Supplementary data

Table 4. Summary of outcome data of included studies

First author/ year	Trial name	Surgery type	Regimen	No. of patients randomized	No. of VTEs	No. of major bleeding	No. of major/clinically relevant bleeding
Bauer 2001	PENTAMAKS	Knee	Fondaparinux 2.5 mg q.d.	526	45	11	11
			Enoxaparin 30 mg b.i.d	523	101	1	1
Eriksson 2001	PENTHIFRA	Hip	Fondaparinux 2.5 mg q.d.	849	52	18	18
			Enoxaparin 40 mg q.d.	862	119	19	19
Turpie 2002	PENTATHLON	Hip	Fondaparinux 2.5 mg q.d.	1,138	48	20	20
			Enoxaparin 30 mg b.i.d.	1,137	66	11	11
Lassen 2002	EPHESUS	Hip	Fondaparinux 2.5 mg q.d.	1,155	37	47	47
			Enoxaparin 40 mg q.d.	1,154	85	32	32
Lassen 2007	APROPOS	Knee	Apixaban 2.5 mg b.i.d.	153	10	0	0
			Enoxaparin 30 mg b.i.d.	152	17	0	0
Lassen 2009	ADVANCE-1	Knee	Apixaban 2.5 mg b.i.d.	1,599	101	11	46
			Enoxaparin 30 mg b.i.d.	1,596	97	22	69
Lassen 2010	ADVANCE-2	Knee	Apixaban 2.5 mg b.i.d.	1,528	145	9	53
			Enoxaparin 40 mg q.d.	1,529	243	14	72
Lassen 2010	ADVANCE-3	Hip	Apixaban 2.5 mg b.i.d.	2,708	24	22	129
			Enoxaparin 40 mg q.d.	2,699	73	18	134
Eriksson 2007	RE-MODEL	Knee	Dabigatran 150 mg q.d.	708	212	9	57
			Dabigatran 220 mg q.d.	694	182	10	50
			Enoxaparin 40 mg q.d.	699	193	9	46
Eriksson 2007	RE-NOVATE	Hip	Dabigatran 150 mg q.d.	1,174	73	15	70
			Dabigatran 220 mg q.d.	1,157	51	23	71
			Enoxaparin 40 mg q.d.	1,162	60	18	58
Ginsberg 2009	RE-MOBILIZE	Knee	Dabigatran 150 mg q.d.	877	218	5	27
			Dabigatran 220 mg q.d.	862	187	5	28
			Enoxaparin 30 mg b.i.d.	876	163	12	33
Eriksson 2011	RE-NOVATE II	Hip	Dabigatran 220 mg q.d.	1,036	61	14	37
			Enoxaparin 40 mg q.d.	1,019	69	9	29
Eriksson 2006	ODIXa-HIP	Hip	Rivaroxaban 10 mg q.d.	142	12	1	4
			Enoxaparin 40 mg q.d.	160	27	3	8
Eriksson 2008	RECORD-1	Hip	Rivaroxaban 10 mg q.d.	2,266	16	6	71
			Enoxaparin 40 mg q.d.	2,275	54	2	56
Kakkar 2008	RECORD-2	Hip	Rivaroxaban 10 mg q.d.	1,252	15	1	41
			Enoxaparin 40 mg q.d.	1,257	75	1	34
Lassen 2008	RECORD-3	Knee	Rivaroxaban 10 mg q.d.	1,154	79	7	40
			Enoxaparin 40 mg q.d.	1,277	164	6	34
Turpie 2009	RECORD-4	Knee	Rivaroxaban 10 mg q.d.	1,584	65	10	46
			Enoxaparin 30 mg b.i.d.	1,564	94	4	34
Fuji 2014	STARS E-3	Knee	Edoxaban 30 mg q.d.	360	22	4	22
			Enoxaparin 20 mg b.i.d.	365	41	1	13
Fuji 2015	STARS J-V	Hip	Edoxaban 30 mg q.d.	307	6	2	8
			Enoxaparin 20 mg b.i.d.	303	17	6	11

VTE = venous thromboembolism, q.d = once daily, b.i.d. = twice daily. The number of VTE was the sum of symptomatic/asymptomatic deep vein thrombosis and symptomatic non-fatal pulmonary embolism.

Table 5. Comparison of 7 interventions regarding major bleeding and clinically relevant non-major bleeding by using network odds ratios in the first analysis set (including two regimen groups of enoxaparin) as a sensitivity analysis

Outcome	Enoxaparin 30 mg b.i.d.	Enoxaparin 40 mg q.d.	Apixaban 2.5 mg b.i.d	Dabigatran 150 mg q.d.	Dabigatran 220 mg q.d.	Fondaparinux 2.5 mg q.d.
Major bleeding						
Enoxaparin 40 mg q.d.	0.86 (0.52–1.43)					
Apixaban 2.5 mg b.i.d.	0.70 (0.40–1.22)	0.82 (0.50–1.33)				
Dabigatran 150 mg q.d.	0.68 (0.36–1.29)	0.79 (0.47–1.33)	0.97 (0.49–1.91)			
Dabigatran 220 mg q.d.	0.95 (0.52–1.73)	1.11 (0.71–1.74)	1.36 (0.73–2.55)	1.41 (0.84–2.36)		
Fondaparinux 2.5 mg q.d.	1.32 (0.75–2.31)	1.54 (1.02–2.31)[a]	1.88 (1.02–3.48)[a]	1.95 (1.02–3.72)[a]	1.38 (0.76–2.53)	
Rivaroxaban 10 mg q.d.	1.47 (0.69–3.15)	1.71 (0.85–3.45)	2.10 (0.93–4.74)	2.17 (0.93–4.74)	1.54 (0.69–3.47)	1.11 (0.50–2.46)
Clinically relevant non-major bleeding						
Enoxaparin 40 mg q.d.	0.93 (0.68–1.26)					
Apixaban 2.5 mg b.i.d.	0.78 (0.57–1.07)	0.84 (0.68–1.03)				
Dabigatran 150 mg q.d.	1.20 (0.83–1.73)	1.29 (0.99–1.70)	1.54 (1.11–2.14)[a]			
Dabigatran 220 mg q.d.	1.08 (0.75–1.54)	1.16 (0.90–1.50)	1.38 (1.00–1.90)[a]	0.90 (0.69–1.16)		
Fondaparinux 2.5 mg q.d.	NA	NA	NA	NA	NA	
Rivaroxaban 10 mg q.d.	1.16 (0.84–1.61)	1.25 (1.00–1.58) [a]	1.49 (1.11–2.00) [a]	0.97 (0.69–1.36)	1.08 (0.77–1.51)	NA

95% confidence intervals are displayed in parenthesis. Row interventions (numerator) were compared to column intervention (denominator).
q.d. = once daily, b.i.d. = twice daily, NA = not applicable (due to lack of data).
[a] Statistically significant. Odds ratio >1 favors column-defining treatment.

Table 6. Comparison of 7 interventions regarding major bleeding and clinically relevant non-major bleeding by using network odds ratios in the second analysis set (including edoxaban) as a sensitivity analysis

Outcome	Enoxaparin various dose	Apixaban 2.5 mg b.i.d	Dabigatran 150 mg q.d.	Dabigatran 220 mg q.d.	Fondaparinux 2.5 mg q.d.	Rivaroxaban 10 mg q.d.
Major bleeding						
Apixaban 2.5 mg b.i.d.	0.77 (0.49–1.22)					
Dabigatran 150 mg q.d.	0.76 (0.45–1.27)	0.98 (0.49–1.95)				
Dabigatran 220 mg q.d.	1.08 (0.69–1.68)	1.39 (0.74–2.62)	1.42 (0.84–2.38)			
Fondaparinux 2.5 mg q.d.	1.48 (1.00–2.19)	1.91 (1.04–3.52)	1.95 (1.02–3.72)	1.37 (0.75–2.51)		
Rivaroxaban 10 mg q.d.	1.63 (0.82–3.22)	2.10 (0.93–4.78)	2.14 (0.91–5.03)	1.51 (0.67–3.41)	1.10 (0.50–2.43)	
Edoxaban 30 mg q.d.	0.79 (0.21–2.98)	1.03 (0.25–4.17)	1.05 (0.25–4.32)	0.74 (0.18–2.98)	0.54 (0.14–2.12)	0.49 (0.11–2.16)
Clinically relevant non-major bleeding						
Apixaban 2.5 mg b.i.d	0.83 (0.68–1.01)					
Dabigatran 150 mg q.d.	1.28 (0.98–1.66)	1.54 (1.11–2.14)				
Dabigatran 220 mg q.d.	1.15 (0.89–1.47)	1.38 (1.00–1.90)	0.90 (0.69–1.16)			
Fondaparinux 2.5 mg q.d.	NA	NA	NA	NA		
Rivaroxaban 10 mg q.d.	1.23 (0.99–1.54)	1.49 (1.11–2.00)[a]	0.97 (0.69–1.36)	1.08 (0.77–1.50)	NA	
Edoxaban 30 mg q.d.	1.44 (0.76–2.71)	1.73 (0.89–3.37)	1.13 (0.57–2.24)	1.26 (0.64–2.48)	NA	1.17 (0.60–2.28)

For footnotes, see Table 5.

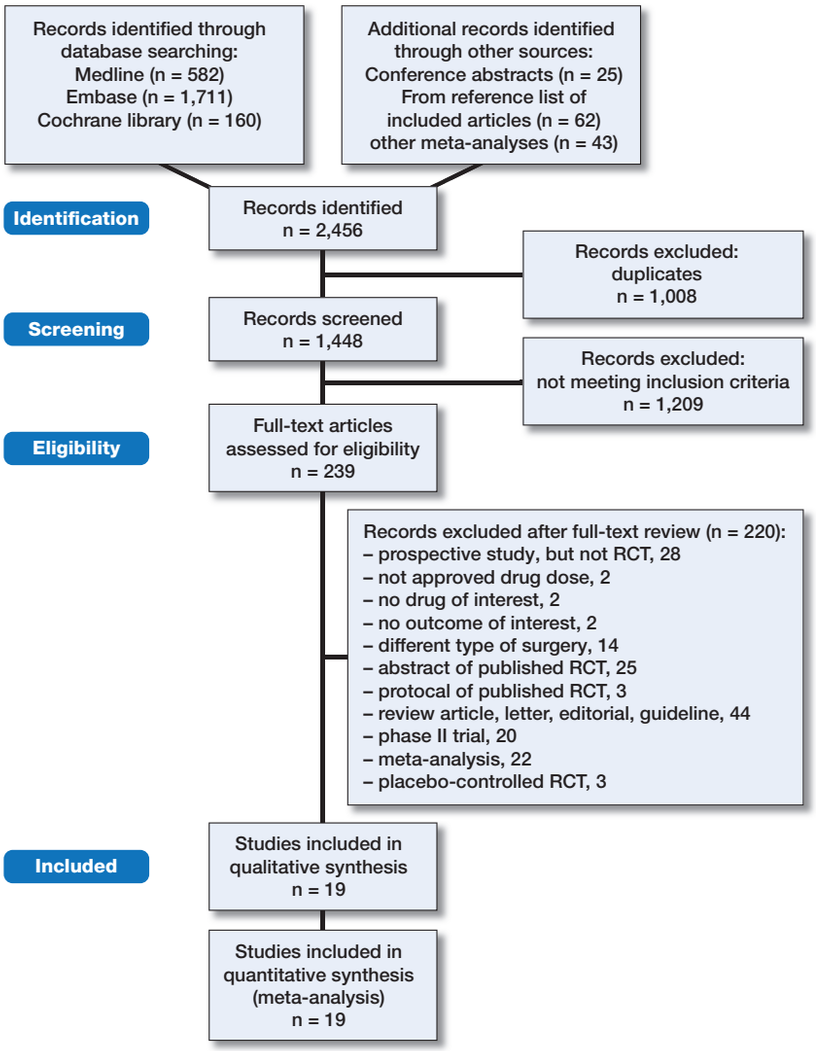

Figure 1. PRISMA flow diagram of articles search and selection.

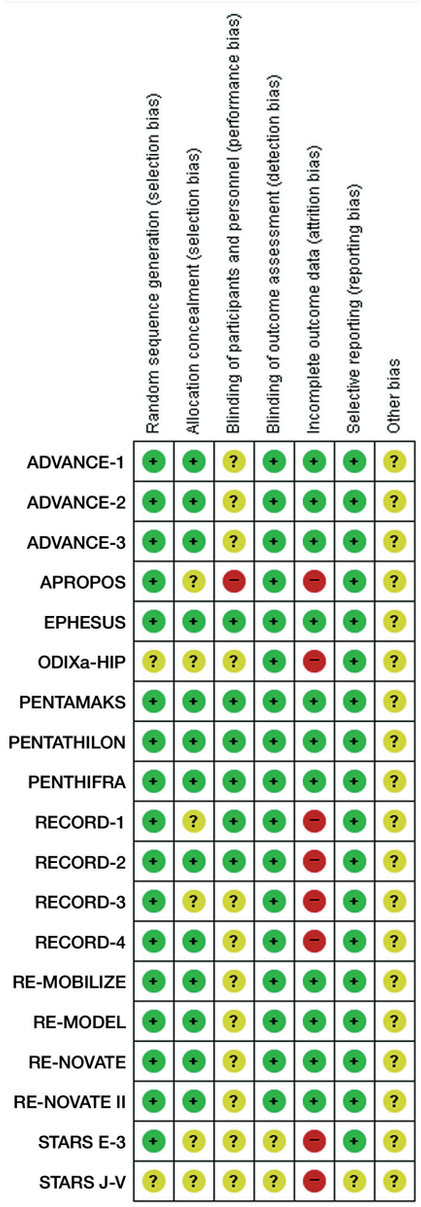

Figure 2. Risk of bias assessment of individual studies.

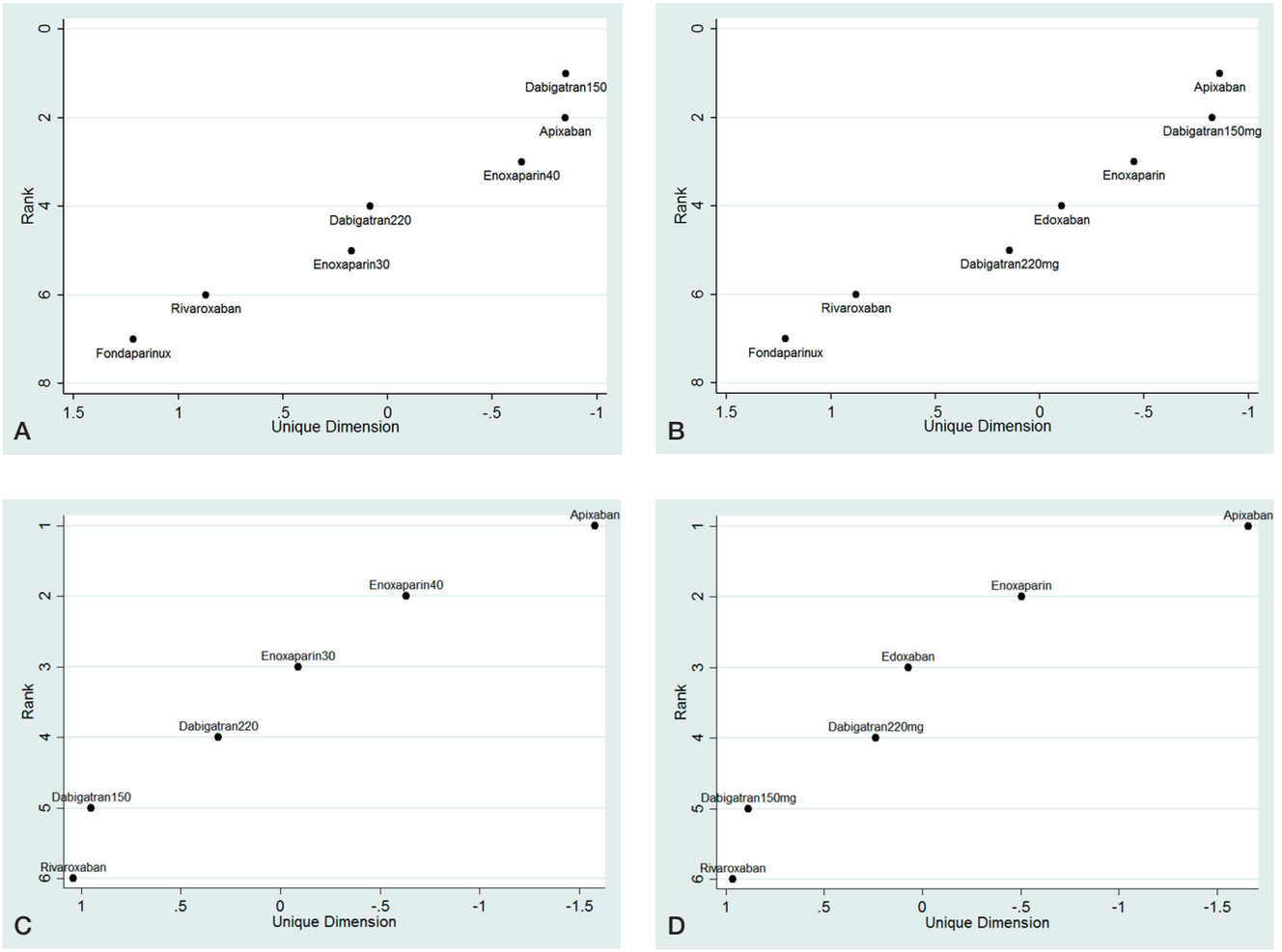

Figure 5. Ranking plots of the anticoagulants network based on the analysis of the surface under the cumulative ranking curve (SUCRA) values for major bleeding and clinically relevant non-major bleeding in the first and second analyses set, respectively. Each dot was located according to the two SUCRA values of each drug for the outcomes. The larger SUCRA values mean the better the rank of the drug regimen. The drug located in the right upper corner has higher SUCRA values for the outcome and is regarded as the preferred of the drugs compared.
A. Sensitivity analysis 1.1. Major bleeding in the first analysis set.
B. Sensitivity analysis 1.2. Major bleeding in the second analysis set.
C. Sensitivity analysis 2.1. Clinically relevant non-major bleeding in the first analysis set.
D. Sensitivity analysis 2.2. Clinically relevant non-major bleeding in the second analysis set.

Search strategies

1. (enoxaparin) OR (low-molecular-weight heparin) OR (fondaparinux) OR (dabigatran) OR (robaroxaban) OR (apixaban) OR (edoxaban) OR (factor Xa) OR (pentasaccharide)
2. ((hip) OR (knee)) AND ((arthroplasty) OR (replacement) OR (prosthe*))
3. (low extremity surgery) OR (orthopedic surgery) OR (orthopaedic surgery)
4. 2 or 3
5. 1 and 4

List of studies included in our network meta-analysis

Bauer K A, Eriksson B I, Lassen M R, Turpie A G. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001; 345 (18): 1305-10.

Eriksson B I, Bauer K A, Lassen M R, Turpie A G. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med 2001; 345 (18): 1298-304.

Eriksson B I, Borris L C, Dahl O E, Haas S, Huisman M V, Kakkar A K, Muehlhofer E, Dierig C, Misselwitz F, Kalebo P. A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. Circulation 2006; 114 (22): 2374-81.

Eriksson B I, Borris L C, Friedman R J, Haas S, Huisman M V, Kakkar A K, Bandel T J, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008; 358 (26): 2765-75.

Eriksson B I, Dahl O E, Huo M H, Kurth A A, Hantel S, Hermansson K, Schnee J M, Friedman R J. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double-blind, non-inferiority trial. Thromb Haemost 2011; 105 (4): 721-9.

Eriksson B I, Dahl O E, Rosencher N, Kurth A A, van Dijk C N, Frostick S P, Kalebo P, Christiansen A V, Hantel S, Hettiarachchi R, Schnee J, Buller H R. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost 2007a; 5 (11): 2178-85.

Eriksson B I, Dahl O E, Rosencher N, Kurth A A, van Dijk C N, Frostick S P, Prins M H, Hettiarachchi R, Hantel S, Schnee J, Buller H R. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet 2007b; 370 (9591): 949-56.

Fuji T, Fujita S, Kawai Y, Nakamura M, Kimura T, Fukuzawa M, Abe K, Tachibana S. Efficacy and safety of edoxaban versus enoxaparin for the prevention of venous thromboembolism following total hip arthroplasty: STARS J-V. Thromb J 2015; 13: 27.

Fuji T, Wang C J, Fujita S, Kawai Y, Nakamura M, Kimura T, Ibusuki K, Ushida H, Abe K, Tachibana S. Safety and efficacy of edoxaban, an oral factor Xa inhibitor, versus enoxaparin for thromboprophylaxis after total knee arthroplasty: the STARS E-3 trial. Thromb Res 2014; 134 (6): 1198-204.

Ginsberg J S, Davidson B L, Comp P C, Francis C W, Friedman R J, Huo M H, Lieberman J R, Muntz J E, Raskob G E, Clements M L, Hantel S, Schnee J M, Caprini J A. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. J Arthroplasty 2009; 24 (1): 1-9.

Kakkar A K, Brenner B, Dahl O E, Eriksson B I, Mouret P, Muntz J, Soglian A G, Pap A F, 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; 372 (9632): 31-9.

Lassen M R, Ageno W, Borris L C, Lieberman J R, Rosencher N, Bandel T J, Misselwitz F, Turpie A G. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008; 358 (26): 2776-86.

Lassen M R, Bauer K A, Eriksson B I, Turpie A G. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. Lancet 2002; 359 (9319): 1715-20.

Lassen M R, Davidson B L, 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; 5 (12): 2368-75.

Lassen M R, Gallus A, Raskob G E, Pineo G, Chen D, Ramirez L M. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Engl J Med 2010a; 363 (26): 2487-98.

Lassen M R, Raskob G E, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet 2010b; 375 (9717): 807-15.

Lassen M R, Raskob G E, Gallus A, Pineo G, Chen D, Portman R J. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med 2009; 361 (6): 594-604.

Turpie A G, Bauer K A, Eriksson B I, Lassen M R. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. Lancet 2002; 359 (9319): 1721-6.

Turpie A G, Lassen M R, Davidson B L, Bauer K A, Gent M, Kwong L M, Cushner F D, Lotke P A, Berkowitz S D, Bandel T J, Benson A, Misselwitz F, Fisher W D. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet 2009; 373 (9676): 1673-80.