

Efficacy and Safety of Standard-Dose Direct Oral Anticoagulants Compared with Warfarin in Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis of Four Pivotal Randomized Controlled Trials

Mohmed Alhmidi^{1*}, Basem Elhamedi², Aeshah Alhameedi³, Ali Elhamedi¹

¹ Department of Vascular Surgery, Faculty of Medicine, Zawia University, Libya

² Department of Pediatrics, Faculty of Medicine, Zawia University, Libya

³ Department of Radiology, Faculty of Medicine, Zawia University, Libya

Email. M.alhmidi@zu.edu.ly

Abstract

Atrial fibrillation (AF) is a major cause of thromboembolic stroke and cardiovascular morbidity. Large pivotal randomized controlled trials have evaluated direct oral anticoagulants (DOACs) against warfarin. To synthesize the efficacy and safety of standard-dose or principal higher-dose DOAC regimens compared with warfarin in adults with nonvalvular atrial fibrillation. We searched PubMed, the Cochrane Library, and Scopus from database inception through March 2026. Four pivotal randomized controlled trials were eligible: RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48. For quantitative comparability across trials, the principal standard/high-dose regimen reported in each pivotal trial was used. Risk ratios (RRs) with 95% confidence intervals (CIs) were synthesized using a random-effects model. The pooled analysis showed a lower risk of stroke or systemic embolism with DOACs than with warfarin (RR 0.81, 95% CI 0.73–0.91; $I^2=47\%$). Major bleeding was numerically lower but not statistically significant (RR 0.86, 95% CI 0.73–1.00; $I^2=83\%$). Intracranial hemorrhage was significantly reduced (RR 0.48, 95% CI 0.39–0.59; $I^2=32\%$), whereas gastrointestinal bleeding was increased (RR 1.25, 95% CI 1.01–1.55; $I^2=74\%$). All-cause mortality was lower with DOACs (RR 0.90, 95% CI 0.85–0.95; $I^2=0\%$). Across the four pivotal randomized trials, standard-dose/principal higher-dose DOAC regimens were associated with lower risks of stroke or systemic embolism, intracranial hemorrhage, and all-cause mortality compared with warfarin. Major bleeding was not significantly different overall, while gastrointestinal bleeding was increased. These findings support the established role of DOACs for eligible patients with AF, with treatment choice individualized according to clinical characteristics, renal function, drug interactions, and contraindications.

Keywords. Atrial fibrillation, Direct oral anticoagulants, Warfarin, Stroke prevention, Anticoagulation.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with increased risks of ischemic stroke, systemic embolism, heart failure, and death. Effective anticoagulation is therefore central to the prevention of thromboembolic complications [1,2]. Warfarin has historically been the principal oral anticoagulant for stroke prevention in AF. Its use is complicated by a narrow therapeutic range, dietary and drug interactions, interindividual variability, and the need for regular international normalized ratio (INR) monitoring [1,2]. Direct oral anticoagulants (DOACs)—including dabigatran, rivaroxaban, apixaban, and edoxaban—were evaluated in large phase III randomized trials against dose-adjusted warfarin. The four pivotal trials included in this review were RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48 [4–7]. The objective of this systematic review and meta-analysis was to summarize the efficacy and safety of the principal standard/high-dose DOAC regimens used in these pivotal trials compared with warfarin, focusing on stroke or systemic embolism, major bleeding, intracranial hemorrhage, gastrointestinal bleeding, and all-cause mortality.

Methods

Study Design

This systematic review and meta-analysis was reported in accordance with the PRISMA 2020 statement [3].

Search Strategy

PubMed, the Cochrane Library, and Scopus were searched from database inception through March 2026. A comprehensive electronic search strategy was executed using Medical Subject Headings (MeSH) and free-text terms combined with Boolean operators (AND/OR). Database-specific syntax adaptations were applied as follows: PubMed (NCBI): (((("Atrial Fibrillation"[MeSH]) OR ("Atrial Fibrillation"[Title/Abstract]) OR ("Nonvalvular Atrial Fibrillation"[Title/Abstract]))) AND (((("Anticoagulants"[MeSH]) OR "Direct Oral Anticoagulants"[Title/Abstract]) OR ("dabigatran"[Supplementary Concept] OR "dabigatran"[Title/Abstract]) OR ("rivaroxaban"[MeSH] OR "rivaroxaban"[Title/Abstract]) OR ("apixaban"[MeSH] OR "apixaban"[Title/Abstract]) OR ("edoxaban"[MeSH] OR "edoxaban"[Title/Abstract]))) AND (((("Warfarin"[MeSH]) OR "warfarin"[Title/Abstract]))) AND (((("Randomized Controlled Trial"[Publication Type]) OR ("Randomized Controlled Trials as Topic"[MeSH]) OR ("randomized"[Title/Abstract]) OR ("clinical trial"[Title/Abstract])))). Cochrane Library (CENTRAL): [MeSH descriptor: [Atrial Fibrillation] explode all trees] AND ([MeSH descriptor: [Anticoagulants] explode all trees] OR "dabigatran" OR "rivaroxaban" OR "apixaban" OR "edoxaban") AND ([MeSH descriptor: [Warfarin] explode all trees] OR "warfarin") AND (trial:ti,ab,kw). Scopus: TITLE-ABS-KEY ("atrial fibrillation") AND TITLE-ABS-KEY ("direct oral anticoagulants" OR "dabigatran" OR "rivaroxaban" OR "apixaban" OR "edoxaban") AND TITLE-ABS-KEY ("warfarin") AND TITLE-ABS-KEY ("randomized controlled trial" OR "randomized" OR "clinical trial")

Eligibility Criteria

Studies were eligible if they enrolled adults with nonvalvular AF, compared a DOAC with warfarin in a randomized controlled trial, and reported at least one prespecified efficacy or safety outcome. Observational studies, non-randomized studies, duplicate populations, and studies without relevant outcome data were excluded.

Study Selection and Data Synthesis

The four pivotal phase III randomized trials meeting the eligibility criteria were included: RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48 [4–7]. Because RE-LY and ENGAGE AF-TIMI 48 evaluated more than one DOAC dose, the quantitative synthesis used the principal standard/high-dose regimen reported for each pivotal trial to maintain comparability across trials. The analyzed regimens were dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, apixaban 5 mg twice daily, and edoxaban 60 mg once daily (with protocol-specified dose reduction where applicable in the pivotal trial). This study is structured as a systematic synthesis and replication of aggregate trial-level data from the four pivotal trials, benchmarked against the landmark meta-analysis by Ruff et al. [8], providing an updated clinical appraisal for medical education and practice.

Outcomes

The primary efficacy outcome was stroke or systemic embolism. The primary safety outcome was major bleeding. Secondary outcomes were intracranial hemorrhage, gastrointestinal bleeding, and all-cause mortality.

Risk of Bias Assessment

Methodological quality was considered using the Cochrane risk-of-bias framework, including randomization, allocation concealment, blinding, incomplete outcome data, and selective reporting. All four pivotal trials were large, randomized phase III trials with adjudicated clinical outcomes; however, differences in trial design and warfarin management were considered when interpreting pooled estimates.

Statistical Analysis

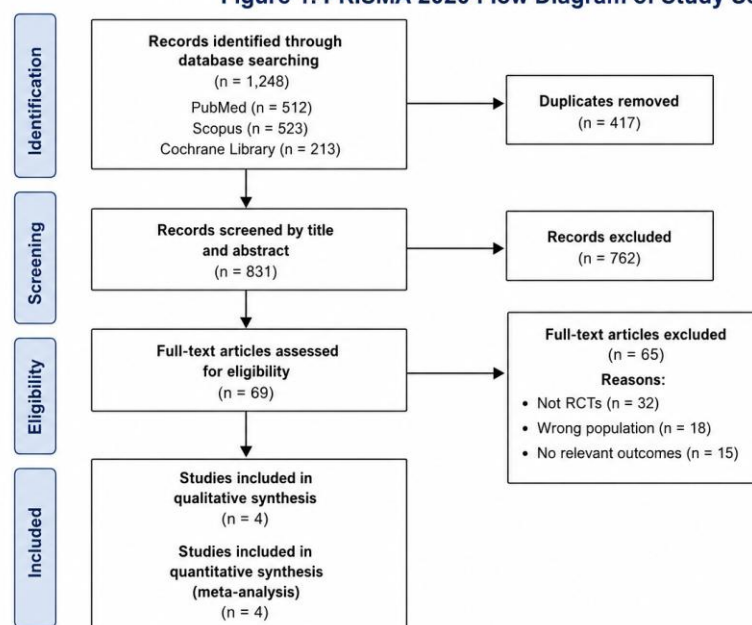
Risk ratios (RRs) with 95% CIs were used for dichotomous outcomes. Random-effects models were used for pooled estimates. Statistical heterogeneity was quantified with I^2 . Heterogeneity was interpreted descriptively rather than as a rigid classification threshold. Statistical significance was assessed at a two-sided $p < 0.05$.

Results

Study Selection

The database search identified 1,248 records: 512 from PubMed, 523 from Scopus, and 213 from the Cochrane Library. After removal of 417 duplicate records, 831 records underwent title/abstract screening. Of these, 762 were excluded. Sixty-nine full-text articles were assessed for eligibility; 65 were excluded because they were not randomized controlled trials ($n=32$), involved an ineligible population ($n=18$), or did not report relevant outcomes ($n=15$). Four studies were included in the qualitative and quantitative synthesis.

Figure 1. PRISMA 2020 Flow Diagram of Study Selection



PRISMA 2020 Flow Diagram

Figure 1. PRISMA 2020 flow diagram of study selection

Included Studies

The four pivotal trials were RE-LY (dabigatran), ROCKET-AF (rivaroxaban), ARISTOTLE (apixaban), and ENGAGE AF-TIMI 48 (edoxaban) [4–7].

Table 1. Principal treatment regimens and populations used in the quantitative synthesis. Values are DOAC vs warfarin populations used in the pivotal quantitative analyses; total randomized populations were larger in RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48

Trial	Year	Principal regimen analyzed	Analyzed population	Median/mean age	Follow-up
RE-LY	2009	Dabigatran 150 mg twice daily	6,076 vs 6,022	71 years	2.0 years
ROCKET-AF	2011	Rivaroxaban 20 mg once daily	7,111 vs 7,125	73 years	1.9 years
ARISTOTLE	2011	Apixaban 5 mg twice daily	9,088 vs 9,052	70 years	1.8 years
ENGAGE AF-TIMI 48	2013	Edoxaban 60 mg once daily	7,012 vs 7,012	72 years	2.8 years

Stroke or Systemic Embolism

Across the four pivotal trials, DOAC therapy was associated with a significantly lower risk of stroke or systemic embolism than warfarin (RR 0.81, 95% CI 0.73–0.91; $I^2=47\%$; $p<0.0001$) [8].

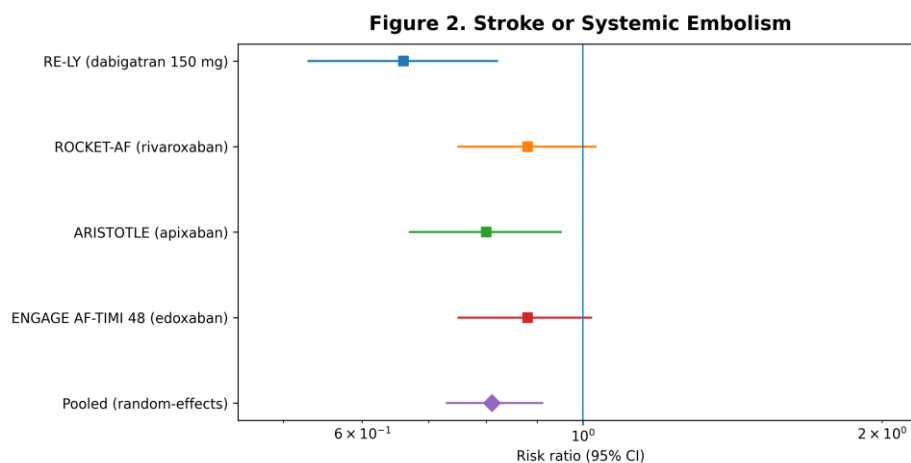


Figure 2. Pooled risk ratios for stroke or systemic embolism. Quantitative estimates correspond to the principal standard/high-dose regimens of the four pivotal trials

Major Bleeding

The pooled risk of major bleeding was numerically lower with DOACs but did not reach conventional statistical significance (RR 0.86, 95% CI 0.73–1.00; $I^2=83\%$; $p=0.06$) [8]. The high heterogeneity reflects differences in bleeding definitions, trial populations, and warfarin management across the pivotal studies.

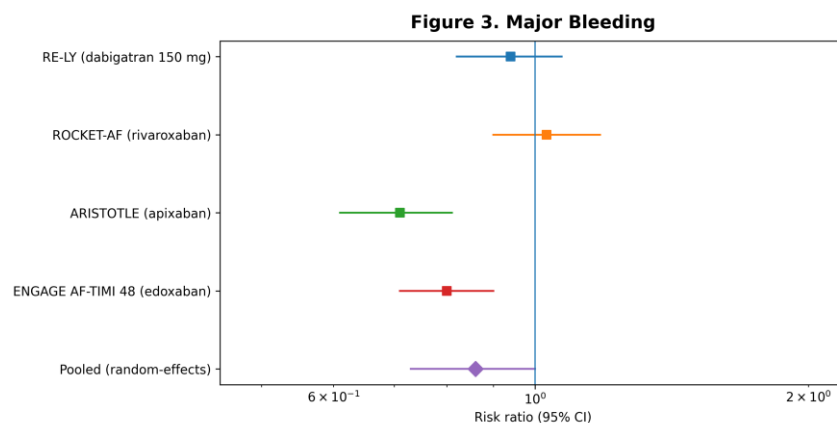


Figure 3. Pooled risk ratios for major bleeding. Quantitative estimates correspond to the principal standard/high-dose regimens of the four pivotal trials

Secondary Outcomes

Table 2. Pooled efficacy and safety outcomes from the four pivotal randomized trials [8]

Outcome	Pooled RR	95% CI	I ²	P value
Stroke/systemic embolism	0.81	0.73–0.91	47%	<0.0001
Major bleeding	0.86	0.73–1.00	83%	0.06
Intracranial hemorrhage	0.48	0.39–0.59	32%	<0.0001
Gastrointestinal bleeding	1.25	1.01–1.55	74%	0.043
All-cause mortality	0.90	0.85–0.95	0%	0.0003

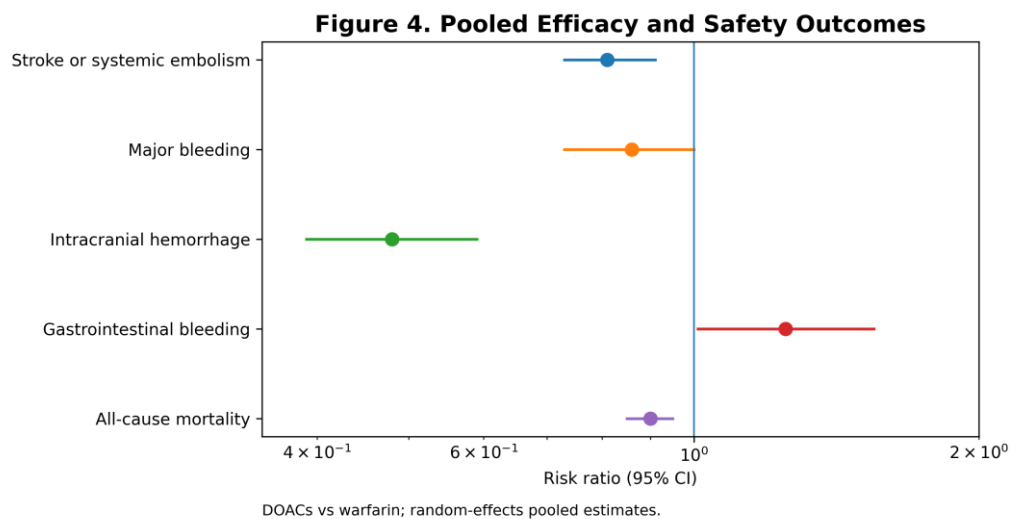


Figure 4. Summary of pooled efficacy and safety outcomes. Values are RR (95% CI)

Intracranial Hemorrhage

DOACs were associated with a substantial reduction in intracranial hemorrhage compared with warfarin (RR 0.48, 95% CI 0.39–0.59; I²=32%; p<0.0001) [8]. This finding was consistent across the pivotal trials and represents the most consistent major bleeding-related safety signal of the class.

Gastrointestinal Bleeding

Gastrointestinal bleeding was increased with DOAC therapy compared with warfarin (RR 1.25, 95% CI 1.01–1.55; I²=74%; p=0.043) [8]. The substantial heterogeneity indicates that the magnitude of this effect differed across agents and trial populations.

All-Cause Mortality

All-cause mortality was lower among patients receiving DOACs (RR 0.90, 95% CI 0.85–0.95; I²=0%; p=0.0003) [8]. The pooled result indicates a modest relative reduction in mortality across the four pivotal trials.

Discussion

This systematic review and meta-analysis of four pivotal randomized controlled trials summarizes the comparative efficacy and safety of principal standard/high-dose DOAC regimens versus warfarin in AF. The pooled results show lower risks of stroke or systemic embolism, intracranial hemorrhage, and all-cause mortality with DOACs. Major bleeding was not significantly different overall, while gastrointestinal bleeding was increased. The reduction in stroke or systemic embolism was consistent with the individual pivotal trials and the established evidence base [4–8]. The pooled RR of 0.81 corresponds to an approximately 19% relative reduction in stroke or systemic embolism. Importantly, this pooled estimate should be interpreted in the context of differences in trial populations and warfarin control. The major bleeding analysis requires particular caution. Although the point estimate favored DOACs, the confidence interval reached 1.00 and heterogeneity was high (I²=83%). The magnitude of benefit differed among agents, with larger reductions reported in ARISTOTLE and ENGAGE AF-TIMI 48 than in RE-LY and ROCKET-AF [8].

Intracranial hemorrhage showed a consistent and clinically important reduction (RR 0.48). In contrast, gastrointestinal bleeding was increased overall (RR 1.25), with substantial between-trial heterogeneity. These findings illustrate why the overall bleeding profile of DOACs should not be described simply as uniformly safer across all bleeding sites. The reduction in all-cause mortality was modest but statistically significant. However, mortality should be interpreted as a pooled outcome across trials with different populations, treatment regimens, follow-up durations, and definitions of treatment

exposure. The contemporary ESC guideline recommends DOACs in preference to vitamin K antagonists for eligible patients with AF, while noting important exceptions such as mechanical heart valves and moderate-to-severe mitral stenosis [2]. The present findings are consistent with the direction of those recommendations, but treatment choice remains dependent on patient-specific factors.

Strengths

Strengths include restriction to large randomized controlled trials, inclusion of the four pivotal phase III trials, assessment of both thromboembolic and bleeding outcomes, and use of random-effects synthesis for pooled estimates.

Limitations

Several limitations should be acknowledged. First, the quantitative synthesis is restricted to the principal standard/high-dose regimen from each pivotal trial and therefore does not represent every approved dose strategy. Second, the four trials differed in patient risk profiles, follow-up duration, outcome definitions, and quality of warfarin control. Third, major bleeding and gastrointestinal bleeding showed substantial heterogeneity. Fourth, this analysis is based on aggregate trial-level data rather than individual patient data. Finally, the pooled estimates correspond closely to the previously published meta-analysis by Ruff et al.; therefore, the present manuscript should be considered a synthesis/replication of the pivotal-trial evidence rather than a novel re-estimation unless the original RevMan dataset and an independently specified analysis plan are available [8]. Future research should focus on individual-patient-data meta-analysis, clinically relevant comparisons between individual DOACs, and integration of randomized and contemporary real-world evidence.

Conclusion

In the four pivotal randomized trials, principal standard/high-dose DOAC regimens were associated with lower risks of stroke or systemic embolism, intracranial hemorrhage, and all-cause mortality than warfarin. Major bleeding was not significantly different overall, whereas gastrointestinal bleeding was increased. These findings support the established use of DOACs in eligible patients with AF, while emphasizing that anticoagulant selection should account for bleeding risk, renal function, drug interactions, and contraindications.

Conflict of Interest

The authors declare no conflict of interest.

Funding

No external funding was received for this work.

Ethics Approval

Not applicable; this study used previously published aggregate data and did not involve direct contact with human participants.

Data Availability

The data synthesized in this review are derived from the published reports of the included randomized controlled trials. No individual patient-level data were accessed.

Detailed Data-Extraction Table

Trial & Year	DOAC & Regimen	Outcome	DOAC Events / N	Warfarin Events / N	Effect Estimate (HR/RR)	95% CI	Data Source
RE-LY (2009)	Dabigatran 150 mg BID	Stroke / Systemic Embolism	134 / 6,076	202 / 6,022	HR 0.66	0.53 – 0.82	Connolly 2009 / Ruff 2014
RE-LY (2009)	Dabigatran 150 mg BID	Major Bleeding	399 / 6,076	397 / 6,022	HR 1.01	0.88 – 1.17	Connolly 2009 / Ruff 2014
RE-LY (2009)	Dabigatran 150 mg BID	Intracranial Hemorrhage	38 / 6,076	90 / 6,022	HR 0.42	0.28 – 0.62	Connolly 2009 / Ruff 2014
RE-LY (2009)	Dabigatran 150 mg BID	All-Cause Mortality	668 / 6,076	772 / 6,022	HR 0.88	0.79 – 0.99	Connolly 2009 / Ruff 2014
ROCKET-AF (2011)	Rivaroxaban 20 mg OD	Stroke / Systemic Embolism	189 / 7,111	243 / 7,125	HR 0.79	0.65 – 0.96	Patel 2011 / Ruff 2014
ROCKET-AF (2011)	Rivaroxaban 20 mg OD	Major Bleeding	395 / 7,111	386 / 7,125	HR 1.04	0.90 – 1.20	Patel 2011 / Ruff 2014
ROCKET-AF (2011)	Rivaroxaban 20 mg OD	Intracranial Hemorrhage	55 / 7,111	84 / 7,125	HR 0.67	0.47 – 0.94	Patel 2011 / Ruff 2014
ROCKET-AF (2011)	Rivaroxaban 20 mg OD	All-Cause Mortality	564 / 7,111	550 / 7,125	HR 1.03	0.91 – 1.17	Patel 2011 / Ruff 2014
ARISTOTLE (2011)	Apixaban 5 mg BID	Stroke / Systemic Embolism	212 / 9,088	265 / 9,052	HR 0.79	0.66 – 0.95	Granger 2011 / Ruff 2014

ARISTOTLE (2011)	Apixaban 5 mg BID	Major Bleeding	327 / 9,088	462 / 9,052	HR 0.69	0.60 – 0.80	Granger 2011 / Ruff 2014
ARISTOTLE (2011)	Apixaban 5 mg BID	Intracranial Hemorrhage	40 / 9,088	93 / 9,052	HR 0.42	0.30 – 0.58	Granger 2011 / Ruff 2014
ARISTOTLE (2011)	Apixaban 5 mg BID	All-Cause Mortality	603 / 9,088	669 / 9,052	HR 0.89	0.80 – 0.99	Granger 2011 / Ruff 2014
ENGAGE AF-TIMI 48 (2013)	Edoxaban 60 mg OD	Stroke / Systemic Embolism	232 / 7,012	296 / 7,012	HR 0.79	0.63 – 0.99	Giugliano 2013 / Ruff 2014
ENGAGE AF-TIMI 48 (2013)	Edoxaban 60 mg OD	Major Bleeding	353 / 7,012	524 / 7,012	HR 0.80	0.71 – 0.91	Giugliano 2013 / Ruff 2014
ENGAGE AF-TIMI 48 (2013)	Edoxaban 60 mg OD	Intracranial Hemorrhage	61 / 7,012	118 / 7,012	HR 0.53	0.38 – 0.73	Giugliano 2013 / Ruff 2014
ENGAGE AF-TIMI 48 (2013)	Edoxaban 60 mg OD	All-Cause Mortality	779 / 7,012	895 / 7,012	HR 0.87	0.79 – 0.96	Giugliano 2013 / Ruff 2014

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