Prediction of Cardiovascular Events and All-Cause Mortality With Brachial-Ankle Elasticity Index

A Systematic Review and Meta-Analysis

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Abstract—Brachial-ankle elasticity index (baEI; also known as brachial-ankle pulse wave velocity) has been proposed as a surrogate end point for cardiovascular disease. We performed a meta-analysis of longitudinal cohort studies for determining the ability of baEI to predict risk of cardiovascular events and all-cause mortality and dissecting factors influencing this predictive ability. Multiple online databases, reference lists from retrieved articles, and abstracts from international cardiovascular conventions were searched until April 2012. Longitudinal cohort studies that reported associations of baEI with clinical risk were included. Of the 18 studies included (8169 participants; mean follow-up, 3.6 years), 15 reported results on total cardiovascular events (5544 individuals), 7 on cardiovascular mortality (2274 individuals), and 9 on all-cause mortality (5097 individuals). The pooled relative risks for total cardiovascular events, cardiovascular mortality, and all-cause mortality were 2.95 (95% CI, 1.63–5.33), 5.36 (95% CI, 2.17–13.27), and 2.45 (95% CI, 1.56–3.86), respectively, for subjects with high versus low baEI (all $P<0.001$). An increase in baEI by 1 m/s corresponded with an increase of 12%, 13%, and 6% in total cardiovascular events, cardiovascular mortality, and all-cause mortality, respectively. We conclude that baEI is associated with increased risk of total cardiovascular events and all-cause mortality. Issues such as expansion of data to non-Asian populations, validation of path length estimation, determination of reference values, and prospective comparison with carotid-femoral pulse wave velocity remain to be resolved. **(*Hypertension*. 2012;60:556-562.)** ● **Online Data Supplement**

Key Words: brachial-ankle pulse wave velocity ■ cardiovascular risk ■ cardiovascular disease ■ mortality ■ prediction ■ meta-analysis ■ arterial stiffness

Arterial stiffness is increasingly recognized as a surrogate end point for cardiovascular (CV) disease and is associated with presence of CV risk factors and atherosclerotic disease.[1] Arterial stiffness can be measured with noninvasive, reproducible, and relatively inexpensive techniques, and, thus, it is suitable for large-scale studies. Carotid-femoral pulse wave velocity (PWV; cfPWV) is considered the gold-standard method for assessing aortic stiffness[2] and predicts future CV events and all-cause mortality in a strong and independent manner.[3]

Brachial-ankle PWV, calculated as the ratio of the distance between the brachial and the tibial artery divided by the transit time between these 2 arteries, has been proposed as an additional arterial biomarker of CV risk. PWV is classically referred to "segmental stiffness." Because of the complexity of the anatomic course of the brachial-ankle arterial system, it is unclear whether the term brachial-ankle PWV is appropriate to define any particular segmental stiffness or whether it is just the ratio of a virtual brachial-ankle distance and the measurement of the brachial-ankle transit time. For this reason, this index will be referred to as the brachial ankle elasticity index (baEI) in the current article. Use of this index has been popularized primarily in East Asian countries over the past 13 years and has been shown in cross-sectional comparisons to be associated with CV risk factors and function, as well as CV disease (CVD), in a similar to cfPWV fashion.[4–8] A number of studies examined the ability of baEI to predict the risk of future CV events and total mortality. In addition, the Japanese guidelines for the management of hypertension suggested the measurement of cfPWV or baEI as a tool for assessment of subclinical target organ damage.[9]

Although baEI has been generally shown to have a predictive role based on the results of individual studies,[10–27] no overall quantitative estimate of this role exists. Furthermore, the studies that investigated the predictive role of baEI involved different populations. Moreover, the sizes of the

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populations studied were highly diverse and, thus, gave rise to dissimilar risk estimates. In addition, because most published studies yielded positive results, publication bias may have been involved. Finally, an important issue is whether the predictive ability of baEI extends beyond CV events. Accordingly, we conducted the present systematic review and meta-analysis with the primary aim to provide an overview of relevant cohort studies and to calculate robust quantitative estimates of the predictive value of baEI for different outcomes. Second, we investigated whether publication bias or quality of studies could have affected the true predictive ability of baEI. Third, we evaluated the effect of different baseline CV risk factors on the predictive ability of baEI.

Materials and Methods

The meta-analysis was conducted according to the checklist of the Meta-Analysis of Observational Studies in Epidemiology.[28] The outcomes of interest were as follows: (1) total CV events (CV deaths and nonfatal CV events); (2) CV mortality; and (3) all-cause mortality. We refer to the online-only Data Supplement for an expanded version of this section.

Data Sources and Searches

Studies evaluating relationships of baEI with the risk of future clinical events were drawn from a systematic review of the English and non-English literature in the PubMed, Cochrane, and Embase databases until April 2012. Reference lists from retrieved articles and abstracts from international CV conventions were also sought.

Study Selection

Studies were deemed eligible if they were full-length publications in peer-reviewed journals or abstracts in CV international conventions; evaluated baEI; and reported a combined CV outcome or CV mortality or all-cause mortality. Otherwise, no restriction criteria were imposed with regard to the type or the size of the population studied.

Data Extraction

The literature search, selection of studies, and extraction of data were done independently by 2 reviewers. Disagreements were resolved by consensus. For each study, we recorded a risk estimate for baEI. Numeric data appearing in the articles were used.

Quality Assessment

We evaluated the quality of the included studies by assessing selection bias, detection bias, and attrition bias.

Data Synthesis and Analysis

The risk estimates of each study were reported as a hazard ratio, relative risk (RR), odds ratio, or dichotomous frequency data. We treated hazard ratios as RRs. Because no uniform cutoff values are available for baEI, patients were allocated to the high baEI or low baEI group according to cutoffs provided by each study. When available, we used the adjusted risk estimates from multivariate models.

We performed meta-analyses of studies investigating baEI to obtain the pooled RRs separately for total CV events, CV mortality, and all-cause mortality. The proportion of inconsistency across studies not explained by chance was quantified with the I^2 statistic. Heterogeneity between subgroups was calculated with the Cochran Q test.[29] When significant heterogeneity ($P<0.05$) existed among studies, the random-effects model was used to obtain the pooled RRs. We also calculated adjusted RRs per absolute baEI difference (1 m/s) for all of the clinical end points in addition to the calculation of RR of high versus low stiffness groups in each study. Risk estimates between subgroups were compared with a test of interaction.[30] The RRs and CIs of individual studies were illustrated with forest plots. To estimate the contribution of continuous study moderators to the overall heterogeneity, we ran a metaregression analysis with fixed-effect estimates. The presence of publication bias was investigated graphically by funnel plots of precision, the Duval and Tweedie trim-and-fill method,[31] and the classic fail-safe N method. All of the analyses were performed with Comprehensive Meta Analysis version 2 (Biostat, Englewood, NJ).

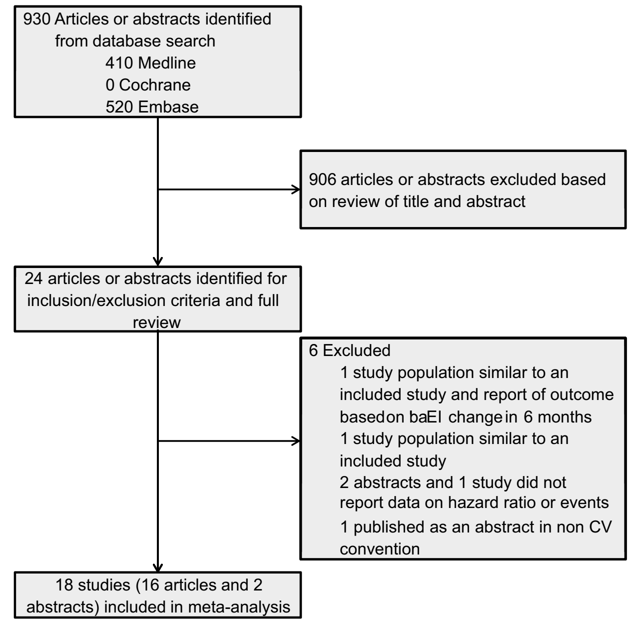

Figure 1. Flowchart of selection of studies for inclusion in meta-analysis.

Results

Literature Search

The results of the literature search are shown in Figure 1. We retrieved 930 articles from our preliminary search. Of these, 24 articles were identified for full review. After full review, 6 studies were excluded (Figure 1).[32–37]

Study Characteristics

Our meta-analysis included 16 original articles and 2 abstracts assessing relationships of baEI with total CV events, CV mortality, and all-cause mortality. In total, the included studies analyzed 8169 subjects. Details of the individual studies are shown in Table S1, available in the online-only Data Supplement. Of the 18 studies included (8169 participants; mean follow-up, 3.6 years), 15 reported results on total CV events (5544 individuals), 7 on CV mortality (2274 individuals), and 9 on all-cause mortality (5097 individuals).

Shape of the Association Between baEI and Clinical Events

Analysis of the 4 studies[16,18,20,23] reporting tertiles for all-cause mortality showed that the pooled RRs increase in a stepwise, linear-like fashion from the first to the third tertile (please see Figure S1).

Meta-Analysis

baEI and Total CV Events

The magnitude of risk for total CV events in individuals who had high baEI was significantly higher compared with the

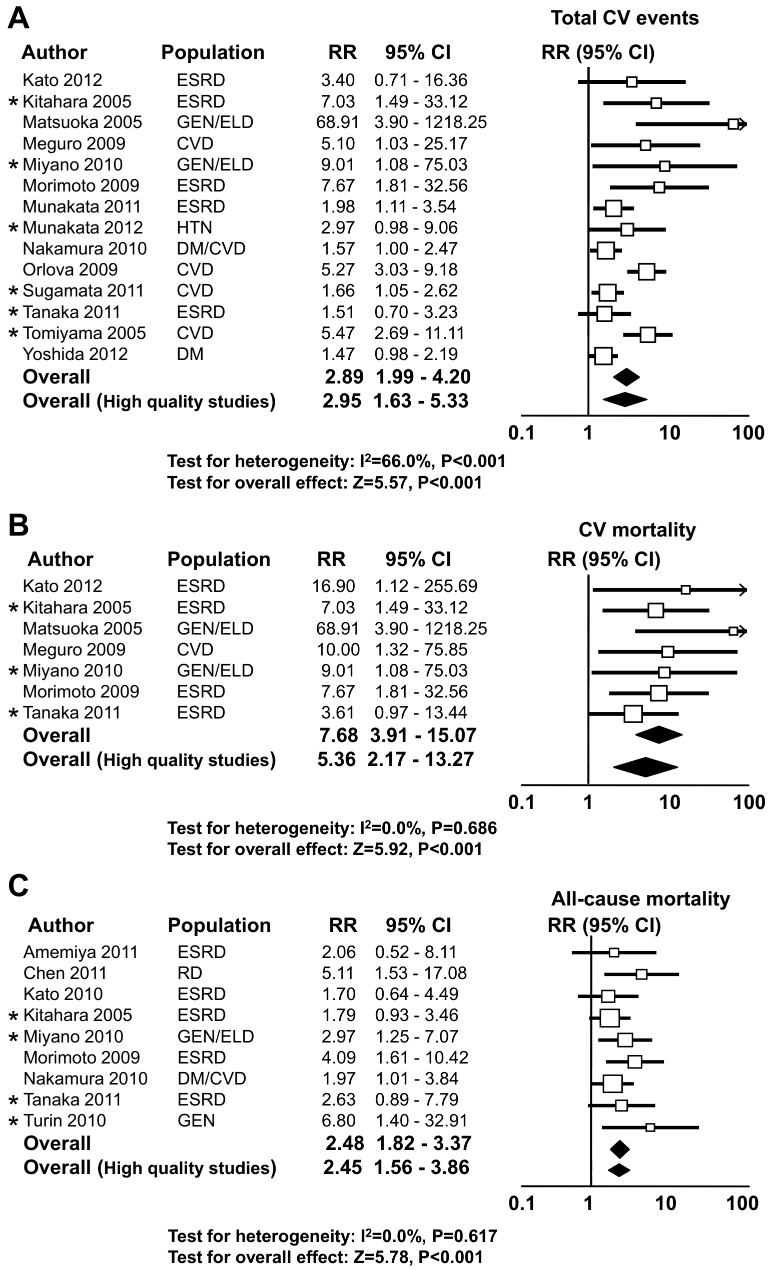

Figure 2. Relative risk (RR) and 95% CI for high brachial-ankle elasticity index (baEI) and clinical events. RR and 95% CI for high baEI and total cardiovascular (CV) events (**A**), CV mortality (**B**), and all-cause mortality (**C**). Studies are listed alphabetically. Boxes represent the RR and lines represent the 95% CI for individual studies. The diamonds and their width represent the pooled RRs and the 95% CI, respectively. CVD indicates cardiovascular disease; DM, diabetes mellitus; GEN, general population; ELD, elderly; ESRD, end-stage renal disease; RD, renal disease; HTN, hypertensives. *High quality studies.

risk of individuals with low baEI (RR, 2.89 [95% CI, 1.99–4.20]; Figure 2A). By applying a sensitivity analysis, we excluded low-quality studies based on our quality assessment, without significant changes in our final results for total CV events (RR, 2.95 [95% CI, 1.63–5.33]; $P<0.001$).

Because we observed significant heterogeneity ($I^2=66.0\%$; $P<0.001$) between the included studies, we conducted between-study subgroup analyses and found that the RR for high baEI varied between different populations (please see Figure S2). The pooled RR of total CV events for an increase in baEI by 1 m/s was 1.12 (95% CI, 1.05–1.19), corresponding with a risk increase of 12% ($Z=3.42$, $P=0.001$; $I^2=73.1\%$, $P=0.005$).[10,12,14,17,22]

To further investigate the incremental predictive role of baEI over and beyond baseline conventional risk factors, we performed a sensitivity analysis in which we included studies[11,16,20,24,26] that had adjusted for most (≥5 of 6) conventional risk factors, namely, age, sex, smoking, diabetes mellitus, dyslipidemia, or cholesterol levels and hypertension or blood pressure (as opposed to the remainder of the studies[10,12–15,17,19,25,27] that had adjusted for ≤4). RR in studies that adjusted for most CV risk factors[11,16,20,24,26] (RR, 2.01 [95% CI, 1.34–3.01] for studies that adjusted for most CV risk factors versus RR, 3.43 [95% CI, 2.02–5.81] for studies that adjusted for <5 CV risk factors) was lower to the overall combined estimated risk but still remained statistically significant and did not differ from the overall combined risk of studies that adjusted for <5 CV risk factors ($P=0.29$).

baEI and CV Mortality

The magnitude of risk in individuals who had high baEI was significantly higher compared with the risk of individuals with low baEI. The pooled RRs for baEI were 7.68 (95% CI, 3.91–15.07) for CV mortality (Figure 2B). By applying a sensitivity analysis, we excluded the low-quality studies based on our quality assessment, with the overall estimate for total CV events (RR, 5.36 [95% CI, 2.17–13.27]; $P<0.001$) becoming lower but still a significant one. The pooled RR of CV mortality for an increase in baEI by 1 m/s was 1.13 (95% CI, 1.06–1.20), corresponding with a risk increase of 13% ($Z=3.96$, $P<0.001$; $I^2=0.0\%$, $P=0.941$).[12,14,17]

In a sensitivity analysis similar to the one for total CV events, RR in studies that adjusted for most CV risk factors[11,16,20] (RR, 5.55 [95% CI, 2.17–14.22] for studies that adjusted for most CV risk factors versus RR, 10.82 [95% CI, 4.11–28.50] for studies[12–14,17] that adjusted for <5 CV risk factors) was lower to the overall combined estimated risk but still remained statistically significant and did not differ from the overall combined risk of studies that adjusted for <5 CV risk factors ($P=0.33$).

baEI and All-Cause Mortality

The magnitude of risk in individuals who had high baEI was significantly higher compared with the risk of individuals with low baEI. The pooled RRs were 2.48 (95% CI, 1.82–3.37) for all-cause mortality (Figure 2C). By applying a sensitivity analysis, we excluded low-quality studies based on our quality assessment, without significant changes in our final results for all-cause mortality (RR, 2.45 [95% CI, 1.56–3.86]; $P<0.001$). There was no significant difference in RR between different populations.

The pooled RR of all-cause mortality for an increase in baEI by 1 m/s was 1.06 (95% CI, 1.02–1.10), corresponding with a risk increase of 6% ($Z=2.81$, $P=0.005$; $I^2=0.0\%$, $P=0.732$).[14,17,21]

For additional sensitivity analyses regarding clinical end points please see the online-only Data Supplement.

Publication Bias

The funnel plot was asymmetrical at the bottom (please see Figure S3) for all of the clinical end points, suggesting an absence of small studies with small or negative risk estimates in our meta-analysis, either because of publication bias or because of a true inexistence of negative studies (absence of publication bias). The trim-and-fill method imputed missing studies and recalculated our pooled risk estimate. The imputed RRs were 2.42 (95% CI, 1.67–3.51), 5.93 (95% CI, 3.23–10.90), and 2.26 (95% CI, 1.68–3.05) for total CV events, CV mortality, and all-cause mortality, respectively, which are lower than our original risk estimates but are still significant. Importantly, the results of the fail-safe N test of our pooled analysis are 316, 63, and 76, respectively, which are reassuring. The fail-safe N test computes the number of missing studies (with a mean effect of 0) that would need to be added to the analysis to yield a statistically nonsignificant overall effect, and it is unlikely that there are >22 (316/14=22.6), 9 (63/7=9), and 8 (76/9=8.4) unpublished or undiscovered studies for every 1 study that we found for total CV events, CV mortality, and all-cause mortality, respectively. These findings suggest that the apparent publication bias is insufficient to affect our results or interpretations in a meaningful way.

Metaregression Analysis

Age at enrollment was not a predictor of the magnitude of the log RR for total CV events ($P=0.128$) in the whole population.[10–17,19,20,25,26] However, there were differences according to the group of patients studied. Specifically, age was inversely significantly related to the predictive role of high baEI for total CV events in end-stage renal disease (ESRD) patients[11,14,16,20,25] and CVD patients,[10,13,15,19] indicating that baEI is a stronger determinant of prognosis in younger ESRD and CVD patients ($P=0.029$ and $P=0.005$, respectively; please see Figure S4) The percentage of diabetics in 9 studies[10,11,13,14,16,17,19,20,27] showed a significant inverse association with the predictive value of high baEI ($P<0.001$; please see Figure S4). In particular, diabetes mellitus percentage was inversely significantly related to the predictive role of high baEI for total CV events in CVD patients,[10,13,19] indicating that baEI is a stronger determinant of prognosis in nondiabetics with CVD ($P=0.002$). In accordance, both hemoglobin A1c[14,17,19] and blood glucose[10,17,19,26] were inversely significantly related to the predictive role of high baEI for total CV events ($P=0.012$ and $P=0.004$, respectively).

Discussion

In this systematic review and meta-analysis, we pooled baEI data for 8169 subjects from 18 studies, who were followed up for a mean of 3.6 years. Our study is the first meta-analysis to investigate in a thorough manner the predictive role of baEI and to assess factors influencing this predictive ability. Our principal finding is that subjects with high baEI compared with patients with low baEI have 3-fold higher risk for total CV events, 5-fold higher risk for CV mortality, and 2.5-fold higher risk for all-cause mortality, respectively. An increase in baEI by 1 m/s corresponds with an increase of 12%, 13%, and 6% in total CV events, CV mortality, and all-cause mortality. Finally, the predictive ability of subjects with high baEI is higher in younger patients with ESRD and CVD and lower in diabetics.

Strengths and Limitations of the Present Meta-Analysis

Few narrative reviews[38] and editorials,[39] including the Japanese guidelines for management of hypertension, have commented on the possible predictive role of baEI. However, the present study is the first meta-analysis to provide robust pooled estimates of this role. An important strength of our study is the exhaustive search strategy that likely enabled us to capture most, if not all, relevant studies. Furthermore, as a meta-analysis, the present study overcomes the potentially biased inclusion and weighing of results that may appear in reviews when interpreting the available evidence. In addition, we dealt with the heterogeneous quality of studies, as well as with potential publication bias.

In the majority of studies, patients with high baEI were in most cases older, had higher blood pressure, and were more often diabetic or dyslipidemic. Thus, it is reasonable to assume that patients with high baEI were a priori at higher baseline risk than patients with low baEI patients. However, most prospective studies have dealt with this potential limitation by adjusting for the potential confounders between patients with low baEI and high baEI. Furthermore, as it was shown in our relevant sensitivity analysis, RR in studies that adjusted for most conventional risk factors was lower but not substantially different from the overall combined risk.

In this analysis, we used aggregate data as reported in published articles (or calculated from other data provided in the articles) rather than data for individual patients. Accordingly, we did not deal with potential methodologic problems of the original studies. Furthermore, the ability of baEI to discriminate, calibrate, and reclassify risk could not be assessed. None of the included studies provided robust estimates of the discriminatory and reclassification power of baEI beyond classic risk factors or Framingham risk score. Second, although CV mortality and all-cause mortality were uniformly defined, the definition of total CV events differed among the studies included in analysis. Third, it must be stressed that all but one[15] of the studies were conducted on Asian subjects, thus the application of our findings cannot be extrapolated to non-Asian subjects.

baEI: Clinical Implications

Our results support the potential of baEI as a biomarker of risk that can amalgamate the effect of CV factors on the arterial tree. Improvement of baEI either by pharmacological or lifestyle interventions, per se, might be beneficial in terms of prognosis in high-risk groups; however, such data are limited.[40] Mechanisms explaining its predictive value can be inferred by its associations with arterial and overall CV performance. baEI is associated with left ventricular function,[41] left ventricular hypertrophy,[6,42] and impaired coronary perfusion.[43] Furthermore, baEI is an independent predictor of longitudinal increases in BP, as well as of new onset of hypertension and microalbuminuria.[44,45]

An interesting finding of our analysis is that baEI is a predictor of all-cause mortality in addition to CV outcomes. Although pathophysiological explanations are not readily identifiable, this could reflect the existence of common pathogenetic mechanisms, such as inflammation, aging, and oxidative stress, over a wide range of conditions.

Further dissection of our findings provided interesting information. The predictive ability of baEI for clinical events is higher in younger patients with ESRD or CVD. Explanations may include a "selection" phenomenon, with ESRD and CVD survivors who reach an older age being less vulnerable to the harmful effects of arterial stiffening, as shown previously for cfPWV as well.[3] Nevertheless, identification of high baEI in younger patients may suggest the existence of an aggressive arterial disease.

baEI: Theoretical and Methodologic Considerations

Ease of use of the technique for measurement of baEI has assisted popularization of the technique. However, both theoretical and technical considerations exist.

Although baEI may predominantly be determined by central (elastic) artery stiffness, its values that are higher than cfPWV or PWV of the arteries of the upper and lower limbs[4,46] indicate that it may be determined by stiffness of distal peripheral arteries. Among parameters of arterial stiffness, aortic PWV was the primary independent correlate of baEI,[47] explaining 58% of the total variance in baEI, and an additional 23% of the variance was explained by femoral-ankle PWV.[48] Accordingly, the pertinent question is whether addition of segments of the arterial tree that differ markedly in terms of geometry, structure, and function, as well as the influence of age and sex,[49,50] adds to the predictive value of aortic stiffness or rather "dilutes" its predictive ability. Importantly, whereas aortic PWV has a proven predictive ability, this is not the case for the stiffness of upper or lower limb arteries.[51,52] Scarce data that compare baEI with cfPWV exist. Two cross-sectional studies showed that both predict prevalent CVD and CV complications.[4,5] Only 1 abstract investigated the prospective predictive role of both indices demonstrating a superiority of cfPWV.[33] It cannot be overemphasized that the 2 indices should not be used interchangeably, and large prospective studies should be conducted comparing the prognostic role of each.

Path length is calculated using anthropometric data (height-based formulas) rather than the actual "above the body" distances, and this may introduce error in terms of actual stiffness of an individual subject. Furthermore, anthropometric data are derived from a Japanese population, rendering the applicability to other populations questionable.[8,53,54] Inherent to this consideration is the need for the determination of reference values as has been done for cfPWV.[55]

Predictive ability may differ and applicability may be limited in specific conditions where arteries of smaller caliber are affected, such as in diabetes mellitus or in peripheral arterial disease, where the pressure wave may be delayed and distorted when traveling toward the periphery. In line with this, predictive value is lower in diabetics, as we showed in our analysis. Furthermore, in patients with low ankle-brachial index, baEI has shown inconsistent results, and for this reason several studies have excluded such patients.

Perspectives

Our findings showing that baEI predicts risk of total CV events and all-cause mortality are potentially applicable to clinical practice and call for extension to other disease states and population groups. Indeed, potential for a universal clinical applicability awaits prospective studies and standardized assessment of path length in non-Asian populations, as well as determination of reference values. Furthermore, it should be stressed that baEI cannot be used interchangeably with cfPWV, and prospective studies that compare these 2 indices are warranted.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Our study extends and integrates evidence from 18 studies (8,169 participants, mean follow-up 3.6 years), and it is the first to demonstrate that brachial-ankle elasticity index (baEI) is an independent predictor of clinical end points and the role of cardiovascular risk factors on the predictive ability of baEI.

What Is Relevant?

- Our findings are potentially applicable to clinical practice and call for extension to other disease states and population groups.

Summary

baEI is associated with increased risk of total cardiovascular events and all-cause mortality. Issues such as expansion of data to non-Asian populations, validation of path length estimation, determination of reference values and prospective comparison with carotid-femoral pulse wave velocity remain to be resolved.