

ORIGINAL REPORT

# Safety and efficacy of new oral anticoagulants and low-molecular-weight heparins compared with aspirin in patients undergoing total knee and hip replacements

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## ABSTRACT

**Background** There has been much debate recently on the best type of thromboprophylaxis following elective total joint replacement surgery.

**Objective** This study aims to compare rates of venous thromboembolism (VTE), gastro-intestinal (GI) bleeding and mortality events, with use of new oral anticoagulants (NOAC) or low-molecular-weight heparins (LMWHs) compared with aspirin in patients undergoing total joint replacement.

**Methods** A population-based retrospective cohort study was performed using the Clinical Practice Research Datalink. Patients  $\geq 18$  years of age who had undergone total knee ( $n = 3261$ ) or hip replacement (THR ( $n = 4016$ )) between 2008 and 2012 were included. Within this population, three cohorts were selected, based on their first prescription within the 35-day period after surgery: use of NOACs only, LMWHs only and aspirin only. Incidence rates were calculated, and Cox proportional hazard models were fitted to estimate the risk of VTE, GI bleeding and all-cause mortality with the use of NOACs and LMWHs compared with aspirin use after total knee replacement and THR. We statistically adjusted our analyses for lifestyle factors, comorbidities and concomitant drug use.

**Results** Total knee replacement and THR patients currently on LMWHs had higher risk of VTE (HR = 17.2 (6.9–43.0) and HR = 39.5 (18.0–87.0), respectively), GI bleeding (HR = 20.9 (1.9–232.3) and HR = 2.0 (0.2–17.2), respectively) and all-cause mortality (HR = 4.3 (1.7–12.4) and HR = 4.0 (2.4–6.7), respectively). NOAC use was associated with an increased risk of GI bleeding in patients undergoing THR surgery.

**Conclusions** In contrast to previous studies, we found an increased risk of VTE, GI bleeding and all-cause mortality with the use of LMWHs compared with aspirin. Risk of GI bleeding was increased with the use of NOACs compared with aspirin use after THR surgery. Copyright © 2016 John Wiley & Sons, Ltd.

**KEY WORDS**—new oral anticoagulants; aspirin; low-molecular-weight heparins; GI bleeding; venous thromboembolism; mortality; epidemiology; pharmacoepidemiology

Received 16 February 2016; Revised 26 July 2016; Accepted 7 August 2016

## INTRODUCTION

Osteoarthritis (OA) is the most prominent cause of pain and disability in the UK.<sup>1</sup> Based on 7-year

consultation prevalence in general practice, an estimated 8.75 million people have sought treatment for pain associated with OA. This is one-third of the people aged 45 years and over in the UK.<sup>1</sup> Between 1990 and 2010, in the UK, the prevalence of disability due to OA increased by 15%.<sup>2</sup> Total joint replacements (TJR), such as total hip replacement (THR) or total knee replacement (TKR), substantially improve

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quality of life in these patients.<sup>3</sup> However, potentially fatal venous thromboembolic (VTE) events may occur in up to 4.3% following this drastic surgical procedure.<sup>4</sup> Intensive antithrombotic treatment up to 35 days has therefore been suggested, but this may in turn result into life-threatening major bleedings such as gastro-intestinal (GI) bleeding and haemorrhagic stroke.<sup>4</sup> Clinical trials have reported a major bleeding incidence of approximately 2% following THR or TKR surgery.<sup>5</sup>

There has been much debate recently on the best type of thromboprophylaxis following THR or TKR surgery, in particular in terms of bleeding risk.<sup>6–9</sup> Low-molecular-weight heparins (LMWHs) have gained popularity over the past decades but can only be administered subcutaneously. The recently introduced direct thrombin inhibitors and direct factor Xa inhibitors (e.g. dabigatran and rivaroxaban) combine advantages of vitamin K antagonists, aspirin (a platelet aggregation inhibitor) and LMWHs. They can be orally administered and do not require international normalised ratio monitoring. Several randomised controlled trials (RCT) studying the safety and efficacy profiles of these new oral anticoagulants (NOACs) compared with LMWHs have been conducted. However, there is limited information on the safety profile of NOAC and LMWH use compared with aspirin in real practice. Although, on average, aspirin is used as antithrombotic therapy in 14% of TJR surgeries, this has not been extensively evaluated.<sup>10</sup> Currently, clinicians cannot evaluate an individual patient's risk of major bleeding when they undergo THR or TKR surgery. It is therefore important to address long-term safety in a population-based setting.

The aim of this study was to compare rates of VTE events, GI bleeding events and mortality, with the use of NOACs or LMWHs compared with aspirin in patients undergoing THR or TKR surgery. We hypothesised that NOAC and LMWH use would be associated with more bleeding, but less thrombotic events.

## METHODS

The study protocol was approved by the Independent Scientific Advisory Committee, protocol number: 13\_218R.

### *Data source*

A population-based retrospective cohort study was performed using the Clinical Practice Research Datalink (CPRD). CPRD collates the computerised

medical records of general practitioners (GP). GPs play a key role in the UK healthcare system, as they are responsible for primary healthcare and specialist referrals. Patients are semi-permanently affiliated with a practice that centralises the medical information from the GPs, specialist referrals and hospitalisations. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and major outcomes.

### *Study population*

The study population comprised all patients aged 18 years or older who underwent a primary THR or TKR surgery from January 2008 until 31 October 2012. This time frame was chosen because NOACs have been registered for anticoagulant therapy after TKR and THR in Europe since 2008. The date of THR or TKR surgery was selected as index date. Each patient was then followed until the end of valid of data collection (a patient's transfer out of practice or 1 November 2012), the date of death or when an outcome of interest occurred. When death was considered an outcome of interest, it was not part of the definition of censoring. Patients with documented pregnancy in the year prior to surgery were excluded from analysis (Figure 1).

### *Exposure*

Three cohorts were selected, based on their first prescription within the 35-day period after surgery: use of NOACs (direct thrombin inhibitors/direct factor Xa inhibitors) only, LMWHs only and aspirin only. Patients without identified drug use, due to missing data on thromboprophylaxis, were excluded. Concomitant use of NOACs and aspirin was categorised as NOAC use. Concomitant use of LMWHs and aspirin was categorised as LMWH use. This classification was chosen because it is more likely that in these cases, the exposure to NOACs or LMWHs is associated with TJR, whereas the aspirin prescription was either additional or for another indication. Exposure to both a NOAC and a LMWH is highly unlikely. Therefore, patients with concomitant use of these drugs any time during follow-up were also excluded. Patients with a NOAC, LMWH or an aspirin prescription 6 months prior to TJR were excluded (Figure 1). In addition to product codes, we used anonymised free text recordings during the 10 days before/after surgery. This time window was based on the mean duration of hospital stays after TJRs, as reported in the National Registry of Hospitalisations of England

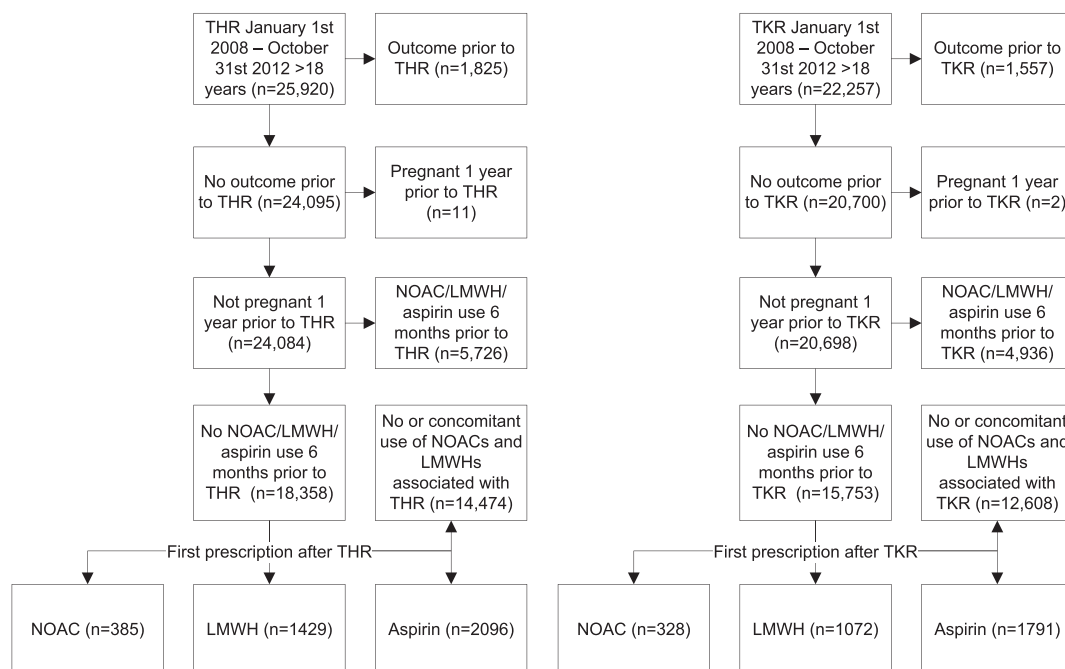


Figure 1. Flowchart depicting the selection of the study population. THR, total hip replacement; TKR, total knee replacement; LMWH, low-molecular-weight heparin; NOAC, new oral anticoagulant

(2008–2013).<sup>11</sup> Use of anonymised free text has previously proven to be an effective method to increase detection rate of exposure to hospital-prescribed medications.<sup>12</sup> We expected that the duration of initial thromboprophylaxis would take either 14 days (TKR) or 35 days (THR) based on the summary of product characteristics. Exposure was classified as a time-dependent variable, that is, it could vary over follow-up time. At the start of each 7-day period, exposure to a thromboprophylactic drug in the 14 days (TKR) or 35 days (THR) prior to this period was assessed. Exposure within this period was classified as current use. When the prescription was not renewed within 7 days after its estimated date of cessation, a patient became a past user. When a new prescription was received, a past user became a current user again.

### Outcomes

All patients were followed up until the occurrence of GI bleeding (Table S1), VTE (Table S2) or all-cause mortality. Patients with a documented history of these outcomes, except all-cause mortality, were excluded from analysis (Figure 1).

### Covariates

Risk factors for each outcome were identified based on literature and used as potential confounders. Potential

confounders were assessed in a time-dependent manner, with the exception of smoking status, body mass index (BMI), socio-economic status (SES) and alcohol use. We divided total follow-up into 7-day intervals. Information on time-dependent potential confounders was determined at the start of each time interval. All variables were treated as categorical variables (with the exception of age), and we used dummy indicator variables to account for missing data.

Covariates per outcome:

#### (1) *Gastrointestinal bleeding*

Age and sex; presence of GI ulcers, gastritis, duodenitis, oesophagitis, oesophageal and gastric varices, and atrial fibrillation in the entire previous history; and use of antithrombotic agents (vitamin K antagonists and antiplatelet drugs), use of non-steroidal anti-inflammatory drugs, use of systemic glucocorticoids, use of selective serotonin reuptake inhibitors, use of antihypertensives, use of statins, use of antidiabetics and use of acid suppressants (PPIs or histamine-2 receptor antagonists) in the previous 6 months.

#### (2) *Venous thromboembolism (VTE)*

Age, sex, SES, smoking status and BMI; presence of varicose veins, inflammatory bowel disease, fractures, heart failure, ischemic stroke, cerebrovascular diseases, atrial fibrillation, cancer and chronic

obstructive pulmonary disease in the entire previous history; and use of hormone replacement therapy, use of tamoxifen, use of anticoagulants (vitamin K antagonists, antiplatelet drugs (aspirin excluded)), use of non-steroidal anti-inflammatory drugs and use of contraceptives in the previous 6 months.

### (3) *All-cause mortality*

Age, sex, SES, BMI, smoking status and alcohol use; presence of cancer, chronic obstructive pulmonary disease, pneumonia, cardiovascular disease and cerebrovascular disease in the entire previous history; and use of antidiabetics, use of statins, use of antihypertensives and use of antibiotics in the previous 6 months.

### *Statistical analysis*

Person-years (PY) of follow-up were calculated by adding all person-time from the start date to either the date of outcome or to the date of censoring, if no outcome had occurred. The incidence rates (IR) of the outcomes were estimated as the number of events per 1000 PY. In case of sufficient amount of events, time-varying Cox proportional hazard models were used to estimate the hazard ratios (HRs) for outcomes with past, or current use of LMWHs, and NOACs compared with current aspirin use. HRs were adjusted, in a time-dependent manner, for age, sex and potential confounders, as specified per outcome in the previous section, which showed a >5% change in the beta-coefficient of current use, or when consensus about inclusion existed within the team of researchers, supported by clinical evidence from literature. In the case of insufficient number of events, categories were combined (e.g. past NOAC users were combined with current NOAC users). In the case of insufficient number of events, we were unable to conduct analyses adjusted by more than two confounders (age and sex). Sensitivity analyses were conducted taking into account VTE events occurring >30 days after surgery only.

## RESULTS

Baseline characteristics of THR (NOAC:  $n=385$ ; LMWH:  $n=1429$ ; aspirin:  $n=2096$ ) and TKR patients (NOAC:  $n=328$ ; LMWH:  $n=1072$ ; aspirin:  $n=1791$ ) are presented in Table 1. NOACs were prescribed to relatively young patients, whereas aspirin was prescribed to a relatively older group of patients. Between 62.0% and 62.6% of the THR patients and between 55.3% and 61.6% of the TKR were women. In both the TKR and the THR patients, aspirin users were

more likely to have been diagnosed with previous comorbidities and consequently used more drugs.

GI bleedings occurred more often in patients currently on thromboprophylaxis when compared with patients who had stopped using thromboprophylaxis or patients without documented use of thromboprophylaxis (Table 2). IRs of GI bleeding in THR and TKR patients currently on thromboprophylaxis were 4.6 and 4.5 per 1000 PY, respectively. In the THR group, GI bleedings mostly occurred with the use of NOACs (IR = 22.1/1000 PY; HR = 9.4 (confidence interval (CI) = 1.1–82.0)). In the TKR patients, events mostly occurred with the use of LMWHs (IR = 31.9/1000 PY; HR = 20.9 (CI = 1.9–232.3)). In past users, the differences were not statistically significant.

Venous thromboembolics occurred more often in patients currently on thromboprophylaxis when compared with patients who had stopped using thromboprophylaxis (Table 3). IRs of VTE in THR and TKR patients currently on thromboprophylaxis were 31.1 and 45.4 per 1000 PY, respectively. In the THR group, these VTEs mostly occurred with the use of LMWHs (IR = 260.2/1000 PY; adjusted HR = 39.5 (CI = 18.0–87.0)). In the TKR patients, VTEs mostly occurred with the use of LMWHs (IR = 402.9/1000 PY; adjusted HR = 17.2 (CI = 6.9–43.0)). Sensitivity analyses only taking VTE events occurring >30 days after surgery into account revealed similar results when compared with the primary analyses (Table S3) in THR patients. In THR patients, IR of VTE with current use of LMWHs was 187.5/1000 PY, and adjusted HR was 30.6 (CI = 13.3–70.4)). In the TKR patients, IR of VTE with current use of LMWHs was 548.2/1000 PY, and adjusted HR was 51.2 (CI = 13.1–200.4)). Patients currently on thromboprophylaxis died more often when compared with patients who had stopped using thromboprophylaxis (Table 4). IRs of all-cause mortality in THR and TKR patients currently on thromboprophylaxis were 47.1 and 32.9 per 1000 PY, respectively. In the THR group, all-cause mortality mostly occurred with the current use of LMWHs (IR = 106.7/1000 PY; adjusted HR = 4.0 (CI = 2.4–6.7)). In the TKR patients, all-cause mortality mostly occurred with the use of LMWHs (IR = 79.3/1000 PY; adjusted HR = 4.5 (CI = 1.7–12.4)).

## DISCUSSION

This study shows that TKR and THR patients currently on LMWHs had higher IRs of VTE and all-cause mortality compared with current aspirin users. Moreover, risk of VTE and all-cause mortality was



Table 1. Baseline characteristics of patients using NOACs, LMWHs or aspirin associated with total hip and knee replacements

Characteristic	Total hip replacement			Total knee replacement		
	NOAC	LMWH	Aspirin	NOAC	LMWH	Aspirin
Characteristic	<i>n</i> = 385 (%)	<i>n</i> = 1429 (%)	<i>n</i> = 2096 (%)	<i>n</i> = 328 (%)	<i>n</i> = 1072 (%)	<i>n</i> = 1791 (%)
Follow-up (mean; <i>y</i> (SD))	1.6 (1.1)	2.2 (1.3)	2.7 (1.3)	1.7 (1.0)	2.3 (1.4)	2.9 (1.3)
Age (mean; <i>y</i> (SD))	66.7 (11.3)	68.5 (11.6)	70.9 (11.7)	68.0 (9.3)	67.9 (10.0)	69.6 (9.6)
Females (%)	241 (62.6)	893 (62.5)	1300 (62.0)	202 (61.6)	653 (60.9)	990 (55.3)
Socio-economic status						
Low	66 (17.1)	233 (16.3)	274 (13.1)	61 (18.6)	182 (17.0)	212 (11.8)
Low-medium	61 (15.8)	253 (17.7)	266 (12.7)	65 (19.8)	188 (17.5)	235 (13.1)
Medium	45 (11.7)	212 (14.8)	196 (9.4)	43 (13.1)	188 (17.5)	189 (10.6)
Medium-high	30 (7.8)	141 (9.9)	143 (6.8)	17 (5.2)	87 (8.1)	158 (8.8)
High	22 (5.7)	111 (7.8)	90 (4.3)	22 (6.7)	70 (6.5)	105 (5.9)
Missing	161 (41.8)	479 (33.5)	1127 (53.8)	120 (36.6)	357 (33.3)	892 (49.8)
Body mass index, most recent prior to index date (mean. kg/m <sup>2</sup> [SD])	28.2 (5.7)	27.6 (5.4)	27.1 (5.1)	29.8 (5.4)	30.1 (5.7)	29.8 (5.4)
<20.0 kg/m <sup>2</sup>	108 (28.1)	449 (31.4)	699 (33.3)	55 (16.8)	183 (17.1)	328 (18.3)
20.0–24.9 kg/m <sup>2</sup>	120 (31.2)	496 (34.7)	752 (35.9)	120 (36.6)	380 (35.4)	647 (36.1)
25.0–29.9 kg/m <sup>2</sup>	97 (25.2)	266 (18.6)	391 (18.7)	89 (27.1)	257 (24.0)	478 (26.7)
>30.0 kg/m <sup>2</sup>	37 (9.6)	127 (8.9)	140 (6.7)	51 (15.5)	214 (20.0)	277 (15.5)
Missing	23 (6.0)	91 (6.4)	114 (5.4)	13 (4.0)	38 (3.5)	61 (3.4)
Alcohol consumption						
Yes	285 (74.0)	1087 (76.1)	1485 (70.8)	264 (80.5)	794 (74.1)	1295 (72.3)
No	74 (19.2)	225 (15.7)	475 (22.7)	51 (15.5)	224 (20.9)	402 (22.4)
Unknown	26 (6.8)	117 (8.2)	136 (6.5)	13 (4.0)	54 (5.0)	94 (5.2)
Smoking status						
Non-smoker	159 (41.3)	698 (48.8)	951 (45.4)	159 (48.5)	490 (45.7)	804 (44.9)
Ex-smoker	165 (42.9)	544 (38.1)	907 (43.3)	149 (45.4)	477 (44.5)	811 (45.3)
Current smoker	61 (15.8)	185 (12.9)	237 (11.3)	20 (6.1)	104 (9.7)	176 (9.8)
Unknown	0 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Drug use in the 6 months prior to index date (%)						
VKA	5 (1.3)	130 (9.1)	87 (4.2)	6 (1.8)	106 (9.9)	65 (3.6)
Antiplatelet (excluding aspirin)	5 (1.3)	32 (2.2)	188 (9.0)	7 (2.1)	29 (2.7)	146 (8.2)
Antihypertensives	173 (44.9)	635 (44.4)	1205 (57.5)	153 (46.6)	555 (51.8)	1105 (61.7)
Statins	86 (22.3)	321 (22.5)	764 (36.5)	92 (28.0)	316 (29.5)	733 (40.9)
Antidiabetics	21 (5.5)	77 (5.4)	123 (5.9)	18 (5.5)	81 (7.6)	136 (7.6)
PPI	131 (34.0)	483 (33.8)	915 (43.7)	131 (39.9)	423 (39.5)	840 (46.9)
H2RA	11 (2.9)	41 (2.9)	93 (4.4)	9 (2.7)	43 (4.0)	71 (4.0)
Tamoxifen	4 (1.0)	5 (0.3)	4 (0.2)	4 (1.2)	9 (0.8)	5 (0.3)
SSRI's	30 (7.8)	108 (7.6)	185 (8.8)	23 (7.0)	80 (7.5)	160 (8.9)
Systemic corticosteroids	21 (5.5)	92 (6.4)	126 (6.0)	16 (4.9)	73 (6.8)	121 (6.8)
NSAIDs	159 (41.3)	570 (39.9)	755 (36.0)	138 (42.1)	472 (44.0)	718 (40.1)
NSAIDs COX-selective	13 (3.4)	51 (3.6)	73 (3.5)	15 (4.6)	45 (4.2)	66 (3.7)
NSAIDs non-selective	151 (39.2)	537 (37.6)	699 (33.3)	123 (37.5)	439 (41.0)	669 (37.4)
Antibiotics	102 (26.5)	482 (33.7)	693 (33.1)	112 (34.1)	429 (40.0)	603 (33.7)
Contraceptives	1 (0.3)	9 (0.6)	3 (0.1)	0 (0.0)	3 (0.3)	1 (0.1)
Hormone replacement therapy	12 (3.1)	30 (2.1)	31 (1.5)	3 (0.9)	40 (3.7)	28 (1.6)
Comorbidities ever before index date (%)						
Cancer	1 (0.3)	21 (1.5)	15 (0.7)	0 (0.0)	6 (0.6)	15 (0.8)
GI ulcers	11 (2.9)	55 (3.8)	97 (4.6)	16 (4.9)	64 (6.0)	98 (5.5)
Gastric and oesophageal varices	1 (0.3)	1 (0.1)	2 (0.1)	0 (0.0)	3 (0.3)	0 (0.0)
Oesophagitis	35 (9.1)	129 (9.0)	169 (8.1)	37 (11.3)	113 (10.5)	186 (10.4)
Gastritis/duodenitis	31 (8.1)	85 (5.9)	148 (7.1)	25 (7.6)	79 (7.4)	143 (8.0)
Varicose veins	65 (16.9)	220 (15.4)	331 (15.8)	55 (16.8)	202 (18.8)	315 (17.6)
IBD	11 (2.9)	18 (1.3)	24 (1.1)	3 (0.9)	19 (1.8)	21 (1.2)
Fractures	115 (29.9)	463 (32.4)	812 (38.7)	77 (23.5)	317 (29.6)	477 (26.6)
Atrial fibrillation	13 (3.4)	83 (5.8)	186 (8.9)	7 (2.1)	65 (6.1)	128 (7.1)
Heart failure	5 (1.3)	30 (2.1)	62 (3.0)	2 (0.6)	25 (2.3)	62 (3.5)
Ischemic stroke	0 (0.0)	7 (0.5)	34 (1.6)	1 (0.3)	5 (0.5)	22 (1.2)
Cerebrovascular diseases	8 (2.1)	49 (3.4)	199 (9.5)	9 (2.7)	36 (3.4)	136 (7.6)
COPD	18 (4.7)	96 (6.7)	110 (5.2)	11 (3.4)	66 (6.2)	111 (6.2)
Pneumonia	11 (2.9)	45 (3.1)	84 (4.0)	13 (4.0)	27 (2.5)	62 (3.5)

NOAC, new oral anticoagulants; LMWHs, low-molecular-weight heparins; SD, standard deviation; VKA, vitamin K antagonist; SSRI, selective serotonin re-uptake inhibitor; NSAID, non-steroidal anti-inflammatory drug; IBD, inflammatory bowel disease; COPD, chronic obstructive pulmonary disease.

Table 2. Risk of GI bleeding following thromboprophylaxis after total hip and knee replacement surgeries

	Total hip replacement			Total knee replacement		
	GI bleeding IR (per 1000 PY)	Age/sex adjusted HR (95%CI)	Fully adjusted HR (95%CI)	GI bleeding IR (per 1000 PY)	Age/sex adjusted HR (95%CI)	Fully adjusted HR (95%CI)
No thromboprophylaxis	1.9	0.6 (0.1–2.7)	—	3.6	1.5 (0.2–12.9)	—
Past thromboprophylaxis	1.6	0.6 (0.2–1.8)	—	3.8	2.3 (0.3–17.1)	—
By type of thromboprophylaxis						
NOAC	1.7	1.0 (0.1–8.9)	—	7.3	5.7 (0.6–51.6)*	—
LMWH	2.0	0.7 (0.2–2.6)	—	2.4	1.6 (0.2–13.2)	—
Aspirin	1.3	0.5 (0.1–1.8)	—	4.2	2.4 (0.3–17.8)	—
Current thromboprophylaxis	4.6	—	—	4.5	—	—
By type of thromboprophylaxis						
NOAC	22.1	9.4 (1.1–82.0)	—	0.0	—	—
LMWH	5.3	2.0 (0.2–17.2)	—	31.9	20.9 (1.9–232.3)	—
Aspirin	3.9	Referent	—	1.7	Referent	—

\*Includes person time of current NOAC users because of lack of events in current NOAC group.

CI, confidence interval; GI, Gastro-intestinal; IR, incidence rate; HR, hazard ratio; NOAC, new oral anticoagulant; LMWH, low-molecular-weight heparin.

Table 3. Risk of VTE following thromboprophylaxis after total hip and knee replacement surgeries

	Total hip replacement			Total knee replacement		
	VTE IR (per 1000 PY)	Age/sex adjusted HR (95%CI)	Fully adjusted HR (95%CI) <sup>†</sup>	VTE IR (per 1000 PY)	Age/sex adjusted HR (95%CI)	Fully adjusted HR (95%CI) <sup>‡</sup>
No thromboprophylaxis	56.7	9.3 (4.5–19.5)	10.1 (4.8–21.5)	53.3	3.6 (1.6–7.8)	3.5 (1.6–7.6)
Past thromboprophylaxis	9.4	1.5 (0.7–3.1)	1.5 (0.7–3.3)	13.0	0.9 (0.4–2.0)	0.9 (0.4–2.0)
By type of thromboprophylaxis						
NOAC	1.7	0.3 (0.0–2.7)	0.4 (0.0–3.0)	3.6	0.3 (0.1–1.5)*	0.3 (0.1–1.4)*
LMWH	11.4	1.5 (0.7–3.4)	1.6 (0.7–3.6)	15.1	1.1 (0.5–2.5)	1.0 (0.4–2.3)
Aspirin	9.1	1.6 (0.7–3.4)	1.6 (0.7–3.6)	13.1	0.9 (0.4–2.1)	1.0 (0.4–2.2)
Current thromboprophylaxis	31.1	—	—	45.4	—	—
By type of thromboprophylaxis						
NOAC	22.1	4.4 (0.6–35.5)	4.7 (0.6–37.9)	0.0	—	—
LMWH	260.2	39.2 (18.0–85.0)	39.5 (18.0–87.0)	402.9	18.9 (7.6–46.9)	17.2 (6.9–43.0)
Aspirin	6.0	Referent	Referent	12.3	Referent	Referent

\*Includes person time of current NOAC users due to lack of events in current NOAC group.

<sup>†</sup>Adjusted for age and sex. Drug use in previous 6 months: vitamin K antagonists.

<sup>‡</sup>Adjusted for age, sex and socio-economic status. Drug use in previous 6 months: vitamin K antagonists, antiplatelets.

VTE, venous thromboembolic events; IR, incidence rate; HR, hazard ratio; NOAC, new oral anticoagulant; LMWH, low-molecular-weight heparin.

significantly higher in current LMWH users compared with current aspirin users. TKR patients currently on LMWHs had a higher risk of GI bleedings compared with patients currently on aspirin, whereas THR patients currently on LMWHs had a similar risk compared with patients currently on aspirin. THR patients currently on NOACs had a higher risk of GI bleedings, but a similar risk of VTE compared with current aspirin users.

To our knowledge, safety and efficacy of NOACs and LMWHs compared with aspirin after TJR have previously been assessed in three studies. One observational study ( $n=258$ ) and two ( $n=120$  and  $n=324$ ) RCT have been reported on this subject. No significant differences in the incidence of VTE or major bleeding were found in the studies by Jiang *et al.*,<sup>13</sup> and Sindali *et al.*,<sup>14</sup> A lower incidence of deep venous thrombosis with the use of rivaroxaban compared with LMWH or

aspirin use was reported in the study by Zou *et al.*,<sup>15</sup> Traditional meta-analyses and indirect network meta-analyses of RCTs addressing the safety and efficacy of NOACs compared with LMWHs generally presented similar or better safety and efficacy of NOACs compared with LMWHs.<sup>16–18</sup> However, it should be mentioned that low-dose (150 mg daily) dabigatran was associated with an increased risk of VTE compared with enoxaparin<sup>16</sup> and rivaroxaban was associated with an increased risk of bleeding.<sup>17</sup> Finally, mortality rates are similar in NOAC users compared with LMWH users.<sup>16–18</sup>

The present study has several strengths. This is the first study addressing the safety and efficacy of NOACs and LMWHs compared with aspirin use in a large population-based database. This enabled us to assess the risk of VTE, GI bleeding and all-cause mortality associated with NOAC and LMWH use

Table 4. Risk of all-cause mortality following thromboprophylaxis after total hip and knee replacement surgeries

	Total hip replacement			Total knee replacement		
	All-cause mortality IR (per 1000 PY)	Age/sex adjusted HR (95%CI)	Fully adjusted HR <sup>†</sup> (95% CI)	All-cause mortality IR (per 1000 PY)	Age/sex adjusted HR (95%CI)	Fully adjusted HR <sup>‡</sup> (95%CI)
No thromboprophylaxis	0.0	—	—	0.0	—	—
Past thromboprophylaxis	19.5	0.7 (0.5–1.0)	0.8 (0.6–1.1)	13.1	0.5 (0.3–0.9)	0.6 (0.3–1.0)
By type of thromboprophylaxis						
NOAC*	6.7	0.3 (0.1–0.7)	0.3 (0.1–0.8)	7.2	0.3 (0.1–0.8)	0.3 (0.1–0.9)
LMWH	17.9	0.7 (0.5–1.0)	0.7 (0.5–1.1)	14.6	0.6 (0.3–1.1)	0.7 (0.4–1.2)
Aspirin	22.6	0.8 (0.6–1.1)	0.9 (0.6–1.2)	13.0	0.5 (0.3–0.9)	0.6 (0.3–1.0)
Current thromboprophylaxis	47.1	—	—	32.9	—	—
By type of thromboprophylaxis						
NOAC	0.0	—	—	0.0	—	—
LMWH	106.7	4.0 (2.4–6.6)	4.0 (2.4–6.7)	79.3	4.3 (1.6–11.7)	4.5 (1.7–12.4)
Aspirin	41.1	Referent	Referent	28.9	Referent	Referent

\*Includes person time of current NOAC users due to lack of events in current NOAC group (for HR calculations only).

<sup>†</sup>Adjusted for age, sex, BMI, socio-economic status, smoking and alcohol use; drug use in previous 6 months: antihypertension and antibiotics; history of comorbidity ever before: cancer, pneumonia, atrial fibrillation, heart failure, ischemic strokes and cerebrovascular events.

<sup>‡</sup>Adjusted for age, sex, smoking and alcohol use; drug use in previous 6 months: antihypertensives, statins and antibiotics; history of comorbidity ever before: atrial fibrillation, heart failure and cancer.

IR, incidence rate; HR, hazard ratio; NOAC, new oral anticoagulant; LMWH, low-molecular-weight heparin.

compared with aspirin use in 4016 THR and 3261 TKR patients. Granted we were unable to accurately assess these risks, the generated data may be of use in future studies. Data from multiple studies, such as the present, with limited follow-up time and few events should be collected and combined in future meta-analyses. These meta-analyses will eventually be of sufficient power to generate clinically relevant results, limiting the need to conduct expensive trials.

The risks presented in this study are different when compared with previous research. In contrast to the previously reported similar or better safety and efficacy profile of NOACs and LMWHs compared with aspirin, we found a similar or increased risk of VTE, GI bleeding and all-cause mortality. The difference between our study and previous work is probably due to some limitations in our study. First, because of a relatively low detection rate of drug exposure, we were unable to capture sufficient outcome events to properly compare safety and efficacy of NOACs and LMWHs compared with aspirin. The CPRD is a GP-based database; therefore, hospital-prescribed drugs, without the need of a repeat prescription by a GP, are likely to be under registered. Efforts were made to increase detection rate by including data from anonymised free text notes. Using this approach, we were able to increase the detection of exposure by 57% on average. Furthermore, exposure may be differentially reported in patients who did experience some kind of adverse event compared with those who did not. Second, our study showed unexpectedly high IRs of VTE with the use of LMWHs, which is unexpected because LMWHs are also indicated for the treatment of acute

VTE events such as deep venous thrombosis and pulmonary embolism. This would suggest that our results may have been influenced by reversed causality, that is, the incidence of VTE is not likely to be the result of LMWH use, but rather LMWH use is the result of the occurrence of a VTE event. In other words, timing of registration of the VTE event and registration of LMWH prescription may have been distorted. Possibly, the registration of VTE was delayed relative to the LMWH prescription. This type of information bias may especially occur in the case of acute events. We therefore conducted sensitivity analyses only taking VTE events occurring >30 days after surgery into account. These analyses revealed similar results when compared with the primary analyses. This was expected because the initial problem regarding reverse causality still remains. Third, although we made an effort to correct for relevant covariates, confounding is of considerable concern in an observational study. However, because of limited number of events, we were inherently limited in the inclusion of potential confounders when analysing the risk of GI bleeding. Time-varying propensity score adjusted methods, such as marginal structural models, could have been used to overcome this limitation. However, the assumptions associated with these models may not all be met and consequently result in the introduction of bias. Fourth, we categorised concomitant use of a NOAC (or a LMWH) and aspirin as NOAC (or LMWH) use. We did not differentiate between combined users and NOAC (or LMWH) only users because of low number of events. In future, larger studies, this may be an interesting topic to assess.

In contrast to previous studies, we found an increased risk of VTE, GI bleeding and all-cause mortality with the use of LMWHs compared with aspirin. Risk of GI bleeding was increased with the use of NOACs compared with aspirin use after THR surgery. However, we would like to stress that these results should be interpreted with great care. Based on the results presented in this study, comparison of the safety and efficacy of NOACs and LMWHs after TKR or THR cannot be made accurately. However, the data generated could contribute to future studies and meta-analyses addressing these topics.

## ETHICS STATEMENT

This study protocol was approved by the Independent Scientific Advisory Committee (ISAC), protocol number: 13\_218R.

## CONFLICT OF INTEREST

All authors have completed the Unified Competing Interest form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

## KEY POINTS

- In this study, the use of low-molecular-weight heparins compared with aspirin after total knee replacement was associated with an increased risk of gastro-intestinal bleeding, venous thromboembolism and all-cause mortality.
- The use of low-molecular-weight heparins compared with aspirin after total hip replacement was associated with an increased risk of venous thromboembolism and all-cause mortality.
- The use of new oral anticoagulants after total hip replacement was associated with an increased risk of gastro-intestinal bleeding, compared with aspirin.

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## SUPPORTING INFORMATION

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