

# Time-Varying Association of Individual BP Components with eGFR in Late-Stage CKD

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## Abstract

**Background and objectives** The association of individual BP components with changes in eGFR in patients with late-stage CKD is unknown. The objectives of our study were to examine the associations of systolic BP, diastolic BP, and pulse pressure with continuous temporal changes in eGFR and an eGFR decline  $\geq 30\%$  in late-stage CKD.

**Design, setting, participants, & measurements** We performed a retrospective cohort study (2010–2015) of patients with CKD in a multidisciplinary CKD clinic with an eGFR  $\leq 30$ . The associations of repeat measures of BP (systolic BP, diastolic BP, and pulse pressure) with eGFR were examined using general linear mixed models. The associations of BP components and eGFR decline  $\geq 30\%$  were examined with time-varying Cox models.

**Results** In total, 1203 patients were followed for a median of 548 days (interquartile range, 292–913), with an average of 6.7 visits and BP measures per patient. Mean baseline systolic BP, diastolic BP, pulse pressure, and eGFR were 139.2 mmHg, 73.2 mmHg, 64.9 mmHg, and 16.8 ml/min, respectively. Systolic BP and diastolic BP measures over time were statistically significantly associated with changes in eGFR ( $P < 0.001$ ), whereas pulse pressure was not. Patients with extremes of systolic BP ( $< 105$  or  $> 170$ ) and high diastolic BP ( $> 90$ ) measures were at a higher risk of GFR decline  $\geq 30\%$  (systolic BP  $< 105$ : hazard ratio, 1.51; 95% confidence interval, 0.98 to 2.34; systolic BP  $> 170$ : hazard ratio, 1.62; 95% confidence interval, 1.05 to 2.49; referent systolic BP = 121–130; diastolic BP = 81–90: hazard ratio, 1.40; 95% confidence interval, 0.99 to 1.86; diastolic BP  $> 90$ : hazard ratio, 1.83; 95% confidence interval, 1.21 to 2.77; referent diastolic BP = 61–70). The findings were consistent after multiple sensitivity analyses. Pulse pressure was not significantly associated with risk of eGFR decline.

**Conclusions** In patients referred to a multidisciplinary care clinic with late-stage CKD, only extremes of systolic BP and elevations of diastolic BP were associated with eGFR decline.

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## Introduction

Elevated BP is a well established risk factor for CKD progression (1). Randomized, controlled trials and observational studies consistently show that BP above recommended targets increases the risk of adverse outcomes (2–10). Despite evidence for BP control, considerable uncertainty still exists in patients with stage 4/5 CKD, because they are often excluded from trials or if included, present only in small numbers (8,9,11). Additionally, the model of care has changed with the introduction of widely available multidisciplinary CKD clinics. Whether this influences the relationship between BP control and the progression of CKD remains unknown. Indeed, evidence to date focuses on ESRD as opposed to declines in GFR. Understanding the role of BP in CKD progression is important. Declining GFR is not only associated with ESRD but also, associated with higher mortality, cardiac events, infection, and hospitalizations (12). Moreover, in an era of the late-stage CKD population becoming increasingly elderly, a significant proportion of patients may not choose dialytic therapies and

instead, may opt for conservative care (13,14). Examining the role of elevated BP may aid in determining optimal targets in late-stage CKD to retard progression of CKD and avoid complications associated with declining GFR.

Few studies have examined the specific associations of BP on changes in GFR accounting for repeat measures (time varying) (2,6). Changes in numerous clinical and laboratory factors, such as albumin, proteinuria, serum phosphate, and BP measures, have been associated with ESRD and may affect the decline in GFR in late-stage CKD (2,15–17). Recently, the Chronic Renal Insufficiency Cohort (CRIC) showed a dramatic alteration in the risk of ESRD by accounting for repeat time-varying factors (6).

To address these knowledge gaps, we set out to examine the time-varying associations of BP indexes (systolic BP [SBP], diastolic BP [DBP], and pulse pressure [PP]) with eGFR in patients with stage 4/5 CKD managed in a multidisciplinary clinic. Specifically, we examined the associations of SBP, DBP and PP with changes in eGFR over time as well as

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their association with time to decline  $\geq 30\%$  in late-stage CKD.

## Materials and Methods

### Study Cohort

This is a retrospective cohort study of patients who were followed in a multidisciplinary tertiary care hospital CKD clinic from January of 2010 to November of 2015 (18). The tertiary care specialty CKD clinic serves a catchment area of approximately 1.2 million individuals in Ottawa, Canada. The first clinic visit was deemed the date of study entry. Patients are seen in the clinic regularly, with a frequency between every 2 weeks and twice per year depending on clinician perception of need. Referral criteria to the multidisciplinary tertiary care hospital CKD were (1) a diagnosis of CKD and (2) an eGFR  $< 30$  ml/min per 1.73 m<sup>2</sup> or a rapid decline in kidney function (calculated using the Modification of Diet in Renal Disease [MDRD] formula) (19).

The clinic is staffed by a multidisciplinary team, including physicians, nurses, dietitians, pharmacists, and social workers specializing in patients approaching ESRD. Patients are referred to the clinic by their primary nephrologists in anticipation of ESRD. There are standardized treatment procedures for vaccinations, physician consensus regarding anemia management, preferred medications, and BP targets. The study was reviewed and approved by the Ottawa Health Sciences Network Research Ethics Board.

### Data Collection

Data were abstracted from clinical charts and electronic medical records for all patients by trained personnel starting in January of 2010. Data are routinely validated by random audit of 5% of entries every 6 months with  $> 95\%$  data accuracy (18). Variables collected include demographics (age and sex), cause of CKD, comorbidities (coronary artery disease, congestive heart failure, diabetes, malignancy, and peripheral vascular disease), outcomes with dates (death and dialysis initiation), longitudinal laboratory measures (hemoglobin, potassium, phosphate, proteinuria, eGFR calculated by MDRD equation, and albumin), physiologic parameters (BP and body mass index), and medications.

### Outcomes and Exposures

The main predictors of interest were SBP, DBP, and PP. At each clinic visit, BP was measured once by a trained nurse using the auscultatory method. BP measurements were made with patients in the sitting position after 15 minutes of rest with an appropriately fitted BP cuff and the cuff placed directly on the skin. The main outcomes of interest for this study were (1) change in eGFR and (2) eGFR decline  $\geq 30\%$  from baseline. Change in eGFR (in milliliters per minute per 1.73 m<sup>2</sup>) was examined using repeated measures of eGFR analyzed as a continuous variable. eGFR decline  $\geq 30\%$  was examined as the time to decline of  $\geq 30\%$  from baseline analyzed as a categorical variable. The eGFR was measured at each study visit and calculated by the four-variable MDRD equation (19). Demographics and comorbidities (coronary artery disease, congestive heart failure, malignancy, peripheral vascular disease, and diabetes mellitus) were obtained by clinical

history of a previous diagnosis. Cause of CKD was on the basis of the responsible nephrologists' diagnosis.

### Statistical Analyses

Baseline descriptive statistics for the total analytic cohort classified by any eGFR decline of  $\geq 30\%$  are presented as mean and SD for continuous variables and frequency and proportion for categorical variables. Because proteinuria measures available were 24-hour urine collections, albumin-to-creatinine ratio (ACR), or protein-to-creatinine ratio, we categorized proteinuria as minimal (ACR  $< 30$  mg/g, protein-to-creatinine ratio  $< 27$  mg/g, or 24-hour urine protein  $< 0.03$  g/d), mild (ACR = 30 to  $< 150$  mg/g, protein-to-creatinine ratio = 27 to  $< 120$  mg/g, or 24-hour urine protein = 0.03–0.3 g/d), moderate (ACR = 150–350 mg/g, protein-to-creatinine ratio = 120–300 mg/g, or 24-hour urine protein = 0.3–3 g/d), or severe (ACR  $> 350$  mg/g, protein-to-creatinine ratio  $> 300$  mg/g, or 24-hour urine protein  $> 3$  g/d). If multiple proteinuria measures were available at the same visit, the lowest value was used. Baseline differences between groups were tested using chi-squared tests for categorical variables and two-sample *t* tests for continuous variables. The time-varying associations between the predictors SBP, DBP, and PP and the outcome (continuous eGFR) were analyzed using separate general linear mixed effects regression models estimated using Restricted Maximum Likelihood (20). Fixed effects of interest in each model were time defined in years since the first clinic visit; continuous measures of SBP, DBP, and PP; and their interactions with time. To allow for nonlinear trends in eGFR, time was modeled using restricted cubic splines, with five knots fitted at the 5th, 25th, 50th, 75th, and 95th percentiles of time corresponding to values of 1, 48, 168, 411, and 952 days, respectively. Additional statistical methods details are presented in Supplemental Material. To avoid exclusion of participants due to missing covariates, multiple imputation was performed before analysis using a Markov Chain Monte Carlo algorithm (the data augmentation algorithm) (21). To illustrate the associations of individual BP components with eGFR over time, modeled eGFR trajectories were plotted with BP variables set at the 5th, 50th, and 95th percentiles (SBP: 105, 140, and 170, respectively; DBP: 50, 70, and 90, respectively; and PP: 35, 60, and 100, respectively) (20). All remaining continuous covariates were set to their median values, whereas categorical covariates were set to their mode. The association of SBP, DBP, and PP with time to eGFR decline  $\geq 30\%$  was examined using Cox proportional hazards models for all participants ( $n = 1203$ ). For simplicity of interpretation, BP components were categorized at approximately the 5th, 25th, 50th, 75th, and 95th percentiles and modeled at baseline on cohort entry and with time-updated values. Patients were censored at study end ( $n = 287$ ), at ESRD ( $n = 540$ ), at death ( $n = 141$ ), at loss to follow-up ( $n = 20$ ), if they moved out of the province ( $n = 33$ ), or if they received a preemptive transplant ( $n = 8$ ). All statistical analyses were conducted using SAS v.9.4.

## Results

### Study Cohort

Our analytic cohort included  $n = 1203$  adult patients ( $> 18$  years old) for a total of 6123 unique observations

**Table 1. Characteristics of the CKD cohort and differences between patients with and without eGFR decline  $\geq 30\%$** 

| Characteristic                                | <i>n</i> =1203 | eGFR Decline $\geq 30\%$ , <i>n</i> =494 | No eGFR Decline $\geq 30\%$ , <i>n</i> =709 | <i>P</i> Value |
|---|----------------|--|---|----------------|
| <b>Demographics</b>                           |                |  |   |                |
| Women   | 40.6 (489)     | 37.9 (187)                               | 42.6 (302)                                  | 0.11           |
| Age, yr                                       | 65.9 SD 14.9   | 62.7 SD 15.1                             | 68.2 SD 14.3                                | <0.001         |
| Body mass index, kg/m <sup>2</sup>            | 30.1 SD 7.0    | 29.8 SD 6.7                              | 30.3 SD 7.3                                 | 0.18           |
| <b>Cause of CKD</b>                           |                |  |   |                |
| Diabetes                                      | 33.5 (403)     | 41.1 (203)                               | 28.2 (200)                                  | <0.001         |
| Ischemic nephropathy                          | 18.7 (225)     | 12.3 (61)                                | 23.1 (164)                                  |                |
| GN  | 14.0 (168)     | 18.8 (93)                                | 10.6 (75)                                   |                |
| Other   | 33.8 (406)     | 27.7 (137)                               | 38.1 (270)                                  |                |
| <b>Comorbidities</b>                          |                |  |   |                |
| Coronary artery disease                       | 33.2 (399)     | 29.8 (147)                               | 35.5 (252)                                  | 0.04           |
| Congestive heart failure                      | 27.3 (328)     | 21.9 (108)                               | 31.0 (220)                                  | <0.001         |
| Hypertension                                  | 92.8 (1116)    | 94.7 (468)                               | 91.4 (648)                                  | 0.03           |
| Peripheral vascular disease                   | 19.5 (234)     | 18.8 (93)                                | 19.9 (141)                                  | 0.66           |
| Hyperlipidemia                                | 73.9 (889)     | 73.7 (364)                               | 74.0 (525)                                  | 0.89           |
| Stroke  | 13.8 (166)     | 11.3 (56)                                | 15.5 (110)                                  | 0.04           |
| Diabetes mellitus                             | 59.6 (717)     | 59.1 (292)                               | 59.9 (425)                                  | 0.81           |
| Cigarette smoker                              | 14.3 (172)     | 15.2 (76)                                | 13.7 (96)                                   | 0.45           |
| Malignancy                                    | 14.4 (172)     | 11.7 (58)                                | 16.1 (114)                                  | 0.04           |
| ACE/ARB                                       | 51.9 (624)     | 56.7 (280)                               | 48.5 (344)                                  | 0.01           |
| <b>Laboratory</b>                             |                |  |   |                |
| Baseline eGFR, ml/min per 1.73 m <sup>2</sup> | 16.8 SD 5.5    | 14.8 SD 4.0                              | 18.2 SD 5.9                                 | <0.001         |
| Bicarbonate, mEq/L                            | 23.8 SD 4.5    | 23.4 SD 3.6                              | 24.1 SD 5.0                                 | 0.03           |
| Albumin, g/dl                                 | 3.6 SD 0.6     | 3.5 SD 0.6                               | 3.6 SD 0.6                                  | 0.03           |
| Hemoglobin, g/L                               | 11.0 SD 1.6    | 11.1 SD 1.6                              | 11.0 SD 1.6                                 | 0.06           |
| Potassium, mEq/L                              | 4.6 SD 0.6     | 4.6 SD 0.6                               | 4.5 SD 0.6                                  | 0.06           |
| Phosphate, mg/dl                              | 4.3 SD 0.9     | 4.3 SD 0.9                               | 4.3 SD 0.9                                  | 0.43           |
| Proteinuria categories                        |                |  |   | <0.001         |
| Minimal                                       | 24.3 (212)     | 13.0 (49)                                | 32.9 (163)                                  |                |
| Mild  | 25.9 (226)     | 34.5 (130)                               | 19.4 (96)                                   |                |
| Moderate                                      | 25.9 (226)     | 28.9 (109)                               | 23.6 (117)                                  |                |
| Severe  | 25.9 (226)     | 34.5 (130)                               | 19.4 (96)                                   |                |
| Mean baseline SBP, mmHg                       | 139.2 SD 21.6  | 141.1 SD 21.7                            | 136.0 SD 21.3                               | <0.001         |
| <b>Distribution of baseline SBP (% , N)</b>   |                |  |   |                |
| SBP $\leq 120$                                | 20.9 (234)     | 17.3 (81)                                | 23.5 (153)                                  | 0.001          |
| SBP 121–139                                   | 35.6 (398)     | 31.6 (148)                               | 38.4 (250)                                  |                |
| SBP $\geq 140$                                | 43.5 (487)     | 51.1 (239)                               | 38.1 (248)                                  |                |
| Mean SBP over time, mmHg                      | 134.7 SD 13.6  | 137.8 SD 15.2                            | 134.4 SD 14.2                               | <0.001         |
| Mean baseline DBP, mmHg                       | 73.2 SD 12.6   | 75.2 SD 12.2                             | 71.7 SD 12.8                                | <0.001         |
| <b>Distribution of baseline DBP (% , N)</b>   |                |  |   |                |
| DBP $\leq 60$                                 | 17.5 (195)     | 12.0 (56)                                | 21.4 (139)                                  | <0.001         |
| DBP 61–89                                     | 72.6 (811)     | 76.0 (355)                               | 70.2 (456)                                  |                |
| DBP $\geq 90$                                 | 9.9 (111)      | 12.0 (56)                                | 8.5 (55)                                    |                |
| Mean DBP over time, mmHg                      | 70.3 SD 7.9    | 72.5 SD 9.5                              | 70.1 SD 9.0                                 | <0.001         |
| Mean baseline PP, mmHg                        | 64.9 SD 19.4   | 65.9 SD 20.1                             | 64.3 SD 18.8                                | 0.18           |
| <b>Distribution of baseline PP (% , N)</b>    |                |  |   |                |
| PP $\leq 50$                                  | 26.4 (295)     | 25.9 (121)                               | 26.8 (174)                                  | 0.44           |
| PP 51–69                                      | 35.5 (396)     | 33.4 (156)                               | 36.9 (240)                                  |                |
| PP $\geq 70$                                  | 38.1 (426)     | 40.7 (190)                               | 36.3 (236)                                  |                |
| Mean PP over time, mmHg                       | 64.4 SD 11.2   | 65.3 SD 15.6                             | 64.3 SD 14.6                                | 0.13           |

Values are presented as mean with SD or percentage and frequency. Missing total data (eGFR: 1.2%, SBP: 3.3%, DBP: 3.6%, PP: 3.6%, hemoglobin: 2.1%, potassium: 0.8%, bicarbonate: 5.1%, albumin: 6.4%, phosphate: 4.8%, and proteinuria: 19.2%). ACE/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; SBP, systolic BP; DBP, diastolic BP; PP, pulse pressure.

(Supplemental Figure 1). Study exclusions were patients followed for <30 days (*n*=6 patients and 11 observations) and observations after 4 years (143). The median follow-up time was 548 days (interquartile range, 292–913), and time between visits was 101 (range =30–727). The mean (range)

of number of BP measures per patient was 6.7 (1–17). Among the participants, 85.1% had data up to 6 months, 67.6% had data up to 1 year, and 33.9% had data for up to 2 years. The median eGFR at first clinic visit was 17.4 ml/min per 1.73 m<sup>2</sup> (interquartile range, 14.3–21.1),

**Table 2. General linear mixed effects regression model of the association between the individual components of BP (systolic BP, diastolic BP, and pulse pressure) and eGFR for splines of time**

| Variable                              | Estimate<br>(Change in eGFR) | P Value | Variable      | Estimate<br>(Change in eGFR) | P Value | Variable     | Estimate<br>(Change in eGFR) | P Value |
|---------------------------------------|------------------------------|---------|---------------|------------------------------|---------|--------------|------------------------------|---------|
| Intercept                             | 15.54                        | <0.001  | Intercept     | 15.34                        | <0.001  | Intercept    | 15.69                        | <0.001  |
| SBP                                   | -0.02                        | <0.001  | DBP           | -0.06                        | <0.001  | PP           | -0.01                        | 0.24    |
| SBP×1–48 d                            | 0.14                         | 0.004   | DBP×1–48 d    | 0.32                         | <0.001  | PP×1–48 d    | 0.05                         | 0.34    |
| SBP×49–168 d                          | -6.97                        | 0.02    | DBP×49–168 d  | 13.08                        | 0.01    | PP×49–168 d  | -3.56                        | 0.26    |
| SBP×169–411 d                         | 10.22                        | 0.02    | DBP×169–411 d | 18.49                        | 0.02    | PP×169–411 d | 5.51                         | 0.24    |
| SBP×411–952 d                         | -3.50                        | 0.04    | DBP×411–952 d | -5.43                        | 0.06    | PP×411–952 d | -2.27                        | 0.20    |
| P value for nonlinearity <sup>a</sup> | <0.001                       |         |               | <0.001                       |         |              | <0.001                       |         |
| P value for interaction <sup>b</sup>  | <0.001                       |         |               | <0.001                       |         |              | 0.49                         |         |

Models are adjusted for age at cohort entry, sex, and baseline comorbidities (coronary artery disease, congestive heart failure, malignancy, hypertension, peripheral vascular disease, diabetes, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use) as well as repeat measures of hemoglobin, albumin, phosphate, potassium, bicarbonate, and proteinuria. eGFR is in milliliters per minute per 1.73 m<sup>2</sup>. SBP, systolic BP; DBP, diastolic BP; PP, pulse pressure.

<sup>a</sup>P values represent statistical significance testing of likelihood ratios for models containing nonlinearity terms for time compared with linearity terms for time.

<sup>b</sup>P values represent statistical significance testing of likelihood ratios for models containing terms for interactions with BP and time compared with no interactions.

with 99% of patients having an eGFR of 30 ml/min per 1.73 m<sup>2</sup> or less.

**Study Characteristics**

Characteristics of study participants are presented in Table 1. Participants with an eGFR decline ≥30% were younger (mean age =63 versus 68 years old) with diabetes or GN more likely as the cause of CKD and more severe proteinuria. There was a lower prevalence of a history of coronary artery disease, congestive heart failure, stroke, and malignancy among those with eGFR≥30% declines. The use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) at baseline was more common among those with an eGFR decline (57% versus 49%). The use of ACE inhibitors or ARBs decreased over time from baseline use of 51.9%–39.7% on the last clinic visit. The mean baseline bicarbonate and serum albumin were lower among those with an eGFR≥30% decline. The mean baseline eGFR was lower among those with a decline (14.8 versus 18.2). The mean baseline SBP, DBP, and PP for the total cohort were 139, 73, and 65 mmHg, respectively, with SBP and DBP baseline values being significantly higher among those with an eGFR decline ≥30%. The SBP, DBP, and PP varied over clinic visits with SDs of 13, 7, and 11 mmHg, respectively. The percentage with baseline SBP≥140 was 51.1% versus 38.1% among those with and without ≥30% eGFR decline, whereas the percentage with baseline DBP ≥90 mmHg was 12.0% versus 8.5% in the two groups.

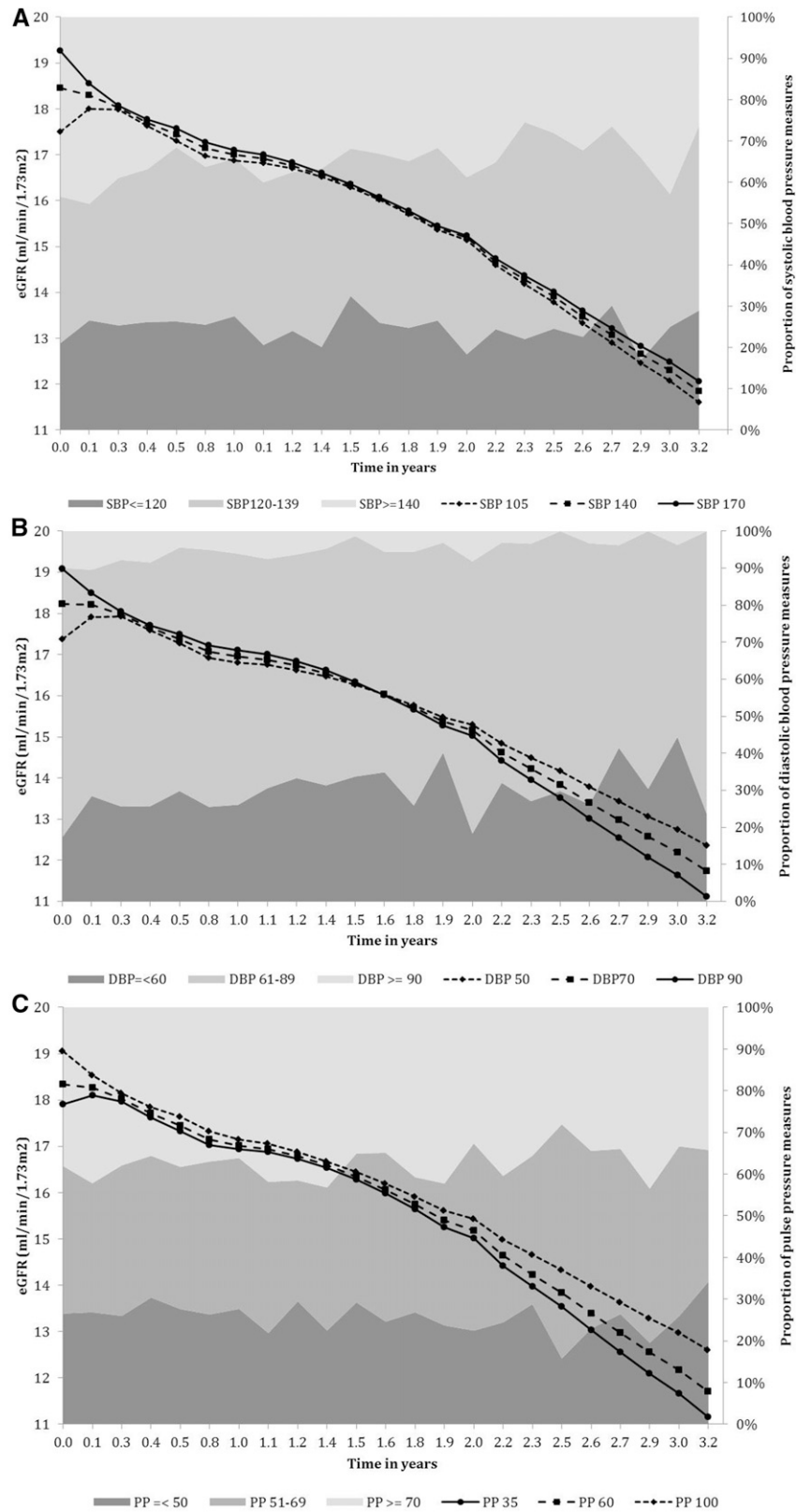
**Time-Varying Associations of BP and eGFR**

The crude proportions of extreme BP measures at cross-sections of time 0, 6, 12, 18, and 24 months were as follows: SBP<105 (21.1, 26.3, 27.6, 32.5, and 18.4, respectively), SBP≥170 (43.4, 31.5, 34.2, 31.8, and 38.8, respectively), DBP<50 (17.4, 29.9, 26.1, 33.8, and 18.4, respectively), DBP>90 (9.9, 4.4, 6.1, 1.3, and 8.2, respectively), PP<35 (26.5, 27.6, 27.7, 29.2, and 22.4, respectively), and PP>100 (38.1, 38.3, 36.2, 35.1, and 32.7, respectively). The summarized results from the adjusted linear mixed models are presented in Table 2, with full models presented in Supplemental Tables 1–3. All BP components (SBP, DBP, and PP) were nonlinearly associated with eGFR over time (P<0.001). SBP and DBP were associated with changes in eGFR (P values of <0.001 for both) over time, whereas PP was not (P=0.49). Results were consistent in two sensitivity analyses: (1) excluding ESRD and patients who died and (2) excluding the first clinic eGFR value (Supplemental Table 4).

The modeled time-varying associations with each BP component are presented in Figure 1. Overall, the eGFR declined over time, with sharper periods of decline early after cohort entry and after roughly 2 years of clinic follow-up. Patients with higher BP values had higher eGFRs at their baseline clinic visit. Extremes of BP showed similar trajectories of eGFR decline, with the mean eGFR separations at 3 years between SBP of 170/105, DBP of 90/50, and PP of 100/35 mmHg of 0.40, 1.24, and 1.31 ml/min per 1.73 m<sup>2</sup>, respectively. Overall higher BPs were associated with the largest declines in eGFR after 1–2 years of follow-up.

**BP Indices and the Risk of an eGFR Decline >30%**

An eGFR decline ≥30% occurred in 494 (41.4%) of the study participants during the study period for a crude rate



**Figure 1. | Predicted eGFR trajectories by levels of (A) systolic BP (SBP), (B) diastolic BP (DBP), and (C) pulse pressure (PP) with overlay distribution of proportion of BP measures over time.** (A) The lines indicate the predicted eGFR trajectories at SBPs of 105, 140, and 170 mmHg (the 5th, 50th, and 95th percentiles, respectively) from a linear mixed model with covariates set to their median values. The shaded areas represent the distributions of SBP measures ( $\leq 120$ , 121–139, and  $\geq 140$ ) during follow-up. Analysis adjusted for age, sex, cause of CKD, malignancy, coronary artery disease, congestive heart failure, peripheral vascular disease, diabetes mellitus at baseline, angiotensin-converting



**Table 3. The hazard ratios of categories of systolic BP, diastolic BP, and pulse pressure for eGFR decline ≥30% at the first clinic visit and time varying**

| BP Component, mmHg                         | Baseline Unadjusted HR (95% CI) | Baseline Adjusted HR <sup>a</sup> (95% CI) | Time-Varying Unadjusted HR (95% CI) | Time-Varying Adjusted HR <sup>b</sup> (95% CI) |
|--|---------------------------------|--|-------------------------------------|--|
| <b>Systolic BP (P=0.02<sup>c</sup>)</b>    |                                 |  |                                     |  |
| <105                                       | 0.84 (0.49 to 1.41)             | 0.86 (0.51 to 1.46)                        | 1.28 (0.84 to 1.95)                 | 1.51 (0.98 to 2.34)                            |
| 105–120                                    | 0.95 (0.69 to 1.31)             | 1.02 (0.73 to 1.41)                        | 0.79 (0.58 to 1.05)                 | 0.85 (0.62 to 1.15)                            |
| 121–130                                    | Referent                        | Referent                                   | Referent                            | Referent                                       |
| 131–140                                    | 1.10 (0.82 to 1.48)             | 1.08 (0.81 to 1.46)                        | 1.12 (0.87 to 1.46)                 | 1.07 (0.81 to 1.41)                            |
| 141–170                                    | 1.31 (1.01 to 1.70)             | 1.24 (0.95 to 1.63)                        | 1.46 (1.15 to 1.84)                 | 1.14 (0.88 to 1.48)                            |
| >170                                       | 1.27 (0.88 to 1.84)             | 1.19 (0.81 to 1.75)                        | 2.41 (1.62 to 3.60)                 | 1.62 (1.05 to 2.49)                            |
| <b>Diastolic BP (P=0.05<sup>c</sup>)</b>   |                                 |  |                                     |  |
| <50  | 0.47 (0.22 to 1.00)             | 0.55 (0.26 to 1.17)                        | 0.89 (0.56 to 1.42)                 | 0.93 (0.57 to 1.52)                            |
| 51–60                                      | 0.77 (0.55 to 1.06)             | 0.94 (0.67 to 1.31)                        | 1.06 (0.83 to 1.36)                 | 1.07 (0.83 to 1.39)                            |
| 61–70                                      | Referent                        | Referent                                   | Referent                            | Referent                                       |
| 71–80                                      | 1.04 (0.82 to 1.32)             | 0.96 (0.76 to 1.23)                        | 1.21 (0.96 to 1.53)                 | 1.06 (0.82 to 1.37)                            |
| 81–90                                      | 1.25 (0.97 to 1.60)             | 1.06 (0.81 to 1.40)                        | 1.67 (1.28 to 2.18)                 | 1.40 (0.99 to 1.86)                            |
| >90  | 1.20 (0.84 to 1.72)             | 0.91 (0.62 to 1.33)                        | 2.68 (1.87 to 3.82)                 | 1.83 (1.21 to 2.77)                            |
| <b>Pulse pressure (P=0.80<sup>c</sup>)</b> |                                 |  |                                     |  |
| <35  | 1.13 (0.71 to 1.84)             | 0.91 (0.56 to 1.49)                        | 1.30 (0.82 to 2.08)                 | 1.36 (0.83 to 2.24)                            |
| 36–50                                      | 1.05 (0.79 to 1.41)             | 0.98 (0.73 to 1.31)                        | 1.03 (0.78 to 1.36)                 | 1.07 (0.79 to 1.44)                            |
| 51–60                                      | Referent                        | Referent                                   | Referent                            | Referent                                       |
| 60–75                                      | 1.06 (0.80 to 1.40)             | 1.07 (0.80 to 1.41)                        | 1.15 (0.88 to 1.50)                 | 1.13 (0.85 to 1.50)                            |
| 76–100                                     | 1.23 (0.94 to 1.63)             | 1.24 (0.93 to 1.66)                        | 1.45 (1.11 to 1.88)                 | 1.19 (0.89 to 1.59)                            |
| >100                                       | 1.16 (0.73 to 1.84)             | 1.30 (0.81 to 2.08)                        | 1.17 (0.69 to 1.97)                 | 1.09 (0.60 to 1.97)                            |

HR, hazard ratio; 95% CI, 95% confidence interval.

<sup>a</sup>Data were adjusted for age, sex, cause of CKD, malignancy, coronary artery disease, congestive heart failure, peripheral vascular disease, diabetes mellitus, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, and baseline measures of hemoglobin, bicarbonate, phosphate, potassium, albumin, and proteinuria. Number of events (GFR decline ≥30%) =494.

<sup>b</sup>Data were adjusted for age, sex, cause of CKD, malignancy, coronary artery disease, congestive heart failure, peripheral vascular disease, diabetes mellitus, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, and time-updated measures of hemoglobin, bicarbonate, phosphate, potassium, albumin, and proteinuria.

<sup>c</sup>P value represents the association of each BP component over time modeled as a continuous variable.

of 34.5/100 patient-years. Crude and adjusted hazard ratios (HRs) for the risk of an eGFR decline ≥30% by categorical BP components at baseline and when using time-varying associations are presented in Table 3. In the adjusted analyses, baseline SBP (P=0.44), DBP (P=0.39), and PP (P=0.41) were not significantly associated with the risk of an eGFR decline >30%. After accounting for these variables as time-varying associations, however, a significant association was observed for SBP (P=0.02), and a borderline significance was observed for DBP (P=0.05). For SBP, a U-shaped relationship was observed, with a higher

hazard at both extremes of SBP<105 (HR, 1.51; 95% confidence interval [95% CI], 0.98 to 2.34) and SBP>170 (HR, 1.62; 95% CI, 1.05 to 2.49) compared with a referent category of SBP=121–130 mmHg. For DBP, there was no significantly higher hazard with low DBP but a graded higher hazard with elevated DBP (DBP =81–90: HR, 1.40; 95% CI, 0.99 to 1.86; DBP>90: HR, 1.83; 95% CI, 1.21 to 2.77; referent DBP =61–70 mmHg). Time-varying PP was not associated with eGFR declines (P=0.80).

To examine the sensitivity of the results to the presence of patients reaching ESRD or death before an eGFR decline

enzyme (ACE)/angiotensin receptor blocker (ARB) use, and time-updated measures of hemoglobin, bicarbonate, phosphate, potassium, albumin, and proteinuria. (B) The lines indicate the predicted eGFR trajectories at DBPs of 50, 70, and 90 mmHg (the 5th, 50th, and 95th percentiles, respectively) from a linear mixed model with covariates set to their median values. The shaded areas represent the distributions of DBP measures (<60, 61–89, and >90) during follow-up. Analysis adjusted for age, sex, cause of CKD, malignancy, coronary artery disease, congestive heart failure, peripheral vascular disease, diabetes mellitus at baseline, ACE/ARB use, and time-updated measures of hemoglobin, bicarbonate, phosphate, potassium, albumin, and proteinuria. (C) The lines indicate the predicted eGFR trajectories at PPs of 35, 60, and 100 mmHg (the 5th, 50th, and 95th percentiles, respectively) from a linear mixed model with covariates set to their median values. The shaded areas represent the distributions of PP measures (<50, 51–69, and >70) during follow-up. Analysis adjusted for age, sex, cause of CKD, malignancy, coronary artery disease, congestive heart failure, peripheral vascular disease, diabetes mellitus at baseline, ACE/ARB use, and time-updated measures of hemoglobin, bicarbonate, phosphate, potassium, albumin, and proteinuria.

( $n=494$ ; informative censoring), additional models were performed (results not shown). Both early and late censoring models for ESRD and mortality did not substantively alter the results.

## Discussion

We found that repeat measures of all individual BP components (SBP, DBP, and PP) were associated with eGFR and that these associations changed over time for SBP and DBP. Higher mean BPs were associated with small continuous declines in eGFR that were more apparent after 1–2 years of follow-up. Extremes of SBP and elevated DBP were associated with a higher risk of declines in eGFR  $\geq 30\%$ . These findings were only identified after accounting for time-varying associations and consistent after accounting for informative censoring. Taken together, these findings show that the association of BP and eGFR in late-stage CKD is complex and only apparent with repeat measures of both BP and eGFR. Our findings illustrate that the avoidance of extremes of SBP and elevations in DBP may retard the loss of eGFR.

The relationship between elevated BP and the risk of ESRD has been well established (1,22). Our findings are consistent with previous reports; however, the association of BP with eGFR was only detectable at extremes of BP. This may be due to our cohort or our focus on declines of eGFR as opposed to the need for dialysis. Dialysis as an outcome overlooks an important contingent of patients, specifically those who choose conservative, nondialytic care and those with longer time horizons of eGFR decline who may experience complications. In our cohort, 40% had not reached an end point after 14 months. Our findings suggest that a wider range of BPs with avoidance of extremes may be safe in CKD with respect to the loss of eGFR, an observation that warrants further investigation.

Numerous studies have examined the association of BP and ESRD, but few have examined the associations of BP with eGFR changes in CKD stage 4/5 (2,5,23–25); de Goeij *et al.* (26), examining baseline BP in 547 (mean eGFR =13.1 ml/min) patients with CKD, showed an association between elevated SBP and DBP and monthly eGFR declines. The African American Study of Kidney Disease and Hypertension randomized, controlled trial examined usual (141/85 achieved) versus low (128/78) BP on the slope of eGFR decline in 1094 patients (mean eGFR =46 ml/min per 1.73 m<sup>2</sup>) and found no difference in eGFR decline (11). In a study examining only baseline BP components in patients with milder degrees of CKD, Rifkin *et al.* (27) reported an inverse relationship with elevated blood components (SBP and PP) and eGFR decline. Similar to our findings, they found that SBP had the strongest association with eGFR decline, and in models adjusting for all BP components, SBP remained independently associated with eGFR. Our study examined a larger cohort of patients with more advanced CKD (mean eGFR =17), incorporated repeat measures for both BP and eGFR, and lastly, examined the associations of SBP/DBP and eGFR changes over time. These methodological differences and our study cohort may explain why we did not show any significant associations with baseline BP measures and eGFR and our associations were only detected for extremes of SBP and elevated DBP.

A report from the CRIC illustrated the importance of time-updated measures of SBP and the risk of ESRD. The longitudinal-adjusted HR of ESRD for SBP >140 mmHg was 3.4-fold compared with 1.5-fold when only the baseline SBP was considered (6). Similarly, we showed marked differences between the associations of baseline measures of BP and their time-varying associations. The lack of association between an elevated baseline BP and GFR declines may reflect successful therapeutic interventions or falsely elevated measures due to measurement error or white coat effect.

A recent growing body of evidence shows differing individual eGFR trajectories in late-stage CKD (13,28). Our study illustrates that BP indices are associated with differing eGFR trajectories over time but that the clinical associations may be only modest. Although more variation was observed across levels of DBP and SBP relative to PP on eGFR trajectories, the overall differences in eGFR decline over time were small. Furthermore, the relationship with BP on eGFR over time is nonlinear, undergoing dynamic changes especially at higher levels of eGFR.

Strengths of our study include the use of well validated data, a unique cohort of patients with late-stage CKD undergoing multidisciplinary care, the use of time-varying covariates, and eGFR as the study outcome. We modeled changes in BP using nonlinear methods both continuously and as a clinically meaningful decline. Our findings were consistent and robust in a series of sensitivity analyses where we accounted for informative censoring after exclusion of patients with ESRD and mortality and exclusion of the first eGFR value at referral. Our study did have some limitations. Our study did not directly address whether BP extremes led to eGFR declines or vice versa. It is plausible that elevations in BP may be leading to eGFR loss or conversely, that individuals with eGFR loss experience elevations in BP. There were considerable missing data on proteinuria (19.2%), although the majority was in patients with existing measures of <1 g/d, and low levels of proteinuria tend to remain stable over time (15). The BPs were not obtained by 24- or 48-hour ambulatory measures. They reflected pragmatic measures obtained in a clinic setting and were measured by trained health care workers. There were relatively few measures at some extremes of BP. There is a possibility of a referral bias, because physicians or patients may have declined referral to the CKD clinic, and they may be more likely to choose conservative therapies. We only accounted for ACE inhibitors and ARB use and did not account for all possible antihypertensives. Lastly, we did not use statistical models that account for time-varying confounding, such as inverse probability of treatment weighting, that may biased the findings toward the null.

In conclusion, in patients with late-stage (4/5) CKD cared for in a multidisciplinary clinic, extremes of SBP and elevated DBP were associated with steeper declines in eGFR and a higher risk of an eGFR decline of  $\geq 30\%$ . Avoidance of extremes of SBP and elevated DBP may limit the progression of CKD.

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## Disclosures

None.

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**Supplemental Table 1:** General linear mixed effects regression model of the systolic blood pressure (exposure) and eGFR.

| <b>Variable</b>    | <b>Estimate</b> | <b>P</b> |
|--------------------|-----------------|----------|
| Intercept          | 15.54           | <0.001   |
| SBP                | -0.02           | <0.001   |
| Time1              | -0.56           | 0.58     |
| Time2              | -99.80          | 0.09     |
| Time3              | 164.98          | 0.06     |
| Time4              | -81.83          | 0.01     |
| SBP x time1        | 0.14            | 0.004    |
| SBP x time2        | -6.97           | 0.02     |
| SBP x time3        | 10.22           | 0.02     |
| SBP x time4        | -3.50           | 0.04     |
| Hemoglobin         | -0.04           | <0.001   |
| Bicarbonate        | -0.06           | 0.003    |
| Phosphate          | 5.27            | <0.001   |
| Potassium          | 0.05            | 0.26     |
| Albumin            | 0.04            | 0.02     |
| Proteinuria        |                 |          |
| None               | 0.03            | 0.86     |
| Minimal            | 0.15            | 0.34     |
| Moderate           | referent        |          |
| Severe             | -0.08           | 0.64     |
| ACE/ARB            | 1.18            | <0.001   |
| Male               | -0.71           | 0.02     |
| Age                | 0.03            | 0.02     |
| CAD                | 0.42            | 0.26     |
| CHF                | 1.05            | 0.006    |
| PVD                | 0.26            | 0.52     |
| Diabetes           | 0.48            | 0.23     |
| Malignancy         | 0.59            | 0.17     |
| Cause of CKD       |                 |          |
| Diabetes           | -1.19           | 0.02     |
| Ischemia           | 0.27            | 0.55     |
| Glomerulonephritis | 0.51            | 0.22     |
| Other              |                 |          |

SBP systolic blood pressure, ACE angiotensin converting enzyme inhibitor, ARB angiotensinogen receptor blocker, CAD coronary artery disease, CKD congestive heart failure, PVD peripheral vascular disease, CKD chronic kidney disease. The time values (labelled time1-time4) represent splines of time at values of 1, 48, 168, 411 and 952 days of follow up.

**Supplemental Table 2:** General linear mixed effects regression model of the diastolic blood pressure (exposure) and eGFR.

| <b>Variable</b>    | <b>Estimate</b> | <b>P</b> |
|--------------------|-----------------|----------|
| Intercept          | 15.34           | <0.001   |
| DBP                | -0.06           | <0.001   |
| Time1              | -0.06           | 0.95     |
| Time2              | -124.44         | 0.04     |
| Time3              | 200.91          | 0.02     |
| Time4              | -93.89          | 0.005    |
| DBP x time1        | 0.32            | <0.001   |
| DBP x time2        | 13.08           | 0.01     |
| DBP x time3        | 18.49           | 0.02     |
| DBP x time4        | -5.43           | 0.06     |
| Hemoglobin         | -0.03           | <0.001   |
| Bicarbonate        | -0.06           | <0.001   |
| Phosphate          | 5.24            | <0.001   |
| Potassium          | 0.04            | 0.29     |
| Albumin            | 0.04            | 0.01     |
| Proteinuria        |                 |          |
| None               | 0.03            | 0.86     |
| Minimal            | 0.14            | 0.37     |
| Moderate           | Referent        |          |
| Severe             | -0.08           | 0.67     |
| ACE/ARB            | 1.16            | <0.001   |
| Male               | -0.67           | 0.03     |
| Age                | 0.02            | 0.07     |
| CAD                | 0.44            | 0.23     |
| CHF                | 1.03            | 0.007    |
| PVD                | 0.30            | 0.46     |
| Diabetes           | 0.53            | 0.18     |
| Malignancy         | 0.62            | 0.15     |
| Cause of CKD       |                 |          |
| Diabetes           | -1.20           | 0.01     |
| Ischemia           | 0.28            | 0.54     |
| Glomerulonephritis | 0.54            | 0.19     |
| Other              | Referent        |          |

DBP diastolic blood pressure, ACE angiotensin converting enzyme inhibitor, ARB angiotensinogen receptor blocker, CAD coronary artery disease, CKD congestive heart failure, PVD peripheral vascular disease, CKD chronic kidney disease. The time values (labelled time1-time4) represent splines of time at values of 1, 48, 168, 411 and 952 days of follow up.

**Supplemental Table 3:** General linear mixed effects regression model of the pulse pressure (exposure) and eGFR.

| <b>Variable</b>    | <b>Estimate</b> | <b>P</b> |
|--------------------|-----------------|----------|
| Intercept          | 15.69           | <0.001   |
| PP                 | -0.01           | 0.24     |
| Time1              | -1.19           | 0.24     |
| Time2              | -68.92          | 0.24     |
| Time3              | 119.77          | 0.18     |
| Time4              | -66.39          | 0.05     |
| PP x time1         | 0.05            | 0.34     |
| PP x time2         | -3.56           | 0.26     |
| PP x time3         | 5.51            | 0.24     |
| PP x time4         | -2.27           | 0.20     |
| Hemoglobin         | -0.04           | <0.001   |
| Bicarbonate        | -0.06           | <0.001   |
| Phosphate          | 5.30            | <0.001   |
| Potassium          | 0.04            | 0.29     |
| Albumin            | 0.03            | 0.02     |
| Proteinuria        |                 |          |
| None               | 0.17            | 0.82     |
| Minimal            | 0.18            | 0.26     |
| Moderate           | Referent        |          |
| Severe             | 0.11            | 0.56     |
| ACE/ARB            | 1.18            | <0.001   |
| Male               | -0.70           | 0.02     |
| Age                | 0.03            | 0.02     |
| CAD                | 0.42            | 0.26     |
| CHF                | 1.01            | 0.01     |
| PVD                | 0.26            | 0.51     |
| Diabetes           | 0.47            | 0.24     |
| Malignancy         | 0.60            | 0.17     |
| Cause of CKD       |                 |          |
| Diabetes           | -1.15           | 0.02     |
| Ischemia           | 0.27            | 0.55     |
| Glomerulonephritis | 0.53            | 0.20     |
| Other              | Referent        |          |

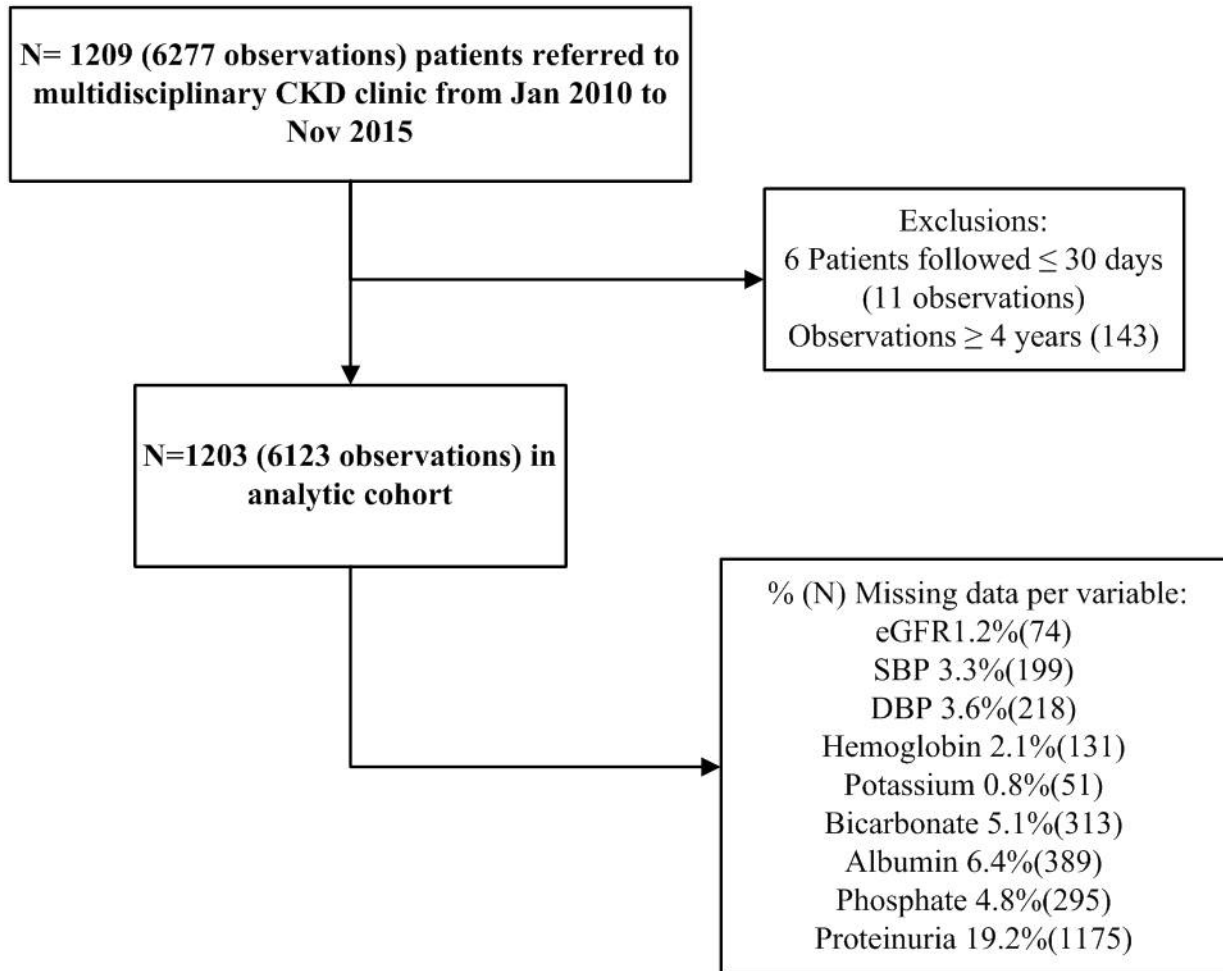
PP pulse pressure, ACE angiotensin converting enzyme inhibitor, ARB angiotensinogen receptor blocker, CAD coronary artery disease, CKD congestive heart failure, PVD peripheral vascular disease, CKD chronic kidney disease. The time values (labelled time1-time4) represent splines of time at values of 1, 48, 168, 411 and 952 days of follow up.

**Supplementary Table 4:** Results of sensitivity analyses for non-linearity and changes over time on the association of individual blood pressure components and eGFR.

| Model                              | Non-linearity                                    |         | Change over time                                 |         |
|------------------------------------|--|---------|--|---------|
|                                    | Difference in -2 log likelihood between models * | P value | Difference in -2 log likelihood between models # | P value |
| <b>SBP:</b>                        |  |         |  |         |
| Full model (N=1203)                | 40.1   | <0.001  | 27.1   | <0.001  |
| ESKD/death excluded (N=681)        | 36.3   | <0.001  | 11.1   | 0.03    |
| First eGFR value excluded (N=1203) | 30.2   | <0.001  | 10.6   | 0.03    |
| <b>DBP:</b>                        |  |         |  |         |
| Full model (N=1203)                | 47.3   | <0.001  | 31.4   | <0.001  |
| ESKD/death excluded (N=681)        | 46.8   | <0.001  | 29.6   | <0.001  |
| First eGFR value excluded (N=1203) | 29.4   | <0.001  | 12.0   | 0.02    |
| <b>PP:</b>                         |  |         |  |         |
| Full model (N=1203)                | 32.4   | <0.001  | 3.4  | 0.49    |
| ESKD/death excluded (N=681)        | 28.5   | <0.001  | 2.1  | 0.72    |
| First eGFR value excluded (N=1203) | 30.1   | <0.001  | 2.8  | 0.60    |

All models adjusted for age, sex, cause of chronic kidney disease, malignancy, coronary artery disease, congestive heart failure, peripheral vascular disease, diabetes mellitus at baseline, ACE/ARB use and time-updated measures of hemoglobin, bicarbonate, phosphate, potassium, albumin and proteinuria. \* degrees of freedom =6, # degrees of freedom =4. SBP systolic blood pressure ESKD end stage kidney disease eGFR estimated glomerular filtration rate DBP diastolic blood pressure PP pulse pressure

**Supplemental Figure 1: Study cohort.**





### **Additional statistical methods:**

#### *Time-varying associations of blood pressure and eGFR*

The time-varying associations between continuous eGFR and each of SBP, DBP and PP were analyzed using separate general linear mixed effects regression models, estimated using Restricted Maximum Likelihood (REML)(20). Fixed effects of interest in each model were: time, defined in years since the first clinic visit; continuous measures of SBP, DBP and PP; and their interactions with time. To allow for non-linear trends in eGFR, time was modelled using restricted cubic splines with 5 knots fitted at the 5<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 95<sup>th</sup> percentiles of time corresponding to values of 1, 48, 168, 411, and 952 days, respectively. Statistical significance testing for non-linearity versus linearity were conducted using likelihood ratio tests. Denominator degrees of freedom were calculated using the Kenward Roger method(20). Random coefficients were specified for subject and time to account for correlations in repeated measures on the same subjects. Repeat measures of each blood pressure component were tested for associations of changes over time with repeat measures of eGFR using likelihood ratio tests. All analyses were adjusted for age at cohort entry, gender, and baseline comorbidities (coronary artery disease, congestive heart failure, malignancy, hypertension, PVD, diabetes,), as well as repeat measures of hemoglobin, albumin, phosphate, potassium, bicarbonate and proteinuria. All continuous covariates were grand mean centred prior to analysis. Multi-collinearity among baseline predictors were assessed using a variable clustering algorithm with a cut point for proportion of variation explained set at 70% (22). To avoid exclusion of subjects due to missing covariates, multiple imputation was performed prior to analysis using a Markov Chain Monte Carlo algorithm (the data augmentation algorithm) (21). Ten multiple

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imputation datasets were generated with all variables included in analytical models specified as predictors in the multiple imputation model. Analyses were carried out for each multiple imputation dataset and pooled across datasets using Rubin's rules (23).

To illustrate the associations of individual BP components and eGFR over time, modelled eGFR trajectories were plotted with blood pressure variables set at the 5<sup>th</sup>, 50<sup>th</sup> and 95<sup>th</sup> percentiles (SBP:105, 140, 170, DBP:50, 70, 90, PP: 35, 60, 100)(20). All remaining continuous covariates were set to their median values, while categorical covariates were set to their mode. In a sensitivity analysis, models were repeated excluding observations from patients who reached ESKD prior to a  $\geq 30\%$  decline in GFR or who died (n=681) for the linear mixed models. This was to avoid bias in our estimates as a number of participants may have been referred to clinic immediately prior to ESKD initiation.

#### *Blood pressure indices and the risk of a GFR decline > 30%*

The association of SBP, DBP and PP with time to eGFR decline  $\geq 30\%$  was examined using Cox proportional hazards models for all participants (N=1203). For simplicity of interpretation, blood pressure components were categorized at approximately the 5<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 95<sup>th</sup> percentiles and modelled at baseline upon cohort entry and with time-updated values. The interval considered as a normal range was classified as the reference category. Both crude and adjusted hazard ratios were estimated, adjusting for the same covariates as in the linear mixed models. The proportional hazards assumption was checked by examining Schoenfeld residuals(24). Patients were censored at study end (n=287), at ESKD (n=540), at death (n=141), at loss to follow-up (n=20), if they moved out

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of province (n=33) or received a pre-emptive transplant (n=8). To assess the potential influence of informative censoring, we employed the method by Allison where additional models were created censoring the competing event (ESKD or death) i.) at the time of the event of interest (eGFR decline $\geq$ 30%) or ii.) the longest event time (4 years) and comparing the two(24).