Direct oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation and bioprosthetic valves: A meta-analysis

Yujiro Yokoyama, MD,[a] Alexandros Briasoulis, MD, PhD,[b] Hiroki Ueyama, MD,[c] Makoto Mori, MD,[d] Masao Iwagami, MD, MPH, PhD,[e] Naoki Misumida, MD,[f] Hisato Takagi, MD, PhD,[g] and Toshiki Kuno, MD, PhD[h]

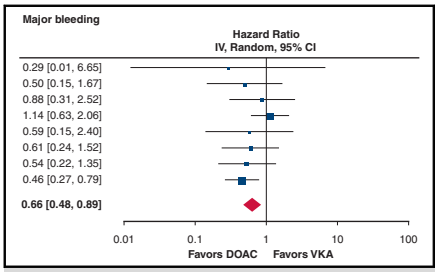
ABSTRACT

Background: The optimal anticoagulation strategy for patients with bioprosthetic valves and atrial fibrillation remains uncertain. We conducted a meta-analysis using updated evidence comparing direct anticoagulants (DOACs) and vitamin K antagonists (VKAs) in patients with bioprosthetic valves and atrial fibrillation.

Methods: Medline and Embase were searched through March 2021 to identify randomized controlled trials (RCTs) and observational studies investigating the outcomes of DOAC therapy and VKA therapy in patients with bioprosthetic valves and atrial fibrillation. The outcomes of interest were all-cause death, major bleeding, and stroke or systemic embolism.

Results: Our analysis included 4 RCTs and 6 observational studies enrolling a total of 6405 patients with bioprosthetic valves and atrial fibrillation assigned to a DOAC group (n = 2142) or a VKA group (n = 4263). Pooled analysis demonstrated the similar rates of all-cause death (hazard ratio [HR], 0.90; 95% confidence interval [CI], 0.77-1.05; $P = .18$; $I^2 = 0\%$) in the DOAC and VKA groups. However, the rate of major bleeding was significantly lower in the DOAC group (HR, 0.66; 95% CI, 0.48-0.89; $P = .006$; $I^2 = 0\%$), whereas the rate of stroke or systemic embolism was similar in the 2 groups (HR, 0.72; 95% CI, 0.44-1.17; $P = .18$; $I^2 = 39\%$).

Conclusions: DOAC might decrease the risk of major bleeding without increasing the risk of stroke or systemic embolism or all-cause death compared with VKA in patients with bioprosthetic valves and atrial fibrillation. (J Thorac Cardiovasc Surg 2023;165:2052-9)



DOAC was associated with lower risk of bleeding compared with VKA in patients with bioprosthetic valves and atrial fibrillation.

CENTRAL MESSAGE

Direct oral anticoagulant therapy was associated with lower risk of bleeding without increasing the risk of ischemic events compared with vitamin K antagonists in patients with bioprosthetic valves and atrial fibrillation.

PERSPECTIVE

Our analysis of 4 randomized controlled trials and 5 observational studies showed an association between direct oral anticoagulant therapy and lower rates of major bleeding without increasing the risk of stroke or systemic embolism or all-cause death compared to vitamin K antagonists in patients with bioprosthetic valves and atrial fibrillation.

See Commentaries on pages 2060 and 2061.

From the [a]Department of Surgery, St. Luke's University Health Network, Bethlehem, Pa; [b]Division of Cardiovascular Diseases, University of Iowa Hospitals and Clinics, Iowa City, Iowa; [c]Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, New York, NY; [d]Division of Cardiac Surgery, Yale School of Medicine, New Haven, Conn; [e]Department of Health Services Research, University of Tsukuba, Tsukuba, Japan; [f]Division of Cardiovascular Medicine, Gill Heart and Vascular Institute, University of Kentucky, Lexington, Ky; [g]Department of Cardiovascular Surgery, Shizuoka Medical Center, Shizuoka, Japan; and [h]Department of Cardiology, Montefiore Medical Center, Albert Einstein Medical College, New York, NY.

Received for publication April 12, 2021; revisions received July 15, 2021; accepted for publication July 16, 2021; available ahead of print July 29, 2021.

Address for reprints: Toshiki Kuno, MD, PhD, Department of Cardiology, Montefiore Medical Center, Albert Einstein Medical College, 111 East 210th St, Bronx, NY 10467–2401 (E-mail: tkuno@montefiore.org).

0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2021.07.034

Abbreviations and Acronyms

CI = confidence interval
DOAC = direct anticoagulant
HR = hazard ratio
INR = international normalized ratio
RCT = randomized controlled trial
VKA = vitamin K antagonist

Scanning this QR code will take you to the table of contents to access supplementary information.

Patients with bioprosthetic valve and atrial fibrillation require anticoagulation to prevent thromboembolic events, although the most effective therapeutic strategy is still uncertain. Direct oral anticoagulants (DOACs) are safe and efficacious alternatives to vitamin K antagonists (VKAs) for anticoagulation in patients with atrial fibrillation.[1] However, the guidelines recommend against using DOACs in patients with bioprosthetic valves, although supporting evidence is lacking.[2] A recent randomized controlled trial (RCT) showed noninferiority of rivaroxaban compared with VKAs at 12 months in patients with bioprosthetic mitral valves and atrial fibrillation.[3] Similarly, a recent meta-analysis of 4 RCTs showed similar rates of ischemic events, bleeding, and all-cause deaths with DOAC therapy and VKA therapy in patients with bioprosthetic valve and atrial fibrillation[4]; however, among the 4 RCTs, 2 trials were post hoc studies, and 1 trial was terminated prematurely because of low enrollment, and thus the update study is still warranted. We conducted a meta-analysis using updated evidence comparing DOAC therapy and VKA therapy in patients with bioprosthetic valves and atrial fibrillation.

METHODS

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement standards (Online Data Supplement).[5] Given the nature of our study, Institutional Review Board approval and informed written consent for publication were not required. A review protocol does not exist for this analysis.

Eligibility Criteria

Included studies met the following criteria: the study design was an RCT or an observational study, the study population comprised patients with atrial fibrillation and bioprosthetic valves, enrolled patients were assigned to a DOAC group and a VKA group, and outcomes included either all-cause mortality, major bleeding, or systemic embolism or stroke.

Information Sources and Search

All RCTs and observational studies that investigated the outcomes of DOAC therapy and VKA therapy in patients with bioprosthetic valves and atrial fibrillation were identified using a 2-level strategy. First, the Medline and Embase databases were searched through March 31, 2021, using Web-based search engines (PubMed and OVID). Search terms included "bioprosthesis or bioprosthetic or transcatheter aortic valve," "DOAC or NOAC or oral anticoagulants or edoxaban or apixaban or rivaroxaban or dabigatran," and "atrial fibrillation." We did not apply any language limitations.

Study Selection and Data Collection Process

Relevant studies were identified through a manual search of secondary sources, including references of initially identified articles, reviews, and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analyses. Two independent and blinded authors (Y.Y. and T.K.) conducted a literature search and reviewed the search results separately to select the studies based on our inclusion and exclusion criteria. Disagreements were resolved by consensus.

Data Items

We sought data according to the PICOS framework as follows: P (population), patients with atrial fibrillation and biprosthesis; I (intervention), DOAC; C (comparison), VKA; O (outcome), all-cause mortality, major bleeding, and systemic embolism or stroke; and S (study type), RCTs and observational studies.

Risk of Bias in Individual Studies

Study quality was assessed independently by 2 blinded authors (Y.Y. and T.K.) using the Cochrane Collaboration risk of bias 2.0 tool for RCTs[6] and the Newcastle–Ottawa Scale for observational studies.[7] Disagreements were resolved by consensus.

Summary Measures

The primary outcome of interest was all-cause mortality, and the secondary efficacy outcome was systemic embolism or stroke. The primary safety outcome was major bleeding. We accepted the criterion of major bleeding from each study. Systemic embolism or stroke was defined as ischemic stroke, systemic embolism, and/or transient ischemic attack. Hazard ratios (HRs) of each outcome were extracted from each trial.

Synthesis of Results

RevMan version 5.3 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to combine HRs in a random-effects model. A P value of <.05 was considered statistically significant.

Risk of Bias Across Studies and Additional Analyses

ProMeta 3 (https://idostatistics.com/prometa3/) was used to perform sensitivity analyses and examine funnel plot asymmetry. Funnel plot asymmetry suggesting publication bias was assessed mathematically using Egger's linear regression test.[8] Significant heterogeneity was considered to be present when the I^2 index was >50% or P for heterogeneity was <.05. Sensitivity analyses were performed by limiting patients with surgical bioprostheses.

RESULTS

Study Selection

Our analysis included 4 RCTs[3,9-11] and 6 observational studies[12-17] that enrolled a total of 6405 patients with bioprosthetic valves and atrial fibrillation assigned to the DOAC group (n = 2142) or the VKA group (n = 4263) (Figure 1).

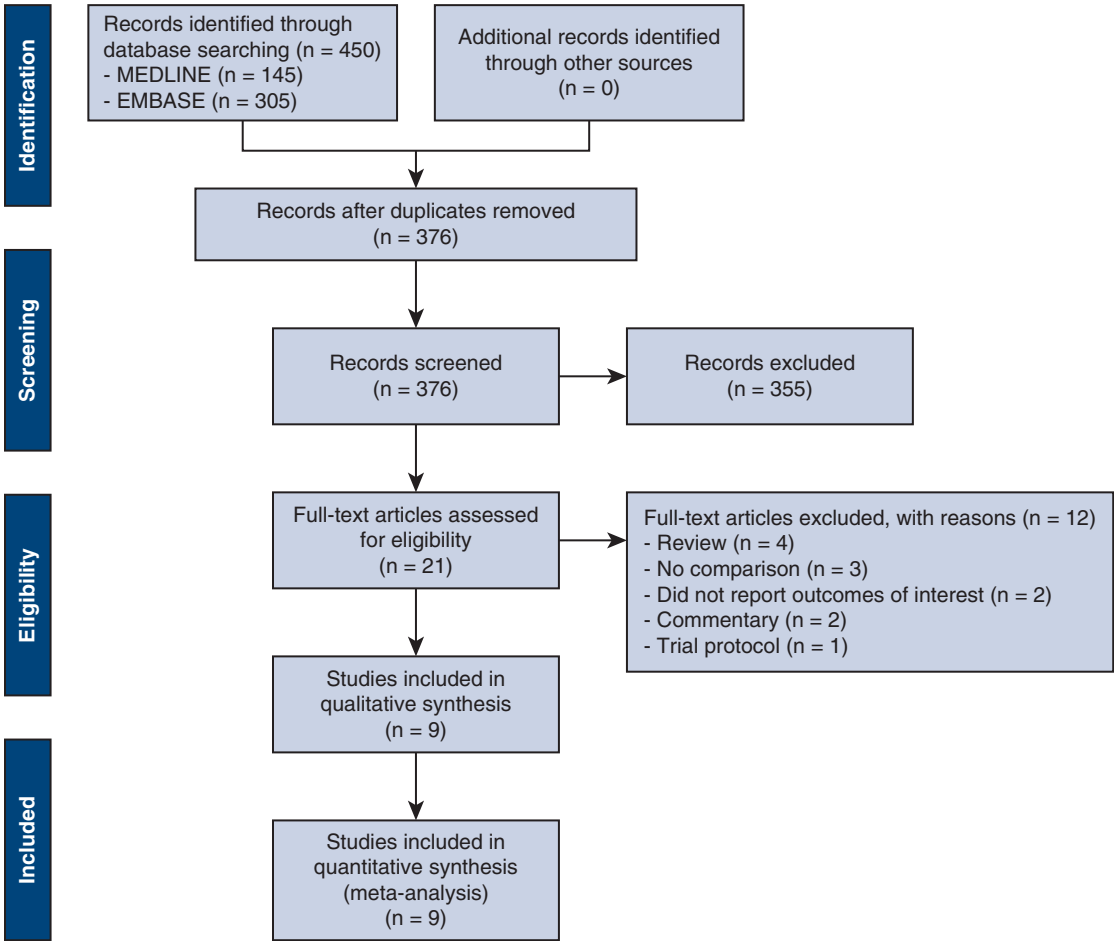


FIGURE 1. Workflow for selecting eligible articles according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria in search of original studies for this meta-analysis.

Study Characteristics

Among the observational studies, propensity-score matching was used in 2,[14,17] inverse probability of treatment weighting was used in 2,[15,16] Cox regression model was used in 1,[13] and the 1 was a prospective study without adjustment.[12] Study profiles and patient characteristics are summarized in Tables 1 and 2. In all the RCTs, the VKA dose was adjusted to maintain a target international normalized ratio (INR) of 2.0 to 3.0. In the RCTs, the DOAC regimens included 110 mg of dabigatran twice daily,[9] 60 mg of edoxaban daily,[10] 5 mg of apixaban twice daily,[11] or 20 mg of rivaroxaban daily.[3] Among the observational studies, apixaban was used in 1 study[12]; dabigatran, rivaroxaban, apixaban, and edoxaban were used in 2 studies[13,17]; and dabigatran, rivaroxaban, and apixaban were used in 2 studies.[14,16] The DOAC regimen was not described in 1 observational study.[15] The approaches to bioprosthesis implantation included 1 surgical aortic valve replacement,[16] 1 surgical mitral valve replacement,[3] 5 surgical aortic and/or mitral valve replacements,[6-8,11] 3 transcatheter aortic valve replacements,[12,13,15] and 1 surgical or transcatheter aortic and/or mitral valve replacement.[10]

Risk of Bias Within Studies

The quality of RCTs and observational trials is summarized in Figure E1 and Table E1. The definitions of major bleeding and systemic embolism or stroke in the various studies are shown in Table E2.

Results of Individual Studies and Synthesis of Results

Pooled analysis demonstrated the similar rates of all-cause death (HR, 0.90; 95% CI, 0.77-1.05; $P = .18$; $I^2 = 0\%$) between the DOAC and VKA groups (Figure 2). However, the rates of major bleeding were significantly lower in the DOAC group (HR, 0.66; 95% CI, 0.48-0.89; $P = .006$; $I^2 = 0\%$) (Figure 3), whereas the rates of stroke or systemic embolism were similar in the 2 groups (HR, 0.72; 95% CI, 0.44-1.17; $P = .18$; $I^2 = 39\%$) (Figure 4). All the outcomes were consistent between the RCTs and the observational studies (P for

TABLE 1. Study profiles

Study	Year	Period	Follow-up	Design	Adjustment	Approach	DOAC regimen
Durães et al[9]; DAWA	2016	2013-2014	90 d	RCT	N/A	TAVR/SMVR	Dabigatran 110 mg twice daily
Carnicelli et al[10]; ENGAGE AF-TIMI 48	2017	2008-2010	2.8 y	RCT	N/A	SAVR (n = 60), SMVR (n = 131)	Edoxaban 60 mg daily
Seeger et al[12]	2017	2013-2014	1 y	Cohort	N/A	TAVR	Epixaban
Guimarães et al[11]; ARISTOTLE	2019	2006-2010	1.6 y	RCT	N/A	SAVR (n = 73), SMVR (n = 26), DVR (n = 5)	Apixaban 5 mg twice daily
Butt et al[13]	2021	2012-2017	1.9 y	Cohort	Cox	TAVR	Dabigatran, rivaroxaban, or apixaban
Russo et al[14]	2019	2013-2018	2.2 y	Cohort	PSM	AVR (n = 128), MVR (n = 132)	Dabigatran, rivaroxaban, apixaban, or edoxaban
Kawashima et al[15]	2020	2013-2017	N/A	Cohort	IPTW	TAVR	N/A
Guimarães et al[3]; RIVER	2020	2016-2019	1 y	RCT	N/A	SMVR	Rivaroxaban 20 mg daily
Duan et al[16]	2021	2011-2020	2.9 y	Cohort	IPTW	SAVR (n = 1724), SMVR (n = 943)	Dabigatran, apixaban, or rivaroxaban
Mannacio et al[17]	2021	2013-2019	3.2 y	Cohort	PSM	SAVR	Dabigatran, rivaroxaban, apixaban, or edoxaban

DOAC, Direct oral anticoagulant; *RCT*, randomized controlled trial; *N/A*, not available; *TAVR*, transcatheter aortic valve replacement; *SMVR*, surgical mitral valve replacement; *SAVR*, surgical aortic valve replacement; *DVR*, dual valve replacement; *PSM*, propensity score matched; *AVR*, aortic valve replacement; *MVR*, mitral valve replacement; *IPTW*, Inverse probability of treatment weighting.

interaction = .77, I^2 = 0 for all-cause deaths; *P* for interaction = .78, I^2 = 0 for major bleeding; and *P* for interaction = .36, I^2 = 0 for stroke).

Additional Analysis

The sensitivity analysis after limiting patients with surgical bioprosthesis showed the similar rates of all-cause death (HR, 0.87; 95% CI, 0.74-1.05; *P* = .15; I^2 = 0%) and stroke or systemic embolism (HR, 0.63; 95% CI, 0.36-1.12; *P* = .12; I^2 = 39%) between the DOAC and VKA groups (Figures E2 and E3), whereas the rates of major bleeding were significantly lower in the DOAC group (HR, 0.53; 95% CI, 0.35-0.79; *P* = .002; I^2 = 0%) (Figure E4).

Risk of Bias Across Studies

Publication bias was assessed using funnel plots (Figure E5), which showed no evidence of publication bias.

DISCUSSION

Our analysis demonstrates the lower rates of major bleeding in the DOAC group compared with the VKA group in patients with bioprosthetic valves and atrial fibrillation

TABLE 2. Patient characteristics

Patient	DOAC	VKA	Age, y	Female sex, %	DM, %	HTN, %	MI, %	Stroke, %	CHF, %	CKD, %	CHA2DS2-VASc score	HAS-BLED score	Antiplatelet, %
27	15	12	47	63	4	48	N/A	30	N/A	N/A	N/A	0	N/A
133	63	70	75	37	N/A	N/A	N/A	76	N/A	N/A	3	2.7	34
156	87	69	73	39	23	85	16	22	35	5	N/A	N/A	32
735	219	516	82	46	21	88	N/A	20	47	10	5	3.3	82
260	130	130	66	44	21	33	7	24	16	N/A	3.1	1.2	7
503	227	276	84	67	24	76	6	14	N/A	76	5.1	2.7	69
1005	500	505	59	60	14	61	5	13	39	2	2.6	1.6	9
2672	439	2233	N/A	N/A	N/A	53	21	13	75	78	N/A	N/A	32
642	321	321	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0

DOAC, Direct oral anticoagulant; *VKA*, vitamin K antagonist; *DM*, diabetes mellitus; *HTN*, hypertension; *MI*, myocardial infarction; *CHF*, congestive heart failure; *CKD*, chronic kidney disease; *N/A*, not available.

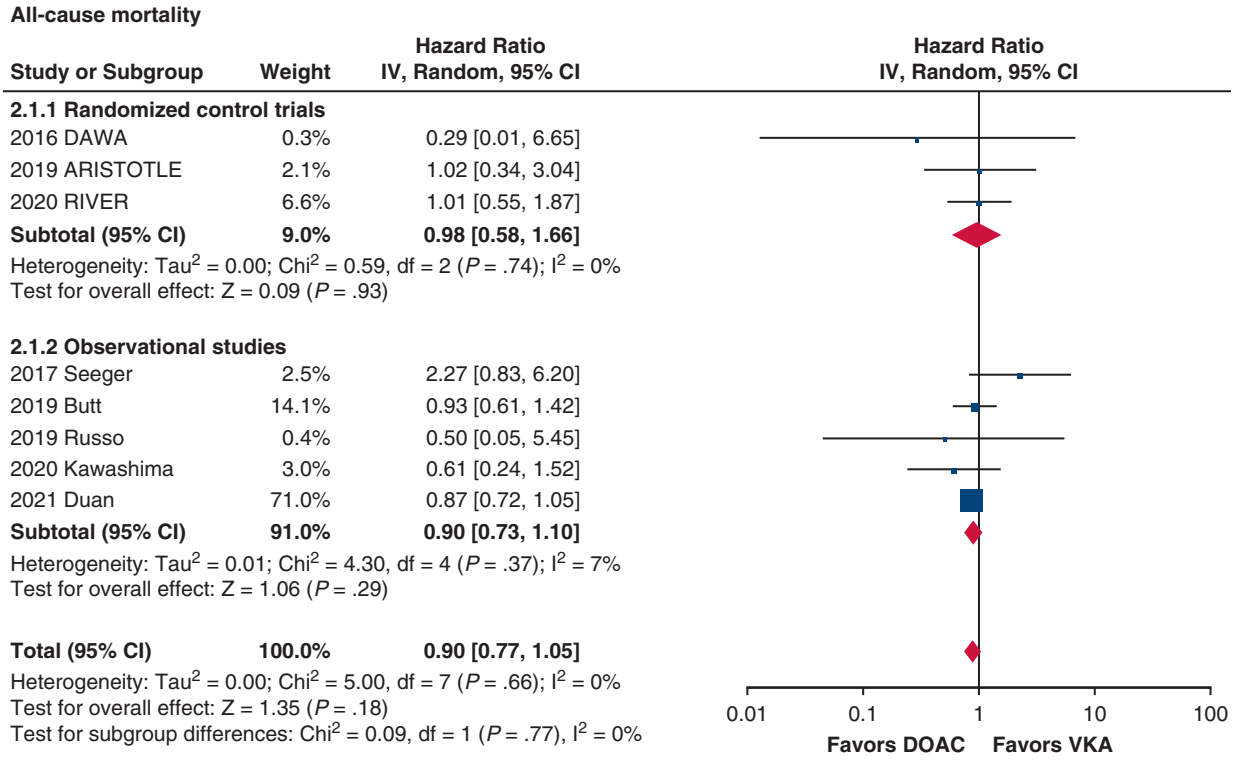


FIGURE 2. Comparison of all-cause deaths for direct oral anticoagulant (*DOAC*) and vitamin K antagonist (VKA) therapy in patients with a bioprosthetic valve and atrial fibrillation using a random-effects model. (Left) Studies analyzed with their corresponding hazard ratios (HRs) and 95% confidence intervals (*CIs*). (Right) Forest plot of the data. The *horizontal lines* represent the values within the 95% CI of the underlying effects. The *vertical line* indicates an HR of 1. *IV,* Inverse variance.

(Figure 5). The rates of all-cause death and stroke or systemic embolism were similar in the 2 groups.

Anticoagulation strategies for patients with bioprosthetic valves and atrial fibrillation are complicated, because bioprosthetic valves and atrial fibrillation cause thromboembolic complications via different mechanisms.[18] Antithrombic strategies for patients with bioprosthetic valves have been evolving. Data from the Danish National Patient Registry show higher rate of stroke, thromboembolic events, and cardiovascular deaths in the early postsurgical period after bioprosthetic aortic valve replacement in patients not treated with VKAs compared with those treated with VKAs[19]; however, given the very low risk of thromboembolism in bioprosthetic valve recipients without another indication for anticoagulation, guidelines recommend aspirin monotherapy or 3 to 6 months of VKA after bioprosthetic valve implantation.[2,20] This recommendation applies to both mitral and aortic valve replacement,[2] although anticoagulation therapy is more frequently used in recipients of mitral valve replacement compared with recipients of aortic valve replacement.[21] Among patients without a bioprosthetic valve who have atrial fibrillation, the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial showed that rivaroxaban was noninferior to VKA for the prevention of stroke or systemic embolism.[1]

Among patients with bioprosthetic valves and atrial fibrillation, the efficacy and safety of DOAC therapy were assessed in subgroup analyses of large-scale RCTs.[10,11] The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial showed no significant differences between apixaban and warfarin for major bleeding or stroke/systemic embolism for patients with bioprosthetic valves and atrial fibrillation; however, only 156 of the 18,201 patients had bioprosthetic valves in the original trial.[11] Similarly, the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) trial demonstrated that treatment with low-dose edoxaban had a similar rate of stroke/systemic embolism but a lower rate of major bleeding compared with VKA therapy in patients with bioprosthetic valves and atrial fibrillation, although only 133 of 21,105 patients had bioprosthetic valves in this trial.[10] The recent RIVER (Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation) trial including 1005 patients with bioprosthetic mitral valves and atrial fibrillation demonstrated the

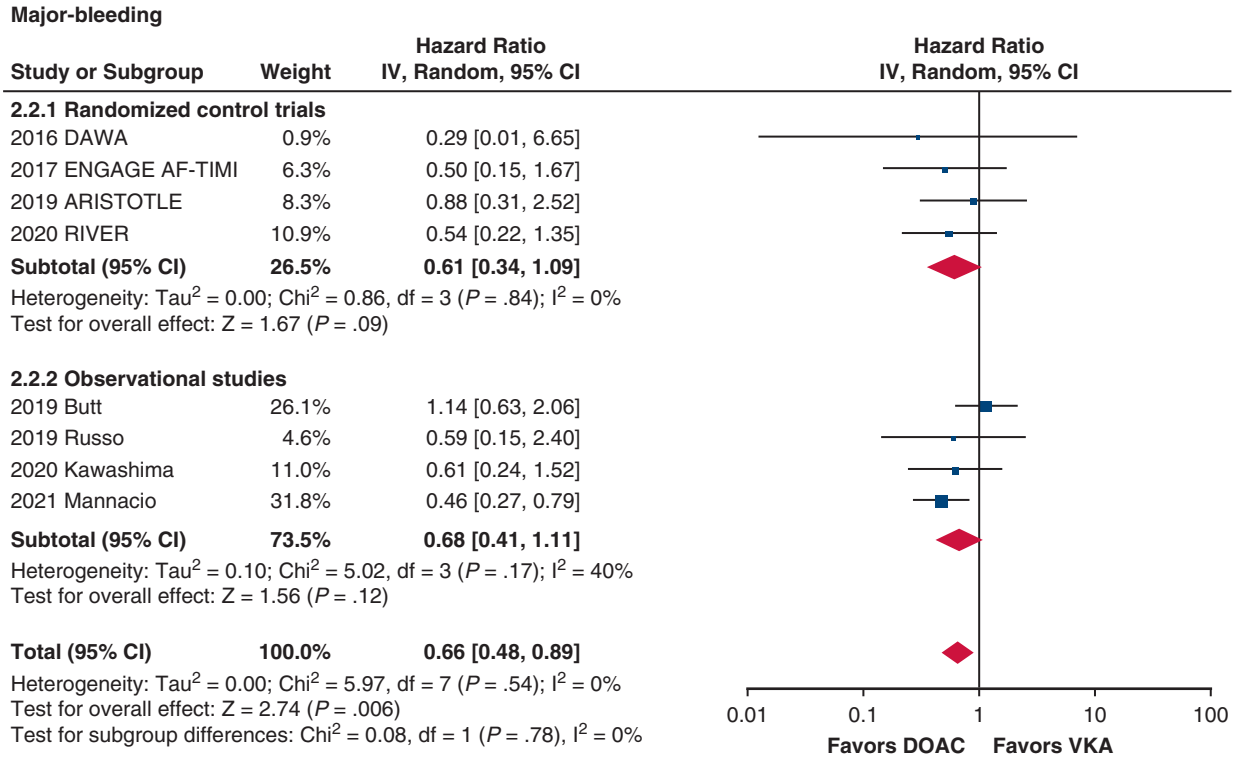


FIGURE 3. Comparison of major bleeding for direct oral anticoagulant (*DOAC*) and vitamin K antagonist (*VKA*) therapy in patients with a bioprosthetic valve and atrial fibrillation using a random-effects model. (Left) Studies analyzed with their corresponding hazard ratio (HRs) and 95% confidence intervals (*CIs*). (Right) Forest plot of the data. The *horizontal lines* represent the values within the 95% CI of the underlying effects. The *vertical line* indicates an HR of 1. *IV*, Inverse variance.

noninferiority of rivaroxaban compared with VKA in terms of death, cardiovascular events, and major bleeding at 12 months.[3] Furthermore, it showed a 46% reduction in major bleeding (HR, 0.54; 95% CI, 0.21-1.35), although this did not reach statistical significance.

A recent meta-analysis of 4 RCTs did not show significant differences in outcomes between DOAC and VKA[4]; however, 2 of the RCTs were post hoc analyses and 1 RCT was terminated prematurely, which might have been underpowered. In the present meta-analysis, we included observational studies, and the results showed a significant decrease in major bleeding with DOAC therapy compared with VKA therapy without a significant interaction among the HRs from RCTs and observational studies in the outcomes of major bleeding (P for interaction = .78; $I^2 = 0$).

The higher bleeding rates with VKA therapy might be related to the target INR in our analysis (2.0-3.0), given that a lower INR (2.0-2.5) might be associated with less bleeding compared with a higher INR (>2.5) in patients with nonvalvular atrial fibrillation,[22] and the same theory might apply to patients with bioprosthetic valves. Our results suggest that DOAC has a more favorable safety outcome compared with VKA while maintaining similar efficacy in preventing valve thrombosis and intracardiac thrombus in the setting of atrial fibrillation. Furthermore, because DOACs do not require monitoring of INR and are less influenced by food or concomitant medication than VKAs, DOAC therapy is an attractive alternative for many patients with a bioprosthetic valve and atrial fibrillation, suggesting guideline adjustments.[2,20] Further large-scale RCTs comparing DOAC and VKA therapy are warranted in those patients, especially with an INR of 2 to 2.5, which could provide a balance between efficacy and safety.

This study has several limitations. First, we included 4 different regimens in the DOAC group and did not assess the efficacy and safety of each DOAC regimen. Second, we included patients with both aortic and mitral bioprosthetic valves, including those with transcatheter aortic valve replacement, although optimal strategies might differ for these patients. However, the sensitivity analysis limiting patients with surgical bioprostheses showed similar results. Third, our analysis included 5 observational studies and 2 trials that were subgroup analyses of RCTs, in which the compared subgroups were not randomized[7,8] and thus is subject to selection bias and confounders from these study designs. However, 5 of the 6 observational studies were determined to have a low risk of bias. Furthermore, patients

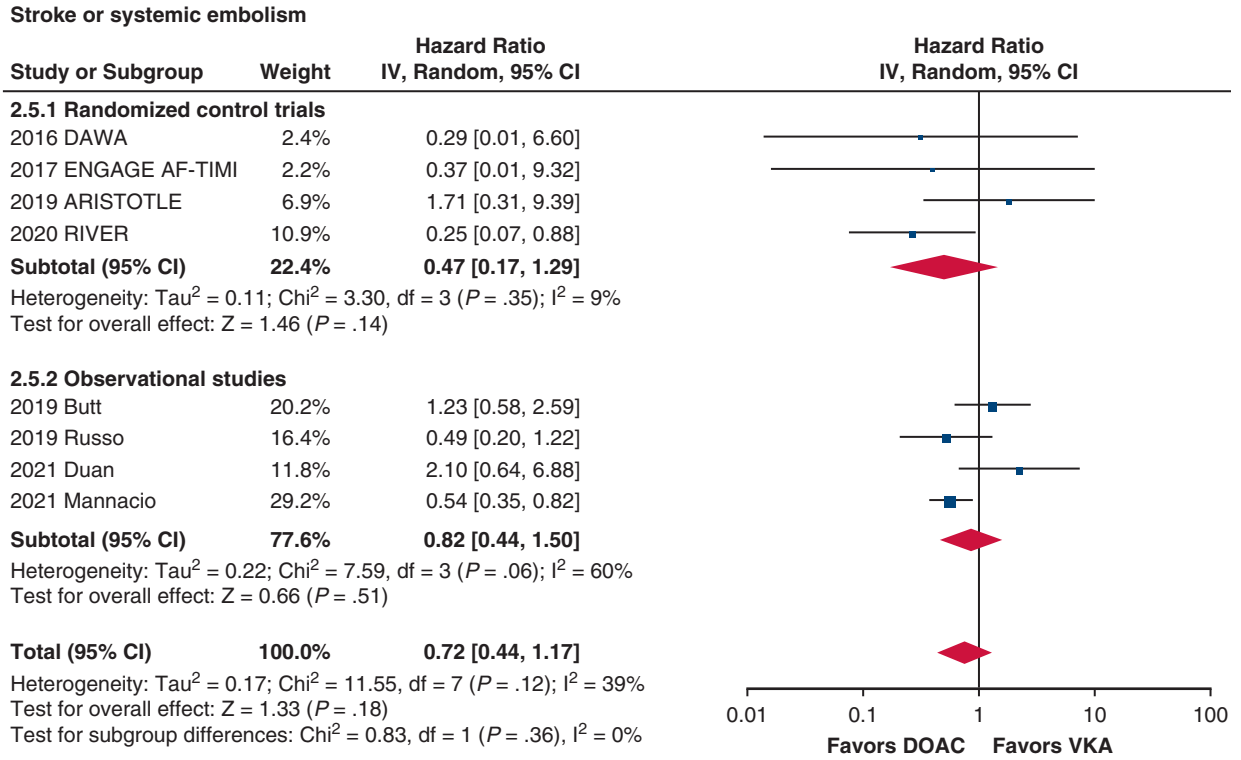


FIGURE 4. Comparisons of stroke or systemic embolism for direct oral anticoagulant (*DOAC*) and vitamin K antagonist (*VKA*) therapy in patients with a bioprosthetic valve and atrial fibrillation using a random-effects model. (Left) Studies analyzed with their corresponding hazard ratio (HRs) and 95% confidence intervals (*CI*s). (Right) Forest plot of the data. The *horizontal lines* represent the values within the 95% CI of the underlying effects. The *vertical line* indicates an HR of 1. *IV*, Inverse variance.

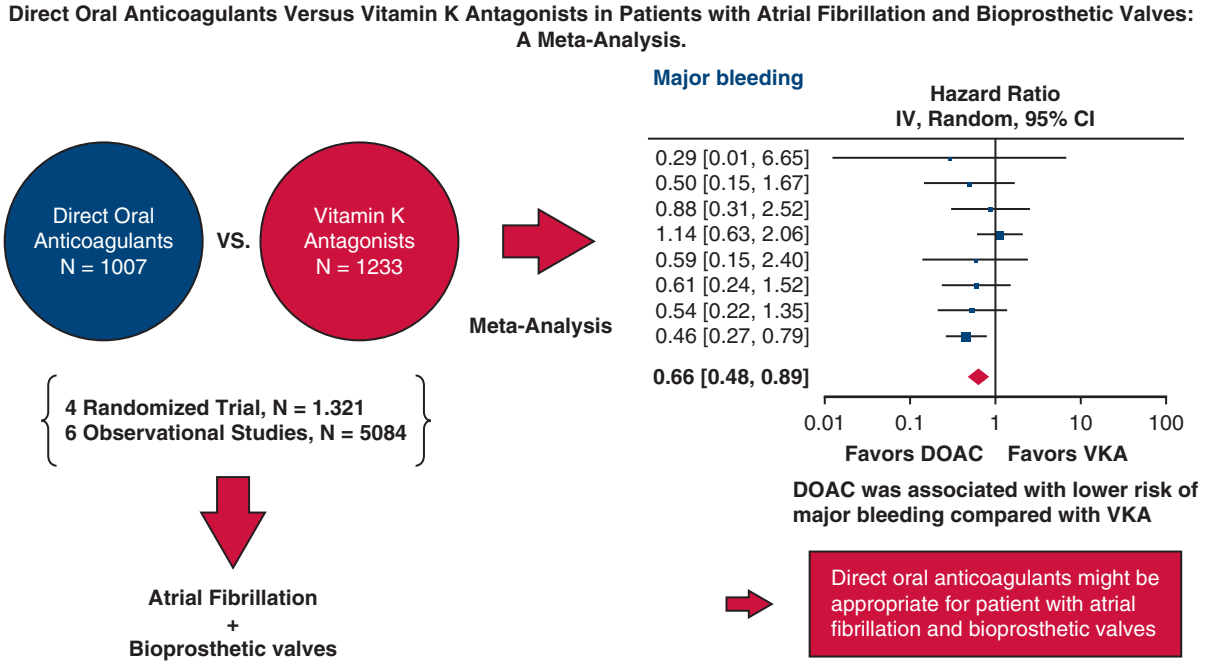


FIGURE 5. A meta-analysis of 4 randomized control trials and 6 observational studies comparing direct oral anticoagulants (*DOACs*) versus vitamin K antagonists (*VKAs*) for patients with atrial fibrillation and a bioprosthetic valve showing lower major bleeding with DOACs compared to VKAs. *IV*, Inverse variance; *CI*, confidence interval.

with recent (≤3 months) valve replacement were excluded in the 2 RCTs[10,11] and 1 observational study.[17] Considering that perioperative thromboembolic risk is time-dependent after bioprosthetic valve replacement,[23] the underlying thromboembolic risk in these studies might have differed from that in the other studies. Finally, the follow-up periods in the included studies were relatively short, and future trials with long-term follow-up are warranted.

CONCLUSIONS

Our findings indicate that DOAC therapy might decrease the risk of major bleeding without increasing the risk of stroke or systemic embolism or all-cause death compared with VKA in patients with bioprosthetic valves and atrial fibrillation.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

References

1. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883-91.
2. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP III, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Thorac Cardiovasc Surg*. 2021;162:e183-353.
3. Guimarães HP, Lopes RD, de Barros E Silva PGM, Liporace IL, Sampaio RO, Tarasoutchi F, et al. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. *N Engl J Med*. 2020;383:2117-26.
4. Kheiri B, Przybylowicz R, Simpson TF, Alhamoud H, Osman M, Dalouk K, et al. Meta-analysis of direct oral anticoagulants in patients with atrial fibrillation and bioprosthetic valves. *Am J Cardiol*. 2021;142:140-1.
5. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6:e1000100.
6. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
7. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital Research Institute. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed January 28, 2021.
8. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-34.
9. Durães AR, de Souza Roriz P, de Almeida Nunes B, Albuquerque FP, Vieira de Bulhões F, de Souza Fernandes AM, et al. Dabigatran versus warfarin after bioprosthesis valve replacement for the management of atrial fibrillation postoperatively: DAWA pilot study. *Drugs R D*. 2016;16:149-54.
10. Carnicelli AP, De Caterina R, Halperin JL, Renda G, Ruff CT, Trevisan M, et al. Edoxaban for the prevention of thromboembolism in patients with atrial fibrillation and bioprosthetic valves. *Circulation*. 2017;135:1273-5.
11. Guimarães PO, Pokorney SD, Lopes RD, Wojdyla DM, Gersh BJ, Giczewska A, et al. 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. *Clin Cardiol*. 2019;42:568-71.
12. Seeger J, Gonska B, Rodewald C, Rottbauer W, Wöhrle J. Apixaban in patients with atrial fibrillation after transfemoral aortic valve replacement. *JACC Cardiovasc Interv*. 2017;10:66-74.
13. Butt JH, De Backer O, Olesen JB, Gerds TA, Havers-Borgersen E, Gislason GH, et al. Vitamin K antagonists vs. direct oral anticoagulants after transcatheter aortic valve implantation in atrial fibrillation. *Eur Heart J Cardiovasc Pharmacother*. 2021;7:11-9.
14. Russo V, Carbone A, Attena E, Rago A, Mazzone C, Proietti R, et al. Clinical benefit of direct oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation and bioprosthetic heart valves. *Clin Ther*. 2019;41:2549-57.
15. Kawashima H, Watanabe Y, Hioki H, Kozuma K, Kataoka A, Nakashima M, et al. Direct oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation after TAVR. *JACC Cardiovasc Interv*. 2020;13:2587-97.
16. Duan L, Doctor JN, Adams JL, Romley JA, Nguyen LA, An J, et al. Comparison of direct oral anticoagulants versus warfarin in patients with atrial fibrillation and bioprosthetic heart valves. *Am J Cardiol*. 2021;146:22-8.
17. Mannacio VA, Mannacio L, Antignano A, Mauro C, Mastroroberto P, Musumeci F, et al. New oral anticoagulants versus warfarin in atrial fibrillation after early post-operative period in patients with bioprosthetic aortic valve. *Ann Thorac Surg*. March 17, 2021 [Epub ahead of print].
18. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369:1206-14.
19. Mérie C, Køber L, Skov Olsen P, Andersson C, Gislason G, Skov Jensen J, et al. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. *JAMA*. 2012;308:2118-25.
20. Mori M, Gan G, Bin Mahmood SU, Deng Y, Mullan CW, Assi R, et al. Variations in anticoagulation practice following bioprosthetic aortic and mitral valve replacement and repair. *J Am Coll Cardiol*. 2020;76:2412-3.
21. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739-91.
22. Odén A, Fahlén M, Hart RG. Optimal INR for prevention of stroke and death in atrial fibrillation: a critical appraisal. *Thromb Res*. 2006;117:493-9.
23. Russo A, Grigioni F, Avierinos JF, Freeman WK, Suri R, Michelena H, et al. Thromboembolic complications after surgical correction of mitral regurgitation incidence, predictors, and clinical implications. *J Am Coll Cardiol*. 2008;51:1203-11.

Key Words: bioprosthetic valve, atrial fibrillation, vitamin K antagonist, direct oral anticoagulant

ADULT

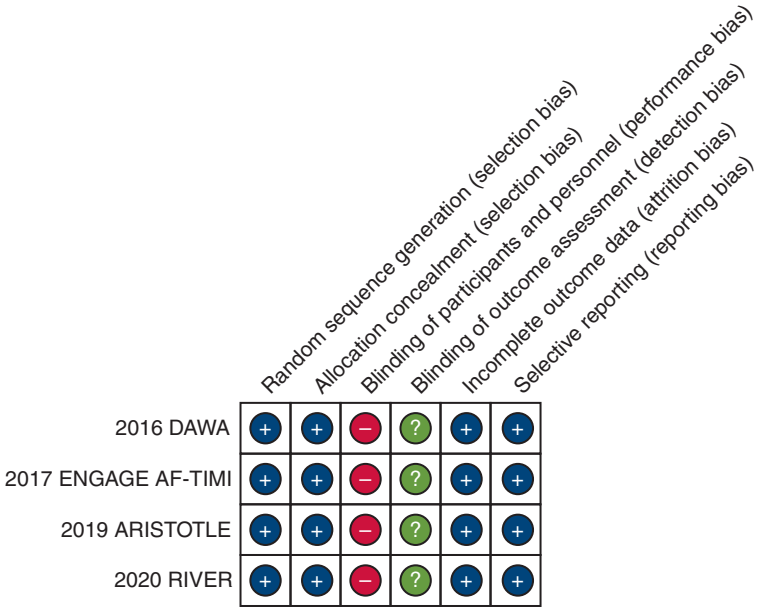


FIGURE E1. Risk of bias summary according to the Cochrane Collaboration Manual. *Green* indicates unclear risk; *blue*, low risk.

All-cause mortality for surgical bioprosthesis

Study or Subgroup	log [Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
2.7.1 Randomized control trials				
2016 DAWA	–1.2321	1.595	0.3%	0.29 [0.01, 6.65]
2019 ARISTOTLE	0.0169	0.5582	2.6%	1.02 [0.34, 3.04]
2020 RIVER	0.01	0.3143	8.2%	1.01 [0.55, 1.87]
Subtotal (95% CI)			**11.1%**	**0.98 [0.58, 1.66]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.59$, df = 2 ($P = .74$); $I^2 = 0\%$				
Test for overall effect: Z = 0.09 ($P = .93$)				
2.7.2 Observational studies				
2019 Russo	–0.6931	1.2185	0.5%	0.50 [0.05, 5.45]
2021 Duan	–0.1393	0.0959	88.3%	0.87 [0.72, 1.05]
Subtotal (95% CI)			**88.9%**	**0.87 [0.72, 1.05]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.21$, df = 1 ($P = .65$); $I^2 = 0\%$				
Test for overall effect: Z = 1.49 ($P = .14$)				
Total (95% CI)			**100.0%**	**0.88 [0.74, 1.05]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.97$, df = 4 ($P = .91$); $I^2 = 0\%$				
Test for overall effect: Z = 1.44 ($P = .15$)				
Test for subgroup differences: $Chi^2 = 0.17$, df = 1 ($P = .68$), $I^2 = 0\%$				

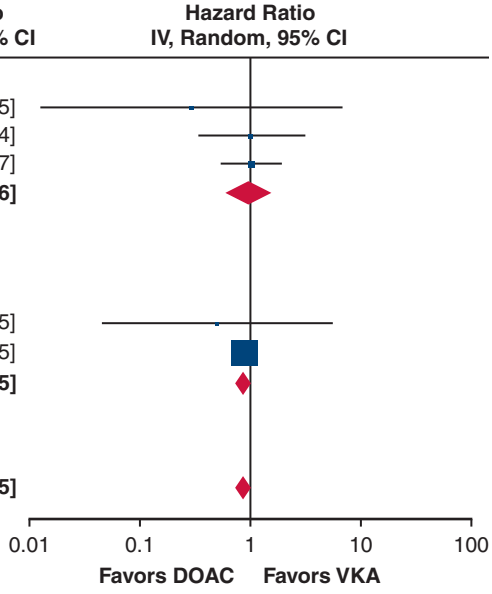


FIGURE E2. Comparison of all-cause deaths with direct oral anticoagulant (*DOAC*) and vitamin K antagonist (*VKA*) therapy in patients with a surgical bioprosthetic valve and atrial fibrillation using a random-effects model. (Left) Studies analyzed with their corresponding hazard ratios (HRs) and 95% confidence intervals (*CIs*). (Right) Forest plot of the data. The *horizontal lines* represent the values within the 95% CI of the underlying effects. The *vertical line* indicates an HR of 1. *SE*, Standard error; *IV*, inverse variance.

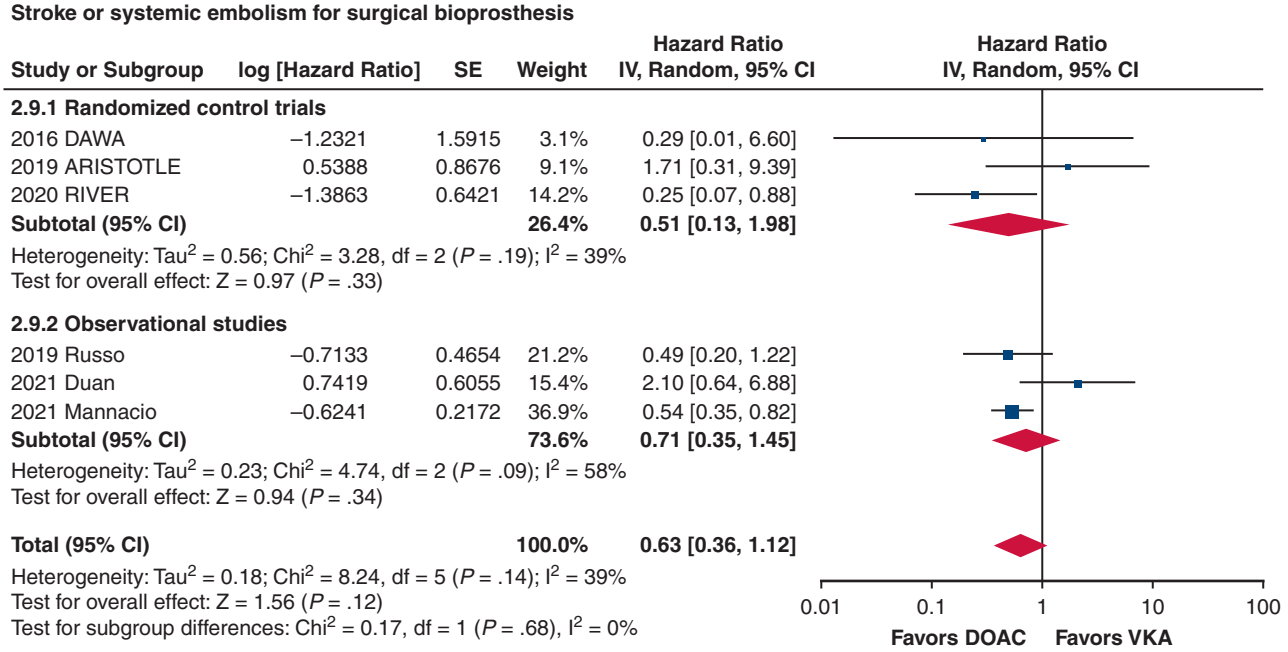


FIGURE E3. Comparisons of stroke or systemic embolism with direct oral anticoagulant (*DOAC*) and vitamin K antagonist (*VKA*) therapy in patients with a surgical bioprosthetic valve and atrial fibrillation using a random-effects model. (Left) Studies analyzed with their corresponding hazard ratios (HRs) and 95% confidence intervals (*CIs*). (Right) Forest plot of the data. The *horizontal lines* represent the values within the 95% CI of the underlying effects. The *vertical line* indicates an HR of 1. *SE*, Standard error; *IV*, inverse variance.

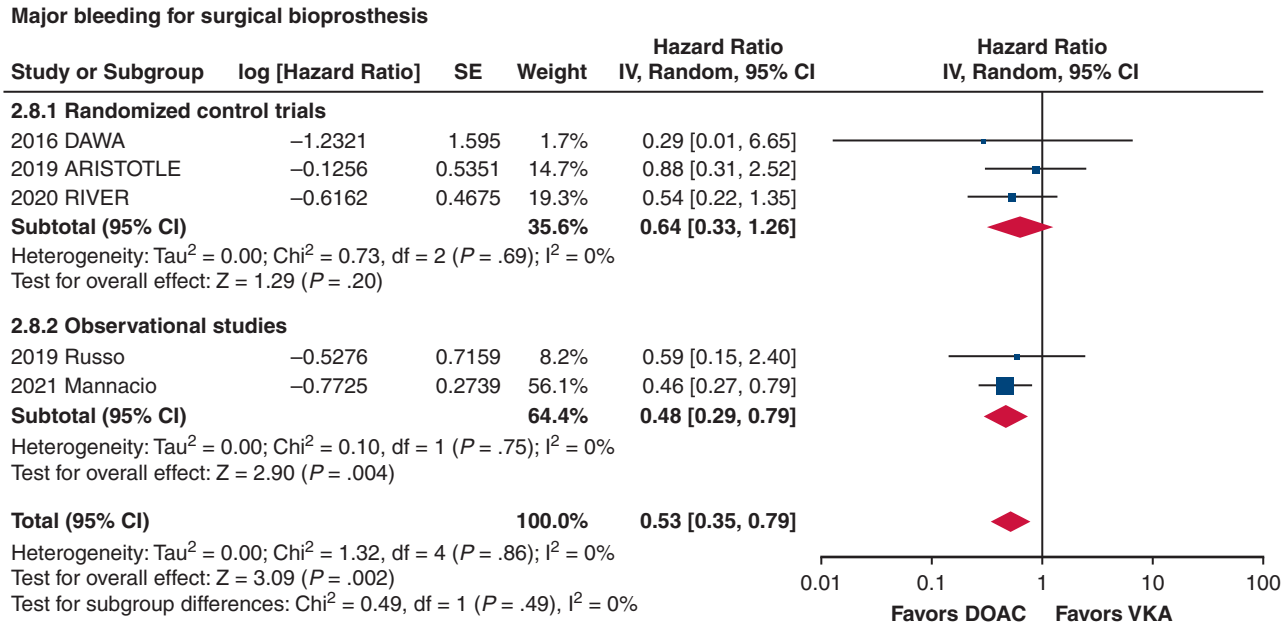


FIGURE E4. Comparisons of major bleeding with direct oral anticoagulant (*DOAC*) and vitamin K antagonist (*VKA*) therapy in patients with a surgical bioprosthetic valve and atrial fibrillation using a random-effects model. (Left) Studies analyzed with their corresponding hazard ratios (HRs) and 95% confidence intervals (*CIs*). (Right) Forest plot of the data. The *horizontal lines* represent the values within the 95% CI of the underlying effects. The *vertical line* indicates an HR of 1. *SE*, Standard error; *IV*, inverse variance.

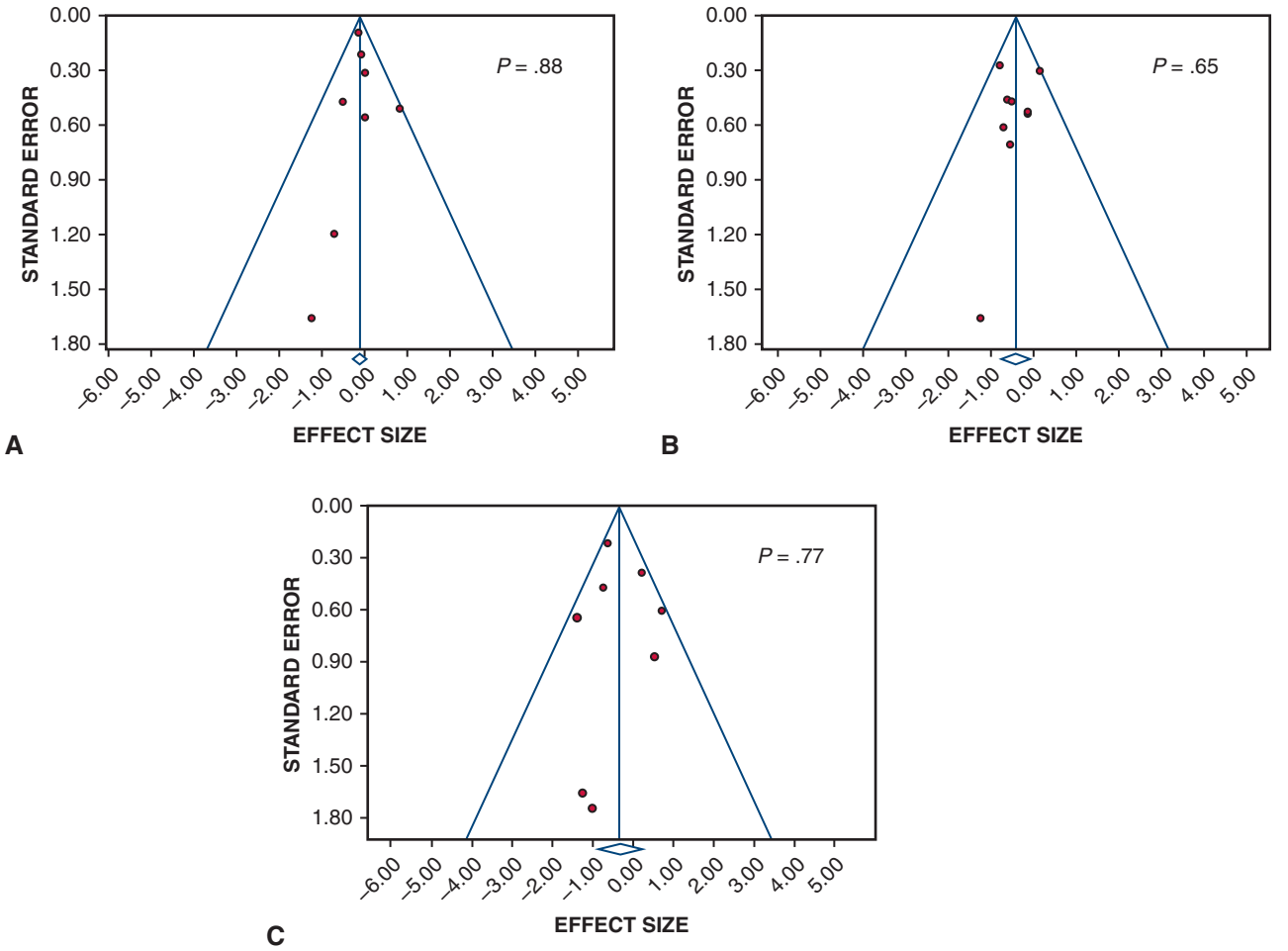


FIGURE E5. Funnel plot for each outcome for all-cause deaths (A), major bleeding (B), and stroke or systemic embolism (C).

TABLE E1. Quality assessment based on the Newcastle–Ottawa Scale (range, 1-9)

Study	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Absence of outcome at start of study	Comparability of cohorts	Outcome assessment	Length of follow-up	Adequacy of follow-up	NOS score
Seeger et al[12]	1	1	1	1	0	1	1	1	7
Butt et al[13]	1	1	1	1	2	1	1	1	9
Russo et al[14]	1	1	1	1	2	1	1	1	9
Kawashima et al[15]	1	1	1	1	2	1	1	0	8
Duan et al[16]	1	1	1	1	2	1	1	1	9
Mannacio et al[17]	1	1	1	1	2	1	1	1	9

An NOS score ≥8 is considered low risk; 6-7, moderate risk; and ≤5, high risk. *NOS*, Newcastle–Ottawa Scale.

TABLE E2. Definitions of major bleeding and systemic thromboembolism or stroke in each study

Study	Major bleeding	Stroke or systemic embolism
Durães et al[9]; DAWA	N/A	Stroke or systemic embolism
Carnicelli et al[10]; ENGAGE AF-TIMI 48	International Society for Thrombosis and Haemostasis definition	Stroke or systemic embolism
Seeger et al[12]	N/A	N/A
Guimarães et al[11]; ARISTOTLE	International Society for Thrombosis and Haemostasis definition	Stroke or systemic embolism
Butt et al[13]	Bleeding leading to a hospital admission	Stroke, TIA, or systemic embolism
Russo et al[14]	Fatal bleeding or symptomatic bleeding in a critical area or organ, or bleeding causing a decrease in hemoglobin level of 2 g/dL or leading to transfusion of ≥2 units of whole blood or red blood cells	Stroke, TIA, or systemic embolism
Kawashima et al[15]	Valve Academic Research Consortium: 2 criteria	N/A
Guimarães et al[3]; RIVER	Bleeding Academic Research Consortium	N/A
Duan et al[16]	N/A	Stroke, TIA, or systemic embolism
Mannacio et al[17]	Intracranial, major intestinal, or urinary bleeding	Stroke, TIA, or systemic embolism

N/A, Not available; *TIA*, transient ischemic attack.