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Systematic Review

Outcomes and Safety of Direct Oral Anticoagulants (DOACs) versus Vitamin K Antagonists (VKAs) amongst Patients with Valvular Heart Disease (VHD): A Systematic Review and Meta-Analysis

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Abstract: Background: Both valvular heart disease (VHD) and atrial fibrillation (AF) frequently coexist. AF is an important cause of arrhythmias with a definitive cardiovascular morbidity. The use of either vitamin K antagonists (VKAs/warfarin) or direct oral anticoagulants (DOACs) (also known as new oral anticoagulants (NOACs)) has been the mainstay for preventing stroke and systemic embolism in patients with VHD and/or AF, and this has been broadly discussed. However, there are limited studies on anticoagulation therapy for patients with valvular atrial fibrillation (VAF). The main aim of this meta-analysis was to evaluate the outcomes (stroke–vascular events and intracranial bleeding) following DOAC and VKA treatment amongst patients with VAF. Methods: We identified clinical trials and observational studies published in the last 10 years. A systematic review and a meta-analysis were performed to evaluate the outcomes of patients with valvular atrial fibrillation following DOAC vs. VKA treatment. Data evaluation was performed using Review Manager 5.4; the endpoints were stroke–vascular events and intracranial bleeding following DOAC and VKA treatment amongst VAF patients. Risk ratios (RR) were evaluated with 95% confidence intervals. Using random effects models, forest plots were obtained. Heterogeneity was assessed by using the I^2 statistic. Results: Eight studies were included in this metanalysis, and a total of fifteen thousand two hundred and fifteen patients (DOAC (8732) and VKA (6483)) were pooled. We found a significant risk reduction in stroke–vascular events when using DOACs in comparison with using VKAs (pooled RR: 0.76; 95% CI: 0.64–0.90, $p = 0.002$). A total of 14862 patients (DOAC (8561) and VKA (6301)) were pooled from a total of six studies for intracranial bleeding. We found a significant risk reduction in terms of intracranial bleeding when using DOACs in comparison with using VKAs (pooled RR: 0.43; 95% CI: 0.24–0.77, $p \leq 0.05$). Conclusions: When compared to VKAs, DOAC agents were found to have less risk of stroke–vascular events and intracranial bleeding. Further prospective studies are essential to establish the efficacy and safety of DOAC agents in patients with various subtypes of VAF.

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1. Introduction

Globally, in 2010, the age-adjusted prevalence of atrial fibrillation (AF) was reported in approximately 33 million people [1]. In elderly patients, both valvular heart disease (VHD) and AF are seen commonly, and they frequently coexist [2]. AF is one of the most common clinically important arrhythmias with a definitive cardiovascular morbidity, and it has up to a five-fold risk of a stroke and systemic embolization [3,4]. the use of either vitamin K antagonists (VKAs/warfarin) or direct oral anticoagulants (DOACs) (also known as new oral anticoagulants (NOACs)) has been the mainstay in and is crucial for preventing stroke and systemic embolism in patients with VHD and/or AF [5,6] because they have been shown to reduce both the risk of the event and the mortality as well [7–9].

Despite the pertinent usage of these treatments, a high incidence of thromboembolic events, about 1–4% per year, and a notable risk of bleeding, ranging from 2% to 9% per year, has been reported [10]. Also, the presence of any contraindications or inconvenience regarding to the constant monitoring of the international normalized ratio (INR) to ensure an optimal level of medication or to maintain the narrow therapeutic index could be linked to the suboptimal use or underutilization of VKA therapy in AF patients [11,12].

Since 2009, non-VKA oral anticoagulants (DOACs) have been approved for stroke prevention in patients with AF [7,13]. Each of the DOAC agents, dabigatran, rivaroxaban, apixaban, and edoxaban, have been reported to be at least as safe and effective as warfarin [13]. Since then, DOACs have rapidly replaced warfarin for stroke prevention in AF patients. This could be attributed to their ease of use, wide therapeutic index, and lack of a necessity for continuous monitoring when compared with using warfarin [13,14]. So far, there is only limited evidence from randomized trials recommending the use of VKAs for patients with bioprosthetic valves [15–17]. A few subgroup analyses, however, were performed based on trials, and they have reported on the efficacy and safety of various DOACs among patients with atrial fibrillation and a bioprosthetic mitral valve [10,18,19].

In view of the requirement of long-term anticoagulation in patients with atrial fibrillation and a bioprosthetic valve or VHD, it is essential to find out which of the two standards of treatments (DOACs vs. VKAs) would be more effective compared to the other. The primary objective of this study was to review the published literature and compare the overall efficacy and safety of various DOACs and VKAs in terms of treating valvular atrial fibrillation (VAF) patients (AF + VHD).

2. Methods

Our systematic review and meta-analysis were carried out according to the standards established by the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines and the MOOSE (meta-analysis of observational studies in epidemiology) protocol to evaluate the outcomes of patients with valvular atrial fibrillation following treatment with DOACs vs. VKAs. For our meta-analysis, we chose articles on dabigatran, rivaroxaban, edoxaban, and apixaban (DOACs) as the intervention group and on warfarin (VKA) as the control group.

The primary aim of the study was to evaluate all-cause mortality among patients with valvular atrial fibrillation (VAF) (atrial fibrillation of valvular (mitral and aortic) heart disease and bioprosthetic origin) following treatment with DOACs or VKAs. The secondary aim of the study was to evaluate stroke and life-threatening bleeding following intervention and control.

2.1. Endpoint Definitions

We defined VAF as AF developing in the setting of mild mitral valve stenosis or aortic valve stenosis and/or in the presence of an artificial (bioprosthetic only) heart valve [20]. Stroke was defined as a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH) [21]. Major bleeding was defined based on International Society on Thrombosis and Haemostasis and included: (a) fatal bleeding; (b) bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; and/or (c) bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more or leading to the transfusion of two or more units of whole blood or red cells [22].

2.2. Search Criteria

We followed the PRISMA guidelines and the MOOSE protocol in conducting the systematic review and meta-analysis comparing the outcomes of VAF following the use of DOACs vs. VKAs. Articles on Pubmed were searched using the following keywords: ((((((valvular atrial fibrillation [Title/Abstract]) OR (VAF [Title/Abstract])) OR (valvular AF [Title/Abstract])) OR (atrial fibrillation with bioprosthetic valve [Title/Abstract])) OR (atrial fibrillation with mechanical valve [Title/Abstract])) OR (atrial fibrillation with mechanical heart valves [Title/Abstract])) OR (atrial fibrillation with mitral stenosis [Title/Abstract]) AND ((((((((((Oral anticoagulants vs. Warfarin [Title/Abstract]) OR (DOAC vs. Warfarin [Title/Abstract])) OR (DOACs vs. Warfarin [Title/Abstract])) OR (rivaroxaban vs. Warfarin [Title/Abstract])) OR (rivaroxaban [Title/Abstract])) OR (apixaban [Title/Abstract])) OR (Oral anticoagulants [Title/Abstract])) OR (Warfarin [Title/Abstract])) OR (Warfarin [Title/Abstract])) OR (Factor Xa inhibitor [Title/Abstract])) OR (VKA [Title/Abstract])) OR (vitamin K antagonist [Title/Abstract]) to identify clinical trials and observational studies with data on the outcomes of VAF amongst the different types of DOACs and VKAs from the last 10 years.

2.3. Inclusion Criteria

Only clinical trials and observational studies published in the last 10 years with data on valvular atrial fibrillation amongst the adult population and with an intervention comparison between DOACs and VKAs were considered in our meta-analysis.

2.4. Exclusion Criteria

Patients with moderate-to-severe mitral stenosis and mechanical valve placement were excluded. Studies/articles other than clinical trials and observational studies, non-human, non-English, and non-full-text studies were also excluded.

2.5. Study Selection Strategy

Using the above eligibility criteria and keywords, we screened the abstracts and evaluated them for their inclusion in our meta-analysis. BI and GP screened abstracts independently, and any disagreement was resolved by UP. From the screened abstracts, full-length articles were obtained and studied individually for their eligibility in the quantitative analysis (meta-analysis). Figure 1 describes the study selection process.

2.6. Data Extraction

Data on the study name, design, duration, sample size, population characteristics (country, mean/median age in years, and sex (%)), type of intervention (DOAC vs. VKA), and outcomes (mortality, stroke, and major bleeding) were collected using a standard template, and any disagreement was resolved by BI and UP. Table 1 describes the data we collected for this meta-analysis.

2.7. Statistical Analysis

An Excel sheet was used to collect the data, and the Review Manager version 5.3 software was used to analyze the data. We performed random effects models to estimate the pooled effect size (pooled odds ratio) and the 95% confidence interval (95% CI). Forest plots were obtained. $p < 0.05$ was considered statistically significant. Heterogeneity (I^2 values) was identified, and $I^2 > 75\%$ represented a high heterogeneity. In such circumstances, sensitivity analysis was performed, and studies with a higher variability were removed using a funnel plot. A risk of bias analysis was performed and described using the Newcastle–Ottawa scale (NOS).

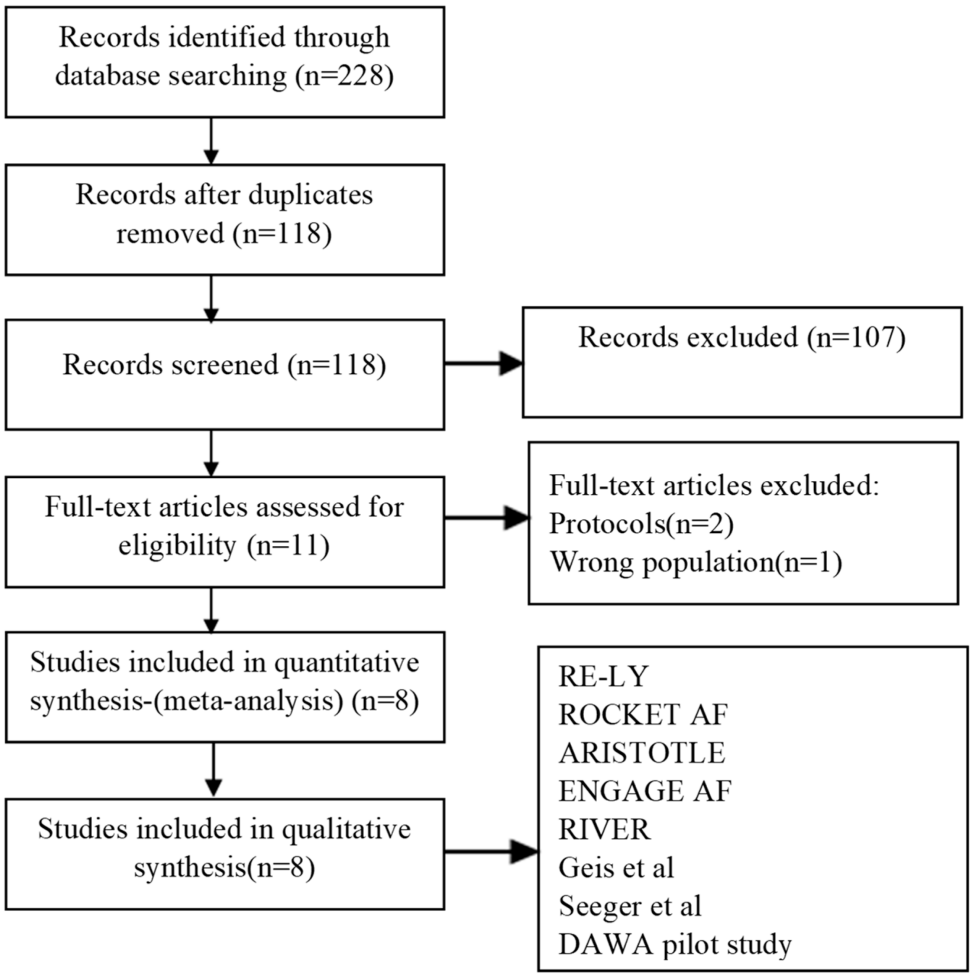

Figure 1. Study Selection Process.

Table 1. Study characteristic including designs, demographics, interventions, and outcomes.

Study Name, Year	Country	Study Design	Population	Sample Size	Mean/Median Age (Years)	Female (%)	Intervention (DOAC vs. VKA)	Outcomes (Events) (Events in NOAC vs. Events in VKA)
RE-LY Ezekowitz et al., (2014) [23]	USA	Prospective, randomized trial	Atrial fibrillation and valvular heart disease	3950	74.0 (68.0, 79.0)	40.7%	Dabigatran vs. warfarin (2645 vs. 1305)	All-cause mortality (226/2645 vs. 122/1305) Stroke (77/2645 vs. 49/1305) Major bleeding (209/2645 vs. 132/1305) Intracranial bleeding (16/2645 vs. 24/1305)
Rocket AF Breithardt et al., (2014) [24]	USA	Multicenter, international, double-blind, double-dummy, randomized trial	Atrial fibrillation and valvular heart disease	2003	75 (68.0, 79.0)	39.4%	Rivaroxaban vs. warfarin (968 vs. 1035)	All-cause mortality (100/968 vs. 112/1035) Stroke (38/968 vs. 50/1035) Major bleeding (88/968 vs. 68/1035) Intracranial bleeding (13/968 vs. 12/1035)
ARISTOTLE Avezum et al., (2015) [18]	USA	Randomized, double-blind trial	Atrial fibrillation and valvular heart disease	4808	71 (64.0, 77.0)	40.3%	Apixaban vs. warfarin (2438 vs. 2370)	All-cause mortality (222/2438 vs. 215/2370) Stroke (60/2438 vs. 87/2370) Major bleeding (99/2438 vs. 119/2370) Intracranial bleeding (10/2438 vs. 34/2370)
ENGAGE AF-TIMI De Caterina, et al., (2017) [19]	USA	Randomized, double-blind, double-dummy trial	Atrial fibrillation and co-existing valvular heart disease	2824	71.8 $\pm$ 9.4	42.2%	Edoxaban vs. warfarin (1869 vs. 955)	All-cause mortality (308/1869 vs. 147/955) Stroke (82/1869 vs. 50/955) Major bleeding (99/1869 vs. 89/955) Intracranial bleeding (11/1869 vs. 34/2370)

Table 1. *Cont.*

Study Name, Year	Country	Study Design	Population	Sample Size	Mean/Median Age (Years)	Female (%)	Intervention (DOAC vs. VKA)	Outcomes (Events) (Events in NOAC vs. Events in VKA)
RIVER trial Guimarese et al., (2020) [25]	Brazil	Phase 4, multicenter, randomized, noninferiority, open-label design with blinded adjudication of outcomes	Atrial fibrillation and bioprosthetic mitral valve	1005	59.3 ± 12.1	60.4%	Rivaroxaban vs. warfarin (500 vs. 505)	All-cause mortality (20/500 vs. 20/505) Stroke (3/500 vs. 12/505) Major bleeding (7/500 vs. 13/505) Intracranial bleeding (0/500 vs. 5/505)
Geis et al., (2018) [26]	Germany	Prospective cohort	Post TAVI	326	83.1 ± 5.3	51%	DOAC vs. VKA (154 vs. 172)	All-cause mortality (12/154 vs. 11/172) Stroke (5/154 vs. 2/172) Major bleeding (3/154 vs. 3/172) Intracranial bleeding
Seeger et al., (2016) [27]	Germany	Prospective cohort	Post TAVR	272	81.3 ± 5.9	40.5%	Apixaban vs. VKA (141 vs. 131)	All-cause mortality at 12 months (19/81 vs. 6/50) Stroke at 12 months (1/81 vs. 1/50) Major bleeding (5/141 vs. 7/131) Intracranial bleeding (1/141 vs. 0/131)
DAWA pilot, Durães et al., (2016) [10]	Brazil	Phase II, prospective, open label, randomized, pilot study	Bioprosthetic mitral and/or aortic valve replacement and post-op AF	27	Not given (intervention group—48.8 ± 10.4, control group—45.7 ± 6)	63%	Dabigatran vs. warfarin (15 vs. 12)	All-cause mortality (0/15 vs. 1/12) Stroke (0/15 vs. 1/12) TIA (1/15 vs. 0/12) Major bleeding (1/15 vs. 2/12) Intracranial bleeding

3. Results

In the last 10 years (From January 2011 until present), using the inclusion and exclusion criteria, we narrowed the articles examined down eight articles (both observational studies and clinical trials). The utilization of DOACs was about 57.5% (8670/15,074) of this pooled population.

3.1. Stroke–Vascular Events

The meta-analysis conducted with eight studies showed an incidence of stroke–vascular events of 3.4% (519/15,074) with a higher incidence following VKA use (3.9%; 252/6404) compared to DOAC use (3.1%; 267/8670). We found a 24% risk reduction (pooled RR: 0.76, 95% CI: 0.64–0.90, $p = 0.002$) when using DOACs in comparison with using VKAs with a 0% interstudy variability ($I^2 = 0\%$, p for $I^2 = 0.49$, $chi^2 = 6.43$, $tau^2 = 0$) (Figure 2).

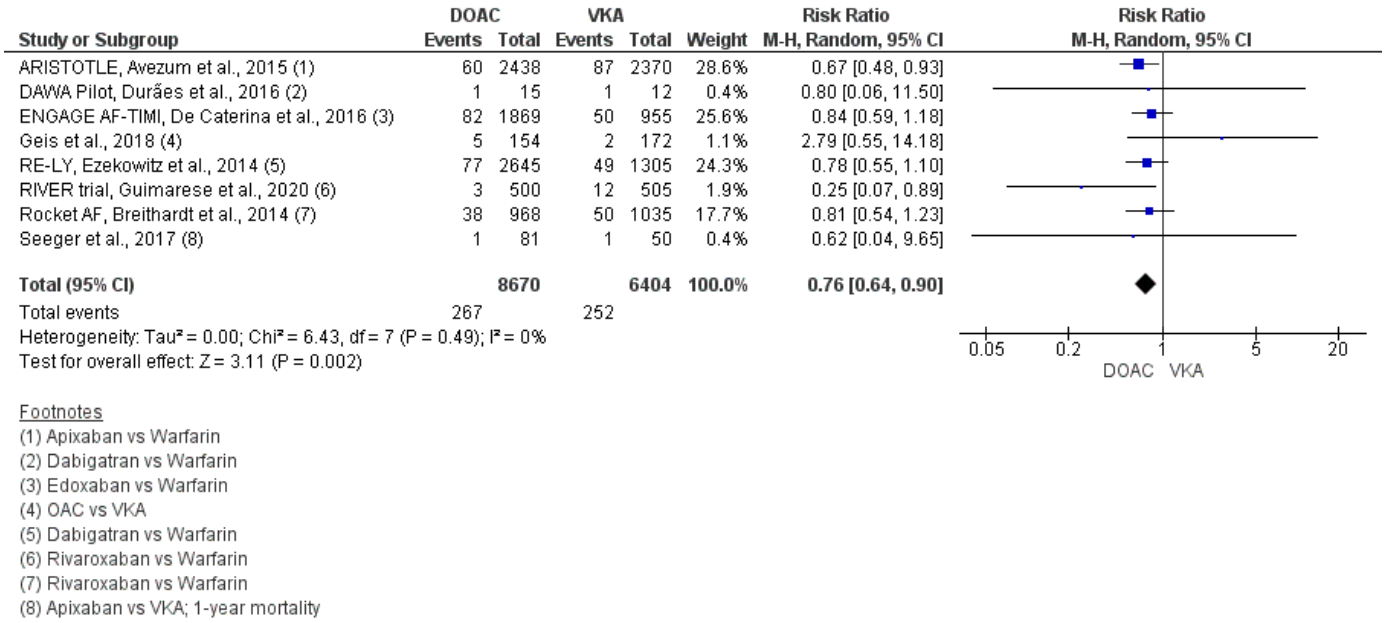

Figure 2. Forest plot for risk of stroke–vascular events after DOAC therapy.

3.2. All-Cause Mortality

A total of eight studies including fifteen thousand and seventy-four participants were pooled for the meta-analysis of all-cause mortality. DOAC therapy was associated with an RR of 1.01 (95% CI: 0.92–1.11, $p = 0.91$) compared to VKA therapy with a 0% interstudy variability ($I^2 = 0\%$, p for $I^2 = 0.70$, $chi^2 = 4.69$, $tau^2 = 0$) (Figure 3). For this outcome, we found no significant difference between the two groups.

3.3. Major Bleeding

For major bleeding after DOAC therapy, a total of 15,213 participants were pooled in our analysis. The incidence of major or life-threatening bleeding was 511 out of 8730 (5.85%) with DOAC therapy compared to 433 out of 6483 (6.67%) with VKA therapy. The RR for major bleeding after DOAC therapy was 0.80 (95% CI: 0.61–1.04, 0.1)) ($I^2 = 64\%$) (Figure 4).

3.4. Intracranial Bleeding

In this meta-analysis, six out of the eight studies provided intracranial bleeding as part of their secondary outcome. A total of 14,862 participants were pooled in our analysis. The incidence of intracranial bleeding was 0.96% (143/14862) overall. Interestingly, ARISTOTLE reported the highest number of events among the VKA arm. We found a 57% risk reduction in intracranial bleed in the DOAC arm compared to the VKA arm. The pooled risk ratio

was 0.43 (95% CI: 0.24–0.77, $p \leq 0.05$) without interstudy statistical variation in terms of the heterogeneity analysis ($I^2 = 55\%$, p for $I^2 = 0.05$, $chi^2 = 11.03$, $tau^2 = 0.25$) (Figure 5).

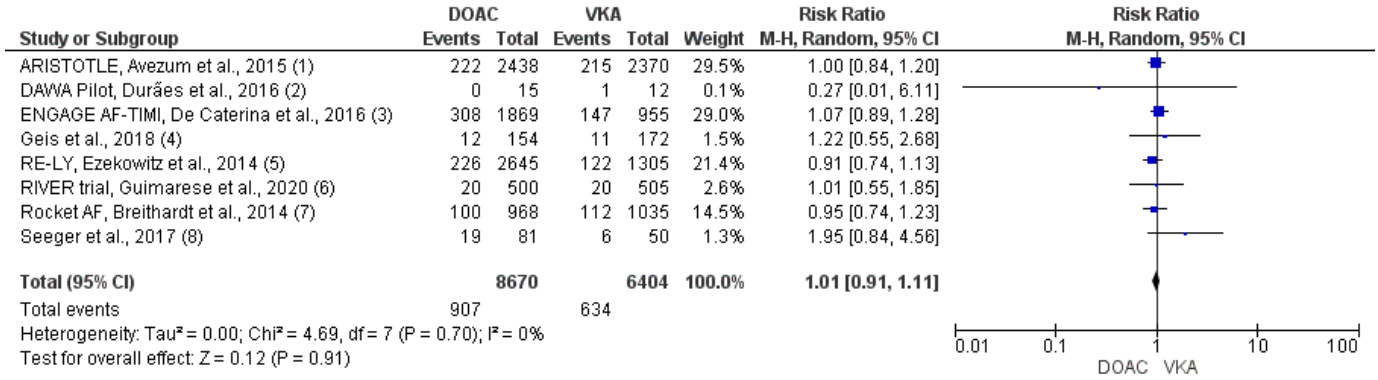

Figure 3. Forest plot for all-cause mortality after DOAC therapy.

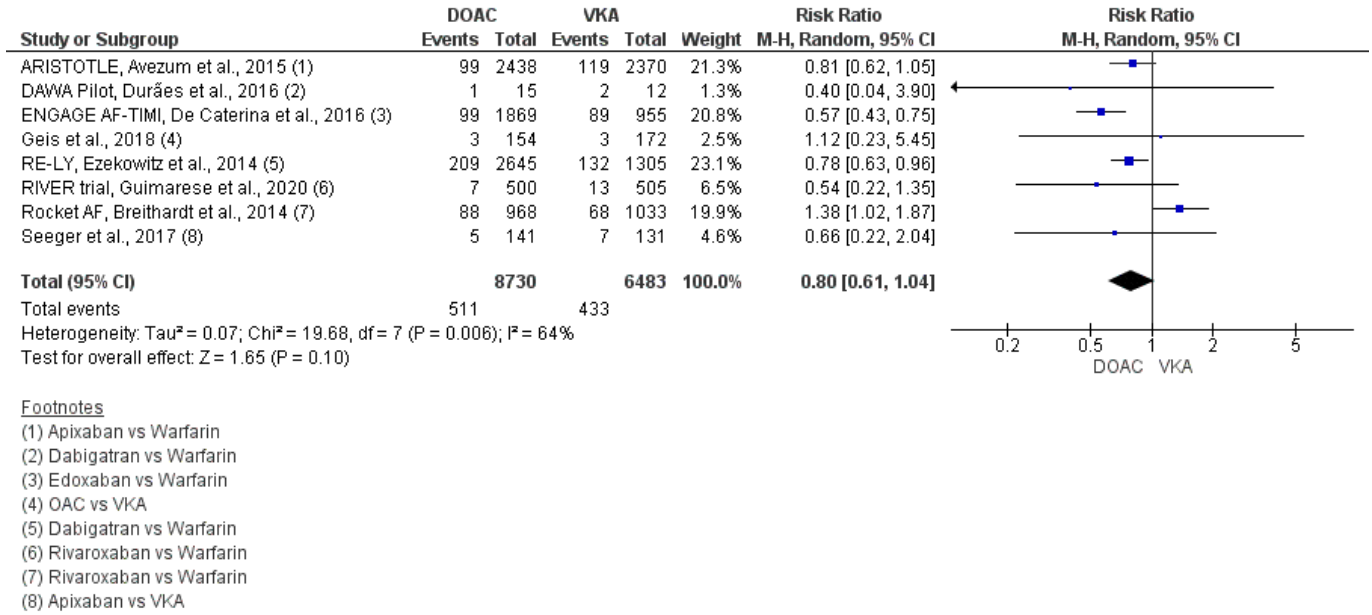

Figure 4. Forest plot for major bleeding after DOAC therapy.

3.5. Composite Poor Outcome Overall Event

We pooled all the events from the eight studies for composite poor outcomes. A total of 15,074 participants were pooled for the total incidence of events; there were a total 1750 events noted in the DOAC arm compared to 1410 events in the VKA arm. The incidence was 20.1% (1750/8670) in the DOAC arm compared to 22% (1410/6404) in the VKA arm. The composite events included all-cause mortality, stroke–vascular events, major bleeding, and intracranial bleeding. The ENGAGE AF-TIMI trial reported the highest number of events, with the incidence of overall events measuring 26.7% and 31.7% in the DOAC and VKA arms, respectively. The pooled RR of composite events was 0.89 (95% CI:

0.80–1.00, $p = 0.05$) with no statistical variation in terms of heterogeneity ($I^2 = 54\%$, p for $I^2 = 0.03$, $chi^2 = 15.12$, $tau^2 = 0.01$) (Figure 6).

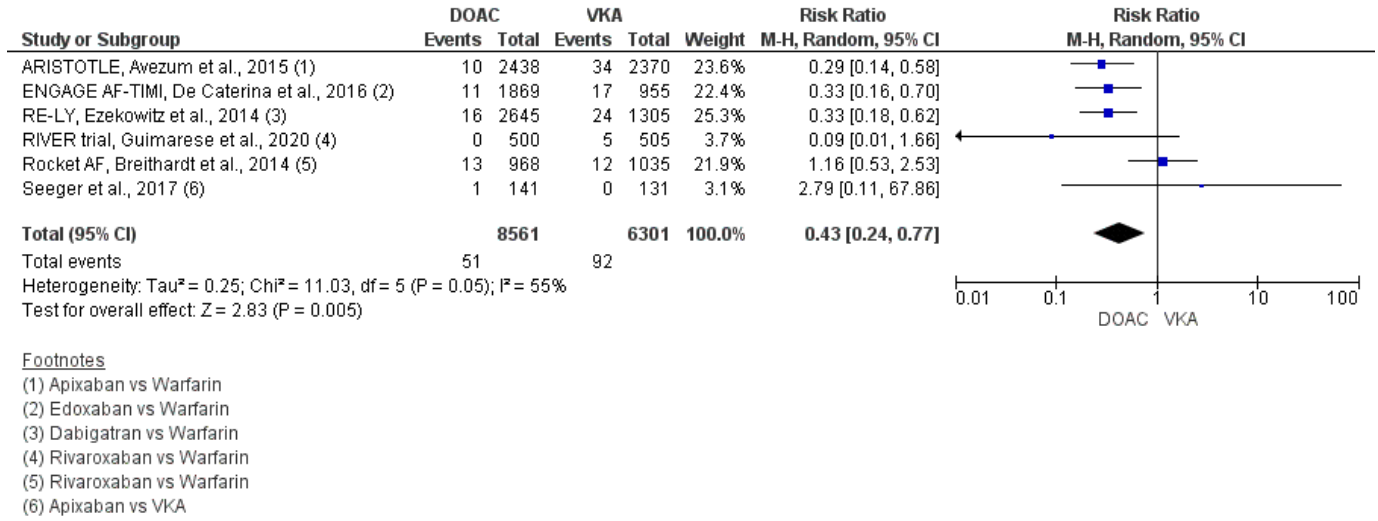

Figure 5. Forest plot for intracranial bleeding after DOAC therapy.

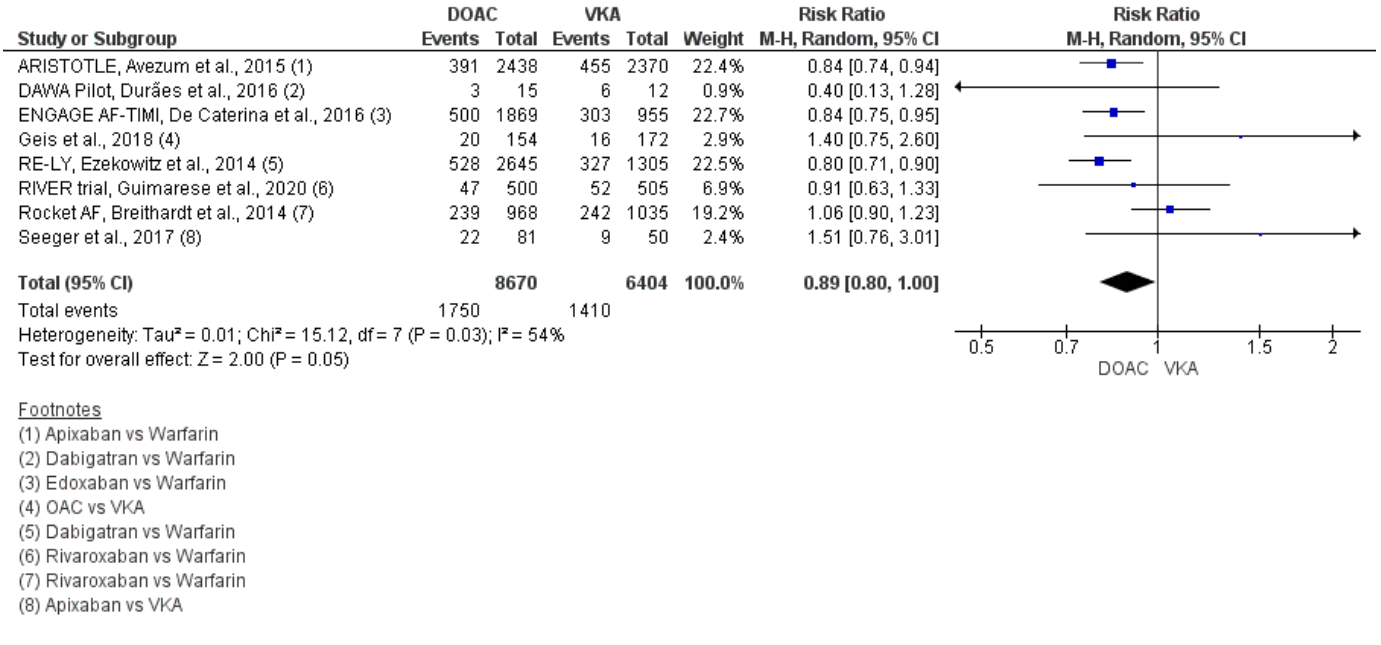

Figure 6. Forest plot for composite poor outcome after DOAC therapy.

4. Discussion

The main findings of this systematic review and meta-analysis include the following: (a) DOAC agents were found to significantly reduce the risk of stroke–vascular events, intracranial bleeding, and poor composite outcome in patients with VAF when compared to VKA agents. (b) However, there was no difference in all-cause mortality and major bleeding when comparing VAF patients who received DOACs to patients who received VKAs.

In individuals with VAF, prior randomized clinical trials comparing different DOAC agents or different doses of the same DOAC agent to VKAs found no significant difference in mortality [10,18,19,23,24]. The results of our study were consistent with the mortality outcomes in these studies. Major bleeding was another outcome, in which a significant difference was not found along with all-cause mortality between DOACs and VKAs in our study. The high heterogeneity identified with regards to major bleeding in our study was

due to the ROCKET-AF study [24], where rivaroxaban was associated with a higher risk of major bleeding than warfarin.

The beneficial effect of DOACs in preventing stroke and thromboembolic events was noted as a 24% risk reduction in our study Similarly, in recent meta-analyses, the risk reduction was noted to be about 35%, 22%, and 30% [28–30]. Likewise, the beneficial effect of DOACs in lowering the risk of intracranial bleeding was also consistent with these recent meta-analysis studies. The risk reduction in the other meta-analyses was 65%, 49%, and 53% [28–30], and it was 49% in our study. For this analysis, we included only six of the eight studies.

From the eight studies, the participants were pooled for the total incidence of events or composite poor outcomes. While 20.1% in the DOAC arm had composite poor outcomes, the VKA arm had 22% of the same. Among the studies, the ENGAGE AF-TIMI trial [19] had the highest number of events, and the incidence of overall events, which measured 26.7% and 31.7% in the DOAC and VKA arms, respectively, was noted to be statistically significant.

In patients with VHD and atrial fibrillation who do not have rheumatic mitral stenosis or mechanical valves, the ACC/AHA guidelines support an individualized decision between using NOACs and VKAs [31]. Large cohort studies have validated the CHADs-VASc2 and HAS-BLED scores, proving their utility in making decisions in this group [32]. The ACC/AHA 2020 recommendations advocate using NOACs instead of VKAs in patients with atrial fibrillation with a bioprosthetic valve > 3 months after implantation or native VHD except mitral stenosis [31]. Dabigatran use has been linked to an increased risk of thromboembolism and intracranial bleeding in patients receiving a mechanical valve replacement [33]. Interestingly, the RIVER trial, which compared the safety and efficacy of the use of DOACs with VKAs in patients with AF and patients with mitral bioprosthetic valves concluded that rivaroxaban was non-inferior to warfarin [25].

A large multi-center prospective study, i.e., the DAWA study, was initiated to study this comparison between the use of DOACs and VKAs in patients with bioprosthetic valves; however, the study was terminated due to low enrolment [10]. More studies comparing the use of other DOACs vs. VKAs in patients with atrial fibrillation with mitral stenosis or mechanical valves are imperative.

Our study has some limitations. First, the inconsistency in the inclusion and exclusion criteria of the included studies due to the absence of complete agreement regarding the terms “valvular AF” and “nonvalvular AF” might have caused the occurrence of heterogeneity in some of the estimated outcomes. Secondly, the baseline features were not categorized based on thrombo-embolic risk, which is one of this study’s major flaws. This could have understated the protective effects of VKAs if higher-risk patients were initially included in a separate cohort. Thirdly, the pooled population included in our analysis was heterogeneous since we utilized both post hoc analyses of large RCTs and observational studies. Additionally, in view of the class effect of DOAC agents, we decided to evaluate studies that used different DOAC agents or different doses of the same DOAC agents [19,23] against VKAs. Thus, the collective outcome analyses might have underestimated or overestimated the benefit of the results we found.

5. Conclusions

Due to their limited drug interactions and similar efficacy and safety profile in the prevention of stroke, systemic embolism, and intracranial hemorrhage, DOAC agents have become an admirable substitute for VKAs. Our study supports the use of DOACs in patients with atrial fibrillation and VHD, excluding those with mechanical valve replacement and mitral stenosis. The use of DOAC agents should be cautiously applied in patients considered to have a very high thrombotic risk. Hence, further prospective studies are essential to establish the efficacy and safety of various doses of DOAC agents in patients with various subtypes of VAF. Also, further simultaneous prospective studies between DOAC agents could help to stratify their usage according to their profile of side effects better.

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