Todd, F., Yeomans, D., Whitehouse, M. R., & Matharu, G. (2021). Does venous thromboembolism prophylaxis affect the risk of venous thromboembolism and adverse events following primary hip and knee replacement? A retrospective cohort study. *Journal of Orthopaedics*, *25*, 301-304. https://doi.org/10.1016/j.jor.2021.05.030

Does venous thromboembolism prophylaxis affect the risk of venous thromboembolism and adverse events following primary hip and knee replacement? A retrospective cohort study.

Abstract

Background

The optimum chemical venous thromboembolism (VTE) prophylactic agents following total hip and knee replacement (THR and TKR) remain unknown. NICE recommends multiple agents, including direct oral anticoagulants (DOACs), low-molecular weight heparin (LMWH), and aspirin. We assessed whether VTE prophylaxis affected the risk of VTE and adverse events following primary THR and TKR.

Materials and Methods

We reviewed 982 elective primary THRs (59%) and TKRs (41%) at a large tertiary centre during 2018. The primary outcome was any VTE (DVT and/or PE) within 90-days. Secondary outcomes were adverse events within 90-days (major bleeding and wound complications). The association between VTE prophylaxis and outcomes was assessed.

Results

The overall prevalence of VTE and adverse events were 2.7% (n=27) and 15.2% (n=136) respectively. The most common agents used were DOAC +/- LMWH (50.7%, n=498), followed by aspirin +/- LMWH (35.5%, n=349) and LMWH alone (4.7%, n=46). The risk of VTE (aspirin+/-LMWH=3.7%, DOAC=2.0%, LMWH=2.2%) was not significantly different between agents (p=0.294). The risk of any adverse event was significantly higher (p<0.001)

with aspirin +/- LMWH (16.1%; n=56) and LMWH (28.3%; n=13) compared with DOACs +/- LMWH (7.0%; n=35) in TKRs only, there was no differences between agents for adverse events in THRs (p=0.644).

Conclusions

Choice of thromboprophylaxis did not influence the risk of VTE following primary THR and TKR. DOACs (+/- LMWH) were associated with the lowest risk of adverse events. Large multicentre trials are still needed to assess the efficacy and safety of these agents following THR and TKR.

Keywords: venous thromboembolism; thromboprophylaxis; total hip replacement; total knee replacement; wound complication

Introduction

Primary total hip and knee replacement (THR and TKR) are commonly performed worldwide, and are both clinically and cost-effective interventions for treating painful arthritis (1). A recognised complication of these operations is venous thromboembolism (VTE) (2). Rates for post-operative VTE vary, but can be up to 5% for deep vein thrombosis (DVT) and 2% for pulmonary emboli (PE) (3).

In addition to the substantial financial cost of treatment, VTE events can result in prolonged hospital admissions and carry significant morbidity and risk of mortality (4-6). Consequently, thromboprophylaxis forms an integral part of perioperative management for patients undergoing THR and TKR. A number of different agents are used for VTE prophylaxis including aspirin, low molecular weight heparin (LMWH), and direct oral anticoagulant agents (DOACs). However, the optimum chemical venous thromboembolism (VTE) prophylactic agents following THR and TKR remain unknown. There are pros and cons of each agent. Aspirin is a popular option due to low cost, known efficacy and clinician familiarity (7, 8). Similarly, LMWH is an established agent for thromboprophylaxis (9), although it requires subcutaneous administration, which after discharge may incur additional district nurse costs if patients are unable to manage this in the community (10). DOACs such as dabigatran and rivaroxaban act as direct inhibitors of coagulation factors and provide an alternative oral option, however the cost of these agents is substantial, and concerns have been raised about increased risks of bleeding (11).

Data exists to support the efficacy of each agent (aspirin, LMWH, and DOACs) in preventing VTE following THR and TKR. A recent meta-analysis of 13 randomised

controlled trials concluded that in terms of clinical effectiveness and safety profile, aspirin did not differ statistically significantly from other anticoagulants used for VTE prophylaxis after THR and TKR (12). In addition, large observational studies have demonstrated aspirin to be at least as effective as other agents for VTE prevention in both primary THR and TKR (3, 13, 14).

The 2018 National Institute for Health and Care Excellence (NICE) guidelines recommend a choice of three main VTE prophylaxis agents (aspirin, LMWH or DOACs) for patients undergoing elective primary THR or TKR, although for THR the use of aspirin should be preceded by 10 days of LMWH monotherapy (15). The lack of a standardised regimen and the addition of aspirin as a new agent since 2010 guidelines is reflected in clinical practice, with choice of post-operative thromboprophylaxis being heterogeneous between centres and across the country (16-19).

Given the recent changes to NICE guidance, our aims were to determine (1) the risk of VTE and adverse events at our institution following primary THR and TKR, and (2) whether the risk of VTE and adverse events were influenced by VTE prophylaxis used.

Materials and Methods

We reviewed all patients undergoing primary elective THR and TKR at a UK tertiary centre between 1st January 2018 and 31st December 2018. Partial knee replacements (unicompartmental and patella-femoral), THR for fracture, and revision hip and knee surgery cases were excluded. 982 operations were identified which were eligible for study inclusion.

Our primary outcome was any VTE (DVT and/or PE) within 90 days of surgery. Secondary outcomes were adverse events of chemical thromboprophylaxis occurring within 90 days of surgery and included: major bleeding (gastrointestinal and cerebral), wound problems (ooze, superficial and deep infections, haematoma) and further surgery. All reoperations on the joint relating to post-operative wound and prothesis complications within the timeframe were included. Data was also collected on length of hospital stay.

Hospital electronic records were reviewed by two authors (FT and DY). Authors did not review the same records, so no formal interobserver reliability assessment was performed. Data on chemical thromboprophylaxis was obtained from pharmacy records on discharge from hospital in addition to hospital drug charts and was grouped into three categories: aspirin with or without a preceding course of (+/-) LMWH, DOAC (+/-) LMWH, and LMWH alone. The aspirin +/- LMWH group included aspirin monotherapy for hips and 10 days of LMWH followed by 28 days of aspirin alone for knees. Choice of regimen was made by the respective consultant in charge of the patient's care.

VTE and adverse events were identified by a systematic search of hospital databases for each patient. Imaging (computerised tomography pulmonary angiography and/or venous ultrasonography), discharge/outpatient letters, hospital readmissions and emergency department visit records were all reviewed and recorded. All positive VTE events were reviewed and corroborated by the other author.

Statistical analysis

In the whole cohort, the effect of VTE prophylaxis on VTE and adverse events was assessed using: (1) 2-sided Fisher's exact test (as some cells had an expected frequency under 5), and (2) logistic regression (with aspirin +/- LMWH being the reference group). In the whole cohort, the effect of VTE prophylaxis on length of stay was assessed using: (1) the Kruskal-Wallis test (as length of stay data was not normally distributed), and (2) linear regression (with aspirin +/- LMWH being the reference group). Analyses were repeated separately in THR and TKR patients, however regression analyses could not be repeated as the number of VTEs and adverse events were too few to permit meaningful analysis when the cohort was subdivided by the joint replaced. In all analyses p-values of less than 0.05 were considered statistically significant, and 95% confidence intervals were calculated.

Results

We identified 982 primary THRs and TKRs during the study period, of which 586 (59.7%) were performed on females and 396 (40.3%) on males. Mean age at surgery was 69.2 years (range 17-97 years). DOAC +/- LMWH was the most common regimen (n=498, 50.7%), followed by aspirin +/- LMWH (n=349, 35.5%) and LMWH alone (n=46, 4.7%). There were a further 89 patients (9.1%) who received alternative thromboprophylaxis, such as those on clopidogrel or warfarin preoperatively.

Risk of VTE

The overall risk of any VTE event was 2.8% (n=27), of which 22 were DVTs and 7 PEs (two patients had both DVT and PE). No PEs were fatal. The risk of VTE was 3.7%

(n=13) with aspirin +/- LWMH, 2.0% (n=10) with DOAC +/- LWMH and 2.2% (n=1) with LMWH alone. The remaining VTE events were in patients receiving alternative thromboprophylaxis. There was no significant difference in the risk of VTE between aspirin and the other two treatments in the whole cohort (p=0.294). This finding was confirmed in the logistic regression analysis (DOAC odds ratio (OR)=0.53, 95% CI=0.23-1.22, p=0.136; LMWH OR=0.57, 95% CI=0.07-4.50, p=0.597).

Adverse events

In the whole cohort, the risk of any adverse event was significantly higher (p<0.001) with aspirin +/- LMWH (16.1%; n=56) and LMWH alone (28.3%; n=13) compared with DOACs +/- LMWH (7.0%; n=35). Logistic regression analysis demonstrated that aspirin had a significantly higher risk of any adverse events compared with DOACs (DOAC OR=0.40, 95% CI=0.25-0.62, p<0.001); LMWH had a higher risk of any adverse events compared with aspirin (LMWH OR=2.06, 95% CI=1.02-4.16, p=0.044).

For specific complications in the whole cohort, major bleeding within 90 days of surgery occurred in three patients. Two suffered gastrointestinal bleeds (one on LWMH alone, and one on a DOAC with LMWH). One patient on a DOAC with LMWH suffered a haemorrhagic stroke.

In the whole cohort, the risk of wound ooze was significantly higher (p<0.001) with aspirin +/- LMWH (12.3%, n=43) and with LMWH alone (13.0%, n=6) compared with DOAC +/- LMWH (4.2%, n=21). The risk of further surgery was significantly higher (p<0.001) with LMWH alone (15.2%, n=7) compared with aspirin +/- LMWH (4.0%, n=14), and compared with DOAC +/- LMWH (2.4%, n=12). The risk of wound

infection (p=0.067) and haematoma (p=0.743) was not significantly different between VTE prophylaxis agents. The risk of specific complications by VTE prophylaxis agents are summarised below (Table 1).

Complication	Aspirin +/- LMWH	DOAC +/- LMWH	LMWH alone	Total
GI bleed	0 (0%)	1 (0.2%)	1 (2.2%)	2 (0.2%)
Haemorrhagic stroke	0 (0%)	1 (0.2%)	0 (0%)	1 (0.1%)
Wound ooze	43 (12.3%)	21 (4.2%)	6 (13.0%)	70 (7.8%)
Wound infection	5 (1.4%)	7 (1.4%)	3 (6.5%)	15 (1.7%)
Haematoma	6 (1.7%)	8 (1.6%)	1 (2.2%)	15 (1.7%)
Further surgery	14 (4.0%)	12 (2.4%)	7 (15.2%)	33 (3.7%)

Table 1 Adverse events for the whole cohort.

Length of hospital stay

The length of hospital stay was significantly shorter (p=0.003) in patients receiving aspirin +/- LMWH (median 4 days, interquartile range (IQR) 3-6 days), and in patients receiving DOAC +/- LMWH (median 4 days, IQR 3-6 days), compared with those receiving LMWH alone (median 6 days, IQR 4-8 days). This finding did not reach statistical significance in the linear regression model (DOAC +/- LMWH coefficient = 0.73 days, 95% CI= -0.15 to 1.60 days, p=0.102; LMWH alone coefficient = 1.55 days, 95% CI= -0.41 to 3.51 days, p=0.122).

Analysis of THRs only

In THRs, the risk of VTE was 0.96% (n=5), and the risk of any adverse event was 4.8% (n=25). There was no difference in the risk of VTE (p=0.471) or adverse events (p=0.644) between the different VTE prophylactic agents in THR patients. The length of hospital stay was significantly shorter (p=0.046) in THR patients receiving aspirin +/- LMWH (median 4 days, IQR 3-5 days), and in THR patients receiving DOAC +/- LMWH (median 4 days, IQR 3-6 days), compared to THR patients receiving LMWH alone (median 5 days, IQR 4-7 days).

Analysis of TKRs only

In TKRs, the risk of VTE was 5.1% (n=19), and the risk of any adverse event was 21.3% (n=79). There was no difference in the risk of VTE (p=0.781) between the different VTE prophylactic agents in TKR patients. For TKRs the risk of adverse events was significantly different (p<0.001) between the VTE prophylaxis agents, with more adverse events observed with LMWH alone (55.0%, n=11) and aspirin +/- LMWH (21.5%, n=51), compared with DOAC +/- LMWH (14.9%, n=17). This relationship was generally seen for each specific complication: wound ooze (25% LMWH alone, 16.5% aspirin +/- LMWH, 7.9% DOAC +/- LMWH), haematoma (5% LMWH alone, 2.5% aspirin +/- LMWH, 1.8% DOAC +/- LMWH), further surgery (30% LMWH alone, 5.5% aspirin +/- LMWH, 5.3% DOAC +/- LMWH), and wound infection (15% LMWH alone, 1.7% aspirin +/- LMWH, 1.8% DOAC +/- LMWH).

The length of hospital stay was significantly shorter (p=0.008) in TKR patients receiving aspirin +/- LMWH (median 4 days, IQR 3-6 days), and in TKR patients

receiving DOAC +/- LMWH (median 5 days, IQR 3-7 days), compared to TKR patients receiving LMWH alone (median 6 days, IQR 4-8.5 days).

Discussion

We observed that VTE prophylaxis agents did not influence the risk of VTE following primary THR and TKR at our centre. However, DOACs (+/- LMWH) were associated with the lowest risk of adverse events compared with aspirin (+/-LMWH) and compared with LMWH alone. This difference was driven by wound complications and mainly seen following TKRs (rather than THRs). There was an overall higher incidence of VTE and adverse events after primary TKR compared with THR.

Our finding that VTE rates were not influenced by choice of thromboprophylaxis is reflected throughout the literature. A recent meta-analysis by Matharu et al. (12) included 13 RCTs (n=6060) to investigate the efficacy of aspirin versus other anticoagulants in THRs and TKRs. Pooled analysis demonstrated no significant difference (relative risk (RR) 1.12 for aspirin, 95% CI 0.78-1.62) in the risk of VTE by prophylactic agent. Subgroup analysis confirmed no difference in VTE risk between patients receiving aspirin versus LMWH (RR 0.76, 95% CI 0.37-1.56), and those receiving aspirin versus rivaroxaban +/- LMWH (RR 1.52, 95% CI 0.56-1.42).

We observed that the use of DOACs resulted in a reduced risk of adverse events compared with the other agents, with further analysis demonstrating that this finding was specific to wound complications in TKR patients. This would also explain the findings regarding a higher incidence of further surgery in the LMWH alone group, given the increasing risk of wound complications. There have previously been concerns about the excess bleeding risk associated with DOACs in smaller studies, including

wound problems (20). However more recent large database and registry studies have not observed a difference between the risk of adverse events and wound problems between the commonly used VTE prophylactic agents (3, 14, 19). This is confirmed in a recent meta-analysis of RCTs (12). It is unclear why DOACs had a lower risk of adverse events in our study, and may relate to only a small subgroup of patients in this study receiving LMWH alone (which was associated with much higher risk of adverse events compared with other agents). It is recommended further studies are needed to assess the risk profile of DOACs relative to other agents.

Our subgroup analysis also demonstrated a higher risk of VTE after TKR compared with THR. This finding is consistent with the literature (5, 21) and, although not fully elucidated, may represent differences in the use of tourniquets, (22) bandaging, intra-operative positioning and better post-operative mobilisation in post-operative THR cohorts (23).

We observed similar bleeding risks between agents in both THA and TKRs, with absolute numbers remaining small, reflecting rates seen in similar cohorts (24). Concerns have been raised regarding the higher risk of intra- and post-operative bleeding with DOAC use (3, 25). However effect sizes are often small, with other studies demonstrating no statistical differences (12, 14, 26), suggesting a comparative safety profile in line with our study.

On a departmental level, cost-effectiveness is a deciding factor in choice of prophylactic regimen. As an established agent, aspirin remains the cheapest option at £0.015 per day per patient (local pharmacy data) versus LMWH (£0.82 per day per patient) and the more expensive DOACs (£1.92 per day per patient). This needs to be offset against the

cost of treating post-THR/TKR VTE events, estimated between £295-£457 for post-operative DVTs and £992 for PEs (27). Given the low incidence of VTE, aspirin remains an attractive option from a cost perspective.

We observed that the choice of thromboprophylaxis influenced length of hospital stay, with the LMWH alone group demonstrating a longer stay in hospital than the aspirin (+/- LMWH) and DOAC groups. This perhaps relates to the increasing wound problems and need for further surgery in the LMWH alone group. Direct RCT comparisons of our three agents and their effect on length of stay are lacking. We identified a single recent trial that demonstrated no difference in length of stay between dalteparin and aspirin (28), however the trial was halted prematurely due to difficulties in patient recruitment.

Whilst our study utilises a large cohort studied recruited over a year with 90-day follow up, our work has some limitations. As a single centre study, the use of thromboprophylactic regimens may not be generalisable to other centres. The rates of VTE and complications may also differ at our centre compared with others, which may also limit generalisability. Finally, some of our analyses were subject to small numbers, given relatively few outcome events occurred within 90-days of surgery, but this is consistent with the literature (12).

Despite the slightly higher risk of adverse events, aspirin remains a choice on the formulary for suitable patients due to cost effectiveness and similar efficacy for preventing VTE. We will continue to monitor our rates of VTE and adverse events and adjust our guidance accordingly.

In conclusion, with the numbers available, VTE prophylaxis agents did not influence the risk of VTE following primary THR and TKR at our centre. However, DOACs (+/-

LMWH) were associated with the lowest risk of adverse events compared with aspirin (+/-LMWH) and compared with LMWH alone. This finding was predominantly driven by wound complications in TKR patients. Large multicentre trials are still needed to assess the efficacy and safety of these three VTE prophylactic agents following primary THR and TKR, with any future recommendations also considering the health economics of different treatment regimes.

Word Count

2531 words

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