

# The Systolic Blood Pressure Difference Between Arms and Cardiovascular Disease in the Framingham Heart Study

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## ABSTRACT

**BACKGROUND:** An increased interarm systolic blood pressure difference is an easily determined physical examination finding. The relationship between interarm systolic blood pressure difference and risk of future cardiovascular disease is uncertain. We described the prevalence and risk factor correlates of interarm systolic blood pressure difference in the Framingham Heart Study (FHS) original and offspring cohorts and examined the association between interarm systolic blood pressure difference and incident cardiovascular disease and all-cause mortality.

**METHODS:** An increased interarm systolic blood pressure difference was defined as  $\geq 10$  mm Hg using the average of initial and repeat blood pressure measurements obtained in both arms. Participants were followed through 2010 for incident cardiovascular disease events. Multivariable Cox proportional hazards regression analyses were performed to investigate the effect of interarm systolic blood pressure difference on incident cardiovascular disease.

**RESULTS:** We examined 3390 (56.3% female) participants aged 40 years and older, free of cardiovascular disease at baseline, mean age of 61.1 years, who attended a FHS examination between 1991 and 1994 (original cohort) and from 1995 to 1998 (offspring cohort). The mean absolute interarm systolic blood pressure difference was 4.6 mm Hg (range 0-78). Increased interarm systolic blood pressure difference was present in 317 (9.4%) participants. The median follow-up time was 13.3 years, during which time 598 participants (17.6%) experienced a first cardiovascular event, including 83 (26.2%) participants with interarm systolic blood pressure difference  $\geq 10$  mm Hg. Compared with those with normal interarm systolic blood pressure difference, participants with an elevated interarm systolic blood pressure difference were older (63.0 years vs 60.9 years), had a greater prevalence of diabetes mellitus (13.3% vs 7.5%), higher systolic blood pressure (136.3 mm Hg vs 129.3 mm Hg), and a higher total cholesterol level (212.1 mg/dL vs 206.5 mg/dL). Interarm systolic blood pressure difference was associated with a significantly increased hazard of incident cardiovascular events in the multivariable adjusted model (hazard ratio 1.38; 95% CI, 1.09-1.75). For each 1-SD-unit increase in absolute interarm systolic blood pressure difference, the hazard ratio for incident cardiovascular events was 1.07 (95% CI, 1.00-1.14) in the fully adjusted model. There was no such association with mortality (hazard ratio 1.02; 95% CI 0.76-1.38).

**CONCLUSIONS:** In this community-based cohort, an interarm systolic blood pressure difference is common and associated with a significant increased risk for future cardiovascular events, even when the absolute difference in arm systolic blood pressure is modest. These findings support research to expand clinical use of this simple measurement.

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**KEYWORDS:** Cardiovascular disease; Cardiovascular risk; Interarm blood pressure difference

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An increased interarm systolic blood pressure difference is usually defined as 10 mm Hg or greater<sup>1,2</sup> and can be found in up to 24% of healthy individuals.<sup>3-6</sup> It has been suggested that identification of interarm systolic blood pressure difference is crucial for appropriate identification and treatment of hypertension,<sup>7-9</sup> for clinical decision-making and surveillance.<sup>1,10-13</sup> Interarm systolic blood pressure differences have been studied in patients in primary care settings,<sup>14-16</sup> in patients with various manifestations of vascular disease,<sup>17-19</sup> and in population-based cohorts.<sup>3,6,16</sup> It has been found to correlate with classic and novel cardiovascular risk factors and may be predictive of cardiovascular events. Nevertheless, data on the epidemiology of interarm systolic blood pressure difference are relatively scarce.<sup>3,6,16,17</sup> While an association between interarm systolic blood pressure difference and mortality was noted in 3 small prospective studies and a meta-analysis that pooled data from 20 older studies,<sup>14,15,17,18,20</sup> the evidence for an association with cardiovascular disease is less consistent.<sup>20</sup> The objectives of this study were to describe the distribution of interarm systolic blood pressure difference and risk factor correlates in the Framingham Heart Study (FHS) original and offspring cohorts and to determine the association between interarm systolic blood pressure difference and incident cardiovascular events and all-cause mortality.

## METHODS

### Study Participant Sample

Methods of recruitment have been described previously for participants from the original cohort and the offspring study cohort of the FHS.<sup>21,22</sup>

From the original FHS cohort of 5209 that was recruited in 1948,<sup>23</sup> 1026 men and women attended an FHS examination between 1991 and 1994. There also were 3532 men and women from the offspring study cohort who attended the sixth offspring cycle examination from 1995 to 1998. Of the 4558 total original and offspring cohort participants, 494 were excluded because they did not have a blood pressure measurement in both arms. Of the remaining participants, 66 participants <40 years old and 608 with prevalent cardiovascular disease were excluded. The Institutional Review Board at Boston University Medical Center approved the examination content, and informed consent was obtained from study participants at the time of their examination.

### Interarm Systolic Blood Pressure Measurement

For the purpose of calculating the interarm systolic blood pressure difference, brachial systolic blood pressure measurements were obtained as part of an ankle-brachial index

measurement by trained technicians according to a standard protocol after participants lay supine for at least 5 minutes. Measurements were taken in the sequence of right arm, left arm, right ankle, and left ankle and repeated twice. If the initial and repeat blood pressure differed by >10 mm Hg at any site, a third measurement was taken. When 2 blood pressure measurements were obtained in the same arm, the average blood pressure in that arm was used. The interarm systolic blood pressure difference was defined as the absolute difference between the single or average blood pressure measurements in each arm. An increased interarm systolic blood pressure difference was defined as interarm systolic blood pressure difference  $\geq 10$  mm Hg.<sup>14,18</sup> The maximal difference between arms was used.

## CLINICAL SIGNIFICANCE

- Interarm systolic blood pressure difference (ISBPD) is associated with incident cardiovascular events independent of traditional cardiovascular risk factors in a large community-based cohort.
- Measurement of blood pressure in both arms is important both for accurate blood pressure detection and for cardiovascular risk stratification.

### Definition of Incident Cardiovascular Disease Events and Mortality

Participants were followed through 2010 for the first incident cardiovascular event, defined as coronary heart disease (ie, a fatal coronary event, recognized myocardial infarction and unrecognized myocardial infarction, coronary insufficiency, or angina), a cerebrovascular event (ie, ischemic stroke or transient ischemic attack), intermittent claudication,<sup>24</sup> or congestive heart failure.<sup>25</sup> An unrecognized myocardial infarction was adjudicated when serial changes on the electrocardiogram showed development of pathologic Q waves and neither the participant nor the physician considered the possibility of a myocardial infarction. Mortality data were obtained by review of all medical records including the last hospitalization, nursing home records, personal physical records, and if needed, next-of kin interviews along with death certificate evaluation. All cardiovascular events and deaths in both the original cohort and offspring participants were adjudicated by an end-point committee of 3 senior investigators using the same criteria and all available medical records. Ischemic stroke and transient ischemic attack events were reviewed by a panel of study neurologists.

### Definition of Risk Factor Covariates

Covariates were obtained at the same time as the interarm systolic blood pressure difference measurement. Hypertension was defined as a blood pressure  $\geq 140/90$  mm Hg or the use of antihypertension medications. Body mass index was calculated as the participants' weight in kilograms divided by the participants' height in meters squared. Diabetes mellitus was considered present if the fasting glucose was  $\geq 126$  mg/100 mL (offspring), a nonfasting glucose of  $\geq 200$  mg/dL (original cohort), or if the participant was receiving

treatment with insulin or oral hypoglycemic medications. Total cholesterol was analyzed as a continuous variable. Lipid-lowering therapy was entered into the model as a separate binary variable. Participants were queried at each examination about cigarette smoking, and current smoking was defined as smoking at least one cigarette per day in the year preceding the examination. The 10-year Framingham risk score for general cardiovascular disease was calculated for each participant.<sup>26</sup>

## Statistical Analysis

Descriptive statistics were generated. Continuous measures were summarized using mean and SD. Categorical traits were summarized using percentages. We standardized interarm systolic blood pressure difference (ISBPD) to mean = 0 and SD = 1 because this measure is skewed to the right. Hazard ratios (HRs) for continuous ISBPD were presented for every 1-SD-unit increase in blood pressure. The main exposure, ISBPD, was first analyzed as a binary variable (ie, <10 mm Hg and ≥10 mm Hg); then as a 3-level ordinal variable (<10 mm Hg vs 10 to <15 mm Hg and ≥15 mm Hg), and then as a continuous trait. We tested for linear trend in the hazards across the 3-level ordinal variable. Two-sample *t*-test with pooled variance or unequal variance as indicated was used to compare means between participants who had ISBPD ≥10 mm Hg versus those with ISBPD <10 mm Hg. The chi-squared test was used to compare categorical traits. Age- and sex-adjusted time to first cardiovascular event was analyzed using Kaplan-Meier plots and evaluated using the log-rank chi-squared test.

Next, after confirming the validity of the Cox proportional hazards regression assumptions, 2 Cox models were fitted with ISBPD <10 mm Hg as the referent category. The first

model adjusted for the following variables: age, sex, hypertension, total cholesterol level, high-density lipoprotein cholesterol, cholesterol treatment, presence or absence of diabetes mellitus, and smoking status; and the second model adjusted for the 10-year Framingham risk score for general cardiovascular disease.<sup>26</sup> We also assessed for linear trend using the 3-category ordinal ISBPD variable (ie, ISBPD <10 mm Hg, 10 to <15 mm Hg, and ≥15 mm Hg). Furthermore, similar models were fitted, accounting for familial correlations between the original and offspring cohorts. We used generalized estimating equations to account for the familial correlations within our dataset. Similar analysis approaches were used restricting the sample to hypertensive participants and also using mortality as the outcome.

The predictive utility of the Cox model was examined by comparing the *c*-statistic. The incremental effect of adding ISBPD to the Framingham risk score for predicting cardiovascular outcomes was evaluated with the use of category-based net reclassification improvement index (NRI).<sup>27</sup> The NRI is used to assess how well an exposure “reclassifies” patients from one risk category to another. We calculated NRI using an extension to survival analysis that employs Kaplan-Meier estimates of event probabilities using categories: low risk (0 to <6%), intermediate risk (6% to 20%), or high risk (>20%). A large NRI indicates that the additional exposure causes a large improvement in reclassification.

## RESULTS

Our final study sample included 3390 participants; mean age of 61.1 ± 11.3 years, 56.3% women, followed for an average of 13.3 years. The median ISBPD was 3 (interquartile range 2.6) mm Hg, and 317 (9.4%) participants had an ISBPD ≥10 mm Hg (Table 1). The distribution of

**Table 1** Age and Sex-Adjusted Comparison of Baseline Variables by Interarm Systolic Blood Pressure Difference

Variable	ISBPD <10 mm Hg (n = 3073*)	ISBPD ≥10 mm Hg (n = 317*)	P-Value
Age†	60.9 (11.3)	63.0 (11.5)	.002
Male (%)†	1343 (43.7)	137 (43.2)	.87
Body mass index kg/m <sup>2</sup>	27.4 (4.8)	29.6 (6.2)	<.001
SBP mm Hg	129.3 (19.3)	136.3 (20.3)	<.001
DBP mm Hg	74.9 (9.8)	76.3 (9.9)	.02
Hypertension (%)	1249 (40.6)	184 (58.0)	<.001
HTN treatment (%)	789 (25.7)	137 (43.6)	<.001
Total cholesterol mg/dL	206.5 (39.3)	212.1 (40.2)	.17
HDL cholesterol mg/dL	51.8 (16.2)	51.2 (16.9)	.53
Triglycerides mg/dL	137.8 (135.2)	151.2 (105.8)	.004
Lipid lowering treatment (%)	282 (9.2)	38 (12.0)	.10
Diabetes mellitus (%)	229 (7.5)	42 (13.3)	.003
Current cigarette use (%)	426 (13.9)	39 (12.3)	.44
Ever cigarette use (%)	1384 (45.0)	137 (43.2)	.54
Framingham 10-year risk score	12.3 (10.6)	15.2 (12.1)	<.001

DBP = diastolic blood pressure; HDL = high-density lipoprotein; HTN = hypertension; ISBPD = interarm systolic blood pressure difference; SBP = systolic blood pressure.

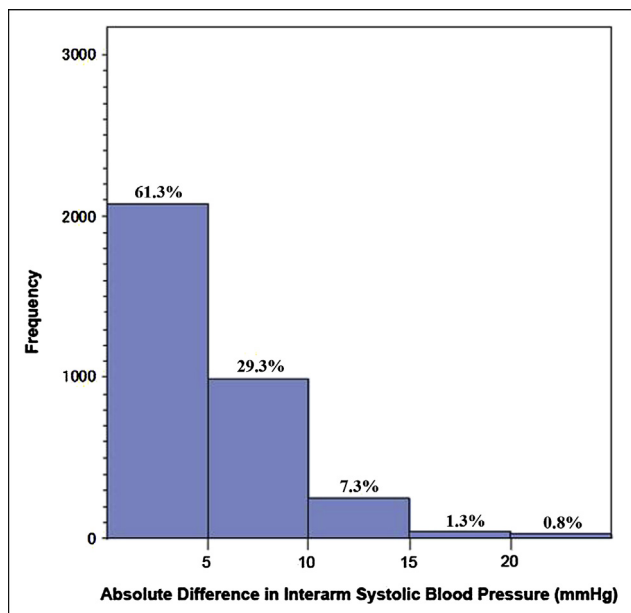
\*Percentages were calculated from the available number of participants in a particular category.

†Not age- and sex-adjusted.

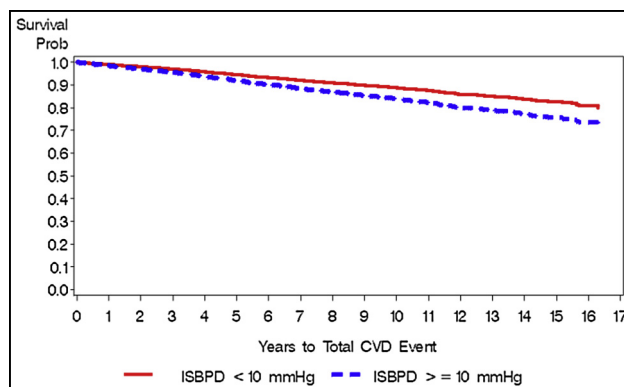
systolic blood pressure difference between arms in the sample is shown in **Figure 1**. There were 3073, 246, and 71 participants with ISBPD of <10 mm Hg, 10 to <15 mm Hg and  $\geq 15$  mm Hg, respectively.

Overall, 598 participants (17.6%) experienced a first cardiovascular event, including 83 (26.2%) participants with an increased ISBPD. The overall incidence rate of total cardiovascular disease was 17.64 per 1000 person-years (95% confidence interval [CI], 16.25-19.11). Age- and sex-adjusted Kaplan-Meier plots stratified by binary ISBPD (<10 mm Hg vs  $\geq 10$  mm Hg) are shown in **Figure 2** and show that the ISBPD  $\geq 10$  mm Hg category had a significantly higher probability for incident cardiovascular event than the ISBPD <10 mm Hg category (log-rank test chi-squared = 18.2,  $P < .0001$ ).

An ISBPD  $\geq 10$  mm Hg was associated with a significantly increased hazard of incident cardiovascular events in the multivariable adjusted Cox models (HR 1.38; 95% CI, 1.09-1.75) (**Table 2**). There was no change in the hazard with adjustment for Framingham risk score. In a multivariable model, an ISBPD  $\geq 15$  mm Hg was associated with an increased hazard of incident cardiovascular events (HR 1.47; 95% CI, 0.93-2.32). There was a statistically significant linear trend with increasing ISBPD category ( $P = .009$  in the multivariable adjusted model). An ISBPD  $\geq 10$  mm Hg also was associated with a significantly increased hazard of incident cardiovascular events in a subgroup analysis of 1433 hypertensive participants (HR 1.50; 95% CI, 1.14-1.97, in the multivariable model). In similar analyses for total mortality, there were no significant associations (**Table 2**). For each 1-SD increase in absolute ISBPD, the HR for incident cardiovascular events was 1.07 (95% CI, 1.00-1.14) in the multivariable-adjusted model



**Figure 1** Distribution of absolute interarm systolic blood pressure difference.



**Figure 2** Age- and sex-adjusted Kaplan-Meier plot for incident cardiovascular events in 3390 participants with or without an interarm systolic blood pressure difference (ISBPD)  $\geq 10$  mm Hg (log-rank test chi-squared  $P < .0001$ ).

(**Table 3**). There was no significant sex interaction with ISBPD. Adjustment for familial clustering did not materially alter the results.

We examined model performance and the utility of ISBPD in reclassification of overall risk for incident cardiovascular disease. Both the c-statistic for a multivariable model that included ISBPD and a multivariable model that did not include ISBPD were 0.74 (95% CI, 0.72-0.76). Category-based net reclassification for improvement changed significantly with ISBPD (NRI 0.021;  $P = .02$ ). The net reclassification is presented in **Table 4**.

## DISCUSSION

In this large, prospective, community-based cohort of middle-age men and women free of cardiovascular disease, an increased ISBPD was found to be present in nearly 10% of individuals, and is associated with increased levels of traditional cardiovascular risk factors. Furthermore, an increased ISBPD is associated with an increased risk for incident cardiovascular events, independent of traditional cardiovascular risk factors. This association is consistent when ISBPD was examined as a binary and as a continuous variable, and showed a positive linear trend across categories of increasing ISBPD. This is the first community-based cohort study to show such an association.

While we did not examine the anatomical correlates of increased ISBPD, our findings are consistent with previous publications linking subclavian artery stenosis to increased cardiovascular risk<sup>3,28</sup> and are indirectly consistent with studies linking increased ISBPD with subclavian artery stenosis. Indeed, ISBPD  $> 10$  mm Hg has been shown to have a high sensitivity,<sup>29,30</sup> yet a low specificity<sup>31</sup> for angiographically significant subclavian artery stenosis. Furthermore, in 2 population-based studies, subclavian artery stenosis has been found to correlate with conventional risk factors for atherosclerosis.<sup>6,16</sup> While a recent meta-analysis did not find a correlation between an ISBPD  $\geq 15$

**Table 2** Hazard Ratios of an Incident Cardiovascular Event or Mortality According to ISBPD Category

	BP Category	Incident CVD HR (95% CI)	Mortality HR (95% CI)
Primary analysis for ISBPD $\geq 10$ mm Hg:			
MV adjusted*	<10 referent	1.00	1.00
	$\geq 10$ mm Hg	1.38 (1.09-1.75)	1.02 (0.76-1.38)
Framingham 10-year risk score	<10 referent	1.00	1.00
	$\geq 10$ mm Hg	1.38 (1.09-1.75)	0.98 (0.72-1.33)
Analysis for ISBPD categories 10 to <15 mm Hg and $\geq 15$ mm Hg:			
MV adjusted*	<10 referent	1.00	1.00
	10 to <15 mm Hg	1.36 (1.04-1.77)	0.99 (0.71-1.39)
	$\geq 15$ mm Hg	1.47 (0.93-2.32)	1.11 (0.62-1.99)
	Trend <i>P</i> -value	.009	.82
Framingham 10-year risk score	<10 referent	1.00	1.00
	10 to <15 mm Hg	1.32 (1.01-1.72)	0.95 (0.67-1.35)
	$\geq 15$ mm Hg	1.62 (1.02-2.56)	1.05 (0.57-1.95)
	Trend <i>P</i> -value	.005	.97

BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; ISBPD = interarm systolic blood pressure difference; MV = multivariable.

\*Adjusted for age, sex, smoking status, diabetes mellitus, hypertension, high-density lipoprotein cholesterol/total cholesterol ratio, and cholesterol treatment.

mm Hg and a known pre-existing diagnosis of cardiovascular disease when pooling 6 studies,<sup>20</sup> subclavian artery stenosis has been shown to correlate with ischemic heart disease as detected by stress myocardial single-photon emission computed tomography.<sup>32</sup>

In 6743 participants free of clinical cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis (MESA) an ISBPD  $\geq 15$  mm Hg was found in 307 (4.5%) and correlated with subclinical measures of cardiovascular disease.<sup>3</sup> Consistent with our findings, the MESA participants with an increased ISBPD tended to be older, more likely to have diabetes mellitus and hypertension, and were more obese than participants with a normal ISBPD. An increased ISBPD was found to correlate with markers of atherosclerosis including peripheral artery disease (ankle-brachial index  $\leq 0.9$ ), an increase in carotid intima-media thickness, and a high coronary calcium score. Mortality and cardiovascular events were not assessed.

Several small prospective studies in cohorts of selected participants and a single meta-analysis previously described

an association between ISBPD and both all-cause and cardiovascular mortality,<sup>14,17,18,20</sup> however, an association with cardiovascular disease in those studies was inconsistent.<sup>20</sup> In a prospective study of 230 hypertensive patients (mean age 68.1 years) who were followed for a median of 9.8 years in a primary care setting, 55 (23%) had an ISBPD  $\geq 10$  mm Hg.<sup>14</sup> An ISBPD  $\geq 10$  mm Hg was associated with incident CV events and with all-cause mortality, and there also was an increase of 5%-6% in the incidence of mortality for each 1-mm-Hg increase in ISBPD. In another prospective cohort recruited from 2 clinics, 421 consecutive patients (mean age 62.9 years), 95% of whom were men, were followed for a median of 5.6 years. Mortality was 31% and associated with an increase in ISBPD.<sup>18</sup> In contrast, overall mortality in our study occurred in 12.2% over a longer period of time. Incident cardiovascular disease was not reported in this study. These 2 studies were small and selective, focusing on patients with hypertension or renal disease, making them less useful for drawing general conclusions. Adequately, in the secondary analysis in the subset of our study participants with hypertension, we observed a significant association between ISBPD and incident cardiovascular events. Finally, in another study combining 3 cohorts, 1778 subjects were recruited from both noninvasive vascular diagnostic laboratories and the community, and followed for a median of 9.4 years.<sup>17</sup> In a fully adjusted model accounting for cardiovascular risk factors and for baseline cardiovascular disease, an ISBPD  $\geq 15$  mm Hg demonstrated only increasing but not significant hazards for cardiovascular mortality (HR 1.43; 95% CI, 0.93-2.18). Incident cardiovascular disease was again not reported, the study population was enriched with high-risk patients being evaluated in vascular laboratories, and cause of death was adjudicated based on death certificate data. As expected, our study

**Table 3** Standardized ISBPD: Risk-factor-adjusted Relative Risk of a First Cardiovascular Event According to ISBPD

Stratification	HR (95% CI)*	<i>P</i> -Value
MV adjusted†	1.07 (1.00-1.14)	.04
Framingham 10 year risk score	1.08 (1.02-1.15)	.02

CI = confidence interval; HR = hazard ratio; ISBPD = interarm systolic blood pressure difference; MV = multivariable.

\*For every 1-SD-unit increase in blood pressure.

†Adjusted for age, sex, smoking status, diabetes mellitus, hypertension, high-density lipoprotein cholesterol/total cholesterol ratio and cholesterol treatment.

**Table 4** Net Reclassification Stratified by CVD Events

Risk Category without ISBPD	No CVD Event (n = 2783)			Incident CVD Event (n = 593)		
	Risk Category with ISBPD					
	<6%	6%-20%	>20%	<6%	6%-20%	>20%
<6%	543	16	0	177	6	0
6%-20%	23	1465	20	5	260	7
>20%	0	26	690	0	4	134

CVD = cardiovascular disease; ISBPD = interarm systolic blood pressure difference.

participants were of lower risk, and it is not surprising that our HR for cardiovascular events were lower. Our lower-risk population also may have been underpowered to detect a mortality association with ISBPD. Post hoc power calculations revealed that with 489/3390 deaths, 50 of which occurred in the ISBPD  $\geq 10$  mm Hg, we only had 22% and 76% power to detect HRs of 1.2 and 1.5, respectively. For the association with mortality, our HR was low and not significant. Furthermore, of the deaths in our cohort, most were not cardiovascular disease related, further limiting our ability to assess an association with ISBPD.

Potential limitations of the present study include sequential, as opposed to simultaneous, blood pressure measurements,<sup>2,7,33-35</sup> and blood pressure measurements during one encounter as opposed to an average of separate encounters.<sup>34,36,37</sup> Nonetheless, in a cohort in which the prevalence of ISBPD  $> 10$  mm Hg was 40%, the ISBPD was roughly stable, despite repeated measurements,<sup>18</sup> and in 2 studies comparing sequential and simultaneous measurements, the ISBPD differences were well below the 10 mm Hg threshold that we have used.<sup>35,38</sup> Given that our results have shown significant and consistent prognostic value, they are unlikely to represent random variation. Furthermore, sequential blood pressure measurement is the accepted method of measuring arm blood pressures in clinical practice,<sup>39</sup> making our results clinically applicable. Strengths of the present study include its large community-based sample, a comprehensive directly measured covariate assessment, and validated cardiovascular events and deaths. Finally, the significant category-based net reclassification improvement index suggests statistically significant, albeit small, enhancement of incident cardiovascular event prediction beyond traditional risk factors by considering ISBPD.

In conclusion, in this community-based cohort, an ISBPD was common and was associated with a significant increase in risk for cardiovascular events even after adjustment for cardiovascular risk factors. Even modest differences in clinically measured systolic blood pressures in the upper extremities reflect on cardiovascular risk. This study supports the potential value of identifying the ISBPD as a simple clinical indicator of increased cardiovascular risk. Blood pressure is easily obtained in an office setting, and our findings support recommendations for measurement of blood pressure in both arms, both for accurate blood pressure detection and for detection of ISBPD.

Our findings support research to expand clinical use of this simple measurement.

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