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Direct oral anticoagulation in atrial fibrillation and heart valve surgery—a meta-analysis and systematic review

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Abstract

Aims: Oral anticoagulation with direct oral anticoagulants (DOAC) could provide an alternative to vitamin K antagonists (VKA) for patients with atrial fibrillation (AF) undergoing bioprosthetic heart valve replacement or valve repair.

Methods and results: The aim of this meta-analysis was to review the safety and efficacy of DOAC in patients with surgical implanted bioprosthetic heart valves or valve repairs and AF including data from six clinical trials with a total of 1,857 patients. The efficacy and safety data of DOAC and VKA were pooled to perform random-effects meta-analyses using the Mantel–Haenszel method with pooled risk ratios (RR) and 95% confidence interval (CI). A trial sequential analysis (TSA) was performed to assess statistical robustness. Death caused by cardiovascular cause or thromboembolic events were comparable (RR 0.67, 95% CI: 0.42–1.08; $p = 0.10$) as DOAC significantly reduced the risk for major bleeding (RR 0.55, 95% CI: 0.35–0.88; $p = 0.01$) and thromboembolic stroke or systemic embolism rates (RR 0.54, 95% CI: 0.32–0.90; $p = 0.02$). Rates for intracranial bleeding and hemorrhagic stroke (RR 0.27, 95% CI: 0.07–0.99; $p = 0.05$) show a trend toward fewer events in the DOAC group. Outcomes for major or minor bleeding events and all-cause mortality were comparable for DOAC and VKA.

Conclusion: Cumulative data analysis reveals that DOAC may provide an effective and safe alternative to VKA in patients with AF after surgically implanted bioprosthetic heart valves or repair with AF. Within a relatively heterogeneous study population, this meta-analysis shows a risk reduction of major bleedings and thromboembolic stroke or systemic embolisms for DOAC.

Keywords: apixaban, atrial fibrillation, dabigatran, direct oral anticoagulation (DOAC), edoxaban, heart valve, rivaroxaban, vitamin K antagonist

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Introduction

Lifelong oral anticoagulation is recommended for patients with a surgically implanted bioprosthetic heart valve and atrial fibrillation (AF).[1,2] ESC/EACTS guidelines recommend oral anticoagulation after bioprosthetic heart valve replacement and other indications for anticoagulation without a clear recommendation for a specific oral anticoagulant (class I, level b). The recent ESC/EACTS guidelines from 2021 recommend that DOACs should be considered over VKA after three months following the surgical implantation of a biological heart valve in patients with AF (class IIa, level b).[2] ACC/AHA guidelines recommend anticoagulatory therapy with VKA for patients who run a low risk of bleeding after surgical implanted bioprosthesis either in the aortic or in the mitral position for at least three months (class IIa, level B-NR).[1] The use of direct oral anticoagulants (DOAC) for patients directly after heart valve surgery is not

recommended in recent guidelines. As an alternative oral anticoagulation to VKA, DOAC have been approved for several indications including non-valvular AF, VTE, PE, and non-MS valvular AF. The direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban have been judged non-inferior to VKA concerning the prevention of stroke in patients with non-valvular AF and favorable outcomes regarding bleeding complications.[3–6] DOAC do not require a routine monitoring or measurement of blood coagulation parameters, have fewer drug-drug and no food interactions, and thus lead to an improved patient satisfaction and compliance.[7,8] For further information, please see Supplementary material (Table 1). However, DOAC have thus far not been approved for patients who have undergone biological valve replacement or repair with or without additional indication for anticoagulation (e.g., AF), but promising results have been reported recently.[9] To evaluate recent data and encourage further research on the efficacy and safety of DOAC after heart valve surgery in patients with AF, we conducted a systematic review and meta-analysis.

Methods

Data sources and search strategy

This systematic review and meta-analysis was conducted using the 'Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines' (PRISMA) to assure a reproducible literature research and synthesis[10] (Figure 1) and was registered at PROSPERO (International prospective register of systematic reviews, ID257411). Studies investigating DOAC *versus* VKA in patients with AF after bioprosthetic valve replacement or valve repair were searched. An electronic search through the databases PubMed (https://pubmed.ncbi.nlm.nih.gov) and Web of Science (https://apps.webofknowledge.com) including MEDLINE, KCI Korean Journal Database, Russian Science citation index, and Scielo citation index has been performed on April 30, 2021. For search terms and Boolean operators, please see Supplemental material.

Study selection and data extraction

The following inclusion criteria for studies were applied: prior 'left-sided' heart valve surgery with either bioprosthetic aortic valve replacement, bioprosthetic mitral valve replacement, mitral valve repair using an annuloplasty device, or the combination of the aforementioned surgeries. Studies comparing oral VKA anticoagulation with DOAC were included, regardless of any combined antiplatelet therapy. In addition, the patients were required to have a history of any type of AF (paroxysmal, persistent, and permanent). Studies only reporting on patients after surgical valve repair without or less than 50% of patients with AF in either the DOAC or VKA group were excluded to diminish heterogeneity. The authors S.G. and E.K. independently conducted the study selection by screening titles and abstracts. Potentially relevant studies were analyzed using the full texts, and any disagreements over the appropriateness of inclusion were resolved by consulting the author T.W. Case reports or series as well as reviews and meta-analyses were excluded. Studies reporting on transcatheter aortic valve implantation or transcatheter mitral valve interventions were excluded.

Studies included, with name of the study, the design, patients' characteristics, control anticoagulant (VKA) and DOAC with type and dosage as well as the concomitant use of antiplatelet therapy and type of valve surgery were retrieved. A risk of bias assessment of included trials was performed using the Cochrane Collaboration's tool (Supplemental material, Figure S1).[11] There was no patient or public involvement due to the character of this study as a meta-analysis.

Outcomes

The primary outcome was defined as death caused by cardiovascular or thromboembolic events. The secondary outcome was defined as major bleeding in accordance with the definition of the International Society of Thrombosis and Haemostasis and the criteria of the Thrombolysis in Myocardial Infarction (TIMI) and Bleeding Academic Research Consortium (BARC) or the Valve Academic Research Consortium (VARC), if applicable. The combination of the primary and secondary outcomes was calculated to assess the net clinical outcome. Furthermore, we conducted sub-analyses for thromboembolic stroke and systemic embolism, intracranial bleeding or hemorrhagic stroke, all-cause mortality, cardiovascular mortality, and any bleeding event. In a subsequent

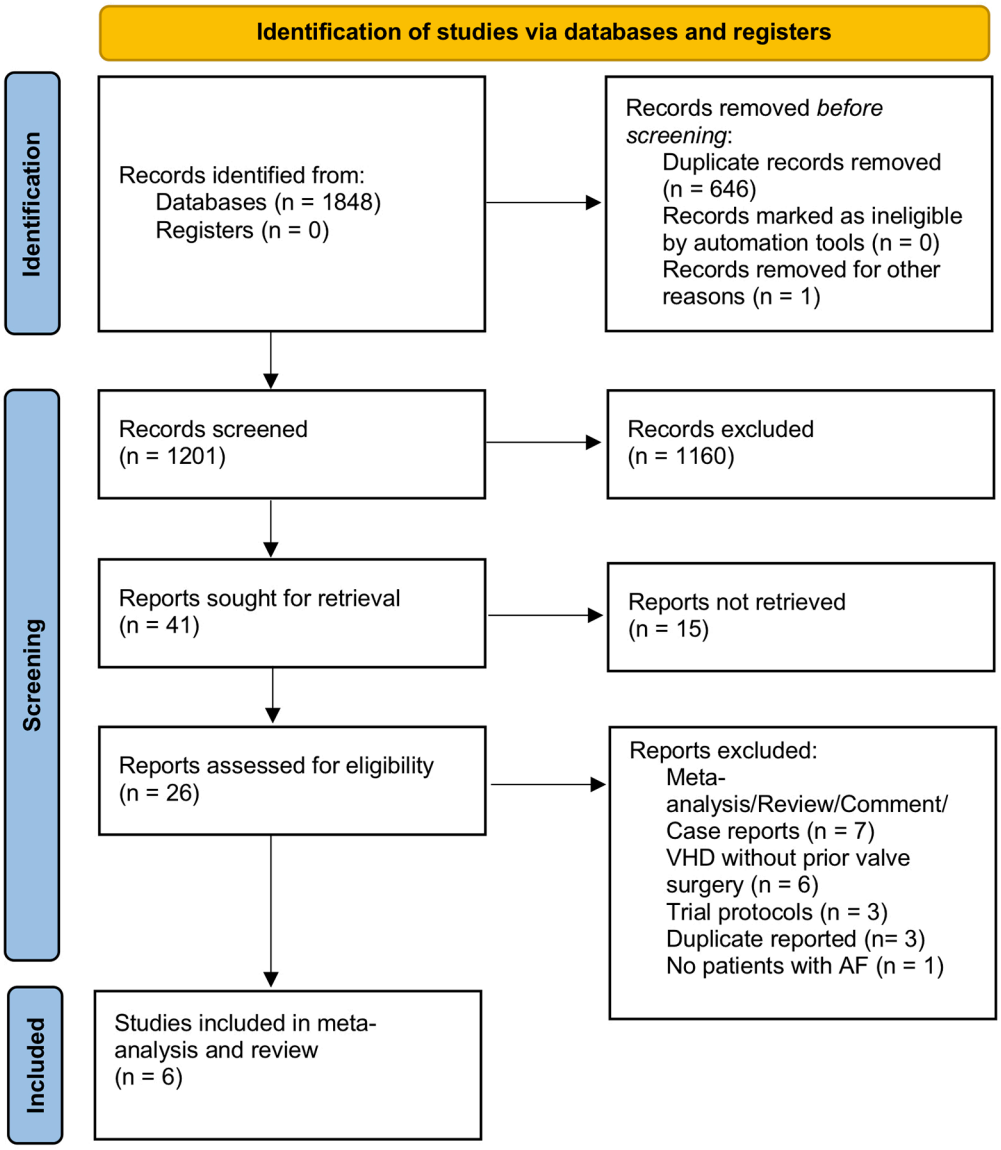

Figure 1. Study selection. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers.
AF, atrial fibrillation; VHD, valvular heart disease.

analysis, we calculated the reported outcomes for patients with biological prostheses and/or valve repair and for biological valve replacements alone.

Statistical analysis

Statistical analyses were performed using the *Review Manager (RevMan)* software (version5.4.1, The Cochrane Collaboration, 2020). Dichotomous variables were used concerning the number of participants with events and total number of participants in the DOAC and VKA control groups to perform the risk ratio random-effects meta-analyses by the Mantel–Haenszel method.[12] Weights of each and every individual study were calculated using the Mantel–Haenszel method. Forest plots with pooled risk ratios (RR) and 95% confidence interval (CI) were used to display the outcomes (M-H, random, 95% CI) as observational studies with different follow-up times were included in this meta-analysis.[13] The results were considered statistically significant

when $p < 0.05$. To quantify possible heterogeneity, the I^2-statistic was calculated to estimate the percentage of total variation between studies and is defined as follows: $I^2 < 30\%$=low-heterogeneity; $30\% < I^2 < 75\%$=moderate-heterogeneity; and $I^2 > 75\%$=considerable-heterogeneity.[14] Trial sequential analyses (TSA) were conducted for outcomes to explore whether or not pooled data were powered to assess for groups of interest using TSA version 0.9.5.10beta (Copenhagen Trial Unit, Center for Clinical Intervention Research, Copenhagen, Denmark, 2011).[15,16]

The calculation of the required information was based on a type-I error with an alpha (two-sided) of 5% and power of 80%. The relative risk reduction was based on pooled outcome data included in the analysis as well as the incidence of events in the control (VKA) group and heterogeneity. To interpret the power of outcomes, either significance with a minimum sample size had to be reached or crossing trial of the monitoring boundary with respect to alpha occurred. The data for bioprosthetic aortic valve replacement, bioprosthetic mitral valve replacement, and mitral valve repair were pooled for the reported outcome data and analyses with or without mitral valve repair were conducted if applicable. The outcomes for different dosages of DOAC were pooled into a single estimate, as differentiated outcome reports on single dosages were not available in most studies and then pooled with other trials included in the analysis.

Results

Studies included

Six studies [9,17–21] with a total of 1,857 patients after left-sided heart valve surgery (biological aortic and/or biological mitral valve replacement, mitral valve repair in two studies) and AF were included in this meta-analysis to evaluate the efficacy and safety of DOAC ($n = 962$) as a potential alternative to VKA ($n = 895$) anticoagulation. For the study selection process, which is in accordance with the guideline for reporting systematic reviews (PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only), see Figure 1.[22]

Three open-label RCTs,[9,18,20] two double-blinded RCTs[17,19] and one retrospective cohort study (propensity score match)[21] were included. Table 1 displays the study design of the evaluated studies.

This meta-analysis and systematic review represents the largest analysis of this topic. In relation to the novelty use of anticoagulation other than VKA with limited literature, multiple DOAC and various follow-up timeframes had to be included. Patients' baseline characteristics with respect to their bleeding risk and prior clinical events are presented in Table 2.

Primary outcome analysis—death caused by cardiovascular cause or thromboembolic events

Considering death caused by cardiovascular cause or thromboembolic events, quantitative analyses revealed 3.2% *versus* 4.8% (3.3% *versus* 5.4% without mitral valve repair) of all cases in the DOAC and VKA groups. The qualitative synthesis with pooled data analysis for patients after bioprosthetic heart valve replacement or mitral valve repair (RR 0.67, 95% CI: 0.42–1.08; $p = 0.10$) showed no differences between the groups with regard to the defined primary outcome analysis (Figure 2).

The subgroup analysis after excluding valve repair patients (RR 0.60, 95% CI: 0.35–1.04; $p = 0.07$) showed trend toward lower mortality due to cardiovascular or thromboembolic events with DOAC (Supplemental material, Figure S2). The analyzed data showed no heterogeneity ($I^2 = 0\%$). For the bioprosthetic heart valve group including patients with mitral valve repair, a cumulative evidence of 35% of the minimum required information size with 4,710 patients was reached as displayed in the TSA graph (Supplemental material, Figure S3). No further analysis was required as no statistically significant differences between DOAC and VKA were found.

Secondary outcome analysis—major bleeding

Patients with DOAC exhibited significantly fewer major bleeding events when compared to VKA with 3.0% in the DOAC group and 4.9% in the VKA group (RR 0.55, 95% CI: 0.35–19 0.88; $p = 0.01$), as shown in Figure 3. In patients without valve repair (Supplemental material, Figure S3), major bleeding events were 2.5% in the

Table 1. Study designs of included studies.

Trial	Design	Cohort	DOAC	Control	OAC initiation	AVR	MVR	MVre	Follow-up
Dabigatran Versus Warfarin After Bioprosthesis Valve Replacement for the Management of Atrial Fibrillation Postoperatively: DAWA Pilot Study; Durães et al.[18]	Open-label RCT	$n = 27$	Dabigatran 110 mg bid	Warfarin INR 2–3	Time interval of at least 3 at months*	Yes	Yes	No	3 months
Edoxaban for the Prevention of Thromboembolism in Patients with Atrial Fibrillation and Bioprosthetic Valves, ENGAGE AF-TIMI 48, Carnicelli et al.[17]	Double-blinded RCT	$n = 191$	Edoxaban 60/30 mg od	Warfarin INR 2–3	n.a. / different period of time between valve surgery and OAC initiation	Yes	Yes	No	2.8 years
Efficacy and safety of apixaban vs warfarin in patients with atrial fibrillation and prior bioprosthetic valve replacement or valve repair: Insights from the ARISTOTLE trial; Guimarães et al. [19]	Double-blinded RCT	$n = 156$	Apixaban 5/2.5 mg bid	Warfarin INR 2–3	n.a. / different period of time between valve surgery and OAC initiation	Yes	Yes	Yes	1.8 years
Clinical Benefit of Direct Oral Anticoagulants Versus Vitamin K Antagonists in Patients with Atrial Fibrillation and Bioprosthetic Heart Valves; Russo et al.[21]	Retrospective cohort study (propensity score matching)	$n = 260$ after PS	Apixaban 5 mg bid Dabigatran 150 mg bid Edoxaban 60 mg od Rivaroxaban 15/20 mg od	Warfarin, Acenocoumarol INR 2-3	n.a. / different period of time between valve surgery and OAC initiation	Yes	Yes	No	2.2 years
Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve, RIVER trial; Guimaraes et al.[9]	Open-label RCT	$n = 1005$	Rivaroxaban 15/20 mg od	Warfarin INR 2–3	Heterogenous time interval #	No	Yes	No	1 year
Efficacy and safety of edoxaban in patients early after surgical bioprosthetic valve implantation or valve repair: A randomized clinical trial, ENAVLE study; Shim et al.[20]	Open-label RCT	$n = 218$	Edoxaban 60/30 mg od	Warfarin, INR 2-3	Both before discharge	Yes	Yes	Yes	3 months

AVR, aortic valve replacement; bid, bis in die/twice a day; INR, International normalized ratio; MVR, mitral valve replacement; MVre, mitral valve repair; n.a., not available; OAK, oral anticoagulation; od, once daily; RCT, randomized controlled trial.
*'at least 3 months after bioprosthesis replacement and with AF post- operatively';[18] # 'the interval between mitral valve surgery and randomization was less than 3 months for 18.8% of the patients, between 3 months and less than 1 year for 16.8%, between 1 year and less than 5 years for 32.2%, and 5 years or more for 30.6%; data were missing for 1.6% of the patients'[9]

Table 2. Baseline characteristics of patients from included studies.

Study ID	Male	Age, years	AF	HAS-BLED score	CHADS2 score	Prior stroke / TIA	Prior major bleed
Durães et al.[18]	33% / 42%	45 /45 (median)	Postoperatively	0 (0-1) (median)	Not reported	27% / 33%	Not reported
Carnicelli et al.[17]	63% (all)	75 (all, median)	Paroxysmal: 25% (all of ENGAGE AF-TIMI 48)	2.7 ± 1.1 (mean)	3.0 ± 1.0 (mean)	21% (all)	Not reported
Guimarães et al.[19]	61% / 61%	72 / 74 (median)	Paroxysmal: 20% / 19% Non-paroxysmal: 81% / 81%	⩾ 3: 36% / 33%	⩾ 3: 35% / 33%	28% / 17%	29% / 28%
Russo et al.[21]	57% / 55%	66 ± 9 (all, mean)	Non-valvular AF (not reported)	2.3 ± 1.2 / 2.4 ± 1.1 (mean)	3.1 ± 1.1 / 3.2 ± 1.2 (mean)	23% / 25%	5% (all)
Guimaraes et al.[9]	38% / 41%	59 ± 2 / 59 ± 12 (mean)	Paroxysmal: 23% / 22% Permanent: 62% / 61% Persistent: 11% / 12% Flutter 4% / 5%	1.6 ± 0.6 / 1.6 ± 0.9 (mean)	2.7 ± 1.5 / 2.5 ± 1.3 (mean)	15% / 16%	Not reported
Shim et al.[20]	61% / 60%	> 74: 57% / 56%	No classification	> 2: 52% (all)	Not reported	22% / 25%	16% (all)

AF, atrial fibrillation and TIA, transient ischemic attack.

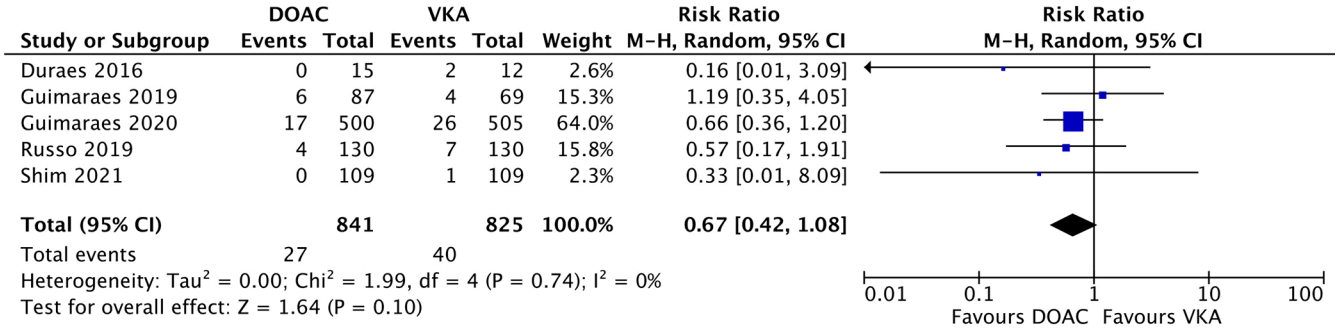

Figure 2. Forest plot with pooled estimates regarding death from cardiovascular cause or thromboembolic events.
CI, confidence interval; DOAC, direct oral anticoagulation; M-H, Mantel–Haenszel; VKA, vitamin K antagonist.

DOAC group *versus* 5.0% in the VKA group (RR 0.43, 95% 2 CI: 0.25–0.77; $p < 0.01$). No statistical heterogeneity was obtained between the reported groups ($I^2 = 0\%$). The cumulative evidence for major bleeding events in the cohort including mitral valve repair reached 79% of the required 2,347 patients. As displayed in the TSA graph, cumulative estimates were robust to determine a premature statistically significant result in accordance with the O'Brien-Fleming analysis (Supplemental material, Figure S5).

Secondary analyses

Thromboembolic stroke or systemic embolism rates were significantly decreased for patients after biological heart valve replacement or mitral valve repair when anticoagulated with a DOAC (2.4%) in comparison with VKA (4.1%) anticoagulation (RR 0.54, 95% CI: 0.32–0.90; $p = 0.02$; $I^2 = 0\%$), please see Figure 4. After biological heart valve replacement without valve repair patients, DOAC also performed better (2.5% *versus* 4.7%) in the prevention of stroke or systemic embolism (RR 0.47, 95% CI: 0.26–0.83; $p < 0.01$; $I^2 = 0\%$), shown in Supplemental material, Figure S6.

Rates for intracranial bleeding in patients after biological heart valve replacement with or without mitral valve repair did not differ significantly between DOCA and VKA, but showed a trend toward fewer events in the DOAC groups

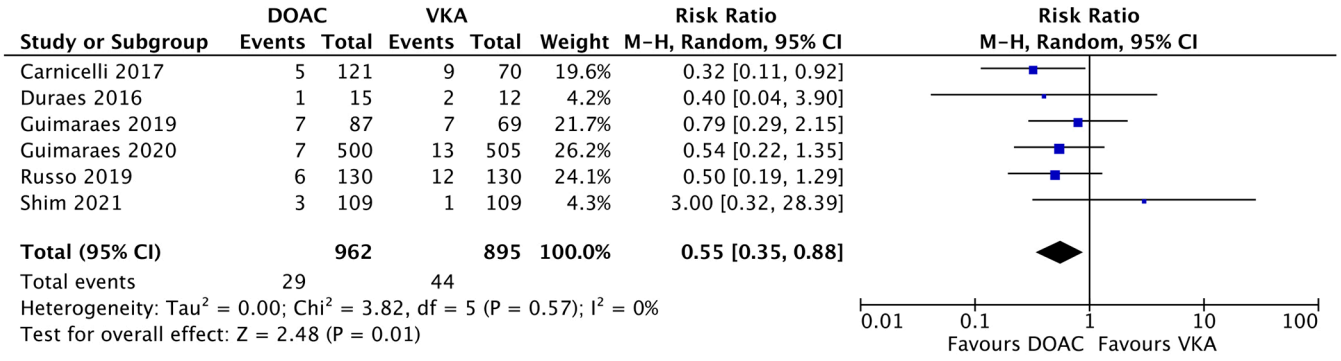

Figure 3. Forest plot with pooled estimates regarding major bleeding. DOAC, direct oral anticoagulation; CI, confidence interval; M-H, Mantel–Haenszel; VKA, Vitamin K antagonist.

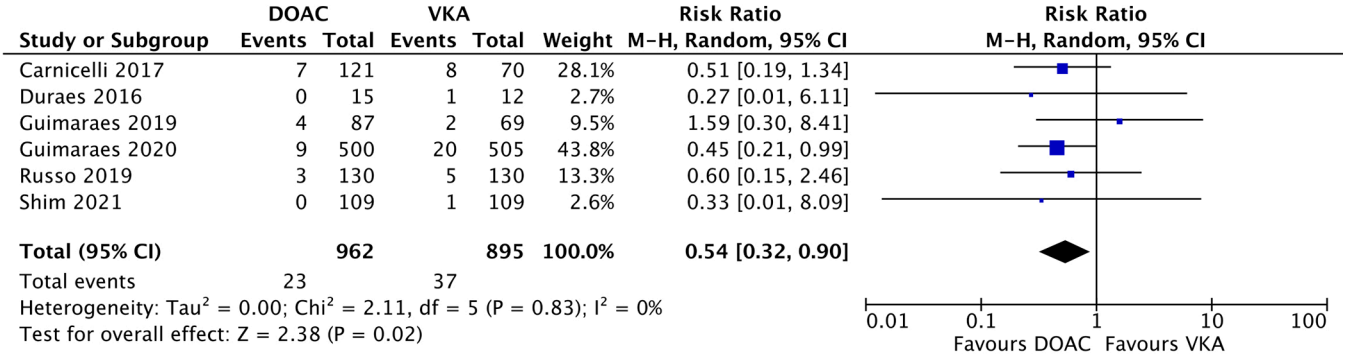

Figure 4. Forest plot with pooled estimates regarding thromboembolic stroke or systemic embolism.
CI, confidence interval; DOAC, direct oral anticoagulation; M-H, Mantel–Haenszel; VKA, vitamin K antagonist.

(Supplemental material, Figures S7 and S8). Of note, the confidence interval for intracranial bleeding was 0.07–0.99, which might be explained by the low event rate of $n = 2$ in the DOAC group. Furthermore, outcomes for any bleeding events, all-cause, and cardiovascular mortality were comparable (Supplemental material, Figure S9–S14).

Pooled analysis of the primary and secondary outcome

The combined analysis of death caused by cardiovascular or thromboembolic events and major bleeding revealed 6.0% in the DOAC group and 7.6% in the VKA group for patients after valve replacement and repair (RR 0.81, 95% CI: 0.52–1.25; $p = 0.34$; $I^2 = 18\%$) and 5.4% *versus* 7.7% without valve repair patients (RR 0.70, 95% CI: 0.29–1.68; $p = 0.42$; $I^2 = 52\%$), as shown in Figure 5 and Supplemental material, Figure S15. Statistical heterogeneity was present in the sub-analysis for patients without mitral valve repair.

Discussion

The main findings of this meta-analysis and systematic review were as follows: (1) DOAC and VKA anticoagulation were comparable with regard to death caused by cardiovascular or thromboembolic events in patients after heart valve surgery and AF. (2) A sub-analysis of thromboembolic stroke or systemic embolism rates showed a significant risk reduction by DOAC in both patient cohorts. (3) The major bleeding risk was significantly reduced by DOAC with a clear trend toward fewer hemorrhagic

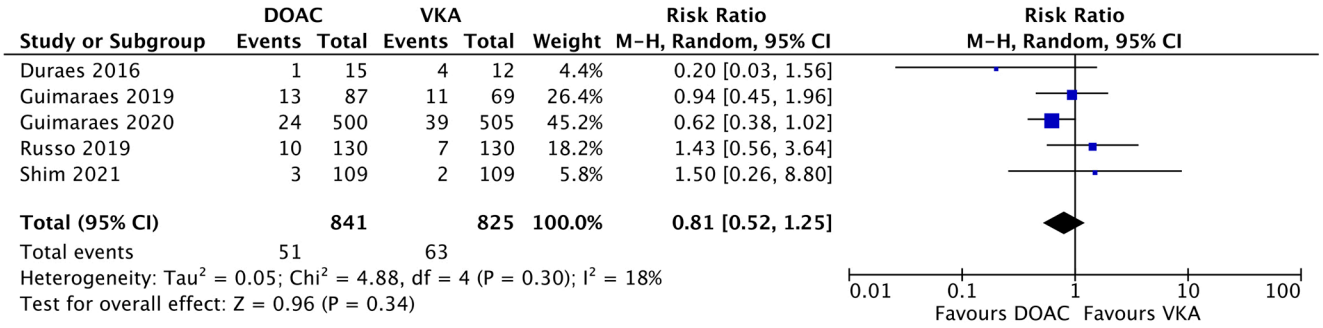

Figure 5. Forest plot with pooled estimates regarding death from cardiovascular cause or thromboembolic events and major bleeding.
CI, confidence interval; DOAC, direct oral anticoagulation; M-H, Mantel–Haenszel; VKA, vitamin K antagonist.

stroke or intracranial bleeding events, as the number of overall bleeding events was unaffected in the relatively small subgroup. (4) All-cause mortality, cardiovascular mortality, and rates for the combination of the primary and secondary outcome analysis did not differ between DOAC and VKA. Overall, the analyzed studies showed no significant heterogeneity except for one case.

Comparison with other reviews

Existing meta-analysis and systematic reviews addressed the use of DOAC in patients with valvular heart disease,[23–25] but only one review conducted a sub-analysis including patients after biological heart valve implantation.[26] Within this meta-analysis, only a very limited number of patients with a biological heart valve prosthesis were analyzed, including only three studies.[17–19]

By contrast, we conducted a comprehensive meta-analysis and systematic review of the literature including patients after heart valve surgery with biological valves and mitral valve repair as they have an indication for oral anticoagulation with respect to recent larger trials.

A large meta-analysis including patients of the initial AF studies with the FXa inhibitors and dabigatran investigating the effect of DOAC in comparison with VKA and valvular heart disease (native heart valve disease and also including patients after valve surgery) failed to show a beneficial effect of DOAC with regard to stroke or systemic embolism; however, lower event rates for major bleeding were reported.[23]

In contrast to this, another meta-analysis and systematic review including both patients with native valvular heart disease and bioprosthetic valve implantation with AF showed a significant risk reduction for both endpoints with stroke or systemic thrombo-embolization and major bleeding.[24]

In line with our findings, Malik *et al.*[26] reported lower rates for stroke or systemic embolism in patients with valvular heart disease as defined above. Due to higher rates of major bleeding events for patients with valvular heart disease in the Rocket-AF trial,[4] DOAC did not perform better than VKA, also leading to a high heterogeneity in this analysis.[26] The sub-analysis for patients with bioprosthetic heart valves and AF showed no differences between DOAC and VKA with respect to clinical outcomes with stroke or systemic embolism and major bleeding, which might be biased by a low power of the analysis and limited number of patients included.[26]

No other meta-analysis comparing DOAC with VKA in patients after heart valve surgery with bioprosthetic heart valves and prior mitral valve repair with AF was identified.

Comparison with studies not included

Early findings concerning the use of DOAC reporting on the efficacy and safety in patients with biological heart valves or prior valve repair showed a low incidence for thromboembolism and major bleeding,[21] and an increasing trend for the off-label use of DOAC in this patient population was detected.[27] The use of the factor Xa

inhibitor rivaroxaban in patients after mitral valve repair showed no cerebrovascular events or major bleeding in a one-year follow-up study. Clinically relevant non-major bleeding events were comparable to VKA. With regard to a low incidence of AF between 14% and 17% and focusing on mitral valve repair, this study would have biased the present meta-analyses but points toward the potential use of DOAC after valve surgery.[28] Two studies investigating the use of DOAC after surgical valve replacement with biological prostheses irrespective of atrial fibrillation, with AF rates between 35% and 39%[29] and between 45% and 65%,[30] reported on comparable thromboembolism rates to VKA of 2.4%[30] and 3.8%.[29] Findings for major bleeding events differed with 0%[29] and 7.1%,[30] but both did not reach statistically significant differences in comparison with VKA. Concomitant antiplatelet therapy was administered in $>90\%$ both studies.[29,30] The subgroup analysis of a study comparing the factor Xa inhibitors rivaroxaban, apixaban, and VKA in patients with valvular heart disease which included 389 patients with bioprosthetic heart valve showed no significant difference for all-cause mortality, stroke or systemic embolism and major bleeding. For major bleeding, the authors showed a trend toward a risk reduction in the FXa inhibitor group as the sub-analysis may have been underpowered.[31] A recent retrospective study with a total of 2,672 patients included examined the effect of DOAC compared to VKA in patients with AF and bioprosthetic heart valves with respect to thromboembolic events and bleeding complications. The composite of ischemic stroke, systemic embolism, and transient ischemic attack did not differ between DOAC and VKA, but patients' risk for the safety outcome presented by intracranial hemorrhage, gastrointestinal bleed, and other bleeding was significantly reduced by DOAC. All-cause mortality was comparable between the groups.[32] Detailed outcome data with absolute numbers of events were not available on request to the authors, which led to an exclusion of the discussed articles.[31,32]

Clinical implications

The findings of this meta-analysis and outcomes reported by the discussed literature encourage the further investigation of DOAC in patients after (1) biological heart valve replacement or repair and AF as an alternative anticoagulation to VKA and (2) should also be considered as temporary anticoagulation for patients undergoing either mitral valve replacement or repair. Importantly, it is unclear whether anticoagulation with DOAC is also efficacious and safe in the early postoperative course and in long-term use. Furthermore, reduced dosages of DOAC in relation to, for example, impaired renal function need to be investigated carefully and a strict monitoring of these patients is mandatory. The comparison of normal a dosed DOAC and reduced anticoagulation therapy has been evaluated by Steffel *et al.* in 'Randomized, Double-Blind Comparison of Half-Dose Versus Full-Dose Edoxaban in 14,014 Patients with Atrial Fibrillation' from the ENGAGE AF-TIMI 48 trial. The reduced dose of edoxaban led to fewer bleeding events, including life-threatening bleeding and hemorrhagic stroke, but showed a higher incidence of thromboembolic events with stroke and systemic embolism,[33] if these findings from the AF collective can be transferred to patients with a biological heart valve or valve repair remains unclear and needs to be assessed systematically.

Strengths and limitations of the study

The results are limited by the method of our study as a meta-analysis and in association with the individually included studies. Furthermore, different study types had to be included due to a lack of data in the literature on account of the newness of the discussed topic. The ENAVLE study by Shim, C.Y. *et al* did not have AF as a defined inclusion criterion and, therefore, differs in comparison with the other included studies. The authors decided to include this particular study because of the high rate of AF of 60-62% (paroxysmal AF in 24-25% and persistent AF of 35-38%) in the study groups. Even if the inclusion criteria of the mentioned study did not comment AF, the selected study population reflects the typical patient undergoing a biological heart valve replacement and, therefore, adds important information to the discussion. Different DOAC (direct thrombin inhibitor and direct FXa inhibitors) and dosages (reduced dosages in patients with renal impairment) were pooled together assuming a class effect, which has to be examined further with regard to both the efficacy in preventing thromboembolic events and the safety aspect regarding bleeds. In addition, the included studies showed very heterogenous time frames of OAC initiation after surgery or did not report on the time of OAC initiation, which plays a crucial clinical role. Due

to a heterogeneity in the definition of bleeding events in the included study, a clear categorization of reported bleeding events is not possible. Accordingly, to this point this study shows methodological heterogeneity and the efficacy and safety of separate DOAC need to be assessed further to determine class differentiations as these disparities cannot be ruled out with respect to the recent level of research. Different surgical techniques including biological aortic and mitral valve replacement as well as mitral valve repair were included as they all have an indication for anticoagulation and DOACs may provide an alternative to VKA. Nevertheless, a sub-analysis without mitral valve repair patients was also conducted. Besides, this meta-analysis is the largest to report on the use of DOAC in patients after heart valve surgery and AF and TSA were performed to determine the robustness of reported results and diminish heterogeneity. Importantly, there is still hidden heterogeneity due to a lack of prospective clinical trials addressing this topic and further research is fundamental.

Conclusion

In patients with bioprosthetic heart valves and AF, DOAC were statistically comparable with regard to outcome rates for death caused by cardiovascular or thromboembolic events, but showed a risk reduction of 33% and 40% if valve repair patients were excluded. The major bleeding risk was reduced significantly in both groups when compared to VKA as well as rates for thromboembolic stroke or systemic embolism. There were no risk increases in patients receiving DOAC after heart valve surgery and AF as also displayed by the pooled efficacy and safety analysis for death from cardiovascular cause or thromboembolic events and major bleeding, resulting in a statistically irrelevant risk reduction of 19% (30%) in the DOAC group.

Key messages

What is already known? Direct oral anticoagulation (DOAC) is already proven safe and efficacious with a widespread use in patients with atrial fibrillation (AF).

What does this study add? This systematic review of literature and meta-analysis is the first to exclusively investigate the use of DOAC in patients with AF and heart valve surgery (biological heart valve replacement and/or valve repair). DOAC show a significant risk reduction of major bleedings and thromboembolic stroke or systemic embolisms in comparison with vitamin k antagonists (VKA).

How might this impact on clinical practice? Positive findings support the further investigation of DOAC in patients after heart valve surgery and AF. DOAC might be an alternative to VKA anticoagulation in this patient population.

Author contributions

Stephen Gerfer: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing–original draft; Writing–review & editing.

Ilija Djordjevic: Investigation.

Kaveh Eghbalzadeh: Data curation.

Navid Mader: Formal analysis; Methodology.

Thorsten Wahlers: Supervision.

Elmar Kuhn: Conceptualization; Data curation; Formal analysis; Investigation; Supervision; Writing – original draft.

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Conflict of interest statement

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Supplemental material

Supplemental material for this article is available online.

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