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REVIEW PAPER

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Cardio-ankle vascular index and cardiovascular disease: Systematic review and meta-analysis of prospective and cross-sectional studies

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The cardio-ankle vascular index (CAVI) is a new measure of arterial stiffness that reflects the stiffness from the ascending aorta to the ankle arteries, and demonstrates little dependence on blood pressure during the evaluation. However, a comprehensive assessment of the association of CAVI with cardiovascular disease (CVD) has not been reported. We performed a systematic review to assess the association between CAVI and CVD. We searched for both prospective and cross-sectional studies using MEDLINE, Embase, and Cochrane from inception until April 11, 2017. We pooled the results using random-effects models. Among 1519 records, we identified nine prospective studies (n = 5214) and 17 cross-sectional eligible studies (n = 7309), with most enrolling high CVD risk populations in Asia. All nine prospective studies investigated composite CVD events as an outcome (498 cases including coronary events and stroke) but modeled CAVI inconsistently. The pooled adjusted hazard ratio for CVD events per 1 standard deviation increment of CAVI in four studies was 1.20 (95% CI: 1.05-1.36, $P = 0.006$). Of the 17 cross-sectional studies, 13 studies compared CAVI values between patients with and without CVD and all reported significantly higher values in those with CVD (pooled mean difference in CAVI values 1.28 [0.86-1.70], $P < 0.001$). This systematic review suggests a modest association between CAVI and incident CVD risk, and highlights the need for studies assessing CAVI as a predictor of CVD in the general population and non-Asian countries.

1 | INTRODUCTION

Arterial stiffness, an important material property of the arterial wall, is of increasing interest for several reasons.[1] It has been shown to predict cardiovascular disease (CVD) beyond traditional risk factors.[2] Moreover, arterial stiffness is likely to predate hypertension and target organ damage, which has important implications for early identification of individuals at a high risk of CVD.[3]

There are several parameters that measure arterial stiffness. Given a body of evidence about the prognostic value and correlations with cardiovascular risk factors, there is a general consensus that carotid-femoral pulse wave velocity (cfPWV) is a reference standard measure of arterial stiffness.[2,4,5] However, to measure cfPWV, probes often need to be placed on both the carotid and femoral arteries, which can be uncomfortable for some individuals and may require them to expose the groin area depending on devices

used. Also, obtaining a good waveform for the measurement can be challenging in some individuals (eg, those with obesity) and in general, is highly operator dependent.[6] Accordingly, the use of cfPWV has been limited primarily to research applications.

The cardio-ankle vascular index (CAVI) is a new parameter of arterial stiffness[7] derived from the cardio-ankle pulse wave velocity and acknowledged in the 2015 American Heart Association Scientific Statement for Improving and Standardizing Vascular Research,[8] with several unique logistical and conceptual properties. First, it is measured simply using blood pressure cuffs placed in both arms and ankles and a microphone on the chest, without requiring probes on the neck or groin, and is mostly operator independent.[9] Second, CAVI reflects the stiffness of the entire aorta (including the ascending segment), and the femoral, popliteal, and tibial arteries, and measures the increase in arterial stiffness occurring from end-diastole to end-systole.[7,10] A significant association has been reported between cfPWV and CAVI.[11] Moreover, it has been reported that CAVI is less affected by blood pressure at the time of measurement compared to PWV, as CAVI is based on the stiffness parameter β, the exponent of the pressure-volume relationship.[10,12] Reproducibility of CAVI is also good.[13]

Despite these unique properties, the effectiveness of CAVI as a predictor of CVD and death has only been assessed by small studies,[14-22] hindering robust conclusions. Therefore, we performed a systematic review and meta-analysis of studies reporting associations between CAVI and CVD. Since the identification of potent predictors of CVD risk has often resulted from studies comparing the predictors between persons with and without CVD (eg, natriuretic peptide, which was originally found to be useful for diagnosing heart failure but later identified as a potent predictor of incident heart failure), we also investigated cross-sectional studies comparing CAVI values between those with and without CVD.

2 | METHODS

2.1 | Literature search strategy

We included prospective and cross-sectional studies that performed CAVI assessment among adults aged 18 years or older and had data on CVD outcomes during follow-up or the status of CVD concurrently with CAVI data. We restricted our analysis to studies with at least 20 CVD events or 20 patients with CVD. We did not find any randomized controlled trials or case-control studies in our literature search. We excluded case reports, case series, conference abstracts, review articles, and articles not written in English. We did not implement any restrictions for the year of publication.

Our primary outcomes of interest were CVD outcomes, including coronary heart disease (myocardial infarction, angina pectoris, and coronary revascularization based on percutaneous coronary intervention or coronary artery bypass grafting), stroke, or heart failure. Since CVD is a leading cause of death in many countries,[23] we also included all-cause mortality when reported. As noted above, we also included cross-sectional studies with information on the status of the CVD events.

We searched MEDLINE, Embase, and Cochrane for relevant articles on April 11, 2017, using the search strategy detailed in Data Supplement S1. Given a limited number of studies with data on CAVI, we searched for terms related to CAVI (ie, cardio ankle vascular index, cardioankle vascular index, cardiac ankle vascular index, CAVI) without adding terms indicating CVD outcomes.

2.2 | Study selection

Our search results were exported to EndNote X7 reference manager (Clarivate Analytics; Thomson Reuters, Philadelphia, PA), and duplicates were removed by an author (ND). The remaining articles were uploaded to Covidence (Melbourne, Australia). Two independent reviewers (ND and EK) reviewed all titles and abstracts. Any discrepancy was solved by discussion or a third reviewer (KM). Subsequently, the same two independent reviewers (ND and EK) reviewed all papers included in the full-text screen and recorded reasons for any exclusions in this step.

2.3 | Data collection and quality assessment

Data Supplement S2 summarizes data elements extracted in our systematic review. Two reviewers (ND and EK) extracted the elements from each eligible study to Excel (Microsoft Office Professional Plus 2016, Microsoft Corporation, Redmond, WA). Any discrepancy was solved by discussion or a third reviewer (KM).

We examined the risk of bias in prospective studies using the Newcastle Ottawa Quality Assessment Scale (NOS) for cohort studies (Data Supplement S3).[24] The scale assesses aspects of methodology in observational studies related to study quality, including nine items grouped into three major categories: selection (four items, one star for each), comparability (one item, up to two stars), and outcomes (three items, one star for each). The maximum score was nine stars, and six stars or more were regarded as high quality. For cross-sectional studies, we applied an adapted form of the NOS (Data Supplement S3).[25] The maximum score was ten, and seven points were used to identify studies with high quality.[26] Two reviewers (ND and EK) worked independently, and any disagreement was resolved by discussion.

2.4 | Data synthesis and analysis

We pooled the results from prospective studies with a similar methodology for modeling or categorizing CAVI, whenever there were two or more studies with eligible data. Specifically, for the studies modeling CAVI as a continuous variable, we pooled hazard ratio (HR) according to 1 standard deviation (SD) increment of CAVI, whenever possible. When CAVI was analyzed categorically, we pooled the HR for the highest compared with the lowest category in each study since the exact categorization varied across studies.[27] We pooled HRs for composite CVD and total mortality, separately. We conducted a random-effects meta-analysis to estimate pooled HRs and their 95% confidence intervals (CIs). If available, we included the HR that most extensively adjusted for

covariates in each study. If adjusted estimates were not reported, we used the unadjusted results. All tests were two-sided at an alpha-level of 0.05, and analyses were performed with Stata version 14 (StataCorp, LLC, College Station, TX).

Cross-sectional studies were analyzed in Review Manager version 5.3 (Cochrane Collaboration, Oxford, UK) with random-effects models to estimate the mean difference in CAVI values between those with and without CVD. The potential of publication bias in cross-sectional studies was investigated visually by funnel plots.[28] We repeated the analysis for coronary artery disease (1, 2, 3 vessel disease vs. no vessel disease). We also performed a sensitivity analysis removing studies with low NOS scores (NOS score <6 for prospective studies and <7 for cross-sectional studies). Heterogeneity among studies was assessed using the I^2 statistic. An I^2 > 75% was considered indicative of high heterogeneity.[29]

3 | RESULTS

3.1 | Description of studies

3.1.1 | Search results

A total of 1519 records were identified from MEDLINE, Embase, Cochrane, and discussion with experts. After removing duplicates, 991 records were assessed in the title and abstract screening. Nine hundred and twenty-seven records did not meet the inclusion criteria, leaving 64 records for full-text screening. Of those, 38 were excluded after the full-text review due to various reasons (eg abstracts but not full articles or no relevant outcomes), and 26 studies met the eligibility criteria for qualitative synthesis (Figure 1). Of those, 20 studies met the criteria of high quality, whereas six studies (one prospective study and five cross-sectional studies) did not (Table S1).

3.1.2 | Prospective studies

Out of the 26 included studies, nine were prospective studies and included 5214 participants.[14-22] All studies were relatively recent (2010 or later). Seven studies were from Japan,[15-18,20-22] and the other two were from China[14] and Lithuania.[19] Most studies were relatively small, and there were only two studies that enrolled more than 1000 participants (n = 2106[19] and 1003[21]). All studies investigated participants with high-risk profiles for CVD, such as those with hypertension, diabetes, kidney disease, and a history of CVD. The average age of participants ranged from 52 to 69 years (Table 1).

Of the nine prospective studies, most had an average follow-up time of less than five years, and the longest average follow-up time was 6.7 years (Table 1). A total of 498 cases of composite CVD were reported from the nine studies,[14-22] although the exact definition of composite CVD varied across the studies (Table S2). Also, different thresholds were used for categorizing CAVI (Table 2). Of the nine

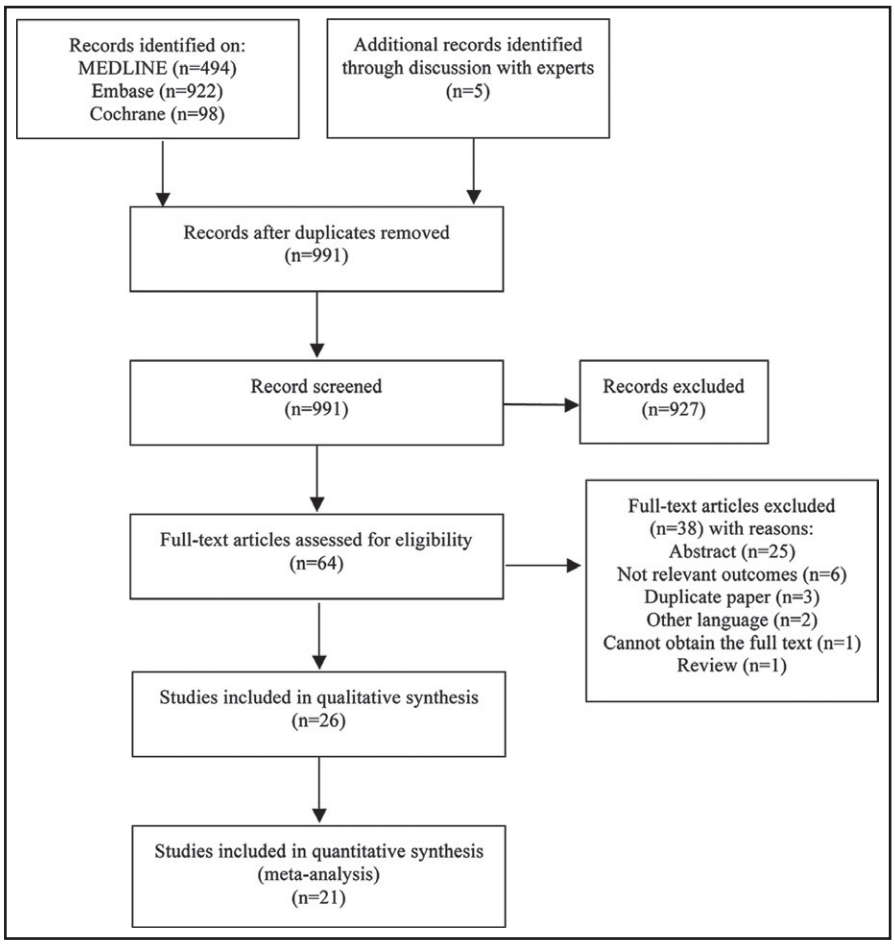

FIGURE 1 Flow diagram of study selection

TABLE 1 Summary of prospective studies included in systematic review

Study	Year	Region	Sample size	Population characteristics
Chung	2015	China	626	Diabetic patients
Kato	2010	Japan	194	Patients on chronic hemodialysis
Kato	2012	Japan	135	Patients on chronic hemodialysis
Kubota	2011	Japan	400	Patients with hypertension, diabetes, dyslipidemia
Kusunose	2016	Japan	114	At least 2 cardiovascular risk factors including hypertension, diabetes, dyslipidemia, smoking, or a history of CVD including myocardial ischemia, stroke, or heart failure
Laucevicius	2015	Lithuania	2106	Metabolic syndrome subjects without overt atherosclerotic disease
Otsuka	2014	Japan	211	CAD patients with impaired CAVI
Sato	2016	Japan	1003	Metabolic disorders including diabetes mellitus, hypertension, and dyslipidemia
Satoh-Asahara	2015	Japan	425	Obese Japanese outpatients consecutively enrolled in a multi-center study (obese defined as BMI ≥25)

Study	Age (y)	Male (%)	HTN (%)	Current smoking (%)	SBP	DBP	CVD (%)	Diabetes (%)	Follow-up (y)
Chung	64 ± 9	46	80	26	136 ± 15	80 ± 10	8	100	4.1
Kato	64 ± 12	65	–	19	139 ± 26	80 ± 15	20	20	3.3
Kato	60 ± 11	67	–	22	139 ± 23	83 ± 13	13	36	5.3
Kubota	69 ± 12	63	54	20	136 ± 19	–	0	58	2.3
Kusunose	69 ± 11	78	86	29	131 ± 19	75 ± 11	60	32	4.3
Laucevicius	54 ± 6	38	–	24	–	–	0	19	3.8
Otsuka	65 ± 10	56	73	26	145 ± 23	84 ± 10	100	55	2.9
Sato	63 ± 11	51	52	22	137 ± 22	81 ± 12	0	51	6.7
Satoh-Asahara	52 ± 14	45	62	17	140 ± 19	84 ± 12	0	49	5.0

BMI, body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; HTN, hypertension; SBP, systematic blood pressure.

studies, six reported significant associations between higher CAVI values and elevated CVD risk (Table 2).[14,17,19-22] Three studies examined total mortality as an outcome, and none of them found a significant association (Table 2).[14-16]

Four prospective studies examined CAVI as a continuous exposure for the risk of composite CVD.[18,19,21,22] The pooled HR for composite CVD per 1SD increment in CAVI value was 1.20 (95% CI: 1.05-1.36, $P = 0.006$, $I^2 = 0.0\%$) (Figure 2). Three studies allowed us to pool the estimates comparing the highest vs. lowest CAVI category,[14,16,17] and the pooled HR of composite CVD was not significant (1.34 [0.95-1.87], $P = 0.092$, $I^2 = 25.2\%$, $P = 0.263$; Figure 3). The three studies used different thresholds for high vs. reference CAVI (≥9-10 vs. <8-9, respectively). For total mortality, the pooled HR of two studies for highest vs. lowest CAVI category was 1.10 (0.85-1.43) (Figure S1).

3.1.3 | Cross-sectional studies

Of 17 cross-sectional studies[7,30-46] (n = 7,309) investigating CAVI values in patients with and without CVD (Table S3), 11 were from Japan,[7,33-38,41-44] two were from South Korea,[39,40] and the remaining studies were from China,[45] Thailand,[46] Turkey,[30] and Czech Republic.[31] Most studies were small, and only one study[46] had a sample size of more than 1,000 participants. The average age of participants ranged from 56 to 71 years.

Despite varying definitions of CVD across studies (Table S4), all 17 studies reported significant associations between CAVI and CVD (Table S5).[7,30,32,34-38,42-46] When we explored the 13 studies comparing CAVI values in individuals with and without CVD, the pooled mean difference in CAVI values was significantly positive at 1.28 (0.86-1.70) (Figure 4). This pattern was generally consistent for coronary heart disease[7,30,31,34-37,43,45,46] and stroke[42,43] (Table S5). The funnel plot for the mean difference in CAVI values against their standard errors did not indicate publication bias (Figure S2).

Three studies[34,35,38] evaluated the number of diseased coronary arteries and CAVI values, and all reported significantly higher CAVI values among those with two- or three-vessel disease compared with those without coronary artery stenosis (Figure S3). However, an evident dose-response relationship across one-, two-, and three-vessel disease was only shown in two studies.[34,38]

After removing the studies with low NOS score, the pooled HR for composite CVD (Figure S4) and the mean difference in CAVI

TABLE 2 Summary of prospective study results on the association between CAVI and outcomes

Study	Year	No. of events	CAVI categorization	Reference standard	HR (95% CI) for total mortality	HR (95% CI) for composite CVD
Chung	2015	98 CVD (24 death, 10 ACS, 34 stroke, and 42 coronary revascularization)	<9, ≥9	CAVI < 9	CAVI ≥ 9: Unadjusted HR 1.07 (0.82, 1.41)	CAVI ≥ 9: Unadjusted HR **1.23 (1.07, 1.42)** Adjusted HR[a] **1.18 (1.00, 1.38)**
Kato	2010	39 death (25 CV death), 15 non-fatal CVD	Tertiles: <8.3, 8.3-10.6, ≥10.7	1st tertile (CAVI < 8.3)	Unadjusted HR 2nd tertile 1.25 (0.54, 2.90) 3rd tertile 1.45 (0.64, 3.26)	Unadjusted HR 2nd tertile 0.61 (0.19, 1.96) 3rd tertile 1.34 (0.45, 4.02)
Kato	2012	32 death (22 CV death), 37 fatal and non-fatal CV events.	Tertiles: <8.0, 8.0-9.8, ≥9.9	1st tertile (CAVI < 8.0)	Unadjusted HR 2nd tertile 1.2 (0.5, 3.1) 3rd tertile 2.0 (0.9, 4.8)	Unadjusted HR for CVD mortality 2nd tertile 0.98 (0.28, 3.37) 3rd tertile 2.59 (0.91, 7.34) Adjusted HR[b] for CVD mortality 2nd tertile 0.69 (0.28, 1.70) 3rd tertile 1.51 (0.47, 4.85) Unadjusted HR for CVD events 2nd tertile 1.01 (0.40, 2.54) 3rd tertile 2.02 (0.90, 4.54) Adjusted HR[b] for CVD events 2nd tertile 0.91 (0.34, 2.44) 3rd tertile 1.50 (0.59, 3.84)
Kubota	2011	49 CVD (17 CAD, 32 strokes, no death)	<9, 9-9.9, ≥10	CAVI < 9		Adjusted HR[c] for CVD 9-9.9 1.47 (0.70, 3.08) ≥10 **2.11 (1.02, 4.38)** Adjusted HR[d] for CVD 9-9.9 1.38 (0.65, 2.97) ≥10 **2.25 (1.02, 4.95)**
Kusunose	2016	35 MACE	CAVI per SD	CAVI per SD		Unadjusted HR for MACE 1.12 (0.77, 1.63)
Laucevicius	2015	93 CVD (55 MI, 38 stroke)	CAVI per SD	CAVI per SD		Unadjusted HR **1.26 (1.03, 1.55)** Adjusted HR[e] 1.12 (0.9, 1.4)
Otsuka	2014	28 CVD (2 CV death, 4 non-fatal MI, 12 unstable angina, 5 recurrent angina pectoris requiring coronary revascularization, 5 stroke)	–	Normal CAVI		Adjusted HR[f] persistently impaired CAVI **3.3 (1.47, 8.59)** second CAVI **1.8 (1.18, 2.74)**
Sato	2016	46 death (6 CV death, 40 other causes), 90 CVD (41 MI, 20 unstable angina pectoris, 29 stable angina pectoris)	CAVI per 1 increment	CAVI per 1 increment		Adjusted HR[g] **1.126 (1.006, 1.259)**

(*Continues*)

values between those with and without CVD (Figure S5) remained essentially unchanged.

4 | DISCUSSION

This systematic review identified a total of 26 studies exploring the relationship between CAVI and CVD, and most of them explicitly investigated high CVD risk populations. Of note, most of the studies were relatively small (n < 1000) and performed in Asia. Nine were prospective studies, and their pooled results showed a modest association between CAVI and incident CVD events but not with all-cause mortality. Nonetheless, the follow-up time was generally short (mostly <5 years) probably because CAVI is a relatively new technique. In the 17 cross-sectional studies, CAVI values were higher in those with prevalent CVD than those without.

Study	Year	No. of events	CAVI categorization	Reference standard	HR (95% CI) for total mortality	HR (95% CI) for composite CVD
Satoh-Asahara	2015	15 CHD, 7 stroke, and 6 arteriosclerosis obliterans	CAVI per 1 increment	CAVI per 1 increment		Unadjusted HR **1.70 (1.32, 2.20)** Adjusted HR[h] **1.49 (1.04, 2.13)**

ACS, acute coronary syndrome; CAD, coronary artery disease; CAVI, cardio-ankle vascular index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MACE, major adverse cardiovascular events; SD, standard deviation. Kato 2010 and Kato 2012 studied the same population. Significant results are in bold.

Adjusted confounders:

[a]Sex, age, history of hypertension, dyslipidemia, smoking, peripheral arterial disease, family history of coronary heart disease, body mass index, known duration of diabetes, fasting plasma glucose, hemoglobin A1c, and serum creatinine level.

[b]age, gender and diabetes mellitus.

[c]Age and sex.

[d]Age, sex, smoking, hypertension, diabetes mellitus, dyslipidemia, and chronic kidney disease.

[e]Age, sex, fasting glucose.

[f]Diabetes, multi-vessel CAD, second baPWV.

[g]Gender, age, smoking, diabetes mellitus, hypertension, obesity (BMI ≥ 25 kg/m^2), and dyslipidemia.

[h]Age, gender, BMI, current smoking, and presence of hypertension, dyslipidemia, and diabetes.

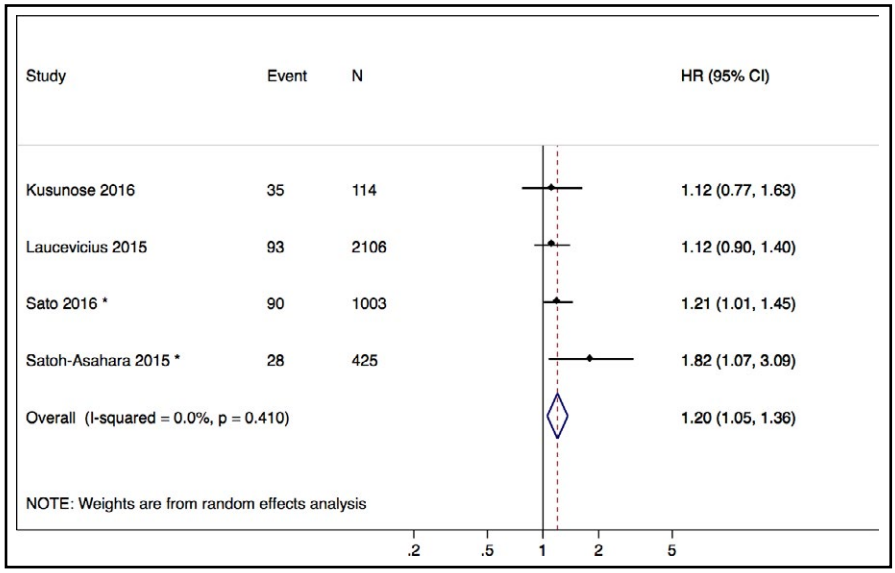

FIGURE 2 Hazard ratios (HR) of cardiovascular events for 1 standard deviation (SD) increment of cardio-ankle vascular index (CAVI). The bars/diamond and their width represent the HRs and the 95% CI, respectively. *Converted from HR per 1 increment

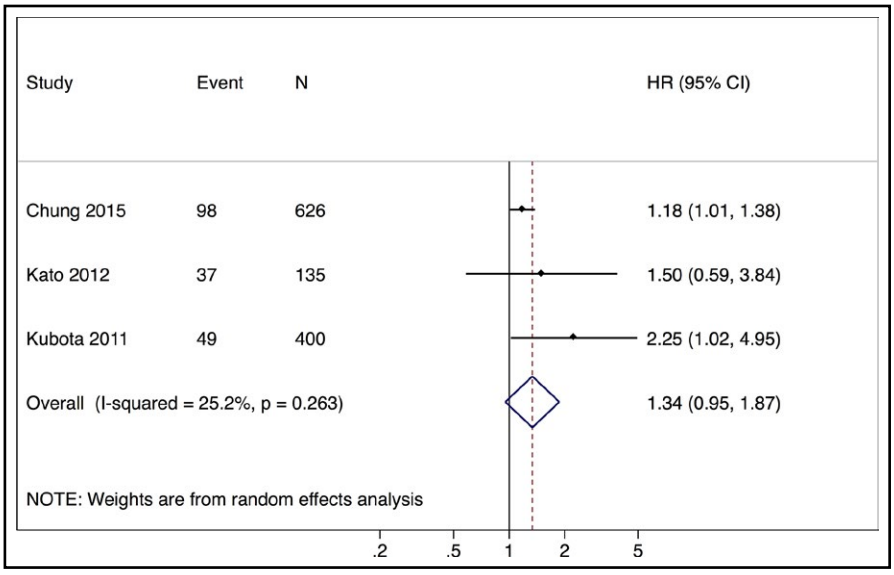

FIGURE 3 Hazard ratios (HR) of cardiovascular events for the highest vs. the lowest category of cardio-ankle vascular index (CAVI). Compared CAVI categories: ≥ vs <9 in Chung 2015; ≥9.9 vs <8.0 in Kato 2012; and ≥10 vs <9 in Kubota 2011

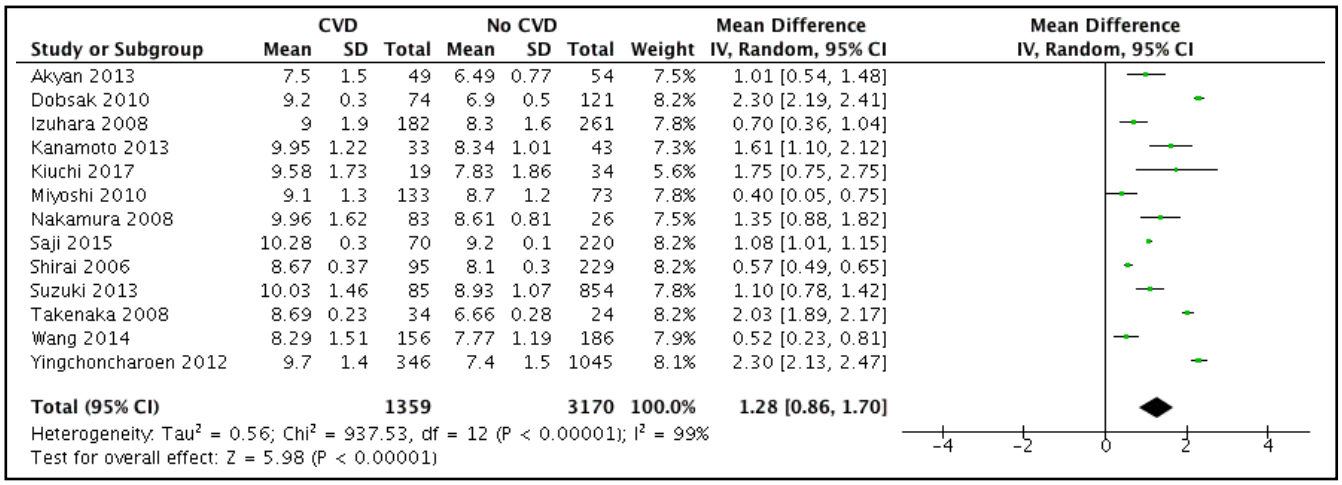

FIGURE 4 Mean difference in cardio-ankle vascular index (CAVI) among those with and without cardiovascular disease (CVD)

Since CAVI assesses arterial stiffness, an important pathophysiological aspect in the development of CVD, it is not surprising that prospective studies in our systematic review demonstrated more evident associations with CVD than with all-cause mortality. This pattern has been observed for other measures of arterial stiffness including cfPWV (currently considered the noninvasive reference standard measure of arterial stiffness).[2,47] Additionally, previous cross-sectional studies in our review consistently reported higher values of CAVI among patients with CVD than those without.

None of three studies in our review investigating CAVI and all-cause mortality found significant associations. This observation is in contrast to previous systematic reviews demonstrating significant associations of some arterial stiffness parameters, such as cfPWV[2] and brachial-ankle pulse wave velocity (baPWV),[48] with mortality. However, it should be noted that the three studies exploring the CAVI-mortality relationship investigated selected populations, such as patients on dialysis.[15,16] Therefore, large prospective studies with diverse study populations assessing the CAVI-mortality relationship are warranted.

CAVI is an alternative approach to measuring arterial stiffness, and it overcomes some drawbacks of measuring cfPWV. Specifically, the measurement of cfPWV can be time-consuming. Also, the acquisition of a good carotid and femoral artery pulses is generally operator dependent and is sometimes difficult for clinical staff.[49] Moreover, some patients may feel uncomfortable exposing the inguinal area during the test.[50] Furthermore, the carotid-femoral path does not include the ascending aortic segment, which may demonstrate the earliest changes during arterial aging and disease. In contrast, CAVI does not require a probe assessment in the groin and has little operator dependence. Other potential advantages of CAVI include reportedly being less influenced by the blood pressure at the time of measurement.[7] Also, CAVI may have superior reproducibility to PWV in several vascular beds.[7,51] CAVI reflects the stiffness from the ascending aorta to the ankle arteries and thus may be a comprehensive marker of systemic arterial stiffness.[11]

On the other hand, the inclusion of leg artery stiffness may be considered a caveat of CAVI since the elastic artery stiffness (ie, aortic stiffness), but not the muscular artery stiffness (ie, leg artery stiffness), appears to be independently associated with cardiovascular risk.[4] Therefore, the inclusion of muscular segments may not contribute much to the prognostic value of CAVI. Nonetheless, the practical implications of this issue in CVD risk assessments are still unclear and require future investigations. Also, we should keep in mind that several studies have reported that baPWV, a parameter of arterial stiffness including leg arteries, predicts CVD risk independently of traditional risk factors.[48]

There are some limitations in our study. Due to inconsistent methods of modeling/categorizing CAVI among studies, we could only pool HRs from a few studies for each outcome although we identified a total of nine prospective studies. Consequently, although some experts suggest a CAVI value of 8 or 9 as the appropriate cut-off value to separate low, medium, and high risk,[38,52-54] we could not meaningfully explore these categories in our study. Also, the cut-off values of the pooled studies were inconsistent. In addition, studies were mainly from Asian countries, limiting generalizability to other racial/ethnic groups. Finally, we did not include non-English studies.

To our knowledge, this is the first systematic review investigating the association of CAVI and CVD outcomes. CAVI was higher in patients with CVD than those without. In terms of the prospective prognostic value of CAVI, we found a limited number of studies, but they indicated a modest association between CAVI and CVD risk. Since most previous studies examined high CVD risk patients from Asia, future studies in the general population and in non-Asian countries are needed.

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CONFLICT OF INTEREST

KM received honorarium from Fukuda Denshi outside of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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