Clinical trials of antithrombotics for thrombosis prevention in elective major knee surgery

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1 direct factor Xa inhibitors

Trial	Treatments	Patients	Trials design and methods
apixaban vs enoxaparin (europe regimen)			
ADVANCE 2 , 2010 [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
rivaroxaban vs enoxaparin (europe regimen)			
RECORD 3 , 2008 [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
apixaban vs enoxaparin (US regimen)			
APROPOS 2.5mg , 2007 [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
rivaroxaban vs enoxaparin (US regimen)			
ODIXa-KNEE , 2005 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
RECORD 4 , 2009 [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

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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

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]

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

2 Low molecular weight heparin

Trial	Treatments	Patients	Trials design and methods
ardeparin vs placebo			
Levine , 1996 n=122/124 follow-up: 14 days	ardeparin 50/kgx2 +elastic stockings versus Placebo+elastic stockings	Knee	double blind
enoxaparin vs placebo			
Leclerc , 1991 n=65/64 follow-up: 14 days	Enoxaparin 3000 x2 versus Placebo	Knee	double blind

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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]

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]

3 oral direct thrombin inhibitor

Trial	Treatments	Patients	Trials design and methods
ximelagatran vs Dalteparin			
METHRO I , 2002 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

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Trial	Treatments	Patients	Trials design and methods
ximelagatran vs Enoxaparin			
METHRO III , 2002 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
Phase II (Heit) , 2001 n=600 follow-up: 612 days	Ximelagatran 8, 12, 18 or 24 mgorally 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
EXPRESS , 2003 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
dabigatran 150mg vs enoxaparin (europe regimen)			
RE-MODEL (150mg) , 2007 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
dabigatran 220mg vs enoxaparin (europe regimen)			
RE-MODEL (220mg) , 2007 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
dabigatran 150mg vs enoxaparin (US regimen)			
RE-MOBILIZE (150mg) , 2008 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
dabigatran 220mg vs enoxaparin (US regimen)			
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

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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]

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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

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]

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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

RE-MOBILIZE (220mg), 2008:

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4 platelet aggregation inhibitors

Trial	Treatments	Patients	Trials design and methods
Aspirin vs placebo			
McKenna-I , 1980 n=24/12 follow-up: 2 weeks	Aspirin 975mg or 3900mg daily versus placebo	total knee replacement	Parallel groups double-blind

References

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]

5 synthetic oligosaccharide

Trial	Treatments	Patients	Trials design and methods
fondaparinux vs enoxaparin			
L8635 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
PENTAMAKS (Bauer) , 2001 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

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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]

6 About TrialResults-center.org

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