

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

A Systematic Review and Meta-Analysis

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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 noninterventional observational studies compared to cohorts derived from randomized clinical trials (RCTs). The pooled recurrence risk was 7.20% per year after stroke despite anticoagulation.

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

(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).

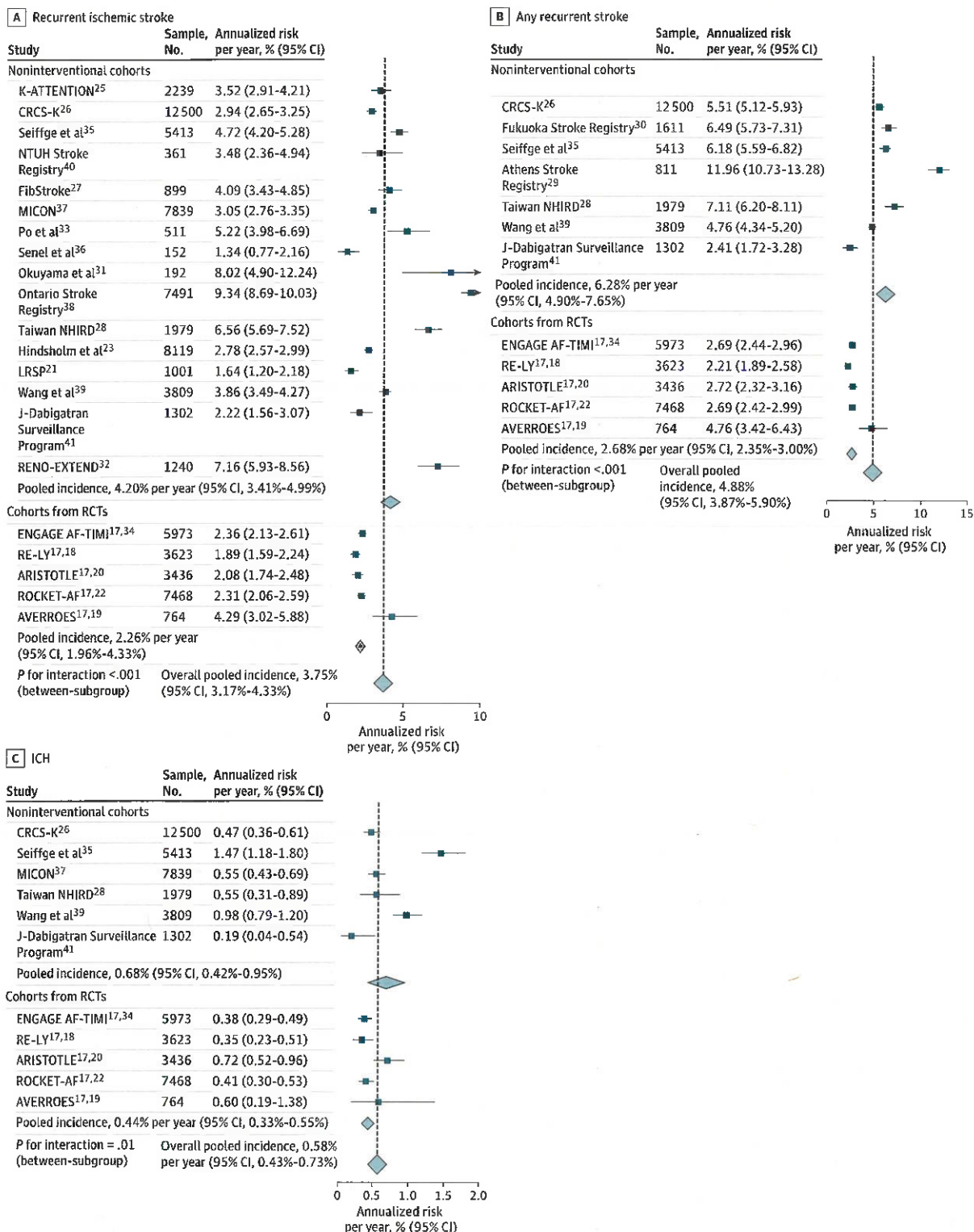
Discussion

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-

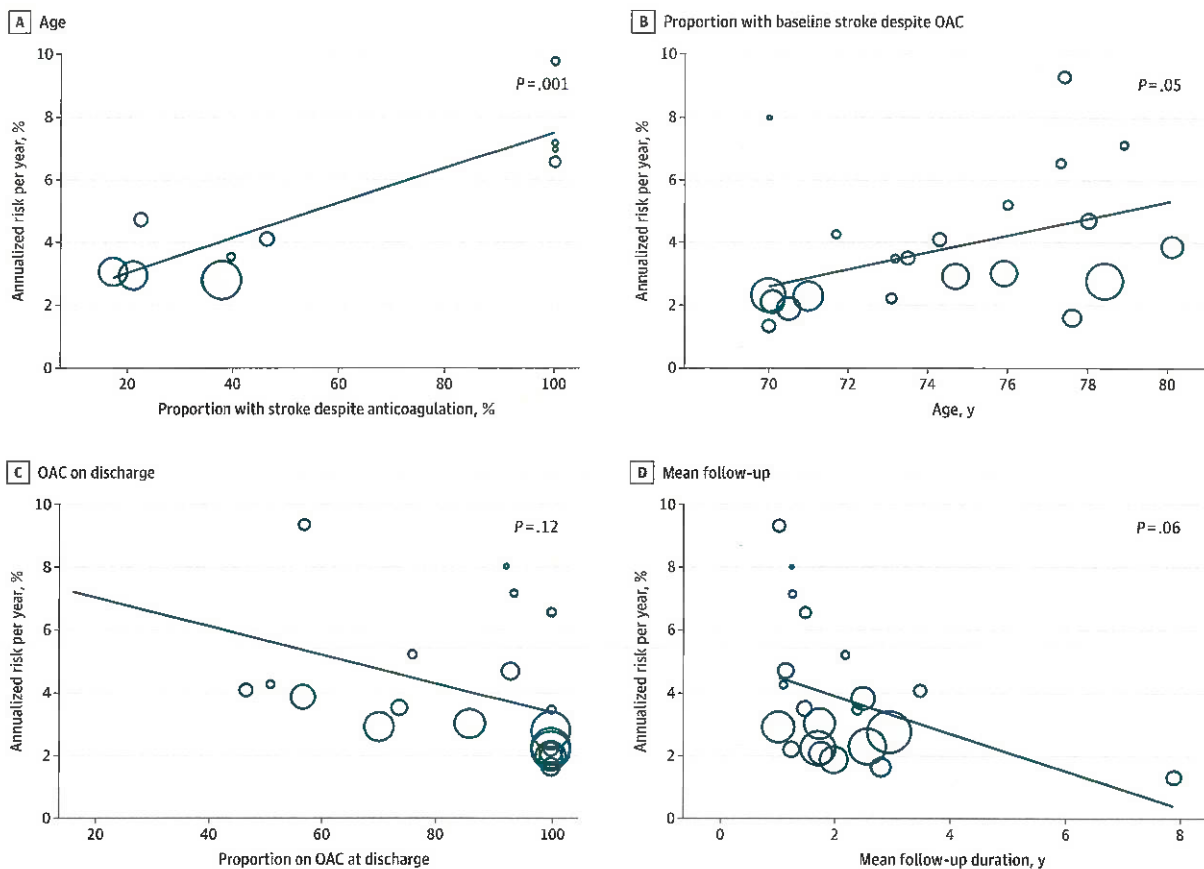
Figure 1. Annualized Risk of Recurrent Stroke



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



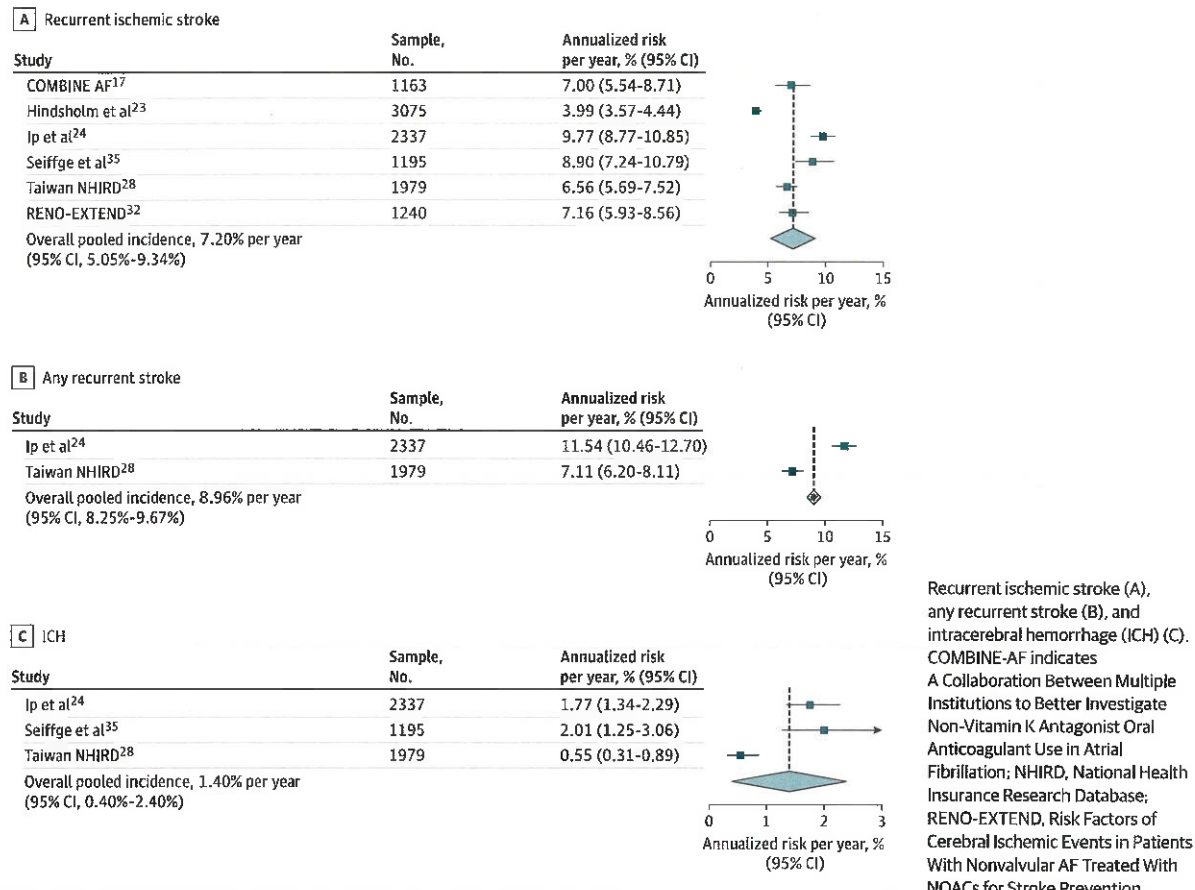
Data are presented according to age (A), proportion with baseline stroke despite oral anticoagulant (OAC) (B), OAC on discharge (C), and mean follow-up (D). The center of the bubbles indicates the annualized risk for each study, with

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 LAOO 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 pLAOO in addition to OAC in patients with stroke despite anticoagulation. The LAOS-IV (The Fourth Left Atrial Appendage Occlusion Study) trial (NCT05963698) will compare the addition of pLAOO to OAC with OAC alone in patients with high CHA₂DS₂-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 $\pm$ 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
<i>ACA</i> anterior cerebral artery, <i>AICA</i> anterior inferior cerebellar artery, <i>ASA</i> anterior spinal artery, <i>CN</i> cranial nerve, <i>MCA</i> middle cerebral artery, <i>PCA</i> posterior cerebral artery, <i>PICA</i> posterior inferior cerebellar artery, <i>SCA</i> superior cerebellar artery, <i>TIA</i> transient ischemic attack, <i>VA</i> vertebral artery, <i>VB</i> 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

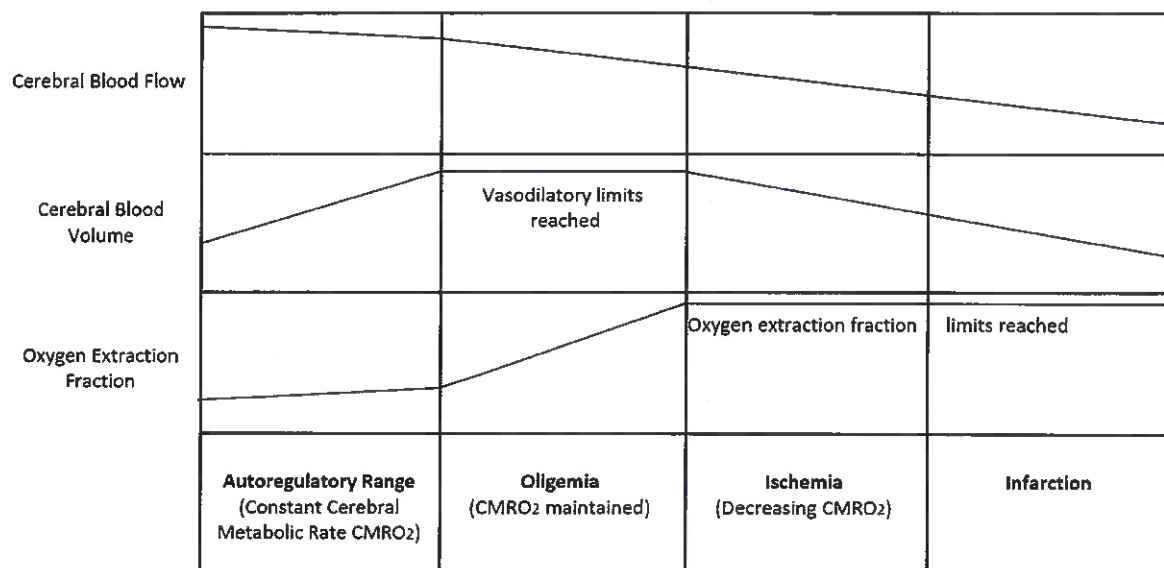


Fig. 1 Stages of cerebral hypoperfusion

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).

neurorehabilitation upper extremity interventions studied 1307 randomized control trials conducted between 1993 and 2021 (59,879 subjects with mean sample size of 46 patients per trial) [28, 29]. The six most commonly used interventions included robotics; virtual reality allowing subjects to interact with objects and virtually rendered environments and scenarios;

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.

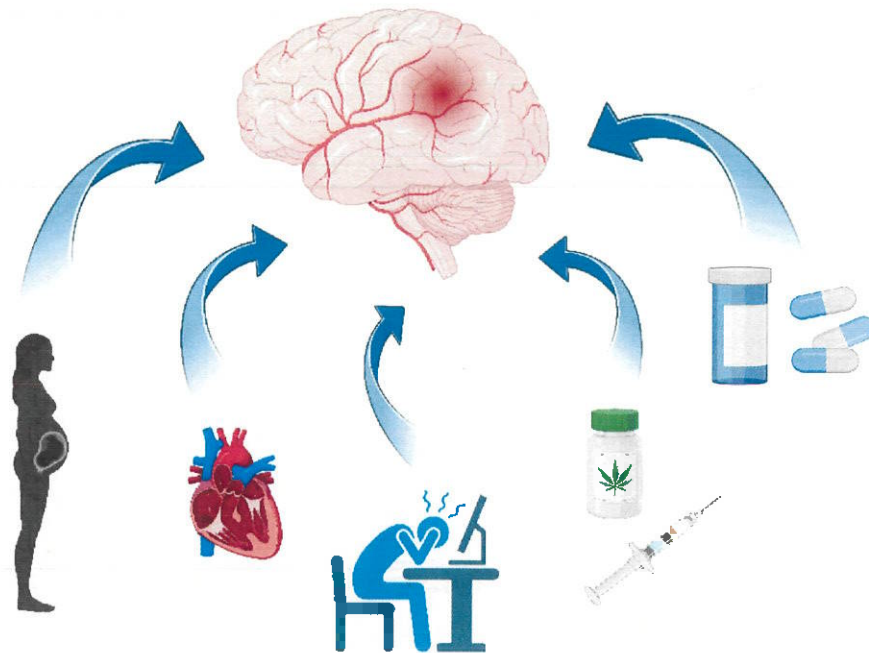


Figure 1. Specific risk factors for stroke in the young population are pregnancy and post-partum state, patent foramen ovale, migraines, recreational drug use, and oral contraceptives.

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.

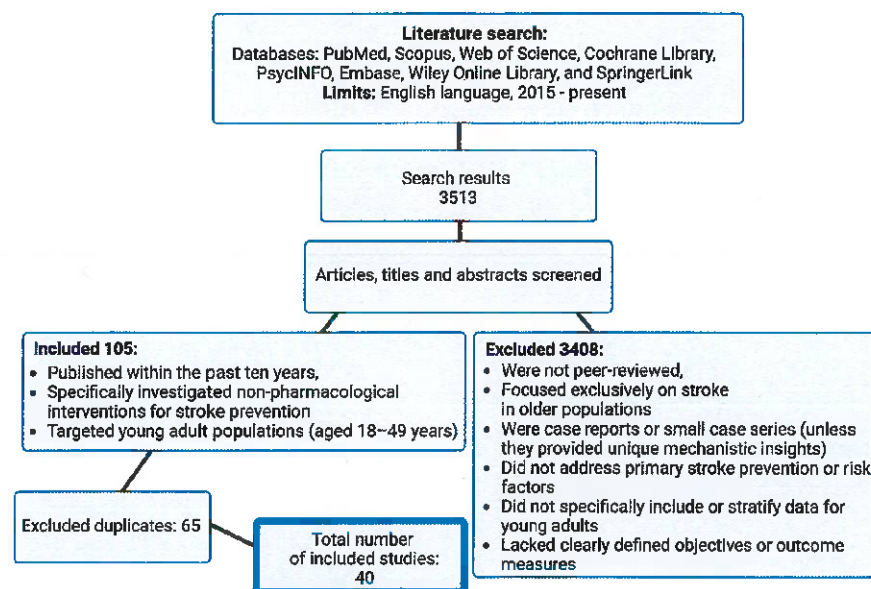


Figure 2. Summarizing the literature search, screening, and selection process for studies included in the review on non-pharmacological stroke prevention in young adults.

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].

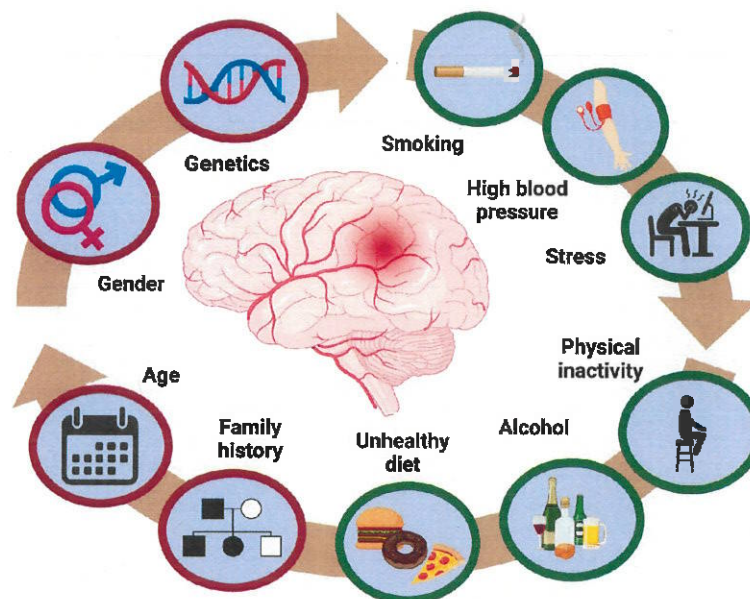


Figure 3. Schematic presentation of modifiable and non-modifiable risk factors for strokes in young adults.

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
Putaalaa 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%; $P=0.78$).

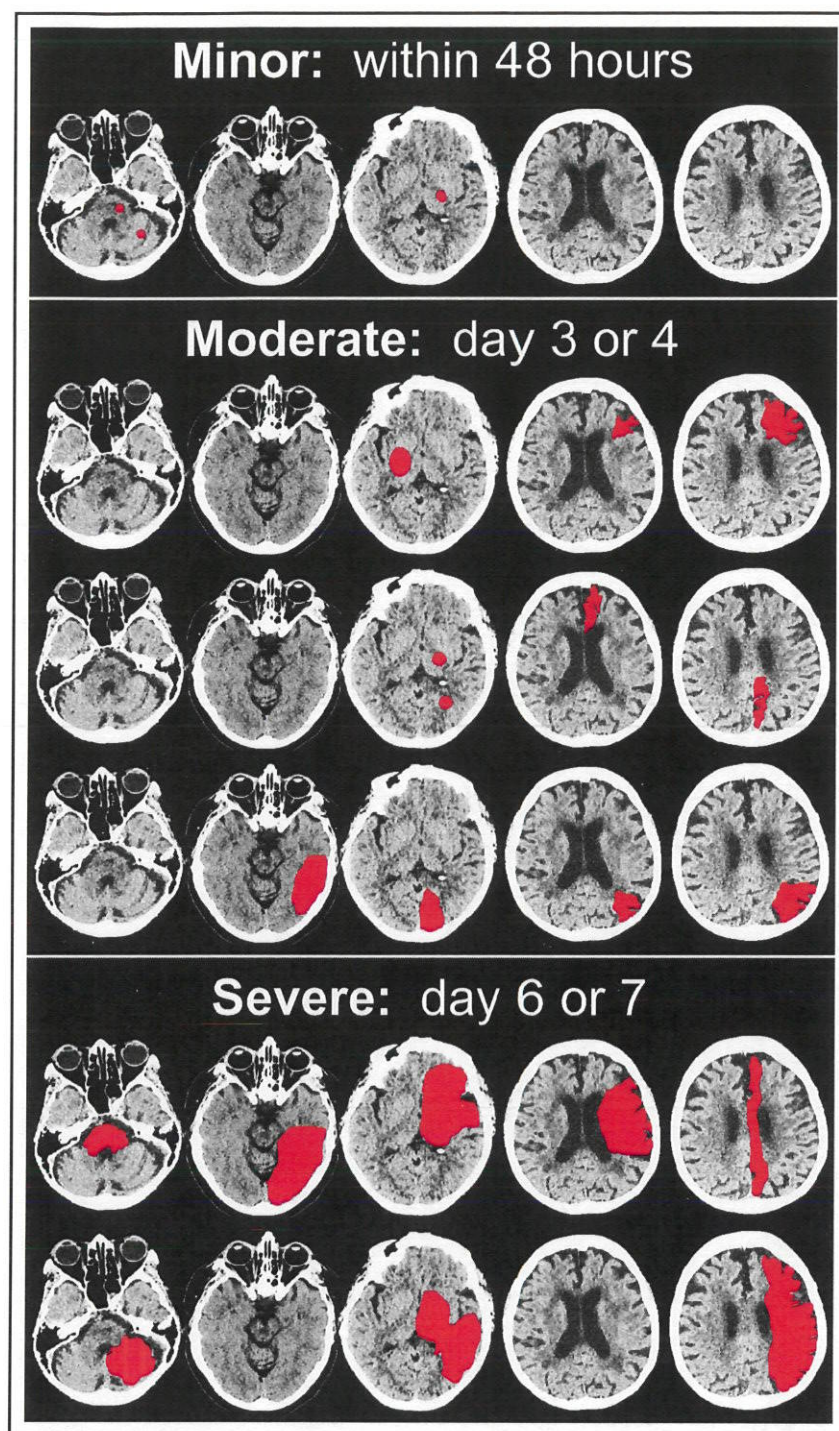


Figure. Example of ELAN (Early Versus Late Initiation of Direct Oral Anticoagulants in Post-Ischemic Stroke Patients With Atrial Fibrillation) stroke classification scheme.

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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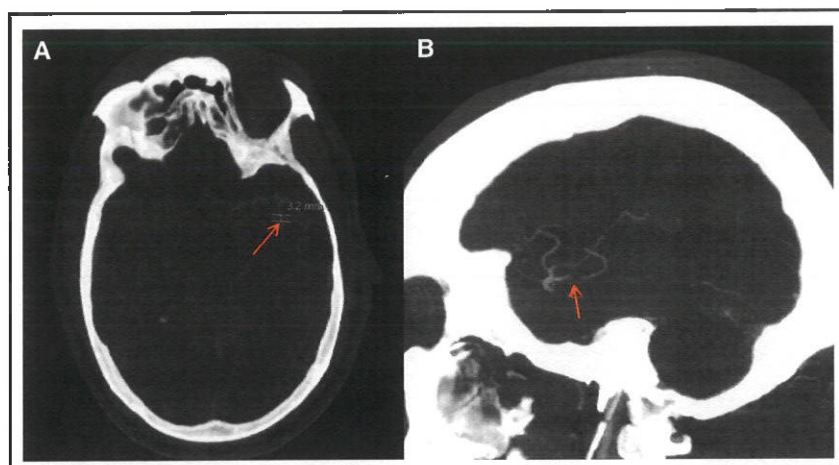


Figure 1. Imaging demonstrating M2 occlusion of left middle cerebral artery.

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,

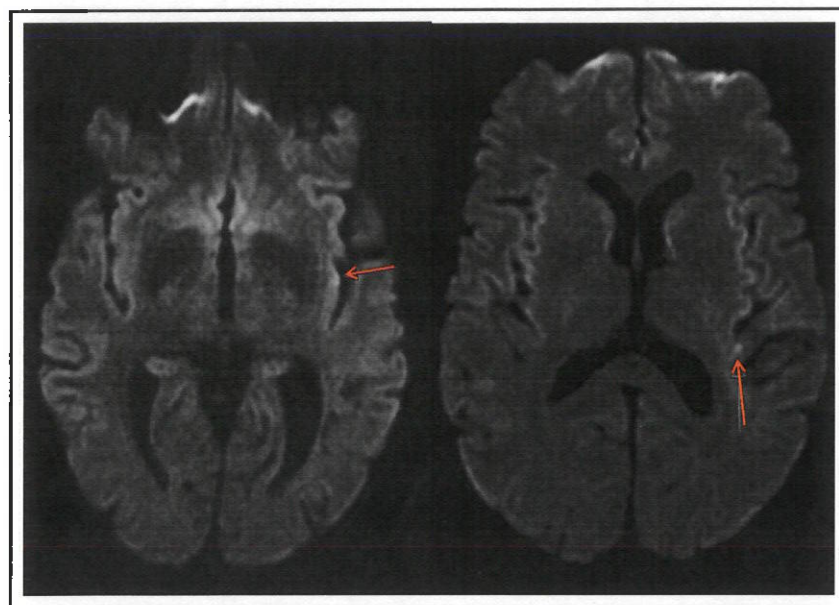


Figure 2. Axial images of magnetic resonance imaging (MRI) brain diffusion weighted imaging (DWI) sequence with arrows indicating small acute infarcts in the left middle cerebral artery territory.

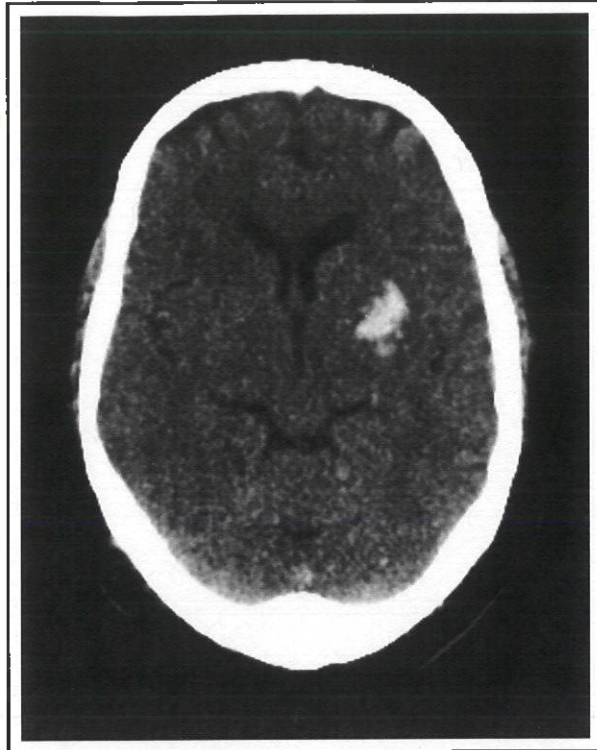


Figure 3. Computed tomography of the head demonstrates a left basal ganglia hemorrhage.

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-Embolism 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-Embolism 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-Embolism 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.

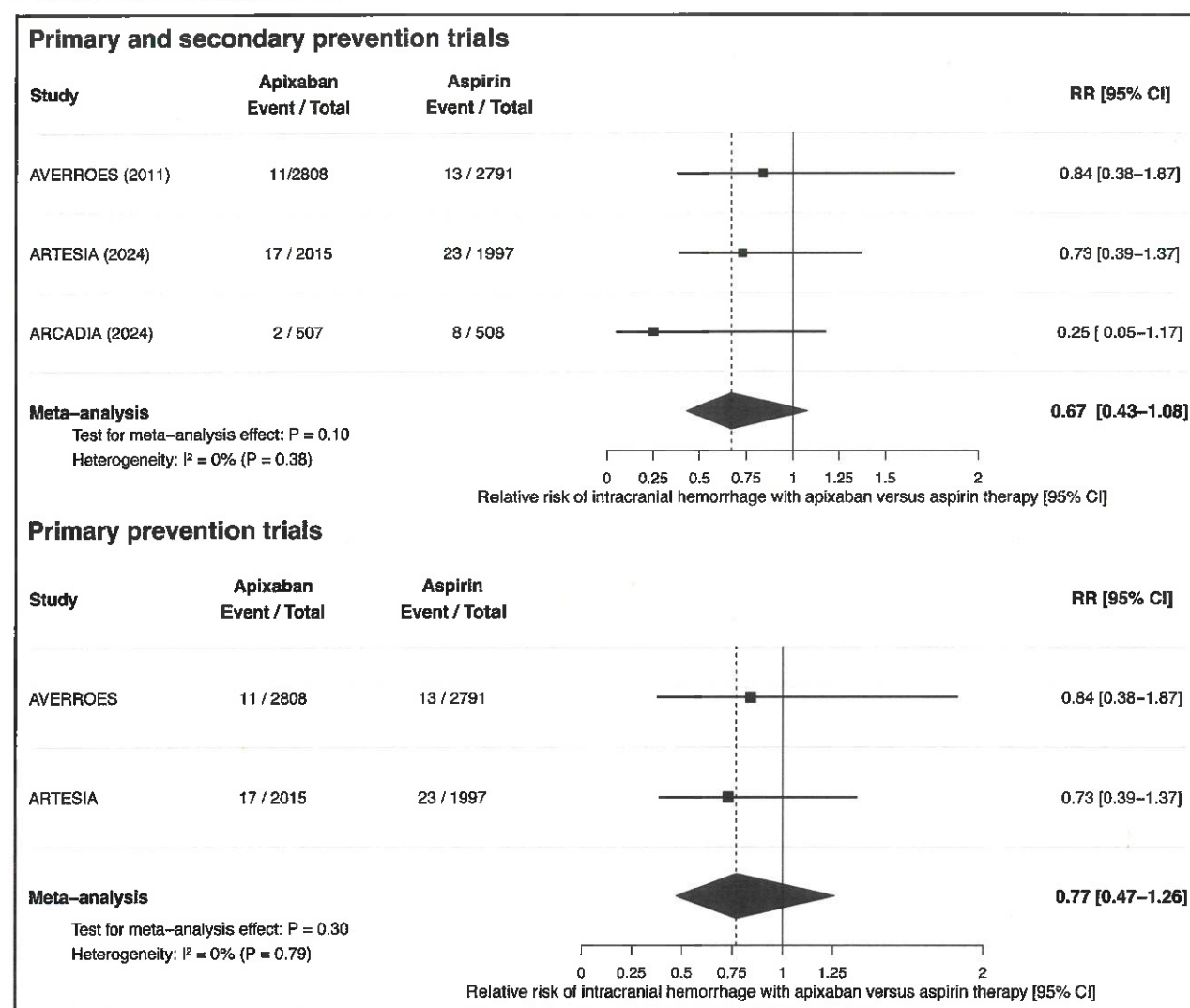


Figure 1. Meta-analysis of relative risk (RR) of intracranial hemorrhage with apixaban vs aspirin therapy.

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

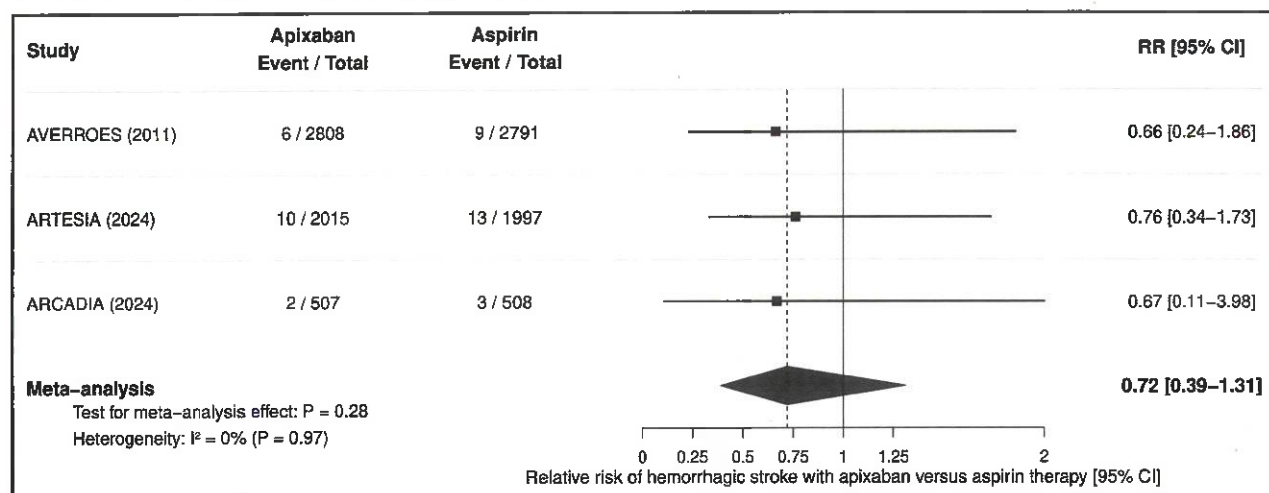


Figure 2. Meta-analysis of relative risk (RR) of hemorrhagic stroke with apixaban vs aspirin therapy.

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-Embolic 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. Daghlis designed the study with input from all authors. Dr Daghlis and Dr Lieberman performed study screening and data extraction. Dr Daghlis 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 (SeLECT₂₀)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

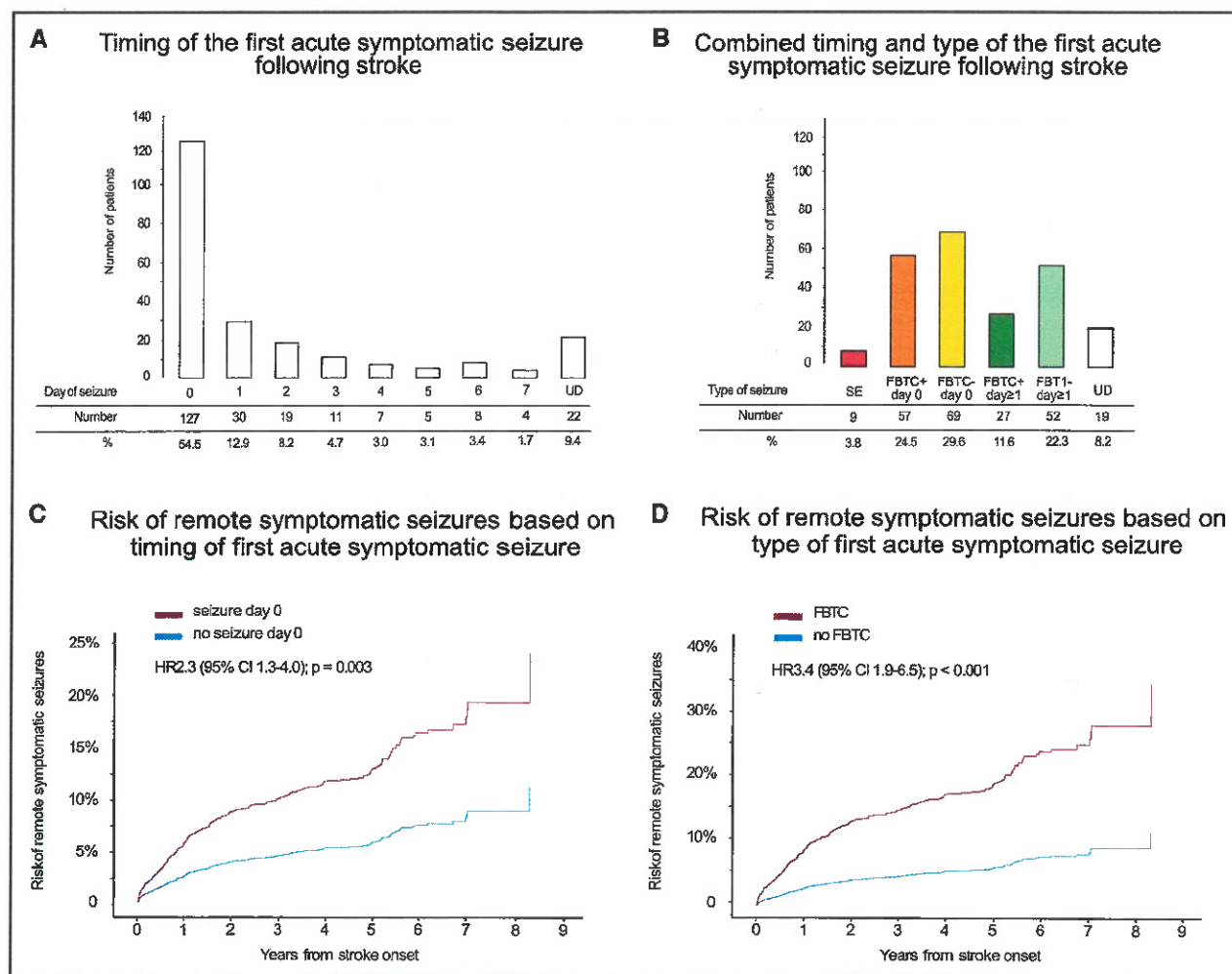


Figure 1. Characterization of acute symptomatic seizures (ASyS) timing and type.

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 (SeLECT₂₀) 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 SeLECT₂₀ score (Figure 3; SeLECT₂₀ score 3 to 4, $P<0.001$; SeLECT₂₀ score 5 to 6, $P=0.10$).

Thus, the SeLECT₂₀ model may not adequately capture the risk of epilepsy in those with ASyS. To overcome these limitations, we updated the SeLECT₂₀ 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

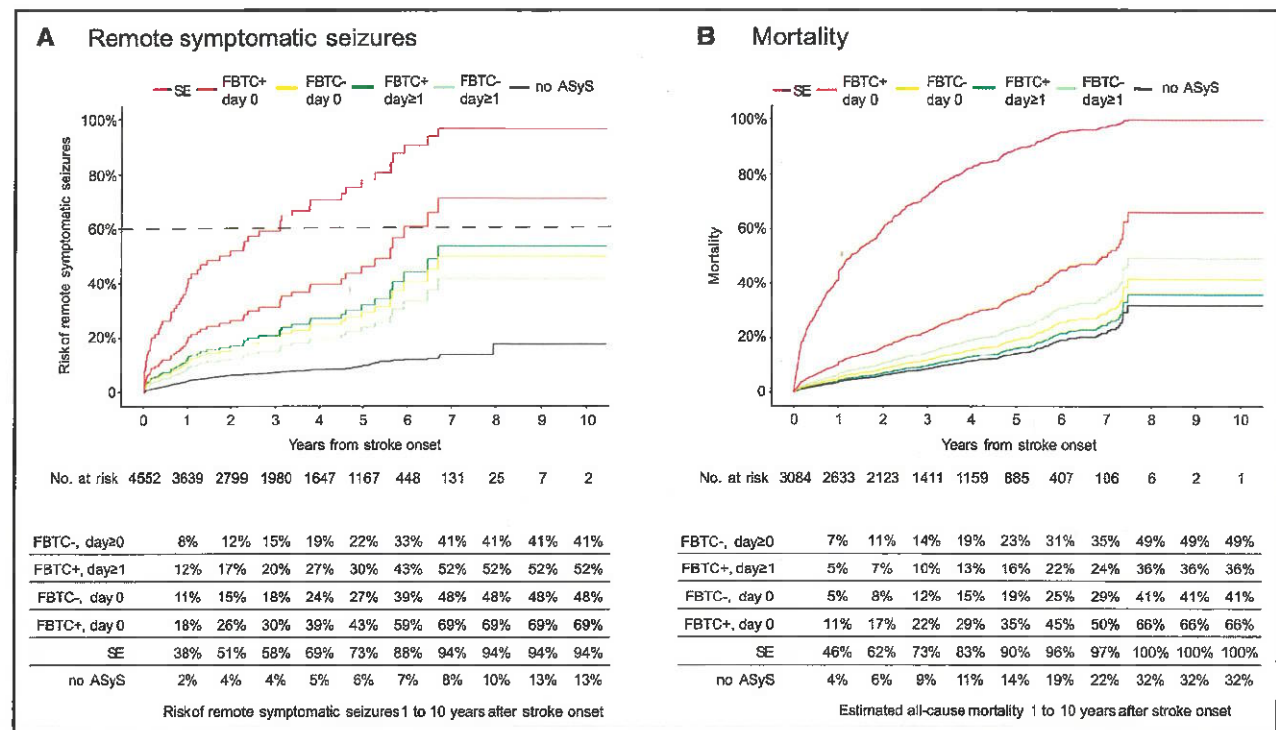


Figure 2. Risk of poststroke epilepsy or mortality following acute symptomatic seizures (ASyS) after stroke.

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 antiepilepsy 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 SeLECT_{2.0} 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 SeLECT_{2.0} 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 SeLECT_{2.0} 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 SeLECT_{2.0} 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 SeLECT_{2.0} 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

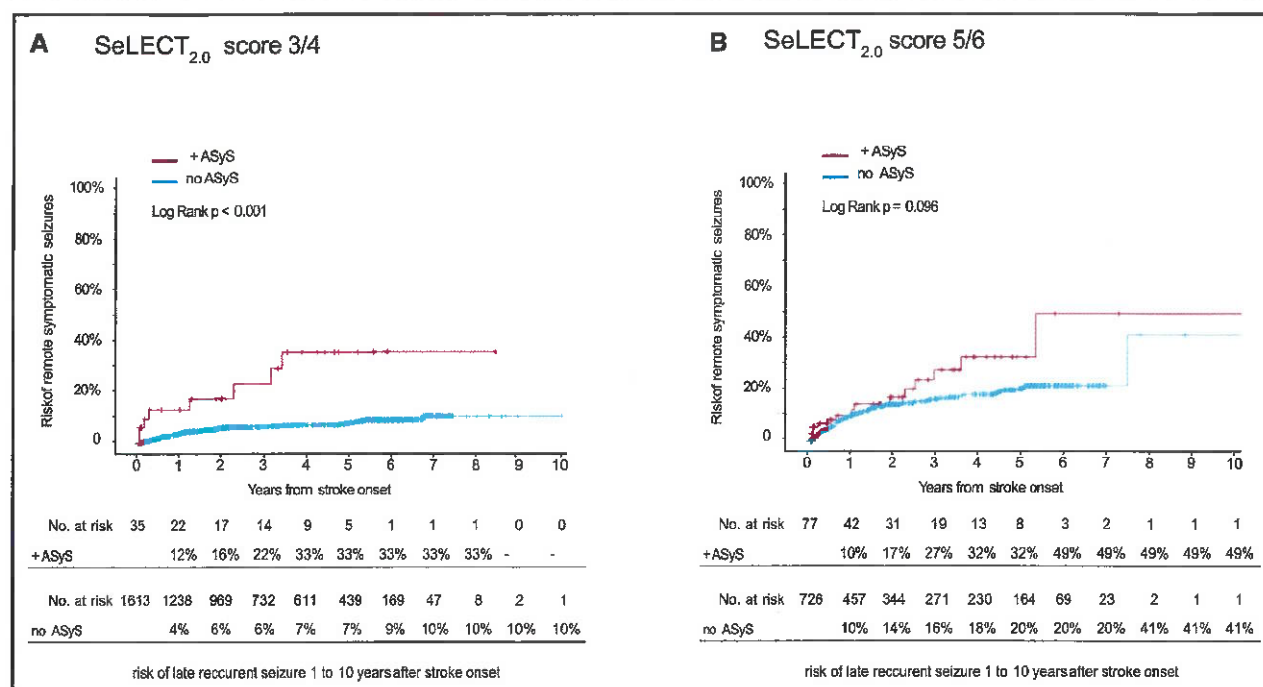


Figure 3. Risk of epilepsy in individuals with or without acute symptomatic seizures (ASyS) having a similar SeLECT_{2.0} score. Kaplan-Meier estimates ($n=4552$) of the time to poststroke epilepsy in those with a SeLECT_{2.0} score of 3 to 4 (A) or 5 to 6 (B) points. Separate curves are shown for individuals 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.

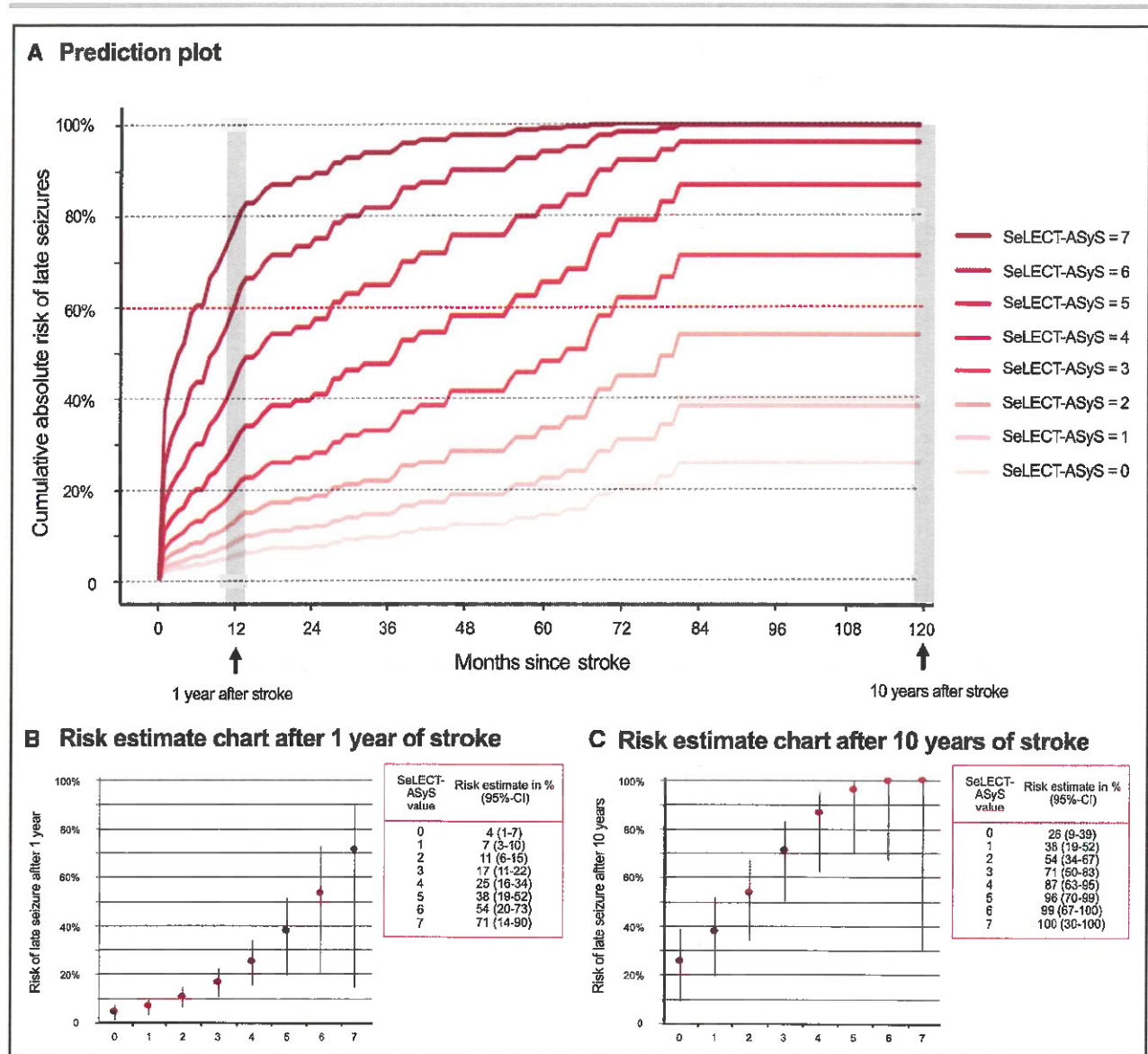


Figure 4. Predicted risk of poststroke epilepsy according to a new prognostic model in stroke survivors with acute symptomatic seizures.

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 SeLECT_{2.0}'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 SeLECT_{2.0} 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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The podcast and transcript are available at <https://www.ahajournals.org/str/podcast>.

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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

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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 (≈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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Decision-Making for Endovascular Thrombectomy in Patients With Large Vessel Occlusions and Mild Neurological Deficit: A Consensus Statement

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Acute ischemic stroke patients with mild deficits (National Institutes of Health Stroke Scale [NIHSS] of 0–5) but confirmed large vessel occlusions (LVO) present a clinical challenge for endovascular thrombectomy (EVT) decisions due to limited evidence and the absence of clear guidelines. A Delphi consensus was conducted at the 2024 5T (Teamwork, Training, Technology, Technique, Transport) Think Tank conference with 40 international stroke experts. Following a systematic literature review, three iterative Delphi rounds were employed to explore EVT decision-making in strokes due to LVO with low NIHSS. Data were collected through surveys and in-person discussions, focusing on disability evaluation, imaging markers, procedural risk, and outcome scales. Consensus was achieved on key factors influencing EVT decisions. Experts emphasized the importance of symptom-specific disability (e.g., aphasia, vision loss) over NIHSS scores alone. Early neurological deterioration (END) was perceived as main concern in this patient population. Imaging markers such as proximal occlusion, poor collaterals, and large penumbra were expected to be predictors of END. The anticipated technical difficulty and patient-specific factors, such as independence and quality of life, also guided decisions. The Potential of rtPA for Ischemic Strokes With Mild Symptoms (PRISMS) trial definition of disabling deficits and the 9-level modified Rankin Scale were favored as outcome measures for future studies. EVT decisions for acute ischemic strokes with mild deficit but proven LVO require nuanced, individualized approaches beyond NIHSS thresholds. Disability assessment, imaging-based risk evaluation, and patient-centered discussions are critical for optimizing outcomes, emphasizing the need for further research and standardized guidelines.

Keywords Stroke; Thrombectomy; Low NIHSS; Mild deficit; Large-vessel occlusion; Early neurological deterioration

Introduction

Acute stroke patients with mild deficits (baseline National Institutes of Health Stroke Scale [NIHSS] of 0–5) but proven large vessel occlusion (LVO) present a clinical treatment dilemma. The evidence on benefit from endovascular thrombectomy (EVT) is very limited; the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) and Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial (EXTEND-IA) trials included a total of 14 patients with NIHSS scores of 0–5.^{1,2} No clear guideline recommendations for EVT in patients with low NIHSS exist, and EVT decisions are made on a case-by-case basis, with high variability among practitioners and institutions.³ Two randomized trials are currently ongoing to investigate the effect of EVT in anterior circulation LVO stroke with low NIHSS: Endovascular Therapy for Low NIHSS Ischemic Strokes (EN-DOLow, NCT04167527) and Minor Stroke Therapy Evaluation (MOSTE, NCT03796468).

With up to 30% of stroke patients with LVO reported to present with an NIHSS <6,⁴ this minor stroke subset of patients with LVO is not small. It is estimated that 30%–40% will remain disabled at 90 days,^{5,6} and this proportion doubles in the 20% of

patients in whom early neurological deterioration (END) occurs.⁷ Observational data on EVT for minor stroke remain inconclusive, with reports ranging from clinical benefit to harm, including elevated rates of symptomatic intracranial hemorrhage.^{8–11} The risk/benefit ratio seems to differ based on the risk of END, the occlusion location, and size of the ischemic territory at risk. Currently, no randomized trials are specifically testing the safety and efficacy of EVT in stroke due to vertebrobasilar occlusion and medium vessel occlusion (MeVO) with low NIHSS, although several ongoing and recently completed EVT trials for stroke due to MeVO do include patients with low NIHSS.¹²

Even when the results of these trials are available, the question of EVT benefit in the minor stroke (low NIHSS) population remains complex. Heterogeneity in outcome may be influenced by within-NIHSS score variation: a total NIHSS score of 3 can be caused by severe aphasia as well as facial droop and loss of sensation—but the former will be more likely to lead to a much higher disability burden than the latter. Heterogeneity may be further influenced by the modified Rankin Scale (mRS) score itself, which is traditionally used as the primary outcome in EVT trials, but may not be sensitive enough to detect small but meaningful differences in long-term post-EVT outcomes in minor stroke patients. The individual impact of any neurological loss of func-

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tion will differ from patient to patient—for example, hemianopia in a truck driver is much more detrimental compared to hemianopia in a retiree whose vision was impaired to begin with.¹³ The inflection point in the risk/benefit ratio may vary according to the arterial lesion location: patients with a proximal occlusion and a large territory at risk may have more potential benefit with revascularization. In contrast, the predicted benefit may be smaller in the setting of an MeVO, where there will be a smaller territory at risk, or when extensive ischemic changes are already present at baseline. Even a slight increase in complication rates could tip the balance against EVT.

A simple total NIHSS score threshold for EVT decision-making does not take the anticipated complexity of the endovascular procedure into account. EVT decisions in this setting are therefore more complex and require a more nuanced approach as compared to major stroke due to LVO with more severe deficits.

During the 2024 5T (Teamwork, Training, Technology, Technique, Transport) Think Tank conference, this topic was discussed following a live modified Delphi consensus approach. In preparation for the live session, a systematic literature search had been performed. We summarized the results of the literature search and synthesized the expert opinions of the 31 participating neurointerventionalists, neurologists, and neurosurgeons on the topic of EVT for low NIHSS LVO stroke.

Methods

5T Think Tank attendees and sponsoring

This Delphi consensus was conducted as part of the 5T Think Tank that was held in September 2024 in Banff, Alberta, Canada. The 5T Think Tank is an annual 3-day in-person meeting of in-

ternational experts in the field of neurology and neurointervention (neurologists, radiologists, and neurosurgeons). Every year, the latest research and future developments in the field of interventional stroke therapy are discussed. Focus is laid on areas with lacking or unclear evidence. The meeting is by invitation only. The selection of 5T attendees focused on representing a diverse spectrum of specialists regarding geography, sub-specialties, and gender. The 5T Think Tank is sponsored by Medtronic, Stryker, Terumo, Cerenovus, and Penumbra in equal parts. However, the industry did not control the guest list, the choice of topics, or the content of the presentations. The preparation and analysis of the Delphi rounds were conducted by 5T Think Tank attendees unaffiliated with and independent from the sponsors.

Delphi methodology

The Delphi method is a structured, iterative forecasting technique incorporating feedback loops.¹⁴ In the medical field, it has been used to develop interim treatment guidelines and standardize patient care in the absence of strong evidence, serving as a provisional approach until sufficient data supports evidence-based practices.¹⁵ The Delphi method relies on a panel of individuals with content expertise that answers a series of questions with controlled opinion feedback, the goal being to assess expert opinions and achieve consensus among the respondents. In this study, the Delphi technique was applied to identify aspects influencing decision-making to undergo EVT in patients with low NIHSS strokes due to LVO or MeVO. Figure 1 shows the key elements of the Delphi methodology that were used in this study.

Literature search

In preparation for the Delphi consensus, a scoping literature

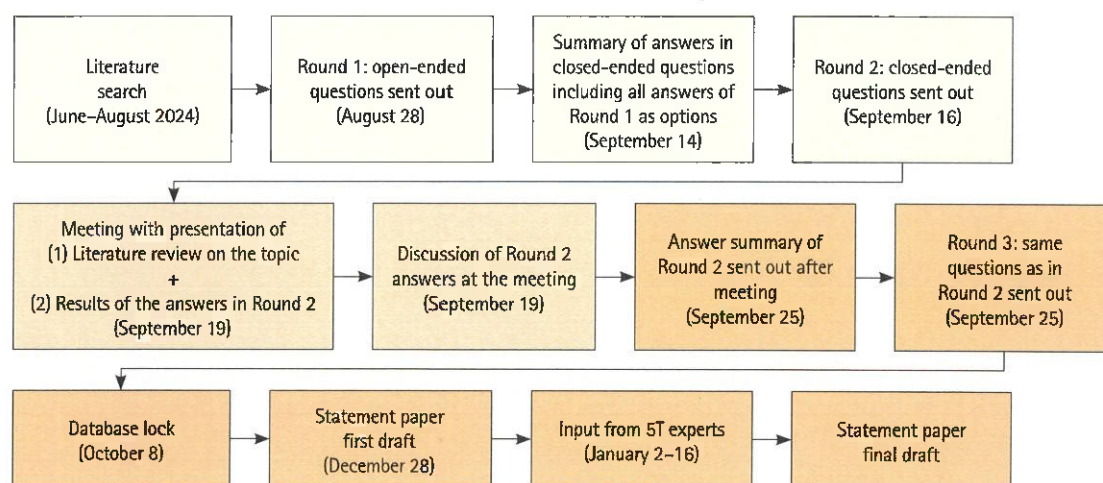


Figure 1. Delphi methodology and processes used for this manuscript. Arrows indicate the chronological order of the process elements. Light orange boxes represent pre-5T meeting activities, medium orange boxes denote in-person meeting steps, and dark orange boxes indicate post-meeting tasks. 5T, Teamwork, Training, Technology, Technique, Transport.

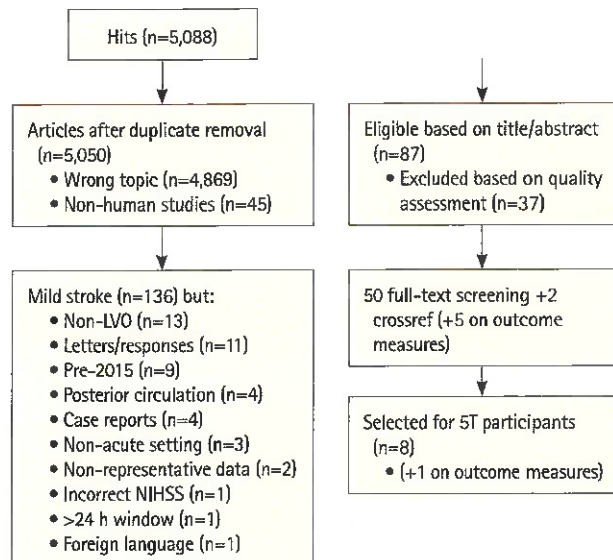


Figure 2. Flowchart of the scoping literature search in preparation of the meeting. LVO, large vessel occlusion; NIHSS, National Institutes of Health Stroke Scale; 5T, Teamwork, Training, Technology, Technique, Transport.

search was performed to identify key publications on EVT in LVO and MeVO in the anterior circulation with low NIHSS (see search strategy in Figure 2). Neurointerventional treatment of posterior circulation occlusions comes with different challenges compared to the anterior circulation, which can significantly affect how treatment decisions are made. We chose to exclude posterior circulation occlusions to keep the questions simpler and get clearer answers during the Delphi process. The purpose of this literature search was to identify high-quality prospective and retrospective cohort studies and ongoing trials focused on EVT for LVO or MeVO with low NIHSS. One of the coauthors (MK) summarized and presented the results of this search during the live session. A list of the publications selected for presentation during the meeting can be found in Supplementary Table 1.

Round 1

After a scoping review of literature, 5T attendees were asked the following five open-ended questions via email prior to the in-person meeting, inquiring about decision-making on EVT treatment and suitable outcome measures in patients with low NIHSS (0–5) due to LVO or MeVO stroke:

- (1) Would you, and if yes, how would you account for different levels of disability within one NIHSS score (e.g., NIHSS 3 aphasia vs. NIHSS 3 sensory+facial movement) when considering EVT?
- (2) Would you, and if yes, how would you account for different levels of disability impact based on individual patient factors/professions (e.g., hemianopia in a truck driver, arm

drift in a professional musician) when considering EVT?

- (3) How would you identify low NIHSS patients with a high risk of early neurological deterioration without EVT?
- (4) What are your thoughts on the risk-benefit balance of EVT in low NIHSS patients?
- (5) Which outcome measure(s) would be the most suitable for assessing intravenous thrombolysis (IVT)/EVT benefit in patients with baseline NIHSS 0–5?

These questions were intentionally broad, and phrased as open-ended questions, to encourage discussion and brainstorming, and ensure that all relevant points for future rounds are captured. All questions referred to stroke patients with a low NIHSS (0–5) due to LVO or MeVO.

Rounds 2 and 3

Rounds 2 and 3 consisted of 15 closed-ended questions that were drafted based on the round 1 open-ended questions. They aimed to examine the group's attitudes towards EVT decision-making in low NIHSS MeVO and LVO stroke in more concrete, practical terms. The questions in rounds 2 and 3 were identical. Round 2 questions were sent out to participants via email prior to the in-person meeting. Prior to round 3, the results of round 2 were presented and discussed at the meeting. All original questions from rounds 2 and 3 can be found in Supplementary Materials.

Data collection and analysis

An online survey tool (Qualtrics.com) was used for data collection. Respondent's email addresses were recorded to prevent duplicate responses. The first two rounds were conducted prior to the meeting.

During the 5T Think Tank in-person meeting, the current evidence on the topic was presented as well as a summary of the answers from round 1. Thereafter followed a 90-minute discussion. The second round was closed after this session, and the answers of round 2 were summarized and distributed to all participants. All participants then reviewed the results of the second round in detail before answering the questions of round 3.

Frequent reminders were sent out shortly after the meeting to achieve the same response rate in all rounds. Thereafter, the database was locked, and data analysis was performed by two think tank attendees (SLB and AS), who did not participate in the consensus themselves.

Consensus in multiple-choice questions was defined based on the type of response allowed. For questions permitting multiple answers, consensus required at least 70% agreement among participants. When only a single answer could be selected, a minimum of 50% agreement on one option was considered sufficient.

cient. For binary questions, such as yes/no, consensus was defined as at least 70% agreement. This approach is similar to the previous Delphi consensus in the field of neurointervention.^{16–18}

No approval by an institutional review board was necessary for this study. By participating in the survey, respondents have agreed to their data being analyzed in an anonymized form.

Results

Response data were collected from September 18 to October 9, 2024. Of the 40 ST Think Tank attendees with expertise in stroke medicine, 31 (78%) responded to rounds 1 and 2, and 29 (73%) responded to round 3. A list of the Delphi participants can be found in the Supplementary Material. Participants had the option to skip questions if they felt the topic was outside their area of expertise. As a result, the number of responses varies across questions.

Delphi results round 1

Question 1: Would you, and if yes, how would you account for different levels of disability within one NIHSS score (e.g., NIHSS 3 aphasia vs. NIHSS 3 sensory+facial movement) when considering EVT?

All respondents indicated that they use no fixed NIHSS cut-off in clinical practice to decide whether a patient should receive EVT. In patients with low NIHSS, debilitating symptoms lead to more aggressive management, while less severely disabling symptoms may be managed conservatively. There was agreement that not all NIHSS categories represent the same level of disability per NIHSS point. Categories such as vision loss and aphasia were considered more disabling deficits, while facial droop and sensory deficits were generally considered less disabling and, thus, less likely to trigger a decision in favor of EVT.

Question 2: Would you, and if yes, how would you account for different levels of disability impact based on individual patient factors/professions when considering EVT?

While many respondents stated that they include occupation, age, baseline functional status, quality of life (QoL), and level of independence as factors in their EVT decision-making, others were critical of this individualized approach: they felt that this approach is often based upon assumptions, as history-taking is typically crude in a hyper-acute setting. Therefore, many times this level of patient history is not readily available. It was also noted that the inherent desire to help a patient when we have more specific details about how a stroke will affect them can also bias decision-making towards overly aggressive or con-

servative treatment decisions.¹⁹ Some felt that individual patient factors should only be accounted for after discussing with the patient (or a proxy) how they would manage and adapt if they had to continue living with the present disability in their daily life. Other respondents perceived EVT to be much safer today than in the past, so they tend to offer it to most patients if technically feasible. Finally, some participants stated they treat all patients with LVO who are still working due to the risk of END.

Question 3: How would you identify low NIHSS patients with a high risk of early neurological deterioration without EVT?

Respondents listed the following indicators for END: worsening upon orthostatic challenge, large perfusion deficit on imaging that does not match the clinical symptoms, low collateral flow reserve, fluctuating NIHSS score/symptoms, long clot length, proximal occlusion of a major intracranial vessel, potential embolic stroke origin/multiple artery occlusions, incomplete circle of Willis, high blood pressure, diabetes, and elderly patients. Five (16%) respondents felt that any low NIHSS patient with LVO was at risk of secondary neurological deterioration, and as this often leads to significant disability, all low NIHSS individuals with LVO should be treated. One of these respondents mentioned they treat all LVOs that are not determined to be from intracranial atherosclerotic disease (ICAD) because ICAD markedly increases the risk of the intervention.

Question 4: What are your thoughts on the risk-benefit balance of EVT in low NIHSS patients?

The responses again reflected a wide range of perspectives, highlighting the complexity and nuance of decision-making in this subgroup. Factors felt to decrease the benefit of EVT in low NIHSS stroke patients with LVOs were ICAD, distal location of arterial vessel occlusion, simultaneous treatment with intravenous tenecteplase or alteplase, and low degree of disability. Factors felt to increase the benefit of EVT in low NIHSS stroke patients were young patient age, aphasia as a symptom, an experienced interventionalist performing the EVT, and any indicators of a high risk of secondary neurological deterioration or if the latter could not be reliably detected due to, for example, organizational structures of the hospital. Two respondents (6%) felt that there was nearly always a benefit of EVT.

Question 5: Which outcome measure(s) would be the most suitable for assessing IVT/EVT benefit in patients with baseline NIHSS 0–5?

Some respondents felt that the mRS traditionally used in stroke trials in ordinal or dichotomized form was also appropriate for low NIHSS patients. However, the majority of experts suggested

other scales that could be combined with the mRS if necessary, such as a QoL scale (e.g., EuroQol 5-Dimension 5-Level [EQ-5D-5L]) or early neurological improvement on the NIHSS scale.

Delphi results rounds 2 and 3

Detailed results of rounds 2 and 3 are presented in Table 1. There was consensus that a hard NIHSS cut-off alone is not a good basis for deciding on EVT treatment for low NIHSS patients. Ninety-six percent of respondents felt that EVT decision should rather be based on the degree of disability that the symptoms cause. Ninety percent thought that the degree of disability should always be discussed with the patient and/or family despite the additional time lost for discussion. When deciding on the threshold of disability to qualify for EVT, 18/30 (60%) in round 2 and 19/29 (66%) in round 3 favored any decrease in baseline functional status that prevents the patient from exerting their main daily activity, which is favorably determined by the patient.

Disabling symptoms

The expert panel agreed that aphasia and vision loss were the symptoms on the NIHSS scale with the largest impact on QoL and the functional status of a patient.

There was consensus (16/29 [55%] strongly agree, 11/29 [38%] somewhat agree) that these symptoms should have more weight on EVT decision-making than their actual NIHSS score. For patients with aphasia, the expert panel reached consensus that this symptom alone suffices to justify the indication for EVT.

Study measures of disability in low NIHSS stroke patients

The panelists reached a consensus that the Potential of rtPA for Ischemic Strokes With Mild Symptoms (PRISMS) trial's operational definition of the presence or absence of disabling deficits offered the best measure of disability in prospective studies involving low NIHSS stroke patients.

After an extensive discussion of possible outcome measures of long-term functional outcome, the expert panel chose the 9-level mRS (currently under development in the StrokeNet Thrombectomy Endovascular Platform [STEP] trial, <https://www.nihstroke.net.org/trials/step-trial/master>) as the most appropriate outcome measure of trials involving low NIHSS LVO/MeVO stroke patients. This was followed by a combination of the ordinal mRS and another scale (rank 2), dichotomous mRS of 0 (rank 3), and a QoL scale (rank 4). The panel felt that the ordinal mRS alone was the least appropriate outcome measure for this patient population (Supplementary Table 2).

Imaging features

The expert panel agreed that the anticipated technical difficul-

ty of the EVT and the occlusion location should be accounted for when deciding on EVT in low NIHSS patients. There was disagreement among the group on whether or not to take ASPECTS into account for decision-making, as it is virtually always high in low NIHSS patients.

Patient characteristics/treatment goals

Among the mentioned patient characteristics that potentially influence decision-making for EVT in low NIHSS stroke patients ≤65 years, QoL and independence without treatment emerged as the most important factors for EVT decisions in patients with low NIHSS. Ability for social interaction holds moderate importance. Interestingly, 9/29 (31%) respondents rated the discussion with patient or family without fixed parameters highest, while 10/29 (34%) chose it as the least important among the presented characteristics. Detailed results are presented in Table 1.

In patients >65 years, level of independence without treatment and QoL without treatment remained the most important parameters, similar to the general population, but with stronger emphasis.

Elaborating reasons not to take individual patient factors into account when deciding on EVT in low NIHSS stroke patients, there was only consensus on the statement that "history-taking was typically crude in a hyper-acute setting, therefore such decisions are based on assumptions that could be wrong."

Early neurological deterioration

The risk for END in low NIHSS LVO/MeVO stroke was generally perceived as moderate by 18/28 (64%) and high by 6/28 (21%) of the experts in round 3. The panel agreed that no single clinical or imaging factor was extremely useful as an indicator for END. However, by round 3 there was consensus that a large penumbra, low collateral flow reserve, a proximal occlusion location, and fluctuating symptoms were the most reliable predictors of END. Additionally, orthostatic neurological deterioration, high blood pressure, multiple occlusions, an incomplete circle of Willis, and a long clot length were felt to be somewhat useful as indicators of an increased risk of END. There was agreement that diabetes and potential embolic origin of the stroke were not useful predictors of an increased END risk. Detailed results are provided in Supplementary Table 3.

Risk-benefit balance of EVT

There was consensus that some patients with low NIHSS despite LVO benefit more from EVT than others. The expert panel agreed that patients with aphasia, poor collaterals, or with a proximal clot have a great net benefit of EVT. Combining round 3 votes for a small and great perceived benefit of EVT, there was consen-

Table 1. Summary of round 2 and round 3 questions and answers

Question	Answer options	Answers		Final consensus achieved?
		Round 2	Round 3	
Do you agree that the decision for or against EVT in low NIHSS stroke patients should not be based on a hard NIHSS cut-off?	- Strongly agree - Somewhat agree - Somewhat disagree - Strongly disagree	18/30 (60%) 6/30 (20%) 4/30 (13%) 2/30 (7%)	20/29 (69%) 6/29 (21%) 1/29 (3%) 2/29 (7%)	Yes
Do you agree that the decision for or against EVT in low NIHSS stroke patients should be based on the degree of disability that the symptoms cause?	- Strongly agree - Somewhat agree - Somewhat disagree - Strongly disagree	16/30 (53%) 9/30 (30%) 2/30 (7%) 3/30 (10%)	23/29 (79%) 5/29 (17%) 0 1/29 (3%)	Yes
To determine if the disability is high enough to qualify for EVT, which of the following should be the measure?	(A) Decreased baseline functional status such that main daily activity cannot be exerted. (B) Significantly impaired QoL (as per patient).	(A) 18/30 (60%) (B) 12/30 (40%)	(A) 19/29 (66%) (B) 10/29 (34%)	Yes
To determine if the disability is high enough to qualify for EVT, which of the following applies:	(A) Should only be an expert judgement. (B) Has to be discussed with patient and/or family.	(A) 5/29 (17%) (B) 24/29 (83%)	(A) 3/29 (10%) (B) 26/29 (90%)	Yes
Rate your degree of agreement with the following statements about disabling symptoms: (A) Aphasia should always be treated with EVT (if LVO/MeVO) if a benefit of the treatment can be expected. (B) For treatment decision, aphasia should get more weight/points on the NIHSS score. (C) For treatment decision, vision loss/field cut should get more weight/points on the NIHSS score.	- Strongly agree - Somewhat agree - Somewhat disagree - Strongly disagree	- Technical difficulty occurred, thus the results are not valid for the 2nd round	- (A) 14/29 (48%), (B) 16/29 (55%), (C) 6/29 (21%) - (A) 13/29 (45%), (B) 11/29 (38%), (C) 17/29 (59%) - (A) 2/29 (7%), (B) 2/29 (7%), (C) 4/29 (14%) - (A) 0/29 (0%), (B) 0/29 (0%), (C) 2/29 (7%)	(A) No (B) Yes (C) Yes
In a prospective study on EVT in patients with low NIHSS, how should disability be assessed and weighed?	(A) Use a simple description of the deficit and give it a number of NIHSS points reached in this category (e.g., aphasia; motor deficit/unable to walk; sensory deficit; visual deficit). (B) Don't necessarily differentiate different levels of disability, but just differentiate presence/absence of disability. (C) Use the PRISMS trial operational definition of the presence or absence of disabling deficits: Disabling is "defined as either inability to return to work or perform basic activities of daily living based on current deficits."	(A) 10/30 (33%) (B) 3/30 (10%) (C) 17/30 (57%)	(A) 5/29 (17%) (B) 1/29 (3%) (C) 23/29 (79%)	Yes
Which of the following factors should be accounted for when deciding over EVT in low NIHSS patients?	(A) Anticipated technical difficulty of EVT. (B) Level of occlusion. (C) ASPECTS in the territory responsible for the (disabling) symptoms.	Strongly agree: (A) 16/29 (55%), (B) 10/29 (36%), (C) 10/29 (34%) Somewhat agree: (A) 9/29 (31%), (B) 12/29 (43%), (C) 10/29 (34%) Somewhat disagree: (A) 3/29 (10%), (B) 5/29 (18%), (C) 5/29 (17%) Strongly disagree: (A) 1/29 (3%), (B) 1/29 (4%), (C) 4/29 (14%)	Strongly agree: (A) 8/29 (28%), (B) 12/29 (41%), (C) 10/29 (34%) Somewhat agree: (A) 18/29 (62%), (B) 15/29 (52%), (C) 12/29 (41%) Somewhat disagree: (A) 1/29 (3%), (B) 1/29 (3%), (C) 6/29 (21%) Strongly disagree: (A) 2/29 (7%), (B) 1/29 (3%), (C) 1/29 (3%)	(A) Yes (B) No (C) No

Table 1. Continued

Question	Answer options	Answers		Final consensus achieved?
		Round 2	Round 3	
For EVT decision in low NIHSS stroke patients which of the following parameters is the most important in patients <65 years?	Profession alone; profession+hobbies; profession+age; QoL without treatment; level of independence without treatment; no fixed parameters, always discuss with patient or proxy.	The 3 top choices: – No fixed parameters: 11/29 (38%) – QoL without treatment: 8/29 (28%) – Level of independence without treatment: 4/29 (14%)	The top 3 ranks: 1. Level of independence without treatment, 2. No fixed parameters, 3. QoL without treatment	Yes
For EVT decision in low NIHSS stroke patients which of the following parameters is the most important in patients >65 years?	Ability for social interaction; QoL without treatment; level of independence without treatment; no fixed parameters, always discuss with patient or proxy.	The 3 top choices: – No fixed parameters: 11/27 (41%) – QoL without treatment: 7/27 (26%) – Level of independence without treatment: 6/27 (22%)	The top 3 ranks: 1. Level of independence without treatment, 2. No fixed parameters, 3. QoL without treatment	Yes
Mark your agreement with the following statements: individual patient factors should NOT be taken into account when deciding on EVT in low NIHSS stroke patient because...	– Strongly agree	– (A) 3/26 (12%), (B) 2/26 (8%), (C) 2/28 (7%), (D) 3/27 (11%)	– (A) 3/28 (11%), (B) 1/28 (4%), (C) 4/28 (14%), (D) 4/28 (14%)	(A) No (B) No (C) No (D) No
(A) History-taking is typically crude in a hyper-acute setting, therefore such decisions are based on assumptions that could be wrong.	– Somewhat agree	– (A) 12/26 (46%), (B) 8/26 (31%), (C) 11/28 (39%), (D) 11/27 (41%)	– (A) 17/28 (61%), (B) 11/28 (39%), (C) 13/28 (46%), (D) 14/28 (50%)	
(B) The risk of EVT is generally low and should be done anyway if possible.	– Somewhat disagree	– (A) 5/26 (19%), (B) 10/26 (38%), (C) 11/28 (39%), (D) 10/27 (37%)	– (A) 4/28 (14%), (B) 11/28 (39%), (C) 9/28 (32%), (D) 7/28 (25%)	
(C) This information could lead us to be overly aggressive or conservative in our treatment decision.	– Strongly disagree	– (A) 6/26 (23%), (B) 6/26 (23%), (C) 4/28 (14%), (D) 3/27 (11%)	– (A) 4/28 (14%), (B) 5/28 (18%), (C) 2/28 (7%), (D) 3/28 (13%)	
(D) Any patient who is still working/of working age should be treated.				
How high would you estimate the risk of neurological deterioration in low NIHSS LVO/MeVO stroke patients without EVT?	– Low risk – Moderate risk – High risk	4/28 (14%) 17/28 (61%) 7/28 (25%)	4/28 (14%) 18/28 (64%) 6/28 (21%)	Yes
Do you think the benefit of EVT is always given in low NIHSS LVO/MeVO stroke patients?	– Yes – No	3/28 (11%) 25/28 (89%)	2/28 (7%) 26/28 (93%)	Yes

EVT, endovascular thrombectomy; NIHSS, National Institutes of Health Stroke Scale; QoL, quality of life; LVO, large vessel occlusion; MeVO, medium vessel occlusion; PRISMS, Potential of rTPA for Ischemic Strokes With Mild Symptoms; ASPECTS, Alberta Stroke Program Early CT Score.

such that the net benefit was greater than the risks in patients with poor collaterals, orthostatic deterioration, aphasia, and a proximal clot. There was consensus that the risk of EVT surpasses potential benefits when the clot is poorly accessible (15/28, 54%). Detailed results are presented in Supplementary Table 4.

Recommendations guiding treatment decisions in low NIHSS LVO/MeVO patients are summarized in Table 2.

Discussion

Prudence regarding EVT in low NIHSS patients originates from the delicate balance of the risks of EVT that may not be counterbalanced by the possible benefits in patients with minimal

impairment. Absence of level 1 evidence leaves the decision on treatment of low NIHSS stroke patients to the discretion of the clinicians.

This Delphi consensus session among international experts on interventional stroke treatment suggests that the decision in favor or against EVT in low NIHSS stroke patients with LVO or MeVO is often not solely based on a strict NIHSS cut-off, but rather an individualized decision based on the degree of disability and if possible, based on the patient's perspective. Presumed QoL and independence without treatment were key factors swaying treatment decisions. The majority of the expert panel relied on discussions with the patient to arrive at a personalized decision whenever possible.

Table 2. Summary of recommendations guiding EVT treatment decisions in low NIHSS LVO/MeVO patients

No.	Recommendation
1	In stroke patients with LVO and low NIHSS, treatment decision should be guided by anticipated technical difficulty of EVT and the degree of disability defined as inability to return to work or perform basic activities of daily living. It should not be guided by a strict NIHSS cut-off.
2	The level of disability that warrants the risk of EVT should ideally be determined through a discussion with the patient and/or their family. When such a discussion is not possible, disability was considered sufficient to justify EVT if the current symptoms result in a decreased baseline functional status that prevents the patient from performing their main daily activities.
3	For EVT treatment decisions, aphasia and vision loss/field cut should be regarded as highly disabling symptoms that may justify intervention even in patients with low NIHSS scores.
4	The risk of END in low NIHSS LVO/MeVO stroke patients not undergoing EVT was considered moderate.

END, early neurological deterioration; EVT, endovascular thrombectomy; LVO, large vessel occlusion; MeVO, medium vessel occlusion; NIHSS, National Institutes of Health Stroke Scale.

However, the following factors were identified that influence the decision in a certain direction:

Disabling symptoms

While the NIHSS scale is a well-established measure of neurological deficits, the degree of disability within the total score can vary substantially. In the present analysis, aphasia and vision loss were considered the most disabling symptoms captured on the NIHSS scale, particularly compared to sensory deficits that contribute a similar number of points to the score. It has previously been shown that aphasia significantly affects functional outcome, mood, QoL, social participation and the ability to return to work.²⁰⁻²³ Additionally, aphasia is often co-occurring with dysphagia—a symptom that is not captured on the NIHSS but that has a severe impact on QoL, and increases the likelihood of associated complications such as pneumonia.^{24,25}

Vision loss is less straightforward. For instance, the disability caused by vision loss was rated with 0.60 disability adjusted life year (DALY; 0=no disability, 1=maximal disability similar to death) in the original Global Burden of Disease (GBD) study in 1990,²⁶ and with 0.19 DALY in the 2010 GBD study.²⁷ The reason for the large difference between the two studies likely lies in the questions asked during the assessment: while the original GBD study focused on introduced impairment and need for assistance, the 2010 GBD study asked “how sick” a completely blind person was.²⁸ Although blindness can lead to significant impairment, one would not necessarily consider a visually impaired person as “sick.”²⁸ Interestingly, there appears to be a difference in disability depending on the age somebody turns blind: vision loss in older adults is associated with reduced QoL, increased risk of cognitive impairment, and greater difficulties in performing daily activities.²⁹ Additionally, older adults with visual impairment have an increased risk of falls, and thus, with associated morbidity.³⁰

The expert panel felt that the degree of disability introduced through aphasia and vision loss justifies EVT if their presence as isolated symptoms was resulting in the low NIHSS.

However, there is a potential bias here, as proprioceptive and kinesthetic functions, which depend on sensation and may initially present with subtle impairments, can later become more overt during the recovery phase and still lead to significant disabling effects.

The discussion among the expert panel acknowledged that even seemingly mild symptoms can be associated with a high degree of disability for certain individuals. For example, facial palsy in a professional trumpet player can lead to full invalidity. McDonough et al.¹³ have shown that such factors in fact play a role in real-world decision-making on EVT for low-NIHSS patients with MeVOs. However, in our analysis, there was consensus that the importance of the profession and hobbies is surpassed by the QoL and the level of independence. Even though some deficits may be debilitating for someone's profession, they may still not justify risking a patient's independence. It was argued that taking “low-level disability” into account for EVT decision-making in low NIHSS patients may underestimate the risk of the intervention. Considering individual patient factors could thus lead interventionalists to be overly aggressive or conservative in their treatment decision. Additionally, the term “individual patient factors” is not trivial, taking into account that essential skillsets of a housewife or a retired person with caregiving responsibilities ought to be equally considered as a profession.

The experts thus coincided that differentiating disability versus no disability was most appropriate approach for selecting patients who qualify for EVT, but the final decision should be guided by the discussion with the patient or their proxy.

A measure of disability is needed that can be efficiently applied in the time-sensitive setting of stroke care. To date, such scores have been implemented in prospective trials, but are not yet common in real-world practice. The expert panel agreed that the PRISMS trial's operational definition of the presence or absence of disabling deficits was currently the most appropriate: “disabling is defined as either inability to return to work or perform basic activities of daily living based on current deficits.”³¹

In terms of long-term outcomes for trial settings, experts expressed their concern that a single conventional outcome measure of stroke patients, such as the ordinal mRS, may not be granular enough to reliably measure differences in treatment effect in patients who had a low NIHSS to begin with. A combination of two established scores was proposed as a pragmatic solution to capture small changes in neurological deficit. However, the results of the survey at the end of each Delphi round reflect that experts would prefer a single, new score tailored to patients with mild to moderate disability (i.e., a low NIHSS score).

Anticipated technical difficulty

The potential benefit of an EVT encompasses the alleviation of current symptoms, the prevention of long-term sequelae (e.g., pneumonia resulting from dysphagia), and the mitigation of END. Conversely, the risk associated with the intervention reflects a combination of technical complexity, the interventionalist's expertise, and individual patient characteristics.

Factors known to increase the risk of an intervention are, among others, the need for multiple passes with thrombectomy devices,³² a fibrin-rich clot composition,³³ and underlying ICAD.³⁴ Those still cannot be reliably predicted based on routine imaging, nor are they modifiable in a given patient with acute stroke. The interventionalist's experience is positively correlated with recanalization rates and inversely correlated with the duration of the procedure,³⁵ but this, again, is a non-modifiable factor in the acute setting.

The expert panel agreed that the anticipated technical difficulty of EVT was mostly a function of the accessibility of the clot—mainly defined by occlusion location and presence of ICAD—as well as the interventionalist's experience. Individual patient characteristics such as age and diabetes mellitus were thought to have a lower priority when estimating the risk of EVT.

END/risk without treatment

END is a frequent phenomenon of neurological worsening of ≥ 4 NIHSS points within 24 hours after a baseline assessment or treatment.³⁶ Its incidence lies between 9%–10% in strokes due to LVO, and it is a reliable predictor of poor outcome in stroke patients.^{36,37} Risk factors for END include age, glucose level at admission, symptom onset to treatment time, high systolic blood pressure, history of hypertension, diabetes mellitus, atrial fibrillation, and large artery atherosclerosis.³⁶ Collateral status is the only imaging-based risk factor for END.

END in low NIHSS patients likely has a larger impact on functional outcome compared to high-NIHSS patients. Hence, the identification of risk factors for END in the low NIHSS LVO population is of particular interest.

The expert panel agreed that poor collaterals, a large penumbra on perfusion imaging, proximal occlusion location, and fluctuating symptoms were the most reliable predictors for END in low NIHSS LVO/MeVO patients. That is, the panel relied on imaging markers for which limited evidence is available, and their value to predict END has yet to be studied.

Interestingly, to date, there is no convincing evidence that EVT actually reduces the risk of END compared to IVT, as there seems to be a similar incidence among patients treated with EVT and IVT only.^{36,38} Of note, however, rescue EVT in case of END seems to improve outcomes.³⁹ In the discussion among the expert panel it was brought up that, given the known time-sensitive nature of stroke, the potential harm of END in low NIHSS LVO/MeVO patients is higher in institutions that cannot guarantee close neurological monitoring. This could thus be a valuable consideration for triage and transport decisions.

Of note, despite its correlation with poor outcome in stroke patients, END is just an intermediary endpoint, and as such, a surrogate for the final 90-day outcome. As not all cases of END result in long-term disability, further research is needed to identify patients who benefit from END treatment or prevention.

Limitations

Delphi consensus sessions are conducted on topics with little or no evidence, and thus represent opinions of the experts surveyed. The selective group of participants may not represent the global perspective on EVT in low NIHSS patients. Recommendations may not apply to all healthcare systems due to variations in resources, expertise, and patient demographics. The study is qualitative and does not provide definitive recommendations. The conclusions drawn are interim, reflect the opinions of the Delphi panel members only, and may change upon completion of ENDOLOW, MOSTE, and other ongoing trials. For example, the 9-level mRS, selected as the most suitable outcome measure for trials involving low NIHSS LVO/MeVO stroke patients, has not yet been published or validated. As a result, its suitability will need to be evaluated once evidence is available.

Conclusions

This Delphi consensus panel suggests that a single, universal NIHSS cut-off may not be appropriate to guide EVT decisions in low NIHSS LVO and MeVO stroke. Instead, factors such as the degree of disability, anticipated technical difficulty, and the risk of END should be taken into account. The panel emphasized the importance of patient-centered discussions and individualized treatment approaches, and highlighted critical gaps in evidence,

including the need for more robust predictors of END in low NIHSS populations. These findings provide an interim framework for clinicians while awaiting results from ongoing randomized trials.

Supplementary materials

Supplementary materials related to this article can be found online at <https://doi.org/10.5853/jos.2025.00304>.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: SLB, AS, JMO, MDH. Study design: SLB, AS, JMO. Methodology: SLB, JMO, MDH. Data collection: SLB, AS. Investigation: SLB, MK, AS, JMO. Statistical analysis: SLB, JMO. Writing—original draft: SLB, MK, AS, JMO. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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Supplementary Table 1. List of the publications selected for presentation during the meeting

No.	Publications
1	Seners P, Perrin C, Lapergue B, Henon H, Debais S, Sablot D, et al; MINOR-STROKE Collaborators. Bridging therapy or IV thrombolysis in minor stroke with large vessel occlusion. <i>Ann Neurol</i> 2020 Jul;88(1):160–169. doi: 10.1002/ana.25756. Epub 2020 May 14. PMID: 32350929.
2	Lin CH, Saver JL, Ovbiagele B, Tang SC, Lee M, Liebeskind DS. Effects of endovascular therapy for mild stroke due to proximal or M2 occlusions: meta-analysis. <i>J Neurointerv Surg</i> 2023 Apr;15(4):350–354. doi: 10.1136/neurintsurg-2022-018662. Epub 2022 Mar 15. PMID: 35292565; PMCID: PMC10086511.
3	Schwarz G, Bonato S, Lanfrancini S, Matusevicius M, Ghione I, Valcamonica G, et al. Intravenous thrombolysis + endovascular thrombectomy versus thrombolysis alone in large vessel occlusion mild stroke: a propensity score matched analysis. <i>Eur J Neurol</i> 2023 May;30(5):1312–1319. doi: 10.1111/ene.15722. Epub 2023 Feb 24. PMID: 36746650.
4	Wang P, Chen W, Chen C, Bivard A, Yu G, Parsons MW, et al; INSPIRE. Association of perfusion lesion variables with functional outcome in patients with mild stroke and large vessel occlusion managed medically. <i>Neurology</i> 2023 Feb 7;100(6):e627–e638. doi: 10.1212/WNL.000000000000201498. Epub 2022 Oct 28. PMID: 36307224; PMCID: PMC9946183.
5	Dunne T, Patel K, Siegler JE. How low do we go? NIHSS in anterior circulation thrombectomy decision-making. <i>Stroke Vasc Interv Neurol</i> 2024;4(5):e001212. doi: 10.1161/SVIN.123.001212.
6	Xu Y, Liu X, Li H. A comparison of endovascular therapy and medical management in patients with large vessel occlusion mild stroke treated between 2015 and 2023: a systematic review and meta-analysis. <i>J Stroke Cerebrovasc Dis</i> 2024 Jul;33(7):107721. doi: 10.1016/j.jstrokecerebrovasdis.2024.107721. Epub 2024 Apr 13. PMID: 38616013.
7	Seners P, Ben Hassen W, Lapergue B, Arquizan C, Heldner MR, Henon H, et al; MINOR-STROKE Collaborators. Prediction of early neurological deterioration in individuals with minor stroke and large vessel occlusion intended for intravenous thrombolysis alone. <i>JAMA Neurol</i> 2021 Mar 1;78(3):321–328. doi: 10.1001/jamaneurol.2020.4557. PMID: 33427887; PMCID: PMC7802007.
8	Heitkamp C, Winkelmeier L, Flottmann F, Schell M, Knip H, Brooks G, et al; German Stroke Registry-Endovascular Treatment (GSR-ET). Thrombectomy patients with minor stroke: factors of early neurological deterioration. <i>J Neurointerv Surg</i> 2025 Jul 14;17(8):796–802. doi: 10.1136/jnis-2024-021930. PMID: 38991731; PMCID: PMC12322444.
9	Romano JG, Gardener H, Campo-Bustillo I, Khan Y, Tai S, Riley N, et al; MaRISS Investigators. Predictors of outcomes in patients with mild ischemic stroke symptoms: MaRISS. <i>Stroke</i> 2021 Jun;52(6):1995–2004. doi: 10.1161/STROKEAHA.120.032809. Epub 2021 May 5. PMID: 33947209; PMCID: PMC9254134.

Supplementary Table 2. Number of panelist votes for ranking outcome measures to assess IVT/EVT benefit in patients with baseline NIHSS 3–5

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Rank 9
mRS 0–1	5	6	3	5	5	0	3	0	2
mRS 0	6	5	3	4	5	4	0	2	0
Ordinal mRS alone	1	0	5	4	3	4	7	2	3
Ordinal mRS in combination with another score.	2	4	3	5	5	4	0	4	2
9-level mRS with 1a, 1b, 2a, and 2b levels (under development in STEP trial).	8	5	3	4	3	4	1	0	1
QoL scale	5	2	6	3	3	5	2	2	1
NIHSS	0	2	3	1	1	3	8	6	5
Delta-NIHSS (baseline NIHSS minus 30 d NIHSS)	1	4	2	3	2	2	3	10	2
Delta mRS	1	1	1	0	2	3	5	3	13

Panelists were asked to assign a rank/priority to the outcome measures to assess IVT/EVT benefit in patients with baseline NIHSS 3–5 in a trial setting. The number of votes per rank for the outcome measures listed in the first column is shown. Rank 1=highest priority; Rank 9=lowest priority.

EVT, endovascular thrombectomy; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; STEP trial, StrokeNet Thrombectomy Endovascular Platform trial; NIHSS, National Institutes of Health Stroke Scale; QoL, quality of life.

Supplementary Table 3. Round 3 ratings regarding usefulness of different indicators for END risk

	Not useful at all	Slightly useful	Extremely useful
How useful are the following factors to identify low NIHSS LVO/MeVO patients with high risk of END without EVT?			
Orthostatic challenge	1	20	8
Any low NIHSS patient with LVO is at risk. Secondary deterioration often leads to disability → all low NIHSS individuals with LVO should be treated.	8	16	5
Any LVO not determined to be from ICAD.	9	12	8
Older age	13	14	2
Incomplete circle of Willis	8	19	2
Multiple occlusions	3	15	11
Long clot length	5	15	9
Large penumbras	2	6	21
Proximal occlusion of major intra-cranial vessel	1	5	23
Potential embolic origin	12	13	3
Low collateral flow reserve (=poor collaterals)	3	9	17
High blood pressure	6	17	6
Diabetes	16	12	0
Fluctuating symptoms	1	9	19

END, early neurological deterioration; EVT, endovascular thrombectomy; ICAD, intracranial atherosclerotic disease; LVO, large vessel occlusion; MeVO, medium vessel occlusion; NIHSS, National Institutes of Health Stroke Scale.

Supplementary Table 4. Perceived risk–benefit balance of EVT in low NIHSS LVO patients (Round 3 responses, stratified by patient and treatment characteristics; number of panelist votes)

	Risk is higher than benefit	No benefit, no risk	Small net benefit	Great net benefit
How do you rate the benefit of EVT in low NIHSS patients with...				
Ipsilateral ICAD	8	4	13	3
Poor collaterals	2	3	6	17
Orthostatic deterioration	0	2	12	14
Aphasia	0	2	7	19
Distal clot (MeVO)	6	4	14	3
Proximal clot (LVO)	0	0	6	22
Poor accessibility of clot	15	4	9	0
After TNK application	0	8	14	6
If EVT is performed by an experienced interventionalist	0	1	9	17
If EVT is performed by an un-experienced interventionalist	15	5	8	0
Disabling symptoms	0	0	9	19
Young patient	0	3	8	17

Round 3 answers are shown to how participants perceive the risk–benefit balance of EVT in low NIHSS LVO patients stratified for different patient or treatment characteristics. The number of votes from panelists are shown per patient or treatment characteristic.

EVT, endovascular thrombectomy; ICAD, intracranial atherosclerotic disease; LVO, large vessel occlusion; MeVO, medium vessel occlusion; NIHSS, National Institutes of Health Stroke Scale; TNK, tenecteplase.

SPECIAL REPORT

Every Minute Counts: A Paradigm Shift in ICH: Perspectives and Recommendations From the Fourth Hemorrhagic Stroke Academia Industry (HEADS) Roundtable

The HEADS-4 Participants*

ABSTRACT: The HEADS-4 (Fourth Hemorrhagic Stroke Academia Industry) roundtable discussed topics related to the importance of time in the diagnosis and treatment of intracerebral hemorrhage. The goal was to address the shortcomings in current evidence and identify priorities for research to provide stronger data to support implementation of code intracerebral hemorrhage initiatives. The meeting focused on these aspects of intracerebral hemorrhage: diagnosis in the field; reversal of coagulopathy; blood pressure lowering; surgical evacuation; and reorganizing systems of care.

GRAPHIC ABSTRACT: A [graphic abstract](#) is available for this article.

Key Words: blood pressure ■ cerebral hemorrhage ■ glial fibrillary acidic protein ■ hematoma ■ hemorrhagic stroke

The HEADS (Hemorrhagic Stroke Academia Industry) roundtable was established in 2017 to regularly update priorities and benchmark standards for research in various aspects of intracerebral hemorrhage (ICH).^{1–3} The HEADS-4 (Fourth HEADS) roundtable was held in Sydney, Australia, on March 27, 2025, immediately before the ninth World Intracranial Hemorrhage Conference. The focus of HEADS-4 was on increasing recognition that ICH is a medical emergency, where every minute counts, similar to its counterpart of acute ischemic stroke, reinforcing recent calls to establish protocols for code ICH.^{3,4} HEADS-4 participants discussed the following topics: (1) rapid diagnosis of ICH in the field; (2) reversal of coagulopathy; (3) blood pressure (BP) lowering after ICH; (4) surgical evacuation of ICH; and (5) reorganizing ICH systems of care. This article consolidates the perspectives and recommendations of HEADS-4 participants, with the aim of highlighting shortcomings in the available evidence and need for

research to provide stronger data to expand implementation of initiatives, such as Code ICH, to improve the management of patients who experience this devastating disease.

PATHOPHYSIOLOGY SUPPORTING THE CONCEPT OF TIME IS BRAIN IN ICH

ICH involves primary injury from hematoma formation, tissue disruption, and hematoma expansion (HE) leading to mass effect, elevated intracranial pressure, and neurological deficits and secondary injury from downstream cascades initiated by hemoglobin-degradation and plasma products derived from the hematoma that damages neurological tissue from neuroinflammation, cell death, and edema formation.⁵ These processes are closely related and linked to neurological deterioration, death, and disability after ICH.^{6,7}

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

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*A list of all HEADS-4 Participants is given in the Appendix.

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Studies have clearly shown that HE is a time-dependent process, where both the likelihood and severity of HE are greatest within the first few hours after ICH,^{6,8} and slightly longer in patients with anticoagulation-associated ICH.⁹ Emerging evidence indicates that hemolysis of erythrocytes, neuroinflammation, and secondary injury also occur early, within the first few hours, but last for days-to-weeks, after ICH.^{10,11} These chronopathophysiological considerations support the concept that time is brain in ICH, where interventions targeting ICH-related mass effect, HE, and secondary injury are likely to be most effective when implemented as early as possible after the onset of ICH.

Indeed, the neutral results of several previous trials provide indirect support in favor of an earlier intervention in ICH. For example, trials of hemostatic agents, such as activated recombinant factor VIIa¹² and tranexamic acid,¹³ have shown that while these interventions can reduce HE when administered within 4 to 8 hours after ICH, they did not result in improved long-term outcome. To address this issue, the ongoing FASTEST (Factor VIIa for Acute Hemorrhagic Stroke Administered at Earliest Time; URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT03496883) and TICH-3 (Tranexamic Acid for Hyperacute Primary Intracerebral Haemorrhage; URL: <https://fundingawards.nihr.ac.uk>; Unique identifier: NIHR129917) were designed to investigate the effects of these hemostatic agents on HE and clinical outcomes when administered within 2 hours from ICH onset in FASTEST and 4.5 hours in TICH-3. Similarly, BP lowering within 4.5 to 6 hours from ICH had only a modest effect on functional outcome in the INTERACT2 (Second Intensive BP Reduction in Acute Cerebral Hemorrhage Study)¹⁴ and no effect in the ATACH II trial (Second Antihypertensive Treatment of Acute Cerebral Hemorrhage).¹⁵ Although minimally invasive surgical evacuation of the hematoma within 72 hours in the MISTIE-III trial (Third Minimally Invasive Surgery Plus Recombinant Tissue Plasminogen Activator for ICH Evacuation)¹⁶ did not result in improved outcome, evacuation within 24 hours in the subsequent ENRICH trial (Early Minimally Invasive Removal of Intracerebral Hemorrhage)¹⁷ showed improved long-term outcome on the utility-weighted modified Rankin Scale, albeit predominantly in patients with lobar ICH. It is unclear whether the difference in outcomes between MISTIE-III and ENRICH was primarily related to onset-to-evacuation time, technique, or design and choice of primary end point. The neutral results of previous ICH trials may have been influenced, at least in part, by time delays in the initiation of interventions. It is interesting to note that several post hoc and meta-analyses of the aforementioned interventions have suggested improved outcomes from an earlier treatment.^{18–20}

The impact of time on pharmacological treatments targeting secondary brain injury is less clear. The therapeutic

time window in preclinical studies varied from 24 to 72 hours.^{21,22} In the i-DEF trial (Deferoxamine in ICH),²³ there was no difference in outcomes when treatment was initiated within <12 versus 12 to 24 hours after ICH. Secondary brain injury after ICH involves multiple pathways that evolve spatially and temporally, and neuroinflammation may have detrimental or beneficial effects over time.²⁴ The sequence of events and time window of medical therapies targeting secondary injury in patients requires further evaluation.

RAPID DIAGNOSIS OF ICH IN THE FIELD

The ability to quickly diagnose ICH in the prehospital setting is an essential prerequisite to initiate appropriate time-sensitive treatments and inform triage decisions. However, relying solely on clinical features to diagnose ICH is problematic, as many of these features overlap with other stroke types or mimics. Several predictive models, using historical and clinical features, have been proposed to differentiate ICH from ischemic stroke and mimics.²⁵ However, the diagnostic accuracy of these models is moderate at best.

Portable computed tomography scanners deployed in mobile stroke units aid reliable detection of ICH in the ambulance. However, the high costs and limited availability of mobile stroke units (few hospitals in fewer countries) restricts the widespread utilization of this diagnostic strategy. In addition, currently available portable scanners are too heavy (>700 kg) and require large mobile stroke units, limiting their use in metro and large regional settings. Lightweight scanners are needed for standard ambulances and medical aircraft.

There is an unmet need to develop novel, low-cost, point-of-care tests or portable devices for the detection of ICH in the ambulance and prehospital settings. Several technologies have been previously evaluated, including transcranial ultrasound, portable electroencephalography, and near-infrared spectroscopy. However, several limitations of these technologies included the modest discriminatory abilities between stroke types, reliability in detecting small ICH, and in differentiating conditions such as hemorrhagic transformation of ischemic infarcts or tumors from primary ICH.²⁶ Progress in recent years has revealed several promising technologies for detecting ICH. A portable, compact, ultralightweight (<50 kg) 0.1 Tesla magnetic resonance imaging Axana has been developed by Wellumino employing pulsed gradient-free mapping, thus eliminating the need for bulky gradient coils for rapid imaging at the bedside. Axana is currently undergoing preclinical testing in Australia and is expected to commence first-in-human trials in 2025. Micro-X is utilizing a carbon nanotube x-ray technology to develop a small, light (70 kg), and fast computed tomography Micro-X computed tomography equipped with 21 high voltage array

mini-tubes and a unique curved detector to fit in small ambulances and aircraft. EMVision Medical Devices Ltd utilizes electromagnetic, ultra-high frequency, radio wave technology to develop a portable, point-of-care, lightweight scanner (EMU, weighing about 100 kg) and a stroke helmet or first responder (<15 kg). In a pre-validation 2-center study, involving 307 participants with suspected acute stroke, the EMU device was able to differentiate between stroke types and detect ICH with an overall sensitivity of 92% and specificity of 85%. A large multicenter, prospective, diagnostic performance study using the EMU device is currently underway in Australia and the United States (URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT06999122). Improvements in digital connectivity for data sharing and image viewing are essential to enhance the effectiveness of these imaging techniques.

Besides imaging-based devices, the use of blood biomarkers, in particular GFAP (glial fibrillary acidic protein), is a promising marker for rapid prehospital diagnosis of ICH and differentiation from ischemic stroke. In a prospective study of 143 patients admitted to the emergency department with acute coma, GFAP plasma concentrations, using prehospital blood samples drawn by rescue services, were significantly elevated in patients with ICH (3352 pg/mL) compared with other causes (43 pg/mL).²⁷ When using a cutoff value of 101 pg/mL, sensitivity for identifying ICH was 94%, specificity 78.9%, positive predictive value 71.6%, and negative predictive value 95.9%. A subsequent study in 353 patients presenting within 6 hours of acute stroke-like symptoms (DETECT [Rapid Diagnosis of Intracerebral Hemorrhage in Patients With Acute Stroke by Measuring Prehospital GFAP Levels on a Point-of-Care Device]) showed that the median prehospital GFAP levels were 208 pg/mL in patients with ICH compared with 30 pg/mL in ischemic stroke.²⁸ Moreover, age-specific cutoff values were defined to identify ICH with a high positive predictive value. For patients with moderate to severe neurological deficit (National Institutes of Health Stroke Scale score >6), GFAP values below 30 pg/mL were able to rule out ICH with a negative predictive value of 100% (95% CI, 93.7%–100%). The integration of clinical predictors alongside GFAP levels may improve the prediction of ICH. In a study of 209 patients with suspected stroke, of whom 5% with a final diagnosis of ICH, clinical predictors alone achieved an area under the curve of 0.74 (95% CI, 0.60–0.88), whereas GFAP alone resulted in an area under the curve of 0.83 (95% CI, 0.69–0.99), but when combined clinical predictors and GFAP, the area under the curve was significantly enhanced to a value of 0.90 (95% CI, 0.79–0.98).²⁹ Several validation studies testing the feasibility and accuracy of GFAP plasma level measurements using a point-of-care device in the ambulance are underway.³⁰

SUMMARY AND RECOMMENDATIONS

- There is an unmet need to develop novel portable imaging technologies, point-of-care tests, and artificial intelligence-based algorithms for reliable and rapid diagnosis of ICH in the prehospital setting.
- ICH detection in the field could revolutionize treatment and is a top research priority.

REVERSAL OF COAGULOPATHY

In high-income countries now, ≈15% to 20% of patients with acute ICH are taking an oral anticoagulant (OAC),³¹ and this is likely to increase in the coming decades with the aging of populations. OAC-associated ICH is associated with greater risk for HE, worse outcomes, and higher mortality.^{31,32} Thus, it is intuitive to reverse OAC as soon as possible in these patients. Professional guidelines, such from the American Heart Association/American Stroke Association and the European Stroke Organization, provide recommendations for reversal of various OACs, including vitamin K antagonists and direct OACs. While evidence suggests that early reversal of anticoagulation is associated with less HE, whether this effect translates into improved outcomes after ICH is less robust. In the INCH trial (INR Normalization in Coumadin-Induced Intracerebral Hemorrhage),³³ 50 patients were randomized to either fresh frozen plasma (n=23) or prothrombin complex concentrate (n=27). International normalized ratio was normalized to ≤1.2 within 3 hours in 18 (67%) of patients treated with prothrombin complex concentrate compared with 2 (9%) of patients treated with fresh frozen plasma. Although mortality was lower in prothrombin complex concentrate-treated patients (19% versus 35%), the difference was not statistically significant. However, earlier and faster international normalized ratio normalization was associated with significantly less HE. In the ANNEXA-I trial (Andexanet for factor Xa Inhibitor-Associated Acute ICH), where patients with an ICH while taking a factor Xa inhibitor were randomized to andexanet or usual care, which included background use of prothrombin complex concentrate, the median time from hospital presentation to initiation of treatment was 2.1 hours (interquartile range [IQR], 1.5–2.9) in the andexanet group and 2.3 h (1.7–3.1) in the usual care group. A larger proportion of andexanet-treated patients (67% versus 53.1%) met the criteria for the primary end point (hemostatic efficacy, defined as HE ≤35% after 12 hours, an increase <7 points on the National Institutes of Health Stroke Scale, and no receipt of rescue therapy).³⁴ The between-group difference appeared to be driven by differences in HE, where HE ≤35% was seen in 76.7% of patients in the andexanet group compared with 64.4% in the usual care group. However, there were no appreciable differences between the treatment groups in modified Rankin Scale

(mRS) scores or mortality at 30 days. Idarucizumab, the best available therapeutic option for reversing the anticoagulant effect of the direct thrombin inhibitor, dabigatran, has been only investigated in a single-arm study in which 19% of the participants had ICH, and the effect of treatment on HE or functional outcome was not evaluated.³⁵ Despite this evidence gap with respect to clinical outcomes, future trials will be complicated by at least a perceived lack of clinical equipoise regarding reversal of OAC in patients with ICH.

A retrospective cohort study of 9492 patients with OAC-associated ICH in the American Heart Association/American Stroke Association Get With The Guidelines Stroke Quality Improvement Registry found that a door-to-treatment with a reversal agent time of ≤ 60 minutes was associated with decreased mortality and discharge to hospice, but no difference in good functional outcome (mRS score, 0–3) at discharge.³⁶ However, this study was limited by the exclusion of many patients with OAC-associated ICH ($n=7973$) in whom the time of reversal was not recorded or data were missing, raising the strong influence of selection bias.

SUMMARY AND RECOMMENDATIONS

- Although current evidence indicates that several anticoagulation reversal agents can restore hemostatic efficacy and reduce HE, it remains unclear whether this translates into improved overall net clinical benefit in OAC-associated ICH.
- More research is required to define the optimal timing of OAC reversal and effect on clinical outcome, and of the clinical and imaging characteristics of patients with OAC-associated ICH who are most likely to benefit from anticoagulation reversal.

BP LOWERING

A recent pooled analysis of individual patient data from 16 randomized controlled trials investigating intensive BP lowering in 5761 patients with acute ICH showed that earlier achievement and maintenance of systolic BP 120 to 140 mmHg was significantly associated with a lower likelihood of death or dependency (mRS score, 3–6: odds ratio, 0.98 [95% CI, 0.97–0.99]) and HE at 24 hours (odds ratio, 0.98 [95% CI, 0.96–1.00]).³⁷ These findings align with a growing body of literature and post hoc analyses from INTERACT2 and ATACH II^{18,19}; larger systolic BP reductions within the first hour postrandomization in INTERACT2 were associated with lower odds of poor outcome,¹⁸ and in ATACH II, ultra-early BP reduction (≤ 2 hours after symptom onset) was associated with reduced HE and improved 90-day functional outcome.¹⁹ The prehospital INTERACT4 trial showed that early lowering of systolic BP to 130 to 140 mmHg in the ambulance,

within a median of 61 minutes (IQR, 41–93) from symptom onset, was associated with increased death and disability among patients with ischemic stroke, but clearly beneficial in patients with ICH (mRS score, 3–6: odds ratio, 0.75 [95% CI, 0.60–0.92]).³⁸ Both hematoma volumes at hospital presentation and postadmission HE appeared lower in the actively treated group. The results of an individual patient data meta-analysis of all 4 INTERACT studies have shown that the greatest benefits on HE and functional recovery occurred when BP lowering was initiated within 3 hours of symptom onset.³⁹ Other studies have confirmed the safety of intensive BP lowering after ICH, with no increase in ischemic diffusion-weighted imaging lesions seen on magnetic resonance imaging.⁴⁰ These findings underscore the time-dependent benefit of BP lowering in ICH, but also the importance of early identification of ICH in the prehospital setting. INTERACT4 is an important proof-of-concept study, but as it was limited to the Chinese context, further confirmatory studies in other settings are needed.

SUMMARY AND RECOMMENDATIONS

- Accumulating evidence supports the time-dependent benefit of early intensive BP lowering in ICH.
- Time-to-BP treatment and achieved systolic target (130–140 mmHg) should be incorporated in ongoing stroke registries and quality improvement programs.
- Confirmation of the beneficial effects of very early prehospital BP lowering seen in INTERACT4 in other health care settings is encouraged.
- As most patients enrolled in the INTERACT studies had small-to-medium-sized deep ICH and were treated with urapidil (an α -1 adrenergic receptor antagonist and serotonin agonist), more data are required on the benefit of BP lowering in large and lobar ICH, and whether there is heterogeneity in the effects of different BP-lowering agents on outcomes.

SURGICAL EVACUATION OF ICH

A recent Cochrane review assessing whether the effects of surgery in patients with spontaneous ICH differ according to the surgical technique found low-certainty evidence that minimally invasive surgery may increase the chance of good functional outcome (risk ratio, 1.36 [95% CI, 1.18–1.58]) and moderate-certainty evidence that it may reduce 30-day case fatality (risk ratio, 0.62 [95% CI, 0.47–0.81]), whereas evidence was very uncertain that craniotomy with hematoma evacuation may increase the chance of good functional outcome (risk ratio, 1.41 [95% CI, 0.77–2.55]) or reduce 30-day fatality (risk ratio, 0.68 [95% CI, 0.46–1.00]).⁴¹ It is logical to assume that interventions that aim to decompress the hematoma would be most beneficial

when delivered within the first few hours after ictus, by minimizing mechanical injury from HE and secondary injury from blood product toxicity. Indeed, previous small studies and meta-analyses suggest that early evacuation is associated with better outcomes.^{20,42,43} Surgical trials that attempted evacuation after 24 hours from ICH onset did not demonstrate improvements in long-term functional outcome,^{16,44} whereas in the ENRICH trial, there was improved utility-weighted modified Rankin Scale scores at 180 days, mostly in patients with lobar ICH from an early evacuation within 24 hours (median time to surgery was 16.8 hours [IQR, 11–21]). However, as randomized controlled trials directly comparing earlier versus later intervention have not been performed, it remains unclear whether ultra-early evacuation (eg, <8 hours) could provide a greater net benefit over potential harms, particularly in basal ganglia locations where the rich vascular supply and proximity to the lateral ventricles could lead to early HE and intraventricular extension, both of which are major determinants of poor outcome. While an earlier study evaluating craniotomy for ICH within 4 hours of onset was stopped prematurely because of increased postoperative bleeding and mortality,⁴⁵ recent data from the Dutch ICH Surgery Trial pilot study, which evaluated the safety of minimally invasive endoscopy-guided evacuation within a median time of 6 hours and 43 minutes from symptom onset, did not demonstrate safety concerns and showed that early surgery can effectively reduce ICH volume at 24 hours (IQR, 50–89) by $\approx 78\%$.⁴⁶ Similarly, data from a prospective, single-arm, phase II study, which enrolled 10 patients at 2 centers in Australia, showed that minimally invasive endoscopy-guided evacuation within a median time of 531 minutes (IQR, 437–628) from ICH onset was not associated with surgical safety concerns.⁴⁷ The median mRS score at 6 months was 4 (IQR, 3–6), with 30% achieving a good score of 0 to 3. Several ongoing and planned randomized controlled trials of minimally invasive surgery for ICH in the ultra-early and early time windows are currently underway.

The positive results of ENRICH may also be attributed to the smaller residual hematoma volumes and higher percentage of postoperative hematoma volume of ≤ 15 mL compared with other trials.^{16,17} In ENRICH, the mean percent reduction in hematoma volume after surgery from baseline was 73.2 ± 37.8 mL, with a mean volume after the completion of surgery of 14.9 ± 21.7 mL. A volume of ≤ 15 mL after completion of surgery was observed in 72.7% of patients. Although available evidence suggests that minimally invasive surgery may be most beneficial when performed within 24h of onset in patients with lobar ICH of ≤ 30 mL utilizing a trans-sulcal, channel-based para-fascicular approach, more investigations are needed to assess whether different approaches and ICH volume should be utilized based on ICH location and volume, and time course.

Magnetic resonance imaging–based biomarker development to map out relatively healthy white matter tracts within the hematoma is ongoing⁴⁸ and could help to further refine and guide surgical evacuation techniques, particularly for basal ganglia ICH. Healthy white matter within hematoma has been shown to aid in hematoma healing in animal models as mediators of macrophage propagation and need preservation in human ICH evacuation strategies.⁴⁹

SUMMARY AND RECOMMENDATIONS

- Uncertainty exists over the optimal timing of minimally invasive ICH evacuation and whether it varies depending on ICH location (lobar versus deep).
- Emerging evidence suggests that earlier minimally invasive evacuation is safe and offers greater benefits.
- Several ongoing and planned randomized controlled trials of minimally invasive surgery in patients with ICH in variable time windows and with various techniques are underway.
- Planned and future trials of early/ultra-early minimally invasive surgical evacuation should consider evaluation of both lobar and deep ICH.
- Future studies should evaluate the effect of different minimally invasive surgery approaches based on ICH volume, location, and time course.

REORGANIZING ICH SYSTEMS OF CARE

Recognizing the importance of immediate and specialized evaluation and treatment of patients with ICH has led to increased focus on fast-care bundle approach combining simple therapeutic protocols of BP lowering, temperature and glucose control, and reversal of coagulopathy.^{4,50,51} Bundled care increases compliance with best practices, and its implementation in hospitals in low- and middle-income countries has been shown to improve clinical outcome in acute ICH.⁵¹ The ongoing I-CATCHER trial (International Care Bundle Evaluation in Cerebral Hemorrhage Research) is currently evaluating the implementation and efficacy of a broader, more structured, and time-driven in-hospital care bundle, in a wide range of hospital settings, predominantly in high-income countries.⁵² The proposed bundle includes early systolic BP reduction to <140 mm Hg, reversal of coagulopathy, early avoidance of withdrawal of care, contact pathways to neurosurgery and intensive care within <30 minutes from ICH detection, and treatments for hyperglycemia and fever within 24 hours.

An argument can be made that a focus on hospital-based care bundles alone is unlikely to be sufficient to improve outcomes for patients with ICH. Optimization of triage systems and transfers is also a priority. Data from various national registries indicate that most ICH

patients arrive at a local hospital by ambulance within hours of symptom onset. Many of these hospitals lack specialized stroke expertise, and interhospital transfers to comprehensive stroke centers are common. Yet, there has been no universally agreed-upon standardized or dedicated ICH systems of care. Worldwide, stroke triage/bypass systems are mainly organized for ischemic stroke workflow to deliver reperfusion therapies. These triage algorithm systems often rely on prehospital stroke severity scales, such as FAST (Face, Arm, Speech, Time to call 911), Los Angeles Prehospital Stroke Scale, and Cincinnati Prehospital Stroke Scale, which were developed to identify acute ischemic stroke and not for ICH. In the SSTS (Stockholm Stroke Triage System) project, which used a modified FAST scale allowing for arm or leg weakness, 172 patients with ICH were initially triage-negative, that is, they were routed to a primary stroke center instead of a comprehensive stroke center based on their prehospital assessment.⁵³ A larger proportion of patients with ICH were triaged to comprehensive stroke centers in systems using the RACE (Rapid Arterial Occlusion Evaluation) and the ACT-FAST (Ambulance Clinical Triage for Acute Stroke Treatment) large vessel occlusion screening scales.⁵⁴ The RACE-plus (Transfer to the Closest Local Stroke Center vs Direct Transfer to Endovascular Stroke Center of Acute Stroke Patients With Suspected Large Vessel Occlusion-Plus) algorithm was recently introduced to improve prehospital identification of ICH. However, there is an overall paucity of studies investigating the sensitivity and specificity of commonly used prehospital scales to identify ICH. Moreover, patients with ICH often present with headaches, seizures, or altered level of consciousness, and may not be identified as a stroke.

A secondary analysis of the RACECAT trial (Transfer to the Closest Local Stroke Center vs Direct Transfer to Endovascular Stroke Center of Acute Stroke Patients With Suspected Large Vessel Occlusion in the Catalan Territory) showed that direct transfer to an endovascular-capable comprehensive stroke center resulted in reduced chances of functional independence at 90 days compared with transfer to the nearest local stroke center for patients who received a final diagnosis of ICH.⁵⁵ However, it is important to realize that this trial population did not represent all patients with ICH, and that the results were dependent on the specific characteristics of the Catalanian stroke health care system, in which the local stroke centers are located >30 minutes from an endovascular-capable center. Network characteristics may vary significantly across different regions; thus, there needs to be cautious interpretation of the application of these findings outside Catalonia, Spain, especially in areas where primary and comprehensive stroke centers are in close proximity.

There is a need to implement and maintain organized systems of care for optimizing ICH workflow. The use of biomarkers and advanced mobile imaging technology

may potentially circumvent some of the aforementioned challenges. Emerging artificial intelligence-guided ICH detection software and group notification/communication systems have been shown to streamline ICH diagnosis and transfer process and to decrease time-to-treatment in ICH.⁵⁶ The use of novel point-of-care computing technologies that can enable fast detection of ICH and facilitate efficient transfer of data to the health information system with real-time data in the ambulance and emergency room settings for triaging patients for right care has the potential to revolutionize ICH systems of care. These approaches are currently being evaluated in the POC4TRIAGE project (Point of Care Devices for Urgent Care Triage; <https://poc4triage.eu>). Similarly, the EU UMBRELLA project (European Union Umbrella Project; <https://umbrellaproject.eu>) aims to integrate real world stroke data leveraging state-of-the-art digital technologies, including communication systems, imaging techniques, and wearable devices to build a federated data platform to serve as the basis for the creation and validation of artificial intelligence-based predictive models allowing for advanced personalized diagnosis, risk prediction, and treatment decisions for stroke patients.

Changes to the in-hospital ICH workflow and infrastructure may also be needed to facilitate rapid treatment of ICH. For example, unlike traditional operating rooms, having dedicated rooms within the emergency department that can be used for angiography and endovascular and minimally invasive surgical, can facilitate immediate surgical interventions such as hematoma evacuation.

SUMMARY AND RECOMMENDATIONS

- Adopting care bundles and time-based metrics for acute treatment of ICH is strongly encouraged.
- Current prehospital stroke severity scales may not be sensitive to stratify or diagnose ICH. Further studies are needed to determine which scale, if any, is best, and to develop new scales to facilitate ICH detection.
- There is limited data on the impact of prehospital strategies and triage destination on ICH outcomes. More studies are needed to evaluate whether dedicated systems of care specific for ICH will translate into improved outcomes.
- Utilizing novel digital technologies, including communication systems, imaging techniques, point-of-care testing, and artificial intelligence-based predictive models in the prehospital setting, can form the foundation to develop innovative ICH systems of care to expedite treatment.

CONCLUSIONS

Evidence is accumulating that the efficacy of several interventions for ICH is time-dependent and that their

Table. Summary of the Key HEADS-4 Recommendations

Diagnosis of ICH in the prehospital setting	Improved ICH detection in the field can revolutionize ICH treatment and is a top research priority. There is an unmet need to develop novel portable imaging technologies, point-of-care tests, and AI-based algorithms that can reliably and quickly facilitate the diagnosis of ICH in the prehospital setting.
Reversal of coagulopathy	There is a need for more studies to evaluate the optimal timing of anticoagulation reversal and its effect on long-term outcomes, and clinical and imaging characteristics of patients with OAC-associated ICH who are most likely to benefit from anticoagulation reversal.
BP lowering	Accumulating evidence supports the time-dependent benefit of early intensive BP lowering after ICH. Confirmation of the beneficial effects of ultra-early BP lowering in the ambulance seen in INTERACT4 in other systems and settings is encouraged. As most patients enrolled in the INTERACT studies had small-to-medium-sized deep ICH and were treated with urapidil (an alpha-1 adrenergic receptor antagonist and serotonin agonist), more data are required on the benefit of BP lowering in large and lobar ICH, and whether there is heterogeneity in the effects of different BP-lowering agents on outcomes.
Surgical evacuation	The optimal timing of minimally invasive ICH evacuation and whether it varies depending on ICH location (lobar vs deep) is uncertain. Emerging evidence suggests that earlier minimally invasive evacuation may be more beneficial. Planned and future trials of early and ultra-early minimally invasive surgical evacuation should consider evaluation of both lobar and deep ICH locations. Future studies should evaluate the effect of different MIS approaches based on ICH volume, location, and time course.
ICH systems of care	The adoption of care bundles and time-based metrics for acute treatment of ICH is strongly encouraged. Currently existing prehospital stroke severity scales may not be sensitive to stratify or diagnose ICH. Further studies are needed to determine which scale, if any, is best and to develop new scales to facilitate ICH detection. There is limited data on the impact of prehospital strategies and triage destination on ICH outcomes. More studies are needed to evaluate whether dedicated systems of care specific to ICH will translate into improved outcomes. Utilizing novel digital technologies, including communication systems, imaging techniques, point-of-care testing, and AI-based predictive models in the prehospital setting can form the foundation to develop innovative ICH systems of care to expedite treatment.

AI indicates artificial intelligence; BP, blood pressure; HEADS-4, Fourth Hemorrhagic Stroke Academia Industry; ICH, intracerebral hemorrhage; INTERACT, Intensive BP Reduction in Acute Cerebral Hemorrhage Study; MIS, minimally invasive surgery; and OAC, oral anticoagulant.

integration within a bundle of care improves compliance with best practices to improve outcomes. Expedited diagnosis and treatment of ICH requires parallel improvements in prehospital identification of ICH, its systems of care, and workflow. More studies are needed to address these challenges and pertinent knowledge gaps. It is our hope that the HEADS-4 recommendations (Table) will help to advance the field and to improve outcomes for the many patients with ICH around the world.

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Supplemental Material

Detailed List of HEADS-4 Participants

APPENDIX

HEADS-4 Participants

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TOPICAL REVIEW

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Left Atrial Appendage Occlusion and Its Role in Stroke Prevention

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ABSTRACT: Atrial fibrillation is a frequent cardiac arrhythmia and is associated with an increased risk of cardioembolic stroke. The left atrial appendage is a finger-like extension originating from the main body of the left atrium and the main location of thrombus formation in patients with atrial fibrillation. Surgical or percutaneous left atrial appendage occlusion (LAAO) aims at preventing clot formation in the left atrial appendage. Here, we describe available surgical and percutaneous approaches to achieve LAAO and discuss the available evidence for LAAO in patients with atrial fibrillation. We discuss LAAO and its role in stroke prevention in 2 frequent scenarios of cerebrovascular medicine: LAAO as a potential alternative to oral anticoagulation in patients with a history of intracranial hemorrhage or at high risk of intracranial bleeding, and LAAO as add-on therapy to direct oral anticoagulant therapy in patients with breakthrough stroke despite anticoagulation. Finally, we provide an outlook on currently ongoing trials that will provide further evidence in the next years.

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

Key Words: anticoagulants ■ atrial appendage ■ atrial fibrillation ■ embolic stroke ■ intracerebral hemorrhage

Atrial fibrillation (AF) is one of the most common cardiac rhythm disorders and is associated with increased risks of morbidity and mortality.¹ Although AF is relatively uncommon in middle-aged adults, it affects nearly 10% of individuals over the age of 80 years.² Moreover, AF is an important independent risk factor for stroke.³ Several risk stratification schemes, such as CHADS₂ and CHA₂DS₂-VASC, and most recently, CHA₂DS₂-VA,⁴ have been developed to evaluate and quantify the individual risk of stroke in patients with AF.

Up to 25% of all ischemic strokes are associated with AF.⁵ Stroke survivors with a concomitant diagnosis of AF are more likely to experience a recurrent stroke than those without AF.⁶ AF-associated ischemic strokes tend to be more severe and are more likely to be disabling or fatal than strokes unrelated to AF. This is presumably mediated by a high rate of cardioembolic large vessel occlusions,⁷ resulting in larger-sized cerebral infarcts, a higher likelihood of hemorrhagic

transformation, and more severe initial neurological impairment.^{8,9}

The left atrial appendage (LAA) plays a crucial role in cardiac thrombus formation. LAA occlusion (LAAO) is a promising approach to reduce the risk of cardioembolic stroke. In this review, we summarize the available evidence for LAAO for stroke prevention in patients with AF.

PRINCIPLES OF STROKE PREVENTION IN PATIENTS WITH AF

Stroke prevention is a cornerstone of AF management,¹⁰ and an integral part of the AF-CARE (Atrial Fibrillation - Care, Avoid, Reduce and Evaluate) pathway suggested in the recently published 2024 European Society of Cardiology (ESC) Guidelines for the management of AF⁴ and the 2023 American Cardiology Conference/American Heart Association/American College of Clinical Pharmacy/Heart Rhythm Society (ACC/AHA/ACCP/

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HRS) Guideline for the Diagnosis and Management of Atrial Fibrillation.¹¹ Oral anticoagulation is the mainstay to prevent ischemic stroke and thromboembolism in patients with AF and risk factors.^{12,13} Antiplatelet therapy (eg, aspirin) alone provides a $\approx 20\%$ risk reduction¹² but is not recommended for stroke prevention in patients with AF, because oral anticoagulation is much more effective.¹³

The evidence for oral anticoagulation in patients with AF is based on 6 pivotal randomized trials enrolling 2900 patients that established the efficacy and safety of dose-adjusted warfarin for stroke prevention more than 3 decades ago.¹³ Here, warfarin reduced stroke by 64%. Between 2009 and 2013, another 4 randomized controlled trials enrolling a total of 71 683 patients with AF demonstrated the noninferiority of 1 oral thrombin inhibitor, dabigatran, and 3 oral factor Xa inhibitors, apixaban, rivaroxaban, and edoxaban, compared with warfarin for stroke prevention.¹⁴ This led to strong recommendations for the use of oral anticoagulation in patients with AF and high risk for stroke, with a preference for the direct oral anticoagulants due to their favorable safety profile and ease of use.^{15–17}

Although oral anticoagulation is the gold standard for stroke prevention in patients with AF, there are certain scenarios where alternative or additional measures for stroke protection could be considered. These include (1) patients with a (recent) history of bleeding, particularly intracerebral hemorrhage (ICH) or who are at high risk of bleeding (ie, cerebral amyloid angiopathy [CAA]^{18,19}), (2) patients unwilling to take oral anticoagulation, and (3) patients who may benefit from additional protection on top of oral anticoagulation.²⁰

LAA AND ITS ROLE IN INTRACARDIAC THROMBUS FORMATION

The LAA is a finger-like extension originating from the main body of the left atrium. There are considerable variations in LAA size and shape and the anatomic relationship with adjacent cardiac and extracardiac structures.²¹ The LAA morphology has been classified into 4 major types: chicken wing, cactus, windsock, and cauliflower, with the former 2 predominating.²²

Several studies have reported that the majority of thrombi forming in the left atrium originate from the LAA: for example, 75% of all left atrial thrombi in a sample of patients with AF undergoing heart surgery,²³ 82% in a sample of patients with AF who had a recent stroke,²⁴ and up to 91% in patients with nonvalvular AF free of stroke.²⁵ Both transesophageal echocardiography (Figure 1) and cardiac computed tomography (Figure 2) are sensitive and specific for LAA thrombus detection.²⁶ In patients with acute stroke and AF, a thrombus can be found in the LAA in a significant proportion of patients, ranging between 8%²⁴ and 15%.²⁷ A recently presented

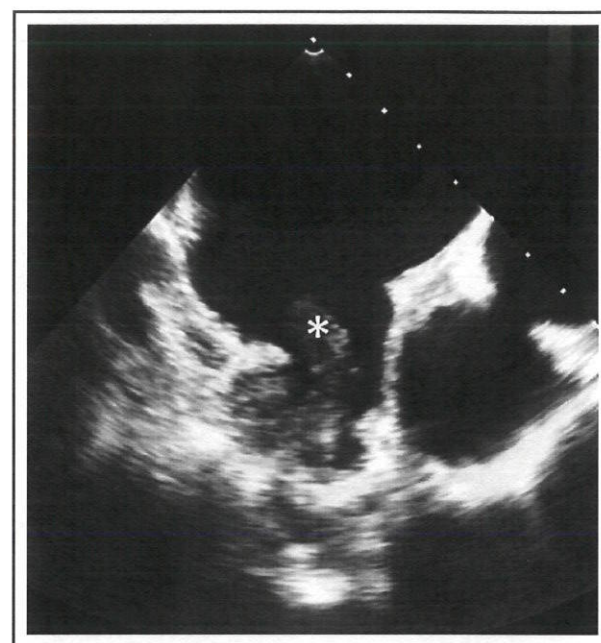


Figure 1. Example of a thrombus (*) in the left atrial appendage on transesophageal echocardiography.

study (Sposato et al, World Stroke Congress 2024) found that in patients presenting with acute ischemic stroke, single-phase, nongated computed tomography angiography extended to the heart identified cardioaortic thrombi in 8.8% of all patients, most frequently LAA thrombi in patients with AF.

Therefore, the LAA represents a biologically plausible target for stroke prevention. Several approaches with the aim of reducing the risk of stroke by means of excluding or occluding the LAA have been developed.^{28–30} These include surgical excision, endocardial, or epicardial suture during concomitant cardiac surgery, epicardial exclusion



Figure 2. Example of a thrombus (*) in the left atrial appendage (LAA) on cardiac computed tomography.

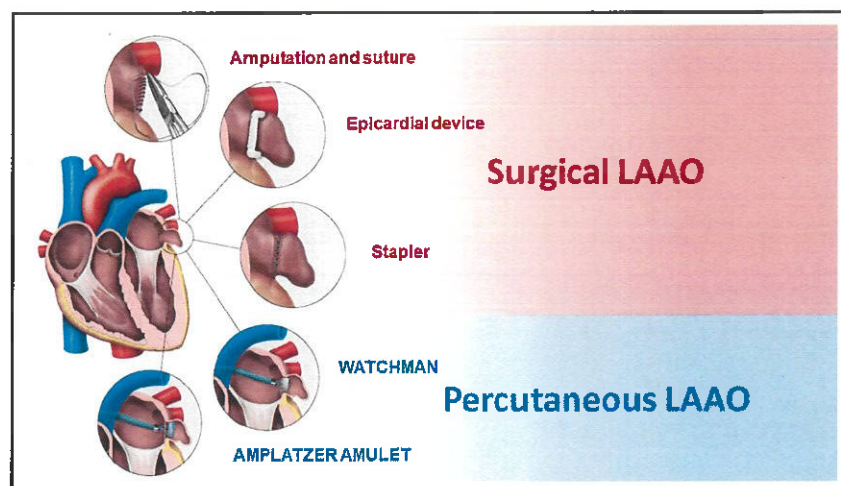


Figure 3. Commonly used surgical and percutaneous approaches to left atrial appendage occlusion (LAAO; clockwise): (1) surgical amputation and suture closure (cut and sew), (2) surgical stapler occlusion, (3) epicardial closure device (eg, AtriClip), (4) percutaneous closure device (Amplatzer Amulet), and (5) percutaneous closure device (WATCHMAN FLX).

by stapling or clips, or endovascular occlusion by percutaneous intervention (Figure 3).

EVIDENCE FOR SURGICAL LAAO

Until recently, the evidence for surgical occlusion of the LAA was largely limited to data from observational studies.³¹ In 2021, the LAAOS III (Left Atrial Appendage Occlusion Study) provided solid evidence for stroke risk reduction with concomitant surgical LAAO.³² This trial enrolled patients with AF undergoing cardiac surgery for another indication. LAAOS III included 4770 patients (9% with prior stroke) who were randomized 1:1 to occlusion or no occlusion of the LAA during cardiac surgery (66.7% valve procedure, 21.0% isolated coronary artery bypass graft). The technique for surgical LAAO was left at the discretion of the treating surgeon (55.7% cut and sew, 11.2% stapler, and 15.1% closure device; Figure 3). During a mean follow-up of 3.8 years, there was a 33% relative risk reduction in the primary end point of ischemic stroke or systemic embolism in patients assigned to receive LAAO (hazard ratio, 0.67 [95% CI, 0.53–0.85]). This benefit was observed in addition to usual care, with >75% of patients in both groups receiving oral anticoagulation with a vitamin K antagonist or a direct oral anticoagulant at any point during the trial. A prespecified secondary analysis found that stroke risk reduction with LAAO was independent of anticoagulation therapy in LAAOS III.³³ Patients who continued anticoagulation therapy throughout the study had the lowest risk of stroke (2.2% in patients who continued anticoagulation after LAAO versus 7.5% in patients who stopped anticoagulation after LAAO).³³ This finding highlights the potential of a combined mechanical/pharmacological approach to stroke prevention in patients with AF.

The results of LAAOS III have led to class I recommendations for surgical LAAO in addition to oral anticoagulation in patients with AF undergoing cardiac surgery

to prevent stroke and thromboembolism in the most recent 2023 ACC/AHA/ACCP/HRS and 2024 ESC Guidelines for the management of AF.^{4,34} The results of LAAOS III do not support surgical LAA occlusion as a standalone replacement for oral anticoagulation and do not support surgical LAAO in patients without another indication for cardiac surgery.

EVIDENCE FOR PERCUTANEOUS LAAO

Percutaneous LAAO may represent an alternative to surgical LAAO. There are currently 2 devices for percutaneous LAAO that were approved by the US Food and Drug Administration based on 3 randomized trials that enrolled a total of 2992 patients.^{35–37} Approval mechanisms for medical devices differ from those for novel drugs, and device studies typically enroll only a fraction of participants enrolled in drug trials.

The Food and Drug Administration approval of the first-generation WATCHMAN LAAO device (Boston Scientific, Marlborough, MA) is based on results from the PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic PROTECTION in Patients With Atrial Fibrillation) and PREVAIL (WATCHMAN Left Atrial Appendage System for Embolic PROTECTION in Patients With Atrial Fibrillation) randomized noninferiority trials, testing the device against warfarin.^{35,36} PROTECT AF, published in 2009, enrolled 707 patients with AF and a CHADS₂ score ≥1 who were randomized in a 2:1 fashion to percutaneous LAAO (n=463) or warfarin (target international normal ratio, 2.0–3.0; n=244).³⁶ Patients randomized to the device arm were treated with warfarin and aspirin for 45 days after implantation, then received dual antiplatelet therapy with aspirin and clopidogrel until the 6-month visit, and then aspirin alone indefinitely thereafter. The primary end point was a composite of all-cause stroke, systemic embolism, or cardiovascular or unexplained death. During a mean follow-up of 18 months, 21 patients (4.5%) in the device group and

18 patients (7.4%) in the warfarin group had a primary end point event (rate ratio, 0.62 [95% credible interval, 0.35–1.25]; *P* value for noninferiority <0.001), driven by a reduction in hemorrhagic stroke and cardiovascular or unexplained death. The rate of ischemic stroke was numerically higher in the device group (2.2 versus 1.6 per 100 patient-years, rate ratio, 1.34 [95% credible interval, 0.60–4.29]).³⁶

PREVAIL, published in 2014, enrolled 407 patients with AF and a CHADS₂ score ≥2, or a CHADS₂ score of 1 with a least 1 additional risk factor.³⁵ Study participants were randomized 2:1 to percutaneous LAAO (*n*=269) or warfarin (*n*=138). The coprimary efficacy end points were (1) a composite of all-cause stroke, systemic embolism, cardiovascular, or unexplained death and (2) all-cause stroke or systemic embolism >7 days after randomization. The postimplant antithrombotic regimen was identical to that used in PROTECT AF. At 18 months, the rates for the first coprimary efficacy end point were 6.4% in the device arm and 6.3% in the warfarin group (rate ratio, 1.07 [95% credible interval, 0.57–1.89], not meeting the prespecified noninferiority criteria). Rates of the second coprimary efficacy end point were 2.5% versus 2.0%, meeting noninferiority. The overall rate of ischemic stroke was higher in the device group (1.9% versus 0.7%).³⁵ Subsequent longer-term follow-up results from both PROTECT AF and PREVAIL have been published.³⁸ In a meta-analysis of patient-level data, the rate of the composite of stroke, systemic embolism, or cardiovascular death was 2.8% and 3.4% per year in patients randomized to percutaneous LAAO and warfarin, respectively. Corresponding rates of ischemic stroke or systemic embolism were 1.6% versus

1.0%, and of major bleeding were 3.1% and 3.5%, respectively.

The company's second-generation device, WATCHMAN FLX, was evaluated in a prospective, nonrandomized, single-arm study that enrolled 400 patients with AF and "a rationale for a nonpharmacological approach to stroke prevention."³⁹ The postimplant antithrombotic regimen was direct oral anticoagulation (with a recommendation for apixaban or rivaroxaban) and aspirin for 45 days, then dual antiplatelet therapy with aspirin and clopidogrel until the 6-month visit, and then aspirin alone indefinitely thereafter. The study met both its primary safety (death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring cardiac surgery) and efficacy performance goals (peri-device flow ≤5 mm on transesophageal echocardiography, assessed at 12 months). At 2 years, the annualized rate of ischemic stroke in patients undergoing implantation of a WATCHMAN FLX device was 1.7%.³⁹

The Food and Drug Administration approval of the Amplatzer Amulet LAA Occluder (Abbott, Green Oaks, IL) is based on a randomized noninferiority trial testing the device against the first-generation WATCHMAN system.³⁷ The Amulet IDE trial (Amplatzer Amulet Left Atrial Appendage Occluder IDE Trial) enrolled 1878 patients with AF and an "appropriate rationale to seek a nonpharmacological alternative." Patients were randomized 1:1 to 1 of the 2 devices. The 3 coprimary end points were (1) a safety composite of procedure-related complications, major bleeding, or all-cause death at 12 months; (2) an effectiveness composite of ischemic stroke or systemic embolism at 18 months; and (3) the rate of successful LAA occlusion on transesophageal echocardiography

Table 1. Observational Studies of LAAO in Patients With a History of Intracranial Hemorrhage

	Horstmann et al ⁴⁰	Gilhofer et al ⁴⁰	Pouru et al ⁴¹	Ajmal et al ⁴²	Hucker et al ⁴³	Hutt et al ⁴⁴	Renou et al ⁴⁵	Tzikas et al ⁴⁶
Study design	Observational, prospective	Observational, retrospective	Observational, retrospective	Observational, retrospective	Observational, retrospective	Observational, retrospective	Observational, prospective	Observational, prospective
Study population	20 patients with AF and a history of lcrH	138 patients with and history of lcrH	104 patients with and history of lcrH	16 patients with AF and a history of lcrH	63 patients with AF and a history of lcrH	38 patients with AF and a history of lcrH	46 patients with AF and a history of lcrH	198 patients with AF and a history of lcrH
Type of intracranial bleeding	5 SDH/SAH; 16 ICH	78 SDH/SAH; 64 ICH	32 SDH/SAH; 69 ICH	9 SDH/SAH; 7 ICH	23 SDH/SAH; 44 ICH	15 SDH/SAH; 23 ICH	46 ICH	Not reported
CHA ₂ DS ₂ -VASc	4.5	4.4	4.7	4.5	4.9	5.0	5.2	4.5
HAS-BLED	4.7	3.7	3.3	4	3.5	4.2	4.0	3.5
Comparator	None	None	None	None	95 patients without a history of lcrH	None	None	849 patients without a history of lcrH
Intervention	LAAO	LAAO	LAAO	LAAO	LAAO	LAAO	LAAO	LAAO
Antithrombotic treatment after LAAO	3 mo DAPT+lifelong APT	1–6 mo DAPT+6 mo APT	<6 mo of APT post-LAAO	DOAC+AT for 45 d, DAPT for 6 mo, lifelong APT	Mixed (51% DOAC, 19% DAPT, 43% OAC+APT)	DOAC for 45 d, DAPT for 6 mo, lifelong APT	6 mo APT, 56% lifelong APT	APT lifelong
Follow-up	Mean 14 mo	Median 15 mo	Median 3.6 y	Mean 13 mo	6 mo	Median 13 mo	Mean 13 mo	Mean 18 mo
Rate of ischemic stroke/thromboembolism	0	1.8%/y	3.4%/y	0	0	0	4.3%/y	Not reported
Rate of ICH	0	1.5%/y	1.9%/y	0	0	0	2%/y	Not reported

AF indicates atrial fibrillation; APT, single antiplatelet therapy; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; ICH, intracerebral hemorrhage; lcrH, intracranial hemorrhage; LAAO, left atrial appendage occlusion; OAC, oral anticoagulation; SAH, subarachnoid hemorrhage; and SDH, subdural hematoma.

Table 2. Summary of Ongoing Randomized Controlled Trials in Patients With AF Assessing Safety and Efficacy of LAAO in Different Patient Populations

Trial name	Patients with high risk of ischemic stroke		Patients with high risk of bleeding		
	ELAPSE	LAAOS-4	ASAP-TOO	STROKE-CLOSE	CLEARANCE
Trial number	https://www.clinicaltrials.gov ; Unique identifier: NCT05976685	https://www.clinicaltrials.gov ; Unique identifier: NCT05963698	https://www.clinicaltrials.gov ; Unique identifier: NCT02928497	https://www.clinicaltrials.gov ; Unique identifier: NCT02830152	https://www.clinicaltrials.gov ; Unique identifier: NCT04298723
Patient population	AF and breakthrough stroke	AF and CHA ₂ DS ₂ -VASC score ≥ 4	Patients with AF not deemed suitable for OAC	Patients with AF with a history of IcaH (<6 mo)	Patients with AF with a history of IcaH (>6 wk)
Interventional group	LAAO (any device)+DOAC	LAAO (WATCHMAN)+OAC	LAAO (WATCHMAN)	LAAO (Amulet)	LAAO (WATCHMAN)
Comparator group	DOAC alone	OAC alone	APT or no AT	OAC or APT or no AT	DOAC
Primary outcome	Recurrent ischemic stroke, SE, or CVD (superiority)	Ischemic stroke or SE (superiority)	Ischemic stroke or SE (superiority)	Stroke (ischemic or hemorrhagic), SE, life-threatening or major bleeding, or all-cause mortality (superiority)	CVD, stroke (ischemic or hemorrhagic), SE, or bleeding (BARC type 2–5)
Sample size	482–1000	4000	481	750	550
Estimated completion	2029	2029	2025	2030	2025

AF indicates atrial fibrillation; AT, antithrombotic treatment; APT, antiplatelet agent; ASAP-TOO, Assessment of the WATCHMAN Device in Patients Unsuitable for Oral Anticoagulation; BARC, Bleeding Academic Research Consortium; BMT, best medical therapy; CATALYST, Amplatzer Amulet LAAO vs NOAC; CLEARANCE, Comparison of LAA-Closure vs Oral Anticoagulation in Patients With NVAF and Status Post Intracranial Bleeding; CLOSURE-AF, Left Atrial Appendage CLOSURE in Patients With Atrial Fibrillation Compared to Medical Therapy; COMPARE-LAAO, Left Atrial Appendage Occlusion for AF Patients Unable to Use Oral Anticoagulation Therapy; CVD, cardiovascular death; DOAC, direct oral anticoagulants; ELAPSE, Early Closure of Left Atrial Appendage for Patients With Atrial Fibrillation and Ischemic Stroke Despite Anticoagulation Therapy; IcaH, intracranial hemorrhage; LAA-KIDNEY, Left Atrial Appendage Closure in Patients With Non-Valvular Atrial Fibrillation and End-Stage Chronic KIDNEY Disease; LAAO, left atrial appendage occlusion; LAAOS-4, The Fourth Left Atrial Appendage Occlusion Study; OAC, oral anticoagulation; OCCLUSION-AF, Left Atrial Appendage Occlusion Versus Novel Oral Anticoagulation for Stroke Prevention in Atrial Fibrillation; SE, systemic embolism; STROKE-CLOSE, Prevention of Stroke by Left Atrial Appendage Closure in Atrial Fibrillation Patients After Intracerebral Hemorrhage; and TIA, transient ischemic attack.

at 45 days. The Amulet device was noninferior to the WATCHMAN device for safety (14.5% versus 14.7% at 12 months) and efficacy (2.8% in both groups at 18 months), both *P* values for noninferiority <0.001. The rate of successful LAA occlusion at 45 days was high in both groups (98.9% versus 96.8%, *P*=0.003 for superiority).³⁷ The rate of major bleeding at 12 months was similar in both groups (10.6% with Amulet and 10.0% with WATCHMAN), with the majority being nonprocedure related (7.9% and 8.0%, respectively). However, the rate of procedure-related complications was higher with Amulet compared with WATCHMAN (4.5% versus 2.5%, *P*=0.02), primarily driven by an increase in pericardial effusion/tamponade.³⁷

Unresolved issues in percutaneous LAAO include the potential of peri-device leak, device-related thrombus formation, and uncertainty regarding the optimal postimplant antithrombotic regimen.⁴⁰

High-quality evidence in support of percutaneous LAAO beyond the regulatory trials is sparse. The 402-patient PRAGUE-17 trial (Interventional Left Atrial Appendage Closure vs Novel Anticoagulation Agents in Patients With Atrial Fibrillation Indicated for Long-Term Anticoagulation) claimed noninferiority of percutaneous LAAO with any approved device with direct oral anticoagulation for a primary end point that consisted of both efficacy and safety events.⁴¹ Several observational

studies aimed at comparing percutaneous LAAO versus oral anticoagulation have been published, but carry an immense risk of bias.^{42–44} The recent OPTION trial (Left Atrial Appendage Closure After Ablation for Atrial Fibrillation) enrolling 1600 patients with AF undergoing catheter ablation found that, compared with direct oral anticoagulation therapy, percutaneous LAAO was superior for a safety end point of nonprocedure-related major or clinically relevant nonmajor bleeding and noninferior for an efficacy end point of all-cause mortality, ischemic stroke or systemic embolism.⁴⁵ However, the observed rate of ischemic stroke or systemic embolism was low ($\approx 0.5\%$ per year in both groups), and the trial was not powered to demonstrate noninferiority of LAAO for the prevention of thrombotic events. In addition, only a fraction of participants (10.8%) had a history of ischemic stroke or transient ischemic attack, limiting the applicability of these findings to patients with (recent) stroke.

LAAO IN PATIENTS WITH CEREBROVASCULAR DISEASE AT HIGH RISK OF INTRACRANIAL BLEEDING

One appealing scenario for the use of LAAO for stroke prevention is as an alternative to standard of care oral

Table 2. Continued

			Patients without contraindications for OAC		
COMPARE LAAO	CLOSURE-AF	LAA-KIDNEY	CHAMPION-AF	CATALYST	Occlusion-AF
https://www.clinicaltrials.gov ; Unique identifier: NCT04676880	https://www.clinicaltrials.gov ; Unique identifier: NCT03463317	https://www.clinicaltrials.gov ; Unique identifier: NCT05204212	https://www.clinicaltrials.gov ; Unique identifier: NCT04394546	https://www.clinicaltrials.gov ; Unique identifier: NCT04226547	https://www.clinicaltrials.gov ; Unique identifier: NCT03642509
Patients with AF not deemed suitable for OAC	AF with CHA ₂ DS ₂ -VASC ≥2, HAS-BLED ≥3 or prior IcaH	AF with end-stage renal disease, with or without hemodialysis	Patients with AF recommended for OAC therapy	Patients with AF recommended for OAC therapy	Patients with AF with prior ischemic stroke or TIA
LAAO (any device)	LAAO (any device)	LAAO (Amplatzer or Amulet)	LAAO (WATCHMAN)	LAAO (Amulet)	LAAO (any device)
ATP or no AT	OAC	OAC or BMT	DOAC alone	DOAC alone	DOAC alone
Stroke (ischemic, hemorrhagic, or undetermined; superiority)	Stroke (ischemic or hemorrhagic), SE, major bleeding (BARC type 3–5), or CVD (superiority)	Net clinical benefit, defined as, time to first stroke (including ischemic or hemorrhagic strokes), SE, CVD, or major bleeding (BARC 3–5)	Stroke, SE, or CVD (noninferiority)	Ischemic stroke, SE, or CVD (noninferiority)	Stroke (ischemic or hemorrhagic), SE, major bleeding, or all-cause mortality
609	1512	430	3000	2650	750
2026	2025	2028	2027	2029	2030

anticoagulation in people with AF at increased risk of bleeding. There are several cerebrovascular comorbidities that potentially increase the risk of intracranial bleeding, for example, a history of ICH, a diagnosis of CAA, or cerebral microbleeds.

ICH is a devastating disease and is associated with high rates of permanent disability and death.^{46–49} Patients with AF are at increased risk for ICH secondary to oral anticoagulation use,^{13,50} likely mediated by the concomitant presence of bleeding-prone cerebral small vessel disease.⁵¹ AF and ICH share common risk factors, resulting in up to 25% of all patients with ICH having AF.⁵²

In general, the risk of recurrent ICH depends on the underlying cause of the ICH ranging between 1.3% and 7.4% annually,⁴⁷ with the highest risk of recurrence among those with CAA.⁵³ In patients with CAA free of ICH, the risk of ICH is also elevated as it is in patients with cerebral microbleeds but without a formal diagnosis of CAA.⁵⁴ Whether and how oral anticoagulation increases these incremental risks is currently unknown.^{55,56}

Several small randomized controlled trials compared restarting versus avoiding anticoagulation in patients with ICH but results were mainly exploratory.^{57,58} A recent individual patient data meta-analysis demonstrated that anticoagulation significantly reduces the risk of ischemic stroke, systemic embolism, and cardiovascular death (similar to the risk reduction observed in patients with AF

without ICH), but the effect on recurrent ICH was uncertain with numerically higher numbers of recurrent ICH in patients who restarted anticoagulation.¹⁸ From a patient and physician's perspective, reinitiating oral anticoagulation after an ICH event is frequently associated with fear.⁵⁶ However, when comparing the estimated risks of an ICH associated with oral anticoagulation and of a cardioembolic stroke in the absence of oral anticoagulation, the anticipated benefit of reinitiating treatment is generally felt to outweigh the risk, with both the American Stroke Association, and the American College of Chest Physicians guidelines suggest the decision be tailored to the individual patient.⁵⁹

The pivotal trials comparing LAAO with warfarin^{35,36} or direct oral anticoagulants⁴¹ excluded patients unsuitable for anticoagulation therapy (ie, with a history of ICH), and it is uncertain whether the results from these trials apply also to patients with a history of ICH, CAA, or cerebral microbleeds. Therefore, evidence on this topic is currently limited to observational data only.

LAAO Among Patients With Prior ICH

Several retrospective^{60–64} and prospective^{19,65,66} observational studies assessed the risk of recurrent ICH and ischemic thromboembolic complications. Table 1 summarizes key findings of these studies. Most studies included

a mixed population of intracranial bleedings including subdural hematoma, subarachnoid hemorrhage, and intraparenchymal/ICH with diverging follow-up periods and heterogeneous postinterventional antithrombotic treatments. Overall, 8 individual studies included 268 patients with a history of ICH. Overall, procedural success of LAAO was good, and the observed rates of both ischemic stroke/systemic embolism and recurrent ICH after LAAO were low. Post-LAAO antithrombotic therapy was heterogeneous, including short periods of oral anticoagulation or dual antiplatelet therapy and mostly lifelong single antiplatelet therapy (aspirin). Only 2 studies included a comparator group which was patients with AF who received LAAO without a history of ICH and none included any comparator arm for patients with AF and a history of ICH (ie, no treatment, antiplatelet, or anticoagulation therapy without LAAO). Overall, the risk of bias for published studies is significant due to selection and reporting bias, and study quality was low.

LAAO in Patients With Cerebral Microbleeds or a Diagnosis of CAA

Cerebral microbleeds are magnetic resonance imaging-defined lesions indicating recent or old microhemorrhages.⁵⁴ They are increasingly found in the context of cerebrovascular disease or dementia.⁵⁴ Some of them may be due to CAA but the underlying spectrum of causes is heterogeneous.⁶⁷ They are usually indicators of advanced cerebrovascular disease and associated with a high risk of both ICH and ischemic stroke.^{54,68} CAA is characterized by amyloid-beta deposits in small leptomeningeal vessels leading to vessel fragility and bleeding.⁶⁹ The diagnosis of CAA may include cerebral microbleeds using the Boston 2.0 criteria.⁷⁰

Percutaneous LAAO might have a role in this particularly vulnerable subset of patients with AF and a diagnosis of CAA. Recently, a large randomized trial assessing the role of oral anticoagulation with edoxaban in patients with AF and prior intracranial hemorrhage has stopped the recruitment of patients entering the trial with lobar intracranial hemorrhage and convexity subarachnoid hemorrhage, subtypes of intracranial hemorrhage that are often associated with CAA. After a safety review of the first 699 study participants, the Data and Safety Monitoring Board made a recommendation to stop oral anticoagulation and to not enroll any additional patients with these intracranial hemorrhage subtypes, due to an observed unacceptably high risk of hemorrhagic stroke in this group.⁷¹ In the absence of high-quality evidence, percutaneous LAAO might be an alternative for these patients, but the optimal postimplantation antithrombotic regimen remains unclear. A multicenter, observational study based out of Vanderbilt⁷² included patients with AF and probable CAA, with at least 1 lobar hemorrhage without severe hypertension, who had undergone percutaneous LAAO using any commercially available device.

Patients with a history of symptomatic ICH or who were otherwise high risk were placed on single or dual antiplatelet therapy for 6 weeks after the closure procedure while patients who had previously tolerated anticoagulation were continued for 6 weeks after the procedure. In this small study of 26 patients, 1 patient had an ischemic stroke, and another patient had a recurrent ICH.⁷²

LAAO IN PATIENTS WITH BREAKTHROUGH STROKE

Approximately 40% of all AF-related ischemic strokes occur in patients who are already on therapy with oral anticoagulants (breakthrough strokes).⁷ The risk of recurrent stroke is particularly high in those patients, with annualized rates of recurrent stroke ranging between 5% and 9%.^{10,20,73–76} Although approximately one-quarter of breakthrough strokes are related to non-AF-related stroke causes,^{77,78} the majority are cardioembolic in origin but only in part related to medication errors (ie, off-label dosing, noncompliance).⁷⁷ Current treatment strategies include switching anticoagulants between different agents or adding antiplatelet agents, without any high-quality evidence that any of these strategies reduce the risk of recurrent ischemic stroke.^{20,77,79,80} Therefore, additional treatment options are warranted. A recent matched cohort study compared 433 patients with AF who underwent LAAO after a breakthrough stroke (or systemic embolism/LAA thrombus) despite anticoagulation therapy with 433 patients with AF who continued oral anticoagulation alone after a breakthrough stroke.⁸¹ The risk of recurrent stroke was lower in patients who received LAAO compared with anticoagulation alone (hazard ratio, 0.33 [95% CI, 0.19–0.58]; $P < 0.001$). In this study, only 33% of patients continued anticoagulation therapy after LAAO. Among patients who received LAAO, the rate of recurrent stroke was numerically lower in those who continued anticoagulation therapy compared with those who stopped anticoagulation. Given the findings from LAAOS III where patients who continued anticoagulation after LAAO had the lowest risk of ischemic stroke,³³ these results suggest that combining LAAO with oral anticoagulation therapy may provide the highest risk reduction for recurrent ischemic stroke, but confirmation of this hypothesis in a randomized trial is warranted.

ONGOING TRIALS

The available evidence for percutaneous LAAO for stroke prevention is largely based on a few, relatively small randomized controlled trials with several limitations. Emerging evidence from observational studies suggests that LAAO could be a useful tool in several specific patient populations, as outlined above. Several randomized controlled trials are ongoing to evaluate the efficacy and safety of LAAO in patients with an increased risk of bleeding, as an

alternative for long-term direct oral anticoagulation therapy in patients without a contraindication and as combined therapy on top of direct oral anticoagulants in patients with a high risk of ischemic stroke (Table 2).

CONCLUSIONS

Surgical LAAO is proven to reduce the risk of stroke or systemic embolism in patients with AF undergoing cardiac surgery for another indication. Percutaneous LAAO is promising, but evidence from randomized controlled trials supporting its use is limited. However, LAAO may have great potential for several selected patient groups. Ongoing trials will determine whether percutaneous LAAO is safe and effective as an alternative to long-term anticoagulation therapy in patients with an increased risk of bleeding or a history of ICH, as an add-on to direct oral anticoagulation in patients with breakthrough stroke despite anticoagulation therapy and as an alternative to long-term anticoagulation therapy in patients without contraindications. All efforts should be made to maximize enrollment in ongoing trials to strengthen the evidence base for percutaneous LAAO.

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REVIEW

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Management of acute ischemic stroke in the emergency department: optimizing the brain

Latha Ganti^{1,2*}

Abstract

Acute ischemic stroke is a devastating condition that afflicts more than 12 million people every year. Globally, stroke is the 2nd leading cause of death and 3rd leading cause of disability worldwide. While not all patients can avail themselves of existing acute therapies, all patients can benefit from brain optimization measures. This paper details the 12 steps in the management of acute ischemic stroke in the emergency department.

Keywords Acute ischemic stroke, Blood pressure management, Thrombolysis

Introduction

As of 2019, stroke claimed 3.29 million lives worldwide. That number is expected to increase further to 4.90 million by year 2030 [1]. Stroke is a leading cause of both death and disability worldwide, and the emergency department (ED) is often the initial point of care for these patients. The approach outlined in this manuscript provides a structured and comprehensive framework for managing AIS in the ED, highlighting brain optimization measures for patients who are not eligible for thrombolysis or thrombectomy. This focus on optimizing care for the vast majority of stroke patients—who do not qualify for acute interventions—addresses a significant gap in current stroke management protocols.

The only FDA-approved therapy for acute ischemic stroke (AIS) is tissue plasminogen activator (t-PA), based on the National Institutes of Neurologic Diseases Institute study [2]. Approved in 1996, t-PA is administered as

alteplase at a dose of 0.9 mg/kg with 10% as a bolus and the remainder as an infusion. More recently, tenecteplase (at a dose of 0.4 mg/kg as a single bolus) is being used despite not having official FDA clearance for the treatment of AIS. This is due to the ease of administration and either equivalent or superior outcomes with regard to the rate of symptomatic hemorrhage, functional outcome at 90 days, and reperfusion grade after thrombectomy [3]. However, only 3–8.5% of potentially eligible patients receive thrombolytic therapy [4]. For patients with an arterial occlusion in the proximal middle cerebral artery or basilar artery, thrombectomy is another acute therapeutic intervention. A 2019 study performed at a comprehensive stroke center (CSC) found that only seven out of one hundred AIS patients were eligible for thrombectomy according to the 2018 guidelines by the American Heart Association (AHA), highlighting that a majority of AIS patients are thrombectomy-ineligible [5].

Considering the statistics above, approximately 90% of acute ischemic stroke patients do not receive any acute therapeutic options. Some of this gap may be corrected by improving patients' knowledge about stroke [6], including providing language-specific education [7, 8]. Despite this relatively large proportion of patients ineligible or unable to obtain thrombolysis or thrombectomy,

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ACUTE ISCHEMIC STROKE CARE MAP	
1	Determine time of onset of symptoms
2	Obtain noncontrast brain CT
3	Calculate NIHSS
4	Check glucose. If <60 mg/dL, give D50
5	Maintain oxygen >94%
6	Check temperature, treat fever
7	Obtain Neurology consult
8	Keep patient NPO, dysphagia screen
9	Give aspirin, unless ICH or true allergy
10	BP: maintain MAP > 100 mmHg with saline or pressors if necessary; do not lower BP unless > 220/110 mmHg unless concurrent emergency or tPA candidate
11	Obtain ancillary testing (labs, ECG)
12	Do not anticoagulate

Fig. 1 Acute stroke care map. Graphic designed by Latha Ganti on Canva.com. CT= computed tomography; NIHSS= National Institutes of Health Stroke Scale; D50= dextrose 50%; ICH= intracerebral hemorrhage; MAP= mean arterial pressure; ECG= electrocardiogram

there are many things physicians can do to optimize the actively infarcting brain. This paper will review the 12 steps in the management of acute ischemic stroke after the patient arrives at the emergency department, with a focus on brain optimization measures. This paper does not discuss the many factors that influence *which* ED the patient is transported to.

Review

The acute ischemic stroke care map is summarized in Fig. 1.

Time is brain (Fig. 2) [9]. Therefore, the emergency department evaluation of the acute stroke patient must occur swiftly as well as accurately.

Step 1: ascertain the time of onset of symptoms

The first step is to determine the time of onset of symptoms, as this effectively determines whether a patient is a tPA candidate or not. For patients who woke up with stroke symptoms, the time of onset is traced back to the last known well time, which would be when they went to bed. This is still the definition being used, even though there is good data to suggest that acute ischemic strokes, like myocardial infarctions, likely happen in the hour before awakening [10].

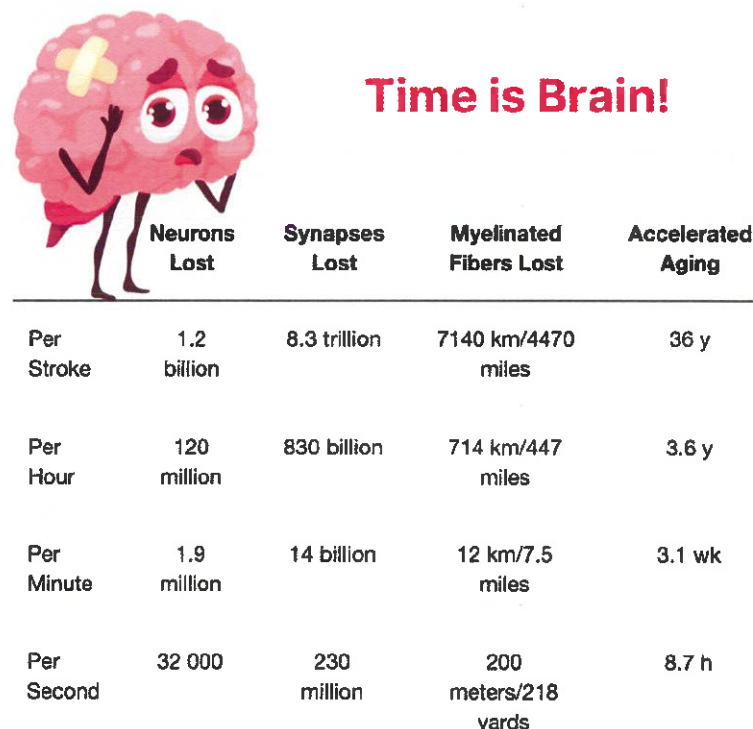


Fig. 2 Time is Brain Quantified. Data from [9]. Graphic designed by Latha Ganti on Canva.com

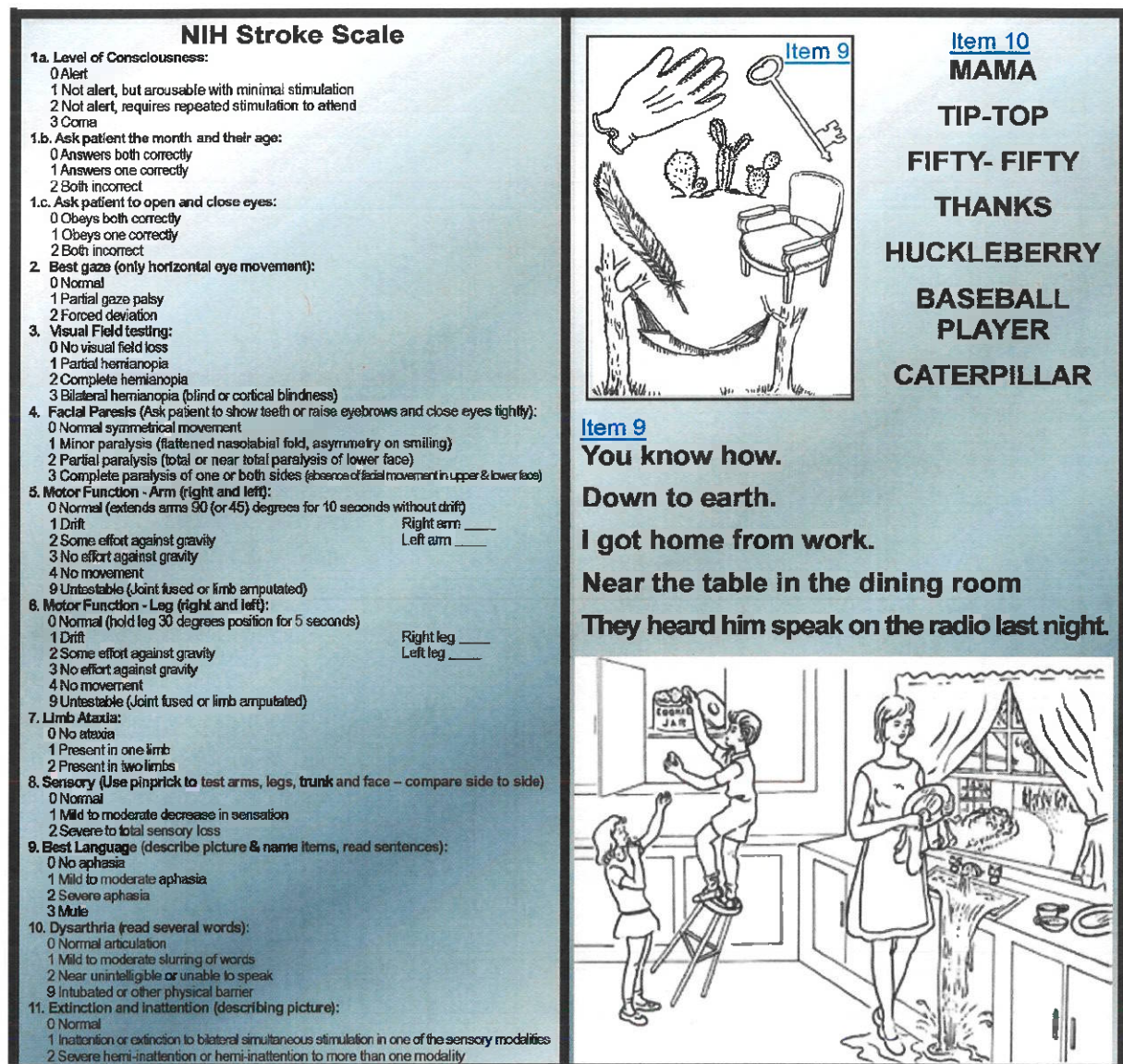


Fig. 3 A summary of the National Institutes of Health Stroke Scale [10]

Step 2: obtain non-contrast brain CT

The next step is to obtain a non-contrast brain CT. The purpose of this scan is to look for intracerebral hemorrhage (ICH), which is an absolute contraindication for thrombolysis. Only a non-contrast brain CT is needed to decide whether or not to administer tPA. CT angiography is used to look for occlusions amenable to thrombectomy, but advanced imaging should not delay tPA administration, as it is accepted that the earlier in their stroke course an eligible patient receives t-PA, the better their outcome [11].

Step 3: Perform the National Institutes of Health Stroke Scale (NIHSS)

The clinical assessment (history, general examination, and neurological examination) remains the cornerstone of the evaluation. The use of a stroke rating scale, preferably the NIHSS, is recommended [11]. The NIHSS is a 42-point scale, with higher numbers indicating worse neurologic deficits. This scale has been widely adopted in the United States, as part of hospital-wide stroke quality initiatives, and free training on the scale is available (Fig. 3).

Step 3a: If a patient is a tPA candidate, prepare thrombolytic for administration.

Step 4: check rapid bedside glucose

Hypoglycemia

Glucose is the major cerebral energy substrate in the adult brain. It is critical for synaptic activity that relies on the complex metabolic interactions between neurons and astrocytes [12]. Hypoglycemia thus disturbs cerebral metabolism, and for this reason, the brain is considered especially vulnerable to hypoglycemia due to its high metabolic demand, reliance on glucose as a primary fuel, and minimal fuel stores [12]. Hypoglycemia can mimic ischemic stroke [13]; for this reason, a rapid glucose test is the only lab test that should be performed before administering intravenous tPA [11]. Recurrent hypoglycemia has also been shown to be detrimental to brain function [14].

Hyperglycemia

Hyperglycemia has been associated with adverse prognosis following AIS [15] and is considered a marker of a more severe stroke. A review of hyperglycemia in acute ischemic stroke [16] reports that experimental data suggest that elevated blood glucose may directly contribute to infarct expansion through several maladaptive metabolic pathways, and postulate that treatment with insulin may mitigate these adverse effects. However, a Cochrane review by the same team found no evidence that tight glycemic control with insulin resulted in improved outcomes. This review included 11 randomized controlled trials and 1583 patients and found no benefit in terms of functional outcome, death, or improvement in final neurological deficit but significantly increased the number of hypoglycemic episodes. Indeed, patients whose glucose levels were maintained within a tight range with intravenous insulin experienced a greater risk of symptomatic and asymptomatic hypoglycemia [17]. Interestingly, hyperglycemia at acute stroke presentation may often represent occult diabetes [18]. A Mayo Clinic study of 446 patients reports that patients with hyperglycemia exhibited significantly greater stroke severity ($P=0.002$) and greater functional impairment ($P=0.004$) than those with normoglycemia. Patients with hyperglycemia were 2.3 times more likely to be dead at 90 days compared to those with normal glucose ($P<0.001$). Among the patients without a prior history of diabetes, patients with hyperglycemia were 3.4 times more likely to die within 90 days ($P<0.001$) [18]. Persistent hyperglycemia (>200 mg/dL) during the first 24 h is an independent predictor for ischemic stroke expansion and poor neurological outcome [11].

Step 5: check room air oxygen saturation

The goal of oxygen therapy is to prevent hypoxia, which can potentially worsen the brain injury caused by ischemia. Partial airway obstruction, hypoventilation, aspiration pneumonia, and atelectasis are the most common causes of hypoxia in the AIS patient. Supplemental oxygen should be provided to maintain oxygen saturation $>94\%$. Nonhypoxic patients with acute ischemic stroke do not need supplemental oxygen therapy [11]. There is also no evidence that hyperbaric oxygen provides any benefit for the routine AIS patient. There is potentially a role for hyperbaric oxygen for a stroke secondary to air embolization [19].

Step 6: check temperature

Pyrexia is a common phenomenon following AIS as well as intracerebral hemorrhage (ICH). It is associated with worse clinical outcomes, including longer length of stay (LOS), higher mortality, and disability [20].

A retrospective cohort study of 9366 patients with AIS found that peak temperature in the first 24 h $<37^{\circ}\text{C}$ and $>39^{\circ}\text{C}$ was associated with an increased risk of in-hospital death compared to normothermia [19].

The source of the fever should be ascertained. It could be secondary to concurrent infection such as pneumonia or urinary tract infection, or it may be a manifestation of cerebral disturbance, as is common with brainstem strokes. Regardless of etiology, it is important to treat fever. The best way to do this is with oral or rectal aspirin. The rectal route is preferred if a swallow screen is not cleared or there is any concern for dysphagia. Acetaminophen can also be used to treat fever and comes in both oral and rectal forms; however, aspirin has the added advantage of reducing the risk of future ischemic events. While targeted temperature management is popular for cardiac arrest, devices such as cooling helmets have not shown a clear benefit in AIS, based on a systematic review of 46 cooling helmet studies [21]. Controversial data exists regarding hypothermia and insufficient evidence exists to recommend hypothermia for the treatment of patients with AIS according to a Cochrane review of 426 patients [22].

Step 7: neurology consultation (if available)

While the decision of whether or not to give tPA is well within the emergency physician's domain, in a busy emergency department, having an additional colleague to help with the acute stroke patient can be extremely helpful. In a prospective cohort of 107 patients, an emergency department-based study reported that the lack of a dedicated stroke team was significantly associated with longer door-to-needle times for stroke management [23].

Table 1 Antihypertensive drug options for treating hypertension in acute ischemic stroke (> 220/110 mmHg in non-tPA candidates and > 185/105 mmHg in t-PA candidates; caveats for concurrent select hypertensive emergencies)

Drug	Dose	Onset of action	Elimination half life	Duration of action	Contra-indications	Caution
Labetalol	10–20 mg IV over 1–2 min, may repeat 1 time	2–5 min	5.5 h	4 h	Bradycardia, 2nd or third-degree heart block, severe asthma	
Clevidipine	1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h	2–4 min	1 min	5–15 min		Lipid emulsification can result in hypertriglyceridemia
Nicardipine	5 mg/h IV, titrate up by 2.5 mg/h every 5–15 min, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits	5–10 min	40–60 min	15–90 min	Severe aortic stenosis	Cumulative doses can result in cyanide toxicity
Enalaprilat	1.25 mg/dose given over 5 min every 6 h	<15 min	35 h	6 h	history of angioedema related to an ACE inhibitor; bilateral renal artery stenosis	Not easily titratable, long half life

Optimal BP in acute ischemic stroke: MAP between 90–130 mmHg

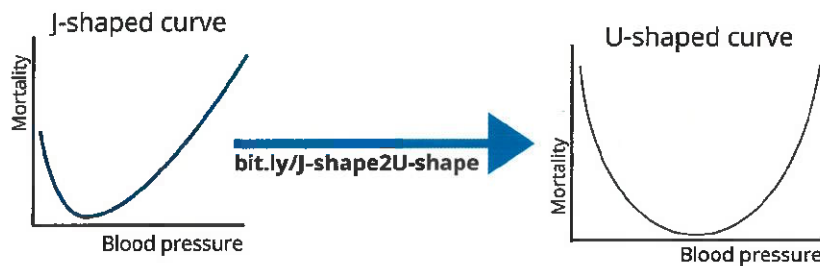


Fig. 4 The “sweet spot” for blood pressure in acute ischemic stroke follows a U-shaped curve [32]

Consultation could occur in person or via telemedicine depending on the local hospital resources.

Step 8: keep patients NPO (nothing per ore)

It is important to keep acute stroke patients NPO, because impairments of swallowing are associated with a high risk of aspiration pneumonia and increased risk of death. A review of 42 studies with 26,366 participants found that post-stroke dysphagia was associated with a higher pooled odds ratio (OR) for risk of pneumonia 4.08 (95% CI, 2.13–7.79) and mortality 4.07 (95% CI, 2.17–7.63) [24]. Patients with infarctions of the brain stem, multiple strokes, major hemispheric lesions, or depressed consciousness are at the greatest risk for aspiration [25]. Risk factors for aspiration include an abnormal gag reflex, impaired voluntary cough, dysphonia, incomplete oral-labial closure, more severe strokes, and cranial nerve palsies. It is important to note that a preserved gag reflex may not indicate safety with swallowing.

Step 9: Antiplatelet agents

A Cochrane review covering 11 studies involving 42,226 participants reported that treatment with aspirin 160–325 mg resulted in decreased odds of death or dependency at six-month follow-up. The number needed to treat is 79, so for every 1000 people treated with aspirin, 13 people would avoid death or dependency [26]. For patients who have an ischemic stroke while already on aspirin therapy, an alternate antiplatelet agent such as clopidogrel is given. Studies have also investigated the use of dual antiplatelet therapy (DAPT). A Cochrane review encompassing 15 studies and 17,091 patients found that DAPT was more effective in reducing stroke recurrence but increased the risk of hemorrhage compared to a single antiplatelet agent. However, the systematic review concluded that the benefit in the reduction of stroke recurrence seems to outweigh the harm of dual antiplatelet agents initiated in the acute setting and continued for one month [27]. Based on these data, the

AHA recommends that in patients presenting with a high risk minor stroke or transient ischemic attack, treatment for 21 days with dual antiplatelet therapy (aspirin + clopidogrel) initiated within 24 h can be beneficial for early secondary stroke prevention for a period of up to 90 days from symptom onset [11].

Step 10: blood pressure management

The normal cerebral blood flow (CBF) in the human brain is approximately 50–60 mL per 100 g of tissue per minute [28]. When cerebral blood flow drops to 50%, synaptic transmission stops, and cerebral energy use decreases by 50%. This represents the penumbra area of an infarct. At this point, autoregulation fails and the ischemic brain becomes dependent on systemic circulation for perfusion [29]. Autoregulation is the brain's ability to maintain its cerebral perfusion pressure irrespective of what is happening to the systemic blood pressure. Once autoregulation fails, cerebral perfusion pressure (CPP) is directly dependent on systemic blood pressure [30]. Therefore, decreasing systolic blood pressure in acute ischemic stroke can be detrimental to the

Table 2 Contraindications to t-PA for acute ischemic stroke

Evidence of intracerebral hemorrhage (ICH) on non-contrast brain CT scan or any history of ICH in the past

Ischemic stroke within the last 3 months
Severe head trauma within 3 months
Signs and symptoms consistent with subarachnoid hemorrhage
Gastrointestinal (GI) malignancy or GI bleed within 21 days
Coagulopathy: platelet count < 100,000/mm ³ , INR > 1.7, aPTT > 40 s, PT > 15 s
Dose of low molecular weight heparin taken in last 24 h
Dose of direct thrombin inhibitor or factor Xa inhibitor taken in last 48 h
Presence of infective endocarditis, intracranial neoplasm, or aortic arch dissection

Recommendations summarized from [10]. CT Computed tomography, INR International normalized ratio, aPTT activated partial thromboplastin time, PT Prothrombin time

ischemic brain, extending the area of infarct. This is why one should not acutely decrease blood pressure in acute ischemic stroke. Emergency administration of an antihypertensive agent should be withheld in ischemic stroke unless the systolic blood pressure is greater than 220 mm Hg or the diastolic blood pressure is greater than 120 mm Hg. Additional indications for acute antihypertensive administration would include if there is a concurrent hypertensive emergency (such as acute aortic dissection) or if the patient is a tPA candidate [11]. If the patient is a t-PA candidate, then the blood pressure should be lowered to 185/110 mmHg. When a blood pressure-lowering agent is given, it should be lowered no more than 15% in the acute period. Several antihypertensive agents are available [Table 1], but none of them have been compared

in randomized controlled trials. Rather, they are consensus-based guidelines. Agents that are not recommended for blood pressure treatment in acute ischemic stroke are hydralazine and nitroglycerin, due to their vasodilatory properties that can result in an extension of the area of infarct. Hydralazine raises intracranial pressure, which, together with its effect upon systemic blood pressure, reduces cerebral perfusion pressure [31]. It is important to note that in the majority of patients, a decline in blood pressure occurs within the 1st few hours after stroke without any specific medical treatment.

In addition to elevated blood pressure, the lower end of blood pressure is also equally important. A Mayo Clinic study of 357 consecutive ED patients was one of the first to demonstrate the detrimental impact of low

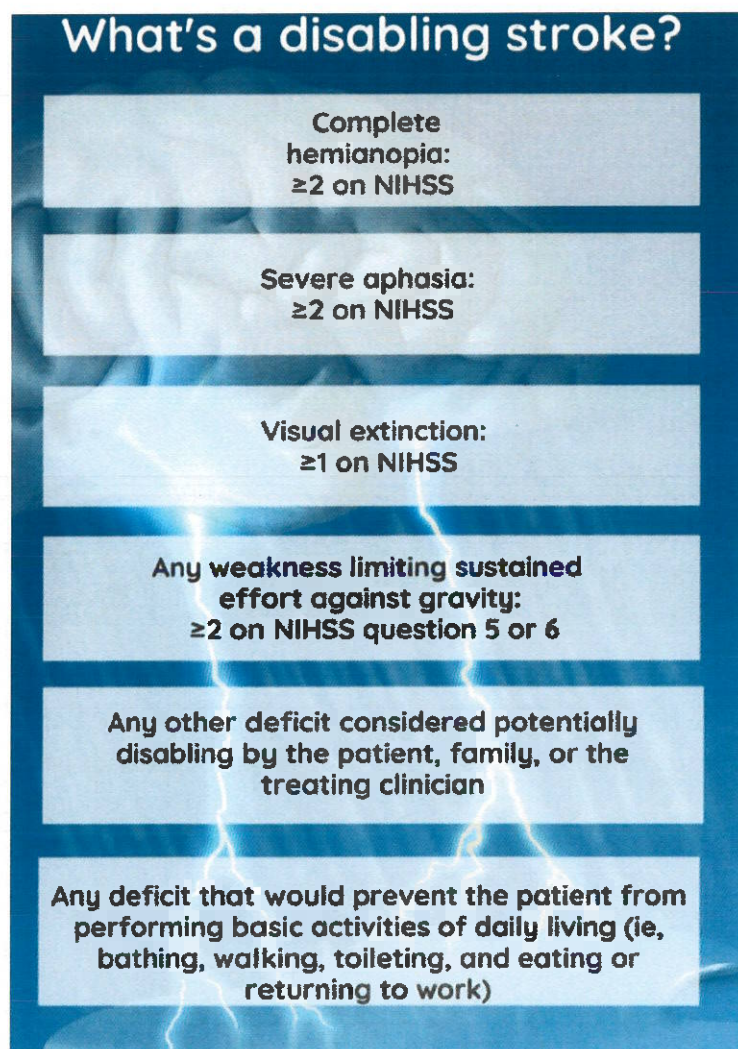


Fig. 5 Elements of a non-disabling stroke. Infographic designed by Latha Ganti on Canva.com based on data from [34]

pressure on acute stroke outcomes. The study reported that patients with low BP (dBP <70, sBP <155, or MAP <100 mm Hg) were significantly more likely to die within 90 days than those with BP in the normotensive or mildly hypertensive range (dBP 70 to 105, sBP 155 to 220, MAP 100 to 140 mm Hg). These associations were significant even after adjusting for age, sex, and NIHSS score [32]. This led to the paradigm shift of thinking of the blood pressure and stroke outcome as a U-shaped curve, rather than a J-shaped curve (Fig. 4). This study was followed by several other similar studies leading to the updated American Stroke Association (ASA) recommendation supporting the treatment of low blood pressure with intravenous fluids and/or pressors as needed to maintain systemic perfusion levels necessary to support organ function [11].

Step 11: Obtain ancillary testing

Ancillary studies can decipher systemic conditions that may mimic or cause stroke or identify systemic conditions that may influence therapeutic options. Routine labs in the evaluation of acute ischemic stroke include a complete blood count (CBC), electrolyte panel, liver function tests (LFTs), coagulation studies, and sometimes troponin level measurement. Many patients receive their primary diagnosis of hypertension, diabetes, hypothyroidism, or heart disease at the time of presentation for acute stroke. Because the medications utilized to treat these conditions are cleared either through the kidney or the liver, having a chemistry panel and LFTs are useful to provide a baseline. Determination of the platelet count and, in patients taking

warfarin or with liver dysfunction, the prothrombin time (PT) and international normalized ratio (INR) is important. A CBC can reveal leukocytosis or anemia, both of which can exacerbate symptoms or provide clues to other underlying conditions. An electrocardiogram is also routinely obtained in an acute stroke evaluation.

Step 12: do not anticoagulate

Until about 20 years ago, acute ischemic strokes would receive prompt anticoagulation. Since then, a Cochrane review including 28 trials involving 24,025 participants [33] has informed us that early administration of anticoagulants does not lower the risk of early recurrent stroke, even among patients with cardioembolic stroke. Anticoagulants do not lessen the risk of neurological worsening. There is also no adequate data to demonstrate the efficacy of anticoagulants in potentially high-risk groups such as patients with intracardiac or intraarterial thrombi, making no early anticoagulation a level I recommendation by the American Stroke Association (ASA) [11]. Current data do not support the routine use of any of the currently available anticoagulants for acute ischemic stroke.

Thrombolytics

Patient who present within 4.5 h of symptom onset should be considered for thrombolytic therapy. Indications include age of 18 years or older, being within the drug time window, and having signs and symptoms compatible with a stroke. Several contraindications to thrombolysis exist [Table 2].

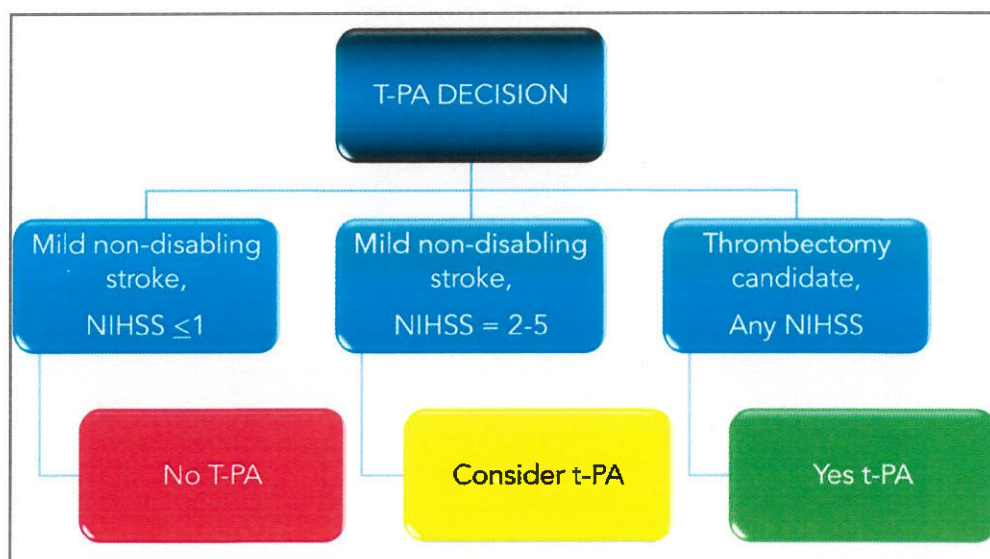


Fig. 6 algorithm for treatment of mild acute Ischemic strokes with NIHSS < 6

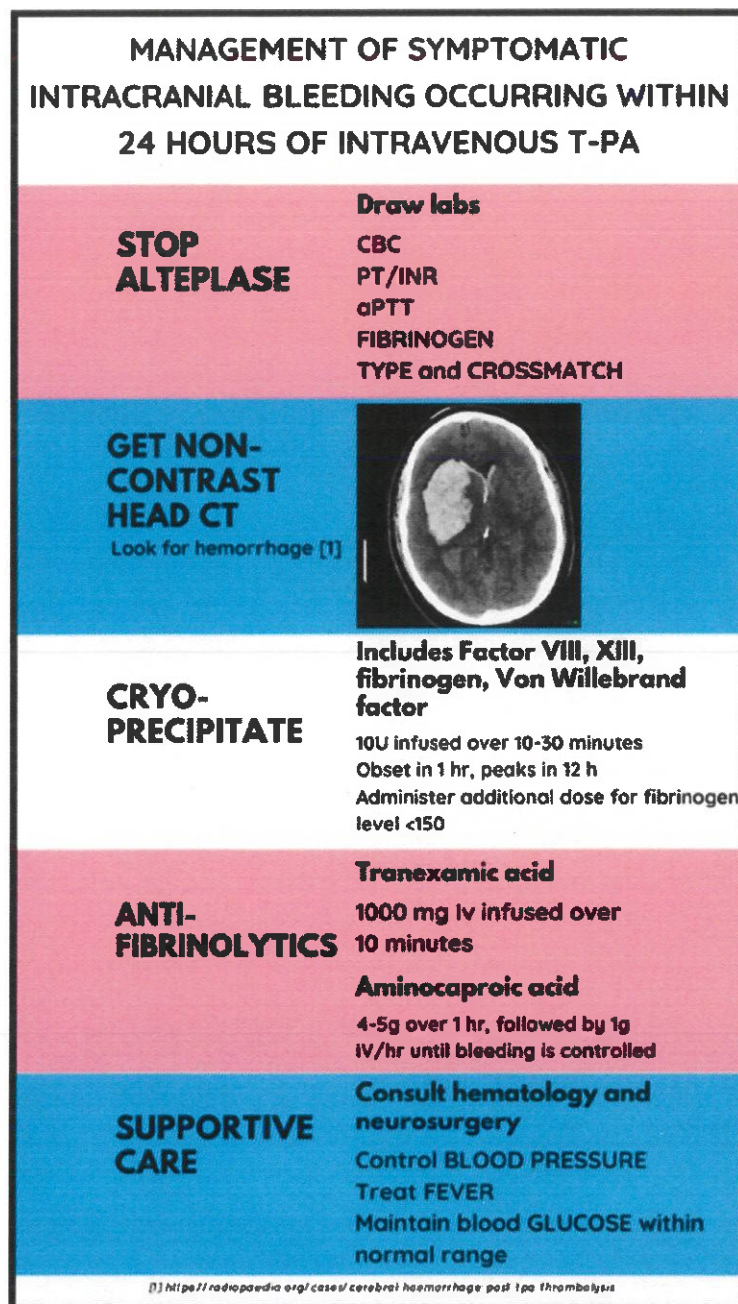


Fig. 7 Management of symptomatic intracranial hemorrhage in the first 24 h after alteplase administration. Infographic designed by Latha Ganti on Canva.com based on data from [11]

Over the last few guideline iterations, the number of contraindications for t-PA has decreased, leading to more widespread use. For the first time, however, this latest guideline [11] adds a contraindication – the presence of a mild *non-disabling* stroke; administering t-PA to these patients is not recommended as it may actually cause

harm. This recommendation is informed by the PRISMS study, a double-blind, controlled, randomized, multicenter trial of 313 patients with NIHSS 0–5 and non-disabling stroke presentations with a baseline modified Rankin score of 0–1. This study showed no clear benefit with tPA over aspirin for non-disabling strokes and an

increased risk for brain hemorrhage with tPA [34]. While it is sometimes difficult to define what is non-disabling, there is agreement on what constitutes a disabling stroke (Fig. 5).

This was followed by a study of an Austrian Stroke Unit prospective registry (ASUR) comprising 39 Austrian stroke units, $N=140,000$, that dichotomized patients into those with mild strokes NIHSS 0–1 and NIHSS 2–5 [35]. This study reports that early neurological deterioration occurred in 10% of the intravenous thrombolysis (IVT) arm vs. no-IVT arm, patients undergoing IVT experienced more significant shifts in mRS and had increased mortality after 8 months and were less likely to have a NIHSS of 0 at discharge and mRS of 0 at 3 months.

The MaRISS study [36] also examined mild strokes in 1736 patients with NIHSS 0–5 using registry-based data from over 100 hospitals in the Get with the Guidelines® database. After adjusting for age, sex, race/ethnicity, and baseline NIHSS, investigators did not identify an effect of alteplase on the primary outcome (mRS 0–1 at 90 days) but did find an association with Stroke Impact Scale-16 in the restricted sample of baseline NIHSS score 3–5. Figure 6 summarizes the t-PA treatment decision for mild strokes.

One known and feared complication of thrombolysis in AIS is symptomatic intracranial hemorrhage [37]. The typical incidence quoted is ~6% [2], but this risk is higher for those with certain co-morbidities [38]. A 2023 systematic review of 105 studies concluded that there is moderate level evidence for the following being associated with a greater risk of ICH after thrombolysis for AIS: higher NIHSS, older age, diabetes, hyperglycemia, difficult-to-control hypertension, early ischemic changes on initial CT, larger areas of infarct, atrial fibrillation, antiplatelet therapy, or anticoagulant therapy. This review also found the same moderate level of evidence for leukoaraiosis, proteinuria, and elevated levels of fibrinogen, creatinine, and homocysteine, which are traditionally not included in the standard risk assessment [39]. When symptomatic ICH following thrombolysis does occur, a non-contrast brain CT is obtained to ascertain the extent of bleeding. Cryoprecipitate and antifibrinolytic therapy are given to control hemorrhage. Brain optimization measures discussed above are instituted, and specialty consultations are obtained as appropriate (Fig. 7).

Rarely, t-PA administration can result in an allergic reaction, usually manifested as angioedema. In this case, the t-PA (alteplase or tenecteplase) is immediately discontinued, if still infusing. This is followed up by standard ED treatment of histamine-mediated allergic reactions including 125 mg methylprednisolone IV, 50 mg diphenhydramine IV, and sometimes an intravenous H_2 blocker.

Angioedema can also result from a bradykinin-mediated mechanism, which is treated with a C1-esterase inhibitor, ecallanotide, or icatibant, as available. Fresh frozen plasma may be given if no bradykinin-mediated angioedema medications are available [40].

Conclusion

An acute ischemic stroke is the ultimate medical emergency with more than a million neurons lost every minute. Thrombolysis and thrombectomy are two acute interventions with demonstrated efficacy. However, these are only options for a select minority of emergency department AIS patients – those who are at the right place at the right time. Patients need to present within a few hours of symptom onset and/or have a clot in a location amenable to thrombectomy. Nonetheless, brain optimization measures, including optimizing blood pressure, glucose, oxygen, and temperature and being mindful of ancillary studies are part of the acute stroke care map that can benefit *all* stroke patients.

Authors' contributions

LG drafted the manuscript.

Funding

No funding was received for this study.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Competing interests

Dr. Ganti has an editorial role at Springer.

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ORIGINAL CONTRIBUTION

Management Strategies for Early Neurological Deterioration in Noncardioembolic Ischemic Stroke

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BACKGROUND: Early neurological deterioration (END) is a frequent complication of acute ischemic stroke. Although END worsens clinical outcomes, standardized treatment strategies remain undefined, resulting in variability in clinical practice. This study examines real-world treatment patterns for END and compares the effects of different strategies on neurological and functional outcomes.

METHODS: This study analyzed data from a nationwide, prospective, multicenter stroke registry in South Korea, including patients with noncardioembolic stroke who developed END due to stroke progression between January 2019 and August 2024. END was defined as new or worsening neurological symptoms meeting National Institutes of Health Stroke Scale criteria (≥ 2 -point total or ≥ 1 point in consciousness or motor subscores) with radiological confirmation. Patients were classified into conservative management, antithrombotics change, and induced hypertension (iHTN). The primary outcomes were neurological improvement, defined as a ≥ 2 -point reduction in the National Institutes of Health Stroke Scale score, and 3-month functional outcome measured by modified Rankin Scale ordinal shift. Secondary outcomes included good functional recovery (modified Rankin Scale score, 0–2) and composite vascular events (death, stroke, and myocardial infarction). Multivariable analyses adjusted for age, sex, prestroke modified Rankin Scale, initial National Institutes of Health Stroke Scale score, vascular risk factors, the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification, acute thrombolysis, and laboratory covariates.

RESULTS: Among 3067 patients with END due to stroke progression, 1840 (60.0%) received conservative management, 747 (24.4%) underwent antithrombotic changes, and 480 (15.7%) were treated with iHTN. Neurological improvement occurred in 34.2% of patients, with the highest in the iHTN group (41.5%) compared with the conservative (32.2%) and antithrombotics change groups (34.4%; $P < 0.001$). In adjusted analyses, iHTN increased the odds of neurological improvement (adjusted odds ratio, 1.55 [95% CI, 1.25–1.92]) and a favorable 3-month modified Rankin Scale shift (adjusted odds ratio, 1.24 [95% CI, 1.03–1.48]) compared with conservative management, particularly in patients with large artery atherosclerosis. Antithrombotics change showed no significant association with neurological or functional recovery.

CONCLUSIONS: In patients with noncardioembolic ischemic stroke who developed END due to stroke progression, iHTN was associated with favorable clinical outcomes.

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

Key Words: fibrinolytic agents ■ hypertension ■ ischemic attack, transient ■ ischemic stroke ■ thrombosis

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Nonstandard Abbreviations and Acronyms

aOR	adjusted odds ratio
CRCS-K	Clinical Research Collaboration for Stroke-Korea
END	early neurological deterioration
HR	hazard ratio
iHTN	induced hypertension
LAA	large artery atherosclerosis
mRS	modified Rankin Scale
NI	neurological improvement
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
SVO	small vessel occlusion
TOAST	Trial of Org 10172 in Acute Stroke Treatment

Early neurological deterioration (END) occurs in ≈10% to 40% of patients during the acute ischemic stroke and is strongly associated with prolonged hospitalization, long-term disability, and increased mortality.^{1–4} Despite its clinical importance, treatment strategies for END remain largely empiric. In current practice, management decisions are often based on individual clinician preference rather than standardized guidelines, resulting in considerable variability in care.^{5,6} Moreover, there is a notable lack of high-quality evidence comparing the effectiveness of different treatment approaches, highlighting the need for systematic investigation.

When systemic medical causes are excluded, END is commonly attributed to stroke progression, recurrence of stroke, symptomatic hemorrhagic transformation, or malignant edema, with stroke progression being the most frequent cause.^{5,7,8} END due to stroke progression is typically driven by infarct expansion or perilesional edema due to hypoperfusion or thrombus propagation.^{8,9} Based on this pathophysiology, treatment strategies such as induced hypertension (iHTN) or the intensification of antithrombotic therapy have been proposed to augment cerebral perfusion and potentially confer neuroprotective benefits.

Although limited studies suggest that these strategies may improve neurological outcomes in patients with END,^{10–12} their clinical application remains inconsistent, and clear guidance, particularly in the context of noncardioembolic stroke, is lacking. Most importantly, the comparative effectiveness of these different treatment approaches has not been systematically assessed in real-world practice.

Therefore, this study aimed to address this evidence gap by focusing on patients with noncardioembolic ischemic stroke who develop END due to stroke progression. We investigate the real-world practice of 3 commonly

applied management strategies, conservative treatment, change in antithrombotic therapy, and iHTN, and compare their associations with early neurological improvement (NI) during hospitalization and functional outcomes at 3 months.

METHODS

Data Availability

The data used in this study are available upon reasonable request following the submission of a legitimate academic research proposal to be assessed by the Clinical Research Collaboration for Stroke-Korea (CRCS-K) Steering Committee. One may request to contact the corresponding author regarding data availability.

Study Design and Subjects

This study was conducted using data from the CRCS-K registry, a prospective, multicenter, nationwide, Web-based database that includes consecutive patients with acute stroke or transient ischemic attack admitted to 20 academic hospitals across South Korea. Detailed information on the CRCS-K registry has been reported previously.^{13,14} Regular monitoring and systematic audits were performed to ensure and enhance data quality. Prospective collection of information on END management began in January 2019.

Eligible patients met the following criteria: (1) admission for an acute cerebrovascular event between January 2019 and August 2024; (2) a diagnosis of acute ischemic stroke or transient ischemic attack within 7 days of symptom onset; (3) classification as having noncardioembolic stroke according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria¹⁵; (4) documented occurrence of END during hospitalization; and (5) END specifically attributed to stroke progression. Patients were excluded if END was due to symptomatic hemorrhagic transformation, malignant cerebral edema, or other nonischemic causes. In addition, cases were excluded if END management involved intracranial pressure control (eg, hyperosmolar therapy, decompressive craniectomy, or hypothermia), reperfusion therapy, or bypass surgery. The flowchart of the study is presented in [Figure S1](#).

This study was conducted and reported in accordance with the Strengthening of Reporting of Observational Studies in Epidemiology guidelines.

Definition of END and Subtypes

END was defined as any new neurological symptoms or worsening of neurological status meeting at least 1 of the following criteria: (1) an increase in the total National Institutes of Health Stroke Scale (NIHSS) score by >2 points; (2) an increase in the NIHSS subscore for level of consciousness by >1 point; or (3) an increase in the NIHSS subscore for motor function by >1 point. These changes had to occur during hospitalization due to the index stroke and within 3 weeks of symptom onset.^{16,17}

In our study, we included patients with END attributable to stroke progression, as this is the most frequent mechanism of END and represents a potentially modifiable target for therapeutic intervention.⁸ END attributable to stroke

progression was defined as deterioration caused by progressive ischemia, swelling of the infarcted tissue, or perilesional edema in the initially affected vascular territory, as confirmed on follow-up imaging. The neurological worsening had to persist for more than 24 hours. We used an END cohort previously described in the literature, where neurological worsening due to nonvascular causes (eg, seizures, infections, or medical complications) was systematically categorized separately and excluded from the definition of END applied in this study.⁸

END Management

END management strategies were classified into 3 categories. The conservative group included patients who continued preexisting medications without change, underwent dose reductions or discontinuation, or received intravascular volume expansion after the onset of END. The antithrombotics change group comprised patients with whom antithrombotic therapy was modified after the occurrence of END. This included switching to a different combination of oral antiplatelet regimen, adding additional medication to the ongoing antithrombotic therapy, or initiating parenteral anticoagulants or antithrombotics such as direct thrombin inhibitors or glycoprotein IIb/IIIa inhibitors. The iHTN group was defined as those who received intravenous vasopressors to raise systolic blood pressure, generally by 10% to 20% above baseline levels, according to each participating center's protocol, which was informed by prior studies.¹¹ In South Korea, there are currently no standardized guideline recommendations for the management of END. The use of various treatment strategies, including iHTN, was determined at the discretion of each treating physician and participating center.

Data Collection

Demographic, clinical, and laboratory data were collected prospectively. NIHSS scores were assessed at admission by the attending physician and re-evaluated by the stroke physician or stroke team whenever neurological changes were observed. Stroke subtypes were classified according to the TOAST criteria as large artery atherosclerosis (LAA), small vessel occlusion (SVO), undetermined cause, or other determined cause.¹⁵ The classification of ischemic stroke subtypes was based on magnetic resonance imaging–based algorithms.¹⁶ The modified Rankin Scale (mRS) score and poststroke vascular events (stroke, myocardial infarction, and death) were prospectively assessed at 3 months after discharge by physicians and nurses at participating centers who were trained and certified in a standardized manner through a Web-based education system. Structured clinic visits or telephone interviews were conducted according to the predefined protocol. Regular on-site audits and data monitoring by the outcome adjudication committee ensured data quality and intercenter consistency. A detailed description of these standardized assessment procedures has been reported previously.^{13,14} To further examine the robustness of our findings, subgroup analyses were performed for the primary outcomes according to baseline characteristics that could plausibly influence treatment selection or outcomes, including age (<70 versus ≥70 years), the presence of hypertension, the presence of coronary heart disease, and baseline NIHSS score (≤4 versus >4).

Outcome

The primary outcomes were (1) NI, defined as an improvement of >2 points in the NIHSS score between the time of END and discharge and (2) the 3-month functional outcome assessed using an ordinal shift analysis of the mRS. Secondary outcomes included good functional outcome at 3 months (defined as mRS score, 0–2), composite vascular outcome comprising stroke recurrence, myocardial infarction, and all-cause death, as well as the individual components of this composite outcome. Subgroup analyses of the primary outcomes were also performed according to the TOAST classification.

Ethic Statement

Clinical information was collected from the CRCS-K registry with approval from the local institutional review boards of all participating centers. A waiver for informed consent was provided because of study subject anonymity and minimal risk to the participants. The current study was approved by local institutional review boards at all participating centers, including Chonnam National University Hospital (CNUH-2025-234).

Statistical Analysis

Baseline characteristics and outcomes were compared among the different END management groups using the χ^2 test, the ANOVA, or the Kruskal-Wallis test, as appropriate for the type of variable. The following parameters had missing data that were substituted using median values: hemoglobin (0.03%), low-density lipoprotein (0.5%), and glycated hemoglobin (1.0%). The event probabilities of NI during hospitalization, ordinal shift in mRS scores at 3 months, good functional outcome (mRS score, 0–2), and 3-month vascular outcomes were estimated using the Kaplan-Meier method, and differences among the groups were assessed using the log-rank test. These analyses were performed both in the overall cohort and within subgroups based on stroke subtype.

Odds ratios (ORs) or hazard ratios (HRs) with 95% CIs were calculated for the following outcomes: NI during hospitalization, ordinal shift in the mRS score at 3 months, good functional outcome (mRS score, 0–2), and 3-month vascular outcomes. Binary logistic regression analysis was used for NI and good functional outcome, while ordinal logistic regression was applied for the analysis of mRS shift. The Cox proportional hazards model was used to evaluate 3-month vascular outcomes. All analyses were performed separately for each END management group. Covariate adjustments included age, sex, prestroke mRS, initial NIHSS, comorbidities (history of hypertension, diabetes, prior stroke, dyslipidemia, and coronary heart disease), TOAST classification, acute thrombolytic therapy, and any variables with a *P* value <0.1 in baseline comparisons.

Two-sided *P* <0.05 was considered statistically significant. All statistical analyses were conducted using R software with the rms package (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria) and SAS, version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

General Characteristics

The mean follow-up duration of patients was 90.7±7.8 days. A total of 3067 patients (age, 70.0±13.0 years;

male, 58.0%) with END due to stroke progression were included in the analysis. Of these, 1840 (60.0%) were managed conservatively, 747 (24.4%) underwent antithrombotic changes, and 480 (15.7%) were treated with iHTN. The median NIHSS score was 4 (2–6) at admission, 7 (4–9) at the time of END, and 6 (3–9) at discharge. According to the TOAST classification, LAA was the most frequent subtype, accounting for 54.5% of patients ($n=1670$).

Across the treatment groups, the antithrombotic change group had a lower NIHSS score at admission (median, 3 [2–6]) compared with the conservative group (4, [2–7]) and the iHTN group (4, [2–6]; $P<0.001$). The history of hypertension was more common in the conservative (71.7%) and antithrombotic change (71.1%) groups, and less common in the iHTN group (59.4%; $P<0.001$). Coronary heart disease was most prevalent in the conservative group (9.4%) and least in the iHTN group (4.0%; $P<0.001$). The iHTN group had the highest proportion of LAA subtype (64.0%; $P<0.001$). Acute reperfusion therapy was most frequently performed in the conservative group (18.2%; $P<0.001$; Table 1).

Primary Outcomes

Among the total study population, 1049 (34.2% [95% CI, 32.5–35.9]) achieved NI. The proportion of patients with NI was 32.2% (95% CI, 30.1–34.4) in the conservative group, 34.4% (95% CI, 31.0–37.9) in the antithrombotic change group, and 41.5% (95% CI, 37.0–46.0) in the iHTN group, with differences observed among groups ($P<0.001$). While the median 3-month mRS score was similar across groups (3 [interquartile range, 2–4]), the overall distribution differed ($P<0.001$; Table 2).

In the crude analysis, patients in the iHTN group were more likely to achieve NI compared with those in the conservative group (OR, 1.49 [95% CI, 1.21–1.83]) and also showed greater improvement in functional outcomes (OR, 1.55 [95% CI, 1.30–1.84]). The antithrombotic change group did not show an association with NI but was associated with improved functional outcomes (OR, 1.28 [95% CI, 1.10–1.48]). After adjustment for potential confounders, only the iHTN group remained significantly associated with increased odds of NI (adjusted OR [aOR], 1.55 [95% CI, 1.25–1.92]) and a favorable functional outcome shift (aOR, 1.24 [95% CI, 1.03–1.48]) compared with the conservative group (Table 3). Groupwise differences in mRS distributions are illustrated in Figure 1.

Secondary Outcomes

Overall, 1134 (37.0% [95% CI, 35.3–38.7]) of patients achieved a good functional outcome (mRS score, 0–2) at

3 months. The iHTN group had the highest rate at 42.1% (95% CI, 37.6–46.6), with a difference observed across treatment groups ($P=0.015$; Table 2). In crude analysis, patients in the iHTN group were more likely to achieve a good functional outcome compared with conservative management (OR, 1.34 [95% CI, 1.09–1.64]), but this association was not statistically significant after multivariable adjustment (aOR, 1.17 [95% CI, 0.92–1.48]; Table 3).

Composite vascular events within 3 months occurred in 294 (9.7% [95% CI, 8.6%–10.7%]) of all patients, with event rates of 11.3% (95% CI, 9.8%–12.7%) in the conservative group, 8.2% (95% CI, 6.3%–10.2%) in the antithrombotic change group, and 5.9% (95% CI, 3.8%–8.0%) in the iHTN group, showing a difference among groups ($P<0.001$). Overall mortality was 6.5% (95% CI, 5.6%–7.3%), with event rates of 8.1% (95% CI, 6.9%–9.4%) in the conservative group, 4.8% (95% CI, 3.3%–6.4%) in the antithrombotic change group, and 2.6% (95% CI, 1.1%–4.0%) in the iHTN group ($P<0.001$). The incidence of recurrent stroke and myocardial infarction was low across all groups, with no differences observed (Table 2).

In the crude analysis, both the antithrombotic change group (HR, 0.72 [95% CI, 0.54–0.96]) and the iHTN group (HR, 0.51 [95% CI, 0.34–0.76]) were associated with a lower risk of composite vascular events compared with the conservative group. Similarly, both the antithrombotic change group (HR, 0.57 [95% CI, 0.40–0.83]) and the iHTN group (HR, 0.30 [95% CI, 0.17–0.55]) were associated with reduced mortality risk. However, after multivariable adjustment, iHTN was associated with a lower risk of mortality (adjusted HR, 0.50 [95% CI, 0.28–0.92]), whereas no significant association was observed in composite vascular events (adjusted HR, 0.67 [95% CI, 0.45–1.01]). In the antithrombotic change group, the risk differences observed in the crude analysis were no longer evident after adjustment for confounders (Table 4). Survival curves for vascular outcomes are presented in Figure 2.

Outcomes According to TOAST Classification

In patients with LAA ($n=1670$), the iHTN group showed higher rates of good mRS score (0–2) at 3 months (42.0% versus 31.1%; $P=0.002$) and NI (41.4% versus 31.9%; $P=0.007$) compared with the conservative group. For those with SVO ($n=604$), the proportion of NI was higher in the iHTN group (42.7% [95% CI, 33.3%–52.5%]) compared with the conservative (28.9% [95% CI, 24.1%–34.0%]) and antithrombotic change groups (30.4% [95% CI, 23.3%–38.2%]). However, there was no difference in the proportion of patients achieving a good functional outcome at 3 months across the treatment groups. Among patients with undetermined cause or other determined cause ($n=793$), neither NI

Table 1. General Characteristics According to END Management

Variable	Total	Conservative	Antithrombotics change	iHTN	P value
Number	3067	1840 (60.0%)	747 (24.4%)	480 (15.7%)	
Age, y; mean±SD	70.0±13.0	70.2±13.1	69.7±13.0	69.6±12.2	0.560
Male, n (%)	1778 (58.0)	1087 (59.1)	417 (55.8)	274 (57.1)	0.288
Initial NIHSS, median (IQR)	4 (2–6)	4 (2–7)	3 (2–6)	4 (2–6)	<0.001
NIHSS score at END, median (IQR)	7 (4–9)	7 (4–10)	6 (4–9)	7 (5–9)	0.001
Discharge NIHSS score, median (IQR)	6 (3–9)	6 (3–9)	5 (3–8)	5 (3–8)	<0.001
Prestroke mRS score, median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	<0.001
History of TIA, n (%)	48 (1.6)	28 (1.5)	13 (1.7)	7 (1.5)	0.902
History of stroke, n (%)	593 (19.3)	365 (19.8)	144 (19.3)	84 (17.5)	0.513
History of CHD, n (%)	254 (8.3)	173 (9.4)	62 (8.3)	19 (4.0)	<0.001
History of HTN, n (%)	2136 (69.6)	1320 (71.7)	531 (71.1)	285 (59.4)	<0.001
History of DM, n (%)	1206 (39.3)	746 (40.5)	288 (38.6)	172 (35.8)	0.151
History of dyslipidemia, n (%)	1165 (38.0)	726 (39.5)	271 (36.3)	168 (35.0)	0.109
Smoking, n (%)					0.328
None	2054 (67.0)	1223 (66.5)	510 (68.3)	321 (66.9)	
Current	722 (23.5)	429 (23.3)	170 (22.8)	123 (25.6)	
Ex-smoking	291 (9.5)	188 (10.2)	67 (9.0)	36 (7.5)	
History of antiplatelet, n (%)	791 (25.8)	483 (26.3)	198 (26.5)	110 (22.9)	0.290
History of HTN medication, n (%)	1551 (50.6)	956 (52.0)	376 (50.3)	219 (45.6)	0.047
History of statin medication, n (%)	750 (24.5)	464 (25.2)	166 (22.2)	120 (25.0)	0.263
History of other lipid med, n (%)	135 (4.4)	82 (4.5)	34 (4.6)	19 (4.0)	0.871
History of DM medication, n (%)	865 (28.2)	533 (29.0)	202 (27.0)	130 (27.1)	0.515
TOAST, n (%)					<0.001
LAA	1670 (54.5)	975 (53.0)	388 (51.9)	307 (64.0)	
SVO	604 (19.7)	336 (18.3)	158 (21.2)	110 (22.9)	
UD	151 (4.9)	112 (6.1)	27 (3.6)	12 (2.5)	
OD	642 (20.9)	417 (22.7)	174 (23.3)	51 (10.6)	
Acute treatment, n (%)					<0.001
None	2584 (84.3)	1506 (81.8)	651 (87.1)	427 (89.0)	
IVT	291 (9.5)	191 (10.4)	66 (8.8)	34 (7.1)	
IAT	137 (4.5)	102 (5.5)	21 (2.8)	14 (2.9)	
IVT+IAT	55 (1.8)	41 (2.2)	9 (1.2)	5 (1.0)	
Laboratory, mean±SD					
WBC	8.2±3.1	8.3±3.2	8.1±2.9	7.9±2.7	0.010
Hemoglobin	13.7±1.9	13.7±1.9	13.7±1.9	13.8±1.7	0.499
Platelet	233.2±71.1	232.0±71.7	235.1±71.8	234.9±67.7	0.519
Creatinine	0.97±0.80	0.99±0.85	1.00±0.86	0.88±0.36	0.014
Fasting glucose	131.6±53.6	132.7±54.8	134.4±55.2	122.9±44.8	<0.001
LDL-C	113.2±41.6	113.0±42.4	113.6±39.2	113.5±41.9	0.923
HbA1c	6.5±1.5	6.5±1.6	6.5±1.6	6.4±1.3	0.131
SBP	160.2±29.1	160.6±30.1	159.0±28.1	160.5±26.8	0.430

P values are calculated by the χ^2 test, the ANOVA, and the Kruskal-Wallis Test. CHD indicates coronary heart disease; DM, diabetes; END, early neurological deterioration; HbA1c, glycated hemoglobin; HTN, hypertension; IAT, intra-arterial thrombectomy; iHTN, induced hypertension; IQR, interquartile range; IVT, intravenous thrombolysis; LAA, large artery atherosclerosis; LDL-C, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OD, other cause; SBP, systolic blood pressure; SVO, small vessel occlusion; TIA, transient cerebral ischemia; TOAST, Trial of Org 10172 in Acute Stroke Treatment; UD, undetermined cause; and WBC, white blood cell.

nor 3-month functional outcomes differed significantly between treatment strategies. The rate of composite vascular events was lower in the iHTN group (4.8%

[95% CI, 0%–10.1%]) compared with the conservative (16.7% [95% CI, 13.5%–19.9%]) and antithrombotic change groups (11.1% [95% CI, 6.7%–15.5%]; Table 5).

Table 2. Event Rate of Primary and Secondary Outcomes According to END Management

	All	Conservative	Antithrombotics change	iHTN	P value
Neurological improvement during hospitalization (NIHSS score improvement ≥ 2)					
No. of events	1049	593	257	199	
Event rate, % (95% CI)	34.2 (32.5–35.9)	32.2 (30.1–34.4)	34.4 (31.0–37.9)	41.5 (37.0–46.0)	<0.001
Ordinal shift for 3-mo mRS score*					
Median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	<0.001
Good functional outcome at 3 mo (mRS score, 0–2)					
No. of events	1134	647	285	202	
Event rate, % (95% CI)	37.0 (35.3–38.7)	35.2 (33.0–37.4)	38.2 (34.7–41.7)	42.1 (37.6–46.6)	0.015
Composite vascular events (including all-cause mortality, recurrent stroke, and myocardial infarction)					
No. of events	294	205	61	28	
Event rate, % (95% CI)	9.7 (8.6–10.7)	11.3 (9.8–12.7)	8.2 (6.3–10.2)	5.9 (3.8–8.0)	<0.001
All-cause mortality					
No. of events	194	147	35	12	
Event rate, % (95% CI)	6.5 (5.6–7.3)	8.1 (6.9–9.4)	4.8 (3.3–6.4)	2.6 (1.1–4.0)	<0.001
Stroke recurrence					
No. of events	89	51	23	15	
Event rate, % (95% CI)	3.0 (2.4–3.6)	2.9 (2.1–3.7)	3.2 (1.9–4.4)	3.2 (1.6–4.7)	0.911
Myocardial infarction					
No. of events	32	23	8	1	
Event rate, % (95% CI)	1.1 (0.7–1.4)	1.3 (0.8–1.8)	1.1 (0.3–1.8)	0.2 (0.0–0.6)	0.133

Adjusted variables: male, age, initial NIHSS score, prestroke mRS score (0–1), history of hypertension, history of diabetes, history of stroke, history of coronary heart disease, history of dyslipidemia, treatment history of hypertension, TOAST classification, acute reperfusion therapy, WBC, creatinine, and fasting glucose level. END indicates early neurological deterioration; iHTN, induced hypertension; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; TOAST, Trial of Org 10172 in Acute Stroke Treatment; and WBC, white blood cell.

*The ordinal shift across the range of mRS scores toward a better outcome, for which the treatment effect is reported as a common OR with the 95% CI.

In patients with LAA, iHTN was associated with NI compared with the conservative group (aOR, 1.57 [95% CI, 1.19–2.06]), as well as with greater odds of achieving a favorable mRS shift (aOR, 1.46 [95% CI, 1.16–1.84]) and good functional outcome at 3 months (aOR, 1.40 [95% CI, 1.03–1.89]). Among patients with SVO, iHTN was also associated with NI (aOR, 1.88 [95% CI, 1.16–3.05]) but not with functional outcomes. Among patients with undetermined cause or other determined cause, no significant associations were observed between treatment strategy and 3-month functional outcomes (Table 6).

Subgroup Analysis

Subgroup analyses were conducted for the 3-month mRS ordinal shift (Table S1; Figure S2) and NI (Table S2; Figure S3). Overall, iHTN tended to be associated with more favorable outcomes across subgroups. For the mRS ordinal shift, the beneficial effect of iHTN did not differ according to baseline hypertension ($P_{\text{interaction}}=0.865$) or coronary heart disease ($P_{\text{interaction}}=0.550$), indicating that the association was consistent regardless of these comorbidities. In contrast, a significant interaction was observed for baseline NIHSS severity ($P_{\text{interaction}}=0.029$),

suggesting that the magnitude of the effect may vary by initial stroke severity. Nevertheless, iHTN was associated with a favorable direction of outcome compared with other treatment strategies in both subgroups (NIHSS score ≤ 4 and >4). For NI, no significant interactions were observed with any of the tested variables.

DISCUSSION

In this nationwide study using the CRCS-K registry, we analyzed over 3000 patients with END attributed to stroke progression. Among these patients, approximately one-quarter underwent changes in antithrombotic therapy, and iHTN was implemented in about 15% of patients with END. Compared with conservative management, iHTN was significantly associated with greater improvement in NIHSS scores at discharge and a favorable shift in the 3-month mRS distribution. These associations were particularly evident in patients with the LAA subtype. Our findings suggest that iHTN may offer potential clinical benefit in the management of progressive END and provide a basis for hypothesis generation and future prospective investigations.

Although prior research has addressed END management, real-world treatment approaches remain

Table 3. Clinical Outcomes According to END Management

	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Primary outcomes				
Neurological improvement during hospitalization (NIHSS score improvement ≥ 2)				
Conservative management	1 (Ref)		1 (Ref)	
Antithrombotics change	1.10 (0.92–1.32)	0.286	1.17 (0.97–1.40)	0.964
Induced hypertension	1.49 (1.21–1.83)	<0.001	1.55 (1.25–1.92)	<0.001
Ordinal shift for 3-mo mRS score*				
Conservative management	1 (Ref)		1 (Ref)	
Antithrombotics change	1.28 (1.10–1.48)	0.001	1.02 (0.87–1.19)	0.809
Induced hypertension	1.55 (1.30–1.84)	<0.001	1.24 (1.03–1.48)	0.023
Secondary outcomes				
Good functional outcome at 3 mo (mRS score, 0–2)				
Conservative management	1 (Ref)		1 (Ref)	
Antithrombotics change	1.14 (0.95–1.36)	0.151	0.97 (0.79–1.19)	0.760
Induced hypertension	1.34 (1.09–1.64)	0.005	1.17 (0.92–1.48)	0.197

Adjusted variables: male, age, initial NIHSS score, prestroke mRS score (0–1), history of hypertension, history of diabetes, history of stroke, history of coronary heart disease, history of dyslipidemia, treatment history of hypertension, TOAST classification, acute reperfusion therapy, WBC, creatinine, and fasting glucose level. END indicates early neurological deterioration; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odd ratio; TOAST, Trial of Org 10172 in Acute Stroke Treatment; and WBC, white blood cell.

*The ordinal shift across the range of mRS scores toward a better outcome, for which the treatment effect is reported as a common OR with the 95% CI.



heterogeneous and lack clearly defined standards.⁵ In our registry-based analysis reflecting real-world clinical practice, $\approx 60\%$ of patients with END were managed conservatively, including approaches such as volume expansion. This likely reflects the complex and heterogeneous mechanisms underlying progressive END, as well as the absence of established efficacy for specific treatment strategies in previous studies.^{9,19} In this challenging clinical context, our findings provide supporting evidence for the potential benefit of selecting treatment strategies, as certain approaches were associated with better outcomes.

In our study, iHTN was implemented in $\approx 15\%$ of patients with END following noncardioembolic stroke, indicating its relatively infrequent use in clinical practice. However, compared with conservative management, iHTN was associated with a 55% higher likelihood of achieving NI and a 24% greater likelihood of a favorable shift in functional outcome at 3 months. Given the significant associations between iHTN and the primary outcomes, NI and mRS shift, iHTN may be more favorably associated with overall neurological recovery after END. These results support a previous randomized clinical trial conducted in patients who developed END following ischemic stroke due to LAA or SVO.¹¹ In that trial, iHTN increased the likelihood of achieving NI (defined as a ≥ 2 -point improvement in NIHSS) by 57% and functional independence at 3 months by 75% compared with placebo. A subgroup analysis showed that these effects were particularly pronounced in patients with SVO. Unlike previous studies, we found that iHTN

was associated with better outcomes in patients with LAA within this cohort. Furthermore, because we focused on post-END management and excluded patients who underwent EVT after END, these findings suggest that iHTN may represent a potential therapeutic option for patients with LAA with END in whom EVT is not feasible. Notably, despite higher initial NIHSS scores, the iHTN group had $\approx 50\%$ lower mortality compared with other treatment strategies, addressing previous safety concerns such as thrombus propagation or hemorrhagic transformation.²⁰ By contrast, although iHTN was associated with NIHSS score improvement in patients with SVO, this did not lead to better functional outcomes, possibly due to the higher baseline severity in our study; only 37.0% achieved a good functional outcome at 3 months.

In clinical practice, changes in antiplatelet or antithrombotic therapy, including intravenous agents, are often considered after END although evidence remains limited. In our study, antithrombotic therapy was modified in approximately a quarter of patients after END. Compared with conservative management, the antithrombotic change group was not significantly associated with either NI or improved functional outcomes. This may be due to the substantial heterogeneity of the group, which included a wide range of therapeutic approaches, making it difficult to isolate the effect of any single antithrombotic intervention. Accordingly, further studies are warranted to evaluate the efficacy of specific, clearly defined antithrombotic strategies in the management of END.

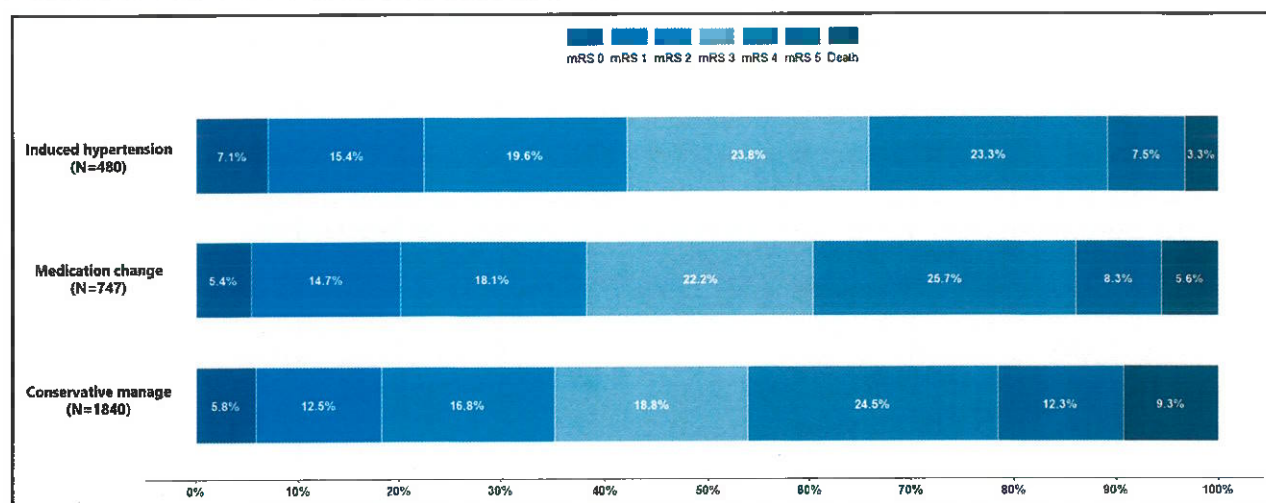


Figure 1. Modified Rankin Scale (mRS) distribution at 3 months according to early neurological deterioration management.

In a previous study involving predominantly LAA and SVO subtypes, intravenous argatroban administered after END was associated with a modest benefit for good functional outcome at 3 months (risk ratio, 1.10 [95% CI, 1.00–1.20]). However, interpretation of these results is limited due to the use of a broad outcome definition (mRS score, 0–3).¹⁰ Tirofiban has also been reported to yield better outcomes than aspirin in patients without large or medium vessel occlusion.¹² In that study, 40.2% of patients had END or stroke progression, suggesting possible relevance, although the effect of tirofiban in the END-specific subgroup was not clearly demonstrated.

Intravenous antithrombotic agents have been explored as potential strategies following END; however, clear evidence supporting their efficacy remains limited. Further studies are needed to clarify the role of specific antithrombotic strategies in the management of END. Although dual-antiplatelet therapy is the standard treatment in the acute phase of ischemic stroke,²¹ some clinicians have attempted to add a third agent after END. However, triple-antiplatelet therapy increases the risk of bleeding without improving clinical outcomes.²²

Our findings provide clinical insight into the management of END, for which treatment strategies remain

Table 4. Vascular Outcomes According to END Management

	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Composite vascular events (including all-cause mortality, recurrent stroke, and myocardial infarction)				
Conservative management	1 (Ref)		1 (Ref)	
Antithrombotics change	0.72 (0.54–0.96)	0.025	0.87 (0.65–1.16)	0.348
Induced hypertension	0.51 (0.34–0.76)	<0.001	0.67 (0.45–1.01)	0.055
All-cause mortality				
Conservative management	1 (Ref)		1 (Ref)	
Antithrombotics change	0.57 (0.40–0.83)	0.003	0.79 (0.54–1.13)	0.188
Induced hypertension	0.30 (0.17–0.55)	<0.001	0.50 (0.28–0.92)	0.024
Stroke recurrence				
Conservative management	1 (Ref)		1 (Ref)	
Antithrombotics change	1.09 (0.67–1.79)	0.725	1.08 (0.66–1.78)	0.750
Induced hypertension	1.10 (0.62–1.96)	0.738	1.10 (0.61–1.98)	0.759
Myocardial infarction				
Conservative management	1 (Ref)		1 (Ref)	
Antithrombotics change	0.85 (0.38–1.90)	0.693	0.93 (0.41–2.09)	0.853
Induced hypertension	0.16 (0.02–1.22)	0.077	0.16 (0.02–1.19)	0.072

Adjusted variables: male, age, initial NIHSS score, prestroke mRS score (0–1), history of hypertension, history of diabetes, history of stroke, history of coronary heart disease, history of dyslipidemia, treatment history of hypertension, TOAST classification, acute reperfusion therapy, WBC, creatinine, and fasting glucose level. END indicates early neurological deterioration; HR, hazard ratio; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment; and WBC, white blood cell.

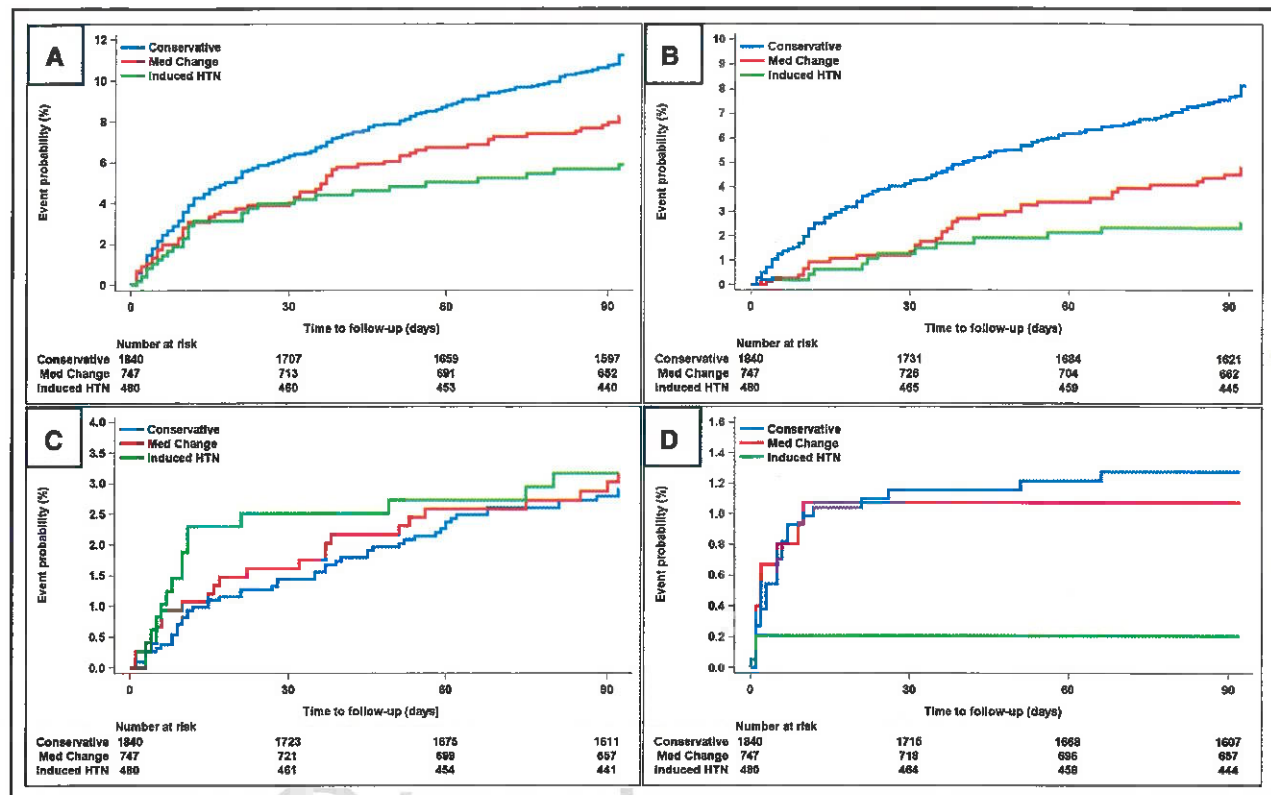


Figure 2. Survival curve for 3-month vascular outcome.

A, Composite vascular outcome. B, All-cause mortality. C, Stroke. D, Myocardial infarction. HTN indicates hypertension.

largely undefined. In particular, we observed a favorable association between iHTN and improved outcomes in patients with END, suggesting that more proactive interventions may be beneficial in progressive END. Although our study was not specifically designed to define which patients should or should not receive iHTN, the TOAST subgroup analyses yielded clinically meaningful signals. Patients with END due to LAA appeared to experience both neurological and functional benefits, suggesting that this subgroup may be more likely to respond

favorably. However, these findings should not be interpreted as a recommendation to uniformly increase blood pressure in all patients with END. While several studies have reported on the safety of iHTN after END, some have also raised concerns that the risk of complications such as intracerebral hemorrhage may increase.^{20,23,24} The potential benefits of iHTN are likely to depend on baseline hemodynamic status and individual patient characteristics, underscoring the need for a tailored rather than a one-size-fits-all approach.

Table 5. Event Rates According to TOAST Classification

Stroke subtype	Outcome	Conservative	Antithrombotics change	Induced hypertension	P value
LAA (n=1670)	Good mRS score at 3-mo (0–2) event rate, % (95% CI)	31.1 (28.2–34.1)	34.5 (29.8–39.5)	42.0 (36.4–47.8)	0.002
	Improvement of NIHSS ≥ 2 event rate, % (95% CI)	31.9 (29.0–34.9)	36.3 (31.5–41.3)	41.4 (35.8–47.1)	0.007
	Composite vascular outcome event rate, % (95% CI)	11.4 (9.4–13.4)	8.5 (5.7–11.3)	7.2 (4.3–10.1)	0.066
SVO (n=604)	Good mRS score at 3-mo (0–2) event rate, % (95% CI)	48.5 (43.1–54.0)	44.3 (36.4–52.4)	47.3 (37.7–57.0)	0.682
	Improvement of NIHSS ≥ 2 event rate, % (95% CI)	28.9 (24.1–34.0)	30.4 (23.3–38.2)	42.7 (33.3–52.5)	0.023
	Composite vascular outcome event rate, % (95% CI)	2.4 (0.8–4.0)	3.9 (0.8–7.0)	2.8 (0.0–5.8)	0.648
UD+OD (n=793)	Good mRS score at 3-mo (0–2) event rate, % (95% CI)	34.2 (30.2–38.4)	30.8 (24.5–37.7)	33.3 (22.0–46.3)	0.689
	Improvement of NIHSS ≥ 2 event rate, % (95% CI)	35.0 (30.9–39.2)	33.8 (27.3–40.8)	39.7 (27.6–52.8)	0.695
	Composite vascular outcome event rate, % (95% CI)	16.7 (13.5–19.9)	11.1 (6.7–15.5)	4.8 (0.0–10.1)	0.014

P values are calculated by the χ^2 test and the log-rank test. END indicates early neurological deterioration; LAA, large artery atherosclerosis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OD, other cause; SVO, small vessel occlusion; TOAST, Trial of Org 10172 in Acute Stroke Treatment; and UD, undetermined cause.

Table 6. Clinical Outcomes According to TOAST Classification

Subtype	Group	Ordinal shift for good mRS score*	P value	Good mRS score at 3 mo (0–2)	P value	NIHSS score improvement (≥2)	P value
LAA (n=1670)	Conservative management	1 (Ref)		1 (Ref)		1 (Ref)	
	Antithrombotics change	1.16 (0.93–1.43)	0.184	1.15 (0.87–1.52)	0.338	1.26 (0.78–1.62)	0.071
	Induced hypertension	1.46 (1.16–1.84)	0.002	1.40 (1.03–1.89)	0.030	1.57 (1.19–2.06)	0.001
SVO (n=604)	Conservative management	1 (Ref)		1 (Ref)		1 (Ref)	
	Antithrombotics change	0.90 (0.64–1.28)	0.557	0.91 (0.59–1.41)	0.676	1.08 (0.69–1.68)	0.72
	Induced hypertension	1.12 (0.75–1.67)	0.594	1.08 (0.651–1.78)	0.774	1.88 (1.16–3.05)	0.009
UD+OD (n=793)	Conservative management	1 (Ref)		1 (Ref)		1 (Ref)	
	Antithrombotics change	0.85 (0.63–1.14)	0.282	0.74 (0.49–1.10)	0.139	1.03 (0.72–1.47)	0.867
	Induced hypertension	0.84 (0.53–1.34)	0.469	0.66 (0.35–1.24)	0.204	1.20 (0.69–2.09)	0.509

Adjusted variables: male, age, initial NIHSS score, prestroke mRS score (0–1), history of hypertension, history of diabetes, history of stroke, history of coronary heart disease, history of dyslipidemia, treatment history of hypertension, TOAST classification, acute reperfusion therapy, WBC, creatinine, and fasting glucose level. END indicates early neurological deterioration; LAA, large artery atherosclerosis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OD, other cause; OR, odds ratio; SVO, small vessel occlusion; TOAST, Trial of Org 10172 in Acute Stroke Treatment; UD, undetermined cause; and WBC, white blood cell.

*The ordinal shift across the range of mRS scores toward a better outcome, for which the treatment effect is reported as a common OR with the 95% CI.

While conservative management remains prevalent in clinical practice, our findings underscore the urgent need for evidence-based guidelines to inform treatment decisions following END. To date, previous studies have focused on identifying risk factors for END^{25,26} and exploring various preventive strategies to reduce its occurrence.^{27–33} While these efforts have emphasized prevention, our study focused on therapeutic approaches after the onset of END. Moving forward, a comprehensive approach that includes early risk stratification, prevention, and timely intervention will be essential to improving outcomes in patients at risk of END.

This study has several limitations. First, due to its retrospective observational study design, the possibility of residual confounding cannot be entirely excluded, despite adjustment for multiple potential covariates. Second, detailed information on emerging acute-phase treatments intended to prevent END was not available. Although such therapies may have influenced outcomes, they are still supported by limited evidence, and their use is likely to have been infrequent within this cohort. Third, treatment strategies were not randomly assigned. Therefore, the decision to initiate iHTN or modify antithrombotic therapy was likely influenced by clinicians' assessments of stroke severity or patient prognosis, introducing a potential indication bias. In particular, the antithrombotics change group likely represents a heterogeneous set of therapeutic decisions, and some patients in the conservative group may not have received active END management due to clinical contraindications. Likewise, patients in the iHTN group may have been selectively chosen based on the absence of significant cardiovascular comorbidities because vasopressors are generally avoided in conditions such as coronary artery disease. However, in our subgroup analyses, the beneficial association of iHTN was observed regardless of the presence of coronary heart disease or hypertension, suggesting that the influence of these comorbidities on the

interpretation of our results is likely to be limited. Finally, as this was a cohort study, the treatment regimens, including the choice of agents, dosages, and target blood pressure levels, could not be standardized. Although most participating centers generally performed iHTN based on protocols from prior clinical trials,¹¹ variations across centers were still possible. Furthermore, we could not evaluate the absolute blood pressure values before and after treatment nor ascertain whether patients achieved the target blood pressure thresholds. Nevertheless, this study systematically evaluated real-world treatment patterns and outcomes following END in a large-scale, nationwide cohort, providing clinically relevant insights into current practice and potential therapeutic directions.

In conclusion, this study demonstrated that iHTN applied after the occurrence of progressive END in patients with noncardioembolic stroke was significantly associated with better neurological recovery and more favorable functional outcomes. Given the retrospective nature of the study, these results should be considered hypothesis-generating, and further validation through prospective randomized controlled trials is warranted.

ARTICLE INFORMATION

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The authors report no conflicts. The authors confirm that this manuscript complies with all instructions to authors and confirm that authorship requirements have been met, and the final manuscript was approved by all authors. The authors confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. We followed the Strengthening the Reporting of Observational Studies in Epidemiology statement checklist for the report of an observational cohort study.

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Stroke

FIRST PROOF ONLY

CLINICAL AND POPULATION SCIENCES

Neurostimulant Use for Rehabilitation and Recovery After Stroke: A Narrative Literature Review

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BACKGROUND: Stroke often results in significant impairments across various domains, including movement, language, cognition, and mood. Neurostimulants have been proposed as potential therapeutic interventions to enhance recovery in these areas.

METHODS: This narrative literature review examines clinical trials investigating the efficacy of neurostimulants in poststroke recovery. It evaluates outcomes related to aphasia, motor deficits, cognition, fatigue, and depression.

RESULTS: The qualitative analysis included 34 trials testing the following neurostimulants: methylphenidate (n=6), amphetamines (n=8), memantine (n=2), modafinil (n=2), levodopa (n=14), amantadine (n=1), bromocriptine (n=3), and ropinirole (n=1). Of the 34 studies, 31 were randomized, placebo-controlled (double-blind, n=27; single-blind, n=2; unblinded n=2), 2 were randomized and not placebo-controlled, and 1 was not randomized. Study design was either multiarm (n=23), crossover (n=10), or used subjects as their own control (n=1). Mean sample size was 49.4 (5–593).

CONCLUSIONS: Current evidence suggests that memantine may be effective for aphasia, although few phase III trials exist, whereas bromocriptine and amphetamines lack sufficient evidence for long-term recovery of aphasia. Levodopa may improve motor aphasia but has not shown long-term benefits for motor recovery. Similarly, ropinirole has not been shown to improve poststroke motor outcomes. Methylphenidate has limited efficacy for cognitive improvement but may enhance poststroke functionality and mood. Modafinil may help with poststroke fatigue. In conclusion, there are promising results of positive effects of neurostimulants with few side effects, though studies are limited by heterogeneous designs and small sample sizes. Neurostimulant efficacy must be assessed in conjunction with specific rehabilitation modalities as part of larger, well-designed studies to best understand their effects on impairment.

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

Key Words: amphetamines ■ aphasia ■ cognition ■ levodopa ■ memantine ■ motor skills disorders ■ stroke

Although motor deficits are widely recognized as a source of poststroke disability, cognitive and behavioral changes are also common and disabling. There are few available, effective rehabilitation treatments. Stem cell therapy, monoclonal antibodies, and robot-assisted therapies have not shown efficacy, are expensive, and have significant risks.^{1–4} Rehabilitation therapies remain the standard of care for

the improvement of poststroke cognitive, motor, and behavioral deficits, but they are time and resource-intensive and often dependent on nonclinical factors such as insurance status and geographic accessibility.⁵ In addition, these therapies provide limited benefits.⁴ And despite, these therapies, between 2015 and 2035 direct, medical, and stroke-related costs will more than double.⁶ Pharmacological agents are a promising

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Nonstandard Abbreviation and Acronym

MIDAS	Modafinil in Debilitating Fatigue After Stroke
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adjunct to traditional rehabilitation strategies to optimize plasticity and possibly reduce costs.

Stimulants have been investigated in animal studies and clinical trials as potential enhancers of natural mechanisms of repair and plasticity via their actions on adrenergic, dopaminergic, and glutamatergic systems.^{7,8} The clinical usefulness of these adjuncts is challenging to interpret due to heterogeneity in study design, drug timing relative to the stroke, dose of the drug, outcomes measured, and variability in stroke recovery from patient to patient. Hence, it is unclear how these drugs may be helpful for clinical recovery.⁵

This narrative review summarizes the published studies related to poststroke recovery and neurostimulants with a particular focus on methylphenidate, dextroamphetamine, memantine, modafinil, and dopaminergic agents including levodopa, amantadine, bromocriptine, and ropinirole.

METHODS

A MEDLINE search was performed to identify prospective clinical trials that examined the effect of a stimulant (methylphenidate, dextroamphetamine, memantine, modafinil, levodopa, amantadine, bromocriptine, and ropinirole) on poststroke recovery, including both ischemic and hemorrhagic strokes as well as subarachnoid hemorrhage. Studies published in or before November 2024 were included. All data supporting the findings of this study are publicly available on MEDLINE. Although this is a narrative review, to more clearly standardize our approach, the search terms and Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram are included in the Figure. Relevant publications advanced to full-text review. A trial was ultimately included if it (1) studied human patients after ischemic or hemorrhagic stroke, (2) identified and measured a poststroke deficit, and (3) had at least 2 treatment arms where one arm received the drug and the other received standard of care or placebo. We considered acute to be within 2 to 3 weeks after stroke onset, subacute to be within 6 months, and chronic to be beyond 6 months.⁹ The protocols and outcomes of each study were assessed and compared. Study outcomes were categorized as showing improvement or no improvement based on whether authors reported better outcomes with a pharmacological agent.¹⁰ Indeed, we need to use this classification as one of the faults of many of these studies was that few indicated if their outcomes were clinically significant rather than just statistically significant. Finally, trials were assessed for the quality of the randomization, placebo, and reporting processes via the Jadad score.¹¹ Jadad scores range from 0 to 5, with 5 being the highest quality study based on the robustness of randomization, blinding, and accounting for patient follow-up. Jadad scores do not, as a weakness of the score, consider

power. H.C. and neurovascular attending A.R. jointly calculated the scores for each article. A.R. had final say over scores.

The trials were grouped by the type of outcome studied by the trialists, which had not been predetermined before the literature search: aphasia, motor impairment, cognitive impairment, fatigue, and depression.

RESULTS

The MEDLINE database search yielded 860 publications, of which 34 met the inclusion criteria (Figure).

Aphasia

A total of 9 studies were found on aphasia in poststroke patients, all of which were double-blinded, placebo-controlled trials (Table 1). The most common pharmacological adjuncts used were dopaminergic agents, including bromocriptine ($n=3$) and levodopa/carbidopa ($n=3$). Other studies were for amphetamines ($n=2$) and memantine ($n=1$).

There was only one study in the acute phase, by Ashtary et al,¹² and the rest were in the subacute or chronic phase of stroke.

Bromocriptine

Bromocriptine is a postsynaptic dopaminergic agent thought to improve nonfluent aphasia via its action on the frontal lobe.

Ashtary et al,¹² Sabe et al,¹³ and Bragoni et al¹⁴ investigated the effect of bromocriptine on nonfluent aphasia in acute (Ashtary et al) and chronic stroke (Sabe et al and Bragoni et al; Table 1). Bragoni et al¹⁴ found a small positive effect of bromocriptine on verbal latency and reading comprehension, and the other 2 studies were negative.^{12,13} Bragoni et al¹⁴ concluded that bromocriptine may improve speech initiation and comprehension via dopaminergic stimulation, though they could not exclude that improvement was secondary to prolonged practice with the therapy modality as opposed to the treatment.¹⁴

These 3 studies all suffered from low power ($N=38$, $N=7$, $N=5$).^{12–14} Bragoni et al¹⁴ had the smallest number of subjects ($N=5$) and were unable to recruit women.¹⁴ Their study design was further limited by the absence of randomization and distinct placebo and experimental treatment arms, earning a Jadad score of 2 out of 5 (as compared with 4 for Sabe et al¹³ and 5 for Ashtary et al¹²). Sabe et al¹³ utilized a crossover trial which, despite a washout period, cannot exclude carryover effects from active treatment. Although there was heterogeneity in dosage (varying between 10 mg and 60 mg/d) and timing of administration of bromocriptine for all 3 studies, undesirable side effects were common including dystonic movements, visual hallucinations, nausea, and syncope (Table 1).

In conclusion, 1 of the 3 studies showed improvement in language markers in chronic stroke with bromocriptine

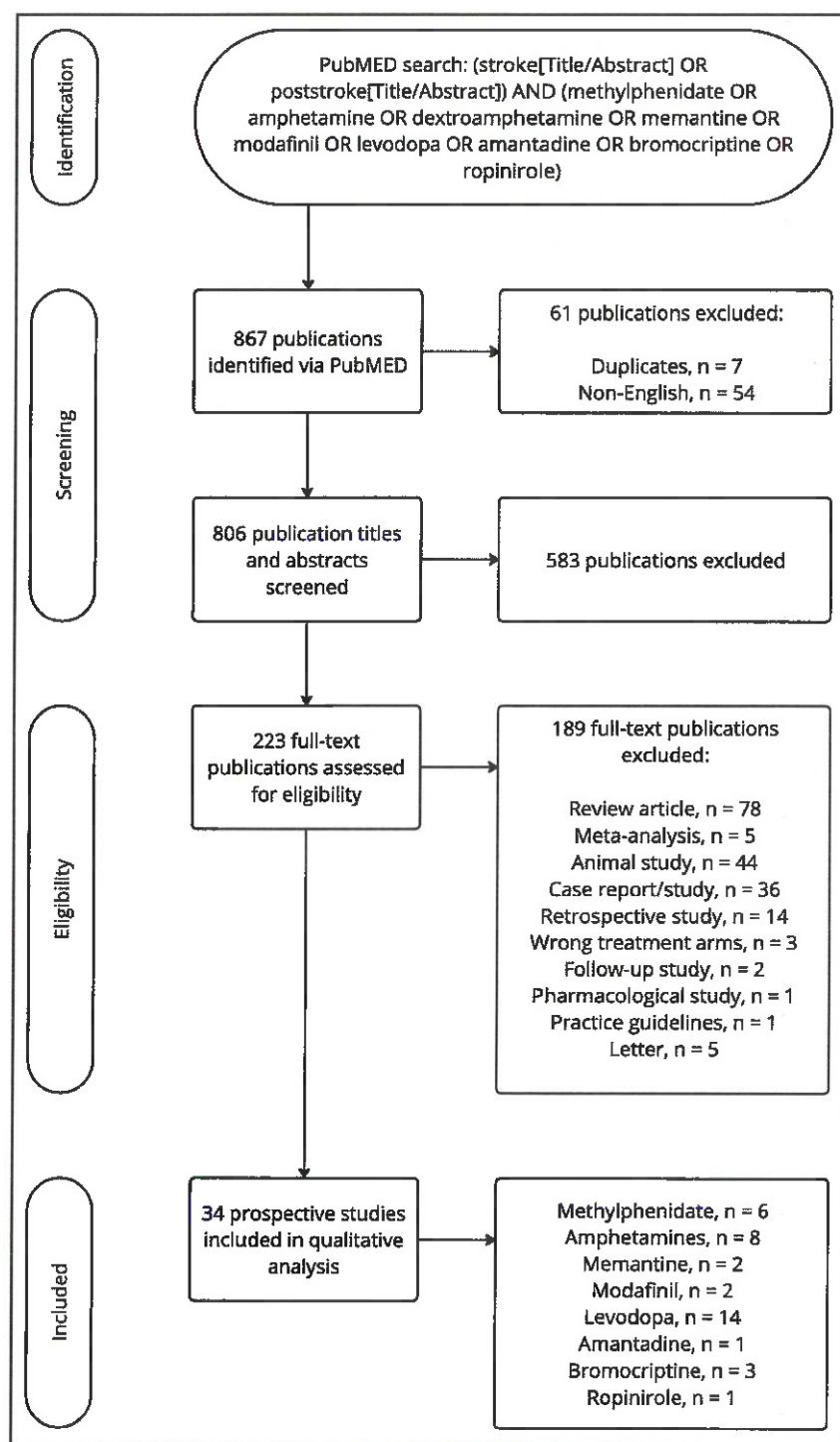


Figure. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Three of the 34 studies included in the final analysis tested >1 agent.

therapy+speech therapy. However, its design is too poor and power too low to draw conclusions. Altogether, the current evidence does not support the use of bromocriptine to improve aphasia after stroke.

Levodopa

Levodopa, a precursor to dopamine, increases levels of both dopamine and norepinephrine, in the brain.²⁰ Dopaminergic stimulation in the prefrontal cortex may help

improve the planning and execution of prefrontal cortex-driven behaviors, such as coordination of movements associated with speaking.⁷

Seniów et al,⁷ Breitenstein et al,¹⁵ and Leemann et al¹⁶ examined the effect of levodopa or levodopa/carbidopa on aphasia in subacute (Seniów et al and Leemann et al) and chronic (Breitenstein et al) stroke (Table 1). Seniów et al⁷ interestingly found that only patients with frontal lesions showed improvement.⁷ The other 2 studies were

Table 1. Trials on Aphasia in Poststroke Patients With at Least 2 Treatment Arms, Where One Arm Is a Neurostimulant, and the Other Is Placebo or Standard of Care

Study	Study type	Poststroke period	Time since stroke	Type of stroke or other injury	Deficit	Drug	Dose
Ashtary et al ¹² Iran	Randomized, double-blind, placebo-controlled trial	Acute (inpatient)	NR	NR	Aphasia (nonfluent, nonspecified)	Bromocriptine	10 mg (starting dose 2.5 mg/d, max dose 3 mo)
Sabe et al, ¹³ Argentina	Randomized, double-blind, placebo-controlled trial	Chronic	>1 y	Ischemic (n=5), closed head injury (n=2)	Aphasia (nonfluent and fluent)	Bromocriptine	60 mg (starting dose 3.75 mg/d, max dose 2 wk)
Bragoni et al, ¹⁴ Italy	Double-blind, placebo-controlled trial	Chronic	>6 mo	NR	Aphasia (nonfluent, chronic, all types)	Bromocriptine	30 mg TID (starting dose 2.5 mg, max dose 3 mo)+ domperidon 30 mg TID
Seniów et al, ⁷ Poland	Randomized, double-blind, placebo-controlled trial	Subacute	2–8 wk	NR	Aphasia (frontal language area lesion, that is, motor aphasia)	Levodopa/benserazide	100/25 mg
Breitenstein et al, ¹⁵ Germany	Randomized, double-blind, placebo-controlled trial	Chronic	>1 y	Ischemic	Aphasia (all types, 8/10 lesions in the midbrain dopaminergic system)	Levodopa/carbidopa	100/25 mg
Leemann et al, ¹⁶ Switzerland	Randomized double-blind, placebo-controlled, crossover study	Subacute	2–9 wk	Ischemic (n=8), traumatic brain injury (n=3), central venous thrombosis (n=1)	Aphasia (anomia)	Levodopa/benserazide	100/25 mg
Walker-Batson et al, ¹⁷ United States	Randomized, double-blind, placebo-controlled trial	Subacute	16–30 d	Ischemic	Aphasia (all types; all left middle cerebral artery)	Dextroamphetamine	10 mg

Patients	Treatment	Outcome studied	Assessments	Results	Adverse drug effects	Outcome	Jadad score
38 (bromocriptine: n=19, mean age, 54.4 [11.4] y; placebo: n=19, mean age, 52.8 [14.4] y); 18 women total	4 mo of upitration of daily bromocriptine or placebo	Standardized Persian language test, global aphasia score	0, 8, and 16 wk	Bromocriptine did not improve nonfluent aphasia more than placebo.	None	No improvement	5
7 (with crossover; mean age, 54 [range, 30–79] y; 3 women)	6 wk of daily bromocriptine or placebo with crossover after a washout period of 3 wk	No. of content words, content units, and pauses >3 s during the description of a figure, verbal naming, verbal fluency, Controlled Oral Word Association test, Boston Naming test	Weekly	No significant benefits of bromocriptine over placebo in any of the variables examined.	Dystonic movements on the hemiparetic side (n=2), nausea (n=1), and lack of energy (n=1)	No improvement	4
5 (mean age, 60.2 [range, 54–65] y; 0 women)	Multiple phases: 2 mo of placebo+domperidon and speech therapy, 2 mo of bromocriptine+domperidon and speech therapy, 2 mo of bromocriptine+domperidon, then washout	Standardized Italian language test, others	After each phase	Bromocriptine only had a positive effect on reading comprehension and verbal latency, 2 of the 4 parameters improved overall (dictation ($P<0.004$), reader comprehension ($P<0.003$), repetition ($P<0.01$), verbal latency ($P<0.01$)).	Nausea (n=3), syncope (n=1), atrial fibrillation (n=1, subject dropped out), and visual hallucinations (n=1, subject dropped out)	Improvement (in 2 areas only)	2
39 (levodopa: n=20, mean age, 52.7 [range, 26–69] y, 4 women; placebo: n=19, mean age, 59 [range, 37–71] y, 10 women)	Levodopa or placebo therapy 30 min before speech and language therapy sessions conducted 45 min every weekday for 3 wk	BDAE	Pretreatment and posttreatment	Improved performance with levodopa in some but not all BDAE subsets (verbal fluency [6.3 vs 2.32, $P=0.011$], repetition of phrases and sentences of high frequency [2.45 vs 1.16, $P=0.028$], and repetition of words [2.2 vs 1.53, $P=0.05$]).	None	Improvement (in 3 areas only)	3
10 (with crossover; mean age not reported, age range, 34–67 y; 3 women)	2 wk of levodopa/carbidopa or placebo daily 90 min before language training with crossover after washout of 4 wk	Naming accuracy and verbal communication	Immediately and 4 wk after each condition, and 6 mo after phase 1	No additive effect of levodopa.	None	No improvement	4
12 (with crossover; mean age, 62.3 [range, 41–76] y; 4 women)	2 wk of levodopa or placebo on the morning of computer-assisted therapy and speech therapy, 1-wk washout, crossover	Naming performance on items trained with computer-assisted therapy or not trained	Baseline, once after each 2-wk period	No difference in performance between levodopa and placebo.	NR	No improvement	4
21 (amphetamine: n=12, mean age, 51.8 y, 6 women; placebo: n=9, mean age, 61.3 y, 2 women)	10 sessions over 5 wk of dextroamphetamine or placebo before speech therapy	PICA	Baseline, 1 wk off the drug, 6 mo after onset	Improved PICA scores with dextroamphetamine 1 wk after treatment ($P=0.0153$), even after correction for initial aphasia severity ($P=0.0974$) and age ($P=0.2771$). Difference between groups not maintained at 6 mo.	None	Improvement	4

(Continued)

Table 1. Continued

Study	Study type	Poststroke period	Time since stroke	Type of stroke or other injury	Deficit	Drug	Dose
Keser et al, ¹⁸ United States	Randomized, crossover double-blind, placebo-controlled trial	Chronic	14–233 mo	Ischemic	Aphasia (chronic nonfluent)	Dextroamphetamine	10 mg
Berthier et al, ¹⁹ United Kingdom	Randomized, double-blind, placebo, parallel-group trial with an open-label extension phase	Chronic	>1 y	Ischemic (82%), hemorrhagic	Aphasia (all types)	Memantine	20 mg/d (5 mg starting dose, weekly increments of 5 mg)

Unless otherwise specified, dosage is daily. BDAE indicates Boston Diagnostic Aphasia Examination; CAL, Communicative Activity Log; max, maximum; NR, not reported by article authors; PICA, Porch Index of Communicative Abilities; tDCS, transcranial direct current stimulation; WAB-AQ, Western Aphasia Battery-Aphasia Quotient; and WAB-R, Western Aphasia Battery-Revised.

negative.^{15,16} In a smaller study on chronic aphasia, Breitenstein et al¹⁵ could not show similar improvement due to possibly a ceiling effect, where maximal improvement was reached with high-intensity therapy and could not be improved upon by levodopa, or possibly to decline in brain plasticity in the chronic poststroke period as compared with the subacute stroke period.¹⁵ Leemann et al,¹⁶ who also could not show improvement in language with levodopa, additionally theorized a delay between levodopa administration and therapy session in their study could have reduced the drug's efficacy.¹⁶

With regards to quality, the studies by Seniów et al,⁷ Breitenstein et al,¹⁵ and Leemann et al¹⁶ are inadequately powered given the small number of patients enrolled (N=38, N=10, N=12, respectively). Their Jadad scores are not very strong at 3, 4, and 4 for Seniów et al,⁷ Breitenstein et al,¹⁵ and Leemann et al,¹⁶ respectively; however, the latter 2 have a crossover design which is weaker than the multiarm trial utilized by Seniów et al.^{7,15,16} Doses of levodopa/carbidopa were similar in all 3 studies (100/25 mg), but they were administered 30 minutes before training for Seniów et al,⁷ 90 minutes before for Breitenstein et al,¹⁵ and in the morning of training days (timing not specified) for Leemann et al.¹⁶ Seniów et al⁷ and Breitenstein et al¹⁵ reports no side effects, whereas Leemann et al¹⁶ does not mention if there were side effects or not. All 3 studies had more men than women. Comparison of the 3 studies is limited by their different end point scales.

To date, no study has shown consistent improvement across multiple language measures with

levodopa. Of the 3 small and heterogeneous studies found, only Seniów et al⁷ showed improvement in some (but not all) language markers in subacute stroke with levodopa therapy+speech therapy. The study is limited by low power, poorly described randomization procedures, and more severe initial aphasia in the levodopa group. Altogether, the current evidence for levodopa is inconclusive.

Amphetamines

Amphetamines increase the release of norepinephrine, dopamine, and serotonin in the brain. The mechanism through which amphetamines may enhance stroke recovery is unclear but possibly involves enhanced repair processes at the level of the synapse (eg, by increasing the density of synapses) or increased alertness after stroke.^{21–23}

Walker-Batson et al¹⁷ and Keser et al¹⁸ examined the effect of amphetamines on aphasia in subacute (Walker-Batson et al) and chronic (Keser et al) stroke (Table 1). Walker-Batson et al¹⁷ found improvement in language with amphetamines after 5 weeks but the difference with placebo was not significant at 6 months. An inadequately powered study may account for this, or it may be that the addition of a drug cannot improve upon the impact of 30 hours of intensive therapy, as the authors suggest. Keser et al¹⁸ also found improvement with amphetamine as compared with placebo with a single session of speech therapy and transcranial direct current stimulation but could not make firm conclusions on the long-term effects of their single-session intervention.¹⁸

Patients	Treatment	Outcome studied	Assessments	Results	Adverse drug effects	Outcome	Jadad score
10 (with crossover; mean age, 56.4 [range, 34–82] y; 6 women)	1 session of dextroamphetamine or placebo before tDCS and simultaneous speech and language therapy, 1-wk washout period, crossover for 1 session	WAB-R	Before and after tDCS, both weeks	Improved aphasia quotient ($P=0.02$) and language quotient ($P=0.008$) of the WAB-R with dextroamphetamine.	None	Improvement	4
28 (memantine: $n=14$, mean age, 53.7 [range, 36–65] y, 7 women; placebo: $n=14$, mean age, 48.5 [range, 40–66] y, 3 women)	16 wk of memantine or placebo, 2 wk of same drug with constraint-induced aphasia therapy, 2 wk of drug alone, 4 wk of washout, 24 wk open-label extension phase of memantine	WAB-AQ and CAL	Weeks 16, 18, 20, 24, and 48	Improved (WAB-AQ) score in the memantine group at week 16 ($P=0.002$), week 18 ($P=0.0001$), week 20 ($P=0.005$), and at the washout assessment ($P=0.041$), and improved CAL score at week 18 ($P=0.040$). Beneficial effects maintained long-term, and patients who switched to memantine from placebo experienced a benefit ($P=0.02$).	None	Improvement	5

These studies are both underpowered ($N=21$, $N=10$).^{17,18} Their Jadad scores were both 4 out of 5. The same doses of dextroamphetamine were used, although over 5 weeks for Walker-Batson et al¹⁷ and over 1 session for Keser et al,¹⁸ which complicates the comparison. In addition, whereas Walker-Batson et al¹⁷ studied subacute stroke, Keser et al¹⁸ focused on patients with chronic stroke (>6 months) in whom they consider maximal spontaneous recovery to have been reached. Finally, the studies used different scales to measure end points. Still, both studies reported improvements in their primary end points without side effects. Benefits either did not last (Walker-Batson et al¹⁷) or were unlikely to endure due to the short duration of the intervention (Keser et al¹⁸).

Thus, amphetamines may be helpful in the recovery of poststroke aphasia, but the effects are likely short-lived.

Memantine

Glutamate-induced neurotoxicity in cerebral ischemia may contribute to the decline in cognition, language, and memory.²⁴ *N*-methyl-D-aspartate receptor antagonists like memantine are hypothesized to protect the brain from glutamate-induced neurotoxicity after stroke^{25,26} and may help improve poststroke symptoms like aphasia.^{27–29}

Berthier et al¹⁹ examined the effect of memantine on aphasia in chronic stroke, with positive results (Table 1). They then conducted a 24-week open-label extension of the trial, in which both groups received memantine, and where both groups demonstrated continued improvement. Although natural recovery from aphasia over time

could not be ruled out, the improvement seen in patients several years poststroke suggested to the authors a genuine effect from the drug.

This study had a Jadad score of 5 out of 5 but was underpowered ($N=28$).¹⁹ Treatment arms were not significantly different in baseline demographics; however, the placebo group tended to have longer time since stroke ($P=0.053$), which could raise questions about the validity of the study results.

Memantine may have potential to enhance aphasia recovery in the long-term, although there is only one, underpowered, randomized, placebo-controlled trial to support this finding.

Motor

A total of 19 studies were found on motor recovery in poststroke patients that met our inclusion criteria (Table 2). The pharmacological adjuncts used were levodopa/carbidopa ($n=10$), methylphenidate ($n=4$), amphetamines ($n=6$), memantine ($n=1$), and ropinirole ($n=1$). Of note, one study used levodopa or amphetamines⁴¹ and another used methylphenidate or levodopa.⁴⁶

There were 8 studies that recruited patients in the acute phase of stroke. Patients were otherwise recruited in the subacute or chronic phases of stroke.

Levodopa

Levodopa has been widely studied in poststroke motor recovery. Levodopa is hypothesized to improve motor memory formation, although the mechanism is unclear.³³

Table 2. Trials on Motor Deficits in Poststroke Patients With at Least 2 Treatment Arms, Where One Arm Is a Neurostimulant and the Other Is Placebo or Standard of Care

Study	Study type	Poststroke period	Time since stroke	Type of stroke or other injury	Deficit	Drug	Dose	Patients
Scheidtmann et al, ³⁰ Germany	Randomized, double-blind, placebo-controlled trial	Subacute	3 wk–6 mo	Ischemic	Motor (hemiplegia)	Levodopa/carbidopa	100 mg, carbidopa dose unspecified	47 (levodopa: n=22, mean age, 58 [14] y, 11 women; placebo: n=25, mean age, 66 [9], 10 women)
Masihuzzaman et al, ³¹ Bangladesh	Randomized, not placebo, controlled trial	NR	NR	Ischemic (72%), hemorrhagic	Motor (hemiplegia)	Levodopa	125 mg	97 (levodopa+physiotherapy: n=51, mean age, 54.7 [15.1] y; no levodopa+physiotherapy: n=46, mean age, 58.1 [14.7] y; sex not reported)
Das et al, ³² Bangladesh	Randomized, not placebo, controlled trial	NR	NR	Ischemic (78%), hemorrhagic	Motor (hemiplegia)	Levodopa	110 mg	120 (levodopa: n=60, mean age, 59.0 [11.6] y, 17 women; placebo: n=60, mean age, 57.1 [12.4] y, 16 women)
Floel et al, ³³ Germany	Randomized, double-blind, placebo-controlled, crossover trial	Chronic	1–8 y	Ischemic (88%), hemorrhagic	Motor (paresis, MRC scale <2)	Levodopa/carbidopa	100/25 mg	9 (with crossover; mean age, 66.1 [9.5] y, 3 women)
Rösler et al, ³⁴ Germany	Randomized, double-blind, placebo-controlled trial	Chronic	1.5–8.3 y	NR	Motor (arm hemiparesis, MRC scale <2)	Levodopa/carbidopa	100/25 mg	18 (with crossover; mean age, 66.4 [6.8] y, 5 women)
Restemeyer et al, ³⁵ Germany	Randomized, double-blind, placebo-controlled crossover trial	Chronic	0.75–20 y	Ischemic	Motor deficit (hand paresis (degree of strength: 4–4+ on MRC scale))	Levodopa/carbidopa	100/25 mg levodopa/carbidopa+50 mg domperidone to prevent nausea	10 (with crossover; mean age, 62 [12] y, 6 women)
Acler et al, ³⁶ Italy	Randomized, single-blinded, placebo-controlled crossover trial	Chronic	10–48 mo	Ischemic	Motor (hemiparesis)	Levodopa/carbidopa	100/25 mg	10 (with crossover; mean age, 70 [8] y, 5 women)
Ford et al, ³⁷ United Kingdom	Randomized, double-blind, placebo-controlled trial	Acute to subacute	5–42 d	Ischemic (80–90%), hemorrhagic (excluding subarachnoid hemorrhage)	Motor (RMI score <7)	Levodopa/carbidopa	100/25 mg	593 (levodopa/carbidopa: n=308, mean age, 67.5 [13.6] y, 121 women; placebo: n=285, mean age, 69.6 [12.7] y, 108 women)
Walker-Batson et al, ³⁸ United States	Randomized, single-blinded, placebo-controlled clinical trial	Subacute	16–30 d	Ischemic	Motor (hemiplegia)	Dextroamphetamine	10 mg	10 (amphetamine: n=5, mean age, 61.2 [range, 48–73] y, 4 women; placebo: n=5, mean age, 67.8 [range, 62–71] y, 2 women)
Schuster et al, ³⁹ Switzerland	Randomized, double-blind, placebo-controlled trial	Subacute	14–60 d	Ischemic	Motor (CMSA score 1–5 in arm, hand, leg, or foot).	Dextroamphetamine	10 mg	16 (dextroamphetamine+physiotherapy: n=7, mean age, 70.3 [10] y, 5 women; placebo+physiotherapy: n=9, mean age, 65.2 [17] y, 3 women)

Treatment	Outcome studied	Assessments	Results	Adverse drug effects	Outcome	Jadad score
3 wk of daily levodopa or placebo+physiotherapy, then 3 wk of physiotherapy (1 h per weekday) only	RMA	Every week for 6 wk	Improved RMA scores after 3 wk of levodopa as compared with placebo, regardless of initial degree of impairment ($P<0.004$), and still superior at 6 wk ($P<0.020$).	Nausea ($n=1$)	Improvement	4
Levodopa or no levodopa before physiotherapy every 2 wk for 8 wk (4 visits total)	RMI	Every 2 wk	Improved RMI scores with levodopa irrespective of stroke subtypes ($P<0.001$).	NR	Improvement	1
Low-dose levodopa given 1.5 h before physiotherapy once every 2 wk for 8 wk	MRC grading and RMI scores	Every 2 wk	Improved MRC and RMI scores at each visit with levodopa compared with no levodopa.	NR	Improvement	1
2 sessions of levodopa or placebo 60 min before training separates by at least 24 h	Motor memory (% of transcranial magnetic stimulation-evoked movements in the training target zone)	Each session	Percentage of evoked thumb movements falling in the training target zone was higher in levodopa group than in placebo ($P=0.014$).	NR	Improvement	3
3 doses of levodopa/carbidopa or placebo before 1 session of procedural motor learning	Difference in reaction times between random and sequential elements, Modified Ashworth Scale for grading spasticity, RMA for upper arm	Each session	Levodopa significantly improved procedural motor learning as compared with placebo ($P<0.05$).	Dizziness ($n=1$), fatigue ($n=4$), and nausea ($n=3$) with statistically similar frequencies in treatment and nontreatment groups.	Improvement	4
Two sessions of levodopa or placebo before physiotherapy and TMS	Motor studies (Nine-Hole-Peg Test, a dynamometer measuring grip strength, and the Action Research Arm Test), TMS studies	Before drug, 45 min after drug, after physiotherapy	No improvement in motor function nor change in motor excitability as tested by TMS.	NR	No improvement	4
5 wk of levodopa or placebo (no physiotherapy) with pretreatment and posttreatment motor assessments and transcranial magnetic stimulation recordings from the affected and unaffected hemisphere	RMA, Nine-Hole Peg Test, 10-m walking test, and transcranial magnetic stimulation studies	Before and after 5 wk	Improved walking speed ($P<0.01$) and manual dexterity ($P<0.01$) with levodopa and lengthened cortical silent period over the affected hemisphere ($P<0.01$), whereas no changes were found in the placebo group.	Muscle stiffness ($n=2$)	Improvement	4
6 wk of levodopa/carbidopa or placebo 45–60 min before routine physiotherapy and occupational therapy	Ability to walk at least 10 meters independently at 8 wk ($RMI>7$), Nottingham Extended Activities of Daily Living Scale, others	8 wk, 6 mo, 12 mo	No improved ability to walk independently with levodopa/carbidopa (odds ratio, 0.78 [95% CI, 0.53–1.15]) at 8 wk.	Vomiting after study drug (6.2% in levodopa/carbidopa group vs 3.2% in placebo)	No improvement	5
10 sessions of physical therapy where patients received dextroamphetamine or placebo every fourth day	FM	Each session, 1 wk after drug stopped, and 3, 6, and 12 mo	Improved FM scores at 1 wk and 12 mo after drug discontinuation ($P=0.047$).	Sleeplessness ($n=1$) on 15 mg, dose decreased to 10 mg thereafter	Improvement	4
5 wk of dextroamphetamine or placebo before physiotherapy 2 d per week, multidisciplinary inpatient rehabilitation	CMSA	Baseline, every week for 5 wk, and at follow-up 1 wk, 6 mo, and 12 mo after intervention	Improvement in activities of daily living ($P=0.023$) and arm function ($P=0.020$) subscales, but not impairment, hand, foot, leg subscales of CMSA with dextroamphetamine.	None	Improvement (in 2 subscales only)	5

(Continued)

Table 2. Continued

Study	Study type	Poststroke period	Time since stroke	Type of stroke or other injury	Deficit	Drug	Dose	Patients
Sprigg et al, ⁴⁰ United Kingdom	Randomized, double-blind, placebo-controlled trial	Acute to subacute	3–30 d	Ischemic	Motor (mRS score <3 and Scandinavian Stroke Scale score <6)	Dextroamphetamine	10 mg	33 (amphetamine: n=17, mean age, 69 [12] y, 6 women; placebo: n=16, mean age, 73 [11] y, 12 women)
Sonde and Löök, ⁴¹ Sweden	Randomized, double-blind, placebo-controlled clinical trial	Acute	5–10 d	Ischemic	Motor (hemiplegia)	Levodopa or amphetamine	20 mg amphetamine or 100 mg levodopa or 10 mg amphetamine+50 mg levodopa	25 (amphetamine: n=7, mean age, 78.3 [9.1] y, 3 women; levodopa: n=4, mean age, 78.8 [3.9] y, 2 women; amphetamine/levodopa: n=7, mean age, 76.9 [8.4] y, 6 women; placebo: n=7, mean age, 77.6 [5.7] y, 2 women)
Gladstone et al, ⁴² Canada	Randomized, double-blind, placebo-controlled trial	Acute	5–10 d	Ischemic (>90%), hemorrhagic	Motor (hemiparesis)	Dextroamphetamine	10 mg	67 (dextroamphetamine: n=31, mean age, 67.8 [16.2] y, 15 women; placebo: n=36, mean age, 67.8 [13.9] y, 16 women)
Goldstein ⁴³ United States	Double-blind, block-randomized, placebo-controlled trial	Acute to subacute	10–30 d	Ischemic	Motor	Dextroamphetamine	10 mg	64 (dextroamphetamine: n=32, mean age, 67.5 [IQR, 57.0–77.5] y, 13 women; placebo: n=32, mean age, 65.5 [IQR, 56.0–75.0] y, 16 women)
Wang et al, ⁴⁴ United States	Randomized, double-blind, placebo-controlled pilot study	Acute to subacute	<1 mo	Ischemic	Motor (hand deficits)	Methylphenidate	20 mg	9 (methylphenidate: n=3, mean age, 43.3 y, 1 woman; tDCS: n=3, mean age, 51.7 y, 1 woman; both: n=3, mean age, 63.6 y, no women)
Tardy et al, ⁴⁵ France	Randomized, crossover, double-blind, placebo-controlled trial	Acute to subacute	9–35 d	Ischemic (88%), hemorrhagic	Motor (hemiparesis)	Methylphenidate	20 mg	8 (with crossover; mean age, 60 [range, 46–70] y, no women)
Lokk et al, ⁴⁶ Iran	Randomized, double-blind, placebo-controlled trial	Subacute	15–180 d	Ischemic	Motor (hemiparesis)	Methylphenidate or levodopa	20 mg methylphenidate or 125 mg levodopa	78 (methylphenidate: n=19, mean age, 64.1 [10.8] y, 10 women; levodopa: n=20, mean age, 66.3 [9.5] y, 6 women; methylphenidate+levodopa: n=19, mean age, 60.2 [9.1] y, 8 women; placebo: n=20, mean age, 65.3 [9.6] y, 6 women)
Cramer et al, ⁴⁷ United States	Randomized, double-blind, placebo-controlled trial	Subacute to chronic	1–12 mo	Ischemic, hemorrhagic	Motor (mRS score <2 and FM scores 23–83/100)	Ropinirole	4 mg (starting dose 0.25 mg with up titration)	33 (ropinirole+physiotherapy: n=17, mean age, 63 [13] y, 6 women; placebo+physiotherapy: n=16, mean age, 60 [15] y, 4 women)
Beladi Moghadam et al, ⁴⁸ Iran	Randomized, not blinded or placebo-controlled, trial	Acute	<24 h	Ischemic	Functionality	Memantine	20 mg 3× daily for 5 d, then 20 mg daily for 3 mo	53 (memantine: n=24, mean age, 75 [6.4] y; control: n=29, mean age 71 [5.9] y) sex NR

Unless otherwise specified, the dosage is daily. BI indicates Barthel index; CMSA, Chedoke-McMaster Stroke Assessment; FM, Fugl-Meyer; fMRI, functional magnetic resonance imaging; IQR, interquartile range; MRC, Medical Research Council; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NR, not reported by article authors; RMA, Rivermead Motor Assessment; RMI, Rivermead Mobility Index; tDCS, transcranial direct current stimulation; and TMS, transcranial magnetic stimulation.

Treatment	Outcome studied	Assessments	Results	Adverse drug effects	Outcome	Jadad score
11 sessions of inpatient physiotherapy where patients received dextroamphetamine or placebo 1–2 h before with 3–4 d separation	FM, BI, mRS	Days 35, 90	Amphetamine did not improve motor function (FM) at 90 d. Functional outcome (BI and mRS) did not differ between treatment groups.	Increases in blood pressure and heart rate in amphetamine group	No improvement	4
10 sessions of physiotherapy over 2 wk, with patients receiving drugs or placebo 1 h before session	FM and BI for activities of daily living	Baseline, at the end of the 10th session and at follow-up, 3 mo after stroke onset	No additional improvement in FM or BI with drug treatment.	None	No improvement	5
5 wk of dextroamphetamine or placebo coupled with physiotherapy twice per week	FM	Baseline, after each session, 6 wk, 3 mo	Motor scores improved during treatment in both groups, but there was no significant difference in FM scores between the amphetamine and placebo groups ($P=0.35$).	None	No improvement	5
6 sessions of physical therapy, patients received dextroamphetamine or placebo 1 h before, every 4 d+standard rehabilitation	FM	3 mo after stroke onset	No relative improvement in FM scores with dextroamphetamine as compared with placebo 3 mo after stroke.	None	No improvement	5
1 d of tDCS alone, methylphenidate alone, or both	Motor recovery, cortical excitability, Purdue Pegboard Test	After intervention	Improved Purdue pegboard gain scores with tDCS+methylphenidate than tDCS alone ($P=0.017$) or methylphenidate alone ($P=0.01$).	None	Improvement	4
1 session of motor tests and fMRI after either methylphenidate or placebo, with crossover to the other drug 7 d later	Finger-tapping test, hand grip strength, target pursuit task, fMRI	Baseline, 7 d	Improvement after methylphenidate compared with placebo in finger-tapping test ($P=0.009$), but not hand grip or target pursuit task.	Psychostimulation ($n=1$)	Improvement(in one measure only)	5
3-wk regimen of physiotherapy and daily methylphenidate or levodopa or placebo therapy	FM, BI, and NIHSS	Baseline, 15, 90, 180 d	No additional improvement in FM, BI, or NIHSS at 3 and 6 mo with active drugs as compared with placebo, however mean change over 6 mo in BI ($P=0.011$) and NIHSS ($P=0.001$) scores was significantly greater in the active drug groups.	None	Improvement(but not in motor scores)	5
9 wk of daily ropinirole or placebo coupled with 90-min physiotherapy sessions twice weekly during weeks 6–9.	Gait velocity (primary); safety, gait endurance, and FM (secondary)	Weeks 9 and 12	Gains in gait velocity did not differ by treatment assignment.	None	No improvement	5
Standard of care stroke treatment with or without addition of memantine for 3 mo	NIHSS, BI, and serum concentrations of matrix metalloproteinases as neuronal damage biomarkers (primary)	3 d, 5 d, and 3 mo	Memantine significantly improved the neurological function of the patients over the first few days of the study according to NIHSS ($P<0.0001$) and from day 5 to 3 mo according to BI ($P=0.002$) as compared with placebo.	Nausea without vomiting (10.52%)	Improvement in functionality	3

One early study by Scheidtmann et al³⁰ supported the claim that levodopa enhances physiotherapy outcomes in the subacute poststroke period (Table 2).

The trial by Scheidtmann et al³⁰ used a multiarm treatment protocol, had low power and a Jadad score of 4, and reported all side effects (1 case of nausea).³⁰

Two larger trials by Masihuzzaman et al³¹ and Das et al,³² who are from 1 group, later echoed the finding that levodopa can enhance physiotherapy outcomes (Table 2).

Trials by both Masihuzzaman et al³¹ and Das et al³² used a multiarm treatment protocol, but Masihuzzaman et al did not control with placebo. The trials by Masihuzzaman et al³¹ and Das et al³² are larger than the trial by Scheidtmann et al³⁰; however, they provide fewer details about their study population and methodology, and both earned a Jadad score of 1 (Scheidtmann et al score is 4).^{30–32} Neither report on safety nor tolerability. Neither report on time since stroke. Masihuzzaman et al³¹ did not report on the sex of participants. Age was comparable across both studies. Choice of end point measures was also comparable.

Together, these studies suggest some evidence that levodopa can enhance physiotherapy outcomes.

There were 4 studies on levodopa's effect on motor recovery in patients with chronic stroke.

Floel et al³³ found that levodopa possibly enhances the formation of motor memories in chronic stroke (Table 2). The same group later published a larger trial, by Rösner et al,³⁴ again demonstrating improved procedural motor learning with levodopa. Of note, mobility and strength assessments of the affected limb were not improved, which could suggest a lack of clinical significance.

Despite the small sample sizes of studies by both Floel et al³³ and Rösner et al,³⁴ Rösner et al demonstrated that they had adequate power. These 2 studies had Jadad scores of 3 and 4, respectively.^{33,34} Both utilized a cross-over design. The age, sex, and time since stroke of both participant pools were comparable. The dose of levodopa was not comparable as the trial by Rösner et al³⁴ had 3 doses of levodopa as compared with 2 in the trial by Floel et al³³. Side effect frequency was similar in the placebo and levodopa groups.³⁴ Floel et al³³ did not comment on side effects.

By contrast, Restemeyer et al³⁵ found no improvement with levodopa before physiotherapy and transcranial magnetic stimulation in chronic stroke (Table 2).

The study by Restemeyer et al³⁵ utilized a crossover design, had low power (N=10), and earned a Jadad score of 4 out of 5. The authors do not mention if there were side effects.

The last study on levodopa for motor recovery in patients with chronic stroke was by Acler et al,³⁶ and they had positive results after 5 weeks even without physiotherapy (Table 2).

The study by Acler et al³⁶ utilized a crossover design, had low power (N=10), and earned a Jadad score of 4 out of 5.

Although the above 4 studies are limited by their sizes, they suggest patients with chronic stroke may benefit from levodopa-enhanced physiotherapy sessions. It is not clear how long-lasting this effect may be, nor if it would affect motor actions not practiced during training sessions.

To test the hypothesis that levodopa helps with long-term motor memories, Ford et al³⁷ studied 593 patients with acute and subacute stroke over 12 months after levodopa administration (Table 2). It failed to show a lasting positive improvement in ability to walk at 12 months with levodopa.³⁷

This prospective, multiarm treatment study by Ford et al³⁷ was adequately powered, earned a Jadad score of 5, and reported all side effects (nausea in both groups).³⁷

In summary, levodopa may enhance motor memory and performance during training sessions with repeated administration before physiotherapy. One large, randomized controlled trial provides high-quality evidence that levodopa may not produce lasting improvements in motor function and memory formation.

Amphetamines

Amphetamines were the first compounds to be studied in motor rehabilitation after stroke, but multiple large-scale studies found amphetamines to bring little benefit and multiple undesirable side effects.

Walker-Batson et al³⁸ and Schuster et al³⁹ examined the effect of amphetamines on motor recovery in subacute stroke (Table 2). Walker-Batson et al³⁸ found improvement with amphetamines at 1 week and 12 months after drug discontinuation, although it is not clarified if the difference was significant at other time points during the study.³⁹ Schuster et al³⁹ found improvements in activities of daily living and arm (although not hand, foot, and leg) function with amphetamines.³⁹

Studies by both Walker-Batson et al³⁸ and Schuster et al³⁹ had low power (N=10, N=16), a multiarm treatment protocol, and high Jadad scores (4 and 5, respectively).^{38,39} The dose in both studies was 10 mg, only on days of physiotherapy, about twice a week. Side effects were described as sleeplessness in 1 patient in the study by Walker-Batson et al³⁸ and none in the study by Schuster et al.³⁹ The trial by Schuster et al³⁹ had poor interrater reliability.³⁹ Finally, the 2 trials used different scales.

The positive findings above were not replicated by 4 larger studies (Sprigg et al,⁴⁰ Sonde and Lökk,⁴¹ Gladstone et al,⁴² and Goldstein⁴³), despite all studies administering similar doses of the drug and having similar protocols (Table 2).

In these 4 studies, only multiarm treatment protocols were utilized, Jadad scores were either 4 or 5, and all side effects were reported.^{40–43} Subjects in the amphetamine group in the study by Sprigg et al⁴⁰ were more likely to be male.⁴⁰

In conclusion, despite early evidence in smaller studies that amphetamines might enhance Fugl-Meyer scores in patients with lasting arm or leg deficits, at least 4 newer and larger trials have failed to show a positive effect when amphetamines are given in the acute or subacute period of stroke. Moreover, these have fallen out of favor due to concern for adverse effects including insomnia, increases in heart rate and blood pressure, and psychiatric stimulation.

Methylphenidate

Methylphenidate is an indirect dopamine and norepinephrine agonist thought to have a positive effect on poststroke cognition, motivation, and mood.^{45,49,50}

Grade et al,⁵¹ Wang et al,⁴⁴ and Tardy et al⁴⁵ examined the effect of methylphenidate on motor recovery in acute (Grade et al) to subacute (Wang et al and Tardy et al) stroke (Table 2). The earliest study of methylphenidate for stroke recovery, by Grade et al,⁵¹ demonstrated improvements in depression and motor function with methylphenidate in patients with acute stroke⁵¹ (see sections Depression and Methylphenidate).

In the acute to subacute period, Wang et al⁴⁴ showed methylphenidate and transcranial direct current stimulation could improve hand motor deficits.⁴⁴ In a similar study, Tardy et al⁴⁵ showed improvement in a finger-tapping test with methylphenidate.⁴⁵

The studies by Wang et al⁴⁴ and Tardy et al⁴⁵ are small (N=9, N=8) and unlikely to be adequately powered.^{44,45} In addition, both studies utilized single-day administrations. The Jadad scores were 4 and 5 respectively. The study population of Tardy et al⁴⁵ was older than Wang et al⁴⁴ and did not have any women, as opposed to the study by Wang et al.

The largest study on methylphenidate to date, by Lökk et al,⁴⁶ showed no difference in activities of daily living and motor outcomes at 6 months with methylphenidate or levodopa versus placebo⁴⁶ (Table 2).

The quality of the trial by Lökk et al⁴⁶ was notable for having multiple arms with similar demographics, a large sample size (although power calculations are not included in the methodology), and a Jadad score of 5.⁴⁶ No side effects were reported.

Although there are some promising results in smaller and shorter studies on methylphenidate, 1 large, randomized trial has failed to show that methylphenidate improved motor and functional recovery after stroke (when given in the 6 months after stroke onset).

Ropinirole

Ropinirole is a dopaminergic agent comparable to levodopa.⁴⁷

Cramer et al⁴⁷ examined the effect of ropinirole on motor recovery in chronic stroke but found no additional improvement in gait velocity with ropinirole (Table 2).

The study by Cramer et al⁴⁷ had a multiarm treatment protocol with a Jadad score of 5.⁴⁷ No side effects were reported. The treatment arms had similar demographics.

The multiple negative trials for ropinirole and levodopa in motor recovery, taken together with the similarity of their mechanisms of action, suggest enhancing dopaminergic tone in the early stages of stroke recovery may not improve motor outcomes.

Memantine

As mentioned above, memantine is a *N*-methyl-D-aspartate receptor antagonist thought to help in cerebral ischemia.

One randomized, controlled trial on memantine was available. Beladi Moghadam et al⁴⁸ examined the effect of memantine on motor recovery in acute stroke and showed memantine could improve functionality scores at 3 months (Table 2).

The study by Beladi Moghadam et al⁴⁸ had a poor Jadad score of 3.⁴⁸ There was no placebo group. As this was a pilot trial, the number of participants was based on expert opinions and not powered based on other studies.

In conclusion, this trial provides initial evidence that memantine can improve functionality after stroke, though its results should be confirmed in better-designed studies.

Cognition

As compared with the extensive data available on aphasia and motor deficits, far fewer studies addressed global cognition. Only one study was identified on cognitive recovery in poststroke patients (methylphenidate, n=1; Table 3).

Methylphenidate

Luauté et al⁵² sought to evaluate whether methylphenidate could improve neglect in patients with subacute stroke (Table 3). Methylphenidate was similar to placebo in improving spatial neglect, likely due to success of a prism adaptation exercise used by the authors. Methylphenidate did have a positive effect on scores for activities of daily living. The authors suggested this may be due to methylphenidate's positive effect on mood, executive function, or fatigue.

The study by Luauté et al⁵² was adequately powered and earned a Jadad score of 5.⁵² Only 4 out of the 21 participants were women; however, the 2 treatment arms were comparable in terms of age and sex. The study drug was well tolerated.

In conclusion, there is some evidence to suggest that methylphenidate improves functionality after stroke, possibly via an effect on mood, executive function, or fatigue, though there is insufficient evidence to say it improves cognition.

Fatigue

Three studies on poststroke fatigue met our inclusion criteria (amantadine, n=1; modafinil, n=2; Table 3). Two are

Table 3. Trials on Cognition, Fatigue, and Depression in Poststroke Patients With at Least 2 Treatment Arms, Where One Arm Is a Neurostimulant, and the Other Is Placebo or Standard of Care

Study	Study type	Poststroke period	Time since stroke	Type of stroke or other injury	Deficit	Drug	Dose	Patients
Lauauté et al, ⁵² France	Randomized, double-blind, placebo-controlled trial	Subacute to chronic	2.6–12 mo	Ischemic/hemorrhagic	Neglect	Methylphenidate	10 mg twice a day	21 (methylphenidate: n=13, median age 58.9 [range, 48.1–67.9] y, 2 women; placebo: n=8, median age 55.55 [range, 29.3–62.8] y, 2 women)
Akçıl et al, ⁵³ Turkey	Randomized, unblinded, controlled trial	Acute	Upon admission	Hemorrhagic (subarachnoid)	Glasgow Coma Scale score <8/15	Amantadine	200 mg IV for 5 d, then 100 mg oral twice a day for 25 d	12 (amantadine: n=5, mean age, 50.6 [11.9] y, 2 women; control: n=7, mean age, 54.6 [8.4] y, 3 women)
Poulsen et al, ⁵⁴ Denmark	Randomized, double-blind, placebo-controlled trial	Acute	<14 d	Ischemic/hemorrhagic (ischemic in the modafinil group, 85% in control)	Fatigue	Modafinil	400 mg (200 mg if ≥65 y)	41 (modafinil: n=21, mean age, 69 [range, 62–79] y, 10 women; placebo: n=20, mean age, 71 [range, 65–82] y, 12 women)
Bivard et al, ⁵⁵ Australia	Randomized, double-blind, placebo-controlled trial	Subacute to chronic	3–38 mo	Ischemic/hemorrhagic (91% ischemic)	Fatigue (MFI score of ≥60)	Modafinil	200 mg	36 (with crossover; mean age, 63 [15] y, 14 women)
Grade et al, ⁵¹ United States	Randomized, double-blind, placebo-controlled trial	Acute	18 d (mean)	Ischemic/hemorrhagic	Depression, cognition, and motor	Methylphenidate	5 mg for 1 d, 10 mg for 1 d, then 5 mg added every 3 d	21 (methylphenidate: n=10, mean age, 69.8 [3.6] y, 6 women; placebo: n=11, mean age, 72.6 [3.5] y, 4 women)
Delbari et al, ⁵⁶ Iran (see Lokk et al ⁴⁶)	Randomized, double-blind, placebo-controlled trial	Subacute	15–180 d	Ischemic	Depression and cognition	Methylphenidate or levodopa	20 mg of either methylphenidate or placebo, combined with 125 mg levodopa or placebo	78 (methylphenidate: n=19, mean age, 64.1 [10.8] y, 10 women; levodopa: n=20, mean age, 66.3 [9.5] y, 6 women; methylphenidate+levodopa: n=19, mean age, 60.2 [9.1] y, 8 women; placebo: n=20, mean age, 65.3 [9.6] y, 6 women)

Unless otherwise specified, dosage is daily. CRS-R indicates Coma Recovery Scale–Revised; DASS, Depression, Anxiety, and Stress Scale; DRS, Disability Rating Scale; FIM, Functional Independence Measure; FMS, Fugl-Meyer Scale; FSS, Fatigue Severity Scale; HAM-D, Hamilton Depression Rating Scale; MFI-20, Multidimensional Fatigue Inventory 20; M-FIM, modified Functional Independence Measure; MMSE, Mini-Mental State Exam; MOCA, Montreal Cognitive Assessment; NR, not reported by article authors; SS-QoL, Stroke-Specific Quality of Life; and ZDS, Zung Self-Rating Depression Scale.

in the acute phase of stroke, and one is in the subacute to chronic phase.

Amantadine

Amantadine, a dopaminergic modulator (and a weak *N*-methyl-D-aspartate receptor antagonist), is often used for fatigue and amotivation in neurological disorders, notably traumatic brain injuries, and minimally conscious states, or for hyperkinesism in parkinsonism.⁵⁷

Although there were no trials of amantadine for poststroke fatigue, Akçıl et al⁵³ evaluated the impact of amantadine on patients with acute subarachnoid hemorrhage and found improved poststroke wakefulness and reduced disability (Table 3).

The trial by Akçıl et al⁵³ was underpowered (N=12).⁵³ There was no significant difference in terms of sex and age between the amantadine and control group. The trial

did not have a placebo arm, for a total Jadad score of 3. Side effects were not reported.

Given its utility in the world of traumatic brain injuries and coma as a wakefulness agent,⁵⁸ the possibility of using amantadine to ameliorate poststroke fatigue warrants further evaluation.

Modafinil

Modafinil is another wakefulness-promoting agent which acts via atypical dopaminergic receptors.^{59,60}

Poulsen et al⁵⁴ and Bivard et al⁵⁵ examined the impact of modafinil on poststroke fatigue in acute (Poulsen et al) and subacute to chronic (Bivard et al) stroke (Table 3). Poulsen et al⁵⁴ could not show improvement with modafinil, although fatigue improved in both groups. In contrast, the MIDAS trial (Modafinil in Debilitating Fatigue After Stroke) by Bivard et al⁵⁵ showed a positive

Treatment	Outcome studied	Assessments	Results	Adverse drug effects	Outcome	Jadad score
Prism adaptation exercises (days 12–15) with concurrent methylphenidate or placebo (days 11–15)	FIM score, Bergego scale	7, 15, 22, 45 d	No difference in spatial neglect, however, there was long-term functional improvement in FIM ($P=0.0318$) and on Bergego scale ($P=0.0204$) induced by methylphenidate combined with prism adaptation.	None	Improvement in functionality, not neglect	5
Standard of care subarachnoid hemorrhage treatment with or without addition of daily amantadine for 30 d	CRS-R and DRS	Baseline, 5, 90, 180 d	CRS-R was higher, and DRS lower for the amantadine group than standard care on day 5, and at months 3 and 6 (all $P<0.03$).	NR	Improvement	3
90 d of treatment with modafinil or placebo, 4 assessment time points over 180 d	MFI-20 (primary), FSS, SS-QoL, language	Baseline, 30, 90, 180 d	No difference in MFI-20 at 90 d ($P=0.3$), but fatigue improved by full FSS ($P=0.019$) and FSS-7 ($P=0.04$), and SS-QoL work/productivity ($P=0.007$), language ($P=0.012$), upper extremity function ($P=0.02$).	Dizziness ($n=2$), rash ($n=1$)	No improvement (by primary end point)	4
6 wk of modafinil or placebo, 1 wk washout, crossover, 6 wk of therapy	MFI-20, MOCA, the DASS, and the SS-QoL scale	Baseline, 6 wk, 13 wk	Decrease in fatigue by MFI-20 ($P<0.001$), improved quality of life by SS-QoL ($P=0.01$); no difference in MOCA ($P=0.36$) or DASS ($P=0.77$).	Headache ($n=4$), agitation ($n=3$), anxiety ($n=2$), dizziness ($n=2$), nausea ($n=1$)	Improvement	5
3 wk of daily methylphenidate or placebo and physiotherapy	HAM-D ZDS, MMSE, FMS, M-FIM	Baseline, weekly	Methylphenidate group scored lower on HAM-D ($F[1,18]=5.714$; $P=0.028$), lower on the ZDS ($F[1,18]=4.206$; $P=0.055$), higher on the M-FIM ($F[1,18]=5.374$; $P=0.032$), and higher on the FMS ($F[1,9]=4.060$; $P=0.075$) than patients receiving placebo after 3 wk. No difference in MMSE.	NR	Improvement	5
3 wk of physiotherapy and daily methylphenidate or levodopa or placebo therapy	Geriatric Depression Scale, MMSE	Baseline, 15, 90, 180 d	Improvement in mood when compared with placebo only w methylphenidate and levodopa (at 90 d [$P=0.018$] and 180 d [$P=0.006$]). No between-group difference in MMSE.	None	Improvement	5

effect of modafinil on poststroke fatigue in patients with established chronic fatigue after stroke.⁵⁵

The Poulsen et al⁵⁴ and MIDAS trials had a multi-arm treatment protocol and a crossover design, respectively.^{54,55} Sample sizes were 41 and 36, and Jadad scores were 4 and 5, respectively. The drug was poorly tolerated, although puzzlingly even more so at the lower dose and shorter treatment duration of the MIDAS trial. Rash ($n=1$) and dizziness ($n=2$) were reported by Poulsen et al,⁵⁴ and headache ($n=4$), agitation ($n=3$), and anxiety ($n=2$) were reported by Bivard et al.⁵⁵ The trials differed in the time since stroke, with a shorter interval since stroke in the trial by Poulsen et al.⁵⁴

In conclusion, the MIDAS trial offers preliminary evidence for modafinil's efficacy in chronic poststroke fatigue, but the medication had numerous side effects.

Depression

Although depression after stroke is widely studied, there are few trials evaluating the efficacy of stimulants for mood. A total of 2 studies (methylphenidate, $n=1$, methylphenidate or levodopa, $n=1$) were found on the treatment of depression in poststroke patients that met our inclusion criteria (Table 3). One is in the acute phase of stroke, and the other is in the subacute phase.

Methylphenidate or Levodopa

Methylphenidate had some early evidence of potential benefit in poststroke depression and apathy.^{61–65}

Two randomized, controlled trials found that methylphenidate may help with depression in acute (Grade et al⁶¹) and subacute (Delbari et al⁶⁵) stroke, although only when combined with levodopa for the later (Table 3). The

latter authors suggested this may be due to improvements in activities of daily living with methylphenidate and levodopa as they had demonstrated in a prior study cited above.⁴⁶

These studies utilized multiarm treatment protocols and earned Jadad scores of 5.^{51,56} Grade et al⁵¹ do not comment on side effects, but Delbari et al⁵⁶ report that there were none. The doses of methylphenidate were largely similar.

In conclusion, 2 randomized controlled trials on patients with poststroke depression offer equivocal evidence as to the efficacy of methylphenidate in improving mood.

DISCUSSION

In this narrative literature review, we describe the current evidence available on neurostimulants and potential efficacy to ameliorate poststroke aphasia, motor deficits, cognition, fatigue, and depression. We hope our review will serve as a comprehensive and accessible guide on

neurostimulants after stroke for the interested clinician. Other reviews on this topic are numerous but tend to focus on a subclass of medications or a type of poststroke deficit.^{5,21,66–75} For instance, Martinsson et al²¹ focused solely on amphetamines and their effect on poststroke recovery, and Zhang et al⁶⁷ focused solely on the pharmacological treatment of aphasia after stroke.

Our results are summarized in Table 4. In aphasia, there is preliminary evidence of efficacy for some stimulants, such as memantine, but not others, such as amantadine and bromocriptine. Few appropriately powered phase III trials exist. Amphetamines had insufficient evidence to support their efficacy for long-term recovery of aphasia. Levodopa may improve motor aphasia or have an impact on memory encoding of language. Although levodopa may improve motor memory formation in the short-term, larger studies showed that levodopa failed to improve the ability to walk 12 months after stroke.³⁷ Amphetamines and methylphenidate had poor and minimal evidence to support their use for motor recovery. These findings are in line with other published reviews

Table 4. Summary of the Findings

Deficit	Drug	Summary of findings
Aphasia	Bromocriptine (n=3)	One study showed improvement in language markers when combined with speech therapy.
		Poor study design and low power limit conclusions.
		Current evidence does not support bromocriptine for poststroke aphasia.
	Levodopa (n=3)	Evidence is inconclusive but suggests possible benefits in aphasias from frontal lobe lesions.
	Amphetamines (n=2)	Two small, low-power studies suggest short-term benefits for aphasia recovery.
Motor		Long-term effects are unclear.
	Memantine (n=1)	A single small, randomized trial shows potential for long-term aphasia recovery enhancement.
	Levodopa (n=10)	May enhance motor memory during physiotherapy when given before training.
		A large RCT suggests no lasting improvements in motor function or memory formation with daily use.
	Methylphenidate (n=4)	Early studies suggested benefits for motor recovery.
		Four larger, newer trials showed no positive effects in acute/subacute stroke.
		Concerns about side effects (insomnia, increased heart rate, psychiatric stimulation) led to decreased research interest.
	Amphetamines (n=6)	Smaller studies suggest potential benefits for motor recovery poststroke.
		A large RCT found no significant improvement in motor or functional recovery.
	Memantine (n=1)	One open-label trial (no placebo) shows possible functional improvements.
Cognition	Methylphenidate (n=1)	Further well-designed studies are needed.
		Limited evidence exists; 1 negative trial.
		Similar mechanisms with levodopa suggest no benefit in early stroke recovery for motor outcomes.
Fatigue	Amantadine (n=1)	May improve functionality through mood, executive function, or fatigue improvement.
		Insufficient evidence for efficacy in treating neglect.
	Modafinil (n=2)	Potential to address poststroke fatigue, supported by 1 small trial showing improvements in the Coma Recovery Scale after subarachnoid hemorrhage.
		Applicability to other stroke types is unclear.
Depression	Methylphenidate or levodopa (n=2)	MIDAS trial shows efficacy for chronic poststroke fatigue but with side effects.
		No benefit observed in acute stroke.
		Two RCTs on methylphenidate provide mixed evidence for mood improvement
		Suggests a potential link between motor recovery, daily activities, and mood.

MIDAS indicates Modafinil in Debilitating Fatigue After Stroke; n, number of included studies for each drug and deficit pair; and RCT, randomized controlled trial.

on this topic.^{69,71,76,77} With regards to poststroke deficits in cognition and depression, methylphenidate appears to have limited efficacy in poststroke cognitive improvement; however, it may improve poststroke functionality and mood (possibly via an effect on activities of daily living). Finally, modafinil may aid in poststroke fatigue.

The available trials had significant methodological challenges. Many were inadequately powered. In addition, there was considerable heterogeneity across protocols, drug dosages, and timing of drug administration. Jadad scores also varied widely. Differences in participant characteristics, such as age, sex, stroke severity, and time since stroke onset also complicated comparison, as did the lack of standardization in outcome measures and follow-up durations. These limitations highlight the need for larger, well-designed trials to establish definitive findings.

The period after stroke in which patients are recruited matters, as brain plasticity in the acute stroke period seems to be higher than in the chronic stroke period.¹⁵ Therefore, similar interventions may have different results owing to the potential for recovery of the patient. Thus, studies in the early poststroke period must have sufficient power to differentiate natural recovery from pharmacologically enhanced recovery. Our analysis reveals numerous instances where both the intervention and nonintervention groups measurably improved over the early poststroke study period, making a true benefit from the drug harder to observe.^{12,14,19,33,42,46,47}

Still, there are promising results that neurostimulants may have positive effects on stroke rehabilitation with few side effects.⁶⁸ Within the scope of this review, the neurostimulants mentioned are relatively safe and well tolerated, except for amphetamines.^{69,78} Common side effects of dopaminergic agents included nausea and muscle stiffness/dystonia (specifically levodopa and bromocriptine; Tables 1 and 2). Modafinil was associated with anxiety in 2 patients leading to discontinuation of the drug. Methylphenidate had few side effects reported other than psychostimulation in 1 patient. Given that most medications mentioned here are relatively safe, finding an appropriate and efficacious way to introduce them into clinical practice has the potential to greatly improve poststroke outcomes with little risk.

Despite their potential to improve stroke recovery, pharmacological adjuncts have an uncertain place in clinical practice. Large studies suggest that patients who receive these medications do not have significantly different lengths of stay, motor recovery, cognitive recovery, or discharge destination than patients who do not.⁶⁸ Still, it is possible that with optimal patient selection, timing, and dosing, adjunctive therapies may create real and lasting benefits for patients. For instance, if we can use biomarkers, whether blood tests or neuroimaging findings, to identify patients who will respond to these drugs early on, then larger trials might demonstrate efficacy. It

is worth noting that these medications are an adjuvant to rehabilitation therapy and to adequately assess their efficacy, they must be paired with rehabilitation therapy specific to the modality in question.

This review also highlights that stroke rehabilitation continues to be an interdisciplinary endeavor. Novel rehabilitation programs pair highly individualized therapy sessions with computer-assisted trainings and brain stimulation, such as transcranial direct current stimulation and transcranial magnetic stimulation.⁷⁰ Recovery is a complex process and requires mechanism-based approaches to rehabilitation which could involve pharmacotherapy.

Our study is limited by its narrative review format, which does not systematically search and assess all available evidence. Our approach, although valuable for providing a broad overview potentially introduces selection bias and limits the reproducibility of our findings.

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