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From Arterial Stiffness to Inflammation: Peripheral Arterial Disease Screening in Patients with Coronary Artery Disease

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ABSTRACT: Peripheral arterial disease (PAD) frequently coexists with coronary artery disease (CAD) but remains underdiagnosed. This systematic review evaluated evidence supporting an integrative PAD screening strategy combining the cardio-ankle vascular index (CAVI), high-sensitivity C-reactive protein (hs-CRP), and clinical risk profiling in CAD patients. Seven databases were searched according to PRISMA 2020 guidelines. Eligible studies evaluated CAVI, CRP/hs-CRP, or clinical risk characteristics relevant to PAD detection in patients with CAD. Risk of bias was assessed using an adapted QUADAS-2 tool, and thematic narrative synthesis was performed. Twelve studies were included. Elevated CAVI was associated with greater atherosclerotic burden, incident PAD, and angiographically confirmed lower-extremity arterial disease. CAVI pseudonormalization occurred in 76% of above-knee chronic total occlusions, 28% of above-knee stenoses, and 19% of below-knee lesions, defining an important limitation of CAVI-based screening. Higher hs-CRP independently predicted incident PAD and adverse cardiovascular outcomes. Epidemiological studies demonstrated a high prevalence of PAD among patients with CAD, particularly those with type 2 diabetes or chronic kidney disease. No study evaluated an integrated screening model incorporating these components. The evidence supports a multimodal PAD screening strategy integrating CAVI, hs-CRP, and structured clinical risk profiling in patients with CAD.

Prospective validation is warranted before clinical implementation. PROSPERO
Registration: CRD420261426023.

1. INTRODUCTION

Peripheral arterial disease (PAD) is a major manifestation of systemic atherosclerosis, affecting approximately 236 million people worldwide (Fowkes et al., 2013; Song et al., 2019). The burden is greatest in low- and middle-income countries, where access to vascular screening remains limited (Qanitha et al., 2022). Among patients with established coronary artery disease (CAD), PAD affects an estimated 13-22% in primary care-based studies using ankle-brachial index (ABI) screening, with higher prevalence reported in imaging-based studies of selected cardiac populations (Bhatt et al., 2006; Steg et al., 2007).

Both conditions share a common atherosclerotic pathophysiology, characterized by endothelial dysfunction, oxidative stress, and inflammation-driven plaque progression across multiple arterial territories (Criqui and Aboyans, 2015). However, fewer than 25% of patients with PAD receive a formal diagnosis during primary care or cardiac evaluation (Hirsch et al., 2001). When PAD and CAD coexist, the risk of major adverse cardiovascular events (MACE) is substantially higher than with single-territory disease, with annual event rates of approximately 5.6% versus 3.5% at 1-year follow-up in the REACH registry (Steg et al., 2007). These findings underscore that early PAD detection in patients with CAD represents a clinically important unmet need rather than merely a screening consideration.

One important contributor to this diagnostic gap is the limited sensitivity of the ankle-brachial index (ABI). Although an ABI ≤ 0.90 is endorsed by current ESC guidelines as the standard non-invasive diagnostic threshold for PAD, its sensitivity is substantially reduced in populations at highest cardiovascular risk (Mazzolai et al., 2024). In patients with type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), or advanced age, medial arterial calcification can artificially elevate ankle systolic pressure, resulting in falsely normal ABI values despite hemodynamically significant arterial stenosis (Fowkes et al., 2008). Pooled estimates suggest that ABI sensitivity may be as low as 15%-65% in populations with arterial calcification. This limitation is particularly relevant in our population, where the prevalence of T2DM and renal impairment exceeded 30% in our previous cohort (Qanitha et al., 2018).

Structured clinical risk profiling can help identify individuals at high risk of PAD based on established cardiovascular risk factors and comorbidities, making it a practical component of PAD screening. The cardio-ankle vascular index (CAVI) provides complementary information by assessing arterial stiffness independently of blood pressure at the time of measurement. It is derived from pulse wave velocity using the Bramwell–Hill relationship (Shirai et al., 2006). This may be particularly useful in patients with medial arterial calcification, in whom ABI sensitivity is often reduced. CAVI has also been independently associated with the severity of coronary atherosclerosis and adverse cardiovascular outcomes in cardiac populations (Miyoshi et al., 2010; Otsuka et al., 2014).

High-sensitivity C-reactive protein (hs-CRP) provides a complementary measure of systemic inflammation. As an acute-phase reactant, hs-CRP reflects inflammatory activity driven largely by interleukin-6 signaling from activated vascular and immune cells (Brevetti et al., 2010). This inflammatory pathway contributes to atherosclerotic progression across both coronary and peripheral arterial beds. Elevated hs-CRP has been prospectively associated with incident PAD and PAD-related adverse outcomes in high-risk populations (Ridker, 2016).

Existing studies have evaluated these components individually, with some focusing on diagnostic performance and others on cardiovascular prognosis. However, their findings have not been synthesized to determine whether these complementary measures collectively support an integrative PAD screening strategy in patients with CAD. To our knowledge, no previous systematic review has comprehensively evaluated the evidence for such an approach. Therefore, this systematic review and thematic synthesis aimed to evaluate the component-level evidence for combining CAVI, hs-CRP, and structured clinical risk profiling to identify PAD among patients with CAD. The primary objective was to determine whether the existing evidence is sufficiently consistent and robust to warrant prospective validation of an integrated PAD screening model.

2. MATERIALS AND METHODS

2.1 Protocol and Registration

This systematic review was conducted in accordance with the PRISMA 2020 guidelines, and the protocol was prospectively registered in PROSPERO (CRD420261426023).

2.2 Eligibility Criteria

Studies were eligible if they enrolled adults (≥ 18 years) with established CAD confirmed by coronary angiography ($\geq 50\%$ stenosis in ≥ 1 major epicardial artery), documented myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting. Studies of patients at high cardiovascular risk, defined as having ≥ 2 major cardiovascular risk factors or a prior atherosclerotic vascular event, were also eligible.

Eligible index tests or exposures included CAVI, serum CRP or hs-CRP, and structured clinical risk characteristics evaluated as potential variables of an integrated PAD screening strategy or as markers of systemic atherosclerotic risk relevant to PAD detection. Eligible reference standards or outcomes included an ABI ≤ 0.90 measured by Doppler or oscillometric methods, imaging-confirmed PAD ($\geq 50\%$ stenosis in ≥ 1 infra-inguinal segment), incident PAD, or composite cardiovascular outcomes including peripheral vascular events during prospective follow-up. Studies were required to report at least one extractable effect estimate.

We excluded secondary literature (systematic reviews, meta-analyses, narrative reviews, editorials, and guidelines), animal or in vitro studies, case reports or case series ($n < 20$), and studies lacking sufficient statistical detail for data extraction.

2.3 Search Strategy

Systematic searches were conducted in PubMed, Scopus, Embase, the Cochrane Library, ScienceDirect, CINAHL, and Web of Science. Search strategies combined Boolean terms covering four domains: PAD, CAD or high cardiovascular risk, index tests or exposures (CAVI, CRP/hs-CRP, and clinical risk factors), and PAD-related outcomes (ABI, PAD, peripheral vascular events, and hazard ratios). Controlled vocabulary, including MeSH terms in PubMed and Emtree terms in Embase, was incorporated where applicable. The reference lists of all included studies were also manually screened to identify additional eligible studies.

2.4 Study Selection

Three independent reviewers (A.A.S., A.Q., and M.N.Z.) screened all deduplicated records at the title and abstract level. Full-text eligibility was independently assessed by N.P.L. and M.N.Z. Disagreements were resolved through consensus and, when consensus could not be reached, adjudicated by I.M. and H.R.

2.5 Data Extraction

Standardized data extraction forms were pilot-tested on five randomly selected studies and subsequently applied by three reviewers (A.A.S., A.Q., and M.N.Z.). Extracted data included study design, participant characteristics, CAVI device and measurement conditions, CRP assay methodology, clinical risk variables, reference standards or outcome definitions, and reported effect estimates. Discrepancies were resolved through consensus.

2.6 Quality Assessment

All included studies were assessed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool (Whiting et al., 2011), which was selected because the review evaluated candidate markers for PAD detection in a high-risk population. QUADAS-2 assesses risk of bias across 4 domains: Patient Selection, Index Test, Reference Standard, and Flow and Timing, together with applicability concerns.

Because most included studies were cohort or registry-based rather than conventional diagnostic accuracy studies, signaling questions were prespecified and adapted to the study designs in accordance with established QUADAS-2 guidance. The Index Test domain assessed the standardization of CAVI measurements (device, measurement conditions, and operator procedures) or CRP assays (assay methodology and laboratory standards). The Reference Standard domain evaluated the appropriateness and specificity of PAD definitions, including ABI or imaging-confirmed PAD, and the potential for outcome-assessment bias. The Flow and Timing domain assessed completeness of follow-up and the appropriateness of participant exclusions.

All adaptations were prespecified in the registered protocol and incorporated into the data-extraction form. Two reviewers (M.N.Z. and N.P.L.) independently assessed risk of bias, with disagreements resolved by consensus and adjudication by senior reviewers (I.M. and H.R.) when required. Risk of bias was categorized as low, unclear, or high within each QUADAS-2 domain.

2.7 Synthesis

A thematic narrative synthesis was performed according to the framework proposed by (Popay et al. 2006), which included 3 stages: preliminary synthesis, assessment of relationships within and across studies, and evaluation of the robustness of the findings. Three main thematic domains were identified from the included studies and refined through reviewer consensus. A meta-analysis was not performed because of substantial heterogeneity in study populations, study designs, outcome definitions (PAD-specific diagnostic outcomes versus composite cardiovascular events), and index-test protocols, including CAVI measurement conditions, thresholds, and CRP assay methods. Instead, the findings were synthesized narratively to describe the strength, consistency, and clinical relevance of associations across the 3 domains and to assess whether the available evidence supports prospective validation of an integrated PAD screening strategy.

3. RESULTS AND DISCUSSION

3.1 Study Selection

The database searches identified 4,255 records. After removing 1,408 duplicates, 2,847 records underwent title and abstract screening, of which 2,512 were excluded. Full-text assessment was performed for 335 articles, and 323 were excluded for prespecified eligibility criteria. Ultimately, 12 primary studies met the eligibility criteria and were included in this review (Figure 1).

3.2 Characteristics of Included Studies

Twelve primary studies included 180,747 participants from 6 countries (2001–2021). Most were prospective cohorts ($n=8$, 67%), while 4 (33%) were cross-sectional or retrospective studies. Six studies evaluated CAVI in CAD or ACS populations, all from Japan; 2 evaluated hs-CRP in relation to PAD outcomes (United States and Croatia); and 4 examined PAD prevalence and clinical risk factors in CAD or high-risk cardiovascular populations (United States and multinational cohorts). Sample sizes ranged from 206 to 67,888. Among prospective studies, median follow-up was 2.9 years (range, 1.0–6.7 years). Study characteristics are summarized in Table 1.

3.3 Quality Assessment

QUADAS-2 was applied to all 12 included studies. Eight studies (67%) were rated as having low risk of bias across all 4 domains. The most common concern was in the Reference Standard domain (5/12 studies), mainly because prospective cohort studies used composite cardiovascular outcomes rather than PAD-specific diagnostic standards. The Index Test domain was rated as unclear in 3 studies, largely due to limited detail on PAD ascertainment in registry-based data. Full QUADAS-2 assessments are presented in Table 2.

Table 1. Characteristics of the included studies ($n=12$)

Study	Country	Design / N	Theme	Index Test / Exposure	PAD / CV Outcome	Comparator	Key Findings
CAVI ($n=6$)							
Miyoshi 2010 [12]	Japan	Cross-sectional / 206	CAVI	CAVI (VaSera VS-1500)	CAD severity and LV function	IHD vs. Non-IHD group	CAVI: IHD 9.1 ± 1.3 vs non-IHD 8.7 ± 1.2 ($p=0.02$). CAVI independently correlated with CAD severity and LV

							dysfunction by multivariate analysis.
Otsuka 2014 [13]	Japan	Prospective / 211 (follow-up 2.9 years)	CAVI	CAVI (VaSera VS-1500)	CVD events (including peripheral vascular)	Impaired CAVI vs. Normalized CAVI (mean + 1 SD (age/sex-specific)	Higher risk of cardiovascular events (HR 3.30, 95% CI 1.47–8.59; $p < 0.01$). Event-free survival differed significantly ($p = 0.01$).
Gohbara 2016 [18]	Japan	Prospective / 288 ACS (follow-up 15 months)	CAVI	CAVI at discharge (VaSera)	CVD events (CV death, nonfatal MI, nonfatal stroke)	High-CAVI vs. Low-CAVI group (≤ 8.325)	Higher risk of cardiovascular events (19 events [6.6%]; HR 18.00, $p = 0.005$ (95% CI not reported in source).
Kirigaya 2020 [19]	Japan	Prospective / 387 ACS (follow-up 3 years)	CAVI	CAVI post-stabilization	CVD events (CV death, ACS recurrence, HF, stroke)	High-CAVI vs. Low-CAVI group (< 8.35)	Higher risk of MACE with HR 1.91 (95% CI 1.22–2.98) after adjustment for age, LVEF, eGFR, risk factors.
Miyoshi 2021 [20] CAVI-J	Japan	Prospective / 3,028 (follow-up 4 yr)	CAVI	CAVI (VaSera VS-1500)	CVD events (including PAD, ABI ≤ 0.9)	High-CAVI vs. Low-CAVI group (≤ 9.0)	Higher MACE with HR 2.31 (95% CI 1.52–3.50). Incident PAD: OR 2.18 in high-CAVI group.
Hayase 2021 [21]	Japan	Cross-sectional / 96	CAVI	CAVI (VaSera)	PAD anatomy (arteriography gold standard)	CAVI vs. ABI	Pseudonormalization: above-knee CTO 76%, above-knee stenosis 28%, below-knee only 19%. OR: above-knee stenosis 3.1 (95% CI 1.39–7.22); below-knee only 4.56 (95% CI 1.64–14.7).
hs-CRP/CRP (n=2)							
Joosten 2012 [22]	USA	Prospective / 44,985	hs-CRP	Plasma CRP	PAD incidence	CRP quartile	Higher PAD incidence with HR 1.34 (95% CI 1.17–

		(follow-up 20 years)		(validated assay)			1.54) per SD log- CRP.
							Dose-response across quartiles was observed, with higher CRP levels associated with progressively greater PAD risk.
Vrsalović 2015 [23]	Croatia	Prospective / 319 symptomatic PAD (follow-up 24 mo)	CRP	Serum CRP	CVD events (MI, urgent revascularisation, stroke, death)	High vs. Low CRP (≤5 mg/L)	Higher CVD events with HR 1.89 (95% CI 1.18–3.02). Polyvascular disease also independent (HR 1.95, 95% CI 1.23–3.09).
Clinical risk factors (n=4)							
Hirsch 2001 [7] PARTNERS	USA	Cross- sectional / 6,979	Clinical RF	ABI ≤0.9 + clinical RF profiling	PAD (ABI ≤0.9)	No PAD	PAD prevalence 13.0% in CAD patients Predictors: age ≥70, or 50–69 + smoking/DM.
Bhatt 2006 [4] REACH	Multi- national (44 countries)	Cross- sectional / 67,888	Clinical RF	PAD (physician- reported)	PAD co- prevalence in atherothrombosis	No PAD	PAD in CAD patients: 15.9%. PAD in T2DM subgroup: 22.8%. Coexisting PAD was more common in patients aged ≥65 years.
Steg 2007 [5] REACH	Multi- national (44 countries)	Prospective / 55,814 (follow-up 1 years)	Clinical RF	PAD + CAD (physician- reported)	MACE at 1 year	CAD alone	Higher MACE in PAD+CAD (5.6% vs. 3.5% per year, p<0.001)
Diehm 2009 [24] getABI	Germany	Prospective / 6,880 (follow-up 5 years)	ABI + Clinical RF score	ABI + age, DM, smoking, eGFR score	PAD (ABI ≤0.9) + mortality	ABI >0.9	21.5% PAD incidence in high-risk outpatients. A clinical risk score demonstrated moderate discrimination for PAD (C-statistic

0.72). T2DM and CKD patients had highest PAD prevalence (32–41%) and lowest diagnostic sensitivity of ABI

ABI: ankle-brachial index; ACS: acute coronary syndrome; CAD: coronary artery disease; CAVI: cardio-ankle vascular index; CKD: chronic kidney disease; CTO: chronic total occlusion; CVD: cardiovascular disease; DM: diabetes mellitus; EF: ejection fraction; eGFR: estimated GFR; LVEF: left ventricular ejection fraction; MACE: major adverse cardiovascular events; PAD: peripheral arterial disease; RF: risk factors. Superscript numbers refer to the full reference list.

Table 2. QUADAS-2 quality assessment of the included studies

Study	Design	Patient Selection	Index Test*	Reference Standard†	Flow & Timing	Applicability ‡	Overall Quality
CAVI							
Miyoshi 2010	Cross-sectional	L	U §	L	L	AC-L	High
Otsuka 2014	Prospective	L	L	U ¶	U **	AC-L	High
Gohbara 2016	Prospective	L	L	U ¶	L	AC-L	Moderate-High
Kirigaya 2020	Prospective	L	L	U ¶	L	AC-L	High
Miyoshi 2021	Prospective	L	L	U ¶	L	AC-L	High
Hayase 2021	Retrospective	U ††	L	L	L	AC-L	Moderate
hs-CRP/CRP							
Joosten 2012	Prospective cohort	L	L	L	L	AC-L	High
Vrsalović 2015	Prospective	L	L	L	L	AC-L	High
Clinical risk profile							
Hirsch 2001 (PARTNERS)	Cross-sectional	L	L	L	U #	AC-L	High
Bhatt 2006	Cross-sectional	L	U §§	U §§	L	AC-U	Moderate

(REACH)							
Steg 2007	Prospective	L	U §§	U §§	L	AC-U	Moderate
(REACH)							
Diehm 2009	Prospective	L	L	L	L	AC-L	High
(getABI)							

QUADAS-2 domain ratings: L = Low risk of bias; U = Unclear risk of bias; H = High risk of bias. Applicability: AC-L = Low concern; AC-U = Unclear concern. QUADAS-2 applied to all 12 primary studies with pre-specified domain adaptations (see Methods).

*Index Test domain adapted to assess: CAVI device standardization or CRP assay standardization. Reference Standard domain adapted to assess: specificity of outcome definition and adjudicator blinding. §CAVI conditions not fully standardized (Miyoshi 2010). Composite CVD endpoints used as reference standard in prospective studies (not PAD-specific adjudication).

**Follow-up timing unclear. ††Retrospective single-centre (Hayase).

‡‡Cross-sectional, no prospective verification.

§§REACH: physician-reported PAD without standardized ABI protocol.

3.4 Thematic Findings

3.4.1 Theme 1: CAVI in Patients with CAD or ACS

Six studies evaluated CAVI in patients with CAD or acute coronary syndrome (ACS), including 4,360 participants from Japan (Miyoshi et al., 2010; Otsuka et al., 2014; Gohbara et al., 2016; Kirigaya et al., 2020; Miyoshi et al., 2021; Hayase et al., 2021). All studies used the VaSera VS-1500 device (Fukuda Denshi). CAVI thresholds were determined using receiver operating characteristic (ROC) curve analysis within each study rather than applying a prespecified cutoff. The reported thresholds ranged from 8.325 to 8.35, which were below the widely cited upper limit of normal (CAVI >9.0) based on Japanese population reference data (Namekata et al., 2011).

Miyoshi et al. included 206 patients (133 with ischemic heart disease [IHD] and 73 without IHD). CAVI was significantly higher in patients with IHD than in those without IHD (9.1 ± 1.3 vs. 8.7 ± 1.2 ; $p=0.02$) and was independently associated with the severity of coronary atherosclerosis, based on angiographic scoring, as well as left ventricular systolic and diastolic function (Miyoshi et al., 2010). These findings support CAVI as a marker of systemic atherosclerotic burden in patients with CAD.

Otsuka et al. included 211 patients with CAD who underwent PCI in a prospective study with a median follow-up of 2.9 years. Persistently elevated CAVI, defined as exceeding the age- and sex-specific mean + 1 SD at 2 assessments performed 6 months apart, was independently associated with a higher risk of composite cardiovascular events compared with normal CAVI ($p=0.01$). These findings support the prognostic value of serial CAVI assessment in patients with CAD (Otsuka et al., 2014).

In another study, Gohbara et al. evaluated 288 patients with ACS in a prospective study with a median follow-up of 15 months. Using a ROC-derived CAVI cutoff of 8.325, patients were categorized into low-CAVI ($n=135$) and high-CAVI ($n=153$) groups. Because patients with established PAD were excluded, the study evaluated CAVI primarily as a prognostic marker rather than a diagnostic tool for PAD. During follow-up, cardiovascular events occurred in 19 patients (6.6%). High CAVI was independently associated with a higher risk of cardiovascular events ($p=0.005$) (Gohbara et al., 2016).

Meanwhile, Kirigaya et al. evaluated 387 patients with ACS in a prospective study with a median follow-up of 3 years. Using a ROC-derived CAVI cutoff of 8.35, patients were classified into low-CAVI (<8.35 ; $n=177$) and high-CAVI (≥ 8.35 ; $n=210$) groups. The primary endpoint was MACE, defined as cardiovascular death, recurrent ACS, hospitalization for heart failure, or

stroke. High CAVI was independently associated with MACE after adjustment for age, ejection fraction, estimated GFR, and conventional cardiovascular risk factors (adjusted HR, 1.91; 95% CI, 1.22–2.98) (Kirigaya et al., 2020).

The CAVI-J study provided the largest prospective evidence, including 3,028 patients at cardiovascular risk from multiple centers with 4 years of follow-up. CAVI >9.0 was independently associated with MACE, including incident PAD events, after adjustment for conventional cardiovascular risk factors (HR, 2.31; 95% CI, 1.52–3.50). These findings extend the prognostic evidence from smaller ACS studies to a broader cardiovascular-risk population (Miyoshi et al., 2021).

Hayase et al. retrospectively evaluated 96 patients with PAD (ABI <0.90) confirmed by extremity arteriography to assess whether CAVI reflects PAD severity and anatomic distribution (Hayase et al., 2021). Using CAVI <8.0 as the normal threshold, CAVI pseudonormalization occurred in 76% of limbs with above-knee chronic total occlusion (CTO), compared with 28% of limbs with above-knee stenosis and 19% with isolated below-knee lesions. Abnormal CAVI was associated with above-knee stenosis (OR, 3.10; 95% CI, 1.39–7.22) and below-knee lesions (OR, 4.56; 95% CI, 1.64–14.7).

Across the six studies evaluating CAVI, higher CAVI was consistently associated with adverse cardiovascular outcomes in CAD and ACS populations. The varied CAVI thresholds across studies suggest population-specific calibration rather than a single universal cutoff. Based on our literature search, evidence specifically evaluating CAVI in patients with PAD remains limited. However, PAD frequently coexists with CAD and is associated with a substantially higher risk of adverse cardiovascular events, including stroke, myocardial infarction, and cardiovascular death (Bonaca et al., 2021). In the EUCLID trial, nearly half of patients with PAD had atherosclerotic involvement in at least 1 additional vascular territory, underscoring the systemic nature of atherosclerotic disease (Bonaca et al., 2021; Hiatt et al., 2017). Collectively, these findings provide biological and prognostic support for further evaluation of CAVI as a component of an integrated PAD screening strategy.

Two important limitations identified in the previous studies should be considered when designing future validation studies. First, Gohbara et al. excluded patients with established PAD; therefore, the association between CAVI and cardiovascular events reflects prognostic risk stratification in patients with ACS without known PAD rather than its ability to detect PAD (Gohbara et al., 2016). Second, the CAVI pseudonormalization in 76% of limbs with above-knee chronic total occlusion reported by Hayase et al. indicates that CAVI may be less reliable in severe PAD (Hayase et al., 2021). Taken together, these findings suggest that CAVI may have greater utility for detecting early-to-moderate PAD in high-risk patients without advanced limb ischemia. When severe PAD is clinically suspected, additional vascular assessment should be considered regardless of the CAVI value.

These findings are consistent with previous meta-analyses linking arterial stiffness to cardiovascular risk. In a meta-analysis of 9 prospective studies, Matsushita et al. reported an approximately 1.0-unit higher mean CAVI in patients with cardiovascular disease than in those without (Matsushita et al., 2019). Similarly, Vlachopoulos et al. demonstrated that increased arterial stiffness independently predicts cardiovascular events and all-cause mortality across diverse populations (Vlachopoulos et al., 2010). Our review extends this evidence by demonstrating consistent prognostic associations in ACS populations while also identifying an important limitation of CAVI for PAD assessment in severe disease, particularly above-knee chronic total occlusion (Gohbara et al., 2016; Kirigaya et al., 2020; Hayase et al., 2021). Overall, CAVI appears promising as a marker of systemic vascular risk, but its role in PAD screening requires prospective validation across different stages of disease severity.

3.4.2 Theme 2: hs-CRP as an Inflammatory Marker of PAD

Two studies provided direct evidence linking CRP/hs-CRP to PAD or PAD-related cardiovascular outcomes. Joosten et al. analyzed 44,985 men from the Health Professionals Follow-up Study in a prospective cohort with a median follow-up of 20 years, during which 804 incident PAD cases occurred. Each standard-deviation increase in log-transformed plasma CRP was independently associated with incident PAD after multivariable adjustment (HR, 1.34; 95% CI, 1.17–1.54). A dose-response relationship was also observed across CRP quartiles, with a greater risk among participants with elevated CRP combined with T2DM or smoking (Joosten et al., 2012).

Vrsalović et al. prospectively followed 319 consecutive patients with symptomatic PAD and preserved left ventricular ejection fraction for a median of 24 months. During follow-up, 77 patients (24%) experienced MACE. In multivariable Cox regression analysis, CRP >5 mg/L was independently associated with MACE (HR, 1.89; 95% CI, 1.18–3.02; $p < 0.05$) (Vrsalović et al., 2015).

These findings reinforce that hs-CRP is independently associated with incident PAD and MACE in patients with established PAD, supporting the contribution of systemic inflammation to PAD risk. Together with the findings of Joosten et al., they suggest that CRP provides prognostic information complementary to CAVI by reflecting systemic inflammation rather than arterial stiffness.

3.4.3 Theme 3: Clinical Risk Profiling for PAD Detection in CAD Populations

Four epidemiologic studies described the prevalence, determinants, and clinical risk profile of PAD in patients with CAD and other high-risk populations. The PARTNERS study (Hirsch et al.; $n=6,979$ patients from 350 U.S. primary care practices) reported a PAD prevalence of 13.0% among patients with established CAD, compared with 3.7% in the general primary care population (Hirsch et al., 2001). The strongest independent predictors of PAD were age ≥ 70 years or age 50–69 years combined with a history of smoking or T2DM.

The REACH registry (Bhatt et al.; $n=67,888$ outpatients with established atherosclerosis from 44 countries) reported PAD in 15.9% of patients with CAD, with higher prevalence among those with T2DM (22.8%), older age, and active smoking (Bhatt et al., 2006). In a 1-year prospective analysis of 55,814 REACH participants, Steg et al. found that patients with both PAD and CAD had a higher annual MACE rate than those with CAD alone (5.6% vs. 3.5%), demonstrating the increased risk associated with polyvascular disease (Steg et al., 2007).

The getABI study (Diehm et al.; $n=6,880$ German outpatients with ≥ 1 cardiovascular risk factor; prospective; up to 5 years) reported a PAD prevalence of 21.5% in this high-risk population. A clinical risk score incorporating age, T2DM, smoking, and estimated GFR showed moderate ability to identify patients with PAD (C-statistic, 0.72). PAD prevalence was highest among patients with both T2DM and CKD (32%–41%) (Diehm et al., 2009).

This clinical risk profiling further demonstrates that PAD is common among patients with CAD, particularly those with T2DM and CKD, in whom ABI may have reduced diagnostic sensitivity because of medial arterial calcification.

3.4.4 Rationale for an Integrated Screening Strategy and Evidence Gap

Currently, no primary study has directly evaluated an integrated model combining CAVI, hs-CRP, and clinical risk factors for PAD detection in patients with CAD. However, the available evidence for each component provides a rationale for investigating whether their combination improves PAD detection beyond any single measure. CAVI and hs-CRP capture distinct aspects of atherosclerotic disease: CAVI reflects systemic arterial stiffness, whereas hs-CRP reflects systemic inflammation. Their complementary biological information may therefore improve risk stratification when considered together. Clinical risk profiling further provides an estimate of baseline PAD probability before biomarker assessment, which is particularly relevant in patients with CAD, among whom PAD prevalence is relatively high but varies across populations (13%–22%).

The findings support a complementary rather than single-marker approach to PAD screening. Although ABI remains the recommended first-line noninvasive test, its accuracy can be limited by medial arterial calcification, particularly in patients with T2DM, CKD, and advanced age (Criqui and Aboyans, 2015; Diehm et al., 2009). CAVI may provide additional information on arterial stiffness independent of blood pressure (Shirai et al., 2006), while hs-CRP captures the inflammatory component of atherosclerosis (Brevetti et al., 2010; Ridker, 2016). Clinical risk profiling can further help prioritize patients for testing based on readily available risk factors. Thus, these measures may provide complementary information across different stages of the atherosclerotic process and form the basis for a targeted screening strategy in patients with CAD.

To our knowledge, this is the first systematic review to synthesize primary-study evidence on CAVI, hs-CRP, and clinical risk profiling as complementary components of an integrated PAD screening strategy in patients with CAD. The key finding is that no study has yet prospectively evaluated or validated their combined use for PAD detection. This evidence gap highlights the need for prospective studies to determine whether integrating these complementary measures can improve PAD detection beyond conventional clinical assessment and ABI.

The conceptual 3-pathway framework developed from this review (Figure 2) integrates three complementary domains relevant to PAD risk: arterial stiffness (CAVI >9.0), systemic inflammation (hs-CRP >3 mg/L), and clinical risk factors, including age ≥ 65 years, T2DM, smoking, dyslipidemia, and CKD. The framework illustrates how these domains may collectively contribute to PAD detection in patients with CAD. Because the framework has not been prospectively validated, it should be considered hypothesis-generating and used to inform the design of future validation studies rather than clinical decision-making.

3.5 Limitations

Several limitations should be considered. First, all six CAVI studies were conducted in Japan, which may limit generalizability to non-Asian populations with different CAVI reference values, body composition, and arterial stiffness profiles. Second, study designs varied substantially, ranging from a small retrospective single-center study (Hayase, $n=96$) to large multinational prospective registries (REACH, $n=67,888$). Outcome definitions also varied from PAD-specific endpoints to composite cardiovascular outcomes, precluding quantitative meta-analysis. Third, REACH-based studies relied on physician-reported PAD rather than standardized ABI measurements, which may have introduced outcome misclassification.

3.6 Implications for Future Research

The available component-level evidence provides a strong rationale for prospective validation of an integrated PAD screening strategy in patients with CAD. The next step should be a multicenter diagnostic accuracy study evaluating whether combining CAVI, hs-CRP, and clinical risk factors improves PAD detection beyond ABI alone. This approach may be particularly relevant in resource-limited settings where vascular imaging or duplex ultrasonography is not routinely available. CAVI and ABI should be measured using standardized protocols, with CAVI obtained after adequate supine rest and ABI measured in both legs. hs-CRP should be assessed using a standardized high-sensitivity assay, while the clinical model should incorporate prespecified PAD risk factors, including age, T2DM, smoking, dyslipidemia, and CKD. Subgroup analyses should specifically assess patients with T2DM and CKD, in whom ABI may be less reliable because of medial arterial calcification. External validation across geographically and ethnically diverse CAD populations, particularly in low- and middle-income settings, will be essential. If validated, this multimodal strategy could offer a practical and scalable approach for identifying previously unrecognized PAD when advanced vascular imaging is not readily accessible, thereby improving recognition of polyvascular disease in routine CAD care.

4. CONCLUSIONS

This systematic review supports an integrated PAD screening framework combining CAVI, hs-CRP, and clinical risk profiling in patients with CAD. Each component captures a complementary dimension of PAD risk, but no primary study has yet validated their combined use. The proposed framework is therefore hypothesis-generating rather than ready for clinical implementation. Prospective multicenter validation is the critical next step, particularly in patients with T2DM, CKD, and resource-limited settings. If validated, this approach could provide a practical and scalable strategy for detecting previously unrecognized PAD and improving recognition of polyvascular disease in CAD.

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AUTHOR CONTRIBUTIONS

AAS and AQ designed the research study. AQ, PAFD, and HR performed the research. PAFD, HR, and IM provided help and advice on manuscript. AQ, MNZ, and NPL analyzed the data. MNZ and NPL wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

This systematic review did not involve primary data collection from human participants, human tissue, or identifiable human data. No ethical approval or institutional review board oversight was required.

DATA AVAILABILITY STATEMENT

The study selection database, data extraction forms, and quality assessment records are available from the corresponding author upon reasonable request. The protocol of this systematic review is registered in PROSPERO (CRD420261426023).

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Figure Legends:

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart of the study selection

Figure 2. Conceptual framework of three interconnected pathways: vascular stiffness, cardiometabolic burden, and systemic inflammation in PAD screening among patients with CAD

Figure 1

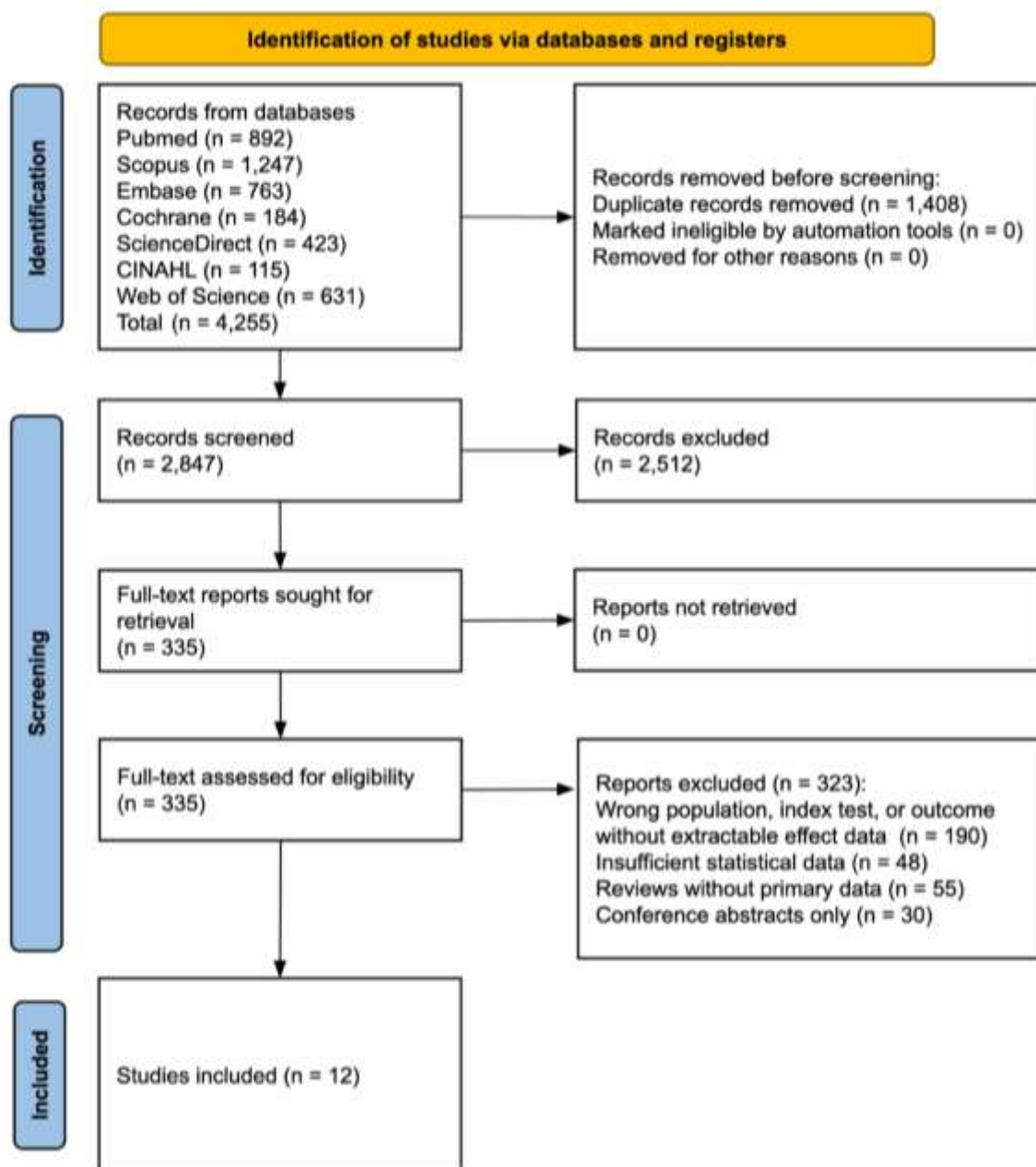
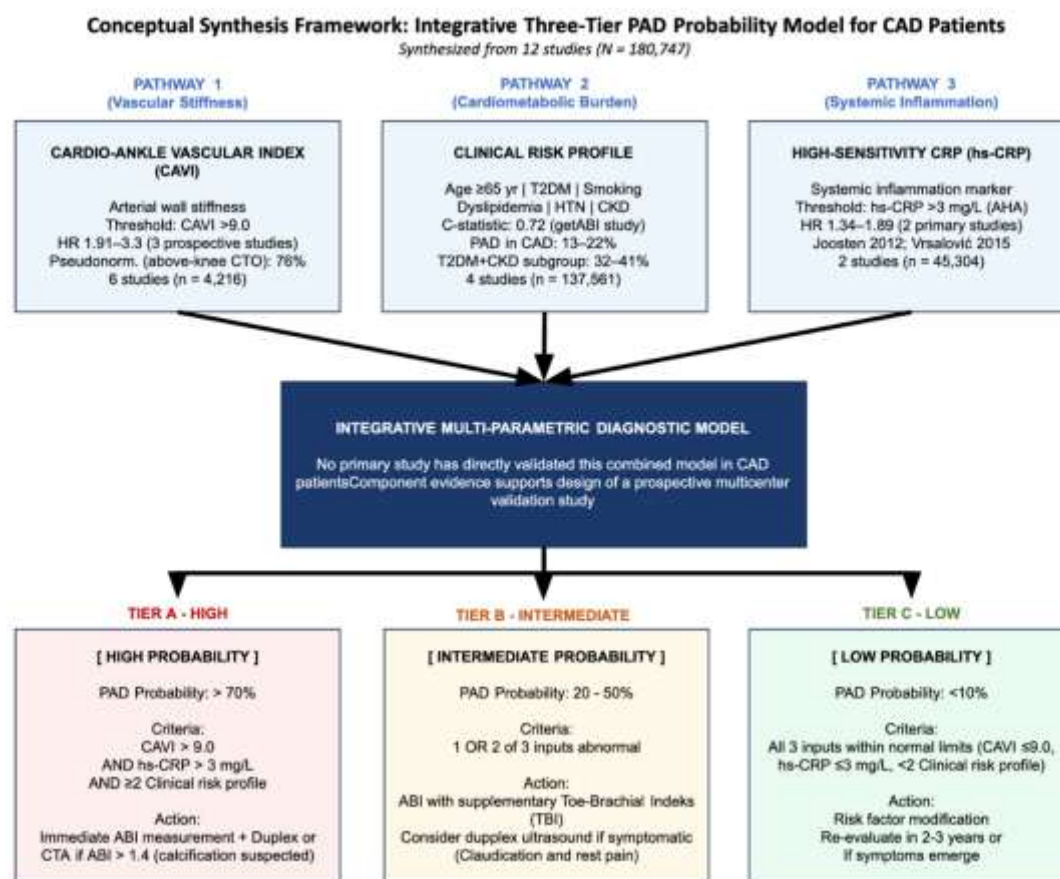


Figure 2



SUPPLEMENTARY MATERIALS

Search strategy

2.3.1 PubMed/MEDLINE search string

("Coronary Artery Disease"[MeSH Terms] OR "Coronary Disease"[MeSH Terms] OR "coronary artery disease"[Title/Abstract] OR "coronary heart disease"[Title/Abstract] OR CAD[Title/Abstract]) AND ("Peripheral Arterial Disease"[MeSH Terms] OR "Ankle Brachial Index"[MeSH Terms] OR "peripheral artery disease"[Title/Abstract] OR "peripheral arterial disease"[Title/Abstract] OR PAD[Title/Abstract] OR "ankle brachial index"[Title/Abstract] OR ABI[Title/Abstract]) AND ("Vascular Stiffness"[MeSH Terms] OR "cardio-ankle vascular index"[Title/Abstract] OR CAVI[Title/Abstract] OR "arterial stiffness"[Title/Abstract]) AND ("C-Reactive Protein"[MeSH Terms] OR "C-reactive protein"[Title/Abstract] OR CRP[Title/Abstract] OR "hs-CRP"[Title/Abstract]) AND ("Sensitivity and Specificity"[MeSH Terms] OR "ROC Curve"[MeSH Terms] OR "diagnostic accuracy"[Title/Abstract] OR sensitivity[Title/Abstract] OR specificity[Title/Abstract] OR AUC[Title/Abstract] OR "predictive value"[Title/Abstract])

2.3.2 Scopus search string

TITLE-ABS-KEY(("coronary artery disease" OR "coronary heart disease" OR CAD) AND ("peripheral artery disease" OR "peripheral arterial disease" OR PAD OR "ankle brachial index" OR ABI) AND ("cardio-ankle vascular index" OR CAVI OR "arterial stiffness") AND ("C-reactive protein" OR CRP OR "hs-CRP") AND ("diagnostic accuracy" OR sensitivity OR specificity OR AUC OR "ROC curve" OR "predictive value"))

2.3.3 Embase (Ovid) search string

1. exp coronary artery disease/ OR (“coronary artery disease” OR “coronary heart disease” OR CAD).mp. 2. exp peripheral arterial disease/ OR exp ankle brachial index/ OR (“peripheral artery disease” OR “peripheral arterial disease” OR PAD OR “ankle brachial index” OR ABI).mp. 3. exp arterial stiffness/ OR (“cardio-ankle vascular index” OR CAVI OR “arterial stiffness”).mp. 4. exp C reactive protein/ OR (“C-reactive protein” OR CRP OR “hs-CRP”).mp. 5. exp diagnostic accuracy/ OR (sensitivity OR specificity OR “diagnostic accuracy” OR AUC OR “ROC curve” OR “predictive value”).mp. 6. 1 AND 2 AND 3 AND 4 AND 5

2.3.4 Cochrane CENTRAL search string

(“coronary artery disease” OR “coronary heart disease” OR CAD) AND (“peripheral artery disease” OR “peripheral arterial disease” OR PAD OR “ankle brachial index” OR ABI) AND (“cardio-ankle vascular index” OR CAVI OR “arterial stiffness”) AND (“C-reactive protein” OR CRP OR “hs-CRP”) AND (sensitivity OR specificity OR “diagnostic accuracy” OR AUC OR “ROC curve”):ti,ab,kw

2.3.5 Web of Science Core Collection search string

TS=((“coronary artery disease” OR “coronary heart disease” OR CAD) AND (“peripheral artery disease” OR “peripheral arterial disease” OR PAD OR “ankle brachial index” OR ABI) AND (“cardio-ankle vascular index” OR CAVI OR “arterial stiffness”) AND (“C-reactive protein” OR CRP OR “hs-CRP”) AND (“diagnostic accuracy” OR sensitivity OR specificity OR AUC OR “ROC curve”))