



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>

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Link to published version (if available):
[10.1016/j.jor.2021.05.030](https://doi.org/10.1016/j.jor.2021.05.030)

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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

1 **Introduction**

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

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

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

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

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

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

39 **Materials and Methods**

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

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

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

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

66 **Statistical analysis**

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

78 **Results**

79 We identified 982 primary THRs and TKRs during the study period, of which 586
80 (59.7%) were performed on females and 396 (40.3%) on males. Mean age at surgery
81 was 69.2 years (range 17-97 years). DOAC +/- LMWH was the most common regimen
82 (n=498, 50.7%), followed by aspirin +/- LMWH (n=349, 35.5%) and LMWH alone
83 (n=46, 4.7%). There were a further 89 patients (9.1%) who received alternative
84 thromboprophylaxis, such as those on clopidogrel or warfarin preoperatively.

85

86 **Risk of VTE**

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

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

95

96 **Adverse events**

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

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

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

112 infection (p=0.067) and haematoma (p=0.743) was not significantly different between
 113 VTE prophylaxis agents. The risk of specific complications by VTE prophylaxis agents
 114 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%)

115 **Table 1 Adverse events for the whole cohort.**

116

117 **Length of hospital stay**

118 The length of hospital stay was significantly shorter (p=0.003) in patients receiving
 119 aspirin +/- LMWH (median 4 days, interquartile range (IQR) 3-6 days), and in patients
 120 receiving DOAC +/- LMWH (median 4 days, IQR 3-6 days), compared with those
 121 receiving LMWH alone (median 6 days, IQR 4-8 days). This finding did not reach
 122 statistical significance in the linear regression model (DOAC +/- LMWH coefficient =
 123 0.73 days, 95% CI= -0.15 to 1.60 days, p=0.102; LMWH alone coefficient = 1.55 days,
 124 95% CI= -0.41 to 3.51 days, p=0.122).

125

126 Analysis of THRs only

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

134

135 Analysis of TKRs only

136 In TKRs, the risk of VTE was 5.1% (n=19), and the risk of any adverse event was
137 21.3% (n=79). There was no difference in the risk of VTE (p=0.781) between the
138 different VTE prophylactic agents in TKR patients. For TKRs the risk of adverse events
139 was significantly different (p<0.001) between the VTE prophylaxis agents, with more
140 adverse events observed with LMWH alone (55.0%, n=11) and aspirin +/- LMWH
141 (21.5%, n=51), compared with DOAC +/- LMWH (14.9%, n=17). This relationship was
142 generally seen for each specific complication: wound ooze (25% LMWH alone, 16.5%
143 aspirin +/- LMWH, 7.9% DOAC +/- LMWH), haematoma (5% LMWH alone, 2.5%
144 aspirin +/- LMWH, 1.8% DOAC +/- LMWH), further surgery (30% LMWH alone,
145 5.5% aspirin +/- LMWH, 5.3% DOAC +/- LMWH), and wound infection (15% LMWH
146 alone, 1.7% aspirin +/- LMWH, 1.8% DOAC +/- LMWH).

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

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

151 **Discussion**

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

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

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

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

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

185 We observed similar bleeding risks between agents in both THA and TKRs, with
186 absolute numbers remaining small, reflecting rates seen in similar cohorts (24).

187 Concerns have been raised regarding the higher risk of intra- and post-operative
188 bleeding with DOAC use (3, 25). However effect sizes are often small, with other
189 studies demonstrating no statistical differences (12, 14, 26), suggesting a comparative
190 safety profile in line with our study.

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

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

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

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

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

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

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

224

225 **Word Count**

226 2531 words

227

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