

LOW MOLECULAR WEIGHT HEPARINS (LMWH) FOR PREVENTION OF VENOUS THROMBOEMBOLISM (VTE) IN TOTAL KNEE ARTHROPLASTY (TKA) PATIENTS

An Evidence Review from the UPHS Center for Evidence-based Practice

September 2009

Matthew D. Mitchell, PhD, Kendal Williams, MD, MPH, Craig A. Umscheid, MD, MSCE

EVIDENCE SUMMARY

1. None of the three expert society guidelines published since 2005 that address anticoagulation in TKA patients express a preference for LMWH over other potential agents or one LMWH product over another.
2. There are no head to head comparison studies of LMWHs that are of sufficient quality to conclude that one is superior to the other for either VTE prevention outcomes or bleeding. A single low quality pre-post study comparing dalteparin to enoxaparin in both TKA and THA patients suggested no difference in either outcome, but this is not sufficient evidence to draw any certain conclusions.
3. Based on evidence of high quality, enoxaparin is more effective than placebo in preventing DVT events and further research is unlikely to change this estimate.
4. Based on evidence of moderate quality, dalteparin is more effective than no prophylaxis in preventing DVT events, but further research may change this estimate.
5. Based on evidence of moderate quality, we cannot conclude that enoxaparin leads to increased bleeding events in TKA patients compared to placebo, but further research may change this estimate.
6. Based on evidence of low quality, we similarly cannot conclude that dalteparin leads to increased bleeding events in TKA patients compared to no prophylaxis, but further research is likely to change the magnitude or direction of this estimate.
7. Based on evidence of moderate quality, fondaparinux is more effective than placebo in preventing venous thromboembolism, but further research may change this estimate. There is no evidence on the effect of fondaparinux on DVT or pulmonary embolism in particular.
8. Based on evidence of moderate quality, fondaparinux significantly increases the risk of major bleeding and reduces the risk of venous thromboembolism and deep vein thrombosis when compared to enoxaparin.

TABLE OF CONTENTS

Background.....	3
Methods	5
Protocol for Systematic Review	5
Search Strategy for Guidelines.....	6
Search Strategy for Systematic Reviews.....	7
Search Strategy for Primary Studies	8
Meta-analysis.....	10
Assessment of evidence quality.....	10
Evidence Review	11
Guidelines.....	11
Systematic Reviews.....	11
Primary Studies.....	12
Direct comparisons of different low-molecular weight heparins.....	12
Studies comparing LMWH to placebo or other controls	13
Bleeding and other adverse events	13
Venous thromboembolism	15
Meta-analysis.....	16
Summary of Primary RCT Results.....	18
Strength of evidence	19
Appendix A—Modified Jadad Scale For RCT Quality	21
Appendix B—GRADE Criteria for Rating a Body of Evidence	22
References.....	23

BACKGROUND

This report reviews evidence on bleeding, venous thromboembolism (VTE), and other outcomes when total knee arthroplasty patients are given low molecular weight heparins (LMWH) and related drugs for prophylaxis of VTE. This is a large class of drugs, some of which are FDA-approved for US marketing (Table 1), others of which are not approved (Table 2), and still others have been withdrawn from the US market (Table 2). They compete with other anticoagulants, particularly warfarin and unfractionated heparin (UFH). LMWH and the related drugs are more specific in their effects than other anticoagulants. They act primarily by inhibiting factor Xa (activated thrombokinase), and to a lesser extent by inhibiting factor IIa (thrombin). The various LMWH products differ in how they are prepared (they all start with unfractionated heparin) and have different balances of inhibitory action, so evidence for the effectiveness and safety of one is not necessarily evidence that is generalizable to all.

This report will focus on the approved drugs (Table 1), and wherever possible will limit the evidence under consideration to studies involving only knee arthroplasty patients. A large body of evidence on these drugs has been obtained from studies of hip arthroplasty patients, but since the balance of VTE and bleeding risks is different for these patients than for knee arthroplasty patients, one should use caution when applying the results from one group to patients in the other group. Since these drugs inhibit blood coagulation, they reduce the risk of thromboembolisms (which can become life-threatening if they migrate to the lung: pulmonary embolism) but they increase the risk of complications related to excessive bleeding. This report will not attempt to find a clinically-optimum balance point between these risks, but will instead discuss the impact of these drugs on each of the risks so the drug that maximizes overall patient safety can be selected.

TABLE 1. LOW MOLECULAR WEIGHT HEPARINS AND RELATED DRUGS ANALYZED IN THIS REPORT

Drug	Alternate names	Trade name	Manufacturer	FDA approved?	Category	Major knee-specific trials
Dalteparin	Tedelparin	Fragmin, Fragmine	Eisai/Pfizer	Yes	LMWH	
Enoxaparin		Lovenox, Clexane	Sanofi Aventis	Yes	LMWH	Enoxaparin Clinical Trials Group (1, 2)
Tinzoparin	Logiparin	Innohep	Celgene	Yes	LMWH	
Fondaparinux		Arixtra	GlaxoSmithKline	Yes	Factor Xa inhibitor	PENTAMAKS (3)

TABLE 2. DRUGS NOT ANALYZED IN THIS REPORT

Drug	Alternate names	Trade name	Manufacturer	FDA approved?	Category	Major knee-specific trials
Ardeparin		Normiflo	Pharmacia	Withdrawn 2000	LMWH	Ardeparin Arthroplasty Study Group (4-6)
Bemiparin		Zibor, Hibor, Ivor	Rovi	No	LMWH	Bemiparin Study Group (7)
Certoparin	Sandoparin	Embolex	Novartis	No	LMWH	
Lomoparin		Orgaran	Schering-Plough	No	LMWH	
Nadroparin		Fraxiparin, Fraxiparine	GlaxoSmithKline	No	LMWH	
Parnaparin	Lowhepa	Fluxum	Alfa Wasserman	No	LMWH	
Reviparin		Clivarine	Abbott	No	LMWH	ECHOS (8)
Apixaban			Bristol-Myers Squibb	Postponed	Factor Xa inhibitor	APROPOS (9) ADVANCE-1 (10)
Betrixaban			Portola	No (phase II)	Factor Xa inhibitor	EXPERT (11), EXPLORE (in progress)
Idraparinux			Sanofi Aventis	No	Factor Xa inhibitor	
Rivaroxaban	BAY 59-7939	Xarelto	Ortho-McNeil	Pending	Factor Xa inhibitor	RECORD 3 (12), RECORD 4 (13)
Danaparin	Danaparoid	Orgaran	Schering-Plough	No	Factor Xa inhibitor	
Ximelagatran	Melagatran	Exanta	AstraZeneca	Withdrawn 2006	Direct thrombin inhibitor	EXULT(14), EXPRESS (15), METHRO (16-18)
Dabigatran		Pradaxa	Boehringer-Ingelheim	No (phase III)	Direct thrombin inhibitor	RE-MODEL (19), RE-MOBILIZE (20), BISTRO II (21)

Red text—drugs withdrawn by their manufacturer for safety or other reasons

METHODS

CENTER FOR EVIDENCE-BASED PRACTICE

PROTOCOL FOR SYSTEMATIC REVIEW

SPECIFIC AIM:

Determine the differences in efficacy and side effects between specific low molecular weight heparin products in patients who are having total knee arthroplasty surgery

METHODS:

Study designs: Controlled trials

Inclusion and exclusion criteria:

Participants: Patients having total knee arthroplasty (TKA): trials including other patients included if no TKA-only trials available

Interventions: Low molecular weight heparins (LMWH), including enoxaparin and dalteparin, and the Factor Xa inhibitor fondaparinux

Comparisons: Placebo, other LMWHs, fondaparinux, warfarin

Outcomes: Venous thromboembolism (including pulmonary embolism, deep vein thrombosis), bleeding, other side effects

Other:

Data collection

Databases: MEDLINE, EMBASE

Study quality: RCTs assessed using modified Jadad scale (Appendix A)

Data extraction: By CEP analyst

Data extraction (calculation of relative risks and confidence intervals, meta-analyses, exploration of heterogeneity):

Using techniques recommended by Cochrane Peripheral Vascular Diseases Group, including random effects meta-analysis of reported risk ratios where there is sufficient data.(22) Quality of evidence rating based on GRADE criteria (Appendix B)

SEARCH STRATEGY FOR GUIDELINES

Searches were completed in June 2008. Both NGC searches found the same three included guidelines, and two of them were also found in the Medline search.

1. NATIONAL GUIDELINE CLEARINGHOUSE

Keyword	Results	Retrieved	Included
Thromboembolism	123	7	3
Knee	81	5	3

2. MEDLINE

Search	Syntax	Results	Retrieved	Included
1	exp thromboembolism/	34,449	–	–
2	exp venous thromboembolism/	809	–	–
3	exp thrombophlebitis/	20,298	–	–
4	exp thrombosis/	117,627	–	–
5	exp venous thrombosis/	36,993	–	–
6	exp postthrombotic syndrome/	36	–	–
7	exp pulmonary embolism/	26,177	–	–
8	(thromboemboli\$ or microthrombus or thrombus or thrombos\$ or thrombilic or thrombotic).ti,ab.	121,065	–	–
9	((pulmonary or lung) adj5 emb\$).ti,ab.	24,632	–	–
10	dvt.ti,ab.	4,320	–	–
11	(thromboprophylaxis or (embolism adj4 prevention)).ti,ab.	1,956	–	–
12	((post-thrombo\$ or postthrombo\$) adj3 syndrome).ti,ab.	838	–	–
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	192,758	–	–
14	exp Arthroplasty, Replacement, Knee/ or exp Arthroplasty/	22,864	–	–
15	(knee adj5 (prosth\$ or repl\$)).ti,ab.	6,203	–	–
16	14 or 15	26,297	–	–
17	exp guideline/ or exp Practice Guideline/ or guideline.mp	39,651	–	–
18	13 and 16 and 17	18	14	2

SEARCH STRATEGY FOR SYSTEMATIC REVIEWS

Searches were completed in June 2008. The Cochrane Library includes two protocols for reviews involving LMWH for knee arthroplasty patients, but none of these reviews are completed, and no estimated completion dates are given. The three systematic reviews identified from the DARE database were all published between 2000 and 2002 and lack all of the relevant evidence that was subsequently published, so they were excluded from further consideration. A technology assessment report on dabigatran in patients undergoing hip or knee surgery is in progress at the NIHR Coordinating Centre for Health Technology Assessment (23). Results are not expected until late 2009.

1. MEDLINE

Search	Syntax	Results	Retrieved	Included
1-13	See Medline search for guidelines	193,476	–	–
14	nadropar\$ OR fraxipar\$ OR enoxapar\$ OR clexane OR lovenox OR daltepar\$ OR fragmin or fragmine OR ardepar\$ OR normiflo OR tinzapar\$ OR logipar\$ OR innohep OR certopar\$ OR sandopar\$ OR revipar\$ OR clivarin OR tedelpar\$ OR bemipar\$ OR hibor OR danapar\$ OR lomopar\$ OR orgaran OR parnapar\$ OR fluxum OR lowhepa.mp	4,374	–	–
15	exp "Review"/	1,457,300	–	–
16	exp Evidence-Based Medicine/ OR systematic review.mp.	47,687	–	–
17	exp Meta-Analysis/ OR meta-analysis.mp.	34,861	–	–
18	15 OR 16 OR 17	1,500,862	–	–
19	13 AND 14 AND 18	523		
20	limit to English language, published 2004-present	174	29	2

2. COCHRANE LIBRARY

Keyword	Reviews	Retrieved	Included
Thromboembolism	41	2	0

3. DARE (DATABASE OF ABSTRACTS OF REVIEWS OF EFFECTS)

Keyword	Reviews	Retrieved
Thromboembolism	101	3

4. HTA (HEALTH TECHNOLOGY ASSESSMENT)

Keyword	Technology assessments	Retrieved	Included
Thromboembolism	24	6	0

SEARCH STRATEGY FOR PRIMARY STUDIES

The initial searches sought controlled trials of low-molecular weight heparins and related drugs in patients undergoing total knee arthroplasty. When no such trials were found for some of the drugs of interest, an additional search was carried out, seeking trials comparing different low-molecular weight heparins in orthopedic populations.

1. MEDLINE

Search	Syntax	Results	Retrieved	Included
1-13	See Medline search for guidelines	193,825	–	–
14	exp Arthroplasty, Replacement, Knee/ or exp Arthroplasty/	23,055	–	–
15	(knee adj5 (prosth\$ or repl\$)).ti,ab.	6,233	–	–
16	14 or 15	26,499	–	–
17	13 and 16	1,574		
18	nadropar\$ OR fraxipar\$ OR enoxapar\$ OR clexane OR lovenox OR daltepar\$ OR fragmin or fragmine OR ardepar\$ OR normiflo OR tinzapar\$ OR logipar\$ OR innohep OR certopar\$ OR sandopar\$ OR revipar\$ OR clivarin OR tedelpar\$ OR bemipar\$ OR hibor OR danapar\$ OR lomopar\$ OR orgaran OR parnapar\$ OR fluxum OR lowhepa.mp	4,388	–	–
19	exp Heparin, Low-Molecular-Weight/	7,489	–	–
20	18 or 19	8,340	–	–
21	17 and 20	411	–	–
22	(randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.	633,545	–	–
23	21 and 22	164	34	6

Search	Syntax	Results	Retrieved	Included
1	exp Arthroplasty, Replacement, Knee/ or exp Arthroplasty/	23,104	–	–
2	(knee adj5 (prosth\$ or repl\$)).ti,ab.	6,248	–	–
3	1 or 2	26,553	–	–
4	fondaparinux.mp.	715	–	–
5	(danapar\$ or orgaran).mp.	347	–	–
6	dalteparin.mp. or exp Dalteparin/ or fragmi\$.mp. or tedelparin.mp.	1,011	–	–
7	enoxaparin.mp. or exp Enoxaparin/ or lovenox.mp. or clexane.mp.	2,426	–	–
8	(tinzipar\$ or logipar\$ or innohep).mp.	53	–	–
9	3 and 4 and 5	1	–	–
10	3 and 4 and 6	4	–	–
11	3 and 4 and 7	44	–	–
12	3 and 4 and 8	0	–	–
13	3 and 5 and 6	0	–	–
14	3 and 5 and 7	1	–	–
15	3 and 5 and 8	0	–	–
16	3 and 6 and 7	23	–	–
17	3 and 6 and 8	1	–	–
18	3 and 7 and 8	1	–	–
19	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	65	1	1

2. EMBASE

Search	Syntax	Results	Retrieved	Included
1	'low molecular weight heparin'/exp/mj	8,246	–	–
2	'rivaroxaban'/exp/mj	93	–	–
3	'melagatran'/exp/mj	130	–	–
4	'dabigatran'/exp/mj	24	–	–
5	1 or 2 or 3 or 4	8,449	–	–
6	'total knee replacement'/exp	7,909	–	–
7	'knee arthroplasty'/exp	4,409	–	–
8	6 or 7	11,745	–	–
9	'venous thromboembolism'/exp	22,835	–	–
10	5 and 8 and 10	139	–	–
11	Remove duplicate records	106	26	2

mj: restrict to articles with search term as major focus

META-ANALYSIS

Where there were multiple RCTs of the same comparison in similar patient populations, we used meta-analytic techniques to try and obtain a summary effect size (risk ratio) and confidence interval. For studies with multiple treatment arms, such as the Japan phase III enoxaparin trial (24), only the arms including the largest daily dose were included. This analysis was done using RevMan 5 software, following the methods used by the Cochrane Peripheral Vascular Diseases Group (22). Heterogeneity of reported results was evaluated with both the chi-square test (critical value of $p < 0.10$ because this statistic lacks power) and the I^2 statistic (critical value of 50%). If significant heterogeneity was observed, summary results were not reported as they may not be valid because they would be combining two different quantities. There was not sufficient evidence for meta-regression or any other analyses to try and ascertain the causes of heterogeneity.

ASSESSMENT OF EVIDENCE QUALITY

The quality of individual randomized trials was assessed using a modified Jadad scale (see Appendix A). The quality of the evidence base for a given question was assessed using the GRADE criteria (Appendix B). The GRADE system assigns a starting quality grade based on the type of evidence (randomized controlled trials vs. other types of trials), then raises or lowers the grade depending on the quality, consistency, precision, and other characteristics of the evidence base. The resulting evidence grade can be used as a guide to how likely it is that additional evidence will change one's conclusions.

EVIDENCE REVIEW

GUIDELINES

Only guidelines published since 2005 were examined, since new drugs continue to be introduced and new clinical trials have been published. The most important recent guidelines are from the American Academy of Orthopedic Surgeons (25, 26) and from the American College of Chest Physicians (27). As pointed out in a subsequent commentary article (28), the guidelines make some differing recommendations. None of the guidelines express a preference for one LMWH over another, and none make mention of tinzaparin.

TABLE 3. COMPARISON OF VTE PROPHYLAXIS GUIDELINES FOR TKA PATIENTS

	ACCP guideline (27) 2008	AAOS guideline (25, 26) 2007	ICSI guideline (29)
Recommended agent(s)	LMWH, fondaparinux, or adjusted-dose VKA. Guideline does not recommend one more highly than another.	Aspirin, LMWH, pentasaccharides, or warfarin. Guideline does not recommend one more highly than another.	Dalteparin, enoxaparin, fondaparinux, or warfarin. Guideline does not recommend one more highly than another.
Aspirin	X	✓	No agreement
Warfarin (VKA)	✓	✓	✓
Unfractionated heparin			X
Target INR for warfarin treatment	2.5 (range 2.0-3.0)	2.0 or less	2.5 (range 2.5-3.0)
Role of mechanical prophylaxis	IPC is an alternative to anticoagulant drug therapy, if done optimally.	Recommended for all patients unless contraindicated.	Recommended for all non-ambulatory patients.
Patients with increased bleeding risk	IPC or VFP until bleeding risk subsides, then drug therapy.	Aspirin or warfarin.	Mechanical prophylaxis only (IPC, VFP, and/or graded compression stockings).
Same as for total hip arthroplasty?	IPC alternative not discussed for hip arthroplasty. No mention of drugs which are not recommended.	No difference in guidelines for knee and hip patients.	Yes

IPC—intermittent pneumatic compression

VFP—venous foot pump

SYSTEMATIC REVIEWS

There were no recent systematic reviews summarizing data on more than one or two low molecular-weight heparins for patients undergoing total knee arthroplasty. Therefore we retrieved and analyzed primary studies on the topic.

PRIMARY STUDIES

For space reasons, separate evidence tables are provided for VTE outcomes (Table 6) and non-VTE outcomes (Table 7). The evidence tables include only studies of FDA-approved low-molecular weight heparins (dalteparin, enoxaparin, and tinzaparin) and factor Xa inhibitors (fondaparinux). Studies of products that are not marketed in the US: bemiparin (7, 30), certoparin, lomoparin, nadroparin (31), rivaroxaban (12, 13, 32), and apixaban (10) are not included in the tables. Cells reporting statistically significant results that favor the study drug are shaded yellow. Cells reporting statistically significant results that favor the control are shaded red. The majority of studies were sponsored or funded by drug manufacturers.

DIRECT COMPARISONS OF DIFFERENT LOW-MOLECULAR WEIGHT HEPARINS

We found no studies comparing one LMWH with another exclusively in total knee arthroplasty patients. There was one retrospective pre post study including both knee and hip arthroplasty patients (33). The investigators reported bleeding (Table 4) and DVT (Table 5) results before and after changing from enoxaparin to dalteparin as their standard DVT prophylaxis. Both bleeding rates and DVT rates decreased, but the decreases were not statistically significant.

The PENTAMAKS trial compared fondaparinux to enoxaparin. It was a well designed and well reported randomized controlled trial, scoring a perfect 9 on the modified Jadad scale for study quality. In this study, patients given fondaparinux had significantly greater risk of major bleeding, but the difference in overall bleeding risk was not significant (Table 4). On the other hand, the patients given fondaparinux had significantly less risk of deep vein thrombosis and significantly fewer venous thromboembolisms in total (Table 5). The effect of fondaparinux instead of enoxaparin was one additional major bleed per 52 patients treated, and one fewer DVT per 7 patients treated. Pulmonary embolisms were too few for the difference in rates to be statistically significant (Table 5).

Another study comparing fondaparinux to enoxaparin measured effects on wound healing, but did not report VTE or bleeding outcomes (34). It found no significant differences between the two drugs. However, a post-hoc analysis by the study authors noted that the study did not have enough patients to statistically prove a one-day or longer delay in healing.

TABLE 4. DIRECT COMPARISONS: NON-VTE OUTCOMES

Study	Design Quality	Patients	Treatment	Results: any bleeding	Major bleeding	Results: Other adverse events	Comment
†-PENTAMAKS (3) 2001	RCT 9	Major knee surgery	2.5 mg fondaparinux qd 30 mg enoxaparin bid 6 hours to 5-9 days after surg.	25/517 20/517 p = NS	11/517 1/517 p = 0.006 RR 11.0 [1.4-84.9]	Death, any cause: 2/517 3/517 p = NS	Major bleeding defined as fatality, bleeding in critical organ, bleeding leading to reoperation, or bleeding index ≥ 2.
†-Krottenberg (33) 2001	Pre post study	TKA (218) THA (243)	Enoxaparin, dose varied Dalteparin, dose varied	6/161 7/300 p = NS	NR	NR	

TABLE 5. DIRECT COMPARISONS: VTE OUTCOMES

Study	Design	Patients	Treatment	All VTE	Pulmonary embolism	Deep vein thrombosis	Proximal DVT	Distal DVT	Comment
†-PENTAMAKS (3) 2001	RCT 9	Major knee surgery	Fondaparinux 2.5 mg qd Enoxaparin 30 mg bid 6 hours to 5-9 days after surg.	45/361 101/363 p < 0.001 RR 0.45 [0.33-0.62]	1/517 4/517 p = NS	45/361 98/361 p < 0.001 RR 0.46 [0.33-0.63]	9/368 20/372 p = 0.05 RR 0.45 [0.21-0.99]	35/372 78/366 p < 0.001 RR 0.44 [0.31-0.64]	DVT figures based on venography. PE based on symptomatic cases.
†-Krotenberg (33) 2001	Pre post study	TKA (218) THA (243)	Enoxaparin, dose varied Dalteparin, dose varied	NR	NR	3/161 1/300 p = NS	NR	NR	

†-Trial sponsored or funded by drug manufacturer

Major bleeding as defined by investigators RR: risk ratio with 95 percent confidence interval

STUDIES COMPARING LMWH TO PLACEBO OR OTHER CONTROLS

With little or no evidence from direct comparisons of low molecular weight heparins, we then analyzed controlled studies of these drugs comparing them to placebo or other anticoagulants in knee replacement patients. The evidence base for these comparisons is small too: only 11 studies met the inclusion criteria, including one non-randomized pre-post study. Study quality of the randomized trials rated from 5 to 9 on our nine-point modified Jadad scale (see Appendix).

BLEEDING AND OTHER ADVERSE EVENTS

None of the studies comparing LMWH or fondaparinux to placebo found significant differences in bleeding or other adverse events (Table 6). One trial (1) found a small but significant increase in bleeding for enoxaparin when compared with warfarin. Major bleeding was also reduced with coumadin, but the effect was not statistically significant.

TABLE 6. PRIMARY STUDIES: NON-VTE OUTCOMES

Study	Design Quality	Patients	Treatment	Results: any bleeding	Major bleeding	Results: Other adverse events	Comment
Fondaparinux							
†-JFSA (35) 2008	RCT 7	TKA	Fondaparinux, varying doses Placebo	12/339 4/87 p = NS	2/339 1/87 p = NS	Severe AE: 1/339 Severe AE: 2/87 No deaths either group	Significant dose dependence for VTE rate, no dose dependence for bleeding rate.

Study	Design Quality	Patients	Treatment	Results: any bleeding	Major bleeding	Results: Other adverse events	Comment
Dalteparin							
Wang (36) 2004	RCT 5	TKA	Dalteparin, dose by weight Indomethacin, 25 mg bid No prophylaxis	0/50 0/49 0/51	0/50 0/49 0/51		Not double-blind (no placebo) 1 indomethacin, 2 control patients given dalteparin for treatment of prolonged INR
Fong (31) 2000	Non-random pre-post study	TKA	Dalteparin, dose by weight No prophylaxis	10/100 8/100 p = 0.46	0/100 0/100 p = NS	Deep infection: 0/100 1/100 No deaths either group	Pre-post design, no blinding No difference in length of stay or recovery time
Enoxaparin							
†–Japan phase III trial (24) 2008	RCT 5	TKA	Enoxaparin 20 mg qd Enoxaparin 40 mg qd Enoxaparin 20 mg bid Placebo	5/89 7/91 13/95 8/89	0/89 1/91 3/95 4/89		
†–ECTG (1) 2001 (initial treatment)	RCT 5	TKA	Enoxaparin 30 mg bid Warfarin (to INR of 2 to 3)	58/173 42/176 p = 0.04 RR 1.40 [1.00-1.97]	9/173 4/176 p = 0.17	Death, any cause: 1/173 3/176 p = NS	No thrombocytopenia observed.
†–Leclerc (37) 1996	RCT 7	TKA	Enoxaparin 30 mg bid Warfarin (to INR of 2 to 3)	104/336 95/334 p = NS	7/336 6/334 p = NS	Death, any cause: 1/336 1/334 p = NS	
†–Leclerc (38) 1992	RCT 9	TKA or osteomy	Enoxaparin 30 mg bid Placebo	4/66 5/65 p = 0.71	0/66 1/65 p = NS	Death, any cause: 1/66 0/65 p = NS	
†–ECTG (39) 1995	RCT 3 (open label)	TKA	Enoxaparin 30 mg bid Unfractionated heparin	46/228 52/225 p = NS	3/228 3/225 p = NS	NR	
Tinzoparin							
†–Hull (40) 1993	RCT 6	TKA	Tinzoparin 75 U/kg Warfarin (to INR of 2 to 3)	14/317 8/324 p = NS	9/317 3/324 p = NS	NR	No significant difference in death rates when TKA, THA patients pooled. Significantly more thrombocytopenia in LMWH group when TKA, THA pooled.

†–Trial sponsored by drug manufacturer

§–specific procedures not reported

Major bleeding as defined by investigators

RR: risk ratio [95 percent confidence interval]

VENOUS THROMBOEMBOLISM

There is evidence from the placebo-controlled trials that fondaparinux and low-molecular weight heparins reduce the risk of deep vein thrombosis and venous thromboembolism (Table 7). At least one trial for each drug evaluated found a significant reduction in the risk of one of these outcomes. None of the trials found a significant effect on pulmonary embolism: this is an infrequent complication so larger studies are necessary to detect a difference in PE rates.

TABLE 7. PRIMARY STUDIES: VTE OUTCOMES

Study	Design Quality	Patients	Treatment	All VTE	PE	DVT	Proximal DVT	Distal DVT	Comment
Fondaparinux									
†-JFSA (35) 2008	RCT 7	TKA	Fondaparinux, varying doses Placebo	62/306 49/75 RR 0.31 [0.24-0.41]	NR	NR	NR	NR	Significant dose dependence for VTE rate, no dose dependence for bleeding rate.
Dalteparin									
Wang (36) 2004	RCT 5	TKA	Dalteparin, dose by weight Indomethacin, 25 mg bid No prophylaxis	25/50 22/49 36/51 RR 0.71 [0.51-0.98]	0/50 0/49 0/51	25/50 22/49 36/51 RR 0.71 [0.51-0.98]	1/50 1/49 3/51 p = NS	24/50 21/49 33/51 p = NS	Not double-blind (no placebo) 1 indomethacin, 2 control pts given dalteparin Tests of significance for LMWH vs. no prophylaxis p < 0.05 for both drugs vs. control
Fong (31) 2000	Non-random (see comment)	TKA	Dalteparin, dose by weight No prophylaxis	0/100 15/100 p < 0.0001 RR 0.03 [0.00-0.53]	0/100 1/100 p = NS	0/100 14/100 p < 0.0001 RR 0.03 [0.00-0.57]	0/100 5/100 p = 0.06	0/100 9/100 p = 0.003 RR 0.05 [0.00-0.89]	Sequential design, no blinding
Enoxaparin									
†-Japan phase III trial (24) 2008	RCT 5	TKA	Enoxaparin 40 mg qd Enoxaparin 20 mg bid Placebo	26/74 25/84 48/79 RR 0.53 [0.40-0.71]	See comment	25/74 25/84 48/79 RR 0.52 [0.39-0.70]	3/74 0/84 6/79 RR 0.25 [0.06-0.97]	NR	Study also included 20 mg qd group Study not powered to measure PE differences between treatment groups. Only three PEs observed in entire study Tests of significance for LMWHs vs. placebo
†-ECTG (1) 2001	RCT 5	TKA	Enoxaparin 30 mg bid Warfarin (to INR of 2 to 3)	44/173 80/176 p = 0.004 RR 0.56 [0.41-0.76]	0/173 1/176 p = NS	44/173 79/176 p = NS	3/173 20/176 p = 0.002 RR 0.15 [0.05-0.50]	41/173 59/176 p = NS	

Study	Design Quality	Patients	Treatment	All VTE	PE	DVT	Proximal DVT	Distal DVT	Comment
†–Leclerc (37) 1996	RCT 7	TKA	Enoxaparin 30 mg bid Warfarin (to INR of 2 to 3)	NR	1/336 3/334 p = NS	76/206 109/211 p = 0.003 RR 0.71 [0.57-0.89]	24/206 22/211 p = NS	NR	DVT figures based on venography. PE based on symptomatic cases.
†–Leclerc (38) 1992	RCT 9	TKA or osteomy	Enoxaparin 30 mg bid Placebo	NR	0/65 1/64 p = NS	11/65 37/64 p < 0.0001 RR 0.29 [0.16-0.52]	0/65 12/64 p < 0.001 RR 0.04 [0.00-0.66]	NR	
†–ECTG (39) 1995	RCT 3 (open label)	TKA	Enoxaparin 30 mg bid Unfractionated heparin	54/145 74/143 p = 0.02 RR 0.72 [0.55-0.94]	0/228 2/225 p = NS	56/228 77/225 p = 0.02 RR 0.72 [0.54-0.96]	5/228 22/225 p < 0.001 RR 0.22 [0.09-0.58]	51/228 54/225 p = NS	All VTE outcome includes only patients who had venography.
Tinzoparin									
†–Hull (40) 1993	RCT 6	TKA	Tinzoparin 75 U/kg Warfarin (to INR of 2 to 3)	NR	0/317 1/324 p = NS	116/258 152/277 p = 0.02 RR 0.82 [0.69-0.97]	20/258 34/277 p = NS	NR	DVT measured with venography. Not all patients had venograms PE based on symptomatic cases

†–Trial sponsored by drug manufacturer

‡–Composite outcome including all deep vein thrombosis, non-fatal pulmonary embolism, and all-cause mortality

RR: Risk ratio [95 percent confidence interval]

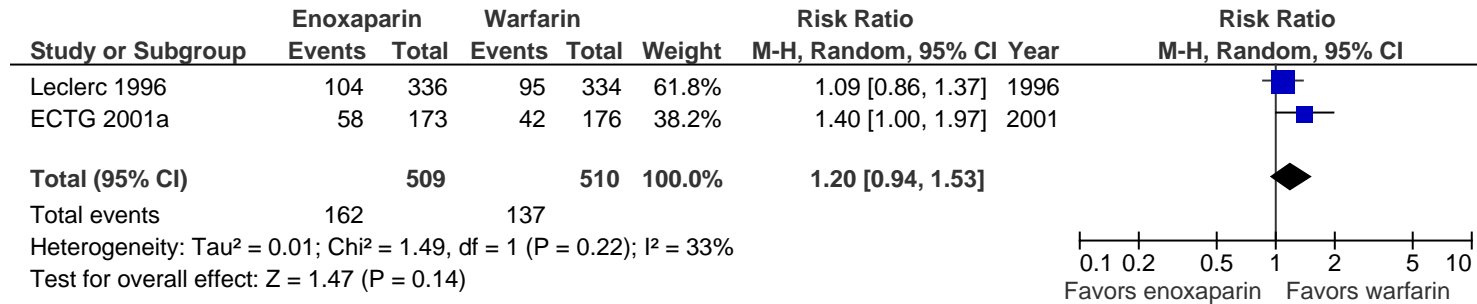
META-ANALYSIS

Only three comparisons of drug and control had more than one trial meeting the inclusion criteria. Within those comparisons, meta-analyses were further limited because not all outcomes were reported in each trial, and in some cases, there were zero total events, making calculation of a risk ratio impossible (Table 8). The meta-analyses revealed considerable heterogeneity among the trials. Differences in patient populations between trials, differences in study design, differences in outcome measurement, and other factors all could have contributed to this heterogeneity.

Meta-regression techniques can help identify the cause of heterogeneous results, but they require considerably more data than is available for low-molecular weight heparins. Absent a means of accounting for the heterogeneity in study results, we must recognize the possibility that the results of all the trials may have been affected by the same differences that gave rise to the heterogeneity seen in the meta-analyses. Thus one should not try to compare bleeding or VTE rates across different placebo-controlled studies to draw conclusions about the relative effects of one LMWH or another.

FIGURE 1. META-ANALYSIS RESULTS: ENOXAPARIN VS. WARFARIN

A—ANY BLEEDING



B—DEEP VEIN THROMBOSIS

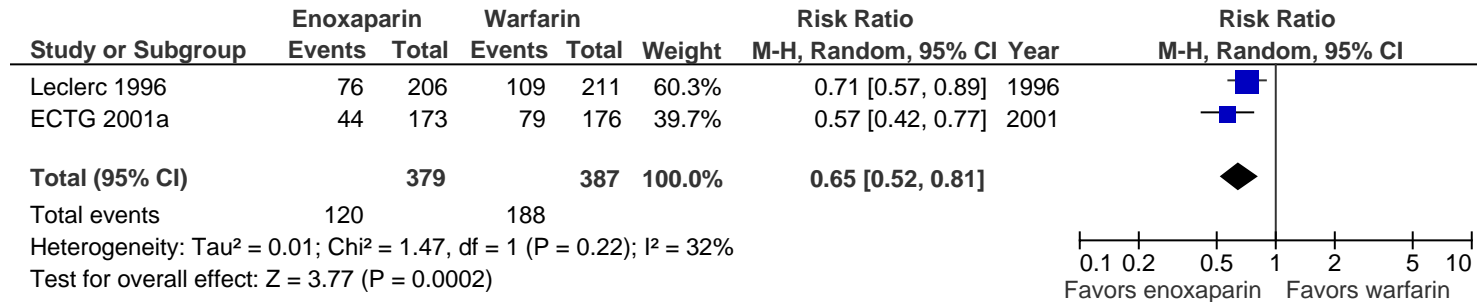
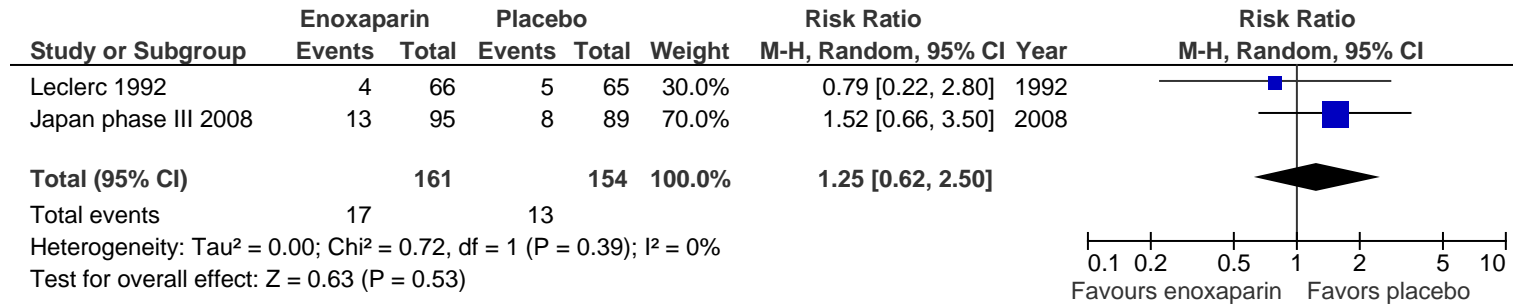
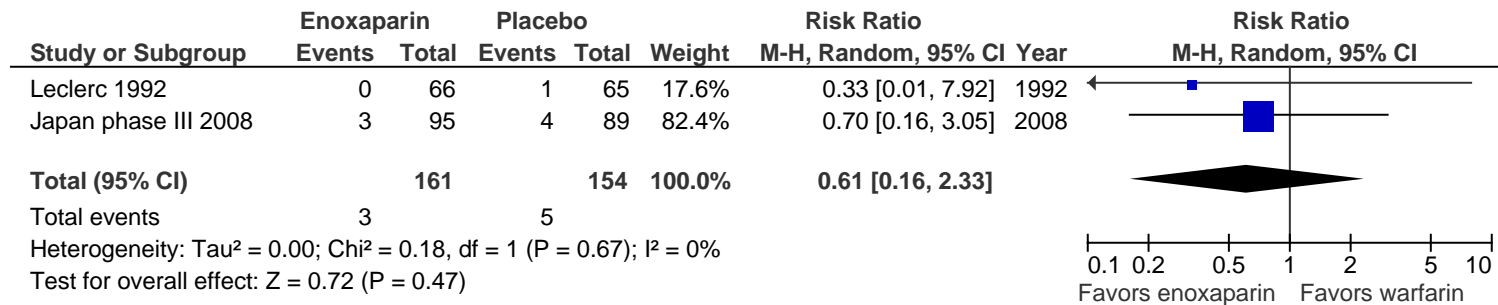


FIGURE 2. META-ANALYSIS RESULTS: ENOXAPARIN VS. PLACEBO

A—ANY BLEEDING



B—MAJOR BLEEDING



C—PROXIMAL DEEP VEIN THROMBOSIS

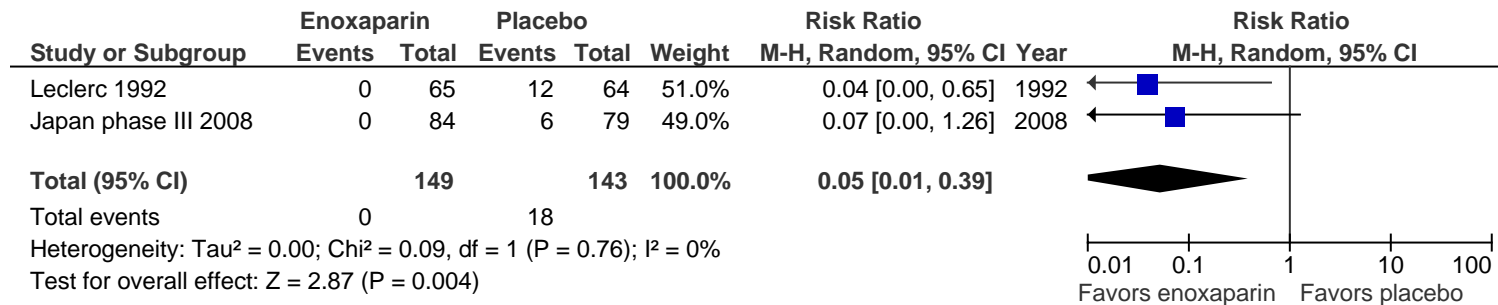


TABLE 8. SUMMARY OF PRIMARY RCT RESULTS

Study drug	Comparison	Studies	Summary risk ratio [95% confidence interval]						
			Any bleeding	Major bleeding	VTE	PE	DVT	Proximal DVT	Distal DVT
Fondaparinux	Enoxaparin	1	1.25 [0.70-2.22]	11.0 [1.43-84.9]	0.45 [0.33-0.62]	0.25 [0.03-2.23]	0.46 [0.33-0.63]	0.45 [0.21-0.99]	0.44 [0.31-0.64]
Fondaparinux	Placebo	1	1.04 [0.27-4.01]	1.04 [0.07-16.3]	0.14 [0.07-0.30]	No data	No data	No data	No data
Dalteparin	No prophylaxis	1	§	§	0.71 [0.51-0.98]	§	0.71 [0.51-0.98]	NS	NS
Enoxaparin	Placebo	2	1.25 [0.62-2.50]	0.61 [0.16-2.33]	0.53 [0.40-0.71]	NS	†	0.05 [0.01-0.39]	No data

Results in *italics* are summary effect sizes from CEP meta-analysis of published results. Summary risk ratios calculated using random-effects methods as recommended by Cochrane Peripheral Vascular Diseases Group.(22) Risk ratios below 1.0 favor study drug, over 1.0 favor comparison. Statistically significant findings shaded yellow if study drug favored, red if control favored

†—Significant heterogeneity among studies. Summary effect size not valid.

§—Study or studies reported zero events in both experimental and control groups, data insufficient for calculation of risk ratio.

NS—Not significant.

TABLE 9. STRENGTH OF EVIDENCE

Comparison	Outcome	Quantity and type of evidence	Findings	Starting grade	Decrease GRADE					Increase GRADE			GRADE of Evidence for Outcome	Overall GRADE of Evidence Base
					Study Quality†	Consistency†	Directness†	Precision†	Publication Bias†	Large Magnitude†	Dose-response	Confounders		
Fondaparinux vs. enoxaparin	Any bleed	1 RCT (3)	No difference	High	0	0	0	-1	0	0	0	0	Moderate	Moderate
	Major bleed*	1 RCT (3)	Increased risk	High	0	0	0	-1	0	0	0	0	Moderate	
	VTE*	1 RCT (3)	Decreased risk	High	0	0	0	-1	0	0	0	0	Moderate	
	DVT	1 RCT (3)	Decreased risk	High	0	0	0	-1	0	0	0	0	Moderate	
	Prox DVT	1 RCT (3)	Decreased risk	High	0	0	0	-1	0	0	0	0	Moderate	
	Distal DVT	1 RCT (3)	Decreased risk	High	0	0	0	-1	0	0	0	0	Moderate	
Enoxaparin vs. dalteparin	Any bleed*	1 pre-post (33)	No difference	Low	0	0	-1	-1	0	0	0	0	Very Low	Very Low
	DVT*	1 pre-post (33)	No difference	Low	0	0	-1	-1	0	0	0	0	Very Low	
Fondaparinux vs. placebo	Any bleed	1 RCT (35)	No difference	High	0	0	0	-2	0	0	0	0	Low	Low
	Major bleed*	1 RCT (35)	No difference	High	0	0	0	-2	0	0	0	0	Low	
	VTE*	1 RCT (35)	Decreased risk	High	0	0	0	-1	0	0	0	0	Moderate	

Dalteparin vs. no prophylaxis	Any bleed	1 RCT (36), 1 pre-post (31)	No difference	High	-1	0	0	-1	0	0	0	0	Low	Low
	Major bleed*	1 RCT (36), 1 pre-post (31)	No difference	High	-1	0	0	-1	0	0	0	0	Low	
	VTE*	1 RCT (36), 1 pre-post (31)	Decreased risk	High	-1	0	0	0	0	0	0	0	Moderate	
	PE	1 RCT (36), 1 pre-post (31)	No difference	High	-1	0	0	-1	0	0	0	0	Low	
	DVT	1 RCT (36), 1 pre-post (31)	Decreased risk	High	-1	0	0	0	0	0	0	0	Moderate	
	Prox DVT	1 RCT (36), 1 pre-post (31)	No difference in either, but suggestive decrease in pre-post	High	-1	0	0	-1	0	0	0	0	Low	
	Distal DVT	1 RCT (36), 1 pre-post (31)	Decreased risk in pre-post, suggestive decrease in RCT	High	-1	0	0	0	0	0	0	0	Moderate	

Enoxaparin vs. placebo	Any bleed	2 RCT (24, 38)	No difference	High	0	0	0	-1	0	0	0	0	Moderate	Moderate
	Major bleed*	2 RCT (24, 38)	No difference	High	0	0	0	-1	0	0	0	0	Moderate	
	VTE*	1 RCT(2, 24)	Decreased risk	High	0	0	0	-1	0	0	0	0	Moderate	
	DVT	2 RCT (24, 38)	Decreased risk	High	0	0	0	0	0	0	0	0	High	
	Prox DVT	2 RCT (24, 38)	Decreased risk	High	0	0	0	0	0	0	0	0	High	
	PE	2 RCT (24, 38)	No difference	High	0	0	0	-2	0	0	0	0	Low	
Enoxaparin vs. warfarin	Any bleed	2 RCT (1, 37)	Increased risk in 1 RCT (1), no difference in 1 RCT (37)	High	0	-2	0	0	0	0	0	0	Low	Moderate
	Major bleed*	2 RCT (1, 37)	No difference	High	0	0	0	-1	0	0	0	0	Moderate	
	VTE*	1 RCT (1)	Decreased risk	High	0	0	0	-1	0	0	0	0	Moderate	
	DVT	2 RCT (1, 37)	Decreased risk	High	0	-1	0	0	0	0	0	0	Moderate	
	Prox DVT	2 RCT (1, 37)	Decreased risk in 1 RCT (1), no difference in 1 RCT (37)	High	0	-2	0	0	0	0	0	0	Low	
	Distal DVT	1 RCT (1)	No difference	High	0	0	0	-1	0	0	0	0	Moderate	
	PE	2 RCT (1, 37)	No difference	High	0	0	0	-2	0	0	0	0	Low	
Enoxaparin vs. UFH	Any bleed	1 RCT (39)	No difference	High	0	0	0	-1	0	0	0	0	Moderate	Low
	Major bleed*	1 RCT (39)	No difference	High	0	0	0	-2	0	0	0	0	Low	
	VTE*	1 RCT (39)	Decreased risk	High	0	0	0	-1	0	0	0	0	Moderate	
	DVT	1 RCT (39)	Decreased risk	High	0	0	0	-1	0	0	0	0	Moderate	
	Prox DVT	1 RCT (39)	Decreased risk	High	0	0	0	-1	0	0	0	0	Moderate	
	Distal DVT	1 RCT (39)	No difference	High	0	0	0	-1	0	0	0	0	Moderate	
	PE	1 RCT (39)	No difference	High	0	0	0	-2	0	0	0	0	Low	
Tinzaparin vs. warfarin	Any bleed	1 RCT (40)	No difference	High	0	0	0	-1	0	0	0	0	Moderate	Low
	Major bleed*	1 RCT (40)	No difference	High	0	0	0	-2	0	0	0	0	Low	
	PE	1 RCT (40)	No difference	High	0	0	0	-2	0	0	0	0	Low	
	DVT*	1 RCT (40)	Decreased risk	High	0	0	0	-1	0	0	0	0	Moderate	
	Prox DVT	1 RCT (40)	No difference	High	0	0	0	-1	0	0	0	0	Moderate	

Evidence strength based on GRADE criteria (Appendix B)

* These outcomes are considered the most critical by those grading the evidence.

† These modifiers can impact the GRADE by 1 or 2 points

APPENDIX A—MODIFIED JADAD SCALE FOR RCT QUALITY

Jadad's components (marked with a "J") and TC Chalmers components (marked with a "C").

Randomization:

1. J Described as randomized?
2. J Randomization appropriately performed?

Blinding:

3. J Study described as double-blinded?
4. C Outcome assessor blinded?
5. J Study participant blinded (e.g. intervention described as indistinguishable, active placebo, identical placebo or dummy)?
6. C Investigator blinded?

Patient attrition:

7. J Attrition described?
8. C Attrition smaller than 10-15% of assigned patients?
9. C Attrition appropriately analyzed (i.e. intention-to-treat analysis for superiority studies)?

J—components from original Jadad scale (41); C—components from Chalmers list (42)

APPENDIX B—GRADE CRITERIA FOR RATING A BODY OF EVIDENCE

Developed by the GRADE Working Group (43-45)

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial—high

Observational study—low

Any other evidence—very low

Criteria for increasing or decreasing level

Reductions

Study quality has serious (–1) or very serious (–2) problems

Important inconsistency in evidence (–1)

Directness is somewhat (–1) or seriously (–2) uncertain

Sparse or imprecise data (–1)

Reporting bias highly probable (–1)

Increases

Evidence of association† strong (+1) or very strong (+2)

Dose-response gradient evident (+1)

All plausible confounders would reduce the effect (+1)

†Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders

Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.

REFERENCES

1. Fitzgerald RH,Jr, Spiro TE, Trowbridge AA, Gardiner GA,Jr, Whitsett TL, O'Connell MB, et al. Prevention of venous thromboembolic disease following primary total knee arthroplasty. A randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. *J Bone Joint Surg Am.* 2001 Jun;83-A(6):900-6.
2. Comp PC, Spiro TE, Friedman RJ, Whitsett TL, Johnson GJ, Gardiner GA,Jr, et al. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. enoxaparin clinical trial group. *J Bone Joint Surg Am.* 2001 Mar;83-A(3):336-45.
3. Bauer KA, Eriksson BI, Lassen MR, Turpie AG, Steering Committee of the Pentasaccharide in Major Knee Surgery,Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med.* 2001 Nov 1;345(18):1305-10.
4. Eriksson BI, Kakkar AK, Turpie AGG, Gent M, Bandel T-, Homering M, et al. Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. *J Bone Jt Surg Ser B.* 2009;91(5):636-44.
5. Heit JA, Berkowitz SD, Bona R, Cabanas V, Corson JD, Elliott CG, et al. Efficacy and safety of low molecular weight heparin (ardepardin sodium) compared to warfarin for the prevention of venous thromboembolism after total knee replacement surgery: A double-blind, dose-ranging study. ardepardin arthroplasty study group. *Thromb Haemost.* 1997 Jan;77(1):32-8.
6. Heit JA, Elliott CG, Trowbridge AA, Morrey BF, Gent M, Hirsh J. Ardepardin sodium for extended out-of-hospital prophylaxis against venous thromboembolism after total hip or knee replacement. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 2000 Jun 6;132(11):853-61.
7. Navarro-Quilis A, Castellet E, Rocha E, Paz-Jimenez J, Planes A, Bemiparin Study Group in Knee,Arthroplasty. Efficacy and safety of bemiparin compared with enoxaparin in the prevention of venous thromboembolism after total knee arthroplasty: A randomized, double-blind clinical trial. *J Thromb Haemost.* 2003 Mar;1(3):425-32.
8. Haas S, Breyer HG, Bacher HP, Fareed J, Misselwitz F, Victor N, et al. Prevention of major venous thromboembolism following total hip or knee replacement: A randomized comparison of low-molecular-weight heparin with unfractionated heparin (ECHOS trial). *Int Angiol.* 2006 Dec;25(4):335-42.
9. Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct factor xa inhibitor, as thromboprophylaxis in patients following total knee replacement. *J Thromb Haemost.* 2007 Dec;5(12):2368-75.
10. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med.* 2009 Aug 6;361(6):594-604.
11. Turpie AG, Bauer KA, Davidson BL, Fisher WD, Gent M, Huo MH, et al. *Thromb Haemost.* 2009 Jan;101(1):68-76.
12. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, et al. *N Engl J Med.* 2008 Jun 26;358(26):2776-86.
13. Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, et al. *Lancet.* 2009 May 16;373(9676):1673-80.
14. Francis CW, Berkowitz SD, Comp PC, Lieberman JR, Ginsberg JS, Paiement G, et al. Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. *N Engl J Med.* 2003 Oct 30;349(18):1703-12.
15. Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Lassen MR, Mouret P, et al. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement: The EXPRESS study. *J Thromb Haemost.* 2003 Dec;1(12):2490-6.

16. Eriksson BI, Arfwidsson AC, Frison L, Eriksson UG, Bylock A, Kalebo P, et al. A dose-ranging study of the oral direct thrombin inhibitor, ximelagatran, and its subcutaneous form, melagatran, compared with dalteparin in the prophylaxis of thromboembolism after hip or knee replacement: METHRO I. MELagatran for THRombin inhibition in orthopaedic surgery. *Thromb Haemost.* 2002 Feb;87(2):231-7.
17. Eriksson BI, Bergqvist D, Kalebo P, Dahl OE, Lindbratt S, Bylock A, et al. Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: The METHRO II randomised trial. *Lancet.* 2002 Nov 9;360(9344):1441-7.
18. Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Mouret P, Rosencher N, et al. Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee replacement. *Thromb Haemost.* 2003 Feb;89(2):288-96.
19. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: The RE-MODEL randomized trial. *J Thromb Haemost.* 2007 Nov;5(11):2178-85.
20. RE-MOBILIZE Writing C, Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, et al. Oral thrombin inhibitor dabigatran etexilate vs north american enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty.* 2009 Jan;24(1):1-9.
21. Eriksson BI, Dahl OE, Buller HR, Hettiarachchi R, Rosencher N, Bravo ML, et al. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: The BISTRO II randomized trial. *J Thromb Haemost.* 2005 Jan;3(1):103-11.
22. Fowkes FGR, Fletcher J, Hiatt WR, Kleijnen J, Leng GC, Maxwell H, et al. Cochrane peripheral vascular diseases group. Fowkes FGR, Fletcher J, Hiatt WR, Kleijnen J, Leng GC, Maxwell H, Middeldorp S, Moneta G, Price JF, Prins MH, Stansby G, Tisi P, Wakefield TW, Watson L, Welch K. Cochrane Peripheral Vascular Diseases Group. About The Cochrane Collaboration: Cochra(TRUNCATED). 2009(2009 Issue 3).
23. National Coordinating Centre for Health Technology Assessment. Dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery (project) (project record). Southampton: The National Coordinating Centre for Health Technology Assessment (NCCHTA); 2009.
24. Fuji T, Ochi T, Niwa S, Fujita S. Prevention of postoperative venous thromboembolism in japanese patients undergoing total hip or knee arthroplasty: Two randomized, double-blind, placebo-controlled studies with three dosage regimens of enoxaparin. *J Orthop Sci.* 2008 Sep;13(5):442-51.
25. American Academy of Orthopaedic Surgeons. Clinical guideline on prevention of pulmonary embolism in patients undergoing total hip or knee arthroplasty. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2007 May 2007.
26. Johanson NA, Lachiewicz PF, Lieberman JR, Lotke PA, Parvizi J, Pellegrini V, et al. Prevention of symptomatic pulmonary embolism in patients undergoing total hip or knee arthroplasty. *J Am Acad Orthop Surg.* 2009 Mar;17(3):183-96.
27. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American college of chest physicians evidence-based clinical practice guidelines (8th edition). *Chest.* 2008 Jun;133(6 Suppl):381S-453S.
28. Eikelboom JW, Karthikeyan G, Fagel N, Hirsh J. American association of orthopedic surgeons and american college of chest physicians guidelines for venous thromboembolism prevention in hip and knee arthroplasty differ: What are the implications for clinicians and patients? *Chest.* 2009 Feb;135(2):513-20.
29. Institute for Clinical Systems Improvement. Health care guideline: Venous thromboembolism prophylaxis. fifth edition. Bloomington, MN: Institute for Clinical Systems Improvement; 2008 October 2008.
30. Otero-Fernandez R, Gomez-Outes A, Martinez-Gonzalez J, Rocha E, Fontcuberta J. Evaluation of the effectiveness and safety of bemiparin in a large population of orthopedic patients in a normal clinical practice. *Clin Appl Thromb Hemost.* 2008;14(1):75-83.

31. Fong YK, Ruban P, Yeo SJ, Lee BP, Lo NN, Seow KH, et al. Use of low molecular weight heparin for prevention of deep vein thrombosis in total knee arthroplasty--a study of its efficacy in an asian population. *Ann Acad Med Singapore*. 2000 Jul;29(4):439-41.
32. Turpie AG, Fisher WD, Bauer KA, Kwong LM, Irwin MW, Kalebo P, et al. BAY 59-7939: An oral, direct factor xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study. *J Thromb Haemost*. 2005 Nov;3(11):2479-86.
33. Krotenberg R, Adler U, Pomeranz B, Miller JD, Russell MW. Dalteparin vs. enoxaparin as prophylaxis for deep-vein thrombosis after total hip or knee arthroplasty: A retrospective analysis. *Am J Phys Med Rehabil*. 2001 Dec;80(12):889-95.
34. Bonneux IM, Bellemans J, Fabry G. Evaluation of wound healing after total knee arthroplasty in a randomized prospective trial comparing fondaparinux with enoxaparin. *Knee*. 2006 Mar;13(2):118-21.
35. Fuji T, Fujita S, Ochi T. Fondaparinux prevents venous thromboembolism after joint replacement surgery in japanese patients. *Int Orthop*. 2008;32(4):443-51.
36. Wang CJ, Wang JW, Weng LH, Hsu CC, Huang CC, Yu PC. Prevention of deep-vein thrombosis after total knee arthroplasty in asian patients. comparison of low-molecular-weight heparin and indomethacin. *J Bone Joint Surg Am*. 2004 Jan;86-A(1):136-40.
37. Leclerc JR, Geerts WH, Desjardins L, Laflamme GH, L'Esperance B, Demers C, et al. Prevention of venous thromboembolism after knee arthroplasty. A randomized, double-blind trial comparing enoxaparin with warfarin. *Ann Intern Med*. 1996 Apr 1;124(7):619-26.
38. Leclerc JR, Geerts WH, Desjardins L, Jobin F, Laroche F, Delorme F, et al. Prevention of deep vein thrombosis after major knee surgery--a randomized, double-blind trial comparing a low molecular weight heparin fragment (enoxaparin) to placebo. *Thromb Haemost*. 1992 Apr 2;67(4):417-23.
39. Colwell CW,Jr, Spiro TE, Trowbridge AA, Stephens JW, Gardiner GA,Jr, Ritter MA. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep venous thrombosis after elective knee arthroplasty. enoxaparin clinical trial group. *Clin Orthop*. 1995 Dec(321):19-27.
40. Hull R, Raskob G, Pineo G, Rosenbloom D, Evans W, Mallory T, et al. A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. *N Engl J Med*. 1993 Nov 4;329(19):1370-6.
41. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary?. *Control Clin Trials*. 1996 Feb;17(1):1-12.
42. Chalmers TC, Smith H,Jr, Blackburn B, Silverman B, Schroeder B, Reitman D, et al. A method for assessing the quality of a randomized control trial. *Control Clin Trials*. 1981 May;2(1):31-49.
43. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ*. 2004 Jun 19;328(7454):1490.
44. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ, et al. Rating quality of evidence and strength of recommendations: What is "quality of evidence" and why is it important to clinicians? *BMJ*. 2008 May 3;336(7651):995-8.
45. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Rating quality of evidence and strength of recommendations: Going from evidence to recommendations. *BMJ*. 2008 May 10;336(7652):1049-51.