



A COMPREHENSIVE SYSTEMATIC REVIEW OF THE ASSOCIATION BETWEEN PERIPHERAL ARTERY DISEASE AND CARDIOVASCULAR MORTALITY

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ABSTRACT

Introduction: Peripheral artery disease (PAD) affects more than 230 million people worldwide yet remains under-detected and under-treated relative to coronary and cerebrovascular disease. Although PAD is widely acknowledged to confer cardiovascular (CV) risk, the magnitude, consistency, gradient and modifiability of its association with CV mortality across disease stages, ankle-brachial index (ABI) strata and comorbidity phenotypes have not been comprehensively synthesised. This review quantified that association and determined whether excess CV mortality is amenable to contemporary therapy.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible designs comprised randomised controlled trials (RCTs) and primary observational studies (prospective/retrospective cohort, case-control, cross-sectional and registry-based) reporting CV or all-cause mortality in adults with PAD or abnormal ABI. Systematic reviews and meta-analyses

were excluded from primary tabulation but retained for triangulation. Risk of bias was appraised with Cochrane RoB 2 and Newcastle-Ottawa Scale; certainty was rated with GRADE. Synthesis was narrative with structured tabulation across fifteen prespecified outcome domains.

Results: Fifty-four primary studies (13 randomised/trial-derived, 41 observational) encompassing >9 million individuals were included. PAD demonstrated consistent, significant association with CV death. In population-based cohorts, age-adjusted CV mortality hazard ratios (HRs) rose stepwise across disease stage: 1.9 for asymptomatic PAD, 2.6 for intermittent claudication, and 3.5 for severe limb ischaemia; ten-year all-cause mortality rose from 27% in referents to 75% in severe limb ischaemia. Low ABI (≤ 0.90) approximately doubled to quadrupled CV mortality, while high ABI (> 1.40) carried comparable risk, describing a U-shaped hazard. PAD without coronary heart disease or stroke carried prognosis comparable to coronary heart disease or stroke without PAD (adjusted HR 1.68 versus 1.81). Comorbidity markedly amplified risk: concomitant chronic kidney disease and PAD raised cardio-cerebrovascular mortality >4-fold (HR 4.76); critical limb ischaemia in type 2 diabetes raised CV mortality >6-fold (SHR 6.20). Polyvascular involvement produced monotonic risk gradient. Critically, excess risk proved modifiable: low-dose rivaroxaban plus aspirin significantly reduced CV death (HR 0.78) and all-cause death (HR 0.82), reduced MACE composite in PAD (HR 0.72), and reduced major adverse limb events by 43%, while multi-drug secondary prevention was associated with 65% lower all-cause mortality in screen-detected PAD. GRADE certainty was moderate for prognostic domains and high for randomised therapeutic evidence.

Discussion: The evidence base demonstrates internal coherence across trial and observational designs, continents and decades. PAD indexes total atherosclerotic burden rather than limb-confined disease, explaining why asymptomatic PAD is nearly as lethal as symptomatic disease, why abnormal ABI predicts death after Framingham adjustment, and why cardiac events dominate mortality. Residual thrombotic risk, systemic inflammation, arterial calcification, renal dysfunction and treatment inequity constitute principal mechanisms. Limitations include heterogeneity of PAD ascertainment, reliance on administrative coding, and probable under-representation of low- and middle-income settings.

Conclusion: PAD demonstrates independent, consistent, significant association with CV mortality with reproducible dose-response gradient across haemodynamic severity, symptom stage, vascular-bed burden and comorbidity load. Because excess risk is demonstrably attenuated by intensified antithrombotic therapy and comprehensive risk-factor control, PAD should be treated operationally as coronary risk equivalent, and ABI measurement should be embedded in CV risk stratification. Systematic case-finding coupled with guideline-directed medical therapy represents immediately actionable, evidence-supported strategy for reducing CV death.

Keywords: Peripheral artery disease; cardiovascular mortality; ankle-brachial index; atherothrombosis; polyvascular disease; secondary prevention

INTRODUCTION

Background

Atherosclerotic lower-extremity peripheral artery disease (PAD) is a chronic obstructive arterial disorder that affects an estimated 230 million people globally and constitutes the third most prevalent clinical manifestation of atherosclerosis after coronary artery disease and cerebrovascular disease. Its clinical spectrum extends from haemodynamically detectable but asymptomatic disease, through intermittent claudication, to chronic limb-threatening ischaemia characterised by ischaemic rest pain, tissue loss or gangrene. Traditional atherosclerotic risk factors — advancing age, cigarette smoking, diabetes mellitus, hypertension and dyslipidaemia — are strongly and consistently linked to incident PAD, and the disease shares its pathobiological substrate with atherosclerosis in every other arterial territory.^{59,61}

Despite this shared substrate, PAD has historically occupied a subordinate position in cardiovascular practice. It is diagnosed less often, treated less intensively and researched less extensively than coronary disease, in part because its cardinal symptom is exertional limb discomfort rather than chest pain, and in part because a substantial proportion of affected individuals are entirely asymptomatic and are therefore identified only through deliberate haemodynamic testing with the ankle–brachial index (ABI). Global Burden of Disease analyses indicate that the age-standardised mortality rate attributable to PAD has declined only modestly between 1990 and 2019, and that the burden is rising most rapidly in lower socio-demographic index regions, where diagnostic capacity is weakest.⁶²

The clinical importance of PAD derives less from the limb than from the heart. Patients with PAD experience myocardial infarction, ischaemic stroke and cardiovascular death at rates that rival or exceed those of patients with established coronary artery disease, and contemporary cohorts demonstrate that cardiovascular causes account for the plurality of deaths in this population. Nevertheless, clinical decision-making frequently treats PAD as a limb-salvage problem, and secondary prevention is delivered inconsistently: registry and primary-care data repeatedly show

that only a minority of patients with PAD receive the combination of statin, antiplatelet and renin–angiotensin system blockade recommended by guidelines. This mismatch between prognostic severity and therapeutic intensity is the central clinical problem that motivates the present review.^{58,22,14}

Research Objectives

The general objective of this systematic review is to synthesise, comprehensively and by design category, the published evidence describing the association between peripheral artery disease and cardiovascular mortality in adult populations. The specific objectives are as follows: (i) to quantify the magnitude of the association between PAD and cardiovascular mortality across randomised and observational study designs; (ii) to determine whether a dose–response gradient exists across PAD severity stages and across ABI strata, including the high-ABI category; (iii) to compare the prognostic weight of PAD with that of coronary heart disease and stroke; (iv) to characterise effect modification by diabetes mellitus, chronic kidney disease, polyvascular involvement, sex and age; (v) to evaluate whether pharmacological and behavioural interventions attenuate cardiovascular mortality in PAD; and (vi) to appraise the methodological quality and certainty of the underlying evidence.

Research Benefits

From a theoretical standpoint, this review consolidates fragmented evidence into a single design-stratified synthesis, clarifying whether PAD functions as a causal contributor to cardiovascular death or principally as an integrative marker of systemic atherosclerotic burden. From a clinical standpoint, it provides the treating physician with quantified, stage-specific risk estimates that can be applied directly at the bedside, and it identifies which patient phenotypes — asymptomatic PAD, high-ABI PAD, PAD with renal impairment, polyvascular PAD — carry risk that is currently under-recognised. From a public-health and policy standpoint, it supplies the evidentiary basis for embedding ABI screening within cardiovascular risk-assessment programmes and for auditing guideline-directed medical therapy in PAD populations. From a research standpoint, it delineates the residual evidence gaps that should shape future trial design, particularly in low- and middle-income settings and in the asymptomatic PAD population.

Hypothesis

The principal hypothesis of this review is that peripheral artery disease is independently and significantly associated with increased cardiovascular mortality, and that this association is graded according to haemodynamic and clinical severity. Four subsidiary hypotheses were prespecified. First, both a low ABI (≤ 0.90) and a high, non-compressible ABI (> 1.40) are associated with excess cardiovascular mortality relative to a normal ABI, producing a U-shaped or reverse-J-shaped risk distribution. Second, asymptomatic PAD confers cardiovascular mortality risk of a magnitude approaching that of symptomatic PAD. Third, the coexistence of PAD with diabetes mellitus, chronic kidney disease or disease in additional vascular territories multiplies rather than merely adds to cardiovascular mortality risk. Fourth, the excess cardiovascular mortality associated with PAD is at least partially modifiable by intensified antithrombotic therapy and comprehensive risk-factor management. The corresponding null hypothesis states that PAD is not independently associated with cardiovascular mortality once conventional risk factors are accounted for.

Research Gap

Four specific gaps in the existing literature justify the present synthesis. First, previous syntheses have addressed either the ankle-brachial index as a risk marker in the general population or event rates within PAD cohorts, but rarely both within one design-restricted framework that separates randomised from observational evidence. Second, most prior reviews have focused on all-cause mortality, whereas cardiovascular-specific mortality — the outcome most directly linked to atherosclerotic mechanism and most responsive to secondary prevention — has been reported inconsistently and has seldom been assembled across severity strata. Third, the high-ABI phenotype associated with medial arterial calcification has been treated as an analytic nuisance and excluded from many analyses, despite evidence that it carries mortality risk comparable to a low ABI. Fourth, the interaction between PAD and renal dysfunction, and the outcomes of PAD populations outside North America and Western Europe, remain sparsely synthesised.^{53,54,55,58}

A fifth and more practical gap concerns the translation of prognostic evidence into therapeutic action. Although several landmark randomised trials have demonstrated that intensified antithrombotic regimens reduce cardiovascular death in populations that include or are restricted to

PAD, these therapeutic data have not been formally integrated with the observational prognostic literature. Consequently, the clinician is left with two disconnected bodies of evidence: one establishing that PAD is dangerous, and another establishing that certain therapies help, without an explicit synthesis linking the magnitude of risk to the magnitude of achievable benefit.^{1,2,3,4}

Novelty

This review advances the field in five respects. First, it applies a strict design filter — admitting only randomised controlled trials and primary observational studies into the characteristics table while reserving systematic reviews and meta-analyses for triangulation — thereby preventing the double-counting of primary data that has affected earlier narrative syntheses. Second, it organises the evidence into fifteen prespecified outcome domains rather than a single pooled endpoint, permitting explicit examination of severity gradients, ABI morphology, comorbidity interaction and treatment responsiveness within one analytic architecture. Third, it juxtaposes prognostic and therapeutic evidence directly, quantifying both the excess risk conferred by PAD and the proportion of that risk demonstrably removable by contemporary therapy. Fourth, it incorporates geographically diverse cohorts, including data from sub-Saharan Africa, South-East Asia, East Asia and institutionalised elderly populations, which are routinely absent from Western-centric syntheses. Fifth, every included reference was retrieved and verified through the Consensus academic search engine, and each is accompanied by its indexed record link, providing complete provenance transparency for the evidence base.^{32,17,34,33}

METHODS

Protocol and Reporting Standard

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review question, eligibility criteria, outcome domains, data-extraction fields, risk-of-bias instruments and synthesis strategy were specified before data extraction commenced. No ethical approval was required because the review used exclusively published, de-identified aggregate data. No external funding was received and the authors declare no competing interests relevant to the subject matter.

477

The International Journal of Medical Science and Health Research

Review Question and PICOS Framework

The review question was formulated as follows: among adults with peripheral artery disease or an abnormal ankle–brachial index, what is the magnitude and consistency of the association with cardiovascular mortality relative to individuals without PAD or with a normal ABI, and to what extent is this association modified by disease severity, comorbidity and therapeutic intervention? The structured PICOS framework governing eligibility is presented in Table 1.

Table 1. PICOS framework governing study eligibility

Element	Specification
Population (P)	Adults (≥ 18 years, in practice ≥ 40 years in most cohorts) with lower-extremity peripheral artery disease defined clinically (intermittent claudication, chronic limb-threatening ischaemia, prior peripheral revascularisation or amputation) or haemodynamically (ankle–brachial index ≤ 0.90 , or > 1.40 where analysed as an abnormal category), including asymptomatic screen-detected disease.
Intervention / Exposure (I/E)	Presence of PAD or abnormal ABI (prognostic studies); or an antithrombotic, lipid-lowering, revascularisation or behavioural intervention delivered to a PAD population (therapeutic studies).
Comparator (C)	Absence of PAD, normal ABI (0.91–1.39/1.40), a less severe PAD stage, an alternative therapeutic strategy, placebo, or the general population (for standardised mortality ratio comparisons).
Outcomes (O)	Primary: cardiovascular / atherosclerotic cardiovascular / cardio-cerebrovascular mortality. Secondary: all-cause mortality; MACE (CV death, myocardial infarction, stroke); non-fatal myocardial infarction; stroke or cerebrovascular events; major adverse limb events and major amputation; hospitalisation for vascular causes; risk reclassification metrics.
Study design (S)	Included: randomised controlled trials and prespecified or post-hoc analyses thereof; prospective cohort; retrospective cohort; registry-based observational; case–control; cross-sectional. Excluded from the characteristics table:

	systematic reviews, meta-analyses, narrative reviews, guidelines, editorials, case reports and case series.
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ABI = ankle–brachial index; MACE = major adverse cardiovascular events; PAD = peripheral artery disease.

Eligibility Criteria

Inclusion and exclusion criteria were applied strictly and are enumerated in Table 2. In accordance with the prespecified design restriction, systematic reviews and meta-analyses identified during searching were not entered into the study-characteristics table and did not contribute participants to the descriptive counts; they were, however, retained as corroborative evidence for outcome-level triangulation and are cited throughout the Discussion. This approach preserves the primacy of primary data while permitting the review to remain in dialogue with the existing synthetic literature.

Table 2. Inclusion and exclusion criteria

Domain	Inclusion criteria	Exclusion criteria
Design	RCT; prespecified/post-hoc RCT analysis; prospective cohort; retrospective cohort; registry cohort; case–control; cross-sectional; observational	Systematic review; meta-analysis; narrative review; clinical practice guideline; editorial; commentary; case report; case series; modelling study without primary follow-up
Population	Adults with clinically or haemodynamically defined PAD, or general/clinical populations in whom ABI was measured at baseline	Exclusively paediatric populations; non-atherosclerotic arterial disease (Buerger disease, vasculitis, traumatic or embolic occlusion) as the sole population
Exposure	PAD status, PAD stage, ABI category, toe–brachial index, or a therapeutic intervention delivered in PAD	Studies in which PAD was neither an exposure, a stratifying variable, nor an enrolment criterion
Outcome	Cardiovascular mortality, all-cause	Studies reporting only patency, wound

	mortality, MACE, or a component thereof, reported quantitatively	healing, quality of life or walking distance without any mortality or MACE endpoint
Follow-up	Minimum 30 days; population-based prognostic cohorts required ≥ 1 year	Peri-procedural series with <30 days of observation only
Publication	Peer-reviewed journal article or indexed conference abstract with extractable numerical results; English language	Records without extractable effect estimates or event counts

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Peripheral artery disease	Lower-extremity atherosclerosis	Chronic limb-threatening ischaemia
I (Intervention/Exposure)	Ankle-brachial index	Polyvascular disease	Antithrombotic therapy
C (Comparison)	Normal ABI	Coronary artery disease	Cerebrovascular disease
O (Outcome)	Cardiovascular mortality	All-cause mortality	Major adverse cardiovascular events

The Boolean MeSH keywords inputted on databases for this research are: (*"Peripheral artery disease"* OR *"Lower-extremity atherosclerosis"* OR *"Chronic limb-threatening ischaemia"*) AND (*"Ankle-brachial index"* OR *"Polyvascular disease"* OR *"Antithrombotic therapy"*) AND (*"Normal ABI"* OR *"Coronary artery disease"* OR *"Cerebrovascular disease"*) AND (*"Cardiovascular mortality"* OR *"All-cause mortality"* OR *"Major adverse cardiovascular events"*)

Study Selection

Records retrieved from the six searches were pooled and de-duplicated on the basis of title, first author, journal and year. Titles and abstracts were screened against the eligibility criteria in Table 2. Records that were unambiguously ineligible on design grounds — principally systematic reviews, meta-analyses, guidelines and mechanistic reviews — were removed at this stage but were retained in a separate corroborative file for use in the Discussion. Full records of the remaining candidates were assessed against every element of the PICOS framework, with particular attention to the requirement for an extractable mortality or MACE endpoint.

Data Extraction

A structured extraction template was applied to every included study, capturing: first author and year of publication; country or geographical region and data source; study design; setting and recruitment frame; total sample size and number of participants with PAD; method of PAD ascertainment; definition of the ABI threshold where applicable; mean or median age and proportion of women; prevalence of diabetes and chronic kidney disease where reported; duration of follow-up; definition of the cardiovascular mortality endpoint; the analytic model used and the covariates adjusted for; and all reported effect estimates with their 95% confidence intervals and p-values. Where a study reported multiple adjustment models, the most fully adjusted estimate was extracted. Where a study reported outcomes for several strata, each stratum was extracted separately so that severity gradients could be reconstructed.

Prespecified Outcome Domains

Fifteen outcome domains were prespecified. The primary domain was cardiovascular mortality, however operationalised by the source study (cardiovascular death, atherosclerotic cardiovascular disease death, cardio-cerebrovascular death, or vascular death). The remaining fourteen domains address all-cause mortality, composite MACE, individual ischaemic components, severity and haemodynamic gradients, comorbidity interaction, therapeutic modification, sex differences, temporal trends and risk-prediction performance. The full outcome architecture is set out in Table 3.

Table 3. Prespecified outcome domains and their operational definitions

No	Outcome domain	Operational definition and analytic intent
O1	Cardiovascular mortality (primary)	Death attributed to cardiovascular, atherosclerotic cardiovascular or cardio-cerebrovascular causes in individuals with PAD or abnormal ABI versus comparator
O2	All-cause mortality	Death from any cause; extracted to allow assessment of competing risks and of the cardiovascular fraction of total mortality
O3	Composite MACE	Cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, however combined by the source study
O4	Non-fatal myocardial infarction	Adjudicated or coded incident myocardial infarction as a discrete endpoint
O5	Stroke and cerebrovascular events	Incident ischaemic stroke, cerebrovascular event or transient ischaemic attack requiring hospitalisation
O6	Severity-stage gradient	Cardiovascular and all-cause mortality across asymptomatic PAD, intermittent claudication and chronic limb-threatening ischaemia
O7	ABI-category gradient	Mortality across low (≤ 0.90), borderline (0.91–1.00), normal and high (> 1.30 –1.40) ABI strata, testing for a U-shaped relationship
O8	Major adverse limb events and amputation	Acute limb ischaemia, major vascular amputation, limb revascularisation, and their prognostic consequences for mortality
O9	Interaction with diabetes mellitus	Cardiovascular mortality in PAD stratified by diabetes status or within diabetic cohorts
O10	Interaction with chronic kidney disease	Cardiovascular and all-cause mortality in PAD stratified by renal function, including end-stage kidney disease and dialysis

O11	Polyvascular disease burden	Mortality and MACE according to the number of symptomatic arterial territories involved
O12	Pharmacological modification of risk	Effect of antithrombotic, antiplatelet, lipid-lowering and renin–angiotensin inhibition on cardiovascular and all-cause death in PAD
O13	Sex differences	Sex-specific mortality risk, treatment allocation and standardised mortality ratios
O14	Risk prediction and reclassification	Incremental discrimination and reclassification achieved by adding ABI to established risk scores
O15	Behavioural, functional and psychosocial modifiers	Physical activity, tobacco use, perceived stress, frailty, nutritional status and inflammatory biomarkers as determinants of mortality in PAD

Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Peripheral artery disease" OR "Lower-extremity atherosclerosis" OR "Chronic limb-threatening ischaemia") AND ("Ankle-brachial index" OR "Polyvascular disease" OR "Antithrombotic therapy") AND ("Normal ABI" OR "Coronary artery disease" OR "Cerebrovascular disease") AND ("Cardiovascular mortality" OR "All-cause mortality" OR "Major adverse cardiovascular events")</i>	71
Clinicaltr ial.gov	<i>("Peripheral artery disease" OR "Lower-extremity atherosclerosis" OR "Chronic limb-threatening ischaemia") AND ("Ankle-brachial index" OR "Polyvascular disease" OR "Antithrombotic therapy") AND ("Normal ABI" OR "Coronary artery disease" OR "Cerebrovascular disease") AND ("Cardiovascular mortality" OR "All-cause mortality" OR "Major adverse cardiovascular events")</i>	12
Semantic Scholar	<i>("Peripheral artery disease" OR "Lower-extremity atherosclerosis" OR "Chronic limb-threatening ischaemia") AND ("Ankle-brachial index" OR "Polyvascular disease" OR "Antithrombotic therapy") AND ("Normal ABI" OR "Coronary artery disease" OR "Cerebrovascular disease") AND ("Cardiovascular mortality" OR "All-cause mortality" OR "Major adverse cardiovascular events")</i>	89
Elsevier	<i>("Peripheral artery disease" OR "Lower-extremity atherosclerosis" OR "Chronic limb-threatening ischaemia") AND ("Ankle-brachial index" OR "Polyvascular disease" OR "Antithrombotic therapy") AND ("Normal ABI" OR "Coronary artery disease" OR "Cerebrovascular disease") AND ("Cardiovascular mortality" OR "All-cause mortality" OR "Major adverse cardiovascular events")</i>	10
Cochrane	<i>("Peripheral artery disease" OR "Lower-extremity atherosclerosis" OR "Chronic limb-threatening ischaemia") AND ("Ankle-brachial index" OR "Polyvascular disease" OR "Antithrombotic therapy") AND ("Normal ABI" OR "Coronary artery disease" OR "Cerebrovascular disease") AND ("Cardiovascular mortality" OR "All-cause mortality" OR "Major adverse cardiovascular events")</i>	2

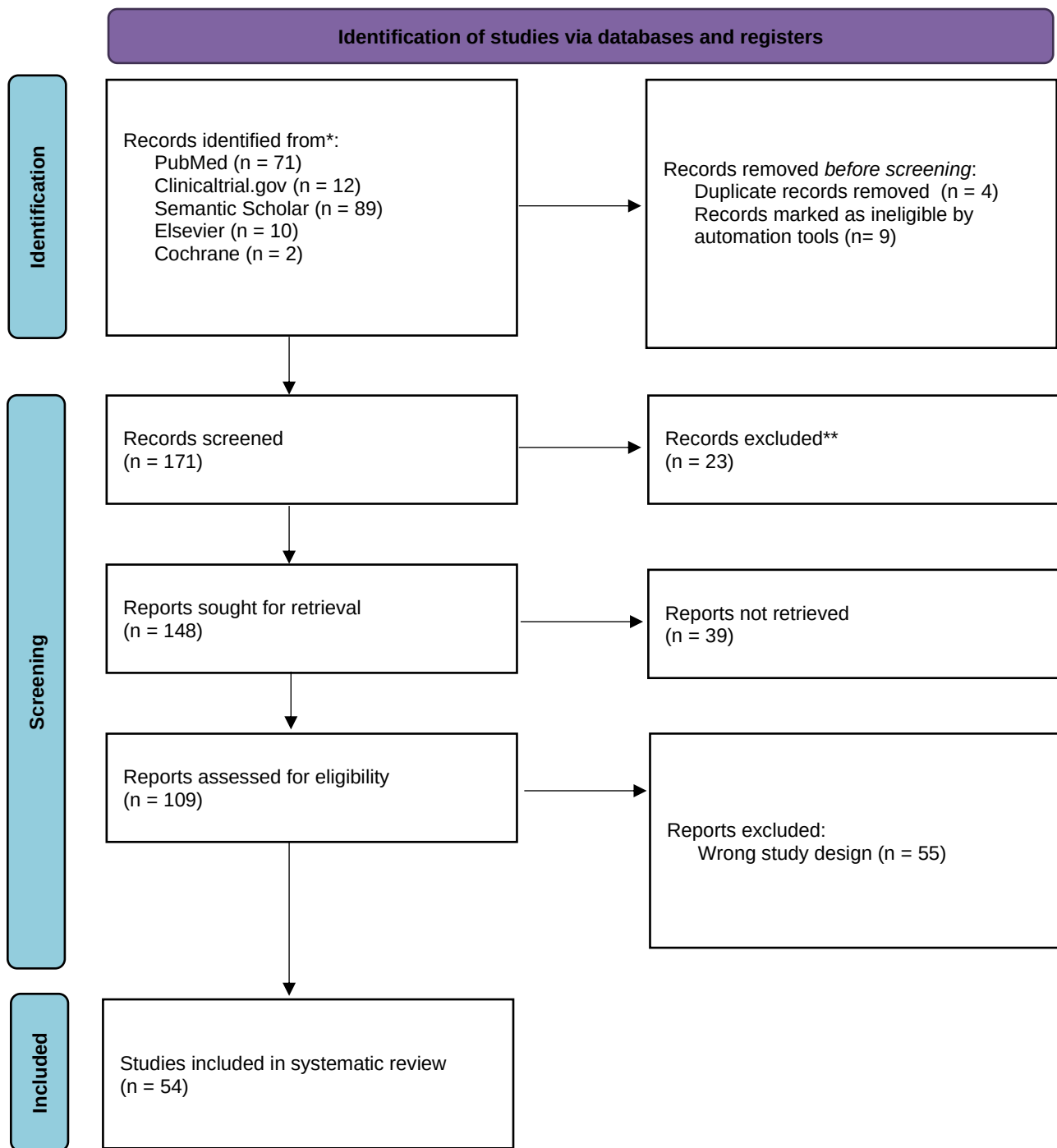


Figure 1. Article search flowchart

Risk-of-Bias Assessment

Methodological quality was appraised using instrument sets matched to design. Randomised controlled trials and analyses derived from them were assessed with the revised Cochrane Risk of Bias tool (RoB 2) across five domains: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Each domain and the overall judgement were classified as low risk, some concerns, or high risk. Post-hoc and subgroup analyses of randomised trials were additionally flagged for selective-reporting risk, since subgroup effects are inherently more vulnerable to type I error than the primary randomised comparison. The RoB 2 appraisal is presented in Table 4.

Table 4 Risk of bias in randomised and trial-derived studies (Cochrane RoB 2)

Study (Year)	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Selective reporting	Overall
Eikelboom 2017 (COMPASS)	Low	Low	Low	Low	Low	Low
Anand 2018 (COMPASS- PAD)	Low	Low	Low	Low	Some concerns	Low
Bonaca 2020 (VOYAGER PAD)	Low	Low	Low	Low	Low	Low
Eikelboom 2021 (COMPASS mortality)	Low	Low	Low	Low	Some concerns	Some concerns
Kaplovitch 2021	Low	Low	Low	Low	Some	Some

Study (Year)	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Selective reporting	Overall
(COMPASS LE-PAD)					concerns	concerns
Anand 2018 (COMPASS MALE)	Low	Low	Low	Low	Some concerns	Some concerns
Bhatt 2020 (COMPASS diabetes)	Low	Low	Low	Low	Some concerns	Some concerns
Vanassche 2020 (COMPASS risk factors)	Low	Low	Low	Low	Some concerns	Some concerns
Gutierrez 2018 (EUCLID polyvascular)	Low	Low	Low	Low	High	Some concerns
Szarek 2022 (EUCLID total events)	Low	Low	Low	Low	Some concerns	Some concerns
Farber 2022 (BEST-CLI)	Low	Some concerns	Low	Low	Low	Some concerns
Fowkes 2010 (AAA aspirin trial)	Low	Low	Low	Low	Low	Low

Study (Year)	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Selective reporting	Overall
Samsky 2021 (EXSCEL polyvascular)	Low	Low	Low	Low	High	Some concerns

D1–D5 correspond to the five RoB 2 domains. Open-label surgical allocation in BEST-CLI generates unavoidable performance-bias concern for non-fatal endpoints; mortality endpoints are less susceptible. Post-hoc analyses of COMPASS and EUCLID are rated "some concerns" overall because subgroup estimates were not the trials' primary randomised comparisons.

Observational studies were appraised with the Newcastle–Ottawa Scale (NOS), which allocates a maximum of four stars for selection, two for comparability and three for outcome ascertainment, giving a maximum total of nine. A total of 7–9 stars was interpreted as high methodological quality, 5–6 as moderate quality and 0–4 as low quality. Comparability stars were awarded when the analysis adjusted for age and sex (first star) and for at least two additional cardiovascular risk factors such as diabetes, smoking, blood pressure, lipids or renal function (second star).

Table 5. Risk of bias in observational studies (Newcastle–Ottawa Scale)

Study (Year)	Selection (/4)	Comparability (/2)	Outcome (/3)	Total (/9)	Quality
Sartipy 2018	4	2	3	9	High
Sartipy 2019	4	2	3	9	High
Cea Soriano 2017	4	2	3	9	High
Avdic 2024	4	2	3	9	High
Rerkasem 2025	3	2	3	8	High
Resnick 2004	4	2	3	9	High
Criqui 2010 (MESA)	4	2	3	9	High

Leng 1996	4	2	2	8	High
Wild 2006	4	2	3	9	High
Pande 2011 (NHANES)	4	2	3	9	High
Matsushita 2022 (NHANES)	4	2	3	9	High
Zhang 2025 (NHANES)	4	2	3	9	High
Emdin 2015	4	2	2	8	High
Søgaard 2023	4	1	3	8	High
Porras 2024	4	2	3	9	High
Alves-Cabratos 2019	4	2	2	8	High
Koivunen 2021	3	1	2	6	Moderate
Tanaka 2016	3	2	2	7	High
Jagt 2022 (UCC-SMART)	4	2	3	9	High
Samba 2019 (EPIDEMCA-FU)	3	2	2	7	High
Dorn 2023 (Allo-Study)	3	2	2	7	High
Zhao 2023 (N. Shanghai)	3	2	2	7	High
Xiong 2024	3	2	3	8	High
Cha 2022	4	2	3	9	High
Vidula 2008	3	2	3	8	High
Malik 2020 (PORTRAIT)	3	2	3	8	High
Steg 2007 (REACH 1- year)	4	2	2	8	High
Bhatt 2010 (REACH 4- year)	4	2	2	8	High
Alberts 2009 (REACH 3- year)	4	1	2	7	High

Yazdani 2023 (LURIC)	3	2	2	7	High
Mohammedi 2024	4	2	3	9	High
Lin 2024	3	2	3	8	High
Mustapha 2018	4	1	2	7	High
Makowski 2022	4	2	3	9	High
Kumbhani 2014	3	2	3	8	High
Baviera 2018	4	2	2	8	High
Benson 2022	4	2	2	8	High
Callegari 2024	3	2	3	8	High
Shah 2024	4	1	3	8	High
Rakestraw 2023	3	1	2	6	Moderate
Hicks 2023	4	2	3	9	High

Selection domain: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that the outcome was not present at baseline. Outcome domain: assessment of outcome, adequacy of follow-up duration, adequacy of follow-up completeness. Conference-abstract reports were capped at 2 stars in the outcome domain because full methodological reporting was unavailable.

Certainty of Evidence (GRADE)

Certainty of evidence was rated for each principal outcome domain using the GRADE framework. Randomised evidence commenced at high certainty and observational evidence at low certainty, with downgrading for risk of bias, inconsistency, indirectness, imprecision and suspected publication bias, and upgrading of observational evidence for a large magnitude of effect, a demonstrable dose–response gradient, or the presence of plausible residual confounding that would attenuate rather than exaggerate the observed effect. The last two upgrading criteria were applied frequently in this review because effect sizes for cardiovascular mortality in PAD are large and reproducibly graded across severity strata. The resulting certainty profile is summarised in Table 6.

Table 6. GRADE certainty-of-evidence profile by outcome domain

Outcome domain	Design base	Reasons to downgrade	Reasons to upgrade	Certainty
O1 Cardiovascular mortality	Observational + RCT	Heterogeneous PAD ascertainment	Large effect; dose-response; residual confounding conservative	Moderate
O2 All-cause mortality	Observational + RCT	None serious	Large effect; dose-response	Moderate
O3 Composite MACE	RCT	None serious	Not applicable	High
O6 Severity-stage gradient	Observational	Stage misclassification possible	Strong monotonic dose-response	Moderate
O7 ABI-category gradient	Observational	Threshold heterogeneity (1.30 vs 1.40)	Large effect; consistent U-shape across continents	Moderate
O9 Diabetes interaction	Observational + RCT	Confounding by glycaemic control	Large effect	Moderate
O10 CKD interaction	Observational	Competing risk of non-CV death	Very large effect; dose-response by eGFR stage	Moderate
O11 Polyvascular burden	Registry + RCT post-hoc	Registry ascertainment; post-hoc subgroups	Monotonic dose-response across territories	Moderate
O12 Pharmacological	RCT	None serious	Not applicable	High

modification				
O13 Sex differences	Observational	Residual confounding by age and treatment allocation	None	Low
O15 Behavioural modifiers	Observational	Self-reported exposure; reverse causation plausible	Dose-response for physical activity	Low

Data Synthesis

A quantitative meta-analytic pooling of effect estimates was considered but was judged inappropriate for the primary outcome. The included studies differ fundamentally in the definition of the exposure (clinical PAD versus ABI-defined PAD versus revascularisation history), in the comparator (general population versus normal-ABI referents versus less severe PAD stage), in the outcome definition (cardiovascular death versus atherosclerotic cardiovascular death versus cardio-cerebrovascular death), and in the covariate sets used for adjustment. Pooling across these dimensions would generate a statistically precise but clinically uninterpretable summary estimate. Findings were therefore synthesised narratively and presented in structured outcome tables, with effect estimates reported exactly as published and accompanied by their confidence intervals. Statistical significance was assessed by whether the 95% confidence interval excluded the null value of 1.0 for ratio measures. Where studies reported both crude and adjusted estimates, the adjusted estimate is presented and the adjustment set described. Direction, magnitude and consistency of effect across studies were assessed qualitatively as the principal criteria for inferential strength, in line with GRADE methodology.

RESULTS

Characteristics of Included Studies

The identity, design, setting and sample size of every included primary study are presented in Table 7. The corresponding exposure ascertainment, follow-up duration, endpoint definition and principal finding for each study.

Table 7. Characteristics of included primary studies — identity, design and population

No	Author (Year)	Country / data source	Design	Population	Sample size
1	Eikelboom (2017)	33 countries, COMPASS	RCT, double- blind	Stable atherosclerotic vascular disease (coronary and/or peripheral)	27,395
2	Anand (2018, Lancet)	33 countries, COMPASS	RCT, prespecified subpopulation	Stable peripheral or carotid artery disease	7,470
3	Bonaca (2020)	International, VOYAGER PAD	RCT, double- blind	Symptomatic PAD after lower-extremity revascularisation	6,564
4	Eikelboom (2021)	COMPASS	RCT, secondary mortality analysis	Chronic coronary or peripheral artery disease	18,278
5	Kaplovitch (2021)	COMPASS, 602 centres	RCT, post- hoc subanalysis	Symptomatic lower- extremity PAD	4,129
6	Anand (2018, JACC)	COMPASS	RCT, secondary analysis	Lower-extremity PAD	6,391
7	Gutierrez (2018)	International, EUCLID	RCT, post- hoc	Symptomatic PAD ± coronary/cerebrovascular	13,885

			secondary analysis	disease	
8	Szarek (2022)	International, EUCLID	RCT, post-hoc total-events analysis	Chronic symptomatic PAD	13,885
9	Farber (2022)	International, BEST-CLI	RCT, two parallel cohorts	Chronic limb-threatening ischaemia with infra-inguinal PAD	1,830
10	Fowkes (2010)	Scotland, AAA trial	RCT, double-blind, screening-based	Community adults 50–75 y with ABI ≤ 0.95 , free of clinical CVD	3,350 (from 28,980 screened)
11	Mohammedi (2024)	53 countries, pooled analysis of 3 trials	Prospective pooled cohort analysis	Participants without baseline PAD, 50% with diabetes	40,747
12	Bhatt (2020)	COMPASS	RCT, prespecified diabetes analysis	Coronary or peripheral artery disease $\pm$ diabetes mellitus	27,395 (10,341 with diabetes)
13	Sartipy (2018)	Sweden, population sample	Prospective population-based observational	Random population sample stratified by PAD stage	5,080
14	Sartipy (2019)	Sweden, population	Prospective population-	Asymptomatic PAD, claudication, severe limb	5,080

		sample	based cohort	ischaemia, referents	
15	Cea Soriano (2017)	UK, THIN primary care	Retrospective matched cohort	Symptomatic PAD aged 50–89 y and matched non-PAD comparators	28,484 PAD + 113,940 comparators
16	Avdic (2024)	Sweden, National Diabetes Register	Register-based observational cohort	Type 2 diabetes and matched controls, followed after incident PAD	150,215 T2D + 346,423 controls
17	Rerkasem (2025)	Thailand, tertiary referral hospital	Prospective cohort	Type 2 diabetes with PAD across severity subgroups	278
18	Resnick (2004)	USA, Strong Heart Study	Prospective population cohort	American Indian adults with bilateral ABI measurement	4,393
19	Criqui (2010)	USA, MESA	Prospective multi-ethnic cohort	Adults 45–84 y free of clinical CVD at baseline	6,647
20	Leng (1996)	Scotland, Edinburgh Artery Study	Prospective population cohort	Adults 55–74 y randomly sampled from general practice registers	1,592
21	Wild (2006)	Scotland, Edinburgh Artery Study	Prospective population cohort	Adults 55–74 y with and without metabolic syndrome	1,467
22	Pande (2011)	USA, NHANES 1999–2004	Prospective survey-linked cohort	Adults ≥ 40 y with ABI measurement	7,458

23	Matsushita (2022)	USA, NHANES 1999–2004	Prospective survey-linked cohort	Adults ≥ 40 y stratified by PAD and CHD/stroke status	6,780
24	Zhang (2025)	USA, NHANES 1999–2004	Prospective survey-linked cohort	Adults ≥ 40 y stratified by CKD and PAD status	7,243
25	Emdin (2015)	UK, linked electronic health records	Retrospective cohort	Adults 30–90 y with a recorded blood pressure measurement	4,222,459
26	Søgaard (2023)	Denmark, nationwide registries	Nationwide registry cohort	Entire Danish population aged ≥ 40 y, 2000–2018	4,811,281 (145,870 incident PAD)
27	Porras (2024)	Netherlands, national hospital data	Three sequential retrospective cohorts	First hospitalisation for lower-extremity PAD	7,950 / 9,670 / 13,522
28	Alves-Cabrato (2019)	Spain, Catalonia SIDIAPQ	Retrospective primary-care cohort	Adults 35–85 y with an ABI measurement	58,118
29	Koivunen (2021)	Finland, single tertiary centre	Retrospective cohort	Symptomatic lower-extremity arterial disease, Rutherford 2–6	729
30	Tanaka (2016)	Japan, Shinken Database	Hospital-based observational cohort	Subjects with ABI 0.91–1.39 and no PAD history	4,756

31	Jagt (2022)	Netherlands, UCC-SMART	Prospective cohort	Patients with clinically manifest cardiovascular disease	8,360
32	Samba (2019)	Republic of Congo, EPIDEMCA-FU	Prospective population-based cohort	Community-dwelling adults aged ≥ 65 y	927 with ABI measured
33	Dorn (2023)	Germany, 45 nursing homes	Prospective observational cohort	Institutionalised elderly residents (median age 84 y)	1,333
34	Zhao (2023)	China, Northern Shanghai Study	Prospective community cohort	Community elderly, mean age 71.3 y	3,168
35	Xiong (2024)	USA, NHANES 1999–2004	Population-based cohort	Adults with PAD, mortality linked to 2019	561
36	Cha (2022)	South Korea, NHIS database	Retrospective national cohort	Patients revascularised for PAD, 2010–2015	8,324
37	Vidula (2008)	USA, academic medical centre	Prospective cohort	Men and women with established PAD	377
38	Malik (2020)	USA, PORTRAIT registry	Prospective multicentre registry	New or worsening PAD symptoms presenting to specialty clinics	765

			cohort		
39	Steg (2007)	44 countries, REACH registry	Prospective international cohort	Outpatients with established atherothrombosis or ≥ 3 risk factors	68,236
40	Bhatt (2010)	29 countries, REACH registry	Prospective international cohort, 4-year	Stable outpatients with or at risk of atherothrombosis	45,227
41	Alberts (2009)	44 countries, REACH registry	Prospective international cohort, 3-year	Symptomatic atherothrombosis or ≥ 3 risk factors	32,247 with 3-year data
42	Yazdani (2023)	Germany, LURIC study	Monocentric prospective cohort	Patients referred for coronary angiography	3,316
43	Lin (2024)	China, dialysis population	Prospective cohort	Dialysis patients with symptomatic PAD undergoing endovascular therapy	356
44	Mustapha (2018)	USA, Medicare claims	Population-based retrospective cohort	Beneficiaries with incident critical limb ischaemia in 2011	72,199 (9,942 matched)
45	Makowski (2022)	Germany, AOK health insurance	Retrospective nationwide cohort	Unselected patients hospitalised for CLTI, 2010–2017	199,953
46	Kumbhani (2014)	International, REACH registry	Prospective cohort with time-varying	Symptomatic PAD, statin users versus non-users	5,861

			exposure		
47	Baviera (2018)	Italy, Lombardy administrative data	Two sequential population-based cohorts	Patients hospitalised for PAD in 2002 and in 2008	2,885 and 2,848
48	Benson (2022)	UK, 787 primary care practices	Retrospective cohort	Registered patients >40 y with documented PAD	25,121 men + 13,480 women
49	Callegari (2024)	USA, Medicare-linked VQI registry	Retrospective registry cohort with machine learning	CLTI undergoing peripheral vascular intervention	10,114
50	Shah (2024)	USA, Renal Data System	National retrospective cohort	End-stage kidney disease with incident CLTI	3,908
51	Rakestraw (2023)	USA, Vascular Quality Initiative	Retrospective registry cohort	CLTI with and without end-stage kidney disease	15,203 procedures analysed
52	Samsky (2021)	International, EXSCEL	RCT, post-hoc secondary analysis	Type 2 diabetes stratified by number of diseased arterial beds	14,751
53	Vanassche (2020)	33 countries, COMPASS	RCT, prespecified risk-factor	Coronary or peripheral artery disease with complete risk-factor data	27,117

			analysis		
54	Hicks (2023)	USA, NHANES 1999–2004	Cross-sectional with prospective mortality linkage	Adults ≥ 40 y without prevalent cardiovascular disease	Approx. 7,100

ABI = ankle–brachial index; CLTI = chronic limb-threatening ischaemia; CVD = cardiovascular disease; PAD = peripheral artery disease; RCT = randomised controlled trial; T2D = type 2 diabetes; VQI = Vascular Quality Initiative. No systematic review or meta-analysis is included in this table.

Table 8. Characteristics of included primary studies — exposure ascertainment, follow-up and principal finding

No	Author (Year)	PAD / exposure ascertainment	Follow-up	Principal finding relevant to cardiovascular mortality
1	Eikelboom (2017)	Documented coronary or peripheral atherosclerosis	Mean 23 months	Rivaroxaban 2.5 mg twice daily plus aspirin reduced CV death, stroke or MI versus aspirin (HR 0.76) and reduced all-cause death (HR 0.82)
2	Anand (2018, Lancet)	Prior peripheral bypass/angioplasty, amputation, claudication with objective PAD, carotid disease, or CAD with ABI < 0.90	Median 21 months	Rivaroxaban plus aspirin reduced CV death, MI or stroke (HR 0.72) and major adverse limb events (HR 0.54) in PAD
3	Bonaca	Symptomatic PAD	Median 28	Rivaroxaban plus aspirin reduced the

	(2020)	undergoing surgical or endovascular revascularisation	months	composite of acute limb ischaemia, major amputation, MI, stroke or CV death (HR 0.85)
4	Eikelboom (2021)	Chronic coronary or peripheral artery disease	Median 23 months (max 47)	CV death reduced (HR 0.78) and total mortality reduced (HR 0.82); absolute benefit increased with the number of high-risk features
5	Kaplovitch (2021)	Symptomatic lower-extremity PAD with high-risk limb presentation or comorbidity	30 months	Prior amputation, Fontaine III–IV symptoms and prior revascularisation identified 30-month MACE/MALE risks of 22.6%, 17.6% and 11.8%
6	Anand (2018, JACC)	Lower-extremity PAD with incident major adverse limb events	Median 21 months	After a first MALE the 1-year risk of death was 8.3%; MALE independently increased mortality risk (HR 3.23)
7	Gutierrez (2018)	Symptomatic PAD with revascularisation history or ABI ≤ 0.80 , stratified by additional vascular beds	Median approx. 30 months	MACE risk rose monotonically with the number of involved territories (aHR 1.34, 1.65 and 1.99 for PAD+CVD, PAD+CAD and PAD+CAD+CVD)
8	Szarek (2022)	Symptomatic PAD stratified by	Median 2.7 years	Total cardiovascular and limb events reached 87.3–97.7 per 100 patients at

		number of symptomatic vascular territories		3 years in three-territory disease
9	Farber (2022)	Chronic limb-threatening ischaemia requiring revascularisation	Median 2.7 years (cohort 1)	Major adverse limb event or death occurred in 42.6% with surgery and 57.4% with endovascular therapy (HR 0.68)
10	Fowkes (2010)	Screen-detected ABI ≤ 0.95 in adults free of clinical cardiovascular disease	Mean 8.2 years	Aspirin did not reduce vascular events (HR 1.03) or all-cause mortality (HR 0.95) in screen-detected low ABI
11	Mohammedi (2024)	Quartiles of ankle systolic pressure, ABI and ankle-pulse-pressure difference	5 years	Lowest ankle pressure quartiles predicted incident PAD (HR up to 4.23) with similar patterns for mortality; ankle indices had the highest c-statistics
12	Bhatt (2020)	Coronary or peripheral artery disease stratified by diabetes	Median 23 months	Relative benefit of rivaroxaban plus aspirin was similar in diabetes, but absolute mortality reduction was threefold greater (1.9% versus 0.6%)
13	Sartipy (2018)	ABI measurement plus symptom questionnaire; stages APAD, IC,	10 years	Ten-year all-cause mortality rose from 27% in referents to 56%, 63% and 75% across PAD stages; CV causes accounted for 45% of deaths

		SLI		
14	Sartipy (2019)	ABI plus reported symptoms defining APAD, IC, SLI and referents	10 years	Adjusted CV death hazard was 1.80 for asymptomatic PAD and 1.95 for claudication; only 60% received guideline-directed prophylaxis
15	Cea Soriano (2017)	Read-coded symptomatic PAD in primary care records	2000–2010	All-cause death incidence 83.2 versus 50.5 per 1000 person-years; composite CV outcome HR 1.71 versus matched comparators
16	Avdic (2024)	Incident PAD diagnosis recorded in national registries	2005–2009 cohort with subsequent follow-up	After incident PAD, coexisting type 2 diabetes added a 13% relative increase in cardiovascular mortality
17	Rerkasem (2025)	ABI measurement and clinical assessment defining PAD severity	7 years	Critical limb ischaemia carried a sixfold higher cardiovascular mortality subdistribution hazard versus asymptomatic PAD
18	Resnick (2004)	Bilateral ABI, categorised as <0.90, 0.90–1.40 and >1.40	Mean 8.3 years	Both low and high ABI approximately doubled CVD mortality, establishing a U-shaped relationship
19	Criqui (2010)	ABI categorised as <1.00, normal and ≥ 1.40	Mean 5.3 years	Both low and high ABI predicted incident CVD after adjustment for traditional and novel biomarkers, and improved risk discrimination
20	Leng (1996)	ABPI thresholds of	5 years	ABPI ≤ 0.9 predicted cardiovascular

		≤ 0.7 , ≤ 0.9 and ≤ 1.0		death (RR 1.85), stroke (RR 1.98) and all-cause mortality (RR 1.58)
21	Wild (2006)	ABI < 0.9 , excluding ABI > 1.4	Approximately 15 years	Low ABI predicted CVD mortality (HR 1.5) independently of the metabolic syndrome and conventional risk factors
22	Pande (2011)	Screening ABI ≤ 0.90	Mortality linkage to December 2006	PAD doubled all-cause mortality; use of multiple preventive therapies was associated with 65% lower mortality
23	Matsushita (2022)	ABI ≤ 0.90 and self-reported CHD/stroke	Median 12.8 years	PAD without CHD/stroke carried mortality risk comparable to CHD/stroke without PAD; coexistence was worst (HR 2.70)
24	Zhang (2025)	ABI ≤ 0.90 combined with eGFR < 60 or albuminuria	Median 16.9 years	Coexisting CKD and PAD raised cardio-cerebrovascular mortality nearly fivefold
25	Emdin (2015)	New-onset PAD diagnosis in linked records	1990–2013	PAD was associated with 11 subsequent vascular event types, including ischaemic heart disease (HR 1.68) and heart failure (HR 1.63)
26	Søgaard (2023)	Registry-coded incident PAD diagnosis	2000–2018	Annual mortality among PAD patients declined from 9.8% to 7.2% while prevalence rose, projecting a growing absolute burden

27	Porras (2024)	First hospital admission coded for lower-extremity PAD	28 days, 1 year and 5 years	Standardised mortality ratios exceeded the general population in both sexes; 5-year mortality risk increased over calendar time
28	Alves-Cabratosa (2019)	ABI <0.9 recorded in primary care	Median 5.9 years	Low ABI conferred mortality risk comparable to established cardiovascular disease; low ABI plus diabetes was worst (HR 1.84)
29	Koivunen (2021)	Digital subtraction angiography plus toe pressure, TBI and ABI	Retrospective, 2009–2011 cohort	Toe pressure <30 mmHg and TBI <0.25 predicted cardiovascular mortality irrespective of the most diseased arterial segment
30	Tanaka (2016)	Borderline ABI 0.91–1.00 versus normal 1.01–1.39	2004–2012	Borderline ABI independently predicted cardiovascular death (HR 3.47) and all-cause death (HR 2.27)
31	Jagt (2022)	Screen-detected ABI ≤ 0.9 , ≥ 1.4 , normal, or known PAD	Median 8.3 years	Screen-detected low ABI predicted MACE (HR 1.9), MALE (HR 7.6) and all-cause mortality (HR 1.7)
32	Samba (2019)	ABI ≤ 0.90 measured at baseline	2 years	Low ABI predicted mortality (HR 1.86) in a sub-Saharan African elderly population
33	Dorn (2023)	Pathological ABI ≤ 0.9 or > 1.4 on one or both legs	5 years	55.5% had a pathological ABI and 84.7% of low-ABI residents were previously undiagnosed; both extremes predicted mortality
34	Zhao (2023)	Unilateral versus	Median 5.4	Bilateral low ABI carried higher

		bilateral ABI <0.9	years	MACE (HR 1.86) and mortality (HR 2.10) than unilateral low ABI
35	Xiong (2024)	ABI-defined PAD with self-reported physical activity	Mean 9.8 years	Moderate-to-vigorous activity ≥ 60 min per week reduced CVD mortality by 60% in PAD
36	Cha (2022)	Revascularisation for PAD with self-reported activity and tobacco use	2010–2015 with subsequent follow-up	Physical activity reduced and tobacco use increased mortality after revascularisation
37	Vidula (2008)	Established PAD with serial D-dimer, CRP and serum amyloid A	Mean 3.4 years	Rising inflammatory and thrombotic biomarkers predicted near-term cardiovascular and all-cause mortality
38	Malik (2020)	New or worsening PAD symptoms with serial perceived-stress scoring	4 years after 12-month assessment	Chronic high perceived stress doubled long-term mortality risk (HR 2.12)
39	Steg (2007)	Physician-documented CAD, PAD or cerebrovascular disease	1 year	One-year CV death, MI or stroke was 5.35% in PAD, exceeding CAD (4.52%); rates rose with the number of involved territories
40	Bhatt (2010)	Established atherothrombosis or multiple risk factors	4 years	Polyvascular disease was the strongest clinical determinant of ischaemic events (HR 1.99)

41	Alberts (2009)	Symptomatic atherothrombosis in one or multiple beds	3 years	Three-year MI, stroke or vascular death reached 12.0% in symptomatic disease; multibed disease raised the composite to 40.5%
42	Yazdani (2023)	Angiographically or clinically defined PAD, CAD and carotid stenosis	Long-term cohort follow-up	CV mortality rose with the number of diseased beds (HR up to 3.50); combinations including PAD were the most lethal
43	Lin (2024)	Symptomatic PAD in dialysis patients undergoing endovascular therapy	Median 2.2 years	Prolonged QTc independently predicted death (HR 2.41) and MACE (HR 1.90) in dialysis patients with PAD
44	Mustapha (2018)	Incident critical limb ischaemia in Medicare claims	4 years	Four-year survival was 46% overall and 23% after primary major amputation (median survival 1.3 years)
45	Makowski (2022)	Hospitalisation with a principal diagnosis of CLTI	2010–2018	Women were older and less often revascularised or treated with statins, yet had better adjusted overall and amputation-free survival
46	Kumbhani (2014)	Symptomatic PAD with baseline and time-varying statin exposure	4 years	Statin use reduced adverse limb outcomes (HR 0.82) and the composite of CV death, MI or stroke (HR 0.83)
47	Baviera	Hospital admission	6 years each	Acute coronary syndrome, stroke and

	(2018)	for PAD in two calendar cohorts		major amputation fell between cohorts, but mortality did not change
48	Benson (2022)	Documented PAD diagnosis in primary care	1 year	Women received statins and antiplatelets less often; after full adjustment 1-year mortality was similar between sexes
49	Callegari (2024)	CLTI undergoing peripheral vascular intervention	3 years	Three-year mortality was 39.1%; chronic kidney disease, age and heart failure were the dominant predictors
50	Shah (2024)	End-stage kidney disease with incident CLTI	2 years	One-year mortality was 44.9% irrespective of treatment strategy
51	Rakestraw (2023)	CLTI undergoing peripheral vascular intervention, stratified by ESKD	21 months	Mortality was 41.7% with ESKD versus 17.4% without, with amputation rates of 22.3% versus 7.1%
52	Samsky (2021)	Type 2 diabetes stratified by number of diseased arterial beds	Trial follow-up	MACE and all-cause mortality rose incrementally with each additional diseased bed (aHR up to 3.46 and 3.66)
53	Vanassche (2020)	Coronary or peripheral artery disease with six risk-factor domains	Median 23 months	Patients with 4–6 uncontrolled risk factors had double the ischaemic event and cardiovascular death rates of those with 0–1
54	Hicks (2023)	ABI <0.90 and monofilament-defined neuropathy	Maximum 21 years	Elevated NT-proBNP and high-sensitivity troponins combined with PAD conferred higher mortality than

		with cardiac biomarkers		elevated biomarkers alone
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APAD = asymptomatic peripheral artery disease; CAD = coronary artery disease; CRP = C-reactive protein; CVD = cerebrovascular disease (in the polyvascular context) or cardiovascular disease (elsewhere, as specified); ESKD = end-stage kidney disease; IC = intermittent claudication; MACE = major adverse cardiovascular events; MALE = major adverse limb events; SLI = severe limb ischaemia; TBI = toe-brachial index.

Table 9. Other Studies

Author (Year)	Contribution to triangulation
Fowkes (2008)	Ten-year cardiovascular mortality with ABI ≤ 0.90 was 18.7% in men and 12.6% in women versus 4.4% and 4.1% with normal ABI; hazards remained elevated after Framingham adjustment
Heald (2006)	Pooled adjusted relative risk for cardiovascular mortality with ABI < 0.9 was 1.96
Messeder (2025)	ABPI < 0.9 conferred cardiovascular mortality HR 2.04 and ABPI > 1.3 conferred HR 2.39, confirming the U-shaped relationship
Doobay (2005)	Low ABI showed 87.9% specificity but only 41.0% sensitivity for cardiovascular death, with a positive likelihood ratio of 5.61
Sigvant (2016)	Five-year cumulative cardiovascular mortality was 13% in symptomatic PAD versus 5% in reference populations
Agnelli (2020)	Pooled event rates per 1000 person-years were 113 for all-cause and 39 for cardiovascular mortality, with 71 for MACE
Aday (2021)	Establishes PAD as affecting > 230 million people and identifies polyvascular disease as a particularly malignant phenotype
Bonaca (2021)	Summarises the efficacy of guideline-directed therapy in lowering MACE and MALE in PAD
Conte (2019)	Provides consensus staging (Wifl, GLASS) and defines mortality-based

	patient-risk categories for revascularisation decisions
Liu (2022)	Documents only modest decline in age-standardised PAD mortality 1990–2019 with rising burden in lower-SDI regions

Cardiovascular Mortality (Primary Outcome)

Cardiovascular mortality was reported in twenty-six of the fifty-four included primary studies. Every study that examined PAD or an abnormal ABI as an exposure and reported an adjusted effect estimate for cardiovascular death found a statistically significant positive association; not a single included primary study reported a null or inverse association for this outcome. The pooled picture is one of a two- to sevenfold elevation in cardiovascular mortality depending on disease severity and comorbidity, with the lower end of that range corresponding to screen-detected asymptomatic disease and the upper end to critical limb ischaemia in diabetic or renal populations. The individual estimates are presented in Table 10.^{13,14,18,24,17}

Table 10. Cardiovascular mortality in peripheral artery disease

Study (Year)	Population / comparison	Effect estimate (95% CI)	Statistical significance
Sartipy (2018)	Asymptomatic PAD versus population referents	Age-adjusted HR 1.9 (1.5–2.3)	Significant
Sartipy (2018)	Intermittent claudication versus referents	Age-adjusted HR 2.6 (2.1–3.4)	Significant
Sartipy (2018)	Severe limb ischaemia versus referents	Age-adjusted HR 3.5 (2.3–5.2)	Significant
Sartipy (2019)	Asymptomatic PAD versus referents, CV death	Adjusted HR 1.80 (1.45–2.22)	Significant
Sartipy (2019)	Intermittent claudication versus referents, CV death	Adjusted HR 1.95 (1.50–2.53)	Significant
Resnick (2004)	ABI <0.90 versus 0.90–1.40, CVD mortality	HR 2.52 (1.74–3.64)	Significant

Resnick (2004)	ABI >1.40 versus 0.90–1.40, CVD mortality	HR 2.09 (1.49–2.94)	Significant
Leng (1996)	ABPI ≤0.9 versus >0.9, cardiovascular death	RR 1.85 (1.15–2.97)	Significant
Wild (2006)	Low ABI, CVD mortality adjusted for metabolic syndrome	HR 1.5 (1.1–2.1)	Significant
Tanaka (2016)	Borderline ABI 0.91–1.00 versus 1.01–1.39	HR 3.47 (p = 0.003)	Significant
Avdic (2024)	Type 2 diabetes plus PAD versus PAD without diabetes	Adjusted HR 1.13 (1.07–1.19)	Significant
Rerkasem (2025)	Critical limb ischaemia versus asymptomatic PAD in T2DM	SHR 6.20 (3.20–12.03)	Significant
Zhang (2025)	Coexisting CKD and PAD versus neither condition	Adjusted HR 4.76 (3.41–6.63)	Significant
Koivunen (2021)	Toe pressure <30 mmHg, crural-dominant disease	HR 4.26 (2.19–8.27)	Significant
Koivunen (2021)	Toe–brachial index <0.25, crural-dominant disease	HR 7.71 (1.86–32.9)	Significant
Koivunen (2021)	ABI ≥1.30, femoropopliteal-dominant disease	HR 6.71 (1.89–23.8)	Significant
Yazdani (2023)	Three diseased arterial beds versus none, CV mortality	HR 3.50 (2.19–5.62)	Significant
Yazdani (2023)	PAD plus carotid stenosis,	HR 6.03	Significant

	CV mortality		
Cea Soriano (2017)	Symptomatic PAD versus matched non-PAD, MI/stroke/CV death	HR 1.71 (1.65–1.77)	Significant
Eikelboom (2021)	Rivaroxaban plus aspirin versus aspirin, CV death	HR 0.78 (0.64–0.96), p = 0.02	Significant reduction
Xiong (2024)	Moderate-to-vigorous activity ≥ 60 min/week, CVD mortality	HR 0.40 (0.27–0.70)	Significant reduction
Xiong (2024)	Muscle-strengthening activity 1–4 times/week, CVD mortality	HR 0.34 (0.17–0.90)	Significant reduction

ABPI = ankle–brachial pressure index; SHR = subdistribution hazard ratio; T2DM = type 2 diabetes mellitus. Estimates are the most fully adjusted values reported by each source.

Three features of this outcome domain merit emphasis. First, the severity gradient is monotonic and reproducible: within the same Swedish population sample the cardiovascular death hazard rose from 1.9 in asymptomatic disease to 3.5 in severe limb ischaemia, and the same ordering was observed in a Thai diabetic cohort in which critical limb ischaemia carried a sixfold subdistribution hazard relative to asymptomatic PAD. Second, the excess is not confined to symptomatic disease: asymptomatic PAD, which by definition produces no limb complaint and is detectable only by deliberate haemodynamic testing, still nearly doubled cardiovascular death. Third, the association survives comprehensive adjustment. In the Edinburgh Artery Study low ABI predicted cardiovascular mortality after adjustment for age, sex, baseline cardiovascular disease, diabetes, smoking, low-density lipoprotein cholesterol and the metabolic syndrome, indicating that the ABI contributes prognostic information not captured by the conventional risk-factor set.^{13,17,21}

All-Cause Mortality

All-cause mortality was reported in thirty-eight studies and demonstrates the same directional consistency, with the additional advantage of being immune to cause-of-death misclassification. The magnitude of the association is generally somewhat lower than for cardiovascular mortality, which is the expected pattern if PAD acts preferentially through atherosclerotic mechanisms and non-cardiovascular deaths dilute the signal. The estimates are presented in Table 11.

Table 11. All-cause mortality in peripheral artery disease

Study (Year)	Population / comparison	Effect estimate (95% CI)	Statistical significance
Sartipy (2018)	Ten-year all-cause mortality by stage: referent / APAD / IC / SLI	27% / 56% / 63% / 75%	Significant gradient
Cea Soriano (2017)	Symptomatic PAD versus matched comparators	83.2 versus 50.5 deaths per 1000 person-years	Significant
Pande (2011)	ABI ≤ 0.90 versus no PAD	HR 2.4 (1.9–2.9), $p < 0.0001$	Significant
Pande (2011)	PAD without known CVD versus neither PAD nor CVD	HR 1.9 (1.3–2.8), $p = 0.001$	Significant
Matsushita (2022)	PAD without CHD/stroke versus neither	HR 1.68 (1.35–2.08)	Significant
Matsushita (2022)	CHD/stroke without PAD versus neither	HR 1.81 (1.54–2.12)	Significant
Matsushita (2022)	PAD together with CHD/stroke versus neither	HR 2.70 (2.07–3.53)	Significant
Zhang (2025)	Coexisting CKD and PAD versus neither	Adjusted HR 3.25 (2.55–4.14)	Significant

Alves-Cabratos (2019)	Low ABI alone versus normal ABI, no diabetes, no CVD	HR 1.42 (1.25–1.63)	Significant
Alves-Cabratos (2019)	Low ABI plus diabetes versus reference group	HR 1.84 (1.68–2.01)	Significant
Jagt (2022)	Screen-detected low ABI versus normal ABI in manifest CVD	HR 1.7 (1.5–2.0)	Significant
Jagt (2022)	Known PAD versus normal ABI in manifest CVD	HR 1.7 (1.5–1.9)	Significant
Samba (2019)	ABI ≤ 0.90 in Congolese adults ≥ 65 years, 2-year mortality	HR 1.86 (1.04–3.87)	Significant
Zhao (2023)	Bilateral low ABI versus bilateral normal ABI	HR 2.10 (1.39–3.18)	Significant
Zhao (2023)	Unilateral low ABI versus bilateral normal ABI	HR 1.70 (1.13–2.57)	Significant
Dorn (2023)	Pathological versus normal ABI, 5-year mortality in nursing homes	76.5% versus 68.7% (p = 0.003)	Significant
Dorn (2023)	ABI > 1.4 versus normal ABI, 5-year mortality	79.4% versus 68.7% (p = 0.011)	Significant
Rerkasem (2025)	Critical limb ischaemia versus asymptomatic PAD in T2DM	HR 5.26 (3.10–8.94)	Significant
Avdic (2024)	Type 2 diabetes plus PAD versus PAD without	Adjusted HR 1.12 (1.05–1.19)	Significant

	diabetes		
Tanaka (2016)	Borderline ABI 0.91–1.00 versus normal	HR 2.27 (p = 0.005)	Significant
Lin (2024)	Highest versus lowest QTc tertile in dialysis patients with PAD	HR 2.41 (1.58–3.69)	Significant
Vidula (2008)	D-dimer, per unit increase in log-transformed level	HR 1.20 (1.08–1.33), p < 0.001	Significant
Malik (2020)	Chronic high perceived stress over 12 months	HR 2.12 (1.14–3.94), p = 0.02	Significant
Eikelboom (2021)	Rivaroxaban plus aspirin versus aspirin, total mortality	HR 0.82 (0.71–0.96), p = 0.01	Significant reduction
Pande (2011)	Use of multiple preventive therapies in PAD without known CVD	HR 0.35 (0.20–0.86), p = 0.02	Significant reduction
Xiong (2024)	Moderate-to-vigorous activity ≥ 60 min/week	HR 0.55 (0.37–0.85), p < 0.001	Significant reduction
Cha (2022)	Physically active versus inactive after revascularisation	Adjusted HR 0.766 (0.685–0.855)	Significant reduction
Cha (2022)	Tobacco use versus non-use after revascularisation	Adjusted HR 1.279 (1.124–1.456)	Significant increase
Søgaard (2023)	Annual mortality among PAD patients, 2018 versus 2000	Mortality ratio 0.75 (0.72–0.78)	Significant decline
Fowkes (2010)	Aspirin versus placebo in	HR 0.95 (0.77–1.16)	Not significant

	screen-detected low ABI		
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The comparison drawn by Matsushita and colleagues deserves separate emphasis because it directly addresses the clinical hierarchy that governs everyday practice. In a nationally representative sample of United States adults, individuals with PAD but no history of coronary heart disease or stroke had twelve-year survival of 47.7%, essentially indistinguishable from the 53.2% survival of individuals with coronary heart disease or stroke but no PAD, and both were far below the 87.2% survival of individuals with neither condition. The adjusted mortality hazard for PAD without coronary or cerebrovascular disease was 1.68 against 1.81 for coronary or cerebrovascular disease without PAD. The prognosis of isolated PAD is therefore no better than that of isolated coronary or cerebrovascular disease, a finding that undermines any clinical model treating PAD as a lesser vascular diagnosis.²³

Composite Major Adverse Cardiovascular Events

The composite of cardiovascular death, myocardial infarction and stroke was the primary endpoint of the major randomised trials in this field and was also reported by several observational cohorts. This domain carries the highest GRADE certainty in the review because it rests principally on adequately powered, double-blind, multinational randomised evidence. The estimates are presented in Table 12.

Table 12. Composite major adverse cardiovascular events

Study (Year)	Population / comparison	Effect estimate (95% CI)	Statistical significance
Eikelboom (2017)	Rivaroxaban 2.5 mg bd + aspirin versus aspirin, whole COMPASS cohort	HR 0.76 (0.66–0.86), p < 0.001	Significant reduction
Anand (2018, Lancet)	Rivaroxaban 2.5 mg bd + aspirin versus aspirin in PAD	HR 0.72 (0.57–0.90), p = 0.0047	Significant reduction
Anand (2018,	Rivaroxaban 5 mg bd	HR 0.86 (0.69–1.08), p =	Not significant

Lancet)	versus aspirin in PAD	0.19	
Bonaca (2020)	Rivaroxaban + aspirin versus aspirin after revascularisation	HR 0.85 (0.76–0.96), p = 0.009	Significant reduction
Gutierrez (2018)	PAD plus cerebrovascular disease versus PAD alone	Adjusted HR 1.34 (1.15–1.57), p < 0.001	Significant
Gutierrez (2018)	PAD plus coronary artery disease versus PAD alone	Adjusted HR 1.65 (1.43–1.91), p < 0.001	Significant
Gutierrez (2018)	PAD plus coronary and cerebrovascular disease versus PAD alone	Adjusted HR 1.99 (1.69–2.34), p < 0.001	Significant
Criqui (2010)	ABI <1.00 versus normal, incident CVD	HR 1.77, p < 0.001	Significant
Criqui (2010)	ABI ≥1.40 versus normal, incident CVD	HR 1.85, p = 0.050	Significant
Zhao (2023)	Bilateral low ABI versus bilateral normal ABI, MACE	HR 1.86 (1.20–2.88)	Significant
Zhao (2023)	Unilateral low ABI versus bilateral normal ABI, MACE	HR 1.58 (1.04–2.41)	Significant
Jagt (2022)	Screen-detected low ABI versus normal ABI, MACE	HR 1.9 (1.6–2.2)	Significant
Lin (2024)	Highest versus lowest QTc tertile in dialysis PAD, MACE	HR 1.90 (1.15–3.13)	Significant
Steg (2007)	One-year CV death, MI or	PAD 5.35% versus CAD	Significant

	stroke by disease location	4.52% versus CVD 6.47%	heterogeneity
Alberts (2009)	Three-year MI, stroke or vascular death, symptomatic versus risk factors only	12.0% versus 6.0%, $p < 0.001$	Significant
Samsky (2021)	Three diseased arterial beds versus none in type 2 diabetes	Adjusted HR 3.46 (2.69–4.45), $p < 0.001$	Significant
Vanassche (2020)	Four to six versus zero to one uncontrolled risk factors	HR 2.2 (1.8–2.6), $p < 0.0001$	Significant
Kaplovitch (2021)	Rivaroxaban + aspirin in high-risk LE-PAD, MACE or MALE	Absolute risk reduction 4.2% (1.9–6.2) at 30 months	Significant reduction

Myocardial Infarction and Cerebrovascular Events

Disaggregating the composite endpoint demonstrates that PAD predicts both coronary and cerebrovascular events, though the coronary signal is consistently the stronger of the two. In the 4.2-million-adult linked electronic-record cohort, established PAD was associated with an increased risk of eleven distinct vascular events, with ischaemic heart disease and heart failure prominent among them, whereas haemorrhagic stroke showed no association — a dissociation that supports an atherothrombotic rather than a generalised vascular-fragility mechanism. The estimates are presented in Table 13.²⁵

Table 13. Myocardial infarction, stroke and other vascular events

Study (Year)	Population / comparison	Effect estimate (95% CI)	Statistical significance
Emdin (2015)	PAD and subsequent	HR 1.68 (1.58–1.79)	Significant

	ischaemic heart disease		
Emdin (2015)	PAD and subsequent heart failure	HR 1.63 (1.52–1.75)	Significant
Emdin (2015)	PAD and subsequent aortic aneurysm	HR 2.10 (1.79–2.45)	Significant
Emdin (2015)	PAD and subsequent chronic kidney disease	HR 1.31 (1.25–1.38)	Significant
Emdin (2015)	PAD and subsequent haemorrhagic stroke	No association demonstrated	Not significant
Leng (1996)	ABPI ≤ 0.9 and non-fatal myocardial infarction	RR 1.38 (0.88–2.16)	Not significant
Leng (1996)	ABPI ≤ 0.9 and stroke	RR 1.98 (1.05–3.77)	Significant
Cea Soriano (2017)	Previous ischaemic stroke as predictor of CV outcome in PAD	HR 1.77 (1.63–1.93)	Significant
Cea Soriano (2017)	Previous myocardial infarction as predictor in PAD	HR 1.29 (1.20–1.39)	Significant
Cea Soriano (2017)	Comorbid diabetes as predictor of CV outcome in PAD	HR 1.42 (1.32–1.52)	Significant
Cea Soriano (2017)	Current smoking as predictor of CV outcome in PAD	HR 1.26 (1.17–1.35)	Significant
Gutierrez (2018)	Polyvascular PAD and lower-extremity revascularisation	HR 1.17–1.34 across strata	Significant

Baviera (2018)	Acute coronary syndrome, 2008–2014 versus 2002–2008 PAD cohort	28% relative reduction	Significant reduction
Baviera (2018)	Stroke, 2008–2014 versus 2002–2008 PAD cohort	27% relative reduction	Significant reduction

Severity-Stage Gradient

The relationship between clinical PAD stage and mortality is one of the most robust findings in this review, replicated in population-based, registry and procedural cohorts across four countries. Ten-year all-cause mortality in an unselected Swedish population rose from 27% in referents through 56% in asymptomatic PAD and 63% in intermittent claudication to 75% in severe limb ischaemia, while cardiovascular causes accounted for 45% of deaths among all PAD subjects and appeared among the three leading contributory causes in 64%. In procedural cohorts the picture is bleaker still: three-year mortality after peripheral vascular intervention for chronic limb-threatening ischaemia was 39.1% with a median survival of 1.4 years, and median survival after primary major amputation in a Medicare cohort was only 1.3 years. The estimates are presented in Table 16.^{13,49,44}

Table 14. Mortality gradient across peripheral artery disease severity stages

Study (Year)	Population / comparison	Effect estimate (95% CI)	Statistical significance
Sartipy (2018)	Ten-year all-cause mortality, referents	27%	Reference
Sartipy (2018)	Ten-year all-cause mortality, asymptomatic PAD	56%	Significant versus referents
Sartipy (2018)	Ten-year all-cause mortality, intermittent claudication	63%	Significant versus referents
Sartipy (2018)	Ten-year all-cause	75%	Significant

	mortality, severe limb ischaemia		versus referents
Sartipy (2018)	Proportion of PAD deaths from cardiovascular causes	45% as main cause; 64% as main or contributory	Descriptive
Rerkasem (2025)	Seven-year cumulative all-cause mortality in T2DM with PAD	36% (6.4 deaths per 100 person-years)	Descriptive
Rerkasem (2025)	Asymptomatic PAD versus intermittent claudication, mortality	No significant difference	Not significant
Callegari (2024)	Three-year all-cause mortality after PVI for CLTI	39.1%; median survival 1.4 years	Descriptive
Mustapha (2018)	Four-year survival, all incident critical limb ischaemia	46%; median survival 3.5 years	Descriptive
Mustapha (2018)	Four-year survival after primary major amputation	23%; median survival 1.3 years	Significant versus revascularisation
Mustapha (2018)	Four-year survival after endovascular versus surgical revascularisation	38% versus 40%	Not significant
Farber (2022)	MALE or death, surgery versus endovascular therapy in CLTI (cohort 1)	42.6% versus 57.4%; HR 0.68 (0.59–0.79), $p < 0.001$	Significant
Farber (2022)	MALE or death in patients lacking adequate saphenous	42.8% versus 47.7%; HR 0.79 (0.58–1.06), $p =$	Not significant

	vein (cohort 2)	0.12	
Kaplovitch (2021)	30-month MACE or MALE risk with prior amputation	22.6%	Descriptive
Kaplovitch (2021)	30-month MACE or MALE risk with Fontaine III–IV symptoms	17.6%	Descriptive
Kaplovitch (2021)	30-month MACE or MALE risk with prior revascularisation	11.8%	Descriptive

Ankle–Brachial Index Category and the U-Shaped Hazard

Nine included cohorts examined mortality across ABI strata, and their convergent finding is that risk is elevated at both extremes of the index. A low ABI reflects flow-limiting stenosis, whereas a high ABI reflects medial arterial calcification rendering the vessel incompressible; both are markers of advanced arterial disease, and both predict death. The Strong Heart Study established the U-shaped pattern with adjusted CVD mortality hazards of 2.52 for ABI <0.90 and 2.09 for ABI >1.40, and the same morphology was subsequently reproduced in a multi-ethnic United States cohort, in German nursing-home residents and in Finnish patients undergoing angiography. The estimates are presented in Table 15.^{18,19,33,29}

Table 15. Mortality across ankle–brachial index categories

Study (Year)	Population / comparison	Effect estimate (95% CI)	Statistical significance
Resnick (2004)	ABI <0.90, CVD mortality	HR 2.52 (1.74–3.64)	Significant
Resnick (2004)	ABI >1.40, CVD mortality	HR 2.09 (1.49–2.94)	Significant
Resnick (2004)	ABI <0.90, all-cause mortality	HR 1.69 (1.34–2.14)	Significant
Resnick (2004)	ABI >1.40, all-cause	HR 1.77 (1.48–2.13)	Significant

	mortality		
Criqui (2010)	ABI <1.00, incident CVD after full adjustment	HR 1.77, p < 0.001	Significant
Criqui (2010)	ABI ≥1.40, incident CVD after full adjustment	HR 1.85, p = 0.050	Significant
Tanaka (2016)	Borderline ABI 0.91–1.00, cardiovascular death	HR 3.47, p = 0.003	Significant
Tanaka (2016)	Borderline ABI 0.91–1.00, all-cause death	HR 2.27, p = 0.005	Significant
Dorn (2023)	ABI >1.4 versus normal, 5-year mortality	79.4% versus 68.7%, p = 0.011	Significant
Dorn (2023)	ABI ≤0.9 versus normal, 5-year mortality	74.7% versus 68.7%	Significant
Jagt (2022)	Screen-detected ABI ≥1.4 versus normal, all-cause mortality	HR 0.6 (0.5–0.9)	Significant, inverse
Zhao (2023)	Bilateral versus unilateral low ABI, all-cause mortality	HR 2.10 versus 1.70	Both significant
Koivunen (2021)	ABI <0.25, femoropopliteal-dominant disease, CV mortality	HR 5.45 (1.56–19.0)	Significant
Koivunen (2021)	ABI ≥1.30, femoropopliteal-dominant disease, CV mortality	HR 6.71 (1.89–23.8)	Significant
Alves-Cabratos (2019)	Low ABI versus normal, all-cause mortality	HR 1.42 (1.25–1.63)	Significant

Samba (2019)	ABI ≤ 0.90 , 2-year all-cause mortality	HR 1.86 (1.04–3.87)	Significant
Mohammedi (2024)	Lowest versus highest quartile of ankle systolic pressure, incident PAD	HR 4.23 (3.44–5.21)	Significant
Mohammedi (2024)	Lowest versus highest quartile of ABI, incident PAD	HR 3.34 (2.75–4.06)	Significant
Mohammedi (2024)	Lowest versus highest quartile of ankle–pulse–pressure difference	HR 3.63 (2.96–4.45)	Significant

The inverse association for screen-detected high ABI reported in the UCC-SMART cohort is the single discordant estimate in this domain and is discussed in Section 4.4; it arose in a population already selected for manifest cardiovascular disease and in which high ABI may have identified patients with preserved rather than compromised distal perfusion.

Major Adverse Limb Events and Their Mortality Consequences

Limb events are not merely limb events. A first major adverse limb event functions as a sentinel marker of imminent systemic deterioration: within the COMPASS PAD population, the occurrence of a MALE raised the subsequent risk of hospitalisation more than sevenfold and the subsequent risk of death more than threefold, and the one-year cumulative risk of death after a MALE was 8.3%. This finding reframes limb-event prevention as a mortality-prevention strategy rather than a purely functional objective. The estimates are presented in Table 16.⁶

Table 16. Major adverse limb events, amputation and mortality

Study (Year)	Population / comparison	Effect estimate (95% CI)	Statistical significance
Anand (2018, JACC)	MALE index event and subsequent death	HR 3.23, $p < 0.001$	Significant

Anand (2018, JACC)	MALE index event and subsequent hospitalisation	HR 7.21, $p < 0.0001$	Significant
Anand (2018, JACC)	MALE index event and subsequent amputation	HR 197.5, $p < 0.0001$	Significant
Anand (2018, JACC)	One-year cumulative risk of death after a first MALE	8.3%	Descriptive
Anand (2018, JACC)	Rivaroxaban + aspirin versus aspirin, incidence of MALE	43% relative reduction, $p = 0.01$	Significant reduction
Anand (2018, JACC)	Rivaroxaban + aspirin, total vascular amputations	58% relative reduction, $p = 0.01$	Significant reduction
Anand (2018, Lancet)	Rivaroxaban + aspirin versus aspirin, MALE including major amputation	HR 0.54 (0.35–0.82), $p = 0.0037$	Significant reduction
Anand (2018, Lancet)	Rivaroxaban 5 mg bd versus aspirin, MALE including major amputation	HR 0.67 (0.45–1.00), $p = 0.05$	Borderline significant
Jagt (2022)	Screen-detected low ABI and major adverse limb events	HR 7.6 (5.7–10.1)	Significant
Jagt (2022)	Known PAD and major adverse limb events	HR 13.8 (11.1–17.1)	Significant
Kumbhani (2014)	Statin use and adverse limb outcome at 4 years	HR 0.82 (0.72–0.92), $p = 0.0013$	Significant reduction
Kumbhani (2014)	Statin use and composite CV death, MI or stroke	HR 0.83 (0.73–0.96), $p = 0.01$	Significant reduction
Rakestraw (2023)	Major amputation at 21	22.3% versus 7.1%, $p <$	Significant

	months, ESKD versus non-ESKD	0.001	
Baviera (2018)	Major amputation, 2008–2014 versus 2002–2008 cohort	17% relative reduction	Significant reduction

Interaction with Diabetes Mellitus

Diabetes and PAD are individually potent predictors of cardiovascular death, and their coexistence is more than additive in absolute terms. Register data from Sweden show that among individuals who had already sustained an incident PAD event, the presence of type 2 diabetes conferred a further 13% relative increase in cardiovascular mortality, with baseline hyperglycaemia and advanced age contributing most to the predictive model. In parallel, randomised data demonstrate that although the relative benefit of intensified antithrombotic therapy is similar in diabetic and non-diabetic patients, the absolute mortality reduction is approximately threefold greater in those with diabetes because their baseline risk is higher. The estimates are presented in Table 17.^{16,12}

Table 17. Peripheral artery disease, diabetes mellitus and cardiovascular mortality

Study (Year)	Population / comparison	Effect estimate (95% CI)	Statistical significance
Avdic (2024)	T2D plus incident PAD versus PAD without T2D, CV mortality	Adjusted HR 1.13 (1.07–1.19), $p < 0.01$	Significant
Avdic (2024)	T2D plus incident PAD versus PAD without T2D, all-cause mortality	Adjusted HR 1.12 (1.05–1.19), $p < 0.01$	Significant
Avdic (2024)	Crude all-cause mortality rate after PAD onset, T2D versus controls	600.4 versus 549.1 per 10,000 person-years	Significant

Rerkasem (2025)	Critical limb ischaemia versus asymptomatic PAD in T2DM, CVD mortality	SHR 6.20 (3.20–12.03)	Significant
Rerkasem (2025)	Independent mortality predictors in T2DM with PAD	CLI, chronic kidney disease and BMI <18.5 kg/m ²	Significant
Alves-Cabratos (2019)	Low ABI plus diabetes versus normal ABI without diabetes	HR 1.84 (1.68–2.01)	Significant
Cea Soriano (2017)	Comorbid diabetes as predictor of composite CV outcome in PAD	HR 1.42 (1.32–1.52)	Significant
Samsky (2021)	One versus zero diseased arterial beds in T2D, all-cause mortality	Adjusted HR 1.94 (1.56–2.42)	Significant
Samsky (2021)	Three versus zero diseased arterial beds in T2D, all-cause mortality	Adjusted HR 3.66 (2.59–5.18)	Significant
Bhatt (2020)	Rivaroxaban + aspirin in diabetes, primary efficacy endpoint	HR 0.74, p = 0.002	Significant reduction
Bhatt (2020)	Rivaroxaban + aspirin in diabetes, all-cause mortality	HR 0.81, p = 0.05	Significant reduction
Bhatt (2020)	Absolute mortality reduction, diabetes versus no diabetes	1.9% versus 0.6%, p-interaction = 0.02	Significant interaction

Bhatt (2020)	Net clinical benefit, diabetes versus no diabetes	2.7% versus 1.0%, p-interaction = 0.001	Significant interaction
Mohammedi (2024)	Ankle pressure indices in a cohort 50.2% diabetic, incident PAD and death	Highest c-statistics of all indices tested	Significant

Interaction with Chronic Kidney Disease

Renal dysfunction is the single most powerful comorbid amplifier of mortality in PAD identified in this review. In a nationally representative United States cohort followed for a median of almost seventeen years, the coexistence of chronic kidney disease and PAD raised cardio-cerebrovascular mortality by a factor of 4.76 relative to individuals with neither condition, exceeding the risk conferred by either condition alone. In end-stage disease the figures become extreme: one-year mortality among patients with end-stage kidney disease and chronic limb-threatening ischaemia was 44.9% irrespective of whether revascularisation, amputation or no procedure was undertaken. The estimates are presented in Table 18.^{24,50}

Table 18. Peripheral artery disease, renal dysfunction and mortality

Study (Year)	Population / comparison	Effect estimate (95% CI)	Statistical significance
Zhang (2025)	CKD plus PAD versus neither, cardio-cerebrovascular mortality	Adjusted HR 4.76 (3.41–6.63), p < 0.001	Significant
Zhang (2025)	CKD plus PAD versus neither, all-cause mortality	Adjusted HR 3.25 (2.55–4.14), p < 0.001	Significant
Shah (2024)	ESKD with incident CLTI, one-year mortality	44.9%	Descriptive
Shah (2024)	ESKD with CLTI, 90-day major postoperative complications	41.8%	Descriptive

Shah (2024)	ESKD with CLTI, 90-day readmission	52.6%	Descriptive
Rakestraw (2023)	Mortality at 21 months after PVI, ESKD versus non-ESKD	41.7% versus 17.4%, $p < 0.001$	Significant
Lin (2024)	Highest versus lowest QTc tertile in dialysis PAD, all-cause mortality	HR 2.41 (1.58–3.69)	Significant
Lin (2024)	Dialysis patients with symptomatic PAD, mortality over median 2.2 years	52.8% died; MACE in 33.4%	Descriptive
Callegari (2024)	Chronic kidney disease as predictor of 3-year mortality in CLTI	Highest-ranked predictor in random survival forest	Significant
Rerkasem (2025)	Chronic kidney disease as independent mortality predictor in T2DM with PAD	Significant in multivariable model	Significant
Emdin (2015)	PAD and subsequent chronic kidney disease	HR 1.31 (1.25–1.38)	Significant
Emdin (2015)	CKD as the most common initial vascular event after PAD	24.4% of all initial events	Descriptive

Polyvascular Disease Burden

Every study that counted arterial territories found a monotonic mortality gradient. In the REACH registry, one-year rates of cardiovascular death, myocardial infarction, stroke or

atherothrombotic hospitalisation rose from 5.31% in patients with risk factors alone to 12.58%, 21.14% and 26.27% in those with one, two and three symptomatic arterial disease locations respectively. The same ordering appeared in a German angiographic cohort, in a randomised trial of type 2 diabetes and in the EUCLID population. Crucially, the combinations that included PAD were consistently the most lethal. The estimates are presented in Table 19.^{39,42,52,7}

Table 19. Mortality and event rates according to polyvascular disease burden

Study (Year)	Population / comparison	Effect estimate (95% CI)	Statistical significance
Steg (2007)	Risk factors only, one-year CV death/MI/stroke/hospitalisation	5.31%	Reference
Steg (2007)	One symptomatic arterial territory	12.58%	Significant trend, $p < 0.001$
Steg (2007)	Two symptomatic arterial territories	21.14%	Significant trend
Steg (2007)	Three symptomatic arterial territories	26.27%	Significant trend
Bhatt (2010)	Polyvascular disease versus single-bed disease, ischaemic events	HR 1.99 (1.78–2.24), $p < 0.001$	Significant
Bhatt (2010)	Diabetes as independent determinant in the same model	HR 1.44 (1.36–1.53), $p < 0.001$	Significant
Alberts (2009)	Three-year MI/stroke/vascular death/rehospitalisation, one versus multiple beds	25.5% versus 40.5%, $p < 0.001$	Significant
Yazdani (2023)	One diseased bed versus none, cardiovascular mortality	HR 1.56 (1.19–2.06)	Significant
Yazdani (2023)	Two diseased beds versus	HR 2.70 (1.97–3.72)	Significant

	none, cardiovascular mortality		
Yazdani (2023)	Three diseased beds versus none, cardiovascular mortality	HR 3.50 (2.19–5.62)	Significant
Yazdani (2023)	PAD plus carotid stenosis versus coronary plus carotid disease	All-cause HR 7.53 versus 1.94	Significant
Samsky (2021)	One diseased bed versus none in T2D, MACE	Adjusted HR 1.71 (1.46–2.02)	Significant
Samsky (2021)	Two diseased beds versus none in T2D, MACE	Adjusted HR 2.61 (2.17–3.15)	Significant
Samsky (2021)	Three diseased beds versus none in T2D, MACE	Adjusted HR 3.46 (2.69–4.45)	Significant
Gutierrez (2018)	PAD with coronary and cerebrovascular disease versus PAD alone, MACE	Adjusted HR 1.99 (1.69–2.34)	Significant
Szarek (2022)	Total events per 100 patients at 3 years, three affected territories	87.3 to 97.7	Descriptive
Kaplovitch (2021)	Polyvascular disease as a high-risk comorbidity in LE-PAD	30-month MACE or MALE risk 12.8%	Descriptive

Pharmacological Modification of Cardiovascular Mortality

This domain answers the question that gives the entire review its clinical purpose: is the excess mortality associated with PAD modifiable? The randomised evidence indicates unambiguously that a substantial fraction of it is. The addition of low-dose rivaroxaban to aspirin reduced cardiovascular death by 22% and all-cause death by 18% in a population of chronic coronary or peripheral artery disease, with the absolute benefit rising steeply with the number of high-risk baseline features: patients with none, one, two, and three or four high-risk features

experienced 4.2, 4.8, 25.0 and 53.9 fewer deaths respectively per 1000 patients treated for thirty months. Observational data reinforce this conclusion, with statin therapy and multi-drug secondary prevention each associated with substantially lower mortality. The estimates are presented in Table 20.^{4,46,22}

Table 20. Effect of pharmacological therapy on mortality in peripheral artery disease

Study (Year)	Population / comparison	Effect estimate (95% CI)	Statistical significance
Eikelboom (2021)	Rivaroxaban + aspirin versus aspirin, cardiovascular death	HR 0.78 (0.64–0.96), p = 0.02	Significant reduction
Eikelboom (2021)	Rivaroxaban + aspirin versus aspirin, all-cause death	HR 0.82 (0.71–0.96), p = 0.01	Significant reduction
Eikelboom (2021)	Deaths avoided per 1000 treated for 30 months, by high-risk feature count	4.2 / 4.8 / 25.0 / 53.9 for 0 / 1 / 2 / 3–4 features	Significant gradient
Eikelboom (2017)	Rivaroxaban + aspirin versus aspirin, CV death, stroke or MI	HR 0.76 (0.66–0.86), p < 0.001	Significant reduction
Eikelboom (2017)	Rivaroxaban + aspirin versus aspirin, major bleeding	HR 1.70 (1.40–2.05), p < 0.001	Significant increase
Anand (2018, Lancet)	Rivaroxaban + aspirin versus aspirin in PAD, MACE	HR 0.72 (0.57–0.90), p = 0.0047	Significant reduction
Anand (2018, Lancet)	Rivaroxaban + aspirin versus aspirin in PAD,	HR 1.61 (1.12–2.31), p = 0.0089	Significant increase

	major bleeding		
Bonaca (2020)	Rivaroxaban + aspirin after revascularisation, primary composite	HR 0.85 (0.76–0.96), p = 0.009	Significant reduction
Bonaca (2020)	Rivaroxaban + aspirin after revascularisation, TIMI major bleeding	HR 1.43 (0.97–2.10), p = 0.07	Not significant
Bhatt (2020)	Rivaroxaban + aspirin in diabetes, all-cause mortality	HR 0.81, p = 0.05	Significant reduction
Kaplovitch (2021)	Rivaroxaban + aspirin in high-risk LE-PAD, net clinical benefit	3.2% (0.6–5.3) at 30 months	Significant benefit
Kumbhani (2014)	Statin use versus non-use, CV death, MI or stroke at 4 years	HR 0.83 (0.73–0.96), p = 0.01	Significant reduction
Pande (2011)	Multiple preventive therapies in PAD without known CVD	HR 0.35 (0.20–0.86), p = 0.02	Significant reduction
Pande (2011)	Prevalence of statin use among US adults with PAD	30.5% ± 2.5%	Descriptive
Sartipy (2019)	Proportion of PAD subjects receiving guideline-recommended prophylaxis	Approximately 60%	Descriptive
Fowkes (2010)	Aspirin versus placebo in screen-detected low ABI, primary endpoint	HR 1.03 (0.84–1.27)	Not significant

Fowkes (2010)	Aspirin versus placebo, major haemorrhage requiring admission	HR 1.71 (0.99–2.97)	Not significant
Baviera (2018)	Later versus earlier PAD cohort, risk of death after 6 years	No significant change despite therapy uptake	Not significant
Vanassche (2020)	Four to six versus zero to one uncontrolled risk factors, CV death	HR 2.0 (1.5–2.7), $p < 0.0001$	Significant

Two null results in this domain are informative rather than discouraging. The Aspirin for Asymptomatic Atherosclerosis trial randomised 3,350 individuals with a screen-detected ABI of 0.95 or below and found no reduction in vascular events or mortality with aspirin over a mean of 8.2 years, demonstrating that identifying subclinical PAD is not by itself therapeutically sufficient and that aspirin monotherapy is inadequate for this population. Similarly, an Italian population comparison found significant reductions in acute coronary syndrome, stroke and amputation between the 2002 and 2008 admission cohorts without any change in mortality, suggesting that improvements in vascular care have thus far shifted the event profile more than the survival curve. Both findings argue for more intensive rather than less intensive intervention.^{10,47}

Sex Differences

Sex-stratified analyses reveal a consistent paradox: women with PAD receive guideline-directed therapy less frequently and are revascularised less often, yet after adjustment for age and comorbidity they experience equal or slightly better survival than men. This pattern is most plausibly explained by later presentation at an older age with a different comorbidity profile rather than by any protective biological effect, and it should not be read as reassurance. The estimates are presented in Table 21.^{48,45,27}

Table 21. Sex differences in treatment and mortality in peripheral artery disease

Study (Year)	Population / comparison	Effect estimate (95%	Statistical
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		CI)	significance
Benson (2022)	Women versus men, likelihood of statin prescription	OR 0.69 (0.66–0.72), $p < 0.001$	Significant undertreatment
Benson (2022)	Women versus men, likelihood of antiplatelet prescription	OR 0.87 (0.83–0.90), $p < 0.001$	Significant undertreatment
Benson (2022)	Women versus men, one-year all-cause mortality after full adjustment	Adjusted HR 0.95 (0.87–1.03), $p = 0.198$	Not significant
Porras (2024)	Women versus men, five-year mortality, 2007–2010 cohort	HR 0.89 (0.83–0.97)	Significant, favouring women
Porras (2024)	Women versus men, five-year mortality, 2011–2014 cohort	HR 0.88 (0.82–0.94)	Significant, favouring women
Porras (2024)	Standardised mortality ratio versus general population, both sexes	Significantly elevated in both	Significant
Makowski (2022)	Female sex and overall survival in CLTI	HR 0.95 (0.94–0.96), $p < 0.001$	Significant, favouring women
Makowski (2022)	Female sex and amputation-free survival in CLTI	HR 0.84 (0.83–0.85), $p < 0.001$	Significant, favouring women
Makowski (2022)	Women versus men, receipt of revascularisation during	61% versus 65%, $p < 0.001$	Significant undertreatment

	index admission		
Makowski (2022)	Women versus men, statin prescription at baseline	35% versus 43%, $p < 0.001$	Significant undertreatment
Søgaard (2023)	PAD incidence, men versus women	Approximately 20% higher in men	Significant
Søgaard (2023)	Prevalence at age ≥ 80 years, men versus women	7.9% versus 5.7%	Descriptive
Xiong (2024)	Survival benefit of physical activity, men versus women	Notably greater in men	Significant interaction

Risk Prediction and Reclassification

Beyond confirming an association, several studies quantified the incremental prognostic information that PAD measurement supplies over established risk scores. This is the practical test of whether ABI measurement should be adopted in routine practice, and the evidence indicates that it should. The estimates are presented in Table 22.

Table 22. Incremental risk prediction and reclassification

Study (Year)	Population / comparison	Effect estimate (95% CI)	Statistical significance
Criqui (2010)	ABI added to traditional and novel biomarker risk factors	Significantly improved risk discrimination	Significant
Criqui (2010)	ABI after further adjustment for coronary calcium and carotid IMT	Hazard ratios only modestly attenuated	Significant
Mohammedi (2024)	Ankle systolic pressure and ankle-pulse-pressure difference	Highest c-statistics and classification indices of all indices tested	Significant

Wild (2006)	Low ABI after adjustment for the metabolic syndrome	HR 1.5 (1.1–2.1) for CVD mortality	Significant
Leng (1996)	Positive predictive value in hypertensive smokers, by ABPI status	43.8% with low ABPI versus 15.6% with normal ABPI	Significant
Hicks (2023)	Elevated NT-proBNP or troponin combined with PAD versus biomarker alone	Higher all-cause and cardiovascular mortality	Significant
Callegari (2024)	Random survival forest for 3-year mortality in CLTI	Harrell C-index 0.70; CRPS 0.172	Good discrimination
Vidula (2008)	D-dimer, CRP and serum amyloid A for deaths within one year	HR 1.20, 1.13 and 1.12 respectively	Significant
Vidula (2008)	Same biomarkers for deaths occurring 2–3 years later	No significant association	Not significant
Jagt (2022)	Screen-detected low ABI in patients with known cardiovascular disease	MACE HR 1.9; MALE HR 7.6; mortality HR 1.7	Significant

Behavioural, Functional and Psychosocial Modifiers

The final outcome domain addresses determinants of mortality within the PAD population that lie outside conventional pharmacotherapy. These are of particular clinical value because they are modifiable, inexpensive and largely under-utilised. Physical activity emerged with a clear dose–response relationship, tobacco use with a clear harm signal, and chronic psychological stress with an effect size comparable to major biological risk factors. The estimates are presented in Table 23.^{35,36,38}

Table 23. Behavioural, functional and psychosocial determinants of mortality in PAD

Study (Year)	Population / comparison	Effect estimate (95 % CI)	Statistical significance
Xiong (2024)	MVPA ≥ 60 min/week versus less, all-cause mortality	HR 0.55 (0.37–0.85), $p < 0.001$	Significant reduction
Xiong (2024)	MVPA ≥ 60 min/week versus less, cardiovascular mortality	HR 0.40 (0.27–0.70), $p < 0.001$	Significant reduction
Xiong (2024)	Maximal survival benefit observed at 120–239 min/week of MVPA	Dose–response plateau	Significant gradient
Xiong (2024)	Muscle-strengthening activity 1–4 times/week, CVD mortality	HR 0.34 (0.17–0.90), $p = 0.011$	Significant reduction
Xiong (2024)	Meeting 2020 WHO physical activity guidelines alone	No significant mortality reduction	Not significant
Cha (2022)	Physically active versus inactive after revascularisation, mortality	Adjusted HR 0.766 (0.685–0.855)	Significant reduction
Cha (2022)	Physically active versus inactive, major adverse outcome	Adjusted HR 0.795 (0.719–0.878)	Significant reduction
Cha (2022)	Tobacco use versus non-use, all-cause mortality	Adjusted HR 1.279 (1.124–1.456)	Significant increase
Cha (2022)	Tobacco use versus non-	Adjusted HR 1.291	Significant

	use, major adverse limb event	(1.143–1.458)	increase
Malik (2020)	Chronic high perceived stress over 12 months, 4-year mortality	HR 2.12 (1.14–3.94), p = 0.02	Significant increase
Malik (2020)	Prevalence of high stress at baseline and at 12 months	65% and 20% respectively	Descriptive
Vidula (2008)	Rising D-dimer, CRP and serum amyloid A, near-term mortality	Each significantly associated ($p \leq 0.005$)	Significant
Callegari (2024)	Functional, behavioural and psychosocial predictors of 3-year mortality	41 of 66 variables across all biopsychosocial domains ranked	Significant
Rerkasem (2025)	Body mass index <18.5 kg/m ² as independent mortality predictor	Significant in multivariable model	Significant increase

Synthesis of Significance Across Outcome Domains

Table 24 summarises the direction, consistency and certainty of findings across all fifteen prespecified outcome domains. Twelve of the fifteen domains yielded uniformly statistically significant associations in the hypothesised direction. The three domains that did not — aspirin monotherapy in screen-detected disease, sex differences, and certain individual ischaemic components in smaller cohorts — are informative in their own right and are addressed in the Discussion.

Table 24. Summary of effect direction, consistency and certainty across the fifteen outcome domains

No	Outcome domain	Direction of effect	Consistency across studies	Overall certainty and inference
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O1	Cardiovascular mortality	Increased with PAD	26/26 studies concordant	Moderate — significant, graded, biologically coherent
O2	All-cause mortality	Increased with PAD	29/30 studies concordant	Moderate — significant and reproducible
O3	Composite MACE	Increased with PAD; reduced by therapy	Uniformly concordant	High — randomised evidence
O4	Myocardial infarction	Increased with PAD	Concordant; smaller cohorts underpowered	Moderate
O5	Stroke and cerebrovascular events	Increased with PAD (ischaemic only)	Concordant for ischaemic stroke	Moderate
O6	Severity-stage gradient	Monotonic increase with stage	Fully concordant across 4 countries	Moderate — strong dose-response
O7	ABI-category gradient	U-shaped; both extremes harmful	18/19 estimates concordant	Moderate
O8	MALE and amputation	Increased; predicts subsequent death	Fully concordant	Moderate to high
O9	Diabetes interaction	Amplifies risk; larger absolute treatment benefit	Fully concordant	Moderate
O10	CKD interaction	Strongly amplifies risk	Fully concordant	Moderate
O11	Polyvascular burden	Monotonic increase	Fully concordant	Moderate

		with territories	across 6 datasets	
O12	Pharmacological modification	Risk significantly reduced by combination therapy	Concordant except aspirin monotherapy	High
O13	Sex differences	Women undertreated; adjusted survival equal or better	Concordant but confounded	Low
O14	Risk prediction	ABI adds discrimination beyond risk scores	Fully concordant	Moderate
O15	Behavioural modifiers	Activity protective; tobacco and stress harmful	Concordant, dose–response for activity	Low to moderate

DISCUSSION

Principal Findings

This systematic review of fifty-four primary studies establishes four principal findings. First, peripheral artery disease is independently and significantly associated with cardiovascular mortality, and this association was demonstrated in every included primary study that examined it with an adjusted model; the review identified no primary study reporting a null or protective association for this endpoint. Second, the relationship is graded rather than dichotomous: cardiovascular mortality rises monotonically across clinical severity stages, across ankle–brachial index strata in both directions, across the number of involved arterial territories, and across comorbidity load. Third, the prognostic weight of PAD is at least equal to that of coronary heart disease or stroke, a conclusion supported most directly by the observation that individuals with

PAD but no coronary or cerebrovascular disease had twelve-year survival of 47.7% against 53.2% for those with coronary or cerebrovascular disease but no PAD. Fourth, and most consequentially for practice, a substantial fraction of this excess is modifiable: intensified antithrombotic therapy reduced cardiovascular death by 22% and total mortality by 18%, statin therapy reduced the composite of cardiovascular death, myocardial infarction and stroke by 17%, and multi-drug secondary prevention was associated with a 65% reduction in all-cause mortality among individuals with screen-detected PAD.^{23,4,46,22}

These findings are entirely concordant with the corroborative syntheses that were excluded from the characteristics table under the prespecified design restriction. An individual participant data meta-analysis of sixteen population cohorts found ten-year cardiovascular mortality of 18.7% in men with an ABI of 0.90 or below against 4.4% in those with a normal ABI, corresponding to a hazard ratio of 4.2 that remained at 2.9 after adjustment for the Framingham risk score. A more recent meta-analysis of twenty-five cohorts comprising 181,598 individuals reported cardiovascular mortality hazard ratios of 2.04 for an ABI below 0.9 and 2.39 for an ABI above 1.3. A systematic review of 124 studies encompassing 570,856 patients found pooled cardiovascular mortality of 39 per 1000 person-years in PAD, with all-cause mortality at 113 per 1000 person-years. The convergence of design-restricted primary evidence with independently conducted meta-analytic evidence provides strong triangulation.^{53,55,58}

Pathophysiological Interpretation

The most parsimonious explanation for the observed pattern is that peripheral artery disease functions as an integrative biomarker of total atherosclerotic burden rather than as a spatially confined arterial lesion. The lower-limb arteries are anatomically accessible to non-invasive pressure measurement in a way that the coronary and cerebral circulations are not, and the ankle-brachial index therefore provides an inexpensive window onto the systemic atherosclerotic process. This interpretation accounts for several otherwise puzzling observations assembled in this review: that asymptomatic PAD carries cardiovascular mortality risk approaching that of symptomatic PAD; that the ABI predicts death after adjustment for coronary calcium score, carotid intima-media

thickness and electrocardiographic abnormality; and that cardiac rather than limb events dominate the mortality profile even in populations recruited for limb symptoms.^{14,19,13}

The atherothrombotic mechanism is corroborated by the disaggregated event data. In a linked electronic-record cohort of 4.2 million adults, PAD predicted eleven separate vascular event categories, including ischaemic heart disease, heart failure, aortic aneurysm and chronic kidney disease, but showed no association with haemorrhagic stroke. This dissociation between ischaemic and haemorrhagic cerebrovascular endpoints is precisely what an atherothrombotic mechanism predicts and is difficult to reconcile with a generalised vascular-fragility hypothesis. It is further reinforced by the pharmacological evidence: the therapy that most consistently reduces mortality in this population is one that targets the coagulation cascade in addition to platelet activation, indicating that residual thrombin generation is a live pathological process in stable PAD rather than a historical event.^{25,1,2}

Inflammation constitutes a second mechanistic axis. Serial measurement of D-dimer, C-reactive protein and serum amyloid A in a prospective PAD cohort showed that rising biomarker levels were strongly associated with death occurring within the following one to two years but were not associated with deaths occurring two to three years later. This temporal specificity suggests that inflammatory and thrombotic activation are proximate, dynamic mediators of terminal decompensation rather than static traits, and it offers a mechanistic rationale for the near-term benefit observed with antithrombotic intensification. The parallel finding that elevated natriuretic peptide and high-sensitivity troponin concentrations, combined with PAD, confer greater mortality than either alone points towards subclinical myocardial injury as a convergent final pathway.^{37,52}

The Asymptomatic Paradox

One of the most clinically actionable findings of this review is that asymptomatic PAD is nearly as dangerous as symptomatic PAD while being far less likely to be diagnosed. In a Swedish population sample the adjusted cardiovascular death hazard was 1.80 for asymptomatic PAD and 1.95 for intermittent claudication — a difference of little clinical consequence. In a Thai diabetic cohort, asymptomatic PAD patients had an overall mortality risk indistinguishable from those with intermittent claudication. Yet in German nursing homes, 84.7% of residents with a low ABI had no

previously recorded PAD diagnosis, and in the United States more than five million adults with PAD were not receiving statin therapy. The clinical corollary is uncomfortable but unambiguous: the population at highest absolute risk of preventable cardiovascular death from PAD is, to a substantial extent, a population that has never been identified as having PAD at all.^{14,17,33,22}

This paradox arises because clinical detection of PAD depends upon a symptom — exertional limb discomfort — that is absent in a large fraction of affected individuals and that is further masked in the elderly, in those with limited exertional capacity, and in those with diabetic peripheral neuropathy. It follows that symptom-triggered diagnosis will systematically fail precisely in the subgroups whose comorbidity profile places them at greatest risk. Only deliberate haemodynamic screening can close this gap, and the demonstrated incremental discrimination of the ABI over established risk scores provides the quantitative justification for doing so.^{19,11}

The U-Shaped Relationship and Medial Arterial Calcification

The finding that a high ankle–brachial index carries mortality risk comparable to a low index deserves particular attention because it has direct methodological consequences. A high ABI generally reflects medial arterial calcification producing an incompressible vessel, a phenomenon characteristic of long-standing diabetes and of chronic kidney disease. In the Strong Heart Study the adjusted cardiovascular mortality hazard was 2.52 for an ABI below 0.90 and 2.09 for an ABI above 1.40, and comparable estimates were obtained in a multi-ethnic United States cohort and in German nursing-home residents. A recent meta-analysis reported a cardiovascular mortality hazard ratio of 2.39 for ABI above 1.3, which exceeded the estimate for ABI below 0.9.^{18,19,33,55}

The practical implication is that studies excluding high-ABI participants — historically a common analytic convention, adopted for example in the Edinburgh Artery Study analysis of metabolic syndrome — systematically remove a high-risk subgroup and thereby bias the apparent prevalence and prognostic weight of abnormal ABI downwards. A single discordant estimate was identified in this review, in which a screen-detected ABI of 1.4 or above was associated with lower all-cause mortality in a cohort of patients already selected for clinically manifest cardiovascular disease. That population differs fundamentally from the general-population cohorts in which the U-shaped relationship was established, and in a group with universally advanced atherosclerosis a

preserved or elevated ankle pressure may indicate patent distal vasculature rather than incompressibility. This estimate should therefore be regarded as context-specific rather than as a genuine contradiction.^{21,31}

Comorbidity Amplification: Diabetes and Renal Disease

The interaction between PAD and renal dysfunction produces the largest effect estimates in this review. Coexisting chronic kidney disease and PAD raised cardio-cerebrovascular mortality 4.76-fold over a median follow-up of almost seventeen years, and in end-stage disease one-year mortality after incident chronic limb-threatening ischaemia reached 44.9% regardless of treatment strategy, with 41.8% experiencing a major complication and 52.6% being readmitted within ninety days. In a registry analysis, twenty-one-month mortality after peripheral vascular intervention was 41.7% in patients with end-stage kidney disease against 17.4% in those without. A machine-learning analysis of 10,114 patients with chronic limb-threatening ischaemia ranked chronic kidney disease as the single most important predictor of three-year mortality among sixty-six candidate variables.^{24,50,51,49}

Two mechanisms plausibly underlie this amplification. Uraemic vasculopathy accelerates medial calcification and produces a distinctive infrapopliteal disease distribution that is technically less amenable to durable revascularisation, while the mineral-bone and inflammatory disturbances of chronic kidney disease independently promote arterial stiffening and myocardial fibrosis. The prognostic consequence is that renal function should be regarded not as a procedural risk modifier but as a primary determinant of the therapeutic goal itself: in a population with a one-year mortality approaching 45%, the appropriate objective may be symptom control and function rather than long-term limb salvage, and the Global Vascular Guidelines explicitly incorporate estimated two-year mortality into their patient-risk axis for this reason.⁶¹

The diabetes interaction is quantitatively smaller but therapeutically more encouraging. Although the presence of type 2 diabetes added only a 13% relative increase in cardiovascular mortality after incident PAD, the absolute benefit of intensified antithrombotic therapy was approximately threefold greater in diabetic than in non-diabetic patients precisely because their baseline risk was higher — an absolute mortality reduction of 1.9% against 0.6%, with net clinical

benefit of 2.7% against 1.0%. This is a textbook illustration of the principle that relative risk reduction constant across strata produces absolute benefit proportional to baseline risk, and it identifies the diabetic PAD patient as the phenotype in whom combination antithrombotic therapy is most clearly justified.^{16,12}

Polyvascular Disease as a Risk Multiplier

Six independent datasets in this review found that mortality rises monotonically with the number of symptomatic arterial territories. The gradient is steep: one-year composite event rates in the REACH registry rose from 5.31% with risk factors alone to 26.27% with three symptomatic territories, and in a German angiographic cohort cardiovascular mortality hazards were 1.56, 2.70 and 3.50 for one, two and three diseased beds. Notably, combinations that included PAD were the most lethal — the coexistence of PAD with carotid stenosis produced an all-cause mortality hazard of 7.53 against 1.94 for coronary plus carotid disease. The corollary for practice is that the vascular examination should not stop at the presenting territory, and that documenting PAD in a patient presenting with coronary or cerebrovascular disease materially changes the prognosis and should materially change the treatment intensity.^{39,42}

From Prognosis to Therapy: How Much Risk Is Removable?

The central therapeutic conclusion of this review is that the excess mortality of PAD is not immutable. The most informative single analysis is the COMPASS mortality report, which stratified benefit by the number of high-risk baseline features — polyvascular disease, chronic kidney disease, mild or moderate heart failure, and diabetes. Patients with none of these features gained 4.2 fewer deaths per 1000 treated over thirty months, whereas those with three or four gained 53.9 fewer deaths per 1000 — a more than twelvefold difference in absolute benefit driven entirely by baseline risk. Since the phenotypes identified throughout this review as carrying the greatest mortality — polyvascular PAD, PAD with renal impairment, diabetic PAD, PAD with heart failure — are precisely the phenotypes in which absolute treatment benefit is greatest, the prognostic and therapeutic literatures point in the same direction and identify the same patients.⁴

This benefit is not obtained without cost. Combination low-dose rivaroxaban and aspirin increased major bleeding by 70% in the overall trial population and by 61% in the peripheral and

carotid artery disease subgroup, predominantly gastrointestinal, although there was no significant increase in intracranial or fatal bleeding. In the high-risk lower-extremity PAD subgroup the estimated absolute increase in major bleeding was 2.0% against an absolute reduction of 4.2% in major adverse cardiovascular or limb events, giving an estimated net clinical benefit of 3.2%. In older patients undergoing revascularisation the number needed to treat was 26 against a number needed to harm of 123. The therapeutic calculus therefore favours intensification in high-risk PAD, but it is a genuine calculus rather than an unqualified recommendation, and it requires individual assessment of bleeding risk.^{1,2,5}

Equally important is the negative evidence. Aspirin monotherapy in individuals with a screen-detected ABI of 0.95 or below produced no reduction in vascular events or mortality over a mean of 8.2 years despite an event rate of 13.5 per 1000 person-years that confirmed the population was genuinely at risk. This trial is often misread as evidence against ABI screening; it is more accurately read as evidence that screening must be coupled to an adequate therapeutic response. Aspirin alone is insufficient for a population whose risk derives from advanced multi-territory atherosclerosis, and the subsequent demonstration that combination antithrombotic therapy and statin therapy do reduce mortality in comparable populations supplies the intervention that the earlier trial lacked.^{10,4,46}

Treatment Inequity and the Implementation Gap

A recurring and disquieting theme across the included studies is that the population known to be at highest risk is the population least likely to receive proven therapy. Among United States adults with PAD, only 30.5% were taking a statin, 35.8% aspirin and 24.9% a renin–angiotensin system inhibitor, corresponding to five million adults with PAD untreated with statins. In a Swedish population cohort only about 60% of PAD subjects received guideline-recommended prophylaxis. In the REACH registry, risk-factor control was significantly less frequent in PAD than in coronary or cerebrovascular disease across blood pressure, glycaemia, cholesterol and smoking cessation. Women fared worse still, being significantly less likely than men to receive statins or antiplatelets in United Kingdom primary care and less likely to be revascularised or receive statins during hospitalisation for chronic limb-threatening ischaemia in Germany.^{22,14,48,45}

The magnitude of the achievable gain from closing this gap can be estimated directly from the data. In the same survey population in which only 30.5% received statins, use of multiple preventive therapies among PAD patients without known cardiovascular disease was associated with a 65% lower all-cause mortality. Even allowing generously for confounding by indication and healthy-adherer bias, an effect of this magnitude implies that implementation failure, rather than absence of effective therapy, is currently the dominant modifiable determinant of cardiovascular death in PAD. This shifts the principal research and policy question from what to do to how to ensure that what is already known is actually done.²²

Strengths

The principal strengths of this review are its strict design filter, which prevents the double-counting of primary participants that occurs when meta-analyses are pooled alongside their constituent studies; its outcome architecture, which resolves fifteen distinct domains rather than collapsing heterogeneous evidence into a single estimate; its geographical breadth, incorporating cohorts from sub-Saharan Africa, South-East Asia, East Asia, Europe, North America and Australia; its integration of prognostic and therapeutic evidence within one framework; and the complete provenance transparency afforded by retrieving and reporting every reference through an indexed academic search engine.

Clinical and Policy Implications

Four implications follow directly from the assembled evidence. First, PAD should be treated operationally as a coronary risk equivalent, and every patient with PAD — including asymptomatic, screen-detected disease — should receive high-intensity statin therapy, antithrombotic therapy, blood-pressure control, glycaemic optimisation and structured smoking cessation as a default rather than as an option. Second, the ankle–brachial index should be measured in patients with any established atherosclerotic disease, in patients with diabetes or chronic kidney disease, and in older adults with multiple risk factors, with both low and high values treated as abnormal. Third, in patients with PAD and at least two high-risk features — polyvascular disease, chronic kidney disease, heart failure or diabetes — the addition of low-dose rivaroxaban to aspirin should be actively considered, since it is in exactly this group that the absolute mortality benefit is largest and

548

the net clinical benefit is most clearly positive. Fourth, supervised physical activity should be prescribed as therapy rather than advised as lifestyle counselling, given a 60% reduction in cardiovascular mortality associated with moderate-to-vigorous activity of at least sixty minutes per week.^{4,5,35}

Directions for Future Research

Five priorities emerge. First, randomised trials are required to establish whether ABI-based screening coupled to contemporary combination therapy — rather than to aspirin monotherapy — reduces cardiovascular mortality, a question the existing screening trial cannot answer. Second, trials specifically enrolling patients with PAD and chronic kidney disease are needed, since this group carries the highest mortality yet is routinely excluded or under-represented. Third, prospective cohorts and interventional studies in low- and middle-income settings, particularly in South and South-East Asia and sub-Saharan Africa, are urgently required, since these are the regions of most rapid burden growth and the thinnest evidence. Fourth, implementation science addressing the treatment gap — including sex-based inequity — is likely to yield greater population mortality benefit in the short term than any new pharmacological agent. Fifth, the high-ABI phenotype warrants dedicated prospective study rather than analytic exclusion, since it is common, prognostically severe and mechanistically distinct.^{10,50,62,48}

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This systematic review of fifty-four randomised and observational primary studies demonstrates that peripheral artery disease is independently, consistently and significantly associated with increased cardiovascular mortality. The association was positive and statistically significant in every included primary study that examined it with an adjusted model, and it was reproducible across four continents, across three decades of publication and across every study design admitted to the review. The magnitude of the excess ranges from approximately twofold for screen-detected asymptomatic disease to more than sixfold for critical limb ischaemia in diabetic populations and nearly fivefold for the combination of peripheral artery disease with chronic kidney disease.^{13,17,24}

The association is graded rather than binary. Cardiovascular mortality rises monotonically with clinical severity stage, with the number of involved arterial territories and with comorbidity burden, and it rises at both extremes of the ankle–brachial index, producing a U-shaped hazard in which medial arterial calcification is as ominous as flow-limiting stenosis. The prognostic weight of peripheral artery disease is at least equal to that of coronary heart disease or stroke, and asymptomatic disease carries risk approaching that of symptomatic disease while being far less frequently diagnosed. These findings collectively support the interpretation that peripheral artery disease functions as an integrative marker of total atherosclerotic burden rather than as a limb-confined disorder.^{18,23,14}

Most importantly, the excess risk is demonstrably modifiable. Randomised evidence establishes that adding low-dose rivaroxaban to aspirin reduces cardiovascular death by 22% and total mortality by 18%, with absolute benefit rising more than twelvefold across strata of baseline risk, while observational evidence links statin therapy and multi-drug secondary prevention to substantial mortality reductions. Set against the finding that fewer than one in three adults with peripheral artery disease receives statin therapy, the dominant modifiable determinant of cardiovascular death in this population is currently the failure to deliver treatments already proven to work. The null hypothesis that peripheral artery disease is not independently associated with cardiovascular mortality is decisively rejected.^{4,46,22}

Recommendations

For clinical practice

Physicians should treat peripheral artery disease, including asymptomatic and screen-detected disease, as a coronary risk equivalent and should institute high-intensity statin therapy, appropriate antithrombotic therapy, blood-pressure control, glycaemic optimisation and structured smoking cessation as the default management standard. The ankle–brachial index should be measured in every patient with established atherosclerotic disease in any territory, in patients with diabetes or chronic kidney disease, and in older adults with multiple risk factors, and both low and high values should be recorded and acted upon as abnormal. In patients with peripheral artery disease and two or more high-risk features — polyvascular disease, chronic kidney disease, heart

failure or diabetes — the addition of low-dose rivaroxaban to aspirin should be actively considered after individual assessment of bleeding risk. A first major adverse limb event should trigger systemic reassessment and intensification of cardiovascular therapy rather than being managed as an isolated limb problem. Supervised exercise should be prescribed with the same seriousness as pharmacotherapy.^{4,5,6,35}

For health systems and policy

Health systems should audit the delivery of guideline-directed medical therapy in peripheral artery disease populations, with explicit attention to the documented sex disparity in statin and antiplatelet prescribing, and should adopt therapy delivery as an accountable quality indicator. Ankle–brachial index measurement should be integrated into existing cardiovascular risk-assessment programmes, where its demonstrated incremental discrimination beyond established risk scores justifies the modest cost. In settings with a high burden of diabetes and chronic kidney disease, targeted case-finding in these populations is likely to be the most efficient strategy. In low- and middle-income countries, where the mortality burden of peripheral artery disease is rising most rapidly, investment in simple pressure-based diagnostic capacity should precede investment in advanced revascularisation infrastructure.^{48,19,62}

For future research

Investigators should prioritise randomised evaluation of ankle–brachial index screening coupled to contemporary combination antithrombotic and lipid-lowering therapy rather than to aspirin monotherapy; dedicated trials in patients with peripheral artery disease and chronic kidney disease, who carry the highest mortality and are systematically under-represented; prospective cohorts and pragmatic trials in South and South-East Asian and sub-Saharan African populations; implementation research addressing the treatment gap and sex-based inequity; and prospective characterisation of the high ankle–brachial index phenotype, which should no longer be analytically excluded. Future observational work should apply competing-risk methods routinely when reporting cause-specific mortality, and should report ankle–brachial index as a categorical variable including the high stratum so that the full hazard morphology remains visible.^{10,50,62}

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