

Variability independent of mean blood pressure as a real-world measure of cardiovascular risk

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Summary

Background Individual-level blood pressure (BP) variability, independent of mean BP levels, has been associated with increased risk for cardiovascular events in cohort studies and clinical trials using standardized BP measurements. The extent to which BP variability relates to cardiovascular risk in the real-world clinical practice setting is unclear. We sought to determine if BP variability in clinical practice is associated with adverse cardiovascular outcomes using clinically generated data from the electronic health record (EHR).

Methods We identified 42,482 patients followed continuously at a single academic medical center in Southern California between 2013 and 2019 and calculated their systolic and diastolic BP variability independent of the mean (VIM) over the first 3 years of the study period. We then performed multivariable Cox proportional hazards regression to examine the association between VIM and both composite and individual outcomes of interest (incident myocardial infarction, heart failure, stroke, and death).

Findings Both systolic (HR, 95% CI 1.22, 1.17–1.28) and diastolic VIM (1.24, 1.19–1.30) were positively associated with the composite outcome, as well as all individual outcome measures. These findings were robust to stratification by age, sex and clinical comorbidities. In sensitivity analyses using a time-shifted follow-up period, VIM remained significantly associated with the composite outcome for both systolic (1.15, 1.11–1.20) and diastolic (1.18, 1.13–1.22) values.

Interpretation VIM derived from clinically generated data remains associated with adverse cardiovascular outcomes and represents a risk marker beyond mean BP, including in important demographic and clinical subgroups. The demonstrated prognostic ability of VIM derived from non-standardized BP readings indicates the utility of this measure for risk stratification in a real-world practice setting, although residual confounding from unmeasured variables cannot be excluded.

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Introduction

Widely available and now increasingly accessible measures of blood pressure (BP) offer ever greater opportunities for cardiovascular risk assessment. In addition to

the degree of BP elevation itself,¹ greater variation in BP levels that are observed from repeated measures is associated with greater cardiovascular risk. Studies of BP variation assessed over a period of days, using devices such as 24-h ambulatory BP monitors, have consistently found higher BP variability to be associated with risk for coronary artery disease, stroke, and cardiovascular

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Research in context

Evidence before this study

We searched PubMed for studies on the validation and use of blood pressure (BP) variability in cardiovascular risk assessment using the search term “BP variability.” No date or language limitations were placed on the search. Study titles were reviewed, with subsequent review of manuscript abstracts and full text, based on relevancy. Multiple BP variability measures were reviewed including standard deviation, coefficient of variation, average real variability and variability independent of the mean. Most studies utilized BP data from cohort or clinical trials rather than real-world settings, where fidelity of measurements is less stringent. Further, the use of measures such as standard deviation and average real variability are correlated with mean BP, limiting the assessment of BP variability’s independent association with cardiovascular outcomes.

Added value of this study

Our study demonstrates the feasibility of leveraging digitally stored BP data, despite its known limited measurement fidelity, to calculate variability independent of the mean, and that this measure retains its predictive capabilities in this setting. Further, our data show that variability independent of the mean is able to predict cardiovascular risk irrespective of age, sex, and predefined clinical comorbidities.

Implications of all evidence available

These results indicate that BP variability independent of the mean can be utilized in real-world clinical settings and is robust to lower fidelity BP measurements recorded outside of clinical trials, although residual confounding from unmeasured variables cannot be excluded. This finding enhances our understanding of the potential use of digitally stored, clinically generated data to further risk stratify patients, using measures not clearly identified or calculated by clinicians alone.

death.^{2–5} Furthermore, variation in visit-to-visit BP measured over years to decades in clinical trials and observational cohort studies have shown similar results.^{6–14} Despite these compelling findings, BP variation is rarely used in clinical practice, due to lack of evidence from real-world patient care settings, where BP data is collected with varying fidelity compared to clinical trials.

The potential utility of assessing BP variation in practice relies on its relation to outcomes, notwithstanding the heterogeneity in how BP data are captured in real-world settings when compared to cohort and clinical trial studies. In particular, BP measures in prospective studies are typically acquired according to rigorous procedures that can involve consistent positioning of the study participant, repeated measurements

performed in the same arm, and measurements performed without a clinician in the room after a pre-specified period of rest. By contrast, the time constraints and logistical demands of real-world patient care preclude adherence to standardized protocols.^{15–18} Therefore, to understand whether BP variability could be not only feasible but also informative as a measure of risk in clinical practice, we used readily available electronic health record (EHR) data to assess BP variability and examine its relation with cardiovascular outcomes across a large unselected cohort of ambulatory patients.

Methods

Study design. We identified a total of 677,996 patients in our health system (large academic medical center in Southern California) who had at least 1 ambulatory visit during which BP was documented in the EHR. Of these individuals, 51,147 patients had at least 1 ambulatory visit with a BP measurement documented every calendar year, from years 2013 through 2016 (i.e. representative of consistent ambulatory care). We defined the ‘clinical assessment period’ (years 2013 through 2016) as the time window during which EHR data were used to calculate BP variability (Figure 1). Prior to and during this period, we used ICD-9 and ICD-10 codes to identify comorbid conditions including diabetes mellitus, chronic kidney disease, coronary artery disease, hypertension, and atrial fibrillation or flutter (Supplemental Table 1). Dyslipidemia was not assessed due to previously recognized limitations in the accuracy of administrative coding, even in combination with laboratory data, when using electronic health records data to identify presence of this condition.¹⁹ We identified age, race/ethnicity, and smoking status at the time of first visit. We also determined if patients were prescribed any antihypertensive medication at any time during the clinical assessment period. For primary analyses, we defined the ‘outcomes surveillance period’ (years 2017 through 2019) as the time window during which ICD-9 and ICD-10 codes were used to identify new-onset cardiovascular events including myocardial infarction, heart failure (both preserved and reduced ejection fraction), and stroke (Figure 1). We identified all-cause death using vital status documented in the EHR. We studied the outcome of all-cause mortality given that we were unable to reliably ascertain specific cause of death for mortality events occurring outside of our health system. All study protocols were approved by the Cedars-Sinai Institutional Review Board with requirement for individual informed consent waived.

Sampling strategy. For primary analyses, we excluded 5469 patients who had stroke, myocardial infarction, or heart failure diagnosed prior to the main outcome surveillance period (before year 2017) or died in 2016 following a visit during which BP was recorded. We further excluded 3196 patients aged <18 years at the

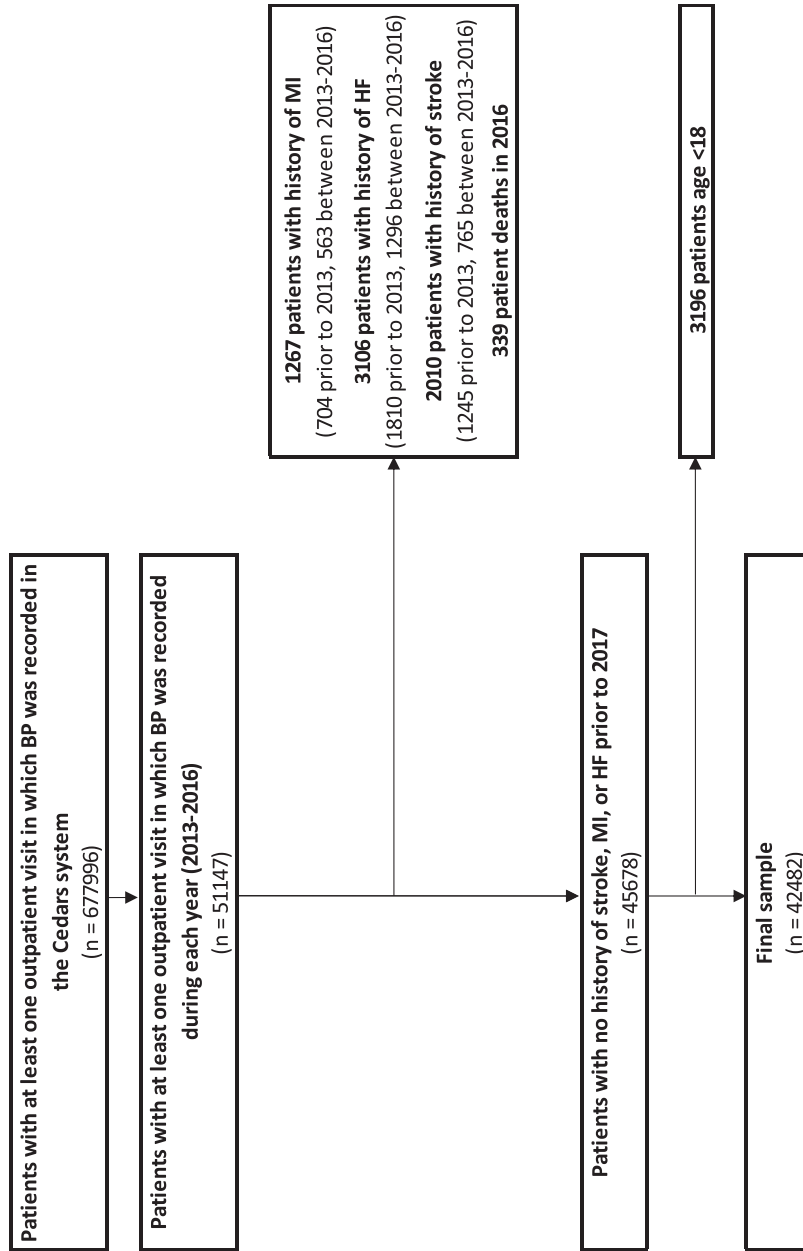


Figure 1. Primary cohort development.

study period start, resulting in a final sample of 42,482 patients who contributed 1117,944 qualifying BP measurements, of which 600,953 occurred during the clinical assessment period (from 2013 through 2016); BP data from this period were used to calculate variability independent of the mean (VIM) for the primary analysis (Figure 1). In order to examine whether our results were sensitive to the choice of outcome surveillance dates, we conducted a sensitivity analysis in which we considered a clinical assessment period from 2013 to 2015 and an extended outcomes surveillance period from years 2016 to 2019. For these analyses, from the 51,147 patients with consistent ambulatory care (from years 2013 to 2016), we excluded 4661 individuals with cardiovascular disease diagnosed prior to year 2015. We further excluded 3198 patients aged <18 years at the first visit. The final sensitivity analysis cohort included 42,388 patients with 449,461 qualifying ambulatory visits during the clinical assessment period.

Blood pressure variability. We extracted the systolic (SBP) and diastolic (DBP) BPs, measured in mmHg, from every outpatient visit at which these were measured during the 'clinical assessment period' (years 2013 through 2016); if multiple BP readings were recorded for a single visit, the SBPs and DBPs for that visit were averaged. We then calculated the VIM for SBP and DBP separately, for all eligible patients, using all BP measurements from 2013 through 2016. Upon careful consideration of the multiple methods previously applied and evaluated for measuring BP variability, we elected to use the VIM method to quantify visit-to-visit BP variability given that alternate measures (e.g. standard deviation, coefficient of variation, and mean real variability) have previously been shown as highly correlated with the mean BP, thus limiting their ability to differentiate from effects of mean BP.^{7,20} The VIM is calculated first as the standard deviation of BP readings divided by the mean BP raised to the power of x , where x is obtained from fitting a nonlinear regression model among the entire sample where standard deviation = $a \times \text{mean}^x$. This quantity is then multiplied by the sample mean BP raised to the power of x . As such,

$$\text{VIM} = \frac{k \times \text{Standard Deviation (SBP)}}{\text{Mean (SBP)}^x}$$

Where,

$$k = \text{Mean}(\text{Mean}(\text{SBP}))^x$$

Since VIM is derived from the distribution of BP within the sample itself, the values of VIM in a given sample cannot be compared to the values from a population with a different distribution of BP values. In general, the value of the VIM is considered a relative, rather than an absolute measure of BP variability given that it is calculated in reference to values derived from

mean BP; a higher value of VIM represents greater variability of visit-to-visit BP readings.²⁰

Statistical analyses. In patients without any documented cardiovascular outcome of interest or death prior to year 2017, we performed multivariable Cox proportional hazards regression to compute hazard ratios (HRs) examining the association between VIM (separately for SBP and DBP) during the clinical assessment period and the development of the primary outcome during the outcome surveillance period. The primary outcome of interest was a composite of new-onset myocardial infarction, heart failure, stroke, or all-cause mortality; secondary analyses considered each of these events separately. For the primary analysis, patients were censored at time of last recorded outpatient visit during which BP was measured or at the end of the outcome surveillance period (December 31, 2019), whichever came first. In secondary analyses of myocardial infarction, heart failure, and stroke, patients were further censored at date of death if they died prior to the end of the study period. All analyses adjusted for age, sex, race/ethnicity, and smoking status along with presence of diabetes mellitus, chronic kidney disease, coronary artery disease, or atrial fibrillation or flutter; all analyses also adjusted for use of antihypertensive medications, the number of visits at which a BP was recorded, and mean SBP and DBP. In secondary analyses, we repeated the primary outcome analyses in subgroups stratified by sex, hypertension status, age (≤ 50 vs > 50 years), diabetes status, chronic kidney disease status, and coronary artery disease status. Clinical conditions were defined based on ICD-9 and 10 codes. In sensitivity analyses, we repeated all models using a clinical assessment period of 2013 to 2015 and an outcomes surveillance period of 2016 to 2019. We conducted all statistical analyses using R (v3.6.1) and considered statistical significance as a two-tailed P value < 0.05 .

Role of the funding source. Funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Authors JE, MD, PB, and SC had direct access to the data. The decision to submit for publication was made by all authors.

Results

Primary analyses. The study cohort had an average age of 53.9 ± 16.4 years with 62.0% women and 60.8% Non-Hispanic White patients. The most common comorbidity was diabetes mellitus (10.7%), followed by coronary artery disease (8.1%), with 24.8% of patients prescribed at least 1 antihypertensive medication at some point during the study period. On average, patients had 14 ± 11 BP measurements documented during outpatient visits with a mean SBP of 123 ± 12 mmHg and DBP of 74 ± 7 mmHg (Table 1).

Characteristic	Overall (n = 42,482)	Female (n = 26,341)	Male (n = 16,141)
Demographic characteristics			
Age, years, mean (SD)	53.88 (16.38)	52.63 (16.67)	55.93 (15.69)
Race/ethnicity, n (%)			
Asian	4052 (9.5)	2834 (10.8)	1218 (7.5)
Hispanic/Latinx	4760 (11.2)	3249 (12.3)	1511 (9.4)
Non-Hispanic Black	5474 (12.9)	3960 (15.0)	1514 (9.4)
Non-Hispanic White	25,840 (60.8)	14,974 (56.8)	10,866 (67.3)
Other ¹	1274 (3.0)	780 (3.0)	494 (3.1)
Unknown	1082 (2.5)	544 (2.1)	538 (3.3)
Smoking status, n (%)			
Current	2076 (4.9)	1035 (3.9)	1041 (6.4)
Former	11,879 (28.0)	6381 (24.2)	5498 (34.1)
Never	28,527 (67.2)	18,925 (71.8)	9602 (59.5)
Clinical characteristics			
Number of BPs recorded during study period, mean (SD)	14.15 (11.06)	14.62 (11.54)	13.38 (10.18)
Renal disease, n (%)	2353 (5.5)	1041 (4.0)	1312 (8.1)
Atrial fibrillation or atrial flutter, n (%)	1864 (4.4)	758 (2.9)	1106 (6.9)
Diabetes mellitus, n (%)	4537 (10.7)	2380 (9.0)	2157 (13.4)
Coronary artery disease, n (%)	3449 (8.1)	1049 (4.0)	2400 (14.9)
BP characteristics			
Antihypertensive use, n (%)	10,546 (24.8)	5311 (20.2)	5235 (32.4)
Mean systolic BP, mean (SD), mmHg	123.78 (12.04)	122.32 (12.72)	126.18 (10.39)
Mean diastolic BP, mean (SD), mmHg	74.13 (7.11)	72.96 (6.88)	76.03 (7.07)
Systolic variation independent of the mean, mean (SD)	10.67 (3.50)	10.93 (3.45)	10.24 (3.55)
Diastolic variation independent of the mean, mean (SD)	7.51 (2.42)	7.64 (2.40)	7.32 (2.44)

Table 1: Demographic and clinical characteristics.

Abbreviations: SD, standard deviation

1. Other race includes American Indian/Alaska Native Hawaiian or other Pacific Islander, and Other.

During the outcomes surveillance period, there were $n = 1572$ new diagnoses of cardiovascular outcomes including myocardial infarction ($n = 338$), heart failure ($n = 816$), and stroke ($n = 418$) in addition to $n = 700$ deaths. In multivariable Cox proportional hazards models, VIM of SBP was associated with an increased risk for the composite outcome of any new cardiovascular disease diagnosis or death (HR, 95% CI 1.22, 1.17–1.28), as well as all disaggregated clinical outcomes (Figure 2A). In stratified analyses, both females (1.18, 1.11–1.25) and males (1.26, 1.18–1.34) demonstrated increased risk of the composite endpoint, without an appreciable difference between sexes ($P = 0.12$). In disaggregated outcome analyses, higher VIM was associated with increased risk of death in both females (1.26, 1.13–1.39) and males (1.42, 1.29–1.56), with the risk being significantly higher for men than for women ($P = 0.03$) (Figure 2B).

Findings for VIM of DBP were similar to those for VIM of SBP. Increasing DBP VIM was associated with greater risk of the composite outcome (1.24, 1.19–1.30) as well as all component clinical endpoints. Associated risk for the composite outcome was elevated in both sexes without a significant difference between females

(1.22, 1.14–1.30) and males (1.26, 1.18–1.34) ($P = 0.47$) (Figure 2C). There were no significant sex-specific differences in any of the distinct clinical endpoints (Figure 2D).

In overall sex-pooled analyses of associations with VIM and the composite outcome, there was an increasing trend in risk of adverse cardiovascular events across deciles of VIM; notably, both mean SBP and DBP values plotted across deciles of VIM were flat (Figure 3).

Secondary analyses. Both SBP and DBP VIM were significantly associated with the composite outcome following stratification by age (≤ 50 years vs > 50 years) and the presence of prespecified clinical comorbidities, including diabetes mellitus, coronary artery disease, renal disease and hypertension (Figure 4). There were no statistically significant differences in the association by age strata or between those with and without the specified clinical conditions. In particular, results were similar for the subgroup of patients with compared to without pre-existing coronary artery disease.

Sensitivity analyses. Characteristics of the sensitivity analysis cohort were similar to those of the primary analysis cohort. During the extended outcomes surveillance period, there were $n = 2368$ new

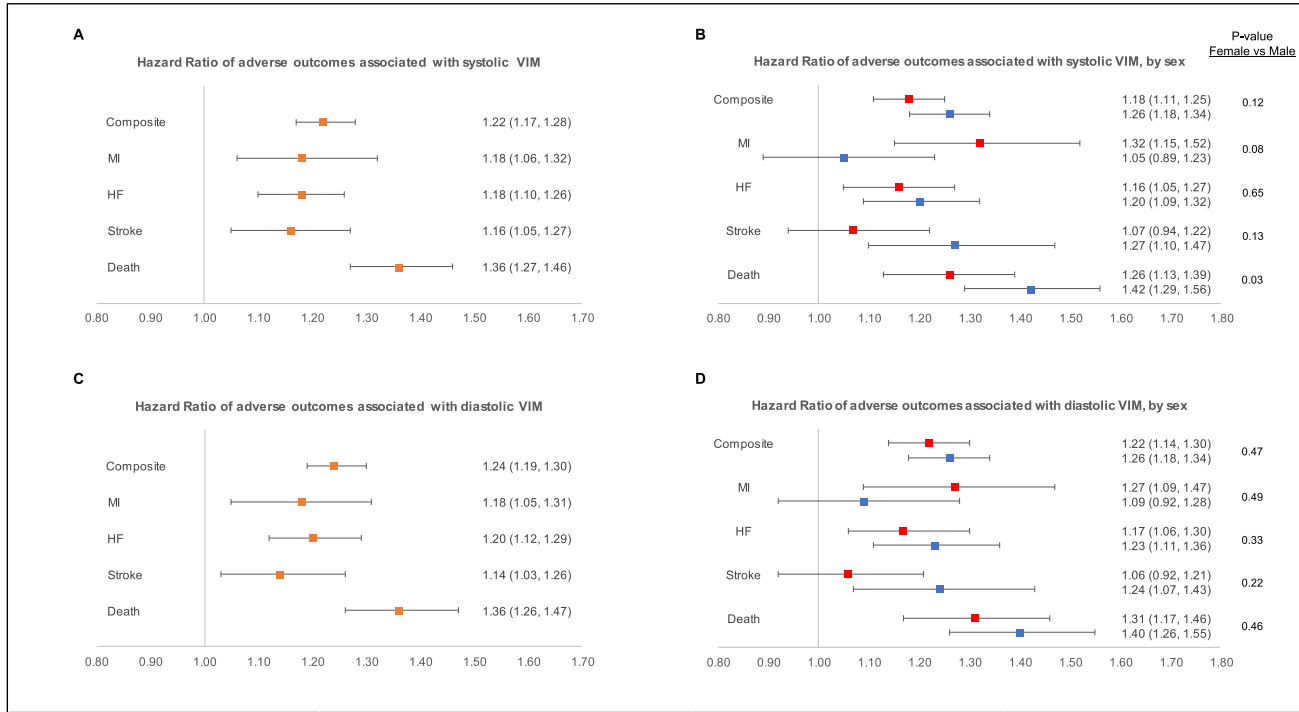


Figure 2. Association of variability independent of the mean BP and new-onset cardiovascular disease or death. Hazard of outcomes of interest associated with (A) systolic BP VIM among the entire cohort, (B) sex-disaggregated systolic BP and VIM, (C) diastolic BP VIM among the entire cohort, (D) sex-disaggregated diastolic BP and VIM. Hazard ratios were calculated using multi-variable Cox proportional hazards regression, controlling for age, sex, race/ethnicity, smoking status, diabetes mellitus, chronic kidney disease, atrial fibrillation or flutter, coronary artery disease, use of antihypertensive medications and the number of visits at which a BP was recorded, as well as mean SBP and DBP. Horizontal black lines represent 95% confidence intervals; colored boxes represent point estimates. P-values in panels B and D represent significance of the interaction term of VIM and sex on each respective outcome. HF, heart failure. MI, myocardial infarction. VIM, variability independent of the mean BP.

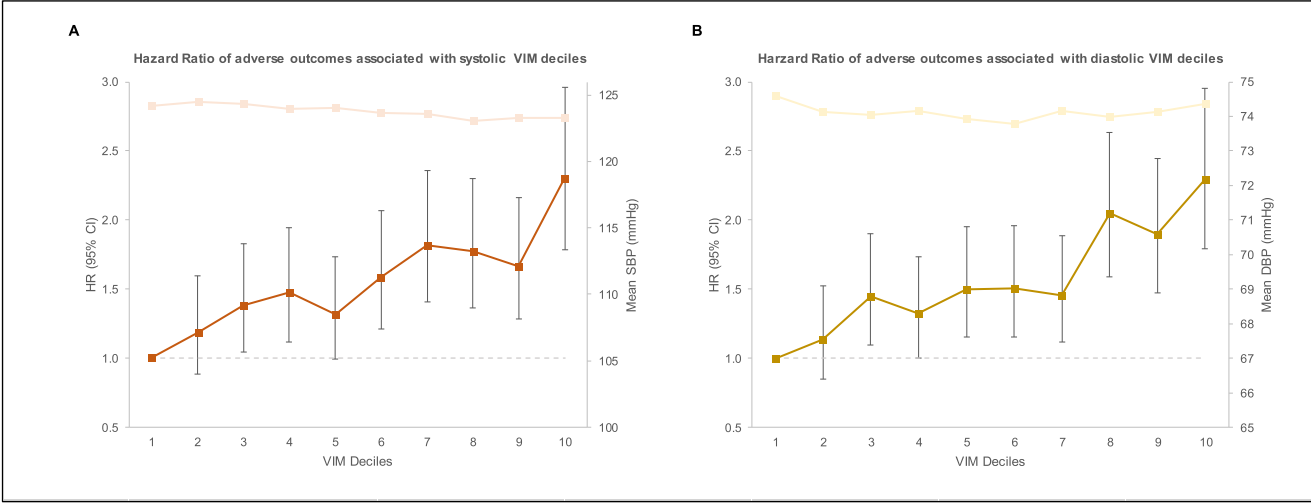


Figure 3. New-onset cardiovascular disease risk or death by decile of variability independent of mean BP. Hazard of composite outcome and (A) mean systolic BP by deciles of systolic BP VIM, and (B) mean diastolic BP by deciles of diastolic BP VIM. VIM, variability independent of the mean. Vertical black lines represent 95% confidence intervals; colored boxes represent point estimates. SBP, systolic BP. DBP, diastolic BP. HR, hazard ratio.

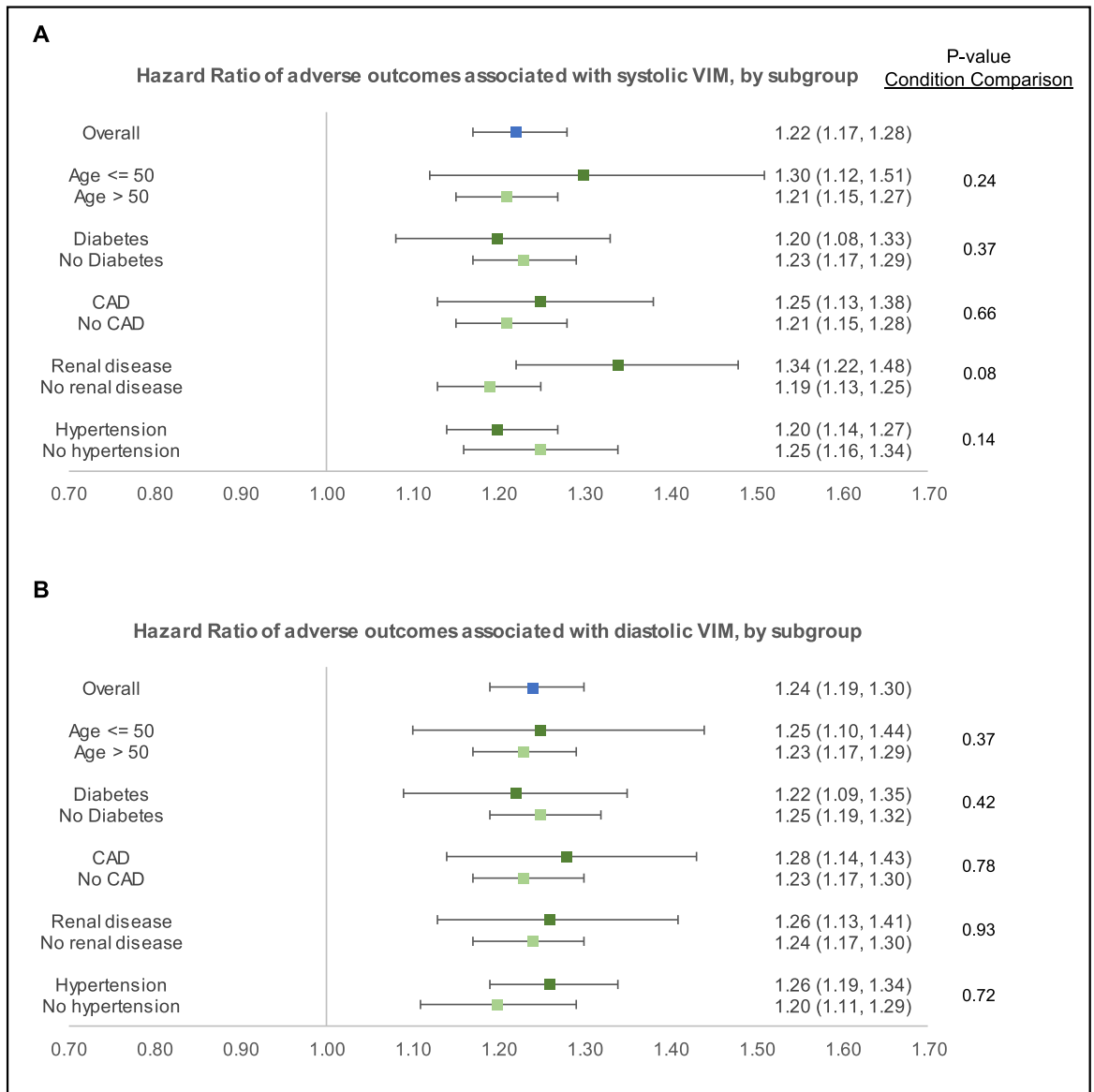


Figure 4. Association of variability independent of the mean BP and new-onset cardiovascular disease or death, stratified by clinical conditions. Hazard of outcomes of interest, stratified by clinical conditions, associated with (A) systolic BP VIM, and (B) diastolic BP VIM. Hazard ratios were calculated using multivariable Cox proportional hazards regression, controlling for age, race/ethnicity, smoking status, diabetes mellitus, chronic kidney disease, atrial fibrillation or flutter, coronary artery disease, use of antihypertensive medications and the number of visits at which a BP was recorded, as well as mean SBP and DBP. Horizontal black lines represent 95% confidence intervals; colored boxes represent point estimates. P-values represent significance of the interaction term of VIM and each clinical condition on new-onset cardiovascular disease or death. VIM, variability independent of the mean BP. CAD, coronary artery disease.

diagnoses of cardiovascular outcomes including myocardial infarction ($n = 504$), heart failure ($n = 1236$), and stroke ($n = 628$), in addition to $n = 961$ all-cause deaths. Both increasing SBP VIM (1.15, 1.11–1.20) and DBP VIM (1.18, 1.13–1.22) were associated with the composite outcome. In sex-aggregated analyses of specific outcomes, both SBP and DBP VIM were also positively associated with heart failure, stroke and

mortality, though only DBP VIM was associated with myocardial infarction (**Supplemental Figure 1A,C**). In sex stratified analyses, increasing SBP VIM and DBP VIM were associated with the composite outcome for both men and women. There were no sex differences in SBP and DBP VIM associations with the composite or distinct cardiovascular outcomes (**Supplemental Figure 1B,D**).

Discussion

In this study of over 42,000 adults, we demonstrate that clinically generated individual-level BP variation captured by the EHR can be reliably quantified in a large patient population and shown to predict cardiovascular outcomes. Importantly, we found that BP variation in this real-world setting is associated with significantly greater risk for new-onset cardiovascular disease independent of mean BP. These findings were consistent for the specific cardiovascular disease types including myocardial infarction, stroke, and heart failure, as well as for all-cause mortality; the findings were also consistent across subgroups categorized by age, sex and clinical comorbidities. In effect, our results indicate that variation in BP data acquired from across a range of clinical venues is both an accessible and informative measure of cardiovascular risk in real-world settings.

The current study extends from prior investigations of BP variability that have relied predominantly on either high-frequency data captured over a short period of time (i.e. 24-h ambulatory BP monitoring) or low-frequency data captured over a long period of time (i.e. cohort study data with BP measured every few years over decades).^{5,6,21} We applied the VIM method of capturing BP variability to the clinical practice setting, not only to test its validity when based on less extreme measurement frequency, but also to evaluate its potential application and utility in a real-world environment. In this setting, we found that VIM predicted not only cardiovascular disease in the near-to-intermediate term but was able to leverage BP data generated from disparate clinical sources to derive more signal than noise. We also showed the prognostic potential of VIM across demographic and clinical subgroups at risk for BP associated adverse outcomes. We recognize that BP variability can arise from many possible etiologies including and not limited to medication non-adherence, medication rebound effects, neurohormonal pathophysiology, in addition to variations in measurement technique. Our results suggest that EHR derived BP data, amidst the multiple potential sources of variation, could yet be used to auto-calculate VIM that may serve as a practical tool for further tailoring approaches to risk stratification in the clinical setting and across a broadly diverse patient population.

Our analyses expand from prior work that relied on protocolized BP data collections in controlled studies. BP protocols in clinical trials, for instance, are typically adherent to guidelines recommendations that patients be seated quietly in a room for at least 5 min, legs uncrossed, and feet on the floor with BP measurements performed and then repeated after 1-2 min.¹ Unfortunately, time constraints and limited training on BP technique results in reduced protocol adherence in the real world.²²⁻²⁵ In fact, a systematic assessment of BP technique found that only 1 out of 159 medical students

correctly performed all aspects of BP measurement.²⁶ Deviations from protocol can result in BP values up to 5 mmHg higher than those obtained in clinical trials.^{15,27} For all these reasons, it is well recognized that BP findings from controlled studies are not always directly applicable to real-world clinical practice. Nonetheless, our findings indicate that EHR derived BP data can be used to calculate and derive prognostic utility from the VIM, as has been shown in prospective clinical studies in which BP measurement is highly protocolized. While prior studies have examined using EHR data to estimate other measures of BP variability,²⁸ our results demonstrate that VIM, a variability measure that overcomes the inherent correlation between standard deviation and BP, can be determined using readily available EHR data. Although these results should not be taken as a reason to forego appropriate BP measurement technique or dismiss the importance of lowering BP, they demonstrate the potential utility of an admittedly imperfect measure for aiding in clinical risk assessment.

Prior work has shown that throughout early adulthood, women on average have lower BP than men,²⁹ although the risk of cardiovascular disease, including stroke, myocardial infarction and heart failure is higher for women at the same BP levels as men.³⁰ In our primary analysis, sex specific differences in the association between VIM at these endpoints were not appreciated, and while the risk of death with higher VIM was found to be greater among men than women, this must be interpreted cautiously given the lack of such a difference in our time shifted sensitivity analysis. Although larger prospective studies are needed to validate our findings, these data indicate that VIM may represent a sex-independent marker of composite cardiovascular risk, at all BP levels, and help to address some of the limitations inherent to assessing mean BP alone which may underestimate risk in females.

Further, the association of increasing VIM with a composite of cardiovascular events and death was consistent across age and clinically comorbid conditions. Importantly, the short to intermediate term risk of elevated BP and cardiovascular events among younger patients is less well understood than for older individuals, with multiple proposed BP thresholds above which risk increases at lower ages. This is similarly true for those with diabetes mellitus, coronary artery disease and renal dysfunction.³¹⁻³⁴ We found that VIM was positively associated with the composite outcome in stratified analyses of each of these subgroups, as well as among patients with a diagnosis of hypertension. These results indicate that VIM may serve as a risk marker independent of mean BP, helping to further clarify risk among populations in whom BP thresholds may vary from the general population. Given the observational nature of our study, performed using medical records

data, future studies are needed to more directly interrogate possible mechanisms underlying our findings. Prior studies have suggested that BP variability promotes cyclical hemodynamic and mechanical stress on the vasculature that can lead to endothelial damage and accelerate the development of subclinical atherosclerosis that precedes clinical cardiovascular events.⁶ Further investigations are needed to understand how BP variability may be more relevant to some forms of cardiovascular disease more than others. Additional studies with more granular data are also needed to ascertain whether certain classes or individual types of antihypertensive medications may influence BP variation among susceptible patients.

Several limitations of our study merit consideration. Interpretation of VIM outside of the population used to calculate its value is difficult due to its reliance on the distribution of BP within the sample itself. As such, we cannot say that a specific amount of variability increases risk more than another, but rather that increased variability overall is associated with adverse outcomes. Residual confounding may also arise from factors such as dyslipidemia, sleep apnea, and physical activity that are associated with both BP variability and cardiovascular risk. This is an important limitation intrinsic to EHR data, wherein all potentially relevant clinical data may not be available such that potential bias related to these unmeasured variables cannot be excluded. Given relative lack of 24-h ambulatory BP monitoring data available for the current analyses, additional investigations are needed to examine how diurnal and nighttime variations in BP may be related to the VIM measures and outcomes studied herein. Further, risk stratification and identification of endpoints were based on EHR and ICD-9/10 data. To minimize effects of potential coding errors, we selected ICD-9/10 codes that are considered the most reliable for cardiovascular outcomes analyses.^{35,36} Residual inaccuracies intrinsic to the data may yet have contributed to non-differential misclassification. We also limited our analysis to only incident cardiovascular disease, excluding those with a documented history of myocardial infarction, heart failure, or stroke prior to the study period. As such, the association of VIM and future recurrent cardiovascular events warrants future investigation. Future work should also examine potential differential associations between VIM and subtypes of the identified cardiovascular events, including differences between heart failure with reduced versus preserved ejection fraction. Many clinical events occurring outside of our health system were later captured within the electronic health record by later treating providers who tend to prioritize documenting prior cardiovascular events given their clinical importance. Nonetheless, it is likely that not all outside occurring events could be captured in this way. To ensure follow-up, we limited our cohort to patients with at least 1 visit annually and those without a history of

pre-identified cardiovascular events, which may limit generalizability to those who either seek care less frequently, change medical systems, or have a history of cardiovascular events. Notwithstanding potential socio-cultural and regional differences, our study cohort was found to be demographically relatively representative of the overall adult US population.³⁷ Because all our analyses were conducted using data from a single health system, additional studies of separate patient cohorts are still needed to validate and assess the generalizability of our findings.

In summary, our results reveal BP variability as an indicator of cardiovascular risk that is not only readily accessible from across a range of clinical practice venues but is also highly prognostic for risk of myocardial infarction, stroke, or heart failure in real-world settings. These findings demonstrate effective translation of a previously under-recognized clinical risk marker from controlled studies into the pragmatic clinical care environment – and offer promise for extension to home-based and remote monitoring applications. Future work is needed to examine even broader digital health applications and also to – across various practical settings – develop and determine the potential of interventions targeting BP variability to lower cardiovascular risk.

Data sharing statement

Due to the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to Cedars-Sinai Medical Center at biodatacore@cshs.org.

Contributors

JEE was involved in Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resource, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Project administration, and Funding acquisition for the manuscript. MD was involved in Methodology, Validation, Formal analysis, Writing - Review & Editing, and Visualization for the manuscript. DO was involved in Methodology and Writing - Review & Editing of the manuscript. PB was involved in Validation, Formal analysis, and Writing - Review & Editing of the manuscript. HJ and CAB were involved in Data Curation and Writing - Review & Editing of the manuscript. MAR, NAB, and FR were involved in Methodology and Writing - Review & Editing of the manuscript. TJN and CMA was involved in Methodology, Resources, and Writing - Review & Editing of the manuscript. SC was involved in Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resource, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization,

Supervision, Project administration, and Funding acquisition for the manuscript.

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Declaration of interests

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101442.

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