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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.

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%)