Thrombosis Research 175 (2019) 102–109

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Resumption of anticoagulant therapy after anticoagulant-related gastrointestinal bleeding: A systematic review and meta-analysis☆

D. Little[a], C. Chai-Adisaksopha[a], C. Hillis[b], D.M. Witt[c], M. Monreal[d], M.A. Crowther[a], D.M. Siegal[a,*]

[a] Department of Medicine, McMaster University, 1280 Main St W, Hamilton, ON L8S 4L8, Canada
[b] Department of Oncology, McMaster University, 1280 Main St W, Hamilton, ON L8S 4L8, Canada
[c] Department of Pharmacotherapy, The University of Utah, 201 Presidents Circle, Salt Lake City, UT 84112, United States
[d] Department of Internal Medicine, Hospital Universitari Germans Trias I Pujol, Carretera de Canyet, s/n, Barcelona 08916, Spain

ARTICLE INFO

Keywords:
Anticoagulants
Gastrointestinal hemorrhage
Hemorrhage
Thromboembolism
Thrombosis

ABSTRACT

Introduction: Oral anticoagulation (OAC) is permanently discontinued in up to 50% of patients following a gastrointestinal (GI) bleed. A previous meta-analysis showed a reduced risk of thromboembolism and death, and a non-statistically significant increased risk of re-bleeding associated with resumption. We conducted an updated meta-analysis to determine the risks of recurrent GI bleeding, thromboembolism, and death in patients who resumed OAC compared to those who did not.

Materials and methods: We searched EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials for new references from January 2014 to September 2017. Randomized controlled trials and observational studies involving adults with OAC-related GI bleeding were included. Risk of bias was assessed using the Cochrane Collaboration's ROBINS-I tool. Pooled relative risk (RR) ratios were calculated using a random-effects model.

Results: We identified 12 observational studies involving 3098 patients. There was an increased risk of recurrent GI bleeding (RR 1.91, 95% CI 1.47–2.48, I^2 = 0%, 11 studies), and a reduced risk of thromboembolism (RR 0.30, 95% CI 0.13–0.68, I^2 = 59.8%, 9 studies) and death (RR 0.51, 95% CI 0.38–0.70, I^2 = 71.8%, 8 studies) in patients who resumed OAC compared to those who did not. Eleven studies were judged to be at serious risk of bias due to confounding.

Conclusions: Resuming OAC after OAC-related GI bleeding appears to be associated with an increase in recurrent GI bleeding, but a reduction in thromboembolism and death. Further prospective data are needed to identify patients for whom the net clinical benefit favours OAC resumption and the optimal timing of resumption.

1. Introduction

Bleeding is the main complication of oral anticoagulation (OAC). The most common site of OAC-related bleeding is gastrointestinal (GI) representing approximately 40% of major OAC-related bleeds [1,2]. The annual risk of GI bleeding reported in contemporary trials in atrial fibrillation (the most frequent indication for OAC) ranges from 0.9% to 1.2% for warfarin and 0.8% to 2.0% for direct oral anticoagulants (DOAC), respectively [3]. The rate of fatal GI bleeds with warfarin is 0.01 per 100 patient-years compared to 0.04 per 100 patient-years with rivaroxaban [4]. Although rates of fatal GI bleeding are low, major gastrointestinal bleeds significantly reduce quality of life for up to nine months after the event [5].

Decisions regarding whether and when to resume OAC require clinicians to weigh the risks of recurrent GI bleeding and thromboembolism. OAC is permanently discontinued in approximately 41% to 51% of patients following a GI bleed emphasizing the clinical uncertainty in this setting [6–9]. Without OAC, the risk of embolism or valve thrombosis with a mechanical valve is 12–22% per year [10]. In patients with atrial fibrillation, the average annual risk of stroke without OAC is 4.5%, which increases to 12% in patients with a history of stroke [11]. Alternatively, resuming OAC within the first 7 days following a GI bleed increases the risk of recurrent GIB compared with resuming OAC after 30 days [9]. In one small retrospective study, 8.3% of patients who

Abbreviations: GI, gastrointestinal; OAC, oral anticoagulation; DOAC, direct oral anticoagulant

☆ Guarantor of the article: Deborah Siegal MD MSc FRCPC.

* Corresponding author at: 50 Charlton Ave. E. F-303, Hamilton, ON L8N 4A6, Canada.
E-mail address: siegald@mcmaster.ca (D.M. Siegal).

https://doi.org/10.1016/j.thromres.2019.01.020
Received 13 November 2018; Received in revised form 3 January 2019; Accepted 28 January 2019
Available online 30 January 2019
0049-3848/

resumed warfarin during the same hospitalization developed recurrent bleeding [12]. In a meta-analysis of 3 observational studies, resumption of OAC (warfarin) following a GI bleed was associated with a significant reduction in thromboembolic events (9.9% vs. 16.4%, HR 0.68, 95% CI 0.52–0.88) and death (24.6% vs. 39.2%, HR 0.76, 95% CI 0.66–0.88), and a non-statistically significant difference in recurrent GI bleeding (10.1% vs. 5.5%, HR 1.20, 95% CI 0.97–1.48) [7]. Since the publication of this meta-analysis, additional studies have become available. We aimed to update the results of our previous systematic review and meta-analysis to determine the risk of recurrent GI bleeding, thromboembolism, and mortality in patients who resume OAC compared to those who do not after GI bleeding.

2. Methods

We updated our previous systematic review and presented the combined results according to guidelines [13,14]. We developed a study protocol before data collection, which was registered on PROSPERO and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017078574.

2.1. Data sources and searches

We searched EMBASE, MEDLINE and the Cochrane Register of Controlled Trials using the same strategy as the prior review (Supplementary Fig. 1) [7]. The combined searches included citations from inception to July 2014 (prior review) and January 2014 to September 2017 (updated review). We also searched conference proceedings of The American Society of Hematology, Digestive Diseases Week, International Society on Thrombosis and Haemostasis, European Hematology Association, American College of Cardiology, American Heart Association, and European Society of Cardiology (August 2014 to January 2018). The reference lists of included articles were manually screened.

2.2. Study selection

Studies were eligible for inclusion if they were (i) randomized controlled trials or observational studies; (ii) included adults (18 years of age or older) with major or clinically relevant non-major GI bleeding while receiving OAC (vitamin K antagonists, dabigatran, rivaroxaban, apixaban or edoxaban) for atrial fibrillation, venous thromboembolism or mechanical heart valves, and (iii) reported recurrent GI bleeding, thromboembolism, and/or mortality for patients who resumed and those who did not resume OAC. Case reports, case series, systematic reviews, editorials, and letters, and studies which did not report outcomes separately for patients in whom OACs were and were not resumed were excluded. Concomitant antiplatelet therapy was allowed. There were no restrictions with respect to duration of follow-up, language, or publication status. Recurrent GI bleeding and thromboembolism were defined as per the individual studies. The most common definition of recurrent GI bleeding was GI bleeding causing a fall in hemoglobin of ≥20 g/L or requiring transfusion of ≥2 units of packed red blood cells. The most common definition of thromboembolism was pulmonary embolism, deep vein thrombosis, stroke, transient ischemic attack, or systemic embolism.

Two independent reviewers (DL, DS) screened titles and abstracts and reviewed full-text articles, including those from the previous review. Disagreements were resolved by consensus and the kappa statistic was calculated to determine agreement for screening and full-text review. Reviewers were not blinded to the study title or authors. For studies with incomplete or unclear data, a minimum of 3 attempts were made to obtain additional data from the corresponding author.

2.3. Data extraction and risk of bias assessments

Data extraction and risk of bias assessments were conducted in duplicate (DS, DL) using a custom electronic data collection form (Microsoft Access®, Microsoft Corporation). Disagreements were resolved by consensus. The following data were extracted: study design, year of publication, study inclusion and exclusion criteria, definitions of outcomes, definitions of resumed and not resumed, types of OAC, indications for OAC, duration of follow-up, timing of OAC resumption, concomitant antiplatelet therapy use, types of GI bleeds, patient characteristics (age, gender, number of patients), thromboembolic events, recurrent GI bleeding, and all-cause mortality.

Risk of bias was assessed by two authors (DL, DS) independently using the Cochrane Risk of Bias for Non-Randomized Studies (ROBINS-I) tool [15]. Study outcomes were thromboembolic events (arterial or venous) and recurrent GI bleeding, as defined in individual studies, and all-cause mortality.

2.4. Statistical analysis

Baseline characteristics were summarized using descriptive statistics. Categorical data were reported as counts and proportions. Continuous data were reported as means with standard deviations (SD) or medians with min-max values. Pooled incidence rates (events per 100 person-years of follow-up) were calculated for individual studies using methods previously described [16]. Pooled relative risk ratios were calculated with 95% confidence intervals (CI) for recurrent GI bleeding, thromboembolic events, and mortality using a random-effects model (STATA, StataCorp). A post-hoc sensitivity analysis was conducted by pooling reported risk ratios which were adjusted for known covariates (Supplementary Tables 1 and 3) and calculated relative risk ratios using the generic inverse variance method (RevMan 5.3,The Nordic Cochrane Centre, Copenhagen) [17]. Heterogeneity was assessed using the I^2 statistic. An I^2 value of 0–40% indicates minor heterogeneity, 30–60% moderate heterogeneity, and 50–90% significant heterogeneity [18]. Funnel plots were generated to assess for publication bias for outcomes reported in 10 or more studies [18]. We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method to assess the certainty of evidence for each outcome [19] and generated a summary of findings table using GRADEpro GDT (McMaster University and Evidence Prime) [20].

The following subgroup analyses were planned a priori to explore sources of heterogeneity: type of oral anticoagulant (vitamin K antagonist or direct oral anticoagulant), timing of OAC resumption (early/ < 30 days after bleed vs. delayed/ > 30 days after bleed), indication for OAC (atrial fibrillation, venous thromboembolism, mechanical heart valve), and type of GI bleed (upper vs. lower source).

3. Results

3.1. Study selection

In addition to the 2055 articles identified in the previous review, we found an additional 2551 articles after removal of duplicates (Fig. 1). Two additional abstracts were included from screening conference abstracts [21,22]. After screening by title and abstract, 24 studies were selected for full text review including the 6 studies screened by full text review in the prior systematic review. Agreement between reviewers after screening by title and abstract was good (kappa 0.71). A total of 13 studies met inclusion criteria. Of the studies meeting inclusion criteria, one study did not report the outcome events and the author was unable to provide additional data therefore it was excluded [23]. Twelve studies were included in the final review. Agreement between reviewers for inclusion after full text review was excellent (kappa 1.0).

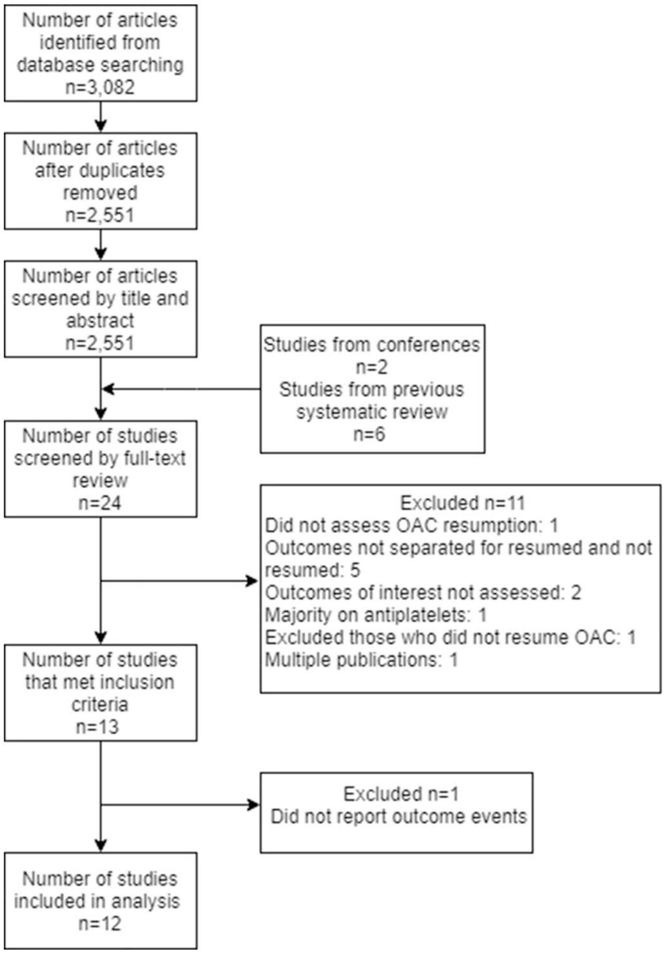

Fig. 1. Flow diagram.
OAC oral anticoagulant.

3.2. Study characteristics

All 12 studies were observational studies (prospective $n = 3$, retrospective $n = 9$) published in English between 2001 and 2017 [8,9,21,22,24–31]. Characteristics of the included studies are shown in Table 1. There was a total of 3098 included patients with median duration of follow-up reported in 10 studies ranging from 90 days to 868 days. There were 1542 patients who resumed OAC (1875.8 patient-years of follow-up) and 1556 patients who did not (578.2 patient-years of follow-up). The number of patients analyzed ranged from 20 to 1329 patients. The average age was reported in 8 studies and ranged from 67 to 80 and 57.2% of patients were male. Among 10 studies reporting the type of OAC prior to GI bleeding, patients received vitamin K antagonists (VKA, $n = 2962$) and direct oral anticoagulants (DOAC, $n = 72$). Ten studies reported the indications for OAC including atrial fibrillation ($n = 1887$), prosthetic heart valves ($n = 126$), venous thromboembolism ($n = 276$), and other indications ($n = 177$). Of the 10 studies reporting the site of GI bleeding, 4 studies included patients with upper GI bleeds, 1 study included patients with lower GI bleeds, and 5 studies included patients with both upper and lower GI bleeds. In total, there were 1072 patients with an upper GI bleed, 1581 patients with a lower GI bleed, and 347 patients with an unknown source of GI bleeding. Median duration of OAC interruption ranged from 1 day to 50 days. Recurrent GI bleeding was reported in 11 studies, thromboembolism in 10 studies, and mortality in 8 studies. The authors of 3 studies kindly provided additional data for analysis [21,22,31].

3.3. Risk of bias

The risk of bias assessment is shown in Supplementary Fig. 2 and Supplementary Table 2. For the outcome of recurrent GI bleeding, 10 studies were judged at serious risk of bias and 1 at unclear risk of bias. For the outcome of thromboembolism, all 9 studies were judged at serious risk of bias. For the outcome of mortality, all 8 studies were judged at serious risk of bias. The main source of potential bias was due to confounding with all outcomes in 11 of the 12 studies judged at serious risk of bias due to confounding.

3.4. Recurrent GI bleeding

Recurrent GI bleeding occurred in 182 of 1387 (13.1%) patients who resumed OAC compared to 70 of 1192 (5.9%) patients who did not. The incidence rate of recurrent GI bleeding in those who resumed OAC was 27.0 per 100 patient-years (95% CI 16.0–39.0; $I^2 = 89.0\%$) compared to 13.0 per 100 patient-years (95% CI 7.0–19.0; $I^2 = 61.2\%$) in those who did not ($p < 0.001$). Resuming OAC was associated with an increased risk of recurrent GI bleeding (RR 1.91, 95% CI 1.47–2.48, $I^2 = 0\%$, 11 studies) (Fig. 2). Sensitivity analysis including adjusted risk ratios (reported in 5 studies) in the pooled risk estimate showed a similar result (Supplementary Table 3). Overall, the evidence that resuming OAC increases recurrent GI bleeding was rated as very uncertain (Table 2)

3.5. Thromboembolism

Thromboembolism occurred in 103 of 1351 (7.6%) patients who resumed OAC compared to 178 of 1157 (15.4%) patients who did not. The incidence rate of thromboembolism in those who resumed OAC compared to those who did not was 4.2 per 100 patient-years (95% CI 0.7–7.7; $I^2 = 92.6\%$) compared to 18.1 per 100 patient-years (95% CI 11.0–25.2; $I^2 = 68.5\%$) respectively ($p < 0.001$). Resuming OAC was associated with a reduced risk of thromboembolism (RR 0.30, 95% CI 0.13–0.68, $I^2 = 59.8\%$, 9 studies) (Fig. 3). The thromboembolism data from Ananthasubramaniam [25] was excluded from analysis given there were no events in either group. Sensitivity analysis including adjusted risk ratios (reported in 4 studies) in the pooled risk estimate showed a similar result (Supplementary Table 3). Overall, the evidence that resuming OAC reduces thromboembolism was rated as very uncertain (Table 2)

3.6. Mortality

In patients who resumed OAC, 299 of 1393 (21.5%) patients died compared to 461 of 1461 (31.6%) patients in those who did not. The incidence rate of death in those who resumed OAC compared to those who did not was 20.0 per 100 patient-years (95% CI 10.0–30.0; $I^2 = 95.8\%$) compared to 50.0 per 100 patient-years (95% CI 20.0–70.0; $I^2 = 72.3\%$) respectively ($p < 0.001$). Resuming OAC was associated with a reduced risk of mortality (RR 0.51, 95% CI 0.38–0.70, $I^2 = 71.8\%$, 8 studies) (Fig. 4). Sensitivity analysis including adjusted risk ratios (reported in 5 studies) in the pooled risk estimate showed a similar result (Supplementary Table 3). Overall, the evidence that resuming OAC reduces mortality was rated as very uncertain (Table 2)

3.7. Publication bias

A funnel plot was constructed for the outcome of recurrent GI bleeding and is shown in Fig. 5. The plot was symmetrical suggesting there was no evidence of publication bias. Funnel plots were not constructed for the other outcomes because there were < 10 studies for each outcome.

Table 1
Characteristics of included studies.

Study	Design	Indication for OAC n (%)	Type of OAC n (%)	Type of GI bleed n (%)	Total patients analyzed n	Antiplatelet use at index bleed n (%)	Resumed n	Did not resume n	Age, yrs Mean (SD) or median (range)	Males n (%)	Follow-up days
Sengupta 2014	Prospective	AF 115 (58) VTE 58 (29) MHV 18 (9) Other 9 (5)	VKA 145 (74) DOAC 25 (13) NR 27 (14)	UGIB 50 (25) LGIB 50 (25) Other 97 (49)	197	ASA 110 (56) Clopidogrel 29 (15)	121	76	75 (65–83)	114 (58)	90
Ananthasubramaniam 2001	Retrospective	MHV 23 (100)	VKA 23 (100)	UGIB 10 (50) LGIB 2 (10) Other 11 (55)	20	NR	19	1	61 (11)	12 (48)	180
Chen 2014	Retrospective	AF 8 (22) VTE 11 (31) MHV 10 (28) Other 7 (19)	VKA 36 (100)	UGIB 19 (53) LGIB 3 (8) Other 14 (39)	36	ASA 4 (11) Clopidogrel 1 (3) Dipyridamole 5 (14)	22	12	74 (12)	19 (53)	NR
Calo 2015	Retrospective	AF 47 (66) VTE 13 (18) MHV 5 (7) Other 5 (7)	VKA 61 (86) Other (NR)	UGIB 71 (100)	71	ASA 17 (24)	36	35	79 (72–84)	44 (62)	365
Lee 2011	Retrospective	Other 58 (100)	VKA 58 (100)	UGIB 58 (100)	58	NR	22	36	63 (2)	33 (57)	NR
Majeed 2017	Retrospective	AF 130 (63) VTE 23 (11) MHV 28 (14) Other 26 (13)	VKA 207 (100)	UGIB 207 (100)	207	Any 65 (31)	121	86	77 (NR)	130 (63)	868
Patel 2017	Retrospective	NR	VKA 607 (100)	LGIB 607 (100)	607	ASA 299 (49) Thienopyridine 71 (12) DAPT 59 (10)	204	403	68 (58–76)	324 (53)	90
Qureshi 2014	Retrospective	AF 1329 (100)	VKA 1329 (100)	UGIB 472 (36) LGIB 725 (55) Other 132 (10)	1329	ASA 323 (24) Other 34 (3)	653	676	75 (11)	700 (53)	720
Nieto 2008	Prospective	VTE 54 (100)	VKA 54 (100)	NR	144	NR	88	56	74 (NR)	72 (50)	90
Witt 2012	Retrospective	AF 223 (50), VTE 108 (24), MHV 42 (10), other 69 (16)	VKA	UGIB 155 (35) LGIB 194 (44) Other 93 (21)	442	ASA 205 (46)	260	182	74 (12)	222 (50)	90
Siau 2016	Retrospective	Any (NR)	VKA (NR) DOAC (NR)	UGIB 30 (100)	30	0	19	11	73 (NR)	21 (69)	286
Marten 2015	Prospective	AF 35 (74) VTE 8 (19) MHV 0 Other 3 (6)	DOAC 47 (100)	NR	47	NR	26	21	78 (10)	29 (62)	426

AF atrial fibrillation, ASA aspirin, DAPT dual antiplatelet therapy, DOAC direct oral anticoagulant, GI gastrointestinal, LGIB lower gastrointestinal bleed, NR not reported, OAC oral anticoagulant, MHV mechanical heart valve, UGIB upper gastrointestinal bleed, VKA vitamin K antagonist, VTE venous thromboembolism.

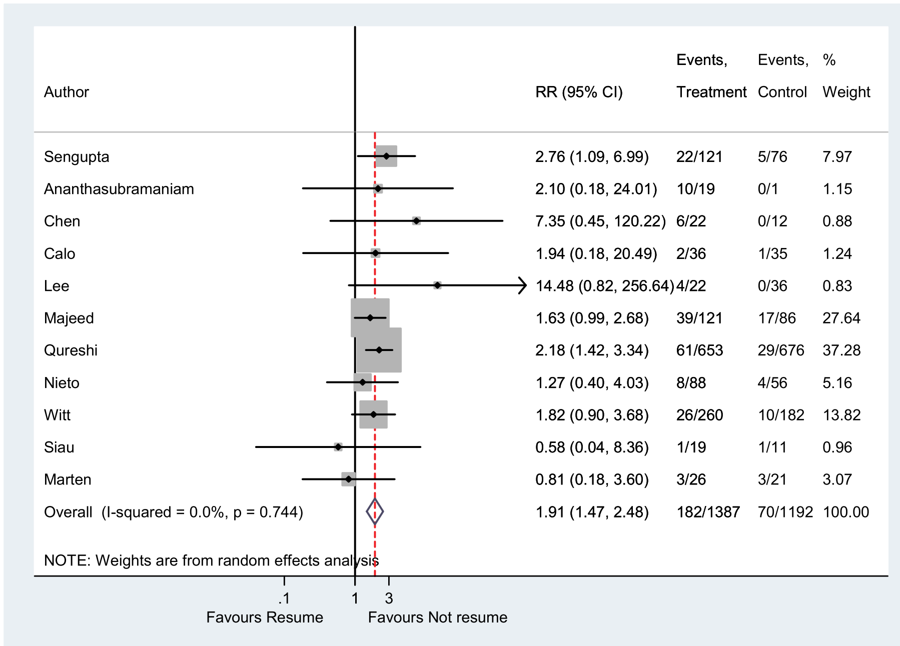

Fig. 2. Recurrent gastrointestinal bleeding.
CI confidence interval, RR relative risk.

3.8. Subgroup analysis

We were unable to explore differences in the risk of outcomes between pre-defined subgroups due to insufficient data. When the pooled analysis was limited to studies involving patients with upper GI bleeds, resuming OAC was associated with a reduced risk of thromboembolism (RR 0.19, 95% CI 0.08–0.45, $I^2 = 0\%$, 3 studies) and mortality (RR 0.70, 95% CI 0.53–0.91, $I^2 = 0\%$, 2 studies), with an increased risk of recurrent GI bleeding (RR 1.69, 95% CI 1.05–2.71, $I^2 = 0\%$, 4 studies) compared to not resuming OAC (Supplementary Figs. 3–5).

Table 2
GRADE summary of findings: Resuming OAC compared to not resuming OAC in patients following OAC-associated GI bleeding.*

Outcomes	Anticipated absolute effects† (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)‡	Comments
	Risk with not resuming OAC	Risk with resuming OAC				
Recurrent GI Bleeding Follow-up: 1177.3 patient-years	59 per 1,000	**112 per 1,000** (86 to 146)	**RR 1.91** (1.47 to 2.48)	2579 (11 observational studies)	⊕◯◯◯ VERY LOW §	Very uncertain if resuming OAC increases risk of recurrent GI bleeding Limitations of risk of bias and observational data
Thromboembolism Follow-up: 2075.0 patient-years	154 per 1,000	**46 per 1,000** (20 to 105)	**RR 0.30** (0.13 to 0.68)	2508 (9 observational studies)	⊕◯◯◯ VERY LOW §‖¶	Very uncertain if resuming OAC reduces risk of thromboembolism Limitations of risk of bias, inconsistency, and observational data
Mortality Follow-up: 3477.8 patient-years	316 per 1,000	**161 per 1,000** (120 to 221)	**RR 0.51** (0.38 to 0.70)	2854 (8 observational studies)	⊕◯◯◯ VERY LOW §‖¶	Very uncertain if resuming OAC reduces mortality. Limitations of risk of bias, inconsistency, and observational data

*Patient or population: Adults with OAC-associated GI bleeding. Setting: Worldwide. Intervention: Resuming OAC. Comparison: Not resuming OAC.
†The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
‡High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
§Serious risk of bias in most studies due to baseline confounding.
‖Heterogeneity evident by visual inspection and I^2 coefficient.

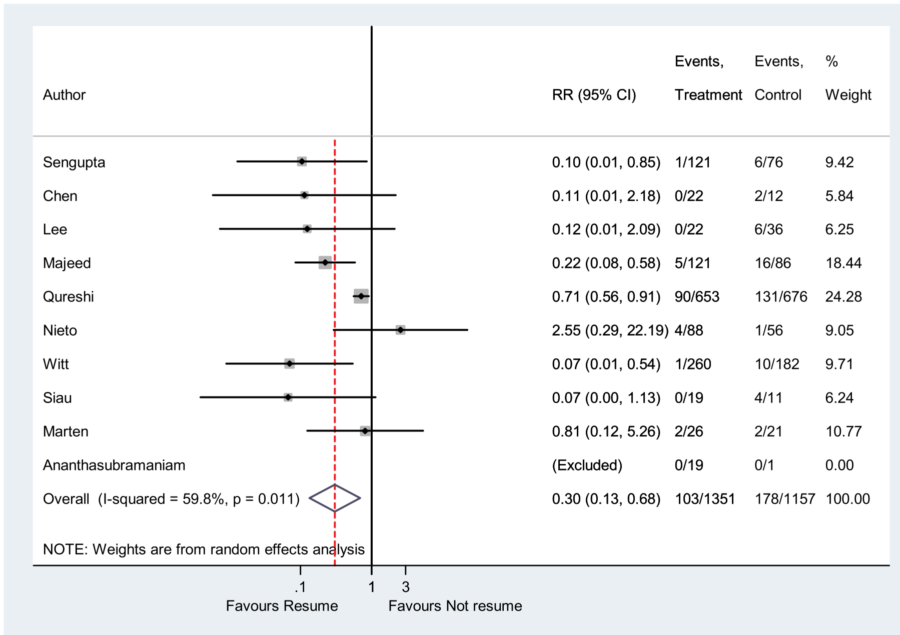

Fig. 3. Thromboembolism.
CI confidence interval, RR relative risk.

4. Discussion

In this updated systematic review and meta-analysis, resuming OAC after an episode of GI bleeding appears to be associated with an increased risk of recurrent GI bleeding (91%), and a reduced risk of thromboembolism (70%) and mortality (49%). Our findings differ from the prior meta-analysis of 3 observational studies which showed a reduced risk of thromboembolism and mortality, but a numerically higher but nonsignificant increase in recurrent GI bleeding in patients who resumed OAC [7]. With the inclusion of 9 additional studies we demonstrated this increase in recurrent GI bleeding to be significant.

The decision whether and when to resume OAC following an episode of OAC-related GI bleeding must balance the risks of thromboembolism and recurrent GI bleeding. Data on the nature and relative influence of factors clinicians consider when making this decision are lacking. Although observational in nature, our data suggest that the net clinical benefit favours resuming OAC with a reduced risk of thromboembolism and death, despite an increase in GI bleeding. Importantly, the clinical impact of GI bleeding and thrombotic events are not equivalent. The case-fatality rate of OAC-related bleeding is 8–13% [16,32,33]. In comparison, the risk of death, institutionalization due to stroke, or disability at 3 months was 41% for all strokes in a European stroke registry [34]. In a large U.S. cohort study, the mortality rate following ischemic stroke was as high as 57% [35].

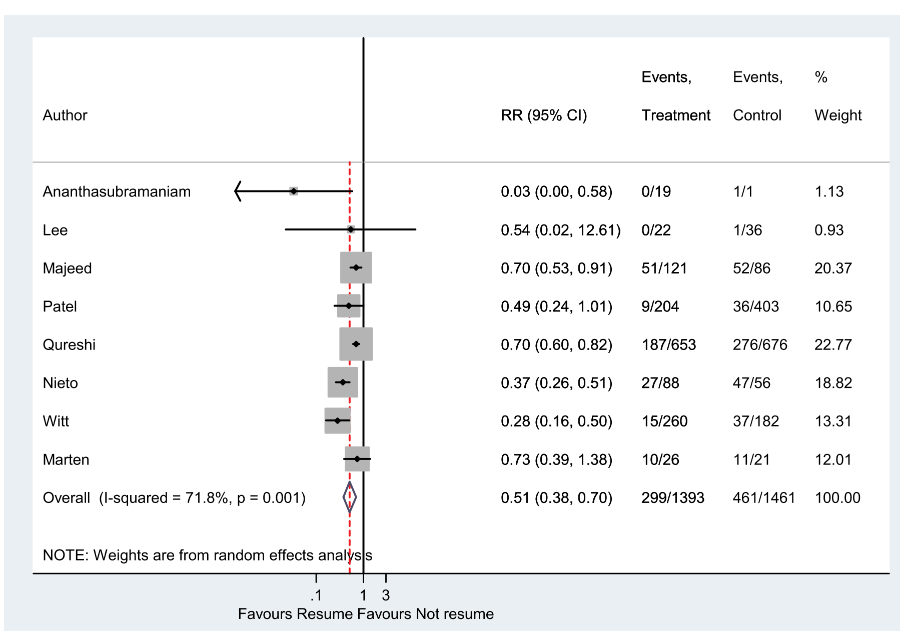

Fig. 4. Mortality.
CI confidence interval, RR relative risk.

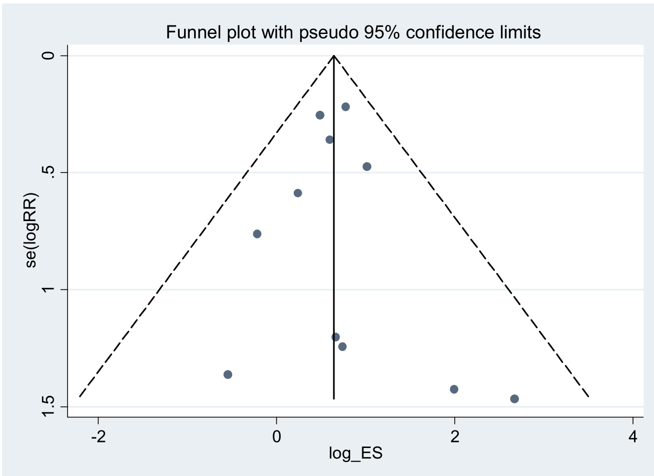

Fig. 5. Funnel Plot for recurrent gastrointestinal bleeding.

Key to the decision to resume OAC is determining the optimal timing for resumption which maximizes benefit and minimizes harm. In our study, the timing of OAC resumption varied widely and outcomes were not reported based on when OAC was resumed. As a result, there were insufficient data to make firm conclusions, but some observations are worth noting. Using a time-dependent analysis, Majeed et al. found that the risk of recurrent GI bleeding was lowest when OAC was resumed between 3 and 6 weeks post-bleed [29]. In Qureshi et al., outcomes were analyzed separately for patients who interrupted OAC for < 7, 7–15, 15–21, 21–30, and > 30 days [9]. Those who resumed OAC within 7 days had an increased risk of recurrent GI bleeding (HR 3.27, 95% CI 1.82–5.91), while those who resumed OAC between 7 and 30 days had a similar risk (7–15 days HR 1.03, 95% CI 0.45–2.35, 15–21 days HR 1.42, 95% CI 0.65–3.11, 21–30 days HR 1.50, 95% CI 0.55–4.04) compared to those who resumed OAC after 30 days. The incidence of thromboembolism was lowest the earlier OAC was resumed (< 7 days 11.6 per 100 person-years vs. > 30 days 20.4 per 100 patient-years). Witt et al. also found that the rate of recurrent GI bleeding was significantly increased when OAC was resumed within the first 1 to 7 days compared to later (12.4% vs. 6.2%, respectively) [8]. Rates of thromboembolism were similar regardless of the duration of OAC interruption and there were no thromboembolic events in patients who resumed OAC within 14 days.

The majority of patients included in our analysis were receiving VKAs therefore caution should be applied when extrapolating these results to patients using DOACs. One study included patients with GI bleeding while on a DOAC ($n = 47$), but outcomes were not reported separately for patients who resumed a DOAC versus a VKA [22]. In this study there was a trend towards reduced rates of thromboembolism (RR 0.81, 95% CI 0.12–5.26) and mortality (RR 0.73, 95% CI 0.39–1.38) in patients who resumed OAC, and a similar frequency of recurrent GI bleeding in those who resumed OAC compared to those who did not resume OAC (11.5% and 14.3%, respectively).

There are several limitations to the present study. First, there was heterogeneity in the pooled estimates for thromboembolism and mortality ($I^2 = 59.8\%$ and 71.8%, respectively). Potential sources of heterogeneity in the pooled estimates of thromboembolism and mortality include the variability in the time to resume OAC length of follow-up, definition of thromboembolism, methods of outcome ascertainment, and other differences in baseline characteristics (e.g. age, indication for OAC, severity of index bleed, use of antiplatelet therapies). To address the differences in length of follow-up we calculated pooled incidence rates adjusted for the duration of follow-up for each treatment group. Outcomes were not separated for patients on concurrent antiplatelet therapy following the index GI bleed. The definition of 'resumed OAC' varied among the studies with no definition provided in 5 studies. There were insufficient data to conduct planned subgroup analyses to explore sources of heterogeneity (type of OAC, timing of OAC resumption, indication for OAC, and type of GI bleed).

Second, we were unable to obtain outcome event data for meta-analysis from a study that otherwise met inclusion criteria [23]. In this study, resuming OAC after GI bleeding was associated with reduced all-cause mortality (HR 0.39, 95% CI 0.34–0.46) and thromboembolism (HR 0.41, 95% CI 0.31–0.54) compared to not resuming antithrombotics (including antiplatelet therapy). Resuming OAC alone was associated with an increased risk of major bleeding (HR 1.37, 95% CI 1.06–1.77) compared to non-resumption of antithrombotic treatment. However, the risk of recurrent GI bleeding was not significantly increased (HR 1.22, 95% CI 0.84–1.77). This study excluded events occurring in the first 90 days, however sensitivity analysis with an exclusion period of 30, 60, or 120 days did not change the results significantly.

Third, all studies were observational with potential risk of bias due to baseline confounding. Possible confounders included age, indication for OAC, source of bleeding, risk of thrombosis, risk of rebleeding, and comorbidities. In the absence of randomization, differences in baseline characteristics which are prognostic for outcomes may have influenced whether OAC was resumed or not. For example, patients felt to be at high-risk of thromboembolism or low-risk of bleeding may have been more likely to resume OAC. In the Majeed 2017 study, more patients with mechanical heart valves resumed OAC than those with atrial fibrillation or venous thromboembolism. In another study, older patients and those without an identifiable source of GI bleeding were less likely to resume OAC [8].

Despite these limitations, this study-level meta-analysis with quality (risk of bias) assessments represents the best available evidence regarding important clinical outcomes in patients who resumed OAC compared to those who did not after OAC-related GI bleeding. As advocated by GRADE methodologists, "clinicians and patients need a best estimate of treatment effect to inform decisions" [36]. However, we acknowledge that the methodological limitations of the included studies reduce our confidence in the estimates of effect as reflected in the certainty of evidence assessments in the GRADE Summary of Findings table (Table 2).

5. Conclusions

Resuming OAC after an OAC-related GI bleed appears to be associated with an increased risk of recurrent GI bleeding, but with a reduced risk of thromboembolism and mortality, although these results should be interpreted with caution due to very low certainty of the evidence. Prospective studies are needed to confirm our findings and clarify the optimal timing to resume OAC. In the absence of high-quality data regarding the optimal timing of resumption and type of OAC in this setting, decision-making should be individualized with discussion about risk and benefit and incorporating patient values and preferences. Research on the values and preferences involved in such decisions is warranted.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.01.020.

Author contributions

D. Little, D. Siegal, and C. Chai-Adisaksopha were involved in the study design. D. Little and D. Siegal were involved in the study selection, data extraction, and risk of bias assessment. D. Siegal, D. Little and C. Chai-Adisaksopha were involved in the data analysis. D. Little drafted the manuscript. D. Little, D. Siegal, C. Chai-Adisaksopha, M. A. Crowther, M. Monreal, D. M. Witt, and C. Hillis revised the manuscript.

Funding

This work was supported by a Heart and Stroke Foundation of Canada ERLI Grant and a Hamilton Health Sciences Research Early Career Award. The funding source was not involved in the design, conduct, analysis, or preparation of the study.

Disclosures

DL, CC, DW, and MM have no conflicts of interest to declare. CH has received honoraria from BMS-Pfizer. DS has received honoraria from BMS-Pfizer, Bayer, Servier and Novartis. MC has received fees for serving on advisory boards for Bayer, Pfizer, the Bristol-Myers Squibb/Pfizer Alliance, LEO Pharma, Asahi Kasei Pharma (AKP) America, Janssen, and Octapharma, fees for serving on data safety monitoring boards from Bayer, the Bristol-Myers Squibb/Pfizer Alliance, and Daiichi-Sankyo, payment for the development of educational presentations from Bayer, Pfizer, Boehringer Ingelheim, Celgene, Alexion, AbbVie, and Ortho Clinical Diagnostics, travel support from Bayer, Pfizer, LEO Pharma, AKP America, Octapharma, and Shire, and grant support and drug supplies for studies from Bayer and LEO Pharma.

All authors approved the final draft submitted to Thrombosis Research.

Writing assistance

None.

Acknowledgments

The authors thank Dr. Grigorios Leontiadis for his suggestions regarding the analysis and reviewing the manuscript. The authors also thank Dr. Keith Siau, Dr. José Nieto, and Luise Tittl for providing additional data for analysis.

References

[1] C.T. Ruff, R.P. Giugliano, E. Braunwald, E.B. Hoffman, N. Deenadayalu, M.D. Ezekowitz, A.J. Camm, J.I. Weitz, B.S. Lewis, A. Parkhomenko, T. Yamashita, E.M. Antman, Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials, Lancet 383 (2014) 955–962.

[2] F. Radaelli, F. Dentali, A. Repici, A. Amato, S. Paggi, E. Rondonotti, J.M. Dumonceau, Management of anticoagulation in patients with acute gastrointestinal bleeding, Dig. Liver Dis. 47 (2015) 621–627.

[3] P. Kirchhof, S. Benussi, D. Kotecha, A. Ahlsson, D. Atar, B. Casadei, M. Castella, H.C. Diener, H. Heidbuchel, J. Hendriks, G. Hindricks, A.S. Manolis, J. Oldgren, B.A. Popescu, U. Schotten, B. Van Putte, P. Vardas, Group ESCSD, 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS, Eur. Heart J. 37 (2016) 2893–2962.

[4] M.W. Sherwood, C.C. Nessel, A.S. Hellkamp, K.W. Mahaffey, J.P. Piccini, E.Y. Suh, R.C. Becker, D.E. Singer, J.L. Halperin, G.J. Hankey, S.D. Berkowitz, K.A.A. Fox, M.R. Patel, Gastrointestinal bleeding in patients with atrial fibrillation treated with rivaroxaban or warfarin: ROCKET AF trial, J. Am. Coll. Cardiol. 66 (2015) 2271–2281.

[5] K. Wang, H. Li, W.J. Kwong, E.M. Antman, C.T. Ruff, R.P. Giugliano, D.J. Cohen, E.A. Magnuson, E.A.-T.T. Investigators, Impact of spontaneous extracranial bleeding events on health state utility in patients with atrial fibrillation: results from the ENGAGE AF-TIMI 48 trial, J. Am. Heart Assoc. 6 (2017) e006703.

[6] J. Raunso, C. Selmer, J.B. Olesen, M.G. Charlot, A.M. Olsen, D.M. Bretler, J.D. Nielsen, H. Dominguez, N. Gadsboll, L. Kober, G.H. Gislason, C. Torp-Pedersen, M.L. Hansen, Increased short-term risk of thrombo-embolism or death after interruption of warfarin treatment in patients with atrial fibrillation, Eur. Heart J. 33 (2012) 1886–1892.

[7] C. Chai-Adisaksopha, C. Hillis, M. Monreal, D.M. Witt, M. Crowther, Thromboembolic events, recurrent bleeding and mortality after resuming anticoagulant following gastrointestinal bleeding. A meta-analysis, Thromb. Haemost. 114 (2015) 819–825.

[8] D.M. Witt, T. Delate, D.A. Garcia, N.P. Clark, E.M. Hylek, W. Ageno, F. Dentali, M.A. Crowther, Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding, Arch. Intern. Med. 172 (2012) 1484–1491.

[9] W. Qureshi, C. Mittal, I. Patsias, K. Garikapati, A. Kuchipudi, G. Cheema, M. Elbatta, Z. Alirhayim, F. Khalid, Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation, Am. J. Cardiol. 113 (2014) 662–668.

[10] E.M. Baudet, V. Puel, J.T. McBride, J. Grimaud, F. Roques, Long-term results of valve replacement with the St Jude Medical Prosthesis, J. Thorac. Cardiovasc. Surg. 109 (1995) 858–870.

[11] R. Hart, L. Pearce, M. Aguilar, Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation, Ann. Intern. Med. 146 (2007) 857–867.

[12] M. Guerrouij, C.S. Uppal, A. Alklabi, J.D. Douketis, The clinical impact of bleeding during oral anticoagulant therapy: assessment of morbidity, mortality and post-bleed anticoagulant management, J. Thromb. Thrombolysis 31 (2011) 419–423.

[13] P. Garner, S. Hopewell, J. Chandler, H. MacLehose, H.J. Schunemann, E.A. Akl, J. Beyene, S. Chang, R. Churchill, K. Dearness, G. Guyatt, C. Lefebvre, B. Liles, R. Marshall, L. Martinez Garcia, C. Mavergames, M. Nasser, A. Qaseem, M. Sampson, K. Soares-Weiser, et al., When and how to update systematic reviews: consensus and checklist, BMJ 354 (2016) i3507.

[14] A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gotzsche, J.P. Ioannidis, M. Clarke, P.J. Devereaux, J. Kleijnen, D. Moher, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration, PLoS Med. 6 (2009) e1000100.

[15] J.A. Sterne, M.A. Hernan, B.C. Reeves, J. Savovic, N.D. Berkman, M. Viswanathan, D. Henry, D.G. Altman, M.T. Ansari, I. Boutron, J.R. Carpenter, A.W. Chan, R. Churchill, J.J. Deeks, A. Hrobjartsson, J. Kirkham, P. Juni, Y.K. Loke, T.D. Pigott, C.R. Ramsay, et al., ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions, BMJ 355 (2016) i4919.

[16] L. Linkins, P. Choi, J.D. Douketis, Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism, Ann. Intern. Med. 139 (2003) 893–900.

[17] Review Manager (RevMan) [Computer Program]. Version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014.

[18] J. Higgin, S. Green (Eds.), Cochrane Handbook for Systematic Review of Interventions. Version 5.1.0 [Updated March 2011], The Cochrane Collaboration, 2011.

[19] G.H. Guyatt, A.D. Oxman, H.J. Schunemann, P. Tugwell, A. Knottnerus, GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology, J. Clin. Epidemiol. 64 (2011) 380–382.

[20] GRADEpro Guideline Development Tool [Software], McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from, http://gradepro.org , Accessed date: December 2018.

[21] K. Siau, J. Hannah, M.M. Widlak, T. Iqbal, N. Bhala, Maintenance of antithrombotic therapy post endoscopy for acute upper gastrointestinal bleeding is associated with improved clinical outcomes, Gastroenterology 150 (2016) S881–S882.

[22] S. Marten, L. Tittl, K. Daschkow, J. Beyer-Westendorf, Pattern and management of ISTH major bleeding complications with DOACs, Blood 126 (2015) 892.

[23] L. Staerk, G.Y. Lip, J.B. Olesen, E.L. Fosbol, J.L. Pallisgaard, A.N. Bonde, A. Gundlund, T.B. Lindhardt, M.L. Hansen, C. Torp-Pedersen, G.H. Gislason, Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study, BMJ 351 (2015) h5876.

[24] N. Sengupta, J.D. Feuerstein, V.R. Patwardhan, E.B. Tapper, G.A. Ketwaroo, A.M. Thaker, D.A. Leffler, The risks of thromboembolism vs. recurrent gastrointestinal bleeding after interruption of systemic anticoagulation in hospitalized inpatients with gastrointestinal bleeding: a prospective study, Am. J. Gastroenterol. 110 (2015) 328–335.

[25] K. Ananthasubramaniam, J. Beattie, H. Rosman, V. Jayam, S. Borzak, How safely and for how long can warfarin therapy be withheld in PHV patients, Chest 119 (2001) 478–484.

[26] W.C. Chen, Y.H. Chen, P.I. Hsu, F.W. Tsay, H.H. Chan, J.S. Cheng, K.H. Lai, Gastrointestinal hemorrhage in warfarin anticoagulated patients: incidence, risk factor, management, and outcome, Biomed. Res. Int. 2014 (2014) 463767.

[27] N.C. Calo, M.A. Mahler, S. Duran, R.C.G. Sueyro, M.L. Gonzalez, M. Marcolongo, D. Manazzoni, D. Nieto, J.A. De Paula, Risk of death and thromboembolism in patients that do not resume anticoagulation after an episode of peptic ulcer bleeding, Gastroenterology 148 (2015) S155.

[28] J.K. Lee, H.W. Kang, S.G. Kim, J.S. Kim, H.C. Jung, Risks related with withholding and resuming anticoagulation in patients with non-variceal upper gastrointestinal bleeding while on warfarin therapy, Int. J. Clin. Pract. 66 (2012) 64–68.

[29] A. Majeed, N. Wallvik, J. Eriksson, J. Hoijer, M. Bottai, M. Holmstrom, S. Schulman, Optimal timing of vitamin K antagonist resumption after upper gastrointestinal bleeding. A risk modelling analysis, Thromb. Haemost. 117 (2017) 491–499.

[30] P. Patel, N. Nigam, N. Sengupta, Resumption of warfarin after hospitalization for lower gastrointestinal bleeding and mortality benefits, J. Clin. Gastroenterol. 0 (0) (2017).

[31] J. Nieto, P. Marchena, R. Guijarro, N. Ruiz-Gimenez, E. Gonzalez-Higueras, T. Camara, M. Monreal, Clinical outcome of patients with major bleeding after venous thromboembolism, Thromb. Haemost. 100 (2008) 789–796.

[32] M. Carrier, G. Le Gal, P. Wells, M. Rodger, Case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism, Ann. Intern. Med. 152 (2010) 578–589.

[33] J.D. Douketis, K. Arneklev, S. Goldhaber, J. Spandorfer, Comparison of bleeding in patients with nonvalvular atrial fibrillation treated with ximelagatran or warfarin, Arch. Intern. Med. 166 (2006) 853–859.

[34] P.U. Heuschmann, S. Wiedmann, I. Wellwood, A. Rudd, A.D. Carlo, Y. Bejot, D. Ryglewicz, D. Rastenyte, C.D.A. Wolfe, Three-month stroke outcome: the European Registers of Stroke (EROS) investigators, Neurology 76 (2011) 159–165.

[35] S. Koton, A.L. Schneider, W.D. Rosamond, E. Shahar, Y. Sang, R.F. Gottesman, J. Coresh, Stroke incidence and mortality trends in US communities, 1987 to 2011, JAMA 312 (2014) 259–268.

[36] M.H. Murad, V.M. Montori, J.P. Ioannidis, R. Jaeschke, P.J. Devereaux, K. Prasad, I. Neumann, A. Carrasco-Labra, T. Agoritsas, R. Hatala, M.O. Meade, P. Wyer, D.J. Cook, G. Guyatt, How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature, JAMA 312 (2014) 171–179.