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VISIT-TO-VISIT VARIABILITY OF BLOOD PRESSURE AND CARDIOVASCULAR DISEASE AND ALL-CAUSE MORTALITY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Keith M. Diaz, **Rikki M. Tanner**, **Louise Falzon**, **Emily B. Levitan**, **Kristi Reynolds**, **Daichi Shimbo**, and **Paul Muntner**
Department of Medicine, Columbia University Medical Center, New York, NY (K.M.D., L.F., D.S.); Department of Epidemiology, University of Alabama at Birmingham, Birmingham, A.L. (R.M.T., E.B.L., P.M.); Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA (K.R.)

Abstract

Visit-to-visit variability (VVV) of blood pressure (BP) has been associated with cardiovascular disease (CVD) and mortality in some but not all studies. We conducted a systematic review and meta-analysis to examine the association between VVV of BP and CVD and all-cause mortality. Medical databases were searched through June 4, 2014 for studies meeting the following eligibility criteria: adult participants; BP measurements at ≥3 visits; follow-up for CVD, coronary heart disease (CHD), stroke, or mortality outcomes; events confirmed via database, death certificate, and/or event ascertainment committee; and adjustment for confounders. Data were extracted by two reviewers and pooled using a random-effects model. Overall, 8,870 abstracts were identified of which 37 studies, representing 41 separate cohorts, met inclusion criteria. Across studies, VVV of systolic BP (SBP) and diastolic BP showed significant associations with outcomes in 181 of 312 (58.0%) and 61 of 188 (32.4%) analyses, respectively. Few studies provided sufficient data for pooling risk estimates. For each 5 mmHg higher SD of SBP, the pooled hazard ratios for stroke across seven cohorts was 1.17 (95% CI:1.07–1.28), for CHD across four cohorts was 1.27 (95% CI:1.07–1.51), for CVD across five cohorts was 1.12 (95% CI:0.98–1.28), for CVD mortality across five cohorts was 1.22 (95% CI:1.09–1.35), and for all-cause mortality across four cohorts was 1.20 (95% CI:1.05–1.36). In summary, modest associations between VVV of BP and CVD and all-cause mortality are present in published studies. However, these findings are limited by the small amount of data available for meta-analysis.

Keywords

blood pressure; blood pressure variability; cardiovascular disease; mortality; systematic review; meta-analysis

Correspondence: Keith M. Diaz, Columbia University Medical Center, 622 West 168th Street, PH9-319, New York, NY 10032, Phone: 212-304-5231, Fax: 212-305-3172, kd2442@columbia.edu.

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INTRODUCTION

In many individuals, blood pressure (BP) varies between clinic visits conducted days, weeks, or months apart. Although long thought to be artifact, recent data suggest that visit-to-visit variability (VVV) of BP is associated with an increased risk for incident coronary heart disease (CHD), stroke, and mortality, independent of mean BP.[1–3] Most noteworthy was a series of publications in *Lancet* and *Lancet Neurology* in 2010 by Rothwell and colleagues who showed that VVV of BP was a strong risk factor for stroke, independent of mean BP.[3–5] These publications stimulated a great deal of interest in VVV of BP as a novel risk factor for cardiovascular disease (CVD). More recent findings, however, have yielded mixed results regarding the association between VVV of BP and risk for future cardiovascular events.[6,7] Given the uncertainty of the association between VVV of BP and CVD risk, we conducted a systematic review and meta-analysis. Our primary objective was to document the association between VVV of BP and CVD, including stroke and CHD, and all-cause mortality. Our secondary objective was to document the methodology (e.g., number of visits, time interval between visits, etc.) used to estimate VVV of BP in published studies.

METHODS

Search Strategy and Selection Criteria

Studies were included if they met the following criteria: (1) adult participants aged 18 years and over, (2) measurement of BP at three or more visits on different days, (3) follow-up for outcomes of incident CVD, CHD, stroke, or mortality, (4) events confirmed via database, death certificate, and/or event ascertainment committee, and (5) adjustment for confounders undertaken in the design or analysis stages of the study. We excluded studies that only assessed BP variability via ambulatory monitoring, did not use a comparison or referent group, or that were reported exclusively in letters to the editor, commentaries, meeting abstracts, editorials, or review articles. There was no restriction on language.

The following databases were searched through June 4, 2014: MEDLINE, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, ProQuest Dissertations & Theses (PQDT), and ClinicalTrials.gov. The MEDLINE search strategy is described in the online-only Data Supplement. Terms for the other databases were adapted accordingly. To supplement the database searches, a PubMed related articles search and a cited reference search through ISI Web of Science were conducted using the included articles identified from the first set of search results. A manual search was also performed using the reference lists from the included articles and the reference lists from review articles produced by the electronic database searches.

Two investigators (KMD and RMT) independently reviewed all identified articles for eligibility using the above criteria. The title and abstract of identified articles were reviewed and those deemed ineligible were excluded. The full-text for the remainder of articles were retrieved and reviewed. Discrepancies on whether to include a study were resolved by discussion including a third investigator (PM).

Data Extraction

Data were abstracted from all articles by two separate investigators (KMD and RMT), independently, using a standardized instrument. Study characteristics (cohort name, sample size, population characteristics, country of origin, outcomes, and follow-up period), VVV measurement methodology (number of visits used to derive VVV, number of BP readings taken at each visit, time interval between visits, BP measurement device, BP indexes assessed, VVV metrics quantified, and whether VVV was analyzed as a continuous and/or categorical variable), and results (e.g., hazard ratios) from fully adjusted models were abstracted for the overall study population and for all subgroups reported. The quality of data abstraction was controlled by comparing the forms of the data abstractors. Discrepancies in data abstraction were resolved by discussion and by a third investigator (PM), when needed. When potentially relevant data were not reported, two attempts were made to contact the corresponding author via email. Any data that were not reported in the full-text and were not provided by the corresponding author are described as "not reported" or "NR". For this manuscript we describe all included articles as "studies". As several studies reported results from multiple populations, the term "cohort" is used to describe each unique population. Finally, for many cohorts, the results from multiple analyses of VVV of SBP or VVV of DBP with an outcome were reported. Therefore, each result is referred to as an "analysis".

Statistical Analyses

Meta-analyses were conducted for VVV of SBP and VVV of DBP modeled as continuous variables. Analyses were restricted to cohorts in which VVV was quantified as the standard deviation (SD) of BP, the most commonly used VVV metric. Pooled hazard ratios (HR) and 95% confidence intervals (CI) were calculated per 5 mmHg higher SD of BP using a random-effects model. Tests for heterogeneity were not conducted because of the small amount of data available for pooling each outcome (range: 2 to 7 cohorts). Publication bias was assessed by funnel plots and with a regression asymmetry test[8] for measures of VVV of BP with >10 analyses (pooling all outcomes).[9] Data analyses were conducted using Stata V11 (Stata Inc., College Station, TX).

RESULTS

The original search identified 6,100 abstracts (Figure 1). Following review of the title and abstract, 6,002 abstracts were excluded. Of the 98 full-text articles retrieved, 42 were review articles, leaving 56 original articles. An additional 4 potentially relevant articles were identified from a manual search of the reference lists from the 42 review articles. Of the 60 original articles reviewed, 34 were excluded leaving 26 original articles. An additional 11 original articles were identified from 2,770 abstracts identified in a supplemental search of other sources (reference lists, related articles search, citations). In total, of the 8,870 abstracts retrieved and reviewed from the original and supplemental searches, 37 studies met the inclusion criteria for abstraction.[1–3,6,7,10–41]

Study Characteristics

The earliest study identified was published in 1983 with 28 studies (32 cohorts) published between 2010 and June 2014 (Table 1). Two studies reported data from multiple cohorts. The study by Rothwell et. al. analyzed data from four cohorts.[3] The study by Poortvliet et. al. reported results for cohorts at two different follow-up lengths: a short-term follow-up cohort (included countries: Ireland, Scotland, the Netherlands) and a long-term follow-up cohort that included the subset of individuals from Scotland.[31] Overall, the 37 included studies comprised 41 different cohorts. Cohort sample sizes ranged from 144 to 58,228 participants. Cohorts included general population/community-based samples (4 cohorts), elderly populations (5 cohorts), individuals with hypertension (11 studies), a history of stroke (5 cohorts), on hemodialysis (8 cohorts), with chronic kidney disease not on hemodialysis (3 cohorts), individuals with type 2 diabetes (4 cohort), and post-menopausal women (1 cohort). A number of countries were represented including populations exclusively from Australia, Hong Kong, Italy, Japan, Korea, Taiwan, the Netherlands, the U.K., and the U.S., as well as aggregated populations from a number of countries.

Visit-to-Visit Variability Metrics

The number of visits used to derive VVV ranged from 3 visits to 156 visits with 13 cohorts using the same number of visits for each participant (Table 2). The number of BP readings per visit was 1 measure (9 cohorts), 2 measures (19 cohorts), 3 measures (8 cohorts), varied (2 cohorts), or was not reported (3 cohorts). Across the cohorts, the time-interval between visits ranged from 2 days to 3–4 years. The time-interval between visits was uniform for 26 cohorts, varied for 13 cohorts, and was not reported for 2 cohorts. Among the included cohorts, 22 reported one measure of VVV (e.g., SD) and 8 reported two measures of VVV (e.g., SD and coefficient of variation [CV]). The remaining cohorts reported more than 2 VVV measures with six different measures of VVV reported for one cohort. The most common measures used to quantify VVV were SD (23 cohorts) and CV (21 cohorts). Nineteen other VVV measures were reported. VVV of SBP was reported in 37 cohorts, VVV of DBP was reported in 21 cohorts, VVV of MAP was reported in 2 cohorts, and VVV of PP was reported in 7 cohorts. VVV of SBP and VVV of DBP were both reported in 20 cohorts.

VVV of SBP and Outcomes

SD of SBP, modeled as a continuous variable, was associated with an increased risk for stroke in 3 of 9 analyses, stroke mortality in 0 of 1 analyses, CHD in 4 of 6 analyses, CHD mortality in 0 of 1 analyses, CVD in 3 of 8 analyses, CVD mortality in 5 of 9 analyses, all-cause mortality in 4 of 7 analyses, and a composite outcome of all-cause mortality/CVD in 1 of 1 analyses (Table 3, left panel). Modeled as a categorical variable, increased risk was present in the highest versus lowest SD of SBP category in the majority of analyses for stroke, CVD, CVD mortality, and all-cause mortality, but not stroke mortality, CHD, or CHD mortality (Table 4, left panel). Mean BP was included as a covariate in 22 of the 24 cohorts (91.7%) which examined SD of SBP and outcomes.

CV of SBP modeled as a continuous variable was associated with each outcome except stroke and CVD mortality in the majority of analyses (Table 3, right panel). Modeled as a

categorical variable, increased risk was present in the highest versus lowest category of CV of SBP in the majority of analyses for stroke, CVD, and all-cause mortality, but not stroke mortality, CHD, or CHD mortality (Table 4, right panel). Results for VVV of SBP using measures other than SD or CV modeled as a continuous variable are presented in Supplemental Table S1 and as categorical variable in Supplemental Table S2.

In total, 181 of 312 (58.0%) analyses showed a positive significant association between VVV of SBP and outcomes (Table 5). Results were similar after excluding studies among hemodialysis patients and studies that quantified VVV of SBP using visits separated by >1 year (Supplemental Table S3). At least one positive significant association was reported in 31 of the 37 cohorts that reported data for VVV of SBP. Meta-analyses of SD of SBP modeled as a continuous variable showed positive significant associations for stroke, CHD, CVD mortality, and all-cause mortality, but not CVD (Figure 2). Funnel plots and regression testing found no evidence of publication bias among the pooled studies for VVV of SBP (p=0.698).

VVV of DBP and Outcomes

SD of DBP was associated with outcomes in 5 of 19 analyses when modeled as a continuous variable (Supplemental Table S4, left panel) and in 12 of 38 analyses when modeled as a categorical variable (Supplemental Table S5, left panel). CV of DBP was associated with outcomes in 12 of 41 analyses (Supplemental Table S4, right panel and Supplemental Table S5, right panel). Results for VVV of DBP metrics other than SD or CV are provided in Supplemental Table S6 for continuous and Supplemental Table S7 for categorical analyses.

In total, 61 of 188 (32.4%) analyses showed a significant positive association between VVV of DBP and outcomes (Table 5). Results were similar after excluding studies among hemodialysis patients and studies that quantified VVV of DBP using visits separated by >1 year (Supplemental Table S3). At least one significant positive association was reported in 11 of the 21 cohorts that reported data for VVV of DBP. A significant negative association was reported in one cohort. Meta-analyses of SD of DBP modeled as a continuous variable showed significant associations for CHD and CVD mortality, but not stroke or all-cause mortality (Supplemental Figure S1).

VVV of PP, VVV of MAP, and Outcomes

Modeled as continuous or categorical variables, VVV of PP metrics (SD, CV, and other) were associated with increased risk in less than 50% of reported analyses (Supplemental Tables S8, S9, and S10). Only two studies evaluated VVV of MAP and outcomes (Supplemental Tables S11 and S12). In total, 10 of 34 (29.4%) analyses showed a significant association between VVV of PP and outcomes and 3 of 5 analyses showed a significant association between VVV of MAP and outcomes (Table 5). Summary results excluding studies among hemodialysis patients and studies that quantified VVV of PP or MAP using visits separated by >1 year are reported in Supplemental Table S3.

DISCUSSION

In this systematic review, we identified 41 cohorts that evaluated the association of VVV of BP with cardiovascular outcomes and/or all-cause mortality. A rigorous meta-analysis to summarize all published data was not possible because of the large heterogeneity in quantifying, defining and reporting VVV. Pooling the available data, statistically significant associations, albeit modest in magnitude, were observed between VVV of SBP and outcomes including stroke, CHD, CVD mortality, and all-cause mortality.

The vast majority of studies we identified reported an increased risk for outcomes with higher VVV of BP in at least one analysis. In many cases, the positive findings within a cohort were accompanied by additional analyses wherein no association was observed. For example, the study by Hastie et al. reported 104 different analyses wherein 24 of 52 (46.1%) analyses for VVV of SBP and 10 of 52 (19.2%) analyses for VVV of DBP showed significant associations with outcomes.[1] The mixed findings within studies underscores a need to more carefully consider negative results. Chance findings as a result of inflation of type I error rates with multiple analyses may also need more rigorous consideration. Nonetheless, the significant associations reported for many different outcomes (stroke, CHD, CVD, all-cause mortality) across many different populations (general population, chronic kidney disease, hypertension, diabetes, hemodialysis patients, etc.) suggests a potential role for VVV of BP as a CVD risk factor. It should be acknowledged that, given the rising and falling fluid volumes in hemodialysis patients, VVV of BP may be a different clinical entity in this population.

This review highlights a need for researchers to use standardized approaches when defining VVV of BP. The number of visits, time interval between visits, and the BP measurement protocols varied widely across studies. For example, the number of visits used to quantify VVV ranged from as few as 3 visits to as many as 156 visits and the time interval between visits ranged from 2 days to 3–4 years. It has been reported that VVV of BP is influenced by the number of visits used to calculate it, the time interval between visits, the BP measurement device, and the number of BP measurements per visit.[42,43] These factors may affect the VVV of BP – outcome associations observed between studies. It has thus been suggested that adjustments should be made for the number of visits used to calculate VVV of BP and the time-interval between visits.[42] Although VVV of BP was derived using the same number of visits for all participants in 13 cohorts and the same time-interval between visits in 26 cohorts, only 2 of the remaining cohorts[20,29] adjusted for these factors. Moreover, there was inadequate description of the methodology used to quantify VVV of BP for several cohorts as the number of visits used to quantify VVV of BP, the time interval between visits, and the number BP measurements per visits were not reported.

A standardized approach to calculating VVV of BP is also needed. A total of 21 different metrics were used to calculate VVV of BP, with many studies reporting multiple metrics. The reporting of multiple metrics has made it challenging to interpret evidence on the association of VVV of BP and outcomes. It has been reported that many of the metrics provide largely redundant information.[44] Therefore, future studies of VVV of BP may benefit from only reporting three metrics: a measure of variation around an individual's

mean BP (SD, CV or SD independent of the mean), a measure of change in BP over time (average real variability or successive variation), and a measure of spikes in BP (peak BP).

VVV of SBP was more often investigated and reported in comparison to VVV of DBP. However, both showed associations with adverse outcomes in the meta-analysis we conducted. Although sparingly studied, VVV of PP and VVV of MAP were also associated with CVD and all-cause mortality in some studies.[10,23,31] These data implicate VVV in all four BP indexes as having potential prognostic value. In the only study to analyze all four BP indexes, Hsieh et al showed VVV of SBP, DBP, and MAP, but not VVV of PP, to be associated with all-cause mortality. In contrast, VVV of PP was the only BP index associated with CVD mortality in this study. Future studies are, therefore, still needed to determine which BP index carries the greatest prognostic information.

Several limitations should be considered when interpreting our findings. First, because of the aforementioned methodological considerations, a meta-analysis including all 41 cohorts was not possible. Second, studies adjusted for different sets of confounders which could have contributed to the heterogeneity of results. Third, given the small number of studies available for pooling we could not perform meta-regression to evaluate factors associated with the heterogeneity of results across studies. Finally, the majority of studies included were secondary analyses of randomized controlled trials or observational studies. Methodological factors that influence VVV of BP (e.g., number of visits, time interval between visits) may have affected the VVV of BP to outcomes association that we report. Future studies using rigorous methodology should be conducted to provide a better assessment of the VVV of BP – outcome association and determine the clinical utility of measuring VVV of BP. As ambulatory BP is considered to have superior prognostic value to clinic BP,[45] another important area for future studies is to determine the clinical relevance of VVV of ambulatory BP.

PERSPECTIVES

In the current systematic review, an association between VVV of BP and CVD and mortality outcomes was present in some but not all studies. When data were available to pool, VVV of SBP was associated with a modest increased risk for stroke, CHD, CVD mortality, and all-cause mortality and VVV of DBP was associated with an increased risk for CHD and CVD mortality. The associations observed across a variety of populations suggest that VVV of BP may be a risk factor for CVD. However, the association between VVV of BP and outcomes that we report is limited by the various number of methodologies used to quantify VVV of BP. Thus, the clinical relevance of VVV of BP should be interpreted cautiously and is still unclear. Additional studies using standardized approaches for estimating VVV of BP are needed to clarify its prognostic value.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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NOVELTY AND SIGNIFICANCE

What is new?

This is the first study to systematically review and meta-analyze the published literature on the association between visit-to-visit variability (VVV) of blood pressure (BP) and health outcomes.

What is relevant?

Pooled estimates showed that VVV of BP was associated with a modest increased risk for cardiovascular disease and all-cause mortality. This finding, however, is limited by the small amount of available data to pool and lack of a standardized approach for estimating VVV of BP. Therefore, caution should be used in intepreting it's clinical relevance.

Summary

Data from published studies suggest that VVV of BP may be a novel cardiovscular risk factor. However, the modest associations from pooled estimates may limit its potential clinical relevance. Additional studies using standardized approaches for estimating VVV of BP are needed to clarfiy its prognositc value.

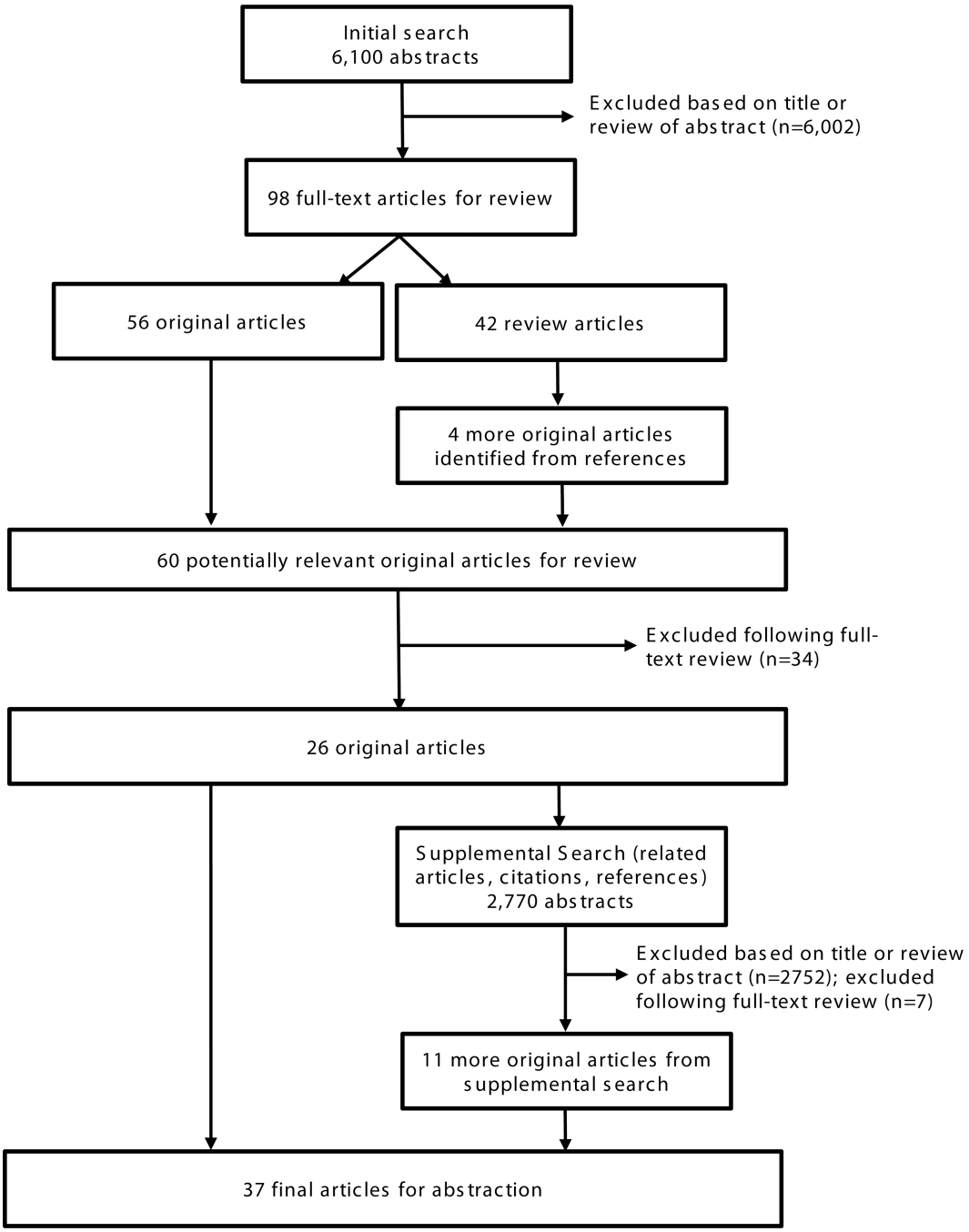

Figure 1.
Flow diagram of article selection for the systematic review.

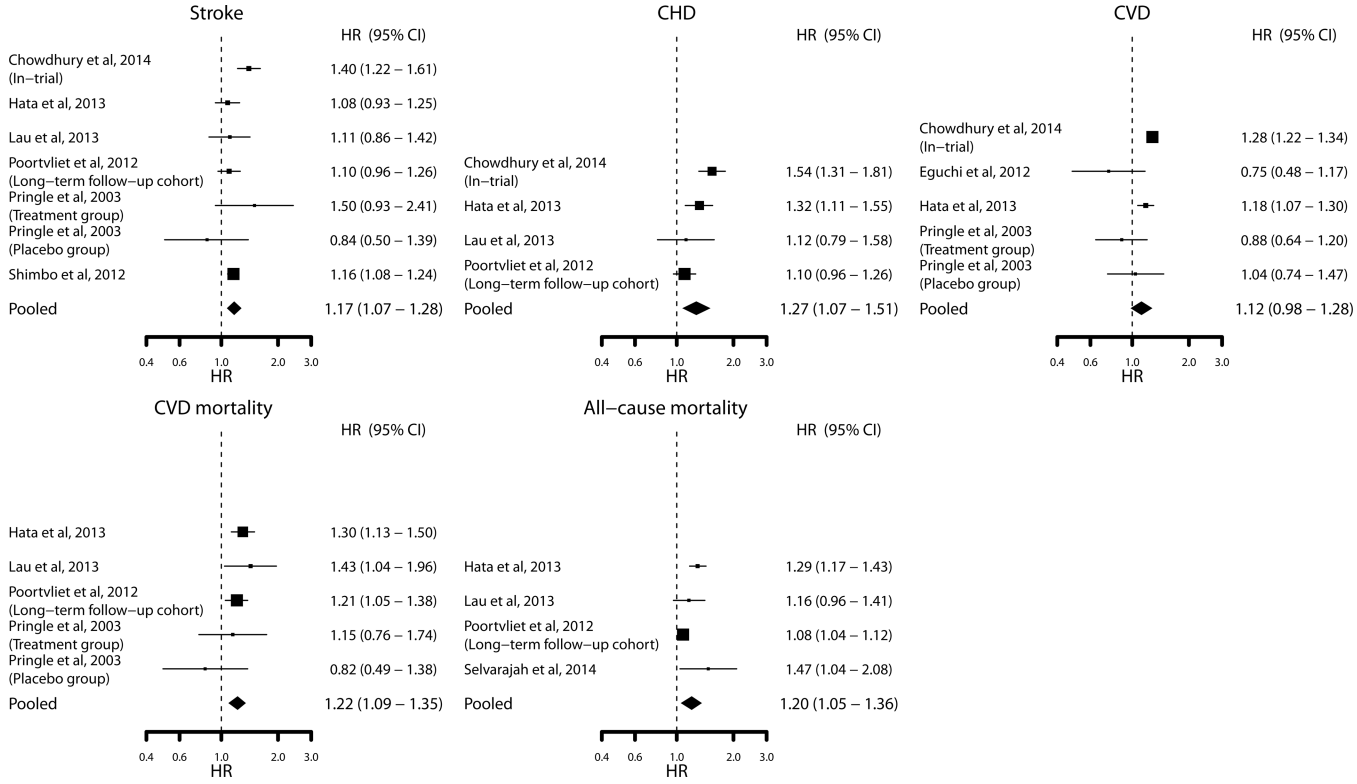

Figure 2.

Association of the standard deviation of systolic blood pressure with outcomes. Sizes of the squares are proportional to the number of events in each study. Vertical lines denote 95% confidence intervals. The width of the diamond shapes represents the 95% confidence intervals in pooled analyses.

Table 1

Characteristics of included cohorts.

Year	First Author	Cohort	Sample Size	Population	Countries	Outcomes	Follow-up Period
2010	Brickman[10]	WHICAP	686	Older adults 65+ years of age	USA	Stroke	4.5 ± 0.8 years (mean)
2008	Brunelli[11]	ArMORR	6,961	Adult hemodialysis patients	USA	All-cause mortality, CVD mortality	185 days (median); range 181–365 days
2012	Carr[12]	MRC Elderly Trial	4,396	Elderly hypertensive patients	UK	CHD, stroke	5.8 years (mean)
2014	Chang[13]	HEMO	1,844	Adult hemodialysis patients	USA	All-cause mortality, CVD mortality	2.5 years (median); IQR 1.3–4.3 years
2014	Chowdhury[14]	ANPB2	In-trial: 5,880 Post-trial: 5,542	Elderly hypertensive patients	Australia	In-trial: CVD (fatal and non-fatal), MI (fatal and non-fatal), stroke (fatal and non-fatal) Post-trial: Fatal CVD, fatal MI, fatal stroke	In-trial: 4.1 years (median) Post-trial: 6.9 years post-trial (median)
2012	Di Iorio[16]	N/A	374	Adult CKD patients	Italy	All-cause mortality	33 ± 21 months (mean)
2013	Di Iorio[15]	N/A	1,088	Adult hemodialysis patients	Italy	All-cause mortality, CVD mortality	5 years (max)
2012	Eguchi[17]	Karatsu-Nishiarita Study	457	Adult hypertensive patients	Japan	Hard CVD (stroke, MI, sudden cardiac death)	66 ± 27 months (mean)
2014	Gao[7]	N/A	2,906	Elderly primary care patients	USA	All-cause mortality, CHD mortality, stroke mortality, stroke or CHD mortality	12.9 years (median); range 2–16 years
1997	Grove[18]	Honolulu Heart	1,433	Middle-age men of Japanese ancestry living in Oahu, HI	USA	CHD	11.6 years (mean)
2013	Hastie[1]	N/A	14,522	Adult hypertensive patients	Scotland	All-cause mortality, CVD mortality, ischemic heart disease mortality, stroke mortality	35 years (max)
2013	Hata, J.[19]	ADVANCE Trial	8,811	Adult type 2 diabetic patients	20 countries from Asia, Australasia,	All-cause mortality, CVD mortality, MI, stroke, major	2.4 years (median)

Year	First Author	Cohort	Sample Size	Population	Countries	Outcomes	Follow-up Period
					Europe, and North America	macrovascular events (composite of stroke, MI, CVD mortality)	
2000	Hata, Y.[20]	N/A	521	Elderly hypertensive patients	Japan	Stroke	1 year
2002	Hata, Y.	N/A	419	Elderly hypertensive patients	Japan	MI	1 year
1983	Hofman[22]	Framingham	3,350	Adult general population	USA	All-cause mortality, CHD, CVD	26 years (max)
2012	Hsieh[23]	N/A	2,161	Adult type 2 diabetic patients	Taiwan	All-cause mortality, CVD mortality	66.7 ± 7.5 months (mean); range 21–80 months
2013	Kawai[24]	NOAH	485	Adult hypertensive patients	Japan	CVD	7.6 ± 2.6 years (mean)
2013	Kim[25]	N/A	2,174	Adult hemodialysis patients	Korea	All-cause Mortality	46.5 months (mean)
2013	Kostis[26]	SHEP	4,736	Elderly with isolated systolic hypertension	USA	CVD Mortality	Range 11.7 – 15.0 years
2013	Lau[27]	N/A	281	Patients with recent lacunar infarct	Hong Kong	ACS, all-cause mortality, CVD mortality, stroke	78 ± 18 months (mean)
2014	Lau[28]	N/A	632	Patients with recent ischemic stroke	Hong Kong	ACS, all-cause mortality, CVD mortality, stroke	76 ± 18 months
2013	Mallamaci[29]	N/A	1,618	Adult CKD patients	Italy	Composite of all-cause mortality and fatal and non-fatal CVD	37 months (median); range 0.3–110 months
2012	Mancia[6]	ELSA	1,521	Adult hypertensive patients	Europe (France, Germany, Greece, Italy, Spain, Sweden, UK	CVD	4 years (max)
2013	McMullan[30]	AASK	908	Adult African Americans with CKD	USA	All-cause mortality, CVD, CVD mortality	52 months (median); 75 months (max)
2011	Muntner[2]	NHANES III	956	Adult general population	USA	All-cause mortality	14 years (median)

Year	First Author	Cohort	Sample Size	Population	Countries	Outcomes	Follow-up Period
2012	Poortvliet (Short Term)[31]	PROSPER	4,819	Elderly adults with or at risk for CVD	Ireland, Scotland, The Netherlands	All-cause mortality, coronary events, stroke (fatal and non-fatal), vascular mortality	3 years (max); 2.3 years (mean)
2012	Poortvliet (Long Term)[31]	PROSPER	1,808	Elderly adults with or at risk for CVD	Scotland	All-cause mortality, coronary events, stroke (fatal and non-fatal), vascular mortality	7.1 years (mean); 9.3 years (max)
2003	Pringle[32]	Syst-Eur	744	Elderly hypertensive patients	Europe (23 countries)	CVD, CVD mortality, stroke	4.4 years (median); range 1–109 months
2012	Rossignol[33]	FOSIDIAL	388	Hemodialysis patients with LVH	France	CVD	2 years (max)
2010	Rothwell[3]	UK-TIA Aspirin Trial	2,006	Patients with recent TIA or stroke	UK	Stroke	10 follow-up visits, occurring every 4 months (median); range 1–20 visits
2010	Rothwell[3]	ASCOT-BPLA Trial	18,530	Adult hypertensive patients	Europe (7 countries)	Coronary events, stroke, composite of coronary events and stroke	10 follow-up visits, occurring every 6 months (median)
2010	Rothwell[3]	ESPS-1 Study	1,247	Patients with recent TIA or stroke (Placebo group)	Europe (6 countries)	Stroke	NR
2010	Rothwell[3]	Dutch-TIA Trial	3,150	Patients with recent TIA or stroke	The Netherlands	Stroke	NR
2014	Selvarajah[34]	N/A	203	Adult hemodialysis patients	England	All-cause mortality	2.0 ± 1.3 years (mean)
2014	Shafi[35]	DEcIDE-ESRD	11,291	Adult hemodialysis patients	USA	All-cause mortality, CVD, CVD mortality	22 months (median); 25th–75th percentile 13–36 months
2012	Shimbo[36]	WHI	58,228	Post-menopausal women	USA	Stroke	5.4 years (median)
2013	Suchy-Dicey[37]	CHS	3,852	Elderly general population	USA	All-cause mortality, stroke, MI	9.9 years (mean)
1999	Tozawa[38]	OKIDS	144	Adult hemodialysis patients	Japan	All-cause mortality, CVD mortality	35.2 ± 8.1 months (mean)

Year	First Author	Cohort	Sample Size	Population	Countries	Outcomes	Follow-up Period
2013	Yinon[39]	HEALS	11,153	Adult general population	Bangladesh	CVD mortality (all and major), CHD mortality, stroke mortality, all-cause mortality	6.5 years (mean)
2007	Zoppini[41]	Verona Diabetes Study	1,128	Adult type 2 diabetic patients	Italy	All-cause mortality, cerebrovascular disease mortality, CVD mortality, ischemic heart disease mortality	10 years (max)
2008	Zoppini[40]	Verona Diabetes Study	1,319	Adult type 2 diabetic patients	Italy	All-cause mortality	10 years (max)

ACS, acute coronary syndrome; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; IQR, interquartile range; LVH, left ventricular hypertrophy; MI, myocardial infarction; N/A, not available; NR, not reported; TIA, transient ischemic attack.

Data in table are sorted in alphabetical order.

Table 2

Methodology for measurement of BP and calculation of visit-to-visit variability.

Year	First Author	Number of Visits to Derive VVV	Number of BP Readings per Visit to Derive VVV	Time Between Visits	Method of BP Assessment	VVV of SBP, DBP, MAP, or PP	VVV Metrics	VVV as continuous	VVV as categorical
2010	Brickman	3	1 (3 taken, but only the 3rd used to calculate VVV)	~2 years (visit 1 to 2: 2.12 ± 0.71 yrs; visit 2 to 3: 2.45 ± 0.65 yrs)	Automated (Dinamap Pro 100)	MAP	SD	No	Yes; 4 groups based on the median split of the mean BP measurement and the median split of the SD across the study
2008	Brunelli	35.9 ± 4.5; range 4–52	1	2 days (visits 3×/week on either Mon./Wed./Fri. or Tues./Thurs./Sat.)	Manual	SBP, DBP	Average residual: intercept ratio	Yes	No
2012	Carr	NR	2	2 weeks for 1st month, monthly for 3 months, every 3 months thereafter	Manual	SBP, DBP	Maximum BP, RSV, standard residual	Yes	No
2014 *	Chang	4.9 ± 1.2; range 3–13	1	8.0 ± 4.7 days; range 3–56 days	Automated (varied devices)	SBP	ARV, CV	Yes	No
2014	Chowdhury	8 (median); range 2–19	2 (3 taken, but only last 2 used)	6 months (mean); 5.5 months (median); IQR 4.5–6.5 months	Manual	SBP	In-trial: ARV, SD Post-trial: SD	Yes	Yes; deciles of VVV
2012	Di Iorio	5	3	~1 month (5 visits over a 4–5 month period)	Semi-automated oscillometric device	SBP	CV	Yes	No
2013	Di Iorio	NR	1	Visits 3×/week	Manual	SBP	CV	Yes	Yes; quartiles of VVV
2012	Eguchi	36.5 ± 22.6; range 1–78	2 (3 taken, but only	1 month	Manual	SBP, DBP	SD	Yes	No

Year	First Author	Number of Visits to Derive VVV	Number of BP Readings per Visit to Derive VVV	Time Between Visits	Method of BP Assessment	VVV of SBP, DBP, MAP, or PP	VVV Metrics	VVV as continuous	VVV as categorical
			last 2 used)						
2014	Gao	35 (median), 39.8 (mean); range 6–258	1	NR (derived from electronic medical records; time interval varied for each participant)	NR	SBP, DBP	Root mean square error	Yes	Yes; 6 groups based on tertile of BP regression slope and quartile of VVV (lowest quartile or all other quartiles)
1997	Grove	3 or 4	2 or 3 (3 at visits 1 and 2; 2 at visits 3 and 4)	~3 years for visits 1–3; ~4 years for visit 4	Manual	SBP	Variance of the residuals	Yes	Yes; quintiles of VVV
2013	Hastie	≥3; Year 1 VVV: 3.6 ± 0.8; Years 2–5 VVV: 7.8 ± 3.2; Years 5–10 VVV: 7.9 ± 3.7	2 (3 taken, but only last 2 used)	≥30 days; Year 1 VVV: 77.9 ± 37.1 days; Years 2–5 VVV: 157.5 ± 111.9 days; 204.1 ± 193.0 days	Manual	SBP, DBP	ARV, CV, SD	No	Yes; quartiles of VVV; 4 groups based on median split of VVV over Year 1 and median split of VVV over Years 2–5
2013	Hata, J.	6	2	1 month between visits 1 and 2, 2 months between visits 2 and 3, every 6 months thereafter	Automated (Omron HEM-705CP)	SBP	CV, Maximum BP, SD	Yes	Yes; deciles of VVV
2000	Hata, Y.	cases: 9.8 ± 2.4; controls: 10.3 ± 2.3	2	~1 month (all visits occurred over 1 year)	Manual	SBP, DBP	BP range, CV, maximum BP change	Yes	No
2002	Hata, Y.	10 ± 2	2	~1 month (all visits occurred over 1 year)	Manual	DBP	CV	Yes	No
1983	Hofman	range 5–7	2	2 years	Manual	SBP	Yearly	Yes	No

Year	First Author	Number of Visits to Derive VVV	Number of BP Readings per Visit to Derive VVV	Time Between Visits	Method of BP Assessment	VVV of SBP, DBP, MAP, or PP	VVV Metrics	VVV as continuous	VVV as categorical
							change, conditional on initial BP level or attained BP level		
2012	Hsieh	15.7 ± 3.4; range 9–23	2	2–6 months	Automated (Omron HEM-1000)	SBP, DBP, MAP, PP	CV, SD	Yes	No
2013	Kawai	6	2	1–2 months	Automated (Omron HEM-705IT or HEM-711)	SBP	SD	No	Yes; High vs. low VVV cut-off determined by ROC curve analysis
2013	Kim	NR	2 (3 taken, but only highest and lowest used)	NR (days between dialysis visits)	NR	SBP, DBP	ARV	No	Yes; high vs. low VVV (cut-off determination NR)
2013	Kostis	15 mean; range 9–33	2	1 month, visits 1–4; every 3 months for all remaining visits	Random zero sphygmomanometer	SBP	rSSR, VABS2, VIM	Yes	No
2013	Lau	12 ± 6; range 3–36	3	3–4 months	Automated (Dinamap PRO100)	SBP, DBP	SD	Yes	Yes, tertiles of VVV
2014	Lau	12 ± 6; range 3–36	3	3–4 months	Automated (Dinamap PRO 100)	SBP, DBP	CV	Yes	Yes, quartiles of VVV
2013	Mallamaci	range 2–7	3	8 ± 5 months	Manual	SBP, DBP	CV, SD	Yes	No
2012	Mancia	7+	3	6 months	Manual	SBP, DBP	CV, SD	Yes	No
2013	McMullan	5	2 (3 taken, but only last 2 used)	2 months	Random zero sphygmomanometer	SBP	SD	Yes	Yes; tertiles of VVV
2011	Muntner	3	2 (3 taken, but only last 2 used)	17 days (median); range 1–48	Manual	SBP, DBP	CV, SD	No	Yes; tertiles of VVV

Year	First Author	Number of Visits to Derive VVV	Number of BP Readings per Visit to Derive VVV	Time Between Visits	Method of BP Assessment	VVV of SBP, DBP, MAP, or PP	VVV Metrics	VVV as continuous	VVV as categorical
2012	Poortvliet (Short Term)	5	NR	3 months	Automated (Omron M4)	SBP, DBP, PP	SD	Yes	Yes; quartiles of VVV
2012	Poortvliet (Long Term)	9	NR	3 months	Automated (Omron M4)	SBP, DBP, PP	SD	Yes	Yes; quartiles of VVV
2003	Pringle	3	2	~1 month	Manual	SBP	SD	Yes	No
2012	Rossignol	17	3	1 week for weeks 1–6; bi-weekly for weeks 6–8; 3 months for all subsequent visits	Manual	SBP, DBP, PP	ARV†, CV, CV of ARV†, residual of the linear fit between SD and mean BP, SD	Yes	No
2010	Rothwell (UK-TIA Aspirin Trial)	2, 4, 6, 8, 10 (separate analyses)	1	4 months	Random zero sphygmomanometer	SBP, DBP	CV, maximum BP, SD, VIM	No	Yes; deciles of VVV
2010	Rothwell (ASCOT-BPLA Trial)	NR	2 (3 taken, but only last 2 used)	6 months	Automated (Omron HEM-705CP)	SBP, DBP	ARV†, CV, maximum BP, RSD, SD, VIM	Yes	Yes; deciles of VVV
2010	Rothwell (ESPS-1 Study)	NR	2 (mean of right and left arms)	3 months	Manual	SBP	CV, SD, VIM	No	Yes; deciles of VVV
2010	Rothwell (Dutch-TIA Trial)	NR	1	4 months	Manual	SBP	CV, SD, VIM	No	Yes; deciles of VVV
2014	Selvarajah	25.00 ± 1.63	NR	2–5 days	Automated oscillometric device (Fresenius 4008S or Nikisso DBB-05)	SBP, DBP	CV, SD, VIM	Yes	Yes; median split
2014	Shafi	32.8 ± 9.3	1	2–3 days	Automated oscillometric device	SBP	SD of residuals from modeled average BP over time	Yes	Yes; tertiles of VVV

Year	First Author	Number of Visits to Derive VVV	Number of BP Readings per Visit to Derive VVV	Time Between Visits	Method of BP Assessment	VVV of SBP, DBP, MAP, or PP	VVV Metrics	VVV as continuous	VVV as categorical
2012	Shimbo	7.9 ± 1.8	2	1 year	Manual	SBP	SD, SDreg	Yes	Yes; quartiles of VVV
2013	Suchy-Dicey	5	2 (3 taken, but only last 2 used)	1 year	Random zero sphygomanometer for visit 1; manual for visits 2–5	SBP, DBP, PP	SDreg	Yes	No
1999	Tozawa	156	1	visits 3x/week over 1 year	Manual	SBP	ΔBP (maximum minus minimum), CV	Yes	Yes; median split
2013	Yinon	3.84 (mean); range 2–4	1, 3 if BP ≥ 140/90 mmHg at 1st measurement (lowest reading of 3 used)	2.2 years (mean)	Automated (Omron HEM 712-C)	SBP	SD	Yes	Yes; tertiles of VVV
2007	Zoppini	6+	3	NR	Manual	PP	CV	Yes	No
2008	Zoppini	7 (median); range 3–31	3	NR	Manual	PP	CV	No	Yes; tertiles of VVV

ARV, average real variability; BP, blood pressure; CV, coefficient of variation; DBP, diastolic blood pressure; IQR, interqua MAP, mean arterial pressure; NR, not reported; PP, pulse pressure; ROC, receiver operating characteristic; rSSR, sum deviations between daily average blood pressure value and the trend-predicted blood pressure; RSD, residual standard successive variance; SBP, systolic blood pressure; SD, standard deviation; SDreg, standard deviation about regression pressure regressed across visits; VABS2, variance of the absolute values of the second differences between successive pressure values; VIM, variance independent of the mean; VVV, visit-to-visit variability.

*The study by Chang et. al. initially appeared online in 2013.

†described as average successive variation (ASV) in original publication.

Data in table are sorted in alphabetical order.

Table 3

Results reported for continuous analysis of standard deviation and coefficient of variation of systolic blood pressure and outcomes.

	Standard deviation		Coefficient of variation	
Study	***HR/OR/RR (95% CI)***	***Units****	***HR/OR/RR (95% CI)***	***Units****
Stroke				
Chowdhury et al, 2014 (In-trial)	1.07 (1.04 – 1.10)	1 mmHg	-	-
Hata, J. et al, 2013	1.08 (0.93 – 1.25)	5 mmHg	1.08 (0.93 – 1.25)	3.4%
Hata, Y. et al, 2000	-	-	1.15 (1.03 – 1.29)	2%
Lau et al, 2013	1.13 (0.83 – 1.52)	6 mmHg	-	-
Lau et al, 2014	-	-	1.02 (0.97 – 1.07)	4%
Poortvliet et al, 2012 (Short-term follow-up cohort)	Not statistically sig. (Data NR)	NR	-	-
Poortvliet et al, 2012 (Long-term follow-up cohort)	1.1 (1.0 – 1.3)	4.88 mmHg	-	-
Pringle et al, 2003 (Treatment group)	1.50 (0.93 – 2.41)	5 mmHg	-	-
Pringle et al, 2003 (Placebo group)	0.84 (0.50 – 1.39)	5 mmHg	-	-
Rothwell et al, 2010 (ASCOT-BPLA ABPM Substudy)	1.69 (1.34 – 2.11)	1 SD	1.78 (1.40 – 2.26)	1 SD
Shimbo et al, 2012	1.16 (1.08 – 1.24)	5 mmHg	-	-
Stroke Mortality				
Yinon et al, 2013	1.51 (0.93 – 2.44)	1 SD of Log	-	-
CHD				
Chowdhury et al, 2014 (In-trial)	1.09 (1.05 – 1.12)	1 mmHg	-	-
Hata, J. et al, 2013	1.32 (1.11 – 1.55)	5 mmHg	1.29 (1.10 – 1.52)	3.4%
Lau et al, 2013	1.14 (0.75 – 1.73)	6 mmHg	-	-
Lau et al, 2014	-	-	0.95 (0.85 – 1.06)	4%
Poortvliet et al, 2012 (Short-term follow-up cohort)	Not statistically sig. (Data NR)	NR	-	-
Poortvliet et al, 2012 (Long-term follow-up cohort)	1.1 (1.0 – 1.3)	5 mmHg	-	-
Rothwell et al, 2010 (ASCOT-BPLA ABPM Substudy)	1.43 (1.23 – 1.67)	1 SD	1.49 (1.27 – 1.75)	1 SD
CHD Mortality				
Yinon et al, 2013	0.78 (0.56 – 1.08)	1 SD of Log	-	-
CVD				
Chowdhury et al, 2014 (In-trial)	1.05 (1.04 – 1.06)	1 mmHg	-	-
Eguchi et al, 2012	0.75 (0.48 – 1.17)	5 mmHg	-	-
Hata, J. et al, 2013	1.18 (1.07 – 1.30)	5 mmHg	1.18 (1.07 – 1.29)	3.4%
Mancia et al, 2012	0.999 (0.952 – 1.048)	NR	0.976 (0.906 – 1.051)	NR
Pringle et al, 2003 (Treatment group)	0.88 (0.64 – 1.20)	5 mmHg	-	-
Pringle et al, 2003 (Placebo	1.04 (0.74 – 1.47)	5 mmHg	-	-

Study	Standard deviation		Coefficient of variation	
	HR/OR/RR (95% CI)	*Units**	*HR/OR/RR (95% CI)*	*Units**
group)				
Rossignol et al, 2012	Not statistically sig. (Data NR)	NR	1.08 (1.03 – 1.14)	NR
Rothwell et al, 2010 (ASCOT-BPLA ABPM Substudy)	1.50 (1.31 – 1.72)	1 SD	1.57 (1.37 – 1.80)	1 SD
CVD Mortality				
Chang et al, 2014	-	-	1.10 (0.89 – 1.37)	10%
Di Iorio et al, 2013	-	-	1.21 (1.05 – 1.33)	NR
Hata, J. et al, 2013	1.30 (1.13 – 1.50)	5 mmHg	1.29 (1.12 – 1.48)	3.4%
Hsieh et al, 2012	1.05 (0.96 – 1.14)	NR	1.08 (0.95 – 1.22)	NR
Lau et al, 2013	1.53 (1.05 – 2.25)	6 mmHg	-	-
Lau et al, 2014	-	-	1.25 (0.99 – 1.57)	4%
Poortvliet et al, 2012 (Short-term follow-up cohort)	Not statistically sig. (Data NR)	NR	-	-
Poortvliet et al, 2012 (Long-term follow-up cohort)	1.2 (1.1 – 1.4)	5 mmHg	-	-
Pringle et al, 2003 (Treatment group)	1.15 (0.76 – 1.74)	5 mmHg	-	-
Pringle et al, 2003 (Placebo group)	0.82 (0.49 – 1.38)	5 mmHg	-	-
Tozawa et al, 1999	-	-	1.78 (0.94 – 3.37)	1%
Yinon et al, 2013 (All CVD Mortality)	1.41 (1.04 – 1.92)	1 SD of Log	-	-
Yinon et al, 2013 (Major CVD Mortality)	1.84 (1.27 – 2.66)	1 SD of Log	-	-
All-Cause Mortality				
Chang et al, 2014	-	-	1.18 (1.02 – 1.36)	10%
Di Iorio et al, 2012 (Before Dialysis Entry)	-	-	1.06 (1.02 – 1.09)	NR
Di Iorio et al, 2012 (Including Time After Dialysis Inception)	-	-	1.05 (1.03 – 1.09)	NR
Di Iorio et al, 2013	-	-	1.02 (0.95 – 1.06)	NR
Hata, J. et al, 2013	1.29 (1.17 – 1.43)	5 mmHg	1.28 (1.16 – 1.40)	3.4%
Hsieh et al, 2012	1.05 (1.01 – 1.09)	NR	1.06 (1.00 – 1.12)	NR
Lau et al, 2013	1.20 (0.96 – 1.51)	6 mmHg	-	-
Lau et al, 2014	-	-	1.23 (1.07 – 1.41)	4%
Poortvliet et al, 2012 (Short-term follow-up cohort)	Not statistically sig. (Data NR)	NR	-	-
Poortvliet et al, 2012 (Long-term follow-up cohort)	1.1 (1.1 – 1.2)	5 mmHg	-	-
Selvarajah et al, 2014	1.08 (1.01 – 1.16)	1 mmHg	1.13 (1.02 – 1.24)	1%
Tozawa et al, 1999	-	-	1.63 (1.05 – 2.53)	1%
Yinon et al, 2013	0.99 (0.82 – 1.74)	1 SD of Log	-	-
Composite of all-cause mortality and fatal and non-fatal CVD				

	Standard deviation		Coefficient of variation	
Study	***HR/OR/RR (95% CI)***	***Units****	***HR/OR/RR (95% CI)***	***Units****
Mallamaci et al, 2013	1.15 (1.03 – 1.27)	5 mmHg	1.17 (1.02 – 1.34)	5%

CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; NR, not reported; OR, odds ratio; RR, relative risk; SD, standard deviation; VVV, visit-to-visit variability.

* Units represented by the measure of association

Dash indicates data were not examined.
For each outcome, data in table are sorted in alphabetical order by first author's last name.

Table 4

Results reported for categorical analysis of standard deviation and coefficient of variation of systolic blood pressure and outcomes.

	Standard deviation			Coefficient of variation		
Study	***HR/OR/RR (95% CI)***	***Levels***	***Comparison***	***HR/OR/RR (95% CI)***	***Levels***	***Comparison***
Stroke						
Chowdhury et al, 2014 (In-trial)	2.78 (1.28 – 6.05)	Deciles	Top decile (≥19.72 mmHg) vs. bottom decile (≤7.07 mmHg)	-	-	-
Hata, J. et al, 2013	1.06 (0.53 – 2.10)	Deciles	Top decile (≥18.1 for placebo group; ≥16.8 for active treatment group) vs. bottom decile (≤5.2 for placebo group; ≤5.0 for active treatment group)	-	-	-
Lau et al, 2013	1 (ref) 0.95 (0.41 – 2.19) 1.14 (0.51 – 2.56)	Tertiles	<13.0 13.0 – 17.5 >17.5	-	-	-
Lau et al, 2014	-	-	-	1 (ref) 0.90 (0.49 – 1.66) 0.68 (0.35 – 1.30) 1.08 (0.60 – 1.93)	Quartiles	<8.6 (ref) 8.6–10.9 11.0–14.2 >14.2
Poortvliet et al, 2012 (Short-term follow-up cohort)	1 (ref) 1.0 (0.6 – 1.6) 1.1 (0.7 – 1.8) 1.2 (0.8 – 1.9)	Quartiles	≤9 (ref) >9 – 12.5 >12.5 – ≤17 >17	-	-	-
Poortvliet et al, 2012 (Long-term follow-up cohort)	1 (ref) 1.0 (0.7 – 1.5) 1.3 (0.9 – 2.0) 1.3 (0.9 – 1.8)	Quartiles	<10.5 (ref) >10.5 – ≤13 >13 – ≤16.5 >16.5	-	-	-
Rothwell et al, 2010 (UK-TIA Aspirin Trial)	4.37 (2.73 – 6.99)	Deciles	Top vs. bottom decile	3.82 (2.54 – 5.73)	Deciles	Top vs. bottom decile
Rothwell et al, 2010 (ASCOT-BPLA Trial, all participants)	2.57 (1.59 – 4.15)	Deciles	Top vs. bottom decile	2.06 (1.28 – 3.31)	Deciles	Top vs. bottom decile
Rothwell et al, 2010 (ASCOT-BPLA Trial, treatment cohorts: amlodipine and atenolol treatment groups combined)	2.54 (1.28 – 5.04)	Deciles	Top vs. bottom decile	2.28 (1.13 – 4.60)	Deciles	Top vs. bottom decile

	Standard deviation			Coefficient of variation		
Study	***HR/OR/RR (95% CI)***	***Levels***	***Comparison***	***HR/OR/RR (95% CI)***	***Levels***	***Comparison***
Rothwell et al, 2010 (ASCOT-BPLA Trial, Amlodipine Treatment Group)	3.80 (1.67 – 8.65)	Deciles	Top vs. bottom decile	3.01 (1.39 – 6.52)	Deciles	Top vs. bottom decile
Rothwell et al, 2010 (ASCOT-BPLA Trial, Atenolol Treatment Group)	4.06 (2.17 – 7.60)	Deciles	Top vs. bottom decile	3.30 (1.83 – 5.94)	Deciles	Top vs. bottom decile
Rothwell et al, 2010 (ESPS-1 Study)	1.78 (1.21 – 2.62)	Deciles	Top vs. bottom decile	2.22 (1.52 – 3.22)	Deciles	Top vs. bottom decile
Rothwell et al 2010 (Dutch TIA Trial)	3.35 (1.63 – 6.87)	Deciles	Top vs. bottom decile	3.41 (1.62 – 7.19)	Deciles	Top vs. bottom decile
Shimbo et al, 2012	1 (ref) 1.39 (1.03 – 1.89) 1.52 (1.13 – 2.03) 1.72 (1.28 – 2.32)	Quartiles	<6 (ref) 6.0 – 8.9 9.0 – 12.9 ≥13.0	-	-	-
Stroke Mortality						
Chowdhury et al, 2014 (Post-trial)	1.90 (0.50 – 7.21)	Deciles	Top decile (≥19.72 mmHg) vs. bottom decile (≤7.07 mmHg)	-	-	-
Hastie et al, 2013 (Year 1)	1 (ref) 1.01 (0.67 – 1.53) 0.80 (0.53 – 1.20) 1.28 (0.87 – 1.88)	Quartiles	<13.87 (ref) 13.87 – 18.20 18.21 – 23.14 >23.15	1 (ref) 0.94 (0.66 – 1.35) 0.99 (0.70 – 1.40) 1.00 (0.71 – 1.42)	Quartiles	<11.0 (ref) 11.0 – 13.0 13.1 – 18.0 >18.0
Hastie et al, 2013 (Years 2–5)	1 (ref) 0.91 (0.55 – 1.52) 0.98 (0.61 – 1.58) 1.65 (1.04 – 2.62)	Quartiles	<12.98 (ref) 12.98 – 17.07 17.08 – 21.80 >21.81	1 (ref) 0.93 (0.58 – 1.49) 1.12 (0.71 – 1.75) 1.49 (0.95 – 2.31)	Quartiles	<9.6 (ref) 9.6 – 10.8 10.9 – 12.3 >12.4
Hastie et al, 2013 (Years 5–10)	1 (ref) 1.19 (0.58 – 2.44) 1.45 (0.75 – 2.83) 1.40 (0.71 – 2.76)	Quartiles	<13.04 (ref) 13.04 – 16.99 17.00 – 21.52 >21.53	1 (ref) 0.96 (0.48 – 1.91) 1.21 (0.62 – 2.36) 1.31 (0.66 – 2.56)	Quartiles	<9.8 (ref) 9.8 – 10.9 11.0 – 12.4 >12.5
Hastie et al, 2013 (Years 10+)	1 (ref) 0.72 (0.21 – 2.54) 1.06 (0.33 – 3.46) 2.39 (0.84 – 6.77)	Quartiles	<13.15 (ref) 13.15 – 17.59 17.60 – 21.81 >21.82	1 (ref) 1.09 (0.34 – 3.48) 1.65 (0.53 – 5.09) 2.29 (0.78 – 6.72)	Quartiles	<9.5 (ref) 9.5 – 11.4 11.5 – 12.6 >12.7
Yinon et al, 2013	1 (ref) 0.70 (0.30 – 1.63) 1.43 (0.73 – 2.79)	Tertiles	<7.36 (ref) 7.36 – 11.49 >11.49	-	-	-
CHD						

	Standard deviation			Coefficient of variation		
Study	***HR/OR/RR (95% CI)***	***Levels***	***Comparison***	***HR/OR/RR (95% CI)***	***Levels***	***Comparison***
Chowdhury et al, 2014 (In-trial)	4.11 (1.87 – 9.06)	Deciles	Top decile (≥19.72 mmHg) vs. bottom decile (≤7.07 mmHg)	-	-	-
Hata, J. et al, 2013	1.55 (0.75 – 3.20)	Deciles	Top decile (≥18.1 for placebo group; ≥16.8 for active treatment group) vs. bottom decile (≤5.2 for placebo group; ≤5.0 for active treatment group)	-	-	-
Lau et al, 2013	1 (ref) 1.16 (0.31 – 4.37) 2.13 (0.62 – 7.35)	Tertiles	<13.0 13.0 – 17.5 >17.5	-	-	-
Lau et al, 2014	-	-	-	1 (ref) 1.06 (0.36 – 3.14) 0.34 (0.08 – 1.51) 0.60 (0.18 – 2.02)	Quartiles	<8.6 (ref) 8.6–10.9 11.0–14.2 >14.2
Poortvliet et al, 2012 (Short-term follow-up cohort)	1 (ref) 0.8 (0.6 – 1.1) 1.0 (0.7 – 1.3) 1.0 (0.8 – 1.3)	Quartiles	≤9 (ref) >9 – 12.5 >12.5 – ≤17 >17	-	-	-
Poortvliet et al, 2012 (Long-term follow-up cohort)	1 (ref) 0.9 (0.6 – 1.3) 1.3 (0.9 – 1.9) 1.2 (0.8 – 1.7)	Quartiles	<10.5 (ref) >10.5 – ≤13 >13 – ≤16.5 >16.5	-	-	-
CHD Mortality						
Chowdhury et al, 2014 (Post-trial)	4.35 (1.18 – 16.06)	Deciles	Top decile (≥19.72 mmHg) vs. bottom decile (≤7.07 mmHg)	-	-	-
Hastie et al, 2013 (Year 1)	1 (ref) 1.24 (0.94 – 1.63) 1.33 (1.01 – 1.74) 1.26 (0.95 – 1.66)	Quartiles	<13.87 (ref) 13.87 – 18.20 18.21 – 23.14 >23.15	1 (ref) 1.23 (0.97 – 1.57) 1.18 (0.93 – 1.50) 1.09 (0.85 – 1.40)	Quartiles	<11.0 (ref) 11.0 – 13.0 13.1 – 18.0 >18.0
Hastie et al, 2013 (Years 2–5)	1 (ref) 0.95 (0.69 – 1.30) 1.14 (0.85 – 1.54) 1.22 (0.90 – 1.65)	Quartiles	<12.98 (ref) 12.98 – 17.07 17.08 – 21.80 >21.81	1 (ref) 1.25 (0.93 – 1.68) 1.28 (0.96 – 1.71) 1.35 (1.01 – 1.82)	Quartiles	<9.6 (ref) 9.6 – 10.8 10.9 – 12.3 >12.4
Hastie et al, 2013 (Years 5–10)	1 (ref) 0.83 (0.55 – 1.25) 0.92 (0.62 – 1.35) 1.12 (0.76 – 1.65)	Quartiles	<13.04 (ref) 13.04 – 16.99 17.00 – 21.52 >21.53	1 (ref) 1.10 (0.73 – 1.64) 1.25 (0.84 – 1.86) 1.23 (0.81 – 1.86)	Quartiles	<9.8 (ref) 9.8 – 10.9 11.0 – 12.4 >12.5
Hastie et al, 2013 (Years 10+)	1 (ref) 1.28 (0.69 – 2.38)	Quartiles	<13.15 (ref) 13.15 – 17.59	1 (ref) 1.06 (0.56 – 2.02)	Quartiles	<9.5 (ref) 9.5 – 11.4

	Standard deviation			Coefficient of variation		
Study	***HR/OR/RR (95% CI)***	***Levels***	***Comparison***	***HR/OR/RR (95% CI)***	***Levels***	***Comparison***
	1.52 (0.82 – 2.81) 1.28 (0.68 – 2.42)		17.60 – 21.81 >21.82	1.73 (0.93 – 3.21) 1.58 (0.83 – 3.02)		11.5 – 12.6 >12.7
Yinon et al, 2013	1 (ref) 0.78 (0.49 – 1.27) 0.89 (0.55 – 1.44)	Tertiles	<7.36 (ref) 7.36 – 11.49 >11.49	-	-	-
CVD						
Chowdhury et al, 2014 (In-trial)	2.18 (1.52 – 3.13)	Deciles	Top decile (≥19.72 mmHg) vs. bottom decile (≤7.07 mmHg)	-	-	-
Hata, J. et al, 2013	1.54 (0.99 – 2.39)	Deciles	Top decile (≥18.1 for placebo group; ≥16.8 for active treatment group) vs. bottom decile (≤5.2 for placebo group; ≤5.0 for active treatment group)	-	-	-
Kawai et al, 2013	1 (ref) 1.96 (1.05 – 4.10)	High vs. low cut-off determined by ROC curve analysis	<8.1 (ref) vs. ≥8.1	-	-	-
McMullan et al, 2013	1 (ref) 1.28 (0.71 – 2.29) 1.23 (0.65 – 2.34)	Tertiles	1.30 – 9.37 (ref) 9.40 – 15.47 15.51 – 55.56	-	-	-
Rothwell et al, 2010 (ASCOT-BPLA Trial, all participants)	1.80 (1.30 – 2.49)	Deciles	Top vs. bottom decile	1.57 (1.14 – 2.16)	Deciles	Top vs. bottom decile
Rothwell et al, 2010 (ASCOT-BPLA Trial, treatment cohorts: amlodipine and atenolol treatment groups combined)	1.94 (1.16 – 3.24)	Deciles	Top vs. bottom decile	1.84 (1.11 – 3.05)	Deciles	Top vs. bottom decile
Rothwell et al, 2010 (ASCOT-BPLA Trial, Amlodipine Treatment Group)	2.85 (1.56 – 5.21)	Deciles	Top vs. bottom decile	3.36 (2.00 – 5.66)	Deciles	Top vs. bottom decile
Rothwell et al, 2010 (ASCOT-BPLA Trial, Atenolol	1.99 (1.25 – 3.18)	Deciles	Top vs. bottom decile	2.05 (1.32 – 3.19)	Deciles	Top vs. bottom decile

	Standard deviation			Coefficient of variation		
Study	***HR/OR/RR (95% CI)***	***Levels***	***Comparison***	***HR/OR/RR (95% CI)***	***Levels***	***Comparison***
Treatment Group)						
CVD Mortality						
Chowdhury et al, 2014 (Post-trial)	2.41 (1.45 – 4.00)	Deciles	Top decile (≥19.72 mmHg) vs. bottom decile (≤7.07 mmHg)	-	-	-
Hastie et al, 2013 (Year 1)	1 (ref) 1.16 (0.94 – 1.43) 1.21 (0.99 – 1.48) 1.28 (1.05 – 1.57)	Quartiles	<13.87 (ref) 13.87 – 18.20 18.21 – 23.14 >23.15	1 (ref) 1.13 (0.94 – 1.35) 1.08 (0.91 – 1.29) 1.04 (0.87 – 1.25)	Quartiles	<11.0 (ref) 11.0 – 13.0 13.1 – 18.0 >18.0
Hastie et al, 2013 (Years 2–5)	1 (ref) 0.94 (0.74 – 1.18) 1.04 (0.83 – 1.30) 1.23 (0.98 – 1.54)	Quartiles	<12.98 (ref) 12.98 – 17.07 17.08 – 21.80 >21.81	1 (ref) 1.07 (0.86 – 1.33) 1.11 (0.89 – 1.36) 1.23 (0.99 – 1.53)	Quartiles	<9.6 (ref) 9.6 – 10.8 10.9 – 12.3 >12.4
Hastie et al, 2013 (Years 5–10)	1 (ref) 0.95 (0.69 – 1.31) 1.02 (0.75 – 1.38) 1.16 (0.86 – 1.58)	Quartiles	<13.04 (ref) 13.04 – 16.99 17.00 – 21.52 >21.53	1.04 (0.77 – 1.40) 1.12 (0.83 – 1.52) 1.19 (0.87 – 1.63)	Quartiles	<9.8 (ref) 9.8 – 10.9 11.0 – 12.4 >12.5
Hastie et al, 2013 (Years 10+)	1 (ref) 1.26 (0.78 – 2.02) 1.36 (0.84 – 2.20) 1.56 (0.98 – 2.50)	Quartiles	<13.15 (ref) 13.15 – 17.59 17.60 – 21.81 >21.82	1 (ref) 1.27 (0.78–2.07) 1.79 (1.11–2.90) 1.69 (1.02–2.77)	Quartiles	<9.5 (ref) 9.5 – 11.4 11.5 – 12.6 >12.7
Hata, J. et al, 2013	2.49 (1.15 – 5.37)	Deciles	Top decile (≥18.1 for placebo group; ≥16.8 for active treatment group) vs. bottom decile (≤5.2 for placebo group; ≤5.0 for active treatment group)	-	-	-
Lau et al, 2013	1 (ref) 2.00 (0.36 – 11.21) 7.64 (1.65 – 35.41)	Tertiles	<13.0 13.0 – 17.5 >17.5	-	-	-
Lau et al, 2014	-	-	-	1 (ref) 1.69 (0.67 – 4.26) 1.64 (0.68 – 3.98) 2.36 (1.02 – 5.49)	Quartiles	<8.6 (ref) 8.6–10.9 11.0–14.2 >14.2
Poortvliet et al, 2012 (Short-term follow-up cohort)	1 (ref) 0.8 (0.5 – 1.2) 1.0 (0.6 – 1.5) 0.9 (0.6 – 1.3)	Quartiles	≤9 (ref) >9 – 12.5 >12.5 – ≤17 >17	-	-	-
Poortvliet et al, 2012 (Long-term follow-up cohort)	1 (ref) 1.1 (0.7 – 1.5) 1.5 (1.0 – 2.1) 1.6 (1.1 – 2.2)	Quartiles	<10.5 (ref) >10.5 – ≤13 >13 – ≤16.5 >16.5	-	-	-

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	Standard deviation			Coefficient of variation		
Study	***HR/OR/RR (95% CI)***	***Levels***	***Comparison***	***HR/OR/RR (95% CI)***	***Levels***	***Comparison***
Yinon et al, 2013 (All CVD Mortality)	1 (ref) 0.56 (0.33 – 0.96) 1.27 (0.85 – 1.92)	Tertiles	<7.36 (ref) 7.36 – 11.49 >11.49	-	-	-
Yinon et al, 2013 (Major CVD Mortality)	1 (ref) 0.69 (0.36 – 1.30) 1.70 (1.03 – 2.82)	Tertiles	<7.36 (ref) 7.36 – 11.49 >11.49	-	-	-
All-Cause Mortality						
Hastie et al, 2013 (Year 1)	1 (ref) 1.09 (0.93 – 1.27) 1.17 (1.01 – 1.36) 1.22 (1.05 – 1.42)	Quartiles	<13.87 (ref) 13.87 – 18.20 18.21 – 23.14 >23.15	1 (ref) 1.10 (0.96 – 1.26) 1.08 (0.95 – 1.24) 1.07 (0.94 – 1.23)	Quartiles	<11.0 (ref) 11.0 – 13.0 13.1 – 18.0 >18.0
Hastie et al, 2013 (Years 2–5)	1 (ref) 0.99 (0.82 – 1.18) 1.13 (0.95 – 1.33) 1.32 (1.11 – 1.56)	Quartiles	<12.98 (ref) 12.98 – 17.07 17.08 – 21.80 >21.81	1 (ref) 1.12 (0.95 – 1.32) 1.13 (0.96 – 1.32) 1.27 (1.08 – 1.50)	Quartiles	<9.6 (ref) 9.6 – 10.8 10.9 – 12.3 >12.4
Hastie et al, 2013 (Years 5–10)	1 (ref) 0.95 (0.75 – 1.21) 1.02 (0.81 – 1.29) 1.26 (0.99 – 1.58)	Quartiles	<13.04 (ref) 13.04 – 16.99 17.00 – 21.52 >21.53	1 (ref) 1.10 (0.87 – 1.38) 1.28 (1.02 – 1.61) 1.37 (1.09 – 1.73)	Quartiles	<9.8 (ref) 9.8 – 10.9 11.0 – 12.4 >12.5
Hastie et al, 2013 (Years 10+)	1 (ref) 1.07 (0.76 – 1.51) 1.12 (0.85 – 1.68) 1.32 (0.94 – 1.84)	Quartiles	<13.15 (ref) 13.15 – 17.59 17.60 – 21.81 >21.82	1 (ref) 1.13 (0.80 – 1.60) 1.73 (1.24 – 2.44) 1.49 (1.04 – 2.13)	Quartiles	<9.5 (ref) 9.5 – 11.4 11.5 – 12.6 >12.7
Hata, J. et al, 2013	2.08 (1.30 – 3.31)	Deciles	Top decile (≥18.1 for placebo group; ≥16.8 for active treatment group) vs. bottom decile (≤5.2 for placebo group; ≤5.0 for active treatment group)	-	-	-
Lau et al, 2013	1 (ref) 1.47 (0.74 – 2.90) 1.97 (1.02 – 3.80)	Tertiles	<13.0 13.0 – 17.5 >17.5	-	-	-
Lau et al, 2014	-	-	-	1 (ref) 1.06 (0.60 – 1.87) 1.18 (0.69 – 2.01) 1.46 (0.88 – 2.43)	Quartiles	<8.6 (ref) 8.6–10.9 11.0–14.2 >14.2
McMullan et al, 2013	1 (ref) 0.77 (0.28 – 2.16) 2.82 (1.14 – 6.95)	Tertiles	1.30 – 9.37 (ref) 9.40 – 15.47 15.51 – 55.56	-	-	-

	Standard deviation			Coefficient of variation		
Study	***HR/OR/RR (95% CI)***	***Levels***	***Comparison***	***HR/OR/RR (95% CI)***	***Levels***	***Comparison***
Muntner et al, 2011	1 (ref) 1.57 (1.07 – 2.18) 1.50 (1.03 – 2.18)	Tertiles	<4.80 (ref) 4.80 – 8.34 ≥8.35	1 (ref) 1.55 (1.09 – 2.22) 1.49 (1.05 – 2.10)	Tertiles	<3.9 3.9 – 6.7 ≥6.8
Poortvliet et al, 2012 (Short-term follow-up cohort)	1 (ref) 1.0 (0.7 – 1.3) 1.1 (0.8 – 1.6) 1.0 (0.8 – 1.4)	Quartiles	≤9 (ref) >9 – 12.5 >12.5 – ≤17 >17	-	-	-
Poortvliet et al, 2012 (Long-term follow-up cohort)	1 (ref) 1.2 (1.0 – 1.5) 1.4 (1.1 – 1.7) 1.5 (1.2 – 1.8)	Quartiles	<10.5 (ref) >10.5 – ≤13 >13 – ≤16.5 >16.5	-	-	-
Selvarajah et al, 2014	1.48 (0.75 – 2.91)	Median split	NR	2.08 (1.04 – 1.16)	Median split	NR
Yinon et al, 2013	1 (ref) 0.57 (0.42 – 0.78) 1.00 (0.78 – 1.31)	Tertiles	<7.36 (ref) 7.36 – 11.49 >11.49	-	-	-

CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; NR, not reported; OR, odds ratio; ROC, receiver operating characteristic; RR, relative risk; VVV, visit-to-visit variability.

Dash indicates data were not examined.

For each outcome, data in table are sorted in alphabetical order by first author's last name.

Table 5

Summary of significant positive associations reported for VVV of systolic blood pressure, diastolic blood pressure, pulse pressure, mean arterial pressure, and outcomes across all analyses.

	SBP				DBP				PP				MAP			
VVV Metrics	***SD***	***CV***	***Other***	***Total***	***SD***	***CV***	***Other***	***Total***	***SD***	***CV***	***Other***	***Total***	***SD***	***CV***	***Other***	***Total***
Modeled as Continuous Variable																
Stroke	3 of 9	2 of 4	8 of 23	13 of 36	0 of 3	1 of 2	2 of 16	3 of 21	1 of 2	-	0 of 2	1 of 4	-	-	-	-
Stroke Mortality	0 of 1	-	0 of 1	0 of 2	-	-	0 of 1	0 of 1	-	0 of 1	-	0 of 1	-	-	-	-
CHD	4 of 6	2 of 3	9 of 22	15 of 31	1 of 3	1 of 2	1 of 14	3 of 19	0 of 2	-	0 of 2	0 of 4	-	-	-	-
CHD Mortality	0 of 1	-	0 of 1	0 of 2	-	-	0 of 1	0 of 1	-	0 of 1	-	0 of 1	-	-	-	-
CVD	3 of 8	3 of 4	7 of 10	13 of 22	1 of 3	0 of 1	0 of 2	1 of 6	0 of 1	0 of 1	-	0 of 2	-	-	-	-
CVD Mortality	5 of 9	2 of 6	4 of 14	11 of 29	1 of 4	0 of 2	1 of 1	2 of 7	2 of 3	1 of 2	-	3 of 5	0 of 1	0 of 1	-	0 of 2
All-Cause Mortality	4 of 7	8 of 9	11 of 12	23 of 28	2 of 5	2 of 3	3 of 5	7 of 13	1 of 3	0 of 2	1 of 2	2 of 7	1 of 1	1 of 1	-	2 of 2
Composite Outcome: All-Cause Mortality and CVD	1 of 1	1 of 1	-	2 of 2	0 of 1	0 of 1	-	0 of 2	-	-	-	-	-	-	-	-
Sub-total	20 of 42	18 of 27	39 of 83	77 of 152	5 of 19	4 of 11	7 of 40	16 of 70	4 of 11	1 of 7	1 of 6	6 of 24	1 of 2	1 of 2	-	2 of 4
Modeled as Categorical Variable																
Stroke	9 of 13	7 of 8	18 of 20	34 of 41	3 of 7	3 of 5	9 of 13	15 of 25	1 of 2	-	-	1 of 2	1 of 1	-	-	1 of 1
Stroke Mortality	1 of 6	0 of 4	1 of 5	2 of 15	0 of 4	0 of 4	1 of 5	1 of 13	-	-	-	-	-	-	-	-
CHD	1 of 5	0 of 1	2 of 2	3 of 8	2 of 3	0 of 1	-	2 of 4	0 of 2	-	-	0 of 2	-	-	-	-
CHD Mortality	1 of 6	1 of 4	5 of 5	7 of 15	0 of 4	0 of 4	0 of 5	0 of 13	-	-	-	-	-	-	-	-
CVD	6 of 8	4 of 4	14 of 15	24 of 27	3 of 4	4 of 4	9 of 12	16 of 20	-	-	-	-	-	-	-	-
CVD Mortality	6 of 11	2 of 5	7 of 7	15 of 23	1 of 7	0 of 5	2 of 5	3 of 17	1 of 2	-	-	1 of 2	-	-	-	-
All-Cause Mortality	7 of 12	5 of 7	7 of 12	19 of 31	3 of 9	1 of 7	4 of 10	8 of 26	1 of 2	1 of 2	-	2 of 4	-	-	-	-
Composite Outcome: All-Cause Mortality/CVD	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sub-total	31 of 61	19 of 33	54 of 66	104 of 160	12 of 38	8 of 30	25 of 50	45 of 118	3 of 8	1 of 2	-	4 of 10	1 of 1	-	-	1 of 1
Total	**51 of 103**	**37 of 60**	**93 of 149**	**181 of 312**	**17 of 57**	**12 of 41**	**32 of 90**	**61 of 188**	**7 of 19**	**2 of 9**	**1 of 6**	**10 of 34**	**2 of 3**	**1 of 2**	-	**3 of 5**

CHD, coronary heart disease; CV, coefficient of variation; CVD, cardiovascular disease; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; VVV, visit-to-visit variability.

Data are presented as the total number of analyses that showed significant positive associations of VVV with outcomes out of the total number of analyses that were reported. For example, '1 of 3' indicates that one out of a total of three analyses reported higher VVV to be associated with an increased risk for outcomes.