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Title: Association between different methods of assessing blood pressure variability and incident cardiovascular disease, cardiovascular mortality and all-cause mortality: a systematic review

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ABSTRACT

BACKGROUND: Blood pressure variability (BPV) is a possible risk factor for adverse cardiovascular outcomes and mortality. There is uncertainty as to whether BPV is related to differences in populations studied, measurement methods or both. We systematically reviewed the evidence for different methods to assess blood pressure variability (BPV) and their association with future cardiovascular events, cardiovascular mortality and all-cause mortality.

METHODS: Literature databases were searched to June 2019. Observational studies were eligible if they measured short-term BPV, defined as variability in blood pressure measurements acquired either over a 24-hour period or several days. Data were extracted on method of BPV and reported association (or not) on future cardiovascular events, cardiovascular mortality and all-cause mortality. Methodological quality was assessed using the CASP observational study tool and data narratively synthesised.

RESULTS: 61 studies including 3,333,801 individuals were eligible. BPV has been assessed by various methods including ambulatory and home-based BP monitors assessing 24-hour, 'day-by-day' and 'week-to-week' variability. There was moderate quality evidence of an association between BPV and cardiovascular events (43 studies analysed) or all-cause mortality (26 studies analysed) irrespective of the measurement method in the short- to longer-term. There was moderate quality evidence reporting inconsistent findings on the potential association between cardiovascular mortality, irrespective of methods of BPV assessment (17 studies analysed).

CONCLUSIONS: An association between BPV, cardiovascular mortality and cardiovascular events and/or all-cause mortality were reported by the majority of studies irrespective of method of measurement. Direct comparisons between studies and reporting of pooled effect sizes was not possible.

Keywords: Blood pressure; Hypertension; Hypotension; Measurement; Variability: Review

Key Points

Blood pressure variability (BPV) has been assessed through various methods across a variety of populations and setting.

BPV is associated with cardiovascular events, cardiovascular mortality and all-cause mortality.

Standardisation in methods of assessment is required to determine a universally agreed measure of BPV.

INTRODUCTION

Blood pressure varies physiologically in response to changes in demand that accompany normal activities and in predictable trends driven by the circadian rhythm.[1] Fluctuations in blood pressure increase with age even in normotensive individuals.[2] This variation in blood pressure is known as blood pressure variability (BPV). There is growing interest in BPV as a risk factor for adverse cardiovascular outcomes and mortality.[1,2] However, studies to date have shown conflicting results, which are potentially related to differences in populations studied and measurement methods.[1-6]

There remains uncertainty on the choice of an optimal method to measure BPV. Blood pressure variability can be analysed using either time domain or frequency domain analysis. Frequency domain analysis requires signal processing skills with which to transform blood pressure signals into different frequency components and to quantify the variance or "power" at each specific frequency. Time domain analysis, which is widely used, evaluates the variability of blood pressure measurements over any specified time period. Various measurement methods have been employed to determine BPV using time domain analysis. The most commonly applied BPV measurement methods include standard deviation (SD), coefficient of variation (CoV) and average real variability (ARV). Newer methods include individual residual variation (IRV), variation independent of the mean (VIM), maximum-minimum difference (MMD), and BPV ratio. While some studies used only one method,[3,4,7-15] many used more than one method.[16-22]

Despite increasing evidence linking increased BPV with poorer outcomes, the pathophysiological process underlying BPV and its relevance in clinical practice remain unclear. Changes in BP between measurements either within the day, day to day or visit to visit may occur from physiological insults from illness or medications, or impaired haemodynamic regulatory systems which is in turn a reflection of overall health status [23] Determination of BPV may therefore be a useful biomarker or prognostication in clinical practice [17,18] Furthermore, the presence of large variations in BPV is likely to influence blood pressure treatment targets and well as clinical decisions on frequency of BP monitoring, which should be individualized in older adults.[24] Therefore a better understanding of the relationship between BPV and cardiovascular and mortality outcomes as well as the available methods of measurements of BPV and their individual relevance in practice may potentially assist in clinical decision making with respect to intensity of treatment.

Few previous systematic reviews have been published investigating the impact of BPV on cardiovascular outcomes.[22,23,25] There has been limited assessment of the differences in cardiovascular outcomes distinguishing the method of BPV measurement. The potential association between different measures of BPV has been previously highlighted.[23] However several new studies have been published which may change the interpretation of these previous studies. The aim of this systematic review was therefore to investigate the association of BPV, stratified by various methods of BPV measurement, with cardiovascular events, cardiovascular mortality and all-cause mortality.

MATERIALS AND METHODS

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines.[26] The PRISMA checklist is **Supplementary File 1**. The review protocol is **Supplementary File 2**.

Search Strategy

A systematic literature search of MEDLINE, EMBASE, OpenGrey and the ClinicalTrials.gov databases was conducted. The search was limited to human studies published in English between 2004 and the search date (3rd June 2019). A 2004 search strategy start date was selected to provide a contemporary analysis of participants managed with current therapies and health services.[23] The search strategy is presented in **Supplementary Table 1** and tailored for each of the search databases. To augment the principal search strategy, a forward citation search was performed for all included studies using the Scopus database. Secondly, a backwards citation search was also conducted through a review of all included study reference lists. Finally, corresponding authors of all potentially eligible studies were contacted and asked to identify any previously omitted studies. No additional citations were identified through these approach.

Identification of Studies

Two investigators (AA-F/TS) screened papers identified from the search for inclusion, firstly by title and abstract, and then full-text screening of shortlisted papers.

Eligibility Criteria

Studies were included if they were:

Population: people who were community-dwelling, hospital or institutional-living. No age restriction was made.

Intervention: measurement of BPV over 24-hours or longer and followed-up adult subjects for more than a year for cardiovascular events, cardiovascular mortality or all-cause mortality. Accordingly, studies which assessed *only* visit-to-visit BPV or beat-to-beat BPV were excluded. Studies assessing 'nocturnal dip' and 'morning surge' variables were excluded as physiologically discrete from random BPV. We did not control by methods of BPV as we wished to assess the impact of methods of assessment on BPV.

Outcome: Cardiovascular events were grouped as composite outcomes including myocardial infarction (MI), stroke, first hospitalisation or diagnosis of heart failure, coronary revascularisation, coronary artery bypass graft, peripheral vascular disease, renal failure with dialysis, transient ischemic attack, acute aortic aneurysm dissection or grafting and angina. As recommended by Mena et al,[16] coronary artery disease was defined by any of the following: MI diagnosed on the basis of at least two of three standard criteria (typical chest pain, electrocardiographic QRS changes, and positive ischemia serum markers) or angina pectoris defined by chest pain, coronary angiography showing hemodynamic significant obstructions or revascularisation procedures. Stroke was diagnosed on the basis of rapid onset of localising neurological deficit lasting 24 hours in the absence of any other disease (or lasting less than 24 hours for transient ischemic attack). Congestive heart failure was diagnosed using McKee criteria.[27]

Design: Review articles, poster abstracts, or otherwise non-observational studies were excluded, as were specific cohorts such as those comprised of patients on dialysis or with previous stroke. Studies which investigated the same databases or geographical area were all included in the review.

Where papers reported the same study or data from the same cohort two or more times, these were grouped and analysed by study to avoid participant double counting.

Data Extraction

Two pairs of two reviewers (AA-F/TS and JS/AE) independently extracted data into a pre-specified data extraction table. Data extracted included: study date and location; cohort size, co-morbidities, age, gender; method of assessing blood pressure; method of assessing outcomes of interest. Data were collected on the association between BPV (24-hours, day-time, night-time) and cardiovascular outcomes. Methods of calculating BPV that were deemed eligible included categorical assessment (high versus low variability) as there are currently no 'gold standards' for defining or measuring BPV, and therefore thresholds are arbitrary at present,[28] SD of blood pressure, and CoV (SD/mean), in addition to the ARV. The ARV was defined as the absolute difference of consecutive blood pressure readings, thereby accounting for the order in-which measurements were obtained.[6] Cardiovascular outcomes included cardiovascular events (including MI), cardiovascular mortality and all-cause mortality.

Quality Assessment

The quality of the studies was assessed using a modified version of the Critical Appraisal Skills Programme (CASP) checklist for cohort studies.[29] For each question, a score of one denoted good performance in that area and zero denoted an unclear method or failure to meet the criterion, resulting in a total score for each paper. Each study was reviewed by two reviewers independently (AA-F/TS and JS/AE).

Disagreements in respect to study eligibility and inclusion, data extraction and quality assessment were resolved through discussion until consensus was reached. Any further disagreements were resolved by the arbitration of a third reviewer (PKM).

A judgement on the quality of the evidence was made specifically by assessing the CASP items and specifically Items 5, 6 (confounding) and 7, 8 (follow-up completion and duration) which were deemed the most important items for this study design by the research team. Quality of evidence was termed through this approach as: 'low', 'moderate' or 'high' quality evidence.

Data Synthesis

The between-study heterogeneity was assessed though analysis of the data extraction tables. This identified substantial variability in the approach to assessing blood pressure and the populations

under-investigation. As a result, it was deemed inappropriate to undertake a meta-analysis of the data.

A narrative analysis reporting hazard ratios was therefore adopted to answer the research questions on different methods of assessing BPV and adverse cardiovascular outcomes. Blood pressure measurements for BPV estimation were obtained through both ambulatory blood pressure monitoring (ABPM) over 24-26 hours as well as home blood pressure monitoring (HBPM) using automated devices over 7-28 days. In BPV obtained from ABPM for instance, blood pressure measurements are usually obtained every 15 minutes during the daily time (16 hours) and 30-minutes at night-time (eight hours). Thus, within 24 hours, there should be around 80 blood pressure measurements for each subject. Multiple formulae are then used to calculate variability. The simplest formula is SD. We presented three methods of estimation of BPV was presented: SD, CoV and ARV. The association between these different assessment methods and the end-points (cardiovascular events/cardiovascular mortality/all-cause mortality) was investigated. This was reported by one of three timepoints i.e. short- (up to 24 hours), medium (24 hours to one-week) and long-term (greater than one-week). Through this, short-term referred to beat-to-beat and within and between hour measurements, medium-term as between day/night or between days (as obtained from HBPM) and long-term as variation over weeks (by clinic, HBPM measurements).

RESULTS

The search strategy identified 4259 unique citations. After title and abstract screening, 362 full-texts were retrieved, resulting in 61 papers which were eligible for inclusion (**Supplementary Figure 1**).

Study Characteristics

A summary of the included study characteristics is presented in **Supplementary Table 2**. Included studies were predominantly cohort studies, performed either prospectively or retrospectively. This included data from 3,333,801 individuals. Mean ages of participants ranged from 47.1 years [30] to 85 years.[31] Mean percentage of females in study cohorts was 45.0% (SD: 19.2) with four studies excluding females [2,6,32,33] and one study excluding males.[34] Follow-up interval ranged from 12 months [9,35,36] to 20 years.[37] Thirty-nine studies were conducted in a hospital setting, [4,8,10,11,14,15,19,25,31,33-36,38-50,52-61,64,69,71] whilst 21 studies were conducted in the

community.[1-3,,5,6,9,12,13,16,20,21,30,37,51,62,63,65-68,70] - This was not documented in one paper.[17]

Forty-two studies specified a specific comorbidity(ies) which were used as eligibility criteria. When used, this was hypertension in 24 studies, [10-12,14-16,19,33,35,38,4-42,45,46,51,54,56,59,60,65,66,69,70] type 2 diabetes in five studies,[4,44,58,62,64] history of or risk factors for cardiovascular disease in five studies,[39,48,49,-50,68] hypertension with coronary artery diseases in one study,[38] five studies recruited participants who had had an ischaemic stroke,[25,36,47,57,61] whilst two studies recruited people with previous transient ischaemic attacks (TIA) or non-disabling stroke.[21,57] One study only excluded participants with a previous stroke.[13] Hsu [37] only recruited normotensive participants. The presence of previous and current medical conditions was not specified in 19 studies.[1,2,3,5,6,8,9,13,17, 21,30,31,34,43, 52,53,55,63,71]

Seventeen (28%) studies separately examined cardiovascular mortality as an endpoint.[2,6,13,16,19,21,25,46-49,53,62,65-67,69] Twenty-six (43%) studies investigated all-cause mortality either as a primary or secondary outcome. [2,5,6,9,13,15,16,19-21,25,42,43,47-49,50,52,53,59,62,64-67,69] Forty-four studies (72%) had a composite 'cardiovascular events' endpoint which included fatal and non-fatal events.[1,3,4,6,8-12,14,17,19,20,25,30-41,43-45,48,50,51,53-55,57,58,60,61,63,64,67,69-71] Twenty-two studies (37%) had a separate outcome for incident stroke.[6,7,15,25,34,36,38-41,44,45,47,48,50,51,53,54,59,63,68,70]

One study assessed for the occurrence of left ventricular abnormalities.[60] One study assessed specifically for chronic heart failure[66] and one assessed chronic heart disease.[53] One study assessed cardiovascular risk.[7] One study post-stroke functional outcome.[61] Asayama et al [19] assessed lacunar infarct as their outcome, detected by computed tomography or magnetic resonance imaging.

Thirty studies (49%) measured blood pressure over 24 to 26 hours (short-term) using ambulatory BP monitors, [1-6,8-12,14-17,33,35-37,40,42,52,54,57,60,61,63,65,67,69]; in 34 studies (56%), 'day-by-day' variability was determined in participants who self-measured blood pressure for 7-28 days with home blood pressure monitors (HBPM) (long-term).[8,13,19-21,25,30,31,34-36,38,39,41,43-51,53,55,58,59,61,62,64,66,68,70,71]

Critical Appraisal

The results of the critical appraisal are presented in **Supplementary Table 3**. The evidence was judged to be of moderate quality overall. Whilst included studies recurrently presented strengths including clearly posing a defined research question (100%), recruiting their cohorts in an acceptable and defined approach (93%), measuring BPV accurately (85%) and then accurately assessing cardiovascular outcomes (74%), the studies less consistently identified important confounding factors (46%), nor accounted for these sufficiently in their adjusted analyses (51%). Subject follow-up was determined as sufficient in 44 studies (72%) and by duration in 44 studies (72%). The results were clearly presented in 44 studies (72%),suitable to implement to general population in 27 studies (44%) and were interpreted with appropriate clinical implications in 43 studies (70%).

Outcomes

Due to the large degree of heterogeneity in methods of BPV measurements as well as the variations of types of BPV measured in both ambulatory, home and office blood pressure measurements, it was not possible to determine individual effect sizes or to report pooled effect sizes. Therefore, the number of studies employing each method as well as the numbers with positive or negative findings were tabulated in detail to provide a source of reference for future researchers **Supplementary Table 4**. A summary of the number of studies reporting each outcome associated with BPV and the number of participants included in these studies are summarised in **Table 1,** with fuller presentation in **Supplementary Table 4.**

Ambulatory Blood Pressure Measurements

Cardiovascular Events

Cardiovascular events were reported in 22 studies, 17 of which reported the presence of associations with at least one systolic BPV (SBPV) variable, while five studies did not record any associations in any SBPV. Six studies reported the presence of associations with diastolic BPV (DBPV) and cardiovascular events, while four studies reported no association. SD was employed by 22 studies to estimate SBPV of which 17 demonstrated positive results, [1,3,4,6,8,9,11,12,14,17,33,35,37,40,57,60,69] while five were negative.[10,36,54,61,63,] Ten studies also evaluated SD-DBPV of which six [6,8,11,17,37,69] were positive and four were negative.[3,11,61] The evidence was graded moderate in quality.

Cardiovascular Mortality

Cardiovascular mortality was reported for medium-term BPV estimations using ABPM for six moderate-quality studies. Three found associations with SBPV and three did not find any associations. Five studies which investigated DBPV showed significant associations and only one showed the absence of association. All five studies used SD, one used CoV and two used ARV. Of the five studies which reported SD-SBPV for ABPM, two were positive [67,69] and four negative.[2,6,16,65] Five studies which reported SD-DBPV were positive [6,16,65,67,69] while one was negative.[2] One for CoV-DBPV [69] was negative, and the ARV studies reported both SBPV and DBPV of which both were positive.[6,67]

Five studies evaluated short-term 24-hour BPV, all used SD-SBPV, from which one was positive [69] and four negative [2,6,16,65]. Of the studies which used SD-DBPV, three were positive [6,65,69] and two negative [2,16]. CoV was used for 24-hour BPV by one negative study for DBPV [69]. Two studies used ARV for 24-hour SBPV and DBPV with positive associations for both.[6,67] Four studies investigated the above for cardiovascular mortality using ABPM. Day-time SBPV was positive for one study [67] and were negative for the rest three studies,[2,16,69] and DBPV positive for three studies [16,67,69] and negative for one.[2] One study was positive for both SBPV and DBPV at night[69] and two negative for both at night.[2,16] Both studies used SD. The evidence was graded moderate in quality.

All-Cause Mortality

Eleven studies evaluated all-cause mortality for medium-term ABPM derived BPV. All studies reported SBPV and nine reported DBPV. Significant associations were reported by six for SBPV and seven for DBPV. Nine used SD, four were positive for SBPV and six for DBPV. Of the 11 studies, six evaluated 24-hour SBPV, one was positive [69] and five negative,[2,16,42, 52,65] while seven evaluation 24-hour DBPV, with three positive [6,65,69] and four negative [2,16,42,52] results. Six studies evaluated either medium-term day-time or night-time BPV, two studies were positive for day-time SBPV [42,67] and three for day-time DBPV [16,42,67], three studies were negative for SBPV for both day and night-time [2,69] but positive for both day and night-time DBPV.[16] One study was positive for day-time SBPV and DBPV and negative for night-time SBPV and DBPV.[42] One study was negative for day-time SBPV and DBPV and positive for night-time SBPV and DBPV.[69] One study which only used night-time SBPV was positive.[15] Only one short-term study used CoV, of which one was negative for SBPV over 24-hours.[15] Three moderate-quality studies used ARV measured over short-term, two were positive for both 24-hour SBPV and DBPV [6,9] and one which only evaluated 24-hour SBPV was negative. The evidence was graded moderate in quality.

Day-to-day or Visit-to-visit Measurements

Cardiovascular Events

Twenty-seven studies evaluated SBPV in day-to-day or visit-visit measurements for cardiovascular events. Both SD and ARV were utilized by one study which evaluated morning, evening, daily and morning to evening variations.[20] This reported significant associations in SBPV and SBPV using both SD and ARV for morning measurements, SD-DBPV, ARV-SBPV and ARV-DBPV more morning measurements and ARV-DBPV for morning to evening measurements.[20]

Twenty-three studies used SD to determine day to day or visit to visit BPV. Twenty studies reported significant associations in SD-SBPV alone,[8,20,30,31,34,36,39,41,43-45,,48,50,51,53,55,61,64,70,71] while four found significant associations in SD-DBPV alone,[20,45,61,70] two found significant associations with both SBPV and DBPV.[61,70] Nine studies employed CoV to evaluate day to day or visit to visit CoV-SBPV or CoV-DBPV. All three studies which evaluated both CoV-SBPV and CoV-DBPV found significant associations with cardiovascular events [58,61,70]. Four studies evaluated only CoV-SBPV, three of which found positive associations [36,39,44] while one did not find any significant association.[38] One studies evaluated day to day or visit to visit CoV-DBPV alone and found no significant association.[20] Overall, the evidence was graded moderate in quality.

Cardiovascular Mortality

Ten of the eleven studies which evaluated day to day or visit to visit BPV reported a significant association cardiovascular mortality and at least one BPV parameter. Eight studies used SD estimations. Two of the eight studies which estimated morning SD-SBPV had positive results [13,21]. Six of the eight studies evaluated day to day or visit to visit SD-SBPV, five of which reported positive results [46,48,49,53,66]. Three of the eight studies evaluated day to day or visit to visit SD-DBPV, with one reporting a positive association [49] and two found no associations [48,62]. One study used CoV for morning SBPV and reported a significant association.[25] Two studies used CoV to estimate day to day or visit to visit SBPV and DBPV one [62] reported negative results for both CoV-SBPV and Co-VDBPV and one [47] a positive association in SBPV but not in DBPV. One study used ARV to estimate morning and evening SBPV with positive results.[19] The evidence was graded moderate to high-quality.

All-Cause Mortality

All-cause mortality was reported in 16 studies, with positive associations in 12 for day to day or visit to visit measurements. One study assessed both SD and ARV for morning, evening, daily and morning-to-evening SBPV and DBPV, with positive associations in all parameters except evening SD-SBPV.[20] Three studies used SD alone for morning SBPV, two were positive [13,21] and one was negative.[25] Five studies evaluated both SD-SBPV and SD-DBPV for day to day or visit to visit measurements, three of which were positive for both [20,49,62] and one for DBPV only [43]. Another four studies evaluated only SD-SBPV for day to day or visit to visit measurements, and all four showed positive associations with all-cause mortality [50,53,64,66]. Two studies evaluated day to day or visit to visit CoV-SBPV and CoV-DBPV, of which one was positive for both CoV-SBPV and Co-V DBPV [62] and one was only positive for CoV-SBPV.[47] One study [59] used only ARV to determine day to day or visit to visit DBPV, which was only positive among individuals with systolic blood pressure ≥140mmHg. Overall, the evidence was graded moderate in quality.

DISCUSSION

There are numerous methods of assessing BPV. Irrespective of method, many more studies have reported an association between BPV and cardiovascular events, cardiovascular mortality and all-cause mortality. It is currently unclear what is the best method to measure BPV.

Our systematic review revealed the presence of considerable diversity in the methods used and inconsistencies in the findings of studies that have assessed the relationship between BPV, adverse cardiovascular and mortality outcomes. Some methods of measurement appear to be more effective in predicting cardiovascular events. For example, in some studies, measuring the SD of night-time diastolic blood pressure tended to out-perform other measures like the SD of day-time 24-hour SD blood pressures in predicting cardiovascular events in the given population. However, it was difficult to find a sufficient volume of evidence with which to establish these trends with the differences in cut-off points or thresholds used, and the multiple subgroups analyses employed by included studies. Given these reasons, it remains unclear what the 'best method' for assessing BPV is.

High or low BPV may represent an irreversible condition where the blood pressure regulatory system is irreparably damaged. This may produce a U- or J-shaped relationship between BPV and cardiovascular outcomes. There has been increasing use of ABPM and HBPM in clinical studies.[72]

These may provide more robust estimates of BPV, as individual clinic blood pressure measurements are merely a snapshot. There are, however, limited advances beyond ABPM and HBPM to date. New technology for continuous measurements is invasive, e.g. requiring arterial line, or not yet fully portable and user-friendly.

The mechanisms underlying the relationship between increased blood pressure variability using both ambulatory measurements, daily home measurements or office visit measurements with cardiovascular endpoints and mortality are unclear. It has been postulated that blood pressure variability may be related to arterial stiffness which increases with age and is exacerbated by the presence of comorbid hypertension and diabetes.[67] However, this may not necessary account for the differences in measurement according to time of day, which may also be driven by hormonal factors. Furthermore, the use of medications with shorter half-lives may also account for variations within the day, while the introduction or withdrawal of medications may account for differences between visits. Nevertheless, increased arterial stiffness, presence of comorbidities, variations in hormonal release and use of medications are all related to poorer clinical outcomes, which may confound this relationship. Fluctuations in blood pressure may results in poorer outcomes in terms of potential increased risk of falls and cognitive deficits with increased exposure to hypotensive episodes as well as potential increased risk of haemorrhagic strokes with surges in blood pressure.[72] The above proposed mechanisms have not been evaluated in available studies, with further research now urgently required. Available evidence does, however, related BPV with target end-organ damage.[71]

This study has some limitations. Firstly, due to the methods adopted in the original studies, it was not possible to collect similar data from a sufficient number of studies to meaningfully pool in a meta-analysis. Therefore, only the number of positive and negative studies were reported rather than pooled effect sizes. Similarly, it was not possible to provide a single or range of effect size or summary statistics, meaning the approach of presenting positive or negative associations was most appropriate. As a novel risk factor, new data collection and analysis methods for BPV continually appear in the literature. Incomplete reporting of results and variations in study format also prevented the pooling of studies in this review. These difficulties have highlighted the potential for the presence of selective reporting in this body of literature, particularly in instances where only significant findings have been reported. Similarly, there is a very high risk of selective analysis or outcome reporting in the manipulation of data grouping or analysis, for example in the creation of categorical groups of variability and whether hazard ratios are calculated per mmHg change or per standard deviation increment. Future studies should therefore be conducted on harmonising the field thereby reducing

heterogeneity to facilitate recommendations based on meta-analyses. Finally, this systematic review only investigated cardiovascular mortality and morbidity outcomes and not outcomes such as syncope, falls or care home admission. These are all important outcomes particularly for older people and require further investigation.

CONCLUSION

An association between BPV and cardiovascular events, cardiovascular mortality and all-cause mortality, has been reported by most published studies irrespective of method of measurement. It was not possible to report pooled effect sizes due to heterogeneity in methods of measurement and analysis. Consensus is required on how best to measure BPV given the reported variability in methods, in order to enable accurate comparisons in future.

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*(As per Author Guidelines, for the full reference list, please refer to **Supplementary File 3**)*

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FIGURE AND TABL LEGENDS

Table 1: Number of studies according to measurement method, outcomes, computation methods and presence or absence of association.

Supplementary Figure 1: PRISMA flow-chart

Supplementary Table 1: Search Strategy (Medline used as an example)

Supplementary Table 2: Characteristics of included studies

Supplementary Table 3: Results of the critical appraisal assessment using the CASP observational study appraisal tool.

Supplementary Table 4: Summary of clinical outcomes associated with blood pressure variability

Supplementary File 1: PRISMA Checklist

Supplementary File 2: Systematic Review Protocol

Supplementary File 3: Supplementary Reference List

DECLARATIONS

Funding: No funding was received to undertake the conduct of this study.

Conflicts of Interest: No author declares a conflict of interest in relation to this paper.

Ethical approval: No ethical approval was required for this study design.

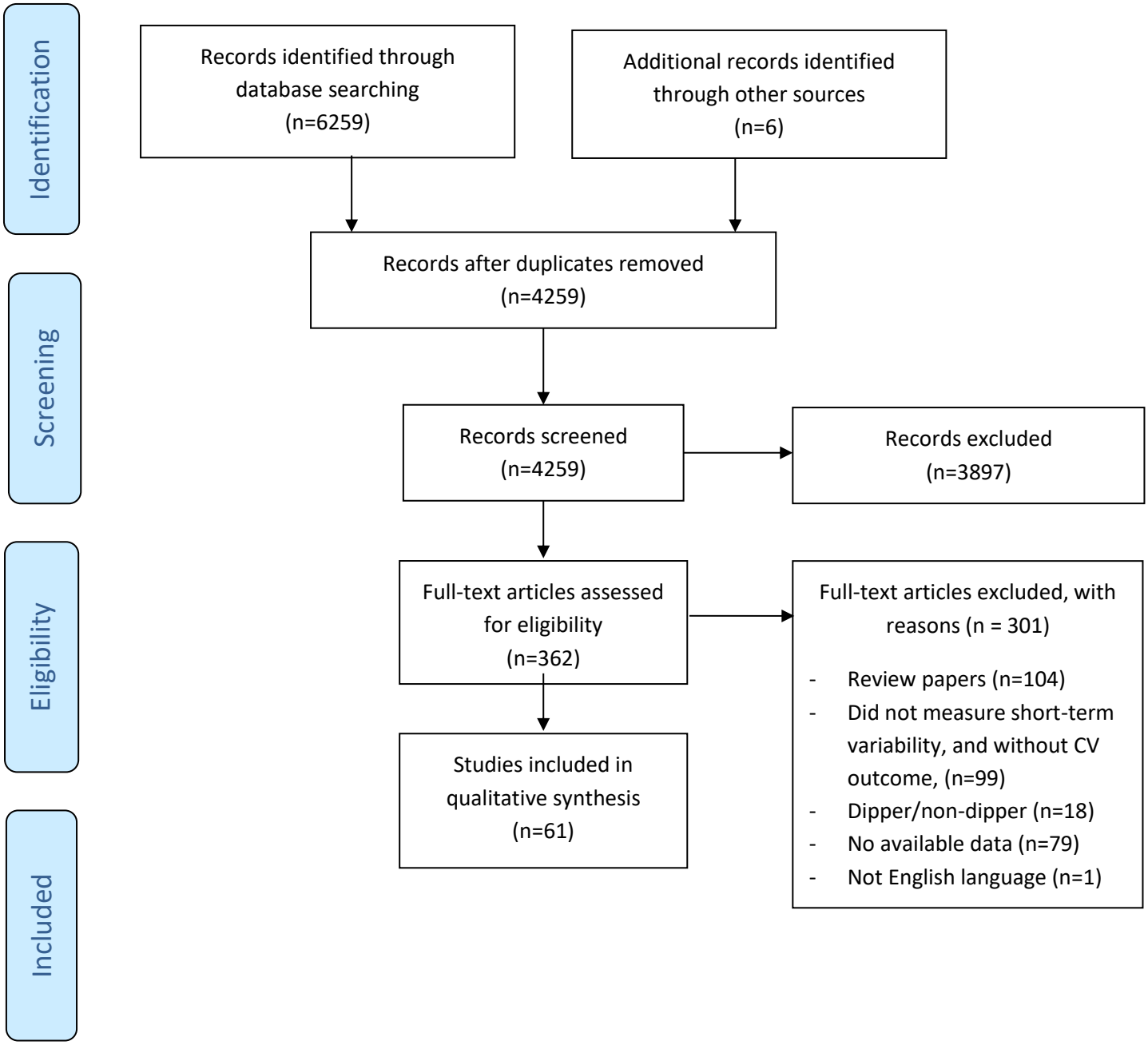
Table 1: Number of studies according to measurement method, outcomes, computation methods and presence or absence of association.

Type of measurement	Outcome	n	Computation methods						ALL	
			SD		CoV		ARV			
			+	-	+	-	+	-	+	-
ABPM	Cardiovascular outcomes	38211	13 (19737)	7 (15489)	2 (2541)	2 (1993)	5 (14457)	1 (229)	17 (32914)	5 (5297)
ABPM	Cardiovascular mortality	21055	5 (19038)	1 (2017)	0 (0)	1 (486)	1 (18092)	0 (0)	5 (19038)	1 (2017)
ABPM	All-cause mortality	27596	7 (22979)	3 (3363)	0 (0)	1 (3433)	3 (19346)	0 (0)	8 (24233)	3 (3363)
ABPM	CV events & all-cause mortality	55129	18 (38797)	10 (10117)	2 (2541)	4 (5912)	6 (23611)	1 (229)	22 (46469)	8 (8660)
Day-to-day/Visit-to-visit	Cardiovascular outcomes	3261113	20 (3230612)	3 (2335)	8 (141324)	2 (3915)	3 (4919)	0 (0)	24 (3258778)	3 (2335)
Day-to-day/Visit-to-visit	Cardiovascular mortality	50796	7 (45038)	1 (2161)	2 (1176)	1 (2161)	1 (2421)	0 (0)	10 (48635)	1 (2161)
Day-to-day/Visit-to-visit	All-cause mortality	198037	9 (171654)	3 (4058)	2 (2817)	2 (4287)	3 (23535)	1 (19248)	12 (193979)	4 (4058)
Day-to-day/Visit-to-visit	CV events & all-cause mortality	3281408	25 (3246629)	3 (2855)	10 (144141)	4 (6992)	4 (24167)	0 (0)	31 (3278417)	3 (2991)
All measurement types	CV events & all-cause mortality	3333801	43 (3288402)	10 (10693)	12 (146682)	6 (10255)	5 (14457)	3 (19477)	53 (3325085)	7 (8716)

SD=standard deviation; CoV=coefficient of variation; ARV=average real variability; ABPM=ambulatory blood pressure measurements; CV=cardiovascular. '+' indicated number of studies with positive associations, '-' indicates number of studies with negative associations. Total number of participants involved for all studies counted in each cell is indicated in parentheses.

For actual references of studies included in the table, please refer to **Supplementary Table 4**.

Supplementary Figure 1: PRISMA flow-chart



Supplementary Table 1: Search Strategy (MEDLINE used as an example)

1. Blood Pressure/
2. Blood Pressure Determination/
3. Blood Pressure Monitoring, Ambulatory/
4. (blood pressure or bp or sbp or dbp).ti,ab.
5. OR/1-4
6. varia*.ti,ab.
7. (variabilit* or variation?)).ti,ab.
8. ((between or within) adj3 visit?).ti,ab.
9. "measure* to measure*".ti,ab.
10. repeat* measure*.ti,ab.
11. within subject?.ti,ab.
12. OR/6-12
13. AND/5,12
14. exp animal/ not human/
15. 13 not 14
16. incidence.sh. or exp mortality/ or follow-up studies.sh. or prognos*.tw. or predict*.tw. or course*.tw.
17. AND/15,16

Supplementary Table 2: Characteristics of included studies

	N	Setting	Gender (% female)	Mean Age (years)	Comorbidities	Blood Pressure Measure	Mean Follow-up	Outcome
Arashi [38]	2049	Hospital	19.8	65.0 ± 9.0	Hypertension with coronary artery disease	BP measured by standard cuff mercury sphygmomanometer after 5 minutes of rest	4.2 years	Stroke, cardiovascular events, cardiovascular mortality, all-cause mortality
Asayama [19]	2421	Hospital	60.9	58.6 (no SD)	Hypertension	HBP 2x per day for 4 weeks	Median: 12 years	All-cause mortality, stroke, cardiovascular events
Bilo [67]	9154	Community	53	54.1±14.3 years	Untreated hypertension individuals	24hr ABPM	6.3 years	Cardiovascular mortality
Bjorklund [3]	872	Community	0	71	Not specified	24hr ABPM every 20 mins	6.6 ±years	Cardiovascular events
Blacher [39]	2501	Hospital	20	62.3±9.0 (with event) 61.2±8.9 (without event)	History of CVD	Twice during patient visit post 5-minute rest	4.2 years	Stroke, cardiovascular events, cardiovascular mortality
Chi [60]	203	Hospital	45	54.1±15.1	Hypertension	Average of 3 office BP measurements after 10-min rest, 24hrs ABPM (every 15min daytime and every 30min nighttime), aortic BP monitoring by software analysis	Not documented	Left ventricular abnormalities
Choi [40]	1230	Hospital	44.3	59.3±12.5 years	Hypertension	Average of 2 BP measurements post 10-minute rest, 24hrs ABPM	4 years	Stroke, cardiovascular event, cardiovascular mortality
Chowdhury [41]	6010	Hospital	51.7	71.9 ± 4.9	Hypertension	At least 3 times during patient visit post 5-minute rest	Median: 4.1 years	Stroke, cardiovascular events, cardiovascular mortality

Chowdhury [42]	508	Hospital	43.1	72±5	Hypertension	26hr ABPM every 30 mins	Median: 10.9 years	Cardiovascular mortality and all-cause mortality
Cui [33]	998	Hospital	0	78.4±12.0	Hypertension	24hr ABPM every 15mins day, every 30 mins night	Not documented	Cardiovascular events
Darabont [30]	1975	Community	52.6	47.1±15.4	Not specified	Automatic oscillometric BP measuring device on first clinic visit anytime and second clinic visit in morning	2 study visits 7-10 days apart	Cardiovascular events
Duan [1]	1526	Community	0	58.6 years	Not specified	HBP at morning and evening for 4 weeks, within 1hr after awakening	12.0 years	Stroke, cardiovascular events, cardiovascular mortality
Eguchi [4]	457	Hospital	62.4	67.0±9.2	Type 2 Diabetes	24 hrs ABPM every 30 mins	67 months	Cardiovascular events
Eguchi [8]	300	Hospital	52	67.8±9.6	Not specified	24 hrs ABPM every 30 mins	54.6 months	Cardiovascular events
Eto [14]	106	Hospital	46	73.9±8.1	Hypertension	24hrs ABPM every 30 mins	Median: 34 months (3-60)	Cardiovascular events
Gao [43]	2906	Hospital	78.7	66±6.2	Not specified	BP measurements from out-patient visits	12.9 years	Cardiovascular mortality, all-cause mortality
Gavish [15]	3433	Hospital	55	56±16	Hypertension	Visit-to-visit BP measured, at least two visits, 3 BP readings measured post 5 mins rest, 24hrs ABPM every 20 mins day, every 20 mins night	7.6 years	Cardiovascular events
Gavish [52]	1246	Hospital	54	56±16	Not specified	24hrs ABPM	5 years	Cardiovascular events, all-cause mortality
Gosmanova [71]	2865157	Hospital	6.1	59.3±13.1 years	Not specified	Clinic BP measurements	8 years	All-cause mortality, cardiovascular events
Hansen [6]	8938	Community	46.8	53 (no SD)	Not specified	24hrs ABPM every 15-30 mins day, every 30-60 mins night	Median: 11.3 years	Stroke, cardiovascular events, cardiovascular mortality, all-cause mortality
Hara [66]	4695	Community	Not documented	Not documented	Hypertension	2 clinic BP measurements	2 years	CHF, cardiovascular events, stroke, all-cause mortality

Hashimoto [13]	902	Community	0	58.6 (no SD)	Not specified	24hrs ABPM every 15-30 mins day, every 30-60 mins night	Median: 13.1 years	Stroke, cardiovascular events, cardiovascular mortality, all-cause mortality
Hata [44]	8811	Hospital	42	66±6	Type 2 Diabetes	Average of 2 valid BP measurements after a 5 mins rest	2.4 years	Stroke, cardiovascular events, cardiovascular mortality, all-cause mortality
Hoshide [68]	4231	Community	53.3	65±11	History of or risk factors for CVD	HBP x3, 2x morning and 1x evening for 14 consecutive days	4 years	Stroke, cardiovascular events
Hsieh [62]	2161	Community	57	63.5±11.9	Type 2 Diabetes	Average of 2 valid BP measurements after a 10-minute rest	66.7 months.	All-cause mortality and cardiovascular mortality
Hsu [37]	1257	Community	46.8	53.1±13.1	Normotensive	Two or more measurements by clinic sphygmomanometer and 24hrs ABPM	20 years	Cardiovascular mortality
Johansson [20]	1866	Community	56.1	56.4 (no SD)	Without a stroke	HBP 2x, morning and evening for seven consecutive days	7.8 years	Cardiovascular events, all-cause mortality
Kawai [45]	485	Hospital	46.8	61.7±11.5	Hypertension	Average of 2 valid BP measurements after a 5 mins rest	7.59 years	Stroke, Cardiovascular events, cardiovascular mortality, all-cause mortality
Kikuya [21]	2455	Community	60.4	59.4±12.3	Not specified	HBP every morning for 4 weeks	11.9 years	All-cause mortality, cardiovascular mortality
Kostis [46]	4736	Hospital	Not documented	Not documented	Hypertension	Zero manometers used for 2 BP measurements after 5 mins of quiet rest	17 years	Cardiovascular mortality
Lau [47]	632	Hospital	47	71±11	Ischaemic Stroke without AF	3 times during patient visit post 5 mins rest	76 months	All-cause and cardiovascular mortality, nonfatal recurrent stroke
Lau [48]	656	Hospital	32	66±10	Diabetes, CVD or cerebrovascular disease	3 times during patient visit post 5 mins rest	81 months	Stroke and cardiovascular mortality

Mancia [2]	2017	Community	Not documented	50.9 (no SD)	Not specified	24hrs ABPM, every 20 minutes	148 months	Cardiovascular events, cardiovascular mortality, all-cause mortality
Men [59]	19 248	Hospital	Not documented	Not documented	Hypertension	Average of 2 valid BP measurements after a 5 mins rest	4.5 years	Stroke
Mena 2005 [16]	312	Community	63	66.9 (no SD)	Hypertension	24hrs ABPM every 15 mins day, every 30 mins night	1.86 years	Cardiovascular events
Mena [9]	1254	Community	43.5	56.6 (no SD)	Not specified	24hrs ABPM every 15-30 mins day and 30-60 mins at night	Median: 12.4 years	Cardiovascular events, all-cause mortality
Mossello [5]	100	Community	66.7	83±10	Not specified	24hrs ABPM every 15 mins day, every 20 mins night	12 months	All-cause mortality
Muntner [53]	25814	Hospital	Not documented	>55 (no mean or SD)	Not specified	Standard BP measuring technique 2x by trained observer	28 months	Stroke, all-cause mortality, CHD, cardiovascular events
Palatini [17]	486	Hospital	46	49 (no SD)	Hypertension	24hrs ABPM every 15 mins day, every 30 mins night	4.74 years	Cardiovascular events
Palatini [69]	7112	Not documented	44	52±15	Not specified	24hrs ABPM	Median: 5.5 years	All-cause mortality, cardiovascular events, cardiovascular mortality
Park [55]	CAMELOT=1677, PREVENT=776	Hospital	Not documented	Not documented	Not specified	2 clinic BP measurements with 2 mins intervals, post 3 mins rest	CAMELOT: 24 months PREVENT:36 months	Cardiovascular Events
Pierdomenico [54]	1088	Hospital	46	42±12 years	Hypertension		4.74±2.4 years	All-cause mortality, cardiovascular mortality, cardiovascular events
Pierdomenico [10]	1472	Hospital	53.1	Not documented	Hypertension	24hrs ABPM every 15 mins day, every 30 mins night	4.88 years	Cardiovascular events
Pierdomenico [11]	1280	Hospital	49	≥40 (no mean or SD)	Hypertension	24hrs ABPM every 15 mins day, every 30 mins night	4.75 years	Cardiovascular events

Poortvliet [49]	5804	Hospital	Not documented	75.2 (no SD)	History of or risk factors for CVD	Clinic BP	3 years (7.1 years available for 1808 subjects)	Cardiovascular events, cardiovascular mortality, all-cause mortality
Pringle [63]	744	Community	26.7	69.5 (no SD)	Not specified	24hrs ABPM every 30 mins, clinic BP	4.4 years	Stroke, cardiovascular events, cardiovascular mortality
Rakugi [56]	4876	Hospital	Not documented	69.6±2.9	Hypertension	Office BP	3.3 years	Cardiovascular events
Rothwell [57]	2435	Hospital	Not documented	Not documented	Previous TIA	24hrs ABPM every 30 mins	Range: 6-30 months	Stroke, risk of stroke, cardiovascular events
Shi [61]	229	Hospital	31.2	66.7±13.0	Ischaemic Stroke	24hrs ABPM, standard mercury sphygmomanometer measurements every morning	24 months	Post-stroke functional outcome
Shimbo [34]	58228	Hospital	100	Range: 50-79 (no mean or SD)	Not specified	Average of 2 BP measurements after 5 mins rest, taken 30 seconds apart	5.4 years	Stroke
Suchy-Dicey [50]	3852	Hospital	59	72±5.0	Risk factors for CVD	Average of 2 BP measurements (from a total of 3 measurements), readings 5 mins apart	9.9 years	Stroke, cardiovascular events, cardiovascular mortality, all-cause mortality
Takao [58]	632	Hospital	17.8	55.7±9.3	Type 2 Diabetes	Four or more BP measurements	11.1 years	Cardiovascular events
Tao [36]	1764	Hospital	32.1	62.4±11.0	Acute ischaemic Stroke or TIA	24hrs ABPM, every 15 mins during daytime and every 30 mins during the night	12 months	Non-fatal recurrent stroke
Veloudi [35]	286	Hospital	53	64 (no SD)	Hypertension	Clinic BP, 7 day HBPM, 24 ABPM	12 months	Cardiovascular events
Verdecchia [12]	2649	Community	47	51 (no SD)	Hypertension	24hrs ABPM every 15 mins	Median: 6 years	Cardiovascular events
Wan [64]	124105	Hospital	55.6	63.2±11.3	Type 2 Diabetes	2 clinic BP measurements with 1 min intervals	24 months	Cardiovascular events, cardiovascular mortality
Webb [25]	520	Hospital	49.1	66±13	TIA or non-disabling stroke	HBP 3x3 daily for 1 week, 24hrs ABPM every 30 mins day and 60 mins night	Range 2-5 years	Stroke, cardiovascular events, cardiovascular mortality, all-cause mortality

Wei [51]	724	Community	33.1	76.6±4.6	Hypertension	Average of 2 BP measurements post 5 to 10 mins rest	4 years	Stroke, cardiovascular events, cardiovascular mortality
Weiss [31]	469	Hospital	59.7	84.9 (no SD)	Not specifd	Day-to-day BP (total of 5-10 BP measurements)	12 months	All-cause mortality
Wu [65]	148	Community	45.4	73.3±2.8	Hypertension	Average of 2 measurements by clinic BP	8.5 years	Cardiovascular events, cardiovascular mortality, all-cause mortality
Yu [70]	122636	Community	54.3	64.1±11.3	Hypertension	Clinic BP	48 months	Stroke

ABPM – ambulatory blood pressure measurement; AF – atrial fibulation; BP – blood pressure; CHD – coronary heart disease; CVD – cardiovascular disease; HBP – high blood pressure, hrs – hours; mins – minutes; SD – standard deviation; TIA – transient ischaemic attack

Supplementary Table 3: Results of the critical appraisal assessment using the CASP observational study appraisal tool

	Arashi [38]	Asayama [19]	Bilo [67]	Bjorklund [3]	Blacher [39]		Chi [60]	Choi [40]	Chowdhury [41]	Chowdhury [42]	Cui [33]	Darabont [30]	Duan [1]	Eguchi [4]	Eguchi [8]	Eto [14]	Gao [43]	Gavish [15]	Gavish [52]	Gosmanova [71]	Hansen [6]	Hara [66]	Hashimoto [13]	Hata [44]	Hoshide [68]	Hsieh [62]	Hsu [37]	Johansson [20]	Kawai [45]	Kikuya [21]
Did the study address a clearly focused issue?	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Was the cohort recruited in an acceptable way?	1	1	1	0	1		1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Was the exposure accurately measured to minimise bias?	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	0	0	1	1	1
Was the outcome accurately measured to	1	1	1	1	1		0	1	1	1	0	0	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	0

minimise bias?																														
Have the authors identified all important confounding factors?	0	1	1	1	0		0	1	1	1	0	0	0	1	1	0	1	0	0	1	1	0	0	0	1	1	1	0	0	0
Have they taken account of the confounding factors in the design and/or analysis?	0	0	1	1	0		0	1	1	1	0	1	0	1	1	0	1	0	0	1	1	0	0	0	1	1	1	0	0	0
Was the follow up of subjects complete enough?	1	0	1	1	1		1	1	1	1	1	1	1	0	0	1	1	0	1	1	0	1	1	1	1	0	1	1	1	1
Was the follow up of subjects long enough?	1	1	1	0	1		0	1	1	1	0	0	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	1	0
Are the results clearly presented ?	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

How precise are the results?	0	1	1	1	1		0	1	1	1	0	0	0	0	1	0	1	1	0	1	1	1	1	1	1	1	1	0	0	0
Can the results be applied to the general population?	1	1	0	0	0		0	1	1	0	0	0	0	0	0	0	1	0	0	0	1	1	1	1	1	1	1	0	1	0
Are clinical implications made?	0	1	1	1	1		0	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0

	Kostis [46]		Lau [47]	Lau [48]	Mancia [2]	Mancia [71]	Men [59]	Mena [16]	Mena [9]	Mossello [5]	Muntner [53]	Palatini [17]	Palatini [59]	Park [55]	Pierdomenico [54]	Pierdomenico [10]	Pierdomenico [11]	Poortvliet [49]	Pringle [63]	Rakugi [56]	Rothwell [57]	Shi [61]	Shimbo [34]	Suchy-Dicey [50]	Takao [58]	Tao [36]	Veloudi [35]	Verdecchia [12]	Wan [64]	Webb [25]	Wei [51]	Weiss [31]	Wu [65]	Yu [70]
Did the study address a clearly focused issue?	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Was the cohort recruited in an acceptable way?	1		1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1
Was the exposure accurately measured to minimise bias?	1		1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1

Was the outcome accurately measured to minimise bias?	0		1	1	1	1	1	0	1	0	1	0	0	1	1	1	0	1	1	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1
Have the authors identified all important confounding factors?	0		0	0	0	0	1	1	0	0	1	1	1	0	1	1	1	1	0	0	0	0	1	1	0	0	0	1	1	0	0	0	1	0
Have they taken account of the confounding factors in the design and/or analysis?	0		0	0	0	0	1	1	0	0	1	1	1	0	1	1	1	1	0	0	0	0	1	1	1	0	0	1	1	1	0	1	1	0
Was the follow up of subjects	1		1	1	1	1	1	0	0	0	1	0	0	0	0	0	1	1	1	0	0	1	1	1	0	1	1	1	1	1	1	1	1	1

complete enough?																																				
Was the follow up of subjects long enough?	1		1	1	1	1	1	0	1	0	1	1	1	0	1	1	1	1	1	1	0	0	1	1	0	0	0	1	1	1	1	0	1	1
Are the results clearly presented?	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1
How precise are the results?	1		1	1	1	0	1	1	1	1	1	1	1	1	0	1	0	1	1	0	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1
Can the results be applied to the general population?	0		0	0	1	1	1	1	1	0	1	1	1	0	0	0	0	1	1	0	0	0	1	1	0	0	0	0	1	0	0	0	1	0	
Are clinical implications made?	0		0	0	0	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	0	0	0	1	1	1	0	0	1	0	

Supplementary Table 4. Summary of clinical outcomes associated with blood pressure variability.

Type of BPV		**Associations**							
ABPM									
Cardiovascular Outcomes		**SD**		**CoV**		**ARV**		**ALL**	
		Present (+)	**Absent (-)**	**+**	**-**	**+**	**-**	**+**	**-**
24h	SBP	6 [1,14,33,35,40,57]	7 [6,9,36, 54,60,61,63]	2 [14,57]	2 [36,61]	4 [6,9,37,60]	1 [61]	10 [1,6,9,14,33,35,37,40,57,60]	4 [36, 54, 61,63]
	DBP		2 [6,61]		2 [61,61]	2 [6,37]	2 [9,61]	2 [6,37]	2 [9,61]
Day	SBP	3 [3,11,14]	5 [9,10,36,57,63]	1 [14]	1 [36]	2 [9,11]		4 [3,9,11,14]	4 [10,36, 57,63]
	DBP		2 [3,11]			1 [11]		1 [11]	1 [3]
Night	SBP	5 [4,8,12,17,69]	6 [3,9,10,11,36,63]		1 [36]			5 [4,8,12,17,69]	6 [3,9,10,11,36,63]
	DBP	3 [8,17,69]	2 [3,11]					3 [8,17,69]	2 [3,11]
ALL	SBP	13 [1,3,4,8,11,12,14,17,33, 35,40,69,57]	8 [6,9,10,36,54,60 ,61,63]	2 [14,57]	2 [36,61]	5 [6,9,11,37 ,60]	1 [61]	17 [1,3,4,6,8,9,11,12,14,17,33,3 5,37,40,57,60,69]	5 [10,36,54,61,63]
	DBP	3 [8,17,69]	4 [3,6,11,61]		1 [61]	3 [6,11,37]	2 [9,61]	6 [6,8,11,17,37,69]	4 [3,9,11,61]
	SBP/ DBP	13 [1,3,4,8,11,12,14,17,33, 35,40,69,57]	7 [6,9,10,36,54,61 ,63]	2 [14,57]	2 [36,61]	5 [6,9,11,37 ,60]	1 [61]	17 [1,3,4,6,8,9,11,12,14,17,33,3 5,37,40,57,60,69]	5 [10,36,54,61,63]

Cardiovascular mortality		**SD**		**CoV**		**ARV**		**ALL**	
		Present (+)	**Absent (-)**	**+**	**-**	**+**	**-**	**+**	**-**
24h	SBP	1 [69]	4 [2,6,16,65]			1 [6]	1 [67]	2 [6,69]	4 [2,16,65,67]
	DBP	3 [6,65,69]	2 [2,16]		1 [69*]	2 [6,67]		4 [6,65,67,69]	2 [2,16]
Day	SBP	1 [67]	3 [2,16,69]					1 [67]	3 [2,16,69]

	DBP	3 [16,67,69]	1 [2]					3 [16,67,69]	1 [2]
Night	SBP	1 [69]	3 [2,16,67]					1 [69]	3 [2,16,67]
	DBP	1 [69]	3 [2,16,67]					1 [69]	3 [2,16,67]
ALL	SBP	2 [67,69]	4 [2,6,16,65]			1 [6]	1 [67]	3 [6,69,67]	3 [2,16,65]
	DBP	5 [6,16,65,67,69]	1 [2]		1 [69*]	2 [6,67]		5 [6,16,65,67,69]	1 [2]
	SBP/ DBP	5 [6,16,65,67,69]	1 [2]		1 [69*]	2 [6,67]		5 [6,16,65,67,69]	1 [2]

All-cause mortality		**SD**		**CoV**		**ARV**		**ALL**	
		Present (+)	**Absent (-)**	**+**	**-**	**+**	**-**	**+**	**-**
24h	SBP	1 [69]	5 [2,16,42,52,65]		1 [15]	3 [6,9,67]		4 [6,9,67,69]	6 [2,15,16,42,52,65]
	DBP	3 [6,65,69]	4 [2,16,42,52]			3 [6,9,67]		5 [6,9,65,67,69]	4 [2,16,42,52]
Day	SBP	2 [42,67]	3 [2,16,69]					2 [42,67]	3 [2,16,69]
	DBP	3 [16,42,67]	2 [2,69]					3 [16,42,67]	2 [2,69]
Night	SBP	2 [15,69]	5 [2,5,16,42,67]					2 [15,69]	5 [2,5,16,42,67]
	DBP	3 [16,67,69]	2 [2,42]					3 [16,67,69]	2 [2,42]
ALL	SBP	4 [15,42,67,69]	5 [2,5,16,52,65]		1 [15]	3 [6,9,67]		6 [6,9,15,42,67,69]	5 [2,5,16, 52,65]
	DBP	6 [6,16,42,65,67,69]	2 [2,52]			3 [6,9,67]		7 [6,9,16,42,65,67,69]	2 [2,52]
	SBP/ DBP	7 [6,15,16,42,65,67,69]	3 [2,5,52]		1 [15]	3 [6,9,67]		8 [6,9,15,16,42,65,67,69]	3 [2,5,52]

All cardiovascular outcomes and mortality for ABPM	**SD**		**CoV**		**ARV**		**ALL**	
	Present (+)	**Absent (-)**	**+**	**-**	**+**	**-**	**+**	**-**

24h	SBP	7 [1,14,33,35,40,57,69]	12 [2,6,9,16,36,42,52,54,60,61,63,65]	2 [14,57]	35 [15,36,61]	5 [6,9,37,60,67]	1 [61]	12 [1,6,9,14,33,35,37,40,57,60,67,69]	10 [2,15,16,36,42,52,54,61,63,65]
	DBP	3 [6,65,69]	5 [2,16,42,52,61]		2 [61,69*]	4 [6,9,37,67]	2 [9,61]	6 [6,9,37,65,67,69]	5 [2,16,42,52,61]
Day	SBP	5 [3,11,14,42,67]	9 [2,9,10,16,36,63,61,69,57]	1 [14]	1 [36]	2 [9,11]		6 [3,9,11,14,42,67]	7 [2,10,16,36,57,63 ,69]
	DBP	4 [16,42,67,69]	35 [2,3,11]			1 [11]		5 [11,16,42,67,69]	2 [2,3]
Night	SBP	6 [4,8,12,15,17,69]	11 [2,3,5,9,10,11,16,36,42,63,67]		1 [36]			6 [4,8,12,15,17,69]	11 [2,3,5,9,10,11,16,36,42,63,67]
	DBP	5 [8,16,17,67,69]	5 [2,3,11,16,42]					5 [8,16,17,67,69]	5 [2,3,11,16,42]
ALL	SBP	16 [1,3,4,8,11,12,14,15,17,33,35,40,42, 57,67,69]	13 [2,5,6,9,10,16,36,52,54,60,61,63,65]	2 [14,57]	35 [15,36,61]	6 [6,9,11,37,60,67]	1 [61]	20 [1,3,4,6,8,9,11,12,14,15,17,33,35,37,40,42,57,60,67,69]	13 [2,5,6,9,10,16,36,52,54,60,61,63,65]
	DBP	8 [6,8,16,17,42,65,67,69]	7 [2,3,6,11,52,61,61]		3 [61,69*,61]	5 [6,9,11,37,67]	2 [9,61]	11 [6,8,9,11,16,17,37,42,65,67,69]	7 [2,3,6,11,52,61,69*]
	SBP/ DBP	18 [1,3,4,6,8,11,12,14,16,17,33,35,40,42,57,65,67,69]	10 [2,5,9,10,36,52,54,60,61,63]	2 [14,57]	4 [15,36,61,69*]	6 [6,9,11,37,60,67]	1 [61]	22 [1,3,4,6,8,9,11,12,14,15,16,17,33,35,37,40,42,57,60,65,67,69]	8 [2,5,10,36,52,54,61,63]

Day-to-day/Visit-to-visit								
Cardiovascular Outcomes	**SD**		**CoV**		**ARV**		**ALL**	
	Present (+)	**Absent (-)**	**+**	**-**	**+**	**-**	**+**	**-**

Morning	SBP	1 [20]		2 [25,68]		2 [19,20]		4 [19,20,25,68]	
	DBP	1 [20]				1 [20]		1 [20]	
Evening	SBP		1 [20]			1 [19]	1 [20]	1 [19]	1 [20]
	DBP		1 [20]				1 [20]		1 [20]
Daily/Visit	SBP	18 [8,30,31,34^{+},36,39,41,43,44,48§,50,51,53,55,61,64,70,71]	4 [20,35,38,48‡]	6 [36,39,44,58,61,70]	1 [38]	2 [20,48§]		20 [8,20,30,31,34^{+},36,39,41,43,44,48§,50,51,53,55,58,61,64,70,71]	3 [35,38,48‡]
	DBP	3 [20,61,70]	2 [35,43]	3 [58,61,70]	1 [20]			4 [20,58,61,70]	2 [35,43]
Morning - Evening	SBP	1 [45]	1 [20]				1 [20]	1 [45]	1 [20]
	DBP	1 [45]	1 [20]			1 [20]		2 [20,45]	
ALL	SBP	20 [8,20,30,31,34^{+},36,39,41,43,44,45,48§,50,51,53,55,61,64,70,71]	3 [35,38,48‡]	8 [25,36,39,44,58,61,68,70]	1 [38]	3 [19,20,48§]		24 [8,19,20,25,30,31,34^{+},36,39,41,43,44,45,48§,50,51,53,55,58,61,64,68, 70,71]	3 [35,38,48‡]
	DBP	4 [20,45,61,70]	2 [35,43]	3 [58,70,61]	1 [20]	1 [20]		5 [20,45,58,70,61]	2 [35,43]
	SBP/ DBP	20 [8,20,30,31,34^{+},36,39,41,43,44,45,48§,50,51,53,55,61,64,70,71]	3 [35,38,48‡]	8 [25,36,39,44,58,61,68,70]	2 [20,38]	3 [19,20,48§]		24 [8,19,20,25,30,31,34^{+},36,39,41,43,44,45,48§,50,51,53,55,58,61,64,67,70,71]	3 [35,38,48‡]

Cardiovascular Mortality		**SD**		**CoV**		**ARV**		**ALL**	
		Present (+)	**Absent (-)**	**+**	**-**	**+**	**-**	**+**	**-**
Morning	SBP	2 [13,21]		1 [25]		1 [19]		4 [13,19,21,25]	
	DBP								
Evening	SBP					1 [19]			
	DBP								
Daily/Visit	SBP	5 [46,48,49,53,66]	1 [62]	1 [47]	1 [62]			6 [46,47,48,49,53,66]	1 [62]

	DBP	1 [49]	2 [48,62]		2 [47,62]			1 [49]	3 [47,48,62]
Morning - Evening	SBP								
	DBP								
ALL	SBP	7 [13,21,46,48,49,53,66]	1 [62]	2 [25,47]	1 [62]	1 [19]		10 [13,19,21,25,46,47,48,49,53,66]	1 [62]
	DBP	1 [49]	2 [62,48]		2 [47,62]			1 [49]	3 [47,48,62]
	SBP/ DBP	7 [13,21,46,48,49,53,66]	1 [62]	2 [25,47]	1 [62]	1 [19]		10 [13,19,21,25,46,47,48,49,53,66]	1 [62]

All-cause mortality		**SD**		**CoV**		**ARV**		**ALL**	
		Present (+)	**Absent (-)**	**+**	**-**	**+**	**-**	**+**	**-**
Morning	SBP	3 [13,20,21]	1 [25]		2 [19,20]			3 [13,20,21]	2 [19,25]
	DBP	1 [20]				1 [20]		1 [20]	
Evening	SBP		1 [20]			1 [19]	1 [20]	1 [19]	1 [20]
	DBP	1 [20]				1 [20]		1 [20]	
Daily/Visit	SBP	7 [20,49,50,53,62,64,66]	2 [43,48]	2 [47,62]		2 [20,59§]	1 [59‡]	9 [20,47,49,50,53,59§,62,64,66]	3 [43,48,59‡]
	DBP	4 [20,43,49,62]	1 [48]	1 [62]	1 [47]	1 [20]		4 [20,43,49,62]	2 [47,48]
Morning - Evening	SBP	1 [20]				1 [20]		1 [20]	
	DBP	1 [20]				1 [20]		1 [20]	
ALL	SBP	9 [13,20,21,62,49,50,64,66,53]	3 [25,43,48]	2 [62,47]	2 [19,20]	3 [19,20,59§]	1 [59‡]	12 [13,19,20,21,47,49,50,53,59§,62,64,66,]	4 [25,43,48,59‡]

	DBP	1 [20]	1 [48]	1 [62]	1 [47]	1 [20]		2 [20,62]	2 [47,48]
	SBP/ DBP	9 [13,20,21,49,50,53,62, 64,66]	3 [25,43,48]	2 [62,47]	2 [19,20]	3 [19,20,59§]	1 [59‡]	12 [13,19,20,21,47,49,50,53,59 §,62,64,66]	4 [25,43,48,59‡]

CoV events & all-cause mortality (day-to-day)		**SD**		**CoV**		**ARV**		**ALL**	
		Present (+)	**Absent (-)**	**+**	**-**	**+**	**-**	**+**	**-**
Morning	SBP	3 [13,20,21]	1 [25]	2 [25,68]	2 [19,20]	2 [19,20]		6 [13,19,20,21,25,68]	
	DBP	1 [20]				1 [20]		1 [20]	
Evening	SBP		1 [20]			1 [19]	1 [20]	1 [19]	1 [20]
	DBP	1 [20]				1 [20]		1 [20]	
Daily	SBP	23 [8,20,30,31,34+,36,39,41, 43,44,46,48§,49,50,51,53, 55,61,62,64,66,70,71]	6 [20,35,38,4 3,62,48‡]	8 [36,39,44,4 7,58,61,62, 70]	2 [38,62]	3 [20,48§,59]		26 [8,20,30,31,34+,36,39,41,43, 44,46,47,48,49,50,51,53,55,5 8,59,61,62,64,66,70,71]	3 [35,38,62]
	DBP	6 [20,43,49,61,62,70]	4 [35,43,48,6 2]	4 [58, 61,62,70]	3 [20,47 ,62]			7 [20,43,49,58,61,62,70]	5 [35,43,47,48,62]
Morning – Evening	SBP	2 [20,45]				1 [20]		2 [20,45]	
	DBP	2 [20,45]				1 [20]		2 [20,45]	
ALL	SBP	25 [8,13,20,21,30,31,34+,36, 39,41,43,44,45,48,49,50,5 1,53,55,61,62,64,66,70,71]	3 [25,35,38]	10 [25,36,39,4 4,47,58,61, 62,68,70]	3 [19,20 ,38]	4 [19,20,48§, 59]		31 [8,13,19,20,21,25,30,31,34+, 36,39,41,43,44,45,46,48,49,5 0,51,53,55,58,59,61,62,64,66 ,68,70,71]	2 [35,38]
	DBP	7 [20,43,62,45,49,70,61]	3 [35,43,48]	4 [58,61,62,7 0]	2 [20,47]	1 [20]		8 [20,43,62,45,49,58,70,61]	4 [35,43,47,48]

	SBP/ DBP	25 [8,13,20,21,30,31,34[+],36, 39,41,43,44,45,48,49,50,5 1,53,55,61,62,64,66,70,71]	3 [25,35,38]	10 [25,36,39,4 4,47,58,61, 62,68,70]	4 [19,20 ,38,47]	4 [19,20,48[§], 59]		31 [8,13,19,20,21,25,30,31,34[+], 36,39,41,43,44,45,46,48,49,5 0,51,53,55,58,59,61,62,64,66 ,68,70,71]	3 [35,38,47]

ABPM & Day-to-day	**SD**		**CoV**		**ARV**		**ALL**	
	Present (+)	**Absent (-)**	**+**	**-**	**+**	**-**	**+**	**-**
SBP	40 [1,3,4,8,11,12,13,14,15,1 7,20,21,30,31,33,34[+],35,3 6,39,40,41,42,43,44,45,4 8,49,50,51,53,55,57,61,6 2,64,66,67,69,70,71]	13 [2,5,6,9,10,16 ,25,38,52,54, 60,63,65]	12 [14,25,36,39 ,44,47 ,57,58,61,62 ,68,70]	5 [15,19,2 0,36,38]	9 [6,9,11,1 9,20,37,4 8[§],59[§],60]	2 [59[‡], 61]	51 [1,3,4,6,8,9,11,12,13,14,15,17, 19,20,21,25,30,31,33,34[+],35,36 ,37,39,40,41,42,43,44,45,46,47 ,48,49,50,51,53,55,57,58,59,60 ,61,62,64,66,67,68,69,70,71]	9 [2,5,10,16,38,52, 54,63,65]
DBP	15 [6,8,16,17,20,42,43,45,49 ,61,62,65,67,69,70]	7 [2,3,11,35,48, 52,61]	4 [58,61,62,70]	4 [20,47,6 1,69*]	5 [6,9,11,2 0,37]	1 [61]	19 [6,8,9,11,16,17,20,37,42,43,62, 45,49,65,69,58,61,67,70]	7 [2,3,11,35,48,52, 61]
SBP/DBP	43 [1,3,4,6,8,11,12,13,14,15, 16,17,20,21,30,31,33,34[+], 35,36,39,40,41,42,43,44, 45,48,49,50,51,53,55,57, 61,62,64,65,66,67,69,70, 71]	10 [2,5,9,10,25,3 8,52,54,60,63]	12 [14,25,36,39 ,44,47,57,58 ,61,62,68,70]	6 [15,19,2 0,38,61, 69*]	5 [6,9,11,3 7,60]	2 [59[‡], 61]	53 [1,3,4,6,8,9,11,12,13,14,15,16, 17,19,20,21,25,30,31,33,34[+],35 ,36,37,39,40,41,42,43,44,45,46 ,47,48,49,50,51,53,55,57,58,59 ,60,61,62,64,65,66,67,68,69,70 ,71]	7 [2,5,10,38,52,54, 63]

ABPM: ambulatory blood pressure monitoring; ARV=average real variability; CoV: coefficient of variance; DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation; *includes 24h, day and night time variations; [†]ischaemic stroke; [‡] stroke in SBP<140mmHg; [§]stroke in SBP≥ 140mmHg.

Supplementary File 1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Intro, Para 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Intro, Para 3, Line 5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Supplementary File 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods, Eligibility Criteria
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, Search Strategy
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods, Identification of Studies
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, Data Extraction

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods, Data Extraction
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods, Quality Assessment
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods, Data Synthesis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods, Data Synthesis

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods, Quality Assessment
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods, Data Synthesis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary Table 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, Paragraph 1
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, Paragraph 5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion, Paragraph 2-4
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Declarations, Funding.

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Supplementary File 2: Systematic Review Protocol

Systematic Review Protocol

Title: Which methods of measurement of short-term blood pressure variation provide the best estimate of cardiovascular outcome? – a systematic review

Lead Researchers: Choon-Hian Goh, Maw Pin Tan & Professor Phyo Myint

Date: 12th December 2014

Background

Variation in blood pressure (BP) levels has long been viewed more as an obstacle to accurate blood pressure measurement than a risk factor itself. However, it is now accepted that variation in systolic and diastolic BP has a physiological basis resulting in non-random fluctuation over seconds, minutes, and even years of measurement, and that these changes may influence the development and progression of cardiovascular, cerebrovascular and renal disease (1). The heterogeneous nature of the existing literature makes it difficult to draw firm conclusions about the significance of variability – there are no standard measures or indices for any type of variation or outcomes. It is already acknowledged that daily variability of blood pressure can affect the diagnosis and treatment of hypertension on the basis of one-off office measurements, and that home and ambulatory blood pressure measurement may give more accurate information (2). Further, if variability proves to be a significant factor in cardiovascular disease, it could bring about a shift in clinical practice towards antihypertensive treatments which not only lower, but also stabilise blood pressure (1).

Measuring variability is difficult because of its close relationship with mean blood pressure, the influence of physical and emotional stimuli, and the frequency with which it is associated with other cardiovascular risk factors such as diabetes(2). Standard deviation is still frequently used to quantify blood pressure variation (BPV), despite the fact it only shows variation relative to the mean blood pressure level. New indices such as average real variability (ARV) and variation independent of the mean (VIM) may prove to more accurately represent the true association between BPV and cardiovascular outcome (3).

Methods

Search Strategy

The literature search began by hand-searching the references of a small number of high-quality papers in the field and reviewing their MeSH terms. These were used to construct searches for Medline and EMBASE databases, limiting to English, humans, and recent papers (published since 2004). The references of relevant reviews will also be hand-searched for appropriate papers. The titles and abstracts of the results will then be screened independently by two team members to produce an agreed-upon list of papers for full-text screen and subsequent critical appraisal.

Eligibility Criteria

Included papers will measure the effect of variability on cardiovascular outcomes such as cardiac death or cardiac events e.g. myocardial infarct or stroke.

Critical Appraisal Methods

Papers will be appraised using the Cochrane risk of bias tool (4) and the CASP tool (5) where applicable.

Data Analysis

A series of study characteristics tables will help to establish the relationships between the method of blood pressure measurement, the index of variability used, and the results of each paper. Two separate tables will show the measurements and indices – these will then be cross-tabulated so that the magnitude of the result in each paper for each combination can be easily viewed. This will be followed by a meta-analysis using RevMan where feasible. Any studies which cannot be meta-analysed will be reported individually.

Impact of Research

It is hoped that following review and meta-analysis, the most effective way of measuring and quantifying short-term blood pressure variation for accurate prediction of cardiovascular outcomes in both short (≤1yr) and longer term (>1 yr) will be determined. This will help to standardise future research leading to a more coherent picture of blood pressure variability as a prognostic tool and as a potential risk factor for cardiovascular diseases.

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Supplementary File 3: Full Reference List

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