UNIVERSITY OF OTTAWA
HEART INSTITUTE
INSTITUT DE CARDIOLOGIE
DE L'UNIVERSITÉ D'OTTAWA

FINAL CLINICAL REPORT

Low Molecular Weight Heparin and Unfractionated Heparin for the Prevention of Venous Thromboembolic Events in Medical and Non-orthopedic Surgical Patients: Clinical Review

December 2016

Authorship

George A. Wells, PhD[1,2]
Shannon Kelly, MSc[1]
Jesse Elliott, MSc[1]
Marc Carrier, MD, MSc, FRCPC[2,3]
William Geerts. MD, FRCPC [4]
Agnes Y. Y. Lee, MD, FRCPC [5]
Amy Johnston, MSc[1]
Zemin Bai, MD, MSc[1]
Becky Skidmore, MLS[6]

Conflicts of Interest

Dr. Marc Carrier received honorariums for speaking engagements from Sanofi-Aventis, Pfizer, Boehringer Ingelheim, LEO Pharma, and Bayer. He received research funding from LEO Pharma and Bristol-Myers Squibb and was a consultant for Scientific Advisory Board meetings for Sanofi-Aventis and LEO Pharma.

No other conflicts of interest were declared.

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Prospero registration

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[1] Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, Ontario
[2] Faculty of Medicine, University of Ottawa, Ottawa, Ontario
[3] Ottawa Hospital Research Institute Ottawa, Ontario
[4] University of Toronto/Sunnybrook Health Sciences Centre, Toronto, Ontario
[5] University of British Columbia and Vancouver Coastal Health, Vancouver, British Columbia
[6] Independent Medical information Scientist, Ottawa, Ontario

EXECUTIVE SUMMARY

Objectives

The objective of this review is to assess the comparative efficacy and safety of low molecular weight heparin (LMWH) compared to unfractionated heparin (UFH) in medical and non-orthopedic surgical patients.

Methods

A protocol was developed with input from clinical experts and the research team. The protocol was registered prior to search initiation and literature screening (PROSPERO CRD4201026946).

The strategy for building and analyzing the evidence base for the prevention of VTEs in medical and non-orthopedic surgical patients consisted of two fundamental steps:

1. Three existing systematic reviews were selected to provide the evidence base for this review following a review of the literature and consultation with clinical experts. We screened all randomized controlled trials (RCTs) included by the existing systematic reviews and individual RCTs of interest were included in this review. Studies were eligible for inclusion in the review if they satisfied the population, intervention, comparator, and study design criteria (Table A). Studies were not excluded based on the absence of outcomes of interest.

2. A pair-wise meta-analysis of randomized evidence conducted relating LMWHs to UFH or direct oral anticoagulants (for surgical patients only) for each efficacy and safety outcome specified in the protocol.

Table A: Summary of Eligibility Criteria

Population	Adult surgical and non-orthopedic medical patients
Interventions	Low molecular weight heparins
Comparators	- Unfractionated heparin, vitamin K antagonists - Direct oral anticoagulants were included as a comparator for surgical patients only
Outcomes: Efficacy	- VTE (including DVT or PE) - Symptomatic and objectively confirmed VTE
Outcomes: Safety	- All-cause death - Bleeding (major, minor, intracranial, all) - Heparin-induced thrombocytopenia - Length of stay in hospital
Study Types	Randomized controlled trials, published in or after 1995
Exclusions	- Phase I or II clinical trials - Patients admitted to the intensive care unit - Patients undergoing surgery for cancer - Patients laparoscopic surgery (day surgery) - Patients undergoing cardiac surgery - Patients undergoing orthopedic surgery

Key Findings

Medical patients:

- Prophylaxis with LMWH resulted in significantly fewer VTE, DVT, and PE events. There were no differences in the risk of bleeding or all-cause death between groups (Table B).

- The odds of VTE and DVT were significantly lower among stroke patients who received LMWH but not among patients with no stroke. There were no differences in the odds of a bleed or all-cause death between patients with stroke or no stroke.

Table B: Evidence Summary for Medical Patients

Efficacy			Safety		
Outcome	**RCTs (no.)**	**OR (95% CI)**	**Outcome**	**RCTs (no.)**	**OR (95% CI)**
VTE	3	0.51* (0.38 to 0.68)	Any bleed	2	0.98 (0.71 to 1.34)
Symptomatic VTE	2	0.36 (0.11 to 1.16)	Major bleed	2	1.92 (0.74 to 4.98)
DVT	3	0.52* (0.39 to 0.69)	Minor bleed	1	0.86 (0.56 to 1.32)
PE	3	0.19* (0.05 to 0.76)	Intracranial hemorrhage	2	0.81 (0.25 to 2.64)
Fatal PE	2	0.67 (0.11 to 4.12)	All-cause death	3	1.00 (0.70 to 1.43)

CI = confidence interval, DVT = deep vein thrombosis, OR = odds ratio, PE = pulmonary embolism, VTE = venous thromboembolism.

Surgical patients:

- There were no differences in the odds of VTE, DVT, or PE between patients who received LMWH or UFH. The odds of any bleeding event or a minor bleed were increased among patients who received LMWH. There were no differences in major bleeding or all-cause death between groups. Caution should be taken in interpreting these findings because only one study was included for this analysis (Table C).

- When one study involving patients with cancer was included in the data analysis, there was no longer a significantly increased odds of increased bleeding. There were no changes to the odds of VTE, PE or DVT.

Table C. Evidence Summary for Surgical Patients

Efficacy			Safety		
Outcome	RCTs (no.)	OR (95% CI)	Outcome	RCTs (no.)	OR (95% CI)

Efficacy			Safety		
Outcome	RCTs (no.)	OR (95% CI)	Outcome	RCTs (no.)	OR (95% CI)
VTE	1	1.00 (0.65 to 1.54)	Any bleed	1	1.72 (1.15 to 2.56)
Symptomatic VTE	1	0.67 (0.11 to 4.00)	Major bleed	1	1.79 (0.82 to 3.92)
DVT	1	1.09 (0.49 to 2.40)	Minor bleed	1	1.65 (1.05 to 2.60)
PE	1	3.01 (0.12 to 73.99)	Intracranial hemorrhage	0	NA
Fatal PE	0	NA	All-cause death	1	2.96 (0.31 to 28.56)

CI = confidence interval, DVT = deep vein thrombosis, OR = odds ratio, PE = pulmonary embolism, VTE = venous thromboembolism.

- HIT was not reported in any of the included trials

Limitations

The results of these analyses should be interpreted with caution because of the limited number of included trials. These trials involved a small number of patients with narrow inclusion criteria, which may limit the generalizability of these findings.

In each of the included trials, outcome assessment was based on DVT, not PE. Because PE is a rare event, it is possible that these trials were underpowered or of insufficient duration to detect PE.

This analysis included trials published between 1995 and the search date of each systematic review used to identify the included trials (2008-2009); as such, any trials published outside of these bounds would not have been captured.

Key messages

- Among medical patients, prophylaxis with LMWH reduces the risk of VTE and DVT with no increased risk of bleeding or death, compared with UFH. There may be differences in the risk of an event between stroke and no stroke populations.

- Among non-orthopedic surgical patients, prophylaxis with LMWH may increase the risk of bleeding, but not major bleeding, compared with UFH. There are no differences in the odds of VTE, DVT, or PE. This finding was based on one trial and should be interpreted with caution.

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Abbreviations

BID	Twice per day
CI	Confidence interval
DVT	Deep vein thrombosis
HIT	Heparin-induced thrombocytopenia
ICH	Intracranial hemorrhage
LMWH	Low molecular weight heparin
NA	Not applicable
NR	Not reported
OR	Odds ratio
PE	Pulmonary embolism
QD	Once per day
RCT	Randomized controlled trial
TID	Three times per day
UFH	Unfractionated heparin
VTE	Venous thromboembolism

1. CONTEXT AND POLICY ISSUES

1.1 Introduction

Venous thromboembolism (VTE), comprised of deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major preventable source of morbidity and mortality among hospitalized patients, with variable risk depending on underlying morbidity (1). The incidence of nosocomial VTE is estimated to be about 1% of admissions. VTE is also associated with increased length of stay among hospitalized patients (2). Risk factors for VTE in hospitalized medical patients include increasing age, previous VTE, thrombophilia, cancer, and immobilization (3). Among patients undergoing abdominal surgery, risk factors for VTE are similar, with higher risk among those undergoing surgery for cancer (4).

Guidelines for the management and prevention of VTE have recommended routine thromboprophylaxis as far back as 1986 (5). In 2016, Accreditation Canada implemented VTE prophylaxis as a required organizational practice for hospitals serving patients 18 and older (https://accreditation.ca/sites/default/files/rop-handbook-2016-en.pdf). Their set of standards stipulates that Canadian hospitals must identify medical and surgical patients who are at risk for VTE and requires that appropriate thromboprophylaxis must be provided. There continue to be knowledge gaps related to the optimal provision of thromboprophylaxis despite a large body of evidence that interventions can safely reduces thromboembolic complications associated with acute illness and surgery (5). While the risk of VTE is well-recognized in surgical patients, prophylaxis to mitigate VTE in medical patients may be underutilized (6).

Choice of thromboprophylaxis modality should be made after careful consideration of both the potential benefits and risks to the patient. Both mechanical (e.g., compression stockings) and pharmacologic (e.g., heparins) options are available. Pharmacologic interventions have been well-studied, and may be more efficacious than physical interventions in those who are not at a high risk for bleeding (5). In the last 35 years, standard pharmacologic thromboprophylaxis has been with unfractionated heparin (UFH), but increasingly, low molecular weight heparins (LMWH) are replacing UFH as there are noted clinical advantages with use. These include fewer daily injections, the ability to treat ambulatory, low-risk patients, a decreased risk of heparin-induced thrombocytopenia, and better efficacy in high-risk patients(7).

Pharmacologic thromboprophylaxis is generally administered to patients in a diverse group of medical and surgical indications, including those with acute medical illness, patients undergoing general, gynecologic, bariatric or orthopedic surgery, and patients with major trauma or spinal cord injuries. The scope of this report was limited to patients undergoing non-orthopedic surgery or hospitalized medical patients.

The anticoagulant products and doses included in the scope of this review reflect the policy questions posed by jurisdictional clients from the Canadian Agency for Drugs and Technologies in Health (CADTH); input from clinical experts was also considered in order to ensure clinical relevance of the report in Canada.

In order to inform policy work within provincial and territorial regional health authorities and hospitals, as well as clinical decisions, a health technology assessment was undertaken. The review was funded by the Drug Safety and Effectiveness Network (DSEN) of the Canadian Institute of Health Research (CIHR) as a collaboration between the University of Ottawa Heart Institute, Cardiovascular Research Methods Centre (UOHI-CRMC) and CADTH. This health technology assessment includes both a

clinical and an economic evaluation. UOHI-CRMC conducted the clinical portion of the review and the related economic evaluation was done by CADTH. This report provides findings from the clinical evaluation; findings from the economic evaluation are available in a supplemental report on the CADTH website (www.cadth.ca).

1.2 Research questions

The focus of this report is on pharmacologic thromboprophylaxis with UFH and LMWH. Two primary research questions were addressed:

1. What is the comparative clinical effectiveness of LMWH versus UFH in the prevention of VTE in medical patients?
2. What is the comparative clinical effectiveness of LMWH versus UFH in the prevention of VTE in non-orthopedic surgical patients?

2. METHODS

The strategy for building and analyzing the evidence base for the prevention of VTEs in medical and surgical patients consisted of two fundamental steps:

1. Selection of randomized controlled trials (RCTs) from a systematic review of the available randomized evidence.

2. A pair-wise meta-analysis of randomized evidence conducted relating LMWHs to UFH or direct oral anticoagulants (surgical patients only) for each of efficacy and safety outcome specified a priori, depending on the availability of evidence.

2.1 Search Strategy

A focused literature search was conducted in PubMed and MEDLINE on August 1, 2015. Following review by two independent review authors, three systematic reviews were identified as comprehensive summaries of the existing evidence base (1, 3, 4). No additional searches were performed.

The systematic reviews identified were:

1. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, Samama CM; American College of Chest Physicians. *Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed*: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl)(4). (Literature search current to Nov. 4, 2009)

2. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR; American College of Chest Physicians. *Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis*. Chest. 2012 Feb;141(2 Suppl)(3). (Literature search current to Nov. 4, 2009)

3. *Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital.* National Clinical Guideline Centre – Acute and Chronic Conditions (UK). Source London: Royal College of Physicians (UK); 2010. National Institute for Health and Clinical Excellence: Guidance (1). (Literature search current to Dec. 10, 2008)

2.2 Selection and Eligibility Criteria

Unique randomized controlled trials (RCTs) considered to be relevant by one study author were retrieved for review and obtained in full-text format from the three included previous systematic reviews (Table 1)(1, 3, 4). The full text of each potentially relevant article was independently assessed by two reviewers, and a final decision made for inclusion. Any uncertainties were resolved by discussion and consensus with a third reviewer and or a content expert. Reviewers did not remain blind to study authors or centre of publication prior to study selection. The draft list of included studies was vetted by clinical experts prior to finalization to ensure all studies met the inclusion criteria and that no key studies had been missed.

Table 1: Eligibility criteria for individual RCTs

Population	**Population A:** Adults undergoing general abdominal surgery ("surgical" patients): includes "general," "mixed" or abdominal-pelvic surgery, urological, gynecological, bariatric surgery **Population B:** Adults considered to be acutely ill medical patients (non-surgical)
Interventions	LMWH products available in Canada, at approved doses: • Enoxaparin 40 mg QD • Dalteparin 5000 U QD • Tinzaparin 3500 or 4500 U QD • Nadroparin 2850 U QD
Comparators	• Unfractionated heparin (5000 BID or TID) • Vitamin K antagonists: warfarin, acenocoumarol • Direct oral anticoagulants (dabigatran, apixaban, edoxaban, rivaroxaban) were included as comparators of interest for general abdominal surgery patients only)
Outcomes: Efficacy	• VTE (DVT, PE, fatal PE) • Clinically relevant VTE (symptomatic and objectively confirmed)
Outcomes: Safety	• All-cause death • Bleeding (major, minor, intracranial, all) • Heparin-induced thrombocytopenia • Length of hospital stay
Study Types	Randomized controlled trials
Exclusions	• Phase I or II clinical trials • Patients admitted to the intensive care unit • Patients undergoing surgery for cancer • Patients laparoscopic surgery (day surgery) • Patients cardiac surgery • Patients undergoing orthopedic surgery • Meeting or conference abstracts with no full-text publication
Note: Crossover RCTs were eligible for inclusion in the review; however, only first-period data were eligible for inclusion in the analysis.	

2.3 Data Extraction and Management

One reviewer extracted data from the included RCTs using a standardized data abstraction form and a second reviewer checked all extracted data for accuracy and completeness. The following attributes of each RCT were entered into a database:

1. Characteristics of trial participants;
2. Study design characteristics;
3. Details on interventions including, but not limited to, dose, frequency, route of administration, duration, and co-medication; and,
4. Each efficacy and safety outcome specified in the project protocol.

The primary peer-reviewed publication for each included RCT was used for data extraction. Where multiple publications for a unique RCT were available (e.g. supplemental online appendices, companion publications or clinical trial registries) the most recently adjudicated data for each outcome of interest was extracted.

2.4 Outcome definitions

Outcomes considered in this review were grouped as efficacy or safety outcomes. Definitions used were vetted by the research team and clinical experts.

2.4.1 Efficacy outcome definitions

VTE: This outcome includes all reported VTE events and combines DVT and/or PE events reported in the primary studies. We also considered PE, DVT and fatal PE separately in the analyses. All reported cases of VTE were extracted, and clinical experts were consulted to ensure comparability in terms of method of diagnosis/confirmation.

Symptomatic VTE: VTE events that were symptomatic and objectively confirmed.

2.4.2 Safety outcome definitions

All-cause death: death from any cause while on treatment.

Major bleeding: clinically overt bleeding associated with at least one of the following:

1) a decrease in hemoglobin levels of at least 2 g/dl;
2) transfusion of 2 or more units of packed red blood cells;
3) intracranial, retroperitoneal or body cavity bleeding;
4) death; or
5) major bleeding episode as defined by individual study investigators.

Minor bleeding: as defined by individual study investigators.

Any bleeding: any event reported as a bleed by individual study investigators.

Intracranial bleeding: as defined by individual study investigators..

Heparin-induced thrombocytopenia: Decrease in platelets greater than 50% or to less than 100 x 109/L and a positive laboratory HIT assay (8).

Length of hospital stay: recorded as reported duration of stay in hospital (days).

Data were extracted and analyzed for the on-treatment period only.

2.5 Risk of Bias Assessment

Risk of study bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias (ROB) for RCTs (7).

2.6 Data Synthesis and Analysis

Included studies were assessed for both clinical and methodological diversity. Clinical diversity was assessed by examining study participants, interventions, and comparators to ensure the appropriateness of pooling. Methodological diversity was also assessed by checking that the studies were similar in terms of study design and risk of bias.

Meta-analyses were undertaken using random-effects models if data were available and sufficiently similar. The effect sizes for the identified dichotomous outcomes were expressed in terms of odds ratios (ORs) and 95% confidence intervals (Cls). The denominator for analyses of efficacy outcomes was the number of randomized patients; safety outcomes were analyzed using the number of patients who received treatment.

2.7 Sensitivity analysis

A secondary sensitivity analysis was performed based on the number of patients who had adequate outcome assessment.

2.7 Subgroup Analysis

No subgroups were identified a priori. However, after review of the included studies, it was decided to explore two subgroups of patients

Two of the medical patient RCTs enrolled patients with a previous stroke (100%) (9, 10) and one RCT specifically excluded patients with a previous stroke (11). A post-hoc subgroup analysis comparing outcomes in patients with and without previous stroke was performed.

In January 2016 the review protocol was expanded to include studies of patients undergoing surgery for cancer. The majority of patients were undergoing abdominal surgery due to cancer. Following the protocol modification, one study was eligible for inclusion (12). Note that this study was identified by clinical experts and was not identified in the three systematic reviews or through additional screening of titles or abstracts.

3. RESULTS: MEDICAL PATIENTS

3.1 Study characteristics

Four RCTs met the inclusion criteria (9-11, 13)(Table 2). Following consult with clinical experts, one study (13) was excluded from data analysis due to method of screening for VTE (via d-dimer assessment) which was considered dissimilar when compared to the other three included studies. Study and patient characteristics were extracted and are reported for this study in Table 2 (Kleber et al. 2003).

Each of the three studies included in data analysis compared the LMWH enoxaparin (40 QD) and UFH (5000 IU BID or TID) (Table 2). No studies reported oral anticoagulants. Two trials involved patients with ischemic stroke (9, 10), while one trial excluded patients with previous stroke (11).

The mean age was between 68 and 74 years in two RCTs (9, 11) and a third (10) did not report mean age; however, 42% of patients in each treatment arm were aged older than 65 years. All studies included populations of patients with prolonged immobility or who were unable to walk unassisted (Table 3). None of the included studies reported the proportion of patients with irritable bowel disease, sepsis, or acute respiratory failure.

Table 2: Study characteristics - RCTs of hospitalized medical patients

Author, year	Country	No. of arms	Design	Duration of treatment	Population	Intervention (no. randomized)	Age, mean (SD)	Male, %	Weight, kg
Hillbom 2002	Finland	2	Randomized, double-blind	10 +/- 2 d or until discharge	Acute ischemic stroke (lower-limb paralysis lasting for at least 24h and necessitating bed rest)	ENOX 40 mg QD (106) UFH 5000 IU TID (106)	68 (12) 69 (10)	64.2% 55.7%	73 (13) 77 (16)
Lechler 1996	Germany, Austria	2	Randomized, double-blind	7 d	Hospitalized medical patients, age >65yr, limited mobility	ENOX 40 mg QD (477) UFH 5000 U TID (482	74 (13) 74 (13)	38.4% 36.9%	66 (15) 66 (16)

Author, year	Country	No. of arms	Design	Duration of treatment	Population	Intervention (no. randomized)	Age, mean (SD)	Male, %	Weight, kg
Sherman 2007	15 countries, including USA and Canada	2	Randomized, open-label	10 d (range 6-14 d)	Acute ischaemic stroke, unable to walk unassisted because of motor impairment, with a score of 2 or more as indicated by National Institutes of Health Stroke Scale for motor function of the leg	ENOX 40 mg QD (884) UFH 5000 U BID (878	42% in each arm were < 65 yr	59% 54%	NR
Kleber 2003 (not included in data analyses)	Germany	2	Randomized, controlled, open-label	10 +/- 2 d	Hospitalized for severe respiratory disease or heart failure, and confined to bed for >2/3 of each day	ENOX 40 mg QD (332) UFH 5000 IU TID (333)	70 (14) 70 (14)	48.2% 55.0%	70 (15) 71 (16)

Note: d = days, yr = year, mg = milligrams, BID = twice per day, ENOX = enoxaparin, NR = not reported, QD = once per day, TID = three times per day, SD = standard deviation, UFH = unfractionated heparin.

The proportion of patients with cancer was less than 15% in both intervention arms of Lechler et al. (11) and Sherman et al. (10) and Hillbom and colleagues (9) did not report this characteristic.

Table 3: Participant characteristics - RCTs of hospitalized medical patients

Author, year	Dose	No. of participants (%)*							
		Coronary artery disease	Acute COPD	Stroke	Thrombo-philia	Prolonged immobility	> 60 yr	Cancer	Previous VTE
Hillbom 2002	ENOX 40 QD UFH 5000 TID	NR	NR	100%	NR	95% 98%	NR	NR	3%‡ 3%
Lechler 1996	ENOX 40 QD UFH 5000 TID	34.2% 35.9%	NR	Excluded	Excluded	100%	87.2% 88.8%	14.7% 12.9%	6.1% 7.7%

Author, year	Dose	No. of participants (%)*							
		Coronary artery disease	Acute COPD	Stroke	Thrombo-philia	Prolonged immobility	> 60 yr	Cancer	Previous VTE
Sherman 2007	ENOX 40 QD UFH 5000 BID	NR	NR	100%	NR	100% unable to walk unassisted	NR	NR	2% 2%
Kleber 2003	ENOX 40 QD UFH 5000 TID	164 (49.4) 169 (50.8)	134 (40.4) 142 (42.6)	Excluded	Excluded	100%	NR	25 (7.5) 16 (4.8)	20 (6.0) 19 (5.7)

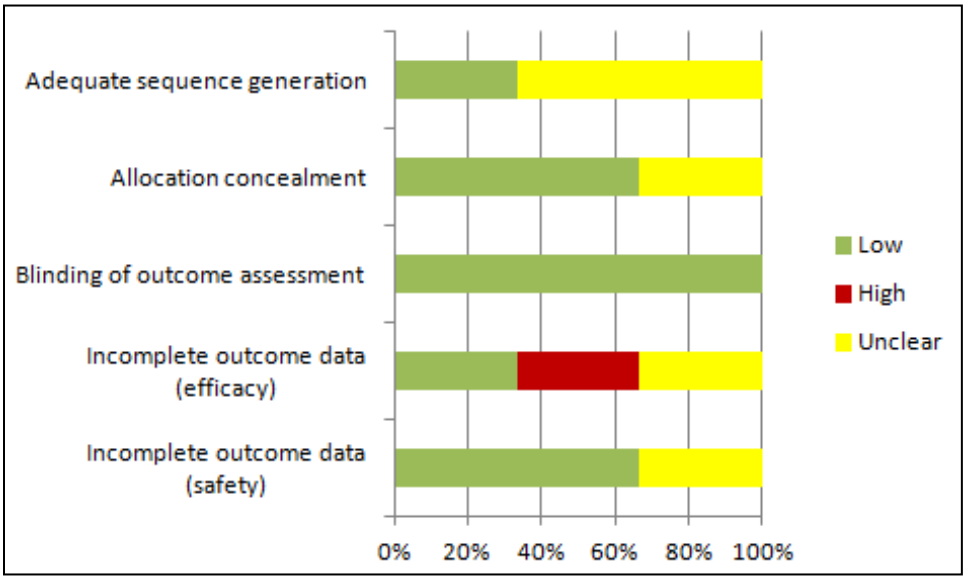
Note: BID = twice per day, ENOX = enoxaparin, NR = not reported, QD = once per day, TID = three times per day, SD = standard deviation, UFH = unfractionated heparin, VTE = venous thromboemoblism.
*Unless otherwise stated
‡DVT only

3.2 Risk of bias

Risk of bias was assessed for each trial included in the data analysis (9-11) (Figure 1, Appendix 1).

Sequence generation was inconsistently reported. In two of three trials, insufficient details were reported to allow judgment of the risk of bias, resulting in a rating of "unclear." Allocation concealment was judged to be at low risk of bias in two studies; one trial reported insufficient data to permit judgment. Blinding was adequate in all three trials. One trial (10) was deemed to be at high risk of bias for incomplete outcome data addressed. In this trial, approximately 25% of participants in each group were excluded from the efficacy population, with about half of these excluded because venography or ultrasonography was not performed.

Figure 1: Risk of bias summary – Medical patients



3.3 Efficacy outcomes

In total, three trials met the criteria for inclusion in data analysis for medical patients (9-11). Each of these trials compared enoxaparin (40 mg/d) to UFH (5000 BID or TID). The number of randomized patients who received treatment was more than 99% in each trial; however, the number of patients who received adequate outcome assessment was between 69% and 82% (Table 4).

Table 4: Summary of efficacy (A) and safety events (B) - RCTs of hospitalized medical patients

A.

STUDY:	Lechler 1996	Hillbom 2002	Sherman 2007
Treatments	UFH 5000 TID ENOX 40 QD	UFH 5000 TID ENOX 40 QD	UFH 5000 BID ENOX 40 QD
No. randomized	482 477	106 106	878 884
No. with appropriate outcome assessment	377 393	73 77	669 666
VTE *	7 1	24 14	121 68
Symptomatic VTE*	NR	4 2	7 2
DVT*	4 1	24 14	118 67
PE	0 4	3 1	6 1
Fatal PE	0 0	1 1	2 1

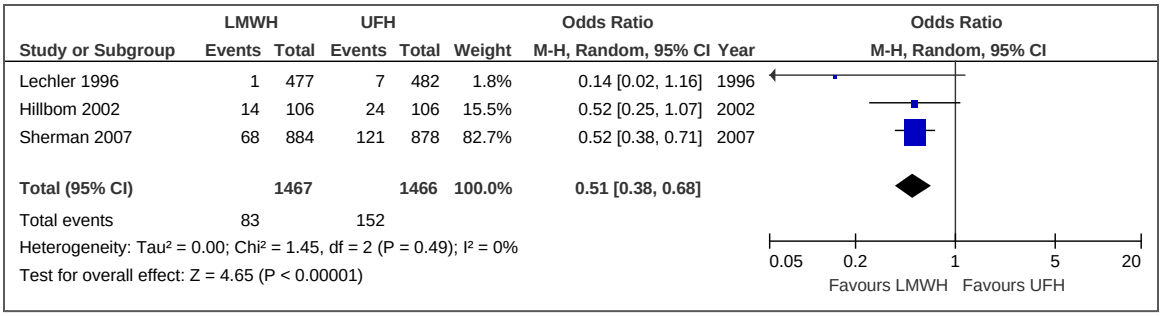
B.

	Lechler 1996	Hillbom 2002	Sherman 2007
Treatments	UFH 5000 TID ENOX 40 QD	UFH 5000 TID ENOX 40 QD	UFH 5000 BID ENOX 40 QD
No. received treatment	482 477	106 106	872 877
Major bleeding*	No. of people 7 2	0 1	6† 11
Minor bleeding*	NR	No. of people 2 2	 48 42
ICH*	NR	0 1	6 4
All-cause death	11 7	8 9	45 48
HIT	NR	NR	NR

Note: BID = twice per day, DVT = deep vein thromboembolism, HIT = heparin-induced thrombocytopenia, ICH = intracranial hemorrhage, NR = not reported, QD = once per day, TID = three times per day, UFH = unfractionated heparin, VTE = venous thromboembolism.
*Number of events unless stated otherwise
†Includes "symptomatic intracranial hemorrhage and major extracranial hemorrhage.

VTE outcomes were pooled for meta-analysis where appropriate. Compared with UFH, use of LMWH was associated with significantly lower odds of VTE (Figure 2, Table 5), with a total of 83 events in the LMWH group (n = 1467) and 152 events in the UFH group (n = 1466). The resulting odds ratio was 0.51 (95% CI: 0.38 to 0.68).

Figure 2: Meta-analysis results for VTE events in medical patients



The odds of DVT and PE were also significantly lower in the LMWH group than in the UFH group (Table 5). There were no significant differences between groups in the odds of fatal PE or symptomatic VTE.

Forest plots for these additional outcomes are provided in Appendix 2.

3.3.1 Sensitivity analysis

When meta-analyses were limited to patients with adequate outcome assessment, the odds of VTE or DVT were significantly lower in the LMWH group than in the UFH group (Table 5). The odds of symptomatic VTE were not significantly different between groups.

3.4 Safety outcomes

The included RCTs varied in the reporting of bleeding events: Hillbom (9) reported the number of people with an event, while Sherman (10) reported the number of events. Lechler (11) reported both the total number of events and the number of people with an event (Table 6). Data in Table 6 reported for both the number of people and the number of events, as appropriate.

Two RCTs reported the number of patients with major bleeding (9, 11) and two RCTs reported the number of major bleeding events (9, 10) (Hillbom (9) reported both number of events and number of people) The odds of a major bleed were not significantly different between patients receiving LMWH and UFH (Table 6, Figure 3) when analyzed by the total number of major bleeds or the number of people with a major bleed.

There were no significant differences between LMWH and UFH in the odds of any bleeding, minor bleeding, intracranial hemorrhage, or all-cause death (Table 6). None of the included studies reported HIT.

Forest plots for each outcome are presented in Appendix 2.

Figure 3: Meta-analysis results for major bleeding in medical patients

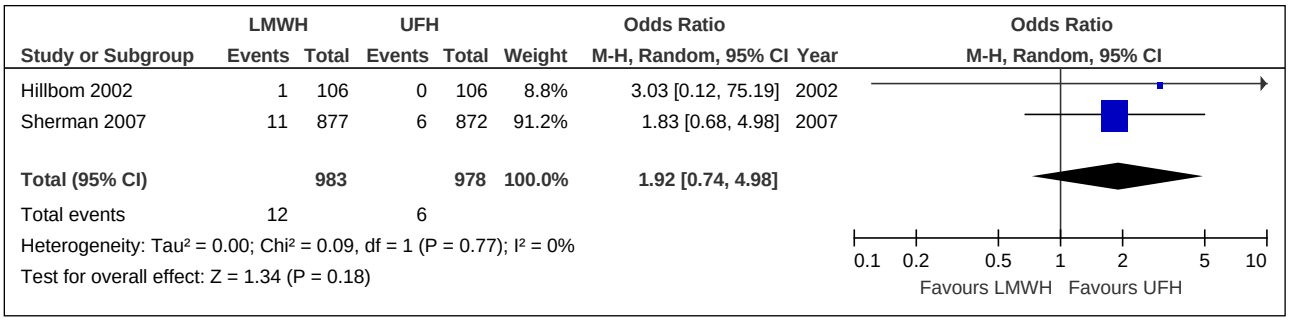


Table 5: Meta-analysis results for medical patients - Efficacy outcomes

Outcome	Studies	Included treatments	No. of events	Based on no. randomized				Based on no. with appropriate outcome assessment‡			
				Denominator	OR (95% CI) (LMWH v. UFH)	SE (logOR)	I^2	Denominator	OR (95% CI) (LMWH v. UFH)	SE (logOR)	I^2
Any VTE	Lechler, Sherman Hillbom	UFH 5000 BID or TID ENOX 40 QD	152 83	1466 1467	**0.51*** **(0.38 to 0.68)**	0.1413	0%	1130 1140	**0.50*** **(0.37 to 0.67)**	0.1440	0%
DVT	Lechler, Sherman Hillbom	UFH 5000 BID or TID ENOX 40 QD	146 82	1466 1467	**0.52*** **(0.39 to 0.69)**	0.1433	0%	1126 1138	**0.51*** **(0.38 to 0.68)**	0.1450	0%
PE total	Lechler, Sherman Hillbom	UFH 5000 BID or TID ENOX 40 QD	13 2	1466 1467	**0.19*** **(0.05 to 0.76)**	0.0134	0%	NA	NA	NA	NA
PE fatal	Hillbom, Sherman	UFH 5000 BID or TID ENOX 40 QD	3 2	984 990	0.67 (0.11 to 4.12)	0.6517	0%	NA	NA	NA	NA
Sympt. VTE	Hillbom, Sherman†	UFH 5000 BID or TID ENOX 40 QD	11 4	984 990	0.36 (0.11 to 1.16)	0.5856	0%	753 747	0.36 (0.11 to 1.15)	0.5862	0%

Note: BID = twice per day, CI = confidence interval, DVT = deep vein thromboembolism, HIT = heparin-induced thrombocytopenia, ICH = intracranial hemorrhage, LMWH = low molecular weight heparin, NR = not reported, OR = odds ratio, PE = pulmonary embolism, QD = once per day, SE = standard error, TID = three times per day, UFH = unfractionated heparin, VTE = venous thromboembolism.
Data are presented for treatment period (data were extracted separately from follow-up period, where possible).
*$p < 0.05$
†Note: Sherman presented data as number of events (not number of people with an event). It was inferred that each person could have no more than one event for the purpose of this analysis.
‡No. with appropriate outcome assessment plus number with a symptomatic event prior to outcome assessment.

Table 6: Meta-analysis results for medical patients - Safety outcomes

Outcome	Measure	Studies	Included treatments	No. of events	No. received treatment	OR (95% CI) (LMWH v. UFH)	SE (logOR)	I^2
Any bleeding	No. of people	Hillbom, Lechler	UFH 5000 TID ENOX 40 QD	15 16	588 583	1.08 (0.53 to 2.20)	0.8367	0%
	No. of events	Lechler, Sherman	UFH 5000 BID or TID ENOX 40 QD	85 84	1354 1361	0.98 (0.71 to 1.34)	0.9092	0%
Major bleeding	No. of people	Hillbom, Lechler	UFH 5000 TID ENOX 40 QD	7 3	588 583	0.60 (0.07 to 5.22)	0.2221	40%
	No. of events	Hilbom Sherman	UFH 5000 BID or TID ENOX 40 QD	6 12	978 983	1.92 (0.74 to 4.98)	0.5021	NA
Minor bleeding	No. people	Hillbom	UFH 5000 TID ENOX 40 QD	2 2	106 106	1.00 (0.14 to 7.32)	1.0096	NA
	No. of events	Sherman	UFH 5000 BID ENOX 40 QD	48 42	872 877	0.86 (0.56 to 1.32)	0.2169	
ICH	No. of events	Hillbom Sherman*	UFH 5000 BID or TID ENOX 40 QD	6 5	978 983	0.81 (0.25 to 2.64)	0.6072	0%
All-cause death	No. of people	Hillbom, Lechler, Sherman	UFH 5000 BID or TID ENOX 40 QD	64 64	1460 1460	1.00 (0.70 to 1.43)	0.1995	NA
HIT	No studies	—	—	—	—	—	—	—

Note: BID = twice per day, CI = confidence interval, DVT = deep vein thromboembolism, HIT = heparin-induced thrombocytopenia, ICH = intracranial hemorrhage, NR = not reported, OR = odds ratio, QD = once per day, SE = standard error, TID = three times per day, UFH = unfractionated heparin, VTE = venous thromboembolism.
*Sherman reported as "minor extracranial hemorrhage"

3.5 Subgroup analyses

Of the included RCTs, two focused on populations of patients with previous stroke (9, 10), while one specifically excluded patients with previous stroke (11).

Among patients with no previous stroke, there were no significant differences in the odds of VTE, DVT, PE, or symptomatic VTE (Table 7). In contrast, the odds of VTE and DVT were significantly lower in the LMWH group compared with the UFH group.

There were no differences in any safety outcomes between the previous stroke and no previous stroke populations: there were no significant differences in the odds of all bleeding, major bleeding, minor bleeding, or all-cause death between LMWH or UFH groups (Table 8).

Intracranial hemorrhage was not reported in the single RCT involving patients without previous stroke (11), and no subgroup comparison was possible between patient with and without a previous stroke for this outcome.

Forest plots for each efficacy and safety outcome for this analysis are presented in Appendix 3.

Table 7: Results of subgroup analysis for medical patients: Stroke v. no stroke – Efficacy outcomes

					Based on no. randomized			Based on no. with appropriate outcome assessment*		
Outcome	**Measure**	**Studies**	**Included treatments**	**No. of events**	**Denominator**	**OR (95% CI) (LMWH v. UFH)**	**I^2**	**Denominator**	**OR (95% CI) (LMWH v. UFH)**	**I^2**
Any VTE	**No stroke**	Lechler	UFH 5000 BID ENOX 40 QD	7 1	482 477	0.14 (0.02 to 1.16)	NA	377 393	0.13 (0.02 to 1.10)	NA
	Stroke	Sherman Hillbom	UFH 5000 BID or TID ENOX 40 QD	145 82	984 990	**0.52*** **(0.39 to 0.69)**	0%	753 747	**0.50** **(0.38 to 0.69)***	0%
DVT	**No stroke**	Lechler	UFH 5000 BID ENOX 40 QD	4 1	482 477	0.25 (0.03 to 2.25)	NA	377 393	0.24 (0.03 to 2.14)	NA
	Stroke	Sherman Hillbom	UFH 5000 BID or TID ENOX 40 QD	142 81	984 990	**0.53*** **(0.39 to 0.70)**	0%	749 745	**0.52*** **(0.38 to 0.69)**	0%
PE (total)	**No stroke**	Lechler	UFH 5000 BID ENOX 40 QD	4 0	482 477	0.11 (0.01 to 2.07)	NA	NA	NA	NA
	Stroke	Sherman Hillbom	UFH 5000 BID or TID ENOX 40 QD	9 2	984 990	0.23 (0.05 to 1.07)	0%	NA	NA	NA
PE (fatal)	**No stroke**	No studies	—	—	—	—	—	—	—	—
	Stroke	Sherman Hillbom	UFH 5000 BID or TID ENOX 40 QD	3 2	984 990	0.67 (0.11 to 4.12)	0%	NA	NA	NA
Symptomatic VTE	**No Stroke**	No studies	—	—	—	—	—	—	—	—
	Stroke	Sherman, Hillbom	UFH 5000 BID or TID ENOX 40 QD	11 4	984 990	0.36 (0.11 to 1.16)	0%	753 747	0.36 (0.11 to 1.15)	0%

Note: BID = twice per day, CI = confidence interval, DVT = deep vein thromboembolism, HIT = heparin-induced thrombocytopenia, ICH = intracranial hemorrhage, NR = not reported, OR = odds ratio, QD = once per day, SE = standard error, TID = three times per day, UFH = unfractionated heparin, VTE = venous thromboembolism.
*No. with appropriate outcome assessment plus number with a symptomatic event prior to outcome assessment.

Table 8: Results of subgroup analysis for medical patients: Stroke v. no stroke - safety outcomes

Outcome	Group	Study	Included treatments	No. of events	No. who received treatment	OR (95% CI) (LMWH v. UFH)	I^2
All bleeding	No Stroke	Lechler (no. of people)	UFH 5000 BID ENOX 40 QD	13 13	482 477	1.01 (0.46 to 2.20)	NA
	Stroke	Hillbom (no. of people)	UFH 5000 TID ENOX 40 QD	2 3	106 106	1.51 (0.25 to 9.25)	NA
		Sherman (no. of events)	UFH 5000 BID ENOX 40 QD	70 69	872 877	0.98 (0.69 to 1.38)	
Major bleeding (no. of events)	No Stroke	No studies	—	—	—	—	—
	Stroke	Hillbom (no. events) Sherman (no. events)	UFH 5000 BID or TID ENOX 40 QD	6 12	978 983	1.92 (0.74 to 4.98)	0%
Major bleeding (no. of people)	No Stroke	Lechler (no. people)	UFH 5000 BID ENOX 40 QD	7 2	482 477	0.29 (0.06 to 1.38)	NA
	Stroke	Hillbom (no. of people)	UFH 5000 TID ENOX 40 QD	0 1	106 106	3.03 (0.12 to 75.19)	NA
Minor bleeding	No Stroke	No studies	—	—	—	—	—
	Stroke	Hillbom (no. of people)	UFH 5000 TID ENOX 40 QD	2 2	106 106	1.00 (0.14 to 7.23)	NA
		Sherman (no. of events)	UFH 5000 BID ENOX 40 QD	48 42	872 877	0.86 (0.56 to 1.32)	
ICH	No Stroke	No studies	—	—	—	—	—
	Stroke	Hillbom Sherman	UFH 5000 TID or BID ENOX 40 QD	6 5	978 983	0.81 (0.25 to 2.64)	0%
All-cause death	No Stroke	Lechler	UFH 5000 BID ENOX 40 QD	11 7	482 477	0.64 (0.25 to 1.66)	NA
	Stroke	Sherman Hillbom	UFH 5000 BID or TID ENOX 40 QD	53 57	978 983	1.07 (0.73 to 1.58)	0%
HIT	No studies	—	—	—	—	—	—

4. RESULTS: SURGICAL PATIENTS

4.1 Study characteristics

Three trials were initially identified that met the PICO criteria (14-16). The trials by Ward (16) and Osman (15) were not included in the analyses as they were felt to not be representative of the general population of surgical patients (Osman: renal transplantation) or because VTE was assessed through use of a surrogate outcome (Ward).

The primary meta-analysis included only the RCT by McLeod (14) and a secondary analysis was performed to include the trial by Bergqvist and colleagues (12). A fourth trial involving patients undergoing surgery for cancer was identified following the protocol modification and included in a post-hoc analysis (12).

The trials by McLeod (14) and Bergqvist (12) compared enoxaparin (40 QD) and UFH (5000 IU TID) (Table 2, Table 9). No studies reported direct or other oral anticoagulants. Mean age was higher in the RCT by Bergqvist (12); however, authors provided baseline characteristics only for patients investigators deemed to be 'evaluable' (56% to 59% of patients randomized). Patients in the RCT by McLeod (14) were undergoing colorectal surgery (35% cancer), while patients in the Bergqvist RCT (12) were all undergoing surgery for abdominal or pelvic cancer.

The trials by both McLeod (14) and Bergqvist (12) allowed the inclusion of patients with previous VTE; however, the proportion of such patients was less than 5% in both studies (Table 10). None of the included RCTs reported the proportion of patients with acute respiratory failure, stroke, sepsis, or thrombophilia.

The surgical characteristics were not well reported in either RCT (Table 11). The mean duration of surgery was similar between the two trials; however, McLeod (14) reported the mean duration of anesthesia while Bergqvist reported the mean duration of the surgical procedure (12).

Table 9: Study characteristics - RCTs of surgical patients

Author, year	Country	No. of study arms	Design	Duration of treatment	Population	Intervention (no. randomized)	Age, mean (SD)	Male, %	Weight
McLeod 2001	Canada	2	Randomized, double-blind	Up to 10 d	Colorectal surgery	ENOX 40 mg QD (674) UFH 5000 IU TID (675)	52 (18) 50 (17)	56% 53%	BMI > 30 13% 16%
Bergqvist 1997	10 countries	2	Randomized, double-blind	10 +/- 2 d	Abdominal or pelvic cancer (gastrointestinal, urological, gynecological)	ENOX 40 mg QD (556) UFH 5000 IU TID (560)	Median (range)* 68 (35-90) 69 (32-91)	52%* 53%	BMI - Median (range)* 24.8 (13.9-41.8) 24.3 (15.9-51.4)
Ward 1998	Australia	2	Randomized; blinding unclear	5d or until full activity resumed	Major gynecological surgery	DALT 5000 QD (280) UFH 5000 BID (286)	55 (17) 55 (16)	NR	NR
Osman 2007	Egypt†	3 (2 of interest)	Randomized, double-blind	1 wk	Non-risky renal transplantation	TINZ 3500 QD (25) UFH 5000 BID (25)	28.3‡ 29.4‡	56%‡ 76%‡	NR

BID = twice daily, DALT = dalteparin, ENOX = enoxaparin, NR = not reported, QD = once daily, SD = standard deviation, TINZ = tinzaparin, UFH = unfractionated heparin.
*Data provided for evaluable patients only.
†Based on affiliation of corresponding author.
‡Transplant recipient.

Table 10: Participant characteristics - RCTs of surgical patients

Author, year	Group	% of participants										
		Heart failure	COPD	Acute respiratory failure	Stroke	Sepsis	IBD	Thrombophilia	Prolonged immobility	> 60 yr	Cancer	Previous VTE
McLeod 2001	ENOX 40 mg QD UFH 5000 TID	NR	NR	NR	NR	NR	43.0 43.6	NR	NR	NR	35.8 34.7	2.7 3.7
Bergqvist 1997*	ENOX 40 QD UFH 5000 TID	9.4 10.6	6.6 5.4	NR	NR	NR	NR	NR	5 (1.6)† 7 (2.2)	76%	100 (inclusion criteria)	4.1 2.2
Ward 1998	DALT 5000 QD UFH 5000 BID	NR	NR	NR	NR	NR	NR	NR	NR	NR	79.2 83.6	NR
Osman 2007	TINZ 3500 QD UFH 5000 BID	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Excluded

BID = twice daily, DALT = dalteparin, ENOX = enoxaparin, NR = not reported, QD = once daily, SD = standard deviation, TINZ = tinzaparin, UFH = unfractionated heparin.
*Data provided for evaluable patients only
† Prolonged immobilization before surgery > 72 h

Table 11: Surgical characteristics - RCTs of surgical patients

Author, year	Intervention	Elective or emergent surgery	Method of anesthesia	Duration of surgery, mean	Mechanical prophylaxis	Post surgical infection	Length of hospital stay, d	Reoperation for bleeding
McLeod 2001	ENOX 40 QD UFH 5000 TID	NR	General	Anesthesia time: 3.9 (1.6) h	None	NR	NR	2 (0.3) 1 (0.2)
Bergqvist 1997*	ENOX 40 QD UFH 5000 TID	Elective	General	Duration of operation: 2 h 59 min (23 min to 12 h 50 min)	NR	NR	NR	NR

Author, year	Intervention	Elective or emergent surgery	Method of anesthesia	Duration of surgery, mean	Mechanical prophylaxis	Post surgical infection	Length of hospital stay, d	Reoperation for bleeding
Ward 1998	DALT 5000 QD UFH 5000 BID	NR; transplant	NR	NR	NR	NR	NR	1 (slipped ligature of artery)
Osman 2007	TINZ 3500 QD UFH 5000 BID	NR	NR	NR	Allowed	NR	NR	NR

BID = twice daily, DALT = dalteparin, ENOX = enoxaparin, NR = not reported, QD = once daily, SD = standard deviation, TINZ = tinzaparin, UFH = unfractionated heparin.

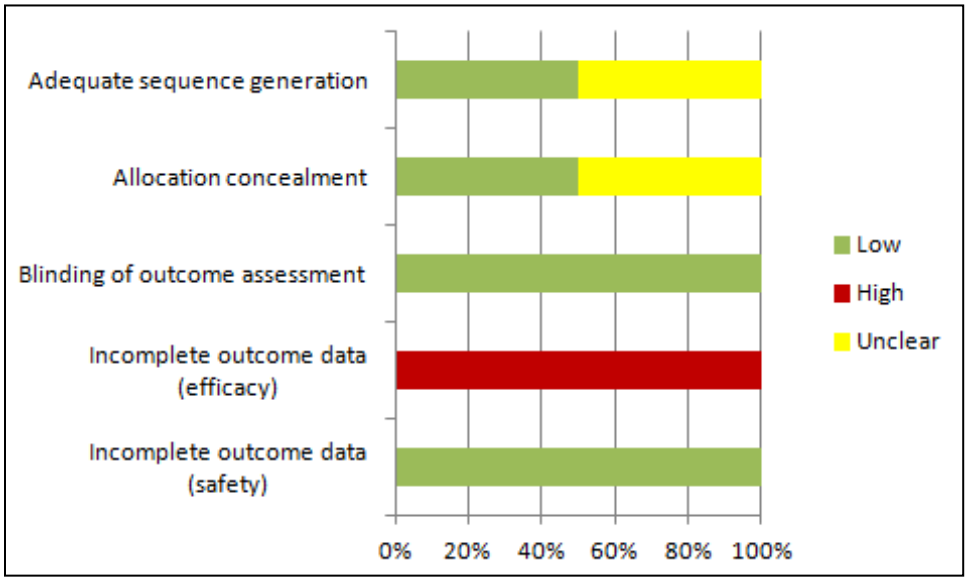
4.2 Risk of bias

Risk of bias was assessed for the McLeod (14) and Bergqvist (12) RCTs.

Both trials were assessed as being at low risk of bias for the domains of blinding and addressing incomplete outcome data for safety (Figure 4). The McLeod RCT was at low risk of bias for sequence generation and allocation concealment, while insufficient data was provided by Bergqvist to permit assessment for either domain.

Both trials were assessed as being at high risk of bias for incomplete outcome data. In both trials, the proportion of patients who completed the trial was less than 80%. In the trial by McLeod and colleagues (14), about 10% of in each group patients withdrew because of 'preference', and about 15% in each group did not receive adequate outcome assessment. In the trial by Bergqvist and colleagues (12), about 40% of randomized patients did not receive adequate outcome assessment and were excluded from the efficacy analysis.

Figure 4: Risk of bias summary — Surgical patients



4.3 Efficacy outcomes

One trial was included in the primary analysis (14). McLeod (14) randomized patients to received enoxaparin (40 mg QD) or UFH (5000 TID). The proportion of randomized patients who received treatment was 95%–97%; however, only ~70% of randomized patients had adequate outcome assessment (

Table 12).

Table 12: Summary of efficacy (A) and safety events (B) - RCTs of surgical patients

A.

	McLeod 2001	Bergqvist 1997
Treatments	UFH 5000 TID ENOX 40 QD	UFH 5000 TID ENOX 40 QD
No. randomized	675 674	560 556
No. with appropriate outcome assessment	468 468	319 312
VTE	44 44	58 46
Symptomatic VTE	3 2	8 4
DVT	12 13	58 46
PE	0 1	2 0
Fatal PE	NR	NR

B.

	McLeod 2001	Bergqvist 1997
Treatments	UFH 5000 TID ENOX 40 QD	UFH 5000 TID ENOX 40 QD
No. who received treatment	643 653	560 555
Any bleeding	42 70	96 104
Major bleeding	10 18	16 23
Minor bleeding	32 52	80 81
ICH	NR	0 0
All-cause death	1 3	7 4
HIT	NR	NR

TID = three times per day, QD = once per day, No. = number, ICH = intracranial hemorrhage, HIT = Heparin-Induced Thrombocytopenia, NR = not reported, PE = pulmonary embolism, VTE = venous thromboembolism, DVT = deep-vein thrombosis,

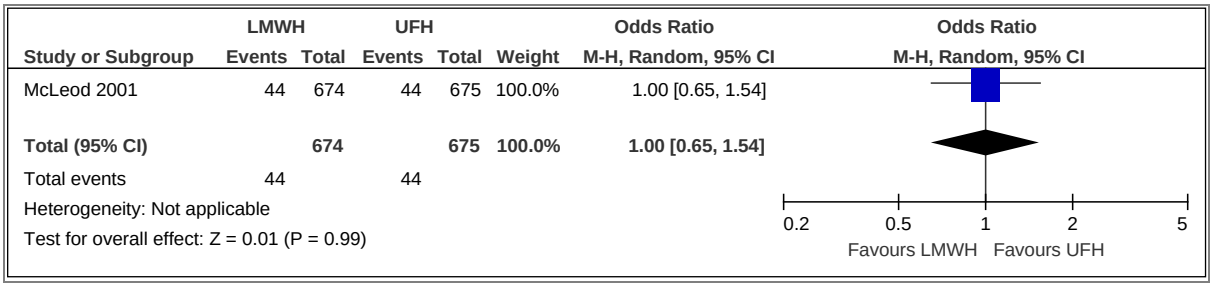
In the trial by McLeod (14), findings showed no significant differences in odds of a VTE event when the LMWH and UFH groups were compared (

Figure 5). Results were similar for DVT, PE, and symptomatic DVT (

Table 13). Fatal PE and HIT were not reported in this study.

Forest plots for each efficacy and safety outcome are presented in Appendix 4.

Figure 5: Meta-analysis results for VTE events in surgical patients



4.3.1 Sensitivity analysis

When patients with adequate outcome assessment were considered in sensitivity analyses, there were no significant difference in the odds of VTE, DVT, or symptomatic VTE between the LMWH or UFH groups (

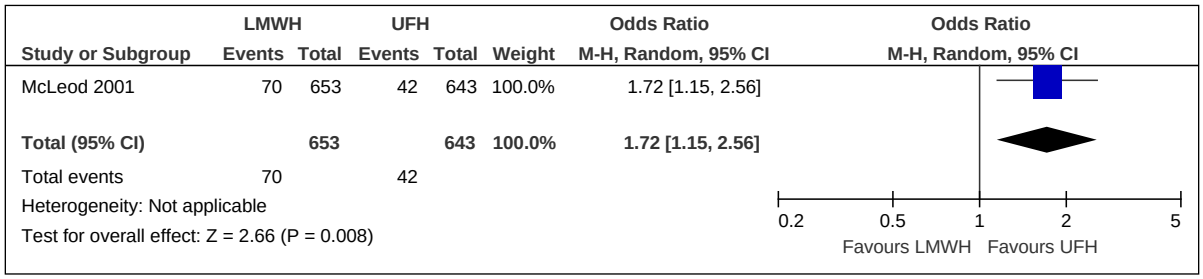
Table 13).

4.4 Safety outcomes

In the trial by McLeod and colleagues (14), the odds of any bleeding event (Figure 6) and the odds of a minor bleed were significantly higher among patients taking LMWH than among those taking UFH (Table 14).

There were no significant differences between groups in the odds of a major bleed or all-cause death. Intracranial hemorrhage and HIT were not reported in this trial.

Figure 6: Any bleeding event — surgical patients



4.5 Additional analysis

In the following analysis, data from the trial by Bergqvist and colleagues (12) was combined with that from McLeod and colleagues (14). The trial by Bergqvist and colleagues (12) was not included in the base case analysis because it was originally not eligible for inclusion based on the PICO statement. The protocol was amended in January 2016 to allow inclusion of trials with 100% cancer patients. Clinical experts identified one trial (12) that met the inclusion criteria.

There were no significant differences in the odds of VTE, DVT, PE, or symptomatic VTE between groups when data from both McLeod and colleagues and Bergqvist and colleagues were considered (Table 15). This was consistent whether the number of patients randomized or with adequate outcome assessment were included in the analysis.

There were also no significant differences in the odds of any bleeding event, major bleeding, minor bleeding, or all-cause death between groups (Table 16). Forest plots for each efficacy and safety outcome are presented in Appendix 5.

Table 13: Results for surgical patients - efficacy outcomes

Outcome *	Studies	Included treatments	No. of events	Based on no. randomized				Based on no. with appropriate outcome assessment†			
				Denominator	OR (95% CI) (LMWH v. UFH)	SE (logOR)	I^2	Denominator	OR (95% CI) (LMWH v. UFH)	SE (logOR)	I^2
Any VTE	McLeod	UFH 5000 TID ENOX 40 QD	44 44	675 674	1.00 (0.65 to 1.54)	0.2205	NA	468 468	1.00 (0.64 to 1.55)	0.224 0	NA
DVT	McLeod	UFH 5000 TID ENOX 40 QD	12 13	675 674	1.09 (0.49 to 2.40)	0.4041	NA	468 468	1.09 (0.49 to 2.40)	0.405 8	NA
PE total	McLeod	UFH 5000 TID ENOX 40 QD	0 1	675 674	3.01 (0.12 to 73.99)	1.6339	NA	NA	NA	NA	NA
PE fatal	No studies	—	—	—	—	—	—	—	—	—	—
Sympto-matic VTE	McLeod	UFH 5000 TID ENOX 40 QD	3 2	675 674	0.67 (0.11 to 4.00)	0.9145	NA	468 468	0.67 (0.11 to 4.00)	0.915 2	NA

Note: CI = confidence interval, DVT = deep vein thrombosis, ENOX = enoxaparin, LMWH = low-molecular weight heparin, NA = not applicable, OR = odds ratio, PE = pulmonary embolism, SE = standard error, UFH = unfractionated heparin, VTE = venous thromboembolism.
*Data are presented for treatment period (data were extracted separately from follow-up period, where possible.
†No. with appropriate outcome assessment plus number with a symptomatic event prior to outcome assessment

Table 14: Results for SURGICAL PATIENTS - safety outcomes

Outcome	Measure	Studies	Included treatments	No. of events	No. received treatment	OR (95% CI) (LMWH v. UFH)	SE (logOR)	I^2
All bleeding	No. of events	McLeod	UFH 5000 TID ENOX 40 QD	42 70	643 653	**1.72** **(1.15 to 2.56)**	0.2074	NA
Major bleeding	No. of events	McLeod	UFH 5000 TID ENOX 40 QD	10 18	643 653	1.79 (0.82 to 3.92)	0.3984	NA
Minor bleeding	No. of events	McLeod	UFH 5000 TID ENOX 40 QD	32 52	643 653	**1.65** **(1.05 to 2.60)**	0.2319	NA
ICH	—	No studies	—	—	—	—	—	—
All-cause death	No. of people	McLeod	UFH 5000 TID ENOX 40 QD	1 3	643 653	2.96 (0.31 to 28.56)	1.1560	NA
HIT	—	No studies	—	—	—	—	—	—

Note: CI = confidence interval, ENOX = enoxaparin, ICH = intra-cerebral hemorrhage, LMWH = low-molecular weight heparin, HIT = heparin induced thrombocytopenia, NA = not applicable, OR = odds ratio, SE = standard error, UFH = unfractionated heparin

Table 15: Additional analyses including Bergqvist RCT (100% cancer patients) - Efficacy outcomes

				Based on no. randomized				Based on no. with appropriate outcome assessment†			
Outcome	**Studies**	**Included treatments**	**No. of events**	**Denominator**	**OR (95% CI) (LMWH v. UFH)**	**SE (logOR)**	**I^2**	**Denominator**	**OR (95% CI) (LMWH v. UFH)**	**SE (logOR)**	**I^2**
Any VTE	McLeod, Bergqvist	UFH 5000 TID ENOX 40 QD	102 90	1235 1230	0.88 (0.65 to 1.18)	0.1506	0%	797 786	0.88 (0.65 to 1.20)	0.1542	0%
DVT	McLeod, Bergqvist	UFH 5000 TID ENOX 40 QD	70 59	1235 1230	0.84 (0.58 to 1.20)	0.1823	0%	793 784	0.84 (0.58 to 1.22)	0.1844	0%
PE total	McLeod, Bergqvist	UFH 5000 TID ENOX 40 QD	2 1	1235 1230	0.74 (0.05 to 10.54)	1.2254	31%	NA	NA	NA	NA
PE fatal	No studies	—	—	—	—	—	—	—	—	—	—
Sympt. VTE	McLeod, Bergqvist	UFH 5000 TID ENOX 40 QD	11 6	1235 1230	0.55 (0.20 to 1.49)	0.5091	0%	787 797	0.55 (0.20 to 1.51)	0.5100	0%

Note: CI = confidence interval, ENOX = enoxaparin, ICH = intra-cerebral hemorrhage, LMWH = low-molecular weight heparin, HIT = heparin induced thrombocytopenia, NA = not applicable, OR = odds ratio, SE = standard error, UFH = unfractionated heparin

Note: Data are presented for treatment period (data were extracted separately from follow-up period, where possible.
*$p < 0.05$
†No. with appropriate outcome assessment plus number with a symptomatic event prior to outcome assessment.

Table 16: Additional analyses including Bergqvist RCT (100% cancer patients) - Safety outcomes

Outcome	Measure	Studies	Included treatments	No. of events	No. received treatment	OR (95% CI) (LMWH v. UFH)	SE (logOR)	I^2
All bleeding	No. of events	McLeod, Bergqvist	UFH 5000 TID ENOX 40 QD	138 174	1203 1208	1.36 (0.89 to 2.07)	0.1221	65%
Major bleeding	No. of events	McLeod, Bergqvist	UFH 5000 TID ENOX 40 QD	26 41	1203 1208	1.59 (0.97 to 2.63)	0.2541	0%
Minor bleeding	No. of events	McLeod, Bergqvist	UFH 5000 TID ENOX 40 QD	112 133	1203 1208	1.27 (0.80 to 2.02)	0.1353	64%
ICH	No. of events	Bergqvist	UFH 5000 TID ENOX 40 QD	0 0	560 555	—	—	—
All-cause death	No. of events	McLeod, Bergqvist	UFH 5000 TID ENOX 40 QD	8 7	1203 1208	0.98 (0.22 to 4.45)	0.5192	36%
HIT	—	No studies	—	—	—	—	—	—

CI = confidence interval, HIT = heparin-induced thrombocytopenia, ICH = intracranial hemorrhage, LMWH = low molecular weight heparin, OR = odds ratio, SE = standard error, UFH = unfractionated heparin.

5. DISCUSSION

Anticoagulants continue to be the primary strategy for the prevention of thrombosis in hospitalized patients, yet there are still knowledge gaps that may contribute to less-than-optimal thromboprophylaxis in certain patients. Decision-making is complex, and must be individualized based on each patients' risk-benefit profile, especially given the potential for bleeding complications. This review aimed to determine the comparative efficacy and safety of pharmacologic thromboprophylaxis with UFH and LMWH in medical and surgical patients.

We found that among medical inpatients, thromboprophylaxis with LMWH resulted in significantly fewer VTE, DVT, and PE events when compared to UFH. There was no difference in the risk of bleeding or all-cause death between the groups. Among surgical patients, there were no differences in the odds of VTE, DVT, or PE between patients who received LMWH or UFH. The odds of any bleeding event or a minor bleed were increased among patients who received LMWH. There were no differences in major bleeding or all-cause death between groups.

The 2012 Antithrombotic Guidelines by the American College of Chest Physicians recommend the use of LMWH, low-dose UFH, or fondaparinux as prophylaxis among hospitalized medical patients at increased risk of VTE (Grade 1B), with the choice between agents based on patient preference, compliance, ease of administration, and cost (3). With respect to the choice between LWMH and UFH, these guidelines found no significant difference in the risk of symptomatic DVT, non-fatal PE, or death (3). Our results were consistent with these findings. However, the guideline also reported a reduced risk of major bleeding (RR 0.48, 95% CI 0.24 to 0.99) associated with the use of LMWH (3). In contrast, we found no difference in the odds of a major bleeding event between LMWH and UFH. This may be, in part, due to differences in the LMWH agents and dosing regimens included in the current review.

Patients with recent stroke are believed to be at increased risk of VTE, potentially due to altered blood flow (1). Of the three trials involving medical patients included in this review, two involved patients with stroke. Among studies involving patients with stroke, we found that the odds of VTE and DVT were significantly lower in the LMWH group compared with the UFH group, with no differences in the risk of bleeding or all-cause death. In the 2010 NICE guidelines, one trial was included that compared LMWH with UFH among patients with stroke (9). NICE also reported a significantly lower odds of DVT, with no difference in the odds of PE, major bleeding, or all-cause mortality (1).

Among non-orthopedic surgical patients, the recommendations in the 2012 Antithrombotic Guidelines by the American College of Chest Physicians (4) are stratified by baseline risk of VTE. Among general and abdominal-pelvic surgery patients at moderate or high risk (but not at high risk of major bleeding), LMWH or UFH are recommended over no prophylaxis (4). For those at high risk of bleeding, mechanical prophylaxis is recommended. Among all surgical patients, the risks of fatal PE, symptomatic VTE, and major bleeding were not significantly different between LMWH and UFH (4). Our findings are consistent with these findings. In addition, we found an increased risk of any bleeding and minor bleeding among patients receiving LMWH. However, our findings should be interpreted with caution because they are based on the results of a single study (14). It is important to note that the higher risk of any bleeding with LMWH reported in this colorectal surgical study is attributable to excess minor bleeding episodes. Rates of intraoperative and post-operative blood loss, mean units of blood transfused, and the proportion of patients requiring transfusions in the study were similar in both

the LMWH and UFH groups. Rates of ecchymosis (bruising) were similar, and high in both treatment groups; however, other minor bleeding events such as wound hematomas, macroscopic rectal bleeds and upper gastrointestinal bleeds were higher in the LMWH group. There may be a number of hereditary or acquired patient risk factors or surgical procedure aspects contributing to the higher rates of minor bleeding with LMWH in this study, but it is not possible to closely examine in detail using the data presented in this study.

Heparin-induced thrombocytopenia was not reported in any of the included RCTs. A 2005 systematic review involving medical patients receiving LMWH or UFH identified 2 RCTs that assessed HIT (17). Both of these trials involved orthopedic surgery (18, 19), with a significantly lower risk of HIT among post-operative patients who received LMWH (OR 0.10, 95% CI 0.01 to 0.2). A 2012 Cochrane review of HIT in post-operative surgical patients (20) also reported a significantly lower risk of HIT among patients who received LMWH (RR 0.24, 95% CI 0.07 to 0.82).

Recently, a retrospective review of patients with HIT at a tertiary-care centre in Toronto, Canada, reported an annual incidence of 16.5 per 10,000 admissions before introduction of an intervention to promote the use of LMWH over UFH (21). After implementation of the intervention, the incidence of HIT decreased to 6.1 per 10,000 admissions, with a 4-fold increase in the use of LMWH during this period. In particular, HIT was reduced by 62% among medical patients, 77% among patients undergoing cardiovascular surgery, and 77% among patients undergoing 'other' surgery. The decrease in HIT in the post-intervention phase was estimated to reduce the costs of HIT by $266,938 at this single centre (CDN, 2007 dollars; 83% reduction).

Limitations

The results of this review should be interpreted with caution because of the limited number of included trials. These studies involved a small number of patients with narrow inclusion criteria, which may limit the generalisability of these findings to the broad group of medical and surgical patients requiring thromboprophylaxis.

Each of the included trials primarily focused on the assessment of DVT events, and PE outcomes were secondary and/or incidental. As PE is less common than DVT, it is likely these trials were underpowered or of insufficient duration to detect PE. As a result, our meta-analysis may be underpowered to assess the association of thromboprophylaxis and this outcome.

This analysis included RCTs published between 1995 and the most recent search date of each systematic review (2008-2009); as such, any trials published outside of these bounds would not have been captured. A cursory search of the literature (April 10, 2016, PubMed) prior to the completion of this review did not locate any RCTs that met our eligibility criteria.

No RCTs of LMWH or UFH compared to the direct oral anticoagulants or vitamin K antagonists met our eligibility criteria. As such, we are unable to contextualize our results comparatively amongst all of the currently available pharmacologic options for thromboprophylaxis.

Conclusions

Based on limited evidence for medical patients, prophylaxis with LMWH reduces the risk of VTE and DVT with no increased risk of bleeding or death, compared with UFH. There may be differences in the risk of an event between stroke and no stroke populations.

In a limited analysis of non-orthopedic surgical patients, prophylaxis with LMWH may increase the risk of bleeding, but not major bleeding, compared with UFH. There are no differences in the odds of VTE, DVT, or PE. This finding was based on one RCT and should be interpreted with caution.

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Appendix 1: Risk of bias judgment

Author, year	Sequence generation	Allocation concealment	Blinding of objective outcome assessment	Incomplete outcome data addressed - efficacy	Incomplete outcome data addressed - safety
Medical patients					
Hillbom	Low	Low	Low	Unclear	Unclear
Lechler	Unclear	Unclear	Low	Low	Low
Sherman	Unclear	Low	Low	High	Low
Surgical patients					
McLeod	Low	Low	Low	High	Low
Bergqvist	Unclear	Unclear	Low	High	Low

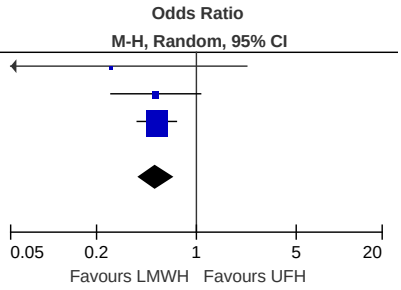
Low = low risk of bias; unclear = not sufficient detail to make judgment; high = high risk of bias

Appendix 2: Forest plots for medical patients

DVT

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Lechler 1996	1	477	4	482	1.7%	0.25 [0.03, 2.25]	1996
Hillbom 2002	14	106	24	106	15.7%	0.52 [0.25, 1.07]	2002
Sherman 2007	67	884	118	878	82.6%	0.53 [0.39, 0.72]	2007
Total (95% CI)		**1467**		**1466**	**100.0%**	**0.52 [0.39, 0.69]**	
Total events	82		146				

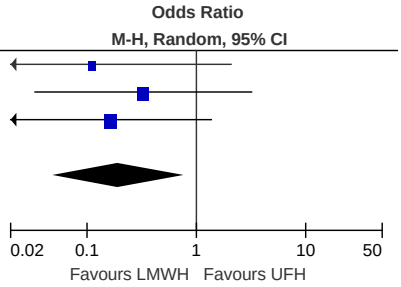
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 2 (P = 0.81); I² = 0%
Test for overall effect: Z = 4.47 (P < 0.00001)



PE

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Lechler 1996	0	477	4	482	22.0%	0.11 [0.01, 2.07]	1996
Hillbom 2002	1	106	3	106	36.2%	0.33 [0.03, 3.20]	2002
Sherman 2007	1	884	6	878	41.9%	0.16 [0.02, 1.37]	2007
Total (95% CI)		**1467**		**1466**	**100.0%**	**0.19 [0.05, 0.76]**	
Total events	2		13				

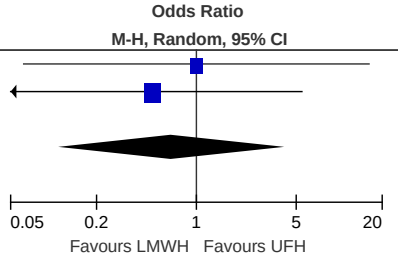
Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.35 (P = 0.02)



Fatal PE

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Hillbom 2002	1	106	1	106	42.7%	1.00 [0.06, 16.20]	2002
Sherman 2007	1	884	2	878	57.3%	0.50 [0.04, 5.48]	2007
Total (95% CI)		**990**		**984**	**100.0%**	**0.67 [0.11, 4.12]**	
Total events	2		3				

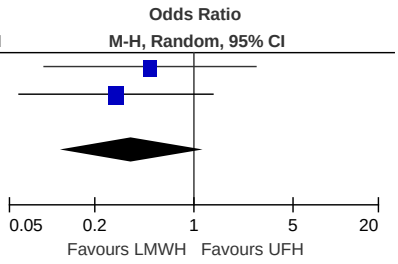
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.66)



Symptomatic VTE

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI
Hillbom 2002	2	106	4	106	45.6%	0.49 [0.09, 2.74]
Sherman 2007	2	884	7	878	54.4%	0.28 [0.06, 1.36]
Total (95% CI)		**990**		**984**	**100.0%**	**0.36 [0.11, 1.16]**
Total events	4		11			

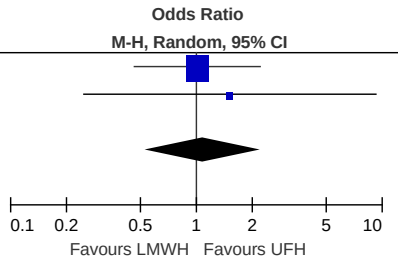
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)



Any bleeding (no. of people with a bleed)

	LMWH		UFH			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Lechler 1996	13	477	13	482	84.4%	1.01 [0.46, 2.20]	1996
Hillbom 2002	3	106	2	106	15.6%	1.51 [0.25, 9.25]	2002
Total (95% CI)		**583**		**588**	**100.0%**	**1.08 [0.53, 2.20]**	
Total events	16		15				

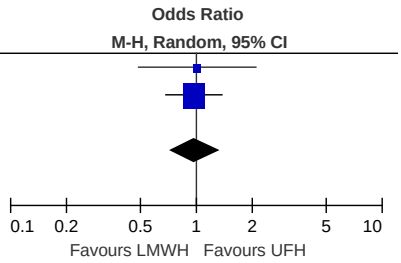
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)



Any bleeding (no. of bleeding events)

	LMWH		UFH			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Lechler 1996	15	477	15	482	18.5%	1.01 [0.49, 2.09]	1996
Sherman 2007	69	884	70	872	81.5%	0.97 [0.69, 1.37]	2007
Total (95% CI)		**1361**		**1354**	**100.0%**	**0.98 [0.71, 1.34]**	
Total events	84		85				

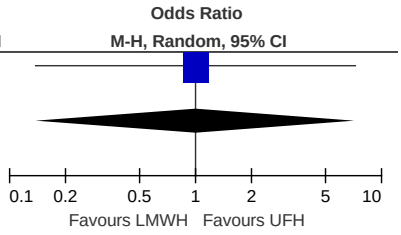
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)



Minor bleeding (no. of people with a bleed)

	LMWH		UFH			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	
Hillbom 2002	2	106	2	106	100.0%	1.00 [0.14, 7.23]	
Total (95% CI)		**106**		**106**	**100.0%**	**1.00 [0.14, 7.23]**	
Total events	2		2				

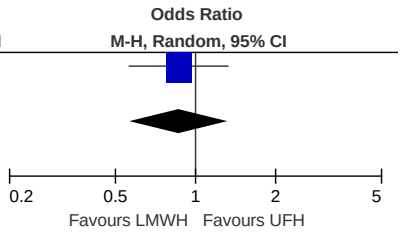
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Minor bleeding (no. of bleeding events)

	LMWH		UFH			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	
Sherman 2007	42	877	48	872	100.0%	0.86 [0.56, 1.32]	
Total (95% CI)		**877**		**872**	**100.0%**	**0.86 [0.56, 1.32]**	
Total events	42		48				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

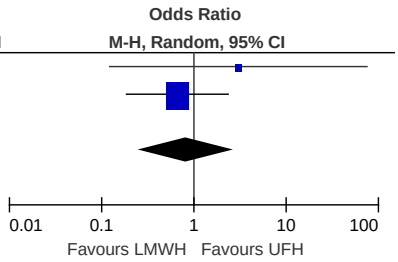


ICH

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI
Hillbom 2002	1	106	0	106	13.5%	3.03 [0.12, 75.19]
Sherman 2007	4	877	6	872	86.5%	0.66 [0.19, 2.35]
Total (95% CI)		**983**		**978**	**100.0%**	**0.81 [0.25, 2.64]**
Total events	5		6			

Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 1 (P = 0.39); I² = 0%

Test for overall effect: Z = 0.35 (P = 0.73)

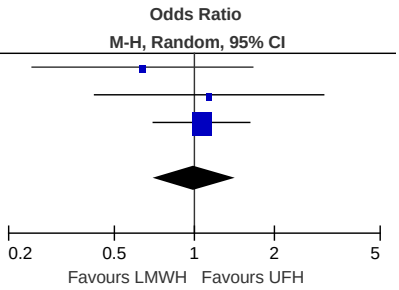


All-cause death

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Lechler 1996	7	477	11	482	14.0%	0.64 [0.25, 1.66]	1996
Hillbom 2002	9	106	8	106	13.0%	1.14 [0.42, 3.07]	2002
Sherman 2007	48	877	45	872	73.1%	1.06 [0.70, 1.62]	2007
Total (95% CI)		**1460**		**1460**	**100.0%**	**1.00 [0.70, 1.43]**	
Total events	64		64				

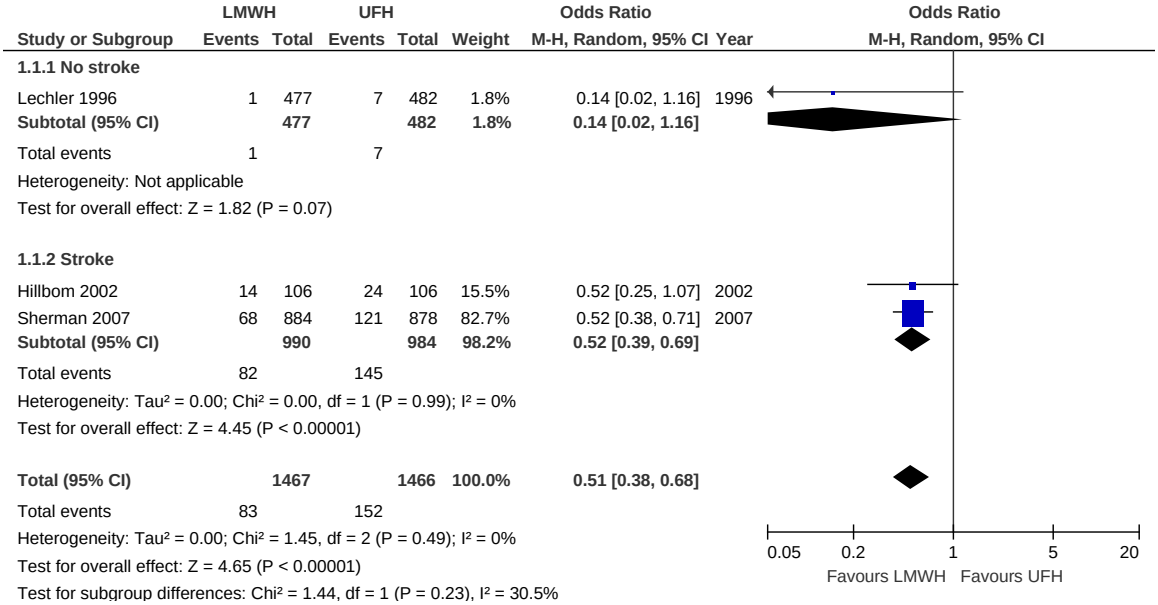
Heterogeneity: Tau² = 0.00; Chi² = 1.00, df = 2 (P = 0.61); I² = 0%

Test for overall effect: Z = 0.00 (P = 1.00)

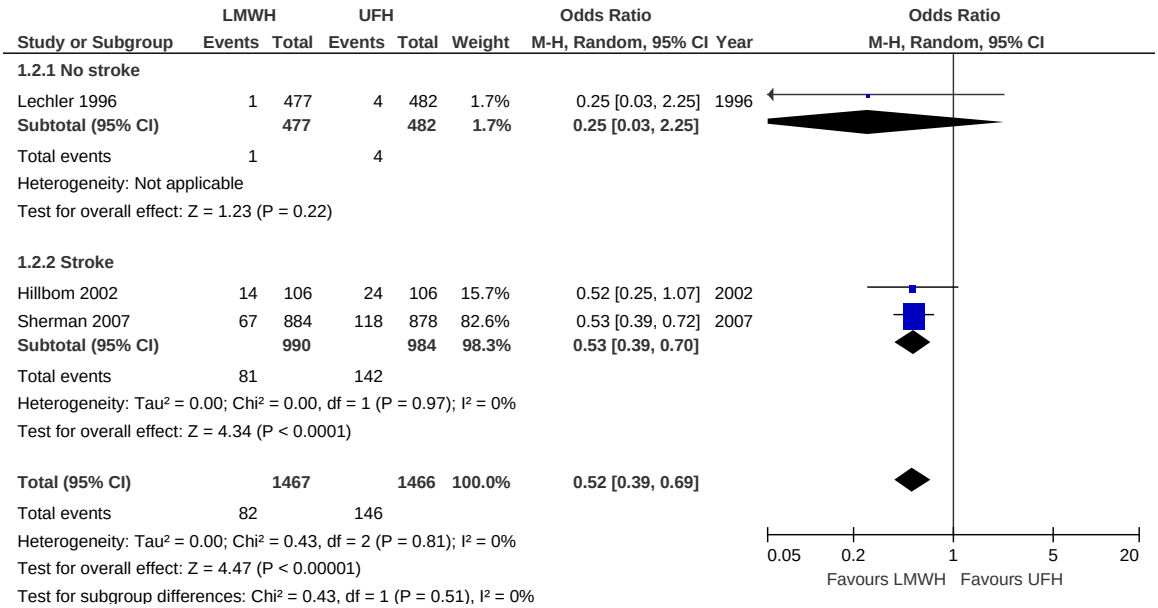


Appendix 3: Forest plots for subgroup analysis of medical patients with and without previous stroke

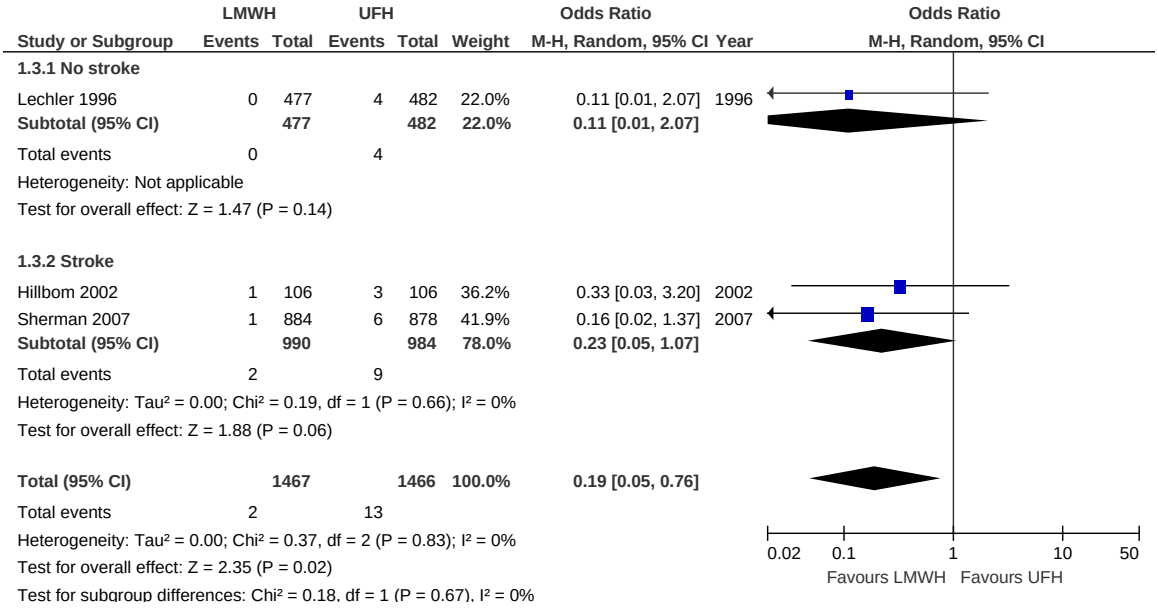
VTE



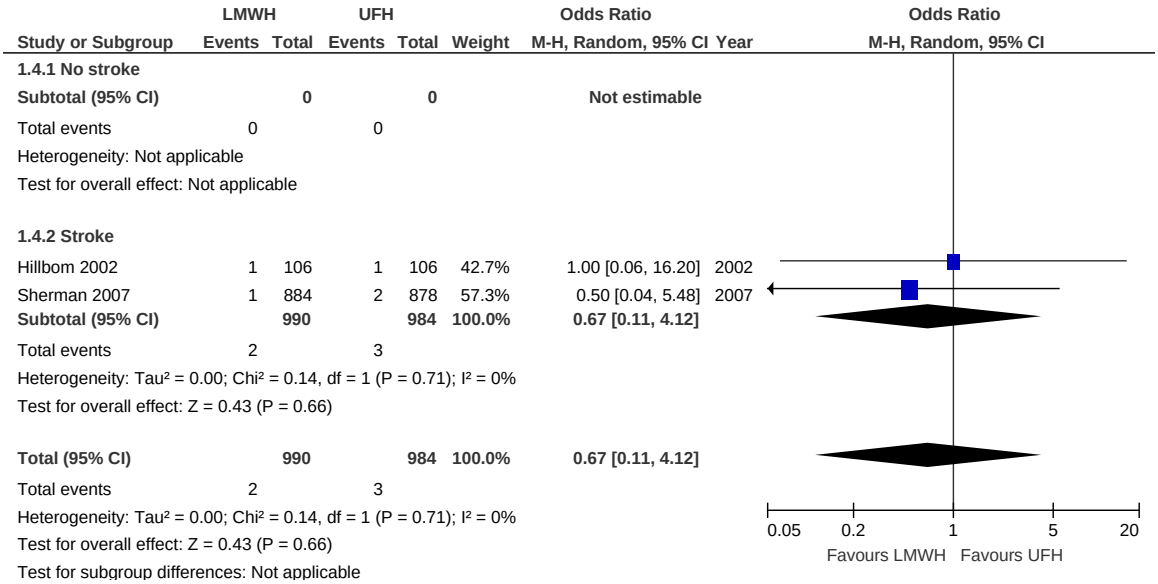
DVT



PE

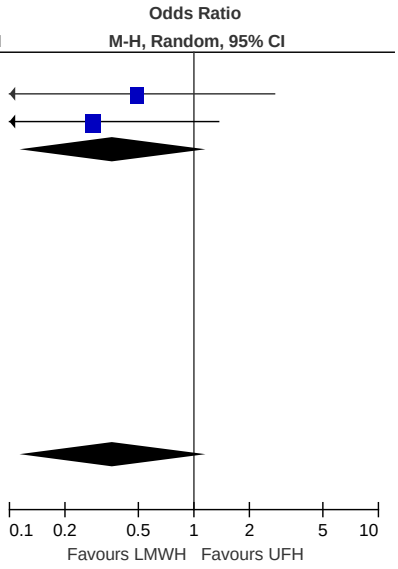

LMWH
UFH
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
1.3.1 No stroke
Lechler 1996 0 477 4 482 22.0% 0.11 [0.01, 2.07] 1996
Subtotal (95% CI) 477 482 22.0% 0.11 [0.01, 2.07]
Total events 0 4
Heterogeneity: Not applicable
Test for overall effect: Z = 1.47 (P = 0.14)
1.3.2 Stroke
Hillbom 2002 1 106 3 106 36.2% 0.33 [0.03, 3.20] 2002
Sherman 2007 1 884 6 878 41.9% 0.16 [0.02, 1.37] 2007
Subtotal (95% CI) 990 984 78.0% 0.23 [0.05, 1.07]
Total events 2 9
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.88 (P = 0.06)
Total (95% CI) 1467 1466 100.0% 0.19 [0.05, 0.76]
Total events 2 13
Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.35 (P = 0.02)
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%
0.02
0.1
1
10
50
Favours LMWH
Favours UFH

Fatal PE


LMWH
UFH
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
1.4.1 No stroke
Subtotal (95% CI) 0 0 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
1.4.2 Stroke
Hillbom 2002 1 106 1 106 42.7% 1.00 [0.06, 16.20] 2002
Sherman 2007 1 884 2 878 57.3% 0.50 [0.04, 5.48] 2007
Subtotal (95% CI) 990 984 100.0% 0.67 [0.11, 4.12]
Total events 2 3
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.66)
Total (95% CI) 990 984 100.0% 0.67 [0.11, 4.12]
Total events 2 3
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.66)
Test for subgroup differences: Not applicable
0.05
0.2
1
5
20
Favours LMWH
Favours UFH

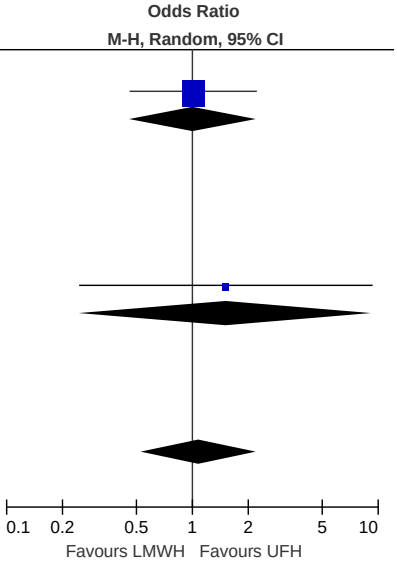
Symptomatic VTE

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI
1.5.1 Stroke						
Hillbom 2002	2	106	4	106	45.6%	0.49 [0.09, 2.74]
Sherman 2007	2	884	7	878	54.4%	0.28 [0.06, 1.36]
Subtotal (95% CI)		**990**		**984**	**100.0%**	**0.36 [0.11, 1.16]**
Total events	4		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 1.71 (P = 0.09)						
1.5.2 No stroke						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**990**		**984**	**100.0%**	**0.36 [0.11, 1.16]**
Total events	4		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 1.71 (P = 0.09)						
Test for subgroup differences: Not applicable						



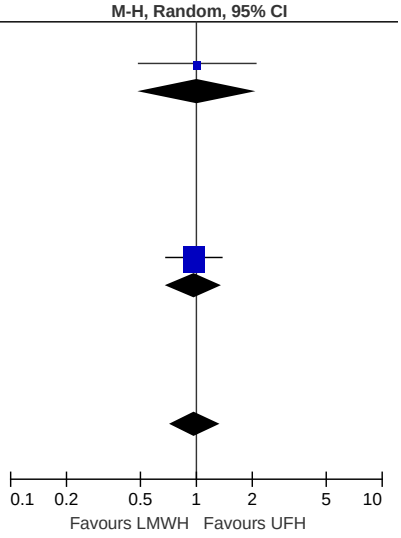
Any bleeding – no. of people with an event

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.7.1 No stroke							
Lechler 1996	13	477	13	482	84.4%	1.01 [0.46, 2.20]	1996
Subtotal (95% CI)		**477**		**482**	**84.4%**	**1.01 [0.46, 2.20]**	
Total events	13		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.03 (P = 0.98)							
1.7.2 Stroke							
Hillbom 2002	3	106	2	106	15.6%	1.51 [0.25, 9.25]	2002
Subtotal (95% CI)		**106**		**106**	**15.6%**	**1.51 [0.25, 9.25]**	
Total events	3		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.45 (P = 0.65)							
Total (95% CI)		**583**		**588**	**100.0%**	**1.08 [0.53, 2.20]**	
Total events	16		15				
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%							
Test for overall effect: Z = 0.20 (P = 0.84)							
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%							



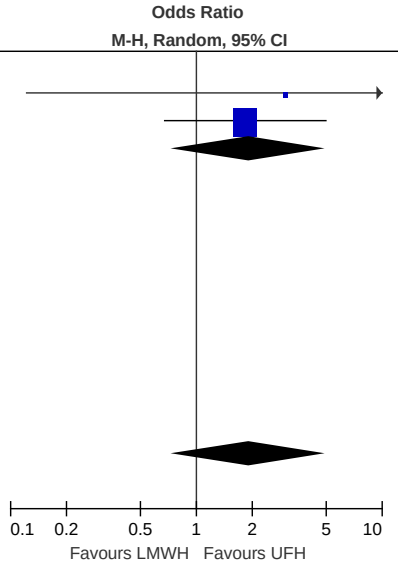
Any bleeding – no. of events

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.8.1 No stroke							
Lechler 1996	15	477	15	482	18.5%	1.01 [0.49, 2.09]	1996
Subtotal (95% CI)		**477**		**482**	**18.5%**	**1.01 [0.49, 2.09]**	
Total events	15		15				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.03 (P = 0.98)							
1.8.2 Stroke							
Sherman 2007	69	884	70	872	81.5%	0.97 [0.69, 1.37]	2007
Subtotal (95% CI)		**884**		**872**	**81.5%**	**0.97 [0.69, 1.37]**	
Total events	69		70				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.17 (P = 0.86)							
Total (95% CI)		**1361**		**1354**	**100.0%**	**0.98 [0.71, 1.34]**	
Total events	84		85				
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%							
Test for overall effect: Z = 0.14 (P = 0.89)							
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%							



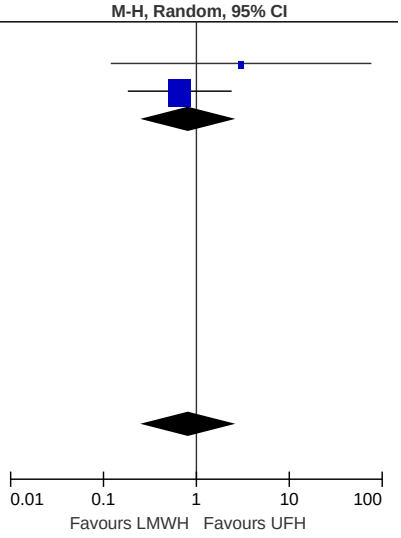
Minor bleeding

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.9.1 Stroke							
Hillbom 2002	1	106	0	106	8.8%	3.03 [0.12, 75.19]	2002
Sherman 2007	11	877	6	872	91.2%	1.83 [0.68, 4.98]	2007
Subtotal (95% CI)		**983**		**978**	**100.0%**	**1.92 [0.74, 4.98]**	
Total events	12		6				
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%							
Test for overall effect: Z = 1.34 (P = 0.18)							
1.9.2 No stroke							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		**983**		**978**	**100.0%**	**1.92 [0.74, 4.98]**	
Total events	12		6				
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%							
Test for overall effect: Z = 1.34 (P = 0.18)							
Test for subgroup differences: Not applicable							



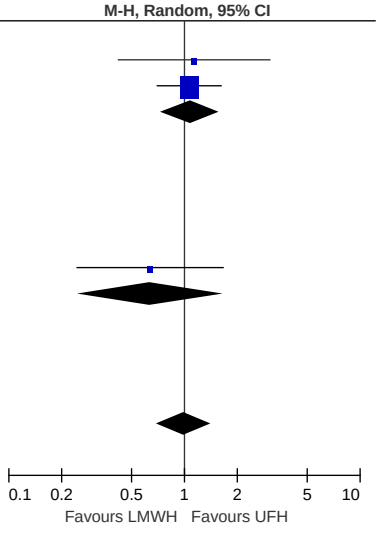
Intracranial hemorrhage

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.13.1 Stroke							
Hillbom 2002	1	106	0	106	13.5%	3.03 [0.12, 75.19]	2002
Sherman 2007	4	877	6	872	86.5%	0.66 [0.19, 2.35]	2007
Subtotal (95% CI)		**983**		**978**	**100.0%**	**0.81 [0.25, 2.64]**	
Total events	5		6				
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 1 (P = 0.39); I² = 0%							
Test for overall effect: Z = 0.35 (P = 0.73)							
1.13.2 No stroke							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		**983**		**978**	**100.0%**	**0.81 [0.25, 2.64]**	
Total events	5		6				
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 1 (P = 0.39); I² = 0%							
Test for overall effect: Z = 0.35 (P = 0.73)							
Test for subgroup differences: Not applicable							



All-cause death

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.12.1 Stroke							
Hillbom 2002	9	106	8	106	13.0%	1.14 [0.42, 3.07]	2002
Sherman 2007	48	877	45	872	73.1%	1.06 [0.70, 1.62]	2007
Subtotal (95% CI)		**983**		**978**	**86.0%**	**1.07 [0.73, 1.58]**	
Total events	57		53				
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.90); I² = 0%							
Test for overall effect: Z = 0.37 (P = 0.71)							
1.12.2 No stroke							
Lechler 1996	7	477	11	482	14.0%	0.64 [0.25, 1.66]	1996
Subtotal (95% CI)		**477**		**482**	**14.0%**	**0.64 [0.25, 1.66]**	
Total events	7		11				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.92 (P = 0.36)							
Total (95% CI)		**1460**		**1460**	**100.0%**	**1.00 [0.70, 1.43]**	
Total events	64		64				
Heterogeneity: Tau² = 0.00; Chi² = 1.00, df = 2 (P = 0.61); I² = 0%							
Test for overall effect: Z = 0.00 (P = 1.00)							
Test for subgroup differences: Chi² = 0.98, df = 1 (P = 0.32), I² = 0%							

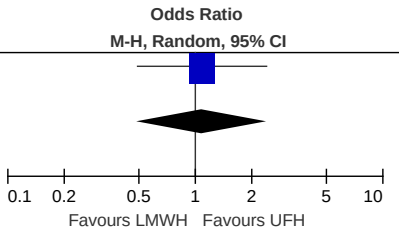


Appendix 4: Forest plots for surgical patients

DVT

	LMWH		UFH			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
McLeod 2001	13	674	12	675	100.0%	1.09 [0.49, 2.40]	2001
Total (95% CI)		**674**		**675**	**100.0%**	**1.09 [0.49, 2.40]**	
Total events	13		12				

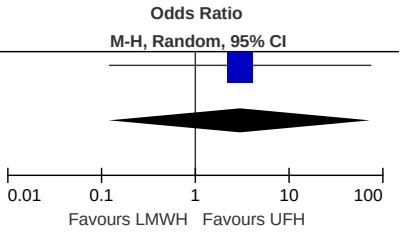
Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.84)



PE

	LMWH		UFH			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
McLeod 2001	1	674	0	675	100.0%	3.01 [0.12, 73.99]	2001
Total (95% CI)		**674**		**675**	**100.0%**	**3.01 [0.12, 73.99]**	
Total events	1		0				

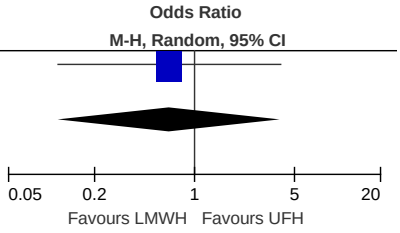
Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)



Symptomatic VTE

	LMWH		UFH			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
McLeod 2001	2	674	3	675	100.0%	0.67 [0.11, 4.00]
Total (95% CI)		**674**		**675**	**100.0%**	**0.67 [0.11, 4.00]**
Total events	2		3			

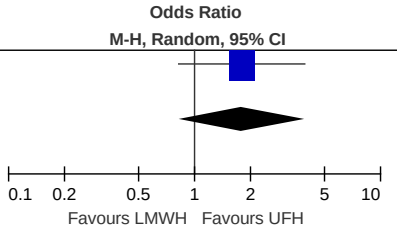
Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)



Major bleeding

	LMWH		UFH			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
McLeod 2001	18	653	10	643	100.0%	1.79 [0.82, 3.92]
Total (95% CI)		**653**		**643**	**100.0%**	**1.79 [0.82, 3.92]**
Total events	18		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.47 (P = 0.14)

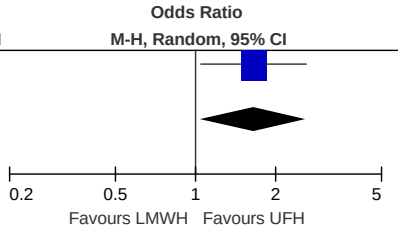


Minor bleeding

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI
McLeod 2001	52	653	32	643	100.0%	1.65 [1.05, 2.60]
Total (95% CI)		**653**		**643**	**100.0%**	**1.65 [1.05, 2.60]**
Total events	52		32			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.16 (P = 0.03)

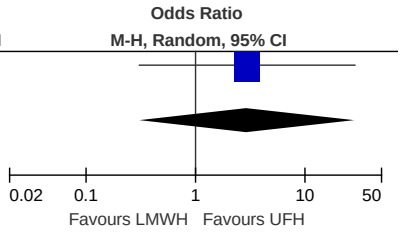


All-cause death

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI
McLeod 2001	3	653	1	643	100.0%	2.96 [0.31, 28.56]
Total (95% CI)		**653**		**643**	**100.0%**	**2.96 [0.31, 28.56]**
Total events	3		1			

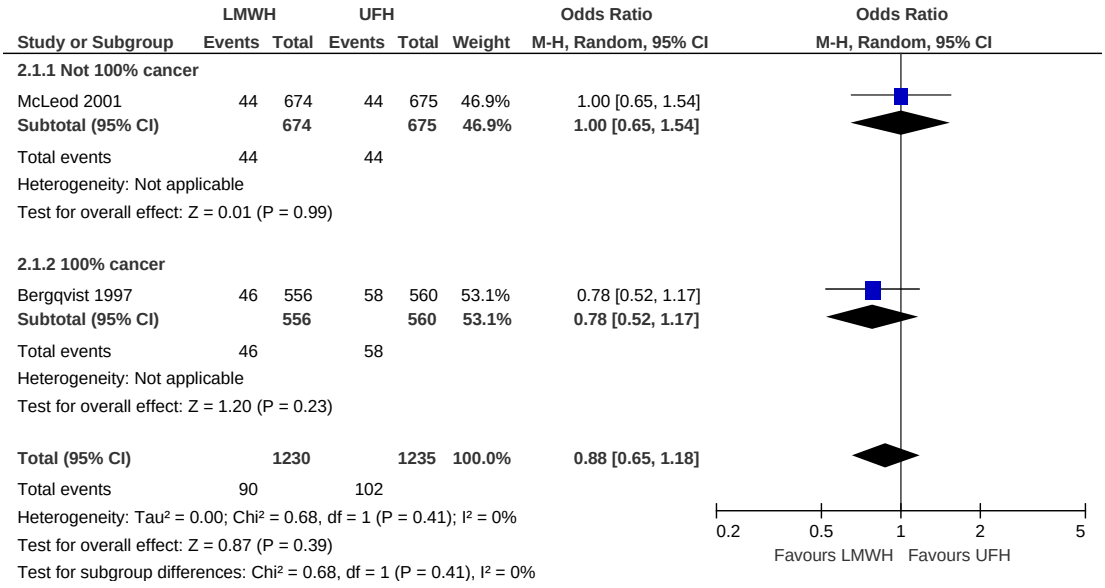
Heterogeneity: Not applicable

Test for overall effect: Z = 0.94 (P = 0.35)

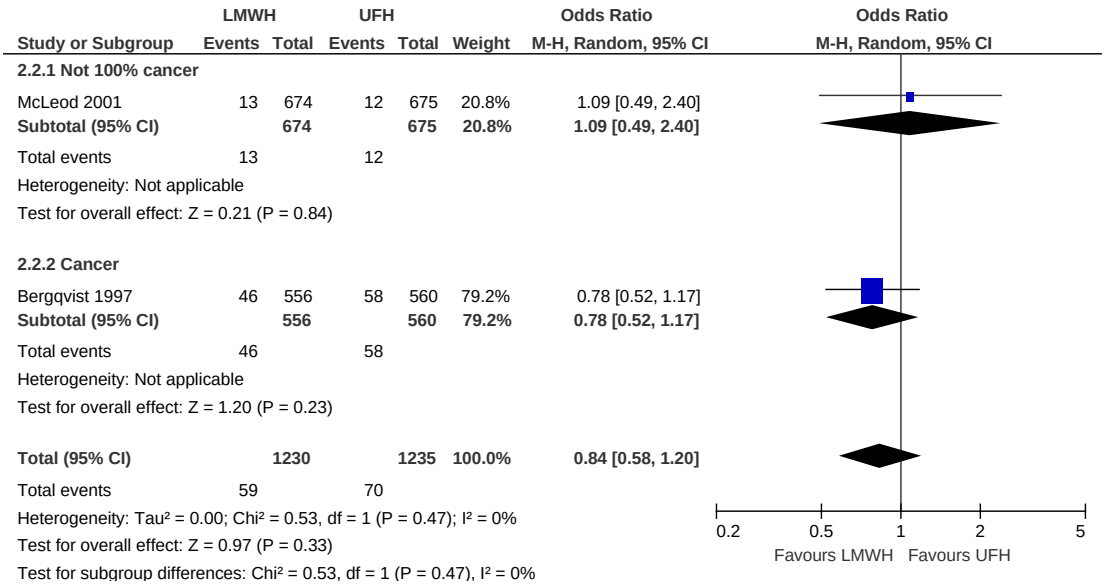


Appendix 5: Forest plot for additional meta-analyses: Surgical patients (100% cancer versus <100% cancer)

VTE

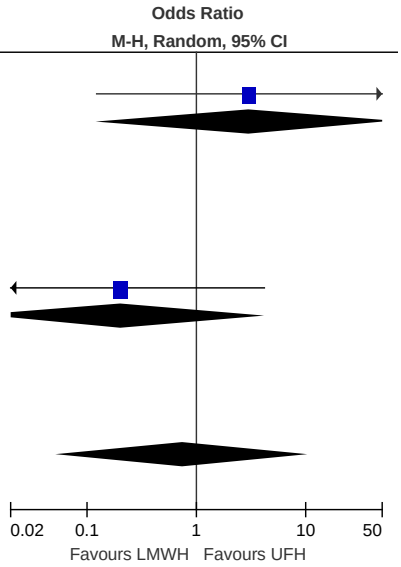


DVT



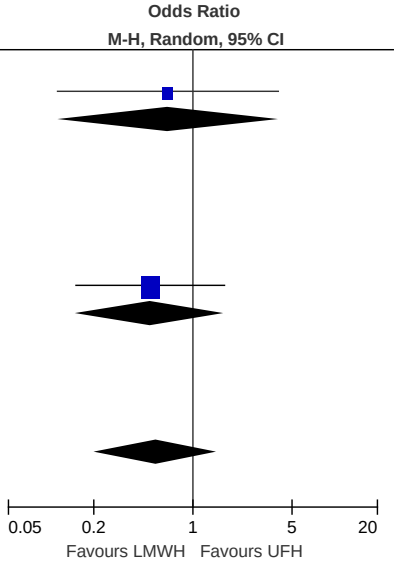
PE

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
2.3.1 Not 100% cancer							
McLeod 2001	1	674	0	675	48.2%	3.01 [0.12, 73.99]	2001
Subtotal (95% CI)		**674**		**675**	**48.2%**	**3.01 [0.12, 73.99]**	
Total events	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.67 (P = 0.50)							
2.3.2 Cancer							
Bergqvist 1997	0	556	2	560	51.8%	0.20 [0.01, 4.19]	1997
Subtotal (95% CI)		**556**		**560**	**51.8%**	**0.20 [0.01, 4.19]**	
Total events	0		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.04 (P = 0.30)							
Total (95% CI)		**1230**		**1235**	**100.0%**	**0.74 [0.05, 10.54]**	
Total events	1		2				
Heterogeneity: Tau² = 1.14; Chi² = 1.45, df = 1 (P = 0.23); I² = 31%							
Test for overall effect: Z = 0.22 (P = 0.82)							
Test for subgroup differences: Chi² = 1.44, df = 1 (P = 0.23), I² = 30.8%							



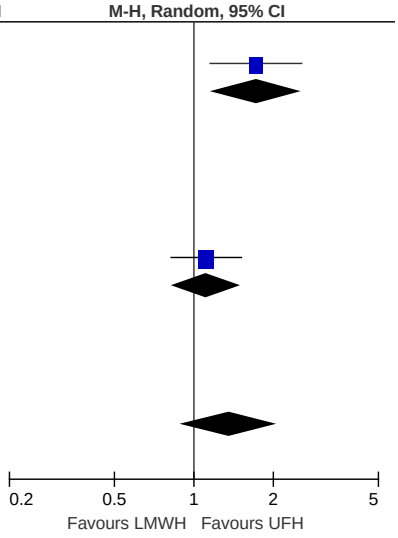
Symptomatic VTE

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI
2.8.1 Not 100% cancer						
McLeod 2001	2	674	3	675	31.2%	0.67 [0.11, 4.00]
Subtotal (95% CI)		**674**		**675**	**31.2%**	**0.67 [0.11, 4.00]**
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
2.8.2 Cancer						
Bergqvist 1997	4	556	8	560	68.8%	0.50 [0.15, 1.67]
Subtotal (95% CI)		**556**		**560**	**68.8%**	**0.50 [0.15, 1.67]**
Total events	4		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						
Total (95% CI)		**1230**		**1235**	**100.0%**	**0.55 [0.20, 1.49]**
Total events	6		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%						



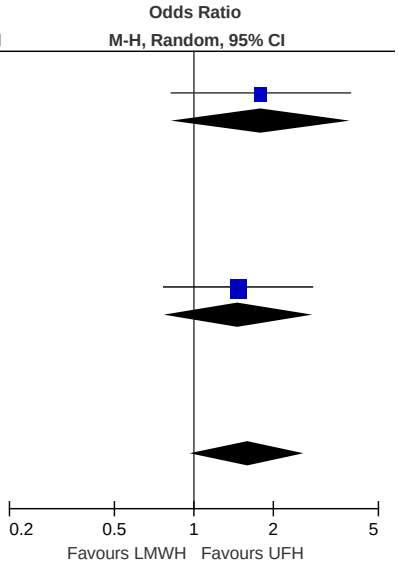
Any bleeding

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI
2.4.1 Not 100% cancer						
McLeod 2001	70	653	42	643	45.4%	1.72 [1.15, 2.56]
Subtotal (95% CI)		**653**		**643**	**45.4%**	**1.72 [1.15, 2.56]**
Total events	70		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.66 (P = 0.008)						
2.4.2 Cancer						
Bergqvist 1997	104	555	96	560	54.6%	1.11 [0.82, 1.51]
Subtotal (95% CI)		**555**		**560**	**54.6%**	**1.11 [0.82, 1.51]**
Total events	104		96			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**1208**		**1203**	**100.0%**	**1.36 [0.89, 2.07]**
Total events	174		138			
Heterogeneity: Tau² = 0.06; Chi² = 2.84, df = 1 (P = 0.09); I² = 65%						
Test for overall effect: Z = 1.42 (P = 0.16)						
Test for subgroup differences: Chi² = 2.84, df = 1 (P = 0.09), I² = 64.8%						



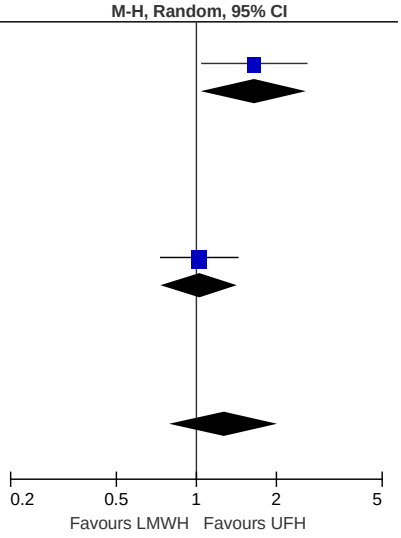
Major bleeding

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI
2.5.1 Not 100% cancer						
McLeod 2001	18	653	10	643	40.9%	1.79 [0.82, 3.92]
Subtotal (95% CI)		**653**		**643**	**40.9%**	**1.79 [0.82, 3.92]**
Total events	18		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						
2.5.2 Cancer						
Bergqvist 1997	23	555	16	560	59.1%	1.47 [0.77, 2.81]
Subtotal (95% CI)		**555**		**560**	**59.1%**	**1.47 [0.77, 2.81]**
Total events	23		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.16 (P = 0.24)						
Total (95% CI)		**1208**		**1203**	**100.0%**	**1.59 [0.97, 2.63]**
Total events	41		26			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 1.83 (P = 0.07)						
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%						



Minor bleeding

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
2.6.1 Not 100% cancer							
McLeod 2001	52	653	32	643	44.6%	1.65 [1.05, 2.60]	2001
Subtotal (95% CI)		**653**		**643**	**44.6%**	**1.65 [1.05, 2.60]**	
Total events	52		32				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.16 (P = 0.03)							
2.6.2 Cancer							
Bergqvist 1997	81	555	80	560	55.4%	1.03 [0.73, 1.43]	1997
Subtotal (95% CI)		**555**		**560**	**55.4%**	**1.03 [0.73, 1.43]**	
Total events	81		80				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.15 (P = 0.88)							
Total (95% CI)		**1208**		**1203**	**100.0%**	**1.27 [0.80, 2.02]**	
Total events	133		112				
Heterogeneity: Tau² = 0.07; Chi² = 2.75, df = 1 (P = 0.10); I² = 64%							
Test for overall effect: Z = 1.00 (P = 0.32)							
Test for subgroup differences: Chi² = 2.75, df = 1 (P = 0.10), I² = 63.6%							



All-cause death

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Odds Ratio M-H, Random, 95% CI
2.7.1 Not 100% cancer						
McLeod 2001	3	653	1	643	32.7%	2.96 [0.31, 28.56]
Subtotal (95% CI)		**653**		**643**	**32.7%**	**2.96 [0.31, 28.56]**
Total events	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.94 (P = 0.35)						
2.7.2 Cancer						
Bergqvist 1997	4	555	7	560	67.3%	0.57 [0.17, 1.97]
Subtotal (95% CI)		**555**		**560**	**67.3%**	**0.57 [0.17, 1.97]**
Total events	4		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
Total (95% CI)		**1208**		**1203**	**100.0%**	**0.98 [0.22, 4.45]**
Total events	7		8			
Heterogeneity: Tau² = 0.49; Chi² = 1.56, df = 1 (P = 0.21); I² = 36%						
Test for overall effect: Z = 0.03 (P = 0.98)						
Test for subgroup differences: Chi² = 1.56, df = 1 (P = 0.21), I² = 35.7%