Hypertension

BLOOD PRESSURE VARIABILITY AND STROKE

Impact of Model Choice When Studying the Relationship Between Blood Pressure Variability and Risk of Stroke Recurrence

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ABSTRACT: Long-term blood pressure variability (BPV), an increasingly recognized vascular risk factor, is challenging to analyze. The objective was to assess the impact of BPV modeling on its estimated effect on the risk of stroke. We used data from a secondary stroke prevention trial, PROGRESS (Perindopril Protection Against Stroke Study), which included 6105 subjects. The median number of blood pressure (BP) measurements was 12 per patient and 727 patients experienced a first stroke recurrence over a mean follow-up of 4.3 years. Hazard ratios (HRs) of BPV were estimated from 6 proportional hazards models using different BPV modeling for comparison purposes. The 3 commonly used methods first derived SD of BP measures observed over a given period of follow-up and then used it as a fixed covariate in a Cox model. The 3 more advanced modeling accounted for changes in BP or BPV over time in a single-stage analysis. While the 3 commonly used methods produced contradictory results (for a 5 mmHg increase in BPV, HR=0.75 [95% CI, 0.68–0.82], HR=0.99 [0.91–1.08], HR=1.19 [1.10–1.30]), the 3 more advanced modeling resulted in a similar moderate positive association (HR=1.08 [95% CI, 0.99–1.17]), whether adjusted for BP at randomization or mean BP over the follow-up. The method used to assess BPV strongly affects its estimated effect on the risk of stroke, and should be chosen with caution. Further methodological developments are needed to account for the dynamics of both BP and BPV over time, to clarify the specific role of BPV. **(*Hypertension*. 2021;78:1520–1526. DOI: 10.1161/HYPERTENSIONAHA.120.16807.)**

• **Data Supplement**

Key Words: blood pressure ■ perindopril ■ proportional hazards models ■ risk factor ■ stroke

Recently, the variability of intraindividual blood pressure (BP) has emerged as a novel risk factor for stroke, independently of the level of absolute or mean BP.[1] Commonly, BP variability (BPV) is described according to its temporality, including beat-to-beat, short, medium and long-term variability. Each timeframe within which BPV is measured is hypothesized to represent different mechanisms,[2] yet each appears to be associated with an increased risk of cardiovascular disease (CVD). In particular, long-term BPV, which is the variability of BP over several years has been shown to be associated with the risk of stroke, independently of mean BP level.[3–9]

The statistical methods used to study long-term BPV raise questions. In many studies, BPV of each patient is first derived as the SD, or some other metric of BPV, of the patient's BP measures observed during the follow-up, often including the period after the occurrence of CVD[10,11] (Stage 1). This unique value of BPV is then taken as the exposure value in a Cox regression model to investigate the association

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Novelty and Significance

What Is New?

- Assessing the impact of strong assumptions (blood pressure variability [BPV] stable over time and measured without error) made in previous studies estimating the association between BPV and risk of stroke.
- Comparing the results with more advanced modeling of BPV accounting for measurement errors.

What Is Relevant?

- The estimated association between BPV and the risk of stroke highly depend on the modeling of BPV.
- The estimated association was much weaker with more advanced methods than with the most commonly used methods.

Summary

Estimating the association between BPV and the risk of cardiovascular events raises several important methodological issues that are likely to strongly bias the results if not appropriately accounted for.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
BPV	BP variability
CVD	cardiovascular disease
HR	hazard ratio
PROGRESS	Perindopril Protection Against Stroke Study

with the risk of CVD (Stage 2). This commonly used 2-stage analytical approach raises 2 important methodological issues. First, the uncertainty of BPV estimates derived in Stage 1 is usually not accounted for in Stage 2, which could produce a biased estimate of the association between BPV and CVD.[12] Second, this method uses, at each time point, BP measures observed after that time point, which is not appropriate in Cox regression models.[13–15] The second issue could be solved by either (1) deriving BPV in an initial exposure window, and then taking this as a baseline value in a Cox model for CVD outcome during the remaining period of follow-up or (2) using a Cox model over the entire follow-up, but taking BPV as a time-dependent variable. However, these 2 options require sufficiently numerous and close BP measurements for each patient. A more robust third option could be to use a joint modeling of BP or BPV and time-to-event.[16] A recent methodological article used such an approach to investigate the association between BPV and CVD.[12] However, the authors assumed that BPV of each patient was stable over time.

In light of these limitations, the aim of this study was to compare the results obtained by joint modeling considering BPV as time-dependent to other used approaches. We used data from the PROGRESS (Perindopril Protection Against Stroke Study), a large randomized, controlled trial on the prevention of stroke recurrence.[17]

METHODS

The data supporting the finds of this study are not available.

Study Population and Design

The study population was composed of all the participants randomized in the PROGRESS who had at least 2 BP measurements from randomization. The design and methods of PROGRESS have been described elsewhere.[17] Briefly, this was a double-blind randomized and controlled trial (RCT), which enrolled 6105 patients with a past history of stroke recruited between May 1995 and November 1997 and followed up for at least 4 years. It was designed to determine the effect of BP lowering therapy with Perindropril, an ACE (angiotensin-converting-enzyme) inhibitor, with or without indapamide, for preventing stroke recurrence. Eligible patients had a history of stroke in the past 5 years before inclusion. After 4-week run-in period, individuals were randomly assigned to receive active therapy by Perindopril, with or without indapamide or placebo.

Outcome

All events were reviewed by an end points adjudication committee and were coded according of the ninth revision of the International Classification of Diseases.[18] The event of interest was the first recurrence of fatal or nonfatal, hemorrhagic or ischemic stroke, whichever came first during the follow-up. Death from other causes was considered as a competing event.

Blood Pressure Assessment

The protocol included 5 visits within the first year and 2 annual visits for the next 4.5 years, with standardized BP measurements at each visit. BP at a specific visit was defined as the mean of the 2 BP measurements performed with a mercury sphygmomanometer, in the seated position after 5 minutes of rest. BPV of each patient was quantified as the SD of BP, using different methods as described below.

Statistical Analysis

Quantitative variables were described by the mean (SD) if they were normally distributed or by the median (interquartile range) if not. Hazard ratios (HRs) of BPV adjusted for

systolic BP at randomization, age, sex, ethnicity (Asian or Non-Asian), randomized treatment group (active treatment or placebo) were estimated from 6 proportional hazards models. Three versions of the Cox model often used in the literature were considered for comparison purpose, as well as a time-dependant Cox model and two joint models, as described below. The time-to-event in each model was the time elapsed between the second BP measurement and the first stroke recurrence. It was right censored at death from a nonstroke cause or at end of study if it occurred before any stroke recurrence, in all models

In the Fixed Cox model, BPV was the SD of all BP measures observed during the entire follow-up including BP measures after stroke recurrence (version A) or excluding them (version B). Both versions A and B of the fixed Cox model thus used future information at each time point (conditioned on the future; Figure).

The First Year Cox model was estimated from the end of the first year of follow-up only. More specifically, this model was estimated using only patients still at risk of a first stroke recurrence at 1 year and thus excluded patients who had a stroke recurrence, died, or were lost of follow-up within the first year. BPV was the SD of all BP measures observed during the first year of follow-up (Figure). This model thus did not condition on the future but was based on a selected population surviving at least 1 year without a stroke.

The Time-Dependent Cox model included BPV as a time-dependent covariate. At each visit, BPV was the SD of current BP measure and all observed previous BP measures.[19] This model did not condition on the future, allowed BPV to vary over time, but assumed that BPV was constant between 2 consecutive visits (Figure).

The Fixed Joint model was a shared random-effect model where the BPV of each patient was the variability of the deviations of all his observed BP measures from his own individual mean BP trajectory over time (Figure). More specifically, individual trajectories of BP over follow-up were modeled using a linear mixed model. The BPV of each patient was estimated from this model and was simultaneously incorporated as a time-constant covariate in a cause-specific proportional hazards model for the first stroke recurrence. The linear mixed model and the proportional hazards model were jointly estimated in a single stage.[12] Technical details are given in the Data Supplement. This model accounted for the evolution of BP over time but assumed that BPV was a stable component of BP over time (Figure).

The Time-Dependent Joint model was also a shared random-effect model but did not assume that the BPV of each

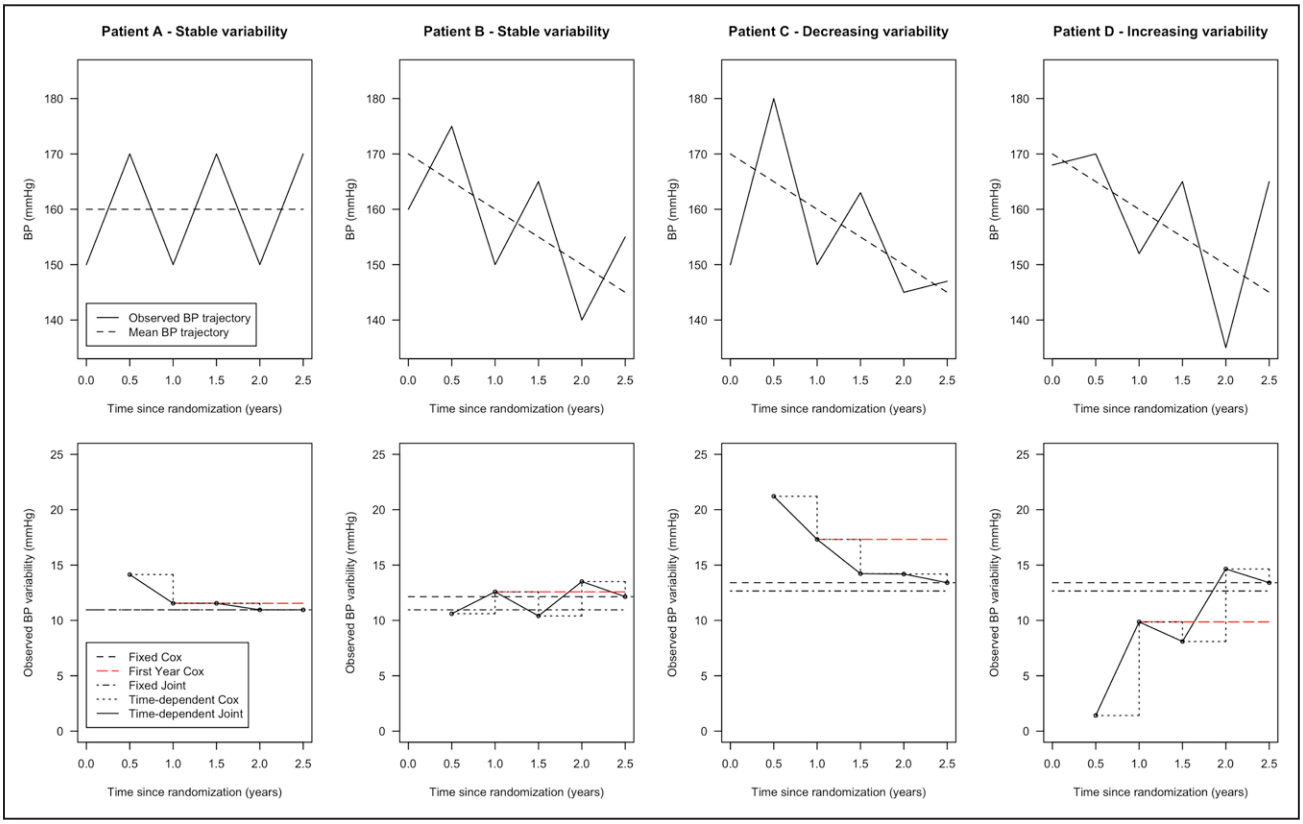

Figure. Systolic blood pressure (BP) (top) and observed BP variability (bottom) of 4 hypothetical patients followed up for 2.5 y with BP measurements every 6 mo and no stroke recurrence.

Top: the solid line represents observed BP trajectory, and the dashed line represents the underlying mean BP trajectory. Bottom: observed BP variability considered in the analytical models. The solid line represents observed BP variability trajectory derived at each time point as the SD of current and past observed BP measurements (time-dependent joint model). The dotted line represents the same BP variability trajectory but constant between 2 consecutive BP measurements (time-dependent Cox model). The dashed line represents the BPV derived as the SD of all observed BP measurements (Fixed Cox model). The long-dashed red line represents the BPV derived as the SD of all BP measurements observed during the first year of follow-up (First Year Cox model). The 2-dashed line represents BPV derived using all BP measurements deviations from the mean BP trajectory (Fixed Joint Model).

patient was stable over time. The linear mixed model directly modeled individual trajectories of SD of observed BP measurements during the follow-up rather than individual trajectories of BP (Figure). The current true value of SD of BP at each time point was estimated from this model and was simultaneously incorporated as a time-dependent covariate in a cause-specific proportional hazards model for the first stroke recurrence. The linear mixed model and the proportional hazards model were also jointly estimated in a single stage.[20] Technical details may be found in the Data Supplement. This model accounted for changes in BPV over time (Figure) but did not specifically model the evolution of BP over time.

It is important to note that the concept of BPV differs between the Fixed Joint model and the other models. In the Fixed Joint model, BPV quantified only fluctuations around the individual mean BP trajectory over time, while in other models, BPV also captures changes in BP over time (Patients A and B in Figure have the same BPV in the Fixed Joint Model, but different BPV in all other models).

Sensitivity Analysis

To assess the robustness of results with respect to the BP level adjustment, we adjusted all models for the mean level of BP over the follow-up rather than for BP at randomization. Note that because the mean level was derived using all BP measures observed up to the first stroke recurrence, this sensitivity analysis implied a conditioning on the future, as done for BPV in the fixed Cox model. Finally, we further adjusted for the delay between qualifying event and randomization in PROGRESS.

The proportional hazards assumption in all Cox's models was verified using Schoenfeld residuals. The linearity of the effect of quantitative variables was verified using penalized splines with 4 *df*. All analysis were performed using R Development Core Team (http://www.R-project.org, version R 3.4.3, accessed November 2017), the JM package version 1.4-8 for the Time-dependent Joint Model,[21] and the JAGS software through rjags and coda packages for the Fixed Joint Model.[22,23]

RESULTS

A total of 6105 patients were randomized in the PROGRESS study,[17] including 6000 patients with at least 2 BP measurements before any stroke recurrence. Patients were mostly elderly (mean age, 63.9 years), male (69.8%) and non-Asian (38.9%) (Table 1). The mean duration of follow-up for the first stroke recurrence was 3.7 years, during which a first stroke recurrence occurred for 693 patients. The median number of BP measurements per patient was 12. On average, mean systolic BP over the follow-up was 138.1 mm Hg (SD, 18.5) (Table 1, Figure S1 in the Data Supplement), and BPV was 11.0 mm Hg (SD, 4.3) (Table 1, Figures S2 through S4). Patients who survived at least 1 year had much less subsequent BP measurements as expected (Table 1).

The association between BPV and the HR of stroke recurrence estimated from the 6 models is shown in Table 2. All estimated HRs are shown for a 5 mm Hg increase in BPV, which approximately corresponded to 1

Table 1. Characteristics of Patients at Randomization and During Follow-Up, PROGRESS Study

Variable	All patients (n=6000)	Patients at risk at 1 y (n=5737)
Treatment group (n, %)	2991 (49.9)	2873 (50.1)
Age at randomization (mean, SD, in y)	63.9 (9.5)	63.7 (9.5)
Male (n, %)	4187 (69.8)	3996 (69.7)
Asian (n, %)	2334 (38.9)	2233 (38.9)
Length of follow-up for the first stroke recurrence (mean, SD in years)	3.7 (1.0)	3.8 (0.8)
Number of patients with at least one stroke recurrence (n, %)	693 (11.6)	493 (8.6)
Number of BP measures per patient over the follow-up for the first stroke recurrence		
Median (IQR)	12 (10–13)	5 (5–6)
<5	305 (5.1)	3645 (63.5)
5–10	920 (15.3)	2094 (36.5)
>10	4775 (79.6)	0
Systolic BP (mean, SD, in mm Hg)		
At randomization	138.1 (18.5)	137.9 (18.3)
Over the follow-up for the first stroke recurrence	138.2 (14.3)	138.1 (14.9)
Systolic BPV (mean, SD, in mm Hg)		
Over the follow-up for the first stroke recurrence in all patients	11.0 (4.3)	11.4 (4.5)
Over the follow-up for the first stroke recurrence in patients with a stroke recurrence	10.8 (4.3)	11.4 (4.7)
Over the follow-up for the first stroke recurrence in patients with a stroke recurrence within the first year	9.6 (5.7)	Not applicable
Over the whole follow-up for patients with a stroke recurrence	12.0 (4.6)	12.5 (4.5)

BP indicates blood pressure; BPV, blood pressure variability; IQR, interquartile range; PROGRESS, Perindopril Protection Against Stroke Study; and SD, standard deviation.

SD of BPV (Table 1, Figure S4). The sample sizes used for the First year Cox model was lower than for the other models (n=5737 versus 6000) because it was restricted to subjects still at risk of stroke recurrence at 1 year. When BPV was calculated as the SD of all BP measures over the whole follow-up, including BP measures after the first stroke recurrence (Fixed Cox Model—version A), an increase of 5 mm Hg in BPV was associated with a 19% increase in the hazard of stroke (HR=1.19 [95% CI, 1.10–1.30]). When excluding BP measures after the stroke recurrence (Fixed Cox Model—version B), the effect of BPV was inverted with a 25% decrease in the hazard of stroke for each 5 mm Hg increase of BPV (HR=0.75 [95% CI, 0.68–0.82]). When BPV was calculated as the SD of BP over the first year of follow-up only (First Year Cox Model), BPV was no longer associated with subsequent stroke (HR=0.99 [95% CI, 0.91–1.08]). When BPV was a time-dependant covariate in a Cox

Table 2. Estimated Effect of BPV on the Risk of Stroke Recurrence, Using Different Representation of BPV in the Models

Models	n	Number of events (first stroke recurrence)	SD (for a 5-mm Hg increase)		
			HR	95% CI	*P* Value
Fixed Cox Model–version A	6000	693	1.19	(1.10–1.30)	<0.001
Fixed Cox Model–version B	6000	693	0.75	(0.68–0.82)	<0.001
First year Cox Model	5737	493	0.99	(0.91–1.08)	0.859
Time-dependent Cox Model	6000	693	1.07	(0.99–1.15)	0.069
Fixed joint model	6000	693	1.07	(0.90–1.27)	…*
Time-dependent joint model	6000	693	1.08	(0.99–1.17)	0.076

HR derived for an increase of 5 mm Hg in the SD of blood pressure, adjusted for age, sex, ethnicity, blood pressure level at randomization, and treatment group. Model 1: Cox model with BPV as a fixed covariate derived using all BP measures observed over the whole follow-up including those after stroke. Model 2: Cox model with BPV as a fixed covariate derived using all BP measures observed up to the first stroke recurrence. Model 3: Cox model with BPV as a fixed covariate derived over the first year of follow-up only. Model 4: Cox model with BPV as a time-dependent covariate. Model 5: joint modeling of blood pressure and hazard of a first stroke recurrence, assuming stable BPV over time. Model 6: joint modeling of BPV and hazard of a first stroke recurrence, considering BPV as a time-dependent biomarker.

*No *P* Value because of Bayesian inference.

model (Time-Dependent Cox Model) or a time-dependent variable in a joint model (Time-Dependent Joint Model), the results were almost identical: an increase of 5 mm Hg in the current value of BPV was associated with a 7% or 8% increase in the hazard of stroke recurrence (HR=1.07 [95% CI, 0.99–1.15] for the Cox model; HR=1.08 [95% CI, 0.99–1.17] for the joint model). When BPV was assumed to be a stable component of BP in a joint model (Fixed Joint Model), an increase of 5 mm Hg in BPV was associated with a 7% increase in the hazard of stroke (HR=1.07 [95% CI, 0.90–1.27], Table 2).

When adjusting for the delay between qualifying event and randomization, or for the mean BP level over the follow-up rather than for BP at randomization, the results were almost the same (Table S1).

DISCUSSION

Our study shows some important discrepancies between the results of the different modeling approaches of BPV. While the Fixed Cox Model version B suggested a significant decrease in the risk of stroke with higher BPV, the other models suggested otherwise: no association (First Year Cox model version A), a marginally significant positive association (Time-dependent Cox Model, Fixed Joint Model, Time-Dependent Joint Model), or a significant stronger positive association (Fixed Cox Model–version A, including BP measures after the first event).

Our results indicating a divergence in the association between BPV and stroke encompassing both reduced and increased risk, raise questions about the most appropriate statistical approach. Theoretically, the results from the 2 joint models are likely to be the more accurate since they both accounted for measurement errors on BP (for the Fixed Joint Model) or BPV (for the Time-Dependent Joint Model). However, in our study, ignoring measurement errors on BPV in the Time-Dependent Cox model produced similar results to those from the Time-Dependent Joint Model. The comparable finding could be explained by the frequent measures of BP in the PROGRESS Study (5 times in the first year and twice thereafter). Assuming that BPV was constant between 2 consecutive BP measures in the Time-Dependent Cox Model might have been appropriate in this study. However, the results of the Time-Dependent Cox Model and Joint model might diverge in studies with less frequent BP measures, when time-dependent BPV would be updated less regularly.

In our study, we found contradictory results between the 2 versions of the Fixed Cox model. It is not surprising that including BP measures after the stroke recurrence (version A) produced the strongest estimated positive association between BPV and stroke, given the strong relationship between post-stroke BPV and recurrent stroke. Indeed, a stroke recurrence may influence BP instability and thus produce a stronger BPV over the entire follow-up than over the follow-up for stroke recurrence (average of 12.6 versus 11.3 mm Hg as shown in Table 1). However, only the variability until the stroke recurrence is likely to cause the stroke recurrence. Using BP measures after the stroke is thus likely to induce an over-estimation bias of the positive association between BPV and stroke. Excluding BP measures after the first stroke recurrence in version B produced an opposite result, that is, a negative association between BPV and stroke. The reason is likely that the first stroke recurrence occurred shortly after randomization for many subjects who had lower BPV. Indeed, 200 over 693 subjects had a first stroke recurrence within the first year (Table 2), and their mean BPV was 9.6 compared with 10.8 mm Hg for all patients with a stroke recurrence (Table 1). This might have led to a spurious protective effect of BPV. The Fixed Joint Model also excluded BP measures after the stroke recurrence and also assumed

constant BPV, but BPV was likely to be much better estimated. Indeed, each subject specific BPV was estimated from a linear mixed model that accounted for the data of all subjects, as well as for the evolution of BP over time and for its measurement's errors. The results from the Fixed Joint Model were actually relatively close to those from the Time-Dependent Joint Model, maybe suggesting that in the PROGRESS study, BPV before the stroke recurrence was almost constant over time for most patients. However, the discrepancy between the Fixed Joint Model and the Time-Dependent Joint Model may be more important in other populations with a lower control of BP. Our results also illustrate the loss of statistical power and potential selection bias when using only the BP measures observed in a first period of follow-up and estimating the association with stroke in the remaining period of follow-up (First Year Cox Model).

The results suggesting a positive association between increased BPV and stroke are consistent with previous studies.[1,5,24] Specifically, the study conducted by Rothwell et al was a secondary analysis of a randomized controlled trial comprised of 2435 patients with a recent transient ischemic attack or stroke. They defined BPV as the SD of systolic BP measures and found an increased risk of stroke recurrence for subjects in the top 10% of BPV compared with those in the bottom (HR=4.84 [95% CI, 3.03–7.74]).[1] In the same way, Tao et al[24] conducted a study which consisted in analysis of risk of stroke recurrence associated with long-term BPV defined as the SD of BP measures in a large cohort composed from >2000 Chinese patients. The authors founded an increased risk of 93.9% of stroke recurrence for the highest quartile of systolic BPV compared with the lower quartile. Those results were also replicated in other population. For example, Shimbo et al[5] studied a large sample of >56 000 postmenopausal women in which a 5 mm Hg increase in BPV (defined as the SD of systolic BP measures) was associated with a 16% increased risk of stroke. Although our results seem to be consistent, the previously studies used a Fixed Cox Model in which BPV calculation excluded measurements after stroke occurrence (Fixed Cox Model version B), and our results differed in this way.

Our study has strength and limitations. First, we used data from a large international randomized controlled trial, including a large number of repeated measures of BP over >4 years. The definition of events was rigorous due to a review by an independent evaluation committee, and BP was accurately measured using the same standardized procedure over the whole follow-up. However, in such a large international trial as PROGRESS, few variables are usually registered, and thus our estimates of the effect of BPV may be affected by residual cofounding. In the main analysis, we adjusted for the BP level at randomization. We further adjusted for the mean BP level over the follow-up in a sensitivity analysis, which showed similar HR and identical discrepancy of results between the different models. However, this sensitivity analysis conditioned on the future and it would be of interest to replicate it using more advanced statistical methods modeling both BP level and BPV dynamically in time. This would allow a better distinction between the effect of BPV from the effect of BP, and thus answer the central question about the role of BPV, that is, an epiphenomenon or a true separate biological property. Another limitation is that the population was restricted to patients with a history of stroke. Although the results of all models were almost identical before and after adjustment for the time interval between qualifying event and randomization, suggesting no strong confounding effect of this variable, it would be of interest to replicate our analytical methods on a more general population. Finally, we studied a heterogeneous group of strokes consisting of both hemorrhagic and ischemic strokes, which may result in reduced estimated association if only one subtype of stroke is related to BPV. However, some authors have shown an increased risk as the BPV increases for both ischemic and hemorrhagic strokes.[25] An alternative option to account for heterogeneous populations in terms of BP trajectories would be to use a joint latent class mixed model instead of a shared random-effects model.[26]

In conclusion, our study illustrates how the methods used to estimate the association between BPV and stroke risk may affect the direction and magnitude of the estimated association, as well as its statistical significance. Because all our analyses relied on real data and not simulated data, it is difficult to determine which methods provided the result the closest to the truth. However, because the time-dependent Cox model and the 2 joints models used much more information and resulted in much more similar results than the 3 other commonly used methods, we may have more confidence in them. The choice between these 3 more advanced modeling of BPV depends on whether one can assume that BPV is a stable component of BP over time, or by contrast a time varying component. If one may assume that BPV is a stable component that should just quantify fluctuations around the patient's mean BP trajectory over time, the most appropriate model from a methodological point of view, among those we investigated, is the Fixed Joint Model. By contrast, if one assumes that BPV may vary over time and that it should dynamically capture changes in both BP and BPV over time, then the time-dependent Joint model may be preferred. The time-dependent Cox model could also be considered as a simpler alternative to the time-dependent Joint model if BP is measured sufficiently closely over time for each patient. In case of doubt, we encourage researchers to use sensitivity analysis with the 2 Joint models and the time-dependent Cox model to assess the robustness of their results. In any case, we recommend not using version A or B of the Fixed Cox model which both naively use future BP measures to explain the present.

PERSPECTIVES

This work highlights important methodological issues when estimating the association between BPV and the risk of cardiovascular events. Our study calls for replication of results on other data and populations, using the same range of analytical methods. This work also invites authors to discuss the definition of BPV, in particular, on whether it should be considered as stable biological component over time or not, and whether it should just quantify fluctuations around patient's mean BP trajectory, or also capture changes in patient's mean BP trajectory over time. Finally, our study also calls for further methodological developments of the joint modeling of BPV and risk of events, accounting correctly for both BP and BPV evolution over time, as well as further studies comparing the predictive performance of the different alternatives for BPV modeling.

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