Stroke

ORIGINAL CONTRIBUTION

Switching From Aspirin Monotherapy After Noncardioembolic Stroke: A Systematic Review and Network Meta-Analysis

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BACKGROUND: Patients who experience an ischemic stroke while on aspirin therapy present a clinical dilemma about optimal long-term secondary prevention. While switching to an alternative antithrombotic agent is often considered, the effectiveness of switching remains uncertain.

METHODS: We conducted a systematic review and network meta-analysis of randomized controlled trials reporting outcomes among patients with ischemic stroke while on aspirin and were either continued on aspirin or switched to an alternative antithrombotic therapy. Alternative antithrombotics included 2 trials of vitamin K antagonists (n=478), 3 trials of dual antiplatelet therapy (n=2229), 3 trials of direct oral anticoagulant (n=2660) monotherapy, and 1 trial of low-dose direct oral anticoagulant added onto aspirin (n=92). We excluded trials of patients with only short-term outcomes of 90 days or fewer, or those with cardioembolic sources of stroke requiring anticoagulation. Our primary outcome was recurrent ischemic stroke; the secondary outcome was a composite of ischemic stroke, myocardial infarction, and vascular death (or all-cause mortality). Outcomes reflect recurrent events measured over a median of ≈19 months (range 11–42 months). In the network portion of this meta-analysis, surface under the cumulative ranking curve rankings and pairwise meta-analyses were used to evaluate and compare the relative efficacy of alternative antithrombotic medications.

RESULTS: Data were available from 9 studies (total N=5459 patients) for the outcome of recurrent ischemic stroke. Switching to another therapy was associated with a pooled relative risk of recurrent stroke of 0.88 (95% CI, 0.76–1.03) compared with continuing aspirin, with minimal heterogeneity (P=0.93; I^2=0). For the composite secondary outcome, 6 studies contributed data, yielding a pooled relative risk of 0.89 (95% CI, 0.72–1.10). In the network meta-analysis, dabigatran, apixaban, and aspirin+low-dose rivaroxaban ranked the highest among antithrombotic alternatives to aspirin, though none were significantly better than continuing aspirin. Rankings were similar when based on posterior estimates from the clinical trials and when using predictive distributions that incorporate between-study variance (ie, expected performance in future settings).

CONCLUSIONS: Among patients experiencing ischemic stroke while taking aspirin, switching to an alternative antithrombotic therapy was not conclusively associated with a reduction in recurrent stroke and composite cardiovascular events. Trials are needed to determine whether specific antithrombotic strategies meaningfully improve outcomes in this high-risk population.

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

Key Words: anticoagulants ■ aspirin ■ ischemic stroke ■ secondary prevention ■ stroke

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Nonstandard Abbreviations and Acronyms

HR	hazard ratio
NMA	network meta-analysis
OR	odds ratio
PRISMA-NMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses
RCT	randomized controlled trial
RR	relative risk
SUCRA	surface under the cumulative ranking

Although aspirin is well established for secondary stroke prevention and widely used in patients with noncardioembolic stroke, the annual recurrence rate in people taking aspirin ranges from 3.3% to 14.5% per year, varying in part in relation to the cause of stroke and comorbidities.[1–3] Thus, there is a high morbidity and mortality burden of recurrent stroke in patients taking aspirin.

Unfortunately, for the large number of patients who have had a stroke while they were already taking aspirin, no randomized controlled trials (RCTs) have specifically evaluated whether switching to an alternative therapy (such as another antiplatelet regimen or an anticoagulant) is more effective as a long-term preventative strategy. Consequently, clinical practice is highly variable. Indeed, a recent American Heart Association Get With The Guidelines study found that nearly 40% of ischemic stroke survivors were taking aspirin monotherapy before their stroke, and 44.4% of them remained on aspirin monotherapy at discharge.[4]

We hypothesized that switching from aspirin to an alternative antithrombotic after noncardioembolic stroke would reduce the risk of recurrent stroke in the long term for those on aspirin at the time of the index stroke. We defined alternative antithrombotics to aspirin as a different antiplatelet or anticoagulant, or having an antiplatelet or anticoagulant added onto aspirin.

We conducted a systematic review and network meta-analysis (NMA) of randomized trials comparing aspirin to alternative antithrombotic regimens for stroke prevention; we focused on studies that provided subgroup data for patients who had their index ischemic stroke while already on aspirin as there are no randomized trials prospectively designed to enroll this specific aspirin-failure population and test long-term switching strategies We then performed a NMA to compare the relative efficacy of these treatments in this specific population.

METHODS

Protocol and Study Design

The original protocol used for this analysis is included in the Supplemental Appendix and registered with PROSPERO (URL: https://www.crd.york.ac.uk/PROSPERO/; Unique identifier: CRD42021279401). A systematic review and NMA were performed on RCTs involving any patients on aspirin before the index ischemic stroke who were then randomized to aspirin or another antithrombotic therapy. An amendment submitted to PROSPERO—not included in the original protocol—extended the study timeline to October 2024 (from 2022), given the numerous trials that were published in those 2 years that would qualify for this analysis. PRISMA-NMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses) were followed.[5] Data will be shared upon request from the corresponding author.

Search Strategy, Selection Criteria, and Data Extraction

We included RCTs comparing aspirin to another antithrombotic regimen after an ischemic stroke. To be included, the trial must have had available data about aspirin use at the time of the index event and outcome data in relation to that exposure. We limited our analysis to trials examining noncardioembolic stroke subtypes. Stand-alone abstracts were included in our search; however, abstract-only records without sufficient data were not included in the meta-analysis.

We excluded studies that specifically enrolled patients with atrial fibrillation or malignancy. In clinical practice, patients with atrial fibrillation or malignancy have a relatively strong indication for anticoagulation. We excluded studies with a follow-up duration of ≤3 months, as we were focused on long-term outcomes, but no upper limit for follow-up was prespecified; patients are expected to be on these medications for the rest of their lives. We also excluded non-English publications.

We searched through the following databases up to October 2024: PubMed, Embase, Scopus, Clinicaltrials.gov, and Cochrane Library, as well as the reference lists of key papers in consultation with experts. When using these databases, we selected for clinical trials only if that feature was available. Our search terms are in the Supplementary Appendix.

Two neurovascular physicians (A.R. and O.K.) screened titles and abstracts of retrieved citations independently. Discrepancies were resolved by discussion and, if no agreement was reached, by a third neurovascular physician (S.E.K.). The 2 investigators (A.R. and O.K.) also rated the methodology for risk of bias using Cochrane's risk of bias 2 (RoB 2) tool for randomized trials (Supplemental Appendix 2).[6] Areas of disagreement were resolved by a third reviewer (S.E.K.) if necessary.

From the eligible studies, we extracted adjusted relative risk (RR) ratios, odds ratios (ORs), or hazard ratios (HRs) and 95% CIs for recurrent ischemic stroke. We excluded trials reporting only outcomes at 3 months or less (in included trials, follow-up ranged from 11 to 42 months). All data were extracted directly from the source manuscript, abstract, its supplementary material, or a published substudy. If the data could not be obtained from the published domain, information was sought by contacting the primary authors.

Outcomes

Our primary outcome was recurrent ischemic stroke. Our secondary outcome was a composite of ischemic stroke, myocardial infarction, and vascular death. If vascular death was not

available, we used all-cause mortality instead. This was done to maximize inclusion of relevant data.

Statistical Analysis

We created a summary statistic and variance for each trial and applied a weight to each trial based on the inverse of the variance. We selected a fixed-effects inverse-variance model given the minimal between-study heterogeneity. We pooled summary statistics from each study. Because there was a lack of transitivity—the assumption that the distribution of important effect modifiers is sufficiently similar across trials so that indirect comparisons are valid—in our qualitative synthesis of the studies, with substantial variation in baseline characteristics, we conducted the quantitative network portion of the analysis as a sensitivity analysis.

Because ischemic stroke is a relatively uncommon outcome across included studies, the absolute event rates were expected to be low, and ORs, HRs, and RRs converge under such conditions.[7] Therefore, we pooled these estimates in a meta-analysis by treating them as approximate RRs. If unpublished data were provided, RRs were calculated directly. SEs were formed using a log RR with its SE. We assessed between-study heterogeneity using Cochran's Q and I^2 statistics and between-study variance (τ^2). Q=3.02 with df=8 (P=0.93), I^2=0, and τ^2 was estimated as 0 based on DerSimonian-Laird methods. On this basis, we used a fixed-effects model for the primary analysis. Recognizing that I^2 can be biased toward 0 with few studies and low event rates, we report Q, I^2, and τ^2 alongside pooled effects and interpret no observed heterogeneity with caution. We also conducted a sensitivity analysis, differentiating studies that included anticoagulation and those that switched patients to another antiplatelet therapy.

All contributing subgroup data sets were 2-arm comparisons versus aspirin; therefore, no special multi-arm adjustment was required.

Regarding the network portion of our meta-analysis, we first conducted a qualitative synthesis that assessed for clinical and methodological heterogeneity as well as transitivity. Transitivity refers to the assumption that treatment comparisons across different studies are valid if the populations, interventions, and outcomes are sufficiently similar. In a NMA, this allows for indirect comparisons between treatments that have not been directly compared in head-to-head trials. In our qualitative synthesis, there was substantial variation in baseline characteristics—such as hypertension and smoking—across these studies. Moreover, there was variability in blinding; multiple studies did not use double-blinding, while others did.[8,9] This suggests intransitivity. Thus, we decided that a quantitative synthesis for a NMA would be a sensitivity analysis rather than the primary analysis.[10] This was done to explore rankings among therapies in the absence of direct comparisons, rather than to make firm conclusions on individual comparisons.

For the NMA, we used a multivariate model with the reference treatment, which was the use of aspirin, as well as a comparison between the nonaspirin treatments. We checked the consistency assumption and found the network was star-shaped. We summarized the network geometry using an aspirin-anchored graph (Figure S2) and tabulated study counts and sample sizes per node and comparison. This structure limited the ability to formally test consistency between direct and indirect comparisons. We also used the surface under the cumulative ranking (SUCRA) to determine the relative rankings of treatments.[11] SUCRA is a method used in NMA to rank treatments. SUCRA values range from 0 to 1, with higher values indicating a higher probability that a treatment is among the most effective or safest options.

Analysis was conducted in STATA version 16 and R.

RESULTS

Study Selection

A systematic search identified a total of 233 191 publications and abstracts using the search terms (see Supplemental Appendix). Due to the high volume of records screened, detailed counts for each reason for exclusion at the title/abstract stage were not retained. However, all exclusions fell under predefined categories specified in the protocol: not RCTs, wrong population, comparator, outcome, or follow-up duration. In particular, even while we prescreened specifically for RCTs using our search terms, a large number of abstracts initially queried were not RCTs. Moreover, the duplicate removal feature on Covidence was not perfect in removing duplicate studies. In addition, plenty of cardiology trials looking at the use of aspirin and other antithrombotics with cardiology-specific outcomes were also screened out manually. Together, this explains the extraordinary decrease from the first to the second round of screening. Thus, of the total number of studies screened, 33 were potentially eligible for inclusion (Figure 1; Table 1). Study-level characteristics for the 33 studies are included in Table S1. Of these 33 publications and abstracts, we obtained sufficient data either from contacting the primary authors or from the publications themselves for 9 studies. We sought additional data from the primary authors of the other 24 studies. Of the 24 contacted, 9 did not reply, and 14 replied that they did not have the data we requested, most often because they did not keep track of whether patients were on aspirin before the index event, or did not have access to the original trial data. In 1 case, most, if not all, the patients were on clopidogrel before and throughout the trial.[18] Thus, only 9 of the 33 potentially eligible trials had either published data that could be used in our analysis or responded to our inquiry and provided unpublished data that matched our requirements. Of the 9 studies included in this study, 4 required us to contact the investigators for unpublished data.

Publication Bias

Statistical heterogeneity across studies was low; the statistical test for heterogeneity was nonsignificant (Q(8)=3.02; P=0.93; I^2=0; τ^2=0), a pattern that is plausible given low event rates and the small number of trials but may also reflect limited power to detect

ORIGINAL CONTRIBUTION

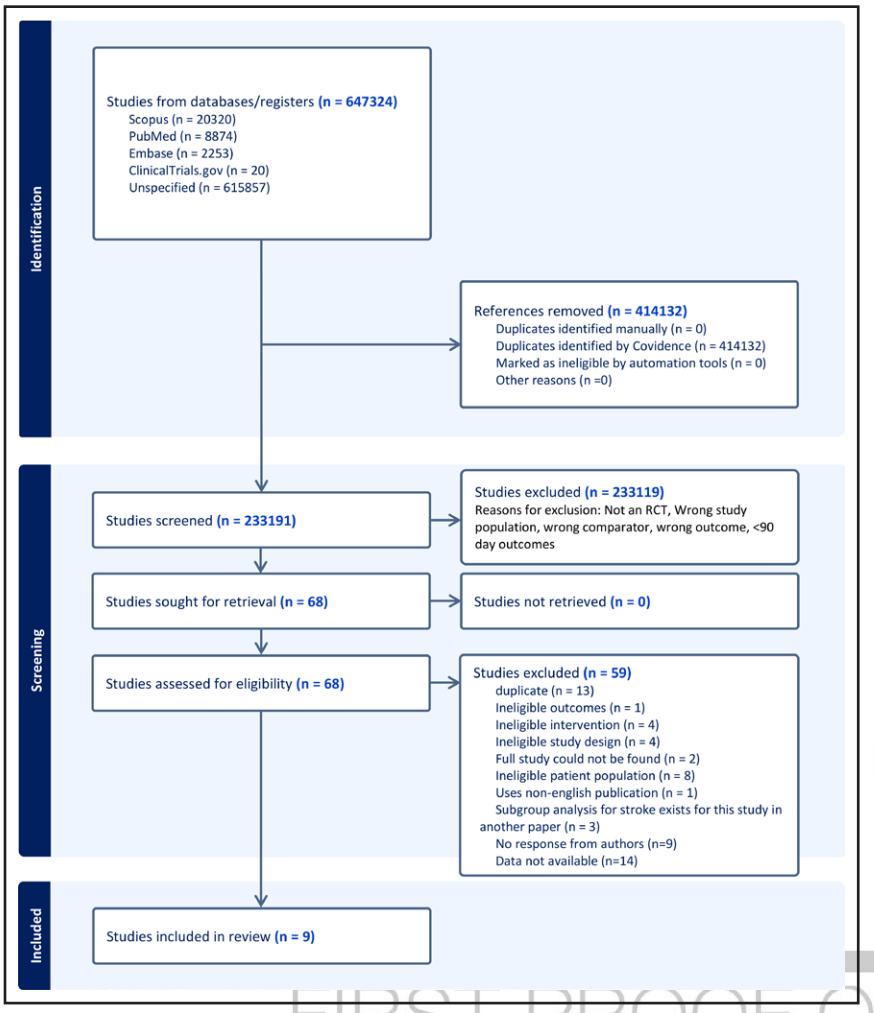

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses) flow diagram illustrating identification, screening, eligibility, and inclusion of randomized controlled trials (RCTs).

heterogeneity. These findings support the use of a fixed-effects inverse-variance model for pooling estimates for primary and secondary outcomes.

A funnel plot (Figure S1) was used to assess the presence of publication bias. Visual inspection of the plot suggested asymmetry, with fewer studies appearing in the lower-right region of the plot, where smaller studies with positive treatment effects would be expected. This pattern may indicate potential small-study effects or publication bias. However, an Egger test did not indicate significant evidence of publication bias (P=0.31).

Of the 9 studies included, no study was judged as high risk on the Cochrane's RoB tool overall. Three of the 9 were overall low risk, and 6 of 9 had overall some concerns, most commonly due to open-label design. Domain-level and overall judgments for each trial are shown in Supplemental Material 1.

Outcomes

For the primary outcome of ischemic stroke, there were 5459 patients from 9 studies. The pooled effect estimate (95% CI) was RR=0.88 (0.76, 1.03). A forest plot with individual and summary estimates is displayed in Figure 2. For the secondary outcome, only 6 of the 9 studies had these data. The pooled effect estimate was RR=0.89 (0.72, 1.10). A forest plot with individual and summary estimates is displayed in Figure 3.

NMA

As our qualitative synthesis noted baseline differences in demographic variables and trial design among the trials, we considered the NMA to be a sensitivity analysis. In our NMA, we created a network plot with aspirin as the comparator group for all treatments (Figure S2), and we combined the warfarin group from WARSS with the vitamin K antagonists from ESPRIT under the label VKA (vitamin K antagonist), as warfarin is a vitamin K antagonist.[19,20]

We then evaluated whether the indirect comparisons in our NMA were consistent with one another. In our analysis, all treatments were compared only to aspirin—there were no studies that directly compared the non-aspirin treatments to each other. This limited our ability to assess whether the indirect comparisons were reliable.

Table 1. Characteristics of Included Studies With Data Available for >90 Days of Follow-Up

Study title	Design	Population in trial	Antithrombotic compared with aspirin	Aspirin dose, mg	Year	No. of patients analyzed/ No. of patients in the original trial	Follow up duration in trial, months	Data availability	Location of patient population
A Randomized Trial of Anticoagulants Versus Aspirin After Cerebral Ischemia of Presumed Arterial Origin (SPIRIT)[9]	Open-label RCT	Patients with recent (<6 mo) minor stroke or TIA of noncardioembolic origin, excluding high-grade carotid stenosis or atrial fibrillation.	Anticoagulation (INR target 3.5) with phenprocoumon, acenocoumarol, or warfarin (referred to as "VKA" [vitamin K antagonists] in the analysis)	30–100	1997	297/1316	14	From investigator	Europe, United Kingdom, Australia
A Comparison of Warfarin and Aspirin for the Prevention of Recurrent Ischemic Strokes (WARSS)[12]	Double blind RCT	Patients with ischemic stroke within 30 d, excluding cardioembolic and high-grade carotid stenosis etiologies.	Warfarin (goal INR 1.4–2.8)	325	2001	181/2206	24	From the published abstract	United States
Aspirin Plus Dipyridamole Versus Aspirin Alone After Cerebral Ischemia of Arterial Origin (ESPRIT)[13]	Open-label RCT	Patients with minor stroke or TIA within 6 mo, presumed arterial origin; excluding those with potential cardiac embolic sources.	Aspirin + dipyridamole	30–325	2006	628/2763	42	From investigator	Europe, United Kingdom, Australia, United States
Study for the Prevention of Small Subcortical Strokes (SPS 3)[1]	Double blind RCT	Patients with symptomatic lacunar stroke in the prior 180 d, without high-grade carotid disease or cardioembolic risk.	Aspirin +clopidogrel	325	2014	838/3020	41	From the published substudy	North America, Latin America, Spain
Navigate ESUS: New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source[14]	Double blind RCT	Patients with nonlacunar ischemic stroke within 7 d–6 mo; no major artery stenosis, and no identified cardiac embolic source.	Rivaroxaban	100	2018	1226/7213	11	From the published substudy	Europe, Asia, North America, Canada, Latin America
RE-SPECT ESUS: Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source[15]	Double blind RCT	Patients with ESUS within 3–6 mo, depending on age and risk factors.	Dabigatran	100	2019	1316/5390	19	From the published substudy	Europe, Asia, North America, and Latin America
Dual Antiplatelet Therapy Using Cilostazol for Secondary Prevention in High-Risk Ischemic Stroke (CSPS.com)[8]	Open-label RCT	High-risk patients with noncardioembolic ischemic stroke on MRI within 8–180 d	Aspirin + cilostazol	81 or 100	2019	763/1884	17	From the published substudy	Japan
Apixaban Versus Aspirin for Embolic Stroke of Undetermined Source (ATTICUS)[16]	Open-label RCT	Patients with ESUS within 3–28 d, enriched for at least 1 atrial fibrillation risk factor (clinical, ECG, or echocardiographic)	Apixaban	100	2023	118/352	12 (primary outcome follow-up)	From investigator	Germany

(*Continued*)

Table 1. Continued

Study title	Design	Population in trial	Antithrombotic compared with aspirin	Aspirin dose, mg	Year	No. of patients analyzed/ No. of patients in the original trial	Follow up duration in trial, months	Data availability	Location of patient population
Combination Antithrombotic Therapy for Recurrent Ischemic Stroke in Intracranial Atherosclerotic Disease (CATIS-ICAD)[17]	Open-label RCT	Patients with ischemic stroke or high-risk TIA due to intracranial stenosis (30% to 99%).	Aspirin + rivaroxaban 2.5 mg BID	81	2023	92/101	20	From investigator	Canada

ASA indicates aspirin; ESUS, embolic stroke of undetermined source; MRI, magnetic resonance imaging; and RCT, randomized controlled trial.

While a global statistical test suggested no inconsistency (*P*=0.42), this finding should be interpreted cautiously because of the limited network structure. Our results depend heavily on indirect comparisons, and without direct head-to-head trials between nonaspirin treatments, there is greater uncertainty around the relative rankings. We also examined a comparison-adjusted funnel plot and found no major evidence of small-study bias.

The relative effect sizes of different treatments were compared with aspirin (Table 2). CSPS.com (aspirin+cilostazol), Atticus (apixaban), and CATIS-ICAD (aspirin+low-dose rivaroxaban) appeared to have the greatest effect on reducing the risk of recurrent ischemic stroke (RR=0.57, 0.58, and 0.58, respectively); however, no significant differences among treatments were observed.

We then created a league table to present pairwise comparisons between different treatments (Table S2). There was no treatment in the network that showed statistical significance in 1 direction over another. To determine the relative rankings of treatments, we used the SUCRA curve to produce rankograms for all treatments. These included the SUCRA treatment ranking, PrBest (Probability of being the best treatment), and the mean rank position. Subsequently, we ran a network rank command to estimate the predictive ranking probabilities. Consequently, we could compare the cumulative ranking plots based on the estimated and predictive ranking probabilities (Table 3). Predictive rankings incorporate uncertainty and reflect how these treatments might perform in future settings.

Treatment rankings suggest that dabigatran, apixaban, and aspirin+low-dose rivaroxaban were the highest-ranked treatments. The poorest performing treatments included aspirin alone, rivaroxaban, and aspirin+cilostazol. The similarity between estimated and predictive ranks suggests these findings are more likely to reflect reality.

Sensitivity Analyses

For sensitivity analyses, we calculated a pooled estimate in just the studies that had patients switch to antiplatelets and just the studies that had patients switch to anticoagulation. In the analysis limited to antiplatelet agents, the pooled estimate for switching from aspirin was RR=0.80 (0.61, 1.06; Figure 4).

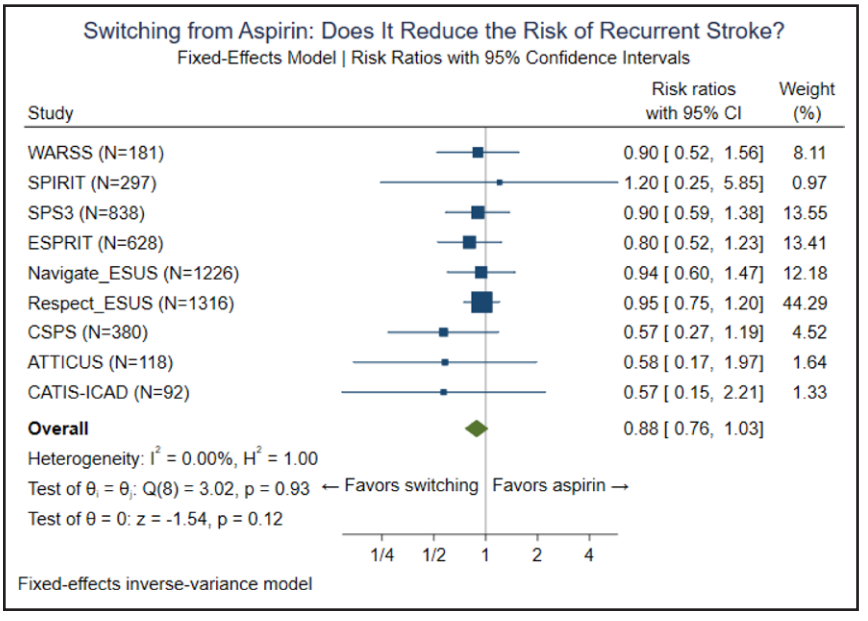

Figure 2. Forest plot showing pooled effect estimate for recurrent ischemic stroke comparing switch vs continue aspirin.
ESUS indicates embolic stroke of undetermined source.

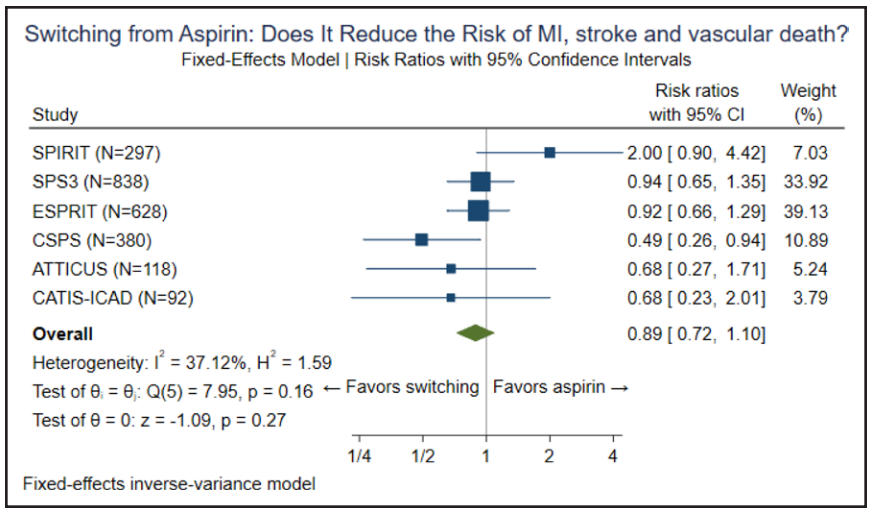

Figure 3. Forest plot showing pooled effect estimate for composite outcome of ischemic stroke, myocardial infarction (MI), and vascular death (or all-cause mortality).

In the analysis limited to anticoagulants, the pooled estimate for switching was RR=0.93 (0.77, 1.12; Figure 5).

DISCUSSION

In our systematic review and NMA, the pooled RR for switching antithrombotic therapies after a patient has a stroke while on aspirin was RR=0.88 (0.76, 1.03). This result suggests there may be a small but clinically important effect on reducing recurrent ischemic stroke risk if the patient is switched to a different regimen. Similar results were found for a composite outcome of ischemic stroke, myocardial infarction, and vascular or all-cause mortality. These findings merit future studies designed to compare these treatment strategies in patients who have a stroke while on aspirin.

In our NMA, we found that dabigatran, apixaban, and aspirin+low-dose rivaroxaban were the highest-ranked treatments for reducing recurrent ischemic stroke. This partially aligns with prior literature. For example, apixaban is a drug with a nearly equivalent bleeding risk to aspirin and strong evidence of efficacy for secondary stroke prevention in atrial fibrillation, even though it has not been shown to be superior to aspirin in patients with embolic stroke of undetermined source.[21,22] Similarly, aspirin and low-dose rivaroxaban as a combination reduced the risk of recurrent ischemic stroke in the COMPASS and COMMANDER-HF trials, and it is a regimen that is used for secondary stroke prevention in patients with vascular disease.[23,24]

Moreover, all of the treatments evaluated in our NMA ranked above aspirin, suggesting that patients who experience a stroke while on aspirin may remain at high risk of recurrence on aspirin.[25,26] While the network findings were inconclusive, they highlight a critical need for further research to identify effective secondary prevention strategies in this high-risk population.

The literature surrounding the choice of antithrombotic therapy in people who have experienced a stroke while taking aspirin is sparse, which is reflected in practice variability. Our protocol (including Figures S3 and S4) describes this gap in detail. Given the high prevalence of aspirin use, even a modest benefit, if present, could translate into a substantial population-level impact.

Table 2. Relative Effect Sizes of Treatments for Network Meta-Analysis

Study	Comparison	RR (95% CI)
SPIRIT and WARSS	VKA vs aspirin	0.93 (0.55–1.56)
SPS3	Aspirin+clopidogrel vs aspirin	0.90 (0.68–1.38)
ESPRIT	Aspirin+dipyridamole vs aspirin	0.80 (0.52–1.23)
Navigate-ESUS	Rivaroxaban vs aspirin	0.94 (0.60–1.47)
Respect-ESUS	Dabigatran vs aspirin	0.95 (0.75–1.20)
CSPS.com	Aspirin+cilostazol vs aspirin	0.57 (0.27–1.19)
ATTICUS	Apixaban vs aspirin	0.58 (0.17–1.97)
CATIS-ICAD	Aspirin+low-dose rivaroxaban vs aspirin	0.57 (0.15–2.21)

ESUS indicates embolic stroke of undetermined source; RR, relative risk; and VKA, vitamin K antagonist.

Table 3. Treatment Rankings: Estimated and Predicted Treatment Rankings From Best Treatments to Worst in Preventing Recurrent Ischemic Stroke, Where a Lower Mean Rank Indicates a Better Treatment

Treatment	Estimated mean rank	Predictive mean rank
Dabigatran	2.8	2.7
Apixaban	3.4	3.5
Aspirin+rivaroxaban	3.5	3.5
Aspirin+dipyridamole	4.6	4.6
Aspirin+clopidogrel	5.6	5.6
VKA	5.9	5.9
Aspirin+cilostazol	6.0	6.1
Rivaroxaban	6.2	6.2
Aspirin	6.9	7.0

VKA indicates vitamin K antagonist.

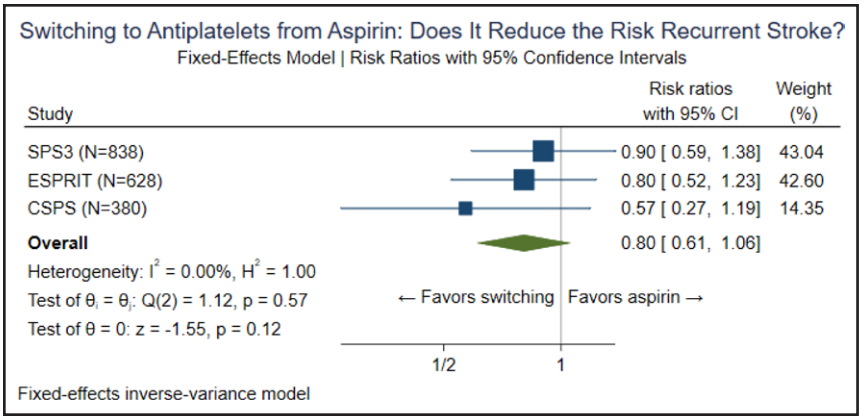

Figure 4. Forest plot showing pooled effect estimate for recurrent ischemic stroke in antiplatelet studies only.

Some observational studies have attempted to answer this question. For instance, in 1 nonrandomized study of 1172 patients, compared with maintaining aspirin monotherapy, switching to another antiplatelet agent was associated with a reduction in the risk of the composite of stroke, myocardial infarction and vascular death (HR, 0.50 [95% CI, 0.27–0.92]) and adding on another antiplatelet agent was also associated with a reduced risk of the composite of stroke, myocardial infarction, and vascular death (HR, 0.40 [95% CI, 0.27–0.72]).[2]

A prior meta-analysis of 5 randomized and nonrandomized studies found that switching to another antiplatelet agent versus aspirin monotherapy was associated with reduced risks of major adverse cardiovascular events (HR, 0.68 [95% CI, 0.54–0.85]) and recurrent stroke (HR, 0.70 [95% CI, 0.54–0.92]).[27] However, over 90% of patients were enrolled in the acute setting, and about half were followed for only 90 days. Given our concern about acute versus long-term differences in aspirin use, this meta-analysis suggests a short-term benefit but is less helpful for addressing whether there is a long-term benefit.

Our study tried to address these limitations by examining only RCTs that followed patients for longer than 90 days. Prior trials such as CHANCE and POINT have demonstrated that short-term dual antiplatelet therapy reduces early recurrence risk.[28,29] However, these trials lacked long-term data beyond 90 days, after which only aspirin monotherapy might be used. Our results, therefore, complement these findings by focusing on the long-term treatment landscape and highlighting the need for trials evaluating optimal maintenance therapy after the acute period.

This provides additional clarity for clinicians faced with aspirin failure, that is, when patients have an event despite aspirin. This may occur due to a poor platelet response to aspirin secondary to genetic mutations as measured by a platelet aggregation assay, which is correlated with a higher risk of recurrent cardiovascular events.[30,31] It also may occur in the setting of increased platelet production, too, which means there is a greater proportion of platelets unexposed to aspirin; or metabolic syndrome, which accelerates platelet turnover and adherence.[31,32] Thus, it might make mechanistic sense for patients to switch to another antithrombotic regimen after a cardiovascular event while on aspirin. Nevertheless, there are likely nuanced differences among patients in this population. Not all of them are physiologically unresponsive to aspirin or respond to alternative antithrombotics. This is further demonstrated by our inconclusive results with over 5000 of these patients.

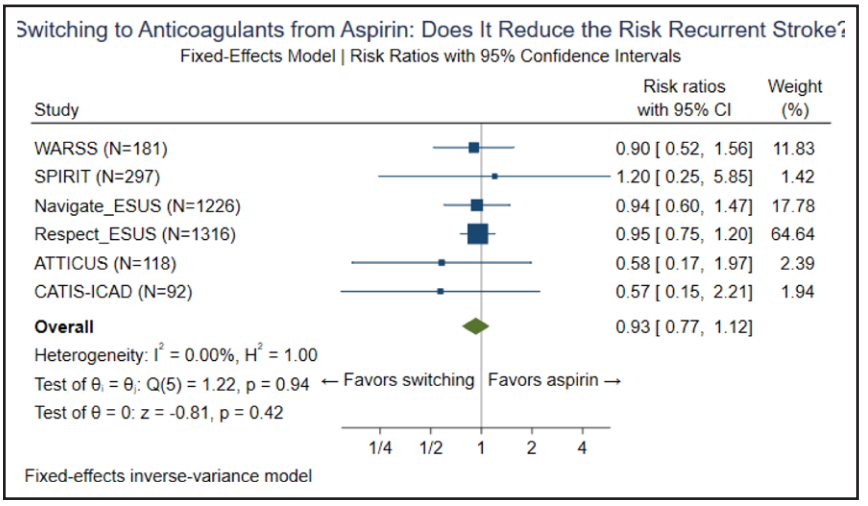

Figure 5. Forest plot showing pooled effect estimate for recurrent ischemic stroke in anticoagulant studies only.
ESUS indicates embolic stroke of undetermined source.

And there are several weaknesses to our approach despite attempting to include only RCTs. First, no trial was prospectively designed to randomize only patients who have had a stroke while already on aspirin; our estimates, therefore, depend on subgroup analyses within broader RCTs, which can limit causal inference for this population. Additionally, many potentially eligible studies did not have the data (or the primary author did not respond to our inquiries) on what antithrombotics patients were taking at the time of the index event. This has been an oversight in many secondary stroke prevention trials, and 1 that we suggest changing. This lack of data may have introduced bias (though the direction and magnitude are uncertain) and decreased our statistical precision. It is also true that in some data sets, patients may have been misclassified as being on aspirin at the time of enrollment rather than on aspirin at the time of the index event. Moreover, it is not clear if some patients were or were not reliably taking aspirin before their index event. This is an important distinction as it might mean there are some patients included in this study who were not on aspirin before stroke onset, biasing results towards the null. Third, this was not an individual patient-level meta-analysis, which constrained our ability to account for reporting inconsistencies, such as variability in raw patient data. It also limited our ability to adjust for baseline characteristics and other potential confounders, such as age and stroke pathogenesis. Indeed, even within different trials, there were patients with different stroke subtypes. It also meant we were unable to include major bleeding in our primary or secondary outcomes due to the inconsistent availability of this data. This limits our ability to assess net clinical benefit, especially in trials where stroke reduction may be offset by higher bleeding risk. It further prevented us from testing whether the effect of the assigned treatment differed based on the baseline treatment, which would have provided a more accurate assessment of our research question. Fourth, there were studies for which we had to substitute all-cause mortality for cardiovascular mortality in our secondary outcome analysis; this introduced inconsistency and likely biased results towards the null by diluting cardiovascular-specific effects. Fifth, the studies with available data spanned a range of nearly 30 years, which means that aspirin doses before enrollment differed across studies and anticoagulants that were higher risk or less effective were used in the earlier studies compared with the later ones. This could have biased our results towards the null by including studies with obsolete antithrombotics. Sixth, multiple data sets were from studies that were not double-blinded.[8,9,33] This may have created some bias away from the null in the results from those studies. Seventh, the NMA was limited by indirect comparisons and potential violations of transitivity. And although we selected trials with follow-up periods exceeding 90 days to focus on long-term secondary prevention, we could not exclude the possibility that recurrent strokes occurred in the early poststroke period—a time of particularly heightened risk. This overlap makes it difficult to fully isolate the long-term effects of antithrombotic strategies, as some of the observed benefits or lack thereof may reflect short-term protection during the initial high-risk window. Furthermore, the absence of observed heterogeneity in our study should not be taken to imply that the included studies are clinically identical. With only 9 studies and low event rates, the power to detect genuine between-study differences is limited. Accordingly, our pooled estimates should be interpreted with his limitation in mind. And last of all, because safety outcomes like major bleeding were not consistently reported, we could not evaluate the net clinical benefit of each strategy.

CONCLUSIONS

This comprehensive systematic review and NMA did not find a significant difference in the risk of recurrent ischemic stroke between patients who switched antithrombotic therapies and those who remained on aspirin after experiencing an ischemic stroke while already on aspirin. However, the point estimates in all analyses favored switching therapies. These findings underscore the need for future stroke prevention trials to evaluate optimal antithrombotic management following ischemic stroke while on aspirin.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S2
Figures S1–S5
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Protocol for Systematic Review and Network Meta-Analysis
Search Strategy and Terms

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