The Association of Blood Pressure Variability with Adverse Outcomes in a Primary Care Chronic Kidney Disease Cohort.

Short title: Blood Pressure Variability and Chronic Kidney Disease in Primary Care

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ABSTRACT

Hypertension is common in individuals with chronic kidney disease and both conditions are associated with adverse outcomes including cardiovascular morbidity. Therefore, it is clinically important to identify methods of risk prediction in individuals with chronic kidney disease. Blood pressure variability has recently emerged as a predictor of cardiovascular events and mortality in the general population, with growing evidence indicating that it may play a similar role in individuals with chronic kidney disease. However, there have been no large studies assessing blood pressure variability in individuals with chronic kidney disease in primary care, where the majority of these patients are managed. Using a retrospective observational study design, we analyzed routinely collected blood pressure readings from 16,999 individuals in The Leicester and County Chronic Kidney Disease cohort. Standard deviation, coefficient of variation and average real variability of systolic blood pressure were used to calculate blood pressure variability. During a median follow-up of 5.0 (IQR 3.3 to 5.0) years, 2053 (12.1%) patients had cardiovascular events, death occurred in 5021 (29.6%) individuals and 156 (0.9%) individuals had endstage kidney disease events. In adjusted models, standard deviation and coefficient of variation were associated with cardiovascular events, all-cause mortality and endstage kidney disease. Average real variability was associated with all-cause mortality and cardiovascular events, but not endstage kidney disease. Blood pressure variability may be an accessible, routinely collected, non-invasive measure for stratifying the risk of adverse events in individuals with chronic kidney disease in a primary care setting.

KEY WORDS

chronic kidney disease, cardiovascular outcomes, cardiovascular disease, endstage renal disease, blood pressure measurement/monitoring

INTRODUCTION

Increased blood pressure variability (BPV) has emerged as a risk factor for mortality and cardiovascular events in the last decade, with some studies claiming a comparable risk profile to cholesterol (1). However, its association with complications in individuals with chronic kidney disease (CKD) is less clear.

Blood pressure had been regarded as a static variable but measures such as ambulatory blood pressure monitoring and visit-to-visit measures can be used to assess short and longer term variability (2). Visit-to-visit blood pressure can be used to calculate variability over a defined time period.

Simple statistical measures such as standard deviation (SD) for all of an individual's blood pressure measurements can give an assessment of BPV and this has been used to evaluate its association with risk in general population studies (3,4,5). Other measures of variation such as coefficient of variation (CoV) and average real variability (ARV) have also been used to measure variability (6). CoV utilises a ratio between the SD and the mean, and so it is theoretically weighted in sensitivity to lower blood pressure values and is used as a method to reduce the influence of mean arterial blood pressure on mortality (3). ARV uses the difference between consecutive blood pressure readings, summates these values and then divides by the number of measurements minus one to give a single value of variability. ARV has shown promise as a measure of BPV, with a number of studies showing its benefit above that of simple SD (7,8,9). ARV is sensitive to sequence order, less sensitive to sampling frequency and progressive trends over time, giving it a potential advantage over other measures of BPV (8).

BPV is well studied within the general population and has been incorporated into risk stratification tools such as QRISK3 (5). Mechanisms that control both short term and long term BPV may be deranged in individuals with CKD owing to the haemodynamic and hormonal function of the renal system (10). Therefore it is important to validate BPV as a marker for cardiovascular events, all-cause mortality and ESKD in individuals with CKD. Evidence is emerging that BPV may have a key role in the progression of CKD (11,12) and worsens as CKD progresses (13). A previous prospective, secondary care nephrology cohort study has shown that long term, but not short term, BPV was associated with cardiovascular events and mortality (11). There are no similar studies conducted in a primary care CKD cohort. This is important, as primary care clinics manage the largest group of CKD patients who are largely asymptomatic from their CKD and do not require secondary care input. Individuals with less severe CKD remain at significantly elevated risk of cardiovascular events, even if their absolute risk of ESKD remains low. Therefore, identification of risk at early stages of CKD may help improve clinical outcomes, particularly those related to cardiovascular disease. Using a non-invasive, routinely collected clinical observation like blood pressure may be a cost-effective and accessible strategy to identify risks in individuals with CKD.

We therefore aimed to investigate in a primary care CKD cohort the association of BPV and its different metrics with cardiovascular, all-cause mortality and endstage kidney disease (ESKD).

METHODS

We analysed data from 'The Leicester City and County Chronic Kidney Disease' cohort (ClinicalTrials.gov Identifier: NCT03135002). All data are reported in line with the STROBE statement for cohort studies (Table S1) (14). Ethical approval for the study was received from the UK's Health Research Authority. The cohort is a primary care observational CKD cohort. Retrospective data, including all clinical blood pressure measures, were extracted from individual practice between 16th January 2017 and 13th March 2018. Information for all adults (≥18 years of age) with one or more Modification of Diet in Renal Disease (MDRD) estimated Glomerular Filtration Rate (eGFR) <65ml/min/1.73m^2 between 1st November 2006 and 1st November 2011 was extracted (Figure 1). For these individuals all serum creatinine data was extracted and used to calculate EPI eGFR (15). If an individual had two EPI eGFRs <60ml/min/1.73m^2 more than 90 days apart they were included in the cohort. Data were anonymised using the web-based CKD management and audit software tool, IMPAKT (16). ESKD at baseline was an exclusion criterion. Proteinuria was assessed using protein-to-creatinine ratio (PCR) and albumin-to-creatinine ratio (ACR). Blood pressure variability for each individual prior to the beginning of the follow-up period was measured using values of systolic blood pressure (SysBP) to calculate mean SysBP prior to baseline, SD, CoV, ARV. Item S1 describes these calculations.

The study's follow-up was between 1st November 2011 and 1st November 2016. Linked primary and secondary care events for cardiovascular events disease, EKSD and mortality events were used to identify outcomes. Cardiovascular events were

defined as acute coronary syndrome and ischaemic stroke. EKSD events were defined as haemodialysis, peritoneal dialysis or kidney transplantation.

Statistical methods

Mean and SD and/or median and interquartile range (IQR) were reported for continuous variables. Counts and percentages were reported for categorical variables. Baseline characteristics were compared by ethnicity using t-tests and chi squared. The Fine and Gray model was used for cardiovascular and ESKD events with the competing risk of all-cause mortality (17). For all-cause mortality the Cox proportional hazards model was used. Linear regression was performed to assess trends in mean population blood pressure during the baseline and follow-up periods.

Multivariable analyses for cardiovascular and all-cause mortality outcomes were adjusted for baseline age, gender, EPI eGFR, ACR, smoking status, body mass index, hypertension diagnosis, systolic and diastolic blood pressure, use of hypertensive medications, diabetes mellitus, cerebrovascular disease, ischaemic heart disease, heart failure and total cholesterol. Due to the relatively low number of events and to avoid model overfitting the multivariable analysis for ESKD was only adjusted for age, gender, EPI eGFR, ACR, hypertension diagnosis, systolic and diastolic blood pressure, and use of hypertensive medications. All definitions for co-morbidities were consistent with those used by the CKD Prognosis Consortium (18).

Multiple imputation was used with the models to account for missing data. One imputation cycle was used for every incomplete case percentage, an approximation of the missing information fractions, up to a maximum of 20 imputations (19). Log transformation was performed of all non-normally distributed variables in the

imputation model, prior to transformation back of imputed values, followed by analysis (19). All statistical analysis was performed using Stata 16.0.

RESULTS

Baseline Characteristics

16,999 patients were included in the cohort. Table 1 shows the demographics of the cohort. 10,187 individuals (59.9%) were female with a mean age of 77.3 years (SD 9.9). A total number of 242,110 SysBP measurements were taken. The mean SysBP measures per patient was 14.2 (SD: 8.8). Mean standard deviation, CoV and ARV were 14.0 mmHg (SD 5.6), 0.10 (SD 0.04) and 13.1mmHg (SD 5.9) respectively. Mean and median eGFR were 48.5 (SD 9.9) and 50 (IQR 40 to 56) ml/min/1.73m^2 respectively. 5,460 (32.1%) of individuals had a missing data value for ACR. During a median follow-up of 5.0 (IQR 3.3 to 5.0) years, 2053 (12.1%) patients had cardiovascular events, death occurred in 5021 (29.6%) individuals and 156 (0.9%) ESKD events.

Trends in Blood Pressure Over Time

A decline in mean population blood pressure was visually observed over time, with a slowing of the decline at later dates(Figure 2). Linear regression confirmed this suggesting a fall in population mean blood pressure of approximately 0.75mmHg per year (beta-coefficient -0.73, 95% CI -0.71 to -0.74, p<0.001). The rate of decline in population mean blood pressure was faster in the baseline period compared to the follow-up period (beta coefficient -1.04,95% (CI: -1.00 to -1.08, p<0.001) compared to -0.51 (95% CI: -0.48 to -0.55, p<0.001)).

Correlation of Blood Pressure Measures

The relationships of baseline SysBP, SD, CoV and ARV were assessed. Scatterplots of their relationship are shown in Figure 3. The variation in baseline SysBP was not predicted by the measures of SysBP variation (R^2 <0.02 for all measures) but SysBP SD variation was predicted by CoV and ARV (R^2 0.93 and 0.64 respectively).

Association with Outcomes

The association of blood pressure measures with outcomes in unadjusted and adjusted analysis are shown in Table 2. Results for all variable in the fully adjusted models are shown in Tables S2, S3 and S4.

Cardiovascular Events

In adjusted analysis, the established risk factors of age, smoking, diabetes mellitus, cerebrovascular disease, ischaemic heart disease and total cholesterol were all associated with cardiovascular disease events (p<0.001 for all variables). EPI eGFR was associated with cardiovascular events (SHR 0.992 per ml/min/1.73m^2, 95% CI 0.988-0.996, p<0.001), but there was limited evidence for an association with ACR (SHR 1.001 per mg/mmol, 95% CI 1.000-1.002, p=0.117). All measures of blood pressure and its variation were directly associated with cardiovascular events in unadjusted analysis (p=0.001 or less for all five measures). Measures of SBV were all associated with cardiovascular events in unadjusted analysis (p<0.001 for all three measures). There was limited evidence for a difference in the magnitude of the association of most recent SysBP measure and the mean of all SysBP prior to the beginning of follow-up (p=0.076 for interaction). A similar lack of relationship was found in an adjusted model (p=0.139 for interaction). All three measures of BPV

were directly associated with cardiovascular events in adjusted analysis (p<0.001 for all three measures).

All-cause Mortality Events

In adjusted analysis, the non-SysBP derived variables of age, male gender, smoking, body mass index, diabetes mellitus, cerebrovascular disease, ischaemic heart disease, heart failure and total cholesterol were all associated with all-cause mortality events. Both eGFR (HR 0.982 per ml/min/1.73m^2, 95% CI 0.979-0.985, p<0.001) and ACR (HR 1.003 per mg/mmol, 95% CI 1.001 to 1.005, p=0.005) were also associated with this group of events. Latest and mean SysBP were inversely associated with all-cause mortality events in unadjusted and adjusted analysis (p<0.001 for all four analyses). There was no evidence for a difference in magnitude of effect between latest SysBP and mean SysBP in either unadjusted (p=0.293 for interaction) or adjusted (p=0.344 for interaction) analysis. All three measures of BPV were associated with a direct relationship with risk of all-cause mortality events (p<0.001 for all unadjusted and adjusted analyses).

Endstage Renal Disease Events

All four established variables for prediction of ESKD events used in the Kidney Failure Risk Equation, age, gender, EPI eGFR and ACR, were associated with events in adjusted analysis (p<0.01 for all four). Unadjusted analysis for ESKD events showed limited evidence for a relationship with latest SysBP (SHR 1.007, 95% CI 0.999-1.016, p=0.094), mean SysBP (SHR 1.014, 95% CI 1.001-1.028, p=0.039) and ARV (SHR 1.160, 95% CI 0.985-1.367, p=0.075). There was stronger evidence for a relationship with SD (SHR 1.240, 95% CI 1.067-1.441, p=0.005) and

CoV (SHR 1.200, 95% CI 1.035-1.391, p=0.016) in unadjusted analysis. Adjusted analysis for ESKD events showed similar patterns of results. Both SD (SHR 1.234, 95% CI 1.029-1.480, p=0.023) and CoV (SHR 1.192, 95% CI 1.006-1.412, p=0.043) had stronger evidence for a relationship with ESKD events than ARV (SHR 1.166, 95% CI 0.943-1.441, p=0.157).

DISCUSSION

The aim of this study was to evaluate the predictive value of BPV measures for outcomes in a primary care CKD cohort. The current data suggest that measures of SysBP and its variability were associated with cardiovascular, all-cause mortality and ESKD events in unadjusted analysis. Similar findings were found in adjusted analysis for cardiovascular and all-cause mortality events. The relationship with ESKD events was less clear and may be related to the relatively limited number (n=156) of these events. SD and CoV may be the better predictors of ESKD events in adjusted analysis. All adjusted models included baseline SysBP as a variable in the model. For non-variability SysBP measures there was no evidence that a mean of all available SysBP measures prior to the beginning of follow-up was better than the latest SysBP measurement. Therefore, in addition to the latest SysBP measurement, SD and CoV may be the better BPV measures associated with outcomes in a primary care CKD cohort. Further, on the basis of parsimony and clinical interpretability, SD may be recommended over CoV as a potential additional predictive variable for the three reported outcomes.

These results reaffirm the outcomes of another similar study in secondary care CKD which showed long term BPV was associated with an increased risk of mortality and cardiovascular events in individuals CKD (12). This current study observed similar results in a larger, primary care cohort. The findings of this are clinically important. Primary care observes a large share of the CKD population. Many of these individuals with CKD, may be asymptomatic and do require management of their CKD in secondary care. Those who continue to be managed in primary care remain at higher risk of poor clinical outcomes, particularly in relation to cardiovascular

disease, when compared to the general population (20). Therefore, it is important that these individuals can have their risk assessed in a primary care setting. Blood pressure is a routinely collected, non-invasive measurement. BPV may therefore be an accessible and potentially cost-effective means to identify risk in these individuals.

Mortality is the most consistently associated outcome with BPV in the surrounding literature (21, 22, 23). Cardiovascular and ESKD events are more inconsistent (20, 22, 23, 24). A study with 114,900 individuals with stage 3-4 CKD and 582 ESKD events showed that higher SD and ARV values predicted ESKD events, although CoV did not (22). In this study, only 156 ESKD events were recorded. It may be that our dataset was under-powered to detect the association between BPV and ESKD events. Alternatively, as seen by other studies, it may be that there is no clinically significant correlation between BPV and ESKD events (21, 22). It remains to be seen if BPV can predict ESKD events in individuals with CKD in future studies.

The study population was in Leicestershire in the United Kingdom. This region has a particularly diverse population with a large proportion of people of ethnicities that carry a higher risk of cardiovascular events (25, 26). The influence of ethnicity on BPV is unclear, but the relationship of ethnicity and cardiovascular events may contribute to the results seen in this study.

Many mechanisms to explain the role of BPV have been suggested, including in individuals with CKD (10). Behavioural phenomena such as exercise levels can acutely influence an individual’s blood pressure (10). Biological modulation of blood pressure may be linked to a variety of factors including blood viscosity, hormonal factors and autonomic nervous system activity (27). Where some of these changes

in SysBP may be appropriate, our results suggest that increased levels of variation may lead to poor cardiovascular outcome and mortality. Further studies are needed to evaluate the biological phenomena that cause appropriate levels of BPV to become detrimental to health in CKD.

There are known limitations of the measures of variability studied in the presented cohort. SD and CoV are closely mathematically related and there was evidence in the current cohort of co-linearity between the variables. CoV is a ratio of SD:mean and therefore varies more at lower absolute values of the measurement. It may have been expected therefore that in the current cohort, with generally well controlled blood pressure, CoV may have been a more sensitive predictor of events than SD. However, we found no evidence for this hypothesis.

ARV emphasises the sequence of measurements in addition to variability, therefore it may provide additional prognostic information. Due to the sequence sensitivity, two individuals with entirely different SysBP profiles can have similar ARV values. Previous studies have demonstrated ARV to be superior to SD in assessing cardiovascular disease risk in hypertensive individuals (*15*). Our study results did not indicate any superiority of the ARV measure. The ARV measure is also less sensitive when frequency of measurement is low (7). The precise minimum number of values needed to satisfy this variable remains unclear.

The correlation between ARV and SD (R^2 =0.64) was not strong. As ARV is less affected by long term changes than SD/CoV, this implies the presence of trends in our data. This was confirmed by graphically comparing population mean SysBP and time (Figure 2) and in linear regression . Population mean SysBP fell by approximately 0.75mmHg per year with a slower decline during the follow-up period.

A likely cause for this may be an age-related SysBP changes. There were differences between SD/CoV and ARV in ESKD outcomes in the unadjusted analysis. This difference was not observed in the adjusted analysis; likely due to adjusting for mean SysBP in the model. However, our follow up period (5 years) may have been too short to appropriately capture the influence of progressive trends. A longer follow up period may have demonstrated differences between ARV and SD/CoV as trends have more time to establish. BPV caused by progressive changes may have an entirely different prognosis to more randomly observed BPV.

Our study has limitations. The minimum number of blood pressure measurements required over a certain period of time to ensure variability as a valid measure is currently not clear. This will affect its clinical utility to identify higher risk individuals in clinical care. The effects of an informative visiting process, such as may be the case in the current data, may also apply. This occurs when measurements are not taken at fixed or random intervals, but instead in relation to clinical events. For instance, an individual with high blood pressure or an acutely unstable condition is likely to seek medical care more often and therefore have more blood pressure measurement than an individual with controlled hypertension and with limited chronic or acute conditions. Conversely, patients in the acute phase of decline are more likely to present to secondary care services, minimising the potential bias in our data. Further studies are needed to establish the practical applications and limitations of BPV as a predictive tool in CKD populations.

In a retrospective observational study, it is difficult to infer the direction of causality. It could be that the general decline in an individual’s condition that precedes cardiovascular events and death would favour an increase in BPV.

Medications factors are also likely to have a major influence on blood pressure variability, with those starting or changing treatments expected to have the greatest BPV. Adjusted analysis included the use of medications prior to the start of follow-up. As we were assessing prognosis and risk of events according to BPV at baseline, we did not include use of medications, or any other variable, as a time varying co-variable throughout the study's follow-up. As with any routinely collected data, there may be differences in how SysBP was measured between sites. There was no standardisation of measurement quality and this may have contributed to BPV. Variations are likely to be minimal, as these were all collected by health care professionals trained to be competent within the National Health Service in the UK. SysBP values were also recorded in a practice, and did not include values measured by patients or values from continuous blood pressure monitoring methods.

In conclusion, the current study has assessed the association of cardiovascular, all-cause mortality and ESKD events with systolic BPV measures in a primary care CKD cohort. The SysBP measures of SD and CoV were associated with these all three event types in adjusted, including baseline SysBP, analysis. On the basis of parsimony and clinical interpretability, the use of SD should be considered for predicting outcomes in individuals with CKD.

AUTHORS CONTRIBUTION

Research idea and study design: SP, LC, RM. Literature review: SP, LC, MS. Data acquisition: DS, JM, RM. Data Analysis: RM. Statistical analysis: RM. Supervision: LG, NJB, RM. Drafting of manuscript: SP, LC, MS and RM

Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors approved the final draft of the manuscript.

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RM was funded by Kidney Research UK from 2015-2018 when the data for the cohort was collected (Grant Number TF2/2015). Other than external peer review of the grant for the study, Kidney Research UK had no role in study design; collection, analysis, and interpretation of data; writing the report; or the decision to submit the current report for publication.

DISCLOSURES

Dr David Shepherd and the University of Leicester own the intellectual property rights for the IMPAKT data tool which was used for data extraction. The authors declare no other relevant disclosures in relation to this study.

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TABLES

Table 1: Baseline characteristics of cohort. Figures in parentheses refer to standard deviation for mean values, interquartile range for medians values and percentage for counts.

Baseline Characteristics	Mean/Median/n
n	16,999
Age, mean	77.4 (19-104)
Female, n	10,187 (59.9)
EPI eGFR, mean	48.5 (11.7)
EPI eGFR, median	50 (40 to 56)
ACR, mean	10.6 (35.6)
ACR, median	2.9 (0.8 to 7.3)
Hypertension, n	16,089 (94.7)
SysBP, mean	134.8 (16.4)
DBP, mean	74.0 (9.9)
SysBP measurements, n	242,110
SysBP measurements per patient, median	13 (9 to 18)
Individual SBP mean, mean	139.6 (12.5)
SD of SysBP, mean	13.4 (5.6)
CoV of SysBP, mean	0.10 (0.04)
ARV of SysBP, mean	13.9 (5.9)
Diabetes Mellitus Type 1, n	238 (1.4)
Diabetes Mellitus Type 2, n	4,549 (26.8)
Cerebrovascular disease, n	2,103 (12.4)
Ischaemic heart disease, n	4,346 (25.6)
Outcomes	
Follow-up years, mean	4.1 (1.5)
Follow-up years, median	5.0 (3.3 to 5.0)
Cardiovascular events, n	2,053 (12.1)
ESKD events, n	156 (0.9)
Death, n	5,021 (29.5)

Table 2: Unadjusted and adjusted analysis of all-cause mortality, cardiovascular and endstage renal disease events and their association with measures of blood pressure variability. Hazard ratio (HR) for all-cause mortality, subdistribution hazard ratio (SHR) for cardiovascular and endstage renal disease events. HR/SHRs for each BPV variable are shown for each standard deviation change in the variable.

Variable	Unadjusted		Adjusted	
	(S)HR (95%CI)	p-value	(S)HR (95%CI)	p-value
	All-cause Mortality Event			
Latest SysBP	0.994 (0.993-0.996)	<0.001	0.993 (0.991-0.995)	<0.001
Mean SysBP	0.995 (0.993-0.997)	<0.001	0.994 (0.991-0.997)	<0.001
SD	1.207 (1.176-1.239)	<0.001	1.079 (1.050-1.109)	<0.001
CoV	1.255 (1.223-1.289)	<0.001	1.103 (1.073-1.134)	<0.001
ARV	1.169 (1.140-1.199)	<0.001	1.078 (1.051-1.109)	<0.001
	Cardiovascular Event			
Latest SysBP	1.005 (1.002-1.007)	0.001	1.003 (1.000-1.006)	0.060
Mean SysBP	1.009 (1.005-1.012)	<0.001	1.007 (1.002-1.011)	0.003
SD	1.188 (1.142-1.236)	<0.001	1.095 (1.050-1.143)	<0.001
CoV	1.174 (1.128-1.222)	<0.001	1.087 (1.042-1.134)	<0.001
ARV	1.170 (1.126-1.215)	<0.001	1.099 (1.054-1.144)	<0.001
	Endstage Renal Disease Event			
Latest SysBP	1.007 (0.999-1.016)	0.094	1.004 (0.992-1.016)	0.512

Mean SysBP	1.014 (1.001-1.028)	0.039	1.010 (0.996-1.024)	0.162
SD	1.240 (1.067-1.441)	0.005	1.234 (1.029-1.480)	0.023
CoV	1.200 (1.035-1.391)	0.016	1.192 (1.006-1.412)	0.043
ARV	1.160 (0.985-1.367)	0.075	1.166 (0.943-1.441)	0.157

FIGURE LEGEND

Figure 1: Diagram showing inclusion criteria, baseline period and follow up period. Extraction of data was conducted retrospectively.

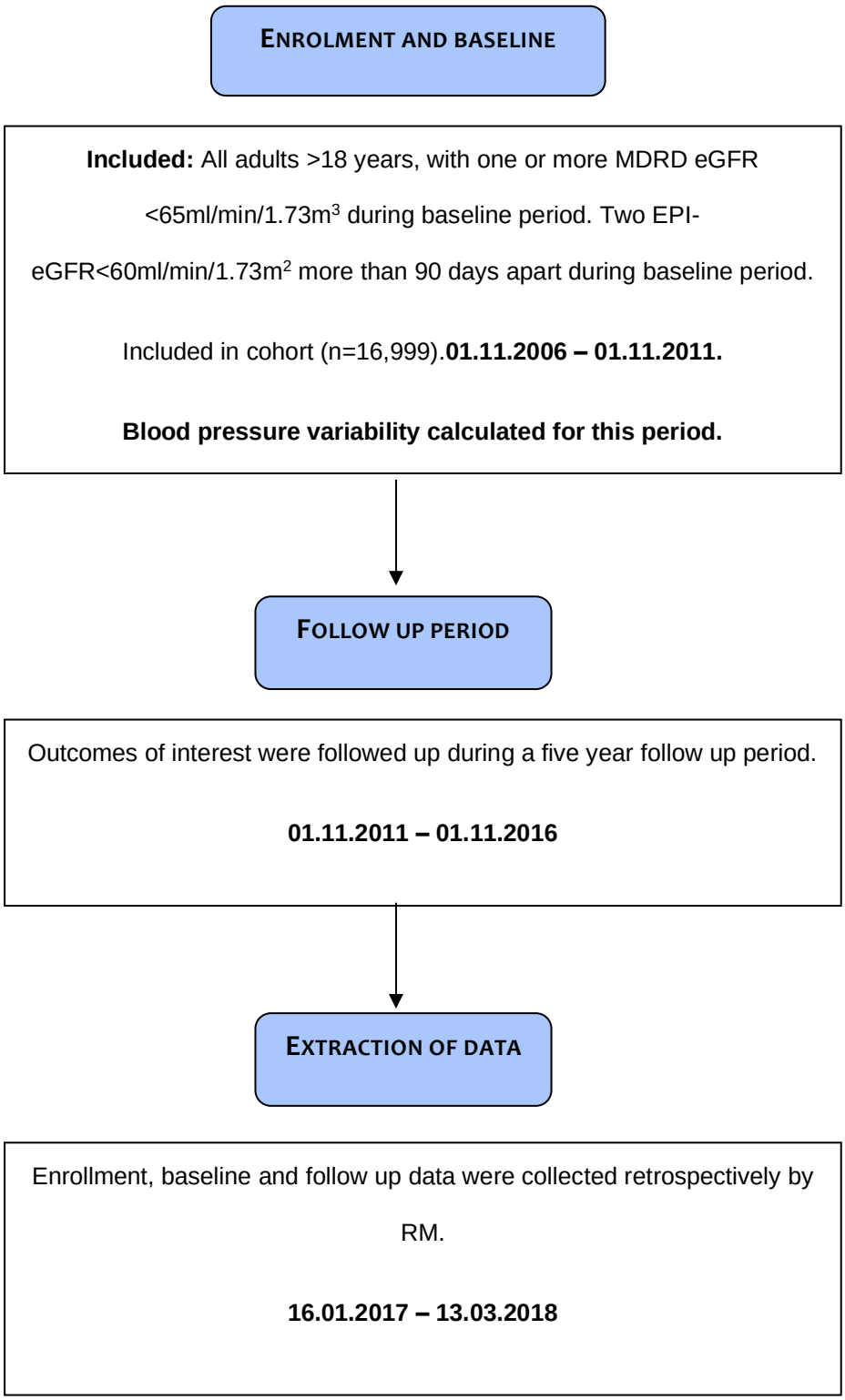


Figure 2: Diagram showing the trend of population mean systolic blood pressure over time, including both baseline and follow-up periods.

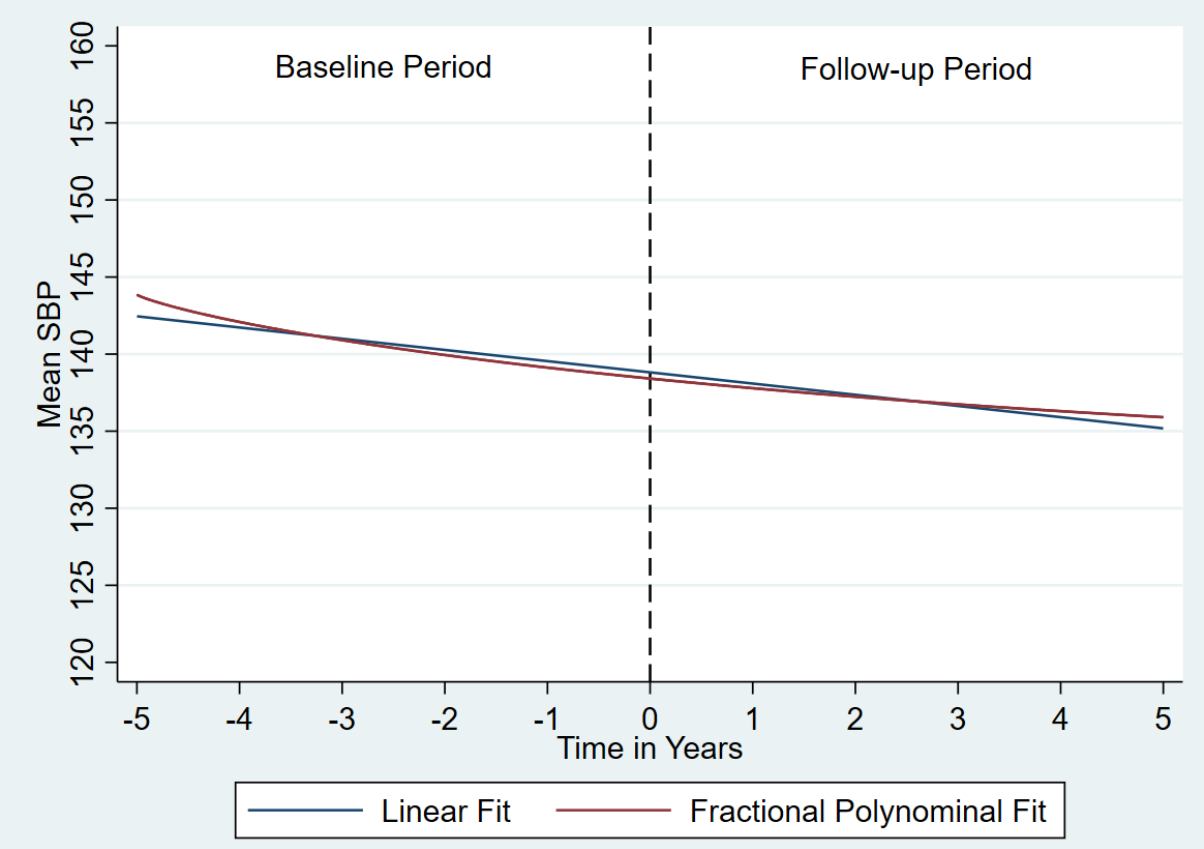
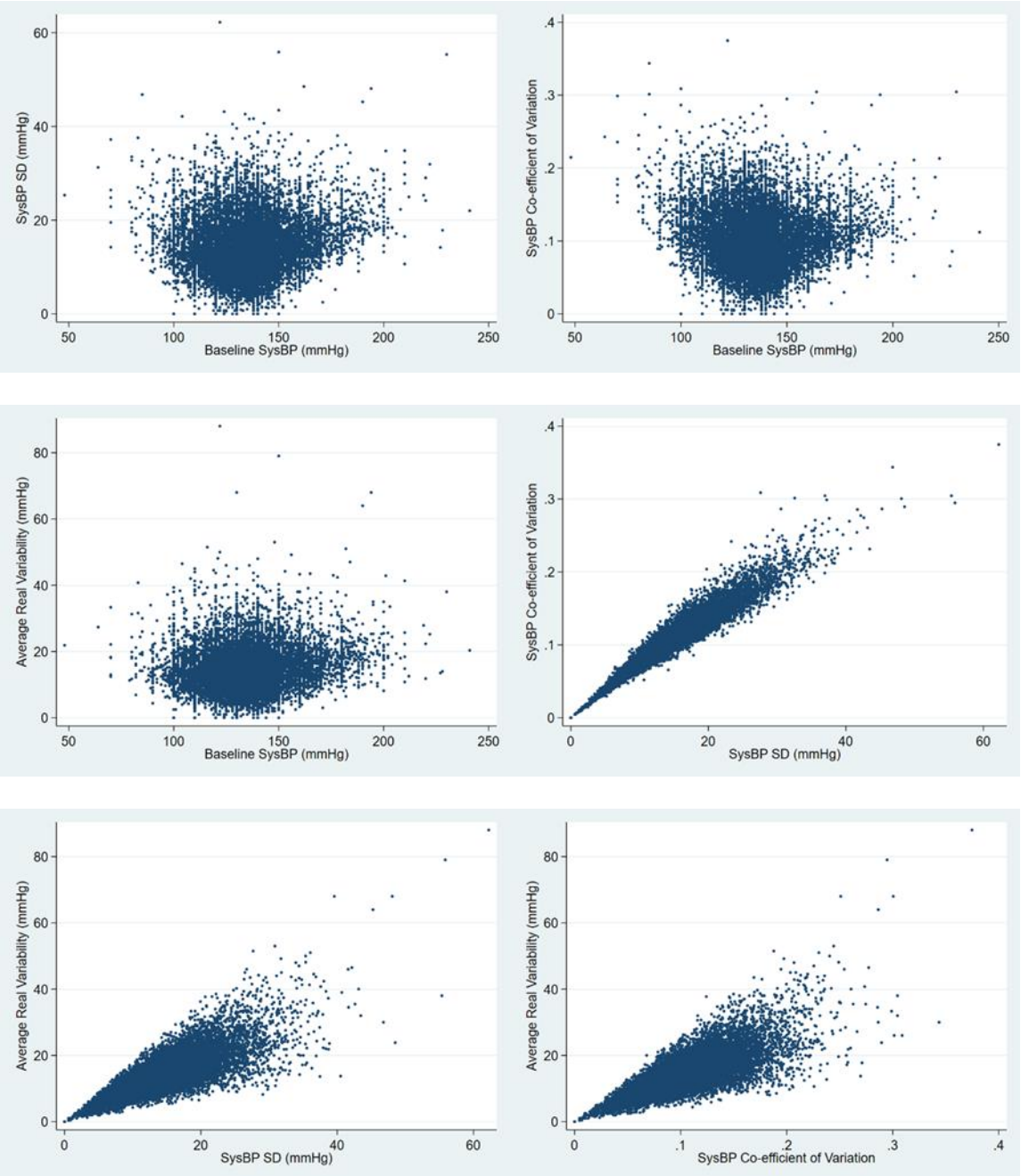


Figure 3: Scatterplots demonstrating the relationship of Baseline SysBP, SD, CoV and ARV



SUPPLEMENTARY MATERIAL

Supplementary Table 1 – STROBE checklist for manuscript.

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Abstract, page 2.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Abstract, pages 2-3.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Introduction, pages 4-5.
Objectives	3	State specific objectives, including any prespecified hypotheses Introduction, page 5.
Methods		
Study design	4	Present key elements of study design early in the paper Methods, pages 6-7.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Methods, page 6.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Methods, page 6.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed Not applicable to our study.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Methods, pages 6-7.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Methods, pages 6-7.
Bias	9	Describe any efforts to address potential sources of bias Methods, page 7.
Study size	10	Explain how the study size was arrived at Methods, page 6. Cohort study with no sample size calculation. Primary care centres clearly defined (ClinicalTrials.gov Identifier: NCT03135002).

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Methods, pages 6-7.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding. Methods, pages 6-7. Statistical Methods section included.
		(*b*) Describe any methods used to examine subgroups and interactions Not applicable.
		(*c*) Explain how missing data were addressed. Methods, pages 6-7. Statistical Methods describes the multiple imputation model.
		(*d*) If applicable, explain how loss to follow-up was addressed. Not applicable.
		(*e*) Describe any sensitivity analyses. Not applicable.
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Results, page 8 and Table 1.
		(b) Give reasons for non-participation at each stage. Not applicable.
		(c) Consider use of a flow diagram. Not presented as described in Results, page 8.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Results, page 8 and Table 1.
		(b) Indicate number of participants with missing data for each variable of interest. Results, page 8 and Table 1.
		(c) Summarise follow-up time (eg, average and total amount). Results, page 8 and Table 1.
Outcome data	15*	Report numbers of outcome events or summary measures over time. Results, page 8 and Table 1.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. Methods, page 7. Results, pages 8,9,10 and Tables 2, S2, S3, S4.
		(*b*) Report category boundaries when continuous variables were categorized.

		Categorisation not performed.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. Not applicable to study.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses. Not applicable.
Discussion		
Key results	18	Summarise key results with reference to study objectives. Discussion, page 11.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. Discussion, pages 12,13.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. Discussion, page 13.
Generalisability	21	Discuss the generalisability (external validity) of the study results. Discussion, pages 11,13.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. Funding declaration, page 14.

Supplementary Item 1 – Supplementary Item 1 – Description of formulae to calculate Standard Deviation, Coefficient of Variation and Average Real Variability.

Blood pressure variability was calculated for each individual using standard deviation (SD), coefficient of variation (CoV) and average real variability (ARV) of all SysBP measures available.

CoV was calculated by dividing an individual's SD by their mean SysBP (μ) value.

$$CoV = \frac{SD}{\mu}$$

ARV was calculated by ascertaining the difference between consecutive SysBP readings (k and k+1), summating these values for each combination of consecutive SysBP measurements and then dividing by the number of measurements minus one.

$$ARV = \frac{1}{n-1}\sum_{k=1}^{n-1}(SBP_{k+1} - SBP_k)$$

Supplementary Table 2 - Adjusted Analysis of the Association between Baseline Data and Cardiovascular Events. All-cause mortality events treated as a competing event. All variables used in the model are reported. All co-morbidity categorical variables use absence of the condition as the comparator and smoking status uses never smoked. SHR – subdistribution hazard ratio, CI – confidence interval. Units: age per year, EPI eGFR per ml/min/1.73m^2, ACR per mg/mmol, body mass index per kg/m^2, blood pressure per mmHg, total cholesterol per mmol/L.

Variable	SHR	95% CI		p-value
		Lower	Upper	
Age	1.038	1.032	1.043	<0.001
Female	0.931	0.846	1.024	0.141
EPI eGFR	0.992	0.988	0.996	<0.001
ACR	1.001	1.000	1.002	0.117
Ex-smoker	1.075	0.976	1.185	0.143
Current smoker	1.467	1.254	1.716	<0.001
Body mass index	0.997	0.988	1.006	0.493
Hypertension	1.115	0.793	1.568	0.531
Use of hypertensive medication	1.205	0.953	1.522	0.119
Systolic blood pressure	1.003	1.000	1.006	0.060
Diastolic blood pressure	1.004	0.999	1.009	0.139
Diabetes mellitus	1.317	1.199	1.448	<0.001
Cerebrovascular disease	1.905	1.708	2.125	<0.001
Ischaemic heart disease	1.497	1.359	1.648	<0.001
Heart failure	1.060	0.923	1.217	0.409
Total cholesterol	1.073	1.033	1.113	<0.001

Supplementary Table 3 – Adjusted Analysis of the Association between Baseline Data and All-cause Mortality. All variables used in the model are reported. All co-morbidity categorical variables use absence of the condition as the comparator and

smoking status uses never smoked. HR – hazard ratio, CI – confidence interval. Units: age per year, EPI eGFR per ml/min/1.73m^2, ACR per mg/mmol, body mass index per kg/m^2, blood pressure per mmHg, total cholesterol per mmol/L.

Variable	HR	95% CI		p-value
		Lower	Upper	
Age	1.098	1.094	1.103	<0.001
Female	0.921	0.865	0.980	0.010
EPI eGFR	0.982	0.979	0.985	<0.001
ACR	1.003	1.001	1.005	0.005
Ex-smoker	1.216	1.143	1.294	<0.001
Current Smoker	1.946	1.757	2.154	<0.001
Body Mass Index	0.991	0.985	0.997	0.004
Hypertension	1.247	1.012	1.536	0.038
Use of hypertensive medication	0.961	0.831	1.111	0.593
Systolic blood pressure	0.993	0.991	0.995	<0.001
Diastolic blood pressure	1.000	0.997	1.003	0.899
Diabetes mellitus	1.259	1.182	1.341	<0.001
Cerebrovascular disease	1.329	1.235	1.430	<0.001
Ischaemic heart disease	1.141	1.072	1.216	<0.001
Heart failure	1.865	1.729	2.011	<0.001
Total cholesterol	0.960	0.932	0.989	0.008

Supplementary Table 4 – Adjusted Analysis of the Association between Baseline Data and Endstage Renal Disease Events. All-cause mortality events treated as a competing event. All variables used in the model are reported. All co-morbidity categorical variables use absence of the condition as the comparator. SHR –

subdistribution hazard ratio, CI – confidence interval. Units: age per year, EPI eGFR per ml/min/1.73m^2, ACR per mg/mmol, blood pressure per mmHg..

Variable	SHR	95% CI		p-value
		Lower	Upper	
Age	0.936	0.924	0.947	<0.001
Female	0.588	0.418	0.828	0.002
EPI eGFR	0.888	0.872	0.903	<0.001
ACR	1.002	1.001	1.004	0.007
Hypertension	0.242	0.028	2.076	0.196
Use of hypertensive medication	3.336	0.443	25.142	0.242
Systolic blood pressure	1.004	0.992	1.016	0.512
Diastolic blood pressure	0.997	0.978	1.016	0.748