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Original research

The effect of new oral anticoagulants and extended thromboprophylaxis policy on hip and knee arthroplasty outcomes: observational study

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ABSTRACT

The efficacy and safety of the new oral anticoagulants (NOAC) and the benefits of extended duration thromboprophylaxis following hip and knee replacements remain uncertain. This observational study describes the relations between thromboprophylaxis policies following hip and knee replacements across England's NHS and patient outcomes between January 2008 and December 2011. From the national administrative database, we analyzed mortality, thromboembolic complications, emergency readmission, and bleeding rates for 201,418 hip and 230,282 knee replacements. There were no differences in outcomes for either LMWH or NOAC. We found no advantage in favor of any single anticoagulation policy or in changing policy. This study supports the American Academy of Orthopaedic Surgeons' recommendation that the choice and duration of thromboprophylaxis prophylaxis be decided by the treating surgeon.
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Introduction

Venous thromboembolism (VTE) is a significant, potentially fatal complication that may occur in patients following total knee arthroplasty (TKA) and total hip arthroplasty (THA). The benefits of providing pharmacological thromboprophylaxis in these patients during their hospital admission have been established [1] and are recommended by the American College of Chest Physicians [2] and the National Institute for Health and Clinical Excellence (NICE) [3,4].

Historically, the options for short and extended duration chemical thromboprophylaxis were limited to oral aspirin, vitamin K antagonists such as warfarin, and low-molecular-weight heparin (LMWH) preparations. Although LMWH has been shown to reduce thromboembolic events, its route of administration by daily subcutaneous injection may be associated with worse compliance and may not be cost-effective [5]. In contrast, the orally administered vitamin K antagonists, whilst having better compliance, require frequent invasive monitoring due to their narrow therapeutic window [6,7].

The introduction of a new generation of oral anticoagulants (NOAC) has combined the benefits of both LMWH and warfarin. Rivaroxaban (Bayer trade name Xarelto) and Apixaban (Bristol-Myers Squibb: Eliquis) are direct oral inhibitors of factor Xa, whereas Dabigatran (Boehringer Ingelheim: Pradaxa) inhibits thrombin. Studies have shown them to be safe and effective, and their ease of administration and lack of monitoring requirement confer the additional benefits of patient compliance and reduce the need for invasive monitoring. As a result, many studies and national guidelines have recommended the use of NOAC in extended VTE prophylaxis for 28–35 days after total hip arthroplasty and for 10–14 days after total knee arthroplasty [2,3,8–12].

Despite these guidelines, the evidence on the ideal duration for all types of extended VTE prophylaxis is limited, and it is unclear whether extended prophylaxis is associated with a significant reduction in morbidity or mortality [13]. Furthermore, it is unclear whether NOAC are associated with lower mortality or morbidity compared with the traditional agents.

The aim of this study was to address the key uncertainties in the literature and in particular to answer the following questions:

1. What are the current thromboprophylaxis policies following total hip and knee arthroplasty in NHS hospitals in England?

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2. Is there an association between the use of different thromboprophylactic prescribing policies and patient morbidity and mortality at 90 days and one year from surgery?
3. Does extended prophylaxis have any benefit in reducing morbidity or mortality in patients undergoing THA and TKA?
4. If a hospital changes its policy, will it also see changes in its rates of morbidity and mortality?
5. Are NOAC safe?

Material and methods

Thromboprophylactic policy

Using postal, email and telephonic questionnaires, we contacted all acute National Health Service (NHS) hospital Trusts in England regarding their VTE prophylactic policy for both hip and knee replacement surgery between January 2008 and December 2011. The questionnaire requested information about the presence or absence of a Trust policy, the chemical agent used, and the duration of use. We also requested information on any changes of policy during that time period.

Patient records

From the national administrative database that covers all admissions to NHS (public) hospitals in England, Hospital Episode Statistics (HES), we extracted admissions for elective THA and TKA between April 2008 and March 2012 using the Office for Population Censuses and Surveys Fourth Revision (OPCS4) primary procedure codes W371, W381, W391, W931, W941, W951 (THA) and W401, W411, W421 (TKA). The data set includes in-hospital deaths, age, sex, postcode (allowing the area-level Carstairs deprivation quintile to be added), 13 secondary diagnosis codes for co-morbidities and complications (allowing the Charlson index of co-morbidity to be derived using our version adapted for the NHS [14]) and 12 operation fields with dates. Patients who underwent surgery in Independent Sector Treatment Centres (ISTCs) were excluded from the analysis to reduce selection bias, as these patients tend to be healthier, have less comorbidity and less severe primary hip and knee pathology than the general NHS patient [15,16].

Outcome measures

We analyzed all-cause mortality in three ways: in-hospital, total within 90 and total within 365 days from the operation date. Unplanned all-cause hospital readmission, VTE and bleeding rates at 90 days were established using the secondary diagnosis fields for the index admission and the primary diagnosis for subsequent admissions within 90 days of discharge following the operation. As patients were clustered within hospitals, hierarchical logistic regression models were fitted, using SAS v9.2 PROC GLIMMIX, adjusting for age, sex, year, comorbidity and deprivation. A number of hospital trusts (organizations that can comprise more than one site) changed their prescribing policy during the study period (63 out of 111 for THA and 71 out of 105 Trusts for TKA). Some trusts were unable to verify the exact date of policy change. Therefore, to reduce misclassification, we excluded from analysis all patient data in the year where the policy change occurred.

Out of hospital deaths were available via linked files provided by the Office for National Statistics with complete dates of death until the end of 2011. For our one-year mortality outcome, we therefore had to exclude operations from 2010/1 onwards to allow one year of follow-up.

We analyzed the 90-day mortality rates for those 37 hospitals that changed from LMWH to NOAC. Hospitals that did not change policy were also included in these models. Due to some national temporal trends in outcome rates, a simple before versus after comparison would have been misleading. Dummy variables to indicate the year were included in the model, and an interaction between policy group and time was fitted. The question of interest was whether hospitals that changed policy registered *greater* (or lesser) improvements in their outcomes after changing than the hospitals that did not change policy. In this too we excluded the year of change due to hospitals' uncertainties over the date of policy change.

P values of under 0.05 were considered statistically significant.

Results

Study groups

From April 2008 through March 2012, 201,418 patients undergoing THA and 230,282 patients undergoing TKA were included. More than two-thirds of patients were aged 65 or over; 60% were female. 29.3% of THA and 33.1% of TKA patients had a non-zero Charlson score.

Survey response rate

Details of the VTE policy for THA and TKA were obtained for 120 and 127 trusts respectively, giving a survey response rate of 80.5% and 86.4% respectively of all NHS Trusts. Of trusts who responded to the survey, 63 out of 111 trusts (57%) reported a change of prescribing policy for THA, whilst 71 out of 105 trusts (68%) reported a change in policy for TKA during the study period. Whilst the majority of trusts used heparin as their choice of VTE prophylaxis following THA or TKA, by the end of the study a significant proportion of trusts had changed from using heparin to NOAC. Aspirin was the least frequently used agent at the start of the study period; all six aspirin-using trusts switched to LMWH by the period's end.

Table 1
Numbers of patients and numbers and crude rates of main 90-day outcomes by thromboprophylaxis policy group for THA and TKA combined

Policy group	Numbers of patients (% of total)	Total mortality (rate as %)	VTE (rate as %)	GI bleed (rate as %)
Aspirin	11,844 (2.7%)	51 (0.4%)	161 (1.4%)	5 (<0.1%)
Unknown (survey non-responder)	116,143 (26.9%)	389 (0.3%)	1451 (1.2%)	95 (0.1%)
NOAC	78,787 (18.3%)	206 (0.3%)	903 (1.1%)	71 (0.1%)
Variable (surgeon-specific within hospital)	37,939 (8.8%)	103 (0.3%)	546 (1.4%)	26 (0.1%)
Heparin – standard	26,193 (6.1%)	113 (0.4%)	402 (1.4%)	17 (0.1%)
Heparin – extended	160,794 (37.2%)	547 (0.3%)	2167 (1.5%)	129 (0.1%)
Total	431,700 (100%)	1409 (0.3%)	5630 (1.3%)	343 (0.1%)

Table 2
Adjusted odds ratios for each outcome by thromboprophylaxis policy group for THA (excluding calendar year of any policy change)

Policy	In-hospital mortality		90d mortality		365d mortality		90d GI bleed		90d readmission		90d VTE	
	OR and CI	*p* value	OR and CI	*p* value	OR and CI	*p* value	OR and CI	*p* value	OR and CI	*p* value	OR and CI	*p* value
Aspirin	0.60 (0.28–1.32)	0.207	0.93 (0.57–1.51)	0.756	1.32 (1.02–1.71)	**0.036**	0 (0–6.93)	0.895	1.01 (0.86–1.19)	0.873	0.88 (0.61–1.27)	0.505
Unknown (survey non-responder)	1.00 (0.75–1.32)	0.974	1.00 (0.80–1.24)	0.968	0.93 (0.81–1.07)	0.329	1.07 (0.73–1.58)	0.729	1.03 (0.94–1.13)	0.488	0.91 (0.77–1.09)	0.313
NOAC	0.82 (0.54–1.25)	0.367	0.98 (0.68–1.41)	0.918	0.96 (0.67–1.39)	0.836	0.94 (0.54–1.62)	0.818	0.99 (0.91–1.07)	0.808	1.03 (0.84–1.25)	0.805
Variable[a]	0.82 (0.49–1.36)	0.443	0.72 (0.48–1.09)	0.118	0.86 (0.66–1.13)	0.277	0.98 (0.50–1.93)	0.956	0.94 (0.84–1.05)	0.276	1.16 (0.91–1.49)	0.223
Heparin – standard	0.81 (0.51–1.29)	0.379	0.93 (0.67–1.29)	0.670	0.90 (0.73–1.10)	0.283	0.89 (0.44–1.81)	0.746	1.00 (0.90–1.11)	0.966	1.17 (0.93–1.46)	0.183
Heparin – extended	1		1		1		1		1		1	

Bold indicates $p < 0.05$.
NOAC = new oral anticoagulants.
[a] Surgeon-specific within the hospital.

Table 3
Adjusted odds ratios for each outcome by thromboprophylaxis policy for TKA (excluding calendar year of any policy change)

policy	In-hospital mortality		90d mortality		365d mortality		90d GI bleed		90d readmission		90d VTE	
	OR and CI	*p* value	OR and CI	*p* value	OR and CI	*p* value	OR and CI	*p* value	OR and CI	*p* value	OR and CI	*p* value
Aspirin	1.15 (0.60–2.20)	0.667	1.14 (0.74–1.75)	0.566	1.08 (0.79–1.49)	0.625	1.13 (0.43–2.98)	0.810	1.05 (0.90–1.21)	0.546	1.12 (0.80–1.57)	0.519
Unknown (survey non-responder)	0.85 (0.63–1.15)	0.302	0.93 (0.76–1.14)	0.504	1.02 (0.88–1.19)	0.771	1.10 (0.73–1.67)	0.639	0.97 (0.90–1.05)	0.448	0.92 (0.77–1.10)	0.347
NOAC	1.03 (0.69–1.53)	0.901	1.24 (0.88–1.74)	0.213	1.16 (0.79–1.70)	0.441	1.16 (0.65–2.07)	0.614	1.04 (0.97–1.12)	0.278	1.06 (0.90–1.26)	0.481
Variable[a]	0.86 (0.52–1.43)	0.569	0.79 (0.51–1.23)	0.298	0.90 (0.62–1.31)	0.583	1.20 (0.60–2.42)	0.607	0.99 (0.90–1.10)	0.921	0.99 (0.79–1.25)	0.943
Heparin - standard	1.20 (0.78–1.85)	0.405	1.05 (0.77–1.43)	0.774	1.09 (0.88–1.34)	0.426	0.70 (0.32–1.53)	0.373	0.92 (0.83–1.01)	0.089	0.97 (0.78–1.21)	0.805
Heparin -extended	1		1		1		1		1		1	

NOAC = new oral anticoagulants.
[a] Surgeon-specific within the hospital.

Table 4
Adjusted odds ratios for each outcome for in-patient heparin compared with extended duration for heparin or new oral anticoagulants, following THA or TKA

Outcome	Measure	THA		TKA	
		Heparin IP	Heparin or NOAC extended	Heparin IP	Heparin or NOAC extended
In-hospital mortality	OR (95% CI)	0.81 (0.51–1.27)	1	1.22 (0.80–1.86)	1
	p value	0.348		0.366	
90d mortality	OR (95% CI)	0.95 (0.69–1.30)	1	1.00 (0.73–1.37)	1
	p value	0.733		0.994	
365d mortality	OR (95% CI)	0.92 (0.76–1.12)	1	1.07 (0.88–1.30)	1
	p value	0.403		0.513	
90d GI bleed	OR (95% CI)	0.78 (0.39–1.56)	1	0.65 (0.30–1.40)	1
	p value	0.485		0.269	
90d Readmission	OR (95% CI)	1.01 (0.91–1.11)	1	0.93 (0.85–1.02)	1
	p value	0.865		0.131	
90d VTE	OR (95% CI)	1.18 (0.95–1.47)	1	1.02 (0.84–1.25)	1
	p value	0.132		0.823	

NOAC = new oral anticoagulants.

Mortality and VTE rates

90-day crude rates for total mortality and coded VTE and GI bleed were low (Table 1). The in-hospital mortality rate was 0.2% after both procedures, and the total 365-day mortality rate was 0.8% for THA and 0.6% for TKA. 9.0% of THA patients and 9.4% of TKA patients were readmitted within 90 days.

The covariate-adjusted outcome rates by policy for the THA and TKA groups are presented in Tables 2 and 3. For THA, in-hospital mortality, 90-day mortality and 90-day VTE rates did not differ significantly between the different policy groups. The 365-day mortality rate in the small aspirin group following THA was significantly higher than in any other group undergoing THA ($p = 0.036$) with OR of 1.32 (1.02–1.71). Analysis for TKA did not show any statistically significant difference between mortality rates and VTE rates for different policy groups.

Hemorrhagic complications and readmissions

The recorded rate of GI bleeding within 90 days and all-cause readmission within 90 days did not differ significantly between different policy groups for either THA or TKA.

Sensitivity analysis for the timing of policy change

As mentioned above, around two-thirds of trusts changed their policy during the period. By excluding the year of change in our primary analysis and reduce the likelihood of misclassifying the policy group, statistical power is reduced. Therefore, a sensitivity analysis was performed by including all patients in the study and assuming that any change in prescribing policy occurred in January of that year. Results were similar to those after excluding the year of change. The only statistically significant difference in outcomes between different policy groups was an increase in the 365-day mortality in the aspirin group following THA ($p = 0.018$) with OR of 1.36 (1.05–1.75).

Table 5
Adjusted odds ratios for 90-day mortality for a thromboprophylaxis policy change from heparin standard or heparin extended to new oral anticoagulants

Policy change	THA		TKA	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Heparin standard to NOAC	1.27 (0.87–1.86)	0.215	1.43 (1.00–2.03)	0.049
Heprain extended to NOAC	0.84 (0.58–1.21)	0.064	0.97 (0.74–1.26)	0.806

NOAC = new oral anticoagulants.

Extended prophylaxis

We compared the outcomes of Trusts using LMWH during the in-patient period only with Trusts who used either LMWH or NOAC in extended duration (Table 4). For THA and TKA, no statistically significant difference was found between the mortality, readmission, GI bleeding and VTE rates of the different policy groups.

Changing policy

We looked at whether a change in prescribing policy led to a change in outcomes. We observed some temporal trends in outcome measure over the period of the study for different policy groups. Therefore, we compared the change in outcomes for hospitals that changed their policy from standard or extended LMWH to NOAC with hospitals that did not change their policy of LMWH (Table 5). We were restricted by small numbers of outcomes in this hospital subset to analyzing the change in 90-day mortality rates. Changing from standard duration LMWH to NOAC was associated with a non-significant increase in 90-day mortality rates in the TKA group, and the confidence interval was wide.

Discussion

The aim of this study was to survey the current thromboprophylaxis policies following total hip and knee arthroplasty in NHS hospitals in England and to determine whether there was any association between the use of different policies and patient outcomes with respect to morbidity and mortality outcomes. We found that the efficacy and safety of LMWH and NOAC were comparable irrespective of their duration of use and that a change in policy did not lead to a demonstrable change in mortality or morbidity rates. We now consider each study question in turn.

What are the current thromboprophylaxis policies following total hip and knee arthroplasty in NHS hospitals in England?

This study highlights the current prophylactic regimes of all hospital trusts in England over a four-year period with a sample of over 400,000 patients. The vast majority of trusts have a policy in place, but there are also a significant number of trusts where the

treatment is down to individual surgeon preference. The most common pharmacological agent used was LMWH. 71 trusts changed their prescribing policy during the period studied (the majority to NOAC), likely in response to the introduction of NICE clinical practice guidelines.

Is there an association between the use of different thromboprophylactic prescribing policies and patient morbidity and mortality at 90 days and one year from surgery?

In our study we found no evidence to support NOAC superiority over LMWH following THA and TKA. Most of the studies that have been able to show a benefit in the use of NOAC have been pharmaceutical-sponsored studies that used a venographic technique to detect asymptomatic VTE. In the RE-MODEL, RE-NOVATE AND RE-NOVATE II trials [8,9,17], dabigatran was shown to be non-inferior to enoxaparin in preventing VTE and in all-cause mortality, whereas pooled analysis of patients from four RECORD phase II clinical trials showed Rivaroxaban to be superior to Enoxaparin in reducing symptomatic DVT and all-cause mortality [18]. However, in clinical practice ultrasonography is more commonly used to confirm the diagnosis of clinically apparent VTE, and it is not certain whether a reduction in asymptomatic VTE correlates with improved patient outcomes. Parvizi et al. have questioned the correlation of asymptomatic DVT with symptomatic PE and found the relationship to be negligible [19]. Our findings suggest that any reported benefits of NOAC observed in these trials may be not borne out in clinical practice on a large scale.

Does extended prophylaxis or a change in policy to extended prophylaxis reduce morbidity and mortality in patients undergoing THA and TKA?

With the recent trend towards extended VTE prophylaxis [20,21], the benefits of such a policy have been called into question. Husted et al. found their rates of VTE with a standard regime were comparable to series using an extended regime and cautioned against the indiscriminate use of an extended VTE prophylaxis policy [13].

Our study showed that the type of prophylaxis used and the duration of treatment had no effect on outcomes following THA or TKA. Furthermore, for those trusts that changed their prescribing policy from a standard to an extended duration, there was no difference in 90-day mortality rates after the change in policy.

Are NOAC safe?

There have been concerns from the orthopadic community that NOAC may be associated with an increased bleeding risk compared with traditional agents. In a systematic review and meta-analysis, Gomez et al. compared the use of LMWH with Rivaroxaban following THA and TKA and concluded that the relative risk of bleeding was higher with the NOAC [22]. Marlow et al. reported similar findings in 2011, albeit with a small study [23]. Surgeons may also be wary of these anticoagulants, as they are not easily reversible compared with LMWH and warfarin. In an analysis of prospectively collected data on English hospital trusts, Jameson et al. reported a significantly higher rate of wound complications with Rivaroxaban compared with LMWH following THA or TKA, with no differences in symptomatic pulmonary emboli or mortality [24].

In 2011, both the UK Department of Health [25] and the United States Centers for Medicare and Medicaid Services [26] implemented a 30-day all-cause readmission penalty following THA and TKA. Thus the identification of anticoagulants that are associated with a reduced bleeding risk and a reduced readmission rate is an important area in optimizing patient outcomes and minimizing the economic burden of these complications to the treating hospital.

Our study found that the use of LMWH and NOAC was comparable in terms of 90-day bleeding rates and 90-day readmission rates for all causes. The mechanism of action of all chemical thromboprophylaxis agents is likely to cause hematomas and extended bleeding from surgical wounds. We did not have information on wound complications, and it is possible that our outcomes were not sensitive enough to detect specific complications associated with NOAC use. However, a policy of using NOACs as chemical thromboprophylaxis was not associated with significantly higher readmission or mortality rates, suggesting that the use of NOACs for chemical thromboprophylaxis in hip and knee replacements is as safe as other anticoagulants.

Strengths and limitations of the study

The study benefits from a large sample size (over 400,000 patients). It had an excellent response rate for the survey, and the fact that the non-response group had similar outcomes to the rest suggests, though cannot prove, that the effect of non-responder bias is small.

The reliability of the HES database is dependent on the accuracy of coding, which is good and improving [27,28]. This database is more accurate when analyzed for hard end points such as mortality and all-cause readmission, but less reliable for secondary diagnoses such as VTE and bleeding if variation in the quality of coding exists. We found 90-day rates of recorded VTE of 1.1% for THA and 1.5% for TKA; our recorded GI bleed rates were 0.1% for both. By comparison, the Global Orthopaedic Registry, containing 15,000 procedures in three years up to 2004 in 13 countries, reported 90-day VTE rates of 0.9% for THA and 1.3% for TKA and 90-day GI bleed rates for 0.1% for THA and 0.2% for TKA [29]. These figures are very similar to ours.

We had limited numbers of events to assess the effect on outcomes when hospitals changed policy and were restricted to considering 90-day mortality. While important, this outcome is much less sensitive than morbidity measures to the effects of changing practice. Regarding outcomes, we chose to use VTE rather than just PE because, while PE is the more important complication than symptomatic DVT, both are complications that thromboprophylaxis should reduce so it is more relevant to use both as an endpoint.

A limitation of our survey is that the presence of a hospital policy does not necessarily equate to full compliance in clinical practice across the hospital [30]. However, this data set shows the link between the stated policy of the hospital and the outcome and is thereby akin to an intention-to-treat analysis, which is standard in clinical trials. A second limitation is that we do not have data on hospital policies on mechanical thromboprophylaxis or on postoperative ultrasonography use. Finally, HES data do not capture activity in primary care, and by only capturing conditions serious enough to warrant readmission, our data may under-estimate the morbidity associated with different prescribing policies. However, we would not expect there to be a relation between policy group and recording levels. It therefore seems unlikely that a bias exists when comparing the outcomes between different policies, though this cannot be ruled out.

Conclusions

This national study reflects recent clinical practice by surgeons across England. Despite clinical practice guidelines advocating the use of extended chemical prophylaxis for joint replacement surgery, we have found no evidence to support this practice. The efficacy and safety of LMWH and NOAC were found to be

comparable irrespective of their duration of use. This study would support the American Academy of Orthopaedic Surgeons' recommendation [31] that the overriding choice and duration of prophylaxis be decided by the treating physician on an individual basis.

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