APPLYING DIFFERENT RESEARCH METHODOLOGIES TO ORAL ANTICOAGULANT MANAGEMENT RESEARCH

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LAY ABSTRACT

Oral anticoagulants (OACs) (blood thinners) are among Canada's most frequently prescribed drugs and a top cause of severe medication-related harm. The objectives of this thesis include (1) to determine the barriers and facilitators for optimal OAC management, (2) to define a potential list for the core outcome set of OACs, and (3) to explore the drug-drug interaction of OACs. First, we applied a scoping review and a qualitative study to explore the barriers and facilitators for OACs management. Then we conducted a systematic survey to address the lack of consensus on outcomes and their definitions for OAC treatment clinical trials. Finally, we used a systematic review and planned a population-based study to address drug-drug interaction related to OACs. Different research approaches, including a systematic review, a systematic survey, a scoping review, a population-based study, and qualitative study, were involved in this thesis.

ABSTRACT

Background and Objectives

Oral anticoagulants (OACs) are among Canada's most frequently prescribed drugs and a top cause of medication-related serious harm leading to emergency department visits, hospitalizations, and fatalities. During the preparation to launch a Canadian Institutes of Health Research (CIHR)-funded randomized controlled trial (RCT) called "Improving Anticoagulant Safety at Hospital Discharge: A Randomized Trial," we faced some issues. First, as the RCT addresses OAC management, we needed to determine the barriers and facilitators for optimal OAC management, which were not identified in our literature search. Second, there is no core outcome set (COS) specific for OACs and the choice of outcomes and their measurement for the trial was not obvious. Finally, the drug-drug interactions between the OACs and other medications are not fully understood, particularly with regards to important clinical outcomes. Identifying the interacting medications and their interaction effect size, is vital to guaranteeing the safety of patients. To address these issues, the objectives of this thesis were: (1) to determine the barriers and facilitators for optimal OAC management, (2) to define the potential list for the COS of OACs, and (3) to explore the drug-drug interaction of OACs.

Methods

Several research approaches, including a systematic review, a systematic survey, a scoping review, a population-based retrospective cohort study with time varying methods, and a qualitative study were applied in this thesis. First, we applied both a synthesis review and qualitative research to explore the barriers and facilitators for OACs management to guarantee the evidence's robustness. Next, we used a systematic survey to address the lack of consensus on outcomes used and their

definitions for OAC treatment clinical trials. Finally, we used a systematic review and planned a population-based study to address drug-drug interaction related to OACs.

Methodologic challenges and innovation

In the scoping review (Chapter 2: Barriers and facilitators to optimal oral anticoagulant management: a scoping review) and the focus group study (Chapter 3: Perceptions on patient education to improve oral anticoagulant management) we employed a qualitative approach. The main methodological challenge for both the scoping review and the focus group focused on the rigorous way to synthesize the themes. In Chapter 4, we used a systematic survey to explore the outcome list for OAC management research. The primary methodological challenge referred to the outcome reporting in the included studies. Not all outcomes performed in the trials can be reported for the space limitation or potential publication bias. In Chapters 5 and 6, a systematic review with meta-analysis and an observational protocol were used to explore the drug-drug interaction for OACs. The main methodological challenge for Chapter 5 was how to evaluate the drug-drug interaction (DDI) evidence systematically. The main methodological challenge for Chapter 6 is to address confounding and bias in a population-based protocol on DOACs drug-drug interaction.

Conclusion

In summary, this standard thesis describes five different background projects to prepare for an OAC management RCT. The papers contribute to the literature by using several research methodologies to provide useful evidence for OAC management and OAC research.

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ABBREVIATIONS

AA: Afreen Ahmad; **AF:** atrial fibrillation; **AH:** Anne Holbrook**; AL:** Alvin Leenus; **B&Fs:** barriers and facilitators; **CG:** Cristian Garcia**; CI:** confidence interval; **CIHR:** Canadian Institutes of Health Research; **CINAHL:** Cumulative Index to Nursing and Allied Health Literature; **COMET:** Core Outcome Measures in Effectiveness Trials; **CONSORT:** the consolidated standards of reporting trials; **COREQ:** consolidated criteria for reporting qualitative research; **COS:** no core outcome set; **DDIs:** drug-drug interactions; **DOACs:** direct-acting antagonist oral anticoagulants; **DS:** Deborah Siegal; **DZ:** Dena Zeraatkar; **FA:** Farah Al-Shalabi; **GI:** gastrointestinal; **GLG:** Gregoire Le Gal; **GP**: general practitioners; **HB:** Harsukh Benipal; **INR:** international normalized ratio; **JL:** Jiayu Liu; **KV:** Kristina Vidug; KW: Kitchener-Waterloo area; **LM:** Lawrence Mbuagbaw; **LN:** Laura Nguyen; **LT:** Lehana Thabane; **MA:** Momina Abbas; **ML:** Munil Lee; **MP:** Michael Paterson; **MW**: Mei Wang; **MW*:** Michael Wong; **MS:** Marilyn Swinton **N/A:** not applicable; **OAC:** oral anticoagulant; **OR:** odds ratio; **PPIs:** proton pump inhibitors; **PSM:** patient self-management; **PST:** patient self testing; **PT:** prothrombin time; **RCT:** randomized controlled trial; **SD:** standard deviation; **SRQR:** the Standards for Reporting Qualitative Research; **STROBE:** Reporting of Observational Studies in Epidemiology; **TIA:** transient ischemic attack; **TTR:** time in therapeutic range; **UK:** United Kingdom, **USA**: United States of America; **VKAs:** vitamin K antagonists; **VTE:** venous thromboembolism**; ZC**: Zhiyuan Chen.

DECLARATION OF ACADEMIC ACHIEVEMENT

Chapter One: Introduction
This chapter is unpublished. MW and AH are the authors.

Chapter Two: Barriers and facilitators to optimal oral anticoagulant management: a scoping review.

This paper has published in Journal of Thrombosis and Thrombolysis. AH led the grant that provided funding. AH and MW designed the methods. MW and ML carried out the initial literature searches. MW, ML and JL performed the study selection and data extraction. MW, AL, and ML performed the study reporting quality assessment. MW did the data analysis and drafted the manuscript. AH, LM, and LT provided several rounds of critical revision for accurate and important intellectual content. All authors critically revised the manuscript for important intellectual content.

Chapter Three: Perceptions on patient education to improve oral anticoagulant management

This chapter is unpublished. AH and MW conceived the study idea. AH and MW contributed substantially to study design, analysis and interpretation of data, as well as drafting the chapter. All authors assisted in drafting the chapter and revised it critically for important intellectual content.

Chapter Four: Are the Correct Outcomes Being Measured in Studies of Oral Anticoagulants? A Systematic Survey

This paper has published in the journal of Thrombosis Research. AH led the grant that provided funding and conceived the study topic. AH and MW designed the methods. MW and ZC carried out the initial literature searches. MW, ZC, and MW* performed study selection and data extraction. MW did the data analysis and drafted the manuscript. AH, DS, GLG, LM, and LT provided several rounds of critical revision for accurate and important intellectual content. All authors critically revised the manuscript for important intellectual content.

Chapter Five: Drug Interactions with Warfarin: A Systematic Review and Meta-analysis

This paper has published in British Journal of Clinical Pharmacology. AH and MW designed the methods. MW, DZ and AA carried out the initial literature searches.

MW, LN, CG, FA, MA, HB, DZ and AA performed the study selection and data extraction. MW, ML, FA, HB, and KV performed the study reporting quality assessment. MW, DZ, AA and AH did the data analysis and drafted the manuscript. AH provided several rounds of critical revision for accurate and important intellectual content.

Chapter Six: The Drug-drug Interactions between Direct Oral Anticoagulant (DOACs) and Proton Pump Inhibitors (PPIs) in Elderly Patients: A Protocol for a Population-Based Retrospective Cohort Study

This chapter is unpublished. AH and MW conceived the study idea. AH and MW contributed substantially to study design, analysis and interpretation of data, as well as drafting the chapter. All authors assisted in drafting the chapter and revised it critically for important intellectual content.

Chapter Seven: Discussion
This chapter is unpublished. MW and AH are the authors.

The work in this thesis was conducted between September 2017 and June 2021.

Chapter One: Introduction

Oral anticoagulants (OACs) include vitamin K antagonists (VKAs) such as warfarin, and direct-acting antagonist oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, apixaban, and edoxaban [1]. OACs are used for the prevention and treatment of venous and arterial thromboembolism [2-6]. For instance, patients with atrial fibrillation (AF) are treated long-term with OACs with the primary purpose of preventing stroke and systemic embolism [7]. For patients with venous thromboembolism (VTE), using OACs is the primary approach to minimize morbidity and mortality [8]. For most cases, OACs need to be chronically used. Regular monitoring of the prothrombin time (PT)/ international normalized ratio (INR) is required for warfarin but not for DOACs [9]. With more than 7 million dispensed prescriptions annually [10], OACs are among Canada's most frequently prescribed drugs [11, 12]. On the other hand, OACs are a top cause of medication-related serious harm leading to emergency department visits, hospitalizations, and fatalities [13, 14]. Because of the critical role OACs play in practice, the research on OACs covers a broad range of areas. In addition to the efficacy and safety of the medication, the management of OACs, economic analysis, and pharmacokinetics are also included in OAC research. Further, both quantitative and qualitative research are used to generate evidence on the OACs.

As in any other field of clinical research, the appropriate methodology is the key to guarantee the quality of the OACs research [15, 16]. Quantitative methods are used to confirm theories and assumptions by factual information. In comparison, qualitative methods are used to understand people's thoughts, concepts, or experiences via qualitative approaches (e.g., focus groups, interviews, case studies, discourse analysis) [17].

Our team is now engaged in a Canadian Institutes of Health Research (CIHR) funded pilot randomized controlled trial (RCT) called "Improving Anticoagulant Safety at Hospital Discharge: A Randomized Trial (NCT02777047)." During the preparation for this RCT, some issues were raised. First, as the RCT is under the scope of OAC management, we need to determine the barriers and facilitators for optimal OAC management, which were not identified in our literature search. Second, there is no core outcome set (COS) specific for OACs. Third, the choice of and their measurement for the trial is an issue. Finally, the drug-drug interaction between the OACs and other medications must be addressed. Defining the related medications and their drug interaction effect size is vital for guarantee the safety of the patients.

To address these issues, the objectives of this thesis are: (1) to determine the barriers and facilitators for optimal OAC management. (2) to define the potential list for the COS of OACs (3) to explore the drug-drug interaction of OACs.

Issue 1: The barriers and facilitators for optimal OAC management

Balancing the benefits of preventing or treating thromboembolic events with the risk of bleeding events is always the primary concern for OAC management [18, 19]. Because of their tremendous benefit in preventing important clinical events (e.g., stroke, thromboembolism) and their high potential for significant harm [13, 14], anticoagulation therapy is one of the most important priorities for improving medication safety. Therefore, OAC management includes assessing the patient's ongoing individual risk of benefits and harms related to OACs, the patient's values and preferences, patient education and training, regular monitoring, patient communication, and prevention or management of adverse complications [20, 21]. At the same time, optimal anticoagulation is likely to improve health outcomes and health care sustainability [22-24].

There are reviews on the barriers for specific aspects of the optimal use of anticoagulants (e.g., after orthopedic surgery, implementation of the guidelines, and underuse of OACs, etc.) [25-28], but no large study or systematic review has outlined the key barriers and facilitators to optimal oral anticoagulation management in general.

The education of patients is thought to be essential to high-quality OAC management. Theoretically, improving patients' knowledge should improve their self-management skills and adherence [29-31]. However, systematic reviews show no high-quality evidence that supplemental patient education improves patient outcomes [32, 33]. At present, most studies were carried out in the era of warfarin as the dominant OAC, and interventions vary on education time, content, format, and target population. Direct-acting oral anticoagulants (DOACs) are the dominant OAC in the current era. Although patient education on OACs is supposed to be provided as part of usual care, there is no consistent guideline or pathway for delivering education to OAC patients, including DOAC content. As patients' education is supposed to be a facilitator of OAC management but complicated in terms of its content, format, and duration, improving education is essential for clinical practice [34, 35].

We applied both a synthesis review and qualitative research to explore the barriers and facilitators for OACs management to guarantee the evidence's robustness. The findings of the two projects have been used in the ongoing RCT directly.

Issue 2: Appropriate outcomes for OAC management research

Different outcomes were measured in the OAC treatment clinical trials, which may cause inconsistencies in the results reported and difficulties in synthesizing those evidence through systematic reviews and meta-analyses [36]. For the present ongoing RCT, appropriate outcomes for OAC management are needed. Standardization of the selection of outcomes is needed to overcome the issue.

The Core Outcome Measures in Effectiveness Trials (COMET) initiative is an international effort to develop and apply COS for clinical trials (http://www.comet-initiative.org/) [37, 38]. Williamson et al. formed the Management Group for the COMET Initiative in 2010. A COS is an agreed minimum of a specific standardized collection of outcomes within a specified setting. The COMET database currently contains 1332 citations of planned, ongoing, and completed work, including guidance on developing, implementing, evaluating, and updating COS [39]. For developing a new COS, COMET advises that the first step is to identify all potentially relevant outcomes in a literature review. After reviewing qualitative data to vet, the original outcome list, a consensus group process is undertaken to finalize the recommended COS [40].

Currently, no consensus outcomes and their definitions are available for OAC treatment clinical trials. Developing a COS will help researchers and clinicians make comparisons of effectiveness between interventions and ensure an evidence-based and patient-centered focus on outcomes and care. A systematic survey was applied to address this issue.

Issue 3: Drug-drug interaction for OACs

Despite its proven efficacy and long history as the gold standard of anticoagulant therapy, warfarin's narrow therapeutic window creates some clinical challenges. Its potential for drug-drug interactions with other medications is a commonly cited reason for the variability of a patient's INR and occasional adverse events [41]. Drug-drug interactions are a common concern for clinicians frequently managing multimorbid disease involving multiple concomitant medications. Since clinical decision support systems frequently base their warnings on quality surrogate data such as drug levels or INR, clinicians need trustworthy evidence to guide their decision-making [42-44].

Regarding the drug interaction for DOACs, no high-quality evidence (e.g., RCTs or systematic reviews) is available on the clinically relevant outcomes for many commonly used medications. The proton pump inhibitors (PPIs) can control acid-

related gastrointestinal (GI) disorders [45]. The evidence for PPIs for treatment of gastroesophageal reflux disease and GI bleeding has been used to support its concomitant use with direct oral anticoagulants (DOACs) [46-50]. However, there is controversy on the effect of PPIs on GI bleedings associated with DOACs. Studies reported that there was no evidence supporting the protective effect of PPIs against dabigatran-related GI bleedings [51, 52]. One large, randomized trial of pantoprazole with low-dose rivaroxaban (5 mg twice daily) shows the use of PPIs does not reduce upper GI bleeding [53].

There remains controversy about the overall net clinical benefit for the PPIs given with the various DOACs (dabigatran, rivaroxaban, apixaban, edoxaban). Besides, there are little high-quality data on the interaction between PPIs and DOACs concerning clinical events. A prospective pilot study demonstrated that the use of dabigatran and PPIs reduces dabigatran plasma levels in patients with atrial fibrillation (AF) [54]. Simultaneously, it was reported that there were no significant changes found concerning the anticoagulant activity of factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) according to PPI exposure [55-57]. Although there are several reports on a potential pharmacodynamic and pharmacokinetic interaction between PPIs and antithrombotic agents connected with an increase of thromboembolic events [58-60], except the decreasing upper GI bleeding, no other clinically meaningful drug-drug interaction (DDIs) with PPIs were reported for DOACs [61-64].

To our knowledge, there is no study explicitly investigating the effect of concomitant PPIs on the clinically relevant outcomes (both clinically relevant bleedings and thromboembolic events) in DOAC treated patients. We applied a systematic review and planned a population-based study to address this issue.

Outline of the thesis

This thesis is a standard one of five projects corresponding with the three issues described above. Therefore, the papers are separated into five different chapters beginning with Chapter 2.

Chapter 2 is a scoping review to identify factors (both barriers and facilitators) associated with the quality of OACs management.

Chapter 3 is a qualitative focus group study as a supplement for Chapter two. The objective of the project was to explore the content and format of patients' education important for providers or patients, and any possible reason that can cause

suboptimal education from the perceptions of providers, patients, and caregivers as a way of improving OAC management in practice.

Chapter 4 is a systematic survey to describe the outcomes used in recent OAC intervention prospective clinical studies. This work will inform the development of a COS for future OAC research, which in the end, will be used in the ongoing RCT as well.

Chapter 5 is a systematic review and meta-analysis to explore the warfarin drug-related interactions with a specific focus on patient-important outcomes.

Chapter 6 is a protocol aimed to explore the risk of thromboembolic adverse events or clinically relevant bleedings in patients having DOACs when concomitant taking PPIs by using a population-based cohort study.

Chapter 7 summarizes the main findings and methodological challenges of Chapters 2 to 6. The implications and limitations of these Five studies are also discussed in Chapter 7.

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Chapter Two: Barriers and facilitators to optimal oral anticoagulant management: a scoping review. Journal of thrombosis and thrombolysis

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Barriers and facilitators to optimal oral anticoagulant management: a scoping review

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Abstract
Oral anticoagulants (OACs) are high alert medications and require high-quality management to optimize health outcomes. The objective of this scoping review was to identify barriers and facilitators (B&Fs) associated with the quality of OAC management. We searched MEDLINE, EMBASE, and CINAHL databases until July 12, 2018, and cross-referenced the bibliographies of the retrieved studies. We included quantitative and qualitative studies that assessed B&Fs to OAC management. The study selection and data extraction processes were performed in duplicate. Analyses included measuring the prevalence of reported B&Fs from studies reporting quantitative data, identifying B&Fs in narrative analyses, and identifying their impact on important outcomes of OAC management. B&Fs were coded and aggregated to higher-level themes using a consensus approach. Factors were described as "key" if they were statistically associated with important outcomes in a randomized trial or observational study. We included 62 studies—three randomized clinical trials (RCTs), 46 observational studies (cross-sectional studies, cohort studies, and case–control studies), 11 qualitative studies, and two mixed-methods studies. Factors identified could be grouped into four themes—therapy-related, patient-related, healthcare provider-related, and health system-related. Key barriers to optimal OAC management were mostly patient-related, whereas interventions focused on education or implementing protocols were shown through RCTs to be effective at improving knowledge scores of OAC patients. While multiple barriers and some facilitators were identified in this review, none was proven to be associated with clinical outcomes. With this in mind, individual physicians may wish to address the key barriers in their practice as a quality improvement initiative but system-wide or policy changes should await high-quality evidence. Future trials should address these factors.
Systematic review registration: PROSPERO CRD42017069043

Keywords Anticoagulants · Barriers · Facilitators · Medication management · Adherence · Scoping review

Introduction

Oral anticoagulants (OACs) are indicated for the treatment and prevention of thromboembolic events, for atrial fibrillation, venous thromboembolism and mechanical heart valves, as well as in perioperative use for many surgical procedures

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and increasingly for cardiovascular risk [1–3]. OACs include vitamin K antagonists (VKAs), primarily warfarin, and the newer direct-acting oral anticoagulants (DOACs), namely dabigatran, rivaroxaban, apixaban, and edoxaban [4, 5]. The overall number of patients receiving OACs has been increasing due to an aging population with resultant increased prevalence of indications as well as expansion of the indications for OACs [6, 7].

The primary concern when treating patients with OACs is balancing the benefits of preventing thromboembolic events with the risk of bleeding events [8, 9]. Anticoagulants are the top cause of medication-related serious harm, in terms of emergency visits, hospitalizations, and fatalities [10, 11]. Because of their tremendous benefit in preventing important clinical events (e.g., stroke, thromboembolism) and their high potential for major harm, anticoagulation therapy is one of the most important priorities for improving medication safety.

OAC management includes assessment of the patient's ongoing individual risk of benefits and harms related to OACs, understanding the patient's values and preferences, patient education and training, regular monitoring, patient communication, and prevention or management of adverse complications [12, 13]. Optimal OAC management means management which leads to the best possible OAC-related health outcomes [14]. Optimal anticoagulation is likely to improve health outcomes and health care sustainability [15–17]. For example, a systematic review of mostly observational studies indicated that specialized anticoagulation clinics might result in the higher time to therapeutic International Normalized Ratio (INR) range compared with usual care for patients taking warfarin. In addition, patient self-testing (PST)/patient self-management (PSM) can result in low mortality rates and decreased incidence of thromboembolism for warfarin users [18]. Systematic reviews of the quality of OAC management in practice suggest considerable room to improve [19, 20]. Based on low time in therapeutic range for warfarin, and anticoagulation therapy-related complications for DOACs, this poor implementation may limit the ability to modify patient-important outcomes [21]. Models of OAC management include hospital outpatient clinics and various forms of community management (family doctor, specialist, pharmacist-assisted primary care, etc.) with certain degrees of PSM [22].

In preparation for a randomized trial to examine a telehealth-supported coordination model for OAC management early post-hospital discharge, we undertook a scoping review of the main barriers that our intervention should address or facilitators that we should invoke. There are reviews on the barriers for specific aspects of the optimal use of anticoagulants (e.g., after orthopedic surgery, implementation of the guidelines, and underuse of OACs, etc.) [23–26], but there is no large study or systematic review outlining the key barriers and facilitators (B&Fs) to optimal oral anticoagulation management in general. The objective of this scoping review is to identify factors, both B&Fs, associated with the quality of OAC management.

Methods

Study registration

This project was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with number CRD42017069043. The scoping review was undertaken using the methodology recommended by Arksey and O'Malley [27]. The scoping study approach requires identifying all relevant literature with all possible study design, charting the data, and finally collating and summarizing the results.

Eligibility criteria

We included both quantitative and qualitative studies as well as experimental and non-experimental study designs. These included randomized controlled trials, non-randomized controlled trials, quasi-experimental, prospective and retrospective cohort studies, case–control studies, analytical cross-sectional studies, case series, individual case reports and descriptive cross-sectional studies. We included only original research in this review. Articles that presented a secondary analysis of data, such as reviews or editorial letters, were excluded. We only included studies conducted on human participants reported in the English language. The outcomes of interest, labeled as 'important outcomes', included thromboembolic or hemorrhagic events, mortality, hospitalizations, participant quality of life, participant satisfaction with care provided or received, knowledge on OAC management (both medication and management), quality of OAC management, and health care utilization and costs, adherence to OAC. Further details (study objective, participants, follow-up, timeline, etc.) on inclusion and exclusion criteria are in Table 1.

Search methods for identification of studies

We conducted electronic searches of the following databases: MEDLINE and EMBASE via OVID, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). We defined three main concepts in our research question: B&Fs, OACs, and management. Search strategies were created and adapted based on assistance from the Health Science Librarians at McMaster University (See Online Appendix 1 for search strategy).

Table 1 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Study design	• Quantitative studies (survey studies, randomized controlled trials, non-randomized trials with or without control group, cohort or case–control studies, cross-sectional studies) • Qualitative studies (qualitative interviews, focus groups, ethnographic observations, qualitative case studies) • Mixed methods studies	• Non-empirical work (editorials, opinion texts, theoretical discussions) • Reviews and meta-analyses (we screened reference lists of those reviews for eligible studies)
Study objective	• A study designed to empirically determine barriers and facilitators • An intervention specifically designed to address a barrier or facilitator to improve oral anticoagulant management	• Studies which only mention B&Fs to OAC management as part of introduction or discussion
Participants	• Adults more than 18 years old who are taking OACs or their caregivers or their health care providers	• Children (less than 18 years old)
Outcomes of Interest	• Thromboembolic or hemorrhagic events • Mortality • Hospitalizations • Participant quality of life • Participant satisfaction with care provided or received • Knowledge of OAC management • Quality of OAC management • Health care utilization and costs • Adherence to OAC	
Follow-up (for relevant studies)	• At least 1 week	• Less than a week
Timeline	• No time restriction	
Publication language	• English	• Non-English

INR international normalized ratio, *TTR* time to therapeutic INR range, *OAC* Oral AntiCoagulant

Grey literature search of Google Scholar was also included in the search. We also explored sources identified by searching the reference list of all the included full-text papers.

Selection of studies

Titles and abstracts were first screened for relevance by two independent reviewers (MW and ML) and full-text articles with potential eligibility were downloaded for further assessment. Two independent reviewers checked the duplicate during both the title and abstract screening stage and the full-text review stage. Disagreements were resolved by discussion between the two reviewers or by adjudication from a third-party reviewer (AH).

Appraisal of study reporting quality

Given the diversity of study designs included, no single appraisal tool to assess the methodological quality (risk of bias) for all the included articles could be found. We, therefore, adopted reporting guidelines specific to each design to appraise the quality and completeness of study reporting [28], as follows: (1) we used the consolidated standards of reporting trials (CONSORT) statement to assess randomized trials [29, 30]; (2) we used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement to assess observational studies [31, 32]; (3) we used the Standards for Reporting Qualitative Research (SRQR) to assess qualitative studies [33]; (4) the final reporting quality was described as the percentage of the number of reporting item divided by the number of total items needed; (5) we did not assess the reporting quality of conference abstracts as there was no reporting guideline and rated them as unclear. Two reviewers independently assessed the methodological reporting quality of the studies. Discrepancies were discussed until consensus was reached.

Data collection and analysis

Screening for relevance and data extraction were performed by two independent reviewers to decrease the likelihood of selection bias [34]. Pre-designed and tested data collection forms were used to extract data from the included studies. We collected information on first author, title, year of publication, publication journal, country of study, study design, type of OACs, sample size, population characteristics, exposure, important outcomes, duration of follow-up, information relating to bias assessment, funding sources for the research, types and characteristics of B&Fs, and outcome statistics in quantitative articles (see details in Online Appendix 2).

The reporting quality of the selected articles was assessed according to specific reporting guideline (CONSORT, STROBE or SRQR) [29–33]. Each item was phrased as a question with the response options: "Yes," "No," "not sufficient" and "not applicable." The percentage of "Yes" out of the total were calculated to evaluate the reporting quality.

We analyzed qualitative and quantitative data separately, and the findings were combined into a final synthesis. First, we synthesized qualitative data to explore the factors that act as B&Fs to oral anticoagulants management. We undertook a using the three stages recommended by Thomas et al. [35]. The process involved coding text and developing initial themes. The exact findings of the identified studies were extracted according to content and meaning, by two review authors independently. In this step, we identified and clustered different types of B&Fs for optimal OAC management. Most of the factors were categorized according to that found in the original papers. To overcome the inconsistency and some overlap of the coding, several rounds of discussion meetings were held. Next, we used the quantitative studies to assess which barriers or facilitators were important to oral anticoagulant management based on the following hierarchy. First, we chose randomized controlled trial (RCT) as the highest level of research design) combined with the importance of the related outcomes (see Table 1). We defined the second level factors shown in observational studies to be significantly associated with at least one of the outcomes of interest. Examples of the statistics results (e.g., odds ratios (OR) and p-values) from the included studies were supplied. Descriptive statistics for individual reporting items and study characteristics items were reported as counts and percentage.

Results

Study characteristics

The literature search yielded 4769 publications from the databases. We added 9 articles from the additional sources. After removal of duplicates, we included 3398 articles for the title and abstract screening, and then 145 for full-text review. There were 62 studies left for the final data analysis (see details in Fig. 1).

The 62 studies were published between January 1995 and July 2018. Three were randomized clinical trials [36–38], 46 were observational studies [39–82], 11 were qualitative studies [83–93], and 2 were mixed methods studies [94, 95]. Half of the studies (n = 31) were conducted in the United States of America, seven studies in Australia and five were in the United Kingdom. Other countries represented include Netherlands (3), Canada (2), Spain (2), China (1), France (1), Germany (1), Greece (1), Israel (1), Japan (1), Qatar (1), and Saudi Arabia (1).

Reporting quality

The overall average reporting quality score of the included 44 full report studies was 62.4% ± 11.9% (mean ± standard deviation) with only three articles scoring 80% or more (see details in Table 2).

Reported B&Fs

The summary of potential B&Fs to oral anticoagulation management is outlined in Table 3 (factors specific for warfarin was marked with *) and more detailed information including mentioned frequency and outcome statistics can be found in Online Appendices 3 and 4. Four themes were identified from the included articles: therapy-related factors (35 items); patient-related factors (35 items); healthcare provider-related factors (30 items) and health system-related factors (41 items). Therapy-related factors included the impact on lifestyle, drug-drug interactions, and reversal problems. We defined the patient-related barriers only for the direct factors attributed to the patients, which included patients' conditions or diseases, patients' attitudes or behaviors, and patient characteristics. Healthcare provider-related factors included health provider characteristics, health provider's attitudes and behaviors. Health system-related factors included healthcare support, patients' expectations of the health system, communication within system, and clinical evidence. None of the studies addressed clinical events, mortality or healthcare utilization as the outcome of interest.

Factors that met the definition of 'key factors' had to have a statistically significant impact on at least one important outcome in an RCT or observational study (see details in Online Appendix 3). We provide representative examples of each key barrier and facilitator below, with statistical information drawn from the source studies.

No RCTs addressed barriers. Three important therapy-related barriers included: (a) any requirement of regular blood tests to monitor the drug (as a barrier against adherence to warfarin ($P < 0.01$)) [94], (b) pill burden (as a barrier to adherence to warfarin for patients feeling they already take too many medications) ($P < 0.05$) [66], and (c) patients with alcoholism (as a barrier to appropriate prescribing of warfarin, adjusted OR 0.59 (95% CI 0.35–0.99)) [61].

We identified ten key patient-related barriers: (a) senior age (> 75 years old, as a barrier to prescribing OACs (not drug specified) when indicated and to gaining knowledge about medication) [45, 49, 50, 54, 61, 63, 64, 80, 94] (see statistical details in Online Appendix 3), (b) language barriers (as a barrier to maintaining TTR (for instance, absolute difference of TTR of 7.2%, $P < 0.05$) [46, 59, 71], (c)

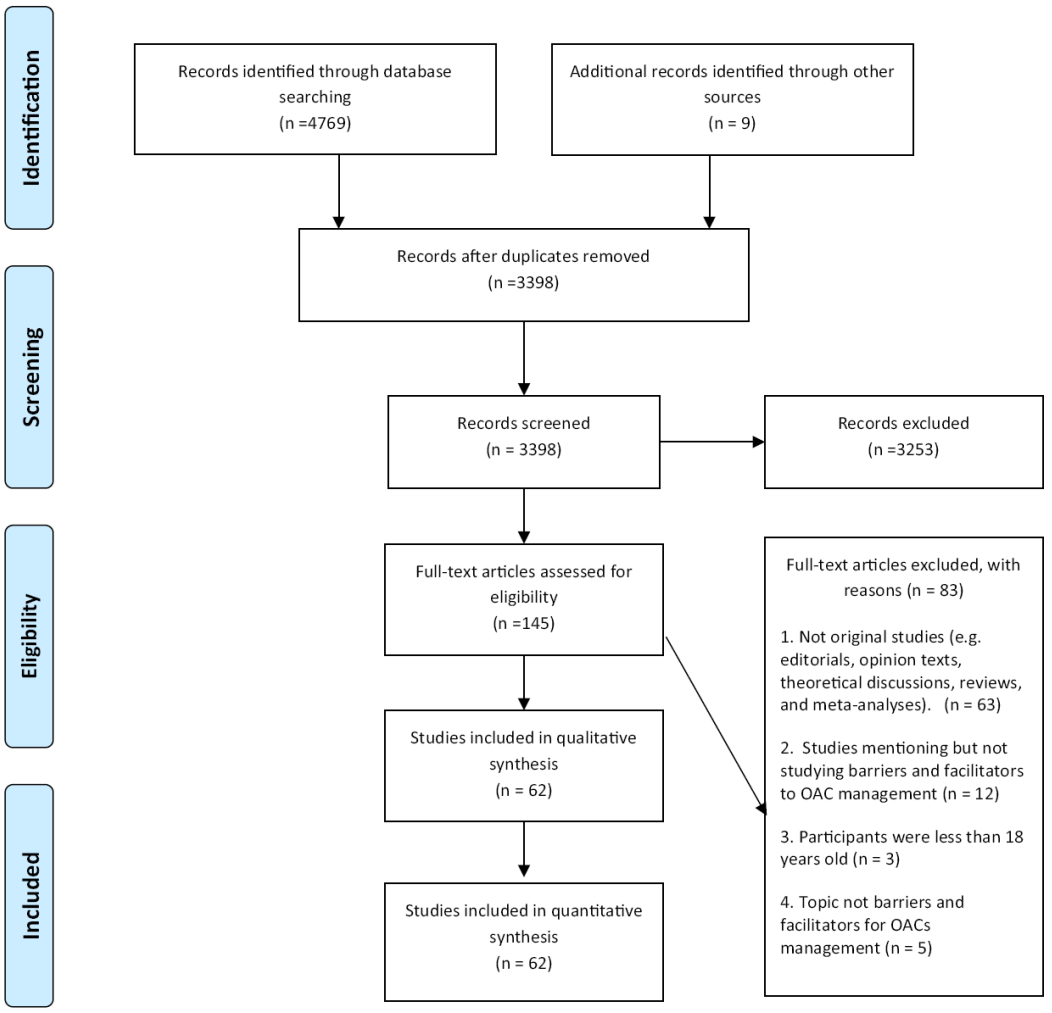

Fig. 1 Flow diagram for article selection

cognitive impairment of patients (as a barrier to adherence to OACs (not drug specified)) [49], (d) comorbidity burden of patients (as a barrier to optimal prescription or compliance with OACs, for instance, the adjusted OR of warfarin users versus nonusers 0.66 (95% CI 0.52–0.84) [49, 61, 65, 69, 94], (e) perceived high fall risk in elderly (as a barrier to optimal prescription with OACs (not drug specified), for instance, the adjusted OR of warfarin users versus nonusers for AF patients 0.61 (95% CI 0.52–0.73)) [61], (f) frailty or poor general health (as a barrier to decreasing the likelihood of patients receiving OACs (not drug specified), for instance, the OR was 12.58 (95% CI 5.82–27.21) for severe disability compared to no disability) [82], (g) concern about bleeding (as a barrier related to noncompliance with OACs, for instance with warfarin ($P < 0.05$)) [94], (h) the behavior of noncompliance (as a barrier to optimal OAC management, for instance, the OR for classifying a noncompliant patient as showing with poor warfarin management quality (TTR < 60.0%) was 1.588, $P < 0.01$) [65], (i) no drug coverage (as a barrier to adherence, for instance, the OR of patients who are noncompliant with warfarin versus patients who are compliant with warfarin was 5.60 (95% CI

Table 2 Characteristics of included studies

Randomized clinical trials (RCT)

Source paper	Full report	Country	Participants (number)	Intervention and control	Study focus	Methodology reporting quality score[§]
Field et al. [36]	Yes	USA	Patients taking warfarin (435)	Intervention: patients received a developed warfarin communication protocol Control: patients continued with usual care	Using communication protocol to improve time in therapeutic range for INR	63.6%
Ryan et al. [37]	Yes	Ireland	Patients taking warfarin (162)	Intervention: patients treated by protocol of supervised patient self-testing Control: Patients treated by conventional anticoagulation management service	Using protocol of supervised patient self-testing to improve time in therapeutic range for INR	66.7%
Chen et al. [38]	No (Abstract)	USA	Patients with AF (90)	Intervention: electronic personal health record-facilitated medication education Control: usual care	Education for improving mean score on knowledge of dabigatran	N/A

Observational studies

Source Paper	Full report	Country	Participants(number)	Design	Study focus	Methodology reporting quality score[#]
Ansell et al. [41]	No (Abstract)	USA	Patients taking warfarin (259)	Cross-sectional study (survey)	Barriers associated with anticoagulation therapy	N/A
Arepally et al. [42]	Yes	USA	Physicians (647)	Cross-sectional study (survey)	Current beliefs, behaviors, and knowledge of practicing physicians for the use of antithrombotic therapies	51.7%
Barrios et al. [43]	Yes	Spain	Health providers (893)	Cross-sectional study (survey)	The barriers and deficiencies present for anticoagulated patients	46.4%
Beyth et al. [45]	Yes	USA	Physicians (80)	Cross-sectional study (survey)	Factors related to the anticoagulation decision-making	50.0%
Bhandari et al. [46]	Yes	USA	Patients taking warfarin (187)	Retrospective cohort study	Time in therapeutic range for INR	62.5%
Bungard et al. [47]	Yes	Canada	Physicians (280)	Cross-sectional study (survey)	Barriers to prescription warfarin	64.3%
Changying et al. [48]	No (Abstract)	China	Physicians (208)	Cross-sectional study (survey)	Physicians' concern about warfarin treatment	N/A
Chen et al. [49]	No (Abstract)	USA	Patients taking OACs (1481)	Retrospective cohort study	Factors associated with receiving anticoagulant treatment	N/A

Table 2 (continued)

Observational studies						
Source Paper	Full report	Country	Participants(number)	Design	Study focus	Methodology reporting quality score[#]
Robson et al. [70]	Yes	UK	Patients with AF (4604)	Pre-post study	To explore if an education program can improve the OACs prescribtion	50.0%
Rodriguez et al. [71]	Yes	USA	Patients taking warfarin (3,770)	Retrospective cohort study	Time in therapeutic range for INR	64.3%
Rose et al. [72]	Yes	USA	Patients taking warfarin (56,490)	Prospective cohort study	Time in therapeutic range for INR	70.0%
Rosenman et al. [74]	Yes	USA	Patients with AF (4180)	Retrospective cohort study	Potential barriers to prescription of warfarin	66.7%
Salinas et al. [75]	No (Abstract)	USA	Health Providers (1024)	Cross-sectional study (survey)	Barriers to using new and emerging therapies to manage patients with AF	N/A
Shen et al. [77]	Yes	Australia	GP (182)	Cross-sectional study (survey)	Factors related to anticoagulant under-utilization for AF	53.6%
Stafford et al. [78]	Yes	Australia	Patients taking warfarin (268)	Prospective cohort study	Warfarin knowledge scores	40.6%
Tan et al. [79]	No (Abstract)	Ireland	Patients with AF (168)	Cross-sectional study (survey)	Barriers for the very elderly with atrial fibrillation on warfarin attending an outpatient anticoagulant monitoring service	N/A
Wilson et al. [80]	Yes	USA	Patients taking OAC (65)	Cross-sectional study (survey)	Barriers for elder patients with anticoagulation therapy	41.4%
Airee et al. [39]	Yes	USA	Patients taking warfarin (100)	Retrospective cohort study	Time in therapeutic range for INR	56.2%
Al Ammari et al. [40]	No (Abstract)	Saudi Arabia	Patients taking warfarin (50)	Retrospective cohort study+Cross-sectional Study(survey)	Time in therapeutic range for INR	N/A
Berger et al. [44]	No (Abstract)	USA	Physicians (22)	Cross-sectional study (survey)+Cohort study	Use of HAS-BLED on decision-making	N/A
Farmakis et al. [54]	No (Abstract)	Greece	Patients with AF (1127)	Prospective cohort study	Predictors of adherence to antithrombotic therapy	N/A
Khudair et al. [62]	Yes	Qatar	Patients taking warfarin (140)	Prospective cohort study	Adherence	78.6%
Orensky et al. [66]	Yes	USA	Patients taking warfarin (75)	Retrospective cohort study	Predictors of noncompliance with warfarin therapy	57.1%
Rosenman et al. [73]	Yes	USA	Patients with AF (187)	Retrospective cohort study	Barriers to using warfarin	63.3%
Sarangpur et al. [76]	No (Abstract)	USA	Patients taking warfarin (291)	Retrospective cohort study	The effect of missed clinic appointments on important clinical outcomes	N/A
Durand et al. [81]	No (Abstract)	UK	Patients on DOACs or Warfarin (501)	Pre-post study	To assess the impact of a program on OAC's management	N/A

Table 2 (continued)

Observational studies						
Source Paper	Full report	Country	Participants(number)	Design	Study focus	Methodology reporting quality score[#]
Cohen et al. [50]	Yes	Israel	Patients with indication of OACs (575)	Retrospective case–control study	Factors influencing warfarin starting use	53.3%
Cruess et al. [51]	Yes	USA	Patients taking warfarin (156)	Prospective cohort study	Specific patient factors that might help explain Warfarin non-adherence at outpatient anticoagulation clinics	59.4%
Edwards et al. [52]	No (Abstract)	USA	Patients on chronic warfarin therapy (63)	Pre-post study	Time in therapeutic range before and after employing an electronic medical record	N/A
Elewa et al. [53]	Yes	USA	Patients on chronic warfarin therapy (260)	Cross-sectional study (survey)	Predictors in determining patients' choice of OACs for stroke prevention	59.4%
Ferguson et al. [55]	Yes	Australia	Cardiovascular nurses (55)	Cross-sectional study (survey)	Barriers in patients with AF	72.4%
Frankel et al. [56]	Yes	USA	Health providers (507)	Cross-sectional study (survey)	Barriers to effective communication and optimal anticoagulation use	55.2%
Gattellari et al. [57]	Yes	Australia	Family physicians (569)	Cross-sectional study (survey)	Barriers to the use of anticoagulation	37.9%
Gross et al. [58]	Yes	USA	General internists (127)	Cross-sectional study (survey)	Factors associated with performing anticoagulant treatment	62.1%
Hong et al. [59]	No (Abstract)	USA	Patients taking warfarin (1715)	Retrospective Cohort study	Time in therapeutic range for INR	N/A
Ingelgard et al. [60]	Yes	USA	Physicians (30)	Cross-sectional study (survey)	The barriers to warfarin use	48.3%
Johnston et al. [61]	Yes	USA	Patients with AF (11,699)	Retrospective cohort study	The predictors of Warfarin use	60.7%
Mæda et al. [63]	Yes	Japan	Physicians (139)	Cross-sectional study (survey)	Factors associated with OACs prescription	51.7%
McCrory et al. [64]	Yes	USA	Physicians (309)	Cross-sectional study (survey)	The barriers to anticoagulation in clinical practice	69.0%
Mueller et al. [65]	Yes	Germany	Patients with AF (417)	Prospective cohort study	Factors associated with poor anticoagulation quality	73.3%
Partington et al. [67]	Yes	Canada	Patients with indication of OACs (106)	Retrospective case–control study	The appropriate use and barriers to oral anticoagulant therapy	67.9%
Peterson et al. [68]	Yes	Australia	GP (711)	Cross-sectional study (survey)	Potential barriers to the use of anticoagulation	65.5%
Platt et al. [69]	Yes	USA	Patients taking warfarin (111)	Prospective cohort study	Factors affecting nonadherence to warfarin	66.7%

Table 2 (continued)

Observational studies						
Source Paper	Full report	Country	Participants(number)	Design	Study focus	Methodology reporting quality score[#]
McGrath et al. [82]	Yes	USA	Patients with ischemic stroke (1405)	Retrospective cohort study	To explore barriers to anticoagulation among older atrial fibrillation (AF) patients	66.7%
van Fessem et al. [96]	No (Abstract)	Netherlands	Patients taking OACs (248)	Pre-post study	To check a quality-improvement project on OACs management	N/A
Redgrift et al. [99]	No (Abstract)	England	Patients with AF (105)	Cross-sectional study (survey)	To explore the common barriers to anticoagulation in AF	N/A
Qualitative studies						
Source Paper	Full report	Country	Participants(number)	Data collection format	Study focus	Methodology reporting quality score*
Bajorek et al. [89]	Yes	Australia	Nurses (11)	Group Interview (Focus group)	The nursing perspective on warfarin use	66.7%
Borg Xuereb et al. [90]	Yes	UK	Physicians (16)	Multi-perspective interpretative phenomenological analyses	Understanding the anticoagulation decision-making	88.3%
Decker et al. [91]	Yes	USA	Health providers (27)	Interview	Barriers to warfarin treatment	88.3%
Drewes et al. [92]	Yes	Netherlands	Anticoagulant clinic specialists (103)	Interview	The barriers to collaboration between care professionals	77.8%
Graves et al. [93]	No (Abstract)	USA	Patients taking warfarin (48)	Cause analysis	The main factor that caused the adverse event of inpatients are taking warfarin	N/A
Kauffman et al. [83]	Yes	USA	Patients taking warfarin (19)	Interview	Patient-specific factors influencing adherence to INR monitoring	88.3%
Kuljis et al. [84]	Yes	UK	Patients taking warfarin (17)	Interview	Patient views, needs, and expectations of an anticoagulation service and the self-testing and management services provided	77.8%
Lowthian et al. [85]	Yes	Australia	Patients taking warfarin (40) and their treating doctors (36)	Interview	Potential weaknesses in the system of managing warfarin therapy	61.1%
Wild et al. [86]	Yes	UK, USA, and Spain	Patients taking vitamin K antagonists (60)	Interview	Patients perspectives on taking vitamin K antagonists	61.1%
Kea et al. [87]	No (Abstract)	Oregon	Emergency department physicians (18)	Interview	Factors that prevent and support OAC prescribing for AF by ED physicians	N/A

Table 2 (continued)

Qualitative studies						
Source Paper	Full report	Country	Participants(number)	Data collection format	Study focus	Methodology reporting quality score*
Vaanholt et al. [88]	No (Abstract)	Netherlands	Patients with AF (48)	Group Interview (Focus group)	Examine patients' reasons for (non-) adherence to oral anticoagulant therapy	N/A
Mixed method studies						
Source Paper	Full report	Country	Participants(number)	Design	Study focus	Methodology reporting quality score #
Arnsten et al. [94]	Yes	USA	Patients taking warfarin (132)	Case–control study + interview	Barriers to compliance with anticoagulation therapy	64.5%
Deplanque et al. [95]	Yes	Austria, Belgium, France, Italy, and Portugal	Patients with indication of OACs (370)	Prospective observational study + interview	Factors associated with performing anticoagulant treatment	56.7%

UK United Kingdom, *USA* United States of America, *AF* atrial fibrillation, *GP* general practitioners, *INR* international normalized ratio, *DOAC* direct oral AntiCoagulant, *OAC* Oral AntiCoagulant

*Percentage of reporting applicable methodology items recording to Standards for Reporting Qualitative Research (SRQR)

#Percentage of reporting applicable methodology items recording to strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

§Percentage of reporting applicable methodology items recording to Consolidated Standards of Reporting Trials (CONSORT)

Table 3 Summary of the barriers and facilitators for optimal OAC management

Category	Barriers	Facilitators
A. Therapy-related		
A1. Impact on lifestyle	• Dietary (or alcohol) restrictions • Changes in routine • Pill burden (patients are already taking too many medications to add another one) • Dosing changes • *Requirement of regular blood tests to monitor the drug • *Transportation barriers • Restricted physical activity when using the drugs	• Dietary freedom (switch from warfarin to dabigatran) • Ensuring type of lifestyle and therapy is matched with patient's capacity to self-manage • Fewer blood tests to monitor the drug (switch from warfarin to dabigatran) • *Regular adherence and INR monitoring • *Facilitate access to INR testing • *Provide INR test reminders in the form of phone calls, letters, and E-mail • *Availability of portable INR monitors
A2. Drug-drug interactions	• Patients taking medication that may interact with OACs • Patients taking medication that may interact with OACs • Patients with alcoholism (or other drug abuses) • Use of Aspirin • Allergy or intolerance to warfarin	
A3. Reversal problems	• Reversibility of anticoagulants • *Difficulty related to reversing	
B. Patient-related		
B1. Patients' condition or diseases	• (History of) cognitive impairment (e.g., dementia, poor cognition, or mental health problem) • Comorbidity burden (e.g., renal disease requiring hemodialysis, renal insufficiency, cancer, hepatic disease, severe anemia, poorly controlled hypertension, paroxysmal AF) • Other conditions 1. Frailty or poor general health 2. Inability for self-care 3. Perceived high fall risk in elderly 4. Limited life expectancy 5. History of alcoholism 6. Active bleeding, risk of bleeding, or history of bleeding 7. Poor memory 8. Inability to comply with therapy 9. Risk of embolus is too low to warrant anti-coagulation • Returned to normal sinus rhythm for AF patients	• Indication of OAC is Stroke/TIA • Having another indication for anticoagulant therapy • History of stroke • Hypertension • Congestive heart failure • Risk factor for thromboembolism • *Patients with therapeutic INR
B2. Patients' attitudes or behaviors	• Concern about bleeding • Concern about bruising • Concern of therapy having negative impact on quality of life • Fear or dislike of lab test (monitoring) • Refusal to the OACS • Averse to taking the pill every day • Averse to attending the clinic • Concerns that the medication is difficult to manage • Non-compliance • Missed clinical appointment Inability to adhere to alcohol restrictions	• Believe health providers' skill, and competence is excellent or very good • Believe taking OACs benefits their health • Believe taking OACs protects their future health • Fear of stroke • Monitoring of adherence (refer to non-compliance)

Table 3 (continued)

Category	Barriers	Facilitators
B3. Patient characteristics	• Demographic characteristics 1. Age (senior) 2. Gender (Male) 3. Ethnicity (non-white) 4. Language barriers • Socioeconomic factors 1. Having full-time job 2. No insurance 3. Education level 4. Lack of social support (e.g. patient living alone) 5. Poor social situation 6. Out of pocket costs • Health Knowledge 1. Drug myth 2. Lack of receptivity to specific details about disease and medication 3. Inability to comprehend medication instructions	• Knowledge of benefits and risk of OACs • Family support & involvement (e.g., married) • Self-management & community support • Without language limitation • Patients' good literacy
C Healthcare provider-related		
C1. Health providers' characteristics	• Lack knowledge related to coagulation • Shortcomings in training • Less experience related to coagulation management	• Health providers' good skill and competence • Experienced with OAC • Impact of clinical trials on their practice of anticoagulant prophylaxis • Cardiologist • More new AF patients
C2. Health provider's attitudes or behaviors	• Concern about bleeding • Concern about litigation • Concern about the monitoring • Concern about patients' advanced age • Clinician reluctance (worry about the AE, don't want to disorder patient's habits) • Concern if patients will be adherent with OACs • Fear of the patient falling • Fear of patients' poor literacy • Concern about reversibility of OACs • Doubt effectiveness or unfamiliar with evidence • Hard to decide whether the benefits of OAC outweigh the risks or vice versa • Belief that aspirin is better alternative • Patient feels physician is not very concerned about them • Poor patient to healthcare provider communication • Difficulty contacting patient in case of urgent dose change • *Harsh language or chastising patients following missed INR tests	• Patients are dependent on physicians • Good communication (including listening, interpreters, written information) • Open discussion and understanding anticoagulation • Assign anticoagulation providers to work with the same patients over time • *Providing reassurance to patients when they have achieved their INR goal • Pharmacy education

1.60–19.20)) [94], and (j) lack of social support (e.g., patient living alone) (as a barrier to optimal prescription or compliance with OACs, for instance, decreasing the likelihood of patients receiving OACs (not drug specified) ($P < 0.05$) [49] and reducing compliance with warfarin ($P < 0.05$) [66]).

For healthcare provider-related barriers, the main barrier was less experience related to coagulation management (not drug specified), OR 0.43 (95% CI 0.23–0.81) [63]. For health system-related barriers, the main barrier found was lack of anticoagulation clinic service (as a

Table 3 (continued)

Category	Barriers	Facilitators
D. Healthcare system-related		
D1. Healthcare support	• No regular physician • The amount of time available in consultations is limited • No time for patients to think in secondary care • The luxury of repeated consultations and rapport-building in primary care • Increased expertise but lack of time in secondary care • Administrative barriers to free prescription • Lack of subsequent monitoring or difficulty in arranging services for monitoring • Lack of anticoagulation clinic services • Delay in lab report	• Nurse or pharmacist-led anticoagulation management service • Warfarin booklets (written information) • Thorough assessment of the patients • A greater utilization of carer support and services • Further support for the primary care setting • Electronic personal health records plus education • Case management • Multi-disciplinary care • Discharge planning • Medication event monitor system • Computer-assisted oral anticoagulant dosage program
D2. Reimbursement and Time Issues	• Inadequate reimbursement for time spent monitoring warfarin	• Adequate reimbursement • More personalized/real-time communication • Pragmatic and collaborative patient-clinician partnerships • Recognition of patient knowledge and expertise as peer educators
D3. Communication within the system	• Breakdown in communication between clinicians and healthcare settings • Inadequate to the exchange of information between patients and providers • Poor provider to provider communication	• Health care organization • Delivery system (re)design • Good GP/GP support • Facilitated telephone communication between nurses and physicians • Improved role clarification
D4. Clinical evidence	• Lack of effective protocols and efficacy data • Lack of clarity of guideline recommendations • Lack of RCT evidence • Lack of consensus as to treatment • Lack of awareness of tools to guide risk assessment	• HAS-BLED score (bleeding assessment score) • Targeted guidelines • Computer software supporting clinical decisions

INR international normalized ratio, *OAC* oral anticoagulant, *AF* atrial fibrillation, *TIA* transient ischemic attack, *GP* general practitioner

*Note: specific for warfarin

barrier to starting anticoagulation with OR 0.50 (95% CI 0.27–0.90)) [49].

For facilitators, three RCTs indicated that interventions based on education or implementing protocols were effective for improving TTR or knowledge score (both medication and management knowledge) of OAC patients (See statistical details in Online Appendix 4) [36–38].

We did not identify any key therapy-related facilitators. Patient-related facilitators included (a) family support and involvement (e.g., patients with family support had better compliance with warfarin, $P < 0.01$) [66], (b) patients' belief that OACs benefit their health (patient-related factor for patients' compliance with OACs; for instance, in patients who were noncompliant with warfarin versus patients who were compliant with warfarin, those who believed taking OACs benefits their health had lower percentages: OR 0.50 (95% CI 0.20–1.10)) [94], and (c) an indication of OAC is stroke/transient ischemic attack (TIA) (patients in this condition were more likely to be adherent with OACs; for instance, in patients who were noncompliant with warfarin versus patients who were compliant with warfarin patients, those whose indication was stroke/TIA had lower percentages. OR 0.20 (95% CI 0.10–0.70)) [94].

The major health provider-related facilitator was health providers' high skill and competence (healthcare provider related factor for patients' compliance with OACs; for instance, if health providers had good skills and competence, patients had lower percentages in noncompliance to warfarin. OR 0.40 (95% CI 0.10–1.00)) [94].

Finally, the system-related facilitator was a dedicated nurse or pharmacist-led anticoagulation management service [health system-related factor for improving warfarin knowledge scores or improving TTR of patients, (for instance, usual care vs. service intervention for TTR control was less effective, $P < 0.01$)] [16, 39, 81, 96].

Discussion

There is a lack of high-quality evidence on barriers and facilitators for OAC management, so it is not entirely clear other than identification of potential factors driving clinical outcomes, how important are the factors identified in this review. Practical clinical questions regarding the management of oral anticoagulation are rarely addressed by randomized trials and tend to focus on surrogate outcomes [12, 97]. To our knowledge, this is the first scoping review on B&Fs for OAC management that summarizes across themes and perspectives. In this scoping review, we identified B&Fs related to broad themes within the following four categories: (1) therapy-related factors, (2) patient-related factors, (3) healthcare provider-related factors, (4) healthcare system-related factors. We found 79 barrier items and 58 facilitator items in total. Overall, the review supports the hypothesis that optimizing complex medications like OACs may require a multi-faceted approach. It is difficult to say which barriers or facilitators are the most important and these may vary by patient. For example, patient education comes up repeatedly as a facilitator yet our scoping review of patient education about OACs did not find improved clinical outcomes [98]. Likewise, health systems are constantly being exhorted to do more for patient management, but each new support program takes funding away from other health interventions.

One critical finding for the included studies was that, other than indirect outcomes (e.g., patients' adherence, patients' knowledge of the medication, the right prescription rate of the OACs), no study addressed the effect of barriers or facilitators on clinical outcomes (e.g. thromboembolic events, bleeds, or death). One of the reasons of this finding may due to the inclusion criteria of the review, which required specific mention of a barrier or facilitator in the objectives of the study. This approach may have missed some factors associated with clinical outcomes. However, the results of the review highlight the need for high-quality evidence addressing B&Fs interventions impact on patient-important outcomes.

The key barriers we found in this review were mostly patient-related factors. For some factors, e.g., senior age (> 75 years old), cognitive impairment of patients, perceived high fall risk in elderly, comorbidity burden of patients, and frailty or poor general health, it is difficult to find strategies to address the barriers. Conversely for language barriers, translators are an effective facilitator to overcome management challenges [59]. To deal with the barrier of requirement of regular blood tests to monitor the drug, the facilitators we found in this scoping review include fewer blood tests to monitor the drug (switch from warfarin to dabigatran), facilitate access to INR testing, provide INR test reminders in the form of phone calls, letters, and E-mail, and availability of portable INR monitors for self-monitoring. For lack of social support (e.g., a patient living alone), the respective facilitator we found was family support and involvement. However, it is apparent that fewer studies focused on facilitators as opposed to barriers, which indicates a research direction in the future.

We chose to perform a scoping review as our study methodology instead of a narrative review or a systematic review for several reasons. First, the topic is broad, which is more suitable for a scoping review than the other two. Second, we used a systematic literature search, which is used in a scoping review, not a narrative review. However, this scoping review has its limitations. First, we focused on studies that explored B&F for OAC management as their objectives. The studies that mentioned barriers or facilitators but not as part of their objectives were not included. We may have also missed some intervention studies on OAC management that addressed barriers or facilitators but did not report them as such. Second, we did not assess the risk of bias of the included papers since this is a scoping review. Instead, we checked the reporting quality of the included articles. The results showed the reporting quality is suboptimal for the included articles. In addition, to some extent, there may exist information and selection bias as the included studies do not always describe the facilitators or barriers explicitly or extensively. Finally, as the original design of the study is to explore the general meaning of B&F of the OAC management, we did not stratify our results by indication of anticoagulation and OAC category, although it is not clear that the B&F would differ by indication. However, extraction processes were performed in duplicate with adjudication to reduce errors. As a result, we believe we identified valid B&Fs for OACs management from the literature we found.

Conclusion

While multiple barriers and some facilitators were identified in this review, none was proven to be associated with clinical outcomes. With this in mind, individual physicians may wish to address the key barriers in their practice as a quality improvement initiative but system-wide or policy changes should await high-quality evidence. Future trials should address these factors.

Addendum

A. Holbrook led the grant that provided funding. A. Holbrook and M. Wang designed the methods. M. Wang and S. Yusuf carried out the initial literature searches. M. Wang, M. Lee and J. Liu performed the study selection and data

extraction. M. Wang, A. Leenus, and M. Lee performed the study reporting quality assessment. M. Wang did the data analysis and drafted the manuscript. A. Holbrook, L. Mbuagbaw, and L. Thabane provided several rounds of critical revision for accurate and important intellectual content. All authors critically revised the manuscript and supplied the final approval of the version to be published.

Compliance with ethical standards

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Appendix 1. Literature search strategy.

1. CINAHL search strategy

Search ID#	Search Terms	Search Options	Last Run Via	Results
S29	S17 AND S26	Limiters - Human Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	177
S28	S17 AND S26	Limiters - English Language Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	414
S27	S17 AND S26	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	416
S26	S20 OR S21 OR S22 OR S23 OR S24 OR S25	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	173,303
S25	"hindrance*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	539
S24	"limit*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	128,778
S23	(MH "Communication Barriers") OR "communication barrier"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	3,572
S22	"obstacle*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases	6,021

			Search Screen - Advanced Search Database - CINAHL	
S21	"facilitator*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	5,789
S20	"barrier*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	42,390
S19	S17 OR S18	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	7,282
S18	"oral anticoagulant*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	1,245
S17	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	6,661
S16	""eliquis""	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	14
S15	""savaysa""	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	7
S14	""edoxaban""	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	129

S13	""apixaban""	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	349
S12	""xarelto""	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	19
S11	(MH "Rivaroxaban") OR "Rivaroxaban"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	618
S10	""pradaxa""	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	28
S9	(MH "Dabigatran Etexilate") OR "dabigatran"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	817
S8	""direct acting oral anticoagulant""	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	12
S7	""coumarin""	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	235
S6	""Orfarin""	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	0
S5	""Coumadin""	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases	157

			Search Screen - Advanced Search Database - CINAHL	
S4	""Jantoven""	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	0
S3	""acenocoumarol""	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	37
S2	(MH "Warfarin") OR "warfarin"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	5,579
S1	""Marevan""	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	0

2. Embase search strategy.

Database: Embase <1974 to 2018 July 12>
Search Strategy:
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1 (warfarin* or acenocoumarol* or (Oral* adj3 (Anticoagula* or Anti-coagula*)) or direct acting oral anticoagulant* or (Marevan* or Jantoven* or Coumadin* or Orfarin*) or coumarin* or dabigatran* or pradaxa* or rivaroxaban* or xarelto* or apixaban* or edoxaban* or savaysa* or eliquis*).mp. or anticoagula*.kw,ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (197181)
2 barrier*.mp. or facilitat*.ti,ab,kw,kf. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (770212)
3 1 and 2 (3752)
4 limit 3 to (english language and humans) (2738)

3. Medline search strategy
Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

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1 (warfarin* or acenocoumarol* or (Oral* adj3 (Anticoagula* or Anti-coagula*)) or direct acting oral anticoagulant* or (Marevan* or Jantoven* or Coumadin* or Orfarin*) or coumarin* or dabigatran* or pradaxa* or rivaroxaban* or xarelto* or apixaban* or edoxaban* or savaysa* or eliquis*).mp. or anticoagula*.kw, ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (113338)

2 barrier*.mp. or facilitat*. ti,ab,kw,kf. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (648017)

3 1 and 2 (1884)

4 limit 3 to (english language and humans) (1199)

Appendix 2. Data extraction form.

Study ID: _____ Reviewer Initials: _____

STUDY INFORMATION

First Author: _____ Year of Publication_____

Title of Article:

_____

Journal Name: _____ Country: _____

METHODS AND RESULTS

Study Setting: _____

Study Design: _____

Category	Barriers	Facilitators	Provider group (N)	Response scale	Statistics results (prevalence, P value, 59% CI, etc.)
			Applicable for quantitative studies		
Therapy-Related					
1.Therapeutic Drug Monitoring and Accompanying Dose Adjustment	•	•	•	•	•
2. Drug–Drug Interactions	•	•	•	•	•
3. Affect lifestyle	•	•	•	•	•
Patient-Related					
1. Physiological factors	•	•	•	•	•

2. Psychosocial factors	•	•	•	•	•
3. Attitudinal behaviors	•	•	•	•	•
4. Social–Economic Factors	•	•	•	•	•
5. Language barrier	•	•	•	•	•
6. Health Knowledge	•	•	•	•	•
7. Comorbidity	•				
8. Other	•				
Healthcare provider – related					
1. Providers' Knowledge of anticoagulation	•	•	•	•	•
2. Doctor patients' relationship	•	•	•	•	•
3. Physician's Attitude	•	•	•	•	•
Health System-Related					
1. Healthcare support	•	•	•	•	•
2. Patients expectation to Health system	•				
3. Communication within system.	•	•	•	•	•

COMMENTS

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_____

Appendix 3. Barriers to oral anticoagulation management.

Category	Barriers	References which mentioned the according item (Sources of the opinion)	References with survey results (Sources of the opinion, results of the survey)	References with association check results (Statistics for association with outcome(s))
A. Therapy-Related Barriers				
A1. Impact on lifestyle	Dietary (or alcohol) restrictions	*Wild et al.* (Patients)	*Ansell et al.* (Patients, 48%)	
	Changes in routine	*Vaanholt et al.* (Patients).		
	Pill burden (patients are already taking too many medications to add another one).	*Decker et al.* (Healthcare providers) *Ingelgard et al.* (Healthcare providers)		*Orensky et al.* (Pill burden lead noncompliance, p=0.039)
	Dosing changes (patients have to remember).		*Ansell et al.* (Patients, 57%)	
	Regular blood tests to monitor the drug	*Borg Xuereb et al.* (Healthcare providers); *Bungard et al.* (Healthcare providers); *Decker et al.* (Healthcare providers)	*Ansell et al.* (Patients, 76%); *Arepally et al.* (Healthcare providers, 43%); *Frankel et al.* (Healthcare providers, 40%)	*Arnsten et al.* (Related to noncompliant with warfarin, P= 0.004.).
	Transportation barriers	*Decker et al.* (Healthcare providers)	*Gross et al.* (Healthcare providers, 1%); *Ingelgard et al.* (Patients, 16.7 %; Healthcare provider, Level of reluctance to prescription, Mean ± SD; 7.30 ± 2.34 (0–10 scale: 0 = not at all reluctant, 10 = very reluctant).)	
	Restricted physical activity when using the drugs			*Arnsten et al.* (Related to noncompliant with warfarin, P= 0.03.)
A2. Drug-drug interactions	Patients taking medication that may interact with OACs.	*Bajorek et al.* (Healthcare providers)	*Gross et al.* (Healthcare providers, 4 %); *Ingelgard et al.* (Healthcare providers, 12.5%); *Ansell*	

			et al. (Patients, 50%); *Tan et al.* (Patients, 61%).	
	Patients with alcoholism (or another drug abuse).	*Peterson et al.* (Healthcare providers); *Rosenman et al.* (Patients)	*Ingelgard et al*. (Healthcare providers, Level of reluctance to prescription, Mean ± SD; 7.30 ± 2.34 (0–10 scale: 0 = not at all reluctant, 10 = very reluctant).); *Shen et al.* (Healthcare providers, 99%)	*Johnston et al.* (The adjusted odds ratio (OR) of warfarin users versus nonusers for AF patients (95%CI): 0.59 (0.35-0.99).)
	Use of Aspirin	*Peterson et al.* (Healthcare providers)	*McGrath et al.* (Patients, 73%)	
	Allergy or intolerance to warfarin		*McGrath et al.* (Patients 1.8%)	
A3. Reversal problems	Reversibility of anticoagulants		*Frankel et al.* (Healthcare providers, 49%)	
	Difficulty related to reversing	*Ingelgard et al.* (Healthcare providers)	*Arepally et al.* (Healthcare providers, 43%)	
B. Patient-Related Barriers				
B1. Patients' condition or diseases	(History of) cognitive impairment (e.g., dementia, poor cognition, mental health problem)	*Bajorek et al.* (Healthcare providers); *Ingelgard et al.* (Patients); *Johnston et al.* (Patients); *Peterson et al.* (Healthcare providers)	*Deplanque et al.* (Healthcare providers, 8.4%); *Gross et al.* (Healthcare providers, 34 %); *Shen et al.* (Healthcare providers, 94%); *McGrath et al.* (Patients, 9.4%).	*Chen et al.* (Decreased the likelihood of patients receiving anticoagulant therapy ($p<0.05$).); *Platt et al.* (For warfarin nonadherence, adjusted OR (95%CI): 2.9 (1.7–4.8).)
	Comorbidity burden (e.g., hepatitis, renal disease requiring hemodialysis, renal insufficiency, cancer, hepatic disease, severe anemia, poorly controlled hypertension, paroxysmal AF)	*Peterson et al.* (Healthcare providers); *Rosenman et al.* (Patients)	*Gross et al.* (Healthcare providers, 5%); *Ingelgard et al.* (Patients, 12.5%); *McGrath et al.* (Patients, 17.1%); *Redgrift et al.* (Healthcare providers, 41.0%).	*Chen et al.* (patients with higher comorbidity burden were less likely to be on anticoagulant treatment (Charlson Comorbidity Index (CCI): 1-2, OR=0.67, 95% CI: 0.55-0.83; CCI=3+, OR=0.61, 95% CI: 0.45-0.81); *Johnston et*

				al. (The adjusted OR of warfarin users versus non users for AF patients (95%CI): 0.66 (0.52-0.84).); *Mueller et al.* (An increased risk of unstable INR values (OR: 3.866, p = 0.002).); *Platt et al.* (For warfarin nonadherence, adjusted OR (95%CI): 1.4 (1.1–1.6).); *Arnsten et al.* (Related to noncompliant with warfarin P= 0.02); *Farmakis et al.* (Less adherence for paroxysmal AF, OR=0.64, p=0.045)
	Other conditions			
	• Poor memory capacity	*Decker et al.* (Healthcare providers)		
	• Frailty or poor general health		*Gross et al.* (Healthcare providers, 15%); *McGrath et al.* (Patients, 19.3%); *Redgrift et al.* (Healthcare providers, 60%).	*Chen et al.* (Decreased the likelihood of patients receiving anticoagulant therapy ($p<0.05$). *McGrath et al.* (On non-use of OAC therapy at discharge, the OR was12.58 (95% CI 5.82–27.21) for severe disability compared to no disability.)
	• Inability for self-care	*Graves et al.* (Patients)		
	• Perceived high fall risk in elderly	*Bajorek et al.* (Healthcare providers); *Decker et al.* (Healthcare providers); *Peterson et al.* (Healthcare providers); *Rosenman et al.* (Patients)	*Bungard et al.* (Healthcare providers, 64%); *Deplanque et al.* (Healthcare givers, 17.8%); *Gattellari et al.* (Healthcare providers, 54.4%); *Gross et al.* (Healthcare providers, 65 %); *Shen et al.* (Healthcare providers, 89%). *Tan et al.* (Patients, 61%); *Ingelgard et al.* (Healthcare providers, Level of reluctance to	*Johnston et al.* (The adjusted OR of warfarin users versus nonusers for AF patients (95%CI): 0.61 (0.52, 0.73).)

			prescription, Mean ± SD; 8.20 ± 1.81 (0–10 scale: 0 = not at all reluctant, 10 = very reluctant).); *McGrath et al.* (Patients, 26.7%)	
	• Limited life expectancy	*Graves et al.* (Patients)		
	• Returned to normal sinus rhythm for AF patients	*Gattellari et al.* (Healthcare providers); *Peterson et al.* (Healthcare providers); *Rosenman et al.* (Patients)		
B2. Patients' attitudes or behaviors	Concern about bleeding	*Decker et al.* (Healthcare providers)	*Ansell et al.* (Patients, 70%); *Ingelgard et al.* (Patients, 12.5%)	*Arnsten et al.* (Related to noncompliant with warfarin, P= 0.04.)
	Concern about bruising	*Decker et al.* (Healthcare providers);	*Ansell et al.* (Patients, 63%); *Tan et al.* (Patients, 61%); *Wild et al.* (Patients, 28.3%)	
	Concern of therapy having negative impact on quality of life		*Bungard et al.* (Healthcare providers, 8.2%)	
	Fear or dislike of lab test (monitoring)	*Decker et al.* (Healthcare providers)	*Ingelgard et al.* (Patients, 29.2 %; Healthcare provider, Level of reluctance to prescription, Mean ± SD; 8.32 ± 2.07 (0–10 scale: 0 = not at all reluctant, 10 = very reluctant).)	
	Refusal to the OACS		*Bungard et al.* (Healthcare providers, 72%); *Deplanque et al.* (Healthcare providers, 4.8%); *Gross et al.* (Healthcare providers, 31%); *McCrory et al.* (Health providers mean rank was 3.6. To rank the potential reasons from 1 (most frequent or important) to 8 (least	

			frequent or important).); *McGrath et al.* (Patients, 14.9%); *Redgrift et al.* (Healthcare providers, 64.8%).	
	Averse to taking the pill every day	*Decker et al.* (Healthcare providers)		
	Averse to attending the clinic	*Decker et al.* (Healthcare providers)		
	Concerns that the medication is difficult to manage	*Decker et al.* (Healthcare providers)		
	Non-compliance	*Graves et al.* (Patients); *Johnston et al.* (Patients); *Kea et al.* (Healthcare providers).	*Gross et al.* (Healthcare providers, 42%); *Rosenman et al.* (Patients, 2.1%); *McGrath et al.* (Patients, 1.8%).	*Mueller et al.* (OR for classifying a patient as showing with poor OAC quality 1.588, p = 0.003)
	Missed clinical appointment			*Sarangpur et al.* (Lower TTR (p=0.0007) • Higher number of appointments for monitoring (p<0.0001) • Higher nonadherence (<0.0001) • Longer duration of therapy (p=0.0009).) *Rose et al.* (61) (45% of patients had at least one monitoring gap; 29% of the gaps contained hospital admissions; patients with more gaps per year recorded lower TTR, P<0 .001)
	Inability to adhere to alcohol restrictions		*Ingelgard et al.* (Healthcare providers, Level of reluctance to prescription, Mean ± SD; 7.40 ± 1.93. (0–10 scale: 0 = not at all reluctant, 10 = very reluctant).)	
	Demographic characteristics			

B3. Patient's characteristics	• *Age (senior)	*Rosenman et al.* (Patients for age> 75)	*Bungard et al.* (Healthcare providers (for > 85 years old patients), 72%); *Deplanque et al.* (Healthcare providers, 15.9%); *Gross et al.* (Healthcare providers, 7%); *Shen et al.* (Healthcare providers, 80%); *McGrath et al.* (Patients, 11%).	*Arnsten et al.* (Patients who are noncompliant with warfarin mean age 53.7: patients who are compliant with warfarin mean age 68.7; P< 0.001.); *Beyth et al.* (Age 75 years or older, adjusted OR (95% CI): 0.15 (0.04, 0.52) for unlikely prescribed); *Chen et al.* (Decreased the likelihood of a patients receiving anticoagulant therapy (p<0.05).); *Cohen et al.* (Compare to <70 patients, >80 patients (adjusted OR (95% CI): 0.306 (0.170–0.551) p<0.001.) are less likely treated with OACs.); *Farmakis et al.* (Less adherence for older age, OR=0.64, p=0.045); *Johnston et al.* (The adjusted OR of warfarin users versus non users for <55 patients (95%CI): 0.73 (0.60, 0.90), for ≥85 patients: 0.41 (0.34-0.49).); *Maeda et al.* (Warfarin prescription, 82 years old versus 68 years old Odds ratio (95%CI):0.31 (0.22 – 0.44).); *McCrory et al.* (75 years elderlies less likely to get OAC than 65 and 55years old (p < 0.01) for all scenarios); *Partington et al.* (Means of age ±SD for warfarin treated for AF versus not treated, 77.7±8.6: 82.0±9.2 (P=0.02).); *Wilson et al.* (A negative relationship was found (P < 0.01), that is, as age increased, knowledge about medication

				and food-drug interaction decreased)
	Gender (Male)			*Arnsten et al.* (Patients who are noncompliant with warfarin versus patients who are compliant with warfarin: OR (95% CI): 3.5 (1.5, 8.2).)
	Ethnicity (non-white)			*Arnsten et al.* (Patients who are noncompliant with warfarin versus patients who are compliant with warfarin: OR (95% CI): 6.4 (1.9, 21.9).); *Bhandari et al.* (TTR was lower for African Americans than for Whites (absolute difference of 8.7%, p<0.001).)
	Language barriers	*Graves et al.* (Patients); *Ingelgard et al.* (Patients)	*Shen et al.* (Less likely to give OAC to non-English speaking background patients in 4/5 scenarios (p<0.001).)	*Bhandari et al.* (Absolute difference of TTR is 7.2%, p<0.05); *Hong et al.* (Adjusted result for TTR difference, LEP patients spent less TTR (−2.1%, 95%CI [−4.1% to −0.04%].). *Rodriguez et al.* (TTR, mean (SD), language barriers: without language barriers = 71.6 (13.1): 74.0 (13.9) (P=0.007).)
	Socioeconomic factors			
	• Working full time	*Vaanholt et al.* (Patients).		*Arnsten et al.* (Patients who are noncompliant with warfarin versus patients who are compliant with warfarin for working full time: OR (95% CI): 5.6 (1.6, 19.2).); *Platt et al.* (For warfarin adherence, compared to currently employed subjects, unemployed OR (95% CI): 0.6 (0.3–1.2)) and retired OR (95% CI): 0.5 (0.3–0.8).)

	• No insurance	*Kea et al.* (Healthcare providers)		*Arnsten et al.* (Patients who are noncompliant with warfarin versus patients who are compliant with warfarin for uninsured has higher OR: OR (95% CI): 5.6 (1.6, 19.2).)
	• Education level			*Platt et al.* (For warfarin nonadherence, compared to greater than high school level education, lower education level has higher OR (95% CI): 1.8 (1.2, 2.7).)
	• Lack of social support (e.g., patient living alone)	*Ingelgard et al.* (Healthcare providers); *Johnston et al.* (Patients); *Kea et al.* (Healthcare providers)	*Deplanque et al.* (Healthcare providers, 6.2%); *Ferguson et al.* (Healthcare providers, 41%);	*Chen et al.* (Decreased the likelihood of patients receiving anticoagulant therapy ($p<0.05$).); *Orensky et al.* (less compliance: P=0.039)
	• Poor social situation	*Decker et al.* (Healthcare providers)		
	• Out of pocket costs		*McCrory et al.* (Health providers mean rank 5.6. To rank the potential reasons from 1 (most frequent or important) to 8 (least frequent or important)	
	Health Knowledge			
	• Drug myth	*Borg Xuereb et al.* (Healthcare providers); *Decker et al.* (Healthcare providers)		
	• lack of receptivity to specific details about disease and medication	*Vaanholt et al.* (Patients).		*Arnsten et al.* (In patients who are noncompliant with warfarin versus patients who are compliant with warfarin fewer information patients has higher OR. OR (95% CI): 4.4 (1.4, 14.2); *Cruess et al.* (Less

				information patients have lower nonadherence: OR (95% CI): 1.11 (1.02/1.21), P= 0.013.)
	• Inability to comprehend medication instructions		*Ingelgard et al.* (Healthcare providers, Level of reluctance to prescription, Mean ± SD. 7.58 ± 1.97. (0–10 scale: 0 = not at all reluctant, 10 = very reluctant).)	
C Healthcare Provider-Related Barriers				
C1. Health providers' characteristics	Lack knowledge related to coagulation	*Drewes et al.* (Healthcare providers); *Kea et al.* (Healthcare providers).	*Arepally et al.* (Healthcare providers, 69%); *Bungard et al.* (Healthcare providers, 1%); *Gattellari et al.* (Healthcare providers, 17.4%)	
	Shortcomings in training	*Ingelgard et al.* (Healthcare providers)	*Barrios et al.* (Healthcare providers, 38%)	
	Years since graduation from medical school	*Kea et al.* (Healthcare providers)		*Maeda et al.* (Warfarin prescription, 1-10 versus >11: OR (95%CI): 0.43 (0.23, 0.81).)
	Less experience managing acute thromboembolism in patients with AF			*Maeda et al.* (Warfarin prescription, less experience versus more experience: OR (95%CI): 0.20 (0.064, 0.60).)
C2. Health provider's attitudes or behaviors	Concern about bleeding		*Bungard et al.* (Healthcare providers, 13%); *Changying et al.* (Healthcare providers, 74%); *Deplanque et al.* (Healthcare providers, 24.7%); *Frankel et al.* (Healthcare providers, 62%)	
	Concern about litigation		*Bungard et al.* (Healthcare providers, 3.0%); *Gross et al.* (Healthcare providers, 2%); *Ingelgard et al.*	

			(Healthcare providers, 12.5%)	
	Concern about the monitoring		*Changying et al.* (Healthcare providers, 65.4%); *Ferguson et al.* (Healthcare providers, 75.0%);	
	Concern about patients' advanced age		*Changying et al.* (Healthcare providers, 44.7%)	
	Clinician reluctance (worry about the AE, don't want to disorder patient's habits)	*Decker et al.* (Healthcare providers); *Kea et al.* (Healthcare providers)		
	Concern if patients will be compliance		*Deplanque et al.* (Healthcare providers, 22.0%); *Ferguson et al.* (Healthcare providers, 71.0%); *Gross et al.* (Healthcare providers, 42%); *Ingelgard et al.* (Healthcare providers, Level of reluctance to prescription, Mean ± SD. 8.50 ± 1.30. (0–10 scale: 0 = not at all reluctant, 10 = very reluctant)	
	Fear of the patient falling		*Ferguson et al.* (Healthcare providers, 71.0%)	
	Fear of patients' poor literacy		*Ingelgard et al.* (Healthcare providers, Level of reluctance to prescription, Mean ± SD. 8.33 ± 2.21. (0–10 scale: 0 = not at all reluctant, 10 = very reluctant)	
	Concern about reversibility of OAC		*Frankel et al.* (Healthcare providers, 49%)	
	Doubt effectiveness or unfamiliar with evidence		*Gattellari et al.* (Healthcare providers,	

			30%); *Salinas et al.* (Healthcare providers, 75% SP & 50% GP)	
	Hard to decide whether the benefits of OAC outweigh the risks or vice versa		*Gattellari et al.* (Healthcare providers, 38.9%); *McCrory et al.* (Health providers, mean rank 6.8. To rank the potential reasons from 1 (most frequent or important) to 8 (least frequent or important)	
	Belief that aspirin is better alternative		*McCrory et al.* (Health providers mean rank 6.8. To rank the potential reasons from 1 (most frequent or important) to 8 (least frequent or important)	
	Patient feels physician is not very concerned about them.			*Arnsten et al.* (In patients who are noncompliant with warfarin versus patients who are compliant with warfarin less concerned patients has higher percentages. OR (95% CI): 3.1 (1.2, 7.8). p=0.01.)
	Poor patient to healthcare provider communication	*Graves et al.* (Patients); *Vaanholt et al.* (Patients).		
	Difficulty contacting patient in case of urgent dose change.		*Ingelgard et al.* (Healthcare providers, Level of reluctance to prescription, Mean ± SD. 7.00 ± 2.33. (0–10 scale: 0 = not at all reluctant, 10 = very reluctant)	
	Harsh language or chastising patients following missed INR tests	*Kauffman et al.* (Patients)		
D. Health System- Related Barriers				

D1. Healthcare support	No regular physician			*Arnsten et al.* (In patients who are noncompliant with warfarin versus patients who are compliant with warfarin no regular physician patients has higher percentages: OR (95% CI): 11.1 (3.6, 50.0). p=0.01.)
	The amount of time available in consultations is limited	*Borg Xuereb et al.* (Healthcare providers)		
	No time for patients to think in secondary care	*Borg Xuereb et al.* (Healthcare providers)	*Bungard et al.* (Healthcare providers, 3.0%)	
	Luxury of repeated consultations and rapport-building in primary care	*Borg Xuereb et al.* (Healthcare providers)		
	Increased expertise but lack of time in secondary care	*Borg Xuereb et al.* (Healthcare providers)		
	Administrative barriers to free prescription		*Barrios et al.* (Healthcare providers, 38.1%)	
	Lack of sub-sequent monitoring or difficulty in arranging services for monitoring	*Graves et al.* (Patients); *Gross et al.* (Healthcare providers); *Ingelgard et al.* (Healthcare providers)	*Barrios et al.* (Healthcare providers, 20.1%);	
	Lack of anticoagulation clinic services		*Gross et al.* (Healthcare providers, 4%)	*Chen et al.* (Lack of anticoagulation clinic services, patients were less likely to be on anticoagulant treatment (OR=0.50, 95% CI: 0.27-0.90)
	Delay in lab report	*Ingelgard et al.* (Healthcare providers)		
D2. Patients expectation to health system	Inadequate reimbursement for time spent monitoring warfarin	*Ingelgard et al.* (Healthcare providers)	*Bungard et al.* (Healthcare providers, 9.0%)	
D3. Communication within the system.	Breakdown in communication between clinicians and healthcare settings	*Decker et al.* (Healthcare providers)		
	Inadequate to the exchange of information.	*Drewes et al.* (Healthcare providers)	*McGrath et al.* (Patients, 3.2%).	
	Poor provider to provider communication	*Graves et al.* (Patients)		
D4. Clinical evidence	Lack of effective protocols and efficacy data		*Arepally et al.* (Healthcare providers, 57%)	

	Lack of clarity of guideline recommendations	*Kea et al.* (Healthcare providers)	*Arepally et al.* (Healthcare providers, 7%)	
	Lack of RCT evidence		*Bungard et al.* (Healthcare providers, 3.0%)	
	Lack of consensus as to treatment.	*Drewes et al.* (Healthcare providers)		
	Lack of awareness of tools to guide risk assessment		*Salinas et al.* (Healthcare providers, 75% SP & 50% GP)	

Abbreviation: INR, international normalized ratio; OAC, oral anticoagulant; AF, atrial fibrillation; TIA, transient ischemic attack; GP, general practitioner; TTR, Time in therapeutic range.

Appendix 4. Facilitators to oral anticoagulation management.

Category	Facilitators	References which mentioned the according item (Sources of the opinion)	References with survey results (Sources of the opinion, results of the survey)	References with association check results (Statistics for association with outcome(s))
A. Therapy-Related Facilitators				
A1. Impact on lifestyle	Ensuring type of lifestyle and therapy is matched with patient's capacity to self-manage	*Ferguson et al.* (Healthcare providers)		
	Dietary freedom (switch from warfarin to dabigatran)		*Elewa et al.* (Patients, Willingness to switch to same efficacy anticoagulant, but without barrier (1 to 5): 4.1 ± 1.25)	
	Deal with regular monitoring			
	•Fewer blood tests to monitor the drug (switch from warfarin to dabigatran).		*Elewa et al.* (Patients, Willingness to switch to same efficacy anticoagulant, but without barrier (1 to 5): 3.9 ± 1.35)	
	•Regular adherence and INR monitoring	*Ferguson et al.* (Healthcare providers)	*Shen et al.* (Healthcare providers, 99%)	
	•Facilitate access to INR testing.	*Ferguson et al.* (Healthcare providers)		
	•Provide INR test reminders in the form of phone calls, letters, and E-mail	*Kauffman et al.* (Patients)		
	•Availability of portable INR monitors	*Peterson et al.* (Healthcare providers)		

B. Patients-Related Facilitators				
B1. Patients' condition or diseases	Indication of OAC is Stroke/TIA	*Beyth et al.* (Healthcare providers); *Borg Xuereb et al.* (Healthcare providers)	*Frankel et al.* (Healthcare providers, 96%)	*Arnsten et al.* (In patients who are noncompliant with warfarin versus patients who are compliant with warfarin patients whose indication was Stroke/TIA has lower percentages. OR (95% CI): 0.2 (0.1, 0.7). p=0.008.)
	Having another indication for anticoagulant therapy			*Beyth et al.* (More warfarin prescription with another indication for anticoagulant therapy, OR (95% CI): 19.7 (4.7, 83.1).)
	History of stroke			*Cohen et al.* (Patients with history of stroke (adjusted OR (95% CI): 1.95 (1.041 to 3.681).) are more likely treated with warfarin.)
	Hypertension			*Johnston et al.* (Predictor of warfarin use, hypertension, OR (95%CI): 1.40 (1.23, 1.59).)
	Congestive heart failure			*Johnston et al.* (Predictor of warfarin use, Congestive heart failure, OR (95%CI), 1.37 (1.20, 1.57).); *Partington et al.* (more likely use warfarin, P=0.02)

	Risk factor for thromboembolism			*Maeda et al.* (Warfarin prescription, with this factor versus without. OR (95%CI): 2.4 (1.8-3.6).)
	Patients with therapeutic INR			*Orensky et al.* (Patients with therapeutic INR (%) lead compliance, P<0.001)
B2. Patients' attitudes or behaviors	Believe health providers' skill, and competence is excellent or very good			*Arnsten et al.* (In patients who are noncompliant with warfarin versus patients who are compliant with warfarin patients who believe their providers have lower percentages. OR (95% CI): 0.4 (0.1, 1.0), P= 0.013.)
	Believe taking OACs benefits their health	*Vaanholt et al.* (Patients).		*Arnsten et al.* (In patients who are noncompliant with warfarin versus patients who are compliant with warfarin patients who believed taking OACs benefits their health has lower percentages: OR (95% CI): 0.5 (0.2, 1.1); P= 0.002.)
	Believe taking OACs protects their future health			*Arnsten et al.* (In patients who are noncompliant with warfarin versus patients who are compliant with warfarin patients who believed

				taking OACs benefits their future health has lower percentages: OR (95% CI): 0.3 (0.1, 0.7); P= 0.008.)
	Fear of stroke	*Borg Xuereb et al.* (Healthcare providers)		
	Monitoring of adherence (refer to non-compliance)	*Khudair et al.* (Patients)		
B3. Patient's characteristics	Knowledge of benefits and risk of OACs	*Ferguson et al.* (Healthcare providers)	*Bungard et al.* (Healthcare providers, 96%); *Gattellari et al.* (Healthcare providers, 30%); *Wild et al.* (Patients, 58%)	
	Family support & involvement (e.g., married).	*Ferguson et al.* (Healthcare providers)		*Orensky et al.* (Patients with Family support lead compliance, P=0.003)
	Self-management & community support	*Ferguson et al.* (Healthcare providers); *Kuljis et al.* (Patients); *Vaanholt et al.* (Patients).		
	Limited English patients (LEP) use a language surrogate or say without language limited		*Shen et al.* (Healthcare providers, 79%)	*Hong et al.* (LEP patients who used a communication surrogate were not statistically different from English-speakers who did not use a surrogate in their percent TTR (−2.5%, 95%CI [−5.0% to 0.01%]) or TDR (1.2%,

				95%CI [−0.6% to 3.0%])
	Patients' good literacy			*Wilson et al.* (As literacy increased, knowledge about medication and food-drug interaction increased, P<0.01)
C. Healthcare Provider-Related Facilitators				
C1. Health providers' characteristics	Health providers' good skill and competence	*Kea et al.* (Healthcare providers)		*Arnsten et al.* (if health providers had good skill and competence, patients have lower percentages in noncompliance. OR (95% CI): 0.4 (0.1, 1.0). P= 0.013.)
	Experienced with OAC			*Beyth et al.* (More warfarin prescription with experienced physicians, OR (95% CI): 2.6 (1.3, 5.2).)
	Impact of clinical trials on their practice of anticoagulant prophylaxis			*Maeda et al.* (Warfarin prescription, with this factor versus without. OR (95%CI): 2.7 (1.4, 5.4).)
	Cardiologist	*Peterson et al.* (Healthcare providers); *McCrory et al.* (Healthcare Providers).		
	More new AF patients	*Peterson et al.* (Healthcare providers)		
C2. Health providers' attitudes or behaviors	Patients are dependent on physicians	*Borg Xuereb et al.* (Healthcare providers)		
	Good communication (including	*Ferguson et al.* (Healthcare providers)		

	listening, interpreters, written information)			
	Open discussion and understanding anticoagulation	*Ferguson et al.* (Healthcare providers)		
	Assign anticoagulation providers to work with the same patients over time	*Kauffman et al.* (Patients)		
	Providing reassurance to patients when they have achieved their INR goal		*Wild et al.* (Patients, 20%)	
	Pharmacy education	*Ferguson et al.* (Healthcare providers)	*Shen et al.* (Healthcare providers, 89%)	
D. Health System-Related Facilitators				
D1. Healthcare support	Nurse or pharmacist-led anticoagulation management service	*Ferguson et al.* (Healthcare providers); *Lowthian et al.* (Healthcare providers)		*Stafford et al.* (Pharmacist-delivered warfarin education was associated with a significant difference between the intervention patients' baseline and day 8 mean warfarin knowledge scores of 64.5% (95% CI, 61.0–68.5%) and 78.0% (95% CI 74.5–81.5%; P < 0.001.). *Airee et al.* (TTR, Control vs. Protocol, P=0.006). *Al Ammari et al.* (Time needed to stabilize INR within the therapeutic range (days ± SD) is

				less. Control group =5.46 ±3.96 vs Intervention group= 3.5 ±2.43). *Durand et al.* 241 new patients from category 1 and 2 are now on appropriate anticoagulation, leading to an interim improvement of 18% (62 to 80%, p<0.0001). *van Fessem et al.* A significant 51% increase in safe preoperative plans (P<0.001).
	Warfarin booklets (written information).	*Bajorek et al.* (Healthcare providers); *Drewes et al.* (Healthcare providers); *Ferguson et al.* (Healthcare providers)		
	Thorough assessment of the patients	*Bajorek et al.* (Healthcare providers); *Drewes et al.* (Healthcare providers); *Ferguson et al.* (Healthcare providers); *Lowthian et al.* (Healthcare providers); *Robson et al.* (Healthcare providers)		
	A greater utilization of carer support and services	*Bajorek et al.* (Healthcare providers)		

	Further support for the primary care setting	*Borg Xuereb et al.* (Healthcare providers)		
	Electronic personal health records plus education			*Edwards et al.* (the proportion of patients with an in-range INR at first clinic visit post-hospitalization increased from 35.8% to 60.3% (p=0.02).). *Chen et al.* (Mean score on knowledge of dabigatran increased, p = 0.007))
	Case management	*Ferguson et al.* (Healthcare providers)		
	Multi-disciplinary care	*Ferguson et al.* (Healthcare providers)		
	Discharge planning	*Kauffman et al.* (Patients)		
	Medication event monitor system	*Platt et al.* (Patients)		
	Computer-assisted oral anticoagulant dosage program			*Ryan et al.* (TTR was significantly higher, median TTR 74% vs 58.6%; z=5.67, P < 0.001.); *van Fessem et al.* (A significant 51% increase in safe preoperative plans (P<0.001).)
D2. Patients expectation to health system	Adequate reimbursement	*Kauffman et al.* (Patients)		
	More personalised/real-time communication	*Kuljis et al.* (Patients)		
	Pragmatic and collaborative patient–clinician partnerships	*Kuljis et al.* (Patients)		

	Recognition of expert patient knowledge and expertise	*Kuljis et al.* (Patients)		
D3. Communication within system.	Health care organization	*Drewes et al.* (Healthcare providers); *Vaanholt et al.* (Patients).		
	Delivery system (re)design	*Ferguson et al.* (Healthcare providers)		
	Good GP/GP support	*Ferguson et al.* (Healthcare providers)		
	Facilitated telephone communication between nurses and physicians			*Field et al.* (TTR: 1. 53.1%: 50.0% adjusted difference: 4.5% (95% CI, 0.3%-8.7%).)
	Improved role clarification	*Lowthian et al.* (Healthcare providers)		
D4. Clinical evidence	HAS-BLED score (bleeding assessment score).	*Ferguson et al.* (Healthcare providers)	*Berger et al.* (Providers, 100% more confidential for their decision.)	
	Targeted guidelines	*Borg Xuereb et al.* (Healthcare providers)		*Robson et al.* (Increased people on anticoagulants ($p<0.001$))
	Computer software supporting clinical decisions			*Robson et al.* (People with CHADS2 VA SC >=1 on antiplatelet decreased ($p<0.001$).)

Abbreviation: INR, international normalized ratio; OAC, oral anticoagulant; AF, atrial fibrillation; TIA, transient ischemic attack; GP, general practitioner

Chapter Three: Perceptions on patient education to improve oral anticoagulant management

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Perceptions on Patient Education to Improve Oral Anticoagulant Management

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Abstract

Objective: To explore the opinions of health care providers and patients on the desired content and format of patient education on oral anticoagulant medication (OAC), in addition to perceived barriers to high-quality patient education.

Data sources: Five focus group discussions in two health regions in Southwestern Ontario from 2017-2018.

Study Design: We applied qualitative descriptive methods in a focus group study on OAC management.

***Data Collection/Extraction methods*:** Five focus group discussions were conducted with 19 patients, 7 caregivers, and 16 health care providers (physicians, nurses, and pharmacists). During the focus groups, data on education were collected and analysed using content analysis as part of a qualitative descriptive approach. Transcripts were analyzed using conventional content analysis.

Principal Findings: We identified the five themes of patient education on OAC management: (i) content of OAC education (rationale, risk, and appropriate drug administration methods), (ii) the best times for providing OAC education (time of OACs initiation along with continuing education), (iii) preferred education delivery strategies (case management targeted patient information summaries from authoritative sources such as Thrombosis Canada and video education), (iv) patient and community pharmacist engagement in OAC education and (v) perceived barriers to optimal patient education (patients depending too much on their health care providers for advice, the limited time patients spend with health care providers, gaps in clear communication between providers, and the lack of a nationally or provincially coordinated OAC management program).

Conclusion: Our focus groups suggest that patients, caregivers and health care providers support the need for education on OACs, including for patients taking DOACs. The optimal combination of content, format, duration, timing, and sources for OAC education requires further research.

Keywords: oral anticoagulants; patient education; focus group; qualitative research.

What is known on this topic

- Education of patients is thought to be critical for high-quality OAC management because improving patients' knowledge has the potential to improve their self-management skills and adherence.
- Systematic reviews show that there is no high-quality evidence that supplemental patient education improves patient outcomes.
- There are several educational theories which provide a framework for patient education but defining the optimal content components, appropriate format, timing, and duration is still an unmet goal in OAC patient education.

What this study adds

- We explored the five themes of patient education on OAC management, including content of OAC education, the best time for OAC education, preferred education delivery strategies, engagement of patients and community pharmacists in education, and barriers to optimal patient education.
- Despite a lack of high-quality evidence showing that patient education can improve clinical outcomes, our findings suggest that patients, caregivers and health care providers support the need for OAC education.
- The optimal combination of content, format, duration, timing, and sources for OAC education requires further research.

INTROCUCTION

Oral anticoagulants (OACs) are highly effective for the prevention and treatment of thromboembolic diseases (Sterne et al., 2017). In addition to the vitamin-K-antagonist (VKA) (e.g., warfarin), the direct oral anticoagulants (DOACs) (e.g., dabigatran, rivaroxaban, apixaban, and edoxaban) are now available. The OAC prescription volume continues to increase in Canada and worldwide (Lippi, Mattiuzzi, Cervellin, & Favaloro, 2017; Weitz et al., 2015). Optimizing the management of OACs is essential, as they are high-risk medications with an attendant risk of bleeding and bleeding-related adverse events (Choi & Douketis, 2012). Education of patients is thought to be critical for high-quality OAC management (Danielle E. Clarkesmith, Pattison, Lip, & Lane, 2013) because theoretically, improving patients' knowledge can improve their self-management skills and adherence (Schwanda & Gruber, 2020; Smet et al., 2018; Steffel et al., 2018).

Patients' management on OAC is complex due to the chronic use, the potentially fatal side effect of bleeding, the multiple comorbidities of older patients, and the frequent procedures requiring reconsideration of OAC (Grille, Martín, & Torregrossa, 2019; Weitz & Pollack, 2015; Werth, Breslin, NiAinle, & Beyer-Westendorf, 2015). Furthermore, the limited time of front-line health care providers increases the challenge of providing high-quality OAC education (Wang et al., 2020). Systematic reviews show that there is a lack of high-quality evidence that supplemental patient education improves patient outcomes (D. E. Clarkesmith, Pattison, Khaing, & Lane, 2017; Paquette et al., 2019; Wong, Schulman, Woodworth, & Holbrook, 2013). However, most studies were carried out in the era of warfarin as the dominant OAC, and the interventions varied in education timing, content, format, and target population. Currently, DOACs are the dominant OAC in many countries (Raschi, Bianchin, De Ponti, De Ponti, & Ageno, 2017). Although DOACs are said to require less monitoring, they still require the same orientation to their benefit, harms, adherence, procedures, drug coverage, and duration (Janzic & Kos, 2017). The aim of patient education is to enable "individuals to make informed decisions about their personal health-related behaviour" (Bellamy, 2004). Several educational theories have provided a framework of patient education, but defining the optimal content components, appropriate format, timing, and duration is still an unmet goal in OAC patient education (Hews-Girard, Guelcher, Meldau, McDonald, & Newall, 2017).

One valid method of exploring important aspects of optimal patient education is to use qualitative research methods to seek input from key stakeholders. To inform our randomized controlled trial evaluating the coordination of OAC management

early post-hospital discharge in adults, we conducted focus groups on barriers and facilitators to optimizing oral anticoagulant therapy management. Since patient education was identified a priori as a likely facilitator for OAC management, we included it as a discussion topic in the focus groups. The objective of this study was to explore the perspectives of patients, caregivers and health care providers on the desired content, timing and format of patient education along with perceived barriers to high-quality patient education.

METHODS

The present study was a data secondary analysis of a focus group study. We followed the principles of qualitative description (Hamilton & Finley, 2019; Neergaard, Olesen, Andersen, & Sondergaard, 2009) and the consolidated criteria for reporting qualitative research (COREQ) guidelines (Tong, Sainsbury, & Craig, 2007). The protocol for this qualitative research was approved by Hamilton Integrated Research Ethics Board (HiREB #1639) and the Tri-Hospital Research Ethics Board for Kitchener-Waterloo-Cambridge (THREB#2017-0635).

Participants

To ensure sufficient diversity of opinion, we recruited patients, caregivers, and health care providers using purposeful sampling in a city (Hamilton) with a tertiary academic medicine centre including thromboembolism specialists, and Kitchener-Waterloo area (KW) with community hospital facilities, in Southwestern Ontario (Luciani, Campbell, Tschirhart, Ausili, & Jack, 2019). The inclusion criteria for patients included current use of OACs, a history of using OACs (but had discontinued taking them) or a refusal of OAC therapy. Eligible caregivers were those with at least 1-year of experience facilitating OAC use on behalf of a patient. Patients and caregivers were recruited from lists provided by investigators' practices. Health care providers were recruited via email or phone invitations from the study investigators. The technique of snowball sampling (a purposive nonprobability approach in which the researcher recruits a few volunteers who, in their turn, recruit other volunteers) (Noy, 2008) was also used until adequate numbers of health care providers were recruited. Our target health care providers were primary or secondary health care providers who prescribe, dispense, or manage OAC therapy. We aimed to balance profession (hematologist, family physician, clinical pharmacologist, thromboembolism nurse, pharmacist), practice location (rural or urban), sex, and working length of time practicing.

Focus groups were conducted separately with patients/caregivers (n=3) and health care providers (n=2) in the two cities between May 2017 to April 2018. The

target sample size for each focus group was 6-8 participants. An over recruitment of 2-4 participants was pursued for each focus group in case there were "no-shows."

Procedure

All focus groups were organized in the two cities at a time and date convenient for the participants and researchers. Before each focus group discussion, all participants signed informed consent forms and completed a brief demographic questionnaire (Appendix I). Each focus group lasted around 2 hours. All focus group discussions were facilitated by an experienced focus group facilitator (MS) with training in qualitative methods and with no prior relationship to the participants. In addition, two other research staff were present to take notes during the discussions and take field notes. All group discussions were digitally recorded, transcribed by a professional transcriptionist and de-identified. Participants received a $25 gift card as an honorarium for their time.

Focus Group Guide

The research team developed semi-structured questions to identify the barriers and facilitators to optimal anticoagulation management. Questions on patient education were asked as an independent section of the guide. Questions for the health care provider focus groups asked about OAC education that patients currently receive, their perceptions of patient understanding about OACs and barriers and facilitators to OAC patient education. The education questions for patients and caregivers focused on their perceptions about their level of knowledge about blood thinners, the education they received when they were first prescribed OACs, barriers to OAC education and their suggestions for OAC education (Appendix II).

Data analysis

Demographic questionnaire data were analyzed using descriptive statistics. Conventional content analysis was used to analyze the focus group transcripts. Two investigators (MS and MW) independently conducted line-by-line open coding and met to develop a preliminary list of codes which was applied to the remaining transcripts (Hsieh & Shannon, 2005). Once coding was complete, the research team met to review coding reports and group codes into categories/themes. NVivo software, version 11.0 (QSR International) was used for data management.

RESULTS

Five focus groups were held, three with patients/caregivers (two in Hamilton and one in Kitchener-Waterloo), and two with healthcare providers (one in Hamilton, one in Kitchener-Waterloo). A total of 42 individuals participated including 19 patients, 7 caregivers, and 16 healthcare providers. Just over half (n=14, 53.8%) of the participants were female and the mean age was 62.2 years (SD=13.9). Most patients (n=18, 94.7%) were currently using OACs, with the most frequent duration of use being more than 3 years. The 16 health care providers included 4 pharmacists (25%), 3 nurses (19%), and 9 physicians (56%). Two-thirds of the healthcare providers (n+12, 75%) were female and the mean age was 48.4 years (SD=8.6). (Table 1).

The content of OAC education (What)

The rationale and benefit for taking OACs

Providers described what information they typically share with their patients. As one hematologist shared:

"*I really spend a lot of time at the beginning helping the patient to understand the medication that they're taking and the reason that they're taking it*"- [hematologist, Hamilton]

A pharmacist explained what content they believed is important for OAC patient education: *"I think the most important factor there would be people who truly understand the outcomes when they do not take medication properly. That they actually understand how the medication is working and what it's really doing.*"- [pharmacist, Kitchener-Waterloo].

In addition, many patients realized the benefits of the OACs for them, for example,

"*I guess the benefits are to live to see another day*" and "*So, basically, it's keeping me from having a stroke or any other issues that could be happening from the clotting. That's my understanding.*"- [patient, Hamilton]

Following the correct dose schedule and monitoring

Both healthcare providers and patients described how important it is to take OACs correctly.

"...if I have to write it down every single day, this is what you do. So, just how to take it, and when to come back." - [family doctor, Kitchener-Waterloo]

As one patient reflected, knowing how to take the medications appropriately is essential for them:

"*I think the number one thing to prevent harm from ourselves is knowing what medications to take…to an extent…knowing how to take the medications appropriately….*"- [patient, Hamilton]

The risks of taking OACs

A provider mentioned the risk of taking OACs as an important component of education:

"*I think that ... you (should) really try to make clear what's a problem…like, what are the signs of bleeding…when do you need to seek help*?" - [nurse, Kitchener-Waterloo]

In addition, patients believe that knowing the risks of OACs is important for them too,

"*Patient knowledge is one of the biggest things because if you do not know, you can't advocate for yourself… As long as the patient knows what the ramifications are of…what the risks are…they can advocate for themselves*."- [patient, Hamilton]

The best time for OAC education (When)

At initiation

Physicians identified the start of OAC therapy as an ideal time for providing patient education:

"...for the initial discussion with the patient. We might be called in with the Resident to have that initial discussion"- [hematologist, Hamilton]

"...at the time when the patient is first prescribed blood thinners, I think it would be very useful if they were given half an hour of a video presentation that covers all bases." – [nurse, Hamilton]

Most patients appreciated the initial education they received:

"…first, I would say that I had an excellent first hematologist. Eleven years ago, Dr. XX really set me up, right off the bat; took the time to explain everything to me; I took notes." – [patient, Hamilton]

Continuing anticoagulation discussion

From the perspective of health care providers, OAC education should be ongoing through their relationship with the patient.

"The initiation conversation is not the same as the maintenance conversation; is not the same as changes in their medical stability or status, changing along the way; is not the same when other medications are started or stopped…." – [family doctor, Kitchener-Waterloo]

"So, it's sort of an ongoing education that happens face to face because people are coming in for routine monitoring…" - [nurse, Hamilton]

"Whenever I re-prescribe a DOAC or warfarin, I go through the discussion again for each medication, why they're taking this." – [family doctor, Hamilton]

From the patient's perspective, continuing education is necessary:

"… knowledge is so important and although we get the initial knowledge when we first start taking this and we are loaded with a lot of information, I think over time we…some of us may become complacent and, perhaps, not remember some of the fine parts." "And we need to be updating our knowledge and, certainly, keeping it current because, otherwise, like everything else, this is so much overload of information that we tend to forget some important aspects of this therapy."- [patient, Hamilton]

Preferred education delivery strategies (How)

Case management approach

For health care providers, case management was a recommended approach.

"It is case management approach … You use the anticoagulation encounter as an opportunity to case-manage the whole situation more broadly."- [nurse, Kitchener-Waterloo]

"... use that opportunity as a face-to-face to say, "Yes, we're here for your Coumadin, but let us talk about your diabetes; let us talk about your heart failure; let us talk about advanced care planning, etc., etc. ..." – [hematologist, Kitchener-Waterloo]

However, the providers also recognized that not all patients have access to a case management approach:

"*I think that we have to be realistic and know that a lot of patients aren't…or that case management approach is not available to a lot of patients. (Murmurs of agreement) ..."* – [family doctor, Hamilton]

Education checklist

Some health care providers mentioned using a checklist as a tool for patient education:

"We actually have a checklist to make sure we don't forget anything." "Our initial checklist is really helpful, but we get to reinforce that information through our relationships with people ongoing, which is very nice." – [nurse, Hamilton]

Handouts/Brochures

Some of the patients appreciate the handouts they received:

"*And they did give me tons of information; I still have all the…the handouts they gave me. They've been awesome."* - [patient, Hamilton]

"I would have appreciated something on…a handout that's sort of explaining the pros and cons of the medication I was taking." – [patient, Hamilton]

The utility of handouts was also confirmed by healthcare providers:

"We've always used paper tools to enhance what we tell them." – [nurse, Hamilton]

However, some providers expressed their concerns about brochures provided by pharmaceutical companies,

"The question is, are they [brochures] better than nothing...They got a bulk shipment of it [handouts] and got a few in storage, they can be outdated…They can be biased. They are very heavily branded." - [family doctor, Kitchener-Waterloo]

Other delivery formats (e.g., a video)

Some other education delivery formats were mentioned:

"*I think we should make it easier to get information to the potential users of the drugs. And I think one of the best…easiest way…is to use a video."* - [patient, Hamilton]

"*It is hard for people to understand those things…I just do not think we really know exactly what tools are useful. Some people are developing tools with the help of patient input to identify what…maybe it is not written information, maybe it is pictures and diagrams…*"- [nurse, Hamilton]

Peer education

Patients expressed their eagerness for the opportunity to communicate with other patients,

"…maybe there's a list of some people that doctor might call and these people that are about to go on warfarin might have the opportunity to talk to somebody that is on it. I could see how that might be helpful for some people." – [patient, Hamilton]

Public awareness

Patients mentioned the importance of increasing public awareness about OACs and their side effects:

"*I really think, you know you see TV commercials, if you are having a stroke, blurred vision, this and that. There is nothing for blood clots…There's no education to tell people, "Oh, you probably have a blood clot. You should go to the Emergency Room."* – [patient, Hamilton]

Thrombosis Canada website

Providers identified the Thrombosis Canada website as a useful resource for patient education:

"There are videos on the Thrombosis Canada website so that's great."- [nurse, Hamilton]

"The Thrombosis Canada website which you can print things off for patients. So, there is every disease that we treat and every drug that we use is available for print off so we can always give that to the patients. And I think we all use those regularly."- [nurse, Hamilton]

The appropriate persons to carry on the education (Who)

Frontline physician at initiation

Patients stated that the frontline doctors should perform the initial education,

"Mainly, though, like, the frontline physician has to be where we get at least the start of our knowledge." – [patient, Hamilton]

"For our education, anyway, it has got to start at the frontline with the doctor that diagnoses us, whether that is a family physician or a hematologist." - [patient, Hamilton]

Community pharmacist potential

Providers described relying on community pharmacists to do some education:

"What's the role for community pharmacy? Huge potential." "it's a matter of family docs developing relationships with pharmacists so that you can trust that they're getting the proper education. (Others agreeing)." - [family doctor, Kitchener-Waterloo]

Patients shared positive experiences with their local pharmacist,

"The pharmacists have been great, too." – [patient, Kitchener-Waterloo]

Self education

Many patients believed that it was their responsibility to educate themselves.

"Take care of yourself and you've really got to answer the questions because they will not give you that." "And educate yourself. Really educate yourself." - [patient, Hamilton]

Another patient shared, *"You cannot depend on, sometimes, like, the pharmacy or…you know, you gotta be on the ball and look after yourself. That's from my experience."* - [patient, Kitchener-Waterloo]

Barriers to patient education.

Lack of necessary education content and effective format

One of the specific barriers identified by health care providers is the limited education that occurs for DOACs.

"*I always worry a little bit about the education with the DOACs compared to Warfarin brings everybody's radars up.*" - [nurse, Hamilton]

"*We actually have, sometimes in an hour, set up to go over everything, like, top to bottom (on Warfarin). Give them the information, everything. But if someone is started on a DOAC, they get the DOAC and they get the two-minute spiel and that's the end of it."* - [specialist, Hamilton]

Some patients not interested in education

A family doctor from the Hamilton focus group recalled one of his patients' words, "*I trust you. You're not going to give me something that's going to kill me, hopefully… so, I might not spend a lot of time educating some people because they don't need it, or they don't want it.*"

Limited time of health care providers for education

One of the common barriers cited is the limited time that health care providers have to spend with patients. As one of the specialists described,

"So, there is very limited time to be able to sit down and have that conversation…" – [specialist, Hamilton]

Poor communication within the healthcare system

Poor communication between specialists and family doctor was mentioned, for instance, a family doctor said,

" *… there's no really good way, other than me filling out these forms and having the desk clerk fax them off and…and who even knows if that happens or if it*

goes to the right person. There is…it is really difficult to communicate from hospital…or even from doctor to doctor…in real time about what's happening. " -[family doctor, Hamilton]

Lack of regional or larger OAC programs

One of the doctors expressed his disappointment in Canada's infrastructure for OAC information compared to that in other countries:

"*So, there is several examples of the patient education platform for anticoagulation that works very well and has very robust outcomes, but we don't use it in Canada because our systems are so fragmented. We do not even have (local) anticoagulation programming…let alone regional, let alone provincial, let alone national." "Is there something better? There is but we don't use it in Canada. …in New Zealand, and Germany, and Sweden, and Iceland, for example, where they have national anticoagulation registries… it's a patient self-management model…and so, for example, in Sweden you've got over two hundred thousand patients registered on the national registry and their time in therapeutic range is over eighty percent. And has been for decades."* -[specialist, Hamilton]

DISCUSSION

Patient education can influence patient behavior and produce changes in attitudes, knowledge, and skills necessary to maintain or improve health (Adams, 2010; Physicians, 2000). Although there is no high-quality evidence that supplemental patient education improves patient outcomes (Clarkesmith, Pattison, Khaing, & Lane, 2017; Paquette et al., 2019; Wong, Schulman, Woodworth, & Holbrook, 2013), understanding the benefits and risks of medications is believed to be an important component for patients' medication adherence (Gellad, Grenard, & Marcum, 2011; Jimmy & Jose, 2011; Timmers et al., 2017). In the present study, our participants (healthcare providers and patients) offered perspectives based on their experiences, about the content, format, and timing of OAC patient education and perceived barriers to OAC patient education.

Patients, caregivers and health care providers agreed that the rationale, risk, and adherence of OACs should be included in patient education. There are no specific Canadian guidelines for OAC patients' education contents. However, the national patient safety goal for anticoagulant therapy was defined by the Joint Commission of the United States (Commission, 2018). According to the Joint Commission, the content of OAC education for patients should include adherence to medication dose and schedule, the importance of follow-up appointments and

laboratory testing, potential drug-drug and drug-food interactions, and the potential for adverse drug reactions. These guidelines are consistent with our findings for the important content of OAC education.

Despite the low quality of the evidence, continuing patient education is thought to be effective in improving patients' knowledge, behaviors, and clinical outcomes (Bzowyckyj, Dow, & Knab, 2017). In the present study, in addition to the initial education given to patients, health care providers described their emphasis on continuing anticoagulation education. Until now, no specific study has focussed on the efficacy of patients' continuing education on OAC management yet. Future high-quality research is needed to explore this topic.

In this study, patients, caregivers, and health care providers expressed the need for a variety of formats for patient education. They described how written education materials (brochures or handouts) may be important but are easily outdated, may have problems with commercial bias, and are not suitable for patients with health literacy barriers (Hersh, Salzman, & Snyderman, 2015). Education videos were also mentioned but still require the same attention to timeliness, freedom from bias, and health literacy. Thrombosis Canada has printed material and educational videos on thromboembolic diseases on each OAC for patients and providers (https://thrombosiscanada.ca/thrombosis-canada-materials/). However, no study has evaluated the utilization of those formats and their effect on patient outcomes. In addition, although there were challenges for OAC case management (Lowery, Haley, & Bussey, 2005), trials have showed the effect of the case management for medical delivery (Hernández-Zambrano et al., 2019; Iliffe et al., 2014). Furthermore, the lack of national thromboembolic programs for patients and lack of public awareness of the thromboembolic disease were identified as barriers by the health care providers and patients, respectively. Unlike cancers and diabetes, public awareness for thromboembolic disease is low globally (Wendelboe et al., 2015). Although there is an annual World Thrombosis Day internationally, it does not appear to be well known or utilized by patients. Similarly, large OAC management programs remain unproven to improve clinical outcomes, add additional health care costs and would further fracture overall medical care.

The traditional education personnel are the health care providers, including the specialists, physicians, and thrombosis nurses, which is consistent with our findings. In addition, we found the potential role that pharmacists can play in continuing OAC education during the OAC maintenance. Both physicians and patients have mentioned the role of pharmacists played in the OAC management in the present study. Although pharmacists are only trained in a few aspects of OAC management, pharmacist-managed anticoagulation programs have been shown to

improve patient knowledge on anticoagulants control, patient quality of life, and patient satisfaction, but no statistical benefit in thromboembolic events or bleeding occurrence (Liang et al., 2020; Verret et al., 2012; Zhou et al., 2016). In addition, patient self-education was suggested by patients in the present study. A randomized controlled trial has showed that the culturally adapted chronic disease self-management programme improved self-efficacy and self-care behaviour in patients with chronic disease (Griffiths et al., 2005). However, high quality evidence is needed to explore the benefit of patient self-education on OAC management.

For the barriers of the OAC education, concerns of communication within the health care system have been mentioned by both the health care providers and patients. This is consistent with our systematic review, which indicates that poor communication is one of the barriers to OAC management (Wang et al., 2020). According to expert opinion, optimal communication between the specialists, family doctors, nurses, and pharmacists is required in a compelling format to deal with transitional care problems, including patient education (Foppe van Mil et al., 2016; Owens et al., 2014). In practice, communication in healthcare can be improved (Kripalani et al., 2007; Vermeir et al., 2015). In addition, a lack of necessary educational content delivered in an effective format was mentioned as another barrier. Warfarin, which has been used in practice for decades, has mature educational content (Wofford, Wells, & Singh, 2008). In this study, both health providers and patients mentioned that more patient education about DOACs would be of benefit, especially when transitioning from warfarin to DOACs. Similar to warfarin education, DOAC patients' education should include the rationale for use (benefits for preventing or treating thrombosis), harms (bleeding), and the importance of adherence to treatment and clinical follow-up (Arthur Allen et al., 2021). Therefore, in practice, it is necessary for health care providers to perform DOAC education following the standard guideline to supply sufficient information on DOACs.

Using focus group discussions and rigorous qualitative research methods, we demonstrated the importance of patient education about OACs to patients and providers and identified key barriers and facilitators to providing education. However, there are some limitations for this study. First, the present study is a secondary analysis of the data, which may affect the saturation of the results (Saunders et al., 2018; Szabo & Strang, 1997). Next, our study results were based on the experiences and perspectives of a small number of health care providers and patients in Hamilton and Kitchener-Waterloo areas, which may not be generalizable to other health care settings or other geographic locations. Finally, there was a potential selection bias for the participants, in those patients and providers who

agreed to participate in the focus groups may have more strongly held views on the topic that they wish to share.

The implications for this study for practice are supplying useful information to health care providers in terms of education contents, formats, appropriate time, education personnel, and possible barriers. RCTs with clearly defined education arms in patients initiating anticoagulation are needed to confirm our statement.

CONCLUSION

Despite a lack of high-quality evidence showing patient education can improve actual clinical outcomes, both patients and health care providers still support its provision, including for patients taking DOACs. It is possible that the best combination of contents, length, timing, source, formats, and avoiding possible barriers of education would improve clinical outcomes but requires further research to clarify.

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Appendix 1A. Baseline Demographics- Health care Providers

IDNO: |__|__|__|__| **Facilitator Initials:** |M|__|S| **Note-taker Initials**: |__|__|__|
Participant sub-group: Health care Providers **Audio**: |__|__|__|
Group number: |__|__| **Date**: June 27, 2017

1. **Age**: _____

2. **Gender:**
   - Male
   - Female

3. **Occupation:**
   - Physician
   - Nurse Practitioner
   - Registered Nurse
   - Pharmacist
   - Other

4. **Name of clinic or institute: _____**

5. **Practice time: _____years**

6. **Specialty (if applicable):_____**

7. **Type of Practice**
   - Inpatient
   - Outpatient
   - Both

8. **Location of Practice**
   - Urban
   - Rural
   - Rural Remote

9. **Involvement in Oral Anticoagulant (OAC) Management** (check all that apply):

- ☐ Prescribe OACs
- ☐ Supervise OAC management for my patients
- ☐ Supervise OAC management on behalf of another health care provider(s)
- ☐ Dispense OACs
- ☐ Advise other HCPs on the management of OACs
- ☐ Manage OACs as part of my job as MRP (Most Responsible Practitioner)
- ☐ Other (please specify):_____

Appendix 1B. Baseline Demographics: Patients/Caregivers

IDNO: |__|__|__|__| **Facilitator Initials:** |__|__|__| **Note-taker Initials**: |__|__|__|

Participant sub-group: Healthcare Providers **Audio**: |__|__|__|

Location: (circle one): Hamilton/Kitchener-Waterloo

Group number: |__|__| **Date**: |__|__|/|__|__|/|__|__|

1. First Name: _____Last Name Initial____

2. City of Residence:

   - ☐ Hamilton
   - ☐ Kitchener-Waterloo

3. Age_____

4. "Blood thinner" (oral anticoagulants-OAC) Status
   - ☐ Previous user
   - ☐ Current user
   - ☐ Refused blood thinner
   - ☐ Caregiver

5. Duration of blood thinner use
   - ☐ 0-6 months
   - ☐ 6 months -1 year
   - ☐ 1-3 years

- 3+ years

6. Reason for use
   - Atrial Fibrillation (irregular heart rhythm)
   - Previous venous thromboembolism (blood clot in leg or lung)
   - Mechanical heart valve
   - Other, please describe: _____

7. Health care provider monitoring my blood thinner
   - Doctor (please select one of the following):
     - Family Physician (GP)
     - Specialist (e.g., Hematologist or Cardiologist or Internal Medicine, etc.)
   - Nurse (please select one of the following):
     - Registered Nurse (RN)
     - Registered Nurse Practioner (RNP)
   - Pharmacist
   - Other: _____
8. Number of previous clotting events (for example, stroke or TIA (mini stroke), pulmonary embolism (lung clot), DVT (leg clot), heart attack, clot on heart valve, clot in major blood vessel supplying leg or arm)
   - 0
   - 1
   - 2
   - 3
   - 4
   - 5 or more

9. Number of previous bleeding events
   - 0
   - 1
   - 2
   - 3
   - 4
   - 5 or more

Appendix 2A. Focus Group Topic Guide- Healthcare Providers

FGD IDNO |__|__|__|__| **Facilitator Initials** |__|__|__| **Note-taker Initials** |__|__|__|
Participant sub-group: Healthcare providers **Digital file**: |__|__|__|
Date |__|__/__|__/__|__| **Location:** (circle one): Hamilton/Kitchener-Waterloo

Introduction

I am _____ from _____
(Facilitator)

There are 2 research staff that will be assisting me today (introduce them and explain their roles)

- ✓ Explain general purpose of the study:
  - *For overall study:* To improve the management of oral anticoagulants, both self-management by patients and provider management, as improved management will advance the safety and effectiveness of the anticoagulants.
  - *For FGD (healthcare providers):* To discuss barriers and facilitators to optimal oral anticoagulant management for patients and for healthcare providers such as adherence, and ideas for improving the management of oral anticoagulants.

- ✓ Aims of the discussion and expected duration (1 hour)
- ✓ Who is involved in the process (other participants)
- ✓ What will happen with the collected information and how the participant/target group will benefit
- ✓ Ask group to endorse the proposed ground rules, for example:
  - Only one person talks at a time.

- It is important for us to hear everyone's ideas and opinions. There are no right or wrong answers to questions – we are interested in learning about your experiences, your opinions, and your ideas
- It is important for us to hear all sides of an issue – if you experience is different from that the group is talking about, we hope that you will share it with us.

✓ Check position and functioning of tape recorders

✓ Confirm that everyone has completed the consent form: ask if there any questions and confirm permission to digitally record the discussion

✓ Describe process for transcription and reason for participants to identify themselves with their first name before they speak and how that name will be replaced with a number in the transcript to protect identity

Domain	**Topic**
Introduction	Could everyone please introduce themselves and their specialty?
Management of anticoagulants	**Health care provider's perspective anticoagulant management** • Thinking about all of your patients who are on oral anticoagulants, I'd like to ask you to think about which patients have the best adherence to taking the medication as prescribed. • Why are these patients doing well with taking their oral anticoagulants? (Probes: patient level factors, support system, think of one patient who is doing really well – what things contribute to their success with taking the oral anticoagulants?) • What other behaviours do you believe are important for high quality patient self-management?

	• What features of healthcare provider management and follow-up of patients are key to high quality OAC management • Thinking about all your patients who are on oral anticoagulants, I'd like to ask you to think about which patients are not adhering to the medications. • Why are these patients not doing well with taking their oral anticoagulants? (Probes: patient level factors, drug side effects, drug interactions, support system, think of one patient who is really having a difficult taking their anticoagulants as prescribed – what challenges do they face?) • What are some of the difficulties you experience with managing these medications in your patients? (Probes: Adequate time and resources for patients to be informed? Think about one of the patients where you are had a very difficult time managing their oral anticoagulants – what made it difficult?) • What things would help you to manage your patients use of anticoagulants more successfully? Probes (patient level factors, system level factors) • What factors help vs. hinder patient compliance with OACs • Can you suggest things that would improve anticoagulation management?
Education	• How are patients educated about oral anticoagulants? • Do you feel you patients understand enough about anticoagulants? • What do you feel are barriers and facilitators to patient education about anticoagulants?

	• Do you find patients receive enough education about anticoagulants?
Communication	• What sorts of communication (face-to-face, phone calls, email) do you think help vs hinder optimal OAC management? (Probe: Are there any specific communication barriers you can think off? communications to and from patients, other HCPs, labs, etc.) • What communication (face-to-face, phone calls, email) would you think helps to ensure the medication you are taking are managed in the best possible way? What types of communications would make management more difficult? Is there any suggestions you have that could improve this?

Appendix 2B. Focus Group Topic Guide- Patients/Caregivers

FGD IDNO |__|__|__|__| **Facilitator Initials** |__|__|__| **Note-taker Initials** |__|__|__|

Participant sub-group: (*circle*): Healthcare providers/Patients
Digital file: |__|__|__|

Date |__|__/__|__/__|__| **Location:** (circle one): Hamilton/Kitchener-Waterloo

Introduction

I am _____ from _____ (Facilitator)

There are 2 research staff that will be assisting me today (introduce them and explain their roles)

- ✓ Explain general purpose of the study:

- *For overall study:* The use of blood thinners, both self-management by patients and your medical team's management, as improved use will advance the safety and effectiveness of the blood thinners which are also known as "anticoagulants

- *For FGD (patients):* To explore the difficulties patients experience when taking blood thinners, things that make it easier to take them and ideas to improve blood thinner use in the future.

✓ Aims of the discussion and expected duration (1 hour)

✓ Who is involved in the process (other participants)

✓ What will happen with the collected information and how the participant/target group will benefit

✓ Emphasize the Facilitator is not a health care professional and cannot answer and questions regarding medications and treatment and that this should be discussed with the healthcare provider.

✓ Emphasize we would like to discuss the experience with blood thinners not the healthcare system in general

✓ Ask group to endorse the proposed ground rules, for example:

- Only one person talks at a time.

- It is important for us to hear everyone's ideas and opinions. There are no right or wrong answers to questions – we are interested in learning about your experiences, your opinions, and your ideas

- It is important for us to hear all sides of an issue – if you experience is different from that the group is talking about, we hope that you will share it with us.

✓ Check position and functioning of tape recorders

✓ Confirm that everyone has completed the consent form: ask if there any questions and confirm permission to digitally record the discussion

Domain	Topic
Introduction	• I'd like to begin by asking each of you to introduce yourself and describe if you are a patient or caregiver. Please also share if you are currently taking blood thinners or have taken them in the past or have refused to take them.
Anticoagulant Knowledge	**Patients/Caregivers perspective on oral anticoagulation management** • We'd like to begin the discussion by talking about "blood thinners," specifically the potential benefits and harms. • Can you start by telling me why you are taking blood thinners or, if you have refused to take them, why the doctor suggested you take them? • Now can you tell me about the potential benefits of blood thinners? • Now can you tell me about the potential harms of blood thinners? • Are you able to take your blood thinners exactly as your doctor? If yes, why? (Probe: What things help you to do this? (Are you comfortable with blood thinners)? Probe (patient level factors, doctor level factors, system level factors, support). If no, why not? (Probe: Comfort level with blood thinners? What things make it difficult for you to take the blood thinners exactly as your doctor has prescribed? What would make it easier for you to take them as prescribed?). • Have you talked about these challenges with your doctor? (Probe why/who not.) • Do you have trouble taking your medication as prescribed? • What types of behaviour do you think prevent you from having your anticoagulants managed in the best possible way? • What behaviours help to make sure anticoagulants are managed in the best possible way? • For those who take blood thinners, have you ever thought about stopping them? If yes, why?

	• For those who have stopped taking blood thinners, would you mind sharing why you stopped taking them? • If your doctor has suggested that you take blood thinners but you have refused to take them can you tell us why you have refused?
Education	• Do you feel you know enough about the blood thinner that you are taking or that your doctor has recommended for you? Probes: what things would you like to more about? Can you share the types or sources of education you have received?
Communication	• What communication (face-to-face, phone calls, email) would you think helps to ensure the medication you are taking are managed in the best possible way? • What communication would make management more difficult? • Is there any suggestions you have that could improve this?

Chapter Four: Are the correct outcomes being measured in studies of oral anticoagulants? A systematic survey

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Review Article

Are the correct outcomes being measured in studies of oral anticoagulants? A systematic survey

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ABSTRACT

Introduction: Oral anticoagulant (OAC) intervention trials have typically included clinical event outcomes. However, there is no standard list of outcomes to be used in OAC research. This study aimed to describe and classify the outcomes used in recent prospective clinical studies involving OACs.

Materials and methods: We searched MEDLINE, EMBASE, and CINAHL databases from January 2009 to July 2019 for prospective studies with an intervention or control group that included one or more oral anticoagulants. We abstracted details about each included study and the outcomes used from the study report and its accompanying protocol. Using the Core Outcome Measures in Effectiveness Trials (COMET) Initiative recommendations, we categorised each outcome into one of five domains (mortality/survival, physiological/clinical, life impact, resource use, and adverse events). Our primary outcome was the prevalence of use of an outcome domain across studies.

Results: We included 70 prospective studies, including 52 randomized controlled trials and 18 prospective cohort studies. A total of 121 different outcomes were reported. The COMET domains were represented in the 70 studies as follows: mortality (63/70, 90.0%); physiological/clinical domain (70/70, 100%), life impact domain (43/70, 61.4%), resource use domain (26/70, 37.1%), and adverse events domain (55/70, 78.6%).

Conclusion: Outcome reporting in prospective studies of OACs more frequently concentrates on mortality, physiological/clinical domains, and adverse events compared to life impact and resource utilization domains, the latter uncommonly used. A priority for future research includes developing a core outcome set (COS) for OAC research that represents all domains.

1. Introduction

Oral anticoagulants (OACs) include vitamin K antagonists (VKAs) such as warfarin, and direct-acting antagonist oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, apixaban and edoxaban [1]. OACs are used for the prevention and treatment of venous and arterial thromboembolism [2–6]. For instance, patients with atrial fibrillation (AF) are treated long-term with OACs with the primary purpose of preventing stroke and systemic embolism [7]. For patients with venous thromboembolism (VTE), using OACs is the main approach to minimize morbidity and mortality [8]. Clinical trials are the mainstay of evaluating effectiveness and safety of medications, and well-developed guidelines for their methodology are available to ensure low risk of bias and high generalizability [9,10].

The Core Outcome Measures in Effectiveness Trials (COMET) initiative is an international effort to develop and apply core outcome sets (COS) for clinical trials (http://www.comet-initiative.org/) [11,12]. This is to ensure that all relevant outcomes are measured, including patient reported outcomes, and improve consistency to add systematic review. The database of all studies relevant to the

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development of core outcome sets for use in clinical trials was developed by COMET Initiative (https://www.comet-initiative.org/studies/). There are many successful examples of COS development in COMET. For instance, the additional endpoints for trials in acute stroke was developed in 2012 [13] and the outcome parameters for trials in atrial fibrillation was set in 2007 [14]. A COS is a consensus-based recommendation for a standardized collection of outcomes to include within a specified disease or condition research program. The COMET database currently contains 1332 citations of planned, ongoing, and completed work, including guidance on developing, implementing, evaluating, and updating COS [15]. For developing a new COS, COMET advises that the first step is to identify all potentially relevant outcomes in a literature review. After reviewing qualitative data to vet, the original outcome list, a consensus group process is undertaken to finalize the recommended COS [16].

A taxonomy for outcomes in medical research has been developed by COMET [17]. This is a 38-item classification system categorised into five domains (mortality/survival domain, physiological/clinical domain, life impact domain, resource use domain, and adverse events/effects domain). This taxonomy is focused on the classification of what, rather than how outcomes are measured. Application of the taxonomy to the core outcome sets in the COMET database revealed that 92% of COS include morbidity and mortality measures. However, quality of life, health resource utilization, patient and provider satisfaction, etc. were used less frequently [17].

Core outcome sets were first championed in rheumatology, as part of an effort to include high quality measurement of disability, function, quality of life, etc., in addition to clinical events (https://omeract.org/) [18]. Core outcome sets in areas of thromboembolic diseases, including stroke, AF, and VTE, have been used to inform several pivotal clinical trials [13,14,19]. However, there is no COS for OAC intervention trials, which have typically concentrated on clinical event outcomes (e.g., stroke, systemic embolism, VTE, mortality, and bleeding events) [8]. Estimated time in therapeutic range (TTR) for the international normalized ratio (INR) is a commonly used surrogate outcome for the effect and safety of vitamin K antagonists (VKA) but has no relevance for DOACs for which there are no monitoring parameters [20]. However, there is no standard list of outcomes to be used in OAC research. This and the lack of a standardized approach for measuring the outcomes in studies of OACs hampers the ability to compare and pool clinical trials. It is not clear that the outcomes most important to patients, providers, or healthcare policymakers are frequently measured. For instance, quality of life, medication compliance, and OAC management quality are important outcomes for patients, physicians, and the health care system, respectively [21–23]. However, they are not often reported in current publications. The development of a COS for OAC studies could be useful to ensure that essential outcomes are assessed, and the pooling of studies is feasible.

This survey aimed to systematically describe the outcomes used in recent OAC intervention prospective clinical studies and categorize them into the five COMET domains. This work will inform the development of a COS for future OAC research. We hypothesize that there is an extensive list of outcomes used in trials involving OACs but that domains beyond clinical events may be under-represented.

Research question. What outcomes (both primary and secondary) were used in prospective studies published between 2009 and 2019, which included adults using any of the oral anticoagulants as an intervention?

2. Methods

2.1. Search strategy and eligibility criteria

We performed a literature search to identify relevant articles published from 2009 onwards. We searched Medline, Embase, and The Cochrane Library. The search strategy included terms for randomized clinical trials (RCTs) or prospective cohort studies, oral anticoagulants [anticoagula$ adj3 oral], Warfarin, acenocoumarol Phenprocoumon, Dabigatran, Apixaban, Rivaroxaban, and Edoxaban with a time limit of January 2009 to July 2019, limited to human studies and the English language (see detailed search strategy in Appendix 1). The studies' eligibility criteria were 1) RCTs and prospective cohort studies, including full reports and/or protocols; 2) participants 18 years of age or older; 3) intervention or control group included one or more OAC; 4) studies measured the efficacy and/or safety related to OAC therapy. Since we were primarily interested in clinical outcomes, studies focused on economic analyses and pharmacokinetics were excluded. We excluded letters, commentaries, and reviews. Conference abstracts were excluded because of their lack of details in outcome measurement.

2.2. Sampling considerations

In order to determine how many studies would be needed, we assumed a proportion of studies reporting any outcome at 5%. Given a margin of error of 5% and a 95% confidence level for a population size of 637 (based on our search), we needed to sample 67 articles, which we rounded up to 70. These computations were done using WinPEPI version 11.65 [24]. A randomized sampling procedure was performed using the Excel randomization function to retrieve corresponding citation numbers. We repeatedly sampled and screened identified citations meeting eligibility criteria until we achieved the target sample size.

2.3. Study selection

Two independent investigators (MW and ZC) performed the selection process in two screening phases: first title and abstract screening, then for those articles that passed, we randomly selected a sample for full-text screening.

The second full-text screening of randomly selected citations was performed to assess eligibility. Articles that did not meet our inclusion criteria during the review were replaced by the following paper from the random sampling list. Our unit of analysis was the whole study, which means the protocol of a study (if available) was used as an appendix of the study. We prefer to include the original studies. If secondary-analysis or sub-study papers were on the list, the original papers and protocols (if available) were identified. Protocols were treated as an independent study unit if the results were still not available.

2.4. Data extraction

Pre-tested data extraction forms were used to extract the data (Appendix 2). Each included article, its protocol (if the included article was a result paper), or its result paper (if the article was a protocol) was searched for using both the reference list and a literature search. We collected information on the first author, year of publication, journal name, the country where a study was conducted, participants, the name of the OAC(s), study objective, and the name of each outcome. The outcome names were recorded exactly as used in the original papers. Terms understood to mean exactly the same were counted as the same outcome. For instance, death due to bleeding and fatal bleeding were categorised to death due to bleeding. For studies reporting the same outcome in 2 places (for example, fatal pulmonary embolism as a thromboembolic outcome and as a mortality outcome), these were only counted under the Mortality domain. Composite outcomes were defined as those where at least two different clinical events (bleeding events, thromboembolic events, and death) were used in a combined outcome. At least two reviewers (MW, ZC, and MWo) with training in clinical research methodology independently extracted the data using a standardized and pilot-tested data collection form.

2.5. Data analysis

After data collection, each outcome measure was classified according to COMET outcome taxonomy in medical research, which includes 38 items in five domains [17]. The details of the five domains and the 38 items can be found in Appendix 3. Information on the types and subtypes of outcomes under each domain was collected. We reported the outcomes named in the original articles, including types and subtypes, according to the frequency (%) assigned to each domain. The prevalence of use of an outcome domain across studies was calculated.

3. Results

3.1. Search results and study characteristics

A total of 13,427 articles were selected through searching electronic databases, and an additional 23 records were identified by cross-checking the bibliographies of retrieved meta-analyses or relevant reviews. After exclusion of duplicates and screening of the titles and abstracts, we identified 637 potentially eligible articles. From these, we randomly selected 70 articles for full-text screening with replacement for subsequently excluded articles (Fig. 1) [25–94].

The basic characteristics and target outcomes extracted from the included studies are listed in Table 1. All 70 included papers were prospective studies, including 52 RCTs and 18 prospective cohort studies (PCS). Twenty-three of the included articles also had protocols available (22 for RCTs and one for PCS), ten of them were protocols (seven for RCTs and three for PCSs) without results, and 37 were reports of results with unavailable protocols (23 for RCTs and 14 for PCSs). More than one-third of the included studies were multinational (22/70, 31.4%). For studies performed in a single country, ten were from Japan (14.2%),5 from China (7.1%), and 4 from Australia (5.7%). Thirty-five studies (50.0%) focused on DOACs, 21 (30.0%) on both DOACs and VKA, 13 studies (18.6%) on VKAs, and one (1.4%) on unspecified OACs. The top three targeted participants were patients with AF (28/70, 40.0%), patients with VTE (e.g., VTE, PE, and DVT) (16/70, 22.9%), and patients having surgery (e.g., knee replacement, mechanical heart valve, lumbar spine surgery, and hip fracture surgery, etc.) (13/70, 18.6%). Six studies (8.6%) were on OAC management. The proportions of the studies in stroke prophylaxis for AF and stroke prophylaxis for DVT or PE were 41.4% (29/70) and 50% (35/70), respectively.

3.2. Reporting of the outcomes in 70 included studies

A total of 121 unique outcomes were reported, with details in Table 1. Only 17 of the studies (24.3%) reported outcomes representing all of the five outcome domains. Nine studies (12.9%) did not report any mortality/survival outcome, 27 (38.6%) did not report on life impact, 44 (62.9%) did not report a resource use domain, and 15 (21.4%) did not report adverse events. In the 70 studies, bleedings, thromboembolism, and mortality outcomes were measured in 69 studies (98.6%), 66 studies (94.3%), and 63 studies (90.0%), respectively. More than half of the included studies (60.0%, 42/70) used a composite outcome. The details of the outcome list in each domain can be found in Table 2.

3.2.1. Outcomes reported within the mortality/survival domain

Mortality outcomes were measured in 63 studies (90.0%). The most frequently reported item in this domain was all-cause death (56/70, 80.0%), followed by cardiovascular death (27/70, 38.6%), death caused by bleeding (27/70, 38.6%), death due to PE (27/70, 38.6%), and VTE-

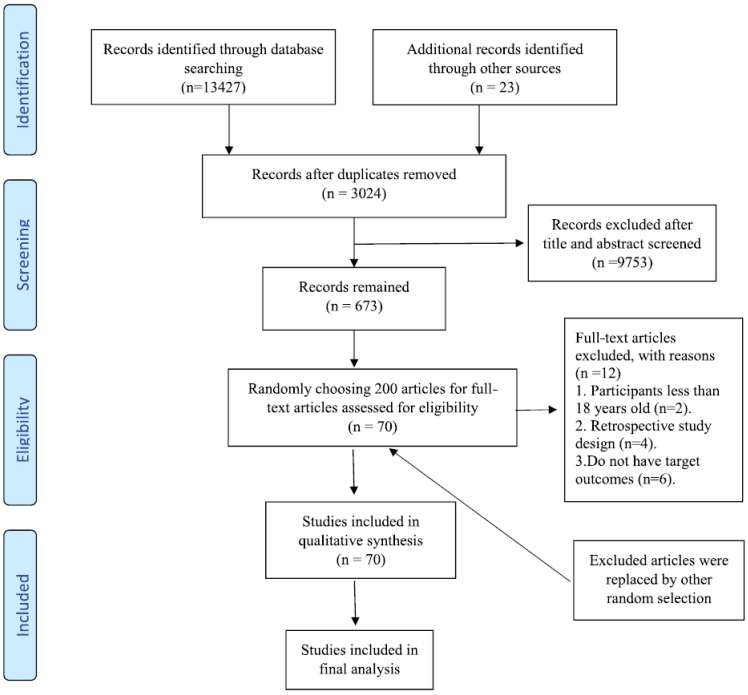

Fig. 1. PRISMA flow diagram detailing the search strategy and results.

Table 1
Characteristics of the included studies in the order of the study selection.

First author, publication year	Country	Study design	Protocol Availability	Participants	Related OAC(s)	Indication(s)	Composite outcome	Outcomes taxonomy domains 1. Mortality/ survival 2. Physiological/ Clinical 3. Life impact 4. Resource use 5. Adverse events
Agnelli et al. 2013 [25]	Australia	RCT	Protocol available	Patients with acute VTE	Apixaban, Enoxaparin, and Warfarin	Treatment of VTE	Yes	1, 2, 3, 4, 5
Breithardt et al. 2014 [26]	USA	RCT	Protocol available	Patients with AF	Rivaroxaban and Warfarin	AF	Yes	1, 2
Bo et al. 2017 [27]	Italy	PCS	Protocol not available	Patients with AF	Warfarin, Dabigatran, Rivaroxaban, and Apixaban	AF	No	1, 2, 4
Buller et al. 2013 [28]	Netherlands	RCT	Protocol available	Patients with symptomatic VTE	Edoxaban and Warfarin	Treatment of VTE	Yes	1, 2, 5
Calkins et al. 2017 [29]	Multiple countries	RCT	Protocol available	Patients scheduled for catheter ablation of AF	Dabigatran and Warfarin	Ablation for AF	Yes	1, 2, 3, 5
Chopard et al. 2018 [30]	France	PCS	Protocol not available	Patients with PE	Rivaroxaban and Apixaban	Treatment of VTE	Yes	1, 2, 4, 5
Connolly et al. 2013 [31]	Canada	RCT	Protocol not available	Patients with AF	Dabigatran	AF	Yes	1, 2, 4, 5
Weitz et al. 2017 [32]	Multiple countries	RCT	Protocol available	Patients with DVT or PE	Rivaroxaban	Treatment of VTE	Yes	1, 2, 5
Giugliano et al. 2013 [33]	Multiple countries	RCT	Protocol available	Patients with AF	Edoxaban and Warfarin	AF	Yes	1, 2, 4, 5
Gulpen et al. 2019 [34]	Netherlands	PCS	Protocol not available	Patients with AF	Apixaban, Edoxaban, Dabigatran, or Rivaroxaban	AF	No	2, 3, 5
Kimpton et al. 2018 [35]	Canada	RCT protocol	Result paper not available	Cancer patients	Apixaban	Prevention of VTE	No	1, 2, 5
Lassen et al. 2010 [36]	Australia	RCT	Protocol not available	Patients after total knee replacement	Apixaban and Enoxaparin	Prevention of VTE	Yes	1, 2, 5
Lavitola et al. 2010 [37]	Brazil	RCT	Protocol not available	Patients with Mitral Valvulopathy and AF	Warfarin	Mitral Valvulopathy and AF	No	2, 3
Onundarson et al. 2015 [38]	Iceland	RCT	Protocol not available	Patients on warfarin	Warfarin	OAC management	Yes	1, 2, 4
Ageno et al. 2017 [39]	Multiple countries	PCS protocol	Result paper not available	Patients with VTE	Dabigatran and Warfarin	Treatment of VTE	No	1, 2, 3, 4, 5
Lee et al. 2017 [40]	South Korea	PCS	Protocol not available	Patients with AF	Warfarin and Dabigatran	AF	Yes	1, 2, 4
Ogawa et al. 2011 [41]	Japan	RCT	Protocol not available	Patients with AF	Apixaban and Warfarin	AF	Yes	1, 2, 3, 5
Poli et al. 2019 [42]	Italy	PCS	Protocol not available	Patients with AF	Warfarin and DOACs	AF	No	1, 2
Saji et al. 2016 [43]	Japan	PCS	Protocol not available	Patients with AF	Warfarin and DOACs	AF	Yes	1, 2
Sakamoto et al. 2019 [44]	Japan	RCT protocol	Result paper not available	Patients with AF	Edoxaban	AF	Yes	1, 2, 3, 4, 5
Xing et al. 2017 [45]	China	RCT	Protocol not available	Elderly patients with AF	Warfarin	AF	No	2, 5
Beyer-Westendorf et al. 2017 [46]	Germany	RCT	Protocol available	Patients with Superficial venous thrombosis	Rivaroxaban	Prevention of thromboembolic complications	Yes	1, 2, 5
Mirdamadi et al. 2014 [47]	Iran	RCT	Protocol not available	Patients underwent total knee arthroplasty	Dabigatran	Prevention of VTE	No	1, 2, 3
Cohen et al. 2018 [48]	Multiple countries	PCS protocol	Result paper not available	Patients with VTE	Edoxaban	Treatment of VTE	No	1, 2, 3, 4, 5
Duraes et al. 2018 [49]	Brazil	RCT protocol	Result paper not available	Patients with mechanical heart valve	Rivaroxaban and Warfarin	Prevention of thromboembolic complications	No	1, 2, 3
Engelberger et al. 2015 [50]	Switzerland	PCS	Protocol not available	Patients with AF	Rivaroxaban	AF	Yes	2, 3, 5

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Table 1 (*continued*)

First author, publication year	Country	Study design	Protocol Availability	Participants	Related OAC(s)	Indication(s)	Composite outcome	Outcomes taxonomy domains 1. Mortality/ survival 2. Physiological/ Clinical 3. Life impact 4. Resource use 5. Adverse events
Du et al. 2015 [51]	China	RCT	Protocol not available	Patients after lumbar spine surgery	Rivaroxaban	Prevention of VTE after surgery	Yes	1, 2
Fuji et al. 2014 [52]	Japan	RCT	Protocol not available	Patients undergoing hip fracture surgery	Edoxaban	Prevention of embolism	Yes	1, 2, 5
Okumura et al. 2017 [53]	Japan	RCT protocol	Result paper not available	Elderly patients with AF	Edoxaban	AF	Yes	1, 2, 5
Yasuda et al. 2019 [54]	Japan	RCT	Protocol available	Patients with AF	Rivaroxaban	AF	Yes	1, 2, 3, 4, 5
Prochaska et al. 2017 [55]	Germany	PCS	Protocol available	Patients on OACs	OACs (not specified)	OAC management	Yes	1, 2, 3, 4, 5
Falamić et al. 2019 [56]	Croatia	RCT	Protocol not available	Patients on warfarin	Warfarin	OAC management	No	2, 3, 4, 5
Passman et al. 2016 [57]	USA	PCS	Protocol not available	Elderly rural patients on NOACs with non-permanent AF	NOACs (not specified)	OAC management	No	1, 2, 3
Christensen et al. 2011 [58]	Denmark	RCT	Protocol not available	Patients on OACs	OACs (not specified)	OAC management	No	1, 2, 3, 4, 5
Alexander et al. 2011 [59]	Multiple countries	RCT	Protocol available	Patients with acute coronary syndrome	Apixaban	Prevention of acute ischemic events	Yes	1, 2, 3, 5
Homma et al. 2012 [60]	Multiple countries	RCT	Protocol available	Patients with Heart Failure and Sinus Rhythm	Warfarin	Prevention of stroke and death for patients with heart failure	Yes	1, 2, 3, 4, 5
Hoffmeyer 2017 [63]	Switzerland	PCS	Protocol not available	Patients with fracture-related surgery	Rivaroxaban	Prevention of VTE after surgery	No	1, 2, 5
Ferro et al. 2018 [61]	Multiple countries	RCT protocol	Result paper not available	Patients with cerebral venous thrombosis	Dabigatran and Warfarin	Prevention VTE	Yes	2
Buller et al. 2012 [62]	Multiple countries	RCT	Protocol available	Patients with PE	Rivaroxaban	Treatment of PE	Yes	1, 2, 3, 4, 5
Hoshi et al. 2017 [64]	Japan	RCT protocol	Result paper not available	Patients with AF	Apixaban	AF	Yes	1, 2, 3, 4, 5
Paikin et al. 2011 [65]	Multiple countries	RCT	Protocol available	Patients with AF	Warfarin and Dabigatran	AF	Yes	1, 2, 3, 4
Chen et al. 2012 [66]	China	RCT	Protocol not available	Patients with AF	Warfarin	AF	No	1, 2, 3
Lee et al. 2013 [67]	Multiple countries	RCT protocol	Result paper not available	Patients with cancer, and DVT and/or PE	Warfarin	Prevention cancer-associated thrombosis	Yes	1, 2, 4, 5
Cannon et al. 2017 [68]	Multiple countries	RCT	Protocol available	Patients with AF	Warfarin and Dabigatran	AF	Yes	1, 2, 5
Kobayashi et al. 2017 [69]	Japan	RCT	Protocol not available	Patients with osteoarthritis or osteonecrosis	Edoxaban	Prevention of VTE after surgery	No	1, 2
Mega et al. 2009 [70]	Multiple countries	RCT	Protocol not available	Patients with ACS	Rivaroxaban	Prevention of VTE in patients with ACS	Yes	1, 2, 5
Anderson et al. 2018 [71]	Canada	RCT	Protocol available	Patients after hip or knee arthroplasty	Rivaroxaban	Prevention of VTE after surgery	Yes	1, 2, 3, 4, 5
Tang et al. 2017 [72]	China	RCT	Protocol not available	Patients after internal fixation of hip fracture	Rivaroxaban	Prevention of VTE after surgery	No	1, 2, 5
Washam et al. 2019 [73]	Japan	RCT	Protocol available	Patients with AF	Apixaban and Warfarin	AF	Yes	1, 2, 3, 5
Nilsson et al. 2014 [74]	Denmark	PCS	Protocol not available	Persons prescribed VKA	VKA (not specified)	OAC management	No	1, 2, 5
Yamashita et al. 2017 [75]	Japan	PCS	Protocol not available	Patients with AF	DOAC and Warfarin	AF	No	2
Devereaux et al. 2018 [76]	Multiple countries	RCT	Protocol available	Patients with myocardial injury after non-cardiac surgery	Dabigatran	Prevention of VTE after surgery	Yes	1, 2, 3, 4, 5
Connolly et al. 2013 [77]	Multiple countries	RCT	Protocol not available	Patients with AF	Betrixaban and Warfarin	AF	No	1, 2, 5
		RCT			Warfarin	Treatment of PE	Yes	1, 2, 3, 5

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Table 1 (*continued*)

First author, publication year	Country	Study design	Protocol Availability	Participants	Related OAC(s)	Indication(s)	Composite outcome	Outcomes taxonomy domains 1. Mortality/ survival 2. Physiological/ Clinical 3. Life impact 4. Resource use 5. Adverse events
Buller et al. 2012 [78]	Multiple countries		Protocol not available	Patients with acute PE				
Haas et al. 2019 [79]	Germany	PCS protocol	Result paper not available	Patients with AF	NOAC and VKA (not specified)	AF	No	2, 3, 5
Enajat et al. 2009 [80]	Netherlands	RCT	Protocol not available	Patients with AF	Phenprocoumon	AF	No	2, 3, 5
Zannad et al. 2018 [81]	Multiple countries	RCT	Protocol available	Patients with heart failure, sinus rhythm, and coronary disease	Rivaroxaban	Prevention of TE in patients with heart failure, sinus rhythm, and coronary disease	Yes	1, 2, 4, 5
Duan et al. 2016 [82]	China	RCT	Protocol not available	Patients with PE	Rivaroxaban	Treatment of PE	No	1, 2, 3, 4, 5
Goette et al. 2016 [83]	Multiple countries	RCT	Protocol available	Patients undergoing cardioversion of AF	Edoxaban and Warfarin	AF	Yes	1, 2, 3, 4, 5
Lavau-Denes et al. 2013 [84]	France	RCT	Protocol not available	Cancer patients	Warfarin	Prevention of catheter related DVT	No	1, 2, 3, 4, 5
Nakamura et al. 2015 [85]	Multiple countries	RCT	Protocol available	Patients with cancer, and DVT and/or PE	Edoxaban and Warfarin	Treatment of VTE	Yes	1, 2, 3, 4, 5
Gage et al. 2019 [86]	USA	RCT	Protocol available	Patients undergoing hip or knee arthroplasty	Warfarin	Treatment of VTE or death	Yes	1, 2, 3, 5
Vranckx et al. 2019 [87]	Multiple countries	RCT	Protocol available	Patients with AF	Edoxaban and Warfarin	AF	Yes	1, 2, 3, 5
Yhim et al. 2019 [88]	South Korea	PCS	Protocol not available	Patients with cancer, and DVT and/or PE	Rivaroxaban	Treatment of VTE	No	1, 2, 3, 4
Konigsbrugge et al. 2016 [89]	Australia	PCS	Protocol not available	Patients with AF	VKA, Dabigatran, Rivaroxaban, and Apixaban	AF	No	1, 2, 3, 4
Verdecchia et al. 2018 [90]	Italy	PCS	Protocol not available	Patients with AF	Dabigatran	AF	Yes	1, 2, 3
Eikelboom et al. 2013 [91]	Multiple countries	RCT	Protocol available	Patients with mechanical heart valves	Warfarin and Dabigatran	Prevent TE in patients with mechanical heart valves	Yes	1, 2, 3, 4, 5
Lassen et al. 2009 [92]	Australia	RCT	Protocol not available	Patients after knee replacement	Apixaban	Prevention of VTE after surgery	No	1, 2, 5
Romera et al. 2009 [93]	Spain	RCT	Protocol not available	Patients with acute DVT	Acenocoumarol	Treatment of DVT	No	1, 2
Schulman et al. 2009 [94]	Multiple countries	RCT	Protocol not available	Patients with acute VTE	Dabigatran and Warfarin	Treatment of VTE	Yes	1, 2, 3, 5

Abbreviation: ACS acute coronary syndrome, AF atrial fibrillation, CRNMB Clinically relevant nonmajor bleeding, CRP C-reactive protein, DOAC Direct oral anticoagulants, DVT deep-vein thrombosis, INR the international normalized ratio, NOAC Non-Vitamin K antagonist oral anticoagulants, OAC oral anticoagulants, PCS prospective cohort study, PE pulmonary embolism, RCT randomized controlled trial; TE thromboembolism, USA United States of America, VKA Vitamin K antagonists, VTE Venous thromboembolism

related death (17/70, 24.3%).

3.2.2. *Outcomes reported within physiological/clinical domain*

All included studies reported outcomes in the physiological/clinical domain, with a wide variety of specific outcomes. The top five subtypes of outcomes within this category included bleeding, pharmacokinetic and pharmacodynamic endpoints, venous thromboembolism, arterial thromboembolism, and any thromboembolic events, conditions, or diseases after thromboembolism (Table 2).

Many different bleeding types and bleeding sites were reported as bleeding outcomes. Within 10 different types of bleeding, the top three most frequently used bleeding types were major bleeding (61/70, 87.1%), any bleeding (46/70, 67.1%), and clinically relevant nonmajor bleeding (CRNMB) (32/70, 45.7%), (Table 2). For descriptions of major bleeding, the top three were major bleeding (59/61, 96.7%), major bleeding associated with a reduction in hemoglobin concentration (4/61, 6.6%), and critical site major bleeding (4/61, 6.6%). Twenty-four different bleeding sites were reported, with the top three (as reported) being intracranial bleeding (35/70, 50.0%), gastrointestinal bleeding (29/70, 41.4%), and hemorrhagic stroke (17/70, 24.3%) (Table 2). Several subtypes were found in each bleeding sites. The top three for intracranial bleeding were intracranial bleeding (including all kinds of intracranial bleeding) (23/35, 65.7%), intracranial major bleeding (13/35, 37.1%), and intracerebral bleeding (3/35, 8.6%), while the top three for gastrointestinal bleeding were gastrointestinal major bleeding (11/29, 37.9%), gastrointestinal bleeding (3/29, 10.3%), and gastrointestinal minor bleeding (2/29, 6.9%).

The vascular outcomes included VTE (43/70, 61.4%), arterial

Table 2
Outcome summary for the 70 prospective oral anticoagulants studies (including protocols if available) based on the 38 items taxonomy for outcomes in medica research [17,106].

Outcome domains	Categories	Outcome using frequency in the first 70 included studies
Death	1. Mortality/survival (Includes overall (all-cause) survival/mortality and cause-specific survival/mortality, as well as composite survival outcomes that include death (e.g., disease-free survival, progression-free survival, amputation-free survival)	• All-cause death (80.0%, 56/70) • Cardiovascular death (38.6%, 27/70) • Death caused by bleeding (38.6%, 27/70) • Death due to PE (28.6%, 20/70) • VTE related death (24.3%, 17/70) • Death due to other causes (nonvascular) (20.0%, 14/70) • Death caused from stroke (15.7%, 11/70) 1. Death due to any stroke (72.7%,8/11) 2. Death due to ischemic stroke (18.2%, 2/11) 3. Death due to hemorrhagic stroke (9.1%, 1/11) • Death due to cancer (11.4%, 8/70) • Death due to infectious disease (5.7%, 4/70) • Death due to AE (5.7%, 4/70) 1. Death due to treatment related AEs (75.0%, 3/4) 2. Death due to treatment related AEs (25.0%, 1/4) • Death due to HF (4.3%, 3/70) • Death due to thromboembolism (2.9%, 2/70) • Death due to DVT (2.9%, 2/70) • Undetermined death (2.9%, 2/70) • Death due to respiratory failure (1.4%, 1/70) • Death not related to anticoagulation (1.4%, 1/70)
Physiological/ Clinical (Physiological/clinical outcomes include measures of physiological function, signs and symptoms, as well as laboratory (and other scientific) measures relating to physiology and are categorised according to the underlying cause/body system.)	2. Blood and lymphatic system outcomes	*Bleeding type • Major bleeding (87.1%, 61/70) 1. Major bleeding (96.7%, 59/61) 2. Major bleeding that induced hemoglobin decreasing (6.6%, 4/61) 3. Critical site major bleeding (6.6%, 4/61) 4. Critical site nonfatal major bleeding (4.9%, 3/61) 5. Major bleeding that induced blood transfusion ≥2 units (4.9%, 3/61) 6. TIMI major bleeding (3.3%, 2/61) 7. Noncritical site nonfatal major bleeding (3.3%, 2/61) 8. Life-threatening major bleeding (1.6%, 1/61) 9. Symptomatic nonfatal major bleeding (31.6%, 1/61) • Any bleeding (67.1%, 46/70) • CRNMB (45.7%, 32/70) • Minor bleeding (35.7%, 25/70) • Nonserious (nonmajor) bleeding (18.6%, 13/70) • Life-threatening bleeding (17.1%, 12/70) • Clinically relevant bleeding (8.6%, 6/70) • Severe hemorrhagic events (8.6%, 6/70) • Severity of the bleeding (2.9%, 2/70) • Mild hemorrhagic events (2.9%, 2/70) Bleeding sites (63.3%, 19/30) • Intracranial bleeding (50.0%, 35/70) 1. Intracranial bleeding (65.7%, 23/35) 2. Intracranial major bleeding (37.1%, 13/35) 3. Intracerebral bleeding (8.6%, 3/35) 4. Nonfatal intracranial bleeding (8.6%, 3/35) 5. Nonfatal intracranial major bleeding (8.6%, 3/35) 6. Symptomatic intracranial bleeding (2.9%, 1/35) 7. Major intracerebral bleeding (2.9%, 1/35) • Gastrointestinal bleeding (41.4%, 29/70) 1. Gastrointestinal major bleeding (37.9%, 11/29) 2. Gastrointestinal bleeding (10.3%, 3/29) 3. Gastrointestinal minor bleeding (6.9%, 2/29) 4. Nonfatal gastrointestinal major bleeding (3.4%, 1/29) 5. Nonsurgical site gastrointestinal major bleeding (3.4%, 1/29) 6. Nonsurgical site gastrointestinal CRNMB (3.4%, 1/29) 7. Gastrointestinal CRNMB (3.4%, 1/29) 8. Nonsurgical site gastrointestinal bleeding (3.4%, 1/29) 9. Severe gastrointestinal bleeding (3.4%, 1/29) 10. Mild gastrointestinal bleeding (3.4%, 1/29) 11. Upper gastrointestinal bleeding (3.4%, 1/29) 12. Lower clinically significant gastrointestinal bleeding (3.4%, 1/29) 13. Lower non-clinically significant gastrointestinal bleeding (3.4%, 1/29)

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Table 2 (*continued*)

Outcome domains	Categories	Outcome using frequency in the first 70 included studies
		14. Lower gastrointestinal bleeding (3.4%, 1/29)
		• Hemorrhagic stroke (24.3%, 17/70)
		1. Hemorrhagic stroke (94.1%, 16/17) 2. Symptomatic hemorrhagic infarction (5.9%, 1/17)
		• Nose bleeding (Epistaxis) (15.7%, 11/70)
		1. Nose bleeding (36.4%, 4/11) 2. Nose minor bleeding (45.5%, 3/11) 3. Nose CRNMB (45.5%, 3/11) 4. Mild epistaxis (9.1%, 1/11)
		• Retroperitoneal Bleeding (14.3%, 10/70)
		1. Retroperitoneal major bleeding (60.0%, 6/10) 2. Retroperitoneal bleeding (20.0%, 2/10) 3. Nonfatal retroperitoneal major bleeding (Critical site) (20.0%, 2/10) 4. Nonfatal retroperitoneal bleeding (Critical site) (10.0%, 1/10) 5. Nonfatal retroperitoneal major bleeding (10.0%, 1/10) 6. Retroperitoneal major bleeding (Critical site) (10.0%, 1/10)
		• Intraocular or retinal bleeding (14.3%, 10/70)
		1. Intraocular major bleeding (40.0%, 4/10) 2. Intraocular bleeding (20.0%, 2/10) 3. Nonfatal intraocular major bleeding (20.0%, 2/10) 4. Intraocular major bleeding (critical site) (10.0%, 1/10) 5. Intraocular minor bleeding (critical site) (10.0%, 1/10)
		• Hematoma (14.3%, 10/70)
		1. Hematoma (40.0%, 4/10) 2. Minor hematoma (20.0%, 2/10) 3. Major Hematoma (10.0%, 1/10) 4. Nonfatal major hematoma (10.0%, 1/10) 5. Surgical site major hematoma (10.0%, 1/10) 6. Surgical site CRNMB hematoma (10.0%, 1/10) 7. Nonsurgical site CRNMB hematoma (10.0%, 1/10) 8. Surgical site hematoma (10.0%, 1/10) 9. Nonsurgical site hematoma (10.0%, 1/10)
		• Urogenital bleeding or Haematuria (12.9%, 9/70)
	Laboratory parameters (for example, from blood samples) and scientific measures (for example, pharmacokinetic outcomes) should be classified within the physiological domain that captures the reason for the assessment (rather than within the Blood and lymphatic system domain, for example).	1. Minor Haematuria (44.4%, 4/9) 2. Haematuria (10.0%, 1/10) 3. Major haematuria (10.0%, 1/10) 4. Blood urine present (CRNMB) (10.0%, 1/10) 5. Nonfatal major haematuria (10.0%, 1/10) 6. Nonsurgical haematuria (CRNMB) (10.0%, 1/10) 7. Blood urine present (10.0%, 1/10) 8. Renal bleeding (10.0%, 1/10)
		• Intramuscular bleeding (10.0%, 7/70)
		1. Intramuscular major bleeding (42.9%, 3/7) 2. Intramuscular bleeding (28.6%, 2/7) 3. Nonfatal Intramuscular major bleeding (14.3%, 1/7) 4. Intramuscular major bleeding (critical site) (14.3%, 1/7)
		• Pericardial bleeding (8.6%, 6/70)
		1. Pericardial major bleeding (66.7%, 4/6) 2. Pericardial major bleeding (critical site) (16.7%, 1/6) 3. Nonfatal pericardial major bleeding (16.7%, 1/6)
		• Traumatic bleeding (8.6%, 6/70)
		1. Contusion (16.7%, 1/6) 2. Traumatic minor hemorrhage (33.3%, 2/6) 3. Traumatic major hemorrhage (16.7%, 1/6) 4. Bite mark (16.7%, 1/6) 5. Eczema nummular (16.7%, 1/6)
		• Intraarticular bleeding (7.1%, 5/70)

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Table 2 (*continued*)

Outcome domains	Categories	Outcome using frequency in the first 70 included studies
		1. Intraarticular major bleeding (40.0%, 2/5) 2. Intraarticular bleeding (20.0%, 1/5) 3. Nonfatal intraarticular major bleeding (Critical site) (20.0%, 1/5) 4. Haemarthrosis (major bleeding) (20.0%, 1/5)
		• Bruising or ecchymosis or purpura or Hemorrhage subcutaneous (7.1%, 5/70)
		1. Purpura (minor bleeding) (50.0%, 1/5) 2. Surgical site bruising or ecchymosis (major bleeding) (20.0%, 1/5) 3. Nonsurgical site bruising or ecchymosis (major bleeding) (20.0%, 1/5) 4. Nonsurgical site bruising or ecchymosis (bleeding) (20.0%, 1/5) 5. Surgical site bruising or ecchymosis (nonmajor bleeding) (20.0%, 1/5) 6. Surgical site bruising or ecchymosis (bleeding) (20.0%, 1/5)
		• Intrathoracic bleeding (Hemoptysis) (7.1%, 5/70)
		1. Hemoptysis major bleeding (critical site) (20.0%, 1/5) 2. Nonfatal intrathoracic major bleeding (20.0%, 1/5) 3. Nonfatal intrathoracic major bleeding (critical site) (20.0%, 1/5) 4. Intrathoracic major bleeding (critical site) (20.0%, 1/5) 5. Intrathoracic CRNMB, (nonsurgical site) (20.0%, 1/5)
		• Surgical site bleeding (5.7%,4/70)
		1. Surgical site bleeding (50.0%, 2/4) 2. Surgical site major bleeding (25.0%, 1/4) 3. Bleeding incision complications (25.0%, 1/4)
		• Extracranial bleeding (5.7%, 4/70)
		1. Extracranial bleeding (75.0%, 3/4) 2. Minor extracranial bleeding (25.0%, 1/4) 3. Major extracranial bleeding (25.0%, 1/4)
		• Hematochezia (melaenas) (4.3%, 3/70)
		1. Hemorrhoidal minor bleeding (66.7%, 2/3) 2. Hematochezia (33.3%, 1/3)
		• Intraspinal bleeding or Intrathecal bleeding (4.3%, 3/70)
		1. Major intraspinal bleeding (66.7%, 2/3) 2. Major intrathecal bleeding (33.3%, 1/3)
		• Subconjunctival hemorrhage or Conjunctive bleeding (2.9%, 2/70)
		1. Subconjunctival minor bleeding (100%, 2/2) 2. Subconjunctival CRNMB (50%, 1/2)
		• Nonsurgical site bleeding (2.9%, 2/70)
		1. Nonsurgical site major bleeding (50.0%, 1/2) 2. Nonsurgical site CRNMB bleeding (50.0%, 1/2) 3. Nonsurgical site bleeding (50.0%, 1/2)
		• Gingival bleeding or mouth bleeding (minor bleeding) (2.9%, 2/70) • Hemorrhoidal minor bleeding (2.9%, 2/70) • Mucosal major bleeding (1.4%, 1/70) • Other sites (20.0%, 14/70)
	Pharmacokinetic and Pharmacodynamic end points	• INR or TTR (38.6%, 27/70) • Plasma OAC levels (15.7%, 11/70) • D-dimer (14.3%, 10/70) • Activated partial thromboplastin time (aPTT) (11.4.7%, 8/70) • Prothrombin time (PT) (10.0, 7/70) • C-reactive protein (CRP) (5.7%, 4/70) • Hematology Profile (5.7%, 4/70) • Anti-factor Xa (4.3%, 3/70) • Prothrombin Time and International Normalized Ratio (PT/INR) (4.3%, 3/70) • Prothrombin Fragment 1 + 2 (4.3%, 3/70) • Fibrinogen (FIB) (2.8%, 2/70) • Population PK of DU-176 (1.4%, 1/70) • P-selectin (1.4%, 1/70)

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Table 2 (*continued*)

Outcome domains	Categories	Outcome using frequency in the first 70 included studies
		• Thrombin time (TT) (1.4%, 1/70) • Prothrombinase induced clotting time (PICT) (1.4%, 1/70) • Soluble fibrin (SF) (1.4%, 1/70) • Thrombin antithrombin complex (TAT) (1.4%, 1/70) • Plasminogen activator inhibitor 1 (PAI-1) (1.4%, 1/70) • Fibrinogen degradation products (FDP) (1.4%, 1/70) • Asymmetric dimethylarginine (ADMA) (1.4%, 1/70) • Von Willebrand factor (vWF) (1.4%, 1/70) • Soluble CD40 ligand (1.4%, 1/70) • Thrombin generation (TG) (1.4%, 1/70) ˆLab tests or physical examination
		• Blood pressure 10.0%, 7/70) • Height and weight (BMI) (8.6, 6/70) • Laboratory test panel (8.6, 6/70) • Electrocardiography (ECG) (7.1, 5/70) • Heart rate (7.1, 5/70) • Hemoglobin (Hb) (5.7%, 4/70) • Vital signs (5.7%, 4/70) • Platelet (4.3%, 3/70) • Stroke risk (CHADS2 and CHA2DS2-VASC) (4.3%, 3/70) • Blood count (RBC, Hb, Ht, Plt, and WBC) (2.9%, 2/70) • Total cholesterol (1.4%, 1/70) • low-density lipoprotein cholesterol (LDL) (1.4%, 1/70) • High-density lipoprotein cholesterol (HDL) (1.4%, 1/70)
	3. Cardiac outcomes	Diseases
		• Cardiovascular events (including bleedings) (15.7%, 11/70) • Atrial Fibrillation (AF) (5.7%, 4/70) • Heart failure (HF) (32.9%, 2/70) • Cardioversion and sinus rhythm maintenance (1.4%, 1/70) ˆLab test
		• BNP Brain natriuretic peptide test (2.9%, 2/70) • NT-pro BNP (2.9%, 2/70) • HS-Troponin I (1.4%, 1/70)
	4. Congenital, familial and genetic outcomes	Not applicable.
	5. Endocrine outcomes	ˆLab test
		• HbA1c glycosylated hemoglobin (4.3%, 3/70) • Blood glucose (mg/dL) (2.9%, 2/70)
	6. Ear and labyrinth outcomes 7. Eye outcomes 8. Gastrointestinal outcomes 9. General outcomes	Not applicable.
	10. Hepatobiliary outcomes	Diseases
		• Liver dysfunction (28.6%, 20/70) ˆLab test
		• Liver function test (28.6%, 20/70)
	11. Immune system outcomes	Not applicable.
	12. Infection and infestation outcomes	Disease
		• Infection (4.3%, 3/70)
	13. Injury and poisoning outcomes	Not applicable.
	14. Metabolism and nutrition outcomes	
	15. Musculoskeletal and connective tissue outcomes	• Bone fractures (2.9%, 2/70) • Severe osteoporosis (1.4%, 1/70)
	16. Outcomes relating to neoplasms: benign, malignant and unspecified (including cysts and polyps). Outcomes relating to neoplasms include those related to non-solid and solid tumours.	Malignancies (1.4%, 1/70)
	17. Nervous system outcomes	Not applicable.
	18. Pregnancy, puerperium and perinatal outcomes (Pregnancy, puerperium and perinatal domain extends to outcomes relating to breastfeeding and weaning.)	ˆLab test • Pregnancy test (8.6, 6/70)
	19. Renal and urinary outcomes	Diseases Drug related renal dysfunction (20.0%, 14/70) ˆLab test
		• Renal function test (20.0%, 14/70)
		1. Creatinine Clearance) (85.7%, 12/14) 2. Cystatine C (Renal function) (7.1%, 1/14) 3. (Microscopic) Urinalysis (7.1%, 1/14)

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Table 2 (*continued*)

Outcome domains	Categories	Outcome using frequency in the first 70 included studies
	20. Reproductive system and breast outcomes 21. Psychiatric outcomes (Psychiatric outcomes include all those relating to mental health conditions and associated behaviours (e.g. addictions and behavioural problems)). 22. Respiratory, thoracic and mediastinal outcomes 23. Skin and subcutaneous tissue outcomes	Not applicable.
	24. Vascular outcomes	Venous thromboembolism • Pulmonary embolism (PE) (51.4%, 36/70) 1. PE (72.2%, 26/36) 2. Nonfatal PE (19.4%, 7/36) 3. Symptomatic PE (16.7%, 6/36) 4. Nonfatal symptomatic PE (16.7%, 6/36) 5. Proximal PE (5.6%, 2/36) 6. Proximal symptomatic PE (2.8%, 1/36) 7. Asymptomatic PE (2.8%, 1/36) • VTE (42.8%, 30/70) 1. VTE (76.7%, 23/30) 2. Symptomatic VTE (36.7%, 11/30) 3. Nonfatal symptomatic VTE (6.7%,2/30) 4. Asymptomatic VTE (3.3%,1/30) 5. Severe VTE (3.3%,1/30) 6. Nonfatal VTE (3.3%,1/30) 7. Major VTE (3.3%,1/30) • Deep-vein thromboembolism (DVT) (40.0%, 28/70) 1. DVT (85.7%, 24/28) 2. Symptomatic DVT (42.9%, 12/28) 3. Asymptomatic DVT (17.9%, 5/28) 4. Proximal DVT (17.9%, 5/28) 5. Nonfatal DVT (7.1%, 2/28) 6. Distal DVT (7.1%, 2/28) 7. Proximal symptomatic DVT (7.1%, 2/28) 8. Proximal asymptomatic DVT (3.6%, 1/28) 9. Nonfatal symptomatic DVT (3.6%, 1/28) 10. Distal asymptomatic DVT (3.6%, 1/28) • VTE sites (10.0%, 7/70) 1. Superficial vein thrombosis (SVT) (28.6%, 2/7) 2. Cerebral VTE (28.6%, 2/7) 3. Lower-limb thrombosis (28.6%, 2/7) 4. Ophthalmic-vein thrombosis (28.6%, 2/7) 5. Splenic VTE (14.3%, 1/7) 6. Portal VTE (14.3%, 1/7) 7. Mesenteric VTE (14.3%, 1/7) 8. Hepatic VTE (14.3%, 1/7) 9. Renal VTE (14.3%, 1/7) 10. Gonadal VTE (14.3%, 1/7) 11. VTE extension towards the saphenofemoral junction (14.3%, 1/7) 12. Upper-limb thrombosis (14.3%, 1/7) 13. Prosthetic valve thrombus (14.3%, 1/7) 14. Other VTEs (28.6%, 2/7) Arterial thromboembolism • Stroke (Cerebral infarction) (62.9%, 44/70) 1. Stroke (90.9%, 40/44) 2. Ischemic stroke (63.6%, 28/44) • Ischemic stroke (96.4%, 27/28) • Nonfatal ischemic stroke (7.1%, 2/28) 3. Disabled stroke (6.8%, 3/44) 4. Undetermined stroke (6.8%, 3/44) 5. Nonfatal stroke (4.5%, 2/44) 6. Nondisabled stroke ((4.5%, 2/44) 7. Nonfatal nondisabled stroke (2.3%, 1/44) • MI (52.9%, 37/70)

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Table 2 (*continued*)

Outcome domains	Categories	Outcome using frequency in the first 70 included studies
		1. MI (97.3%, 36/37) 2. Nonfatal MI (8.1%, 3/37) 3. Asymptomatic MI (2.7%, 1/37)
		• Systemic embolic events (SEE) (42.9%, 30/70)
		1. SEE (96.7%, 29/30) 2. Nonfatal SEE (6.7%, 2/30)
		• Transient ischemic attack (TIA) (22.9%, 16/70) • Any ischemic event (17.1%, 12/70)
		1. Any ischemic event (83.3%, 10/12) 2. Peripheral ischemic event (16.7%, 2/12)
		• Peripheral arterial occlusion (5.7%, 4/70) • (Unstable) Angina (4.3%, 3/70) • Acute coronary syndrome (ACS) (5.7%, 4/70) • Non-central nervous system embolism (2.9%, 2/70) • Asymptomatic Cerebral embolism (ACE) (1.4%, 1/70) • Stent thrombosis (7.1%, 5/70)
		Any thromboembolic event
		• Any thromboembolic event (17.1%, 12/70)
		1. Any ischemic event (83.3%, 10/12) 2. Peripheral ischemic event (16.7%, 2/12) 3. Cerebral thromboembolic event (8.3%, 1/12)
		Conditions or diseases after thromboembolism
		• Thrombocytopenia (5.7%, 4/70) • Post-thrombotic syndrome (PTS) (2.9%, 2/70) • Chronic thromboembolic pulmonary hypertension (CTEPH) (1.4%, 1/70) • Degree of thrombus regression (1.4%, 1/70)
Life impact	Functioning	• Modified Rankin Scale score (mRS) (10.0%, 7/70)
	25. Physical functioning 26. Social functioning 27. Role functioning 28. Emotional functioning/wellbeing	Not applicable.
	29. Cognitive functioning	Cognitive status (1.4%, 1/70)
	30. Global quality of life (Includes only implicit composite outcomes measuring global quality of life)	Quality of life (11.4%, 8/70)
		• Patient-reported quality of life (62.5%, 5/8) • Healthcare resource utility (37.5%, 3/8) • Alcohol use (12.5%, 1/8)
	31. Perceived health status (Subjective ratings by the affected individual of their relative level of health)	Not applicable.
	32. Delivery of care	• Adherence/compliance (38.6%, 27/70) • Withdraw from the study (including stopping the medication) (18.6%, 13/70) • Patient/carer satisfaction (emotional rather than financial burden) (7.1%, 5/70) • Anticoagulant utilization (4.3%, 3/70) • Physician satisfaction (1.4%, 1/70) • Warfarin dose adjustment frequency (1.4%, 1/70)
	33. Personal circumstances (Outcomes relating to patient's finances, home and environment)	Not applicable.
Resource use	34. Economic: general outcomes (e.g., cost, resource use) not captured within other specific resource use domains	• Health care utilization (2.9%, 2/70) • Cost-effective assessment (2.9%, 2/70)
	35. Hospital: outcomes relating to inpatient or day case hospital care (e.g. duration of hospital stays, admission to ICU)	• Hospitalization (31.4%, 22/70)
		1. All cause hospitalization (40.9%, 9/22)
		• All cause hospitalization (88.9%, 8/9) • Readmission for all cause (22.2%,2/9)
		2. Hospitalization stays (27.3%, 6/22) 3. Cardiovascular hospitalization (27.3%, 6/22)
		• Cardiovascular hospitalization (66.7%, 4/6) • Readmission for cardiovascular diseases (33.3%, 2/6)
		4. Hospitalization for Heart failure (18.2%, 4/22) 5. Hospitalization due to bleeding (9.1%, 2/22) 6. Hospitalization due to unstable angina (4.5%, 1/22)

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Table 2 (*continued*)

Outcome domains	Categories	Outcome using frequency in the first 70 included studies
	36. Need for further intervention: outcomes relating to medication (e.g. concomitant medications, pain relief), surgery (e.g. caesarean delivery, time to transplantation) and other procedures (e.g. dialysis-free survival, mode of delivery)	Need further intervention • Coronary revascularization (5.7%, 4/70) • Concomitant treatment (1.4%, 1/70) • Coronary artery bypass graft (1.4%, 1/70) • Surgery for superficial-vein thrombosis (1.4%, 1/70) • Amputation (1.4%, 1/70)
	37. Societal/carer burden: outcomes relating to financial or time implications on carer or society as a whole (e.g., need for home help, entry to institutional care, effect on family income)	Not applicable.
Adverse events	38. Adverse events/effects (Includes outcomes broadly labelled as some form of unintended consequence of the intervention (e.g., adverse events/effects, adverse reactions, safety, harm, negative effects, toxicity, complications, sequelae). Specifically named adverse events should be classified within the appropriate taxonomy domain above with an additional level of categorisation which identifies that this outcome is being considered as an adverse event.)	• Adverse events/effects (78.6%, 55/70) 1. Any AE (67.3%, 37/55) • All cause AE (86.5%, 32/37) • Drug related AE (51.4%, 19/37) • Any AE led to medication discontinuation (21.6%, 8/37) • Treatment related AE (27.0%, 10/37) • Treatment-emergent AE (5.4%, 2/37) • Treatment not related AE (2.7%, 1/37) 2. Serious AE (23.6%, 13/55) • All serious AE (92.3%, 12/13) • Drug related serious AE (23.1%, 3/13) • Treatment related serious AE (23.1%, 3/13) 3. AE Severity (18.2%, 10/55) 4. AE required further intervention (3.6%, 2/55) 5. Non-serious AE (3.6%, 2/55) 6. Unexpected AE (1.8%, 1/55)

Note: *Having definition diversity under the same outcome. ^ some of the lab tests acted as a monitoring measurement.
Abbreviation: OAC oral anticoagulants, VTE venous thromboembolism, DVT deep thromboembolism, AE adverse events, PE Pulmonary embolism, HF heart failure, MI myocardial infarction, TIMI Thrombolysis in Myocardial Infarction, CRNMB Clinically relevant nonmajor bleeding, INR international normalized ratio, TTR time in therapeutic range, AE adverse events/effects.

thromboembolism (52/70, 74.3%), any thromboembolic event (12/70, 17.1%), and conditions or diseases after thromboembolism (8/70, 11.4%). The top three subtypes of the VTE were PE (36/70, 51.4%), VTE (all types of VTE) (30/70, 42.8%), and DVT (28/70, 40.0%). Several subtypes were found under the outcomes of PE, VTE, and DVT. For PE, the top three subtypes were PE (all types of PE) (26/36, 72.2%), nonfatal PE (7/36, 19.4%), and symptomatic PE (6/36, 16.7%); for VTE, they were any VTE (23/30, 76.7%), symptomatic VTE (11/30, 36.7%), and nonfatal symptomatic VTE (2/30, 6.7%); and for DVT, they were any DVT (24/28, 85.7%), symptomatic DVT (12/28, 42.9%), and symptomatic DVT (5/28, 17.9%). The top three arterial thromboembolism were stroke (cerebral infarction) (44/70, 62.9%), myocardial infarction (MI) (37/70, 52.9%), and systemic embolic events (SEE) (30/70, 42.9%). There were also several subtypes under each arterial thromboembolism (see other details in Table 2).

Pharmacokinetic and pharmacodynamic endpoints were found in 38 studies, most commonly INR or TTR (27/70, 38.6%), plasma OAC levels (11/70, 15.7%), and D-dimer (10/70, 14.3%). Blood tests for liver dysfunction and renal dysfunction were reported in 20 (28.6%) and 14 (20%) studies, respectively. The most reported physical examination or lab measures in the included studies were blood pressure (7/70, 10.0%), height and weight (or BMI) (6/70, 8.6%), and laboratory test panel (6/70, 8.6%).

3.2.3. *Outcomes reported within the life impact domain*

Outcomes in this domain were found in 43 studies (61.4%). Three types of outcomes were observed - delivery of care (21/70, 30.0%), quality of life (8/70, 11.4%), and cognitive status (1/70, 1.4%). For delivery of care, subtypes included adherence/compliance (27/70, 38.6%), withdrawal from the study (13/70, 18.6%), patient/carer satisfaction (emotional rather than a financial burden) (5/70, 7.1%), anticoagulant utilization (3/70, 4.3%). For quality of life, they were patient-reported quality of life (5/8, 62.5%), healthcare resource utilization (3/8, 37.5%), and alcohol use (1/8, 12.5%).

3.2.4. *Outcomes reported within the resource use domain*

Outcomes in this domain were measured in 26 studies (37.1%). Four types of outcomes were found in this domain, which were hospitalization (22/70, 31.4%), health care utilization (2/70, 2.9%), cost-effective assessment (2/70, 2.9%), and need for further intervention (6/70, 8.6%). The top three subtypes of hospitalization were all cause hospitalization (9/22, 40.9%), length of hospital stay (6/22, 27.3%), and cardiovascular hospitalization (6/22, 27.3%). The most common need for further intervention outcome was coronary revascularization (4/70, 5.7%).

3.2.5. *Outcomes reported within the adverse events domain*

Adverse events/effects (AEs) were assessed in 55 studies (64.3%). The top three types of AEs were any AE (37/55, 67.3%), serious AE (13/55, 23.6%), and AE Severity (10/55, 18.2%). The top three subtypes of any AE were all cause AE (32/37, 86.5%), drug related AE (19/37, 51.4%) and any AE led to medication discontinuation (8/37, 21.6%). The common subtypes for serious AE included all serious AE (12/13, 92.3%), drug related serious AE (3/13, 23.1%), and treatment related serious AE (3/13, 23.1%).

4. Discussion

This is the first known systematic survey of outcomes measured in prospective studies of OACs. We found that outcomes in the mortality, physiological/clinical, and adverse events domains were more frequently used. There were fewer outcomes measured in the life impact

and resource use domains. For instance, there were only eight studies (11.4%) looking at patient-reported quality of life (life impact domain). From the patient and caregiver's perspective, quality of life is an essential part of the effect of the medications [95]. The lack of evidence in the domain of life impact is a cause for concern. In terms of the resource use domain, only a few included studies explored the health care utilization (three studies) and cost-effective assessment (two studies). This might be partly because we excluded articles that focused only on economic outcomes. Since only 90 of 10,030 (0.9%) titles screened were studies on economics, it was unlikely that they would be represented in the randomly selected 70. Nonetheless, health technology assessment is a valuable component of randomized trials, critical to inform drug reimbursement decisions, [96].

We found that there are many outcomes used in prospective studies of OACs. For instance, bleeding, thromboembolism, and mortality outcomes were measured in 69 (98.6%), 66 (94.3%), and 63 studies (90.0%), respectively. In terms of safety outcomes of the OACs, the most frequently reported bleeding outcomes were major bleeding, any bleeding, and CRNMB; the most frequently reported bleeding sites were intracranial, gastrointestinal, and hemorrhagic stroke. Second, in terms of the efficacy outcomes of the OACs, we found that mortality and thromboembolism types were well represented. All-cause mortality is arguably the most important among mortality outcomes, and was commonly reported on, less so many outcome-specific or site-specific fatal outcomes. For thromboembolism outcomes, most frequently reported were stroke (62.9%, 44/70) and myocardial infarction (MI) (52.9%, 37/70). For pharmacokinetic and pharmacodynamic endpoints, the most frequently used items were INR or TTR, plasma OAC levels, and D-dimer. For drug-related adverse effect monitoring, liver dysfunction and renal dysfunction were always included. Next, our study revealed that the use of composite outcomes was common, presumably because this yields higher event rates and more statistical power.

Although we included several studies of anticoagulation management [38,55–58,74]. no specific outcomes assessing the quality of OAC management were found. As the optimal management of anticoagulation could improve health outcomes and health care sustainability [97–99], it will be important to generate a series of reliable and accurate outcomes for OAC management in future methodological studies.

Consensus regarding which outcomes to measure and how to measure them is important. First, the process implies that experts agree on which outcomes are the most important to patients, clinicians, and policymakers. This is the role of COMET which is to develop and apply COS for clinical trials. Second, consensus around important outcomes allows trialists to be more efficient with their study resources. Third, common important outcomes are critical to high impact systematic reviews where meta-analysis requires not only the same outcome but also same measurement method (i.e., mean event rate or number of patients with at least one event). There are few publications examining which outcomes are used or should be used in studies of OAC therapy. In 2018, a systematic review reported on the outcomes measured in clinical trials of non-valvular AF. In this paper, they found that clinical trials of anticoagulation therapy reported 82 outcomes from 18 outcome domains, most of which are similar to our findings [100].

Aside from rheumatologic conditions, core outcome sets are relatively common in disease-related research. However, they are not common for medication-related research; COSMOS lists a core outcome set and a study using the COS for polypharmacy in older people [101,102]. Regulatory guidance determines the outcomes measured in research on new medications. The International Council for Harmonisation (ICH) develops guidelines collaboratively with the regulatory authorities and pharmaceutical industry. According to the Tripartite Guideline for Structure and Content of Clinical Study Reports, the appropriate measurements of efficacy or safety should be standard, i.e., widely used and generally recognised as reliable, accurate, and relevant [103]. This standard understandably emphasizes mortality and morbidity outcomes but misses some key domains which determine ongoing effectiveness, safety, and access, including quality of life, ability to adhere, satisfaction with effect.

Limitations of the present study include the following considerations. First, we may have missed some important outcomes, as we excluded studies focused only on economic analysis or pharmacokinetics. However, these are unlikely to yield useful clinical efficacy or safety outcomes. Second, the definition of each outcome varied across the studies and we account for the different versions of outcomes using the same label according to their meaning. For example, most of the studies defined the major bleeding and CRNMB according to the International Society on Thrombosis and Haemostasis (ISTH) criteria but others used TIMI definitions [70,104,105]. Next, outcomes considering patient and other stakeholder perspectives are important components for a COS. However, the present project did not explore the specific outcomes needed from this perspective. We only found that the reporting of the domain of "life impact" is suboptimal. Finally, this study did not address the validity and reliability of each outcome, which would be an important consideration for a core outcome.

The results of this survey will provide information useful for developing COS for OAC research by a consensus process in the future. This would involve qualitative studies to be sure that stakeholder experts are able to offer and comment on potential core outcomes, followed by a formal consensus panel review.

5. Conclusion

Outcome reporting in prospective studies of OACs more frequently concentrates on mortality, physiological/clinical domains, and adverse events compared to life impact and resource utilization domains. A priority for future research would be to develop a core outcome set (COS) for OAC research.

CRediT authorship contribution statement

A. Holbrook led the grant that provided funding. A. Holbrook and M. Wang designed the methods. M. Wang and Z. Chen carried out the initial literature searches. M. Wang, Z. Chen, and M. Wong performed study selection and data extraction. M. Wang did the data analysis and drafted the manuscript. A. Holbrook, D. Siegal, G. Le Gal, L. Mbuagbaw, and L. Thabane provided several rounds of critical revision for accurate and important intellectual content. All authors critically revised the manuscript and supplied the final approval of the version to be published.

Ethics approval and consent to participate

The present project is a systematic survey based on the review of publicly reported literature, which did not require ethics review.

Consent for publication

Not applicable as this is a retrospective study.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Canada, and the Chair on Diagnosis of Venous Thromboembolism at the Department of Medicine, University of Ottawa.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to thank all the involved study investigators for dedicating their time and skills to completing this study.

Appendix 1. Strategies for literature research

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
_____

1. (oral anti*coagula* or dabigatran or rivaroxaban or apixaban or edoxaban or warfarin or phenprocoumon).mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (43735)
2. limit 1 to (humans and english and yr = "2009 -Current") (17167)
3. clinical trial.pt. (516775)
4. randomized.ab. (447967)
5. placebo.ab. (199012)
6. trial.ti. (201154)
7. randomly.ab. (313970)
8. 3 or 4 or 5 or 6 (1015002)
9. 2 and 8 (2338)

****
Database: Embase <1974 to 2019 July 02>
Search Strategy:
_____

1. (oral anti*coagula* or dabigatran or rivaroxaban or apixaban or edoxaban or warfarin or phenprocoumon).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (118818)
2. limit 1 to (humans and english and yr = "2009 -Current") (64310)
3. clinical trial.pt. (0)
4. randomized.ab. (643980)
5. placebo.ab. (282128)
6. trial.ti. (273968)
7. randomly.ab. (413579)
8. 3 or 4 or 5 or 6 (931181)
9. 2 and 8 (5770)

****
Cochrane Library
Date Run: 04/07/2019 08:11:45
Comment: outcomes
ID Search Hits
#1 oral anti*coagula* or dabigatran or rivaroxaban or apixaban or edoxaban or warfarin or phenprocoumon with Publication Year from 2009 to present, in Trials 5319

Appendix 2. Data collection form

Study ID: ____ Reviewer Initials: _____
STUDY INFORMATION
First Author: _____ Year of Publication_____
Title of Article: _____
Journal Name: _____ Country: _____
METHODS
Participants:
Sample Size: Total_____.

The intervention_____
The control _____
RESULTS
Primary outcomes: XXX, XXX

Outcomes	Category	Definition	Measurement	Measuring time point	Follow-up	Statistical analysis

COMMENTS
Word Count:

Appendix 3. A taxonomy developed for outcomes in medical research

Core area	Outcome domain	Explanation
Death		Includes overall (all-cause) survival/mortality and cause-specific survival/mortality, as well as composite survival outcomes that include death (e.g., disease-free survival, progression-free survival, amputation-free survival)
	1. Mortality/survival	
Physiological/ clinical	**Physiological/clinical**	Physiological/clinical outcomes include measures of physiological function, signs and symptoms, as well as laboratory (and other scientific) measures relating to physiology and are categorised according to the underlying cause/body system.
	2. Blood and lymphatic system outcomes	
	3. Cardiac outcomes	
	4. Congenital, familial and genetic outcomes	*General* outcomes include those affecting the whole body which cannot be attributed to a certain body system e.g., fatigue, chills, flu like symptoms, malaise, anorexia, pain (unspecified, not associated with a particular body system), fever (not attributable to infection), anthropometric measures (e.g. weight), "global" measures, "symptoms" (not associated with a particular body system), "physical health", fitness.
	5. Endocrine outcomes	
	6. Ear and labyrinth outcomes	
	7. Eye outcomes	
	8. Gastrointestinal outcomes	
	9. General outcomes	Pain outcomes are categorised according to underlying cause or body system or within the *General* outcomes domain (if non-specific).
	10. Hepatobiliary outcomes	
	11. Immune system outcomes	Laboratory parameters (for example, from blood samples) and scientific measures (for example, pharmacokinetic outcomes) should be classified within the physiological domain that captures the reason for the assessment (rather than within the *Blood and lymphatic system* domain, for example).
	12. Infection and infestation outcomes	
	13. Injury and poisoning outcomes	
	14. Metabolism and nutrition outcomes	
	15. Musculoskeletal and connective tissue outcomes	*Psychiatric* outcomes include all those relating to mental health conditions and associated behaviours (e.g. addictions and behavioural problems).
	16. Outcomes relating to neoplasms: benign, malignant and unspecified (including cysts and polyps)	*Pregnancy, puerperium and perinatal domain* extends to outcomes relating to breastfeeding and weaning.
	17. Nervous system outcomes	
	18. Pregnancy, puerperium and perinatal outcomes	*Outcomes relating to neoplasms* include those related to non-solid and solid tumours.
	19. Renal and urinary outcomes	Sleep outcomes which relate to clinical signs, symptoms, or lab measures may be classified as *Nervous system*, *Psychiatric* or *Metabolism and nutrition* outcomes, depending on cause. However, outcomes relating to the impact of sleep deprivation, for example, should instead be classified within the relevant functioning domain.
	20. Reproductive system and breast outcomes	
	21. Psychiatric outcomes	
	22. Respiratory, thoracic and mediastinal outcomes	
	23. Skin and subcutaneous tissue outcomes	
	24. Vascular outcomes	
Life impact	**Functioning**	**Impact outcomes**
	25. Physical functioning	*Physical functioning*: impact of disease/condition on physical activities of daily living (for example, ability to walk, independence, self-care, performance status, disability index, motor skills, sexual dysfunction. Health behaviour and management)
	26. Social functioning	*Social functioning*: impact of disease/condition on social functioning (e.g., ability to socialise, behaviour within society, communication, companionship, psychosocial development, aggression, recidivism, participation)
	27. Role functioning	*Role functioning*: impact of disease/condition on role (e.g., ability to care for children, work status)
	28. Emotional functioning/wellbeing	*Emotional functioning/wellbeing*: impact of disease/condition on emotions or overall wellbeing (e.g., ability to cope, worry, frustration, confidence, perceptions regarding body image and appearance, psychological status, stigma, life satisfaction, meaning and purpose, positive affect, self-esteem, self-perception and self-efficacy)
	29. Cognitive functioning	*Cognitive functioning*: impact of disease/condition on cognitive function (e.g., memory lapse, lack of concentration, attention); outcomes relating to knowledge, attitudes and beliefs (e.g., learning and applying knowledge, spiritual beliefs, health beliefs/knowledge)
	30. Global quality of life	Includes only implicit composite outcomes measuring global quality of life
	31. Perceived health status	Subjective ratings by the affected individual of their relative level of health
	32. Delivery of care	Includes outcomes relating to the delivery of care, including adherence/compliance, patient preference, tolerability/acceptability of intervention, withdrawal from intervention (e.g., time to treatment failure), appropriateness of intervention, accessibility, quality and adequacy of intervention, patient/carer satisfaction (emotional rather than financial burden), and process,

(*continued on next page*)

(*continued*)

Core area	Outcome domain	Explanation
		implementation and service outcomes (e.g. overall health system performance and the impact of service provision on the users of services).
	33. Personal circumstances	Outcomes relating to patient's finances, home and environment
Resource use	**Resource use**	*Economic*: general outcomes (e.g., cost, resource use) not captured within other specific resource use domains
	34. Economic	*Hospital*: outcomes relating to inpatient or day case hospital care (e.g., duration of hospital stays, admission to ICU)
	35. Hospital	*Need for further intervention*: outcomes relating to medication (e.g., concomitant medications, pain relief), surgery (e.g., caesarean delivery, time to transplantation) and other procedures (e.g. dialysis-free survival, mode of delivery)
	36. Need for further intervention	*Societal/carer burden*: outcomes relating to financial or time implications on carer or society as a whole (e.g., need for home help, entry to institutional care, effect on family income)
	37. Societal/carer burden	
Adverse events	38. Adverse events/effects	Includes outcomes broadly labelled as some form of unintended consequence of the intervention (e.g., adverse events/effects, adverse reactions, safety, harm, negative effects, toxicity, complications, sequelae). Specifically named adverse events should be classified within the appropriate taxonomy domain above with an additional level of categorisation which identifies that this outcome is being considered as an adverse event.

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Chapter Five: Drug-drug Interactions with Warfarin: A Systematic Review and Meta-analysis

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SYSTEMATIC REVIEW AND META-ANALYSIS

Drug–drug interactions with warfarin: A systematic review and meta-analysis

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Aims: The objective of this paper is to systematically review the literature on drug–drug interactions with warfarin, with a focus on patient-important clinical outcomes.

Methods: MEDLINE, EMBASE and the International Pharmaceutical Abstract (IPA) databases were searched from January 2004 to August 2019. We included studies describing drug–drug interactions between warfarin and other drugs. Screening and data extraction were conducted independently and in duplicate. We synthesized pooled odds ratios (OR) with 95% confidence intervals (CIs), comparing warfarin plus another medication to warfarin alone. We assessed the risk of bias at the study level and evaluated the overall certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Results: Of 42 013 citations identified, a total of 72 studies reporting on 3 735 775 patients were considered eligible, including 11 randomized clinical trials and 61 observational studies. Increased risk of clinically relevant bleeding when added to warfarin therapy was observed for antiplatelet (AP) regimens (OR = 1.74; 95% CI 1.56–1.94), many antimicrobials (OR = 1.63; 95% CI 1.45–1.83), NSAIDs including COX-2 NSAIDs (OR = 1.83; 95% CI 1.29–2.59), SSRIs (OR = 1.62; 95% CI 1.42–1.85), mirtazapine (OR = 1.75; 95% CI 1.30–2.36), loop diuretics (OR = 1.92; 95% CI 1.29–2.86) among others. We found a protective effect of proton pump inhibitors (PPIs) against warfarin-related gastrointestinal (GI) bleeding (OR = 0.69; 95% CI 0.64–0.73). No significant effect on thromboembolic events or mortality of any drug group used with warfarin was found, including single or dual AP regimens.

Conclusions: This review found low to moderate certainty evidence supporting the interaction between warfarin and a small group of medications, which result in increased bleeding risk. PPIs are associated with reduced hospitalization for upper GI bleeding for patients taking warfarin. Further studies are required to better understand drug–drug interactions leading to thromboembolic outcomes or death.

KEYWORDS
drug interaction, meta-analysis, systematic review, warfarin

1 | INTRODUCTION

Warfarin is a vitamin K antagonist (VKA) oral anticoagulant (OAC) commonly prescribed for the prevention of stroke, venous thromboembolism (VTE), and other thromboembolic complications in patients with atrial fibrillation and mechanical heart valves.[1–3] Recently, the introduction of direct oral anticoagulants (DOACs) into clinical practice has decreased the frequency of warfarin prescribing.[4–6] However, warfarin remains the anticoagulant of choice for a significant proportion of patients who wish to stay on it or have conditions which require warfarin, or where the extra cost of DOACs is not supported.[7,8]

Despite its proven efficacy and long history as the gold standard of anticoagulant therapy, warfarin's narrow therapeutic window creates some clinical challenges. Its potential for drug–drug interactions with other medications is a commonly cited reason for the variability of a patient's international normalized ratio (INR) and occasional adverse events.[2] Anticoagulants have consistently been among the top drug families associated with clinical harm requiring emergency medical assessment or hospitalization.[9–11] Furthermore, drug–drug interactions are a common concern for clinicians frequently managing multimorbid disease involving multiple concomitant medications. Since clinical decision support systems frequently base their warnings on quality surrogate data such as drug levels or INR, clinicians need trustworthy evidence to guide their decision-making.[12–14]

Our previous systematic review of the literature found low-quality evidence suggesting multiple foods and drug–drug interactions with warfarin, but the studies focused primarily on surrogate outcomes, chiefly INR.[12] The objective of this systematic review was to update our previous systematic review on warfarin drug-related interactions, with updated methods and a specific focus on patient-important outcomes.

2 | METHODS

This systematic review and meta-analysis were conducted following the requirements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[15] An internal protocol was developed a priori for the project, but the protocol was not registered on PROSPERO.

2.1 | Literature search

A search strategy was developed in consultation with a clinical research librarian. The International Pharmaceutical Abstracts (IPA), MEDLINE and EMBASE databases were searched for this update from January 2004 to August 2019 using relevant medical subject headings (MeSH) and key terms (see the Appendix for full search strategy). Reference lists of relevant systematic reviews were scanned to identify other potentially eligible studies.

2.2 | Study selection

Studies were included in the review if they: (1) were published in the English language, (2) used randomized controlled trials (RCTs) or observational designs (cohort study, case–control study or case series), (3) included at least 25 adult participants receiving warfarin, (4) provided original data reporting on an interaction between warfarin and another drug or combination of drugs available in Canada or the United States, (5) included a warfarin-only control group, (6) evaluated one or more patient-important clinical outcomes: bleeding, thromboembolic events or death, and (7) reported sufficient data to estimate effects, i.e., odds ratio (OR) and corresponding 95% confidence interval (CI) for any eligible patient-important outcome. Exclusion criteria included: (1) studies reporting on children, healthy participants, or drug–drug interactions with food/herbal or alternative medicines, and (2) reviews, commentaries, editorials, protocols, case reports, qualitative research or letters. Review and meta-analysis articles were scanned for additional relevant studies.

Following training and calibration exercises to ensure inter-rater reliability, titles and abstracts of identified citations were assessed for eligibility independently and in duplicate by paired reviewers. Potentially eligible citations were then evaluated as full-texts independently and in duplicate by paired reviewers. All disagreements were resolved by discussion or consultation with a third author.

2.3 | Quality assessment and the certainty of the evidence

We evaluated the risk of bias using the Cochrane risk of bias tool for RCTs, considering the following domains: random sequence generation, blinding of outcome assessment, blinding of participant and personnel, allocation concealment, selective reporting, incomplete outcome and other bias.[16] For observational studies, including data used from RCTs that were not subject to randomization, we applied the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS I) tool.[17] All disagreements between reviewers were resolved through consensus or consultation with a third author.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence for each outcome.[18] The results of the risk of bias for each included study were used to inform a GRADE evidence assessment.[18,19]

2.4 | Primary outcomes

The primary outcomes of the present review include: (1) clinically relevant bleeding (including major bleeding in accordance with International Society on Thrombosis and Haemostasis (ISTH) definitions, non-major clinically relevant bleeding, or bleeding which required the

patient to be hospitalized),[20] (2) thromboembolic events (including stroke or ischaemic stroke, any thromboembolic event, or any systemic thromboembolic event), and (3) all-cause mortality or cardiovascular death.

2.5 | Data extraction

Pairs of reviewers extracted the following study characteristics independently: study design, interacting drug, the sample size of interacting drug and control arms, outcome event number of each arm (if any), and length of follow-up. Interacting drugs were categorized by family (antiplatelets, antimicrobials, non-steroidal anti-inflammatory drugs [NSAIDs], antidepressants, analgesics, cardiovascular, and miscellaneous). The study design was classified as follows: (1) RCT if patients were randomly assigned to study groups which were kept intact for the analysis, (2) prospective cohort if data on outcomes were prospectively collected for the purpose of assessing warfarin drug–drug interactions, (3) retrospective cohort if the analysis was conducted using patient charts, administrative databases or secondary data from other clinical trials, or (4) case–control if patients who developed an outcome were compared with those who had not developed the outcome.

Risk statistics and associated 95% CIs for clinically relevant bleeding, thromboembolic events, and all-cause mortality or cardiovascular death were extracted. If outcomes were reported at multiple time points, only the time point closest to the start of the interacting drug was extracted. All conflicts were resolved by discussion and consensus.

2.6 | Statistical analysis

In studies where event rates were reported without risk statistics, the appropriate risk statistics were manually calculated. When risk statistics were not reported as ORs, ORs and associated 95% CI comparing warfarin plus other medication to warfarin alone were calculated for each outcome from event rates, using Review Manager 5.3. Adjusted ORs with 95% CI comparing warfarin plus other medication to warfarin alone provided in the original paper were directly used in the meta-analysis. *P*-values <0.05 were considered as statistically significant. Between-study heterogeneity was measured using Cochrane's Q-test and the Higgins I^2 statistic (*P*-value < 0.10 or I^2 > 50% was considered as statistically significant heterogeneity).[21] A random-effect model (DerSimonian and Laird method) was generally applied. However, the fixed-effect model was used where there was an absence of between-study heterogeneity (*P* > .10 or I^2 < 50%) or when the number of the analysed studies was too small to estimate the results sensibly. We performed subgroup analyses of medication families within therapeutic categories where possible to check for class effects. Results are presented with medications organized by second-level ATC codes. Forest plots were created using Revman 5.

3 | RESULTS

A total of 42 013 articles were identified through searching electronic databases, and an additional seven records were identified by cross-checking bibliographies of retrieved meta-analyses or relevant reviews. Of these, 588 articles were considered potentially eligible for full-text review, and 72 (*n* = 4 502 273) were included in the final analysis (see Figure 1).[22–93]

The characteristics and target outcomes of the included studies are listed in Table 1. We included 11 RCTs,[22–32] 5 prospective cohort studies,[33–37] 43 retrospective cohort studies,[51–93] and 13 case–control studies.[38–50] The studies included in the final analysis had been conducted in the United States (37.5%, 27/72), Canada (16.7%, 12/72), multiple countries (international studies) (6.9%, 5/72), Japan (6.9%, 5/72), Finland (5.5%, 4/72) and Australia (5.5%, 4/72). A total of 29 unique drugs or drug combinations in seven therapeutic classes were investigated (for details, see Table 1).

Data on clinically relevant bleeding, thromboembolic events and all-cause mortality were available from 68 (94.4%), 27 (37.5%) and 27 (37.5%) studies, respectively. Data on clinically relevant bleeding was available for 141 unique drugs or drug combinations in ten drug classes. There were six unique drugs or drug combinations in four drug classes for thromboembolic events, and seven unique drugs or drug combinations in five drug classes for all-cause mortality (for details, see Table 1).

3.1 | Platelet aggregation inhibitors (antiplatelet agents)

A total of 41 studies reported on antiplatelets including 730 128 patients. Of these studies, 11 (26.8%, 11/41) were RCTs.[22–32] However, the data extracted from four of the RCTs were not subject to randomization.[22,25–27] Four studies (9.8%, 4/41) were prospective cohort studies,[34–37] 24 studies (58.5%, 24/41) were retrospective cohort studies,* and two (4.9%, 2/41) were case–control studies.[49,50] Thirty-eight studies (*n* = 641 736) reported on clinically relevant bleeding, 23 (*n* = 173 393) on thromboembolic events and 27 (*n* = 125 240) on all-cause mortality.

A meta-analysis based on the data from these 38 studies showed that a higher rate of clinically relevant bleeding in the concomitant use of any antiplatelet with warfarin compared to warfarin alone (OR = 1.74; 95% CI 1.56–1.94). Similar results were found in each subgroup analysis (see Figure 2A). Nine RCTs,[23–25,27,27–32] 14 retrospective cohort studies† and one case–control study[49] were identified, which recruited a total of 478 334 patients with the use of aspirin and warfarin compared to warfarin alone. Significantly increased bleeding was observed (OR = 1.50; 95% CI 1.29–1.74). Three retrospective cohort studies[66,70,85] and one case–control study[49] reported on the risk of bleeding with the concomitant use of clopidogrel and warfarin

*50,51,55,57,64–71,75–77,81,82,84,85,87,88,90–93

†51,55,57,64,66,68,71,75,81,84,85,87,90,91

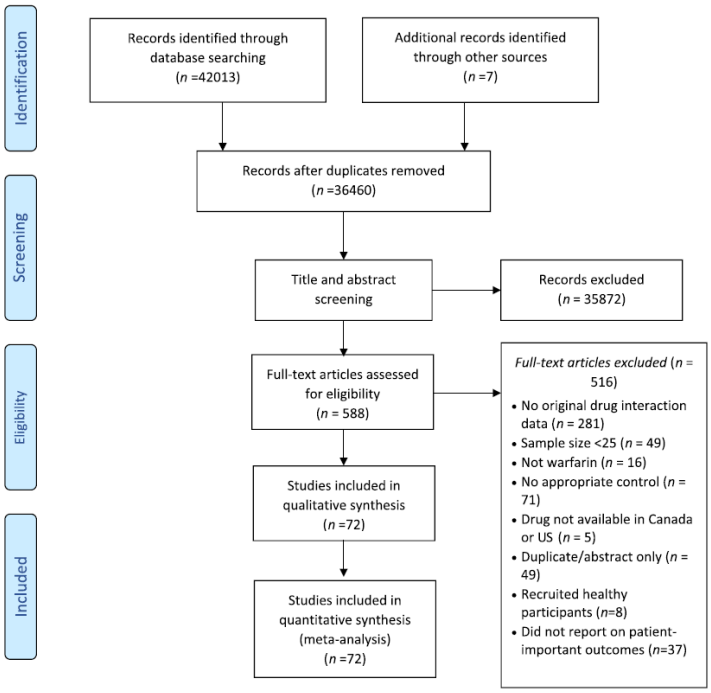

FIGURE 1 PRISMA flow diagram detailing the search strategy and result

compared to warfarin alone with an increased risk of bleeding (OR = 3.55; 95% CI 2.78–4.54). One RCT,[22] one prospective cohort study,[34] and seven retrospective cohort studies[57,64–66,85,90,91] reported on dual antiplatelet therapy (aspirin and clopidogrel or aspirin and ticlopidine). Increased bleeding with unspecified dual antiplatelet therapy and warfarin compared to warfarin alone was also detected (OR = 2.07, 95% CI 1.33–3.21). A similar increase in bleeding was also found based on the results of two RCTs,[22,26] two prospective cohort studies,[34,35] and three retrospective studies[67,77,91] for single unspecified antiplatelets and warfarin compared to warfarin alone (OR = 1.49; 95% CI 1.31–1.69). Four studies reported on the risk of bleeding with mixed antiplatelet regimens (single and dual antiplatelets of aspirin, ticlopidine, clopidogrel or dipyridamole) and warfarin to warfarin alone, with an increased risk for bleeding detected (OR = 1.75; 95% CI 1.44–2.12).[22,34,69,82]

No statistically significant difference in thromboembolic events was found with the concomitant use of any antiplatelet and warfarin compared to warfarin alone (OR = 1.22; 95% CI 0.96–1.56)[‡] (see details for the subgroup analysis in Figure 3A). Compared to warfarin alone, no significant benefit was observed with thromboembolic prevention and the concomitant use of aspirin with warfarin (OR = 1.28; 95% CI 0.93–1.75).[§] Two cohort studies detected no significant difference (OR = 0.80; 95% CI 0.51–1.25) for the occurrence of thromboembolic events with the concomitant use of dual antiplatelets and warfarin compared to warfarin alone.[34,65] The pooling of the results of one RCT, two prospective cohort studies, and one retrospective study for a single unspecified antiplatelet and warfarin compared to warfarin alone yielded no statistically significant difference (OR = 1.28; 95% CI 0.80–2.04).[26,34,35,65] One RCT and two retrospective cohort studies reported on the thromboembolic events with mixed antiplatelets (single and dual antiplatelets) and warfarin compared to warfarin alone. The pooled result shows that there is no statistical difference either (OR = 1.31; 95% CI, 0.93–1.85).[22,34,69]

There was a total of 23 studies that reported on all-cause death for the use of antiplatelet plus warfarin compared to the use of warfarin alone.[¶] According to the pooled results, compared to warfarin alone, the concomitant use of any antiplatelet with warfarin did not have a significant effect on mortality (OR = 1.15; 95% CI 0.93–1.42). Similar results were found in the subgroup analysis based on the types of antiplatelets (see details in Figure 4). For example, no significant benefit was observed in all-cause death for the concomitant use of aspirin with warfarin (OR = 1.25; 95% CI 0.88–1.78) compared to warfarin alone.[#] Four cohort studies detected no significant difference (OR = 1.21; 95% CI 0.49–3.03) for the occurrence of all-cause death

‡22–27,29–32,34–36,55,65,69,71,75,81,84,87
§23–25,27,29–32,55,71,75,81,84,87
¶22–24,28–32,34–36,51,55,64,69,71,76,77,81,84,87,88,90,92,93
#23,24,28,30–32,51,55,64,71,76,81,84,87,90

TABLE 1 Characteristics of the studies included in this review

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
RCTs (11 papers)									
Flaker et al. 2006[24]	Columbia, Canada, France, USA, and Finland	RCT	High-risk patients with nonvalvular AF	3653 (3172, 481)	Aspirin (≤100 mg daily)	16.5 months (mean)	Major bleeding	2.3% (100/3172) vs. 3.9% (25/481)	
							Thromboembolic events	1.55% (49/3172) vs. 1.7% (8/481)	
							Death	2.5% (69/3172) vs. 2.6% (13/481)	
Pengo et al. 2007[28]	Italy	RCT	Patients undergoing heart valve replacement with mechanical prosthesis	198 (104, 94)	Aspirin (100 mg daily)	2 years	Major bleeding	1.9% (2/104) vs. 4.3% (4/94)	RR 2.3 (95% CI 0.3–25.2)
							Death	0 (0/104) vs. 1.1% (1/94)	
Dong et al. 2011[23]	China	RCT	Patients undergoing mechanical heart valvular replacement	1496 (748, 748)	Aspirin (75–100 mg daily)	24 ± 9 months	Bleeding (menorrhagia, nosebleed, bleeding gums, skin ecchymosis, and cerebral haemorrhage)	3.46% (28/748) vs. 3.75% (26/748)	
							Thromboembolic events	3.6% (27/748) vs. 2.1% (16/748)	
							Death	0.4% (3/748) vs. 0.3% (2/748)	
[a]Granger et al. 2011[26]	USA	RCT	Patients with AF	9052 (6391, 2661)	Single antiplatelet (not specify dosage)	1.8 years	Bleeding (no specified)	4.7% (298/6391) vs. 6.2% (164/2661)	
							Thromboembolic events	2.7% (171/6391) vs. 3.5% (94/2661)	
[a]Patel et al. 2011[27]	45 countries	RCT	Patients with nonvalvular AF	7133 (4514, 2619)	Aspirin (not specify dosage)	Median 590 days	Major and clinically relevant nonmajor bleeding	19.7% (891/4514) vs. 21.3% (558/2619)	

(Continues)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
							Thromboembolic events	4.1% (185/4514) vs. 4.6% (121/2619)	
[a]Dans et al. 2013[22]	Philippines	RCT	Patients with AF	6022 (3696, 2326)	Aspirin or clopidogrel or both (not specify dosage)	2 years	Major bleeding	2.8% (104/3696) vs. 4.8% (112/2326)	
							Thromboembolic events	1.47% (54/3696) vs. 2.1% (49/2326)	
							Death	2.28% (83/3696) vs. 3.36% (78/2326)	
				5742 (3696, 2046)	Single antiplatelet (aspirin or clopidogrel) (not specify dosage)		Major bleeding	2.8% (104/3696) vs. 4.6% (94/2046)	
				3976 (3696, 280)	Dual antiplatelets (aspirin or clopidogrel) (not specify dosage)		Major bleeding	2.8% (104/3696) vs. 6.3% (18/280)	
[a]Giugliano et al. 2013[25]	46 countries	RCT	Patients with AF	7036 (4944, 2092)	Aspirin (not specify dosage)	2.8 years	Major bleeding	4.3% (213/4944) vs. 5.9% (124/2092)	
							Thromboembolic events	6.3% (312/4944) vs. 10.1% (212/2092)	
Wang et al. 2014[31]	China	Retrospective cohort study	Patients with postoperative AF following mechanical heart valve replacement	1016 (506510)	Aspirin (75–100 mg daily)	24 months (mean)	Bleeding (skin ecchymosis, nosebleed, bleeding gums, menorrhagia, and cerebral haemorrhage)	3.95% (20/506) vs. 3.53% (18/510)	
							Thromboembolic events	4.35% (22/506) vs. 2.16% (11/510)	
							Death	0.40% (2/506) vs. 0.20% (1/510)	

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
Shah et al. 2016[30]	USA	RCT	Patients with AF	8904 (7146, 1758)	Aspirin (mean dose 99.2 mg daily)	Not specified	Major and clinically relevant nonmajor bleeding	(891/7146, 558/1758)	
							Thromboembolic events	(185/7146, 121/1758)	
							Death	(350/7146, 282/1758)	
Xu et al. 2016[32]	USA	RCT	Patients with atrial fibrillation	6643 (4998, 1645)	Aspirin (≤100 mg daily)	1 year	Major bleeding	2.54%/year (127/4998) vs. 4.38%/year (72/1645)	
							Thromboembolic events	1.49% (74/4998) vs. 1.88%/year (31/1645)	
							Death	2.61%/year (130/4998) vs. 3.56%/year (59/1645)	
Proietti et al. 2018[29]	UK	RCT	AF patients on warfarin	3624 (2904, 720)	Aspirin (not specify dosage)	Median 568 days	Major bleeding	(97/2904) vs. (31/720)	
Prospective cohort studies (5 papers)									
Abdul-Jawad et al. 2016[34]	Canada	Prospective cohort study	Patients with AF	564 (101, 463)	Single antiplatelet (aspirin 80 to 100 mg daily or clopidogrel 75 mg daily)	13 months	Major bleeding and life-threatening bleeding	14.9% (15/101) vs. 25.5% (118/463)	HR 1.97 (95% CI 1.11–3.51)
							Thromboembolic events	5.0% (5/101) vs. 5.0% (23/463)	HR 1.10 (95% CI 0.40–3.02)
							Death	22.8% (23/101) vs. 19.2% (89/463)	HR 0.88 (95% CI 0.54–1.44)
				158 (101, 57)	Duel antiplatelets (aspirin 80 to 100 mg daily and clopidogrel 75 mg daily)		Major bleeding and life-threatening bleeding	14.9% (15/101) vs. 17.5% (10/57)	HR 1.69 (95% CI 0.63–4.54)

(Continues)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
							Thromboembolic events	7.0% (5/101) vs. 5.0% (4/57)	
							Death	22.8% (23/101) vs. 19.3% (11/57)	HR 1.86 (95% CI 0.75–4.59)
				621 (101, 520)	Aspirin, or clopidogrel, or both ((aspirin 80 to 100 mg daily and clopidogrel 75 mg daily)		Major bleeding and life-threatening bleeding	14.9% (15/101) vs. 24.4% (127/520)	HR 1.85 (95% CI 1.05–3.28)
							Thromboembolic events	7.0% (5/101) vs. 5.2% (27/520)	HR 1.25 (95% CI 0.45–3.48)
							Death	22.8% (23/101) vs. 19.2% (100/520)	HR 0.93 (95% CI 0.58–1.50)
Toyoda et al. 2008[35]	Japan	Prospective cohort study	Patients with stroke and cardiovascular diseases	1769 (1298, 471)	Single antiplatelet (aspirin, median dose, 100 mg/d, or ticlopidine; median dose, 200 mg/d, or cilostazol, median dose, 200 mg/d)	19 months (median)	Bleeding (life threatening bleeding, major bleeding and gastrointestinal bleeding)	1.4% (18/1298) vs. 2.8% (13/471)	
							Thromboembolic events	1.1% (14/1298) vs. 3.2% (15/471)	
							Death	1.3% (17/1298) vs. 1.3% (6/471)	
McGrath et al. 2014[36]	Canada	Retrospective cohort study	Patients with AF and ischemic stroke	1522 (850672)	Single antiplatelets (not specify dosage)	3.3 years (median)	Major bleeding	6.5% (55/850) vs. 8.3% (56/672)	HR 1.30 (95% CI 0.94–1.80)
							Thromboembolic events	12.2% (104/850) vs. 11.5% (77/672)	HR 0.93 (95% CI 0.71–1.24)
							Mortality	41.9% (356/850) vs. 41.8% (281/672)	HR 0.94 (95% CI 0.82–1.08)
Kumagai et al. 2017[33]	Japan	Prospective cohort study	Patients with Nonvalvular atrial fibrillation	6404 (4799, 1605)	Statin (not specify dosage)	2 years	Major bleeding	2.1% (99/4799) vs. 2.1% (33/1605)	

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
			and diabetes mellitus				Thromboembolic event	1.6% (78/4799) vs. 1.2% (19/1605)	HR 0.73 (95% CI 0.44–1.20)
							Death	2.8% (135/4799) vs. 1.6% (26/1605)	HR 0.57 (95% CI 0.38–0.87)
Saito et al. 2015[37]	Japan	Prospective cohort study	Outpatients with AF	30 (21, 9)	Antiplatelets (not specified)	1 year	Cerebral microbleeds	23.8% (5/21) vs.33.3% (3/9)	
Retrospective cohort studies (43 papers)									
Shireman et al. 2004[82]	USA	Retrospective cohort study	Patients discharged with AF	10 093 (8131,1962)	Single antiplatelet (aspirin and clopidogrel or ticlopidine, or ticlopidine alone without dosage)	90 days	Major bleeding (intracranial haemorrhage and gastrointestinal bleed)		OR 1.53 (95% CI 1.05–2.22)
Buresly et al. 2005[57]	Canada	Retrospective cohort study	Elderly survivors of acute myocardial infarction	3721 (3314, 407)	Aspirin (most received 300–325 mg/d)	654 days (mean)	Bleeding (not specified)	5.9% (195/3314) vs. 8.4% (34/407)	OR 1.84 (95% CI 1.23–2.76)
				215 (195, 20)	Dual antiplatelets (aspirin and clopidogrel, or aspirin and ticlopidine)			5.9% (12/195) vs. 8.3% (1/12)	
Chung et al. 2005[59]	USA	Retrospective cohort study	Patients on warfarin	1145 (1022, 123)	Selective NSAIDs (celecoxib 100 or 200-mg capsule used once or twice a day or as needed)	n/a	Major bleeding	1.5% (15/1022) vs. 0.8% (1/123)	RR 1.04 (95% CI 0.14–7.85)
Berlowitz et al. 2006[52]	USA	Retrospective cohort study	Chronic heart failure patients on warfarin (66988)	48 520 (29 136, 19 384)	Beta-blocker (metoprolol without dosage specified)	2.2 years	Bleeding (not specified)	3.8% (1095/29136) vs. 4.6% (894/19384)	
				38 114 (29 136, 8978)	Beta-blocker (atenolol			3.8% (1095/29136)	

(Continues)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
					without dosage specified)			vs. 4.0% (357/8978)	
				38 626 (29 136, 9490)	Beta-blocker (carvedilol without dosage specified)			3.8% (1095/29136) vs. 2.4% (225/9490)	
Zhang et al. 2006[89]	USA	Retrospective cohort study	Warfarin users	9926 (9147, 779)	Metronidazole (not specify dosage)	7 days	Bleeding (not specified)	14.2% (1289/9147) vs. 22.7% (177/779)	
				12 532 (9147, 3385)	Cephalosporin (not specify dosage)			14.1% (1289/9147) vs. 17.2% (583/3385)	
				14 053 (9147, 4906)	NSAID/COX-2 (not specify dosage)			14.1% (1289/9147) vs. 14.3% (700/4906)	
				9908 (9147, 761)	Fibric acid derivatives (not specify dosage)			14.1% (1289/9147) vs. 13.1% (100/761)	
				10 407 (9147, 1260)	Amiodarone (not specify dosage)			14.1% (1289/9147) vs. 14.8% (186/1260)	
Holden et al. 2008[68]	Canada	Retrospective cohort study	Haemodialysis patients	139 (89, 50)	Aspirin (not specify dosage)	3.6 years (median)	Major bleeding	5.6% (5/89) vs. 10.0% (5/50)	
Johnson et al. 2008[69]	USA	Retrospective cohort study	Patients with warfarin therapy	4183 (2560, 1623)	Antiplatelets (aspirin, clopidogrel, dipyridamole, or dipyridamole/aspirin, not specify dosage)	6 months	Anticoagulation-related major haemorrhage	0.9% (23/2560) vs. 2.0% (32/1623)	OR 2.06 (95% CI 1.01–4.36)
							Thromboembolic events	0.4% (9/2560) vs. 0.1% (5/1623)	OR 1.48 (95% CI 0.43–5.08)
							Death	0.2% (6/2560) vs. 0.3% (1/1623)	OR 0.18 (95% CI 0.02–1.80)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
Cheetham et al. 2009[58]	USA	Retrospective cohort study	Patients on warfarin	44 613 (36 444, 8169)	Non-selective NSAIDs (not specify dosage)	5 years	Gastrointestinal bleeding that resulted in hospitalization	0.7% (255/36444) *vs.* 2.7% (225/8169)	
				38 045 (36 444, 1601)	Selective NSAIDs (COX-2 inhibitors without specified dosage)			0.7% (255/36444) *vs.* 1.2% (19/1601)	
Hauta-Aho et al. 2009[47]	Finland	Retrospective cohort study	Warfarin-treated in-patients	4010 (3614, 396)	Single antiplatelet (aspirin, dipyridamole, clopidogrel, or ticlopidine without specified dosage)	8.5 years	All bleeding	1.5% (53/3614) *vs.* 3.3% (13/396)	
				4681 (3614, 1067)	Non-selective NSAIDs (no specify dosage)			1.5% (53/3614) *vs.* 4.1% (44/1067)	
				3836 (3614, 222)	Coxib (no specify dosage)			1.5% (53/3614) *vs.* 5.4% (12/222)	
				4442 (3614, 828)	SSRIs (no specify dosage)			1.5% (53/3614) *vs.* 4.2% (35/828)	
				3813 (3614, 199)	Non-SSRIs (no specify dosage)			1.5% (53/3614) *vs.* 2.0% (4/199)	
				5021 (3614, 1407)	CYP2C9 inhibitor (not specify dosage)			1.5% (53/3614) *vs.* 7.4% (104/1407)	
Wallerstedt et al. 2009[46]	Sweden	Retrospective cohort study	Patients on warfarin	234 (117, 117)	SSRIs (not specify dosage)	Control: 584.6 patient-years; intervention: 213.9 patient-years	Clinically relevant bleeding	8.5% (10/117) vs. 9.4% (17/117)	HR 3.49 (95% CI 1.37–8.91)

(Continues)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
Hansen et al. 2010[66]	Denmark	Retrospective cohort study	Patients with AF	111 204 (93 492, 17 712)	Aspirin (75 mg daily)	3.3 ± 2.6 years (mean)	Bleeding (not specified)	3.9% (3642/93492) vs. 6.9% (1209/17712)	HR 1.83 (95% CI 1.72–1.96)
				93 988 (93 492, 496)	Clopidogrel (75 mg daily)			3.9% (3642/93492) vs. 13.9% (69/496)	HR 3.08 (95% CI 2.32–3.91)
				93 900 (93 492, 408)	Dual antiplatelets (aspirin and clopidogrel without specified dosage)			3.9% (3642/93492) vs. 15.7% (64/408)	HR 3.70 (95% CI 2.89–4.76)
Launiainen et al. 2010[74]	Finland	Retrospective cohort study	Warfarin-positive cases	267 (214, 53)	Paracetamol (not specify dosage)	1 year	Major bleeding	12.6% (27/214) vs. 34.0% (18/53)	RR 2.7, $P < .05$
				228 (214, 14)	Tramadol (not specify dosage)			12.6% (27/214) vs. 28.6% (4/14)	RR 2.3, $P > .05$
Yuan et al. 2010[88]	USA	Retrospective cohort study	Patients with heart failure	5266 (3581, 1685)	Single and dual antiplatelets (aspirin, clopidogrel, or both without specified dosage)	12 months	All-cause death	10.0% (358/3581) vs. 6.5% (109/1685)	
Cochran et al. 2011[62]	USA	Retrospective cohort study	Warfarin-treated patients	100 (75, 25)	SSRIs (not specify dosage)	6 months	Major bleeding	5.3% (4/75) vs. 20% (5/25)	OR 4.4 (95% CI 1.1–18.0)
				100 (54, 46)	Any depressants (not specify dosage)			6% (3/54) vs. 13% (5/46)	OR 2.6 (95% CI 0.6–11)
Vitry et al. 2011[85]	Australia	Retrospective cohort study	Veterans who used warfarin	11 892 (11 042, 850)	Aspirin (not specify dosage)	28 days	Bleeding-related hospitalizations	4.1% (453/11042) vs. 5.9% (50/850)	RR 1.44 (95% CI 1.00–2.07)
				11 329 (11 042, 287)	Clopidogrel (not specify dosage)			4.1% (453/11042) vs. 9.8% (28/287)	RR 2.23 (95% CI 1.48–3.36)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
				11 088 (11 042, 46)	Dual antiplatelet (aspirin and clopidogrel not specify dosage)			4.1% (453/11042) vs. 17.4% (8/46)	RR 3.44 (95% CI 1.28–9.23)
				11 176 (11 042, 134)	Aspirin and NSAIDs (antiplatelet +others without specified dosage)			4.1% (453/11042) vs. 4.5% (6/134)	RR 2.5 (95% CI 0.88–7.10)
				11 087 (11 042, 45)	Clopidogrel and NSAIDs (not specify dosage)			4.1% (453/11042) vs. 11.1% (5/45)	RR1.01 (95% CI 0.40–2.53)
				11 071 (11 042, 29)	Co-trimoxazole or trimethoprim (not specify dosage)			4.1% (453/11042) vs. 20.7% (6/29)	RR 5.08 (95% CI 2.00–12.88)
				11 090 (11 042, 48)	Macrolides (not specify dosage)			4.1% (453/11042) vs. 12.5% (6/48)	RR 3.07 (95% CI 1.37–6.90)
				11 358 (11 042, 316)	Antibiotics (not specify dosage)			4.1% (453/11042) vs. 10.1% (32/316)	RR 2.34 (95% CI 1.55–3.54)
				11 651 (11 042, 609)	Selective NSAIDs (celecoxib without specified dosage)			4.1% (453/11042) vs. 4.4% (27/609)	RR 1.07 (95% CI 0.69–1.68)
				12 422 (11 042, 1380)	NSAIDs (not specify dosage)			4.1% (453/11042) vs. 5% (69/1380)	RR 1.19 (95% CI 0.90–1.59)
				11 088 (11 042, 46)	SSRIs (not specify dosage)			4.1% (453/11042) vs. 8.7% (4/46)	RR 2.17 (95% CI 0.81–5.78)
				11 106 (11 042, 64)	Tramadol (not specify dosage)			4.1% (453/11042) vs. 9.4% (6/64)	RR 2.37 (95% CI 0.93–6.01)
				11 080 (11 042, 38)	Amiodarone (not specify dosage)			4.1% (453/11042) vs. 13.2% (5/38)	RR 3.33 (95% CI 1.38–8.0)
				11 121 (11 042, 79)	Thyroid hormones (not specify dosage)			4.1% (453/11042) vs. 8.9% (7/79)	RR 1.66 (95% CI 0.66–4.16)

(Continues)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
Amad et al. 2012[51]	Canada	Retrospective cohort study	Acute coronary syndromes patients	955 (593, 362)	Aspirin (not specify dosage)	n/a	Major bleeding	3.6% (21/593) vs. 1.7% (6/362)	
							Death	6.9% (41/593) vs. 3.6% (13/362)	
Fosbol et al. 2012[64]	USA	Retrospective cohort study	Patients with acute non–ST-segment elevation MI	1834 (563, 1271)	Aspirin (not specify dosage)	1 year	Bleeding-related hospitalizations	13.9% (78/563) vs. 14.3% (182/1271)	
							Death	29.3% (165/563) vs. 25.4% (323/1271)	
				1294 (563731)	Aspirin and clopidogrel (not specify dosage)		Bleeding-related hospitalizations	13.9% (78/563) vs. 14.9% (109/731)	
							Death	29.3% (165/563) vs. 18.2% (133/731)	
Lam et al. 2013[72]	Canada	Retrospective cohort study	Patients with warfarin therapy	14 248 (7124, 7124)	Amiodarone (not specify dosage)	30 days	Bleeding-related hospitalizations	0.3% (23/7124) vs. 0.8% (56/7124)	HR 2.45 (95% CI 1.49–4.02)
Clark et al. 2014[41]	USA	Retrospective cohort study	Patients receiving warfarin	12 006 (6149 vs. 5857)	Oral antibiotics (not specify dosage)	30 days	Clinically relevant bleeding	0.5% (28/6149) vs. 0.7% (39/5857)	
							Thromboembolic events	0.08% (5/6149) vs. 0.1% (6/5857)	
							All-cause death	0.4% (25/6149) vs. 0.5% (29/5857)	
Flaker et al. 2014[63]	International study	Retrospective cohort study	Patients with AF	8944 (7902, 1042)	Amiodarone (not specify dosage)	21.8 months (mean)	Major and clinically relevant nonmajor bleeding	5.0% (397/7902) vs. 4.9% (51/1042)	
							Thromboembolic events	2.9% (227/7902) vs. 3.4% (35/1042)	

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
							All-cause death	6.9% (546/7902) vs. 10.5% (109/1042)	
Lane et al. 2014[73]	USA	Retrospective cohort study	Patients on warfarin	22 272 (20 294, 1708)	Cotrimoxazole (not specify dosage)	n/a	Bleeding-related hospitalizations	0.6% (115/20294) vs. 0.8% (14/1708)	
				22 272 (17 893, 4379)	Ciprofloxacin (not specify dosage)			0.6% (99/17893) vs. 0.7% (30/4379)	
				22 272 (19 740, 2532)	Levofloxacin (not specify dosage)			0.6% (118/19740) vs. 0.4% (11/2532)	
				22 272 (21 982, 290)	Fluconazole (not specify dosage)			0.5% (126/21982) vs. 1.0% (3/290)	
				22 272 (16 514, 5758)	Azithromycin (not specify dosage)			0.6% (96/16514) vs. 0.6% (33/5758)	
				22 272 (21 789, 483)	Clarithromycin (not specify dosage)			0.6% (127/21789) vs. 0.6% (2/483)	
				22 272 (15 677, 6595)	Cephalexin (not specify dosage)			0.6% (95/15677) vs. 0.5% (34/6595)	
				22 272 (20 399, 1873)	Clindamycin (not specify dosage)			0.6% (118/20399) vs. 0.6% (11/1873)	
Lopponen et al. 2014[76]	Finland	Retrospective cohort study	Patients primary intracerebral haemorrhage	157 (140, 17)	Aspirin (not specify dosage)	30 days	Death	50.7% (71/140) vs. 58.8% (10/17)	HR 2.20 (95% CI 0.86–5.64)
				159 (140, 19)	Mixed antidepressants (citalopram, escitalopram, fluoxetine, mirtazapine, or paroxetine without specified dosage)			50.7% (71/140) vs. 78.9% (15/19)	HR 2.10 (95% CI 1.13–3.92)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
Quinn et al. 2014[78]	USA	Retrospective cohort study	Patients with AF	30 949 (30 028, 921) (30 028, 1939)	TCAs (not specify dosage) SSRIs (not specify dosage)	6 years (median)	Major bleeding	1.3% (404/30028) *vs.* 1.3% (12/921) 1.3% (404/30028) *vs.* 2.3% (45/1939)	RR 0.82 (95% CI 0.46–1.46) RR 1.41 (95% 1.04–1.92)
Santos et al. 2014[80]	Brazil	Retrospective cohort study	Patients treated with warfarin for at least 12 months	866 (755, 111)	Amiodarone (23.8 ± 11.3 mg/week)	6.4 years (mean)	Major bleeding	2.5% (19/755) *vs.* 1.8% (2/111)	RR 0.71 (95% CI 0.17–3.03)
Steinberg et al. 2014[83]	USA, Germany, UK	Retrospective cohort study	Patients with nonvalvular AF at high risk of stroke	6779 (6221, 558)	Amiodarone (200–300 mg daily)	23.6 months	Major and clinically relevant nonmajor bleeding Thromboembolic events	20.3% (1261/6221) *vs.*16.5% (92/558) 4.5% (279/6221) *vs.* 2.7% (15/558)	
Ghanbari et al. 2015[65]	USA	Retrospective cohort study	Patients with atrial fibrillation and coronary artery disease who underwent implantable cardioverter defibrillator implantation	13 258 (5264,7994) 7234 (5264,1970)	Single antiplatelet (aspirin, clopidogrel, or ticlopidine without specified dosage) Dual antiplatelet agents (aspirin and clopidogrel, or aspirin and ticlopidine without specified dosage)	30 days	Bleeding (not specified) Thromboembolic events Bleeding (not specified) Thromboembolic events	1.7% (90/5264) *vs.* 2.4% (188/7994) 1.5% (79/5264) *vs.* 1.2% (99/7994) 1.7% (90/5264) *vs.* 3.6% (71/1970) 1.5% (79/5264) *vs.* 1.1% (22/1970)	HR 1.41(95% CI 1.10–1.82) HR 0.83 (95% CI 0.62–1.11) HR 2.18 (95% CI 1.60–2.98) HR 0.73 (95% CI 0.45–1.16)
Bjorck et al. 2016[55]	Sweden	Retrospective cohort study	Patients with nonvalvular AF	39 162 (34 851, 4311)	Aspirin (not specify dosage)	n/a	Major bleeding	3.14% (1094/34851) *vs.* 6.4% (274/4311)	

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
Narum et al. 2016[77]	Norway	Retrospective cohort study	Head trauma patients	57 (53, 4)	Single antiplatelet (not specify dosage)	30 days	Thromboembolic events All-cause death Death	3.3% (1136/34851) vs. 10.1% (437/4311) 3.27% (1143/34851) vs. 5.31% (229/4311) 28.3% (15/53) vs. 50% (2/4)	
Watanabe et al. 2016[87]	Japan	Retrospective cohort study	Patients with AF	6074 (5046, 1025)	Aspirin (not specify dosage)	2 years	Major bleeding Thromboembolic events All-cause death	1.8% (92/5046) vs. 3.0% (31/1025) 1.5% (75/5046) vs. 1.3% (13/1025) 2.2% (109/5046) vs. 3.2% (33/1025)	RR 1.67 (95% CI 1.11–2.50) RR 0.85 (95% CI 0.47–1.53) RR 1.50 (95% CI 1.02–2.21)
Cieri et al. 2017[60]	USA	Retrospective cohort study	Patients after major orthopedic surgery	2380 (1118, 1262)	Enoxaparin (30 mg twice/day and 40 mg/day started 12 hours before surgery)	n/a	Major bleeding Thromboembolic events	0.4% (5/1118) vs. 0.4% (5/1262) 0.4% (5/1118) vs. 0.2% (2/1262)	
Lai et al. 2017[71]	Taiwan	Retrospective cohort study	Dialysis patients with atrial fibrillation and high thromboembolic risk	246 (31, 215)	Aspirin	54.6 ± 30.5 months	Bleeding (hemorrhagic stroke and gastrointestinal bleeding) Thromboembolic events Death	48.3% (15/31) vs. 39.1% (84/215) 9.7% (3/31) vs. 14.4% (31/215) 45.2% (14/31) vs. 41.4% (89/215)	
Lee et al. 2017[75]	Denmark	Retrospective cohort study	Patients with first-time myocardial infarction and AF	46 501 (37 539, 8962)	Aspirin (not specify dosage)	n/a	Bleeding (not specified)	7.1% (2684/37539) vs. 13.9% (1244/8962)	

(Continues)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
							Thromboembolic events	4.8% (1768/37539) vs. 5.9% (527/8962)	
Van Tuyl et al. 2017[84]	USA	Retrospective cohort study	Patients with a HeartMate II left ventricular assist device	76 (32, 44)	Aspirin (81 mg daily)	n/a	Bleeding (actionable and fatal)	21.9% (7/32) vs. 22.7% (10/44)	
							Thromboembolic events	9.4% (3/32) vs. 11.4% (5/44)	
							Death	9.4% (3/32) vs. 4.5% (2/44)	
Bernaitis et al. 2018[53]	Australia	Retrospective cohort study	Patients receiving warfarin for non-valvular AF	3196 (1365, 1831)	Statin (not specify dosage)	6 months	Major bleeding	0.7% (10/1365) vs. 0.8% (15/1831)	
	Singapore			1170 (311, 859)				2.3% (7/311) vs. 0.8% (7/859)	
Boyce et al. 2018[56]	Australia	Retrospective cohort study	Patients receiving warfarin management for AF and DVT	1116 (1065, 51)	Non-selective NSAIDs (not specify dosage)	n/a	Major bleeding	7.1% (76/1065) vs.13.7% (7/51)	
				1100 (1065, 35)	Selective NSAIDs (not specify dosage)			7.1% (76/1065) vs. 11.4% (4/35)	
Inohara et al. 2018[93]	USA	Retrospective cohort study	Intracerebral haemorrhage among patients on warfarin	14 639 (9777, 4862)	Single antiplatelet agent (not specify dosage)	n/a	Death	31.7% (3101/9777) vs. 33.2% (1615/4862)	OR 1.17 (95% CI 1.07–1.28)
				10 174 (9777, 397)	Dual antiplatelet agents (not specify dosage)			31.7% (3101/9777) vs. 47.1% (187/397)	OR 2.13 (95% CI 1.66–2.73)
Gulati et al. 2018[90]	Norway	Retrospective cohort	Users of antithrombotic medications	206 118 (151 966, 54 152)	Aspirin (not specify dosage)	6 years	Intracranial haemorrhage	0.55% (836/151966) vs. 0.75% (406/54152)	
				4964 (4701, 263)			Death	30.3% (1423/4701) vs. 37.6% (99/263)	

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
				159 648 (151 966, 7682)	Dual antiplatelets (aspirin + Clopidogrel without specified dosage)		Intracranial haemorrhage	0.55% (836/151966) vs. 0.85% (65/7682)	
				4718 (4701, 17)			Death	30.3% (1423/4701) vs. 52.9% (9/17)	
Korhonen et al. 2018[70]	Finland	Retrospective cohort study	Patients receiving warfarin	150 847 (92 265, 58 582)	Statins (not specify dosage)		Bleeding-related hospitalizations	1.3% (1218/92265) vs. 1.4% (822/58582)	
				92 674 (92 265, 409)	Clopidogrel (not specify dosage)			1.3% (1218/92265) vs. 5.4% (22/409)	
				93 936 (92 265, 1671)	Clopidogrel + statins (not specify dosage)			1.3% (1218/92265) vs. 3.4% (57/1671)	
Ray et al. 2018[79]	USA	Retrospective cohort study	Patients using individual anticoagulants	813 413 (668 519, 144 914)	Proton pump inhibitors (not specify dosage)		Hospitalization for upper gastrointestinal bleeding	1.13% (7574/668519) vs. 0.74% (1072/144914)	
Bertram et al. 2019[54]	Australia	Retrospective cohort study	Patients receiving warfarin management for AF and DVT	4494 (2493, 2001)	Proton pump inhibitors (not specify dosage)	n/a	Major bleeding	2.4% (60/2493) vs. 1.7% (35/2001)	
Kim et al. 2019[71]	South Korea	Retrospective cohort study	Patients with AF	2500 (1493, 1007)	Aspirin (not specify dosage)	4 years	Vitreous haemorrhage	0.5% (7/1493) vs. 1.1% (11/1007)	
				1654 (1493, 161)	P2Y12 inhibitors (clopidogrel bisulfate, prasugrel, and ticagrelor without specified dosage)			0.5% (7/1493) vs. 0.6% (1/161)	

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TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
				1818 (1493, 325)	Aspirin + P2Y12 inhibitors (not specify dosage)			0.5% (7/1493) vs. 1.8% (6/325)	
LaDuke et al. 2019[92]	USA	Retrospective cohort study	Traumatically injured patients	5748 (3855, 1893)	Antiplatelets (not specify dosage)	5 years	Death	6.2% (240/3855) vs. 8.7% (165/1893)	
Schaefer et al. 2019[81]	USA	Retrospective cohort study	Patients treated with warfarin	3688 (1844, 1844)	Aspirin (≤100 mg daily)	Median 12.8 months	Major bleeding	3.3% (61/1844) vs. 5.7% (105/1844)	
							Thromboembolic events	2.7% (50/1844) vs. 2.3% (42/1844)	
							Death	4.4% (81/1844) vs. 3.7% (68/1844)	
Case control studies (13 papers)									
Battistella et al. 2005[39]	Canada	Case control study	Older patients receiving warfarin	Cases: 17/361; controls: 344/1437	Ocular antibiotics (not specify dosage)	90 days	Upper gastrointestinal bleeding		OR 0.90 (95% CI 0.70–1.3)
				Cases: 24/361; controls: 337/1437	Non-selective NSAIDs (not specify dosage)				OR 1.90 (95% CI 1.40–3.70)
				Cases: 25/361; controls: 336/1437	Selective NSAIDs (Rofecoxib without specified dosage)				OR 2.4 (95% CI 1.7–3.6)
				Cases: 22/361; controls: 339/1437	Selective NSAIDs (celecoxib without specified dosage)				OR 1.70 (95% CI 1.20–3.60)
Kurdyak et al. 2005[42]	Canada	Case control study	Patients with upper gastrointestinal tract bleeding	Cases: 95/1538; controls: 655/15196	SSRIs (not fluoxetine or fluvoxamine without	90 days	Upper gastrointestinal bleeding	9.0% (1443/15984) vs. 12.7% (95/750)	RR 1.1 (95% CI 0.9–1.4)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
					specified dosage)				
				Cases: 41/1538; controls: 245/15196	SSRIs (fluoxetine and fluvoxamine without specified dosage)			9.1% (1497/16448) vs. 14.3% (41/286)	RR 1.2 (95% CI 0.8–1.7)
				Cases: 10/1538; controls: 104/15196	TCAs (not specify dosage)			9.2% (1528/16620) vs. 8.8% (10/114)	RR 0.70 (95% CI 0.40–1.40)
Stroud et al. 2005[48]	Canada	Case control study	Elderly patients on warfarin	Cases: 31/4269; controls: 50/17048	Cefuroxime (not specify dosage)	14 days	Hospitalizations for haemorrhage		OR 1.62 (95% CI 1.28–2.26)
				Cases: 43/4269; controls: 155/17048	Ocular antibiotics (not specify dosage)				OR 0.93 (95% CI 0.77–1.10)
				Cases: 12/4269; controls: 16/17048	Levofloxacin (not specify dosage)				OR 1.21 (95% CI 0.84–2.01)
Douketis et al. 2007[40]	Canada	Case control study	Patients receiving warfarin	Cases: 1518; controls: 15100	Statin (not specify dosage)	2 years	Bleeding (upper gastrointestinal bleed or intracranial bleed)		OR 0.91 (95% CI 0.77–1.07)
Schelleman et al. 2008[45]	USA	Case control	Warfarin users	Cases: 35/11444; controls: 865/568744	Fluconazole (not specify dosage)	5 days	Hospitalization for gastrointestinal bleeding		OR 1.55 (95% CI 1.10–2.20)
				Cases: 104/11444; controls: 3022/568744	Cephalexin (not specify dosage)				OR 1.61 (95% CI 1.32–1.96)
				Cases: 75/11444; controls 2226/568744	Co-trimoxazole (not specify dosage)				OR 1.46 (95% CI 1.16–1.85)

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TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
				Cases: 112/11444; Controls 3907/568744	Amoxicillin (not specify dosage)				OR 1.36 (95% CI 1.12–1.64)
				Cases: 214/11444; controls 3737/568744	Levofloxacin (not specify dosage)				OR 2.23 (95% CI 1.94–2.57)
				Cases: 150/11444; controls 3069/568744	Ciprofloxacin (not specify dosage)				OR 2.05 (95% CI 1.74–2.43)
				Cases: 21/11444; controls 330/568744	Gatifloxacin (not specify dosage)				OR 2.43 (95% CI 1.55–3.81)
Fischer et al. 2010[41]	Canada	Patients on warfarin	Case control	Cases 25/2151; controls 56/21434	Co-trimoxazole (not specify dosage)		Upper gastrointestinal bleeding		OR 3.84; (95% CI 2.33–6.33)
				Cases 31/2151; controls 124/21434	Ciprofloxacin (not specify dosage)				OR 1.94 (95% CI 1.28–2.95)
				Cases 30/2151; controls 209/21434	Amoxicillin or ampicillin (not specify dosage)				OR 1.37 (95% CI 0.92–2.05)
				Cases 11/2151; controls 64/21434	Nitrofurantoin (not specify dosage)				OR 1.40 (95% CI 0.71–2.75)
				Cases 10/2151; controls 81/21434	Ocular antibiotics (not specify dosage)				OR 0.99 (95% CI 0.50–1.93)
				Cases 5/2151; controls 61/21434	Norfloxacin (not specify dosage)				OR 0.38 (95% CI 0.12–1.26)
Schelleman et al. 2010[46]	USA	Case control study	Warfarin users	Cases: 499/12193; controls: 32089/609650	Statins (atorvastatin without specified dosage)	30 days	Gastrointestinal bleeding		OR 1.29 (95% CI 1.04–1.61)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
				Cases: 16/12193; controls: 1835/609650	Statins (Fluvastatin without specified dosage)				OR 1.45 (95% CI 0.68–3.09)
				Cases: 113/12193; controls: 8652/609650	Statins (pravastatin without specified dosage)				OR 0.66 (95% CI 0.38–1.14)
				Cases: 277/12193; controls: 14909/609650	Statins (simvastatin without specified dosage)				OR 1.33 (95% CI 1.00–1.78)
				Cases: 39/12193; controls: 2117/609650	Fenofibrate (not specify dosage)				OR 2.07 (95% CI 0.91–4.69) Data for 31–60 days used due to no data for 1–30 days
				Cases: 67/12193; controls: 3010/609650	Gemfibrozil (not specify dosage)				OR 1.96 (95% CI 1.19–3.24)
Schelleman et al. 2011[47]	USA	Case control study	Warfarin users	Cases: 316/13026; controls: 13850/653209	SSRIs (sertraline without specified dosage)	29 days	Gastrointestinal bleeding		OR 1.18 (95% CI 0.90–1.56)
				Cases: 258/13026; controls: 11932/653209	SSRIs (paroxetine without specified dosage)				OR 1.64 (95% CI 1.27–2.12)
				Cases: 162/13026; controls: 7314/653209	SSRIs (citalopram without specified dosage)				OR 1.73 (95% CI 1.25–2.38)
				Cases: 146/13026; controls: 7109/653209	SSRIs (Escitalopram without specified dosage)				OR 1.19 (95% CI 0.82–1.71)

(Continues)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
				Cases: 114/13026; controls: 5490/653209	SSRIs (fluoxetine without specified dosage)				OR 1.63 (95% CI 1.11–2.38)
				Cases: 122/13026; controls: 5001/653209	TCAs (amitriptyline without specified dosage)				OR 1.47 (95% CI 1.02–2.11)
				Cases: 20/13026; controls: 1147/653209	TCAs (nortriptyline without specified dosage)				OR 1.45 (95% CI 0.68–3.12)
				Cases: 152/13026; controls: 6538/653209	Mirtazapine (not specify dosage)				OR 1.75 (95% CI 1.30–2.35)
				Cases: 77/13026; controls: 4133/653209	Venlafaxine (not specify dosage)				OR 1.43 (95% CI 0.88–2.31)
Baillargeon et al. 2012[38]	USA	Case control study	Older patients receiving warfarin	Cases: 17/798; controls: 8/2394	Azole antifungals (not specify dosage)	1 year	Hospitalization for bleeding		OR 4.57 (95% CI 1.90–11.03)
				Cases: 36/798; controls: 39/2394	Cephalosporin (not specify dosage)				OR 2.45 (95% CI 1.52–3.95)
				Cases: 22/798; controls: 22/2394	Co-trimoxazole (not specify dosage)				OR 2.70 (95% CI 1.46–5.05)
				Cases: 24/798; controls: 35/2394	Macrolides (not specify dosage)				OR 1.86 (95% CI 1.08–3.21)
				Cases: 40/798; controls: 56/2394	Quinolones (not specify dosage)				OR 1.69 (95% CI 1.09–2.62)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
				Cases: 31/798; controls: 50/2394	Penicillin (not specify dosage)				OR 1.92 (95% CI 1.21–2.07)
Pincus et al. 2012[44]	Canada	Case control study	Older patients receiving warfarin	Cases 21/10532; controls 63/40693	Levothyroxine (not specify dosage)	30 days	Hospitalization for bleeding		OR 1.11 (95% CI 0.67–1.86)
Suh et al. 2012[20]	South Korea	Case control study	Patients on warfarin	Cases 95/744; controls 195/2484	Antiplatelets (not specify dosage)	30 days	Bleeding (not specified)		OR 1.56 (95% CI 1.18–1.68)
				Cases 93/744; controls 238/2484	Antidepressants (not specify dosage)				OR 1.28 (95% CI 0.97–1.55)
				Cases 164/744; controls 421/2484	Analgesics (not specify dosage)				OR 1.33 (95% CI 1.07–2.24)
				Cases 42/744; controls 137/2484	Antiarrhythmics (not specify dosage)				OR 1.07 (95% CI 0.74–3.04)
				Cases 226/744; controls 766/2484	Anti-hypertensive agents (not specify dosage)				OR 0.87 (95% CI 0.71–1.19)
				Cases 273/744; controls 777/2484	Lipid-lowering agents (not specify dosage)				OR 1.18 (95% CI 0.98–1.06)
				Cases 141/744; controls 292/2484	Anti-infectives (not specify dosage)				OR 1.76 (95% CI 1.39–2.13)
				Cases 168/744; controls 520/2484	Gastrointestinal agents (not specify dosage)				OR 0.96 (95% CI 0.78–1.65)
				Cases 117/744; controls 414/2484	Thyroids and antithyroid (not specify dosage)				OR 0.89 (95% CI 0.70–2.07)

(Continues)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
Nagata et al. 2015[43]	Japan	Case control study	Patients with lower GI bleeding (LGIB)	Case 20/355: control 95/8221	Proton pump inhibitor (not specify dosage)		Lower gastrointestinal bleeding		OR 1.10 (95% CI 0.40–3.07)
Kean et al. 2018[49]	USA	Case control study	Patients who experienced major bleeding events	Case 62/769: vs. control 15/769	Oxycodone (not specify dosage)	30 days prior to the reference date	Major bleeding		OR 4.5 (95% CI 2.6–8.2)
				Case 37/769: vs. control 12/769	Prochlorperazine (not specify dosage)				OR 3.4 (95% CI 1.8–6.8)
				Case 41/769: vs. control 13/769	Levofloxacin (not specify dosage)				OR 3.3 (95% CI 1.8–6.6)
				Case 23/769: vs. control 7/769	Guaifenesin (not specify dosage)				OR 3.3 (95% CI 1.5–8.3)
				Case 16/769: vs. control 5/769	Clopidogrel (not specify dosage)				OR 3.3 (95% CI 1.3–10.1)
				Case 36/769: vs. control 12/769	Oxybutynin chloride (not specify dosage)				OR 3.1 (95% CI 1.7–6.3)
				Case 15/769: vs. control 5/769	Pregabalin (not specify dosage)				OR 3.1 (95% CI 1.2–9.7)
				Case 26/769: vs. control 9/769	Gemfibrozil (not specify dosage)				OR 3.0 (95% CI 1.4–6.7)
				Case 15/769: vs. control 6/769	Baclofen (not specify dosage)				OR 2.8 (95% CI 1.1–8.1)
				Case 17/769: vs. control 6/769	Calcitriol (not specify dosage)				OR 2.8 (95% CI 1.2–7.9)
				Case 32/769: vs. control 12/769	Metolazone (not specify dosage)				OR 2.7 (95% CI 1.4–5.6)
				Case 10/769: vs. control 2/769	Amoxicillin Clavulanate (not specify dosage)	Within 14 days of the reference date			OR 5.6 (95% CI 1.5–36.7)
				Case 120/769: *vs.* control 53/769	Ferrous sulfate (not specify dosage)	30 days prior to the reference date			OR 2.5 (95% CI 1.8–3.6)
				Case 17/769: vs. control 7/769	Ibuprofen (not specify dosage)				OR 2.4 (95% CI 1.1–6.4)
				Case 16/769: vs. control 3/769					OR 5.3 (95% CI 1.8–23.1)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
					Acetaminophen (not specify dosage)	Within 14 days of the reference date			
				Case 17/769; vs. control 3/769	Hydrocodone-acetaminophen (not specify dosage)				OR 5.8 (95% CI 1.9–25.0)
				Case 30/769; vs. control 14/769	Cephalexin (not specify dosage)	30 days prior to the reference date			OR 2.2 (95% CI 1.2–4.3)
				Case 40/769; vs. control 20/769	Ondansetron (not specify dosage)				OR 2.1 (95% CI 1.2–3.7)
				Case 34/769; vs. control 17/769	Glimepiride (not specify dosage)				OR 2.0 (95% CI 1.1–3.8)
				Case 28/769; vs. control 14/769	Paroxetine (not specify dosage)				OR 2.0 (95% CI 1.1–4.0)
				Case 73/769; vs. control 41/769	Amoxicillin (not specify dosage)				OR 1.9 (95% CI 1.3–2.9)
				Case 38/769; vs. control 20/769	Amiodarone (not specify dosage)				OR 1.9 (95% CI 1.1–3.4)
				Case 42/769; vs. control 23/769	Loperamide (not specify dosage)				OR 1.9 (95% CI 1.1–3.2)
				Case 373/769; vs. control 267/769	Acetaminophen (not specify dosage)				OR 1.8 (95% CI 1.5–2.3)
				Case 66/769; vs. control 39/769	Citalopram (not specify dosage)				OR 1.8 (95% CI 1.2–2.7)
				Case 57/769; vs. control 34/769	Polyethylene glycol 3350 (not specify dosage)				OR 1.7 (95% CI 1.1–2.7)
				Case 11/769; vs. control 2/769	Furosemide (not specify dosage)	Within 14 days of the reference date			OR 11.4 (95% CI 2.2–208.2)
				Case 89/769; vs. control 56/769	Isosorbide mononitrate (not specify dosage)	30 days prior to the reference date			OR 1.7 (95% CI 1.2–2.4)
				Case 259/769; vs. control 190/769	Omeprazole (not specify dosage)				OR 1.6 (95% CI 1.2–1.9)

(Continues)

TABLE 1 (Continued)

First author, year of publication	Country or area	Study design	Study population	Sample size (control arm, interacting drug arm)	Interaction drug name or category (dosage)	Follow-up period	Outcomes	Proportion or incidence rate of outcomes (no. of cases/total)	Risk statistic for warfarin plus other drug (s)
				Case 73/769; *vs.* control 49/769	Allopurinol (not specify dosage)				OR 1.5 (95% CI 1.1–2.3)
				Case 97/769; *vs.* control 67/769	Gabapentin (not specify dosage)				OR 1.5 (95% CI 1.1–2.1)
				Case 194/769; *vs.* control 144/769	Aspirin (not specify dosage)				OR 1.5 (95% CI 1.2–1.9)
				Case 129/769; *vs.* control 99/769	Amlodipine (not specify dosage)				OR 1.4 (95% CI 1.0–1.8)
				Case 11/769; *vs.* control 3/769	Metoprolol tartrate (not specify dosage)	Within 14 days of the reference date			OR 3.7 (95% CI 1.1–16.4)
				Case 11/769; *vs.* control 2/769	Docusate sodium (not specify dosage)				OR 5.4 (95% CI 1.4–35.0)

AF, atrial fibrillation; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin re-uptake inhibitors; RCT, randomized clinical trial; RR, rate ratio; GI, gastrointestinal.
[a]The RCTs for which the extracted drug–drug interaction data between warfarin and aspirin was not subject to randomization.

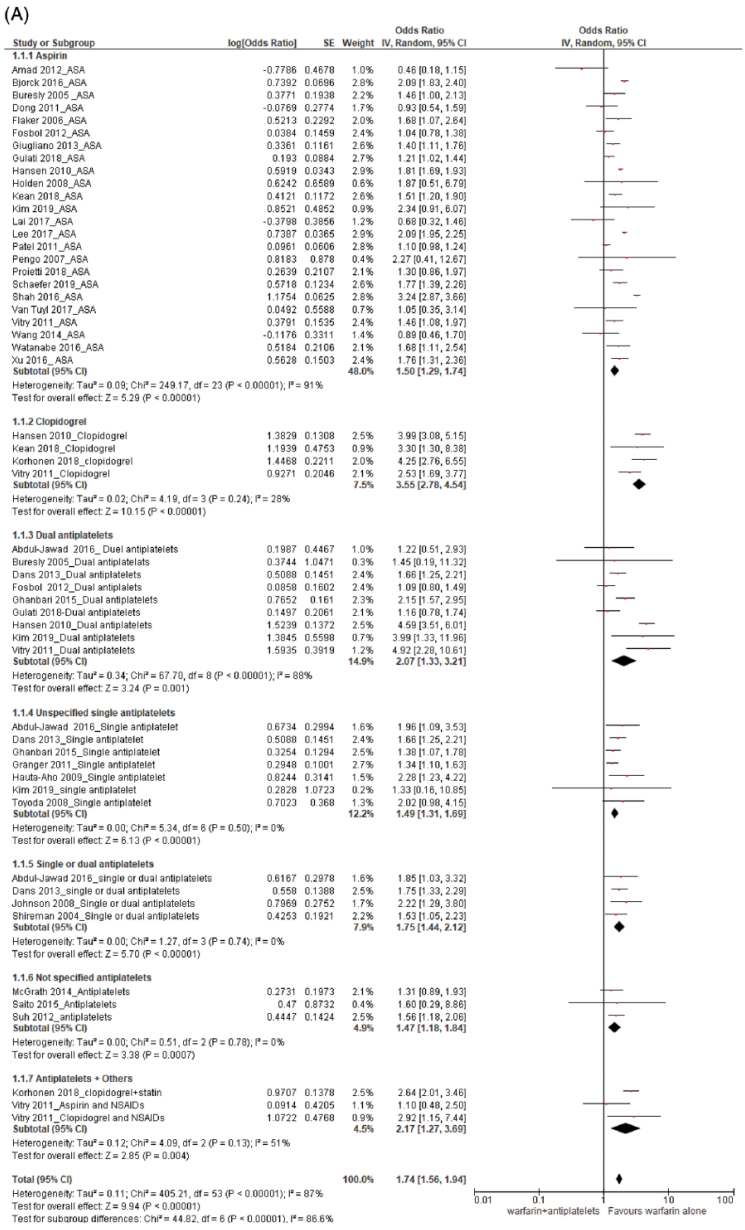

FIGURE 2 (A) Forest plots for bleeding in warfarin interaction with antiplatelets. (B) Forest plots for bleeding in warfarin interaction with antimicrobials. (C) Forest plots for bleeding in warfarin interaction with nonsteroidal anti-inflammatory drugs (NSAIDs). (D) Forest plots for bleeding in warfarin interaction with other analgesics. (E) Forest plots for bleeding in warfarin interaction with antidepressants. (F) Forest plots for bleeding in warfarin interaction with antiarrhythmics. (G) Forest plots for bleeding in warfarin interaction with lipid lowering agents. (H) Forest plots for bleeding in warfarin interaction with PPIs. (I) Forest plots for bleeding in warfarin interaction with thyroids

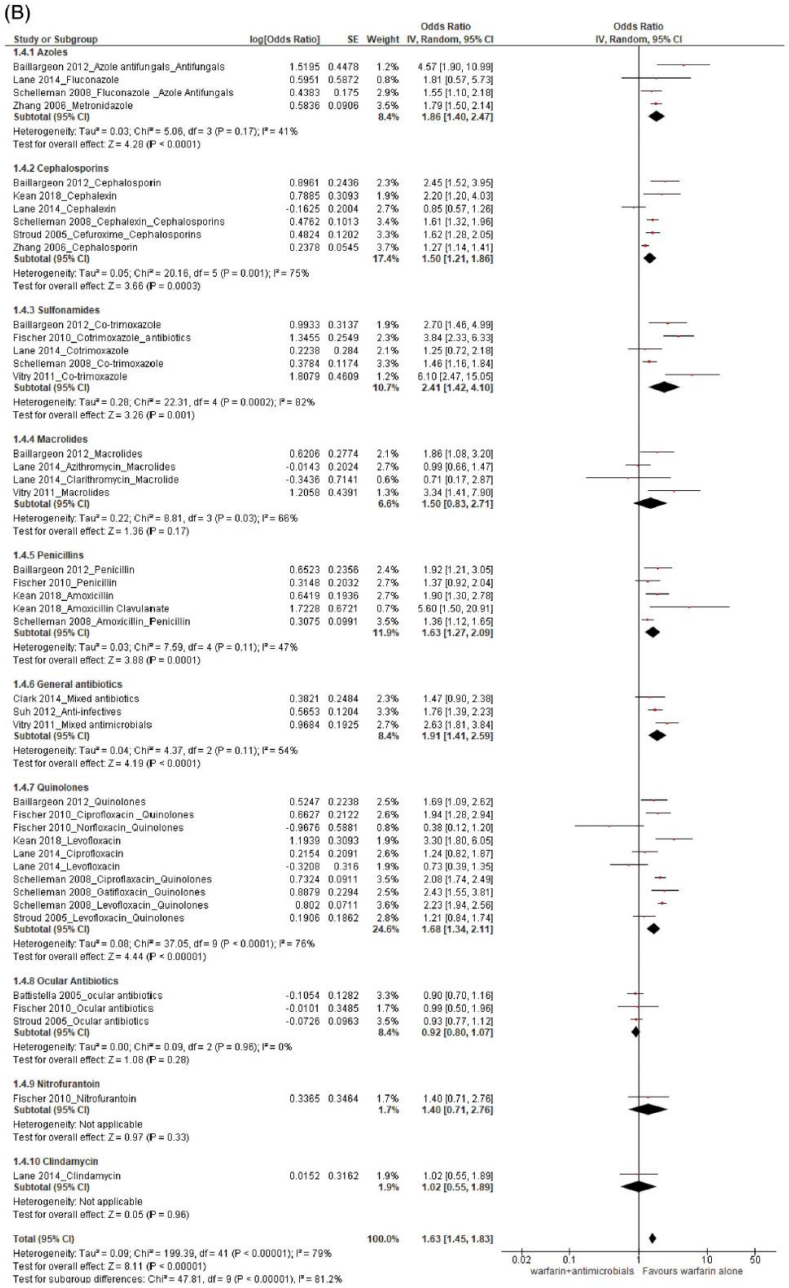

FIGURE 2 (Continued)

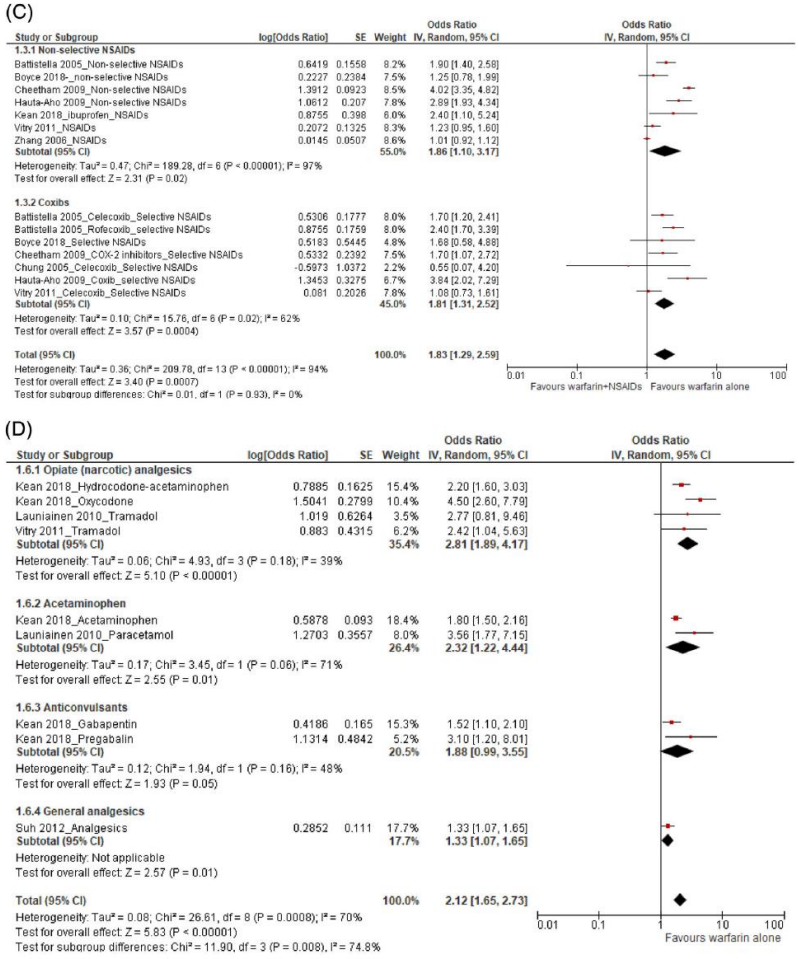

FIGURE 2 (Continued)

with the concomitant use of dual antiplatelets and warfarin compared to warfarin alone.[34,64,90,93] One RCT and three retrospective cohort studies reported on the all-cause death with mixed antiplatelets (single and dual antiplatelets) and warfarin compared to warfarin alone. The pooled result shows that there is no statistically significant difference (OR = 0.84, 95% CI 0.47–1.50).[22,34,69,88] However, pooling results of two prospective cohort studies and two retrospective cohort studies showed that there was significantly more death for warfarin and single unspecified antiplatelet than that for warfarin alone (OR = 1.16; 95% CI 1.06–1.26).[34,35,77,93]

3.2 | Anti-infectives for systemic use (antimicrobials)

A total of 11 studies (n = 717 468)—four retrospective cohort studies (36.4%) and seven case–control studies (63.6%)—reported on patient-important outcomes related to the concomitant use of antimicrobials and warfarin.** Three studies (n = 615 578) reported on azole antifungals,[38,45,73,89] six studies (n = 641 039) on cephalosporins,[38,45,48,49,73,89] five studies (n = 640 308) on

**[38,39,41,45,48,49,61,73,85,89,94]

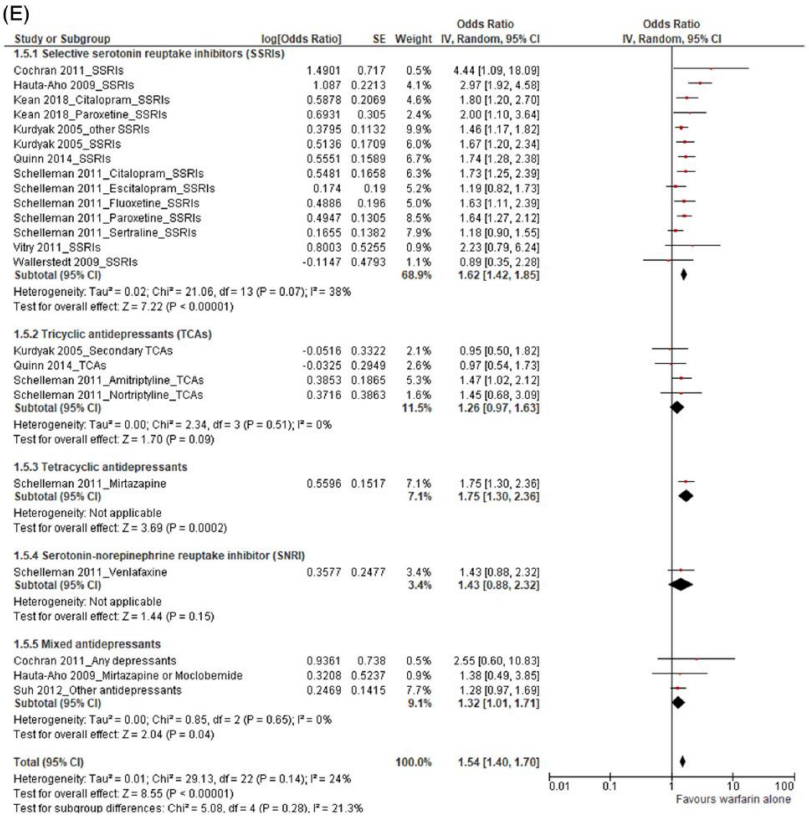

FIGURE 2 (Continued)

sulfonamides,[38,41,45,73,85] three studies (*n* = 36 554) on macrolides,[38,73,85] three studies (*n* = 43 868) on ocular antibiotics,[39,41,48] four studies (*n* = 608 503) on penicillins,[38,41,45,49] six studies (*n* = 652 092) on quinolones,[38,41,45,48,49,73] one study (*n* = 22 272) on lincomycin,[73] one study (*n* = 23 585) on nitrofurantoin[41] and three studies (*n* = 26 592) on unspecified antibiotic therapy.[61,85,94] All 11 studies reported on clinically relevant bleeding, and only one study (*n* = 12 006) on thromboembolic events and all-cause mortality.[61]

Our meta-analysis showed evidence of an increased risk of bleeding with the concomitant use of antimicrobials, all classes combined (OR = 1.63; 95% CI 1.45–1.83). In subgroup analysis (see details in Figure 2B), compared to warfarin alone, there was a statistically significant increased risk of bleeding with the concomitant use of warfarin and azole antifungals (OR = 1.86; 95% CI 1.40–2.47), cephalosporins (OR = 1.50; 95% CI 1.21–1.86), sulfonamides (OR = 2.41; 95% CI 1.42–4.10), penicillins (OR = 1.59; 95% CI 1.14–2.20), amoxicillin (OR = 1.78; 95% CI 1.14–2.79), quinolones (OR = 1.68; 95% CI 1.34–2.11), and with unspecified antibiotic therapy (OR = 1.69; 95% CI 1.27–2.24). However, warfarin plus macrolides (OR = 1.50; 95% CI 0.83–2.71), or ocular antibiotics (OR = 0.92; 95% CI 0.80–1.07), or lincomycin (OR = 1.02, 95% CI 0.55–1.89), or nitrofurantoin (OR = 1.40; 95% CI 0.71–2.76) did not show a significant increase in bleeding compared to warfarin alone.

Only one study reported on the occurrence of thromboembolic events and all-cause death.[61] This study did not specify the class of the antimicrobials. Compared to warfarin alone, no significant difference was found when antimicrobials were combined with warfarin in thromboembolic events or all-cause death.

3.3 | Anti-inflammatory agents for systemic use (nonsteroidal anti-inflammatory drug [NSAIDs])

A total of eight eligible studies (*n* = 84 095)—six (75.0%, 6/8) retrospective cohort studies, and two (25.0%, 2/8) case–control studies—were identified that reported on the potential interaction between

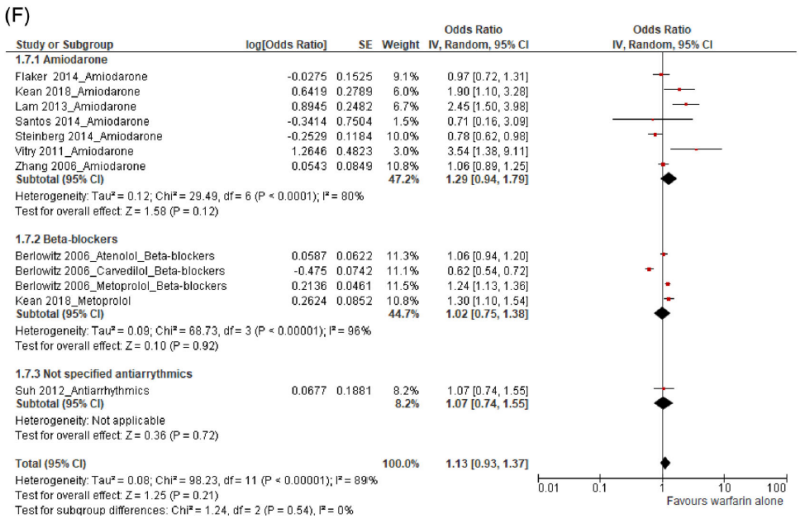

FIGURE 2 (Continued)

NSAIDs and warfarin.[††] All eight studies reported clinically relevant bleeding, and no studies reported on thromboembolic events or all-cause mortality.

According to the meta-analysis, increased risk of bleeding was observed with the concomitant use of NSAIDs, and warfarin compared to warfarin alone (OR = 1.83; 95% CI 1.29–2.59). Similar results were found in each subgroup analysis (see details in Figure 2C). The bleeding risk increased with both non-selective NSAIDs plus warfarin compared to warfarin alone (n = 80 483) (OR = 1.86; 95% CI 1.10–3.17),[‡‡] as well as for Cox-2 NSAIDs plus warfarin compared to warfarin alone (n = 57 575) (OR = 1.81; 95% CI 1.3–2.52).[39,56,58,59,67,85]

3.4 | Analgesics

A total of four studies (n = 16 153) reported on bleedings related to the concomitant use of non-NSAID analgesics and warfarin.[49,50,74,85] Opioid analgesics (n = 12 872) were investigated in three studies.[49,74,85] Acetaminophen was investigated in two studies (n = 1805)[49,74] and anticonvulsants (gabapentin and pregabalin) were reported in one study (n = 1538).[49] One of the studies (n = 3228) did not specify the specific analgesics that they focused on.[50] All four studies reported on clinically relevant bleeding, but no study reported on thromboembolic events and all-cause mortality. According to the meta-analysis, an increased risk was observed for bleeding with the concomitant use of each non-NSAID analgesic and warfarin compared to warfarin alone (details in Figure 2D).

3.5 | Antidepressants

A total of ten studies (n = 736 916)—six (60.0%, 6/10) retrospective cohort studies and four (40.0%, 4/10) case–control studies—reported on the concomitant use of antidepressants and warfarin.[§§] Eight studies (n = 732 363) reported on selective serotonin reuptake inhibitors (SSRIs),[¶¶] three studies (n = 713 918) on tricyclic antidepressants (TCAs),[42,47,78] one study (n = 666 235) on tetracyclic antidepressants (mirtazapine),[47] one study (n = 666 235) on serotonin-norepinephrine reuptake inhibitors (SNRIs),[47] and four studies (n = 7141) on mixed or unspecified antidepressants.[50,62,67,76] All ten studies reported on clinically relevant bleeding. One study (n = 159) reported the all-cause death in patients with intracerebral haemorrhage.[76] No study reported on thromboembolic events or all-cause mortality.

Compared to warfarin alone, there was a statistically significant increased risk of bleeding for SSRIs plus warfarin (OR = 1.62; 95% CI 1.42, 1.85), for mirtazapine plus warfarin (OR = 1.75; 95% CI 1.30, 2.36), and for combined antidepressants plus warfarin (OR = 1.48; 95% CI 1.24, 1.78). However, the risk of bleeding with the concomitant use of TCAs and warfarin (OR = 1.26; 95% CI 0.97, 1.63) or the concomitant use of SNRIs and warfarin (OR = 1.43; 95% CI 0.88, 2.32) was not significantly increased compared to warfarin alone (details in Figure 2E).

††39,49,56,58,59,67,85,89

‡‡39,49,56,58,67,85,89

§§42,47,49,50,62,67,76,78,85,86

¶¶42,47,49,62,67,78,85,86

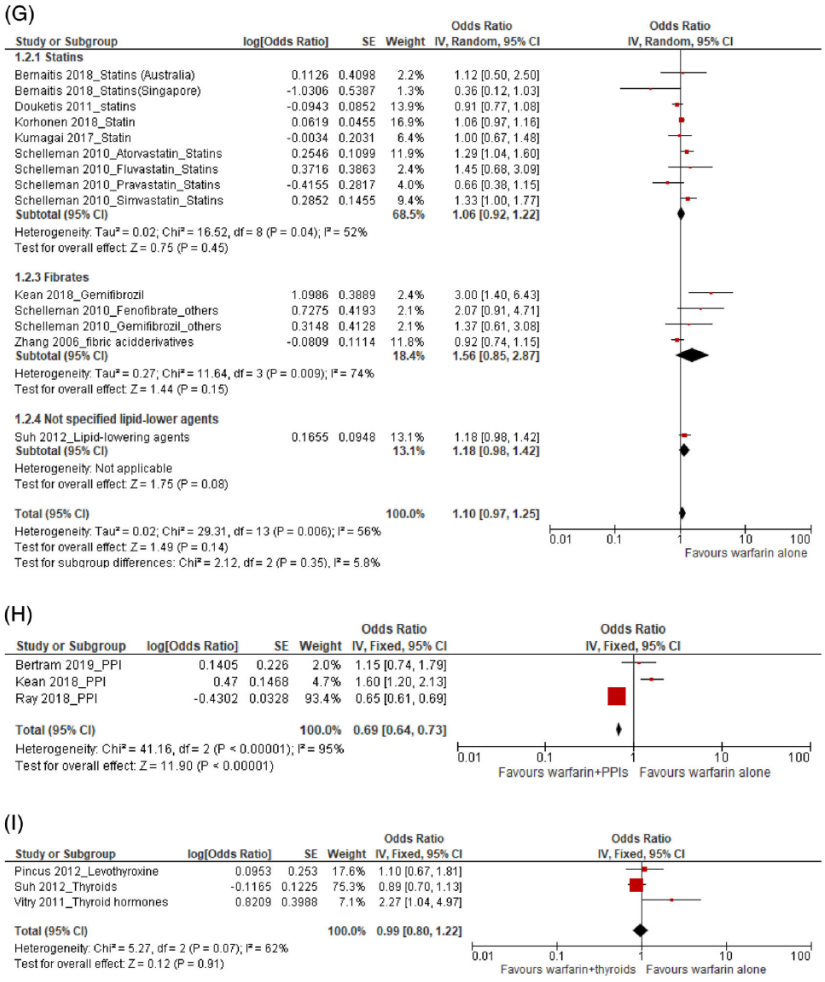

FIGURE 2 (Continued)

One study reported that compared to warfarin alone, the concurrent use of SSRI (or SNRIs) and warfarin increased the case fatality rate for intracerebral haemorrhage (OR = 3.64; 95% CI 1.15, 11.53).[76]

3.6 | Cardiovascular system agents

3.6.1 | Antiarrhythmics

Seven studies (n = 53 844) reported on amiodarone[##] and one study (n = 57 072) on unspecified antiarrhythmics.[50] Based on the results of the meta-analysis, we found that the concurrent use of amiodarone and warfarin did not significantly increase clinically relevant bleeding (OR = 1.29; 95% CI 0.94–1.79) (see Figure 2F) or thromboembolic events (OR = 0.95; 95% CI 0.71–1.28) (see Figure 3B). However, we found a statistical increase for all-cause death with concomitant use of amiodarone and warfarin compared to warfarin alone in patients with atrial fibrillation (OR = 1.60; 95% CI 1.29–1.99).[24]

3.6.2 | Beta blocking agents

Two studies (n = 62 958) reported on beta-blockers, including metoprolol, atenolol and carvedilol.[49,52] Compared to warfarin alone, the

##49,63,72,80,83,85,89

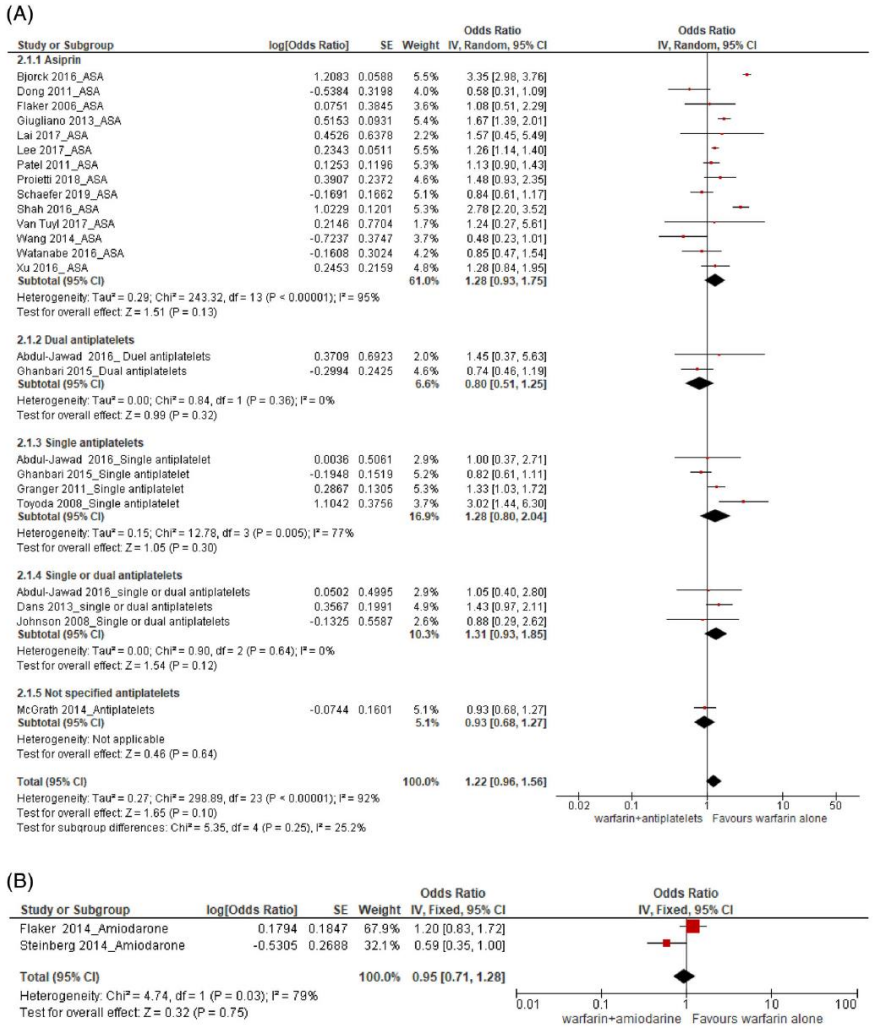

FIGURE 3 (A) Forest plots for thromboembolism events in warfarin interaction with antiplatelets. (B) Forest plots for thromboembolism events in warfarin interaction with amiodarone

concomitant use of beta-blockers and warfarin did not significantly increase clinically relevant bleeding events (OR 1.02, 95% CI 0.75–1.38) (details in Figure 2F).

3.6.3 | Lipid-modifying agents

Five studies (n = 1 421 921) reported on statins.[33,40,46,53,70] All five studies reported rates of clinically relevant bleeding, but only one study (n = 6404) on thromboembolic events and all-cause mortality.[33] Three studies (n = 639,14) reported on fibrates.[46,49,89] All three studies reported clinically relevant bleeding, but no study reported on thromboembolic events or all-cause mortality. One study reported on unspecified lipid-lowering agents.[50]

Neither statin (OR = 1.06; 95% CI 0.92–1.22) nor fibrates (OR = 1.56; 95% CI 0.85–2.87) increased bleeding in patients on warfarin (see details in Figure 2G). Kumagai et al. reported a statistical decrease for all-cause death with concomitant use of statins and

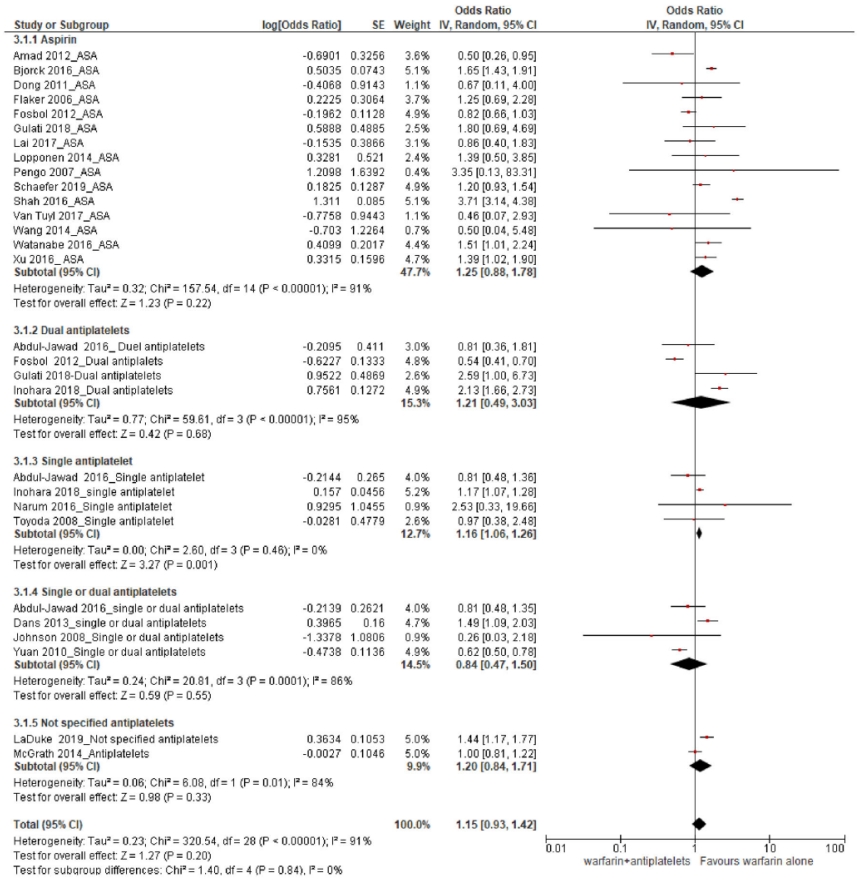

FIGURE 4 Forest plots for all-cause death in warfarin interaction with antiplatelets

warfarin compared to warfarin alone (OR = 0.57; 95% CI 0.37–0.87).[33]

3.6.4 | Others

One study suggested that neither unspecified antihypertensives (OR = 0.87; 95% CI 0.71–1.07) nor unspecified antiarrhythmics (OR = 1.07; 95% CI 0.74–1.55) significantly decreased or increased the bleeding events in patients on warfarin.[50] Another study reported on other cardiovascular agents, including amlodipine (a calcium channel blocker) (OR = 1.40; 95% CI 1.00–1.96), isosorbide mononitrate (a nitrate) (OR = 1.70; 95% CI 1.20–2.41), and the loop diuretics (OR = 1.92; 95% CI 1.29–2.86), which were found to significantly increase bleeding when combined with warfarin.[49]

3.7 | Alimentary tract and metabolism

3.7.1 | Drugs for acid-related disorders

Two retrospective cohort studies (n = 814 727)[54,79] and one case–control study (n = 3228)[49] were identified that reported on the potential interaction between proton pump inhibitors (PPIs) and warfarin. Compared to warfarin alone, significantly decreased risk of bleeding for PPIs plus warfarin (OR = 0.69; 95% CI 0.64–0.73) was detected (see Figure 2H, and further information in Discussion).

3.7.2 | Other gastrointestinal agents

A case–control study supplied data on some other gastrointestinal agents. The antidiarrheal loperamide (OR = 1.90; 95% CI 1.10–3.28),

the laxative polyethylene glycol 3350 (OR = 1.70; 95% CI 1.10–2.70), ondansetron (OR = 2.10; 95% CI 1.20–3.70), prochlorperazine (OR = 3.40; 95% CI 1.80–6.42), and stool softener docusate (OR = 5.40; 95% CI 1.40–20.83) were found associated with increased bleeding rates in patients on warfarin.[49]

3.8 | Others

One retrospective study[85] and two case–control studies[44,50] (*n* = 65 476) reported on thyroid agents and their impact on bleeding. According to the pooled result, no significant difference (OR = 0.99; 95% CI 0.80–1.22) was found for bleeding events with concomitant use of thyroid drugs and warfarin compared to warfarin alone (see Figure 2I).

Three reports on patient-important outcomes related to the concomitant use of other drugs that do not belong to the therapeutic classes described above were also identified. One study (*n* = 5021) reported on a variety of drugs that can inhibit CYP2C9 (e.g., metronidazole, fluconazole, amiodarone, phenytoin, miconazole, sulfamethoxazole, tamoxifen, zafirlukast, gemfibrozil and fluvoxamine).[67] No significant difference was found for bleeding or thromboembolic events. Another study (*n* = 2380) compared enoxaparin plus warfarin to warfarin alone.[60] No significant difference was found for both bleeding and thromboembolic events with a short-term transition period of concomitant use of enoxaparin and warfarin compared to warfarin alone.

A case–control study (*n* = 1538) reported several other medications that potentially have interactions with warfarin.[49] Guaifenesin (OR = 3.30; 95% CI 1.50–8.30), calcitriol (OR = 2.80; 95% CI 1.20–7.90), ferrous sulfate (OR = 2.50; 95% CI 1.80–3.60), glimepiride (OR = 2.00; 95% CI 1.10–3.80), oxybutynin chloride (OR = 3.10; 95% CI 1.70–6.30), baclofen (OR = 2.80; 95% CI 1.10–8.10) and allopurinol (OR = 1.50; 95% CI 1.10–2.30) were associated with an increased bleeding risk in patients on warfarin.

3.9 | Quality of included studies

3.9.1 | Randomized controlled studies

All of the 11 RCTs had an unclear risk of bias in the selection of reported results and a low risk of bias in other domains. For most, we found a low risk of bias for allocation concealment (9/11; 81.8%), blinding of outcome assessment (9/11 studies; 81.8%), incomplete outcome data domain (7/11; 63.6%) and random sequence generation (7/11, 63.6%). More than half of the included studies had some risk of bias due to the lack of adequate blinding of participants and personnel (6/11; 45.5%). This may be due to poor reporting (Table 2A). Since the data extracted from four of these RCTs were not subject to randomization,[22,25–27] they were treated as observational studies for purposes of risk of bias assessment.

3.9.2 | Observational studies

Prospective cohort, retrospective cohort and case–control studies were rated using the ROBINS I assessment. The study quality of the included observational studies was highly variable. Almost all the included observational studies (59/61, 96.7%) had a high risk of confounding. Forty-two studies were thought to have problems with selection bias. For the four RCTs, in which our extracted data were not subject to randomization,[22,25–27] we found a high risk of confounding. See details in Table 2B.

3.9.3 | The certainty of evidence (GRADE)

The evidence varied from low to moderate certainty: the observational study design meant the GRADE rating started as moderate certainty evidence, and almost all studies except the 11 RCTs and three studies[52,70,85] had bias due to confounding. In addition, several pooled results came from significant heterogeneity evidence (see details in Table 3).

4 | DISCUSSION

The present review is an update of our previously published systematic review and a subsequent summary in the 2012 ACCP guidelines on the management of anticoagulant therapy.[2,12,95] The guidelines made a weak recommendation based on low-quality evidence to avoid concomitant ongoing treatment with antiplatelets and NSAIDs, and to be vigilant with monitoring when antibiotics or SSRIs are required for patients on vitamin K antagonist therapy. Another review of warfarin drug–drug interaction reported that the concomitant use of warfarin with other medications, including cotrimoxazole, quinolones, amiodarone, macrolides, SSRIs, platelet aggregation inhibitors, NSAIDs and lipid-lowering agents, was associated with an increased risk of bleeding in patients 65 years and older.[96] Most other reviews have been focused on pharmacokinetic and pharmacodynamic interactions rather than patient-important outcomes.[97] Mechanisms that could influence warfarin's effect include reducing the gastrointestinal absorption of warfarin, inhibition of CYP2C9 which metabolizes the R-isomer, or affecting either vitamin K or the coagulation factors.[98]

In the present systematic review, we improve the quality of the warfarin drug–drug interaction information in several respects: (a) we focus on clinically important outcomes relevant to warfarin—bleeds, thromboembolic events and death, (b) we carried out a broad, comprehensive search on all medications available in Canada or the United States, (c) we completed a rigorous risk of bias assessment, and (d) conclusions are based on higher quality evidence than was previously available. We found an increased risk of clinically relevant bleeding for antiplatelet (AP) regimens, azole antifungals, cephalosporins, sulfonamides, penicillins, quinolones, non-selective NSAIDs, Coxib NSAIDs, opioid analgesics, acetaminophen, mirtazapine, SSRIs,

TABLE 2A Summary assessment of risk of bias for included RCT studies using Cochrane Collaboration's risk of bias tool

	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	
Author (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Anything else, ideally prespecified	Low risk of bias score
Flaker et al. 2006[24]	+/-	+	−	+	+	+/-	+	4/7
Pengo et al. 2007[28]	+	+/-	−	+	−	+/-	+	3/7
Dong et al. 2011[23]	−	+	+/-	+/-	−	+/-	+	2/7
Granger et al. 2011[26,a]	+	+	+	+	+	+/-	+	6/7
Patel et al. 2011[27,a]	+	+	+	+	+	+/-	+	6/7
Dans et al. 2013[22,a]	+	+	+	+	+/-	+/-	+	5/7
Giugliano et al. 2013[25,a]	+	+	+	+	+	+/-	+	6/7
Wang et al. 2014[31]	−	+	+/-	+/-	+/-	+/-	+	2/7
Shah et al. 2016[30]	+	+	+/-	+	+	+/-	+	5/7
Xu et al. 2016[32]	+	+	+	+	+	+/-	+	6/7
Proietti et al. 2018[29]	+/-	+/-	+/-	+	+	+/-	+	3/7

Notes: + for low risk of bias, − for high risk of bias, +/- for unclear bias.
[a]The data extracted from these RCTs were not subject to randomization, therefore risk of bias assessment included with observational studies in Table 2B.

amlodipine, isosorbide mononitrate, loop diuretics, loperamide, polyethylene glycol 3350, ondansetron, docusate, prochlorperazine, guaifenesin, calcitriol, ferrous sulfate, glimepiride, oxybutynin, baclofen and allopurinol. Notably, there was no increased risk of bleeding events found for amiodarone or statins. Data on thromboembolic events and all-cause mortality were available from only 27 (37.5%) of the included studies, with no significant effect related to any drug group used with warfarin, including single or dual AP regimens.

Drug–drug interactions are an important component of medication safety, a constant source of worry for prescribers, and are associated with harm. Unfortunately, the literature on the clinical importance of drug interactions is of poor quality but does suggest that potential drug interactions are very common, affecting 25% to 66% of adult patients depending on the setting, and with an unknown frequency of major harm due to confounding by disease and severity of illness.[99–102] Drug interaction alerts, part of every modern electronic medical record and pharmacy software, are an attempt to improve the safety of drug therapy, including warfarin. However, the knowledge bases behind these alerts are proprietary, not subjected to validation, have questionable accuracy, can have a negative effect on timely therapy, and are only very weakly associated with improved clinical outcomes.[103–106]

In the present review, we provide summaries on clinically relevant outcomes for 141 unique drugs or drug combinations within ten drug classes (antiplatelets, antimicrobials, NSAIDs, other analgesics, antidepressants, cardiovascular agents, lipid-lowering agents, gastrointestinal agents, and others) for drug–drug interactions with warfarin. There are several key clinical messages from this review. First, we have confirmed higher rates of clinically relevant bleeding with the concomitant use of warfarin and antiplatelets, azole antifungals, cephalosporins,

TABLE 2B Summary assessment of the risk of bias for included observational studies using ROBINS-I "risk of bias" tool

Author (year)	Bias due to confounding	Bias in the selection of participants into the study	Bias in the classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in the selection of the reported result	Low risk of bias score
Prospective cohort studies by year								
Toyoda et al. 2008[35]	−	−	+	+	+	+	+	5/7
McGrath et al. 2014[36]	−	+	+	+	+/−	+	+	5/7
Abdul-Jawad et al. 2016[34]	−	+	+	+	+	+	+	6/7
Kumagai et al. 2017[33]	−	−	+	+	+	+	+	5/7
Granger et al. 2011[26,a]	−	+	+	+	+	+	+	6/7
Patel et al. 2011[27,a]	−	+	+	+	+	+	+	6/7
Dans et al. 2013[22,a]	−	+	+	+	+	+	+	6/7
Giugliano et al. 2013[25,a]	−	+	+	+	+	+	+	6/7
Retrospective cohort studies by year								
Shireman et al. 2004[82]	−	−	+	+	+	+	+	5/7
Buresly et al. 2005[57]	−	−	+	+	+	+	+	5/7
Chung et al. 2005[59]	−	−	+	+	+	+	+	5/7
Berlowitz et al. 2006[52]	+	−	+	+	+	+	+	6/7
Zhang et al. 2006[89]	−	−	+	+/−	+	+	+	4/7
Holden et al. 2008[68]	−	−	+	+	+/−	+	+	4/7
Johnson et al. 2008[69]	−	−	+	+	+/−	+	+	4/7
Cheetham et al. 2009[58]	−	+	+	+	+	+	+	6/7
Hauta-Aho et al. 2009[67]	−	−	+	+	+/−	+	+	4/7

(Continues)

TABLE 2B (Continued)

Author (year)	Bias due to confounding	Bias in the selection of participants into the study	Bias in the classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in the selection of the reported result	Low risk of bias score
Wallerstedt et al. 2009[86]	−	+	+	−	+/-	+	+	4/7
Hansen et al. 2010[66]	−	−	+	+	+	+	+	5/7
Launiainen et al. 2010[74]	−	−	−	−	+/-	−	+	1/7
Yuan et al. 2010[88]	−	−	+	+/-	+	+	+	4/7
Cochran et al. 2011[62]	−	−	+	+	+	+	+	5/7
Vitry et al. 2011[85]	+	−	−	+/-	+/-	+	+	3/7
Amad et al. 2012[51]	−	−	+	+	+	+	+	5/7
Fosbol et al. 2012[64]	−	−	+	−	−	+	+	3/7
Lam et al. 2013[72]	−	−	+	+	−	+	+	4/7
Clark et al. 2014[61]	−	−	+	+	+	+	+	5/7
Flaker et al. 2014[63]	−	−	+	+	+	+	−	4/7
Lane et al. 2014[73]	−	+/-	+	+	+/-	+	+	4/7
Lopponen et al. 2014[76]	−	−	+	+	−	+	+	4/7
Quinn et al. 2014[78]	−	−	+	+	+	+	+	5/7
Santos et al. 2014[80]	−	−	+	+	+	+	+	5/7
Steinberg et al. 2014[83]	−	+	+	+	+	+	+	6/7
Ghanbari et al. 2015[65]	−	+	+	−	+	+	+	5/7
Saito et al. 2015[37]	−	+	+	+/-	+	+	+	5/7
Bjorck et al. 2016[55]	−	+	+	+	+	+	+	6/7
Narum et al. 2016[77]	−	−	−	+/-	+	+	+	3/7
Ray et al. 2016[79]	−	+	+	+/-	+/-	+	+	4/7
Watanabe et al. 2016[87]	−	−	+	+/-	+	+	−	3/7

TABLE 2B (Continued)

Author (year)	Bias due to confounding	Bias in the selection of participants into the study	Bias in the classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in the selection of the reported result	Low risk of bias score
Cieri et al. 2017[60]	−	+	+	+	+	+	+	6/7
Lai et al. 2017[71]	−	+	+	+/-	+/-	+	+	4/7
Lee et al. 2017[75]	−	+	+	+	+	+	+	6/7
Van Tuyl et al. 2017[84]	−	+	+	+	+/-	+	+	5/7
Bernaitis et al. 2018[53]	−	−	+	+	−	+	+	4/7
Boyce et al. 2018[56]	−	−	+	+	+	+	+	5/7
Inohara et al. 2018[93]	−	−	+	+	+	+	+	5/7
Korhonen et al. 2018[70]	+	+	+	+	+/-	+	+	6/7
Gulati et al. 2018[90]	−	−	+	+	+	+	+	5/7
Bertram et al. 2019[54]	−	−	+	+	+	+	+	5/7
Kim et al. 2019[91]	−	−	+	+	+	+	+	5/7
LaDuke et al. 2019[92]	−	−	+	+	+	+	+	5/7
Schaefer et al. 2019[81]	−	−	+	+	+	+	+	5/7
Case control studies by year								
Battistella et al. 2005[39]	−	+	+	+	+	+	+	6/7
Kurdyak et al. 2005[42]	−	+	+	+	+/-	+	+	5/7
Stroud et al. 2005[48]	−	−	+	+	+	+	+	5/7
Douketis et al. 2007[40]	−	−	+	−	+	−	+	3/7
Schelleman et al. 2008[45]	−	−	−	+	+	+	+	4/7
Fischer et al. 2010[41]	−	−	+	−	+	+	+	4/7

(Continues)

TABLE 2B (Continued)

Author (year)	Bias due to confounding	Bias in the selection of participants into the study	Bias in the classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in the selection of the reported result	Low risk of bias score
Schelleman et al. 2010[46]	−	−	−	+	+	+	+	4/7
Schelleman et al. 2011[47]	−	−	−	+	+	+	+	4/7
Baillargeon et al. 2012[38]	−	+	+	+	+	+	+	6/7
Pincus et al. 2012[44]	−	−	+	+	+	+	+	5/7
Suh et al. 2012[50]	−	−	+	+	+	+	+	5/7
Nagata et al. 2015[43]	−	+	+	+/−	+	−	+	4/7
Kean et al. 2018[49]	−	−	+	+	+	+	+	5/7

Notes: + for low risk of bias, − for high risk of bias, +/− for unclear bias.
[a]Studies designed as RCTs, but data extracted from those RCTs were not subject to randomization.

sulfonamides, penicillins, quinolones, SSRIs and NSAIDs.[95,96] Second, we found no improvement in the rate of thromboembolic events or mortality when antiplatelets were given with warfarin compared to warfarin alone. Third, while amiodarone had previously been associated with increased INR when administered with warfarin,[63,107] we found no statistically significant increase in clinically relevant bleeding. Fourth, we found a significant decrease in clinically relevant bleeding associated with PPIs plus warfarin, which was not surprising given their widespread use to decrease upper gastrointestinal (GI) bleeding. Despite the common use of PPIs with warfarin in practice to reduce GI bleeding, there is no randomized trial evidence of benefit for clinically relevant bleeding, and there are low-quality reports that PPIs might raise INR by increasing the absorption of warfarin.[54,108] However, this systematic review has clarified that the best available evidence suggests that PPIs reduce the incidence of hospitalization for upper GI bleeding for patients taking warfarin. This is consistent with the findings of another large observational study,[109] which could not be included in the present study due to the reporting of the data. Finally, the lack of evidence on thromboembolic outcomes or fatal outcomes related to drug–drug interactions with warfarin is a serious research gap.

The strengths of this review include its methodological rigour (comprehensive search, duplicate screening and data extraction), detailed review of the quality of evidence, including the risk of bias, and focus on patient-important outcomes. The conclusions of this review are primarily limited by the overall quality of the literature, which is mostly comprised of retrospective, observational studies conducted using administrative databases or post hoc analyses of clinical trials that are at high risk of confounding and selection bias. Only 11 (15.3%) studies were randomized trials, all of which dealt with antiplatelet agents, and for four of them our comparison of interest was not subject to randomization. In addition, some potentially eligible studies may have been missed as our search strategies included the term "interaction" for warfarin. Unfortunately, drug–drug interactions are rarely the topic of randomized trials.

Our previous systematic review of warfarin drug interactions included many studies where adjudication of interaction was based on the INR.[12] The literature has advanced considerably in terms of quality since then, so we chose to concentrate on studies reporting actual clinical outcomes. While the INR (or TTR) is a useful surrogate marker for the clinical monitoring of warfarin,[110] only a portion of warfarin's interactions manifest with a changed INR. Furthermore, the larger and higher quality studies are typically based in real practice where INR is measured only occasionally. Indeed, we found that INR data were completely missing from 51% (37/72) of the included papers. A useful future study could examine the predictive relationship of INR trends with clinical outcomes in drug interactions. As the literature continues to evolve, we will also be able to examine individual drugs within interacting drug families.

The implications of this review are obvious for clinicians and may be encouraging, given the small list of interacting medications associated with bleeding, particularly where the potentially interacting drug does not have haemorrhagic effects of its own. For policymakers, the present results improve the evidence base of

TABLE 3 GRADE evidence profile of drug interactions with warfarin for outcomes of clinically relevant events

		Certainty assessment							
Outcomes	Interaction drugs	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Nn	Aspirin	24	RCTs and observational studies	Serious[a,b,c,d,e]	Serious[f]	Not serious	Not serious	None	
	Clopidogrel	4	Observational studies	Serious[a,b,c,g]	Not serious	Not serious	Not serious	None	
	Dual antiplatelets	9	RCTs and observational studies	Serious[a,b,h,i]	Serious[j]	Not serious	Not serious	None	
	Unspecified single Antiplatelets	7	RCTs and observational studies	Serious[a,b,c,g,h,i]	Not serious	Not serious	Not serious	None	
	Single or dual antiplatelets	4	RCTs and observational studies	Serious[a,b,c,i]	Not serious	Not serious	Not serious	None	
Clinically relevant bleeding	Statins	9	Observational studies	Serious[a,b,c,g,k]	Not serious	Not serious	Not serious	None	
	Fibrates	4	Observational studies	Serious[a,b,g]	Serious[l]	Not serious	Not serious	None	
	NSAIDs	14	Observational studies	Serious[a,b,g]	Serious[m]	Not serious	Not serious	None	
	Various NSAIDs	7	Observational studies	Serious[a,b,g]	Serious[m]	Not serious	Not serious	None	
	NSAIDs - Coxibs	7	Observational studies	Serious[a,b,g]	Serious[n]	Not serious	Not serious	None	
	Azole antifungals	4	Observational studies	Serious[a,b,g]	Not serious	Not serious	Not serious	None	
Clinically relevant bleeding	Cephalosporins	6	Observational studies	Serious[a,b,g]	Serious[o]	Not serious	Not serious	None	
	Sulfonamides	5	Observational studies	Serious[a,b,g,h]	Serious[p]	Not serious	Not serious	None	
	Macrolides	4	Observational studies	Serious[a,b,g]	Serious[q]	Not serious	Not serious	None	
	Ocular antibiotics	3	Observational studies	Serious[a,b,h]	Not serious	Not serious	Not serious	None	
	Penicillins	5	Observational studies	Serious[a,b,g,h]	Not serious	Not serious	Not serious	None	
	Quinolones	10	Observational studies	Serious[a,b,g,h]	Serious[r]	Not serious	Not serious	None	
Clinically relevant bleeding	Selective serotonin reuptake inhibitors (SSRIs)	14	Observational studies	Serious[a,b,g,h]	Not serious	Not serious	Not serious	None	
	Tricyclic antidepressants (TCAs)	4	Observational studies	Serious[a,b,g]	Not serious	Not serious	Not serious	None	
	Opiate (narcotic) analgesics	4	Observational studies	Serious[a,b,g,h,k]	Not serious	Not serious	Not serious	None	
	Acetaminophen	2	Observational studies	Serious[a,b,c,g,h,k]	Serious[s]	Not serious	Not serious	None	
	Amiodarone	7	Observational studies	Serious[a,b,c,g]	Serious[t]	Not serious	Not serious	None	
	Beta-blockers	4	Observational studies	Serious[a,b]	Serious[u]	Not serious	Not serious	None	
Clinically relevant bleeding	Thyroid drugs	3	Observational studies	Serious[a,b,g]	Serious[n]	Not serious	Not serious	None	
	Proton pump inhibitors (PPI)	3	Observational studies	Serious[a,b]	Not serious	Not serious	Not serious	None	
TEE	Aspirin	14	Observational studies	Serious[a,b,c,d,e,i]	Serious[u]	Not serious	Not serious	None	
	Dual antiplatelets	2	Observational studies	Serious[a,h]	Not serious	Not serious	Not serious	None	
	Single antiplatelets	4	Observational studies	Serious[a,b,h,i]	Serious[r]	Not serious	Not serious	None	
	Single or dual antiplatelets	3	Observational studies	Serious[a,b,i]	Not serious	Not serious	Not serious	None	

TABLE 3 (Continued)

Outcomes	Interaction drugs	Certainty assessment							
		№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
All cause death	Aspirin	15	Observational studies	Serious[a,b,c,d,h,i]	Serious[f]	Not serious	Not serious	None
	Dual antiplatelets	4	Observational studies	Serious[a,b,c,h]	Serious[u]	Not serious	Not serious	None
	Single antiplatelet	4	Observational studies	Serious[a,b,g]	Not serious	Not serious	Not serious	None
	Single or dual antiplatelets	4	Observational studies	Serious[a,b,i]	Serious[j]	Not serious	Not serious	None

CI, confidence interval; OR, odds ratio; TEE, thromboembolic events; RCT, randomized controlled trials.

Key:

[a]All included observational studies had a high risk of confounding.

[b]Some observational studies have problems with selection bias.

[c]Bias due to missing data.

[d]Selection bias for RCTs: Bias due to random sequence generation.

[e]Performance bias for RCTs: Blinding of participants and personnel.

[f]I^2 = 91% (I^2 > 50% was considered as statistically significant heterogeneity).

[g]For observational studies: Bias in the classification of interventions.

[h]For observational studies: Bias due to deviations from intended interventions.

[i]Reporting bias for both RCTs and observational studies: Selective reporting.

[j]I^2 = 88% (I^2 > 50% was considered as statistically significant heterogeneity).

[k]For observational studies: Bias in the measurement of outcomes.

[l]I^2 = 74% (I^2 > 50% was considered as statistically significant heterogeneity).

[m]I^2 = 94% (I^2 > 50% was considered as statistically significant heterogeneity).

[n]I^2 = 62% (I^2 > 50% was considered as statistically significant heterogeneity).

[o]I^2 = 75% (I^2 > 50% was considered as statistically significant heterogeneity).

[p]I^2 = 82% (I^2 > 50% was considered as statistically significant heterogeneity).

[q]I^2 = 66% (I^2 > 50% was considered as statistically significant heterogeneity).

[r]I^2 = 76% (I^2 > 50% was considered as statistically significant heterogeneity).

[s]I^2 = 71% (I^2 > 50% was considered as statistically significant heterogeneity).

[t]I^2 = 80% (I^2 > 50% was considered as statistically significant heterogeneity).

[u]I^2 = 96% (I^2 > 50% was considered as statistically significant heterogeneity).

TABLE 3 (Continued)

Outcomes	No. of patients		Effect		Certainty
	Warfarin + other drugs	Warfarin alone	Relative(95% CI)	Absolute(95% CI)	
Nn	4701/103 855 (4.5%)	11 798/374 479 (3.2%)	**OR 1.50** (1.29 to 1.74)	**15 more per 1000** (from 9 more to 22 more)	⨁◯◯◯ Low
	124/1961 (6.3%)	5329/197 568 (2.7%)	**OR 3.55** (2.78 to 4.54)	**63 more per 1000** (from 45 more to 85 more)	⨁⨁⨁◯ Moderate
	312/11 511 (2.7%)	5010/270 931 (1.8%)	**OR 2.07** (1.33 to 3.21)	**19 more per 1000** (from 6 more to 39 more)	⨁⨁◯◯ Low
	591/14 192 (4.2%)	585/21 875 (2.7%)	**OR 1.49** (1.31 to 1.69)	**13 more per 1000** (from 8 more to 18 more)	⨁⨁⨁◯ Moderate
	303/6431 (4.7%)	248/14 488 (1.7%)	**OR 1.75** (1.44 to 2.12)	**12 more per 1000** (from 7 more to 18 more)	⨁⨁⨁◯ Moderate
Clinically relevant bleeding	1782/121 267 (1.5%)	49 201/2 527 722 (1.9%)	**OR 1.06** (0.92 to 1.22)	**1 more per 1000** (from 2 fewer to 4 more)	⨁⨁⨁◯ Moderate
	715/8653 (8.3%)	26 312/1 261 296 (2.1%)	**OR 1.56** (0.85 to 2.87)	**11 more per 1000** (from 3 fewer to 37 more)	⨁⨁◯◯ Low
	1205/20 277 (5.9%)	4003/119 579 (3.3%)	**OR 1.83** (1.29 to 2.59)	**26 more per 1000** (from 9 more to 49 more)	⨁⨁◯◯ Low
	1095/16 965 (6.5%)	2476/63 518 (3.9%)	**OR 1.86** (1.10 to 3.17)	**31 more per 1000** (from 4 more to 75 more)	⨁⨁◯◯ Low
	110/3312 (3.3%)	1527/56 061 (2.7%)	**OR 1.81** (1.31 to 2.52)	**21 more per 1000** (from 8 more to 39 more)	⨁⨁◯◯ Low
	232/1994 (11.6%)	13 605/613 584 (2.2%)	**OR 1.86, (1.40 to 2.47)**	**18 more per 1000** (from 9 more to 31 more)	⨁⨁⨁◯ Moderate
Clinically relevant bleeding	818/13 306 (6.1%)	18 463/627 733 (2.9%)	**OR 1.50** (1.21 to 1.86)	**14 more per 1000** (from 6 more to 24 more)	⨁⨁◯◯ Low
	142/4433 (3.2%)	14 839/635 875 (2.3%)	**OR 2.41** (1.42 to 4.10)	**31 more per 1000** (from 9 more to 66 more)	⨁⨁◯◯ Low
	65/6348 (1.0%)	1450/52 478 (2.8%)	**OR 1.50** (0.83 to 2.71)	**13 more per 1000** (from 5 fewer to 44 more)	⨁⨁◯◯ Low
	70/650 (10.8%)	6711/43 218 (15.5%)	**OR 0.92** (0.80 to 1.07)	**11 fewer per 1000** (from 27 fewer to 9 more)	⨁⨁⨁◯ Moderate
	256/4465 (5.7%)	14 916/604 050 (2.5%)	**OR 1.63** (1.27 to 2.09)	**15 more per 1000** (from 6 more to 26 more)	⨁⨁⨁◯ Moderate
	555/14 854 (3.7%)	44 173/1 843 471 (2.4%)	**OR 1.68** (1.34 to 2.11)	**16 more per 1000** (from 8 more to 25 more)	⨁⨁◯◯ Low
Clinically relevant bleeding	1332/50 829 (2.6%)	68 739/3 375 478 (2.0%)	**OR 1.62** (1.42 to 1.85)	**12 more per 1000** (from 8 more to 17 more)	⨁⨁⨁◯ Moderate
	164/7325 (2.2%)	27 842/1 372 828 (2.0%)	**OR 1.26** (0.97 to 1.63)	**5 more per 1000** (from 1 fewer to 12 more)	⨁⨁⨁◯ Moderate
	28/1616 (1.7%)	559/12 794 (4.4%)	**OR 2.81** (1.89 to 4.17)	**70 more per 1000** (from 36 more to 116 more)	⨁⨁⨁◯ Moderate
	21/822 (2.6%)	43/983 (4.4%)	**OR 2.32** (1.22 to 4.44)	**52 more per 1000** (from 9 more to 125 more)	⨁⨁◯◯ Low
	352/10 173 (3.5%)	3259/43 671 (7.5%)	**OR 1.30** (0.94 to 1.79)	**20 more per 1000** (from 4 fewer to 52 more)	⨁⨁◯◯ Low
	1685/32 660 (5.2%)	3845/88 570 (4.3%)	**OR 1.02** (0.75 to 1.38)	**1 more per 1000** (from 10 fewer to 16 more)	⨁⨁◯◯ Low
Clinically relevant bleeding	145/694 (20.9%)	11 591/64 782 (17.9%)	**OR 1.15** (0.74 to 1.79)	**21 more per 1000** (from 40 fewer to 102 more)	⨁⨁◯◯ Low
	7634/669 090 (0.1%)	1297/145 657 (0.1%)	**OR 1.05** (0.54 to 2.02)	**1 fewer per 1000** (from 2fewer to 1 fewer)	⨁⨁⨁◯ Moderate
TEE	1589/26 863 (5.9%)	3949/107 613 (3.7%)	**OR 1.28** (0.93 to 1.75)	**10 more per 1000** (from 2 fewer to 26 more)	⨁⨁◯◯ Low
	26/2027 (1.3%)	84/5365 (1.6%)	**OR 0.80** (0.51 to 1.25)	**3 fewer per 1000** (from 8 fewer to 4 more)	⨁⨁⨁◯ Moderate
	231/11 589 (2.0%)	269/13 054 (2.1%)	**OR 1.28** (0.80 to 2.04)	**6 more per 1000** (from 4 fewer to 21 more)	⨁⨁◯◯ Low
	81/4469 (1.8%)	68/6357 (1.1%)	**OR 1.31** (0.93 to 1.85)	**3 more per 1000** (from 1 fewer to 9 more)	⨁⨁⨁◯ Moderate

TABLE 3 (Continued)

Outcomes	No. of patients		Effect		Certainty
	Warfarin + other drugs	Warfarin alone	Relative(95% CI)	Absolute(95% CI)	
All cause death	1264/15 197 (8.3%)	2906/63 694 (4.6%)	**OR 1.25** (0.88 to 1.78)	**11 more per 1000** (from 5 fewer to 33 more)	⊕⊕◯◯ Low
	340/1202 (28.3%)	3936/12 119 (32.5%)	**OR 1.21** (0.49 to 3.03)	**43 more per 1000** (from 134 fewer to 268 more)	⊕⊕◯◯ Low
	97/938 (10.3%)	55/1452 (3.8%)	**OR 1.16** (1.06 to 1.26)	**6 more per 1000** (from 2 more to 9 more)	⊕⊕⊕◯ Moderate
	231/6154 (3.8%)	420/9938 (4.2%)	**OR 0.84** (0.47 to 1.50)	**7 fewer per 1000** (from 22 fewer to 20 more)	⊕⊕◯◯ Low

CI, confidence interval; OR, odds ratio; TEE, thromboembolic events; RCT, randomized controlled trials.

Key:

[a]All included observational studies had a high risk of confounding.

[b]Some observational studies have problems with selection bias.

[c]Bias due to missing data.

[d]Selection bias for RCTs: Bias due to random sequence generation.

[e]Performance bias for RCTs: Blinding of participants and personnel.

[f]I^2 = 91% (I^2 > 50% was considered as statistically significant heterogeneity).

[g]For observational studies: Bias in the classification of interventions.

[h]For observational studies: Bias due to deviations from intended interventions.

[i]Reporting bias for both RCTs and observational studies: Selective reporting.

[j]I^2 = 88% (I^2 > 50% was considered as statistically significant heterogeneity).

[k]For observational studies: Bias in the measurement of outcomes.

[l]I^2 = 74% (I^2 > 50% was considered as statistically significant heterogeneity).

[m]I^2 = 94% (I^2 > 50% was considered as statistically significant heterogeneity).

[n]I^2 = 62% (I^2 > 50% was considered as statistically significant heterogeneity).

[o]I^2 = 75% (I^2 > 50% was considered as statistically significant heterogeneity).

[p]I^2 = 82% (I^2 > 50% was considered as statistically significant heterogeneity).

[q]I^2 = 66% (I^2 > 50% was considered as statistically significant heterogeneity).

[r]I^2 = 76% (I^2 > 50% was considered as statistically significant heterogeneity).

[s]I^2 = 71% (I^2 > 50% was considered as statistically significant heterogeneity).

[t]I^2 = 80% (I^2 > 50% was considered as statistically significant heterogeneity).

[u]I^2 = 96% (I^2 > 50% was considered as statistically significant heterogeneity).

decision support and could simplify the many theoretical drug–drug interaction warnings that can interfere with appropriate prescribing. For researchers, rigorously designed studies on warfarin drug–drug interactions are still needed to provide stronger certainty evidence on clinically important interactions, particularly for thromboembolic and fatal outcomes.

5 | CONCLUSION

This review found low to moderate certainty evidence supporting interaction between warfarin and a small group of medications, which result in increased bleeding risk. PPIs are associated with reduced incidence of hospitalization for upper GI bleeding for patients taking warfarin. Further studies are required to better understand drug–drug interactions leading to thromboembolic outcomes or death.

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COMPETING INTERESTS

The authors declare no financial or personal conflict of interest.

CONTRIBUTORS

A.H. and M.W. designed the methods. M.W., D.Z. and A.A. carried out the initial literature searches. M.W., L.N., C.G., F.A., M.A., H.B., D.Z. and A.A. performed the study selection and data extraction. M.W., M.L., F.A., H.B. and K.V. performed the study reporting quality assessment. M.W., D.Z., A.A. and A.H. carried out the data analysis and drafted the manuscript. A.H. provided several rounds of critical revision for accurate and important intellectual content. All authors critically revised the manuscript and supplied final approval of the version to be published.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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APPENDIX I: SEARCH STRATEGY

Embase 1996–present; Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® January 2004–August 2019

1. warfarin.mp. or exp warfarin/
2. interact*.mp.
3. exp drug interaction/or drug interaction*.mp.
4. potentiat*.mp.
5. antagonist*.mp.
6. inhibit*.mp.
7. ae.fs.
8. ai.fs.
9. de.fs.
10. (rat or rats or mouse or mice or murine or sheep or bovine or dog or dogs or cat or cats or cow or cows or primate or primates or frogs).m_titl.
11. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
12. 1 and 11
13. 12 not 10

Database International Pharmaceutical January 2004–August 2019

1. warfarin.mp. or exp warfarin/
2. interact*.mp.
3. (drug interactions or drug interaction*).mp.
4. potentiat*.mp.
5. antagonist*.mp.
6. inhibit.mp.
7. ae.mp.
8. (rats or rat or mice or mouse or murine or sheep or bovine)
9. (dog or dogs or cow or cows or primate or primates or bovine)
10. 2 or 3 or 4 or 5 or 6 or 7
11. 1 and 10
12. 8 and 9
13. 11 not 12

Chapter Six: The Drug-drug Interactions between Direct Oral Anticoagulant (DOACs) and Proton Pump Inhibitors (PPIs) in Elderly Patients: A Retrospective Cohort Study Protocol

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Association of Direct Oral Anticoagulant-Proton Pump Inhibitor Cotherapy with Adverse Outcomes: Protocol for a Population-based Cohort Study

Running title: Drug interaction between DOACs and PPIs

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ABSTRACT

Introduction: Proton pump inhibitors (PPIs) are widely used for secondary prevention of upper gastrointestinal (GI) bleeding. However, there remains controversy about the overall net clinical benefit of PPIs (omeprazole, rabeprazole, pantoprazole, lansoprazole) when co-prescribed with direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, edoxaban). Our objective is to explore the risk of clinically relevant events, including bleeding, thromboembolic events, and death, in patients co-prescribed DOACs and PPIs.

Methods and analysis: The protocol describes a retrospective cohort study of all Ontario residents aged 66 years or older with atrial fibrillation and at least one pharmacy dispensation for a DOAC identified using linked administrative healthcare databases covering 2009 to 2020. Ontario Drug Benefit dispensation records will be used to ascertain PPI exposure during DOAC therapy. The primary outcome is a composite of clinically relevant bleeding, thrombotic events, or all-cause death. Poisson regression with a generalized estimating equation model will be used to calculate the adjusted incidence rate difference, incidence rate ratios 95% confidence interval, adjusting for propensity for PPI use using inverse probability transition weights.

Ethics and dissemination: This research is exempt from REB review under section 45 of Ontario's Personal Health Information Protection Act. We will report our findings in a peer-reviewed biomedical journal and present them at conferences. The study will provide useful evidence to optimize the co-prescription of DOACs and PPIs in practice.

Keywords: Direct oral anticoagulants (DOACs), proton pump inhibitors (PPIs), drug interaction, population-based cohort study.

ARTICLE SUMMARY

Strengths and limitations of this study

- Few studies explicitly investigate the effects of concomitant PPIs on clinically relevant outcomes (e.g., bleeding, thromboembolic events, and death) in patients receiving direct oral anticoagulants (DOACs).

- In this population-based cohort study of seniors, we examine the risk of thromboembolic adverse events, clinically relevant bleeding, and all-cause death in patients prescribed DOACs when concomitant taking PPIs.

- Time-dependent covariates included in Poisson regression models consider the relation of the survival outcome as a function of the change of the covariate.

- As with any observational study, an important limitation is potential for residual confounding.

- As the study is limited to patients aged $\geqslant$66 years, we are unable to generalize the results to younger patients.

INTRODUCTION

Background/rationale

The direct oral anticoagulants (DOACs) refer to the factor Xa inhibitors-rivaroxaban, edoxaban, apixaban, and betrixaban, and the direct thrombin inhibitor-dabigatran.[1] Before introducing DOACs within the last decade, the vitamin-K-antagonist (VKA) warfarin was the only oral anticoagulant used for prevention and treatment of thrombosis.[2] Proton pump inhibitors (PPIs), are H+-K+-blockers, that are used to manage acid-related gastrointestinal (GI) disorders.[3] Currently, there are six PPIs available in Canada: omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and dexlansoprazole. The evidence for PPIs for treating gastroesophageal reflux disease and GI bleeding has been used to indirectly support its concomitant use with DOACs.[4-8] In Canada, with the availability of the DOACs, the proportion of total oral anticoagulant (OAC) prescriptions attributable to warfarin steadily decreased, from 99% in 2010 to around 10% in 2017.[9] [10] According to the 2014 guidelines on AF of the Canadian Cardiovascular Society, most patients for whom an OAC is indicated should receive a DOAC rather than warfarin (strong recommendation, high-quality evidence).[11] At the same time, over 33 million prescriptions of PPIs were dispensed in Canada in 2016, and the number is increasing over time.[12] In 2018, direct factor Xa inhibitors and PPIs were among the top 10 drug classes in terms of public drug program spending in seniors: $316.2 million and $180.8 million, respectively.[13]

In a recent systematic review, we showed an increased risk of bleeding in patients receiving PPI plus warfarin compared to warfarin alone (OR 1.34, 95% CI, 1.22 - 1.47), likely at least partly due to residual confounding.[14] However, controversy remains about the overall net clinical benefit for the PPIs when given with DOACs. Some studies reported no evidence of a protective effect of PPIs against dabigatran-related GI bleeding.[15] [16] One large randomized trial showed that pantoprazole treatment in addition to low dose rivaroxaban did not reduce upper GI bleeding.[17] A prospective pilot study demonstrated that the use of dabigatran with PPIs reduced dabigatran plasma levels in patients with AF.[18] Similarly, it was reported that there were no significant changes found in the anticoagulant activity of factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) according to PPI exposure.[19-21] There are several reports of potential pharmacodynamic and pharmacokinetic interactions between PPIs and antithrombotic agents linked to an increase of thromboembolic event.[22-24] However, except for a lower risk of upper GI bleeding, no other clinically meaningful drug-drug interaction (DDIs) with PPIs were reported for DOACs.[25-28]

There is concern that the use of PPIs may reduce the efficacy of DOACs due to alteration of gastric pH as an acidic environment is required for the dissolution of DOACs; the increase in gastric pH induced by PPIs might affect the solubility and absorption of some of the DOACs (i.e., dabigatran and rivaroxaban).[29] In the RE-LY trial, concomitant use of PPIs reduced dabigatran exposure by 15%, but no significant impact on efficacy outcomes was observed.[30] A pilot RCT reported that a 2-week period of PPI withdrawal leads to a significant increase in dabigatran trough and peak plasma levels in patients with AF.[31]

It is important for clinicians to know whether there are clinically relevant effects of the interaction between PPIs and DOACs when they are co-prescribed. Several studies have considered the effects of cotherapy on GI bleeding.[7 32 33] However, none explicitly investigate the effects of concomitant PPIs on the range of risks and benefits (i.e., clinically relevant gastrointestinal bleeding, thromboembolic events, or death) simultaneously in DOAC-treated patients.

Objectives

The objective of the study is to examine the risk of thromboembolic events, clinically relevant bleeding, and all-cause death in patients concomitantly prescribed DOACs and PPIs.

Our research question is: Among patients receiving DOACs for any indication, does concomitant PPI prescription alter the event rate for the composite outcome (thromboembolic events, clinically relevant bleeding events, and death), compared to not taking PPIs?

METHODS AND ANALYSIS

Study design and data sources

Our study is a population-based cohort study of administrative healthcare data in Ontario, Canada's most populous province. The databases that will be used are listed in Table 1.

We will use Ontario's administrative health databases, which are linked at the person-level using a coded version of the Ontario health insurance number. Prescription drug claims will be identified using the Ontario Drug Benefit Database, which contains comprehensive records of prescriptions dispensed to all Ontarians aged 65 years or older. The Canadian Institute for Health Information (CIHI) Discharge Abstract Database captures diagnostic and procedural information about

hospital admissions. The Ontario Health Insurance Plan Registered Persons Database contains demographic and mortality data. OHIP physician claims data will be used to identify physicians' services. Researchers routinely use these databases to study the clinical consequences of drug-drug interactions.[34 35] International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes and International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes will be used to capture the clinical diagnoses associated with healthcare encounters (see Table 1&Table 2).

Study Population

Ontario residents aged 66 years or older who are newly dispensed a DOAC (dabigatran, rivaroxaban, edoxaban, apixaban, or betrixaban) from 1 January 2009 to 31 March 2020 will be included. As prescription drug information is available for all adults from their 65th birthday in Ontario, including individuals aged 66 years or older will allow for a 1-year lookback period for existing medications. We will exclude patients with a missing or invalid provincial health insurance number, missing age or sex, and prescription for multiple DOACs at entry. Patients will be censored upon death, hospitalization for bleeding or thrombosis, discontinuation of DOAC, switch to other than the entry DOAC, loss of health insurance, or the end of the study period (31 March 2020), whichever occurs first.

Patient and public involvement

No patient involved.

Main Exposures

We will create a DOAC cohort (the control cohort) and a DOAC-PPI co-therapy cohort (the exposure cohort). Drug exposure with doses will be determined from records of dispensation. Exposure to DOACs and PPIs will be treated as time-varying variables. The drug exposure period will be defined according to the combination of the date the prescription is filled and the prescription duration (days supplied).

We will identify a period of continuous DOAC use for each patient, beginning with the first pharmacy claim for a DOAC following the patient's 66th birthday (index date). Our definition of continuous use is a subsequent prescription within 1.5 times the days supplied of the previous DOAC prescription, using a minimum grace period of 30 days. The risk of DOAC-related bleeding, thromboembolic events, or death will be captured only while patients are taking the index DOAC. Thus, all study analyses will be restricted to periods of anticoagulant treatment during

follow-up, defined as the interval from the date the prescription was filled through 1 day after the end of the days of supply, representing approximately two half-lives of the DOACs.

PPI co-therapy will be defined as the period during which gastroprotective effects are most plausible, defined as the interval from filling the prescription (or index date) through the end of the dispensed days of supply. No co-therapy will be defined as person-days with no filled PPI prescription during the observational window.

Main outcomes

The primary outcome will be a composite of clinically relevant bleeding, thrombotic events, or all-cause death. The diagnosis and procedure codes used to define the outcomes can be found in Table 2. Thrombotic events are defined as any thromboembolic event, including myocardial infarction (MI), systemic embolism, ischemic stroke, deep vein thrombosis (DVT), and pulmonary embolism (PE) as captured in hospital discharge abstracts (CIHI-DAD) or emergency department records (NACRS). Clinically relevant bleeding is defined as hospitalization with a most responsible diagnosis, or an emergency department visit with a primary diagnosis of any bleeding. Secondary outcomes include the individual members of the composite primary outcome measure, emergency department visits for the primary outcome, hospitalization for the primary Outcomes will be measured through the records for the hospitalizations and emergency visits registered in the accordingly databases after the index date.

Sample size

We will include up to 26 covariates in the final multivariable Poisson regression models and a minimum of 520 patients (26 covariates × 20) with at least one of the components of the composite outcome (i.e., clinically relevant bleeding, thromboembolic events, or death).[36] To our knowledge, there have been no studies examining rates of the composite outcome of clinically relevant bleeding, thromboembolic events, or death for patients taking DOACs precisely as we have defined them here. However, the sample size is feasible. According to a recently published ICES population-based study, 128,273 patients (average 14,252 annually) were initiated anticoagulation with a DOAC from 2009 to 2017, and 10.5% was reported for the composite outcome (i.e., clinically relevant bleedings, thromboembolic events, and death).[37] If the percentage of co-therapy with PPIs is around 35% (264,447 person-years/ 754,389 person-years as reported by Ray et al.),[7] the patients in the co-therapy cohort can reach 5000 annually in ICES databases. During the 10-year observational windows, there should be around 5,250

patients with at least one component event of the composite outcome. Although it will be more than enough to fulfill our target sample size, we will still include any case eligible to perform the final analysis.

Covariates

The potential confounders include patient demographics [age at cohort entry date, sex, urban/rural (RPDB rural variable) at cohort entry, and socioeconomic status (income quintiles: census-based median neighborhood [Dissemination Area] income quintile) at cohort entry date], indications [AF, thromboembolism, valve replacement/repair comorbidities, hip or knee replacement], Charlson Comorbidity Index at entry date, comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, ischemic stroke, transient ischemic attack, dementia, chronic pulmonary disease, anemia, kidney diseases, and hepatic diseases), components of HAS-B_ED score at cohort entry date (hypertension, abnormal kidney or liver function, stroke, bleeding history, and alcohol use)], CHA2 DS2-VASc Score for AF stroke risk at cohort entry date, and the medications relevant to the outcomes (warfarin (yes/no) within 100 days preceding the index date, former PPIs co-therapy consisted of person-days for patients who filled a PPI prescription in the past year, but whose days of supply ended and, thus, should not benefit from co-therapy.

The potential mediators of the proposed covariates during the following-up period include prescription aspirin (time-varying covariable), antiplatelet agents (time-varying covariable), nonsteroidal anti-inflammatory drugs (time-varying covariable), statins (yes/no), antimicrobials (yes/no), and selective serotonin receptor inhibitors (yes/no). Detailed information on covariates is provided in Table 2.

Bias

To control for confounding, we will include covariables mentioned above in the model to adjust the results. Furthermore, time-varying exposures will help address potential time-varying confounding.[38] For instance, the doses of our primary exposures (DOACS and PPIs) and prescription of other drugs that may affect outcome risk (e.g., NSAIDs and antiplatelet agents) will be captured in a time-varying fashion on a day-to-day basis, and time-dependent Poisson regression models will be used. In addition, any missing data will be dealt with by multiple imputation should observations be missing in more than 10% of cases.[39]

Data collection

The lookback windows include 1) 365 days for defining new DOAC use, 2) 100 days for other related drugs, 3)180 days to 3 years for disease comorbidities and derived indices, and 4) as per the diagnosis dates in ICES-derive chronic disease cohorts.

Baseline data collection will include age at cohort entry, sex, key medical comorbidities (see Table 2), previous GI bleeding history, indications for DOAC, the name of DOAC and PPIs, the first prescription date of DOAC (index date), information for covariates, patients who transfer to other DOAC during the observational window, and the type and date of each outcome.

Data analysis

As this is a population-based study, we will include all eligible Ontario residents. We will compare baseline characteristics of exposures and controls using standardized differences. We computed a set of stabilized inverse probability of treatment (IPT) weight to account for differences in the baseline characteristics (Table 2) between the two cohorts.[40] First, the IPT weights were obtained by fitting a logistic regression model with the primary outcome and the DOACs and PPIs co-therapy as independent variables. Next, we applied IPT weights and assessed balance between the two cohorts by calculating weighted standardized differences, which express the difference of means or prevalence between the two cohorts as a proportion of the pooled standard deviation (SD), with standardized differences above 0.10 considered potentially meaningful. The time-dependent Poisson regression model will then be used to estimate the adjusted incidence of the target outcomes according to both exposure cohort and control cohort with all available covariates using the weighted sample[41] and IPT weight adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) will be obtained. The criterion for statistical significance will be set at alpha = 0.05. All statistical analyses will be performed at ICES using SAS version 9.4 (SAS Institute).

Sensitivity analysis will be performed 1) by excluding patients who did not maintain their original DOAC use assignments during their follow-up, and 2) by excluding patients who re-entered the cohort. Subgroup analysis will be performed according to the different DOACs, PPIs, and indications, respectively (if we have enough data).

ETHICS AND DISSEMINATION

This research is exempt from REB review as the data used in the project is authorized under section 45 of Ontario's Personal Health Information Protection

Act. Upon completion, the results of this population-based study will be submitted to a peer-reviewed biomedical journal for publication and presented at several conferences.

Collaborators Not applicable.

Author Contributions AH and MW obtained the funding and developed the study idea. MW, AH and MP designed the study. MW obtained data permissions and research ethics approvals. LT, DS, and LM contributed to the study design, methodology and analysis plan. AH and DS provided clinical guidance, AH developed the outcome data sets and MP provided expertise in large administrative health databases housed at ICES in designing the study. MW drafted the initial manuscript, and all authors critiqued the protocol manuscript. All authors approve the attached manuscript for publication and are accountable for all aspects of the work.

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Data statement Not applicable.

Disclaimer The conclusions, opinions and statements expressed herein are those of the authors and do not necessarily reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned, externally peer reviewed.

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Table 1. Description of the Ontario databases to be used in the study.

Name of database	Database description
1. Ontario Drug Benefit (ODB) Plan Database	Records of dispensed outpatient prescriptions paid for by the provincial government. The ODB formulary includes a wide range of routine outpatient medications, including the prescription drugs of interest to this study.
2. Canadian Institute for Health Information–Discharge Abstract Database (CIHI-DAD)	The CIHI-DAD collects diagnostic, and procedural variables for each admission to a hospital in Ontario. Coding of primary and secondary diagnoses and inpatient procedures uses the 10th version of the Canadian Modified International Classification of Diseases (ICD-10 CA) for all diagnoses after 2002.
3. Canadian Institute for Health Information–National Ambulatory Care Reporting System (CIHI-NACRS)	The NACRS is compiled by the Canadian Institute for Health Information (CIHI) and contains administrative, clinical (diagnoses and procedures), demographic, and administrative information for all patient visits made to hospital- and community-based ambulatory care centers (emergency departments, day surgery units, hemodialysis units, and cancer care clinics) in Ontario.
4. Ontario Health Insurance Plan (OHIP) Claims History Database	Claims for physician services paid for by the provincial government. It includes a fee code for each service and a diagnosis code for the condition representing the main reason for each service
5. OHIP Registered Persons Database (RPDB)	The RPDB captures information regarding Ontarians' sex, date of birth, postal code, and vital status.
6. Ontario Mental Health Reporting System (OMHRS)	The OMHRS analyzes and reports on information submitted to CIHI about all individuals receiving hospital-based adult mental health services in Ontario.
7. Same Day Surgery Database (SDS)	The SDS summarizes information about same day surgery encounters. Each record contains the procedures undergone as well as clinical information about the individual. The clinical information follows the ICD coding scheme (ICD-9 before 2002 and ICD-10 from 2002 onwards).
8. Corporate Provider Database (CPDB)	This database contains addresses, registration and program eligibility information (e.g.,

	contracts such as primary care group) about individual health care providers, such as physicians.
9. ICES Physician Database (IPDB)	The IPDB contains information about physicians practicing in Ontario. The IPDB includes demographic information about each physician (i.e., age, sex), practice location, physician specialty, services provided, where each physician was trained and year of graduation.
10. Ontario Census Area Profiles (CENSUS)	Ontario-level demographic and statistical data on individuals and households.
11. Postal Code Conversion File (PCCF)	Links postal codes with Census-based area-level variables such as neighborhood income quintiles and urban/rural residence.
12. Ontario Asthma Database (ASTHMA)	ASTHMA contains all Ontario asthma patients identified since 1991.
13. Ontario Congestive Heart Failure Database (CHF)	The CHF database contains all Ontarians with CHF identified since 1991.
14. Ontario Chronic Obstructive Pulmonary Disease Database (COPD)	COPD contains all Ontario COPD patients identified since 1991.
15. Ontario Hypertension Database (HYPER)	HYPER contains all Ontario hypertension patients identified since 1991.
16. Ontario Dementia Database (DEMENTIA)	The Ontario Dementia Dataset is comprised of all Ontario persons who have been identified with Alzheimer's and related dementias in ICES data holdings between the ages of 40 to 110 years.
17. Ontario Crohn's and Colitis Cohort Database (OCCC)	OCCC includes all Ontario patients who were identified with Crohn's disease or Ulcerative Colitis from the ages of 0-105 years.
18. Ontario Diabetes Database (ODD)	The ODD is a population-based disease registry constructed using a validated algorithm based on hospitalizations and physician visits to identify individuals with physician-diagnosed diabetes mellitus in Ontario.
19. Ontario Rheumatoid Arthritis Database (ORAD)	ORAD contains data on all Ontario rheumatoid arthritis patients identified since 1991.
20. Ontario Cancer Registry (OCR)	Patient demographics, cancer diagnosis details, and death information.

Table 2. Variables and their related data sources with codes (if applicable).

Variables	Data source	Codes or specified
Demographics		
Age & sex	RPDB and CENSUS	Not applicable
Income quintile	Statistics Canada and CENSUS	Not applicable
Rural residence	Census Postal Code Conversion File and CENSUS	Not applicable
Indications		
Atrial fibrillation (AF)	NACRS and DAD	ICD10 I48.0, I48.1, I48.2, I48.3, I48.4, I48.9
Thromboembolism	DAD, NACRS, and OHIP	DAD/NACRS ICD10: I26.0, I26.9, I80.1, I80.2, I80.3, I80.8, I80.9, I82.8, I82.9 OHIP Diagnosis Codes: 415, 451
Valve Replacement/Repair	DAD	DAD CCI : • 1HU90 Mitral valve replacement • 1HU80 Mitral valve repair • 1HV90 Aortic valve replacement • 1HV80 Aortic valve repair • 1HT90 Pulmonary valve replacement • 1HT80 Pulmonary valve repair • 1HS90 Tricuspid valve replacement • 1HS80 Tricuspid valve repair • 1HW Valve annulus surgery
Hip or Knee Replacement	DAD	DAD CCI: • 1VA53 implantation of internal device, hip joint • 1VG53 implantation of internal device; knee joint.
Exposures on a day-to-day basis during the following-up period		
Direct oral anticoagulants (DOACs)	ODB	Rivaroxaban, dabigatran, edoxaban, and apixaban

The proton pump inhibitors (PPIs)	ODB	Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and dexlansoprazole.
Comorbidities		
1. Chronic kidney disease (CKD) in the 3 years prior to cohort entry	CIHI-DAD and OHIP	CIHI-DAD: • I12.0 Hypertensive renal disease with renal failure • I13.1 Hypertensive heart and renal disease with renal failure • N03.X Chronic nephritic syndrome • N05.X Unspecified nephritic syndrome • N18.X Chronic renal failure • N19.X Unspecified renal failure • N25.X Disorders resulting from impaired renal tubular function. OHIP: • 403 Hypertensive renal disease • 585 Chronic renal failure;
2. End stage renal disease (ESRD) in the 180 days prior to cohort entry	DAD/NACRS	DAD/NACRS CCI • 1PZ21HQBR • 1PZ21HPD4 • 1PZ21HQBS. • 1PC85LAXXJ transplant; kidney using living donor (allogenic or syngeneic) kidney • 1PC85LAXXK transplant; kidney using cadaver kidney. OHIP Fee Codes • R849 Dialysis - Hemodialysis - Initial & acute.

		• G323 Dialysis - Hemodialysis – Acute, repeat (max 3) • G325 Dialysis - Hemodialysis - Medical component (incl in unit fee) • G32 Dialysis - Chronic, contin. hemodialysis or hemofiltration each • G86 Chronic hemodialysis hospital location • G862 Hospital self-care Chronic hemodialysis • G863 Chronic hemodialysis IHF location • G86 Chronic Home hemodialysis • G866 Intermittent hemodialysis treatment centre • G330 Peritoneal dialysis - Acute (up to 48 hrs) • G331 Peritoneal dialysis - Repeat acute (up to 48 hrs) max. 3 • G332 Peritoneal dialysis - Chronic (up to 48 hrs) [NOT AFTER JAN 2008] • G861 Chronic peritoneal dialysis hospital location • G864 Chronic Home peritoneal dialysis • G082 Continuous venovenous hemodiafiltration • G083 Continuous venovenous haemodialysis

		• G085 Continuous venovenous hemofiltration • G090 Venovenous slow continuous ultrafiltration • G091 Continuous arteriovenous haemodialysis • G092 Continuous arteriovenous hemodiafiltration • G093 Hemodiafiltration - Contin. Init & Acute (repeatx3) • G094 Hemodiafiltration - Contin. Chronic • G095 Slow Continuous Ultra Filtration - Initial & Acute (repeat) • G096 Slow Continuous Ultra Filtration – Chronic • G294 Arteriovenous slow continuous ultrafiltration init and acute • G295 Continuous arteriovenous hemofiltration initial and acute • G333 Home/self-care dialysis • H540 Renal dialysis (outpatient).
3. Liver disease in the 3 years prior to cohort entry	CIHI-DAD and OHIP	CIHI-DAD: B18.x, K70.x, K71.1, K71.3–K71.5, K71.7, K72.x–K74.x, K76.0, K76.2–K76.9, Z94.4 liver disease. OHIP Diagnosis Code: 571 liver disease.
4. Alcoholism in the 3 years prior to cohort entry	CIHI and OHIP	CIHI: F102, G312, G621, G721, I426, K292, K860, Z8640. OHIP Diagnosis Code: 303

5. Dementia in the 3 years prior to cohort entry	Ontario Dementia Database (DEMENTIA)	Not applicable
6. Diabetes in the 3 years prior to cohort entry in the 3 years prior to cohort entry	Ontario Diabetes Dataset (ODD)	Not applicable
7. Hypertension: Ontario Hypertension Database in the 3 years prior to cohort entry	Ontario Hypertension dataset (HYPER)	Not applicable
8. Congestive heart failure (CHF) in the 3 years prior to cohort entry	Congestive Heart Failure (CHF)	Not applicable
9. Active Cancer	OCR, OHIP	Diagnosis in OCR within 1 year OR any of the following OHIP fee codes within 180 days: chemotherapy: G281, G339, G345, G359, G381, G382, G388; and radiation: X310, X311, X312, X313.
10. $CHADS_2$-VASc Score for Atrial Fibrillation Stroke Risk at cohort entry date	As specified for each code related.	1. Congestive heart failure (CHF database): 1 point 2. Hypertension (HYPER database): 1 point 3. Age 65-74 years: 1 point and age 75 years or older: 2 points 4. Diabetes Mellitus (Ontario Diabetes Database): 1 point 5. Previous thromboembolism (codes as following in the preceding 3 years): Any or more than 1 of these codes leads to 2 points. Total score can be 0 or 2. 6. Vascular disease (CAD or PVD: CIHI DAD/NACRS: I25x, I70x, I71x, I73x, I74x, K55.1. OHIP: 412, 451in the preceding 3 years): 1 point 7. Female Sex: 1 point
11. HAS-BLED Score at cohort entry date: HAS-B_ED is HAS-BLED	As specified for each code related.	1. Hypertension (HYPER database): 1 point

without the variable INR (with factors as defined above in the 3-y preceding entry or according to the definition of the ICES-derived cohort)		2. Abnormal renal function (codes for CKD and ESRD) described above): 1 point 3. Abnormal liver function (codes described above): 1 point 4. Stroke or TIA (CIHI-DAD: I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64, I65, I65.0, I65.1, I65.2, I65.3, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.4, I66.8, I66.9 cerebral infarction (ischemic stroke); G45.0, G45.1, G45.2, G45.3, G45.8, G45.9 transient ischemic attack (TIA)): 1 point 5. Bleeding history (bleeding codes described as following in outcome section): 1 point 6. Elderly: Age over 65: 1 point 7. Alcoholism (codes described above): 1 point
12. Charlson Comorbidity Index (using a 3-year lookback).	DAD	Derived using an ICES-developed macro
Potential drug interactions – dispensed in the past 3 months prior to cohort entry		
1. Warfarin: yes/no	ODB	Not applicable
1. Former PPIs co-therapy: yes/no	ODB	Not applicable
	Potential drug interactions – dispensed during the following up period	
1. Non-steroidal anti-inflammatory drugs*: day-to-day basis	ODB	ibuprofen, naproxen, etodolac, nabumetone, indomethacin, rofecoxib, celecoxib, etoricoxib valdecoxib, and meloxicam
2. Selective serotonin reuptake inhibitors (SSRI): yes/no.	ODB	citalopram, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, mirtazapine, trazodone, amitriptyline, nortriptyline, imipramine, and bupropion
3. Amiodarone	ODB	Not applicable

4. Statins: yes/no.	ODB	Atorvastatin, Fluvastatin, Pravastatin, or Simvastatin
5. Aspirin*: day-to-day basis	ODB	Not applicable
6. Antiplatelets: day-to-day basis	ODB	clopidogrel, ticagrelor, dipyridamole, ticlopidine, or prasugrel
7. Antimicrobials: yes/no.	ODB	Fluconazole, Cephalexin, Cefuroxime, Cotrimoxazole, trimethoprim, Macrolides, Azithromycin, Clarithromycin, Macrolides, Ocular Antibiotics, Amoxicillin, Ampicillin, Penicillins, Gatifloxacin, Ciprofloxacin, Norfloxacin, Quinolones, or Levofloxacin
Outcomes		
Bleeding events	CIHI-DAD and CIHI-NACRS	ICD10 • Intracranial haemorrhage: I60, I61, I62.0, I62.1, I62.9, S06.400, S06.401, S06.410, S06.411, S06.420, S06.421, S06.430, S06.431, S06.440, S06.441, S06.490, S06.491, S06.500, S06.501, S06.510, S06.511, S06.520, S06.521, S06.530, S06.531, S06.540, S06.541, S06.590, S06.591, S06.600, S06.601, S06.610, S06.611, S06.620, S06.621, S06.630, S06.631, S06.640, S06.641, S06.690, S06.691 • Eye haemorrhage H35.6, H43.1, H45.0, H11.3, H31.3 • Bleeding of respiratory system: R04.0, R04.1,

		R04.2, R04.8, R04.9, J94.2 • Upper GI bleeding: I85.0, I98.20, I98.3, K22.10, K22.12, K22.14, K22.16, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.80 • Lower GI bleeding and general GI bleeding: K62.5, K55.20, K55.21, K63.80, K92.0, K92.1, K92.2 • Urogenital system bleeding: R31, R310, R311, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N93.0, N93.8, N93.9, N95.0 • Bleeding of muscular and skeletal systems: M25, M25.00, M25.01, M25.02, M25.03, M25.04, M25.05, M25.06, M25.07, M25.08, M25.09 • Others: K66.1, N42.1, R58, T79.2, K66.1, D68.3
Thromboembolic event	CIHI-DAD and CIHI-NACRS	ICD10 • Cerebral infarction (ischemic stroke): I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64, I65, I65.0, I65.1, I65.2, I65.3, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.4, I66.8, I66.9

		• Transient ischemic attack (TIA): G45.0, G45.1, G45.2, G45.3, G45.8, G45.9 • Retinal vascular occlusions: H34.0, H34.1, H34.2, H34.8, H34.9 • Myocardial infarction (MI): I21.1, I21.2, I21.3, I21.4, I21.9, I22.0, I22.1, I22.8, I22.9, I23.0, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8, I24.0, I24.1, I24.8, I24.9 • Pulmonary embolism (PE): I26.0, I26.9 • Vascular disorders of intestine: K55.0, K55.1, K55.9 • Systemic embolism: I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9 • Atherosclerosis: I70.0, I70.1, I70.2, I7020, I7021, I70.8, I70.9 • Nontraumatic ischemic infarction of muscle: M62.2 • Thrombophlebitis: I80.0, I80.1, I80.2, I80.3, I80.8, I80.9, G08 • Other venous embolism and thrombosis: I82.0, I82.1, I82.2, I82.3, I82.8, I82.9, I81, I67.6 • Other peripheral vascular diseases: I73.1, I73.8, I73.9
All cause death	RPDB	Not applicable

Abbreviation: the abbreviation for databases refer to Table 1., CCI for Canadian Classification of Interventions codes.

Appendix. Data collection plan.

Project Initiation This Section must be Completed Prior to Project Dataset(s) Creation	
Project Title:	The Drug-drug Interactions between Direct Oral Anticoagulant (DOACs) and Proton Pump Inhibitors (PPIs) in Elderly Patients: A Population-Based Retrospective Cohort Study
Project TRIM number:	2021 0908 060 000
Research Program:	CDP
Site:	ICES McMaster
Project Objectives:	*Insert Project Objectives as listed in the approved ICES Project PIA* There are therapeutic and convenience advantages to the direct-acting oral anticoagulants (DOACs) compared to warfarin, and the DOAC prescription rates have increased markedly in recent years. In Canada, the direct factor Xa inhibitors and PPIs were each among the top 10 drug classes by public drug prescription program spending on seniors, at $316.2 million and $180.8 million respectively in 2018. In practice, there is widespread use of proton pump inhibitors (PPIs) to treat gastroesophageal reflux disease and for the treatment and prevention of upper gastrointestinal (GI) bleeding in patients taking DOACs, using indirect evidence from previous PPI trials. However, there remains controversy about the overall net clinical benefit for the PPIs (omeprazole, rabeprazole, pantoprazole, lansoprazole) given with the various DOACs (dabigatran, rivaroxaban, apixaban, edoxaban). There is also evidence that the use of PPIs may reduce the efficacy of dabigatran due to alteration of gastric pH as an acidic environment is required for the dissolution. On the other hand, use of pantoprazole with low dose rivaroxaban had no major harm or benefit for preventing upper GI bleeding in a large, randomized trial. Since DOACs are essential but high-risk medications and PPIs are ubiquitous, it is very important to explore broadly the risk of clinically benefit events in patients taking DOACs concomitantly with PPIs. The primary objective of the present study is to explore the risk of the composite outcome of clinically relevant bleeding, thrombotic events, and all-cause death in patients taking PPIs in combination with DOACs compared to those taking DOACs only. A secondary objective is to determine if there is a difference between different DOACs in this risk of events. **Research question:** Among patients receiving DOACs, does concomitant PPIs prescription use change the incidence of the composite of clinically relevant bleeding, thrombotic events, and all-cause death, compared to not taking PPIs?
ICES Project PIA Initial Approval Date:	*The ICES Employee or agent who is responsible for creating the Project Dataset(s) is responsible for ensuring there is an approved ICES Project PIA and verifying the date of approval prior to creating the Project Dataset(s)* 2021-03-17
Principal Investigator (PI):	Mei Wang
Check the applicable box if the PI is an ICES Student/Trainee	☒ ICES Student ☐ ICES Fellow ☐ ICES Post-Doctoral Trainee ☐ Visiting Scholar
Responsible ICES Scientist:	*Name the Responsible ICES Scientist if the PI is not a Full Status ICES Scientist* Michael Paterson

Project Initiation This Section must be Completed Prior to Project Dataset(s) Creation		
Project Team Member(s) Responsible for Project Dataset Creation and/or Statistical Analysis and date joined (list all):	*All person(s) (ICES Analyst, Appointed Analyst, Analytic Epidemiologist, PI, and/or Student) responsible for creating the Project Dataset(s) and/or statistical analysis on the Research Analytics Environment (RAE) and the date they joined the project must be recorded*	
	Mei Wang	2020-09-01
	Michael Paterson	2020-11-14
	Richard Perez	2021-03-10
	Francis Nguyen	2021-03-29
Other ICES Project Team Members and date joined (list all):	*All other Research Project Team Members (e.g., Research Administrative Assistants, Research Assistants, Project Managers, Epidemiologists) and the date they joined the project must be recorded*	
	Anne Holbrook	2020-09-01
	Lehana Thabane	2020-09-01
	Lawrence Mbuagbaw	2020-09-01
	Gary Foster	2020-09-01
	Deborah Siegal	2020-09-01
Confirmation that DCP is consistent with Project Objectives:	*The following individuals must confirm that the ICES Data provided for in this DCP is relevant (e.g., with respect to cohort, timeframe, and variables) and required to achieve the Project Objectives stated in the ICES Project PIA prior to initial Project Dataset creation: 1) PI; 2) Responsible ICES Scientist if the PI is not a Full Status ICES Scientist, or a second ICES Scientist or the Scientific Program Lead if the PI is creating both the DCP and the Project Dataset[s]; 3) ICES Research and Analysis Staff creating the DCP; and 4) ICES Analytic Staff (ICES Employee or agent responsible for creating the Project Dataset[s]). This may be delegated either verbally or via e-mail.*	
	Principal Investigator	☒ 2021-03-29
	Responsible ICES Scientist or Second ICES Scientist/Lead	☒ 2021-03-29
	ICES Research and Analysis Staff Creating the DCP	☒ 2021-03-29
	ICES Analytic Staff	☒ 2021-03-29
Designated ICES Research and Analysis Staff accountable for Project Documentation:	*The person named (ICES staff) is accountable for ensuring that the approved ICES Project PIA, ICES Project PIA Amendments, and DCP are saved on the T Drive, ensuring ICES Project PIA Amendments are submitted as required, ensuring DCP Amendments are documented, and sharing the final DCP with the PI/Responsible ICES Scientist at project completion*	
	Richard Perez	
DCP Creation Date and Author:	*Date DCP was finalized prior to Project Dataset(s) creation*	*Name of person who created the DCP*
	Date	***Name***
	2021-03-29	Mei Wang

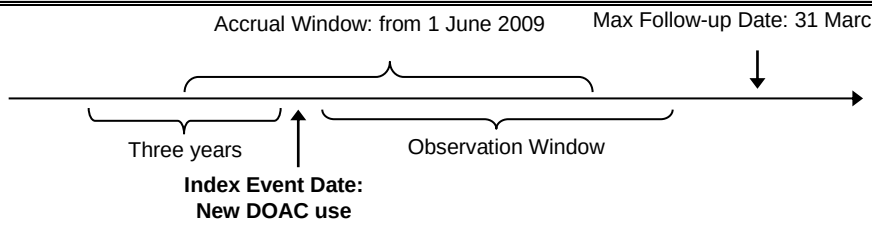
ICES Data This Section must be Completed Prior to Project Dataset(s) Creation	
The ICES Employee or agent who is responsible for creating the Project Dataset(s) must ensure that this list includes only data listed in the ICES Project PIA *Changes to this list after initial ICES Project PIA approval require an ICES Project PIA Amendment*	*Mandatory for all datasets that are available by individual year*
General Use Datasets – Health Services	***Years (where applicable)***
DAD	January 2009 to the latest data available (temporarily 31 March 2020)
NACRS	January 2009 to the latest data available (temporarily 31 March 2020)
ODB	January 2009 to the latest data available (temporarily 31 March 2020)
OHIP	January 2009 to the latest data available (temporarily 31 March 2020)
OMHRS	January 2009 to the latest data available (temporarily 31 March 2020)
SDS	January 2009 to the latest data available (temporarily 31 March 2020)
General Use Datasets – Care Providers	
CPDB	June 2009 to the latest data available (temporarily 31 March 2020)
IPDB	June 2009 to the latest data available (temporarily 31 March 2020)
General Use Datasets – Population	
CENSUS	June 2009 to the latest data available (temporarily 31 March 2020)
RPDB	June 2009 to the latest data available (temporarily 31 March 2020)
General Use Datasets – Coding/Geography	
DIN	June 2009 to the latest data available (temporarily 31 March 2020)
REF	June 2009 to the latest data available (temporarily 31 March 2020)
PCCF	June 2009 to the latest data available (temporarily 31 March 2020)
General Use Datasets - Facilities	
See list	
General Use Datasets - Other	
ASTHMA	June 2009 to the latest data available (temporarily 31 March 2020)
CHF	June 2009 to the latest data available (temporarily 31 March 2020)
COPD	June 2009 to the latest data available (temporarily 31 March 2020)
HYPER	June 2009 to the latest data available (temporarily 31 March 2020)
DEMENTIA	June 2009 to the latest data available (temporarily 31 March 2020)
OCCC	June 2009 to the latest data available (temporarily 31 March 2020)
ODD	June 2009 to the latest data available (temporarily 31 March 2020)
ORAD	June 2009 to the latest data available (temporarily 31 March 2020)
Controlled Use Datasets	
See list	
Other Datasets	

ICES Data This Section must be Completed Prior to Project Dataset(s) Creation	

Project Amendments and Reconciliation			
ICES Project PIA Amendment History (add additional rows as needed):	*Privacy approval date*	*Person who submitted amendment*	*Note that any changes to the list of ICES Data or Project Objectives require an ICES Project PIA Amendment*
	Date	***Name***	***Amendment***
	yyyy-mon-dd		
DCP Amendment History (add additional rows as needed):	*Date DCP amended*	*Person who made the DCP amendment*	*Note that any DCP amendments involving changes to the list of ICES Data or Project Objectives require an ICES Project PIA Amendment*
	Date	***Name***	***Amendment***
	yyyy-mon-dd		
Date Programs/DCP reconciled	*The person(s) creating the dataset and/or analyzing the data are responsible for ensuring that the final DCP reflects the final program(s) when the project is completed*		
	yyyy-mon-dd		

Project Cohort	
Study Design	☒ Cohort study ☐ Matched cohort study ☐ Case-control study ☐ Cross-sectional study ☐ Other (specify):
Index Event / Inclusion Criteria	Ontario residents aged 66 years or older who are newly dispensed a DOAC (rivaroxaban, dabigatran, apixaban, or edoxaban) from June 2009 to the date of latest ICES data available (temporarily March 2020). As prescription drug information is available for all adults older than 65 years in Ontario, inclusion of individuals aged 66 years or older will allow for a 1-year look-back period for existing medications and definition of new use (ie, no use in the preceding 365 d). We will identify a period of continuous DOAC use for each patient, beginning with the first pharmacy claim for a DOAC following the patient's 66th birthday (index date). Our definition of continuous use is a subsequent prescription within 1.5 times the day supply of the previous DOAC prescription, using a minimum grace period of 30 days.
Estimated Size of Cohort (if known)	We will include up to 26 covariates in the final multivariable Poisson regression models and a minimum of 520 patients (26 covariates × 20) with at least one of the components of the composite outcome (i.e., clinically relevant bleeding, thromboembolic events, or death).36 To our knowledge, there have been no studies examining rates of the composite outcome of clinically relevant bleeding, thromboembolic events, or death for patients taking DOACs precisely as we have defined them here. However, the sample size is feasible. According to a recently published ICES population-based study, 128,273 patients (average 14,252 annually) were initiated anticoagulation with a DOAC from 2009 to 2017, and 10.5% was reported for the composite outcome (i.e., clinically relevant bleedings, thromboembolic events, and death).37 If the percentage of co-therapy with PPIs is around 35% (264,447 person-years/ 754,389 person-years as reported by Ray et al.),7 the patients in the co-therapy cohort can reach 5000 annually in ICES databases. During the 10-year observational

Project Cohort	
	windows, there should be around 5,250 patients with at least one component event of the composite outcome. Although it will be more than enough to fulfill our target sample size, we will still include any case eligible to perform the final analysis.
Exclusions (in order)	*Step* Description 1. Missing or invalid health insurance number [ICES Key number (IKN)] 2. Missing age or sex 3. Aged < 66 y at entry 4. History of less than 365 d of OHIP coverage at entry 5. Prescription for multiple DOACs at entry

Project Time Frame Definitions	
	
Accrual Start/End Dates	1 June 2009 to the latest data available. Accrual period is dependent on earliest ODB coverage of DOACs and the latest period for which we have exposure and outcome data – estimated to be 31 March 2020.
Max Follow-up Date	Currently, 31 March 2020.
When does observation window terminate?	Patients leave the cohort on the first of the following dates: 1. End of DOAC use: after 365 days with no filled prescription for any DOAC. (Note: patients may reenter the cohort if they subsequently meet the criteria for entry before the end of the accrual period.) 2. Switch to other than the entry DOAC 3. The date of the data end (currently 31 March 2020) 4. Loss of OHIP, emigration 5. Date of a study endpoint (any hemorrhage, thrombosis, or RPDB death date).
Lookback Window(s)	1. 365 d for defining new DOAC use 2. Various lookbacks for covariates: • 100 d for drugs • 180 d to 3 y for disease comorbidities and derived indices • As per the diagnosis dates in ICES-derive chronic disease cohorts.

Variable Definitions (add additional rows as needed)	
Main Exposure or Risk Factor	Cohort drug exposure is determined from records of filled prescriptions. Periods of drug exposure are defined according to the date the prescription was filled and the dispensed days of supply. Continuous DOAC use is defined as a subsequent prescription within 1.5 times the day supply of the previous DOAC prescription, using a minimum grace period of 30 days. For example, if someone

Variable Definitions (add additional rows as needed)	
	received a prescription of a DOAC for <20 days' supply, look forward 30 days versus if someone received a prescription for 20 or more days' supply look forward 1.5x the day supply. If a person did not receive a subsequent prescription, they discontinued use. **DOACs treatment.** The risk of DOACs-related bleeding should only be present while patients are taking the drug (rivaroxaban, dabigatran, edoxaban, and apixaban). Thus, all study analyses will be restricted to periods of anticoagulant treatment during follow up, defined as the interval from the date the prescription was filled through 1 day after the end of the days of supply, representing approximately two half-lives. **PPI co-therapy.** PPI co-therapy, or person-days on which the patient was likely to be taking the PPIs (i.e., omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, or dexlansoprazole) and thus for which a gastroprotective effect was most plausible, was defined as the interval between the date a PPI prescription was filled through the end of days of supply. No PPI co-therapy was defined as person days with no filled PPI prescription during the observational window.
Primary Outcome Definition	The primary outcome will be a composite of clinically relevant bleeding, thrombotic events, or all-cause death. Definitions (see codes in Table 4): 1. Clinically relevant bleeding: defined as hospitalization (in CIHI DAD) with a most responsible discharge diagnosis (DX10CODE1; dxtype =1, 2; exclude suspect), or an emergency department visit (in NACRS) with main diagnosis of bleeding. 2. Thrombotic events: any of the following arterial or venous thromboembolic events - myocardial infarction (MI), systemic embolism, peripheral embolism, ischemic stroke, deep vein thrombosis (DVT), or pulmonary embolism (PE) as a most responsible discharge diagnosis in CIHI DAD (DX10CODE1; dxtype =1, 2; exclude suspect). 3. All-cause Death: Death date in RPDB.
Secondary Outcome Definition(s)	The secondary outcomes will include clinically relevant bleeding, gastrointestinal (GI) bleeding, upper GI bleeding, thrombotic events, and all-cause death each one. Definitions (see codes in Table 4) 1. Clinically relevant bleeding as described above, with specific subgroups as follows: • Total GI bleeding: Bleeding arising from the esophagus, stomach, duodenum, small intestine, large intestine or colon, rectum, or anus. • Upper GI bleeding: Bleeding arising from the esophagus, stomach, or duodenum. 2. Thrombotic events (as defined above) 3. All-cause death (as defined above)
Covariates	**Indications** 1. Atrial Fibrillation (As coded below in the 5 years preceding cohort entry) NACRS ED visit (source=ed, inclsuspect=F, incluscheduled=F, date=regdate) or DAD inpatient hospitalization (acute=T, inpatient=T, all dxtype, inclsuspect=F, date=ddate) with ICD10 I480 (atrial fibrillation)

Variable Definitions (add additional rows as needed)	
	2. Thromboembolism (As coded below in the 5 years preceding cohort entry) NACRS ED visit (source=ed, inclsuspect=F, incluscheduled=F, date=regdate) or DAD inpatient hospitalization (acute=T, inpatient=T, all dxtype, inclsuspect=F, date=ddate) with ICD10 I26.0, I26.9, I80.1, I80.2, I80.3, I80.8, I80.9, I82.8, I82.9; or OHIP dx 415, 451 3. Valve Replacement/Repair (from Lee et al. 2013) (As coded below in the 5 years preceding cohort entry) DAD INCODE1-20: 1HU90 Mitral valve replacement, 1HU80 Mitral valve repair, 1HV90 Aortic valve replacement, 1HV80 Aortic valve repair, 1HT90 Pulmonary valve replacement, 1HT80 Pulmonary valve repair, 1HS90 Tricuspid valve replacement 1HS80 Tricuspid valve repair, 1HW Valve annulus surgery 4. Hip or Knee Replacement (As coded below in the 35 days preceding cohort entry) DAD INCODE1-20: 1VA53: implantation of internal device, hip joint; 1VG53: implantation of internal device, knee joint 5. Multiple indications (having at least two of the above indications) 6. Others. **Demographics** 1. Age at cohort entry date 2. Sex 3. Urban/rural (RPDB rural variable) at cohort entry 4. Socioeconomic status (income quintiles: Census-based median neighborhood [Dissemination Area] income quintile) at cohort entry date. **Comorbidities (see codes in Table 5)** Captured in DAD, NACRS, and OHIP as of cohort entry using an ICES-derived cohort or with lookback periods as indicated, below. 1. Chronic kidney disease (CKD): 3 years 2. End stage renal disease (ESRD): 180 days. 3. Liver diseases: 3 years 4. Alcoholism: 3 years 5. Dementia: Ontario Dementia Database 6. Diabetes: Ontario Diabetes Database 7. Hypertension: Ontario Hypertension Database 8. Congestive heart failure (CHF): Ontario CHF database 9. Active Cancer: Diagnosis in OCR within 1 year OR any of the following OHIP fee codes within 180 days: chemotherapy: G281, G339, G345, G359, G381, G382, G388; and radiation: X310, X311, X312, X313. **CHA_2DS_2-VASc Score for Atrial Fibrillation Stroke Risk at cohort entry date** 1. Congestive heart failure (CHF database): 1 point 2. Hypertension (HYPER database): 1 point 3. Age 65-74 years: 1 point and age 75 years or older: 2 points 4. Diabetes Mellitus (Ontario Diabetes Database): 1 point 5. Previous thromboembolism (Table 4 in the preceding 3 y): Any or more than 1 of these codes leads to 2 points. Total score can be 0 or 2. 6. Vascular disease (Table 5 in the preceding 3 y): 1 point

Variable Definitions (add additional rows as needed)	
	7. Female Sex: 1 point **HAS-B_ED Score at cohort entry date:** HAS-B_ED is HAS-BLED without the variable INR (with factors as defined above in the 3-y preceding entry or according to the definition of the ICES-derived cohort) 1. Hypertension (HYPER database): 1 point 2. Abnormal renal function: 1 point 3. Abnormal liver function: 1 point 4. Stroke or TIA: 1 point 5. Bleeding history: 1 point 6. Elderly: Age over 65: 1 point 7. Alcoholism: 1 point **Charlson Comorbidity Index (CCI; using a 3-year lookback).**
Other Variables	**Pre-Index related drugs within 100 days preceding the index date.** 1. Warfarin (yes/no) 2. Former PPIs co-therapy consisted of person-days for patients who filled a PPI prescription in the past year, but whose days of supply ended and, thus, should not benefit from co-therapy. Analysis of this person-time permitted assessment of confounding by unmeasured factors associated with receiving a PPI prescription. **Potential interaction drugs during the following up period:** 3. Amiodarone (yes/no) 4. NSAID (time dependent variable) 5. Antiplatelet agent (time dependent variable) 6. Selective serotonin reuptake inhibitor (SSRI) (yes/no) 7. Statins (yes/no) 8. Antimicrobials (yes/no)

Analysis Plan and Dummy Tables (expand/modify as needed)
Descriptive Tables (insert or append dummy tables), e.g.:
Table 1. Baseline characteristics and covariates according to primary/secondary exposure
Table 2. Outcomes according to primary/secondary exposure
Table 3. Description of ICES databases.
Table 4. Excel files for all related ICD-10 codes.
Table 5. DAD/NACRS and OHIP diagnosis and OHIP fee codes for related variables.
Table 6. Clinical and continuity of care variables and data sources variable data.

Statistical Model(s)

Type of model	Time-dependent Poisson regression model
Primary independent variable	DOAC treatment with PPI co-therapy (time-dependent variable)
Dependent variable	The adjusted incidence of composite outcome including clinically important hemorrhages, thromboembolic events, or death.

Analysis Plan and Dummy Tables (expand/modify as needed)	
Covariates	1. Age 2. Sex 3. Indication for DOAC 4. Active cancer 5. Previous thromboembolism 6. CHA_2DS_2VASc score 7. Charlson Comorbidity Index (CCI) 8. Kidney disease 9. Liver disease 10. Pre-Index related drugs. 11. Potential drug interaction therapy 12. GI bleeding history 13. HAS-B_ED score 14. Alcoholism
Data analysis plan	The study analysis requires identifying periods of exposure to oral anticoagulants and PPIs. Because these medications are thought to alter the risk of bleeding only while the patients are taking the drugs, we will track study medication exposure during follow up on a day-by-day basis. As this is a population-based study, we will include all eligible Ontario residents. We will compare baseline characteristics of exposures and controls using standardized differences. We computed a set of stabilized inverse probability of treatment (IPT) weight to account for differences in the baseline characteristics (Table 2) between the two cohorts.40 First, the IPT weights were obtained by fitting a logistic regression model with the primary outcome and the DOACs and PPIs co-therapy as independent variables. Next, we applied IPT weights and assessed balance between the two cohorts by calculating weighted standardized differences, which express the difference of means or prevalence between the two cohorts as a proportion of the pooled standard deviation (SD), with standardized differences above 0.10 considered potentially meaningful. The time-dependent Poisson regression model will then be used to estimate the adjusted incidence of the target outcomes according to both exposure cohort and control cohort with all available covariates using the weighted sample41 and IPT weight adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) will be obtained. The criterion for statistical significance will be set at alpha = 0.05. All statistical analyses will be performed at ICES using SAS version 9.4 (SAS Institute).
Statistical Model(s)	
Type of model	
Outcome	
Matching	
Sensitivity Analyses	Sensitivity analysis will be performed 1) by excluding patients who did not maintain their original DOAC use assignments during their follow-up, and 2) by excluding patients who re-entered the cohort. Subgroup analysis will be performed according to the different DOACs, PPIs, and indications, respectively (if we have enough data).
Type of model	
Primary independent variable	
Dependent variable	

Analysis Plan and Dummy Tables (expand/modify as needed)	
Covariates	

Quality Assurance Activities		
RAE Directory of SAS Programs		
RAE Directory of Final Dataset(s)	*The final analytic dataset for each cohort includes all the data required to create the baseline tables and run all the models. It should include all covariates for all models such as patient risk factors, hospital characteristics, physician characteristics, exposure measures (continuous, categorical) and outcomes. It should include covariates that were considered but didn't make the final cut. This would permit an analyst to easily re-run the models in the future.*	
RAE README file available: ☐Yes ☐No		
Date results of quality assurance tools for final dataset shared with project team (where applicable):		
	%assign	yyyy-mon-dd
	%evolution	yyyy-mon-dd
	%dinexplore	yyyy-mon-dd
	%track / %exclude	yyyy-mon-dd
	%codebook	yyyy-mon-dd
Additional comments:		

References:

Table 1. Baseline characteristics according to primary/secondary exposure.

Patient Characteristic	No PPI Co-therapy					PPI Co-therapy				
	All DOACs	Apixaban	Dabigatran	Rivaroxaban	Edoxaban	All DOACs	Apixaban	Dabigatran	Rivaroxaban	Edoxaban
Patients, No.										
New episodes of anticoagulant treatment, No.										
Person-years of follow-up										
Covariate, person-years (%)										
Age, y 66-74 75-84 ≥85										
Year of cohort entry 2009-2011 2012-2013 2014-2015 2016-2017 2018-2019 2019-										
Sex Male Female										
Income quintiles 1 (Low) 2 3 4 5 (high)										
Rural residence										
Comorbidity										

1. Chronic kidney disease and End stage renal disease 2. Liver diseases. 3. Alcoholism 4. Dementia: Ontario 5. Diabetes: Ontario 6. Hypertension: 7. Congestive heart failure (CHF): 8. Active Cancer: Diagnosis in OCR within 1 year.										
Medications 1. Amiodarone 2. NSAID 3. Antiplatelet agent 4. SSRI 5. Statin **6.** Antimicrobials										
PPIs 1. Omeprazole 2. Esomeprazole 3. Lansoprazole 4. pantoprazole 5. rabeprazole 6. dexlansoprazole		**n/a**	**n/a**	**n/a**	**n/a**					

Table 2. Comparative Incidence of primary outcomes (a composite of clinically relevant bleeding, thrombotic events, or all-cause death) for individual direct oral anticoagulants according to PPI co-therapy.

	No PPI Co-therapy			PPI Co-therapy		
	Primary outcomes, n	**Person-years**	**Adjusted incidence/ 10 000 person-years (95% CI)**	**Primary outcomes, n**	**Person-years**	**Adjusted incidence/**
All DOACs						
Apixaban						
Dabigatran						
Rivaroxaban						
Edoxaban						

Table 3. Description of ICES databases.

Name of database	Database description
21. Ontario Drug Benefit (ODB) Database	Records of dispensed outpatient prescriptions paid for by the provincial government. The ODB formulary includes a wide range of routine outpatient medications, including oral preparations of the prescription drugs of interest to this study.
22. Canadian Institute for Health Information–Discharge Abstract Database (CIHI-DAD)	The CIHI-DAD collects diagnostic, and procedural variables for each admission to a hospital in Ontario. Coding of primary and secondary diagnoses and inpatient procedures uses the 10th version of the Canadian Modified International Classification of Disease system (ICD-10 CA) for all diagnoses after 2002.
23. Canadian Institute for Health Information–National Ambulatory Care Reporting System (CIHI-NACRS)	The NACRS is compiled by the Canadian Institute for Health Information (CIHI) and contains administrative, clinical (diagnoses and procedures), demographic, and administrative information for all patient visits made to hospital- and community-based ambulatory care centers (emergency departments, day surgery units, hemodialysis units, and cancer care clinics) in Ontario.
24. Ontario Health Insurance Plan (OHIP) Claims History Database	Claims for physician services paid for by the provincial government.
25. Registered Persons Database (RPDB)	The RPDB captures information regarding Ontarians' gender, date of birth, postal code, and vital status.
26. Ontario Mental Health Reporting System (OMHRS)	The OMHRS analyzes and reports on information submitted to CIHI about all individuals receiving adult mental health services in Ontario, as well as some individuals receiving services in youth inpatient beds and selected facilities in other provinces.
27. Same Day Surgery Database (SDS)	The SDS summarizes same day surgery information about individuals. Each record contains the procedures undergone as well as clinical information about the individual. The clinical

	information follows the ICD coding scheme (ICD-9 before 2002 and ICD-10 from 2002 onwards).
28. Corporate Provider Database (CPDB)	This data contains addresses, registration and program eligibility information (e.g., contracts such as primary care group) about individual health care providers such as physicians, pharmacists, and other practitioners.
29. ICES Physician Database (IPDB)	The IPDB contains information about physicians practicing in Ontario. The IPDB includes demographic information about each physician (i.e., age, sex), practice location, physician specialty, services provided, where each physician was trained and year of graduation.
30. Ontario Census Area Profiles (CENSUS)	Ontario-level demographic and statistical data on individuals and households.
31. Drug Identification Number (DIN)	The Drugs List data set contains information on drug and product names, subclass information, product codes, drug strength, route of administration, first and last dispensing dates from OD. This data set is used to obtain a list of drug information numbers (DINs) which fall under generic drug names/drug subclasses, to look up properties of a drug such as strength, and to gather information on doses of drug dispensed in an ODB claim.
32. Reference Files (Look-up Tables) (REF)	REF contains detailed information on various geographic variables used in conducting population level analysis and various geographic-related look-up tables. (e.g., Dissemination Area can be linked with other geographic variables such as income quintile)
33. Postal Code Conversion File (PCCF)	Contains macros corresponding to each census year to link the postal codes with the geographic variables based on PCCF+ files since 1996. Geographic variables include neighborhood income quintiles, census division, dissemination area, latitude/longitude, urban/rural.
34. Ontario Asthma dataset (ASTHMA)	ASTHMA collects data, which includes all Ontario asthma patients identified since 1991.

35. Congestive Heart Failure (CHF)	The CHF database contains all Ontario individuals with CHF identified since 1991.
36. Chronic Obstructive Pulmonary Disease (COPD)	COPD contains all Ontario COPD patients identified since 1991, which enables identification of individuals with physician diagnosed COPD in health administrative databases.
37. Ontario Hypertension dataset (HYPER)	HYPER contains all Ontario hypertension patients identified since 1991, for the purposes of including algorithms for identifying cases, validation measures, citations for each cohort creation, data availability, prevalence and incidence flags.
38. Ontario Dementia Database (DEMENTIA)	The Ontario Dementia Dataset is comprised of all Ontario persons who have been identified with Alzheimer's and related dementias in ICES data holdings between the ages of 40 to 110 years.
39. Ontario Crohn's and Colitis Cohort dataset (OCCC)	OCCC includes all Ontario patients who were identified with Crohn's disease or Ulcerative Colitis from the ages of 0-105 years.
40. Ontario Diabetes Dataset (ODD)	The ODD is a population-based disease registry constructed using a validated algorithm based on hospitalizations and physician visits to identify individuals with physician-diagnosed diabetes mellitus in Ontario. ODD data is collected for the purpose of recording physician-diagnosed diabetes cases.
41. Ontario Rheumatoid Arthritis Dataset (ORAD)	ORAD contains data on all Ontario rheumatoid arthritis patients identified since 1991. ORAD collects data for the purpose of improving the accuracy of Canadian health administrative databases in identifying patients with rheumatoid arthritis.

Table 4. all related ICD-10 codes.

Microsoft Excel Worksheet

Table 5. DAD/NACRS and OHIP diagnosis and OHIP fee codes for related variables.

Variables	Data Source and Type of Code
Chronic kidney disease	DAD diagnosis ICD10 I12.0 Hypertensive renal disease with renal failure I13.1 Hypertensive heart and renal disease with renal failure N03.X Chronic nephritic syndrome N05.X Unspecified nephritic syndrome N18.X Chronic renal failure N19.X Unspecified renal failure N25.X Disorders resulting from impaired renal tubular function. OHIP diagnosis 403 Hypertensive renal disease 585 Chronic renal failure
End stage renal disease	DIALYSIS OHIP fee code R849 Dialysis - Hemodialysis - Initial & acute G323 Dialysis - Hemodialysis - Acute, repeat (max 3) G325 Dialysis - Hemodialysis - Medical component (incl in unit fee) G326 Dialysis - Chronic, contin. hemodialysis or hemofiltration each G860 Chronic hemodialysis hospital location G862 Hospital self-care Chronic hemodialysis G863 Chronic hemodialysis IHF location G865 Chronic Home hemodialysis G866 Intermittent hemodialysis treatment centre G330 Peritoneal dialysis - Acute (up to 48 hrs) G331 Peritoneal dialysis - Repeat acute (up to 48 hrs) max. 3 G332 Peritoneal dialysis - Chronic (up to 48 hrs) [NOT AFTER JAN 2008] G861 Chronic peritoneal dialysis hospital location G864 Chronic Home peritoneal dialysis G082 Continuous venovenous haemodialfiltration G083 Continuous venovenous haemodialysis G085 Continuous venovenous haemofiltration G090 Veneovenous slow continuous ultrafiltration G091 Continuous arteriovenous haemodialysis G092 Continuous arteriovenous haemodiafiltration G093 Haemodiafiltration - Contin. Init & Acute (repeatx3) G094 Haemodiafiltration - Contin. Chronic G095 Slow Continuous Ultra Filtration - Initial & Acute (repeat) G096 Slow Continuous Ultra Filtration - Chronic G294 Arteriovenous slow continuous ultrafiltration init and acute G295 Continuous arteriovenous haemofiltration initial and acute G333 Home/self-care dialysis H540 Renal dialysis (outpatient) DAD/NACRS procedure HD: 1PZ21HQBR PD: 1PZ21HPD4 CRRT: 1PZ21HQBS KIDNEY TRANSPLANTATION DAD procedure

	1PC85LAXXJ Transplant, kidney using living donor (allogenic or syngeneic) kidney. 1PC85LAXXK Transplant, kidney using cadaver kidney
Liver disease	CIHI: B18.x, K70.x, K71.1, K71.3–K71.5, K71.7, K72.x–K74.x, K76.0, K76.2–K76.9, Z94.4. OHIP: 571
Alcoholism	CIHI: F102, G312, G621, G721, I426, K292, K860, Z8640. OHIP: 303
Vascular disease	CAD or PVD: CIHI DAD/NACRS: I25x, I70x, I71x, I73x, I74x, K55.1. OHIP: 412, 451

Abbreviations: CCI= Canadian Classification of Health Interventions; DAD: Discharge Abstract Database; ICD-10CM=International Classification of Diseases, 10th Revision; Clinical Modification; NACRS=National Ambulatory Care Reporting System; OHIP=Ontario Health Insurance Plan

Table 6. Clinical and continuity of care variables and data sources variable data.

Variable	Data source
Patients' characteristics	
Age & sex	Registered Persons Database (RPDB)
Income quintile	Statistics Canada
Rural residence	Census Postal Code Conversion File
Indication: Atrial fibrillation	CIHI-DAD, CIHI-NACRS, OHIP
Type of DOAC dispensed at index prescription date: dabigatran, rivaroxaban, apixaban, edoxaban. Type of PPIs dispensed at the index prescription date: omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and dexlansoprazole	ODB
Comorbidities	
Components of CHA2DS2-VASc– looking at the presence of these medical conditions in the 3 years prior to cohort entry	
Congestive heart failure	CHF
Hypertension	HYPER
Prior stroke/transient ischaemic stroke Peripheral vascular disease	CIHI-DAD
Abnormal renal/liver function	CIHI-DAD, OHIP
Prior bleeding	CIHI-DAD
Drugs/alcohol concomitantly	CIHI-DAD, ODB
Charlson comorbidity score	CIHI-DAD
Other comorbidities	
Dementia	DEMENTIA
Delirium	CIHI-DAD, OMHRS
Diagnosis of obesity in the 3 years prior to cohort entry Diagnosis of underweight in the 3 years prior to cohort entry	CIHI-DAD, OHIP
Antiphospholipid syndrome in the 3 years prior to cohort entry	CIHI-DAD
Active cancer	OCR, OHIP
Substance abuse Alcoholic abuse	CIHI-DAD, OMHRS, OHIP
Recent anticoagulant use (120 days)	ODB
Thromboembolic event	CIHI-DAD, CIHI-NACRS
Potential drug interactions – dispensed in the past 3 months prior to cohort entry or during the following up period, unless otherwise specified	

Different drugs dispensed that potentially interact with DOACs • Non-steroidal anti-inflammatory drugs* （ibuprofen, naproxen, etodolac, Nabumetone, indomethacin, Rofecoxib, celecoxib, etoricoxib valdecoxib, and meloxicam） • Selective serotonin reuptake inhibitors (SSRI) (citalopram, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, mirtazapine, trazodone, amitriptyline, nortriptyline, imipramine, and bupropion). • Amiodarone • Statins (Atorvastatin, Fluvastatin, Pravastatin, or Simvastatin) • Aspirin* • Antiplatelets (clopidogrel, ticagrelor, dipyridamole, ticlopidine, or prasugrel) • Antimicrobials (Fluconazole, Cephalexin, Cefuroxime, Cotrimoxazole, trimethoprim, Macrolides, Azithromycin, Clarithromycin, Macrolides, Ocular Antibiotics, Amoxicillin, Ampicillin, Penicillins, Gatifloxacin, Ciprofloxacin, Norfloxacin, Quinolones, or Levofloxacin) Number of drugs dispensed that potentially interact with DOACs	ODB
Outcomes	
Bleeding events	CIHI-DAD, CIHI-NACRS
Thromboembolic event	CIHI-DAD, CIHI-NACRS
All cause death	RPDB

*Over-the-counter use of drug is not captured.

Chapter Seven: Discussion

This thesis focused on a series of projects to prepare for an OAC management RCT, including 1) the barriers and facilitators for optimal OAC management, 2) appropriate outcomes for OAC management research, and 3) drug-drug interaction for OACs. These three important topics were investigated in this manuscript-basis thesis, with specific studies dedicated to exploring each issue. This chapter summarizes the key findings from **Chapters 2 to 6** and discusses the methodological challenges, limitations, and implications of the five studies.

Methodology challenges and innovation

In **Chapters 2 and 3**, we applied a qualitative approach to explore the barriers and facilitators for optimal OAC management. The scoping review (**Chapter 2**) and the focus group study (**Chapter 3**) employed a qualitative approach. The main methodological challenge focused on the rigorous ways to synthesize the themes. Although there is no standard category of influencing factors for OAC management and there are too many factors reported in the existing papers, we followed the principles of qualitative description and the content analysis to synthesize the findings [1, 2]. Content analysis is an analytic method based on an inductive approach to coding, with codes developed directly from the data rather than preconceived categories [3]. Another methodological challenge was how to decide the factors that have potentially overlapping coding. For instance, several items labeled patient-related barriers could be coded as provider-related or system-level barriers. This potential overlap in attribution coding was addressed within the investigator group by discussion and consensus. This is a common issue with qualitative methods. Most of the categories were attributed to the original papers. The scoping review results were checked and confirmed by a focus group study we ran at the same time (Appendix 1). The innovation of the methodology focused on the preparation for an RCT with rigorous qualitative research.

In **Chapter 4**, we used a systematic survey to explore the outcome list for OAC management research. The primary methodological challenge referred to the outcome reporting in the included studies. Not all outcomes performed in the trials can be reported for the space limitation or potential publication bias. A lack of complete and transparent reporting of the investigated trial outcomes is always the kay issue of publication bias [4]. We then included any available protocol in the projects to assess the outcomes used in the included studies integrally. The secondary challenge was to define a valid taxonomy in medical research [5, 6]. This taxonomy

has been validated in another review on outcome reporting from non-valvular atrial fibrillation clinical trials [7].

In **Chapters 5 and 6**, a systematic review with meta-analysis and observational study were used to explore the drug-drug interaction for OACs. The main methodological challenge for **Chapter 5** was how to evaluate the drug-drug interaction (DDI) evidence systematically. The logical steps include 1) assessing the quality of DDI evidence, 2) assessing the severity of the DDI-related clinically important outcomes, and 3) Defining the causality of DDI [8]. We performed those procedures in the present study by the risk of bias assessment (Table 2), effect size evaluation by meta-analysis, and GRADE assessment (Table 3) for each important outcome. The main methodological challenge for **Chapter 6** was to address confounding and bias in a population-based protocol on DOACs drug-drug interaction. First, time-dependent Poisson regression model will be used to estimate the propensity score with all selected confounders forced as covariates [9]. Then, matching will be performed on age, sex, and history of bleeding. Also, the balance on the covariates of interest will be assessed. The methodological innovation was the use of both systematic review and population-studies to generate concrete evidence for drug-drug interaction.

The implication of the studies

According to the scoping review (**Chapter 2**), factors identified could be grouped into four themes— therapy-related, patient-related, healthcare provider-related, and health system-related. Key barriers to optimal OAC management were mostly patient-related, whereas interventions focused on education or implementing protocols were shown through RCTs to improve the knowledge scores of OAC patients but not clinical outcomes. The individual physician may wish to address the key barriers in their practice as a quality improvement initiative, but system-wide or policy changes should await higher quality evidence. For our ongoing OAC management trial, some related factors can be used to optimize the coordination treatment. For instance, review renal function regularly for patients taking DOACs (therapy-related facilitator), ensuring patient knowledge of benefits and risk of OACs (patients-related facilitator), providing reassurance to patients when they have achieved their INR goal (healthcare provider-related facilitator), and case management program (health system-related facilitator) can be tailored into the intervention of the experimental arm.

The qualitative study (**Chapter 3**) provided input content of the patients' OAC education and some barriers to OAC patient education in Ontario. Tailored and effective intervention

programs could be developed based on the findings to improve the OAC patient education in Ontario. In the present study, according to both healthcare providers and patients' opinions, four themes of the important contents of patient education (what, when, who, and how) were explored. Some important barriers, including the patients' attitude, limited time of the health care providers, the poor communication within the system, and lack of national OAC registries, were identified. All those related educational contents can be used to improve the initial education and virtual visits for our ongoing RCT. Besides, the findings of the study supplied a clue to optimal patients' education to improve the OAC management.

The results of the systematic survey (**Chapter 4**) provide valuable information for the development of a cone outcome set (COS) for OAC research by a consensus process in the future (See Appendix II, a protocol for the Delphi study). This would involve qualitative studies to ensure that stakeholder experts can offer and comment on potential core outcomes, followed by a formal consensus panel review. In the meantime, the list of the outcomes supplied a good reference for other OAC research in choosing appropriate outcomes to be used.

The implications for **Chapter 5** (systematic review on warfarin drug-drug interaction) are obvious for clinicians. They may be encouraging, given the small list of interacting medications for warfarin associated with bleeding, particularly where the potentially interacting drug does not have hemorrhagic effects of its own. For policymakers, the present results improve the evidence base of decision support and could simplify the many theoretical drug-drug interaction warnings that can interfere with appropriate prescribing. For researchers, rigorously designed studies on warfarin drug-drug interactions are still needed to provide stronger certainty evidence on clinically important interactions, particularly for thromboembolic and fatal outcomes. Nevertheless, for our ongoing RCT, the effect size of the warfarin drug-drug interaction and the clinically significant drug interaction list supply a useful reference for the intervention.

For **Chapter 6**, the protocol on the drug-drug interactions between DOACs and Proton Pump Inhibitors (PPIs) is meant to complement several studies, including systematic reviews of warfarin drug interaction [10] and population-based studies on other drug interactions with DOACs [11-13]. These, in addition to the present study, will optimize the OACs prescription in practice. The findings of this study will be a good reference for the ongoing RCT as well.

Limitations of the studies

For **Chapter 2&3**, there may exist information and selection bias in the scoping review as the included studies do not always describe the facilitators or barriers explicitly or extensively to some extent. Next, since the study's original design was to explore the general meaning of B&F of the OAC management, we did not stratify our results by the indication for anticoagulation or OAC category, although it is not clear that the B&F would differ by indication. However, extraction processes were performed in duplicate with adjudication to reduce errors. As a result, we believe we identified valid B&Fs for OACs management from the literature we found.

For **Chapter 4**, first, this study did not address the validity and reliability of each outcome, which would be an important consideration for a core outcome. Second, the definition of each outcome varied across the studies, and we only combined outcome descriptions under one term when we were sure that it was the same outcome. Finally, we may have missed some important outcomes, as we excluded studies focused only on economic analysis or pharmacokinetics. However, these are unlikely to yield beneficial clinical efficacy or safety outcomes. As outlined, vetting these outcomes which trials have used against a framework standard of which outcomes should be considered for trials, will be important.

The conclusions of **Chapter 5** (systematic review on warfarin drug-drug interaction) are primarily limited by the overall quality of the literature, which is mainly comprised of retrospective studies conducted using administrative databases or post hoc analyses of clinical trials that are at high risk of confounding and selection bias. In addition, some potentially eligible studies may have been missed as our search strategies included the term "interaction" for warfarin. Unfortunately, drug-drug interactions are rarely the topic of randomized trials. For **Chapter 6** (protocol on DOACs and PPIs interaction), the study will be a retrospective cohort study with the unavoidable problems of observational studies, including confounding, which we may not realize and will not include in the data analysis [14]. In addition, the limitation of the data resources will restrict the target population to senior patients, which will lead the information loss of the patients less than 65 years old.

Conclusion

In summary, this standard thesis describes five different background projects to prepare for an OAC management RCT. The papers contribute to the literature by employing a variety of methods to inform OAC management and OAC research. More investigation may be needed to generalize these findings and explore further methodological issues for OAC trials.

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