Major bleeding during secondary prevention of venous thromboembolism in patients who have completed anticoagulation: a systematic review and meta-analysis

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Summary. *Background:* The risk of major bleeding in patients who have completed anticoagulation therapy for unprovoked venous thromboembolism (VTE) is unknown. *Objective:* To report the major bleeding and fatal bleeding rates in patients randomized to placebo or observation (i.e. no anticoagulation therapy) for the secondary prevention of recurrent VTE. *Patients and methods:* We performed a systematic review and meta-analysis of the literature to summarize the rates of major bleeding and fatal bleeding in patients randomized to placebo or observation during the secondary prevention of VTE. Unrestricted searches of MEDLINE (January 1, 1950 to August 31, 2013), Embase (January 1, 1980 to August 31, 2013), and the Cochrane Register of Controlled Trials using the OVID interface were conducted. Publications from potentially relevant journals were also searched by hand. We used a random-effects model to pool study results and I^2 testing to assess for heterogeneity. *Results:* The analysis included 11 studies and 3965 patients who were followed for a median of 24 months. The overall pooled major bleeding rate was 0.45 per 100 patient-years (95% CI 0.29–0.64, $I^2 = 0\%$), and the overall pooled fatal bleeding rate was 0.14 per 100 patient-years (95% CI 0.057–0.26, $I^2 = 0\%$). *Conclusions:* Patients not receiving anticoagulant therapy for the secondary prevention of VTE experience major bleeding events, and this may have an impact on recommendations for extended treatment in this patient population.

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Introduction

The optimal duration of anticoagulation in patients with unprovoked venous thromboembolism (VTE) is controversial. In these patients, the risk of recurrent events during the first year after anticoagulation is discontinued is between 5% and 10% [1]. The American College of Chest Physicians recommends a minimum of 3 months of anticoagulation therapy and to consider prolonged treatment in patients with low or moderate risk of major bleeding events [1]. To counsel patients, clinicians need accurate estimates of the risks of recurrent VTE and of major bleeding episodes with different therapeutic strategies to ensure that the benefits outweigh the risks of long-term secondary prevention. The risk of major bleeding after completing anticoagulant therapy is unknown in this patient population. Therefore, the incremental risks of major bleeding with various treatment strategies over and above the risk with no anticoagulant therapy are unclear. This systematic review and meta-analysis evaluates the rate of major bleeding episodes in high-risk patients participating in trials for the secondary prevention of recurrent VTE who received placebo or observation only (i.e. no anticoagulant therapy).

Patients and methods

We searched MEDLINE (January 1, 1950 to August 31, 2013), EMBASE (January 1, 1980 to August 31, 2013), and the Cochrane Register of Controlled Trials using the OVID interface. Publications were also sought through a hand-search of potentially relevant journals. There were no restrictions on language, publication year, or type of publication. The search strategy included the MeSH terms *venous thrombosis, pulmonary embolism, aspirin, warfarin,*

and *acenocoumarol*. The following terms were also added to the search strategy: *recurrent venous thromboembolism, oral anticoagulants, dabigatran, rivaroxaban, apixaban,* and *ximelagatran*. The outcomes were major bleeding and fatal bleeding as defined by ISTH [2] or per individual study. The methodological quality was evaluated using the Risk of Bias Assessment Tool from the Cochrane Handbook for randomized trials [3]. The primary measurement was bleeding event rates reported per 100 patient-years stratified according to the underlying treatment strategy with its associated 95% CIs. Pooled measurements were calculated using a random-effects model within the Stats Direct software (version 2.7.9; StatsDirect Ltd, Cheshire, UK). Heterogeneity was assessed using the I^2 test [4].

Results and discussion

Our systematic search identified 636 citations. A total of 11 trials assessing anticoagulation for secondary prevention after VTE were included in the analysis [5–15]. Eight studies were randomized placebo-controlled trials [5–9,11,12,14], two studies compared vitamin K antagonist (VKA) treatment with observation [13,15], and one study compared different durations of VKA therapy (the period of observation for major bleeding and fatal bleeding events after completing a fixed duration of anticoagulation was included in this analysis) [9,10]. All studies were judged to be at low risk of bias according to the risk of bias assessment tool.

A total of 3965 patients were included in our analysis; 3630 were treated with placebo and 335 patients were simply observed for bleeding events (Table 1). The total population was followed for a median of 23.9 months (range 6–40.3 months); the median follow-up for those receiving placebo was 14.3 months (6–25.2 months) and 37.2 months for those enrolled in observation without anticoagulation only arms (32.7–40.3 months). The majority of patients were male (median 57%, range 51%–63%); the mean age varied between 53 and 68 years; and most patients had unprovoked VTE (median 100%, range 57%–100%).

The overall pooled major bleeding rate in patients who have completed anticoagulation for the secondary prevention of recurrent VTE (i.e. no longer on anticoagulant therapy) was 0.45 per 100 patient-years (95% CI 0.29–0.64, I^2 = 0%). The pooled major bleeding rate for patients randomized to placebo was 0.42 per 100 patient-years (95% CI 0.25–0.62, I^2 = 0%), and that for patients randomized to observation was 0.62 per 100 patient-years (95% CI 0.23–1.2, I^2 = 0%) (Fig. 1). Fatal bleeding events were rare with an overall pooled fatal bleeding rate of 0.14 per 100 patient-years (95% CI 0.057–0.26, I^2 = 0%). In the studies reporting sites of major bleeding and fatal bleeding, intracranial hemorrhage (including subdural and subarachnoid bleeding) and gastrointestinal bleeding were most common.

Our systematic review demonstrates that patients not receiving anticoagulant or antiplatelet therapy for the secondary prevention of recurrent VTE also experience major bleeding events. This event rate needs to be accounted for and included in the risk-benefit ratio, along with the previously reported risk of recurrent VTE, on and off anticoagulation, and risk of major bleeding on anticoagulant therapy, when clinicians are deciding on the length of anticoagulation therapy for patients with unprovoked VTE [16–20].

The rate of major bleeding events for patients with VTE on oral anticoagulation has previously been reported to be approximately 2.1 per 100 patient-years (95% CI 1.6–2.6) [17]. Our review reported a risk of major bleeding of 0.45 per 100 patient-years (95% CI 0.29–0.64) for similar patients not receiving anticoagulation therapy. Therefore, the incremental risk of major bleeding associated with anticoagulant therapy is approximately 1.5 per 100 patient-years. A recent systematic review and network meta-analysis reported that the use of VKA was associated with the greatest risk of major bleeding events in comparison to placebo or observation (OR 5.24, 95% credible interval [CrI] 1.78–18.25) [20]. In that review, the new oral anticoagulant apixaban, at two different treatment doses, was associated with the lowest risk of major bleeding events relative to placebo or observation.

It is interesting to note that the rates of major bleeding are higher in patients randomized to observation than those on placebo, although this finding is not significant. This may be attributed to different definitions of major bleeding used among the trials. All three trials randomizing patients to observation were published between 1997 and 2003—that is, before the ISTH criteria were established.

Our review has several strengths and limitations. First, all bleeding events were independently adjudicated; second, there was no heterogeneity identified between studies. Limitations of this study include the relatively small sample size of patients randomized to observation and generalizability to clinical practice. With respect to this latter concern, the patient population was extracted from RCTs. These patients are selected for participation, are likely younger, and generally do not have a history of bleeding events and severe comorbidities as they are often excluded from such studies, which may underestimate the true "real-world" bleeding risk and make our reported rate a conservative estimate. Timing of major bleeding events and known risk factors for major bleeding (antiplatelet use, moderate renal dysfunction, active malignancy, etc.) were not consistently reported in all trials, and therefore subgroup analyses could not be conducted. Last, observational prospective cohort studies were not included in the review. Although this could provide more insight into "real-world" bleeding risks, it may have significantly increased heterogeneity given the potential lack

Table 1 Characteristics of included studies

Study	Patients	Treatment regimen (No. of patients) (group 1 vs. group 2 vs. group 3)	Study design	Follow-up duration (mean)	Mean age (years) Group		
					1	2	3
DURAC 2 (10)	All VTE	Fixed duration VKA† (n = 111) vs. extended duration VKA (n = 116)	Open label, randomized	Fixed duration group followed for 40.3 months	65	64	–
LAFIT (12)	All VTE	Placebo (n = 83) vs. VKA (n = 79)	Double blind, randomized	10 months	58	59	—
WODIT DVT (13)	DVT only	Observation (n = 133) vs. VKA (n = 134)	Open label, randomized	37.2 months	68	67	—
WODIT PE (15)	PE only	Observation (n = 91) vs. VKA (n = 90)	Open label, randomized	32.7 months	61	63	—
PREVENT (14)	All VTE	Placebo (n = 253) vs. Low intensity VKA (n = 255)	Double blind, randomized	2.1 years	53‡	53‡	—
THRIVE III (11)	All VTE	Placebo (n = 611) vs. ximelagatran 24 mg BID (n = 612)	Double blind, randomized	505 days	58	56	—
RESONATE (9)	All VTE	Placebo (n = 659) vs. dabigatran 150 mg BID (n = 684)	Double blind, randomized	6 months	56	56	—
EINSTEIN-EXT (5)	All VTE	Placebo (n = 590) vs. rivaroxaban 20 mg daily (n = 598)	Double blind, randomized	265 days	58	58	—
AMPLIFY-EXT (8)	All VTE	Placebo (n = 826) vs. apixaban 5 mg BID (n = 811) vs. apixaban 2.5 mg BID (n = 840)	Double blind, randomized	12 months	57	56	57
WARFASA (6)	All VTE	Placebo (n = 197) vs. ASA 100 mg daily (n = 205)	Double blind, randomized	23.9 months	62	62	—
ASPIRE (7)	All VTE	Placebo (n = 411) vs. ASA 100 mg daily (n = 411)	Double blind, randomized	37.2 months	54	55	—

ASA, acetyl salicylic acid; DVT, deep vein thrombosis; NR, not reported; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism. *Normal renal function is defined as creatinine clearance ≥ 80 mL min−1 (Cockcroft-Gault). †Standard-dose adjusted VKA unless otherwise indicated. ‡Median age. §Median creatinine clearance (Cockcroft-Gault).
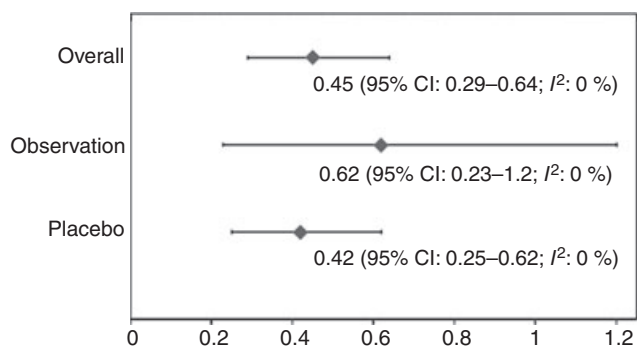

Fig. 1. Forest plot of pooled proportions of major bleeding rates in patients randomized to placebo, observation, and overall (per 100 patient-years).

Overall 0.45 (95% CI: 0.29–0.64; I^2: 0 %)
Observation 0.62 (95% CI: 0.23–1.2; I^2: 0 %)
Placebo 0.42 (95% CI: 0.25–0.62; I^2: 0 %)

of independent adjudication or the use of standardized definitions of major bleeding.

In conclusion, our review suggests that the incidence of major bleeding events is non-negligible in patients receiving no treatment and may change the estimate of the incremental harm-benefit ratio clinicians consider when discussing anticoagulation for secondary prevention of recurrent VTE with patients.

Addendum

Acknowledgements

Men (%)			Unprovoked VTE (%)			Antiplatelet use (%)			Active malignancy (%)			Normal renal function* (%)			Major bleeding events (No.)			Fatal bleeding events (No.)		
Group			Group			Group			Group			Group			Group			Group		
1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
63	59	—	NR	NR	—	NR	NR	—	0	0	—	NR	NR	—	2	10	—	1	2	—
53	68	—	100	100	—	NR	NR	—	NR	NR	—	NR	NR	—	0	3	—	0	0	—
61	55	—	100	100	—	NR	NR	—	0	0	—	NR	NR	—	2	4	—	2	0	—
NR	NR	—	57	55	—	NR	NR	—	0	0	—	NR	NR	—	1	2	—	0	0	—
53	53	—	100	100	—	NR	NR	—	NR	NR	—	NR	NR	—	2	5	—	1	0	—
51	54	—	NR	NR	—	NR	NR	—	5	6	—	110§	114§	—	5	6	—	0	0	—
55	56	—	100	100	—	NR	NR	—	< 1	< 1	—	70	70	—	0	2	—	0	0	—
57	59	—	74	73	—	NR	NR	—	4.4	4.7	—	63	62	—	0	4	—	0	0	—
57	58	58	91	91	93	13	11.8	14.3	2.2	1.1	1.8	68	71	71	4	1	2	0	0	0
62	66	—	100	100	—	0	100	—	0	0	—	NR	NR	—	1	1	—	0	0	—
54	55	—	100	100	—	0	100	—	1	1	—	NR	NR	—	6	8	—	2	0	—

Disclosure of Conflicts of Interest

The authors state that they have no conflicts of interest.

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