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Effectiveness of Aspirin for Stroke Prevention in High-Risk Vascular Patients: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

Maame Ama Owusuaa-Asante, PhD
Department of Health, Wellbeing and Social Care, Oxford Brookes University, GBS Partnership, Birmingham, United Kingdom; and PENKUP Research Institute, Birmingham, United Kingdom

Gordon Mabengban Yakpir, PhD
Faculty of Health, Wellbeing & Social Care, Oxford Brookes University, GBS Partnership, Birmingham Campus, United Kingdom; and PENKUP Research Institute, Birmingham, United Kingdom

Kennedy Oberhiri Obohwemu, PhD
Department of Health, Wellbeing and Social Care, Oxford Brookes University, GBS Partnership, Birmingham, United Kingdom; and PENKUP Research Institute, Birmingham, United Kingdom

Jane Amedzro, MPH
Faculty of Health Sciences, De Montfort University, Leicester, United Kingdom

Osinubi Olusunmola, PhD
Faculty of Health, Wellbeing & Social Care, Global Banking School/Oxford Brookes University, Birmingham, United Kingdom; and PENKUP Research Institute, Birmingham, United Kingdom

Samuel Oluwatosin Adejuyitan, MSc
Doctoral Researcher, School of Business and Creative Industries, University of the West of Scotland, United Kingdom; and PENKUP Research Institute, Birmingham, United Kingdom

Oluwadamilola R. Tayo, MPH
Faculty of Health, Wellbeing & Social Care, Oxford Brookes University, GBS Partnership, Leeds, United Kingdom

Rupali Chauhan, MPH
Faculty of Health, Wellbeing & Social Care, Oxford Brookes University, GBS Partnership, Manchester, United Kingdom

Shubham Sharma, MDS
Independent Researcher, Manchester, United Kingdom

Divya Motupalli, MPHGH
Faculty of Health, Wellbeing & Social Care, Oxford Brookes University, GBS Partnership, Manchester, United Kingdom

Corresponding Author: **Kennedy Oberhiri Obohwemu, PhD**
Department of Health, Wellbeing and Social Care, Oxford Brookes University, GBS Partnership, Birmingham, United Kingdom; and PENKUP Research Institute, Birmingham, United Kingdom

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ABSTRACT

Background: - Stroke remains a leading global public health concern, affecting both developed and developing nations. Approximately 15 million individuals experience a stroke annually, with 6 million resulting in death and 5 million leading to long-term disability. Preventive strategies encompass both pharmacological and non-pharmacological approaches, among which aspirin has been widely studied. This systematic review and meta-analysis aim to evaluate the effectiveness of aspirin in preventing stroke among patients at high risk of vascular

disease.

Methods: - A comprehensive literature search was conducted across Cochrane Library, CINAHL Plus with Full Text, Web of Science, and ScienceDirect. Eligible studies were randomized controlled trials (RCTs) investigating the use of aspirin for stroke prevention in high-risk vascular patients. Multiple reviewers independently conducted data extraction, risk of bias assessment, and quality appraisal, guided by the Centre for Reviews and Dissemination (CRD) and the Cochrane Collaboration standards.

Results: - Seven RCTs met the inclusion criteria, involving a total of 42,918 participants. Although methodological and outcome measurement variations were noted across studies, fixed-effects meta-analysis with a 95% confidence interval revealed a statistically significant benefit of aspirin in stroke prevention. The findings consistently favoured aspirin over other or no interventions.

Discussion: - While the results support the effectiveness of aspirin in reducing stroke incidence in high-risk vascular patients, variations in study design and outcomes highlight the need for caution in interpretation. This review did not address the safety profile or cost-effectiveness of aspirin, which are critical components of clinical decision-making.

Conclusion: - Aspirin appears to be an effective intervention for stroke prevention in individuals at high risk of vascular disease. Future research should explore its safety, long-term outcomes, and economic implications to guide more comprehensive clinical guidelines.

KEYWORDS: - Aspirin, Stroke Prevention, Vascular Disease, Systematic Review, Randomized Controlled Trials, Antiplatelet Therapy

INTRODUCTION

Stroke remains a significant global public health concern, ranking as the second leading cause of death and the third leading cause of disability-adjusted life years (DALYs) worldwide (Feigin et al., 2022). In 2021, approximately 12 million new stroke cases were reported globally, with ischemic strokes accounting for about 7.8 million of these cases (World Stroke Organisation, 2022). The burden of stroke is projected to increase, particularly in low- and middle-income countries, driven by aging populations and the rising prevalence of modifiable risk factors (Jaberinezhad et al., 2022; WHO, 2022; Mosisa et al., 2023).

In the United Kingdom, stroke incidence has been on the rise. NHS England reported a 28% increase in hospital admissions for stroke between 2004 and 2024, reaching over 111,000 admissions annually (NHS, 2024). The economic impact is substantial, with stroke-related costs in the UK estimated at £43 billion in 2025, encompassing healthcare expenditures, social care, and productivity losses (Patel et al., 2018).

Similarly, in the United States, stroke is a leading cause of death and long-term disability. Approximately 795,000 individuals experience a new or recurrent stroke each year, with about 140,000 deaths attributed to stroke annually (CDC, 2024). The prevalence of stroke is increasing among younger adults, highlighting the need for effective prevention strategies (Tsao et al., 2023).

Modifiable risk factors such as hypertension, diabetes mellitus, obesity, smoking, and physical inactivity significantly contribute to stroke risk (Ciumărnean et al., 2021; Nindrea & Hasanuddin, 2023). Lifestyle interventions targeting these factors have been shown to reduce stroke incidence. For instance, adherence to a healthy diet, regular physical activity, and smoking cessation are associated with a lower risk of stroke (Abate et al., 2021; Upoyo, Setyopranoto & Pangastuti, 2021; Libruder et al., 2022).

Pharmacological interventions also play a crucial role in stroke prevention. Low-dose aspirin has been widely used for the primary and secondary prevention of cardiovascular events, including stroke (Christensen et al., 2021; Masson et al., 2022). However, recent evidence suggests that the benefits of aspirin for primary stroke prevention may be limited and must be weighed against the increased risk of bleeding (Berger, 2022). The U.S. Preventive Services Task Force recommends individualized decision-making regarding aspirin use for primary prevention, particularly in older adults (U.S. Preventive Services Task Force, 2022).

Given the global burden of stroke and the evolving evidence on prevention strategies, this systematic review and meta-analysis aim to evaluate the effectiveness of aspirin in preventing stroke among patients at high risk of vascular disease. The findings of this analysis will be crucial in optimizing preventative strategies and ultimately mitigating the devastating impact of stroke on individuals and public health systems globally.

METHODS

Research Aim

This research paper aims to systematically analyse the available evidence on the effectiveness of aspirin in the prevention of stroke among patients at high risk of vascular disease. Specifically, it seeks to identify and evaluate studies that have examined the use of aspirin in stroke prevention, investigate the underlying mechanisms of aspirin as an antiplatelet agent, and critically analyse the findings of these studies to inform clinical practice and future research.

Eligibility criteria

Inclusion criteria:

This systematic review includes the following criteria:

1. Studies published in peer-reviewed journals, other relevant academic publications, as well as unpublished work and grey literature deemed pertinent to the topic.

2. Studies published in English or in other languages with accessible, reliable translations.

3. Studies involving participants with a probable history of stroke or a confirmed clinical diagnosis of stroke.

4. Studies including participants with at least one cardiovascular risk factor.

5. Studies published within the last 20 years to ensure contemporary relevance.

Only randomized controlled trials published between 1996 and 2016 were included in the review to ensure a balance between historical relevance and methodological rigour. RCTs are considered the gold standard for evaluating the efficacy of interventions, as they minimize bias through randomization and controlled comparison groups (Sharma, Srivastav & Samuel, 2020; Zhou et al., 2021). The 20-year timeframe was selected to capture a comprehensive range of high-quality evidence while excluding outdated studies that may no longer reflect current clinical practice or guidelines. This period also aligns with the evolution of stroke prevention strategies and reflects major advancements in antiplatelet therapy, particularly the widespread adoption and evaluation of aspirin in both primary and secondary prevention settings (Mac Grory et al., 2022; Shah, Liu & Yu, 2022).

Exclusion criteria:

Studies were excluded from the review based on the following criteria:

1. Non-randomized study designs.

2. Studies involving patients taking medications deemed incompatible with the trial treatment.

3. Studies including participants currently receiving anticoagulation therapy or those requiring long-term anticoagulation.

4. Studies involving patients with a documented history of hypersensitivity or allergic reactions to aspirin.

Search strategy

The following electronic databases were systematically searched: Cochrane Library, PubMed, CINAHL Plus with Full Text, Web of Science, and ScienceDirect. The search strategy was guided by the Population, Intervention, Comparator, and Outcome (PICO) framework (see Table 1). A combination of relevant keywords and Boolean operators was employed, including the following: Aspirin AND stroke prevention AND patients with high risk of vascular disease; acetylsalicylic acid AND transient ischemic attack AND vascular disease; and stroke AND cerebral attack AND vascular patients. No language restrictions were applied, provided that translated English versions of the studies were accessible.

Table 1: PICO Framework

Research Question	Does aspirin prevent the occurrence of stroke in patients who are at high risk of getting a vascular disease.
Population	The total population consists of patients with stroke, with or without any cerebrovascular events history.
Intervention	Aspirin or Acetylsalicylic acid
Comparator	Placebo, Clopidogrel, Clopidogrel plus Aspirin and Terutroban
Outcome	Stroke prevention
Design	Randomised Controlled Trials (RCTs)
Setting	General Practice, Hospitals

PubMed

The search employed relevant keywords related to aspirin, stroke prevention, and vascular disease. While the search was not limited by language, only translatable and accessible studies were considered. A total of 7,644 articles were initially retrieved. Filters were then applied to restrict results to full-text articles, clinical trials, and studies published within the last 20 years. This refined the pool to 581 studies. However, upon careful screening of titles and abstracts, none of the studies met the eligibility criteria due to irrelevant interventions or ineligible participant characteristics.

CINAHL Plus with Full Text

The CINAHL database was searched using combinations of the keywords: *aspirin*, *stroke prevention*, and *vascular patients*. The search was filtered to include RCTs published within the past 20 years. An initial query yielded 51 studies. Further keyword combinations such as *aspirin*, *stroke prevention*, and *vascular disease* returned 14 results, while the search terms *aspirin*, *stroke*, and *vascular disease* produced 36 results. After reviewing titles and abstracts, 5 studies were deemed eligible and relevant to the topic, while the remaining studies were excluded due to failure to meet the inclusion criteria.

Web of Science

A search was carried out on Web of Science using the terms *aspirin*, *stroke prevention*, and *patients at high risk of vascular disease*. Filters were applied to include only RCTs published within the past 20 years. A total of 557 studies were retrieved. However, after screening for relevance and eligibility, none of the studies met the inclusion criteria for the review.

Cochrane Library

A search of the Cochrane Library was conducted using the keywords *aspirin*, *vascular disease*, and *stroke prevention*, which returned 14 studies. An additional search using *acetylsalicylic acid*, *vascular disease*, and *transient ischemic attack* yielded 6 studies. No language restrictions were applied, and both searches were filtered to include publications from the past 20 years. Following a detailed abstract review, only 1 study was deemed relevant and included in the review.

ScienceDirect

ScienceDirect was searched using the terms *aspirin*, *vascular disease*, and *stroke prevention*, without applying language restrictions. The search yielded 1,133 articles. After applying inclusion criteria and carefully reviewing the abstracts, 1 study was considered relevant to the topic and included in the final analysis.

Following the retrieval of studies across all databases, titles and abstracts were screened for eligibility, and full-text articles were examined for methodological quality. Studies with inadequate methodological rigor were excluded from the review. A detailed summary of the search process and strategies adopted is presented in Table 2. To ensure transparency and reduce the risk of bias, a PRISMA flow diagram has been included to illustrate the selection process, including the number of studies identified, screened, excluded, and ultimately included, along with reasons for exclusion (Page et al., 2021).

Assessment of Heterogeneity

Heterogeneity among the included studies was assessed using the I^2 statistic, which quantifies the percentage of variation across studies that is due to heterogeneity rather than chance. I^2 values were calculated using Review Manager (RevMan) software, and results were interpreted based on established thresholds: 0–40% may not be important; 30–60% may represent moderate heterogeneity; 50–90% may indicate substantial heterogeneity; and 75–100% suggests considerable heterogeneity (Higgins et al., 2011). In cases where only a single study contributed to an outcome comparison, heterogeneity could not be calculated and was marked as "Not Applicable." Depending on the level of heterogeneity identified, either a fixed-effect model (for low or no heterogeneity) or a random-effects model (for moderate to high heterogeneity) was employed to ensure appropriate statistical pooling of results. This approach allowed for a more robust synthesis of evidence by accounting for both within-study and between-study variation where applicable.

RESULTS

A total of 2,463 studies were initially identified through comprehensive searches across multiple electronic databases for the purpose of this review. After removing duplicates and applying preliminary inclusion filters, 1,200 studies were retrieved and screened in greater detail to assess their potential relevance. This stage involved a careful and systematic examination of titles and abstracts to determine alignment with the review's inclusion criteria, which focused on RCTs evaluating the effectiveness of aspirin in stroke prevention among patients at high risk of vascular disease. Following this rigorous screening process, only seven studies were deemed to meet all the eligibility requirements and were subsequently included in the final review. These selected studies formed the evidence base for analysis, synthesis, and interpretation of findings in the context of the research question.

Table 2 outlines the initial study selection process undertaken during the systematic literature search across the five major databases. Each database was searched using a tailored combination of keywords aligned with the study's PICO framework. The keywords were selected to capture the full range of relevant RCTs examining the efficacy of aspirin in stroke prevention among patients with an elevated risk of vascular disease.

Table 2: Initial Study Selection Process

Database **Search**	**Search terms (Keywords)**	**Date assessed** **(2016)**	**Number of studies identified with liberal screening of database**	**Excluded due to non-relevance to inclusion criteria and research question.**	**Studies for more detailed evaluation**	**Limit to the number of years and language restrictions** **(December 2004 to July 2014)**
PUBMED	"Aspirin" "AND stroke prevention" AND "Vascular disease"	21st August to 12th September	581	581	0	Limit to 20 years, no language restrictions.

Database Search	Search terms (Keywords)	Date assessed (2016)	Number of studies identified with liberal screening of database	Excluded due to non-relevance to inclusion criteria and research question.	Studies for more detailed evaluation	Limit to the number of years and language restrictions (December 2004 to July 2014)
	AND "Randomised control trials"					
PUBMED	"Acetylsalicylic acid" AND Transient Ischaemic Attack" AND "High risk patients of vascular disease"	21st August to 12th September	71	71	0	Limit to 20 years, no language restrictions.
CINAHL plus with full text	"Aspirin" AND "Stroke prevention" AND "Vascular patients"	6th October to 10th October	51	50	2	Limit to 20 years, no language restrictions.
"	"Aspirin" AND "Stroke prevention" AND "Vascular disease"	12th October to 14th October	14	14	3	Limit to 20 years, no language restrictions.
CINAHL plus with full text	"Aspirin" AND "Stroke" AND "vascular disease"	12th October to 14th October	36	36	0	Limit to 20 years, no language restrictions.
Web of Science	"Aspirin" AND "Stroke prevention" AND "Patients at high risk of vascular disease"	14th October to 16th October	557	557	0	Limit to 20 years, no language restrictions.
Cochrane Library	"Aspirin" AND Stroke prevention" AND "Vascular disease"	16th October to 18th October	14	12	0	Limit to 20 years, no language restrictions.
	"Acetylsalicylic" AND "Vascular disease" AND	16th October to 18th October	6	6	1	Limit to 20 years, no language restrictions.

Database Search	Search terms (Keywords)	Date assessed (2016)	Number of studies identified with liberal screening of database	Excluded due to non-relevance to inclusion criteria and research question.	Studies for more detailed evaluation	Limit to the number of years and language restrictions (December 2004 to July 2014)
	"Transient Ischaemic"					
Science Direct	"Aspirin" AND Stroke prevention" AND "Vascular disease"	16th October to 18th October	1133	1132	1	Limit to 20 years, no language restrictions.
Total			2463	2455	7	

To enhance transparency and methodological rigour, the study selection process is further illustrated in the PRISMA flow diagram below. This diagram outlines each stage of the review, including the number of records identified through database searches, those screened and excluded, and the final number of studies included for detailed evaluation. The diagram further shows the number of full-text articles assessed for eligibility, the reasons for exclusion at each stage, and the final number of studies included for detailed evaluation. Presenting this information visually, the PRISMA diagram offers a clear, step-by-step depiction of how the final body of evidence was identified and refined, enhancing the transparency, replicability, and credibility of the review process.

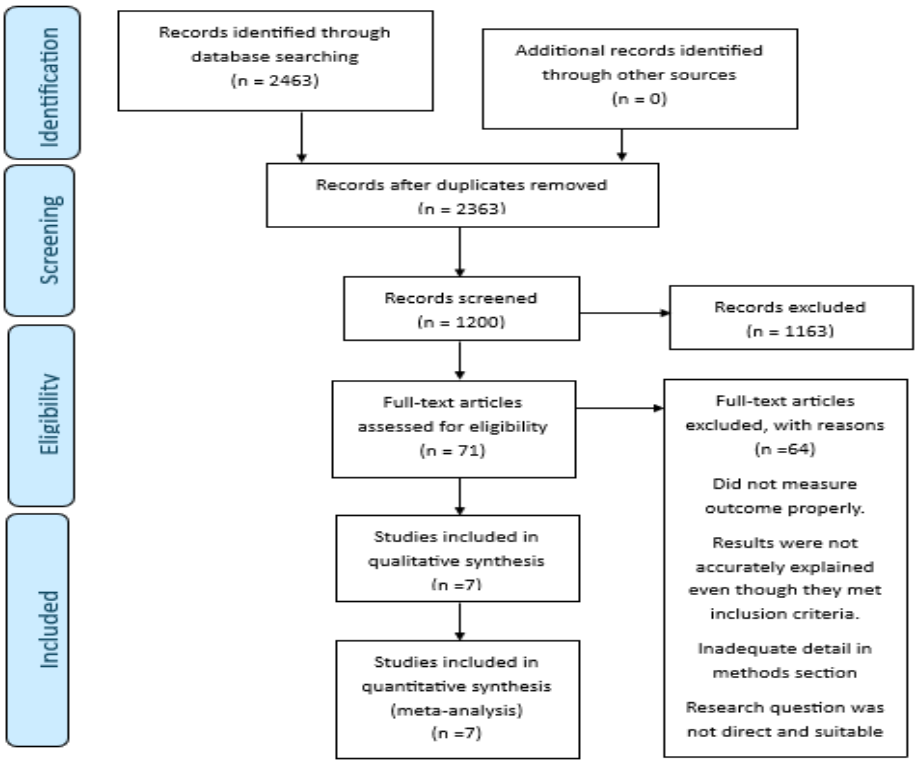

Figure 1: PRISMA Flow chart

Data Extraction

Following the identification of eligible studies, a structured data extraction process was undertaken to systematically collect key information relevant to the research objectives. This process involved extracting details on study design, population characteristics, intervention types, comparison groups, outcome measures, and main findings. Data were extracted using a predefined template to ensure consistency and reduce the risk of errors or omissions. This approach allowed for a clear comparison of study methodologies and results across the included literature. The extracted data are presented in the tables below, offering a concise summary of each study's core attributes and facilitating further synthesis and interpretation of the evidence

Table 3A: Data Extraction Table

Study/Title	Author	Participants	Intervention versus comparison	Outcomes
A Randomized Trial of Low Dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women	Ridker et al., 2005	A total of 39,876 patients	Aspirin versus Placebo	Aspirin group-221 event of stroke. Placebo group-266. Non-statistically significant risk reduction. RR=0.83 95% CI (0.70-0.99) P Value=0.04
Aspirin in the prevention of progressing stroke; a randomised controlled study	Roden-Jullig et al., 2003	Totally 441 patients with 220 assigned to Aspirin and 221 assigned to placebo	Aspirin versus Placebo	Aspirin patients: 15.9% Stroke. Placebo group: 16.7%. Not statistically significant. RR=0.95 (95% CI 0.62-1.45) P Value=0.81
Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events	Bhatt et al., 2006	Total of 15,603 patients assigned to clinical groups	Aspirin+ Clopidogrel versus Aspirin+ placebo	Clopidogrel plus Aspirin:6.8% rate of primary effectiveness. Aspirin plus placebo: 7.3% primary efficacy. (Relative Risk, 0.79; 95% CI, 0.64 to 0.98; P Value=0.03

Study/Title	Author	Participants	Intervention versus comparison	Outcomes
Aspirin Plus Clopidogrel Versus Aspirin Alone after Coronary Artery Bypass Grafting	Kulik et al., 2010	Total of 113 patients	Aspirin+ Clopidogrel versus Aspirin+ placebo	Aspirin+ Clopidogrel did not significantly reduce cardiovascular events compared to Aspirin plus placebo RR=1.2 95% CI 0.35 to 4.3; P Value=0.74
Terutroban versus aspirin in patients with cerebral ischemic events (PERFORM): A randomised, double-blind parallel-group trial	Bousser et al., 2011	19,120 patients with 9562 allocated to Terutroban and 9558 to Aspirin	Aspirin Versus Terutroban	The primary endpoint happened in 1091 (11%) patients getting Terutroban and 1062 (11%) taking Aspirin. RR 0.98, 95% CI 0.90-1.08. P Value=0.74 No indication of a difference between the two drugs for secondary and tertiary endpoints.
Low dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice	Collaborative Group of the primary prevention project, 2001	Total of 4495 people (2583 female with mean age 64.4years)	Aspirin versus Vitamin E	Aspirin reduced the incidence of stroke being statistically significant for cardiovascular death (1.4-0.8%) RR=0.68 (95% CI 0.31-0.99). Cardiovascular events (8.2-

Study/Title	Author	Participants	Intervention versus comparison	Outcomes
				6.3%; 0.68[0.36-1.28] P Value= 0.22
A randomised, blinded trial of Clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE)	CAPRIE, 1996	Total number of 19185 patients with more than 6300 in each clinical group	Aspirin Versus Clopidogrel	Clopidogrel patients: 5.32% risk of stroke annually. RR=1.2(95% CI 1.01-1.24). Aspirin patients: 5.83% risk of stroke annually with Statistical significance with p=0.02

Table 3B: Data Extraction Table

Author and year of study	Study design and aim	Study size				Study Outcomes	
		Intervention group (n)		Control group(n)		RR or OR	CI
Ridker et al. 2005	Randomized controlled trial	19934		19942		0.83	0.69, 0.99
Roden-Jullig et al. 2003	Randomized controlled study	220		221		0.95	0.62 1.45
Bhatt et al. 2006	Randomized controlled trial	7802		7081		0.79	0.64 0.98
Kulik et al. 2010	Randomized controlled trial	56		57		1.2	0.35 4.34
Bousser et al. 2011	Randomized controlled trial	9556		9544		0.98	0.98-1.08
Collaborative group of the primary prevention project, 2011	Randomized controlled trial	2226		2269		0.68	0.36 1.28
CAPRIE, 1996	Randomized controlled trial	9599		9566		1.2	1.01 1.24

Table 3C: Data Extraction Table

Author/year	Duration of trial	Design of study	Country and trial setting	Study size	Characteristics of participants	Period of follow up	Comparison population or control	Outcome measure	Commercial research support
Ridker et al 2005	10 years	Randomized control trial	United States, Boston	39876 patients	Women 45 years or older. Had no history of cancer. Had no history of side effects to any of the study medications. Were not taking Aspirin.	12 months	477-populatio 522-placebo	Prevention of Stroke	National Heart, Lung and Blood Institute and National Cancer Institute, Bethesda
Roden-Jullig et al 2003	1988-1992	Randomized trial, double blinded and placebo controlled	Swedd	441 patients	All of ages with acute Ischaemic stroke confirmed. Should have used antiplatelet drugs including NSAID.	3 months	220-aspirin 221-placebo	Prevention of progressing stroke	Serafimer Hospital Foundation, the County Council of Stockholm, Department of Research, Development and Education. The Claes Groschinsky Foundation, the Loo and Hans Osterman Foundation, the 1987 Foundation for stroke research
Bhatt et al 2006	Between October 1, 2002 and November 14, 2003	Randomized trial, double blinded and placebo	32 different countries	15603 patients	45 years or older. Had documented cerebrovascular disease.	1 month, 3 months and 6	Clopidogrel plus aspirin-7802 Aspirin plus	Prevention of Atherothrombotic events (Stroke, myocardial infarction, death)	Sanofi-Aventis and Bristol-Myers Squibb, National

		controlled				months	placebo-7801		institutes of Health
Kulik et a.,l 2010	May 2006 to July 2009	Randomized	Ottawa, Canada	113 patients	Men 55 or older undergoing coronary artery bypass grafting with SVGs	12 months	Aspirin plus Clopidogrel-56 Aspirin-57	Prevention of Stroke	Physicians' Service incorporated Foundation, Boston Scientific
Bousser et al., 2011	February 22, 2006 and April 7, 2008	A randomized double-blind, parallel group trial	46 countries	19,120 patients	Men and women aged 65 or older. Had Ischaemic stroke	6 months	9562-Terutroban 9558-Aspirin	Prevention of Cerebral Ischaemic Events	Sevier, Sanofi-Aventis, Foundation Bouygues, INSERM and Ministere du travail
Collaborative Group of Primary Prevention Project, 2001	Trial stopped prematurely on ethical grounds	Randomized controlled open 2x2 factorial trial	-	4495 patients	65 years or older, hypertensive, hypercholesterolaemia, diabetes mellitus, family history of myocardial infarction	4 months	Low dose aspirin-2226 Placebo-2269	Prevention of cardiovascular risk	-
CAPRIE, 1996	3 years	Randomized, blinded trial		19185 patients	Diagnosed of Ischaemic stroke, myocardial infarction or symptomatic atherosclerotic peripheral arterial disease	22.8 months	Aspirin-9586 Clopidogrel-9599	Prevention of Ischaemic events (Stroke)	Sanofi and Bristol-Myers Squibb

Quality Appraisal/ Risk of Bias Assessment

To assess the methodological robustness and reliability of the included studies, a formal quality appraisal was conducted. This critical evaluation ensured that only studies with acceptable levels of internal validity, appropriate design, and minimal risk of bias were considered in the synthesis of findings. The appraisal process involved reviewing each study's randomisation methods, blinding procedures, completeness of outcome data, and clarity of reported results. Recognised appraisal tools were employed to systematically evaluate study quality, and studies were assessed independently to minimise the risk of reviewer bias.

The risk of bias in the included studies was assessed using two established tools: the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework and RevMan software provided by the Cochrane Collaboration. The GRADE approach was used to evaluate the overall quality of evidence across studies, considering factors such as study limitations, inconsistency, indirectness, imprecision, and publication bias. Meanwhile, the RevMan tool was employed to generate detailed risk-of-bias assessments for individual studies, focusing on domains including random sequence

generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other potential sources of bias. These assessments allowed for a structured appraisal of the internal validity of the included trials, informing the strength of conclusions drawn from the systematic review. The results of the quality assessment are presented in Fig. 2A and Fig. 2B, providing a transparent account of the strengths and limitations of the evidence base included in this review.

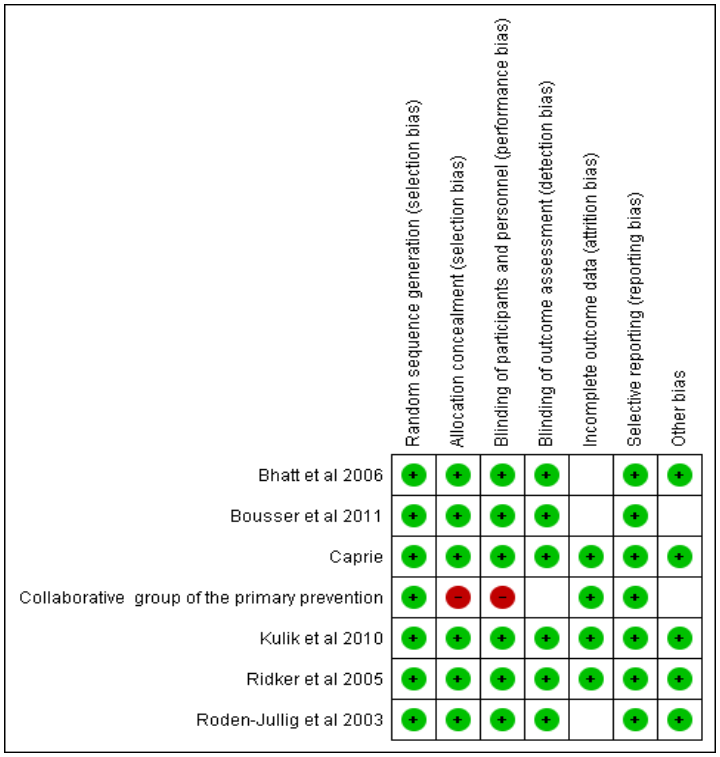

Figure 2A: Risk of Bias Assessment

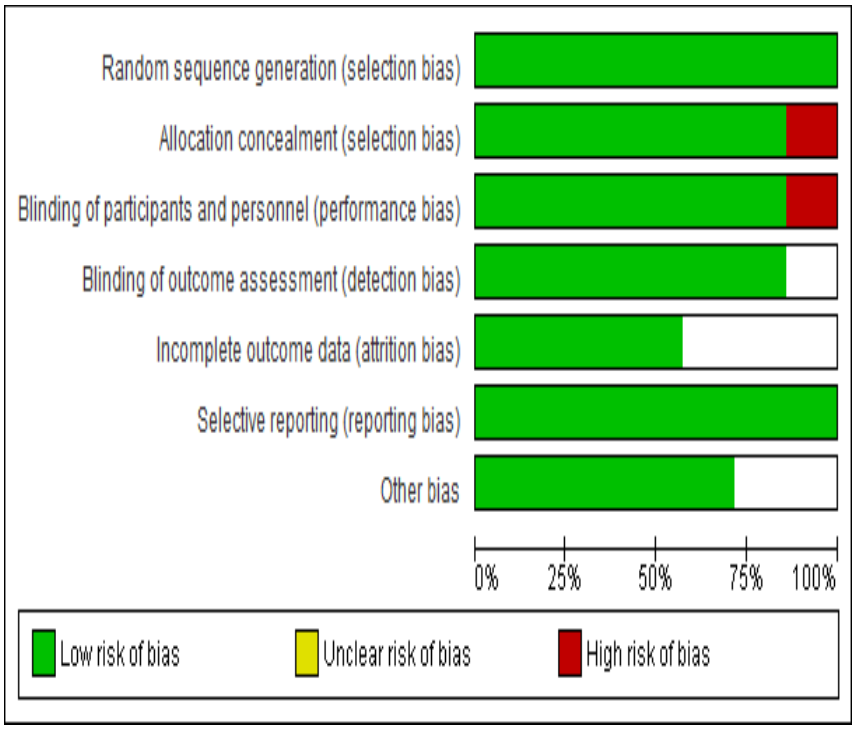

Figure 2B: Risk of Bias Assessment

Table 4 shows that one out of the seven included studies was assessed as having a high risk of bias, primarily due to the lack of blinding of both participants and research personnel, as well as inadequate concealment of treatment allocation. Additionally, four of the remaining six studies were judged to have an unclear risk of bias, attributed to factors such as incomplete outcome data due to participant withdrawal, unblinded outcome assessment, and other methodological concerns that could not be fully resolved from the available informatio

Table 4: Final Outcome of Quality Assessment

	Random sequence generation	Allocation concealment	Binding of participants and	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Bhatt et al., 2006	L	L	L	L	*U*	L	L
Bousser et al., 2011	L	L	L	L	U	L	U
CAPRIE, 1996	L	L	L	L	L	L	L
Collaborative Group of the primary prevention, 2001	L	H	H	U	L	L	U
Kulik et al., 2010	L	L	L	L	L	L	L
Ridker et al., 200	L	L	L	L	L	L	L

Roden-Jullig et al., 2003	L	L	L	L	U	L	L

In addition to the primary risk of bias assessments, the Critical Appraisal Skills Programme (CASP) tool was employed to further evaluate the methodological quality of this systematic review. The CASP checklist (see Table 5) provides a systematic and structured approach to appraising research by guiding reviewers through key domains such as clarity of the research question, appropriateness of study design, rigor of the methodology, transparency in reporting, relevance of results, and implications for practice (Dada et al., 2023; Shaheen et al., 2023). By applying the CASP tool, this review was assessed for its internal coherence, credibility, and overall trustworthiness, ensuring that the synthesis of evidence adhered to established standards of critical appraisal and evidence-based practice.

Table 5: CASP Checklist

Study title	Author	Did the study ask a clearly focused question	Was the treatment randomly assigned to patients	Were the patients, health workers and study personnel blinded	Were the groups similar at the start of the trial	Aside from the experimental intervention were the groups treated equally	Were the patients who entered the trial properly accounted for at its conclusion	How large was the treatment effect	How precise was the estimate of the treatment effect	Can the results be applied in your context or to the local population	Were all clinically important outcomes considered	Are the benefits worth the harms and costs
A Randomised trial of low dose Aspirin in the primary prevention of cardiovascular disease in women	Ridker et al. 2005	YES	YES	YES	YES	YES	YES	Comparatively, aspirin therapy significantly reduced the risk myocardial infarction but had no significant effect on the risk stroke	RR 0.83 95% Confidence Interval, 0.70 to 0.99; P=0.04	YES	YES	YES
Aspirin in the prevention of progressing stroke: A randomised	Roden-Jullig et al. 2003	YES	YES	YES	YES	YES	YES	Aspirin treatment did not significantly reduce the rate of	RR 0.95, 95% Confidence Interval :0.62-1.45, P=0.81	YES	YES	YES

control study								stroke progression.				
Clopidogrel and Aspirin versus Aspirin alone for the prevention of Atherothrombotic Events	Bhatt et al. 2006	YES	YES	YES	YES	YES	YES	Overall, Clopidogrel plus aspirin was not significantly more effective than aspirin alone In reducing rate of stroke.	RR 0.79, 95% Confidence Interval: 0.64–0.98 P=0.03	YES	YES	YES
Aspirin plus Clopidogrel versus Aspirin alone after coronary bypass grafting	Kulik et al. 2010	YES	YES	YES	YES	YES	YES	Clopidogrel plus Aspirin did not show statiscal significance in reducing any form of cardiovascular event compared with aspirin alone	RR 1.2 95% Confidence Interval:0.35-4.34 P=0.7	YES	YES	YES
Terutroban versus Aspirin in patients with cerebral ischaemic events (PERFORM): A Randomised, double blind, parallel-group trial	Bousser et al. 2011	YES	YES	YES	YES	YES	YES	There was no significant evidence between Terutroban and Aspirin for the prevention of any form of stroke	RR 0.98 95% Confidence Interval: 0.90-1.08 P=0.74	YES	YES	YES
Low dose aspirin	Collaborative	YES	YES	YES	YES	YES	YES	Aspirin showed	RR 0.68	YES	YES	YES

and vitamin E in people at cardiovascular risk: a randomised trial in general practice	group of the primary prevention project, 2001							statically significant results in the prevention of all stroke compared to placebo.	95% Confidence Interval: 0.36-1.28 P=0.2		
A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE)	Caprie, 1996	YES	YES	YES	YES	YES	YES	Long term administration of Clopidogrel with vascular disease proved to be more effective than Aspirin in the prevention of any stroke, Myocardial infarction or death from any cause	RR 1.2 95% Confidence Interval: 1.01-1.24 P=0.02	YES	YES	YES

Heterogeneity Assessment

Table 6 presents the heterogeneity values across the included studies comparing aspirin with other interventions for stroke prevention. For two of the studies—CAPRIE (2006) and Bousser et al. (2011)—heterogeneity was not applicable, due to insufficient comparative data and limitations in reported statistical outcomes. Among the studies where heterogeneity could be evaluated, Bhatt et al. (2006) and Kulik et al. (2010) reported I^2 value of 0.45, indicating moderate heterogeneity, while the Collaborative Group for Primary Prevention (2001), Roden-Jullig et al. (2003), and Ridker et al. (2005) yielded a higher I^2 of 0.77, suggesting substantial heterogeneity. These variations in heterogeneity reflect differences in study design, populations, and outcome measures.

For studies demonstrating low to moderate heterogeneity, a fixed-effect model was used to synthesise the results. In contrast, for those with substantial heterogeneity, a random-effects model was employed to account for potential variability across study populations and methodologies. These findings were

taken into consideration when interpreting the pooled effect sizes in the meta-analysis and support the use of a model-specific approach to ensure the robustness of conclusions drawn from the evidence

Table 6: Heterogeneity Assessment

Study	Heterogeneity (I^2 values)
CAPRIE, 2006	Not Applicable
Bousser et al., 2011	Not Applicable
Bhatt et al., 2006 Kulik et al., 2010	0.45 0.45
Collaborative Group for Primary Prevention, 2001 Ridker et al., 2005 Roden-Jullig et al., 2003	0.77 0.77 0.77

Data Analysis

Studies Comparing Aspirin to Placebo

The forest plot below illustrates the comparative analysis of studies included in this review that evaluated the efficacy of aspirin versus placebo in the prevention of stroke. In all the studies represented, participants were randomly assigned to either the experimental group (aspirin) or the control group (placebo). The pooled analysis revealed a relative risk (RR) of 0.84 with a 95% confidence interval (CI) ranging from 0.71 to 0.98. Importantly, the confidence interval does not cross the line of no effect (RR = 1.0), and the p-value associated with the overall effect is less than 0.05, indicating that the observed difference is statistically significant

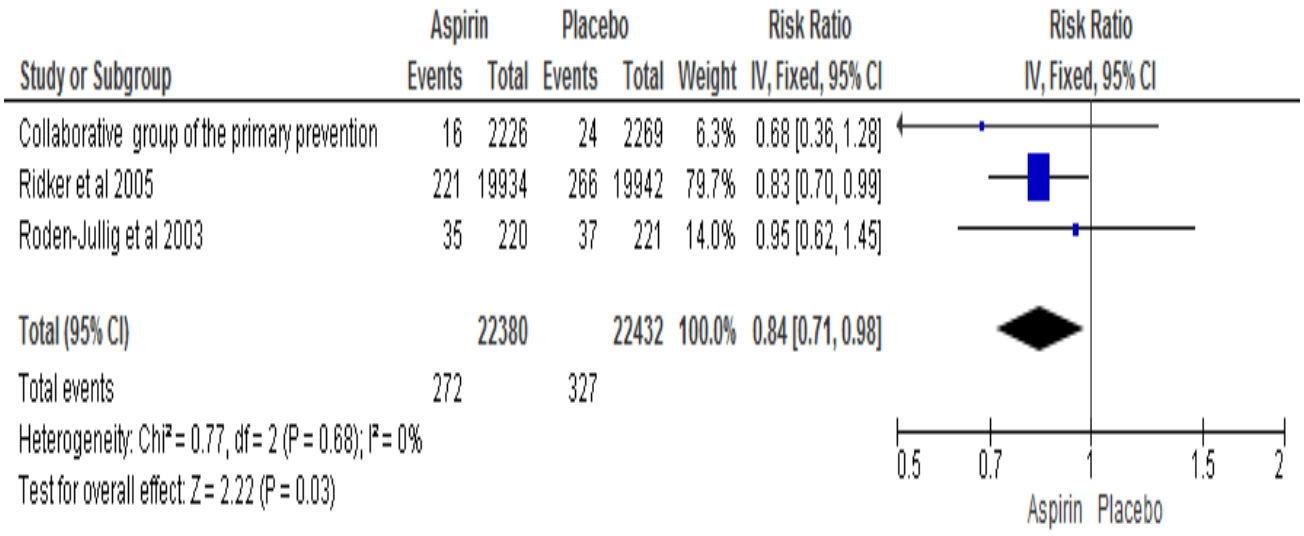

Figure 3: Forest Plot for Studies Comparing Aspirin to Placebo

These findings suggest that aspirin is more effective than placebo in reducing the risk of stroke among individuals at high risk of vascular events. The reduction in relative risk implies a meaningful clinical benefit in favour of aspirin, supporting its role as a preventive pharmacological strategy. This result aligns with prior evidence on the antiplatelet action of aspirin in reducing thrombotic events, further strengthening the argument for its inclusion in stroke prevention protocols for appropriately selected patients (Passacquale et al., 2022). However, the interpretation of these findings must still consider the risk-benefit profile for each individual, particularly in relation to potential bleeding complications associated with aspirin therapy.

The funnel plot (Figure 4) was examined to assess the potential presence of publication bias among the included studies. The plot appeared symmetrical, suggesting that the likelihood of publication bias was minimal. Symmetry in a funnel plot typically indicates that the distribution of study effects is not skewed, and smaller studies with both positive and negative results are equally represented, thereby reducing the probability of selective publication or reporting bias (Nakagawa et al., 2022).

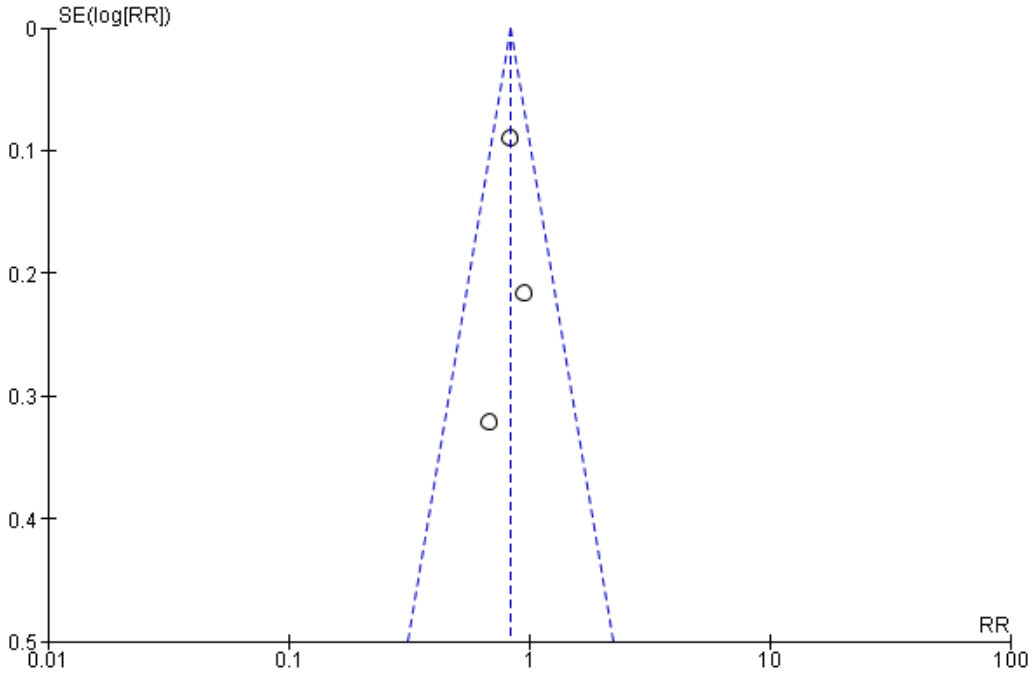

Figure 4: Funnel Plot for Studies Comparing Aspirin to Placebo

However, caution is warranted in interpreting this result. According to Higgins and Green (2011) in the *Cochrane Handbook for Systematic Reviews of Interventions*, funnel plots should be interpreted with care when the number of included studies is fewer than ten. With fewer studies, the power of the funnel plot to detect asymmetry is substantially limited, making any conclusions regarding publication bias unreliable (Kepes, Wang & Cortina, 2023). In this review, only seven studies were included in the final analysis—below the recommended threshold—therefore limiting the robustness of the funnel plot as a diagnostic tool for bias. Consequently, while the plot does not visually indicate the presence of publication bias, definitive conclusions cannot be drawn solely from its appearance due to the small sample size.

Tables 7A, 7B, and 8 present the results of the quality appraisal conducted using the GRADE approach for studies comparing aspirin to placebo in the prevention of stroke among patients at high risk of vascular disease. The GRADE framework was applied to assess the overall certainty of the evidence across key domains, including risk of bias, consistency of results, directness of evidence, precision of estimates, and potential publication bias. This structured evaluation enabled a transparent and systematic judgement of the strength and reliability of the

included evidence. The assessments reported in these tables provide a comprehensive overview of how confident we can be in the effect estimates derived from the included randomized controlled trials, thereby informing clinical decision-making and future research priorities in stroke prevention

Table 7A: GRADE Assessment (I) (Aspirin compared to Placebo)

Aspirin compared to placebo for stroke prevention in patients with high risk of vascular disease

Patient or population: Stroke prevention in patients with high risk of vascular disease

Setting: General practice, hospitals

Intervention: Aspirin

Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Aspirin**				
STROKE PREVENTION follow up: mean 65 months	15 per 1,000	**12 per 1,000** (10 to 14)	**RR 0.83** (0.71 to 0.98)	44812 (3 RCTs)	⨁⨁◯◯ LOW [a,b]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

RR: Risk ratio

Table 7B: GRADE Assessment (II) (Aspirin compared to Placebo)

GRADE Working Group Levels of Evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Patients and personnel were not blinded during allocation of treatment

b. Trial came to a sudden end on ethical grounds

Table 8: GRADE Evidence Profile for Selected Studies (Aspirin compared to Placebo)

Question: Aspirin compared to placebo for stroke prevention in patients with high risk of vascular disease

Setting: General Practice, Hospitals

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aspirin**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
STROKE PREVENTION (follow up: mean 65 months)												
3	randomised trials	serious [a,b]	not serious	not serious	serious	none	272/22380 (1.2%)	327/22432 (1.5%)	**RR 0.83** (0.71 to 0.98)	**2 fewer per 1,000** (from 0 fewer to 4 fewer)	⊕⊕◯◯ LOW [a,b]	

CI: Confidence interval; **RR:** Risk ratio

a. Patients and personnel were not blinded during allocation of treatment

b. Study ended abruptly due to ethical reasons

Studies Comparing Aspirin to Clopidogrel

Figure 5 presents the forest plot comparing studies that evaluated the effectiveness of aspirin versus clopidogrel in preventing stroke among patients at high risk of vascular disease. In these studies, participants were randomly assigned to either the experimental group receiving clopidogrel or the control group receiving aspirin. The overall test of effect produced a relative risk (RR) of 1.12, with a 95% confidence interval (CI) ranging from 1.01 to 1.24. While the confidence interval borders the line of no effect (RR = 1.0), it does not cross it, and the associated p-value is less than 0.05. This result indicates that the observed difference is statistically significant, with clopidogrel demonstrating a modest but measurable superiority over aspirin in reducing stroke risk in the analysed studies.

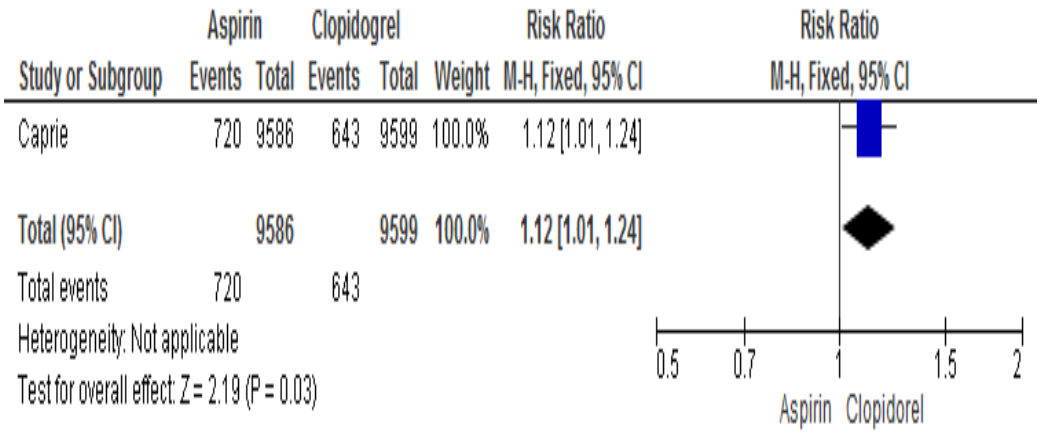

Figure 5: Forrest Plot for Studies Comparing Aspirin to Clopidogrel

As shown in Figure 6 below, the funnel plot demonstrates no apparent evidence of publication bias. The distribution of studies appears symmetrical, suggesting a low likelihood of selective publication or small-study effects that could distort the overall findings. Symmetry in the funnel plot typically indicates that both large and small studies with varying effect sizes are adequately represented in the literature, thereby reducing concerns about reporting bias (Afonso et al., 2024).

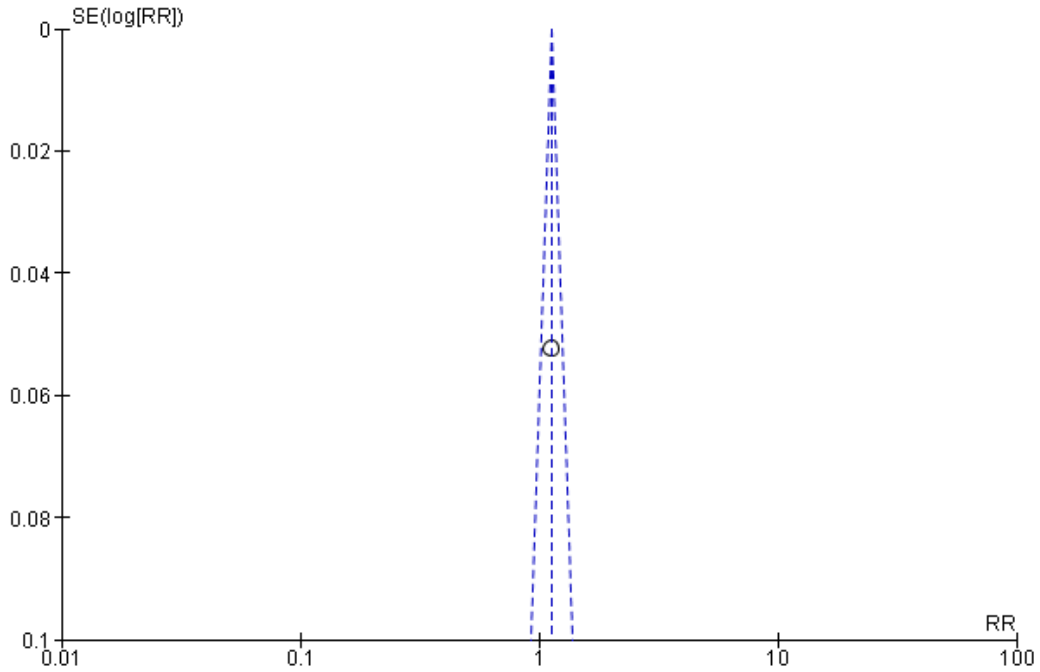

Figure 6: Funnel Plot for Studies Comparing Aspirin to Clopidogrel

However, as stated previously, the reliability of funnel plots in detecting publication bias is limited when the number of included studies is small. Funnel plots should be interpreted with caution when fewer than 10 studies are included, as the power to detect asymmetry is significantly reduced (Higgins and Green, 2011; Kepes, Wang & Cortina, 2023; Afonso et al., 2024). In this review, the number of studies included in the analysis does not meet this threshold. Therefore, although the plot suggests minimal bias, definitive conclusions regarding

the presence or absence of publication bias cannot be drawn with confidence.

Tables 9 and 10 summarise the quality appraisal outcomes using the GRADE methodology for studies comparing aspirin and clopidogrel in the prevention of stroke among individuals at high risk of vascular disease

Table 9: GRADE Evidence Profile (I) (Aspirin compared to Clopidogrel)

Aspirin compared to Clopidogrel for Stroke prevention in patients with high risk of vascular disease

Patient or population: Stroke prevention in patients with high risk of vascular disease

Setting: General Practice, Hospitals

Intervention: Aspirin

Comparison: Clopidogrel

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Clopidogrel	**Risk with Aspirin**				
Stroke prevention	67 per 1,000	**75 per 1,000** (68 to 83)	**RR 1.12** (1.01 to 1.24)	19185 (1 RCT)	⨁⨁⨁⨁ HIGH	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

RR: Risk ratio

GRADE Working Group Levels of Evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 10: GRADE Evidence Profile (II) (Aspirin compared to Clopidogrel)

Question: Aspirin compared to Clopidogrel for Stroke prevention in patients with high risk of vascular disease

Setting: General Practice, Hospitals

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Clopidogrel	Relative (95% CI)	Absolute (95% CI)		
stroke prevention												
1	randomised trials	not serious	not serious	not serious	not serious	none	720/9586 (7.5%)	643/9599 (6.7%)	**RR 1.12** (1.01 to 1.24)	**8 more per 1,000** (from 1 more to 16 more)	⊕⊕⊕⊕ HIGH	

CI: Confidence interval; **RR:** Risk ratio

Studies Comparing Aspirin to Terutroban

Figure 7 presents the forest plot illustrating the comparative analysis of studies evaluating aspirin versus Terutroban in the prevention of stroke among patients with high vascular risk. Participants in the included study were assigned to either the experimental group (Terutroban) or the control group (Aspirin). The overall test of effect yielded a relative risk (RR) of 0.98, with a 95% confidence interval (CI) ranging from 0.90 to 1.08. As the confidence interval crosses the line of no effect (RR = 1.0) and the associated p-value exceeds 0.05, the result is not statistically significant. This suggests that there is no meaningful difference in stroke prevention efficacy between aspirin and Terutroban based on the available data

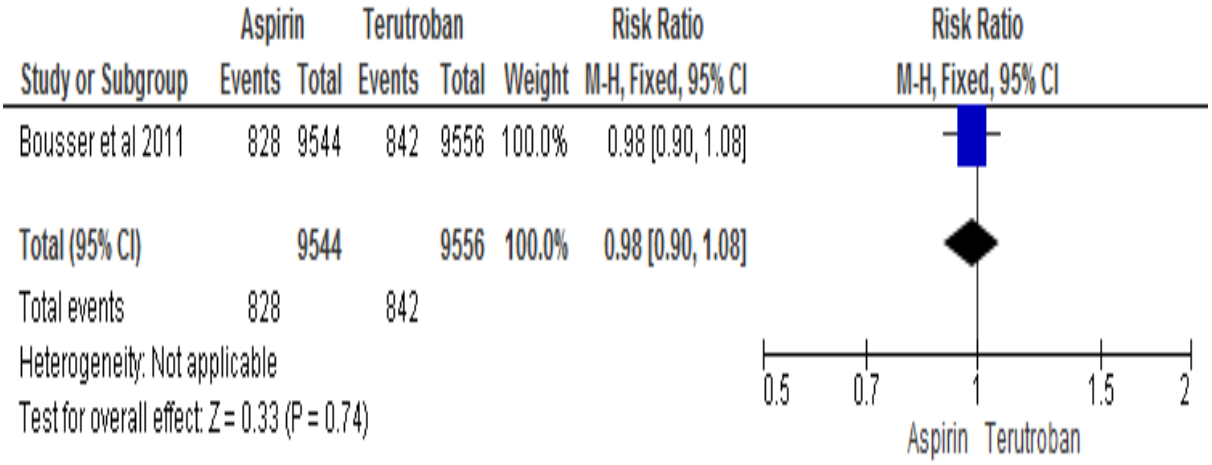

Figure 7: Forest Plot for Studies Comparing Aspirin to Terutroban

The funnel plot (Figure 8) revealed no apparent evidence of publication bias, as indicated by its symmetrical appearance. However, since only a single study was included in this analysis, it is not possible to draw reliable conclusions regarding the presence or absence of publication bias. As noted by Higgins and Green (2011), the interpretation of funnel plots is not recommended when fewer than ten studies are available, due to insufficient statistical power to detect asymmetry.

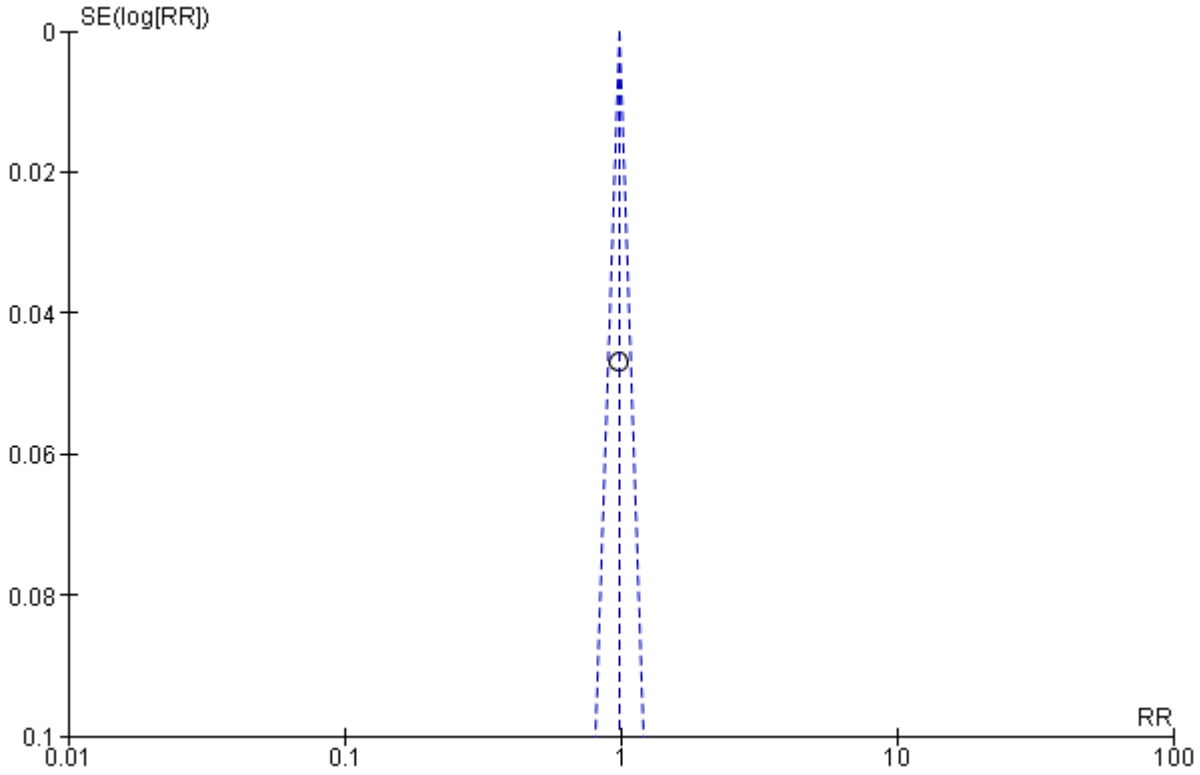

Figure 8: Funnel Plot for Studies Comparing Aspirin to Terutroban

Table 11A and 11B present the GRADE assessments for studies comparing Aspirin to Terutroban in the context of stroke prevention among patients at high risk of vascular disease.

Table 11A: GRADE Assessment (Aspirin compared to Terutroban)

Aspirin compared to Terutroban for stroke prevention in patients with high risk of vascular disease

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Terutroban	**Risk with Aspirin**				
stroke	**Low**		**RR 0.98**	19100	⨁⨁⨁⨁	

Aspirin compared to Terutroban for stroke prevention in patients with high risk of vascular disease

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Terutroban	Risk with Aspirin				
prevention	0 per 1,000	**0 per 1,000** (0 to 0)	(0.90 to 1.08)	(1 RCT)	HIGH	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

RR: Risk ratio

GRADE Working Group Grades of Evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 11B: GRADE Evidence Profile (Aspirin compared to Terutroban)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Terutroban	Relative (95% CI)	Absolute (95% CI)		
stroke prevention												
1	randomised trials	not serious	not serious	not serious	not serious	none	828/9544 (8.7%)	0.0%	**RR 0.98** (0.90 to 1.08)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	

CI: Confidence interval; **RR:** Risk ratio

Studies comparing Aspirin to Clopidogrel Plus Aspirin

Fig. 9 presents the forest plot of included studies comparing aspirin monotherapy to dual antiplatelet therapy (DAPT) with clopidogrel plus aspirin in the prevention of stroke among high-risk vascular patients. In each study, participants were randomly allocated to either the experimental group (clopidogrel plus aspirin) or the control group (aspirin alone). The overall test of effect yielded a relative risk (RR) of 0.80 with a 95% confidence interval (CI) ranging from 0.65 to 0.99. As the confidence interval does not cross the line of no effect (RR = 1.0) and the p-value is less than 0.05, the result is statistically significant

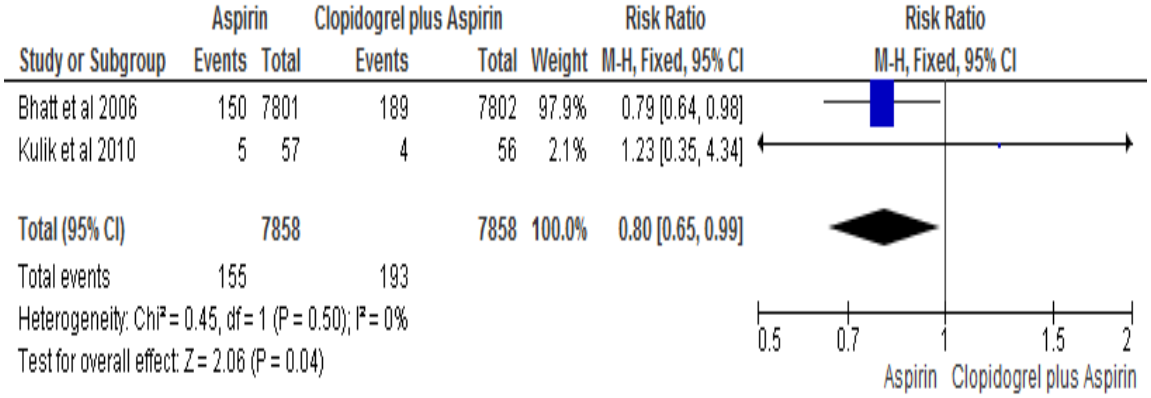

Figure 9: Forrest Plot for Studies Comparing Aspirin to Clopidogrel Plus Aspirin

Fig. 10 below displays the corresponding funnel plot, which does not suggest the presence of publication bias. The plot appears symmetrical, indicating a balanced distribution of study effect sizes, which reduces the likelihood of selective publication or reporting bias. Symmetry in a funnel plot is typically interpreted as a sign that smaller studies are not disproportionately absent from the analysis, thereby supporting the credibility of the pooled findings (Higgins and Green, 2011; Kepes, Wang & Cortina, 2023; Afonso et al., 2024).

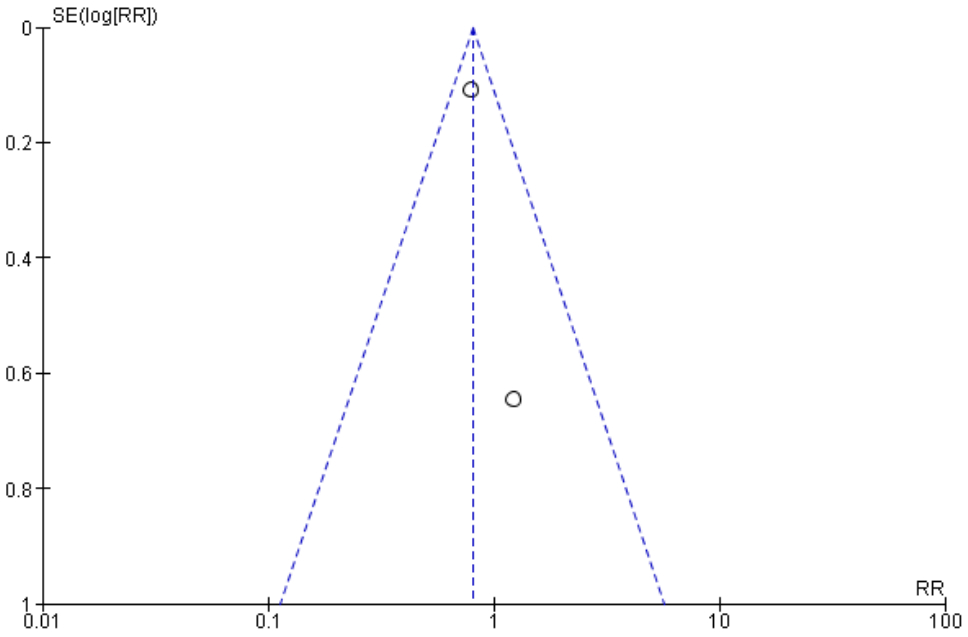

Figure 10: **Funnel Plot (for Studies Comparing Aspirin to Clopidogrel Plus Aspirin) showing no publication bias.**

Tables 12 and 13 present the GRADE assessments for studies comparing Aspirin to Clopidogrel Plus Aspirin in the context of stroke prevention among patients at high risk of vascular disea

Table 12: GRADE Evidence Profile (Aspirin Compared to Clopidogrel Plus Aspirin)

GRADE Evidence Profile (Aspirin compared to Clopidogrel Plus Aspirin)

Aspirin Compared to Clopidogrel Plus Aspirin for stroke prevention in patients with high risk of vascular disease

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Clopidogrel plus Aspirin	**Risk with Aspirin**				
Stroke prevention follow up: mean 20 months	25 per 1,000	**20 per 1,000** (16 to 24)	**RR 0.80** (0.65 to 0.99)	15716 (2 RCTs)	⨁⨁⨁⨁ HIGH	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 13: GRADE Evidence Profile

Question: Aspirin compared to Clopidogrel plus Aspirin for stroke prevention in patients with high risk of vascular disease

Setting: General Practice, Hospitals

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Clopidogrel plus Aspirin	Relative (95% CI)	Absolute (95% CI)		
Stroke prevention (follow up: mean 20 months)												
2	randomised trials	not serious	not serious	not serious	not serious	none	155/7858 (2.0%)	193/7858 (2.5%)	**RR 0.80** (0.65 to 0.99)	**5 fewer per 1,000** (from 0 fewer to 9 fewer)	⊕⊕⊕⊕ HIGH	

CI: Confidence interval; **RR:** Risk ratio

DISCUSSION

This systematic review and meta-analysis explored the effectiveness of aspirin in preventing stroke among patients at high risk of vascular disease. Drawing upon evidence from rigorously selected randomised controlled trials, this review provides a critical synthesis of aspirin's comparative efficacy against other pharmacological interventions, such as placebo, clopidogrel, terutroban, and dual antiplatelet therapy (DAPT). The findings contribute to the ongoing discourse on optimising stroke prevention strategies and inform clinical practice by highlighting both the strengths and limitations of aspirin therapy in various clinical contexts.

When aspirin was compared to placebo, the evidence indicated a statistically significant reduction in the incidence of stroke among high-risk individuals. This supports existing clinical and epidemiological data suggesting that aspirin plays a vital role in secondary stroke prevention (Calderone et al., 2021; Santos-Gallego & Badimon, 2021; Davidson et al., 2022). Although the strength of the evidence was considered low due to methodological concerns in one of the included studies, the direction and consistency of the effect across trials are in line with previous findings that validate aspirin's clinical utility in preventing vascular events (Wang et al., 2022). These findings corroborate earlier research that demonstrated aspirin's superiority over placebo in reducing the risk of stroke and cardiovascular morbidity among individuals with heightened vascular risk (Stiller & Hjemdahl, 2022).

The comparison between aspirin and clopidogrel suggested that clopidogrel may offer superior protective benefits against recurrent stroke. This is particularly relevant in patients who may have contraindications to aspirin or who are at higher risk for gastrointestinal side effects. Previous large-scale clinical trials have similarly concluded that clopidogrel can be more effective than aspirin in specific subgroups, including individuals with diabetes or peripheral artery disease (Bedair et al., 2024; Li et al., 2024). Furthermore, clopidogrel's pharmacodynamic profile, characterised by inhibition of the P2Y12 receptor on platelets, provides a mechanistic rationale for its superior efficacy in certain populations (Camargo et al., 2021).

When compared with terutroban, a newer antiplatelet agent, aspirin demonstrated comparable efficacy, although the results were not statistically significant. While aspirin appeared slightly more effective in reducing stroke events, the small number of studies and limited statistical power restrict the confidence with which conclusions can be drawn. Further investigations are warranted to clarify whether terutroban can serve as

a viable alternative or adjunct to aspirin in specific clinical scenarios.

The analysis of aspirin monotherapy versus dual antiplatelet therapy, comprising aspirin and clopidogrel, revealed that aspirin alone may be equally or more effective in preventing stroke in certain populations. While dual therapy is often considered in acute settings or following specific cardiovascular events, prolonged use carries an increased risk of bleeding without necessarily conferring added protection against stroke (Costa et al., 2023). These findings underscore the importance of patient stratification and duration of therapy when determining the optimal antiplatelet regimen (Khan et al., 2021).

Despite the comprehensive nature of this review, several methodological limitations were identified. There was substantial heterogeneity in study designs, participant characteristics, follow-up durations, and definitions of endpoints across the included trials. These differences could influence the pooled estimates and introduce variability that may affect the overall interpretation of results. Additionally, the included studies varied in their comparator arms—ranging from placebo to active pharmacological agents—thereby complicating direct comparisons and the generalisability of findings.

One study (Collaborative Group of the primary prevention, 2001) exhibited a high risk of bias due to a lack of blinding and inadequate allocation concealment, which negatively influenced the quality assessment and reduced the overall certainty of the evidence. However, to mitigate the potential for bias in this review, the entire process—including study selection, data extraction, risk of bias assessment, and data synthesis—was conducted by multiple independent reviewers. This collaborative approach enhanced the methodological rigour, minimised the risk of selection and confirmation bias, and contributed to the overall reliability and transparency of the findings, in line with previous studies (Sarri et al., 2022).

The applicability of the findings is strengthened by the real-world relevance of the included trials. Studies were conducted in diverse clinical and community settings and involved participants of varying ages, genders, and socio-economic backgrounds. As such, the review findings are broadly applicable to contemporary clinical practice. However, caution should be exercised when extrapolating the results to populations not well represented in the original trials, including individuals with severe comorbidities, advanced age, or those requiring long-term anticoagulation.

These findings are largely consistent with existing literature. Several randomised trials and meta-analyses have affirmed the role of aspirin in reducing the risk of recurrent stroke, though its efficacy in primary prevention remains more contentious (RECOVERY Collaborative Group, 2022; Wang et al., 2022). The overall benefit of aspirin in stroke prophylaxis appears to be context-dependent, with individual patient risk profiles influencing both the potential advantages and the likelihood of adverse effects (Chun et al., 2024). Differences in trial methodologies, patient populations, and outcome measures may account for the observed variability in the literature (Jannati, Patnaik & Banerjee, 2024).

While this review reinforces the role of aspirin as an effective agent for secondary stroke prevention among patients with high vascular risk, the superiority of alternative agents such as clopidogrel in certain contexts suggests that antiplatelet therapy should be personalised. Ongoing research should focus on improving adherence, refining risk stratification tools, and expanding access to high-quality stroke prevention interventions, particularly in resource-limited settings. Strengthening trial designs and ensuring greater representation of diverse populations will also be critical for enhancing the applicability and equity of future findings in stroke prevention.

CONCLUSION

This systematic review and meta-analysis critically examined the evidence surrounding the use of aspirin for stroke prevention in patients with a high risk of vascular disease. The findings underscore aspirin's effectiveness in reducing stroke incidence compared to placebo, affirming its role as a cornerstone in secondary prevention strategies. However, when evaluated against other antiplatelet and antithrombotic agents such as clopidogrel, dual antiplatelet therapy, and terutroban, the comparative efficacy of aspirin varied, with some evidence suggesting superiority of alternatives in

specific clinical scenarios.

The review also highlighted important limitations in the existing literature, including heterogeneity in trial designs, variation in outcome measures, and methodological weaknesses such as risk of bias and insufficient blinding. These factors necessitate cautious interpretation of the pooled results. Furthermore, while the review process employed rigorous and transparent methodology with input from multiple independent reviewers, the limited number of high-quality studies and variations in sample populations indicate that more robust and inclusive research is needed.

The findings support the continued use of aspirin in clinical practice, particularly for patients with established vascular disease or those at significant risk of recurrent cerebrovascular events. However, they also reinforce the need for personalised treatment approaches that consider individual risk profiles, tolerability, and potential for adverse effects. Future research should prioritise head-to-head comparisons of antiplatelet agents, incorporate pharmacogenomic insights, and aim to address gaps in evidence—especially in underrepresented populations and resource-limited settings.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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