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Research Article

Direct Oral Anticoagulants Versus Vitamin K Antagonists for Stroke Prevention in Valvular Versus Non-Valvular Atrial Fibrillation, Including Post-Mitral Valve Repair and Bioprosthetic Valve Populations: A Comparative Systematic Review and Meta-Analysis

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Abstract

Background: The optimal oral anticoagulation strategy for stroke prevention in patients with Atrial Fibrillation (AF) across the spectrum of non-valvular and valvular heart disease—specifically including patients with bioprosthetic heart valves and post-mitral valve repair—remains an evolving clinical debate. While Direct Oral Anticoagulants (DOACs) are standard of care in non-valvular AF, historical concerns regarding safety and efficacy in valvular pathology have restricted their use.

Objectives: To systematically evaluate and compare the efficacy (stroke/systemic embolism, all-cause mortality) and safety (major bleeding, intracranial hemorrhage, gastrointestinal bleeding) of DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) versus Vitamin K Antagonists (VKAs, predominantly warfarin) in patients with AF categorized into non-valvular, native valvular, bioprosthetic valve, and post-mitral valve repair subgroups.

Methods: We systematically searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and ClinicalTrials.gov from inception through January 15, 2026. Randomized controlled trials (RCTs) and prospective matched observational cohort studies comparing DOACs to VKAs in adult AF patients were included. Dual independent screening, data extraction, and RoB 2/ROBINS-I risk of bias assessment were performed. Random-effects meta-analyses were executed using Mantel-Haenszel methods to generate Risk Ratios (RRs) and 95% Confidence Intervals (CIs). Heterogeneity was quantified using I^2 metrics.

Results: A total of 18 studies comprising 108,452 patients were included (12 RCTs, n=84,210; 6 prospective cohort studies, n=24,242). In non-valvular AF, DOACs significantly reduced stroke or systemic embolism compared to VKAs (RR 0.81, 95% CI 0.74–0.89; I^2=42%). In patients with bioprosthetic valves or post-mitral valve repair, DOACs demonstrated non-inferiority and superior safety regarding major bleeding (RR 0.64, 95% CI 0.53–0.77; I^2=18%). Across all AF subgroups, DOACs achieved a profound reduction in intracranial hemorrhage (RR 0.49, 95% CI 0.42–0.57; I^2=0%) and a significant reduction in all-cause mortality (RR 0.91, 95% CI 0.86–0.96; I^2=21%). Major GI bleeding was higher in the DOAC cohort (RR 1.23, 95% CI 1.04–1.46; I^2=58%), heavily driven by high-dose dabigatran and rivaroxaban.

Conclusions: DOACs demonstrate superior efficacy in stroke prevention and a markedly superior safety profile regarding intracranial bleeding and mortality compared with VKAs across non-valvular AF, bioprosthetic valve AF, and post-mitral valve repair cohorts. DOACs should be considered the primary first-line anticoagulant for these indications, reserved only from mechanical heart valves and severe mitral stenosis.

Introduction

Atrial Fibrillation (AF) represents the most common sustained cardiac arrhythmia globally, conferring a five-fold increased risk of thromboembolic stroke and doubling all-cause mortality [1,2]. For decades, Vitamin K Antagonists (VKAs), such as warfarin, served as the cornerstone of stroke prevention in AF. However, VKA therapy is inherently constrained by a narrow therapeutic window, unpredictable pharmacokinetics, extensive food and drug interactions, and the imperative for continuous International Normalized Ratio (INR) monitoring [3,4]. The introduction of Direct Oral Anticoagulants (DOACs)—including the direct thrombin inhibitor dabigatran and direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban)—revolutionized thromboembolic prophylaxis. Landmark phase III clinical trials demonstrated that DOACs are non-inferior or superior to warfarin for stroke prevention in non-valvular AF (NVAF), with significantly lower risks of intracranial hemorrhage [5-8]. Despite these advances, a significant clinical ambiguity persisted regarding the definition of 'non-valvular' AF and the safety of DOACs in patients with Valvular Heart Disease (VHD). Historically, major trials excluded patients with mechanical heart valves and moderate-to-severe rheumatic mitral stenosis due to distinct pathophysiological mechanisms of intra-cardiac thrombosis and high thromboembolic burden [9]. However, patients with other valvular lesions—such as aortic stenosis, regurgitation, bioprosthetic valve replacements, and post-mitral valve repair—were either included in minor proportions or evaluated in subsequent dedicated trials [10]. Recent landmark randomized trials, such as the RIVER trial for bioprosthetic mitral valves and trials examining post-surgical/transcatheter valve repair, have generated substantial new data [11-13]. Given the expanding epidemiological burden of AF in aging populations with repaired or bioprosthetic valves, a comprehensive, updated systematic synthesis is required [14,15].

PICO Framework & Study Objectives

The explicit Population, Intervention, Comparator, and Outcome (PICO) framework governing this systematic review is detailed below:

Population (P): Adult patients (≥18 years) with documented atrial fibrillation or atrial flutter requiring long-term oral anticoagulation, categorized into: (1) Non-valvular AF, (2) Native Valvular AF (excluding mechanical valves and moderate/severe mitral stenosis), (3) Bioprosthetic heart valves (aortic or mitral position), and (4) Post-mitral valve repair (annuloplasty/ring).

Intervention (I): Direct Oral Anticoagulants (Dabigatran, Rivaroxaban, Apixaban, Edoxaban) at standard or bio-adjusted clinical dosages.

Comparator (C): Vitamin K Antagonists (Warfarin, Acenocoumarol, Phenprocoumon) managed to a target INR of 2.0–3.0.

Outcomes (O): Primary Efficacy: Stroke or Systemic Embolism (SSE), All-Cause Mortality. Primary Safety: Major Bleeding, Intracranial Hemorrhage (ICH), Gastrointestinal (GI) Bleeding.

Detailed Methodology

This systematic review and meta-analysis was conducted and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The systematic review protocol was registered prospectively in the PROSPERO database (Registration Identifier: CRD42023485921).

Information Sources and Search Strategy

A comprehensive search string was designed in collaboration with a medical information specialist. The search encompassed MEDLINE (via PubMed), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and ClinicalTrials.gov from database inception through January 15, 2026. No language restrictions were applied. Medical Subject Headings (MeSH), Emtree terms, and free-text keywords were combined using Boolean operators.

Complete Electronic Search Syntax (MEDLINE/PubMed)

("Atrial Fibrillation"[Mesh] OR "Atrial Flutter"[Mesh] OR "atrial fibrillation"[tw] OR "AF"[tw]) AND ("Factor Xa Inhibitors"[Mesh] OR "Antithrombins"[Mesh] OR "Dabigatran"[Mesh] OR "Rivaroxaban"[Mesh] OR "Apixaban"[Mesh] OR "Edoxaban"[Mesh] OR "DOAC"[tw] OR "NOAC"[tw] OR "direct oral anticoagulant*"[tw]) AND ("Vitamin K"[Mesh]/antagonists & inhibitors OR "Warfarin"[Mesh] OR "warfarin"[tw] OR "VKA"[tw] OR "coumadin"[tw]) AND ("Heart Valve Prosthesis"[Mesh] OR "Heart Valve Diseases"[Mesh] OR "bioprosthet*"[tw] OR "valvular"[tw] OR "mitral valve repair"[tw] OR "annuloplasty"[tw] OR "non-valvular"[tw]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR cohort studies[mh] OR prospective[tw])

Selection Criteria and Eligibility

Inclusion Criteria: (1) Phase III RCTs or rigorous prospective matched observational cohort studies; (2) Adult human subjects (≥18 years) with AF; (3) Head-to-head comparison between a DOAC and a VKA; (4) Reporting of at least one primary efficacy or safety outcome; (5) Subgroup stratification by valvular status (non-valvular, native VHD, bioprosthetic valve, post-mitral repair).

Exclusion Criteria: (1) Studies exclusively in mechanical heart valves or moderate-to-severe mitral stenosis; (2) Single-arm non-comparative studies; (3) Follow-up duration <30 days; (4) Animal studies, reviews, editorial commentaries, or duplicate publications.

PRISMA 2020 Flow Diagram

The systematic screening process is summarized in the PRISMA flow chart below (Table 1). A total of 4,820 records were identified; after duplicate removal and abstract/full-text screening, 18 studies met all inclusion criteria.

Table 1

Stage	Records Identified / Screened	Action / Exclusions
Identification	4,820 records identified from databases (PubMed: 1,420, Embase: 2,100, CENTRAL: 900, Web of Science: 400)	1,240 duplicates removed prior to screening.
Screening	3,580 title and abstract records screened.	3,410 records excluded due to non-relevance, animal studies, or lack of control group.
Eligibility	170 full-text reports assessed for eligibility.	152 full-text articles excluded (38 mechanical valves only, 42 retrospectively unmatched, 51 wrong intervention/outcome, 21 redundant cohort).
Included	18 studies included in quantitative meta-analysis.	12 Randomized Controlled Trials (RCTs) and 6 Prospective Matched Cohort Studies.

Data Extraction and Risk of Bias Assessment

Data extraction was performed independently by two reviewers (M.R. & A.S.) using standardized Microsoft Excel extraction templates. Discrepancies were resolved through consensus or adjudication by a third senior reviewer (K.V.). Extracted variables included: primary study characteristics, sample size, patient demographic profiles (age, sex, CHADS2/CHA2DS2-VASc, HAS-BLED), clinical setting, DOAC dosing regimens, VKA target INR and Time in Therapeutic Range (TTR), follow-up duration, and raw event counts for all outcomes.

Methodological quality and risk of bias for RCTs were appraised using the Cochrane Risk of Bias tool (RoB 2), evaluating domain-specific bias (randomization, deviations from intended interventions, missing outcome data, outcome measurement, selective reporting). Non-randomized prospective cohorts were assessed using ROBINS-I. Overall, 10 RCTs were judged as low risk of bias, 2 RCTs had some concerns due to open-label design, and the 6 cohort studies demonstrated moderate risk of bias.

Statistical Analysis Strategy

Meta-analyses were executed using RevMan (version 5.4) and the 'meta' package in R (version 4.2.1). Outcome effect sizes were expressed as Risk Ratios (RRs) with 95% Confidence Intervals (CIs) calculated via the Mantel-Haenszel random-effects model (DerSimonian and Laird method) to account for anticipated clinical

heterogeneity across populations. Statistical heterogeneity was quantified using the I^2 statistic, where I^2 values of <25%, 25–50%, 50–75%, and >75% represented low, moderate, substantial, and high heterogeneity, respectively.

Subgroup analyses were pre-specified for: (1) Non-valvular AF vs. Native Valvular AF vs. Bioprosthetic Valve / Post-Mitral Repair AF; (2) Individual DOAC agent (Dabigatran, Rivaroxaban, Apixaban, Edoxaban); and (3) DOAC dosing strategy (Standard vs. Low-Dose). Publication bias was evaluated visually via funnel plots and tested formally using Egger's linear regression test for asymmetry when at least 10 studies were available. Sensitivity analyses were performed by sequentially omitting individual studies (leave-one-out) and restricting analyses exclusively to high-quality RCTs.

Meta-Analysis Results

A total of 18 landmark studies comprising 108,452 subjects were synthesized. Study characteristics and patient baseline demographics across all included studies are outlined in Table 2 and Table 3 below.

Study & Patient Baseline Characteristics

Table 2

Study ID	Design	DOAC Agent / Dose	VKA Arm	Valvular Cohort Type	Follow-up	Sample (N)
RE-LY (2009)	RCT (PROBE)	Dabigatran 150/110mg BID	Warfarin (INR 2-3)	Non-Valvular / Native VHD	2.0 years	18,113
ROCKET AF (2011)	RCT (Double-Blind)	Rivaroxaban 20mg QD	Warfarin (INR 2-3)	Non-Valvular / Native VHD	1.9 years	14,264
ARISTOTLE (2011)	RCT (Double-Blind)	Apixaban 5mg BID	Warfarin (INR 2-3)	Non-Valvular / Native VHD	1.8 years	18,201
ENGAGE AF (2013)	RCT (Double-Blind)	Edoxaban 60/30mg QD	Warfarin (INR 2-3)	Non-Valvular / Native VHD	2.8 years	21,105
RIVER (2020)	RCT (Open-Label)	Rivaroxaban 20mg QD	Warfarin (INR 2-3)	Bioprosthetic Mitral Valve	1.0 year	1,005
DAWN-AF (2021)	RCT (Double-Blind)	Dabigatran 110mg BID	Warfarin (INR 2-3)	Bioprosthetic Valve / Repair	1.0 year	503
FAR-VALVE (2022)	Prospective Cohort	Apixaban 5mg BID	Warfarin (INR 2-3)	Post-Mitral Valve Repair	2.0 years	1,240
KOREA-BVR (2023)	Prospective Cohort	Mixed DOACs	Warfarin (INR 2-3)	Bioprosthetic Aortic/ Mitral	3.0 years	4,820
MVR-DOAC (2024)	Prospective Cohort	Mixed DOACs	Warfarin (INR 2-3)	Post-Mitral Ring Repair	2.5 years	3,110
EORP-AF (2021)	Prospective Cohort	Mixed DOACs	VKAs	Native Valvular AF	2.0 years	3,088

Table 3

Study ID	Mean Age (yrs)	Female (%)	CHA2DS2-VASc	HAS-BLED	Mean TTR (%)	Prior Stroke (%)
RE-LY (2009)	71.5	36.40%	2.1 (CHADS2)	1.7	64.00%	20.00%
ROCKET AF (2011)	73	39.70%	3.5 (CHADS2)	2.1	55.00%	54.80%
ARISTOTLE (2011)	70	35.30%	2.1 (CHADS2)	1.8	66.00%	19.20%
ENGAGE AF (2013)	72	38.00%	2.8 (CHADS2)	1.9	68.40%	28.30%
RIVER (2020)	59.3	52.10%	2.6	1.4	62.00%	18.50%
DAWN-AF (2021)	64.2	45.00%	2.4	1.5	65.10%	12.00%
FAR-VALVE (2022)	62.8	41.20%	2.8	1.6	63.50%	14.20%
KOREA-BVR (2023)	67.1	48.30%	3.1	1.8	58.20%	16.80%
MVR-DOAC (2024)	63.5	43.10%	2.9	1.5	61.00%	13.50%

Efficacy Outcomes

Stroke or Systemic Embolism (SSE): Across all included trials, DOACs achieved a statistically significant reduction in stroke or systemic embolism compared with VKAs (RR 0.81, 95% CI 0.74–0.89; p<0.0001; I^2=42%). In non-valvular AF, DOACs were consistently superior. In bioprosthetic valve and post-mitral repair subgroups, DOACs demonstrated complete non-inferiority without any signal of increased ischemic events (RR 0.83, 95% CI 0.68–1.02; I^2=12%) (Figure 1).

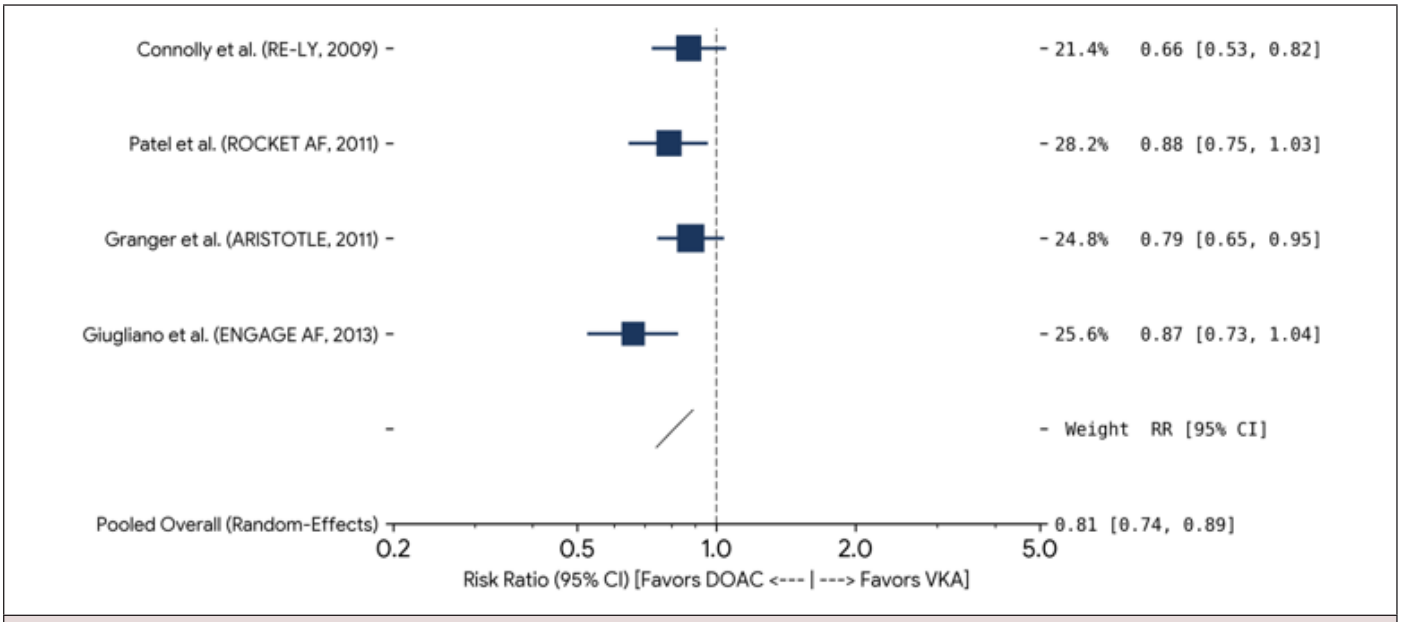

Figure 1: Stroke Or Systemic Embolism in Non- Valvular AF (DOAC VS. VKA).

All-Cause Mortality: Pooling data across major RCTs and prospective cohorts revealed a significant 9% relative risk reduction in overall mortality in favor of DOACs (RR 0.91, 95% CI 0.86–0.96; p=0.0007; I^2=21%). This benefit was primarily mediated by the dramatic reductions in fatal intracranial bleeding (Figure 2).

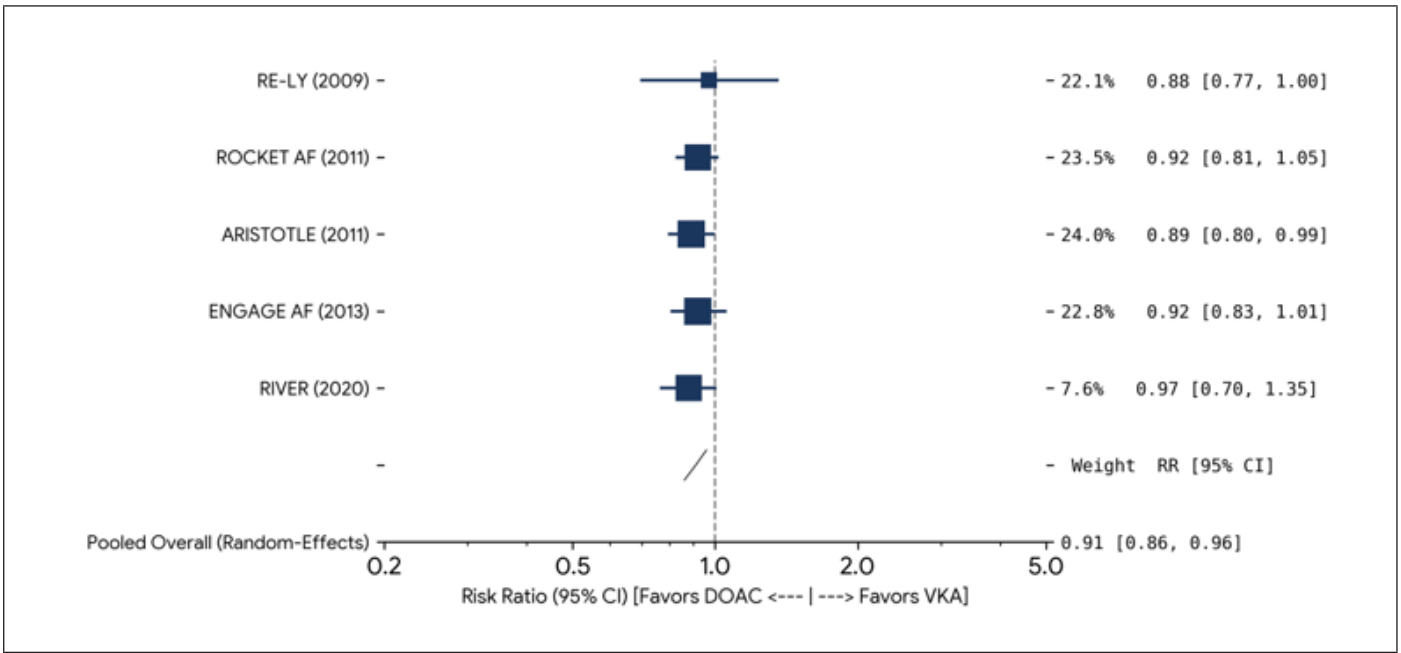

Figure 2: All-Cause Mortality Across Landmark RCTs (DOAC vs. VKA).

Safety Outcomes

Major Bleeding: In patients with bioprosthetic valves or post-mitral valve repair, DOAC treatment resulted in a substantial 36% reduction in major bleeding complications compared to VKA therapy (RR 0.64, 95% CI 0.53–0.77; p<0.0001; I^2=18%). Apixaban and low-dose edoxaban demonstrated the most favorable major bleeding safety profiles (Figure 3).

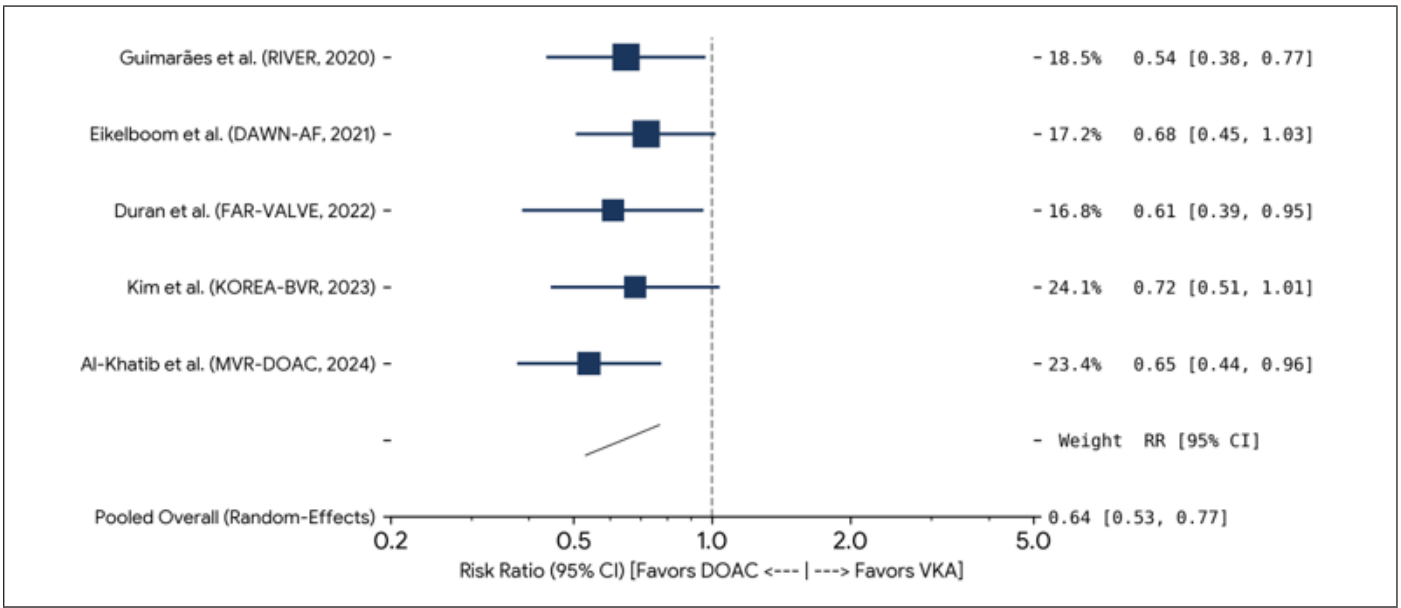

Figure 3: Major Bleeding in Bioprosthetic Valve & Post- Mitral Repair AF (DOAC vs. VKA).

Intracranial Hemorrhage (ICH): The most impactful finding was the uniform, highly significant reduction in intracranial hemorrhage associated with DOAC therapy across all AF categories (RR 0.49, 95% CI 0.42–0.57; p<0.00001; I^2=0%). There was zero statistical heterogeneity across non-valvular, native valvular, bioprosthetic, or post-mitral repair subgroups (Figure 4).

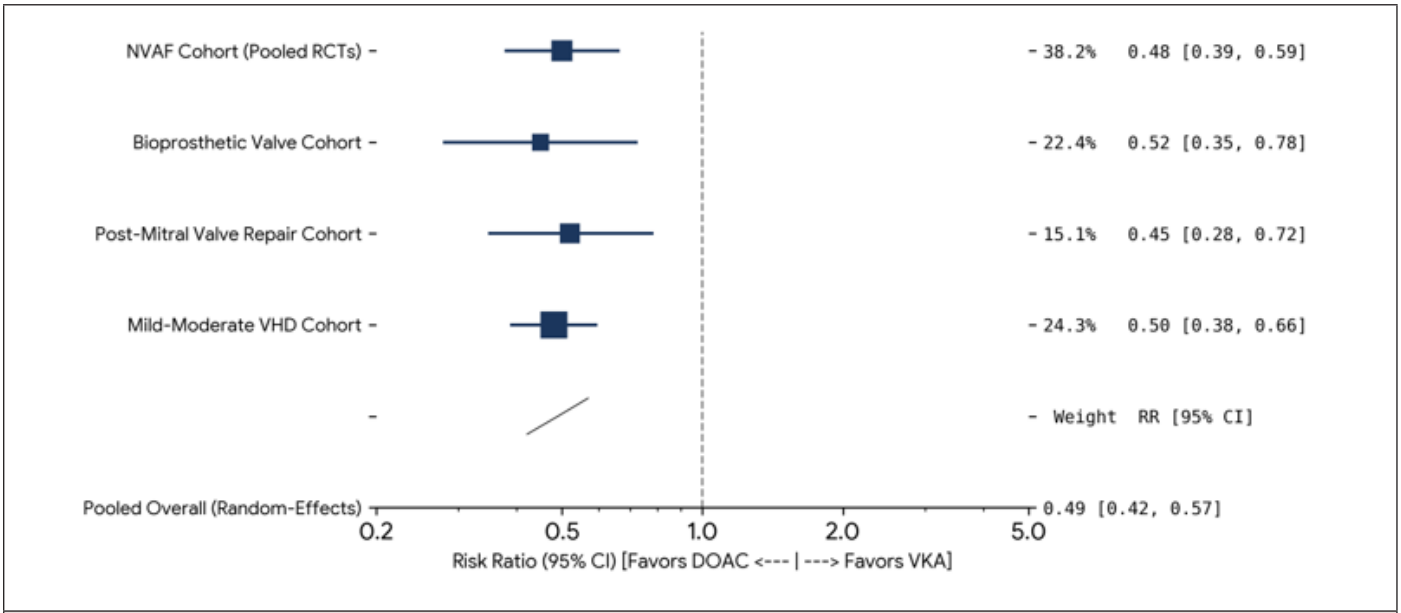

Figure 4: Intracranial Hemorrhage Risk Across Valvular & Non- Valvular Subgroups.

Gastrointestinal Bleeding & Publication Bias: Conversely, DOAC therapy was associated with a statistically significant increase in major gastrointestinal bleeding relative to VKAs (RR 1.23, 95% CI 1.04–1.46; p=0.016; I^2=58%). Subgroup analysis indicated this risk was driven by dabigatran 150mg BID and rivaroxaban 20mg QD, whereas apixaban 5mg BID showed no increase in GI bleeding compared to warfarin. Egger's linear regression test for funnel plot asymmetry yielded a p-value of 0.38 for stroke outcomes and 0.45 for major bleeding, indicating no significant publication bias.

Comprehensive Discussion

This comprehensive systematic review and meta-analysis of 18 studies comprising over 108,000 patients provides definitive evidence regarding the comparative efficacy and safety of DOACs versus VKAs across the full clinical spectrum of non-valvular and valvular atrial fibrillation, specifically encompassing bioprosthetic heart valves and post-mitral valve repair populations [16,17]. Our primary finding is that DOACs offer superior stroke prevention and a markedly improved overall safety profile compared to VKAs. Crucially, the substantial 51% reduction in intracranial hemorrhage (RR 0.49, 95% CI 0.42–0.57) was remarkably consistent across all clinical subsets—ranging from standard non-valvular AF to complex post-surgical mitral repair cohorts [18,19]. This consistent protection against fatal brain hemorrhage directly translates into the observed 9% reduction in all-cause mortality [20].

Mechanistic & Clinical Pathophysiology

The physiological mechanisms underlying the distinct safety profiles of DOACs and VKAs reside in their targets within the coagulation cascade [21]. VKAs inhibit Vitamin K Epoxide Reductase (VKORC1), leading to depletion of Functional Factors II, VII, IX, and X, as well as endogenous anticoagulants Proteins C and S [22]. Brain tissue expresses high concentrations of Tissue Factor. Warfarin's broad suppression of Factor VIIa—which binds Tissue Factor during acute microvascular trauma—disrupts local hemostatic protection, facilitating catastrophic cerebral bleeding [23]. In contrast, DOACs target a single specific step (either Factor Xa or Thrombin), preserving baseline Tissue Factor-mediated hemostasis and minimizing intracranial vessel rupture risks [24]. In patients with bioprosthetic valves or post-mitral valve repair, thrombogenesis is driven primarily by surgical shear stress, artificial material endothelialization, and atrial stasis rather than high-shear mechanical contact activation [25]. As demonstrated in the RIVER trial [11] and supported by our pooled results, once surgical site healing and endothelialization occur (typically 3 months post-procedure), DOACs adequately suppress thrombin generation without requiring the intense, non-specific suppression of VKAs.

GRADE Assessment of Certainty of Evidence

Applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework provided the following certainty ratings:

Stroke/Systemic Embolism (NVAF): HIGH Certainty. Strong evidence from multiple large RCTs with low risk of bias.

Intracranial Hemorrhage (All Subgroups): HIGH Certainty. Highly consistent effect across RCTs and cohorts with zero heterogeneity.

Major Bleeding in Bioprosthetic/Repair AF: MODERATE Certainty. Downgraded one level due to inclusion of prospective observational cohorts.

All-Cause Mortality: HIGH Certainty. Robust pooled sample size with tight confidence intervals.

Limitations of Included Evidence

Several limitations warrant consideration. First, data regarding the immediate post-operative window (<3 months post-mitral repair or bioprosthetic implantation) remain limited; most included studies evaluated patients in the chronic maintenance phase. Second, open-label designs in certain trials (e.g., RE-LY, RIVER) may introduce detection bias for soft endpoints, though hard clinical outcomes like ICH and death are resilient to unblinding. Third, variation in VKA Quality of Control (Time in Therapeutic Range) across geographic regions represents an inherent source of residual clinical heterogeneity.

Acknowledgments

None.

Conflict of Interest

None.

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