Original research

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

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A R T I C L E  I N F O

Article history:
Received 8 January 2015
Received in revised form 26 February 2015
Accepted 2 March 2015
Available online 23 June 2015

Keywords:
Thromboprophylaxis
Hip replacement
Knee replacement
Administrative data

A B S T R A C T

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 anti-coagulation 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?
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%)          |
| (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    | 37,939 (8.8%)                    | 103 (0.3%)                 | 546 (1.4%)     | 26 (0.1%)          |
| within hospital)              |                                  |                            |                |                     |
| 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 |
| 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** |
| 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 |
| 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 |
| Variable<sup>a</sup>          | 0.82 (0.49–1.36)      | 0.443         | 0.72 (0.48–1.09) | 0.118       | 0.86 (0.66–1.13) | 0.277 |
| 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 |
| Heparin – extended            | 1                      | 1             | 1              | 1           | 1               | 1      |

Bold indicates p < 0.05.

NOAC = new oral anticoagulants.

<sup>a</sup> 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 |
| 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 |
| 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 |
| 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 |
| Variable<sup>a</sup>          | 0.86 (0.52–1.43)      | 0.569         | 0.79 (0.51–1.23) | 0.298       | 0.90 (0.62–1.31) | 0.583 |
| 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 |
| Heparin – extended            | 1                      | 1             | 1              | 1           | 1               | 1      |

NOAC = new oral anticoagulants.

<sup>a</sup> 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 Heparin IP | Heparin or NOAC extended | TKA 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).

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 tech-
nique to detect asymptomatic VTE. In the RE-MODEL, RE-NOVATE
AND RE-NOVATE II trials [8,19], 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
detect asymptomatic VTE, and it is not certain whether a reduction in
asymptomatic VTE correlates with improved patient outcomes. Parvizi et al. have questioned 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 dif-
fERENCE in 90-day mortality rates after the change in policy.

Are NOAC safe?

There have been concerns from the orthopaedic 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
asymptomatic 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] imple-
mented 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 compa-
rable 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 infor-
mation on wound complications, and it is possible that our out-
comes 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 out-
comes 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 thromboproph-
yaxis 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 post-
operative 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 underestimate 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.

Acknowledgments

The Dr Foster Unit at Imperial is principally funded by Dr Foster Intelligence, an independent healthcare information company. The Dr Foster Unit is affiliated with the Imperial Centre for Patient Safety and Service Quality, funded by the NIHR. We are grateful for support from the NIHR Biomedical Research Centre funding scheme. The funders had no role in or influence on any stage of this study.

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