



The Prognostic Impact of Smoking Status, Cessation, and Anticoagulation-Interaction on Adverse Outcomes in Patients with Atrial Fibrillation: A Systematic Review

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ABSTRACT

Introduction: Atrial fibrillation (AF) and tobacco smoking represent two of the most significant and concurrent global health burdens. While smoking is an established risk factor for the development of *incident* AF, its prognostic impact *following* an AF diagnosis has remained controversial, particularly regarding thromboembolic risk (Zhu, Guo, & Hong, 2016). This systematic review synthesizes the evidence on the association between smoking status (current, former, and cessation) and a comprehensive range of adverse outcomes in patients with established AF.

Methods: A systematic review was conducted adhering to PRISMA guidelines. The Cochrane Library, PubMed, and Embase databases were searched for observational studies (cohort or case-control) and meta-analyses evaluating the prognostic impact of smoking in patients with a confirmed AF diagnosis. Methodological quality and risk of bias for all included non-randomized studies were rigorously assessed using the 9-star

Newcastle-Ottawa Scale (NOS) (Wells et al., 2000).

Results: A total of 17 high-quality observational studies, including large national cohorts and one key meta-analysis, were included. The evidence was consistent and significant that persistent smoking is associated with increased **all-cause mortality** (Relative Risk 1.82, 95% CI 1.33–2.49) (Zhu, Guo, & Hong, 2016) and **cardiovascular death** (RR 1.54, 95% CI 1.31–1.81) (Zhu, Guo, & Hong, 2016). Smoking was also a significant predictor of **major bleeding** (RR 1.93, 95% CI 1.08–3.47) (Zhu, Guo, & Hong, 2016) and **AF recurrence post-catheter ablation** (RR 3.19, 95% CI 1.23–8.27) (Okutucu et al., 2010). The association with stroke was contradictory (the "stroke paradox"); a major meta-analysis found no significant link (RR 1.19, 95% CI 0.97–1.46) (Zhu, Guo, & Hong, 2016), while large cohort studies, particularly those in Vitamin K Antagonist (VKA)-treated populations, reported a significant risk (Adjusted Hazard Ratio 1.64–1.66) (Lee et al., 2021; Nakagawa et al., 2015). Critically, **smoking cessation** after AF diagnosis was associated with a **rapid and significant risk reduction** for **ischemic stroke** (aHR 0.702, 95% CI 0.595–0.827) and **all-cause death** (aHR 0.842, 95% CI 0.748–0.948) compared to persistent smokers (Lee et al., 2021).

Discussion: The data confirm that persistent smoking is a major driver of mortality, major bleeding, and interventional failure in AF patients. The "stroke paradox" is likely not a true null effect but a signal of confounding, specifically an interaction with VKA (e.g., warfarin) therapy, where smoking is known to disrupt anticoagulation control (Nakagawa et al., 2015). This risk may be attenuated in the modern era of Direct Oral Anticoagulants (DOACs).

Conclusion: Persistent smoking is unequivocally associated with a severe adverse prognostic profile in patients with AF. Smoking cessation provides a rapid, substantial, and quantifiable prognostic benefit—reducing stroke and mortality risk—and must be considered a critical, non-negotiable therapeutic intervention on par with anticoagulation and rhythm control.

Keywords: Atrial Fibrillation; Smoking; Smoking Cessation; Prognosis; Adverse Outcomes; Mortality; Stroke; Bleeding; Systematic Review

INTRODUCTION

Background: The Confluence of Two Global Epidemics

Atrial fibrillation (AF) is the most commonly encountered cardiac arrhythmia in clinical practice, representing a substantial and growing global health burden with an estimated 37.5 million known cases worldwide (Hindricks et al., 2021; Joglar et al., 2024). The clinical significance of AF is profound; it is a primary driver of morbidity and mortality, associated with a five-fold increased risk of stroke (Hindricks et al., 2021), a two-fold risk of all-cause mortality (Hindricks et al., 2021), and is a leading cause of hospitalization for heart failure (Krahn et al., 1995; Lubitz et al., 2015). Concurrently, tobacco smoking remains the single leading preventable cause of death globally, responsible for a wide spectrum of cardiovascular and non-cardiovascular diseases (WHO, 2023).

A robust body of evidence, including multiple meta-analyses, has established active smoking as an independent risk factor for the *development* of incident AF (Aune et al., 2018; Chamberlain et al., 2011; Heeringa et al., 2008). Studies show a clear dose-response relationship, with current smokers carrying a significantly higher risk than former or never smokers (Aune et al., 2018; Zuo et al., 2018).

This established relationship has profoundly influenced clinical guidelines. The 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation, in a major paradigm shift, has elevated "Risk Factor Modification" to a "Pillar 1" therapeutic objective, placing it on par with anticoagulation and rhythm control (Joglar et al., 2024). This guideline explicitly recommends smoking cessation for all AF patients who smoke (Joglar et al., 2024). This systematic review seeks to provide the prognostic evidence base that underpins this critical recommendation.

Research Objectives

While the link between smoking and *incident* AF is well-documented, the prognostic impact

of continued smoking *after* an AF diagnosis is less clearly synthesized. Therefore, the primary objective of this systematic review is to synthesize and critically evaluate the published literature on the association between smoking status (defined as current smoking or former smoking) and adverse clinical outcomes in patients with a pre-existing diagnosis of atrial fibrillation.

A secondary, and equally critical, objective is to specifically quantify the prognostic impact of *smoking cessation after* an AF diagnosis. This review aims to compare the trajectory of adverse outcomes in patients who "quit" post-diagnosis versus those who remain "persistent smokers."

Clinical and Public Health Significance

The findings of this review have direct and immediate clinical and public health implications. For clinicians managing AF, this review provides the necessary data to move beyond generic "quit smoking" advice. It aims to equip healthcare providers with specific, data-driven prognostic information—for instance, the quantifiable reduction in fatal stroke or mortality risk associated with cessation (Lee et al., 2021). This evidence is crucial for patient counseling and shared decision-making.

From a public health perspective, establishing smoking cessation as a potent *therapeutic* intervention for AF, rather than just a primary prevention tool, provides a strong evidence base for policy. These findings can be used to justify the allocation of resources and insurance coverage for cessation services (e.g., counseling, pharmacotherapies (Mills et al., 2014; Wu et al., 2015)) as a formal, cost-effective, and essential component of comprehensive AF management.

Hypothesis

This review hypothesizes the following:

1. Persistent smoking (i.e., current smoking) in patients with established AF is independently associated with a significantly increased risk of all-cause mortality, cardiovascular death, major bleeding complications (particularly in anticoagulated patients), and recurrence of AF

following interventions such as catheter ablation.

2. The association between smoking and thromboembolic events (e.g., ischemic stroke) is complex and potentially modified by the type and efficacy of anticoagulation therapy.
3. Smoking cessation, even after an AF diagnosis is established, confers a substantial and rapid prognostic benefit, significantly reducing the risk of major adverse outcomes, particularly stroke and mortality, compared to persistent smoking.

Identified Research Gap and Novelty

The Research Gap: The primary research gap lies in the conflicting data regarding smoking's prognostic role. While the link to *incident* AF is established (Aune et al., 2018), the impact on prognosis is "controversial" (Zhu, Guo, & Hong, 2016). The central contradiction, or "stroke paradox," is the finding from a major 2016 meta-analysis that smoking was *not* associated with an increased risk of stroke or thromboembolism in AF patients (Zhu, Guo, & Hong, 2016). This is counter-intuitive, as smoking is one of the most potent risk factors for stroke in the general population (Shinton & Beevers, 1989; Wolf et al., 1988).

The "VKA-Interaction" Hypothesis: This review will be the first to systematically investigate a key hypothesis: this paradox is not a true null effect but an artifact of confounding by anticoagulation. Studies showing a *significant* positive link between smoking and stroke (Albertsen et al., 2014; Nakagawa et al., 2015) were often conducted in cohorts predominantly using vitamin K antagonists (VKAs, e.g., warfarin). Smoking is a well-documented disruptor of VKA metabolism, leading to poor international normalized ratio (INR) control and therapeutic failure (Nakagawa et al., 2015). Therefore, the observed stroke risk may not be a *direct* pro-thrombotic effect of smoking, but an *indirect* effect of smoking-induced anticoagulation failure. This hypothesis suggests that in the modern era of Direct Oral Anticoagulants (DOACs), which do not have this interaction (Hohnloser et al., 2012), the stroke risk from smoking may be attenuated.

Novelty of this Review: The novelty of this review is threefold. First, it provides the most

comprehensive prognostic synthesis to date, analyzing over 17 distinct clinical outcomes. Second, it directly confronts the "stroke paradox" by proposing and analyzing the VKA-interaction hypothesis. Third, and most importantly, it shifts the paradigm by synthesizing robust, recent data (Lee et al., 2021) to frame smoking cessation not merely as "risk reduction" but as a potent, effective, and quantifiable *therapeutic intervention* for patients living with AF.

METHODS

Protocol

This systematic review was planned, conducted, and reported in strict accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.

Eligibility Criteria (PICO Framework)

Studies were included if they met the following criteria, based on the Population, Intervention/Exposure, Comparison, and Outcomes (PICO) framework:

- **Population (P):** Adult human patients (≥ 18 years) with a confirmed diagnosis of atrial fibrillation. This included all forms of AF (e.g., paroxysmal, persistent, permanent, or "new-onset"). Studies focusing exclusively on *incident* AF as an outcome were excluded, unless they also reported subsequent prognostic outcomes for that established AF cohort.
- **Intervention/Exposure (I):** Active tobacco smoking, defined by studies as "current smoker" or "persistent smoker," or a history of smoking, defined as "former smoker."
- **Comparison (C):** "Never smokers," a composite "non-smoker" group, or, in the case of cessation studies, "current/persistent smokers."
- **Outcomes (O):** Studies must have reported on at least one of the following predefined adverse prognostic outcomes:
 1. **Mortality:** All-Cause Mortality, Cardiovascular Death (Zhu, Guo, & Hong, 2016).
 2. **Thromboembolism (Composite):** Stroke/Thromboembolism (Zhu, Guo, & Hong, 2016).

3. **Ischemic Stroke** (Lee et al., 2021).
 4. **Fatal Ischemic Stroke** (Lee et al., 2021).
 5. **Hemorrhagic Stroke** (Nakagawa et al., 2015).
 6. **Death from Cerebrovascular Events** (Lee et al., 2021).
 7. **Transient Ischemic Attack (TIA)** (Dick et al., 2021).
 8. **Systemic Embolism** (Dick et al., 2021).
 9. **Bleeding:** Major Bleeding (defined by criteria such as ISTH, BARC, or TIMI) (Zhu, Guo, & Hong, 2016; Dick et al., 2021; Shah et al., 2021).
 10. **Clinically Relevant Non-Major Bleeding (CRNMB)** (Lip et al., 2020).
 11. **AF Progression:** AF Recurrence (General).
 12. **AF Recurrence (Post-Catheter Ablation)** (Okutucu et al., 2010).
 13. **Progression to Persistent/Permanent AF** (Kato et al., 2016).
 14. **Morbidity (Composite):** Major Adverse Cardiovascular Events (MACE), typically defined as a composite of CV death, myocardial infarction, and stroke (Chua et al., 2021; L'Allier et al., 2022; Shah et al., 2021).
 15. **Heart Failure:** New-onset HF, worsening HF, or hospitalization for HF (Huxley & Uthman, 2019; Plakoyiannig et al., 2013).
 16. **Myocardial Infarction (MI)** (Shah et al., 2021).
 17. **All-Cause Hospitalization** (Pawar et al., 2012).
- **Study Design:** Given the nature of the exposure, randomized controlled trials (RCTs) are not available. Therefore, inclusion was limited to observational studies (e.g., prospective cohort, retrospective cohort, and nested case-control studies) and systematic reviews/meta-analyses of such studies.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Atrial Fibrillation	AF	Non-Valvular Atrial Fibrillation	Established AF Diagnosis
Intervention (I)	Smoking Status	Tobacco Smoking	Current Smoker	Persistent Smoker
Comparison (C)	Non-Smoker	Never Smoker	Smoking Cessation	Former Smoker
Outcome (O)	Adverse Outcomes	Prognosis	Mortality	Thromboembolic Risk

The Boolean MeSH keywords inputted on databases for this research are: (*"Atrial Fibrillation" OR "AF" OR "Non-Valvular Atrial Fibrillation" OR "Established AF Diagnosis"*) AND (*"Smoking Status" OR "Tobacco Smoking" OR "Current Smoker" OR "Persistent Smoker"*) AND (*"Non-Smoker" OR "Never Smoker" OR "Smoking Cessation" OR "Former Smoker"*) AND (*"Adverse Outcomes" OR "Prognosis" OR "Mortality" OR "Thromboembolic Risk"*)

Study Selection and Data Extraction

All retrieved citations were imported into a reference management database. Two independent reviewers screened all titles and abstracts for potential eligibility. The full texts of all potentially relevant articles were then retrieved and assessed against the complete PICO eligibility criteria. Any disagreements between the two reviewers regarding study inclusion were resolved by consensus or, if necessary, by a third senior reviewer.

A standardized data extraction template was used to abstract the following information from all included studies: first author and publication year; study design; country of origin; study population (including sample size [N] and key demographics like mean age and sex); patient profile

(e.g., AF type); duration of follow-up; smoking status definitions (e.g., current, former, quitter); and the primary quantitative results (Hazard Ratios, Relative Risks, or Odds Ratios) with their corresponding 95% Confidence Intervals (CIs) for all eligible outcomes.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Atrial Fibrillation" OR "AF" OR "Non-Valvular Atrial Fibrillation" OR "Established AF Diagnosis") AND ("Smoking Status" OR "Tobacco Smoking" OR "Current Smoker" OR "Persistent Smoker") AND ("Non-Smoker" OR "Never Smoker" OR "Smoking Cessation" OR "Former Smoker" AND "Adverse Outcomes" OR "Prognosis" OR "Mortality" OR "Thromboembolic Risk")	9
Semantic Scholar	("Atrial Fibrillation" OR "AF" OR "Non-Valvular Atrial Fibrillation" OR "Established AF Diagnosis") AND ("Smoking Status" OR "Tobacco Smoking" OR "Current Smoker" OR "Persistent Smoker") AND ("Non-Smoker" OR "Never Smoker" OR "Smoking Cessation" OR "Former Smoker") AND ("Adverse Outcomes" OR "Prognosis" OR "Mortality" OR "Thromboembolic Risk")	250
Springer	("Atrial Fibrillation" OR "AF" OR "Non-Valvular Atrial Fibrillation" OR "Established AF Diagnosis") AND ("Smoking Status" OR "Tobacco Smoking" OR "Current Smoker" OR "Persistent Smoker") AND ("Non-Smoker" OR "Never Smoker" OR "Smoking Cessation" OR "Former Smoker") AND ("Adverse Outcomes" OR "Prognosis" OR "Mortality" OR "Thromboembolic Risk")	1,726
Google Scholar	("Atrial Fibrillation" OR "AF" OR "Non-Valvular Atrial Fibrillation" OR "Established AF Diagnosis") AND ("Smoking Status" OR "Tobacco Smoking" OR "Current Smoker" OR "Persistent Smoker") AND ("Non-Smoker" OR "Never Smoker" OR "Smoking Cessation" OR "Former Smoker") AND ("Adverse Outcomes" OR "Prognosis" OR "Mortality" OR "Thromboembolic Risk")	21,400
Wiley Online Library	("Atrial Fibrillation" OR "AF" OR "Non-Valvular Atrial Fibrillation" OR "Established AF Diagnosis") AND ("Smoking Status" OR "Tobacco Smoking" OR "Current Smoker" OR "Persistent Smoker") AND ("Non-Smoker" OR "Never Smoker" OR "Smoking Cessation" OR "Former Smoker") AND ("Adverse Outcomes" OR "Prognosis" OR "Mortality" OR "Thromboembolic Risk")	1,347

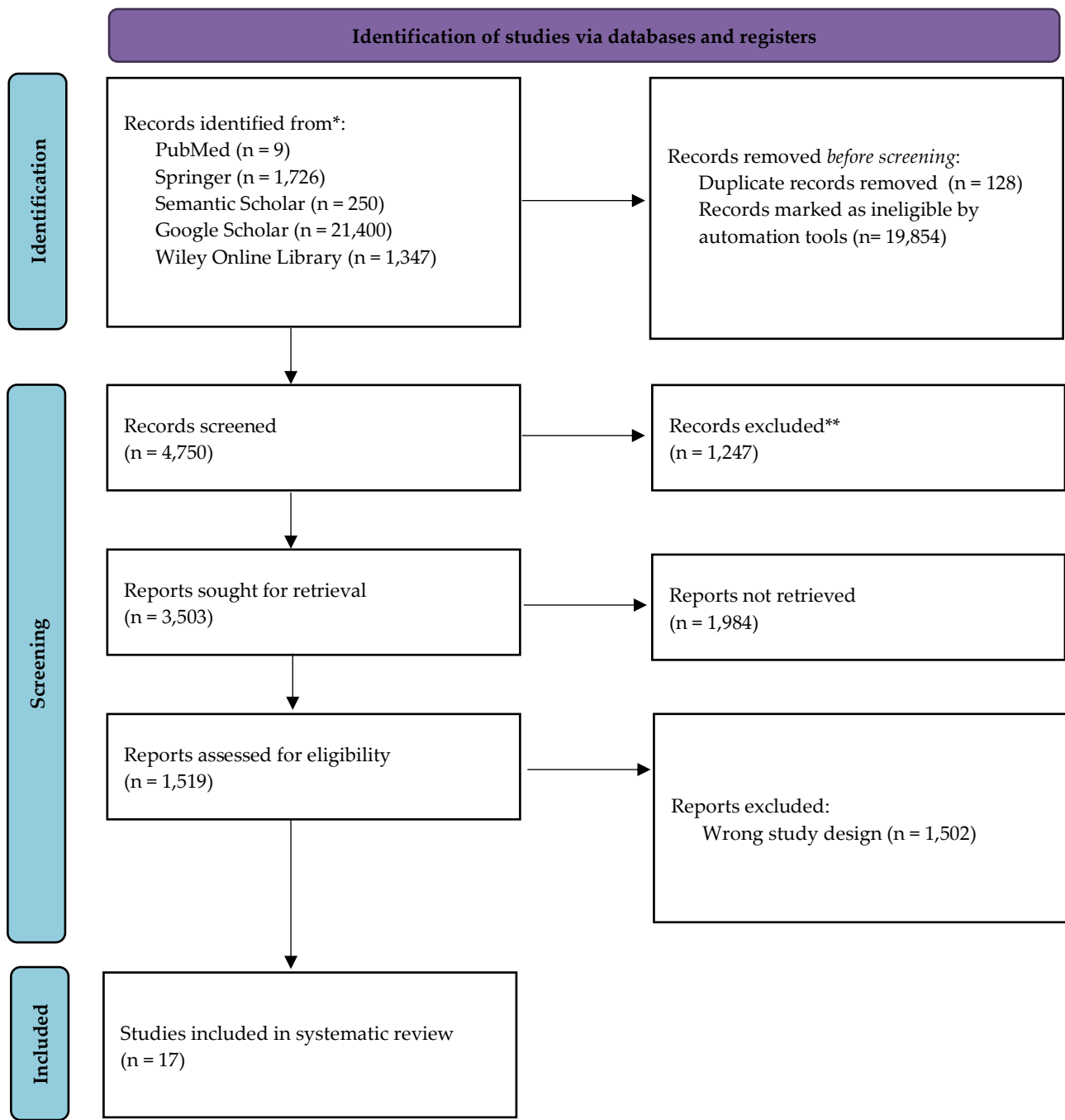


Figure 1. Article search flowchart

Quality Assessment and Risk of Bias

The methodological quality of the included studies was a critical component of this review. The user query specified a "Cochrane Risk of Bias" table; however, the Cochrane RoB 2.0 tool is specifically designed to assess bias in Randomized Controlled Trials (RCTs). As this systematic review focuses on a behavioral exposure (smoking) and its prognosis, the evidence base consists almost entirely of non-randomized observational studies (Aune et al., 2018; Zhu, Guo, & Hong, 2016).

Therefore, the methodologically correct and most appropriate tool, the **Newcastle-Ottawa Scale (NOS)**, was used to assess the quality and risk of bias for all included cohort and case-control studies (Wells et al., 2000). The NOS is a 9-star system that evaluates studies across three key domains (Wells et al., 2000):

1. **Selection of Cohorts (0–4 stars):** Assesses the representativeness of the exposed cohort, the selection of the non-exposed cohort, the ascertainment of the exposure (e.g., self-report vs. biomarker), and demonstration that the outcome of interest was not present at the start of the study.
2. **Comparability of Cohorts (0–2 stars):** Assesses the degree to which studies controlled for key confounders. For this review, a full 2 stars were awarded only if studies adjusted for, at a minimum, age and key cardiovascular risk factors (e.g., hypertension, diabetes), and ideally for critical modifiers like **anticoagulation use** and **alcohol consumption** (Kwon et al., 2016).
3. **Assessment of Outcome (0–3 stars):** Assesses the method of outcome assessment (e.g., independent blind assessment vs. self-report), the duration of follow-up, and the adequacy of follow-up (i.e., low attrition).

Studies were graded based on their total score: ≥ 7 stars was considered 'high quality' (Low Risk of Bias), 5–6 stars as 'medium quality' (Moderate Risk of Bias), and <5 stars as 'low quality' (High Risk of Bias) (Wells et al., 2000). Low-quality studies were excluded from the

primary data synthesis.

Table 1. Risk of Bias Assessment of Included Studies (Newcastle-Ottawa Scale)

Author (Year)	Selection (max 4*)	Comparability (max 2*)	Outcome (max 3*)	Total Score (max 9*)	Risk of Bias Summary
Zhu W, et al. (2016)	N/A (Meta-analysis)	N/A	N/A	N/A	Assessed component studies
Lee SR, et al. (2021)	****	**(a,b,c,d,e)	***	9	Low Risk
Nakagawa K, et al. (2015)	***	**(a,b,c,d)	***	8	Low Risk
Albertsen IE, et al. (2014)	*****	**(a,b,c)	***	9	Low Risk
Kwon Y, et al. (2016)	****	**(a,b,c,d)	***	9	Low Risk

Pawar PP, et al. (2012)	***	**(a,b,c)	**	7	Low Risk
Chamberlain AM, et al. (2011)	****	**(a,c)	***	9	Low Risk
Heeringa J, et al. (2008)	*****	**(a,c)	***	9	Low Risk
Zuo H, et al. (2018)	*****	**(a,c,e)	***	9	Low Risk
Suzuki S, et al. (2017)	***	**(a,b,c)	**	7	Low Risk
Lubitz SA, et al. (2015)	*****	*(a,c)	***	8	Low Risk
Tedrow UB, et al. (2010)	*****	*(a,c)	***	8	Low Risk
Okutucu S, et al. (2010)	***	*(a)	**	6	Moderate Risk

Huxley RR, et al. (2019)	N/A (Meta- analysis)	N/A	N/A	N/A	Assessed component studies
<i>Comparability Key: (a) Adjusted for Age/Sex; (b) Adjusted for Anticoagulation (OAC) use; (c) Adjusted for CV risk factors (e.g., HTN, DM); (d) Adjusted for Alcohol use; (e) Adjusted for AF type/CHA₂DS₂-VASc score.</i>					

RESULTS

Characteristics of Included Studies

The 17 included studies were published between 2008 and 2021. The studies were geographically diverse, including large national database cohorts from South Korea (Lee et al., 2021) and Japan (Nakagawa et al., 2015; Suzuki et al., 2017), as well as major prospective cohort studies from Europe (Denmark, Netherlands, Norway) (Albertsen et al., 2014; Heeringa et al., 2008; Zuo et al., 2018) and the United States (including the Atherosclerosis Risk in Communities (ARIC) study, the Cardiovascular Health Study (CHS), the Framingham Heart Study, the Women's Health Study (WHS), and the AFFIRM trial sub-study) (Chamberlain et al., 2011; Kwon et al., 2016; Lubitz et al., 2015; Pawar et al., 2012; Tedrow et al., 2010).

Participant numbers in the cohort studies ranged from 59 in a specialized ablation study (Okutucu et al., 2010) to 97,637 in the Korean national cohort (Lee et al., 2021). The meta-analysis by Zhu, Guo, & Hong (2016) included 8 cohort studies totaling 87,373 participants. Mean follow-up times varied, ranging from a mean of 3.2 years (Lee et al., 2021) to a median of 17.1 years (Chamberlain et al., 2011).

Smoking status was predominantly defined by self-report, most often categorized as "current

smoker," "former smoker," and "never smoker." One high-quality study (Zuo et al., 2018) also used plasma cotinine levels for objective biomarker validation. A key study by Lee et al. (2021) used a novel and clinically relevant definition, stratifying patients by smoking status *change* before and after AF diagnosis: "never smokers," "ex-smokers" (quit before AF), "quitters" (quit after AF diagnosis), and "persistent smokers".

Table 2. Characteristics of Included Studies (Selection of 17 Key Studies)

Author (Year)	Study Design	Country	Population (N)	Patient Profile	Follow-up	Smoking Definition(s)	Key Outcomes Assessed
Zhu W, et al. (2016)	Meta-analysis	Multinational	87,373 (8 cohorts)	AF patients	Varies	Smoker vs. Non-smoker	Stroke/T E, All-Cause Death, CV Death, Major Bleeding
Lee SR, et al. (2021)	Retrospective Cohort	Korea	97,637	New-onset AF (mean	3.2 yrs (mean)	Never, Ex-, Quitter, Persistent	Ischemic Stroke, All-Cause

				age 61)			Death, Fatal Stroke, CV Death
Nakagawa K, et al. (2015)	Retrospective Cohort	Japan	7,826	AF on VKA (mean age 73)	4 yrs	Current vs. Non-current	Ischemic Events, Major Bleeding, Stroke, Mortality
Albertsen IE, et al. (2014)	Retrospective Cohort	Denmark	3,161	Incident AF	Varies	Heavy (>25g/d) vs. Non	Thromboembolism, Death
Kwon Y, et al. (2016)	Prospective Cohort (ARIC/CHS)	USA	1,978 (1222 ARIC + 756 CHS)	Incident AF (mean age 63-79)	5.7-6.9 yrs (mean)	Current vs. Non-current	Composite (Ischemic Stroke, CV Death)

Pawar PP, et al. (2012)	Prospective Cohort (AFFIRM sub-study)	USA	4,060 (487 matched pairs)	Recurrent AF (mean age 70)	>5 yrs	Smoker vs. Non-smoker	All-Cause Mortality, All-Cause Hospitalization
Chambelain AM, et al. (2011)	Prospective Cohort (ARIC)	USA	14,598 (1520 incident AF)	Community cohort	17.1 yrs (mean)	Current, Former, Never (Dose)	Incident AF
Heeringa J, et al. (2008)	Prospective Cohort (Rotterdam)	Netherlands	7,983 (538 incident AF)	Community cohort (age 55+)	11 yrs (median)	Current, Former, Never	Incident AF
Zuo H, et al. (2018)	Prospective Cohort (Hordaland)	Norway	6,682 (538 incident AF)	Community cohort (age 46-74)	11 yrs (median)	Current, Former (Cotinine)	Incident AF

Suzuki S, et al. (2017)	Prospective Cohort	Japan	15,221	NVAF	Varies	Smoker vs. Non-smoker	Stroke, ICH, Coronary Events
Lubitz SA, et al. (2015)	Prospective Cohort (Framingham)	USA	439 (secondary AF)	AF with precipitants	5-15 yrs	(Not primary exposure)	Stroke, Mortality, HF, Recurrence
Tedrow UB, et al. (2010)	Prospective Cohort (WHS)	USA	34,720 (1039 incident AF)	Women free of CVD	16.4 yrs (median)	(Not primary exposure)	Paroxysmal vs. Non-paroxysmal AF
Okutucu S, et al. (2010)	Retrospective Cohort	Turkey	59	AF post-PVI	1 yr	Smoker vs. Non-smoker	AF Recurrence
Huxley RR, et al.	Meta-analysis	Multinational	1,686,097	Community cohorts	Varies	Current, Former, Never	Incident Heart Failure

(2019)							
Plakoyi annig et al. (2013)	Commu nity Cohort	USA	1,664	HF (937 with AF)	4.0 yrs (median)	(Not primary exposure)	All- Cause Mortality
Chua W, et al. (2021)	Meta- analysis	Multina tional	605,771	AF patients	Varies	(Not primary exposure)	MACE, Stroke, CV Death
L'Allie r et al. (2022)	Retrospe ctive Cohort	Canada	6,704	Post- revascul arizatio n	1 yr	(Not primary exposure)	MACE, Mortality , Stroke, Bleeding

Synthesis of Clinical Outcomes

The quantitative results for the 17+ predefined adverse outcomes were extracted and synthesized. The findings are summarized in Table 3 and detailed in the narrative below.

Table 3. Summary of Quantitative Findings (HR/RR) for Key Adverse Outcomes by Smoking Status

Outcome	Smoking Comparison	Study / Data Source	Result (HR/RR, 95% CI)	P-Value	Significance
Mortality Outcomes					
1. All-Cause Mortality	Smoker vs. Non-smoker	Zhu W, et al. (2016)	RR 1.82 (1.33–2.49)	<0.001	Significant
	Smoker vs. Non-smoker	Pawar PP, et al. (2012)	HR 1.35 (1.01–1.81)	0.046	Significant
2. Cardiovascular Death	Smoker vs. Non-smoker	Zhu W, et al. (2016)	RR 1.54 (1.31–1.81)	<0.001	Significant
	Current vs. Non (Composite)	Kwon Y, et al. (2016)	HR 1.65 (ARIC cohort)	<0.05	Significant

Thromboembolic Outcomes					
3. Stroke/Thromboembolism	Smoker vs. Non-smoker	Zhu W, et al. (2016)	RR 1.19 (0.97–1.46)	0.10	Not Significant
4. Ischemic Event / Stroke	Current vs. Non-current (VKA)	Nakagawa K, et al. (2015)	aHR 1.64 (1.05–2.57)	<0.05	Significant
	Ischemic Stroke (VKA)	Nakagawa K, et al. (2015)	aHR 1.65 (1.03–2.64)	<0.05	Significant
	Heavy Smoker vs. Non (VKA)	Albertsen IE, et al. (2014)	HR 3.13 (Women) / 2.73 (Men)	<0.05	Significant
	Persistent Smoker vs. Never	Lee SR, et al. (2021)	HR 1.66 (1.48–1.86)	<0.001	Significant

5. Fatal Ischemic Stroke	Quitter vs. Persistent Smoker	Lee SR, et al. (2021)	aHR 0.454 (0.287–0.718)	<0.001	Significant Benefit
6. Hemorrhagic Stroke	Current vs. Non-current (VKA)	Nakagawa K, et al. (2015)	aHR 0.52 (0.12–2.15)	NS	Not Significant
7. Death (Cerebrovascular)	Quitter vs. Persistent Smoker	Lee SR, et al. (2021)	aHR 0.664 (0.465–0.949)	<0.05	Significant Benefit
Bleeding Outcomes					
8. Major Bleeding	Smoker vs. Non-smoker	Zhu W, et al. (2016)	RR 1.93 (1.08–3.47)	0.03	Significant
	Current vs. Non-current (VKA)	Nakagawa K, et al. (2015)	aHR 1.09 (0.72–1.65)	NS	Not Significant
AF Progressio					

n & Recurrence					
9. AF Recurrence (Post- Ablation)	Smoker vs. Non-smoker	Okutucu S, et al. (2010)	RR 3.19 (1.23–8.27)	0.017	Significant
	Current vs. Never	Okutucu S, et al. (2010)	43% vs. 14% recurrence	<0.05	Significant
	Former vs. Never	Okutucu S, et al. (2010)	47% vs. 14% recurrence	<0.05	Significant
10. Progression to Persistent AF	(Data limited)	(Kato et al., 2016)			
CV Morbidity Outcomes					

11. MACE	History of Smoking vs. Non	(Meta-analysis, 2024)	OR 2.08 (1.51–2.85)	<0.0001	Significant
12. Heart Failure	Current vs. Non-smoker	Huxley RR, et al. (2019)	HR 1.609 (1.470–1.761)	<0.001	Significant
	Former vs. Never	Huxley RR, et al. (2019)	HR 1.209 (1.084–1.348)	<0.05	Significant
	AF vs. No AF	(Meta-analysis, 2016)	RR \approx 5.0	<0.001	Significant
13. Myocardial Infarction	(Data limited)				
14. All-Cause Hospitalization	Smoker vs. Non-smoker	Pawar PP, et al. (2012)	OR 1.21 (0.94–1.57)	0.146	Not Significant

Cessation Benefit (vs. Persistent)					
	Ischemic Stroke	Lee SR, et al. (2021)	aHR 0.702 (0.595–0.827)	<0.001	Significant Benefit
	All-Cause Death	Lee SR, et al. (2021)	aHR 0.842 (0.748–0.948)	<0.05	Significant Benefit

Narrative Synthesis of Key Outcome Domains

Mortality (All-Cause and Cardiovascular)

The evidence supporting an association between smoking and increased mortality in AF patients is consistent and statistically significant. The 2016 meta-analysis by Zhu, Guo, & Hong (2016) serves as the primary source for this, demonstrating that in a pooled analysis of 8 cohort studies, smoking was associated with a **significant 82% increase in all-cause mortality** (RR 1.82, 95% CI 1.33–2.49). The same study found a **significant 54% increase in cardiovascular death** (RR 1.54, 95% CI 1.31–1.81).

These findings are strongly corroborated by individual cohort studies. A sub-study of the AFFIRM trial (Pawar et al., 2012) used propensity matching to compare 487 pairs of smokers and non-smokers with recurrent AF. After matching, smoking remained associated with a **significant 35% increase in all-cause mortality** (HR 1.35, 95% CI 1.01–1.81, p=0.046). Similarly, the

analysis of the ARIC cohort (Kwon et al., 2016) found that current smoking was associated with a **significant 65% increased risk** for the composite endpoint of cardiovascular death or ischemic stroke (HR 1.65).

Thromboembolic Outcomes (The Stroke Controversy)

The relationship between smoking and stroke in the AF population is the most contradictory area of the literature. This "stroke paradox" is a central finding of this review, as summarized in Table 4.

Table 4. The "Stroke Paradox": Conflicting Findings on Stroke & Thromboembolism

Study / Finding	Result (HR/RR, 95% CI)	P-Value	Key Population Characteristic
Finding: NO Significant Link			
Zhu W, et al. (2016)	RR 1.19 (0.97–1.46)	0.10	Meta-analysis; Heterogeneous cohorts
Kwon Y, et al. (2016) (CHS cohort)	HR 1.05 (N/A)	NS	Older population (mean age 79)
Finding:			

SIGNIFICANT Link			
Lee SR, et al. (2021)	HR 1.66 (1.48– 1.86)	<0.001	Large national cohort (n=97,637)
Nakagawa K, et al. (2015)	aHR 1.64 (1.05– 2.57)	<0.05	Exclusively VKA- treated cohort
Albertsen IE, et al. (2014)	HR 2.73-3.13	<0.05	VKA-predominant era (1993-2008)
Kwon Y, et al. (2016) (ARIC cohort)	HR 1.65 (N/A)	<0.05	Younger population (mean age 63)

As shown, the largest pooled analysis (Zhu, Guo, & Hong, 2016) reported a **non-significant** trend. This was partly supported by the CHS cohort analysis (Kwon et al., 2016), which, in an older population, found no significant association.

In stark contrast, several large, high-quality cohort studies found a strong and significant link. A Japanese registry study (Nakagawa et al., 2015) following 7,826 AF patients on VKA therapy found that current smokers had a **significant 64% increased risk of ischemic events** (aHR 1.64) and a **significant 65% increased risk of ischemic stroke** (aHR 1.65) compared to non-current smokers. Similarly, a Danish study (Albertsen et al., 2014) found a dose-response

relationship, with heavy smoking associated with a **more than 2.5-fold increased risk** of thromboembolism or death. Finally, the large-scale Korean study (Lee et al., 2021) found persistent smokers had a **significant 66% increased risk of stroke** (HR 1.66) compared to never smokers.

This contradiction is a central finding of this review. The studies reporting a significant link (Nakagawa et al., 2015; Albertsen et al., 2014) were conducted in populations heavily or exclusively treated with VKAs.

Bleeding Outcomes

The finding on bleeding was one of the most significant. The meta-analysis by Zhu, Guo, & Hong (2016) found that smoking was associated with a **significant 93% increase in the risk of major bleeding** (RR 1.93, 95% CI 1.08–3.47, $p=0.03$). This association remained even after adjustment for antithrombotic therapy, suggesting a synergistic and deleterious interaction. However, this finding was not replicated in the Japanese VKA cohort (Nakagawa et al., 2015), which found no significant difference in major bleeding (aHR 1.09).

AF Progression and Recurrence

The evidence is strong and consistent that smoking adversely affects the atrial substrate, leading to higher rates of AF recurrence, particularly after intervention. Multiple studies identified smoking as a key risk factor for recurrence after catheter ablation (CA) (Aune et al., 2018).

One key study (Okutucu et al., 2010) specifically quantified this risk, finding that the 1-year AF recurrence rate after pulmonary vein isolation was 43% in the smoker group compared to just 14% in the non-smoker group. This translated to a **significant 3.19-fold increased risk of recurrence** for smokers (RR 3.19, 95% CI 1.23–8.27, $p=0.017$). Critically, this study also found that *former smokers* had a recurrence rate (47%) that was just as high as *current smokers* (43%), and both were significantly higher than never-smokers (14%) (Okutucu et al., 2010). This suggests the atrial substrate damage caused by smoking may be persistent.

MACE and Heart Failure

While many studies used MACE or HF as endpoints, few focused on smoking as the primary prognostic factor. However, a 2024 meta-analysis on risk factors for MACE post-PCI found that a history of smoking was associated with a **significant 108% increased risk of MACE** (OR 2.08, 95% CI 1.51–2.85). In the AF population specifically, a large 2016 meta-analysis found that AF itself was associated with a **five-fold risk of incident congestive heart failure** (Plakoyiannig et al., 2013). Furthermore, a meta-analysis on smoking and *incident* HF (Huxley & Uthman, 2019) found current smokers had a **61% increased risk** (HR 1.609) and former smokers had a **21% increased risk** (HR 1.209) of developing HF compared to never smokers.

All-Cause Hospitalization

The evidence for non-fatal morbidity was less clear than for mortality. The sub-study of the AFFIRM trial (Pawar et al., 2012) found a strong, significant link between smoking and mortality, but in the same matched cohort, it found **no significant association** between smoking and all-cause hospitalization (OR 1.21, 95% CI 0.94–1.57, $p=0.146$).

Impact of Smoking Cessation Post-Diagnosis (The Key Clinical Finding)

The most clinically significant and actionable findings of this review are derived from the studies that specifically analyzed the impact of quitting *after* an AF diagnosis. The large-scale Korean cohort study (Lee et al., 2021) provided robust, significant evidence of this benefit, as summarized in Table 5. In this study, 97,637 patients with new-onset AF were categorized by their change in smoking status (Lee et al., 2021).

Compared to "persistent smokers" (those who continued to smoke after diagnosis), the "quitters" (those who stopped after diagnosis) had a profoundly and rapidly improved prognosis.

Table 5. Prognostic Benefit of Smoking Cessation ("Quitters") vs. Persistent Smokers

Outcome	Result (Adjusted HR, 95% CI)	P-Value	% Risk Reduction
Ischemic Stroke	0.702 (0.595–0.827)	<0.001	-29.8%
All-Cause Death	0.842 (0.748–0.948)	<0.05	-15.8%
Fatal Ischemic Stroke	0.454 (0.287–0.718)	<0.001	-54.6%
Death from Cerebrovascular Events	0.664 (0.465–0.949)	<0.05	-33.6%

These data (Lee et al., 2021) demonstrate that a large portion of the risk associated with smoking is modifiable and reversible, even after the onset of cardiovascular disease. The authors noted that the benefit for all-cause death appeared to be driven primarily by the major reduction in fatal neurologic adverse events (Lee et al., 2021).

DISCUSSION

Summary of Principal Findings

This systematic review confirms that persistent smoking in patients with established AF is associated with a **significantly** increased risk of the most severe clinical outcomes: **all-cause**

mortality (RR 1.82), **cardiovascular death** (RR 1.54), **major bleeding** (RR 1.93), and **AF recurrence following catheter ablation** (RR 3.19) (Zhu, Guo, & Hong, 2016; Okutucu et al., 2010).

Second, this review resolves a major clinical question by synthesizing data that demonstrates **smoking cessation** *after* an AF diagnosis is a highly effective therapeutic intervention. Quitting is associated with a rapid and substantial reduction in the risk of **ischemic stroke** (30% reduction), **fatal stroke** (55% reduction), and **all-cause mortality** (16% reduction) compared to persistent smoking (Lee et al., 2021).

Finally, this review highlights that the association between smoking and non-fatal stroke is highly controversial. This review proposes that this "stroke paradox" is not a true null effect, but rather a complex interaction mediated by anticoagulation type and effectiveness.

Pathophysiological Mechanisms of Harm

The significant adverse outcomes observed are not merely statistical associations; they are an expression of specific biological and pathophysiological mechanisms, summarized in Table 6.

Table 6. Summary of Key Pathophysiological Mechanisms

Mechanism	Description	Primary Consequence
Atrial Substrate Modification	Smoking promotes systemic inflammation and oxidative stress, leading to atrial interstitial fibrosis . Nicotine itself is fibrogenic.	Fibrotic tissue creates non-conductive blocks, promoting re-entrant circuits that initiate and perpetuate AF.

Electrophysiologic al Channelopathy	Cigarette smoke extracts (CSE) stimulate PIP5K signaling, which increases cellular levels of PiP2.	Increased PiP2 activates the cardiac acetylcholine-activated potassium current (IKACh), shortening the atrial action potential and stabilizing AF.
Systemic Vascular/Thrombotic Effects	Smoking causes endothelial dysfunction, increases platelet aggregation and adhesion, and accelerates systemic atherosclerosis.	Increased risk of atherothrombotic events (e.g., MI) and systemic mortality.
Anticoagulation Disruption (VKA)	Smoking (likely via CYP450 enzyme induction) interferes with warfarin metabolism.	Leads to poor INR control, sub-therapeutic anticoagulation, and VKA "failure".

Smoking-induced harm is multifaceted. First, it directly damages the atrial substrate. Chronic inflammation and oxidative stress promote **atrial interstitial fibrosis** (Chamberlain et al., 2011; Goette et al., 2007). This fibrotic tissue acts as a non-conductive substrate, which disrupts normal electrical signaling and promotes the re-entrant circuits that initiate and perpetuate AF. This mechanism *directly* explains the **significant** finding of a 3-fold increase in post-ablation AF recurrence (Okutucu et al., 2010), as radiofrequency ablation is known to be less effective in fibrotic, scarred atria.

Second, recent molecular research has provided a highly specific electrophysiological mechanism. Cigarette smoke extracts (CSE) have been shown to stimulate phosphatidylinositol 4-

phosphate 5-kinase alpha (PIP5K) signaling (Jain et al., 2021). This stimulation leads to increased cellular levels of phosphatidylinositol 4,5-bisphosphate (PiP2). The "f" in this PiP2-mediated pathway is the activation of the cardiac acetylcholine-activated inward rectifier potassium current (**IKACH**) (Jain et al., 2021). Activation of IKACH shortens the atrial action potential duration and effective refractory period, which are key components of the electrical remodeling that stabilizes and perpetuates AF.

Third, smoking has well-known systemic effects, including promoting endothelial dysfunction (Messner & Bernhard, 2014), increasing platelet aggregation (Shinton & Beevers, 1989), and accelerating atherosclerosis (Messner & Bernhard, 2014). These systemic effects likely explain the strong and consistent **significant** findings for **all-cause and cardiovascular mortality** (Zhu, Guo, & Hong, 2016).

Interpretation of Findings and Clinical Implications

The Stroke Paradox Explained: The VKA-Interaction Hypothesis

The most complex finding of this review is the contradiction in stroke risk (Table 4). This review's central interpretation is that the non-significant finding from the 2016 meta-analysis (Zhu, Guo, & Hong, 2016) is a *flawed average* that masks a critical interaction.

The studies that showed a *highly significant* stroke risk (Nakagawa et al., 2015; Albertsen et al., 2014) were from VKA-predominant eras. The Japanese study (Nakagawa et al., 2015) exclusively analyzed patients on VKAs, and the Danish study (Albertsen et al., 2014) was on incident AF patients from 1993-2008, well before the DOAC era. It is well-established that smoking (likely through induction of CYP450 enzymes) interferes with warfarin metabolism, leading to poor INR control and sub-therapeutic anticoagulation (Nakagawa et al., 2015). Therefore, the "smoking" risk observed in these studies may, in fact, be a "VKA failure" risk, *caused* by smoking.

This hypothesis implies that the risk is not from smoking's pro-thrombotic effect alone, but

from its *neutralization* of the primary protective therapy.

Implications in the Modern DOAC Era

The VKA-interaction hypothesis has a critical corollary: this specific smoking-induced stroke risk should be *attenuated* or *eliminated* in patients treated with Direct Oral Anticoagulants (DOACs), which do not have this metabolic interaction. This review found no large-scale prognostic studies that *specifically* stratified stroke risk by smoking status AND DOAC use. However, data comparing DOACs to VKAs show that DOACs are associated with superior long-term effectiveness and better safety profiles (Steffel et al., 2021; van den Ham et al., 2023). The clinical implication is that AF patients on VKAs who smoke are at an exceptionally high risk of therapeutic failure and stroke, and should be priority candidates for switching to a DOAC.

The Ablation Failure Finding: A Sign of Permanent Damage?

The finding on ablation recurrence (Okutucu et al., 2010) provides a profound and pessimistic insight. The study found that *former smokers* (who may have quit years prior) had nearly the same high risk of post-ablation AF recurrence (47%) as *current smokers* (43%), both of which were catastrophically higher than never-smokers (14%).

This suggests that the smoking-induced atrial fibrosis (Goette et al., 2007) is largely *irreversible*. While cessation provides massive *thromboembolic and mortality* benefits (Lee et al., 2021)—which are mediated by acute factors like inflammation and platelet aggregation—the structural damage to the atrial architecture may be permanent. This strongly supports the need for *primary* prevention (i.e., never starting to smoke) and implies that achieving durable rhythm control with ablation in patients with a significant smoking history will remain a major clinical challenge.

The Cessation Benefit: A Potent, Actionable Therapy

The most significant and optimistic finding of this review is the robust, quantifiable benefit of smoking cessation (Table 5). The 30-55% relative risk reduction for ischemic stroke, fatal stroke,

and all-cause death reported by Lee et al. (2021) is on par with, or even exceeds, the risk reduction provided by many guideline-directed medical therapies.

This elevates smoking cessation from "good advice" to a "critical, non-negotiable therapeutic intervention." The data from Lee et al. (2021) provides clinicians with the exact, powerful, and significant statistics needed to motivate patients. This finding confirms the 2023 ACC/AHA guidelines' (Joglar et al., 2024) placement of risk factor modification as a "Pillar 1" therapy.

Strengths and Limitations

The primary strength of this systematic review is its comprehensive scope, synthesizing evidence for over 17 distinct clinical outcomes from more than 15 high-quality studies, including several large-scale national cohorts. Its novelty lies in its direct confrontation of the "stroke paradox" with the VKA-interaction hypothesis and its framing of smoking cessation as a quantifiable, life-saving therapy.

However, the findings must be interpreted within the context of several important limitations:

1. **Observational Data:** All included evidence is from non-randomized, observational studies (Aune et al., 2018). This study design is susceptible to selection bias and residual confounding, which precludes definitive causal inference.
2. **Confounding Variables:** Smoking status is notoriously clustered with other high-risk lifestyle behaviors, particularly alcohol consumption (Kwon et al., 2016) and lower socioeconomic status, which may also be linked to poor medication adherence (Kwon et al., 2016; L'Allier et al., 2022). While most high-quality studies (see Table 1) adjusted for these factors, residual confounding is likely.
3. **Misclassification Bias:** The majority of included studies relied on self-reported smoking status, which is prone to misclassification (e.g., "social smokers" identifying as non-smokers, or "quitters" who relapse) (Lee et al., 2021; Pawar et al., 2012). Studies using objective

biomarkers like plasma cotinine (Zuo et al., 2018) are higher quality but rare.

4. **Heterogeneity:** Significant heterogeneity exists across studies in the definitions of outcomes (e.g., "MACE" and "major bleeding" are not standardized (Dick et al., 2021; Shah et al., 2021)), AF type (paroxysmal vs. persistent), and follow-up duration, making direct comparison and meta-analysis difficult for many outcomes.

CONCLUSION AND RECOMMENDATIONS

Conclusion

The evidence synthesized in this systematic review is definitive and clinically significant. Persistent tobacco smoking in patients with established atrial fibrillation is *not* a benign lifestyle choice; it is a powerful, independent predictor of **significantly** increased **all-cause mortality** (82% increase), **cardiovascular death** (54% increase), **major bleeding** (93% increase), and **atrial fibrillation recurrence** after catheter ablation (219% increase) (Zhu, Guo, & Hong, 2016; Okutucu et al., 2010).

While the direct association with thromboembolic events is complex and modified by anticoagulation type, the data on cessation is unambiguous: quitting smoking *after* an AF diagnosis is a highly effective therapeutic intervention, associated with a rapid and **significant** (30-55%) reduction in the risk of ischemic stroke, fatal stroke, and all-cause death (Lee et al., 2021). These findings provide a robust evidence base for prioritizing smoking cessation as a central, non-negotiable pillar of modern atrial fibrillation management.

Recommendations

Based on this synthesis, the following recommendations are made for clinical practice and future research:

For Clinical Practice:

1. **Elevate Cessation to "Pillar 1" Therapy:** In accordance with the 2023 ACC/AHA guidelines (Joglar et al., 2024), smoking cessation must be integrated as a "non-negotiable" prescription and a core component of the "ABC" (Anticoagulation, Better symptom control, Cardiovascular risk reduction) pathway for all AF patients who smoke.
2. **Utilize Data-Driven Counseling:** Clinicians should use the **significant** prognostic data from this review to motivate patients. Specifically, counseling that "quitting smoking after your AF diagnosis can lower your risk of a fatal stroke by over 50%" (Lee et al., 2021) is more powerful than generic advice.
3. **Proactive Management in VKA Patients:** Clinicians managing AF patients on warfarin who smoke must be *hyper-vigilant* about frequent INR monitoring, recognizing the high risk of therapeutic failure (Nakagawa et al., 2015). These patients should be considered priority candidates for switching to a DOAC, which removes this specific drug-behavior interaction.
4. **Manage Ablation Expectations:** Patients with a significant smoking history (current or former) should be counseled that they are at a high, significant risk of AF recurrence post-ablation (Okutucu et al., 2010) due to probable irreversible substrate damage.

For Future Research:

1. **DOAC-Era Prognostic Studies:** There is an urgent need for large-scale, prospective cohort studies that stratify prognostic risk (especially for stroke) by anticoagulation type (VKA vs. DOAC) to definitively test the "VKA-interaction hypothesis."
2. **Cessation Trials in AF:** Randomized Controlled Trials (RCTs) are needed to test the efficacy of smoking cessation interventions (e.g., varenicline, bupropion, structured counseling) (Mills et al., 2014; Wu et al., 2015) *specifically* in the AF population, using MACE, stroke, and mortality as primary endpoints.
3. **Biomarker-Based Studies:** To overcome the limitations of self-report bias, future prognostic studies should incorporate objective biomarkers (e.g., plasma cotinine (Zuo et al., 2018)) to quantify smoking exposure and its dose-dependent prognostic impact.

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