ORIGINAL RESEARCH

OUTCOMES AND QUALITY

Prognostic Value of Cardio-Ankle Vascular Index for Cardiovascular and Kidney Outcomes

Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND Arterial stiffness causes cardiovascular disease and target-organ damage. Carotid-femoral pulse wave velocity is regarded as a standard arterial stiffness metric. However, the prognostic value of cardio-ankle vascular index (CAVI), which is mathematically corrected for blood pressure, remains understudied.

OBJECTIVES The purpose of this study was to determine the association of CAVI with cardiovascular and kidney outcomes.

METHODS PubMed, Scopus, and Web of Science were searched until May 6, 2023, for longitudinal studies reporting the association of CAVI with mortality, cardiovascular events (CVEs) (including death, acute coronary syndromes, stroke, coronary revascularization, heart failure hospitalization), and kidney function decline (incidence/progression of chronic kidney disease, glomerular filtration rate decline). Random-effects meta-analysis was performed. Studies were assessed with the "Quality in Prognostic Studies" tool.

RESULTS Systematic review identified 32 studies (105,845 participants; follow-up range: 12-148 months). Variable cutoffs were reported for CAVI. The risk of CVEs was higher for high vs normal CAVI (HR: 1.46 [95% CI: 1.22-1.75]; $P < 0.001$; $I^2 = 41\%$), and per SD/unit CAVI increase (HR: 1.30 [95% CI: 1.20-1.41]; $P < 0.001$; $I^2 = 0\%$). Among studies including participants without baseline cardiovascular disease (primary prevention), higher CAVI was associated with first-time CVEs (high vs normal: HR: 1.60 [95% CI: 1.15-2.21]; $P = 0.005$; $I^2 = 65\%$; HR per SD/unit increase: 1.28 [95% CI: 1.12-1.47]; $P < 0.001$; $I^2 = 18\%$). There was no association between CAVI and mortality (HR = 1.31 [0.92-1.87]; $P = 0.130$; $I^2 = 53\%$). CAVI was associated with kidney function decline (high vs normal: HR: 1.30 [1.18-1.43]; $P < 0.001$; $I^2 = 38\%$; HR per SD/unit increase: 1.12 [95% CI: 1.07-1.18]; $P < 0.001$; $I^2 = 0\%$).

CONCLUSIONS Higher CAVI is associated with incident CVEs, and this association is present in the primary prevention setting. Elevated CAVI is associated with kidney function decline. (JACC Adv 2024;3:101019) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ABBREVIATIONS AND ACRONYMS

CAVI = cardio-ankle vascular index

cfPWV = carotid femoral pulse wave velocity

CKD = chronic kidney disease

CVD = cardiovascular disease

CVEs = cardiovascular events

eGFR = estimated glomerular filtration rate

Large artery stiffness has emerged as a causal risk factor for cardiovascular disease (CVD), target-organ damage, and a predictor of mortality.[1-3] Carotid-femoral pulse wave velocity (cfPWV) has been considered the gold standard for the noninvasive assessment of arterial stiffness.[4] However, the pursuit for alternative markers of arterial stiffness has continued. The cardio-ankle vascular index (CAVI) was introduced as a novel alternative metric of arterial stiffness, which is derived from the heart ankle pulse wave velocity through a mathematical correction for blood pressure dependence at the time of measurement.[5] Additionally, CAVI is easily measured in clinical settings and exhibits high reproducibility, which may reduce its measurement variability and enhance its reliability.[6,7] Notably, cfPWV neglects the ascending aorta, which is the most distensible aortic segment and plays a crucial role in ventricular-arterial interaction.[8] On the other hand, CAVI uses the heart-to-ankle transit time, including both the aorta (from the heart to aortic bifurcation) and a long muscular arterial segment (femoral to ankle). Due to these differences, data regarding cfPWV cannot be readily extrapolated to CAVI, and more studies focused on the role of CAVI as a prognostic biomarker are needed.

A previous systematic review and meta-analysis in 2019 aimed to explore the relationship between CAVI and CVD. However, a notable limitation was that 19 out of the 28 included studies were cross-sectional, limiting the ability to establish a definitive prognostic association.[9] Multiple additional longitudinal studies have been published since this meta-analysis was performed. In addition, the previous meta-analysis did not analyze kidney outcomes (such as kidney function decline), which is important given that the kidneys are thought to be the prime target organs of large artery stiffening, due to its low local microvascular resistance, which exposes the microcapillaries to central pulsatility.[8] Finally, the previous meta-analysis analyzed the prognostic value of CAVI in both primary prevention and secondary prevention settings, whereas the proposed clinical value of arterial stiffness measurements may lie predominantly in identifying higher risk individuals for primary prevention.[8]

The present systematic review and meta-analysis aims to investigate the prognostic value of CAVI for prediction of incident cardiovascular events (CVEs), mortality, and kidney function decline.
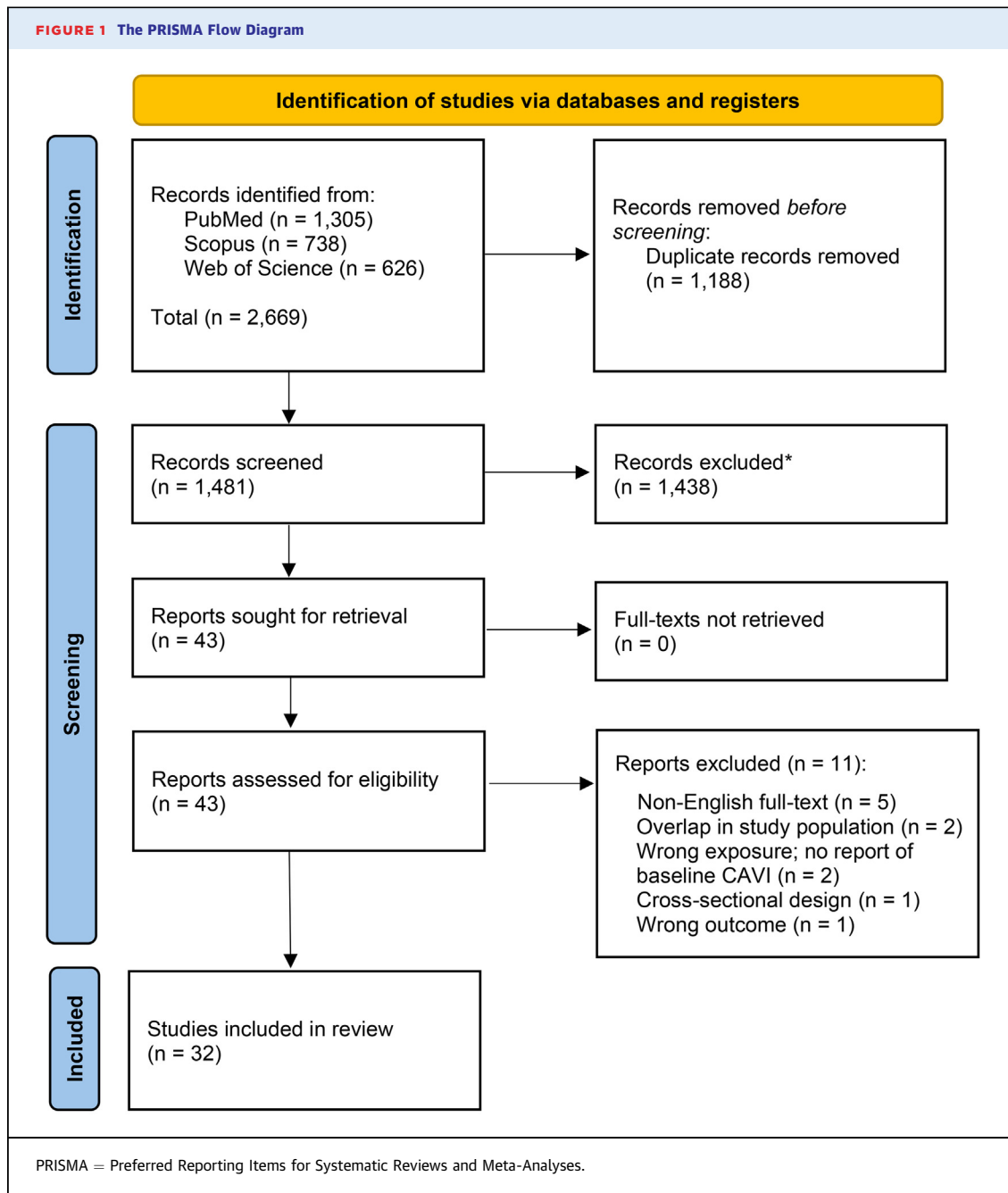
METHODS

The methodology and reporting of this systematic review and meta-analysis conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the reporting guidelines for Meta-analyses of Observational Studies (MOOSE).[10,11] Since Institutional Review Board and ethics committee approvals were obtained for each included study, no additional approval was required for this review of aggregate published data. The protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO; CRD42023430708).

SEARCH AND STUDY SELECTION. A systematic search was conducted in PubMed, Scopus, and Web of Science, covering records from the date of database inception until May 6, 2023. Key terms of the search strategy were "CAVI", "arterial stiffness", "death", "cardiovascular events", "renal function", and "prediction". The search strings for each database are available in the supplementary materials/search strategy. Detection of duplicate records and screening of titles and abstracts were performed using the Rayyan web application (Rayyan Systems, Inc, Cambridge, Massachusetts).[12]

Studies were selected based on the following eligibility criteria: 1) original longitudinal studies—including cohorts, case-control studies, randomized trial data, or registries. Cross-sectional studies and non-original publications (eg, reviews, editorials, letters, conference abstracts) were excluded; 2) measurement of the study exposure, CAVI, at baseline and as a predictor of outcomes; and 3) report of prognosis data about association of baseline CAVI with future outcomes, including mortality, CVEs, and kidney function decline (outcomes are defined below).

Studies with non-English full texts were excluded. To ensure inclusion of independent data sets, in case of suspected overlaps in study populations where data for the same outcome from the same participants were reported in multiple publications, only 1 of the published records was included. Overlap was judged based on recruitment sites, dates, eligibility criteria, population characteristics, and reported outcomes. Selection between such publications was based on recency, larger sample size, and report of statistics required for meta-analysis.

DATA EXTRACTION. Predesigned electronic data collection forms were used to extract the following information: study publication year, design (cohort, case-control, registry; prospective vs retrospective;

FIGURE 1 The PRISMA Flow Diagram

Identification of studies via databases and registers

Identification

Records identified from:
  PubMed (n = 1,305)
  Scopus (n = 738)
  Web of Science (n = 626)

Total (n = 2,669)

Records removed *before screening*:
  Duplicate records removed (n = 1,188)

Screening

Records screened
(n = 1,481)

Records excluded*
(n = 1,438)

Reports sought for retrieval
(n = 43)

Full-texts not retrieved
(n = 0)

Reports assessed for eligibility
(n = 43)

Reports excluded (n = 11):
  Non-English full-text (n = 5)
  Overlap in study population (n = 2)
  Wrong exposure; no report of baseline CAVI (n = 2)
  Cross-sectional design (n = 1)
  Wrong outcome (n = 1)

Included

Studies included in review
(n = 32)

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

single-center vs multicenter), country, study affiliation, number of participants, population eligibility criteria, age, sex, CAVI measurement method, mean CAVI, handling of CAVI in the analytic models (categorical or continuous; selected cut-point and its rationale in case of categorization), follow-up duration, definitions of outcome measures, and covariates used in multivariable models.

Predefined study outcomes were mortality (including all-cause death or CV death), CVEs (including death, acute coronary syndromes, stroke, coronary revascularization, heart failure hospitalization), and kidney outcomes (incidence/progression of chronic kidney disease [CKD], or estimated glomerular filtration rate [eGFR] decline). CKD was defined as eGFR <60 mL/min/1.73 m². A further decline in eGFR defined CKD progression. Heterogeneous definitions of kidney outcomes were expected in the literature. All outcomes were binary. A composite of the outcomes was considered based on the reporting

TABLE 1 Study Characteristics

First Author, Year	Design	Country	Population	n	Age, y	Male	Abnormal CAVI	Mean CAVI	Outcome(s)	Duration of Follow-Up
Kubota et al, 2011	Prospective observational, single-center	Japan	Patients with HTN, DM, DLP, or CVD	400	68.7 ± 10.7	252 (63%)	≥9	NR	CVEs (CAD events, stroke)	27.2 ± 4.6 months
Kato et al, 2012	Retrospective observational, single-center	Japan	Patients on chronic hemodialysis	135	60 ± 11	91 (67%)	≥8	9.7 ± 3	All-cause death, CV death, CVEs (MI, stroke, SCD, HF)	63 ± 4 months
Maebuchi et al, 2013	Prospective observational, single-center	Japan	Patients with HTN, DM, DLP, or CVD	369	67.3 ± 8.5	248 (67%)	≥8	NR	Occurrence of CKD (defined as new dipstick proteinuria and eGFR <60 mL/min/1.73 m^2)	22 ± 9 months
Chung et al, 2015	Retrospective case-control, single-center	Taiwan	Age >35 y with DM without CVD	626	64 ± 9	288 (46%)	≥9	8.8 ± 1.4	CVEs (death, ACS, ischemic stroke, coronary revascularization)	4.10 ± 0.36 y
Laucevičius et al, 2015	Retrospective, population-level registry	Lithuania	Patients with metabolic syndrome without CVD	2,106	53.83 ± 6.17	799 (38%)	Per SD	7.92 ± 1.43	CVEs (MI, stroke/TIA, SCD)	3.5 ± 1.7 y
Satoh-Asahara et al, 2015	Prospective observational, multicenter	Japan	Outpatients with obesity; without CVD	425	51.5 ± 14.1	189 (44%)	Per unit	7.6 ± 1.5	CVEs (MI, PCI, stroke/TIA, arteriosclerosis obliterans)	5 y
Kusunose et al, 2016	Prospective observational, single-center	Japan	Patients with ≥2 CVD-RFs or CVD	114	69 ± 11	89 (78%)	Per SD	8.5 ± 1.5	CVEs (CV death, MI, coronary revascularization, acute pulmonary edema, stroke), rapid kidney function decline (annual decline ≥5 mL/min/1.73 m^2)	51 months
Yuta Sato et al, 2016	Prospective observational, single-center	Japan	Individuals without CVD with metabolic disorders (DM, HTN, DLP)	1,003	62.5 ± 11.2	514 (51%)	per unit	9.25 ± 1.61	Nonfatal MI or angina pectoris	6.7 ± 1.6 y
Hitsumoto et al, 2018	Prospective observational, single-center	Japan	Patients with CKD and no history of CVEs	460	74 ± 12	152 (33%)	>10	9.7	CVEs (CV death, MI, ischemic stroke, and HFH)	60.1 months
Kim et al, 2019	Prospective observational, multicenter	USA	Adults without prevalent CVD	2,755	75 ± 5	39%	≥13	Median 13 (IQR 11.8-14.2)	CVEs (CHD, HF, stroke), all-cause death	4.4 y
Itano et al, 2020	Prospective registry of employee health checkups	Japan	Population of employees undergoing checkups	24,297	46.2 ± 13.0	14,461 (60%)	per SD & ≥8.1	7.5 ± 1.0	CKD incidence (expressed as HR, defines as new proteinuria and eGFR <60 mL/min/1.73 m^2), rapid eGFR decline (expressed as OR, defined as annual decline ≥3 mL/min/1.73 m^2)	3.1 y
Kirigaya et al, 2020	Prospective observational, single-center	Japan	Patients with ACS who underwent CAG	387	64.6 ± 9	323 (83%)	≥8.35	8.5 ± 1.2	CVEs (CV death, recurrence of ACS, HFH, stroke), CV death	62 months
Satirapoj et al, 2020	Prospective observational, single-center	Thailand	Age ≥18 y with CVD or ≥45 y with ≥2 CVD RFs	352	67.8 ± 10.1	61%	≥8	9.4 ± 1.4	Rapid GFR decline (annual decline ≥5 mL/min/1.73 m^2)	1 y
Jeong et al, 2021	Retrospective registry, single-center	South Korea	Registry data of participant age ≥18 y without ESRD	8,701	60.4 ± 11.4	50%	>7.7	8.47 ± 1.21	Kidney disease progression (defined as doubling of serum creatinine, ≥50% decline in eGFR, or development of ESRD), ESRD: receiving dialysis or kidney transplantation	7 y

TABLE 1 Continued

First Author, Year	Design	Country	Population	n	Age, y	Male	Abnormal CAVI	Mean CAVI	Outcome(s)	Duration of Follow-Up
Limpijankit et al, 2021	Prospective survey among employees	Thailand	Employees with ASCVD RFs but without CVD symptoms	3,630	57.4 ± 7.3	73%	≥9	NR	CVEs (CV death, MI, stroke)	12.4 ± 0.6 y
Miyoshi et al, 2021	Prospective observational, multicenter	Japan	Patients aged 45-74 y with CVD RFs	2,938	63.2 ± 8	2001 (68%)	Per unit and >9.5	NR	CVEs (CV death, MI, stroke), all-cause death	4.9 y
Murakami et al, 2021	Retrospective observational, multicenter	Japan	Patients undergoing chronic hemodialysis	209	60 ± 11	129 (62%)	Per SD and ≥9.15	8.8 ± 1.3	All-cause death	6 y
Shinohara et al, 2021	Retrospective observational, single-center	Japan	Patients undergoing AFCA with successful PVI	193	Median: 64.9	139 (72%)	Per unit	Median 8.5	Recurrence of atrial arrhythmia (AF/AT)	31.3 months
Sumin et al, 2021	Retrospective observational, single-center	Russia	Patients who underwent elective CABG	238	Median normal CAVI: 56.5; High CAVI: 62	183 (77%)	≥9	NR	CVEs (all-cause death, MI, stroke/TIA, PCI, carotid endarterectomy, PE, CV hospitalization)	5 y
Watanabe et al, 2021	Prospective observational, single-center	Japan	Patients with HF hospitalization	223	Median low CAVI: 58; High CAVI: 69	178 (80%)	≥8.9	Median low CAVI: 7.31; high CAVI: 9.62	CVEs (all-cause death, HFH, ischemic coronary events)	1,623 d
Yasuharu et al, 2021	Prospective observational, community residents	Japan	General population sample	7,249	59.8 ± 12.6	34%	Per unit	7.91 ± 1.15	CVEs (first-ever MI, CABG, PCI, stroke)	8.53 y
Yu Sato et al, 2021	Prospective observational, single-center	Japan	Patients with HF hospitalization	557	Median low CAVI: 65.5; high CAVI: 73.0	356 (64%)	≥9.64	Median low CAVI: 7.9; High CAVI: 10.4	Stroke	1415 d
Aiumtrakul et al, 2022	Prospective observational, multicenter	Thailand	Age ≥45 with ≥3 atherosclerosis RFs or established CVD	4,898	65.6 ± 8.6	2,743 (56%)	≥8	8.8 ± 0.9	Kidney function decline (defined as eGFR decline >40%, or decline <15 mL/min/1.73 m^2, or doubling of serum creatinine, initiation of dialysis), all-cause death, CV death	60 months
Nagayama et al, 2022a	Urban residents' health examinations, retrospective	Japan	General population volunteers	27,864	Median without eGFR decline: 45; with decline: 61	12,369 (44%)	Per SD and ≥8	Median without eGFR decline: 7.5; with decline: 8.4	Kidney function decline (defined as eGFR decline <60 mL/min/1.73 m^2)	3.5 ± 1.7 y
Nagayama et al, 2022b	Urban residents' health examinations, retrospective	Japan	General population volunteers	5438	Median: 48	2368 (44%)	≥8	Median AF: 8.7; no AF: 7.6	Incidence of AF	4 y
Okamoto et al, 2022	Retrospective observational, single-center	Japan	With ≥1 CVD RF but without CVD	554	68 ± 9	64%	>9	8.8 ± 1.3	CVEs (CV death, MI, stroke, coronary revascularization, HFH)	4.3 y
Rerkasem et al, 2022	Prospective observational, multicenter	Thailand	Patients with HIV on ART age ≥50 y; no previous CVEs	347	57.7 ± 5.4	42%	Per unit and ≥8	8.2 ± 0.8	CVEs (all-cause death, HFH, MI, ischemic stroke, CV interventions	5.3 y
Sobajima et al, 2022	Prospective observational, single-center	Japan	Patients who underwent TAVI for severe AS	149	84.7 ± 5.6	36 (24%)	≥9	9.64 ± 1.36	HF readmission	726 d

TABLE 1 Continued

First Author, Year	Design	Country	Population	n	Age, y	Male	Abnormal CAVI	Mean CAVI	Outcome(s)	Duration of Follow-Up
Spronck et al, 2022	Prospective observational, single-center	USA	Patients referred for CMR; with/ without HF	154	64.9 ± 10.8	146 (95%)	Per SD	NR	Composite endpoint of death or HFH	2.56 y
Sumin et al, 2022	Retrospective observational, single-center	Russia	Patients who underwent elective CABG	274	Median normal CAVI: 57; high CAVI: 63	209 (76%)	≥9	NR	CVEs (All-cause death, MI, stroke/TIA, coronary revascularization, carotid endarterectomy, PAD intervention, PPM), CV death	10 y
Limpijankit et al, 2023	Retrospective observational, single-center	Thailand	With moderate to high ASCVD risk or stable chest pain	8,687	59.0 ± 8.4	37%	≥9	8.9 ± 2.2	CVEs (CV death, MI, stroke)	9.9 ± 2.4 y
Miki et al, 2023	Retrospective observational, single-center	Japan	Patients who underwent TAVI for severe AS	113	83.5 ± 4.6	43 (38%)	≥9.3	NR	CV death, HFH	2.3 y

ACS = acute coronary syndrome; AF = atrial fibrillation; AFCA = atrial fibrillation catheter ablation; ART = anti-retroviral therapy; AS = aortic stenosis; ASCVD = atherosclerotic cardiovascular disease; AT = atrial tachycardia; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CAG = coronary angiography; CAVI = cardio-ankle vascular index; CHD = coronary heart disease; CKD = chronic kidney disease; CMR = cardiac magnetic resonance; CV = cardiovascular; CVD = cardiovascular disease; CVEs = cardiovascular events; DLP = dyslipidemia; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HF = heart failure; HFH = heart failure hospitalization; HIV = human immunodeficiency virus; HTN = hypertension; MI = myocardial infarction; NR = not reported; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PPM = permanent pacemaker; PVI = pulmonary vein isolation; RFs = risk factors; SCD = sudden cardiac death; TAVI = transcatheter aortic valve intervention; TIA = transient ischemic attack.

of included publications. According to the statistical models and reporting of each study, unadjusted and/or adjusted HRs and/or ORs were entered into datasheets. Additionally, for studies with dichotomized exposure, data for 2×2 tables were extracted if they were available. Studies that specifically reported recruiting participants without prior CVD or participants from a healthy general population were considered as "primary prevention" studies in subgroup analyses.

RISK OF BIAS ASSESSMENT. The risk of bias in studies was assessed using the QUIPS (Quality In Prognosis Studies) tool.[13] QUIPS is a comprehensive tool specifically designed to evaluate the risk of bias in prognostic studies in 6 domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each domain was evaluated and a judgment of unclear, low, moderate, or high risk of bias was assigned accordingly. The risk of bias assessment was performed by 2 reviewers (H.T. and O.E.). Disagreements were resolved through discussion with a third reviewer (J.C.).
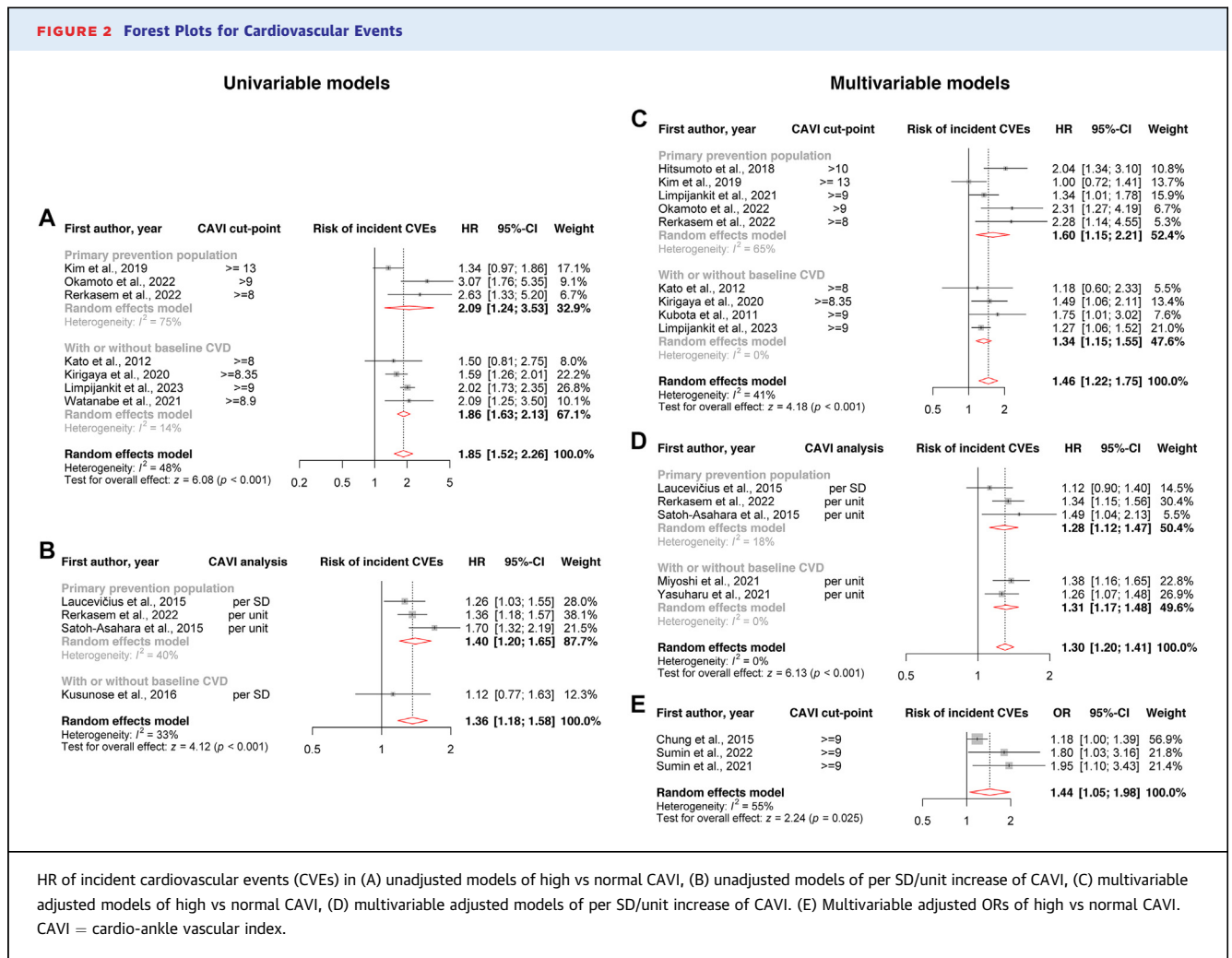
STATISTICAL ANALYSIS. Studies were grouped based on categorical or continuous handling of the study predictor in statistical models. For studies which reported results for more than 2 categorical levels of CAVI, an intra-study fixed-effects meta-analysis was used to calculate the appropriate effect size and obtain dichotomous exposure groups.[14-20] If

more than 1 multivariable model was reported, estimates from the most comprehensive model were used based on the number of covariates and model performance metrics (if available). Study results were pooled using the frequentist framework random-effects models to calculate pooled HRs or ORs with corresponding 95% CIs. Between-study heterogeneity was assessed with the Higgins' I^2 statistic, with $I^2 \geq 50\%$ indicating severe heterogeneity. The τ^2 was estimated with the DerSimonian-Laird method. A subgroup analysis was performed to determine the association of CAVI with outcomes among studies with a primary prevention population. Publication bias was evaluated through visual assessment of contour-enhanced funnel plots and applying the Egger's test. All statistical analyses were conducted using R (version 4.1.3, R Foundation for Statistical Computing) and packages "meta" and "metafor."

RESULTS

The systematic search identified 32 eligible studies with 105,845 participants (**Figure 1**).[14-45] The majority of the studies (27/32) were conducted in East Asian countries (Japan = 20, Thailand = 5, Russia = 2, USA = 2, Lithuania = 1, South Korea = 1, Taiwan = 1). Most studies had a prospective design (19/32). Notably, 9 studies reported data from a primary prevention population,[17,23,25,31,32,34,35,43,44] while the rest included a mix of participants with or without prior CVD. All but 1 study used commercial VaSera devices

FIGURE 2 Forest Plots for Cardiovascular Events

HR of incident cardiovascular events (CVEs) in (A) unadjusted models of high vs normal CAVI, (B) unadjusted models of per SD/unit increase of CAVI, (C) multivariable adjusted models of high vs normal CAVI, (D) multivariable adjusted models of per SD/unit increase of CAVI. (E) Multivariable adjusted ORs of high vs normal CAVI. CAVI = cardio-ankle vascular index.

(Fukuda Denshi, Tokyo, Japan) to measure CAVI.[17] Study characteristics are presented in detail in **Table 1**. Details of eligibility criteria and CAVI measurement methods are shown in Supplemental Table 1. Risk of bias assessments are demonstrated in Supplemental Table 2.

INCIDENT CARDIOVASCULAR EVENTS. Incidence of a composite of fatal and nonfatal CVEs was reported in 18 studies (N = 31,548).[16-18,21-25,27,31,32,35,39-44] In meta-analysis of CVEs, pooled HR of unadjusted results was 1.85 (95% CI: 1.52-2.26; $P < 0.001$; $I^2 = 48\%$; N = 13,088) (**Figure 2A**) for high vs low CAVI groups, and 1.36 (95% CI: 1.18-1.58; $P < 0.001$; $I^2 = 33\%$; N = 2,992) (**Figure 2B**) per increases in SD/units of CAVI. In adjusted multivariable models, CAVI was associated with incident CVEs when studies used cut-points of CAVI (HR: 1.46, 95% CI: 1.22-1.75; $P < 0.001$; $I^2 = 41\%$; N = 17,355) (**Figure 2C**), and when considering SD/unit increases in CAVI (HR: 1.30, 95% CI: 1.20-1.41; $P < 0.001$; $I^2 = 0\%$; N = 13,065) (**Figure 2D**). Meta-

regression did not show an association between effect size and follow-up duration (Supplemental Figures S1 and S2). The covariates that were included in the multivariable models in each study are shown in Supplemental Table 3. Combining results from 3 studies that reported adjusted ORs showed an association between CAVI and incident CVEs (OR: 1.44, 95% CI: 1.05-1.98; $P < 0.025$; $I^2 = 55\%$; N = 1,138) (**Figure 2E**).

In the subgroup of studies with primary prevention populations (ie, those without prevalent CVD at baseline), higher CAVI was associated with risk of CVEs in both categorical (HR: 1.60, 95% CI: 1.15-2.21; $P = 0.005$; $I^2 = 65\%$; N = 7,746) (**Figure 2C**) and continuous handling of the CAVI variable (HR = 1.28, 95% CI: 1.12-1.47; $P < 0.001$; $I^2 = 18\%$; N = 2,878) (**Figure 2D**).

Individual components of the CVEs were available from studies. However, because of heterogeneity in reporting and inadequacy of data, meta-analysis was

TABLE 2 Narrative Reporting of Study Results Not Included in Meta-Analyses

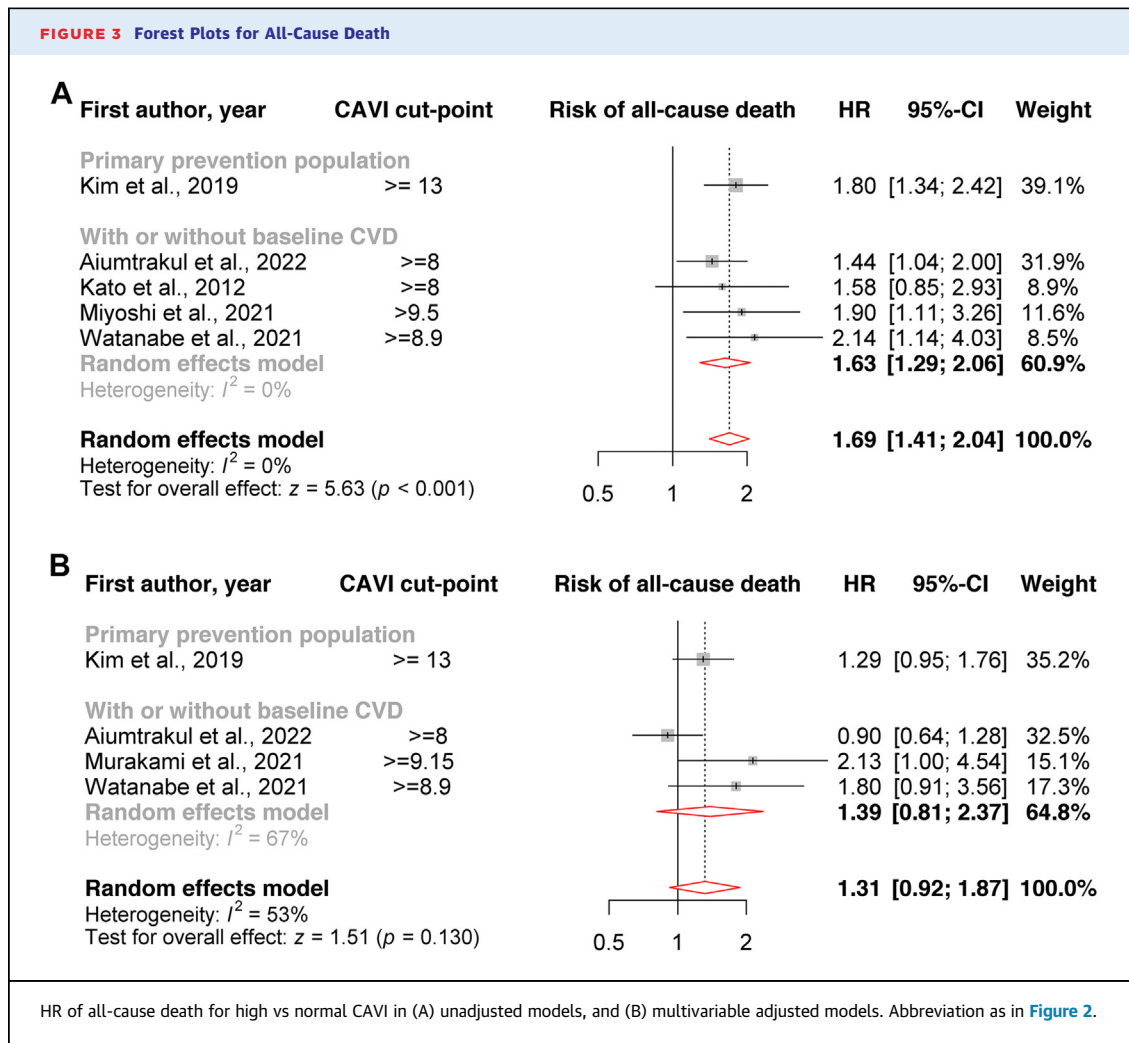| Outcome	First Author, Year	Population	CAVI Cut point	Duration of Follow-Up	Results
Acute coronary syndrome	Chung et al, 2015	Age >35 y with DM without CVD	≥9	4.10 ± 0.36 y	Unadjusted OR: 1.35, 95% CI: 0.99-1.85
Myocardial infarction	Miyoshi et al, 2021	Patients aged 45-74 y with CVD RFs	>9.5	4.9 y	Unadjusted HR: 1.13, 95% CI: 0.42-3.02
Myocardial infarction/angina	Yuta Sato et al, 2016	Individuals without CVD with metabolic disorders (DM, HTN, DLP)	Per unit	6.7 ± 1.6 y	Adjusted HR: 1.13, 95% CI: 1.01-1.26
Ischemic coronary events	Watanabe et al, 2021	Patients with HF hospitalization	≥8.9	1,623 d	Unadjusted HR: 1.15, 95% CI: 0.34-3.95
Coronary revascularization	Chung et al, 2015	Age >35 y with DM without CVD	≥9	4.10 ± 0.36 y	Unadjusted OR: 1.25, 95% CI: 1.03-1.51 Adjusted OR: 1.21, 95% CI: 0.98-1.5
Stroke	Chung et al, 2015	Age >35 y with DM without CVD	≥9	4.10 ± 0.36 y	Unadjusted OR: 1.08, 95% CI: 0.86-1.36 Adjusted OR: 1.12, 95% CI: 0.86-1.46
	Miyoshi et al, 2021	Patients aged 45-74 y with CVD RFs	>9.5	4.9 y	Unadjusted HR: 2.07, 95% CI: 1.1-3.91
	Yu Sato et al, 2021	Patients with HF hospitalization	≥9.64	1,415 d	Unadjusted HR: 3.02, 95% CI: 1.35-6.73 Adjusted HR: 3.6, 95% CI: 1.27-10.21
Atrial fibrillation	Nagayama et al, 2022b	General population volunteers	≥8	4 y	Adjusted HR: 5.27, 95% CI: 1.6-17.3
Recurrence of atrial fibrillation/ atrial tachycardia	Shinohara et al, 2021	Patients undergoing AFCA with successful PVI	Per unit	31.3 months	Unadjusted HR: 1.17, 95% CI: 0.99-1.39 Adjusted HR: 1.44, 95% CI: 1.17-1.78
Death or heart failure hospitalization	Spronck et al, 2022	Patients referred for CMR; with/without HF	per SD	2.56 y	Unadjusted HR: 1.58, 95% CI: 1.14-2.2 Adjusted HR: 1.44, 95% CI: 1.01-2.06
	Miki et al, 2023	Patients who underwent TAVI for severe AS	≥9.3	2.3 y	Normal CAVI group: 8 out of 85 participants High CAVI group: 3 out of 28 participants
Heart failure hospitalization	Miki et al, 2023	Patients who underwent TAVI for severe AS	≥9.3	2.3 y	Normal CAVI group: 5 out of 85 participants High CAVI group: 1 out of 28 participants
	Sobajima et al, 2022	Patients who underwent TAVI for severe AS	≥9	726 d	Unadjusted HR: 1.55, 95% CI: 1.03-2.3 Adjusted HR: 1.62, 95% CI: 1.07-2.46
All-cause death	Chung et al, 2015	Age >35 y with DM without CVD	≥9	4.10 ± 0.36 y	Unadjusted OR: 1.07, 95% CI: 0.82-1.41
	Sumin et al, 2022	Patients who underwent elective CABG	≥9	10 y	Adjusted OR: 1.91, 95% CI: 0.97-3.77

Abbreviations as in Table 1.

not possible for these outcomes. Narrative reporting of study results is shown in **Table 2**.

MORTALITY. Data for all-cause mortality was available in 8 studies (12,058 participants).[14,16,17,27,28,40,41,43] Pooled unadjusted results showed that all-cause death was higher in high baseline CAVI groups vs low baseline CAVI (HR: 1.69, 95% CI: 1.41-2.04; $P < 0.001$; $I^2 = 0\%$; N = 10,949) (**Figure 3A**). However, this association was not observed in the analysis of adjusted results (HR: 1.31, 95% CI: 0.92-1.87; $P = 0.130$; $I^2 = 53\%$; N = 8,085) (**Figure 3B**). All studies reported categorization of CAVI in the analyses, but the study by Murakami et al also reported HRs per SD increase of CAVI (adjusted HR: 1.60, 95% CI: 1.11-2.3).[28] Among studies reporting incidence of all-cause death, there was only 1 primary prevention study, which did not show a significant association (adjusted HR: 1.29, 95% CI: 0.95-1.76).[17] Two studies reported ORs for the risk of all-cause death.[40,43] However, they were not included in meta-analysis due to critical differences in design (**Table 2**).

Incident CV death was reported in 6 studies (N = 8,745).[14,16,21,26,27,40] All 6 studies reported categorization of CAVI with cut-points, and none of them were primary prevention studies. Unadjusted HRs available from 3 studies showed an association between CAVI and risk of CV death (HR: 2.84, 95% CI: 1.89-4.28; $P < 0.001$; $I^2 = 2\%$; N = 3,460) (**Figure 4A**). However, this association was not demonstrated using adjusted HRs from 2 studies (HR: 1.42, 95% CI: 0.62-3.29; $P = 0.408$; $I^2 = 65\%$; N = 522) (**Figure 4B**). Moreover, pooled unadjusted OR was calculated from 2×2 tables available from 3 studies, which did not show an association between CAVI and incident CV death (unadjusted OR: 1.51, 95% CI: 0.64-3.58; $P = 930$; $I^2 = 73\%$; N = 5,285) (**Figure 4C**).

KIDNEY FUNCTION DECLINE. Kidney function decline was reported in 7 studies (N = 66,595), with varying outcome definitions (**Table 1**).[14,15,19,20,22,29,45] Baseline eGFR ranged between 51 and 87 mL/min/1.73 m². Pooled unadjusted HR for dichotomous CAVI exposure groups from 2 studies was 1.50
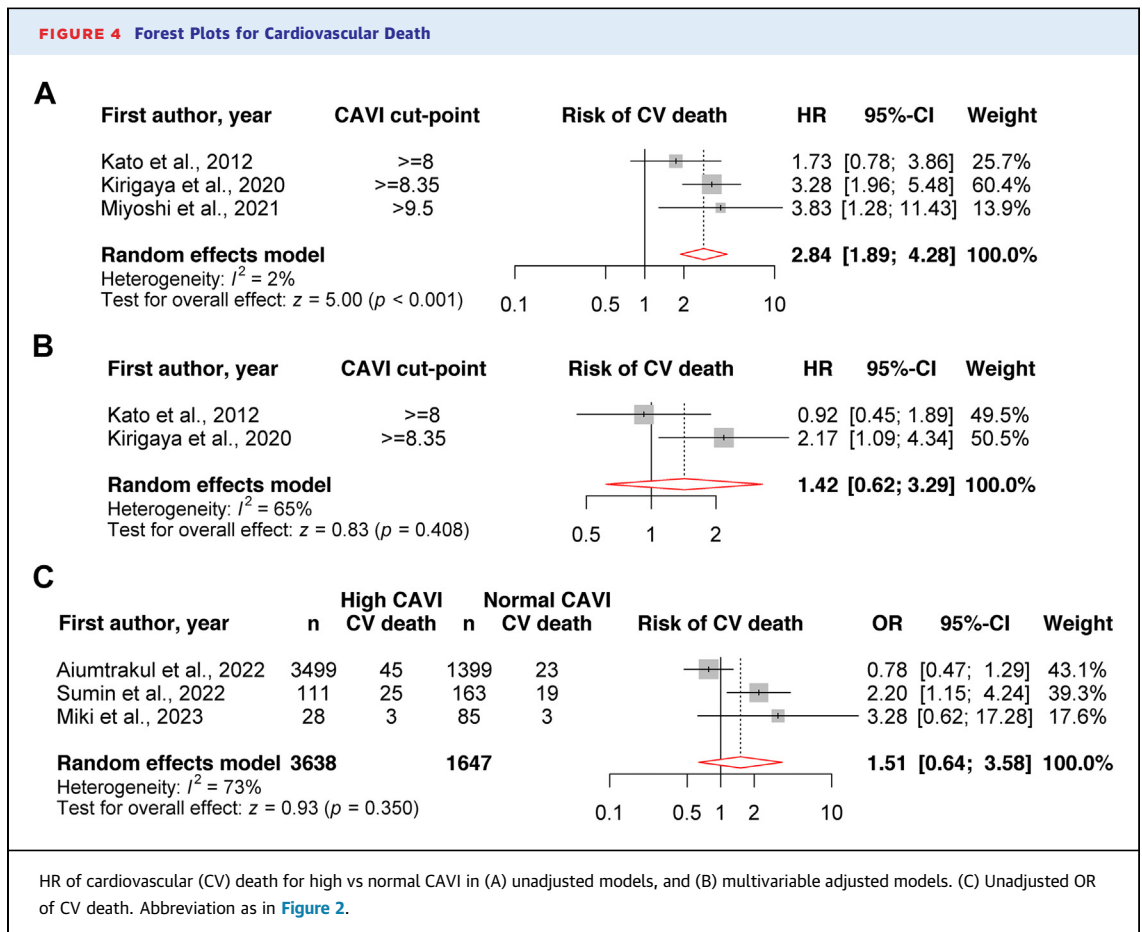
FIGURE 3 Forest Plots for All-Cause Death

HR of all-cause death for high vs normal CAVI in (A) unadjusted models, and (B) multivariable adjusted models. Abbreviation as in **Figure 2**.

(95% CI: 1.05-2.14; P = 0.024; I² = 90%; N = 13,599) (**Figure 5A**). The study by Kusunose et al reported unadjusted HR per SD increase of CAVI, and therefore was not included in the meta-analysis (HR: 1.52, 95% CI: 1.01-2.28). Adjusted results showed a significant association between higher CAVI and kidney dysfunction outcomes when CAVI was considered as a categorical (HR = 1.30, 95% CI: 1.18-1.43; P < 0.001; I² = 38%; N = 65,760) or a continuous variable (HR: 1.12, 95% CI: 1.07-1.18; P < 0.001; I² = 0%; N = 52,161) (**Figure 5B**). In the meta-analysis of 3 studies which reported adjusted ORs, CAVI was associated with kidney outcomes (OR: 1.67, 95% CI: 1.01-2.76; P = 0.046; I² = 71%; N = 25,018) (**Figure 5C**).

PUBLICATION BIAS. There was concern for publication bias for adjusted HRs of CVEs when considering CAVI as a dichotomous exposure (Egger's P = 0.098, Supplemental Figure 5. No significant publication bias was detected for other analytical models (Supplemental Figures 3 to 11).

DISCUSSION

This systematic review included 32 longitudinal studies investigating the role of CAVI as a prognostic marker, although significant heterogeneities were present in terms of study design and analytical methods. Our meta-analysis showed an association between CAVI and the risk of CVEs in both unadjusted and adjusted models. Additionally, CAVI was an independent predictor of CVEs among participants without baseline CVD, defined as the primary prevention subgroup. The latter is an important consideration, given that the primary prevention setting is particularly relevant for the potential clinical application of arterial stiffness measurements.[8] Although univariable models indicated an association with all-cause and CV death, pooling adjusted results revealed no association between CAVI and mortality. Furthermore, CAVI was a predictor of kidney function decline (a clinically important but less studied

FIGURE 4 Forest Plots for Cardiovascular Death

HR of cardiovascular (CV) death for high vs normal CAVI in (A) unadjusted models, and (B) multivariable adjusted models. (C) Unadjusted OR of CV death. Abbreviation as in **Figure 2**.
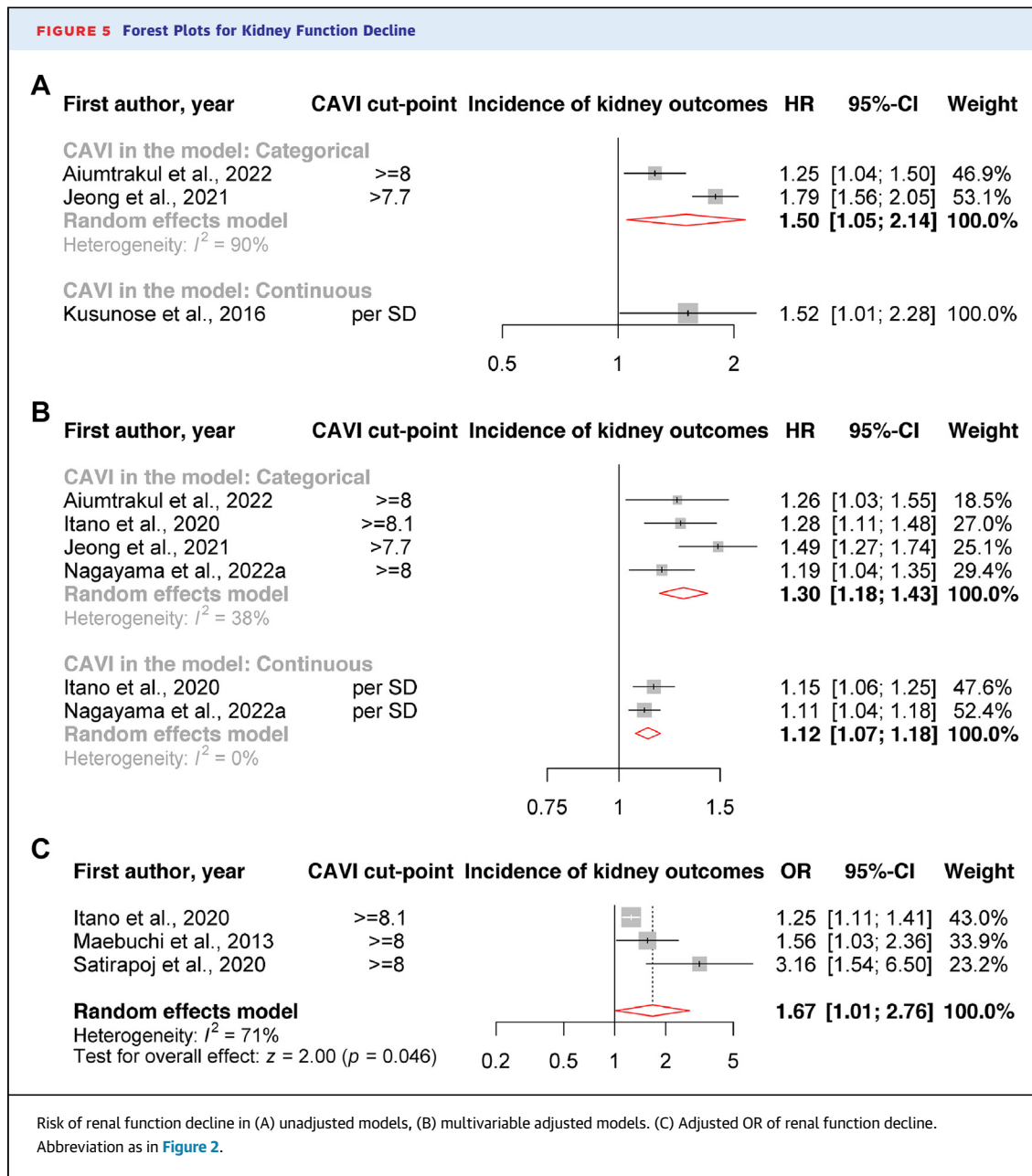
outcome of arterial stiffening), consistent with the detrimental effects of large artery stiffening on the kidneys (**Central Illustration**). Overall, by including a larger number of participants from multiple studies, this review enhances the statistical power and generalizability of the findings compared to individual studies in the literature.

CARDIOVASCULAR EVENTS AND MORTALITY. Considering the deleterious effects of large artery stiffness and abnormal pulsatile hemodynamics on the left ventricle and the microvasculature of various target organs,[8] the finding that CAVI predicts CVEs is not surprising. However, this review did not demonstrate an independent association between CAVI and all-cause death or even CV death. This is in contrast to data from previous studies that showed both cfPWV and brachial ankle PWV are associated with an increased risk of death.[46,47] Such differences may be due to the inclusion of a large non-aortic segment in the measurement of CAVI, which may confound the association, or may be related to the correction for blood pressure involved in its computation.[38] Further

studies are required to investigate more selective metrics of aortic stiffening, such as the cardio-femoral vascular index, an analogous index which only includes the heart to femoral segment. Furthermore, it is important to note that the studies included in this review that report mortality outcomes selected high-risk participants or individuals with comorbidities, such as patients with recent heart failure hospitalizations, or those receiving chronic hemodialysis.[28,41] This may have impacted the associations due to the presence of competing causes of death among these populations. In addition, including high-risk populations may introduce a potential collider bias. Finally, we note that larger sample sizes and a longer duration of follow-up may be necessary to detect an association between CAVI and mortality.
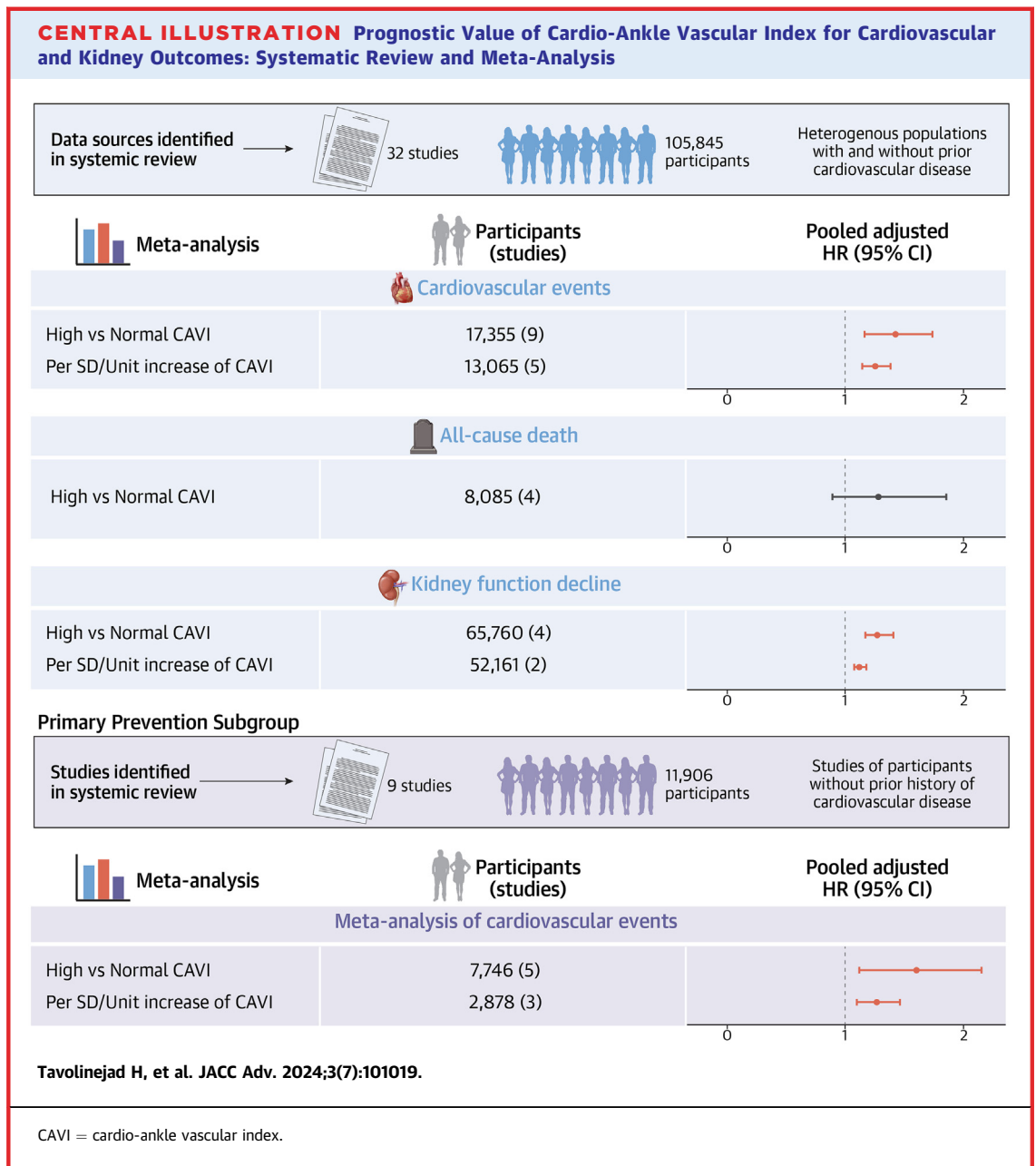
An interesting aspect of this study was the investigation of the prognostic role of CAVI in the setting of primary prevention of CVEs. A previous systematic review and meta-analysis in 2019 found that most of the published studies included participants with established CVD.[9] In our meta-analysis, a larger

FIGURE 5   Forest Plots for Kidney Function Decline

Risk of renal function decline in (A) unadjusted models, (B) multivariable adjusted models. (C) Adjusted OR of renal function decline. Abbreviation as in **Figure 2**.

number of studies including participants without prevalent CVD at baseline were identified, and subgroup analyses among these studies revealed a significant association between CAVI and first-time CVEs. Previous research has established that cfPWV is an independent predictor of CVEs and all-cause mortality in the general population that improves risk classification on top of conventional risk factors.[3,46] Based on our findings and by considering the large samples and moderately long duration of follow-up in primary prevention studies

(3.5-12 years), CAVI may be similarly useful as a prognostic tool, which could in turn guide decision-making in specific primary prevention settings.[8] This is further supported by data showing that, in addition to the prognostic value of a single baseline CAVI measurement, longitudinal changes in CAVI may predict incident CV risk.[48,49]

CAVI is correlated with various other CVD risk factors. It is known that large artery stiffness leads to isolated systolic hypertension.[8] A recent study of 34,649 normotensive adults found that high CAVI is

CENTRAL ILLUSTRATION Prognostic Value of Cardio-Ankle Vascular Index for Cardiovascular and Kidney Outcomes: Systematic Review and Meta-Analysis

Data sources identified in systemic review → 32 studies | 105,845 participants | Heterogenous populations with and without prior cardiovascular disease

Meta-analysis	Participants (studies)	Pooled adjusted HR (95% CI)
Cardiovascular events		
High vs Normal CAVI	17,355 (9)	
Per SD/Unit increase of CAVI	13,065 (5)	
All-cause death		
High vs Normal CAVI	8,085 (4)	
Kidney function decline		
High vs Normal CAVI	65,760 (4)	
Per SD/Unit increase of CAVI	52,161 (2)	

Primary Prevention Subgroup

Studies identified in systemic review → 9 studies | 11,906 participants | Studies of participants without prior history of cardiovascular disease

Meta-analysis	Participants (studies)	Pooled adjusted HR (95% CI)
Meta-analysis of cardiovascular events		
High vs Normal CAVI	7,746 (5)	
Per SD/Unit increase of CAVI	2,878 (3)	

Tavolinejad H, et al. JACC Adv. 2024;3(7):101019.

CAVI = cardio-ankle vascular index.

associated with new-onset hypertension.[50] On the other hand, large artery stiffness is exacerbated in the presence of other CVD risk factors.[2] CAVI may reflect these associations and combine the cumulative impact of various risk factors on the arterial wall, in addition to the effects of nonclassical risk factors.[51] Importantly, only a few studies have reported prognostic model performance after CAVI is added to conventional risk factors,[27,29,31,35] and there are few comparisons between CAVI and other metrics of arterial stiffness.[16,17,21,22,28] This should be the focus of future research.

There is insufficient evidence about the appropriate cut-points of CAVI and heterogeneity exists among published data, as several studies derive cut-points from small and highly selected samples. It is

crucial to note that the available evidence indicates racial and/or ethnic differences in normative CAVI values.[52] Moreover, the impact of increasing age and prevalent CVD risk factors on CAVI may also differ based on race and/or ethnicity.[53] Therefore, further studies should be done to better explore the impact of race, ethnicity, and other demographic factors on optimal cut-points for risk prediction.

KIDNEY OUTCOMES. We found that CAVI can serve as a marker of kidney function decline, regardless of the presence or absence of underlying CKD. This is consistent with the known effects of arterial stiffness on aortic pressure pulsatility, which can be transmitted to low-resistance, high-flow microvascular beds such as the kidney glomeruli. In addition to the putative role of large artery stiffness on renal vascular damage, CKD can contribute to the worsening of arterial stiffness through various mechanisms, including the upregulation of the renin-angiotensin-aldosterone axis, sympathetic activation, and vascular calcification in advanced stages of disease.[54,55]

It has been shown that large artery stiffness is associated with incident CKD, as well as progression of CKD toward end-stage renal disease.[56,57] However, the specific utility of CAVI in this context has not been thoroughly investigated. While our findings suggest that CAVI can be used to evaluate the risk of future decline in kidney function, it is important to consider that the studies included in our review varied in terms of baseline eGFR, definitions of kidney function decline, and adjustments for relevant covariates, such as hypertension.

STRENGTHS AND LIMITATIONS. The substantial number of studies included in this review collectively demonstrate the potential of CAVI as a prognostic biomarker. However, it is important to acknowledge that most included studies included East Asian populations. To investigate the generalizability of these findings, and considering potential ethnic differences in CAVI values, further research is required among non-Asian subjects, with a focus on establishing normative data and assessing the prognostic role of CAVI. Of note, ongoing studies in the United States (including the Multi-Ethnic Study of Atherosclerosis) have included CAVI measurements and will provide important data from North American populations.

Heterogeneities were observed in population characteristics, outcome definitions, follow-up duration, and settings. We addressed these differences by rigorously selecting studies for meta-analysis and by reporting study features in detail. Moreover, there were significant variations in statistical models and the covariates that were used. This may influence the robustness of the conclusion that CAVI predicts outcomes independent of conventional risk factors.

CONCLUSIONS

This systematic review and meta-analysis demonstrates that high baseline CAVI is independently associated with incident CVEs and kidney function decline. Moreover, CAVI was a predictor of first-time CVEs among subjects without prior history of CVD. We did not find an independent association between CAVI and the risk of all-cause or CV mortality. Studies are needed to further investigate the prognostic role of CAVI, particularly in the setting of primary prevention.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Arterial stiffening is a known cause of cardiovascular disease and target organ damage. Novel markers are needed for prognostic evaluation focused on vascular health. CAVI, which is derived from haPWV through a mathematical correction for blood pressure values at the time of its measurement, can be easily measured and shows good reproducibility. This review of the contemporary evidence showed significant associations between higher CAVI and future incident cardiovascular events, and predicted declines in kidney function. Furthermore, in a subgroup of studies involving participants without previous cardiovascular disease, higher CAVI was an independent predictor of first-time incident cardiovascular events,

highlighting its value as a prognostic tool in the primary prevention setting.

TRANSLATIONAL OUTLOOK: The prognostic value of arterial stiffness metrics is particularly relevant in the setting of primary prevention to assist in clinical decision making in various scenarios. Future longitudinal studies with appropriate follow-up durations are needed among individuals without a history of cardiovascular disease to further assess the utility of CAVI in predicting first-time cardiovascular events independent of conventional risk factors. Additionally, while this study highlights the association of CAVI with kidney function decline, the role of CAVI in assessing and predicting other target-organ damage phenotypes should be investigated in the future.

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KEY WORDS cardio-ankle vascular index, cardiovascular, CAVI, vascular stiffness, mortality

APPENDIX For search strategy and supplemental tables and figures, please see the online version of this paper.