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Title	Aspirin compared to enoxaparin or rivaroxaban for thromboprophylaxis following hip and knee replacement.
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Publication date	2020-04-23
Original Citation	Ni Cheallaigh, S., Fleming, A., Dahly, D., Kehoe, E., O'Byrne, J. M., McGrath, B., O'Connell, C. and Sahm, L. J. (2020) 'Aspirin compared to enoxaparin or rivaroxaban for thromboprophylaxis following hip and knee replacement', International Journal of Clinical Pharmacy, 42, pp. 853-860. doi: 10.1007/s11096-020-01032-1
Type of publication	Article (peer-reviewed)
Link to publisher's version	https://link.springer.com/article/10.1007/s11096-020-01032-1 - 10.1007/s11096-020-01032-1
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Download date	2026-11-03 01:26:28
Item downloaded from	https://hdl.handle.net/10468/10260

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Title

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

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.

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

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 (± 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 post-operative 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.

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.

Key Words

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

Main Text

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 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 trials [11, 2]. The National Institute for Health and Care Excellence (NICE) updated their guidelines in March 2018 and now include aspirin as an option for VTE prophylaxis following elective total hip replacement (THR) and total knee replacement (TKR) [16]. In contrast, a recent Australian Evidence Review [17] found the evidence to be equivocal with regard to aspirin for VTE prophylaxis.

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.

Aim of the Study

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

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

Ethics Approval

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

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 post-operative 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.

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).

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. Post-discharge 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.

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].

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

VTE rates and 95% confidence intervals (CIs) were estimated using Poisson 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 ±1.0%. The authors were confident that the ±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/m^2), 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).

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

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/m^2 (± 5.6 kg/m^2)) 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.

Information on the regimen prescribed was available for 6,418 participants (98.01%). No VTE occurred in patients for whom data on the thromboprophylaxis regimen

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

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

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). The results were not appreciably different in those with a history of VTE vs those without (though our study would not have been well-powered to detect any clinically meaningful differences, given that only 5% of our sample had a history of VTE). A history of PE was associated with an increased risk of post-operative VTE (0.87% vs. 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 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 DVT and 6.38 (2.66 – 15.32; p<0.001) for PE specifically.

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

Discussion

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

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. Additionally, the rates of DVT and PE were almost identical. The rate of VTE in the modified rivaroxaban group was lower at 0.66%. However, both the adjusted and unadjusted risk difference between these groups suggests the two treatments are equivalent. No clinically significant difference existed between the groups, since the difference in VTE rate between the groups was less than the clinically significant difference we proposed of 1%.

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 aspirin 160mg daily, similar to the dose used in our study (150mg daily), and a similar VTE rate of 1.1% was reported in the aspirin group, as well as similar DVT and PE rates of 0.73% and 0.39% respectively. A pooled analysis of data from 14 RCTs by Brown [26] found no statistically significant difference between aspirin and LMWH regimens, and reported symptomatic DVT rates of 0.96% for aspirin and 1.28% for 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 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 (AD 1%, 95% CI −0.5-2.5%, p<0.001), though the reported VTE rate in the aspirin group was much lower than in our study at 0.3%; this may have been due to small sample size. The meta-analysis conducted by An *et al* in 2016 [27] concluded that aspirin, both alone and in multimodal regimens, resulted in a DVT rate of 1.2% and a PE rate of 0.6%. The DVT rate observed in our study is lower than expected from An *et al's* results, however the PE rate is similar.

The rate of symptomatic VTE in the modified rivaroxaban group is similar to the rate 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 of rivaroxaban followed by aspirin (81mg daily), reported a VTE rate of 0.7% and 0.64% in the respective groups, showing non-inferiority of the aspirin regimen (AD 0.06%, 95% CI −0.55-0.66%, p<0.001). Though the overall VTE rates reported by 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 rivaroxaban. They found a significant reduction in PE rates with rivaroxaban

(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, however the difference was not found to be significant in our study. Zou *et al* [25] 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 (p=0.017). This large difference may be due to (i) the inclusion of asymptomatic DVT 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* [19] found that, compared with aspirin, rates of asymptomatic DVT in TKR were lower with rivaroxaban. However, they found insufficient evidence to demonstrate an effect on symptomatic DVT or PE, which are outcomes of clinical importance.

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, 38] the proportion of patients with a history of VTE ranged from 1.22% [36] to 3.99% [35]. Some studies excluded these participants [4, 23, 14, 8, 9, 24, 25]. Therefore, participants in our study may be considered a higher risk population in comparison to other studies. Since history of VTE was the strongest risk factor for post-operative VTE in our patients, consideration should be given to those with a prior VTE when assessing risk and prescribing thromboprophylaxis. Of note, the Australian Evidence Review on the topic specified that aspirin should only be considered in patients 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 and adverse event effects in relevant subgroups of patients e.g. race/ethnicity, body weight, tobacco use, presurgical use of antiplatelet drugs or warfarin.

Limitations

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 clinicians cannot be excluded, as the data were not entered specifically for the purpose of this study. Due to the nature of the data source used, there was a small proportion 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 was not possible to determine compliance with thromboprophylaxis post-discharge, and it was assumed that most participants continued the regimen initially prescribed. These factors were consistent across the entire study population and should not influence the comparison of outcomes between treatment groups. Other confounding factors not recorded on the electronic record, such as inflammatory state, 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.

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.

Acknowledgements

The authors would like to thank all the staff in Cappagh National Orthopaedic Hospital who contributed to the study, particularly the Department of Anaesthetics the

277 Department of Orthopaedic Surgery, and the staff in the Pharmacy Department, Pre-
278 Assessment Clinic and Joint Register.

279 Funding

280 No funding was received for this study.

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

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

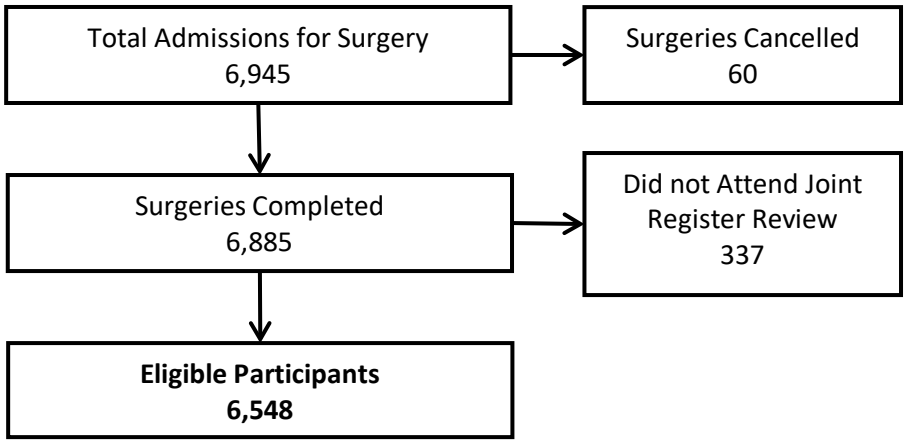


Figure 1. Participants Included and Excluded from the Study

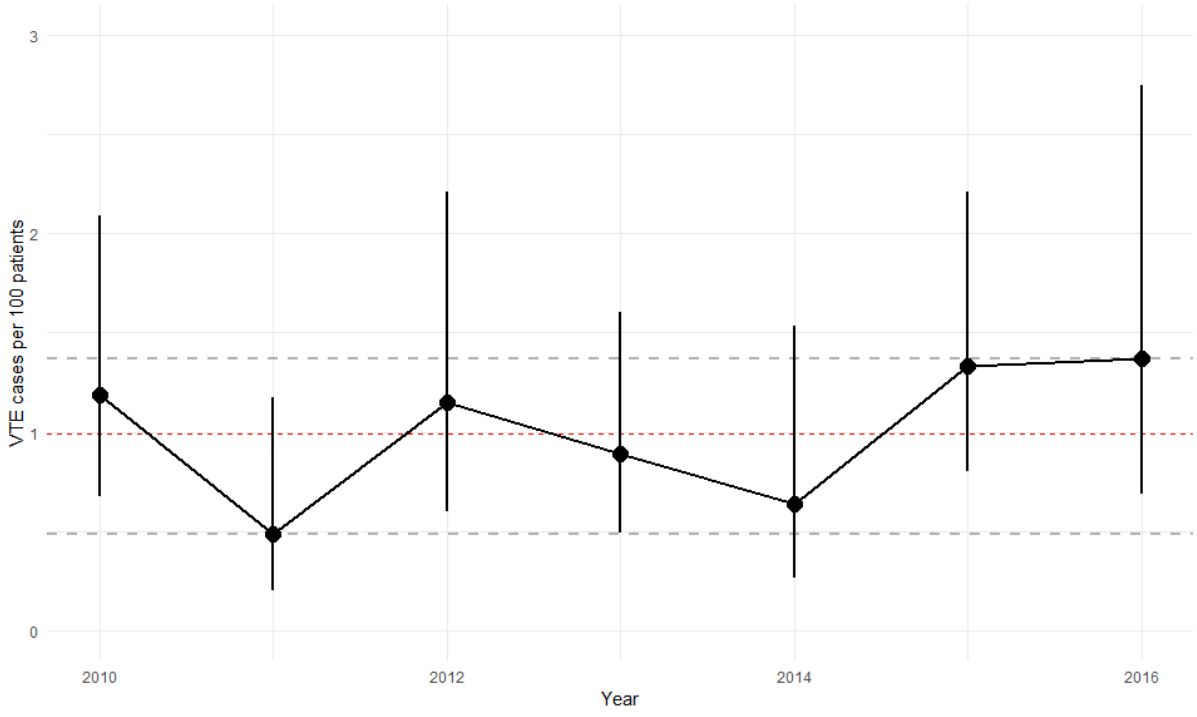


Figure 2: Yearly VTE incidence (with 95% CIs), regardless of VTE prophylaxis.