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Titolo della tesi

Visit-to-visit Systolic Blood Pressure Variability and Clinical Implications in a High-Risk Hypertensive Population: an Analysis of the SPRINT Data

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Summary

Abstract

Aim. The prognostic significance of blood pressure variability (BPV) for the occurrence of cardiovascular (CV) events and mortality is still debated. Differences in its methodological assessment and in patients' characteristics have been both indicated as potential explanations to the discrepant findings. We used the Systolic Blood Pressure Intervention Trial (SPRINT) dataset to explore this unresolved issue.

Methods. We applied three protocols that differed by timing and number of study visits to calculate the same index (coefficient of variation, CoV, %) of long-term (visit-to-visit) systolic BPV: 1) quarterly until outcome occurrence, including monthly assessment during the 3-months titration period; 2) quarterly until outcome occurrence, excluding titration period; and 3) quarterly for 1 year, excluding titration period. Outcomes of interest were primary events and all-cause mortality. Crude and progressively adjusted Cox proportional hazard models were used to assess the risk of outcomes according to the three estimates of visit-to-visit systolic BPV.

Results. An optimal visit-to-visit systolic BPV associated with lower incidence of the primary outcome (CoV 5-10%) and all-cause mortality (CoV ≤8%), or any of the two (CoV 5-11%), was identified according to the first two estimates only. This effect was independent of mean systolic BP. Optimal visit-to-visit systolic BPV appeared to confer additional protection to intensive BP lowering. Conversely, different BPV apparently worsened CV risk among standard-treated patients. Clinical correlates of suboptimal BPV included older age, female gender, non-White ethnicity, smoke, and pre-existing CV and renal disease.

Conclusions. Visit-to-visit systolic BPV might add prognostic value to the estimation of CV risk in high-risk, non-diabetic hypertensive patients, but the protocol adopted for its calculation is crucial. An effort to standardize BPV assessment is worthwhile.

Keywords

Population Biologic Variability; Blood Pressure; Hypertension; Research Methodology; Cardiovascular Diseases; Mortality

The Systolic Blood Pressure Intervention Trial (SPRINT)

and the *SPRINT Data Analysis Challenge*

The Systolic Blood Pressure Intervention Trial (SPRINT) was a randomized, controlled, open-label trial conducted between 2010 and 2013 at 102 clinical sites organized into 5 clinical center networks in the United States and Puerto Rico [1]. It compared intensive management of systolic blood pressure (target, <120 mm Hg) with standard management (target, <140 mm Hg) in high-risk, non-diabetic hypertensive participants aged 50 years and older. Sponsored by the National Heart, Lung, and Blood Institute (NHLBI), the National Institute on Aging, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute of Neurological Disorders and Stroke, the trial was stopped early in 2015, after a median follow-up of 3.26 years of the planned average of 5 years, because of a significantly lower rate of cardiovascular (CV) events with intensive compared to standard management [1].

In January 2016, the International Committee of Medical Journal Editors proposed a plan on sharing clinical trial data to the purpose of acknowledging the potential value of this approach for the benefit of patients and the advancement of science [2]. In fact, often patients participate in clinical trials at great risk to themselves, and researchers and analysts are expected to use the relative data in a responsible way to advance medicine.

To clarify the complexities and promote the potential benefits of data sharing, the New England Journal of Medicine (NEJM) and the Harvard Medical School Department of Biomedical Informatics started a project aimed at challenging the possibility of

maximizing data extraction from real clinical trial data by simply opening them to external researchers [3].

A first step was to identify a clinical trial data set that could be mined for new purposes. The SPRINT trial, whose main results have been published in November 2015 by the NEJM, was selected to this aim. Thus, the NHLBI and the SPRINT Data Coordinating Center joined the NEJM's effort to show how clinical trial data can be used to identify additional advances in human health: together, they co-sponsored an international contest that became known as the *SPRINT Data Analysis Challenge* [2].

The *SPRINT Data Analysis Challenge* was meant to challenge clinical trialists, data analysts, and any other interested party to reanalyze the published SPRINT data, either alone or in combination with other publicly available data, to derive new insights or ideas, and to generate new findings with the potential to improve the general understanding of disease or patient care.

Individuals and institutions interested in participating in the *Challenge* were required to obtain ethics committee approval (or an exemption) and sign a data use agreement in order to request and receive the data [2]. The SPRINT Investigators and the NHLBI's BioLINCC repository made the SPRINT data available in November 2016 to those who had gone through this first step. After receiving the data set, participants had to qualify to enter the *SPRINT Data Analysis Challenge* by proving that they could answer one of two questions that required possession and use of the data (**box 1**) [2]. Then, the real challenge began: to identify a novel biologic or clinical finding using the SPRINT data [2].

Entries were judged on the basis of novelty, applicability to clinical practice, and soundness of methods by 15 recognized experts who represented the three primary constituencies — clinical trialists, data analysts, and patients. In addition to being reviewed by one representative from each constituency, all entries were opened to the public for voting [2]. At the end of the contest, participants of the *SPRINT Data Analysis Challenge* could then propose their work for publication, independent of the contest classification.

A total of 279 groups from around the world requested the data, 205 of them completed BioLINCC's process, 218 individuals and teams entered the qualifying round, 200 qualified for the main event, and 143 entries were received for the *Challenge Round* by the deadline of February 14, 2017 (**Figure 1**) [2]. The participants were quite diverse in terms of both geographic origin, extent of experience in clinical research, and background (academia, industry, regulatory agencies), with about 107 institutions from 26 countries being represented [2].

Nearly a third of the 143 entries were analyses based on the individual's blood pressure measurements over time. A quarter of the entries were benefit–risk calculators. Another portion consisted of subgroup analyses using one or more of the baseline characteristics of the patients to parse risk levels. The remaining entries were a variety of types of analyses such as using patients' medications or medication adjustments to determine their risk level or examining race and center effects in SPRINT. Several entrants used an additional data set, most often the data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [2]. A survey of people who either entered the *SPRINT Data Analysis Challenge* or intended to do so

revealed that the major barriers to entry were time constraints and difficulties obtaining ethics committee approval [2].

By correctly qualifying to the first steps, we became one of the 143 teams worldwide who had the possibility to propose their findings and compete for the award (**Figure 1**). Our new finding consisted in an analysis on the distribution of CV risk in SPRINT based on participants' diastolic blood pressure (BP) profile. The analysis was tested in the population overall and in predefined subgroups based on pre-existing chronic kidney disease (CKD) and CV disease (CVD). We observed a J-curve phenomenon in participants with pre-existing CKD and CVD, but not in those without these conditions, a finding that supports the importance of patients' clinical characteristics in shaping their CV risk profile. These findings were published in the *Journal of the American Society of Hypertension* (JASH) [4] and were accompanied by an Editorial of the Journal's Editor-in-Chief, Dr. Daniel Levy [5], who stated:

> "... This new study provides further support for the risks associated with a low attained diastolic blood pressure in patients receiving antihypertensive treatment who have either pre-existing cardiovascular disease or chronic kidney disease. The authors are to be congratulated for their clever use of the public release SPRINT dataset to test a long-standing controversy in clinical medicine. ..."

The sharing of clinical trial data is a complex issue and an important obligation to clinical trial participants, centered around the question whether a clinical trial data set could be used by other investigators to produce new findings. Technological advances and extensive analytic resources have provided the necessary tools to the community of researchers in the medical field for maximizing information extracted from long-lasting clinical trials that require economic investment and human commitment. The *SPRINT Data Analysis Challenge* brought together teams of clinical trialists and data analysts and demonstrated that when they work together, they can develop new ideas.

The present work represents a further development of the research approach initiated under the *SPRINT Data Analysis Challenge*.

Box 1. ***Qualifying Round: Answer One Question Using SPRINT Data.***

QUESTION*: What is the sample size and the mean for the systolic blood pressure at the last recorded [post-baseline] study visit for each participant by treatment arm (Intensive and Standard)?*

ANSWER. The statistical analysis was performed with R environment v.3.2.2 through "stat" package, according to the following procedure.

The last available, post-baseline visit for each participant was included (n=9249). A-priori exclusion of SBP missing values was applied (n=1, maskID S32412). Among the remaining 9248 participants, data analysis revealed 8 outliers with a numeric value for SBP comprised between 0 and 3 mmHg at their last visit (maskID S02523, S05662, S10460, S16441, S20422, S58370, S76600, and S78737).

From this basis, three different approaches were adopted for the calculation of sample size and mean SBP by treatment arm:

1. Using the dataset as selected (n=9248)
2. Excluding the incoherent data (SBP ≤ 3 mmHg; n=8) from the dataset
3. Using, for each of the 8 outliers and the missing SBP value, the last useful SBP value recorded (at 12M for S02523, 15M for S05662, 6M for S10460, 3M for S16441, 6M for S20422, 2M for S58370, 12M for S76600, and 1M for S78737). However, it was not possible to include S32412 because his/her last useful SBP data referred to RZ.

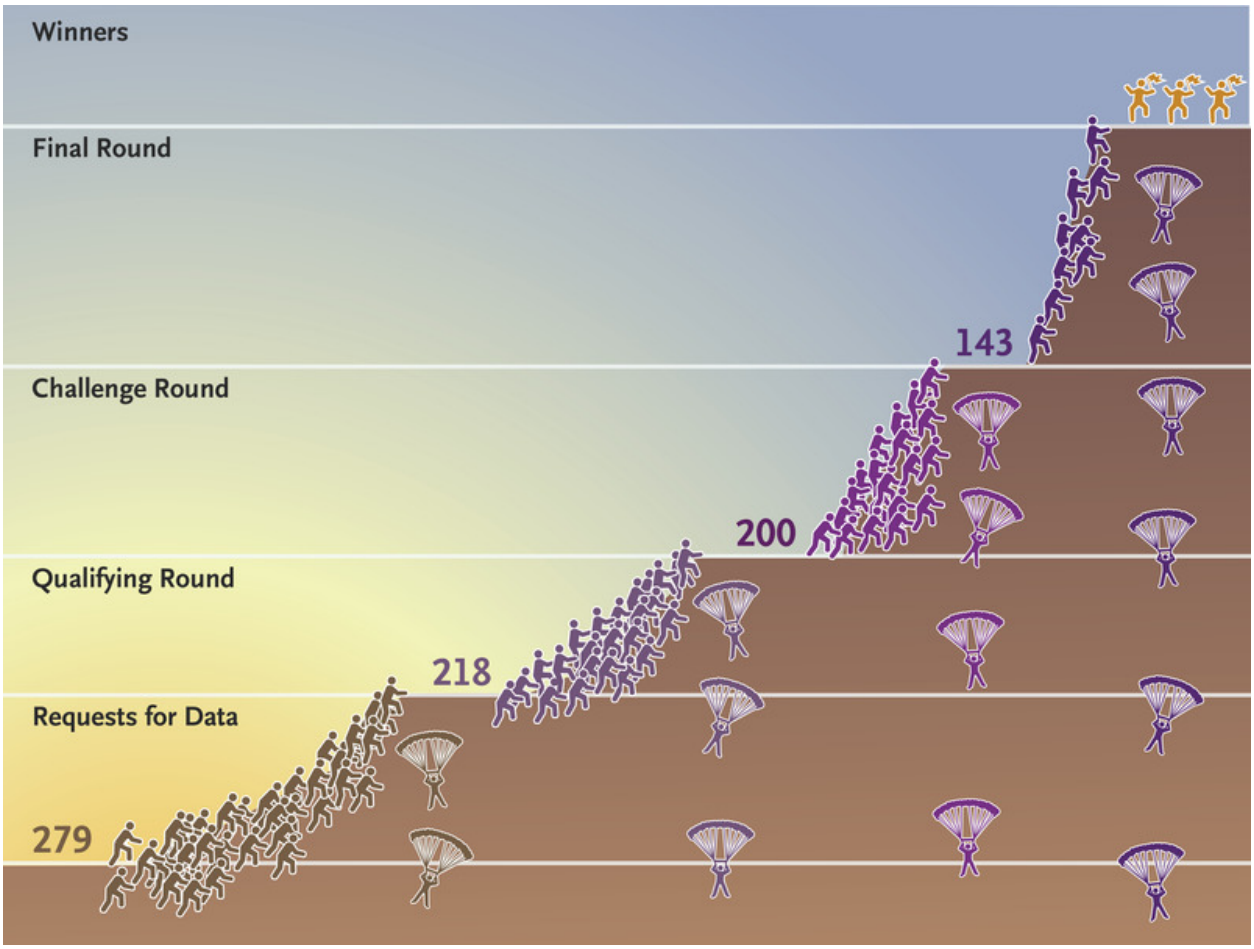
According to these three approaches, respectively, the answer can be summarized as follows:

Group	Sample Size	Mean SBP
INTENSIVE 0	n=4616	133.79±14.25 mmHg
INTENSIVE 1	n=4632	119.78±14.62 mmHg

Group	Sample Size	Mean SBP
INTENSIVE 0	n=4612	133.90±13.71mmHg
INTENSIVE 1	n=4628	119.88±14.20 mmHg

Group	Sample Size	Mean SBP
INTENSIVE 0	n=4616	133.90±13.71 mmHg
INTENSIVE 1	n=4632	119.89±14.21 mmHg

Figure 1. Qualifying steps in the SPRINT Data Analysis Challenge. From "Perspective: Learning What We Didn't Know — The SPRINT Data Analysis Challenge".



Blood Pressure Variability:

Assessment and Clinical Relevance

Blood pressure (BP) is a dynamic measure, characterized by continuous fluctuations over time spans that range from seconds to minutes, days, and years [6,7]. The size and patterns of these variations define the term BP variability (BPV) [8]. BPV is the result of a complex interplay between environmental (i.e. seasons, altitude), physical (i.e. posture, volemia, sleep), and emotional (i.e. stress) challenges that are able to induce BP changes, and biological regulatory mechanisms (e.g. vasoactive substances, vascular compliance, baroreflex activity, central nervous system influences) that are aimed at maintaining homeostasis [6]. By finely regulating BP levels in response to the changing demands of different organs, these mechanisms are intended to ensure a constantly adequate organ perfusion [6]. In addition, BPV might reflect the effect of external determinants, as observed among patients on antihypertensive medications, where drug classes, timing/intensity of BP treatment, and relative adherence can all influence BP behavior [7,9,10].

Thus, BPV represents a dynamic and characteristic physiologic feature of the cardiovascular (CV) system. In parallel, it could be seen as a source of noise affecting the assessment of the individual's real BP level [6]. Consistent evidence now supports its role as an independent predictor of CV risk, to the point that it has also attracted interest as a possible target for pharmacological treatment [6,8,11]. In fact, although representing an adaptive response to different stimuli under physiological conditions, BPV may also reflect alterations in CV regulatory mechanisms that may affect CV prognosis. In

particular, there is evidence supporting a prognostic importance of short-term BPV for the occurrence of CV and fatal events [12,13]. Similarly, sustained increase in long-term BPV appears to have detrimental effects on CV events and mortality [14–16], independent of medication adherence [17], although other evidence has questioned these findings [18–20]. A variety of methodological approaches for the assessment of BPV have been used in these analyses, potentially leading to conflicting results even when the same population was examined [21,22]. In addition, different degrees of total CV risk in the examined populations might explain the inhomogeneous predictive power of BPV in different clinical settings [23].

Principal indices of BPV

Indices for BPV assessment can be classified into two main groups: those assessing overall BPV, and those for the estimation of specific BPV patterns (**Table 1**). The former include:

a) *spectral indices*, obtained by decomposing very-short term BPV in its components oscillating at different frequencies (high-, low-, and very low-frequency); they yield information on the autonomic control of circulation, baroreflex function, and respiratory mechanics [24];
b) *'residual' BPV*, representing the fast BP fluctuations that remain after exclusion of the slower components of the 24 hours BP profile using Fourier spectral analysis, and expressing the tendency of BP to vary erratically throughout the day and night [25];

c) measures of *dispersion* of average BP values over a given time window [24], namely *standard deviation* (SD) and related indices, which have been developed to overcome the dependency of SD on trends in BP changes and on average BP. They include the *weighted 24 hours SD* (wSD, calculated as the average of daytime and nighttime SD corrected for the respective duration of day and night); the *coefficient of variation* (CoV, calculated as SD*100/BP mean); and the *variability independent of the mean* (VIM, which is based on nonlinear regression analysis);

d) estimates that take into account the *sequence* of measurements over time [24]: *average real variability* (ARV, computed as the average of the absolute differences between consecutive BP readings over 24 hours); *time rate of BP fluctuations* (similar to ARV, but quantified as a function of time to incorporate information on the speed of BP changes); and *interval weighted SD* (similar to SD, it attributes proportional weights to time intervals between BP recordings);

e) *instability* indices that take into account extreme BP readings within a given time window, like *range* (maximum and minimum BP), *peak and trough values*, *peak size* (maximum-mean BP) and *trough size* (mean-minimum BP); they are affected by instability and prone to artifacts more than other indices [24].

Specific BPV patterns are those associated with the day/night cycle, and can be better captured by ABPM and related indices [24]. The most reliable is the *nocturnal BP fall* [(daytime-nighttime BP)*100/daytime BP], which allows to categorize patients into 4 categories: normal dippers (nocturnal fall in BP between 10-20%); reduced dippers (nocturnal fall in BP<10%); extreme dippers (nocturnal BP fall>20%); and reverse

dippers (increase in nighttime BP compared to daytime values). Other specific BPV indices of debated clinical value due to lack of standard assessment methods include *morning BP surge* (i.e. difference between the lowest nocturnal BP value and the highest BP measure after awakening), *siesta dipping* (BP fall related to afternoon nap), and *postprandial BP fall* (possible expression of autonomic failure).

The few studies directly comparing the prognostic value of different estimates of BPV did not provide clear indications as to which index should be preferred. At present, the indices supported by the strongest outcome evidence include ARV or wSD for 24-hour BPV, and SD, CoV or VIM for mid- and long-term BPV [6,24].

Very Short-Term and Short-Term BPV

These types of BPV occur within seconds (on a beat-by-beat basis) to hours (over 24 hours), and are amenable to be captured by ambulatory BP measurement (ABPM) [11]. In physiologic conditions, they typically represent a homeostatic response to specific stimuli mediated by neural (i.e., central sympathetic drive and its reflex modulation by arterial and cardio-pulmonary reflexes), humoral (catecholamines, insulin, angiotensin II, bradykinin, endothelin-1, nitric oxide), vascular (i.e., elastic properties of arteries), and rheological (i.e., blood viscosity) mechanisms [11,26,27]. However, their sustained increases may also reflect alterations in regulatory mechanisms (i.e., enhanced sympathetic drive and impaired baroreflex function), which may occur in several conditions, including in the presence of endothelial dysfunction, arterial hypertension, CKD, sleep breathing disorders (i.e., obstructive sleep apnea), and insulin resistance.

Arterial hypertension was intuitively one of the scenarios where the clinical relevance of very short- and short-term BPV was first shown. Cross-sectional and longitudinal evidence indicated greater prevalence, incidence and severity of hypertension-mediated target organ damage — especially prevalent early impaired left ventricular systolic function, incident left ventricular hypertrophy, and progression of microalbuminuria and CKD — in hypertensive subjects with higher short-term BPV, namely nondippers or reverse dippers, and even after accounting for differences in mean BP levels [28,29]. In addition, despite some persistent debate, subjects with a nondipping or reverse dipping pattern have been shown to be at an increased risk of CV events and mortality compared to dippers [30]. The same was observed for subjects with increased morning BP surge [31].

Several human studies on clinical pharmacology indicated that antihypertensive treatment may have a favorable impact on BPV by means of a proportional decrease in both BP SD and mean BP values [11]. Other evidence from animal and human studies, indeed, supported the possibility that the benefit of specific drug classes (i.e., calcium antagonists, third generation beta-blockers) over organ damage was possibly due to improved baroreflex sensitivity and consequent reduced BPV, besides their effect on mean BP levels. In fact, antihypertensive medications have different performances in terms of mean BP reduction and relative distribution over 24 hours [11]. Quantitative measures of this performance include the trough/peak (T/P) ratio, the smoothness index (SI), and the treatment-on-variability index (TOVI). The T/P ratio is derived from ABPM recordings by dividing the BP changes at the end of the dosing interval by those observed at the maximum effect of the drug [32]. Its precision is affected by the short time

intervals examined. This limitation is addressed by the SI, which is calculated as the ratio between the average of the 24 hourly BP changes induced by a given medication and the SD of hourly reductions based on before-treatment and on-treatment ABPM [33]. Telmisartan, amlodipine and ramipril appear to have a particularly favorable SI. In addition, higher SI (>1) has been associated with regression of cardiac hypertrophy and slower progression of carotid artery wall thickness. Finally, in order to account for the circadian BP fluctuations, as well as for the dependence of BP SD on mean BP levels, the TOVI was introduced as the ratio between the average of the 24 hourly BP reductions by treatment and the wSD [34]. This index is in substantial agreement with SI in terms of informative power, and both indicated a better BPV profile in the course of combination therapy compared to single drug treatment [34].

Mid-term BPV

Day-by-day BPV appears to be particularly affected by behavioral factors (i.e. working days versus weekend, sedentary lifestyle, excessive alcohol intake, cigarette smoking), as well as traditional and new CV risk factors (i.e. gender, age, body mass index [BMI], diabetes, CVD, heart rate and its variability, self-reported insomnia and sleep duration) [11]. Improper dosing, titration, and adherence to antihypertensive treatment also contribute to increased mid-term BPV.

This type of BPV can be assessed by performing ABPM over consecutive days (i.e., during 48 hours or more), or by home BP monitoring (HBPM). The first is not usually practical and feasible for both patients and medical staff, but has the advantage of providing nighttime BP and a considerable number of readings. HBPM is widely

available, well accepted, and allows early changes to antihypertensive therapy based on BP consistency over relatively short time spans, but the large variety of protocols and indices proposed for the assessment of BPV prevents specific recommendations on the methodology, prognostic importance, and wide clinical applications of this technique.

In spite of the variety of the possible mid-term BPV assessment methods (including SD, CoV, VIM, and ARV), consistent evidence supports the prognostic importance of this variable in terms of subclinical organ damage and CV morbidity/mortality [35–39], with few exceptions [40,41].

Long-term and very-long-term BPV

These attributes refer to BPV assessed in the medical office on a visit-to-visit basis, conventionally occurring on intervals of less or more than 5 years, respectively.

BPV in the long term appears to be mostly affected by treatment-related factors (i.e. reduced compliance), reproducibility of BP assessment (i.e. measurement errors), and possibly by seasonal changes.

Most of the studies examining the prognostic power of long-term BPV used SD and CoV as the relative assessment indices, although all the dispersion and sequence indices are appropriate [6]. However, identifying a standard method to obtain reproducible and valid estimates of visit-to-visit BPV and the optimal interval between visits remains a matter of debate, given the heterogeneity in the number of BP measurements and the between-visits intervals among the studies so far conducted on this topic [6,11]. In addition, office BP assessments can be affected by the so called “white coat effect”, i.e.

an alarm reaction that can falsely alter BP values. To overcome these issues, ABPM and, even more, HBPM have been proposed as valuable alternatives. HBPM in particular can be considered as a valuable tool to assess visit-to-visit BPV. According to this, the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines suggest that HBPM should be performed with a semiautomatic, validated BP monitor, for at least 3 days and preferably for 6–7 consecutive days before each clinic visit, in 2 measurement sessions (morning and evening) of 2 readings each, performed 1–2 minutes apart and taken in a quiet room after 5 minutes of rest in the sitting position, with back and arm supported [42]. The relative average could then be used to assess BPV.

Independent of the methods used and of mean BP values, a bunch of evidence has shown increasing values of visit-to-visit BPV to be associated with diastolic dysfunction, systemic vasculopathy (endothelial dysfunction, increased carotid intima-media thickness, arterial stiffness, and atherosclerosis) [43,44], development and progression of albuminuria and renal disease [45], white matter lesions and brain infarctions, and impairment in cognitive function [46,47].

Compared to short-term indices of BPV, visit-to-visit BPV has been shown to be a better predictor of CV prognosis (i.e. occurrence of cerebrovascular and coronary fatal/non-fatal events, all-cause mortality) independent of mean BP [48,49]. This can be due to the fact that it reflects the degree of BP control and the BP burden for the CV system in the long term, which definitely has a greater impact on CV outcomes than very-short-term or short-term BP fluctuations. The prognostic importance of long-term BPV was particularly evident in treated hypertensive individuals, in diabetics with and

without CKD, among post-menopausal women, and in patients with prior cerebrovascular events, while it provided little or no contribution to CV risk prediction when baseline risk was residual [11]. Further, some antihypertensive medications (i.e. calcium channel blockers) appear to be more effective than others (i.e. first and second generation beta-blockers) in reducing intraindividual BPV, although this effect was shown to be dependent on baseline CV risk [50]. These observations support the added value of long-term BPV to average BP levels in CV risk stratification in subjects at high CV risk, suggesting that the protective effect of antihypertensive treatment depends not only on the degree, but also on the consistency of BP control over time.

Table 1. Principal indices of blood pressure variability.

Overall	
BPV Index	**Type of BPV assessed**
Frequency:	
- Spectral indices (HF, LF, VLF)	Short-term BPV
- Residual variability	Very short-term BPV (spectral analysis)
Dispersion:	
- Standard deviation (SD)	Short-term BPV
- Coefficient of variation (CV)	Mid-term BPV
- Variability independent of the mean (VIM)	Long-term BPV
- Weighted 24h SD (wSD)*	
Sequence:	
- Average Real Variability (ARV)	Short-term BPV
- Interval Weighted SD (wSD)	Mid-term BPV
- Time rate of BP fluctuations**	Long-term BPV
Instability:	
- Range (Maximum-minimum BP)	Short-term BPV
- Peak size (Maximum BP)	Mid-term BPV
- Trough size (Mean-minimum BP)	

Specific patterns of BPV	
Nocturnal BP fall Night/day ratio Morning blood pressure surge (MBPS) Afternoon siesta dipping Postprandial blood pressure fall	Short-term BPV

Aim

Based on current gaps in evidence regarding standardized metrics and protocols for the assessment of BPV, including the minimum number of measures and visits and the optimal intervals between them, the current study aimed at exploring this unresolved issue using the SPRINT trial available dataset.

Thus, we applied different criteria of timing and number of study visits to the same index of long-term BPV assessment to test the prognostic value of visit-to-visit systolic BPV, and the relevant clinical correlates, in the specific high-risk, non-diabetic hypertensive population enrolled in the SPRINT trial.

Methods

Study population

Details of the SPRINT trial design and protocol have been previously described. Briefly, SPRINT is a 2-arm, multicenter, randomized clinical trial designed to test whether a systolic BP <120 mmHg compared to <140 mmHg reduces CV events and mortality in high-risk, non-diabetic, non-stroke, US multiethnic hypertensive patients aged at least 50 years [51].

Participants with at least 2 available systolic BP measurements besides the randomization visit were included in this analysis.

As an analysis of existing, de-identified data, this study was deemed exempt from review by the local Institutional Review Board.

Outcomes of interest

The outcomes of interest included the first occurrence of a *primary event* (a composite of adjudicated myocardial infarction [MI], acute coronary syndrome not resulting in MI [non-MI ACS], stroke, acute decompensated heart failure [HF], or death from CV diseases [CVD]; or each single component), *all-cause mortality*, and their combination as defined by the SPRINT protocol, i.e. the occurrence of *any of the two*.

Definition of visit-to-visit systolic BPV

BP measurement technique in SPRINT has been recapitulated elsewhere [52]. All SPRINT sites were provided with the Professional Digital Blood Pressure Monitor (Omron Healthcare, Lake Forest, IL®) model 907XL for BP measurement in the trial.

Visit-to-visit systolic BPV was expressed as systolic BP coefficient of variation (CoV, %), individually computed as standard deviation (SD) of mean systolic BP divided by mean systolic BP and multiplied by 100 [21,53]. Since CoV is affected by the number of BP measurements [54], we defined as CoV accuracy (%) the normalized variable derived for each individual as the ratio of the available and the expected BP readings to events. Three protocols in terms of number and timing of study visits were used to calculate visit-to-visit systolic BPV.

In the first approach (overall analysis), all the available office systolic BP measurements until the occurrence of the combined outcome of a primary event or all-cause mortality (i.e. monthly assessment during the 3-months titration period excluding randomization, then quarterly) were used. There was no threshold of CoV accuracy as inclusion criteria.

The second approach (sensitivity analysis) was based on the observations that BP remained relatively stable after the titration period (i.e. the 3-month visit) [21], and that between-treatment separation in the incidence of the primary outcome and total mortality occurred at the first and the second year of follow-up, respectively [51]. Thus, visit-to-visit systolic BPV was derived separately for primary and fatal events from all available BP readings registered quarterly after the titration period until the outcome,

excluding patients who experienced a primary event before the first year or died before the second year, and those with CoV accuracy<100%.

Finally, in order to test the consistency of different methods of BPV assessment [21], we used a third approach (restricted analysis) where visit-to-visit systolic BPV was calculated quarterly during the first year after the titration period (i.e. based on the 3-, 6-, 9- and 12-month visits), excluding patients with a primary event within the first year or who died before the second year, and those missing any of these measurements (i.e. CoV accuracy<100%).

Statistical analysis

All analyses were conducted using R [55]. Differences in demographic characteristics were evaluated with unpaired *t* tests for continuous variables and χ^2 tests for categorical variables. The Benjamini–Hochberg method was used to control for multiple hypothesis testing [56].

Cox proportional hazard models with penalized smoothing splines (three degrees of freedom) were used to explore the potential non-linear association between visit-to-visit systolic BPV and the hazard ratio (HR; 95% confidence interval [CI]) for the outcomes of interest. Analyses were replicated for the three approaches used to calculate visit-to-visit systolic BPV. To this aim, we first identified the range of visit-to-visit systolic BPV associated with the lowest (HR<1) crude risk of events (defined as "optimal" BPV) in each setting. The extremes of the range were rounded to the nearest integer. Adjusted HRs (95% CI) were then calculated with progressively adjusted Cox proportional models (model 1: treatment arm; model 2: additional inclusion of systolic

BP, age ≥75 years, gender, race, pre-existing cardiovascular disease [CVD] and chronic kidney disease [CKD], smoke, number of medications throughout the study) using the optimal BPV as reference. The number of covariates was limited to avoid possible overfitting [21]. Stratification by treatment arm was also performed. Information on single drugs classes and adherence to treatment was not available.

As anticipated, between-treatment separation in the incidence of the primary outcome and total mortality occurred at the first and the second year of follow-up, respectively [51]. Thus, participants who experienced a primary event before the first year or died before the second year were excluded in the sensitivity and restricted analyses, where these outcomes were examined separately. In the overall analysis, where the occurrence of any of the two outcomes — as defined by the SPRINT protocol — was examined, these time thresholds could not be applied.

Data were analyzed as recorded, without imputation for missing data.

Statistical significance was set at $p<0.05$.

Results

Overall analysis

Of the 9361 participants enrolled in SPRINT, 9120 (97.4%) had complete data for this analysis. The range of visit-to-visit systolic BPV associated with the lowest crude risk of the combined outcome of primary events or all-cause mortality was 5–11% (**Figure 1, panel A**). The majority of patients (N=6297) belonged to that range. They tended to be younger, non-smokers White men from the standard group, with lower systolic BP (-0.91 mmHg), higher serum glucose, better renal function, less CVD or CKD, more BP readings, and greater CoV accuracy; they were on less BP medications, and more likely to be on aspirin and to achieve BP goal (**Table 1**).

Compared to SPRINT patients with optimal BPV, the crude HR for the occurrence of the combined outcome of primary events or all-cause mortality among those with different systolic BPV was 1.70 (95% CI 1.5–2.0; p<0.001) (**Table 2**). The univariate and multivariate analyses confirmed the crude findings (**Table 2**). Further correction for CoV accuracy did not modify the adjusted results (data not shown).

The Kaplan-Meyer curve for the combined outcome of primary events or all-cause mortality showed that participants in the intensive treatment arm with optimal BPV had the lowest cumulative hazard, while the opposite occurred among standard-treated patients with different BPV (**Figure 2, panel A**; **Table 3**). Different BPV was associated with greater risk of the combined outcome of primary and fatal events, independent of treatment arm (**Table 4**).

Sensitivity analysis

After exclusion of participants who experienced a primary outcome before the first year (N=489), and of those with CoV accuracy <100% (N=2765, **Figure 3**), visit-to-visit systolic BPV associated with the lowest crude risk of an event among the remaining 5937 participants was 5–10% (**Figure 1, panel B**). It was based on a mean of 12.5±2.8 study visits. The crude HR for the primary outcome outside that range was 1.60 (95% CI 1.30–2.00; p<0.001). Similar findings were observed in the univariate analysis. The risk persisted after multivariate adjustment (HR 1.47, 95% CI 1.15–1.87; p=0.002), particularly influenced by older age, history of CVD or CKD, and number of BP medications (**Table 5**).

When the single components of the primary outcome were examined, only the adjusted risk of MI and HF remained significant (**Table 6**).

The Kaplan-Meyer curve for the primary outcome showed a better risk profile among participants in the intensive treatment arm with optimal BPV compared to those in any other stratum (**Figure 2, panel B**), included intensive-treated participants with suboptimal BPV (**Table 3**, **Table 4**).

After exclusion of participants who experienced a fatal outcome before the second year (N=858) and of those with CoV accuracy <100% (N=2831, **Figure 4**), the range of visit-to-visit systolic BPV associated with the lowest risk of all-cause mortality among the remaining 5802 participants was ≤8% (**Figure 1, panel C**). It was based on a mean of 12.9±2.4 study visits. The crude HR for a fatal event above that cutoff was 2.50 (95% CI 1.60–4.00; p<0.001). The multivariate adjusted HR was 2.11 (95% CI 1.30–3.40; p=0.003) (**Table 5**). Clinical correlates of different BPV reflected what observed overall. The Kaplan-Meyer curve for all-cause mortality and relative pairwise

comparisons showed that participants in the standard treatment arm with different BPV had significant greater cumulative hazard compared to any other strata (**Figure 2, panel C, Table 3**). This was also confirmed in the survival analysis (full adjusted HR 4.95, 95% CI 2.06-11.9, p<0.001) (**Table 4**).

Restricted analysis

When visit-to-visit systolic BPV was calculated based on 4 pre-defined BP measurements on 7888 participants [21], the relative range associated with the lowest crude risk of a primary event was ≤10% and that for all-cause mortality was ≤8% (**Figure 5, panel A and B**). The crude and adjusted HRs for the primary outcome were not significantly increased above the cutoff of 10% (**Table 7**). Conversely, the crude and univariate HR (1.50, 95% CI 1.10–1.90; p=0.003), but not the multivariate HR (1.27, 95% CI 0.98–1.66; p=0.071), for all-cause mortality were increased above the cutoff of 8% (**Table 7**).

Discussion

Our findings indicate that an optimal visit-to-visit systolic BPV exists in a high-risk hypertensive population like the one enrolled in SPRINT with regards to the risk of primary and fatal events, but strictly depending on the relative calculation method. In particular, the optimal range of BPV associated with the lowest risk of the combined outcome of CV events and all-cause mortality was 5-11%. Results remained significant after the sensitivity analysis, where stringent inclusion criteria were applied in terms of study visits selection and CoV accuracy, as well as after multiple adjustments incorporating mean systolic BP. Optimal BPV appeared to confer additional protection to intensive BP lowering, while suboptimal BPV further worsened CV risk in standard-treated patients. However, the results lost significance in the restricted analysis, where only 4 quarterly BP assessments recorded during the first year were included. Clinical correlates of suboptimal BPV in our analyses included older age, female gender, non-White ethnicity, smoke, and pre-existing CVD and CKD.

Our results are in line with data from several clinical trials and meta-analyses supporting an exceeding risk of CV outcomes and mortality in association with high BPV [57–60]. Specifically, a recent meta-analysis of 24 clinical trials and prospective studies on non-dialysis adults showed that long-term (clinic) systolic BPV was associated with 10-18% higher risk of mortality and CV events over and above the effect of mean BP [61]. Another recent meta-analysis of 23 high-quality cohort studies on 107,434 hypertensive patients at different CV risk and a median follow-up time of 11 years confirmed that visit-to-visit systolic BPV was an independent predictor of long-term mortality and CV events [62]. A secondary analysis of the Antihypertensive and Lipid-Lowering Treatment to

Prevent Heart Attack Trial (ALLHAT), which enrolled 42,418 hypertensive adults aged ≥55 years with ≥1 additional risk factor for CVD, also agrees with our findings [57]. BPV was calculated as the intra-individual SD of systolic BP across 7 follow-up visits. Results indicated 25-58% higher risk of CV events among participants in the highest versus the lowest quintile of SD of systolic BP; in parallel, a graded association between higher SD of systolic BP and increased risk for all-cause mortality was described, which was similar to our findings.

In seeming contrast with our overall results and sensitivity analyses is the restricted analysis. Previous findings on the same population had excluded a significant association of quintiles of visit-to-visit systolic BPV with the composite primary outcome, while showing some association with all-cause mortality [21]. While the lower number of included study visits might trivially explain the observed discrepancy, another possible explanation is that the upper cutoffs of the reference ranges of BPV that we identified, namely 10% for the primary outcome and 8% for total mortality, incorporated the first three to four quintiles according to previous findings (**Figure 5, panel A and B**). Potentially, this would blunt any possible significant difference among contiguous quintiles. Conversely, differences between extreme quintiles would be more likely visible.

SPRINT enrolled older, high-risk hypertensive patients with increased atherosclerotic burden. Arterial stiffness that is typical of atherosclerosis might be regarded as a potential major contributor to our findings [63]. In fact, elderly hypertensives typically have wide BP swings that stem from impaired stretching of baroreceptors, secondary to arterial stiffness. The consequent diminished autonomic signaling leads to

failure to regulate BP in response to the appropriate stimuli, translating into inappropriate (i.e. excessive) BPV. Possible clinical correlates of this phenomenon include postural hypotension and episodic hypertension [63,64]. The high prevalence of older age and pre-existing CVD, as well as the observation of a greater risk of MI, among participants with suboptimal BPV reinforce this hypothesis.

It is also possible that suboptimal BPV is mediated by subclinical inflammation [65], which is typical of atherosclerosis as well as of a variety of conditions with impact on CV health [66–71]. This phenomenon might at least in part explain the increased burden of non-CVD mortality in the examined patients with suboptimal BPV. Major causes of non-CVD mortality in SPRINT included death from cancer, infections, acute/chronic diseases (i.e. pulmonary, gastrointestinal), and hemodialysis-related complications [51], all of which display a certain extent of inflammatory burden.

The stratified analysis by treatment arm adds information of interest to the available evidence regarding the prognostic importance of BPV beyond that of mean BP. In fact, the gain in terms of reduced risk among intensively treated patients with optimal BPV, together with the further worsening of CV risk among standard-treated patients in the opposite situation, supports the importance of visit-to-visit systolic BPV independent of mean BP in this population. Thus, it appears that this variable adds value to the estimation of CV risk [72] in a high-risk hypertensive population, like the one enrolled in SPRINT. This is in line with existing literature supporting the independent prognostic value of BPV in different clinical and demographic settings [13,61,73,74].

Our study is not without limitations. Information on timing in BP measurements and drug intake at different visits, medications types and doses, as well as patient

adherence to treatment was not available to the present study. Our analysis may have been underpowered to detect associations between inappropriate BPV and the single components of the primary outcome other than MI and HF, or it is possible that the same become evident at different stages in the disease process than is detectable after the follow-up period available to this analysis; further, prior established risk of each single outcome might affect the probability to observe significant results. In addition, as anticipated, analytical differences among the available studies on this topic, as well as the BP measurement method in SPRINT compared to other studies [75], should be considered when interpreting the relative findings [59,61,62].

Our study has some important strengths. First, it was conducted on a well-defined, large sample of a high-risk multiethnic hypertensive population. Second, BP measurements and outcomes incidence were carefully ascertained in SPRINT. Third, a sensitivity analysis was performed to exclude the most active titration period and the primary or fatal events attributable to pre-trial conditions. In addition, all the available study visits until the occurrence of an event were included, at the same time introducing a measure of CoV accuracy. Finally, stratification by treatment arm was performed and data were tested with multiple adjustments, including mean systolic BP.

Conclusions

In conclusion, an optimal visit-to-visit systolic BPV appears to exist and to add prognostic value to the estimation of CV risk, independent of systolic BP mean, in a high-risk, non-diabetic hypertensive population like the one enrolled in SPRINT, but the methodological approach to its calculation is crucial. Given the potential impact on CV risk estimation, an effort to standardize BPV assessment is worthwhile.

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References

1. Group TSR, The SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *New England Journal of Medicine* 2015; 373: 2103–2116.

2. Burns NS, Miller PW. Learning What We Didn't Know - The SPRINT Data Analysis Challenge. *N Engl J Med* 2017; 376: 2205–2207.

3. Drazen JM, Morrissey S, Malina D, et al. The Importance - and the Complexities - of Data Sharing. *The New England journal of medicine* 2016; 375: 1182–1183.

4. Del Pinto R, Pietropaoli D, Ferri C. Diastolic blood pressure and risk profile in renal and cardiovascular diseases. Results from the SPRINT trial. *J Am Soc Hypertens* 2018; 12: 513–523.e3.

5. Levy D. Editor's Page. *J Am Soc Hypertens* 2018; 12: 483.

6. Parati G, Stergiou GS, Dolan E, et al. Blood pressure variability: clinical relevance and application. *J Clin Hypertens* 2018; 20: 1133–1137.

7. Mancia G. Short- and long-term blood pressure variability: present and future. *Hypertension* 2012; 60: 512–517.

8. Parati G, Ochoa JE, Lombardi C, et al. Assessment and management of blood-pressure variability. *Nature Reviews Cardiology* 2013; 10: 143–155.

9. Parati G, Stergiou GS, Dolan E, et al. Blood pressure variability: clinical relevance and application. *J Clin Hypertens* 2018; 20: 1133–1137.

10. Del Pinto R, Ferri C. Hypertension Management at Older Age: An Update. *High Blood Press Cardiovasc Prev* 2019; 26: 27–36.

11. Parati G, Ochoa JE, Lombardi C, et al. Blood pressure variability: assessment, predictive value, and potential as a therapeutic target. *Curr Hypertens Rep* 2015; 17: 537.

12. Verdecchia P, Angeli F, Gattobigio R, et al. Impact of blood pressure variability on cardiac and cerebrovascular complications in hypertension. *Am J Hypertens* 2007; 20: 154–161.

13. Muntner P, Shimbo D, Tonelli M, et al. The relationship between visit-to-visit variability in systolic blood pressure and all-cause mortality in the general population: findings from NHANES III, 1988 to 1994. *Hypertension* 2011; 57: 160–166.

14. Men X, Sun W, Fan F, et al. China Stroke Primary Prevention Trial: Visit-to-Visit

Systolic Blood Pressure Variability Is an Independent Predictor of Primary Stroke in Hypertensive Patients. *J Am Heart Assoc*; 6. Epub ahead of print 13 March 2017. DOI: 10.1161/JAHA.116.004350.

15. Ohkuma T, Woodward M, Jun M, et al. Prognostic Value of Variability in Systolic Blood Pressure Related to Vascular Events and Premature Death in Type 2 Diabetes Mellitus: The ADVANCE-ON Study. *Hypertension* 2017; 70: 461–468.

16. Muntner P, Whittle J, Lynch AI, et al. Visit-to-Visit Variability of Blood Pressure and Coronary Heart Disease, Stroke, Heart Failure, and Mortality: A Cohort Study. *Ann Intern Med* 2015; 163: 329–338.

17. Kronish IM, Lynch AI, Oparil S, et al. The Association Between Antihypertensive Medication Nonadherence and Visit-to-Visit Variability of Blood Pressure: Findings From the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Hypertension* 2016; 68: 39–45.

18. Mancia G, Schumacher H, Böhm M, et al. Relative and Combined Prognostic Importance of On-Treatment Mean and Visit-to-Visit Blood Pressure Variability in ONTARGET and TRANSCEND Patients. *Hypertension* 2017; 70: 938–948.

19. Chang TI, Reboussin DM, Chertow GM, et al. Visit-to-Visit Office Blood Pressure Variability and Cardiovascular Outcomes in SPRINT (Systolic Blood Pressure Intervention Trial). *Hypertension* 2017; 70: 751–758.

20. Schutte R, Thijs L, Liu Y-P, et al. Within-subject blood pressure level--not variability--predicts fatal and nonfatal outcomes in a general population. *Hypertension* 2012; 60: 1138–1147.

21. Chang TI, Reboussin DM, Chertow GM, et al. Visit-to-Visit Office Blood Pressure Variability and Cardiovascular Outcomes in SPRINT (Systolic Blood Pressure Intervention Trial). *Hypertension* 2017; 70: 751–758.

22. Mezue K, Goyal A, Pressman GS, et al. Blood pressure variability predicts adverse events and cardiovascular outcomes in SPRINT. *J Clin Hypertens* 2018; 20: 1247–1252.

23. Mancia G, Facchetti R, Parati G, et al. Visit-to-visit blood pressure variability, carotid atherosclerosis, and cardiovascular events in the European Lacidipine Study on Atherosclerosis. *Circulation* 2012; 126: 569–578.

24. Dorobantu M, Mancia G, Grassi G, et al. *Hypertension and Heart Failure: Epidemiology, Mechanisms and Treatment*. Springer, 2018.

25. Mancia G, Bombelli M, Facchetti R, et al. Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. *Hypertension* 2007; 49: 1265–1270.

26. Mancia G, Parati G, Pomidossi G, et al. Arterial baroreflexes and blood pressure and heart rate variabilities in humans. *Hypertension* 1986; 8: 147–153.

27. Conway J, Boon N, Davies C, et al. Neural and Humoral Mechanisms Involved in Blood Pressure Variability. *Journal of Hypertension* 1984; 2: 203–208.

28. Parati G, Pomidossi G, Albini F, et al. Relationship of 24-Hour Blood Pressure Mean and Variability to Severity of Target-Organ Damage in Hypertension. *Journal of Hypertension* 1987; 5: 93–98.

29. Frattola A, Parati G, Cuspidi C, et al. Prognostic value of 24-hour blood pressure variability. *J Hypertens* 1993; 11: 1133–1137.

30. Hansen TW, Li Y, Boggia J, et al. Predictive Role of the Nighttime Blood Pressure. *Hypertension* 2011; 57: 3–10.

31. Metoki H, Ohkubo T, Kikuya M, et al. Prognostic Significance for Stroke of a Morning Pressor Surge and a Nocturnal Blood Pressure Decline. *Hypertension* 2006; 47: 149–154.

32. Omboni S, Parati G, Zanchetti A, et al. Calculation of trough: peak ratio of antihypertensive treatment from ambulatory blood pressure: methodological aspects. *Journal of Hypertension* 1995; 13: 1105–1112.

33. Parati G, Omboni S, Rizzoni D, et al. The smoothness index: a new, reproducible and clinically relevant measure of the homogeneity of the blood pressure reduction with treatment for hypertension. *J Hypertens* 1998; 16: 1685–1691.

34. Parati G, Dolan E, Ley L, et al. Impact of antihypertensive combination and monotreatments on blood pressure variability: assessment by old and new indices. Data from a large ambulatory blood pressure monitoring database. *J Hypertens* 2014; 32: 1326–1333.

35. Matsui Y, Ishikawa J, Eguchi K, et al. Maximum Value of Home Blood Pressure. *Hypertension* 2011; 57: 1087–1093.

36. Ushigome E, Fukui M, Hamaguchi M, et al. The coefficient variation of home blood pressure is a novel factor associated with macroalbuminuria in type 2 diabetes mellitus. *Hypertension Research* 2011; 34: 1271–1275.

37. Hoshide S, Yano Y, Shimizu M, et al. Is home blood pressure variability itself an interventional target beyond lowering mean home blood pressure during anti-hypertensive treatment? *Hypertension Research* 2012; 35: 862–866.

38. Kikuya M, Ohkubo T, Metoki H, et al. Day-by-Day Variability of Blood Pressure and Heart Rate at Home as a Novel Predictor of Prognosis. *Hypertension* 2008; 52: 1045–1050.

39. Johansson JK, Niiranen TJ, Puukka PJ, et al. Prognostic value of the variability in home-measured blood pressure and heart rate: the Finn-Home Study. *Hypertension* 2012; 59: 212–218.

40. Schutte R, Thijs L, Liu Y-P, et al. Within-Subject Blood Pressure Level—Not Variability—Predicts Fatal and Nonfatal Outcomes in a General Population. *Hypertension* 2012; 60: 1138–1147.

41. Okada T, Matsumoto H, Nagaoka Y, et al. Association of home blood pressure variability with progression of chronic kidney disease. *Blood Pressure Monitoring* 2012; 17: 1–7.

42. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018; 39: 3021–3104.

43. Shimbo D, Shea S, McClelland RL, et al. Associations of aortic distensibility and arterial elasticity with long-term visit-to-visit blood pressure variability: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Hypertens* 2013; 26: 896–902.

44. Diaz KM, Veerabhadrappa P, Kashem MA, et al. Relationship of visit-to-visit and ambulatory blood pressure variability to vascular function in African Americans. *Hypertens Res* 2012; 35: 55–61.

45. Okada H, Fukui M, Tanaka M, et al. Visit-to-visit blood pressure variability is a novel risk factor for the development and progression of diabetic nephropathy in patients with type 2 diabetes. *Diabetes Care* 2013; 36: 1908–1912.

46. Havlik RJ, Foley DJ, Sayer B, et al. Variability in Midlife Systolic Blood Pressure Is Related to Late-Life Brain White Matter Lesions. *Stroke* 2002; 33: 26–30.

47. Nagai M, Hoshide S, Ishikawa J, et al. Visit-to-visit blood pressure variations: new independent determinants for cognitive function in the elderly at high risk of cardiovascular disease. *J Hypertens* 2012; 30: 1556–1563.

48. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *The Lancet* 2010; 375: 895–905.

49. Mancia G, Messerli F, Bakris G, et al. Blood Pressure Control and Improved Cardiovascular Outcomes in the International Verapamil SR-Trandolapril Study. *Hypertension* 2007; 50: 299–305.

50. Mancia G, Facchetti R, Parati G, et al. Visit-to-visit blood pressure variability in the European Lacidipine Study on Atherosclerosis: methodological aspects and effects of antihypertensive treatment. *J Hypertens* 2012; 30: 1241–1251.

51. SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* 2015; 373:

2103–2116.

52. Johnson KC, Whelton PK, Cushman WC, et al. Blood Pressure Measurement in SPRINT (Systolic Blood Pressure Intervention Trial). *Hypertension* 2018; 71: 848–857.

53. Ushigome E, Fukui M, Hamaguchi M, et al. The coefficient variation of home blood pressure is a novel factor associated with macroalbuminuria in type 2 diabetes mellitus. *Hypertens Res* 2011; 34: 1271–1275.

54. Kelley K. Sample size planning for the coefficient of variation from the accuracy in parameter estimation approach. *Behav Res Methods* 2007; 39: 755–766.

55. Website, R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available online at https://www.R-project.org/. (accessed 11 November 2019).

56. Haynes W. Benjamini–Hochberg Method. In: *Encyclopedia of Systems Biology*. Springer, New York, NY, 2013, pp. 78–78.

57. Muntner P, Whittle J, Lynch AI, et al. Visit-to-Visit Variability of Blood Pressure and Coronary Heart Disease, Stroke, Heart Failure, and Mortality: A Cohort Study. *Ann Intern Med* 2015; 163: 329–338.

58. Huang C, Dhruva SS, Coppi AC, et al. Systolic Blood Pressure Response in SPRINT (Systolic Blood Pressure Intervention Trial) and ACCORD (Action to Control Cardiovascular Risk in Diabetes): A Possible Explanation for Discordant Trial Results. *J Am Heart Assoc*; 6. Epub ahead of print 13 November 2017. DOI: 10.1161/JAHA.117.007509.

59. Diaz KM, Tanner RM, Falzon L, et al. Visit-to-visit variability of blood pressure and cardiovascular disease and all-cause mortality: a systematic review and meta-analysis. *Hypertension* 2014; 64: 965–982.

60. Wu C, Shlipak MG, Stawski RS, et al. Visit-to-Visit Blood Pressure Variability and Mortality and Cardiovascular Outcomes Among Older Adults: The Health, Aging, and Body Composition Study. *Am J Hypertens* 2017; 30: 151–158.

61. Stevens SL, Wood S, Koshiaris C, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2016; 354: i4098.

62. Wang J, Shi X, Ma C, et al. Visit-to-visit blood pressure variability is a risk factor for all-cause mortality and cardiovascular disease: a systematic review and meta-analysis. *J Hypertens* 2017; 35: 10–17.

63. Ziegler MG. Atherosclerosis and Blood Pressure Variability. *Hypertension* 2018; 71: 403–405.

64. Townsend RR, Chang TI, Cohen DL, et al. Orthostatic changes in systolic blood pressure among SPRINT participants at baseline. *J Am Soc Hypertens* 2016; 10: 847–856.

65. Tatasciore A, Zimarino M, Renda G, et al. Awake blood pressure variability, inflammatory markers and target organ damage in newly diagnosed hypertension. *Hypertens Res* 2008; 31: 2137–2146.

66. Pietropaoli D, Del Pinto R, Ferri C, et al. Poor Oral Health and Blood Pressure Control Among US Hypertensive Adults: Results From the National Health and Nutrition Examination Survey 2009 to 2014. *Hypertension* 2018; 72: 1365–1373.

67. Pietropaoli D, Del Pinto R, Ferri C, et al. Definition of hypertension-associated oral pathogens in NHANES. *J Periodontol* 2019; 90: 866–876.

68. Del Pinto R, Ferri C. Inflammation-Accelerated Senescence and the Cardiovascular System: Mechanisms and Perspectives. *Int J Mol Sci*; 19. Epub ahead of print 22 November 2018. DOI: 10.3390/ijms19123701.

69. Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002; 420: 860–867.

70. Cobo G, Lindholm B, Stenvinkel P. Chronic inflammation in end-stage renal disease and dialysis. *Nephrol Dial Transplant* 2018; 33: iii35–iii40.

71. Del Pinto R, Wright JT, Monaco A, et al. Vitamin D and blood pressure control among hypertensive adults: results from NHANES 2001-2014. *J Hypertens*. Epub ahead of print 9 September 2019. DOI: 10.1097/HJH.0000000000002231.

72. Del Pinto R, Pagliacci S, De Feo M, et al. Prevalence of hypertension and associated cardiovascular risk factors among pharmacies customers: an Italian nationwide epidemiological survey. *Eur J Prev Cardiol* 2019; 2047487319851301.

73. Wan EYF, Fung CSC, Yu EYT, et al. Association of Visit-to-Visit Variability of Systolic Blood Pressure With Cardiovascular Disease and Mortality in Primary Care Chinese Patients With Type 2 Diabetes—A Retrospective Population-Based Cohort Study. *Diabetes Care* 2017; 40: 270–279.

74. Sarafidis PA, Loutradis C, Karpetas A, et al. The association of interdialytic blood pressure variability with cardiovascular events and all-cause mortality in haemodialysis patients. *Nephrol Dial Transplant* 2019; 34: 515–523.

75. Kjeldsen SE, Lund-Johansen P, Nilsson PM, et al. Unattended Blood Pressure Measurements in the Systolic Blood Pressure Intervention Trial. *Hypertension* 2016; 67: 808–812.

Tables

Table 1. Demographic and clinical characteristics of the SPRINT patients included in the overall analysis by visit-to-visit systolic BPV.

Characteristics	Visit-to-visit Systolic BPV		p-value
	5-11%	Different %	
N	6297	2823	
CoV to event (mean (SD))	7.91 (1.62)	10.38 (5.14)	<0.001
Intensive arm (%)	3076 (48.8)	1494 (52.9)	<0.001
Women (%)	2083 (33.1)	1144 (40.5)	<0.001
Age (mean (SD))	67.69 (9.18)	68.34 (9.83)	0.002
Age ≥75 years (%)	1683 (26.7)	863 (30.6)	<0.001
Race (%)			<0.001
Black	1776 (28.2)	928 (32.9)	
Hispanic	628 (10.0)	334 (11.8)	
Other	118 (1.9)	50 (1.8)	
White	3775 (59.9)	1511 (53.5)	

BMI (mean (SD))	29.90 (5.66)	29.84 (5.99)	0.647
10-year CV risk (mean (SD))	19.95 (10.58)	20.33 (11.39)	0.122
eGFR (mean (SD))	72.30 (20.22)	70.65 (21.30)	<0.001
Serum glucose (mean (SD))	99.06 (13.43)	98.28 (13.71)	0.011
Serum cholesterol (mean (SD))	189.81 (40.77)	190.58 (42.15)	0.409
Smoking habits (%)			0.001
Never	2795 (44.4)	1221 (43.3)	
Former	2724 (43.3)	1168 (41.4)	
Current	772 (12.3)	432 (15.3)	
Pre-existing CVD (%)	1185 (18.8)	639 (22.6)	<0.001
Pre-existing CKD (%)	1684 (26.7)	886 (31.4)	<0.001
Taking aspirin (%)	3259 (51.9)	1391 (49.3)	0.028
Taking statin (%)	2747 (43.9)	1218 (43.5)	0.752
N. of BP medications (mean (SD))	1.81 (1.03)	1.90 (1.04)	<0.001
Achieved treatment goal (%)	4106 (65.2)	1672 (59.2)	<0.001
SBP until event* (mean (SD))	128.24 (9.86)	128.95 (10.39)	0.002
DBP until event* (mean (SD))	71.76 (9.17)	71.47 (9.49)	0.168

Expected BP readings to event (mean (SD))	15.02 (3.45)	14.15 (4.17)	<0.001
Available BP readings to event (mean (SD))	14.43 (3.15)	13.79 (3.87)	<0.001
CoV accuracy (mean (SD))	93.94 (13.53)	90.88 (18.01)	<0.001
Primary events or all-cause mortality (%)	404 (6.4)	294 (10.4)	<0.001
Primary events (%)	304 (4.8)	216 (7.7)	<0.001
All-cause mortality (%)	193 (3.1)	138 (4.9)	<0.001

BPV, blood pressure variability; CoV, coefficient of variation; SD, standard deviation; BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; CVD, CV disease; CKD, chronic kidney disease; SBP, systolic BP; DBP, diastolic BP.

* randomization excluded.

Table 2. **Overall analysis showing the association of visit-to-visit systolic BPV with the occurrence of the combined outcome of primary events or all-cause mortality.** The reference range for visit-to-visit systolic BPV is 5-11%.

Model 1: adjusted for treatment arm; model 2: further adjusted for systolic BP, age ≥75 years, gender, race, pre-existing cardiovascular/chronic kidney disease, smoke, number of medications throughout the study.

Model	HR (95% CI)	p-value
Crude	1.70 (1.50-2.00)	<0.001
Model 1	1.70 (1.50-2.00)	<0.001
Model 2	1.58 (1.35-1.84)	<0.001

BP, blood pressure; CoV, coefficient of variation; HR, hazard ratio; CI, confidence interval.

Table 3. **Pairwise comparisons of the cumulative hazards across strata of treatment arms by BPV using log-rank test.** The reference range of visit-to-visit systolic BPV is 5-11% for the combination of primary outcome and all-cause mortality, 5-10% for the primary outcome, and ≤8% for all-cause mortality. P-values are adjusted using the Benjamini-Hochberg method.

Outcome	Comparisons			
Combination of primary outcome and all-cause mortality		**I** ^{ref}	**I** ^{differ}	**S** ^{ref}
	I ^{differ}	<0.001	-	-
	S ^{ref}	0.03	0.03	-
	S ^{differ}	<0.001	0.0012	<0.001
Primary outcome		**I** ^{ref}	**I** ^{differ}	**S** ^{ref}
	I ^{differ}	0.008	-	-
	S ^{ref}	0.015	0.53	-
	S ^{differ}	<0.001	0.05	0.008
All-cause mortality		**I** ^{ref}	**I** ^{differ}	**S** ^{ref}
	I ^{differ}	0.092	-	-
	S ^{ref}	0.362	0.362	-
	S ^{differ}	<0.001	0.019	<0.001

I, intensive; S, standard; BP, blood pressure; ref, reference range of systolic BPV for the outcome of interest; differ, different systolic BPV.

Table 4. Association of visit-to-visit systolic BPV with the specified outcomes across strata of treatment arms by BPV. The reference range of visit-to-visit systolic BPV is 5-11% for the combination of primary outcome and all-cause mortality, 5-10% for the primary outcome and ≤8% for all-cause mortality. HRs (95% CI) are full adjusted according to model 2 (treatment arm, systolic BP, age ≥75 years, gender, race, pre-existing cardiovascular/chronic kidney disease, smoke, number of medications throughout the study).

Strata	Combination of primary outcome and all-cause mortality		Primary outcome		All-cause mortality	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
I ^{ref}	reference	-	reference	-	reference	-
I ^{differ}	1.40 (1.11-1.76)	0.004	1.49 (1.03-2.17)	0.036	1.69 (0.78-3.70)	0.186
S ^{ref}	1.08 (0.86-1.37)	0.5	1.50 (0.97-2.31)	0.068	2.06 (0.79-5.40)	0.141
S ^{differ}	1.88 (1.46-2.41)	<0.001	2.17 (1.39-3.39)	<0.001	4.95 (2.06-11.9)	<0.001

I, intensive; S, standard; BP, blood pressure; ref, reference range of visit-to-visit systolic BPV for the outcome of interest; differ, different systolic BPV.

Table 5. Sensitivity analyses showing the association of visit-to-visit systolic BPV with the specified outcomes. The reference range of systolic BPV is 5-10% for the primary outcome and ≤8% for all-cause mortality.

Model 1: adjusted for treatment arm; model 2: further adjusted for systolic BP, age ≥75 years, gender, race, pre-existing cardiovascular/chronic kidney disease, smoke, number of medications throughout the study.

Model	Primary outcome		All-cause mortality	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Crude	1.60 (1.30-2.00)	<0.001	2.50 (1.60-4.00)	<0.001
Model 1	1.60 (1.30-2.10)	<0.001	2.50 (1.60-4.10)	<0.001
Model 2	1.47 (1.15-1.87)	0.002	2.11 (1.30-3.40)	0.003

BP, blood pressure; HR, hazard ratio; CI, confidence interval.

Table 6. Association of visit-to-visit systolic BPV with the single components of the primary outcome. The reference range of systolic BPV is 5-10%. HRs (95% CI) are full adjusted according to model 2 (treatment arm, systolic BP, age ≥75 years, gender, race, pre-existing cardiovascular/chronic kidney disease, smoke, number of medications throughout the study).

Outcome	HR (95% CI)	p-value
MI	1.60 (1.09-2.36)	0.017
HF	1.68 (1.06-2.66)	0.027
Stroke	1.39 (0.84-2.30)	0.196
Non-MIACS	0.92 (0.45-1.90)	0.812
CVD death	1.12 (0.58-2.13)	0.730

BP, blood pressure; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; HF, heart failure; non-MIACS, non-myocardial infarction acute coronary syndrome; CVD, cardiovascular disease.

Table 7. Overall analysis showing the association of visit-to-visit systolic BPV with the specified outcomes in the restricted analysis. The reference range of systolic BPV is ≤10% for the primary outcome and ≤8% for all-cause mortality.
Model 1: adjusted for treatment arm; model 2: further adjusted for systolic BP, age ≥75 years, gender, race, pre-existing cardiovascular/chronic kidney disease, smoke, number of medications throughout the study.

Model	Primary outcome (n=7,888)		All-cause mortality (n=8,014)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Crude	1.20 (0.99-1.60)	0.066	1.50 (1.10-1.90)	0.003
Model 1	1.3 (0.99-1.60)	0.062	1.50 (1.10-1.90)	0.003
Model 2	1.05 (0.83-1.34)	0.676	1.27 (0.98-1.66)	0.071

BP, blood pressure; HR, hazard ratio; CI, confidence interval.

Figure legends

Figure 1. Identification of the optimal visit-to-visit systolic BPV using penalized cubic splines. Panel A: overall analysis on the combined outcome of primary events or all-cause mortality; panel B: sensitivity analysis on the primary outcome; panel C: sensitivity analysis on all-cause mortality. The visit-to-visit systolic BPV associated with the lowest risk of events, rounded to the nearest integer, is identified by the red lines (panel A: 5-11%; panel B: 5-10%; panel C: ≤8%).

SBP, systolic blood pressure; HR, hazard ratio.

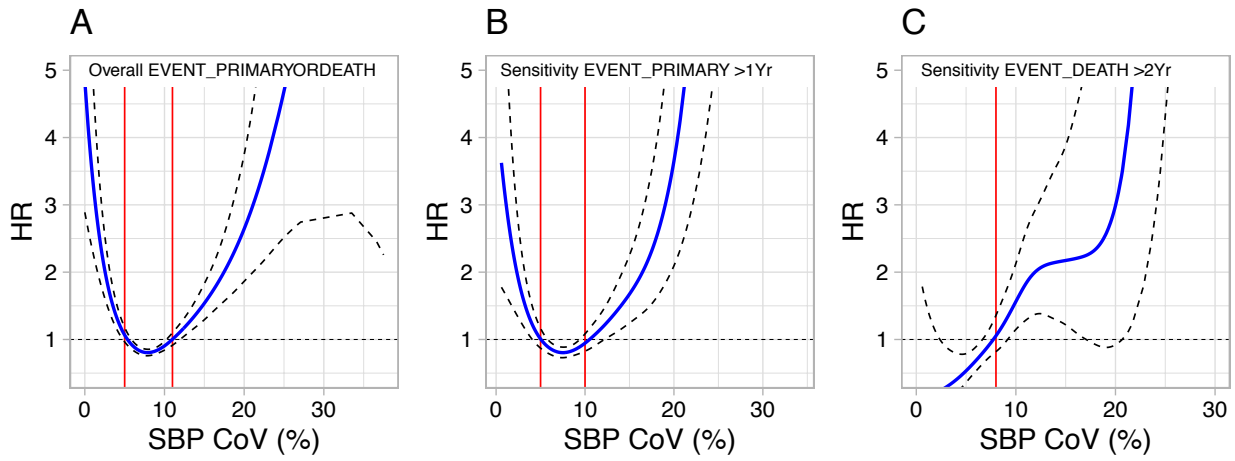


Figure 2. Kaplan-Meyer curves showing the crude cumulative hazard of events stratified by treatment arm and visit-to-visit systolic BPV. Panel A: combined outcome of primary events or all-cause mortality; panel B: primary outcome; panel C: all-cause mortality. Note the different magnitude in the crude cumulative hazard among the outcomes of interest. See Table 3 for pairwise comparisons and Table 4 for adjusted hazard ratios.

I, intensive. S, standard.

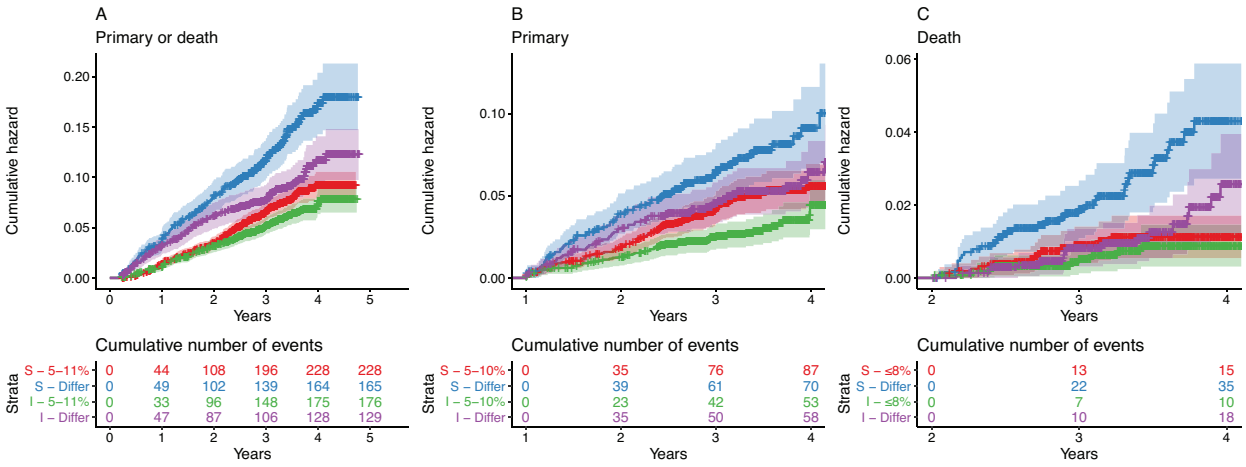


Figure 3. Penalized cubic splines of the risk of the primary outcome by visit-to-visit systolic BPV according to CoV accuracy ranges (0-25%; 26-50%; 51-75%; 76-99%; and 100%). Note the progressive narrowing of the 95% CI (dotted line) from panel A (CoV accuracy: 0-25%) to E (CoV accuracy: 100%). The visit-to-visit systolic BPV associated with the lowest risk of primary events (crude HR<1), rounded to the nearest integer, is identified by the red lines (5-10%) in panel E.

SBP, systolic blood pressure; CoV, coefficient of variation; HR, hazard ratio; CI, confidence interval.

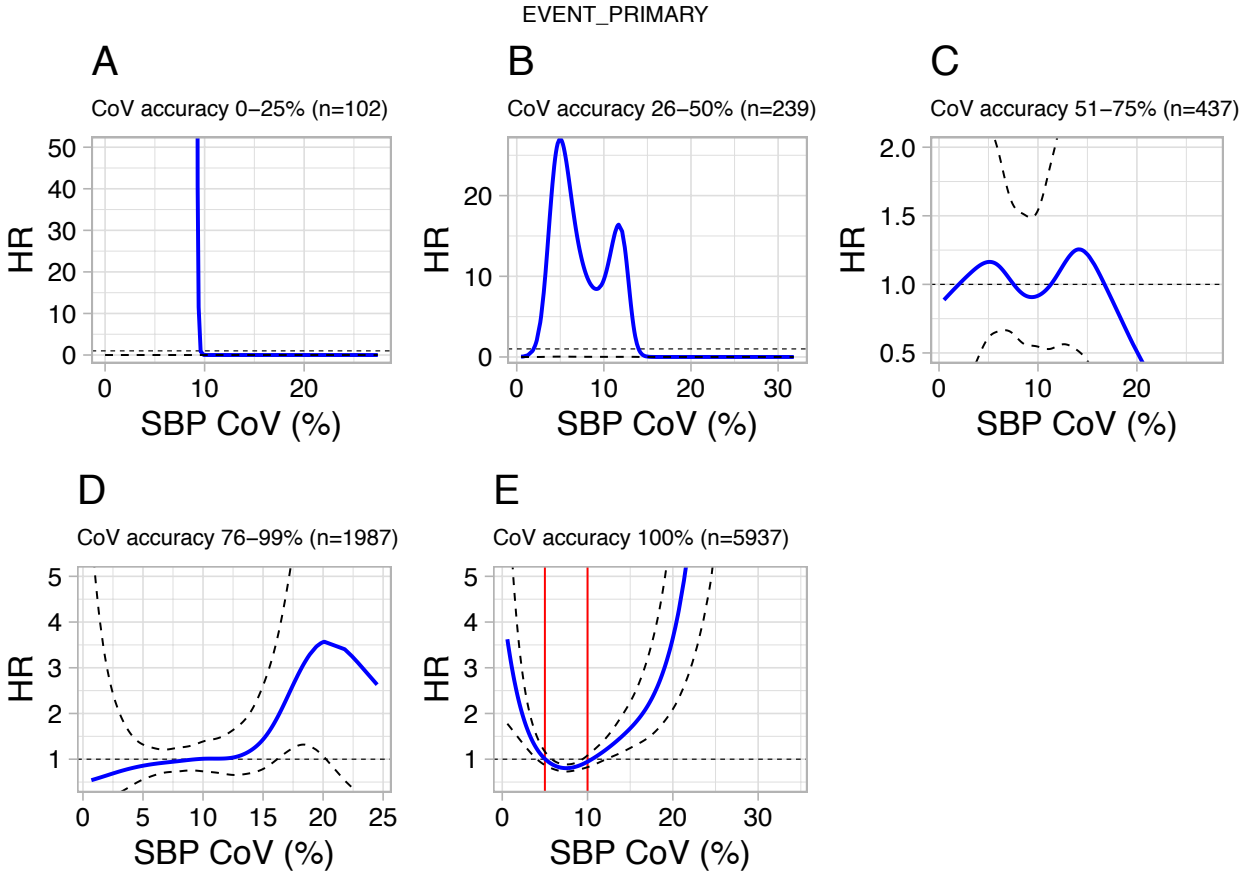


Figure 4. Penalized cubic splines of the risk of all-cause mortality by visit-to-visit systolic BPV according to CoV accuracy ranges (0-25%; 26-50%; 51-75%; 76-99%; and 100%). Note the progressive narrowing of the 95% CI (dotted line) from panel A (CoV accuracy: 0-25%) to E (CoV accuracy: 100%). The visit-to-visit systolic BPV associated with the lowest risk of all-cause mortality (crude HR<1), rounded to the nearest integer, is identified by the red lines (≤8%) in panel E.

SBP, systolic blood pressure; CoV, coefficient of variation; HR, hazard ratio; CI, confidence interval.

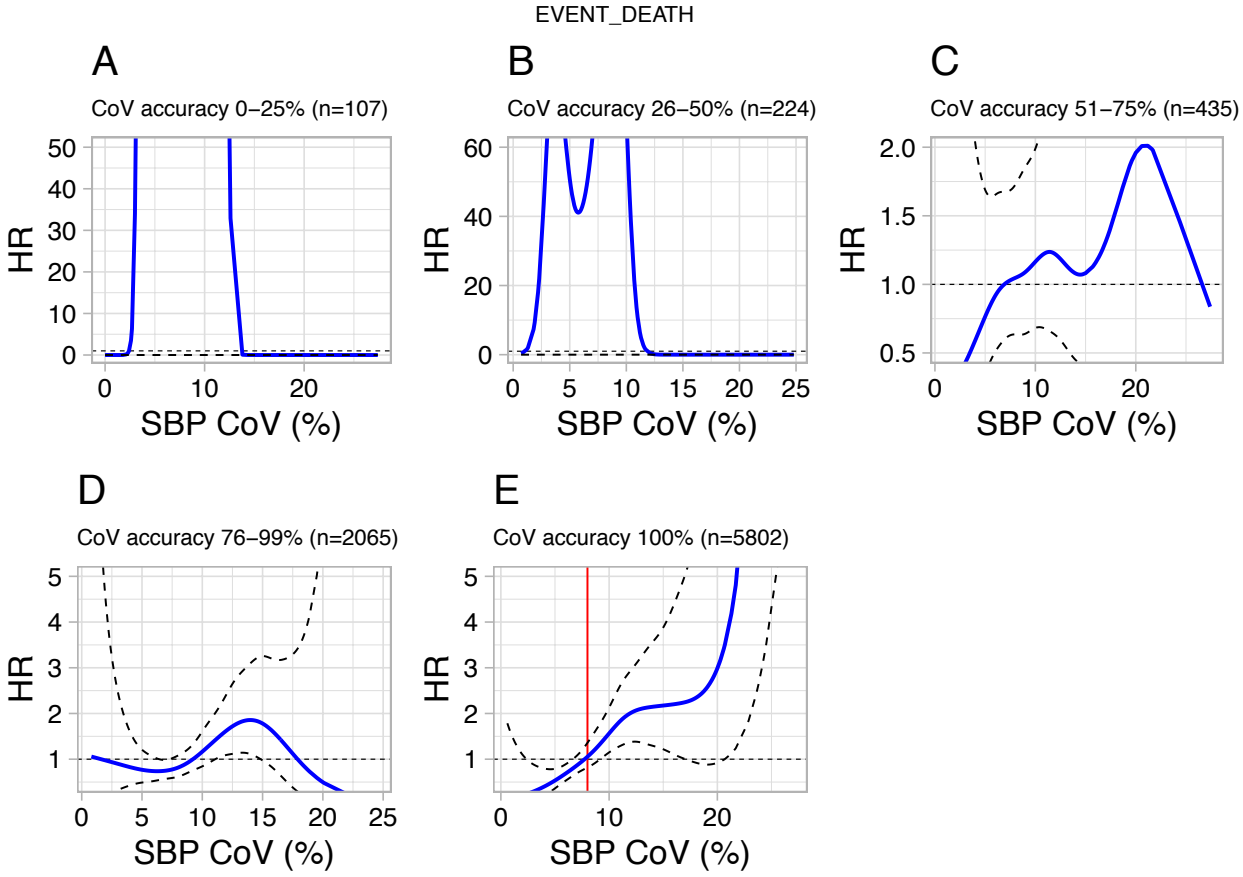
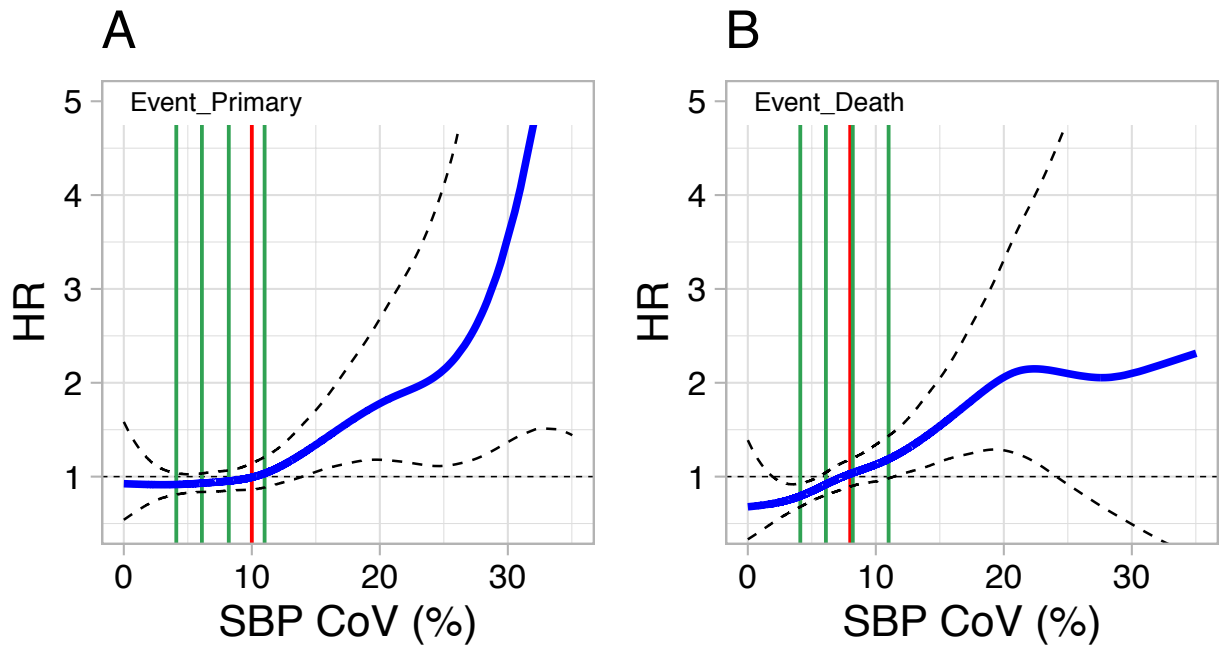


Figure 5. Penalized cubic splines of the risk of primary events (panel A) and all-cause mortality (panel B) by visit-to-visit systolic BPV calculated on 4 BP readings (3-, 6-, 9-, and 12-month visits). Green bars identify quintiles of BPV (4.1, 6.1, 8.2, 11%), while the red bars identify the cutoff of BPV, rounded to the nearest integer, associated with the lowest risk (crude HR<1) of a primary event (≤10%) and all-cause mortality (≤8%) according to our restricted analysis.

SBP, systolic blood pressure; HR, hazard ratio.



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Con il cuore colmo,

Grazie!!!