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Expert Review of Clinical Pharmacology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierj20

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To cite this article: Adane Teshome Kefale, Woldesellassie M. Bezabhe & Gregory M. Peterson (2023) Clinical outcomes of oral anticoagulant discontinuation in atrial fibrillation: a systematic review and meta-analysis, Expert Review of Clinical Pharmacology, 16:7, 677-684, DOI: 10.1080/17512433.2023.2223973

To link to this article: https://doi.org/10.1080/17512433.2023.2223973

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
2023, VOL. 16, NO. 7, 677–684
https://doi.org/10.1080/17512433.2023.2223973

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META-ANALYSIS

Clinical outcomes of oral anticoagulant discontinuation in atrial fibrillation: a systematic review and meta-analysis

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ABSTRACT

Introduction: Oral anticoagulants (OACs) should generally be continued lifelong in patients with atrial fibrillation (AF) to ensure optimal benefits, unless contraindications arise. However, discontinuation of OACs might occur for various reasons, potentially affecting clinical outcomes. In this review, we synthesized evidence on the clinical outcomes following OAC discontinuation in patients with AF.

Methods: We conducted a systematic review and meta-analysis using PubMed, Embase and Scopus. Cohort or case–control studies were included if data were available on clinical outcomes of OAC discontinuation, compared with continuation, in patients with AF. A random-effect meta-analyses were conducted for key outcomes of stroke, mortality, and major bleeding.

Results: Eighteen observational studies having a total of 283,418 patients were included. Discontinuation significantly increased the risk of stroke (hazard ratio [HR] 1.88; 95% confidence interval [CI] 1.58–2.23), all-cause (HR 1.90; 95% CI 1.40–2.59) and cardiovascular (HR 1.83; 95% CI 1.06–3.18) mortality. The risk of major bleeding was not significantly different between the discontinued and continued groups (HR 1.04; 95% CI 0.72–1.52).

Conclusions: Discontinuation of OAC therapy was associated with an increased risk of stroke and mortality, with no difference in the risk of major bleeding. Acknowledging heterogeneity among the studies, the findings underline the need to ensure continuity of OAC therapy in patients with AF to prevent thrombotic complications and associated mortality.

PROSPERO registration number: CRD42020186116

ARTICLE HISTORY
Received 23 February 2023
Accepted 5 June 2023

KEYWORDS
Anticoagulants; discontinuation; persistence; outcomes; stroke; mortality; hospitalization; atrial fibrillation

1. Introduction

Atrial fibrillation (AF) is the most common cardiac rhythm disorder, affecting over 60 million people worldwide in 2019 [1]. AF is associated with an up to five-fold increase in the risk of stroke. It also increases the risk of systemic embolism, myocardial infarction, heart failure, and death [2]. However, a large proportion of thrombotic complications associated with AF can be prevented with tailored initiation and continuous use of oral anticoagulants (OACs), either vitamin K antagonists (VKAs) or direct-acting oral anticoagulants (DOACs) [3].

Following the initiation of an OAC, patients are expected to continuously take the medication, usually lifelong, unless contraindicated. However, the continuation of OACs remains a challenge in clinical practice, even after the introduction of DOACs, with their advantages such as lack of interactions with foods, fewer interactions with drugs, fixed daily dosing, and absence of frequent laboratory monitoring compared to VKAs [4,5]. Discontinuation may be associated with an increased risk of thromboembolic stroke and transient ischemic attack (TIA) [5–8], adverse cardiovascular outcomes, and mortality [8,9]. The effects of discontinuation are more likely to be rapid in DOAC users as these drugs have short half-lives [10].

Prior reviews have focused on rates of persistence with different OACs, with little attention to the clinical consequences of discontinuation [4,5]. Ozaki and colleagues [5] attempted to review outcomes of non-persistence but included only a single study, with studies published since. We aimed to systematically review and meta-analyze the outcomes of OAC discontinuation in patients with AF to synthesize updated evidence relevant to clinical practice.

2. Methods

2.1. Search strategy

AK searched articles in three databases (i.e. Medline via PubMed, Embase via Ovid, and Scopus) using key search terms related to OACs (warfarin, apixaban, dabigatran, rivaroxaban, edoxaban) AND persistence OR discontinuation AND AF. The databases were searched on 19 October 2021, with an update on 16 December 2022. A research librarian was consulted to map search terms and search techniques for different databases. Each database was searched using the most appropriate syntax for the search function (**Supplemental Method 1**). The reference lists of articles initially included in the review were examined to locate any potential studies not captured in the database searches.

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/17512433.2023.2223973

Searching, retrieving, collection, screening, and assessment were carried out according to the PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analyses) guideline [11]. The review protocol was registered with PROSPERO (Registration No: CRD42020186116).

2.2. Selection criteria

We included original studies, published in English, that had been conducted in people with AF (aged ≥18 years) and reported one or more clinical outcomes (listed below) following non-persistence with OAC therapy, compared with persistence. Reviews, conference abstracts, study protocols, case reports, case series, guidelines, commentaries, and editorials were excluded from the review. The details of the exclusion criteria are presented in **Supplemental Method 2**.

2.3. Study screening and data extraction

Two reviewers independently screened abstracts and full texts. AK screened all articles, while WB and GP screened half of the articles each. AK extracted data, with cross-checking by WB and GP. Any disagreement between reviewers was resolved through discussion. Reasons for the exclusion of articles were documented. Pertinent information about study characteristics, inclusion criteria, exclusion criteria, statistical methods, patient characteristics, treatment details, and outcomes of interest were extracted from each article.

2.4. Outcomes

The clinical outcomes of OAC discontinuation in patients with AF included all-cause mortality, cardiovascular (CV) mortality, thromboembolic events (systemic embolism (SE), stroke, TIA, myocardial infarction (MI)), and bleeding events (major bleeding, gastrointestinal bleeding, clinically significant non-major bleeding) as reported in the original studies. Hospitalization was a secondary outcome.

2.5. Quality assessment

Two independent reviewers assessed the quality of included studies using the Joanna Briggs Institute's (JBI) meta-analysis of statistics assessment and review instrument (MAStaRI) tool [12]. The JBI tool consists of 11 items to assess representativeness, exposure/outcome measures, confounding control, and statistical methods. Any disagreement was resolved through discussion. Items were structured with possible answers of 'yes', 'no' 'unclear' or 'not applicable'. Based on the response to each JBI item, studies were rated as high, moderate, or low quality if they scored a total of 'yes' responses of ≥7, 4–6, or <4, respectively [13].

2.6. Statistical analysis and data synthesis

Patients' and studies' characteristics were summarized using descriptive statistics. We meta-analyzed stroke, major bleeding, and mortality outcomes (all-cause and cardiovascular). We used hazard ratios (HRs) and odds ratios (ORs) for cohort studies and case–control studies, respectively, to estimate the pooled values. Martinez et al. [6] reported stroke using relative risk (RR); we approximated it as an OR given that the risk of stroke in patients treated with an OAC is usually less than 3% per year [14,15]. With a case–control study design and low cumulative incidence of an outcome (<10%), RR could be approximated to and interpreted as OR and vice versa [16,17]. Jackevicius et al. [8] assessed the risk of stroke following the discontinuation of dabigatran and rivaroxaban separately; we first estimated the combined risk before inclusion in the meta-analysis. Studies by Garcia-Rodriguez et al. [18] and Holthuis et al. [19] separately described the outcomes of patients from two (i.e. UK and Denmark) and three (i.e. Germany, Italy, and the Netherlands) countries, respectively; we treated these as two and three independent studies during the meta-analysis.

Studies that assessed hospitalization used different summary statistics to report findings [20–23], making it difficult to meta-analyze into a single-point estimate. We used descriptive narration to summarize the findings related to this outcome.

The pooled estimate was calculated for each clinical outcome using an inverse variance random effect model [24]. The log of HRs or ORs and the corresponding standard errors were computed from ratios and 95% confidence intervals (CIs), extracted from respective studies. The model was constructed based on these computed data. Heterogeneity among studies was assessed using Higgins' I^2 and Cochran's Q [25]. Heterogeneity was considered significant when I^2 was >60% [24]. The reasons for heterogeneity were explored through sensitivity analysis, using the 'leave-one-out method.' Pooled values were reported as point estimates with a 95% CI, and a statistical significance of $p < 0.05$. Publication bias assessment using funnel plot asymmetry analysis was not performed as there were fewer than 10 studies in each respective meta-analysis [24]. Analysis was carried out using RevMan (Version 5.4.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). Data, not meta-analyzed, was descriptively narrated.

3. Results

3.1. Study selection

The initial search of the three databases identified 6,926 potential studies. After removing 2,072 duplicates, we screened titles and abstracts of 4,854, which resulted in 49 articles eligible for full-text screening. Of those, 31 articles were excluded as they did not meet the inclusion criteria. Finally, data extracted from 18 studies were included in this systematic review, of which 14 were included in the meta-analysis (Figure 1).

3.2. Study characteristics

The studies included were mostly from the US ($n = 8$) [20–23,26–28], and two registry studies were conducted in multiple countries across five continents [29,30]. Garcia Rodriguez et al. [18] and Holthuis et al. [19] used data

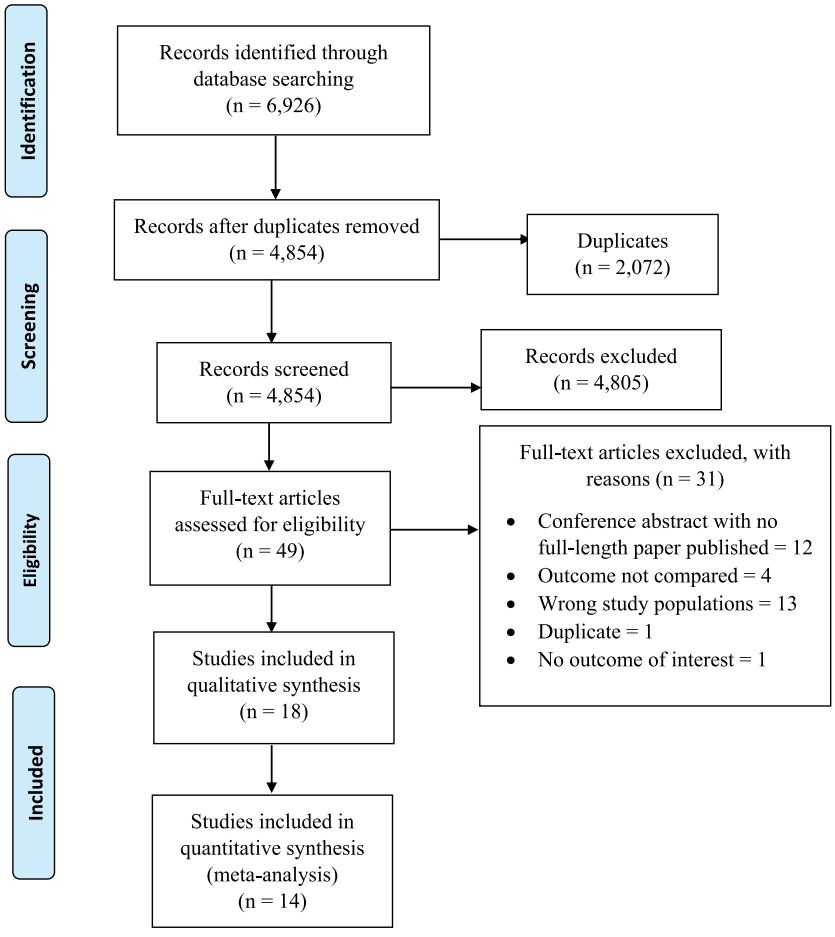


Figure 1. PRISMA flowchart of the study selection process.

derived from two and three countries, respectively. In total, data from 283,418 patients were extracted from 15 retrospective cohort studies (four nested case–control within the cohort) [6,8,18–20,22,23,26–28,31–35] and three prospective registry studies [21,29,30] (Table 1). One study included both valvular and non-valvular AF [21], with all other studies only including non-valvular AF [6,8,18–20,22,23,26–35].

The majority of studies included patients who initiated a VKA ($n = 8$) [6,20,22,26–28,32,34]. Four studies enrolled patients who started either a VKA or a DOAC [18,21,30,31], with six studies using data from patients who initiated a DOAC [8,19,23,29,33,35]. Two publications were based on the same study and reported different outcomes of interest [22,27].

Quality assessment using the JBI tool demonstrated that studies included in the analysis were high quality, with an overall score of ≥9 for each study (**Supplemental Table S1**).

3.3. Patient characteristics

Studies mostly covered the general adult population [6,18–22,26,27,29,30,32,33,35], while a few focused on special groups with AF such as elderly [8,34], patients with cognitive impairment [28], HAS-BLED [Hypertension, Abnormal renal/liver function, Bleeding history, Labile international normalized ratio, Elderly and Drugs/alcohol use] score ≥3 [31], veterans [28], and patients with COVID−19 [23]. The mean age was between 67 and 80.7 years [8,26], and females comprised 1.4% to 52.8% [8,28]. The mean CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke/TIA, Vascular disease, Sex category) score was between 2.8 and 4.3 [6,35]. Hypertension was the most common comorbid condition reported by the studies, in 52.9% to 95% of patients [22,28] (**Supplemental Tables 2 and 3**).

3.4. Clinical outcomes of discontinuation

3.4.1. Summary of major clinical outcomes

The most common clinical outcomes reported were stroke ($n = 15$) [6,8,18,19,21,26–35], followed by all-cause mortality ($n = 8$) [21,23,28,30–32,34,35] and hospitalization ($n = 4$) [20–23]. In six studies [8,21,30–32,35], composite adverse outcomes (usually a combination of thrombotic events and mortality) were also reported. In all studies, except one [29], regardless of the type of OAC, discontinuation was associated with 1.35 to 3.55 and 1.14 to 3.43 times increased risk of stroke and mortality, respectively, compared to continuation of OAC. The risk of hospitalization was lower in the persistent patients in three studies [20,22,23], with no significant difference in one study [21] (**Supplemental Table S3**). Except for one study [31], the risk of major bleeding did not show a significant difference after discontinuation [21,27,28,34].

Table 1. Characteristics of studies included in the review.

Study	Reference	Country	Sample size	Study design	Data source	Definition of non-persistence	Type of OAC
Chao et al.	[31]	Taiwan	4,777	Retrospective cohort	National health insurance database	Discontinuation for >90 days	VKA, DOAC
Cools et al.	[30]	35 countries	23,882	Prospective cohort	GARFIELD-AF Registry	Discontinuation for ≥7 days	VKA, DOAC
Deitelzweig et al.	[26]	USA	16,253	Retrospective cohort	Optum research database	Discontinuation for >60 days plus no INR measurement at least every 42 days	Warfarin
Deitelzweig et al.	[20]	USA	7,808	Retrospective cohort	Integrated delivery network of anticoagulation clinics	Discontinuation for >60 days plus no INR measurement at least every 42 days	Warfarin
Deitelzweig et al.	[23]	USA	7,869	Retrospective cohort	Optum research database	Discontinuation for >30 days	Apixaban
Gallego et al.	[32]	Spain	529	Retrospective cohort	A hospital anticoagulation clinic	Discontinuation other than temporary interruption for procedures	Acenocoumarol
Garcia Rodiguez et al.	[18]	UK and Denmark	10,763	Retrospective cohort with nested case–control	IMRD for the UK and 5 linked Danish registries	Discontinuation for >30 days	VKA, DOAC
Holthuis et al.	[19]	Germany, Italy and the Netherlands	12,798	Retrospective cohort with nested case–control	PHARMO, ARS and InGef databases	Discontinuation for >30 days	DOAC
Jackevicius et al.	[8]	Canada	25,976	Retrospective cohort	Hospital admissions linked with claims data	Discontinuation for ≥14 days	DOAC
Jackson et al.	[21]	USA	10,005	Prospective cohort	ORBIT registry	Patient-reported cessation	VKA, DOAC
Komen et al.	[33]	Sweden	2,704	Retrospective cohort with nested case–control	Stockholm healthcare database	Discontinuation for >91 days	DOAC
Martinez et al.	[6]	UK	2,626	Retrospective cohort with nested case–control	Clinical practice research Datalink	Discontinuation for >30 days	VKA
Orkaby et al.	[28]	USA	2,572	Retrospective cohort	VARIA database	90 days or more without INR measurement	Warfarin
Pamela et al.	[34]	Australia	3,219	Retrospective cohort	Hospital morbidity data	Had at least one supply of 50 warfarin tablets before the index admission but not within 1 year after discharge	Warfarin
Paquette et al.	[29]	44 countries	4,589	Prospective cohort	GLORIA-AF registry	Discontinuation for >30 days	Dabigatran
Spivey et al.	[27]	USA	27,000	Retrospective cohort	Marketscan database	Discontinuation for >45 days or no evidence of INR monitoring at least every 42 days	Warfarin
Spivey et al.	[22]	USA	27,000	Retrospective cohort	Marketscan database	Discontinuation for >45 days or no evidence of INR monitoring at least every 42 days	Warfarin
Toorop et al.	[35]	Netherlands	93,048	Retrospective cohort	Dutch national statistics	Discontinuation for >100 days	DOAC

ARS: Agenzia Regionale di Sanità della Toscana; DOAC: Direct-acting oral anticoagulant; GARFIELD-AF: Global Anticoagulant Registry in the Field- Atrial Fibrillation; GLORIA-AF: Global Registry on Long-Term Oral Anti-thrombotic Treatment In Patients With Atrial Fibrillation; IMRD: IQVIA Medical Research Data; INR: international normalized ratio; ORBIT: Outcomes Registry for Better Informed Treatment; UK: United Kingdom; U.S.A: United States of America; VARIA: Veterans AffaiRs Study to Improve Anticoagulation; VKA: Vitamin K antagonist.

In an Australian study that enrolled patients who survived 1 year and beyond after being hospitalized due to AF and discharged from hospital [34], unlike most other studies, the authors defined persistence as patients who received warfarin before admission to the hospital and at least one supply in the 12 months after discharge. Patients were categorized as discontinued if they were supplied with warfarin before the index hospital admission but not during the 12 months after being discharged. Patients who survived 1 year after hospital discharge were followed-up for 3 years. Compared to persistent patients, those who discontinued warfarin had a higher incidence of thrombotic events (stroke/systemic embolism 2.7 vs. 1.6 per 100 person-years, $p = 0.017$). Persistent patients also had better survival probability than those who discontinued at 3 years post-discharge (65% vs. 77%, $p = 0.05$). The rate of bleeding was not different between the two groups (1.6 vs. 2.0 per 100 patient-years, $p = 0.45$).

In the prospective GARFIELD-AF registry of 23,882 patients, those who discontinued an OAC had a higher risk of MI (HR 1.85; 95% CI 1.09–3.13) and a composite of non-hemorrhagic stroke/SE/MI/all-cause death (HR 1.67; 95% CI 1.35–2.08) and death/non-hemorrhagic stroke/SE (HR 1.66; 95% CI 1.31–2.09). However, there was no significant difference in CV mortality between the two groups (HR 1.37; 95% 0.80–2.35) [30], unlike a study from the United States (CV mortality HR 2.40; 95% CI 1.47–3.39) [21]. The Taiwanese study reported an increased risk of composite adverse outcomes (stroke, intracranial hemorrhage, major bleeding or all-cause mortality) (HR 1.30; 95% 1.14–1.52)

following discontinuation of OAC therapy in patients with a HAS-BLED score ≥ 3 [31].

3.4.2. Stroke and thrombotic events

We performed two separate meta-analyses to pool results from 13 studies, including nine cohort studies using HR [8,21,26–28,30–32,35] and four case–control studies using OR [6,18,19,33]. The pooled estimate demonstrated a doubling risk of stroke when an OAC was discontinued in patients with AF (HR 1.88; 95% CI 1.58–2.23, $I^2 = 69\%$ and OR 2.11; 95% CI 1.69–2.65, $I^2 = 86\%$) (Figure 2a).

Heterogeneity among studies was significant ($I^2 = 69\%$ and 86%), reflecting variability in factors such as how non-persistence was defined and the follow-up periods. In some studies, moreover, TIA was reported with stroke [8,21,26,32] and Deitezweig et al. [26] included all strokes without differentiating between ischemic and hemorrhagic types, with the remaining studies (12 of 13 studies meta-analyzed) reported only ischemic strokes (alone or in combination with TIA/systemic thromboembolism) [6,8,18,19,21,27,28,30–33,35]. In addition, two studies reported ischemic stroke combined with systemic thromboembolism [21,30]. All aforementioned factors, along with a diversity of study populations, were probably the major sources of the observed heterogeneity. We did a subgroup analysis for studies reported in HR using the 'leave-one-out method' to identify the study principally contributing to the heterogeneity. It was shown that most of the heterogeneity was a result of a single study [8], as the I^2 decreased from 69% to 33% when it was excluded from the analysis (**Supplemental Figure S1**). Subgroup analysis was not feasible for the OR group since only a few studies were identified.

3.4.3. Mortality

We pooled the hazard of death from the findings of seven studies [21,23,28,30–32,35]. The discontinued patients had a 1.9 times higher risk of death from any cause (HR 1.90; 95% CI 1.40–2.59, $I^2 = 96\%$) (Figure 2b).

We also performed a meta-analysis to examine the effect of discontinuation on CV mortality, based on data from two large prospective studies [21,30] that enrolled a total of 33,887 patients. There was an increased risk of CV mortality in the discontinued group (HR 1.83; 95% CI 1.08–3.18, $I^2 = 56\%$) compared with those who continued OAC (Figure 2c).

3.4.4. Major bleeding

Three studies had data for meta-analysis for major bleeding [21,28,31]. The pooled estimate revealed no significant difference in major bleeding between the two groups (HR 1.04; 95% CI 0.72–1.52, $I^2 = 85\%$) (Figure 2d).

4. Discussion

This systematic review covered the clinical consequences of OAC discontinuation in AF, using data from 283,418 patients extracted from 18 studies. Discontinuation was associated with nearly two times increased risk of stroke and mortality, with no significant difference in the risk of major bleeding, compared to the persistent use of OACs. A previous review, noting that it included data from a single study of DOAC users [5], showed a much higher risk of stroke following discontinuation (HR 4.55; 95% CI 2.80–7.39) [5]. In our review, warfarin or other VKA users were predominant. The risk of hospitalization was higher in discontinued patients in three large studies, with total participants of 42,677 patients [20,22,23]. In contrast, a study of 10,005 patients did not find a difference in hospitalization risk [21]. Although it was difficult to calculate the pooled estimate for a reliable conclusion, due to the use of different effect measures in the studies, there was a strong correlation between discontinuation and a higher risk of hospitalization (1.23 to 1.4 times higher among discontinuers) in the three studies [20,22,23].

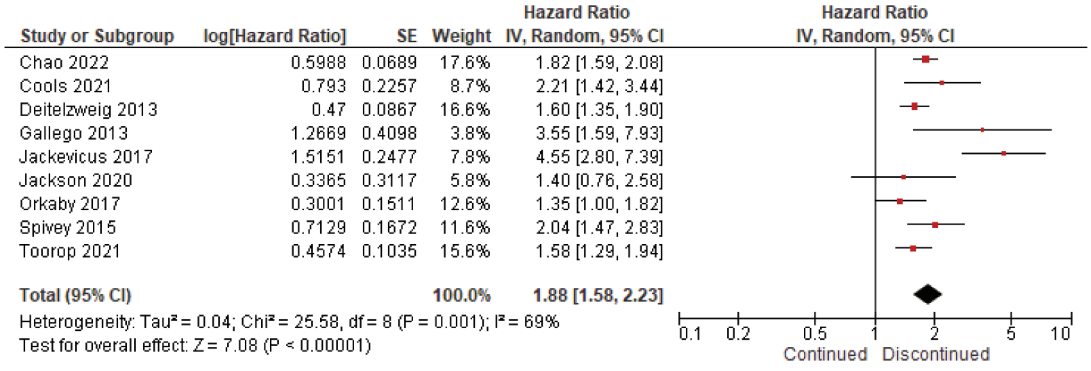
The thromboprophylaxis benefits of OAC therapy on stroke and mortality have been well documented in randomized clinical trials [36–38]. OACs can prevent more than two-thirds of AF-associated strokes when appropriately initiated and maintained [39,40]. Guidelines recommend continuous use in AF patients with moderate to high risk of stroke [41–43], unless contraindications arise. In practice, however, maintaining therapy can be a challenge due to the fear of bleeding and other adverse events associated with OACs [44,45]. A recent review reported non-persistence with DOACs in nearly a third of patients [5], and this is typically worse in VKA users [4].

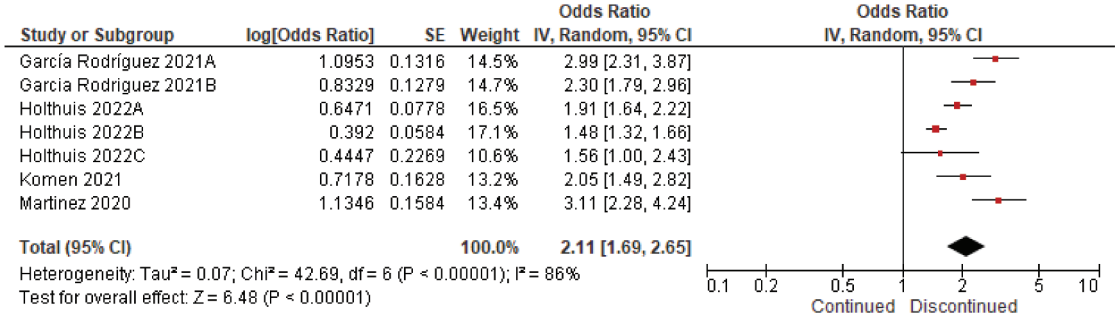
One of the common reasons for the discontinuation of OACs is the anticipated risk of major bleeding [29,46], or the occurrence of minor bleeding, which should not necessarily require discontinuation [47]. This review suggested no significant benefit of discontinuing OACs to prevent bleeding events. It would be reasonable to temporarily withhold an OAC in patients who experienced severe bleeding. However, it should not be the sole reason for prolonged discontinuation of an OAC; as confirmed in this review, the risk of thrombotic events post-discontinuation outweigh the prevention of bleeding [47]. From the patients' perspective, avoiding stroke using OACs is valued more than the risk of major bleeding [48], with patients preferring to accept up to four bleeds to prevent one stroke [49]. As with OAC initiation, the decision to discontinue therapy for clinical reasons should be a trade-off and needs a cautious balancing of risk and benefit.

The major concern that arises from a meta-analysis of observational studies is heterogeneity among studies. The heterogeneity in this review might be a result of variations in study populations, outcome definition, OAC type, follow-up period and definition of discontinuation. In the meta-analysis for stroke following discontinuation, the heterogeneity was apparently due to one study [8]. The study differed from others in terms of the study population (age >65 years), very short discontinuation period (14 days), higher baseline stroke risk, and type of OAC (included patients who started either dabigatran or rivaroxaban).

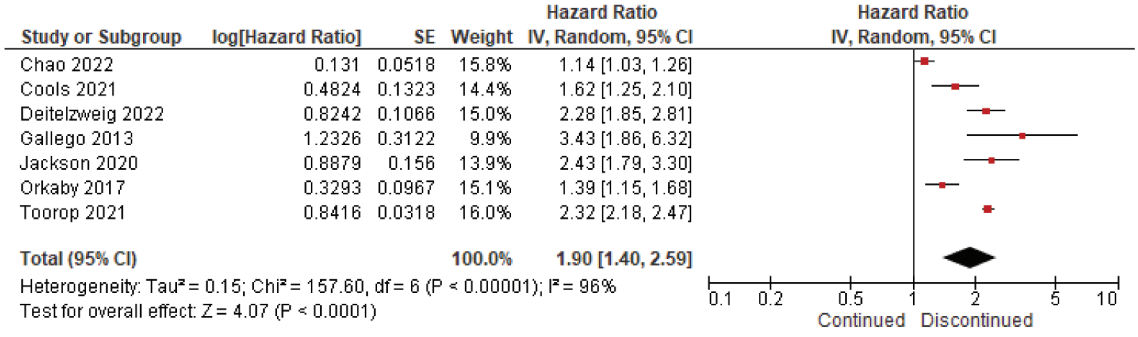
Despite the studies employing various statistical or design approaches (e.g. matching) to control for confounding, the inherent nature of observational studies makes it difficult to preclude confounding. Of the studies included in the review, seven used matching along with regression analysis to control confounding [6,19,22,23,27,28,31]. The remaining studies employed multivariable regression (logistic or Cox proportional

a. Stroke (Top panel, Cohort studies, bottom panel: case-control studies)

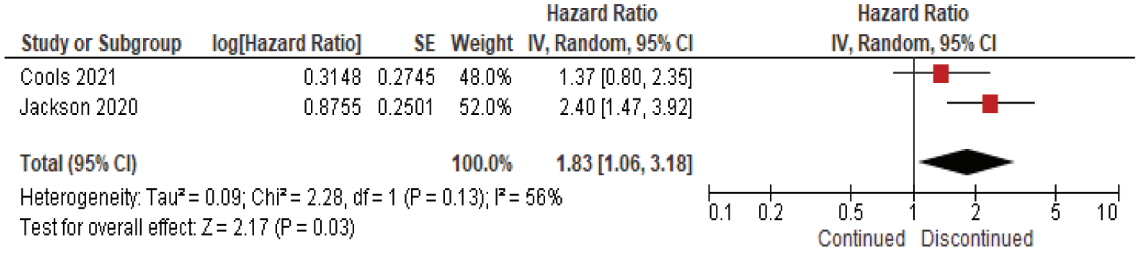




b. All-cause mortality



c. CV mortality



d. Major bleeding

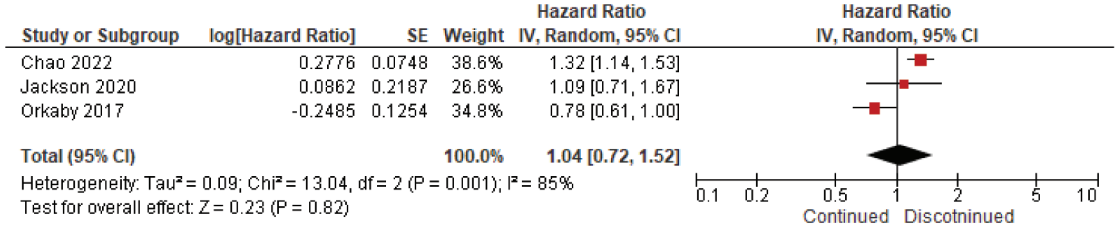


Figure 2. Forrest plots: a. Stroke, b. All-cause mortality, c. Cardiovascular mortality, d. Major bleeding.

model) for confounding control [8,18,20,21,26,29,30,32–35]. There could still be residual confounding to be considered in interpreting the findings. The comparative effect of discontinuation of each OAC type on clinical outcomes needs to be specifically addressed in future studies. Moreover, only two and three studies were included for CV mortality and major bleeding meta-analyses, respectively. Thus, further studies may be needed to complement the findings of this review. Given the observational studies reviewed and the significant heterogeneity, the interpretation of findings should be done with caution.

5. Conclusion

In this systematic review of relatively heterogeneous studies, discontinuation of OACs was associated with a higher risk of stroke, all-cause mortality, and CV mortality, with minimal effect on major bleeding events. Discontinuation was also associated with an increased risk of hospitalization in three out of four studies with that outcome.

Acknowledgments

We would like to thank the University of Tasmania research librarians for their help in developing the search strategy. Adane Kefale was supported by a Tasmanian Graduate Scholarship living allowance and tuition fee offset.

Funding

This paper was not funded.

Author contributions

AT Kefale conducted searching, screening, data extraction, quality assessment, and drafted the manuscript. GM Peterson and WM Bezabhe screened and appraised articles and cross-checked the extracted data. All authors contributed to the conceptualization and design of the review. GM Peterson and WM Bezabhe critically reviewed and revised the manuscript. All authors approved the final version for publication.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Data availability statement

All data are available in the manuscript or the supplemental files.

Reviewer dislcosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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