from 18.4% to 32.7% in the placebo groups and 19.5% to 34.8% in the treatment groups, exclusive of the Vedovati 2014), may have affected the study end point.

Some differences were identified regarding trial design. Three studies were double-blinded and placebo-controlled (Bergqvist 2002; Jørgensen 2002; Kakkar 2010), whereas three reported assessor-blinded evaluations of the venous system (Lausen 1998; Rasmussen 2006; Vedovati 2014). The trial from Sakon et al did not explicitly describe if the objective VTE endpoint assessment was assessor-blinded (Sakon 2010). Differences regarding patient characteristics were also present. Five studies included only cancer patients (Bergqvist 2002; Jørgensen 2002; Kakkar 2010; Sakon 2010; Vedovati 2014), whereas the trials by Lausen and Rasmussen also considered patients undergoing surgery for both benign and malignant diseases (Lausen 1998; Rasmussen 2006). These two studies included a substantial proportion of patients with benign disease (Rasmussen 2006: 42%) and (Lausen 1998: 31%). It was not possible to make a comparison between these two patients groups, because no separate data were provided. Additionally, only one study (Vedovati 2014) performed laparoscopic surgery. The number of patients included in this trial was not large enough to make a reliable comparison between the different open and minimally invasive techniques. Multiple studies have reported that laparoscopic surgery induces a similar postoperative hypercoaguable state when compared to open surgery, however, the degree and duration of the hypercoagulability is not yet

well understood (Diamantis 2007; Nguyen 2001; Tsiminikakis 2009). It is possible that the increased number of minimally invasive surgical procedures (Rahr 1999; SAGES 2007) and the current trend for fast-track recovery (Kehlet 2005) following gastrointestinal surgery may lower the risk of postoperative VTE. Because patients undergoing minimally invasive abdominal or pelvic surgeries may have shorter lengths of hospitalization, these patients might presumably receive a shorter time of sufficient thromboprophylaxis. Future clinical trials will need to evaluate this additional variable when assessing patient VTE risk and the appropriate duration of thromboprophylaxis.

Potential biases in the review process

Trial author involvement in review (review author MSR).

Agreements and disagreements with other studies or reviews

This version agrees with the findings of the prior version of this review, demonstrating a benefit to extended prophylaxis with LMWH after abdominal or pelvic surgery.

AUTHORS' CONCLUSIONS

Implications for practice

Administration of low molecular weight heparin (LMWH for) ≥14 days compared to inpatient only prophylaxis after major abdominal or pelvic surgery significantly reduces the incidence of venous thromboembolism (VTE) without jeopardizing safety, and should be utilized.

Unfractionated heparin and LMWH in general surgery patients has been shown to likely be comparable in efficacy for thromboprophylaxis (Geerts 2001; Geerts 2004; Gould 2012; Mismetti 2001). However, LMWH allows once-daily injection and carries a lesser risk of heparin-induced thrombocytopenia (Jørgensen 1993). Although LMWHs belong to the same drug category, the use of single drug variations in terms of anticoagulant profiles may have added some bias in this analysis. However, the number of patients included in each trial was not large enough to make a reliable comparison between the different types of LMWHs. This review was limited to exclusively LMWH and did not assess unfractionated heparin, vitamin K antagonists, oral direct thrombin inhibitors or oral factor Xa inhibitors for prolonged surgical thromboprophylaxis. The emerging use of oral anticoagulants may help improve the barriers related to compliance, however, clinical studies evaluating abdominal and pelvic surgical patient populations are limited at this time (Sakon 2012).

Implications for research

Future research of optimizing VTE thromboprophylaxis should include patients undergoing laparoscopic surgery under a fast track, enhanced recovery protocol. New antithrombotic drugs with oral administration might improve the ease and compliance of prolonged thromboprophylaxis and should be studied to determine if they are of equal efficacy as LMWH.

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Caitlin Bakker, Information specialist, University of Minnesota Bio-Medical Library.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bergqvist 2002

Methods	RCT, double-blinded, venography
Participants	Patients undergoing elective, open, curative surgery for malignant disease of the gastrointestinal (excluding esophagus) tract, genitourinary tract or female reproductive organs.
Interventions	LMWH (enoxaparin 40 mg, total treatment period of 25 to 31 days) or placebo.
Outcomes	LMWH 165 Placebo167
Notes	ENOXACAN II trial. Follow-up period 3 months. Complete follow-up. All patients were scheduled for bilateral venography. Adequate definitions of VTE and bleeding complications were described in the paper. Venography performed between 25 and 31 days.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in the manuscript. Randomization stratified according to the country where institution was located.

Bergqvist 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described in manuscript.
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo-controlled double-blind study. Patients, healthcare providers, data collectors, outcome assessors, and data analysts were blinded.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described in manuscript.
Incomplete outcome data (attrition bias) All outcomes	High risk	Eighty-one (32.7%) patients in placebo group and 88 (34.8%) patients in experimental group excluded due to lack of adequate venography.
Selective reporting (reporting bias)	Unclear risk	Modified intention-to-treat analysis of patients reaching an evaluable VTE end point (venogram or objection verification of symptomatic VTE).
Other bias	Low risk	The study appears to be free of other sources of bias.

Jørgensen 2002

Methods	RCT, double-blinded, venography.
Participants	Patients undergoing curative surgery for abdominal or pelvic cancer.
Interventions	LMWH (tinzaparin 3500 IU, total treatment period of 28 days) or placebo.
Outcomes	LMWH 58 Placebo 50
Notes	Unpublished data. Presented as an abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated allocation.
Allocation concealment (selection bias)	Unclear risk	Not described in abstract.
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo-controlled double-blind study. Patients, healthcare providers, data collectors, outcome assessors and data analysts were blinded.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described in abstract.
Incomplete outcome data (attrition bias)	High risk	Study terminated prematurely due to lack of funding and high attrition rate (rate not reported).

Jørgensen 2002 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Intention-to-treat analysis of patients reaching an evaluable VTE end point (venogram or objection verification of symptomatic VTE). Adequate definitions of VTE and bleeding complications were described.
Other bias	High risk	Premature termination of trial. Full details of study unclear because Abstract only. Bilateral venography performed on day 28 to 35.

Kakkar 2010

Methods	RCT, double-blinded, placebo-controlled, venography.
Participants	Patients undergoing elective, open, curative or palliative surgery for malignant disease of the gastrointestinal (excluding esophagus) tract, genitourinary tract or female reproductive organs.
Interventions	LMWH (bemiparin 3500 IU, total treatment period of 24 to 32 days), or placebo.
Outcomes	LMWH 248 Placebo 240
Notes	CANBESURE trial. Follow-up 74 to 90 days after randomization. Follow-up complete. All patients were scheduled for bilateral venography. Adequate definitions of VTE and bleeding complications were described in the paper. Venography performed on day 18 to 22, two days before the last LMWH injection.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated allocation.
Allocation concealment (selection bias)	Unclear risk	Not described in the manuscript.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled. All deaths and symptomatic VTE events centrally evaluated by independent blinded committee. Venograms blinded and centrally evaluated by independent committee. Bleeding events adjudicated by an independent data safety monitoring board.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo injection 0.9% sodium chloride, 0.2 mL.
Incomplete outcome data (attrition bias) All outcomes	High risk	Sixty-seven (21.3%) patients in experimental group, 70 (22.6%) patients excluded due to inadequate venography.
Selective reporting (reporting bias)	Unclear risk	Modified intention-to-treat population, included all randomized patients who received at least one dose of randomized treatment and had an assessable

Kakkar 2010 *(Continued)*

		venogram, or documented symptomatic VTE, or died during the double-blind period.
Other bias	Low risk	The study appears to be free of other sources of bias.

Lausen 1998

Methods	RCT, assessor-blinded, venography.
Participants	Patients undergoing major abdominal or non-cardiac thoracic surgery for either malignant or benign diseases.
Interventions	LMWH (tinzaparin 3500 IU, total treatment period 28 days) or no treatment.
Outcomes	LMWH 58 Control 60
Notes	There was no defined follow-up period. All patients were scheduled for bilateral venography. An adequate definition of VTE was described in the paper. No definition of bleeding complications was given in the paper, but bleeding episodes were described. Venography performed on day 28.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated allocation list.
Allocation concealment (selection bias)	Unclear risk	Not described in the manuscript.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Assessor-blinded evaluation of the venograms by two radiologists. Patients, healthcare providers and data-analysts were not blinded.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study, patients not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study terminated prematurely due to lack of funding. Of 176 eligible patients (87 in extended prophylaxis group and 89 in control group), 29 (33.3%) excluded in experimental group and 29 (32.6%) in the control group.
Selective reporting (reporting bias)	Unclear risk	Modified intention-to-treat analysis of patients reaching an evaluable VTE end point (venogram or objection verification of symptomatic VTE).
Other bias	Unclear risk	No definition for bleeding complications was specified.

Rasmussen 2006

Methods	RCT, assessor blinded, venography.
Participants	Patients undergoing major abdominal surgery for either malignant or benign diseases.
Interventions	LMWH (dalteparin 5000 IU, total treatment period 28 days) or no treatment.
Outcomes	LMWH 165 Control 178
Notes	Follow-up period 3 months. Complete follow-up. All patients were scheduled for bilateral venography. Adequate definitions of VTE and bleeding complications were described in the paper. Venography performed on day 28.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated allocation list.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open-label study with assessor-blinded evaluation of the venograms. Patients, healthcare providers and data-analysts were not blinded.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	High risk	Forty-four (19.8%) patients in control group and 40 (19.5%) patients in experimental group excluded.
Selective reporting (reporting bias)	Unclear risk	Modified intention-to-treat analysis of patients reaching an evaluable VTE end point (venogram or objection verification of symptomatic VTE).
Other bias	Low risk	The study appears to be free of other sources of bias.

Sakon 2010

Methods	RCT, assessor interpretation of venography or ultrasonography not described.
Participants	Patients undergoing elective, curative laparotomy for cancer of > 45 minutes duration with a life expectancy of > 6 months after surgery.
Interventions	LMWH (enoxaparin 20 mg twice daily for 14 days) or no treatment.
Outcomes	LMWH/IPC = 113 IPC = 38

Sakon 2010 *(Continued)*

Notes	The study used patients receiving mechanical prophylaxis (IPC) as a reference group for VTE incidence during the study period, but was not intended to be compared statistically with the enoxaparin group. In the total treated population, (n = 109) LMWH mean treatment duration was 10.5 +/- 3.3 days, and in the modified-intention-to-treat population (n = 83), LMWH mean treatment duration was 11 +/- 2.8 days. The defined follow-up period was 14 days following venography (day 28 +/- 5). All patients were scheduled for bilateral venography on day 14 after surgery. Adequate definitions of VTE and bleeding complications were described in the paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized in a 3:1 ratio (LMWH to IPC), method not stated in the manuscript.
Allocation concealment (selection bias)	Unclear risk	Not described in the manuscript.
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study, no stated blinding of VTE objective end points or primary safety end point (bleeding).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	High risk	26 patients (23.9%) in LMWH group and 7 patients (18.4%) in IPC group excluded from total treated population due to inadequate VTE assessment or measurement.
Selective reporting (reporting bias)	Unclear risk	Modified intention-to-treat analysis of patients reaching an evaluable VTE end point (venogram or objection verification of symptomatic VTE).
Other bias	High risk	Study and editorial support financially supported by Sanofi-Aventis K.K., Japan. The principle investigator (MS) reported conflict of interest with Sanofi-Aventis (Japan), GlaxoSmithKline (Japan), Astellas, and Bayer pharmaceutical companies.

Vedovati 2014

Methods	RCT, assessor-blinded, compression ultrasonography.
Participants	Patients undergoing elective laparoscopic surgery for colorectal cancer.
Interventions	LMWH (enoxaparin 4000 IU in 79% allocated to extended prophylaxis, dalteparin 5000 IU in 21% allocated to extended prophylaxis, total treatment period 27 to 31 days).
Outcomes	LMWH 112 Control 113
Notes	LMWH prophylaxis medication varied prior to randomization to extended duration LMWH prophylaxis (enoxaparin 4000 UI or dalterparin 5000 UI or nadroparin 2850 IU). The study was interrupted after the results of the interim analysis showed a reduction in the rate of VTE in patients assigned to extended prophylaxis ($P < 0.01$).

Vedovati 2014 *(Continued)*

	Compression ultrasonography day 26 to 30.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Centralized randomization, method not stated in manuscript.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Compression ultrasonography evaluated by blinded investigator. Unclear if data-analysts blinded.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and presumably caregivers not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Terminated prematurely after interim analysis showed a reduction in the rate of VTE in patients assigned to extended prophylaxis.
Selective reporting (reporting bias)	Low risk	Intention-to-treat analysis on all patients with at least 26 days of follow up and at least one dose of medication; it appears all randomized patients met these parameters.
Other bias	Low risk	The study appears to be free of other sources of bias.

IPC: intermittent pneumatic compression; IU: international units: LMWH: low molecular weight heparin; RCT: randomized controlled trial; VTE: venous thromboembolism.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Corr 2015	Cohort study using historical control patients.
Downs 2012	Phase 2 open-label, non-randomized (single-group assignment) trial using fondaparinux days 1-28 with duplex ultrasonography of the lower extremities between days 28-35. Results are not published. Recruitment was completed January 2009 (n = 44), of which 17 patients did not complete the study. Of the 27 remaining patients, 0 patients were diagnosed with a VTE at week 4, although 1 patient of the 33 patients who received at least one dose of fondaparinux (and could be assessed for adverse events) experienced a pulmonary embolism and 1 developed a retroperitoneal hematoma.
GlaxoSmithKline 2009	Phase 3 trial enrollment reported as complete (n = 127) February 2007. No results reported. No duration of LMWH or objective VTE measurement defined in protocol.
Huh, 2017	Terminated due to poor enrollment (total patients, n = 7; 4 in control arm, 3 in experimental). No statistical analysis performed.
Krasinski 2014	Prospective, non-randomized trial.

Study	Reason for exclusion
Rasmussen 2003	Double publication. Data included in the Rasmussen 2006 trial.
Rasmussen 2003a	Publication is a review and not a primary trial.
Sakon 2012	Extended prophylaxis using an oral direct factor Xa inhibitor (Darexaban, YM150).
Schmeler 2013	Cohort study using historical control patients.

LMWH: low molecular weight heparin; VTE: venous thromboembolism.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Zheng 2017

Methods	Randomized parallel controlled trial.
Participants	Patients with gynecologic malignancy diagnosis undergoing surgery.
Interventions	Graduated compression stocking and/or intermittent pneumatic compression and/or LMWH.
Outcomes	Ultrasound diagnosis of VTE.
Notes	Duration of LMWH duration not specified in protocol. Date of trial registration 30 October 2015. Each of 4 arms of trial anticipate 250 patients enrolled. Study contact zhangzhenyu@coga.org.cn, telephone +86 13801237287

LMWH: low molecular weight heparin; VTE: venous thromboembolism.

Characteristics of ongoing studies *[ordered by study ID]*

Campanini 2017

Trial name or title	Rivaroxaban or placebo for extended antithrombotic prophylaxis after laparoscopic surgery for colorectal cancer: a randomized, double blind, placebo-controlled study
Methods	Randomized, parallel assignment, triple-blinded.
Participants	Diagnosis of colorectal cancer (any stage), elective laparoscopic surgery planned.
Interventions	Postoperative LMWH then oral rivaroxaban for 3 weeks versus placebo for 3 weeks.
Outcomes	Composite of symptomatic objectively confirmed VTE, asymptomatic ultrasonography-confirmed DVT or VTE-related death.
Starting date	May 3, 2017
Contact information	cecilia.becattini@unipg.it
Notes	Rivaroxaban is a direct Factor Xa inhibitor.

DVT: deep venous thrombosis; LMWH: low molecular weight heparin; VTE: venous thromboembolism.

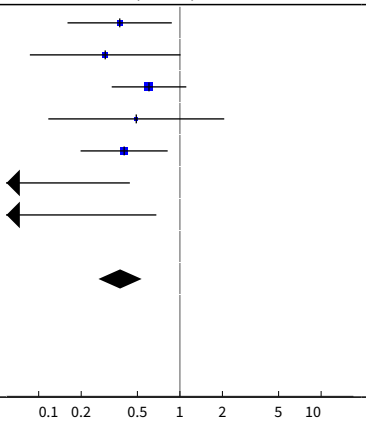
DATA AND ANALYSES

Comparison 1. LMWH versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All VTE	7	1728	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.26, 0.54]
2 All DVT	7	1728	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.27, 0.55]
3 Proximal DVT	7	1728	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.10, 0.47]
4 Symptomatic VTE	7	1728	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.08, 1.11]
5 Bleeding complications	7	2239	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.67, 1.81]
6 All VTE (Subgroup analysis open only)	6	1503	Odds Ratio (M-H, Fixed, 95% CI)	0.42 [0.29, 0.60]
7 All DVT (Subgroup analysis open only)	6	1503	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.30, 0.62]
8 All VTE (Sensitivity analysis unpublished)	6	1620	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.27, 0.56]
9 All DVT (Sensitivity analysis unpublished)	6	1620	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.27, 0.58]
10 Mortality at 90 days	7	1881	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.72, 1.84]

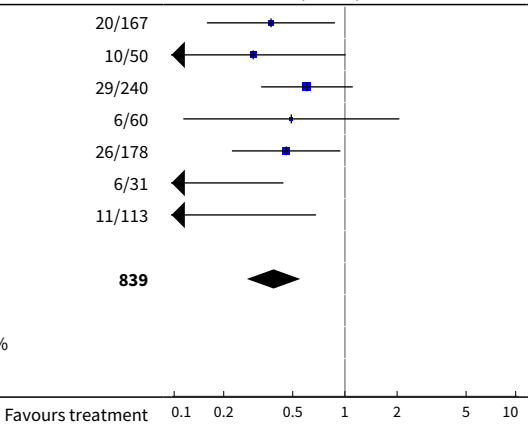
Analysis 1.1. Comparison 1 LMWH versus placebo, Outcome 1 All VTE.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bergqvist 2002	8/165	20/167		17.58%	0.37[0.16,0.88]
Jørgensen 2002	4/58	10/50		9.29%	0.3[0.09,1.01]
Kakkar 2010	19/248	29/240		25.29%	0.6[0.33,1.11]
Lausen 1998	3/58	6/60		5.2%	0.49[0.12,2.06]
Rasmussen 2006	12/165	29/178		24.04%	0.4[0.2,0.82]
Sakon 2010	1/83	6/31		8.02%	0.05[0.01,0.44]
Vedovati 2014	0/112	11/113		10.59%	0.04[0,0.68]
Total (95% CI)	**889**	**839**		**100%**	**0.38[0.26,0.54]**
Total events: 47 (Treatment), 111 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.33, df=6(P=0.22); I^2=27.93%					
Test for overall effect: Z=5.41(P<0.0001)					



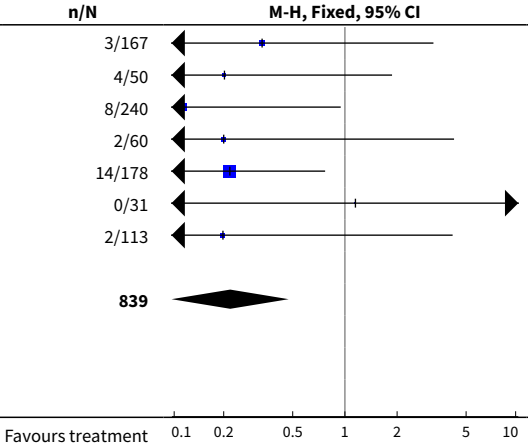
Analysis 1.2. Comparison 1 LMWH versus placebo, Outcome 2 All DVT.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bergqvist 2002	8/165	20/167		18.02%	0.37[0.16,0.88]
Jørgensen 2002	4/58	10/50		9.53%	0.3[0.09,1.01]
Kakkar 2010	19/248	29/240		25.93%	0.6[0.33,1.11]
Lausen 1998	3/58	6/60		5.33%	0.49[0.12,2.06]
Rasmussen 2006	12/165	26/178		22.1%	0.46[0.22,0.94]
Sakon 2010	1/83	6/31		8.22%	0.05[0.01,0.44]
Vedovati 2014	0/112	11/113		10.86%	0.04[0,0.68]
Total (95% CI)	**889**	**839**		**100%**	**0.39[0.27,0.55]**
Total events: 47 (Treatment), 108 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.39, df=6(P=0.21); I^2=28.5%					
Test for overall effect: Z=5.23(P<0.0001)					



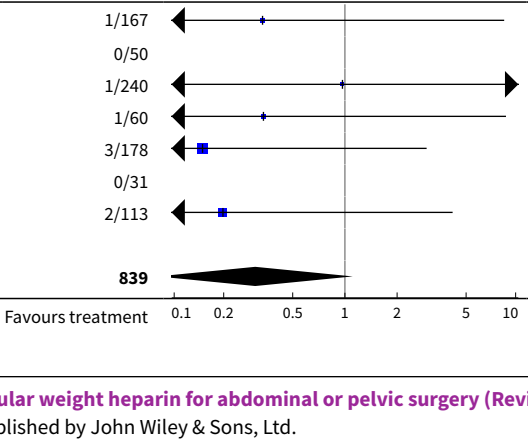
Analysis 1.3. Comparison 1 LMWH versus placebo, Outcome 3 Proximal DVT.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bergqvist 2002	1/165	3/167		8.68%	0.33[0.03,3.24]
Jørgensen 2002	1/58	4/50		12.37%	0.2[0.02,1.87]
Kakkar 2010	1/248	8/240		23.72%	0.12[0.01,0.95]
Lausen 1998	0/58	2/60		7.14%	0.2[0.01,4.26]
Rasmussen 2006	3/165	14/178		38.74%	0.22[0.06,0.77]
Sakon 2010	1/83	0/31		2.08%	1.15[0.05,28.86]
Vedovati 2014	0/112	2/113		7.26%	0.2[0.01,4.18]
Total (95% CI)	**889**	**839**		**100%**	**0.22[0.1,0.47]**
Total events: 7 (Treatment), 33 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.5, df=6(P=0.96); I^2=0%					
Test for overall effect: Z=3.84(P=0)					



Analysis 1.4. Comparison 1 LMWH versus placebo, Outcome 4 Symptomatic VTE.

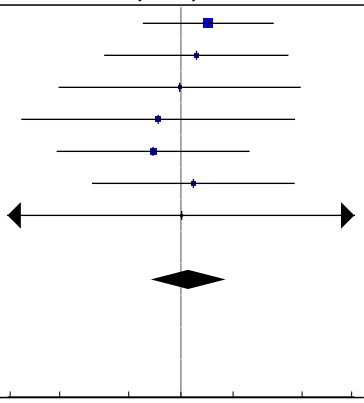
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bergqvist 2002	0/165	1/167		15.17%	0.34[0.01,8.29]
Jørgensen 2002	0/58	0/50			Not estimable
Kakkar 2010	1/248	1/240		10.33%	0.97[0.06,15.56]
Lausen 1998	0/58	1/60		14.93%	0.34[0.01,8.49]
Rasmussen 2006	0/165	3/178		34.27%	0.15[0.01,2.96]
Sakon 2010	0/83	0/31			Not estimable
Vedovati 2014	0/112	2/113		25.29%	0.2[0.01,4.18]
Total (95% CI)	**889**	**839**		**100%**	**0.3[0.08,1.11]**



Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Total events: 1 (Treatment), 8 (Control)					
Heterogeneity: Tau²=0; Chi²=0.96, df=4(P=0.92); I²=0%					
Test for overall effect: Z=1.8(P=0.07)					

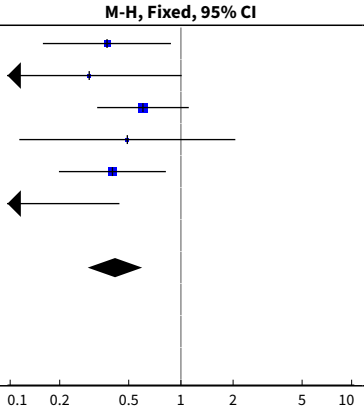
Analysis 1.5. Comparison 1 LMWH versus placebo, Outcome 5 Bleeding complications.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bergqvist 2002	13/253	9/248		28.94%	1.44[0.6,3.43]
Jørgensen 2002	6/93	5/94		15.62%	1.23[0.36,4.17]
Kakkar 2010	3/315	3/310		10.05%	0.98[0.2,4.91]
Lausen 1998	2/75	3/84		9.25%	0.74[0.12,4.55]
Rasmussen 2006	4/193	6/202		19.27%	0.69[0.19,2.49]
Sakon 2010	10/109	3/38		13.56%	1.18[0.31,4.53]
Vedovati 2014	1/112	1/113		3.31%	1.01[0.06,16.33]
Total (95% CI)	**1150**	**1089**		**100%**	**1.1[0.67,1.81]**
Total events: 39 (Treatment), 30 (Control)					
Heterogeneity: Tau²=0; Chi²=1.12, df=6(P=0.98); I²=0%					
Test for overall effect: Z=0.38(P=0.7)					



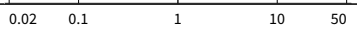
Analysis 1.6. Comparison 1 LMWH versus placebo, Outcome 6 All VTE (Subgroup analysis open only).

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bergqvist 2002	8/165	20/167		19.66%	0.37[0.16,0.88]
Jørgensen 2002	4/58	10/50		10.39%	0.3[0.09,1.01]
Kakkar 2010	19/248	29/240		28.28%	0.6[0.33,1.11]
Lausen 1998	3/58	6/60		5.81%	0.49[0.12,2.06]
Rasmussen 2006	12/165	29/178		26.89%	0.4[0.2,0.82]
Sakon 2010	1/83	6/31		8.97%	0.05[0.01,0.44]
Total (95% CI)	**777**	**726**		**100%**	**0.42[0.29,0.6]**
Total events: 47 (Treatment), 100 (Control)					
Heterogeneity: Tau²=0; Chi²=5.48, df=5(P=0.36); I²=8.69%					
Test for overall effect: Z=4.75(P<0.0001)					



Analysis 1.7. Comparison 1 LMWH versus placebo, Outcome 7 All DVT (Subgroup analysis open only).

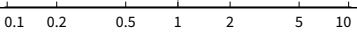
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bergqvist 2002	8/165	20/167		20.22%	0.37[0.16,0.88]
Jørgensen 2002	4/58	10/50		10.69%	0.3[0.09,1.01]
Kakkar 2010	19/248	29/240		29.09%	0.6[0.33,1.11]
Lausen 1998	3/58	6/60		5.98%	0.49[0.12,2.06]
Rasmussen 2006	12/165	26/178		24.79%	0.46[0.22,0.94]
Sakon 2010	1/83	6/31		9.23%	0.05[0.01,0.44]
Total (95% CI)	**777**	**726**		**100%**	**0.43[0.3,0.62]**
Total events: 47 (Treatment), 97 (Control)					
Heterogeneity: Tau²=0; Chi²=5.45, df=5(P=0.36); I²=8.3%					
Test for overall effect: Z=4.55(P<0.0001)					



Favours treatment — Favours control

Analysis 1.8. Comparison 1 LMWH versus placebo, Outcome 8 All VTE (Sensitivity analysis unpublished).

Study or subgroup	Favours treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bergqvist 2002	8/165	20/167		19.38%	0.37[0.16,0.88]
Kakkar 2010	19/248	29/240		27.88%	0.6[0.33,1.11]
Lausen 1998	3/58	6/60		5.73%	0.49[0.12,2.06]
Rasmussen 2006	12/165	29/178		26.5%	0.4[0.2,0.82]
Sakon 2010	1/83	6/31		8.84%	0.05[0.01,0.44]
Vedovati 2014	0/112	11/113		11.68%	0.04[0,0.68]
Total (95% CI)	**831**	**789**		**100%**	**0.38[0.27,0.56]**
Total events: 43 (Favours treatment), 101 (Control)					
Heterogeneity: Tau²=0; Chi²=8.05, df=5(P=0.15); I²=37.92%					
Test for overall effect: Z=5.07(P<0.0001)					

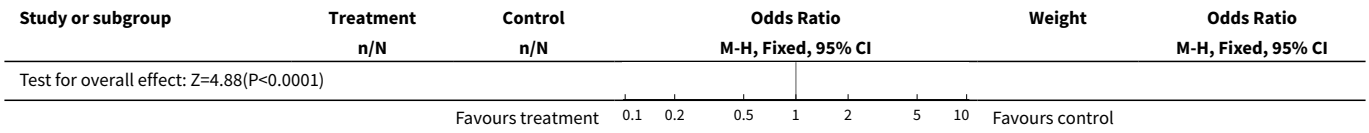


Favours treatment — Favours control

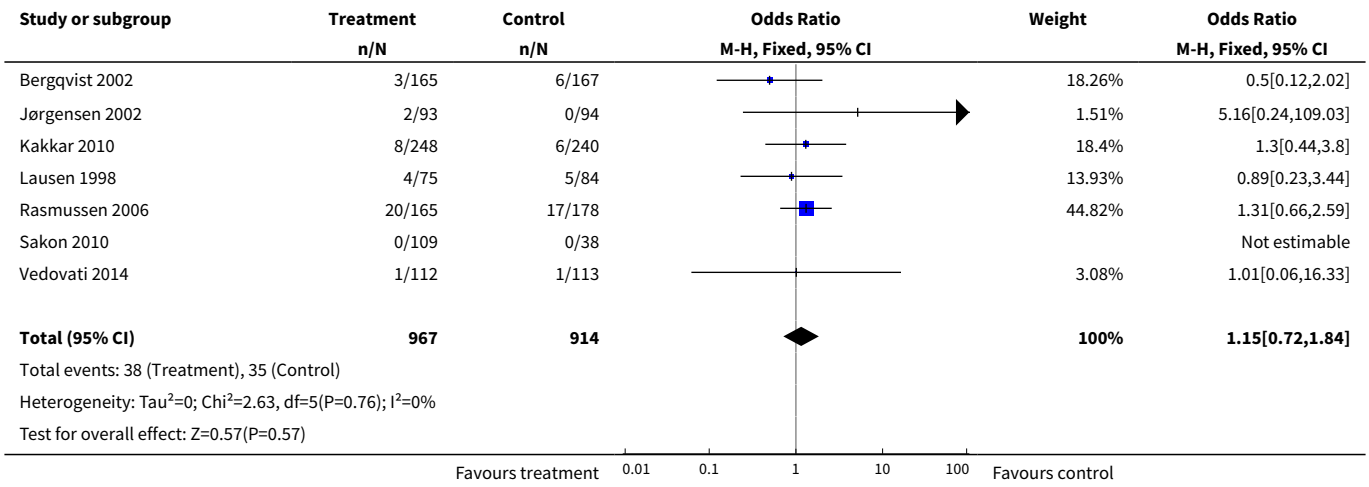
Analysis 1.9. Comparison 1 LMWH versus placebo, Outcome 9 All DVT (Sensitivity analysis unpublished).

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bergqvist 2002	8/165	20/167		19.92%	0.37[0.16,0.88]
Kakkar 2010	19/248	29/240		28.66%	0.6[0.33,1.11]
Lausen 1998	3/58	6/60		5.89%	0.49[0.12,2.06]
Rasmussen 2006	12/165	26/178		24.43%	0.46[0.22,0.94]
Sakon 2010	1/83	6/31		9.09%	0.05[0.01,0.44]
Vedovati 2014	0/112	11/113		12%	0.04[0,0.68]
Total (95% CI)	**831**	**789**		**100%**	**0.4[0.27,0.58]**
Total events: 43 (Treatment), 98 (Control)					
Heterogeneity: Tau²=0; Chi²=8.06, df=5(P=0.15); I²=37.95%					

Favours treatment — Favours control



Analysis 1.10. Comparison 1 LMWH versus placebo, Outcome 10 Mortality at 90 days.



APPENDICES

Appendix 1. Appendix: Cochrane Central Register of Controlled Trials (CENTRAL)

general near/3 surgery (MESH) OR abdom* near/3 (MESH) OR pelvi* near/3 (MESH) OR gynecolo* near/3 (MESH)

AND thrombos* OR thromboemb* OR embol* or "Embolism and Thrombosis" (MESH)

Appendix 2. Appendix: Embase (Ovid) 1947 to October 2017

1	'general surgery' OR 'abdominal surgery' OR 'pelvic surgery' OR 'gynecologic surgery'
2	'abdominal surgery'/exp
3	'general surgery'/exp
4	'pelvis surgery'/exp
5	'gynecologic surgery'/exp
6	#1 OR #2 OR #3 OR #4 OR #5
7	thrombo* OR thromboem* OR embol*
8	'thrombosis'/exp OR 'thrombosis prevention'/exp

(Continued)

9	'thromboembolism'/exp
10	'embolism'/exp
11	#7 OR #8 OR #9 OR #10
12	'prophylaxis' OR 'prophylactic' OR 'prevention' OR 'preventative' OR 'chemoprophylaxis' OR 'antithrombotic prophylaxis' OR 'reduction' OR anticoag* OR 'heparin' OR 'thromboprophylaxis'
13	'prevention'/exp OR 'thrombosis prevention'/exp
14	'heparin'/exp
15	'anticoagulant agent'/exp
16	#12 OR #13 OR #14 OR #15
17	'prolonged' OR 'long term' OR 'duration' OR 'late' OR 'extended' OR 'discharge'
18	#6 AND #11 AND #16 AND #17
19	'crossover procedure':de OR 'double blind procedure':de OR 'randomized controlled trial':de OR 'single blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti
20	#18 AND #19

Appendix 3. Appendix: PUBMED 1967 to October 2017

((((((((((("general surgery" OR "General Surgery" [MESH] OR "abdominal surgery" OR "Abdomen/surgery" [MESH] OR "pelvic surgery" OR "Pelvis/surgery" [MESH] OR "gynecologic surgery" OR "Gynecologic Surgical Procedures" [MESH])))) AND ((({("general surgery" OR "General Surgery" [MESH] OR "abdominal surgery" OR "Abdomen/surgery" [MESH] OR "pelvic surgery" OR "Pelvis/surgery" [MESH] OR "gynecologic surgery" OR "Gynecologic Surgical Procedures" [MESH])))) AND ((thrombos* OR thromboesm* OR embol* OR "Embolism and Thrombosis" [MESH]))))) AND ((((((((("general surgery" OR "General Surgery" [MESH] OR "abdominal surgery" OR "Abdomen/surgery" [MESH] OR "pelvic surgery" OR "Pelvis/surgery" [MESH] OR "gynecologic surgery" OR "Gynecologic Surgical Procedures" [MESH])))) AND ((thrombos* OR thromboesm* OR embol* OR "Embolism and Thrombosis" [MESH])}}}) AND ((("general surgery" OR "General Surgery" [MESH] OR "abdominal surgery" OR "Abdomen/surgery" [MESH] OR "pelvic surgery" OR "Pelvis/surgery" [MESH] OR "gynecologic surgery" OR "Gynecologic Surgical Procedures" [MESH])))) AND ("antithrombotic prophylaxis" OR reduction OR anticoag* OR "prevention and control" [MESH Subheading] OR heparin OR "Heparin, Low-Molecular-Weight" [MESH Terms] OR Anticoagulants [MESH Terms] OR thromboprophylaxis)))) AND ((prolonged OR "long term" OR duration OR late OR extended OR discharge [MESH Terms]) OR "administration and dosage" [MESH Subheading])))))) AND ((((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab] OR randomised[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])))

Appendix 4. AppendixL LILACS 1967 to October 2017

(MH:"General Surgery" OR MH:"Cirugfa General" OR MH:"Cirurgia Geral" OR TW:"General Surgery" OR TW:"Cirugia General" OR TW:"Cirurgia Geral" OR MH:H02.403.810.300) AND (TW:Embolism OR TW:Thrombosis OR TW:Embolia OR TW:Trombosis OR MH:"Embolia y Trombosis" OR TW:Embolia OR TW:Trombose OR MH:"Embolia e Trombose" OR MH:C14.907.355)

Appendix 5. Appendix: Clinicaltrials.gov

Condition/ Disease: embolism OR thrombosis

Other Terms: general surgery OR abdominal surgery OR pelvic surgery OR pelvis surgery OR gynecologic surgery

Terms	Search Results*	Entire Database**
Synonyms		
general surgery	401 studies	31,181 studies
surgery	401 studies	31,181 studies
surgery	403 studies	39,899 studies
Surgical	98 studies	15,174 studies
operations	25 studies	4,764 studies
invasive procedures	8 studies	413 studies
operative procedures	3 studies	133 studies
operative therapy	--	41 studies
Surgically	--	975 studies
general	72 studies	39,430 studies
Global	8 studies	12,389 studies
Generalised	--	98 studies
Generalized	--	1,089 studies
Generalizes	--	4 studies
abdominal surgery	11 studies	695 studies
abdomen surgeries	--	2 studies
abdominal operations	--	39 studies
abdominal	25 studies	6,805 studies
Abdomen	2 studies	1,444 studies
abd	1 studies	273 studies
Abdominopelvis	--	1 studies
pelvic surgery	1 studies	103 studies
pelvic	8 studies	2,907 studies
Pelvis	1 studies	711 studies
pelvis surgery	--	0 studies
pelvis	8 studies	2,908 studies

(Continued)

pelvic	7 studies	2,423 studies
intrapelvic	--	4 studies
gynecologic surgery	2 studies	203 studies
Gynecological Surgeries	1 studies	90 studies
Gynecologic Surgical Procedure	--	12 studies
Gynecological Surgical Procedure	--	3 studies
gynecologic	6 studies	1,155 studies
Gynaecologic	--	64 studies
embolism	367 studies	1,764 studies
Embolus	20 studies	49 studies
thrombosis	385 studies	2,004 studies
Blood Clots	21 studies	78 studies
Thrombi	20 studies	141 studies
Blood Clotting	8 studies	32 studies
thrombotic disorder	--	3 studies

--	No studies found
*	Number of studies in the search results containing the term or synonym
**	Number of studies in the entire database containing the term or synonym

Appendix 6. Appendix 5: WHO ICTRP

Condition: Embolism OR Thrombosis

Intervention: heparin OR antithrombotic prophylaxis OR prevention

Appendix 7. Data Extraction Form

Data collection form

Study ID
Notes

General Information

Date form completed *(dd/mm/yyyy)*
Name/ID of person extracting data
Reference citation (e.g. Medline)
Study author contact details
Publication type *(e.g. full report, abstract, letter)*
Notes:

Study eligibility

Study Characteristics	Eligibility criteria	Eligibility criteria met?			Location in text or source
		Yes	No	Unclear	
Type of study	Randomized controlled trials (RCT)				
	Quasi-experimental studies including quasi-randomized trials				
	Observational studies including cohort, case-control and cross-sectional studies.				
Participants	Abdominal or pelvic operations (benign or malignant pathology)				
Type of intervention	LMWH for extended duration (>= 14 days)				
Types of comparison	LMWH <14 days or other method of thromboprophylaxis				
Types of outcome measures	Primary outcome: VTE, or pulmonary embolism within 30 days of surgery Secondary outcome: Bleeding complications				
Types of determinants	Determinants of concern are: 1) Socioeconomic status - assessed by income, expenditure, household characteristics and/or assets, occupational or contractual status – and education (highest level of education completed, years of schooling, literacy);				

(Continued)

	2) Geographic (euclidian distance - km - to a health center, travel time, location - rural vs. urban residence); 3) Demographic (ethnicity, marital status, immigration status).
Results	Quantitative results of the association between potential determinants and postnatal care services utilization

INCLUDE	EXCLUDE
Reason for exclusion	
Notes:	

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Characteristics of included studies

Methods

	Descriptions as stated in report/paper
Aim of study	
Design	
Study Setting (single/multi-instituional)	
Start date	
End date	
Duration of participation	
Notes:	

Participants

	Description	Location in text or source *(pg & ¶/fig/table)*
Population description		
Setting and context		
Inclusion criteria		

(Continued)

Exclusion criteria		
Method of recruitment of participants		
Informed consent obtained	Yes No Unclear	
Total no. of participants		
Withdrawals and exclusions		
Missing data		
Outcome(s) Definition, measure & classification	Primary outcome – VTE or PE	
	Secondary outcomes 1) Bleeding complication	
Confounding factors/ effect modifiers accounted for		
Results (specify, e.g. OR, RR, IRR) (specify the reference group)	Crude	
	Adjusted	
Authors' reported limitations of study's methods/results		
Scientific quality (specify tool, e.g. modified EPHPP tool)		
Notes:		

Other information

Study funding sources *(including role of funders)*		
Possible conflicts of interest *(for study authors)*		
	Description as stated in report/paper	**Location in text or source**
Key conclusions of study authors		
References to other relevant studies		
Notes:		

WHAT'S NEW

Date	Event	Description
14 October 2019	Amended	Minor changes to abstract to increase clarity.

HISTORY

Protocol first published: Issue 3, 2003
Review first published: Issue 1, 2009

Date	Event	Description
13 May 2019	Amended	Correction of typographical error.
21 February 2019	New citation required and conclusions have changed	Review amended in order to include mortality as an outcome.
21 February 2019	Amended	Review amended according to comment and author response.
28 October 2017	New citation required and conclusions have changed	Update of the version published in the Cochrane Library 2009, Issue 1. Three new studies identified and included.
28 October 2017	New search has been performed	New version submitted.
30 June 2008	Amended	Converted to new review format.
8 January 2008	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

SIF structured the work, extracted the data, completed data entry and analysis and wrote the final manuscript.
RSK and CCJ extracted data and proofread the manuscript.
MSR, BS, MRK and RDM proofread the manuscript.

DECLARATIONS OF INTEREST

MSR is a member the advisory board of Pfizer, Denmark.

One author has been investigators on three of the randomized trials included in this review update (Rasmussen 2006).

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

After recommendation from the editorial team, 'pelvic surgery' has been added to the title.

INDEX TERMS

Medical Subject Headings (MeSH)

Abdomen [surgery]; Anticoagulants [*therapeutic use]; Drug Administration Schedule; Heparin, Low-Molecular-Weight [*therapeutic use]; Pelvis [surgery]; Postoperative Complications [epidemiology] [prevention & control]; Postoperative Hemorrhage [epidemiology] [*prevention & control]; Randomized Controlled Trials as Topic; Venous Thromboembolism [epidemiology] [*prevention & control]

MeSH check words

Humans