medical sciences

Systematic Review

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

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Abstract

Background/Objectives: Chronic venous disease (CVeD) has been associated with circulating abnormalities and cardiovascular outcomes, but these constructs do not establish generalized arterial dysfunction. We assessed the directness and consistency of the primary evidence. Methods: MEDLINE, Embase, Scopus, and CENTRAL were searched from inception to 31 August 2026 (PROSPERO CRD420261433873). Primary human evidence was synthesized without meta-analysis; local mechanisms and traditional risk-factor correlates were mapped separately. Results: The search identified 26,811 records. The reconciled synthesis retained 163 reports (95 assessed in full text and 68 from abstracts); 17 potentially eligible reports await classification. Domains overlapped: 84 reports addressed circulating markers, 13 systemic vascular function or structure, 22 clinical cardiovascular associations, 32 longitudinal outcomes, and 18 genetic causal inference. The descriptive map contained 815 coded reports. Direct vascular-function evidence comprised 10 small reports; 3 additional reports assessed arterial structure/disease. Venous thromboembolism associations were predominantly positive but heterogeneous by setting and event. Mortality associations included higher, null, and inverse findings with non-equivalent comparators; inverse findings in selected chronic-wound populations did not establish protection. No study evaluated incremental cardiovascular risk prediction. Excluding abstract-only reports left fewer positive functional reports and changed the composition of several outcome groups. Certainty of the observational associations was very low. Conclusions: The evidence supports associations with circulating changes and some venous thrombotic outcomes but does not establish generalized arterial dysfunction or added cardiovascular predictive value. Interpretation is constrained by confounding, selected populations, overlapping datasets, incomplete source documentation, and reports awaiting classification.

Keywords: chronic venous disease; varicose veins; venous insufficiency; systemic vascular dysfunction; endothelial function; inflammation; venous thromboembolism; cardiovascular disease; mortality; Mendelian randomization

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1. Introduction

Chronic venous disease (CVeD) is one of the most prevalent disorders of the circulatory system, affecting a substantial proportion of the adult population and representing a considerable clinical and socioeconomic burden [1–4]. It encompasses a spectrum of abnormalities, most commonly of the lower extremities, arising primarily from sustained venous hypertension and valvular dysfunction [5,6]. To avoid ambiguity, chronic venous disease is abbreviated as CVeD throughout this review, and cardiovascular disease is written in full.

At the cellular level, venous hypertension and altered shear stress promote endothelial activation, leukocyte adhesion, oxidative stress, release of cytokines and matrix metalloproteinases, and remodeling of the venous wall and valves [1,5]. These pathways overlap with those implicated in arterial disease, which has led to the hypothesis that CVeD may be a manifestation, or a marker, of a broader systemic vascular disorder [7,8]. However, local venous abnormalities do not by themselves demonstrate generalized vascular dysfunction, and CVeD shares several determinants with cardiovascular disease, including age, obesity, physical inactivity, and hypertension, which are important potential confounders.

Recent meta-analyses have pooled observational associations between CVeD and cardiovascular outcomes [9,10]. Whether these associations are supported by direct evidence of systemic vascular dysfunction, by longitudinal data, or by incremental prognostic value has not been systematically examined. The aim of this systematic review was therefore to evaluate the directness of the primary evidence linking CVeD with systemic vascular dysfunction and cardiovascular disease, distinguishing circulating markers, directly measured systemic vascular function, cardiovascular comorbidity, longitudinal outcomes, incremental risk prediction, and genetic causal-inference evidence and to place this evidence in the context of the local venous pathobiology.

2. Materials and Methods

2.1. Protocol and Registration

This systematic review was conducted and reported in accordance with the PRISMA 2020 statement [11]. The protocol was registered in PROSPERO (CRD420261433873; submitted on 26 June 2026 and registered on 28 June 2026). The complete search strategies and record counts are reported in File S1 (Table S1), and all deviations from the registered protocol, with their date, justification, and potential influence, are listed in Table S2 (File S2). The main deviations were as follows: the searches were re-run during peer review with a single reproducible strategy covering MEDLINE, Embase, and Scopus, with CENTRAL added; Google Scholar, listed in the protocol, was not searched because its results cannot be exported or reproduced in full; no language restriction was applied (protocol: English only); secondary publications were used only for context rather than for qualitative synthesis; local mechanistic and experimental animal studies were summarized in an evidence map rather than synthesized study by study; risk of bias was assessed with design-specific tools instead of the Newcastle–Ottawa Scale and ROBINS-I; the evidence domains used to structure the synthesis were defined after registration.

2.2. Information Sources and Search Strategy

MEDLINE (via PubMed), Embase (Elsevier), Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to 31 August 2026; the searches were executed on 5 November 2026, and records published after 31 August 2026 were removed. The strategy combined a CVeD block (controlled vocabulary and free text for chronic venous disease, insufficiency or disorder, varicose veins, venous ulcer, venous insufficiency, venous reflux, and CEAP) with a broad outcome block covering inflamma-

tion, endothelial function, oxidative stress, matrix metalloproteinases, microcirculation, circulating biomarkers, systemic vascular function (flow-mediated dilation, pulse-wave velocity, arterial stiffness, intima–media thickness, ankle–brachial index, coronary calcium), cardiovascular disease and events, mortality, venous thromboembolism, risk prediction, and Mendelian randomization. No language, design, or species limits were applied; Embase conference abstracts and trial-registry records were not exported. The complete strategies, as executed, and the number of records retrieved from each source are reported in Supplementary File S1. Because the revised search was designed to be exhaustive and reproducible, reference lists were not hand-searched, and forward citation tracking was not repeated (Table S2); instead, the 20 studies included in the original submission were cross-checked against the new search results (Section 3.1).

This search replaced the combination of an earlier search (to 30 November 2023) and a focused update reported in the original submission. When re-executed, the earlier strategy could not reproduce the record counts originally reported because it included subject headings that encompass venous disease itself (e.g., "Cardiovascular Diseases" [MeSH]) and ambiguous abbreviations (e.g., "CVI"). The corrected strategy is reported in full so that it can be reproduced.

2.3. Selection Process

Records were deduplicated by PubMed identifier, DOI and normalized title. Claude Opus 5.5 (Anthropic; claude-opus-5-5) assisted formulation and description of the database-specific search strategies; researchers reviewed and approved the strategies. Initial screening, classification, and extraction also used an assisted workflow, with stage-specific prompts and human oversight described in File S3. The expanded human validation covered 521 distinct records from 572 initial abstract/classification exclusions. The original workbooks contain 174 assessments by M.L.D.R.-S., 173 by E.V.C., and 174 by I.A.D.R. Of these, 432 discordant records were resolved by consensus between M.L.D.R.-S. and I.A.D.R.: 18 were sent to retrieval, 130 to the map, and 284 excluded. The other 89 assessments were concordant exclusions. Fifty-one initial exclusions were outside the expanded validation and retained their initial disposition; complete reassessment of all 572 is not claimed. María Lourdes del Río-Solá and Iván Alejandro Díaz Rengifo independently verified the eligibility and principal extracted data of all 163 included reports. Discrepancies were resolved by consensus between these two investigators. This final verification includes the three reports retained after the NR clarification. Available full texts were used where retrieved; otherwise, verification was limited to the abstract, with unreported data retained as NR or unclear. Exact prompts, access to sources and oversight by stage are reported in File S3.

Full texts were sought through PubMed Central, open-access publishers, institutional access reported in the original workflow and author-supplied files. The current source ledger records 120 full-text assessments and 140 abstract-based assessments among 278 reports sought; 18 reports remained without sufficient retrieved information. Two duplicate report records were subsequently removed, leaving 258 unique assessed reports: 120 with full text and 138 with abstract-based information. Among the retained reports, 95 were assessed in full text and 68 from abstracts. A full-text label identifies source availability; the final independent human verification of eligibility and principal extracted data is described in Section 2.3, and item-level risk-of-bias documentation is recorded separately in File S4. Availability of a full text is recorded separately from whether it resolves eligibility.

2.4. Eligibility Criteria and Scope

The population comprised adults with CVeD (varicose veins, chronic venous insufficiency, CEAP C1–C6, venous leg ulcer, or primary venous reflux). Primary human studies

were eligible for the study-level synthesis if they addressed at least one of the following: (Domain 2) circulating biomarkers of inflammation, endothelial activation, oxidative stress, coagulation, or matrix turnover measured in peripheral blood and compared with participants without venous disease; (Domain 3) vascular function or structure measured directly outside the affected venous territory; (Domain 4) the association between CVeD and cardiovascular disease; (Domain 5) incident cardiovascular events, venous thromboembolism, or mortality; (Domain 6) incremental cardiovascular risk prediction; or (Domain 7) genetic causal inference (Mendelian randomization or another explicit causal-inference design) linking CVeD with cardiovascular diseases, cardiovascular risk factors, or inflammatory mediators.

Domain 1 was mapped descriptively and included local venous wall/valve, local blood, skin/ulcer tissue or fluid, experimental animal mechanisms, circulating-marker studies without a non-venous comparator, and traditional risk factors examined only as correlates of CVeD. Primary reports were not moved into the systemic synthesis solely because they reported a positive result. Secondary publications, conference abstracts, case reports/small case series, and populations or outcomes outside the criteria were excluded. Changes made during revision are dated and justified in Table S4. An unnamed exact puncture vein was recorded NR and did not itself exclude a basal blood-cell/plasma comparison with healthy or normal controls. This is an eligibility judgment, not a newly demonstrated anatomical sampling fact. Specifically local/occlusion experiments, an unconfirmed non-venous comparator or an inseparable eligible population were treated differently: 17 reports remain awaiting classification, outside the principal synthesis, with the missing requirement listed individually. Three basal blood-comparison reports were retained with NR details. Tissue stimulated and cultured-cell results were separated from basal circulating measures. Clarification from investigators could change an awaiting report's status; no author contact or response is claimed.

2.5. Data Extraction

Country, source, setting, design, population and comparator definitions, sample sizes, exposure, outcomes, follow-up, events/group values, estimates, adjustment, direction, limitations, funding, and source locations were extracted by stable report identifier (CID). The reconciled workbook in File S4 retains 163 reports and separate tables for 17 awaiting classification, 66 exclusions, 18 retrieval failures, and 2 late duplicate records. Shared cohorts, health-record networks, claims databases, and GWAS resources were identified where documented. Reports are the unit of the counts below; the 163 reports are not assumed to represent 163 independent studies, and a single defensible count of independent populations was not established.

2.6. Definitions

Four types of evidence beyond the affected venous territory were distinguished and not considered interchangeable: (i) circulating markers, which may reflect systemic inflammation or activation but do not by themselves demonstrate generalized vascular dysfunction; (ii) directly measured vascular function outside the affected venous territory (flow-mediated dilation, pulse-wave velocity, augmentation index, cardio-ankle vascular index, systemic microvascular reactivity), the only category described as direct evidence of systemic vascular dysfunction; (iii) vascular structure and subclinical arterial disease (intima–media thickness, coronary artery calcium, ankle–brachial index, or peripheral artery disease), which indicate arterial disease rather than functional impairment; and (iv) cardiovascular clinical outcomes (prevalent disease, incident events, mortality), which are clinical outcomes rather than measures of vascular function. Venous thromboembolism was analyzed separately

from arterial outcomes because it shares venous stasis pathways with CVeD. Mendelian randomization studies estimate associations of genetically predicted exposures and were analyzed as a separate category.

2.7. Risk-of-Bias Assessment

Risk of bias was assessed with the design-specific NOS, JBI, and genetic instrumental-variable/STROBE-MR frameworks [12–14], mapped to selection/instrument relevance, confounding/comparability, measurement/outcome, and other concerns. A column was high concern if any mapped item was not met, unclear if all mapped items were insufficiently reported, some concern if any were partial/unclear and none not met, and low only if all were met. An abstract-only item assessment could not produce a low-concern column. Source availability and the source of each item judgment are distinguished in File S4. Missing information was not treated as proof of low risk or of a methodological failure. The 265 previously unrecorded item-specific pointers in 56 full-text reports were reconciled against the available main articles; 20 item judgments were corrected and column ratings recalculated. Ge and Levin retain explicitly limited assessments because supplementary methods could not be accessed; methods not verifiable in the main text remain unclear. The documentary reconciliation is distinguished from the final independent verification of eligibility and principal extracted data by M.L.D.R.-S. and I.A.D.R. The new Choi report was assessed from the retrieved article; the three new basal-blood inclusions remain conservatively assessed from abstracts.

2.8. Synthesis and Certainty of Evidence

Because designs, populations, exposures, comparators, outcome definitions, adjustments, and data sources were not exchangeable, a structured synthesis without meta-analysis was used, following SWiM [15]. Seven complementary domains were distinguished: D1 descriptive map; D2 circulating markers; D3 direct systemic vascular function and structure, reported separately; D4 clinical cardiovascular associations; D5 longitudinal outcomes; D6 incremental cardiovascular prediction; and D7 genetic causal inference. They are evidence categories rather than a hierarchy of causal strength. Direction labels distinguish unadjusted/matched comparisons, adjusted associations, effects not retained after adjustment, within-person treatment changes, reverse-direction associations, and genetic estimates. Report-level marker patterns are descriptive, not significance-based estimates of an overall effect. Outcome-specific counts and sensitivity restricted to reports assessed in full text are provided in Table S12 and File S4. Observational certainty started at low and was downgraded for serious bias; inconsistency, indirectness, and imprecision were considered separately for each outcome [16]. No upgrade for a large association was applied in the presence of detection bias, misclassification, or residual confounding. Clinical longitudinal outcomes, cross-sectional comorbidity, reverse-direction findings, composite outcomes, and genetic correlation were not pooled or counted as interchangeable evidence.

3. Results

3.1. Study Selection

The searches identified 26,811 records (PubMed 6324; Embase 12,626; Scopus 7051; CENTRAL 810). Removing 9797 duplicates and 121 post-cutoff records left 16,893 for title screening; 14,861 were excluded by title, and 430 secondary reports set aside. Of 1602 abstracts, 510 were initially excluded; 1092 were classified, with 770 sent to the map, 62 initially excluded, and 260 sent to retrieval. Reconsideration of the 572 initial abstract/classification exclusions added 130 map records and 18 retrieval candidates; 424 remained excluded (284 adjudicated discordances, 89 concordant human exclusions, and 51 with no further

human reassessment documented). Thus, 1602 records balance as 900 initially allocated to the map, 278 sought for retrieval, and 424 excluded. After further recovery, there were 120 full-text and 140 abstract-based assessments, with 18 retrieval failures. Removal of 2 late duplicate records left 258 unique reports assessed: 163 retained, 17 awaiting classification, 12 transferred to the map, and 66 excluded (Figure 1; Table S9). The 163 retained reports comprise 95 full texts and 68 abstracts. Domains overlap: D2 84, D3 13, D4 22, D5 32, and D7 18; none addressed incremental cardiovascular prediction. No independent-study count is asserted.

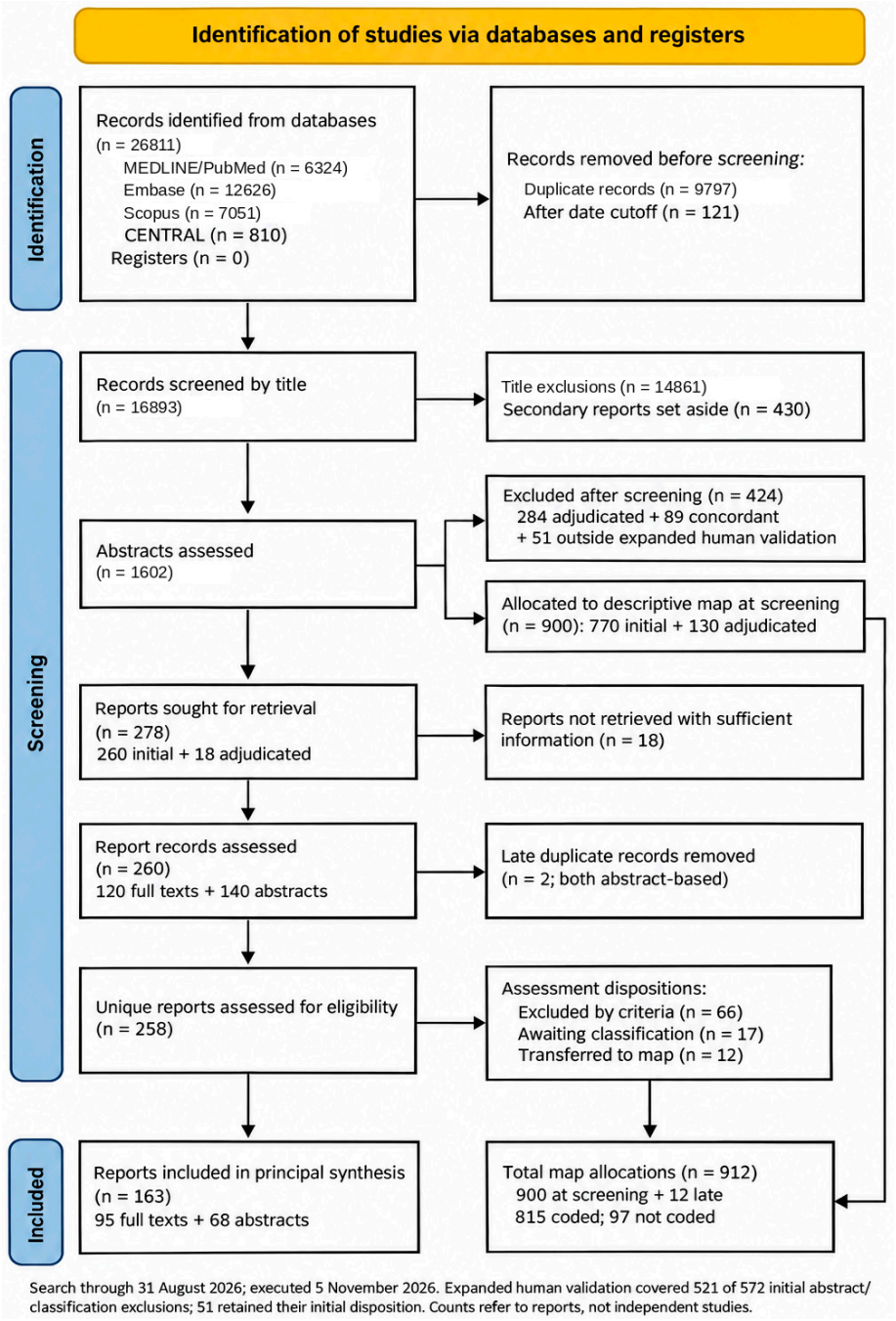


Figure 1. Reconciled PRISMA 2020 selection flow. Initial exclusion, human validation/adjudication, source availability, late duplicate removal, reports awaiting classification, and late map transfer are shown separately. The map received 900 records at screening and 12 after detailed assessment; 815 were coded and 97 not coded. Report counts do not imply independent populations.

3.2. Evidence Map of Local Venous Pathobiology

The descriptive evidence map contains 815 coded reports: 803 previously coded and 12 reassigned during eligibility reconciliation. Of 912 total allocations (900 at screening and 12 after detailed assessment), 97 were not coded. The historical 770-to-711 difference was 38 absent abstracts, 9 duplicate records, 9 without CVeD-specific data, and 3 without extractable data. A further 130 adjudicated map allocations yielded 92 coded and 38 not coded, explaining the preceding 900-to-803 difference. Individual map and non-coded records, compartments, and themes are in File S4 (Table S10 summary). The map informs biological plausibility; it is not a set of direct systemic-function studies and was not assigned study-level certainty.

3.3. Circulating Biomarkers (Domain 2)

Eighty-four reports addressed circulating markers [17–100]. Report-level patterns were 52 positive, 23 mixed, 7 null, and 2 inverse; these labels do not imply that every measured analyte was elevated or that changes were causal. Markers, cellular phenotypes, assays, and comparator selection varied substantially. Some reports showed lower or unchanged measures, including marker-specific discordance in elastase/alpha1-antitrypsin and lower baseline serum MMP-9. Basal comparisons were kept separate from pre-/post-treatment changes, diagnostic ROC analyses, local tissue measurements, and stimulated-cell responses. Chen, Zhang, and Bianciardi were retained for their basal blood comparisons with healthy/normal controls while the exact puncture site remained NR. In Takai, inconsistent blood-versus-skin descriptions prevented treating MMP-9/tryptase as confirmed circulating measures; the qualitative plasma substance-P comparison was recorded separately. Detailed extractions, source labels, and caveats are in File S4 (Table S11).

3.4. Systemic Vascular Function and Structure (Domain 3)

Thirteen reports addressed systemic vascular function or arterial structure/disease [101–113] (Table 1). Ten included functional measurements such as FMD, arterial stiffness, or systemic microvascular reactivity; three addressed ABI/PAD or coronary calcium, which are structural/disease constructs. Among the functional reports, 7 had a positive extraction-defined pattern, 1 mixed finding, and 2 null findings. These were mostly small and incompletely adjusted; positive unadjusted severity associations were not treated as independent adjusted effects. The uncontrolled Nóbrega study reported no significant post-operative FMD change; its aggregate values and published interval could not be reconciled into a valid paired estimate (Table 1). Evidence of arterial disease or circulating activation was not interpreted as direct proof of generalized endothelial dysfunction.

In the study of brachial flow-mediated dilation before and 6 months after varicose-vein surgery (42 of 50 enrolled patients analyzed) [111], %FMD was 4.20 ± 1.30% before and 4.56 ± 1.25% after surgery (labelled mean ± SD in the text and tables, median in the abstract; $p = 0.819$), a difference between the reported group means of +0.36 percentage points (post-minus pre-operative). The published change (0.36 ± 8.8%) and its 95% confidence interval (−3.604 to 2.870) could not be reconciled: the interval is centered on −0.37, which may reflect the opposite direction of subtraction, but this is not specified, and the pre- and post-operative columns are labelled n = 50 and n = 42 despite the stated paired analysis. We report this as an inconsistency in the original publication and did not recalculate a paired estimate. The study showed no statistically significant change in this uncontrolled sample and cannot establish whether baseline function was impaired. Most Domain 3 studies were small, used clinically selected controls, and adjusted incompletely for shared risk factors; 4 of 13 reports could be assessed only from the abstract.

Table 1. Studies of vascular function and of vascular structure or subclinical arterial disease measured outside the affected venous territory (Domain 3).

Study	Construct	Design; Country; n (CVeD/Comparator)	Measurement	Main Finding (as Reported)	Direction of Finding	Source; RoB
Ardron et al., 1991 [101]	Function	Age- and sex-matched case-control, cross-sectional; Australia (Melbourne; site not explicitly stated); geriatric research institute; 15/15 age- and sex-matched healthy controls	Laser Doppler flux: axon reflex, acetylcholine, and nitroprusside responses on forearm and foot	No forearm (systemic) effect estimate; foot axon reflex $t = 6.88$, $p < 0.001$ (paired t test), unadjusted	No difference (matched)	FT; S/L/S/S
Reghunan-danan et al., 1995 [102]	Function	Case-control, cross-sectional comparison; India (presumed); setting NR; 20 VV/20 age-matched normal subjects	Femoral–dorsalis pedis PWV; BP; lipid profile	PWV significantly higher in VV ($p < 0.001$); no difference in BP or lipids; values NR	Worse in CVeD (age-matched; unadjusted)	Abs; U/S/S/S
Moro et al., 2013 [103]	Function	Cross-sectional proof-of-concept; Italy (Rome); university personnel volunteers, University Campus Bio-Medico; 14/25 healthy volunteers without venous reflux	Brachial FMD and shear-normalized FMD (nFMD), blinded sonographer	Age- and gender-adjusted LS means FMD 15.4% vs. 23.2%; CI not reported; all associations confirmed after adjustment	Worse in CVeD (age- and sex-adjusted)	FT; S/L/L/L
Ozpelit et al., 2015 [104]	Function	Comparative cross-sectional; Turkey (presumed); setting NR; 48 CVD (C4–C6)/39 matched healthy volunteers	Central aortic pressure, augmentation index, PWV; echocardiography with tissue Doppler	Central aortic pressure, augmentation index, PWV slightly higher in CVD; values NR	Worse in CVeD (matched; unadjusted)	Abs; S/S/S/U
Komarów et al., 2015 [105]	Function	Cross-sectional case-control; Poland (presumed); primary clinical measurement; 131 CVD (C0s–C3)/84 healthy volunteers	Brachial artery flow-mediated dilatation (FMD, %)	Group difference $p < 0.05$; FMD negatively correlated with CEAP severity; unadjusted	Worse in CVeD and with CEAP severity (unadjusted)	Abs; S/S/S/U
Aykan et al., 2016 [106]	Function	Cross-sectional, CVI vs. healthy controls; Turkey (Trabzon); single-center outpatient clinic; 87/86 healthy controls	CAVI (VaSera VS-1000), ABI, BP, echocardio-graphic LVEF, and LV mass index	Multivariable logistic regression for CVI: CAVI aOR 2.033 (95% CI 1.493–2.768), $p < 0.001$; ABI aOR 0.003 (0.001–0.137); CAVI > 7.9 AUC 0.791 (0.723–0.849)	Worse in CVeD (adjusted)	FT; S/S/S/S
Gurfinkel' et al., 2017 [108]	Function	Uncontrolled before-after study of Venarus; Russia; outpatient phlebology, Moscow; 34 CVI/no control group (pre-treatment values)	Nail-bed capillaroscopy, arterial stiffness indices, endothelial function	Symptoms reduced in all; edema subgroup showed increased capillary velocity and improved endothelial function; values NR	Within-person change after treatment (uncontrolled)	Abs; U/H/S/U

Table 1. *Cont.*

Study	Construct	Design; Country; n (CVeD/Comparator)	Measurement	Main Finding (as Reported)	Direction of Finding	Source; RoB
Dogdus et al., 2018 [109]	Function	Cross-sectional case-control; Turkey; hospital clinic, prospective clinical measurements; 62 CVD C3–C5/48 age-, sex-, BMI-matched healthy subjects	Arterial stiffness (PWV, augmentation index) by 24-h oscillometric ABPM; central BP	Multivariable logistic (CVI as outcome): PWV OR 5.36 (95% CI 2.35–12.26); Aix OR 4.69 (1.86–11.84); TG OR 2.96 (1.34–6.55); PWV > 9.2 AUC 0.826	Worse in CVeD (adjusted)	FT; S/S/S/S
Nogueira et al., 2023 [110]	Function	Cross-sectional analytic study; Brazil (Belo Horizonte); vascular surgery outpatient clinics of 2 hospitals; 35 CEAP C4–C6/35 CEAP C1–C3 (severity strata; no non-CVeD group)	Peripheral and central BP; PWV, augmentation pressure, AIx@75 by brachial oscillometry	Spearman rho PWV–CEAP 0.62, unadjusted; stepwise linear regression for PWV retained age 0.11 (0.10; 0.12), SAPp and AP; CEAP not independent	Correlated with CEAP; not independent after adjustment	FT; S/S/S/S
Nóbrega et al., 2024 [111]	Function	Prospective uncontrolled before–after study; Portugal; tertiary center; CEAP C3–C6 surgical candidates; 50 enrolled, 42 analysed/NA (pre–post within patients)	Brachial artery %FMD before and 6 months after surgery (blinded post-operative assessor)	No statistically significant change ($p = 0.819$); published change and CI inconsistent	No statistically significant within-person change after surgery (uncontrolled)	FT; S/H/S/H
Matic et al., 2016 [107]	Structure/ disease	Cross-sectional; Serbia; tertiary angiology/ dermatovenereology referral center, Clinical Center of Vojvodina; 112 CVI/50 referred patients without CVI	PAD (ABPI ≤ 0.9); hypertension	PAD severe CVI vs. controls OR 3.375 (95% CI 1.125–10.12), unadjusted; severe vs. mild + controls aOR 3.109 (1.062–9.103)	More PAD in severe CVeD (adjusted)	FT; L/S/L/S
Jiang et al., 2024 [112]	Structure/ disease	Cross-sectional analysis of BEST study baseline; China (Beijing); single vascular medicine center; 192/2450 subjects without LECVD	LEAD (ABI < 0.9); hypertension, CHD, stroke, DM; fasting lipids, HbA1c, homocysteine	LEAD and LECVD: crude OR 4.062 (95% CI 3.008–5.485); aOR 2.937 (95% CI 1.956–4.411), $p < 0.001$; hypertension univariable OR 1.541 (1.147–2.069)	More PAD in CVeD (adjusted)	FT; S/L/S/S

Table 1. *Cont.*

Study	Construct	Design; Country; n (CVeD/Comparator)	Measurement	Main Finding (as Reported)	Direction of Finding	Source; RoB
Tomita et al., 2025 [113]	Structure/ disease	Retrospective comparative cross-sectional study; Japan; single center; 234 CVI/234 sex- and age-matched AF patients undergoing ablation	Coronary artery calcium score (CACS) on non-contrast CT	Multivariable linear regression: CVI beta 143.6 (95% CI 63.7–223), $p < 0.001$	Higher in CVeD (adjusted)	FT; H/S/S/S

Values as reported in the source. Construct: function, flow-mediated dilation, arterial stiffness (pulse-wave velocity, augmentation index, cardio-ankle vascular index) or microvascular reactivity; structure/disease, intima–media thickness, coronary artery calcium, ankle–brachial index or peripheral artery disease. Direction of finding distinguishes unadjusted (or matched-only) comparisons, adjusted associations, associations not retained after adjustment, and within-person changes after treatment in uncontrolled studies. FT, full text; Abs, abstract only. RoB columns: selection/confounding/measurement/other (L, low; S, some; H, high concern; U, unclear). Abbreviations: ABI, ankle–brachial index; CACS, coronary artery calcium score; CAVI, cardio-ankle vascular index; CEAP, Clinical, Etiological, Anatomical, and Pathophysiological classification; CVeD, chronic venous disease; FMD, flow-mediated dilation; NR, not reported; PAD, peripheral artery disease; PWV, pulse-wave velocity.

3.5. Cardiovascular Disease (Domain 4)

Twenty-two reports addressed clinical cardiovascular associations [99,107,112,114–132] (Table S5). Cardiovascular conditions, ascertainment, and reference groups differed. The domain includes comorbidity and reverse-direction evidence, not only prevalent disease: in Mok, prior heart failure predicted later recognition of varicose veins, rather than varicose veins predicting incident heart failure. Studies reporting only hypertension or other traditional factors as correlates of CVeD were mapped; the D4 labels were also removed from three retained reports whose eligible contribution lay in D2 or D5. Associations were positive, null, or mixed by condition and severity; selected wound-care comparators, convenience samples, diagnosis codes, and incomplete adjustment constrain interpretation.

3.6. Longitudinal Outcomes (Domain 5)

Thirty-two reports examined longitudinal outcomes [99,122,128,133–161] (Table 2). Eleven contributed a VTE association: seven positive, one mixed by DVT/PE component, and three null. Müller-Bühl's registry association had uncertain temporal ordering and is distinguished from the stricter incident-event evidence. Population claims and EHR cohorts generally reported higher venous-thrombotic risk; estimates were weaker or null in critically ill patients, for autopsy-confirmed PE, and in a small short-term cohort. Thirteen reports contributed all-cause mortality findings: seven positive, one mixed, three null, and two inverses. Higher estimates in population, registry, and advanced-CEAP cohorts coexisted with null results, stage-dependent directions, and inverse estimates in selected nursing-home/chronic-wound populations. Yıldırım reported equal crude in-hospital mortality proportions (13.2% in each group), not an adjusted mortality association. Choi's venous-ulcer indicator was inversely associated with death before amputation within a chronic-wound cohort (A1 HR 0.69, 95%CI 0.63–0.75; A2 HR 0.66, 0.59–0.74); this is not a comparison with healthy/general-population controls and does not establish protection. Different populations, reference groups, and time horizons were not pooled.

Table 2. Longitudinal studies of incident cardiovascular events, venous thromboembolism, and mortality in chronic venous disease (Domain 5).

Study	Design; Country; Follow-Up	Exposure; n (CVeD/ Comparator)	Outcome (s)	Events or Rates	Estimate (95% CI)	Adjustment	Source; RoB
Royal et al., 1978 [140]	Prospective cohort; UK; RCGP Oral Contraception Study, ~1400 general practices; follow-up: 34,482/14,769/47,084 woman-years by OC group	GP-recorded varicose veins; severe = operated varicosities; NR VV/NR women without VV	First idiopathic DVT and superficial venous thrombosis	Excess DVT risk in OC users with VV ~165 per 100,000 users per year (1 in 600 vs. 1 in 1500)	DVT approx. 2-fold (significant in OC users only); superficial thrombosis significantly increased, rising with severity	Indirect standardization for age, parity, smoking, social class	FT; S/L/S/S
Ducimetiere et al., 1981 [133]	Prospective cohort; France; Paris Prospective Study, male employees; follow-up: average 6.6 years	Varicose veins at baseline examination; NR VV/NR men without VV (total cohort 7432)	Incident intermittent claudication, hard CHD, angina pectoris	NR	Not reported numerically: significantly higher risk of intermittent claudication and, in lower social class, hard CHD; no association with angina	NR	Abs; S/U/U/S
Goldhaber et al., 1983 [144]	Prospective community cohort, autopsy-confirmed PE cases vs. participants; USA; Framingham Heart Study; follow-up: up to 26 years	Varicose veins on physical examination at exam 1 or 2; NR/NR participants without varicose veins (3470 analyzed)	Major acute PE confirmed at autopsy	61 major PE at autopsy; varicose veins in major PE 11% men/42% women vs. entry 11%/28%	Logistic coefficients for varicose veins, no OR: multivariate vs. entry cohort men −0.079 (Z −0.41), women 0.058 (Z 0.25), both NS	Age, systolic BP, total cholesterol, cigarette use, glucose, relative weight (sex-specific models)	FT; S/L/L/H
Brand et al., 1988 [134]	Prospective community cohort of incident VV and CV events; USA; Framingham Study; follow-up: 16 years	Incident varicose veins at biennial examination; 396 men, 629 women/1257 men, 1753 women without VV	Two-year incidence of CHD, CHF, stroke, intermittent claudication; CV risk factors	Age-adjusted CHD per 1000: women 34.0 vs. 22.4, $p < 0.05$; men 47.6 vs. 40.7; CHF women 13.7 vs. 8.3	No HR/OR reported; excess CHD in women ($p < 0.05$) not significant after controlling for body mass and systolic BP	Age; CHD in women also body mass and SBP	FT; L/S/L/S

Table 2. *Cont.*

Study	Design; Country; Follow-Up	Exposure; n (CVeD/ Comparator)	Outcome (s)	Events or Rates	Estimate (95% CI)	Adjustment	Source; RoB
Nelzén et al., 1997 [150]	Prospective cohort with matched population controls; Sweden (Skaraborg county); population-based leg ulcer study; follow-up: 5 years; no patients lost	Venous or mixed venous-arterial leg ulcer (Nelzén groups 1–2); 206/382 age- and sex-matched population controls	5-year all-cause survival; relative risk of death; ulcer healing at 54 months	5-year survival 63% venous ulcers vs. 68% controls ($p = 0.53$); venous ulcers healed at 54 months 72/135 (54%)	RR of death vs. matched controls: venous ulcers 1.2 (95% CI 0.8–1.6); arterial 2.0 (1.5–2.7); other 1.7 (1.2–2.3); age/sex matched only	Age and sex matching only; no multivariable adjustment	FT; L/H/L/L
Scott et al., 2004 [159]	Prospective cohort of initially healthy men; USA (greater Boston); VA Normative Aging Study; follow-up: mean 21.7 years (range 3–35)	VV on physical inspection before CHD, as time-varying covariate; 569/1708 men without VV before CHD	Incident symptomatic CHD: nonfatal MI, angina pectoris or cardiac death	Symptomatic CHD 98/569 (17.2%) with VV vs. 363/1708 (21.2%) without; log-rank $p = 0.0001$	Time-dependent Cox: VV adjusted RR 0.64 (95% CI 0.5–0.8), $p = 0.0004$ (n = 1570)	Age, BMI, BP, cholesterol, diabetes, family history, smoking, alcohol, education	FT; H/L/L/S
Mäkivaara et al., 2007 [160]	Prospective population cohort (questionnaire); Finland; Tampere general population aged 40, 50, 60; follow-up: 5 years	Self-reported varicose veins (validated questionnaire); NR VV/NR without VV (4903 respondents)	New arterial disease (angina, MI, PAD, cerebrovascular disease); new hypertension	New arterial disease more frequent with VV; counts NR	Incidence OR arterial disease 2.0 (95% CI 1.5–2.7; n = 3032); new hypertension 1.0 (0.8–1.3; n = 2915)	NR	Abs; S/U/S/S
Takahashi et al., 2008 [152]	Retrospective cohort; USA (Minnesota); nursing-home residents with chronic ulcers; follow-up: 6 months	Prior clinical diagnosis of venous insufficiency (no CEAP); 45 with venous insufficiency/366 without	All-cause mortality at 6 months	Deaths 4/45 vs. 107/366 (derived from Table 1)	Age/sex-adjusted OR 0.24 (95% CI 0.08–0.67); multivariable OR 0.18 (0.05–0.61)	Age, sex; ulcer number, hemoglobin, BMI, HF, PVD, dementia, cancer, others	FT; S/L/L/S

Table 2. *Cont.*

Study	Design; Country; Follow-Up	Exposure; n (CVeD/ Comparator)	Outcome (s)	Events or Rates	Estimate (95% CI)	Adjustment	Source; RoB
Mäkivaara et al., 2009 [122]	Prospective population cohort with baseline cross-sectional analysis; Finland; Tampere postal questionnaire survey; follow-up: 5 years	Questionnaire-reported varicose veins; NR VV/NR without VV (total 4903)	Prevalent and incident congestive heart failure (CHF)	CHF prevalence 2.9% with VV vs. 1.9% without; incidence 4.9 vs. 2.6 per 1000 person-years	Prevalence: OR 1.6 (1.0–2.3); age-sex adjusted OR 1.2 (0.8–1.9). Incidence: IDR 1.9 (1.1–2.9); age-sex adjusted IOR 2.5 (1.4–4.6); multivariable IOR 2.1 (1.1–4.0)	Age, sex, BMI, arterial disease, hypertension	Abs; H/S/H/S
Rahman et al., 2011 [142]	Retrospective record-linkage cohort; England (former Oxford region); ORLS hospital admissions linked to deaths, 1963–1999; follow-up: up to 1999 from index admission; mean NR	First hospital day-case/inpatient episode coded as varicose veins; 43,724 hospital-treated VV/464,533 minor-condition reference cohort	Admission or death with CHD, MI, HF, PE, DVT, stroke, SAH, AAA	Observed/expected: CHD 2713/2940.4; MI 1434/1595.7; HF 1379/1328.1; PE 524/486.2; DVT 458/395.7; AAA 231/206.3	Standardized rate ratios: DVT 1.20 (1.08–1.33); PE 1.10 (0.99–1.21); CHD 0.91 (0.88–0.95); MI 0.89 (0.84–0.94); AAA 1.14 (0.99–1.30)	Indirect standardization for sex, age band, calendar year, district; no CV risk factors	FT; S/S/L/S
Müller-Bühl et al., 2012 [136]	Registry association; ordering of VV and DVT not established in available abstract	VV coded ICD-10 I83.9; 2357 VV/80,588 primary care patients without VV	DVT association; not confirmed first incident DVT after VV	DVT 132/2357 (5.6%) vs. 728/80,588 (0.9%), $p < 0.0001$	VV aOR 7.33 (95% CI 6.14–8.74) for DVT	Age, sex, surgery, hospitalization, CHF, malignancy, pregnancy, hormones, infection, previous DVT	Abs; S/S/S/S
Königsbrügge et al., 2013 [139]	Prospective cohort; Austria; Vienna Cancer and Thrombosis Study (CATS), Vienna General Hospital; follow-up: Median 590 days (IQR 234–731); max 2 years	Clinically visible/palpable VV (CEAP ≥ C2) at inclusion; 160 VV/1110 cancer patients without VV	Adjudicated symptomatic or fatal VTE	VTE 22/160 (13.8%) vs. 76/1110 (6.8%); cumulative incidence at 365 days 12.7% vs. 7.0%	Adjusted SHR 2.10 (95% CI 1.29–3.41), $p = 0.003$; univariable SHR 2.01 (1.26–3.21)	Age, sex, BMI, new vs. progressive cancer, prior VTE, prior thrombophlebitis; Fine–Gray	FT; S/L/L/S

Table 2. *Cont.*

Study	Design; Country; Follow-Up	Exposure; n (CVeD/ Comparator)	Outcome (s)	Events or Rates	Estimate (95% CI)	Adjustment	Source; RoB
Chang et al., 2018 [135]	Retrospective PS-matched cohort; Taiwan; NHI claims linked to National Register of Deaths; follow-up: median 7.3–7.8 years	Diagnosed varicose veins (ICD-9-CM 454); 212,984 VV/212,984 PS-matched controls	Incident DVT, PE, PAD	Per 1000 PY: DVT 6.55 vs. 1.23; PE 0.48 vs. 0.28; PAD 10.73 vs. 6.22	PS-matched HR: DVT 5.30 (95% CI 5.05–5.56); PE 1.73 (1.54–1.94); PAD 1.72 (1.68–1.77); DVT with ≥1 y follow-up 3.98 (3.77–4.21)	PS: age, sex, index year, HT, DM, COPD, hyperlipidemia, malignancy, HF, IHD, stroke, CKD	FT; L/S/S/L
Wu et al., 2020 [141]	Retrospective PS-matched cohort; Taiwan; NHI claims database (LHID2000); follow-up: Up to 12 years; median NR	Claims-based VV diagnosis, severity grades 1–3; 4644 VV/17,760 PS-matched controls	All-cause mortality; MACE (ACS, CHF, ischemic stroke, DVT, PE)	Deaths grade 3: 136 (9.01%) vs. 266 (4.65%); 9-year survival 93.5% vs. 95.6%	Mortality aHR 1.37 (95% CI 1.19–1.57); MACE aHR 2.05 (1.89–2.23); grade 3 mortality aHR 1.83 (1.48–2.27); grade 3 DVT + PE aHR 38.42 (16.38–90.13)	PS matching (age, sex, hypertension, diabetes, hyperlipidaemia, CAD); Cox for COPD, cancer, AF, HF	FT; S/S/L/S
Kreft et al., 2020 [147]	Claims cohort emulating a target trial, new-diagnosis design; Germany; AOK statutory health insurance sample aged ≥ 50; follow-up: up to 12 years (2004–2015)	Incident ICD-10-GM diagnosis of VLU (I83.0, I83.2) or PTS (I87.0); 4673 VLU, 1869 PTS/232,738, and 235,542 non-incident insurees	All-cause mortality	Age-standardized mortality per 100 PY: VLU 7.02, PTS 4.34, total population 2.80	VLU HR 1.36 (1.31–1.42), $p < 0.001$; PTS HR 1.06 (0.98–1.13), $p = 0.135$, adjusted; adding sepsis and embolism, VLU HR 1.09 (1.05–1.14)	Age, sex, multimorbidity; second-stage models add pulmonary embolism and sepsis	FT; S/L/L/L
Prochaska et al., 2021 [128]	Population-based prospective cohort (Gutenberg Health Study); Germany (Mainz); validation in MyoVasc heart-failure cohort; follow-up: mean 6.4 ± 1.6 years (GHS)	Photograph-based CEAP clinical class; CVI defined as C3–C6; 4603 CVI C3–C6/906 CEAP C0, no venous disease	Prevalent CVD composite and CV risk factors; all-cause death	Prevalent CAD 2.9% C0 vs. 7.7% C3 vs. 10.1% C4–C6; PAD 1.6% vs. 5.7% vs. 9.9%; 540 GHS deaths	CVI vs. C0: prevalent CVD PR 1.46 (1.16–1.84) risk-factor adjusted; all-cause death HR 1.46 (1.19–1.79) fully adjusted; MyoVasc HR 1.51 (1.11–2.05)	Age, sex, CV risk factors, CVD, cancer, CV medication; MyoVasc also NT-proBNP	FT; L/L/L/L

Table 2. *Cont.*

Study	Design; Country; Follow-Up	Exposure; n (CVeD/ Comparator)	Outcome (s)	Events or Rates	Estimate (95% CI)	Adjustment	Source; RoB
Salenius et al., 2021 [146]	Retrospective register-based matched cohort; Finland; Tampere tertiary dermatology records, national death register; follow-up: median 7 years (patients) vs. 10 years	VLU diagnosis code at tertiary dermatology clinic; 1924 VLU/NR matched population references	All-cause and cause-specific mortality	1526 deaths among 1924 VLU; median survival 9 years	All-cause mortality HR 1.49 (95% CI 1.41–1.59); ischemic heart disease HR 1.38 (1.23–1.56); diabetes HR 5.81 (3.80–8.89); matched only	Matching on age, sex, residence only	FT; S/H/L/L
Singh et al., 2022 [158]	Prospective cohort, within-CVeD severity comparison; Australia; 2 outpatient vascular centers, Townsville; follow-up: median 3.09 years (IQR 1.09–8.14)	CEAP clinical class (duplex-confirmed CVD); 774 CVeD/C2 reference (n = 326) within cohort	First MACE (MI, stroke, cardiovascular death)	35 MACE: C2 6, C3 10, C4 2, C5 4, C6 13 ($p < 0.001$)	aHR vs. C2: C6 3.03 (1.02–9.03), C5 2.04 (0.54–7.75), C3 1.86 (0.64–5.42); severe (C5–C6) vs. mild (C2–C4) aHR 2.37 (1.12–5.04)	Age, sex, diabetes, hypertension, CHD, stroke, smoking, ACEi, aspirin, statin	FT; H/L/L/S
Hu et al., 2022 [154]	Retrospective population-based cohort, 1:4 age/sex frequency-matched; Taiwan; NHIRD Longitudinal Health Insurance Database; follow-up: Up to 31 Dec 2013; mean NR	First diagnosis of varicose veins (ICD-9-CM 454); 5579/22,316 age- and sex-matched non-VV	Incident atrial fibrillation (ICD-9-CM 427.31)	AF 4.82 vs. 3.47 per 1000 PY (197 vs. 558 events)	Crude HR 1.39 (1.18–1.64); aHR 1.23 (1.04–1.45); age ≤ 64 aHR 1.82 (1.34–2.47); women aHR 1.34 (1.06–1.69)	Age, sex, HF, hypertension, diabetes, hyperlipidemia, CHD, COPD, stroke, VTE, other comorbidities	FT; L/L/L/S
Lee et al., 2023 [157]	Retrospective nationwide claims cohort, 1:1 propensity-score matched; Taiwan; NHIRD; follow-up: mean 4.49 ± 2.63 years (VV)	VV (ICD-9-CM 454.XX) with ≥3 outpatient diagnoses; 56,898/56,898 PS-matched never-VV beneficiaries	Incident mitral valve regurgitation (ICD-9-CM 424.0)	MR 9.10 vs. 5.61 per 1000 PY (2326 vs. 1422 cases)	Crude HR 1.62 (1.52–1.73); aHR 1.63 (1.52–1.74); age 20–39 aHR 2.13 (1.71–2.65); ≥3 annual VV visits aHR 10.64 (9.57–11.82)	PS matching plus Cox adjustment for age, sex, cardiometabolic comorbidities, AF, HF, stroke, cancer	FT; S/L/S/S

Table 2. *Cont.*

Study	Design; Country; Follow-Up	Exposure; n (CVeD/ Comparator)	Outcome (s)	Events or Rates	Estimate (95% CI)	Adjustment	Source; RoB
McBane et al., 2024 [149]	Retrospective cohort; USA; Mayo Clinic vascular laboratory database with National Death Index; follow-up: median 2.84 years	CEAP clinical class (worst limb); calf muscle pump EF by air plethysmography; 3431 with CEAP recorded (cohort 5913)/NR referent CEAP 3	All-cause mortality (National Death Index)	431 deaths overall; 10-year mortality 14.2% (CMP EF ≥ 50%) to 38.7% (EF < 10%)	aHR vs. CEAP 3: CEAP 0–1 0.2 (0.1–0.5); CEAP 2 0.5 (0.3–0.8); CEAP 4 1.2 (0.9–1.5); CEAP 5–6 1.4 (1.0–1.8); CMP EF 10–19% vs. ≥50%: HR 2.4 (1.7–3.3)	Age, sex, neuropathy, AF, pulmonary hypertension, smoking, dyslipidemia, CKD, Charlson index	FT; S/L/L/S
Choi et al., 2024 [155]	Retrospective population-based cohort, 1:3 PS matching; South Korea; NHIS-HEALS claims and screening; follow-up: Median 10.06 years (IQR 9.43–10.44)	≥2 claims ICD-10 I83.0–I83.2 (severe) or I83.9 (mild); 24,557 VV among 2,680,971 participants (PSM 20,736/62,208)	Incident AF (ICD-10 I48)	After PSM: 802/20,736 VV (4.06/1000 PY) vs. 2072/62,208 (3.46/1000 PY)	aHR 1.13 (95% CI 1.06–1.21) before PSM; HR 1.17 (1.08–1.27) after PSM; severe VV 1.18 (1.10–1.26), mild VV 1.08 (1.03–1.13) after PSM	Age, sex, BMI, income, smoking, alcohol, activity, hypertension, diabetes, dyslipidemia, comorbidities; PSM	FT; S/L/L/S
Kudryavtseva et al., 2024 [145]	Prospective observational cohort; Russia (Moscow); women with AF on DOACs at university centers; follow-up: 12 months	CEAP C2–C6 on duplex ultrasound; secondary contrast CVI C3–C6; 28/27 no CVeD or CEAP C0–C1	VTE (DVT, PE, superficial vein thrombophlebitis) during 12 months	VTE 3/28 (10.7%) vs. 0/27, $p = 0.236$; DVT 1 vs. 0; SVT 2 vs. 0; PE 0 vs. 0	No ratio estimate; Fisher exact $p = 0.236$ (C2–C6 vs. control); CVI C3–C6 in 3/3 with VTE vs. 5/52 without, $p = 0.002$; unadjusted	Unadjusted	FT; S/H/S/S
Hsieh et al., 2025 [156]	Retrospective PS-matched (1:4) cohort; Taiwan; NHIRD 2-million beneficiary claims sample; follow-up: to Dec 2018; median NR	Claims-based VV diagnosis; no severity data; 23,238 VV/92,952 PS-matched non-VV	Stroke (ischemic and hemorrhagic), hospital admission primary diagnosis	Stroke 2555 (13.15/1000 PY) vs. 8799 (11.16/1000 PY)	Stroke aHR 1.16 (1.11–1.21); excluding first 6 months aHR 1.13 (1.08–1.19); <1 year aHR 1.34 (1.19–1.50); VV management vs. none aHR 0.82 (0.70–0.96)	Age, sex, income, urbanization, comorbidities (hypertension, diabetes, CAD, AF), aspirin, metformin, statin	FT; L/S/L/S

Table 2. *Cont.*

Study	Design; Country; Follow-Up	Exposure; n (CVeD/Comparator)	Outcome (s)	Events or Rates	Estimate (95% CI)	Adjustment	Source; RoB
Kim et al., 2025 [153]	Retrospective population-based cohort, 1:5 PS matching; South Korea; NHIS-HEALS claims and screening; follow-up: median 13.33 years (IQR 10.4–16.26)	≥2 VV claims (ICD-10 I83.0–I83.2, I83.9, I86.8); 5008 VV/385,428 without VV (PSM: 5004 vs. 25,020)	Incident heart failure (≥2 claims ICD-10 I50)	55,023 HF cases overall (14.0%); HF incidence without VV 1240.589/100,000 PY after PSM; VV-group rates NR	aHR 1.174 (1.089–1.265) before PSM; aHR 1.171 (1.070–1.283) after PSM; Fine–Gray SHR 1.146 (1.034–1.270) after PSM	Age, sex, BMI, income, smoking, alcohol, physical activity, comorbidities, Charlson index; PSM	FT; S/L/L/L
Moderegger et al., 2025 [137]	Retrospective PS-matched cohort; USA; TriNetX EHR network, 58 healthcare organizations; follow-up: Up to ~20 years from index	ICD-10-CM CVD codes recorded twice, ≥12 months apart; 442,057 CVD/442,057 PS-matched controls	SVT, DVT, PE, all-cause mortality	DVT 7.38% vs. 2.308%; PE 3.269% vs. 1.623%; death 14.581% vs. 7.951%; SVT 1.601% vs. 0.086%	HR in PS-matched cohorts (univariate Cox): DVT 3.283 (3.209–3.359); PE 2.017 (1.96–2.076); death 1.806 (1.783–1.83); SVT 18.945 (17.082–21.012)	PSM: age, sex, hypertension, dyslipidemia, diabetes, IHD, CKD, nicotine dependence, BMI, contraceptives	FT; S/L/S/S
Caride-Miana et al., 2025 [151]	Population-based cohort; Spain; national health survey linked to death registry; follow-up: 6.4 years	Self-reported varicose veins in the legs; 2432 self-reported VV/12,152 without	All-cause mortality	Deaths 271/2432 (11.1%) vs. 1075/12,152 (8.8%); $p < 0.001$, unadjusted	No HR reported; varicose veins not retained in the adjusted Cox model	Unadjusted for VV (not retained in multivariable model)	FT; H/H/L/S
Shen et al., 2025 [138]	Retrospective 1:1 PS-matched cohort, active comparator; multinational; TriNetX federated EHR network; follow-up: Mean 1560 ± 1410 days (VV)	ICD-10 I83 diagnosis (no CEAP severity); 297,629 VV/297,629 matched acute tonsillitis	Incident PE, PAD, DVT	PE 2.5% vs. 2.2%; PAD 3.4% vs. 2.3%; DVT 2.6% vs. 1.1%	PSM Cox HR: PE 1.17 (95% CI 1.13–1.21); PAD 1.53 (1.48–1.58); DVT 2.48 (2.38–2.59)	PSM: age, sex, race, hypertension, diabetes, hyperlipidemia, COPD, AF, HF, IHD, CKD, stroke	FT; H/L/S/S
Chervonski et al., 2026 [148]	Retrospective cohort from prospective registry; USA; single-center VQI Varicose Vein Registry; follow-up: Mean 2.8 (VLU) vs. 3.0 (non-VLU) years	VLU history (C5–C6) vs. non-VLU (C2–C4); 632 VLU (C5–C6)/6452 non-VLU (C2–C4)	All-cause mortality	Deaths 23/632 (3.6%) vs. 46/6452 (0.7%), $p < 0.001$	VLU: crude HR 5.03 (2.96–8.53); aHR 2.01 (1.00–4.01), $p = 0.049$. C6 vs. C2: aHR 3.40 (1.08–10.69)	Age, sex, race, prior VV treatment, anticoagulation, rVCSS, deep venous reflux	FT; S/S/L/S

Table 2. *Cont.*

Study	Design; Country; Follow-Up	Exposure; n (CVeD/ Comparator)	Outcome (s)	Events or Rates	Estimate (95% CI)	Adjustment	Source; RoB
Yıldırım et al., 2026 [143]	Retrospective cohort; USA; single-center ICU, MIMIC-IV v3.1 electronic health records; follow-up: Index hospitalization (median ~3.9 days)	Administrative ICD codes for CVD (cross-admission look-back); 544 CVeD/28,197 ICU patients without CVD	In-hospital VTE (DVT or PE); PE and DVT separately	VTE 38/544 (7.0%) vs. 1741/28,197 (6.2%); PE 3.7% vs. 2.9%; DVT 4.4% vs. 4.1%; complicated CVD VTE 5/30 (16.7%)	VTE aOR 1.10 (0.77–1.52); PS-matched OR 1.24 (0.84–1.84); PE aOR 1.31 (0.83–2.07); DVT aOR 0.98 (0.65–1.49); complicated CVD aOR 2.90 (1.09–7.08)	Age, sex, SAPS-II, Charlson, ventilation, vasopressors; 1:3 PS matching	FT; S/L/S/S
Salim et al., 2026 [99]	Retrospective EHR study with nested matched case-control and Cox analyses; UK; CPRD GOLD/Aurum, WSIC, UK Biobank; follow-up: UKB median 11.5 years	Coded chronic venous disease by CEAP-grouped clinical class (C2–C6); Aurum C2 223,961, C6 89,452/447,884, 178,864 age/sex-matched controls without venous codes	CV conditions; CRP and hematological markers; all-cause mortality	UKB mortality 28% C5/C6 vs. 7.3% controls, $p < 0.001$; CRP > 5.00 mg/L OR 1.41 (1.23–1.61)	Aurum OR vs. controls: coronary disease C2 12.36 (9.59–15.93), C6 20.05 (14.09–28.55); hypertension C2 0.68 (0.62–0.75); C6 mortality HR 1.39 (1.23–1.58)	Age and sex matching; survival models include age, gender, CCI score, region	FT; S/S/L/S
Choi JS et al., 2025 [161]	Retrospective multistate cohort; USA; median 2.28 y (IQR 0.80–5.24)	Time-updated venous-ulcer history; 3715 at entry/6399 at exit; total 52,916 chronic-wound patients	Death before amputation; all-cause, not CV-specific	Venous-ulcer indicator versus its negation within a selected chronic-wound cohort	A1 HR0.69 (0.63–0.75); A2 HR0.66 (0.59–0.74)	Demographics, wound/infection histories, PVDm and chronic-disease composite; A1 diabetes; A2 DFU/HbA1c	FT; S/S/L/S

Values as reported in the source; "NR", not reported. Reports from the same cohort (Tampere, Framingham, German primary-care database) are linked in Table S5; several Taiwanese and Korean cohorts used overlapping national insurance databases. FT, full text; Abs, abstract only. RoB columns: selection/confounding/measurement/other (L, low; S, some; H, high concern; U, unclear). Abbreviations: AF, atrial fibrillation; CEAP, Clinical, Etiological, Anatomical, and Pathophysiological classification; CHD, coronary heart disease; CI, confidence interval; DVT, deep vein thrombosis; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease; PE, pulmonary embolism; PS, propensity score; SHR, subdistribution hazard ratio; VLU, venous leg ulcer; VTE, venous thromboembolism; VV, varicose veins.

For subsequent cardiac and arterial outcomes, five clinical reports addressed heart failure (three positive, two null), two atrial fibrillation (both positive), four PAD/intermittent claudication (three positive, one null), six coronary disease/MI or coronary mortality (two positive, one mixed, one null, two inverse), and four stroke (two positive, two null). Full-text restriction changed some group compositions (Table S12). Coronary mortality, incident CHD, socioeconomic subgroups, and composites were distinguished. Mäkivaara's composite arterial-disease estimate was not counted as coronary-specific evidence. Mitral regurgitation and MACE were reported separately; composites containing VTE were not interpreted as purely arterial outcomes. Selected longitudinal effect estimates are displayed in Figure 2. Absolute risks, code-based exposure/outcomes, residual confounding, clinical selection and overlapping databases limit clinical inference.

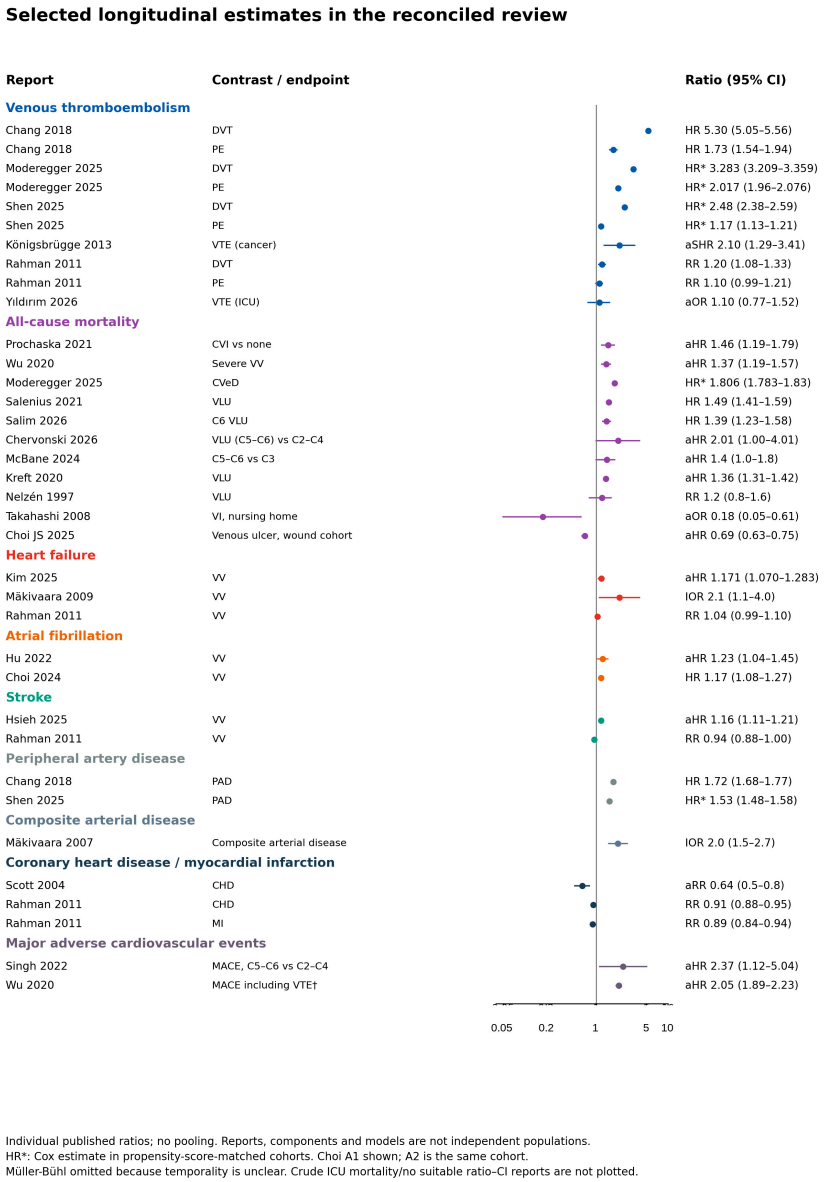


Figure 2. Selected published longitudinal estimates without pooling. Clinical endpoints and composite outcomes are shown separately. Estimates from the same report are not independent cohorts. Müller-Bühl is omitted because temporality is unclear. Choi A1 is shown; A2 uses the same cohort. Ratios with no reported confidence interval are not plotted. Source studies: [99,122,128,135,137–139,141–143,146–150,152–156,158–161].

3.7. Risk Prediction (Domain 6)

No eligible study evaluated whether adding CVeD status or severity to an established cardiovascular risk model improved discrimination, calibration, reclassification, or clinical utility. A genetic risk score for venous thromboembolism improved discrimination of CVeD itself [162], which is not cardiovascular risk prediction.

3.8. Genetic Causal Inference

Eighteen reports used an eligible genetic causal-inference design [163–180] (Table 3). Anthropometric traits, smoking, selected inflammatory proteins, and immune-cell activation phenotypes were examined as genetically predicted exposures for varicose veins; some reports examined venous/cardiac outcomes in the opposite direction. Genetic-score association alone and varices-of-other-sites phenotypes were not counted as eligible causal CVeD evidence. The published Levin version was used for eligibility; unverified preprint-only numerical MR statements were withdrawn, and genetic correlations were treated as contextual, not clinical MR effects. Shared UK Biobank/FinnGen resources, instrument selection, multiple testing, pleiotropy, and sample overlap limit interpretation. These estimates are not observed clinical treatment effects or validation of added cardiovascular prediction. In Song et al. [174], the estimates from Figure 5 of that publication are distinguished from the subset surviving directionality, pleiotropy, and LCV analyses. Its VV-to-phlebitis significance shading conflicts with a confidence interval crossing 1; this is retained as a source-reporting inconsistency, not resolved by inference.

Table 3. Eligible genetic causal-inference reports. Genetic correlations and genetic-score associations are not treated as interchangeable with causal estimates.

Study	Exposure → Outcome	Main Estimate (as Reported)	Source; RoB
Shadrina et al., 2019 [163]	Genetic instruments for 2221 traits: anthropometrics, BP, CAD risk factors, proteins → VV (I83); genetic correlation with DVT, BP, and other traits	MR estimates NR in main text; smoking rg = 0.16; replication significant only for height	FT; L/S/S/H
Yuan et al., 2021 [164]	Genetically predicted BMI, T2D, BP, smoking, alcohol, coffee, micronutrients; height → Varicose veins (ICD-8/9 454, ICD-10 I83)	OR per SD: BMI 1.39 (1.27–1.52); height 1.34 (1.25–1.43); smoking initiation 1.12 (1.04–1.22); SBP per 10 mmHg 0.87 (0.79–0.96), attenuated after MVMR	FT; L/S/S/S
He et al., 2022 [165]	Genetically predicted BMI, height, education, insulin, metformin, smoking, alcohol, DVT → Varicose veins	IVW OR: BMI 1.008 (1.005–1.010); height 1.009 (1.007–1.011); insulin 0.858 (0.794–0.928); metformin 0.944 (0.904–0.985); linear-probability scale	FT; S/S/H/H
Shadrina et al., 2022 [166]	Genetically predicted plasma CD209 (2 IVs) and MICB (1 IV) → Varicose veins of lower extremities (ICD codes)	CD209 → VV OR 1.08 (95% CI 1.05–1.10), $p = 5.9 \times 10^{-11}$, Phet = 0.80; MICB → VV OR 1.13 (1.07–1.18), not replicated	FT; S/S/L/S

Table 3. *Cont.*

Study	Exposure → Outcome	Main Estimate (as Reported)	Source; RoB
Li et al., 2022 [167]	Genetic liability to VV: 21 SNPs, R2 15.0%, mean F 120.92 → Lower-extremity DVT, PE, VTE (FinnGen)	VV → DVT IVW OR 1.173 (1.070–1.286); MVMR adjusted for height and BMI 1.104 (1.035–1.177); validation 1.107 (1.041–1.178); no causal effect on PE or VTE	FT; L/S/S/S
Constantinescu et al., 2023 [168]	Genetic liability to varicose veins (2 SNPs) and lower-extremity VV (16 SNPs) → Self-reported DVT (UK Biobank)	IVW log RR: 1.90 (1.30–2.50) [16 SNPs], $p = 2.36 \times 10^{-7}$; 3.40 (2.31–4.49) [2 SNPs], $p = 5.13 \times 10^{-7}$	FT; S/S/S/S
Levin et al., 2023 [169]	Anthropometric exposures and plasma proteins → Varicose veins; published-version MR distinguished from genetic correlation	Published report: anthropometric IVW MR (Figure 4b of that publication, Supplementary Table S10) and proteome-wide MR. Estimates from the preprint are not substituted for unverified published-version estimates.	FT; S/S/S/S
Lin et al., 2023 [170]	Genetically predicted inflammatory mediator IRF3 → Varicose veins; protein-specific causal analysis	IRF3 OR per SD 1.12 (95% CI 1.07–1.18). Other proteome-screening targets are not treated as eligible inflammatory mediators solely because they appear in the same study.	FT; L/S/S/H
Guo et al., 2024 [171]	Genetically predicted varicose veins (86 SNPs) → Heart failure	IVW OR 1.03 (95% CI 1.01–1.06), $p = 0.009$; LDSC rg 0.1726184, $p = 0.0001$; reverse MR (HF → VV) not significant	FT; L/S/S/L
Du et al., 2024 [172]	Genetically predicted educational attainment; mediators BMI, BMR, hip and waist circumference → Varicose veins, VTE, phlebitis	Higher EA linked to lower VV, VTE, and phlebitis risk; obesity traits increase VV risk and mediate EA effects; numbers NR	Abs; U/U/U/S
Min et al., 2024 [173]	Genetically predicted levels of 91 circulating inflammatory proteins → Varicose veins	IVW OR per SD: CASP-8 1.074 (1.010–1.143); VEGF-A 1.050 (1.012–1.090); 4EBP1 0.938 (0.880–0.999); MMP-10 0.953 (0.910–0.998)	FT; S/S/S/H
Song et al., 2024 [174]	Genetic liability to VV and seven arterial/venous vascular diseases (bidirectional) → Genetic correlation and causal estimates between VV and vascular diseases	Initial Figure 5 of that publication IVW: VV → PAD OR 1.15 (1.04–1.27); VV → VTE 1.11 (1.03–1.18); VTE → VV 1.15 (1.04–1.27). These are not all sensitivity/LCV-confirmed effects; see File S4.	FT; L/S/S/H

Table 3. *Cont.*

Study	Exposure → Outcome	Main Estimate (as Reported)	Source; RoB
Xu et al., 2025 [175]	Genetically predicted obesity (SNP instruments) → Lower limb venous ulcers; mediation by inflammatory proteins	Obesity significantly increased venous ulcer risk (OR NR); mediators CCL19, hGDNF, IL-12B, TNFRSF9	Abs; U/U/S/S
Nian et al., 2025 [176]	731 immune cell traits (genetic instruments, $p < 1 \times 10^{-5}$) → Varicose veins (ICD-based, FinnGen)	IVW OR: CD86 on myeloid DC 1.05 (1.03–1.08); SSC-A on lymphocytes 1.06 (1.03–1.09); CD39 + CD4+ Treg 0.98 (0.97–0.99); CD39 + CD8br 1.04 (1.02–1.05)	FT; S/S/S/H
Zhang et al., 2025 [177]	Genetically predicted levels of 731 immune cell traits → Varicose veins (ICD-coded, FinnGen R10); reverse MR to immune traits	IVW OR: CD86 on myeloid DC 1.052 (1.025–1.078); CD33 on CD33 + HLA-DR + CD14dim 1.020 (1.010–1.030); BAFF-R on IgD-CD24- B cell 0.963 (0.946–0.980); reverse MR null after FDR	FT; S/S/S/H
Chen et al., 2025 [178]	Genetic liability to varicose veins → Atrial fibrillation; reverse direction AF → VV	VV → AF IVW OR 1.1571 (95% CI 1.0810–1.2384), $p = 2.59 \times 10^{-5}$; reverse MR no causal effect	Abs; U/S/H/S
Ge et al., 2025 [179]	Genetic liability to varicose veins → Atrial fibrillation; reverse AF to VV; multi-omics mediators	VV to AF IVW OR 1.092 (95% CI 1.064–1.121), $p = 3.74 \times 10^{-11}$; reverse AF to VV OR 1.012 (0.961–1.066), $p = 0.644$	FT; U/S/U/S
Xia et al., 2026 [180]	Genetically predicted waist–hip ratio, body fat percentage, waist circumference, basal metabolic rate → Varicose veins and other peripheral vascular diseases (AD, AAA, TAA, PAD, DVT)	Waist–hip ratio protective for varicose veins: OR 0.79, $p = 5.057 \times 10^{-6}$ (CI NR); VV-specific estimates for other exposures NR	Abs; U/U/S/S

Estimates are odds ratios per unit increase in the genetically predicted exposure unless stated otherwise. FT, full text; Abs, abstract only. RoB columns (Mendelian randomization framework): instrument relevance/independence and population structure/phenotype and sample overlap/pleiotropy and sensitivity (L, low; S, some; H, high concern; U, unclear). Abbreviations: AF, atrial fibrillation; BMI, body mass index; DVT, deep vein thrombosis; HF, heart failure; IVW, inverse-variance weighted; MVMR, multivariable Mendelian randomization; rg, genetic correlation; VTE, venous thromboembolism; VV, varicose veins.

3.9. Risk-of-Bias Findings

Risk-of-bias concerns differed by design. Longitudinal reports were affected by coded exposures/outcomes, detection bias, incompletely controlled frailty/obesity/activity, selected clinical comparators, and overlapping databases. Marker and functional studies were small, heterogeneous, and often incompletely adjusted. Of 84 D2 reports, 43 were abstract-based; of 13 D3 reports, 4 were abstract-based. Instrument strength, pleiotropy, phenotype definition, shared samples, and sensitivity analyses affected genetic reports. Table S6 and File S4 report judgments, sources of assessment, and column ratings. All 265 previously missing item pointers were recorded from 56 main articles, with 20 judgment corrections. The inaccessible supplementary methods of Ge and Levin remain a documented uncertainty rather than an inferred methodological finding.

3.10. Certainty of Evidence

The GRADE-informed certainty of the observational biomarker, functional, clinical cardiovascular, and longitudinal associations was very low (Tables 4 and S8). Observational evidence began at low certainty and was downgraded for serious risk of bias; large association size did not justify an upgrade when detection bias, misclassification, residual confounding, or clinical selection remained. Further outcome-specific concerns included inconsistent clinical directions, non-equivalent comparators, indirectness, and imprecision in small functional studies. These judgments were reconsidered in the full-text subsets. Genetic causal-inference studies were evaluated separately with the instrumental-variable framework rather than assigned a clinical-effect GRADE rating. No certainty rating was assigned to an absent incremental-prediction evidence base.

Table 4. Summary of findings and GRADE-informed certainty of the evidence, with the sensitivity synthesis restricted to reports assessed in full text.

Outcome (Domain)	Evidence (Reports)	Direction and Magnitude	Main Limitations	Full-Text Reports Only	Certainty
Venous thromboembolism	11 reports	7 positive, 1 mixed, 3 null	Detection, code misclassification, residual confounding, EHR overlap; one uncertain temporal sequence.	10 reports: 6 positive, 1 mixed, 3 null	Very low
All-cause mortality	13 reports	7 positive, 1 mixed, 3 null, 2 inverse	Frailty/comorbidity, stage, and selected wound/ICU comparators; not CV-specific; different horizons.	13 reports: 7 positive, 1 mixed, 3 null, 2 inverse	Very low
Heart failure	5 reports	3 positive, 2 null	Residual confounding/coded diagnoses; five forward clinical reports; reverse-direction and genetic evidence separate.	4 reports: 2 positive, 2 null	Very low
Atrial fibrillation	2 reports	2 positive	Two coded-diagnosis cohorts; detection/residual confounding and shared resources.	2 reports: 2 positive	Very low
Peripheral artery disease	4 reports	3 positive, 1 null	Clinical claudication/PAD definitions differ; confounding and detection bias; cross-sectional ABI findings separate.	3 reports: 2 positive, 1 null	Very low

Table 4. *Cont.*

Outcome (Domain)	Evidence (Reports)	Direction and Magnitude	Main Limitations	Full-Text Reports Only	Certainty
Coronary heart disease/myocardial infarction	6 reports	2 inverse, 1 null, 1 mixed, 2 positive	Incident CHD, coronary death, and subgroup results differ; inverse estimates not causal protection.	5 reports: 2 inverse, 1 null, 2 positive	Very low
Stroke	4 reports	2 positive, 2 null	Different phenotypes and ascertainment; residual confounding and inconsistent direction.	4 reports: 2 positive, 2 null	Very low
Circulating biomarkers	84 reports	7 null, 52 positive, 23 mixed, 2 inverse	Small convenience samples, assay/marker, and comparator heterogeneity; 43 abstract-based reports.	41 reports: 3 null, 26 positive, 11 mixed, 1 inverse	Very low
Direct systemic function	10 reports	2 null, 7 positive, 1 mixed	Small studies, incomplete adjustment, severity associations, and uncontrolled treatment change; no generalized causal inference.	6 reports: 2 null, 3 positive, 1 mixed	Very low
Vascular structure/disease	3 reports	3 positive	ABI/PAD and coronary calcium are arterial disease constructs, not direct functional impairment.	3 reports: 3 positive	Very low
Clinical cardiovascular associations	22 reports	14 positive, 4 null, 4 mixed	Mixed designs/temporal directions, comorbidity, and selected comparators; traditional factors alone not D4.	8 reports: 5 positive, 2 mixed, 1 null	Very low
Incremental CV prediction	0 reports	No added discrimination/calibration/reclassification or utility tested	Diagnostic prediction of CVeD or wound progression is a different question.	Not applicable	Not rated

Observational evidence starts at low certainty; serious bias prevents magnitude-based upgrading. Direction counts describe eligible estimate patterns, not pooled effects or independent studies. Functional assays are separate from arterial structure/disease; clinical, reverse-direction, composite and genetic evidence are not combined. Full-text-only counts and reasons are in Tables S8 and S12 and the outcome matrix in File S4.

3.11. Sensitivity Synthesis Restricted to Full-Text Reports

Restriction to 95 full-text reports changed the evidence composition rather than demonstrating that every result was unchanged. D2 was reduced from 84 to 41 reports (52/23/7/2 positive/mixed/null/inverse became 26/11/3/1). Direct-function reports fell from 10 to 6 (7/1/2 positive/mixed/null became 3/1/2), whereas all 3 structural/disease reports remained. The VTE subset had 10 of 11 reports; excluding the abstract-based temporally uncertain registry estimate left 6 positive, 1 mixed, and 3 null patterns. All 13 mortality reports remained, preserving the heterogeneous findings and selected comparator inverse estimates. HF had 4 of 5, PAD 3 of 4, coronary outcomes 5 of 6, AF 2 of 2, and stroke 4 of

4 clinical reports retained. Very-low clinical certainty remained because source availability did not remove confounding, selection, overlap, imprecision, or inconsistent outcomes (Table S12).

4. Discussion

This review distinguishes abundant local mechanistic evidence from circulating associations, direct systemic-function measurements, clinical disease, longitudinal outcomes, prediction, and genetic inference. The 163 retained reports show a varied rather than uniform pattern. Venous-thrombotic associations are more consistent than arterial outcomes but vary by setting and event. Direct functional evidence is small and confounded, and full-text restriction reduces its positive-report representation. The available studies do not establish a generalized venous-to-arterial causal pathway or incremental cardiovascular predictive value.

The association with venous thromboembolism is the most consistent and is biologically coherent, although detection bias and exposure misclassification limit certainty: venous stasis, endothelial injury, and a prothrombotic state are shared features of CVeD and thrombosis. Genetic correlation and Mendelian randomization data also support a link between varicose veins and venous thromboembolism [167,169]. This association, however, reflects shared venous pathways rather than generalized arterial disease, and composite outcomes that include venous thromboembolism should not be interpreted as evidence of arterial risk.

Mortality findings require attention to population and comparator. Higher estimates in advanced CVeD or population cohorts coexist with null adjusted findings, stage-dependent directions and inverse associations in selected wound-care populations. Choi compared time-varying venous-ulcer history within patients who already had chronic wounds; Takahashi studied nursing-home residents with ulcers of mixed etiology. These contrasts are not interchangeable with CVeD versus healthy controls and do not establish a protective venous effect. Age, immobility, frailty, cardiac congestion, comorbidity, healthcare contact, and coding may influence both CVeD ascertainment and outcomes. Modest HF/AF associations and selected genetic findings do not resolve these biases; inverse coronary associations likewise should not be interpreted as causal protection.

Recent meta-analyses pooled observational associations with cardiovascular outcomes [9,10]. The present review differs in its separation of local, circulating, functional, clinical, longitudinal, predictive, and genetic evidence; in its treatment of venous thromboembolism as distinct from arterial outcomes; in its design-specific risk-of-bias assessment; and in its outcome-level certainty appraisal. A structured comparison with previous reviews [7–10] is provided in Table S13. Secondary reviews were excluded from the synthesis for a methodological reason—they are not independent primary evidence and could lead to double counting—irrespective of their funding; separately, funding and conflicts of interest were extracted for all included studies and considered as a potential source of sponsorship-related bias using the same criteria.

The review has important limitations. Initial selection and extraction used an assisted workflow. Although two investigators independently verified eligibility and principal extracted data for all 163 included reports and resolved discrepancies by consensus, expanded validation of excluded records covered 521 of 572 initial abstract/classification exclusions; 51 were not included in this additional validation. Sixty-eight retained reports were verified from abstracts, so human verification could not resolve methods or numerical details absent from those sources. The previously missing 265 item pointers were reconciled; supplementary methods for Ge and Levin remain inaccessible, so related unverified methods are conservatively unclear. Seventeen potentially eligible reports await classification and could alter findings if clarified. Some historical workflow details cannot be independently

authenticated from retained technical logs (File S3). Several criteria and synthesis choices were refined after registration. Overlapping cohorts/claims/EHR/GWAS resources preclude treating reports as independent replications; an independent-study count was not established. Heterogeneity prevented defensible pooling, and publication/reporting bias cannot be excluded.

Future studies should use standardized clinical CEAP assessment, adjudicated cardiovascular outcomes, and adjustment for obesity, physical activity, and frailty; separate venous from arterial outcomes; and test whether CVeD adds incremental predictive value to established cardiovascular risk models.

5. Implications for Clinical Practice

CVeD encounters can be used to address established cardiovascular risk factors according to usual preventive care, while venous disease is managed under current venous guidance [181,182]. The associations in this review do not by themselves establish an indication for additional arterial investigations, a causal cardiovascular risk factor, or the incorporation of CVeD into cardiovascular-risk calculators.

6. Conclusions

The reconciled primary evidence comprises 163 reports plus 17 awaiting classification. It supports heterogeneous circulating changes and associations with some venous-thrombotic outcomes, with very-low certainty for clinical associations. Mortality and arterial findings differ by setting, comparator, and adjustment. Direct evidence of systemic functional impairment is limited and inconsistent; structural arterial disease is a separate construct. No study establishes incremental cardiovascular-risk prediction. The findings do not support treating CVeD as a proven causal arterial risk factor or adding it to cardiovascular-risk models.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/medsci14080806/s1; File S1, Full electronic search strategies as executed, record counts, and record handling (Table S1); File S2, Methods and supplementary results (protocol deviations, eligibility changes, clinical cardiovascular associations, risk of bias, evidence map, circulating markers, full-text sensitivity and previous-review comparison; Tables S2 and S4–S13); File S3, Model-assisted workflow and human verification; Annex S3A, Retained prompts and criteria (accompanying File S3; Table S3); File S4, Reconciled 163-report extraction, item-level risk of bias, outcome matrix, evidence map, exclusions, awaiting classification, retrieval failures, human rescreening and sensitivity analyses. The individual 20-report adjudication annex is incorporated into File S2. File S5, PRISMA_2020_Checklist.

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