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Heparins and mechanical methods for thromboprophylaxis in colorectal surgery (Review)

Wille-Jørgensen P, Rasmussen MS, Andersen BR, Borly L

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[Intervention Review]

Heparins and mechanical methods for thromboprophylaxis in colorectal surgery

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ABSTRACT

Background

Colorectal surgery implies higher risk of postoperative thromboembolic complications as deep venous thrombosis (DVT) and pulmonary embolism (PE) than general surgery. The best prophylaxis in general surgery is heparin and graded compression stockings. No systematic review on combination prophylaxis or on thrombosis prophylaxis in colorectal surgery has been published.

Objectives

To compare the incidence of postoperative thromboembolism after colorectal surgery using prophylactic methods focussing on heparins and mechanical methods alone and in combinations.

Search methods

Electronic searches was performed in PUBMED, EMBASE, LILACS and the Cochrane Library. Abstract books from major congresses were handsearched as were reference lists from previously performed reviews.

Selection criteria

RCT or CCT comparing prophylactic interventions and/or placebo. Outcomes were ascending venography, 125 I-fibrinogen uptake test, ultrasound methods, pulmonary scintigraphy. Studies, using thermographic methods, other isotopic methods, plethysmographic methods, and purely clinical methods as the only diagnostic measure were excluded. 558 studies were identified - 477 were excluded. Only 3 of the identified studies focused exclusively on colorectal surgery. Studies of general surgery contain considerable numbers of colorectal patients. The authors of 66 studies in general and/or abdominal surgery were contacted for retrieving the results from the colorectal patients. Answers were received from very few. 19 studies entered this review.

Data collection and analysis

All studies and all data extraction were performed by at least two of the authors. Outcome was deep venous thrombosis and/or pulmonary embolism. Analysis of bleeding complications were unfeasible. 12 meaningful outcomes were analysed by means of the fixed effects model with Peto Odds Ratios.

Main results

Heparins versus no treatment: Any kind of heparincompared to no treatment or placebo (comparison 07.03, 11 studies). Heparin is better in preventing DVT and/or PE with a Peto Odds ratio at 0.32 (95% Confidence Interval 0.20-0.53)

Unfractionated heparin versus low molecular weight heparin (comparison 08.03, 4 studies). The two treatments were found equally effective in preventing DVT and/or PE with a Peto Odds ratio 1.01 (95% Confidence Interval 0.67-1.52).
Mechanical methods (comparison 10.3, 2 studies).The combination of graded compression stockings and LDH is better than LDH alone in preventing DVT and/or PE with a Peto Odds ratio at 4.17 (95% Confidence Interval 1.37-12.70).

Authors' conclusions

The optimal prophylaxis in colorectal surgery is the combination of graduated compression stockings and low-dose unfractionated heparin. The unfractionated heparin can be replaced with low molecular weight heparin.

PLAIN LANGUAGE SUMMARY

A combination of graduated compression stockings and heparin seems to be the optimal prophylaxis for patients undergoing colorectal surgery.

Patients undergoing surgery of the large bowel and the rectum have a considerable risk of developing vascular complications expressed as venous thrombosis and/or thrombosis in the lungs (pulmonary embolism). These complications can lead to lifelong impaired venous function in the legs or occasionally sudden postoperative death. In order to avoid these complications, patients are often treated with blood-thinning medicine (anticoagulation) and graded compression stockings during operation. A combination treatment of Heparin and TED-stockings have been proved effective in general surgery. This review demonstrates that this combined treatment also is effective within the high-risk group of patients undergoing surgery of the large bowel or rectum.

BACKGROUND

Colorectal surgery implies a specific high risk for postoperative thromboembolic complications (TE) in form of deep venous thrombosis (DVT) and pulmonary embolism (PE) as compared to general surgery (Wille-Jørgensen 1988, Torngren 1982, Wille-Jørgensen 1990, Kjaergaard 1985). The reason for this is unknown. Pelvic dissection and/ or the peroperative positioning of the patients has been suggested. The different types of prophylaxis have been very well documented both in respect of many RCT´s and in systematic and unsystematic reviews (Collins et al 1988, Clagett 1988, Wille-Jørgensen 1991, Leizorovicz 1992, Nurmohammed 1992, Jørgensen 1993, Clagett 1995). Most of these reviews have dealt with the efficacy of various forms of heparin, and the overall conclusions are that low molecular weight heparin (LMWH) is an effective form of prophylaxis and perhaps better than unfractionated heparin. The latter question is addressed in a current Cochrane Review Protocol (Leizorovicz 1997). One investigation indicates, that a better prophylaxis can be obtained in patients with malignant disease, using a higher dose of LMWH (Bergqvist 1995). Mechanical compression in forms of graded compression stockings and/or intermittent compression devices are effective (Wille-Jørgensen 1991), and a systematic Cochrane Review on the efficacy of graded compression stockings in all kind of surgery has recently been included in The Cochrane Library (Amarigiri 2000). A better prophylaxis can be obtained by the use of a combination of medical and mechanical prophylaxis (Wille-Jørgensen 1991). The use of this combination has not yet been subject to a systematic review as well as a systematic review never previously addressed the problems with thromboprophylaxis in the group of patients undergoing colorectal surgery.

OBJECTIVES

To compare the incidence of postoperative thromboembolism after colorectal surgery having used different prophylactic methods focussing on various heparins and heparanoids and mechanical methods and their combinations.
It was the plan to stratify the studies in pre- or postoperative start of prophylaxis, but due to few studies this was not possible.

METHODS

Criteria for considering studies for this review

Types of studies

RCT or CCT comparing minimum two of the mentioned prophylactic interventions and/or placebo. The randomizations should have taken place before start of treatment. As diagnostic measures ascending venography, 125 I-fibrinogen uptake test, ultrasound/doppler methods, pulmonary scintigraphy, or autopsy should have been used for the whole population. Studies, using thermographic methods, other isotopic methods than the 125 I-fibrinogen uptake test, plethysmographic methods, and purely clinical methods as the only diagnostic measure have been excluded.
As expected only few of the identified studies exclusively focused on colorectal surgery. On the other hand most of the studies in general surgery contain a considerable number of patients having colorectal surgery performed. The primary authors and/or the sponsoring pharmaceutical companies of studies in general and/or abdominal surgery were contacted in order to make them report the results from the colorectal patients exclusively.
The start and end (in time) of the prophylaxis must have been stated

The studies should have described the mortality within 30 days. If this information is not available, it was sought directly from authors, but was very seldom obtained.

Types of participants

Patients undergoing major colorectal surgery for cancer or benign diseases. The participants had to be over 18 years of age. Major surgery implied:
Resections with or without anastomosis, diverting stomas. Excluded were endoscopic and/or transanal procedures.

Types of interventions

A: Unfractionated heparin (5000 IU b.i.d. or t.i.d)
B: Low-molecular weight heparins in different doses
C: Any kind of heparin + graded compression stockings
D: Any kind of heparin + Intermittent pneumatic compression
E: Intermittent compression alone
F: Placebo or untreated

The comparisons are listed in the tables of comparisons section

Types of outcome measures

The outcome was either DVT, PE, fatal PE or total mortality, evaluated within a standardized postoperative time (preferably 30 days for mortality and 7-14 days for DVT/PE).
The TE were diagnosed in an objective way using either mandatory venography, 125I-fibrinogen-uptake test, or Doppler-ultrasound, pulmonary perfusion/ventilation scans and/or autopsy.
The evaluations of the outcomes should at least be blinded against the prophylactic treatment given (assessor-blinding), if a double-blind method was not used.
It was the intention to include both intention to treat analyses and fulfilled protocol analysis. Due to the collected data, we were only able to perform the latter.

Search methods for identification of studies

See: Collaborative review group search strategy:
Electronic searches goes back to 1966 (in PUBMED, 1967 in LILACS and 1980 in EMBASE). The general search strategy, described by the Cochrane Colorectal Cancer Group was used in MEDLINE and The Cochrane Library as well as a comparable search strategy in EMBASE-search. A search for randomised clinical trials (RCT) and controlled clinical trials (CCT) was done. The specialised search used the terms:

colorectal or
colonic or
rectal or
general surgery or
abdominal surgery

and

thrombos* or thromboem*
and

prophylaxis or prevention

The electronic searches searched up to May 2003.

In order to identify more studies, the personal bibliographic register belonging to Peer Wille-Jørgensen, Denmark, was hand searched. The reference-lists form major review articles from 1990 were scrutinized. All references from previously performed meta-analyses were crossed-checked with the other searches . The abstract books of the Congresses arranged by The International Society on Thrombosis and Haemostasis as well as The Mediterrenean League aganist Thrombosis were consulted back to 1976.

Data collection and analysis

All identified trials were reviewed independently by two authors in order to validate the scientific approach and to evaluate, whether the trial could be included. Following data were extracted by minimum two authors: Type of prophylaxis, type of endpoint (DVT, PE, TE, and fatal PE), bleeding listed as major and minor bleeding events, bleeding in ml, per- and postoperative transfusion requirements. The definition of major and minor bleeding events followed the individual authors.
If both authors disagreed on study-validity and/or data extraction consensus was obtained. This happened in two occasions. The bleeding episodes were so inhomogeneous described that it was not possible to relate these complications to the colorectal patients. An analysis of bleeding exclusively on colorectal patients was thus omitted.

The authors of trials on general surgery were contacted by "snail-mail" and E-mail (if possible) in order to stratify their individual trial results in colorectal surgery and other surgery.

Following pharmaceutical companies were asked for the colorectal data from the studies on general surgery and abdominal surgery.

- Leo Chemicals (Denmark) (tinzaparine)
- Pharmacia (Sweden) (dalteparine)
- Aventis (France, USA) (enoxaparine)
- Choay (France) (fraxiparine)
- Alfa (Italy) (Fluxum)
- Knoll (Germany) (reviparine)

The process of getting the colorectal data out of the studies describing general surgery was extremely slow with a very modest outcome. It was thus decided to finish the review with the results obtained. Studies from which the results after colorectal surgery could not be obtained were not excluded, but placed in the category: Studies awaiting assessment, giving the authors an extra chance to answer our requests.

The results from each trial were entered into the RevMan 4.1 module and analysed as binomial data for the thromboembolic endpoints. We used the fixed effects model for the metaanalyses. When performing the analyses studies, different types of low-molecular weight heparins were only entered into the same analysis if the dose of LMWH was judged to be comparable in anti-Xa units (20 mg enoxaparine equalize 2500 anti-Xa units) and presuming the control groups were uniform.
In studies evaluating the efficacy of mechanical prophylaxis, medical prophylaxis (or none) should be the same in both the treated group and the control group within one study, but could vary between studies.
It was allowed, that the type of diagnostic objective measures differed across trials, as long as it was uniformly applied within the individual study to all patients.

As it is known, that there is a great interobserver variation in the evaluation of the endpoints used in prophylactic trials, which substantially can influence the incidence of TE (Wille-Jørgensen 1992), no comparisons across trials between apparently equal groups from different trials were thus made (e.g.. The incidence of DVT after two different LMWH´s in two different studies with apparently equal control groups and diagnostics)

The trials were checked for heterogeneity, when performing the analyses.

RESULTS

Description of studies

The electronic searches and the handsearch revealed 558 studies. Of these 464 were excluded by the primary selection because they did not include colorectal patients, did not address prophylaxis, were not RCT or CCT, or obviously represented double publications of RCT. Fifteen other studies were excluded in the second round due to various reasons listed in the list of excluded studies. In 66 occasions primary authors and/or sponsoring pharmaceutical companies were contacted in order to obtain the colorectal data. This process was only successful in 4 cases, despite several reminders and personal contacts. No authors directly stated that they did not want to give the information, in three cases the authors stated that the data were lost. Studies from which the results after colorectal surgery could not be obtained were not excluded, but placed in the category: Studies awaiting assessment, giving the authors an extra chance to answer our requests. In 19 studies data were useable.

In three studies the material consisted of colorectal patients only (Ho 1999, Mcleod 2001, Wille-Jørgensen 1986), while colorectal data were extracted from 16 studies. The bleeding episodes for colorectal patients only could be defined in two studies (Ho 1999, Mcleod 2001). Ten studies tested any kind of heparin versus no treatment or placebo in a total of 641 patients. Four studies tested unfractionated heparin versus LMWH in a total of 1183 patients and four studies investigated mechanical methods in various combinations in a total of 130 patients.

In 15 studies the 125I-fibrinogen uptake test was the primary screening method for DVT, supplied with confirmatory venography in 5 studies. Mandatory venography was used in one (the largest) study (Mcleod 2001) while Doppler-ultrasound was used in three studies. The number of PE was listed in only 4 studies, all based on clinical suspicion. Total mortality was mentioned in two studies and 30 days follow up was available in two studies. No studies described the autopsy frequency.

Details of the individual studies are listed in table of included studies.

Risk of bias in included studies

Demographic data were described sufficiently and equally balanced between treatment groups of colorectal cancer patients in three studies only (Ho 1999, Wille-Jørgensen 1986, Mcleod 2001).

Seven of the 19 studies used a double-blind design, three other studies were assessor-blinded - in the remaining nine studies blinding was not documented/adressed in the report. Allocation concealment was judged adequate in 10 studies and unclear in nine. Only three studies included a modified intention to treat analysis, reporting all patients with a primary outcome, irrespectivly of treatment received.

Details of the individual studies are listed in table of included studies.

No effort was done in order to rank the studies according to methodological quality.

Effects of interventions

The total material gave opportunity to perform 12 different meaningful comparisons. The most important are highlighted in this text session. The detailed analyses can be studied in metaview.

Heparins versus no treatment:
Unfractionated heparin (LDH) gives a better prophylaxis against DVT and/or PE than does no treatment or placebo (comparison 03.03, 8 studies, 292 patients) with an overall Peto Odds Ratio at 0.35 (95% Confidence Interval 0.20-0.62) with no significant heterogeneity in the analyses. Also low molecular weight heparin (LMWH) seems better than no treatment or placebo in preventing DVT (Peto Odds ratio 0.17 (95% Confidence Interval 0.05-0.54) (comparison 06.01, 3 studies, 349 patients).
When any kind of heparin is compared to no treatment or placebo (comparison 07.03, 11 studies, 641 patients) heparin is better in preventing DVT and/or PE with a Peto Odds ratio at 0.32 (95% Confidence Interval 0.20-0.53) with no significant heterogeneity in the analyses.

LDH versus LMWH:
Four studies addressed this question (comparison 08.03, 1183 patients) and the two treatments were found equally effective in preventing DVT and/or PE (Peto Odds ratio 1.01 (95% Confidence Interval 0.67-1.52).

Mechanical methods:
There was not sufficient data to evaluate intermittent pneumatic compression or graded compression stockings (comparison 09.01, 11.01, and 12.01) neither against no treatment nor heparin.
The combination of graded compression stockings and LDH is better than LDH alone in preventing DVT and/or PE (comparison 10.3, 2 studies, 111 patients) (observe inverse analysis)) with a Peto Odds ratio at 4.17 (95% Confidence Interval 1.37-12.70).

The data on PE alone as outcome parameter were too sparse to draw any conclusions.

DISCUSSION

During the performance of this review, the primary protocol was violated several times due to unexpected distribution of and limited access to data. The violations were:
- doppler-ultrasound was permitted as screening parameter, as it was considered that the limited sensitivity of this type of investigation in asymptomatic patients (Mantoni 1997, Dauzat 1997) was equally distributed among the randomised groups.
- neiher analysis of total mortality and/or fatal PE nor intention to treat analyses were performed due to lack of data.
- some non-blinded studies were included.
No analyses of bleeding complications due to heterogeneity between the method of computing and the fact, that the data were unaccessible for colorectal patients in most studies, thus loosing the ability to balance between efficacy and safety.

These violations of the protocol might invalidate this review. Some studies not fulfilling the original selection criteria were included, as the overall scientific methodology were judged to be reasonable free of bias, and the results were considered to important to leave out. If we have followed the original crieteria for selection only 10 studies had been included, but the overall results and conclusions would not have been altered.

When evaluating the efficacy of thromboprophylaxis it has been a methodological demand to screen all patients with an objective method as most postoperative TE are asymptomatic. One could argue, that this is evaluating a treatment with a surrogate parameters, as the individual patient do not care, whether he/she experience an asymptomatic TE. The most relevant endpoint would be symptomatic DVT and/or PE, perhaps even fatal PE and/or total mortality. This would demand very large trials (up to 50,000 in each treatment arm), but feasible in a multi centre setup. The largest thromboprophylactic trial ever performed is to our knowledge German and showed that the incidence of fatal PE and total mortality was the same after prophylaxis with either unfractionated heparin or LMWH (Haas 1999). There is although a proportionality between the incidence of fatal PE and asymptomatic TE (Wille-Jørgensen 1991), and it is shown that venous function often is impaired after even asymptomatic DVT, giving rise to chronic venous insufficiency (Siragusa 1997, Andersen 1991). Although not optimal, studies using sensitive screening methods can in our opinion be used in evaluating the efficacy of various prophylactic methods.

There was no significant statistical heterogeneity among the studies, but the meta-analysis performed on all heparins versus no treatment or placebo (comparison 07) should be taken with some reserve, due to methodological heterogeneity between the studies. Also one should account for the different drugs and control groups being used in this analysis. As 10 out of 11 studies point in the same direction the conclusion that heparin works is although considered valid.

The analyses are invalidated by the many missing data, as we were unable to retrieve data of colorectal patients from the primary authors but the results obtained are in agreement with other reviews dealing with general surgery as a whole (Wille-Jørgensen 1991) except for one point. We were not able to find any difference between LMWH and LDH. Nurmohammed (Nurmohammed 1992) found LMWH to be more effective in orthopaedic surgery but not convincingly in general surgery a comprehensive meta-analysis. This analysis is although to be taken with care due to severe heterogeneity. In a systematic review where meta-analysis was omitted due to the heterogeneity (Jørgensen 1993), it was concluded that the two treatments do not differ substantially. The efforts in retrieving the inaccessible data will continue and this review will be updated whenever new data on colorectal patients are at hand.

In the investigations with the combination regimens (Wille-Jørgensen 1986, Wille-Jorgensen 1991) unfractionated heparin was used. There are no investigations in general surgery where

the combination of LMWH and stockings has been investigated, but there is no reason to believe that different results would be obtained, if the unfractionated heparin was replaced by LMWH in the combination regimens. The combination regimen seems to be the best, but there are limited data available and the data all come the same author. An investigation in general surgery using a paired design with stockings on one leg only (randomised to left or right), thus comparing legs and not persons also showed a significant better effect of the combination as compared with unfractionated heparin alone (Törngren 1980). Due to the design this study was not included in the analysis, but the result supports our conclusion. Two of the studies awaiting assessment investigates the combination therapy (Borow 1983, Moser 1976). The first find a significant better effect of the combination as compared to heparin alone and the latter could not show any significance in a small sample size. Although these missing data comprise a publication bias, this is not considered to alter the conclusion.

There are other ways to prevent postoperative DVT and/or PE than heparins and stockings. Aspirin has during the last couple of years been shown to be somewhat effective (Collaborative 1994), but seemingly not as effective as heparins. No valid comparisons have to our knowledge been made between aspirin and heparins.

AUTHORS' CONCLUSIONS

Implications for practice

Both unfractionated heparin and low molecular weight heparin can be used as effective prophylaxis against postoperative thromboembolic complications after colorectal surgery. The optimal prophylaxis in colorectal surgery seems to be the combination of graded compression stockings and low-dose unfractionated heparin. The unfractionated heparin can likely be replaced with low molecular weight heparin.

Implications for research

Further effort to retrieve colorectal results from the many studies on general surgery should be continued. Large randomised trials evaluating the use of the combination regime versus monotherapy with fatal pulmonary embolism as outcome should be performed.

ACKNOWLEDGEMENTS

The few primary authors (Maressi 1993, Onarheim 1986) who supplied us with original data are greatly acknowledged.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Butson 1981

Methods	RCT. Sealed envelopes. Not blinded. (Controlgroup = no treatment). No primary stratification of colorectal patients.

Butson 1981 *(Continued)*

Participants	Elective general surgery patients. 119 randomized. Non excluded. Leaving 119 patients in per protocol analysis as well as in intention to treat analysis. Subgroup of 24 colorectal patients were distributed with respectively 63 % and 37 % in the two treatment arms.
Interventions	Intermittent compression: Intermittent compression peroperatively and untill ambulant. Most of the patients 24 to 48 hours postoperatively. Control: No treatment.
Outcomes	Thromboembolic events: DVT Bleeding events: Not described. Diagnosis: radiofibrinogen uptake test every day up to 14 days postoperatively or untill discharge. If positive test then confirmed with venography.
Notes	Both intention to treat- and per protocol analysis. Unbalanced distribution of colorectal patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Covey 1975

Methods	RCT. Coded vials. Patient-, surgeon- and outcome-assessor blinded. No primary stratification of colorectal patients.
Participants	Elective general surgery patients. 105 randomized. Non excluded. Leaving 105 patients in per protocol analysis as well as in intention to treat analysis. Subgroup of 20 colorectal patients were distributed with respectively 45% and 55% in the two treatment arms.
Interventions	LDH: 5000 U unfractionated heparin preoperatively and x2 postoperatively for 8 days or until discharge. Control group: Placebo
Outcomes	Thromboembolic events: DVT Bleeding events: Not described. Diagnosis: radiofibrinogen uptake test, until 8 th day.
Notes	No missing patients. Balanced distribution of colorectal patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Fricker 1988

Methods	RCT. Unclear randomizing procedure. Not blinded. No primary stratification of colorectal patients.

Fricker 1988 *(Continued)*

Participants	Elective cancer general surgery. 80 randomized patients. Non excluded. Leaving 80 patients in per protocol analysis as well as in intention to treat analysis. Subgroup of 6 colorectal patients were distributed with respectively 33% and 67% in the two treatment arms.
Interventions	LDH: 5000 IU unfractionated heparin preoperatively and x3 postoperatively for ten days. LMWH: 2500 anti-Xa units (lowdose) preoperatively and 5000 anti-Xa units (mediumdose) x1 for ten days postoperatively.
Outcomes	Thromboembolic events: PE Bleeding events: Not specified in colorectal patients Diagnosis: Radiofibrinogen uptake test. Positiv test confirmed by phlebography. PE: Clinically, confirmed by scintigraphy.
Notes	Both intention to treat- and per protocol analysis. Unbalanced distribution of colorectal patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Gallus 1976

Methods	RCT. Sealed envelopes. Surgeon blinded. Not patient nor outcome-assessor blinded. (Controlgroup = no treatment). No primary stratification of colorectal patients.
Participants	Elective general surgery patients. 820 randomized patients. Non excluded. Leaving 820 patients in per protocol analysis as well as in intention to treat analysis. Subgroup of 90 colorectal patients were distributed with respectively 49 % and 51 % in the two treatment arms.
Interventions	LDH: 5000 units of unfractionated heparin preoperatively and x3 postoperatively for seven days . Control: No treatment
Outcomes	Thromboembolic events: DVT Bleeding events: Not specified in colorectal patients. Diagnosis: radiofibrinogen uptake test, 1 to 7 th day.
Notes	Intention to treat analysis. Balanced distribution of colorectal patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ho 1999

Methods	RCT. Sealed envelopes. Surgeon blinded. Not patient nor outcome-assessor blinded. (Controlgroup = no treatment)

Ho 1999 *(Continued)*

Participants	Elective surgical colorectal patients. 320 randomized patients. 17 excluded in LMWH group. Leaving 303 patients in per protocol-analysis.
Interventions	LWMH: Enoxaparin 20 mg pre- operatively and 40 mgx1 postoperatively at least 4 days or until ambulant. Control: No treatment.
Outcomes	Thromboembolic:DVT, PE, Fatal PE, overall mortality. Bleeding: Intraoperativly bloodlosses, drainage output, number of bloodtransfusions and postopera- tively related complications. Diagnosis: Clinical every day and doppler ultrasound on 3 th and 5 th post- operative day
Notes	17 patients missing. No intention to treat analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Joffe 1976

Methods	RCT. Computer generated list. Not blinded. No primary stratification of colorectal patients.
Participants	Elective general surgery patients. 220 randomized patients. 17 excluded. Leaving 203 patients in per protocol analysis. Subgroup of 17 colorectal patients were distributed with respectively 47%, 18 % and 35% in the three treatment arms. Treatment arm with pentosan excluded from this analysis. Leaving 14 colorectal patients in analysis.
Interventions	LDH:5000 units of unfractionated heparin preoperatively and x3 postoperatively for seven days. Pentosan: 50 mg preoperatively and x2 postoperatively for seven days. Control group: No treatment.
Outcomes	Thromboembolic events: DVT. Bleeding events:Not specified in colorectal patients. Diagnosis: Radiofibrinogen uptake test
Notes	17 patients missing. No intention to treat analysis. Unbalanced distribution of colorectal patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Koppenhagen 1992

Methods	RCT. Unclear randomizing procedure. Patient, surgeon and outcome-assessor blinded. No primary stratification of colorectal patients.

Koppenhagen 1992 *(Continued)*

Participants	Elective surgical abdominal patients. 673 randomized patients. 20 excluded. Leaving 653 in per protocol- analysis. Subgroup of 195 colorectal patients distributed with respectively 53% and 47% in the two treatment arms.
Interventions	LWMH: 3000 anti Xa units (medium dose) pre- operatively and 3000 anti Xa units plus two placebo injections daily for a mean of 7.5 postoperative days. LDH: 5000 units of unfractionated heparin pre- operatively and x3 postoperatively for a mean of 7.4 days.
Outcomes	Thromboembolic: DVT. PE, fatal PE and overall mortality not described in colorectal patients. Bleeding: not specified in colorectal patients. Diagnosis: Either radiofibrinogen uptake test or phlebography. Daily.
Notes	20 patients missing. No intention to treat analysis. Balanced distribution of colorectal patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kosir 1996

Methods	RCT. Unclear randomizing procedure. Not blinded. No primary stratification of colorectal patients.
Participants	Elective general surgery patients. Subgroup of 12 colorectal patients. 137 randomized patients. 29 excluded. Leaving 108 in per protocol analysis. Subgroup of Colorectal patients were distributed with respectively 17 % , 25% and 58 % in the three treatment group.
Interventions	Intermittent compression: Intermittent compression peroperatively and for 48 hours postoperatively. LDH: 5000 units of unfractionated heparin preoperatively and x2 postoperatively for seven days. Control: No treatment.
Outcomes	Thromboembolic events: DVT Bleeding events: Not described. Diagnosis: Doppler ultrasound at 1 th, 3 th and 30 th day.
Notes	29 missing patients. No intention to treat analysis. Unbalanced distribution of colorectal patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lahnborg 1974

Methods	RCT. Coded vials. Patient-, surgeon- and outcome-assessor blinded. No primary stratification of colorectal patients.

Lahnborg 1974 *(Continued)*

Participants	Elective general surgery patients. 112 randomized patients. Non excluded. Leaving 112 patients in per protocol analysis as well as in intention to treat analysis. Subgroup of 19 colorectal patients were distributed with respectively 58 % and 42 % in the two treatment arms.
Interventions	LDH: 5000 U unfractionated heparin preoperatively and x2 postoperatively for five days. Control: Placebo injection.
Outcomes	Thromboembolic events: DVT, PE and TE. Bleeding events: Not described. Diagnosis: Radiofibrinogen uptake test.
Notes	No missing patients. Balanced distribution of colorectal patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Maressi 1993

Methods	RCT. Unclear randomization procedure. Open study
Participants	Elective gastrointestinal patients
Interventions	LMWH: 3,825 I aXa Units preoperatively Control: No treatment
Outcomes	DVT defined as positive FUT
Notes	Half of postive FUT were verified by venography

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Mcleod 2001

Methods	RCT. Computer generated randomization. Patient-, surgeon- and outcome-assesor blinded. Multicentric studie.
Participants	Elective colorectal patients. 1349 patients randomized. 413 excluded. Leaving 936 patients in per protocol analysis.
Interventions	LDH: 5000 U unfractionated heparin preoperatively and x2 postoperatively. Duration not stated. LMWH: 40 mg enoxaparin X 1 plus saline injection X 1. Duration was up to 10 days.
Outcomes	Thromboembolic events: DVT or PE Bleeding events: Major bleeding events.

Mcleod 2001 *(Continued)*

	Diagnosis: Venography on 5 th to 9 th day.
Notes	413 missing patients. No intention to treat analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Negus 1980

Methods	RCT. Sealed envelopes. Patient-, surgeon- and outcome-assessor blinded. No primary stratification of colorectal patients.
Participants	Elective general surgery patients. 105 enrolled, 95 randomized patients. 10 patients excluded before randomizing procedure. Leaving 95 patients in per protocol analysis. Subgroup of 33 colorectal patients were distributed with respectively 42 % and 58 % in the two treatment arms.
Interventions	Heparin: Iv. heparin 1IU/kgxh peroperatively, the first 48 hours and uptil five days postoperatively. Control group: Iv. saline
Outcomes	Thromboembolic events: TE. Covering both DVT and PE. Bleeding events: Not specified in colorectal patients. Diagnosis: Radiofibrinogen uptake test, every second day until 6 th or 8 th postoperative day.
Notes	10 patients missing. No intention to treat analysis. Balanced distribution of colorectal patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Nicolaides 1983

Methods	RCT. Sealed envelopes. Not blinded. No primary stratification of colorectal patients.
Participants	Elective surgical abdominal patients. 150 randomized patients. Non excluded. Leaving 150 patients in per-protocol analysis as well as in intention to treat analysis. Subgroup of 31 colorectal patients were distributed with respectively 26%, 35% and 39 % in the three treatment arms.
Interventions	Electrical calf stimulation: Peroperatively. LDH: 5000 units of unfractionated heparin preoperatively and x2 postoperatively untill discharge. Intermittent compression/stockings: Intermittent compression peroperatively and at least for 72 hours postoperatively. When ambulant; TED- stockings.
Outcomes	Thromboembolic events: DVT. PE, fatal PE and overall mortality not described. Bleeding: Not described. Diagnosis: Radiofibrinogen uptake test, daily
Notes	No missing patients. 3 treatmentgroups.

Nicolaides 1983 *(Continued)*

	Balanced distribution of colorectal patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Onarheim 1986

Methods	RCT. Unclear randomizing procedure. Patient-, surgeon- and outcome-assessor blinded. No primary stratification of colorectal patients.
Participants	Elective surgical abdominal patients. 52 randomized patients. 1 patient excluded. Leaving 51 in per protocol analysis. Subgroup of 46 colorectal patients were distributed with respectively 48% and 52% in the two treatment arms.
Interventions	LMWH: 5000 anti-x-activated (medium dose) units preoperatively and x1 plus placebo x1 postoperatively for six days. LDH: 5000 U unfractionated heparin preoperatively and eigth o´cloc p.m. at the day of surgery and x2 postoperatively for six days.
Outcomes	Thromboembolic events: DVT Bleeding events: Not specified in colorectal patients. Diagnosis: Radiofibrinogen uptake test every day or every second day for at least 7 days.
Notes	1 missing patient. Balanced distribution of colorectal patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Rem 1975

Methods	RCT. Sealed envelopes. Surgeon blinded. Not patient nor outcome-assessor blinded. (Control group = no treatment). No primary stratification of colorectal patients.
Participants	Elective surgical abdominal- and urological patients. 212 randomized patients. 22 excluded patients in LDH arm and 12 excluded patients in no treatment arm. Leaving 178 patients in per protocol analysis. Subgroup of 31 colorectal patients were distributed with respectively 61% and 39% in the two treatment arms.
Interventions	LDH: 5000 units of unfractionated heparin preoperatively and x3 postoperatively for at least 7 days. Control: No treatment.
Outcomes	Thromboembolic events: DVT. Bleeding: Not specified in colorectal patients Diagnosis: Rradiofibrinogen uptake test, daily
Notes	34 patients missing. No intention to treat analysis.

Rem 1975 *(Continued)*

	Unbalanced distribution of colorectal patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Torngren 1978

Methods	RCT. Coded vials. Patient-, surgeon- and outcome-assessor blinded. No primary stratification of colorectal patients.
Participants	Elective surgical abdominal patients. 175 randomized patients. From the three arm were respectively excluded 3, 4 and 1 patient. Leaving 167 patients in per protocol analysis. Subgroup of 107 colorectal patients were distributed with respectively 38%, 30% and 32 % in the three arms.
Interventions	LDH: 5000 u unfrationated heparin preoperatively and x2 postoperatively for 6 to 8 days. HDH: 25000 u unfrationated heparin preoperatively and x2 postoperatively for 6 to 8 days. Control group: Placebo
Outcomes	Thromboembolic events: DVT Bleeding events: Not specified in colorectal patients. Diagnosis: Radiofrbinogen uptake test performed at a mean of 10.5 days.
Notes	8 missing patients. No intention to treat analysis. Balanced distribution of colorectal patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Valle 1988

Methods	RCT. Unclear randomizing procedure. Patient-, surgeon- and outcome-assessor blinded. No primary stratification of colorectal patients.
Participants	Elective general surgery patients. 100 randomized patients. Non excluded. Leaving 100 patiens in per protocol analysis as well as in intention to treat analysis. Subgroup of 11 colorectal patients were distributed with respectively 55 % and 45 % in the two arms.
Interventions	LMWH: 7500 anti-x-activated (highdose) preoperatively and x1 postoperatively for seven days. Control group: Placebo
Outcomes	Thromboembolic events:DVT Bleeding events: Not specified in colorectal patients. Diagnosis: Clinically and doppler sonography.
Notes	Balanced distribution of colorectal patients.

Risk of bias

Valle 1988 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Wille-Jørgensen 1986

Methods	RCT. Computergenerated list. Not blinded.
Participants	Elective colorectal patients. 86 patients randomized. 5 excluded in LDH - and 3 excluded in LDH+TED group. Leaving 78 patients in per protocol analysis.
Interventions	LDH: 5000 U unfractionated heparin preoperatively and x2 for seven days postoperatively. LDH+TED stockings: Same as above. Also stockings until ambulant.
Outcomes	Tromboembolic events: DVT, PE and TE Bleeding events: Not described. Diagnosis: Radiofibrinogen uptake test on 1,3, 5 and 7 th postoperative day. If positive then confirmed with phlebography.
Notes	8 patients missing. No intention to treat analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Wille-Jørgensen 1991

Methods	RCT. Sealed envelopes. Not consecutive. Not blinded. No primary stratification of colorectal patients.
Participants	Acute abdominal patients. 276 randomized patients. 3 excluded in LDH arm, 15 excluded in LDH+TED arm and 13 excluded in Dextran+TED arm. Leaving 244 patients in per protocol analysis. Subgroup of 51 colorectal patients were distributed with respectively 31%, 33 % and 35% in the three treatment arms. Treatment arm with Dextran+TED were excluded from this analysis. Leaving 33 colorectal patients in analysis. One arm with dextran is excluded from this analysis. Leaving 160 patients for this analysis. Of these 18 were excluded. Subgroup of 33 colorectal patients were distributed with respectively 49 % and 51 % in the two remaining treatment arms.
Interventions	LDH: 5000 U unfractionated heparin preoperatively and x2 for seven days postoperatively. LDH+TED stockings: Same as above. Also stockings until ambulant.
Outcomes	Tromboembolic events: TE Bleeding events: Not specified in colorectal patients. Diagnosis: Radiofibrinogen uptake test on 1,3, 5 and 7 th postoperative day. If positive then confirmed with phlebography.
Notes	18 patients missing. No intention to treat analysis. Balanced distribution of colorectal patients.

Risk of bias

Wille-Jørgensen 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

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

Study	Reason for exclusion
Bounameaux 1993	Colorectal patients not specified. Author contacted. Unable to help.
Browse 1974	Alternate leg. Not possible to include in meta-analysis.
Comerota 1986 A	Colorectal patients not specified. Author contacted. Answered that it was not possible to recollect data. Data more than 15 years old.
Ellis 1982	Colorectal patients not specified. Author contacted. Answered that colorectal data was never specified.
Gallus 1993	Colorectal patients not specified. Author contacted. Answered that it was not possible to recollect data.
Kakkar 1993	Double-publication.
Mcleod 1995	Possible that some of the patients in the abstract are reused in; Mcleod RS, Geerts WH, Sniderman K et al. Thromboprophylaxis after colorectal surgery - results of a randomized, double-blind comparison of low dose heparin and enoxaparin. Thrombosis and Haemostasis. juni, suppl. 1997:753 no PD3078.
No author 1984	May contain patients from other studies. Not possible to identify colorectal patients.
Rasmussen 1988	Fullfill all criteria but not valid diagnostic methods. Tc-plasmin test.
Strand 1975	The per protocol analysis operates with 102 surgical procedures in 100 patients. It is not possible to identify the patient/patients which act as duplicates
Torngren 1982	Historical controlgroup.
Törngren 1980	Alternate leg. Not possible to include in meta-analysis.

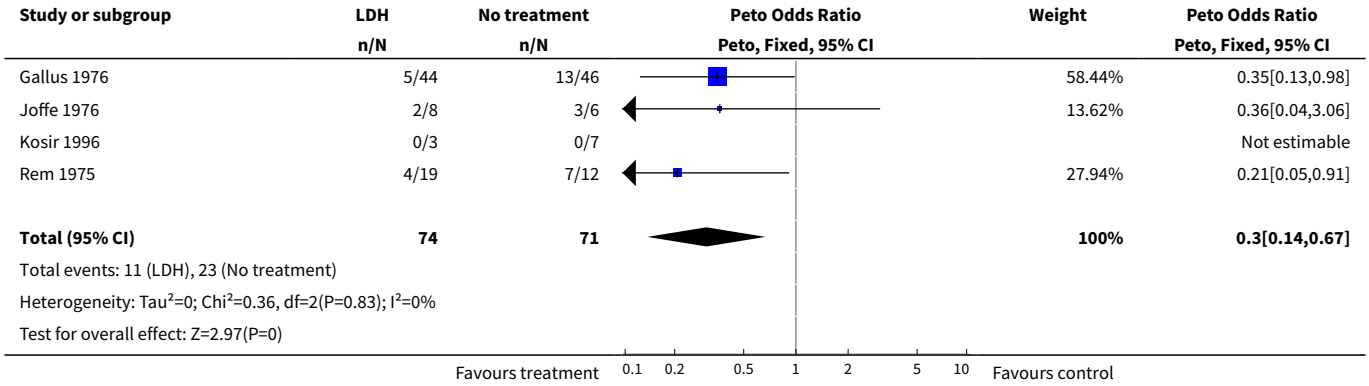
DATA AND ANALYSES

Comparison 1. Thromboembolic events (TE). LDH vs. no treatment.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DVT	4	145	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.14, 0.67]
2 PE, no studies	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 DVT and/or PE. Same as in "DVT".	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

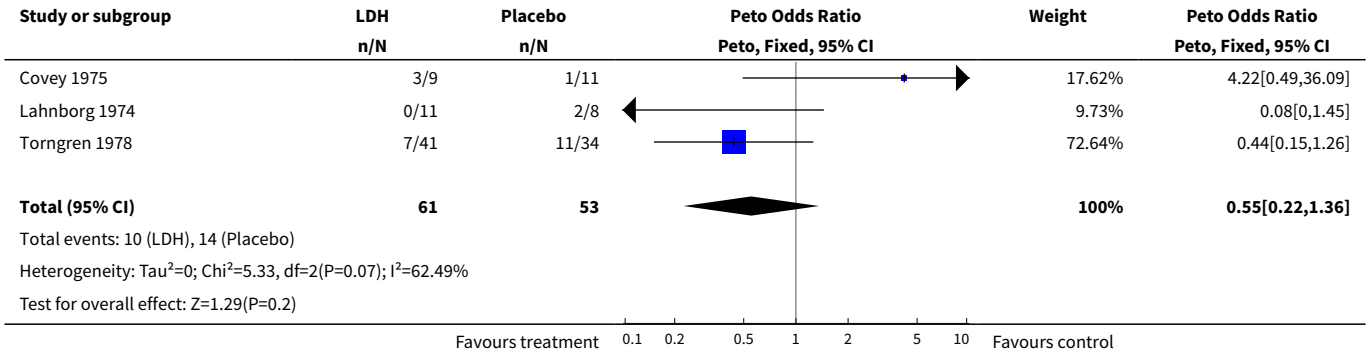
Analysis 1.1. Comparison 1 Thromboembolic events (TE). LDH vs. no treatment., Outcome 1 DVT.



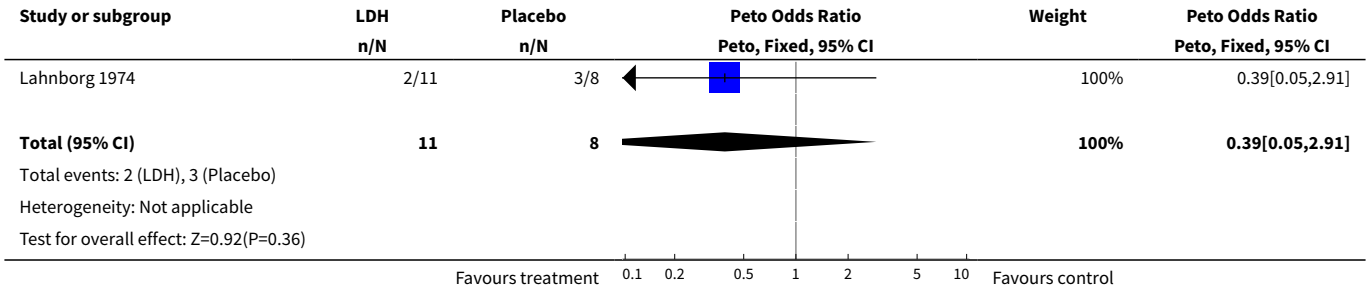
Comparison 2. Thromboembolic events (TE). LDH vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DVT	3	114	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.22, 1.36]
2 PE	1	19	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.39 [0.05, 2.91]
3 DVT and/or PE.	4	147	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.46 [0.21, 0.98]

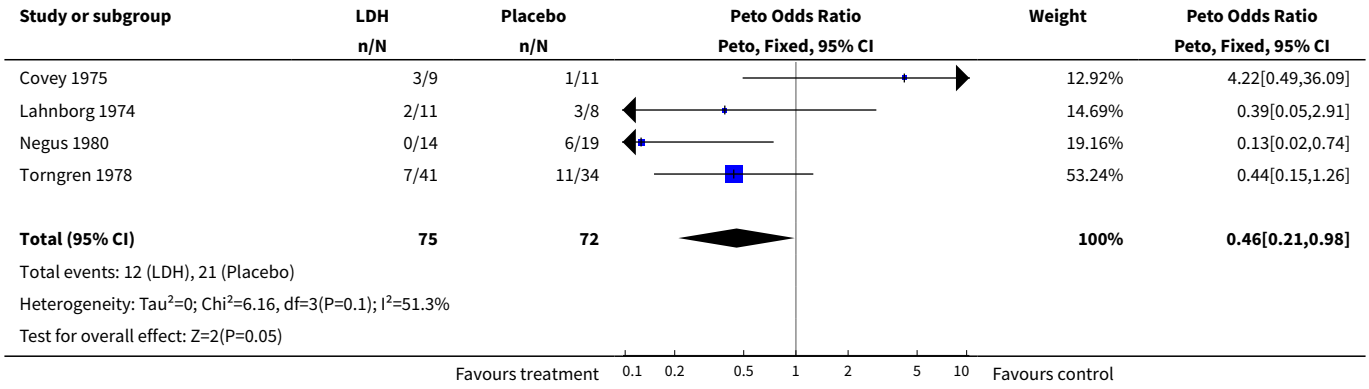
Analysis 2.1. Comparison 2 Thromboembolic events (TE). LDH vs. placebo, Outcome 1 DVT.



Analysis 2.2. Comparison 2 Thromboembolic events (TE). LDH vs. placebo, Outcome 2 PE.



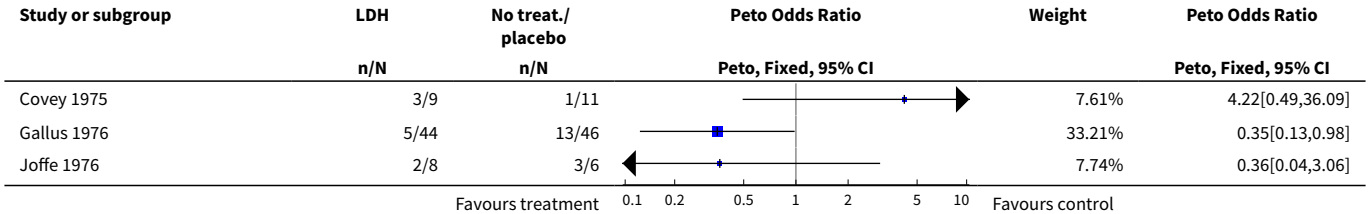
Analysis 2.3. Comparison 2 Thromboembolic events (TE). LDH vs. placebo, Outcome 3 DVT and/or PE..

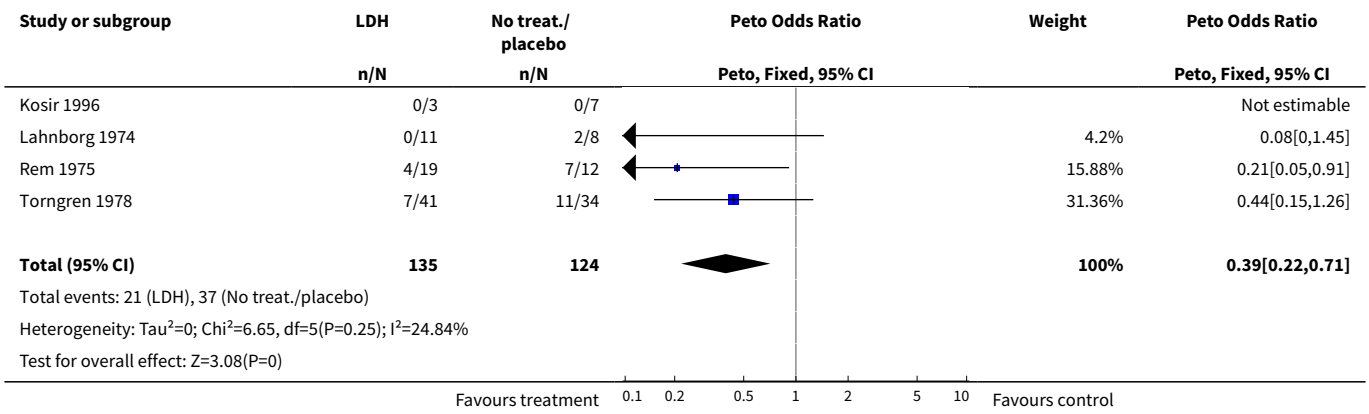


Comparison 3. Thromboembolic events (TE). LDH vs. no treatment or placebo

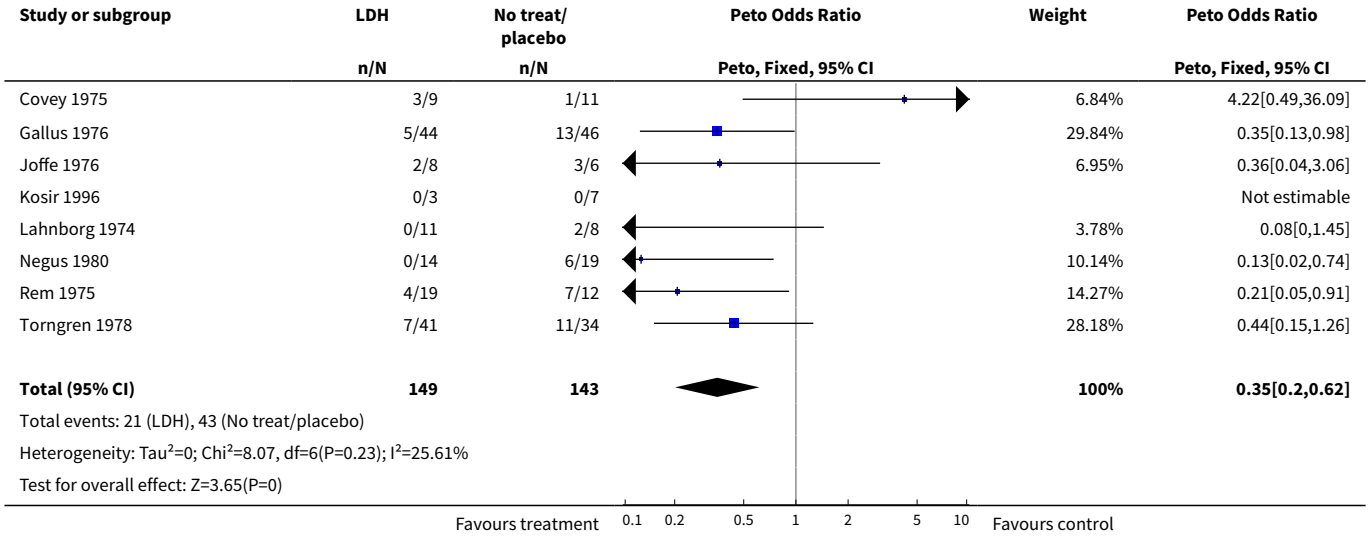
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DVT	7	259	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.39 [0.22, 0.71]
2 PE, same as LDH versus no treat/placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 DVT and/or PE.	8	292	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.20, 0.62]

Analysis 3.1. Comparison 3 Thromboembolic events (TE). LDH vs. no treatment or placebo, Outcome 1 DVT.





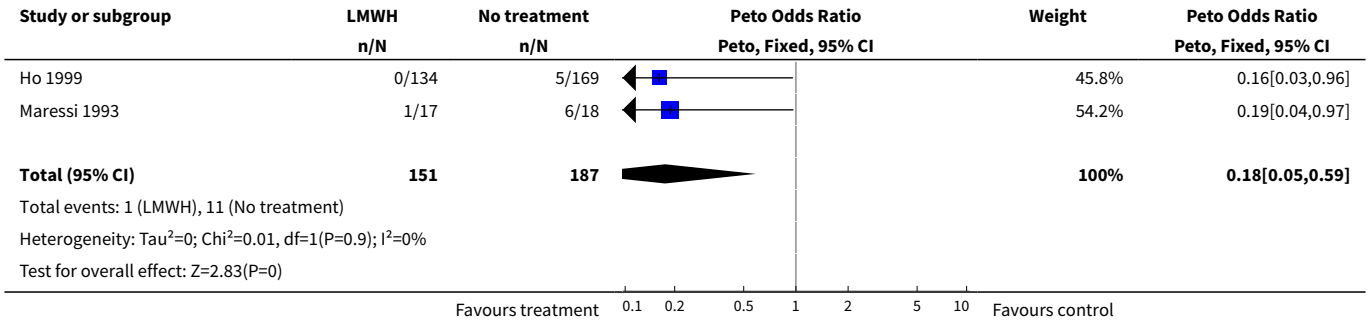
Analysis 3.3. Comparison 3 Thromboembolic events (TE). LDH vs. no treatment or placebo, Outcome 3 DVT and/or PE..



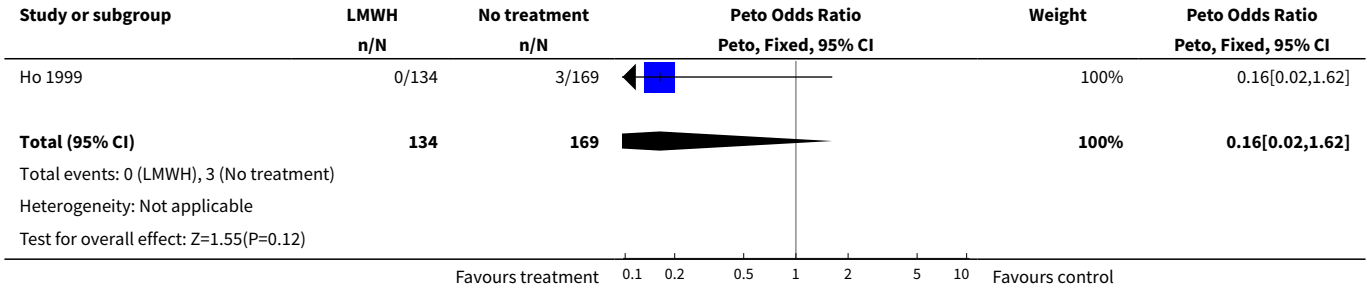
Comparison 4. Thromboembolic events (TE). LMWH vs. no treatment.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DVT	2	338	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.18 [0.05, 0.59]
2 PE	1	303	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.02, 1.62]
3 DVT and/or PE.	2	338	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.18 [0.05, 0.59]

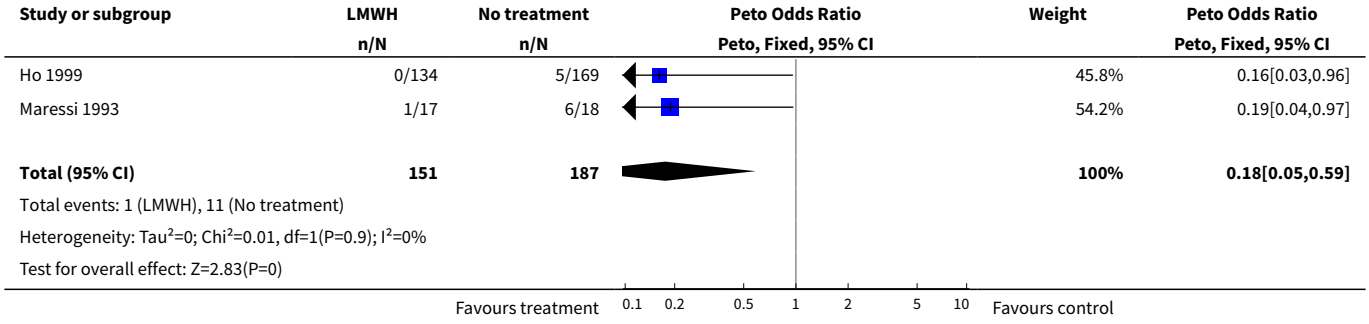
Analysis 4.1. Comparison 4 Thromboembolic events (TE). LMWH vs. no treatment., Outcome 1 DVT.



Analysis 4.2. Comparison 4 Thromboembolic events (TE). LMWH vs. no treatment., Outcome 2 PE.



Analysis 4.3. Comparison 4 Thromboembolic events (TE). LMWH vs. no treatment., Outcome 3 DVT and/or PE..

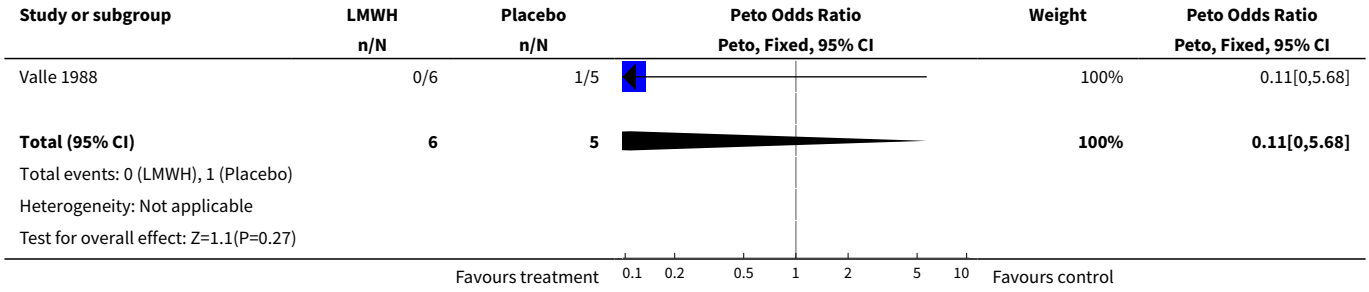


Comparison 5. Thromboembolic events (TE). LMWH vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DVT	1	11	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.11 [0.00, 5.68]
2 PE, no studies	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 DVT and/or PE. Same as in "DVT".	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

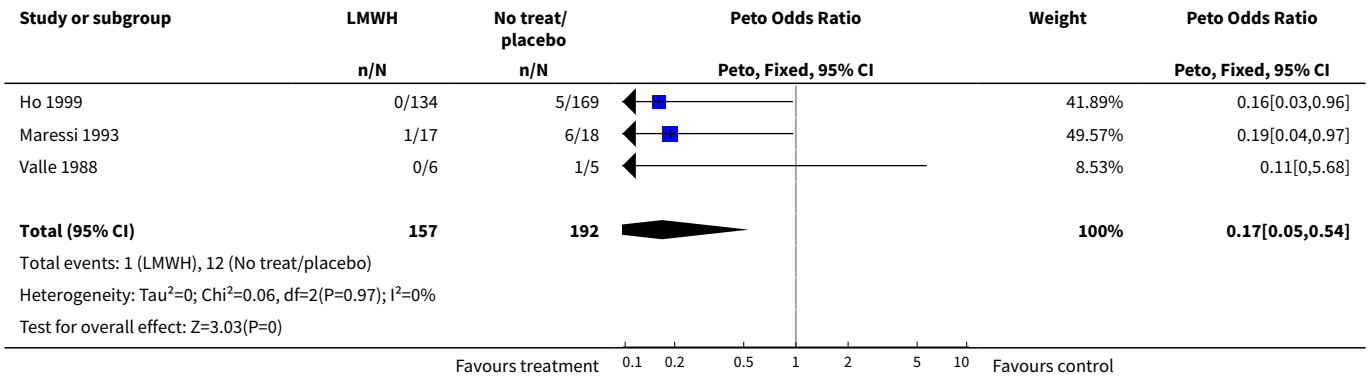
Analysis 5.1. Comparison 5 Thromboembolic events (TE). LMWH vs. placebo, Outcome 1 DVT.



Comparison 6. Thromboembolic events (TE). LMWH vs. no treatment or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DVT	3	349	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.17 [0.05, 0.54]
2 PE, same as LMWH versus no treatment	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 DVT and/or PE, same as LMWH versus no treatment or placebo / DVT	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Thromboembolic events (TE). LMWH vs. no treatment or placebo, Outcome 1 DVT.

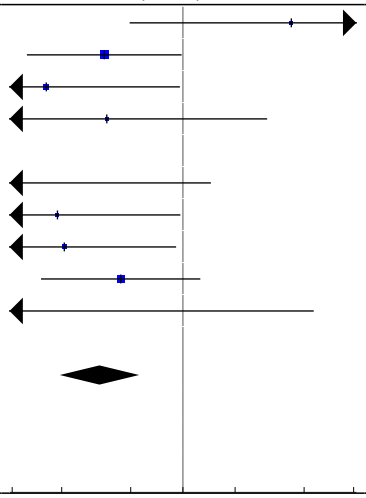


Comparison 7. Thromboembolic events (TE). LDH or LMWH vs. no treatment or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DVT	10	608	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.20, 0.56]
2 PE	2	322	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.27 [0.06, 1.21]
3 DVT and/or PE.	11	641	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.32 [0.20, 0.53]

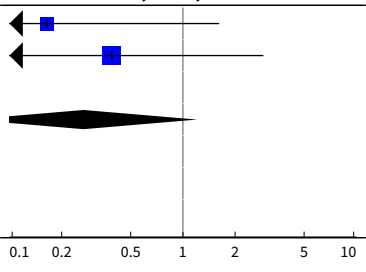
Analysis 7.1. Comparison 7 Thromboembolic events (TE). LDH or LMWH vs. no treatment or placebo, Outcome 1 DVT.

Study or subgroup	LDH or LMWH n/N	No treat. and Placeb n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Covey 1975	3/9	1/11		6.01%	4.22[0.49,36.09]
Gallus 1976	5/44	13/46		26.25%	0.35[0.13,0.98]
Ho 1999	0/134	5/169		8.78%	0.16[0.03,0.96]
Joffe 1976	2/8	3/6		6.12%	0.36[0.04,3.06]
Kosir 1996	0/3	0/7			Not estimable
Lahnborg 1974	0/11	2/8		3.32%	0.08[0,1.45]
Maressi 1993	1/17	6/18		10.39%	0.19[0.04,0.97]
Rem 1975	4/19	7/12		12.55%	0.21[0.05,0.91]
Torngren 1978	7/41	11/34		24.79%	0.44[0.15,1.26]
Valle 1988	0/6	1/5		1.79%	0.11[0,5.68]
Total (95% CI)	**292**	**316**		**100%**	**0.33[0.2,0.56]**
Total events: 22 (LDH or LMWH), 49 (No treat. and Placeb)					
Heterogeneity: Tau^2=0; Chi^2=8.35, df=8(P=0.4); I^2=4.24%					
Test for overall effect: Z=4.12(P<0.0001)					

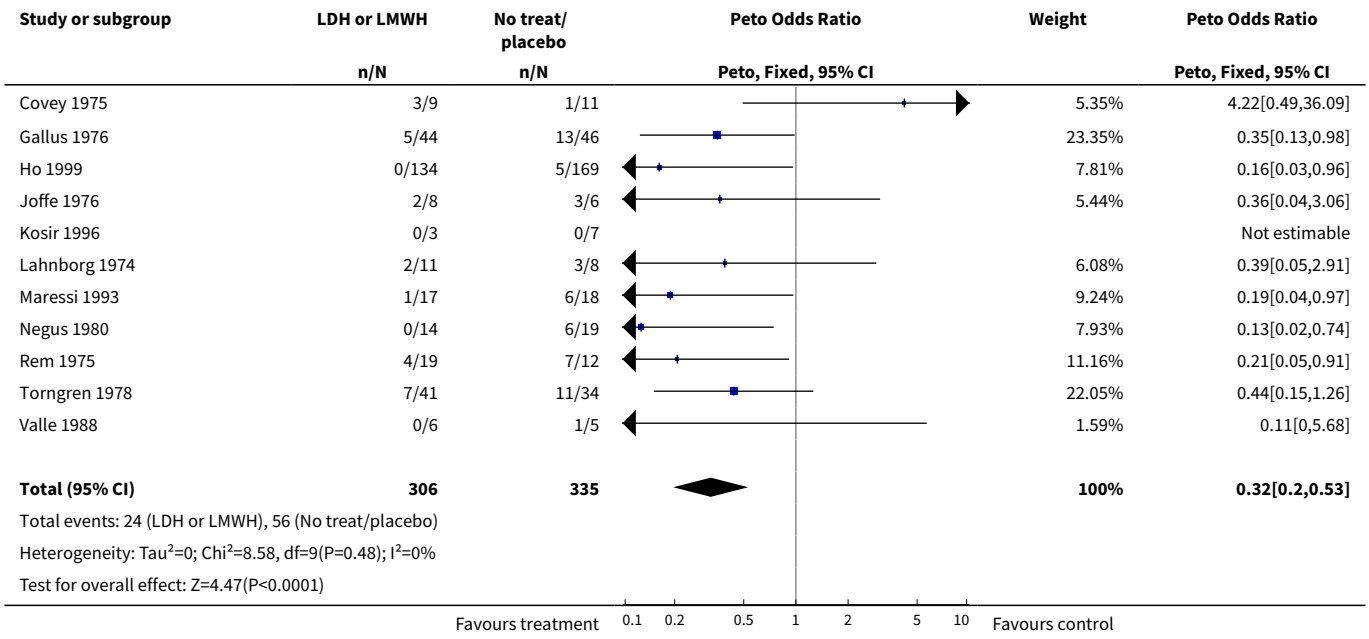


Analysis 7.2. Comparison 7 Thromboembolic events (TE). LDH or LMWH vs. no treatment or placebo, Outcome 2 PE.

Study or subgroup	LDH or LMWH n/N	No treat/ placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Ho 1999	0/134	3/169		43.68%	0.16[0.02,1.62]
Lahnborg 1974	2/11	3/8		56.32%	0.39[0.05,2.91]
Total (95% CI)	**145**	**177**		**100%**	**0.27[0.06,1.21]**
Total events: 2 (LDH or LMWH), 6 (No treat/placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.31, df=1(P=0.58); I^2=0%					
Test for overall effect: Z=1.71(P=0.09)					



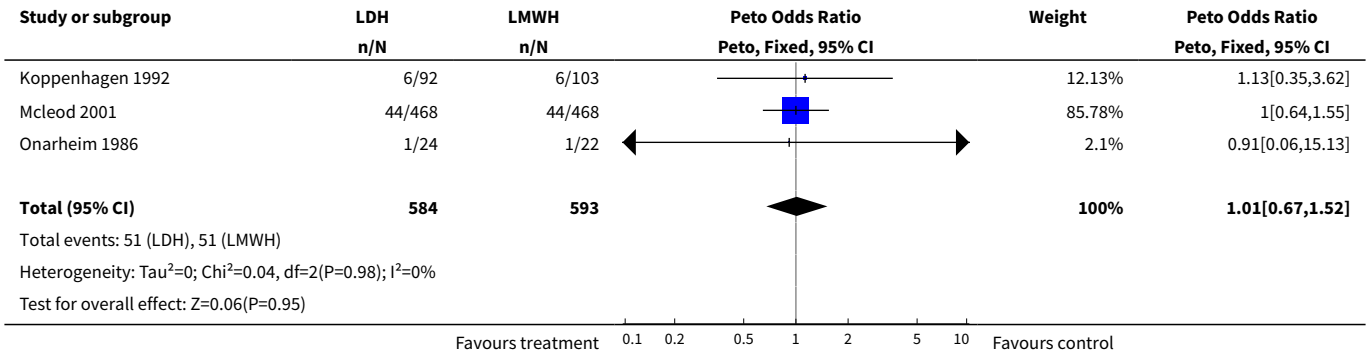
Analysis 7.3. Comparison 7 Thromboembolic events (TE). LDH or LMWH vs. no treatment or placebo, Outcome 3 DVT and/or PE..



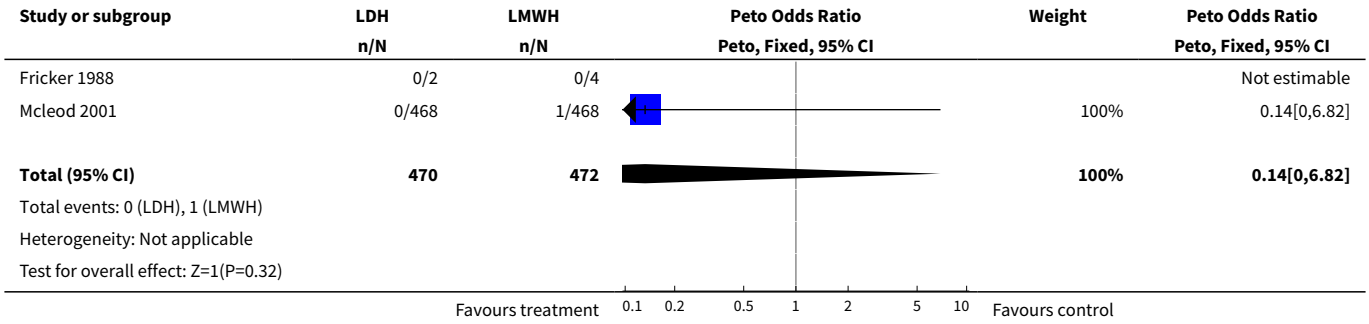
Comparison 8. Thromboembolic events (TE). LDH vs. LMWH

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 DVT	3	1177	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.67, 1.52]
2 PE	2	942	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.82]
3 DVT and PE.	4	1183	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.67, 1.52]

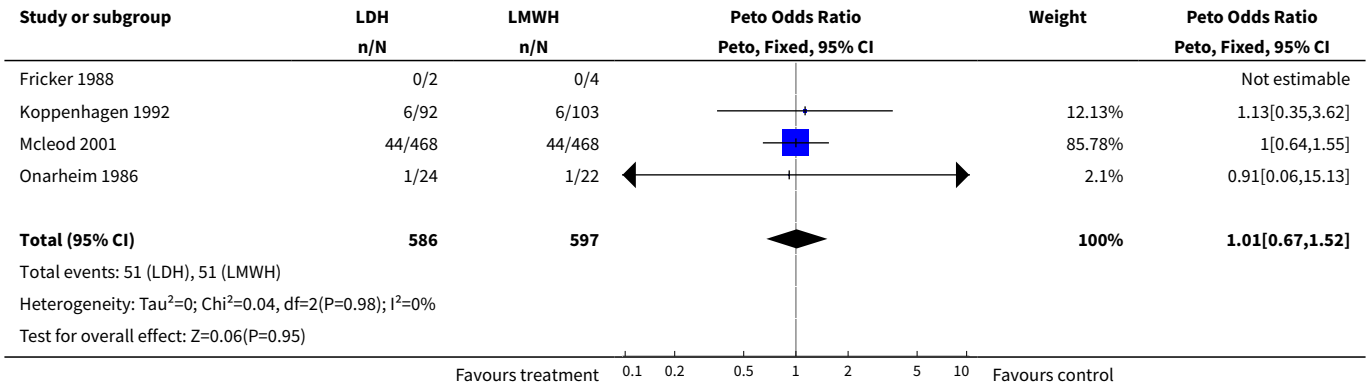
Analysis 8.1. Comparison 8 Thromboembolic events (TE). LDH vs. LMWH, Outcome 1 DVT.



Analysis 8.2. Comparison 8 Thromboembolic events (TE). LDH vs. LMWH, Outcome 2 PE.



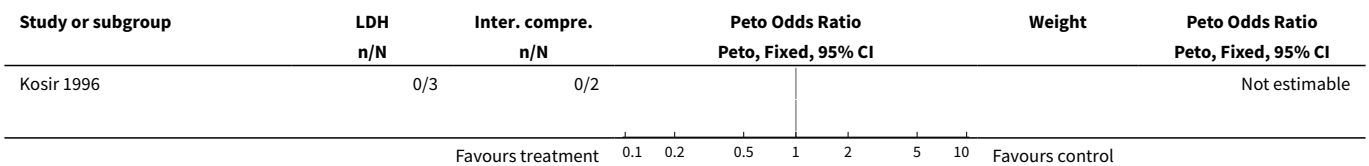
Analysis 8.3. Comparison 8 Thromboembolic events (TE). LDH vs. LMWH, Outcome 3 DVT and PE..

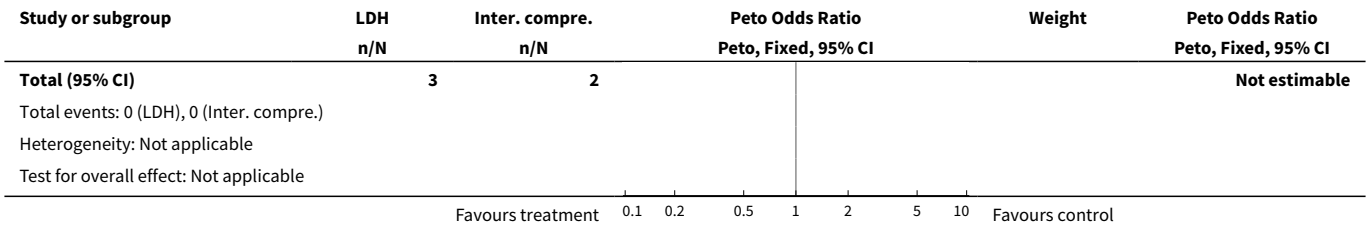


Comparison 9. Thromboembolic events (TE). LDH versus IPC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DVT	1	5	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 PE, no studies	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 DVT and/or PE. Same as in "DVT".	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 9.1. Comparison 9 Thromboembolic events (TE). LDH versus IPC, Outcome 1 DVT.

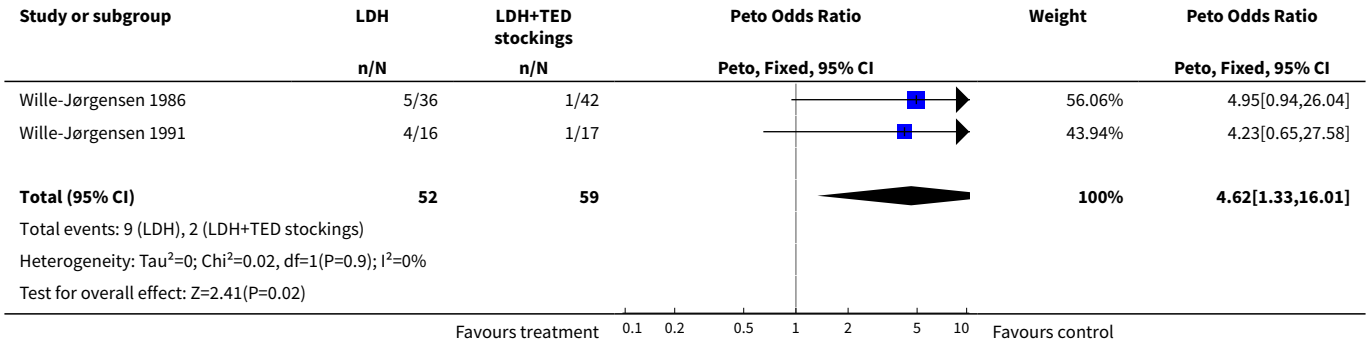




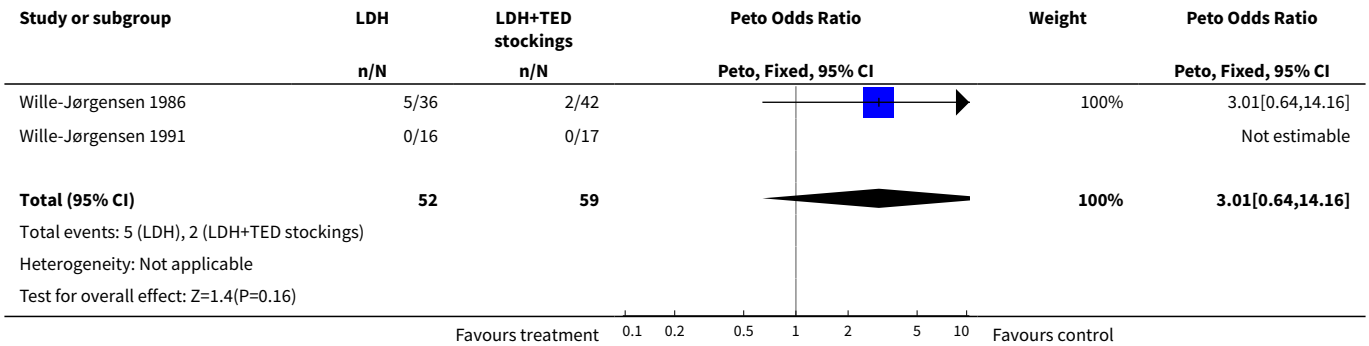
Comparison 10. Thromboembolic events (TE). LDH vs. LDH+TED

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 DVT	2	111	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.62 [1.33, 16.01]
2 PE	2	111	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.01 [0.64, 14.16]
3 DVT and/or PE.	2	111	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.17 [1.37, 12.70]

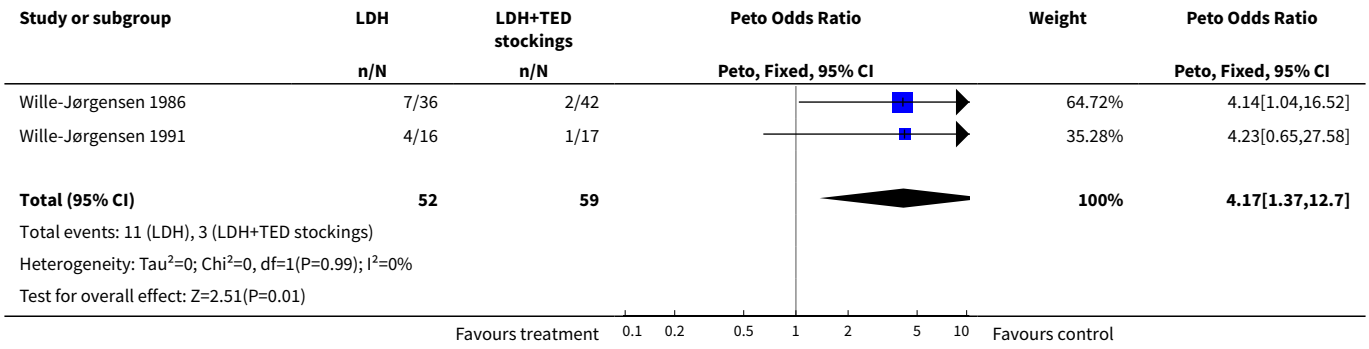
Analysis 10.1. Comparison 10 Thromboembolic events (TE). LDH vs. LDH+TED, Outcome 1 DVT.



Analysis 10.2. Comparison 10 Thromboembolic events (TE). LDH vs. LDH+TED, Outcome 2 PE.



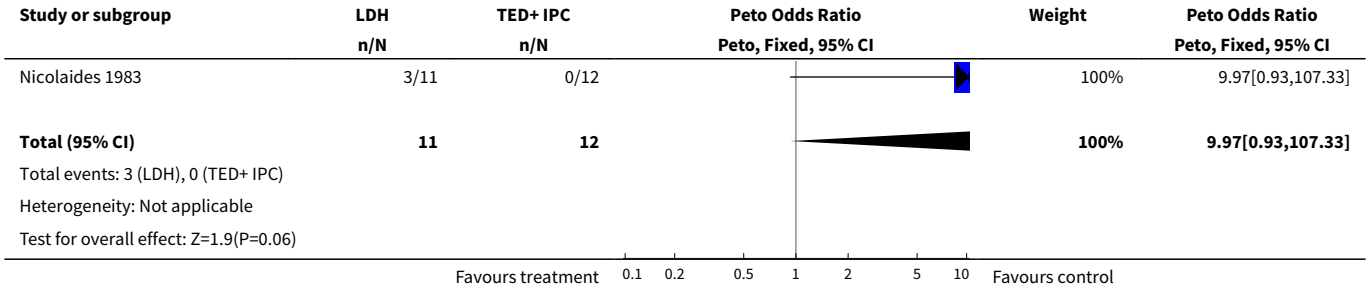
Analysis 10.3. Comparison 10 Thromboembolic events (TE). LDH vs. LDH+TED, Outcome 3 DVT and/or PE..



Comparison 11. Thromboembolic events (TE). LDH vs. TED + IPC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DVT	1	23	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.97 [0.93, 107.33]
2 PE, no studies	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 DVT and/or PE. Same as in "DVT".	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 11.1. Comparison 11 Thromboembolic events (TE). LDH vs. TED + IPC, Outcome 1 DVT.

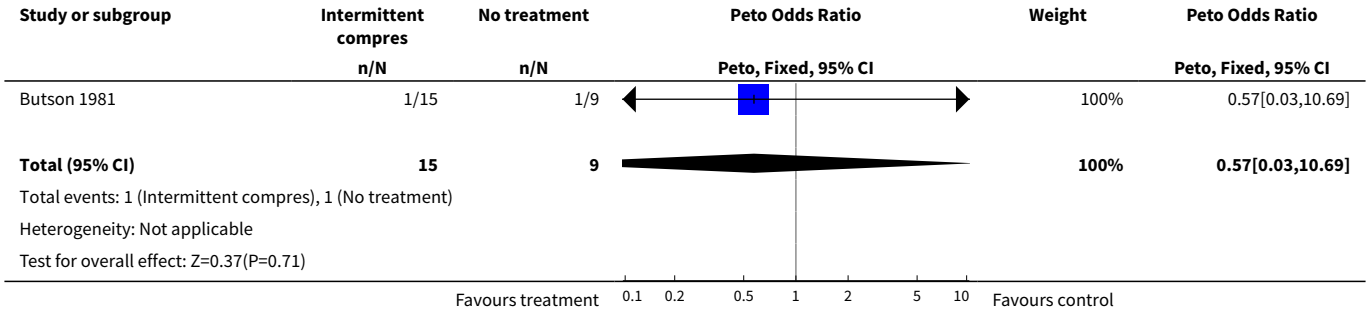


Comparison 12. Thromboembolic events (TE). IPC vs. no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DVT	1	24	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.57 [0.03, 10.69]
2 PE, no studies	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 DVT and/or PE. Same as in "DVT".	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 12.1. Comparison 12 Thromboembolic events (TE). IPC vs. no treatment, Outcome 1 DVT.



FEEDBACK

Safety and effectiveness of thromboprophylaxis

Summary

Submitted by David Cundiff, MD, July 11 2007 - Email Address: dkcundiff3@verizon.net

The conclusions of this review are based on surrogate endpoints (bilateral venography and noninvasive DVT assessment tests) rather than clinical endpoints (total mortality, pulmonary embolism fatalities, symptomatic venous thromboembolism). The small number of patients involved in the studies (< 2,000) made it impossible to reach meaningful conclusions about safety (e.g., bleeding and heparin induced thrombocytopenia with thrombosis) and efficacy. The called for large randomized trials with fatal pulmonary embolism as outcome will probably never be done. Since fatal pulmonary emboli occurs in only about 1-2 cases per 10,000 hospital discharges,1 it would take over 200,000 subjects to do such a trial. The closest study to such a mammoth RTC was a retrospective analysis of about 80,000 hospitalized patients reported by Goldhaber and colleagues in 2000 (1). They looked for the development of VTE during the index hospitalization and up to 30 days after discharge. Of the 384 VTE cases found, 201 had received prophylaxis and 183 had not. Twelve of the 13 fatal pulmonary emboli (FPE) cases occurred in patients receiving anticoagulant prophylaxis.
Goldhaber's study provides evidence that will never be found in RCTs with n < 20,000 (i.e., all reported RCTs): anticoagulant prophylaxis very likely increases the risk of death. A possible mechanism is rebound hypercoagulation.
Neither heparin nor LMWHs are evidence-based to be safe or effective as thromboprophylaxis after colorectal surgery (2;3).

Undisclosed financial conflict of interest:
Dr. Wille-Jorgensen has received research funding from Novartis (4) and co-authored a Pfizer-funded dalteparin (Fragmin) thromboprophylaxis trial (5).

Reference list:
1. Goldhaber SZ, Dunn K, MacDougall RC. New Onset of Venous Thromboembolism Among Hospitalized Patients at Brigham and Women's Hospital Is Caused More Often by Prophylaxis Failure Than by Withholding Treatment. Chest. 2000;118:1680-1684.
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1994;72(2):222-226.
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5. Rasmussen MS, Jorgensen LN, Wille-Jorgensen P, et al. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. J Thromb Haemost. 2006; 4(11):2384-2390.

Submitter agrees with default conflict of interest statement: I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Submitted by contact author Peer Wille-Jørgensen, July 17 2007

The discussion on surrogate end-points in research on thrombosis prophylaxis has been long. In my opinion there is overwhelming evidence, that if you lower the incidence of subclinical DVT, you will also lower the incidence of clinical DVT and Fatal PE (1) - but for statistical reasons it might be difficult to lower the total postoperative mortality. Also an indirect proof of the relation between subclinical DVT and later postphlebitic syndrome has been established (2) Latest evidence is seen in the research on the efficacy of long-term postoperative prophylaxis, in which the same trials the extended prophylaxis lower the incidence of both subclinical and clinical DVT (3;4).
As the diagnosis of pulmonary embolism very seldom is established before death (5) retrospective analysis of incidences of postoperative fatal PE is of very little value even thoug the number of patients is large. Another investigation from one department found although an association between fatal PE and omission of prophylaxis(6).
I agree, that a prospective randomised trial with total mortality as endpoint is unfeasible. We must not althoug forget that the efficacy of heparin prophylaxis against fatal Postoperative PE was established in a methodologically correctly performed trial more than 30 years ago(7).
Taken these facts in mind I still mean that the use of postoperative prophylaxis is evidence based, and for comparing different methods the use of venography for detecting subclinical DVT as endpoint is scientifically acceptable.

Concerning my conflict of interest. I have participtated in several partly industry-sponsored trials on thrombosis prophylaxis, but never have gained any personal financial benefits from it.

Peer Wille-Jørgensen

Reference List

(1) Kakkar VV. Fibrinogen Uptake Test for Detection of Deep Vein Thrombosis - A review of Current Practice. Sem Nucl Med 1977; 7:229-244.
(2) Wille-Jorgensen P, Jorgensen LN, Crawford M. Asymptomatic postoperative deep vein thrombosis and the development of postthrombotic syndrome. A systematic review and meta-analysis. Thromb Haemost 2005; 93(2):236-241.
(3) Hull RD, Pineo GF, Stein PD, Mah AF, MacIsaac SM, Dahl OE et al. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: A systematic review. Ann Int Med 2001; 135(10):858-869.
(4) Dahl OE. Continuing out-of-hospital prophylaxis following major orthopaedic surgery: what now? Haemostasis 2000; 30 Suppl 2:101-105.
(5) Hauch O, Jorgensen LN, Khattar SC, Teglbjaerg CS, Wahlin AB, Rathenborg P et al. Fatal pulmonary embolism associated with surgery. An autopsy study. Acta Chir Scand 1990; 156(11-12):747-749.
(6) Rasmussen MS, Wille-Jorgensen P, Jorgensen LN. Postoperative fatal pulmonary embolism in a general surgical department. Am J Surg 1995; 169(2):214-216.
(7) Kakkar VV, Corrigan TP, Fossard DP, Sutherland I, Thiewell J. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. Reappraissal of Results of International Multicenter Trial. Lancet 1977; i:567-569.

Contributors

David Cundiff and Peer Wille-Jørgensen

Cundiff reply to the 2007 feedback from authors

Summary

Date of Submission: 22-Jul-2008
Name: David K. Cundiff, MD
Email Address: dkcundiff3@verizon.net
Personal Description: Occupation Physician

Feedback: I thank Dr. Wille-J?rgensen for the reply.

The clinical relevance of the surrogate endpoint of asymptomatic DVT prevention with anticoagulants correlating with a lower incidence of clinical DVT and fatal PE is hardly settled by Kakkar?s 1977 article in the Seminars of Nuclear Medicine, ?Fibrinogen Uptake Test for Detection of Deep Vein Thrombosis? review?1 (reference 1 of the reply).

While you have demonstrated a positive correlation between asymptomatic post operative DVT with later postphlebitic syndrome,2 this does not prove that post phlebitic syndrome is prevented by prophylactic anticoagulants. It may be that rebound hypercoagulation related DVT after stopping heparin increases VTE and subsequently the post phlebitic syndrome.

Regarding the efficacy of long-term postoperative prophylaxis with orthopaedic procedures, RCTs comparing heparins for 6-10 days post op versus extending the prophylaxis for an additional 3-4 weeks at home generally do not have data on outcomes after the completion of the extended prophylaxis. This misses outcome events due to post heparin rebound hypercoagulability. In the six RCTs reviewed by Hull and colleagues,3 none had an unanticoagulated arm to see the effect of short term prophylaxis itself. This meta-analysis included only 1953 patients and fatal PE occurred in only 2/862 placebo-treated patients (possibly due to rebound hypercoagulability) versus 0/1091 who received extended prophylaxis. This makes the Goldhaber study,4 about which Dr. Wille-J?rgensen had no comment, particularly relevant. Out of about 80,000 hospitalizations of patients followed for at least 2 months (i.e., capturing rebound hypercoagulability events), 12/13 cases of fatal PE occurred in patients given prophylaxic anticoagulants.

Regarding the reference to the data on the association between fatal PE and omission of prophylaxis from the Bispebjerg Hospital, University of Copenhagen, Denmark,5 despite the statistical significance of the data ($p < .05$), little can be concluded from an observational study with 20 cases of post operative fatal PE out of 4881 surgeries. The abstract of this study states, ?Antithrombotic prophylaxis was applied routinely according to standard instructions.? At least some of those not given antithrombotic prophylaxis may have had contraindications.

In a much larger study of autopsy verified fatal PE cases of all surgical patients in Malmo, Sweden, during the period from 1951 to 1988 in whom pulmonary emboli were found at autopsy (391 cases),6 the incidence of previous prophylaxis with anticoagulants in people with autopsy-proven FPE increased from 50% in 1971-1975 to 76% in 1976-1980, 85% in 1979-1983, and 94% in 1984-1988. The overall incidence of venous thromboembolism in this hospital had not changed from 1957 to 1987.7 Again, these data suggest the possibility of rebound hypercoagulability causing FPE.

While methodologically correct for its time, the ?International Multicentre Trial?8 was before the era of early mobilization and mechanical VTE prophylaxis. The followup period was only until discharge from hospital, so the deaths due to rebound hypercoagulation on stopping the heparin were missed.

1. Kakkar VV. Fibrinogen Uptake Test for Detection of Deep Vein Thrombosis - A review of Current Practice. Sem Nucl Med. 1977;7:229-244.
2. Wille-Jorgensen P, Jorgensen LN, Crawford M. Asymptomatic postoperative deep vein thrombosis and the development of postthrombotic syndrome. A systematic review and meta-analysis. Thromb Haemost. 2005;93(2):236-241.
3. Hull RD, Pineo GF, Stein PD, et al. Extended Out-of-Hospital Low-Molecular-Weight Heparin Prophylaxis against Deep Venous Thrombosis in Patients after Elective Hip Arthroplasty: A Systematic Review. Ann Intern Med. 2001;135:858-869.
4. Goldhaber SZ, Dunn K, MacDougall RC. New Onset of Venous Thromboembolism Among Hospitalized Patients at Brigham and Women? s Hospital Is Caused More Often by Prophylaxis Failure Than by Withholding Treatment. Chest. 2000;118:1680-1684.
5. Rasmussen MS, Wille-Jorgensen P, Jorgensen LN. Postoperative fatal pulmonary embolism in a general surgical department. Am J Surg. 1995;169(2):214-216.
6. Lindblad B, Eriksson A, Bergqvist D. Autopsy-verified pulmonary embolism in a surgical department: analysis of the period from 1951 to 1988. British Journal of Surgery. 1991;78(7):849-852.
7. Lindblad B, Sternby NH, Bergqvist D. Incidence of venous thromboembolism verified by necropsy over 30 years. BMJ. 1991;302(6778):709-711.
8. Kakkar VV, Corrigan TP, Fossard DP, Sutherland I, Thirwell J. Prevention of Fatal Postoperative pulmonary embolism by low doses of heparin. Reappraisal of results of international multicentre trial. Lancet. 1977;1(8011):567-569.

Reply

"David Cundiff might be correct that a rebound effect exsists after stop of heparin for prophylaxis, but it is still theoretically and based on non-solid epidemiological data only. We still belive that the evidence for using heparin - also in prolonged prophylaxis is owerwhelming".

on behalf of the authors

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Contributors

David Cundiff and Peer Wille-Jørgensen

WHAT'S NEW

Date	Event	Description
23 July 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 1998
Review first published: Issue 3, 2001

Date	Event	Description
28 August 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Peer Wille-Jørgensen came with the idea, structured the work, extracted data and made the final manuscript. Bettina R. Andersen and Morten S. Rasmussen did the literature-search and extracted data. Lars Borly retrieved extra data from authors, made the data-entry, and the analysis. Morten S. Rasmussen and Lisbeth S. G. Mathiesen did the literature search and latest update. Peer Wille-Jørgensen did the final editing work.

DECLARATIONS OF INTEREST

One of the reviewers (Morten Schnack Rasmussen) was part time during the review process working as a research fellow on longterm thrombosis prophylaxis. His salary was partly paid for by Pharmacia/Upjohn - a company which produces one of the compounds, which potentially occur in this review. The current review has no connection to his work as a research fellow, despite being in the same scientific area. The company had no influence on the review. No conflict of interest is considered to exist in this respect.
The three other reviewers have no economical connection to the pharmaceutical industry with respect to this review, thus no conflict of interest exists.
The primary reviewer has two papers included in the analyses.

SOURCES OF SUPPORT

Internal sources

- H:S Central Research Fund, Denmark.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Colorectal Surgery; Anticoagulants [*therapeutic use]; Bandages; Confidence Intervals; Heparin [*therapeutic use]; Heparin, Low-Molecular-Weight [therapeutic use]; Odds Ratio; Postoperative Complications [*prevention & control]; Pulmonary Embolism [*prevention & control]; Venous Thrombosis [*prevention & control]

MeSH check words

Humans