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Residual Risk of Recurrent Stroke Despite Anticoagulation in Patients With Atrial Fibrillation
A Systematic Review and Meta-Analysis

John J. McCabe, PhD; Yuen Cheung, MB; Marianne Foley, MB; Stephen O. Brennan, MB; Jane Buckley, MB; Pol Camps Renom, PhD; Tim Cassidy, MD; Ronan Collins, MD; Eamon Dolan, MD; Gerrit M. Grosse, MD, PhD; Joseph Harbison, MD; Kirstyn James, MD; Kayvan Khadjooi, MD; Isuru Induruwa, PhD; Mira Katan, MD; Senan Maher, MB; Margaret O'Connor, MD; Martin O'Donnell, PhD; Francisco Purroy, PhD; Padraig Synott, MB; Peter J. Kelly, MD

IMPORTANCE Atrial fibrillation (AF) is a leading cause of stroke, and oral anticoagulants (OAC) reduce this risk. However, there are limited data on the residual risk of recurrent stroke in patients with AF.

OBJECTIVE To determine the recurrent stroke risk in patients with AF by performing a systematic review and meta-analysis.

DATA SOURCES Eligible studies were identified by searching Ovid MEDLINE and Embase from inception (Ovid: January 1946; Embase: January 1970) until January 2025.

STUDY SELECTION Eligible studies enrolled patients with prior ischemic stroke and AF, reported information on incidence of recurrent stroke, and had follow-up data for 1 or more years. Three reviewers independently screened abstracts and performed full-text reviews.

DATA EXTRACTION AND SYNTHESIS Data extraction was performed by 2 reviewers and independently verified by a third. Incidence rates were pooled using random-effects meta-analysis. Analysis was repeated in patients whose qualifying event occurred despite OAC. Study quality was assessed using the Quality In Prognosis Studies tool.

MAIN OUTCOMES AND MEASURES The primary outcome was recurrent ischemic stroke. The secondary outcomes were any recurrent stroke (ischemic stroke or intra-cerebral hemorrhage [ICH]) and ICH during follow-up.

RESULTS A total of 23 studies were identified, which included 78 733 patients and 140 307 years of follow-up. The median proportion of OAC use across studies was 92%. The pooled incidence of recurrent ischemic stroke was 3.75% per year (95% CI, 3.17%-4.33%). The risk was higher in noninterventional observational cohorts (4.20% per year; 95% CI, 3.41%-4.99%) compared with randomized clinical trials (2.26% per year; 95% CI, 1.96%-2.57%) (*P* value for interaction <.001). The risk of any recurrent stroke was 4.88% per year (95% CI, 3.87%-5.90%), and the risk of ICH was 0.58% per year (95% CI, 0.43%-0.73%). In patients with stroke despite OAC, the risk was 7.20% per year (95% CI, 5.05%-9.34%) for ischemic stroke, 8.96% per year (95% CI, 8.25%-9.67%) for any stroke, and 1.40% per year (95% CI, 0.40%-2.40%) for ICH.

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis, even with modern prevention therapy, the residual recurrence risk after AF-related stroke is high, with an estimated 1 in 6 patients experiencing a recurrent ischemic stroke at 5 years. These data demonstrate an urgent need to improve our understanding of the biological processes responsible for recurrence, improve risk stratification, and develop new secondary prevention strategies after AF-related stroke.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: John J. McCabe, PhD, Health Research Board Stroke Clinical Trials Network Ireland, University College Dublin Clinical Research Centre, Catherine McAuley Centre, Nelson Street, Dublin 7, Ireland (mccabej1@tcd.ie).

As of 2021, the worldwide prevalence of stroke approached 94 million.[1] Atrial fibrillation (AF) is mechanistically implicated in approximately 1 in 3 ischemic strokes,[2] and absolute case numbers of both AF[3] and AF-related stroke[4] are anticipated to dramatically increase due to population aging. Oral anticoagulants (OACs) are the cornerstone of stroke prevention in AF. Anticoagulation reduces stroke risk by 60%, with an absolute incidence of just 1% to 2% per year observed in the intervention arm of pivotal randomized clinical trials (RCTs).[5-9] However, recurrent stroke in AF despite optimal prevention therapy is an emerging unmet clinical need. Recent reports show that stroke despite OAC now accounts for almost 40% of AF-related strokes.[10] It is well established that prior stroke is the single most important risk factor for future stroke in patients with AF.[11] Despite this, there are limited data pertaining to the residual risk of stroke recurrence after AF-related stroke. Accurate quantification of this risk is critically important for patient counseling, prioritization of further research in secondary prevention, and for public health planning. In the present systematic review and meta-analysis, we aimed to establish the residual risk of recurrent stroke in patients with AF, which we derived from study-level estimates.

Key Points

Question What is the residual risk of recurrent stroke in patients with atrial fibrillation (AF)?

Findings In this systematic review and meta-analysis, the incidence of recurrence after AF-related stroke was 3.75% per year, but this risk was twice as high in noninterventional observational studies compared to cohorts derived from randomized clinical trials (RCTs). The pooled recurrence risk was 7.20% per year after stroke despite anticoagulation.

Meaning The residual recurrence risk after AF-related stroke remains unacceptably high despite modern secondary prevention, emphasizing the urgent need for new therapeutic strategies and RCTs in this patient population.

Methods

Systematic Review Protocol and Manuscript Preparation

The protocol for the systematic review was prespecified and published on PROSPERO (CRD42024587253). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines were followed.[12]

Eligibility Criteria and Search Strategy

Eligible studies had the following criteria: (1) included 50 or more patients with ischemic stroke or transient ischemic attack and paroxysmal, persistent, or permanent AF; (2) reported data on recurrent stroke (ischemic or any stroke) from which the incidence rate of recurrent stroke could be reliably recorded (eAppendix 2 in Supplement 1); (3) were cohort studies or data taken from RCTs; and (4) had follow-up for 1 or more years. Studies that only reported composite outcomes (eg, recurrent stroke and death) or surrogate outcomes or studies from which the incidence could not be reliably calculated were excluded.

Our search used a combination of medical subject headings and free text search terms in Ovid MEDLINE (which spans from January 1946 to January 2025) and Embase (January 1970 to January 2025) (eAppendix 1 in Supplement 1). We searched conference abstracts and reference lists of relevant articles to identify other eligible study reports. Three reviewers (J.M., Y.C., and M.F.) independently screened abstracts and performed full-text reviews. Uncertainties regarding eligibility were resolved by consensus.

Assessment of Study Quality

The Quality In Prognosis Studies (QUIPS) tool was used to assess the risk of bias and was adjudicated by 2 investigators (Y.C. and M.F.) (eAppendix 3 in Supplement 1).[13] A third reviewer adjudicated in the event of a conflict in ratings.

Data Extraction

Data extraction was performed using a standardized template by 2 reviewers (Y.C. and M.F.) and independently verified for accuracy by a third reviewer (J.M.). Key information collected included study location, design, years of study, demographics, OAC use, AF burden, follow-up duration, number of recurrent stroke events, and event subtypes (ischemic stroke, intracerebral hemorrhage [ICH]).

Outcomes

The primary outcome was first recurrent ischemic stroke during follow-up. The secondary outcomes were any recurrent stroke (ischemic or hemorrhagic) and ICH. The primary analysis included all cohorts of patients with a history of AF-related stroke. In a secondary analysis, we estimated the risk of recurrence after stroke despite anticoagulation.

Statistical Analysis

Continuous data were summarized as means with standard deviations or medians with interquartile ranges. In the primary analysis, the pooled annualized incidence across all studies was determined using random-effects meta-analysis. Statistical heterogeneity was calculated using the I^2 statistic.[14] Where possible, meta-regression was performed to determine the association between key secondary predictors and the primary outcome. Prespecified subgroup analyses according to study design and risk of bias were performed. We performed a sensitivity analysis restricted to studies with very high proportion of discharge OAC use (≥90%) and studies without high risk of bias in any domain. For the key secondary analysis, the risk of recurrent stroke was separately calculated in patients who had experienced stroke despite anticoagulation. We investigated for small study effects by visual inspection of funnel plots for asymmetry and using the Egger test.[15] Stata version 17.0 (StataCorp) software was used for statistical analyses. The metaprop command was used to perform random-effects meta-analysis and to test for interstudy and between-subgroup heterogeneity.[16] P values were 2-tailed, and a $P<.05$ was considered significant.

Table. Study Characteristics

Source	Year	Prospective (design)	Multi-centered	Location	Sample	OAC, No. (%)	Mean follow-up, y	Events, No.[a]
Athens Stroke Registry[29]	2001	Yes (OC)	Yes	Greece	811	100 (12.3)	3.18	308
FibStroke[27]	2008	No (OC)	Yes	Finland	899	419 (46.6)	3.48	128
Taiwan National Health Insurance Research Database[28]	2016	No (OC)	Yes	Taiwan	1979	1979 (100)	1.47	191
Hindsholm et al[23]	2018	No (OC)	Yes	Denmark	8119	8119 (100)	2.94	663
ENGAGE AF-TIMI[34]	2009	Yes (RCT)	Yes	International	5973	5973 (100)	2.57	363
CRCS-K[26]	2015	Yes (OC)	Yes	Korea	12 500	8779 (70.2)	1.0	367
RE-LY[17,18]	2006	Yes (RCT)	Yes	International	3623	3623 (100)	1.98	136
ARISTOTLE[17,20]	2008	Yes (RCT)	Yes	International	3436	3436 (100)	1.75	125
NTUH Registry[40]	2016	No (OC)	No	Taiwan	361	361 (100)	2.39	30
LRSP[21]	2017	No (OC)	No	Slovenia	1001	1001 (100)	2.80	46
ROCKET-AF[17,22]	2008	Yes (RCT)	Yes	International	7468	7468 (100)	1.71	295
AVERROES[17,19]	2008	Yes (RCT)	Yes	International	764	390 (51.0)	1.10	36
Wang et al[39]; Ip et al[24]	2018	No (OC)	Yes	Hong Kong	3809	2156 (56.6)	2.50	368
MICON[37]	NS	Yes (OC)[b]	Yes	International	7839	6753 (86.1)	1.72	412
Seiffge et al[35]	2016	Yes (OC)[b]	Yes	International	5413	4929 (92.8)	1.13	289
K-ATTENTION[25]	2014	Yes (OC)	Yes	South Korea	2239	1653 (73.8)	1.46	115
Fukuoka Stroke Registry[30]	2011	Yes (OC)	Yes	Japan	1611	1464 (90.9)	2.4	251
Po and Lin[33]	2015	Yes (OC)	No	Taiwan	511	389 (76.1)	2.18	58
Senel and Karadeniz[36]	2006	No (OC)	No	Turkey	152	NS	7.88	16
Ontario Stroke Registry[38]	2008	No (OC)	Yes	Canada	7491	4260 (56.9)	0.87	700
Okuyama et al[31]	2005	Yes (OC)	No	Japan	192	176 (91.7)	1.23	19
RENO-EXTEND[32]	2019	Yes (OC)	Yes	International	1240	1240 (100)	1.25	111
J-Dabigatran Surveillance Program[41]	2012	Yes (OC)	Yes	Japan	1302	1302 (100)	1.24	36

Abbreviations: ARISTOTLE, Apixaban for Reduction in Stroke and Other Thrombo-embolic Events in Atrial Fibrillation; AVERROES, Apixaban vs Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; CRCS-K, Clinical Research Collaboration for Stroke in Korea; ENGAGE AF-TIMI, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction; K-ATTENTION, Korean Atrial Fibrillation Evaluation Registry in Ischemic Stroke Patients; LRSP, Ljubljana Registry of Secondary Stroke Prevention; MICON, Microbleeds International Collaborative Network; NS, not stated; NTUH, National Taiwan University Hospital; OAC, oral anticoagulant; OC, observational cohort; RCT, randomized clinical trial; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; RENO-EXTEND, Risk Factors of Cerebral Ischemic Events in Patients With Nonvalvular AF Treated With NOACs for Stroke Prevention; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; TIA, transient ischemic attack.

[a] Events refers to recurrent ischemic stroke.

[b] Indicates study was an individual participant data analysis of observational cohorts.

Results

Study Selection

The search returned 5989 records, of which 25 study reports from 23 eligible studies were identified (eFigure 1 in Supplement 1).[17-41] Characteristics of included studies are summarized in the **Table**.[17-41] Of the 23 studies, 18 were observational cohort studies and 5 were observational data derived from subgroup analyses of RCTs. Eight studies were retrospective. We included data from 2 large individual participant data (IPD) meta-analyses.[35,37] The combined sample size across studies was 78 733 patients with 140 307 cumulative patient-years of follow-up. Of the 23 cohorts, 9 were performed in Asia (n = 24 504), 5 in Europe (n = 10 982), 1 in North America (n = 7491), and 8 enrolled across 2 or more continents (n = 35 756). The proportion of patients discharged receiving OAC varied substantially (12.1%-100%), with a median proportion of 92% across studies. Baseline characteristics of included patients across studies are summarized in eTable 1 in Supplement 1.

Study Quality

The risk of bias assessment for included studies is summarized in eTable 2 in Supplement 1. Three studies were deemed at high risk of bias in 1 or more domains (eAppendix 3 in Supplement 1). Outcome assessment was the most frequent source of bias, with 6 of 23 studies rated at moderate risk and 3 of 23 studies at high risk.

Residual Risk of Recurrent Stroke

A total of 21 studies reported data for the primary outcome during follow-up, during which time there were 4504 events. The pooled incidence of recurrent ischemic stroke was 3.75% per year (95% CI, 3.17%-4.33%), with substantial statistical heterogeneity (I^2 = 97%). The risk was significantly higher in patients included in noninterventional cohort studies (4.20% per year; 95% CI, 3.41%-4.99%) compared to those enrolled in RCTs

(2.26% per year; 95% CI, 1.96%-2.57%) (*P* for interaction <.001) (**Figure 1**). On meta-regression analysis, between-study differences in the incidence of recurrent stroke were associated with increasing age (β coefficient, 1.0028; 95% CI, 1.0000-1.0005) and stroke despite OAC (β, 1.0006; 95% CI, 1.0003-1.0008). There was a nonsignificant trend toward association between follow-up duration and recurrence (β, 0.9940; 95% CI, 0.9879-1.0002; *P* = .06), but no association with poststroke OAC use, study year, CHA_2DS_2-VASc, or prior stroke (**Figure 2**; eFigures 2-4 in Supplement 1).

A total of 12 studies reported data for the outcome of any recurrent stroke (ischemic or hemorrhagic), for which there were 3445 events. The incidence rate of any recurrent stroke was 4.88% per year (95% CI, 3.87%-5.90%), with substantial between-study statistical heterogeneity (I^2 = 98%) (Figure 2). Again, the risk was substantially higher in noninterventional cohorts (6.28% per year; 95% CI, 4.90%-7.65%) than in cohorts derived from RCTs (2.68% per year; 95% CI, 2.35%-3.00%) (*P* for interaction <.001). Eleven studies provided data on ICH during follow-up, of which there were 519 events. Overall, the risk of ICH was 0.58% per year (95% CI, 0.43%-0.73%; I^2 = 88.7%). The risk of ICH was nonsignificantly lower in observational data from RCTs (0.44% per year; 95% CI, 0.33%-0.55%) than in noninterventional observational studies (0.68% per year; 95% CI, 0.42%-0.95%) (*P* for interaction = .10) (Figure 1).

Recurrence Risk After Stroke Despite Anticoagulation

Six studies provided data separately for patients who had experienced a stroke despite OAC, 1 of which was a pooled IPD from 5 pivotal RCTs.[17,23,24,28,32,35] In total, there were data for 10 989 patients and 1106 recurrent ischemic strokes. The pooled incidence rate of the primary outcome was 7.20% per year (95% CI, 5.05%-9.34%; I^2 = 97%) in patients who had already had a stroke while taking OAC. The risk of any recurrent stroke during follow-up was 8.96% per year (95% CI, 8.25%-9.67%; 2 studies), and the risk of ICH was 1.40% per year (95% CI, 0.40%-2.40%; I^2 = 93%; 3 studies) (**Figure 3**).

Projected 5-Year Recurrence Risk

Based on these pooled estimates, the 5-year cumulative risk of first recurrent ischemic stroke in patients with AF was estimated to be 17.4%. The projected risk for any stroke (ischemic or hemorrhagic) was 22.1%. In patients who experience stroke despite OAC, the risks of recurrent ischemic or any stroke were anticipated to be 31.2% and 37.5%, respectively (eTable 3 in Supplement 1).

Subgroup and Sensitivity Analyses

The risk of recurrent ischemic stroke was lower in studies rated at high risk of bias in 1 or more domains (1.97% per year; 95% CI, 1.06%-2.87%) compared to those with low or moderate bias (4.03% per year; 95% CI, 3.40%-4.65%) (*P* for interaction <.001) (eFigure 5 in Supplement 1). The pooled risk was similar in prospective (3.25% per year; 95% CI, 2.82%-3.68%) and retrospective studies (4.32% per year; 95% CI, 2.30%-6.35%) (*P* for interaction = .31) (eFigure 6 in Supplement 1). In a sensitivity analysis after exclusion of studies with baseline OAC use of less than 90%, the risk of recurrent ischemic stroke was 3.16% per year (95% CI, 2.60%-3.72%; I^2 = 96%) (eFigure 5 in Supplement 1), risk of any stroke was 4.01% per year (95% CI, 3.03%-4.99%; I^2 = 98%), and risk of ICH was 0.55% per year (95% CI, 0.36%-0.75%; I^2 = 90%).

Small Study Effects

There was evidence of small study effects on visual inspection for funnel asymmetry and using the Egger test (β, 5.67; 95% CI, 0.86-10.50; *P* = .02) (eFigure 8 in Supplement 1).

Discussion

In this systematic review and meta-analysis, we provide contemporary estimates for the risk of recurrent stroke in patients with AF. We report several key findings. First, despite high OAC use, we report a residual recurrent ischemic stroke risk of approximately 4% per year. Consequently, we estimate that 1 in 6 patients with AF will experience a recurrent ischemic stroke at 5 years. Second, the risk of recurrent stroke was 2-fold greater for patients included in noninterventional cohorts compared to those enrolled in RCTs, indicating a higher risk in real-world practice than appreciated previously. Third, patients with AF who have a stroke despite OAC use are a very high-risk patient group, with a stroke recurrence risk approaching 9% per year. Taken together, these data indicate that the current treatment paradigm for secondary prevention of stroke in AF is suboptimal. Future research is urgently needed to identify patients at greatest risk and develop new therapeutic strategies to reduce this residual risk.

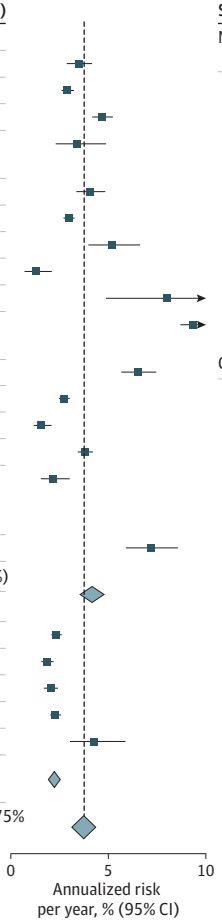
AF represents a growing threat to population health. AF cases almost doubled from 2010 to 2019,[42] and the lifetime risk of AF now approaches 1 in 3 individuals.[43] Stroke due to AF is associated with substantial disability. For instance, compared to stroke events due to other mechanisms, AF-related stroke is associated with a higher incidence of large vessel occlusion, poor functional outcome, and poststroke dementia.[44,45] Our results demonstrating a high residual recurrence risk strongly suggest that anticoagulation alone may be inadequate for long-term secondary prevention after AF-related stroke. Indeed, due to this high event rate, RCTs evaluating emerging prevention measures after stroke due to AF are likely to be feasible. These data should encourage investigators and funders to pursue definitive intervention studies that are urgently required to improve outcomes in these patients.

Several promising therapeutic avenues for secondary stroke prevention have emerged.[46] Percutaneous left atrial appendage occlusion (pLAAO) is an alternative strategy to OAC in patients whom anticoagulation is contraindicated.[47] However, data from the LAAOS-III (Left Atrial Appendage Occlusion Study III) trial provided proof of concept that surgical LAAO provides additional benefit for stroke prevention when added to anticoagulation in patients undergoing cardiothoracic surgery.[48] While these data cannot be directly extrapolated to patients with a history of prior stroke, they do provide a compelling rationale that select high-risk patients after AF-related stroke may derive sufficient benefit from LAAO to

Figure 1. Annualized Risk of Recurrent Stroke

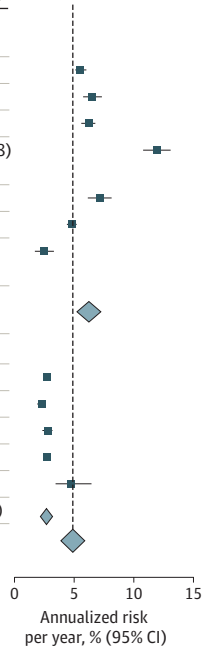
A Recurrent ischemic stroke

Study	Sample, No.	Annualized risk per year, % (95% CI)
Noninterventional cohorts		
K-ATTENTION[25]	2239	3.52 (2.91-4.21)
CRCS-K[26]	12 500	2.94 (2.65-3.25)
Seiffge et al[35]	5413	4.72 (4.20-5.28)
NTUH Stroke Registry[40]	361	3.48 (2.36-4.94)
FibStroke[27]	899	4.09 (3.43-4.85)
MICON[37]	7839	3.05 (2.76-3.35)
Po et al[33]	511	5.22 (3.98-6.69)
Senel et al[36]	152	1.34 (0.77-2.16)
Okuyama et al[31]	192	8.02 (4.90-12.24)
Ontario Stroke Registry[38]	7491	9.34 (8.69-10.03)
Taiwan NHIRD[28]	1979	6.56 (5.69-7.52)
Hindsholm et al[23]	8119	2.78 (2.57-2.99)
LRSP[21]	1001	1.64 (1.20-2.18)
Wang et al[39]	3809	3.86 (3.49-4.27)
J-Dabigatran Surveillance Program[41]	1302	2.22 (1.56-3.07)
RENO-EXTEND[32]	1240	7.16 (5.93-8.56)
Pooled incidence, 4.20% per year (95% CI, 3.41%-4.99%)		
Cohorts from RCTs		
ENGAGE AF-TIMI[17,34]	5973	2.36 (2.13-2.61)
RE-LY[17,18]	3623	1.89 (1.59-2.24)
ARISTOTLE[17,20]	3436	2.08 (1.74-2.48)
ROCKET-AF[17,22]	7468	2.31 (2.06-2.59)
AVERROES[17,19]	764	4.29 (3.02-5.88)
Pooled incidence, 2.26% per year (95% CI, 1.96%-4.33%)		
P for interaction <.001 (between-subgroup)	Overall pooled incidence, 3.75% (95% CI, 3.17%-4.33%)	



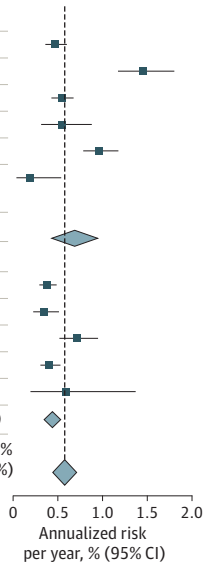
B Any recurrent stroke

Study	Sample, No.	Annualized risk per year, % (95% CI)
Noninterventional cohorts		
CRCS-K[26]	12 500	5.51 (5.12-5.93)
Fukuoka Stroke Registry[30]	1611	6.49 (5.73-7.31)
Seiffge et al[35]	5413	6.18 (5.59-6.82)
Athens Stroke Registry[29]	811	11.96 (10.73-13.28)
Taiwan NHIRD[28]	1979	7.11 (6.20-8.11)
Wang et al[39]	3809	4.76 (4.34-5.20)
J-Dabigatran Surveillance Program[41]	1302	2.41 (1.72-3.28)
Pooled incidence, 6.28% per year (95% CI, 4.90%-7.65%)		
Cohorts from RCTs		
ENGAGE AF-TIMI[17,34]	5973	2.69 (2.44-2.96)
RE-LY[17,18]	3623	2.21 (1.89-2.58)
ARISTOTLE[17,20]	3436	2.72 (2.32-3.16)
ROCKET-AF[17,22]	7468	2.69 (2.42-2.99)
AVERROES[17,19]	764	4.76 (3.42-6.43)
Pooled incidence, 2.68% per year (95% CI, 2.35%-3.00%)		
P for interaction <.001 (between-subgroup)	Overall pooled incidence, 4.88% (95% CI, 3.87%-5.90%)	



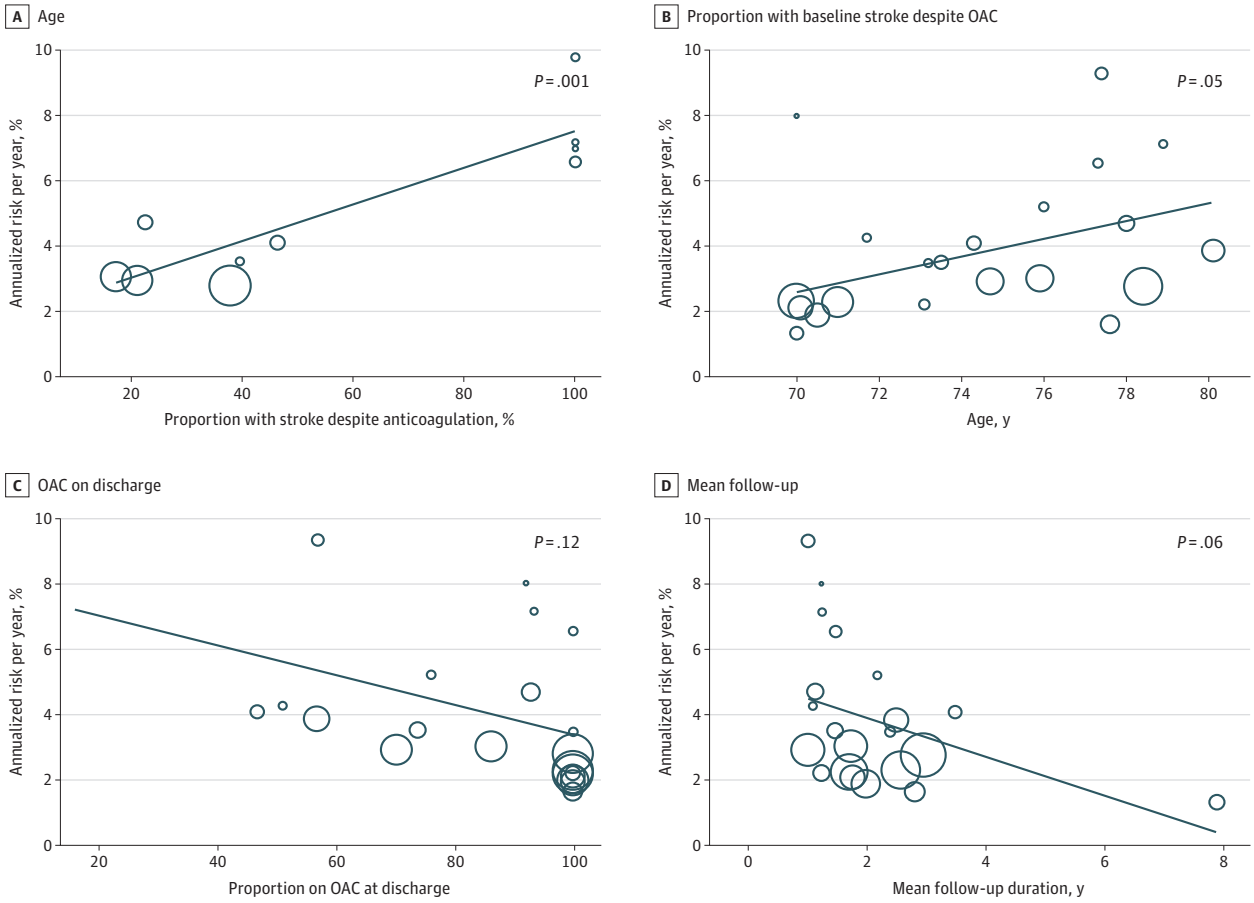
C ICH

Study	Sample, No.	Annualized risk per year, % (95% CI)
Noninterventional cohorts		
CRCS-K[26]	12 500	0.47 (0.36-0.61)
Seiffge et al[35]	5413	1.47 (1.18-1.80)
MICON[37]	7839	0.55 (0.43-0.69)
Taiwan NHIRD[28]	1979	0.55 (0.31-0.89)
Wang et al[39]	3809	0.98 (0.79-1.20)
J-Dabigatran Surveillance Program[41]	1302	0.19 (0.04-0.54)
Pooled incidence, 0.68% (95% CI, 0.42%-0.95%)		
Cohorts from RCTs		
ENGAGE AF-TIMI[17,34]	5973	0.38 (0.29-0.49)
RE-LY[17,18]	3623	0.35 (0.23-0.51)
ARISTOTLE[17,20]	3436	0.72 (0.52-0.96)
ROCKET-AF[17,22]	7468	0.41 (0.30-0.53)
AVERROES[17,19]	764	0.60 (0.19-1.38)
Pooled incidence, 0.44% per year (95% CI, 0.33%-0.55%)		
P for interaction = .01 (between-subgroup)	Overall pooled incidence, 0.58% per year (95% CI, 0.43%-0.73%)	



Recurrent ischemic stroke (A), any recurrent stroke (B), and intracerebral hemorrhage (ICH) (C); results were also stratified by study design (randomized clinical trial [RCT] vs noninterventional observational cohorts). LRSP, Ljubljana Registry of Secondary Stroke Prevention; MICON, Microbleeds International Collaborative Network; NHIRD, National Health Insurance Research Database; NTUH, National Taiwan University Hospital.

Figure 2. Meta-Regression Analysis



Data are presented according to age (A), proportion with baseline stroke despite oral anticoagulant (OAC) (B), OAC on discharge (C), and mean follow-up (D). The center of the bubbles indicates the annualized risk for each study, with the size of the bubble inversely proportional to the standard error. The solid blue line is the fitted regression line.

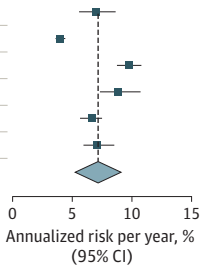
justify the intervention. The ELAPSE (Early Closure of Left Atrial Appendage for Patients With Atrial Fibrillation and Ischemic Stroke Despite Anticoagulation Therapy) trial (NCT05976685) will test this hypothesis by evaluating the potential benefit of pLAAO in addition to OAC in patients with stroke despite anticoagulation. The LAAOS-IV (The Fourth Left Atrial Appendage Occlusion Study) trial (NCT05963698) will compare the addition of pLAAO to OAC with OAC alone in patients with high CHA_2DS_2-VASc and sustained AF. Other mechanical interventions might include carotid filter placement to prevent large cardioembolic thrombi reaching the brain, which will be investigated in the INTERCEPT (Carotid Implants for Prevention of Stroke Recurrence from Large Vessel Occlusion in Atrial Fibrillation Patients Treated with Oral Anticoagulation) trial (NCT05723926). The restoration of sinus rhythm in patient with AF using anti-arrhythmic drugs or catheter ablation was shown to lower the risk of major adverse cardiovascular events (MACE), including stroke, in the EAST-AFNET 4 (Early Rhythm-Control Therapy in Patients with Atrial Fibrillation) trial.[49] A subgroup analysis of patients with prior stroke demonstrated findings consistent with the main analysis, but the absolute risk reduction was much greater due to a higher residual risk in patients with stroke.[50] The EAST-STROKE (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial in Acute STROKE) trial (NCT05293080) will now evaluate the efficacy of early rhythm control for secondary prevention of MACE after AF-related stroke. Other pharmacological therapies aimed at reducing stroke in AF could target inflammatory pathways. Mendelian randomization studies have shown that genetic downregulation of interleukin 18 (IL-18) signaling prevents cardiac remodeling and lowers the risk of AF, cardioembolic stroke, and heart failure.[51] While IL-18 may be a potential druggable target in AF, compelling preclinical work has also demonstrated that inhibition of the NLRP3 inflammasome (upstream of IL-18) may also be a promising therapeutic avenue.[52] Apart from new treatments, multifaceted poststroke interventions that enhance behavioral factors, medication adherence, and improved goal-directed care of cardiovascular risk factors also should be considered for future trial design.

While our data indicate a high risk of recurrent stroke across the population of AF-related stroke, individual risk prediction tools are clearly needed to identify those at highest risk.

Figure 3. Annualized Risk of Recurrence After Stroke Despite Anticoagulation

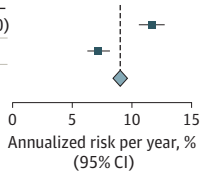
A Recurrent ischemic stroke

Study	Sample, No.	Annualized risk per year, % (95% CI)
COMBINE AF[17]	1163	7.00 (5.54-8.71)
Hindsholm et al[23]	3075	3.99 (3.57-4.44)
Ip et al[24]	2337	9.77 (8.77-10.85)
Seiffge et al[35]	1195	8.90 (7.24-10.79)
Taiwan NHIRD[28]	1979	6.56 (5.69-7.52)
RENO-EXTEND[32]	1240	7.16 (5.93-8.56)
Overall pooled incidence, 7.20% per year (95% CI, 5.05%-9.34%)		



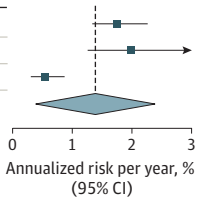
B Any recurrent stroke

Study	Sample, No.	Annualized risk per year, % (95% CI)
Ip et al[24]	2337	11.54 (10.46-12.70)
Taiwan NHIRD[28]	1979	7.11 (6.20-8.11)
Overall pooled incidence, 8.96% per year (95% CI, 8.25%-9.67%)		



C ICH

Study	Sample, No.	Annualized risk per year, % (95% CI)
Ip et al[24]	2337	1.77 (1.34-2.29)
Seiffge et al[35]	1195	2.01 (1.25-3.06)
Taiwan NHIRD[28]	1979	0.55 (0.31-0.89)
Overall pooled incidence, 1.40% per year (95% CI, 0.40%-2.40%)		



Recurrent ischemic stroke (A), any recurrent stroke (B), and intracerebral hemorrhage (ICH) (C). COMBINE-AF indicates A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation; NHIRD, National Health Insurance Research Database; RENO-EXTEND, Risk Factors of Cerebral Ischemic Events in Patients With Nonvalvular AF Treated With NOACs for Stroke Prevention.

However, existing tools, such as CHA_2DS_2-VASc, perform poorly in secondary prevention cohorts.[53] We have recently reported that biomarkers of atrial cardiopathy, small vessel disease, and neuroimaging evidence of prior infarction are each associated with stroke recurrence in patients with AF.[54] However, there are limited data on the value of blood biomarkers (eg, natriuretic peptides) and LAA morphology for determining recurrent stroke in AF,[54] which may yet be shown to provide added value in risk prediction. Collaborative efforts are required to identify new biomarkers for risk prediction after AF-related stroke. This is important, because improved stratification of patients into high-risk and medium-risk groups could help select patients for more intensive secondary prevention measures and inform RCT design.

Stroke despite anticoagulation was associated with a very high risk of recurrence in our analysis. Recent registry data have also shown that most of these patients are appropriately anticoagulated at the time of event.[55] Previous work has shown that patients with stroke despite anticoagulation are older, have a greater burden of cardiovascular risk factors, and have more advanced atrial remodeling compared with patients who are OAC naive at the time of stroke. However, 24% to 35% of these cases have evidence of a competing stroke etiology, and atherosclerotic mechanisms predominate.[56,57] This suggests that the reasons for stroke despite anticoagulation are complex, and an individualized approach to patient care is mandated. Future work should focus on improving our understanding of the biological signatures associated with true OAC failure, specifically in patients who are adherent to OAC therapy and who do not have competing stroke mechanisms. Existing nonrandomized data suggest that switching OAC is ineffective at reducing recurrence, and the addition of anti-platelets increases bleeding risk.[58] However, recent registry data suggest that LAAO may lower the residual stroke risk, thereby furthering the rationale for planned RCTs of LAAO in this high-risk group.[59]

Our work provides important updated information on ICH risk in patients taking OAC after AF-related stroke. The risk of ICH for patients enrolled in RCTs was less than 1 in 200 per year. However, the risk in noninterventional observational cohorts was higher (approximately 1 in 147), and the ICH risk in patients with ischemic stroke despite OAC was 1.4% per year (1 in 70). The higher risk in noninterventional studies is important, as it reflects a greater risk in real-world practice than previously known and emphasizes the importance of modifiable risk factor control for ICH in patients taking OAC, especially blood pressure optimization. The reasons for these risk disparities are unclear but may relate to older age, a higher burden of small vessel disease, and cardiovascular risk factors in

patients enrolled in noninterventional cohorts compared to those typically enrolled in RCTs.

Strengths and Limitations

Our study has several strengths. We provide up-to-date information on the natural history of a condition implicated in 1 in 3 strokes, which has huge public health implications. Our estimates were derived from 23 studies identified by systematic review, encompassing 78 000 patients with over 140 000 years of follow-up. These data are informative for counseling patients and provide a strong justification for RCTs of emerging prevention strategies. We acknowledge that our manuscript has limitations. There was significant statistical heterogeneity in the pooled estimates, which should be considered when interpreting the results. However, high heterogeneity is a frequent occurrence in meta-analyses of single proportions due to differences in population-specific risk factors, geography, and time period when the study was performed, but heterogeneity is also commonly observed due to low variance in point estimates of proportional data.[60] Moreover, this heterogeneity was at least partially explained by several important study-level factors, including proportion of patients with stroke despite OAC, study design, age of participants, and follow-up duration. It is important to note that we were unable to reliably identify patient-specific risk factors for recurrence by meta-regression, which might be more informative for clinical practice. We note that recurrence was lower in studies at risk of bias, so the true risk may even be higher than our estimates suggest. Although the median proportion of patients taking OAC at discharge was high across studies, almost no study provided data on long-term adherence to anticoagulation, some studies had a relatively low baseline use of OACs, and there was also no information on risk factor control during follow-up. These factors may explain some of the residual risk observed. It is also unlikely that all recurrences were due to AF, and other mechanisms are likely in play. However, irrespective of the source of the residual risk, the annualized risk of recurrence is unacceptably high, and efforts to lower it are paramount. Furthermore, we performed a sensitivity analysis, which, even after excluding studies with less than 90% OAC use, demonstrated a high risk of recurrence. We did not have sufficient data to investigate whether the risk of recurrent stroke differs in patients with AF detected after stroke compared with known AF prior to stroke, and this should be the focus of future work.

Conclusions

In this systematic review and meta-analysis, we have demonstrated a high residual risk of recurrent stroke in patients with AF despite modern secondary prevention, including anticoagulation. It is now an urgent research priority to improve our understanding of the biological mechanisms underpinning stroke recurrence in AF and to develop new risk prediction tools to identify patients at greatest risk. These data also provide a clear rationale for future trials of emerging prevention therapies in this high-risk group.

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Author Affiliations: Health Research Board Stroke Clinical Trials Network Ireland, Dublin, Ireland (McCabe, Cheung, Foley, Brennan, Buckley, Cassidy, Collins, Dolan, Harbison, James, Maher, O'Connor, O'Donnell, Synott, Kelly); School of Medicine, University College Dublin, Dublin, Ireland (McCabe, Cheung, Foley, Brennan, Buckley, Synott, Kelly); Stroke Service, Department of Geriatric Medicine, Mater Misericordiae University Hospital, Dublin, Ireland (McCabe, Cheung, Foley, Brennan, Buckley, Cassidy, Synott); Department of Neurology, Institute of Biomedical Research Sant Pau, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain (Renom); Department of Geriatric Medicine, St Vincent's University Hospital, Dublin, Ireland (Cassidy); Department of Geriatric Medicine, Tallaght University Hospital, Dublin, Ireland (Collins); Department of Geriatric Medicine, James Connolly Hospital, Dublin, Ireland (Dolan); Department of Neurology and Stroke Center, University Hospital Basel, Basel, Switzerland (Grosse, Katan); Department of Geriatric Medicine, St James's Hospital, Dublin, Ireland (Harbison); Department of Geriatric Medicine, Cork University Hospital, Cork, Ireland (James); Department of Clinical Neurosciences, Addenbrooke's Hospital, University of Cambridge, Cambridge, United Kingdom (Khadjooi, Induruwa); Department of Geriatric Medicine, Limerick University Hospital, Limerick, Ireland (O'Connor); College of Medicine, Nursing and Health Sciences, University of Galway and University Hospital Galway, Galway, Ireland (O'Donnell); Stroke Unit, Department of Neurology, Hospital Universitari Arnau de Vilanova de Lleida, Lleida, Spain (Purroy); Stroke Service, Department of Neurology, Mater Misericordiae University Hospital, Dublin, Ireland (Kelly).

Author Contributions: Dr McCabe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: McCabe, Cheung, Camps-Renom, Induruwa, Khadjooi, Maher.
Acquisition, analysis, or interpretation of data: McCabe, Cheung, Foley, Brennan, Buckley, Cassidy, Collins, Dolan, Grosse, Harbison, James, Katan, O'Connor, O'Donnell, Purroy, Synnott, Kelly.
Drafting of the manuscript: McCabe, Cheung, Cassidy, Khadjooi, Kelly.
Critical review of the manuscript for important intellectual content: McCabe, Cheung, Foley, Brennan, Buckley, Camps-Renom, Collins, Dolan, Grosse, Harbison, Induruwa, James, Katan, Khadjooi, Maher, O'Connor, O'Donnell, Purroy, Synnott, Kelly.
Statistical analysis: McCabe, Grosse.
Administrative, technical, or material support: McCabe, Cassidy, James, Katan, Kelly.
Supervision: Camps-Renom, Collins, Katan, Kelly.

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