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1 Title

Aspirin compared to enoxaparin or rivaroxaban for thromboprophylaxis following hip
and knee replacement.

4 Abstract

Background: The risk of venous thromboembolism following major orthopaedic
surgery is among the highest for all surgical specialties. Our hospital guidelines for
thromboprophylaxis following elective primary total hip or knee replacement are
based on American College of Chest Physicians guidance. The most recent change to
local guidelines was the introduction of the extended aspirin regimen as standard
thromboprophylaxis.

11 Objective: To establish the appropriateness of this regimen by comparing venous
12 thromboembolism rates in patients receiving extended aspirin to previous regimens.

13 Setting: The largest dedicated orthopaedic hospital in Ireland

Methods: This was a retrospective cohort study. Data were collected from patient
 record software. All eligible patients undergoing primary total hip or knee replacement
 between 1st January 2010 and 30th June 2016 were included.

Main Outcome Measure: Venous thromboembolism up to six months post-operatively.

Results: Of the 6,548 participants (55.3% female, mean age 65.4 years (\pm 11.8 years, 55.8% underwent total hip replacement), venous thromboembolism occurred in 65 (0.99%). Venous thromboembolism rate in both the inpatient enoxaparin group (n=961) and extended aspirin group (n=3,460) was 1.04% and was 0.66% in the

modified rivaroxaban group (n=1,212). Non-inferiority analysis showed the extended aspirin regimen to be equivalent to the modified rivaroxaban regimen. History of venous thromboembolism was the only significant demographic risk factor for postoperative venous thromboembolism (0.87% vs. 3.54%, p=0.0002).

Conclusion: In daily clinical practice, extended aspirin regimen is at least as effective as modified rivaroxaban for preventing clinically important venous thromboembolism among patients undergoing hip or knee arthroplasty who are discharged from the hospital without complications. Aspirin can be considered a safe and effective agent in the prevention of venous thromboembolism after total hip or total knee replacement.

32 Impact of findings on practice

- The findings of this study, along with other emerging evidence, is pertinent to
 Clinical Pharmacists when advising on patient care and developing local
 guidelines on VTE prophylaxis.
- This study should encourage future work to establish the efficacy of aspirin for
 VTE prophylaxis in a robust RCT setting, and also to investigate potential
 benefits in reducing bleeding complications.
- Aspirin thromboprophylaxis may offer a cost-effective alternative to
 practitioners who may fear non-adherence to therapy in their patients due to
 financial difficulties.
- 42

43 Key Words

44 arthroplasty, replacement, hip, knee, aspirin, enoxaparin, rivaroxaban, venous45 thromboembolism

46 Main Text

47 Introduction

The American College of Chest Physicians (ACCP) have calculated the cumulative rate of non-fatal symptomatic VTE in the first 35 days after surgery as 1.8% in patients treated with low-molecular-weight heparin (LMWH) and 4.3% in untreated patients [1]. Reported symptomatic VTE rates with aspirin or multimodal aspirin regimens range from 0.1%-4.17% [2-12], with rivaroxaban range from 0.47%-1.4% [13, 14, 10, 15, 11] and with enoxaparin range from 0.65%-2.5% [13, 5, 15].

Until recently, the evidence supporting the effectiveness of aspirin in this setting is 54 55 based mainly on observational and registry studies [1]. Evidence is now emerging from randomised controlled trials (RCTs), most notably the EPCAT-1 and EPCAT-2 56 trials [11, 2]. The National Institute for Health and Care Excellence (NICE) updated 57 58 their guidelines in March 2018 and now include aspirin as an option for VTE prophylaxis following elective total hip replacement (THR) and total knee 59 replacement (TKR) [16]. In contrast, a recent Australian Evidence Review [17] found 60 the evidence to be equivocal with regard to aspirin for VTE prophylaxis. 61

Guidelines in our hospital in use at the time of the study were based on ACCP guidance
[1]. A timeline of the changes to local guidance can be seen in Table 1. The current
standard thromboprophylaxis regimen in the hospital is the extended aspirin regimen.

65 Aim of the Study

To establish whether aspirin is an appropriate agent for thromboprophylaxis in ourpatient population by comparing the rate of VTE six months' post-surgery in patients

receiving extended aspirin to those receiving the previous regimens of inpatientenoxaparin or the modified rivaroxaban regimen.

70 Ethics Approval

71 Ethical approval was granted by the hospital Ethics Committee (reference
72 CAPP/2017/ETH/SH-DCEO-0021).

73 Methods

The study site is the largest dedicated orthopaedic hospital in Ireland, with 2,717 inpatients admitted in 2016, and specialises in elective arthroplasty. The Joint Register was established in our hospital in 2004, and its purpose is to record and monitor postoperative outcomes, including VTE [18].

This is a retrospective cohort study, whereby patients were grouped according to the
type of thromboprophylaxis prescribed. The rate of VTE in each group was the
outcome of interest.

81 Inclusion and Exclusion Criteria

An interval sampling method was used whereby all patients who underwent elective primary TKR or THR within the study period, 1st January 2010 to 30th June 2016, were included. Each surgery represented one unit of study; if a patient underwent more than one procedure during the study period, they appeared more than once in the dataset. Patients were excluded if:

- Their surgery was cancelled after admission.
- They did not attend their six-month Joint Register appointment (as the required information was not available for these patients).

4

Data were collected from Bluespier[®]; the hospital's electronic patient record software.
It was determined whether participants developed a VTE using their electronic file.
Pre-discharge VTE was recorded as an inpatient complication by a clinician. Postdischarge VTE was recorded on the report generated at the six-month Joint Register
review.

The data were exported as a Microsoft Excel[®] report, cleaned and pseudonymised.
Patients were allocated to a thromboprophylaxis group on an intention to treat (ITT)
basis, according to the instructions in their Theatre notes, discharge letter or discharge
prescription.

99 Statistical methods

Treatment group allocation was on an ITT basis, and this is similar to the approach
taken in a clinical trial setting. A similar approach was used in Hamilton *et al's* study
[4].

103 Categorical patient characteristics were described by their counts and percentages in
104 each category. Continuous characteristics were described by their means and SDs,
105 medians and IQRs, and total ranges.

106 VTE rates and 95% confidence intervals (CIs) were estimated using Poisson107 regression.

We evaluated the equivalence (and thus non-inferiority) of *the Extended aspirin regimen* to *Modified rivaroxaban regimen* based on the risk difference for VTE, using a margin of $\pm 1.0\%$. The authors were confident that the $\pm 1.0\%$ margin of difference in the rate of outcome (VTE) between regimens would represent clinical acceptability and is supported by Wilson *et al* [19]. We reported both the unadjusted and adjusted risk differences and respective 90% confidence intervals (which is the equivalent of
two one-sided tests [TOST], each with alpha = 0.05 [20]. Covariate adjustment was
made using the standardized risk difference estimated with a marginal structural
binomial regression model [21]. The covariates were age (years), sex, body mass index
(BMI kg/m²), any history of VTE (none vs Deep Vein Thrombosis [DVT] vs
Pulmonary Embolism [PE]), and procedure (TKR vs THR). Patients with missing
covariate data were excluded from the adjusted risk difference models.

In addition to the head to head comparison between *Modified rivaroxaban regimen* and *Enoxaparin, then aspirin* and we similarly evaluated the equivalence in the VTE risk difference between patients seen from 2010 to 2012 and those seen from 2013 to 2016, irrespective of the actual VTE prophylaxis received. This was because the *Extended aspirin regimen* was almost always used from 2013 on, and very rarely used before 2013 (see supplemental figure 1).

126 All analysis were conducted using the R Project for Statistical Computing v3.4.3 [22]

127 **Results**

Of the 6,945 patients admitted during the study period, 6,548 (55.3% female, 55.8%
THR, mean age was 65.4 years (± 11.8years) and mean BMI was 30.3kg/m² (± 5.6 kg/m²)) were eligible for inclusion. Reasons for exclusion are shown in Figure 1.
Demographics are outlined in Table 2 with the percentages reported calculated based upon participants for whom data were available.

133 Information on the regimen prescribed was available for 6,418 participants (98.01%).

134 No VTE occurred in patients for whom data on the thromboprophylaxis regimen

prescribed were missing. The proportion of participants allocated to each treatmentgroup is summarised in Table 2.

137 Sixty-five participants had a VTE (0.99% of 6,548). VTE rates and 95% CIs across 138 study all years are given in Figure 2. The unadjusted VTE risk difference comparing 139 the *Extended aspirin regimen* to *Modified rivaroxaban regimen* (n = 4,673) was 0.38% 140 with a 90% TOST CI of -0.096% to 0.86%, which suggests equivalence between the 141 two (i.e. the CI falls within the margin interval of \pm 1%).

The unadjusted VTE risk difference comparing patients seen in 2010-2012 (inpatient enoxaparin, rivaroxaban or modified rivaroxaban) to those seen in 2013-2016 (extended aspirin) was 0.12% with a 90% TOST CI of -0.28% to 0.52%, suggesting equivalence in VTE risk between the two time periods (n = 6548).

146 In demographic analysis, history of VTE was identified as the only statistically and clinically significant risk factor for post-operative VTE (0.87% vs. 3.54%, p=0.0002). 147 The results were not appreciably different in those with a history of VTE vs those 148 without (though our study would not have been well-powered to detect any clinically 149 meaningful differences, given that only 5% of our sample had a history of VTE). A 150 151 history of PE was associated with an increased risk of post-operative VTE (0.87% vs. 152 5.56%, p=0.0004). The increase in risk was not as large with a history of DVT but was statistically significant (0.87% vs. 2.46% p=0.037). When history of VTE was 153 154 adjusted for other demographic variables (age, sex and BMI) the adjusted OR was 3.56 (95% CI 1.77–7.14; p<0.001) for any VTE history, and 2.13 (0.76–6.00; p=0.152) for 155 DVT and 6.38 (2.66 – 15.32; p<0.001) for PE specifically. 156

157 The VTE rates in the inpatient enoxaparin, modified rivaroxaban and extended aspirin 158 groups are shown in Table 3. The demographics of each group are detailed in the 159 supplementary material.

160 **Discussion**

161 The results indicate that, when known confounding factors are accounted for, there 162 was no significant difference in the effectiveness of these regimens in the prevention 163 of VTE, therefore the extended aspirin regimen is an appropriate thromboprophylaxis 164 regimen for our patients.

165 There was no difference in the incidence of VTE between the extended aspirin and inpatient enoxaparin groups, with reported VTE rates of 1.04% in both groups. 166 167 Additionally, the rates of DVT and PE were almost identical. The rate of VTE in the 168 modified rivaroxaban group was lower at 0.66%. However, both the adjusted and unadjusted risk difference between these groups suggests the two treatments are 169 equivalent. No clinically significant difference existed between the groups, since the 170 difference in VTE rate between the groups was less than the clinically significant 171 difference we proposed of 1%. 172

Reported symptomatic VTE rates with aspirin or multimodal aspirin regimens range
from 0.1%-4.17% [2-12], with rivaroxaban ranging from 0.47%-1.4% [13, 14, 10, 15,
11], and with enoxaparin regimens ranging from 0.65%-2.5% [13, 5, 15]. Our results
fall within the expected range based on these studies.

In keeping with our findings, eight studies found no significant difference in VTE rates
between aspirin and LMWH regimens [2, 3, 5-7, 23-25]. Wilson *et al's* recent
systematic review [19] found no evidence of a difference in VTE rates between aspirin

and LMWH-treated groups. The Pulmonary Embolism Prevention (PEP) trial [9] used 180 aspirin 160mg daily, similar to the dose used in our study (150mg daily), and a similar 181 VTE rate of 1.1% was reported in the aspirin group, as well as similar DVT and PE 182 rates of 0.73% and 0.39% respectively. A pooled analysis of data from 14 RCTs by 183 Brown [26] found no statistically significant difference between aspirin and LMWH 184 regimens, and reported symptomatic DVT rates of 0.96% for aspirin and 1.28% for 185 186 LMWH groups (p=0.057, RR 1.33, 95% CI 0.99-1.78), and PE rates of 0.62% for aspirin and 0.45% for LMWH groups (p=0.13, RR 0.73, 95% CI 0.49-1.09). In 187 188 comparison, DVT rates were lower in our study and PE rates were similar. Anderson et al's RCT [2] reported that a multimodal aspirin regimen was non-inferior to LMWH 189 (AD 1%, 95% CI -0.5-2.5%, p<0.001), though the reported VTE rate in the aspirin 190 group was much lower than in our study at 0.3%; this may have been due to small 191 sample size. The meta-analysis conducted by An et al in 2016 [27] concluded that 192 aspirin, both alone and in multimodal regimens, resulted in a DVT rate of 1.2% and a 193 PE rate of 0.6%. The DVT rate observed in our study is lower than expected from An 194 et al's results, however the PE rate is similar. 195

196 The rate of symptomatic VTE in the modified rivaroxaban group is similar to the rate 197 of 0.5% reported with rivaroxaban in a meta-analysis by Gómez-Outes et al [28]. A recent RCT by Anderson *et al* [11], comparing rivaroxaban to a multimodal regimen 198 of rivaroxaban followed by aspirin (81mg daily), reported a VTE rate of 0.7% and 199 0.64% in the respective groups, showing non-inferiority of the aspirin regimen (AD 200 0.06%, 95% CI -0.55-0.66%, p<0.001). Though the overall VTE rates reported by 201 202 Anderson *et al* are lower than observed in our study, they reach similar conclusions. Rath et al [10] compared aspirin 150mg daily, the same dose used in our study, to 203 rivaroxaban. They found a significant reduction in PE rates with rivaroxaban 204

205 (p=0.0084) but no significant difference in symptomatic DVT rates. These are similar to our findings, where a larger reduction was seen in PE rates compared to DVT rates, 206 however the difference was not found to be significant in our study. Zou et al [25] 207 208 found a much larger difference in DVT rates between aspirin (100mg daily) and rivaroxaban groups (16.36% vs. 2.94%), and this was statistically significant 209 (p=0.017). This large difference may be due to (i) the inclusion of asymptomatic DVT 210 211 in their outcome measure, which was not included in our study, (ii) the use of a lower dose of aspirin, or (iii) the small sample size. In their systematic review Wilson et al 212 213 [19] found that, compared with aspirin, rates of asymptomatic DVT in TKR were lower with rivaroxaban. However, they found insufficient evidence to demonstrate an 214 effect on symptomatic DVT or PE, which are outcomes of clinical importance. 215

Potential confounding factors were generally well balanced between the groups investigated by our study, reducing their impact on the comparison of agents. Additional analysis was completed to account for confounding factors and the adjusted results were similar to the unadjusted results. The advances in post-operative management and decrease in length of stay (LOS) over the study period may have had a positive impact in reducing VTE rates, and this may be a confounding factor in comparing the inpatient enoxaparin group to the extended aspirin group.

The overall demographics of the study population were similar to that observed in other studies and registries. The demographic analysis found that a history of VTE was associated with a four-fold higher risk of post-operative VTE, and the risk in participants with a history of PE was six times higher than in those without prior VTE, reflecting the literature [29-33]. This remained the case when history of VTE was adjusted for other demographics (age, sex and BMI). No other demographic risk factor was found to be statistically or clinically significant in this study. Just under 5%

(n=311) of participants had a history of VTE. In other similar studies [2, 34-37, 15, 230 38] the proportion of patients with a history of VTE ranged from 1.22% [36] to 3.99% 231 [35]. Some studies excluded these participants [4, 23, 14, 8, 9, 24, 25]. Therefore, 232 participants in our study may be considered a higher risk population in comparison to 233 other studies. Since history of VTE was the strongest risk factor for post-operative 234 VTE in our patients, consideration should be given to those with a prior VTE when 235 236 assessing risk and prescribing thromboprophylaxis. Of note, the Australian Evidence Review on the topic specified that aspirin should only be considered in patients 237 238 without major risk factors for VTE or bleeding, therefore patients with a history of VTE would be excluded [20]. Future research should evaluate differences in treatment 239 240 and adverse event effects in relevant subgroups of patients e.g. race/ethnicity, body 241 weight, tobacco use, presurgical use of antiplatelet drugs or warfarin.

242 Limitations

243 As this was an observational study, it was not possible to establish the effectiveness of the regimen. The possibility of errors occurring in entry of data to Bluespier[®] by 244 245 clinicians cannot be excluded, as the data were not entered specifically for the purpose 246 of this study. Due to the nature of the data source used, there was a small proportion 247 of missing data. VTE may have been under-reported, as our study data were collected retrospectively from a computer database reliant on physician and patient reporting. It 248 249 was not possible to determine compliance with thromboprophylaxis post-discharge, and it was assumed that most participants continued the regimen initially prescribed. 250 251 These factors were consistent across the entire study population and should not influence the comparison of outcomes between treatment groups. Other confounding 252 factors not recorded on the electronic record, such as inflammatory state, 253 254 haematological disorders and malignancy, could not be included for when adjusting the results to account for demographics. There were no data available on bleeding rates
with the regimens used in the study, therefore this should be investigated in future
research.

258 Conclusion

It can be concluded that the extended aspirin regimen is appropriate for thromboprophylaxis following elective primary TKR and THR. There was no difference between the extended aspirin and inpatient enoxaparin groups, which both had VTE rates of 1.04%. The modified rivaroxaban group had a lower VTE rate of 0.66%, but the difference in comparison with the extended aspirin group was not statistically significant and was not considered clinically significant.

This study identified an overall low VTE rate of 0.99% in our patient population. History of VTE was identified as a strong independent risk factor for post-operative VTE, particularly PE, and this was statistically and clinically significant. No other significant risk factors were identified.

The findings of this study have implications locally in confirming the equivalence of our current standard thromboprophylaxis regimen to previously used regimens. This study adds to the growing evidence supporting the use of aspirin for thromboprophylaxis in the orthopaedic setting. Aspirin may be particularly advantageous in terms of cost-saving and accessibility.

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281 **Conflicts of Interest**

282 The authors have no conflicts of interest to declare

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Table 1: Thromboprophylaxis Regimens in CNOH

Timeline	Regimen Name	Reason for introduction of regimen	Regimen Details
Up to 2010	Inpatient Enoxaparin Regimen	ACCP guidance with limited oral alternatives [39]	Enoxaparin 40mg OD commenced 12 hours post- operatively, and continued until discharge

2010	Rivaroxaban Regimen	Introduction of DOACs to market Implementation of ACCP and NICE guidance on extended thromboprophylaxis [39, 30]	Rivaroxaban10mg OD commenced 6-10 hours post-operatively, and continued for 14 days (TKR) or 35 days (THR)
2010-2012	Modified Rivaroxaban Regimen	Reports of wound complications with rivaroxaban regimen locally and in literature [40, 41]	Enoxaparin 40mg OD commenced 12 hours post- operatively for three doses, followed by rivaroxaban 10mg OD for 14 days (TKR) or 35 days (THR)
2013 - Present	Extended Aspirin Regimen	Reports of major bleeding with modified rivaroxaban regimen locally ACCP guidance on aspirin [1]	Enoxaparin 40mg OD commenced 12 hours post- operatively for three doses, followed by aspirin 150mg OD for 28 days

DOACs = Direct Acting Oral Anticoagulants, OD = Once Daily

			Median	(Min,
Variable	Ν	Mean SD	[IQR]	Max)
Sex	6548			
Males		2928		
		(44.7%)		
Female		3620		
		(55.3%)		
Age (years)	6548	65.4 ± 11.8	66 (58, 74)	(13, 95)
65+ years	6548			
No		2829		
		(43.2%)		
Yes		3719		
		(56.8%)		
BMI (kg/m ²)	6173	30.3 ± 5.6	30 (26, 34)	(13, 51)
Obese (BMI $\geq 30 \text{kg/m}^2$)	6173			
No		2950		
		(47.8%)		
Yes		3223		
		(52.2%)		
Length of stay (days)	6548	5.9 ± 10.3	5 (4, 7)	(0, 522)
Procedure	6548		. (., .)	(*,*==)
TKR	00.0	2897		
		(44.2%)		
THR		3651		
		(55.8%)		
VTE type	6548	(001070)		
None	00.0	6483 (99%)		
DVT before discharge		4 (0.1%)		
PE before discharge		14 (0.2%)		
DVT at 6 months		28 (0.4%)		
PE at 6 months		19 (0.3%)		
Anticoagulant	6225	(0.070)		
None	0220	3971		
1.042		(63.8%)		
Aspirin		1810		
7.6pm		(29.1%)		
Other		444 (7.1%)		
History of VTE	6265	(,,)		
None	0205	5954 (95%)		
DVT		203 (3.2%)		
PE		108 (1.7%)		
VTF prophylaxis	6418	100 (1.770)		
Extended aspirin regimen	0110	3460		
Entenace aspirin regimen		(53.9%)		
Innatient Enovaparin		961 (15%)		
Modified rivaroyaban		1212		
regimen		(18.9%)		
Other*		785 (12 2%)		
Other		105 (12.270)		

Table 2 : Demographics of Study Population

*The majority of this group consisted of patients taking regular anticoagulants or antiplatelets other than aspirin who resumed their usual medications in place of a standard regimen. A small proportion consisted of patients who received rivaroxaban as per product licence.

Table 3 Rates of VTE in Treatment Group

Thromboprophylaxis Regimen	Number	VTE n (%)						
	in Group			TADE	DUT			
		I otal VIE	I otal DV I	I otal PE	DVI	PE Before	DVI at	PE at Joint
					Before	Discharge	Joint	Register
					Discharge		Register	
Inpatient Enoxaparin Regimen	961	10 (1.04%)	5 (0.52%)	5 (0.52%)	1 (0.10%)	3 (0.31%)	4 (0.42%)	2 (0.21%)
(up to 2010)								
Modified Rivaroxaban	1,212	8 (0.66%)	4 (0.33%)	4 (0.33%)	0 (0%)	2 (0.17%)	4 (0.33%)	2 (0.17%)
Regimen (2010-2012)								
		p=0.154*						
Extended Aspirin Regimen	3,460	36 (1.04%)	17 (0.49%)	19 (0.55%)	1 (0.03%)	5 (0.14%)	16 (0.46%)	14 (0.40%)
(2013-present)								

*compared to extended aspirin

Figures



Figure 1. Participants Included and Excluded from the Study



Figure 2: Yearly VTE incidence (with 95% CIs), regardless of VTE prophylaxis.