Longitudinal Assessment of Blood Pressure in Late Stage Chronic Kidney Disease

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Synopsis

The worldwide population of patients with chronic kidney disease (CKD) is growing, with estimated prevalence at 12-15% of adults. Of particular concern are those with late stage CKD, defined as an estimated glomerular filtration rate (eGFR)of less than 30 ml/min/1.73m^2, as they are susceptible to the highest risk of adverse outcomes such as progression to end stage kidney disease (ESKD), cardiovascular disease and all-cause mortality (1, 2). As such, late stage CKD patients are often managed in specialized clinics with set clinical targets, standardized education and multi-disciplinary care(3). A key clinical target for therapeutic intervention and prevention of the progression of CKD is blood pressure (BP) reduction(4). Yet, multiple relevant questions remain regarding the strength and nature of association of BP with clinical outcomes in late stage CKD. As the risks of hypotension-related complications are high in late stage CKD, it remains unclear whether strict BP control delays CKD progression in a real world clinic population(5). Furthermore, it is unclear how to appropriately specify the nature of the longitudinal association between BP and clinical outcomes of ESKD and mortality. The overall objective of this thesis is to examine the longitudinal association of BP and adverse clinical outcomes in a cohort of 1203 patients (mean eGFR 17.8 ml/min/1.73m^2; mean of 6.7 BP measures per patient) with late stage CKD. In our first paper we examined the association of repeat measures of BP with CKD progression, defined as a decline in eGFR. When modeling eGFR using longitudinal linear regression, we found that its over-time trajectory was non-linear and that this trajectory was modified by BP; thus, we found a significant time-dependant association between BP and eGFR. When modeling time to eGFR decline ≥ 30% using Cox proportional hazards regression with categorized BP specified as a time-dependent

exposure, BP was significantly associated with risk of eGFR decline; in particular, extremes of low and high systolic blood pressure (SBP) and high diastolic blood pressure (DBP) significantly increased the risk of eGFR decline. In our second paper, we examined different methods of modelling longitudinal BP and its association with time to mortality and ESKD. We found that elevations in SBP and DBP, in particular, when expressed as current (most recent visit), lag (previous visit), and cumulative exposure were significantly associated with increased risk of ESKD while low SBP (current, lag and cumulative exposure) was significantly associated with increased risk of mortality. Baseline BP measures were not statistically significantly associated with any outcomes. In patients with more moderate ranges of SBP (121-140) or DBP (60-85) at baseline, a subsequent rise to >160 or > 85 respectively, was associated with an increased risk of ESKD. Thus, longitudinal BP measures in late-stage CKD are significantly associated with adverse outcomes and convey important information beyond baseline BP measures.

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Author Contributions

Manuscript one:

Author contributions: MMS, MT contributed to the study design and conception. MMS and MT drafted the manuscript which was critically revised by all authors. MMS, MT, DM, DZ, BM, AA, MR, SH contributed to the analysis and interpretation of the data. MMS was responsible for the statistical analyses.

Manuscript two:

Author contributions: MMS, MT contributed to the study design and conception. MMS and MT drafted the manuscript which was critically revised by all authors. MMS, MT, DM, DZ, BM, AA, MR, SH contributed to the analysis and interpretation of the data. MMS was responsible for the statistical analyses.

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Glossary

ACE angiotensinogen converting enzyme

ARB angiotensin receptor blocker

BP blood pressure

CAD coronary artery disease

CHF congestive heart failure

CI confidence interval

CKD chronic kidney disease

CRIC Chronic Renal Insufficiency Cohort

DBP diastolic blood pressure

eGFR estimated glomerular filtration rate

ESKD end stage kidney disease

HR hazard ratio

IQR interquartile range

IPTW inverse probability of treatment weighting

KDIGO Kidney disease improving global outcomes

KFRE kidney risk failure equation

MDCKD multidisciplinary chronic kidney disease clinic

MDRD modified diet in renal disease

mmHg millimetres of mercury

PP pulse pressure

PVD peripheral vascular disease

RAAS renin angiotensin aldosterone system

REML residual estimated maximum likelihood

SBP systolic blood pressure

TD time-dependent

Chapter 1: Overview and Objectives

Problem

The worldwide population of CKD is growing with appropriately 10-15% of the adult population affected(1). The recognized international definition of CKD is "kidney damage for greater than or equal to 3 months, as defined by structural or functional abnormalities of the kidney, with or without a decreased glomerular filtration rate(GFR) or GFR less than 60 ml/min/1.73m^2 for greater than or equal to 3 months, with or without kidney damage." (4) The current staging system of CKD, based on the risk of end stage kidney disease (ESKD), incorporates the estimated glomerular filtration rate (eGFR) and proteinuria. Late stage CKD, for the purposes of this document will then be defined as an eGFR ≤ 30 ml/min/1.73m^2, and is associated with the onset of metabolic complications related to chronic kidney disease and adverse clinical outcomes in patients (6-9).

The role of blood pressure control in late-stage CKD remains controversial. Previous studies in patients with less advanced CKD demonstrate an association between elevated BP and ESKD and a J-shaped association between BP and mortality(10). However, the few studies examining its importance in late-stage CKD are limited by not accounting for longitudinal measures of BP or only examining the clinical outcome of ESKD.

Purpose and rationale

As BP is an important therapeutic target, there is a pressing need to better understand its role in late-stage CKD. The over-arching objective of this thesis is to delineate the association between BP and clinical outcomes (eGFR, ESKD and all-cause

mortality) using more sophisticated longitudinal modelling strategies and differing means of quantitating BP. A more thorough understanding of the role of BP in late-stage CKD would allow us to better tailor therapy to patients at high risk of complications and risk of adverse outcomes.

Objectives

The two specific objectives of this thesis are:

1) To examine the associations of longitudinal measures of individual BP components (SBP, DBP and PP) with the decline in eGFR.
2) To examine the associations of varying means of quantifying longitudinal BP with ESKD and all-cause mortality.

Overview of Submitted Thesis and Manuscripts

We begin with a review of the relevant literature regarding BP and CKD (Chapter 2 Background). This chapter outlines the problem of CKD and current classification schema, current care models for CKD, a summary of key studies of BP and CKD, the individual BP components, longitudinal modelling of BP and methodological means of quantitating longitudinal exposures. Chapter 3 addresses thesis objective 1: "To determine the association of longitudinal measures of individual BP components (SBP, DBP and PP) with the decline in eGFR" and includes the manuscript "The time-varying association of individual blood pressure components with estimated glomerular filtration rate in late

stage chronic kidney disease" that has been accepted for publication in the Clinical Journal of the American Society of Nephrology (impact factor 2015 4.7). Chapter 4 addresses thesis objective 2: "To examine the associations of differing means of quantifying longitudinal BP with ESKD and all-cause mortality" and includes the submitted manuscript "Longitudinal blood pressure exposures in late-stage chronic kidney disease and the risk of end stage kidney disease or mortality (Best BP in CKD Study)". Chapter 5 presents a summary of the thesis, key findings and identifies areas of future research.

Chapter 2: Background

Introduction

In Canada, an estimated 12% of the adult population are affected by CKD(2). The recognized international definition of CKD is "kidney damage for greater than or equal to 3 months, as defined by structural or functional abnormalities of the kidney, with or without a decreased GFR or GFR less than 60 ml/min/1.73m^2 for greater than or equal to 3 months, with or without kidney damage."(4) The current staging system of CKD, based on the risk of end stage kidney disease (ESKD), incorporates the estimated glomerular filtration rate (eGFR) and proteinuria. Late stage CKD, for the purposes of this document will then be defined as an eGFR ≤ 30 ml/min/1.73m^2, and is associated with an increased risk of adverse clinical outcomes in patients.

Modern CKD care: the multidisciplinary clinic

The cut-off of ≤30 ml/min/1.73m$_2$ is significant as it is associated with the onset of metabolic and clinical complications and is often the earliest time point for potential dialysis planning. Specifically, with the onset of ESKD (defined as eGFR ≤ 15 ml/min/1.73m^2) patients may require dialytic therapies or kidney transplantation for survival. Safe, patient-orientated care requires a series of informed decisions to optimize the transition to ESKD such as vascular access planning, dialysis modality suitability and selection, living-related kidney donor assessment and patient education. Over the past decade newer care models were adopted to address the specific needs of the late stage CKD population. Multi-disciplinary, inter-professional clinics with standardized approaches to assessment, treatment and education were created(3). These approaches demonstrate

improvements in rates of kidney transplantation, adoption of home modalities, optimized vascular access and all-cause mortality (11-17).

The largest growing demographic with late-stage CKD is the elderly (age > 65 years)(18). Patients of advanced age are more often frail, with more co-morbid illnesses and are more likely to choose not to undergo either dialysis or transplantation with the understanding their life expectancy may shorten(19). Despite this more conservative care approach, preserving kidney function is still an important therapeutic target to prevent uremia and its related illnesses such as infection, accelerated cardiovascular disease and mortality (20, 21).

Blood pressure in CKD

At present there are limited therapies for established CKD with blood pressure control being one of the most studied, evidence-based targets for reduction of kidney disease progression (22). Multiple observational and randomized controlled trials clearly demonstrate that a reduction of blood pressure can delay the onset of dialysis, cardiovascular disease and mortality in the CKD population (23-26). Despite the large amount of evidence for BP reduction there is a growing body of studies demonstrating potential harm(5). Concerns and complications due to blood pressure reduction are greatest in the elderly population, coincidentally the same cohort with the highest likelihood of choosing not to initiate dialysis with ESKD (5, 27, 28).

To date a large number of observational studies (summarized below) have examined the association between BP and CKD. Limitations of these studies include i)

examining only single, baseline measures of BP(29-36), ii) including patients with minor CKD(10, 30, 31, 37), iii) limited adjustment for important confounders, and v) not accounting for different mechanisms of end-organ injury related to BP.

The association of BP and eGFR decline

The majority of studies to date have focused exclusively on the need for dialysis or receipt of a kidney transplant as a study outcome (29, 33, 35, 36, 38). As mentioned above, such studies systematically exclude the fastest growing contingent of patients (those with advanced age) who choose not to undergo renal replacement therapy(39). The effect of stringent blood pressure control on GFR reduction in patients with late-stage kidney disease remains controversial. Indeed there are few studies examining the effect of blood pressure on eGFR reduction as opposed to the need for renal replacement therapy. Rifkin *et al* reported an inverse relationship with elevated blood components (SBP, DBP and PP) and eGFR decline in a cohort of 4,365 patients with mild CKD(30). In adjusted linear models, they reported declines of 0.10 to 0.15 ml/min/year per 10 mm Hg increment increase depending on the BP component examined. De Goeil *et al* examining 547 late stage (mean eGFR 13.1 ml/min/1.73m^2) CKD patients and reported an adjusted decline in eGFR of 0.04-0.05 per month per 10 mmHg increase in SBP and DBP (29). Hanratty *et al* examined 43, 305 patients with mild CKD (mean eGFR of 82) finding a 0.2 ml/min/1.73m^2 decline in eGFR per year for an increase in SBP of 10 mmHg. In contrast, The African American Study of Kidney Disease and Hypertension (ASK) randomized controlled trial examined usual (141/85 achieved) versus low (128/78) blood pressure on the slope of eGFR decline in

1094 patients (mean eGFR 46 ml/min/1.73m^2)(40). They reported no difference in the mean eGFR slope over 4 years between the usual and low BP groups.

The importance of individual components of blood pressure in CKD

The individual components of blood pressure (systolic, diastolic and pulse pressure) are representative of different physiological processes. However the relative importance of each blood pressure component in CKD on clinical outcomes remains unclear. Palit *et al* examined 1099 late stage CKD (mean eGFR 18±7 ml/min/1.73m^2) patients and found higher SBP and DBP, but not PP, to be associated with the need for renal replacement therapy(38). There were no associations detected between individual BP components and all-cause mortality. In patients with less severe CKD (mean eGFR 38 ml/min/1.73m^2), Agrawal detected SBP, but not DBP, to be associated with the need for renal replacement therapy and mortality and it was a J-shaped association for mortality (lower and higher SBP were associated with increases in mortality)(33). De Goeji *et al* reported that elevations of either SBP or DBP were associated with an eGFR decline and renal replacement therapy(29). Rifkin *et al* reported that only SBP and PP, but not DBP were associated with eGFR decline in patients with mild CKD(30). Perrelta *et al* and Bell *et al* reported that all three components were associated with ESKD in community cohorts (35, 36). Furthermore Bell *et al* found J-shaped associations between each of SBP and DBP with incidence of ESKD.

Examining different longitudinal blood pressure exposures and clinical outcomes

The exact nature of the underlying relationship between longitudinal BP exposure and outcomes is unknown. As such differing methods of exposure may be more reflective of distinct physiological processes. Longitudinal BP measures could provide information on two distinct processes. Elevations in BP may be casual, leading to progressive kidney damage due to arteriosclerosis and nephron loss. In this schema, chronic or cumulative exposure to BP may better capture the association between BP and adverse clinical outcomes (41, 42). Alternatively, with the progression of kidney disease and nephron loss, patients may accumulate sodium and fluid leading to elevations in BP. This scenario of reverse causality may be best captured with time-dependent measures examining the association of a more recent BP or a change from baseline measure with clinical outcomes. Furthermore if associations were similar and consistent between baseline measures and more complex longitudinal models, there may be a preference towards baseline measures and less model complexity. Previous studies have demonstrated conflicting results on the importance and use of differing longitudinal exposures in chronic disease. Wald *et al* examined abnormalities in mineral metabolism in 1,846 chronic hemodialysis patients. Cumulative measures of calcium and phosphorous were more consistently associated with clinical outcomes than time-dependant or baseline measures(43). Reinikainen *et al* examined differing quantitation of risk factors and their association with cardiovascular mortality in a longitudinally followed cohort of 1711 men(42). Models incorporating cumulative risk factors demonstrated better discrimination relative to time-dependent models. Hanratty *et al* reported associations between SBP and incidence of CKD quantitating SBP separately as baseline, time-dependent and time-weighted exposures

(cumulative) demonstrating associations with all three methods in a cohort of patients with mild CKD(37). In contrast, Barbour *et al* examining different longitudinal exposures for proteinuria reporting time-dependant measures to best prognosticate clinical outcomes in glomerulonephritis(44).

Table 1: Summary of key observational studies examining blood pressure (BP) components and clinical outcomes in chronic kidney disease (CKD)

Study	Cohort	Exposure:				Mean eGFR*	Outcome	Findings
		BP measure	Definition	How modelled	Model used			
Hanratty *et al(37)*	43,305 Kaiser Permanente	SBP	Continuous and categorical	Time-dependent and cumulative, non-linear	Cox proportional hazards regression	82	Incident CKD (eGFR decline)	Increased SBP associated with incident CKD (-0.2 eGFR per year for increase in 10 mmHg)
De Goeij *et al(29)*	508 patients 8 hospitals Netherlands	SBP, DBP	Continuous	Baseline	Linear regression and Cox proportional hazards regression	13.1	eGFR decline; ESKD	Increased 10 mmHg SBP 0.04 eGFR decline per month; increase 10 mm hg DBP 0.05 eGFR decline per month; both SBP and DBP associated with ESKD
Rifkin e*t al(30)*	4,365 Cardiovascular health study	SBP, DBP, PP	Continuous	Baseline	Linear and logistic regression	77-82	eGFR decline	SBP and PP significant; DBP not significant
Kovesdy *et al(31)*	77,765 US veterans	SBP	Continuous and categorical	Time-dependent, non-linear	Cox proportional hazards regression	48	All-cause mortality	Low SBP associated with increased mortality
Bansal *et al(45)*	1,705 CRIC	SBP	Continuous	Baseline, non-linear	Cox proportional hazards regression	25	All-cause mortality	SBP not associated with mortality
Agrawal (33)	218 veterans, single center	SBP, DBP	Categorical	Baseline, non-linear	Cox proportional hazards regression	38	ESKD, all-cause mortality	SBP and DBP J-shaped with ESKD and mortality
Palit *et al(34)*	1,099 Homocysteine in Kidney and ESKD study (HOST)	SBP, DBP, PP	Categorical	Baseline	Cox proportional hazards regression	18	ESKD, all-cause mortality, cardiovascular events (CVE)	SBP/DBP/PP no association with mortality; SBP/DBP no

Study	Cohort	Exposure:				Mean eGFR*	Outcome	Findings
		BP measure	Definition	How modelled	Model used			
								association with CVE; highest PP with CVE; highest SBP and DBP with ESKD
Kovesdy *et al(10)*	651,749 Veterans	SBP, DBP	Categorical	Time-dependent, non-linear	Cox proportional hazards regression	50.4	All-cause mortality	SBP and DBP J-shaped relationship with mortality
Anderson *et al(46)*	3,708 CRIC	SBP	Categorical	Time-dependent	Marginal structural model	45	ESKD, halving of eGFR from baseline	Time-updated high SBP associated with higher ESKD compared to baseline SBP
Bell *et al(36)*	2,772 (REGARDS); stroke incidence population study; oversample Southern USA	SBP, DBP, PP	Categorical	Baseline, non-linear	Cox proportional hazards regression	47.3	ESKD	Elevated SBP, PP, DBP associated; J-shaped SBP and DBP
Peralta *et al(35)*	16, 129 KEEP; large community study	SBP, DBP, PP	Continuous and Categorical	Baseline	Cox proportional hazards regression	48.2	ESKD	All 3 associated with ESKD

eGFR in ml/min/1.73m^2

Chapter 3: The association of repeat blood pressure measures with kidney function in late stage chronic kidney disease

This chapter incorporates the manuscript "The time-varying association of individual blood pressure components with estimated glomerular filtration rate in late stage chronic kidney disease"

Manish M Sood MD, Ayub Akbari MD MSc, Doug Manual MD PhD, Marcel Ruzicka MD PhD, Swapnil Hiremath MD MSc, Deborah Zimmerman MD MSc, Brenden McCormick MD, Monica Taljaard PhD.

Introduction

The optimal, safe levels of blood pressure in patients with late stage CKD remains controversial. This is especially relevant in the growing elderly CKD population, who may more often choose conservative, non-dialysis therapies. Furthermore the association of individual blood pressure components and declines in eGFR assessed longitudinally is unknown.

Background

Despite the current evidence in support of blood pressure control, considerable uncertainty still exists in stage 4/5 CKD as such patients are often excluded from trials or if included, are present only in small numbers (40, 47, 48). Additionally, the model of care has changed with the introduction of widely available multidisciplinary CKD clinics(3). Whether this influences the relationship of blood pressure control and the progression of CKD remains unknown. As well, the majority of evidence to date focuses on the need for dialysis as opposed to declines in glomerular filtration rate. Understanding the role of blood pressure on CKD progression is important. Declining GFR is not only associated with ESKD but is also associated with an increase in mortality, cardiac events, infection and hospitalizations(49). 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 opt for conservative care (19, 50). Examining the role of elevated blood pressure 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 effects of blood pressure on longitudinal changes in GFR (31, 46). Changes in numerous clinical and laboratory factors such as albumin, proteinuria, serum phosphate and blood pressure measures, have been associated with end stage kidney disease (ESKD) and may impact the decline in GFR in late stage CKD(7, 8, 31, 51). Recently the Chronic Renal Insufficiency Cohort (CRIC) demonstrated a dramatic alteration in the risk of ESKD by accounting for repeat, time-varying factors (46).

Study Objectives

To address these knowledge gaps, we set out to examine the time-varying associations of blood pressure indexes (systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP)) with eGFR in stage 4/5 CKD patients managed in a multidisciplinary clinic. Specifically, we examined the associations of SBP, DBP and PP with changes in eGFR over time, as well as their association with time to decline ≥ 30 % in late stage CKD.

Summary of findings

In this retrospective cohort study of patients with late stage CKD, we found that eGFR trajectories were non-linear over time, and that repeat measures of individual blood pressure components (SBP, DBP) were significantly associated with these non-linear eGFR trajectories. Higher blood pressures were associated with steeper declines in eGFR within the first 6 months after referral to a multidisciplinary CKD clinic with more gradual linear

changes afterwards. Extremes of systolic and elevated diastolic blood pressures were associated with increased risks of declines in eGFR ≥ 30%. These associations were only identified when modeling these exposures as time-varying effects and were consistent after accounting for informative censoring. Taken together, these findings demonstrate the continued importance of SBP and DBP on eGFR decline even among patients in late stage CKD.

Conclusions

In conclusion, in late stage (4/5) CKD patients cared for in a multidisciplinary clinic, extremes of SBP and elevated DBP were associated with steeper declines in eGFR. These findings underscore the importance of maintaining target blood pressures in low levels of eGFR to limit the progression of CKD.

Limitations

There was considerable missing data on proteinuria (19.2%) although the majority was in patients with existing measures of less than 1 g/day and low levels of proteinuria tend to remain stable over time(51). Further we performed multiple imputations with 10 iterations under a multivariate model. The blood pressures measures were not obtained by the 24 or 48 hour automated ambulatory method. They reflected pragmatic measures obtained in a clinic setting and were measured by trained health care providers. The majority of the study population was Caucasian and this may limit generalizability to other

cohorts. There is a possibility of a referral bias as physicians or patients may have declined referral to the CKD clinic and they may be more likely to choose conservative therapies.

Manuscript One

Time-varying association of individual blood pressure components with estimated glomerular filtration rate in late stage chronic kidney disease

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Abstract:

Background and objectives: The association of individual blood pressure components on changes in eGFR in late stage CKD patients are unknown. The objectives of the current study are to examine the association of systolic (SBP), diastolic blood pressure (DBP) and pulse pressure (PP) with continuous temporal changes in eGFR and with an eGFR decline ≥ 30% in late stage CKD.

Design, settings, participants and measurements: Retrospective cohort study (2010-2015) of CKD patients in a multidisciplinary CKD (MDCKD) clinic with an eGFR ≤ 30. The associations of repeat measures of blood pressure (SBP, DBP and PP) with eGFR were examined using general linear mixed models. The associations of blood pressure components and eGFR decline ≥ 30% were examined with time-varying Cox models.

Results: 1203 patients were followed for a median of 548 days (IQR 292 to 913) with an average of 6.7 visits and blood pressure measures per patient. Mean baseline SBP, DBP, PP and eGFR were 139.2, 73.2, 64.9 mmHg and 16.8 ml/min, respectively. SBP and DBP measures over time were statistically significantly associated with changes in eGFR ($p<0.001$) whereas PP was not. Patients with extremes of SBP (<105 or >170)and high DBP (>90) measures were at a higher risk of GFR decline ≥30% [SBP <105: HR 1.51(95%CI 0.98-2.34), SBP >170 : HR 1.62 (95%CI 1.05-2.49) referent SBP 121-130, DBP 81-90: HR 1.40 (95%CI 0.99-1.86), DBP>90:HR 1.83(95%CI 1.21-2.77), referent DBP 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 SBP and elevations of DBP were associated with eGFR declines.

Introduction:

Elevated blood pressure is a well-established risk factor for chronic kidney disease (CKD) progression(4). Randomized controlled trials and observational studies consistently demonstrate that blood pressure above recommended targets increases the risk of adverse outcomes(10, 23, 26, 31, 45-48, 52). Despite evidence for blood pressure control considerable uncertainty still exists in stage 4/5 CKD as they are often excluded from trials or if included, present only in small numbers (40, 47, 48). Additionally the model of care has changed with the introduction of widely available multidisciplinary CKD clinics. Whether this influences the relationship of blood pressure control and the progression of CKD remains unknown. Indeed evidence to date focuses on ESKD as opposed to declines in glomerular filtration rate. Understanding the role of blood pressure on CKD progression is important. Declining GFR is not only associated with ESKD but is also associated with higher mortality, cardiac events, infection and hospitalizations(49). More over in an era of the late-stage CKD population becoming increasingly elderly, a significant proportion of patients may not choose dialytic therapies and instead opt for conservative care (19, 50). Examining the role of elevated blood pressure 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 blood pressure on changes in GFR accounting for repeat measures (time-varying) (31, 46). Changes in numerous clinical and laboratory factors such as albumin, proteinuria, serum phosphate and blood pressure measures, have been associated with end stage kidney disease and may impact the decline

in GFR in late stage CKD(7, 8, 31, 51). Recently the Chronic Renal Insufficiency Cohort (CRIC) demonstrated a dramatic alteration in the risk of ESKD by accounting for repeat, time-varying factors (46).

To address these knowledge gaps, we set out to examine the time-varying associations of blood pressure indexes (systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP)) with eGFR in stage 4/5 CKD patients managed in a multidisciplinary clinic. Specifically, we examined the associations of SBP, DBP and PP with changes in eGFR over time, as well as their association with time to decline ≥ 30 % in late stage CKD.

Methods

Study Cohort

This is a retrospective cohort study of patients who were followed in a multidisciplinary tertiary care hospital CKD (MDCKD)clinic from January, 2010 to Nov 2015 (53). 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 two weeks to twice per year depending on clinician perception of need. Referral criteria to the MDCKD i) a diagnosis of CKD and ii) eGFR less than 30 ml/min/1.73m^2 or a rapid decline in kidney function (calculated using the MDRD formula)(54).

The clinic is staffed by a multi-disciplinary 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 blood pressure 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 January 2010. Data are routinely validated by random audit of 5% of entries every six months with > 95% data accuracy(53). Variables collected include demographics (age, sex, gender), cause of CKD, co-morbidities (coronary artery disease, congestive heart failure, diabetes, malignancy, peripheral vascular disease), outcomes with dates (death, dialysis initiation) and longitudinal laboratory measures (hemoglobin, potassium, phosphate, proteinuria, eGFR calculated by MDRD equation, albumin), physiologic parameters (blood pressure, BMI), and medications.

Outcomes and exposures:

The main predictors of interest were SBP, DBP and PP. At each clinic visit, blood pressure was measured once by a trained nurse using the ausculatory method. Blood pressure measurements were made with patients in the sitting position, after 15 minutes of rest, with an appropriately fitted blood pressure 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 ≥30% from baseline. Change in eGFR (in ml/min/1.73m^2) was examined using repeated measures of eGFR analyzed as a continuous variable. eGFR decline ≥30% was examined as the time to decline of ≥30% from baseline analyzed as a categorical variable. The eGFR was measured at each study visit and calculated by the 4 variable MDRD equation(54). 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 chronic kidney disease was based on the responsible nephrologists' diagnosis.

Statistical analysis

Baseline descriptive statistics for the total analytic cohort and classified by any eGFR decline of ≥30% are presented as mean and standard deviation for continuous variables and frequency and proportion for categorical variables. As proteinuria measures available were either 24-hour urine collections, albumin to creatinine or protein to creatinine ratios, we categorized proteinuria as minimal (ACR<30 mg/g, PCR<27 mg/g, 24 hour urine protein <0.03 gram per day), mild (ACR 30-<150 mg/g, PCR 27-<120, 24 hour urine protein 0.03 - 0.3 gram per day), moderate (ACR 150-350 mg/g, PCR 120-300 mg/g, 24 hour urine protein 0.3 -3 gram per day) or severe (ACR>350 mg/g, PCR>300 mg/g, 24hr urine protein >3 grams per day). 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 (REML)(55). 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^{th}, 25^{th}, 50^{th}, 75^{th} and 95^{th} percentiles of time corresponding to values of 1, 48, 168, 411, and 952 days, respectively. Additional statistical methods details are presented in the supplement. To avoid exclusion of participants due to missing covariates, multiple imputation was performed prior to analysis using a Markov Chain Monte Carlo algorithm (the data augmentation algorithm) (56). 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^{th}, 50^{th} and 95^{th} percentiles (SBP:105, 140, 170, DBP:50, 70, 90, PP: 35, 60, 100)(55). All remaining continuous covariates were set to their median values, while categorical covariates were set to their mode. The association of SBP, DBP and PP with time to eGFR decline ≥ 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^{th}, 25^{th}, 50^{th}, 75^{th} and 95^{th} percentiles and modelled at baseline upon cohort entry and with time-updated values. 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 of province (n=33) or received a pre-emptive 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) comprising a total of 6123 unique observations (see Supplementary Figure 1). Study exclusions were patients followed for less than 30 days (n=6 patients, 11 observations), and observations after 4 years (143). The median follow up time was 548 days (IQR 292 to 913) and time between visits 101 (range 30-727). The mean (range) of number of blood pressure measures per patient were 6.7 (1-17). Among the participants, 85.1% had data up to 6 months, 67.6% up to one year, and 33.9% for up to two years. The median eGFR at first clinic visit was 17.4 ml/min/1.73m^2 (IQR 14.3-21.1) with 99% of patients having an eGFR of 30 ml/min/1.73m^2 or under.

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) with diabetes or glomerulonephritis 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 ACE inhibitors or ARBs at baseline was more common among those with an eGFR decline (57 vs 49%). The use of ACE inhibitors or ARBs decreased over time from baseline use of 51.9% to

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 blood pressures significantly higher among those with an eGFR decline ≥ 30%. The SBP, DBP and PP varied over clinic visits with standard deviations 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, while percentage with baseline DBP ≥ 90 mmHg was 12.0% versus 8.5 % in the two groups.

Time-varying associations of blood pressure 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, 18.4) , SBP ≥170 (43.4, 31.5, 34.2, 31.8, 38.8), DBP < 50 (17.4, 29.9, 26.1, 33.8, 18.4), DBP>90 (9.9, 4.4, 6.1, 1.3, 8.2), PP < 35 (26.5, 27.6, 27.7, 29.2, 22.4) and PP >100 (38.1, 38.3, 36.2, 35.1, 32.7). The summarized results from the adjusted linear mixed models are presented in Table 2 with full models presented in supplementary Tables 1-3. All blood pressure components (SBP, DBP, PP) were non-linearly 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: i) excluding ESKD and patients with died and ii) excluding the first clinic eGFR value (see Supplementary table 4).

The modelled time-varying associations with each blood pressure component are presented in Figure 1a-c. 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 blood pressure values had higher eGFRs at their baseline clinic visit. Extremes of blood pressure demonstrated similar trajectories of eGFR decline with the mean eGFR separation at 3 years between SBP 170/105, DBP 90/50 and PP 100/35 mmHg of 0.40, 1.24 and 1.31 ml/min/1.73m^2, respectively. Overall higher blood pressures were associated with the largest declines in eGFR after 1-2 years of follow up.

Blood pressure 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 of 34.5 per 100 patient years. Crude and adjusted hazard ratios for the risk of an eGFR decline ≥30% by categorical blood pressure 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 borderline significance 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%CI 0.98-2.34) and SBP>170 (HR 1.62, 95%CI 1.05-2.49) compared to 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%0.99-

1.86), DBP>90: HR 1.83(95%CI 1.21-2.77), referent DBP 61-70 mmHg]. Time –varying pulse pressure was not associated with eGFR declines (p=0.80).

To examine the sensitivity of the results to the presence of patients reaching ESKD or death prior to an eGFR decline (n=494) (informative censoring), additional models were performed (results not shown). Both early and late censoring models for ESKD and mortality did not substantively alter the results.

Discussion:

We found repeat measures of all individual blood pressure components (SBP, DBP, PP) were associated with eGFR and these associations changed over time for SBP and DBP. Higher mean blood pressures were associated with small continuous declines in eGFR that were more apparent after 1-2 years of follow up. Extremes of systolic and elevated diastolic blood pressures were associated with a higher risk of declines in eGFR ≥ 30%. These findings were only identified after accounting for time-varying associations and were consistent after accounting for informative censoring. Taken together, these findings demonstrate the association of blood pressure 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 blood pressure and the risk of ESKD has been well established (4, 57). 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, non-dialytic care and those with longer time horizons of eGFR decline who may experience complications. In our cohort, 40% had not reached an endpoint after 14 months. Our findings suggest a wider range of blood pressures 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 blood pressure and ESRD but few have examined the associations of blood pressure on eGFR changes in CKD stage 4/5 (10, 31, 33, 35, 36). De Goeil *et al* examining baseline BP in 547 (mean eGFR 13.1 ml/min) CKD patients demonstrated an association between elevated SBP and DBP and monthly eGFR declines(29). The African American Study of Kidney Disease and Hypertension (AASK) randomized control trial examined usual (141/85 achieved) versus low (128/78) blood pressure on the slope of eGFR decline in 1094 patients (mean eGFR 46 ml/min/1.73m2)and found no difference in eGFR decline(40). In a study examining only baseline BP components in patients with milder degrees of CKD, Rifkin *et al* reported an inverse relationship with elevated blood components (SBP and PP) and eGFR decline (30). Similar to our findings they found 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 demonstrate any significant associations

with baseline BP measures and eGFR and associations were only detected for extremes of SBP and elevated DBP.

A report from the Chronic Renal Insufficiency Cohort (CRIC) illustrated the importance of time-updated measures of SBP and the risk of ESKD. The longitudinal adjusted hazard ratio of ESRD for SBP>140 mmHg was 3.4-fold compared to 1.5-fold when only the baseline SBP was considered(46). Similarly, we demonstrated marked differences between the associations of baseline measures of blood pressure versus their time-varying associations. The lack of association between an elevated baseline blood pressure 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 demonstrates differing individual eGFR trajectories in late stage CKD (50, 58). Our study illustrates blood pressure indices are associated with differing eGFR trajectories over time yet 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 blood pressure on eGFR over time is non-linear; undergoing dynamic changes especially at higher levels of eGFR.

Strengths of our study include the use of well validated data, a unique cohort with late stage CKD and undergoing multidisciplinary care, the use of time varying covariates, and eGFR as the study outcome. We modelled changes in blood pressure using non-linear 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 ESKD and mortality and excluding 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, individuals with eGFR loss experience elevations in BP. There was considerable missing data on proteinuria (19.2%) although the majority was in patients with existing measures of less than 1 g/day and low levels of proteinuria tend to remain stable over time(51). The blood pressures were not obtained by 24 or 48 hours 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 blood pressure. There is a possibility of a referral bias as 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 angiotensin receptor blocker use and not all possible anti-hypertensives. 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 towards the null.

In conclusion, in late stage (4/5) CKD patients 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 ≥ 30%. Avoidance of extremes of SBP and elevated DBP may limit the progression of CKD.

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Table 1: Characteristics of CKD cohort and differences between patients with and without eGFR decline **≥ 30%**

Characteristic	**N=1203**	**eGFR decline ≥30% (N=494)**	**No eGFR decline ≥30% (N=709)**	**P value**
Demographics:				
Female Sex	40.6 (489)	37.9 (187)	42.6 (302)	0.11
Age (years)	65.9 SD 14.9	62.7 SD 15.1	68.2 SD 14.3	<0.001
Body mass index (kg/m^2)	30.1 SD 7.0	29.8 SD 6.7	30.3 SD 7.3	0.18
Cause of CKD:				<0.001
Diabetes	33.5 (403)	41.1 (203)	28.2 (200)	
Ischemic nephropathy	18.7(225)	12.3 (61)	23.1 (164)	
Glomerulonephritis	14.0(168)	18.8(93)	10.6(75)	
Other	33.8(406)	27.7 (137)	38.1 (270)	
Comorbidities:				
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
Laboratory:				
Baseline eGFR (ml/min/1.73m^2)	16.8 SD 5.5	14.8 SD4.0	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	11.0SD 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
Distribution of baseline SBP (%, N)				
SBP ≤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 ≥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

Distribution of baseline DBP (%, N)				
DBP ≤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 ≥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
Distribution of baseline PP (%, N)				
PP ≤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 ≥ 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

[a] Values presented as mean with standard deviation or percentage and frequency. [b] 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%, proteinuria 19.2%) [c] Abbreviations: N number % percentage CKD chronic kidney disease ACE/ARB angiotensin converting enzyme inhibitor/angiotensin II receptor blocker eGFR estimated glomerular filtration rate ml millilitre min minute m metre mEq milliequivalent L liter dL decaliter g gram kg kilogram mmHg millimeter of mercury SD standard deviation

Table 2: General linear mixed effects regression model of the association between the individual components of blood pressure (systolic, diastolic and pulse pressure) and estimated glomerular filtration rate for splines of time.

Variable	Estimate (change in eGFR)	P	Variable	Estimate (change in eGFR)	P	Variable	Estimate (change in eGFR)	P
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 x 1-48 days	0.14	0.004	DBP x 1-48 days	0.32	<0.001	PP x 1-48 days	0.05	0.34
SBP x 49-168 days	-6.97	0.02	DBP x 49-168 days	13.08	0.01	PP x 49-168 days	-3.56	0.26
SBP x 169-411 days	10.22	0.02	DBP x 169-411 days	18.49	0.02	PP x 169-411 days	5.51	0.24
SBP x 411-952 days	-3.50	0.04	DBP x 411-952 days	-5.43	0.06	PP x 411-952 days	-2.27	0.20
P value for non-linearity[a]	<0.001			<0.001			<0.001	
P value for change over time[b]	<0.001			<0.001			0.49	

Models adjusted for age at cohort entry, gender, and baseline comorbidities (coronary artery disease, congestive heart failure, malignancy, hypertension, PVD, diabetes,), ACE/ARB use as well as repeat measures of hemoglobin, albumin, phosphate, potassium, bicarbonate and proteinuria.

[a]P values represent statistical significance testing of likelihood ratios for models containing nonlinearity terms for time compared with linearity terms for time.

[b]P values represent statistical significance testing of likelihood ratios for models containing terms for time-varying BP compared with non-time-varying terms.

Abbreviations: eGFR estimated glomerular filtration rate (in ml/min/1.73m^2) SBP systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure

Table 3: The hazard ratio of categories of SBP, DBP and PP for eGFR decline ≥ 30% at the first clinic visit and time-varying.

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

[a] Data adjusted for age, sex, cause of chronic kidney disease, malignancy, coronary artery disease, congestive heart failure, peripheral vascular disease, diabetes mellitus, ACE_ARB use and baseline measures of hemoglobin, bicarbonate, phosphate, potassium, albumin and proteinuria. Number of events (GFR decline≥30%) =494.

[b]Data adjusted for age, sex, cause of chronic kidney disease, malignancy, coronary artery disease, congestive heart failure, peripheral vascular disease, diabetes mellitus, ACE_ARB use and time-updated measures of hemoglobin, bicarbonate, phosphate, potassium, albumin and proteinuria.

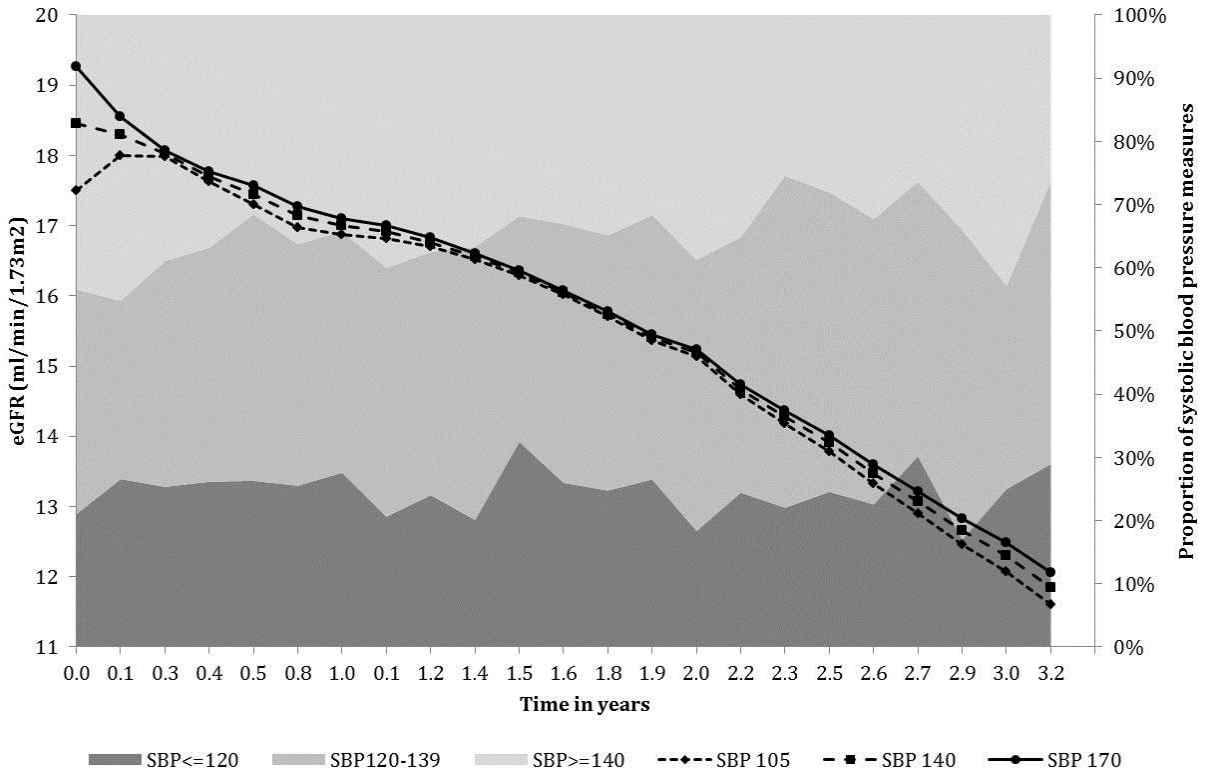
[c] P values represent the association of each BP component over time modelled as a continuous variable

Abbreviations: mmHg millimeters of mercury, HR hazard ratio, CI confidence interval N number % percentage.

Figure Legends

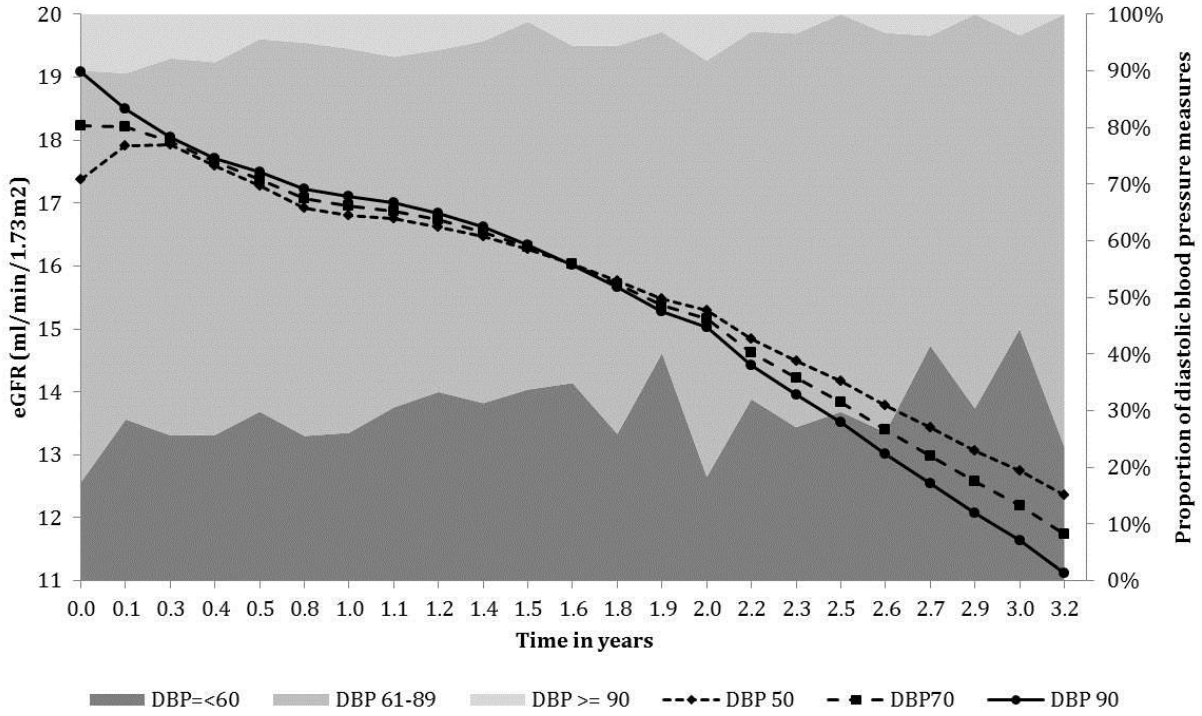
Figure 1: Predicted eGFR trajectories by levels of a) systolic (SBP), b) diastolic (DBP) and c) pulse pressure (PP) with overlay distribution of proportion of blood pressure measures over time.

a)



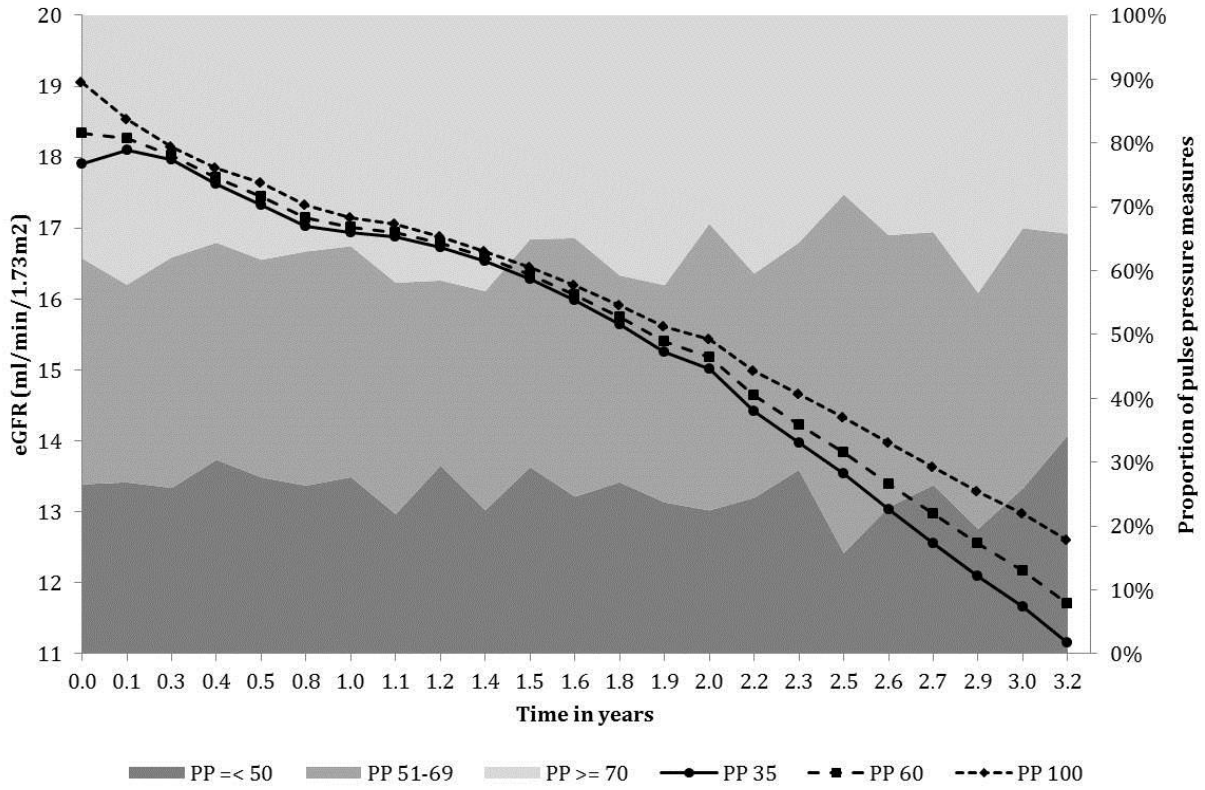
The lines indicate the predicted eGFR trajectory at systolic blood pressures of 105, 140 and 170 mmHg (the 5th, 50th and 95th percentiles) from a linear mixed model with covariates set to their median values. The shaded areas represent the distribution of systolic blood pressure measures (≤120, 121-139, ≥140) during follow up. Analysis 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.

b)



The lines indicate the predicted eGFR trajectory at diastolic blood pressures of 50, 70, and 90 mmHg (the 5th, 50th and 95th percentiles) from a linear mixed model with covariates set to their median values. The shaded areas represent the distribution of diastolic blood pressure measures (<60, 61-89, >90) during follow up. Analysis 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.

c)



The lines indicate the predicted eGFR trajectory at pulse pressures of 35, 60 and 100 mmHg (the 5th, 50th and 95th percentiles) from a linear mixed model with covariates set to their median values. The shaded areas represent the distribution of pulse pressure measures (<50, 51-69, >70) during follow up. Analysis 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.

Chapter 4: Blood pressure exposure in late stage CKD and the risk of end stage kidney disease or all-cause mortality

This chapter incorporates the manuscript "**Longitudinal blood pressure in late-stage chronic kidney disease and the risk of end stage kidney disease or mortality (BEST BP in CKD Study)".**

Manish M Sood MD, Ayub Akbari MD MSc, Doug Manual MD PhD, Marcel Ruzicka MD PhD, Swapnil Hiremath MD MSc, Deborah Zimmerman MD MSc, Brenden McCormick MD, Monica Taljaard PhD.

Introduction

It is unclear how to appropriately specify the nature of the longitudinal association between BP and clinical outcomes of end stage kidney disease (ESKD) and mortality.

Background

Elevations in systolic and diastolic blood pressure are known to be associated with an increased risk of adverse outcomes in chronic kidney disease (CKD) (30, 31, 35, 36, 38). As such, blood pressure control is an important therapeutic target to aid in the progression of CKD and cardiovascular mortality. Despite a large body of evidence in patients with milder degrees of CKD, there remains limited evidence on the optimal blood pressure target in patients with late stage (eGFR < 30) CKD(29, 32, 38).

Numerous previous studies have examined the association between baseline blood pressure and end stage kidney disease (ESKD) or mortality (29, 33-36, 45). However, it is unclear how to appropriately specify the nature of the association between BP and adverse outcomes in longitudinal studies. Different methods of accounting for the effects of blood pressure may better mimic the pathophysiological processes leading to end organ damage. For example, accounting for cumulative exposure based on all follow up blood pressure measures to date may better quantify the temporal effect of hypertension on end-organs. Conversely the current (or most recent) BP measure in a clinic visit often forms the basis for clinical decision making and choices regarding therapeutics. To avoid the risk of reverse causation when using the current BP measurement in time-dependent modeling, an earlier

BP measure (or visit immediately preceding the most recent one, termed "lag") may be appropriate to reduce ambiguity in the causal ordering. A lag BP value would be clinically relevant as it may allow for changes in therapy potentially reducing the risk of an adverse outcome. Lastly, rises or falls in blood pressure from baseline, often based on changes in therapy or clinical status, may be associated with outcomes. Systematic examination of differing methods of longitudinal BP in late-stage CKD may provide insight into casual mechanisms of BP-dependent organ injury.

Study Objectives

Our aim was to examine differing methods of accounting for BP and their association with adverse outcomes. Specifically, we examined the association of SBP and DBP as a single measure at baseline into cohort entry and as four methods accounting for repeat (longitudinal) time-dependent BP measures as follows: 1) current (most recent) clinic visit, 2) lag one visit (visit immediately preceding the most recent one), 3) cumulative (average of all previous measurements to date), and 4) change from baseline to the most recent visit with the clinical outcomes of ESKD and all-cause mortality. We hypothesized that longitudinal measures of BP would be more strongly associated with all-cause mortality or ESKD in late stage CKD patients.

Summary of findings

In a total of 1203 patients with a mean baseline eGFR of 17.77, there were 540 (44.8%, 24.7/100 pt-yrs) cases of ESKD and 141 (11.7%, 6.5/100 pt-yrs) deaths. For SBP, current (SBP> 160 HR 1.67 95%CI 1.26-2.21), cumulative (SBP > 160 HR 1.58 95%CI 1.07-2.35) and a rise to > 160 from baseline 120-160 (HR 1.60 95%CI 1.15-2.23) were significantly associated with increased risk of ESKD. Similarly, elevated DBP was significantly associated with increased risk of ESKD when modelled as current (DBP > 85 HR 1.47 95%CI 1.12-1.95), lag (DBP>85 HR 1.63 95%CI 1.23-2.16), cumulative (DBP>85 HR 2.15 95%CI 1.49-3.09), or change from baseline (rise to >85 from a baseline of 60-85 HR 1.62 95%CI 1.15-2.29). Low SBP (<120) was associated with all-cause mortality when examined as current (HR 1.59), lag (HR 1.37) or cumulative (HR 1.76). For DBP, only cumulative >85 was associated with mortality (HR 2.75). Neither baseline SBP or DBP were significantly associated with any outcomes.

Conclusions

In late stage CKD, persistently high or rises in SBP > 160 or DBP > 85 are associated with ESKD whereas baseline BP measures did not convey information regarding risk.

Limitations

Despite over 10 years of data, there were relatively few deaths in some categories of exposure. We may have underestimated the risk of ESKD as the study cohort included individuals whom may have reached ESKD but did not receive renal replacement therapy (conservative care). We categorized BP measures at clinically relevant cut-points and did

not explore possible non-linear associations with outcomes. Our study cohort includes a referred group of patients from a distinct geographic region that may limit generalizability. Blood pressure was measured once per visit which is reflective of real world practice but may not be as accurate as the average of multiple readings. Lastly, our findings require validation in other study cohorts.

Manuscript Two

Longitudinal blood pressure in late-stage chronic kidney disease and the risk of end stage kidney disease or mortality (BEST BP in CKD Study)

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References: 25

Abstract

Whether different methods of quantitating blood pressure in late chronic kidney disease better mimic pathophysiological processes and clinical outcomes remains unclear. In a retrospective study, we determined the association of BP with end stage kidney disease and all-cause mortality with BP modelled at baseline vs. longitudinally with time-varying Cox models as: a) current (most recent) clinic visit, b) lag (visit immediately preceding the current one), c) cumulative (average of all previous measurements), and d) change from baseline to the most recent visit. Among 1203 (6913 visits) study patients the mean age and baseline eGFR were 66 and 18 ml/min/1.73m^2, and 40% were female. Each patient had a mean of 6.7 BP measurements, 540 (44.8%) reached end stage kidney disease and 141 (11.7%) died. For SBP > 160, current (HR 1.67 95%CI 1.26-2.21), cumulative (HR 1.58 95%CI 1.07-2.35) and a rise to > 160 from baseline 120-160 (HR 1.60 95%CI 1.15-2.23) were associated with end stage kidney disease. Similarly, DBP >85 was associated with end stage kidney disease when modelled as current (HR 1.47 95%CI 1.12-1.95), lag (HR 1.63 95%CI 1.23-2.16), cumulative (HR 2.15 95%CI 1.49-3.09), or change from baseline (rise to >85 from a baseline of 60-85 HR 1.62 95%CI 1.15-2.29). Low SBP (<120) was significantly associated with increased risk of mortality as current (HR 1.59), lag (HR 1.37) or cumulative exposure (HR 1.76). For DBP, only cumulative >85 was significantly associated with mortality (HR 2.75). These findings were consistent in a sensitivity analysis examining for informative censoring. Thus, in late stage chronic kidney disease, persistently high or rises in SBP or DBP are associated with risk of end stage kidney disease whereas baseline BP measures did not convey information regarding risk.

Keywords: chronic kidney disease, renal insufficiency, dialysis, end stage kidney disease, end stage renal disease, systolic blood pressure, diastolic blood pressure, longitudinal blood pressure, time-varying Cox

Introduction:

Elevations in systolic blood pressure (SBP) and diastolic blood pressure (DBP) are known to be associated with an increased risk of adverse outcomes in chronic kidney disease (CKD)(1-7). As such, blood pressure (BP) control is an important therapeutic target to aid in the progression of CKD and cardiovascular mortality (8). Despite a large body of evidence in patients with milder degrees of CKD, there are few studies on the effects of BP in patients with late stage (eGFR < 30 ml/min) CKD (5, 9-11).

BP control and the optimal means of evaluating BP in late stage CKD remains controversial. Numerous studies report conflicting associations between a single baseline BP and end stage kidney disease (ESKD) or mortality (1, 9, 10, 12, 13, 14). In real world clinical practice, Physicians often consider multiple, additional scenarios regarding BP information and their relation to the need for dialysis or mortality. For example, decision-making and changes in pharmacologic agents are often determined by the most recent BP value observed in a given clinic visit. However, an earlier BP measurement such as the visit immediately preceding the most recent one (termed “lag”) may allow for early changes in therapy potentially reducing the risk of an adverse outcome. Physicians may consider averaging all previous BP measures up to the most recent as this may better mimic the temporal effect of hypertension injury on end organs. Lastly, Physicians may consider the

ability to achieve and maintain a reasonable level of BP control since entering their care (changes from baseline) as a means to offset adverse outcomes.

As BP control is crucially important in late stage CKD, we set out to systematically examine differing methods of accounting for BP and their association with adverse outcomes. Specifically, we examined the association of SBP and DBP as a single measure at baseline into cohort entry and as four methods accounting for repeat (longitudinal) time-dependent BP measures as follows: 1) current (most recent) clinic visit, 2) lag one visit (visit immediately preceding the most recent one), 3) cumulative (average of all previous measurements to date), and 4) change from baseline to the most recent visit with the clinical outcomes of ESKD and all-cause mortality. We hypothesized that longitudinal measures of BP would be more strongly associated with all-cause mortality or ESKD in late stage CKD patients.

Methods

Study Cohort

This is a retrospective cohort study using prospectively collected data on N=1209 adult patients (>18 years) followed in a hospital CKD clinic from January 2010 to November 2015 (15). The tertiary care, specialty CKD clinic serves a catchment area of approximately 1.2 million individuals in Ottawa, Canada. The clinic is staffed by a multi-disciplinary care 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. Timing of transfer is at the discretion

of the primary nephrologist with 99% of patients entering the clinic with an eGFR < 30mL/min/1.73 m^2 (calculated using the MDRD formula). The first clinic visit was deemed the date of study entry. Patients are seen in the clinic regularly, sometimes as often as every two weeks and at a minimum twice a year, though the exact interval is left to the discretion of the clinician. There are standardized treatment procedures for vaccinations and consensus regarding anemia, blood pressure targets and preferred medications and all patients use a decision aid regarding modality selection. Patient information was de-identified prior to analysis. The study was reviewed and approved by the Ottawa Hospital Research Ethics Board.

Data collection

Data were abstracted from clinical charts and electronic medical records by trained clerks starting January 2010 and validated by random audit of 5% of entries every six months with > 95% accuracy. Variables collected include demographics (age, sex, race), cause of CKD, co-morbidities (coronary artery disease, congestive heart failure, diabetes, peripheral vascular disease, malignancy), outcomes with dates (death, dialysis initiation) and longitudinal measures of laboratory measures (hemoglobin, phosphate, potassium, bicarbonate, proteinuria, eGFR, albumin), physiologic parameters (blood pressure), and medications. Comorbidities were defined by self-report or clinical documentation based on the medical chart.

Exposures and Outcomes:

The main exposures of interest were SBP and DBP. At each clinic visit, resting blood pressure was measured once by a trained nurse using a mercury sphygmomanometer. Blood pressure measurements were made with patients in the sitting position, after 5 minutes of rest, with an appropriately fitted blood pressure cuff and the cuff placed directly on the skin.

Blood pressure measures (SBP, DBP) were examined at baseline at cohort entry and by four longitudinal time-dependent measures: current, lag, cumulative and change from baseline. Time dependent measures included all values over the follow up period and examine the association of an outcome and the BP measure taken at the most recent clinic measure. Lag measures examine the association of an outcome and the BP measure from the clinic visit immediately before the most recent measure. Cumulative measures the average all the previous BP measures up to the most recent measurement. Change from baseline examines how subsequent BP measures change relative to the first (baseline) BP measure at cohort entry. The main outcomes of interest for this study were ESKD, defined by the initiation of dialysis or pre-emptive transplantation (n=8), or all-cause mortality.

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 chronic kidney disease was based on the most responsible nephrologists' diagnosis.

Statistical analysis

The 2-year kidney failure risk equation (KRFE) (model 3: age, sex, eGFR and the albumin to creatinine ratio) was used to estimate the risk of ESKD(16). Proteinuria was categorized as minimal (ACR<30 mg/g, PCR<27 mg/g), mild (ACR30-149 mg/g, PCR 27-150, 24 hour urine protein <0.3 gram per day), moderate (ACR 150-350 mg/g, PCR 151-300 mg/g, 24 hour urine protein 0.3 -3 gram per day) or severe (ACR>350 mg/g, PCR>300 mg/g, 24hr urine protein >3 grams per day). The various SBP and DBP distributions were examined graphically.

We examined the association of blood pressure (SBP and DBP) with ESKD or all-cause mortality separately using time to event models. BP was modelled categorically (SBP: <120, 121-140, 141-160, > 160, DBP: <60, 60-75, 76-85, >85) as previous studies reported U-shaped associations with BP and outcomes in CKD(4, 17). Models were created to examine the association of SBP or DBP measures as baseline or as time-dependent measures, where time-dependent measures were expressed as current, lag, cumulative or change from baseline. All exposures except baseline were analyzed using extended Cox proportional hazards models to account for longitudinal (time-dependent) measures. To examine change from baseline, baseline and subsequent measures of BP were categorized with the number of categories determined by the distribution of events.

All ESKD models were adjusted for age, sex, cause of CKD, comorbidities (coronary artery disease, congestive heart failure, peripheral vascular disease, diabetes, malignancy), repeat measures of laboratory values (proteinuria, hemoglobin, albumin, potassium, phosphate, bicarbonate), baseline eGFR, baseline BP and the number of anti-hypertensive medications. All-cause mortality models were adjusted for age, sex, comorbidities

(congestive heart failure, diabetes, and malignancy), baseline BP and laboratory values (albumin, phosphate). Mortality models examining BP as a change from baseline were adjusted for age; CHF, albumin and phosphate as they demonstrated the strongest association with mortality. Model fit was examined by the Akaike Information Criteria (AIC). Patients were censored at the outcomes of interest (681), at study end (287), at loss to follow-up (20) or if they moved out of province (33). In a sensitivity analysis we examined for informative censoring by excluding i) all observations for patients who died in models when the outcome was ESKD and ii) all observations for who patients who reached ESKD in models when the outcome was death.

To avoid exclusion of subjects due to missing covariates, multiple imputation was performed prior to analysis. The imputations were generated using a Markov Chain Monte Carlo algorithm (the data augmentation algorithm)(18). Ten multiple imputation datasets were generated with all variables included in analytical models specified as predictors in the multiple imputation model(19). Analyses were carried out for each multiple imputation dataset and pooled across datasets using Rubin's rules. All analyses were conducted with SAS 9.4.

Results:

Study cohort

Our cohort included N=1203 adult patients (>18 years) comprising a total of 6123 unique observations (see Supplementary Figure 1). Study exclusions were patients

followed for less than 30 days (n=6 patients, 11 observations), and observations after 4 years (143). The median follow up time was 1.49 (IQR 0.8-2.45) years and time between visits 101 (range 30-727) days. The mean (range) of number of blood pressure measures per patient were 6.7 (1-17) with 98% of patients having 2 or more measures. Missing data was all less than 6% of measures with the exception being proteinuria at 19.7%.

The median eGFR at first clinic visit was 17.77 ml/min/1.73m^2 (IQR 14.3-21.1) with 99% of patients having an eGFR of 30 ml/min/1.73m^2 or under (see Table 1). The mean patient age at cohort entry was 65.6 years. The majority of patients were Caucasian, men with a mean BMI of 30.1. The most common identified causes of CKD were diabetes, ischemic nephropathy and glomerulonephritis. Hypertension, diabetes and cardiac disease were common comorbidities and nearly half of patients were on RAS blockade at cohort entry. The degree of proteinuria was evenly distributed across categories with the highest proportion in those with severe proteinuria. Nearly one-third of patients had a 2-year kidney failure risk of > 15% by the KFRE.

The baseline distribution of SBP was <120 (18%), 121-140 (39.7%), 141-160 (26.4%) and >160 (16.0%) and for DBP was <60 (21.5%), 60-75 (39.8%), 76-85 (24.4%) and >85 (14.3%) in mmHg. For most current measure, SBP and DBP, roughly 70% of measures were between SBP 120-160 and DBP 60-85. This was similar for lag BP measures. For cumulative blood pressures, there were fewer patients with extremes of SBP (>160) or DBP (>85) with <5% of participants in these categories by 1 year of follow up. For BP changes from baseline, the majority were within the ranges of SBP 121-160 or DBP 60-85.

Association of SBP and DBP modelled as baseline and time-dependent exposures (current, lag, cumulative and change from baseline) with ESKD

The crude number of events and estimated hazard ratios for each type of exposure (expressed as baseline, most recent, lag, cumulative, change from baseline) with ESKD are presented in Figure 1 and Table 2. Neither baseline SBP nor baseline DBP were significantly associated with ESKD. Covariates associated with ESKD in the time-varying models included albumin, hemoglobin, phosphate, baseline eGFR, baseline BP, age and sex (all $p<0.001$). Current SBP > 160 was significantly associated with ESKD in the time-dependent model (HR 1.67 95%CI 1.26-2.21, referent SBP 121-140), the cumulative model (HR 1.58 95%CI 1.07-2.35, referent SBP 121-140) but not the lag model (HR 1.15 95%CI 0.85-1.55, referent SBP 121-140). A change from baseline SBP of 120-160 to a subsequent SBP > 160 was significantly associated with ESKD (HR 1.60- 95%CI 1.15-2.23, referent SBP 121-140) whereas a persistently low SBP (<120) was significantly associated with a lower ESKD risk (HR 0.55 95%CI 0.35-0.87, referent SBP 121-140). Elevated DBP was significantly associated with ESKD in all longitudinal models. Current DBP > 85 was significantly associated with ESKD in the time-dependent model (HR 1.47 95%CI 1.12-1.95, referent 60-75), the lag model (HR 1.63 95%CI 1.23-2.16, referent 60-75) and the cumulative model (HR 2.15 95%CI 1.49-3.09, referent 60-75). A baseline DBP of 60-85 with a subsequent DBP >85 was significantly associated with ESKD (HR 1.62 95%CI 1.15-2.29) whereas a persistently elevated DBP > 85 was associated with a higher ESKD risk (HR 1.54 95%CI 1.09-2.18, referent DBP 60-85). In a sensitivity analysis excluding patients who died, there were minimal changes in the point estimates for the association of SBP/DBP with ESKD (SEE Supplementary Table 5). Model fit as determined by AIC was lowest for the

change from baseline model for SBP (5757) and the cumulative model for DBP (5759) (SEE Supplementary Table 6).

Association of SBP and DBP modelled as baseline and time dependent exposures (current, lag, cumulative and change from baseline) with all-cause mortality

The crude number of events and estimated hazard ratios for each type of exposure (expressed as baseline, current, lag, cumulative, change from baseline) with all-cause mortality are presented in Table 3 for SBP and Table 4 for DBP. As for ESKD, neither baseline SBP nor baseline DBP were significantly associated with mortality. Covariates associated with mortality in the time-varying models included albumin, age, baseline eGFR, baseline BP, CHF, malignancy (all p <0.001), hemoglobin (p=0.04), and phosphate (p=0.03). Current SBP < 120 was significantly associated with mortality in the time-dependent model (HR 1.59 95%CI 1.04-2.44 referent SBP 121-140), the lag model (HR 1.37 95%CI 0.91-2.09 referent SBP 121-140), the cumulative model (HR 1.76 95%CI 1.10-2.82, referent SBP 121-140) and if persistently low (HR 2.28 95%CI 1.38-3.77, referent SBP 120-140). Only cumulative DBP > 85 was significantly associated with mortality (HR 2.75 95%CI 1.05-7.20) albeit in a small number of events (6). In a sensitivity analysis excluding patients with ESKD, there were slight changes in the point estimates for the association of SBP/DBP with all-cause mortality for the current, lag and cumulative models (SEE Supplementary Table 5). However the overall trend of the point estimates was similar and the changes were within the confidence intervals of the original estimates. For the change from baseline model, the HR increased from 2.85 to 2.28 for patients with baseline SBP < 120 and change

< 120 (results now shown). Model fit was lowest for the cumulative models for both SBP (1572) and DBP (1578) (see Supplementary Table 6).

Discussion:

In a unique cohort of late stage CKD patients followed longitudinally in an outpatient clinic, we examined the association of differing repeat measures of SBP and DBP exposure with ESKD and all-cause mortality. We found elevations in SBP and DBP to be consistently associated with ESKD whereas persistently low SBP was associated with all-cause mortality. For SBP > 160 mmHg, time-dependent measures (current, cumulative and rises in SBP from baseline) were significantly associated with ESKD while for DBP all longitudinal measures >85 mmHg were associated with ESKD. All longitudinal measures of SBP < 120 mmHg were associated with mortality. Baseline BP measures were not significantly associated with any outcomes. Interestingly, for patients with more moderate ranges of SBP (121-140 mmHg) or DBP (60-85 mmHg) at baseline, a subsequent rise >160 mmHg or > 85 mmHg was associated with an increased risk of ESKD. Furthermore, DBP>85 mmHg, on the previous second last clinic visit (lag) was associated with a higher ESKD risk suggesting the possibility of therapeutic interventions as a means of reducing the ESKD risk. The results were consistent when accounting for informative censoring. Overall these findings demonstrate for patients with late stage CKD, that the risk of ESKD or mortality is significantly associated with longitudinal blood pressure measures with the differing means of quantitating BP conferring additional and potentially useful information.

In our comprehensive assessment of longitudinal blood pressure measures, we found thresholds for blood pressure values and adverse clinical outcomes that are consistent with previous studies in CKD. Hanratty *et al* examined the association of SBP and incident CKD in 43, 305 patients at a private healthcare network(20). They found a time-weighted higher SBP to be associated with eGFR decline and the cumulative incidence of CKD started to increase with a time-varying SBP > 140 mmHG. Anderson *et al* reported data on 3708 patients with CKD from the Chronic Renal Insufficiency Cohort (CRIC) with a baseline mean eGFR of 45 ml/min(21). They found a greater than doubling in the adjusted risk of ESKD when examining repeat measures of SBP ≥ 140 mmHg compared to baseline (HR repeat measures 3.37 versus HR baseline 1.46) using marginal structural models (MSM). MSM uses inverse probability of treatment weighting (IPTW) to provide average casual treatment effects. Our study differs from previous studies as we examined a broader array of methods for quantitating BP exposures and we examined this relationship in late stage CKD (eGFR < 30). Nevertheless in our study we identified similar SBP thresholds associated with ESKD risk with SBP > 160 mmHg.

To our knowledge, ours is the first study to report the consistent association between longitudinal DBP and ESKD. Previous studies report conflicting results regarding the association between DBP and ESKD(1-3, 5, 9, 12). We found DBP >85 mmHg to be consistently and strongly associated with ESKD across a range of different models with adjusted hazards ranging from 1.5-2.2 (referent DBP 60-75mmHg). Whether this finding is specific to the late-stage CKD population requires further investigation.

A higher ESKD risk with a rise in BP from baseline is a unique and novel observation. CKD patients who enter the speciality clinic with BPs in more conventional ranges (SBP 120-160 mmHg, DBP 60-85 mmHg) with subsequent measures that rise are at a higher ESKD risk. The association of higher BP and ESKD has previously been reported with the traditional paradigm being elevations in BP accelerate end organ damage and the progression of CKD. However we demonstrated the relationship between BP and ESKD in CKD is more complex as a late rise in BP is associated with ESKD onset. This raises the intriguing possibility of reverse causality as the rise in BP may be a sign of increasing ECF volume expansion with declining kidney function. A rise in BP is known to increase the risk of adverse events in the general population. Verdecchia *et al* reported a rise from baseline BP to be associated with stroke and myocardial infarction in 25, 620 patients from the ONTARGET cohort(22). The importance of a rising DBP is reinforced by the observation that a lag DBP (the measure prior to the last clinic visit) >75 mmHg is associated with ESKD. In the general population, a reduction from baseline BP is associated with a reduction in stroke risk but we did not observe any benefit from a reduction of moderate baseline BP to subsequent lower levels on ESKD or all-cause mortality(22). These observations are highly clinically relevant, as a rise in BP should prompt consideration of imminent ESKD. Furthermore interventions to lower a rising BP in late-stage CKD as a means of delaying ESKD remain a possibility and warrant further investigation.

Kovesdy *et al* examined SBP and DBP using time-dependent Cox models in 651, 749 US Veterans with mean eGFR 50 ml/min/m^2 for the risk of all-cause mortality(17). They found a higher mortality risk if BP was outside of 130-159/70-89 mmHg. In contrast, we found the association of SBP and all-cause mortality to vary based on the method of

quantitation and only in lower (<120) ranges of SBP. Our lack of U-shaped relationship with mortality may be due to our unique study cohort of late-stage CKD patients or smaller cohort size. In our sensitivity analysis, after exclusion of patients who reached ESKD, the risk of all-cause mortality for baseline SBP< 120 and repeat SBP <120 increased from 2.28 to 2.85. In contrast, in the ESKD model excluding patients who died the HR remained similar demonstrating a lower ESKD risk. These findings suggest patients with persistently low SBP are heterogeneous with some demonstrating a protective benefit whereas in others its a sign of poor health.

Previous studies have demonstrated conflicting results on the importance and use of differing longitudinal exposures in chronic disease. Wald *et al* examined abnormalities in mineral metabolism in 1,846 chronic hemodialysis patients(23). Cumulative measures of calcium and phosphorous were more consistently associated with clinical outcomes than time-dependant or baseline measures. Reinikainen *et al* examined differing quantitation of risk factors and their association with cardiovascular mortality in a longitudinally followed cohort of 1711 men(24). Models incorporating cumulative risk factors demonstrated better discrimination relative to time-dependent models. Hanratty *et al* reported associations between SBP and incidence of CKD quantitating SBP separately as baseline, time-dependent and time-weighted exposures (cumulative) demonstrating associations with all three methods in a cohort of patients with mild CKD(20). In contrast, Barbour *et al* examining different longitudinal exposures for proteinuria reporting time-dependant measures to best prognosticate clinical outcomes in glomerulonephritis(25). We demonstrated the strongest associations with cumulative exposures to longitudinal BP with no baseline BP measures demonstrating statistical significance.

Strengths of our study include a unique cohort of real world late stage CKD patients, multiple BP measures per patient, the use of a validated database, the large number of covariates adjusted for in our analyses and methodology that accounts for differing longitudinal measures of BP exposure. Our study did have some potential limitations. Despite over 10 years of data, there were relatively few deaths in some categories of exposure. We may have underestimated the risk of ESKD as the study cohort included individuals whom may have reached ESKD but did not receive renal replacement therapy (conservative care). We categorized BP measures at clinically relevant cut-points and did not explore possible non-linear associations with outcomes. Our study cohort includes a referred group of patients from a distinct geographic region that may limit generalizability. Blood pressure was measured once per visit which is reflective of real world practice but may not be as accurate as the average of multiple readings. Lastly, our findings require validation in other study cohorts.

Perspectives:

Different methods of quantitating longitudinal BP yields different information regarding late-stage CKD patients risk of ESKD or all-cause mortality. Elevations of SBP >160 mm Hg and DBP > 85 mmHg were associated with a higher risk of ESKD and SBP <120 mmHg with all-cause mortality. An elevation of SBP or DBP from baseline is associated with a higher ESKD risk, a novel finding that may be represent potential therapeutic targets of intervention. These findings demonstrate the importance of considering the longitudinal course of blood pressure for determining the risk of adverse events in patients with late stage kidney disease.

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Disclosures: none

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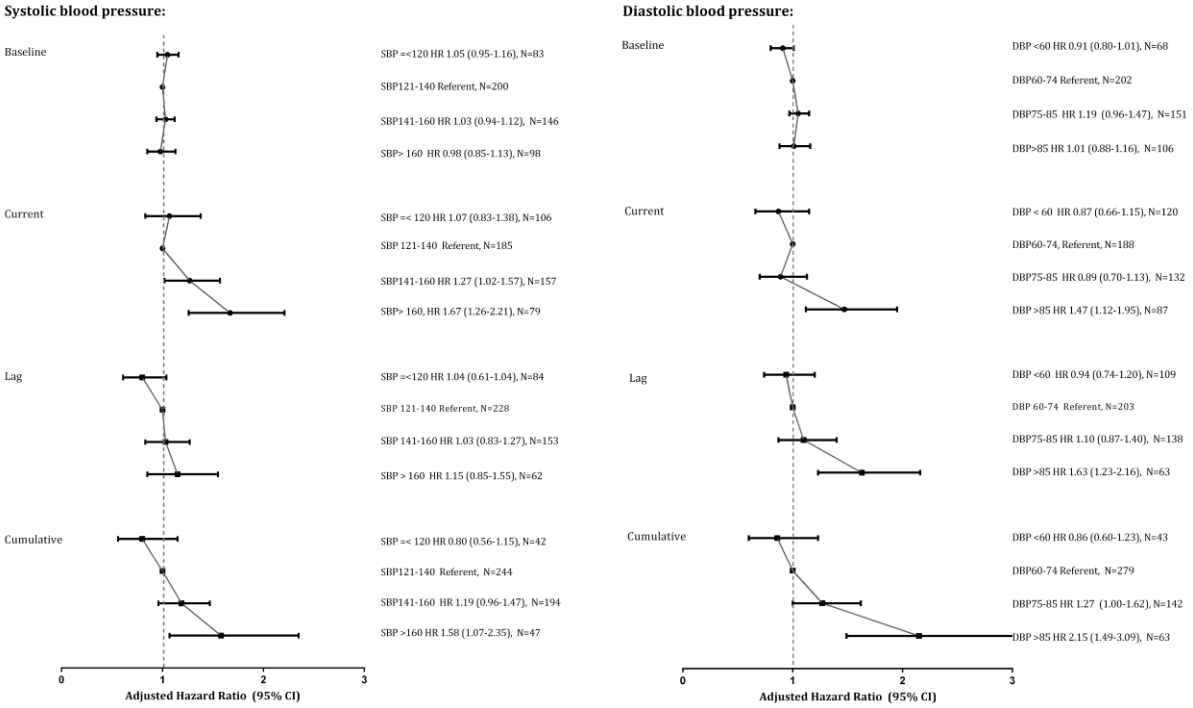
Table 1: Baseline characteristics of the late stage chronic kidney disease study cohort.

Characteristic	N=1203
Demographics:	
Sex (female)	40.2%
Age (years)	65.6±14.5
Body mass index	30.06±7.96
Race:	
Caucasian	75.6%
Cause of CKD:	
Diabetes	33.9%
Ischemic nephropathy	18.6%
Glomerulonephritis	14.0%
Other	34.0%
Comorbidities:	
Coronary artery disease	33.4%
Congestive heart failure	27.7%
Hypertension	92.8%
Peripheral vascular disease	19.1%
Diabetes mellitus	59.0%
Cigarette smoker	15.0%
Malignancy	14.4%
ACE/ARB	48.4%
Laboratory:	
eGFR (ml/min/1.73m^2)	17.77±6.15
Bicarbonate (mmol/L)	24.02±3.46
Albumin (g/L)	35.69±5.53
Hemoglobin (g/L)	110.51±15.90
Potassium (mmol/L)	4.47±0.60
Phosphate (mmol/L)	1.34±0.30
Proteinuria categories	
Minimal	22.5%
Mild	22.6%
Moderate	25.0%
Severe	30.0%
Kidney risk failure equation:	
<5%	25.4%
5-10%	26.5%
10-15%	16.2%
>15%	32.8%

[a] Values presented as mean ± standard deviation or percentage. [b] Missing data imputed for 10 iterations by a Markov Chain Monte Carlo algorithm (eGFR 1.1%, SBP 3.3%, DBP 3.6%, hemoglobin 2.1%, potassium 0.8%, bicarbonate 4.9%, albumin 6.0%, phosphate 4.6%, proteinuria 19.7%) [c] The KRFE was used to calculate the 2-year risk of kidney failure (model 3: age, sex, eGFR and UCR) based on baseline variables. [d] Abbreviations: N number % percentage CKD chronic kidney disease ACE/ARB angiotensin converting enzyme inhibitor/angiotensin II receptor blocker eGFR estimated glomerular filtration rate ml millilitre min minute m metre mmol millimole L litre g grams

Figure 1: Adjusted association of end stage kidney disease with a) systolic blood pressure and b) diastolic blood pressure at baseline, current, lag and cumulative measures.



All ESKD models were adjusted for age, sex, cause of CKD, comorbidities (coronary artery disease, congestive heart failure, peripheral vascular disease, diabetes, malignancy), repeat measures of laboratory values (proteinuria, hemoglobin, albumin, potassium, phosphate, bicarbonate), baseline eGFR, baseline BP and the number of anti-hypertensive medications. Abbreviations: SBP systolic blood pressure, DBP diastolic blood pressure, HR hazard ratio.

Table 2: Adjusted association of change from baseline systolic blood pressure (SBP) and diastolic blood pressure with end-stage kidney disease.

Exposure	BP categories (mmHg)	Number of events (% total)	HR (95% CI)	P value
Systolic Blood Pressure change from baseline:				
Baseline <120	Repeat measure < 120	26 (4.9)	**0.55 (0.35-0.87)**	**0.0389**
	Repeat measure 120-160	55 (10.4)	0.95 (0.70-1.29)	0.5764
	Repeat measure > 160	5 (1.0)	0.81 (0.33-2.00)	0.6123
Baseline 120-160	Repeat measure < 120	74 (14.0)	1.11 (0.84-1.46)	0.5211
	Repeat measure 120-160	227 (43.1)	Referent	
	Repeat measure > 160	44 (8.4)	**1.60 (1.15-2.23)**	**0.0062**
Baseline > 160	Repeat measure < 120	6 (1.1)	1.31 (0.61-2.80)	0.7060
	Repeat measure 120-160	60 (11.4)	0.94 (0.71-1.25)	0.5228
	Repeat measure > 160	30 (5.7)	1.37 (0.91-2.06)	0.1238
Diastolic Blood Pressure change from baseline:				
Baseline <60	Repeat measure < 60	30 (5.7)	0.80 (0.54-1.18)	0.1178
	Repeat measure 60-85	28 (5.3)	1.08 (0.72-1.61)	0.6006
	Repeat measure > 85	4 (0.8)	1.49 (0.54-4.12)	0.6386
Baseline 60-85	Repeat measure < 60	84 (15.9)	1.00 (0.76-1.30)	0.9043
	Repeat measure 60-85	235 (44.6)	Referent	
	Repeat measure > 85	**41 (7.8)**	**1.62 (1.15-2.29)**	**0.0302**
Baseline > 85	Repeat measure < 60	6 (1.1)	1.03 (0.45-2.32)	0.9752
	Repeat measure 60-85	57 (10.8)	1.03 (0.75-1.39)	0.7879
	Repeat measure > 85	**42 (8.0)**	**1.54 (1.09-2.18)**	**0.0071**

Models adjusted for age, sex, cause of CKD, comorbidities (coronary artery disease, congestive heart failure, peripheral vascular disease, diabetes, malignancy), laboratory values (proteinuria, albumin, hemoglobin, potassium, phosphate, and bicarbonate), baseline eGFR, baseline BP and the number of anti-hypertensive medications. Abbreviations: mmHg millimetre of mercury, HR hazard ratio, CI confidence intervals.

Table 3: Adjusted association of systolic blood pressure (SBP) modelled at baseline, current, lag, cumulative and change from baseline with all-cause mortality.

Exposure	SBP categories	Number of events (%)	HR (95%CI)
Baseline:			
	≤120	42 (30.7)	0.84 (0.47-1.53)
	121-140	52 (38.0)	Referent
	141-160	28 (20.4)	1.40 (0.78-2.52)
	>160	15 (11.0)	1.78 (0.62-5.10)
Time-dependent:			
Current:			
	≤120	52 (37.7)	**1.59 (1.04-2.44)**
	121-140	43 (31.2)	Referent
	141-160	33 (23.9)	1.52 (0.95-2.41)
	>160	10 (7.3)	1.27 (0.63-2.56)
Lag:			
	≤120	47 (34.1)	**1.37 (0.91-2.09)**
	121-140	49 (35.5)	Referent
	141-160	29 (21.0)	1.18 (0.73-1.89)
	>160	13 (9.4)	1.42 (0.74-2.70)
Cumulative:			
	≤120	36 (26.1)	**1.76 (1.10-2.82)**
	121-140	55 (39.9)	Referent
	141-160	38 (27.5)	1.63 (1.02-2.62)
	>160	9 (6.5)	3.03 (1.34-6.87)
Change from baseline:*			
Baseline ≤ 120	Repeat measure <120	27 (19.6)	**2.28 (1.38-3.77)**
	Repeat measure 120-140	8 (5.8)	0.80 (0.35-1.80)
	Repeat measure > 140	7 (5.1)	1.38 (0.61-3.12)
Baseline > 120	Repeat measure <120	25 (18.1)	1.40 (0.81-2.41)
	Repeat measure 120-140	35 (25.4)	Referent
	Repeat measure > 140	36 (26.1)	1.17 (0.73-0.88)

All models adjusted for age, sex, comorbidities (congestive heart failure, diabetes, malignancy), laboratory values (albumin, phosphate), baseline BP except * that was adjusted for age, congestive heart failure, albumin, phosphate, baseline BP only. Abbreviations: SBP systolic blood pressure, mmHg millimetre of mercury, HR hazard ratio, CI confidence intervals.

Table 4: Adjusted association of diastolic blood pressure (DBP) modelled at baseline, current, lag, cumulative and change from baseline with all-cause mortality.

Exposure	DBP categories	Number of events (%)	HR (95%CI)
Baseline:			
	<60	40 (29.2)	1.11 (0.62-1.97)
	60-75	59 (43.1)	Referent
	75-85	30 (21.9)	1.10 (0.60-2.01)
	>85	8(5.8)	0.99 (0.34-2.84)
Time-dependent:			
Current:			
	<60	55 (39.9)	0.99 (0.67-1.46)
	60-75	59 (42.8)	Referent
	75-85	15 (10.9)	0.78 (0.44-1.36)
	>85	9 (6.5)	1.25 (0.60-2.60)
Lag:			
	<60	54 (39.1)	1.15 (0.78-1.71)
	60-75	53 (38.4)	Referent
	75-85	21 (15.2)	0.98 (0.59-1.64)
	>85	10 (7.3)	1.19 (0.60-2.37)
Cumulative:			
	<60	37 (26.8)	0.94 (0.58-1.52)
	60-75	79 (57.3)	Referent
	75-85	16 (11.6)	1.07 (0.59-1.94)
	>85	6 (4.4)	**2.75 (1.05-7.20)**
Change from baseline*:			
Baseline ≤ 75	Repeat measure < 60	47 (34.1)	1.15 (0.77-1.73)
	Repeat measure 60-85	50 (36.2)	Referent
	Repeat measure > 85	3 (2.2)	1.00 (0.31-3.24)
Baseline > 75	Repeat measure < 60	8 (5.8)	1.28 (0.58-2.83)
	Repeat measure 60-85	24 (17.4)	1.21 (0.72-2.05)
	Repeat measure > 85	6 (4.4)	2.04 (0.85-4.91)

All models adjusted for age, sex, comorbidities (congestive heart failure, diabetes, malignancy), laboratory values (albumin, phosphate), baseline BP except * that was adjusted for age, congestive heart failure, albumin, phosphate, baseline BP only. Abbreviations: DBP diastolic blood pressure, mmHg millimetre of mercury, HR hazard ratio, CI confidence intervals.

Chapter 5: Discussion

Summary

In this thesis, we examined various methods of modelling longitudinal blood pressure and its association with adverse clinical outcomes in a unique clinical cohort of patients with late-stage CKD managed in a multidisciplinary clinic. Building on a literature review highlighting the relevant knowledge gaps (Chapter 2), we first examined the association of individual blood pressure components with progression of CKD (Chapter 3, manuscript 1) followed by different methods of quantifying longitudinal blood pressure and its association with ESKD or all-cause mortality (Chapter 4, manuscript 2). In this chapter, we will discuss the relevant findings, limitations and future research considerations for this work.

Novel Findings

The first objective of this thesis was to examine the time-varying associations of blood pressure components with CKD progression as defined by continuous eGFR decline or eGFR decline ≥ 30%. Our first study identified the following novel results: i) repeat, longitudinal BP measures were significantly associated with eGFR decline whereas baseline BP was not, ii) SBP and DBP were significantly associated with eGFR decline whereas PP was not, iii) SBP and DBP changed over time, and iv) only extremes of SBP (<105 or >150 mmHg) and elevated DBP (>90 mmHg) were significantly associated with eGFR declines ≥ 30%. The second objective of this thesis was to examine differing methods of longitudinally modelling BP and their association with ESKD or all-cause mortality. Our second study identified the following novel results: i) repeat, longitudinal BP measures were significantly

associated with ESKD whereas baseline measures were not, ii) elevated SBP (>160 mmHg) and DBP (>85 mmHg) were significantly associated with ESKD, iii) low SBP (<120 mmHG) was significantly associated with all-cause mortality, and iv) a subsequent rise from a more moderate SBP or DBP at baseline was significantly associated with ESKD.

Limitations

Our thesis did have some noteworthy limitations. As our study was observational in nature, we were unable to determine causality and were limited to associations. Our study cohort, although unique, was limited to a given demographic of patients from our clinics catchment area and may not be generalizable to all populations. Referral bias may be present as we were unable to determine if all patients with eGFR <30 were referred or attended a clinic visit. As there are no accepted high level evidence standards for the composition and care delivery of multidisciplinary CKD care clinics, our practice patterns may differ from other care models of CKD. Our primary exposure, BP was measured in a standardized, appropriate manner yet different personal were involved in the measurement and variation in techniques may have occurred. Further, the impractical but optimal method of measure, ambulatory BP measures was not used. There was a significant amount of missing data for proteinuria (19.2%) but this may reflect clinical relevance as the majority were in patients with low levels of proteinuria that tend to remain stable over time. We lacked relevant information on i) patient choices regarding conservative care, ii) cause of ESKD, iii) functional status, iv) hospitalization, or v) BP-related adverse effects.

Despite the large study cohort there were relatively few deaths that limited the ability to adjust for all relevant covariates.

Future Research

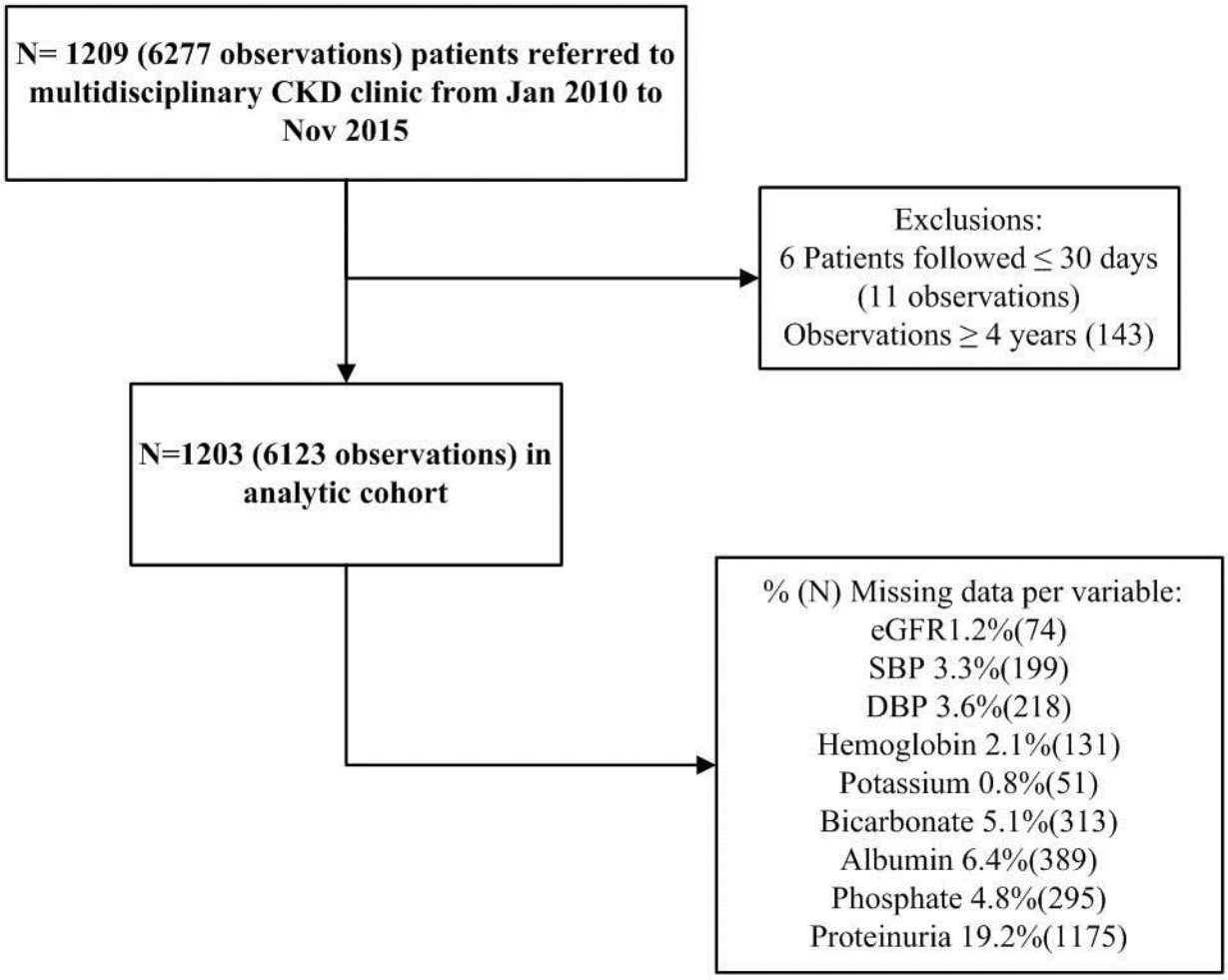
Our findings require confirmation in other cohorts. Other areas of investigation include examination of BP targets in patients managed strictly with conservative care, longitudinal modelling of BP in dialysis and kidney transplantation populations, and the role of BP in other clinical outcomes such as cardiac disease.

Conclusion

Our findings highlight the complexity both analytically and pathophysiological that BP conveys in CKD. We demonstrated that longitudinal BP is associated with adverse clinical outcomes consistent with previous literature. However, a higher risk of outcomes was only evident at extremes of BP allowing for a potential broader target for blood pressure in late-stage CKD. We demonstrated a rise from more moderate ranges of BP incurs a higher risk of ESKD. Overall in this thesis, we present the most comprehensive evaluation of longitudinal blood pressure and its association with clinical outcomes in late stage CKD to date.

Appendices:

Supplemental Figure 1: Study cohort.



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

Variable	Estimate	P
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.

Variable	Estimate	P
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.

Variable	Estimate	P
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.

	Non-linearity		Change over time	
Model	Difference in -2 log likelihood between models *	P value	Difference in -2 log likelihood between models #	P value
SBP:				
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
DBP:				
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
PP:				
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

Additional statistical methods for Manuscript 1:

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)(55). 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^{th}, 25^{th}, 50^{th}, 75^{th} and 95^{th} 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(55). 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% (59). 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) (56). Ten multiple 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 (60).

To illustrate the associations of individual BP components and eGFR over time, modelled eGFR trajectories were plotted with blood pressure variables set at the 5th, 50th and 95th percentiles (SBP:105, 140, 170, DBP:50, 70, 90, PP: 35, 60, 100)(55). 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 ≥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.

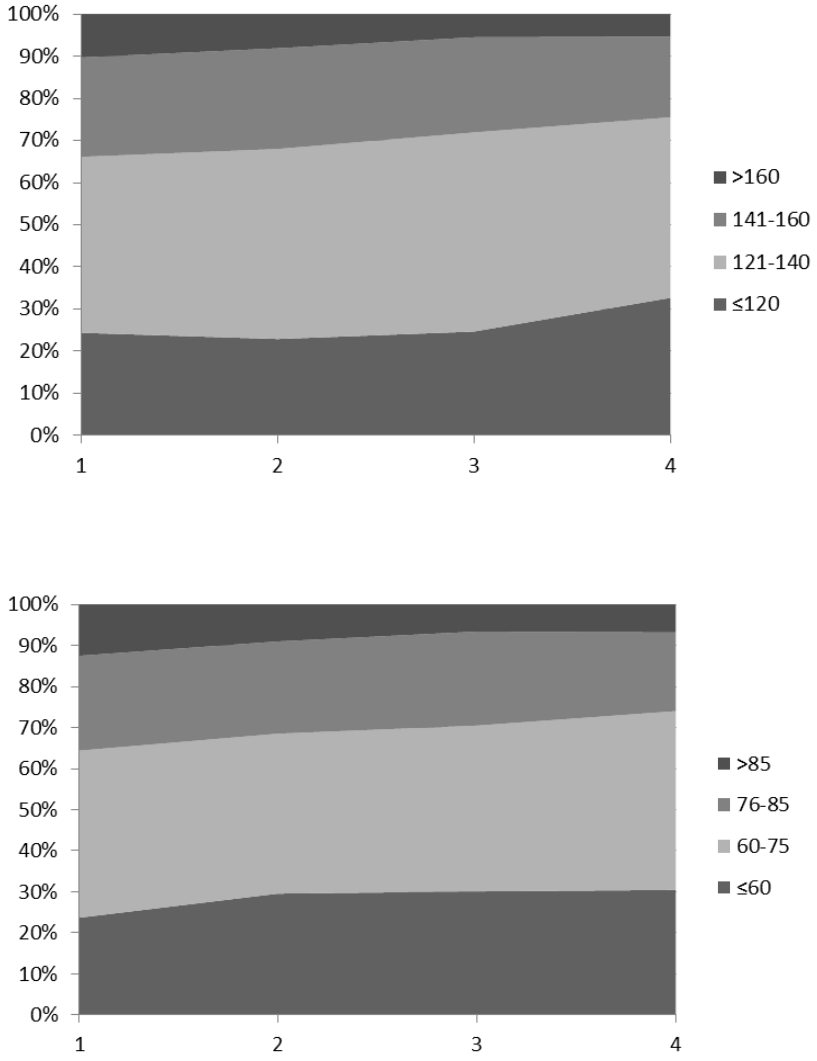
Blood pressure indices and the risk of a GFR decline > 30%

The association of SBP, DBP and PP with time to eGFR decline ≥ 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 5th, 25th, 50th, 75th and 95th 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

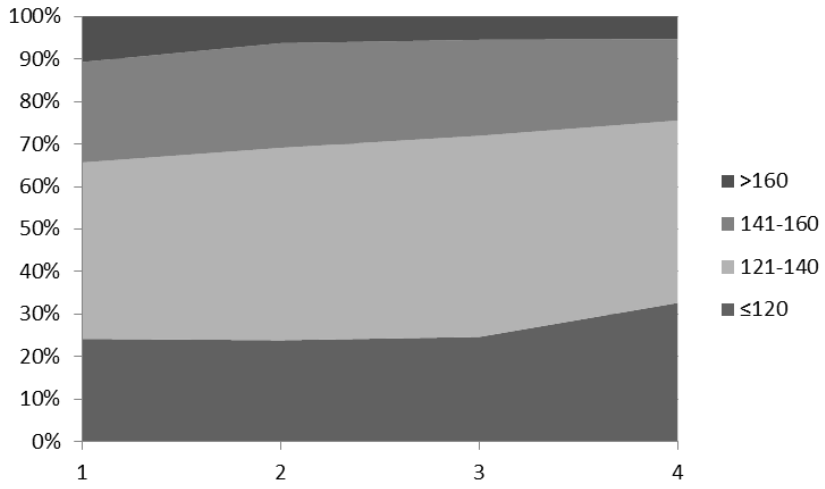
checked by examining Schoenfeld residuals(61). Patients were censored at study end (n=287), at ESKD (n=540), at death (n=141), at loss to follow-up (n=20), if they moved out of province (n=33) or received a pre-emptive transplant (n=8). To assess the potential influence of informative censoring, we employed 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≥30%) or ii.) the longest event time (4 years) and comparing the two(61).

Supplementary Figure 2: Distribution of systolic (SBP) and diastolic blood pressure (DBP) readings during follow up period in years for a) time-dependent measures b) lag measures, c) cumulative measures d) changes from baseline measures.

a)



b)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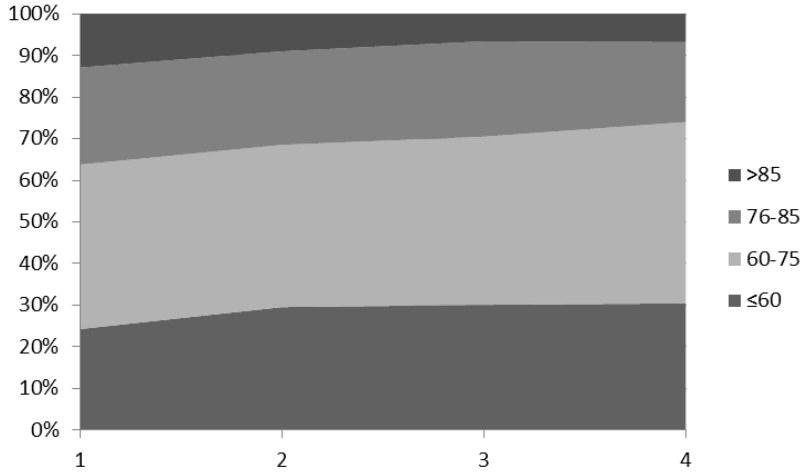
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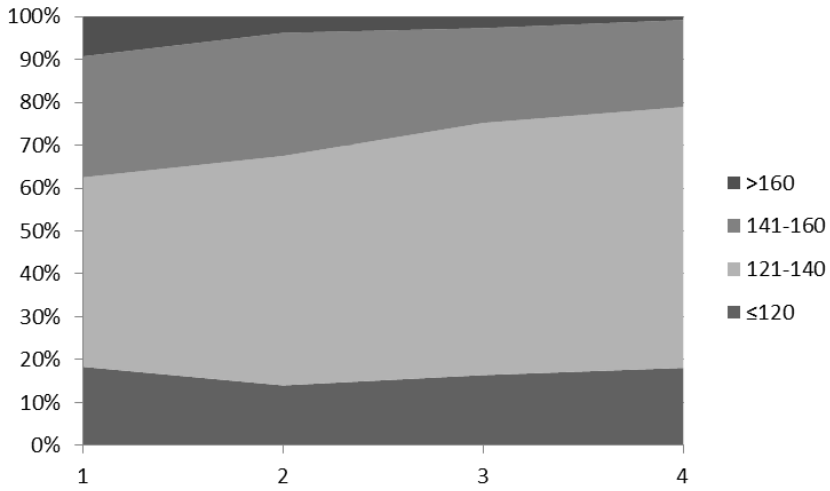
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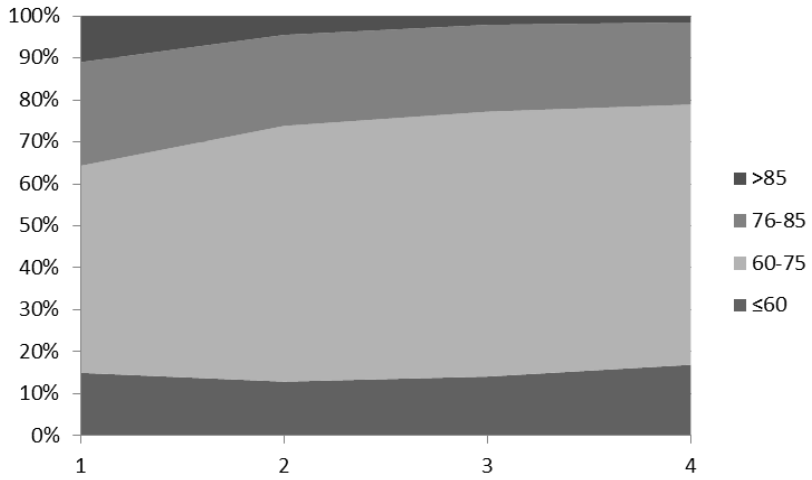
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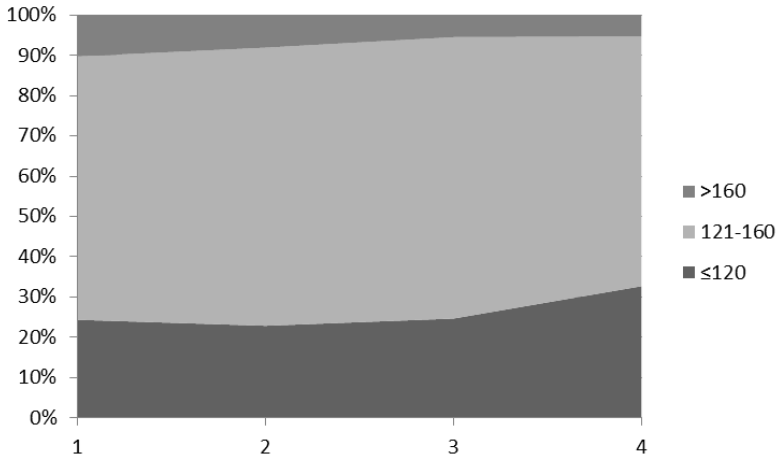
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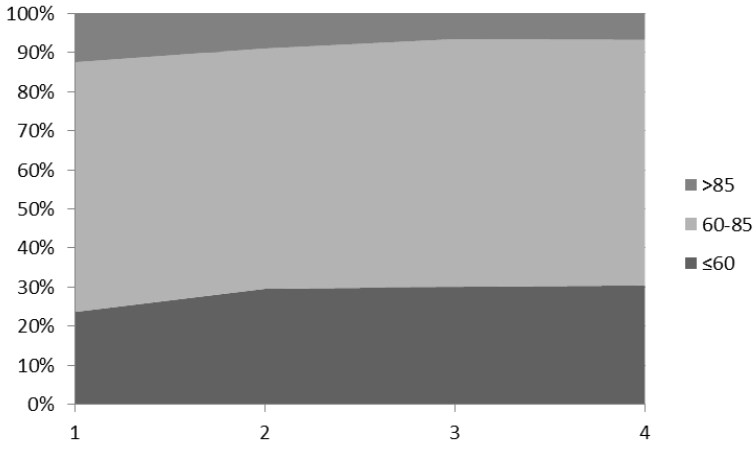
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Supplemental Table 5: The results of a sensitivity analysis to examine for informative censoring of the association of systolic and diastolic blood pressure with ESKD and death. In the ESKD models all patients who died were excluded and in all-cause mortality models all patients with ESKD were excluded.

SBP ESKD*	**Current (HR 95%CI)**	**Lag (HR 95%CI)**	**Cumulative (HR 95%CI)**
<120	1.09 (0.85-1.41)	0.81 (0.62-1.05)	0.81 (0.56-1.16)
120-140	Referent	Referent	Referent
141-160	1.30 (1.04-1.61)	1.07 (0.86-1.32)	1.19 (0.96-1.48)
>160	1.69 (1.28-2.24)	1.17 (0.87-1.58)	1.61 (1.09-2.38)
DBP ESKD*	**Current (HR 95%CI)**	**Lag (HR 95%CI)**	**Cumulative (HR 95%CI)**
<60	0.88 (0.66-1.16)	0.86 (0.68-1.09)	0.83 (0.58-1.19)
60-74	Referent	Referent	Referent
75-84	0.91 (0.72-1.15)	1.28 (1.02-1.61)	1.29 (1.01-1.64)
>85	1.50 (1.14-1.98)	1.58 (1.19-2.09)	2.24 (1.56-3.23)
SBP Death**	**Current (HR 95%CI)**	**Lag (HR 95%CI)**	**Cumulative (HR 95%CI)**
<120	1.44 (0.94-2.22)	1.28 (0.84-1.94)	1.50 (0.94-2.39)
120-140	Referent	Referent	Referent
141-160	1.51 (0.95-2.41)	1.04 (0.64-1.67)	1.61 (0.99-2.60)
>160	1.59 (0.79-3.20)	1.50 (0.79-2.86)	3.50 (1.55-7.92)
DBP Death**	**Current (HR 95%CI)**	**Lag (HR 95%CI)**	**Cumulative (HR 95%CI)**
<60	0.91 (0.83-1.19)	1.07 (0.72-1.58)	0.89 (0.55-1.43)
60-74	Referent	Referent	Referent
75-84	0.84 (0.65-1.07)	0.94 (0.56-1.57)	1.05 (0.57-1.94)
>85	1.28 (0.88-1.84)	1.13 (0.56-2.28)	2.93 (1.12-7.68)

* adjusted for age, sex, cause of CKD, comorbidities (coronary artery disease, congestive heart failure, peripheral vascular disease, diabetes, malignancy), laboratory values (proteinuria, albumin, hemoglobin, potassium, phosphate, and bicarbonate), baseline eGFR, baseline BP and the number of anti-hypertensive medications.

** adjusted for age, sex, comorbidities (congestive heart failure, diabetes, malignancy), laboratory values (albumin, phosphate) and baseline BP.

Abbreviations: SBP systolic blood pressure, DBP diastolic blood pressure, ESKD end stage kidney disease, HR hazard ratio, CI confidence intervals.

Supplemental Table 6: Model fit by Akaike Information Criterion (AIC) for the association of systolic and diastolic blood pressure with ESKD and death.

ESKD*			
SBP model	**AIC**	**DBP model**	**AIC**
Current	5765	Current	5765
Lag	5770	Lag	5759
Cumulative	5769	Cumulative	5759
Change from baseline	5758	Change from baseline	5773
All-cause mortality**			
SBP model	**AIC**	**DBP model**	**AIC**
Current	1574	Current	1580
Lag	1581	Lag	1580
Cumulative	1572	Cumulative	1578
Change from baseline***	1584	Change from baseline***	1590

* adjusted for age, sex, cause of CKD, comorbidities (coronary artery disease, congestive heart failure, peripheral vascular disease, diabetes, malignancy), laboratory values (proteinuria, albumin, hemoglobin, potassium, phosphate, and bicarbonate), baseline eGFR, baseline BP and the number of anti-hypertensive medications.

** adjusted for age, sex, comorbidities (congestive heart failure, diabetes, malignancy), laboratory values (albumin, phosphate), baseline BP except *** that was adjusted for age, CHF, albumin, phosphate, baseline BP only.

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