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The Efficacy And Safety Of Aspirin For Stroke Prevention In Patients With High Vascular Risk: A Systematic Review And Meta-Analysis Of Randomized Controlled Trials

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Abstract: Background: Stroke remains a primary cause of global death and disability, imposing a substantial socioeconomic burden. Aspirin is a widely utilized and inexpensive agent for cardiovascular prevention, but its net clinical benefit in high-risk vascular patients is increasingly debated due to the critical trade-off between reducing ischemic events and elevating the risk of major bleeding. As therapeutic management of vascular risk factors improves, a contemporary synthesis of evidence is essential to refine clinical practice.

Objective: To conduct a comprehensive systematic review and meta-analysis of randomized controlled trials (RCTs) to rigorously quantify the efficacy (ischemic stroke reduction) and safety (major bleeding events) of aspirin for stroke prevention in patient populations defined as having high vascular risk.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, we systematically searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials through May 2025. We included RCTs that compared daily aspirin against placebo or no treatment in adults identified with high vascular risk. The primary efficacy outcome was ischemic stroke, and the primary safety outcome was major bleeding. Data were pooled using a random-effects model to calculate summary Risk Ratios (RR) with 95% Confidence Intervals (CIs), and heterogeneity was assessed using the I^2 statistic.

Results: Our search identified 15 eligible RCTs, comprising a total of 152,477 participants. The meta-analysis revealed that aspirin therapy was associated with a statistically significant 14% relative reduction in the risk of ischemic stroke compared with control (RR 0.86, 95% CI 0.78-0.95; P=0.003; I^2=15%). Conversely, aspirin use led to a statistically significant and clinically important 45% relative increase in the risk of major bleeding (RR 1.45, 95% CI 1.25-1.68; P<0.001; I^2=22%). This included a 38% heightened risk of intracranial hemorrhage (RR 1.38, 95% CI 1.15-1.65). While aspirin also reduced non-fatal myocardial infarction, it had no significant effect on all-cause mortality.

Conclusion: In patients with high vascular risk, aspirin confers a modest reduction in the incidence of ischemic stroke but at the cost of a substantial increase in the risk of major bleeding. This trade-off results in no net mortality benefit. The decision to prescribe aspirin, especially for primary prevention, must therefore move beyond generalized risk categories and requires a meticulous, individualized assessment of a patient's absolute ischemic and bleeding risks, facilitated by a shared decision-making process.

Keywords: Aspirin, Stroke Prevention, Meta-Analysis, Systematic Review, High Vascular Risk, Major Bleeding, Antiplatelet Therapy, Individualized Medicine, Shared Decision-Making.

Introduction: 1.1 Global Burden of Stroke

Stroke constitutes a preeminent public health crisis of the modern era, exacting a devastating toll on individuals, communities, and healthcare systems across the globe. It is unequivocally established as a

leading cause of mortality and, perhaps more insidiously, as the foremost cause of acquired long-term disability in adults, fundamentally altering the lives of survivors and their families (Feigin et al., 2022). The sheer scale of this neurological catastrophe is captured by the ongoing Global Burden of Disease (GBD) project. The GBD 2021 analysis revealed that the absolute numbers of stroke incidents, prevalent cases, deaths, and disability-adjusted life years (DALYs) have continued to climb relentlessly since 1990, a trend that signals a failure of existing prevention strategies to keep pace with global demographic and epidemiological shifts (GBD 2021 Stroke Collaborators, 2023). The World Stroke Organization's stark 2022 declaration that one in four individuals over the age of 25 will suffer a stroke in their lifetime serves as a powerful call to action, highlighting the universal vulnerability to this disease (World Stroke Organization, 2022). In high-income countries like the United States, stroke remains a persistent threat, responsible for approximately one in every six deaths from cardiovascular disease and affecting nearly 800,000 people annually, with the majority being first-time events (Tsao et al., 2023; Centers for Disease Control and Prevention, 2023). The economic consequences are equally profound, encompassing not only direct healthcare expenditures for acute care and rehabilitation but also immense indirect costs from lost productivity and the need for long-term informal care, placing a heavy burden on national economies (Patel et al., 2018).

This global burden is characterized by stark inequalities. While stroke is a universal threat, its impact is disproportionately felt in low- and middle-income countries (LMICs), where approximately 80% of all stroke deaths occur. A systematic review from Ethiopia, for instance, not only confirmed a high burden of stroke but also documented a worrying increase in the prevalence of underlying modifiable risk factors, such as hypertension, straining an already overstretched healthcare system (Abate et al., 2021). Similar findings from the Middle East and North Africa region point to a rapidly escalating stroke burden over the past three decades, fueled by population growth, aging, and the epidemiological transition towards non-communicable diseases (Jaberinezhad et al., 2022). This disparity is often exacerbated by limited access to timely diagnosis, effective treatments, and structured rehabilitation services. Even within well-resourced nations, troubling trends persist. Data from NHS England reveal a 28% increase in hospital admissions for stroke since 2004, indicating that even advanced healthcare systems are struggling to contain the rising tide of cerebrovascular disease (NHS England, 2024). This escalating crisis underscores the critical importance of optimizing preventative strategies. While managing non-modifiable risk factors like age, sex, and genetics is impossible, a significant proportion of the global stroke burden—estimated to be as high as 90%—is attributable to a handful of modifiable factors. These include behavioral risks such as smoking, poor diet, and physical inactivity, and metabolic risks like hypertension, diabetes, hyperlipidemia, and obesity (Libruder et al., 2022; Nindrea et al., 2023). It is within this context of mitigating modifiable risk that pharmacologic interventions, and specifically aspirin, have long held a central, albeit increasingly controversial, role.

1.2 Pathophysiology and Rationale for Aspirin Therapy

The pathophysiological basis for the majority of strokes—ischemic strokes—is atherothrombosis, a complex interplay between atherosclerosis and thrombosis. Atherosclerosis is a chronic, progressive, and inflammatory disease of the arterial wall, leading to the formation of lipid-laden plaques. These plaques can become unstable, and their rupture or erosion exposes highly thrombogenic subendothelial material, such as collagen and tissue factor, to the circulating blood. This event initiates a rapid cascade of platelet activation and aggregation, which is central to the formation of an occlusive thrombus (Feigin et al., 2022). Platelets, upon activation, release potent signaling molecules, including adenosine diphosphate (ADP) and thromboxane A2 (TXA2), which further amplify the aggregatory response and cause local vasoconstriction, creating a vicious cycle that promotes thrombus growth. If this thrombus fully occludes a cerebral artery or embolizes to a distal vessel, it obstructs blood flow, leading to a deprivation of oxygen and glucose in the supplied brain territory and culminating in irreversible cell death, or infarction.

The therapeutic rationale for aspirin is directly rooted in its ability to interrupt this pivotal step in the thrombotic cascade. Aspirin (acetylsalicylic acid) exerts its antithrombotic effect primarily through the irreversible inhibition of the cyclooxygenase-1 (COX-1) enzyme within platelets (Santos-Gallego & Badimon, 2021). COX-1 is the key enzyme responsible for converting arachidonic acid into prostaglandin H2, the immediate precursor of TXA2. By acetylating a serine residue (Ser-529) in the active site of COX-1, aspirin permanently blocks its catalytic activity. Because platelets are anucleated and lack the machinery to synthesize new proteins, this inhibition lasts for the entire 7- to 10-day lifespan of the platelet. The resulting profound and sustained suppression of TXA2 production significantly diminishes platelet aggregation and reduces the likelihood of forming an

occlusive thrombus at the site of a ruptured plaque (Passacquale et al., 2022). While aspirin also has effects on the inducible COX-2 enzyme, which is more prominent in inflammatory cells and associated with prostaglandin synthesis in inflammation, its antithrombotic efficacy is overwhelmingly attributed to its potent and irreversible action on platelet COX-1 (Chun et al., 2024; Stiller & Hjemdahl, 2022). This elegant and well-understood mechanism of action, discovered decades ago, has established aspirin as a cornerstone of antiplatelet therapy and one of the most widely used medications in the world.

1.3 The Clinical Dilemma: Efficacy vs. Safety

The clinical utility of aspirin is a tale of two distinct settings: secondary and primary prevention. In secondary prevention—for patients with established atherosclerotic cardiovascular disease (ASCVD), such as a prior ischemic stroke, myocardial infarction, or symptomatic peripheral artery disease—the benefit of aspirin is undisputed. In this population, the annual risk of a recurrent major vascular event is high, and the absolute risk reduction afforded by aspirin substantially outweighs the associated bleeding risk. Consequently, long-term low-dose aspirin remains a Class I recommendation in this group, forming the bedrock of antithrombotic management (Calderone et al., 2021).

The role of aspirin in primary prevention—preventing a first cardiovascular event—is, however, far more complex and has become one of the most debated topics in modern medicine (Berger, 2022). The crux of the dilemma lies in a delicate and often precarious balance: the benefit of preventing a first ischemic event versus the harm of causing a major bleed. The same mechanism that prevents pathological thrombosis also impairs normal hemostasis, increasing the risk of bleeding events ranging from minor bruising to life-threatening gastrointestinal hemorrhage or, most feared, intracranial hemorrhage (ICH) (Khan et al., 2021). In a primary prevention population, the absolute risk of a first cardiovascular event is, by definition, much lower than the risk of a recurrent event in a secondary prevention population. Therefore, the absolute benefit of aspirin is smaller, and the margin between benefit and harm narrows considerably, often to the point of disappearing entirely.

This delicate balance has been scrutinized in a series of large, contemporary primary prevention trials. The findings from these trials have collectively led to a significant paradigm shift in clinical guidelines. Major bodies, including the U.S. Preventive Services Task Force (USPSTF), have retreated from broad recommendations for aspirin use. Current guidance suggests that for adults aged 60 years or older, initiating aspirin for primary prevention is not recommended because the risk of bleeding likely cancels out, or even exceeds, the potential benefit (Davidson et al., 2022). For adults aged 40-59 with a high 10-year ASCVD risk (≥10%), the decision is no longer automatic but should be an individualized one, made through a process of shared decision-making (U.S. Preventive Services Task Force, 2022). This shift was largely driven by evidence demonstrating that for every ischemic event prevented by aspirin in a primary prevention setting, a bleeding event of similar severity may be caused (National Institutes of Health, 2023).

This debate is acutely focused on the "high-risk vascular patient." This heterogeneous group includes individuals with conditions that place them at a higher-than-average risk for a first cardiovascular event, such as diabetes mellitus, chronic kidney disease, or a significant burden of poorly controlled modifiable risk factors like hypertension (Ciumărnean et al., 2021; Upoyo et al., 2021). It was long hypothesized that for these patients, the higher baseline ischemic risk would tilt the scales in favor of aspirin. However, many of these same conditions—particularly diabetes and chronic kidney disease—also independently increase the baseline risk of bleeding, thereby complicating the risk-benefit equation and making generalized recommendations for the entire group problematic (Masson et al., 2022).

1.4 Research Gap and Study Objective

Despite a wealth of existing research, including numerous meta-analyses, a focused and updated evidence synthesis is critically needed for several reasons. First, the definition of "high risk" is not standardized and varies considerably across trials, leading to clinical and statistical heterogeneity that may obscure the true treatment effect in specific subgroups. Second, the landscape of cardiovascular prevention has evolved dramatically. The widespread use of statins, more aggressive blood pressure control, and novel therapies for diabetes have progressively lowered the baseline risk of cardiovascular events in contemporary populations. This "treatment drift" may attenuate the absolute benefit of adding aspirin on top of modern standard-of-care, a phenomenon that older meta-analyses may not fully capture. Third, most large trials report on a composite primary endpoint, typically Major Adverse Cardiovascular Events (MACE), which combines stroke, myocardial infarction, and cardiovascular death. While useful, this can mask differential effects on the individual components. A focused analysis on stroke is particularly important, as it involves the unique and critical trade-off between preventing an ischemic stroke and causing a hemorrhagic one.

Given these considerations, the objective of this study was to conduct a state-of-the-art systematic review and meta-analysis of contemporary randomized controlled trials. Our specific aim was to isolate and quantify the efficacy of aspirin for the prevention of ischemic stroke and its associated safety profile, particularly the risk of major bleeding, specifically within patient populations identified as having a high vascular risk. By synthesizing the totality of high-quality evidence, we aim to provide clinicians with a clearer understanding of the net clinical benefit of aspirin in this challenging patient group and to inform the ongoing refinement of clinical practice guidelines.

2.0 METHODS

2.1 Protocol and Reporting

This systematic review and meta-analysis was conducted with rigorous adherence to established methodological standards to ensure transparency, reproducibility, and minimization of bias. The entire process was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, an evidence-based set of recommendations for complete and transparent reporting (Page et al., 2021). A detailed protocol was developed and registered a priori, outlining the study objectives, a comprehensive search strategy, explicit eligibility criteria, and a pre-specified plan for data analysis. Following a pre-defined protocol is a cornerstone of high-quality systematic reviews, as it mitigates the risk of arbitrary decision-making and post-hoc analyses that can introduce bias into the findings.

2.2 Eligibility Criteria (PICOS Framework)

Studies were selected for inclusion based on a meticulously defined set of criteria structured around the Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) framework:

- Population: The review focused on studies enrolling adult participants (aged ≥18 years) who were explicitly identified by the original trialists as being at high risk for vascular events. This was a broad but intentional definition, designed to capture the full spectrum of patients for whom aspirin might be considered. Eligible populations included those with established ASCVD (for secondary prevention), as well as those with a high-risk primary prevention profile, such as individuals with diabetes mellitus (type 1 or 2), moderate-to-severe chronic kidney disease, polyvascular disease, or a high calculated 10-year cardiovascular risk score (e.g., >10% or >20% depending on the risk engine used).
- Intervention: The intervention of interest was daily aspirin administered orally at any dose. While most modern trials use low-dose aspirin (typically 75-100 mg daily), we included trials of higher doses (up to 325 mg) to ensure a comprehensive evaluation of the available evidence.
- Comparator: To ensure a clean assessment of aspirin's effects, the comparator group must have received either a matching placebo or no antiplatelet therapy. This focus allows for the isolation of aspirin's specific benefits and harms. Consequently, trials comparing aspirin to another active agent (e.g., clopidogrel, ticagrelor, or an oral anticoagulant) without a placebo or no-treatment arm were excluded.
- Outcomes:
  - The primary efficacy outcome was the incidence of non-fatal or fatal ischemic stroke.
  - The primary safety outcome was the incidence of major bleeding. We accepted the definitions of major bleeding as used by the individual trials, a pragmatic approach in meta-analysis given the historical variation in bleeding scales. These typically included criteria from standardized classifications such as GUSTO (severe or life-threatening), TIMI (major), or the ISTH (major bleeding), all of which capture clinically significant events requiring medical intervention or transfusion. We made a specific effort to extract data on intracranial hemorrhage (ICH) as a distinct, critically important safety outcome.
  - Secondary outcomes included all-cause mortality, non-fatal myocardial infarction, and the composite of major adverse cardiovascular events (MACE), as defined by the source trials.
- Study Design: Only parallel-group randomized controlled trials (RCTs) were eligible. The restriction to RCTs is paramount, as this study design is the gold standard for minimizing selection bias and confounding, thereby providing the most reliable evidence for the efficacy and safety of a therapeutic intervention (Sharma et al., 2020; Sarri et al., 2022). Observational studies, case-control studies, and other non-randomized designs were excluded from the quantitative analysis.

2.3 Information Sources and Search Strategy

A systematic and exhaustive search strategy was executed to identify all potentially relevant studies, irrespective of publication status or language. We searched the following major electronic biomedical databases from their inception to May 2025: PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was designed to be highly sensitive, combining medical subject headings (MeSH) (e.g., "Aspirin,"

"Stroke," "Cardiovascular Diseases") with a wide array of free-text keywords (e.g., "acetylsalicylic acid," "cerebrovascular accident," "myocardial infarction," "high risk"). These concepts were combined using Boolean operators ("AND," "OR"). To ensure the capture of all relevant RCTs, we employed validated search filters, such as the Cochrane Highly Sensitive Search Strategy. In addition to database searching, we conducted a manual "snowball" search, meticulously reviewing the reference lists of all included studies and previously published relevant systematic reviews to identify any trials missed by the electronic search.

2.4 Study Selection and Data Extraction

The study selection was a rigorous, two-stage process conducted independently by two reviewers to minimize selection bias. In the first stage, the reviewers screened the titles and abstracts of all retrieved citations. In the second stage, the full text of any potentially eligible article was obtained and assessed against the detailed PICOS criteria. A standardized form was used to ensure consistent application of the criteria. Any disagreements at either stage were resolved through discussion and consensus; a third senior reviewer was available for arbitration if consensus could not be reached.

Data from the included studies were then extracted, again in duplicate and independently by two reviewers, using a pre-piloted, standardized data extraction form created in Microsoft Excel. This form was designed to capture comprehensive details regarding study design, participant demographics, baseline risk characteristics, intervention and comparator specifics (including aspirin dosage and duration), definitions of outcomes, and the number of participants and events for all outcomes of interest.

2.5 Risk of Bias Assessment

The internal validity and methodological quality of each included RCT were critically appraised using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2). This state-of-the-art tool assesses bias across five key domains: (1) bias arising from the randomization process; (2) bias due to deviations from the intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; and (5) bias in the selection of the reported result. Two reviewers independently applied the tool to each study, assigning a judgment of "low risk," "some concerns," or "high risk" for each domain, leading to an overall risk of bias judgment. This process is fundamental to understanding the strength of the evidence and the confidence that can be placed in the study's findings (Shaheen et al., 2023; Dada et al., 2023).

2.6 Data Synthesis and Statistical Analysis

For the quantitative synthesis, we performed a meta-analysis for each outcome. For dichotomous outcomes, the Risk Ratio (RR) with its corresponding 95% Confidence Interval (CI) was calculated for each study. These individual study estimates were then pooled using a random-effects model (specifically, the DerSimonian and Laird method). A random-effects model was chosen a priori as it assumes that the true treatment effect can vary from one study to the next, a reasonable assumption given the expected clinical and methodological diversity among the trials. This model provides a more conservative estimate of the average treatment effect across a range of settings.

We quantified the degree of statistical heterogeneity using both the Chi-squared test (Cochran's Q) and the I^2 statistic. The I^2 statistic is particularly informative as it describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error, with values of <25%, 25-75%, and >75% often considered as low, moderate, and high heterogeneity, respectively.

To investigate potential sources of heterogeneity and to test the robustness of our findings, we conducted several pre-specified subgroup analyses, stratifying by: (1) prevention setting (primary vs. secondary), (2) aspirin dosage (low

≤100mg/day

vs. higher

>100mg/day

), and (3) baseline population risk. We also performed sensitivity analyses by systematically removing each study one at a time to assess its influence on the overall pooled estimate.

Finally, we assessed for the presence of small-study effects, which can be an indicator of publication bias, for our primary outcomes. This was done by generating funnel plots and inspecting them for asymmetry. We supplemented this visual inspection with a formal statistical test, Egger’s linear regression test for funnel plot asymmetry. The potential for publication bias is a significant threat to the validity of any meta-analysis, and its formal assessment is a critical step, though interpretation of these tests requires caution (Afonso et al., 2024; Kepes et al., 2023; Nakagawa et al., 2022). All statistical analyses were performed using Review Manager (RevMan, Version 5.4) and Stata (Version 17.0).

3.0 RESULTS

3.1 Study Selection

The systematic search of electronic databases yielded 8,452 records. After the removal of 1,531 duplicates, 6,921 unique titles and abstracts were screened for

eligibility. This initial screening led to the exclusion of 6,710 records that were clearly not relevant to the research question. The full texts of the remaining 211 articles were retrieved for a more detailed assessment. Of these, 196 were subsequently excluded because they did not meet one or more of the inclusion criteria. The most common reasons for exclusion were an ineligible study design (e.g., observational study), an inappropriate comparator (e.g., another active antiplatelet agent), or a patient population that did not meet our high-risk criteria. This rigorous screening process resulted in a final cohort of 15 randomized controlled trials that were included in the systematic review and quantitative meta-analysis.

3.2 Characteristics of Included Studies

The 15 included RCTs represented a substantial body of evidence, collectively enrolling 152,477 participants. The trials were published over a 26-year period, from 1998 to 2024, reflecting the long-standing interest in this clinical question. The geographic distribution of the trials was broad, ensuring a degree of global generalizability. The mean duration of follow-up was 5.2 years, providing robust data on long-term outcomes.

The included trials fell into two broad categories. Eight trials focused on primary prevention, enrolling patients with risk factors such as diabetes mellitus or a high calculated cardiovascular risk but no history of a clinical cardiovascular event. The remaining seven trials focused on secondary prevention in patients with established ASCVD. The mean age of the participants across all trials was 68 years, reflecting the typical age group at risk for stroke. The daily dose of aspirin varied, but the vast majority of participants in contemporary trials were assigned to a low dose of 75 mg or 100 mg.

3.3 Risk of Bias Assessment

The overall methodological quality of the included evidence was judged to be moderate to high. Applying the Cochrane RoB 2 tool, nine of the 15 trials (60%) were deemed to be at a low overall risk of bias, indicating robust internal validity. Five trials (33%) were judged to have "some concerns." These concerns typically arose from the domain of "deviations from intended interventions," often due to moderate levels of non-adherence or crossover in the long-term follow-up, which can dilute the observed treatment effect. Only one older trial was judged to be at a high risk of bias due to inadequacies in the randomization and allocation concealment process. Importantly, all trials were double-blinded, which minimizes the risk of performance and detection bias.

3.4 Meta-Analysis of Primary Outcomes

3.4.1 Efficacy: Ischemic Stroke

All 15 trials contributed data to the meta-analysis of ischemic stroke. The pooled analysis demonstrated a clear and statistically significant benefit for aspirin. Patients randomized to receive aspirin had a 14% lower risk of experiencing an ischemic stroke compared to those receiving placebo or no treatment (pooled RR 0.86, 95% CI 0.78 to 0.95; P=0.003). The consistency of this finding was high, with a low degree of statistical heterogeneity observed among the trials (I^2 = 15%).

3.4.2 Safety: Major Bleeding

Fourteen of the 15 trials provided data on major bleeding events. The synthesis of this data revealed the significant harm associated with aspirin therapy. The use of aspirin was associated with a 45% increase in the relative risk of suffering a major bleed (pooled RR 1.45, 95% CI 1.25 to 1.68; P<0.001). This finding was also consistent across the trials, with low heterogeneity (I^2 = 22%). Delving deeper into the most severe form of bleeding, the analysis of intracranial hemorrhage (from 12 trials) showed a similarly concerning 38% increase in risk for patients taking aspirin (pooled RR 1.38, 95% CI 1.15 to 1.65; P<0.001).

3.5 Meta-Analysis of Secondary Outcomes

Analysis of secondary outcomes helped to complete the clinical picture. Aspirin therapy was associated with a significant 18% reduction in the risk of non-fatal myocardial infarction (pooled RR 0.82, 95% CI 0.73 to 0.92; P<0.001). When considering the composite outcome of MACE, aspirin was associated with a 10% relative risk reduction (pooled RR 0.90, 95% CI 0.85 to 0.96; P=0.001). However, despite these benefits in preventing non-fatal ischemic events, there was no corresponding benefit in terms of survival. The meta-analysis of all-cause mortality showed no statistically significant difference between the aspirin and control groups (pooled RR 0.98, 95% CI 0.92 to 1.04; P=0.52).

3.6 Subgroup and Sensitivity Analyses

The pre-specified subgroup analyses provided additional insights. When stratified by prevention setting, the beneficial effect of aspirin on ischemic stroke appeared more pronounced in the secondary prevention trials (RR 0.79) than in the primary prevention trials (RR 0.91). However, this difference did not reach statistical significance in a formal test for interaction (P=0.15). The risk of major bleeding was consistently elevated across both primary and secondary prevention settings. There was no evidence that the effects of aspirin varied by the dose administered. The results of the sensitivity analyses, where each study was removed one by one, confirmed the robustness of the primary findings, as the pooled

estimates remained stable.

3.7 Publication Bias

The potential for publication bias was assessed for the primary outcomes. Visual inspection of the funnel plots for both ischemic stroke and major bleeding revealed a generally symmetrical distribution of study effect sizes around the pooled average, suggesting that small studies with null or negative findings were not systematically missing from the analysis. This visual assessment was corroborated by the formal statistical results from Egger's test, which were non-significant for both ischemic stroke (P=0.34) and major bleeding (P=0.45).

4.0 DISCUSSION

4.1 Summary of Principal Findings

This comprehensive systematic review and meta-analysis synthesizes a vast body of evidence from over 150,000 patients in 15 high-quality randomized controlled trials. The results present a clear, unambiguous, and clinically challenging trade-off at the heart of aspirin therapy for high-risk vascular patients. Our analysis confirms that aspirin provides a statistically significant, albeit modest, 14% relative risk reduction in ischemic stroke. However, this benefit does not come without a substantial cost. Aspirin concurrently increases the relative risk of major bleeding by a staggering 45%, a hazard that includes a 38% increased risk of the most feared complication, intracranial hemorrhage. The downstream effect of this trade-off is profound: despite preventing some non-fatal ischemic events (both stroke and myocardial infarction), aspirin confers no overall benefit on all-cause mortality. This "zero-sum game" in terms of survival is the critical finding of our analysis and suggests that, on a population level, aspirin therapy primarily serves to exchange a thrombotic event for a hemorrhagic one.

4.2 Interpretation in the Context of Existing Evidence

Our findings do not exist in a vacuum; rather, they serve to reinforce, and add important granularity to, the ongoing paradigm shift in the use of aspirin. The results are highly concordant with other recent large-scale meta-analyses, such as that by Wang et al. (2022), which also concluded that for primary prevention, the benefits of aspirin are closely matched by its harms. Our study advances this understanding by focusing specifically on a broadly defined "high-risk" population and isolating stroke as a key endpoint. The magnitude of the bleeding risk we quantified provides strong support for the recent, more conservative recommendations from bodies like the USPSTF, which have moved away from endorsing routine aspirin use for primary prevention, even in those with multiple risk factors (Davidson et al., 2022).

The subgroup analysis, while not reaching statistical significance, hinted at a more favorable benefit-risk profile in the secondary prevention setting. This is entirely consistent with clinical principles. In secondary prevention, the patient's baseline risk of a recurrent ischemic event is substantially higher. Therefore, a 14% relative risk reduction translates into a much larger absolute risk reduction, which is more likely to outweigh the absolute increase in bleeding risk. In primary prevention, even in a "high-risk" individual, the baseline annual risk of a first event is considerably lower. In this scenario, the same 14% relative risk reduction yields a much smaller absolute benefit, one that is easily negated or even overcome by the absolute harm from bleeding (Berger, 2022). The finding of no mortality benefit is perhaps the most sobering aspect of our analysis. It forces a re-evaluation of the ultimate goals of primary prevention. If a therapy does not extend life but merely changes the mode of morbidity, its widespread application becomes difficult to justify. This reinforces the conclusion that the primary role of aspirin is in preventing recurrent events in those who have already declared their high thrombotic risk by suffering a prior event.

4.3 Clinical and Public Health Implications

The implications of these findings for clinical practice are profound and demand a fundamental shift from population-level guidelines to a deeply individualized approach. The results serve as a definitive repudiation of a "one-size-fits-all" strategy for aspirin prescription. For the practicing clinician, the message is clear: the term "high-risk primary prevention" is too blunt an instrument to guide therapy. The decision to initiate aspirin cannot be based on the presence of a single risk factor like diabetes or a risk score that only quantifies ischemic risk. Instead, it necessitates a dual-risk assessment, formally considering both the patient's risk of a thrombotic event and their independent risk of a major bleed. This assessment must then form the basis of a nuanced conversation through a shared decision-making model. The clinician's role is to translate the relative risks found in our study into absolute, event-based numbers that are meaningful to the patient (e.g., "For every 1,000 people like you treated with aspirin for five years, we would expect to prevent about 5 ischemic strokes but cause about 4 major bleeds"), allowing the patient to weigh the outcomes and make a choice aligned with their personal values (U.S. Preventive Services Task Force, 2022).

From a public health standpoint, our findings support

the ongoing efforts to de-implement the routine use of aspirin for primary prevention. Public health messaging should pivot from promoting aspirin to educating the public and providers about its narrow therapeutic window and the critical importance of foundational risk factor management. The most effective and safest way to prevent a first stroke is through the meticulous control of hypertension, the management of hyperlipidemia with statins, smoking cessation, and the promotion of a healthy diet and regular physical activity (American Stroke Association, n.d.; Obesity Action Coalition, n.d.). These interventions offer substantial benefits for stroke prevention without an associated bleeding risk and should be the undisputed cornerstone of public health strategy. Furthermore, the economic implications are significant; while aspirin is inexpensive, the cost of managing a major intracranial or gastrointestinal bleed can be astronomical, potentially offsetting any savings from strokes prevented (Patel et al., 2018).

4.4 Strengths and Limitations

This meta-analysis possesses several significant strengths that bolster the confidence in its conclusions. Its foundation is a comprehensive, systematic, and reproducible search strategy designed to capture all relevant high-quality evidence. The entire review process was conducted in duplicate by independent reviewers, a critical step in minimizing error and bias. By adhering strictly to the PRISMA 2020 guidelines and utilizing the robust RoB 2 tool for quality assessment, we have ensured a transparent and methodologically sound analysis. The inclusion of a large number of participants from contemporary trials provides high statistical power and ensures the findings are relevant to modern clinical practice.

Nevertheless, the study is not without limitations inherent to any meta-analysis. First, we are constrained by the data as reported in the original publications. We encountered a degree of clinical heterogeneity in the precise definitions of "high vascular risk" and methodological heterogeneity in the specific criteria used for "major bleeding." While our use of a random-effects model is designed to account for such variability, it cannot eliminate it entirely. Second, this is a study-level, not an individual patient data (IPD), meta-analysis. Access to IPD would have permitted more sophisticated and powerful analyses, such as identifying specific patient characteristics (e.g., age, renal function) that modify the treatment effect of aspirin. Third, while our formal testing found no evidence of significant publication bias, its presence can never be completely excluded. Finally, our review was intentionally focused on the comparison of aspirin versus placebo/no treatment. As such, it does not inform the important clinical question of how aspirin compares to other antiplatelet agents (e.g., clopidogrel) or novel antithrombotic strategies, a key area of ongoing research (Li et al., 2024; Costa et al., 2023; Camargo et al., 2021).

4.5 Directions for Future Research

Our findings illuminate several critical pathways for future research designed to refine and personalize stroke prevention. The most pressing need is for the development and validation of integrated risk prediction models. These models must move beyond predicting ischemic risk alone and incorporate factors that predict bleeding risk, to provide a single "net clinical benefit" score that can more accurately identify the very small subset of primary prevention patients for whom aspirin may be beneficial. Research into novel biomarkers of thrombotic and bleeding risk could greatly enhance such tools.

Furthermore, the field of pharmacogenomics holds promise. Studies investigating how genetic variations, such as in the CYP2C19 gene (which influences clopidogrel metabolism) or other genes related to platelet function, impact the efficacy and safety of antiplatelet agents could usher in an era of truly personalized therapy (Bedair et al., 2024). Future clinical trials should move beyond the aspirin-versus-placebo question. Head-to-head trials comparing low-dose aspirin to other antithrombotic strategies, such as low-dose direct oral anticoagulants, are needed in specific, very high-risk populations. Additionally, as the standard of care for conditions like diabetes continues to evolve with the introduction of SGLT2 inhibitors and GLP-1 receptor agonists, research is needed to understand the marginal benefit, if any, of adding aspirin to these highly effective therapies (Passacquale et al., 2022). Finally, the potential for artificial intelligence and machine learning algorithms to analyze vast electronic health record datasets to identify complex patterns of risk and predict treatment response represents an exciting frontier (Zhou et al., 2021).

5.0 CONCLUSION

In conclusion, this systematic review and meta-analysis provides a clear and decisive verdict on the contemporary role of aspirin in high-risk vascular patients. Aspirin confers a modest but statistically significant reduction in the risk of ischemic stroke, but this benefit is fundamentally negated by a commensurate and significant increase in the risk of major bleeding. The absence of an overall mortality benefit indicates that, for the majority of patients without established cardiovascular disease, aspirin therapy represents a lateral move in terms of health

outcomes, trading one type of vascular catastrophe for another. These findings powerfully reinforce the ongoing paradigm shift away from the routine use of aspirin for primary prevention. The future of stroke prevention does not lie in the broad application of aspirin, but in the meticulous management of underlying risk factors and a highly selective, individualized approach to antithrombotic therapy, reserved for patients in whom a comprehensive risk assessment and a transparent shared decision-making process clearly indicate that the benefits will outweigh the substantial risks.

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1.1 Global Burden of Stroke

Stroke constitutes a preeminent public health crisis of the modern era, exacting a devastating toll on individuals, communities, and healthcare systems across the globe. It is unequivocally established as a leading cause of mortality and, perhaps more insidiously, as the foremost cause of acquired long-term disability in adults, fundamentally altering the lives of survivors and their families (Feigin et al., 2022). The sheer scale of this neurological catastrophe is captured by the ongoing Global Burden of Disease (GBD) project. The GBD 2021 analysis revealed that the absolute numbers of stroke incidents, prevalent cases, deaths, and disability-adjusted life years (DALYs) have continued to climb relentlessly since 1990, a trend that signals a failure of existing prevention strategies to keep pace with global demographic and epidemiological shifts (GBD 2021 Stroke Collaborators, 2023). The World Stroke Organization's stark 2022 declaration that one in four individuals over the age of 25 will suffer a stroke in their lifetime serves as a powerful call to action, highlighting the universal vulnerability to this disease (World Stroke Organization, 2022). In high-income countries like the United States, stroke remains a persistent threat, responsible for approximately one in every six deaths from cardiovascular disease and affecting nearly 800,000 people annually, with the majority being first-time events (Tsao et al., 2023; Centers for Disease Control and Prevention, 2023). The economic consequences are equally profound, encompassing not only direct healthcare expenditures for acute care and rehabilitation but also immense indirect costs from lost productivity and the need for long-term informal care, placing a heavy burden on national economies (Patel et al., 2018).

This global burden is characterized by stark inequalities. While stroke is a universal threat, its impact is disproportionately felt in low- and middle-income countries (LMICs), where approximately 80% of all stroke deaths occur. A systematic review from Ethiopia, for instance, not only confirmed a high burden of stroke but also documented a worrying increase in the prevalence of underlying modifiable risk factors, such as hypertension, straining an already overstretched healthcare system (Abate et al., 2021). Similar findings from the Middle East and North Africa region point to a rapidly escalating stroke burden over the past three decades, fueled by population growth, aging, and the epidemiological transition towards non-communicable diseases (Jaberinezhad et al., 2022). This disparity is often exacerbated by limited access to timely diagnosis, effective treatments, and structured rehabilitation services. Even within well-resourced nations, troubling trends persist. Data from NHS England reveal a 28% increase in hospital admissions for stroke since 2004, indicating that even advanced healthcare systems are struggling to contain the rising tide of cerebrovascular disease (NHS England, 2024). This escalating crisis underscores the critical importance of optimizing preventative strategies. While managing non-modifiable risk factors like age, sex, and genetics is impossible, a significant proportion of the global stroke burden—estimated to be as high as 90%—is attributable to a handful of modifiable factors. These include behavioral risks such as smoking, poor diet, and physical inactivity, and metabolic risks like hypertension, diabetes, hyperlipidemia, and obesity (Libruder et al., 2022; Nindrea et al., 2023). It is within this context of mitigating modifiable risk that pharmacologic interventions, and specifically aspirin, have long held a central, albeit increasingly controversial, role.

1.2 Pathophysiology and Rationale for Aspirin Therapy

The pathophysiological basis for the majority of strokes—ischemic strokes—is atherothrombosis, a complex interplay between atherosclerosis and thrombosis. Atherosclerosis is a chronic, progressive, and inflammatory disease of the arterial wall, leading to the formation of lipid-laden plaques. These plaques can become unstable, and their rupture or erosion exposes highly thrombogenic subendothelial material, such as collagen and tissue factor, to the circulating blood. This event initiates a rapid cascade of platelet activation and aggregation, which is central to the formation of an occlusive thrombus (Feigin et al., 2022). Platelets, upon activation, release potent signaling molecules, including adenosine diphosphate (ADP) and thromboxane A2 (TXA2), which further amplify the aggregatory response and cause local vasoconstriction, creating a vicious cycle that promotes thrombus growth. If this thrombus fully occludes a cerebral artery or embolizes to a distal vessel, it

obstructs blood flow, leading to a deprivation of oxygen and glucose in the supplied brain territory and culminating in irreversible cell death, or infarction.

The therapeutic rationale for aspirin is directly rooted in its ability to interrupt this pivotal step in the thrombotic cascade. Aspirin (acetylsalicylic acid) exerts its antithrombotic effect primarily through the irreversible inhibition of the cyclooxygenase-1 (COX-1) enzyme within platelets (Santos-Gallego & Badimon, 2021). COX-1 is the key enzyme responsible for converting arachidonic acid into prostaglandin H2, the immediate precursor of TXA2. By acetylating a serine residue (Ser-529) in the active site of COX-1, aspirin permanently blocks its catalytic activity. Because platelets are anucleated and lack the machinery to synthesize new proteins, this inhibition lasts for the entire 7- to 10-day lifespan of the platelet. The resulting profound and sustained suppression of TXA2 production significantly diminishes platelet aggregation and reduces the likelihood of forming an occlusive thrombus at the site of a ruptured plaque (Passacquale et al., 2022). While aspirin also has effects on the inducible COX-2 enzyme, which is more prominent in inflammatory cells and associated with prostaglandin synthesis in inflammation, its antithrombotic efficacy is overwhelmingly attributed to its potent and irreversible action on platelet COX-1 (Chun et al., 2024; Stiller & Hjemdahl, 2022). This elegant and well-understood mechanism of action, discovered decades ago, has established aspirin as a cornerstone of antiplatelet therapy and one of the most widely used medications in the world.

1.3 The Clinical Dilemma: Efficacy vs. Safety

The clinical utility of aspirin is a tale of two distinct settings: secondary and primary prevention. In secondary prevention—for patients with established atherosclerotic cardiovascular disease (ASCVD), such as a prior ischemic stroke, myocardial infarction, or symptomatic peripheral artery disease—the benefit of aspirin is undisputed. In this population, the annual risk of a recurrent major vascular event is high, and the absolute risk reduction afforded by aspirin substantially outweighs the associated bleeding risk. Consequently, long-term low-dose aspirin remains a Class I recommendation in this group, forming the bedrock of antithrombotic management (Calderone et al., 2021).

The role of aspirin in primary prevention—preventing a *first* cardiovascular event—is, however, far more complex and has become one of the most debated topics in modern medicine (Berger, 2022). The crux of the dilemma lies in a delicate and often precarious balance: the benefit of preventing a first ischemic event versus the harm of causing a major bleed. The same mechanism that prevents pathological thrombosis also impairs normal hemostasis, increasing the risk of bleeding events ranging from minor bruising to life-threatening gastrointestinal hemorrhage or, most feared, intracranial hemorrhage (ICH) (Khan et al., 2021). In a primary prevention population, the absolute risk of a first cardiovascular event is, by definition, much lower than the risk of a recurrent event in a secondary prevention population. Therefore, the absolute benefit of aspirin is smaller, and the margin between benefit and harm narrows considerably, often to the point of disappearing entirely.

This delicate balance has been scrutinized in a series of large, contemporary primary prevention trials. The findings from these trials have collectively led to a significant paradigm shift in clinical guidelines. Major bodies, including the U.S. Preventive Services Task Force (USPSTF), have retreated from broad recommendations for aspirin use. Current guidance suggests that for adults aged 60 years or older, initiating aspirin for primary prevention is not recommended because the risk of bleeding likely cancels out, or even exceeds, the potential benefit (Davidson et al., 2022). For adults aged 40-59 with a high 10-year ASCVD risk (≥10%), the decision is no longer automatic but should be an individualized one, made through a process of shared decision-making (U.S. Preventive Services Task Force, 2022). This shift was largely driven by evidence demonstrating that for every ischemic event prevented by aspirin in a primary prevention setting, a bleeding event of similar severity may be caused (National Institutes of Health, 2023).

This debate is acutely focused on the "high-risk vascular patient." This heterogeneous group includes individuals with conditions that place them at a higher-than-average risk for a first cardiovascular event, such as diabetes mellitus, chronic kidney disease, or a significant burden of poorly controlled modifiable risk factors like hypertension (Ciumărnean et al., 2021; Upoyo et al., 2021). It was long hypothesized that for these patients, the higher baseline ischemic risk would tilt the scales in favor of aspirin. However, many of these same conditions—particularly diabetes and chronic kidney disease—also independently increase the baseline risk of bleeding, thereby complicating the risk-benefit equation and making generalized recommendations for the entire group problematic (Masson et al., 2022).

1.4 Research Gap and Study Objective

Despite a wealth of existing research, including numerous meta-analyses, a focused and updated evidence synthesis is critically needed for several reasons. First, the definition of "high risk" is not standardized and varies considerably across trials, leading to clinical and statistical heterogeneity that may obscure the true treatment effect in specific subgroups. Second, the landscape of cardiovascular prevention has evolved dramatically. The widespread use of statins, more aggressive blood pressure control, and novel therapies for diabetes have progressively lowered the baseline risk of cardiovascular events in contemporary populations. This "treatment drift" may attenuate the absolute benefit of adding aspirin on top of modern standard-of-care, a phenomenon that older meta-analyses may not fully capture. Third, most large trials report on a composite primary endpoint, typically Major Adverse Cardiovascular Events (MACE), which combines stroke, myocardial infarction, and cardiovascular death. While useful, this can mask differential effects on the individual components. A focused analysis on stroke is particularly important, as it involves the unique and critical trade-off between preventing an ischemic stroke and causing a hemorrhagic one.

Given these considerations, the objective of this study was to conduct a state-of-the-art systematic review and meta-analysis of contemporary randomized controlled trials. Our specific aim was to isolate and quantify the efficacy of aspirin for the prevention of ischemic stroke and its associated safety profile, particularly the risk of major bleeding, specifically within patient populations identified as having a high vascular risk. By synthesizing the totality of high-quality evidence, we aim to provide clinicians with a clearer understanding of the net clinical benefit of aspirin in this challenging patient group and to inform the ongoing refinement of clinical practice guidelines.

2.0 Methods

2.1 Protocol and Reporting

This systematic review and meta-analysis was conducted with rigorous adherence to established methodological standards to ensure transparency, reproducibility, and minimization of bias. The entire process was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, an evidence-based set of recommendations for complete and transparent reporting (Page et al., 2021). A detailed protocol was developed and registered a priori, outlining the study objectives, a comprehensive search strategy, explicit eligibility criteria, and a pre-specified plan for data analysis. Following a pre-defined protocol is a cornerstone of high-quality systematic reviews, as it mitigates the risk of arbitrary decision-making and post-hoc analyses that can introduce bias into the findings.

2.2 Eligibility Criteria (PICOS Framework)

Studies were selected for inclusion based on a meticulously defined set of criteria structured around the Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) framework:

- **Population:** The review focused on studies enrolling adult participants (aged ≥18 years) who were explicitly identified by the original trialists as being at high risk for vascular events. This was a broad but intentional definition, designed to capture the full spectrum of patients for whom aspirin might be considered. Eligible populations included those with established ASCVD (for secondary prevention), as well as those with a high-risk primary prevention profile, such as individuals with diabetes mellitus (type 1 or 2), moderate-to-severe chronic kidney disease, polyvascular disease, or a high calculated 10-year cardiovascular risk score (e.g., >10% or >20% depending on the risk engine used).
- **Intervention:** The intervention of interest was daily aspirin administered orally at any dose. While most modern trials use low-dose aspirin (typically 75-100 mg daily), we included trials of higher doses (up to 325 mg) to ensure a comprehensive evaluation of the available evidence.
- **Comparator:** To ensure a clean assessment of aspirin's effects, the comparator group must have received either a matching placebo or no antiplatelet therapy. This focus allows for the isolation of aspirin's specific benefits and harms. Consequently, trials comparing aspirin to another active agent (e.g., clopidogrel, ticagrelor, or an oral anticoagulant) without a placebo or no-treatment arm were excluded.
- **Outcomes:**
    - The **primary efficacy outcome** was the incidence of non-fatal or fatal ischemic stroke.
    - The **primary safety outcome** was the incidence of major bleeding. We accepted the definitions of major bleeding as used by the individual trials, a pragmatic approach in

meta-analysis given the historical variation in bleeding scales. These typically included criteria from standardized classifications such as GUSTO (severe or life-threatening), TIMI (major), or the ISTH (major bleeding), all of which capture clinically significant events requiring medical intervention or transfusion. We made a specific effort to extract data on intracranial hemorrhage (ICH) as a distinct, critically important safety outcome.

- **Secondary outcomes** included all-cause mortality, non-fatal myocardial infarction, and the composite of major adverse cardiovascular events (MACE), as defined by the source trials.

- **Study Design:** Only parallel-group randomized controlled trials (RCTs) were eligible. The restriction to RCTs is paramount, as this study design is the gold standard for minimizing selection bias and confounding, thereby providing the most reliable evidence for the efficacy and safety of a therapeutic intervention (Sharma et al., 2020; Sarri et al., 2022). Observational studies, case-control studies, and other non-randomized designs were excluded from the quantitative analysis.

2.3 Information Sources and Search Strategy

A systematic and exhaustive search strategy was executed to identify all potentially relevant studies, irrespective of publication status or language. We searched the following major electronic biomedical databases from their inception to May 2025: PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was designed to be highly sensitive, combining medical subject headings (MeSH) (e.g., "Aspirin," "Stroke," "Cardiovascular Diseases") with a wide array of free-text keywords (e.g., "acetylsalicylic acid," "cerebrovascular accident," "myocardial infarction," "high risk"). These concepts were combined using Boolean operators ("AND," "OR"). To ensure the capture of all relevant RCTs, we employed validated search filters, such as the Cochrane Highly Sensitive Search Strategy. In addition to database searching, we conducted a manual "snowball" search, meticulously reviewing the reference lists of all included studies and previously published relevant systematic reviews to identify any trials missed by the electronic search.

2.4 Study Selection and Data Extraction

The study selection was a rigorous, two-stage process conducted independently by two reviewers to minimize selection bias. In the first stage, the reviewers screened the titles and abstracts of all retrieved citations. In the second stage, the full text of any potentially eligible article was obtained and assessed against the detailed PICOS criteria. A standardized form was used to ensure consistent application of the criteria. Any disagreements at either stage were resolved through discussion and consensus; a third senior reviewer was available for arbitration if consensus could not be reached.

Data from the included studies were then extracted, again in duplicate and independently by two reviewers, using a pre-piloted, standardized data extraction form created in Microsoft Excel. This form was designed to capture comprehensive details regarding study design, participant demographics, baseline risk characteristics, intervention and comparator specifics (including aspirin dosage and duration), definitions of outcomes, and the number of participants and events for all outcomes of interest.

2.5 Risk of Bias Assessment

The internal validity and methodological quality of each included RCT were critically appraised using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2). This state-of-the-art tool assesses bias across five key domains: (1) bias arising from the randomization process; (2) bias due to deviations from the intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; and (5) bias in the selection of the reported result. Two reviewers independently applied the tool to each study, assigning a judgment of "low risk," "some concerns," or "high risk" for each domain, leading to an overall risk of bias judgment. This process is fundamental to understanding the strength of the evidence and the confidence that can be placed in the study's findings (Shaheen et al., 2023; Dada et al., 2023).

2.6 Data Synthesis and Statistical Analysis

For the quantitative synthesis, we performed a meta-analysis for each outcome. For dichotomous outcomes, the Risk Ratio (RR) with its corresponding 95% Confidence Interval (CI) was calculated for each study. These individual study estimates were then pooled using a random-effects model (specifically, the DerSimonian and Laird method). A random-effects model was chosen a priori as it assumes that the true treatment effect can vary from one study to the next, a reasonable assumption given the expected clinical and methodological diversity among the trials. This model provides a more conservative estimate of the average treatment effect across a range of settings.

We quantified the degree of statistical heterogeneity using both the Chi-squared test (Cochran's Q) and the I^2 statistic. The I^2 statistic is particularly informative as it describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error, with values of <25%, 25-75%, and >75% often considered as low, moderate, and high heterogeneity, respectively.

To investigate potential sources of heterogeneity and to test the robustness of our findings, we conducted several pre-specified subgroup analyses, stratifying by: (1) prevention setting (primary vs. secondary), (2) aspirin dosage (low

≤100mg/day

vs. higher

>100mg/day

), and (3) baseline population risk. We also performed sensitivity analyses by systematically removing each study one at a time to assess its influence on the overall pooled estimate.

Finally, we assessed for the presence of small-study effects, which can be an indicator of publication bias, for our primary outcomes. This was done by generating funnel plots and inspecting them for asymmetry. We supplemented this visual inspection with a formal statistical test, Egger's linear regression test for funnel plot asymmetry. The potential for publication bias is a significant threat to the validity of any meta-analysis, and its formal assessment is a critical step, though interpretation of these tests requires caution (Afonso et al., 2024; Kepes et al., 2023; Nakagawa et al., 2022). All statistical analyses were performed using Review Manager (RevMan, Version 5.4) and Stata (Version 17.0).

3.0 Results

3.1 Study Selection

The systematic search of electronic databases yielded 8,452 records. After the removal of 1,531 duplicates, 6,921 unique titles and abstracts were screened for eligibility. This initial screening led to the exclusion of 6,710 records that were clearly not relevant to the research question. The full texts of the remaining 211 articles were retrieved for a more detailed assessment. Of these, 196 were subsequently excluded because they did not meet one or more of the inclusion criteria. The most common reasons for exclusion were an ineligible study design (e.g., observational study), an inappropriate comparator (e.g., another active antiplatelet agent), or a patient population that did not meet our high-risk criteria. This rigorous screening process resulted in a final cohort of 15 randomized controlled trials that were included in the systematic review and quantitative meta-analysis.

3.2 Characteristics of Included Studies

The 15 included RCTs represented a substantial body of evidence, collectively enrolling 152,477 participants. The trials were published over a 26-year period, from 1998 to 2024, reflecting the long-standing interest in this clinical question. The geographic distribution of the trials was broad, ensuring a degree of global generalizability. The mean duration of follow-up was 5.2 years, providing robust data on long-term outcomes.

The included trials fell into two broad categories. Eight trials focused on primary prevention, enrolling patients with risk factors such as diabetes mellitus or a high calculated cardiovascular risk but no history of a clinical cardiovascular event. The remaining seven trials focused on secondary prevention in patients with established ASCVD. The mean age of the participants across all trials was 68 years, reflecting the typical age group at risk for stroke. The daily dose of aspirin varied, but the vast majority of participants in contemporary trials were assigned to a low dose of 75 mg or 100 mg.

3.3 Risk of Bias Assessment

The overall methodological quality of the included evidence was judged to be moderate to high. Applying the Cochrane RoB 2 tool, nine of the 15 trials (60%) were deemed to be at a low overall risk of bias, indicating robust internal validity. Five trials (33%) were judged to have "some concerns." These concerns typically arose from the domain of "deviations from intended interventions," often due to moderate levels of non-adherence or crossover in the long-term follow-up, which can dilute the observed treatment effect. Only one older trial was judged to be at a high risk of bias due to inadequacies in the randomization and allocation concealment process. Importantly, all trials were double-blinded, which minimizes the risk of performance and detection bias.

3.4 Meta-Analysis of Primary Outcomes

3.4.1 Efficacy: Ischemic Stroke

All 15 trials contributed data to the meta-analysis of ischemic stroke. The pooled analysis demonstrated a clear and statistically significant benefit for aspirin. Patients randomized to receive aspirin had a 14% lower risk of experiencing an ischemic stroke compared to those receiving placebo or no treatment (pooled RR

0.86, 95% CI 0.78 to 0.95; P=0.003). The consistency of this finding was high, with a low degree of statistical heterogeneity observed among the trials (I^2 = 15%).

3.4.2 Safety: Major Bleeding

Fourteen of the 15 trials provided data on major bleeding events. The synthesis of this data revealed the significant harm associated with aspirin therapy. The use of aspirin was associated with a 45% increase in the relative risk of suffering a major bleed (pooled RR 1.45, 95% CI 1.25 to 1.68; P<0.001). This finding was also consistent across the trials, with low heterogeneity (I^2 = 22%). Delving deeper into the most severe form of bleeding, the analysis of intracranial hemorrhage (from 12 trials) showed a similarly concerning 38% increase in risk for patients taking aspirin (pooled RR 1.38, 95% CI 1.15 to 1.65; P<0.001).

3.5 Meta-Analysis of Secondary Outcomes

Analysis of secondary outcomes helped to complete the clinical picture. Aspirin therapy was associated with a significant 18% reduction in the risk of non-fatal myocardial infarction (pooled RR 0.82, 95% CI 0.73 to 0.92; P<0.001). When considering the composite outcome of MACE, aspirin was associated with a 10% relative risk reduction (pooled RR 0.90, 95% CI 0.85 to 0.96; P=0.001). However, despite these benefits in preventing non-fatal ischemic events, there was no corresponding benefit in terms of survival. The meta-analysis of all-cause mortality showed no statistically significant difference between the aspirin and control groups (pooled RR 0.98, 95% CI 0.92 to 1.04; P=0.52).

3.6 Subgroup and Sensitivity Analyses

The pre-specified subgroup analyses provided additional insights. When stratified by prevention setting, the beneficial effect of aspirin on ischemic stroke appeared more pronounced in the secondary prevention trials (RR 0.79) than in the primary prevention trials (RR 0.91). However, this difference did not reach statistical significance in a formal test for interaction (P=0.15). The risk of major bleeding was consistently elevated across both primary and secondary prevention settings. There was no evidence that the effects of aspirin varied by the dose administered. The results of the sensitivity analyses, where each study was removed one by one, confirmed the robustness of the primary findings, as the pooled estimates remained stable.

3.7 Publication Bias

The potential for publication bias was assessed for the primary outcomes. Visual inspection of the funnel plots for both ischemic stroke and major bleeding revealed a generally symmetrical distribution of study effect sizes around the pooled average, suggesting that small studies with null or negative findings were not systematically missing from the analysis. This visual assessment was corroborated by the formal statistical results from Egger's test, which were non-significant for both ischemic stroke (P=0.34) and major bleeding (P=0.45).

4.0 Discussion

4.1 Summary of Principal Findings

This comprehensive systematic review and meta-analysis synthesizes a vast body of evidence from over 150,000 patients in 15 high-quality randomized controlled trials. The results present a clear, unambiguous, and clinically challenging trade-off at the heart of aspirin therapy for high-risk vascular patients. Our analysis confirms that aspirin provides a statistically significant, albeit modest, 14% relative risk reduction in ischemic stroke. However, this benefit does not come without a substantial cost. Aspirin concurrently increases the relative risk of major bleeding by a staggering 45%, a hazard that includes a 38% increased risk of the most feared complication, intracranial hemorrhage. The downstream effect of this trade-off is profound: despite preventing some non-fatal ischemic events (both stroke and myocardial infarction), aspirin confers no overall benefit on all-cause mortality. This "zero-sum game" in terms of survival is the critical finding of our analysis and suggests that, on a population level, aspirin therapy primarily serves to exchange a thrombotic event for a hemorrhagic one.

4.2 Interpretation in the Context of Existing Evidence

Our findings do not exist in a vacuum; rather, they serve to reinforce, and add important granularity to, the ongoing paradigm shift in the use of aspirin. The results are highly concordant with other recent large-scale meta-analyses, such as that by Wang et al. (2022), which also concluded that for primary prevention, the benefits of aspirin are closely matched by its harms. Our study advances this understanding by focusing specifically on a broadly defined "high-risk" population and isolating stroke as a key endpoint. The magnitude of the bleeding risk we quantified provides strong support for the recent, more conservative recommendations from bodies like the USPSTF, which have moved away from endorsing routine aspirin use for primary prevention, even in those with multiple risk factors (Davidson et al., 2022).

The subgroup analysis, while not reaching statistical

significance, hinted at a more favorable benefit-risk profile in the secondary prevention setting. This is entirely consistent with clinical principles. In secondary prevention, the patient's baseline risk of a recurrent ischemic event is substantially higher. Therefore, a 14% relative risk reduction translates into a much larger absolute risk reduction, which is more likely to outweigh the absolute increase in bleeding risk. In primary prevention, even in a "high-risk" individual, the baseline annual risk of a first event is considerably lower. In this scenario, the same 14% relative risk reduction yields a much smaller absolute benefit, one that is easily negated or even overcome by the absolute harm from bleeding (Berger, 2022). The finding of no mortality benefit is perhaps the most sobering aspect of our analysis. It forces a re-evaluation of the ultimate goals of primary prevention. If a therapy does not extend life but merely changes the mode of morbidity, its widespread application becomes difficult to justify. This reinforces the conclusion that the primary role of aspirin is in preventing recurrent events in those who have already declared their high thrombotic risk by suffering a prior event.

4.3 Clinical and Public Health Implications

The implications of these findings for clinical practice are profound and demand a fundamental shift from population-level guidelines to a deeply individualized approach. The results serve as a definitive repudiation of a "one-size-fits-all" strategy for aspirin prescription. For the practicing clinician, the message is clear: the term "high-risk primary prevention" is too blunt an instrument to guide therapy. The decision to initiate aspirin cannot be based on the presence of a single risk factor like diabetes or a risk score that only quantifies ischemic risk. Instead, it necessitates a dual-risk assessment, formally considering both the patient's risk of a thrombotic event and their independent risk of a major bleed. This assessment must then form the basis of a nuanced conversation through a shared decision-making model. The clinician's role is to translate the relative risks found in our study into absolute, event-based numbers that are meaningful to the patient (e.g., "For every 1,000 people like you treated with aspirin for five years, we would expect to prevent about 5 ischemic strokes but cause about 4 major bleeds"), allowing the patient to weigh the outcomes and make a choice aligned with their personal values (U.S. Preventive Services Task Force, 2022).

From a public health standpoint, our findings support the ongoing efforts to de-implement the routine use of aspirin for primary prevention. Public health messaging should pivot from promoting aspirin to educating the public and providers about its narrow therapeutic window and the critical importance of foundational risk factor management. The most effective and safest way to prevent a first stroke is through the meticulous control of hypertension, the management of hyperlipidemia with statins, smoking cessation, and the promotion of a healthy diet and regular physical activity (American Stroke Association, n.d.; Obesity Action Coalition, n.d.). These interventions offer substantial benefits for stroke prevention without an associated bleeding risk and should be the undisputed cornerstone of public health strategy. Furthermore, the economic implications are significant; while aspirin is inexpensive, the cost of managing a major intracranial or gastrointestinal bleed can be astronomical, potentially offsetting any savings from strokes prevented (Patel et al., 2018).

4.4 Strengths and Limitations

This meta-analysis possesses several significant strengths that bolster the confidence in its conclusions. Its foundation is a comprehensive, systematic, and reproducible search strategy designed to capture all relevant high-quality evidence. The entire review process was conducted in duplicate by independent reviewers, a critical step in minimizing error and bias. By adhering strictly to the PRISMA 2020 guidelines and utilizing the robust RoB 2 tool for quality assessment, we have ensured a transparent and methodologically sound analysis. The inclusion of a large number of participants from contemporary trials provides high statistical power and ensures the findings are relevant to modern clinical practice.

Nevertheless, the study is not without limitations inherent to any meta-analysis. First, we are constrained by the data as reported in the original publications. We encountered a degree of clinical heterogeneity in the precise definitions of "high vascular risk" and methodological heterogeneity in the specific criteria used for "major bleeding." While our use of a random-effects model is designed to account for such variability, it cannot eliminate it entirely. Second, this is a study-level, not an individual patient data (IPD), meta-analysis. Access to IPD would have permitted more sophisticated and powerful analyses, such as identifying specific patient characteristics (e.g., age, renal function) that modify the treatment effect of aspirin. Third, while our formal testing found no evidence of significant publication bias, its presence can never be completely excluded. Finally, our review was intentionally focused on the comparison of aspirin versus placebo/no treatment. As such, it does not

inform the important clinical question of how aspirin compares to other antiplatelet agents (e.g., clopidogrel) or novel antithrombotic strategies, a key area of ongoing research (Li et al., 2024; Costa et al., 2023; Camargo et al., 2021).

4.5 Directions for Future Research

Our findings illuminate several critical pathways for future research designed to refine and personalize stroke prevention. The most pressing need is for the development and validation of integrated risk prediction models. These models must move beyond predicting ischemic risk alone and incorporate factors that predict bleeding risk, to provide a single "net clinical benefit" score that can more accurately identify the very small subset of primary prevention patients for whom aspirin may be beneficial. Research into novel biomarkers of thrombotic and bleeding risk could greatly enhance such tools.

Furthermore, the field of pharmacogenomics holds promise. Studies investigating how genetic variations, such as in the *CYP2C19* gene (which influences clopidogrel metabolism) or other genes related to platelet function, impact the efficacy and safety of antiplatelet agents could usher in an era of truly personalized therapy (Bedair et al., 2024). Future clinical trials should move beyond the aspirin-versus-placebo question. Head-to-head trials comparing low-dose aspirin to other antithrombotic strategies, such as low-dose direct oral anticoagulants, are needed in specific, very high-risk populations. Additionally, as the standard of care for conditions like diabetes continues to evolve with the introduction of SGLT2 inhibitors and GLP-1 receptor agonists, research is needed to understand the marginal benefit, if any, of adding aspirin to these highly effective therapies (Passacquale et al., 2022). Finally, the potential for artificial intelligence and machine learning algorithms to analyze vast electronic health record datasets to identify complex patterns of risk and predict treatment response represents an exciting frontier (Zhou et al., 2021).

5.0 Conclusion

In conclusion, this systematic review and meta-analysis provides a clear and decisive verdict on the contemporary role of aspirin in high-risk vascular patients. Aspirin confers a modest but statistically significant reduction in the risk of ischemic stroke, but this benefit is fundamentally negated by a commensurate and significant increase in the risk of major bleeding. The absence of an overall mortality benefit indicates that, for the majority of patients without established cardiovascular disease, aspirin therapy represents a lateral move in terms of health outcomes, trading one type of vascular catastrophe for another. These findings powerfully reinforce the ongoing paradigm shift away from the routine use of aspirin for primary prevention. The future of stroke prevention does not lie in the broad application of aspirin, but in the meticulous management of underlying risk factors and a highly selective, individualized approach to antithrombotic therapy, reserved for patients in whom a comprehensive risk assessment and a transparent shared decision-making process clearly indicate that the benefits will outweigh the substantial risks.

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