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ORIGINAL ARTICLE

Direct Oral Anticoagulants Versus Vitamin K Antagonists in Patients Undergoing Cardioversion for Atrial Fibrillation: a Systematic Review and Meta-analysis

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Abstract

Background Clinical guidelines recommend peri-cardioversion anticoagulation in patients with atrial fibrillation (AF). We performed a systematic review and meta-analysis to compare the safety and efficacy of direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs) in patients with AF undergoing cardioversion.

Methods We searched CENTRAL, MEDLINE, and EMBASE for randomized controlled trials (RCTs) and observational studies comparing DOACs to VKAs in patients undergoing cardioversion for AF. We performed title, abstract, and full-text screening, data extraction, and risk of bias evaluation independently and in duplicate. We pooled data using a random effects model and evaluated the overall quality of evidence using Grading of Recommendations Assessment, Development and Evaluation.

Results We identified three eligible RCTs ($n = 5203$) and 21 observational studies ($n = 11{,}855$). The three RCTs and four observational studies were at low risk of bias. In RCTs (mean follow-up, 30 days), thromboembolic events occurred in 0.18% of patients receiving DOACs, as compared with 0.55% receiving VKAs (relative risk [RR] 0.40, 95% CI [0.13, 1.24], moderate quality). Major bleeding occurred in 0.42% of patients receiving DOACs as compared with 0.64% receiving VKAs (RR 0.62, 95% CI [0.28, 1.35], moderate quality), and death occurred in 0.28% of patients receiving DOACs as compared with 0.38% receiving VKAs (RR 0.70, 95% CI [0.23, 2.10], low quality). Confidence in the estimates of effect for observational studies was very low.

Conclusion DOACs peri-cardioversion in patients with AF appears safe from both a bleeding and thromboembolic risk perspective. Available evidence supports the use of DOACs as standard of care peri-cardioversion in patients with AF.

Keywords Cardiology · Cardioversion · Anticoagulation · Thrombosis · Stroke

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Introduction

Atrial fibrillation (AF) is the most common heart rhythm disorder [1]. It independently increases the risk of ischemic stroke by four to five times and is an independent risk factor for heart failure and death [2, 3]. In rate-controlled patients with symptomatic AF, guidelines recommend electrical or chemical cardioversion to improve symptoms and quality of life [4–9]. As such, anticoagulation is strongly recommended before and after electrical cardioversion for AF with duration ≥ 48 h [4, 10, 11]. Oral anticoagulation therapy is recommended for at least 3 weeks prior and for at least 4 weeks after cardioversion [5, 6, 12]. Warfarin, a vitamin K antagonist (VKA), has been extensively studied for stroke prophylaxis. However, VKAs require ongoing dosing management to maintain a therapeutic INR, and cardioversion may be delayed when INR levels are subtherapeutic. By contrast, direct oral anticoagulants (DOACs) have a more rapid onset and consistent level of anticoagulation [13]. In fact, guidelines suggest DOACs, instead of VKAs, for patients with AF [5, 6, 12, 14].

At a tissue level, oxidative stress and expression of adhesion molecules, along with reduction in nitrous oxide, seem to play a role in atrial thrombogenesis among patients with AF [15, 16]. Interestingly, these factors can be mitigated by factor Xa inhibitors—a type of DOAC [17]. Furthermore, large randomized controlled trials (RCTs) have demonstrated the non-inferiority of DOACs to VKAs for stroke prophylaxis in patients with AF [18–21]. Additionally, in 2014, Ruff et al. published a meta-analysis demonstrating a significant reduction in stroke (19%) and all-cause mortality (10%) with the use of DOACs, compared to VKAs, in patients with AF [22]. European registries have already demonstrated increased prescription and uptake of DOACs [23]. Given their convenience, we wanted to establish DOACs' safety and efficacy in patients with AF undergoing cardioversion. As such, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) and observational studies comparing the impact of DOACs and VKAs on thromboembolism, bleeding, mortality, and thrombus detection on transesophageal echocardiography (TEE) in patients with AF undergoing electrical cardioversion.

Methods

We registered our protocol with PROSPERO (CRD42018089256).

Identification of Studies We searched Cochrane CENTRAL, MEDLINE, and EMBASE from inception to December 2017. We screened clinicaltrials.gov, WHO ICTRP, and the ISRCTN Register for completed and ongoing, but yet unpublished studies. We reviewed conference proceedings from the American Association for Thoracic Surgery, European Association for Cardio-Thoracic Surgery, Society of Thoracic Surgeons, American Heart Association, American College of Cardiology, and European Society of Cardiology meetings within the past 2 years. We did not apply language restrictions.

Study Inclusion and Selection We performed title and abstract screening independently and in duplicate using the Covidence online software [24]. If a reviewer deemed a study relevant, it was retrieved for full-text review. We resolved disagreements regarding eligibility through discussion or third-party arbitration. Eligible studies met the following criteria:

1. population: adults (≥ 18 years of age) with AF undergoing electrical cardioversion;
2. intervention: DOAC;
3. comparator: VKA or VKA plus adjunct;
4. outcomes: thromboembolism, bleeding, mortality, and thrombus on TEE; and,
5. design: RCT or observational.

Data Collection and Management We performed data extraction independently and in duplicate using pre-piloted forms. If there was a discrepancy, a third party reviewed the data. We contacted study authors to obtain additional information when required.

Risk of Bias Assessment for Randomized Controlled Trials Risk of bias (ROB) was evaluated as "low," "likely low," "high," or "likely high" using the Cochrane Collaboration tool [25]. Two independent reviewers assessed each trial in six domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selective reporting, and other sources of bias. If all aspects were considered to have "low" or "likely low" risk of bias, we considered the study to be "low" risk. If even one aspect or more was considered to have "likely high" risk of bias, we considered the paper to be "unclear" risk. Studies with at least one aspect considered to have "high" risk of bias were considered to be "high" risk.

Assessment of Risk of Bias in Included Observational Studies We used the CLARITY tools to assess the risk of bias in observational studies [26].

Summary Measures of Treatment Effect and Unit of Analysis We evaluated the clinical and methodological heterogeneity of included studies to assess whether pooling data was appropriate. We performed analyses using Review Manager 5.3 (RevMan 5.3) [27]. We expected heterogeneity among studies and applied a random effects model to pool relevant results and summarize the evidence. We analyzed RCTs and observational studies separately [28]. We presented dichotomous outcomes as relative

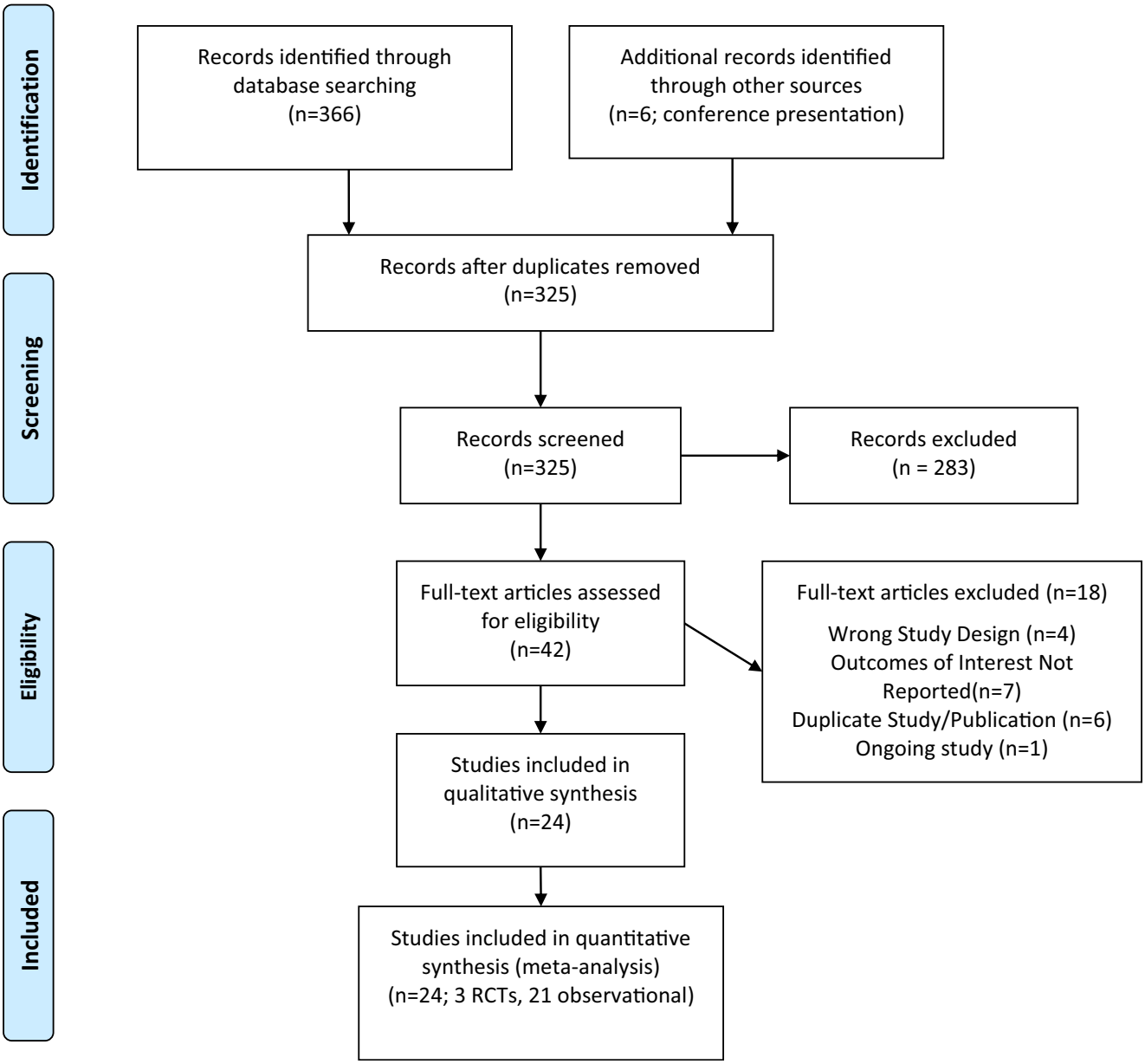


Fig. 1 PRISMA systematic review flow diagram for study selection

risks (RR) and continuous variables as mean differences (MD) with 95% confidence intervals (CI).

Assessment of Heterogeneity We used the chi-square test for homogeneity and the I^2 statistic to assess heterogeneity.

Publication Bias We inspected the funnel plots for publication bias if, for an outcome, 10 or more studies were pooled.

Subgroups We pre-specified the following subgroups to explain possible heterogeneity within data:

1. Mechanism of action: factor Xa versus direct thrombin inhibitors
2. Risk of bias: high and unclear versus low risk of bias

Assessment of Confidence in Pooled Effect Estimates We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of the evidence for each outcome [29]. We separated the GRADE assessment for RCTs and observational studies.

Results

Figure 1 summarizes the screening and study selection process. We identified 325 citations for title and abstract screening. Of

Table 1 Risk of bias for randomized controlled trials

	Goette et al.	Ezekowitz et al.	Cappato et al.
Bias domain	Authors' judgement		
Random sequence generation (selection bias)	Low	Likely low	Low
Allocation concealment (selection bias)	Likely low	Low	Likely low
Blinding of participants and personnel (performance bias)	Low	Low	Low
Blinding of outcome assessment (detection bias)	Low	Low	Low
Incomplete outcome data (attrition bias) All outcomes	Low	Low	Likely low
Selective reporting (reporting bias) All outcomes	Low	Low	Low
Other bias	Low	Low	Low

these, we reviewed the full text of 43 studies. Six additional studies were found during the gray literature search; one of these, a randomized controlled trial, is currently ongoing [30]. A total of three RCTs and 21 observational studies were included in our final analysis [18, 31–54]. The RCTs were all multicenter and evaluated factor Xa inhibitors only. They reported thromboembolism, bleeding, mortality, and thrombus on TEE. Nineteen observational studies reported thromboembolisms, 18 reported bleeding, 11 reported thrombus on TEE, and seven reported mortality. Three observational studies were post-hoc analyses of larger multi-center trials evaluating DOACs versus VKAs in patients with AF [34, 40, 46].

The three RCTs included a total of 5203 patients with AF undergoing elective cardioversion (Appendix 1) [31–33]. Ezekowitz et al. compared apixaban to VKAs and unfractionated heparin, while Goette et al. compared edoxaban to warfarin and enoxaparin [32, 33]. Cappato et al. compared rivaroxaban to warfarin only [31]. The mean follow-up was 30 days.

The 21 observational studies included 11,855 patients with AF undergoing elective cardioversion (Appendix 1). Seven observational studies compared VKAs with dabigatran, one study compared VKAs with apixaban, another compared VKAs with edoxaban, and 12 studies compared warfarin with two or more DOACs. The follow-up ranged from 30 days to 2 years.

All RCTs (Table 1) and four observational studies (Table 2) were considered to be at low risk of bias. Seventeen observational studies were considered to be at high risk of bias in the absence of matching of patients or adjustment for prognostic variables (Table 2).

Thromboembolism (Fig. 2) In RCTs, the incidence of thromboembolism was 0.18% with DOACs and 0.55% with VKAs (RR 0.40, 95% CI [0.13, 1.24], $p = 0.11$, $I^2 = 7\%$, moderate-quality evidence). We downgraded the quality of evidence for serious imprecision (Table 3). Observational studies, however, suggested that DOACs were associated with a significantly lower incidence of thromboembolic events compared to VKAs (RR 0.51, 95% CI [0.26, 0.99], $p = 0.05$, $I^2 = 27\%$, very low-quality evidence). We downgraded the quality of evidence for serious risk of bias (Table 4).

Bleeding (Fig. 3) In RCTs, 1.8% of patients receiving DOACs experienced bleeding, compared with 2.5% of patients receiving VKAs (RR 0.85, 95% CI [0.58, 1.23], $p = 0.38$, $I^2 = 0\%$, moderate-quality evidence). Results were consistent when we limited our analysis to major bleeding, as reported in all three RCTs (RR 0.62, 95% CI [0.28, 1.35], $p = 0.23$, $I^2 = 0\%$, moderate-quality evidence). We downgraded the quality of evidence for bleeding and major bleeding due to serious imprecision (Table 3). Appendix 2 summarizes the definitions of bleeding used in the included RCTs. Observational studies, however, suggested that DOACs were associated with a significantly lower incidence of bleeding compared to VKAs (RR 0.59, 95% CI [0.34, 1.00], $p = 0.05$, $I^2 = 34\%$, very low-quality evidence). We downgraded the quality of evidence in observational studies due to serious risk of bias (Table 4).

Mortality (Fig. 4) In RCTs, the incidence of mortality was 0.3% in patients receiving DOACs compared to 0.4% among patients on VKAs. Mortality did not differ significantly between groups in RCTs (RR 0.70, 95% CI [0.23, 2.10], $p = 0.52$, $I^2 = 5\%$, low-quality evidence) or observational studies (RR 0.87, 95% CI [0.42, 1.78], $p = 0.69$, $I^2 = 0\%$, very low-quality evidence). The quality of evidence for RCTs was downgraded due to very serious imprecision (Table 3). The quality of evidence for observational studies was downgraded due to serious risk of bias and serious imprecision (Table 4).

Table 2 Risk of bias of observational studies

	Selection of exposed and non-exposed cohorts from same population?	Confident in assessment of exposure?	Confident that outcome of interest not present at start of study?	Exposed and unexposed groups matched or statistically adjusted for all prognostic variables?	Confident in assessment of presence or absence of prognostic factors?	Confident in assessment of outcome?	Adequate follow-up?	Similar co-interventions between groups?
Flaker et al.	Definitely yes	Definitely yes	Definitely yes	Probably yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
Nagarakanti et al.	Definitely yes	Definitely yes	Definitely yes	Probably yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
Plitt et al.	Definitely yes	Definitely yes	Definitely yes	Probably yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
Russo et al.	Definitely yes	Definitely yes	Definitely yes	Probably yes	Definitely yes	Definitely yes	Definitely yes	Probably yes
Arujuna et al.	Probably yes	Definitely yes	Definitely yes	Definitely no	Probably yes	Definitely yes	Probably yes	Probably yes
Barysiene et al.	Definitely yes	Definitely yes	Definitely yes	Definitely no	Probably yes	Definitely yes	Probably yes	Probably yes
Basto et al.	Probably yes	Definitely yes	Definitely yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably yes
Carrizo et al.	Definitely yes	Definitely yes	Definitely yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably yes
Chirino Navarta et al.	Definitely yes	Definitely yes	Definitely yes	Definitely no	Definitely yes	Definitely yes	Probably yes	Probably yes
Cohen et al.	Definitely yes	Definitely yes	Probably yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably yes
Femia et al.	Definitely yes	Definitely yes	Definitely yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably yes
Irmer et al.	Definitely yes	Definitely yes	Probably yes	Definitely no	Probably yes	Definitely yes	Definitely yes	Probably yes
Kalejs et al.	Definitely yes	Definitely yes	Definitely yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably yes
Keltner et al.	Probably yes	Probably yes	Probably yes	Definitely no	Definitely no	Probably yes	Probably yes	Probably yes
Kochhauser et al.	Definitely yes	Definitely yes	Definitely yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably yes
Pallisgaard et al.	Definitely yes	Definitely yes	Probably yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably yes
Persidskikh et al.	Probably yes	Probably yes	Definitely yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably yes
Serpytis et al.	Probably yes	Probably yes	Definitely yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably yes
Sharif et al.	Definitely yes	Probably yes	Probably yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably yes
Verma et al.	Probably yes	Probably yes	Probably yes	Definitely no	Probably yes	Probably no	Probably yes	Probably yes
Zylla et al.	Probably yes	Probably yes	Probably yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably yes

Table 3 GRADE table, summarizing the evaluation of the quality of evidence in randomized controlled trials

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)		
Thromboembolism												
3	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	5/2850 (0.2%)	13/2353 (0.6%)	RR 0.40 (0.13 to 1.24)	3 fewer per 1000 (from 1 more to 5 fewer)	⨁⨁⨁◯ moderate	Critical
Major bleeding												
3	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	12/2850 (0.4%)	15/2353 (0.6%)	RR 0.62 (0.28 to 1.35)	2 fewer per 1000 (from 2 more to 5 fewer)	⨁⨁⨁◯ Moderate	Critical
Mortality												
3	Randomized trials	Not serious	Not serious	Not serious	Very serious[b]	None	8/2850 (0.3%)	9/2353 (0.4%)	RR 0.70 (0.23 to 2.10)	1 fewer per 1000 (from 3 fewer to 4 more)	⨁⨁◯◯ low	Critical
Any bleeding												
3	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	52/2850 (1.8%)	58/2353 (2.5%)	RR 0.85 (0.58 to 1.23)	4 fewer per 1000 (from 6 more to 10 fewer)	⨁⨁⨁◯ moderate	Important
Thrombus on TEE												
3	Randomized trials	Not serious	Not serious	Serious	Serious[a]	None	98/1419 (6.9%)	83/1232 (6.7%)	RR 1.07 (0.80 to 1.42)	5 more per 1000 (from 13 fewer to 28 more)	⨁⨁◯◯ low	Not important

CI, confidence interval; *RR*, risk ratio

[a] Wide 95% CI

[b] Extremely wide 95% CI

Table 4 GRADE table, summarizing the evaluation of the quality of evidence in observational studies

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOACs	VKAs	Relative (95% CI)	Absolute (95% CI)		
Thromboembolism												
19	Observational studies	Serious[a]	Not serious	Not serious	Not serious	None	29/6536 (0.4%)	41/4994 (0.8%)	RR 0.51 (0.26 to 0.99)	4 fewer per 1000 (from 0 fewer to 6 fewer)	⨁◯◯◯ very low	Critical
Any bleeding												
18	Observational studies	Serious[a]	Not serious	Not serious	Serious[b]	Serious[c]	47/6410 (0.7%)	62/4688 (1.3%)	RR 0.59 (0.34 to 1.00)	5 fewer per 1000 (from 0 more to 9 fewer)	⨁◯◯◯ very low	Important
Mortality												
7	Observational studies	Serious[a]	Not serious	Not serious	Serious[b]	None	16/1797 (0.9%)	21/1843 (1.1%)	RR 0.87 (0.42 to 1.78)	1 fewer per 1000 (from 7 fewer to 9 more)	⨁◯◯◯ very low	Critical
Thrombus on TEE												
11	Observational studies	Serious[a]	Not serious	Serious	Not serious	None	123/3267 (3.8%)	124/2433 (5.1%)	RR 0.61 (0.39 to 0.97)	20 fewer per 1000 (from 2 fewer to 31 fewer)	⨁◯◯◯ very low	Not important

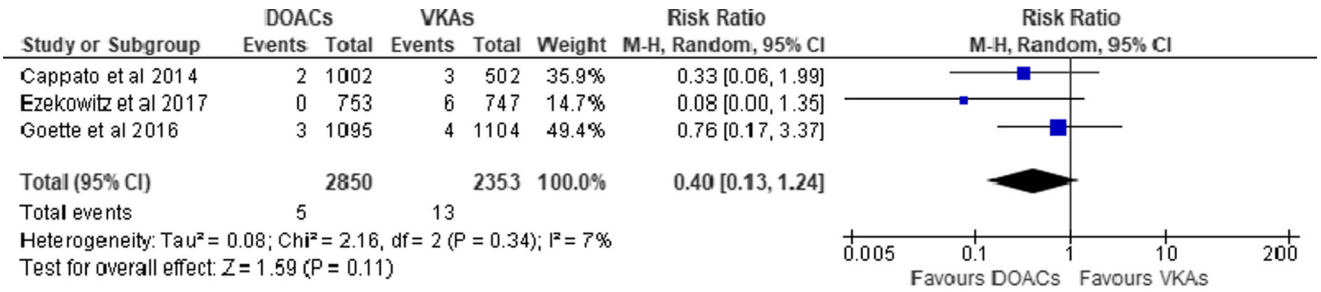
CI, confidence interval; *RR*, risk ratio

[a] Only 4 observational studies are low risk of bias. And, estimate effects are opposite to RCTs

[b] Wide 95% CI

[c] Publication bias suspected

a Randomized controlled trials



b Observational studies

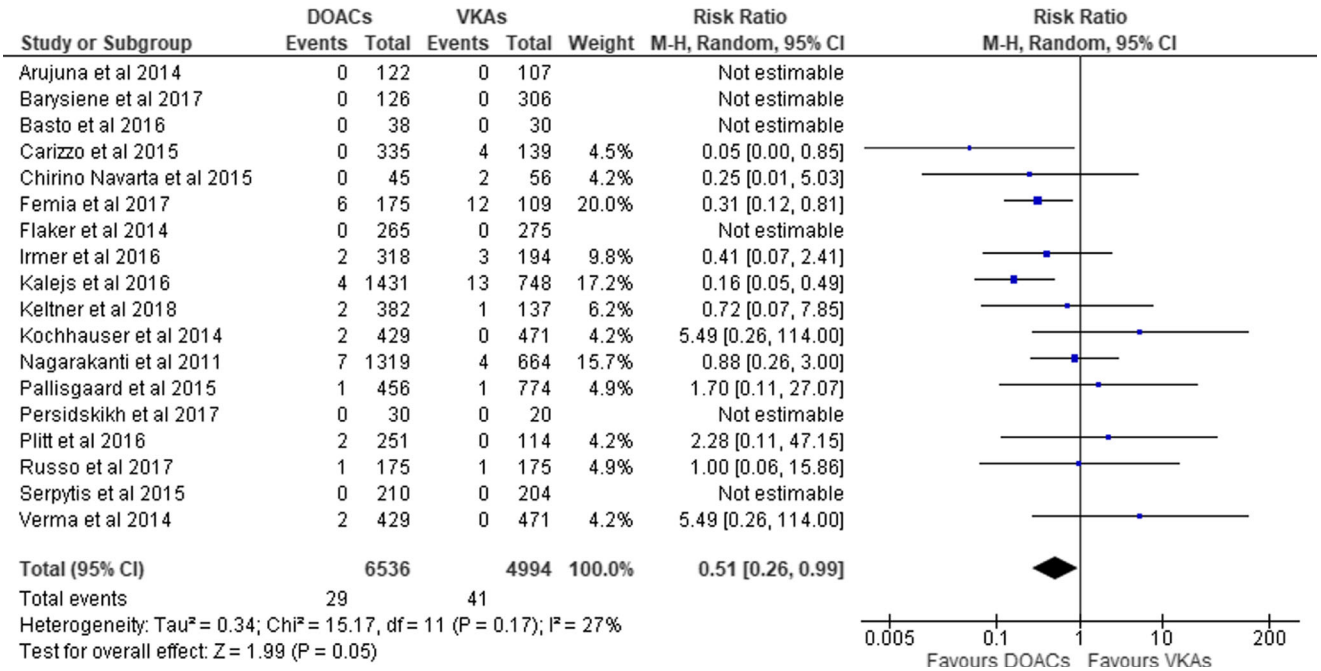


Fig. 2 Forest plot demonstrating thromboembolic events for DOACs and VKAs with or without adjuncts. Square markers represent point estimate of risk ratios (RR) for individual studies, with square size proportional to the weight given to each study in the meta-analysis. Horizontal lines indicate 95% confidence intervals (CI). The solid diamond represents the estimated 95% confidence interval for effect size of all meta-analyzed data

Thrombus on TEE (Fig. 5) The risk of thrombus on TEE did not differ significantly between groups in RCTs (RR 1.07, 95% CI [0.80, 1.42], $p = 0.65$, $I^2 = 0\%$, low-quality evidence). The quality of evidence was downgraded for serious imprecision and indirectness (Table 3). Observational studies demonstrated a significantly lower risk of thrombus on TEE in patients receiving DOACs compared to patients on VKAs (RR 0.61, 95% CI [0.39, 0.97], $p = 0.08$, $I^2 = 43\%$, very low-quality evidence). The quality of evidence was downgraded for serious risk of bias, imprecision, and indirectness (Table 4).

Subgroup Analyses

Factor Xa Inhibitors vs Direct Thrombin Inhibitors Subgroup analysis of factor Xa inhibitors versus other types of DOACs was not possible because all RCTs evaluated factor Xa inhibitors and, for observational studies, study-level data were not available for the different types of DOACs.

High vs Low Risk of Bias All RCTs were at low risk of bias. As such, we were unable to pursue this subgroup analysis. Four observational studies were deemed to be at low risk of bias,

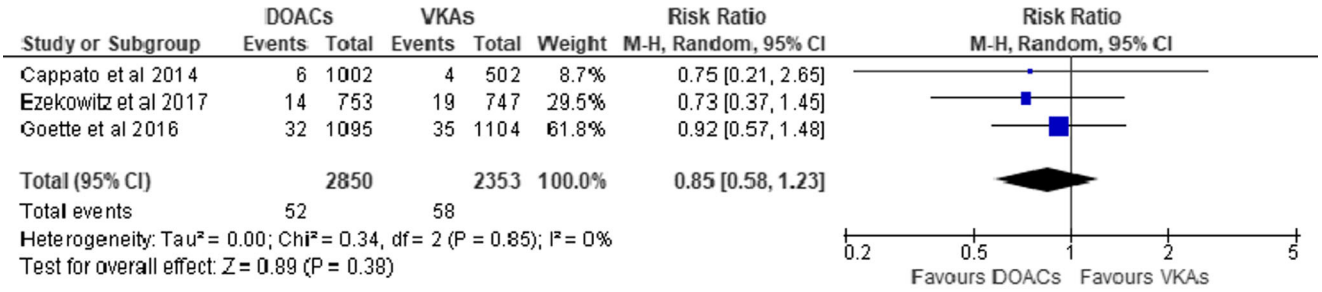
while the rest were determined to be at high risk of bias; as such, sensitivity analyses were conducted (Appendix 3). The tests for subgroup differences were not statistically significant for thromboembolic events ($p = 0.19$), mortality ($p = 0.73$), and thrombus on TEE ($p = 0.42$). For bleeding events, however, the risk was significantly different in studies at low risk of bias (RR 1.37, 95% CI [0.57, 3.32]) compared to studies at high risk of bias (RR 0.46, 95% CI [0.26, 0.82]) ($p = 0.04$). The studies at a higher risk of bias involve significant confounding variables, especially around patient selection; patients at higher risk of bleeding were likely prescribed VKAs, allowing for ongoing monitoring and reversibility, if needed.

Publication Bias Publication bias was evaluated for observational outcomes of thromboembolic events, bleeding events, and thrombus on TEE (Appendix 4). Bias was suspected for bleeding events on visual inspection.

Discussion

This systematic review and meta-analysis of RCTs and observational studies included 17,008 patients with AF undergoing cardioversion. Thromboembolism, bleeding, and mortality did not differ significantly in RCTs based on whether patients received DOACs or VKAs. Observational studies demonstrated a

a Randomized controlled trials



b Observational studies

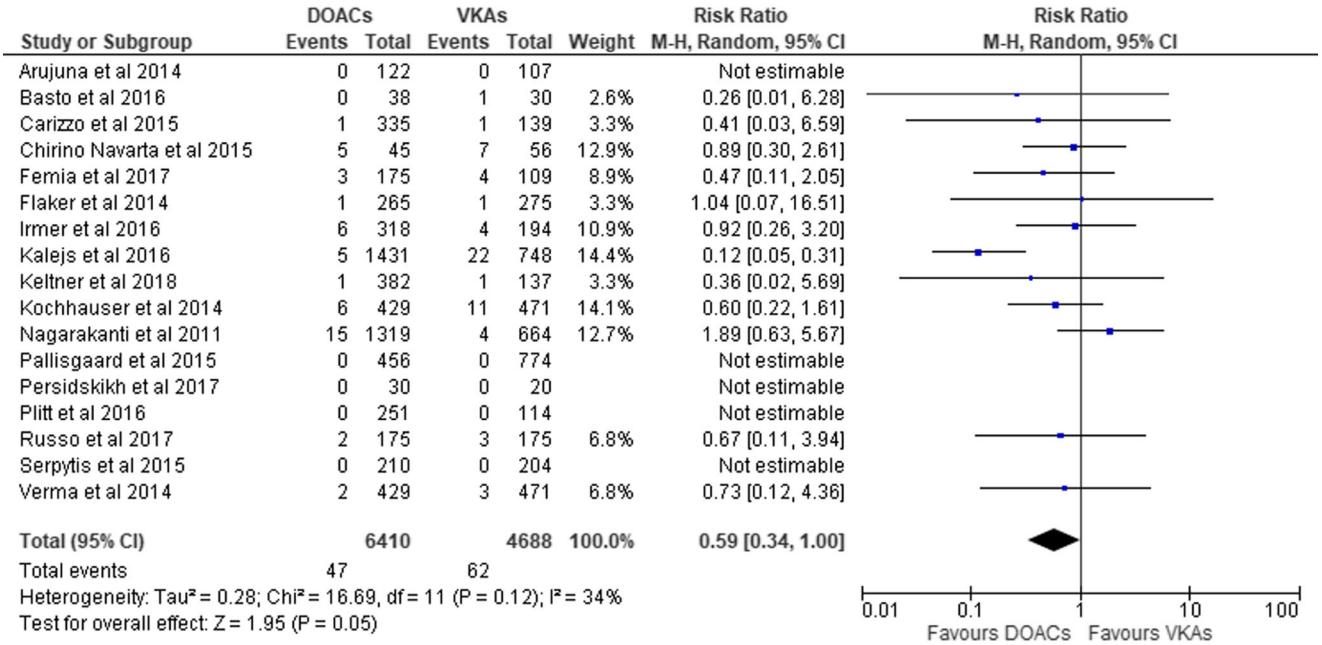


Fig. 3 Forest plots demonstrating bleeding events for DOACs and VKAs with or without adjuncts. Square markers represent point estimate of risk ratios (RR) for individual studies, with square size proportional to the weight given to each study in the meta-analysis. Horizontal lines indicate 95% confidence intervals (CI). The solid diamond represents the estimated 95% confidence interval for effect size of all meta-analyzed data

significantly lower incidence of thromboembolism and bleeding among patients receiving DOACs. And, while observational studies are mired with selection bias and confounding factors likely influence results, clinical trials do not always provide sufficient information. RCTs may have—as was the case here—small and select study populations, and well-monitored adherence, which do not reflect real-world conditions [55].

Studying anticoagulation-related adverse events pericardioversion is challenging. With thromboembolic event rates of 0.3% with DOACs and 0.4% with VKAs—as observed in both RCTs and observational studies in this meta-analysis—a trial aiming to demonstrate a 25% relative risk reduction in thromboembolism would require over 100,000 participants to achieve 80% power (alpha = 0.05). While non-inferiority designs may seem like an interesting alternative, underpowered non-inferiority designs are inherently biased towards non-inferiority. Given these challenges, this meta-analysis, summarizing the totality of available evidence surrounding DOACs in patients with AF undergoing cardioversion, is likely to remain the best evidence to guide clinicians. The RCT-derived evidence for DOACs pericardioversion in patients with AF is reassuring with point estimates that favor DOACs when evaluating patient-important outcomes such as mortality, thromboembolism, and bleeding.

From a practical perspective, VKAs have significant disadvantages: food and drug interactions, increased hemorrhagic risk in older patients, and requirement for INR monitoring [56, 57]. When prescribing VKAs in patients undergoing cardioversion, guidelines strongly recommend an INR range of 2 to 3 [5, 6, 12]. Maintenance of an INR in the therapeutic range is challenging, especially early after initiating VKA treatment [58]. Large, multicenter trials comparing VKAs to DOACs have reported times in therapeutic range between 55 and 65% [18–20, 59]. Meanwhile, in the first month of VKA therapy, time in the therapeutic range was only 51% to 58% in similar, multi-center trials [60–62]. Less time in the therapeutic range has been associated with a higher risk of bleeding and death [63]. The time in the therapeutic range achieved in RCTs is known to be higher than that in observational studies, suggesting that the safety and efficacy of VKAs

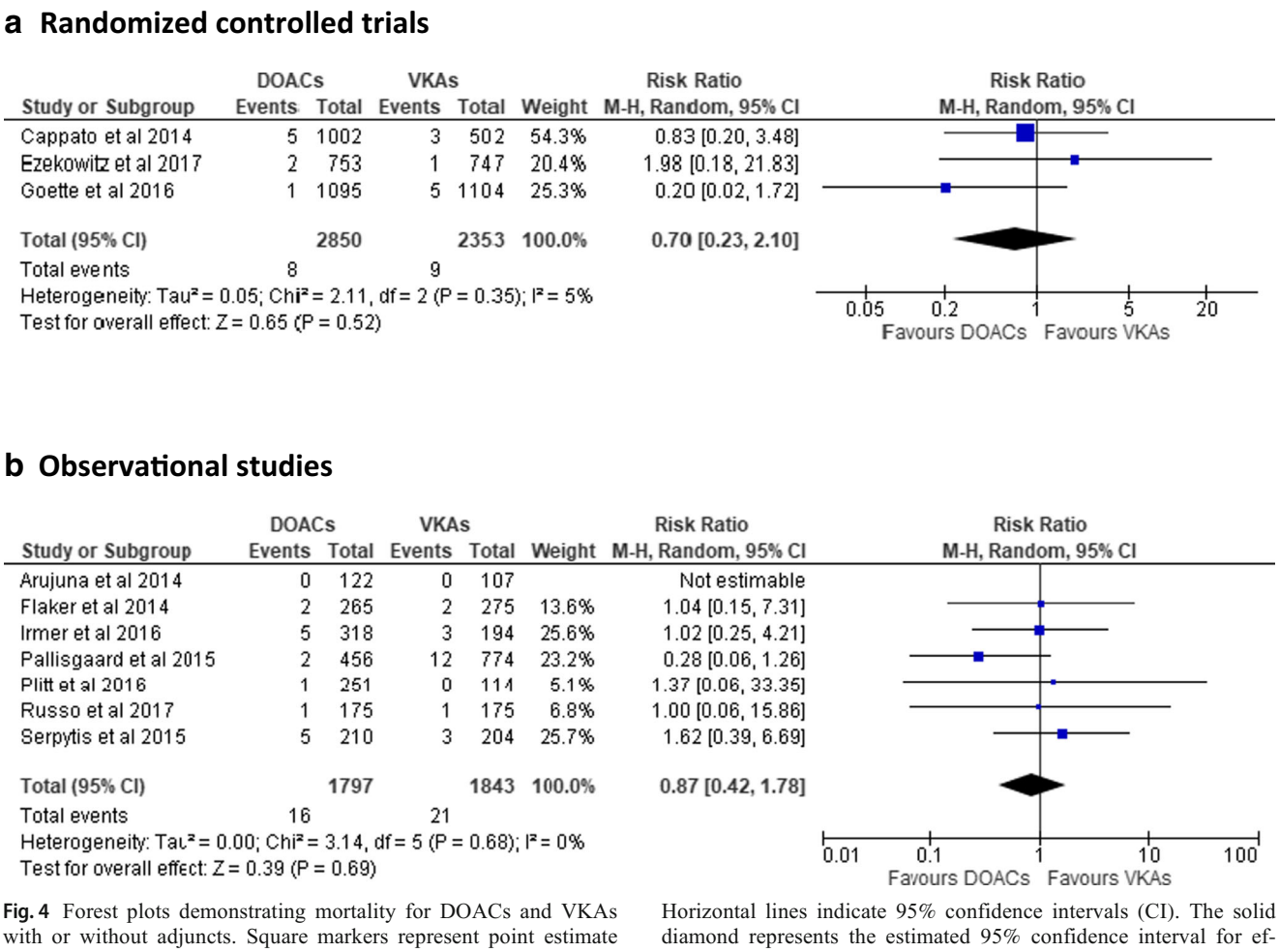


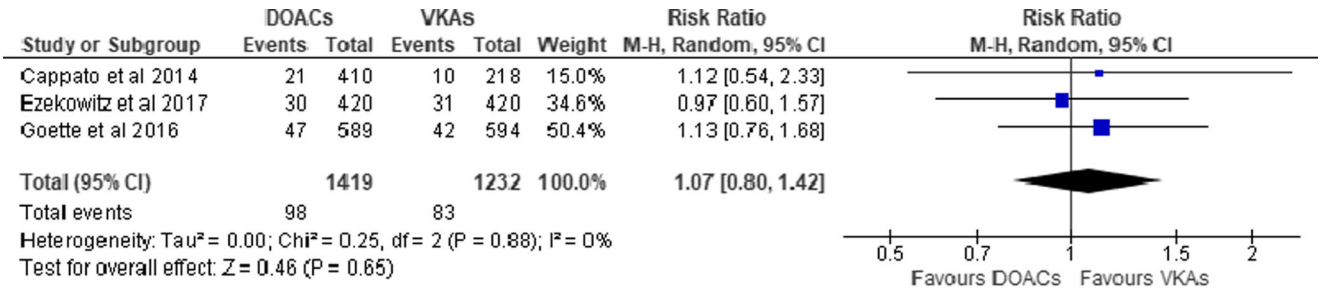
Fig. 4 Forest plots demonstrating mortality for DOACs and VKAs with or without adjuncts. Square markers represent point estimate of risk ratios (RR) for individual studies, with square size proportional to the weight given to each study in the meta-analysis. Horizontal lines indicate 95% confidence intervals (CI). The solid diamond represents the estimated 95% confidence interval for effect size of all meta-analyzed data

portrayed in RCTs may exceed results in the "real world" [64]. Subtherapeutic INRs are particularly important peri-cardioversion as they may lead to procedure cancellations, transoesophageal echocardiograms, and delays that impact patient quality of life, all at costs to the healthcare system [36]. In the X-Vert trial, for example, there was a significant increase of 22 days in median days to cardioversion with VKAs compared to rivaroxaban [31].

In contrast, DOACs carry a predictable therapeutic effect, do not require routine monitoring, and have fewer drug or food interactions [65]. Concerns with using DOACs revolve around the lack of widely available reliable reversal agents with patients and physician concerns about the management of life-threatening bleeding [66]. With an incidence of major bleeding of 0.004% with DOACs in RCTs, these events are rare peri-cardioversion and, based on our pooled estimate of risk, potentially less frequent with DOACs compared to VKAs. This is consistent with the results of larger RCTs with longer follow-up in patients with AF where DOACs decreased the risk of major bleeding when compared with warfarin [67].

Two distinct populations of patients undergo cardioversion. A majority of patients who undergo cardioversion require life-long oral anticoagulation [31, 33, 68]. Among such patients, DOACs are shown to be as effective as VKAs, while being safer, with lower rates of life-threatening bleeds [67]. A recent survey of AF patients treated with DOACs and VKAs as outpatients demonstrated a significantly greater patient satisfaction among those taking DOACs, without any impact on adherence [69]. Our results suggest that these benefits can be extended to the cardioversion period, especially in the 15–25% of patients who undergo cardioversion and do not need long-term oral anticoagulation per current guidelines [32, 33, 68]. These patients are invariably younger and are often more active, and given that there is no evidence of compromise in overall effect, DOACs should be favored for their convenience and predictability.

a Randomized controlled trials



b Observational studies

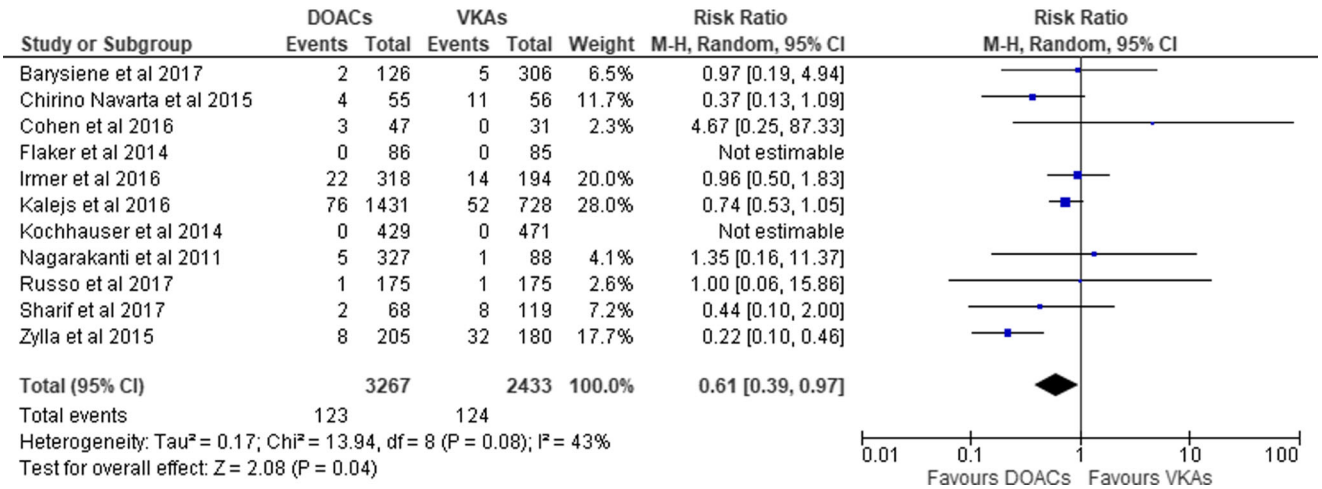


Fig. 5 Forest plot demonstrating thrombus on transesophageal echo for DOACs and VKAs with or without adjuncts. Square markers represent point estimate of risk ratios (RR) for individual studies, with square size proportional to the weight given to each study in the meta-analysis. Horizontal lines indicate 95% confidence intervals (CI). The solid diamond represents the estimated 95% confidence interval for effect size of all meta-analyzed data

Strengths and Limitations

Our systematic review and meta-analysis has several strengths: pre-registration, a comprehensive search strategy, the inclusion of randomized and observational data, and a rigorous evaluation of the quality of evidence. Furthermore, unlike a previous meta-analysis on the topic, we divided observational and RCT data [70]. Our review and meta-analysis also has limitations. First, included studies evaluated different DOACs against VKAs, and some used adjuncts, like low molecular weight or unfractionated heparin, to the VKAs. Although this may lead to clinical heterogeneity, it also reflects clinical practice. Second, despite including all available evidence, the number of participants remains insufficient to evaluate for differences in patient-important outcomes between DOACs and VKAs. Third, the definitions for bleeding, and major bleeding, varied among studies.

Conclusions

Based on moderate-quality data from RCTs and very low-quality observational data, the results of our systematic review and meta-analysis suggest that using DOACs peri-cardioversion in patients with atrial fibrillation appears to be safe from both a bleeding and thromboembolic risk perspective. Available evidence supports the use of DOACs as standard of care for peri-cardioversion in patients with atrial fibrillation.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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