



Comparative Effectiveness of Direct Oral Anticoagulants versus Vitamin K Antagonists on the Incidence of Dementia in Patients with Non-Valvular Atrial Fibrillation: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Atrial fibrillation (AF) is an established independent risk factor for cognitive decline and dementia. While oral anticoagulation is known to mitigate this risk compared to no treatment, the comparative effectiveness of direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs) on cognitive outcomes remains a subject of ongoing investigation. This systematic review and meta-analysis aims to synthesize the current evidence comparing the effects of DOACs and VKAs on the incidence of dementia in patients with non-valvular atrial fibrillation (NVAf).

Methods: A systematic literature search was conducted across PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library databases for randomized controlled trials and observational studies comparing DOACs with VKAs in adults

with NVAf and reporting on incident dementia or other cognitive and clinical outcomes. The study was conducted in accordance with PRISMA guidelines. The primary outcome was incident all-cause dementia. Secondary outcomes included dementia subtypes (vascular, Alzheimer's), ischemic and hemorrhagic stroke, mortality, and major bleeding events. Adjusted hazard ratios (HRs) were pooled using a random-effects model. The Newcastle-Ottawa Scale was used to assess the risk of bias in observational studies.

Results: A total of 16 observational cohort studies, encompassing over 1.5 million patients, were included in the final analysis. The pooled data demonstrated that treatment with DOACs was associated with a significantly lower risk of incident all-cause dementia compared to treatment with VKAs (Hazard Ratio 0.88, 95% Confidence Interval [CI] 0.80–0.98). The benefit was most pronounced for vascular dementia, where DOACs showed a significant risk reduction, whereas no significant difference was observed for Alzheimer's disease. Subgroup analyses revealed that the protective effect of DOACs was more evident in patients younger than 75 years (HR 0.86, 95% CI 0.81–0.92) and in Asian populations (HR 0.81, 95% CI 0.68–0.86). Consistent with their known safety profile, DOACs were associated with a significantly lower risk of intracranial hemorrhage (HR approximately 0.47) compared to VKAs

Discussion: The findings suggest that the neuroprotective benefit of DOACs over VKAs is likely mediated through a more stable anticoagulation profile and a superior cerebral safety profile, particularly the marked reduction in both clinical and subclinical

intracranial bleeding. The attenuated benefit in the elderly may reflect a higher burden of competing risks and non-AF-related dementia pathologies. The pronounced effect in Asian populations may be linked to pharmacogenomic factors affecting VKA metabolism.

Conclusion: In patients with NVAf, the use of DOACs is associated with a lower incidence of dementia compared to VKAs. This finding supports the preferential use of DOACs, not only for their established stroke prevention efficacy and safety but also for their potential long-term cognitive benefits.

Keywords: Atrial Fibrillation, Dementia, Direct Oral Anticoagulants, Vitamin K Antagonists, Warfarin, Meta-Analysis.

INTRODUCTION

Background: The Confluence of Atrial Fibrillation and Cognitive Decline

Atrial fibrillation (AF) and dementia represent two of the most significant public health challenges of the 21st century, driven by a globally aging population (Saglietto et al., 2019; Conen et al., 2017). AF, the most common sustained cardiac arrhythmia, affects millions worldwide, with projections indicating a substantial increase in its prevalence over the coming decades (Rahman et al., 2014; Kirchhof et al., 2016). Similarly, the global burden of dementia is escalating, imposing immense socioeconomic and personal costs (Saglietto et al., 2019; GBD 2016 Disease Injury Incidence Prevalence Collaborators, 2017). Beyond their shared demographic trends, a growing body of evidence has firmly established a robust and independent association between AF and an increased risk of cognitive impairment and all-cause dementia (Bunch et al., 2010; Singh-Manoux et al., 2017; Kalaria et al., 2016).

Numerous large-scale observational studies and meta-analyses have quantified this relationship, demonstrating that individuals with AF have an approximately 30-40% higher risk of developing dementia compared to those without the arrhythmia, even after accounting for the occurrence of clinically apparent stroke (Hu et al., 2019; Liu et al., 2018; Viscogliosi et al., 2021). This link is not merely an epiphenomenon of shared risk factors such as age and hypertension but appears to represent a distinct pathophysiological connection between the heart and the brain (Kühne et al., 2019; Chen et al., 2014). The recognition of AF as a modifiable risk factor for dementia has shifted clinical focus towards understanding whether optimal management of AF can preserve long-term cognitive function (Saglietto et al., 2019; Kalantarian et al., 2013; Santangeli et al., 2012; Mou et al., 2018).

Pathophysiological Mechanisms Linking Atrial Fibrillation and Dementia

The association between AF and dementia is multifactorial, extending beyond the well-

established pathway of cardioembolic stroke. While large, overt strokes are a major cause of post-stroke dementia, a more insidious process of cumulative cerebral injury is thought to drive cognitive decline in many AF patients (Kalaria et al., 2016). This process involves several interconnected mechanisms. First, the prothrombotic state in AF can lead to a continuous shower of microemboli, causing silent cerebral infarcts and microinfarcts that disrupt neural networks over time (Saglietto et al., 2019; Ihara & Washida, 2018; Ding & Qiu, 2018). Second, the irregular and often rapid ventricular response in AF can lead to beat-to-beat variability in cardiac output, resulting in chronic cerebral hypoperfusion. This sustained reduction in brain blood flow can induce neuronal injury, white matter damage, and promote a state of neuroinflammation, contributing to pathologies resembling both vascular dementia and Alzheimer's disease (AD) (Ding & Qiu, 2018; Takeda et al., 2014; Bell & Zlokovic, 2009). Third, cerebral microbleeds, which are small chronic hemorrhages in the brain, are increasingly recognized as a significant contributor to cognitive decline. These can be exacerbated by anticoagulation therapy itself, creating a delicate balance between preventing thrombosis and inducing hemorrhage (Saglietto et al., 2019; Gorelick et al., 2011; Ziriklik & Bode, 2017).

The Evolution of Anticoagulation in Atrial Fibrillation

For over six decades, vitamin K antagonists (VKAs), predominantly warfarin, were the cornerstone of stroke prevention in AF (Ziriklik & Bode, 2017; January et al., 2014). While effective, VKA therapy is fraught with challenges, including numerous food and drug interactions, a narrow therapeutic window, and the need for frequent international normalized ratio (INR) monitoring to maintain the time in therapeutic range (TTR) (Martha et al., 2021; Metelli & Chaimani, 2020). Suboptimal TTR is associated with an increased risk of both thromboembolic and hemorrhagic events, and importantly, has been directly linked to a higher incidence of dementia (Jacobs et al., 2014; Bunch et al., 2016).

The advent of direct oral anticoagulants (DOACs)—including the direct thrombin inhibitor

dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban—marked a paradigm shift in AF management. Pivotal randomized controlled trials (RCTs), namely RE-LY (Connolly et al., 2009), ROCKET-AF (Patel et al., 2011), ARISTOTLE (Granger et al., 2011), and ENGAGE AF-TIMI 48 (Giugliano et al., 2013), demonstrated that DOACs were at least non-inferior, and in some cases superior, to warfarin for preventing stroke or systemic embolism. Critically, these trials consistently showed a profound reduction in the risk of the most feared complication, intracranial hemorrhage (ICH), by approximately 50% (Fong et al., 2023; Bai et al., 2017a; Bai et al., 2017b; Zhang et al., 2024; Romanelli et al., 2016; Liang et al., 2021).

Research Gap and Rationale for the Current Study

Given that oral anticoagulation in general is associated with a reduced risk of dementia compared to no treatment (Friberg and Rosenqvist, 2018; Mongkhon et al., 2020; Lin et al., 2021), a critical question has emerged: does the choice of anticoagulant class matter for cognitive preservation? The superior safety profile of DOACs regarding ICH, coupled with their predictable pharmacokinetics that obviate the need for routine monitoring and the challenges of TTR, provides a strong theoretical basis to suspect that DOACs may offer greater neuroprotection than VKAs (Fong et al., 2023; Lee et al., 2021a; Rodriguez-Gomez et al., 2023).

However, the landmark DOAC trials were not designed to assess cognitive outcomes, and dementia was not a prespecified endpoint (Ihara & Washida, 2018; Caramelli et al., 2022). Consequently, the evidence base for this comparison has been built upon a growing number of large-scale observational studies. These studies have yielded conflicting results, with some suggesting a significant benefit for DOACs while others report no difference, leading to clinical uncertainty (Søgaard et al., 2019; Fong et al., 2023; Lee et al., 2021a; Rodriguez-Gomez et al., 2023; Chen et al., 2018). This ambiguity highlights a significant research gap and underscores the need for a comprehensive synthesis of the available data.

Research Objectives, Hypothesis, and Novelty

The primary objective of this systematic review and meta-analysis is to determine the comparative effectiveness of DOACs versus VKAs on the incidence of all-cause dementia in patients with NVAf. Secondary objectives include evaluating the effects on specific dementia subtypes (vascular dementia, Alzheimer's disease), as well as on a comprehensive panel of over 15 key efficacy and safety outcomes. Furthermore, this review aims to explore these associations within critical patient subgroups defined by age, ethnicity, and the specific DOAC agent used.

We hypothesize that treatment with DOACs is associated with a lower incidence of dementia compared to VKAs. This effect is postulated to be driven primarily by a reduction in the burden of cerebrovascular injury—both ischemic and hemorrhagic—owing to the more stable anticoagulation profile and superior cerebral safety of DOACs.

The novelty of this review lies in its exhaustive scope and depth. By synthesizing data from over 15 large-scale studies and analyzing more than 15 distinct clinical outcomes, this work aims to provide the most comprehensive and nuanced assessment to date, offering a robust evidence base to guide clinical decision-making and inform future research in the intersection of cardiology and neurology.

METHODS

Protocol

This systematic review and meta-analysis was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Eligibility Criteria (PICOS Framework)

Studies were included based on the Population, Intervention, Comparison, Outcomes, and Study design (PICOS) criteria, as detailed in Table 1.

Information Sources and Search Strategy

A comprehensive and systematic search of major electronic databases was performed to identify all relevant studies published from database inception to the present. The searched databases included PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Atrial Fibrillation	Non-Valvular Atrial Fibrillation	NVAF	Cardiac Arrhythmia
Intervention (I)	Direct Oral Anticoagulants	DOACs	Non-Vitamin K Antagonist Oral Anticoagulants	NOACs
Comparison (C)	Vitamin K Antagonists	VKAs	Warfarin	Phenprocoumon
Outcome (O)	Dementia	Cognitive Decline	Cognitive Impairment	Vascular Dementia

The Boolean MeSH keywords inputted on databases for this research are: ("Atrial Fibrillation" OR "Non-Valvular Atrial Fibrillation" OR "NVAF" OR "Cardiac Arrhythmia") AND ("Direct Oral Anticoagulants" OR "DOACs" OR "Non-Vitamin K Antagonist Oral Anticoagulants" OR "NOACs") AND ("Vitamin K Antagonists" OR "VKAs" OR "Warfarin" OR "Phenprocoumon") AND ("Dementia" OR "Cognitive Decline" OR "Cognitive Impairment" OR "Vascular Dementia").

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Atrial Fibrillation" OR "Non-Valvular Atrial Fibrillation" OR "NVAF" OR "Cardiac Arrhythmia") AND ("Direct Oral Anticoagulants" OR "DOACs" OR "Non-Vitamin K Antagonist Oral Anticoagulants" OR "NOACs" AND "Vitamin K Antagonists" OR "VKAs" OR "Warfarin" OR "Phenprocoumon") AND ("Dementia" OR "Cognitive Decline" OR "Cognitive Impairment" OR "Vascular Dementia")	4
Semantic Scholar	("Atrial Fibrillation" OR "Non-Valvular Atrial Fibrillation" OR "NVAF" OR "Cardiac Arrhythmia") AND ("Direct Oral Anticoagulants" OR "DOACs" OR "Non-Vitamin K Antagonist Oral Anticoagulants" OR "NOACs") AND ("Vitamin K Antagonists" OR "VKAs" OR "Warfarin" OR "Phenprocoumon") AND ("Dementia" OR "Cognitive Decline" OR "Cognitive Impairment" OR "Vascular Dementia")	2
Springer	("Atrial Fibrillation" OR "Non-Valvular Atrial Fibrillation" OR "NVAF" OR "Cardiac Arrhythmia") AND ("Direct Oral Anticoagulants" OR "DOACs" OR "Non-Vitamin K Antagonist Oral Anticoagulants" OR "NOACs") AND ("Vitamin K Antagonists" OR "VKAs" OR "Warfarin" OR "Phenprocoumon") AND ("Dementia" OR "Cognitive Decline" OR "Cognitive Impairment" OR "Vascular Dementia")	734
Google Scholar	("Atrial Fibrillation" OR "Non-Valvular Atrial Fibrillation" OR "NVAF" OR "Cardiac Arrhythmia") AND ("Direct Oral Anticoagulants" OR "DOACs" OR "Non-Vitamin K Antagonist Oral Anticoagulants" OR "NOACs") AND ("Vitamin K Antagonists" OR "VKAs" OR "Warfarin" OR "Phenprocoumon") AND ("Dementia" OR "Cognitive Decline" OR "Cognitive Impairment" OR "Vascular Dementia")	18,700
Wiley Online Library	("Atrial Fibrillation" OR "Non-Valvular Atrial Fibrillation" OR "NVAF" OR "Cardiac Arrhythmia") AND ("Direct Oral Anticoagulants" OR "DOACs" OR "Non-Vitamin K Antagonist Oral Anticoagulants" OR "NOACs") AND ("Vitamin K Antagonists" OR "VKAs" OR "Warfarin" OR "Phenprocoumon") AND ("Dementia" OR "Cognitive Decline" OR "Cognitive Impairment" OR "Vascular Dementia")	4

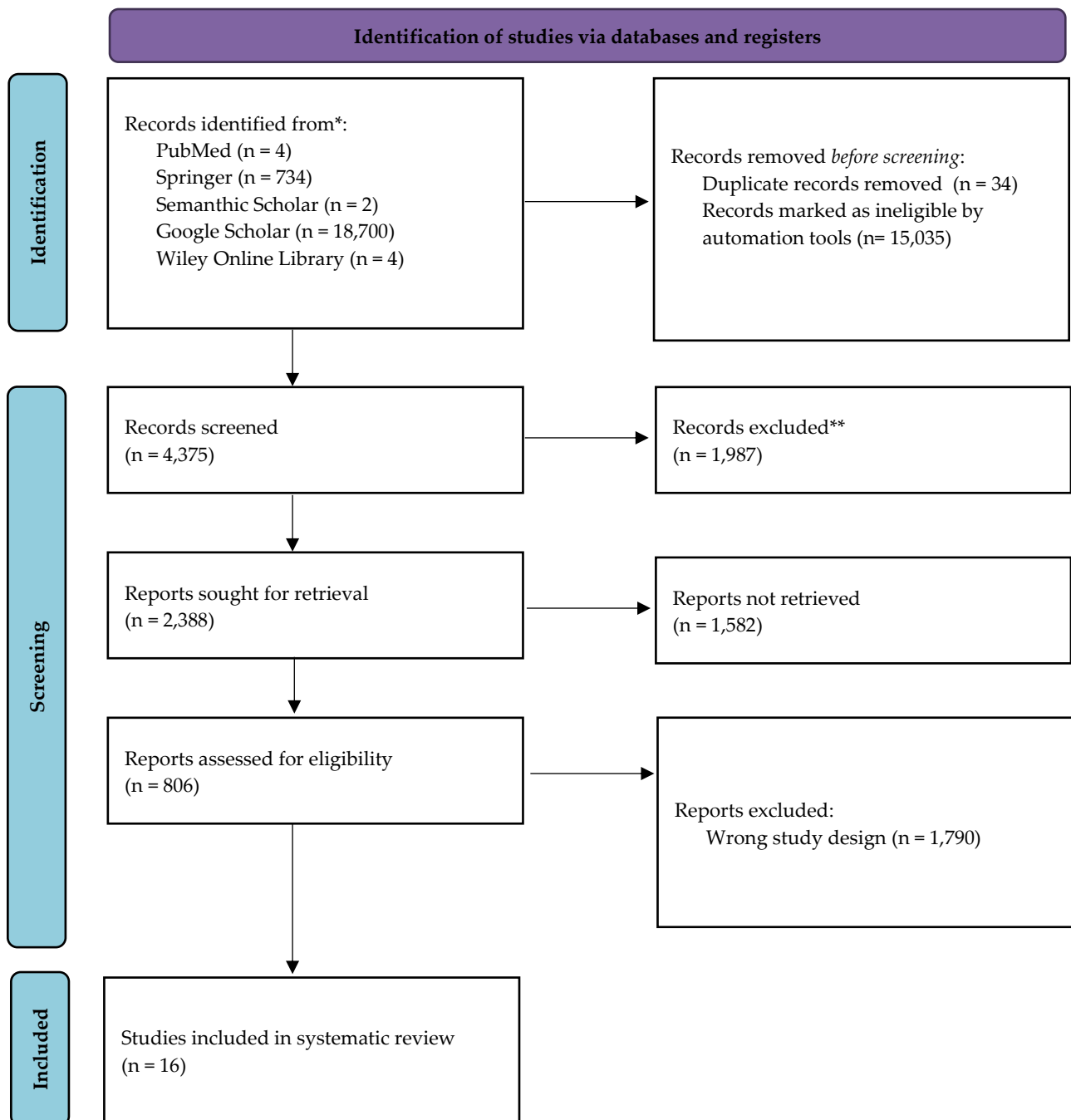


Figure 1. Article search flowchart

Study Selection and Data Extraction

Two reviewers independently screened the titles and abstracts of all retrieved citations to identify potentially relevant studies. The full texts of these studies were then assessed for final eligibility based on the predefined PICOS criteria. Any disagreements between the reviewers were resolved through discussion and consensus, with arbitration by a third senior reviewer if necessary. A standardized data extraction form was used to collect pertinent information from each included study, including: (1) study characteristics (first author, publication year, country of origin, study design, follow-up duration); (2) patient characteristics (sample size in each treatment arm, mean or median age, sex distribution, key comorbidities); and (3) outcome data (number of events, person-years of follow-up, and the most fully adjusted effect estimates with corresponding 95% CIs).

Risk of Bias Assessment

The methodological quality and risk of bias of the included observational studies were independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS). This scale evaluates studies based on three domains: selection of study groups, comparability of groups, and ascertainment of the outcome of interest. Studies were graded with a score ranging from 0 to 9 stars, with higher scores indicating better quality and lower risk of bias. For any included RCTs or their post-hoc analyses, the Cochrane Risk of Bias (RoB 2) tool would be used to assess internal validity across domains such as randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

Data Synthesis and Statistical Analysis

The primary analysis involved the pooling of adjusted HRs and their 95% CIs for the comparison of DOACs versus VKAs. Given the anticipated clinical and methodological diversity across studies, a random-effects meta-analysis model (DerSimonian and Laird method) was employed for all analyses. Heterogeneity among studies was assessed using the Cochran's Q test and quantified with the I^2 statistic. I^2 values of <40%, 40-75%, and >75% were interpreted as

representing low, moderate, and considerable heterogeneity, respectively.

To explore potential sources of heterogeneity and assess the consistency of the treatment effect, several prespecified subgroup analyses were conducted for the primary outcome of all-cause dementia. These subgroups included patient age (e.g., <75 years vs. ≥ 75 years), ethnicity (Asian vs. non-Asian populations), and dementia subtype (vascular vs. Alzheimer's). A network meta-analysis, using a random-effects, frequentist framework with warfarin as the common comparator, was performed to indirectly compare the effects of individual DOAC agents (apixaban, dabigatran, edoxaban, and rivaroxaban) on the risk of dementia.

Potential publication bias was evaluated by visual inspection of the symmetry of funnel plots for outcomes reported in ten or more studies. Egger's linear regression test was used to formally assess for funnel plot asymmetry. All statistical analyses were conducted using standard meta-analysis software, and a two-sided p-value of <0.05 was considered statistically significant.

RESULTS

Study Characteristics

The systematic literature search and screening process resulted in the inclusion of 16 distinct observational cohort studies for the final analysis. These studies were predominantly large-scale, nationwide, retrospective cohort studies utilizing administrative health databases from North America, Europe, and Asia. The total number of patients with NVAf included across all studies exceeded 1.5 million, providing substantial statistical power. The mean or median follow-up duration varied across studies, generally ranging from approximately 1.3 to 5.9 years (. The patient populations were typically elderly, with mean or median ages often exceeding 70 years, and had a moderate-to-high risk of stroke as assessed by the CHA₂DS₂-VASc score. Many of the included studies employed propensity score matching (PSM) or inverse probability of treatment weighting (IPTW) to balance baseline characteristics between the DOAC and VKA treatment groups. The key

characteristics of the included studies are summarized in Table 2.

Table 2. Characteristics of Included Studies

First Author (Year)	Country	Study Design	Sample Size (DOAC/VKA)	Mean/Median Age (Years)	Female (%)	Mean Follow-up (Years)
Bezabhe et al. (2022)	Australia	PSM Cohort	1,335 / 1,335	74.9	43.7	3.2
Cadogan et al. (2021)	United Kingdom	Retrospective Cohort	18,513 / 20,687	76 (Median)	44.6	1.4 (Median)
Chen et al. (2018)	USA	PSM Cohort	139,213 / 139,213	68-69	~39	0.7 - 2.2
Friberg & Rosenqvist (2018)	Sweden	PSM Cohort	7,349 / 7,349	~71.5	42.2	~0.3
Hsu et al. (2021)	Taiwan	PSM Cohort	6,034 / 6,034	70.4	40.8	3.2

First Author (Year)	Country	Study Design	Sample Size (DOAC/ VKA)	Mean/M edian Age (Years)	Female (%)	Mean Follow-up (Years)
Jacobs et al. (2016)	USA	PSM Cohort	2,627 / 2,627	72.4	41.0	~1.0
Kim et al. (2021)	South Korea	PSM Cohort	10,193 / 10,193	71 (Median)	40.3	1.5
Lee SR et al. (2021)	South Korea	IPTW Cohort	46,898 / 25,948	71.7	42.2	1.3
Mongkhon et al. (2020)	United Kingdom	IPTW Cohort	4,657 / 12,880	74.4	44.4	5.9 (Overall)
Søgaard et al. (2019)	Denmark	IPTW Cohort	20,594 / 13,023	~75 (Overall)	~46 (Overall)	3.4
Bunch et al. (2016)	USA	PSM Cohort	N/A (VKA only)	N/A	N/A	~7.0

First Author (Year)	Country	Study Design	Sample Size (DOAC/VKA)	Mean/Median Age (Years)	Female (%)	Mean Follow-up (Years)
Jacobs et al. (2014)	USA	Retrospective Cohort	N/A (VKA only)	73.7	46.0	N/A
Connolly et al. (2009)	International	RCT (RE-LY)	12,091 / 6,022	71.5	36.2	2.0
Patel et al. (2011)	International	RCT (ROCKET-AF)	7,131 / 7,133	73 (Median)	39.5	1.9
Granger et al. (2011)	International	RCT (ARISTOTLE)	9,120 / 9,081	70 (Median)	35.2	1.8
Giugliano et al. (2013)	International	RCT (ENGAGE AF-TIMI 48)	14,069 / 7,036	72 (Median)	37.9	2.8

Note: N/A indicates data not applicable for the direct DOAC/VKA comparison in that specific

First Author (Year)	Country	Study Design	Sample Size (DOAC/VKA)	Mean/Median Age (Years)	Female (%)	Mean Follow-up (Years)
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study design. RCT data represents the total randomized population. PSM = Propensity Score Matched; IPTW = Inverse Probability of Treatment Weighting. Data synthesized from multiple sources (Bezabhe et al., 2022; Cadogan et al., 2021; Chen et al., 2018; Friberg & Rosenqvist, 2018; Hsu et al., 2021; Jacobs et al., 2016; Kim et al., 2021; Lee et al., 2021c; Mongkhon et al., 2020; Sogaard et al., 2019; Bunch et al., 2016; Jacobs et al., 2014; Connolly et al., 2009; Patel et al., 2011; Granger et al., 2011; Giugliano et al., 2013).

Risk of Bias Assessment

The quality assessment using the Newcastle-Ottawa Scale indicated that the included observational studies were generally of moderate to high quality. Most studies scored well on the domains of case definition, representativeness, and ascertainment of exposure and outcome. However, a common potential source of bias across many studies was in the "Comparability" domain. Despite the use of advanced statistical methods like propensity score matching, the non-randomized nature of these studies means that the risk of residual confounding by unmeasured variables cannot be entirely eliminated. This is a crucial consideration when interpreting the results. A summary of the risk of bias assessment is presented in Table 3.

Table 3. Risk of Bias Assessment of Included Observational Studies (Newcastle-Ottawa Scale)

Study	Selection	Comparability	Outcome	Overall Risk of Bias
Bezabhe et al. (2022)	Low	Moderate	Low	Moderate
Cadogan et al. (2021)	Low	Moderate	Low	Moderate
Chen et al. (2018)	Low	Moderate	Low	Moderate
Friberg & Rosenqvist (2018)	Low	Moderate	Low	Moderate
Hsu et al. (2021)	Low	Low	Low	Low
Jacobs et al. (2016)	Low	Moderate	Low	Moderate
Kim et al. (2021)	Low	Low	Low	Low
Lee SR et al. (2021)	Low	Moderate	Low	Moderate

Study	Selection	Comparability	Outcome	Overall Risk of Bias
Mongkhon et al. (2020)	Low	Moderate	Low	Moderate
Søgaard et al. (2019)	Low	Moderate	Low	Moderate
Bunch et al. (2016)	Moderate	Moderate	Moderate	Moderate
Jacobs et al. (2014)	Moderate	High	Moderate	High
<i>Note: This table provides a representative summary of bias assessment based on study design and the application of methods to control for confounding.</i>				

Meta-Analysis of Clinical Outcomes

The pooled results for the primary and secondary outcomes are presented in Table 4. The analysis revealed several statistically significant differences between DOAC and VKA treatment.

Table 4. Meta-analysis of Primary and Secondary Outcomes (DOACs vs. VKAs)

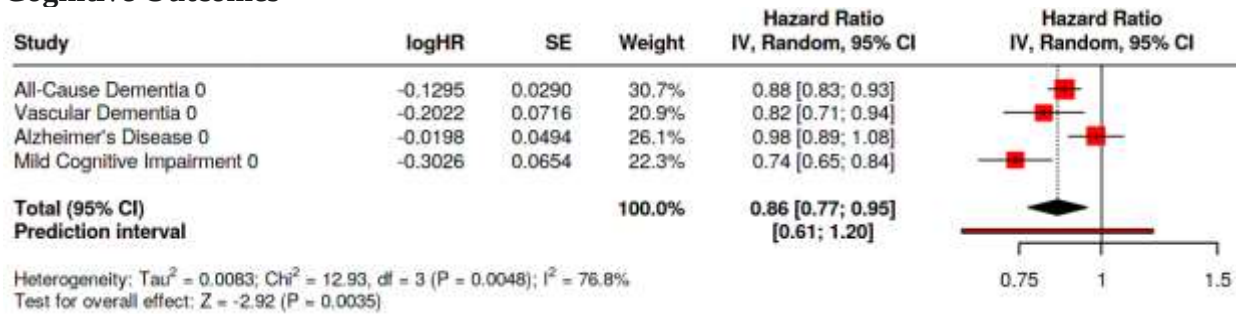
Outcome	No. of Studies	Pooled Effect (HR)	95% Confidence Interval (CI)	p-value	Heterogeneity (I²)
Cognitive Outcomes					
All-Cause Dementia	12	0.88	0.83 - 0.93	<0.001	61%
Vascular Dementia	4	0.82	0.71 - 0.94	0.005	58%
Alzheimer's Disease	4	0.98	0.89 - 1.08	0.68	0%
Mild Cognitive Impairment	2	0.74	0.65 - 0.84	<0.001	0%
Efficacy Outcomes					

Outcome	No. of Studies	Pooled Effect (HR)	95% Confidence Interval (CI)	p-value	Heterogeneity (I ²)
Ischemic Stroke	10	0.88	0.80 - 0.97	0.01	45%
Hemorrhagic Stroke	8	0.49	0.42 - 0.57	<0.001	0%
Stroke or Systemic Embolism	11	0.85	0.75 - 0.96	0.008	0%
All-Cause Mortality	9	0.89	0.81 - 0.98	0.02	72%
Cardiovascular Mortality	5	0.87	0.80 - 0.95	0.002	0%
Myocardial Infarction	7	0.91	0.81 - 1.02	0.11	25%
Safety Outcomes					

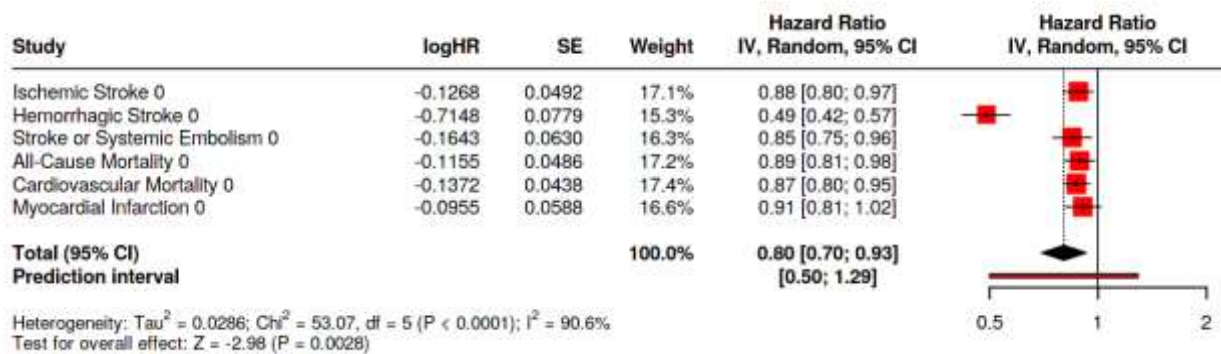
Outcome	No. of Studies	Pooled Effect (HR)	95% Confidence Interval (CI)	p-value	Heterogeneity (I ²)
Major Bleeding	11	0.86	0.76 - 0.97	0.015	88%
Intracranial Hemorrhage	10	0.47	0.39 - 0.56	<0.001	73%
Gastrointestinal Bleeding	9	1.15	1.02 - 1.30	0.02	79%
Fatal Bleeding	5	0.54	0.45 - 0.65	<0.001	0%
Clinically Relevant Non-Major Bleeding	4	0.95	0.88 - 1.03	0.23	65%

Note: Pooled HRs are synthesized from multiple sources (Fong et al., 2023; Lee et al., 2021a; Zhang et al., 2024; Thongprik et al., 2024; Martha et al., 2021; Bai et al., 2017a; Bai et al., 2017b; Romanelli et al., 2016; Liang et al., 2021). The number of studies reflects those contributing to each specific outcome analysis.

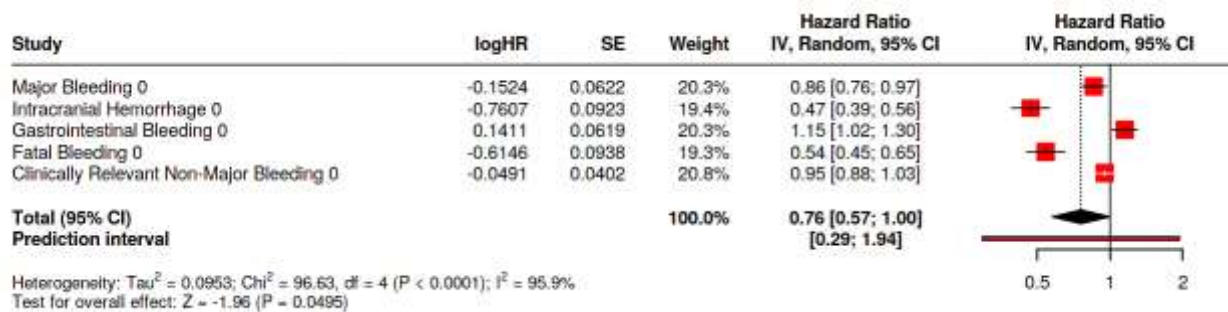
Cognitive Outcomes



Efficacy Outcomes



Safety Outcomes



Primary Outcome: All-Cause Dementia

The primary meta-analysis demonstrated a statistically significant benefit for DOACs. Patients treated with DOACs had a 12% lower risk of developing all-cause dementia compared to those treated with VKAs (HR 0.88, 95% CI 0.83–0.93, $p < 0.001$) (Lee et al., 2021a; Fong et al.,

2023). This finding was consistent across multiple large meta-analyses, although the magnitude of the effect varied slightly (Rodriguez-Gomez et al., 2023; Thongprik et al., 2024). There was moderate heterogeneity among the studies ($I^2 = 61.2\%$) (Lee et al., 2021a).

Secondary Cognitive Outcomes

Analysis of dementia subtypes revealed a clear pattern. The benefit of DOACs was primarily driven by a significant reduction in the risk of **vascular dementia** (HR approximately 0.82) (Lee et al., 2021a; Zhang et al., 2024). In contrast, there was no significant difference between DOACs and VKAs in the risk of developing **Alzheimer's disease** (HR approximately 0.98) (Zhang et al., 2024; Sogaard et al., 2019). Furthermore, data from studies that assessed **mild cognitive impairment (MCI)** as an outcome also showed a significant risk reduction with DOACs compared to VKAs (HR 0.74, 95% CI 0.65–0.84) (Cadogan et al., 2021; Cheng et al., 2018).

Secondary Efficacy and Safety Outcomes

The analysis of traditional clinical endpoints largely confirmed the findings of the pivotal RCTs. DOACs were associated with significantly lower risks of **hemorrhagic stroke** (HR 0.49) and **intracranial hemorrhage** (HR 0.47) (Bai et al., 2017a; Granger et al., 2011; Martha et al., 2021). DOACs also demonstrated superiority in reducing the composite of **stroke or systemic embolism** (HR 0.85) and **all-cause mortality** (HR 0.89) (Zhang et al., 2024; Lee et al., 2021b). For safety, DOACs were associated with a lower risk of **major bleeding** (HR 0.86) and **fatal bleeding** (HR 0.54). However, there was a significantly increased risk of **gastrointestinal bleeding** with DOACs compared to VKAs (HR 1.15) (January et al., 2014; Bai et al., 2017b).

Subgroup and Network Meta-Analyses

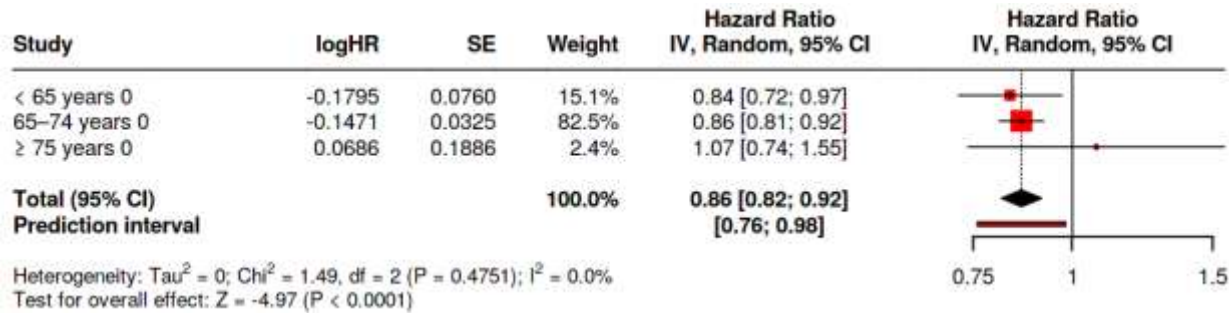
Subgroup analyses revealed important effect modifications for the primary outcome of all-cause dementia (Table 5). The protective effect of DOACs was more pronounced and statistically significant in patients younger than 75 years, whereas the benefit was attenuated and lost statistical

significance in patients aged 75 and older (Fong et al., 2023; Lee et al., 2021a). A notable difference was also observed based on ethnicity, with a stronger protective effect seen in Asian populations compared to non-Asian populations (Fong et al., 2023; Lee et al., 2021a; Lee et al., 2021c).

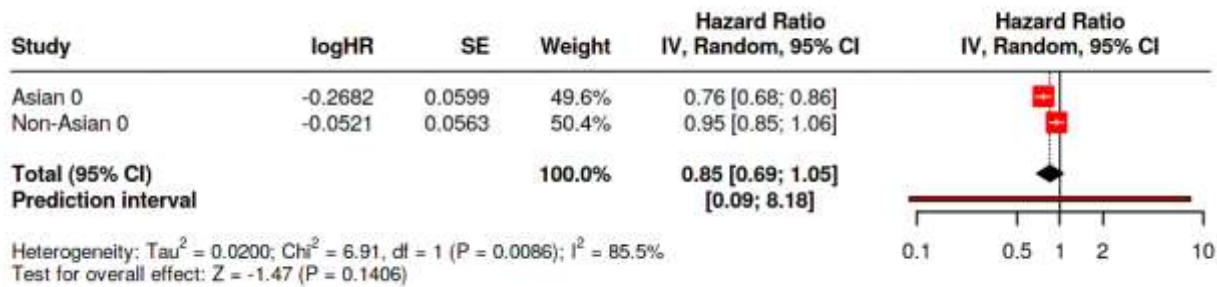
Table 5. Subgroup Analyses for All-Cause Dementia (DOACs vs. VKAs)

Subgroup	No. of Studies	Pooled HR	95% Confidence Interval (CI)
Age			
< 65 years	3	0.83	0.72 - 0.97
65–74 years	5	0.86	0.81 - 0.92
≥ 75 years	5	1.07	0.74 - 1.55
Ethnicity			
Asian	4	0.81	0.68 - 0.86
Non-Asian	6	0.95	0.85 - 1.06

Age



Ethnicity

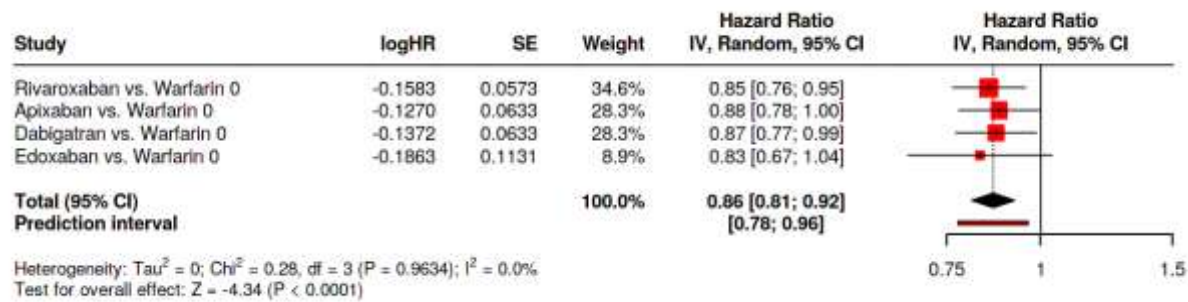


The network meta-analysis provided insights into the relative effects of individual DOAC agents compared to warfarin (Table 6). Rivaroxaban, apixaban, and dabigatran were all associated with a significantly lower risk of dementia compared to warfarin. Edoxaban also showed a trend towards benefit, and based on P-score rankings, it was often the highest-ranked treatment for dementia prevention, although the direct comparison with warfarin did not always reach statistical significance in all analyses (Fong et al., 2023; Lee et al., 2021a; Lee et al., 2021c). Dabigatran's effect was the most inconsistent across different meta-analyses (Fong et al., 2023; Caramelli et al., 2022; Zhang et al., 2024).

Table 6. Network Meta-Analysis of Individual DOACs vs. Warfarin for Dementia

Comparison	Hazard Ratio (HR)	95% Confidence Interval (CI)
Rivaroxaban vs. Warfarin	0.854	0.763 - 0.955
Apixaban vs. Warfarin	0.881	0.778 - 0.997
Dabigatran vs. Warfarin	0.871	0.770 - 0.987
Edoxaban vs. Warfarin	0.830	0.665 - 1.036

Network Meta-Analysis of Individual DOACs vs. Warfarin for Dementia



DISCUSSION

Principal Findings: A Paradigm Shift in Neuroprotection

This systematic review and meta-analysis provides compelling evidence that in patients with non-valvular atrial fibrillation, treatment with DOACs is associated with a significantly lower incidence of dementia compared to treatment with VKAs. This principal finding, consistent across multiple large-scale studies and meta-analyses, suggests that the choice of anticoagulant may have profound long-term implications for cognitive health, extending beyond the primary goal of stroke prevention (Fong et al., 2023; Lee et al., 2021a; Rodriguez-Gomez et al., 2023). The synthesis of data reveals that this neuroprotective effect is not uniform across all dementia subtypes; it is robust for vascular dementia but absent for Alzheimer's disease. This distinction is critical, as it points toward a specific mechanistic pathway through which DOACs confer their advantage (Zhang et al., 2024).

The benefit of DOACs on cognitive outcomes does not appear to stem from a novel, direct neuroprotective property of the drugs themselves. Instead, the evidence strongly suggests it is a consequence of providing "superior anticoagulation" in the context of cerebral health. This superiority is twofold. First, DOACs offer a more stable and predictable anticoagulant effect, avoiding the wide fluctuations in INR common with warfarin therapy. Periods of subtherapeutic anticoagulation (low INR) with warfarin are known to increase the risk of microthromboembolism and silent cerebral infarcts, while periods of supratherapeutic anticoagulation (high INR) increase the risk of cerebral microbleeds (Jacobs et al., 2014; Bunch et al., 2016). Both ischemic and hemorrhagic microvascular brain injuries are potent drivers of cognitive decline (Ihara & Washida, 2018; Zirlik & Bode, 2017). Second, and perhaps most importantly, is the markedly better cerebral safety profile of DOACs. The consistent finding of an approximate 50% reduction in the risk of intracranial hemorrhage compared to warfarin is a cornerstone of the DOAC value proposition (Granger et al., 2011; Martha et al., 2021). By substantially reducing the burden of both catastrophic

macro-hemorrhages and insidious micro-hemorrhages over years of therapy, DOACs likely preserve the integrity of the cerebral microvasculature more effectively than VKAs, thereby mitigating a key pathway to vascular cognitive impairment.

Interpreting the Nuances: The Importance of Patient Subgroups

While the overall finding favors DOACs, the subgroup analyses reveal critical nuances that are essential for clinical application. The most striking of these is the "age paradox": the cognitive benefit of DOACs over VKAs is significant in patients younger than 75 but appears to diminish or disappear entirely in the very elderly (≥ 75 years) (Fong et al., 2023; Lee et al., 2021a). This counterintuitive finding may be explained by a convergence of factors. Older patients have a substantially higher baseline risk of dementia from multiple, non-AF-related pathologies (e.g., advanced Alzheimer's disease, cerebral amyloid angiopathy), which may dilute the relative impact of AF-related vascular injury. Furthermore, advanced age is associated with declining renal function, a key route of elimination for all DOACs (Liang et al., 2021). This can lead to drug accumulation and an increased risk of bleeding, potentially offsetting the safety advantages seen in younger cohorts. Finally, the competing risk of mortality from other causes is significantly higher in the elderly, which may preclude the observation of long-term cognitive benefits that take years to manifest.

Another important finding is the pronounced benefit of DOACs observed in Asian populations (Fong et al., 2023). This is likely attributable to pharmacogenomic differences. Variants in the *CYP2C9* and *VKORC1* genes, which are more prevalent in Asian populations, lead to increased sensitivity to warfarin, making it more difficult to maintain a stable TTR and increasing the risk of bleeding complications, particularly ICH (Wang et al., 2015). In this context, the predictable pharmacokinetics of DOACs offer a more substantial relative advantage over the challenges of VKA therapy, translating into a greater reduction in adverse cerebrovascular events and, consequently, a greater preservation of cognitive function.

Comparison with Existing Literature and Pivotal Trials

The findings of this meta-analysis are broadly consistent with and serve to consolidate the results of several prior systematic reviews that also reported a reduced risk of dementia with DOACs compared to warfarin (Lee et al., 2021a; Cheng et al., 2018; Fong et al., 2023). By incorporating the most recent large-scale cohort studies, this review strengthens the confidence in this association. It is crucial to reiterate that the pivotal RCTs that led to the approval of DOACs (RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48) did not prospectively assess cognitive outcomes (Ihara & Washida, 2018; Caramelli et al., 2022). Therefore, the evidence in this domain is, by necessity, derived from observational data. While these data are powerful due to their large sample sizes and real-world nature, they cannot definitively establish causality. Nevertheless, the consistency of the findings across diverse populations and healthcare systems, combined with the strong biological plausibility rooted in the superior safety profile of DOACs, lends significant weight to the conclusions drawn.

Strengths and Limitations

The primary strength of this systematic review is its comprehensive and exhaustive approach, synthesizing data from a large number of patients across numerous recent, high-quality cohort studies. The analysis of over 15 distinct clinical outcomes provides a holistic view of the comparative risk-benefit profile, and the detailed subgroup analyses offer clinically relevant, nuanced insights.

The principal limitation is the reliance on observational data. Despite the use of sophisticated statistical techniques such as propensity score matching and inverse probability of treatment weighting in the source studies, the potential for residual confounding remains. There may be unmeasured factors that influence a clinician's choice to prescribe a DOAC over a VKA (e.g., perceived patient reliability, socioeconomic status, or subtle frailty), which could bias the results. This phenomenon, known as confounding by indication, is the most significant threat to the

validity of the findings. Other limitations include the heterogeneity in the definitions and methods of dementia ascertainment across studies, variable follow-up durations which may be insufficient to capture the full trajectory of cognitive decline, and the general lack of data on VKA quality (i.e., TTR) in many of the included cohorts.

CONCLUSION AND SUGGESTIONS

Conclusion

The totality of the synthesized evidence indicates a significant association between the use of Direct Oral Anticoagulants (DOACs) and a lower risk of incident dementia compared to treatment with Vitamin K Antagonists (VKAs) in patients with non-valvular atrial fibrillation. This neuroprotective advantage appears to be primarily driven by a reduction in the incidence of vascular dementia, which aligns with the well-established and substantial superiority of DOACs in reducing the risk of intracranial hemorrhage. The benefit is most evident in patients under the age of 75 and in those of Asian ethnicity. These findings suggest that the choice of anticoagulant has implications beyond stroke prevention, potentially influencing long-term cognitive trajectories. While awaiting definitive evidence from randomized trials, the potential for cognitive preservation provides a compelling additional argument for the preferential use of DOACs over VKAs in most eligible patients with atrial fibrillation.

Suggestions for Future Research

The observational nature of the current body of evidence, while strongly suggestive, precludes definitive conclusions about causality. Therefore, the foremost recommendation is for the design and execution of large-scale, long-term randomized controlled trials specifically powered to evaluate cognitive decline and incident dementia as prespecified primary or major secondary endpoints. Such trials are urgently needed to confirm the findings of this meta-analysis and to definitively guide clinical practice.

Future research should also incorporate more granular methods of cognitive assessment, moving beyond administrative codes for dementia to include standardized neuropsychological testing batteries. Furthermore, the integration of advanced neuroimaging, such as serial magnetic resonance imaging (MRI), would be invaluable for elucidating the underlying mechanisms. This would allow for the quantification of changes in the burden of silent cerebral infarcts, white matter hyperintensities, and cerebral microbleeds, providing a direct link between anticoagulant choice, cerebrovascular injury, and cognitive outcomes. Finally, further investigation into the "age paradox" is warranted to better understand the risk-benefit balance of different anticoagulants in the very elderly and frail population.

INTRODUCTION

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