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Warfarin versus Direct Oral Anticoagulants in Patients with Artificial Heart Valves-A Systematic Review & Meta-Analysis

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Abstract

Background and Purpose: Anti-thrombotic efficacy of Direct Oral Anticoagulants (DOAC) after Mechanical (MHV) and Tissue (THV) valve replacement is unclear.

Methods: We systematically reviewed English language publications (randomized trials and observational studies; Inception- May 2022) that compared the clinical outcome of adults (>18 years) that received Warfarin or DOAC an anti-thrombotic therapy after MHV or THV replacement for bleeding and stroke.

Results: Eight studies (n=183167, 38% female; mean study duration 37.5 months) met inclusion criteria. Mechanical and tissue (bioprosthetic) heart valves (MHV and THV) were represented in 14.7% and 85.3% of patients respectively. Overall, warfarin led to 22% more major bleeding (OR=1.22, 95% CI= [1.05, 1.41], p=0.01) and 72% more ischemic stroke (OR=1.72, 95% CI= [1.1, 2.68], p=0.02) compared to DOACs. Bleeding, all-cause mortality, TIA, systemic embolism, and stroke rates were comparable between study groups. Among patients with THV, warfarin led to 33% more major bleeding than DOACs (OR=1.33, 95% CI= [1.06, 1.66]); however, among MHV patients, strokes rates were much higher in the DOAC treated cohort.

Conclusion: Overall, in patients with AHV, warfarin led to more major bleeding and ischemic stroke than DOACs; the overall risks were similar in all bleeding, all-cause mortality, systemic embolism, TIA, and all-strokes. DOACs reduced the risk of ischemic stroke and major bleeding in patients with BPHV, but not MHV. DOAC risk for all-stroke and major bleeding was higher than warfarin in MHV patients.

Keywords: DOAC; Warfarin; Artificial heart valves; Mechanical; Tissue; Meta-analysis

Key Messages

What is already known on this topic: While Direct Oral Anticoagulants (DOACs) use in patients with atrial fibrillation is well established their benefit as antithrombotic therapy after valve replacement is uncertain.

What this study adds: We observed that data is limited to small studies with few event rates that limit interpretability. However, summary evidence suggests that DOAC are associated with higher adverse events after mechanical valve replacement but may be acceptable after tissue valve replacement.

How might this study affect research, practice or policy: This study clearly demonstrates that DOAC therapy is not the recommended antithrombotic regime post-mechanical valve replacement? Limited pooled summary data suggests that bleeding and stroke rates may be lower with DOAC compared to warfarin post-tissue valves. However, this possible benefit should be evaluated in future larger trials.

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Introduction

The American Heart Association recommends life-long use of oral vitamin K antagonists as anti-thrombotic therapy in patients undergoing Mechanical Valve Replacement (MHV) [1]. In the past decades, both surgeons and patients seem to prefer THV over MHV. The recent rapid expansion of trans-catheter valve options has made using THV even more attractive as they provide the opportunity for future non-surgical valve-in-valve procedures [2,3]. While oral warfarin therapy is clearly required to avoid thrombotic events with mechanical valves, its need after THV is less clear. In fact, a nationwide study from the US reported that only 87% tissue valve recipients were on warfarin patients [4]. In fact, a study reports increasing off-label use of DOAC as anti-thrombotic therapy after THV [5]. Plausible reasons for this trend may be that unlike warfarin, DOAC therapy is a fixed dose regime, has less drug and food interactions, and does not need repeated blood tests [6].

Prior meta-analyses that studied patients with non-valvular atrial fibrillation and acute venous thrombo-embolism have clearly demonstrated lower stroke and bleeding rates with DOAC when compared to warfarin [7,8]. At present dabigatran, rivaroxaban, apixaban, and edoxaban are all approved for treatment in venous thrombo-embolism and stroke prophylaxis in Non-Valvular Atrial Fibrillation (NVAF) [9].

The question of DOAC use in patients with atrial fibrillation and Artificial Heart Valves (AHV) is uncertain in clinical practice. The American College of Chest Physicians and American College of Cardiology/American Heart Association guidelines recommend VKAs as the preferred agent for patients with mechanical heart valves [9].

There is paucity of evidence in current literature on the benefits and harms of DOACs in mechanical heart valves. The RE-ALIGN trial ended early, as mechanical heart valve patients in the dabigatran group experienced excess bleeding and thromboembolic events [10]. With bioprosthetic heart valves, use of DOACs has been more acceptable, though it is still a relatively non-standard clinical practice. For example, the ENAVLE trial investigated the efficacy of edoxaban in patients soon after bioprosthetic valve implantation or valve repair [11]. It found edoxaban noninferior to warfarin in preventing thromboembolism and statistically non-significant inferiority of edoxaban in major bleeding. Another study in patients with bioprosthetic valves also found DOACs effective for thromboembolic events, at the expense of increased bleeding [12]. The results of the RIVER trial showed low and similar numbers of major bleeding between warfarin and rivaroxaban in patients with bioprosthetic heart valves [13]. The number of major bleeding incidents was lower for the rivaroxaban group. Given the limited evidence supporting the use of DOACs in mechanical and bioprosthetic heart valves, the aim of this study was to investigate the difference in efficacy and risks of DOACs and warfarin in patients with AHV.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to design, conduct and report this systematic review [14].

Study design

Search Strategy and Inclusion Criteria: A medical librarian (DA) conducted a systematic search of databases (Inception through May 2022) using concepts such as "mechanical heart valve", "bioprosthetic heart valve", "bleed", "novel anticoagulant" and "apixaban or dabigatran or rivaroxaban" to identify peer-reviewed original research studies that compared the clinical outcome (details provided later) of adult patients (>18 years) receiving DOAC or warfarin as anti-thrombotic prophylaxis after Mechanical (MHV) or Tissue (THV) replacement (Supplementary Appendix). We included studies irrespective of valve design or manufacturer. We included both randomized trials and observational studies, but excluded editorial, letters to the editor and other articles that did not present original research. For inclusion in our review, studies had to provide data on both agents. We included studies irrespective of follow-up duration and carefully reviewed included studies to ensure non-duplication of patient data. We primarily used PubMed, CINHAL, and Clinicaltrials.gov as our search engines and supplemented this strategy with a manual review of the citation information of included studies. We provide the full search strategy for PubMed is provided in the supplementary appendix.

Exclusion Criteria: We excluded studies that included patient's post-valve repair or did not compare warfarin with DOACs. We also excluded studies that did not report clinical endpoints, namely at least one of the 7 outcome measures chosen (ischemic stroke, all-stroke, TIA, systemic embolism, major bleeding, all-cause mortality, all bleeding).

Two authors (YS, US) independently reviewed titles, abstracts, and finally full-text articles to decide which studies were to be selected for systematic review and meta-analysis. We resolved disagreements/conflicts regarding study inclusion by consensus of all co-authors; the kappa statistic was 0.9.

Data abstraction & Study Quality: We used pre-specified columns to collect data from all studies. We used the 5-item Jadad scale (score 5 indicates high-quality study; 0 indicates low-quality study) and the Newcastle-Ottawa scale (higher score out of 9 indicates high-quality) to evaluate study quality for randomized trials and observational studies respectively [15-17].

Statistical analysis

We combined individual study results using the Odds Ratio (OR) as the summary estimate. We used a random effects model and the Mantel Hanzel weighting method to obtain the pooled estimate. We tested for statistical significance at the 95% confidence level and graphically presented results as forest plots. We analyzed data such that if the pooled OR was greater than 1, then the result favored DOAC therapy. We quantified residual heterogeneity between studies using the I^2 statistic and considered an $I^2 \geq 75\%$ as significant [18]. We carefully analyzed differences between study groups as a possible source of heterogeneity and performed meta-regression to provide potential explanations.

We pre-specified the following subgroup analyses: (i) based on valve type (mechanical and tissue heart valves, (ii) based on study type (RCT and Retrospective Cohort Study), and (iii) based on follow-up duration (short-term: less than 1 year, long-term: 1 year or longer).

Exclusion sensitivity analysis (Leave-one-out technique) was performed to analyze the contribution of each study to the overall result. Exclusion sensitivity plots were generated to illustrate the odds ratios for the variables and each study exclusion. We used R 4.2.2 (packages: Meta, metafor, ckbplotr, forestplot) and Mix 2.0 Pro (Biostat XL) for analyses and graphs.

Table 1: Overview of studies included in our review.

Author	Type	Year	Country	Mean Age	Sex (%Female)	Valve	Type of DOAC (%)	N warfarin	N DOAC	Pre-op AF/ Flutter #	Approximate Outcome Assessment
Eikelboom et al. [10]	RCT	2013	Multinational	56	35	Mechanical	Dabigatran (100)	84	168	72	12 weeks
Guimaraes et al. [13]	RCT	2020	Brazil	59	60	Bioprosthetic	Rivaroxaban (100)	505	500	1005	12 months
Duraes et al. [23]	RCT	2020	Brazil	44	61	Mechanical	Rivaroxaban (100)	21	23	12	90 days
Pasciolla et al. [24]	Retro Cohort	2020	United States	73	44	Bioprosthetic	Dabigatran (1) Apixaban (68) Rivaroxaban (31)	70	127	102	6 months
Duan et al. [25]	Retro Cohort	2021	United States	N/A	39	Bioprosthetic	Dabigatran (82) Apixaban (14) Rivaroxaban (4)	2233	439	2672	12 months
Piepiorka-Broniecka et al. [26]	RCT	2022	Poland	67	46	Bioprosthetic	Apixaban (100)	25	25	13	3 months
Mannacio et al. [27]	Retro Cohort	2022	Italy	69	41	Bioprosthetic	Dabigatran (30) Apixaban (25) Rivaroxaban (27) Edoxaban (17)	692	340	0	3 years
Kalra et al. [4]	Retro Cohort	2021	United States	62	38	Mechanical & Bioprosthetic	Unspecified	74581	6828	27,696	N/A

AF: Atrial Fibrillation; DOAC: Direct Oral Anticoagulant; N/A: Not Applicable; RCT: Randomized Controlled Trial; Retro: Retrospective Cohort Study

Publication bias was visually assessed with funnel plots and the Begg's and Eggers' tests [19,20]. Trim and fill method was used for imputation of missingness of studies in the funnel plot [21]. A p value of <0.05 was considered significant. The "trim and fill" algorithm was used for adjustment of the pooled estimate for publication bias if the bias found was significant [21].

Results

Overview of studies: From 184 titles and 14 full-text publications, we included 8 studies (4 RCT and 4 retrospective cohort studies; 183,167 patients) for systematic review and meta-analysis [4,10,13,22-26]. Two studies (n=296) exclusively included patients with MHV while five studies (n=4956) included only those that had prior THV replacement. Four studies (n=1351) were randomized trials while the other four (n=181816) were observational studies. The mean age of patients included in the studies ranged between 45 and 74 years and women comprised between 35% and 61% of the study cohorts. While 4 studies reported early results (<1 year follow-up), 3 studies reported data with a longer follow-up duration (range: min 1 to 3 years). The PRISMA flowchart of literature search and study selection is provided in Figure 1. Overall, study quality was moderate, and most had limited interpretability due to small sample sizes and consequently few event rates (Table S4, S5). All studies that reported data regarding the use of DOAC as anti-thrombotic therapy after MHV replacement were randomized trials (Table 1). Kalra et al. reported a very small number of patients receiving only DOAC after MHV but their data source and study design did not allow authors to clearly state the indication for DOAC therapy.

Study endpoints

Bleeding rates from 5 studies (n=4023 patients) were comparable for both drugs [OR: 1.24 (0.55, 2.79)] (Figure 2). We observed significant heterogeneity for this pooled estimate (I^2 83%) and therefore performed a separate analysis according to the study duration. We observed that the pooled result remained consistent after analyzing studies reporting short-term (<1 year) and long-term data (>1 year) separately. Combining data from 6 studies, we observed that major bleeding rates were higher in patients receiving warfarin therapy [OR: 1.22 (1.05, 1.41); I^2=4%] (Figure 2). On pooling data from 6 studies (85,579 patients), stroke rates were comparable between warfarin and DOAC treated patients [OR: 0.95 (0.40, 2.88); I^2=73%] (Figure 3). However, on limiting the analysis to only studies that reported data in MHV patients, stroke rates were much higher in patients treated with DOAC. We did not observe any association between the prevalence of atrial fibrillation and the differential occurrence of stroke between DOAC and warfarin treated patients (meta-regression p-value 0.24). We observed that ischemic stroke rates [OR: 1.73 (1.11, 2.70)] were higher with warfarin therapy, while embolic event rates were similar [OR: 0.68 (0.20, 2.31)], as were TIA events [OR: 0.94 (0.61, 1.44)] (Figure 3). All-cause mortality was similar in both groups [OR: 1.98 (0.93, 4.19)] (Figure S7).

In results limited to only patients receiving THV replacement, we observed that major bleeding and ischemic stroke rates were higher in the warfarin treated group, while pooled event rates for other endpoints (bleeding, stroke, TIA, all-cause mortality) were comparable in both drug groups (Table S6).

Temporal Analysis: We performed subgroup analysis according to study duration and pooled data as short-term (less than 1 year follow-up) or long-term (greater than 1 year follow-up). These analyses support the overall pooled results, briefly we did not observe any meaningful difference in event rates between the DOAC and warfarin treated groups for stroke as well as bleeding (Figure S1). We could not pool data regarding short-term stroke as all studies that qualified has zero event rates in the warfarin arms [10,22,23]. This clearly indicates that in the short-term (<1 year until outcome assessment) DOACs led to higher all-stroke than warfarin (Table S6, S7).

Sensitivity Analyses: We performed further sensitivity analyses to evaluate our primary observations and evaluated publication bias among studied endpoints (Tables S1-S3). All sensitivity analyses support our primary findings (Figure 2, 3).

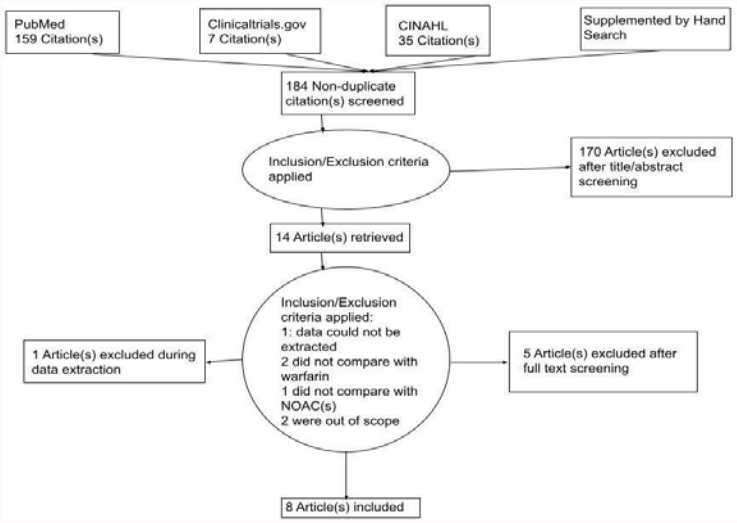

Figure 1: PRISMA flowchart of literature search and study selection is provided.

Table 2: Study Characteristics.

ID	Type	PMID	Author	Year	Country	Valve	Type of NOAC	N	Pre-op AF/Flutter #	Jadad Score¶	Newcastle-Ottawa Score ‖	Approximate Outcome Assessment
1	RCT	23991661	Eikelboom et al.	2013	Multinational	Mechanical	Dabigatran	252	72	3/5	N/A	12 weeks
2	RCT	33196155	Guimaraes et al.	2020	Brazil	Bioprosthetic	Rivaroxaban	1005	1005	3/5	N/A	12 months
3	RCT	33150497	Duraes et al.	2020	Brazil	Mechanical	Rivaroxaban	44	12	3/5	N/A	90 days
4	Retro Cohort	32607688	Pasciolla et al.	2020	United States	Bioprosthetic	Dabigatran, Apixaban, Rivaroxaban	197	102	N/A	6/9 (***°°***)	6 months
5	Retro Cohort	33529622	Duan et al.	2021	United States	Bioprosthetic	Dabigatran, Apixaban, Rivaroxaban	2672	2672	N/A	7/9 (***°****)	12 months
6	RCT	34897639	Piepiorka-Broniecka et al.	2022	Poland	Bioprosthetic	Apixaban	50	13	2/5	N/A	3 months
7	Retro Cohort	33744222	Mannacio et al.	2022	Italy	Bioprosthetic	Dabigatran, Apixaban, Rivaroxaban, Edoxaban	1032	0	N/A	8/9 (***°*****)	3 years
8	Retro Cohort	33683332	Kalra et al.	2021	United States	Mechanical & Bioprosthetic	Unspecified	177915	27,696	N/A	3/9 (***°°°°°)	N/A

AF: Atrial Fibrillation; NOAC: Novel Oral Anticoagulant; N/A: Not Applicable; PMID: PubMed ID; RCT: Randomized Controlled Trial: Retro: Retrospective
¶ Details of Jadad scoring in Supplementary material
‖Details of Newcastle Ottawa scoring in Supplementary material

Discussion

We conducted a systematic review and meta-analysis to compare clinical events in patients treated with warfarin or DOAC as anti-thrombotic therapy after heart valve replacement. Overall, we observed paucity of available data. Most studies were small, observational cohort studies that were likely not powered to answer this question. Our primary, pooled analysis showed that DOACs are at least noninferior to warfarin in treating patients after tissue valve replacement; however, stroke rates are substantially higher for DOAC treated patients after mechanical valve replacement.

Our results are consistent with prior studies that evaluated DOAC therapy for other anti-thrombotic indications [27-29]. In prior meta-analyses that studied patients with AF, DOACs, compared to warfarin, showed a lower risk of hemorrhagic stroke, all-cause mortality, and intracranial hemorrhage in patients with AF [30,31]. Our study supports prior evidence and also demonstrates that data supporting the use of DOAC therapy after valve replacement is very limited. At present, while limited by small sample size, there is very little positive evidence to support the use of DOAC as anti-thrombotic therapy after MHV replacement [10]. The few randomized trials that have investigated this issue have all reported substantially higher stroke rates in DOAC treated MHV patients, especially on the background that a large multi-national phase II trial was prematurely stopped due to unacceptably high bleeding and stroke rates with DOAC therapy in MHV patients (cite). We found two other studies that were registered to investigate the use of DOAC in patients after MHV replacement. One study (CATHAR) was prematurely terminated (exact reasons not specified in clinicaltrials.gov portal) but reported that rivaroxaban was safely used in 10 low-risk patients post-mechanical aortic valve replacement [32]. Another more ambitious phase IV trial that will study the use of apixaban *vs.* warfarin is registered but not yet opens to enrollment [33]. Therefore, despite improved prosthetic valve design, lower profile, and in-built mechanisms to prevent thromboembolic

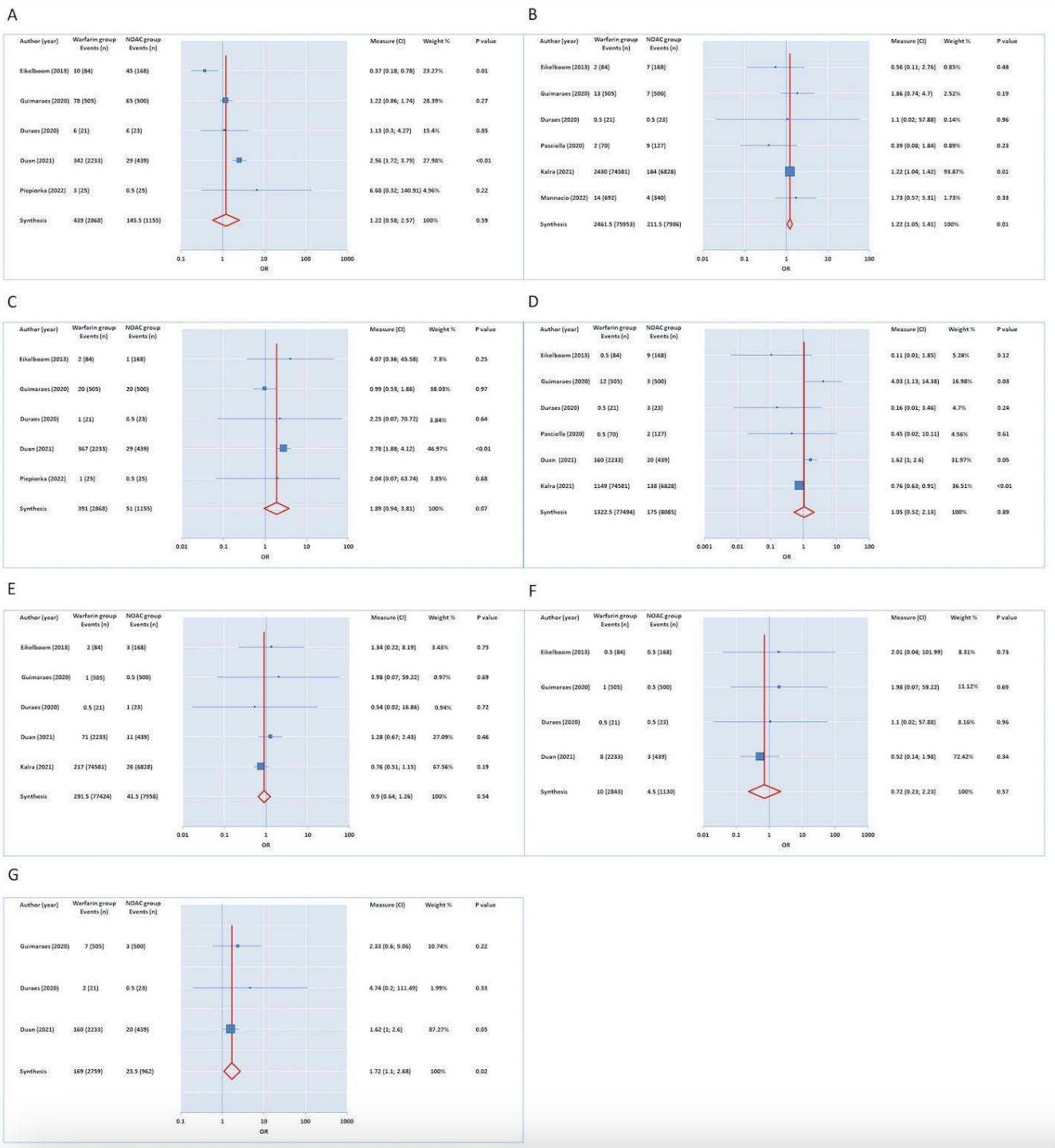

Figure 2: Pooled Forest Plots.
For all bleeding, major bleeding, stroke, ischemic stroke, Transient Ischemic Attack (TIA), systemic embolism (embolic stroke) OR (lower and upper end of 95% CI)

complications, warfarin continues to the anti-thrombotic drug of choice for mechanical valves.

But an equally important message that our study provides is that DOAC therapy is safe and as effective as warfarin in preventing stroke after THV replacement. Given the many advantages of DOAC therapy over warfarin, our study provides important evidence supporting the continued use of DOAC's for tissue valves. The 2017 AHA update recommended the short term (3 months) use of warfarin as anti-thrombotic therapy after THV replacement in low bleeding-risk patients; therefore, in this situation, our meta-analysis demonstrated that DOAC therapy is a safe alternative.

While we agree that the robustness of our results is severely limited by the small amount of data available, we have been able to confirm our results using different sensitivity analyses like the trim-fill and leave-one-out approaches. We have also investigated the temporal of our data using subgroup analyses and reported results

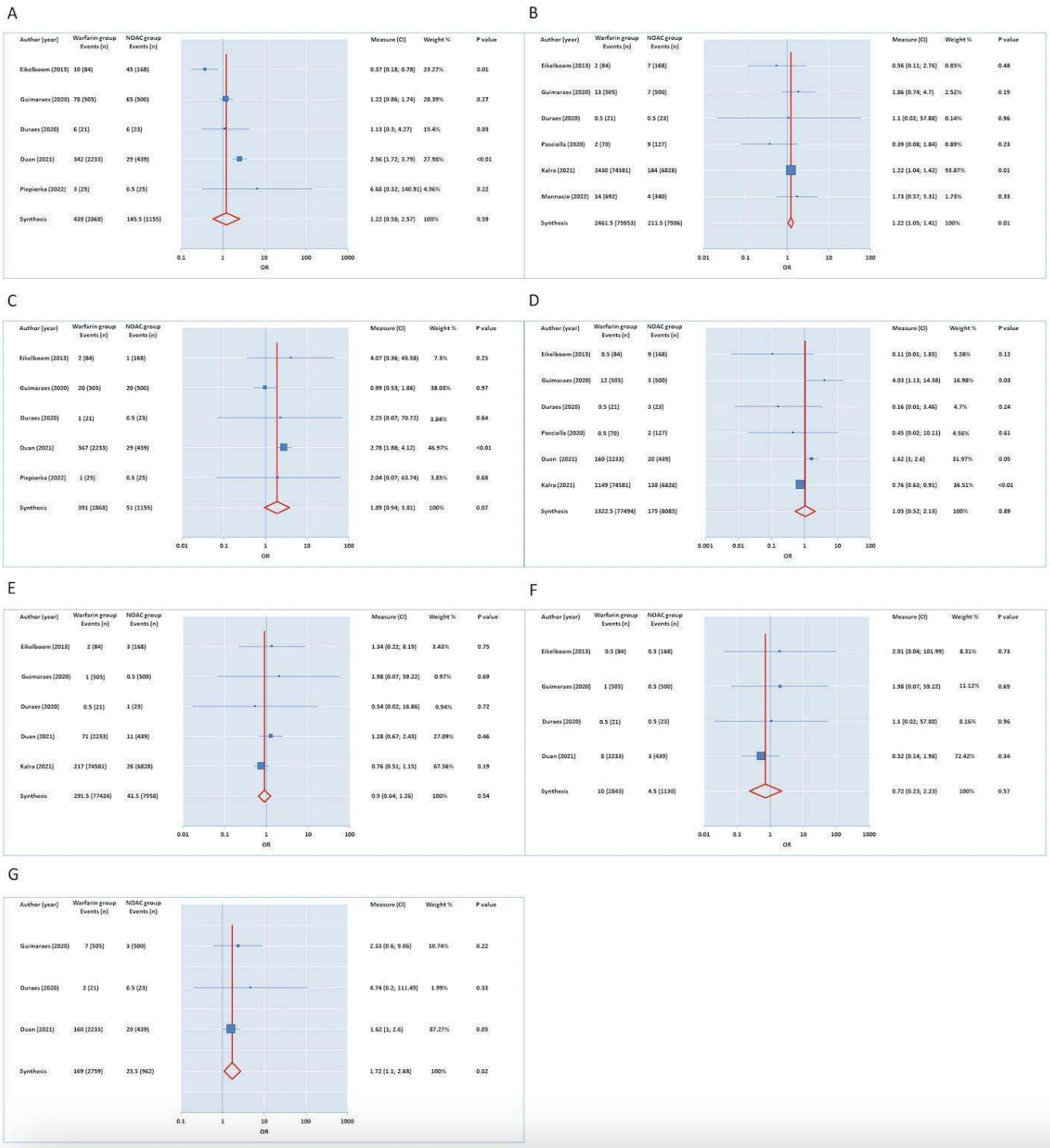

Figure 3: Tissue Valve Subgroup Forest Plots.
For all bleeding, all stroke, major bleeding, ischemic stroke, TIA, all-cause mortality OR (lower and upper end of 95% CI)

separately for tissue and mechanical valves. We agree that it would be pertinent to clinical practice to further be able to separate and report results according to valve position. It is clear from prior evidence that thromboembolic issues are of more concern for prosthetic mitral rather than aortic valves. Thus, we feel that future studies need to address these important issues. We have witnessed a rapid increase in the use of Trans-Catheter Aortic Valve Replacement (TAVR) as the primary procedure for aortic stenosis; however, this brings to attention complications and failures of TAVR that often need to be addressed by surgical aortic valve replacement (https://www.jacc.org/doi/10.1016/j.jacc.2020.08.048). Thus, anti-thrombotic therapy after valve replacement remains an important contemporary issue in the current era of expanding trans-catheter valve technology.

Conclusion

Current evidence comparing DOAC and warfarin as anti-thrombotic therapy after prosthetic valve replacement is limited to few small observational studies with paucity of randomized data.

Table 3: Primary and subgroup syntheses.

Outcomes	I^2 (%)	p value	OR [95% CI]
All bleeding	83	0.59	1.22 [0.58, 2.57]
All bleeding (B)		0.07	1.87 [0.94, 3.72]
All bleeding (M)		0.29	0.56 [0.19, 1.63]
All bleeding comparison (B *vs.* M)		0.17	3.35 [0.59, 19.11]
All bleeding (RCT)		0.83	0.91 [0.39, 2.12]
All bleeding (retro)		<0.01	2.56 [1.72, 3.79]
All bleeding comparison (RCT *vs.* retro)		0.1	0.36 [0.1, 1.22]
Major bleeding	0	0.01	1.22 [1.05, 1.41]
Major bleeding (B)		0.01	1.33 [1.06, 1.66]
Major bleeding (M)		<0.01	0.35 [0.18, 0.67]
Major bleeding comparison (B *vs.* M)		<0.01	3.78 [1.6, 8.94]
Major bleeding (RCT)		0.44	1.36 [0.62, 2.99]
Major bleeding (retro)		0.45	1.18 [0.77, 1.79]
Major bleeding comparison (RCT *vs.* retro)		0.8	1.16 [0.35, 3.86]
All-cause mortality	48	0.07	1.89 [0.94, 3.81]
All-cause mortality (B)		0.23	1.74 [0.71, 4.26]
All-cause mortality (M)		0.23	3.35 [0.46, 24.22]
All-cause mortality comparison (B *vs.* M)		0.65	0.52 [0.03, 9.21]
All-cause mortality (RCT)		0.69	1.13 [0.62, 2.04]
All-cause mortality (retro)		<0.01	2.78 [1.88, 4.12]
All-cause mortality comparison (RCT *vs.* retro)		0.07	0.41 [0.15, 1.08]
All stroke	72	0.89	1.05 [0.52, 2.13]
All stroke (B)		0.37	1.35 [0.7, 2.59]
All stroke (M)		0.02	0.28 [0.1, 0.79]
All stroke comparison (B *vs.* M)		0.07	4.81 [0.89, 26.05]
All stroke (RCT)		0.63	0.49 [0.03, 8.44]
All stroke (retro)		0.94	1.03 [0.52, 2.02]
All stroke comparison (RCT *vs.* retro)		0.68	0.48 [0.01, 16.44]
Ischemic stroke	0	0.02	1.72 [1.1, 2.68]
Ischemic stroke (B)		0.02	1.68 [1.07, 2.64]
Ischemic stroke (M)		0.33	4.74 [0.2, 111.49]
Ischemic stroke comparison (B *vs.* M)		0.57	0.35 [0.01, 13.07]
Ischemic stroke (RCT)		0.12	2.7 [0.78, 9.35]
Ischemic stroke (retro)		0.05	1.62 [1, 2.6]
Ischemic stroke comparison (RCT *vs.* retro)		0.56	1.67 [0.3, 9.21]
TIA	0	0.54	0.9 [0.64, 1.26]
TIA (B)		1	1 [0.7, 1.42]
TIA (M)		0.35	0.55 [0.16, 1.94]
TIA comparison (B *vs.* M)		0.47	1.8 [0.36, 9.03]
TIA (RCT)		0.78	1.23 [0.29, 5.22]
TIA (retro)		0.76	0.93 [0.57, 1.51]
TIA comparison (RCT *vs.* retro)		0.78	1.32 [0.19, 9.21]
Systemic embolism	0	0.57	0.72 [0.23, 2.23]
Systemic embolism (B)		0.46	0.62 [0.18, 2.15]
Systemic embolism (M)		0.78	1.49 [0.09, 24.25]
Systemic embolism comparison (B *vs.* M)		0.67	0.42 [0.01, 23.34]

Systemic embolism (RCT)		0.64	1.67 [0.19, 14.43]
Systemic embolism (retro)		0.34	0.52 [0.14, 1.98]
Systemic embolism comparison (RCT *vs.* retro)		0.52	3.19 [0.1, 104.58]

B: Bioprosthetic Valves; CI: Confidence Interval; I^2, I^2 Statistic Expressed as %; M: Mechanical Valves; OR: Odds Ratio; RCT: Randomized Controlled Trial; retro: retrospective cohort study

Review of available literature clearly demonstrates that DOAC are harmful in patients' post-mechanical valve replacement but are non-inferior to warfarin in patients receiving tissue valves. Future large, randomized data is needed to support these preliminary observations and specifically report data by prosthetic valve position.

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References

1. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the heart rhythm society. J Am Coll Cardiol. 2019;74(1):104-32.
2. Bartus K, Litwinowicz R, Sadowski J, Filip G, Kowalewski M, Suwalski P, et al. Bioprosthetic or mechanical heart valves: Prosthesis choice for borderline patients? Results from 9,616 cases recorded in Polish national cardiac surgery registry. J Thorac Dis. 2020;12(10):5869-78.
3. Isaacs AJ, Shuhaiber J, Salemi A, Isom OW, Sedrakyan A. National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. J Thorac Cardiovasc Surg. 2015;149(5):1262-9. e63.
4. Kalra A, Raza S, Jafry BH, King HE, Lahorra JA, Svensson LG, et al. Off-label use of direct oral anticoagulants in patients receiving surgical mechanical and bioprosthetic heart valves. JAMA Netw Open. 2021;4(3):e211259.
5. Russo V, Attena E, Mazzone C, Esposito F, Parisi V, Bancone C, et al. Nonvitamin K antagonist oral anticoagulants use in patients with atrial fibrillation and bioprosthetic heart valves/prior surgical valve repair: A multicenter clinical practice experience. Semin Thromb Hemost. 2018;44(4):364-9.
6. Rose DK, Bar B. Direct oral anticoagulant agents: Pharmacologic profile, indications, coagulation monitoring, and reversal agents. J Stroke Cerebrovasc Dis. 2018;27(8):2049-58.
7. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: A systematic review and meta-analysis. J Thromb Haemost. 2014;12(3):320-8.
8. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. Lancet. 2014;383(9921):955-62.
9. Chen A, Stecker E, B AW. Direct oral anticoagulant use: A practical guide to common clinical challenges. J Am Heart Assoc. 2020;9(13):e017559.
10. 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(13):1206-14.
11. Shim CY, Seo J, Kim YJ, Lee SH, De Caterina R, Lee S, et al. Efficacy and safety of edoxaban in patients early after surgical bioprosthetic valve implantation or valve repair: A randomized clinical trial. J Thorac Cardiovasc Surg. 2023;165(1):58-67.e4.
12. Yadlapati A, Groh C, Malaisrie SC, Gajjar M, Kruse J, Meyers S, et al. Efficacy and safety of novel oral anticoagulants in patients with bioprosthetic valves. Clin Res Cardiol. 2016;105(3):268-72.
13. Guimaraes HP, Lopes RD, de Barros ESPGM, 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(22):2117-26.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
15. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.
16. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-5.
17. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane handbook for systematic reviews of interventions version 6.3 Cochrane; 2022.
18. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I^2 index? Psychol Methods. 2006;11(2):193-206.
19. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088-101.
20. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
21. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000;56(2):455-63.
22. Duraes AR, de Souza Lima Bitar Y, Schonhofen IS, Travassos KSO, Pereira LV, Filho JAL, et al. Rivaroxaban versus warfarin in patients with mechanical heart valves: Open-label, proof-of-concept trial-the RIWA study. Am J Cardiovasc Drugs. 2021;21(3):363-71.
23. Pasciolla S, Zizza LF, Le T, Wright K. Comparison of the efficacy and safety of direct oral anticoagulants and warfarin after bioprosthetic valve replacements. Clin Drug Investig. 2020;40(9):839-45.
24. 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.
25. Piepiorka-Broniecka M, Michalski TA, Figatowski T, Wojtowicz A, Jurowiecki J, Stanska A, et al. NOAC versus warfarin in the treatment of atrial fibrillation during the first three months after bioprosthetic aortic valve replacement. Cardiol J. 2022;29(2):355-7.
26. Mannacio VA, Mannacio L, Antignano A, Mauro C, Mastroroberto P, Musumeci F, et al. New oral anticoagulants versus warfarin in atrial fibrillation after early postoperative period in patients with bioprosthetic aortic valve. Ann Thorac Surg. 2022;113(1):75-82.
27. Dalia T, Lahan S, Ranka S, Goyal A, Zoubek S, Gupta K, et al. Warfarin versus direct oral anticoagulants for treating left ventricular thrombus: A systematic review and meta-analysis. Thromb J. 2021;19(1):7.
28. Martha JW, Pranata R, Raffaelo WM, Wibowo A, Akbar MR. Direct acting

oral anticoagulant *vs.* Warfarin in the prevention of thromboembolism in patients with non-valvular atrial fibrillation with valvular heart disease-A systematic review and meta-analysis. Front Cardiovasc Med. 2021;8:764356.

29. Silverio A, Di Maio M, Prota C, De Angelis E, Radano I, Citro R, et al. Safety and efficacy of non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: Systematic review and meta-analysis of 22 studies and 440 281 patients. Eur Heart J Cardiovasc Pharmacother. 2021;7(FI1):f20-9.

30. Jia B, Lynn HS, Rong F, Zhang W. Meta-analysis of efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation. J Cardiovasc Pharmacol. 2014;64(4):368-74.

31. Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. Am J Cardiol. 2012;110(3):453-60.

32. Roost E, Weber A, Alberio L, Englberger L, Reineke D, Keller D, et al. Rivaroxaban in patients with mechanical heart valves: A pilot study. Thromb Res. 2020;186:1-6.

33. Antithrombotic Strategy Based on Clinical Events and 4D-CT for Patients After TAVR.