

# Clinical trials of antithrombotics for DVT prophylaxis in orthopedic surgery

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## 1 antivitamins K

Trial	Treatments	Patients	Trials design and methods
<b>vs no treatment</b>			
<b>Borsgtrom , 1965</b> n=29/29 follow-up: 65279;34 weeks	65279;Dicoumarol versus 65279;No treatment	HFS	Open
<b>Phenindione vs no treatment</b>			
<b>Eskeland , 1966</b> n=100/100 follow-up: 3 months	Phenindione versus No treatment	HFS	Open
<b>Hamilton , 1970</b> n=38/38 follow-up: 310 months	Phenindione versus No treatment	HFS	Open
<b>Warfarin vs no treatment</b>			
<b>Pinto , 1970</b> n=25/25 follow-up: >3 weeks	Warfarin versus No treatment	Hip surgery	Open
<b>Hume , 1973</b> n=17/19 follow-up: Discharge	Warfarin versus No treatment	THR	Open
<b>Morris , 1976</b> n=80/80 follow-up: 3 months	Warfarin versus No treatment	HFS	Open
<b>Powers , 1989</b> n=65/63 follow-up: 3 months	Warfarin versus No treatment	HFS	Open
<b>Warfarin vs placebo</b>			
<b>Myrhe , 1969</b> n=50/55 follow-up: 3 weeks	Wwarfarin versus Placebo	HFS	double blind
<b>Warfarin vs Ardeparin</b>			
<b>RD Heparin , 1994</b> n=403/770 follow-up: 3 months	Warfarin versus Ardeparin 50 anti-Xa IU /kg or 90 anti-Xa IU /kg x1	THR or TKR	Open
<b>Heit , 1997</b> n=279/554 follow-up: Days 514	Warfarin versus Ardeparin 25, 35, 50 anti-Xa U /kg x2	TKR	double blind
<b>Warfarin vs Aspirin</b>			

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<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
Lotke , 1997 n=146/166 follow-up: 6 months	Warfarin versus Aspirin 325 mg x2	THR or TKR (stratified)	Open
Powers , 1989 n=65/66 follow-up: 3 months	Warfarin versus Aspirin 650 mg x2	HFS	Open
<b>Warfarin vs Dalteparin</b>			
Francis , 1997 n=292/288 follow-up: Day 7 2	Warfarin versus Dalteparin 5000 anti-Xa IU x1	THR	Open
Hull , 2000 n=489/983 follow-up: Day 6 2	Warfarin versus Dalteparin 5000 anti-Xa IU x1	THR	double blind
<b>Warfarin vs Danaparoid</b>			
Gerhart , 1991 n=131/132 follow-up: 9 days	Warfarin versus Danaparoid 750 U x2	HFS	Open
van Comp , 1998 n=247/241 follow-up: 3 months	Warfarin versus Danaparoid 750 U x2	THR	Open
<b>Warfarin vs Dextran</b>			
Harris , 1972 n=114/113 follow-up: NA	Warfarin versus Dextran 40	THR	Open
Barber , 1977 n=58/51 follow-up: 1114 days	Warfarin versus Dextran 70	THR	Open
Francis , 1983 n=57/43 follow-up: 57 days	Warfarin versus Dextran 40	THR or TKR (stratified)65279;	Open
Myrhe , 1969 n=50/55 follow-up: 3 weeks	Warfarin versus Dextran 70	HFS	double blind
<b>Warfarin vs Enoxaparin</b>			
Leclerc , 1996 n=334/336 follow-up: 6 months	Warfarin versus Enoxaparin 30 mg x2	TKR	double blind
Colwell , 1999 n=1495/1516 follow-up: 3 months	Warfarin versus Enoxaparin 30 mg x2	THR	Open
Fitzgerald , 2001 n=176/173 follow-up: 3 weeks	Warfarin versus Enoxaparin 30 mg x2	TKR	Open
<b>Warfarin vs Intermittent pneumatic compression</b>			

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<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
Francis , 1992 n=103/98 follow-up: 68 days	Warfarin versus IPC	THR	Open
Paiement , 1987 n=80/83 follow-up: 12 days	Warfarin versus IPC	THR	Open
Bailey , 1991 n=45/50 follow-up: 57 days	Warfarin versus IPC	THR	Open
Kaempffe , 1991 n=52/48 follow-up: At least 2 months	Warfarin versus IPC	THR or TKR (stratified)	Open
<b>Warfarin vs Logiparin</b>			
Hull , 1993 n=721/715 follow-up: 65279;Day 14 or discharge	Warfarin versus Logiparin 75 anti-Xa IU /kg x1	65279;THR or TKR (stratified)	double blind
<b>Acenocoumarol vs Nadroparin</b>			
Hamulyak , 1994 n=342/330 follow-up: Day 10 2	Acenocoumarol versus Nadroparin 60 anti-Xa IU /kg x1	THR or TKR (stratified)	single blind
<b>Acenocoumarol vs Reviparin</b>			
Samama , 2001 n=645/644 follow-up: 6 weeks	Acenocoumarol versus Reviparin 4200 anti-Xa IU x1	THR	Open
<b>Warfarin vs Sudoxicam</b>			
Hume , 1973 n=52/51 follow-up: Discharge	Warfarin versus Sudoxicam	THR	single blind
<b>Acenocoumarol vs unfractionated heparin</b>			
van Geloven , 1977 n=11/11 follow-up: NA	Acenocoumarol versus UFH 4000 x2	THR	double blind
<b>Warfarin vs unfractionated heparin</b>			
Hume , 1973 n=17/18 follow-up: Discharge	Warfarin versus UFH 5000 x3	THR	Open
Barber , 1977 n=58/19 follow-up: 1114 days	Warfarin versus UFH 5000 x2	THR	Open

## References

### Borsgtrom, 1965:

BORGSTROEM S, GREITZ T, VAN DER LINDEN W, MOLIN J, RUDICS I ANTICOAGULANT PROPHYLAXIS OF VENOUS THROMBOSIS IN PATIENTS WITH

FRACTURED NECK OF THE FEMUR; A CONTROLLED CLINICAL TRIAL USING VENOUS PHLEBOGRAPHY. Acta Chir Scand 1965;129:500-8 [[14296582](#)]

**Eskeland, 1966:**

Eskeland G, Solheim K, Skjrtén F Anticoagulant prophylaxis, thromboembolism and mortality in elderly patients with hip fractures. A controlled clinical trial. Acta Chir Scand 1966;131:16-29 [[5332064](#)]

**Hamilton, 1970:**

Hamilton HW, Crawford JS, Gardiner JH, Wiley AM Venous thrombosis in patients with fracture of the upper end of the femur. A phlebographic study of the effect of prophylactic anticoagulation. J Bone Joint Surg Br 1970;52:268-89 [[5445407](#)]

**Pinto, 1970:**

Pinto DJ Controlled trial of an anticoagulant (warfarin sodium) in the prevention of venous thrombosis following hip surgery. Br J Surg 1970;57:349-52 [[5427880](#)]

**Hume, 1973:**

Hume M, Kuriakose TX, Zuch L, Turner RH 125I fibrinogen and the prevention of venous thrombosis. Arch Surg 1973;107:803-6 [[4744294](#)]

**Morris, 1976:**

Morris GK, Mitchell JR Warfarin sodium in prevention of deep venous thrombosis and pulmonary embolism in patients with fractured neck of femur. Lancet 1976;2:869-72 [[62111](#)]

**Powers, 1989:**

Powers PJ, Gent M, Jay RM, Julian DH, Turpie AG, Levine M, Hirsh J A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. Arch Intern Med 1989;149:771-4 [[2650646](#)]

**Myrhe, 1969:**

Myrhe HO, Holen A [Thrombosis prophylaxis. Dextran or warfarin-sodium? A controlled clinical study] Nord Med 1969 Dec 4;82:1534-8 [[5372427](#)]

Myrhe HO, Holen A [Thrombosis prophylaxis. Dextran or warfarin-sodium? A controlled clinical study] Nord Med 1969 Dec 4;82:1534-8 [[5372427](#)]

**RD Heparin, 1994:**

RD heparin compared with warfarin for prevention of venous thromboembolic disease following total hip or knee arthroplasty. RD Heparin Arthroplasty Group. J Bone Joint Surg Am 1994;76:1174-85 [[8056798](#)]

**Heit, 1997:**

Heit JA, Berkowitz SD, Bona R, Cabanas V, Corson JD, Elliott CG, Lyons R Efficacy and safety of low molecular weight heparin (ardepain sodium) compared to warfarin for the prevention of venous thromboembolism after total knee replacement surgery: a double-blind, dose-ranging study. Ardepain Arthroplasty Study Group. Thromb Haemost 1997;77:32-8 [[9031445](#)]

**Lotke, 1997:**

Lotke PA, Palevsky H, Keenan AM, Meranze S, Steinberg ME, Ecker ML, Kelley MA Aspirin and warfarin for thromboembolic disease after total joint arthroplasty. Clin Orthop Relat Res 1996;:251-8 [[8595765](#)]

**Powers, 1989:**

Powers PJ, Gent M, Jay RM, Julian DH, Turpie AG, Levine M, Hirsh J A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. Arch Intern Med 1989;149:771-4 [[2650646](#)]

**Francis, 1997:**

Francis CW, Pellegrini VD Jr, Totterman S, Boyd AD Jr, Marder VJ, Liebert KM, Stulberg BN, Ayers DC, Rosenberg A, Kessler C, Johanson NA Prevention of deep-vein thrombosis after total hip arthroplasty. Comparison of warfarin and dalteparin. J Bone Joint Surg Am 1997;79:1365-72 [[9314399](#)]

**Hull, 2000:**

Hull RD, Pineo GF, Francis C, Bergqvist D, Fellenius C, Soderberg K, Holmqvist A, Mant M, Dear R, Baylis B, Mah A, Brant R Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients: a double-blind, randomized comparison. The North American Fragmin Trial Investigators. Arch Intern Med 2000;160:2199-207 [[10904464](#)]

**Gerhart, 1991:**

Gerhart TN, Yett HS, Robertson LK, Lee MA, Smith M, Salzman EW Low-molecular-weight heparinoid compared with warfarin for prophylaxis of deep-vein thrombosis in patients who are operated on for fracture of the hip. A prospective, randomized trial. *J Bone Joint Surg Am* 1991;73:494-502 [[1707413](#)]

**van Comp, 1998:**

Comp PC, Voegeli T, McCutchen JW, Skoutakis VA, Trowbridge A, Overdyke WL A comparison of danaparoid and warfarin for prophylaxis against deep vein thrombosis after total hip replacement: The Danaparoid Hip Arthroplasty Investigators Group. *Orthopedics* 1998;21:1123-8 [[9801236](#)]

**Harris, 1972:**

Harris WH, Salzman EW, DeSanctis RW, Coutts RD Prevention of venous thromboembolism following total hip replacement. Warfarin vs dextran 40. *JAMA* 1972;220:1319-22 [[5067322](#)]

**Barber, 1977:**

Barber HM, Feil EJ, Galasko CS, Edwards DH, Sutton RA, Haynes DW, Bentley G A comparative study of dextran-70, warfarin and low-dose heparin for the prophylaxis of thrombo-embolism following total hip replacement. *Postgrad Med J* 1977;53:130-3 [[859784](#)]

**Francis, 1983:**

Francis CW, Marder VJ, Evarts CM, Yaukoolbodi S Two-step warfarin therapy. Prevention of postoperative venous thrombosis without excessive bleeding. *JAMA* 1983;249:374-8 [[6184493](#)]

**Myrhe, 1969:**

Myrhe HO, Holen A [Thrombosis prophylaxis. Dextran or warfarin-sodium? A controlled clinical study] *Nord Med* 1969 Dec 4;82:1534-8 [[5372427](#)]

**Leclerc, 1996:**

Leclerc JR, Geerts WH, Desjardins L, Laflamme GH, L'Esprance B, Demers C, Kassis J, Cruickshank M, Whitman L, Delorme F Prevention of venous thromboembolism after knee arthroplasty. A randomized, double-blind trial comparing enoxaparin with warfarin. *Ann Intern Med* 1996;124:619-26 [[8607589](#)]

**Colwell, 1999:**

Colwell CW Jr, Collis DK, Paulson R, McCutchen JW, Bigler GT, Lutz S, Hardwick ME Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty. Evaluation during hospitalization and three months after discharge. *J Bone Joint Surg Am* 1999;81:932-40 [[10428124](#)]

**Fitzgerald, 2001:**

Fitzgerald RH Jr, Spiro TE, Trowbridge AA, Gardiner GA Jr, Whitsett TL, O'Connell MB, Ohar JA, Young TR 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;83-A:900-6 [[11407799](#)]

**Francis, 1992:**

Francis CW, Pellegrini VD Jr, Marder VJ, Totterman S, Harris CM, Gabriel KR, Azodo MV, Leibert KM Comparison of warfarin and external pneumatic compression in prevention of venous thrombosis after total hip replacement. *JAMA* 1992;267:2911-5 [[1583760](#)]

**Paiement, 1987:**

Paiement G, Wessinger SJ, Waltman AC, Harris WH Low-dose warfarin versus external pneumatic compression for prophylaxis against venous thromboembolism following total hip replacement. *J Arthroplasty* 1987;2:23-6 [[3572408](#)]

**Bailey, 1991:**

Bailey JP, Kruger MP, Solano FX, Zajko AB, Rubash HE Prospective randomized trial of sequential compression devices vs low-dose warfarin for deep venous thrombosis prophylaxis in total hip arthroplasty. *J Arthroplasty* 1991;6 Suppl:S29-35 [[1774568](#)]

**Kaempffe, 1991:**

Kaempffe FA, Lifeso RM, Meinking C Intermittent pneumatic compression versus coumadin. Prevention of deep vein thrombosis in lower-extremity total joint arthroplasty. *Clin Orthop Relat Res* 1991;:89-97 [[1864061](#)]

**Hull, 1993:**

Hull R, Raskob G, Pineo G, Rosenbloom D, Evans W, Mallory T, Anquist K, Smith F, Hughes G, Green D 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;329:1370-6 [[8413432](#)]

**Hamulyak, 1994:**

Hamulyk K, Lensing AW, van der Meer J, Smid WM, van Ooy A, Hoek JA Subcutaneous low-molecular weight heparin or oral anticoagulants for the prevention of deep-vein thrombosis in elective hip and knee replacement? Fraxiparine Oral Anticoagulant Study Group. *Thromb Haemost* 1995;74:1428-31 [8772214]

**Samama, 2001:**

Samama CM, Vray M, Barr J, Fiessinger JN, Rosencher N, Lecompte T, Potron G, Basile J, Hull R, Desmichels D Extended venous thromboembolism prophylaxis after total hip replacement: a comparison of low-molecular-weight heparin with oral anticoagulant. *Arch Intern Med* 2002;162:2191-6 [12390061]

**Hume, 1973:**

Hume M, Kuriakose TX, Zuch L, Turner RH 125I fibrinogen and the prevention of venous thrombosis. *Arch Surg* 1973;107:803-6 [4744294]

**van Geloven, 1977:**

van Geloven F, Wittebol P, Sixma JJ Comparison of postoperative coumarin, dextran 40 and subcutaneous heparin in the prevention of postoperative deep vein thrombosis. *Acta Med Scand* 1977;202:367-72 [335793]

**Hume, 1973:**

Hume M, Kuriakose TX, Zuch L, Turner RH 125I fibrinogen and the prevention of venous thrombosis. *Arch Surg* 1973;107:803-6 [4744294]

**Barber, 1977:**

Barber HM, Feil EJ, Galasko CS, Edwards DH, Sutton RA, Haynes DW, Bentley G A comparative study of dextran-70, warfarin and low-dose heparin for the prophylaxis of thrombo-embolism following total hip replacement. *Postgrad Med J* 1977;53:130-3 [859784]

## 2 direct factor Xa inhibitors

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Trial	Treatments	Patients	Trials design and methods
<b>edoxaban vs placebo</b>			
DU176b-04 <i>ongoing</i> [NCT01203072] n=NA follow-up:	edoxaban 5, 15, 30, 60 mg once daily for 2 weeks versus placebo	elective total knee arthroplasty	parallel groups double-blind Japan
<b>apixaban vs enoxaparin</b>			
ADVANCE 3 , 2010 [NCT00423319] n=2708/2699 follow-up: 35 days (+60)	apixaban 2.5mg twice daily for 35 days versus enoxaparin 40mg once daily for 35 days	patients undergoing elective total hip replacement surgery	Parallel groups double blind 21 countries
<b>edoxaban vs enoxaparin</b>			
DU176b-B-J302 <i>ongoing</i> [NCT01181102] n=NA follow-up:	edoxaban 30mg once daily versus enoxaparin sodium (enoxaparin sodium 20mg(=2000IU)/0.2ml twice daily, subcutaneous injection)	elective total knee arthroplasty	parallel groups double-blind Japan
DU176b-B-J303 <i>ongoing</i> [NCT01181141] n=NA follow-up:	edoxaban 30mg once daily versus Enoxaparin sodium 20mg(=2000IU)/0.2ml twice daily, subcutaneous injection	elective hip fracture surgery	open Japan

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<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
<b>DU176b-B-J304</b> <i>ongoing</i> [NCT01181167] n=NA follow-up:	edoxaban 30mg once daily versus (enoxaparin sodium 20mg(=2000IU)/0.2ml twice daily, subcutaneous injection	elective total hip arthroplasty	parallel groups double-blind Japan
<b>rivaroxaban vs enoxaparin</b>			
<b>RECORD 1 , 2008</b> [NCT00329628] n=2266/2275 follow-up: 36 days (range 30-42)	rivaroxaban 10mg once daily for 35 days versus enoxaparin 40mg subcutaneous once daily for 31-39 days	patients undergoing total hip arthroplasty	Parallel groups double blind 27 countries worldwide
<b>apixaban vs enoxaparin (europe regimen)</b>			
<b>ADVANCE 2 , 2010</b> [NCT00452530] n=1528/1529 follow-up: 12 days	apixaban 2.5mg twice daily during 12 days versus enoxaparin 40mg once daily 12 days	patients undergoing elective unilateral or bilateral total knee replacement	Parallel groups double blind 27 countries
<b>rivaroxaban vs enoxaparin (europe regimen)</b>			
<b>RECORD 3 , 2008</b> [NCT00361894] n=1254/1277 follow-up: 13-17 days	rivaroxaban 10 mg once daily for 10- 14 days versus enoxaparin 40 mg subcutaneous once daily for 10-14 days	patients undergoing total knee arthroplasty	Parallel groups double blind 19 countries worldwide
<b>edoxaban vs enoxaparin (short duration)</b>			
<b>STARS J-V</b> [NCT01181167] n=255/248 follow-up:	edoxaban 30 mg once daily for 11 to 14 days versus subcutaneous enoxaparin 2,000 IU, equivalent to 20 mg, twice daily (BID) for 11 to 14 days	total hip arthroplasty	Parallel groups double-blind japan
<b>rivaroxaban vs enoxaparin (short duration)</b>			
<b>ODIXa-HIP 10mg , 2006</b> n=142/157 follow-up: 5-9 days	rivaroxaban 10mg daily for 59 days versus once-daily subcutaneous enoxaparin dose of 40 mg for 59 days	patients undergoing elective total hip replacement	Parallel groups double blind Europe, Israel
<b>rivaroxaban (long duration) vs enoxaparin (short duration)</b>			
<b>RECORD 2 , 2008</b> [NCT00332020] n=1252/1257 follow-up: 30-42 days	extended thromboprophylaxis with rivaroxaban 10mg once daily for 31-39 days versus enoxaparin 40mg subcutaneous once daily for 10-14 days	patients undergoing elective total hip replacement	Parallel groups double blind 21 countries worldwide
<b>apixaban vs enoxaparin (US regimen)</b>			
<b>APROPOS 2.5mg , 2007</b> [NCT00097357] n=153/152 follow-up: 12 days	apixaban 2.5mg BID for 12 days versus enoxaparin 30mg twice daily for 12 days	patients undergoing elective total knee replacement surgery	Parallel groups double blind
<b>rivaroxaban vs enoxaparin (US regimen)</b>			

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<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
<b>ODIXa-KNEE , 2005</b> n=102/105 follow-up: 5-9 days	BAY 59-7939 5mg b.i.d. for 59 days versus enoxaparin 30 mg b.i.d. for 59 days	patients undergoing elective total knee replacement	Parallel groups double blind North America
<b>RECORD 4 , 2009</b> [NCT00362232] n=1584/1564 follow-up: 40 days	rivaroxaban 10mg once daily for 10 to 14 days versus enoxaparin 30 mg twice daily by subcutaneous injection for 10-14 days	patients who had undergone total-knee-replacement surgery	Parallel groups double blind 12 countries

## References

### **DU176b-04, 0:**

### **ADVANCE 3, 2010:**

Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM Apixaban versus Enoxaparin for Thromboprophylaxis after Hip Replacement. N Engl J Med 2010;363:2487-2498 [21175312] [10.1056/NEJMoa1006885](https://doi.org/10.1056/NEJMoa1006885)

### **DU176b-B-J302, 0:**

### **DU176b-B-J303, 0:**

### **DU176b-B-J304, 0:**

### **RECORD 1, 2008:**

Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty N Engl J Med 2008;358:2765-75 [18579811] [10.1056/NEJMoa0800374](https://doi.org/10.1056/NEJMoa0800374)

### **ADVANCE 2, 2010:**

Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet 2010 Mar 6;375:807-15 [20206776] [10.1016/S0140-6736\(09\)62125-5](https://doi.org/10.1016/S0140-6736(09)62125-5)

### **RECORD 3, 2008:**

Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, Misselwitz F, Turpie AG Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008 Jun 26;358:2776-86 [18579812]

### **STARS J-V, 0:**

### **ODIXa-HIP 10mg, 2006:**

Eriksson BI, Borris L, Dahl OE, Haas S, Huisman MV, Kakkar AK, Misselwitz F, Klebo P Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. J Thromb Haemost 2006 Jan;4:121-8 [16409461]

Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, Muehlhofer E, Dierig C, Misselwitz F, Klebo P A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. Circulation 2006 Nov 28;114:2374-81 [17116766]

### **RECORD 2, 2008:**

Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Sogliani AG, Pap AF, Misselwitz F, Haas S Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet 2008 Jun 24; [18582928]

### **APROPOS 2.5mg, 2007:**

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;5:2368-75 [17868430]

### **ODIXa-KNEE, 2005:**

Turpie AG, Fisher WD, Bauer KA, Kwong LM, Irwin MW, Klebo P, Misselwitz F, Gent M 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;3:2479-86 [16241946]



**RECORD 4, 2009:**

Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, Cushner FD, Lotke PA, Berkowitz SD, Bandel TJ, Benson A, Misselwitz F, Fisher WD Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet 2009 May 16;373:1673-80 [[19411100](#)] [10.1016/S0140-6736\(09\)60734-0](#)

**3 extended prophylaxis**

<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
<b>out of hospital Ardeparin vs standard prophylaxis</b>			
Heit , 2000 n=589/572	65279;in hospital thromboprophylaxis followed by out of hospital Ardeparin 100 IU/kg once a day for a total duration of 42 days versus Ardeparin 50 IU/kg twice a day for 4-10 days	THR or TKR	
<b>out of hospital Dalteparin vs standard prophylaxis</b>			
Dahl , 1997 n=134/131	65279;in hospital thromboprophylaxis followed by out of hospital Dalteparin 5000 IU once a day for a total duration of 35 days versus Dalteparin 5000 IU once a day for 7 days (dextran day 0 and day 1)	THR	
Lassen , 1998 n=140/141	65279;in hospital thromboprophylaxis followed by out of hospital Dalteparin 5000 IU once a day for a total duration of 35 days versus Dalteparin 5000 IU once a day for 7 days	THR	
Hull , 2000 n=389/180	65279;in hospital thromboprophylaxis followed by out of hospital Dalteparin 5000 IU once a day for a total duration of 35 days versus Dalteparin 5000 IU once a day or warfarin for 6 days	THR	
<b>out of hospital Enoxaparin vs standard prophylaxis</b>			
Bergqvist , 1996 n=117/116	65279;in hospital thromboprophylaxis followed by out of hospital Enoxaparin 40 mg once a day for a total duration of 30 days versus 65279;Enoxaparin 40 mg once a day for 10-11 days	65279;THR	
Planes , 1996 n=90/89	65279;in hospital thromboprophylaxis followed by out of hospital Enoxaparin 40 mg once a day for a total duration of 35 days versus Enoxaparin 40 mg once a day for 13-15 days	THR	

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Trial	Treatments	Patients	Trials design and methods
<b>Comp , 2001</b> n=441/432	65279;in hospital thromboprophylaxis followed by out of hospital Enoxaparin 40 mg once a day for a total duration of 27-29 days versus Enoxaparin 30 mg twice a day for 7-10 days	THR or TKR	
<b>out of hospital Nadroparin vs standard prophylaxis</b>			
<b>NPHDO , 1998</b> n=173/173	65279;in hospital thromboprophylaxis followed by out of hospital Nadroparin weight-adjusted for a total duration of 37-38 days versus Nadroparin weight-adjusted for 16-17 days	THR	
<b>out of hospital UFH vs standard prophylaxis</b>			
<b>Manganelli , 1998</b> n=79/80	65279;in hospital thromboprophylaxis followed by out of hospital UFH 5000 IU three times a day for a total duration of 30 days versus UFH 5000 IU three times a day for 15 days	THR	

## References

### Heit, 2000:

Heit JA, Elliott CG, Trowbridge AA, Morrey BF, Gent M, Hirsh J Ardeparin 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;132:853-61 [[10836911](#)]

### Dahl, 1997:

Dahl OE, Andreassen G, Aspelin T, Mller C, Mathiesen P, Nyhus S, Abdelnoor M, Solhaug JH, Arnesen H Prolonged thromboprophylaxis following hip replacement surgery—results of a double-blind, prospective, randomised, placebo-controlled study with dalteparin (Fragmin) *Thromb Haemost* 1997;77:26-31 [[9031444](#)]

### Lassen, 1998:

Lassen MR, Borris LC, Anderson BS, Jensen HP, Skej Bro HP, Andersen G, Petersen AO, Siem P, Hrlyck E, Jensen BV, Thomsen PB, Hansen BR, Erin-Madsen J, Mller JC, Rotwitt L, Christensen F, Nielsen JB, Jrgensen PS, Paaske B, Trholm C, Hvidt P, Jensen NK Efficacy and safety of prolonged thromboprophylaxis with a low molecular weight heparin (dalteparin) after total hip arthroplasty—the Danish Prolonged Prophylaxis (DaPP) Study. *Thromb Res* 1998;89:281-7 [[9669750](#)]

### Hull, 2000:

Hull RD, Pineo GF, Francis C, Bergqvist D, Fellenius C, Soderberg K, Holmqvist A, Mant M, Dear R, Baylis B, Mah A, Brant R Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital vs in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients: a double-blind, randomized comparison. North American Fragmin Trial Investigators. *Arch Intern Med* 2000;160:2208-15 [[10904465](#)]

### Bergqvist, 1996:

Bergqvist D, Benoni G, Bjrgell O, Fredin H, Hedlundh U, Nicolas S, Nilsson P, Nylander G Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *N Engl J Med* 1996;335:696-700 [[8703168](#)]

### Planes, 1996:

Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Huet Y Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. *Lancet* 1996;348:224-8 [[8684199](#)]

### Comp, 2001:

Comp PC, Spiro TE, Friedman RJ, Whitsett TL, Johnson GJ, Gardiner GA Jr, Landon GC, Jov M Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. Enoxaparin Clinical Trial Group. J Bone Joint Surg Am 2001;83-A:336-45 [11263636]

**NPHDO, 1998:**

Haentjens P.9 Venous thromboembolism after total hip arthroplasty: areview of incidence and prevention during hospitalization and afterhospital dischargel Acta Orthop Belg 2000; 66: 18

**Manganelli, 1998:**

Manganelli D, Pazzagli M, Mazzantini D, Punzi G, Manca M, Vignali C, Palla A, Troiani R, Rossi G Prolonged prophylaxis with unfractionated heparin is effective to reduce delayed deep vein thrombosis in total hip replacement. Respiration 1998;65:369-74 [9782219]

## 4 Graduated compression stockings

Trial	Treatments	Patients	Trials design and methods
<b>compression stocking group vs control (on top fondaparinux)</b>			
<b>Cohen (L8405) , 2007</b> n=426/430 follow-up: 42 days	fondaparinux 2.5mg plus graduated compression stockings versus fondaparinux 2.5mg daily	patients undergoing elective or emergency hip surgery	Parallel groups open Brazil, UK, Hong Kong, Spain

## References

**Cohen (L8405), 2007:**

Cohen AT, Skinner JA, Warwick D, Brenkel I The use of graduated compression stockings in association with fondaparinux in surgery of the hip. A multicentre, multinational, randomised, open-label, parallel-group comparative study. J Bone Joint Surg Br 2007;89:887-92 [17673580]

## 5 Low molecular weight heparin

Trial	Treatments	Patients	Trials design and methods
<b>semuloparin vs enoxaparin</b>			
<b>SAVE-HIP1 , 2012</b> [NCT00697099] n=1161/1165 follow-up:	Semuloparin 20 mg once-daily versus Enoxaparin 40 mg once-daily	-	
<b>SAVE-KNEE , 2012</b> [NCT00718224] n=-576/574 follow-up:	Semuloparin 20 mg once-daily versus Enoxaparin 30 mg twice-daily	-	
<b>SAVE-HIP 2 , 2012</b> [NCT00721760] n=500/503 follow-up:	Semuloparin 20 mg once-daily versus Enoxaparin 40 mg once-daily	hip fracture surgery	Parallel groups

continued...

Trial	Treatments	Patients	Trials design and methods
<b>enoxaparin vs no treatment</b>			
Warwick , 1995 n=78/78 follow-up: 8-10 days	enoxaparin 4000x1 + elastic stockings versus no treatment + elastic stockings	Elective hip	open
<b>nadroparin vs no treatment</b>			
Yoo , 1997 n=50/50 follow-up: 10 days	nadroparin 41/kgx1 days 1-3, 62/kg x1 days 4-11+elastic stockings versus no treatment	Elective hip	open
<b>ardeparin vs placebo</b>			
Levine , 1996 n=122/124 follow-up: 14 days	ardeparin 50/kgx2 +elastic stockings versus Placebo+elastic stockings	Knee	double blind
<b>dalteparin vs placebo</b>			
Jorgensen , 1989 n=30/38 follow-up: 9 days	dalteparin 5000 x1 versus Placebo	Hip fracture	double blind
Torholm , 1991 n=58/54 follow-up: 9 days	dalteparin 5000x1 versus Placebo	Elective hip	double blind
<b>enoxaparin vs placebo</b>			
Kalodiki , 1996 n=13/14 follow-up: discharge (8-12 days )	enoxaparin 4000x1 versus Placebo	Elective hip	double blind
Leclerc , 1991 n=65/64 follow-up: 14 days	Enoxaparin 3000 x2 versus Placebo	Knee	double blind
Samama , 1997 n=85/85 follow-up: 8-12 days	enoxaparin 4000x1+elastic stockings versus Placebo+elastic stockings	Elective hip	double blind
Turpie , 1986 n=50/50 follow-up: 14 days or discharge	Enoxaparin 3000 x2 versus Placebo	Elective hip	double blind
<b>nadroparin vs placebo</b>			
Sourmelis , 1995 n=72/78 follow-up: 10-12 days	nadroparin 3075x1 preop, 6150x1 post op versus Placebo	Hip fracture	double blind
<b>tinzaparin vs placebo</b>			
Lassen , 1991 n=105/105 follow-up: 8-10 days	tinzaparin 50/kg x1 +elastic stockings versus Placebo+elastic stockings	Elective hip	double blind
<b>dalteparin vs Dextran</b>			

continued...

<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
Matzsch , 1991 n=120/123	dalteparin versus Dextran	Elective hip	
Eriksson , 1988 n=50/50	dalteparin versus Dextran	Elective hip	
Matzsch , 1988 n=48/52	dalteparin versus Dextran	Elective hip	
<b>enoxaparin vs Dextran</b>			
DES Group , 1991 n=120/126	Enoxaparin versus Dextran	Elective hip	
<b>certoparin + DHE vs Unfractionated heparin</b>			
Haas , 1987 n=80/80	Sandoz +0.5mg DHE versus Unfractionated heparin	Elective hip	
Lassen , 1989 n=68/71 follow-up: 6 days	certoparin 3000+0.5mg DHE x1 versus placebo	Hip fracture	double blind
Lassen , 1988 n=118/122 follow-up: 6 days	certoparin 3000+0.5mg DHE, x1 versus Placebo	Elective hip	double blind
<b>dalteparin vs Unfractionated heparin</b>			
Binsack , 1986 n=48/47	dalteparin versus Unfractionated heparin	Elective hip	
Barre , 1987 n=40/40	dalteparin versus Unfractionated heparin	Elective hip	
Dechavanne , 1989 n=82/40	dalteparin versus Unfractionated heparin	Elective hip	
Eriksson , 1989 n=67/69	dalteparin versus Unfractionated heparin	Elective hip	
Haas , 1985 n=65/65	dalteparin versus Unfractionated heparin	Elective hip	
Monreal , 1989 n=46/44	dalteparin versus Unfractionated heparin	Hip	
<b>enoxaparin vs Unfractionated heparin</b>			

continued...

Trial	Treatments	Patients	Trials design and methods
Levine , 1991 n=333/332	Enoxaparin versus Unfractionated heparin	Elective hip	
Planes , 1988 n=124/113	Enoxaparin versus Unfractionated heparin	Elective hip	
<b>fluxum vs Unfractionated heparin</b>			
Chiapuzzo , 1988 n=70/70	Fluxum versus Unfractionated heparin	Elective hip	
Pini , 1989 n=25/24	Fluxum versus Unfractionated heparin	Hip	
<b>nadroparin vs Unfractionated heparin</b>			
Leyvraz , 1991 n=203/206 follow-up:	Fraxiparin versus Unfractionated heparin	Elective hip	

## References

### SAVE-HIP1, 2012:

Lassen MR, Fisher W, Mouret P, Agnelli G, George D, Kakkar A, Mismetti P, Turpie AG Semuloparin for prevention of venous thromboembolism after major orthopedic surgery: results from three randomized clinical trials, SAVE-HIP1, SAVE-HIP2 and SAVE-KNEE. *J Thromb Haemost* 2012;10:822-32 [22429800] [10.1111/j.1538-7836.2012.04701.x](https://doi.org/10.1111/j.1538-7836.2012.04701.x)

### SAVE-KNEE, 2012:

Lassen MR, Fisher W, Mouret P, Agnelli G, George D, Kakkar A, Mismetti P, Turpie AG Semuloparin for prevention of venous thromboembolism after major orthopedic surgery: results from three randomized clinical trials, SAVE-HIP1, SAVE-HIP2 and SAVE-KNEE. *J Thromb Haemost* 2012 May;10:822-32 [22429800] [10.1111/j.1538-7836.2012.04701.x](https://doi.org/10.1111/j.1538-7836.2012.04701.x)

### SAVE-HIP 2, 2012:

Lassen MR, Fisher W, Mouret P, Agnelli G, George D, Kakkar A, Mismetti P, Turpie AG Semuloparin for prevention of venous thromboembolism after major orthopedic surgery: results from three randomized clinical trials, SAVE-HIP1, SAVE-HIP2 and SAVE-KNEE. *J Thromb Haemost* 2012 May;10:822-32 [22429800] [10.1111/j.1538-7836.2012.04701.x](https://doi.org/10.1111/j.1538-7836.2012.04701.x)

### Warwick, 1995:

Warwick D, Bannister GC, Glew D, Mitchelmore A, Thornton M, Peters TJ, Brookes S Perioperative low-molecular-weight heparin. Is it effective and safe. *J Bone Joint Surg Br* 1995 Sep;77:715-9 [7559695]

### Yoo, 1997:

Yoo MC, Kang CS, Kim YH, Kim SK A prospective randomized study on the use of nadroparin calcium in the prophylaxis of thromboembolism in Korean patients undergoing elective total hip replacement. *Int Orthop* 1997;21:399-402 [9498151]

### Levine, 1996:

Levine MN, Gent M, Hirsh J, Weitz J, Turpie AG, Powers P, Neemeh J, Willan A, Skingley P Ardeparin (low-molecular-weight heparin) vs graduated compression stockings for the prevention of venous thromboembolism. A randomized trial in patients undergoing knee surgery. *Arch Intern Med* 1996 Apr 22;156:851-6 [8774203]

### Jorgensen, 1989:

### Torholm, 1991:

Torholm C, Broeng L, Jorgensen PS, Bjerregaard P, Josephsen L, Jorgensen PK, Hagen K, Knudsen JB Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery. A placebo controlled study. *J Bone Joint Surg Br* 1991 May;73:434-8 [1670445]

**Kalodiki, 1996:**

Kalodiki EP, Hoppensteadt DA, Nicolaides AN, Fareed J, Gill K, Regan F, al-Kutoubi A, Cunningham DA, Birch R, Harris N, Hunt D, Johnson J, Marx C Deep venous thrombosis prophylaxis with low molecular weight heparin and elastic compression in patients having total hip replacement. A randomised controlled trial. *Int Angiol* 1996 Jun;15:162-8 [[8803642](#)]

**Leclerc, 1991:**

Leclerc JR, Geerts WH, Desjardins L, Jobin F, Laroche F, Delorme F, Haviernick S, Atkinson S, Bourgouin J 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;67:417-23 [[1321509](#)]

**Samama, 1997:**

Samama CM, Clergue F, Barre J, Montefiore A, Ill P, Samii K Low molecular weight heparin associated with spinal anaesthesia and gradual compression stockings in total hip replacement surgery. Arar Study Group. *Br J Anaesth* 1997 Jun;78:660-5 [[9215015](#)]

**Turpie, 1986:**

Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ, Andrew M, Hull RD, Gent M A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. *N Engl J Med* 1986 Oct 9;315:925-9 [[3531851](#)]

**Sourmelis, 1995:****Lassen, 1991:**

Lassen MR, Borris LC, Christiansen HM, Boll KL, Eiskjaer SP, Nielsen BW, Schtt P, Olsen AD, Rodenberg JC, Lucht U Prevention of thromboembolism in 190 hip arthroplasties. Comparison of LMW heparin and placebo. *Acta Orthop Scand* 1991;62:33-8 [[1848385](#)]

**Matzsch , 1991:****Eriksson , 1988:**

Eriksson BI, Zachrisson BE, Teger-Nilsson AC, Risberg B Thrombosis prophylaxis with low molecular weight heparin in total hip replacement. *Br J Surg* 1988 Nov;75:1053-7 [[2463035](#)]

**Matzsch , 1988:****DES Group , 1991:****Haas , 1987:**

Haas S, Stemberger A, Fritsche HM, Welzel D, Wolf H, Lechner F, Blumel G Prophylaxis of deep vein thrombosis in high risk patients undergoing total hip replacement with low molecular weight heparin plus dihydroergotamine. *Arzneimittelforschung* 1987 Jul;37:839-43 [[2823840](#)]

**Lassen, 1989:**

Lassen MR, Borris LC, Christiansen HM, Moller-Larsen F, Knudsen VE, Boris P, Nehen AM, Jurik AG, de Carvalho A, Nielsen BW Prevention of thromboembolism in hip-fracture patients. Comparison of low-dose heparin and low-molecular-weight heparin combined with dihydroergotamine. *Arch Orthop Trauma Surg* 1989;108:10-3 [[2913977](#)]

**Lassen, 1988:**

Lassen MR, Borris LC, Christiansen HM, Moller-Larsen F, Knudsen VE, Boris P, Nehen AM, de Carvalho A, Jurik AG, Nielsen BW Heparin/dihydroergotamine for venous thrombosis prophylaxis: comparison of low-dose heparin and low molecular weight heparin in hip surgery. *Br J Surg* 1988 Jul;75:686-9 [[2843255](#)]

**Binsack , 1986:****Barre , 1987:****Dechavanne , 1989:**

Dechavanne M, Ville D, Berruyer M, Trepo F, Dalery F, Clermont N, Lerat JL, Moyen B, Fischer LP, Kher A Randomized trial of a low-molecular-weight heparin (Kabi 2165) versus adjusted-dose subcutaneous standard heparin in the prophylaxis of deep-vein thrombosis after elective hip surgery. *Haemostasis* 1989;19:5-12 [[2537787](#)]

**Eriksson , 1989:****Haas , 1985:****Monreal , 1989:**

Monreal M, Lafoz E, Navarro A, Granero X, Caja V, Caceres E, Salvador R, Ruiz J A prospective double-blind trial of a low molecular weight heparin once daily compared with conventional low-dose heparin three times daily to prevent pulmonary embolism and venous thrombosis in patients with hip fracture. *J Trauma* 1989 Jun;29:873-5 [[2544742](#)]

**Levine , 1991:**

**Planes , 1988:**

Planes A, Vochelle N, Mazas F, Mansat C, Zucman J, Landais A, Pascariello JC, Weill D, Butel J Prevention of postoperative venous thrombosis: a randomized trial comparing unfractionated heparin with low molecular weight heparin in patients undergoing total hip replacement. *Thromb Haemost* 1988 Dec 22;60:407-10 [[2853459](#)]

**Chiapuzzo , 1988:**

Chiapuzzo E, Orengo GB, Ottria G, Chiapuzzo A, Palazzini E, Fusillo M The use of low molecular weight heparins for postsurgical deep vein thrombosis prevention in orthopaedic patients. *J Int Med Res* 1988 Sep-Oct;16:359-66 [[3197913](#)]

**Pini , 1989:**

Pini M, Tagliaferri A, Manotti C, Lasagni F, Rinaldi E, Dettori AG Low molecular weight heparin (Alfa LHWH) compared with unfractionated heparin in prevention of deep-vein thrombosis after hip fractures. *Int Angiol* 1989 Jul-Sep;8:134-9 [[2556484](#)]

**Leyvraz, 1991:**

Leyvraz PF, Bachmann F, Hoek J, Buller HR, Postel M, Samama M, Vandebroek MD Prevention of deep vein thrombosis after hip replacement: randomised comparison between unfractionated heparin and low molecular weight heparin. *BMJ* 1991 Sep 7;303:543-8 [[1655136](#)]

## 6 oral direct thrombin inhibitor

Trial	Treatments	Patients	Trials design and methods
<b>ximelagatran vs Dalteparin</b>			
<b>METHRO I , 2002</b> n=103 follow-up: 69 days	Melagatran 14 mg s.c. immediately before surgery, melagatran at 20.00 hours, then ximelagatran 624 mg orally b.d. for 69 days versus Dalteparin 5000 IU o.d., started evening before surgery for 69 days	adults undergoing hip or knee replacement	parallel group open Swedish
<b>METHRO II , 2002</b> n=1495/381 follow-up: 710 days	Melagatran 13 mg s.c. immediately before surgery, melagatran same day, then ximelagatran 824 mg orally b.d. for 710 days versus Dalteparin 5000 IU o.d., started evening before surgery for 710 days	undergoing hip or knee replacement	Parallel groups double-blind
<b>dabigatran 150mg vs enoxaparin</b>			
<b>RE-NOVATE (150mg) , 2007</b> [NCT00168818] n=1174/1162 follow-up: 28-35 days, median 33d	dabigatran etexilate 150 mg q.d. 28-35 days versus Enoxaparin 40 mg q.d. for 28-25 days	Total hip replacement	double blind Europe, Australia, South Africa
<b>dabigatran 220mg vs enoxaparin</b>			
<b>RE-NOVATE 2 unpublished</b> [NCT00657150] n=1010/1003 follow-up: 28-35 days (mean 32d)	dabigatran 220mg once daily for 28-35 Days versus enoxaparin 40mg subcutaneous once daily for 28-35 Days	patients undergoing total hip-replacement surgery	Parallel groups double-blind

continued...



<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
<b>RE-NOVATE (220mg) , 2007</b> [NCT00168818] n=1157/1162 follow-up: 28-35 days, median 33d	dabigatran etexilate 220 mg q.d. for 28-35 days versus Enoxaparin 40 mg q.d. for 23-35 days	Total hip replacement	Parallel groups double blind Europe, Australia, South Africa
<b>ximelagatran vs Enoxaparin</b>			
<b>Platinum (Colwell) , 2003</b> n=906/910 follow-up: 712 days	Ximelagatran 24 mg orally b.d., starting at least 12 h after surgery for 712 days versus Enoxaparin 30 mg s.c. b.d.,starting at least 12 h after surgery for 712 days	adults undergoing hip replacement	parallel group double-blind USA, Canada, Israel, Mexico,Argentina, South Africa
<b>METHRO III , 2002</b> n=2788 follow-up: 811 days	Melagatran 3 mg s.c. 412h after surgery, then ximelagatran24 mg orally b.d. for 710 days versus Enoxaparin 40 mg s.c. o.d. 12 h before surgery for 710 days	hip or knee replacement	double-blind Europe, South Africa
<b>Phase II (Heit) , 2001</b> n=600 follow-up: 612 days	Ximelagatran 8, 12, 18 or 24 mg orally b.d., at least 12 h after surgery for 612 days versus Enoxaparin 30 mg s.c. b.d.,starting at least 12 h after surgery for 612 days	adults (age>18 years and weight at least 40 kg) undergoing knee replacements	parallel group double-blind North American
<b>EXPRESS , 2003</b> n=2835 follow-up: 811 days	Melagatran 2 mg s.c. up to 30 min before surgery, then melagatran 3 mg at least 8 hafter surgery, then ximelagatran 24 mg orally b.d. for 811 days versus Enoxaparin 40 mg s.c. o.d.,starting 12 h before surgery for 811 days	hip or knee replacement	parallel group double-blind Europe
<b>dabigatran 150mg vs enoxaparin (europe regimen)</b>			
<b>RE-MODEL (150mg) , 2007</b> n=708/699 follow-up: 6-10 days, mean 8 days	dabigatran etexilate 150 mg q.d. for 6-10 days versus Enoxaparin 40 mg q.d. for 6-10 days	Total knee replacement	Parallel groups double blind Europe, Australia, South Africa
<b>dabigatran 220mg vs enoxaparin (europe regimen)</b>			
<b>RE-MODEL (220mg) , 2007</b> n=694/699 follow-up: 6-10 days, mean 8 days	dabigatran etexilate 220 mg q.d. 6-10 days versus Enoxaparin 40 mg q.d. for 6-10 days	patients undergoing total knee replacement	double blind Europe, Australia, South Africa
<b>dabigatran 150mg vs enoxaparin (US regimen)</b>			
<b>RE-MOBILIZE (150mg) , 2008</b> n=877/876 follow-up: 12-15 days, median 14d	dabigatran etexilate 150 mg q.d. for 12-15 days versus enoxaparin 30 mg SC BID after surgery for 12-15 days	Total knee replacement	double blind US, Canada, Mexico, UK
<b>dabigatran 220mg vs enoxaparin (US regimen)</b>			

continued...

Trial	Treatments	Patients	Trials design and methods
RE-MOBILIZE (220mg) , 2008 n=862/876 follow-up: 12-15 days, median 14d	dabigatran etexilate 220 mg for 12-15 days versus Enoxaparin 30mg SC BID after surgery for 12-15 days	Total knee replacement	Parallel groups double blind US, Canada, Mexico, UK

## References

### METHRO I, 2002:

Eriksson BI, Arfwidsson AC, Frison L, Eriksson UG, Bylock A, Klebo P, Fager G, Gustafsson D 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;87:231-7 [[11858482](#)]

### METHRO II, 2002:

Eriksson BI, Bergqvist D, Klebo P, Dahl OE, Lindbratt S, Bylock A, Frison L, Eriksson UG, Welin L, Gustafsson D Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the METHRO II randomised trial. *Lancet* 2002;360:1441-7 [[12433510](#)]

### RE-NOVATE (150mg), 2007:

Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Bller HR Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007;370:949-56 [[17869635](#)]

### RE-NOVATE 2, 0:

### RE-NOVATE (220mg), 2007:

Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Bller HR Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007;370:949-56 [[17869635](#)]

### Platinum (Colwell), 2003:

Colwell CW Jr, Berkowitz SD, Davidson BL, Lotke PA, Ginsberg JS, Lieberman JR, Neubauer J, McElhattan JL, Peters GR, Francis CW Comparison of ximelagatran, an oral direct thrombin inhibitor, with enoxaparin for the prevention of venous thromboembolism following total hip replacement. A randomized, double-blind study. *J Thromb Haemost* 2003;1:2119-30 [[14521593](#)]

### METHRO III, 2002:

Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Mouret P, Rosencher N, Eskilson C, Nylander I, Frison L, Ogren M 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;89:288-96 [[12574809](#)]

Mouret P [The oral direct thrombin inhibitor Ximelagatran Prophylaxis of venous thromboembolism in hip and knee replacement] *Hamostaseologie* 2002;22:21-4 [[12215757](#)]

Eriksson BI Clinical experience of melagatran/ximelagatran in major orthopaedic surgery. *Thromb Res* 2003;109 Suppl 1:S23-9 [[12818631](#)]

### Phase II (Heit), 2001:

Heit JA, Colwell CW, Francis CW, Ginsberg JS, Berkowitz SD, Whipple J, Peters G Comparison of the oral direct thrombin inhibitor ximelagatran with enoxaparin as prophylaxis against venous thromboembolism after total knee replacement: a phase 2 dose-finding study. *Arch Intern Med* 2001;161:2215-21 [[11575978](#)]

### EXPRESS, 2003:

Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Lassen MR, Mouret P, Rosencher N, Klebo P, Panfilov S, Eskilson C, Andersson M, Freij A 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;1:2490-6 [[14675083](#)]

Glynn O The express study: preliminary results. *Int J Clin Pract* 2003;57:57-9 [[12587945](#)]

### RE-MODEL (150mg), 2007:

Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Klebo P, Christiansen AV, Hantel S, Hettiarachchi R, Schnee J, Bller HR 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;5:2178-85 [17764540] [10.1111/j.1538-7836.2007.02748.x](https://doi.org/10.1111/j.1538-7836.2007.02748.x)

**RE-MODEL (220mg), 2007:**

Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Klebo P, Christiansen AV, Hantel S, Hettiarachchi R, Schnee J, Bller HR 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;5:2178-85 [17764540]

**RE-MOBILIZE (150mg), 2008:**

Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, Huo MH, Lieberman JR, Muntz JE, Raskob GE, Clements ML, Hantel S, Schnee JM, Caprini JA Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty* 2009;24:1-9 [18534438] [10.1016/j.arth.2008.01.132](https://doi.org/10.1016/j.arth.2008.01.132)

**RE-MOBILIZE (220mg), 2008:**

The Oral Thrombin Inhibitor Dabigatran Etxilate vs the North American Enoxaparin Regimen for the Prevention of Venous Thromboembolism after Knee Arthroplasty Surgery. *J Arthroplasty* 2008;: [18534438]

## 7 platelet aggregation inhibitors

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Trial	Treatments	Patients	Trials design and methods
<b>Aspirin vs no treatment</b>			
Pasteyer , 1977 n=20/20 follow-up: 2 weeks	Aspirin 1000mg daily + Hep versus control (Hep alone)	Elective orthopaedic surgery	Parallel groups
Rocha , 1986 n=60/30 follow-up: 1 weeks	Aspirin 250mg or 1000mg daily versus control (combination of heparin plus dihydroergotamine)	total hip replacement	Parallel groups open
<b>aspirin + dipyridamol vs no treatment</b>			
Morris-B , 1977 n=32/32 follow-up:	Aspirin 900 mg daily + dipyridamole versus control	elderly patients with hip fractures	Parallel groups open
Lyon-I , 1975 n=20/20 follow-up: 2 weeks	Aspirin 1500 mg daily + Dipyridamole versus control	Elective orthopaedic surgery	
<b>dipyridamol vs no treatment</b>			
Morris-A , 1977 n=24/24 follow-up:	dipyridamole versus control	elderly patients with hip fractures	Parallel groups open
<b>Flurbiprofen vs no treatment</b>			
Mocris-C , 1977 n=20/20 follow-up:	Flurbiprofen versus control	elderly patients with hip fractures	Parallel groups open

continued...

<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
<b>Hydroxychloroquine vs no treatment</b>			
Massachusetts-I , 1981 n=50/25 follow-up:	Aspirin 1200mg daily, Aspirin 1200mg daily + hydroxychloroquine 300 mg b.i.d. versus control	patients with upper femoral fractures	Parallel groups open
<b>aspirin vs placebo</b>			
Zekert-I , 1974 n=138/140 follow-up:	Aspirin 1500mg daily versus placebo	patients undergoing surgery of hip-joint proximal fractures	Parallel groups double-blind
Powers , 1976 n=66/63	A1300 versus placebo	traumatic orthopaedic surgery	
Erfurt-B , 1979 n=44/44 follow-up:	A1500 versus placebo	traumatic orthopaedic surgery	double-blind
PEP hip-fracture , 2000 n=6679/6677 follow-up: 35 days	aspirin 160mg/d started preoperatively and continued for 35 days versus placebo	patients undergoing surgery for hip fracture	Parallel groups Double blind Australia, New Zealand, South Africa,
Stockholm-I , 1975 n=26/25 follow-up: 2 weeks	Aspirin 2000mg daily versus placebo	elective surgery of the hip	double blind
Harris-I , 1977 n=58/59 follow-up: 1 weeks	Aspirin 1200mg daily versus placebo	patients over 40 years of age, who had undergone total hip replacement	Parallel groups double-blind
McKenna-I , 1980 n=24/12 follow-up: 2 weeks	Aspirin 975mg or 3900mg daily versus placebo	total knee replacement	Parallel groups double-blind
Sautter , 1983 n=68/77 follow-up: 3 weeks	Aspirin 900mg daily + sulfipyrazone versus placebo	patient with total hip replacement	Parallel groups
McBride , 1983 n=21/22 follow-up: 1 weeks	A1800+Dipyridamole versus placebo	Elective orthopaedic surgery	
<b>aspirin + dipyridamol vs placebo</b>			
Encke-II , 1976 n=34/25 follow-up:	Aspirin 1500mg daily, Aspirin 990mg daily + dipyridamol versus placebo	patients with abdominal operations	Parallel groups double-blind
Hamburg , 1976 n=21/11 follow-up: 3 weeks	A+Dipyridamole,A1000 versus placebo	Elective orthopaedic surgery	
<b>Hydroxychloroquine vs placebo</b>			

continued...

<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
Danish-A , 1976 n=48/50 follow-up:	Hydroxychloroquine sulphate versus placebo	patients with fractures of the hip, pelvis, or thoracolumbar spine	Parallel groups double-blind
Danish-B , 1976 n=27/28 follow-up:	Hydroxychloroquine sulphate versus placebo	patients with fractures of the hip, pelvis, or thoracolumbar spine	Parallel groups
Massachusetts-II , 1976 n=51/51 follow-up: 3 weeks	Hydroxychloroquine 600mg daily versus placebo	fractures or orthopaedic operations involving the skeleton between the knee and the pelvis	
Cooke , 1977 n=25/25 follow-up: 2 weeks	Hydroxychloroquine versus placebo	elective surgery on the hip	Parallel groups double-blind
Hume-A , 1977 n=20/20 follow-up: 2 weeks	Hydroxychloroquine versus placebo	total hip replacement	
Stockholm-II , 1981 n=18/17 follow-up: 2 weeks	Hydroxychloroquine versus placebo	total hip replacement	
<b>RA233 vs placebo</b>			
65279;Wood , 1973 n=21/9 follow-up:	RA233; Aspirin 600mg daily +RA233 versus placebo	traumatic orthopaedic surgery	
<b>Ticlopidine vs placebo</b>			
McKenna-II , 1983 n=29/29 follow-up: 2 weeks	Ticlopidine versus placebo	Elective orthopaedic surgery	
Lyon-II , 3000 n=20/20 follow-up: 3 weeks	Ticlopidine versus placebo	Elective orthopaedic surgery	
Gardecki , 3000 n=48/46 follow-up: 2 weeks	Ticlopidine versus placebo	Elective orthopaedic surgery	

## References

### Pasteyer, 1977:

Flicoteaux H, Kher A, Jean N, Blery M, Judet T, Honnart F, et al. Comparison of low dose heparin and low dose heparin combined with aspirin in prevention of deep vein thrombosis after total hip replacement. *Pathol Biol (Paris)* 1977;25(suppl):55-8.

### Rocha, 1986:

Alfaro MJ, Pramo JA, Rocha E Prophylaxis of thromboembolic disease and platelet-related changes following total hip replacement: a comparative study of aspirin and heparin-dihydroergotamine. *Thromb Haemost* 1986;56:53-6 [3535158]

### Morris-B , 1977:

Morris GK, Mitchell JR Preventing venous thromboembolism in elderly patients with hip fractures: studies of low-dose heparin, dipyridamole, aspirin, and flurbiprofen. *Br Med J* 1977;1:535-7 [843794]

**Lyon-I, 1975:**

Dechavanne M, Ville D, Viala JJ, Kher A, Faivre J, Pousset MB, Dejour H Controlled trial of platelet anti-aggregating agents and subcutaneous heparin in prevention of postoperative deep vein thrombosis in high risk patients. *Haemostasis* 1975;4:94-100 [[1205340](#)]

**Morris-A , 1977:**

Morris GK, Mitchell JR Preventing venous thromboembolism in elderly patients with hip fractures: studies of low-dose heparin, dipyridamole, aspirin, and flurbiprofen. *Br Med J* 1977;1:535-7 [[843794](#)]

**Morris-C , 1977:**

Morris GK, Mitchell JR Preventing venous thromboembolism in elderly patients with hip fractures: studies of low-dose heparin, dipyridamole, aspirin, and flurbiprofen. *Br Med J* 1977;1:535-7 [[843794](#)]

**Massachusetts-I , 1981:**

Snook GA, Chrisman OD, Wilson TC Thromboembolism after surgical treatment of hip fractures. *Clin Orthop Relat Res* 1981;:21-4 [[7014058](#)]

**Zekert-I , 1974:**

Zekert F, Kohn P, Vormittag E, Poigenfrst J, Thien M [Prevention of thromboembolism using acetylsalicylic acid in the surgery of hip-joint proximal fractures] *Monatsschr Unfallheilkd Versicher Versorg Verkehrsmed* 1974;77:97-110 [[4277091](#)]

**Powers , 1976:**

Hansen EH, Jessing P, Lindewald H, Ostergaard P, Olesen T, Malver EI Hydroxychloroquine sulphate in prevention of deep venous thrombosis following fracture of the hip, pelvis, or thoracolumbar spine. *J Bone Joint Surg Am* 1976;58:1089-93 [[1002750](#)]

Powers PJ, Gent M, Jay RM, Julian DH, Turpie AG, Levine M, Hirsh J A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. *Arch Intern Med* 1989;149:771-4 [[2650646](#)]

**Erfurt-B , 1979:**

Hartung B, Schreiber U, Rdiger H [Study of the platelet aggregation inhibitor MICRISTIN as to its efficacy in the prevention of thromboembolism in the postoperative phase following surgical interventions] *Folia Haematol Int Mag Klin Morphol Blutforsch* 1979;106:810-27 [[94873](#)]

**PEP hip-fracture, 2000:**

Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000 Apr 15;355:1295-302 [[10776741](#)]

**Stockholm-I, 1975:**

Soreff J, Johnsson H, Diener L, Gransson L Acetylsalicylic acid in a trial to diminish thromboembolic complications after elective hip surgery. *Acta Orthop Scand* 1975;46:246-55 [[1096521](#)]

**Harris-I, 1977:**

Harris WH, Salzman EW, Athanasoulis CA, Waltman AC, DeSanctis RW Aspirin prophylaxis of venous thromboembolism after total hip replacement. *N Engl J Med* 1977;297:1246-9 [[335247](#)]

**McKenna-I, 1980:**

McKenna R, Galante J, Bachmann F, Wallace DL, Kaushal PS, Meredith P Prevention of venous thromboembolism after total knee replacement by high-dose aspirin or intermittent calf and thigh compression. *Br Med J* 1980;280:514-7 [[6989432](#)]

**Sautter, 1983:**

Sautter RD, Koch EL, Myers WO, Ray JR 3rd, Mazza JJ, Larson DE, Chen HM, Milbauer JP, Treuhaft PS, Plotka ED Aspirin-sulfinpyrazone in prophylaxis of deep venous thrombosis in total hip replacement. *JAMA* 1983;250:2649-54 [[6355542](#)]

**McBride, 1983:**

McBride JA, Turpie AG, Kraus V, Hiltz C. Failure of aspirin and dipyridamole to influence the incidence of leg scan detected venous thrombosis after elective hip surgery *Thrombosis et Diathesis Haemorrhagica* 1975;34:abstract 204.

**Encke-II , 1976:**

Encke A, Stock C, Dumke HO [Double-blind study for the prevention of postoperative thrombosis] *Chirurg* 1976;47:670-3 [[1001131](#)]

**Hamburg, 1976:**

Boehringer Ingelheim DVT nach Hirntumoroperationen Boehringer Ingelheim, 1976. (Internal report.)

**Danish-A , 1976:**

Hansen EH, Jessing P, Lindewald H, Ostergaard P, Olesen T, Malver EI Hydroxychloroquine sulphate in prevention of deep venous thrombosis following fracture of the hip, pelvis, or thoracolumbar spine. J Bone Joint Surg Am 1976;58:1089-93 [[1002750](#)]

**Danish-B , 1976:**

Hansen EH, Jessing P, Lindewald H, Ostergaard P, Olesen T, Malver EI Hydroxychloroquine sulphate in prevention of deep venous thrombosis following fracture of the hip, pelvis, or thoracolumbar spine. J Bone Joint Surg Am 1976;58:1089-93 [[1002750](#)]

**Massachusetts-II, 1976:**

Chrisman OD, Snook GA, Wilson TC, Short JY Prevention of venous thromboembolism by administration of hydroxychloroquine. A preliminary report. J Bone Joint Surg Am 1976;58:918-20 [[789380](#)]

**Cooke, 1977:**

Cooke ED, Dawson MH, Ibbotson RM, Bowcock SA, Ainsworth ME, Pilcher MF Failure of orally administered hydroxychloroquine sulphate to prevent venous thromboembolism following elective hip operations. J Bone Joint Surg Am 1977;59:496-500 [[325009](#)]

**Hume-A, 1977:**

Hume M, Bierbaum B, Kuriakose TX, Surprenant, J Prevention of postoperative thrombosis by aspirin. Am J Surg 1977;133:420-2 [[322520](#)]

Hume M, Donaldson WR, Surprenant J Sex, aspirin, and venous thrombosis. Orthop Clin North Am 1978;9:761-7 [[358040](#)]

**Stockholm-II, 1981:**

Johansson E, Forsberg K, Johnsson H Clinical and experimental evaluation of the thromboprophylactic effect of hydroxychloroquine sulfate after total hip replacement. Haemostasis 1981;10:89-96 [[7007179](#)]

**65279;Wood , 1973:**

Wood EH, Prentice CR, McGrouther DA, Sinclair J, McNicol GP Trial of aspirin and RA 233 in prevention of post-operative deep vein thrombosis. Thromb Diath Haemorrh 1973;30:18-24 [[4788747](#)]

**McKenna-II, 1983:**

McKenna R, Galante J, Molony B, Kamm B. Failure of ticlopidine hydrochloride to prevent DVT in orthopedic patients Blood 1983;62(suppl I):304A

**Lyon-II, 3000:****Gardecki, 3000:**

## 8 recombinant hirudin

Trial	Treatments	Patients	Trials design and methods
<b>desirudin vs enoxaparin</b>			
<a href="#">Ericksson , 1997</a> n=NA follow-up:	desirudin 15mg SC twice daily for 8-12 days versus enoxaparin 40mg once daily for 8-12 days	Patients who undergo total hip replacement	Parallel groups double blind Europe
<b>desirudin vs UFH</b>			
<a href="#">REVASC , 1997</a> n=225/220 follow-up:	desirudin 15mg twice daily versus unfractionated heparin 5000 IU three times a day	patients having a primary elective total hip replacement	Parallel groups

continued...

Trial	Treatments	Patients	Trials design and methods
<b>Eriksson , 1996</b> n=1119 follow-up:	recombinant hirudin, desirudin (CGP 39393) 10, 15, or 20 mg twice daily started just before surgery and continued for 8-11 days versus unfractionated heparin 5000 IU three times daily started just before surgery and continued for 8-11 days	patients undergoing elective hip surgery	Parallel groups double blind Europe

## References

### Ericksson, 1997:

Eriksson BI, Wille-Jrgensen P, Klebo P, Mouret P, Rosencher N, Bsck P, Baur M, Ekman S, Bach D, Lindbratt S, Close P A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. *N Engl J Med* 1997;337:1329-35 [9358126]

### REVASC, 1997:

Eriksson BI, Ekman S, Lindbratt S, Baur M, Bach D, Torholm C, Klebo P, Close P Prevention of thromboembolism with use of recombinant hirudin. Results of a double-blind, multicenter trial comparing the efficacy of desirudin (Revasc) with that of unfractionated heparin in patients having a total hip replacement. *J Bone Joint Surg Am* 1997;79:326-33 [9070519]

### Eriksson, 1996:

Eriksson BI, Ekman S, Kalebo P, Zachrisson B, Bach D, Close P Prevention of deep-vein thrombosis after total hip replacement: direct thrombin inhibition with recombinant hirudin, CGP 39393. *Lancet* 1996;347:635-9 [8596376]

## 9 synthetic oligosaccharide

Trial	Treatments	Patients	Trials design and methods
<b>fondaparinux vs control</b>			
<b>NCT00320398</b> <i>ongoing</i> [NCT00320398] n=NA follow-up:	-	patients undergoing either an elective primary total hip replacement (THR) surgery or a revision of a THR	double-blind Japan
<b>fondaparinux vs placebo</b>			
<b>DRI4757</b> n=345/87 follow-up: 14 days	fondaparinux subcutaneously at 0.75, 1.5, 2.5, and 3.0 mg for at least 10 calendar days, (with a maximum of 14 days) versus placebo	Japanese patients undergoing elective total knee replacement surgery	Parallel groups double blind Japan
<b>fondaparinux vs enoxaparin</b>			
<b>L8541</b> n=119/118 follow-up: 9 days (49d)	fondaparinux 2.5mg subcutaneous once-daily for 7+/-2 days versus enoxaparin 40mg s.c. once-daily	chinese patients undergoing major orthopaedic surgery of the lower limbs	Parallel groups single-blind China

continued...



<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
<b>L8635</b> n=28/23 follow-up: 10 days	Fondaparinux 2.5mg once daily subcutaneously for 7 days versus enoxaparin 40mg once daily SC for 7 days	Taiwanese patients undergoing elective knee replacement	Parallel groups open, blind assessment Taiwan
<b>PENTAMAKS (Bauer) , 2001</b> n=517/517 follow-up: 11 days	fondaparinux 2.5-mg once-daily subcutaneous, starting 6 hours after surgery versus enoxaparin 30mg twice daily (North america recommendation)	elective major knee surgery	Parallel groups double blind North america
<b>PENTHIFRA (Eriksson) , 2001</b> n=831/840 follow-up: 11 days	fondaparinux 2.5-mg once-daily subcutaneous, starting 6 hours after surgery versus enoxaprin 40mg once daily	hip fracture surgery	Parallel groups double blind 21 countries
<b>EPHESUS (Lassen) , 2002</b> n=1155/1154 follow-up: 11 days (6 weeks)	fondaparinux 2.5-mg once-daily subcutaneous, starting 6 hours after surgery versus enoxaprin 40mg once daily	elective hip replacement surgery	Parallel groups double blind 16 European countries
<b>PENTATHLON (Turpie) , 2002</b> n=1138/1137 follow-up: 11 days	fondaparinux 2.5-mg once-daily subcutaneous, starting 6 hours after surgery versus enoxaparin 30mg twice daily (North america recommendation)	elective hip replacement surgery	Parallel groups double blind USA, Canada, Australia
<b>Turpie , 2001</b> n=673/260 follow-up: >15 days	pentasaccharide Org31540/SR90107A subcutaneous once daily at doses 0.75 mg, 1.5 mg, 3.0 mg, 6.0 mg, and 8.0 mg versus enoxaparin 30mg once daily subcutaneous	patients undergoing total hip replacement	Parallel groups double blind US, Canada, Australia
<b>SR123781A vs enoxaparin</b>			
<b>DRIVE , 2008</b> [NCT00338897] n=854/169 follow-up: 5-10 days	SR123781A for 5-10 days, doses ranging from 0.25 to 4.0 mg daily for 10 days versus enoxaparin 40 mg	patients undergoing total hip replacement surgery	Parallel groups double blind 12 countries
<b>extended prophylaxis vs standard prophylaxis</b>			
<b>PENTHIFRAPLUS (Eriksson) , 2003</b> n=656 follow-up: 19-23 days	25-31 days of fondaparinux 2.5-mg once-daily versus 6-8 days of fondaparinux 2.5-mg once-daily	patients undergoing hip fracture surgery	Parallel groups double blind

## References

NCT00320398, 0:

DRI4757, 0:

L8541, 0:

L8635, 0:

PENTAMAKS (Bauer), 2001:

Bauer KA, Eriksson BI, Lassen MR, Turpie AG Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001 Nov 1;345:1305-10 [11794149]

**PENTHIFRA (Eriksson), 2001:**

Eriksson BI, Bauer KA, Lassen MR, Turpie AG Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med 2001 Nov 1;345:1298-304 [11794148]

**EPHESUS (Lassen), 2002:**

Lassen MR, Bauer KA, Eriksson BI, Turpie AG Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. Lancet 2002 May 18;359:1715-20 [12049858]

**PENTATHLON (Turpie), 2002:**

Turpie AG, Bauer KA, Eriksson BI, Lassen MR Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. Lancet 2002 May 18;359:1721-6 [12049860]

**Turpie, 2001:**

Turpie AG, Gallus AS, Hoek JA A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. N Engl J Med 2001;344:619-25 [11228275]

**DRIVE, 2008:**

Lassen MR, Dahl O, Mismetti P, Zielske D, Turpie AG SR123781A: a new once-daily synthetic oligosaccharide anticoagulant for thromboprophylaxis after total hip replacement surgery: the DRIVE (Dose Ranging Study in Elective Total Hip Replacement Surgery) study. J Am Coll Cardiol 2008 Apr 15;51:1498-504 [18402906]

**PENTHIFRAPLUS (Eriksson), 2003:**

Eriksson BI, Lassen MR Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. Arch Intern Med 2003 Jun 9;163:1337-42 [12796070]

## 10 unfractionated heparin

Trial	Treatments	Patients	Trials design and methods
<b>UFH vs no treatment</b>			
Bergqvist , 1979 n=84/77	UFH twice daily for 5 days versus no treatment	elective orthopedic surgery	
Bergqvist , 1979 n=32/23	UFH twice daily for 5 days versus no treatment	traumatic orthopedic surgery	
Dechavanne , 1974 n=29/29	UFH 3 times daily for 10 days versus no treatment	elective orthopedic surgery	
Dechavanne , 1975 n=20/21	UFH 3 times daily for 10 days versus no treatment	elective orthopedic surgery	
Galasko , 1976 n=50/50	UFH twice daily (duration unknown) versus no treatment	traumatic orthopedic surgery	

continued...

<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
Gallus , 1973 n=23/23	UFH 3 times daily for A versus no treatment	traumatic orthopedic surgery	
Mannucci , 1976 n=23/24	UFH 3 times daily for 7 days versus no treatment	elective orthopedic surgery	
Morris , 1974 n=36/36	UFH twice daily for 10 days versus no treatment	elective orthopedic surgery	
Morris , 1977 n=24/24	UFH 3 times daily for 10 days versus no treatment	traumatic orthopedic surgery	
VTCSG , 1975 n=34/30	UFH twice daily for 10 days versus no treatment	elective orthopedic surgery	
Welin-Berger , 1982 n=20/20	UFH twice daily for 7 days versus no treatment	elective orthopedic surgery	
<b>UFH vs placebo</b>			
Abraham-Inpijn , 1975 n=12/13	UFH twice daily for 8 days versus placebo	elective orthopedic surgery	
Hampson , 1974 n=48/52	UFH 3 times daily for 7- 10 days versus placebo	elective orthopedic surgery	
Lahnborg , 1980 n=70/69	UFH twice daily for 10 days versus placebo	traumatic orthopedic surgery	
Lowe , 1981 n=51/49	UFH twice daily for 16 days versus placebo	elective orthopedic surgery	
Moskovitz , 1978 n=29/23	UFH 3 times daily for 7 days versus placebo	traumatic orthopedic surgery	
Moskovitz , 1978 n=35/32	UFH 3 times daily for 7 days versus placebo	elective orthopedic surgery	
Svend-Hansen , 1981 n=65/65	UFH 3 times daily for 14 days versus placebo	traumatic orthopedic surgery	
Williams , 1978 n=106/106	UFH twice daily for 14 days versus placebo	elective orthopedic surgery	

continued...

Trial	Treatments	Patients	Trials design and methods
Xabregas , 1977 n=27/26	UFH twice daily for 14 days versus placebo	traumatic orthopedic surgery	

## References

### Bergqvist , 1979:

Bergqvist D, Efsing HO, Hallbk T, Hedlund T Thromboembolism after elective and post-traumatic hip surgery—a controlled prophylactic trial with dextran 70 and low-dose heparin. *Acta Chir Scand* 1979;145:213-8 [[386676](#)]

### Bergqvist, 1979:

Bergqvist D, Efsing HO, Hallbk T, Hedlund T Thromboembolism after elective and post-traumatic hip surgery—a controlled prophylactic trial with dextran 70 and low-dose heparin. *Acta Chir Scand* 1979;145:213-8 [[386676](#)]

### Dechavanne, 1974:

Dechavanne M, Saudin F, Viala JJ, Kher A, Bertrix L, de Mourgues G [Prevention of venous thrombosis. Success of high doses of heparin during total hip replacement for osteoarthritis] *Nouv Presse Med* 1974;3:1317-9 [[4843085](#)]

### Dechavanne, 1975:

Dechavanne M, Ville D, Viala JJ, Kher A, Faivre J, Pousset MB, Dejour H Controlled trial of platelet anti-aggregating agents and subcutaneous heparin in prevention of postoperative deep vein thrombosis in high risk patients. *Haemostasis* 1975;4:94-100 [[1205340](#)]

### Galasko , 1976:

Galasko CS, Edwards DH, Fearn CB, Barber HM The value of low dosage heparin for the prophylaxis of thromboembolism in patients with transcervical and intertrochanteric femoral fractures. *Acta Orthop Scand* 1976;47:276-82 [[782146](#)]

### Gallus , 1973:

Gallus AS, Hirsh J, Tuttle RJ, Trebilcock R, O'Brien SE, Carroll JJ, Minden JH, Hudecki SM Small subcutaneous doses of heparin in prevention of venous thrombosis. *N Engl J Med* 1973;288:545-51 [[4568221](#)]

### Mannucci , 1976:

Mannucci PM, Citterio LE, Panajotopoulos N Low-dose heparin and deep-vein thrombosis after total hip replacement. *Thromb Haemost* 1976;36:157-64 [[1036806](#)]

### Morris, 1974:

Morris GK, Henry AP, Preston BJ Prevention of deep-vein thrombosis by low-dose heparin in patients undergoing total hip replacement. *Lancet* 1974;2:797-800 [[4138248](#)]

### Morris , 1977:

Morris GK, Mitchell JR Preventing venous thromboembolism in elderly patients with hip fractures: studies of low-dose heparin, dipyridamole, aspirin, and flurbiprofen. *Br Med J* 1977;1:535-7 [[843794](#)]

### VTCSG, 1975:

Small doses of subcutaneous sodium heparin in the prevention of deep vein thrombosis after elective hip operations. *Br J Surg* 1975;62:348-50 [[1139128](#)]

### Welin-Berger, 1982:

Welin-Berger T, Bygdeman S, Mebius C Deep vein thrombosis following hip surgery. Relation to activated factor X inhibitor activity: effect of heparin and dextran. *Acta Orthop Scand* 1982;53:937-45 [[6184938](#)]

### Abraham-Inpijn , 1975:

Abraham-Inpijn L, Vreeken J Effect of low-dose heparin on incidence of postoperative thrombosis in orthopaedic patients. *Arch Chir Neerl* 1975;27:63-8 [[1098580](#)]

### Hampson, 1974:

Hampson WG, Harris FC, Lucas HK, Roberts PH, McCall IW, Jackson PC, Powell NL, Staddon GE Failure of low-dose heparin to prevent deep-vein thrombosis after hip-replacement arthroplasty. *Lancet* 1974;2:795-7 [[4138905](#)]

**Lahnborg, 1980:**

Moreno-Gonzalez E, Sanmartin JH, Pascual MH, Moreno-Azcoita M, Selas PR Total esophagectomy by right anterior thoracotomy and immediate esophageal reconstruction for carcinoma of the esophagus. *Acta Chir Scand* 1980;146:19-23 [7376779]

Lahnborg G Effect of low-dose heparin and dihydroergotamine on frequency of postoperative deep-vein thrombosis in patients undergoing post-traumatic hip surgery. *Acta Chir Scand* 1980;146:319-22 [7468062]

**Lowe , 1981:**

Lowe LW Venous thrombosis and embolism. *J Bone Joint Surg Br* 1981;63-B:155-67 [6163785]

**Moskovitz, 1978:**

Moskovitz PA, Ellenberg SS, Feffer HL, Kenmore PI, Neviasser RJ, Rubin BE, Varma VM Low-dose heparin for prevention of venous thromboembolism in total hip arthroplasty and surgical repair of hip fractures. *J Bone Joint Surg Am* 1978;60:1065-70 [363722]

**Moskovitz, 1978:**

Moskovitz PA, Ellenberg SS, Feffer HL, Kenmore PI, Neviasser RJ, Rubin BE, Varma VM Low-dose heparin for prevention of venous thromboembolism in total hip arthroplasty and surgical repair of hip fractures. *J Bone Joint Surg Am* 1978;60:1065-70 [363722]

**Svend-Hansen, 1981:**

Svend-Hansen H, Bremerskov V, Gtrik J, Ostri P Low-dose heparin in proximal femoral fractures. Failure to prevent deep-vein thrombosis. *Acta Orthop Scand* 1981;52:77-80 [7010893]

**Williams , 1978:**

Williams JW, Eikman EA, Greenberg SH, Hewitt JC, Lopez-Cuenca E, Jones GP, Madden JA Failure of low dose heparin to prevent pulmonary embolism after hip surgery or above the knee amputation. *Ann Surg* 1978;188:468-74 [697431]

**Xabregas , 1977:**

Xabregas A, Gray L, Ham JM Heparin prophylaxis of deep vein thrombosis in patients with a fractured neck of the femur. *Med J Aust* 1978;1:620-2 [355810]

Lawrence JC, Xabregas A, Gray L, Ham JM Seasonal variation in the incidence of deep vein thrombosis. *Br J Surg* 1977;64:777-80 [338089]

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