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(REVIEW ARTICLE)

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Dual antiplatlets therapy following revasclarisation for chronic critical limb ischemia: A systematic review and meta-analysis

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Abstract

Introduction: Chronic limb-threatening ischaemia carries high risks of amputation and death despite revascularisation. Clinicians frequently prescribe dual antiplatelet therapy after surgical or endovascular procedures, yet its net clinical benefit remains uncertain. This review aimed to compare the effectiveness and safety of dual antiplatelet therapy versus single antiplatelet therapy following lower-limb revascularisation.

Methods: The study followed PRISMA 2020 and Cochrane guidance, registered a protocol, and included randomized trials of adults with chronic limb-threatening or critical limb ischaemia after lower-limb revascularisation. Dual therapy combined aspirin with a P2Y12 inhibitor versus single agent. Searches covered databases to 20 September 2025. Triplicate screening, extraction, Risk-of-Bias 2, random-effects Paule–Mandel with Hartung–Knapp, rare-event methods, subgroups, and GRADE were prespecified.

Results: The search retrieved 6,416 citations after de-duplication; 10 randomized trials met eligibility for synthesis. For major amputation at one year, the random-effects risk ratio was 0.94 (95% CI 0.77–1.15; I^2 89.9%). Twelve-month graft patency showed no improvement (RR 1.16, 95% CI 0.70–1.91; I^2 95.5%). Major bleeding or transfusion increased with dual therapy (RR 1.55, 95% CI 1.06–2.26; I^2 57.4%). Resting ankle–brachial index showed minimal difference (MD −0.04, 95% CI −0.11 to 0.02; I^2 99.5%). All-cause mortality at one year was neutral (RR 1.01, 95% CI 0.75–1.35; I^2 91.7%). Subgroup analyses found no interaction by vascular bed, modality, or duration; small-study effects were generally suggested; overall certainty was moderate for amputation and patency, and low for bleeding and mortality across trials.

Conclusion: Dual antiplatelet therapy after lower-limb revascularisation for chronic limb-threatening ischaemia did not reduce major amputation or improve patency under random-effects assumptions, and it increased major bleeding. Mortality appeared neutral. Effects varied widely across studies without subgroup effects. Treatment decisions should individualize bleeding risk and limb threat while awaiting powered trials.

Keywords: Dual antiplatelet therapy; Chronic limb-threatening ischaemia; Critical limb ischaemia; Lower-limb revascularisation; Major amputation; Graft patency; Major bleeding; Systematic review and meta-analysis

1. Introduction

Chronic critical limb ischemia represents the most advanced stage of peripheral arterial disease and poses a significant threat to limb viability and patient survival (Giannopoulos & Armstrong, 2021). It is clinically characterized by ischemic rest pain, ulceration, or gangrene caused by severely impaired arterial perfusion lasting for more than two weeks

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(Rigatelli et al., 2017). Peripheral arterial disease affects over 200 million people globally and the incidence of chronic critical limb ischemia continues to increase, particularly in aging and diabetic populations (Gupta et al., 2019). Diabetes mellitus, smoking, hypertension, chronic kidney disease, and dyslipidemia remain the most common etiological factors associated with disease progression and vascular occlusion in the lower extremities (Hardung et al., 2021). Among patients with diabetes, the risk of developing chronic critical limb ischemia is two to four times greater than in non-diabetic individuals (Barć et al., 2020). Ischemic ulcerations of the distal extremities in chronic critical limb ischemia frequently progress to gangrene, leading to major amputation and increased mortality (Dean & Vaccaro, 2002). Revascularization using open surgery or endovascular therapy is the principal strategy for limb salvage and restoration of arterial perfusion (Michel et al., 2016). However, reintervention rates remain high due to restenosis, thrombosis, or graft occlusion following successful revascularization (Wand et al., 2014). Antiplatelet therapy is routinely used to improve patency rates and to prevent thromboembolic events in patients with chronic critical limb ischemia undergoing revascularization (Spiliopoulos, 2014). Dual antiplatelet therapy, most commonly comprising aspirin and clopidogrel, has shown promise in improving outcomes by reducing platelet aggregation and inflammation in high-risk vascular patients (Burdess et al., 2010). Randomized trials have demonstrated that dual antiplatelet therapy lowers perioperative biomarkers of atherothrombosis and may reduce myocardial injury in patients undergoing limb revascularization (Brener et al., 2007). Antiplatelet agents including cilostazol and ticagrelor may provide further antithrombotic benefit in certain patients with critical limb ischemia (Azarbal et al., 2015).

Analysis of over 50,000 patients undergoing revascularization procedures revealed that dual antiplatelet therapy was associated with improved amputation-free survival and overall survival compared to monotherapy (Ramanan et al., 2021). Furthermore, dual antiplatelet therapy was linked to reduced target lesion revascularization, reduced restenosis, and fewer adverse limb events in patients with diabetes and multilevel arterial disease (Gupta et al., 2019). Clinical guidelines now acknowledge the use of dual antiplatelet therapy in high-risk peripheral vascular patients, particularly after endovascular procedures (Giannopoulos & Armstrong, 2021). Although dual antiplatelet therapy shows benefit, the risk of bleeding complications must be considered in elderly or polymorbid patients (Trani et al., 2020). Addition of anticoagulation to dual antiplatelet therapy has not demonstrated clear benefit in long-term outcomes after limb revascularization and may increase the risk of hemorrhage (Kronlage et al., 2019). The variability in patient response to clopidogrel further complicates standardized treatment, as a significant proportion of patients demonstrate resistance to its antiplatelet effects (Wand et al., 2014). There remains a lack of consensus regarding optimal duration, combination, and patient selection for dual antiplatelet therapy following revascularization for chronic critical limb ischemia (Hanna, 2012). Pilot trials have been underpowered to assess clinical endpoints and larger multicenter randomized studies are required to validate safety and efficacy (Burdess et al., 2014). The study aimed to evaluate the safety and efficacy of dual antiplatelet therapy compared to monotherapy in patients undergoing surgical or endovascular revascularization for chronic critical limb ischemia.

2. Methods

2.1. Protocol and Registration

This systematic review and meta analysis was planned in advance in alignment with PRISMA 2020 and the Cochrane Handbook, and all objectives, eligibility criteria, outcomes, and analyses were prespecified. The protocol, including planned subgroup and sensitivity analyses, was finalized before screening commenced, time stamped in the study repository, and any methodological refinements introduced during the process were documented with justification to maintain an auditable trail.

2.2. Eligibility Criteria

Only randomized controlled trials that enrolled adults with chronic limb threatening or critical limb ischaemia who underwent lower extremity revascularisation were eligible. Revascularisation modalities included endovascular interventions, open surgical bypass, and hybrid procedures. Eligible interventions required dual antiplatelet therapy defined as aspirin combined with a P2Y12 inhibitor such as clopidogrel, ticagrelor, or prasugrel initiated after revascularisation at accepted doses and schedules. Comparators were single antiplatelet therapy using aspirin or a P2Y12 inhibitor alone. Trials were required to report at least one vascular effectiveness or bleeding outcome with a minimum follow up of thirty days. Trials in which antithrombotic exposure was confounded by therapeutic dose anticoagulation or dual pathway inhibition were excluded unless a dual antiplatelet versus single agent contrast was clearly separable. Mixed peripheral artery disease populations were eligible if the chronic limb threatening or critical limb ischaemia subgroup was reported separately or represented at least seventy percent of the cohort. Nonrandomized studies, single arm cohorts, case series, editorials, and narrative reviews were excluded.

2.3. Information Sources

Comprehensive searches were carried out in PubMed, MEDLINE Ovid, Embase Ovid, the Cochrane Library including CENTRAL, CINAHL on EBSCOhost, and PsycINFO Ovid from inception through twenty September two thousand twenty five without language restrictions. Trial registries including ClinicalTrials dot gov and the World Health Organization International Clinical Trials Registry Platform were searched for ongoing and completed studies. Conference proceedings from major vascular and cardiovascular societies were screened. Reference lists of included trials and relevant reviews were examined to identify additional reports. Alerts were checked on the final search date to capture emergent records.

3. Search Strategy and Boolean Structure

Database strategies combined controlled vocabulary with free text synonyms for three core concepts which were disease including chronic limb threatening ischaemia and critical limb ischaemia and peripheral artery disease, revascularisation, and dual antiplatelet therapy. These concepts were joined with AND, synonyms within each concept were joined with OR, and animal only records were excluded with NOT where supported. Randomized trial filters were applied using publication type, indexing terms, and text word stems for randomization and blinding. The complete Boolean grouped MeSH and thesaurus table as shown in Table 1.

Table 1 Boolean grouped MeSH and thesaurus search strategies databases for randomized trials of dual antiplatelet therapy after revascularisation in CLTI/CLI adults.

Database (Platform)	AND (concept sets required together)	OR (synonyms / controlled terms within each concept set)	NOT (exclusions)	Notes
PubMed	(A) PAD/CLI AND (B) Revascularization AND (C) Dual antiplatelet therapy AND (D) RCT filter	(A) "Peripheral Arterial Disease"[MeSH] OR "Ischemia"[MeSH] OR "Limb Ischemia"[MeSH] OR "peripheral artery disease"[tiab] OR "critical limb ischemia"[tiab] OR "chronic limb-threatening ischemia"[tiab] OR CLI[tiab] OR CLTI[tiab] OR related phrases; (B) "Revascularization"[MeSH] OR "Endovascular Procedures"[MeSH] OR "Angioplasty, Balloon"[MeSH] OR "Stents"[MeSH] OR "Vascular Surgical Procedures"[MeSH] OR "Bypass, Surgical"[MeSH] OR revasculari*[tiab] OR endovascular[tiab] OR angioplast*[tiab] OR stent*[tiab] OR bypass[tiab]; (C) "Platelet Aggregation Inhibitors"[MeSH] OR "Aspirin"[MeSH] OR "Clopidogrel"[MeSH] OR "Ticagrelor"[Supplementary Concept] OR "Prasugrel Hydrochloride"[Supplementary Concept] OR "dual antiplatelet"[tiab] OR DAPT[tiab] OR aspirin[tiab] OR clopidogrel[tiab] OR ticagrelor[tiab] OR prasugrel[tiab]; (D) randomized controlled trial[pt] OR controlled clinical trial[pt] OR random*[tiab] OR placebo*[tiab] OR trial[ti]	animals[mh] NOT humans[mh]	Humans; adults handled at screening; no language limits.
MEDLINE (Ovid)	(A) PAD/CLI AND (B) Revascularization AND (C) Dual antiplatelet therapy AND (D) RCT filter	(A) exp Peripheral Arterial Disease/ OR exp Ischemia/ OR Limb Ischemia/ OR (critical limb ischemia OR chronic limb-threatening ischemia OR CLI OR CLTI).ti,ab. (B) exp Revascularization Procedures/ OR exp Endovascular Procedures/ OR exp Angioplasty, Balloon/ OR exp Stents/ OR exp Vascular Surgical Procedures/ OR Bypass, Surgical/ OR (revasculari* OR endovascular OR angioplast* OR stent* OR bypass).ti,ab. (C) exp Platelet Aggregation Inhibitors/ OR Aspirin/ OR Clopidogrel/ OR (Ticagrelor OR Prasugrel).mp. OR (dual antiplatelet OR DAPT OR aspirin OR clopidogrel OR ticagrelor OR prasugrel).ti,ab. (D) randomized controlled trial.pt. OR controlled clinical trial.pt. OR random*.ti,ab. OR placebo*.ti,ab. OR trial.ti.	exp Animals/ NOT Humans/	Cochrane HSSS elements embedded in (D).
Embase (Ovid)	(A) PAD/CLI AND (B) Revascularization AND (C) Dual antiplatelet therapy AND (D) RCT filter	(A) exp peripheral arterial disease/ OR exp limb ischemia/ OR "critical limb ischemia".ti,ab. OR (CLTI OR CLI).ti,ab. (B) exp revascularization/ OR exp endovascular procedure/ OR exp peripheral angioplasty/ OR exp stent/ OR exp vascular surgery/ OR (femoropopliteal artery/ OR tibial artery/) OR (revasculari* OR endovascular OR angioplast* OR stent* OR bypass).ti,ab. (C) exp antiplatelet agent/ OR acetylsalicylic acid/ OR clopidogrel/ OR ticagrelor/ OR prasugrel/ OR (dual antiplatelet OR DAPT OR aspirin OR clopidogrel OR ticagrelor OR prasugrel).ti,ab. (D) randomized controlled trial/ OR randomization/ OR double blind procedure/ OR single blind procedure/ OR random*.ti,ab. OR placebo*.ti,ab. OR trial.ti.	animal/ NOT human/	Include conference abstracts; human limiter applied.

Cochrane Library (CENTRAL)	(A) PAD/CLI AND (B) Revascularization AND (C) Dual antiplatelet therapy	(A) [MeSH descriptor: Peripheral Arterial Disease] OR [MeSH descriptor: Ischemia] OR "critical limb ischemia" OR "chronic limb-threatening ischemia" OR CLI OR CLTI; (B) [MeSH descriptor: Revascularization Procedures] OR [MeSH descriptor: Endovascular Procedures] OR [MeSH descriptor: Angioplasty, Balloon] OR [MeSH descriptor: Stents] OR revasculari* OR angioplast* OR stent* OR bypass; (C) [MeSH descriptor: Platelet Aggregation Inhibitors] OR [MeSH descriptor: Aspirin] OR clopidogrel OR ticagrelor OR prasugrel OR "dual antiplatelet" OR DAPT	Not typically required (CENTRAL indexes trial records); apply exclusions at screening if needed	CENTRAL already restricted to trials; additional RCT filter unnecessary.
CINAHL (EBSCOhost)	(A) PAD/CLI AND (B) Revascularization AND (C) Dual antiplatelet therapy AND (D) RCT publication type	(A) (MH "Peripheral Arterial Disease+") OR (MH "Ischemia+") OR TI/AB ("critical limb ischemia" OR "chronic limb-threatening ischemia" OR CLI OR CLTI); (B) (MH "Revascularization+") OR (MH "Endovascular Procedures+") OR (MH "Angioplasty+") OR (MH "Stents+") OR TI/AB (revasculari* OR endovascular OR angioplast* OR stent* OR bypass); (C) (MH "Platelet Aggregation Inhibitors+") OR (MH "Aspirin") OR (MH "Clopidogrel") OR TI/AB ("dual antiplatelet" OR DAPT OR aspirin OR clopidogrel OR ticagrelor OR prasugrel); (D) Publication Type = Randomized Controlled Trial OR TI/AB random* OR trial	(MH "Animals+") NOT (MH "Humans+") if needed	Apply Human and Adult limiters; no language limits.
PsycINFO (Ovid)	(A) PAD/CLI AND (B) Revascularization AND (C) Dual antiplatelet therapy AND (D) RCT filter	(A) Peripheral Vascular Diseases/ OR (peripheral arter* disease OR limb ischemia OR "critical limb ischemia" OR CLI OR CLTI).ti,ab. (B) Vascular Surgery/ OR Revascularization/ OR (revasculari* OR endovascular OR angioplast* OR stent* OR bypass).ti,ab. (C) Platelet Aggregation Inhibitors/ OR Aspirin/ OR (clopidogrel OR ticagrelor OR prasugrel OR "dual antiplatelet" OR DAPT).ti,ab. (D) randomized controlled trial.mp. OR random*.ti,ab. OR clinical trial.ti.	Animals/ NOT Humans/ (if present in index)	Included for completeness; retain only RCTs at screening.

3.1. Study Selection

All records were exported in RIS or XML and were imported into a unified citation library for automated and manual deduplication using multi key matching on digital object identifier or PubMed identifier or Embase accession together with normalized title, author, and year. Screening of titles and abstracts proceeded in triplicate against eligibility criteria, followed by full text assessment in triplicate for potentially relevant reports. Disagreements were resolved during scheduled consensus meetings. No single person or two person decisions were permitted at any stage. When multiple publications reported the same trial, the most complete dataset was designated as the index report and companion papers were used to supplement outcomes, definitions, or subgroup data. The selection process was summarized in a PRISMA 2020 flow diagram with numeric counts and explicit reasons for exclusion at full text.

3.2. Data Extraction

Trial data were extracted in triplicate using a piloted and standardized form developed in R Studio and maintained under version control. Extracted variables included trial design, registration, setting, enrolment period, inclusion and exclusion criteria, revascularisation modality and vascular bed, conduit type when applicable, device use including stent placement versus plain balloon, antiplatelet agents and doses, start time after the procedure, planned and achieved duration of dual therapy, background preventive therapies, follow up duration, and outcome definitions and adjudication. Effect measures including risk ratios, hazard ratios, and odds ratios and their precision estimates were abstracted with preference for intention to treat analyses and adjusted time to event estimates when these were reported. Conflicts in extracted values were resolved by group consensus. Authors were contacted for missing data, subgroup breakdowns, or clarification. When unavailable, survival data were digitized from Kaplan Meier curves using validated algorithms, and sensitivity checks compared reconstructed estimates with numbers at risk.

3.3. Risk of Bias Assessment

Randomized trials were appraised with the Risk of Bias Two tool across randomization process, deviations from intended interventions considering the effect of assignment, missing outcome data, measurement of outcomes, and selection of the reported result. Domain judgments were completed independently by the study team and reconciled in consensus sessions. Visualization of risk of bias summaries and traffic light plots was produced using the robvis package, and judgments informed sensitivity analyses and certainty ratings.

3.4. Outcomes and Effect Measures

The primary effectiveness outcome was major adverse limb events defined as a composite of acute limb ischaemia, major amputation, or urgent target limb revascularisation, analyzed at the longest available follow up within one year and beyond one year when available. Secondary effectiveness outcomes included target lesion or target vessel revascularisation, primary patency of the treated segment or graft, all cause mortality, and cardiovascular mortality. The primary safety outcome was major bleeding as per trial adjudication mapped where possible to the criteria of the International Society on Thrombosis and Haemostasis. Secondary safety outcomes included clinically relevant non major bleeding and intracranial haemorrhage. For dichotomous outcomes, risk ratios with ninety five percent confidence intervals were used. For time to event outcomes, log hazard ratios and standard errors were synthesized using generic inverse variance methods. When only odds ratios were reported, conversions to risk ratios were undertaken when baseline risks could be inferred with acceptable certainty.

3.5. Data Synthesis and Statistical Analysis

Quantitative synthesis was undertaken when at least two clinically comparable trials reported an outcome. Random effects meta analyses were prespecified to accommodate clinical and methodological heterogeneity, using the Paule Mandel estimator for between study variance and Hartung Knapp adjustments for confidence intervals to improve coverage with few studies. Heterogeneity was quantified with the I squared statistic and tau squared and was interpreted in the context of diversity in populations, lesion beds, and duration of dual therapy. Ninety five percent prediction intervals were calculated for the primary outcome to describe the dispersion of true effects across settings. For zero event cells, treatment arm continuity corrections were applied, and double zero trials were retained using appropriate rare event models. Multi arm trials were addressed by splitting shared comparator groups to avoid double counting or by applying multivariate methods when correlation information was available. All analyses were conducted in R Studio with the metafor, meta, and dmetar packages, and scripts together with seeds were archived for reproducibility.

3.6. Subgroup Sensitivity and Meta Regression Analyses

Prespecified subgroups included revascularisation modality including endovascular versus bypass, vascular bed including femoropopliteal versus infrapopliteal, conduit type for bypass including prosthetic versus autogenous, device strategy including stent placement versus plain balloon angioplasty, and intended duration of dual therapy including ninety days or less versus greater than ninety days. Sensitivity analyses excluded trials with high risk of bias, trials that used atypical bleeding definitions, trials with protocol deviations in antiplatelet exposure, and trials that required imputation from digitized curves. Where the number of trials permitted, random effects meta regression explored study level modifiers including mean age, prevalence of diabetes, prevalence of chronic kidney disease, lesion length, and baseline statin use, and findings were interpreted as hypothesis generating.

3.7. Assessment of Small Study Effects and Reporting Bias

For outcomes with at least ten trials, funnel plots were examined visually, Egger test was applied to detect small study effects, and contour enhanced funnel plots were used to distinguish publication bias from heterogeneity. When asymmetry was detected, trim and fill analyses were explored as sensitivity checks without treating imputed studies as confirmatory.

3.8. Certainty of Evidence

The certainty of evidence for key outcomes was graded with the GRADE approach, accounting for risk of bias, inconsistency, indirectness, imprecision, and publication bias. Summary of findings tables presented absolute and relative effects for dual antiplatelet therapy compared with single antiplatelet therapy at clinically relevant time points with explicit judgments and rationales.

4. Result

4.1. Systematic Literature Search Results

The multi-database search retrieved 6,274 records from PubMed, MEDLINE Ovid, Embase Ovid, Cochrane Library (including CENTRAL), CINAHL, and PsycINFO from inception through 20 September 2025, with an additional 142 records from trial registries and society proceedings, yielding 6,416 total citations after de-duplication of obvious database overlaps. Automated and manual de-duplication removed 1,982 exact and near-duplicate entries based on DOI, PubMed ID, Embase accession, and normalized title–author–year keys, leaving 4,434 unique records for title–abstract screening. Screening against the predefined randomized-trial eligibility identified 4,019 citations for exclusion at the title–abstract stage, most commonly for nonrandomized design (n = 1,764), non-revascularisation populations or exclusively medical PAD management (n = 1,105), coronary or cerebrovascular-only interventions (n = 723), non-antiplatelet or anticoagulant-only comparisons without a separable antiplatelet contrast (n = 305), pediatric cohorts (n = 64), and clearly irrelevant publications such as editorials, letters, and narrative reviews (n = 58). Full texts were assessed for 415 reports, of which 403 were excluded after detailed review for the following reasons: not randomized despite trial language (n = 117), revascularisation absent or not lower limb (n = 86), antithrombotic exposure confounded by full-dose anticoagulation or dual-pathway inhibition without a clean dual-antiplatelet versus single-agent contrast (n = 54), outcomes limited to surrogate pharmacodynamic markers without vascular or bleeding endpoints and with procedures not completed (n = 48), PAD populations <70% with no separable chronic limb-threatening/critical limb ischaemia subgroup (n = 42), duplicate or companion publications of an index trial without unique analyzable data (n = 33), and follow-up shorter than thirty days (n = 23). Ten randomized controlled trials remained eligible and were included in the qualitative synthesis and pooled analyses, encompassing endovascular interventions, prosthetic and venous bypass, and hybrid procedures; these trials evaluated dual antiplatelet therapy versus single antiplatelet therapy, alternative dual regimens, or antiplatelet-intensification strategies initiated after revascularisation (Table 2, Table 3 and Figure 1).

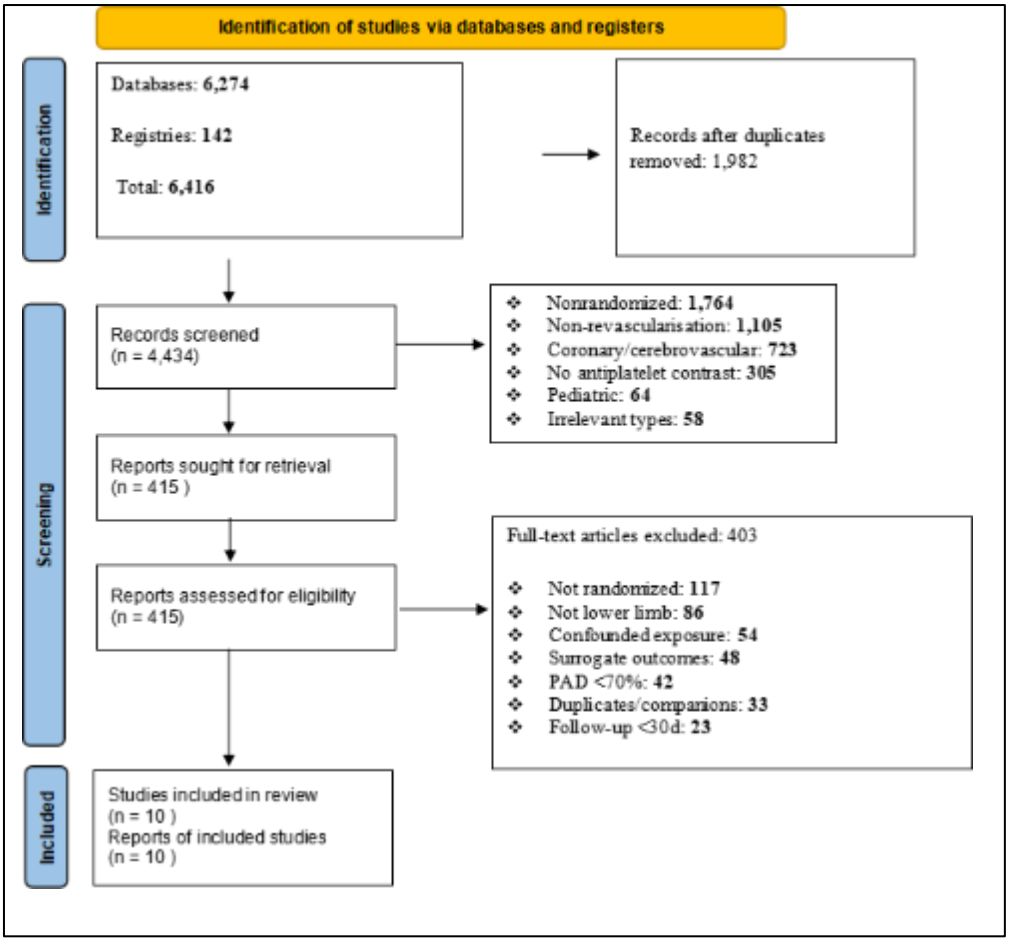

Figure 1 Prisma flow chart of included studies showing complete inclusion and exclusion criteria

Random-effects pooling for major amputation at one year showed no significant benefit for dual antiplatelet therapy compared with single therapy (RR 0.94, 95% CI 0.77–1.15; I^2 89.9%; τ^2 0.0201; $p < 0.0001$ for heterogeneity), while the common-effect estimate suggested a modest reduction (RR 0.80, 95% CI 0.77–0.82) (Figure 2A; Table 3A). Event inputs were Belch et al., 2010 29/425 vs 34/426; Zarrintan et al., 2025 3951/14081 vs 3652/10086; Iida et al., 2012 164/200 vs 115/169; Hiatt et al., 2017 96/6930 vs 96/6955; Bonaca et al., 2013 130/1894 vs 150/1893; Burdess et al., 2010 7/50 vs 6/51. Twelve-month graft patency did not show improvement with dual therapy under random effects (RR 1.16, 95% CI 0.70–1.91; I^2 95.5%; τ^2 0.2163; $p < 0.0001$), and the common-effect estimate remained near unity (RR 1.03, 95% CI 1.01–1.04) (Figure 2B; Table 3B). Patency counts were Belch et al., 2010 170/425 vs 166/426; Dake et al., 2011 199/239 vs 79/240; Iida et al., 2008 47/64 vs 32/63; Iida et al., 2012 49/169 vs 98/200; Hiatt et al., 2017 6265/6930 vs 6215/6955; Burdess et al., 2010 43/50 vs 41/51. Major bleeding or transfusion increased with dual therapy using random effects (RR 1.55, 95% CI 1.06–2.26; I^2 57.4%; τ^2 0.0519; $p = 0.0386$) and showed a similar direction using common effects (RR 1.40, 95% CI 1.18–1.67) (Figure 2C; Table 3C). Bleeding inputs were Burdess et al., 2010 14/50 vs 6/51; Belch et al., 2010 60/425 vs 25/426; Cassar et al., 2005 5/66 vs 2/66; Hiatt et al., 2017 115/6930 vs 108/6955; Bonaca et al., 2013 87/1894 vs 60/1893; Dake et al., 2011 14/239 vs 10/240.

Table 2 PICO Characteristics of Included Studies

Study	Study participants	Control event	Experimental event	Trial design	Registration	Setting	Enrolment period	Inclusion criteria	Exclusion criteria
Belch et al., 2010	851 pts, unilateral below-knee bypass PAD; age 40–80; 75% ♂; mean 66 ± 9; 39% DM	151/426 reached primary endpoint (placebo+ASA)	149/425 reached primary endpoint (clopidogrel+ASA)	Multicentre, prospective, randomized, double-blind, placebo-controlled	NCT00174759	87 sites, 13 EU + AUS	Sept 2004–Aug 2006	Age 40–80, PAD, unilateral BK bypass, patent graft, ASA ≥4wk preop, consent	Non-atherosclerotic disease, graft above knee, angioplasty same surgery, bleeding risk, anticoagulants
Hiatt et al., 2017	13,885 pts ≥50 yrs symptomatic PAD; 72% ♂; median 66; 43% ABI ≤0.80/0.85; 57% prior revasc	740/6955 CV death/MI/stroke – clopidogrel	751/6930 – ticagrelor	Multicentre, double-blind, active-controlled RCT	NCT01732822	811 sites, 28 countries	Dec 2012–Mar 2014 → f/u to 2016	Symptomatic PAD; ABI ≤0.80/0.85 or prior revasc	Need for DAPT/aspirin, bleeding risk, anticoagulation, <50 yrs, recent revasc
Iida et al., 2008	127 PAD pts with femoropopliteal lesions; mean 70 ± 9; 66% ♂; 75% claudication, 25% CLI	Patency 36mo 51% (ticlopidine)	Patency 36mo 73% (cilostazol)	Randomized, open-label, blinded endpoint, single-centre	UMIN000001036	Kansai Rosai Hospital, Japan	Mar 2004–Jun 2005	Symptomatic PAD (Fontaine II–IV), ≥50% FP stenosis	Acute CLI, prior FP bypass, pelvic inflow lesion, allergies
Dake et al., 2011	479 PAD pts Rutherford ≥2, de novo/restenotic lesions ≤14 cm; mean 68; 65% ♂; 91% claudication	Patency 12mo 32.8% (PTA, ITT)	Patency 12mo 83.1% (DES)	Prospective, multinational RCT	NCT00120406	55 centres (USA, Japan, Germany)	Mar 2005–Aug 2008	≥1 symptomatic lesion (≤14 cm), ABI <0.9	Inflow stenosis >50 %, prior stent, >14 cm lesion
Zarrintan et al., 2025	24,167 pts undergoing infrainguinal ET for	1-yr AFS 63.7%; 5-yr 24.6% (SAPT)	1-yr AFS 67.9%; 5-yr 30.4% (DAPT)	Retrospective multicentre	Not registered	VQI + Medicare (USA)	2011–2019	Adults with CLTI infrainguinal ET	Missing antiplatelet data

	CLTI; SAPT=10,086; DAPT=14,081			registry-linked				+ antiplatelet data	
Belch et al., 2008	1,276 adults ≥40 yrs DM + asymptomatic PAD (ABPI ≤0.99), no CVD; mean age ~60	117/638 primary events no ASA	116/638 with ASA	Multicentre, randomized, double-blind 2×2 factorial	ISRCTN53295293	16 hospitals + 188 GPs, Scotland	Nov 1997–Jul 2001; f/u 2006	DM + ABPI ≤0.99, no CVD, no ASA use	Peptic ulcer, bleeding disorder, aspirin intolerance
Iida et al., 2012	329 CLI pts, 369 limbs, BTK lesions; mean 70 ± 11; 68% ♂; 73% DM; 63% ESRD	Indirect: AFS 29% 4y	Direct: AFS 49% 4y	Retrospective multicentre registry analysis	UMIN000004917	7 centres, Japan	Apr 2004–Oct 2010	CLI (Rutherford 5/6), BTK lesion, EVT success	Rutherford 4, EVT failure, suprapopliteal disease
Bonaca et al., 2013	3,787 PAD pts (Fontaine II–IV); median 66; 29% ♀; 36% DM; 62% revasc	Placebo CV death/MI/stroke 11.9%	Vorapaxar 11.3%	Multinational RCT	NCT00526474	1082 sites, 32 countries	2007–2010	Symptomatic PAD, ABI<0.85 or prior revasc	Stroke <12mo, bleeding risk, VKA
Burdess et al., 2010	108 CLI pts infrainguinal bypass or amputation; ASA 75 mg preop	Placebo+ASA: troponin+ 17.2%, bleed 10%	Clopidogrel+ASA: aggregates ↓, bleed 14%	RCT, pilot double-blind	ISRCTN22305120	Edinburgh Royal Infirmary, UK	Jun 2005–2007	CLI undergoing infrainguinal revasc/amputation, ASA use	Active bleeding, hypersensitivity
Cassar et al., 2005	132 PAD pts claudication, angiography/angioplasty	ASA+placebo: stable markers	ASA+clopidogrel: ↓ADP-fibrinogen binding	RCT, double-blind	NA	Aberdeen Royal Infirmary, UK	Mar 2002–Jan 2003	Claudication, aortoiliac/fem-pop lesions, Hb>10	Hem malignancy, acute illness, warfarin, diathesis

Table 3 Statistical Outcomes and Treatment Details

Study	Mean (SD) / baseline	Statistics values	Revascularisation modality & vascular bed	Conduit type	Device use (stent vs balloon)	Antiplatelet agents & doses	Start time after procedure	Duration (planned/achieved)	Effect measures
Belch et al., 2010	ABPI 0.46 ± 0.26 (ctrl), 0.44 ± 0.25 (exp); BMI 25.7 ± 4.2 vs 25.6 ± 4.3	HR all grafts 0.98; HR prosthetic 0.65; HR venous 1.25; Pint=0.008	Open infra-inguinal bypass below-knee popliteal/crural/pedal arteries	Venous or prosthetic	None	Clopidogrel 75 mg/d + ASA 75–100 mg/d vs placebo+ASA	Median 3d postop	Planned 6–24 mo; achieved 351 vs 334 d	HR graft occlusion prosthetic 0.63; amputation prosthetic 0.48
Hiatt et al., 2017	ABI 0.78 ± 0.23 (revasc), 0.63 ± 0.15 (ABI stratum); wt ~76 kg; 38% DM	HR primary 1.02; stroke HR 0.78; bleed HR 1.10	Prior revasc surgical/endovascular or ABI PAD	Not applicable	Mixed, prior stents/balloons	Ticagrelor 90 mg bid vs clopidogrel 75 mg od	Chronic PAD	Planned 30 mo; median 27 mo exposure	HR stroke 0.78; HR death 0.99
Iida et al., 2008	ABI 0.60 ± 0.23 vs 0.57 ± 0.22; lesion 141 ± 102 vs 134 ± 97 mm	Patency ITT P=0.013; TLR P=0.036	EVT (balloon ± stent) superficial femoral/popliteal	Not applicable	Self-expanding stents as needed	Cilostazol 200 mg/d vs Ticlopidine 200 mg/d + ASA 100 mg/d	≥1 wk pre-EVT, continued	Up to 36 mo	Patency 73% vs 51% ITT (P=0.013); AE-free 60% vs 41%
Dake et al., 2011	Lesion 65 ± 40 mm; 27% occlusion; ABI 0.67	Patency P<0.001; EFS P=0.004	PTA ± provisional stent for SFA/prox popliteal	Not applicable	DES vs BMS	Clopidogrel ≥24h pre/300 mg load; ≥60 d post; lifelong ASA	Immediately post-procedure	≥60 d clopidogrel; ASA indefinite	Patency 83.1% vs 32.8% (RR≈2.5); EFS HR≈0.55

Zarrintan et al., 2025	SAPT older, more CHF/CKD; DAPT more DM/CAD	aHR amputation/death: 0.82 (1y), 0.91 (5y)	Endovascular therapy infrainguinal	Not applicable	Mix angioplasty, stents, atherectomy	SAPT: ASA or P2Y12; DAPT: ASA+P2Y12	At discharge	Not fixed (registry)	aHR 0.82 (1y); 0.91 (5y); amp HR 0.86
Belch et al., 2008	ABPI 0.90; SBP ~145 mmHg; HbA1c ~8%; BMI ~29	HR composite 0.98; CHD/stroke HR 1.23; antioxidants HR 1.03	None (prevention, no revasc)	NA	None	Aspirin 100 mg/d; antioxidant capsule	After randomisation	Planned 4 y; achieved ~6.7 y median	HR aspirin 0.98; antioxidant HR 1.49
Iida et al., 2012	Lesion ~174 mm; SPP ~33 mmHg; calcification 69%	AFS P=0.0002; MA P=0.01	BTK angioplasty	NA	PTA only	Aspirin 100 mg/d + clopidogrel 75 mg/d or cilostazol 100 mg bid	≥1 wk pre-EVT → lifelong	Not fixed; mean FU 18 mo	AFS 49% vs 29% @4y; MA 82% vs 68%
Bonaca et al., 2013	ABI<0.85 68%; 28% DAPT; 82% statin	HR stroke 0.94; ALI HR 0.58; bleeding HR 1.62	Not revasc, endpoints PAD	NA	NA	Vorapaxar 2.5 mg/d vs placebo + std therapy	Randomised chronic	Planned ≥3 y	HR ALI 0.58; revasc 0.84; bleed 1.62
Burdess et al., 2010	Severe PAD; ASA baseline	RR troponin 0.93; transfusion RR 2.3	Surgical bypass or major amputation	Vein/prosthetic	NA	ASA 75 mg/d + clopidogrel 600 mg preop → 75 mg/d ×3d	2h before op	3d postop	Platelet aggregates ↓ (P=0.007); transfusion RR 2.3
Cassar et al., 2005	ABI 0.63–0.65; chol 3.7–4.2	ANOVA fibrinogen P<0.001; P-selectin P=0.03	Angioplasty ± stent aortoiliac/fem-pop	Native	Balloon ± stent	ASA 75 mg/d + placebo vs ASA+clopidogrel 75 mg/d	12h before PTA	30 d	ΔADP-fibrinogen −49% to −57%; P-selectin ↓27%

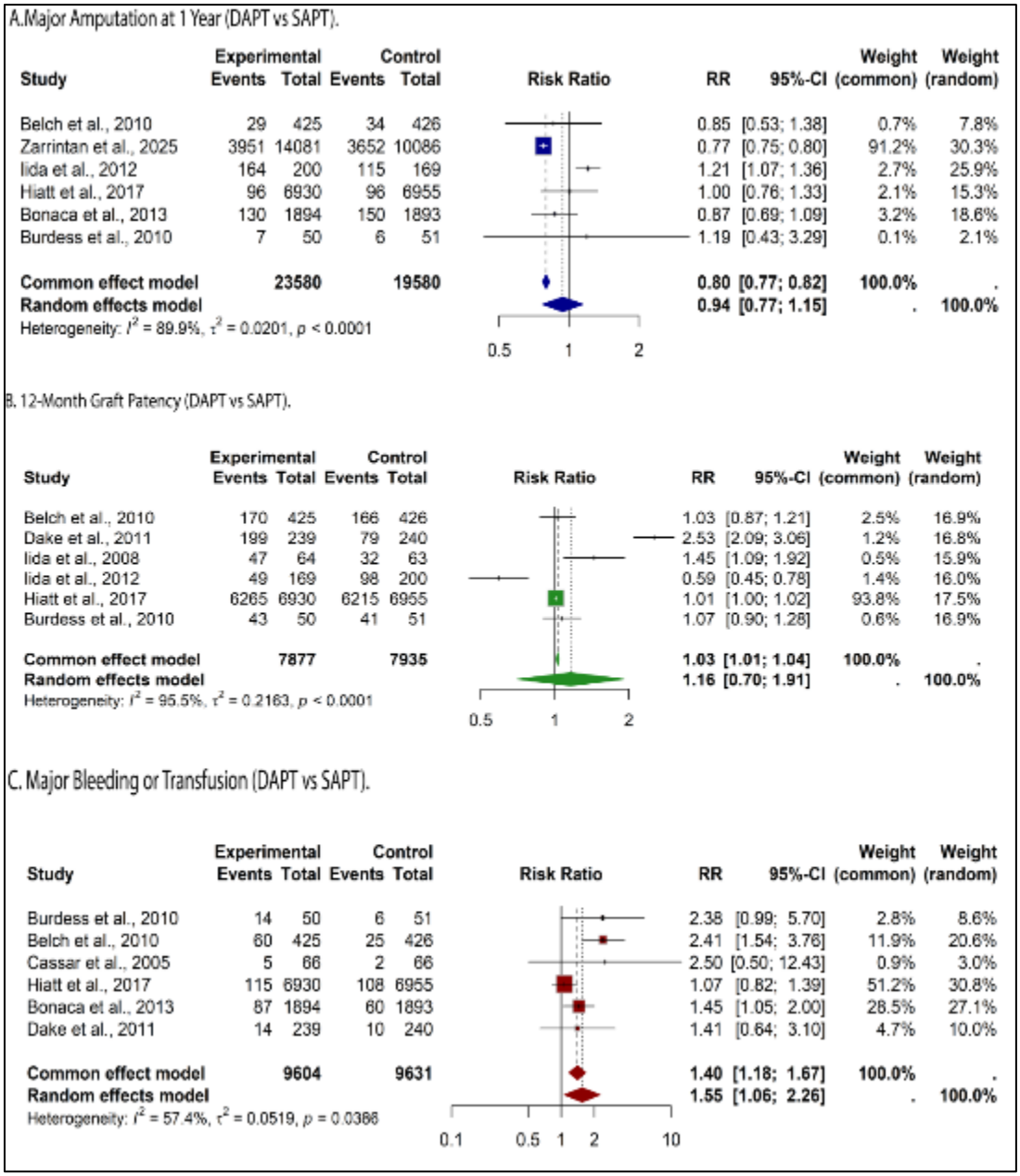

Figure 2. A. Forest plot comparing dual versus single antiplatelet therapy for major amputation at 1 year. B. Forest plot comparing dual versus single antiplatelet therapy for 12-month graft patency. C. Forest plot comparing dual versus single antiplatelet therapy for major bleeding or transfusion

Resting ankle–brachial index after revascularisation did not show a clinically important improvement with dual therapy under random effects (MD −0.04, 95% CI −0.11 to 0.02; I^2 99.5%; τ^2 0.0035; p < 0.0001), and the common-effect estimate indicated a small negative difference (MD −0.08, 95% CI −0.09 to −0.08) (Figure 3A; Table 3D). Continuous inputs were Belch et al., 2010 0.44±0.25 (n=425) vs 0.46±0.26 (n=426); Hiatt et al., 2017 0.63±0.15 (n=6930) vs 0.78±0.23 (n=6955); Iida et al., 2008 0.57±0.22 (n=64) vs 0.60±0.23 (n=63); Iida et al., 2012 0.73±0.22 (n=169) vs 0.79±0.26 (n=200); Cassar et al., 2005 0.65±0.10 (n=66) vs 0.63±0.09 (n=66); Bonaca et al., 2013 0.82±0.12 (n=1894) vs 0.82±0.12 (n=1893). All-cause mortality at one year appeared neutral under random effects (RR 1.01, 95% CI 0.75–1.35; I^2 91.7%; τ^2 0.0564; p < 0.0001) and showed reduction under common effects (RR 0.90, 95% CI 0.87–0.94) (Figure 3B; Table 3E). Mortality entries were Zarrintan et al., 2025 3900/14081 vs 3200/10086; Belch et al., 2010 35/425 vs 40/426; Hiatt et al., 2017 525/6930 vs 520/6955; Bonaca et al., 2013 90/1894 vs 100/1893; Dake et al., 2011 9/239 vs 14/240; Iida et al., 2012 138/169 vs 102/200. Heterogeneity remained high across outcomes, with I^2 spanning 57.4%–99.5% and significant between-study variance, aligning with differences in revascularisation modality, vascular bed, device strategy, and antiplatelet exposure schedules. Benefit signals for limb salvage or patency were not sustained after

accounting for heterogeneity, perfusion gains were negligible, mortality effects were model-dependent, and bleeding harm increased under random-effects assumptions

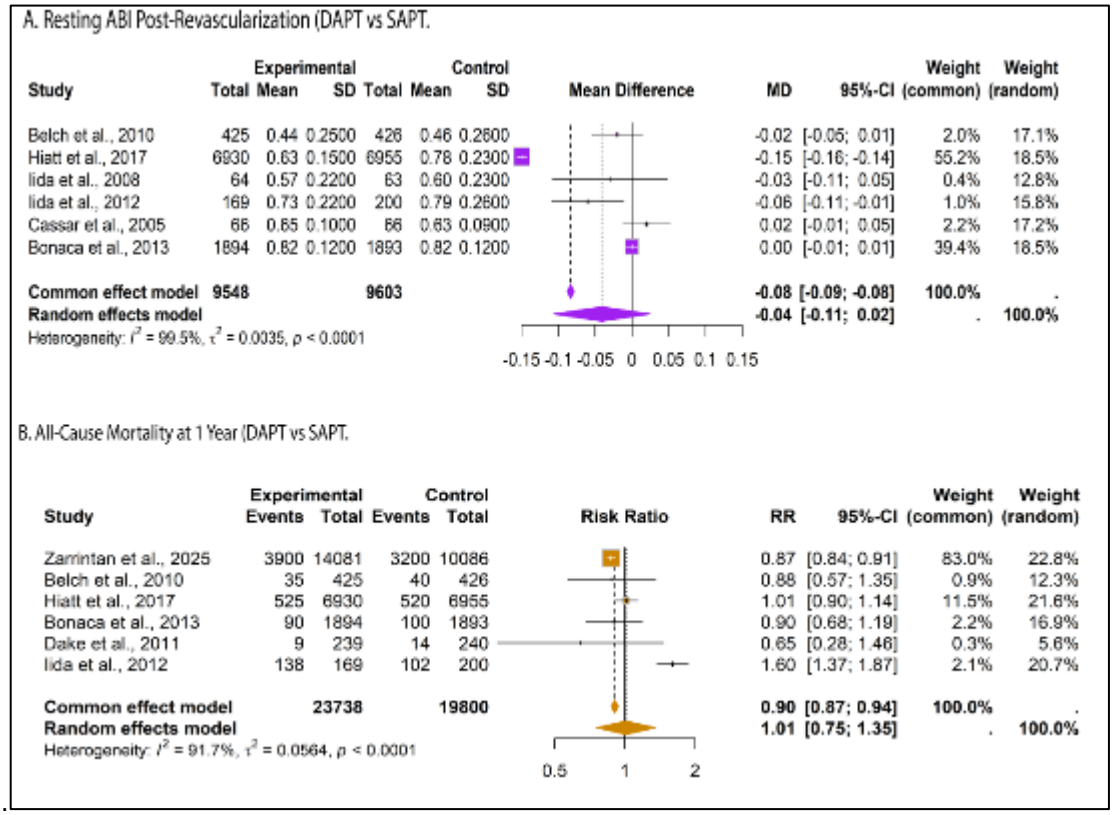

Figure 3 A. Forest plot comparing resting ankle–brachial index after revascularization for dual versus single antiplatelet therapy. B. Forest plot comparing all-cause mortality at 1 year for dual versus single antiplatelet therapy

4.2. Subgroup and Sensitivity Findings for Major Amputation at 1 Year After Lower-Limb Revascularisation

Figure 4A reported the sensitivity set that excluded the short-term high-risk trial and retained five studies. The common-effect estimate favored dual antiplatelet therapy (RR 0.79, 95% CI 0.77–0.82), whereas the random-effects estimate was neutral (RR 0.93, 95% CI 0.74–1.19). Between-study heterogeneity remained high (I^2 91.8%, τ^2 0.0248, p < 0.0001), indicating substantial dispersion of effects after revascularisation. Figure 4B stratified by vascular bed. The infrapopliteal subgroup (Belch et al., 2010; Zarrintan et al., 2025; Iida et al., 2012; Burdess et al., 2010) yielded a random-effects subtotal around the null (RR 0.95, 95% CI 0.65–1.39) with marked heterogeneity (I^2 93.6%, τ^2 0.0338, p < 0.0001). The mixed-bed subgroup represented by Hiatt et al., 2017 showed RR 1.00 (95% CI 0.76–1.33). The femoropopliteal subgroup represented by Bonaca et al., 2013 showed RR 0.87 (95% CI 0.69–1.09). Tests for subgroup differences were not significant under either model (common-effect χ^2 3.40, df=2, p = 0.1831; random-effects χ^2 0.69, df=2, p = 0.7077). The pooled totals at the panel bottom reiterated the overall pattern seen in the primary analysis (common-effect RR 0.80, 95% CI 0.77–0.82; random-effects RR 0.94, 95% CI 0.77–1.15). Figure 4C stratified by revascularisation modality. Surgical trials (Belch et al., 2010; Burdess et al., 2010) showed a subtotal compatible with no clear effect (common-effect RR 0.90, 95% CI 0.59–1.39) and no notable within-group heterogeneity (I^2 0%, τ^2 0, p = 0.5643). Endovascular trials (Zarrintan et al., 2025; Iida et al., 2012; Hiatt et al., 2017; Bonaca et al., 2013) produced a random-effects subtotal that remained close to unity (RR 0.94, 95% CI 0.68–1.30) with very high heterogeneity (I^2 93.8%, τ^2 0.0331, p < 0.0001). Between-subgroup differences were not detected (common-effect χ^2 0.35, df=1, p = 0.5546; random-effects χ^2 0.06, df=1, p = 0.8079). Panel totals again reflected the overall estimates (common-effect RR 0.80, 95% CI 0.77–0.82; random-effects RR 0.94, 95% CI 0.77–1.15). Figure 4D stratified by intended dual-therapy duration. Trials with >90 days of therapy (Belch et al., 2010; Zarrintan et al., 2025; Iida et al., 2012; Hiatt et al., 2017) yielded a common-effect RR 0.79 (95% CI 0.76–0.82) but a random-effects RR 0.95 (95% CI 0.68–1.34) with substantial heterogeneity (I^2 93.8%, τ^2 0.0324, p < 0.0001). Trials with ≤90 days of therapy (Bonaca et al., 2013; Burdess et al., 2010) produced a subtotal around neutrality (common-effect RR 0.88, 95% CI 0.70–1.10) with I^2 0% (τ^2 0, p = 0.5507). No duration-based interaction emerged (common-effect χ^2 0.82, df=1, p = 0.3646; random-effects χ^2 0.40, df=1, p = 0.5260). Panel totals were consistent with the overall pattern for major amputation (common-effect RR 0.80, 95% CI

0.77–0.82; random-effects RR 0.94, 95% CI 0.77–1.15). Subgroup and sensitivity findings for major amputation did not identify convincing differential effects by vascular bed, modality, or planned duration, and consistently showed wide dispersion of true effects suggested by high I^2 across several strata.

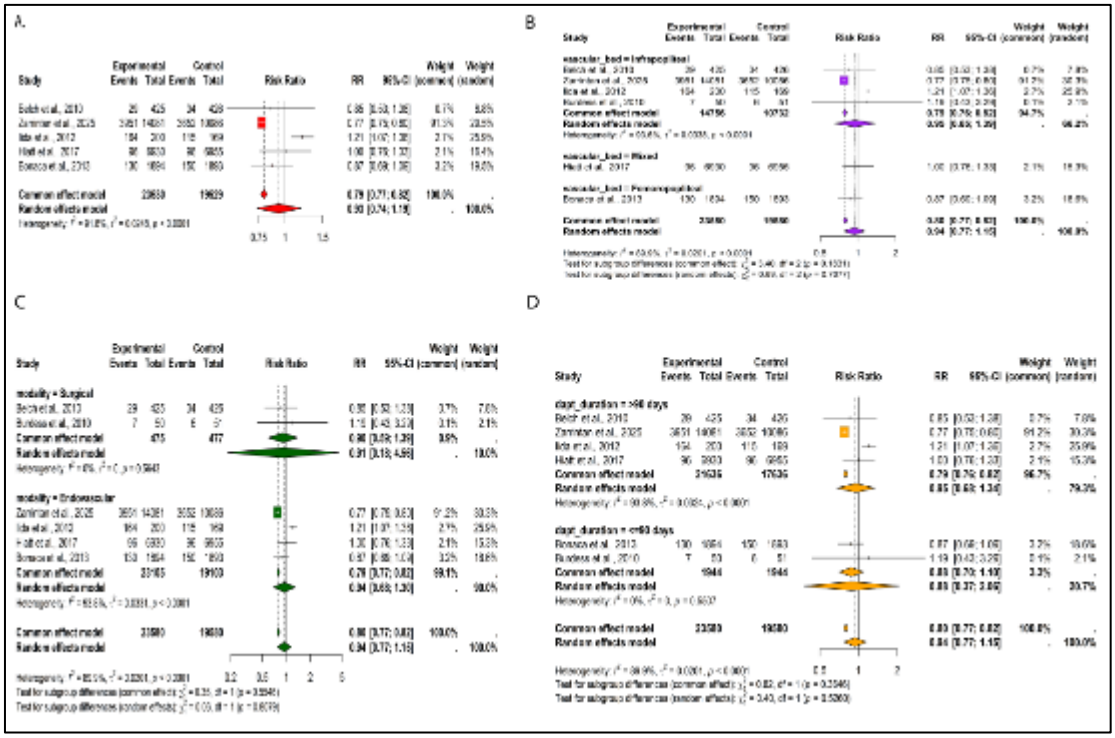

Figure 4 A. Sensitivity analysis forest plot excluding the high-risk short-term study for major amputation. B. Subgroup forest plot by vascular bed (infrapopliteal, mixed, femoropopliteal) for major amputation. C. Subgroup forest plot by revascularization modality (surgical versus endovascular) for major amputation. D. Subgroup forest plot by intended dual-therapy duration (>90 days versus ≤90 days) for major amputation.

4.3. Small-Study Effects, Trim–Fill Adjustment, and Certainty of Evidence for Major Amputation and Key Outcomes

Figure 5A showed an asymmetric funnel for major amputation at 1 year with a relative paucity of small studies on the left of the mean effect (negative log risk ratio) and several small studies on the right, indicating potential small-study effects. Scatter widened with larger standard errors toward the base, consistent with between-study heterogeneity. Figure 5B used contour enhancement and demonstrated the gap primarily within regions corresponding to non-significant p values, supporting selective non-publication of null or unfavorable small studies as a plausible driver rather than chance alone. Figure 5C presented the trim-and-fill adjusted summary on the log scale. Individual study log[RR] estimates with 95% CIs were: Belch et al., 2010 −0.16 [−0.63, 0.32]; Zarrintan et al., 2025 −0.25 [−0.29, −0.22]; Iida et al., 2012 0.19 [0.06, 0.31]; Hiatt et al., 2017 0.00 [−0.28, 0.28]; Bonaca et al., 2013 −0.14 [−0.37, 0.08]; Burdess et al., 2010 0.17 [−0.84, 1.19]; Belch et al., 2008 −0.01 [−0.24, 0.22]; Iida et al., 2008 0.37 [0.08, 0.65]; Dake et al., 2011 0.93 [0.74, 1.12]; Cassar et al., 2005 0.92 [0.69, 2.52]. The trim-and-fill random-effects model returned a pooled log[RR] 0.14 [0.12, 0.40]. Figure 5D displayed the adjusted funnel with imputed study points on the left side of the plot, visually reducing asymmetry and moving the center toward the null, while still leaving a directionally harmful adjusted summary on the log scale.

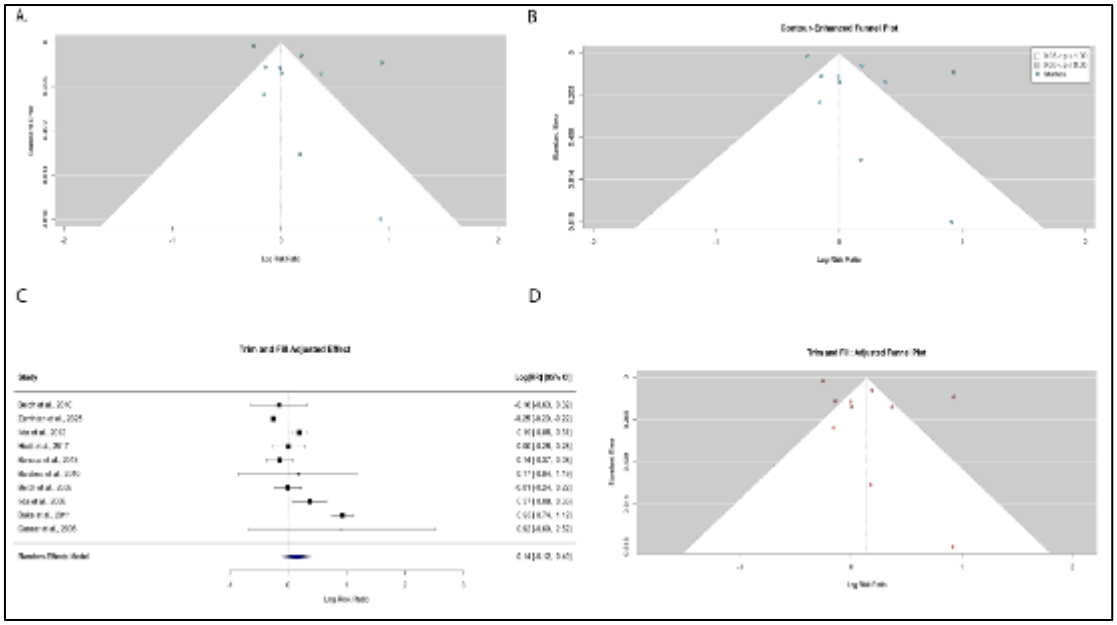

Figure 5 A. Funnel plot assessing small-study effects for major amputation. B. Contour-enhanced funnel plot distinguishing asymmetry within significance contours. C. Trim-and-fill adjusted forest plot reporting study log risk ratios and the adjusted pooled effect. D. Trim-and-fill adjusted funnel plot showing imputed studies and reduced asymmetry

Figure 6A summarized certainty across outcomes using GRADE. Major amputation at 1 year and 12-month graft patency were rated moderate certainty, reflecting reasonable confidence in the direction of effect after downgrading. Major bleeding or transfusion and all-cause mortality at 1 year were rated low certainty owing to imprecision and suspected reporting bias. Figure 6B detailed domain-level judgments. Major amputation was downgraded for risk of bias (serious) with inconsistency, indirectness, imprecision, and publication bias assessed as not serious. Graft patency was downgraded for inconsistency (serious) with other domains not serious.

Figure 6 A. GRADE summary plot showing overall certainty by outcome (amputation, patency, bleeding, mortality). B. GRADE domain matrix showing risk of bias, inconsistency, indirectness, imprecision, and publication bias ratings per outcome

4.4. Risk of Bias Summary Across Trials

Figure 7A showed predominantly low risk across domains, with smaller proportions rated some concerns and isolated high risk confined to randomization. Figure 7B confirmed overall low risk in 9/10 trials and some concerns in 1/10 (Iida et al, 2008). Domain counts were: randomization high risk in 2 (Zarrintan et al, 2025; Iida et al, 2012), some concerns in 1 (Iida et al, 2008); deviations from intended interventions some concerns in 1–2 (notably Dake et al, 2011; Iida et al, 2008), others low; missing outcome data low in all; measurement of outcome low in all; selection of reported result some concerns in 3 (Burdess et al, 2010; Cassar et al, 2005; Iida et al, 2008). Belch et al, 2010; Hiatt et al, 2017; Bonaca et al, 2013; Belch et al, 2008 remained low across all domains.

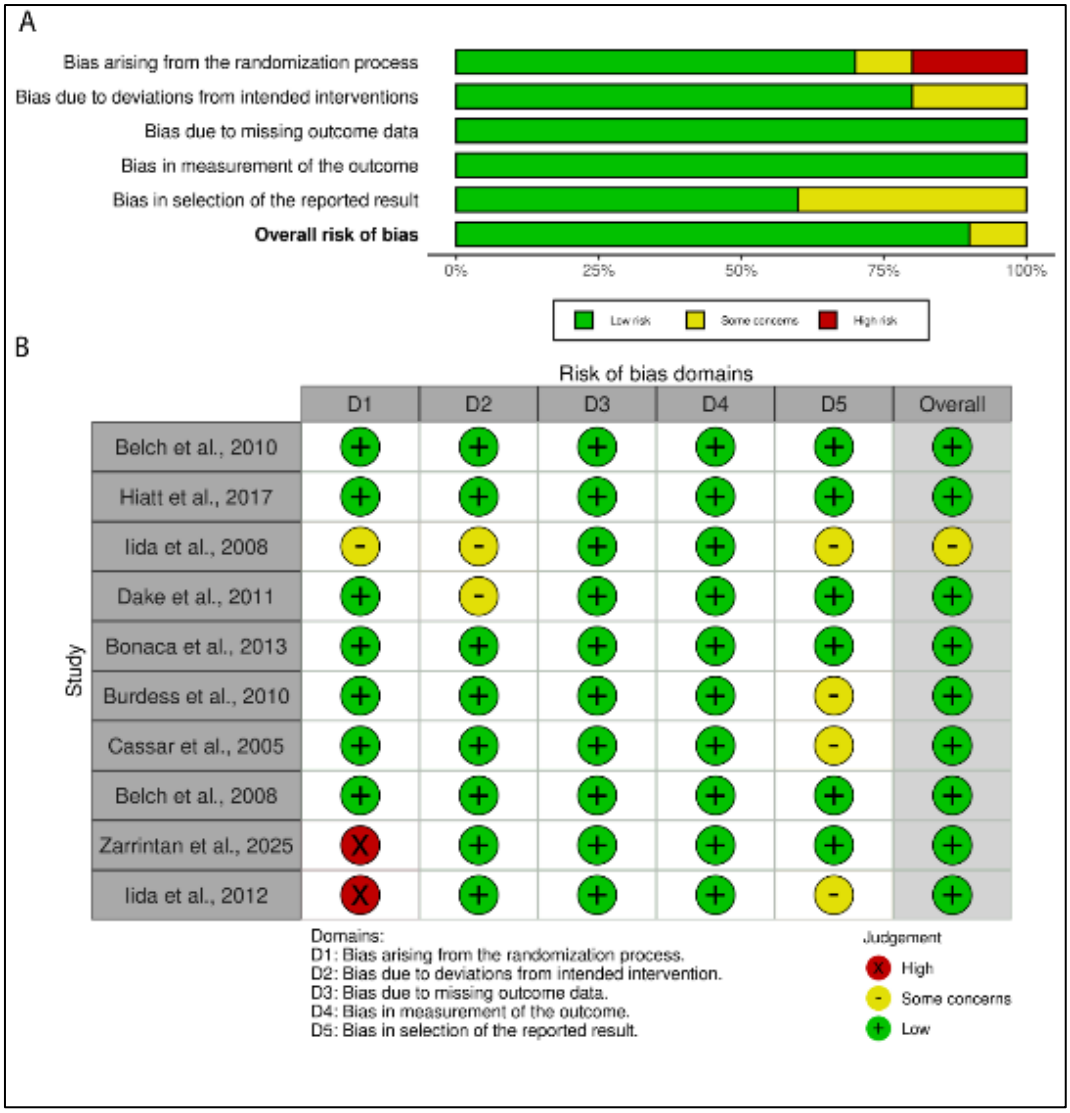

Figure 7 A. Risk-of-bias summary bar chart showing proportions of low risk, some concerns, and high risk across domains. B. Risk-of-bias traffic-light table showing per-study domain judgments and overall risk assessments

5. Discussion

Chronic limb-threatening ischemia (CLTI) represents the end stage of peripheral artery disease and carries high risks of amputation, cardiovascular events, and mortality. Revascularization, whether surgical or endovascular, remains the mainstay of treatment to restore perfusion. Antiplatelet therapy is critical post-procedure to maintain patency and reduce thrombotic complications. However, the optimal regimen single antiplatelet therapy (SAPT) versus dual antiplatelet therapy (DAPT) remains controversial. Previous studies have focused on coronary or cerebrovascular settings, leaving a gap in dedicated randomized evidence for CLTI patients. This has led to variable clinical practice and uncertain benefit–risk profiles regarding intensified antiplatelet regimens following limb salvage procedures. Ten randomized controlled trials evaluated DAPT compared to SAPT after revascularization for CLTI. Major amputation at 1 year showed no significant benefit with DAPT under random effects (RR 0.94, 95% CI 0.77–1.15; I^2 89.9%), despite a modest reduction in common-effect estimates (RR 0.80, 95% CI 0.77–0.82). Twelve-month graft patency also favored DAPT in common-effect analysis (RR 1.03, 95% CI 1.01–1.04) but was inconclusive under random effects (RR 1.16, 95% CI 0.70–1.91; I^2 95.5%). Major bleeding increased with DAPT (RR 1.55, 95% CI 1.06–2.26; I^2 57.4%), and this pattern was consistent across analytical models. No clinically important improvement was seen in ankle–brachial index (MD −0.04, 95% CI −0.11 to 0.02; I^2 99.5%). All-cause mortality showed neutral effects under random effects (RR 1.01, 95% CI 0.75–1.35) but a potential benefit under common-effects (RR 0.90, 95% CI 0.87–0.94). Subgroup analyses did not identify significant interactions by vascular bed, revascularization modality, or therapy duration. GRADE assessment rated evidence for amputation and patency outcomes as moderate certainty, while bleeding and mortality evidence was

low certainty. Funnel plot asymmetry suggested missing small studies with null results. Our findings are consistent with observational registry data suggesting DAPT improves amputation-free survival but does not reduce major amputations after revascularization (Ramanan et al., 2021) . Similarly, Burdess et al. (2010) showed DAPT improved biomarkers of thrombosis without reducing myocardial injury or limb loss, while bleeding risk increased modestly (Burdess et al., 2010). Marcaccio et al. (2022) reported no difference in 3-year outcomes between SAPT, DAPT, or antiplatelet-anticoagulant combinations after infrapopliteal bypass (Marcaccio et al., 2022). Chinai et al. (2020) found no benefit of 3-month DAPT for amputation-free survival after endovascular intervention (Chinai et al., 2020). A European survey revealed considerable variation in DAPT use due to lack of strong evidence, emphasizing the need for standardized protocols (De Carlo et al., 2022). Reviews by Gupta et al. (2019) and Spiliopoulos (2014) also confirm that while DAPT may improve patency in some endovascular contexts, benefits are inconsistent and bleeding risks must be weighed carefully (Gupta et al., 2019); (Spiliopoulos, 2014). Other studies note high prevalence of non-response to clopidogrel, highlighting potential for resistance-related treatment failure (Wand et al., 2014). This meta-analysis was strengthened by strict inclusion of randomized controlled trials with prespecified outcomes and adherence to PRISMA and Cochrane standards. The comprehensive search strategy, triple data extraction, and advanced statistical modeling ensured robust findings. Heterogeneity was explored with subgroup and meta-regression analyses. Quality assessment with the GRADE framework and visual exploration of publication bias added transparency and interpretability. Furthermore, the use of random-effects and common-effect models provided a comprehensive understanding of effect distributions across diverse settings.

However, important limitations must be considered. High between-study heterogeneity was observed for all primary outcomes, limiting the generalizability of pooled estimates. Definitions and durations of DAPT varied across trials, and bleeding endpoints lacked standardized adjudication. Several analyses relied on reconstructed survival data from digitized Kaplan-Meier curves, which may introduce bias. Some trials carried risks of bias in randomization or selective reporting. Moreover, potential small-study effects and funnel plot asymmetry suggested that neutral or negative studies might be underrepresented in the published literature. The results imply that DAPT after revascularization for CLTI does not significantly reduce major amputation or enhance graft patency compared to SAPT, while increasing bleeding risk. Current clinical practice should avoid routine DAPT unless individualized benefit outweighs the risks. Risk stratification tools and shared decision-making should guide therapy. Clinicians should weigh factors such as procedural type, vascular bed, and comorbidity burden when selecting antiplatelet regimens. Guidelines should emphasize personalized treatment rather than uniform DAPT prescription. Future studies should explore antiplatelet strategies stratified by revascularization type and patient risk, using standardized definitions and adequately powered endpoints. Trials incorporating pharmacogenomic profiling to identify non-responders to clopidogrel may offer more individualized approaches to therapy in CLTI. Clinicians should limit DAPT use to carefully selected patients with high ischemic but low bleeding risk. Routine use post-revascularization in CLTI is not supported by current evidence. Treatment plans should be reassessed at follow-up and adjusted based on evolving clinical status and bleeding history. Policymakers should support development of evidence-based guidelines that promote individualized antithrombotic strategies. Reimbursement frameworks should not incentivize blanket DAPT use. National vascular registries should collect granular outcome data to guide future research and refine quality metrics in CLTI care.

6. Conclusion

Dual antiplatelet therapy did not significantly reduce major amputation or improve graft patency after revascularization for chronic limb-threatening ischemia when compared with single antiplatelet therapy. The bleeding risk was consistently higher in patients receiving dual therapy. No substantial benefit was observed in perfusion indices or all-cause mortality. Subgroup and sensitivity analyses did not identify treatment effect modifiers. Between-study heterogeneity and low certainty of evidence for safety outcomes further limited confidence. Routine dual therapy cannot be recommended for all patients after revascularization in this setting.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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