

# Prognostic Significance of Visit-to-Visit Systolic Blood Pressure Variability: A Meta-Analysis of 77,299 Patients

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In recent clinical investigations, visit-to-visit systolic blood pressure (SBP) variability was proven as a predictor of cardiovascular events and all-cause mortality. However, inconsistent results exist in this association. A meta-analysis of 13 prospective studies was conducted to evaluate the prognostic value of visit-to-visit SBP variability by different parameters in 77,299 patients with a mean follow-up of 6.3 years. The pooled age- and mean SBP-adjusted hazard ratios (HRs) for all-cause mortality were 1.03 (95% confidence interval [CI], 1.02–1.04;  $P < .001$ ) per 1-mm Hg

increase in SBP standard deviation (SD) and 1.04 (1.02–1.06,  $P < .001$ ) per 1% in SBP coefficient of variation, and the corresponding values of cardiovascular mortality were 1.10 (1.02–1.17,  $P < .001$ ) and 1.01 (0.99–1.03,  $P = .32$ ), respectively. Moreover, a 1-mm Hg increase in SD was significantly associated with stroke, with an HR of 1.02 (1.01–1.03,  $P < .001$ ). Visit-to-visit SBP variability, independent of age and mean SBP, is a predictor of cardiovascular and all-cause mortality and stroke. *J Clin Hypertens (Greenwich)*. 2015;17:107–115. © 2015 Wiley Periodicals, Inc.

High blood pressure (BP) is considered a worldwide public crisis. On April 7, 2013, Professor Margaret Chan, the director of the World Health Organization (WHO), demonstrated that hypertension affects more than 1 billion people worldwide and leads to more than 9 million deaths per year.<sup>1</sup> In this respect, accurate and appropriate BP measurement and control are currently important.

It is well accepted that 24-hour BP is superior to office BP in the association of target organ damage and in the prediction of future cardiovascular events and mortality.<sup>2–4</sup> This method is also currently recommended by the latest guideline of the European Society of Hypertension.<sup>5</sup> Through 24-hour BP monitoring, BP variability (BPV) can be derived and provide significant but modest prognostic information, independent of mean BP. For instance, Hansen and colleagues<sup>6</sup> reported in 8938 patients from the International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (IDACO) study that 24-hour BPV was an independent and significant predictor of cardiovascular and all-cause mortality.

More recently, Rothwell and colleagues<sup>7,8</sup> indicated in the UK Transient Ischemic Attack Trial (UK-TIA) and

Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) study that visit-to-visit systolic BPV (SBPV), a long-term SBP variation, could provide significant prognostic value, independent of average SBP, to predict future cardiovascular events and mortality, especially the prediction of stroke. However, inconsistent results exist in this association,<sup>9,10</sup> especially when this long-term SBPV was frequently assessed by different parameters and in various populations.

Therefore, a meta-analysis was conducted by integrating the longitudinal clinical studies to assess the predictive value of visit-to-visit SBPV in different settings, namely standard deviation (SD), coefficient of variation (CV), variability independent of the mean (VIM), and average real variability (ARV) for cardiovascular events and all-cause mortality.

## METHODS

### Literature Search

Electronic databases were searched via PubMed and EMBASE through November 2013 using Medical Subject Heading “blood pressure” and “variability” or Text Word “blood pressure variability” or Text Word “blood pressure variation” in combination with the Medical Subject Heading “hypertension/complications,” “cardiovascular diseases/mortality,” “fatal outcome,” “cerebrovascular accident,” “myocardial infarction,” “survival analysis,” or “proportional hazards models.” Data sources were also identified through manually searching the references of articles.

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## Study Eligibility

Studies were deemed eligible if they: (1) were full-length publications in peer-reviewed journals, (2) assessed visit-to-visit SBPV, (3) were prospective studies and reported a combined cardiovascular outcome or cardiovascular or total mortality. Studies were excluded from the meta-analysis if they provided risk estimates from populations that were shared with other included publications. No exclusion criterion was imposed with regard to population characteristics (general or populations with risk factors or diseases), sample size, or follow-up duration. Since there was only one study investigating the visit-to-visit SBPV in the VIM and ARV modes, we only calculated the hazard ratios (HR) per 1-unit increase in VIM and per 1-mm Hg increase in ARV but did not perform the meta-analysis.

## Extraction of Data

Two independent investigators (CT and YZ) abstracted information on all variables listed in Table I and all relevant effect estimates with 95% confidence interval (CI). In a few studies not reporting numeric data, risk estimates were derived by calculating the survival curves or requesting corresponding authors of those papers for unpublished data.

## Outcomes

The main outcomes of interest were (1) all-cause mortality, (2) cardiovascular mortality, and (3) total cardiovascular events, including myocardial infarction, stroke, revascularization, and aortic syndromes.

## Parameters of SBPV

SBPV was quantified using SD, CV, VIM, or ARV.<sup>3,8,11–14</sup> SD and CV were calculated by the formulas as:

$$SD = \sqrt{\sum_{k=1}^n (BP_k - \overline{BP})^2 / (n - 1)} \quad \text{and} \quad CV = SD / \overline{BP}$$

where  $k$  ranges from 1 to  $n$ ,  $SBP_k$  is one SBP measurement,  $\overline{BP}$  is mean SBP and  $n$  is the number of SBP readings.

## Statistical Analysis

Quantitative and qualitative variables were presented as means±SD and numbers (percentages), respectively. HRs for 1-mm Hg change were calculated with the corresponding root the original value. For instance, if the original HR for 5-mm Hg change was 1.12, the HR for 1-mm Hg change would be the fifth root of 1.12, and that is 1.02. The most extensively adjusted HRs and 95% CI from each original study were used to summarize individual risk estimates in order to address confounding. The proportion of inconsistency across studies not explained by chance was quantified with the  $I^2$  statistic. Heterogeneity between subgroups was calculated with Cochran's Q test.<sup>15</sup> When significant heterogeneity existed among studies, the random-effects model was used to obtain the pooled HR. A fixed-effects model was used when heterogeneity was absent. The HRs and CIs of comparable studies were illustrated with forest plots.

Meta-regression was conducted in age (>60 vs ≤60 years), study region (Europe, other), population (general, end-stage renal disease [ESRD], diabetes mellitus [DM], coronary artery disease), sample size (>1000 participants vs ≤1000 participants), and follow-up duration (>6 vs ≤6 years) to explore predefined sources of heterogeneity of our main findings.

Sensitivity analysis was conducted to assess the influence of each study on the overall effect by repeating the meta-analysis while removing one study at a time.

Publication biases were investigated graphically by funnel plots of precision, and its implications for the results were assessed by the Duval and Tweedie trim-and-fill method and the classic fail-safe N method.<sup>16</sup>

All analyses were performed with Comprehensive Meta-Analysis Version 2 (Biostat, Englewood, NJ).<sup>17</sup> All tests in the analysis were two-sided and statistical significance was set at  $P \leq .05$ .

## RESULTS

### Eligible Studies

A total of 846 potential eligible publications were identified, which were narrowed by preliminary review to 41 relevant original articles. Then, several investigations were further excluded because of the cross-sectional study design ( $n=11$ ) or report of the endpoints other than cardiovascular events or death ( $n=15$ ) or without a conventional index for SBPV ( $n=1$ ) or home BPV ( $n=2$ ).<sup>18,19</sup> Finally, 13 longitudinal studies assessing the association of cardiovascular events and all-cause mortality with visit-to-visit SBPV were deemed eligible for the meta-analysis.<sup>9,20–31</sup> Figure 1 shows the literature research process by chart flow.

### Baseline Characteristics

Characteristics of all selected studies are detailed in Table I. A total of 77,299 patients were included with a mean follow-up of 6.3 years. All studies were published since 2011 and the mean/median follow-up ranged from 2.8 to 14 years. Various study populations were included such as patients with hypertension, DM, ESRD, and coronary artery disease, and also patients from the general population. All-cause mortality was evaluated in nine studies,<sup>9,20,22–27,29</sup> cardiovascular mortality in four studies,<sup>9,22,26,27</sup> and stroke in three studies.<sup>9,29,31</sup> Age, sex, and other cardiovascular risk factors were adjusted in most studies (Table I).

### Prognostic Value of Visit-to-Visit SBPV

**All-Cause Mortality.** Six studies reported the relationship between all-cause mortality and visit-to-visit SBPV assessed by SD with nonsignificant heterogeneity in the overall analysis. The combined HR (95% CI) among 11,485 individuals was 1.03 (1.02–1.04,  $P < .001$ ) per 1-mm Hg increase of visit-to-visit SBPV SD (Table II and Figure 2).

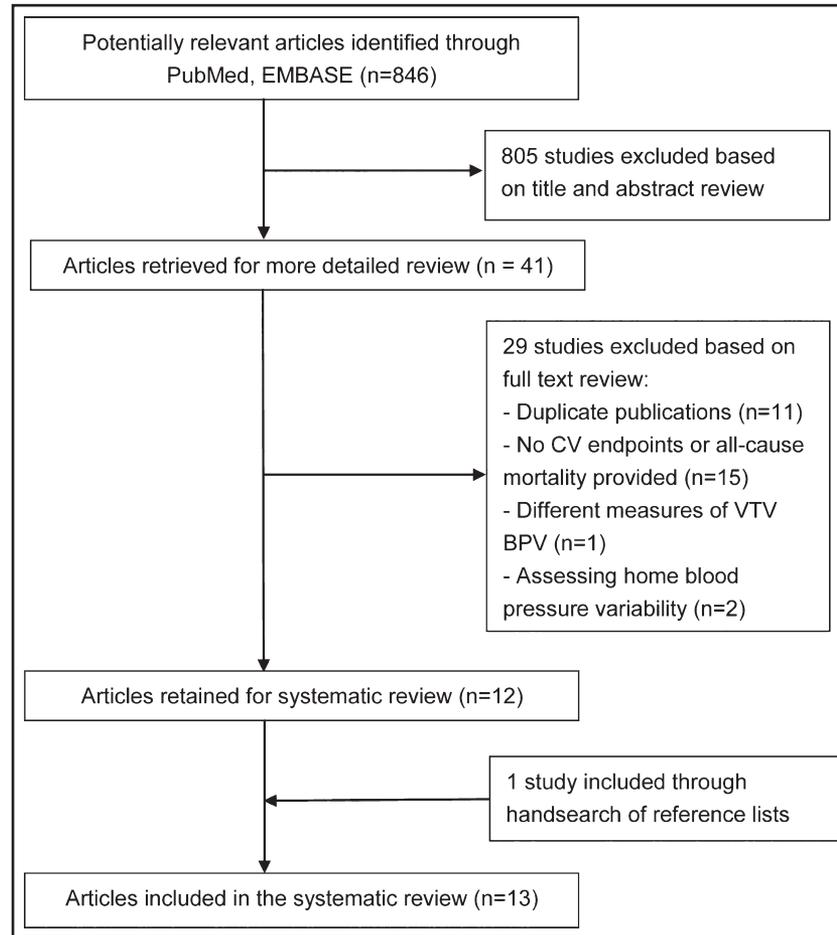
Moreover, five studies reported the relationship between all-cause mortality and visit-to-visit SBPV

TABLE I. Study Characteristics							
Reference (Year)	Population (Sample Size)	Country	Age, y	Men, %	Follow-up Duration, y	SBPV Parameters	Deaths and Events
Muntner and colleagues (2011) <sup>20</sup>	General (n=956)	US	47.4±17.7	49.5	14.0	7.7 (SD)	240 deaths
Poortvliet and colleagues (2012) <sup>29</sup>	Patients with risk factors for CV* diseases (n=1808)	Scotland, Ireland, and the Netherlands	75.2±3.4	48.5	7.1	14.1±4.9 (SD)	735 deaths, 245 strokes, 808 CV* events
Hsieh and colleagues (2012) <sup>22</sup>	Diabetes mellitus (n=2161)	China	63.5±11.9	43.0	5.6	–	119 deaths
Di Iorio and colleagues (2012) <sup>23</sup>	ESRD without CV diseases (n=374)	Italy	76.0±11.0	62.0	2.8	9.7 (SD)	209 deaths
Mallamaci and colleagues (2012) <sup>24</sup>	ESRD (n=1618)	Italy	64.0±12.0	59.0	–	11.0±6.0 (SD)	169 deaths, 202 nonfatal CV* events
Suchy-Dacey and colleagues (2013) <sup>25</sup>	General (n=3852)	US	72.0±5.0	41.0	9.9	9.0±5.0 (SD)	844 deaths, 195 strokes
Schutte and colleagues (2012) <sup>9</sup>	General (n=2944)	Belgium	44.9	49.3	12.3	–	164 CV* deaths, 401 deaths, 49 strokes
Chang and colleagues (2013) <sup>26</sup>	ESRD (n=1844)	US	57.6	43.8	2.5	9.9±4.6 (CV)	869 deaths, 408 CV* deaths
Di Iorio and colleagues (2013) <sup>27</sup>	ESRD (n=1088)	Italy	64.8±12.4	58.6	5.0	10.9±3.7 (SD)	641 deaths, 482 CV* deaths
Eguchi and colleagues (2012) <sup>28</sup>	Hypertension (n=457)	Japan	67.0±9.2	37.6	5.6	13.7±4.6 (SD)	58 CV* events
Rosignol and colleagues (2012) <sup>21</sup>	ESRD (n=388)	France	66.8	52.4	2.0	10.4±3.3 (CV)	32.7% CV* events
Shimbo and colleagues (2012) <sup>31</sup>	Postmenopausal women (n=58,288)	US	–	0.0	5.4	10.9±4.5 (SD)	997 strokes
Mancia and colleagues (2012) <sup>30</sup>	Hypertension (n=1521)	Europe	55.8±7.4	55.8	4.0	5.7 (CV)	–

**TABLE 1. Study Characteristics (Continued)**

Reference (Year)	Key Characters to Define SBPV			Major Adjustment
	No. of Visits	Time Interval	No. of BP Readings per Visit	
Muntner and colleagues (2011) <sup>20</sup>	–	0.6 months	–	Age, sex, CAD, mean SBP and PP, and use of antihypertensive therapy
Poortvliet and colleagues (2012) <sup>29</sup>	–	3 months	–	Age, sex, smoking, BMI, mean SBP
Hsieh and colleagues (2012) <sup>22</sup>	–	2–6 months	2	Age, sex, BMI, mean SBP and DBP, glucose, HbA <sub>1c</sub> , BMI, lipid profiles, creatinine, GFR
Di Iorio and colleagues (2012) <sup>23</sup>	–	1–1.25 months	–	Age, sex, DM, mean SBP and DBP, GFR, lipid profiles
Mallamaci and colleagues (2012) <sup>24</sup>	–	–	–	Age, sex, smoking, BMI, CAD, DM, GFR, mean SBP, antihypertensive therapy
Suchy-Dicey and colleagues (2013) <sup>25</sup>	5	12 months	≥2	Age, sex, smoking, BMI, DM, mean SBP, lipid profiles
Schutte and colleagues (2012) <sup>9</sup>	–	2–4 weeks	5	Sex, age, smoking, BMI, CAD, glucose, mean SBP, lipid profiles
Chang and colleagues (2013) <sup>26</sup>	–	–	–	Age, sex, DM, mean SBP
Di Iorio and colleagues (2013) <sup>27</sup>	–	0.3 weeks	–	Age, sex, BMI, DM, mean SBP, DBP and PP, creatinine
Eguchi and colleagues (2012) <sup>28</sup>	6	1 month	–	Age, sex, smoking, BMI, DM, mean SBP, creatinine, lipid profiles
Rossignol and colleagues (2012) <sup>21</sup>	17	1 week–3 months	3	Age, CAD, DM, mean SBP
Shimbo and colleagues (2012) <sup>31</sup>	>15	4 months	2	Age, smoking, BMI, CAD, DM, mean SBP, antihypertensive therapy
Mancia and colleagues (2012) <sup>30</sup>	6	1 month	3	Age, sex, smoking, DM, mean BP, lipid profiles

Abbreviations: ARV, average real variability; BMI, body mass index; BP, blood pressure; BPV, blood pressure variability; CAD, coronary artery disease; CV, coefficient of variation; CV<sup>2</sup>, cardiovascular; DBP, diastolic blood pressure; DM, diabetes mellitus; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HR, heart rate; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation VIM, variability independent of the mean. – indicates that data were absent in the original article. Continuous variables are presented as mean±SD.



**FIGURE 1.** Flow diagram of selection strategy. BPV indicates blood pressure variability; CV, cardiovascular; VTV, visit-to-visit.

Outcomes	SD (per 1-mm Hg Increase)			CV (per 1%)			VIM (per 1 unit)			ARV (per 1-mm Hg Increase)		
	n	HR	95% CI	n	HR	95% CI	n	HR	95% CI	n	HR	95% CI
All-cause mortality	6	1.03	1.02–1.04 <sup>a</sup>	5	1.04	1.02–1.06 <sup>a</sup>	1	1.00	0.97–1.03	1	1.02	0.97–1.06
Cardiovascular mortality	2	1.10	1.02–1.17 <sup>a</sup>	2	1.01	0.99–1.03	1	1.03	0.99–1.09	1	1.04	0.97–1.12
Cardiovascular events	–	–	–	2	1.05	1.00–1.10 <sup>b</sup>	1	1.02	0.99–1.05	1	1.04	0.99–1.09
Stroke	2	1.02	1.01–1.03 <sup>a</sup>	–	–	–	1	1.04	0.96–1.14	1	1.05	0.90–1.22

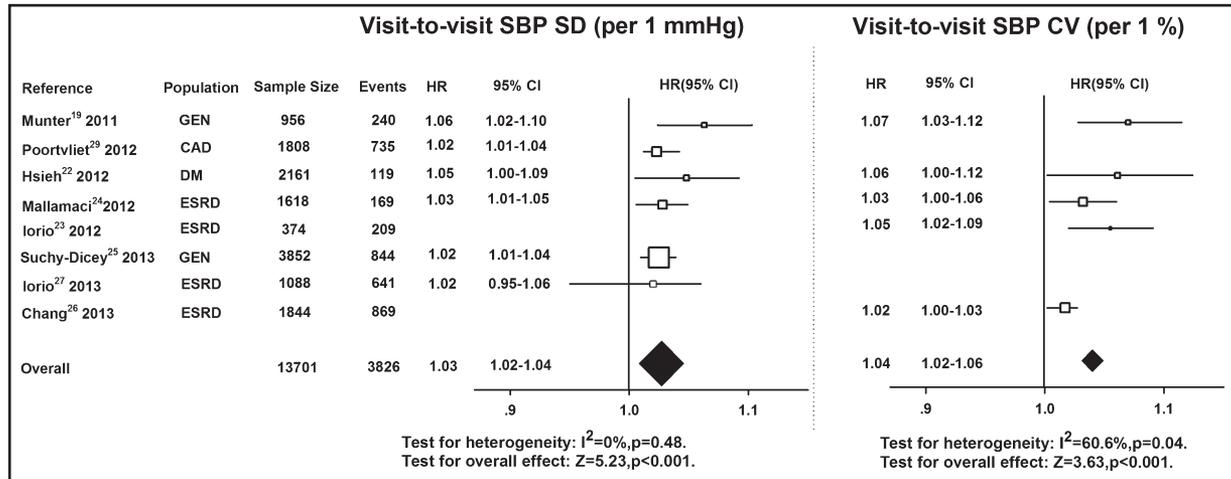
Abbreviations: ARV, average real variability; CV, coefficient of variation; n, numbers of included studies; SD, standard deviation; VIM, variability independent of the mean. Data were pooled hazard ratios. – indicates only one paper was found for the association. <sup>a</sup> $P \leq .001$ . <sup>b</sup> $P \leq .05$ .

assessed by CV, but with significant heterogeneity. The combined HR (95% CI) among 6952 individuals was 1.04 (1.02–1.06,  $P < .001$ ) per 1% in CV for all-cause mortality (Table II and Figure 2).

One study reported the relationship between all-cause mortality and visit-to-visit SBPV assessed by VIM and ARV. The HRs (95% CI) were 1.00 (0.97–1.03) and 1.02 (0.97–1.06) per 1-unit increase in VIM and per

1-mm Hg increase in ARV, respectively, for all-cause mortality (Table II).

**Cardiovascular Mortality.** Two studies reported the relationship between cardiovascular mortality and visit-to-visit SBPV assessed by SD, with nonsignificant heterogeneity. The combined HR (95% CI) among 3249 individuals was 1.10 (1.02–1.17,  $P < .001$ ) per



**FIGURE 2.** Forest plot of hazard ratios (HRs) of the visit-to-visit systolic blood pressure (SBP) standard deviation (SD) and coefficient of variation (CV) with all-cause mortality. HR and 95% confidence interval (CI) for all-cause mortality per 1-mm Hg increase in SBP SD (the left) or per 1% in SBP CV (the right). Boxes and solid lines indicate HR and 95% CI, respectively, for each study, and the diamonds and their width indicate the pooled HR and the 95% CI, respectively. GEN indicates general; CAD, coronary artery disease; DM, diabetes mellitus; ESRD, end-stage renal disease.

1-mm Hg increase in SD for cardiovascular mortality (Table II and Figure 3).

Two studies reported the relationship between cardiovascular mortality and visit-to-visit SBPV assessed by CV, without significant heterogeneity. The combined HR (95% CI) was 1.01 (0.99–1.03,  $P=.32$ ) per 1% increase in CV for cardiovascular mortality (Table II and Figure 3).

Nonsignificant findings were observed for cardiovascular mortality in the only study investigating the visit-to-visit SBPV by VIM or ARV (Table II).

**Cardiovascular Events and Stroke.** Two studies reported the relationship between cardiovascular events and visit-to-visit SBPV assessed by CV, without significant heterogeneity. The combined HR (95% CI) among

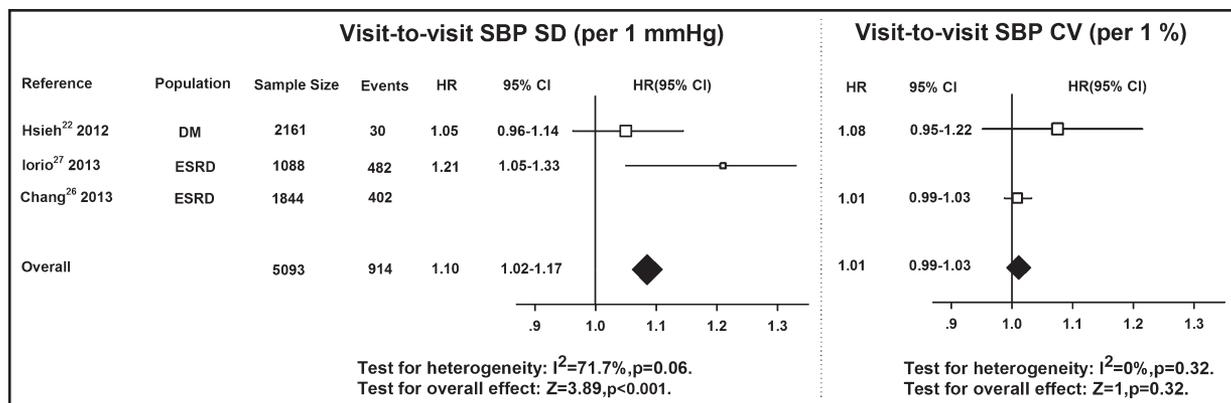
1909 individuals was 1.05 (1.00–1.10,  $P=.046$ ) per 1% increase in CV for cardiovascular events (Table II).

Two studies reported the relationship between stroke and visit-to-visit SBPV assessed by SD, without significant heterogeneity. The combined HR (95% CI) among 60,096 individuals was 1.02 (1.01–1.03,  $P<.001$ ) per 1-mm Hg increase in SD for stroke (Table II and Figure 4).

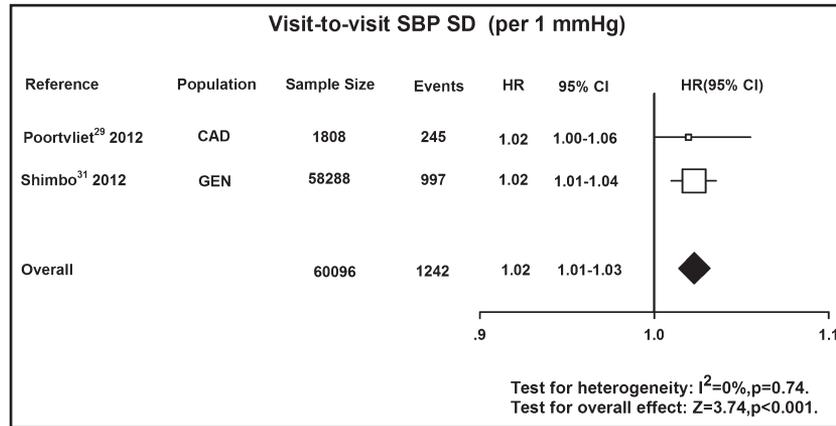
Nonsignificant findings were observed for cardiovascular events and stroke in the only study investigating the visit-to-visit SBPV by VIM or ARV (Table II).

**Sensitivity Analysis**

Meta-regression was conducted in various populations ( $P=.73$ ), different age groups ( $>60$  years and  $\leq 60$  years,  $P=.071$ ), study region (Europe and others,  $P=.45$ ),



**FIGURE 3.** Forest plot of hazard ratios (HRs) of the visit-to-visit systolic blood pressure (SBP) standard deviation (SD) and coefficient of variation (CV) with cardiovascular mortality. HR and 95% confidence interval (CI) for cardiovascular mortality per 1-mm Hg increase in SBP SD (the left) or per 1% in SBP CV (the right). Boxes and solid lines indicate HR and 95% CI, respectively, for each study, and the diamonds and their width indicate the pooled HR and the 95% CI, respectively. DM indicates diabetes mellitus; ESRD, end-stage renal disease.



**FIGURE 4.** Forest plot of hazard ratios (HRs) of the visit-to-visit systolic blood pressure (SBP) standard deviation (SD) with stroke. HR and 95% confidence interval (CI) for stroke per 1-mm Hg increase in SBP SD. Boxes and solid lines indicate HR and 95% CI, respectively, for each study, and the diamonds and their width indicate the pooled HR and the 95% CI, respectively. CAD indicates coronary artery disease; GEN, general.

sample size ( $>1000$  and  $\leq 1000$ ,  $P=.071$ ), and follow-up duration ( $>6$  years and  $\leq 6$  years,  $P=.56$ ). As shown in Table III, the findings, in terms of significant association of all-cause mortality with visit-to-visit SBPV, remained unaltered in these subgroup analyses. Furthermore, the HR values between different subgroup analyses were compared, but with a nonsignificant difference ( $P\geq .071$ , Table III).

Sensitivity analysis was conducted to assess the influence of each study on the overall effect by repeating the meta-analysis while removing one study at a time. Our findings remained unaltered in both the above-mentioned analyses.

**Publication Bias**

The funnel plots for the association of cardiovascular and all-cause mortality and stroke with visit-to-visit

SBPV were not asymmetric. The trim-and-fill method imputed missing studies and recalculated the pooled risk estimate. The imputed HRs were not substantially different from the initial estimates, suggesting the absence of significant publication bias.

**DISCUSSION**

The present meta-analysis indicates that visit-to-visit SBPV, independent of mean SBP, is a strong predictor of all-cause and cardiovascular mortality and stroke. Specifically, a 1-mm Hg increase in SD was significantly associated with a 3% higher risk of all-cause mortality, 10% higher risk of cardiovascular mortality, and 2% higher risk of stroke. A 1% increase in CV was significantly associated with a 4% higher risk of all-cause mortality, 1% higher risk of cardiovascular mortality, and 5% higher risk of cardiovascular events.

It is well accepted that office BP is a strong and independent predictor of cardiovascular events and mortality,<sup>32-34</sup> but it sometimes cannot accurately reflect patients’ out-of-office BP or real-world BP. In this respect, 24-hour ambulatory BP monitoring certainly overcomes this limitation and provides more pronounced prognostic value than office BP measurement.<sup>2-4</sup> In the IDACO study, although 24-hour ambulatory SBPV acted as an independent predictor of cardiovascular and all-cause mortality, the incremental prognostic value, independent of 24-hour mean BP, was only about 1%.<sup>6</sup> However, in the present analysis with adjustment for mean BP level, the incremental prognostic values of visit-to-visit SBPV, per 1-mm Hg SD, were 10% and 3% for cardiovascular and all-cause mortality, respectively. Herein, prognostic value of visit-to-visit SBPV is considerable, as compared with 24-hour ambulatory SBPV. It, therefore, is valuable for routine assessment in clinical practice and merits further investigation.

From a methodological viewpoint, SBPV measurements may vary by different time windows, such as beat-to-beat

Variable	Studies	HR (95% CI)	P Value	P Value <sup>a</sup>	
Age, y	>60	5	1.03 (1.02-1.03)	<.001	.071
	≤60	1	1.06 (1.02-1.10)	–	
Study region	Europe	3	1.02 (1.01-1.03)	<.001	.45
	Other	3	1.02 (1.01-1.04)	<.001	
Population	General	2	1.03 (1.02-1.04)	<.001	.73
	ESRD	2	1.03 (1.01-1.05)	.008	
	DM	1	1.05 (1.01-1.09)	.03	
	CAD	1	1.02 (1.01-1.04)	–	
Sample size	>1000	5	1.03 (1.02-1.03)	<.001	.071
	≤1000	1	1.06 (1.02-1.10)	–	
Follow-up time, y	>6	4	1.03 (1.02-1.04)	<.001	.56
	≤6	2	1.04 (1.00-1.08)	.03	

Abbreviations: SD, standard deviation; ESRD, end-stage renal disease; DM, diabetes mellitus; CAD, coronary artery disease. Data were pooled HRs. <sup>a</sup>P value obtained using meta-regression.

SBPV, daily or 24-hour SBPV, and long-term SBPV (weekly, monthly, or even yearly).<sup>35</sup> Moreover, the underlying mechanisms, clinical significance, and prognostic implications may differ between the types of SBPV according to their time windows. Specifically, short-term SBP variations, in beat-to-beat or 24-hour settings, mainly reflect the influences of central and reflex autonomic modulation, elastic properties of arteries, and the effects of humoral, rheological, and emotional factors of diverse nature and duration.<sup>36–39</sup> On the other hand, long-term SBPV or visit-to-visit SBPV may reflect the effect and adherence of antihypertensive treatment and seasonal change.<sup>20,40,41</sup> In real-world clinical practice, treatment adherence is of great importance to antihypertensive therapy, but currently there is no appropriate index for physicians to monitor patients' medication adherence. Some data suggest visit-to-visit SBPV, independent of SBP level, may theoretically represent patients' adherence to antihypertensive treatment.<sup>42–45</sup> Therefore, physicians, especially general practitioners, are suggested to record patients' SBP at each visit and calculate patients' visit-to-visit SBPV in terms of monitoring their medication adherence and predicting future adverse cardiovascular events.

Several points merit further consideration for the interpretation of the present findings. First, it is a meta-analysis in 77,299 patients from 13 clinical trials covering various populations such as the general population and patients with hypertension, DM, or ESRD. No significant heterogeneity was observed in most cases, except the association of all-cause mortality with visit-to-visit SBPV assessed by CV ( $I^2=60.6\%$ ,  $P=.038$ ). However, only five relevant studies were considered in this analysis, which were conducted in ordinary patients and patients with DM and ESRD, respectively.<sup>20,22–24,26</sup> The significant heterogeneity may contribute to the relatively small sample size and different characteristics of participants.

Second, visit-to-visit SBPV can be calculated by several methods, namely SD, CV, VIM, and ARV, with the first two widely used. However, the SD is highly dependent on mean SBP. Rothwell and colleagues,<sup>8,11</sup> therefore, proposed to use SBPV VIM and ARV instead, which might be better predictors of cardiovascular outcome beyond SBP level. In this meta-analysis, SBPV SD in the visit-to-visit setting seems to be superior to others in predicting cardiovascular and all-cause mortality and stroke, independent of mean SBP. This finding may be attributable to the extensive use of this index and more included studies. In this respect, the prognostic value of VIM and ARV in the visit-to-visit setting, as well as their comparisons with SD, merits future investigation.

Third, in addition to different indices, the number of visits, the number of SBP measurements at each visit and the time interval between visits were different between or even within the included studies. In the Trial of Preventing Hypertension (TROPHY) study, the SD of SBP increased with more visits, with more SBP recordings at each visit, and with longer time intervals between

two visits.<sup>46</sup> Those parameters differed between studies in this meta-analysis, and even a subgroup analysis is not available. This needs to be considered in the interpretation of the findings of the present paper, and a standardized assessment procedure for the definition of visit-to-visit SBPV is warranted.

### Study Strengths and Limitations

Strengths of the present study are the large sample size with a mean follow-up of 6.3 years, as well as extensive calculation of various parameters to assess patients' long-term SBPV.

It has been acknowledged that the limitation of this study is within the fact that this analysis used aggregate data as reported or calculated in published articles rather than data of individual patients. Also, there might be a risk of publication bias, but this was nonsignificant in the study. With a total sample size of 77,299, the number of studies included in the subgroup analysis is too small, especially for the visit-to-visit SBPV VIM and ARV. Some investigators indicated that the prognostic value of visit-to-visit SBPV may be more pronounced in patients with high cardiovascular risk compared with those with low risk.<sup>30</sup> However, in the present analyses, HRs of the long-term SBPV were constantly significant either in the general population or in patients with renal dysfunction or diabetes. No obvious discrepancies were detected.

### CONCLUSIONS

In 77,299 patients, visit-to-visit SBPV, independent of mean SBP and age, is a predictor of cardiovascular and all-cause mortality and stroke. These findings remained unaltered after subgroup analysis, regardless of different populations studied and follow-up durations. However, visit-to-visit SBPV may also be influenced by patients' emotional or hormonal change, dietary intervention, and measurement circumference, which are difficult to be adjusted. Additional clinical investigations, especially on the standardized protocol for SBPV assessment, are highly warranted.

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