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Prolonged thromboprophylaxis with Low Molecular Weight heparin for abdominal or pelvic surgery

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ABSTRACT

Background
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 thromboprophylaxis after surgery remains controversial. Some studies suggest that patients undergoing major abdominal surgery benefit from prolongation of the thromboprophylaxis to 1 month after surgery. No systematic review on prolonged thromboprophylaxis after major abdominal or pelvic surgery has been published.

Objectives
To evaluate the efficacy and safety of prolonged thromboprophylaxis with LMWH for at least 1 month after abdominal or pelvic surgery with thromboprophylaxis administered during the in-hospital period only in preventing late VTE.

Search strategy
Electronic searches were performed January 2008 in the Medline, Embase, Lilacs, and the Cochrane Central Register of Controlled Trials. Abstract books from major congresses addressing thromboembolism were hand searched, as were reference lists from studies of relevance.

Selection criteria
We assessed both randomised and non-randomised controlled clinical trials comparing prolonged thromboprophylaxis with any anti-thrombotic agent with placebo and/or thromboprophylaxis during the admission period only. The patient population in the trials were patients undergoing abdominal or pelvic surgery. The outcome measures included VTE (deep venous thrombosis (DVT) or pulmonary embolism (PE)) as assessed by objective means (ascending bilateral venography, ultrasonography, pulmonary ventilation/perfusion scintigraphy, spiral CT scan or autopsy). Studies exclusively reporting on clinical diagnosis of VTE, without objective confirmation were excluded.

Data collection and analysis
The identification of studies and data extraction were performed by the authors. Outcomes were VTE (DVT or PE) assessed by objective means. Safety outcome were defined as bleeding complications and mortality within 3 months after surgery.
Main results

The search exclusively detected trials evaluating prolonged thromboprophylaxis with LMWH as compared to control or placebo. 133 studies were found in the searches, of which only 4 were found eligible for inclusion, and 129 were excluded. The incidence of overall VTE after major abdominal or pelvic surgery was 14.3% (95% confidence interval 11.2% - 17.8%) in the control group as compared to 6.1% (95% CI 4.0% - 8.7%) in the patients receiving out-of-hospital LMWH. This difference was statistically significant, Peto Odds Ratio 0.41 (95% CI 0.26 -0.63), P < 0.0005. Prolonged thromboprophylaxis with LMWH was also associated with a statistically significant reduction of even the incidence of symptomatic VTE from 1.7% (95% CI 0.8% - 3.4%) in the control group to 0.2 % (95% CI 0.0% - 1.2%) in patients receiving prolonged thromboprophylaxis, Peto Odds ratio 0.22 (95% CI 0.06 -0.80), P = 0.02. The respective incidence of bleeding in the control and LMWH group were 3.7% (95% CI 2.4% -5.5%) and 4.1% (95% CI 2.7% - 6.0%), Peto Odds ratio 1.11 (95% CI 0.62 - 1.97), P = 0.73. There was no significant heterogeneity detected as regards to outcome parameters reported in the included trials.

Authors’ conclusions

Prolonged thromboprophylaxis with LMWH significantly reduces the risk of VTE compared to thromboprophylaxis during hospital admittance only, without increasing bleeding complications after major abdominal or pelvic surgery.

PLAIN LANGUAGE SUMMARY

Prolonged administration of low molecular weight heparin lowers the number of blood clots in the lower limbs after operation in the abdomen or pelvis

Patients subjected to major surgery of the abdomen are at considerable risk of developing blood clots in the veins of the lower limbs. These clots may detach and develop clots in the lungs and cause sudden death. Clots in the limbs may impair the venous function leading to a life-long tendency to swollen legs and leg ulceration. In order to avoid these complications patients are often offered protective medicine during the first week after surgery, but patients are probably at risk of developing clots up to one month after surgery. This review suggests that prophylaxis should be administered for at least one month after surgery.

BACKGROUND

Abdominal surgery leads to a hypercoagulable state, indicating an increased risk for DVT (Iversen 2002). The activation of the coagulation system last for at least 14 days (Galster 2000) and unpublished data suggests that patients remain in a hypercoagulable state for at least one month after surgery. Dahl et al. reported that discontinuation of thromboprophylaxis one week after hip surgery resulted in a second wave of coagulation and fibrinolysis activation (Dahl 1995). Administration of extended thromboprophylaxis with LMWH lowers the markers of coagulation (Arnesen 2003). After major abdominal surgery a similar activated condition lasted until after discharge and was significantly more pronounced for patients with malignant compared to benign disease (Rahr 1994).

Patients undergoing major abdominal or pelvic surgery are at increased risk of developing postoperative venous thromboembolic complications (VTE). The incidence of deep vein thrombosis (DVT) following abdominal surgery in the absence of thromboprophylaxis is 19 to 29% in high risk patients (Geerts 2001). Several methods to reduce VTE have been implemented clinically. Thromboprophylaxis with unfractionated or low-molecular weight heparin (LMWH) administered for the first postoperative week in general surgical patients reduces the incidence of VTE (Geerts 2001).

Prospective cohort studies have revealed an incidence of postoperative DVT as high as 25% four to six weeks after surgery (Sørensen 1990, Scurr 1988, Clarke-Pearson 1984), and a 0.13 - 0.63% incidence of pulmonary embolism (PE) of (Kiil 1978, Huber 1992). A small, randomised study including general surgical patients showed a non-significant reduction in the incidence of DVT as assessed by bilateral venography 28 days after surgery, following four weeks versus one week of thromboprophylaxis with a LMWH (Lausen 1998). A larger double-blind multicentre study with a comparable design reported a significant reduction of DVT in patients with abdominal or pelvic cancer after prolongation of prophylactic administration of LMWH (Bergqvist 2002). The optimal duration of thromboprophylaxis in general surgery remains controversial.

The efficacy of unfractionated heparin and LMWH in general
surgery is comparable but thromboprophylaxis with LMWH allows once daily injection and carries a lesser risk of heparin-induced thrombocytopenia (Jørgensen 1993).

The efficacy of prolonged thromboprophylaxis in patients undergoing major abdominal or pelvic surgery has not previously been systematically reviewed.

OBJECTIVES

The purpose of this systematic review was to evaluate the efficacy and safety of prolonged thromboprophylaxis with different prophylactic methods in preventing late VTE when compared to thromboprophylaxis administered during the first week after surgery.

Late VTE was defined as VTE occurring from the 7th post-operative day and until 3 months postoperatively.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or non-randomised controlled clinical trials comparing prolonged thromboprophylaxis interventions with in-hospital prophylaxis and later placebo or no treatment were considered. Objective diagnostic methods were mandatory for the screening in all patients. Studies with symptomatic outcome measures were included if objectively confirmed.

Types of participants

Patients undergoing general abdominal or pelvic surgery for cancer or benign disease. The surgical procedures included both laparotomies and laparoscopies.

Types of interventions

Trials reporting the use of the following interventions were considered:

A: LMWH (different doses)
B: Unfractionated heparin (5,000 IU s.c. b.i.d or t.i.d)
C: Mechanical methods (graded compression stockings, sequential compression devices)
D: Vitamin K antagonists (phenprocoumon or acenocoumarol)

The prophylactic intervention to patients allocated to prolonged thromboprophylaxis should be continued for at least 14 days after surgery.

Types of outcome measures

The primary outcomes included the incidence of DVT, PE or fatal PE within 30 days after surgery and the postoperative 3-months mortality rate. The efficacy outcome includes both symptomatic and asymptomatic DVT and PE. VTE was to be verified by a mandatory objective test. These included venography, ultrasound/Doppler examination, ventilation-perfusion lung scintigraphy, spiral CT scan or autopsy. The secondary outcomes were symptomatic VTE, verified by mandatory objective test, bleeding complications and mortality. During the analyses, it became apparent that mortality was an important outcome and was thus included as a secondary outcome. Bleeding complications were defined as major or minor bleeding according to the definition in the primary studies. Safety outcome measures were evaluated from reported transfusions requirements.

The evaluations of the outcomes should be blinded with regard to the prophylactic treatment given (assessor-blinded), if a double-blind method was not applied.

Search methods for identification of studies

An electronic search was conducted January 2008, by an experienced trial search coordinator, in Pubmed from 1967, in Lilacs from 1967, in Embase from 1980 and the Cochrane Central Register of Controlled Trials. The general search strategy described by the Cochrane Colorectal Cancer Group was used in Medline and the Cochrane Central Register of Controlled Trials as well as a comparable search strategy in the Embase-search. A search for both randomised and non-randomised controlled clinical trials was done. The bibliography of each trial report were checked for additional references. Primary authors of RCTs were contacted, if necessary, for clarification of data. The reference-lists from major review articles from 1990 were scrutinized. All references from previously performed meta-analyses were cross-checked with the other searches. The abstract books of the congresses arranged by The International Society on Thrombosis and Haemostasis as well as The Mediterranean League against Thrombosis were consulted back to 1976.

The general search strategy for the databases:
general surgery OR abdominal surgery
AND thrombos* OR thromboem*
AND prophylaxis OR prophylactic OR prevention
AND prolonged OR long term OR duration OR late

The above search strategy were combined with the following to identify randomised controlled trials in Pubmed and Cancer Lit:

1: Randomised-controlled-trial in PT
2: Randomised-controlled-trials
3: Random*
4: Double-blind-method  
5: Single-blind-method  
6: #1 OR #2 OR #3 OR #4 OR #5  
The general search strategy were combined with the following to identify randomised controlled trials in Embase:  
1: explode ‘clinical trial’ / all subheadings  
2: explode ‘controlled study’ / all subheadings  
3: randomisation- / all subheadings  
4: ‘case-control-study’ / all subheadings  
5: #2 NOT #4  
6: #1OR #3 OR #5  
7: random* OR clin*  
8: #6 OR #7  

**RESULTS**

**Description of studies**

See: Characteristics of included studies; Characteristics of excluded studies.  
The primary search performed revealed 132 studies, of which 94 were excluded by reviewing the title 38 were selected to be evaluated by the abstract, of these 5 met the inclusion criteria. 33 studies were excluded 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 hand searching and only as an abstract presentation, and is thus reported as unpublished data (Jørgensen 2002).

Thus, three RCTs published as papers and one RCT published as an abstract met the inclusion criteria of this review and were included in the meta-analysis (Bergqvist 2002; Lausen 1998; Rasmussen 2006; Jørgensen 2002). The trial of Bergqvist et al. was a double-blinded RCT, while the trials of Rasmussen et al. and Lausen et al. were open-labelled trials with blinded assessment of the venograms. The publication of Jørgensen et al. consisted of a meta-analysis of the material from the Lausen et al. trial and unpublished data from a double-blind RCT. Both of these trials were terminated prematurely due to lack of funding. The data from the Lausen et al. trial was entered in the present analysis once, thus the data obtained from the Jørgensen et al. study will be the unpublished data from that meta-analysis.

**Risk of bias in included studies**

Details of the individual studies are listed in the table of included studies.
Methodological quality of included studies/ Quality assessment. All the trials defined an ITT-analysis of the outcome data as those patients who entered the randomised phase of the study and had an evaluable efficacy end-point. None of the studies provided information of number of transfusions.

Lausen et al. trial:
Randomisation: Computer-generated allocation list
Concealment: Adequate with sealed envelopes.
Blinding: Open-label study with assessor-blinded evaluation of the venograms. Patients, healthcare providers and data-analyst were not blinded.
Patients characteristics: Patients undergoing major abdominal surgery or non cardiac thoracic surgery for either benign or malignant disease
ITT-analysis: Patients were included in the final analysis if they have reached an evaluable VTE end point (venogram or objective verification of symptomatic VTE)
Completeness of follow-up: There was no defined follow-up period.
Early stoppage of a trial: The study was terminated prematurely due to lack of funding.
Outcome definition: 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.

Bergqvist et al. trial:
Randomisation: Not described in the paper
Concealment: Not described in the paper.
Blinding: Placebo-controlled double blind study. Patients, healthcare providers, data collectors, outcome assessors and data analysts were blinded.
Patients characteristics: Patients undergoing major abdominal or pelvic surgery for either benign or malignant disease
ITT-analysis: Patients was included in the final analysis if they have reached an evaluable VTE end point (venogram or objective verification of symptomatic VTE).
Completeness of follow-up: Follow-up period 3 months. Complete follow-up.
Outcome definition: All patients were scheduled for bilateral venography. Adequate definitions of VTE and bleeding complications were described. However, the planned interim analysis performed with the 328 patients included in the study did not reveal any significant difference between the two treatment groups. In order to perform a meta-analysis with the results of the study of Lausen et al. (also specifically evaluating the effect of tinzaparin) the venograms were re-evaluated by the same radiologists who assessed the venograms in the study by Lausen et al.
No effort was done in order to rank the studies according to methodological quality.

Effects of interventions
No studies reporting on the prolonged use of unfractionated heparin, oral anticoagulants or mechanical methods were identified. The search provided the opportunity to compare LMWH with placebo or no treatment with the following out-come parameters: Overall VTE, proximal DVT, all DVT, symptomatic VTE, bleeding complications and mortality.
LMWH versus placebo or no treatment: The incidence of VTE after major abdominal or pelvic surgery was 14.3% (95% Confidence Interval 11.2% - 17.8%) in the control group as compared to 6.1% (95% CI 4.0% - 8.7%) in the patients receiving out-of-hospital LMWH. This difference was statistically significant (comparison 0.01), Peto Odds ratio 0.41 (95% CI 0.26 -0.63), P < 0.0001. The number of patients needed to treat (NNT) to avoid 1 case of VTE was 13 (95% CI 9 - 24). Prophylaxis with LMWH as compared to control also offered better
DISCUSSION

This meta-analysis supports that prolonged thromboprophylaxis with LMWH as compared with in-hospital prophylaxis significantly reduces the risk of major VTE in patients undergoing major abdominal or pelvic surgery. Although the included studies only reported a small number of symptomatic VTE, prolonged administration of LMWH was associated with significantly fewer cases of symptomatic VTE than found in the group allocated to short term thromboprophylaxis. This benefit was archived without a concomitant increase in bleeding complications. The studies included in the present meta-analysis were not designed to detect a reduction of PE or mortality. As such a trial would demand a huge number of patients it is not likely to be performed. In the present meta-analysis there was no significant difference in the mortality rate between the two allocation groups.

The studies included in this meta-analysis were all designed on "surrogate" end points based on mandatory bilateral venography carried out late after surgery. There has been much debate on the clinical relevance of asymptomatic cases of DVT detected in this way. Most of these cases are confined to the lower leg veins and have only a limited potential for progression or embolization. However, even asymptomatic postoperative DVT is associated with a 59% relative risk increment of developing late post-thrombotic syndrome compared with patients without postoperative DVT (Wille-Jørgensen 2005). Furthermore, a highly significant association was found between asymptomatic proximal DVT, detected by compression ultrasound, and the 90-days mortality in medical patients (Vaitkus 2007). This is in agreement with a large autopsy series reporting that fatal PE is seldom preceded by symptomatic DVT (Lindblad 1991). In the published orthopedic studies of extended thromboprophylaxis with LMWH it has been demonstrated, that the relative reduction of asymptomatic DVT as assessed by venography also translated into a corresponding reduction of symptomatic DVT (Hull 2001; Eikelboom 2001) as observed in the present meta-analysis. Based on these observations it is our opinion that asymptomatic VTE does have clinical importance, thus representing more than a "surrogate" end point.

Compliance in prolonged thromboprophylaxis are an important issue. Two of the included studies described a very high rate (more than 97% of the patients) of compliance (Lausen 1998; Rasmussen 2006) while compliance were not reported in the other studies (Bergqvist 2002; Jørgensen 2002). 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/or of the symptomatic VTE events occurring during the follow-up period of the Bergqvist trial (Bergqvist 2002) did not alter the conclusions of this meta-analysis.

There was no significant statistical heterogeneity among the studies, but some differences were identified regarding the design: Two studies were double-blinded and placebo-controlled whereas the other 2 reported assessor-blinded evaluations of the venograms. Although LMWHs belong to the same drug category the single drug differs in terms of anticoagulant profiles and this could cause some bias in the meta-analysis. However, the number of patients included in each trial were to small to make a reliable comparison between the different LMWHs. There were also differences regarding patient characteristics: Two studies included only high risk cancer patients (Bergqvist 2002; Jørgensen 2002) whereas the trials by Lausen and Rasmussen also considered patients subjected to general surgery for benign or malignant disease (Lausen 1998; Rasmussen 2006). It was not possible to make a comparison between these 2 patients groups, because no separate data was provided from patients with and without cancer in the two last manuscripts.

It is possible that the increased number of minimally invasive surgical procedures (Rahr 1999) and the current trend for fast-track recovery (Kehlet 2005) following gastrointestinal surgery may lower the risk of postoperative VTE. Laparoscopic procedures, however, also cause activation of the coagulation system and cases of VTE have been reported. The fact that these patients are often subjected to a shorter time of sufficient thromboprophylaxis due to early hospital discharge is a potential modern clinical dilemma. In the recently published “Guidelines for DVT prophylaxis during laparoscopic surgery” (SAGES 2007) the authors advocate for a...
patient risk factor stratification in accordance with the American College of Chest Physicians (ACCP) Guidelines (Geerts 2004). Until randomised trials including patients undergoing fast track surgery and laparoscopic procedure are available the use of thromboprophylaxis according to ACCP guidelines is recommended.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

Administration of LMWH for 4 weeks compared to 5-7 days of after major abdominal or pelvic surgery significantly reduces the incidence of VTE without jeopardizing safety.

**Implications for research**

Future research of VTE complications should include patients undergoing laparoscopic surgery under fast track regime. Furthermore larger studies including a large number of patients making clinical outcomes measures possible are needed. New antithrombotic drugs with oral administration will soon be available and might ease the implication of prolonged thromboprophylaxis.

**ACKNOWLEDGEMENTS**

CCCG editorial office for conversion of the review to the required RM5 format.

**REFERENCES**

References to studies included in this review

**Bergqvist 2002** (published data only)


**Jørgensen 2002** (unpublished data only)


**Lausen 1998** (published data only)


References to studies excluded from this review

**Rasmussen 2006** (published data only)


**Rasmussen 2003** (published data only)


**Rasmussen 2003a** (published data only)

Additional references

Arnesen 2003

Clarke-Pearson 1984

Dahl 1995

Eikelenboom 2001

Galster 2000

Geerts 2001

Geerts 2004

Huber 1992

Hull 2001

Iversen 2002
Iversen LH, Thorlaisius-Ussing O. Relations of coagulation test abnormalities to tumour burden and postoperative DVT in resected colorectal cancer. Thrombosis Haemostasis 2002;87:402–8.

Jørgensen 1993

Kehl 2005

Kiil 1978

Lindblad 1991

Rahr 1994

Rahr 1999

SAGES 2007

Scurr 1988

Sørensen 1990

Vairkus 2007

Wille-Jørgensen 1992

Wille-Jørgensen 2005

* Indicates the major publication for the study
### CHARACTERISTICS OF STUDIES

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

**Bergqvist 2002**

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**Methods**
RCT, double-blinded, venography

**Participants**
Patients undergoing surgery for abdominal or pelvic cancer

**Interventions**
LMWH (enoxaparin 40 mg) or placebo

**Outcomes**
LMWH 165
Placebo 167

**Notes**

**Risk of bias**

**Jørgensen 2002**

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**Methods**
RCT, double-blinded, venography

**Participants**
Patients undergoing curative surgery for abdominal or pelvic cancer

**Interventions**
LMWH (tinzaparin 3500 IE) or placebo

**Outcomes**
LMWH 58
Placebo 50

**Notes**
Unpublished data.

**Risk of bias**
<table>
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<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
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<tr>
<td>Lausen 1998</td>
<td>RCT, assessor-blinded, venography</td>
<td>Patients undergoing major abdominal or non cardiac thoracic surgery for either malignant or benign diseases</td>
<td>LMWH (tinzaparin 3500 IE) or no treatment</td>
<td>LMWH 58</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Control 60</td>
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<tr>
<td>Rasmussen 2006</td>
<td>RCT, assessor blinded, venography</td>
<td>Patients undergoing major abdominal surgery for either malignant or benign diseases</td>
<td>LMWH (dalteparin 5000 IE) or no treatment</td>
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**Characteristics of excluded studies**  
[ordered by study ID]
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## Data and Analyses

### Comparison 1. LMWH versus placebo

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<td>1 All VTE</td>
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<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
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<td>2 All DVT</td>
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<td>901</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.43 [0.27, 0.66]</td>
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<tr>
<td>3 Proximal DVT</td>
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<td>901</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
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<td>4 Symptomatic VTE</td>
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<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.22 [0.06, 0.80]</td>
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<td>5 All VTE (Sensitivity analysis)</td>
<td>3</td>
<td>793</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.42 [0.27, 0.68]</td>
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<tr>
<td>6 Symptomatic VTE (Sensitivity analysis)</td>
<td>3</td>
<td>793</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.14 [0.02, 0.82]</td>
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<td>7 Bleeding complications</td>
<td>4</td>
<td>1242</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>1.11 [0.62, 1.97]</td>
</tr>
<tr>
<td>8 Mortality</td>
<td>4</td>
<td>1021</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>1.12 [0.65, 1.93]</td>
</tr>
</tbody>
</table>

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

Review: Prolonged thromboprophylaxis with Low Molecular Weight heparin for abdominal or pelvic surgery

Comparison: 1 LMWH versus placebo

Outcome: 1 All VTE

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio (Peto, Fixed, 95% CI)</th>
<th>Weight</th>
<th>Peto Odds Ratio (Peto, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergqvist 2002</td>
<td>8/165</td>
<td>20/167</td>
<td>3.12 %</td>
<td>0.40 [0.18, 0.86]</td>
<td></td>
</tr>
<tr>
<td>Jrgensen 2002</td>
<td>4/58</td>
<td>10/50</td>
<td>1.48 %</td>
<td>0.32 [0.10, 0.97]</td>
<td></td>
</tr>
<tr>
<td>Lausen 1998</td>
<td>3/58</td>
<td>6/60</td>
<td>1.02 %</td>
<td>0.51 [0.13, 1.96]</td>
<td></td>
</tr>
<tr>
<td>Rasmussen 2006</td>
<td>12/165</td>
<td>29/178</td>
<td>4.38 %</td>
<td>0.43 [0.22, 0.82]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>446</strong></td>
<td><strong>455</strong></td>
<td>100.0 %</td>
<td><strong>0.41 [0.26, 0.63]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 27 (Treatment), 65 (Control)

Heterogeneity: $\chi^2 = 0.32$, df = 3 ($P = 0.96$); $I^2 = 0.0$

Test for overall effect: $Z = 4.09$ ($P = 0.000043$)
### Analysis 1.2. Comparison 1 LMWH versus placebo, Outcome 2 All DVT.

**Review:** Prolonged thromboprophylaxis with Low Molecular Weight heparin for abdominal or pelvic surgery

**Comparison:** 1 LMWH versus placebo

**Outcome:** 2 All DVT

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio Weight</th>
<th>Peto Odds Ratio Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peto,Fixed,95% CI</td>
<td>Peto,Fixed,95% CI</td>
</tr>
<tr>
<td>Bergqvist 2002</td>
<td>8/165</td>
<td>20/167</td>
<td>32.1 % 0.40 [0.18, 0.86]</td>
<td></td>
</tr>
<tr>
<td>Jrgensen 2002</td>
<td>4/58</td>
<td>10/50</td>
<td>15.3 % 0.32 [0.10, 0.97]</td>
<td></td>
</tr>
<tr>
<td>Lausen 1998</td>
<td>3/58</td>
<td>6/60</td>
<td>10.5 % 0.51 [0.13, 1.96]</td>
<td></td>
</tr>
<tr>
<td>Rasmussen 2006</td>
<td>12/165</td>
<td>26/178</td>
<td>42.2 % 0.48 [0.24, 0.93]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>446</td>
<td>455</td>
<td>100.0 % 0.43 [0.27, 0.66]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 27 (Treatment), 62 (Control)

Heterogeneity: Chi² = 0.47, df = 3 (P = 0.93); I² = 0%

Test for overall effect: Z = 3.83 (P = 0.00013)

---

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

**Review:** Prolonged thromboprophylaxis with Low Molecular Weight heparin for abdominal or pelvic surgery

**Comparison:** 1 LMWH versus placebo

**Outcome:** 3 Proximal DVT

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio Weight</th>
<th>Peto Odds Ratio Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peto,Fixed,95% CI</td>
<td>Peto,Fixed,95% CI</td>
</tr>
<tr>
<td>Bergqvist 2002</td>
<td>1/165</td>
<td>3/167</td>
<td>14.7 % 0.37 [0.05, 2.64]</td>
<td></td>
</tr>
<tr>
<td>Jrgensen 2002</td>
<td>1/58</td>
<td>4/50</td>
<td>17.8 % 0.24 [0.04, 1.47]</td>
<td></td>
</tr>
<tr>
<td>Lausen 1998</td>
<td>0/58</td>
<td>2/60</td>
<td>7.4 % 0.14 [0.01, 2.23]</td>
<td></td>
</tr>
<tr>
<td>Rasmussen 2006</td>
<td>3/165</td>
<td>14/178</td>
<td>60.1 % 0.28 [0.10, 0.74]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>446</td>
<td>455</td>
<td>100.0 % 0.27 [0.13, 0.57]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 5 (Treatment), 23 (Control)

Heterogeneity: Chi² = 0.34, df = 3 (P = 0.95); I² = 0%

Test for overall effect: Z = 3.41 (P = 0.00066)
**Analysis 1.4. Comparison 1 LMWH versus placebo, Outcome 4 Symptomatic VTE.**

Review: Prolonged thromboprophylaxis with Low Molecular Weight heparin for abdominal or pelvic surgery

Comparison: 1 LMWH versus placebo

Outcome: 4 Symptomatic VTE

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio Peto,Fixed,95% CI</th>
<th>Weight</th>
<th>Peto Odds Ratio Peto,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergqvist 2002</td>
<td>1/165</td>
<td>4/167</td>
<td>55.4 % 0.30 [0.05, 1.75]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jrgensen 2002</td>
<td>0/58</td>
<td>0/50</td>
<td>0.0 % 0.0 [0.0, 0.0]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lausen 1998</td>
<td>0/58</td>
<td>1/60</td>
<td>11.2 % 0.14 [0.00, 7.06]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasmussen 2006</td>
<td>0/165</td>
<td>3/178</td>
<td>33.4 % 0.14 [0.01, 1.40]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>446</strong></td>
<td><strong>455</strong></td>
<td><strong>100.0 % 0.22 [0.06, 0.80]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1 (Treatment), 8 (Control)

Heterogeneity: Chi² = 0.30, df = 2 (P = 0.86); I² = 0%

Test for overall effect: Z = 2.29 (P = 0.022)

---

**Analysis 1.5. Comparison 1 LMWH versus placebo, Outcome 5 All VTE (Sensitivity analysis).**

Review: Prolonged thromboprophylaxis with Low Molecular Weight heparin for abdominal or pelvic surgery

Comparison: 1 LMWH versus placebo

Outcome: 5 All VTE (Sensitivity analysis)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio Peto,Fixed,95% CI</th>
<th>Weight</th>
<th>Peto Odds Ratio Peto,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergqvist 2002</td>
<td>8/165</td>
<td>20/167</td>
<td>36.6 % 0.40 [0.18, 0.86]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lausen 1998</td>
<td>3/58</td>
<td>6/60</td>
<td>11.9 % 0.51 [0.13, 1.96]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasmussen 2006</td>
<td>12/165</td>
<td>29/178</td>
<td>51.5 % 0.43 [0.22, 0.82]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>388</strong></td>
<td><strong>405</strong></td>
<td><strong>100.0 % 0.42 [0.27, 0.68]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 23 (Treatment), 55 (Control)

Heterogeneity: Chi² = 0.09, df = 2 (P = 0.96); I² = 0%

Test for overall effect: Z = 3.59 (P = 0.00033)
### Analysis 1.6. Comparison 1 LMWH versus placebo, Outcome 6 Symptomatic VTE (Sensitivity analysis).

**Review**: Prolonged thromboprophylaxis with Low Molecular Weight heparin for abdominal or pelvic surgery

**Comparison**: 1 LMWH versus placebo

**Outcome**: 6 Symptomatic VTE (Sensitivity analysis)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>Peto,Fixed,95% CI</td>
<td></td>
<td>Peto,Fixed,95% CI</td>
</tr>
<tr>
<td>Bergqvist 2002</td>
<td>0/165</td>
<td>1/167</td>
<td>20.1 %</td>
<td>0.14</td>
<td>[0.00, 6.90]</td>
</tr>
<tr>
<td>Lausen 1998</td>
<td>0/58</td>
<td>1/60</td>
<td>20.1 %</td>
<td>0.14</td>
<td>[0.00, 7.06]</td>
</tr>
<tr>
<td>Rasmussen 2006</td>
<td>0/165</td>
<td>3/178</td>
<td>59.8 %</td>
<td>0.14</td>
<td>[0.01, 1.40]</td>
</tr>
</tbody>
</table>

**Total (95% CI)** 388 / 405 = 100.0 % 0.14 [0.02, 0.82]

Total events: 0 (Treatment), 5 (Control)

Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² = 0.0%

Test for overall effect: Z = 2.18 (P = 0.029)

### Analysis 1.7. Comparison 1 LMWH versus placebo, Outcome 7 Bleeding complications.

**Review**: Prolonged thromboprophylaxis with Low Molecular Weight heparin for abdominal or pelvic surgery

**Comparison**: 1 LMWH versus placebo

**Outcome**: 7 Bleeding complications

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>Peto,Fixed,95% CI</td>
<td></td>
<td>Peto,Fixed,95% CI</td>
</tr>
<tr>
<td>Bergqvist 2002</td>
<td>13/253</td>
<td>9/248</td>
<td>45.7 %</td>
<td>1.43</td>
<td>[0.61, 3.36]</td>
</tr>
<tr>
<td>Jrgensen 2002</td>
<td>6/93</td>
<td>5/94</td>
<td>22.6 %</td>
<td>1.23</td>
<td>[0.36, 4.13]</td>
</tr>
<tr>
<td>Lausen 1998</td>
<td>2/75</td>
<td>3/84</td>
<td>105 %</td>
<td>0.74</td>
<td>[0.13, 4.41]</td>
</tr>
<tr>
<td>Rasmussen 2006</td>
<td>4/193</td>
<td>6/202</td>
<td>21.2 %</td>
<td>0.70</td>
<td>[0.20, 2.44]</td>
</tr>
</tbody>
</table>

**Total (95% CI)** 614 / 628 = 100.0 % 1.11 [0.62, 1.97]

Total events: 25 (Treatment), 23 (Control)

Heterogeneity: Chi² = 1.09, df = 3 (P = 0.78); I² = 0.0%

Test for overall effect: Z = 0.35 (P = 0.73)
### Analysis 1.8. Comparison 1 LMWH versus placebo, Outcome 8 Mortality.

Review: Prolonged thromboprophylaxis with Low Molecular Weight heparin for abdominal or pelvic surgery

Comparison: 1 LMWH versus placebo

Outcome: 8 Mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio Peto,Fixed 95% CI</th>
<th>Weight</th>
<th>Peto Odds Ratio Peto,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergqvist 2002</td>
<td>3/165</td>
<td>6/167</td>
<td>16.8 % 0.51 [ 0.14, 1.92 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jrgensen 2002</td>
<td>2/93</td>
<td>0/94</td>
<td>3.8 % 7.55 [ 0.47, 121.63 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lausen 1998</td>
<td>4/75</td>
<td>5/84</td>
<td>16.3 % 0.89 [ 0.23, 3.41 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasmussen 2006</td>
<td>20/165</td>
<td>17/178</td>
<td>63.2 % 1.31 [ 0.66, 2.58 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)** 498 523 100.0 % 1.12 [ 0.65, 1.93 ]

Total events: 29 (Treatment), 28 (Control)

Heterogeneity: Chi² = 3.47; df = 3 (P = 0.33); I² = 13%

Test for overall effect: Z = 0.41 (P = 0.68)

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**WHAT’S NEW**

Last assessed as up-to-date: 20 October 2008.

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0.1 0.2 0.5 1.0 2.0 5.0 10.0

Favours treatment Favours control

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**HISTORY**


Review first published: Issue 1, 2009

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8 January 2008 New citation required and conclusions have changed Substantive amendment

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Prolonged thromboprophylaxis with Low Molecular Weight heparin for abdominal or pelvic surgery (Review) 16

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CONTRIBUTIONS OF AUTHORS
Morten Schnack Rasmussen came with the idea, structured the work, extracted the data, made the data-entry and the analysis and made the final manuscript.

Peer Wille-Jørgensen extracted data and proof read the manuscript

Lars N Jorgensen extracted data and proof read the manuscript

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

All three authors has been investigators on three of the randomised trials included in this review (Lausen 1998; Jørgensen 2002; Rasmussen 2006)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW
After recommendation from the editorial team, 'pelvic surgery' has been added to the title