Title

Ankle-brachial index and subsequent risk of incident and recurrent cardiovascular events in older adults: The Atherosclerosis Risk in Communities (ARIC) study

Authors

Wang, Frances M
Yang, Chao
Ballew, Shoshana H
et al.

Publication Date

2021-11-01

DOI

10.1016/j.atherosclerosis.2021.09.028

Peer reviewed

HHS Public Access

Author manuscript

Atherosclerosis. Author manuscript; available in PMC 2022 November 01.

Published in final edited form as:

Atherosclerosis. 2021 November ; 336: 39–47. doi:10.1016/j.atherosclerosis.2021.09.028.

Ankle-brachial index and subsequent risk of incident and recurrent cardiovascular events in older adults: The Atherosclerosis Risk in Communities (ARIC) study

Frances M. Wang[1], **Chao Yang**[1], **Shoshana Ballew**[1], **Corey A. Kalbaugh**[2], **Michelle L. Meyer**[3], **Hirofumi Tanaka**[4], **Gerardo Heiss**[3], **Matthew Allison**[5], **Maya Salameh**[1], **Josef Coresh**[1], **Kunihiro Matsushita**[1]

[1]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA

[2]Clemson University, Clemson, SC, USA

[3]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[4]University of Texas at Austin, Austin, TX, USA

[5]University of California San Diego, San Diego, CA, USA

Abstract

Background and aims: The ankle-brachial index (ABI) is a diagnostic test for screening for and/or detecting peripheral artery disease (PAD), as well as a risk enhancer in the AHA/ACC guidelines on the primary prevention of atherosclerotic cardiovascular disease (ASCVD). However, our understanding of the association between ABI and cardiovascular risk in contemporary older populations is limited. Additionally, the prognostic value of ABI among individuals with prior ASCVD is not well understood.

Address for Correspondence: Kunihiro Matsushita, 2024 E. Monument Street, Suite 2-600, Baltimore, Maryland 21287, kuni.matsushita@jhu.edu.

CRediT author statement

Frances M. Wang: Conceptualization, Methodology, Formal analysis, Data Interpretation, Writing - Original Draft, Writing - Review & Editing, Visualization.
Chao Yang: Conceptualization, Formal analysis, Data Interpretation, Writing - Review & Editing.
Shoshana Ballew: Data Interpretation, Writing - Review & Editing.
Corey A. Kalbaugh: Data Interpretation, Writing - Review & Editing.
Michelle L. Meyer: Data Interpretation, Writing - Review & Editing.
Hirofumi Tanaka: Data Collection, Data Interpretation, Writing - Review & Editing.
Gerardo Heiss: Data Collection, Data Interpretation, Writing - Review & Editing.
Matthew Allison: Data Interpretation, Writing - Review & Editing.
Maya Salameh: Data Interpretation, Writing - Review & Editing.
Josef Coresh: Data Collection, Data Interpretation, Resources, Interpretation, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.
Kunihiro Matsushita: Conceptualization, Methodology, Investigation, Resources, Data Collection, Data Interpretation, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interests

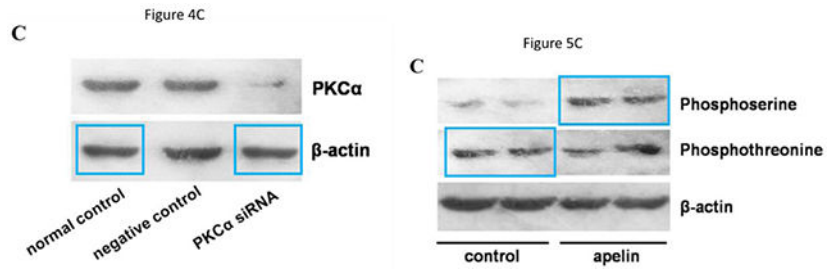
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Methods: Among 5,003 older adults at ARIC visit 5 (2011-2013) (4,160 without prior ASCVD [median age 74 years, 38% male], and 843 with ASCVD [median age 76 years, 65% male]), we quantified the association between ABI and the risk of heart failure (HF), and composite coronary heart disease and stroke (CHD/stroke) using multivariable Cox regression models.

Results: Over a median follow-up of 5.5 years, we observed 400 CHD/stroke events and 338 HF cases (242 and 199 cases in those without prior ASCVD, respectively). In participants without a history of ASCVD, a low ABI ≤0.9 (relative to ABI 1.11-1.20) was associated with both CHD/stroke and HF (adjusted hazard ratios 2.40 [95% CI: 1.55-3.71] and 2.23 [1.40-3.56], respectively). In those with prior ASCVD, low ABI was not significantly associated with CHD/stroke, but was with HF (7.12 [2.47-20.50]). The ABI categories of 0.9-1.2 and >1.3 were also independently associated with increased HF risk. Beyond traditional risk factors, ABI significantly improved the risk discrimination of CHD/stroke in those without ASCVD and HF, regardless of baseline ASCVD.

Conclusions: Low ABI was associated with CHD/stroke in those without prior ASCVD and higher risk of HF regardless of baseline ASCVD status. These results support ABI as a risk enhancer for guiding primary cardiovascular prevention and suggest its potential value in HF risk assessment for older adults.

Graphical Abstract



Keywords

ankle-brachial index; atherosclerotic cardiovascular disease; older adults; risk assessment

1. Introduction

The ankle-brachial index (ABI), the ratio of systolic blood pressure in the ankle to that of the arm, is a simple procedure for detecting peripheral artery disease (PAD).[1] In addition to its value in identifying PAD, a low ABI has also been repeatedly shown as a strong, independent predictor of atherosclerotic cardiovascular disease (ASCVD) and mortality.[2–4] Accordingly, the American Heart Association/American College of Cardiology (AHA/ACC) clinical guidelines list ABI ≤0.9 as a risk enhancer to refine predicted ASCVD risk and guide primary prevention among individuals without a history of ASCVD.[5, 6]

However, there are limitations in our understanding of the prognostic value of ABI for cardiovascular disease (CVD) in older adults. Although stroke and CHD have been extensively investigated in this context,[7–9] the association of ABI values with heart failure

(HF) in older adults, one of the most common adverse CVD outcomes in this population, is understudied.[10] Also, to our knowledge, no studies have evaluated whether ABI can predict CVD outcomes in older adults with prior ASCVD,[6, 10, 11] despite the high prevalence of older adults with a history of this condition. These are crucial knowledge gaps since the importance of risk classification for HF outcomes and for patients with prior ASCVD is sharply increasing[6] due to the availability of effective new therapies such as SGLT2 inhibitors and PCSK9 inhibitors.

Thus, in this study, we evaluated the association between ABI and risk of CVD outcomes, including HF, in a contemporary cohort of community-dwelling older adults, both with and without prevalent ASCVD. We also assessed whether ABI could improve risk prediction of CVD outcomes beyond traditional ASCVD predictors.

2. Patients and methods

2.1 Study population and design

The Atherosclerosis Risk in Communities (ARIC) Study is a community-based cohort of 15,792 participants aged 45 to 64 years at visit 1 during 1987-1989.[12] Participants were recruited from four communities in the United States (Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland). Our analysis used data from ARIC visit 5 (2011-2013), since this was the first visit that measured ABI in both legs and was the first visit after 2000.

Among the 6,538 participants at visit 5, we excluded participants with race other than Black or White (n=18), missing ASCVD history (n=107), missing ABI (n=801), and missing baseline covariates (n=609), yielding a final study population of 5,003 participants. This study was approved by the Institutional Review Board of all centers involved in the study, including the field centers, coordinating center, and central laboratories. Informed consent was obtained from all participants.

2.2 Collection of baseline information

Demographic and behavioral information was collected by a trained interviewer. Age, sex, race, education, income, and smoking status were self-reported. Participants were asked to bring their medications to the study visit, which were coded by trained study personnel. Education and family income were collected at visit 1. All other variables were collected at visit 5.

Brachial artery blood pressure was measured three times in sitting position after a 5-minute rest period by certified technicians using an automatic sphygmomanometer (OMRON HEM-907 XL), and the average of the last two readings was recorded. Blood sample collection was performed during the study visit using a standardized protocol.[13] Total cholesterol and high-density lipoprotein cholesterol (HDL-C) were determined according to standards set by the National Cholesterol Education Program.[14] Diabetes mellitus was defined as a fasting glucose ≥7.0 mmol/L, non-fasting glucose ≥11.1 mmol/L, self-reported diagnosis of diabetes by a physician, or use of antidiabetic medications. Body mass index (BMI) was calculated as weight divided by height squared.

2.3 Definition of baseline ASCVD status

In accordance to the AHA/ACC 2018 cholesterol management guidelines, prevalent ASCVD at baseline included coronary heart disease (CHD) (myocardial infarction or coronary revascularization), stroke, and symptomatic peripheral artery disease (PAD).[6] History of ASCVD was based on self-report at ARIC visit 1 (1987-1989) and any relevant events between visits 1 and 5 (2011-2013) were identified through active surveillance.[12] CHD and stroke events were adjudicated by the ARIC Morbidity and Mortality Classification Committee, as detailed below. PAD was based on hospitalization records and International Classification of Diseases (ICD)-9 codes according to prior literature.[15]

2.4 Ankle-brachial index measurement

Using an automatic oscillometric device (OMRON VP-1000 plus (Kyoto, Japan)), and at five minute intervals, resting systolic blood pressures were measured with the participant in the supine position, twice for each arm and ankle. For each side, ABI was calculated as the ratio of ankle systolic blood pressure to brachial systolic blood pressure, using the higher measurement of the respective right or left brachial systolic blood pressure as the denominator. The average of the two ABI measurements for each leg was recorded. The lower ABI of the right and left measures was generally used in this analysis; however, if the higher ABI measure was greater than 1.3 and the lower ABI was normal (1.0-1.3), we used the higher ABI value (>1.3) in our analysis to avoid eliminating potential information on arterial non-compressibility.[16]

2.5 Cardiovascular outcomes during follow-up

Primary outcomes of interest were CHD, stroke, and acute decompensated HF that occurred from baseline (visit 5, 2011-2013) to December 31, 2017, which were identified based on annual participant telephone follow-up, hospitalization records, and death certificate data adjudicated by a physician panel. CHD was defined as 1) definite coronary death and 2) definite or probable myocardial infarction.[17] Stroke was defined as definite and probable stroke.[18] Given that CHD and stroke are atherosclerotic subtypes, we primarily analyzed them together (CHD/stroke) but also examined them individually in secondary analyses. We defined HF as cases classified as definite or probable acute decompensated HF.[19] In secondary analyses, we defined HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) as ejection fraction <50% and ≥50%, respectively.

2.6 Statistical analysis

We stratified the participants into those with and without a history of ASCVD for all analyses. Baseline characteristics of each group were assessed by ABI category (≤0.90, 0.91-1.00, 1.01-1.10, 1.11-1.20, 1.21-1.30, or >1.30). The association between continuous ABI and incidence rates of CHD/stroke and HF outcomes after adjustment for age, sex, and race were evaluated using Poisson regression models with 5-knot restricted cubic splines (knots at the 5^{th}, 27.5^{th} , 50^{th}, 72.5^{th}, and 95^{th} percentile[20]). We used multivariable Cox proportional hazards models to quantify the association between ABI categories and subsequent risk of CHD/stroke and HF, after adjusting for traditional CVD risk factors.[21]

The ABI category with the lowest risk was selected as a reference. In secondary analyses, we evaluated the associations between ABI with each CHD, stroke, HFpEF, and HFrEF separately.

To determine whether the association between ABI and both CHD/stroke and HF were consistent across demographic and clinical subgroups, we conducted stratified analyses and tested for interaction by age (<75 and ≥75), sex, race, HF history (for CHD/stroke), diabetes, hypertension, and current smoking status. For these subgroup analyses, we modeled ABI by every 0.1-unit decrement after excluding participants with ABI >1.30, since we observed a J-shaped association between ABI and CVD as presented below.

Harrell's C-statistic and the categorical net reclassification index (NRI) were used to determine whether ABI improved risk discrimination of each of the outcomes beyond traditional predictors. For the categorical NRIs, in those without ASCVD history, we used risk cutoffs of 2.5%, 3.75%, and 10% (half of the 10-year risk cutoffs in the AHA/ACC cholesterol clinical guidelines[22] since the median follow-up of this study was ~5 years) for CHD/stroke, and halved the risk cutoffs respectively for individual CHD and stroke outcomes, accordingly. Based on the similar total number of events between CHD/stroke and HF, we applied the same cutoffs for CHD/stroke on HF. In those with a history of ASCVD, we tripled the risk cutoffs used in those without history of ASCVD, according to the ~3-times higher incidence rate of CVD outcomes in this population from our data. In secondary analyses, we also evaluated the added value of ABI over predicted risk based on the 10-year ASCVD risk calculated from the AHA/ACC Pooled Cohort Equation (PCE).[23]

Two-sided *p*-values <0.05 were considered statistically significant, and 95% confidence intervals were reported. All analyses were performed using Stata version 16.1 (StataCorp LP, College Station, Texas) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

At baseline, there were 4,160 participants without ASCVD (median age 74 years and 38% males) and 843 participants with ASCVD (median age 76 years, 65% males). In participants without a history of ASCVD, 5.8% had an ABI ≤0.9, 8.9% had an ABI 0.91-1.00, and 8.5% had an ABI >1.30. The corresponding estimates of participants with an ASCVD history were 15.4%, 11.2%, and 10.8%, respectively. Regardless of the baseline status of ASCVD, participants with lower ABI tended to be Black, on cholesterol medication, current smokers, have less education, and have lower family income (Table 1). Additionally, in those without a history of ASCVD, participants with lower ABI tended to be diabetic and on hypertension medication. Across both ASCVD groups, those with an ABI >1.30 were more likely to be male and White.

Over a median follow-up of 5.5 years, we observed 400 CHD/stroke and 338 HF events (242 CHD/stroke and 199 HF cases in those without prior ASCVD). Regardless of baseline ASCVD history, there was a J-shaped association between ABI and demographically-adjusted incidence rate of CHD/stroke and HF (Figure 1). In those without ASCVD, the

risk gradients between low ABI <0.9 and normal ABI were ~2-fold for both CHD/stroke and HF (Figure 1A and B). However, in those with a history of ASCVD, the risk gradient was greater for HF (~5-fold as shown in Figure 1D) than for CHD/stroke (~2-fold in Figure 1C). The lowest incidence rates of CHD/stroke and HF were observed around ABI 1.20 in participants without history of ASCVD and between ABI 1.21-1.30 in those with history of ASCVD. These associations remained largely consistent when separately analyzing CHD and stroke rates across ABI (Supplemental Figure 1).

After accounting for traditional CVD risk factors, in those without a history of ASCVD, low ABI (≤0.9) was significantly associated with a 2-fold increased risk of both CHD/stroke and HF, relative to ABI 1.11-1.20 (Table 2). For CHD/stroke, even the borderline low ABI 0.91-1.00, as well as ABI 1.01-1.10, had an adjusted hazard ratio of ~1.5 for CHD/stroke (1.50 [95% CI 0.94-2.40] and 1.45 [1.04-2.02], respectively). However, high ABI >1.30 was not significantly associated with an increased risk of CHD/stroke and HF.

In those with a history of ASCVD, adjusting for traditional CVD risk factors, there were no evident associations between ABI and risk of CHD/stroke. However, ABI was robustly associated with HF. Specifically, a low ABI showed adjusted hazard ratio for HF of 7.12 (95% CI 2.47-20.50), relative to ABI 1.21-1.30. Borderline low ABI 0.91-1.00 and even ABI 1.01-1.20 were also significantly associated with increased risk of HF (6.55 [2.24-19.17] and 4.81 [1.68-13.75], respectively). On the other end of the ABI spectrum, high ABI >1.30 was also associated with an increased adjusted hazard ratio of HF (3.12 [1.00-9.73]).

When we assessed CHD and stroke separately, the results remained wholly consistent with the aforementioned findings, but low ABI appeared to be more strongly associated with incident CHD than stroke in those without history of ASCVD (Supplemental Table 1). After categorizing HF into HFpEF and HFrEF, and despite limited statistical power, results were also similar across HF type (Supplemental Table 2). The results were also generally consistent when using a broader reference category of ABI 1.01-1.30 and breaking down the ≤0.9 by 0.1 increments (Supplemental Table 3). Sensitivity analyses adjusting additionally for 3-level smoking status (current, former, never) and additional types of medications (i.e., lipid lowering medication and aspirin) yielded consistent results (Supplemental Table 4).

The associations between ABI with CHD/stroke and HF were mostly consistent within subgroups, including sex and smoking. For CHD/stroke outcomes, the only significant interactions were found in subgroups without a history of ASCVD, where the association between ABI and CHD/stroke was stronger in those who were Black, had diabetes, and had hypertension compared to their counterparts (Figure 2). When examining subgroup associations for HF, the only significant interaction was found by age in those without ASCVD history, where the association between ABI and HF was stronger in age <75 than in age ≥75 (Figure 3). No significant subgroup interactions were identified in those with history of ASCVD.

In our study population, the C-statistics of base models with traditional CVD predictors ranged from 0.61-0.70 for CHD/stroke and HF (Table 3). Adding ABI to these models significantly improved the C-statistics for both CHD/stroke and HF in those without

ASCVD. A significantly positive NRI was also seen for CHD/stroke. Overall, the prediction improvement was most evident for CHD in this population. For those with ASCVD, ABI significantly improved the C-statistic for prediction of HF but not CHD/stroke. However, NRIs were significantly positive for both CHD/stroke and HF in this population. Largely consistent results were observed when evaluating the predictive improvement of adding ABI to calculated ASCVD risk in participants without history of ASCVD (Supplemental Table 5).

4. Discussion

In this large prospective cohort study of community-dwelling older adults, we observed that low ABI (≤0.9), diagnostic of PAD, was independently associated with both incident CHD/stroke and HF in those without ASCVD. Even a borderline low ABI (0.91-1.00) and an ABI 1.01-1.10 conferred an ~50% increase in the risk of CHD/stroke in this population. Additionally, in those with a history of ASCVD, low ABI, borderline low ABI (0.91-1.00), and an ABI 1.01-1.10 (*vs.* 1.21-1.30) were robustly and independently associated with a higher risk of HF but not necessarily recurrent ASCVD. Notably, the high ABI group also tended to have a greater risk of CVD, though the results were only statistically significant for HF outcomes in the ASCVD group. These associations were largely similar across demographic and clinical subgroups. The addition of ABI beyond traditional predictors significantly improved the risk prediction of CHD/stroke and HF in participants with and without ASCVD, but the improvement was most evident for CHD in those without ASCVD and for HF in those with ASCVD.

Our findings on the contemporary associations between ABI and incident CHD/stroke in the older adult population without history of ASCVD are consistent with earlier studies from the 1980s-1990s.[7–9] Since the medical environment has changed substantially in the last few decades (e.g. increased statin use and prevalence of diabetes and general improvements in medical therapy), our contemporary study is of value in the era of modern medicine.[10, 24, 25] Additionally, in this population, we identified an elevated risk of CHD/stroke in those with borderline low ABI (0.91-1.00) and even ABI 1.01-1.10. In the context of primary prevention, these results support the value of low ABI as a cardiovascular risk enhancer, as recommended in the 2018 AHA/ACC Guideline on the Management of Blood Cholesterol.[6] Our results also highlight the prognostic value of borderline ranges of ABI.

Additionally, this study identified a robust association between PAD and HF in community-dwelling older adults, regardless of ASCVD history. This observation is consistent with a few prior studies showing the association between PAD and the subsequent risk of incident HF.[8, 26] Several theories on the physiological link between PAD and HF can be considered. For example, there is evidence that PAD represents complex pathophysiology of both micro- and macro-vascular diseases,[27–29] which may indicate similar processes in the myocardium thereby predisposing the development of subsequent HF.[30, 31] Indeed, the involvement of microvascular disease has been shown to play an important role in cardiac diastolic dysfunction.[31] Likewise, low ABI is a marker of systemic atherosclerosis which can contribute to the development of heart failure.[32] Additionally, PAD has been associated with reduced left ventricular ejection fraction.[33] Since the value of classifying HF risk is

sharply increasing due to SGLT2 inhibitors, ABI can inform the risk classification of HF in older adults.

The elevated risk of cardiovascular outcomes according to high ABI has been reported in several previous studies, presenting a J-shaped association between ABI and adverse outcomes.[34, 35] There are a few plausible mechanisms behind this observation. High ABI often results from uncompressible ankle arteries due to medial calcification and thus can represent systemic arterial stiffness and vascular aging.[32] Also, a high prevalence of significant lower extremity obstructive disease has been reported in individuals with a high ABI.[36] In our contemporary cohort of older adults, a high ABI was significantly associated with an increased risk of HF only in those with history of ASCVD. This may reflect the importance of vascular-ventricular coupling for the development of HF in this high-risk population. Although a high ABI is not recognized as a risk enhancer in current AHA/ACC clinical guidelines, our results suggest high ABI as a potential indicator of HF risk in the ASCVD population.

There are several limitations of our study. First, for calculating ABI, we measured systolic blood pressures using an oscillometric device, which has been reported to result in potential misclassification compared to the currently recommended Doppler probe approach.[37] This seems likely to overall weaken the observed association in our study. On the other hand, the use of an oscillometry-derived ABI has been previously validated and potentially has more clinical and research scalability due to its ease of use.[37] Second, there was a relatively small number of participants with a history of ASCVD. As such, some of the effect estimates had wide confidence intervals and were conservative in terms of statistical significance. Third, since this study was conducted in a bi-racial cohort, generalizability of these results to other racial or ethnic groups is limited. Fourth, despite efforts to adjust for important covariates, there may be residual confounding, and we cannot be certain about the direction of bias. Also, participants who were sicker or had worse PAD and higher risk of CVD were less likely to attend the relevant study visit, which would lead to an underestimation of the true association of ABI with CVD risk.

On the other hand, there are also several strengths of this study, including 1) a large overall sample size which can increase precision, 2) contemporary multi-racial cohort that is more generalizable to current clinical settings compared to prior studies from the 1980-1990s where the clinical patterns were quite different, 3) standardized data collection and outcomes adjudication which reduce imprecision/random error of our study variables, and 4) active surveillance for outcome ascertainment, reducing the potential for selection bias from loss to follow-up.

In conclusion, in a contemporary cohort of community-based older adults, lower ABI was consistently and robustly associated with an increased risk of CHD/stroke in those without prevalent ASCVD and with HF regardless of ASCVD history. These findings support the use of low ABI as a risk enhancer in helping guide primary prevention for CHD/stroke and suggest that ABI may be a strong, non-invasive predictor for assessing HF risk in older adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank the staff and participants of the ARIC study for their important contributions.

Financial support

The ARIC study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), Department of Health and Human Services, under contract numbers HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, and HHSN268201700004I. F.W. received support from the NIH T32 institutional training grant (T32 HL007024).

References

[1]. Gerhard-Herman MD, Gornik HL, Barrett C, et al. , 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, J Am Coll Cardiol, 2017;69:e71–e126. [PubMed: 27851992]

[2]. Vogt MT, McKenna M, Wolfson SK, et al. , The relationship between ankle brachial index, other atherosclerotic disease, diabetes, smoking and mortality in older men and women, Atherosclerosis, 1993;101:191–202. [PubMed: 8379964]

[3]. Criqui MH, McClelland RL, McDermott MM, et al. , The ankle-brachial index and incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis), J Am Coll Cardiol, 2010;56:1506–1512. [PubMed: 20951328]

[4]. Resnick HE, Lindsay RS, McDermott MM, et al. , Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study, Circulation, 2004;109:733–739. [PubMed: 14970108]

[5]. Arnett DK, Blumenthal RS, Albert MA, et al. , 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines, Circulation, 2019;140:e596–e646. [PubMed: 30879355]

[6]. Grundy SM, Stone NJ, Bailey AL, et al. , 2018 AHA/ACC/AACVPR/AAPA/ABC/ ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol, Circulation, 2018:CIR0000000000000625.

[7]. Murabito JM, Evans JC, Larson MG, et al. , The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham Study, Arch Intern Med, 2003;163:1939–1942. [PubMed: 12963567]

[8]. Newman AB, Shemanski L, Manolio TA, et al. , Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group, Arterioscler Thromb Vase Biol, 1999;19:538–545.

[9]. Abbott RD, Rodriguez BL, Petrovitch H, et al. , Ankle-brachial blood pressure in elderly men and the risk of stroke: the Honolulu Heart Program, J Clin Epidemiol, 2001;54:973–978. [PubMed: 11576807]

[10]. Virani SS, Alonso A, Benjamin EJ, et al. , Heart Disease and Stroke Statistics—2020 Update: A Report From the American Heart Association, Circulation, 2020; 141:e139–e596. [PubMed: 31992061]

[11]. Curry SJ, Krist AH, Owens DK, et al. , Screening for Peripheral Artery Disease and Cardiovascular Disease Risk Assessment With the Ankle-Brachial Index: US Preventive Services Task Force Recommendation Statement, JAMA, 2018;320:177–183. [PubMed: 29998344]

[12]. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators, Am J Epidemiol, 1989;129:687–702. [PubMed: 2646917]

[13]. Papp AC, Hatzakis H, Bracey A, et al. , ARIC hemostasis study--I. Development of a blood collection and processing system suitable for multicenter hemostatic studies, Thromb Haemost, 1989;61:15–19. [PubMed: 2526384]

[14]. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report, Circulation, 2002;106:3143–3421. [PubMed: 12485966]

[15]. Matsushita K, Kwak L, Yang C, et al. , High-sensitivity cardiac troponin and natriuretic peptide with risk of lower-extremity peripheral artery disease: the Atherosclerosis Risk in Communities (ARIC) Study, Eur Heart J, 2018;39:2412–2419. [PubMed: 29579246]

[16]. ARIC Manual 2 Home and Field Center Procedures ARIC Visit 5 and NCS Study Protocol. 2013 [cited 2021 Apr. 13]; Available from: https://sites.cscc.unc.edu/aric/sites/default/files/public/manuals/Manual%202%20Home%20and%20Field%20Center%20Procedures.pdf, In.

[17]. White AD, Folsom AR, Chambless LE, et al. , Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience, J Clin Epidemiol, 1996;49:223–233. [PubMed: 8606324]

[18]. Rosamond WD, Folsom AR, Chambless LE, et al. , Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort, Stroke, 1999;30:736–743. [PubMed: 10187871]

[19]. Rosamond WD, Chang PP, Baggett C, et al. , Classification of heart failure in the atherosclerosis risk in communities (ARIC) study: a comparison of diagnostic criteria, Circ Heart Fail, 2012;5:152–159. [PubMed: 22271752]

[20]. Harrell FE Jr, Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis, Springer, 2015.

[21]. Newson R, Confidence intervals for rank statistics: Somers' D and extensions, The Stata Journal, 2006;6:309–334.

[22]. Grundy SM, Stone NJ, Bailey AL, et al. , 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, J Am Coll Cardiol, 2019;73:e285–e350. [PubMed: 30423393]

[23]. Goff DC, Lloyd-Jones DM, Bennett G, et al. , 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, J Am Coll Cardiol, 2014;63:2935–2959. [PubMed: 24239921]

[24]. Salami JA, Warraich HJ, Valero-Elizondo J, et al. , National Trends in Nonstatin Use and Expenditures Among the US Adult Population From 2002 to 2013: Insights From Medical Expenditure Panel Survey, J Am Heart Assoc, 2018;7.

[25]. Qato DM, Wilder J, Schumm LP, et al. , Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs 2011, JAMA Intern Med, 2016;176:473–482. [PubMed: 26998708]

[26]. Gupta DK, Skali H, Claggett B, et al. , Heart failure risk across the spectrum of ankle-brachial index: the ARIC study (Atherosclerosis Risk In Communities), JACC Heart Fail, 2014;2:447–454. [PubMed: 25194293]

[27]. Olin JW and Sealove BA, Peripheral artery disease: current insight into the disease and its diagnosis and management, Mayo Clin Proc, 2010;85:678–692. [PubMed: 20592174]

[28]. Yang C, Kwak L, Ballew SH, et al. , Retinal microvascular findings and risk of incident peripheral artery disease: An analysis from the Atherosclerosis Risk in Communities (ARIC) Study, Atherosclerosis, 2020;294:62–71. [PubMed: 31812251]

[29]. Beckman JA, Duncan MS, Damrauer SM, et al. , Microvascular Disease, Peripheral Artery Disease, and Amputation, Circulation, 2019;140:449–458. [PubMed: 31280589]

[30]. McDermott MM, Liu K, Criqui MH, et al. , Ankle-brachial index and subclinical cardiac and carotid disease: the multi-ethnic study of atherosclerosis, Am J Epidemiol, 2005;162:33–41. [PubMed: 15961584]

[31]. Taqueti VR and Di Carli MF, Clinical significance of noninvasive coronary flow reserve assessment in patients with ischemic heart disease, Curr Opin Cardiol, 2016;31:662–669. [PubMed: 27652814]

[32]. Wilkins JT, McDermott MM, Liu K, et al. , Associations of noninvasive measures of arterial compliance and ankle-brachial index: the Multi-Ethnic Study of Atherosclerosis (MESA), Am J Hypertens, 2012;25:535–541. [PubMed: 22357412]

[33]. Rizvi S, Kamran H, Salciccioli L, et al. , Relation of the ankle brachial index to left ventricular ejection fraction, Am J Cardiol, 2010;105:129–132. [PubMed: 20102904]

[34]. Fowkes FG, Murray GD, Butcher I, et al. , Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis, JAMA, 2008;300:197–208. [PubMed: 18612117]

[35]. O'Hare AM, Katz R, Shlipak MG, et al. , Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study, Circulation, 2006;113:388–393. [PubMed: 16432070]

[36]. Aboyans V, Ho E, Denenberg JO, et al. , The association between elevated ankle systolic pressures and peripheral occlusive arterial disease in diabetic and nondiabetic subjects, J Vasc Surg, 2008;48:1197–1203. [PubMed: 18692981]

[37]. Aboyans V, Criqui MH, Abraham P, et al. , Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association, Circulation, 2012;126:2890–2909. [PubMed: 23159553]

Highlights

- Ankle-brachial index (ABI), the ratio of systolic blood pressure in the ankle to that of the arm, is a diagnostic indicator of peripheral artery disease and a risk enhancer in the ACC/AHA clinical guidelines on the primary prevention of atherosclerotic cardiovascular disease.
- In older adults, lower ABI is robustly associated with an increased risk of CHD/stroke in those without ASCVD and with heart failure regardless of ASCVD history.
- These findings support the use of low ABI as a risk enhancer in helping guide primary prevention for CHD/stroke.
- With the increasing relevance of HF risk classification in the context of SGLT2 inhibitors, ABI may be a strong, non-invasive predictor for assessing HF risk in older adults, particularly in those with history of ASCVD.

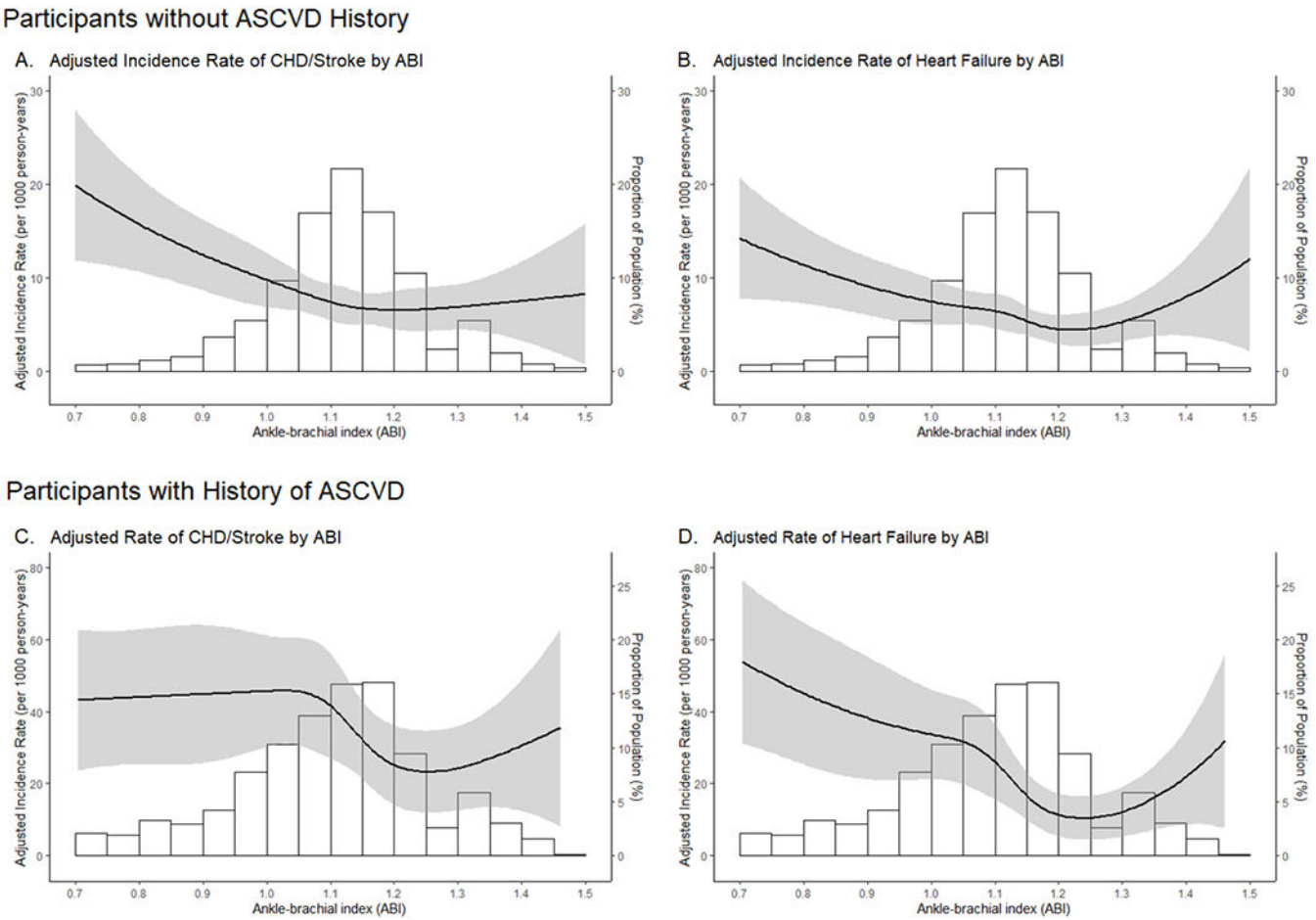


Figure 1.

Adjusted[a] incidence rates of CHD/stroke and heart failure by ABI for participants with and without history of ASCVD.

[a]Adjusted by age, sex, race.

ABI = ankle-brachial index, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease

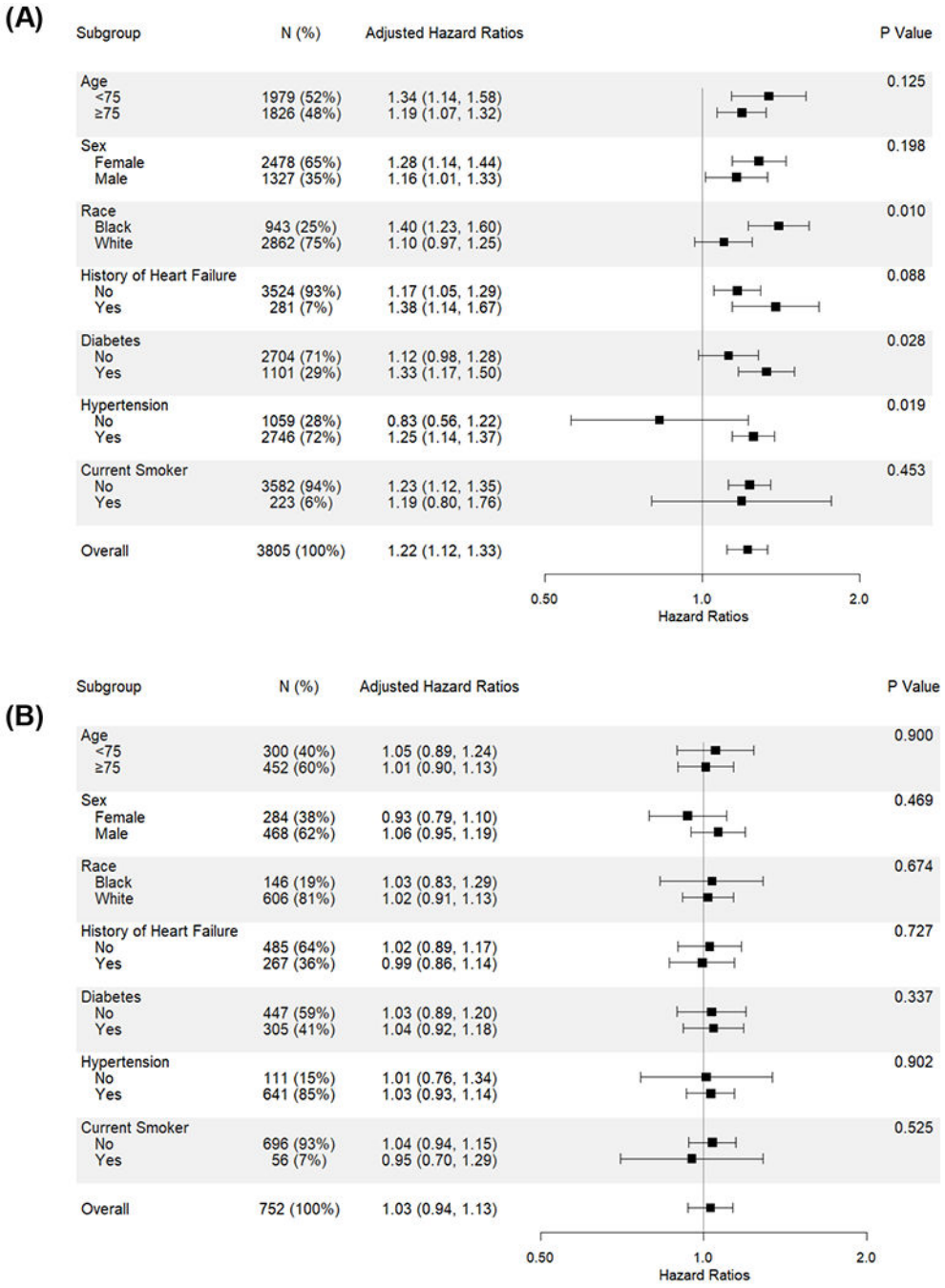


Figure 2.

Subgroup analyses: adjusted[a] hazards ratios of CHD/stroke for each 0.1 increase of ABI in participants with ABI ≤1.3 (A) without ASCVD history and (B) with history of ASCVD.

[a]Adjusted for age, race, sex, smoking status, systolic blood pressure, hypertension medication usage, total cholesterol, HDL-C, and diabetes.

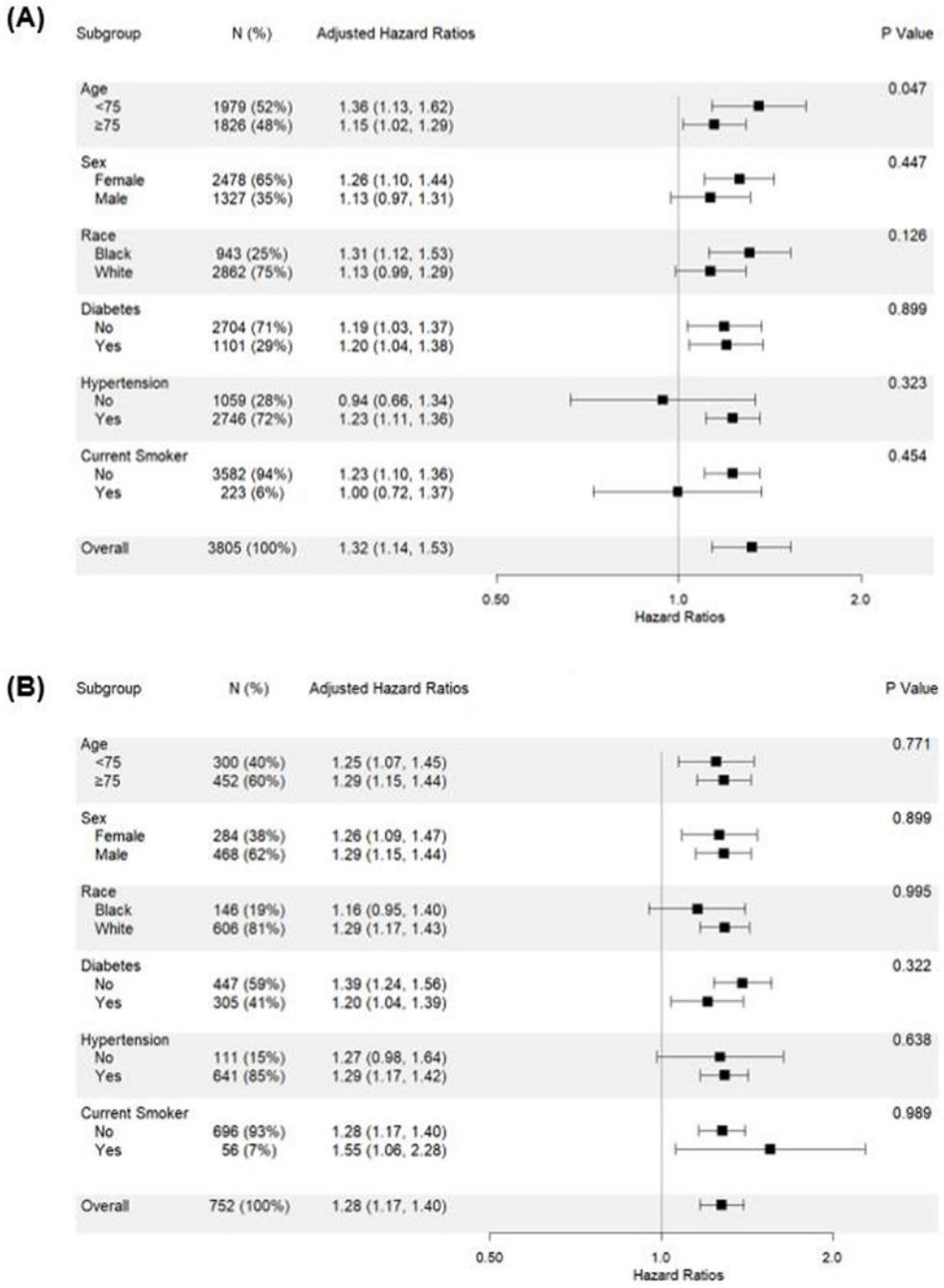


Figure 3.

Subgroup analyses: adjusted[a] hazards ratios of HF for each 0.1 increase of ABI in participants with ABI ≤1.3 (A) without ASCVD history and (B) with history of ASCVD.

[a]Adjusted for age, race, sex, smoking status, systolic blood pressure, hypertension medication usage, total cholesterol, HDL-C, and diabetes.

Table 1.

Study participant characteristics according to baseline ABI category

	Overall	ABI Category					
		≤ 0.90	0.91-1.00	1.01-1.10	1.11-1.20	1.21-1.30	>1.30
No ASCVD history							
N	4160	242	371	1088	1580	524	355
Age, years [IQI]	74 [71, 78]	77 [72, 82]	74 [71, 79]	74 [71, 78]	74 [71, 78]	74 [71, 78]	74 [71, 79]
Male (%)	1576 (37.9)	90 (37.2)	86 (23.2)	267 (24.5)	589 (37.3)	295 (56.3)	249 (70.1)
White (%)	3178 (76.4)	123 (50.8)	237 (63.9)	761 (69.9)	1269 (80.3)	472 (90.1)	316 (89.0)
Systolic blood pressure, mmHg (SD)	130 (17)	134 (20)	129 (18)	130 (18)	130 (17)	130 (17)	127 (16)
Diastolic blood pressure, mmHg (SD)	67 (10)	65 (11)	66 (10)	68 (11)	67 (10)	66 (10)	65 (10)
Hypertension medication (%)	2920 (70.2)	209 (86.4)	282 (76.0)	808 (74.3)	1050 (66.5)	349 (66.6)	222 (62.5)
Diabetes (%)	1195 (28.7)	99 (40.9)	120 (32.3)	321 (29.5)	419 (26.5)	142 (27.1)	94 (26.5)
BMI, kg/m^2 (SD)	28.5 (5.4)	28.9 (5.9)	29.5 (6.6)	28.9 (5.7)	28.0 (5.0)	27.8 (4.7)	28.6 (4.9)
Total cholesterol, mmol/L (SD)	4.8 (1.1)	4.8 (1.1)	4.9 (1.1)	4.9 (1.0)	4.9 (1.1)	4.7 (1.0)	4.6 (1.0)
HDL-C, mmol/L (SD)	1.4 (0.4)	1.3 (0.3)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	1.4 (0.3)	1.3 (0.3)
Cholesterol medication (%)	2111 (50.7)	132 (54.5)	193 (52.0)	562 (51.7)	783 (49.6)	268 (51.1)	173 (48.7)
Current smoker (%)	239 (5.7)	34 (14.0)	51 (13.7)	61 (5.6)	64 (4.1)	13 (2.5)	16 (4.5)
Education (%)[a]							
Grade school	145 (3.5)	17 (7.0)	15 (4.0)	51 (4.7)	43 (2.7)	11 (2.1)	8 (2.3)
Some high school	356 (8.6)	39 (16.1)	50 (13.5)	106 (9.7)	124 (7.9)	22 (4.2)	15 (4.2)
High school	1382 (33.2)	80 (33.1)	128 (34.5)	396 (36.4)	529 (33.5)	157 (30.0)	92 (26.0)
Vocational school	352 (8.5)	20 (8.3)	31 (8.4)	85 (7.8)	132 (8.4)	55 (10.5)	29 (8.2)
College	1305 (31.4)	63 (26.0)	100 (27.0)	292 (26.8)	544 (34.5)	174 (33.2)	132 (37.3)
Graduate/professional school	617 (14.8)	23 (9.5)	47 (12.7)	158 (14.5)	206 (13.1)	105 (20.0)	78 (22.0)
Family income, $ (%)[a]							
<12000	292 (7.4)	37 (16.1)	46 (13.1)	91 (8.9)	94 (6.3)	14 (2.8)	10 (3.0)
12,000-24,999	652 (16.6)	69 (30.0)	73 (20.8)	194 (19.0)	219 (14.7)	59 (11.7)	38 (11.4)
25,000-34,999	703 (17.9)	46 (20.0)	79 (22.5)	190 (18.6)	261 (17.5)	77 (15.3)	50 (15.0)
35,000-49,999	886 (22.6)	33 (14.3)	68 (19.4)	242 (23.7)	349 (23.4)	120 (23.8)	74 (22.2)
≥50,000	1396 (35.5)	45 (19.6)	85 (24.2)	304 (29.8)	567 (38.1)	234 (46.4)	161 (48.3)
History of ASCVD							
N	843	130	94	183	251	94	91
Age, years [IQI]	76 [72, 81]	79 [73, 83]	77 [73, 81]	76 [71, 81]	77 [73, 80]	74 [71, 77]	77 [73, 81]
Male (%)	547 (64.9)	77 (59.2)	52 (55.3)	97 (53.0)	167 (66.5)	75 (79.8)	79 (86.8)
White (%)	689 (81.7)	86 (66.2)	76 (80.9)	140 (76.5)	218 (86.9)	86 (91.5)	83 (91.2)
Systolic blood pressure, mmHg (SD)	130 (19)	133 (21)	129 (19)	128 (18)	130 (19)	130 (16)	125 (17)
Diastolic blood pressure, mmHg (SD)	63 (11)	62 (12)	62 (11)	64 (12)	65 (11)	66 (12)	61 (10)
Hypertension medication (%)	789 (93.6)	127 (97.7)	82 (87.2)	174 (95.1)	238 (94.8)	82 (87.2)	86 (94.5)
Diabetes (%)	349 (41.4)	62 (47.7)	33 (35.1)	68 (37.2)	104 (41.4)	38 (40.4)	44 (48.4)

	Overall	ABI Category					
		≤ 0.90	0.91-1.00	1.01-1.10	1.11-1.20	1.21-1.30	>1.30
BMI, kg/m^2 (SD)	28 (5)	28 (5)	29 (6)	29 (5)	28 (5)	29 (5)	29 (6)
Total cholesterol, mmol/L (SD)	4.1 (1.0)	4.4 (1.1)	4.2 (1.1)	4.2 (1.0)	4.1 (0.9)	4.0 (0.8)	3.7 (0.9)
HDL-C, mmol/L (SD)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.4)	1.22 (0.4)	1.2 (0.3)
Cholesterol medication (%)	681 (80.8)	97 (74.6)	70 (74.5)	146 (79.8)	210 (83.7)	76 (80.9)	82 (90.1)
Current smoker (%)	57 (6.8)	19 (14.6)	8 (8.5)	18 (9.8)	8 (3.2)	3 (3.2)	1 (1.1)
Education (%)[a]							
Grade school	48 (5.7)	16 (12.3)	4 (4.3)	13 (7.1)	8 (3.2)	2 (2.1)	5 (5.6)
Some high school	107 (12.7)	22 (16.9)	10 (10.8)	30 (16.4)	28 (11.2)	7 (7.4)	10 (11.1)
High school	266 (31.6)	38 (29.2)	30 (32.3)	66 (36.1)	84 (33.5)	28 (29.8)	20 (22.2)
Vocational school	78 (9.3)	13 (10.0)	9 (9.7)	13 (7.1)	19 (7.6)	14 (14.9)	10 (11.1)
College	240 (28.5)	28 (21.5)	30 (32.3)	45 (24.6)	73 (29.1)	32 (34.0)	32 (35.6)
Graduate/professional school	102 (12.1)	13 (10.0)	10 (10.8)	16 (8.7)	39 (15.5)	11 (11.7)	13 (14.4)
Family income, $ (%)[a]							
<12,000	70 (8.6)	26 (20.6)	6 (6.5)	26 (14.6)	8 (3.3)	3 (3.3)	1 (1.1)
12,000-24,999	132 (16.2)	31 (24.6)	21 (22.8)	26 (14.6)	34 (14.2)	9 (9.8)	11 (12.6)
25,000-34,999	160 (19.7)	24 (19.0)	18 (19.6)	37 (20.8)	44 (18.4)	22 (23.9)	15 (17.2)
35,000-4,9999	193 (23.7)	21 (16.7)	21 (22.8)	43 (24.2)	67 (28.0)	21 (22.8)	20 (23.0)
≥50,000	259 (31.8)	24 (19.0)	26 (28.3)	46 (25.8)	86 (36.0)	37 (40.2)	40 (46.0)

[a]In those with no history of ASCVD, education and family income were missing in 3 and 231 participants, respectively. In those with history of ASCVD, education and family income were missing in 2 and 29 participants, respectively.

Values are median [IQI], mean (SD), or count (%) as noted.

ABI = ankle-brachial index, ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, IQI = interquartile interval

Table 2.

Adjusted hazard ratios[a] of adverse cardiovascular events by ABI

	ABI category					
	≤ 0.90	**0.91-1.00**	**1.01-1.10**	**1.11-1.20**	**1.21-1.30**	**>1.30**
No ASCVD History						
CHD/stroke	**2.40 (1.55-3.71)**	1.50 (0.94-2.40)	**1.45 (1.04-2.02)**	1 (reference)	1.06 (0.67-1.68)	1.14 (0.68-1.91)
Heart failure	**2.23 (1.40-3.56)**	1.48 (0.91-2.42)	1.03 (0.70-1.52)	1 (reference)	1 (0.61-1.63)	1.16 (0.67-2.00)
History of ASCVD						
CHD/stroke	1.02 (0.52-2.01)	1.67 (0.85-3.27)	1.37 (0.73-2.56)	1.06 (0.58-1.96)	1 (reference)	0.90 (0.42-1.93)
Heart failure	**7.12 (2.47-20.50)**	**6.55 (2.24-19.17)**	**4.81 (1.68-13.75)**	**3.01 (1.06-8.58)**	1 (reference)	**3.12 (1.00-9.73)**

[a]Adjusted for predictors in the AHA/ACC ASCVD risk score (age, race, sex, smoking status, systolic blood pressure, hypertension medication usage, total cholesterol, HDL-C, and diabetes).

ABI = ankle-brachial index, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease

Bolded values denote statistical significance.

Table 3.

Improvements in predictive ability after adding ABI to predictors in the AHA/ACC ASCVD risk score.

No ASCVD history	Base model C statistic[a]	Δ C statistic adding ABI	Categorical NRI
CHD/stroke	0.670 (0.636, 0.705)	**0.012 (0.000, 0.024)**	**0.062 (0.007, 0.120)**
Heart failure	0.696 (0.662, 0.729)	**0.014 (0.000, 0.029)**	0.036 (−0.043, 0.109)
Coronary heart disease	0.696 (0.653, 0.739)	**0.029 (0.004, 0.054)**	**0.120 (0.019, 0.220)**
Stroke	0.642 (0.589, 0.694)	0.011 (−0.007, 0.029)	0.063 (−0.022, 0.153)
History of ASCVD			
CHD/stroke	0.640 (0.594, 0.686)	0.009 (−0.008, 0.026)	0.130 (0.046, 0.213)
Heart failure	0.606 (0.555, 0.657)	0.066 (0.017, 0.114)	0.294 (0.175, 0.425)
Coronary heart disease	0.650 (0.594, 0.706)	0.013 (−0.006, 0.032)	0.090 (0.017, 0.172)
Stroke	0.650 (0.577, 0.723)	0.034 (−0.013, 0.082)	0.079 (−0.107, 0.268)

[a]Includes predictors in the AHA/ACC ASCVD risk score (age, race, sex, smoking status, systolic blood pressure, hypertension medication usage, total cholesterol, HDL-C, and diabetes).

ABI = ankle-brachial index, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease, NRI = net reclassification index

Bolded values denote statistical significance.