medical sciences

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Supplementary Materials

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

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File S1. Full electronic search strategies as executed, record counts, and record handling.
PROSPERO registration: CRD420261433873.
Search period: database inception to 31 August 2026 (publication date). Searches executed on 5 November 2026; records published after 31 August 2026 were removed after export.

1. Overview

A single strategy was developed for MEDLINE (PubMed) and translated to Embase (Elsevier, Emtree), Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). The strategy combined a chronic venous disease block (controlled vocabulary and free text) with a broad outcome block covering local and circulating pathobiology, systemic vascular function, cardiovascular disease and events, mortality, venous thromboembolism, risk prediction, and Mendelian randomization. No language, design, or species limits were applied. In Embase, conference abstracts were excluded in the search line and trial-registry records were not exported.

This strategy replaced the strategy reported in the original submission. When re-executed, the earlier PubMed strategy retrieved approximately 53,000 records, far more than originally reported, because it contained subject headings that encompass venous disease itself (e.g., "Cardiovascular Diseases" [MeSH], which includes vascular and venous diseases) and ambiguous abbreviations (e.g., "CVI", "CVD"). In the revised strategy, "Cardiovascular Diseases" [MeSH] was replaced by narrower headings for heart, coronary, cerebrovascular, and peripheral arterial disease, arteriosclerosis, and hypertension; the abbreviations were removed; and "Varicose Veins" [MeSH] was not exploded, to exclude esophageal and other non-limb varices.

2. Records retrieved

Table S1. Records retrieved per source and record handling.

Source / step	Records	Notes
MEDLINE (PubMed)	6324	Exported in MEDLINE format
Embase (Elsevier)	12,626	Conference abstracts excluded in the strategy
Scopus	7051	Exported in RIS/CSV format
CENTRAL (Cochrane Library)	810	Trials; exported in RIS format
Total identified	**26,811**	
Duplicates removed	9797	Matched on PMID, DOI, and normalized title (Python)

Source / step	Records	Notes
Published after 31 August 2026	121	Removed after export
Unique records screened	**16,893**	See PRISMA flow diagram (Figure 1)

Deduplication: records sharing a PubMed identifier, a digital object identifier, or a normalized title (lowercase ASCII alphanumeric characters, first 150 characters; titles longer than 25 characters) were linked transitively into clusters; each cluster was screened once, using the longest available title and abstract. Publication date was taken from PubMed (year and month) or, for records not in PubMed, from the Embase record date; records from 2026 without a determinable month were retained.

3. Search strategies as executed

3.1. MEDLINE via PubMed

Searched 5 November 2026; publication-date limit included in the search line; 6324 records.

("Venous Insufficiency"[MeSH Terms] OR "Varicose Veins"[MeSH Terms:noexp] OR "Varicose Ulcer"[MeSH Terms] OR "chronic venous disease*"[tiab] OR "chronic venous insufficienc*"[tiab] OR "chronic venous disorder*"[tiab] OR "varicose vein*"[tiab] OR "venous ulcer*"[tiab] OR "venous leg ulcer*"[tiab] OR "venous insufficiency"[tiab] OR "venous reflux"[tiab] OR "CEAP"[tiab]) AND ("Endothelium, Vascular"[MeSH Terms] OR "Inflammation"[MeSH Terms] OR "Oxidative Stress"[MeSH Terms] OR "Matrix Metalloproteinases"[MeSH Terms] OR "Microcirculation"[MeSH Terms] OR "Vascular Remodeling"[MeSH Terms] OR "Leukocytes"[MeSH Terms] OR "Cytokines"[MeSH Terms] OR "C-Reactive Protein"[MeSH Terms] OR "Interleukins"[MeSH Terms] OR "Tumor Necrosis Factor-alpha"[MeSH Terms] OR "von Willebrand Factor"[MeSH Terms] OR "Fibrin Fibrinogen Degradation Products"[MeSH Terms] OR "endothelial dysfunction"[tiab] OR "endothelial activation"[tiab] OR "endothelial function"[tiab] OR "inflammation"[tiab] OR "inflammatory marker*"[tiab] OR "inflammatory mediator*"[tiab] OR "oxidative stress"[tiab] OR "matrix metalloproteinase*"[tiab] OR "MMP"[tiab] OR "microcirculation"[tiab] OR "microvascular"[tiab] OR "vascular remodeling"[tiab] OR "leukocyte*"[tiab] OR "C-reactive protein"[tiab] OR "CRP"[tiab] OR "interleukin*"[tiab] OR "IL-6"[tiab] OR "IL-1"[tiab] OR "tumor necrosis factor"[tiab] OR "TNF"[tiab] OR "cytokine*"[tiab] OR "von Willebrand factor"[tiab] OR "D-dimer"[tiab] OR "ICAM"[tiab] OR "VCAM"[tiab] OR "adhesion molecule*"[tiab] OR "nitric oxide"[tiab] OR "shear stress"[tiab] OR "prothrombotic"[tiab] OR "systemic vascular dysfunction"[tiab] OR "Heart Diseases"[MeSH Terms] OR "Coronary Disease"[MeSH Terms] OR "Cerebrovascular Disorders"[MeSH Terms] OR "Peripheral Arterial Disease"[MeSH Terms] OR "Arteriosclerosis"[MeSH Terms] OR "Hypertension"[MeSH Terms] OR "Atherosclerosis"[MeSH Terms] OR "Mortality"[MeSH Terms] OR "Venous Thromboembolism"[MeSH Terms] OR "Myocardial Infarction"[MeSH Terms] OR "Stroke"[MeSH Terms] OR "Heart Failure"[MeSH Terms] OR "cardiovascular disease*"[tiab] OR "cardiovascular risk"[tiab] OR "cardiovascular outcome*"[tiab] OR "cardiovascular event*"[tiab] OR "cardiovascular morbidity"[tiab] OR "cardiovascular mortality"[tiab] OR "atherosclerosis"[tiab] OR "atherosclerotic"[tiab] OR "mortality"[tiab] OR "all-cause mortality"[tiab] OR "thromboembolic"[tiab] OR "thromboembolism"[tiab] OR "myocardial infarction"[tiab] OR "stroke"[tiab] OR "arterial disease"[tiab] OR "vascular risk"[tiab] OR "systemic vascular"[tiab] OR "Vascular Stiffness"[MeSH Terms] OR "Pulse Wave Analysis"[MeSH Terms] OR "Carotid Intima-Media Thickness"[MeSH Terms] OR "Ankle Brachial Index"[MeSH Terms] OR "flow-mediated dilat*"[tiab] OR "flow mediated dilat*"[tiab] OR "pulse wave velocity"[tiab] OR "arterial stiffness"[tiab] OR "augmentation index"[tiab] OR "intima-media thickness"[tiab] OR "reactive hyperemia"[tiab] OR "peripheral arterial tonometry"[tiab] OR "ankle-brachial index"[tiab] OR "coronary artery calcium"[tiab] OR "microvascular function"[tiab] OR "Risk Assessment"[MeSH Terms] OR "ROC Curve"[MeSH Terms] OR "prediction model*"[tiab] OR "risk score*"[tiab] OR "prognostic model*"[tiab] OR "reclassification"[tiab] OR "C-statistic"[tiab] OR "c statistic"[tiab] OR "decision curve"[tiab] OR "incremental value"[tiab] OR "Mendelian Randomization Analysis"[MeSH Terms] OR "mendelian randomi*"[tiab] OR "genetic instrument*"[tiab]) AND ("1800/01/01"[Date - Publication] : "2026/08/31"[Date - Publication])

3.2. Embase (Elsevier, embase.com)

Searched 5 November 2026; 12,626 records; records published after 31 August 2026 removed after export.

('chronic venous insufficiency'/exp OR 'leg varicosis'/exp OR 'venous leg ulcer'/exp OR ('chronic venous disease*' OR 'chronic venous insufficienc*' OR 'chronic venous disorder*' OR 'varicose vein*' OR 'venous ulcer*' OR 'venous leg ulcer*' OR 'venous insufficiency' OR 'venous reflux' OR ceap):ti,ab) AND ('endothelium'/exp OR 'inflammation'/de OR 'oxidative stress'/exp OR 'matrix metalloproteinase'/exp OR 'microcirculation'/exp OR 'vascular remodeling'/exp OR 'leukocyte'/exp OR 'cytokine'/exp OR 'C reactive protein'/exp OR 'tumor necrosis factor'/exp OR 'von Willebrand factor'/exp OR 'fibrin degradation product'/exp OR 'heart disease'/exp OR 'coronary artery disease'/exp OR 'cerebrovascular disease'/exp OR 'peripheral occlusive artery disease'/exp OR 'atherosclerosis'/exp OR 'hypertension'/de OR 'mortality'/exp OR 'venous thromboembolism'/exp OR 'arterial stiffness'/exp OR 'pulse wave velocity'/exp OR 'arterial wall thickness'/exp OR 'ankle brachial index'/exp OR 'flow mediated vasodilatation'/exp OR 'risk assessment'/exp OR 'mendelian randomization analysis'/exp OR ('endothelial dysfunction' OR 'endothelial activation' OR 'endothelial function' OR inflammation OR 'inflammatory marker*' OR 'inflammatory mediator*' OR 'oxidative stress' OR 'matrix metalloproteinase*' OR mmp OR microcirculation OR microvascular OR 'vascular remodeling' OR leukocyte* OR 'c reactive protein' OR crp OR interleukin* OR 'il-6' OR 'il-1' OR 'tumor necrosis factor' OR tnf OR cytokine* OR 'von willebrand factor' OR 'd-dimer' OR icam OR vcam OR 'adhesion molecule*' OR 'nitric oxide' OR 'shear stress' OR prothrombotic OR 'systemic vascular dysfunction' OR 'cardiovascular disease*' OR 'cardiovascular risk' OR 'cardiovascular outcome*' OR 'cardiovascular event*' OR 'cardiovascular morbidity' OR 'cardiovascular mortality' OR atherosclerosis OR atherosclerotic OR mortality OR 'all-cause mortality' OR thromboembolic OR thromboembolism OR 'myocardial infarction' OR stroke OR 'arterial disease' OR 'vascular risk' OR 'systemic vascular' OR 'flow-mediated dilat*' OR 'flow mediated dilat*' OR 'pulse wave velocity' OR 'arterial stiffness' OR 'augmentation index' OR 'intima-media thickness' OR 'reactive hyperemia' OR 'peripheral arterial tonometry' OR 'ankle-brachial index' OR 'coronary artery calcium' OR 'microvascular function' OR 'prediction model*' OR 'risk score*' OR 'prognostic model*' OR reclassification OR 'c-statistic' OR 'c statistic' OR 'decision curve' OR 'incremental value' OR 'mendelian randomi*' OR 'genetic instrument*'):ti,ab) NOT 'conference abstract'/it

3.3. Scopus

Searched 5 November 2026; 7051 records; records published after 31 August 2026 removed after export.

TITLE-ABS-KEY("chronic venous disease*" OR "chronic venous insufficienc*" OR "chronic venous disorder*" OR "varicose vein*" OR "venous ulcer*" OR "venous leg ulcer*" OR "venous insufficiency" OR "venous reflux" OR ceap) AND TITLE-ABS-KEY("endothelial dysfunction" OR "endothelial activation" OR "endothelial function" OR inflammation OR "inflammatory marker*" OR "inflammatory mediator*" OR "oxidative stress" OR "matrix metalloproteinase*" OR mmp OR microcirculation OR microvascular OR "vascular remodeling" OR leukocyte* OR "c-reactive protein" OR crp OR interleukin* OR "il-6" OR "il-1" OR "tumor necrosis factor" OR tnf OR cytokine* OR "von willebrand factor" OR "d-dimer" OR icam OR vcam OR "adhesion molecule*" OR "nitric oxide" OR "shear stress" OR prothrombotic OR "systemic vascular dysfunction" OR "cardiovascular disease*" OR "cardiovascular risk" OR "cardiovascular outcome*" OR "cardiovascular event*" OR "cardiovascular morbidity" OR "cardiovascular mortality" OR atherosclerosis OR atherosclerotic OR mortality OR "all-cause mortality" OR thromboembolic OR thromboembolism OR "myocardial infarction" OR stroke OR "arterial disease" OR "vascular risk" OR "systemic vascular" OR "heart failure" OR "atrial fibrillation" OR "coronary artery disease" OR "flow-mediated dilat*" OR "flow mediated dilat*" OR "pulse wave velocity" OR "arterial stiffness" OR "augmentation index" OR "intima-media thickness" OR "reactive hyperemia" OR "peripheral arterial tonometry" OR "ankle-brachial index" OR "coronary artery calcium" OR "microvascular function" OR "prediction model*" OR "risk score*" OR "prognostic model*" OR reclassification OR "c-statistic" OR "decision curve" OR "incremental value" OR "mendelian randomi*" OR "genetic instrument*") AND PUBYEAR < 2027

3.4. CENTRAL (Cochrane Library)

Searched 5 November 2026 (title, abstract, keywords); 810 records; records published after 31 August 2026 removed after export.

((chronic NEXT venous NEXT (disease* OR insufficienc* OR disorder*)) OR (varicose NEXT vein*) OR (venous NEXT ulcer*) OR (venous NEXT leg NEXT ulcer*) OR "venous insufficiency" OR "venous reflux" OR ceap) AND (endothelial OR endothelium OR inflammation OR inflammatory OR "oxidative stress" OR metalloproteinase* OR mmp OR microcirculation OR microvascular OR "vascular remodeling" OR leukocyte* OR "c-reactive protein" OR crp OR interleukin* OR cytokine* OR "tumor necrosis factor" OR tnf OR "von willebrand factor" OR "d-dimer" OR icam OR vcam OR (adhesion NEXT molecule*) OR "nitric oxide" OR "shear stress" OR prothrombotic OR (cardiovascular NEXT (disease* OR risk OR outcome* OR event* OR morbidity OR mortality)) OR atherosclerosis OR atherosclerotic OR mortality OR thromboembolic OR thromboembolism OR "myocardial infarction" OR stroke OR "arterial disease" OR "vascular risk" OR "systemic vascular" OR "heart failure" OR "atrial fibrillation" OR "coronary artery disease" OR (flow NEXT mediated NEXT dilat*) OR "pulse wave velocity" OR "arterial stiffness" OR "augmentation index" OR "intima-media thickness" OR "reactive hyperemia" OR "peripheral arterial tonometry" OR "ankle-brachial index" OR "coronary artery calcium" OR (prediction NEXT model*) OR (risk NEXT score*) OR (prognostic NEXT model*) OR reclassification OR "c-statistic" OR "decision curve" OR (mendelian NEXT randomi*))

4. Screening workflow

The searches identified 26,811 records (PubMed 6,324; Embase 12,626; Scopus 7,051; CENTRAL 810). Removing 9,797 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 1,602 abstracts, 510 were initially excluded; 1,092 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 1,602 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 two 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. Historical initial classifier allocations are distinguished from the final reconciled flow; the 521 human validation records and all 432 adjudications are supplied in File S4.