Blood pressure variability and cardiovascular disease: A systematic review and meta-analysis

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Abstract

Objective: Variability in blood pressure (BP) has been increasingly recognized as an independent risk factor for cardiovascular disease (CVD) over and above mean BP. Conflicting results from previous studies reflect heterogeneity of approach and failure to consider confounders. We systematically reviewed studies quantifying the associations of long (clinic), mid- (home) and short term (ambulatory) BP variability, independent of mean BP, with CVD events and mortality.

Data Sources: Medline, Embase, Cinahl and Web of Science were searched to 15th February 2016 for full text articles in English.

Eligibility criteria for selecting studies: Prospective cohort studies or clinical trials in adults were included, except those in haemodialysis patients, where the condition may directly impact BP variability. Standardized hazard ratios were extracted and, if there was little risk of confounding, combined using random effects meta-analysis in main analyses. Outcomes included all-cause and CVD mortality and CVD events. Measures of variability included standard deviation, coefficient of variation, variation independent of mean and average real variability but not night dipping or day-night variation.

Results: Forty-one papers representing nineteen observational cohort studies and seventeen clinical trial cohorts, and forty-six separate analyses were identified. Clinic, home and ambulatory BP variability was studied in twenty-four, four and fifteen papers respectively (two studied both clinic and ambulatory variability). Results from twenty-three analyses were excluded from main analyses due to high risks of confounding. Increased long-term variability in clinic systolic BP was associated with risk of all-cause mortality (HR=1.15, 95% CI [1.09 to 1.22]), CVD mortality (HR=1.18, 95% CI [1.09 to 1.28]), CVD events (HR=1.18, 95% CI [1.07 to 1.30]), coronary heart disease (HR=1.10, 95% CI [1.04 to 1.16]) and stroke (HR=1.15, 95% CI [1.04 to 1.27]). Increased mid-term (home) systolic BP variability and short-term daytime systolic BP variability were also associated with all-cause mortality (HR=1.15, 95% CI [1.06 to 1.26] and HR=1.10 95% CI [1.04 to 1.16]).

Conclusions: Long-term clinic BP variability is associated with cardiovascular and mortality outcomes, over and above the effect of mean BP. Associations are similar in magnitude to those of cholesterol measures with CVD. Limited data for home/ ambulatory variability showed similar associations. Future work should focus on the clinical implications of BP variability assessment and avoid the common confounding pitfalls observed to date.

Systematic review registration: PROSPERO ID: CRD42014015695.

Print abstract

Study question: We reviewed the literature to determine if long (clinic), mid- (home) and short term (ambulatory) blood pressure (BP) variability are associated with cardiovascular and mortality outcomes, independent of mean BP.

Methods: Databases were searched to 15th February 2016 for prospective cohort studies or clinical trials in adults with at least 2500 person-years follow-up. Standardized hazard ratios were extracted and, if there was little evidence risk of confounding, combined using random effects meta-analysis. Outcomes included all-cause and cardiovascular mortality and cardiovascular events. Measures of variability included standard deviation, coefficient of variation, variation independent of mean and average real variability.

Study answer and limitations: Methodological errors are present in approximately half of prospective studies of BP variability. When considering good quality studies only, long-term clinic BP variability is associated with cardiovascular and mortality outcomes, over and above the effect of mean BP. Associations are similar in magnitude to those of cholesterol measures with cardiovascular disease. Limited data for home/ ambulatory BP variability showed similar associations.

What this study adds: This is the first review to compare the evidence of an association of long, mid- and short-term BP variability with cardiovascular outcomes. It is the first review to consider the methodological flaws of previous studies, showing that the association of long term (clinic) blood pressure variability with future cardiovascular disease is found even in studies that avoid errors.

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Study registration: PROSPERO ID: CRD42014015695.

Summary box

What is already known on this topic

- It is well-established that patients with high blood pressure are at higher risk of future cardiovascular disease.
- Some studies have also suggested that patients with higher variability in blood pressure over time are at higher risk than patients with the same mean level of blood pressure.
- It is not clear whether this risk depends on the method of measurement of variability and few have correctly accounted for mean blood pressure or changes in treatment.

What this study adds

- Methodological errors are present in approximately half of prospective studies of blood pressure variability but the association of long term (clinic) blood pressure variability with future cardiovascular disease is found even in studies that avoid errors.
- Mid- and short term blood pressure variability measured at home or by ambulatory monitoring has been little studied comparatively, but shows similar associations with outcomes.

Introduction

Blood pressure is a leading risk factor for cardiovascular disease.[1,2] Most studies have used mean blood pressure (BP) as the indicator of risk, measured in clinic or "out of office" settings.[3–5] However, BP shows marked oscillations over the short and long term.[6] Historically, variability has been viewed as inhibiting accurate measurement of mean BP and as a phenomenon to be overcome by improved monitoring.[7] BP variability has also been recognised as a potential risk factor in its own right for at least two decades.[8,9] In 2010 an analysis of three cohort studies and two randomized trials found that long-term BP variability was a predictor of stroke and coronary events in high risk patients.[10]

However, understanding BP variability has been hampered by statistical and clinical methodological issues. Some studies of variability have not adjusted for mean BP, potentially confounding high variability with high mean blood pressure.[11,12] Others, in using 24-hour mean to adjust for daytime variability, may have turned high daytime variability into a surrogate marker for nocturnal or 24-hour BP.[13] Further studies have defined variability on the basis of measurements taken during follow-up, but analysed it as a baseline risk factor,[14–16] potentially introducing problems of informative censoring or immortal time bias.[17] Informative censoring occurs when reasons for loss to follow-up are confounded with the exposure (e.g. if individuals with extreme or erratic BP are withdrawn from studies due to safety concerns). Immortal time bias can occur if individuals are required to have a certain number of BP measurements in order to be included in analysis for mortality outcomes. The time up until their qualifying measurement becomes 'immortal time' since, by definition, death could not occur earlier.

Other studies fail to use consistent BP monitoring equipment over time, to define a consistent BP measurement protocol or to account for medication change, leaving doubt as to the source of any observed variability.[14,18,19] Measurement at different times of the day[20] or year,[21] in different arms,[22] or using inconsistent cuff sizes[23] can affect accurate measurement, thereby

inducing variability. We reviewed prospective studies that quantified the associations of BP variability with cardiovascular events and mortality, independent of mean BP, in adults. Our main analysis focused on studies meeting pre-specified methodological criteria, so that any apparent effect of BP variability was likely to be a true independent effect.

Methods

The protocol for this review has been published (http://www.crd.york.ac.uk/PROSPERO/, PROSPERO ID: CRD42014015695).

Study selection

Medline, Embase, Cinahl and Web of Science were searched to 15th February 2016 for full text articles in English, describing trials and prospective cohort studies, which assessed the association of (i) long term variability measured through clinic BP monitoring, (ii) mid- term variability measured through home BP monitoring and (iii) short term variability measured through ambulatory BP monitoring with cardiovascular outcomes in adults (Supplement, Table e1). Studies included in recent systematic reviews,[24–27] were also screened. Titles and abstracts were scrutinised by two reviewers (SW/SS and KL/KC) with adjudication by a third (RM).

Inclusion and exclusion criteria

Studies had to consider at least one of the following outcomes: (i) all-cause mortality, (ii) cardiovascular events (including stroke, myocardial infarction, coronary heart disease, and heart failure) or (iii) cardiovascular mortality (including sudden death). Studies assessing intermediate outcomes only (e.g. “arterial intima-media” thickness) or concerning “nocturnal dipping” or “day-night variation” were excluded, since these have been considered previously.[28]

Studies in disease specific populations (e.g. diabetes) were included, except those in haemodialysis patients where changes in BP (intradialysis hypo- and hypertension[29,30]) are common and have been shown to be associated with hospitalisation and mortality.[31,32]

Included studies had at least 2500 person-years of follow-up. BP variability was assessed in the long, mid- or short term in clinics, at home or through ambulatory BP monitoring respectively. Studies of clinic monitoring had to measure visit-to-visit variability over at least five clinic visits.[10] Studies of home monitoring had to consider day-by-day variability over at least twelve measurements on at least three days.[33] For ambulatory, studies had to assess variability over up to 24-hours with at least fourteen daytime readings.[33]

Data extraction

Study and patient characteristics data were extracted independently by two reviewers (SS/SW and KL/RM), as were statistical results (SS and KC/RS) using pre-specified forms (Table e2). Hazard ratios (HRs) for every variability measure and outcome were extracted. The HR from the analysis with the greatest adjustment for confounders but containing only a single variability measure was extracted. Where required data were not available, this was requested by contacting the study authors by email.

Data analysis and statistical methods

Hazard ratios were converted to standardized HRs, using a general method for regression models (Table e3).[34] Briefly, a standardized log-HR was calculated as the log-HR per unit of standardized exposure (the exposure divided by its sample standard deviation). These were pooled using a random-effects meta-analysis, stratified by outcome. Separate analyses were performed for each

time period of variability (long, mid-, or short-term). Heterogeneity was assessed using the Chi-squared test and the I-squared statistic.

Where studies used multiple variability measures, HRs were included in analysis according to the following hierarchy (preferred to least preferred): standard deviation (SD), coefficient of variation (CV), variation independent of mean (VIM), average real variability (ARV), standardised residual (SR), root successive variance (RSV) and other. Where HRs were calculated using data from the same primary study but reported in different papers, the most recently published HR was included. Hazard ratios for study subgroups were combined before inclusion.

Risk of bias was assessed using the QUIPS tool[35] by two independent reviewers (SS and RS), with adjudication by a third (RM). Information about other potential confounders, specific to studies of variability were also extracted (Table e2, indicated by *). Consistency of BP measurement with respect to device, cuff size, personnel and measurement is important to prevent inducing variability. The impact of other potential confounders may be adjusted for during analyses. We decided (a-priori) to include in main analyses only HRs which were correctly adjusted for the equivalent mean BP level (e.g. adjusted for mean systolic daytime BP if variability was assessed for daytime systolic BP), where outcome ascertainment took place after the BP measurement period and, for studies involving antihypertensive treatment, if at least 80% of patients were adherent to medication, did not change treatment during the measurement period or if patients were censored at the point of treatment change. We carried out secondary analyses including all studies.

Publication bias was assessed by Egger's test.[36] However, since this has low power for small numbers of studies, we also calculated of the number of null effect studies of mean weight that would need to be included in meta-analyses to result in a non-significant pooled effect (known as "failsafe N").[37]

Patient involvement

Two lay representatives contribute to the design and content of the NIHR Programme Grant from which this work arose. Results from this work will be presented as part of the wider programme at regular steering group meetings.

Results

Searches identified 5861 references. Removal of duplicates and screening by two reviewers yielded forty-one full-text articles for inclusion (Figure 1). These forty-one papers represented nineteen observational cohort studies and seventeen clinical trial cohorts, and forty-six separate analyses (Table e4). Twenty-four papers[10,14–16,18,19,38–55] studied long-term variability (i.e. of clinic BP), four[56–59] studied mid-term variability (home BP) and fifteen[10–13,41,60–69] studied short-term variability (ambulatory). The number of participants per study ranged from 457[41] to 58,228[53] and follow-up ranged from 2514 person-years[41] to 101,011 person-years.[61]

Study design and analysis characteristics

Consistency of BP measurement with respect to cuff size, arm, device and personnel was unclear or had the potential to introduce variability (e.g. mercury sphygmomanometers and changing personnel) in all of the thirty-six included studies (Table e5). Similarly, potential for confounding was introduced due to the analysis (or was unclear) in all forty-six separate analyses. Results from twenty-three analyses were excluded from our main analyses based on the three pre-specified criteria: eight analyses failed to correctly adjust for mean BP, fifteen did not account for significant medication change during the measurement period and twenty did not separate the measurement and follow-up periods. Results from 4 analyses (3 studies) were not reported in sufficient detail to allow data extraction.

QUIPS risk of bias

Using QUIPS, the majority of the forty-six analyses were rated at moderate risk of bias for study participation, often due to inclusion criteria based on BP readings and a potential for regression to

the mean effects (Table 6). Eighteen analyses were at high risk of bias because the measurement period for BP variability was confounded with follow-up (seventeen) and one[67] failed to report non-significant results. All of the analyses rated at high risk of bias using QUIPS were excluded from our main analysis based on the assessments in Table e5.

i) Long term variability measured through clinic BP monitoring

Twenty-four papers reported results from twenty-one studies that measured long-term BP variability in clinic. Results from three studies[44,48,52] were not presented in sufficient detail for extraction.

Eight studies examined long term systolic BP variability and all-cause mortality, of which four had sufficiently low risk of bias to be included in the main analysis (Figure 2, standardized HR = 1.15, 95% CI [1.09 to 1.22]). Heterogeneity between studies (I-squared = 70.7%, p=0.017), was reduced after removal of a study in patients with previous stroke or vascular disease[43]: this did not significantly alter results (HR = 1.12, 95% CI [1.08 to 1.16]; I-squared=34.9%, p=0.215).

Three studies assessing BP variability and CVD mortality showed a significant relationship (Figure e1, HR=1.18; 95 % CI [1.09 to 1.28]) but only a single study examining CVD events was suitable for inclusion (Figure e2, HR=1.18; 95% CI [1.07 to 1.30]).

Fourteen studies reported results for stroke events, of which six were included in the main analysis (Figure 3; HR = 1.15, 95% CI [1.04 to 1.27]; I-squared = 82.1%, p<0.001). Results were similar after removal of the HR from the UK-TIA trial[70] which removed the heterogeneity (HR=1.10, 95% CI [1.05 to 1.14]; I-squared=0.0%, p=0.618).

Results for CHD events and myocardial infarction showed similar results (Figures e3, e4). Across all outcomes, secondary analysis including results from all studies regardless of risk of bias did not alter results.

ii) Mid-term variability measured through home BP monitoring

Four papers reported results from two studies that measured mid-term variability in home BP. All four papers were of sufficient quality to be included in main analyses, but a lack of data from distinct studies meant it was only possible to perform formal meta-analysis for the all-cause mortality outcome. Systolic BP variability was a significant predictor of death when BP was measured in the morning, evening, or both (Figure 4, e.g. HR for increases in combined BP variability = 1.15, 95% CI [1.06 to 1.26]). Study level results for other outcomes are given in the online supplement (Table e7).

iii) Short term variability measured through ambulatory BP monitoring

Fifteen papers examined short-term variability in ambulatory BP in eleven distinct studies. We were unable to include results from many studies (Ohasama[13,56,57] and ULSAM[11]/ Ohasama,[13,56,57] Eguchi et al.,[41] Verdecchia et al.,[69] and Pierdomenico at al.[65–67]) due to overlap with two large studies (IDACO/ ABP-International) which combined results across cohorts.

Three studies examined daytime systolic BP variability and all-cause mortality of which two were included in the main analysis (Figure 5; HR per = 1.10, 95% CI [1.04 to 1.16]). Four studies examined daytime BP variability and CVD mortality and analysis of three studies with low risk of bias showed a significant association (Figure e5, HR = 1.12; 95% CI [1.03 to 1.21]). Daytime BP variability was also significantly associated with increased risk of stroke (Figure e6; HR = 1.11, 95% CI [1.01 to 1.21]). Results for all three outcomes were unchanged in secondary analysis including results from all studies.

No associations were found between BP variability and CVD (Figure e7) or CHD events (Figure e8), although results became significant in secondary analyses. Results for night-time and 24-hour systolic ambulatory BP are detailed in the online supplement (Figures e9 to e18).

Publication bias

There was no evidence of publication bias for any outcome in relation to clinic, home or ambulatory systolic BP variability as judged by Egger's test. Significant findings for clinic systolic BP variability would remain unchanged for all outcomes even if at least 20 null-effect studies were included in meta-analyses, except for myocardial infarction where only a single null-effect study would be required. Results for home BP variability would become non-significant after the addition of a single null-effect study and those for ambulatory BP variability would become non-significant by the addition of between 1 and 6 null effect studies, depending on outcome and period of measurement.

Discussion

Principle findings

This review has systematically assessed the literature for the association of long, mid- and short-term blood pressure variability with cardiovascular outcomes and mortality. Long-term variability in clinic BP measurements is significantly associated with all-cause and CVD mortality, CVD events, stroke and myocardial infarction, independent of mean BP. Mid- and short term variability are also associated with mortality and limited data for other outcomes also broadly support an association with cardiovascular outcomes. Across all analyses (clinic, home and ambulatory), the hazard ratios for coronary heart disease events were smaller than those for stroke, suggesting that the effect observed for CVD events – as with mean blood pressure - may be driven primarily by cerebrovascular events.

Strengths in relation to the literature

This review is the largest to date on this topic, including data from over 400,000 individuals, and is the first to combine results from long, mid- and short-term BP measurement allowing comparison. It is the first review to isolate studies addressing the methodological issues that are particular to variability research. We have shown that although there is now considerable evidence on this topic, the majority of studies are of poor quality and/or poorly reported. By limiting our main analysis to studies that avoid potential sources of confounding, this review confirms that the apparent prognostic value of BP variability is a true prospective association and can be demonstrated even in studies with low risk of bias.

This is the first review to use standardized hazard ratios to overcome the diversity of variability measures used in primary studies, and hence combine more data.[24,25] For example, our meta-analysis for long term variability and stroke events includes fourteen studies, more than double the number in previous analyses. This review also had sufficient data for meta-analysis of the effect of short term ambulatory BP variability on outcomes, which was a limitation of a previous work.[28]

Finally, this review is the first to demonstrate the robustness of results to unpublished null-effect studies across long, mid- and short-term BP variability. Whilst results for long-term BP variability may be considered conclusive, results for mid-and short-term variability are more susceptible to publication bias and may warrant further investigation.

Limitations

Included studies were primarily in older adults and those at elevated risk of CVD (e.g. due to hypertension) and conducted in European or East Asian populations. Hence the applicability of our findings to younger or healthier people and other ethnic groups is unknown. Studies in patients with a history of cerebrovascular events reported the largest HRs but significant associations remained after removal of these studies from analyses, and so findings remain applicable to those free from

cerebrovascular disease. In studies in hypertensive patients,[14,40,69] blood pressure variability could be confounded by entry criteria (regression-to-the-mean) and treatment.[71] However, such effects would diminish rather than exaggerate hazard ratios for variability, and so our overall conclusions are sound.

Lack of data from distinct cohorts prevented formal meta-analyses for many outcomes with respect to mid-term (home) BP variability. A previous review was similarly limited by paucity of data,[26] despite broader inclusion criteria. Our meta-analyses for short-term ambulatory BP variability were also dominated by two large studies. Despite these caveats, results supported an effect of shorter term variability on cardiovascular outcomes, and pooled hazard ratios were similar to those observed for long-term variability. We were unable to determine if findings varied with timing and frequency of measurement.

In several analyses, there was significant heterogeneity between studies, potentially due to outlying studies in specific populations (e.g. previous vascular disease) or to approximations necessary during data extraction, such as conversion from categorical (e.g. from deciles[10] or tertiles[49]) to continuous scale. However, not all converted hazard ratios were outliers,[13,65] and we verified our conversion method in simulated data (not shown). Significant heterogeneity could be reduced by removal of outlier studies but did not significantly alter the results.

In some cases, few studies contributed to main analyses and the validity of these meta-analyses is debateable. Secondary analysis utilising data from all studies regardless of quality greatly increased the amount of available data but did not materially change results. Only three[44,48,52] otherwise eligible studies failed to contribute any quantitative data, despite contact with authors.

In general, there was poor reporting of study factors that may confound the relationship between BP variability and outcomes. Although studies were excluded from main analyses based on the three most important factors (pre-specified) it was not feasible to do this for all factors. Further

adjustment for confounders might be possible using individual patient data but was beyond the scope of this review. The importance of consideration and reporting of such confounding factors in future work regarding BP variability (and variability in other biological measures) should be emphasized. Although our results indicate that these may be less important in the assessment of BP variability, they may prove instrumental in other clinical areas.

Clinical implications

The mechanism linking blood pressure variability to cardiovascular events is not well understood. Short term blood pressure variability is affected by behavioural, emotional and postural influences on cardiovascular physiology and cardiac rhythm.[72,73] Arterial stiffness contributes to both short[74,75] and long term variability.[73,76,77] Meanwhile poor control of blood pressure resulting in changes to antihypertensive medication also affects variability.[72] Use of certain classes of antihypertensive medication has also been linked with increased visit-to-visit variability[78] and may not be entirely explained by adherence.[79]

The estimated standardized hazard ratio for the effect of long term BP variability on CVD mortality was 1.18. For comparison, the effect of mean BP on CVD mortality reported in a previous meta-analysis[3] corresponds to a standardised hazard ratio of approximately 1.7 (assuming between-person standard deviation of 15 mmHg). Note that the latter standardized hazard ratio for mean BP is not adjusted for BP variability, whereas the former (for BP variability) is adjusted for mean, showing the additional prognostic value of variability over and above the mean. This supports the results of recent work demonstrating the improved discrimination of models including short-term night-time ambulatory BP variability[64] or long-term clinic BP variability[39], over and above traditional risk factors.

How does BP variability compare with other risk factors for CVD? A recent review[80] found that the standardized hazard ratio for increases in cholesterol on CVD events varied between 1.14 and 1.25 in

primary prevention groups, depending on the measure of cholesterol considered (total cholesterol, triglycerides etc.). Hence variability in BP has similar prognostic value to cholesterol measures (standardized HR for long term BP variability on CVD events=1.18).

BP variability is not easily assessed clinically, and it is unclear if certain measures of variability should be preferred. Some measures could be calculated by hand (e.g. ARV) but others could be automatically calculated by electronic health records. This would enable physicians to account for both BP mean and variability concurrently when assessing cardiovascular risk. For example, assuming a standard deviation of SD of SBP of 5 mmHg, an individual with variable BP readings (139, 132 and 125 mmHg, Mean = 132, SD = 7) could be considered at 18% greater risk of CVD events, compared to a similar person with stable BP (134, 130 and 132 mmHg, Mean=132, SD=2). This may be particularly important for patients with highly variable, but comparatively low mean BP or for whom traditional cardiovascular risk estimates lie close to treatment thresholds. Further work is needed to determine the feasibility of obtaining such additional information, and the clinical impact on subsequent risk management.

In summary long-term clinic BP variability in adults is associated with cardiovascular and mortality outcomes, over and above the effect of mean BP. Mid-term (home) and short-term (ambulatory) BP variability is also associated with all-cause mortality but the association with CVD outcomes requires further investigation in novel cohorts.

Contributors

SS, SW, RS, RM and PG helped to design the study. SS, SW, KL, KC and RM carried out article screening. SS, SW, KL, KC, RS and RM extracted data. SS, KC and RS carried out statistical analyses. SS drafted the original manuscript and all authors revised the paper. SS is the guarantor. The authors thank Derek Shaw and David Yeomans, patient representatives, for their contribution to the design and content of the NIHR Programme Grant from which this work arose.

Competing interest statement

All authors have completed the Unified Competing Interest form atwww.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: i) SS is funded by the National Institute for Health Research School for Primary Care Research (NIHR SPCR), ii) RM has received grants and personal fees from Omron and grants from Lloyds Pharmacy, outside the submitted work; PG reports grants from National Heart Foundation, Australia, outside the submitted work, iii) no other relationships or activities that could appear to have influenced the submitted work. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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Ethical approval

Not required for systematic review of existing studies.

Data sharing

Data extracted from the studies included in this review are available from the corresponding author on request.

Transparency

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained

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References

1 Lim SS, Vos T, Flaxman AD, *et al.* A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**:2224–60. doi:10.1016/S0140-6736(12)61766-8

2 Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;**338**:1245.

3 Lewington S, Clarke R, Qizilbash N, *et al.* Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**360**:1903–13.

4 Conen D, Bamberg F. Noninvasive 24-h ambulatory blood pressure and cardiovascular disease: A systematic review and meta-analysis. *J Hypertens* 2008;**26**:1290–9.

5 Ward AM, Takahashi O, Stevens R, *et al.* Home measurement of blood pressure and cardiovascular disease: Systematic review and meta-analysis of prospective studies. *J Hypertens* 2012;**30**:449–56.

6 Grassi G, Bombelli M, Brambilla G, *et al.* Total Cardiovascular Risk, Blood Pressure Variability and Adrenergic Overdrive in Hypertension: Evidence, Mechanisms and Clinical Implications - Springer. *Curr Hypertens Rep* 2012;**14**:333–8. doi:10.1007/s11906-012-0273-8

7 Takahashi O, Glasziou PP, Perera R, *et al.* Blood pressure re-screening for healthy adults: What is the best measure and interval. *J Hum Hypertens* 2012;**26**:540–6.

8 Frattola A, Parati G, Cuspidi C, *et al.* Prognostic value of 24-hour blood pressure variability. *J Hypertens* 1993;**11**:1133–7.

9 Grove JS, Reed DM, Yano K, *et al.* Variability in systolic blood pressure - A risk factor for coronary heart disease? *Am J Epidemiol* 1997;**145**:771–6.

10 Rothwell PM, Howard SC, Dolan E, *et al.* Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010;**375**:895–905. doi:10.1016/S0140-6736(10)60308-X

11 Bjorkland K, Lind L, Berglund L, *et al.* Prognostic significance of 24-h ambulatory blood pressure characteristics for cardiovascular morbidity in a population of elderly men. *J Hypertens* 2004;**22**:1691–7.

12 Gavish B, Ben-Dov IZ, Kark JD, *et al.* The association of a simple blood pressure-independent parameter derived from ambulatory blood pressure variability with short-term mortality. *Hypertens Res* 2009;**32**:488–95. doi:10.1038/hr.2009.39

13 Kikuya M, Hozawa a., Ohokubo T, *et al.* Prognostic Significance of Blood Pressure and Heart Rate Variabilities : The Ohasama Study. *Hypertension* 2000;**36**:901–6. doi:10.1161/01.HYP.36.5.901

14 Kawai T, Ohishi M, Ito N, *et al.* Alteration of vascular function is an important factor in the correlation between visit-to-visit blood pressure variability and cardiovascular disease. *J Hypertens* 2013;**31**:1387–95; discussion 1395. doi:10.1097/HJH.0b013e328360f796

15 Gao S, Hendrie HC, Wang C, *et al.* Redefined blood pressure variability measure and its association with mortality in elderly primary care patients. *Hypertension* 2014;**64**:45–52. doi:10.1161/HYPERTENSIONAHA.114.03576

16 Lau K-K, Wong Y-K, Teo K-C, *et al.* Long-term prognostic implications of visit-to-visit blood pressure variability in patients with ischemic stroke. *Am J Hypertens* 2014;**27**:1486–94. doi:10.1093/ajh/hpu070

17 Lévesque LE, Hanley JA, Kezouh A, *et al.* Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ* 2010;**340**:b5087. doi:10.1136/bmj.b5087

18 Suchy-Dicey AM, Wallace ER, Mitchell SVE, *et al.* Blood pressure variability and the risk of all-cause mortality, incident myocardial infarction, and incident stroke in the cardiovascular health study. *Am J Hypertens* 2013;**26**:1210–7. doi:10.1093/ajh/hpt092

19 Wei Y, Jin Z, Shen G, *et al.* Effects of intensive antihypertensive treatment on Chinese hypertensive patients older than 70 years. *J Clin Hypertens (Greenwich)* 2013;**15**:420–7. doi:10.1111/jch.12094

20 Pickering TG, Harshfield G a, Kleinert HD, *et al.* Blood pressure during normal daily activities, sleep, and exercise. Comparison of values in normal and hypertensive subjects. *JAMA* 1982;**247**:992–6. doi:10.1001/jama.247.7.992

21 Modesti PA, Morabito M, Bertolozzi I, *et al.* Weather-related changes in 24-hour blood pressure profile: effects of age and implications for hypertension management. *Hypertension* 2006;**47**:155–61. doi:10.1161/01.HYP.0000199192.17126.d4

22 Lane D, Beevers M, Barnes N, *et al.* Inter-arm differences in blood pressure: when are they clinically significant? *J Hypertens* 2002;**20**:1089–95.

23 Linfors EW. Spurious Hypertension in the Obese Patient. *Arch Intern Med* 1984;**144**:1482. doi:10.1001/archinte.1984.00350190188032

24 Diaz KM, Tanner RM, Falzon L, *et al.* Visit-to-Visit Variability of Blood Pressure and Cardiovascular Disease and All-Cause Mortality: A Systematic Review and Meta-Analysis. *Hypertension* 2014;**64**:965–82. doi:10.1161/HYPERTENSIONAHA.114.03903

25 Tai C, Sun Y, Dai N, *et al.* Prognostic significance of visit-to-visit systolic blood pressure variability: a meta-analysis of 77,299 patients. *J Clin Hypertens (Greenwich)* 2015;**17**:107–15. doi:10.1111/jch.12484

26 Stergiou GS, Ntineri A, Kollias A, *et al.* Blood pressure variability assessed by home measurements: a systematic review. *Hypertens Res* 2014;**37**:565–72. doi:10.1038/hr.2014.2

27 Manning LS, Rothwell PM, Potter JF, *et al.* Prognostic Significance of Short-Term Blood Pressure Variability in Acute Stroke: Systematic Review. *Stroke* 2015;**46**:2482–90. doi:10.1161/STROKEAHA.115.010075

28 Taylor KS, Heneghan CJ, Stevens RJ, *et al.* Heterogeneity of Prognostic Studies of 24-hour Blood Pressure Variability: Systematic Review and Meta-Analysis. *PLoS One* 2015;**10**:e0126375. doi:10.1371/journal.pone.0126375

29 Daugirdas JT. Pathophysiology of dialysis hypotension: An update. *Am J Kidney Dis* 2001;**38**:S11–7. doi:10.1053/ajkd.2001.28090

30 Inrig JK. Intradialytic hypertension: a less-recognized cardiovascular complication of hemodialysis. *Am J Kidney Dis* 2010;**55**:580–9. doi:10.1053/j.ajkd.2009.08.013

31 Inrig JK, Oddone EZ, Hasselblad V, *et al.* Association of intradialytic blood pressure changes with hospitalization and mortality rates in prevalent ESRD patients. *Kidney Int* 2007;**71**:454–61. doi:10.1038/sj.ki.5002077

32 Inrig JK, Patel UD, Toto RD, *et al.* Association of blood pressure increases during hemodialysis with 2-year mortality in incident hemodialysis patients: a secondary analysis of the Dialysis Morbidity and Mortality Wave 2 Study. *Am J Kidney Dis* 2009;**54**:881–90. doi:10.1053/j.ajkd.2009.05.012

33 National Institute for Health and Care Excellence. Hypertension: Clinical management of primary hypertension in adults (NICE CG127). National Institute for Health and Care Excellence 2011.

34 Bring J. How to Standardize Regression Coefficients. *Am Stat* 1994;**48**:209–13.

35 Hayden JA, van der Windt DA, Cartwright JL, *et al.* Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;**158**:280–6. doi:10.7326/0003-4819-158-4-201302190-00009

36 Egger M, Smith GD, Schneider M, *et al.* Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34. doi:10.1136/bmj.315.7109.629

37 Rosenberg MS. The file-drawer problem revisited: A general weighted method for calculating-safe numbers in meta-analysis. *Evolution (N Y)* 2005;**59**:464–8. doi:10.1111/j.0014-3820.2005.tb01004.x

38 Arashi H, Ogawa H, Yamaguchi JI, *et al.* Impact of Visit-to-Visit Variability and Systolic Blood Pressure Control on Subsequent Outcomes in Hypertensive Patients

With Coronary Artery Disease (from the HIJ-CREATE Substudy). *Am J Cardiol* 2015;**116**:236–42. doi:10.1016/j.amjcard.2015.04.011

39 Blacher J, Safar ME, Ly C, *et al.* Blood pressure variability: cardiovascular risk integrator or independent risk factor? *J Hum Hypertens* 2015;**29**:122–6. doi:10.1038/jhh.2014.44

40 Carr MJ, Bao Y, Pan J, *et al.* The predictive ability of blood pressure in elderly trial patients. *J Hypertens* 2012;**30**:1725–33.

41 Eguchi K, Hoshide S, Schwartz JE, *et al.* Visit-to-visit and ambulatory blood pressure variability as predictors of incident cardiovascular events in patients with hypertension. *Am J Hypertens* 2012;**25**:962–8.

42 Hara A, Thijs L, Asayama K, *et al.* Randomised double-blind comparison of placebo and active drugs for effects on risks associated with blood pressure variability in the Systolic Hypertension in Europe trial. *PLoS One* 2014;**9**:e103169. doi:10.1371/journal.pone.0103169

43 Hata J, Arima H, Rothwell PM, *et al.* Effects of visit-to-visit variability in systolic blood pressure on macrovascular and microvascular complications in patients with type 2 diabetes mellitus: The advance trial. *Circulation* 2013;**128**:1325–34. doi:10.1161/CIRCULATIONAHA.113.002717

44 Hsieh Y-T, Tu S-T, Cho T-J, *et al.* Visit-to-visit variability in blood pressure strongly predicts all-cause mortality in patients with type 2 diabetes: A 5·5-year prospective analysis. *Eur J Clin Invest* 2012;**42**:245–53.

45 Kostis JB, Sedjro JE, Cabrera J, *et al.* Visit-to-visit blood pressure variability and cardiovascular death in the Systolic Hypertension in the Elderly Program. *J Clin Hypertens (Greenwich)* 2014;**16**:34–40. doi:10.1111/jch.12230

46 Lau KK, Wong YK, Chan YH, *et al.* Visit-to-visit blood pressure variability as a prognostic marker in patients with cardiovascular and cerebrovascular diseases - Relationships and comparisons with vascular markers of atherosclerosis. *Atherosclerosis* 2014;**235**:230–5. doi:10.1016/j.atherosclerosis.2014.04.015

47 Mallamaci F, Minutolo R, Leonardis D, *et al.* Long-term visit-to-visit office blood pressure variability increases the risk of adverse cardiovascular outcomes in patients with chronic kidney disease. *Kidney Int* 2013;**84**:381–9. doi:10.1038/ki.2013.132

48 Mancia G, Facchetti R, Parati G, *et al.* Visit-to-visit blood pressure variability in the European Lacidipine Study on Atherosclerosis: Methodological aspects and effects of antihypertensive treatment. *J Hypertens* 2012;**30**:1241–51.

49 McMullan CJ, Bakris GL, Phillips R a, *et al.* Association of BP variability with mortality among African Americans with CKD. *Clin J Am Soc Nephrol* 2013;**8**:731–8. doi:10.2215/CJN.10131012

50 Muntner P, Whittle J, Lynch AI, *et al.* Visit-to-Visit Variability of Blood Pressure and Coronary Heart Disease, Stroke, Heart Failure, and Mortality. *Ann Intern Med* 2015;**163**:329. doi:10.7326/M14-2803

51 Poortvliet RKE, Ford I, Lloyd SM, *et al.* Blood Pressure Variability and Cardiovascular Risk in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). *PLoS One* 2012;**7**.

52 Rossignol P, Girerd N, Gregory D, *et al.* Increased visit-to-visit blood pressure variability is associated with worse cardiovascular outcomes in low ejection fraction heart failure patients: Insights from the HEAAL study. *Int J Cardiol* 2015;**187**:183–9. doi:10.1016/j.ijcard.2015.03.169

53 Shimbo D, Newman JD, Aragaki AK, *et al.* Association between annual visit-to-visit blood pressure variability and stroke in postmenopausal women: Data from the Women's health initiative. *Hypertension* 2012;**60**:625–30.

54 Yu J, Kong Q, Schoenhagen P, *et al.* The prognostic value of long-term visit-to-visit blood pressure variability on stroke in real-world practice: A dynamic cohort study in a large representative sample of Chinese hypertensive population. *Int J Cardiol* 2014;**177**:995–1000. doi:10.1016/j.ijcard.2014.09.149

55 Rakugi H, Ogihara T, Saruta T, *et al.* Preferable effects of olmesartan/calcium channel blocker to olmesartan/diuretic on blood pressure variability in very elderly hypertension. *J Hypertens* 2015;**33**:2165–72. doi:10.1097/HJH.0000000000000668

56 Asayama K, Kikuya M, Schutte R, *et al.* Home blood pressure variability as cardiovascular risk factor in the population of ohasama. *Hypertension* 2013;**61**:61–9. doi:10.1161/HYPERTENSIONAHA.111.00138

57 Hashimoto T, Kikuya M, Ohkubo T, *et al.* Home blood pressure level, blood pressure variability, smoking, and stroke risk in Japanese men: the Ohasama study. *Am J Hypertens* 2012;**25**:883–91.

58 Johansson JK, Niiranen TJ, Puukka PJ, *et al.* Prognostic value of the variability in home-measured blood pressure and heart rate: the Finn-Home Study. *Hypertension* 2012;**59**:212–8. doi:10.1161/HYPERTENSIONAHA.111.178657

59 Kikuya M, Ohkubo T, Metoki H, *et al.* Day-by-day variability of blood pressure and heart rate at home as a novel predictor of prognosis: the Ohasama study. *Hypertension* 2008;**52**:1045–50.

60 Gavish B, Bursztyn M. Blood pressure and heart period variability ratios derived from 24-h ambulatory measurements are predictors of all-cause mortality. *J Hypertens* 2015;**33**:491–8. doi:10.1097/HJH.0000000000000459

61 Hansen TW, Thijs L, Li Y, *et al.* Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. *Hypertension* 2010;**55**:1049–57. doi:10.1161/HYPERTENSIONAHA.109.140798

62 Mancia G, Bombelli M, Facchetti R, *et al.* Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. *Hypertension* 2007;**49**:1265–70. doi:10.1161/HYPERTENSIONAHA.107.088708

63 Mena LJ, Maestre GE, Hansen TW, *et al.* How many measurements are needed to estimate blood pressure variability without loss of prognostic information? *Am J Hypertens* 2014;**27**:46–55. doi:10.1093/ajh/hpt142

64 Palatini P, Reboldi G, Beilin LJ, *et al.* Added predictive value of night-time blood pressure variability for cardiovascular events and mortality: the Ambulatory Blood Pressure-International Study. *Hypertension* 2014;**64**:487–93. doi:10.1161/HYPERTENSIONAHA.114.03694

65 Pierdomenico SD, Di Nicola M, Esposito AL, *et al.* Prognostic value of different indices of blood pressure variability in hypertensive patients. *Am J Hypertens* 2009;**22**:842–7. doi:10.1038/ajh.2009.103

66 Pierdomenico SD, Lapenna D, Di Tommaso R, *et al.* Blood pressure variability and cardiovascular risk in treated hypertensive patients. *Am J Hypertens* 2006;**19**:991–7.

67 Pierdomenico SD, Lapenna D, Bucci A, *et al.* Blood pressure variability and prognosis in uncomplicated mild hypertension. *Am Heart J* 2005;**149**:934–8. doi:10.1016/j.ahj.2004.06.029

68 Pringle E, Phillips C, Thijs L, *et al.* Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. *J Hypertens* 2003;**21**:2251–7.

69 Verdecchia P, Angeli F, Gattobigio R, *et al.* Impact of blood pressure variability on cardiac and cerebrovascular complications in hypertension. *Am J Hypertens* 2007;**20**:154–61. doi:10.1016/j.amjhyper.2006.07.017

70 Farrell B, Godwin J, Richards S, *et al.* The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry* 1991;**54**:1044–54.

71 Yudkin PL, Stratton IM. How to deal with regression to the mean in intervention studies. *Lancet* 1996;**347**:241–3. doi:10.1016/S0140-6736(96)90410-9

72 Parati G, Ochoa JE, Lombardi C, *et al.* Assessment and management of blood-pressure variability. *Nat Rev Cardiol* 2013;**10**:143–55. doi:10.1038/nrcardio.2013.1

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

74 García-García Á, García-Ortiz L, Recio-Rodríguez JI, *et al.* Relationship of 24-h blood pressure variability with vascular structure and function in hypertensive patients. *Blood Press Monit* 2013;**18**:101–6. doi:10.1097/MBP.0b013e32835ebc58

75 Schillaci G, Bilo G, Pucci G, *et al.* Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: findings from 2 large databases. *Hypertension* 2012;**60**:369–77. doi:10.1161/HYPERTENSIONAHA.112.197491

76 Nagai M, Hoshide S, Ishikawa J, *et al.* Visit-to-visit blood pressure variations: new independent determinants for carotid artery measures in the elderly at high risk of cardiovascular disease. *J Am Soc Hypertens* 2011;**5**:184–92. doi:10.1016/j.jash.2011.03.001

77 Okada H, Fukui M, Tanaka M, *et al.* Visit-to-visit variability in systolic blood pressure is correlated with diabetic nephropathy and atherosclerosis in patients with type 2 diabetes. *Atherosclerosis* 2012;**220**:155–9. doi:10.1016/j.atherosclerosis.2011.10.033

78 Webb AJ, Fischer U, Mehta Z, *et al.* Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet* 2010;**375**:906–15.

79 Muntner P, Levitan EB, Joyce C, *et al.* Association Between Antihypertensive Medication Adherence and Visit-to-Visit Variability of Blood Pressure. *J Clin Hypertens* 2013;**15**:112–7.

80 Perera R, Clarke P, Farmer A, *et al.* Optimal strategies for monitoring lipid levels in patients at risk or with cardiovascular disease: best marker for monitoring and cost-effectiveness of different monitoring frequencies. *Health Technol Assess (Rockv)* 2015;**19**.

Figure 1: Study screening flowchart

Figure 2: Random effects meta-analysis of standardized hazard ratios (HRs) for increases in clinic systolic blood pressure (BP) variability and all-cause mortality

Legend: SD: Standard deviation, SR: Standardized residual, CV: Coefficient of variation, VIM: Variation independent of the mean, RMSE: Root mean squared error.

Figure 3: Random effects meta-analysis of standardized hazard ratios (HRs) for increases in clinic systolic blood pressure (BP) variability and stroke events

Legend: SD: Standard deviation, SR: Standardized residual, CV: Coefficient of variation, VIM: Variation independent of the mean, RMSE: Root mean squared error.

Figure 4: Random effects meta-analysis of standardized hazard ratios (HRs) for increases in home systolic blood pressure (BP) variability and all-cause mortality

Legend: SD: Standard deviation, VIM: Variation independent of the mean.

Figure 5: Random effects meta-analysis of standardized hazard ratios (HRs) for increases in ambulatory systolic blood pressure (BP) variability and all-cause mortality

Legend: ARV: Average real variability, SD: Standard deviation.