scientific reports

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Aspirin for the extended prevention of venous thromboembolism: a meta-analysis and trial sequential analysis

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Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major complication following surgery and in high-risk scenarios. Aspirin may provide an alternative for extended VTE prophylaxis, but its risk-benefit profile remains unclear. We conducted a systematic review and meta-analysis of randomized controlled trials, following PRISMA guidelines, to evaluate aspirin's efficacy and safety for extended VTE prevention. Subgroup analyses included primary and secondary prevention, provoked and unprovoked VTE, and low-dose aspirin. Pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated using a random-effects model, and trial sequential analysis was used to assess the robustness of the evidence. Five trials including 68,554 patients were analyzed. Aspirin (100–160 mg) significantly reduced the risk of VTE, DVT, PE, and VTE-related mortality compared to placebo, particularly in primary prevention and provoked VTE cases. No benefit was observed in secondary prevention, while some benefit emerged for unprovoked VTE, limited to overall VTE risk. Low-dose aspirin (100 mg) did not significantly reduce the incidence of VTE, DVT, or PE. Aspirin increased the risks of overall and major bleeding but did not elevate blood transfusion requirements or major cardiovascular events. These findings suggest that prolonged aspirin therapy may have a role in extended VTE prevention, particularly in patients at risk for provoked VTE. However, careful patient selection remains crucial, and further studies are needed to refine its indications and optimal dosing strategy.

Keywords Aspirin, Venous thromboembolism, Venous thrombosis, Deep vein thrombosis, Pulmonary embolism

Venous thromboembolism (VTE), encompassing pulmonary embolism (PE) and deep vein thrombosis (DVT), is a significant complication after major surgery, but also in other high-risk conditions such as prolonged immobilization, active malignancy, trauma, obesity, and critical illness requiring intensive care[1,2]. Thromboprophylaxis typically includes subcutaneous heparin injections or mechanical compression methods, with post-discharge duration recommendations varying by surgery type[2] For patients with a history of VTE, recurrence may occur after discontinuing anticoagulant therapy, even following the recommended long-term treatment of at least three months[1,2]. In such cases, thromboembolic risk often persists beyond the standard period of antithrombotic therapy[1,2]. Low-dose aspirin could provide a simpler oral option for extended VTE prevention, exceeding the guideline-recommended thromboprophylaxis duration[1,2].

However, conflicting data exist in the literature regarding the true risk-benefit profile of aspirin in VTE prevention. A study suggests that low-dose aspirin for secondary prevention can reduce the risk of PE and DVT by approximately one-third during high-risk periods for VTE[3]. Conversely, another study found that long-term, low-dose aspirin did not prevent VTE in initially healthy women[4]. While one study indicated that aspirin administered for secondary prevention reduces VTE recurrence without increasing the risk of major bleeding[5], another study did not observe a significant reduction in VTE recurrence with aspirin for secondary prevention, though it noted a decrease in major vascular events (e.g., myocardial infarction, stroke, cardiovascular death)[6].

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In contrast, another study reported that perioperative aspirin for primary prevention in noncardiac surgery increased the risk of major bleeding without reducing rates of death or nonfatal myocardial infarction, underscoring the complex risk-benefit profile of aspirin[7].

This study aims to quantify the overall effect of aspirin in the extended prevention of VTE, addressing the controversy regarding its risk-benefit profile across various patient conditions, including primary and secondary prevention, as well as provoked and unprovoked VTE. This evidence is crucial for guiding decision-making by weighing the benefits of reducing VTE, mortality—particularly VTE-related mortality—and cardiovascular events against the increased bleeding risks. The study is particularly relevant for extended VTE prophylaxis in high-risk patients and examines whether aspirin use for primary and secondary prevention, provoked and unprovoked VTE can impact outcomes.

Methods

The protocol for this meta-analysis was registered in the PROSPERO database on 26 July 2024, bearing the identification number CRD42024557218. A meta-analysis of available randomised controlled trials (RCTs) was conducted with strict adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist[8].

The inclusion criteria for this systematic review and meta-analysis were based on the PICOS (Population, Intervention, Comparison, Outcomes, Study Design) framework. Briefly, the review focused on adult patients receiving aspirin for VTE prevention, including overall VTE as the primary outcome, with further sub-analyses assessing primary prevention (e.g., surgical patients at risk of VTE) and secondary prevention (e.g., patients with a history of VTE after discontinuation of anticoagulation), compared to those receiving placebo or no treatment.[1–7] Outcomes assessed included the incidence of provoked[3,7] and unprovoked VTE[4–6,9], major and non-major bleeding[5–7,10], blood transfusion, cardiovascular adverse events (AEs)[6,7,9,10], and mortality, which was analyzed as all-cause mortality, cardiovascular mortality, and VTE-related mortality. Only prospective RCTs in English were eligible. Full details on the PICOS criteria and definitions are provided in the Supplementary Material (SM) 1.

Search strategy

A comprehensive literature search was conducted in PubMed, Scopus, and EMBASE, covering publications up to August 19, 2024, and updated on November 10, 2024. Relevant Medical Subject Headings (MeSH) terms and keywords were combined strategically, using Boolean operators to refine results. Full search details, including term combinations and filters, are provided in SM1. To ensure comprehensive coverage, the reference lists of reviewed studies were also examined to identify any potentially overlooked studies.

Study selection, data extraction and data retrieval

Titles and abstracts of articles identified through the initial search strategy were independently evaluated by two authors (MC, ET) to filter out unrelated studies. The full texts of the remaining studies were then reviewed for compatibility with the established inclusion criteria. Data extraction was also carried out independently by the same two authors using specially designed forms for each study. Any disagreements during the study selection, data extraction, or trial evaluation were resolved by a third author (EC) who was not involved in the initial literature search. Additionally, two other authors (TP, FZ), who had not participated in the initial search or data extraction, conducted a manual review and assessment of each selected study to verify the extracted data and ensure the integrity of the final dataset.

Quality assessment and certainty of evidence assessment

The quality assessment of the included RCTs was independently conducted by two authors (MC, ET) using the Risk of Bias 2 (RoB 2) tool[11]. This tool evaluates potential bias across five critical domains: the randomisation process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Each domain is assessed using "signaling questions" designed to identify potential sources of bias. Responses to these questions are used in an algorithm to assign a risk of bias rating for each domain, categorized as "low," "high," or "some concerns." An overall risk of bias assessment is then provided for each study. Disagreements in initial evaluations were resolved through consultation with a third author (EC).

The certainty of evidence was evaluated using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) framework for meta-analyses[12]. Quality of Evidence (QoE) is classified into four levels: high (⊕⊕⊕⊕), moderate (⊕⊕⊕⊖), low (⊕⊕⊖⊖), or very low (⊕⊖⊖⊖). Initially rated as high due to their RCT design, evidence quality may be downgraded based on factors such as risk of bias (e.g., inadequate blinding or allocation concealment), inconsistency (assessed by variance in effect estimates using statistical measures like tau [τ], tau-squared [τ^2], and I-squared [I^2]), indirectness (e.g., differences in study populations, interventions, or outcomes from those of primary interest), imprecision (indicated by wide 95% confidence intervals or estimates near the null effect), and publication bias (e.g., assessed through funnel plots, leave-one-out diagnostics, and Egger's test for asymmetry).

Statistical analysis

The meta-analysis was conducted using a frequentist framework, applying both random effects and fixed effects models to calculate the relative risk (RR) and corresponding 95% confidence intervals (CI) for binary outcome data. The random effects model was preferred in this meta-analysis to account for potential variability across studies. The Mantel–Haenszel method was used to compute the fixed effects estimate for dichotomous data. For the random effects model, inverse-variance weighting was applied using the DerSimonian and Laird method to

handle heterogeneity. In cases where studies reported zero events, a continuity correction of 0.5 was added to frequencies when computing the RR.

Heterogeneity was assessed using the I^2 statistic, with significance interpreted at $p < 0.1$ for the Q test. I^2 values were categorized as low (< 25%), moderate (25-50%), or high (> 50%)[13]. To further quantify heterogeneity, τ was computed to assess the standard deviation of effect sizes across studies, indicating variability beyond chance. Additionally, τ^2 estimated the variance of true effect sizes between studies, though precise estimation was challenging due to the limited number of studies. The Q test confirmed significant heterogeneity, providing further insight into the variability of the meta-analysis results. Publication bias was assessed through visual inspection of funnel plots[14]. Outliers identified from leave-one-out diagnostics, such as Cook's distances, were evaluated to determine influential studies. Egger's test for asymmetry was performed only for analyses with 10 or more studies; a p-value < 0.1 indicated potential publication bias, while a p-value ≥ 0.1 suggested negligible risk.

Trial Sequential Analysis (TSA) was conducted to evaluate the stability and reliability of cumulative meta-analysis results on the effect of aspirin versus placebo or no treatment in preventing VTE. This analysis focused on general, primary and secondary prevention, provoked and unprovoked VTE outcomes, including low-dose aspirin. TSA helps control for random errors by applying monitoring boundaries and assessing type I and II errors[15]. The proportion of events in the control group, the proportion of events in the aspirin group, the highest observed relative risk reduction (RRR), and the minimum information size (MIS) from the literature[3–7] were used to obtain the Trial Sequential Monitoring Boundary (TSMB) and Diversity Adjusted Required Information Size (DARIS). Further details are provided in SM1.

Sensitivity analyses were conducted to evaluate the robustness of results across different outcome types (primary and secondary VTE, provoked and unprovoked VTE) and aspirin dosages (low-dose).

The Number Needed to Treat for Benefit (NNTB) and the Number Needed to Treat for Harm (NNTH) were calculated to assess the net clinical benefit of aspirin in VTE prevention. NNTB was derived from the absolute risk reduction (ARR) for thrombotic outcomes, and NNTH from the absolute risk increase (ARI) for bleeding events. The NNTB/NNTH ratio was also computed to evaluate the balance between efficacy and safety.

All statistical analyses were conducted using R software version 4.1.0 (2021-05-18). Meta-analytical computations were performed using the "*meta*" package, including the calculation of the NNTB and NNTH using the specific *"nnt()"* function. Trial Sequential Analysis (TSA) computations utilized the *"ldbounds"* and *"rpact"* libraries. P-values were two-tailed, with statistical significance set at < 0.05 in accordance with standard convention.

Results

Paper selection

Of the 5527 reports initially identified, 5522 were excluded, leaving 5 RCTs with a total of 68,554 patients for inclusion.[3–7] The PRISMA flow diagram is in Fig. 1.

Study characteristics

Details of the included RCTs are in Table 1[3–7]. Among participants, 34,274 were assigned to treatment (aspirin), and 34,280 to control (placebo)[3–7]. Approximately 96.6% of patients were in primary prevention for overall VTE[3,4,7], while only 40% were in primary prevention for DVT and PE[3,7]. Conversely, approximately 3.4% of patients were in secondary prevention for overall VTE[4–6], while only 1.8% were in secondary prevention for DVT and PE[3,7]. Overall, 59.9% of patients received low-dose aspirin (100 mg) for VTE prevention[4–7]. Regarding VTE type, 25.4% of patients were treated for provoked VTE[3,7], and 40% for unprovoked VTE[5,6]. Allocation between aspirin and placebo groups was nearly equal across all subgroups.

Risk of bias assessment

The RoB 2 assessment conducted on the included RCTs[3–7] indicated a low risk of bias across all domains (Fig. 2), with well-defined randomisation, allocation concealment, and blinding. No deviations or selective reporting were observed. Overall, the risk of bias across all studies was low, confirming their strong methodological quality. Further details on the RoB 2 assessment can be found in SM2.

Endpoints

The primary endpoint of this meta-analysis was the incidence of newly diagnosed symptomatic VTE, including both DVT and PE. Secondary endpoints included all-cause mortality, cardiovascular mortality, VTE-related mortality, major bleeding, and other safety outcomes such as stroke, hemorrhagic stroke, and major cardiovascular adverse events. These endpoints were pre-specified according to the study protocol and align with international guideline recommendations.

Primary endpoint

Aspirin (100–160 mg) significantly reduced VTE (RR [95%CI] = 0.80 [0.72; 0.90], $P < 0.001$; moderate QoE), DVT (RR [95%CI] = 0.82 [0.71; 0.95], $P = 0.010$; moderate QoE), and PE (RR [95%CI] = 0.79 [0.66; 0.95], $P = 0.014$; moderate QoE) compared to placebo (Table 2; Fig. 3)[3–7]. In the sub-analysis, aspirin significantly reduced the incidence of primary VTE, DVT, and PE compared to placebo (Table 3)[3,4,7], but showed no significant benefit in preventing secondary VTE, DVT, or PE (Table 4)[4–6].

Aspirin was effective in reducing provoked VTE, including both its components, DVT and PE, compared to placebo[3,7], and also showed a significant benefit for unprovoked VTE overall, although not for its components (DVT and PE) (Tables S1-S2 in SM3)[5,6]. Low-dose aspirin (100 mg) did not significantly reduce VTE, DVT, or PE compared to placebo (Table S3 in SM3)[4–7].

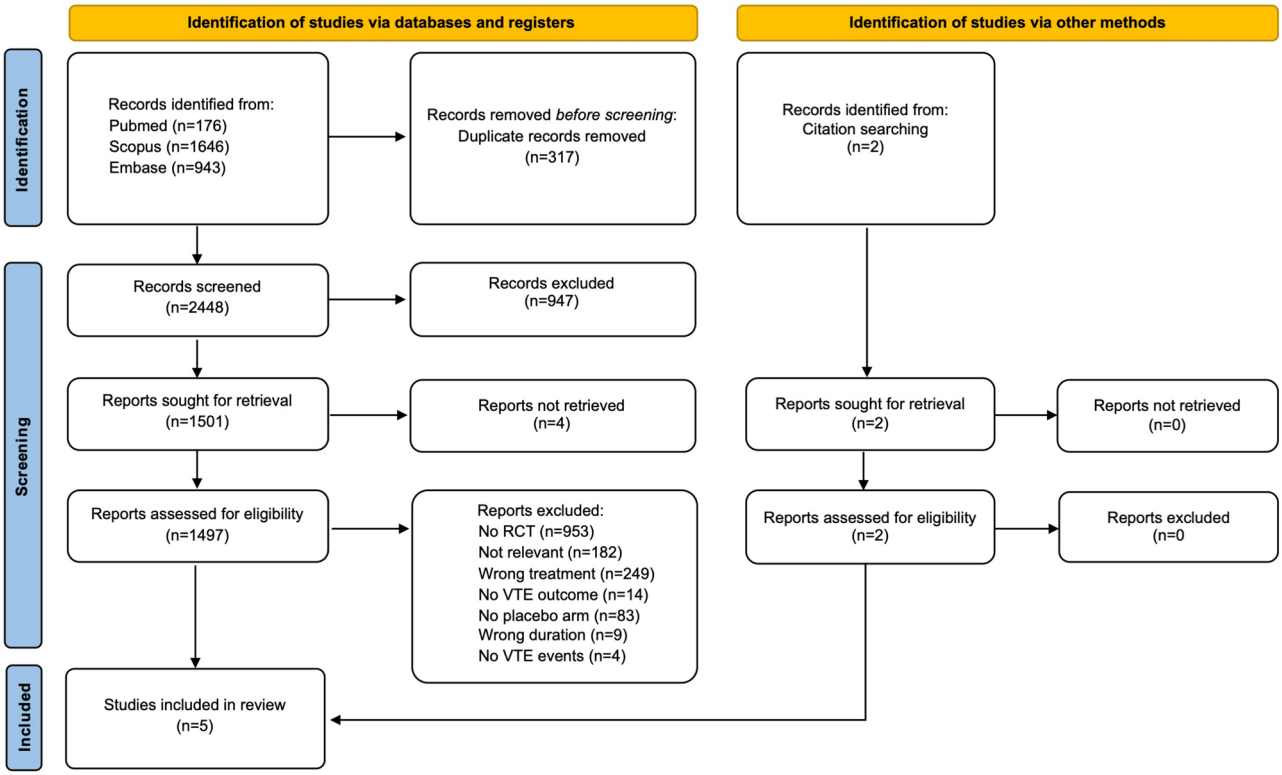

Fig. 1. The PRISMA flow diagram of the study selection process.

Study (year)	Country	Setting	VTE Type	Patients (aspirin/control)	Aspirin regimen	Study duration	Follow up	Primary endpoint	Secondary endpoint
PEP Trial (2000)	Multicenter	Orthopedic surgery	Primary provoked	Hip fracture (6617/6620)	160 mg/die vs. placebo	35 days	35 days for fatal events until hospital discharge for non-fatal events	Symptomatic DVT	PE, MI, stroke, death, complications comprising bleeding events
PEP Trial (2000)	Multicenter	Orthopedic surgery	Primary provoked	Elective arthroplasty (2047/2041)	160 mg/die vs. placebo	35 days	35 days for fatal events until hospital discharge for non-fatal events	Symptomatic DVT	PE, MI, stroke, death, complications comprising bleeding events
Women's Health Study (2007)	United States	Outpatients Primary and secondary prevention	Unspecified unprovoked (mainly first events)	Women > 45 years old (19934/19942)	100 mg alternate days vs. placebo	10 years	Every 6 month in the first year, annually thereafter	DVT or PE	Death aspirin's adverse effects
WARFASA (2012)	Multicenter	Outpatients, secondary prevention after 6–18 months of anticoagulation	Secondary unprovoked	Previous VTE (205/197)	100 mg/die vs. placebo	2 years	Every 3 month in the first year, every 6 months thereafter	VTE recurrence (DVT or PE)	Death, MI, unstable angina, stroke, TIA, acute limb ischemia, bleeding
ASPIRE (2012)	Multicenter	Outpatients, secondary prevention after initial anticoagulation	Secondary unprovoked	Previous VTE (411/411)	100 mg/die vs. placebo	2–4 years	1 month and 6 months after randomization and every 6 months thereafter	VTE recurrence (DVT or PE)	Death, MI, unstable angina, stroke, major vascular events, bleeding
POISE-2 (2014)	Multicenter	Non-cardiac surgery	Primary provoked	Non-cardiac surgery (4998/5012)	200 mg pre-surgery, then 100 mg/die for 30 days vs. placebo	30 days	30 days after randomization	Death or non-fatal MI	Death, PE, DVT, bleeding, stroke, cardiac revascularization, infection

Table 1. Characteristics of studies considered for review and meta-analysis. *VTE* venous thrombo-embolism, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *MI* myocardial infarction, *TIA* transient ischemic attack.

Fig. 2. Risk of bias (RoB) 2 assessment. RoB2 traffic light (**A**) and RoB2 summary (**B**) of included RCTs.

Secondary endpoints

Aspirin (100–160 mg) did not significantly affect all-cause or cardiovascular mortality (Table 2)[3,5–7], but significantly reduced VTE-related mortality (RR [95%CI] = 0.44 [0.26; 0.75], $P = 0.002$; moderate QoE) compared to placebo (Table 2)[3,5,6]. This reduction was consistent for primary prevention and provoked VTE (RR [95%CI] = 0.42 [0.24; 0.72], $P = 0.006$; moderate QoE) (Table 3 and Table S1 in the SM3)[3,7], but not for secondary prevention (Table 4)[5,6], unprovoked VTE (Table S2 in the SM3)[5,6] or low-dose low-dose aspirin (100 mg) in VTE prevention (Tables S3 in the SM3)[5–7].

Aspirin (100–160 mg) was associated with increased overall bleeding (RR [95%CI] = 1.13 [1.10; 1.16], $P < 0.0001$; moderate QoE) and major bleeding (RR [95%CI] = 1.18 [1.07; 1.30], $P < 0.0001$; moderate QoE)[3–7], without increasing transfusion rates, compared to placebo (Table 2)[3,4]. Sub-analyses were consistent across primary prevention[3,7] and provoked VTE[3,7], but not for secondary prevention and unprovoked VTE (Tables 3 and 4; Tables S1-S2 in SM3)[5,6]. Low-dose aspirin also increased bleeding risks in the context of VTE prevention compared to placebo (Table S3 in SM3)[4–7].

Aspirin did not significantly increase stroke (RR [95%CI] = 1.10 [0.86; 1.41], $P = 0.417$; moderate QoE)[3–7] and, specifically, haemorrhagic stroke (RR [95%CI] = 0.95 [0.26; 3.38], $P = 0.449$; low QoE)[3,4], and did not reduce major cardiovascular AEs (RR [95%CI] = 0.92 [0.83; 1.03], $P = 0.162$; low QoE)[3–7], cardiac AEs (RR [95%CI] = 1.03 [0.79; 1.35], $P = 0.773$; low QoE)[3,5–7], or myocardial infarction (RR [95%CI] = 1.03 [0.86; 1.24], $P = 0.700$; low QoE) compared to placebo (Table 2)[3,5–7]. Findings were consistent in primary[3,7] and secondary prevention (Tables 3 and 4)[5,6], provoked[3,7] and unprovoked[5,6] VTE (Tables S1-S3 in SM3), and with low-dose aspirin (100 mg) used in VTE prevention (Tables S3 in the SM3)[4–7]. However, for secondary prevention and unprovoked VTE, aspirin was linked to lower major cardiovascular AEs (RR [95%CI] = 0.71 [0.57; 0.90], $P = 0.004$; moderate QoE) compared to placebo (Table 4)[5,6].

Forest plots are provided in SM4, while funnel plots and leave-one-out diagnostic charts identifying highly influential studies are in SM5. These plots assess aspirin's efficacy and safety compared to placebo in

Variable	RR	[95% CI]	z	*P*-value	τ^2	τ	I^2	*P* at Q test	QoE
Efficacy									
VTE[3–7]	**0.80**	**[0.72; 0.90]**	**− 3.58**	**< 0.001**	**0**	**0**	**42.0% [0.0%; 77.0%]**	**0.125**	⊕⊕⊕⊖ **Moderate**†
DVT[3–7]	**0.82**	**[0.71; 0.95]**	**− 2.55**	**0.010**	**0**	**0**	**0.0% [0.0%; 74.6%]**	**0.439**	⊕⊕⊕⊖ **Moderate**†
PE[3–7]	**0.79**	**[0.66; 0.95]**	**− 2.45**	**0.014**	**0**	**0**	**31.3% [0.0%; 72.1%]**	**0.201**	⊕⊕⊕⊖ **Moderate**†
All-cause mortality[3,5–7]	0.97	[0.86; 1.09]	− 0.44	0.655	0	0	0.0% [0.0%; 79.2%]	0.973	⊕⊕⊕⊖ Moderate‡
Cardiovascular mortality[3,5–7]	0.92	[0.78; 1.08]	− 0.98	0.322	0	0	0.0% [0.0%; 79.2%]	0.840	⊕⊕⊖⊖ Low†‡
VTE-related mortality[3,5,6]	**0.44**	**[0.26; 0.75]**	**− 3.05**	**0.002**	**0**	**0**	**0.0% [0.0%; 84.7%]**	**0.877**	⊕⊕⊕⊖ **Moderate**†
Safety									
Bleeding[3–7]	**1.13**	**[1.10; 1.16]**	**10.41**	**< 0.001**	**0**	**0**	**12.2% [0.0%; 77.7%]**	**0.337**	⊕⊕⊕⊖ **Moderate**†
Major bleeding[3–7]	**1.18**	**[1.07; 1.30]**	**3.31**	**< 0.001**	**0**	**0**	**0.0% [0.0%; 74.6%]**	**0.601**	⊕⊕⊕⊖ **Moderate**†
Trasfusion[3,4]	1.15	[0.86; 1.53]	0.95	0.337	0.046	0.216	63.5% [0.0%; 89.6%]	0.064	⊕⊕⊖⊖ Low*‡
Stroke[3–7]	1.10	[0.86; 1.41]	0.81	0.417	0	0	0.0% [0.0%; 74.6%]	0.923	⊕⊕⊕⊖ Moderate‡
Haemorrhagic stroke[3,4]	0.95	[0.26; 3.38]	− 0.07	0.936	0.449	0.670	26.9% [0.0%; 99.9%]	0.242	⊕⊕⊖⊖ Low*‡
Major cardiovascular AEs[3–7]	0.92	[0.83; 1.03]	− 1.39	0.162	0.006	0.079	39.1% [0.0%; 75.8%]	0.145	⊕⊕⊖⊖ Low*‡
Cardiac AEs[3,5–7]	1.03	[0.79; 1.35]	0.28	0.773	0.036	0.191	9.3% [0.0%; 81.1%]	0.353	⊕⊕⊖⊖ Low*‡
Myocardial infarction[3,5–7]	1.03	[0.86; 1.24]	0.38	0.700	0.004	0.067	26.3% [0.0%; 70.7%]	0.246	⊕⊕⊖⊖ Low†‡

Table 2. Efficacy and safety of aspirin compared to placebo in preventing VTE. *RR* relative risk, *95%CI* 95% confidence interval, *z* z-score measures how many standard deviations a data point is from the mean, τ^2 between-study variance in random-effects meta-analysis, τ standard deviation estimate of effect sizes in random-effects meta-analysis, I^2 measures percentage variation across studies due to heterogeneity, *Q test* Cochran's Q test assesses heterogeneity among study results, *QoE* quality of evidence. *Downgraded one level for inconsistency (such as heterogeneity of estimates of effects across trials)[12]. †Although a low I^2 value usually suggests low heterogeneity, the quality of evidence for this observation remains uncertain. This uncertainty arises from a broad I^2 confidence interval, which hints at potential undetected heterogeneity. Despite the reported absence of between-study variance ($\tau^2 = 0$) and no variation in effect estimates ($\tau = 0$), and an I^2 of 0%, the QoE for the outcome was prudently downgraded one level[12]. ‡Downgraded one level for Imprecision (for example, 95% confidence intervals are wide and include or are close to null effect)[12] High QoE (⊕⊕⊕⊕): The authors are very confident that the true effect lies close to that of the estimate of the effect. Moderate QoE (⊕⊕⊕⊖): The authors 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 QoE (⊕⊕⊖⊖): The authors' confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect[12].

VTE prevention. The funnel plots indicate no significant publication bias, while the leave-one-out diagnostics confirm that the exclusion of influential studies does not substantially alter the overall results, supporting the robustness of the meta-analysis. The Quality of Evidence (QoE) for the outcomes is summarised in Tables 2, 3 and 4 and in SM3 [Tables S1–S3]).

In the TSA, cumulative z-scores crossed the monitoring boundaries for several VTE types, providing firm evidence of aspirin's benefit in general, primary, provoked, and secondary VTE prevention (overall outcome), while evidence for unprovoked VTE and low-dose aspirin (100 mg) were conclusive but not firm (Table 5 and SM3 [Table S4]). Cumulative z-scores for DVT, PE, and VTE-related mortality indicated firm or conclusive evidence for general and primary prevention, and for provoked VTE. In contrast, evidence was inconclusive for some outcomes in secondary and unprovoked VTE, and in low-dose aspirin treatment (Table 5 and SM3 [Table S4]). TSA graphs supporting these findings are provided in SM6.

The NNTB/NNTH ratio analysis across low, moderate, and high baseline risk levels confirms a favorable benefit–risk profile of extended aspirin therapy in VTE prevention. This finding was consistent in subgroup analyses for primary and provoked VTE prevention, particularly in higher-risk populations, while the benefit was limited or uncertain in secondary, unprovoked, and low-dose aspirin settings (SM7).

Discussion

Our meta-analysis assessed the overall role of aspirin in VTE prevention, with additional analyses for primary and secondary prevention. Due to the limited number of RCTs, we conducted a pooled analysis but performed subgroup analyses where feasible to distinguish provoked from unprovoked VTE. Our meta-analysis demonstrates that extended aspirin therapy (100 to 160 mg) significantly reduces the risk of VTE, DVT, and PE compared to placebo, especially in primary prevention in surgical patients. Aspirin is effective in reducing the risk of provoked VTE, including both DVT and PE, and also shows a significant benefit for unprovoked VTE overall, although not for its individual components. Low-dose aspirin (100 mg) does not significantly reduce the risk of VTE, DVT, or PE. While aspirin does not impact overall or cardiovascular mortality, it significantly reduces VTE-related mortality. Aspirin use at any dose increases the risk of bleeding but does not elevate blood transfusion requirements. These effects were consistent for primary prevention and provoked VTE but not for

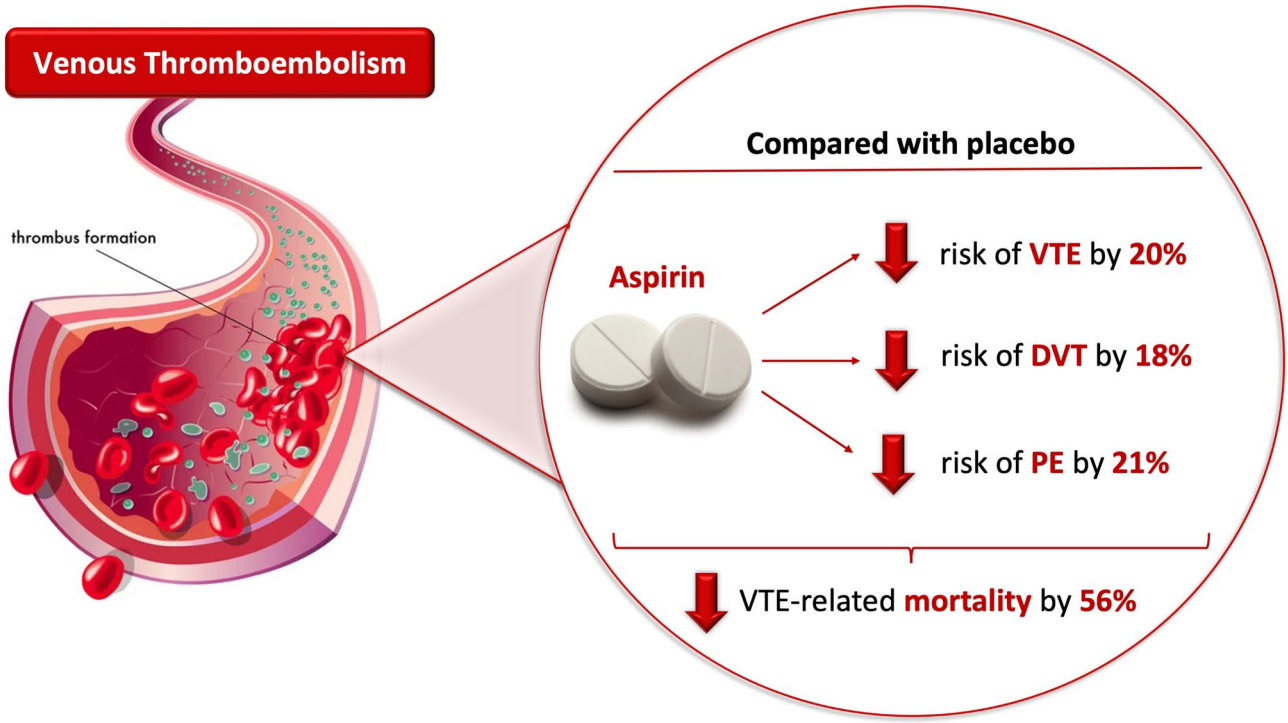

Fig. 3. Summary of main results. Aspirin reduces the risk of venous thromboembolism (VTE) by 20%, deep vein thrombosis (DVT) by 18%, pulmonary embolism (PE) by 21%, and VTE-related mortality by 56% compared with placebo. Illustration elements adapted from Depositphotos™ (licensed image provider), used under extended license permitting academic publication.

secondary prevention, unprovoked VTE, or low-dose aspirin use. Importantly, aspirin does not increase the risk of stroke or haemorrhagic stroke, nor does it reduce major cardiovascular events, except in secondary prevention and unprovoked VTE, where a significant reduction in major cardiovascular events was observed.

While the POISE-2 trial found no significant reduction in VTE for primary prevention in noncardiac surgery[7], pooled analyses indicate a one-third reduction in symptomatic provoked VTE in noncardiac surgery[16]. Extending aspirin (100–160 mg) after stopping antithrombotic prophylaxis may be appropriate for patients with risk factors (e.g., history of VTE, thrombophilia, obesity, malignancy), particularly for those unable or unwilling to use anticoagulants[2], which remain superior in reducing VTE occurrence, making aspirin a secondary option in such cases[1,2] Postoperative VTE events in high-risk surgical patients[17], such as those with obesity[18], often occur weeks after surgery[17,18], typically after stopping prophylaxis[18], underscoring the potential benefit of aspirin use beyond the initial short-term prophylaxis period (4–14 days) or even the extended antithrombotic prophylaxis phase (19–42 days)[2] Aspirin's low cost and convenient oral administration make it an appealing option, especially as early ambulation, while crucial, is insufficient to prevent VTE,[19] necessitating a careful balance between the benefits of aspirin and its associated bleeding risks[2]. Recent multicenter trial evidence shows aspirin prescribed at discharge is noninferior to low-molecular-weight heparin in preventing mortality and major thromboembolic events in extremity fractures, highlighting its role in thromboprophylaxis[20]. Previous studies reported no significant difference in overall mortality between extended- and standard-course antithrombotic prophylaxis[2]. Our meta-analysis demonstrated that prolonged aspirin, administered beyond the 19–42 days recommended by guidelines after major surgery[2], significantly reduced VTE, DVT, PE, and VTE-related mortality in primary prevention and provoked VTE. However, the duration of aspirin therapy varied across studies. In the PEP Trial, aspirin was administered for 35 days, but most VTE events were recorded within the first 16 days of hospitalization[3]. In the POISE-2 Trial, aspirin was given for 30 days[7]. While these findings support aspirin use beyond the initial prophylaxis period, further studies are needed to assess its efficacy beyond 42 days in primary prevention.

Regarding secondary prevention, the INSPIRE analysis showed a 42% reduction in recurrent VTE risk after adjusting for treatment adherence[9] However, our findings did not confirm a statistically significant benefit of aspirin in reducing overall VTE risk in secondary prevention, although some effect cannot be excluded due to wide confidence intervals. This is consistent with guidelines that consider aspirin as an option for patients who refuse or cannot tolerate oral anticoagulants for extended prophylaxis[21] Aspirin use should also be reconsidered when anticoagulant therapy is discontinued, as it may have been stopped when anticoagulation began, requiring a balance between its benefits and bleeding risks[1,2]. In line with our results, aspirin showed a significant benefit in preventing unprovoked VTE overall, although not for its individual components (DVT and PE), suggesting that aspirin may have a limited role in this setting. Nevertheless, anticoagulation remains the standard of care for secondary prevention[2].

Variable	RR	[95% CI]	z	*P*-value	τ^2	τ	I^2	*P* at Q test	QoE
Efficacy									
VTE[3,4,7]	**0.80**	**[0.70; 0.92]**	**− 3.13**	**0.001**	**0**	**0**	**45.8% [0.0%; 82.0%]**	**0.136**	⊕⊕⊕⊖ **Moderate**[†]
DVT[3,7]	**0.72**	**[0.56; 0.92]**	**− 2.61**	**0.009**	**0**	**0**	**0.0% [0.0%; 89.6%]**	**0.964**	⊕⊕⊕⊖ **Moderate**[†]
PE[3,7]	**0.73**	**[0.54; 0.97]**	**− 2.12**	**0.034**	**0.004**	**0.066**	**54.5% [0.0%; 87.0%]**	**0.111**	⊕⊕⊕⊖ **Moderate**[*]
All-cause mortality[3,7]	0.97	[0.86; 1.09]	− 0.42	0.676	0	0	0.0% [0.0%; 89.6%]	0.839	⊕⊕⊖⊖ Low[†‡]
Cardiovascular mortality[3,7]	0.93	[0.79; 1.09]	− 0.85	0.398	0	0	0.0% [0.0%; 89.6%]	0.823	⊕⊕⊖⊖ Low[†‡]
VTE-related mortality[3]	**0.42**	**[0.24; 0.72]**	**− 3.16**	**0.001**	**0**	**0**	**0.0% [0.0%; 99.9%]**	**0.889**	⊕⊕⊕⊖ **Moderate**[†]
Safety									
Bleeding[3,7]	**1.17**	**[1.01; 1.37]**	**2.15**	**0.031**	**0.009**	**0.097**	**19.8% [0.0%; 91.7%]**	**0.287**	⊕⊕⊕⊖ **Moderate**[†]
Major bleeding[3,7]	**1.13**	**[1.00; 1.28]**	**2.11**	**0.034**	**0.001**	**0.039**	**0.0% [0.0%; 89.6%]**	**0.382**	⊕⊕⊕⊖ **Moderate**[†]
Trasfusion[3]	1.04	[0.73; 1.49]	0.25	0.802	0.048	0.219	71.3% [0.0%; 93.5%]	0.062	⊕⊕⊖⊖ Low[*‡]
Stroke[3,7]	1.04	[0.75; 1.43]	0.25	0.803	0	0	0.0% [0.0%; 89.6%]	0.771	⊕⊕⊖⊖ Low[†‡]
Cardiovascular AEs[3,7]	0.98	[0.90; 1.06]	− 0.43	0.664	0	0	0.0% [0.0%; 89.6%]	0.456	⊕⊕⊖⊖ Low[†‡]
Cardiac AEs[3,7]	1.06	[0.96; 1.16]	1.26	0.207	0	0	0.0% [0.0%; 89.6%]	0.647	⊕⊕⊖⊖ Low[†‡]
Myocardial infarction[3,7]	1.02	[0.88; 1.18]	0.37	0.711	0	0	43.3% [0.0%; 83.0%]	0.171	⊕⊕⊖⊖ Low[†‡]

Table 3. Efficacy and safety of aspirin compared to placebo in preventing primary VTE. *RR* relative risk, *95%CI* 95% confidence interval, *z* z-score measures how many standard deviations a data point is from the mean, τ^2 between-study variance in random-effects meta-analysis, τ standard deviation estimate of effect sizes in random-effects meta-analysis, I^2 measures percentage variation across studies due to heterogeneity, *Q test* Cochran's Q test assesses heterogeneity among study results, *QoE* quality of evidence. *Downgraded one level for inconsistency (such as heterogeneity of estimates of effects across trials)[12]. [†]Although a low I^2 value usually suggests low heterogeneity, the quality of evidence for this observation remains uncertain. This uncertainty arises from a broad I^2 confidence interval, which hints at potential undetected heterogeneity. Despite the reported absence of between-study variance ($\tau^2 = 0$) and no variation in effect estimates ($\tau = 0$), and an I^2 of 0%, the QoE for the outcome was prudently downgraded one level[12]. [‡]Downgraded one level for Imprecision (for example, 95% confidence intervals are wide and include or are close to null effect)[12]. High QoE (⊕⊕⊕⊕): The authors are very confident that the true effect lies close to that of the estimate of the effect. Moderate QoE (⊕⊕⊕⊖): The authors 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 QoE (⊕⊕⊖⊖): The authors' confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect[12].

Consistent with other meta-analyses[20,22–24], we found no benefits in reducing overall or cardiovascular mortality, which could have meaningful implications for clinical practice. In the context of VTE prophylaxis, aspirin may offer survival benefits, particularly for patients at high VTE risk[20,22–24], warranting its careful consideration despite the associated bleeding risks. Although caution is advised for healthy individuals without atherosclerosis—where aspirin may slightly reduce myocardial infarction risk but increase major bleeding[23],—this finding underscores its potential value in targeted high-risk populations.

While effective in reducing VTE, aspirin's bleeding risk is a concern. The INSPIRE analysis showed no significant bleeding difference between aspirin and control groups,[9] but other evidence suggests caution. A pooled analysis of two RCTs found an 18% higher bleeding risk with aspirin in non-cardiac surgery patients,[16] and recent meta-analyses for primary prevention of cardiovascular events show a 40% increase in major bleeding risk[22] Our meta-analysis identified a 13% increase in major bleeding with aspirin, though not linked to stroke, specifically haemorrhagic stroke, nor to all-cause or cardiovascular mortality. Nevertheless, caution around intracranial haemorrhage remains, with meta-analyses reporting a 30%[22], 33%[23], or 34% increased risk of haemorrhagic stroke[24] These findings underscore the importance of balancing the benefits of VTE prevention with the associated bleeding risks. The NNTB/NNTH ratio supports a favorable benefit–risk profile, particularly in high-risk patients undergoing primary prevention or with provoked VTE. Nonetheless, careful patient selection remains essential.

Comprehensive data on aspirin's impact on major cardiovascular events indicate potential benefits in reducing cardiovascular incidents by 9%[22] or 11%[24], with a decrease in myocardial infarction by 13%[20], 15%[24], or 18%[23]. Additionally, aspirin has been associated with a 6%[23] or 12%[22] decrease in ischaemic stroke. While data from individual RCTs suggest potential benefits[3,7], our analysis found that aspirin reduced major cardiovascular adverse events only in the context of secondary prevention and unprovoked VTE. A pooled analysis indicated a substantial 34% reduction in these events with aspirin[9], and our findings showed a 29% reduction. However, no significant benefit was observed in primary prevention and provoked VTE. Furthermore, within the context of VTE prevention, aspirin did not demonstrate any effect in reducing the risk of cardiac adverse events or myocardial infarction across any of the conditions explored. While our analysis did not show significant cardiovascular benefits of low-dose aspirin (100 mg/day) in VTE prevention, evidence from sensitivity analyses indicates that aspirin at doses of 100 mg or less daily is associated with reductions in composite cardiovascular

Variable	RR	[95% CI]	z	*P*-value	τ^2	τ	I^2	*P* at Q test	QoE
Efficacy									
VTE[4–6]	**0.83**	**[0.54; 1.28]**	**− 0.82**	**0.410**	**0.093**	**0.305**	**53.6% [0.0%; 86.7%]**	**0.115**	⊕⊕⊖⊖ Low*‡
DVT[5,6]	0.73	[0.45; 1.19]	− 1.23	0.217	0.059	0.244	47.5% [0.0%; 99.9%]	0.167	⊕⊕⊖⊖ Low*‡
PE[5,6]	0.65	[0.42; 1.03]	− 1.82	0.068	0	0	0.0% [0.0%; 99.9%]	0.345	⊕⊕⊖⊖ Low†‡
All-cause mortality[5,6]	0.94	[0.53; 1.68]	− 0.19	0.850	0	0	0.0% [0.0%; 99.9%]	0.704	⊕⊕⊖⊖ Low†‡
Cardiovascular mortality[5,6]	0.55	[0.18; 1.65]	− 1.06	0.290	0	0	0.0% [0.0%; 99.9%]	0.670	⊕⊕⊖⊖ Low†‡
VTE-related mortality[5,6]	0.98	[0.13; 6.93]	− 0.02	0.984	0	0	0.0% [0.0%; 99.9%]	0.984	⊕⊕⊖⊖ Low†‡
Safety									
Bleeding[5,6]	1.47	[0.71; 3.06]	1.05	0.291	0	0	0.0% [0.0%; 99.9%]	0.467	⊕⊕⊖⊖ Low†‡
Major bleeding[5,6]	1.27	[0.47; 3.41]	0.49	0.622	0	0	0.0% [0.0%; 99.9%]	0.828	⊕⊕⊖⊖ Low†‡
Stroke[5,6]	0.97	[0.31; 3.08]	− 0.04	0.970	0	0	0.0% [0.0%; 99.9%]	0.528	⊕⊕⊖⊖ Low†‡
Cardiovascular AEs[5,6]	**0.71**	**[0.57; 0.90]**	**− 2.83**	**0.004**	**0**	**0**	**0.0% [0.0%; 99.9%]**	**0.875**	⊕⊕⊕⊖ **Moderate**†
Cardiac AEs[5,6]	0.64	[0.24; 1.74]	− 0.86	0.392	0.194	0.441	36.6% [0.0%; 99.9%]	0.209	⊕⊕⊖⊖ Low*‡
Myocardial infarction[5,6]	0.50	[0.14; 1.75]	− 1.07	0.284	0	0	0.0% [0.0%; 99.9%]	0.410	⊕⊕⊖⊖ Low†‡

Table 4. Efficacy and safety of aspirin compared to placebo in preventing secondary VTE. *RR* relative risk, *95%CI* 95% confidence interval, *z* z-score measures how many standard deviations a data point is from the mean, τ^2 between-study variance in random-effects meta-analysis, τ standard deviation estimate of effect sizes in random-effects meta-analysis, I^2 measures percentage variation across studies due to heterogeneity, *Q test* Cochran's Q test assesses heterogeneity among study results; *QoE* quality of evidence. *Downgraded one level for inconsistency (such as heterogeneity of estimates of effects across trials)[12]. †Although a low I^2 value usually suggests low heterogeneity, the quality of evidence for this observation remains uncertain. This uncertainty arises from a broad I^2 confidence interval, which hints at potential undetected heterogeneity. Despite the reported absence of between-study variance ($\tau^2 = 0$) and no variation in effect estimates ($\tau = 0$), and an I^2 of 0%, the QoE for the outcome was prudently downgraded one level[12]. ‡Downgraded one level for Imprecision (for example, 95% confidence intervals are wide and include or are close to null effect)[12] High QoE (⊕⊕⊕⊕): The authors are very confident that the true effect lies close to that of the estimate of the effect. Moderate QoE (⊕⊕⊕⊖): The authors 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 QoE (⊕⊕⊖⊖): The authors' confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect[12].

outcomes, including a 13% reduction in ischemic stroke, an 11% reduction in total stroke, and a 13% reduction in myocardial infarction[24]. These benefits appear more pronounced in specific populations, such as individuals under 65 years of age and those with a BMI ≥ 25, with similar bleeding risks[22,24]. Additionally, patients with a low 10-year MACE% risk saw more cardiovascular benefits from aspirin use than those at high risk[22].

Strengths and limitations of the study

By conducting multiple sensitivity analyses, this meta-analysis tested the robustness of the results, reinforcing their clinical relevance. A comprehensive literature review contributed to a robust dataset, and focusing exclusively on adult RCTs improved the applicability of the findings to this specific population.

However, the study has limitations. It did not assess varying aspirin dosages or long-term adherence, which could impact the risk-benefit balance. Important factors such as comorbidities and postoperative care variations were inconsistently reported, possibly influencing outcome interpretation. While major bleeding definitions align with existing literature[10], minor bleeding requires broader criteria to meet recent definitions of clinically relevant non-major bleeding[25]. Many RCTs predate this consensus[25], limiting exact conformity. Additionally, only one study reported gastrointestinal bleeding outcomes[4], constraining the assessment of GI bleeding risks with aspirin for VTE prevention.

Although statistical heterogeneity was acceptable, clinical heterogeneity remains a limitation of our study. Variability in follow-up duration, aspirin regimens, and clinical settings among the included trials may affect the generalizability of our findings. Nevertheless, the consistency of results across studies supports the overall robustness of our conclusions.

Higher RRR thresholds in TSA, based on the maximum reported values, ensure robustness but may overlook some significant results. Lower RRR thresholds could provide a more nuanced view of aspirin's effects.

The NNTB and NNTH estimates are based on aggregated trial data and may not fully capture differences across patient subgroups. Further studies are needed to refine patient selection criteria.

Excluding non-RCT studies and grey literature may risk publication bias despite the benefits of focusing on peer-reviewed research. Current guidelines recommend DOACs for prolonged VTE treatment. Lastly, our meta-analysis aimed to address a gap in the literature by evaluating aspirin as an alternative in patients unable or unwilling to take anticoagulants. Since this was not a network meta-analysis, direct comparisons with DOACs were not included.

Variable	MIS	PC	RRR	TSMBC	DARIS	Results
Aspirin compared to placebo in preventing VTE						
VTE[5]	68,554	0.22	0.37	Yes	706	**Firm evidence**
DVT[5]	68,554	0.14	0.45	Yes	754	**Firm evidence**
PE[3]	68,554	0.01	0.43	Yes	11,003	Conclusive
VTE-related mortality[3]	68,554	0.00	0.58	Yes	13,206	Conclusive
Aspirin compared to placebo in preventing primary VTE						
VTE[3]	27,454	0.02	0.36	Yes	9970	**Firm evidence**
DVT[3]	27,454	0.01	0.29	Yes	21,006	**Firm evidence**
PE[3]	27,454	0.24	0.3	Yes	12,095	Conclusive
VTE-related mortality[3]	27,454	0.00	0.58	No	10,997	Conclusive
Aspirin compared to placebo in preventing secondary VTE						
VTE[5]	1224	0.21	0.37	Yes	2471	**Firm evidence**
DVT5	1224	0.14	0.45	Yes	1556	Conclusive
PE5	1224	0.07	0.23	Yes	6373	Inconclusive
VTE-related Mortality3	1224	0.00	0.57	No	10,393	Inconclusive

Table 5. Trial sequence analysis to detect relative risk reduction in VTE, DVT, PE and VTE-related mortality, with α = 5% and power = 80%. *VTE* venous thromboembolism, *DVT* deep vein thrombosis, *PE* pulmonary embolism. A cumulative, sequential z score curve was constructed and used to evaluate the adequacy of the evidence. *MIS* information size in meta-analyses, *PC* proportion of the event in the control group, established based on literature[3–7]; *RRR* relative risk reduction, set a priori based on literature[3–7]; *TSMBC* trial sequential monitoring boundary crossed, *DARIS* diversity adjusted relative information size. It's the required information size adjusted for heterogeneity among studies. The highest RRR observed in the literature[3–7] was used for the treatment compared to the control, ensuring a more conservative and reliable final result. Inconclusive results suggest that further trials are likely to influence conventional meta-analysis results, or that there is a risk of random errors, potentially leading to false-positive results.

Conclusion

Our meta-analysis suggests that extended aspirin therapy (compared to placebo) may reduce the risk of VTE, DVT, and PE, particularly in primary prevention and provoked VTE, and possibly in unprovoked VTE overall, while also highlighting an increased risk of bleeding. These findings support aspirin's potential role in thromboprophylaxis as an alternative in selected patients, especially when anticoagulation is contraindicated or refused. However, the heightened bleeding risk underscores the importance of careful patient selection and monitoring. Future studies should further explore the risk–benefit balance and optimal patient selection.

Data availability

All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication. The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Received: 17 December 2024; Accepted: 12 May 2025
Published online: 17 May 2025

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Acknowledgements

Acknowledgments: The authors thank Nevio Dubbini for his valuable support in statistical analysis and Rosalinda Russo for her valuable support in search strategy. Permissions have been granted.

Author contributions

Conceptualization, M.C.; methodology, M.C., E.T.; software, M.C.; validation, M.C., E.T., T.P., F.Z., E.C., P.N.; P.S.; formal analysis, M.C., E.T.; investigation, M.C., E.T., T.P., F.Z., E.C.; resources, M.C., E.T., T.P., F.Z., E.C., P.N., P.S.; data curation, M.C., E.T., T.P., F.Z., E.C., P.N., P.S.; writing—original draft preparation, M.C.; writing—review and editing M.C., E.T., T.P., F.Z., E.C., P.N., P.S.; visualization, M.C., E.T.; supervision, M.C., P.N.; P.S.; project administration, M.C. P.N. and P.S. equally contributed to the manuscript. All authors have read and agreed to the published version of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Institutional review board statement

The network meta-analysis protocol was registered prospectively under the PROSPERO identification number CRD42024557218, and strict adherence PRISMA checklist was ensured in the preparation of this manuscript.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that no generative AI tools or AI-assisted technologies were used in the preparation of this manuscript.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-02171-z.

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