Efficacy and safety of rivaroxaban thromboprophylaxis after arthroplasty of the hip or knee: retrospective cohort study

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ABSTRACT

INTRODUCTION Venous thromboembolism (VTE) is a potentially fatal complication of hip arthroplasty and knee arthroplasty. The National Institute for Health and Care Excellence recommend rivaroxaban for VTE prevention. Amid concerns over bleeding complications, the modified thromboprophylaxis policy of Chelsea and Westminster Hospital (CWH; London, UK) advises enoxaparin given after surgery in the inpatient setting followed by rivaroxaban upon hospital discharge. This retrospective study investigated the efficacy and safety of rivaroxaban in this novel, modified venous-prophylaxis regimen in a surgical orthopaedic cohort at CWH.

METHODS A total of 479 patients who received modified thromboprophylaxis treatment at CWH after hip arthroplasty or knee arthroplasty between April 2013 and October 2014 formed the study cohort. Seven outcomes based on efficacy and safety while undergoing treatment with rivaroxaban were investigated: symptomatic deep-vein thrombosis (DVT), pulmonary embolism (PE), death, stroke, myocardial infarction (MI), major bleeding episodes (MBEs) and non-major bleeding episodes (NMBEs). Median follow-up was 369 days. Fisher's exact and Mann–Whitney *U*-tests were adopted to identify associations with these outcomes.

RESULTS Prevalence of symptomatic PE, DVT, death, stroke and MI during treatment was zero. One (0.2%) MBE and nine (1.9%) NMBEs occurred. The MBE (a wound haematoma) required a return to theatre for aspiration. Off-treatment VTEs occurred in four (0.8%) patients after completion of a course of rivaroxaban, and were associated with known risk factors.

CONCLUSIONS Rivaroxaban is an effective and safe anticoagulant for thromboprophylaxis after hip arthroplasty or knee arthroplasty if used in a modified regimen involving enoxaparin administered in the inpatient setting followed by rivaroxaban upon hospital discharge.

KEYWORDS

Venous thromboembolism – Replacement – Arthroplasty – Rivaroxaban – Knee – Hip

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Venous thromboembolism (VTE) is a potentially fatal complication of hip arthroplasty and knee arthroplasty. VTE commonly manifests as deep-vein thrombosis (DVT) and pulmonary embolism (PE).¹ Despite adequate thromboprophylaxis with low-molecular-weight heparin (LMWH) or direct/indirect inhibitors of factor Xa or factor IIa, a meta-analysis involving 44,844 cases found that $\approx 0.5\%$ and $\approx 1\%$ of patients after hip arthroplasty and knee arthroplasty, respectively, suffered symptomatic VTE before hospital discharge.² This prevalence increases ≤ 35 days after surgery, reaching 1.25% for symptomatic DVT and 0.55% for PE on LMWH after major orthopaedic surgery.¹

Rivaroxaban is a direct inhibitor of factor Xa and is given via the oral route. Rivaroxaban was introduced into guidelines set by the UK National Institute for Health and Care Excellence (NICE) in 2009. Rivaroxaban is given for VTE prophylaxis after hip replacement surgery or knee replacement surgery in adults for 35 days or 14 days, respectively.³ NICE

recommended rivaroxaban after four large multicentre phase-III randomised controlled trials (RCTs), RECORD 1–4, showed rivaroxaban to be superior to enoxaparin with regard to efficacy.^{4–7} The composite of DVT, PE and mortality occurred less frequently in patients taking rivaroxaban compared with enoxaparin: 1.1% vs 3.7% after hip arthroplasty⁴ and 9.6% vs 18.9% after knee arthroplasty.⁶ Furthermore, an extended duration of rivaroxaban was more efficacious than short-course enoxaparin,⁵ as was a once-daily regimen of rivaroxaban compared with a twice-daily regimen of enoxaparin.⁷

RCTs present their own limitations with respect to evaluation of the clinical impact of rivaroxaban upon VTE prevention. For example, stringent criteria for patient selection can produce study samples that represent the intended population for the drug inaccurately, thereby compromising the applicability of RCT results to routine practice.⁸ This scenario calls for regular studies to validate their conclusions in real-life

clinical contexts. In the UK, observational studies have primarily investigated rivaroxaban regimens that commence on or within 24 hours of the day of surgery, and have revealed a high prevalence of bleeding and haemorrhagic wound complications relative to LMWH.^{9–11} Consequently, the modified thromboprophylaxis policy of our institution hospital (Chelsea and Westminster Hospital (CWH), London, UK) advises an initial inpatient course of LMWH (s.c.) postoperatively, then switching to rivaroxaban (p.o.) upon hospital discharge. Our single-centre study aimed to investigate the efficacy and safety of rivaroxaban thromboprophylaxis after hip arthroplasty and knee arthroplasty when used as part of this novel, modified anticoagulation regimen in a cohort of surgical orthopaedic patients in the UK.

Methods

This retrospective cohort study was conducted in a 470-bed teaching hospital (CWH) in accordance with the UK Good Clinical Practice code (clinical governance CAPP 924). All adult patients dispensed rivaroxaban (10mg) after elective or emergency, primary or revision, hip arthroplasty or knee arthroplasty between 1 April 2013 and 1 October 2014, were included. Patients not fulfilling these criteria were excluded from the study. Patients were identified using the dispensing records for rivaroxaban of the CWH pharmacy.

Prevalence of seven primary outcomes during rivaroxaban treatment were investigated: imaging-confirmed symptomatic pulmonary embolism (PE), imaging-confirmed symptomatic DVT, myocardial infarction (MI), stroke, death, major bleeding episodes (MBEs), and non-major bleeding episodes (NMBEs). “Major bleeding” was defined in accordance with recommendations from the Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis as a bleed that was fatal, occurred in a critical area or organ, resulted in a fall in haemoglobin of $\geq 20\text{g/l}$, required at least two units of blood transfusion, or a surgical-site bleed necessitating return to theatre for open, arthroscopic or endovascular intervention.¹² “Non-major bleeding” encompassed all other types of bleeding. Secondary outcomes comprised the prevalence of off-treatment PE and DVT after completion of rivaroxaban courses until the end of follow-up.

Demographic data and details of inpatient admission were obtained from electronic records. Data comprised comorbidities, medication history, operative records, blood results, and thromboprophylaxis management. The follow-up period began on the day of hospital discharge (day-1 of the rivaroxaban course) and ended on 1 February 2015 for all patients. It entailed review of all correspondence from orthopaedic clinics, discharge summaries from readmissions, and imaging reports of five investigations if they occurred after rivaroxaban had been initiated: computed tomography of the pulmonary arteries, ultrasound Doppler of the lower limbs, ventilation-perfusion scans, echocardiography and endoscopy of the gastrointestinal tract.

Guidelines for VTE prophylaxis from CWH recommend mechanical thromboprophylaxis in combination with one of two pharmacological options after elective replacement

Table 1 Patient characteristics, procedural information and blood results in the inpatient setting

General	
Female sex – <i>n</i> (%)	293 (61.2)
Age – years median (IQR)	70 (61–75)
Elective – <i>n</i> (%)	446 (93.1)
Duration of stay – days median (IQR)	5 (4–7)
Procedure – <i>n</i> (%)	
Primary hip arthroplasty	247 (51.6)
Primary knee arthroplasty	205 (42.8)
Revision hip arthroplasty	13 (2.7)
Revision knee arthroplasty	14 (2.9)
Medical history – <i>n</i> (%)	
Hypertension	222 (46.3)
Diabetes mellitus	50 (10.4)
Ischaemic heart disease	25 (5.2)
COPD	15 (3.1)
Atrial fibrillation	11 (2.3)
Previous VTE	8 (1.7)
Chronic kidney disease	3 (0.6)
Congestive cardiac failure	1 (0.2)
Medication history – <i>n</i> (%)	
ACEI/ARB	149 (31.1)
Statin	141 (29.4)
Gastric protection	126 (26.3)
CCB	100 (20.9)
Aspirin	48 (10.0)
Thiazide	41 (8.6)
Clopidogrel	6 (1.3)
Anti-retroviral	6 (1.3)
Anticoagulation	0 (0.0)
Blood results upon hospital discharge – median (IQR)	
Haemoglobin – g/l	104 (94.0–113.0)
Platelets – $\times 10^9/\text{l}$	231 (184.8–289.5)
PT – s	10.4 (10.1–10.8)
APTT – s	25.2 (23.6–26.8)
Urea – mmol/l	4.65 (3.6–6.1)
Creatinine – $\mu\text{mol/l}$	68 (60.0–80.8)
eGFR – ml/min/1.73 m ²	84 (70.0–91.0)
Bilirubin – $\mu\text{mol/l}$	11 (8.0–15.0)
Alanine aminotransferase – iU/l	20 (15.0–30.0)

ACEI = angiotensin-converting enzyme inhibitor;
ARB = angiotensin receptor blocker; IQR = interquartile range;
COPD = chronic obstructive pulmonary disease;
PT = prothrombin time;
APTT = activated partial thromboplastin time;
eGFR = estimated glomerular filtration rate;
CCB = calcium channel blocker

of the hip or knee. Option one is rivaroxaban (10mg, once daily (OD)) to start 6–10 hours postoperatively and to continue for 35 days after hip arthroplasty or 14 days after knee arthroplasty. Option two is enoxaparin (40mg OD) to start 6–12 hours postoperatively and to continue for the

remainder of hospital admission. In the latter, enoxaparin is replaced by rivaroxaban (10mg OD) upon hospital discharge to achieve a cumulative duration of anticoagulation of 35 days after hip arthroplasty and 14 days after knee arthroplasty. This particular regimen was chosen by CWH to promote greater compliance with postoperative anticoagulation after the introduction of rivaroxaban into NICE guidelines. The regimen of enoxaparin (s.c.) during inpatient stay was familiar to the clinical team, and so minimised confusion in hospital, whereas switching to rivaroxaban (p.o.) upon hospital discharge meant patients could self-administer rivaroxaban conveniently. The guideline for emergency hip replacement comprised mechanical prophylaxis and enoxaparin (40mg OD) only continuing for 28 days after surgery.

Statistical analyses

SPSS v22.0 (IBM, Armonk, NY, USA) was used for data analyses. Fisher's exact test was used to identify associations between categorical variables and outcomes in view of small

numbers. The Mann-Whitney *U*-test was used to compare continuous variables and outcomes. Data are presented as medians accompanied by interquartile ranges. $p < 0.05$ (two sided) was considered significant.

Results

Four-hundred and seventy-nine patients formed the study cohort (Table 1 and Fig 1). Median follow-up was 369 (range, 116–756) days. All patients (including emergency cases) followed option 2 of the thromboprophylaxis protocol of CWH (Fig 2a and 2b). Routine assessment of VTE and bleeding risk for 477 patients upon hospital admission revealed that 464 had one or more risk factor for VTE and 109 had one or more risk factor for bleeding.

Primary outcomes

VTE, death, stroke or MI did not occur during rivaroxaban treatment. One (0.2%) MBE and nine (1.9%) NMBEs took place on or within 48 hours of stopping rivaroxaban. The

After completion of the rivaroxaban course until the end of follow-up, four (0.8%) off-treatment VTE events were observed (Supplementary Table 3). They consisted of three PEs (0.6%) and one DVT (0.2%) on days 2, 41, 67 and 5, respectively, after stopping rivaroxaban. The PE on day-41 resulted in death. These VTE events were associated with a history of atrial fibrillation ($p=0.003$), chronic kidney disease ($p=0.025$), high platelet count ($p=0.029$), prolonged stay in hospital ($p=0.041$), long treatment course of enoxaparin

Supplementary Table 2 Factors associated with bleeding events on treatment or within 48 hours of stopping rivaroxaban (significant <i>p</i> -values are emboldened)			
	Bleed (<i>n</i>=10)	No bleed (<i>n</i>=469)	<i>p</i>
Female sex – <i>n</i> (%)	6 (60)	287 (61.2)	1.000
Age – years median(IQR)	75 (15)	69 (14)	0.123
Elective – <i>n</i> (%)	10 (100)	436 (93)	1.000
Hip arthroplasty* – <i>n</i> (%)	3 (30)	257 (54.8)	0.198
Duration of stay – days median (IQR)	5 (2)	5 (3)	0.384
Medical history			
Hypertension – <i>n</i> (%)	4 (40)	218 (46.5)	0.758
Diabetes – <i>n</i> (%)	0 (0)	50 (10.7)	0.609
IHD – <i>n</i> (%)	2 (20)	23 (4.9)	0.091
COPD – <i>n</i> (%)	1 (10)	14 (3.0)	0.275
AF – <i>n</i> (%)	0 (0)	11 (2.3)	1.000
Previous VTE – <i>n</i> (%)	1 (10)	7 (1.5)	0.156
CKD – <i>n</i> (%)	0 (0)	3 (0.6)	1.000
CCF – <i>n</i> (%)	0 (0)	1 (0.2)	1.000
Drug history			
ACEI/ARB – <i>n</i> (%)	3 (30)	146 (31.1)	1.000
Statin – <i>n</i> (%)	4 (40)	137 (29.2)	0.490
Gastric protection – <i>n</i> (%)	3 (30)	123 (26.3)	0.727
CCB – <i>n</i> (%)	1 (10)	99 (21.1)	0.696
Aspirin – <i>n</i> (%)	2 (20)	46 (9.8)	0.264
Thiazide – <i>n</i> (%)	2 (20)	39 (8.3)	0.208
Clopidogrel – <i>n</i> (%)	0 (0)	6 (1.3)	1.000
Anti-retroviral – <i>n</i> (%)	1 (10)	5 (1.1)	0.119
Anticoagulation – <i>n</i> (%)	0 (0)	0 (0)	n/a
Blood results upon hospital discharge			
Haemoglobin – g/l, median (IQR)	101.5 (50.55)	104 (19)	0.904
Platelets – $\times 10^9/l$, median (IQR)	245 (120.75)	231 (104.5)	0.668
PT – s, median (IQR)	10.7 (0.6)	10.4 (0.7)	0.275
APTT –s, median (IQR)	23.9 (3.2)	25.2 (3.2)	0.028
Urea – mmol/l, median (IQR)	6.15 (4.33)	4.6 (2.4)	0.094
Creatinine – $\mu\text{mol/l}$, median (IQR)	83.5 (38.5)	68 (20)	0.075
eGFR – ml/min/1.73 m ² , median (IQR)	75.5 (32.75)	84 (21)	0.064
Bilirubin – $\mu\text{mol/l}$, median (IQR)	10 (7)	11 (7)	0.999
ALT – iU/l, median (IQR)	24 (21.25)	20 (15)	0.584
Inpatient thromboprophylaxis			
AES <12 hours, – <i>n</i> (%)	1 (10)	31 (6.6)	0.503
AES 12–24 hours, – <i>n</i> (%)	3 (30)	189 (40.3)	0.747
AES >24 hours – <i>n</i> (%)	1 (10)	48 (10.4)	1.000
AES not administered – <i>n</i> (%)	5 (50)	201 (42.9)	0.751
Enoxaparin <12 hours – <i>n</i> (%)	9 (90)	392 (83.6)	1.000
Enoxaparin 12–24 hours – <i>n</i> (%)	1 (10)	30 (6.4)	0.491

	Bleed (<i>n</i> =10)	No bleed (<i>n</i> =469)	<i>p</i>
Enoxaparin >24 hours – <i>n</i> (%)	0 (0)	46 (9.8)	0.609
Enoxaparin not administered – <i>n</i> (%)	0 (0)	1 (0.2)	1.000
Enoxaparin duration – days median (IQR)	5 (1)	4 (3)	0.575
Outpatient thromboprophylaxis			
Rivaroxaban start day ^o – days median (IQR)	6 (1)	6 (4)	0.653
Rivaroxaban duration (hip) – days median (IQR)	30***	31 (3)	0.510
Rivaroxaban duration (knee) – days median (IQR)	9 (2)	10 (3)	0.278
Total anticoagulation			
Total anticoagulation (hip) – days median (IQR)	35***	35 (1)	0.653
Total anticoagulation (knee) – days median (IQR)	14 (2)	14 (1)	0.110

*Composite of primary and revision hip arthroplasties. ***n*=1 patient so the value is absolute rather than median, no IQR. ****n*=3 patients so the IQR was not available. ^oNumber of days after surgery that rivaroxaban was commenced.

IHD = ischaemic heart disease; COPD = chronic obstructive pulmonary disease; AF = atrial fibrillation; VTE = venous thromboembolism; CKD = chronic kidney disease; CCF = congestive cardiac failure; ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB = calcium channel blocker; PT = prothrombin time; APTT = activated partial thromboplastin time; eGFR = estimated glomerular filtration rate; ALT = alanine aminotransferase; AES = anti-embolism stocking; IQR = interquartile range

(*p*=0.034) and later start day for rivaroxaban (*p*=0.04), whereas an association with previous VTE could not be excluded (*p*=0.065). Despite comorbidities, no patients were taking anticoagulation before hospital admission. Three of these patients did not receive anti-embolism stockings during inpatient admission, but all four were administered enoxaparin within 12 hours of their surgical procedure. One stroke occurred ≈60 days after rivaroxaban completion against a background of atrial fibrillation and previous VTE, and this patient died later. Risk assessment upon hospital admission showed that patients in whom these secondary outcomes occurred had one or two risk factors for VTE.

Discussion

Our study is the first in the UK to investigate the efficacy and safety of rivaroxaban in a modified thromboprophylaxis regimen involving enoxaparin given in the inpatient setting followed by rivaroxaban given in the outpatient setting after hip arthroplasty or knee arthroplasty.

We found no cases of symptomatic VTE (composite of PE and DVT) or death during rivaroxaban treatment. Of ten (2.1%) bleeding events that occurred during or within 48 hours of stopping rivaroxaban, only one (0.2%) was classified as a MBE and necessitated a return to theatre.

Pooled analyses of the four RECORD phase-III trials^{4–7} quoted a prevalence of a composite of symptomatic VTE and all-cause mortality during rivaroxaban treatment to be 0.5%¹⁵ to 0.6%.^{14–16} Bleeding events during or within 48 hours of cessation of rivaroxaban occurred at a prevalence of 7.02%,¹⁷ with MBEs comprising 0.3–0.5%.^{15,14,17} NMBEs took place in 5.6% of patients.¹⁵

After the RECORD RCTs, various studies focused on the efficacy of anticoagulation protocols consisting exclusively of rivaroxaban after hip arthroplasty or knee arthroplasty. In a single-centre prospective study of 206 patients

administered rivaroxaban (10mg) after knee replacement in 2010 in the UK, 1.5% of patients developed symptomatic VTE and 1.9% of patients returned to theatre as a result of wound oozing or haematoma.¹¹ In another single-centre cohort in Dresden (Germany), the prevalence of in-hospital symptomatic VTE was 2.1% among 1,043 patients receiving rivaroxaban (10mg) venous prophylaxis after hip replacement or knee replacement between 2010 and 2011.¹⁸ Prevalence of MBE was 2.9%, which included 0.38% of patients who needed to return to theatre.

Other UK studies have primarily investigated the bleeding risk associated with rivaroxaban if commenced within 24 hours of the surgical procedure, while also reporting on the prevalence of VTE as a secondary outcome. A multi-centre prospective study involving 2,762 patients in the UK taking rivaroxaban after hip arthroplasty or knee arthroplasty identified a prevalence of MBE of 1.05% and a prevalence of wound complications of 3.84%, which included (but was not exclusive to) wound haematoma. Symptomatic VTE at 90 days occurred in 0.72% of cases.¹⁹ In another UK centre of 559 patients taking rivaroxaban compared with 489 patients taking enoxaparin after hip replacement or knee replacement, nine compared with zero patients had to return to theatre as a result of wound haematoma, respectively. PE occurred in 0.9% of patients taking rivaroxaban.⁹ An observational study of 202 patients across two UK centres receiving rivaroxaban after elective hip arthroplasty or knee arthroplasty elicited four patients (2.0%) who had a NMBE in addition to three patients who sustained haematomas (1.5%) that required a return to theatre. No other MBEs, PEs or deaths occurred, but 1% of patients suffered DVT.¹⁰ All of these studies, in which rivaroxaban was commenced in the immediate postoperative period, demonstrated a higher prevalence of bleeding and return to theatre than that obtained with our modified anticoagulation regimen. Therefore, a prospective study is warranted to compare these two protocols directly.

Supplementary Table 3 Factors associated with off-treatment VTE events after completion of a course of rivaroxaban (significant <i>p</i> -values are emboldened)			
	VTE (<i>n</i>=4)	No VTE (<i>n</i>=475)	<i>p</i>
Female sex – <i>n</i> (%)	2 (50)	291 (61.3)	0.644
Age – years median (IQR)	72.5 (25)	70 (14)	0.308
Elective – <i>n</i> (%)	3 (75)	443 (93.3)	0.249
Hip arthroplasty* – <i>n</i> (%)	1 (25)	259 (54.5)	0.336
Duration of stay – days median (IQR)	9.5 (12)	5 (3)	0.041
Medical history			
Hypertension – <i>n</i> (%)	2 (50)	220 (46.3)	1.000
Diabetes mellitus – <i>n</i> (%)	2 (50)	48 (10.1)	0.056
IHD – <i>n</i> (%)	1 (25)	24 (5.1)	0.194
COPD – <i>n</i> (%)	0 (0)	15 (3.2)	1.000
AF – <i>n</i> (%)	2 (50)	9 (1.9)	0.003
Previous VTE – <i>n</i> (%)	1 (25)	7 (1.5)	0.065
CKD – <i>n</i> (%)	1 (25)	2 (0.4)	0.025
CCF – <i>n</i> (%)	0 (0)	1 (0.2)	1.000
Drug history			
ACEI/ARB – <i>n</i> (%)	1 (25)	148 (31.2)	1.000
Statin – <i>n</i> (%)	2 (50)	139 (29.3)	0.585
Gastric protection – <i>n</i> (%)	2 (50)	124 (26.1)	0.284
CCB – <i>n</i> (%)	1 (25)	99 (20.8)	1.000
Aspirin – <i>n</i> (%)	1 (25)	47 (9.9)	0.245
Thiazide – <i>n</i> (%)	0 (0)	41 (8.6)	1.000
Clopidogrel – <i>n</i> (%)	0 (0)	6 (1.3)	1.000
Anti-retroviral – <i>n</i> (%)	0 (0)	6 (1.3)	1.000
Anticoagulation – <i>n</i> (%)	0 (0)	0 (0)	n/a
Blood results upon hospital discharge			
Haemoglobin – g/l, median (IQR)	108 (30)	104 (19)	0.833
Platelets – $\times 10^9/l$, median(IQR)	307 (2.8)	231 (104)	0.029
PT – s, median (IQR)	10.65 (0.85)	10.4 (0.7)	0.635
APTT –s, median (IQR)	23.5 (3.13)	25.2 (3.2)	0.272
Urea – mmol/l, median (IQR)	9.05 (5.35)	4.60 (2.38)	0.06
Creatinine – $\mu\text{mol/l}$, median (IQR)	103 (71.25)	68 (20)	0.212
eGFR – ml/min/1.73 m ² , median (IQR)	68 (54)	84 (21)	0.378
Bilirubin – $\mu\text{mol/L}$ median (IQR)	16.5 (19)	11 (7)	0.229
ALT – iU/L median (IQR)	23 (19.5)	20 (15)	0.667
Inpatient thromboprophylaxis			
AES <12 hours – <i>n</i> (%)	0 (0)	32 (6.7)	1.000
AES 12-24 hours – <i>n</i> (%)	1 (25)	191 (40.1)	0.653
AES >24 hours – <i>n</i> (%)	0 (0)	49 (10.2)	1.000
AES not administered – <i>n</i> (%)	3 (75)	203 (42.7)	0.319
Enoxaparin <12 hours – <i>n</i> (%)	4 (100)	397 (83.6)	0.100
Enoxaparin 12–24 hours – <i>n</i> (%)	0 (0)	31 (6.5)	1.000

	VTE (n=4)	No VTE (n=475)	p
Enoxaparin >24 hours – n (%)	0 (0)	46 (9.7)	1.000
Enoxaparin not administered – n (%)	0 (0)	1 (0.2)	1.000
Enoxaparin duration – median days (IQR)	9.5 (10)	4 (3)	0.034
Outpatient thromboprophylaxis			
Rivaroxaban start day ^o –day median (IQR)	10.5 (10)	6 (5)	0.04
Rivaroxaban duration (hip) – days (IQR)	16**	31 (3)	0.1
Rivaroxaban duration (knee) – days median (IQR)	11***	10 (3)	0.933
Total anticoagulation			
Total anticoagulation (hip) –days(IQR)	33**	35(1)	0.118
Total anticoagulation (knee) – days median (IQR)	15***	14 (1)	0.333

*Composite of primary and revision hip arthroplasty. **n=1 patients so the value is absolute rather than median, no IQR. ***n=3 patients so the IQR was not available. ^oNumber of days after surgery that rivaroxaban was commenced.
IHD = ischaemic heart disease; COPD = chronic obstructive pulmonary disease; AF = atrial fibrillation; VTE = venous thromboembolism; CKD = chronic kidney disease; CCF = congestive cardiac failure; ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB = calcium channel blocker; PT = prothrombin time; APTT = activated partial thromboplastin time; eGFR = estimated glomerular filtration rate; ALT = alanine aminotransferase; AES = anti-embolism stocking; IQR = interquartile range

Our secondary outcome, off-treatment VTE events, occurred in patients with known risk factors, including atrial fibrillation and previous VTE. Major orthopaedic surgery alone conveys a high risk of VTE,¹ and our findings highlight the importance of caring for patients with additional risk factors for thromboembolism on an individual basis. Thus, attention is drawn to the poor compliance with anti-embolism stockings observed in the present study as a preventable aetiological factor in these patients. Furthermore, The ROCKET-AF²⁰ and EINSTEIN-extension²¹ studies have shown the efficacy of rivaroxaban (20mg) as another solution for patients with atrial fibrillation or a history of VTE, respectively, and have attained NICE approval.^{22,23} Longer durations of hospital stay are also known to contribute to VTE by reducing patient mobility,^{24,25} observations that are consistent with the findings from our cohort. Due to the nature of the CWH guidelines for thromboprophylaxis, these longer durations of admission translated to anticoagulation regimens comprising proportionally more enoxaparin relative to rivaroxaban, which provides one explanation why VTE was also associated with longer courses of enoxaparin and later start dates of rivaroxaban. Though they themselves may be a possible cause, the confounding impact exerted by reduced ambulation in these patients negates the clinical validity of independent conclusions that can be drawn. Finally, chronic kidney disease and higher platelet counts upon hospital discharge were also found in VTE patients. Chronic kidney disease is a well-cited aetiological factor,²⁶ whereas increased platelet counts can contribute to thrombosis through an increase in blood viscosity (one of the three constituents of Virchow's triad). This phenomenon is seen in chronic myeloproliferative disorders, including essential thrombocythaemia.²⁷ A larger study cohort is needed to confirm the relevance of the associations identified in our study, particularly for bleeding events (in which the association

with lower APTT values shown in our cohort contradicts those from other studies).

To appreciate fully the clinical importance of the comparably low prevalence of symptomatic VTE and bleeding in our cohort, the seven main limitations of the present study must be considered carefully. First, the study focused on the efficacy and safety of rivaroxaban only in a modified thromboprophylaxis regimen that comprised enoxaparin and rivaroxaban. Only primary outcomes that occurred after hospital discharge were measured because this was when rivaroxaban was commenced. Prevalence of outcomes during inpatient stay (while patients were on enoxaparin) was not measured. Second, data on thromboprophylaxis in the inpatient setting were extracted from electronic prescribing records. Such records detail the prevalence of administration of prescribed medications, but such treatments may have been administered without prescription. This phenomenon could account for the low prevalence of use of anti-embolism stockings seen in our study. Third, all patients were prescribed and dispensed rivaroxaban, but the prevalence of patient compliance was not determined. Fourth, the end of follow-up was fixed at 1 February 2015, so the duration of follow-up varied between patients (which could have accounted for some of the unavailable clinic letters). Fifth, readmissions to our hospital were a key component of follow-up, but we did not take into account presentations to (or investigations at) other hospitals, which was a potential source of missed outcomes. Sixth, patients received enoxaparin and rivaroxaban at different points of their thromboprophylaxis course, so attributing the causes of adverse events to a specific treatment was difficult. Finally, statistical associations were found using appropriate tests, but the clinical relevance of such findings (and the importance of subsequent conclusions) were difficult to determine because of the small numbers of outcomes observed.

Many of these limitations were secondary to the retrospective nature of this study. Consequently, the sources used for data collection were not tailored specifically towards the outcomes of this study.

Conclusions

Our retrospective cohort study showed a modified thromboprophylaxis regimen of rivaroxaban taken in the outpatient setting following enoxaparin taken in the inpatient setting to be an effective and safe option after hip arthroplasty or knee arthroplasty. Prevalence of on-treatment symptomatic VTE, mortality and bleeding was lower than that reported in similar UK studies of rivaroxaban-exclusive thromboprophylaxis courses. Our findings call for greater vigilance in ensuring compliance with mechanical thromboprophylaxis if contraindications are absent, particularly in patients with pre-existing risk factors who are likely to require individualised thromboprophylaxis regimens.

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