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Invited Review Article

Long-term systolic blood pressure variability independent of mean blood pressure is associated with mortality and cardiovascular events: A systematic review and meta-analysis

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ABSTRACT

The association between long-term systolic blood pressure variability (SBPV) and cardiovascular (CV) outcomes after being adjusted with mean blood pressure (BP) is questionable. This systematic review aims to evaluate the associations between mean BP adjusted long-term SBPV and CV outcomes. A systematic search was conducted on PubMed, Scopus, and Science Direct on January 4, 2023. A total of 9,944,254 subjects from 43 studies were included in this meta-analysis. Long-term SBPV increased the risk of all-cause mortality (HR 1.21 [95%CI 1.16-1.25], I^2=100%), CV mortality (HR 1.10 [95%CI 1.07-11.4], I2 = 90%), MACE (HR 1.10 [1.07-1.13], I^2 = 91%), cerebrovascular stroke (HR 1.22 [1.16-1.29], I^2=100%), and myocardial infarction (HR 1.13 [95%CI (1.07-1.19)], I^2=91%). European populations generally had higher risk compared to other continents. In conclusion, long-term SBPV is associated with all-cause mortality, CV mortality, MACE, MI, and stroke. Poor outcomes related to long-term SBPV seem more dominated by cerebrovascular than coronary events.

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Introduction

High blood pressure (BP) is one of the longest and largest epidemics in the world.[1] It is a pivotal risk factor in the development of various cardiovascular diseases.[2,3] Hypertension affected one out of three adults globally.[2,3] The diagnosis of hypertension involves recording an office systolic blood pressure (SBP) $\geq$ 140 mm Hg and/or diastolic blood pressure (DBP) $\geq$90 mm Hg,[2,4] which should be confirmed by several office BP readings 1-4 weeks apart when ambulatory BP monitoring (ABPM) or home blood pressure monitoring (HBPM) is not available.[2,3] The value of mean BP is correlated with the risk of cardiovascular complications.[2,3,5]

Controlling mean BP is required to decrease the risk of various cardiovascular complications.[2–4] However, cardiovascular complications remain high even though the BP has been controlled.[6,7] This suggests that other factors besides mean BP are involved, including systolic blood pressure variability (SBPV). SBPV is a continuous and dynamic fluctuation in BP levels throughout a lifetime.[8] The value of BPV is correlated with mean BP and is associated with cardiovascular complications.[8,9] However, whether high SBPV or high mean BP is associated with cardiovascular complications is unknown. There is a discrepancy between studies for this issue.[10–12] Adjusting the value of SBPV with mean BP is essential to answer that question. Thus, collecting published evidence of relevant topics is necessary. This systematic review aims to evaluate the association between long-term BP variability after adjustment to at least mean BP and various cardiovascular outcomes.

Materials and methods

This systematic review was conducted in accordance with the guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)[13] (Table S1). Furthermore, the protocol for this review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO), with registration number CRD42023389113.

Eligibility criteria

We included prospective studies in our analysis. The selection of studies followed these criteria: (1) evaluating the risk of long-term SBPV on outcomes of interest in the adult population, (2) using hazard ratios that have been adjusted with at least for mean BP, and (3) including at least three SBP measurements. We considered both hypertensive (whether receiving treatment or not) and non-hypertensive populations, provided that the studies met these inclusion criteria. However, we excluded patients undergoing hemodialysis due to the association between intradialytic BP fluctuations, commonly observed in such patients, and worsened outcomes.[14,15]

Further details about the specific outcomes of interest are available in the outcome measures section. In this context, long-term SBPV refers to the variation between clinic visit-to-visit SBP measurements. Measurements obtained through HBPM and ABPM were excluded as they represent short- and mid-term SBPV. Studies with inappropriate designs (such as case reports, case series, and reviews), irrelevant populations or outcomes, unobtained full text (e.g., posters), and non-English language articles were excluded from our analysis.

Search strategy and selection of studies

On January 4, 2023, a systematic search was undertaken across several specified databases, i.e., PubMed, ProQuest, Scopus, and ScienceDirect. The literature search involved the utilization of a set of predetermined keywords, which were (“Blood pressure" OR "systolic blood pressure") AND ("variation" OR "variability") AND ("Stroke" OR "coronary heart disease" OR "myocardial infarction" OR "cardiovascular event" OR "mortality"). The keywords employed are outlined in Table S2. In addition, we also searched relevant articles by manual search. Article searching, retrieval, and screening were performed by three independent reviewers (P.B.T.S., A.D.L., and M. E.S). Any discrepancies during this process will be resolved together by consensus. Articles with relevant titles and abstracts during this process would be included for full-text assessment.

Data extraction

We extracted the following data from each included study: first author name; name of the study; name and type of study; publication year; number of participants; age; male percentage; proportion of patients with antihypertensive medication; source of population (country/ies and regio/regions); mean BP; frequency of BP measurement; length of follow-up; reported unit of SBPV and outcome(s) of interest. We also extracted the names of the studies. When two or more papers were sourced from the same studies, we chose papers that reported the largest number of participants and the longest follow-up duration. Among the multiple adjusted hazard ratios presented, we prioritized selecting the hazard ratio that had been adjusted with the greatest number of confounders. We initiated communication with the corresponding author when the required data were unavailable. Studies featuring different expression units of SBPV were included in our analysis, as these units could be rescaled to standardized hazard ratios (sHR) and subsequently subjected to separate analyses.[16] However, we established a prioritization hierarchy for the units of SBPV based on the following sequence: standard deviation (SD), coefficient of variation (CoV), root of successive variance (RSV), standardized residual (SR), variance of independent mean (VIM), and other units.

Quality assessment

All the included studies underwent further assessment using the Quality in Prognosis Studies (QUIPS) tools developed by Hayden et al. in 2013.[17] The rationale for employing QUIPS tools lies in their capacity to evaluate the methodological quality of prognostic studies independent of specific study designs. This characteristic renders them applicable to both observational studies and clinical trials. The QUIPS tools encompass six domains: study participation, study attrition, measurement of prognostic factors, measurement of outcomes, control of confounding variables, and appropriate statistical analysis and reporting.[17] Three independent investigators (P. B.T.S., A.D.L., and M.E.S.) executed the quality assessment process. Should any discrepancies arise during this evaluation phase, the investigators would collaboratively resolve them.

Outcome measure

The primary focus of this systematic review was to analyze the correlation between SBPV and all-cause mortality. Secondary objectives encompassed the association between BPV and (1) CV mortality, (2) major cardiovascular events (MACEs), (3) myocardial infarction (MI), and (4) stroke. All outcomes would be expressed using the sHR. Standard deviations of individual studies were utilized to pool different exposure data.

Statistical analysis

The hazard ratios collected in the extraction sheet would be rescaled to sHR for each unit of exposure.[16] The exposure was defined as the BPV value divided by the standard deviation. This approach made it feasible to calculate pooled risk estimates across different exposures, considering that various studies might report differing exposures.[16] Furthermore, this methodology allowed us to pool distinct units of BPV and present them in the forest plots, which analyzed the outcomes associated with each unit of BPV as well as their combinations. In instances where papers only provided subgroup hazard ratios, they would be aggregated to encompass a significantly higher number of participants.[18] Subsequently, the sHR was transformed into a standardized beta-coefficient[19], and its standard error was computed to facilitate the pooling of sHR.[20] Statistical analysis was conducted using Review Manager 5.4[21] and R Software ver. 4.2.2.

Results

Study selection process and quality assessment

From the previously mentioned database, a retrieval of 8736 records was conducted. Subsequent removal of 3220 duplicates ensued. Following the titles and abstracts screening, 101 articles with potential were chosen for review. After exploring citations, 18 additional studies were included for comprehensive full-text evaluation. Following this detailed examination, 43 studies met the predetermined inclusion criteria. The procedure for selecting studies for this review was meticulously elucidated in the PRISMA flow diagram, including explanations for study exclusions (Fig. 1).

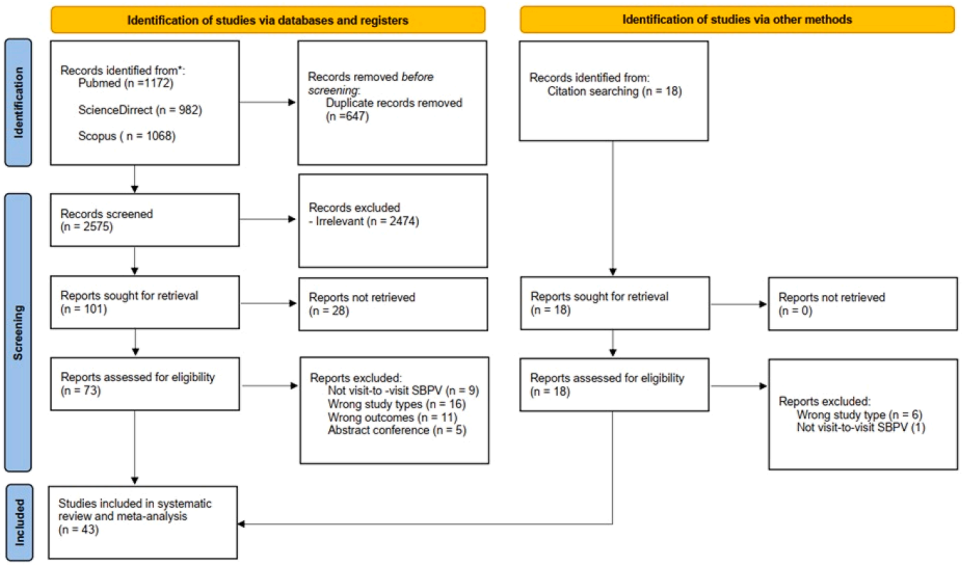

Fig. 1. PRISMA flow diagram of the study selection process.

Furthermore, we conducted a comprehensive quality assessment of the included studies using the QUIPS tool. Our study included a total of 43 individual studies, consisting of 23 observational studies and 21 clinical trials. In study participation domain, 12 studies were found to have a moderate risk of bias, while 31 studies demonstrated a low risk of bias. In terms of study attrition, 23 studies exhibited a low risk of bias, 19 displayed a moderate risk, and only one was assessed as having a high risk of bias. A total of 29 studies were rated as having a low risk of bias in the domain of measuring prognostic factors, while 14 were assessed as having a moderate risk. In the domain of outcome measurement, 31 studies were deemed to have a low risk of bias, while 9 were considered to have a moderate risk, and 3 were found to have a high risk of bias. For the study confounding domain, 33 studies demonstrated a low risk of bias, 9 were evaluated as having a moderate risk, and was identified as having a high risk of bias. Lastly, regarding the appropriate statistical analysis and reporting domain, 38 studies were rated as having a low risk of bias, while 5 studies were found to have a moderate risk. Further details on QUIPS quality assessment of those included studies are provided in Table S3.

Study characteristics

This review included a total of 43 studies,[9,10,28–37,11,38–47,12,48–57,22,58,59,23–27] comprising 9,944,254 patients, concerning SBPV and its association with our outcomes of interest (Table S4). The follow-up period varied from 1 year[11,44,60] to 9 years.[48,53] Most of the studies were from Asian countries (n = 14), followed by North American (n = 11), European (n = 6), and multicontinental countries (n = 6). SD, CoV, VIM, SR, ARV, MMD, CIM, rSSR, and VABS2 were the measures used to account for SBPV across our included studies, with SD being the predominant reported measure in 86.1 % (37/43) of studies. Further details are provided in Table S4.

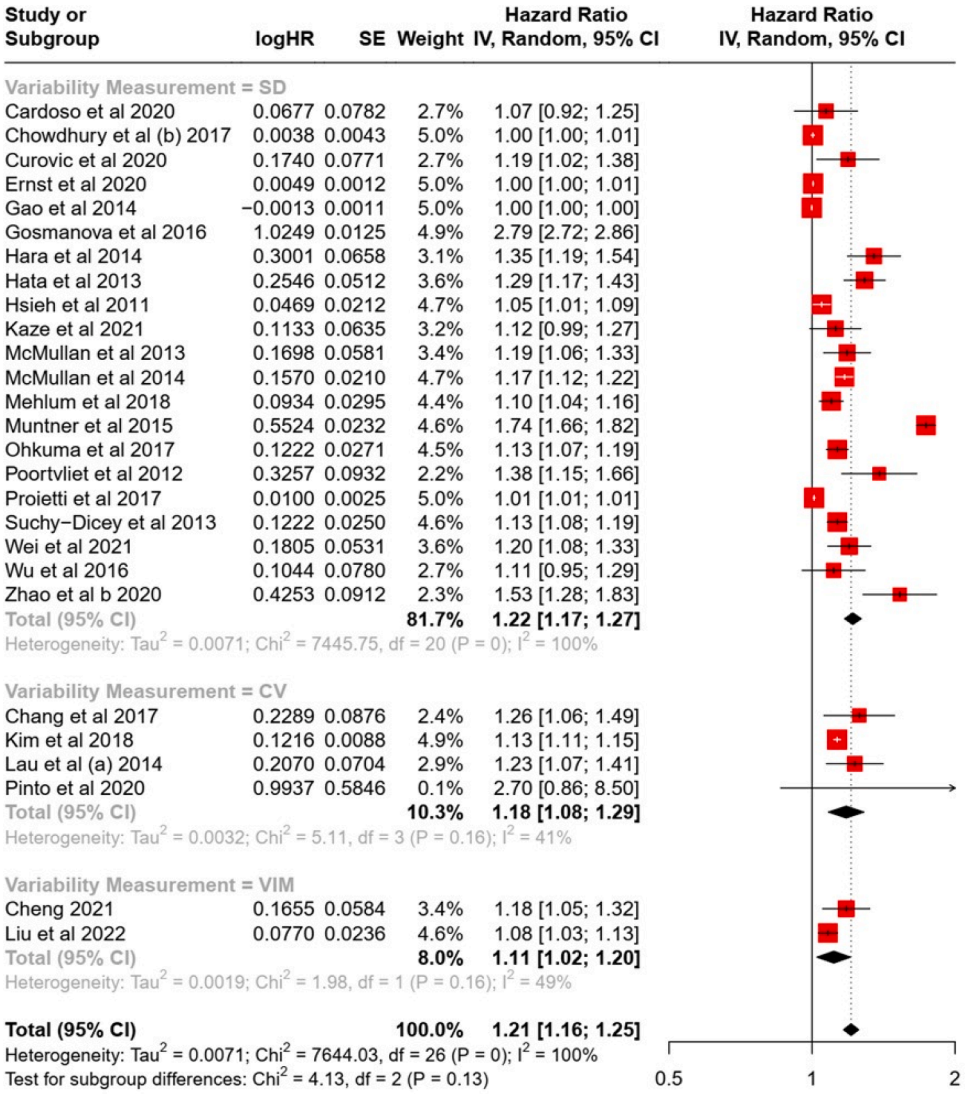

Fig. 2. Forest Plot of SBPV and sHR of All-cause Mortality.

Visit-to-visit systolic BP variability and primary outcomes

All-cause mortality

A total of 27 studies were noted concerning the association of visit-to-visit SBPV to the hazard of all-cause mortality, which was at least adjusted for mean BP. Our pooled analysis confirmed a significant association between this SBPV and all-cause mortality, with a pooled sHR of 1.21 (95 %CI 1.16 – 1.25, I^2=100 %). This significance was also supported by our subgroup analysis on the types of employed variability measurements. Simultaneously, this analysis explained the reduction in heterogeneity in studies utilizing the CV and VIM while revealing high heterogeneity in studies using SD as the measure of SBPV (Fig. 2). Furthermore, our subgroup analysis based on the continents of included studies observed that the pooled sHR from North American studies was higher than the overall pooled sHR (1.31 vs 1.21), which also left significant between-study heterogeneity in this group (Figure S1).

We conducted a leave-one-out sensitivity analysis, systematically excluding each included study one by one. However, this approach did not significantly reduce between-study heterogeneity, as demonstrated in Figure S2. Subsequently, an analysis to identify publication bias revealed a notable bias (observed funnel plot asymmetry and Egger's test p<0.05). In response, we performed a trim-and-fill analysis, resulting in an adjusted new estimate of sHR at 1.03 (95 %CI 0.99 - 1.07, I^2=100 %), as depicted in Figure S3.

Cardiovascular mortality

Out of 43 studies that were included in the analysis, 19 of them investigated CV mortality outcomes. Our observations indicated that the pooled sHR for CV mortality stood at 1.10 (95 %CI 1.07 – 11.4, I^2= 90 %). We identified that the source of between-study heterogeneity was likely derived from studies that employed SD as the measure of SBPV (I^2=91 %) (Fig. 3). Furthermore, upon conducting subgroup analysis based on the continents of origin of the studies, significant heterogeneities persisted within the Asian, North American, and multicontinental subgroups' pooled estimates (I^2<50%). Notably, Asian studies exhibited a higher pooled sHR compared to the general sHR (Figure S4).

Leave-one-out sensitivity analysis was conducted, and none of the omitted studies significantly reduced heterogeneity (Figure S5). A publication bias analysis was performed and found a significant influence of this bias (Egger's test p <0.05), which led to the conduction of trim-and-fill analysis (Figure S6), generating a new adjusted sHR of 1.02 (95 %CI 0.99 – 1.06, I^2 = 92 %).

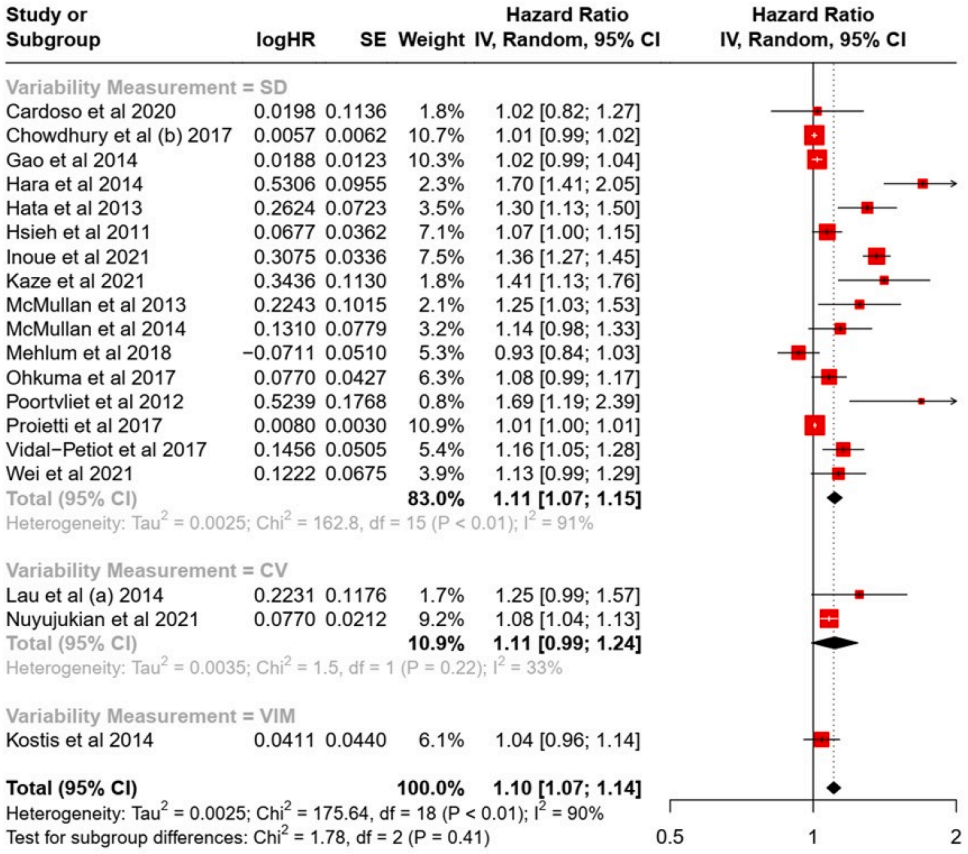

Fig. 3. Forest Plot of SBPV and sHR of Cardiovascular Mortality.

Major Adverse Cardiovascular Events (MACE)

A total of 23 studies that met the criteria for quantitative analysis of MACE outcomes were identified. Our pooled analysis revealed that SBPV increased the hazard of experiencing MACEs by 1.1 times compared to those without this risk factor (sHR 1.10 [1.07 – 1.13], $I^2 = 91$ %) (Fig. 4). Similar to previous analyses, studies using SD as the measure of variability remained the primary contributor to the overall between-study heterogeneity. In subgroup analyses based on continents, significant heterogeneity persisted. However, we observed that European studies' pooled sHR was higher than the general sHR (1.21 vs 1.1) (Figure S7).

Interestingly, the leave-one-out sensitivity analysis observed a marked reduction in overall heterogeneity after excluding Ernst et al. without compromising the overall pooled sHR, which was 1.11 (95%CI 1.08 – 1.12, I^2=75%) (Figure S8). Publication bias analysis, however, indicated the presence of its influence on the pooled estimate (Funnel plot asymmetry and Egger's test p<0.05). This led to the execution of a trim-and-fill analysis, resulting in a new adjusted estimate of 1.03 (95%CI 1.00 - 1.06, $I^2 = 91$%) (Figure S9).

Myocardial infarction

We noted that SBPV was associated with myocardial infarction, a finding supported by the pooled results of 12 studies. Patients with SBPV exhibited a heightened hazard, 1.13 times higher, for experiencing a myocardial infarction (sHR 1.13 [95 %CI (1.07 – 1.19)], I^2=91 %). Nearly all studies utilized SD as the measure of variability (Fig. 5). Subgroup analysis based on study continents indicated that studies where patients were sourced from multiple continents were likely the source of heterogeneity ($I^2 = 91$ %) (Figure S10).

Leave-one-out sensitivity analysis further found that a marked reduction of heterogeneity was observed by excluding the study by Vishram et al. (91 % vs 70 %) (Figure S11). Moreover, trim-and-fill methods were done as the funnel plot appeared asymmetric and the Egger's regression test p <0.05, resulting in a newly adjusted sHR of 1.02 (0.97 – 1.07, $I^2 = 91$ %) (Figure S12).

Stroke

Of the 43 studies, 24 were eligible for the meta-analysis of stroke outcomes. We observed an increased hazard of experiencing a

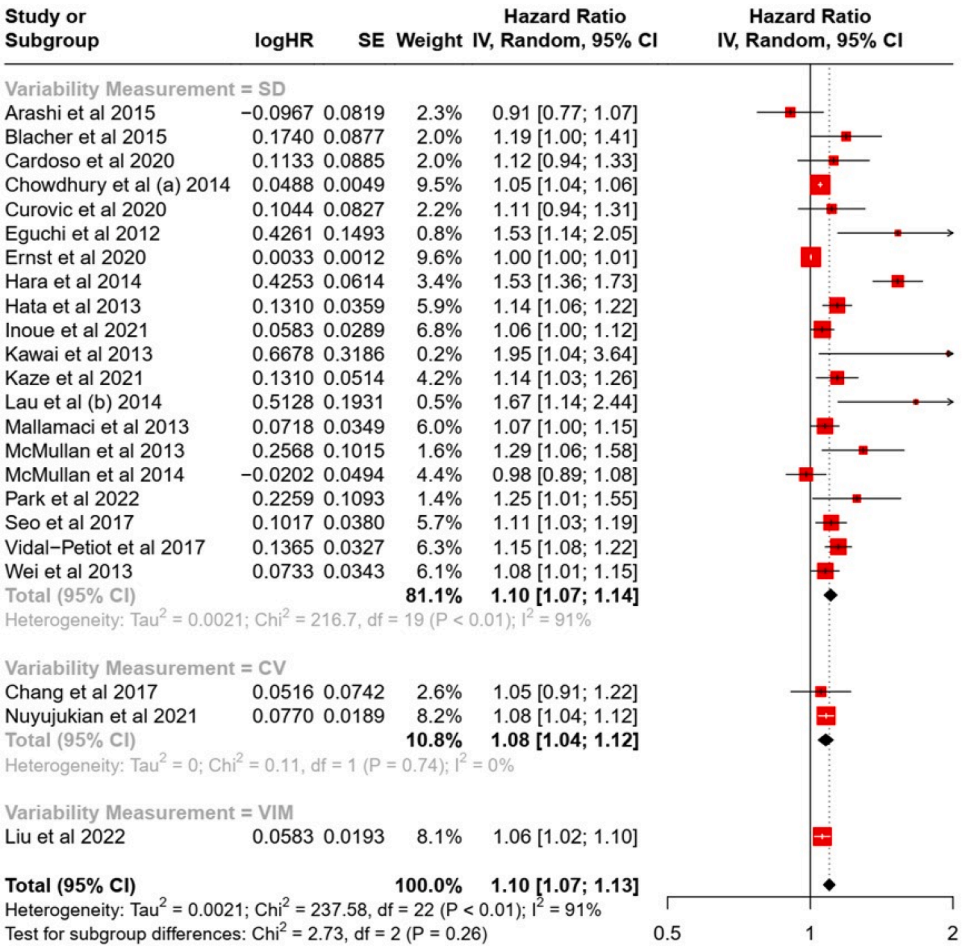

Fig. 4. Forest Plot of SBPV and sHR of MACEs.

stroke in patients with the SBPV risk factor compared to those without (sHR 1.22 [1.16 – 1.29], I^2=100 %). Significant overall heterogeneity was noted, potentially stemming from the higher heterogeneity observed in studies that employed SD as the variability measure (Fig. 6). Subgroup analysis based on continents also failed to fully elucidate the overall heterogeneity, even though the pooled sHR in the studies from Europe and North America was higher than the overall pooled sHR (Figure S13).

Leave-one-out sensitivity analysis did not reveal a significant reduction in heterogeneity after iteratively excluding individual studies (Figure S14). Additionally, the publication bias analysis revealed an insignificant influence of this bias, as the Egger's regression test failed to yield a significant result (Figure S15).

Discussion

This meta-analysis included 9,944,254 participants from 43 studies to evaluate the association between long-term SBPV and individual outcomes. Our finding showed that long-term SBPV is significantly associated with a higher risk of all-cause mortality (Fig. 2). In addition, long-term SBPV is also associated with CV outcomes (Fig. 3). Controlling the BP has been one of the primary targets to reduce morbidity and mortality among the population.[3,61] However, the mortality and CV events remain substantially high even after the BP is under control according to the current guidelines target,[3,61,62] suggesting the other factors' contribution to patient outcomes.

Our meta-analysis revealed that SBPV contributes to higher mortality and CV outcomes even after adjusted for mean BP and comorbidities (Fig. 3). An increase in mean BP is correlated with an increase in BPV value[63], which became one of the main factors contributing to higher morbidity and mortality in patients with more elevated BP. While it is known that high BP induces endothelial dysfunction due to increased wall stress levels,[64,65] the oscillation (variation) of shear stress could also modify endothelial biology and lead to endothelial dysfunction.[66–68] That may explain why high long-term SBPV is significantly associated with poorer CV outcomes independent of mean BP.

Previous studies showed that high SBPV is associated with coronary plaque progression[69] and an increase in white matter lesions in patients with intracerebral atherosclerosis.[70] This meta-analysis showed that SBPV is associated with a higher risk of MI and stroke after being adjusted with mean BP and comorbidities (Figs. 5 and 6). Interestingly, we found that the risk of stroke is higher than MI (22% vs 13%). This suggests higher mortality and CV events due to high SBPV are driven by cerebrovascular than coronary events. The previous meta-analysis showed that BP variability is significantly associated with dementia and cognitive dysfunction.[71] In patients with ischemic stroke, high SBPV increases the risk of recurrent stroke.[72] However, this meta-analysis could not specifically compare the incidence between first and recurrent strokes.

Subgroup analysis revealed that the European population generally had higher hazards for all outcomes compared to other population sources (Table S4). While SPBV in the Australian population was generally not significantly associated with all outcomes except MI (Table S4). This may indicate the differences in ethnic response or sensitivity to SBPV. It is supported by reports from previous studies that showed no significant differences in SBPV among ethnicities.[36,73–75] As a comparison, some ethnicities/races have higher morbidity and mortality among hypertensive patients.

SBPV correlates with arterial stiffness.[76] Some conditions associated with arterial stiffness, such as aging and chronic kidney disease, also increase SBPV but not DBPV.[76,77] The long-term SBPV is influenced by behavioral and environmental factors that probably affect the neural-hormonal system that regulates the CV system.[77] Long-term SBPV is also affected by hypertension

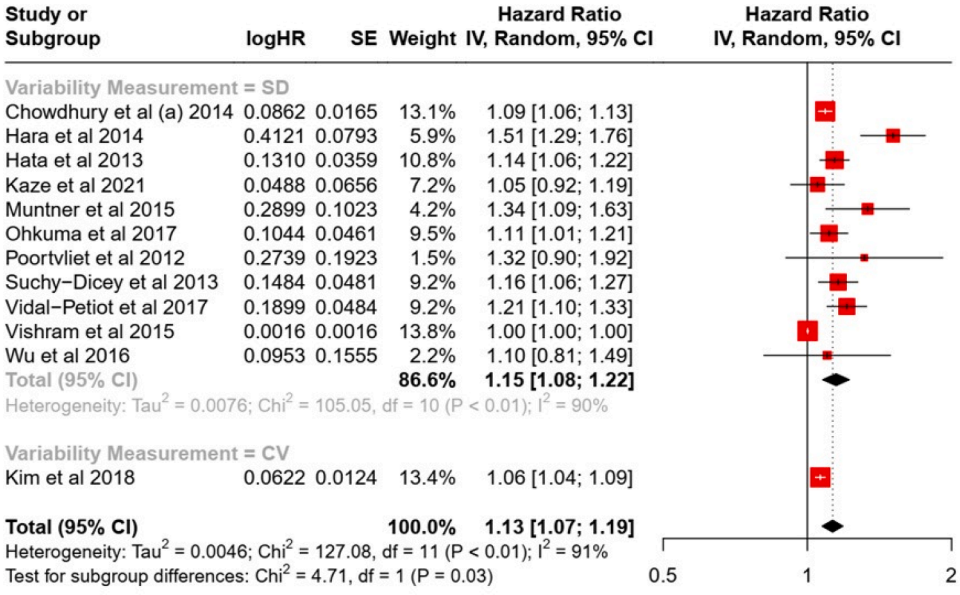

Fig. 5. Forest Plot of SBPV and sHR of Myocardial Infarction.

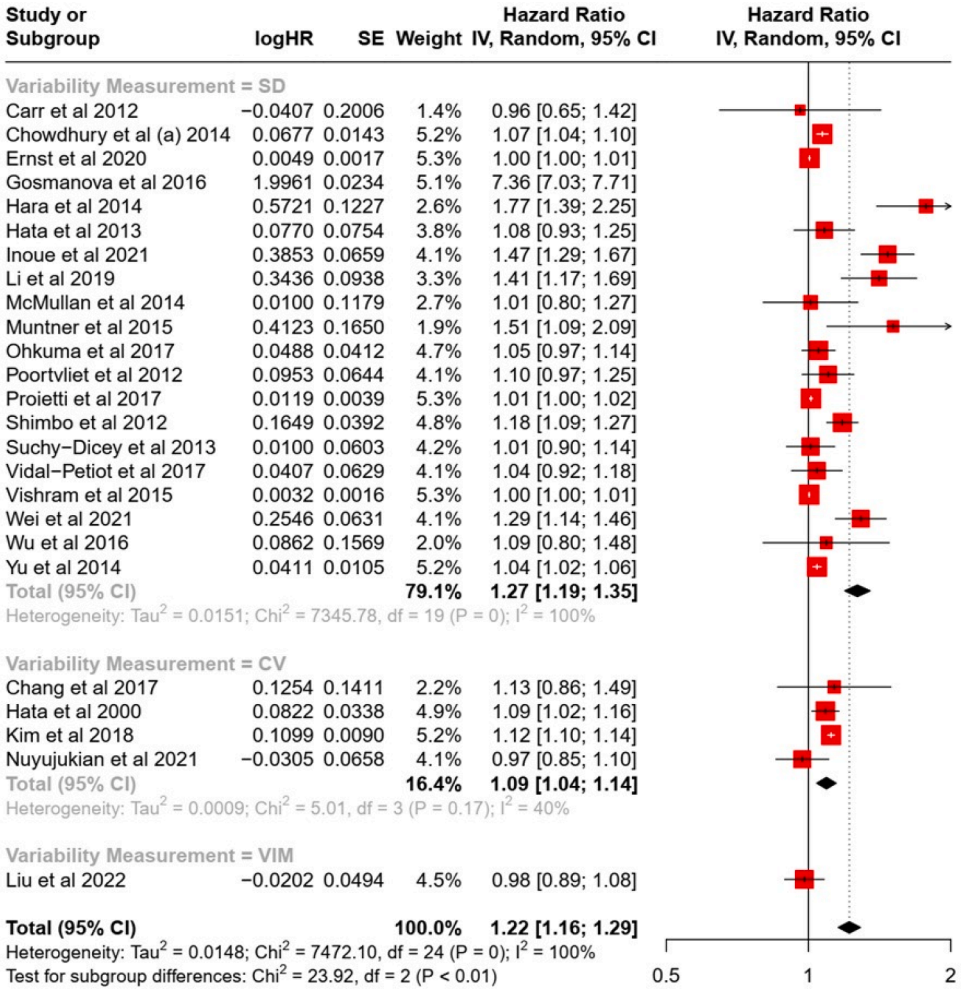

Fig. 6. Forest Plot of SBPV and sHR of Stroke.

medication, such as adherence to treatment, dose/titration, and mechanism of antihypertensive drugs. Antihypertensive drug with a high smoothness index, the homogeneity index of antihypertensive drug effects over 24 hours, reduces short-term BPV and organ regression in hypertension patients.[77,78] Some long-acting dihydropyridine calcium channel blockers like long-acting amlodipine or a combination of long-acting amlodipine-telmisartan are known to have a high smooth index.[77,78] In comparison, short-acting antihypertensive medication is correlated with higher BPV.[77] Although reduction of BPV value is proportionally correlated with reduction of mean BP,[79] the use of high smooth index antihypertensive drugs may further decrease the risk of morbidity and mortality as SBPV is a poor prognostic factor independent of mean BPV. However, there is no specific recommendation from the currently available guidelines regarding this issue.[80,3,61,81]

We acknowledge that this systematic review has some limitations. There was substantial heterogeneity between studies. This may be due to different subjects included in this study, such as the general population,[41] hypertensive patients[27,56], chronic kidney disease[40,49,82], cerebrovascular disease,[9,57,83] coronary artery disease,[83] and vascular disease.[11] However, leaving-one-out sensitivity analysis did not significantly change the result. This also suggests that long-term SBPV is a poor prognostic factor in healthy populations as well as patients with a history of CV disease. In addition, the source population of the included studies is elderly (mean age >50 years old in all studies). Therefore, the generalizability of this meta-analysis to the healthy and young population is questionable. Finally, this is one of the most extensive meta-analyses to evaluate the association between long-term SBPV and various CV outcomes by combining different parameters of SBPV using standardized hazard ratios.[19,20]

Conclusion

After being adjusted with mean BP and comorbidities, long-term SBPV is still associated with all-cause mortality, CV mortality, MACE, stroke, and MI. Concerning visit-to-visit SBPV as prognostic factors, cerebrovascular events may play a more significant role than coronary events. Some ethnicities/races seem to have higher CV and mortality risks due to long-term SBPV. A large, prospective,

well-designed study is needed to confirm the findings of this study.

CRediT authorship contribution statement

Pandit Bagus Tri Saputra: Conceptualization, Methodology, Formal analysis, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration. **Ariikah Dyah Lamara:** Validation, Resources, Data curation, Writing – original draft, Writing – review & editing. **Mahendra Eko Saputra:** Validation, Resources, Data curation, Writing – original draft, Writing – review & editing. **Diar Pasahari:** Validation, Resources, Data curation, Writing – original draft, Writing – review & editing. **Roy Bagus Kurniawan:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Makhyan J. Al Farabi:** Methodology, Resources, Writing – original draft, Writing – review & editing. **Chaq El Chaq Zamzam Multazam:** Formal analysis, Resources, Writing – original draft, Writing – review & editing. **Yudi Her Oktaviono:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision. **Firas F. Alkaff:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cpcardiol.2023.102343.

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