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1 **Title**

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

4 **Abstract**

5 **Background:** The risk of venous thromboembolism following major orthopaedic
6 surgery is among the highest for all surgical specialties. Our hospital guidelines for
7 thromboprophylaxis following elective primary total hip or knee replacement are
8 based on American College of Chest Physicians guidance. The most recent change to
9 local guidelines was the introduction of the extended aspirin regimen as standard
10 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

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

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

19 **Results:** Of the 6,548 participants (55.3% female, mean age 65.4 years (\pm 11.8 years,
20 55.8% underwent total hip replacement), venous thromboembolism occurred in 65
21 (0.99%). Venous thromboembolism rate in both the inpatient enoxaparin group
22 (n=961) and extended aspirin group (n=3,460) was 1.04% and was 0.66% in the

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

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

32 **Impact of findings on practice**

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

42

43 **Key Words**

44 arthroplasty, replacement, hip, knee, aspirin, enoxaparin, rivaroxaban, venous
45 thromboembolism

46 **Main Text**

47 **Introduction**

48 The American College of Chest Physicians (ACCP) have calculated the cumulative
49 rate of non-fatal symptomatic VTE in the first 35 days after surgery as 1.8% in patients
50 treated with low-molecular-weight heparin (LMWH) and 4.3% in untreated patients
51 [1]. Reported symptomatic VTE rates with aspirin or multimodal aspirin regimens
52 range from 0.1%-4.17% [2-12], with rivaroxaban range from 0.47%-1.4% [13, 14, 10,
53 15, 11] and with enoxaparin range from 0.65%-2.5% [13, 5, 15].

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

62 Guidelines in our hospital in use at the time of the study were based on ACCP guidance
63 [1]. A timeline of the changes to local guidance can be seen in Table 1. The current
64 standard thromboprophylaxis regimen in the hospital is the extended aspirin regimen.

65 **Aim of the Study**

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

68 receiving extended aspirin to those receiving the previous regimens of inpatient
69 enoxaparin 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**

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

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

81 Inclusion and Exclusion Criteria

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

86 Patients were excluded if:

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

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

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

99 **Statistical methods**

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

108 We evaluated the equivalence (and thus non-inferiority) of *the Extended aspirin*
109 *regimen* to *Modified rivaroxaban regimen* based on the risk difference for VTE, using
110 a margin of $\pm 1.0\%$. The authors were confident that the $\pm 1.0\%$ margin of difference
111 in the rate of outcome (VTE) between regimens would represent clinical acceptability
112 and is supported by Wilson *et al* [19]. We reported both the unadjusted and adjusted

113 risk differences and respective 90% confidence intervals (which is the equivalent of
114 two one-sided tests [TOST], each with alpha = 0.05 [20]. Covariate adjustment was
115 made using the standardized risk difference estimated with a marginal structural
116 binomial regression model [21]. The covariates were age (years), sex, body mass index
117 (BMI kg/m²), any history of VTE (none vs Deep Vein Thrombosis [DVT] vs
118 Pulmonary Embolism [PE]), and procedure (TKR vs THR). Patients with missing
119 covariate data were excluded from the adjusted risk difference models.

120 In addition to the head to head comparison between *Modified rivaroxaban regimen*
121 and *Enoxaparin, then aspirin* and we similarly evaluated the equivalence in the VTE
122 risk difference between patients seen from 2010 to 2012 and those seen from 2013 to
123 2016, irrespective of the actual VTE prophylaxis received. This was because the
124 *Extended aspirin regimen* was almost always used from 2013 on, and very rarely used
125 before 2013 (see supplemental figure 1).

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

127 **Results**

128 Of the 6,945 patients admitted during the study period, 6,548 (55.3% female, 55.8%
129 THR, mean age was 65.4 years (\pm 11.8years) and mean BMI was 30.3kg/m² (\pm 5.6
130 kg/m²)) were eligible for inclusion. Reasons for exclusion are shown in Figure 1.
131 Demographics are outlined in Table 2 with the percentages reported calculated based
132 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

135 prescribed were missing. The proportion of participants allocated to each treatment
136 group 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 $\pm 1\%$).

142 The unadjusted VTE risk difference comparing patients seen in 2010-2012 (inpatient
143 enoxaparin, rivaroxaban or modified rivaroxaban) to those seen in 2013-2016
144 (extended aspirin) was 0.12% with a 90% TOST CI of -0.28% to 0.52%, suggesting
145 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
147 clinically significant risk factor for post-operative VTE (0.87% vs. 3.54%, p=0.0002).
148 The results were not appreciably different in those with a history of VTE vs those
149 without (though our study would not have been well-powered to detect any clinically
150 meaningful differences, given that only 5% of our sample had a history of VTE). A
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
153 statistically significant (0.87% vs. 2.46% p=0.037). When history of VTE was
154 adjusted for other demographic variables (age, sex and BMI) the adjusted OR was 3.56
155 (95% CI 1.77–7.14; p<0.001) for any VTE history, and 2.13 (0.76–6.00; p=0.152) for
156 DVT and 6.38 (2.66 – 15.32; p<0.001) for PE specifically.

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
166 inpatient enoxaparin groups, with reported VTE rates of 1.04% in both groups.
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
169 unadjusted risk difference between these groups suggests the two treatments are
170 equivalent. No clinically significant difference existed between the groups, since the
171 difference in VTE rate between the groups was less than the clinically significant
172 difference we proposed of 1%.

173 Reported symptomatic VTE rates with aspirin or multimodal aspirin regimens range
174 from 0.1%-4.17% [2-12], with rivaroxaban ranging from 0.47%-1.4% [13, 14, 10, 15,
175 11], and with enoxaparin regimens ranging from 0.65%-2.5% [13, 5, 15]. Our results
176 fall within the expected range based on these studies.

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

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

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

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

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

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

230 (n=311) of participants had a history of VTE. In other similar studies [2, 34-37, 15,
231 38] the proportion of patients with a history of VTE ranged from 1.22% [36] to 3.99%
232 [35]. Some studies excluded these participants [4, 23, 14, 8, 9, 24, 25]. Therefore,
233 participants in our study may be considered a higher risk population in comparison to
234 other studies. Since history of VTE was the strongest risk factor for post-operative
235 VTE in our patients, consideration should be given to those with a prior VTE when
236 assessing risk and prescribing thromboprophylaxis. Of note, the Australian Evidence
237 Review on the topic specified that aspirin should only be considered in patients
238 without major risk factors for VTE or bleeding, therefore patients with a history of
239 VTE would be excluded [20]. Future research should evaluate differences in treatment
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
244 of the regimen. The possibility of errors occurring in entry of data to Bluespier[®] by
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
248 retrospectively from a computer database reliant on physician and patient reporting. It
249 was not possible to determine compliance with thromboprophylaxis post-discharge,
250 and it was assumed that most participants continued the regimen initially prescribed.
251 These factors were consistent across the entire study population and should not
252 influence the comparison of outcomes between treatment groups. Other confounding
253 factors not recorded on the electronic record, such as inflammatory state,
254 haematological disorders and malignancy, could not be included for when adjusting

255 the results to account for demographics. There were no data available on bleeding rates
256 with the regimens used in the study, therefore this should be investigated in future
257 research.

258 **Conclusion**

259 It can be concluded that the extended aspirin regimen is appropriate for
260 thromboprophylaxis following elective primary TKR and THR. There was no
261 difference between the extended aspirin and inpatient enoxaparin groups, which both
262 had VTE rates of 1.04%. The modified rivaroxaban group had a lower VTE rate of
263 0.66%, but the difference in comparison with the extended aspirin group was not
264 statistically significant and was not considered clinically significant.

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

269 The findings of this study have implications locally in confirming the equivalence of
270 our current standard thromboprophylaxis regimen to previously used regimens. This
271 study adds to the growing evidence supporting the use of aspirin for
272 thromboprophylaxis in the orthopaedic setting. Aspirin may be particularly
273 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]	Rivaroxaban 10mg 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

Table 2 : Demographics of Study Population

Variable	N	Mean SD	Median [IQR]	(Min, 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 ≥30kg/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		2897 (44.2%)		
THR		3651 (55.8%)		
VTE type	6548			
None		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			
None		3971 (63.8%)		
Aspirin		1810 (29.1%)		
Other		444 (7.1%)		
History of VTE	6265			
None		5954 (95%)		
DVT		203 (3.2%)		
PE		108 (1.7%)		
VTE prophylaxis	6418			
Extended aspirin regimen		3460 (53.9%)		
Inpatient Enoxaparin		961 (15%)		
Modified rivaroxaban regimen		1212 (18.9%)		
Other*		785 (12.2%)		

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

*compared to extended aspirin

Figures

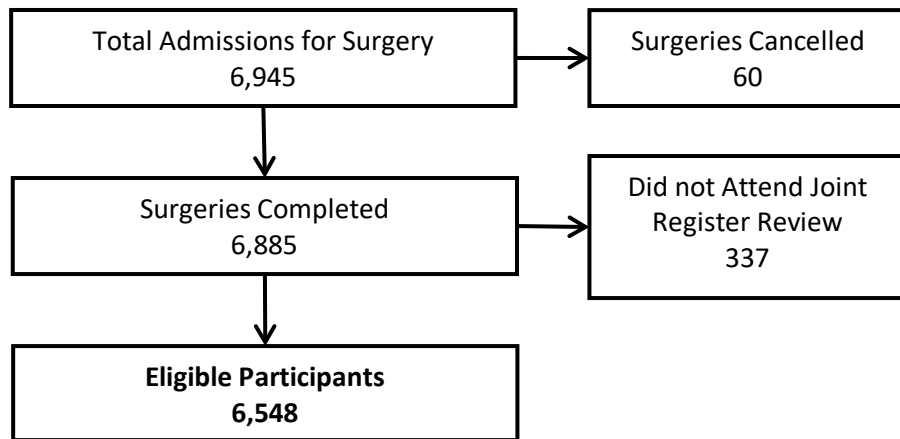


Figure 1. Participants Included and Excluded from the Study

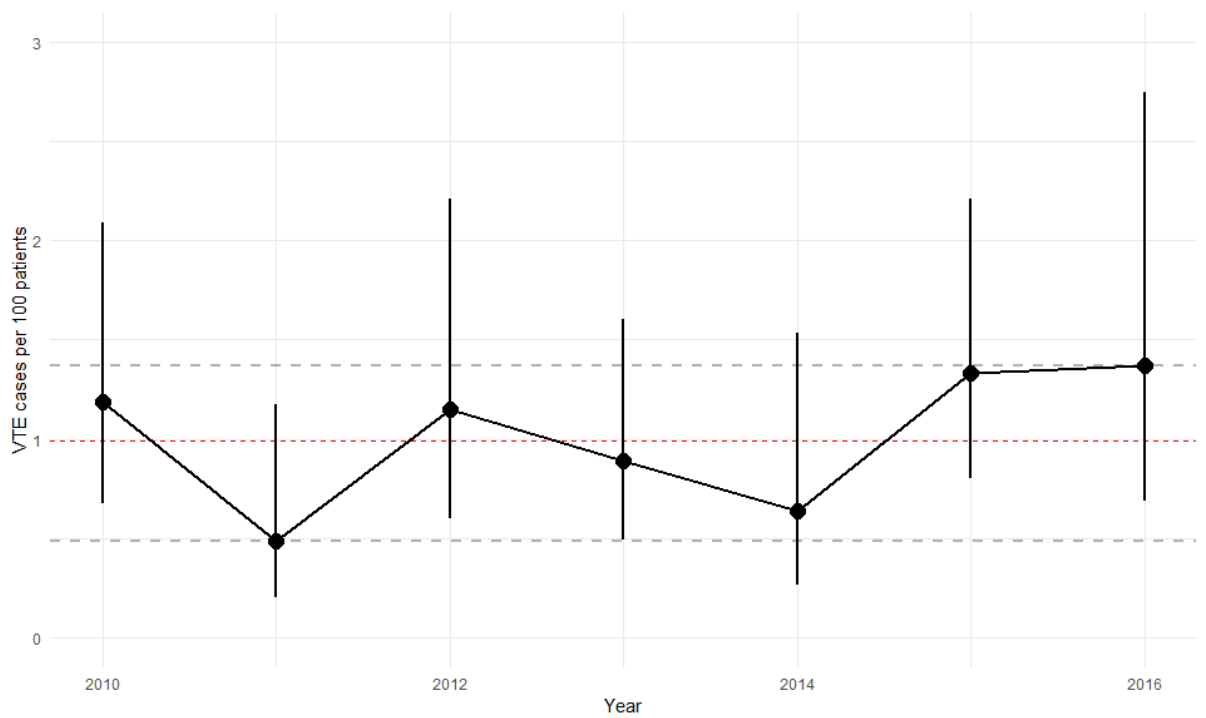


Figure 2: Yearly VTE incidence (with 95% CIs), regardless of VTE prophylaxis.