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ORIGINAL RESEARCH

Discordant Values in Lower Extremity Physiologic Studies Predict Increased Cardiovascular Risk

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BACKGROUND: Ankle-brachial indexes (ABI) are a noninvasive diagnostic tool for peripheral arterial disease and a marker of increased cardiovascular risk. ABI is calculated using the highest systolic blood pressure of the 4 ankle arteries (bilateral dorsalis pedis and posterior tibial). Accordingly, patients may be assigned a normal ABI when the result would be abnormal if calculated using one of the other blood pressure readings. Cardiovascular outcomes for patients with discordant ABIs are undescribed.

METHODS AND RESULTS: We performed a retrospective study of patients who underwent ABI measurement for any indication between January 1996 and June 2018. Those with normal ABIs (1.00–1.39) were included. We compared patients with all 4 normal ABIs (calculated using all 4 ankle arteries; n=15 577, median age 64.0 years, 54.4% men) to those with discordant ABIs (at least 1 abnormal ABI ≤0.99; n=2095, median age 66.0 years, 47.8% men). The outcomes assessed were ischemic stroke, myocardial infarction, and all-cause mortality. Compared with patients with concordant normal ABIs, patients with discordant ABIs were older; women; smoked; and had chronic kidney disease, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, hypertension, or prior stroke. Patients with discordant ABIs had a greater risk of myocardial infarction (hazard ratio [HR], 1.31; 95% CI, 1.10–1.56), ischemic stroke (HR, 1.53; 95% CI, 1.37–1.72), and all-cause mortality (HR, 1.27; 95% CI, 1.16–1.39), including after adjustment for baseline comorbidities.

CONCLUSIONS: Discordant ABI results were associated with an increased risk of myocardial infarction, stroke, and all-cause mortality in the studied population. Clinicians should examine ABI calculations using all 4 ankle arteries to better characterize a patient's cardiovascular risk.

Key Words: ankle-brachial index ■ peripheral artery disease ■ cardiovascular disease risk factors

The ankle-brachial index (ABI) is a simple, noninvasive study to assess for peripheral arterial disease (PAD). The index is calculated by dividing the highest systolic blood pressure from the dorsalis pedis or posterior tibial artery by that of the brachial artery. ABIs define PAD with reasonable accuracy and have been shown to predict cardiovascular events and mortality.[1–5] Abnormal ABIs in asymptomatic patients have been associated with a higher incidence of death, myocardial infarction (MI), and stroke.[6] Patients may be classified as having a normal ABI when 1 ankle artery systolic blood pressure is normal while the other ipsilateral ankle artery pressure is reduced or abnormal—a condition hereafter referred to as discordant ABI. Little attention is given to discordant ABI calculations, again referring to those patients who had a normal ABI reported, but also had an abnormal ABI calculated using the lower of the 2 systolic blood pressures from the ankle arteries for that extremity. We question whether discordant ABIs are a marker of increased

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CLINICAL PERSPECTIVE

What Is New?

- This study evaluates the cardiovascular and mortality risks associated with a discordant ankle-brachial index (ABI), referring to patients who had a normal ABI reported but had at least 1 abnormal ABI (<1.0) using the 4 ankle arteries.
- We show that discordant ABI is associated with incident myocardial infarction, stroke, and all-cause mortality in the studied population, including in models adjusted for baseline cardiovascular risk factors.

What Are the Clinical Implications?

- We suggest that clinicians review normal lower extremity physiologic studies for the presence of discordant ABI measurements to better characterize a patient's cardiovascular risk.
- Our results may encourage more aggressive screening and treatment of traditional modifiable cardiovascular risk factors in patients with discordant ABIs.

Nonstandard Abbreviations and Acronyms

ABI	ankle-brachial index
CAD	coronary artery disease
CKD	chronic kidney disease
HR	hazard ratio
MI	myocardial infarction
PAD	peripheral arterial disease

cardiovascular and mortality risks and as such should be given consideration when making clinical decisions.

METHODS

We conducted a retrospective review of patients who had an ABI performed at Mayo Clinic. We identified all patients who had ABIs performed for any indication between January 1996 and June 2018, excluding patients younger than 18 years of age and those who did not provide research authorization. The cohort was then limited to those with normal ABIs of 1.00 to 1.39. We manually reviewed the ABI reports to assess the 4 ABI calculations performed to derive the reported ABI (the highest of the 2 calculated ABIs for each leg is standardly reported). The 4 ABIs correspond to the 4 ankle arteries (bilateral tibial and dorsalis pedis), specifically the systolic blood pressure at each ankle artery over the corresponding brachial artery systolic blood pressure. Those with discordant ABIs, meaning at least 1 abnormal ABI calculated using the 4 ankle arteries (whereas the ABI reported for each leg was normal), were identified. Abnormal was defined as ABI ≤0.99. Specifically, those with 1 abnormal ABI (other ipsilateral ABI and 2 ABIs in the opposite leg were normal) or 1 abnormal ABI in both legs were classified as discordant (whereas patients with 2 normal ABIs for each leg were considered normal).

The research complies with the guidelines for human studies and was conducted ethically. The Mayo Clinic institutional review board approved this study. The review type was classified as minimal risk; therefore, the requirement for informed consent was waived. The data that support the findings of the study are available from the corresponding author upon reasonable request.

Variables Assessed

Baseline characteristics for the cohort were assessed and included age, sex, smoking history (current or prior smoker), coronary artery disease (CAD), chronic kidney disease (CKD), chronic obstructive pulmonary disease, diabetes mellitus, atrial fibrillation, hyperlipidemia, hypertension, and history of prior MI or ischemic stroke. The CKD variable was limited to CKD stage ≥3, including end-stage renal disease or dialysis. There were no missing data for the baseline variables assessed. Baseline (prior to ABI) use of the following medications was also assessed: aspirin, other antiplatelet agent (clopidogrel, ticagrelor, prasugrel), anticoagulant (warfarin or nonvitamin K anticoagulant), and statin. The outcomes assessed were ischemic stroke, MI, and all-cause mortality.

International Classification of Diseases, Ninth Revision (*ICD-9*) and *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnostic codes were used to define the baseline medical conditions and outcomes for extraction from inpatient and outpatient medical records (Table S1). Mortality data were obtained from the electronic medical records. Random samples of both stroke and MI outcomes were manually verified through a review of the electronic medical record (Data S1).

Statistical Analysis

Mean and SD, median and range, or absolute number and percentage were used to describe the continuous and categorical patient characteristics. Wilcoxon rank-sum test and chi-square tests of significance were employed to compare those with normal and discordant ABIs. Bonferroni correction ($\alpha=0.05/3$) was used to adjust for multiple testing. A P value <0.05 was considered statistically significant. Hazard regression analysis was conducted to calculate hazard ratios (HRs) with 95% CIs for the outcomes of

interest, comparing the group with discordant ABIs versus those with normal ABIs. This analysis was also completed with 2 adjusted models. The first adjusted for age and sex, and the second adjusted for age, sex, diabetes mellitus, CKD stage 3 or greater including end-stage renal disease or dialysis, CAD, hypertension, hyperlipidemia, and smoking history. Multivariate hazard regression analysis was performed to assess the baseline variables associated with each outcome for those with normal and those with discordant ABIs. Variables significant in the univariate regression were included in the multivariate analysis. All statistical analyses were performed with SAS version 9.4 software (SAS Institute Inc., Cary, NC).

RESULTS

A total of 40 174 patients were identified who underwent ABI measurement, and 17 672 of these patients had an overall normal ABI reported and were included in the study. Of those, 2095 (11.9%) had discordant ABIs and were compared with those who did not have discordant ABIs (n=15 577). The median ABI value for those with discordant ABIs was 0.97 (range, 0–0.99). The median ABI for those with normal ABIs was 1.10 (range, 1.00–1.39). The median follow-up for the cohort was 36.3 months (interquartile range, 95.0 months).

Baseline Characteristics

The baseline characteristics for the groups of patients with normal and discordant ABIs are shown in Table 1. There were no significant differences in race or ethnicity between the groups. Most of the assessed baseline comorbidities were significantly more prevalent in the discordant ABI group. Patients with discordant ABIs were more likely to be older (median age 66.0 versus 64.0 years), women (52.2% versus 45.6%; $P<0.0001$), smokers (44.2% versus 40.2%; $P<0.0001$), and have a history of CKD (6.3% versus 5.0%; $P=0.01$), CAD (32.4% versus 28.2%; $P<0.0001$), chronic obstructive pulmonary disease (3.9% versus 2.4%; $P<0.0001$), diabetes mellitus (24.2% versus 21.6%; $P=0.007$), hypertension (51.7% versus 49.3%; $P=0.04$), and prior ischemic stroke (4.2% versus 2.9%; $P<0.0001$). There were no significant differences in the prevalence of atrial fibrillation, hyperlipidemia, prior MI, or prior stroke between the groups. There were no significant differences in the baseline drugs assessed (aspirin or antiplatelet, anticoagulant, or statin therapies).

Outcomes

There was a total of 1007 ischemic strokes (5.7%), 1068 MIs (6.0%), and 4033 deaths (23.5%, n=489 missing data) in the cohort after the index date (ABI measurement). The combined outcome count in the cohort was 6167 (34.9%). Compared with those with normal ABIs, the discordant ABI group had a high percentage of ischemic stroke (6.6% [n=139] versus 5.6% [n=868]), MI (7.1% [n=149] versus 5.9% [n=919]), and death (26.4% [n=544] versus 23.1% [n=3489]).

Compared with those with normal ABIs, those with discordant ABIs had a significantly increased risk of MI (HR, 1.31; 95% CI, 1.10–1.56), stroke (HR, 1.26; 95% CI, 1.05–1.51), and all-cause mortality (HR, 1.27; 95% CI, 1.16–1.39) as shown in Table 2. The analysis remained significant with similar HRs when adjusting for baseline comorbidities (Table 2).

Table 1. Baseline Characteristics of Patients With Normal and Discordant ABIs

	Normal ABI (N=15 577)	Discordant ABI (N=2095)	*P* Value
Median age, y (range in y)	64.0 (18.0–102.0)	66.0 (18.0–96.0)	<0.0001
Male sex, n (%)	8472 (54.4)	1001 (47.8)	<0.0001
Smoking history, n (%)	6173 (39.6)	927 (44.2)	<0.0001
CAD, n (%)	4388 (28.2)	679 (32.4)	<0.0001
CKD, n (%)	777 (5.0)	131 (6.3)	0.01
COPD, n (%)	370 (2.4)	81 (3.9)	<0.0001
Diabetes mellitus, n (%)	3369 (21.6)	508 (24.2)	0.007
Atrial fibrillation, n (%)	1622 (10.4)	243 (11.6)	0.10
Hyperlipidemia, n (%)	6447 (41.4)	870 (41.5)	0.90
Hypertension, n (%)	7676 (49.3)	1083 (51.7)	0.04
MI, n (%)	603 (3.9)	99 (4.7)	0.06
Stroke, n (%)	450 (2.9)	87 (4.2)	<0.0001
Aspirin, n (%)	3848 (24.7)	532 (25.4)	0.49
Antiplatelet, n (%)	701 (4.5)	101 (4.8)	0.51
Anticoagulant, n (%)	1256 (8.1)	180 (8.6)	0.41
Statin, n (%)	3382 (21.7)	449 (21.4)	0.77

P values were calculated by 2-sample *t* tests and chi-square tests for continuous and categorical variables, respectively. ABI indicates ankle-brachial index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; and MI, myocardial infarction.

Predictors of MI, Ischemic Stroke, and All-Cause Mortality

Multivariate modeling for both normal and discordant ABI groups evaluating baseline risk factors for the outcomes of MI, ischemic stroke, and all-cause mortality is shown in Tables 3 through 5, respectively. Univariate modeling for the 3 outcomes is shown in Tables S2 through S4. The most predictive risk factors for the 3 outcomes were similar among the discordant and ABI

Table 2. HRs for the Outcomes of Interest Comparing Patients With Discordant and Normal Ankle-Brachial Indexes

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*	Adjusted HR (95% CI)†
Ischemic stroke	1.26 (1.05–1.51)	1.23 (1.03–1.47)	1.20 (1.00–1.44)
Myocardial infarction	1.31 (1.10–1.56)	1.29 (1.09–1.54)	1.21 (1.01–1.44)
All-cause mortality	1.27 (1.16–1.39)	1.19 (1.08–1.30)	1.15 (1.05–1.26)

HR indicates hazard ratio.
*Adjusted for age and sex.
†Adjusted for age, sex, diabetes mellitus, chronic kidney disease stage 3 or greater, coronary artery disease, hypertension, hyperlipidemia, and smoking history.

cohorts, although the HR magnitude varied as did the full array of predictive variables.

DISCUSSION

Study Outcomes

Our study in a large cohort found that those with discordant ABIs compared with normal ABIs had a significantly higher risk of MI, ischemic stroke, and all-cause mortality. Discordant ABI measurements independently predicted these outcomes when adjusted for baseline comorbidities. A substantial percentage (12%) of patients reported as having normal ABIs had discordant indexes. PAD has been strongly associated with cardiovascular outcomes. Patients with PAD, including PAD defined by abnormal ABI, have increased risk of MI, stroke, cardiovascular mortality, and all-cause mortality compared with those without PAD.[7–9] Our results suggest that a similar relationship exists for those with discordant ABIs.

There was a fairly high percentage of patients who experienced the outcomes of interest in the cohort, likely reflecting the high baseline comorbidity of patients who are referred for ABI testing. However, mortality and cardiovascular event rates were less than that seen in patients with PAD, especially those with prior CAD or stroke.[4,10]

Table 3. Multivariate Regression Analysis for Myocardial Infarction Comparing Patients With Discordant and Normal ABIs

Variable	Normal ABI, HR (95% CI)	Discordant ABI, HR (95% CI)
Age	1.01 (1.01–1.02)*	1.02 (1.01–1.04)*
Male	1.07 (0.93–1.24)*	1.02 (0.72–1.46)*
Diabetes mellitus	1.23 (1.06–1.41)*	1.47 (1.04–2.09)*
CKD	1.74 (1.39–2.17)*	1.64 (0.96–2.80)
CAD	2.02 (1.72–2.36)*	1.69 (1.17–2.45)*
Hypertension	1.29 (1.09–1.52)*	0.90 (0.60–1.35)
Hyperlipidemia	0.76 (0.65–0.90)*	0.93 (0.62–1.37)
Smoker	1.16 (1.02–1.33)*	0.89 (0.63–1.26)
COPD	1.08 (0.75–1.55)	0.63 (0.23–1.78)
Atrial fibrillation	1.26 (1.05–1.51)*	1.26 (0.81–1.95)

Variables significant in the univariate regression were included in the multivariate analysis. ABI indicates ankle-brachial index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; and HR, hazard ratio.
*Significant *P* value (<0.05), calculated by type 3 Wald.

Baseline Status of Patients With Discordant and Normal ABIs

We noted that baseline comorbidities were higher in the group of patients with discordant ABIs. Many of these risk factors are associated with PAD. Age, diabetes mellitus, and smoking have most commonly been associated with PAD of the identified risk factors.[11,12] Additional traditional risk factors include hyperlipidemia, hypertension, and metabolic syndrome.[13] Renal disease has also been associated with incident PAD.[13,14] CAD is a risk factor for PAD given both conditions are manifestations of atherosclerosis, although PAD is often unrecognized in those with CAD.[15–17]

Our study interestingly found that women had a higher prevalence of discordant ABIs than men, which may support that women are more likely to have underrecognized cardiovascular risk. The women in the study were younger than the men in both the normal and discordant ABI groups (mean age in the discordant group,

Table 4. Multivariate Regression Analysis for Ischemic Stroke Comparing Patients With Discordant and Normal ABIs

Variable	Normal ABI, HR (95% CI)	Discordant ABI, HR (95% CI)
Age	1.02 (1.01–1.02)*	1.02 (1.00–1.03)*
Male	1.10 (0.95–1.27)	…
Diabetes mellitus	1.27 (1.09–1.48)*	1.03 (0.70–1.50)
CKD	1.05 (0.79–1.40)	…
CAD	1.28 (1.10–1.50)*	0.94 (0.65–1.35)
Hypertension	1.30 (1.11–1.53)*	1.58 (1.02–2.43)*
Hyperlipidemia	1.13 (0.97–1.31)	1.83 (1.22–2.73)*
Smoker	…	…
COPD	1.43 (0.98–2.07)	1.38 (0.63–3.01)
Atrial fibrillation	1.43 (1.19–1.73)*	2.04 (1.33–3.12)*

Variables significant in the univariate regression were included in the multivariate analysis. Empty cells indicate that the variable was not significant in the univariate analysis. ABI indicates ankle-brachial index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; and HR, hazard ratio.
*Significant *P* value (<0.05), calculated by type 3 Wald.

Table 5. Multivariate Regression Analysis for All-Cause Mortality Comparing Patients With Discordant and Normal ABIs

Variable	Normal ABI, HR (95% CI)	Discordant ABI, HR (95% CI)
Age	1.06 (1.05–1.06)*	1.04 (1.04–1.05)*
Male	1.31 (1.22–1.41)*	1.24 (1.04–1.49)*
Diabetes mellitus	1.43 (1.32–1.55)*	1.52 (1.26–1.83)*
CKD	2.23 (1.97–2.52)*	2.34 (1.77–3.09)*
CAD	1.36 (1.26–1.47)*	1.39 (1.15–1.68)*
Hypertension	0.99 (0.91–1.06)	0.99 (0.81–1.21)
Smoker	1.12 (1.05–1.20)*	…
COPD	1.58 (1.31–1.89)*	1.36 (0.87–2.13)
Atrial fibrillation	1.49 (1.36–1.62)*	1.55 (1.25–1.94)*

Variables significant in the univariate regression were included in the multivariate analysis. Hyperlipidemia did not remain significant and was not included in the model for either ABI group. Empty cells indicate that the variable was not significant in the univariate analysis. ABI indicates ankle-brachial index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; and HR, hazard ratio.

*Significant *P* value (<0.05), calculated by type 3 Wald.

60.32±17.56 versus 64.16±13.68). Research has shown a similar prevalence of PAD between men and women overall, with a higher prevalence in men at younger ages.[18,19] Women appear to present later, have higher rates of asymptomatic and unrecognized disease, and continue to be underrepresented in PAD studies.[16,19]

There was no significant difference in the prevalence of atrial fibrillation between the groups. Studies offer conflicting results regarding the association between atrial fibrillation and PAD.[20,21] The lack of difference between groups in the baseline use of aspirin and antiplatelet agent, anticoagulation, and statin therapies likely reflects the similar prevalence of hyperlipidemia, atrial fibrillation and prior major bleeding (8.4% in those with normal ABI versus 7.9% in those with discordant ABI, *P*=0.46). However, both groups may have been undertreated given the high prevalence of baseline cardiovascular disease or risk, which may be especially relevant in those with discordant ABIs given our study findings.

Predictors of Study Outcomes

Traditional cardiovascular risk factors were associated with MI, ischemic stroke, and all-cause mortality in both the normal and discordant ABI groups. However, there were several differences in predictive variables between groups, which may point to the importance of particular comorbidities in predicting adverse cardiovascular events in those with discordant ABIs. For instance, diabetes mellitus may be an especially impactful risk factor for MI in patients with discordant ABIs compared with those with normal ABIs. PAD patients with diabetes mellitus are at higher risk for rapid progression of their PAD and development of cardiovascular outcomes than PAD patients without diabetes mellitus.[22]

Study Implications

We found that patients with discordant ABIs at our institutions had a higher risk of MI, ischemic stroke, and death, even after adjusting for baseline comorbidities. Our results may encourage more aggressive traditional risk factor modifications in patients with discordant ABIs. Tailored to individual patients, clinicians could consider more intensive lifestyle modifications, therapies to promote smoking cessation, more potent lipid-lowering therapy, tighter hypertension and glycemic controls, and aspirin use for the primary prevention of cardiovascular events if the benefits were felt to outweigh the harms given that this population represents a higher risk group. We do not suggest regarding a discordant ABI as a diagnosis of PAD (to warrant treatment as such) or as a finding to provoke invasive testing. A discordant ABI measurement may be a precursor to PAD. Future research could assess for incident PAD in this population as well as claudication and limb ischemia. Future research may also evaluate noncompressible ABIs (>1.4) and abnormal ABIs (≤0.9) as comparators. Another comparator of interest is discordant ABIs with a greater degree of abnormality (ie, ≤0.9); we hypothesize that more abnormal discordant ABIs would convey greater risk for the outcomes studied.

LIMITATIONS

Limitations of this study include that it is retrospective with variable follow-up. All patients who underwent ABI testing were included. Whether testing was done for screening purposes was not noted. Testing was limited to resting ABI. Exercise ABI and toe-brachial index were not assessed, perhaps leading to a misclassification of disease in some patients. We did not assess functional capacity or its decline in the cohort. *ICD-9* and *ICD-10* diagnosis codes were used to define baseline variables and outcomes, although manual validation indicated comparable accuracy with that of previous studies. Outcomes that occurred outside of the Mayo Clinic healthcare system would not have been included. The cohort was predominantly white, which may reduce the generalizability of our results. Despite these limitations, the study is unique, examining a previously unstudied variable that appears to represent a significant and independent marker of cardiovascular risk.

CONCLUSIONS

PAD remains a common but underdiagnosed and undertreated disease, including in patients with known ischemic heart disease.[13,16] PAD confers a high risk of cardiovascular events and mortality, with similar risks

for both symptomatic and asymptomatic diseases.[23] To our knowledge, this is the first study to examine cardiovascular risk associated with discordant ABIs in a large cohort referring to studies that reported an overall normal ABI but had at least 1 abnormal reading based on an assessment of the 4 ankle arteries. Discordant ABIs appear to better characterize a patient's risk for MI, ischemic stroke, and all-cause mortality in our population. The prevalence of discordant ABIs in the cohort was sizable, indicating a potentially large, unrecognized fraction of the community that may benefit from more intensive cardiovascular risk factor modification. Accordingly, discordant values should be reported for all ABI studies. Given our study findings, clinicians should be cognizant of discordant ABI values and their potential clinical implications.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Data S1
Tables S1–S4
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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Manual verification of outcomes

We randomly selected a sample of patients from the cohort that had incident MI or ischemic stroke during the study period as defined by ICD codes to assess the accuracy of ICD coding for these outcomes. 25 patients for each outcome were evaluated. For each of the 50 selected patients, manual review of the chart was performed by two independent reviewers. Hospital and clinic notes, as well as relevant diagnostic studies (i.e. brain imaging or angiogram for stroke, heart catheterization or echocardiogram or EKG for MI) were reviewed within a week of the diagnosis date of the outcome by ICD coding. The outcome was noted to be inaccurate (by ICD coding) if either there was no mention of the outcome in the notes or testing or it was noted to be a historical diagnosis. ICD coding for MI was found to be 96% accurate (24/25). Coding for ischemic stroke was found to be 88% accurate (22/25). The accuracy noted was superior to the median diagnostic accuracy of diagnostic coding (including ICD-9 and ICD-10) noted in a systematic review (83.2%, IQR: 67.3-92.1%).[24]

Table S1. ICD-9 and ICD-10 codes used to define baseline characteristics and outcomes.

Variable	ICD-9	ICD-10
Diabetes	250	E11.00
	250.0	E11.01
	250.00	E11.21
	250.01	E11.22
	250.02	E11.29
	250.03	E11.311
	250.1	E11.319
	250.10	E11.321
	250.11	E11.321
	250.12	E11.3211
	250.13	E11.3212
	250.2	E11.3213
	250.20	E11.3219
	250.21	E11.329
	250.22	E11.329
	250.23	E11.3291
	250.3	E11.3292
	250.30	E11.3293
	250.31	E11.3299
	250.32	E11.331
	250.33	E11.331
	250.4	E11.3311
	250.40	E11.3312
	250.41	E11.3313
	250.42	E11.3319
	250.43	E11.339
	250.5	E11.339
	250.50	E11.3391
	250.51	E11.3392
	250.52	E11.3393
	250.53	E11.3399
	250.6	E11.341
	250.60	E11.341
	250.61	E11.3411
	250.62	E11.3412
	250.63	E11.3413
	250.7	E11.3419
	250.70	E11.349
	250.71	E11.349
	250.72	E11.3491
	250.73	E11.3492
	250.8	E11.3493

	250.80 250.81 250.82 250.83 250.9 250.90 250.91 250.92 250.93	E11.3499 E11.351 E11.351 E11.3511 E11.3512 E11.3513 E11.3519 E11.352 E11.3521 E11.3522 E11.3523 E11.3529 E11.353 E11.3531 E11.3532 E11.3533 E11.3539 E11.354 E11.3541 E11.3542 E11.3543 E11.3549 E11.355 E11.3551 E11.3552 E11.3553 E11.3559 E11.359 E11.359 E11.3591 E11.3592 E11.3593 E11.3599 E11.36 E11.37 E11.37X1 E11.37X2 E11.37X3 E11.37X9 E11.39 E11.40 E11.41 E11.42 E11.43 E11.44 E11.49 E11.51 E11.52 E11.59

		E11.610 E11.618 E11.620 E11.621 E11.622 E11.628 E11.630 E11.638 E11.641 E11.649 E11.65 E11.69 E11.8 E11.9 E10.10 E10.11 E10.21 E10.22 E10.29 E10.311 E10.319 E10.321 E10.321 E10.3211 E10.3212 E10.3213 E10.3219 E10.329 E10.329 E10.3291 E10.3292 E10.3293 E10.3299 E10.331 E10.331 E10.3311 E10.3312 E10.3313 E10.3319 E10.339 E10.339 E10.3391 E10.3392 E10.3393 E10.3399 E10.341 E10.341 E10.3411 E10.3412

		E10.3413 E10.3419 E10.349 E10.349 E10.3491 E10.3492 E10.3493 E10.3499 E10.351 E10.351 E10.3511 E10.3512 E10.3513 E10.3519 E10.352 E10.3521 E10.3522 E10.3523 E10.3529 E10.353 E10.3531 E10.3532 E10.3533 E10.3539 E10.354 E10.3541 E10.3542 E10.3543 E10.3549 E10.355 E10.3551 E10.3552 E10.3553 E10.3559 E10.359 E10.359 E10.3591 E10.3592 E10.3593 E10.3599 E10.36 E10.37 E10.37X1 E10.37X2 E10.37X3 E10.37X9 E10.39 E10.40 E10.41

		E10.42 E10.43 E10.44 E10.49 E10.51 E10.52 E10.59 E10.610 E10.618 E10.620 E10.621 E10.622 E10.628 E10.630 E10.638 E10.641 E10.649 E10.65 E10.69 E10.8 E10.9
CKD	403.01 403.11 403.91 404 404.13 585 585.3 585.4 585.5 585.6 996.56 996.68 V45.1 V45.11 V45.12 V56 V56.0 V56.1 V56.2 V56.3 V56.31 V56.32 V56.8	I12.0 I13.11 I13.2 N18.3 N18.4 N18.5 N18.6 N18.9 T85.691A T85.691D T85.691S T85.71XA T85.71XD T85.71XS Z49.01 Z49.02 Z49.31 Z49.32 Z91.15 Z99.2
CAD	414 414 414	I25.10 I25.110 I25.111

	414.01 414.02 414.03 414.04 414.05 414.06 414.07 414.1 414.1 414.11 414.12 414.19 414.2 414.3 414.4 414.8 414.9	I25.118 I25.119 I25.2 I25.3 I25.41 I25.42 I25.5 I25.6 I25.700 I25.701 I25.708 I25.709 I25.710 I25.711 I25.718 I25.719 I25.720 I25.721 I25.728 I25.729 I25.730 I25.731 I25.738 I25.739 I25.750 I25.751 I25.758 I25.759 I25.760 I25.761 I25.768 I25.769 I25.790 I25.791 I25.798 I25.799 I25.810 I25.811 I25.812 I25.82

		I25.83 I25.84 I25.89 I25.9
Hypertension	401 401.0 401.1 401.9 402 402.0 402.00 402.01 402.1 402.10 402.11 402.9 402.90 402.91 403 403.0 403.00 403.01 403.1 403.10 403.11 403.9 403.90 403.91 404 404.0 404.00 404.01 404.02 404.03 404.1 404.10 404.11 404.12 404.13 404.9 404.90 404.91 404.92 404.93 405	H35.031 H35.032 H35.033 H35.039 I10 I11.0 I11.9 I12.0 I12.9 I13.0 I13.10 I13.11 I13.2 I15.0 I15.1 I15.2 I15.8 I15.9 I16 I16.0 I16.1 I16.9 I67.4

	405.0 405.01 405.09 405.1 405.11 405.19 405.9 405.91 405.99 437.2 796.2	
Hyperlipidemia	272 272.0 272.1 272.2 272.3 272.4	E78.0 E78.0 E78.00 E78.01 E78.1 E78.2 E78.3 E78.4 E78.5
COPD	491 491.0 491.1 491.2 491.20 491.21 491.22 491.8 491.9 492	J44.0 J44.1 J44.9 J43.2
Atrial fibrillation	427.3 427.31 427.32	I48.0 I48.1 I48.2 I48.3 I48.4 I48.91 I48.92
Major bleeding	456.0 456.20 578.0 578.1 578.9 530.21 531.0 531.00 531.01 531.2	I60.9 I61.9 I62.00 I62.01 I62.02 I62.03 I62.1 I62.9 K92.0 K92.1

	531.20	K92.2
	531.21	K29.01
	531.4	K29.21
	531.40	K29.31
	531.41	K29.41
	531.6	K29.51
	531.60	K29.61
	531.61	K29.71
	532.0	K29.81
	532.00	K29.91
	532.01	K28.0
	532.2	K28.2
	532.20	K28.4
	532.21	K28.6
	532.4	K27.0
	532.40	K27.2
	532.41	K27.4
	532.6	K27.6
	532.60	K26.0
	532.61	K26.2
	533.0	K26.4
	533.00	K26.6
	533.01	K25.0
	533.2	K25.2
	533.20	K25.4
	533.21	K25.6
	533.4	K22.11
	533.40	K22.6
	533.41	I85.01
	533.6	I85.11
	533.60	K31.811
	533.61	K31.82
	534.0	K57.11
	534.00	K57.13
	534.01	K57.31
	534.2	K57.33
	534.20	K66.1
	534.21	K62.5
	534.4	K55.21
	534.40	M25.00
	534.41	M25.011
	534.6	M25.012
	534.60	M25.019
	534.61	M25.021
	535.01	M25.022
	535.11	M25.029
	535.21	M25.031
	535.31	M25.032
	535.41	M25.039

	535.51	M25.041
	535.61	M25.042
	535.71	M25.049
	562.02	M25.051
	562.03	M25.052
	562.12	M25.059
	562.13	M25.061
	530.7	M25.062
	530.82	M25.069
	537.83	M25.071
	537.84	M25.072
	569.3	M25.073
	569.85	M25.074
	568.81	M25.075
	430	M25.076
	431	M25.08
	432	S06.4X0A
	432.0	S06.4X0D
	432.1	S06.4X0S
	432.9	S06.4X1A
	852	S06.4X1D
	852.0	S06.4X1S
	852.00	S06.4X2A
	852.01	S06.4X2D
	852.02	S06.4X2S
	852.03	S06.4X3A
	852.04	S06.4X3D
	852.05	S06.4X3S
	852.06	S06.4X4A
	852.09	S06.4X4D
	852.1	S06.4X4S
	852.10	S06.4X5A
	852.11	S06.4X5D
	852.12	S06.4X5S
	852.13	S06.4X6A
	852.14	S06.4X6D
	852.15	S06.4X6S
	852.16	S06.4X7A
	852.19	S06.4X7D
	852.2	S06.4X7S
	852.20	S06.4X8A
	852.21	S06.4X8D
	852.22	S06.4X8S
	852.23	S06.4X9A
	852.24	S06.4X9D
	852.25	S06.4X9S
	852.26	S06.5X0A
	852.29	S06.5X0D
	852.3	S06.5X0S

	852.30	S06.5X1A
	852.31	S06.5X1D
	852.32	S06.5X1S
	852.33	S06.5X2A
	852.34	S06.5X2D
	852.35	S06.5X2S
	852.36	S06.5X3A
	852.39	S06.5X3D
	852.4	S06.5X3S
	852.40	S06.5X4A
	852.41	S06.5X4D
	852.42	S06.5X4S
	852.43	S06.5X5A
	852.44	S06.5X5D
	852.45	S06.5X5S
	852.46	S06.5X6A
	852.49	S06.5X6D
	852.5	S06.5X6S
	852.50	S06.5X7A
	852.51	S06.5X7D
	852.52	S06.5X7S
	852.53	S06.5X8A
	852.54	S06.5X8D
	852.55	S06.5X8S
	852.56	S06.5X9A
	852.59	S06.5X9D
	853	S06.5X9S
	853.0	S06.6X0A
	853.00	S06.6X0D
	853.01	S06.6X0S
	853.02	S06.6X1A
	853.03	S06.6X1D
	853.04	S06.6X1S
	853.05	S06.6X2A
	853.06	S06.6X2D
	853.09	S06.6X2S
	853.1	S06.6X3A
	853.10	S06.6X3D
	853.11	S06.6X3S
	853.12	S06.6X4A
	853.13	S06.6X4D
	853.14	S06.6X4S
	853.15	S06.6X5A
	853.16	S06.6X5D
	853.19	S06.6X5S
	423.0	S06.6X6A
	459.0	S06.6X6D
	596.7	S06.6X6S
	599.71	S06.6X7A

	719.1 719.10 719.11 719.12 719.13 719.14 719.15 719.16 719.17 719.18 719.19 784.8 786.3	S06.6X7D S06.6X7S S06.6X8A S06.6X8D S06.6X8S S06.6X9A S06.6X9D S06.6X9S R04 R04.0 R04.1 R04.2 R04.8 R04.81 R04.89 R04.9 I31.2 R58 R31.0
MI	410 410.0 410.00 410.01 410.02 410.1 410.10 410.11 410.12 410.2 410.20 410.21 410.22 410.3 410.30 410.31 410.32 410.4 410.40 410.41 410.42 410.5 410.50 410.51 410.52 410.6 410.60 410.61	I21.01 I21.02 I21.09 I21.11 I21.19 I21.21 I21.29 I21.3 I21.4 I21.9 I21.A I21.A1 I21.A9 I22.0 I22.1 I22.2 I22.8 I22.9 I23.0 I23.1 I23.2 I23.3 I23.4 I23.5 I23.6 I23.7 I23.8

	410.62 410.7 410.70 410.71 410.72 410.8 410.80 410.81 410.82 410.9 410.90 410.91 410.92	
Stroke	433.01 433.21 433.31 433.81 433.91 434.01 434.11 434.91	I63.00 I63.011 I63.012 I63.013 I63.019 I63.02 I63.031 I63.032 I63.033 I63.039 I63.09 I63.10 I63.111 I63.112 I63.113 I63.119 I63.12 I63.131 I63.132 I63.133 I63.139 I63.19 I63.20 I63.211 I63.212 I63.213 I63.219 I63.22 I63.231 I63.232 I63.233 I63.239 I63.29 I63.30 I63.311

		I63.312 I63.313 I63.319 I63.321 I63.322 I63.323 I63.329 I63.331 I63.332 I63.333 I63.339 I63.341 I63.342 I63.349 I63.39 I63.40 I63.411 I63.412 I63.413 I63.419 I63.421 I63.422 I63.423 I63.429 I63.431 I63.432 I63.433 I63.439 I63.441 I63.442 I63.449 I63.49 I63.50 I63.511 I63.512 I63.513 I63.519 I63.521 I63.522 I63.523 I63.529 I63.531 I63.532 I63.533 I63.539 I63.541 I63.542 I63.543 I63.549

		I63.59 I63.6 I63.8 I63.9

CAD: coronary artery disease, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, MI: myocardial infarction

Table S2. Univariate regression analysis for myocardial infarction comparing patients with discordant and normal ankle-brachial indices.

Variable	**Normal ABI** HR (95% CI)	**Discordant ABI** HR (95% CI)
Age	**1.03 (1.02-1.03)**	**1.03 (1.02-1.04)**
Male	**1.85 (1.61-2.12)**	**1.86 (1.31-2.64)**
Diabetes	**2.01 (1.75-2.30)**	**2.07 (1.45-2.97)**
CKD	**2.99 (2.42-3.70)**	**2.30 (1.32-4.01)**
CAD	**4.10 (3.59-4.69)**	**2.95 (2.09-4.17)**
Hypertension	**2.59 (2.24-3.01)**	**1.78 (1.23-2.57)**
Hyperlipidemia	**1.97 (1.72-2.25)**	**1.83 (1.29-2.59)**
Smoker	**1.46 (1.29-1.67)**	1.24 (0.88-1.75)
COPD	**2.09 (1.46-2.99)**	1.33 (0.49-3.63)
Atrial fibrillation	**2.13 (1.79-2.54)**	**2.24 (1.44-3.47)**

ABI: ankle-brachial index, CAD: coronary artery disease, CI: confidence interval, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, HR: hazards ratio
Bold indicates significant p-value (<0.05), calculated by Type 3 Wald.

Table S3. Univariate regression analysis for ischemic stroke comparing patients with discordant and normal ankle-brachial indices.

Variable	**Normal ABI** HR (95% CI)	**Discordant ABI** HR (95% CI)
Age	**1.03 (1.02-1.03)**	**1.03 (1.02-1.04)**
Male	**1.34 (1.17-1.54)**	1.26 (0.90-1.78)
Diabetes	**1.53 (1.32-1.77)**	**1.53 (1.05-2.22)**
CKD	**1.48 (1.12-1.96)**	0.85 (0.37-1.92)
CAD	**1.85 (1.62-2.12)**	**1.70 (1.21-2.40)**
Hypertension	**1.83 (1.59-2.11)**	**2.49 (1.67-3.69)**
Hyperlipidemia	**1.60 (1.40-1.84)**	**2.54 (1.76-3.66)**
Smoker	1.07 (0.94-1.23)	1.21 (0.86-1.71)
COPD	**1.97 (1.36-2.85)**	**2.67 (1.23-5.80)**
Atrial fibrillation	**2.01 (1.68-2.40)**	**2.88 (1.91-4.34)**

ABI: ankle-brachial index, CAD: coronary artery disease, CI: confidence interval, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, HR: hazards ratio
Bold indicates significant p-value (<0.05), calculated by Type 3 Wald.

Table S4. Univariate regression analysis for all-cause mortality comparing patients with discordant and normal ankle-brachial indices.

Variable	**Normal ABI** HR (95% CI)	**Discordant ABI** HR (95% CI)
Age	**1.07 (1.06-1.07)**	**1.05 (1.04-1.06)**
Male	**1.57 (1.46-1.68)**	**1.66 (1.38-1.99)**
Diabetes	**1.48 (1.38-1.60)**	**1.61 (1.33-1.96)**
CKD	**2.53 (2.25-2.85)**	**2.73 (2.05-3.65)**
CAD	**1.97 (1.84-2.11)**	**1.85 (1.55-2.21)**
Hypertension	**1.50 (1.40-1.61)**	**1.62 (1.34-1.96)**
Hyperlipidemia	0.98 (0.91-1.04)	1.06 (0.88-1.26)
Smoker	**1.13 (1.06-1.21)**	1.01 (0.85-1.21)
COPD	**2.61 (2.18-3.11)**	**2.37 (1.48-3.77)**
Atrial fibrillation	**2.64 (2.43-2.87)**	**2.62 (2.09-3.27)**

ABI: ankle-brachial index, CAD: coronary artery disease, CI: confidence interval, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, HR: hazards ratio
Bold indicates significant p-value (<0.05), calculated by Type 3 Wald.