

Residual Risk of Recurrent Stroke Despite Anticoagulation in Patients With Atrial Fibrillation

A Systematic Review and Meta-Analysis

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 Supplemental content

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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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 AF³ and AF-related stroke⁴ 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.

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

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 noninterventive 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.

(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 ($\geq 90\%$) 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 pa-

tients 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 post-stroke OAC use, study year, CHA₂DS₂-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 in-

teraction = .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).

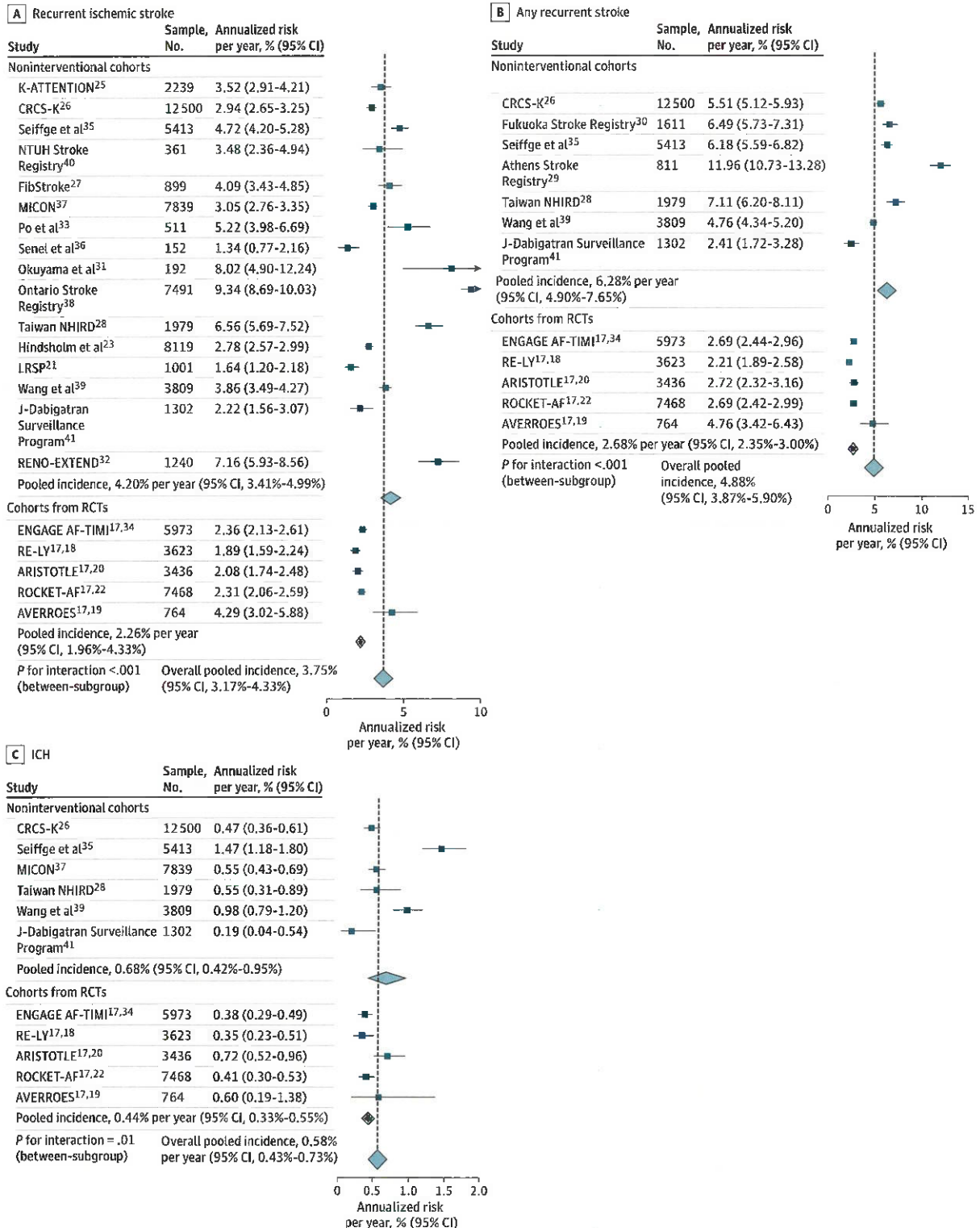
Discussion

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 pro-

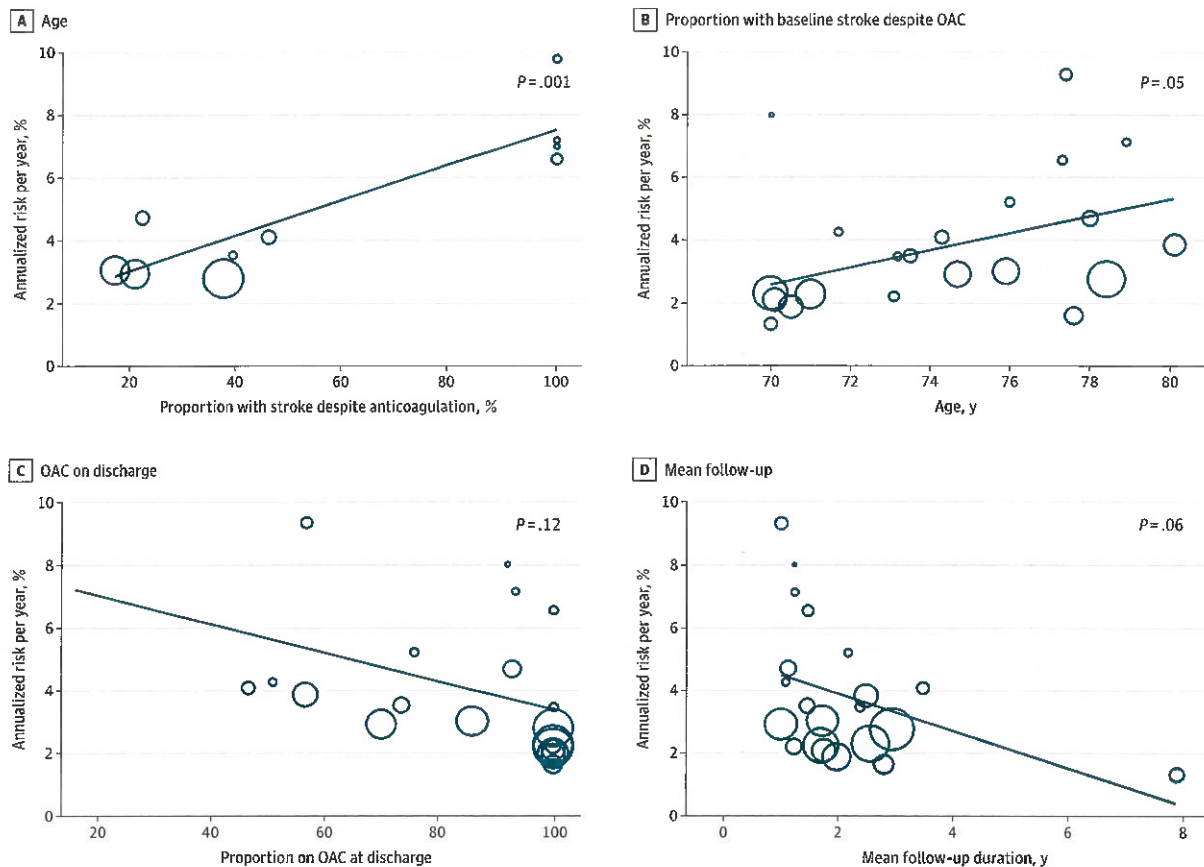
Figure 1. Annualized Risk of Recurrent Stroke



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



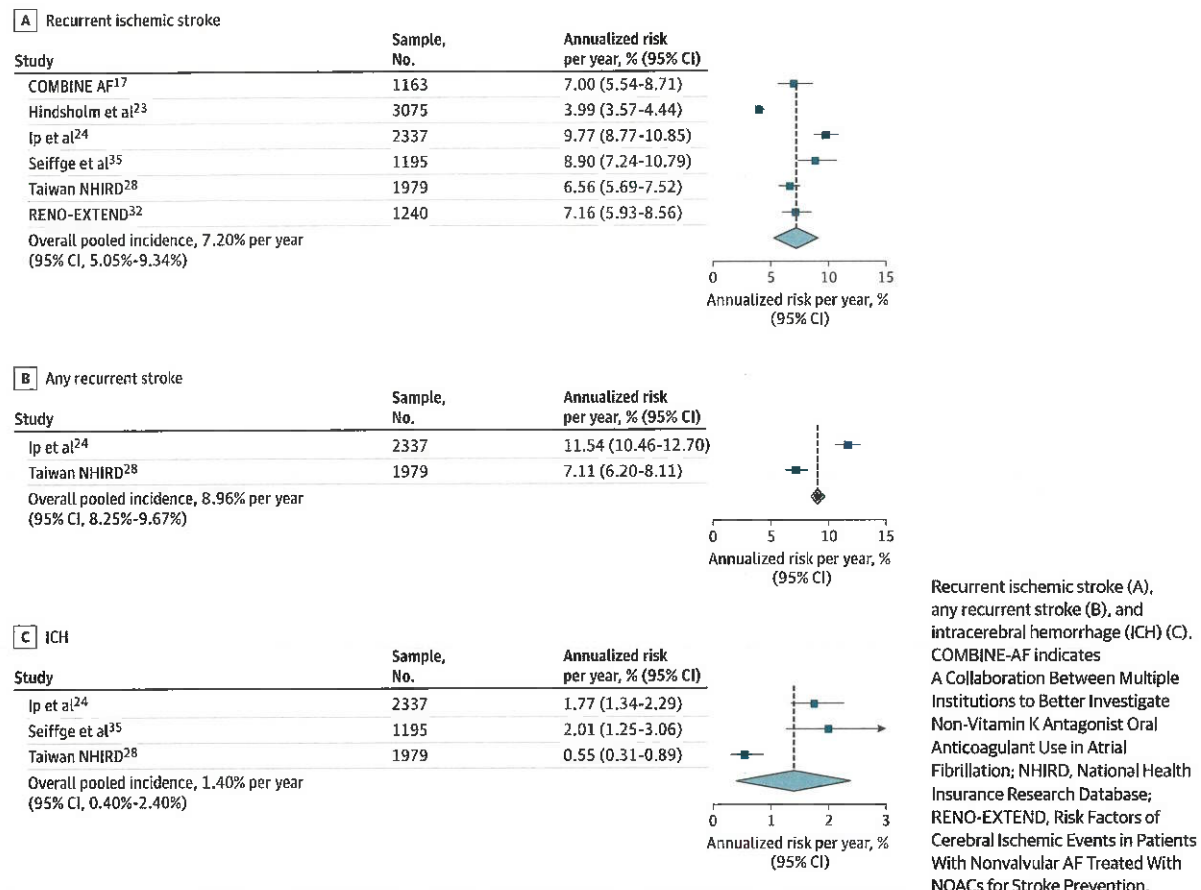
Data are presented according to age (A), proportion with baseline stroke despite oral anticoagulant (OAC) (B), OAC on discharge (C), and mean follow-up (D). The center of the bubbles indicates the annualized risk for each study, with

the size of the bubble inversely proportional to the standard error. The solid blue line is the fitted regression line.

vide a compelling rationale that select high-risk patients after AF-related stroke may derive sufficient benefit from LAAO to 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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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.

Figure 3. Annualized Risk of Recurrence After Stroke Despite Anticoagulation



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. However, existing tools, such as CHA₂DS₂-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 non-randomized 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 modifi-

able 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 stud-

ies 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.

ARTICLE INFORMATION

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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.

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REVIEW

Advances in Ischemic Stroke Treatment: Current and Future Therapies

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ABSTRACT

This review summarizes current concepts in our understanding of stroke anatomy, pathophysiology of cerebral hypoperfusion, and collateral circulation. It also provides an evidence-based update in stroke trials and treatments assessed using PRISMA guidelines. Intravenous thrombolysis, endovascular thrombectomy for anterior circulation strokes, blood pressure control after endovascular thrombectomy, and medical management principles are discussed. Endovascular thrombectomy and medical therapy improves functional independence at 90 days in anterior circulation strokes even in late windows up to 24 h post symptom onset regardless of infarct core size. Intensive systolic blood pressure control acutely post thrombectomy is associated with harm and worse outcomes. This review also provides an evidence-based update on neurorehabilitation strategies with emerging interventions such

as brain–computer interface and robotics having the potential to maximize neuroplasticity for potential improvement and recovery post stroke.

Keywords: Evidence-based update; Stroke trials; Stroke syndromes; Collateral circulation; Thrombolytic therapy; Endovascular thrombectomy; Stroke neurorehabilitation; Brain–body interactions

Key Summary Points

Stroke is a leading cause of adult-onset disability with over half of stroke survivors beyond 6 months dependent on others for at least one activity of daily living.

Evidence-based review of randomized controlled trials for treatment of anterior circulation strokes shows significant improvement in functional independence at 90 days after endovascular thrombectomy plus medical therapy in patients with stroke with symptom onset up to 24 h.

Evidence-based review of randomized controlled trials investigating blood pressure control after endovascular thrombectomy reveals harm and more functional disability with intensive systolic blood pressure control under 140 mmHg.

Evidence-based review of neurorehabilitation randomized controlled trials post stroke demonstrates that intensive and repetitive training is key for motor improvement.

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INTRODUCTION

Stroke is a leading cause of adult-onset disability. Over half of stroke survivors beyond 6 months are dependent on others for at least one activity of daily living. Annually, there are over 12 million incident cases of stroke, of which 65% are ischemic strokes. Patients with stroke with symptomatic steno-occlusive disease have a risk of recurrent stroke of at least 10–15% within 5 years. Globally, stroke accounts for over seven million deaths each year [1]. Modifiable risk factors include blood pressure management, blood glucose and cholesterol control, physical activity, weight management, and environmental exposure such as air pollution. Acute ischemic stroke is a heterogeneous disease with various stroke subtypes, including atherothrombotic infarct involving large vessel occlusions, cardioembolic infarct, lacunar infarct involving penetrating arteries and perforators, subcortical infarct without clear etiology, and infarct of unusual etiology such as hypercoagulable states, vasculitis, genetic disorders, and dissection [2, 3]. This review provides an evidence-based update for current and future therapies for ischemic stroke.

METHODS

The study authors independently searched PubMed and Embase from 2020 to 2025 using search terms “stroke” and “randomized controlled trials”. Identified systematic reviews and meta-analyses were assessed on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Studies that were methodologically rigorous and had clinically impactful and generalizable results were selected for this review. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

STROKE-RELATED SCALES

The modified Rankin scale (mRS) is a functional assessment scale measuring the degree of

disability or dependence in patients with stroke. It is a 7-point scale ranging from 0 (no symptoms) to 6 (death). (Table 1) [4].

The National Institutes of Health Stroke Scale (NIHSS) is a 15-item neurological examination used to assess stroke severity and changes in clinical status. The NIHSS score ranges from 0 to 42, scoring areas including level of consciousness, eye movements (gaze deviation), visual fields, facial weakness, motor strength, limb ataxia and coordination, sensory loss, language function (dysphasia/aphasia), speech clarity (dysarthria), and neglect/inattention (hemispatial neglect) (Table 2) [4]. NIHSS scores of ≥ 10 are 73% sensitive and 74% specific for predicting the presence of large vessel occlusion [5]. However, this scoring system may underestimate the severity of posterior circulation strokes.

Intravenous thrombolysis and mechanical thrombectomy are standards of care for treatment of acute ischemic stroke, with angiographic goal of mTICI (modified Treatment in Cerebral Infarction) score of 2b whereby revascularization is achieved in over 50% of subdivisions of the involved major vascular territory (Table 3) [5–7].

CEREBRAL HYPOPERFUSION AND COLLATERAL CIRCULATION

Cerebral ischemia may ensue in the setting of cerebral hypoperfusion. Traditional stroke syndromes are summarized in Table 4. In addition to cerebral ischemic symptomatology pertaining to the affected vascular territory, orthostatic symptoms, syncope, transient global amnesia, episodic limb shaking, and watershed infarction are possible.

Several clinical factors affect the extent of cerebral hypoperfusion in the setting of ischemia. They include (1) extent of hemodynamic impairment and cardiac status, (2) cerebral autoregulatory impairment and extent of compensatory cerebral collateral circulation, (3) presence of metabolic syndrome of hypertension, hyperlipidemia, and insulin resistance, and (4) brain–body interactions affecting

Table 1 Modified Rankin scale (mRS)

mRS	Daily function
0	No symptoms
1	No significant disability
2	Slight disability, independent but unable to carry out all previous ADL
3	Moderate disability, can walk independently but requires help with ADL
4	Moderately severe disability, not independent with ADL
5	Severe disability, full-time nursing care
6	Death

ADL activities of daily living

Table 2 Stroke severity based on NIHSS score

NIHSS score	Stroke severity
0	No stroke symptoms
1–4	Minor stroke
5–15	Moderate stroke
16–20	Moderate to severe stroke
21–42	Severe stroke

Table 3 Modified thrombolysis in cerebral infarction (mTICI) grading system

mTICI score	Description
0	No reperfusion
1	Minimal reperfusion
2a	Partial reperfusion < 50% of major vascular territory
2b	Partial reperfusion > 50% of major vascular territory
3	Complete reperfusion with filling of all distal branches

blood oxygen carrying capacity and delivery (including coagulation status, anemia, other hematologic disorders, systemic infection and sepsis, renal and hepatic disorders).

In states of misery perfusion, compensatory cerebral vasodilation is not possible as the cerebral autoregulatory capacity is exhausted and, as a result, cerebral blood flow decreases proportionally with cerebral perfusion pressure (Fig. 1, Table 5).

Possible cerebral collateral circulation routes include (1) contralateral internal carotid artery (ICA) through anterior communicating artery, (2) posterior circulation via posterior communicating artery, (3) leptomeningeal or pial collaterals, (4) collateral circulation from external carotid artery (ECA) with retrograde flow and connections with ophthalmic artery, extracranial connections between external carotid artery (ECA) or vertebral artery (VA) branches and distal internal carotid artery (ICA), (5) collaterals through dural meningeal arteries to cortical arteries, (6) anterior cerebral artery (ACA)–posterior cerebral artery (PCA) connections via the limbic loop, and (7) anterior spinal artery collaterals with the vertebrobasilar circulation. Collateral circulation may be graded as good if major vascular branches of the involved territory are visualized distal to occlusion. Collateral circulation may be graded as moderate if some branches are shown, and poor if only distal branches are reconstituted [8].

THROMBOLYTIC THERAPY

Tissue plasminogen activator (tPA), or alteplase, is the gold standard thrombolytic agent given within 4.5 h of stroke symptom onset [1]. Alteplase binds to fibrin, a mesh-like protein in clots and acts within the endogenous fibrinolytic cascade to convert plasminogen to plasmin, the enzyme that dissolves fibrin resulting in clot dissolution. Its dosage is 0.9 mg/kg, with 10% as a bolus given over 1 min and 90% as an infusion over 60 min. The maximum dosage is 90 mg. Other than bleeding complications, alteplase may rarely lead to anaphylactic reaction due to complement cascade activation and

Table 4 Stroke syndromes**CAROTID**

- (1) Asymptomatic bruit
- (2) TIAs: transient monocular blindness, weakness, numbness, speech/language disturbance
- (3) Sudden deficit in MCA and/or ACA territory
- (4) Progressive or stepwise hemispheric deficits (watershed infarction)

MIDDLE CEREBRAL ARTERY (MCA) stroke syndromes

- (a) MCA—entire territory
 - Contralateral gaze palsy, hemiplegia, hemisensory loss, spatial neglect, hemianopsia
 - (Left) global aphasia
- (b) MCA—deep branches
 - Contralateral hemiplegia, hemisensory loss
 - (Left) transcortical motor (non-fluent aphasia, intact repetition) and/or sensory (receptive) aphasia
 - Lacunar syndromes—pure motor hemiparesis, sensorimotor stroke
- (c) MCA—para-sylvian branches
 - Contralateral weakness and sensory loss of face and hand
 - (Left) conduction aphasia, apraxia, Gerstmann syndrome (dys-/a-graphia, dys-/a-calculia, finger agnosia, left–right disorientation)
 - (Right) constructional dyspraxia
- (d) MCA—superior division
 - Contralateral hemiplegia, hemisensory loss, gaze palsy, spatial neglect
 - (Left) Broca's aphasia
- (e) MCA—inferior division
 - Contralateral hemianopsia or upper quadrantanopsia
 - (Left) Wernicke's aphasia
 - (Right) constructional dyspraxia

ANTERIOR CEREBRAL ARTERY (ACA) stroke syndromes

- (a) ACA—entire territory
 - Contralateral hemiplegia
 - Abulia
 - Incontinence
 - Transcortical motor aphasia or motor and sensory aphasia
 - Limb dyspraxia

Table 4 continued**(b) ACA—distal branches**

Contralateral weakness of leg, hip, foot, shoulder
 Sensory loss in foot
 Transcortical motor aphasia or motor and sensory aphasia
 Limb dyspraxia

(c) ACA—deep branches

Lacunar syndromes—pure motor hemiparesis, sensorimotor stroke

(d) ACA—anterior choroidal branches

Hemiparesis, hemisensory abnormalities, hemianopia

Midbrain stroke syndromes**(a) Midbrain basis (Weber syndrome)**

PCA branches, top of basilar
 CN3 fascicles—ipsilateral 3rd palsy (ptosis, no eye adduction, no up/downgaze ± dilated pupil)

(b) Midbrain tegmentum (Claude syndrome)

PCA branches, top of basilar
 CN3 fascicles—ipsilateral 3rd palsy
 Red nucleus, superior cerebellar peduncle fibers—contralateral ataxia

(c) Midbrain basis and tegmentum (Benedikt syndrome)

PCA branches, top of basilar
 CN3 fascicles—ipsilateral 3rd palsy
 Cerebral peduncle—contralateral hemiparesis
 Red nucleus, substantia nigra, superior cerebellar peduncle fibers—contralateral ataxia, tremor, involuntary movements

Pons stroke syndromes**(a) Medial pontine basis (dysarthria hemiparesis—pure motor hemiparesis)**

Basilar artery (paramedian branches), ventral territory
 Corticospinal/bulbar tracts—contralateral face/arm/leg weakness, dysarthria

(b) Medial pontine basis (ataxic hemiparesis)

Basilar artery (paramedian branches), ventral territory
 Corticospinal/bulbar tracts—contralateral face/arm/leg weakness, dysarthria
 Pontine nuclei/pontocerebellar fibers—contralateral ataxia (occasional ipsilateral ataxia)

(c) Medial pontine basis and tegmentum (Foville syndrome)

Basilar artery (paramedian branches), ventral and dorsal territories
 Corticospinal and corticobulbar tracts—contralateral face/arm/leg weakness, dysarthria
 Facial colliculus—ipsilateral face weakness, ipsilateral horizontal gaze palsy

Table 4 continued

(d) Medial pontine basis and tegmentum (Pontine wrong-way eyes syndrome)
Basilar artery (paramedian branches), ventral and dorsal territories
Corticospinal and corticobulbar tracts—contralateral face/arm/leg weakness, dysarthria
Abducens nucleus/paramedian pontine reticular formation—ipsilateral horizontal gaze palsy
(e) Medial pontine basis and tegmentum (Millard–Gubler syndrome)
Basilar artery (paramedian branches), ventral and dorsal territories
Corticospinal and corticobulbar tracts—contralateral face/arm/leg weakness, dysarthria
CN7 fascicles—ipsilateral face weakness
(f) Medial pontine basis and tegmentum (other regions)
Basilar artery (paramedian branches), ventral and dorsal territories
Medial lemniscus—contralateral decreased position and vibration sense
Medial longitudinal fasciculus—internuclear ophthalmoplegia (affected eye impaired adduction)
(g) Lateral caudal pons (AICA)
Middle cerebellar peduncle—ipsilateral ataxia
Vestibular nuclei—vertigo, nystagmus
Trigeminal nucleus and tract—ipsilateral facial decreased pain and temperature sense
Spinothalamic tract—contralateral body decreased pain and temperature sense
Descending sympathetic fibers—ipsilateral Horner syndrome
(h) Lateral caudal pons (other regions)
Labyrinthine artery—inner ear, ipsilateral hearing loss
(i) Dorsolateral rostral pons (SCA)
Superior cerebellar peduncle and cerebellum—ipsilateral ataxia
Other lateral tegmental structures (variable)—variable features of AICA syndrome (lateral tegmental involvement)
Medulla stroke syndromes
(a) Medial medulla
Paramedian VA, ASA
Pyramidal tract—contralateral arm/leg weakness
Medial lemniscus—contralateral decreased position/vibration
CN12 nucleus/fascicles—ipsilateral tongue weakness
(b) Lateral medulla (Wallenberg syndrome)
PICA, VA
Inferior cerebellar peduncle, vestibular nuclei—ipsilateral ataxia, vertigo, nystagmus, nausea
Trigeminal nucleus, tract—ipsilateral facial decreased pain and temperature sense
Spinothalamic tract—contralateral body decreased pain and temperature sense
Descending sympathetic fibers—ipsilateral Horner syndrome

Table 4 continued

Nucleus ambiguus—hoarseness, dysphagia

Nucleus solitarius—ipsilateral decreased taste

VA stroke syndromes

(a) Subclavian steal

Asymptomatic

May present as VB TIAs (dizziness, slurred speech, faintness, imbalance)

(b) Extracranial VA

Asymptomatic

May present as VB TIAs

(c) Intracranial VA

Lateral medullary syndrome (Wallenberg syndrome)

Medial medullary syndrome (tongue paralysis, contralateral hemiplegia)

Hemi-medullary infarction

PICA infarction (dorsolateral medulla and lower half of cerebellum)

Basilar artery stroke syndromes

(a) Basilar occlusion

Often preceding TIAs

At onset headaches, dizziness, paresthesia, confusion followed by CN palsies

Neuro-ophthalmologic abnormalities (such as vertical skew, oscillopsia, downbeat nystagmus), ataxia, quadriparesis/plegia, locked-in syndrome, coma

(b) Lacunes

Pure motor hemiparesis, dysarthria-clumsy hand, pure sensory stroke, sensorimotor stroke

(c) Paramedian and short circumferential arteries

Crossed syndromes with ipsilateral CN palsy

Contralateral motor, sensory or sensorimotor deficits

Neuro-ophthalmologic abnormalities, dysarthria, ataxia

Long circumferential arteries stroke syndromes

(a) SCA

Limb ataxia, dysarthria, CN4 palsy (diplopia worse in downgaze), Horner syndrome, contralateral thermoanalgesia

(b) AICA

Limb and trunk ataxia, CN7 and 8 palsies, Horner syndrome, contralateral hemiplegia and hemisensory loss

(c) PICA

Pseudovestibular syndrome, nystagmus, trunk and limb ataxia, lateral medullary syndrome

Table 4 continued

(d) Top of basilar occlusion
Abnormal pupils, convergence, vertical eye movements, CN3 palsy, hemiplegia/quadruplegia, sensory loss, ataxia, hypersomnolence, inattention, abnormal behavior, confusion, hallucinations, memory loss, visual defects, abnormal movements
(e) Thalamic infarcts
Abulia, memory loss, dysphasia, dyspraxia (anterolateral infarction)
Hypersomnolence, coma, abnormal vertical eye movements and convergence, disorientation, amnesia, dysphasia (anteromedial infarction)
Pure sensory stroke, sensorimotor stroke, Dejerine–Roussy syndrome (lateral infarction)
Visual field defects (dorsal and lateral geniculate body infarction)

POSTERIOR CEREBRAL ARTERY (PCA) stroke syndromes

(a) PCA—deep and superficial territory
Part of syndrome of top of basilar
(b) PCA—deep territory
Thalamopeduncular infarcts
(c) PCA—superficial branches
Cortical blindness
Visual field defects (homonymous hemianopia, altitudinal hemianopia, quadrantanopia)
Abnormal color vision, palinopsia, micropsia
Visual agnosia, pure alexia, hemidyslexia, prosopagnosia, memory deficits, topographic disorientation, amnesic aphasia

Lacunar stroke syndromes

(a) Pure motor hemiparesis—MCA lenticulostriates (posterior limb of internal capsule) or basilar paramedian pontine arteries (basis pontis): unilateral face, arm, leg weakness
(b) Pure sensory stroke—PCA thalamogeniculate arteries (ventral posterolateral thalamus): unilateral hypoesthesia, paraesthesia, dysesthesia of face, arm, leg
(c) Sensorimotor stroke—MCA lenticulostriates, PCA thalamoperforators (thalamocapsular region): combined hemiparesis and hemisensory loss involving unilateral face, arm, leg without cortical signs such as neglect, aphasia
(d) Ataxic hemiparesis—MCA lenticulostriates (corona radiata, posterior limb of internal capsule), basilar pontine perforators (basis pontis): hemiparesis and ipsilateral limb ataxia affecting leg more than arm (dysarthria common)
(e) Dysarthria-clumsy hand syndrome—MCA lenticulostriates (anterior limb or genu of internal capsule), basilar paramedian pontine perforators (basis pontis): dysarthria and unilateral hand clumsiness affecting fine motor (mild face, arm weakness)
(f) Mixed syndromes—combinations of above syndromes

ACA anterior cerebral artery, *AICA* anterior inferior cerebellar artery, *ASA* anterior spinal artery, *CN* cranial nerve, *MCA* middle cerebral artery, *PCA* posterior cerebral artery, *PICA* posterior inferior cerebellar artery, *SCA* superior cerebellar artery, *TIA* transient ischemic attack, *VA* vertebral artery, *VB* vertebrobasilar

mast cell degranulation as plasminogen is converted to plasmin. Tissue plasminogen activator is absolutely contraindicated in active internal bleeding within the past 21 days, intracranial hemorrhage, clinical presentation suggestive of subarachnoid hemorrhage, suspected aortic dissection, recent cranial or spinal surgery within the past 3 months, recent head trauma or stroke within the past 3 months, bleeding diathesis with platelets <100,000, heparin within 48 h, elevated aPTT (activated partial thromboplastin time), use of anticoagulants and INR (international normalized ratio) >1.7, use of direct thrombin inhibitors or direct factor Xa inhibitors, intracranial vascular malformations or neoplasms, severe uncontrolled hypertension (>185/110), suspected or confirmed endocarditis, abnormal blood glucose (<50 mg/dL or 2.8 mmol/L), and extensive stroke demonstrated on cranial imaging [7] (Table 6).

Tenecteplase is a bioengineered form of alteplase, given as a single bolus injection of 0.25 mg/kg up to 25 mg, with higher fibrin selectivity and longer half-life 20–25 min compared to alteplase of 4–6 min. Emerging evidence suggests that tenecteplase may be non-inferior to alteplase [9–11].

ENDOVASCULAR THROMBECTOMY FOR ANTERIOR CIRCULATION STROKES

Between 2015 and 2023, 15 randomized controlled trials were performed (3897 patients), 13 of which were multicenter trials, investigating the efficacy of endovascular thrombectomy and medical treatment for anterior circulation strokes in patients with symptom onset up to 24 h [12–19]. Pooled analysis showed endovascular thrombectomy plus medical therapy was significantly associated with functional independence (OR 2.19, 95% CI 1.81–2.64, $p < 0.00001$, $I^2 = 46\%$). Patients with both large infarct cores (ASPECTS 3–5, core volumes 50–100 mL) and small infarct cores (ASPECTS >6, core volumes <70 mL) treated with endovascular thrombectomy plus medical

therapy showed significant improvement in functional independence at 90 days for both large core strokes (OR 2.50, 95% CI 1.76–3.54, $p < 0.00001$, $I^2 = 26\%$) and small core strokes (OR 2.27, 95% CI 1.67–3.08, $p < 0.00001$, $I^2 = 57\%$). Fourteen of these trials (3806 patients) assessing differences in symptomatic intracerebral hemorrhage found no significant difference between the two arms with homogeneous effect (OR 1.31, 95% CI 0.94–1.83, $p = 0.11$, $I^2 = 0\%$) (Table 6).

BLOOD PRESSURE CONTROL AFTER ENDOVASCULAR THROMBECTOMY

A recent meta-analysis of four randomized control trials pooling 1516 patients showed that, after successful endovascular thrombectomy with mTICI >2b reperfusion, intensive blood pressure control with systolic BP <140 mmHg was associated with harm and more functional disability (mRS >3 or death) at 90 days (OR 1.75, 95% CI 1.36–2.25, $p < 0.00001$, $I^2 = 0\%$), with no difference in symptomatic intracerebral hemorrhage or mortality between the two groups [20, 21]. Intensive blood pressure control after endovascular thrombectomy blunts autoregulatory responses and decreases cerebral blood flow to oligemic regions and collateral flow to penumbra (Table 6).

MEDICAL MANAGEMENT PRINCIPLES

Medical management strategies are essential for patients with stroke in order to optimize cerebral perfusion and prevent recurrent ischemic events. Identification of stroke etiology would be important as short-term prognosis of cardioembolic and atherothrombotic strokes may be worse as a result of large infarct size, stroke recurrence risk, and systemic complications from altered brain-body interface [2, 3].

Individualized blood pressure targets are used to avoid both hypoperfusion and reperfusion injury, with systolic blood pressure targets of 140–180 mmHg for acute stages and 130–160 mmHg for subacute stages. Clinical attention to fluid status is required to maintain appropriate plasma oncotic pressures and cerebral perfusion. Antiplatelet therapy is prescribed for those with atherosclerotic disease or perforator events, whereby anticoagulant therapy is used for those with embolic strokes secondary to cardiac arrhythmias [4, 7, 22, 23].

Management of altered brain–body interactions is necessary to mitigate potential secondary injury cascades. Treatment strategies include (1) maintaining hemodynamic and cardiac stability, (2) optimizing cerebral oxygen delivery (e.g., avoidance of anemia), (3) glycemic control, (4) goal-directed therapy for sepsis, (5) optimizing renal perfusion, and (6) avoiding coagulopathy and encephalopathy due to underlying multisystemic involvement, particularly hepatic and renal impairment [24, 25].

NEUROREHABILITATION POST STROKE

Intensive and repetitive training is a key factor for lower extremity motor improvement and recovery post stroke. Bilateral task performance enables expansion of bilateral sensorimotor cortices, supplementary motor areas, cingulate motor areas, dorsal premotor cortices, and posterior parietal cortices [26, 27]. Robot-assisted gait training developed since 1980 facilitates neuroplasticity. Neural networks and circuits develop to facilitate communication between motor and sensory pathways. In a systematic review of 28 randomized controlled trials (1251 participants), robot-assisted gait training using exoskeleton and end-effector robots within 3 months of stroke significantly and positively stimulates lower extremity function in patients with stroke in the domains of gait speed, walking distance, cadence, and balance [26, 27].

Neuroplasticity is also crucial for upper extremity motor recovery post stroke whereby new neural circuits form in perilesional tissue as well as the non-lesional hemisphere to compensate for lost motor function. A systematic review synthesizing the most frequently used

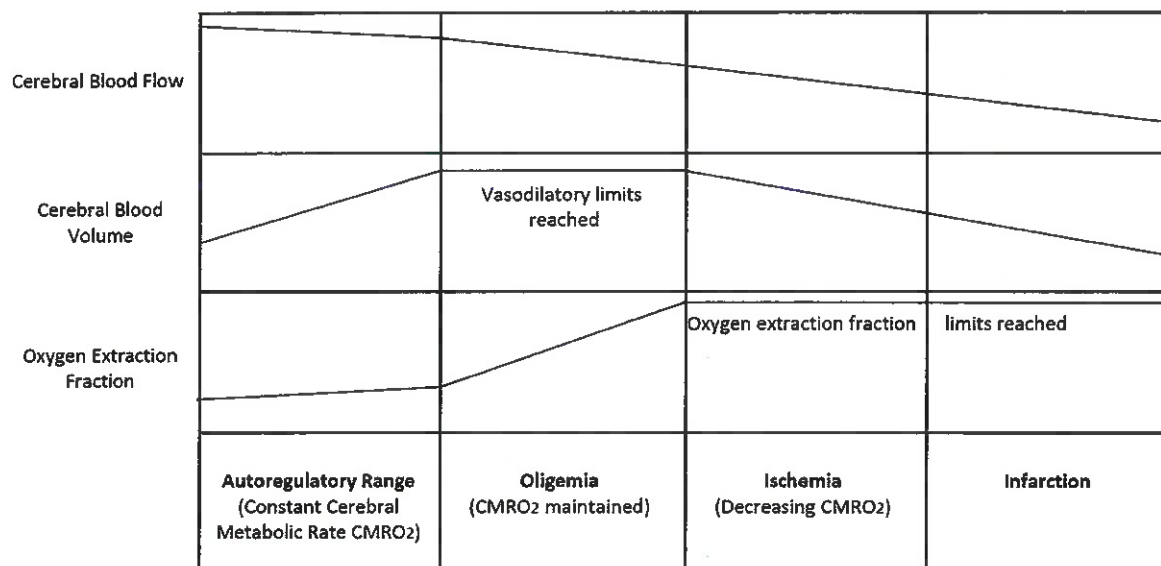


Fig. 1 Stages of cerebral hypoperfusion

Table 5 Cerebrovascular mean flow velocities

	Normal MFV (cm/s)
Artery	
ICA siphon	< 70
MCA M1–M2	< 80
ACA A1	< 80
BA	< 50
VA	< 60
PCA	< 50
Arterial stenosis (50%)	
ICA siphon, ACA (A1)	> 90
MCA M1–M2	> 100
BA-VA-PCA	> 70

MFV mean flow velocity, *ICA* internal carotid artery, *MCA* middle cerebral artery, *ACA* anterior cerebral artery, *BA* basilar artery, *VA* vertebral artery, *PCA* posterior cerebral artery

neuromuscular electrical stimulation; repetitive transcranial magnetic stimulation for activation of neural networks; therapist-guided task-specific training; and botulinum toxin injections for treatment of focal spasticity [28–30] (Table 6).

neuromuscular electrical stimulation; repetitive transcranial magnetic stimulation for activation of neural networks; therapist-guided task-specific training; and botulinum toxin injections for treatment of focal spasticity [28–30] (Table 6).

Efficacy of brain–computer interface (BCI) technology in post-stroke upper extremity rehabilitation was evaluated in a systematic review of 12 randomized controlled trials involving 298 patients whereby BCI coupled with existing therapies enhanced both short- and long-term upper limb motor functional recovery. Electroencephalography (EEG) is the most commonly used modality for signal acquisition in BCI-based stroke rehabilitation whereby the patient with stroke uses mental motor imagery to visualize moving an affected upper limb. Specific EEG band powers, for instance, beta rhythms, decrease over sensorimotor regions before motor task, followed by event-related desynchronization to minimum during task, and recovery resynchronization after task. Signals are then processed, extracted, and sent to wearable robots by providing assistive forces to complete the desired movements of the affected limbs toward the targeted task [27–30].

LIMITATIONS

Variation in study population demographics and pathophysiology of study subjects may lead to differing clinical responses to stroke

Table 6 Key evidence-based updates in ischemic stroke interventions

Topic	Key findings
Thrombolysis	Alteplase (tPA) is gold standard for thrombolysis within 4.5 h of symptom onset Tenecteplase, single bolus with longer half-life, may be non-inferior
Endovascular thrombectomy	Endovascular thrombectomy and medical therapy improves functional independence at 90 days in anterior circulation strokes even in late windows up to 24 h post symptom onset regardless of infarct core size
Blood pressure management post-thrombectomy	Intensive systolic blood pressure control (< 140 mmHg) acutely post thrombectomy is associated with harm and worse outcomes
Neurorehabilitation	Intensive and repetitive training is key to motor recovery Robot-assisted gait training improves lower limb function post stroke. Emerging interventions such as brain–computer interface and robotics enhance motor recovery

interventions. This, in turn, may affect local clinical practice patterns and heterogeneity in treatment guidelines across healthcare organizations worldwide.

CONCLUSION

This review summarizes current concepts in our understanding of stroke anatomy, pathophysiology, and evidence-based updates through various stroke trials and treatments. Evidence-based review of randomized controlled trials for treatment of anterior circulation strokes shows significant improvement in functional independence after endovascular thrombectomy plus medical therapy in patients with stroke with symptom onset up to 24 h. Intensive systolic blood pressure control after endovascular thrombectomy has been demonstrated to cause harm and more functional disability. Intensive and repetitive training is key for motor improvement during neurorehabilitation post stroke. Ongoing clinical studies in strategies to downregulate neuroinflammation may help mitigate secondary injury cascades after stroke.

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Declarations

Conflict of Interest. Benjamin W. Y. Lo and Hitoshi Fukuda have nothing to disclose.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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Review

Stroke in Young Adults: An Overview and Non-Pharmacological Preventive Strategies

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Abstract: Stroke is one of the most common causes of death and disability worldwide, with significant impact on both physical and cognitive health. Although strokes are less common in young adults, they still occur in this population, particularly in those with certain comorbidities, such as Autosomal Dominant Polycystic Kidney Disease (ADPKD). Despite the lack of specific guidelines for stroke prevention in young adults, certain preventive measures can be implemented. Smoking cigarettes is the most significant stroke risk factor in this group. Additionally, psychosocial stress, often exacerbated by academic, career, and financial pressures, is emerging as a modifiable risk factor for stroke in young adults. Key preventive measures include dietary changes, management of underlying health conditions, incorporating regular physical activity into daily routines, smoking cessation, and effective stress management techniques such as mindfulness-based stress reduction (MBSR) and cognitive-behavioral therapy (CBT). Promoting mental health awareness, directing public health campaigns toward young adults, educating them on recognizing stroke symptoms and administering first aid, and improving the quality of healthcare for this population all play a vital role in preventing stroke in young adults.

Keywords: stroke; young adults; prevention; ischemic stroke; hemorrhagic stroke; smoking cessation; mental health; public health



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1. Introduction

Stroke is the second most common cause of death worldwide and is the primary cause of long-term physical and cognitive impairments in adults [1,2]. The risk factors for strokes in young adults are generally very similar to traditional risk factors for strokes in the general population. However, there are a couple of risk factors that are pathognomonic for the younger population of adults. Among those are recreational drug use, migraines, oral contraceptive use, pregnancy and post-partum state, and patent foramen ovale [2]. Defining an age cutoff can be challenging and sometimes arbitrary, but previously published studies and registries often classify young adults as those under 50 years of age [3]. The prevalence of stroke varies significantly between the United States and Europe. In the US, young adults account for approximately 10–15% of all strokes, with the incidence of stroke in adults aged 20–44 rising from 17 to 28 per 100,000 people between 1993 and 2015. In Europe, for adults

under 55, the incidence of ischemic stroke has increased from 10.7 per 100,000 to 18.1 per 100,000. Globally, the rates of ischemic stroke among young adults differ widely, ranging from as low as 5.8 per 100,000 in central Italy to 97.7 per 100,000 in China [4]. Although there are no specific recommendations or guidelines for primary or secondary stroke prevention in young adults, strokes in this population are largely preventable by addressing modifiable risk factors [3]. Despite older studies suggesting that strokes in younger adults were less severe and had a better prognosis, studies have shown a higher mortality risk in this group, emphasizing the need for further research to improve preventive measures and treatments aimed at reducing stroke risk and improving long-term outcomes for these patients [5].

This emphasizes the urgent need for improved prevention and treatment strategies to mitigate stroke risk and enhance long-term outcomes in this population.

Figure 1 illustrates specific risk factors that are more prevalent or unique to the young adult population, including pregnancy and the post-partum state, patent foramen ovale, migraines, recreational drug use, and oral contraceptive use. Recognizing and addressing these factors is crucial for effective stroke prevention in this demographic.

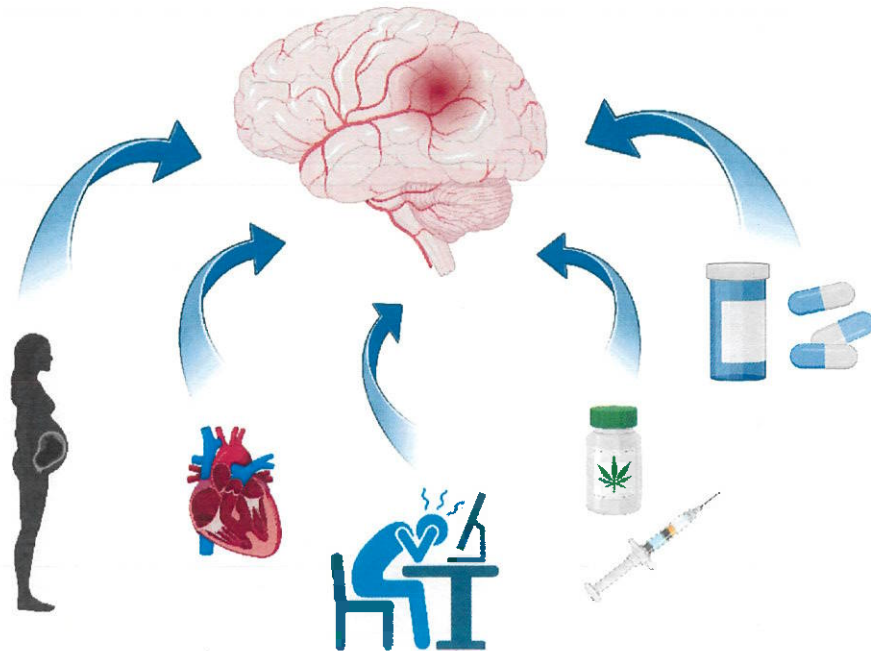


Figure 1. Specific risk factors for stroke in the young population are pregnancy and post-partum state, patent foramen ovale, migraines, recreational drug use, and oral contraceptives.

2. Materials and Methods

This review synthesizes evidence from a wide range of sources, including observational studies, clinical trials, and emerging interventions, to provide a comprehensive overview of stroke prevention in young adults. A narrative review approach was chosen for its flexibility in integrating diverse types of evidence, including epidemiological data, interventional studies, and mechanistic insights. This methodology is particularly well-suited for addressing multifactorial conditions such as stroke, where risk factors, prevention strategies, and therapeutic approaches are continuously evolving.

A comprehensive search of peer-reviewed English-language literature was conducted across multiple databases, including PubMed, Scopus, Web of Science, Cochrane Library, PsycINFO, Embase, Wiley Online Library, and SpringerLink. The primary search terms encompassed “stroke in young adults”, “stroke risk factors”, and “stroke prevention strategies”. The initial search yielded 3513 studies. After screening titles and abstracts and apply-

ing inclusion and exclusion criteria, 105 studies were considered eligible for full-text review. Of these, 40 studies met all inclusion criteria and were ultimately selected for detailed analysis in this review. Inclusion criteria were defined to incorporate studies that (a) were published within the past ten years (2015–2025), with exceptions made for older studies of significant clinical relevance; (b) specifically investigated non-pharmacological interventions for stroke prevention; and (c) targeted young adult populations (aged 18–49 years). Exclusion criteria encompassed studies that (a) were not peer-reviewed; (b) focused exclusively on stroke in older populations; (c) were case reports or small case series, unless they provided unique mechanistic insights; (d) did not address primary stroke prevention or relevant risk factors; (e) did not specifically include or stratify data for young adults; and (f) lacked clearly defined objectives and outcome measures. In cases where multiple similar studies existed, preference was given to systematic reviews or meta-analyses unless more recent primary research offered updated findings. This review synthesizes current knowledge on stroke risk factors in young adults and explores potential non-pharmacological strategies for primary stroke prevention. By integrating findings from existing literature and recent clinical investigations, it critically evaluates established preventive approaches, assesses emerging interventions, and identifies research gaps. Particular emphasis is placed on lifestyle modifications, stress management, and cognitive rehabilitation as key non-pharmacological strategies to mitigate stroke risk in this population. Furthermore, ongoing clinical trials are analyzed to highlight recent advancements and address unmet needs in stroke prevention among young adults. A structured summary of the search results and study selection process is presented in Figure 2. All figures, including the graphical abstract, were created using the BioRender platform (www.biorender.com, accessed on 5 March 2025), to visually represent proposed mechanisms and intervention strategies.

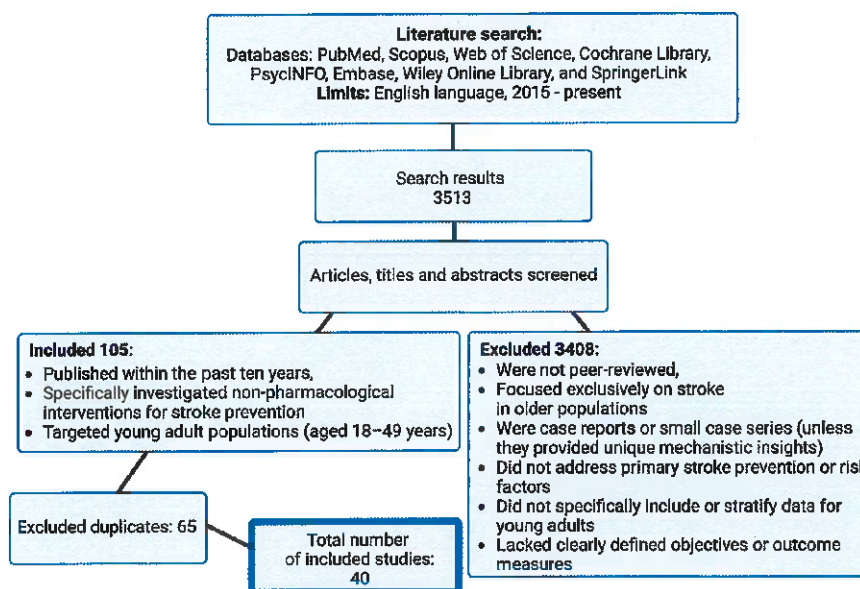


Figure 2. Summarizing the literature search, screening, and selection process for studies included in the review on non-pharmacological stroke prevention in young adults.

3. Overview of Strokes

3.1. Definition and Classification

Stroke is an urgent neurological condition caused by an acute focal injury of the central nervous system (CNS) [6,7]. Strokes can be classified into two main categories: ischemic and hemorrhagic, which includes intracerebral hemorrhage and subarachnoid

hemorrhage [6,7]. Ischemic strokes represent the majority of acute strokes, occurring by an obstruction of small and large arteries, either by atherosclerosis or cardiac-embolism, or athero-thromboembolism [8]. The other etiology is also a significant cause of ischemic stroke, also in younger patients, like an extracranial and intracranial dissection [8]. These changes result in restricted blood flow to the brain. Intracerebral hemorrhages cause about 15% of acute strokes. They can be deep, lobar, or cerebellar. Most commonly, deep hemorrhages occur from atherosclerosis and untreated arterial hypertension, while lobar hemorrhages usually result from cerebral amyloid angiopathy [8]. Importantly, macrovascular lesions (vascular malformations, cavernomas, aneurysms) can be a significant cause of intracerebral strokes in younger patients [8]. Subarachnoid hemorrhage is, in most cases, caused by a spontaneously ruptured aneurysm, but it can also occur from recreational drug use, coagulopathy, and arteriovenous malformations [9]. Transient ischemic attacks (TIAs) are more common in older adults, but they can occur in younger individuals as well. This is defined as the onset of an episode of focal neurological deficit, resulting from focal cerebral ischemia, with a complete resolution within 24 h since occurrence [10]. A recent study has shown that younger patients who have suffered an ESUS (Embolic Stroke of Undetermined Source) have a significant risk of recurrent stroke/TIA (15% over 15 years) [11]. Lacunar strokes are a subtype of ischemic strokes, representing around 25% of them. They occur due to the obstruction of small penetrating arteries that supply deep brain structures (basal ganglia, thalamus, and internal capsule) [11]. In younger adults, lacunar strokes are often associated with diabetes and hypertension, which are major risk factors for small vascular lesions [12]. In younger adults with diabetes, lacunar strokes are often associated with a higher prevalence of intracranial atherosclerotic stenosis and peripheral vascular disease, reflecting broader manifestations of systemic atherosclerosis [13]. Additional significant etiologies of stroke in this population include both inflammatory and non-inflammatory arteriopathies such as fibromuscular dysplasia, as well as monogenic conditions like Fabry disease and CADASIL [14].

Classic clinical representation of an acute stroke consists of difficulty standing or walking, changes in vision, sudden weakness or droopiness of the face, sudden weakness or numbness of extremities, difficulty speaking, and slurred speech. The most common differential diagnoses that can mimic an acute stroke are seizures, conversion disorder, migraine, and hypoglycemia [15,16]. The classification of strokes is essential for adequate diagnosis and treatment [17]. The TOAST classification system categorizes ischemic strokes based on etiology, which can guide treatment decisions and help predict outcomes [17]. Additionally, numerous specific prognostic scales are commonly used to assess long-term prognosis and outcomes [18]. Proper understanding of classification and clinical presentation of an acute stroke is essential for individualized treatment plan and ensuring the best outcomes for the patient [17,18].

3.2. Epidemiology and Risk Factors

Stroke is a very significant global socioeconomic burden, with an incidence of 10.3 million cases per year, as well as 113 million disability adjusted life years (DALY) lost each year [19]. Studies have shown a significant decrease in stroke incidence and mortality in high-income countries, while there have been no notable changes in middle- and low-income countries [20]. Furthermore, a significant growth in disparities has been noted between high-income countries (HIC) and low- and middle-income countries (LMIC), showing a 42% decrease in stroke incidence in HIC and a 100% increase in LMIC [19]. Disparities between different subgroups have been noted too, stroke being more common in men compared to women, and at the same time showing that young and middle-aged women are at higher lifetime risk of stroke compared to men [20]. Given that the majority

of acute strokes occur in patients over 50 years of age, it is alarming to note that 10–15% of strokes are reported in the population aged 18–50 [21]. Additionally, the newest research discovered that the global incidence rate of ischemic stroke will rise up to 89.32 per 100,000 population by the year 2030, which further highlights the urgency for effective both prevention and treatment modalities [21]. Timely thrombolytic treatment and mechanical thrombectomy have been shown to significantly improve recovery outcomes in young ischemic stroke patients compared to older individuals [22], further emphasizing the benefits of early intervention in this group.

Major stroke risk factors can be categorized as modifiable and non-modifiable [23]. Sex, age, and race are considered non-modifiable, whereas hypertension, smoking, and physical inactivity are among the modifiable risk factors [24]. Other modifiable and non-modifiable risk factors are illustrated in Figure 3. Recent population-based studies in young adults emphasize that modifiable risk factors, particularly low physical activity, hypertension, and smoking, account for the majority of stroke risk in this group. In a large German case-control study, physical inactivity alone explained up to 60% of stroke risk in adults under 55 [25]. Similarly, U.S. data showed that smoking and hypertension were the strongest contributors in White and Black populations, respectively [26]. Hypertension is a very common and significant major risk factor for an acute stroke occurrence, accounting for 25% to 50% of cases [27]. A recent study assessed the risk probability of stroke in patients with hypertension and noted it was very high in both males and females (91% and 70.7%, respectively), and remains high with the persistence of hypertension [28]. Frequent alcohol consumption is a greater risk factor for acute strokes as well. Recent research has shown that moderate and high alcohol intakes are associated with increased odds for stroke, but low intake is not [29]. On the other hand, some older studies indicated that light alcohol consumption can somewhat reduce the risk of a stroke in men, specifically ischemic stroke [30,31]. Risk factors can also be classified as short-term or triggers, such as stress or infections; intermediate-term, such as hypertension and hyperlipidemia; and long-term risk factors—sex, age, and race [24]. Besides the ones mentioned, it is important to note other significant risk factors for stroke: elevated cholesterol levels, diabetes, atrial fibrillation, and obesity, although they are more commonly associated with older populations [32,33].

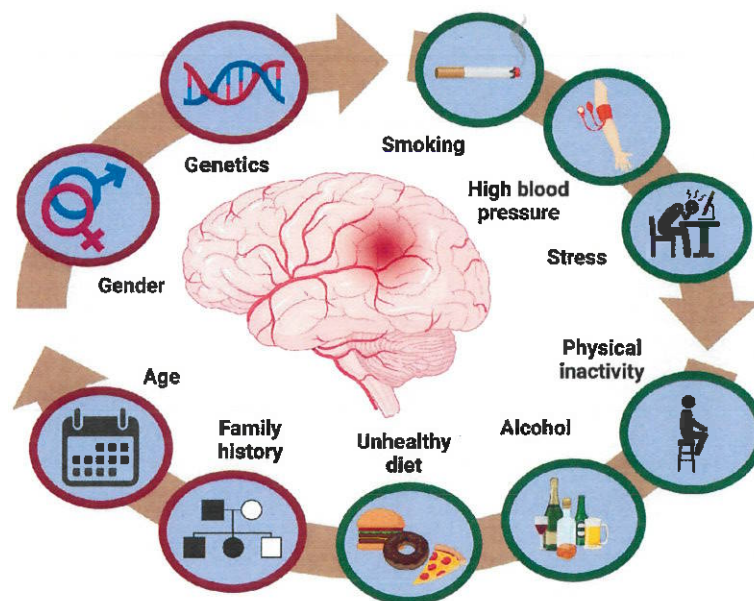


Figure 3. Schematic presentation of modifiable and non-modifiable risk factors for strokes in young adults.

Autosomal Dominant Polycystic Kidney Disease (ADPKD) as a Significant Stroke Risk in Young Adults

Autosomal dominant polycystic kidney disease (ADPKD) is associated with an increased risk of cerebrovascular events, including both ischemic and hemorrhagic strokes, particularly in younger individuals. Studies indicate that patients with ADPKD have a 1.4-fold greater risk of stroke compared to the general population, with this risk being especially pronounced in young adults [34]. Unruptured intracranial aneurysms (UIAs) are significantly more prevalent in this population, with a prevalence ratio of 6.9 compared to individuals without comorbidities [35]. Patients with ADPKD have a markedly increased risk of developing intracranial aneurysms, largely due to impaired vessel wall elasticity and abnormal polycystin expression. These aneurysms frequently occur at arterial bifurcations and are estimated to be 4–5 times more prevalent in ADPKD patients than in the general population [36]. The most relevant contributing factors include early-onset hypertension and the presence of intracranial aneurysms [37,38].

Recent research further emphasizes the neurological burden of ADPKD by highlighting the presence of cerebral microbleeds (CMBs), which are considered markers of small vessel disease and may signal early cerebrovascular injury. A 2025 case-control study reported deep cerebral microbleeds in 20% of individuals with ADPKD, while none were observed in matched controls, even after adjustments for age, sex, and renal function [39]. The results point to a disease-specific susceptibility to microvascular pathology. Such evidence supports the application of advanced neuroimaging modalities, including susceptibility-weighted imaging (SWI) and high-resolution MRI, particularly in symptomatic young adults with ADPKD.

Due to this elevated cerebrovascular risk, screening strategies are essential, especially for early detection of UIAs before rupture. According to current KDIGO 2025 guidelines, magnetic resonance angiography (MRA) or computed tomography angiography (CTA) is recommended for ADPKD patients with a family history of subarachnoid hemorrhage (SAH), those working in high-risk occupations, or individuals undergoing major surgery or pregnancy [38].

Hypertension is the most significant modifiable contributor to stroke in ADPKD and often presents early, sometimes even during adolescence. It becomes more prevalent with age, and studies estimate that up to 60–70% of patients develop hypertension early in the disease course [40,41]. Left ventricular hypertrophy (LVH) is also frequently observed in these patients, even at a young age, and early vascular changes have been reported in normotensive individuals with ADPKD. Furthermore, patients with ADPKD have a higher prevalence of coronary artery aneurysms and cardiac valvular abnormalities compared to the general population [34]. Intensive blood pressure control has been shown to slow cyst growth, preserve renal function, and reduce cardiovascular and cerebrovascular risk. First-line pharmacologic therapy typically includes renin–angiotensin system blockers (e.g., ACE inhibitors or ARBs), with additional lifestyle interventions such as dietary sodium restriction, smoking cessation, and regular aerobic activity recommended to improve outcomes [42]. Interestingly, vascular abnormalities in ADPKD may not be solely driven by hypertension. Polycystins, encoded by the PKD1 and PKD2 genes, are thought to maintain arterial wall integrity. Animal models have shown that loss of polycystins leads to vessel fragility and spontaneous hemorrhage, suggesting a direct role in vascular stability [34]. Additionally, dysregulation of the mTOR pathway—commonly observed in ADPKD due to polycystin-1 dysfunction—may further contribute to vascular remodeling and disease progression [34].

UIAs are a well-documented vascular manifestation of ADPKD, with prevalence rates ranging from 9 to 23%, markedly higher than in the general population. These aneurysms

are also more likely to rupture at a younger age, typically around 10 years earlier than in individuals without ADPKD [43]. Subarachnoid hemorrhage (SAH) resulting from aneurysm rupture is one of the most severe complications in ADPKD, representing a major cause of neurological morbidity in these patients [36]. Individuals with a family history of aneurysmal SAH have a particularly high risk of developing intracranial aneurysms. Siblings of affected patients have been shown to have an increased risk for both unruptured aneurysms and SAH, further supporting the need for targeted screening [44]. Additionally, postmenopausal women may be at increased risk due to the decline of estrogen's vascular protective effects [36].

In addition to guideline-based recommendations, some experts advocate broader screening strategies. A recent study identified a 5% prevalence of UIAs in individuals aged 35 and older with hypertension and a history of smoking. Although only a small proportion of these aneurysms required preventive intervention, the findings highlight the potential benefits of targeted screening in selected subgroups [45]. Screening can help identify small aneurysms that may not require immediate treatment but should be followed longitudinally through imaging surveillance due to their potential for future growth or rupture [36]. Despite these clear associations, many young adults with ADPKD remain unscreened for cerebrovascular risk, particularly in primary care settings [46]. While recent studies have supported universal screening as a strategy that may increase quality-adjusted life years, others caution that such an approach may not be universally appropriate due to risks of overdiagnosis, psychological burden, healthcare costs, and variability in available expertise [36].

Given the rising incidence of stroke among young adults—a group often underrepresented in stroke-related research—early identification and targeted prevention of high-risk conditions like ADPKD are essential.

3.3. Screening and Early Detection

Many young adults with stroke may not recognize early warning signs or seek medical attention promptly, contributing to delays in diagnosis and treatment. This population often underestimates their risk for vascular disease, leading to missed opportunities for prevention and early intervention [47]. This low-risk perception among younger adults presents a significant barrier to timely diagnosis and prevention efforts, often resulting in delayed care and missed opportunities for intervention [48]. Numerous screening tests are used for stroke detection, but specific data on their effectiveness in young adults are still limited. Studies have shown that the most commonly misdiagnosed acute stroke in this population is posterior circulation stroke [49]. One reason for this misdiagnosis may be the use of the FAST (Face, Arm, Speech, Time) screening test, which is less sensitive to posterior strokes and often leads to delayed diagnosis and treatment. A recent study demonstrated that FAST missed 38% of posterior circulation strokes [50]. It is recommended to use additional diagnostic tools, such as MRI, to improve early detection of posterior circulation strokes in young adults, which could significantly improve outcomes and help reduce long-term disabilities in these patients [51].

4. Clinical Studies on Stroke in Young Adults: Treatment and Outcomes

Multiple studies and randomized controlled trials have contributed to a more nuanced understanding of stroke in young adults, emphasizing both the effectiveness of standard acute-phase therapies and the importance of age-specific prevention and rehabilitation approaches (Table 1).

Table 1. Key clinical studies on strokes in young adults: treatments and outcomes.

Study (Author, Year)	Study Design	Sample Size	Key Findings	Limitations
Brouwer et al. (2022) [52]	Prospective registry (MR CLEAN)	3256 (310 aged 18–49)	Endovascular thrombectomy: 61% of young patients achieved mRS 0–2 at 90 days; mortality was lower than older group (7% vs. 32%)	Observational design; no control group
Putala et al. (2009) [53]	Retrospective cohort	48 young adults	IV thrombolysis yielded excellent 3-month outcomes; no deaths reported	Small sample size; retrospective bias
Dutta et al. (2021) [54]	Population-based case-control	2242 total (1090 cases, 1152 controls)	No significant association between marijuana use and early ischemic stroke	Self-reported exposure; residual confounding
Aycock et al. (2023) [55]	Feasibility RCT	30 African American young adults	Improved stroke risk perception and health behaviors via SCORRE intervention	Pilot nature; short duration and small cohort
Lo et al. (2021) [56]	RCT protocol	Target: 208	Narrative-based skills-building aims to improve reintegration and self-efficacy	Results pending; study ongoing
Chan et al. (2021) [57]	RCT	Target: 154	Expressive arts therapy improved mood, stress, and QoL in young survivors	Generalizability limited; long-term outcomes not yet assessed
Singhal et al. (2013) [49]	Expert consensus	N/A	10–15% of ischemic strokes occur in young adults; highlighted diagnostic delays	No original data; relies on expert opinion

A large national registry demonstrated that endovascular thrombectomy is a safe and effective option for younger patients with large vessel occlusion, with 61% achieving functional independence at 90 days and significantly lower mortality (7%) compared to older adults (32%) [52]. The more favorable outcomes in this group may be partly explained by lower comorbidity rates and increased neuroplastic potential.

Intravenous thrombolysis with alteplase (rtPA) has also shown strong efficacy in younger individuals. In a retrospective analysis of patients aged 16 to 49, none died during a three-month follow-up period, and a majority reached favorable functional outcomes [53]. This supports the early use of thrombolytic therapy in this demographic and confirms the relevance of standard acute-phase treatments, provided they are administered without delay.

When it comes to lifestyle factors, the connection between marijuana use and ischemic stroke has been explored in a population-based case-control study including over 2000 individuals aged 15 to 49. After controlling for common confounders such as tobacco use and hypertension, no significant association was found. However, a trend toward higher risk was observed among those using marijuana weekly or more often [54]. While not conclusive, this points to a possible dose–response relationship that warrants further investigation.

Preventive strategies tailored to younger populations have also been the focus of recent interventions. One theory-driven, nurse-led program developed for young African American adults incorporated multimedia education, personalized risk assessment, and behavioral self-monitoring over six weeks. Participants reported enhanced risk perception and adopted healthier habits, including improved diet and increased physical activity [55]. Such culturally responsive approaches show promise in addressing modifiable risk factors in vulnerable subgroups.

Rehabilitation research has begun to move beyond physical recovery, recognizing the unique psychosocial impact of stroke in younger adults. A structured, skills-based program focusing on narrative work and coping strategies led to improvements in self-efficacy, emotional well-being, and community reintegration [56]. In addition, expressive arts-based therapy, involving activities such as visual arts and group reflection, produced measurable improvements in emotional resilience, social support, and spiritual well-being, alongside reductions in stress markers like salivary cortisol [57]. These integrative models reflect a broader, more holistic view of recovery [57].

Despite these advances, stroke in young adults continues to be under-recognized in acute care settings. A recent consensus statement noted that up to 15% of ischemic strokes occur in those under 50, yet atypical presentations such as isolated dizziness or headache often led to diagnostic delays [49]. This highlights the need for increased awareness among clinicians and the development of age-specific diagnostic protocols that better capture the variability of stroke presentations in this population [49].

Taken together, these findings point to several key conclusions. First, young adults clearly benefit from standard reperfusion therapies when diagnosed in a timely manner, underscoring the need for clinical vigilance in emergency settings. Second, lifestyle interventions and targeted education appear particularly effective in reducing stroke risk in this group, especially when adapted to cultural and social contexts. Third, the long-term psychosocial consequences of stroke in young adults call for integrative rehabilitation strategies that extend beyond physical therapy to include mental health support, identity recovery, and community reintegration.

Altogether, current evidence reinforces that stroke in young adults is not simply a milder form of the disease seen in older individuals. Unique risk factors, recovery patterns, and psychosocial outcomes define this group as a distinct clinical category. To improve both immediate and long-term outcomes, future efforts must focus on tailored diagnostics, culturally sensitive prevention, and comprehensive rehabilitation strategies that reflect the realities of younger stroke survivors.

4.1. Comparative Insights: Stroke in Younger vs. Older Adults

Age-based comparisons of stroke incidence, clinical presentation, risk profiles, and outcomes have revealed substantial differences between younger and older adults, underscoring the need for more individualized approaches across the care continuum.

Over the past two decades, stroke incidence has shifted considerably. While rates have declined among adults over 55, a marked increase has been observed in younger populations. Between 2002 and 2018, ischemic stroke rose by 67% in individuals under 55, contrasting with a 15% decrease in older adults [58]. The upward trend in this age group appears closely tied to the rising prevalence of modifiable risk factors such as hypertension, obesity, and type 2 diabetes conditions that were once more commonly associated with older patients [58].

Symptom variability adds complexity to clinical assessment in early-onset stroke. In one hospital-based analysis, adults aged 18 to 50 more frequently presented with fluctuating or progressive neurological deficits compared to those over 50 [59]. Atypical symptoms,

including isolated headache, dizziness, or seizure, often lead to misdiagnosis or delays in care. Given the narrower diagnostic lens often applied in younger individuals, emergency settings must adapt to recognize early signs more effectively [59].

Differences in comorbidities and inpatient outcomes have also been documented. Older adults with stroke typically present with higher rates of atrial fibrillation, prior cerebrovascular events, and chronic hypertension, all of which contribute to elevated in-hospital mortality and greater dependence at discharge [60]. In contrast, younger patients, though generally healthier, still face considerable functional challenges. Their likelihood of achieving independence at discharge, however, tends to be higher, likely due to better baseline health, shorter time to treatment, and greater neuroplasticity [60].

Stroke subtype and underlying etiology also vary with age. In individuals under 50, lacunar and cryptogenic strokes are more frequently encountered, while strokes due to large artery atherosclerosis or cardio-embolism are more common in older patients [61]. These differences point to the importance of age-adapted diagnostic approaches and tailored secondary prevention strategies.

Large-scale hospitalization data from the United States further support the growing significance of stroke in younger adults. Among more than four million ischemic stroke admissions recorded between 2003 and 2014, nearly 5% involved individuals aged 18 to 45 [62]. Alongside traditional cardiovascular risk factors, a wide range of non-conventional contributors, including HIV infection, autoimmune disease, and congenital heart defects, was associated with stroke in this group [62]. Such complexity highlights the need for comprehensive screening protocols that go beyond standard cardiovascular parameters.

Findings from sub-Saharan Africa offer an important global perspective. In a Tanzanian cohort, one-third of stroke patients were aged 45 or younger, with a higher prevalence of hemorrhagic stroke among younger individuals compared to older counterparts [63]. Key risk factors included undiagnosed hypertension, HIV infection, hormonal contraceptive use, elevated LDL cholesterol, and sickle cell disease. Despite high overall 30-day mortality, individuals in early adulthood had comparatively better survival outcomes [63]. These observations reflect the dual burden of communicable and non-communicable conditions and point to the importance of integrating stroke risk assessment into broader public health strategies, particularly in resource-limited settings. Similar patterns emerged in another retrospective analysis, where nearly one in five stroke patients were aged 18 to 45 [64]. Hemorrhagic events were again more prevalent among younger adults (21.5% vs. 11.6%, $p = 0.011$). While hypertension was the leading risk factor across all ages, diabetes mellitus and dyslipidemia were also present in the younger group, though to a lesser extent than in older individuals [64]. Their findings suggest that vascular risk accumulates earlier than often assumed, making a strong case for preventive strategies such as early cardiovascular screening and lifestyle intervention beginning in early adulthood. A comparative overview of these studies is presented in Table 2, highlighting key differences in stroke incidence, clinical features, risk factor profiles, and outcomes between younger and older adults.

Taken together, these studies demonstrate that stroke in younger adults is not a milder version of the disease seen in older populations but a distinct clinical entity. From differences in pathophysiology and risk exposure to variation in clinical presentation and recovery trajectories, early-onset stroke demands a differentiated clinical and public health response. Tailored diagnostic frameworks, targeted prevention efforts, and rehabilitation strategies that account for social, vocational, and psychological realities are critical to improving long-term outcomes in this growing patient population.

Table 2. Comparison of stroke characteristics, risk factors, and outcomes between younger and older adults across key clinical studies.

Study (Author, Year)	Population	Comparison Focus	Younger Adults	Older Adults
Li et al., 2022 [58]	National registry data, USA (2002–2018)	Incidence trend	↑ 67% ischemic stroke incidence under 55	↓ 15% incidence in ≥55
Huggins et al., 2020 [59]	432 stroke inpatients (18–50 vs. >50)	Symptom presentation	43% had fluctuating/progressive symptoms	27% had fluctuating/progressive symptoms
Fonarow et al., 2010 [60]	>500,000 ischemic stroke admissions	Comorbidities and short-term outcomes	Fewer comorbidities; lower in-hospital mortality; better functional recovery	More AF, prior stroke, HTN; higher mortality
Lutski et al., 2017 [61]	Ischemic stroke registry	Functional outcome and etiology	70% mRS ≤ 2; more lacunar/cryptogenic strokes	Lower favorable outcome; more atherosclerosis/cardio-embolism
Patel et al., 2021 [62]	4.2M AIS admissions (USA, 2003–2014)	Risk factors	More obesity, drug use, HIV, congenital heart disease, autoimmune disorders	More traditional risk factors (HTN, AF, CA)
Matuja et al., 2020 [63]	369 stroke patients in Tanzania	Risk profile and mortality	42.3% hemorrhagic stroke; HTN, HIV, contraception, sickle cell, LDL ↑; 49.1% 30-day mortality	27.2% hemorrhagic stroke; 67.2% 30-day mortality
Moosa et al., 2021 [64]	513 stroke patients in Bahrain	Stroke type and comorbidities	21.5% hemorrhagic stroke; HTN (43%), DM (24.7%), DL (16.1%)	11.6% hemorrhagic; HTN (74%), DM (63%), DL (32.2%)

4.2. Comparative Summary of Non-Pharmacological Strategies in Young Adults

In addition to clinical and psychosocial interventions, various non-pharmacological strategies have been proposed to reduce stroke risk in young adults. Table 3 summarizes the most relevant findings from studies investigating the effects of dietary patterns, physical activity, stress reduction, educational programs, and behavioral counseling in this population. The comparative format allows visualization of outcomes across diverse populations and study types, highlighting which strategies may be most effective for specific subgroups.

Table 3. Comparative summary of non-pharmacological interventions and outcomes related to stroke prevention or recovery in young adults.

Study (Author, Year)	Intervention	Population	Key Findings	Notes
Aycock et al., 2023 [55]	Nurse-led Health Education	Young African American adults (18–45)	Improved stroke risk perception, increased health behavior adherence	RCT; population-specific
Chan et al., 2021 [57]	Expressive Arts Therapy	Young stroke survivors (Chinese cohort)	Improved mental health, emotional expression and quality of life	RCT; post-stroke focus
Spence, 2018 [65]	Mediterranean-style Diet	General population; data cited for young adults	Associated with significantly reduced stroke incidence in observational studies	Not age-stratified; observational data

Table 3. Cont.

Study (Author, Year)	Intervention	Population	Key Findings	Notes
Reddin et al., 2022 [66]	Stress Reduction/Perceived Control	INTERSTROKE population (includes young adults)	Higher locus of control associated with lower stroke risk	Large-scale observational study
Sobalska et al., 2020 [67]	Dietary Pattern Assessment	Polish young adults (20–45)	Moderate adherence to preventive diets	Cross-sectional; context-dependent
Mälstam et al., 2023 [68]	“Make My Day” Lifestyle Program	Adults aged 45–75 (includes younger subgroup)	Improved physical activity and reduced sedentary behavior	Pilot RCT; not powered to assess stroke incidence
von Sarnowski et al., 2013 [69]	Physical Activity (Leisure-Time)	Young adults (<55), n = 5023	Physical inactivity PAR = 59.7%; most prevalent in women <35	Case-control; specific to young adults
Loucks et al., 2015 [70]	Mindfulness-Based Stress Reduction (MBSR)	Young and middle-aged adults with CV risk	Reduced inflammatory markers; improved autonomic function	Mixed-methods; theoretical and empirical basis
Calderone et al., 2024 [71]	Cognitive–Behavioral Therapy (CBT)	Young adults (pilot study)	Reduced cortisol levels, improved cardiovascular health indicators	Pilot RCT; small sample size
Markidan et al., 2018 [72]	Smoking Cessation Counseling	Young men	Dose-dependent reduction in ischemic stroke risk after quitting	Large population-based study

5. Dietary and Lifestyle Modifications

Recent research highlights the significant role of nutrition in stroke prevention. Diets rich in fruits, vegetables, whole grains, legumes, nuts, and unsaturated fats—such as olive oil—have been consistently associated with a significantly reduced risk of stroke [65,73]. Supporting this, a recent international review confirmed that poor dietary practices, including high consumption of saturated fats and refined sugars, are frequently observed among young stroke patients. These findings underscore the importance of implementing age-specific nutritional counseling as part of primary prevention strategies in younger adults [74]. Furthermore, adherence to a Mediterranean-style diet has been linked to reduced stroke incidence [75]. Fiber-rich foods, particularly legumes and whole grains, help regulate blood pressure and postprandial glucose levels, thereby contributing to stroke risk reduction. In contrast, the consumption of saturated fats—commonly found in processed foods, red meat, and full-fat dairy products—should be minimized, as these can raise cholesterol levels and promote atherosclerosis [76]. In addition, hyperlipidemia, a diet-related metabolic condition, has been found to be significantly associated with ischemic stroke in young adults, reinforcing the importance of early dietary interventions and lipid management [77]. Despite earlier assumptions, studies have shown no clear association between higher intake of vitamins E and C and reduced stroke incidence [78,79].

The relationship between alcohol consumption and stroke risk remains complex. While moderate intake—particularly of red wine—may confer certain cardiovascular benefits, excessive alcohol use is clearly associated with an increased risk of all stroke subtypes, especially intracerebral hemorrhage. The net effect of alcohol may depend on regional consumption patterns, accompanying lifestyle behaviors, and coexisting risk factors [29]. In young adults, episodic heavy drinking has been identified as a notable risk contributor,

with a population-attributable risk of 10.2%, reinforcing the need for alcohol-focused interventions in this demographic [25]. Some potential protective effects of red wine have been attributed to specific polyphenolic compounds with disease-modifying properties [80].

Excessive dietary salt intake is another modifiable factor contributing to both ischemic and hemorrhagic strokes [81]. Even modest reductions in salt intake have been linked to meaningful improvements in cardiovascular health. Among individuals with hypertension, average reductions of 7 mm Hg in systolic and 4 mm Hg in diastolic blood pressure have been observed. In those with resistant hypertension, the effects are even more pronounced—up to 23 mm Hg systolic and 9 mm Hg diastolic [82].

Psychosocial stress is also associated with elevated stroke risk. However, studies indicate that individuals with a greater perceived locus of control—both at work and at home—experience a significantly lower stroke incidence. This suggests that internal resilience and perceived agency may buffer the physiological effects of chronic stress [66]. In parallel, recent data indicate that younger adults are more likely to adopt dietary patterns that at least partially align with established stroke prevention recommendations. Although these findings are not exclusive to the young, they underscore the broader importance of diet quality in reducing stroke risk across all age groups [67].

Beyond individual habits, structured lifestyle intervention programs have shown promise as part of comprehensive prevention strategies for stroke in younger adults. One such example is a randomized pilot study conducted in primary care settings among adults aged 45 to 75 years with moderate-to-high stroke risk. The intervention promoted “engaging everyday activities” (EEAs) to encourage physical activity and reduce sedentary behavior. Although not powered to detect changes in stroke incidence, the program improved participants’ lifestyle behaviors and demonstrated feasibility in real-world clinical practice [68].

These findings highlight the growing importance of not only educating younger adults about healthy lifestyle choices but also developing accessible, real-world programs that support sustainable behavior change.

6. Physical Activity Increase

Regular physical activity provides well-established cardiovascular benefits and plays a critical role in mitigating key stroke risk factors such as hyperlipidemia, obesity, and atherosclerosis [83]. Recent prevention initiatives specifically targeting younger adults have identified insufficient physical activity as a major modifiable behavioral risk factor, reinforcing the need for movement-focused interventions in this population [74].

Data from a case-control study revealed that physical inactivity represented the single most significant contributor to stroke risk in young adults, with a population-attributable risk (PAR) of 59.7% [25]. Elevated risk was evident even among individuals under the age of 35, pointing to the importance of early lifestyle habits in stroke pathogenesis [25]. Findings from a large multicenter study further confirmed the widespread nature of inactivity among young stroke patients. Nearly half (48.2%) of those with ischemic stroke or transient ischemic attack (TIA) reported low levels of physical activity [69]. The prevalence was higher in women (52.7%) than in men (44.1%) and reached its peak in individuals under 35, where 56.5% were inactive [69]. These patterns indicate a particular vulnerability among younger women and suggest that future interventions should incorporate both age- and sex-specific strategies to effectively address physical inactivity in stroke prevention.

A recent meta-analysis has shown that both moderate and high levels of physical activity are associated with a reduced risk of stroke [84]. Subsequent studies have reinforced these findings, recommending at least 40 min of moderate-to-vigorous aerobic exercise, three to four times per week, as an effective preventive measure. While men appear to

benefit more from moderate-intensity activity, women tend to derive greater benefit from lower-intensity forms of exercise [85].

Higher levels of leisure-time physical activity (LTPA) are consistently associated with a lower incidence of stroke. Even lower levels of LTPA—often considered insufficient by standard guidelines—have been shown to contribute to stroke risk reduction [86]. Moreover, increased LTPA is linked to better functional outcomes, including a reduced risk of death or dependency in activities of daily living (ADL) within three months post-stroke [87]. Regular engagement in sports and structured exercise has also been strongly associated with reduced stroke risk, further emphasizing the importance of maintaining an active lifestyle, particularly in younger populations [88,89].

Complementing these findings, a longitudinal cohort study from Sweden demonstrated that excessive body mass index (BMI) gain during adolescence—spanning puberty through early adulthood—is significantly associated with an elevated incidence of stroke by midlife. This effect appears to be mediated, at least in part, by the early development of hypertension [90].

Taken together, these findings strongly support the inclusion of daily physical activity and healthy weight maintenance as central components of stroke prevention strategies targeting young adults.

7. Stress Reduction

Psychosocial stress is a modifiable risk factor for stroke [66]. Although the exact mechanisms remain unclear, research has demonstrated that psychosocial stress significantly increases stroke risk in adults [91]. It contributes to inflammation in blood vessels, oxidative stress, and immune system dysregulation, all of which play crucial roles in the pathophysiology of stroke [91]. Early career stress, marked by financial concerns and job-related pressures, has also been linked to heightened psychological distress, further increasing the risk of various health complications [92].

Interventions aimed at reducing stress, such as mindfulness-based stress reduction (MBSR) and cognitive-behavioral therapy (CBT), have shown promising results in alleviating stress and improving cardiovascular health. Mindfulness practices, in particular, have been found to reduce inflammatory markers and improve psychological well-being, potentially lowering stroke risk by addressing both the mental and physical components of stress [70]. MBSR and CBT help regulate autonomic nervous system activity, reduce sympathetic nervous system hyperactivity, and enhance parasympathetic function, all of which can improve cardiovascular health. Furthermore, these interventions have been shown to lower cortisol levels, a key stress hormone, and improve endothelial function, which may directly influence stroke risk. By enhancing emotional regulation and reducing negative health behaviors associated with stress, MBSR and CBT offer effective approaches to lowering stroke risk [71,93].

8. Cessation of Smoking

Tobacco smoking remains one of the most significant and preventable risk factors for stroke in young adults. A large case-control analysis estimated that smoking contributes to approximately 20–30% of all strokes in this age group, with prevalence rates notably higher among younger stroke patients compared to older individuals [26]. Furthermore, data from a European study of adults aged 18–55 indicated that smoking alone accounted for nearly 25% of stroke cases, with a population-attributable risk (PAR) of 27.1% among men [25].

Emerging evidence highlights recreational drug use, particularly cannabis, as another relevant modifiable risk factor in this population. A 2024 systematic review and meta-

analysis of six studies involving over 119 million participants found that cannabis abuse was associated with a modest but statistically significant increase in stroke risk among young adults (adjusted odds ratio ≈ 1.21 after adjusting for smoking and alcohol use) [94].

In addition to its established association with stroke, smoking is a well-recognized high-risk behavior that contributes to cardiovascular disease, multiple forms of cancer, and a range of neurological disorders [95]. Among young adults with stroke, tobacco use is consistently identified as a prominent and preventable risk factor [96]. As a modifiable behavior, smoking plays a central role in both primary and secondary stroke prevention. Evidence indicates that cessation substantially lowers the risk of recurrent vascular events and all-cause mortality [97]. Data from recent research reveal a dose-dependent relationship between cigarette consumption and ischemic stroke risk in young men, suggesting that even smoking reduction—rather than complete cessation—may yield measurable benefits [91]. Despite this, only about half of stroke survivors report quitting or cutting back following the event. Those with coexisting conditions such as depression, anxiety, or alcohol misuse are significantly less likely to change their smoking behavior [86]. Although the benefits of cessation are well documented, overall quit rates remain suboptimal. This may be due, in part, to the limited use of available resources, including evidence-based counseling strategies, behavioral interventions, and pharmacologic therapies aimed at supporting cessation [72,98].

9. Mental Health Improvement

A stable and good mental state has been shown to be a positive factor in reducing stroke risk, with higher levels of emotional vitality strongly correlating with a lower risk of stroke [99]. Mental health disorders, such as depression, are more prevalent in younger stroke patients compared to older patients and may contribute to delayed care-seeking behavior or reduced engagement in preventive measures [25,40]. Furthermore, studies clearly indicate that young stroke survivors are at a significantly higher risk of developing new-onset anxiety and depression compared to older individuals. Specifically, those under the age of 50 are nearly three times more likely to experience anxiety and depression than their older counterparts [100]. Additionally, preventive therapies for depression following stroke have proven to be both effective and safe in reducing post-stroke depression [101]. Given the increased vulnerability of young stroke survivors, physician advice plays a crucial role in secondary prevention for this age group. It has been shown to significantly improve physical activity, which in turn can reduce the risk of further vascular events in younger populations [102]. Research indicates that recreational drug use significantly increases the risk of stroke among young adults. A study from Kasr Al-Ainy Hospital reported that 41% of young stroke patients had substance use disorders. Heroin use disorder was linked to higher mortality, while alcohol, heroin, and cocaine use disorders were associated with poorer stroke outcomes [103]. These findings highlight the importance of counseling young patients on the dangers of recreational drug use as a part of stroke prevention strategies.

10. Public Health Initiatives and Education

The primary objective of stroke prevention is to reduce incidence, long-term disability, and mortality, particularly among younger adults. Achieving this goal requires effective identification, reduction, and management of modifiable risk factors. Although stroke care has not always been a public health priority, the foundational functions of public health—assessment, policy development, and assurance—can enable health agencies to play a central role in improving care quality for stroke and cardiovascular patients [104]. According to the Centers for Disease Control and Prevention (CDC), up to 80% of strokes are

preventable through strategies such as diabetes prevention, smoking cessation, cholesterol and blood pressure control, use of anticoagulants in individuals with atrial fibrillation, and reduced alcohol consumption [105].

School-based educational programs have demonstrated the potential for early prevention. One recent initiative targeting high school students focused on increasing knowledge about stroke prevention, symptom recognition, and emergency response. Knowledge surveys conducted before and after the program revealed significant improvement, with the highest scores observed among students who also took on teaching roles. This peer-teaching approach served as a strong motivator for engagement and retention of information [106].

Despite the promise of such programs, broader implementation often faces real-world challenges. For instance, a survey conducted among African American communities found that participants with higher educational attainment displayed greater awareness of stroke risk factors. However, barriers such as psychosocial stress and financial strain were frequently cited as impediments to prevention. Many respondents also preferred receiving health information in clinical rather than community-based settings [107]. Digital tools have also been explored as accessible and scalable public health solutions. In a multi-country survey across four Arab nations, a brief three-minute online video led to statistically significant improvements in stroke-related knowledge, including recognition of risk factors and warning signs, as well as awareness of the need for prompt medical response. Participants, most of whom were under 55 and held university degrees, cited the visual design, simplicity of language, and cultural relevance as key factors in the video's effectiveness [108]. Mass media campaigns can also play a role in increasing public awareness. In Ireland, the National Stroke Awareness Campaign (Act F.A.S.T.) was associated with improved recognition of stroke symptoms. Among those surveyed 18 months after the campaign, 93% recalled having seen the message, and over 80% were able to correctly identify stroke warning signs. Although only a third remembered the name or slogan of the campaign, more than half stated they would go directly to the hospital upon noticing symptoms—an important behavioral shift [109].

While educational efforts clearly improve awareness, they are often insufficient to produce sustained behavior change or reduce recurrence rates when used alone. Current AHA/ASA guidelines recommend patient education as a component of care but acknowledge that it does not consistently lead to measurable improvements in health behaviors. Greater success has been observed in randomized controlled trials that combine education with physical activity, dietary modification, and individualized counseling. In one trial involving 60 participants, a combination of lifestyle interventions resulted in significant reductions in recurrent stroke or TIA (RR 0.23, 95% CI: 0.07–0.72) and lower all-cause mortality (RR 0.11, 95% CI: 0.01–1.98) over 3.5 years of follow-up. Another trial from Japan, which included 70 participants and integrated exercise, salt restriction, and nutritional counseling, was stopped early due to a significant reduction in the combined outcome of stroke-related mortality and cardiovascular hospitalizations after a median follow-up of 2.9 years [110].

Evidence suggests that lifestyle interventions are most effective when they are interactive, tailored to the individual, and delivered by trained healthcare professionals with sufficient time and resources. However, systematic reviews indicate that the optimal model for reducing recurrent stroke through lifestyle-based strategies is still not well established [110].

For educational initiatives to have a sustained impact, public health efforts should be adaptive, community-informed, and grounded in a multifaceted approach. Integrating clinical counseling, community engagement, and digital technologies offers the best

opportunity to extend reach and improve the long-term effectiveness of stroke prevention programs.

11. Conclusions

Although stroke is less common in young adults, its rising incidence and lasting consequences demand greater clinical and research attention. Unique risk factors in this group, such as recreational drug use, oral contraceptives, and chronic stress, are often under-recognized in current prevention models. Inadequate age-specific screening and prevention guidelines contribute to diagnostic delays and missed opportunities for intervention.

To improve outcomes, future research should focus on developing tailored prevention strategies and evaluating the efficacy of non-pharmacological interventions, such as mindfulness and structured lifestyle programs, through rigorous clinical trials. Despite efforts, many existing RCTs on secondary prevention in high-risk groups show limited success, underscoring the need for more effective, context-sensitive approaches. Addressing upstream social determinants like housing instability, food insecurity, and limited access to care is essential for reducing cardiovascular risk and improving treatment adherence. Integrating social needs assessments into clinical practice may help identify at-risk individuals and guide comprehensive support.

Finally, public health initiatives must include culturally sensitive, age-appropriate education on stroke and mental health, helping young adults recognize risk factors and seek timely care. Aligning prevention efforts with the lived realities of this population is crucial for reducing stroke burden and improving long-term outcomes.

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ADVANCES IN STROKE

Advances in Neurocardiology: Timing of Anticoagulation in Patients With Ischemic Stroke and Atrial Fibrillation

Michelle C. Johansen¹, MD, PhD; Luciano A. Sposato², MD, MBA

During the year when the American Heart Association, an organization that champions the prevention of stroke and heart disease, celebrates its 100th anniversary, it is only fitting that the advances in the field of neurocardiology, a subspecialty that merges both, were exciting and practice changing. We focus the 2025 neurocardiology update on atrial fibrillation (AF), and the timing of initiation of anticoagulation after ischemic stroke, which remains the cornerstone of secondary prevention in these patients.

There is no reader of *Stroke* who has not, over the years, found themselves puzzled about when to resume anticoagulation. The precise timing of initiation post-stroke has been a matter of significant debate due to concerns over the heightened risk of hemorrhagic transformation in the early poststroke period. This, balanced with the risk of embolization in the setting of untreated AF, proved difficult. Traditionally, anticoagulation was delayed to minimize the theorized bleeding risk, often guided by empirical 1-3-6-12-day protocols based on stroke severity (transient ischemic attack: minor, moderate, or severe), mirroring the size of the infarct as this normally is a potent indicator of risk of hemorrhage.¹ Recent evidence, however, has begun to challenge this paradigm, suggesting that earlier initiation of anticoagulation in carefully selected patients may reduce the risk of recurrent thromboembolism without significantly increasing bleeding complications.

We now have perhaps the most compelling advance in this area over the past decades, suggesting that early initiation of anticoagulation after stroke using direct oral

anticoagulants (DOACs), even among patients with large strokes, appears safe and may even reduce the risk of recurrent stroke.

This review does not aim to be exhaustive but to highlight key developments in this area. Studies were included based on the authors' judgment of their clinical relevance and contribution to the current understanding. This narrative review aims to synthesize recent literature on the optimal timing for the initiation of anticoagulation following ischemic stroke in patients with AF. Relevant studies were identified through searches of PubMed and other relevant databases using combinations of keywords such as "atrial fibrillation," "ischemic stroke," "anticoagulation," "antithrombotic therapy," and "timing of initiation." The search was limited to English-language publications and focused on literature published from ≈2015 through 2025, though earlier studies were included when foundational to the topic. Priority was given to randomized controlled trials, as well as high-quality observational studies, meta-analyses, and clinical practice guidelines.

Several recently published randomized controlled trials have specifically examined the optimal timing for initiating DOACs after ischemic stroke in patients with AF (Table). The TIMING trial (Early Versus Delayed Non-Vitamin K Antagonist Oral Anticoagulant Therapy After Acute Ischemic Stroke in Atrial Fibrillation), published in 2022, was a Swedish registry-based, noninferiority randomized controlled trial that included 888 patients with AF who experienced ischemic stroke (median National Institutes of Health Stroke Scale score of 4).⁵ Participants admitted

Key Words: anticoagulants ■ hemorrhage ■ infarction ■ stroke ■ thromboembolism

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Table. Anticoagulation Timing After Ischemic Stroke: Summary of Key Studies

Study	Design	Population	Timing arms	Anticoagulant used	Primary outcome	Key findings	Follow-up duration
ELAN ² (2023)	Multicenter RCT (open label)	2013 pts with AF and acute ischemic stroke	Early: 0–2 d (minor), 3–4 d (moderate), and 6–7 d (major) vs late: 3–4 d (minor), 6–7 d (moderate), and 12–14 d (major), respectively	Primarily DOACs (some VKAs allowed)	Composite of recurrent ischemic stroke, systemic embolism, major bleeding, or death at 30 d	Early initiation was safe across stroke severities, with no increase in bleeding (no formal hypothesis testing)	30 d
OPTIMAS ³ (2024)	Multicenter RCT (pragmatic)	3621 pts with AF and recent ischemic stroke	Early (≤4 d) vs delayed (≥7 d)	DOACs (apixaban and rivaroxaban)	Composite of recurrent ischemic stroke, systemic embolism, or symptomatic ICH at 90 d	Early DOAC initiation was noninferior to delayed initiation, with no difference in bleeding risk	90 d
CATALYST ⁴ (2024)	Meta-analysis	Aggregated data from TIMING, ELAN, OPTIMAS, and START	Early (≤4 d) vs delayed (≥5 d)	DOACs	Composite of recurrent ischemia or hemorrhage	Early anticoagulation generally safe; benefit of early DOAC initiation in ischemic stroke	30 d
TIMING ⁵ (2022)	Registry-based RCT (open-label)	888 pts with AF and ischemic stroke	Early (≤4 d) vs delayed (5–10 d)	DOACs (majority)	Composite of recurrent stroke, symptomatic ICH, or mortality	No significant difference; early treatment was noninferior and safe, with low bleeding risk and numerically lower rates of ischemic stroke	90 d
START ⁶ (2025)	Pragmatic, response-adaptive, phase 2 RCT	200 pts with AF and recent mild-moderate ischemic stroke	Timing stratified by group assignment (days 3–4, day 6, day 10, and day 14)	DOACs	Recurrent ischemic stroke, systemic embolism, or hemorrhage at 30 d	No difference detected, suggestive that an earlier start date is better than later times.	90 d

AF indicates atrial fibrillation; CATALYST, Collaboration on the Optimal Timing of Anticoagulation After Ischemic Stroke and Atrial Fibrillation: Individual Participant Data Meta-Analysis; DOAC, direct oral anticoagulant; ELAN, Early Versus Late Initiation of Direct Oral Anticoagulants in Post-Ischemic Stroke Patients With Atrial Fibrillation; ICH, intracerebral hemorrhage; OPTIMAS, Optimal Timing of Anticoagulation After Acute Ischemic Stroke; pts, patients; RCT, randomized controlled trial; START, Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation; TIMING, Early Versus Delayed Non-Vitamin K Antagonist Oral Anticoagulant Therapy After Acute Ischemic Stroke in Atrial Fibrillation; and VKAs, vitamin K antagonists.

within 72 hours of symptom onset were randomized to start DOAC treatment either early (within 4 days) or later (5–10 days). Early initiation was noninferior to delayed initiation for ischemic stroke recurrence (3.1% versus 4.6%), with no symptomatic intracerebral hemorrhage (ICH) observed in either group. TIMING was, however, terminated prematurely due to slow recruitment.

In 2023, results from the ELAN trial (Early Versus Late Initiation of Direct Oral Anticoagulants in Post-Ischemic Stroke Patients With Atrial Fibrillation) were published.² The timing of DOAC initiation was stratified by infarct size (Figure), which was not centralized but performed at each site, with early initiation defined as within 48 hours for minor (<1.5 cm) or moderate (<1.5 cm cortical location of middle cerebral artery, anterior cerebral artery, or posterior cerebral artery) strokes and on days 6 to 7 for major strokes (>1.5 cm). Thrombolytics or thrombectomy were permitted, as was study-defined petechial hemorrhage within the infarct. Among 2013 patients (1006, early treatment; 1007, later treatment), the primary outcome—a composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic ICH, or vascular death at 30 days—occurred in 2.9% of the early treatment group compared with 4.1% in the late treatment group. Notably, recurrent ischemic stroke rates at 30 days were

also numerically lower in the early group (1.4% versus 2.5%) but not statistically significant with 2 symptomatic ICH events reported in each group. The median National Institutes of Health Stroke Scale score at randomization in this trial was relatively low at 3, and the study group did not include patients on anticoagulation at the time of stroke, so the results cannot be extrapolated to that group.

The OPTIMAS trial (Optimal Timing of Anticoagulation After Acute Ischemic Stroke) was a phase 4 multicenter noninferiority randomized controlled trial, based in the United Kingdom, which used an open-label design with blinded end point adjudication.³ This study was published in 2024 and differed from ELAN primarily in that the size of the infarct on imaging was not used to define stroke severity but rather an online randomization tool stratified participants based on their National Institutes of Health Stroke Scale score (median, 5). This study compared early (within 4 days of stroke onset) versus delayed (7–14 days after onset) initiation of DOACs in 3621 patients with AF. The primary composite end point included recurrent stroke, symptomatic ICH, stroke of undetermined type, or systemic embolism at 90 days. Early initiation was shown to be noninferior to delayed initiation, though it did not demonstrate superiority. Symptomatic ICH was not statistically different between the 2 groups (0.6%, 0.7%; *P*=0.78).

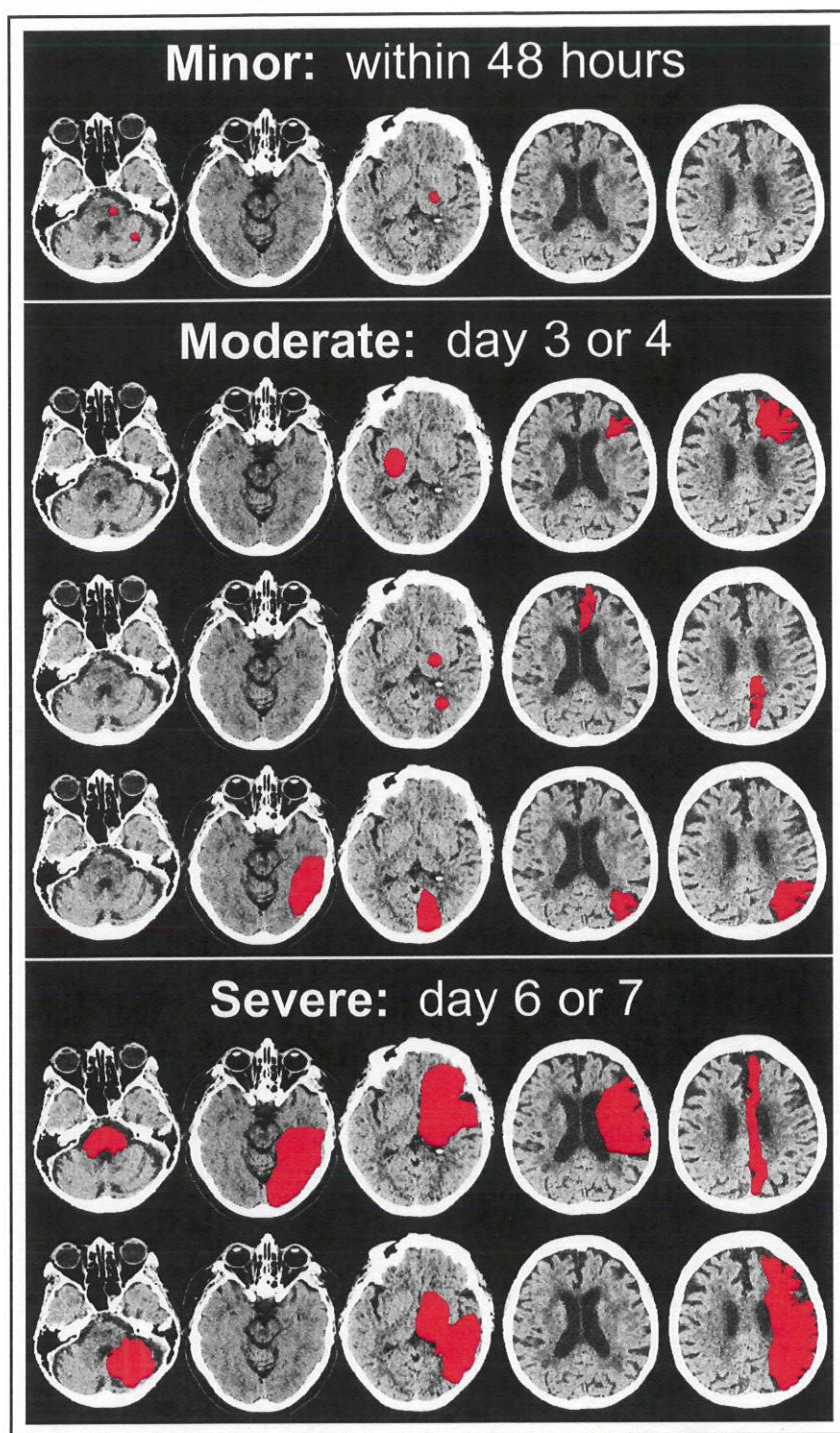


Figure. Example of ELAN (Early Versus Late Initiation of Direct Oral Anticoagulants in Post-Ischemic Stroke Patients With Atrial Fibrillation) stroke classification scheme.

Finally, the CATALYST meta-analysis (Collaboration on the Optimal Timing of Anticoagulation After Ischemic Stroke and Atrial Fibrillation: Individual Participant Data Meta-Analysis) pooled data from TIMING, ELAN, OPTIMAS, and the START study (Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation),⁶ encompassing 5411 patients.⁴ The results of this collaboration have not yet been published but were presented at the World Stroke Congress in 2024. This

analysis evaluated the composite end point of recurrent ischemic stroke, symptomatic ICH, or unclassified stroke at 30 days. The authors found that early DOAC initiation (within 4 days) was associated with a significantly lower incidence of the composite outcome compared with later initiation (≥ 5 days; 2.12% versus 3.02%; odds ratio, 0.70 [95% CI, 0.50–0.98]). Symptomatic ICH rates were low in both groups (0.45% versus 0.40%). At 90 days, event rates remained numerically lower with earlier initiation,

though without statistical significance. There was also no suggestion of a mortality difference between the 2 intervals of DOAC initiation. Their early reported findings also supported the safety and efficacy of initiating DOACs early in patients with AF following acute stroke in various subgroups to include the National Institutes of Health Stroke Scale category, prior anticoagulation, age at the time of stroke, and receipt of reperfusion therapy (although not included in all studies).

The result of this exciting work is that now the majority of evidence supports that the early initiation of oral anticoagulation in patients with ischemic stroke and AF is at the least safe, especially when an imaging correlate is used to assess the risk of hemorrhagic transformation. The evidence also now suggests that earlier initiation of anticoagulation poststroke is likely beneficial to prevent recurrent stroke, a true win-win for the stroke physician.

As a practical approach and one that might be used for public policy and improvement of clinical outcomes, the ELAN Stroke Size Classification Scheme (ELAN publication,² also see the Figure) may serve as a guide for determining the timing of anticoagulation initiation with DOACs for anticoagulant-naïve patients with ischemic stroke with AF. As exciting as this step is in the care of a patient with AF poststroke, there are still limitations to the work done to date, such as a short follow-up period, composite outcomes, studies lacking power to detect a difference, and different enrollment criteria. We encourage a personalized strategy that considers risks and benefits of the individual patient while advocating for earlier initiation of anticoagulation when feasible.

ARTICLE INFORMATION

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ILLUSTRATIVE TEACHING CASES

Section Editors: Sophia Sundararajan, MD, PhD, and Alexis N. Simpkins, MD, PhD, MSCR

Guidelines in Action: Dual Threat—Ischemic and Hemorrhagic Stroke Associated With Substance Use Disorder

Caylee R. McCain, MD; Kelsey Rose Duncan , MD

CASE DESCRIPTIONS

Case 1: Ischemic Stroke Following Cocaine Use

A 48-year-old male with a history of hypertension, well-controlled type 2 diabetes, hyperlipidemia, and prior stroke in the setting of cocaine use presented to the emergency department with aphasia and dysarthria. He had a National Institutes of Health Stroke Scale score of 5 and was last known normal before going to bed 9 hours prior to presentation. His blood pressure was 165 of 110 on arrival, computed tomography of the head did not show evidence of hemorrhage, and computed tomography angiography of the head and neck demonstrated a left M2 occlusion, which correlated with the patient's symptoms (Figure 1). Given the disabling nature of his symptoms, the patient was taken for immediate magnetic resonance imaging of the brain per wake-up stroke protocol. This demonstrated several small acute infarcts along the left arcuate fasciculus and insula (Figure 2), seen on diffusion weighted imaging but not on fluid attenuated inversion recovery. The patient was reexamined following magnetic resonance imaging and found to be clinically improving and able to communicate, with a National Institutes of Health Stroke Scale score of 2. At that time, the patient endorsed cocaine use that morning immediately preceding symptom onset. Thrombolysis was deferred as symptoms were no longer disabling.

Further history revealed that the patient was prescribed daily aspirin and atorvastatin following his prior stroke, but was not taking them consistently. Dual antiplatelet therapy was initiated. Stroke work-up revealed a low-density lipoprotein level of 117 mg/dL and no evidence of atrial fibrillation or diabetes. The patient was counseled regarding cessation of cocaine use and discharged home with outpatient therapies and substance cessation resources. The patient was seen 3 weeks later and had no neurologic deficits. He reported no issues with medication adherence and stopped using cocaine. The patient was de-escalated to aspirin monotherapy. As of his most recent follow-up 6 months after this event, the patient is doing well and remains substance-free.

Case 2: Hemorrhagic Stroke Following Methamphetamine Use

A 61-year-old woman with a history of hypertension, hyperlipidemia, transient ischemic attack years prior, and methamphetamine use disorder presented to the emergency department with right arm weakness, dysarthria, and altered mental status. Her National Institutes of Health Stroke Scale score was 3, and her blood pressure was 173 of 90 on arrival. Computed tomography of the head was performed, demonstrating a left basal ganglia hemorrhage (Figure 3). She endorsed using methamphetamine earlier on the day of presentation as well as several times per month for many years.

She was previously prescribed aspirin following a transient ischemic attack several years prior; however,

See related articles, p e303, e307, e310

Key Words: aphasia ■ dysarthria ■ hemorrhage ■ infarction ■ magnetic resonance imaging

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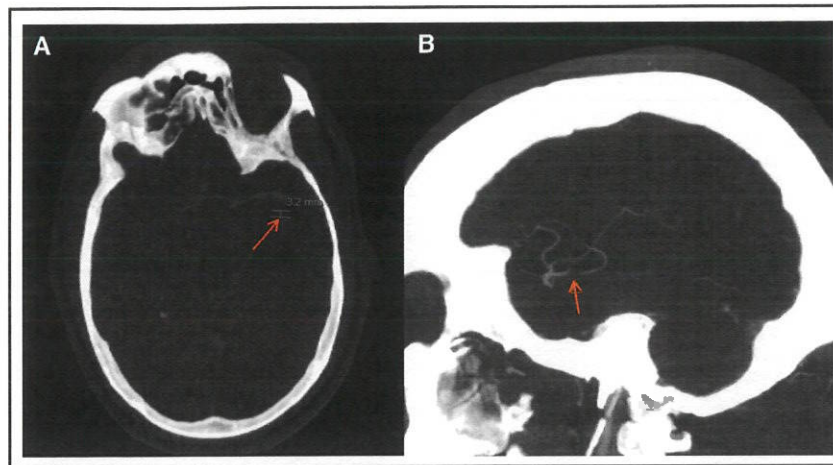


Figure 1. Imaging demonstrating M2 occlusion of left middle cerebral artery.

A, Axial imaging of computed tomography angiography (CTA) head with arrow indicating left M2 occlusion.

B, Sagittal image of CTA head with arrow indicating left M2 occlusion.

she reported difficulty with medication adherence and was not taking any medications regularly. Of note, a urine toxicology screen at the time of her previous transient ischemic attack was found to be positive for amphetamines and cocaine, with an absence of other vascular risk factors at the time. As a result, substance use was a significant suspected contributor to her prior event.

Following identification of the hemorrhage, the patient was admitted to the intensive care unit, and a cardene drip was initiated. She was eventually transitioned to oral antihypertensives for ongoing blood pressure control. Her exam improved over the following days. She was discharged without deficits and given resources on substance use treatment centers, support groups, and local psychologists.

DISCUSSION

The first case demonstrates that while most patients who suffer from ischemic stroke have multiple comorbidities and risk factors, substance use is an important contributor

that should be recognized and addressed. This is especially true in young patients. This patient had previously suffered a stroke in the setting of acute cocaine use, which was thought to be a significant contributor to the cause of his first event. Unfortunately, substance cessation is extremely complex, and it was not until after his second event that this patient received the necessary support and resources to quit cocaine. Getting help for substance use can be difficult due to the socioeconomic obstacles and comorbid health concerns patients with substance use disorders face, and many aspects of their health care may suffer due to cost, stigma, and limited access.

The second case reinforces the complicated nature of substance use and the high incidence of overlapping risk factors that contribute to hemorrhagic stroke. As mentioned in the first case, substance cessation is challenging, often requiring repeated attempts to quit over many years.¹ As health care providers, we must improve our efforts to ensure patients are consistently screened,

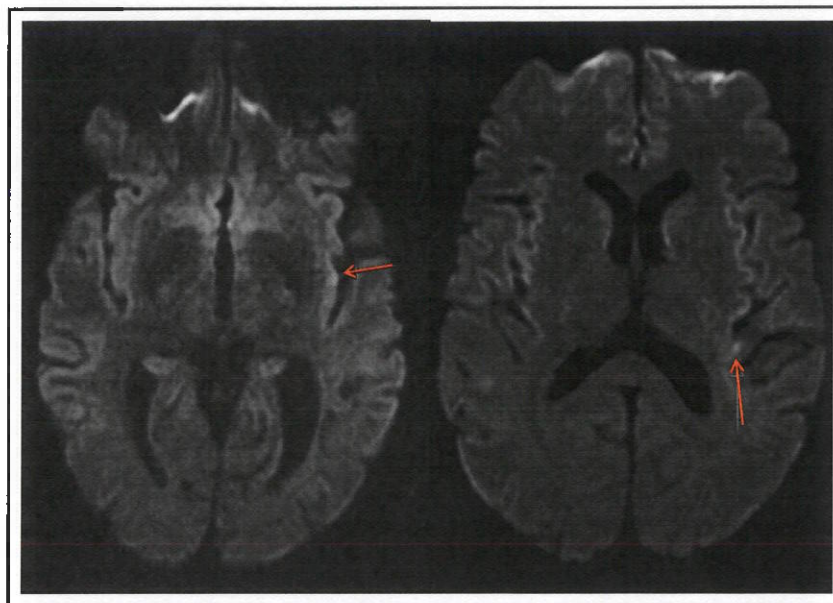


Figure 2. Axial images of magnetic resonance imaging (MRI) brain diffusion weighted imaging (DWI) sequence with arrows indicating small acute infarcts in the left middle cerebral artery territory.

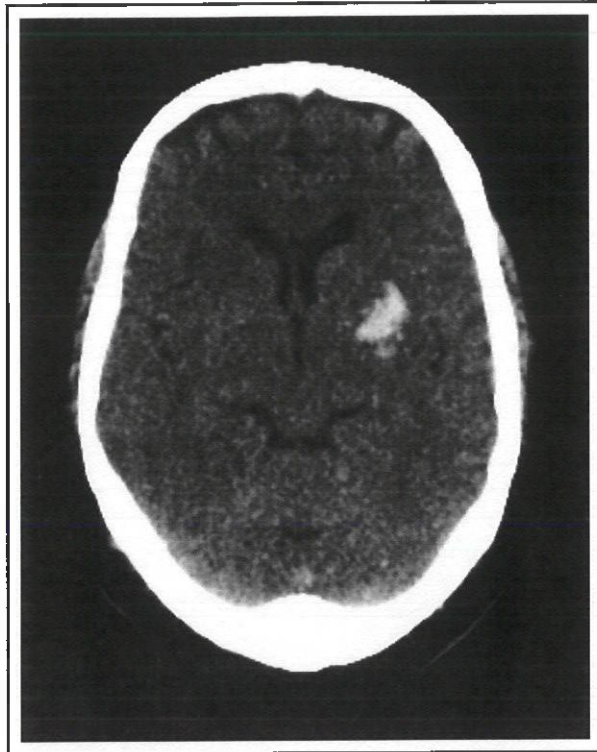


Figure 3. Computed tomography of the head demonstrates a left basal ganglia hemorrhage.

counseled appropriately, and have access to appropriate resources. With this in mind, <https://www.usa.gov/substance-abuse> may serve as a good starting point for providers and patients seeking resources for quitting.

Substance use disorders span a wide range of offending agents, many of which contribute to cerebrovascular dysfunction and injury. The prevalence of illicit substance use among patients with acute ischemic stroke in the United States is 2%; however, it is even higher among men and as high as 20% to 30% among young adult patients with stroke aged 20 to 54.² Up to 62% of patients with stroke have some form of substance misuse when including tobacco and alcohol. Some of the most commonly misused substances include tobacco, alcohol, and marijuana, however, illicit drugs, such as cocaine and amphetamines, impart significant neurovascular risk through several pathophysiological mechanisms.

Central nervous system stimulants induce vasoconstriction of cerebral vasculature by increasing levels of extracellular monoamines, particularly dopamine, which can cause vasospasm in medium and large intracranial arteries as well as microvasculature.³ This can result in a significant reduction in cerebral blood flow and subsequent ischemic stroke. Central nervous system stimulants also cause a rapid increase in intracellular calcium within cerebral vascular smooth muscle cells, leading to vasoconstriction and possible apoptosis.⁴ In addition to triggering hypoperfusion and ischemia in the territory of a constricted vessel, this can contribute to increased blood pressure and hypertensive hemorrhage.

Stimulants, such as cocaine, are also associated with increased platelet activation and aggregation, leading to thrombus formation and infarction. This is partially due to a release of VWF (von Willebrand Factor) from endothelial cells, which promotes platelet adhesion and aggregation.⁵ Endothelial damage and dysfunction can also promote thrombosis and exacerbate vasoconstriction. A population-based case-control study by Cheng et al⁶ investigated cocaine use and risk of ischemic stroke in young adults and found that acute cocaine use in the prior 24 hours was associated with increased risk of stroke even when adjusted for alcohol use, smoking, and hypertension. Additionally, many substances, including cocaine and amphetamines, trigger oxidative stress and inflammatory responses, including the release of cytokines such as TNF α (tumor necrosis factor α) and IL-6 (interleukin 6), which can be prothrombotic in addition to causing further endothelial damage.⁷

A recent article by Hemphill et al⁸ showed that methamphetamine use is more closely associated with hemorrhagic stroke as opposed to ischemic infarct. Cocaine and methamphetamine are both central nervous system stimulants; however, cocaine has a relatively short half-life compared with that of methamphetamine. This may allow for longer vasculature exposure to methamphetamine, resulting in prolonged hypertensive effects and thus further increasing the risk of hemorrhagic stroke.⁹ In addition to increasing blood pressure, stimulants such as amphetamines increase vascular permeability. In cases of overdose, acute amphetamine intoxication is also known to cause hyperthermia and disruption of the blood-brain

Teaching Points

- Screening for substance use disorder is an important part of ischemic and hemorrhagic stroke work-up and prevention.
- Quitting often takes multiple attempts. Once substance use disorder is identified, cessation counseling should be provided in a consistent and nonjudgmental manner.
- Many aspects of a patient's health care may suffer due to stigma and socioeconomic factors associated with substance use disorders. Providers should make every effort to mitigate barriers to care and provide patients with resources for quitting.

barrier, resulting in vasogenic edema and increased hemorrhage risk.

According to the American Heart Association's 2024 Guideline for the Primary Prevention of Stroke, it is recommended that patients with substance use disorders be advised to pursue cessation.¹⁰ Both patients in this series were under the age of 65 and used stimulants chronically. They presented with ischemic and hemorrhagic strokes following use of cocaine and methamphetamine, respectively, which likely contributed to these vascular events. It is probable that a combination of the previously described mechanisms, in addition to the patients' comorbid vascular risk factors, culminated in the ischemic and hemorrhagic strokes described in these cases. This serves to further highlight the importance of substance use counseling and providing patients with information on cessation as an integral part of both primary and secondary stroke prevention.

ARTICLE INFORMATION

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BRIEF REPORT



Risk of Intracranial Hemorrhage With Apixaban Versus Aspirin Therapy: A Meta-Analysis of Randomized Controlled Trials

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BACKGROUND: Oral anticoagulants are superior to antiplatelet agents for preventing cardioembolic stroke but concerns about increased risk of intracranial hemorrhage limit their use. Although rivaroxaban demonstrably increases intracranial bleeding risk compared with aspirin, the comparative risk of intracranial hemorrhage with apixaban versus aspirin remains uncertain. We aimed to clarify this risk through a meta-analysis of randomized controlled trials.

METHODS: We searched PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov for randomized controlled trials comparing apixaban with aspirin for ischemic stroke prevention. Studies were excluded if no intracranial hemorrhage events were reported in either arm. In the primary analysis, we used the Mantel-Haenszel method to meta-analyze the relative risk of intracranial hemorrhage with apixaban versus aspirin therapy. We conducted sensitivity analyses to examine the strength of these findings and to examine the secondary outcome of hemorrhagic stroke (which excludes epidural and subdural hematomas).

RESULTS: Three randomized controlled trials met our inclusion criteria, comprising a total of 10 626 patients and 74 incident intracranial hemorrhage events. In the pooled analysis, the relative risk of intracranial hemorrhage with apixaban versus aspirin therapy was 0.67 [95% CI, 0.43–1.08]; $P=0.10$. These findings were consistent in sensitivity analyses utilizing alternative statistical estimators, in analyses limited to primary prevention trials, and in analyses utilizing the outcome of hemorrhagic stroke (relative risk, 0.72 [95% CI, 0.39–1.31]; $P=0.28$).

CONCLUSIONS: In randomized controlled trials evaluating ischemic stroke prevention, apixaban demonstrated a safety profile comparable—and potentially superior—to aspirin with respect to intracranial hemorrhage risk. These findings warrant a reconsideration of clinical practices that favor aspirin over apixaban due to concerns about intracranial hemorrhage risk.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: apixaban ■ aspirin ■ intracranial hemorrhages ■ ischemic stroke ■ randomized controlled trial

Oral anticoagulation is the most effective therapy for reducing ischemic stroke risk in patients with atrial fibrillation.¹ One of the feared complications of anticoagulation therapy is intracranial hemorrhage, which can result in significant morbidity and mortality.² When intracranial hemorrhage risks are of particular concern, such as in patients with increased fall risk,³ clinicians often substitute oral anticoagulants with aspirin.⁴ This

practice stems from the assumption that aspirin confers lower intracranial bleeding risk. Consequently, direct oral anticoagulants (DOACs) are underprescribed for patients with atrial fibrillation, leaving many inadequately protected against ischemic stroke.³

Although intracranial hemorrhage risks have been shown to be higher for rivaroxaban relative to aspirin,^{5,6} there is uncertainty surrounding associations of other

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Nonstandard Abbreviations and Acronyms

ARCADIA	Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke
ARTESIA	Apixaban for the Reduction of Thrombo-Embolic in Patients With Device-Detected Subclinical Atrial Fibrillation
ASPIRE	Anticoagulation for Stroke Prevention and Recovery After ICH
ATTICUS	Apixaban for the Treatment of Embolic Stroke of Undetermined Source
AVERROES	Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment
DOAC	direct oral anticoagulant
OR	odds ratio
RCT	randomized controlled trial
RR	relative risk

DOACs, such as dabigatran and apixaban, with intracranial hemorrhage. Dabigatran has only been compared with aspirin in a single clinical trial of embolic stroke of undetermined source.⁷ In this trial, the association with intracranial hemorrhage was inconclusive because of wide CIs (odds ratio [OR], 1.00 [95% CI, 0.61–1.64]). A previous meta-analysis⁶ of intracranial hemorrhage risk with apixaban versus aspirin therapy included only the AVERROES trial (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) and was also inconclusive (OR, 0.84 [95% CI, 0.38–1.88]).⁸ Since the publication of this study, several additional randomized controlled trials (RCTs) comparing apixaban with aspirin therapy for ischemic stroke prevention have been reported.^{9–11} The availability of new data provides a compelling rationale to perform an updated synthesis of evidence on the comparative risks of intracranial hemorrhage between these 2 drugs. Findings from this investigation may inform clinical practice and help guide the design of future RCTs evaluating DOAC therapy in patients at high risk for intracranial hemorrhage.

METHODS

Data Availability

Data supporting the findings of this study are presented within the article and are publicly available through the cited references.

Preregistration

This meta-analysis was preregistered (URL: <https://www.crd.york.ac.uk/PROSPERO/>; Unique identifier: CRD42024622622) and conducted according to Preferred Reporting Items of Systematic Reviews and Meta-Analyses guidelines.¹² Our study design and statistical analyses were designed according to best practices from the Cochrane Handbook.¹³

Data Sources and Search Strategy

We searched PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from inception to January 14, 2025. In collaboration with a research librarian, we designed a search strategy for each database, searching titles and abstracts for the following terms: apixaban, Eliquis, aspirin, ASA, acetylsalicylic acid, TIA, transient ischemic attack, ischemic stroke, cerebrovascular accident, stroke, and atrial fibrillation (a full list of search terms is provided in the [Supplemental Methods](#)). We used the Covidence software (www.covidence.org, Melbourne, Victoria, Australia) to aggregate studies, remove duplicates, and screen articles.

Study Eligibility Criteria

Inclusion criteria included (1) RCTs designed to investigate apixaban versus aspirin therapy for the prevention of ischemic stroke, (2) randomization to either apixaban or aspirin at conventional therapeutic dosing, and (3) at least 1 year of mean or median follow-up. We excluded studies that did not exclusively randomize to either apixaban or aspirin (eg, randomization to dual antiplatelet therapy). In keeping with the Cochrane Handbook recommendations, we also excluded studies with no intracranial hemorrhage events reported in either study arm.

Data Abstraction and Risk-of-Bias Assessment

Two reviewers (I.D. and O.J.L.) independently screened titles and abstracts, with a third reviewer (J.C.H.) available to resolve disagreements. For trials meeting our inclusion criteria, we abstracted the following data: trial type (primary or secondary prevention), blinding methodology, trial location, funding source, dosages of apixaban and aspirin, average follow-up duration, intracranial hemorrhage case definition, hemorrhagic stroke case definition, exclusion criteria pertaining to prior intracranial hemorrhage, proportion of patients with prior ischemic stroke or transient ischemic attack, therapy discontinuation rates, mortality rates, and numbers of incident intracranial hemorrhage cases and noncases across each study arm from the intention-to-treat analysis. When information was unavailable in published articles, we contacted study investigators directly. We assessed trial bias using the Cochrane risk-of-bias tool (RoB 2).¹⁴

Statistical Analysis

The primary outcome was the relative risk (RR) of intracranial hemorrhage, which was calculated for each included trial. Given the low incidence rates of this outcome, we used the Mantel-Haenszel method for meta-analysis. This method was selected instead of the inverse-variance weighted method, which can be biased when applied to studies with rare events.¹³ We evaluated heterogeneity using the I^2 statistic and Cochrane Q test.

We performed several secondary and sensitivity analyses. First, we separately meta-analyzed findings from primary and secondary prevention trials of ischemic stroke prevention using the Mantel-Haenszel method. Second, we performed meta-analysis using the Peto OR method, which is another estimator designed to synthesize data from studies involving rare events.^{13,15} Third, to facilitate comparison with prior meta-analyses, we reported estimates using the random-effects inverse-variance weighted method. Finally, we performed a meta-analysis using the outcome of hemorrhagic stroke, a trial outcome limited to intracerebral hemorrhage and occasionally subarachnoid hemorrhage. This analysis was not prespecified in our initial analysis plan.

RESULTS

We screened 939 unique abstracts and identified 2 primary ischemic stroke prevention trials (AVERROES and ARTESIA [Apixaban for the Reduction of Thrombo-Embolic in Patients With Device-Detected Subclinical Atrial Fibrillation]) and 1 secondary ischemic stroke prevention trial (ARCADIA [Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic

Stroke]) that met the inclusion criteria (Figure S1; Table).^{8,10,11} We excluded the ATTICUS trial (Apixaban for the Treatment of Embolic Stroke of Undetermined Source) because it reported no intracranial hemorrhage events in the aspirin and apixaban treatment arms and thus failed to meet our inclusion criteria.⁹ The ARCADIA trial publication only reported intracranial hemorrhage outcomes from the per-protocol population, and so we contacted the lead investigator to obtain intracranial hemorrhage counts for the full intention-to-treat sample. The included trials encompassed 10 626 patients with a mean follow-up ranging from 1.1 to 3.5 years, and with 74 total incident intracranial hemorrhage events. The included RCTs were at low risk-of-bias in all domains assessed by the Cochrane RoB 2 tool.

All 3 trials estimated a lower RR of intracranial hemorrhage with apixaban versus aspirin, although with CIs that crossed the null (Figure 1). In meta-analysis, the pooled RR of intracranial hemorrhage with apixaban versus aspirin was 0.67 ([95% CI, 0.43–1.08]; $P=0.10$; $I^2=0\%$; $P_{het}=0.38$; Figure 1). The pooled RR of intracranial hemorrhage in primary ischemic stroke prevention

Table. Characteristics of Randomized Controlled Trials Selected for Inclusion in the Meta-Analysis

	AVERROES (Connolly et al) ⁸	ARTESIA (Healey et al) ¹¹	ARCADIA (Kamel et al) ¹⁰
Trial type	Primary prevention of stroke in atrial fibrillation	Primary prevention of stroke in subclinical atrial fibrillation	Secondary prevention in ESUS
Trial location	International (36 countries)	International (16 countries)	United States and Canada
Funding source	Industry	Population Health Research Institute and Industry	National Institutes of Health
Blinding	Double blind, double dummy	Double blind, double dummy	Double blind, double dummy
Aspirin dosage	81–324 mg daily	81 mg daily	81 mg daily
Apixaban dosage	5 mg twice daily	5 mg twice daily	5 mg twice daily
Primary outcome	Stroke or systemic embolism	Stroke or systemic embolism	Recurrent stroke
Intracranial hemorrhage definition	Intracranial bleeding	Symptomatic intracerebral hemorrhage or subdural hematoma, excluding ischemic stroke with hemorrhagic transformation	Any symptomatic extravascular blood within the cranium
Hemorrhagic stroke definition	Intracerebral hemorrhage	Intracerebral and subarachnoid hemorrhage	Intracerebral, subarachnoid, and intraventricular hemorrhage
Intracranial hemorrhage exclusion criteria	Serious bleeding in the last 6 mo or at high risk of bleeding	Serious bleeding in the last 6 mo or at high risk of bleeding	History of spontaneous intracranial hemorrhage
Prior anticoagulation exposure, %	14.8% in a month before the trial	Excluded	Excluded
Mean age (SD), y	70 (9.5)	77 (7.7)	68 (10.9)
Female, %	42	36	54
Mean years of follow-up (SD)	1.1 (SD not reported)	3.5 (1.8)	1.8 (1.3)
Prior ischemic stroke or TIA, %	13.6%	8.6%	19.4%
Discontinuation of trial therapy per year, %	Aspirin arm: 20.5% Apixaban arm: 17.9%	Aspirin arm: 16.8% Apixaban arm: 16.7%	Aspirin arm: 25.1% Apixaban arm: 24.5%
Mortality in trial, %	4.48%	17.5%	1.97% (only reported in on-treatment population)

We note that the apixaban dose in these trials was reduced to 2.5 mg twice daily if patients met the established dose-reduction criteria because of age, weight, or kidney function. The percentage of prior stroke or TIA in the ARCADIA trial refers to the events that occurred before the index event leading to trial enrollment. ARTESIA indicates Apixaban for the Reduction of Thrombo-Embolic in Patients With Device-Detected Subclinical Atrial Fibrillation; AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; ARCADIA, Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke; ESUS, embolic stroke of undetermined source; and TIA, transient ischemic attack.

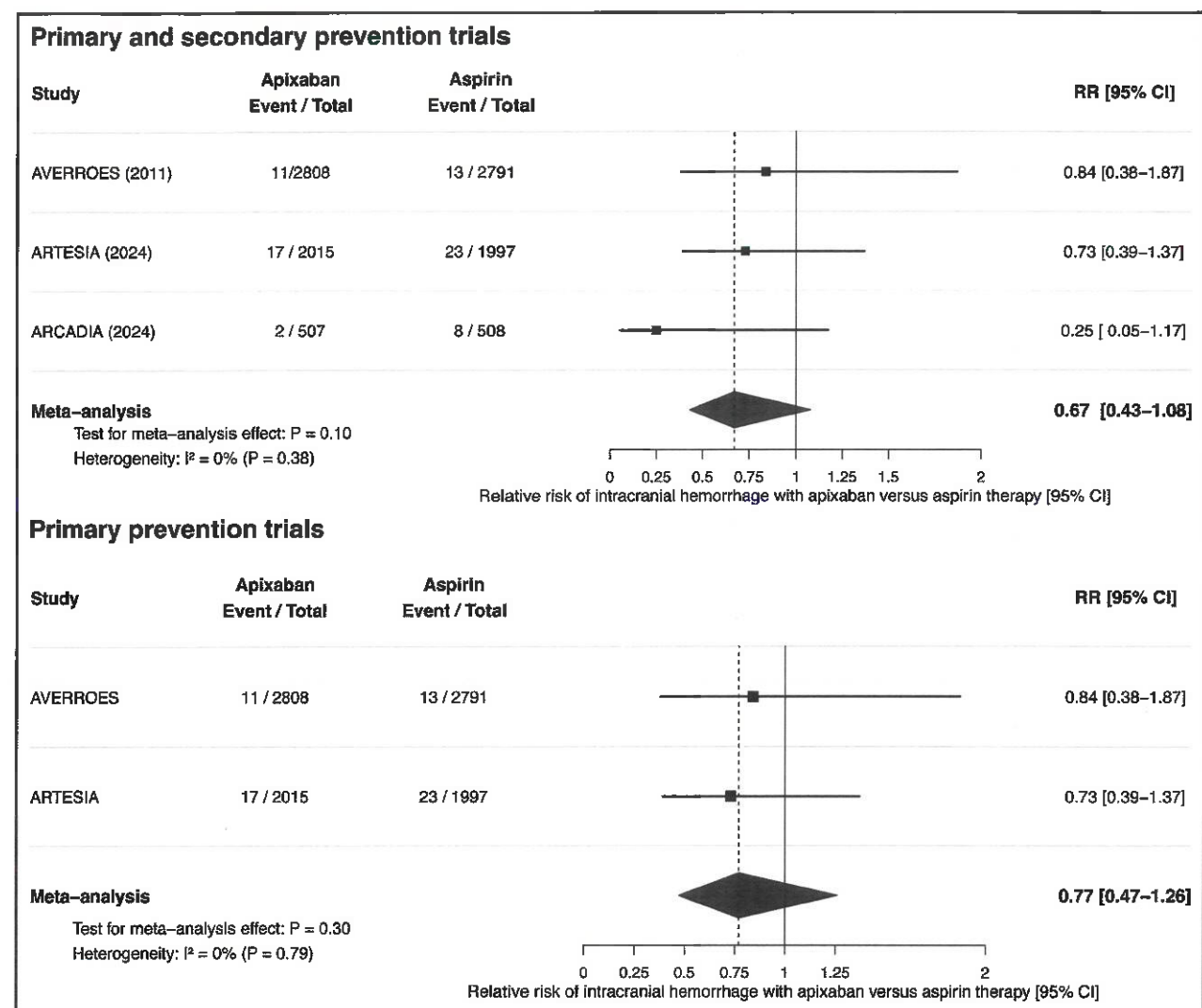


Figure 1. Meta-analysis of relative risk (RR) of intracranial hemorrhage with apixaban vs aspirin therapy.

Displayed are trial-specific RRs of intracranial hemorrhage with apixaban vs aspirin therapy (squares), 95% CIs (bars), and pooled estimates (diamond). We note that the RR calculations, while approximately correct, were not derived from true risks, as patients across the included trials were followed for variable time periods rather than uniform durations. ARCADIA indicates Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke; ARTESIA, Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Subclinical Atrial Fibrillation; and AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment.

trials was 0.77 ([95% CI, 0.47–1.26]; $P=0.30$; $I^2=0\%$; $P_{het}=0.79$; Figure 1).

In sensitivity analyses, the Peto OR method (OR, 0.68 [95% CI, 0.43–1.07]; $P=0.10$) and random-effects inverse-variance weighted method (RR, 0.69 [95% CI, 0.44–1.11]; $P=0.13$) yielded consistent results. The incidence of hemorrhagic stroke was only reported in the AVERROES and ARTESIA trial publications, and so we contacted the ARCADIA lead investigator to obtain hemorrhagic stroke counts across treatment arms (2 in the apixaban arm and 3 in the aspirin arm). Using these data, the pooled RR of hemorrhagic stroke with apixaban versus aspirin therapy was 0.72 ([95% CI, 0.39–1.31]; $P=0.28$; Figure 2).

DISCUSSION

In this updated meta-analysis of ischemic stroke prevention trials, we found that the RR of intracranial hemorrhage is comparable or lower with apixaban compared with aspirin therapy, with CIs ruling out a clinically significant increase in risk. These findings do not provide empirical support for the practice of substituting apixaban with aspirin for the prevention of stroke in atrial fibrillation when clinicians are concerned about intracranial bleeding risk.⁴ This practice replaces a highly effective treatment with one offering minimal benefit, while carrying similar or even greater intracranial hemorrhage risk. Furthermore, our findings, in the context of the known

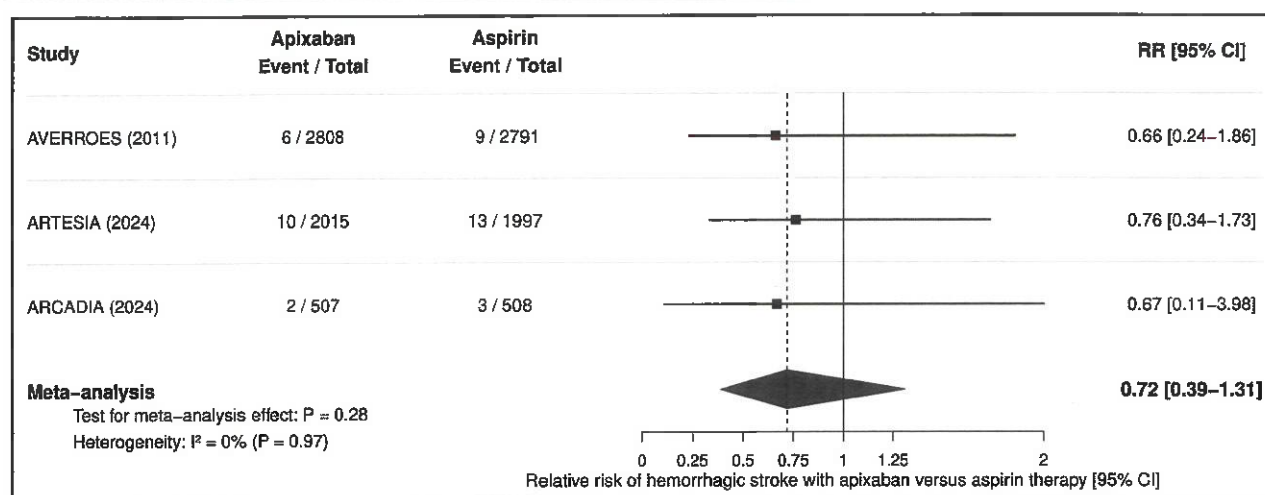


Figure 2. Meta-analysis of relative risk (RR) of hemorrhagic stroke with apixaban vs aspirin therapy.

Displayed are trial-specific RRs of hemorrhagic stroke with apixaban vs aspirin therapy (squares), 95% CIs (bars), and pooled estimates (diamond). We note that the RR calculations, while approximately correct, were not derived from true risks, as patients across the included trials were followed for variable time periods rather than uniform durations. ARCADIA indicates Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke; ARTESIA, Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Subclinical Atrial Fibrillation; and AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment.

increase in intracranial hemorrhage risk with rivaroxaban,⁶ highlight that DOACs have different safety profiles and should not be considered interchangeable. This suggests that trials comparing bleeding risk between antiplatelets and DOACs may be more successful by using apixaban as the comparator DOAC.⁶ Finally, these findings underscore that aspirin is not a benign therapy and should be approached with similar clinical caution as apixaban with respect to increasing intracranial hemorrhage risk.

This study has several strengths. We synthesized evidence from RCTs, which are not susceptible to the biases inherent to observational studies. The trials were well-designed and free of major biases. The consistency of findings across multiple statistical approaches, clinical contexts, and outcomes further strengthens the reliability of our findings. No heterogeneity was detected in any of the analyses. Finally, although not statistically significant, the CIs we estimated excluded clinically meaningful increases in intracranial hemorrhage risk with apixaban.

There are also limitations to consider when interpreting these findings. First, the RCTs included in this meta-analysis excluded or were not enriched for participants with prior intracranial hemorrhage or with intracerebral hemorrhage risk factors, such as cerebral amyloid angiopathy or high microbleed burden. Additional evidence for the relative safety of apixaban versus aspirin therapy in these high-risk populations will be provided by ongoing trials such as ASPIRE (Anticoagulation for Stroke Prevention and Recovery After ICH), which is comparing the efficacy and safety of these agents in patients with recent intracerebral hemorrhage.¹⁶ Second, the point estimate for the RR in ARCADIA was lower than the RR in the primary prevention trials, and it is unclear whether this difference stems from random

variation or indicates a more pronounced reduction in intracranial hemorrhage risk associated with apixaban use in this population. Third, because of data availability and sample size limitations, we were unable to assess heterogeneity by important clinical covariates, such as age, sex, hypertension status, and renal function. Fourth, our RR calculations, although approximately correct, were not derived from true risks, as patients across the included trials were followed for variable time periods rather than uniform durations. Fifth, a meta-analysis of intracranial hemorrhage events from per-protocol subgroups could not be conducted because these data were unavailable in the AVERROES trial. Finally, ARTESIA and ARCADIA combined subarachnoid hemorrhage and intracerebral hemorrhage into a single outcome termed hemorrhagic stroke. We suggest that future anticoagulant trials report subarachnoid and intracerebral hemorrhage separately because of their distinct biologic mechanisms. This differentiation would enable more precise synthesis of evidence in meta-analyses.

CONCLUSIONS

Apixaban is likely at least as safe as aspirin with regard to intracranial hemorrhage risk. Additional research is needed to determine which criteria, if any, would warrant withholding apixaban in favor of aspirin in patients with indications for oral anticoagulation.

ARTICLE INFORMATION

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The podcast and transcript are available at <https://www.ahajournals.org/str/podcast>.

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Dr. Daghlas designed the study with input from all authors. Dr Daghlas and Dr Lieberman performed study screening and data extraction. Dr Daghlas performed statistical analyses and drafted the article. All authors provided critical revisions to the article and approved the final draft.

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None.

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Supplemental Material

Supplemental Methods

Figure S1

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Association of the Timing and Type of Acute Symptomatic Seizures With Poststroke Epilepsy and Mortality

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BACKGROUND: Acute symptomatic seizures (ASyS) increase the risk of epilepsy and mortality after a stroke. The impact of the timing and type of ASyS remains unclear.

METHODS: This multicenter cohort study included data from 9 centers between 2002 and 2018, with a final analysis in February 2024. The study included 4552 adults (2005 female; median age, 73 years) with ischemic stroke and no seizure history. Seizures were classified using International League Against Epilepsy definitions. We examined ASyS occurring within 7 days after stroke. The main outcomes were all-cause mortality and epilepsy. Validation of the updated SeLECT score (SeLECT-ASyS) was performed in 3 independent cohorts (Switzerland, Argentina, and Japan) collected between 2012 and 2024, including 74 adults with ASyS.

RESULTS: The 10-year risk of poststroke epilepsy ranged from 41% to 94%, and mortality from 36% to 100%, depending on ASyS type and timing. ASyS on stroke onset day had a higher epilepsy risk (adjusted hazard ratio [aHR], 2.3 [95% CI, 1.3–4.0]; $P=0.003$) compared with later ASyS. Status epilepticus had the highest epilepsy risk (aHR, 9.6 [95% CI, 3.5–26.7]; $P<0.001$), followed by focal to bilateral tonic-clonic seizures (aHR, 3.4 [95% CI, 1.9–6.3]; $P<0.001$). Mortality was higher in those with ASyS presenting as focal to bilateral tonic-clonic seizures on day 0 (aHR, 2.8 [95% CI, 1.4–5.6]; $P=0.004$) and status epilepticus (aHR, 14.2 [95% CI, 3.5–58.8]; $P<0.001$). The updated SeLECT-ASyS model, available as an application, outperformed a previous model in the derivation cohort (concordance statistics, 0.68 versus 0.58; $P=0.02$) and in the validation cohort (0.70 versus 0.50; $P=0.18$).

CONCLUSIONS: ASyS timing and type significantly affect epilepsy and mortality risk after stroke, improving epilepsy prediction and guiding patient counseling.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: epilepsy ■ ischemic stroke ■ seizures ■ status epilepticus ■ stroke

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Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
ASyS	acute symptomatic seizures
C-statistics	concordance statistics
FBTCS	focal to bilateral tonic-clonic seizure
ILAE	International League Against Epilepsy
PSE	poststroke epilepsy
RSyS	remote symptomatic seizure

Stroke is a major cause of epilepsy in older adults, contributing to over half of new-onset epilepsy cases in individuals aged ≥ 65 years.¹ Poststroke seizures are associated with an increased risk of mortality, poor functional outcomes, disability, and dementia.^{2,3}

Poststroke seizures are categorized into acute symptomatic seizures (ASyS), occurring within the first 7 days after a stroke, and remote symptomatic seizures (RSyS), which are unprovoked seizures occurring later.⁴ ASyS are considered provoked and do not qualify as epilepsy. In contrast, a single or multiple RSyS following ischemic stroke fulfills the International League Against Epilepsy (ILAE) practical definition of epilepsy due to a heightened, $>60\%$ recurrence risk of seizures.⁵

ASyS is a major risk factor for epilepsy and mortality following ischemic stroke.^{3,6} Recent research underscores the heterogeneity among ASyS, suggesting certain subtypes confer higher risks than others.⁷ We have shown that ASyS presenting as status epilepticus carries a markedly elevated risk of epilepsy and mortality compared with short ASyS after ischemic stroke.³ However, there remains a knowledge gap about other characteristics of ASyS that may be associated with an increased risk of seizures or unfavorable outcomes.

We hypothesized that the timing and type of a short ASyS influence the risk of poststroke epilepsy (PSE) and mortality. We assessed this hypothesis using data from a large multicenter registry of poststroke seizures. We implemented this knowledge in an updated prognostic model that improves the prediction of epilepsy following ASyS after ischemic stroke.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

We analyzed both a derivation and a validation cohort of participants. The derivation cohort was drawn from a multicenter registry established as part of the SeLECT study,⁸ consisting of 9 international cohorts ($n=4552$) of adults with neuroimaging-confirmed acute ischemic stroke. We added 3 additional independent international cohorts of people with ASyS following

ischemic stroke as a validation data set by directly approaching investigators with an interest in PSE research. The validation cohort included participants with ASyS following ischemic stroke from 3 additional independent cohorts. We excluded individuals with transient ischemic attacks, a history of seizures or epilepsy, primarily hemorrhagic stroke (eg, primary intracerebral hemorrhage or primary subarachnoid hemorrhage), reinfarction during follow-up, or potentially epileptogenic comorbidities (such as intracranial tumors, cerebral venous thrombosis, severe traumatic brain injury [Glasgow Coma Scale ≤ 8 ; loss of consciousness >24 hours, posttraumatic amnesia >7 days, and significant brain injury on imaging], or prior brain surgery) while retaining patients with a primary ischemic stroke and secondary hemorrhagic transformation. Detailed descriptions of the individual cohorts are provided in the [Supplemental Material](#).

Informed consent, obtained either in written or verbal form (4 cohorts utilized written consent, while 2 cohorts used both written and verbal consent), was acquired. In 3 cohorts consent requirements were waived by the regulatory authorities, as outlined in the [Supplemental Material](#).

Definitions

According to ILAE recommendations, seizures were classified as ASyS (occurring within 7 days after stroke) or RSyS (spontaneous unprovoked seizures >7 days after stroke).⁴ The occurrence of an RSyS was categorized as PSE due to its high seizure recurrence risk, exceeding the 60% risk required for the ILAE pragmatic definition of epilepsy.^{5,8} Status epilepticus was classified according to the revised ILAE definition.⁹ Electrographic status epilepticus was defined according to Salzburg and revised American Clinical Neurophysiology Society criteria.^{10,11} ASyS not qualifying as status epilepticus were defined as short ASyS and classified into subtypes (focal aware, focal with impaired awareness, focal to bilateral tonic-clonic, or undetermined) based on the current ILAE nomenclature.¹² We dichotomized the timing of ASyS into those occurring on the same day as stroke onset (day 0) versus those occurring later because the majority of ASyS occurred on day 0. In individuals with multiple ASyS, we only considered the first reported ASyS. Further definitions are detailed in the [eMethods](#) in the [Supplemental Material](#).

Statistical Analysis

First, we used multivariable Cox proportional hazards regression to assess the relationship between the type and timing of ASyS and the time to PSE or death, while adjusting for covariates (age, sex, National Institutes of Health Stroke Scale score at admission, cortical involvement, involvement of the middle cerebral artery territory, stroke cause, reperfusion treatment, and antiseizure medication treatment after ASyS). Cases were censored at the time of death, first RSyS, or last follow-up. Adjusted risk estimates for PSE or death were obtained from these multivariable Cox regression models. The proportional hazards assumption was assessed using Schoenfeld residuals. In cases where time-varying effects were suggested, complementary analyses were conducted using an accelerated failure time model ([Table S8](#)).

Second, we compared the performance of a previously described prognostic model for PSE (SeLECT_{2.0})³ in stroke survivors with versus without ASyS using concordance statistics (C statistics). We also compared the observed risk of seizures

in those with versus without ASyS having similar SeLECT_{2.0} score strata (3–4 points and 5–6 points) using Kaplan-Meier estimate plots and log-rank tests.

Next, we updated the existing SeLECT_{2.0} model, specifically tailoring it for stroke survivors with ASyS to improve the prediction of PSE in this particularly vulnerable population. Least Absolute Shrinkage and Selection Operator Cox regression was used initially for variable selection, utilizing a penalty function to refine the model.¹³ The regularization parameter lambda in the Least Absolute Shrinkage and Selection Operator regression was selected using k-fold cross-validation ($k=10$). Following the Least Absolute Shrinkage and Selection Operator selection, we used Wald stepwise backward regression as an additional method to identify significant variables and compare them with those selected by Least Absolute Shrinkage and Selection Operator. To account for death as a competing risk, we also used competing risk regression based on Fine and Gray's subdistribution hazard model, which allowed us to calculate the cumulative incidence function for late seizures (see Table S4). We assigned integer values to the retained variables

based on their adjusted hazard ratio (aHR; see Table S5) to calculate a clinical risk score for each study individual.

To evaluate the updated model's discrimination, that is, the ability to distinguish between high- and low-risk cases, we estimated the C statistics (95% CI). Recognizing that prognostic models derived from multivariable regression can exhibit optimism and potentially overestimate predictions when applied to new patient cohorts,¹⁴ we introduced a shrinkage factor. This factor was estimated through 1000 bootstrapped random samples to adjust the C statistics for overoptimism, a technique previously used to enhance model generalizability.^{15,16} We also assessed model calibration, that is, the agreement between predicted and observed risks, using calibration plots (see Figure S5). Perfect calibration is represented by a 45° diagonal line, whereas relevant deviation above or below this line reflects under or overprediction. We used a leave-one-cohort-out strategy for cross-validation of model performance.

Lastly, we computed the change of occurrence of a seizure in the next year, a parameter that may be relevant for assessing the fitness to drive in people with seizures, using the standard

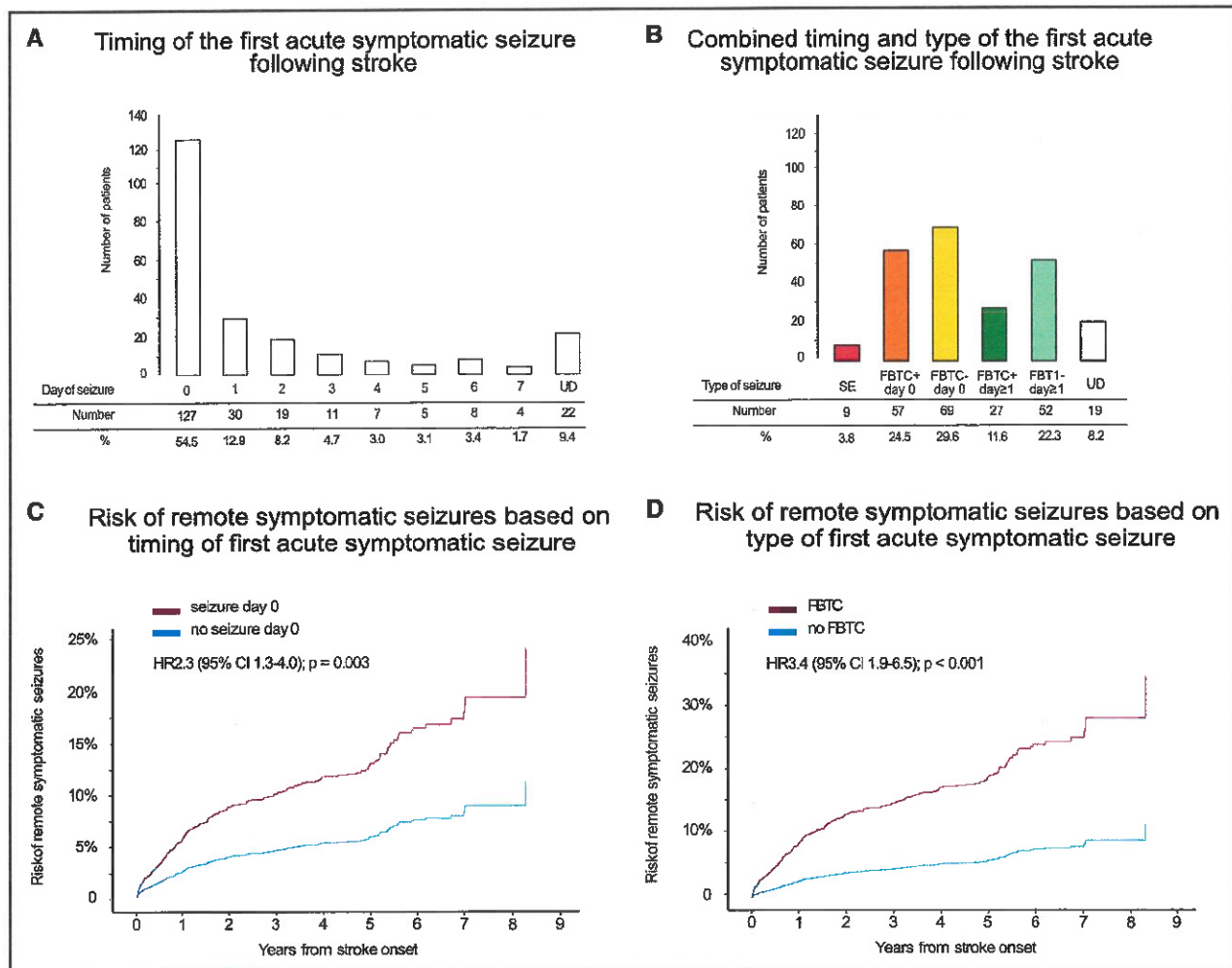


Figure 1. Characterization of acute symptomatic seizures (ASyS) timing and type.

A and **B**, The distribution and stratification of the first ASyS occurring after ischemic stroke. **A** illustrates the timing of ASyS, while **B** combines the timing (day 0 vs other days) with the type of seizure (eg, focal to bilateral tonic-clonic seizure [FBTCs], status epilepticus [SE]). The color coding in **B** aligns with the stratification of ASyS shown in Figure 2. Due to the small number of cases, SE and UD (undetermined/unknown seizure timing) seizures were not further differentiated by timing. **C** and **D**, Kaplan-Meier estimates ($n=4552$) of the time to poststroke epilepsy stratified by ASyS timing (day 0 vs day ≥1; **C**) and type (FBTCs vs other short seizure type; **D**). HR indicates hazard ratio.

statistical definition of conditional risks¹⁷ as detailed previously³² (see Figure S2). Previously proposed change of occurrence of a seizure in the next year thresholds are <20% to 40% for private driving and <2% for professional driving,^{18–20} although these may differ based on local regulations.

All analyses were conducted using R Statistical Software, version 4.0.3, and SPSS, version 26 (IBM), and followed the STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology; Supplemental Material).

RESULTS

The study included 4552 individuals from 9 centers. Their baseline characteristics are shown in Table S1. ASyS occurred in 5% ($n=233$) of participants. The first ASyS was presented on the same day as the stroke (day 0) in 55% ($n=127$; Figure 1A; Table S2). The frequency of ASyS stratified by type and timing is shown in Figure 1B.

Risk of PSE

ASyS on day 0 had a higher risk of PSE (aHR, 2.3 [95% CI, 1.3–4.0]; $P=0.003$; Figure 1C; Table 1) compared with ASyS occurring later after stroke. Other ASyS timing cutoffs did not yield relevant differences in the risk of PSE (Figure S2). Regarding seizure types, ASyS presenting as status epilepticus had the highest risk of PSE (aHR, 9.6 [95% CI, 3.5–26.7]; $P<0.001$), followed by focal to bilateral tonic-clonic seizure (FBTCS; aHR, 3.4 [95% CI, 1.9–6.3]; $P<0.001$; Figure 1D; Table 1) compared with other ASyS types (Figure S4). The full results of the multivariable model and other variables independently associated with PSE (stroke severity, location, and cause) are shown in Table 1.

Stroke survivors with a non-FBTC short ASyS occurring on day 1 or later after stroke had a 41% risk of developing PSE 10 years after stroke, compared with a 69% risk in those having a FBTC short ASyS on day 0 after stroke and a 94% risk in those with acute symptomatic status epilepticus (Figure 2A; Table S2). The 10-year risk of PSE was 13% in stroke survivors without ASyS.

Mortality

A higher risk of all-cause mortality was observed in those with ASyS presenting as FBTCS on day 0 (aHR, 2.8 [95% CI, 1.4–5.6]; $P=0.004$) and those with acute symptomatic status epilepticus (aHR, 14.2 [95% CI, 3.5–58.8]; $P<0.001$). Other subtypes of ASyS were not associated with mortality (Table 2).

Individuals with a stroke and a non-FBTC short ASyS occurring on day 1 or later after stroke had a 49% risk of all-cause mortality 10 years after stroke, compared with a 66% risk in those having a FBTC short ASyS on day 0 after stroke and a 100% risk in those with acute symptomatic status epilepticus (Figure 2B). The overall 10-year risk of all-cause mortality was 32% in those without ASyS.

Table 1. Multivariable Cox Regression Model of Time to First Remote Symptomatic Seizure

Variable	aHR (95% CI)	P value
Demographics		
Age (per 10 y)	0.9 (0.9–1.0)	0.07
Sex, male	1.0 (0.8–1.3)	0.91
Stroke severity at admission		
NIHSS 4–10	1.7 (1.2–2.5)*	<0.001*
NIHSS ≥ 11	4.2 (3.0–5.9)*	<0.001*
Stroke location		
Middle cerebral artery territory involvement	1.5 (1.2–2.1)*	0.02*
Cortical involvement	2.2 (1.7–2.9)*	<0.001*
Stroke cause		
Small-vessel occlusion	1.0 (0.6–1.6)	0.90
Larger-artery atherosclerosis	1.6 (1.2–2.1)*	0.003*
Cardioembolic	0.9 (0.7–1.2)	0.51
Treatment		
Acute reperfusion treatment	0.8 (0.6–1.0)	0.05
Acute symptomatic seizure type		
Seizure occurring on day 0	2.3 (1.3–4.0)*	0.003*
Focal seizure with impaired awareness	1.6 (0.7–3.9)	0.28
Focal to bilateral tonic-clonic seizure	3.4 (1.9–6.3)*	<0.001*
Status epilepticus	9.6 (3.5–26.7)*	<0.001*
Undetermined or unknown seizure type	1.8 (0.7–4.1)	0.20

Data was analyzed using a Cox proportional hazards model in the derivation cohort ($n=4552$). The dependent variable was the time of the first remote seizure. aHR indicates adjusted hazard ratio; and NIHSS, National Institutes of Health Stroke Scale.

*Statistically significant results ($P<0.05$).

Prognostic Modeling

We observed that the performance of a previously published prognostic model predicting the risk of PSE (SeLECT_{2.0}) was low in individuals with ASyS (C statistics, 0.58 [95% CI, 0.49–0.67]; $n=233$) compared with a better performance in the overall cohort (C statistics, 0.75 [95% CI, 0.72–0.78]; $n=4552$). The observed risk of PSE in stroke survivors with ASyS was higher compared with those without ASyS who had a similar SeLECT_{2.0} score (Figure 3; SeLECT_{2.0} score 3 to 4, $P<0.001$; SeLECT_{2.0} score 5 to 6, $P=0.10$).

Thus, the SeLECT_{2.0} model may not adequately capture the risk of epilepsy in those with ASyS. To overcome these limitations, we updated the SeLECT_{2.0} model specifically for those having ASyS after stroke and to implement the above findings on the risk of epilepsy according to ASyS type and timing.

We selected predictors using stepwise backward elimination of a Cox regression model in stroke survivors with ASyS (Table S4). The variables retained in the final model were timing and type of first ASyS, large-vessel atherosclerotic stroke pathogenesis stratified by sex, and stroke involving the cerebral cortex. The calculation of the new model termed SeLECT-ASyS and ranging from 0 to 7 points, is shown in Table 3. The SeLECT-ASyS model

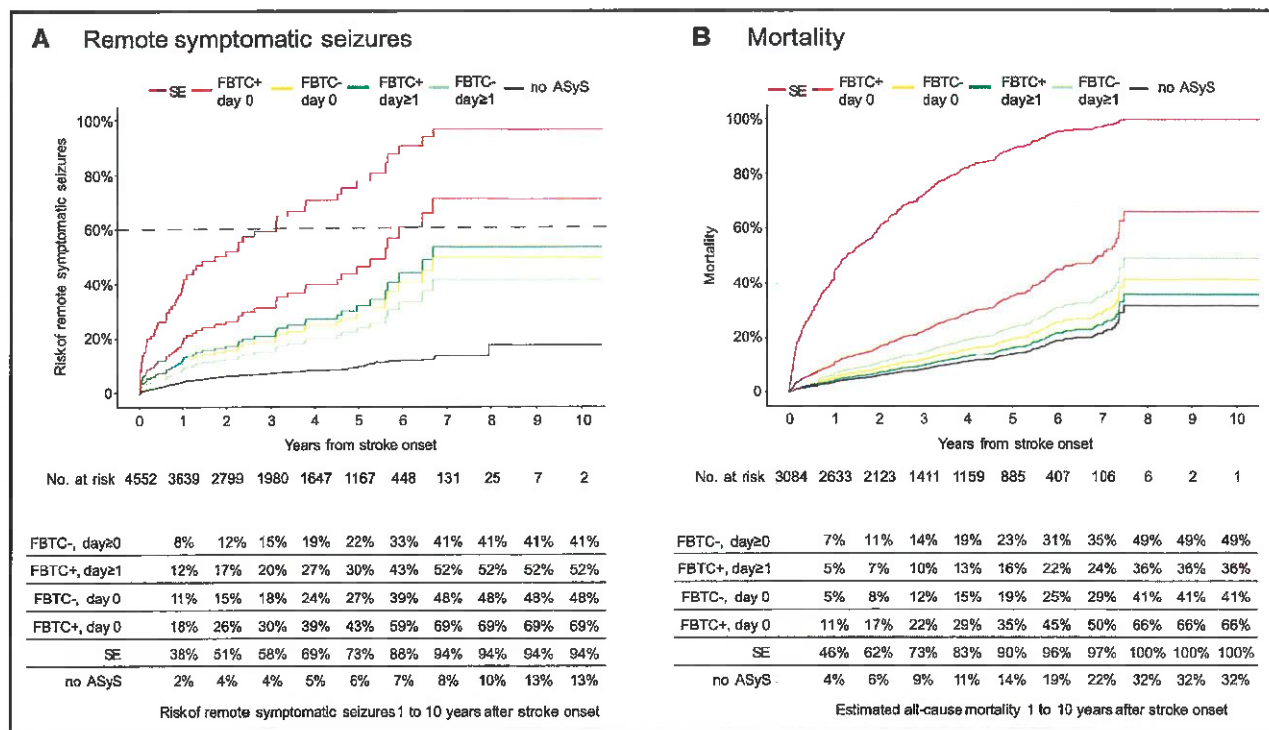


Figure 2. Risk of poststroke epilepsy or mortality following acute symptomatic seizures (ASyS) after stroke.

Data according to the type and timing of ASyS and association with remote symptomatic seizure (RSyS; $n=4552$; **A**) and mortality ($n=3084$; **B**). The tables below each graph display the Kaplan-Meier estimates of the risk of RSyS 1 to 10 years after index stroke according to the type of ASyS. All results were obtained after adjusting for covariates (age, sex, National Institutes of Health Stroke Scale score at admission, cortical involvement, involvement of the middle cerebral artery territory, stroke cause, reperfusion treatment, and antiseizure medication treatment after ASyS). The dotted line denotes the 60% cutoff for the risk of unprovoked seizures used in the International League Against Epilepsy practical clinical definition of epilepsy. FBTCs indicates focal to bilateral tonic-clonic seizure; and SE, status epilepticus.

had better discrimination for time to PSE compared with the original SeLECT₂₀ model (C statistics, 0.68 [95% CI, 0.61–0.76] versus 0.58 [95% CI, 0.49–0.67]; $P=0.02$) in stroke survivors with ASyS. SeLECT-ASyS demonstrated better, near-optimal calibration for long-term outcomes compared with the less optimal calibration of the SeLECT₂₀ model in those with ASyS, although the calibration curves indicated less accuracy for predicting the 1-year occurrence of PSE and lacked data for lower probability outcomes (Figure S5). We cross-validated the results using a leave-one-cohort-out strategy (Table S6). To further support our findings, we evaluated a validation cohort of 74 adults with ASyS following ischemic stroke who met the eligibility criteria (Switzerland, $n=32$; Argentina, $n=23$; and Japan, $n=19$). The baseline characteristics of these individuals are presented in Table S7. In this validation cohort, the SeLECT-ASyS model demonstrated superior discrimination with a C statistics of 0.70 (95% CI, 0.57–0.83) compared with the SeLECT₂₀ model (C statistics, 0.59 [95% CI, 0.44–0.75]; $P=0.18$), indicating better predictive accuracy for RSyS (Figure S6).

The lowest score SeLECT-ASyS value (0 points) predicts a 26% risk (95% CI, 9–39) of PSE 10 years following a stroke, compared with a 100% risk (95% CI, 30–100) for the highest value (7 points; Figure 4). A comparison to the SeLECT₂₀ values for patients without

ASyS is shown in Figure S1. In addition, we updated the values for change of occurrence of a seizure in the next year (Figure S2), a parameter that may be helpful for assessing the risks of safe driving. The new SeLECT-ASyS model was implemented in the SeLECT score smartphone applications available for iOS and Android and the web-based calculator.

Real-World Case Example

A male patient in his 70s presented with an acute ischemic stroke in the right middle cerebral artery territory in 2021, confirmed by neuroimaging. The stroke had cortical involvement and was classified as atherosclerotic in origin (TOAST [Trial of ORG 10172 in Acute Stroke Treatment] classification – type 1). Clinically, he exhibited moderate to severe left-sided hemiparesis, facial palsy, dysarthria, and dysphagia. His National Institutes of Health Stroke Scale score was 25 at the initial evaluation, reduced to 15 following reperfusion therapy.

On the day of admission (day 0), the patient experienced an FBTCs, observed by hospital staff. This event was categorized as an ASyS. Based on the SeLECT₂₀ score, the patient's calculated risk of PSE within 10 years was 30% (95% CI, 13–43) with a total score of 5. However, the updated SeLECT-ASyS model, tailored

Table 2. Multivariable Cox Regression Model of Time to Death

Variable	aHR (95% CI)	P value
Demographics		
Age (per 10 y)	2.2 (2.0–2.4)*	<0.001*
Sex, male	1.2 (1.0–1.4)*	0.05*
Stroke severity at admission		
NIHSS 4–10	1.7 (1.3–2.1)*	<0.001*
NIHSS ≥11	2.4 (1.9–3.1)*	<0.001*
Stroke location		
Middle cerebral artery territory involvement	0.9 (0.8–1.2)	0.64
Cortical involvement	1.0 (0.9–1.3)	0.71
Stroke cause		
Small-vessel occlusion	0.6 (0.4–0.8)*	<0.001*
Larger-artery atherosclerosis	0.7 (0.5–0.9)*	0.02*
Cardioembolic	0.8 (0.7–1.0)	0.07
Treatment		
Acute reperfusion treatment	0.8 (0.7–1.0)*	0.04*
ASM treatment after ASyS	0.5 (0.3–0.9)*	0.03*
Acute symptomatic seizure type		
FBTC–, day>0	1.8 (0.8–4.0)	0.18
FBTC+, day>0	1.2 (0.4–3.7)	0.81
FBTC–, day 0	1.4 (0.7–2.6)	0.32
FBTC+, day 0	2.8 (1.4–5.6)*	0.004*
Status epilepticus	14.2 (3.5–58.8)*	<0.001*

Data was analyzed using a Cox proportional hazards model in the derivation cohort (n=4552). The dependent variable was the time to death of any cause. aHR indicates adjusted hazard ratio; ASM, antiseizure medication; ASyS, acute symptomatic seizures; day 0, same day as stroke onset; FBTC–, other type of short seizure; FBTC+, focal to bilateral tonic-clonic short seizure; and NIHSS, National Institutes of Health Stroke Scale.

*Statistically significant results ($P<0.05$).

specifically for individuals with ASyS, also assigned a score of 5 but predicted a markedly higher 96% (95% CI, 70–99) risk of PSE within 10 years.

Initial treatment included Levetiracetam (500 mg twice daily), which was discontinued upon discharge as the seizure was deemed acute symptomatic. Four months postdischarge, the patient reported recurrent brief episodes of tremors in the left hand, consistent with simple focal seizures. A diagnosis of PSE was made, and Levetiracetam was restarted. Since resuming antiseizure medication, the patient has remained seizure-free.

DISCUSSION

In this study, we investigated the influence of both timing and type of ASyS on the risk of epilepsy and mortality after ischemic stroke. Our findings reveal substantial heterogeneity among ASyS, indicating that events occurring on the day of stroke onset (day 0) and those manifesting as FBTCs or status epilepticus had a higher risk of developing PSE. FBTCs on day 0 and acute symptomatic

status epilepticus had a high, ≥69% risk of epilepsy and a ≥66% risk of mortality (Figure 2).

We also showed that a current state-of-the-art model for predicting PSE (SeLECT_{2.0}) underperformed in stroke survivors with ASyS and confirmed this finding in independent validation cohorts. We implemented our results on the role of timing and types of ASyS in an updated model (SeLECT-ASyS), tailored specifically for stroke survivors experiencing ASyS. This model accurately captures the elevated risks of PSE in this subgroup and significantly outperforms the SeLECT_{2.0} model in those with ASyS. For individuals without ASyS, the SeLECT_{2.0} model remains the appropriate tool for risk prediction, ensuring that each model is applied within its intended population to optimize prognostic accuracy.

We previously showed that acute symptomatic status epilepticus is a predictor of mortality and epilepsy after stroke³ and discussed the potential explanations for this observation. The estimated risks for epilepsy and mortality in the current study are slightly higher compared with our previous study³ because of the completion of long-term (60-month) follow-up in the second largest cohort in the registry (Switzerland (2)) which results in more robust estimates. Building upon our prior research, we demonstrated in this study that ASyS presenting as FBTCs and occurring on day 0 also carry a higher risk of PSE and mortality. There are several potential explanations for this finding.

First, individuals experiencing ASyS early after stroke, that is, on day 0, and ASyS presenting as FBTCs may have a higher predisposition for generating seizures. This genetic or acquired vulnerability,²¹ conceptualized as a low seizure threshold,²² may predispose these individuals to an earlier onset of ASyS and the propagation of seizure activity across hemispheres. Such a low seizure threshold may also heighten the probability of subsequent RSyS during epileptogenesis.²²

Second, the occurrence of ASyS on day 0 and a bilateral spread of seizures could be indicative of a more pronounced proepileptic impact of the stroke. Our previous research suggested that more severe strokes due to large artery atherosclerosis, affecting the middle cerebral artery territory, are more likely to result in PSE.⁶ But, the present study's outcomes were adjusted for these variables, establishing independence from such factors. Other stroke characteristics warrant consideration. At a macroscopic level, the precise localization²³ and connectivity of stroke may contribute to acute seizures and epileptogenesis. Strokes highly connected to the basal ganglia and cerebellum were found to be more likely to cause epilepsy.²⁴ On a microscopic scale, cellular changes that are difficult to detect in vivo in humans, such as neurodegeneration, axonal and synaptic sprouting, blood-brain barrier damage, and inflammation,²¹ may promote acute seizures and epileptogenesis.

Third, disparities between ASyS occurring on day 0 and those manifesting later may be associated with the time-dependent dynamics of pathological mechanisms

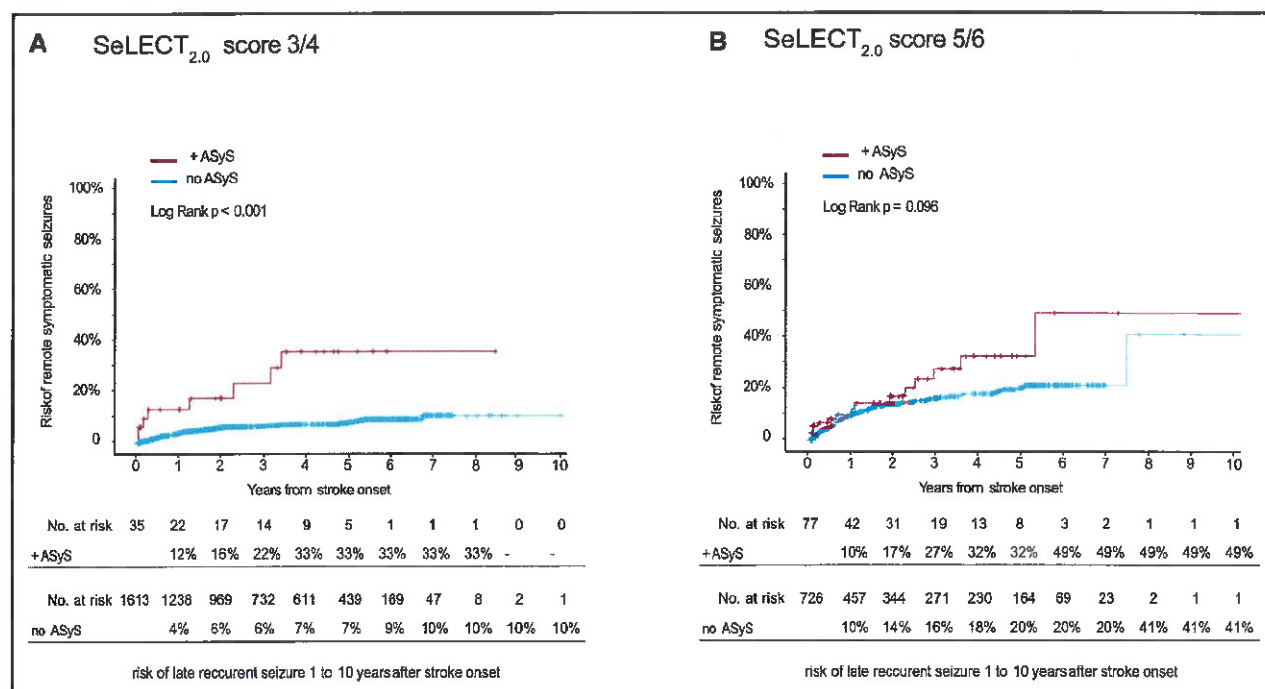


Figure 3. Risk of epilepsy in individuals with or without acute symptomatic seizures (ASyS) having a similar SeLECT_{2.0} score. Kaplan-Meier estimates ($n=4552$) of the time to poststroke epilepsy in those with a SeLECT_{2.0} score of 3 to 4 (A) or 5 to 6 (B) points. Separate curves are shown for individuals with (red) or without (blue) ASyS. Those with a SeLECT_{2.0} score of 3 to 4 who suffered ASyS had a higher risk of poststroke epilepsy (higher risk of remote symptomatic seizures) compared with those without ASyS ($P<0.001$). There was a similar but nonsignificant trend in individuals with a SeLECT_{2.0} score of 5 to 6 who had ASyS compared with those without ($P=0.096$). ASyS is defined as seizures occurring within the first 7 days following ischemic stroke.

following a stroke, such as neuroinflammatory changes and metabolic derangements.²⁵ Consequently, ASyS occurring early might be triggered by distinct mechanisms compared with those occurring later, potentially resulting in variations in the risk of PSE.

Lastly, ASyS may directly or indirectly contribute to epileptogenesis. While this concept has been consistently demonstrated in animal models of status epilepticus, it is less well-established for brief seizures.²⁶ Some experimental evidence suggests that brief convulsive seizures may also contribute to the process of epileptogenesis.^{26–28}

ASyS presenting as FBTCs on day 0 were independently associated with higher mortality after stroke. They may be a marker of significant macro or microscopic neuronal disruption caused by stroke, as discussed above. Furthermore, convulsive seizures have been linked to excitotoxic damage in animal models, potentially contributing to poor outcomes.²⁹ Convulsive seizures may also be associated with injuries, heightened metabolic demand, and aspiration leading to pneumonia, further impacting overall outcomes.

To translate these findings into clinical practice, we incorporated them into an updated prognostic model. Initially, we demonstrated that the current state-of-the-art prognostic model for poststroke seizures, SeLECT_{2.0}, underestimates the risk of PSE in the subset of stroke survivors with ASyS (Figure 3). Stroke survivors with ASyS

represent a distinct group with unique predictors and a heightened risk of epilepsy compared with those without ASyS.³⁰ Subsequently, we updated and validated the SeLECT_{2.0} model, resulting in SeLECT-ASyS, which exhibited superior discrimination and calibration compared with SeLECT_{2.0} in the ASyS subgroup. We also performed internal validation using optimism correction through bootstrapping and cross-validation (Table S6). Furthermore, we also

Table 3. Calculation of the SeLECT-ASyS Score

Variable	SeLECT-ASyS score (points)
Stroke location	
Cortical involvement	1
Stroke cause and sex	
Large artery atherosclerosis, female	1
Large artery atherosclerosis, male	2
Acute symptomatic seizures type	
FBTC–, day≥1	0
FBTC+, day≥1	1
FBTC–, day 0	1
FBTC+, day 0	2
Status epilepticus	4

To calculate an individual's SeLECT-ASyS score, the points associated with each predictor can be added to obtain the total risk score. The total score ranges from 0 to 7 points; day 0 indicates same day as stroke onset; FBTC+, focal to bilateral tonic-clonic short seizure; and FBTC–, other type of short seizure.

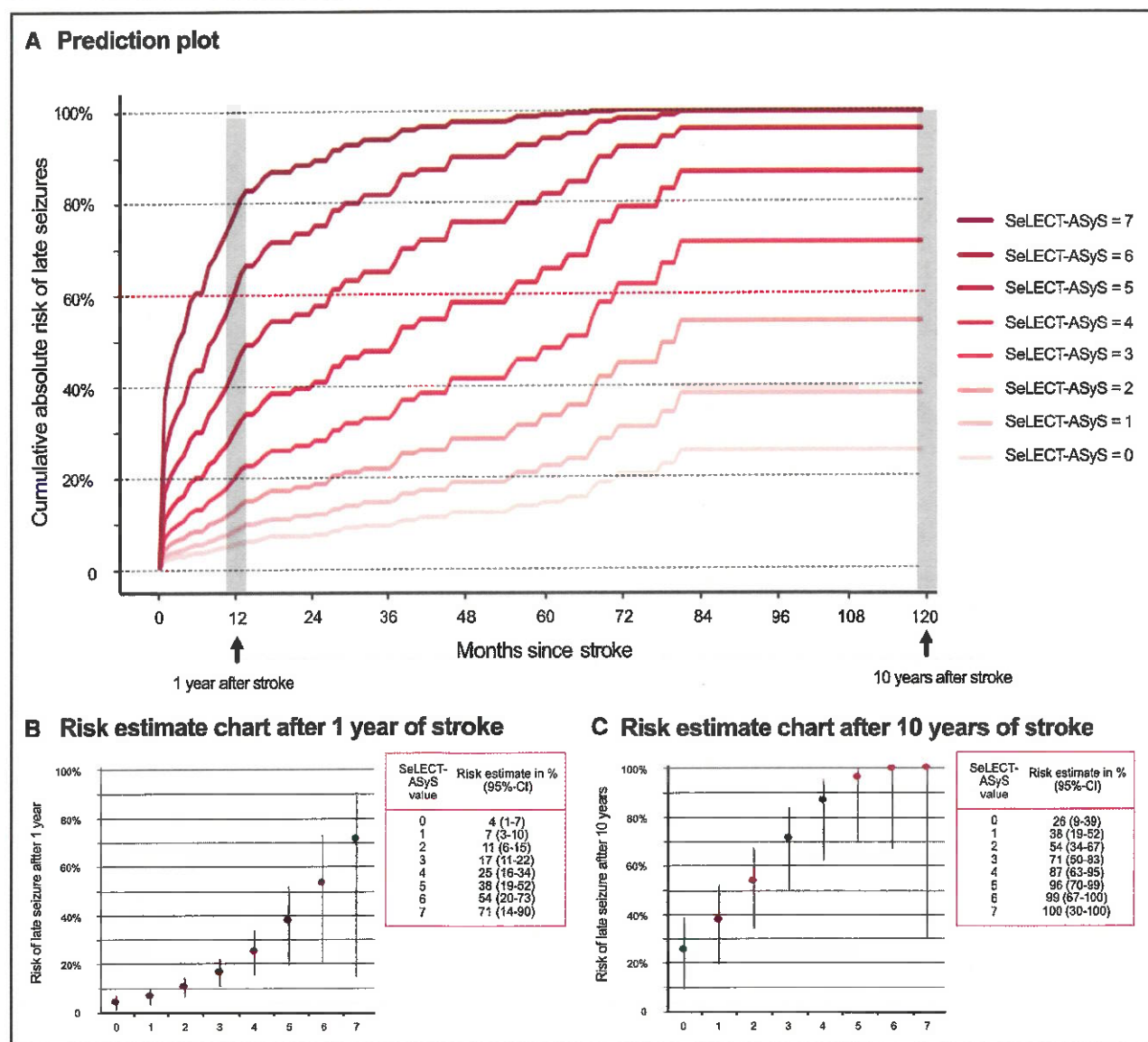


Figure 4. Predicted risk of poststroke epilepsy according to a new prognostic model in stroke survivors with acute symptomatic seizures.

A. The predicted risk of poststroke epilepsy (unprovoked remote symptomatic seizures) is 0 to 120 months after stroke. Each curve represents the estimates for a SeLECT-ASyS value ranging from 0 to 6. Risk estimate charts of late seizures 1 year and 10 years after stroke according to SeLECT-ASyS score values are displayed in **B** and **C**, respectively. Vertical lines indicate 95% CIs.

confirmed SeLECT₂₀'s underperformance in stroke survivors with ASyS in independent external validation cohorts. Consequently, SeLECT-ASyS emerges as the preferred model for prognostication in stroke survivors with ASyS.

The presented case example illustrates marked differences in estimated risks when utilizing SeLECT-ASyS as opposed to SeLECT₂₀ for individuals with ASyS. These differences in risk are clinically meaningful and may have an impact on treatment considerations and the approach to follow-up in such cases. Risk estimates derived from the updated model consistently indicate moderate to high risks of PSE following ASyS (Figure 4). These risks are realistic, as corroborated by the favorable calibration of the model (Figure S5).

The most notable and practically relevant finding is a >60% 10-year risk of epilepsy in stroke survivors with ASyS presenting as FBTCS on day 0 or status epilepticus (28% of all ASyS cases; Figure 1B) and those with SeLECT-ASyS scores ≥ 3 points. This risk level aligns with the ILAE practical definition of epilepsy.⁵ But, it is crucial to acknowledge that this definition requires at least 1 unprovoked seizure occurrence and is, hence, not fully met in cases that suffered only an ASyS. Nevertheless, some clinicians may consider counseling these high-risk cases as if they had epilepsy, potentially recommending primary preventive treatment^{31,32} or extended follow-up. It is important to note, however, that the efficacy of primary preventive treatment after stroke remains unproven. Two ongoing antiepileptogenesis trials in

stroke survivors may offer novel insights into the treatment of cases at high risk of PSE.^{33,34} If such treatments become available, the accurate prediction of the risk of PSE in those with ASyS will become central for the selection of candidates for antiepileptogenic medications.

Our study has several strengths. We assessed one of the largest multicenter cohorts of poststroke seizures. We translated our findings into a user-friendly prognostic model accessible through both smartphone and web applications. The updated model outperforms the current state-of-the-art model and its clinical significance was underscored through an illustrative case.

Our study has limitations. First, despite the inclusion of 9 international cohorts, enhanced statistical power, and generalizability of our results could be further achieved by incorporating data from North America, Asia, or Africa. Second, the practical constraints of performing continuous electroencephalograms in the entire multicenter registry limited our evaluation to clinically apparent seizures, not considering electrographic seizures. Third, the diagnosis of seizures relied largely on clinical observation, and systematic electroencephalogram monitoring was not performed in all cases. This approach may have resulted in an underestimation of seizures with subtle clinical signs. We did not consider purely electrographic events as seizures in this study. Future studies using continuous electroencephalogram monitoring should assess the impact of purely electrographic events on the risk of poststroke seizures. Fourth, data collected in the registry did not differentiate between seizures occurring immediately at stroke onset and those on the same day as the stroke. However, existing studies^{35,36} suggest that the majority of seizures on day 0 align with the immediate onset of the stroke. Fifth, our study lacked data on the discharge National Institutes of Health Stroke Scale score or National Institutes of Health Stroke Scale score assessed 72 hours posttreatment, which may more accurately predict the risk of poststroke seizures.³⁷ Sixth, patients with ASyS may receive antiseizure medication treatment which may impact the risk of subsequent unprovoked seizures. To address this, we corrected all results for antiseizure medication treatment. Lastly, the SeLECT registry did not consistently collect data on the cause of death and long-term disability.

CONCLUSIONS

We demonstrated varying mortality and epilepsy risks based on the type and timing of ASyS following stroke. We implemented these findings in an updated prognostic model (SeLECT-ASyS) that outperformed a previous model and is available as both a smartphone and web application. The 10-year epilepsy risk in those with ASyS presenting as FBTCs on day 0 or status epilepticus and those with SeLECT-ASyS ≥ 3 points exceeded 60%, a cutoff used for the ILAE definition of epilepsy.⁵ These findings have the potential to inform counseling for stroke survivors with ASyS, particularly those with a high (>60%) risk for PSE.

ARTICLE INFORMATION

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Supplemental Material

Supplemental Methods
Tables S1–S8
Figures S1–S6
STROBE Checklist

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COMMENTS AND OPINIONS

American Heart Association Standards for Postacute Stroke Rehabilitation Care

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ABSTRACT: Evidence-based rehabilitation and secondary prevention interventions improve poststroke functional recovery and reduce secondary complications. However, stroke rehabilitation expertise, processes of care, and educational resources vary among sites where postacute care (PAC) is delivered. The American Heart Association developed quality standards based on the American Heart Association 2016 Guidelines for Adult Stroke Rehabilitation and Recovery to address these gaps. An interdisciplinary PAC standards writing committee identified key areas for PAC: quality improvement, medical management, care coordination, patient/caregiver and personnel education, and program management. Subgroups developed draft standards, combining results from a national landscape survey of PAC sites with clinical practice guidelines. The committee then refined the draft standards using a consensus-based process. American Heart Association staff and PAC sites in Montana convened a learning collaborative to gather feedback and provide gap analyses of the standards relative to current practices. Qualitative input from beta testing in Montana and quantitative results from the nationwide survey and Montana sites were analyzed and used to refine the standards further. The national landscape survey demonstrated that most sites do not meet the proposed standards: stroke program oversight structure (78% fall short), stroke rehabilitation leadership (70%), stroke-specific order sets/protocols (61%), and policies requiring staff stroke education (66%). Regarding Montana findings, 41% of the PAC sites have no mechanisms to identify areas of quality improvement specific to their stroke rehabilitation programs, and 59% do not use standardized tools to ensure that performance improvement initiatives are followed. However, with adequate support and resources, most Montana sites stated that they would be able to meet the proposed standards. We conclude that the Stroke PAC Quality Standards are applicable in PAC settings and provide a pathway to improving access to high-quality care for stroke survivors. Outcome studies are needed to confirm anticipated improvements in medical and functional outcomes.

Key Words: patient discharge ■ recovery of function ■ rehabilitation ■ stroke ■ stroke rehabilitation

While acute stroke care has seen important advances toward standardized treatment, the provision of postacute care (PAC) has remained highly variable.^{1,2} Targeted, high-quality poststroke recovery, rehabilitation, and secondary prevention (hereafter abbreviated as simply rehabilitation) interventions can improve recovery of function and reduce the risk of secondary effects and recurrent stroke. Intensive rehabilitation has been found to be associated with lower poststroke mortality rates³ and better functional outcomes.^{4–6}

Across the United States, 47% of all stroke survivors leaving the hospital are discharged home, with the remainder going to skilled nursing facilities (SNFs; 27%), hospital-level inpatient rehabilitation facilities (IRFs; 24%), and long-term care facilities (1%).⁷ However, these percentages vary geographically, both from state to state, and within states. Rural areas in particular provide fewer postacute options, and available facilities may be located great distances from the stroke survivor's family and support network. Geographic proximity

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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has been shown to substantially influence the selection of poststroke facilities and level of care.⁸

The organization and delivery of care in postacute facilities are variable and inconsistent across care delivery settings.⁹ IRFs typically provide at least 3 hours of rehabilitation therapy services per day, as well as frequent physician visits and 24-hour care by registered nurses. Physician or advanced practice provider visits in SNFs are less frequent, nursing care may not include a registered nurse on-site continuously, and the amount of rehabilitation therapy patients receive in SNFs, while varying widely, is generally much lower on average than in IRFs.¹⁰ These more limited resources in many SNFs may contribute to hospital readmissions and suboptimal care coordination and outcomes.

The American Heart Association (AHA) issued Guidelines for Adult Stroke Rehabilitation and Recovery¹¹ that define appropriate evidence-based care for poststroke rehabilitation. The AHA chartered a working group to develop quality standards for postacute stroke rehabilitation with the goal of providing PAC facilities with guidance for the translation of these guidelines into practice. Standards were intended to be relevant and achievable in a broad array of PAC settings, including smaller and more rural facilities with fewer resources, supporting AHA's Mission: Lifeline Stroke Initiative. Mission: Lifeline Stroke is a program for improving stroke outcomes by identifying gaps and reinforcing the use of evidence-based guidelines and quality improvement efforts at a system level across the full continuum of stroke care, including public awareness, prehospital care, hospital care, and PAC.¹²

PHASE 1

In July 2019, the AHA invited experts from AHA national councils and state/regional working groups to form a multidisciplinary writing committee, including members from rural, urban, and suburban areas. This group included physiatrists, physical therapists, occupational therapists, nurses, a neuropsychologist, a social worker, and a speech-language pathologist. Writing group members reviewed all recommendations from the AHA Rehabilitation Guidelines and categorized them, as shown in Table 1.

The writing committee members were divided into subgroups to develop draft standards in each category. Subgroup weekly meetings included discussion on rural versus nonrural facilities and various facility types: IRFs, SNFs, and critical access hospitals (CAHs) with dedicated swing beds for stroke rehabilitation patients. The working group also developed a landscape survey in collaboration with the AHA Certification and Evaluation Team that was distributed to a nationally representative sample of PAC facilities from November 2019 to

Table 1. Summary of PAC Stroke Program Standards

Standard	Description
Program management	Includes recommendations for the systematic and operational oversight of the stroke rehabilitation program by an interprofessional committee
Personnel education	Details essential education components to ensure that staff have the experience and training necessary to monitor and manage stroke rehabilitation patients
Patient/caregiver education and support	Outlines essential education topics and highlights the importance of performing learning that needs assessment and employing the teach-back method
Care coordination	Emphasizes the importance of well-established processes to facilitate transitions to and from any level of care and implements a team-based approach to care during the patient's admission at the PAC facility
Medical management	Addresses availability of key professionals for providing stroke rehabilitation and the necessity of incorporating protocol-driven current evidence-based assessments, screenings, and treatment
Quality improvement	Specifies standardized performance measures and outcome metrics that should be tracked for the stroke rehabilitation population and used to drive performance improvement efforts

PAC indicates postacute care.

January 2020 (Table 2). This 81-item survey asked PAC facilities about their current practices and feedback on the draft standards. The survey was administered online using Qualtrics and distributed to contacts at each of the facilities procured from a third-party vendor. Responses were received from a total of 6.5% of facilities queried after 4 rounds of survey distribution. Facilities were randomly sampled from strata including rural/urban, and rural/urban status was determined using rural zip codes from the Federal Office Of Rural Health Policy.¹³ Note that most (>93%) CAHs in the United States are in rural areas.¹⁴ Conversely, few IRFs are in rural areas in the United States. The number of SNFs ($\approx 15\,300$) in the United States is much larger than the number of IRFs (≈ 1200).¹⁵ The response rates for both types of

Table 2. National Survey Demographics

	CAH (n=185), n (%)	IRF (n=25), n (%)	SNF (n=509), n (%)	Total (N=719), n (%)
Rural	176 (95)	2 (8)	163 (32)	341 (47)
Nonrural	9 (5)	23 (92)	346 (68)	378 (53)
Midwest	93 (50)	6 (24)	166 (33)	265 (37)
Northeast	10 (5)	6 (24)	118 (23)	134 (19)
South	40 (22)	10 (40)	148 (29)	198 (28)
West	42 (23)	3 (12)	77 (15)	122 (17)

CAH indicates critical access hospital; IRF, inpatient rehabilitation facility; and SNF, skilled nursing facility.

facilities are low in the survey, as is the sample size for IRFs, limiting the reliability of the quantitative findings. Survey respondents included nursing directors and chief nursing officers (35%), executive director/chief executive officer (10%), the director of rehabilitation (10%), other administrator/director (14%), the quality office/quality director (5%), the medical director (1%), and other (social work/case management, emergency department coordinator/manager/director, admissions department staff, and so on; 25%). The results identified gaps in program management, patient care, staff and patient education, and certifications, informing the writing committee on areas for additional focus. These gaps were especially evident at CAHs and SNFs. For example, while 68% of IRFs have interprofessional committees that manage their stroke programs, only 17% of SNFs and 29% of CAHs reported having one. The greatest variance among facility types was noted in certifications/accreditations specific to stroke rehabilitation, where 62% of IRFs reported holding certifications compared with only 1% of CAHs and 2% of SNFs (Table 3).

Monthly meetings of the entire writing group were held to share progress and solicit feedback. These meetings included discussions about relevant CMS requirements, current or future payment models, health equity, and educational resources, and training needed to support facilities seeking to achieve compliance with these draft standards. Through a consensus procedure consisting of repeated rounds of group discussions and debate, this first phase produced a draft set of Beta PAC Stroke Program Standards.

PHASE 2

In July 2020, AHA staff convened a learning collaborative with 18 PAC sites in Montana. Participation was voluntary and purposely included various sizes of IRFs, SNFs, and CAHs with swing bed programs, which offer stroke rehab services, to gather feedback and provide gap analyses of the draft standards relative to current

practices. Montana was selected for this learning collaborative due to its rural nature and 3-year statewide Mission: Lifeline Stroke project and contains ≈115 facilities that offer PAC. While concentrating this phase of the project in a single state arguably reduces its nationwide generalizability, this decision reflected the availability of the existing processes and personnel participating in the statewide Mission: Lifeline Stroke project in Montana and also allowed a deeper (rather than a broader nationwide) selection of facilities in a specific region for collaboration in this phase. Qualitative input from beta testing in Montana and quantitative results from the nationwide survey and Montana sites were used to refine the standards further. Notably, 41% of the 18 Montana PAC sites reported that they had no mechanisms for quality improvement for their stroke rehabilitation programs, and 59% did not use standardized tools for performance improvement initiatives. Other areas identified as falling short of the draft standards included availability of Speech/Language therapy at least 5 days/week (38% indicating not meeting this standard), availability of consulting psychologist (43% not meeting this standard), and performing a screening swallowing evaluation within 24 hours of admission (64% not meeting this standard). However, with adequate support and resources, most Montana sites indicated that it would be feasible or very feasible to meet the proposed standards.

In April 2023, the writing committee reconvened in person to finalize the PAC Stroke Program Standards manual, incorporating feedback obtained through the survey and beta testing. The program standards manual was reviewed and approved by the AHA Office of Science and Medicine on June 2, 2023. Table 1 provides an overview of the 6 categories of the final standards, and the detailed standards are provided in the [Supplemental Material](#).¹⁶

PHASE 3

Phase 3 of this project focuses on field-testing these standards in a pilot group of institutions to obtain further

Table 3. National Survey Responses

	CAH	IRF	SNF	Total
	Total, yes (%)	Total, yes (%)	Total, yes (%)	Total, yes (%)
The facility has an interprofessional committee that manages the stroke program	185, 53 (29)	25, 17 (68)	509, 86 (17)	719, 156 (22)
The facility has team members whose main goal is to make the program succeed (eg, stroke champion)	184, 92 (50)	25, 17 (68)	499, 103 (21)	708, 212 (30)
The facility uses standardized stroke-specific order sets/protocols	179, 83 (46)	23, 14 (61)	470, 166 (35)	672, 263 (39)
The facility has a written staff education policy that lists the disciplines and educational requirements for annual stroke education	170, 60 (35)	21, 10 (48)	442, 148 (34)	633, 218 (34)
The education program includes information on managing risk factors and preventing the recurrence of stroke	154, 124 (81)	21, 20 (95)	404, 313 (78)	579, 457 (79)
The facility holds certifications/accreditations specific to stroke rehabilitation	169, 2 (1)	21, 13 (62)	434, 10 (2)	624, 25 (4)

CAH indicates critical access hospital; IRF, inpatient rehabilitation facility; and SNF, skilled nursing facility.

feedback on usability, feasibility, and resources needed. This phase is ongoing with a continued focus on reducing disparities and gaps in access to high-quality care.

SNFs, CAHs, and IRFs in Iowa, Montana, Nebraska, and North Dakota are implementing the Post-Acute Care Stroke Program Standards as part of the Mission: Lifeline Stroke Post-Acute Care Initiative. Over 75 facilities have been recruited to implement the standards over a 3-year timeframe from July 2022 to June 2025. While all 3 types of facilities are participating in this field-testing project, the major focus is on SNFs and CAHs, given their lower level of baseline compliance with these standards and more limited resources.

Participating facilities are provided quality improvement support from AHA throughout the initiatives and have access to the Healthcare Network, an online platform to pose and answer questions among facilities. Facilities are also collecting data quarterly on 6 clinical measures and 3 outcome metrics as outlined in the PAC Stroke Standards manual. Using the Quality and Certification Tool, an online database, they can compare their findings to other participating facilities. These clinical measures were largely sourced from the AHA Clinical Performance Measures for Stroke Rehabilitation Performance Measures¹⁷ tracking data pertaining to patients with aphasia receiving speech therapy, timing of admission assessments, patient education, depression screenings, venous thromboembolism prophylaxis, and follow-up after discharge. Facilities also track the number of stroke rehabilitation survivors, length of stay, and discharge disposition.

Monthly virtual learning collaboratives focus on implementation strategies for each component of the standards, sharing between facilities, and identifying ways to improve postacute stroke care across the region. At the end of the initiative, facilities will provide feedback about the feasibility of implementation and barriers to implementing the program standards.

DISCUSSION

The AHA has identified postacute stroke care as an area of opportunity for standardization of care and quality improvement. Along with the implementation of the PAC Stroke Program Standards at facilities in the Midwest, the AHA plans to gradually expand this initiative to a nationwide postacute stroke care quality program. In parallel, these standards and the experience gained through field testing have informed the AHA in its development of a stroke rehabilitation certification program for SNFs, which launched in February 2024. The 3-year certification is a means by which the AHA offers validation that facilities are implementing and meeting the PAC Stroke Program Standards and requirements. There also is a future opportunity to explore the expansion of these PAC Stroke Program Standards into stroke rehabilitation certifications at other levels of care.

Postacute stroke care quality standardization and certification could increase benefits for patients/caregivers, care organizations, and referral sources. These benefits include improved competency of staff, collaboration, communication and coordination within a system, and improved care and outcomes.

This project has focused on developing standards for postacute stroke care that can be achieved throughout the United States, including less resourced and rural settings. The goal of developing these standards is to define a path for achieving consistent, high-quality postacute and rehabilitative care for stroke survivors, which incorporates evidence-based guidelines. Many of these standards focus on program organization, processes of care, and the structures to monitor and improve quality. These are necessary prerequisites to support further development of outcome-based standards in the future.

When developing standards for practice, there is a balance in calibrating the stringency of the requirements. On one extreme are standards that are easily achieved but do not drive improvement meaningfully. On the other extreme are standards that represent aspirational best practices, but those are not broadly feasible. Overall, the ideal standards may be those that are stringent but at least substantially achievable by most organizations responsible for providing this care. The writing committee believes that it has achieved this goal with these standards, but further field testing is needed.

As with any practice guidelines or standards, there is an expectation that evolving evidence and changes in practice will result in changes over time. All such guidelines and standards should be regarded as snapshots in time, and continuing updates are needed to avoid obsolescence. The ongoing phase 3 of the project will provide helpful data on the feasibility of implementing these standards, as will be feedback from the participants in the AHA's PAC certification program. These sources of data and feedback will be helpful in guiding the development of future versions of these standards.

The ultimate impact will be on the stroke survivor's health and quality of life. The AHA's Mission: Lifeline Stroke programs are already working to minimize stroke death and disability by securing rapid and guideline-directed care for all stroke survivors. By improving care practices and quality standards, the AHA anticipates observing decreased recurrent strokes and hospital readmissions, improved recovery of functionality and independence, and longer, healthier lives.

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Supplemental Material

American Heart Association Post-Acute Care Stroke Program Standards Manual 1.0

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