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Research Article

Direct Oral Anticoagulants versus Warfarin in Patients with Bioprosthetic Heart Valves and Atrial Fibrillation: A Systematic Review and Meta-analysis

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Abstract: Patients with prosthetic heart valves require long-term anticoagulation, and many have concomitant atrial fibrillation (AF). Warfarin has been the standard of care, but direct oral anticoagulants (DOACs) offer predictable pharmacokinetics, fixed dosing and freedom from routine monitoring. Their comparative performance in prosthetic valve populations remains uncertain.
Objectives. To compare the efficacy and safety of DOACs versus warfarin for long-term anticoagulation in adults with mechanical or bioprosthetic heart valves. ***Methods***. This systematic review and meta-analysis followed PRISMA 2020 and was registered in PROSPERO (CRD420251232927). PubMed, Scopus and ClinicalTrials.gov were searched to 30 October 2025. Eligible studies compared a DOAC with warfarin in adults (≥18 years) with mechanical or bioprosthetic valves receiving chronic anticoagulation. Risk of bias was assessed with RoB 2 and ROBINS-I, and certainty with GRADE. Dichotomous outcomes were pooled as odds ratios (ORs) with 95% confidence intervals (CIs) using random-effects meta-analysis (Mantel–Haenszel); heterogeneity was quantified with Cochran's Q and I^2. ***Results.*** Six studies (27,261 patients) were included; all enrolled patients with bioprosthetic valves and AF, and no mechanical valve study was eligible. Three observational studies (810 DOAC, 1,383 warfarin) provided extractable event data. No significant difference was found for thromboembolic stroke (OR 0.90, 95% CI 0.45–1.77; I^2 = 30%), major bleeding (OR 0.93, 95% CI 0.69–1.25; I^2 = 0%), all-cause mortality (OR 1.24, 95% CI 0.91–1.70; I^2 = 0%), minor bleeding (OR 1.12, 95% CI 0.79–1.58; I^2 = 0%) or the composite endpoint (OR 1.08, 95% CI 0.72–1.62; I^2 = 64%). All non-randomised studies were at serious risk of bias, and certainty was very low for every outcome. ***Conclusions.*** In patients with bioprosthetic valves and AF, DOACs and warfarin showed comparable rates of stroke, bleeding and death, supporting DOACs as a reasonable option in selected patients. The evidence is of very low certainty and largely observational. No eligible evidence exists for mechanical valves, in which DOACs remain contraindicated.

Keywords: Direct oral anticoagulants; warfarin; bioprosthetic heart valve; mechanical heart valve; atrial fibrillation; systematic review; meta-analysis

INTRODUCTION

Valvular heart disease is a growing contributor to global cardiovascular morbidity and mortality. As populations age and transcatheter techniques extend valve replacement to patients previously managed medically, the number of people living with a prosthetic heart valve continues to rise. Prosthetic valves divide broadly into mechanical valves, which are durable but highly thrombogenic, and bioprosthetic valves, which carry a lower long-term thrombotic risk but a finite structural lifespan. Atrial fibrillation is common in both groups, particularly among the older patients who typically receive a bioprosthesis, and constitutes an independent indication for oral anticoagulation.

Vitamin K antagonists, principally warfarin, have been the standard of care for decades and reduce thromboembolic complications effectively, but their use is demanding. Warfarin has a narrow therapeutic index, so modest deviations in dosing translate into either thromboembolism or haemorrhage. Keeping the international normalised ratio within range requires frequent venepuncture and clinic attendance, which burdens patients and consumes health system resources. Numerous drug and dietary interactions further destabilise anticoagulation intensity, and time in therapeutic range in routine practice frequently falls short of that achieved under trial conditions. Major bleeding remains a substantial hazard, particularly in the elderly and comorbid populations who most often receive prosthetic valves.

Direct oral anticoagulants (DOACs) address many of these limitations through predictable pharmacokinetics, fixed dosing and the absence of routine monitoring, and have displaced warfarin across most indications in non-valvular atrial fibrillation and venous thromboembolism. Their role in prosthetic valves, however, diverged early and sharply by valve type, and guideline recommendations remain inconsistent in scope and strength. We therefore undertook a systematic review and meta-analysis comparing long-term anticoagulation

with DOACs versus warfarin in adults with mechanical or bioprosthetic heart valve prostheses, evaluating thromboembolic events, major and minor bleeding, all-cause mortality and composite efficacy and safety endpoints.

2. Literature Review

Evidence in mechanical valves is unambiguous and negative. The RE-ALIGN trial, which randomised patients with mechanical aortic or mitral valves to dabigatran or warfarin, was terminated prematurely after an excess of both thromboembolic and bleeding events in the dabigatran arm, and plasma trough concentrations did not correlate with thromboembolic risk. That result established the contemporary contraindication to DOACs in mechanical valves and led to the exclusion of such patients from the pivotal atrial fibrillation trials. A recent meta-analysis of randomised evidence in mechanical valve populations reported a substantially increased risk of ischaemic stroke and thromboembolism with DOACs relative to warfarin. The mechanism is plausible: mechanical valve surfaces activate coagulation predominantly through the contact pathway, initiating factor XII and factor XI activation that warfarin suppresses indirectly by reducing synthesis of multiple clotting factors, but that selective inhibition of thrombin or factor Xa addresses incompletely.

Evidence in bioprosthetic valves has taken the opposite course. Bioprosthetic valves become endothelialised over several months and generate a far lower thrombotic burden, so the dominant indication for anticoagulation in that group is the atrial fibrillation itself rather than the prosthesis. The RIVER trial found rivaroxaban non-inferior to warfarin for a composite of death, major cardiovascular events and major bleeding in patients with atrial fibrillation and a bioprosthetic mitral valve. A valvular subgroup analysis of ENGAGE AF-TIMI 48 preserved the relative efficacy and safety of edoxaban irrespective of valvular disease status. The multicentre prospective BPV-AF Registry reported similar rates of stroke, systemic embolism and major bleeding between warfarin- and DOAC-treated patients, and a large real-world cohort found no difference in either thrombosis or bleeding. Meta-analyses restricted to mitral bioprostheses have reached the same conclusion.

Two gaps persist. First, existing syntheses have generally been confined to a single valve position, a single agent or a single design, and none has attempted to evaluate both mechanical and bioprosthetic valves within one framework using contemporary risk-of-bias instruments and formal certainty assessment. Second, much of the bioprosthetic evidence is observational, in which anticoagulant selection is made by treating physicians rather than by randomisation, so the possibility of confounding by indication has rarely been assessed systematically. This review addresses both.

Materials and Methods

3.1 Protocol and registration

This review was conducted and reported in accordance with the PRISMA 2020 statement and registered prospectively in PROSPERO (CRD420251232927) on 18 November 2025. Institutional review board approval and informed consent were not required, as only published aggregate data were analysed. Four deviations from the registered protocol occurred. Embase and CENTRAL, specified in the protocol, were not searched. ROBINS-I was used in place of the Newcastle-Ottawa Scale for non-randomised studies, as it provides a domain-level assessment of confounding better suited to physician-directed treatment allocation. Funnel plots were planned but not performed, because no outcome included more than three studies and such tests are uninformative below approximately ten. Prespecified subgroup analyses by valve type, individual DOAC agent, follow-up duration and risk score could not be conducted; a post hoc subgroup analysis of major bleeding by bleeding definition was performed instead.

3.2 Search strategy and eligibility criteria

PubMed, Scopus and ClinicalTrials.gov were searched from inception to 30 October 2025, combining Medical Subject Headings and free-text terms across three concepts: population (heart valve, valve replacement, prosthetic valve, mechanical valve, bioprosthetic valve); intervention and comparator (anticoagulant, warfarin, DOAC, NOAC, apixaban, rivaroxaban, dabigatran, edoxaban, vitamin K antagonist); and outcomes (thromboembolism, stroke, valve thrombosis, major bleeding, intracranial haemorrhage, mortality). Reference lists of eligible articles were screened and forward citation tracking performed. The full search strings are provided in Supplementary Appendix A.

Studies were eligible if they enrolled adults aged 18 years or older with a mechanical or bioprosthetic valve prosthesis receiving long-term oral anticoagulation, with valve type and regimen clearly reported; directly compared a DOAC against warfarin or another vitamin K antagonist; reported at least one outcome of interest; and used a randomised, cohort, case-control or registry-based comparative design. Studies were excluded if they were limited to paediatric populations, enrolled only native valve disease, reported mixed valve populations from which prosthetic valve data could not be separated, evaluated only perioperative or bridging anticoagulation, lacked a comparator anticoagulant, or were case reports, narrative reviews, editorials, letters, or animal or in vitro studies.

3.3 Study selection and data extraction

Records were deduplicated and imported into Rayyan. Titles, abstracts and full texts were screened independently by two reviewers, with disagreements resolved by discussion and, where necessary, by a third reviewer. Data were extracted independently by two reviewers using a piloted standardised form and

comprised study characteristics, population characteristics, anticoagulation details, follow-up, and all prespecified outcomes. Where a study reported only adjusted effect estimates without event counts, those estimates were carried into the narrative synthesis and the study was excluded from pooling.

3.4 Risk of bias and certainty of evidence

Randomised evidence was appraised with RoB 2 across five domains and non-randomised evidence with ROBINS-I across seven domains, including confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement and selection of the reported result. Domains were rated low, moderate, serious or critical risk of bias, and the overall judgement for each study was determined by its most serious domain rating. Certainty of evidence for each outcome was assessed using GRADE across risk of bias, inconsistency, indirectness, imprecision and publication bias. Bodies of evidence composed of non-randomised studies began at low certainty and were rated down further where warranted. All assessments were made independently by two reviewers.

3.5 Statistical analysis

Dichotomous outcomes were pooled as odds ratios with 95% confidence intervals using the Mantel-Haenszel method under a random-effects model, selected a priori given the anticipated diversity across registries, valve positions and healthcare settings. Heterogeneity was quantified with Cochran's Q and I^2 and interpreted according to Cochrane guidance. Leave-one-out sensitivity analyses were performed for every pooled outcome. Odds ratios were used in preference to hazard ratios because the included studies reported event counts over differing follow-up periods without consistently available time-to-event data. A two-sided P value below 0.05 was considered significant. Analyses were performed in Review Manager 5.4 (Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

4.1 Study selection and characteristics

The search identified 1,514 records (PubMed n = 1,365; Scopus n = 87; ClinicalTrials.gov n = 62). After removal of 192 duplicates, 1,322 records were screened by title and abstract and 1,306 excluded. Sixteen full texts were assessed and ten excluded, leaving six studies (Figure 1).

The six studies comprised 27,261 patients. Every study enrolled patient with bioprosthetic valves and concomitant atrial fibrillation; no mechanical valve study met the eligibility criteria. Designs comprised one subgroup analysis of a randomised trial, two post hoc substudies of randomised trials, two post hoc subgroup analyses of a prospective observational registry, and one investigator-initiated multicentre observational registry study. Three studies were multinational, two Japanese and one European. Sample sizes ranged from 479 to 21,046 and follow-up from 12 months to a mean of 3.8 years. Characteristics are summarised in Table 1.

Only three studies reported extractable event counts by treatment arm. Amano et al., Miyake et al. and Jochheim et al., comprising 810 patients receiving DOACs and 1,383 receiving warfarin, constitute the entire quantitative evidence base for every pooled analysis below. The remaining three contributed to the narrative synthesis only: Dangas et al. and De Caterina et al. reported no poolable outcome data, and Paparella et al. reported adjusted time-varying hazard ratios without corresponding event counts. Mean age across studies ranged from 70.4 to 85.7 years. Hypertension was the most prevalent comorbidity (75-93%), with heart failure, diabetes and prior stroke also common. Observational studies consistently demonstrated confounding by indication, with DOACs preferentially prescribed to patients with higher thrombotic risk profiles.

Table 1. Characteristics of the included studies.

Author, year	Country	Design	Total n	DOAC n	Control n	Follow-up
Dangas et al., 2025	Multinational	Post hoc on-treatment subanalysis of a randomised, open-label, adjudicator-masked trial (ENVISAGE-TAVI AF)	1,377	713	664	Up to 36 months
Paparella et al., 2025	Multinational, 105 centres	Post hoc substudy of a randomised trial (LAAOS III)	2,645	461	2,184	Mean 3.8 years
Amano et al., 2024	Japan, 16 centres	Post hoc subgroup analysis of a prospective observational registry (BPV-AF Registry)	752	263	489	15.2 ± 4.1 months

Miyake et al., 2022	Japan, 16 hospitals	Post hoc subgroup analysis of a prospective observational registry (BPV-AF Registry)	479	221	258	15.5 ± 4.0 months
Jochheim et al., 2019	Europe, 4 centres	Investigator-initiated multicentre observational registry study	962	326	636	12 months
De Caterina et al., 2017	Multinational	Subgroup analysis of a randomised, double-blind, double-dummy trial (ENGAGE AF-TIMI 48)	21,046	NR	NR	Median 2.8 years

DOAC, direct oral anticoagulant; NR, not reported.

4.2 Primary outcomes

Three observational studies comprising 810 patients receiving DOACs and 1,383 receiving warfarin reported thromboembolic stroke. There was no significant difference between strategies (OR 0.90, 95% CI 0.45 to 1.77; P = 0.75), with low heterogeneity (I^2 = 30%, P = 0.24). Confidence intervals from two studies favoured DOACs and one favoured warfarin, and all crossed unity (Figure 2). In leave-one-out analysis the pooled estimate ranged from 0.59 (95% CI 0.26 to 1.34) to 1.12 (95% CI 0.58 to 2.14), and no configuration produced a significant result.

Major bleeding was reported by the same three studies under two different definitions and was therefore analysed with a post hoc subgroup structure (Figure 3). Among the two studies applying International Society on Thrombosis and Haemostasis criteria in surgical aortic or bioprosthetic valve populations, there was no significant difference (OR 1.11, 95% CI 0.55 to 2.24; P = 0.77; I^2 = 0%). In the transcatheter aortic valve replacement population, where the broader Bleeding Academic Research Consortium type 3-5 definition applied, the result was likewise non-significant (OR 0.89, 95% CI 0.64 to 1.24; P = 0.49). The pooled estimate across all three studies showed no difference (OR 0.93, 95% CI 0.69 to 1.25; P = 0.62) with no heterogeneity (I^2 = 0%), and the test for subgroup differences was not significant (χ^2 = 0.30, df = 1; P = 0.58).

4.3 Secondary outcomes

All-cause mortality was reported by the same three studies. The pooled analysis showed no significant difference (OR 1.24, 95% CI 0.91 to 1.70; P = 0.17) with no heterogeneity (I^2 = 0%). Jochheim et al. contributed the greatest weight (68.2%). Although the point estimate numerically favoured warfarin, the confidence interval was compatible with both a 9% reduction and a 70% increase in the odds of death, and leave-one-out analysis showed that this direction was driven entirely by a single study: omitting Jochheim et al. moved the estimate to 0.94 (95% CI 0.54 to 1.63), whereas omitting either Japanese study left it between 1.21 and 1.36 (Figure 4).

Two studies comprising 589 patients receiving DOACs and 1,125 receiving warfarin reported minor bleeding, with no significant difference between groups (OR 1.12, 95% CI 0.79 to 1.58; P = 0.54) and no heterogeneity (I^2 = 0%) (Figure 5). Composite endpoint definitions varied modestly but generally comprised stroke, systemic embolism, major bleeding, cardiovascular events and all-cause death. The pooled analysis showed no significant difference (OR 1.08, 95% CI 0.72 to 1.62; P = 0.72) with substantial heterogeneity (I^2 = 64%, P = 0.06). Jochheim et al. was the only study with a significant individual result, favouring warfarin (OR 1.53, 95% CI 1.08 to 2.16), and leave-one-out analysis confirmed it as the sole source of heterogeneity: omitting it produced a pooled estimate of 0.87 (95% CI 0.63 to 1.22) with I^2 = 0% (Figure 6).
One study reported that 41.6% of patients in the overall anticoagulation population crossed over or discontinued therapy over a mean of 3.8 years. No study reported hospitalisation for anticoagulation-related complications, quality of life or cost-effectiveness, and time in therapeutic range was reported in only two studies (69.5 ± 35.6% and 68.4%).

4.4 Risk of bias and certainty of evidence

The De Caterina et al. analysis, appraised with RoB 2, was judged at low risk of bias across all five domains, reflecting its randomised design, blinded outcome adjudication, complete follow-up and prespecified analysis plan (Figure 8). All five non-randomised studies were rated at serious risk of bias overall (Figure 7). The dominant concern in every study was confounding, as anticoagulant selection was at physician discretion rather than by randomisation, producing systematic baseline imbalance between arms. Additional concerns comprised participant selection in four studies, deviations from intended interventions in two, unclear blinding of outcome measurement in two, and selective reporting in four, reflecting the post hoc analytic design of most included analyses.

Certainty of evidence was very low for all five pooled outcomes (Table 2). Every quantitative analysis rested exclusively on non-randomised studies, so each body of evidence began at low certainty and was rated down further for serious risk of bias from confounding by indication. Imprecision was an additional concern throughout, with confidence intervals spanning clinically important benefit and harm. Publication bias could not be formally assessed.

Table 2. GRADE summary of findings.

Outcome	Studies (patients)	Pooled OR (95% CI)	Certainty	Reasons for downgrading
Thromboembolic stroke	3 (2,193)	0.90 (0.45–1.77)	Very low	Non-randomised evidence; serious risk of bias (confounding); serious imprecision
Major bleeding	3 (2,193)	0.93 (0.69–1.25)	Very low	Non-randomised evidence; serious risk of bias (confounding); imprecision
All-cause mortality	3 (2,193)	1.24 (0.91–1.70)	Very low	Non-randomised evidence; serious risk of bias (confounding); serious imprecision
Minor bleeding	2 (1,714)	1.12 (0.79–1.58)	Very low	Non-randomised evidence; serious risk of bias (confounding); imprecision
Composite efficacy/safety	3 (2,193)	1.08 (0.72–1.62)	Very low	Non-randomised evidence; serious risk of bias; serious inconsistency (I^2 = 64%); imprecision

CI, confidence interval; OR, odds ratio.

DISCUSSION

In this systematic review and meta-analysis, DOACs and warfarin performed comparably across every outcome examined in patients with bioprosthetic heart valves and atrial fibrillation. Neither strategy was superior for thromboembolic stroke, major bleeding, all-cause mortality, minor bleeding or a composite endpoint. These estimates align with the wider literature, including RIVER, the valvular subgroup of ENGAGE AF-TIMI 48 and prior meta-analyses restricted to mitral bioprostheses. A separate finding is negative in a different sense: despite a search designed to capture both valve types, no study of mechanical valves met the eligibility criteria, so the sharp divergence in guideline treatment of the two populations rests on evidence this review could not synthesise.

Two features of the data qualify the null result. First, the point estimates for mortality and the composite endpoint numerically favoured warfarin, and both were driven by a single European transcatheter registry; removing it moved mortality from 1.24 to 0.94, the composite from 1.08 to 0.87, and eliminated all heterogeneity in the composite outcome. Whether this reflects genuine differences in the transcatheter population, in European prescribing practice, or in outcome ascertainment cannot be determined from aggregate data, but the pooled estimate should not be read as a stable summary of a homogeneous effect. Second, confounding by indication ran through every observational study. Where sicker patients receive the newer agent, an observed null result may conceal a real benefit; where frailer patients are steered towards the drug that avoids clinic attendance, it may conceal a real harm. The direction of this bias cannot be established from the available data, which is why certainty is very low despite the consistency of the findings.

For a patient with a bioprosthetic valve and atrial fibrillation beyond the early postoperative period, these data support a DOAC as a reasonable alternative to warfarin, and the practical advantages are real: fixed dosing, no routine monitoring, fewer dietary constraints and fewer drug interactions. This is particularly relevant for older patients and for health systems where reliable monitoring is difficult to deliver. Adherence reinforces the point, as one study documented crossover or discontinuation in 41.6% of patients over a mean of 3.8 years. Three qualifications apply: the included populations were elderly and comorbid, with routine dose adjustment for renal function, body weight and age; the evidence concerns chronic rather than early postoperative anticoagulation, for which guidelines continue to favour a vitamin K antagonist; and nothing here applies to mechanical valves.

Several limitations constrain interpretation. Only three studies contributed extractable event data, covering 2,193 of the 27,261 patients described, and two of these are post hoc analyses of the same parent registry, raising the possibility of patient overlap. All three were observational and at serious risk of bias. Statistical power was accordingly limited, and confidence intervals for every outcome remained compatible with clinically meaningful benefit or harm. Outcome definitions were heterogeneous, most visibly for major bleeding. Follow-up ranged from 12 months to 3.8 years, and pooling odds ratios across such differing durations disregards the timing of events. Subgroup analyses by individual agent, follow-up duration and risk score could not be performed, and prespecified patient-centred outcomes were reported by no included study. Two protocol-specified databases were not searched, and formal assessment of publication bias was not possible. Finally, atrial fibrillation was the indication for anticoagulation

in all included populations, so these findings do not address patients anticoagulated for the prosthesis alone.

Conclusion

In patients with bioprosthetic heart valves and concomitant atrial fibrillation, direct oral anticoagulants demonstrated efficacy and safety comparable to warfarin, with no significant differences in thromboembolic stroke, major or minor bleeding, all-cause mortality or composite endpoints. These findings support DOACs as a clinically viable alternative in carefully selected patients, given their predictable pharmacological profile and reduced monitoring requirements. The evidence is nonetheless of very low certainty and derives almost entirely from observational studies subject to confounding by indication, and should be interpreted with corresponding caution.

Three recommendations follow. For clinical practice, a DOAC is a reasonable choice for patients with a bioprosthetic valve and atrial fibrillation beyond the early postoperative period, provided dosing is adjusted for renal function, body weight and age and patient selection accounts for bleeding risk; the early postoperative window should continue to be managed with a vitamin K antagonist, and DOACs remain contraindicated in mechanical valves. For research, an adequately powered randomised trial in bioprosthetic valve populations is required, with prespecified thromboembolic and bleeding endpoints, stratification by valve position, agent-level reporting and follow-up beyond three years; trials of factor XI inhibitors represent the most plausible route to progress in mechanical valves, given the contact-pathway mechanism implicated in their thrombogenicity. For reporting, future studies should include hospitalisation, quality of life and cost-effectiveness, none of which was reported by any study in this review.

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