

Thromboembolic events, recurrent bleeding and mortality after resuming anticoagulant following gastrointestinal bleeding

A meta-analysis

Chatree Chai-Adisaksotha¹; Christopher Hillis^{1,2}; Manuel Monreal³; Daniel M. Witt⁴; Mark Crowther^{1,5}

¹Department of Medicine, McMaster University, Hamilton, Canada; ²Department of Oncology, McMaster University, Hamilton, Canada; ³Servicio de Medicina Interna, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; ⁴Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City, Utah, USA; ⁵Hamilton Regional Laboratory Medicine Program, Hamilton, Canada

Summary

Gastrointestinal (GI) bleeding commonly complicates anticoagulant therapy. We aimed to systematically review the published literature to determine the risk of thromboembolism, recurrent GI bleeding and mortality for patients on long-term anticoagulation who experience GI bleeding based on whether anticoagulation therapy was resumed. We performed a systematic review of phase III randomised controlled trials and cohort studies in patients with atrial fibrillation or venous thromboembolism who received oral anticoagulant. We searched MEDLINE, EMBASE and CENTRAL (from 1996-July 2014), conferences abstracts (from January 2006-July 2014) and www.clinicaltrials.gov (up to the last week of July 2014) with no language restriction. Two reviewers independently performed study selection, data extraction and study quality assessment. A total of three studies were included in the meta-analysis. The resumption of warfarin was associated with a sig-

nificant reduction in thromboembolic events (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.52 to 0.88, $p < 0.004$, $I^2 = 82\%$). There was an increase in recurrent GI bleeding but not statistically significant for patients who restarted warfarin compared to those who did not (HR 1.20, 95% CI 0.97 to 1.48, $p = 0.10$, $I^2 = 0\%$). Resumption of warfarin was associated with significant reduction in mortality (HR 0.76, 95% CI 0.66 to 0.88, $p < 0.001$, $I^2 = 87\%$). This meta-analysis demonstrates that resumption of warfarin following interruption due to GI bleeding is associated with a reduction in thromboembolic events and mortality without a statistically significant increase in recurrent GI bleeding.

Keywords

Anticoagulants, bleeding, warfarin, gastrointestinal haemorrhage, thromboembolism

Correspondence to:

Mark Crowther
Rm L208–50 Charlton Ave East
St Joseph's Hospital
Hamilton, ON L8N 4A6, Canada
E-mail: crowthrm@mcmaster.ca

Received: January 21, 2015

Accepted after major revision: April 23, 2015

Epub ahead of print: May 28, 2015

<http://dx.doi.org/10.1160/TH15-01-0063>

Thromb Haemost 2015; 114: 819–825

Introduction

Long-term anticoagulation is broadly used for numerous indications including venous thromboembolism (VTE), stroke and preventing systemic embolism from atrial fibrillation (AF) or prosthetic heart valves. Severe bleeding is an infrequent yet feared side effect of anticoagulant therapy. Gastrointestinal (GI) tract bleeding is a relatively common complication of anticoagulant therapy (1–3). The risk of GI bleeding with long-term warfarin use is estimated to be 0.3–4.5% per year (4, 5). Varying definitions of GI bleeding across studies may contribute to wide range of bleeding rates (6, 7). Concomitant use of antiplatelet agents (aspirin) doubles the risk of GI bleeding when compared to warfarin alone (4). Moreover, the occurrence of anticoagulant (either warfarin, low-molecular-weight heparin or combination with antiplatelet drugs) related GI bleeding is associated with poor clinical outcomes and increased mortality (8).

Supratherapeutic international normalised ratios (INRs) are observed in 56% to 63% of patients presenting with warfarin-associated GI bleeding (3, 9). Initial management of such patients in-

volves withdrawing and/or reversing the anticoagulant effect. (10). However, a retrospective cohort study demonstrated that interrupting anticoagulants resulted in markedly increased risk of death and thromboembolic events, especially the in first 90 days (11). On the other hand, another study reported that restarting warfarin within the first seven days of GI bleeding event was associated with greater risk of recurrent GI bleeding (7). Patients with anticoagulant-associated GI bleeding are challenging given the competing risks for thromboembolic events and recurrent GI bleeding.

Once warfarin is interrupted, clinicians must decide whether to resume anticoagulants or not. This decision is based on two major factors: 1) what is the risk of thromboembolic events if patients continue withholding warfarin; and 2) what is the risk of recurrent GI bleeding if patients resume warfarin?

We aimed to systematically review the published literature to determine the risk of thromboembolism, recurrent GI bleeding and mortality for patients on long-term anticoagulation who experience GI bleeding based on whether anticoagulation therapy was resumed.

Methods

Selection criteria

Studies were included if they met all of the following criteria 1) Randomised controlled trials (RCTs) or cohort studies of adult patients (≥ 18 years) who received oral anticoagulants for treatment of VTE (deep-vein thrombosis [DVT] or pulmonary embolism [PE]) or for primary or secondary stroke and systemic embolism prevention due to AF or a prosthetic heart valve; 2) Patients were on a vitamin K antagonist or non-vitamin K oral anticoagulant [NOAC] (dabigatran, rivaroxaban, apixaban, edoxaban); 3) The study assessed how anticoagulants were managed (interruption or resumption) after the episode of GI bleeding; 4) The study reported thromboembolic events, recurrent GI bleeding and death. Co-prescribing of anti-platelet agents (aspirin or clopidogrel) was allowed. We excluded studies if results were not reported separately for patients where anticoagulants were and were not resumed. The primary outcomes were thromboembolic events (defined as a VTE, stroke, transient ischaemic attack [TIA] or systemic embolisation), recurrent GI bleeding and death from any cause. Recurrent GI bleeding was defined as the occurrence of visualised blood in vomit, gastric aspirate or stool or endoscopic evidence of recent bleeding.

Data sources and searches

Electronic searches were performed in MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) databases. The search strategy for MEDLINE is available in Suppl. Table 1 (available online at www.thrombosis-online.com). The search strategy was slightly modified for the other databases. Articles published from 1996 to July 2014 were eligible for inclusion. No language or publication type restrictions were applied.

A search for unpublished studies was performed in July 2014 using <http://www.clinicaltrials.gov>. We also searched abstract books (January 2006–July 2014) from the congresses of the European Hematology Association (EHA), American Society of Hematology (ASH), International Society on Thrombosis and Haemostasis (ISTH), American College of Cardiology (ACC), American Heart Association (AHA) and European Society of Cardiology (ESC). Reference lists of relevant articles were manually reviewed.

Study selection

Two reviewers (C.C. and C.H.) independently performed the study selection based on the defined inclusion and exclusion criteria. Disagreements were resolved by consensus or through discussion with a third reviewer (M.C.). The kappa statistic was used to assess the agreement between reviewers for study selection. A kappa value between 0.6–0.74 indicates good agreement and a value of 0.75 or more indicates excellent agreement (12). The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for reporting of systematic reviews and meta-analyses of randomised clinical trials was followed (13).

Data extraction

Two reviewers (C.C. and C.H.) independently extracted study data using a standardised data collection form. Discrepancies between reviewers were resolved by consensus or by a third reviewer (M.C.). The following data were extracted from the included studies: study design, year of publication, population characteristics (number of patients, mean or median age and sex), therapeutic indication (VTE, atrial fibrillation, prosthetic heart valve), co-prescribing of antiplatelet agents, mean time in therapeutic range (TTR) during VKA therapy, definition of GI bleeding, follow-up length and outcome measures. Authors of included studies were contacted in order to obtain additional information when necessary.

Quality assessment

Two reviewers (C.C. and C.H.) independently assessed study quality. RCTs were assessed using the methods specified in the Cochrane Collaboration's Tool for Assessing Risk of Bias (12). The Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias in cohort studies (14). This tool focused on the selection of participants between patients who resumed and who did not resume anticoagulant (4 items), comparability of the relevant risk factors of the outcomes and strategies of outcome measurement (2 items) as well as the adequacy of the follow-up period in the included studies (4 items). Each item was rated based on the risk of bias; a high score indicates low risk of bias.

Data synthesis and analysis

Primary analyses

Baseline characteristics of the included studies were summarised using descriptive statistics. Results were pooled to perform an overall comparison between patients who did and did not resume anticoagulation. We calculated a pooled hazard ratio (HR) and corresponding 95% confidence interval (CI) for the outcomes of thromboembolic events, recurrent GI bleeding and death using the generic inverse-variance method (12). A fixed-effects model was applied to the analysis. A fixed-effects model was applied to the analysis in order to avoid small-study effect (small studies are weighted more in a random-effect model). P-values < 0.05 were considered statistically significant. Forest plots were created for each outcome. All analyses were performed using Review Manager (RevMan, version 5.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

Heterogeneity between studies in the pooled analysis was evaluated using the I^2 statistic (10). An I^2 of 0% – 40% indicates minor heterogeneity, 30% – 60% moderate heterogeneity and 50% – 90% substantial heterogeneity. We did not conduct a funnel plot assessment for publication bias as there were less than 10 studies included in the meta-analysis (12).

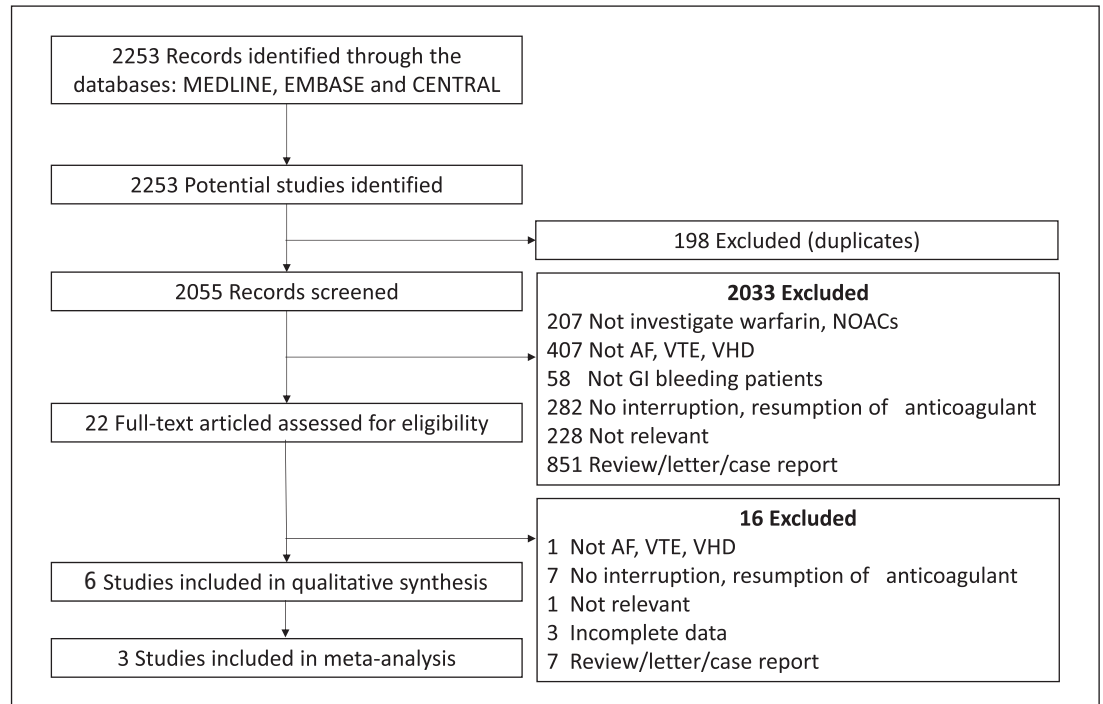


Figure 1: Flow diagram.

Subgroup analyses

A pre-specified *a priori* subgroup analyses was planned to explore sources of heterogeneity, namely the indication for anticoagulation (VTE, AF or prosthetic heart valve) and duration of anticoagulation therapy interruption.

Results

Application of the search strategies yielded 2,253 studies. After elimination of duplicate papers, 2,055 studies were screened based on their title and abstracts. Subsequently, 22 studies were selected for full-text review. Of these, six studies met inclusion criteria. Data were incomplete in four studies. Although every effort was made in order to obtain the data from the authors, only one study provided additional data. Therefore, for comparison of outcomes between patients who resumed anticoagulant and those who did not, only three studies reported complete outcomes including time-to-event data and were considered appropriate for inclusion in the meta-analysis (► Figure 1). Agreement between reviewers before discussion with the third reviewer was excellent (kappa 0.79).

Study characteristics

All three studies were observational (3, 6, 7) (► Table 1). Warfarin was the anticoagulant investigated in all studies except Nieto 2008 (3), which included participants anticoagulated with warfarin, low-molecular-weight heparin, unfractionated heparin and thrombolytic agents. However, only the data from patients with

warfarin-associated GI bleeding were selected for abstraction. Indications for anticoagulation included AF (two studies [6, 7]), VTE (two studies [3, 6]) and prosthetic heart valves (one study [6]). Two studies (3, 6) included patients with multiple indications. Mean patient age ranged from 69.0 to 77.7 years across studies. Median duration of anticoagulation therapy interruption ranged from one to 50 days and median follow-up time was between three and 24 months. Antiplatelet agent co-administration was reported in three studies (3, 6, 7), and was documented in 17% - 83% of patients. The INR at initial presentation was only available from one study (3) and revealed that 63% of presenting INRs were ≥ 3 .

Study quality assessment

The major risk of bias was comparator group dissimilarity (see Suppl. Table 2, available online at www.thrombosis-online.com). All three studies included in the meta-analysis (Nieto 2008 [3], Witt 2012 [6] and Qureshi 2014 [7]) compared patients who resumed warfarin and those who did not. In addition, patients not resuming warfarin in Qureshi 2014 (7) were more likely to have presented at the emergency department and be hospitalised compared to patients resuming warfarin. Likewise, patients not resuming warfarin in Witt 2012 (6) were significantly older than those who did. The follow-up period in the included studies ranged from three to 24 months.

Thromboembolic events

Thromboembolic events occurred in 96 of 970 patients (9.9%) who resumed warfarin and in 146 of 889 (16.4%) patients who did not (► Table 2). The resumption of warfarin was associated with a

Table 1: Characteristics of the included studies.

Study	Design	Anticoagulant	No. of patients		Age, years, Mean (SD)		Male, n (%)		Mean TTR		Indication	Concomitant antiplatelet, n (%)		Duration of withholding warfarin, days, Median (IQR)		Follow-up length (months)
			Resumed	Did not resume	Resumed	Did not resume	Resumed	Did not resume	Resumed	Did not resume		Resumed	Did not resume	Resumed	Did not resume	
Qureshi 2014	Retrospective cohort	Warfarin	653	676	74.8 (10.7)	75.3 (10.7)	364 (55.7)	336 (49.7)	57.5	58	AF	154 (23.5)	169 (25.0)	50.0 (21.0–78.0)	N/A	24
Witt 2012	Retrospective cohort	Warfarin	260	182	71.8 (12.0)	77.7 (11.3)	129 (49.6)	93 (51.1)	50.1	44.4	VTE, AF, PHV	115 (44.2)	90 (49.7)	4.0 (2.0–9.0)	N/A	3
Nieto 2008	Prospective registry	Warfarin	39	15	71.0 (14.0)	69.0 (15.0)	23 (72)	9 (28)	N/A	VTE	5 (12.8)	1 (6.7)	1.0 (0–4.0)	N/A	3	

TTR, time in therapeutic range; AF, atrial fibrillation; VTE, venous thromboembolism; PHV, prosthetic heart valve; N/A, not applicable; IQR, interquartile range; SD, standard deviation.

significant reduction in thromboembolic events (HR 0.68 [95% CI, 0.52 to 0.88], $p = 0.004$, $I^2 = 82\%$) (► Figure 2A). An *a priori* subgroup analysis could not be done because individual patient data regarding indication for anticoagulation and duration of anticoagulation interruption was not retrievable from the original articles.

Recurrent GI bleeding

Recurrent GI bleeding occurred in 99 of 978 (10.1%) patients resuming warfarin and in 49 of 892 (5.5%) patients who did not (► Table 2). The increased rate of recurrent GI bleeding in patients resuming warfarin was not statistically significant when compared to those who did not (HR 1.20 [95% CI, 0.97 to 1.48], $p = 0.10$, $I^2 = 0\%$) (► Figure 2B).

Mortality

Death occurred in 250 of 1,017 (24.6%) patients resuming warfarin and 369 in 940 (39.2%) patients who did not (► Table 2). Resumption of warfarin was associated with significant reduction in mortality (HR 0.76 [95% CI, 0.66 to 0.88], $p = 0.0002$, $I^2 = 87\%$) (► Figure 2C).

Discussion

Our results suggest that among patients receiving long-term warfarin therapy, resumption of anticoagulation following interruption for GI bleeding may reduce the risk of thromboembolic events and mortality without significantly increasing the risk for recurrent GI bleeding. We could only perform a pooled analysis on three studies due to insufficient clinical data reported in the original six papers.

Bleeding during anticoagulant therapy is common. The AF-FIRM study reported bleeding attributable to warfarin in 21% of patients (15). Management of bleeding includes interrupting anticoagulation therapy in many patients. A large prospective registry involving 17,368 patients with acute VTE found that 69% of those experiencing major bleeding interrupted anticoagulation (3). Interrupting anticoagulation therapy can have undesirable consequences. Thromboembolism or death after interruption of warfarin occurred in 8,255 of 48,989 AF patients in a retrospective cohort study in Denmark (11). Another study reported a rate of stroke or systemic embolism of 0.41% per month in patients who temporarily interrupted (3–30 days) anticoagulant therapy (16).

Our study demonstrates that warfarin resumption following GI bleeding is associated with a significant reduction in risk of thromboembolic events – however, there is considerable heterogeneity in the pooled estimate ($I^2 = 82\%$). We planned to perform an *a priori* subgroup analysis based on the hypothesis that the source of heterogeneity might be differences in participants and interventions; however, we were not able to retrieve sufficient clinical data from the original articles to confirm this hypothesis. The more pronounced reduction in thromboembolism and death observed in

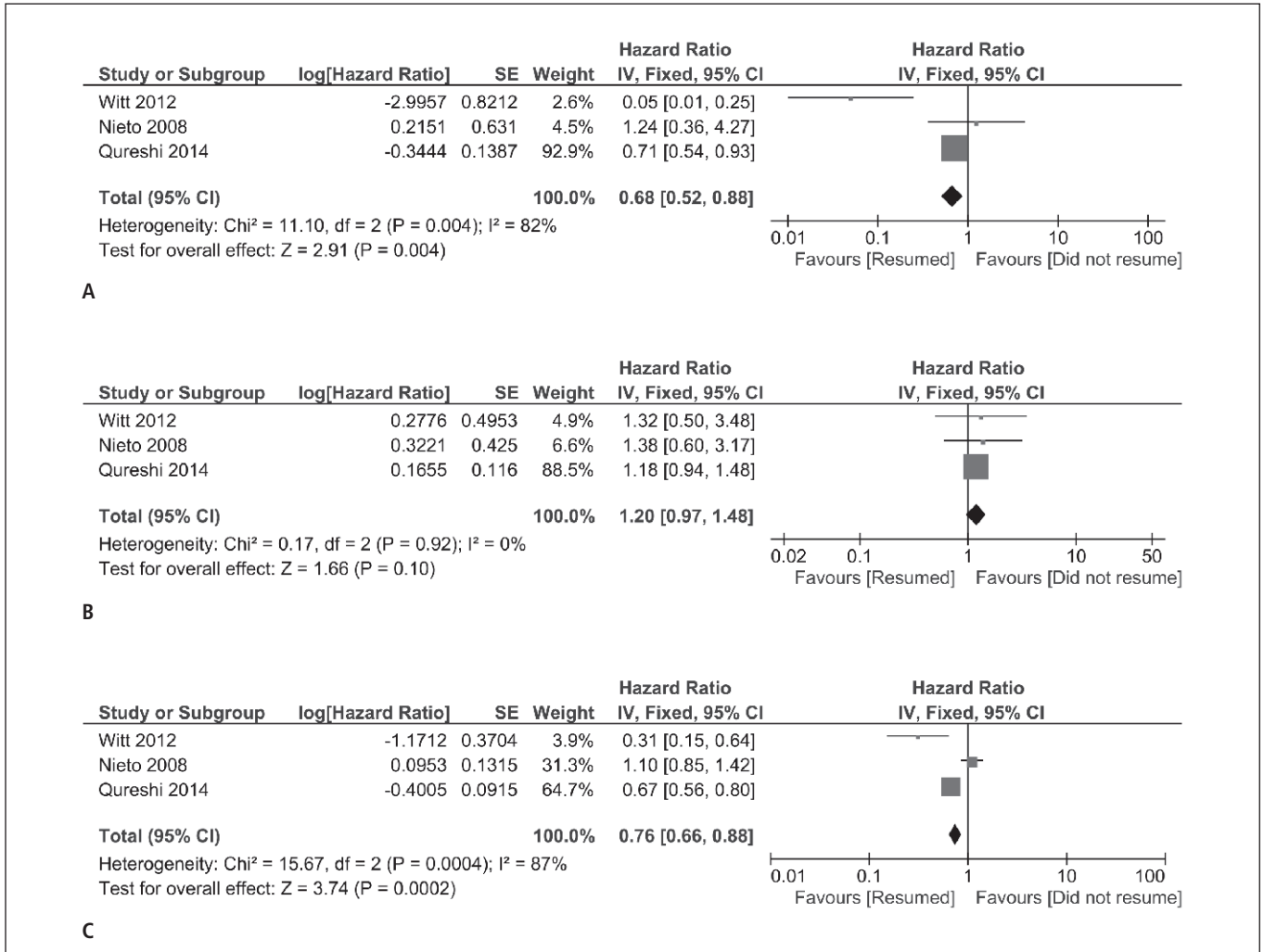


Figure 2: Forrest plot of the estimate effect of thromboembolic event (A), recurrent gastrointestinal bleeding (B) and mortality (C) in a patient who resumed anticoagulant versus a patients who did not resume.

Witt 2012 (6) (► Figure 2A and C) may be because this study included patients with prosthetic valve replacement who were likely at higher risk of thromboembolism and more likely to resume warfarin. Qureshi 2014 (7) and Nieto 2008 (3) excluded patients with prosthetic heart valves. The duration of warfarin interruption also varied between studies, with a median four days (interquartile range [IQR] 2–9) in Witt 2012 (6), one day (IQR, 0–4) in Nieto 2008 (3), and 50 days (IQR, 21–78) in Qureshi 2014 (7).

There was little data to inform analysis of the optimal timing of warfarin resumption; however, a sub-analysis of Qureshi 2014 revealed that the decision to restart warfarin sooner (less than 30 days after an episode of GI bleeding) was associated with lower risk of thromboembolism and death when compared to a decision to restart later (7). Unfortunately, our present study is not able to draw conclusions according to the optimal timing of anticoagulant resumption.

The percentage of patients experiencing recurrent GI bleeding was numerically higher in patients resuming warfarin therapy. However, the HR point estimate of the increased risk in the pooled

What is known about this topic?

- Gastrointestinal (GI) bleeding is a common complication among patients who receive long-term treatment with warfarin.
- Interruption of warfarin following GI bleeding has been shown to result in increasing risk of death and thromboembolic events.
- Resumption of warfarin following GI bleeding may be associated with increased risk of recurrent bleeding.

What does this paper add?

- Pooled analysis of relevant studies confirms that resuming warfarin following GI bleeding is associated lower risk for thromboembolism (32 % relative reduction) and decreased mortality (24 % relative reduction).
- Resuming warfarin was not associated with a significant increase the risk of recurrent GI bleeding.
- Resuming warfarin therapy should be strongly considered for most patients following resolution of GI bleeding.

Author contributions

C.C., M.C., designed the methods; C.C. and C.H. performed study selection, data extraction, study quality assessment and analysis; C.C. drafted the manuscript; C.H., D.M.W., M.M. and M.C. revised the manuscript.

Conflicts of interest

MC discloses having sat on advisory boards for Janssen, Leo Pharma, Portola, and AKP America. MC holds a Career Investigator award from the Heart and Stroke Foundation of Ontario, and the Leo Pharma Chair in Thromboembolism Research at McMaster University. MC's institution has received funding for research projects from Leo Pharma. MC has received funding for presentations from Leo Pharma, Bayer, Celgene, Shire and CSL Behring. MM states that RIETE is sponsored with an unrestricted grant by Sanofi in Spain and by Bayer AG outside Spain. MM discloses having sat on advisory board for Sanofi, Bayer, Leo Pharma, Boehringer Ingelheim and Pfizer. CC, DMW, and CH have no relevant conflicts of interest

References

- Bleeding during antithrombotic therapy in patients with atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators. *Arch Intern Med* 1996; 156: 409–416.
- Majeed A, Hwang HG, Connolly SJ, et al. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. *Circulation* 2013; 128: 2325–2332.
- Nieto JA, Camara T, Gonzalez-Higuera E, et al. Clinical outcome of patients with major bleeding after venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost* 2008; 100: 789–796.
- Coleman CI, Sobieraj DM, Winkler S, et al. Effect of pharmacological therapies for stroke prevention on major gastrointestinal bleeding in patients with atrial fibrillation. *Int J Clin Pract* 2012; 66: 53–63.
- Schelleman H, Brensinger CM, Bilker WB, et al. Antidepressant-warfarin interaction and associated gastrointestinal bleeding risk in a case-control study. *PLoS One* 2011; 6: e21447.
- Witt DM, Delate T, Garcia DA, et al. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding. *Arch Intern Med* 2012; 172: 1484–1491.
- Qureshi W, Mittal C, Patsias I, et al. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation. *Am J Cardiol* 2014; 113: 662–668.
- Hashash JG, Shamseddeen W, Skoury A, et al. Gross lower gastrointestinal bleeding in patients on anticoagulant and/or antiplatelet therapy: endoscopic findings, management, and clinical outcomes. *J Clin Gastroenterol* 2009; 43: 36–42.
- Rubin TA, Murdoch M, Nelson DB. Acute GI bleeding in the setting of supra-therapeutic international normalized ratio in patients taking warfarin: endoscopic diagnosis, clinical management, and outcomes. *Gastrointest Endosc* 2003; 58: 369–373.
- Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Br Med J* 2011; 343: d5928.
- Raunso J, Selmer C, Olesen JB, et al. Increased short-term risk of thromboembolism or death after interruption of warfarin treatment in patients with atrial fibrillation. *Eur Heart J* 2012; 33: 1886–1892.
- Higgins JPT GS, eds. *Cochrane Handbook for Systematic Review of Interventions* Version 5.1.0 [updated March 2011]. ed, The Cochrane Collaboration; 2011.
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Br Med J* 2009; 339: b2700.
- Wells GA SB, O'Connell D, Peterson J, et al. In: *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Accessed July 2014.
- Sherman DG, Kim SG, Boop BS, et al. Occurrence and characteristics of stroke events in the Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (AFFIRM) study. *Arch Intern Med* 2005; 165: 1185–1191.
- Sherwood MW, Douketis JD, Patel MR, et al. Outcomes of temporary interruption of rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: results from the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Circulation* 2014; 129: 1850–1859.
- Desai J, Kolb JM, Weitz JI, et al. Gastrointestinal bleeding with the new oral anticoagulants--defining the issues and the management strategies. *Thromb Haemost* 2013; 110: 205–212.
- Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; 3: 692–694.
- Lip GY, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients. Executive Summary of a Position Document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] Working Group on Thrombosis. *Thromb Haemost* 2011; 106: 997–1011.