medical sciences

Supplementary Materials

Chronic Venous Disease and Systemic Vascular Dysfunction: Mechanistic Links and Cardiovascular Associations—A Systematic Review

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File S2 Methods and supplementary results

This file provides the methods, judgments and selection summaries used in the reconciled manuscript. Complete report extractions, item-level risk-of-bias rationales/source-status flags, map records and individual exclusion/retrieval lists are supplied in the public accompanying File S4, rather than being available only on request. Report counts are not independent-study counts.

Table S2 Protocol deviations

Element	Registered protocol	Final review	Date; justification; potential influence
Title and objectives	CVeD as a marker of systemic vascular dysfunction: implications for cardiovascular risk	Directness of the primary evidence linking CVeD with systemic vascular dysfunction and cardiovascular disease, by evidence domain	July–November 2026; sharpened during drafting and peer review; no change in population or outcomes
Information sources	Embase, Google Scholar, MEDLINE, PubMed, Scopus	MEDLINE (PubMed), Embase, Scopus, CENTRAL; Google Scholar not searched	November 2026; Google Scholar results cannot be exported or reproduced in full; CENTRAL added for trials; possible loss of grey literature indexed only in Google Scholar
Search dates and strategy	No date restriction; strategy not reported	Inception to 31 August 2026; full strategies reported (File S1)	November 2026; the strategy of the original submission (search to 30 November 2023 plus update) could not be reproduced and was replaced at peer review; increased the number of included studies
Language	English only	No language restriction	November 2026; to reduce language bias; non-English reports mostly assessed from the English abstract
Other methods of identifying studies	Forward citation tracking; reference lists; manual search of key journals	Not performed; studies of the original submission cross-checked against the new results	November 2026; replaced by a broad, reproducible database search; possible omission of studies not indexed in the databases

Element	Registered protocol	Final review	Date; justification; potential influence
Selection and extraction	Two reviewers independently, or person/machine combination	Initial classification and extraction used an assisted workflow. M.L.D.R.-S. and I.A.D.R. independently verified eligibility and principal extracted data for all163 retained reports and resolved discrepancies by consensus. Expanded human validation covers521/572 initial abstract/classification exclusions;51 remain outside this additional validation.	13 November2026; final independent verification and consensus confirmed by the corresponding author. Methods §2.3 and S3 describe the workflow; S4 retains record-level sources and dispositions.
Secondary publications	Narrative reviews, consensus documents, and editorials included for qualitative synthesis	Excluded from the synthesis; used only for context	November 2026; to avoid double counting of primary evidence; no effect on included primary studies
Animal and in vitro studies	Excluded unless clinically relevant mechanistic evidence	Local mechanistic and animal studies summarized in an evidence map (Table S10), without study-level appraisal	November 2026; to describe biological plausibility separately from systemic and clinical evidence; not used for conclusions on cardiovascular risk
Comparators	Healthy controls, no CVeD, or severity strata	As registered, except that circulating-biomarker studies (Domain 2) required a comparator without venous disease	November 2026; severity-only comparisons cannot indicate systemic abnormality; such studies were mapped
Outcomes	Primary: systemic vascular dysfunction and cardiovascular risk; secondary: severity, biomarkers, microcirculation, matrix remodeling, quality of life, effects of interventions	Organized into domains (local pathobiology; circulating markers; systemic vascular function; cardiovascular disease; longitudinal outcomes; risk prediction; genetic causal inference); quality of life and treatment efficacy not synthesized	July–November 2026 (post hoc); domain structure defined after registration
Risk of bias	Newcastle–Ottawa Scale and ROBINS-I	Newcastle–Ottawa Scale, JBI checklists, and a Mendelian-randomization framework	November 2026; ROBINS-I is designed for interventions, and most studies were cross-sectional or genetic

Element	Registered protocol	Final review	Date; justification; potential influence
Reporting bias	Not assessed	Considered qualitatively within the certainty assessment	November 2026; no formal test (no meta-analysis)
Certainty of evidence	GRADE	GRADE-informed appraisal per outcome	As registered
Synthesis	Narrative synthesis grouped by predefined themes; no pooling	Structured synthesis without meta-analysis (SWiM) grouped by evidence domain; no pooling	Consistent with protocol; grouping refined post hoc
Review timeline	End date 30 July 2026	Completed November 2026	Extended by peer review
Review team	M.L. del Río-Solá; S. Asensio	M.L. del Río-Solá; I.A. Díaz Rengifo; E. Vargas Castrillón	Team changed after registration; the PROSPERO record is being amended to reflect the current team, sources, language, and methods

Table S4 Eligibility changes during revision

Criterion	Original submission	Revised review	Rationale	Effect on scope
Comparator for circulating biomarkers (Domain 2)	Any circulating-marker study in CVeD, including severity comparisons and local (leg) blood	Peripheral (systemic) blood compared with participants without venous disease	Severity-only comparisons and leg-blood sampling cannot show systemic abnormality	100 systemic-blood marker reports are coded in the map. Individual eligibility exclusions and unresolved comparator/sampling requirements are listed separately in S4 and Table S9; unresolved eligibility is not a demonstrated exclusion.
Local mechanistic studies (vein wall, valve, local blood, leg skin, ulcer tissue)	Included in the study-level synthesis	Summarized in a descriptive evidence map without study-level appraisal	They inform biological plausibility, not systemic or cardiovascular consequences	628 local reports mapped; 9 of the 20 originally included studies reallocated to the map
Experimental animal and in vitro studies	Excluded by protocol, but one animal study included	Evidence map only	Consistency with the protocol; plausibility only	44 animal, 12 animal-and-human, and 29 human-tissue in vitro reports mapped; the originally included animal study was not retrieved and is no longer included

Criterion	Original submission	Revised review	Rationale	Effect on scope
Traditional risk factors as correlates of CVeD	Not explicitly addressed	Evidence map	They describe venous-disease epidemiology, not cardiovascular consequences	Descriptive map only; the current map includes11 late transfers coded as clinical risk-factor associations, separately from75 whole-patient clinical entries (S4).
Secondary publications (reviews, consensus, editorials)	Narrative reviews eligible for qualitative synthesis (protocol)	Excluded from the synthesis; context only	Not independent primary evidence; risk of double counting	430 records set aside; no primary data lost
Conference abstracts	One meeting abstract included	Excluded	Insufficient information for appraisal	1 report excluded (Table S9)
Language	English only (protocol)	No restriction	To reduce language bias	Non-English reports assessed mainly from English abstracts

Current rule and effects on13 November2026: traditional factors alone are mapped; irrelevant genetic-score association and other-site varices are outside D7. Exact puncture-site NR does not itself exclude a basal blood comparison with healthy/normal controls. Of20 uncertain candidates,3 are retained with NR and 17 await classification. Current163 retained reports contribute to D2=84,D3=13,D4=22,D5=32,D7=18. Domain labels were removed from three otherwise retained reports where D4 consisted only of traditional factors. D6 has0 reports.

Table S5 Clinical cardiovascular associations

Twenty-two reports contribute to D4. Baseline comorbidity, prevalent disease, severity comparisons and reverse-direction prospective associations are distinguished; these are not all incident outcomes after CVeD. Complete fields, estimates and sources are in S4 Extraction and Outcome matrix.

Report and CID	Design and contrast	Clinical question
Ammermann F 2020 CID106	Retrospective single-centre cohort (cross-sectional analysis)	Fontaine stage IV PAD; cardiovascular risk factors and comorbidities (CAD, cerebrovascular disease, hypertension) from charts
Fäs J 1973 CID267	Matched-pair case-control comparisons	Prevalence and severity of lower limb arterial occlusions (and reciprocal venous disease in arterial patients)
Augey F 2010 CID274	Prospective case-control (3 years)	Association of HF (and other factors) with stasis ulcer
Jiang S 2024 CID294	Cross-sectional analysis of baseline data from the Beijing Vascular Disease Patients Evaluation Study (BEST, NCT02569268)	LEAD defined by ABI <0.9 (ABI method not detailed); prevalence of hypertension, CHD, stroke, DM; fasting blood indicators including lipids, HbA1c, homocysteine
Mäkivaara LA 2009 CID510	Prospective population cohort (questionnaire-based) with baseline cross-sectional analysis	Prevalent and incident congestive heart failure (CHF)

Report and CID	Design and contrast	Clinical question
Prochaska JH 2021 CID663	Population-based prospective cohort: cross-sectional baseline analysis (Poisson regression, prevalence ratios) + prospective all-cause mortality follow-up (Cox)	D4: prevalent clinically overt CVD (composite of AF, CAD, CHF, MI, PAD, stroke, VTE) and CV risk factors (Poisson PRs); predicted 10-year Framingham CVD risk in 9923 free of CVD. D5: all-cause death (Cox)
Pizano A 2023 CID780	Matched case-control (1:2 by age and sex) with conditional logistic regression	Cardiac/cardiovascular conditions: AF, pulmonary hypertension, right heart failure, PAD, history of PE
Androulakis AE 2004 CID1473	Case-control (CAE cases vs CAD-without-CAE controls vs general population)	Coronary artery ectasia on coronary arteriography (CAE identified in 181/7,510 eligible patients)
Forster OV 2006 CID1551	Cross-sectional comparison within CAD patients (AF vs sinus rhythm)	Atrial fibrillation (persistent/chronic) vs sinus rhythm; connective tissue dysplasia stigmas
Yapan Emren Z 2021 CID1615	Cross-sectional (observational) with risk-factor matching	CEAP distribution, venous reflux; correlation with AF duration and right atrial volume index
Mäkivaara LA 2008 CID2077	Population cohort (prevalence cross-sectional + 5-year incidence)	Prevalent and incident varicose veins
Mok Y 2025 CID4384	Prospective cohort (nested subcohort aged 66–70)	Incident clinically recognized varicose veins (claims-based)
Criqui MH 2007 CID4950	Cross-sectional population study (San Diego Population Study)	Association of CVD history/hypertension/DBP with moderate and severe CVeD (multivariable logistic regression)
Matic M 2016 CID5041	Cross-sectional (referred patients)	PAD defined as ABPI <=0.9 (CW Doppler); hypertension (BP >140/90 confirmed by internist)
Salim S 2026 CID5192	Retrospective longitudinal EHR study with nested matched case-control analyses (conditional logistic regression; machine-learning classifiers in WSIC) and Cox survival analysis	D4: odds of CV conditions/medications (coronary disease, hypercholesterolaemia, hypertension, IHD, angina, arrhythmia, composite CVD) in C2/C6 vs controls. D2: circulating CRP and haematological markers in UKB C5/C6 vs controls. D5: all-cause mortality (ONS-linked) by CEAP class vs matched controls
Takahashi PY 2009 CID5444	Cross-sectional (administrative data)	Associations with comorbidities incl. peripheral vascular disease, congestive heart failure, diabetes, hyperlipidaemia
Margolis DJ 2004 CID5549	Retrospective database study (logistic regression of conditions associated with new VLU onset; case-control type)	Association of CV conditions with recent-onset VLU
Ross M 2019 CID5790	Retrospective observational, cross-sectional comparison of wound types	ACSM CV risk factors, history of CVD, current signs/symptoms of CVD, ACSM risk stratification
Müller-Bühl U 2012 CID7144	Cross-sectional analysis of electronic medical records	Association of cardiovascular diseases (definition NR in abstract) with varicose veins
Mlačak B 1998 CID9719	Cross-sectional comparison	Prevalence of varicose veins

Report and CID	Design and contrast	Clinical question
Komsuoglu B 1994 CID10078	Cross-sectional prevalence/risk-factor study	Association of VV prevalence with congestive heart failure, angina pectoris, hypertension, smoking, diabetes, obesity, hyperlipidaemia
Timilsina R 2021 CID12886	Cross-sectional	Association of VV with hypertension, cardiac infarct ('cardiac infract'), DVT, and other factors

Table S6 Risk of bias and source documentation

Tool	Full-text reports	Abstract-based reports
JBI-ACS	49	46
JBI-QE	1	1
MR-framework	14	4
NOS-case-control	2	12
NOS-cohort	29	5

File S4 Risk of bias supplies 1390 individual item judgments, reasons, derived column ratings and source locations. The 265 previously missing item-specific pointers across 56 full-text reports were reconciled against the main articles, including six complete PDFs newly supplied by the author. Twenty item judgments were corrected and mapped column ratings recalculated; the corresponding manuscript table cells were updated. Ge 2025 and Levin 2023 remain evaluated from the available main articles only because supplementary methods were inaccessible. Unverifiable supplementary methods remain unclear; this limitation is not equated with low risk or a demonstrated failure. Other pre-existing item records are not represented as newly rechecked. Source availability and source actually used for each assessment remain distinct; abstract-only assessments cannot produce a low-concern column.

Table S7 Synthesis without meta analysis

SWiM item	How it was addressed	Location
1. Grouping studies for synthesis	Evidence domains (circulating markers, systemic vascular function, cardiovascular disease, longitudinal outcomes, risk prediction) and genetic causal inference; local pathobiology in an evidence map; within domains, grouping by outcome	Sections 2.4 and 2.8
2. Standardized metric	Effect estimates reported as published (hazard ratio, odds ratio, rate ratio, group means) with 95% CI; no transformation; direction coded for every report	Section2.8; Tables1–4; Tables S8/S12; S4 Extraction and Outcome matrix
3. Synthesis method	Structured tabulation of effect direction and magnitude; pooling not undertaken because exposures, reference groups, and adjustment sets were not exchangeable and several cohorts overlapped	Section 2.8
4. Criteria for prioritizing results	Adjusted over crude estimates; population-based and longitudinal over selected cross-sectional samples; direct measurements over circulating markers; full-text over abstract-only data	Sections 2.6 and 2.8
5. Investigation of heterogeneity	Qualitative exploration by CEAP class (including venous leg ulcer), exposure ascertainment, setting, and overlap of data sources	Sections 3.5 and 3.6

SWiM item	How it was addressed	Location
6. Certainty of evidence	GRADE-informed appraisal per outcome	Section 3.10; Table 4
7. Data presentation	Study-level tables by domain; summary-of-findings table; PRISMA flow diagram	Tables 1–4; Figures 1 and 2; Tables S5 and S9–S11
8. Reporting results	Results reported by domain and outcome with direction, magnitude, precision, and main sources of bias	Sections 3.3–3.10
9. Limitations of the synthesis	Person–machine screening, abstract-only extraction, post hoc structure, absence of pooling, overlapping databases	Section 4

Table S8 Outcome specific certainty judgments

Observational evidence starts at low certainty. For each outcome below, serious bias warrants downgrading to very low; other concerns are specified separately and do not imply a numerical pooled effect. No magnitude upgrade is applied in the presence of bias. Excluding abstracts does not remove the listed design limitations. Genetic inference is assessed separately, not assigned a clinical-effect GRADE rating.

Outcome	Risk of bias	Other GRADE considerations	Upgrade and certainty
Venous thromboembolism	Serious (−1): Detection, code misclassification, residual confounding, EHR overlap; one uncertain temporal sequence.	Not separately downgraded; variation by setting/components remains. Indirectness: selected populations/non-equivalent constructs are kept separate. Not separately downgraded for the larger main estimates; some subgroups imprecise.	Publication bias cannot be excluded; no magnitude upgrade. Very low in all and FT subsets.
All-cause mortality	Serious (−1): Frailty/comorbidity, stage and selected wound/ICU comparators; not CV-specific; different horizons.	Serious: conflicting/null/inverse patterns or non-equivalent clinical settings. Indirectness: selected populations/non-equivalent constructs are kept separate. Not separately downgraded for the larger main estimates; some subgroups imprecise.	Publication bias cannot be excluded; no magnitude upgrade. Very low in all and FT subsets.
Heart failure	Serious (−1): Residual confounding/coded diagnoses; five forward clinical reports; reverse-direction and genetic evidence separate.	Not separately downgraded; variation by setting/components remains. Indirectness: selected populations/non-equivalent constructs are kept separate. Not separately downgraded for the larger main estimates; some subgroups imprecise.	Publication bias cannot be excluded; no magnitude upgrade. Very low in all and FT subsets.
Atrial fibrillation	Serious (−1): Two coded-diagnosis cohorts; detection/residual confounding and shared resources.	Not separately downgraded; variation by setting/components remains. Indirectness: selected populations/non-equivalent constructs are kept separate. Not separately downgraded for the larger main estimates; some subgroups imprecise.	Publication bias cannot be excluded; no magnitude upgrade. Very low in all and FT subsets.
Peripheral artery disease	Serious (−1): Clinical claudication/PAD definitions differ; confounding and detection bias; cross-sectional ABI findings separate.	Not separately downgraded; variation by setting/components remains. Indirectness: selected populations/non-equivalent constructs are kept separate. Not separately downgraded for the larger main estimates; some subgroups imprecise.	Publication bias cannot be excluded; no magnitude upgrade. Very low in all and FT subsets.

Outcome	Risk of bias	Other GRADE considerations	Upgrade and certainty
Coronary heart disease / myocardial infarction	Serious (−1): Incident CHD, coronary death and subgroup results differ; inverse estimates not causal protection.	Serious: conflicting/null/inverse patterns or non-equivalent clinical settings. Indirectness: selected populations/non-equivalent constructs are kept separate. Not separately downgraded for the larger main estimates; some subgroups imprecise.	Publication bias cannot be excluded; no magnitude upgrade. Very low in all and FT subsets.
Stroke	Serious (−1): Different phenotypes and ascertainment; residual confounding and inconsistent direction.	Serious: conflicting/null/inverse patterns or non-equivalent clinical settings. Indirectness: selected populations/non-equivalent constructs are kept separate. Not separately downgraded for the larger main estimates; some subgroups imprecise.	Publication bias cannot be excluded; no magnitude upgrade. Very low in all and FT subsets.
Circulating biomarkers	Serious (−1): Small convenience samples, assay/marker and comparator heterogeneity;43 abstract-based reports.	Serious: conflicting/null/inverse patterns or non-equivalent clinical settings. Indirectness: selected populations/non-equivalent constructs are kept separate. Serious for small studies or imprecise subgroup/functional estimates.	Publication bias cannot be excluded; no magnitude upgrade. Very low in all and FT subsets.
Direct systemic function	Serious (−1): Small studies, incomplete adjustment, severity associations and uncontrolled treatment change; no generalized causal inference.	Serious: conflicting/null/inverse patterns or non-equivalent clinical settings. Indirectness: selected populations/non-equivalent constructs are kept separate. Serious for small studies or imprecise subgroup/functional estimates.	Publication bias cannot be excluded; no magnitude upgrade. Very low in all and FT subsets.
Vascular structure/disease	Serious (−1): ABI/PAD and coronary calcium are arterial disease constructs, not direct functional impairment.	Not separately downgraded; variation by setting/components remains. Indirectness: selected populations/non-equivalent constructs are kept separate. Serious for small studies or imprecise subgroup/functional estimates.	Publication bias cannot be excluded; no magnitude upgrade. Very low in all and FT subsets.
Clinical cardiovascular associations	Serious (−1): Mixed designs/temporal directions, comorbidity and selected comparators; traditional factors alone not D4.	Serious: conflicting/null/inverse patterns or non-equivalent clinical settings. Indirectness: selected populations/non-equivalent constructs are kept separate. Serious for small studies or imprecise subgroup/functional estimates.	Publication bias cannot be excluded; no magnitude upgrade. Very low in all and FT subsets.

Table S9 Selection dispositions

Disposition	Unique assessed reports
Retained principal synthesis	163
Awaiting classification	17
Transferred to descriptive map	12
Excluded by eligibility criteria	66
Total after late duplicate removal	258

Two late duplicate records were removed separately: CID16183 duplicates8085, and 16293 duplicates9300. The second duplicate does not exclude the canonical Turio report, which awaits classification. The66 individual exclusions and their recorded reasons, and the 18 historical retrieval failures after Choi was obtained, are listed in S4. The original assessment had63 exclusions; Zhong was removed from that list and placed in awaiting classification;4 substantive exclusions were added. No uncertain method is represented as a demonstrated failure.

Report and CID	Reason eligibility is unconfirmed	Original source status
Falanga V (1991) CID201	Concurrent non-venous control group is not established; reference values cannot substitute for a comparator.	Resumen y/o ficha; texto completo original no verificado
Signorelli SS (2000) CID424	Systemic versus local blood sampling remains ambiguous in the venous-occlusion experiment.	Resumen y/o ficha; texto completo original no verificado
Serra R (2013) CID582	Controls are described as without ulcers; freedom from venous disease is unconfirmed.	Resumen y/o ficha; texto completo original no verificado
Shields DA (1994) CID662	The venous status of matched controls remains unconfirmed; sampling details are also incomplete.	Resumen y/o ficha; texto completo original no verificado
Zhong et al. (2014) CID1043	Eligible C1/primary-reflux participants cannot be separated from the mixed C0–C1 functional-PPG population.	Texto original completo disponible
Filkor K (2016) CID1177	Controls are defined as without VLU, not as without all relevant venous disease.	Texto original completo disponible
Agius C (2024) CID1453	The venous status of the non-ulcer control group is unconfirmed; CRP remains relevant to eligibility.	Resumen y/o ficha; texto completo original no verificado
Janssens D (1999) CID1483	The control population is insufficiently defined to confirm absence of venous disease.	Resumen y/o ficha; texto completo original no verificado
Shevchenko IuL (2013) CID1544	Control definition and correspondence of the published cohort with the related thesis are unconfirmed.	Resumen y/o ficha; texto completo original no verificado
Triankina SA (2003) CID4355	A concurrent healthy comparator cannot be distinguished from laboratory reference values.	Resumen y/o ficha; texto completo original no verificado
Di Salvo (2010) CID7551	The original report has not been verified sufficiently to establish eligible measures and comparator.	Resumen y/o ficha; texto completo original no verificado
Turio E (2002) CID9300	Primary venous-ulcer results cannot be verified separately from post-thrombotic cases.	Resumen y/o ficha; texto completo original no verificado
Ribeaudeau (1999) CID9581	The venous status of controls and their selection remain unconfirmed.	Resumen y/o ficha; texto completo original no verificado
Crouch, S.P.M. (1994) CID10067	The exact 1994 report is not sufficiently verified; a different 1992 publication cannot substitute for it.	Resumen y/o ficha; texto completo original no verificado
Vanscheidt W (1992) CID10169	Arm sampling is compatible with systemic blood, but the venous status of controls is unconfirmed.	Resumen y/o ficha; texto completo original no verificado
Silva KCN (2025) CID11516	The control venous status and relevant sampling/assay methods are insufficiently documented.	Resumen y/o ficha; texto completo original no verificado

Report and CID	Reason eligibility is unconfirmed	Original source status
Karamalakova YD (2019) CID15720	Blood was collected during surgery; whether it was from the affected local venous territory is unclear.	Texto original completo disponible

Of the 17 awaiting reports, Zhong, Filkor and Karamalakova have full original texts available but still do not establish a required eligibility detail. An unverified/insufficient source is not automatically counted as a retrieval failure. No author correspondence is claimed, and these reports could affect conclusions if later confirmed eligible.

Table S10 Descriptive map

Map pathway	Allocated	Coded	Not coded
Historical initial classification	770	711	59
Adjudication additions	130	92	38
Late transfers from primary synthesis	12	12	0
Total	912	815	97

The first59 comprise 38 absent abstracts,9 duplicate records,9 without CVeD-specific data and 3 without extractable data. S4 Evidence map lists all 815 coded reports and Map not coded all 97 uncoded records. Added traditional risk-factor associations and cultured-cell results remain descriptive; map membership is not evidence of systemic dysfunction.

Table S11 Circulating markers

Report pattern	All reports	Full text only
Positive	52	26
Mixed	23	11
Null	7	3
Inverse	2	1
Total	84	41

The84 individual reports and all extraction fields are provided in S4 Extraction. These categories describe the eligible pattern; they do not imply uniformly higher analytes or causal effects. Cell-associated mRNA/phenotypes, soluble proteins, functional blood assays and stimulated or cultured results are distinguished. Table 1 in Silaghi compares pre/post values; its NS must not replace the separate baseline case-control MMP-9 finding. Druzhkin's ANOVA is between surgical subgroups, not against healthy controls. Takai's MMP-9/tryptase compartment is discordantly reported and is not treated as confirmed circulating data.

Table S12 Full text sensitivity synthesis

Outcome or domain	All reports and pattern	Full text only	Interpretation
Venous thromboembolism	11: 7 positive, 1 mixed, 3 null	10: 6 positive, 1 mixed, 3 null	Very low in both; composition/directions reconsidered.
All-cause mortality	13: 7 positive, 1 mixed, 3 null, 2 inverse	13: 7 positive, 1 mixed, 3 null, 2 inverse	Very low in both; composition/directions reconsidered.

Outcome or domain	All reports and pattern	Full text only	Interpretation
Heart failure	5: 3 positive, 2 null	4: 2 positive, 2 null	Very low in both; composition/directions reconsidered.
Atrial fibrillation	2: 2 positive	2: 2 positive	Very low in both; composition/directions reconsidered.
Peripheral artery disease	4: 3 positive, 1 null	3: 2 positive, 1 null	Very low in both; composition/directions reconsidered.
Coronary heart disease / myocardial infarction	6: 2 inverse, 1 null, 1 mixed, 2 positive	5: 2 inverse, 1 null, 2 positive	Very low in both; composition/directions reconsidered.
Stroke	4: 2 positive, 2 null	4: 2 positive, 2 null	Very low in both; composition/directions reconsidered.
Circulating biomarkers	84: 7 null, 52 positive, 23 mixed, 2 inverse	41: 3 null, 26 positive, 11 mixed, 1 inverse	Very low in both; composition/directions reconsidered.
Direct systemic function	10: 2 null, 7 positive, 1 mixed	6: 2 null, 3 positive, 1 mixed	Very low in both; composition/directions reconsidered.
Vascular structure/disease	3: 3 positive	3: 3 positive	Very low in both; composition/directions reconsidered.
Clinical cardiovascular associations	22: 14 positive, 4 null, 4 mixed	8: 5 positive, 2 mixed, 1 null	Very low in both; composition/directions reconsidered.
Genetic causal inference	18: 9 positive, 9 mixed	14: 6 positive, 8 mixed	Genetic framework; not clinical GRADE

Mortality, AF, stroke and structure/disease retain all their reports. Direct-function positive-pattern reports fall from 7/10 to 3/6, and HF from 3/5 to 2/4; these changes are reported rather than declaring every finding unchanged. VTE temporal uncertainty in Müller-Bühl is separated from strict incident-event inference. Clinical outcome counts omit cross-sectional, reverse-direction and genetic estimates; genetic correlation is context only. Composite arterial disease and MACE including VTE are not coronary-specific estimates. No significance-based vote count substitutes for effect-size synthesis.

Table S13 Previous reviews

Review	Question	Data sources; period	Designs	Studies; synthesis	Contribution and limitations
Del Río-Solá et al., 2026	CVeD and cardiovascular outcomes and traditional risk factors	PubMed, Scopus, Web of Science; January 2011–March 2025	Human observational studies	20 studies (6 in meta-analysis); random-effects meta-analysis	Pooled clinical association; no formal certainty assessment; no separation of local, systemic, and genetic evidence

Review	Question	Data sources; period	Designs	Studies; synthesis	Contribution and limitations
Campello et al., 2026	Arterial–venous continuum (atherosclerosis and CVeD)	Not reported (narrative review)	Human, genetic, and preclinical studies; reviews	Narrative	Conceptual integration; no systematic search or appraisal
De Luca et al., 2026	CVeD and cardiovascular events and mortality	PubMed; 1960–October 2025	Cohorts, registries, case–control; conference abstracts eligible	13 studies; three-level random-effects meta-analysis	Pooled estimates including venous thromboembolism in composite outcomes; industry funded
Abrashev et al., 2025	Endothelial dysfunction in CVeD	PubMed, Europe PMC, Scopus, Web of Science, Google Scholar; 2002–April 2025	Human and in vitro studies; reviews	197 records; narrative	Mechanistic summary; local and systemic compartments not distinguished
Present review	Directness of primary evidence by domain	MEDLINE, Embase, Scopus, CENTRAL; inception–31 August 2026	Primary human studies; local and animal studies mapped	163 retained reports (95 full texts/68 abstracts),17 awaiting classification;815 coded map entries; synthesis without meta-analysis. Independent-study count not established.	Separation of evidence types; venous thromboembolism distinguished from arterial outcomes; design-specific risk of bias; outcome-specific certainty; full-text sensitivity; limitations of68 abstract-based sources explicitly retained.