A QUANTITATIVE ANALYSIS OF THE ROLE OF ANTIHYPERTENSIVE DRUG DOSE ON HYPERTENSION IN CHILDREN WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

Hypertension (HTN) is a highly prevalent and major risk factor for poor cardiovascular and kidney outcomes in chronic kidney disease (CKD). Prior research suggests that HTN is underdiagnosed and undertreated in children with CKD. Risk factors associated with HTN in CKD among children include worsening kidney function, African American race, primary glomerular disease, proteinuria, and non-use of renin-angiotensin-aldosterone system inhibitors (RAASi). However, the effect of antihypertensive dose on blood pressure control in this population is unknown. The objective of this study was to determine the effect of antihypertensive dose on blood pressure control in children with CKD. We hypothesize that uncontrolled hypertension (uHTN) is associated with lower antihypertensive dose.

We developed a novel quantitative tool, the relative dose index (RDI), to analyze the effect of dose on blood pressure control, which expresses subject's daily dose as a ratio

between the current daily dose and the maximum potential daily dose, accounting for age, weight and if indicated, renal dose adjustments. Cumulative RDI (cRDI) is the sum RDI for all antihypertensive agents.

This study was performed on data from the Chronic Kidney Disease in Children (CKiD) study, a large North American multicenter longitudinal study on children with CKD. A preliminary univariate analysis was performed on multiple clinical, demographic and pharmacological variables comparing outcomes of controlled vs. uncontrolled hypertension as well as on absence vs. presence left ventricular hypertrophy (LVH), considered a long-term sequela of uHTN.

A multivariate logistic regression model was developed including relevant covariates. cRDI was not found to be significantly associated with uHTN or LVH, and therefore dose expressed as cRDI may be an indicator of disease severity. Similar to previous findings, non-use of RAASi was associated with uHTN. Non-use of diuretics and non-Caucasian, non-African American race were associated with higher odds of uHTN. Female sex, African American race, and use of a calcium channel blocker, diuretic or beta-blocker were associated with LVH.

This study is the first quantitative analysis of the effect of antihypertensive dose on BP control in children with CKD. The cRDI has potential applications in research areas where multiple drugs are used for a single indication and quantitative analysis of the dose-effect relationship is needed.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Medicine have examined a thesis titled “Quantitative Analysis of the Role of Antihypertensive Drug Dose on Hypertension in Children with Chronic Kidney Disease: A Longitudinal Analysis Based on the CKiD Database,” presented by Benjamin A. Matta, candidate for the Master of Science degree, and certify that in their opinion it is worthy of acceptance.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
ABPM	ambulatory blood pressure monitoring study
ACEi	angiotensin converting enzyme inhibitor
AH	ambulatory hypertension
ARB	angiotensin-receptor blocker
BB	beta-blocker (antihypertensive medication class)
BP	blood pressure
CCB	calcium channel blocker
cRDI	cumulative relative dose index
cHTN	controlled HTN
CKD	chronic kidney disease
CKiD	Chronic Kidney Disease in Children study
RDI	relative dose index
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
HTN	hypertension
IRB	institutional review board
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LVH	left ventricular hypertrophy
LVMI	left ventricular mass index
MH	masked hypertension
NAPRTCS	North American Pediatric Renal Transplant Cooperative Study
NHANES	National Health and Nutrition Examination Survey
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NKF	National Kidney Foundation
RAASi	renin-angiotensin aldosterone system inhibitor
uHTN	uncontrolled HTN
WCH	white-coat hypertension

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CHAPTER 1

INTRODUCTION

Hypertension (HTN) is a major risk factor for developing poor cardiovascular and kidney outcomes in patients with chronic kidney disease (CKD)[1–6]. Children and young adults with CKD have age-specific mortality rates which are more than 130-fold higher than the general US population, largely due to underlying cardiovascular disease[7–9]. It is also one of the few modifiable risk factors for CKD progression. The benefit of strict blood pressure (BP) control, which targets lower BPs than in conventional hypertension management, has been shown to reduce mortality and cardiovascular events in the general population in addition to delaying kidney disease progression in adults and children with CKD[10–12].

Risk factors associated with hypertension in children with CKD include increased rate of decline in kidney function, African American race, primary glomerular disease, increased severity of proteinuria and non-use of RAASi[13]. Left ventricular hypertrophy (LVH) is considered a long-term sequela of uncontrolled hypertension (uHTN), and has been shown to be associated with increased risk for cardiovascular events including myocardial infarction and stroke[14–16].

Due to its complex pathophysiology, involving multiple mechanistic pathways, several classes of antihypertensive agents are used to manage HTN[17]. The importance of strict BP control has been established in adults with CKD and specifically the superiority of

ACE-inhibitors and ARBs (combined, these two classes are known as renin-angiotensin aldosterone system inhibitors; RAASi) over other antihypertensive classes[1,7,18].

Prospective studies in children have been lacking, however. Recently, the ESCAPE trial showed that strict BP control in children with CKD reduced rates of CKD progression when compared with conventional blood pressure management[10,19]. Although RAASi are generally considered the first-line agent for treatment of hypertension in children with CKD, approximately 50-60% require more than one antihypertensive agent to achieve the goal of intensified BP control (<50th percentile)[2], and significant variability exists in the choice of agents used in clinical practice to control blood pressure (BP)[20]. Unfortunately, many with CKD struggle with HTN despite efforts including lifestyle modification of diet and exercise as well as intensive pharmacological management.

Casual blood pressure is the sum of stable basal blood pressure and the variable additional pressure resulting from the patient's current physiological, mental, and metabolic stimuli. Unlike in adults where fixed systolic and diastolic BP cutoffs are used to define elevated casual blood pressure and hypertension (stages 1 and 2), in children, HTN is defined based on blood pressure (BP) percentiles which are derived from population-based data (continuous National Health and Nutrition Examination Survey[21]) and adjusted for age, height and gender.

In 2017, the American Academy of Pediatrics updated the hypertension guidelines providing a new definition of hypertension that is based on BP percentiles from a non-obese pediatric population (Figure 1). This updated definition replaces the previous definition based

on the Fourth Report from 2004[22], which included obese children in the determination of BP percentiles. The new definition also provides for a fixed BP cutoff for children greater than 13 years of age.

	2017 AAP CPG		2004 Fourth Report
	< 13 years	≥ 13 years	
Normal BP	< 90th percentile	< 120/< 80	< 90th percentile
Elevated BP*	≥ 90th to < 95th percentile or 120–129/< 80	120–129/< 80	≥ 90th to < 95th percentile or > 120/80
Stage 1 HTN	≥ 95th to < 95th percentile + 12 mmHg or 130/80 to 139/89	130–139/80–89	≥ 95th to < 99th percentile + 5 mmHg
Stage 2 HTN	≥ 95th percentile + 12 mmHg or ≥ 140/90	≥ 140/90	≥ 99th percentile + 5 mmHg

*Referred to as preHTN in the 2004 Fourth Report

Abbreviations: *AAP*, American Academy of Pediatrics; *BP*, blood pressure; *HTN*, hypertension *CPG*, clinical practice guideline;

Figure 1: Current AAP 2017 vs. Fourth Report 2004 blood pressure classification schemes

The impact of the new definition on BP diagnosis and treatment is unclear at this time, however this study will provide insight into how new the HTN classification scheme impacts diagnosis of HTN in the pediatric CKD population of the CKiD study.

The ambulatory blood pressure monitoring study is an additional clinical tool used to more accurately assess a patient's blood pressure over a 24-hour period at their home, providing an overview of diurnal (awake and sleep) cycles of blood pressure variation. Combining casual BP measurements with ABPM results are used to classify a patient as having normal blood pressure, masked hypertension, white-coat hypertension or ambulatory hypertension using the scheme in Table 1, and described in more detail in the next chapter.

Table 1: Ambulatory blood pressure classification scheme

	Casual blood pressure	
	Normal	Increased
Normal ABPM study	Normal blood pressure	White-coat hypertension
Abnormal ABPM study	Masked hypertension	Ambulatory hypertension

A recent study by Barletta et al (2017) on children with CKD demonstrated that the prevalence of HTN increased between the mid-2000s and 2010s, most strikingly apparent with the use of 24h ambulatory blood pressure monitoring (ABPM) studies that showed a remarkably high percentage of masked hypertension in up to 49% of the cohort. Although designed to determine secular trends rather than serving as an epidemiological study, the significant percentage of those with masked hypertension in both periods of the study led the authors to conclude that HTN in this population is underdiagnosed and likely undertreated[13].

Many questions remain regarding the particular choice and dosing strategy of antihypertensive agents within this high-risk cohort. While evidence in favor of RAASi is available, there remains virtually no data in pediatric patients which compares dosage of medication and if one particular medication dosing strategy is more effective. An intriguing recent Cochrane meta-analysis in adults found that lower dose combinations of blood pressure-lowing medications was at least as effective, and in some cases more effective, than typical antihypertensive dosing strategies and in many cases, associated with fewer side effects[23].

To our knowledge, no studies have been published evaluating the effect of dose on blood pressure control in patients with CKD. Therefore, the objective of this study was to determine the effect of antihypertensive drug dose on blood pressure control and LVH in children using data from the Children with Chronic Kidney Disease (CKiD) Study, the largest North American multicenter longitudinal study of children with chronic kidney disease.

CHAPTER 2

REVIEW OF LITERATURE

Hypertension in patients with chronic kidney disease

Adults and children with CKD have higher rates of cardiovascular morbidity and decline in kidney function if they have hypertension (HTN) compared to those with normal blood pressure. A meta-analysis performed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI)™ Clinical Practice Guidelines for CKD found that 27 of 32 studies on adult populations with various forms of CKD identified a significant relationship between HTN and a more rapid rate of decline in kidney function[24]. Similarly, this relationship was also confirmed among children in a 2003 study based on the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) database, a large longitudinal study of children with kidney disease[25]. In their study, Mitsnefes et al, demonstrated that HTN is a highly significant ($p=0.003$) and independent risk factor for CKD progression. Other risk factors identified in the multivariate Cox regression model included African American ethnicity, older age, acquired kidney disease and eGFR $<50 mL/min/1.73m^2$.

The role of HTN in progression of CKD was similarly shown in the CKiD cohort, with more rapid progression to end-stage kidney disease (ESKD) of 38% and 67% in both

the non-glomerular and glomerular kidney disease cohorts of children with CKD and uncontrolled casual blood pressure, respectively.[3]

Hypertension is associated with higher rates of left ventricular hypertrophy in children with CKD, and children with hypertension are at higher risk of having hypertension as adults[14–16]. In adults, left ventricular hypertrophy is associated with higher rates of cardiovascular morbidity including myocardial infarction and stroke, as well as cardiovascular-related death[26]. Therefore, early identification and management of hypertension may not only benefit children by delaying CKD progression, but also may improve their cardiovascular health as adults.

Epidemiology of hypertension in the pediatric chronic kidney disease population: prevalence and risk factors

The prevalence of HTN in the pediatric CKD population has a significant degree of variability depending on the particular definition of HTN used[20]. Reports from the NAPRTCS and CKiD databases defined solely by baseline measurement of age- height and sex-adjusted systolic or dialystolic BP greater than 95th percentile, estimated that 40% and 54% of the pediatric CKD population have HTN, respectively[25,27]. These are likely underestimates as the ABPM data was not available in either study and therefore they did not take into consideration patients with masked or controlled hypertension[27]. Based on a broader definition including use of antihypertensive agents or blood pressures greater than 2 SD above the mean, HTN was found to be the most common complication in children across all stages of CKD with a prevalence of 70% in a single-center study in Canada[5]. This is likely an

overestimate as this would include non-hypertensive children taking RAASi due to proteinuria.

A study by Flynn et al. showed that characteristics associated with uncontrolled HTN included male sex, shorter duration of CKD, and non-use of RAASi[27]. In that study, among subjects receiving antihypertensive medications, male sex, and absence of RAASi use were associated with uncontrolled HTN. In those who were not using RAASi, other agents including calcium channel blockers (CCB), diuretics, beta-blockers (BB) or other classes of antihypertensive medication were presumably being used to manage HTN.

Ambulatory Blood Pressure Monitoring in the diagnosis and monitoring of hypertension

The ambulatory blood pressure monitoring (ABPM) study is an additional clinical tool to assess blood pressure over a 24-hour period. ABPM has the advantage over clinic BP measurements because it can more accurately assess blood pressure status in the subject's home environment while awake and asleep. Using a combination of casual BP measured in the clinic and the ABPM study, the clinician can differentiate between normotension and masked hypertension on one hand, and between white-coat hypertension (WCH) and ambulatory hypertension on the other hand (Figure 2).

	Casual Blood Pressure			
	<95th percentile		>= 95th percentile	
ABPM mean Blood Pressure	ABPM load		ABPM load	
	<25%	≥25%	<25%	≥25%
<95th percentile	NL	MH	WCH	AH
≥95th percentile	MH	MH	AH	AH

Figure 2: 24-hour ambulatory blood pressure classification scheme
Scheme is based on AHA guidelines[37] and adapted from Samuels et al, 2012).Abbreviations: NL Normotension, MH Masked hypertension, WCH White-coat hypertension; AH Ambulatory hypertension

Masked hypertension with an estimated prevalence of 7% in the general pediatric population[28], but 37-49% in children with CKD (CKiD data), is considered a stronger predictor of ESRD and death in adults compared to casual office BP measurements, and is associated with higher rates of left ventricular hypertrophy in children with CKD[15,29]. Although in a more recent longitudinal analysis of children with CKD, both office and ABPM systolic blood pressure measurements performed similarly in their ability to predict the risk for both left ventricular hypertrophy and progression to end stage kidney disease (ESKD)[30]. The long-term implications of white-coat hypertension is less clear with conflicting evidence. In the study by Agarwal and Andersen, WCH was not found to be associated with increased risk of death or ESKD[29]. On the other hand patients with WCH have been found to have higher rates of metabolic risk factors, left ventricular hypertrophy and have higher rates of progression to ambulatory hypertension compared to normotensive patients[31–33]. Increasingly, ambulatory blood pressure monitoring (ABPM) studies are proving to be effective tools for research on HTN and have improved our understanding of its relationship with various risk factors such as obesity, sodium intake, sedentary lifestyle and

psychological stress, as well as in clinical practice for the diagnosis, management and monitoring of blood pressure status[34–37].

Interpretation of pediatric ABPM studies is widely based on pediatric population-derived normative values published by Soergel et al[38]. The primary parameters used in interpretation of the ABPM study include BP load which is the percentage of BP measurements above the 95th percentile, and BP index, which is the ratio of the average of all BP measurements to the 95th percentile. One should note that the normative values for the ABPM study differ from those of the casual BP measurements, and cannot be used interchangeably. The use of ABPM studies has gained increasing acceptance among clinicians and is now considered standard of care in the evaluation of elevated blood pressure in children[39,40]. Unlike NAPRTCS, the CKiD database includes longitudinal data on antihypertensive medications and 24-hour ambulatory blood pressure monitoring (ABPM) studies. A recent longitudinal multivariate analysis of blood pressure control in the CKiD cohort between 2003 and 2013 showed an increase in the prevalence of HTN based on ABPM studies from 51 to 63%, of which a significant proportion was attributed to MH[13].

Left ventricular hypertrophy: a clinical parameter for monitoring and predicting outcomes among patients with hypertension

Uncontrolled HTN leads to target organ damage that can affect the kidneys, brain, eyes, blood vessels and heart[26]. Left ventricular hypertrophy is a pathophysiological response to HTN which can be monitored over time non-invasively using echocardiography. Both detection of LVH and its reversal after treatment of HTN are useful in guiding management

of HTN and in risk reduction strategies for future cardiovascular events and mortality[15,16,26]. The definition of LVH is based on the left ventricular mass index (LVMI) which in turn is derived from an estimated left ventricular mass that is normalized to height$^{2.7}$ and in adults is defined as LVMI >51g/height(m)$^{2.7}$. The prevalence of LVH is more difficult to establish in children than in adults, as echocardiographic evaluation in children is limited to specific disease-related populations such as children with HTN, CKD, heart disease, diabetes and other high-risk populations. In addition, somatic growth in children is a significant confounding variable in the normalization of LVMI, and therefore a consensus definition of LVH is lacking. LVH in children has been variably defined in the literature using normalization based on body surface area, lean body mass and age-, sex- and height-adjusted percentiles of LVMI height$^{2.7}$, making its prevalence and clinical interpretation difficult[41,42]. An additional limitation in the CKD population is the relatively high prevalence of short stature in this population which results in a positive bias in the determination of LVMI[15,43]. A 2014 longitudinal observational study by Kupferman et al showed that LVH, defined based on a 95th percentile cutoff of age-, sex, and height adjusted LVMI, was associated with higher systolic BP, use of non-RAASi antihypertensive medications, female sex and anemia, in children with CKD after adjusting for covariates of glomerular filtration rate, height, age, CKD diagnosis and duration of CKD[14,30].

The pharmacological treatment of hypertension in children with chronic kidney disease

HTN is a condition that has a complex pathophysiology involving multiple mechanisms including fluid overload, activation of RAAS and sympathetic nervous systems and endothelial dysfunction[2,44] (Figure 3).

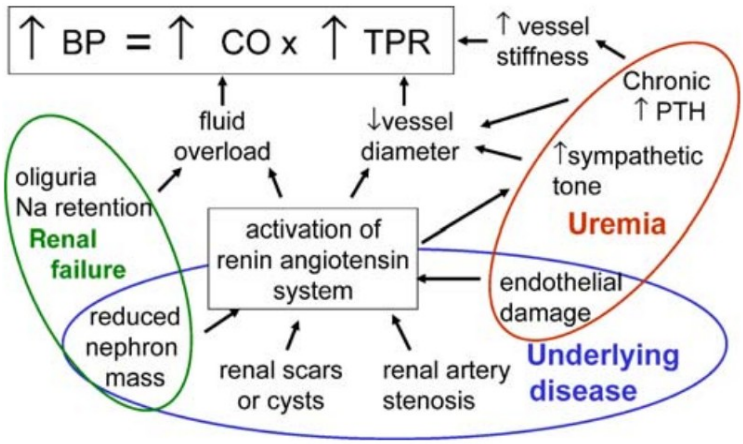


Figure 3: Pathophysiological mechanisms of hypertension in chronic kidney disease
Source: Hadtstein and Schaefer (2008)[2].
Abbreviations: BP blood pressure, CO cardiac output, TPR total peripheral resistance, PTH parathyroid hormone, Na sodium

Currently in the US, pediatric hypertension guidelines published by the American Academy of Pediatrics in 2017 are applicable to the general pediatric population but also address specific high-risk groups within the general population including children with CKD. In the general pediatric population, after a trial of lifestyle modifications including diet and exercise, the choice of a first line pharmacological class or agent among three classes of RAASi, CCB and thiazide diuretics is largely left to the clinician and is based on individual characteristics pertaining to the patient including the etiology of hypertension, cardiovascular

and metabolic risk factors, side effect profile, cost and availability of the agent. Two first-line agents are recommended in patients with stage 2 hypertension.

In the CKD population, the importance of adequate blood pressure control has been established in adults and children. Stricter target BP (ie, <120/80 in adults and <50th percentile in children), have been shown to provide additional benefits in terms of reduced cardiovascular events and delayed CKD progression, however a review of the evidence in the literature is not unanimous regarding the value of lower BP targets. Whereas the benefit of stricter BP control was associated with improved cardiovascular outcomes in the SPRINT[12] trial (adults with high cardiovascular risk) and slower CKD progression in the ESCAPE[10] trial (children with CKD), lower BP targets did not prove beneficial in the ACCORD[45] (adults with type 2 diabetes mellitus) and AASK[1] (African American adults with hypertensive kidney disease) trials. Of note, the AASK trial which also compared efficacy of three antihypertensive drug classes, demonstrated the renoprotective effects in delaying CKD progression with Renin-Angiotensin-Aldosterone System inhibitors (RAASi), compared with either calcium channel blockers (CCB) or beta blocker (BB).

Current guidelines on HTN management in the pediatric CKD popoulation are derived largely from extrapolation from adult RCTs[1,11] and on the ESCAPE trial[10] which showed the benefit of strict blood pressure control. For children with CKD, RAASi are the first line agents recommended in children with CKD stage 3 or higher, or in those with CKD stage 1-2 with proteinuria. This recommendation is consistent with Kidney Disease: Improving Global Outcomes (KDIGO) and Kidney Disease Outcomes Quality Initiative

(KDOQI) guidelines[46,47], two international consortia which have taken a leadership role in setting guidelines in the management of adults and children with chronic kidney disease.

Regarding thresholds for initiation of therapy and target blood pressures, both groups consider BP consistently above the 90th percentile in children with CKD as a critical level of clinical intervention. Whereas KDOQI recommends the 90th percentile as the target of therapy, the KDIGO group considers it the starting point for initiation of therapy, with the target being the 50th percentile or less. This recommendation applies especially in patients with proteinuria where hypertension was associated with an even more rapid decline in kidney function compared to those without proteinuria[13,25,27].

In contrast to the general pediatric population with hypertension, where no clear superiority has been demonstrated among three major classes – RAASi, CCB, and thiazide diuretic – the choice of RAASi as a first-line antihypertensive agent for children with CKD is based on its renoprotective effects resulting in delayed CKD progression as well as reduction of proteinuria which is independently associated with delayed CKD progression[19,48]. Outside of the ESCAPE trial, which was performed on a nearly exclusively European Caucasian pediatric population with CKD, and was designed to compare BP targets and not antihypertensive classes, there are few if any high quality large prospective trials in children with CKD that provide good evidence of the long-term outcome benefits of RAASi over other classes. An Italian study using the largest European database of pediatric CKD (Italkid), found that there was no benefit in taking ACE-inhibitors over other classes of antihypertensive medications in terms of CKD progression among those with hypodysplastic

nephropathy (the most common form of CKD in children. Despite these limitations, in 2012 the KIDGO group suggested (grade 2D: very low quality of evidence) RAASi in hypertensive children with CKD. Aside from the recommendation of RAASi as first line agents in treating HTN in the CKD population, there is no consensus guideline on the use of second-line agents in the management of HTN in CKD, except for the general pediatric (AAP) guidelines which suggest choosing from one of the remaining first line agents (CCB and thiazide diuretic)[39].

HTN can also be caused iatrogenically by several drugs that are used by patients with CKD including steroids[49]. The prevalence of HTN in the CKiD study was relatively high compared to the 2-4% prevalence in the general pediatric population[50], and in a recent publication by Barletta et al, only 37-42% of the cohort were classified as normotensive. In this group, hypertension was classified as masked (37-49%) or confirmed hypertension (13-19%) despite the fact that the majority (65-71%) of children were being managed with antihypertensive agents, including 56-59% with RAASi, 15-17% with calcium channel blockers, and 7-10% with diuretics[13].

Quantitative analysis of antihypertensive dosing and number of agents

While there is strong evidence advocating the benefit of blood pressure control in hypertensive patients overall and in CKD in particular, the question of which dosing strategy should be adopted to achieve both short and long-term therapeutic goals is less clear. Significant variability in response to therapy from different antihypertensive classes has led

to various approaches including combination therapy and monotherapy with systematic rotation of drug class to determine the agent resulting in optimal response[51]. A meta-analysis in 2003 based on adult studies showed that combining antihypertensive agents had an additive effect in terms of the dose-response relationship, with similar efficacy across all major antihypertensive classes with doses as low as 25% of standard dose. At the same time, the adverse effects with combination therapy were less than additive, suggesting a potential benefit of combination therapy starting with lower than standard doses of two or more medications[52]. Combination therapy of two or more antihypertensive agents taken in combination at fixed doses usually lower than standard dose has gained more interest as a means of improving medication adherence, reducing adverse effects and achieving therapeutic goals over monotherapy[53–55].

To our knowledge, however, no study has examined the role of antihypertensive dosing and number of agents in the control of HTN in children with CKD. The wide variability of practices in pharmacological management and dosing of antihypertensive agents, the lack of prospective trials comparing different classes of antihypertensive medications, as well as the methodological challenges in quantitative analysis of dosing in the pediatric population have proven obstacles in further understanding the high prevalence of uHTN in the pediatric CKD population[20].

One measure of standardized medication dose called the Defined Daily Dose (DDD) was developed in the 1980s by the World Health Organization in order to quantify drug utilization across classes for a given condition[56,57]. The DDD is value assigned by the WHO

Collaborating Centre in Oslo, and represents the assumed average maintenance dose per day for a drug used for its main indication in adults. Indicators using the DDD can then be used in quantitative analysis studies to investigate changes in drug utilization in a population over time, compare drug utilization internationally and evaluate the effect of an intervention on drug use. For example one indicator, the DDD per 1000 inhabitants per day is most useful for analysis of utilization of medications used chronically where prescribed doses are similar to the DDD. Importantly, data using DDD give only an estimated consumption rather than an accurate assessment of drug use[56], and are limited by being sensitive to differences between prescribed doses and the corresponding assigned DDD.

CHAPTER 3

METHODOLOGY

Rationale

This study developed from a gap in our current understanding of hypertension in children with CKD. Although hypertension is considered a significant and potent risk factor in the progression of chronic kidney disease and in the development of cardiovascular comorbidities, the high prevalence of HTN in children with CKD, even among those treated with antihypertensive agents has raised the question of underdiagnosis or undertreatment of hypertension in this population[13]. The lack of studies specifically addressing antihypertensive dosing in children provided motivation for this study in furthering development of an integrated strategy for the optimal management of HTN in the setting of CKD.

Antihypertensive dose-response studies using combination therapies have been published for adults[23,52,55,58], showing an additive therapeutic effect with reduced adverse effects. Similar studies are lacking in children and the more importantly in the particularly high-risk pediatric CKD population. To address this gap our group has developed a novel tool for the quantitative analysis of antihypertensive dosing, the relative dose index (RDI), which represents the ratio between the actual daily antihypertensive dose and the maximum daily dose for a given subject, based on age, weight and estimated glomerular filtration rate (eGFR). For details on its definition and rationale refer to RDI section in Study Variables

below. With this new method of standardizing dose in the CKiD cohort, we aim to better understand the factors influencing hypertension among children with CKD.

Our hypothesis was based on the findings from Barletta et al (2017) that hypertension in children with chronic kidney disease is undertreated. As such, we hypothesized that drug dose, as expressed by the cumulative relative dose index for all antihypertensive medications taken by a subject, is lower in children with uHTN (and similarly in MH and AH), and LVH when compared to children with cHTN and without LVH, respectively.

Study design

This cross-sectional observational study was based on data obtained from the CKiD study (Clinicaltrials.gov identifier NCT00327860), which is a multicenter prospective longitudinal observational cohort study of children in North America with mild to moderate chronic kidney disease. Although the parent study remains ongoing with recruitment into a third cohort, a publicly available, fully-de-identified archived dataset is available through the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repository[59]. The NIDDK dataset includes data collected on 586 participants in Cohort 1 and 280 participants in Cohort 2, with comprehensive clinical, demographic, and outcome data through December 31, 2015 archived into the public database. This study was considered exempt from human subjects research due to its de-identified nature, and the study herein was approved by Children's Mercy Kansas City IRB (ID: 18010022).

The CKiD study design and methods have previously been published in detail[40]. Briefly, participants ages 1-16 years with an eGFR between 30 and 90 mL/min per 1.73m^2 were enrolled from 55 pediatric nephrology centers across North America and followed annually. The current manual of procedures, detailed study timeline with covariates of interest, and detailed study protocol can be obtained via the study website[60,61].

A detailed cardiovascular assessment was performed at the third annual study visit (V3) which includes an initial physical exam, echocardiography, and ABPM, and these measures were repeated subsequently at every odd visit (visits 5, 7, 9, etc). Therefore, all measures for this study were taken from the V3 study visit, including socio-demographic, clinical and pharmacological factors of interest.

Study population

CKiD Study Inclusion and Exclusion Criteria[62]:

Inclusion Criteria

- Age between 1 and 16 years (before 17th birthday) for Cohorts 1 and 2; age between 6 months and 16 years (before 17th birthday) for Cohort 3
- Estimated (based on SCr) Schwartz GFR between 30 and 90 ml/min|1.73m^2 for Cohort 1 OR an estimated GFR between 45 and 90 ml/min|1.73m^2 based on the updated Schwartz formula for Cohort 2
- Willingness and ability to provide informed consent and assent

- For Cohort 2, an equal distribution of children with glomerular and non-glomerular causes of disease were enrolled (i.e., 150 within each) and the study placed an upper limit of 60% for the percent of enrolled with non-glomerular disease.

Patients with the non-glomerular diagnoses listed below that meet the initial criteria (i.e., duration of kidney disease less than 5 years, and age between 6 months and 16 years old) are eligible and do not have to meet additional criteria:

- Branchio-oto-Renal Disease/Syndrome
- Cystinosis
- Medullary cystic disease/ juvenile nephronophthisis
- Methylmalonic Acidemia
- Oxalosis
- Polycystic kidney disease (Autosomal recessive)

However, all other patients with non-glomerular diagnoses will require at least two of the following conditions. All conditions except for abnormal imaging/biopsy must have occurred after the initial 6 months of life and must not be secondary to a current or resolving episode of Acute Kidney Injury (AKI):

- significant proteinuria,
    1. Age < 2 years old: urine protein to creatinine ratio > 0.5
    2. Age ≥ 2 years old: urine protein to creatinine ratio > 0.2
- hematuria (for at least 3 months),

- evidence of renal tubular disorders,
- abnormalities detected by kidney biopsy or imaging
- abnormal kidney function
    1. Age < 2 years old: serum creatinine > 0.4 mg/dL
    2. Age ≥ 2 years old: eGFR < 90 ml/min|1.73m^2 (eGFR=41.3 x height[meter]/creatinine[mg/dL])
- Hypertension defined by one of the following:
    1. Documented hypertension noted in the medical record by the physician
    2. Current treatment of hypertension
    3. Blood pressure > 95th percentile for age and gender on at least two occasions

Exclusion Criteria

- Renal, other solid organ, bone marrow or stem cell transplantation
- Dialysis treatment within the past three months
- Cancer diagnosis or HIV diagnosis/treatment within last twelve months
- Current pregnancy or pregnancy within past twelve months
- Inability to complete major data collection procedures
- Current enrollment in a randomized clinical trial in which the specific treatment is unknown
- Not fluent in English or Spanish

- Plans to move out of area of any participating CKiD site (Families can be transferred to another CKiD site if they move)
- History of structural heart disease
- Genetic syndromes involving the central nervous system (e.g., Downs syndrome)
- History of severe to profound mental retardation (i.e., IQ less than 40, significant impairment in adaptive function and/or inability to independently execute self-care skills)

Additional inclusion and exclusion criteria for this study:

- Participants were taking at least one antihypertensive medication at their third visit, and doses for all antihypertensive agents were available
- Measured height, weight and blood pressure
- Required laboratory data: Serum creatinine, serum cystatin-C and serum urea nitrogen levels for calculation of blood pressure percentiles and eGFR (see Table 1)
- Successful 24h ambulatory blood pressure monitoring study
- Left ventricular mass index (LVMI, g/m^2) based on echocardiogram

Specific exclusion criteria for this study:

- Maximum time difference between any two of the physical exam, medication history, echocardiogram and ABPM study exceeding 3 months

Materials

No special materials were used for this study. Data from the CKiD database was imported from relevant files and all analysis was performed using R and RStudio (Versions 3.5.3 and 1.1.463, respectively). Required R libraries were obtained from CRAN Repository[63].

Outcome measures

Blood pressure control was the major outcome of interest and as such was evaluated on three levels:

1) The primary outcome was whether subjects had controlled hypertension (cHTN) or uncontrolled hypertension (uHTN), with the assumption that all patients taking antihypertensive agents had a diagnosis of hypertension. Casual blood pressures which were obtained in the office were assigned percentiles based on the updated 2017 AAP blood pressure guidelines, using the quantile regression algorithm published by Rosner[64,65] and classified as normotensive, masked hypertension (MH), white-coat hypertension (WCH) or ambulatory hypertension (AH) based on the scheme published by Samuels, et al (2012), adapted from AHA guidelines[37] as shown in Figure 2. The rationale for using Samuels' classification is that their classification scheme classifies those who were previously unclassified (normal casual BP, mean ambulatory BP and abnormal BP load) as abnormal, as well as those classified as pre-hypertension based on AHA guidelines, due to the increased

risk of cardiovascular disease in patients with CKD. uHTN was defined as having either masked or ambulatory hypertension.

2) As a secondary outcome, the subclassifications of uHTN were used and BP status was defined as a trichotomous variable with values of controlled hypertension, masked hypertension and ambulatory hypertension.

In contrast to the Fourth Report hypertension guidelines, the updated BP percentiles are based on a pediatric population where obese children (BMI > 95th percentile) were excluded. In addition, fixed adult BP cutoffs are used from a lower age of 13 years (refer to Figure 1). To determine the impact of the new guidelines, cross-tabulations of the study population's BP classification using old and new guidelines was performed for both casual BP classifications (normotensive, elevated BP/pre-hypertension, stage 1 and stage 2 hypertension), as well as ABPM classification (NL Normotensive, WCH white-coat hypertension, MH masked hypertension, and AH ambulatory hypertension). The proportions of subjects reclassified was summarized for each table.

3) As a measure of target organ damage with clinical relevance with respect to hypertension, left ventricular hypertrophy absence vs presence was defined based on LVMI according to the cutoff used by the CKiD study protocol (ie, LVMI > 95th percentile using age-, sex- and height-adjusted normative tables from Khoury et al[41]).

Study variables

Cumulative relative dose index (cRDI)

We developed a new quantitative tool, relative dose index (RDI, Figure 4) which expresses dose as a ratio between the current dose and the maximum potential dose, accounting for age, weight, and if indicated, renal dose adjustments.

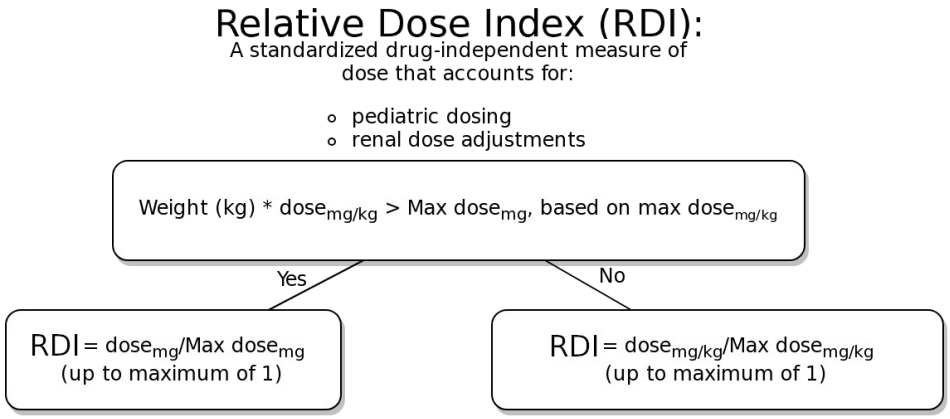


Figure 4: Relative dose index algorithm
A ratio of a subject's current daily dose relative to the maximum potential daily dose is calculated based on standard dosing reference (see Appendix A) and patient age, weight and estimated glomerular filtration rate.

By normalizing dose based on the maximum dose given the individual patient's age, weight and kidney function, the RDI enables a quantitative dose comparison between different antihypertensive medications. Theoretically, based on the study by Law et al (2003) showing the additive BP-lowering effect of antihypertensive doses from different classes of medication, the cumulative effect of multiple antihypertensive agents should be similar to that of the the sum of each individual antihypertensive medication. This cumulative dose is

expressed by adding the RDIs from all antihypertensive medications, and is defined in this study as the cumulative RDI (cRDI).

The maximum RDI for each individual medication was limited to 1, in cases where subjects were taking greater than maximum dose with the assumption that the dose-response curve becomes flattens with increasing supra-maximum doses. The maximum potential dose for each antihypertensive medication was based on pediatric hypertension dose references published in peer-reviewed journals[17,66] when possible, and from Lexicomp Lexi-Drugs[67] for the remaining medications (see Appendix A). Renal dosing adjustments were based on Lexicomp Lexi-Drugs[67].

Socio-demographic, clinical and pharmacological factors

A summary of the variables which were included as potential confounding factors in the analysis of the effect of drug dose (expressed as cRDI) on BP control in the study population is found in Table 2.

Table 2: Covariates included in analysis

Domain	Variable	Type	Value	Notes
Sociodemographic	Age at visit 3	Continuous	Years	Estimated based on year of birth and time at visit 3 (due to de-identified nature of data, precision of age is limited to ±1 year)
	Sex	Binary	Male or female	
	Race	Categorical	Caucasian, African American or other	Self-identified race. Other includes American Indian, native Hawaiian, Asian or multiracial
	Maternal education	Categorical	High school or less, some college or college graduate	
Clinical	Time of CKD onset	Continuous	Years prior to study entry	
	CKD diagnosis	Binary	Glomerular or non-glomerular	
	Proteinuria	Continuous	Urine protein:creatinine ratio (Upc, mg/mg creatinine)	
		1) Ordinal	Normal (Upc<0.5), mild (Upc 0.5-1), moderate (Upc 1-2), severe (Upc > 2)	
		2) Binary	Normal-mild (Upc<1), moderate-severe (Upc>1)	
	Obesity	Continuous	BMI z-score	
		Binary	Obese (BMI ≥ 95th percentile), non-obese (BMI < 95th percentile)	
	Estimated GFR*	Continuous	Based on CKiD formula*	
	CKD stage	Ordinal	1 to 5	Cutoffs for each stage are based on GFR (ml/min/1.73m2): >90, 60-89, 30-59, 15-29, <15
	Hyperkalemia	Binary	Serum potassium level ≤ or > 5mmol/L	
	Family history of hypertension	Binary	Yes or no	
Pharmacological	Current steroid use	Binary	Yes or no	
	Number of antihypertensive agents	Ordinal	1 to 4	
	Cumulative relative dose index	Continuous	Log-transformed for quantitative analysis due to right-skewed distribution	
		Ordinal	Tertiles	
	Mean relative dose index	Continuous	Average RDI for all agents taken per patient	
	Antihypertensive class	Binary	RAASi (includes ACEi and ARB), BB, CCB, diuretic, other	Use or non-use

*Estimated glomarular filtration rate calculated using CKiD formula[70]:

$$eGFR = 39.8 \times \frac{height\,(m)}{Scr\,(mg/dL)}^{0.456} \times \frac{1.8}{cysC\,(mg/L)}^{0.418} \times \frac{30}{BUN\,(mg/dL)}^{0.079} \times 1.076^{male} \times \frac{height\,(m)}{1.4}^{0.179}$$

Statistical Approach

Statistical analysis of relative dose index

Table 2 (see next page) provides an overview of the overall study design and analysis. For each outcome group (cHTN/uHTN, cHTN/MH/AH, and LVH present/absent), the overall study population and each outcome was described based on all the covariates listed in Table 1. Comparisons between outcomes were performed using the appropriate statistical tests based on the type of covariate and outcome and are summarized in Table 3.

Table 3: Statistical tests used in comparing outcome groups

*Outcome type	Covariate type	Statistical test (two-sided)
Dichotomous	Continuous or ordinal	Mann-Whitney U
	Binary or categorical	$\chi 2$ goodness-of-fit
Trichotomous	Continuous or ordinal	Kruskal-Wallis
	Binary or categorical	$\chi 2$ goodness-of-fit

* Outcome types correspond to the number of possible outcomes within each group (ie, Dichotomous – controlled hypertension vs. uncontrolled hypertension, Left ventricular hypertrophy absent vs. present; Trichotomous – controlled hypertension vs. masked hypertension vs. ambulatory hypertension)

Due to its right-skewed distribution in the study population, cRDI was transformed using natural log in subsequent univariate comparisons of outcome groups using t-test and ANOVA, depending on whether the outcome was dichotomous or trichotomous, respectively.

Table 4: Overview of data analysis

Type	Overview	Description
Methodology	1) Blood pressure and hypertension classification a) Comparison old vs new BP percentiles i) Classification of clinic blood pressure ii) Classification of ambulatory blood pressure b) Impact of new BP percentiles and classification criteria on hypertension status c) Secondary outcome of interest: Left ventricular hypertrophy 2) Relative Dose Index (RDI) a) Definition and exploratory survey b) Cumulative and average RDI as new quantitative measures of relative dose 3) Study population selection criteria a) Chronic Kidney Disease in Children (CKiD) Study eligibility criteria b) Inclusion and exclusion criteria for this study	1) a) Definition of hypertension in pediatrics (Fourth Report of 2004 vs American American Academy of Pediatrics 2017) b) Impact of new percentiles and classification scheme on diagnosis of hypertension - Two-way contingency tables for study population of casual blood pressure and ambulatory blood pressure based on Fourth Report vs 2017 AAP c) Left ventricular hypertrophy - Definition based on left ventricular mass index (LVMI) percentile using age, gender and height-adjusted tables from Khoury et al (2009) 2) a) Definition of Relative Dose Index (RDI) i) Algorithm to determine RDI based on subjects age, weight, kidney function and medication ii) Dose reference tables used in calculation of RDI b) Distribution of cumulative RDI among study population 3) a) Overview of CKiD study and eligibility criteria b) Subject selection for this study i) CONSORT flow diagram of study participant exclusions and inclusions ii) Issue of time discrepancy of data collection iii) Venn diagram of overlapping selection criteria
Descriptive statistics and univariate analysis	Summary of covariates from Table 1 *Sociodemographic* - Age (continuous: years) - Sex (binary: male/female) - Race (categorical: Caucasian/African American/other) - Maternal education (categorical: high school/college/graduate) *Clinical* - Onset of kidney disease (continuous: years before study entry) - Primary renal diagnosis (binary: glomerular/non-glomerular) - Proteinuria a) categorical based on urine protein:creatinine ratio: i) normal (<0.5)/mild (0.5-1)/moderate (1-2)/severe (>2) ii) normal-mild/moderate-severe b) continuous (urine protein:creatinine ratio) - Obesity (binary: >95th percentile and continuous: z-score) - Kidney function a) continuous: estimated glomerular filtration rate (mL/min/1.73m^2, using CKiD formula)	Statistical analysis with outcome group comparisons for: 1) Controlled/uncontrolled hypertension 2) Controlled/masked/ambulatory hypertension 3) Left ventricular hypertrophy (present/absent) Summary of results (Tables 1-4, for corresponding outcome groups) - Overall summary of study population (n=240) - Comparison of outcome groups (1-4) to determine potential covariates influencing outcomes: a) Factors with continuous data: mean+/-sd i) Group comparisons with 2 categories (1 and 3): Mann-Whitney U test (two-sided) ii) Group comparisons with 3 categories (2): Kruskal-Wallis test (two-sided) b) Factors with binary or categorical data: count (%) i) Group comparison ($\chi 2$ goodness-of-fit test) → Unadjusted odds ratios (OR) calculated for factors having p-values <0.2 (reference values for each subgroup 'exposure' in OR noted below corresponding table) ii) Comparing odds of outcomes:

Type	Overview	Description
	b) ordinal (chronic kidney disease stage 1-5) - Hyperkalemia (binary: serum potassium level ≤ or > 5mmol/L) - Family history of hypertension (binary: yes/no) *Pharmacological* - Number of antihypertensive agents (ordinal: 1-4) - Relative Dose Index (RDI) a) numeric based on cumulative and average value across agents per subject (cRDI) b) ordinal based on tertile within study population - Use of steroids (binary: yes/no) - Antihypertensive class (binary: RAASi/CCB/diuretic/BB; see abbreviations list)	Odds ratio plot (Forest plot) for unadjusted OR with 95% confidence intervals
Relative dose index: Overall and subgroup analysis	Comparison of each outcome group for cumulative RDI Overall and subgroup analysis 1) Controlled hypertension vs. uncontrolled hypertension (t-test) 2) Controlled hypertension vs. masked hypertension vs ambulatory hypertension (ANOVA) 3) Left ventricular hypertrophy: present vs. absent (t-test)	Results a) Figures: Boxplots of log-transformed cRDI b) Summary Tables: - mean (sd), p-value c) Statistical tests - independent T-test for groups with dichotomous outcomes (1 and 3) - ANOVA for group with trichotmous outcomes (2)
Relative dose index: Multivariate analysis	Multivariate logistic regression based on generalized linear model 1) Controlled hypertension vs uncontrolled hypertension 2) Left ventricular hypertrophy present vs absent Sensitivity analysis a) Exclusion of number of antihypertensive agents	Results a) Table of OR and 95% confidence intervals for each factor in model b) Odds ratio plot of adjusted OR with 95% confidence intervals for outcome groups 1 and 3

For all analyses, a two-sided statistical test was used with alpha 0.05. Results were reported using both exact p-values with 2 significant digits, as well as 95% confidence intervals in order to provide the reader with a combination of useful statistical information necessary to independently interpret results. For binary or categorical variables, $\chi 2$ test for goodness-of-fit was performed to compare between all outcomes groups (cHTN vs uHTN; cHTN vs MH vs AH; LVH absent vs present).

A descriptive summary of the socio-demographic, clinical and pharmacological variables evaluated at the third visit was performed for the overall study population (n=240) alongside a comparison of these covariates between primary and secondary outcomes in Appendix B Tables B1-3.

To determine the direction of association between covariates and dichotomous outcomes, odds ratios with 95% confidence intervals were calculated for covariates having a p-value <0.2. The reference group for the denominator in the odds ratio was noted in each corresponding table. To provide a visual summary of potential confounding covariates, an odds plot was created for all odds ratios with 95% confidence intervals.

Preliminary analysis of cumulative relative dose index

To evaluate whether antihypertensive dosing as expressed by cRDI, differed in each of the outcome groups, a two-sided t-test (for dichotomous outcomes) and ANOVA (for trichotomous outcome group of cHTN/MH/AH) was performed on log-transformed cRDI. Results are shown in boxplots for each outcome comparison.

Subgroup analysis was performed to determine whether covariates interacted with cRDI at each outcome level. Log-transformed cRDI was used for comparisons for all covariate subgroups where the comparison in the descriptive summary (Tables B1-3) yielded a p-value <0.2. Also, a specific a priori analysis was performed on the proteinuria covariates (a) normal/mild/moderate/severe and (b) normal-mild/moderate-severe, in order to assess the potential for bias by indication, because RAASi are indicated as a treatment for proteinuria as well as hyeprtension. T-test and one-way ANOVA tests were performed to comparing cRDI in the dichotmous and trichotomous outcome groups, respectively (cHTN/uHTN; cHTN/MH/AH). No imputation was used in the case of missing data (eg, maternal education, hyperkalemia status and family history of hypertension). Missing data was denoted in Tables B1-B3 (Appendix B) by the presence of a denominator for corresponding covariates.

Interaction between cRDI and number of agents

Because cRDI is defined as the sum of all RDIs for a given subject, the cRDI will be strongly influenced by the number of agents taken. In order to get a better understanding of this relationship, cRDI and average RDI were compared by blood pressure status (cHTN vs. uHTN) and left ventricular hypertrophy status (absent vs. present) and stratified by number of antihypertensive agents. Kruskal-Wallis test was used for statistical comparison between groups.

Multivariate logistic regression models for outcomes

A multivariate analysis was performed using a multivariate generalized linear model logistic regression on the dichotomous outcome groups (cHTN/uHTN, LVH absent/present) to determine the adjusted odds ratios for each of the covariates on the outcomes of interest. Although cRDI did not meet the criteria of $p<0.2$ in the univariate analysis, since the primary focus of this study to examine the effect of antihypertensive dosing on outcomes, it was nevertheless included in all models.

In order to evaluate for multicollinearity, variance inflation factors (VIF) were also calculated and a cutoff of 5 was considered as an indicator of significant collinearity that should be considered for elimination from the model.

Finally, as a sensitivity analysis, models were generated using subjects taking RAASi alone to the exclusion of other antihypertensive classes (n=225) in order to assess for interactions based on antihypertensive class. Tables corresponding to all models are included in the Appendix B for reference.

CHAPTER 4

RESULTS

Subject selection criteria

A CONSORT diagram summarizing the number of subjects included and excluded based on selection criteria described above is shown in Figure 5. Of 708 subjects whose demographic information was obtained in the CKiD database, 651 were present at visit 3. Of these, additional sequential exclusions were made based on unavailability of necessary data or ineligibility for the analysis:

- 36 subjects excluded due to missing BP
- 195 subjects excluded due to unavailable or unsuccessful ABPM studies
- 21 subjects excluded due to eGFR that could not be determined because of missing required parameters (serum creatinine, serum BUN, cystatin C)
- 130 subjects not taking antihypertensive agents. Of these subjects, the proportions normal blood pressure, masked hypertension, ambulatory hypertension and left ventricular hypertrophy present were calculated in Table 5.

Table 5: Outcomes of subjects not taking antihypertensive agents (n=130)

Outcome	n	Proportion
Normotensive	48	0.37
Masked hypertension	52	0.40
Ambulatory hypertension	30	0.23
Left ventricular hypertrophy	26	0.20

- 29 subjects excluded due to incomplete medication dose information
- 20 subjects excluded due to exceeding maximum timespan for data collection at the third visit.

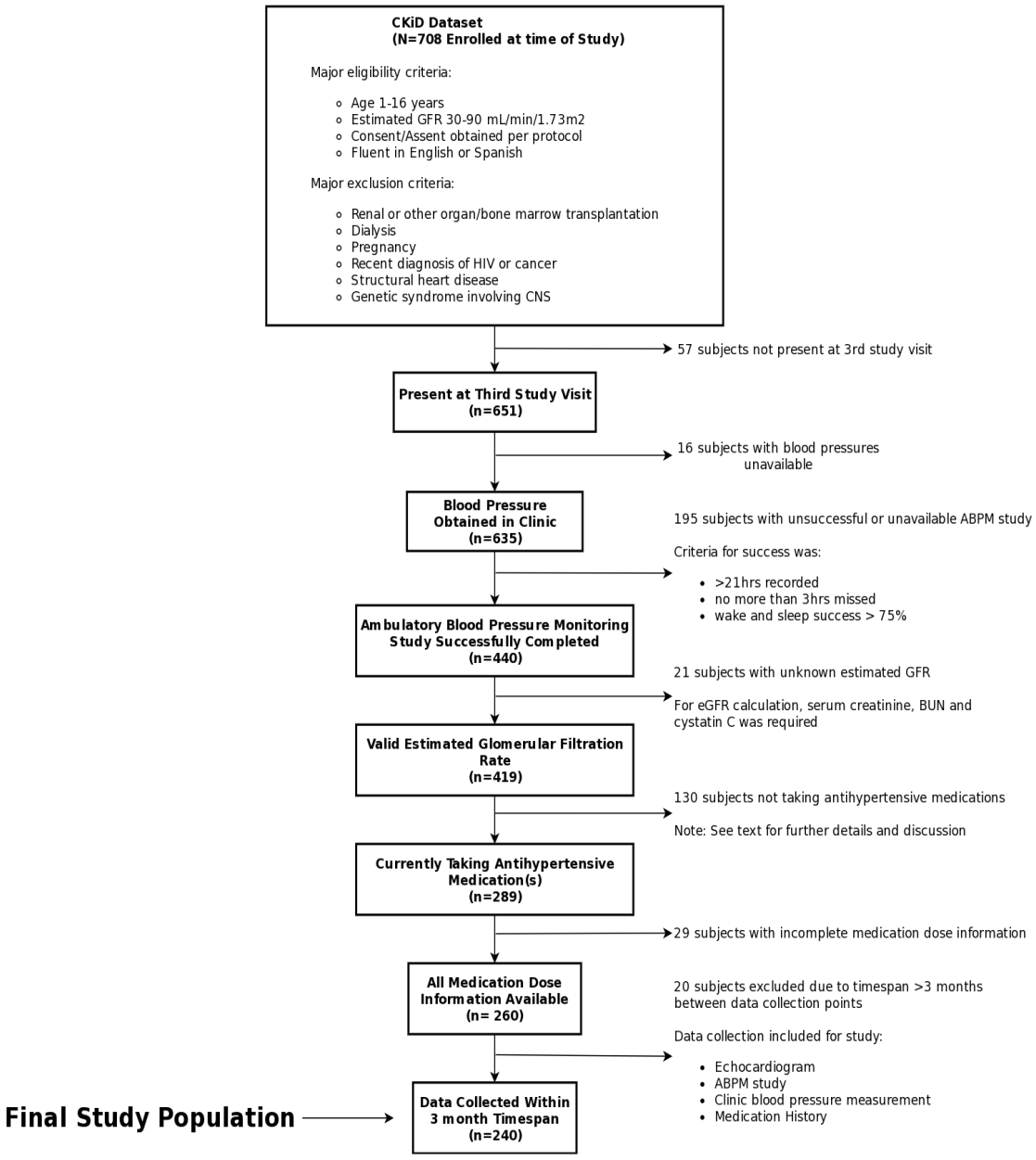
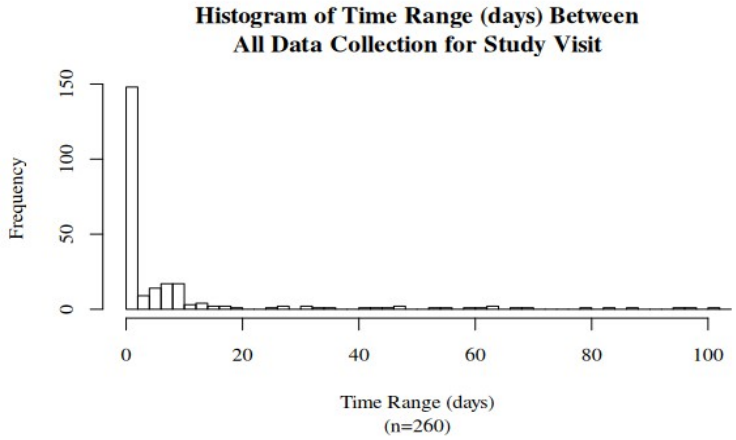


Figure 5: CONSORT flow diagram
Overview of subject inclusion and exclusion based on study selection criteria

To further illustrate the last exclusion, a dumbell plot for each subject and their respective data collection time points as well as a histogram of maximum time difference in days between data collection points was performed (Figure 6). The data collection times used included time of ABPM, echocardiography, medication history and physical exam.

a)



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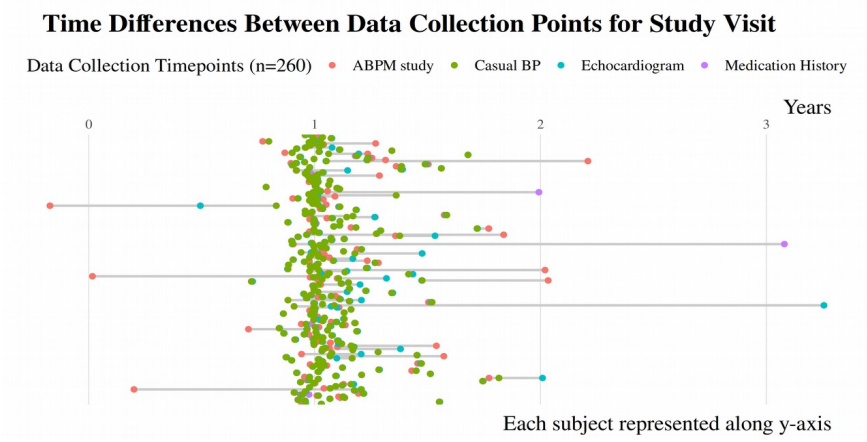

Figure 6: Time differences between data collection at visit 3
a) Histogram of maximum timespan for data collection at visit 3 for 260 eligible subjects. Data collection includes: ABPM, physical exam (casual BP and anthropometric measurements), echocardiogram and medication history. b) Dumbell plot demonstrating timing of data collection for each subject at visit 3. 20 subjects with maximum timespan exceeding 90 days, were excluded from study.
Abbreviations: ABPM ambulatory blood pressure monitoring study

Whereas the vast majority of subjects had all relevant data collected within 1 month, 20 subjects' data exceeded the arbitrary cutoff of 3 months, and were therefore excluded to maintain temporal integrity of the data and validity of the results and analysis.

Since exclusion criteria were additive, rather than sequential, a Venn diagram is useful in providing further insight into the inclusion and exclusion criteria for the study population (Figure 7).

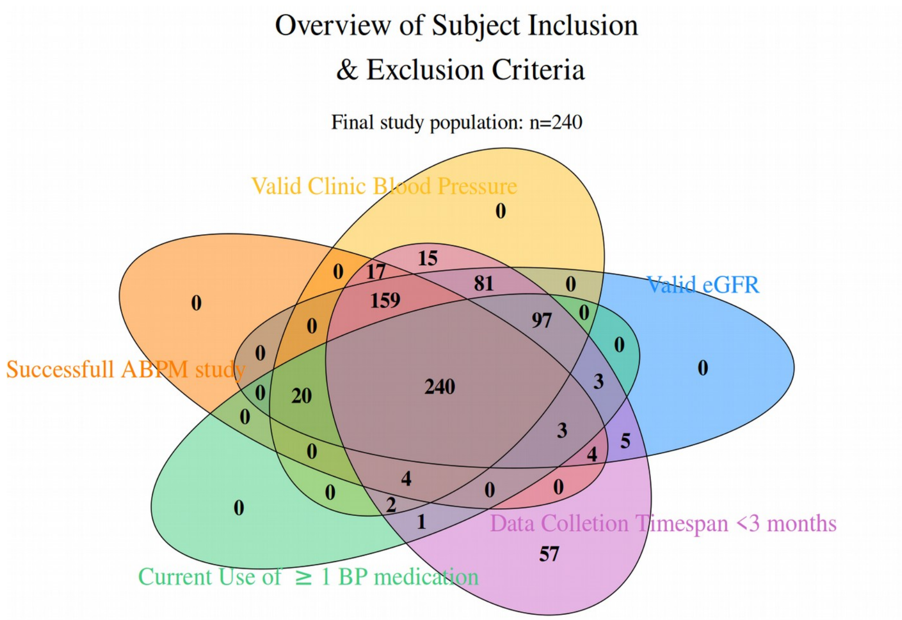

Figure 7: Venn diagram of subject inclusion and exclusion criteria
Regions immediately outside of the central region representing the study population (N=140) represent subjects that meet all criteria except for one. (see text for further explanation)

Regions in the diagram that immediately surround the final study population of 240 subjects, represent subjects that were excluded due to failing to meet a single inclusion criteria. Notable areas with a significant number of exclusion are:

- Not taking any antihypertensive agents (n=159)

- Lack of successful ABPM study (n=97)
- Data collection time span exceeding 3 months (n=20)

These exclusions will be addressed further in the Discussion section.

Overview of antihypertensive medications

The frequencies of each antihypertensive class used by subjects is non-randomly distributed and reflects current guidelines favoring renin-angiotensin aldosterone system inhibitors (RAASi, n=218) in the CKD population (Figure 8), which were followed in descending order by calcium channel blockers (CCB, n=44), diuretics (n=20), beta-blockers (n=12) and others which included alpha-2 stimulators (n=6), sodium channel blockers (n=2) and alpha-1 blockers (n=1).

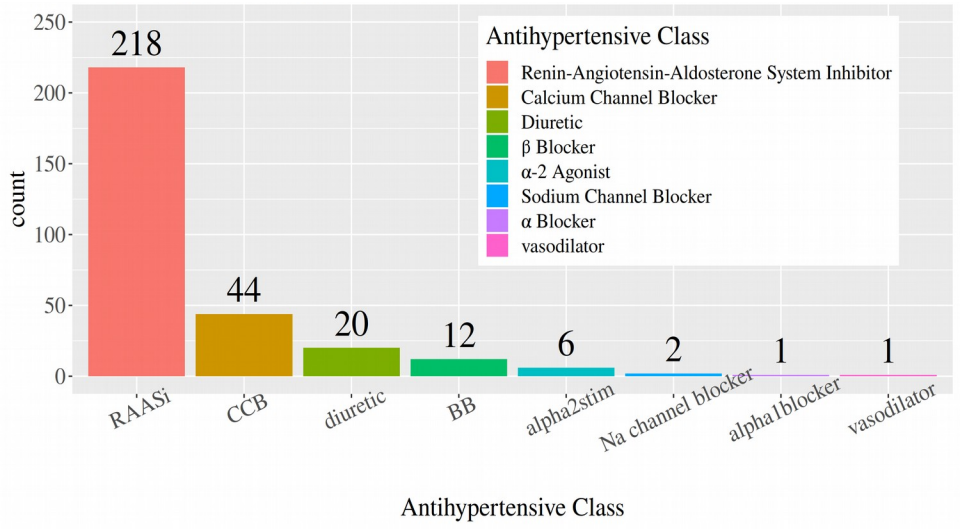

Figure 8: Frequencies of antihypertensive class use in study population
Note that some patients are taking multiple antihypertensive medications. Sodium channel blocker: amiloride

Abbreviations: RAASi Renin-Angiotensin-Aldosterone System Inhibitor, CCB Calcium Channel Blocker, BB Beta-Blocker, alpha2stim central alpha-2 adrenergic agonist

Comparison of Fourth Report and 2017 AAP blood pressure classification schemes

Although the majority of subjects' BP classification remained unchanged with the updated 2017 AAP hypertension classification scheme, compared with the Fourth Report, there were a small but significant number of subjects who were reclassified (Figure 9). Of these, the majority had a more severe classification with the updated guidelines. This was apparent both for the casual BP as well as ambulatory BP classifications.

a) Casual blood pressure classification

4th Report (2004)	American Academy of Pediatrics (2017)				
	Normal	Elevated Blood Pressure	Hypertension Stage 1	Hypertension Stage2	Total
Normal	159	10	0	0	167
Pre-Hypertension	2	24	11	0	37
Hypertension, Stage 1	0	1	22	4	27
Hypertension, Stage 2	0	0	0	7	7
Total	161	35	33	11	240

b) Ambulatory blood pressure classification

4th Report (2004)	American Academy of Pediatrics (2017)				
	Normal	White Coat Hypertension	Masked Hypertension	Ambulatory Hypertension	Total
Normal	102	1	0	0	103
White Coat Hypertension	0	4	0	0	4
Masked Hypertension	0	0	91	10	101
Ambulatory Hypertension	0	0	0	32	32
Total	102	5	91	42	240

Figure 9: Reclassification of blood pressure status using American Academy of Pediatrics (2017) blood pressure guidelines
a) Casual blood pressure classification and b) Ambulatory blood pressure classification. Comparisons are made between AAP 2017[39] and the Fourth Report (2004)[22] for the study population.
Color key: The green shaded areas represent subjects whose classification remained unchanged. Red and blue shaded cells represent subjects who were reclassified to more or less severe BP statuses, respectively.

Of the 240 subjects in the study population, the majority retained the same classification (shaded in green), however 12% and 5% of subjects had their casual BP and

ambulatory BP status, respectively, reclassified with the updated AAP guideline. Of these, almost 90% of the casual BP classification and all of the ambulatory BP classification were reclassified to a more severe category of BP. Only 3 subjects had a less severe casual BP classification (shaded in blue).

Distribution of cumulative relative dose index in the study population

The distribution of cumulative relative dose index (cRDI) in the study population was strongly right-skewed, with a majority of patients having cRDI <0.5 (Figure 10). The maximum cRDI was 3.

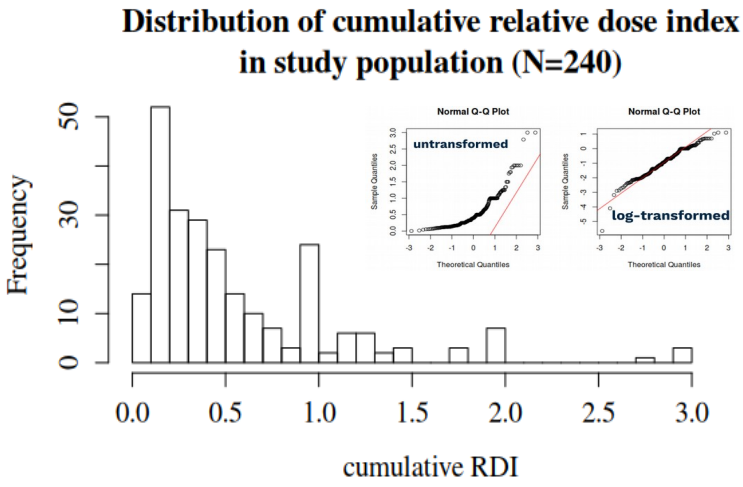

Figure 10: Distribution of cumulative relative dose index (cRDI)
Note the strongly right-skewed distribution. In subgroup analyses, cRDI was log-transformed with statistical significance testing using t-test or ANOVA.Inset: Q-Q plots of untransformed vs. log-transformed cRDI in study population.

Interestingly, review of the dosing of the study population revealed 26 subjects (11%) who had at least one medication dose higher than the recommended dose references. In

addition, 79 subjects (33%) were taking medications that required renal dose adjustment based on the subject's eGFR and medication. The odds of having a medication dosed excessively was 1.3 times higher (95% confidence interval: 0.56-3.02, p=0.54) in these subjects compared to those who did not require renal dose adjustments.

Descriptive summary of study population based on outcomes

A full description of the study population and the various socio-demogrpahic, clinical and pharmacological covariates examined based on blood pressure status and left ventricular hypertrophy outcomes is found in Appendix B (Tables B1-3). In this section, selected covariates which had corresponding p-values of less than 0.2 with respect to each outcome group will be summarized, as they were considered potential confounding variables.

Controlled hypertension vs. uncontrolled hypertension

Unadjusted odds ratios of having uncontrolled hypertension are shown in Figure 11 for covariates with p-values <0.2. Of the covariates examined, the risk factors that were associated with increased odds of having uncontrolled hypertension in descending order included (OR [95% CI]):

1. Current use of calcium channel blockers (6.73 [2.72,16.65])
2. African American race: Compared to Caucasians, the OR for uncontrolled hypertension among this group was 3.33 [CI 1.26,8.75]. Other races (which included

American Indian, Native Hawaiian, Asian or multiracial) also had increased odds of uHTN with OR 2.10 [CI 1.09,4.05].

3. Severe proteinuria (urine protein:creatinine ratio > 2): (2.91 [1.16,7.31])
4. Number of agents: Subjects taking two antihypertensive agents concurrently had OR 2.44 [1.15,5.18] compared to those taking only one agent.
5. Current use of renin-angiotensin-aldosterone inhibitors (RAASi) was associated with OR 0.07 [0.02,0.29] of having uncontrolled HTN compared to those who did not take this class.

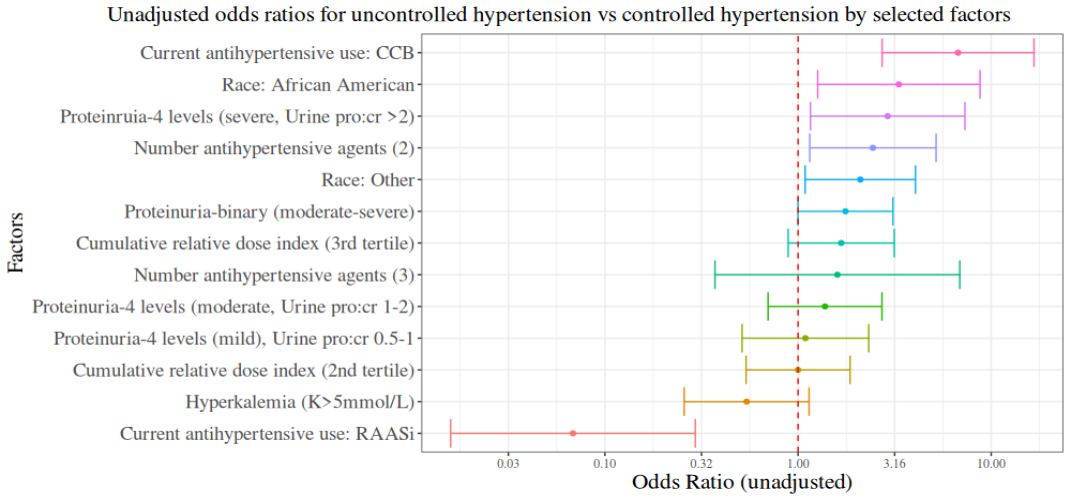

Figure 11: Unadjusted odds ratios of uncontrolled hypertension for selected covariates
Covariates with p-values <0.2 in Table B1 from univariate analysis are shown. Error bars represent 95% confidence intervals.

Reference values for each categorical outcome in parentheses: Race (Caucasian), Proteinuria-4 levels (Normal, urine pro:cr <0.5), Proteinuria-binary (Normal-Mild), Number of agents (1), cumulative relative dose index (1st tertile), Hyperkalemia (K<5 mmol/L), Current antihypertensive use (not using)

Abbreviations: RAASi renin-angiotensin-aldosterone system inhibitor, CCB calcium channel blocker

6. cRDI did not significantly differ among subjects with controlled vs. uncontrolled hypertension (t-test p=0.13, Figure 12).

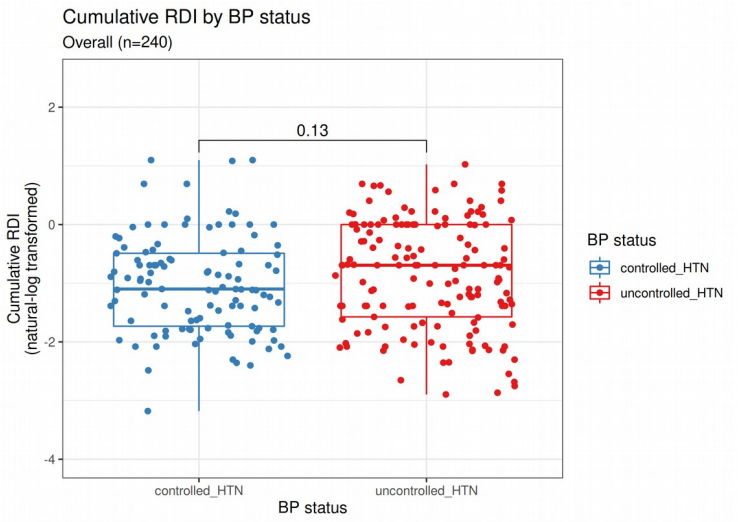

Figure 12: Comparison of cumulative relative dose index by blood pressure status (controlled vs. uncontrolled hypertension)
cRDI was log-transformed and t-test used to compare between controlled vs. uncontrolled hypertension groups. For all boxplots the lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles).The hinges and middle line of the boxplot represent the inter-quartile range (IQR), and median. The upper and lower whiskers extend 1.5 times the IQR from the corresponding hinge.

Table 6 provides a summary of the overall study population and a comparison between controlled vs. uncontrolled hypertension with respect to the selected covariates which had corresponding p-values <0.05.

Table 6: Descriptive summary: Controlled vs. uncontrolled hypertension

Descriptive Statistics	Overall (N = 240)	Controlled Hypertension (n = 107)	Uncontrolled Hypertension (n = 133)	p-value*	OR** [95% CI]
Race, n (%)					
Caucasian	164 (68%)	84 (79%)	80 (60%)	0.0074	
African American	25 (10%)	6 (6%)	19 (14%)		3.33 [1.26,8.75]
Other	51 (21%)	17 (16%)	34 (26%)		2.10 [1.09,4.05]
Proteinuria (Urine protein:creatinine ratio)					
Normal (<0.5)	132 (55%)	65 (61%)	67 (50%)	0.041	
Mild [0.5-1.0)	34 (14%)	16 (15%)	18 (14%)		1.09 [0.51,2.32]
Moderate [1.0-2.0)	46 (19%)	19 (18%)	27 (20%)		1.38 [0.70,2.72]
Severe (>2.0)	28 (12%)	7 (7%)	21 (16%)		2.91 [1.16,7.31]
Normal-Mild (<1.0)	166 (69%)	81 (76%)	85 (64%)	0.05	
Moderate-Severe (>1.0)	74 (31%)	26 (24%)	48 (36%)		1.76 [1.00,3.10]
mean ± sd	0.96 ± 1.48	0.87 ± 1.66	1.03 ± 1.32	0.09	
Number of antihypertensive agents					
1	190 (79%)	93 (87%)	97 (73%)	0.0081	
2	39 (16%)	11 (10%)	28 (21%)		2.44 [1.15,5.18]
3	8 (3%)	3 (3%)	5 (4%)		1.60 [0.37,6.88]
4	3 (1%)	0 (0%)	3 (2%)		+
mean ± sd	1.27 ± 0.58	1.16 ± 0.44	1.35 ± 0.67	0.0081	
Cumulative Relative Dose Index (tertiles & mean)					
1st tertile (low dose)	80 (33%)	39 (36%)	41 (31%)	0.11	
2nd tertile (moderate dose)	80 (33%)	39 (36%)	41 (31%)		1.00 [0.54,1.86]
3rd tertile (high dose)	80 (33%)	29 (27%)	51 (38%)		1.67 [0.89,3.15]
mean ± sd	0.57 ± 0.55	0.52 ± 0.55	0.62 ± 0.54	0.2	
Antihypertensive Drug Class Use, n (%)					
Renin-Angiotensin System Inhibitor	209 (87%)	105 (98%)	104 (78%)	<0.001	0.07 [0.02,0.29]
Calcium Channel Blocker	44 (18%)	6 (6%)	38 (29%)	<0.001	6.73 [2.72,16.65]
Diuretic	20 (8%)	8 (7%)	12 (9%)	0.84	
Beta-blocker	12 (5%)	0 (0%)	12 (9%)	0.0039	+
Other	9 (4%)	0 (0%)	9 (7%)		+

* P-values based on $\chi 2$ goodness-of-fit test for categorical and ordinal covariates. Mann-Whitney U test for continuous and ordinal covariates.

** Unadjusted odds ratios [with 95% confidence intervals] calculated for selected factors with p-values <0.2; Reference categories for odds ratios are italicized. For drug classes, references are non-use of corresponding class.

Controlled hypertension vs. masked hypertension vs. ambulatory hypertension

When uncontrolled hypertension was subdivided into masked and ambulatory hypertension, the following factors were identified as potential confounding factors with p-values <0.2:

1. Race: A significantly disproportionately high proportion of Caucasians had controlled hypertension compared with African Americans and other races ($\chi 2$ test p-value 0.012).
2. Proteinuria: Subjects with severe proteinuria (urine protein:creatinine ratio > 2) were significantly more likely to have masked and ambulatory hypertension (p=0.044).
3. Estimated GFR: There was an inconsistent trend for eGFR, with subjects in the ambulatory hypertension group having the lowest average eGFR (worst kidney function), those with the highest average eGFR in the masked hypertension group, and controlled hypertension with an intermediate average eGFR. One-way ANOVA test was significant (p=0.011) suggesting these results are non-randomly distributed.
4. Number of antihypertensive agents: There was a strong positive association between number of agents and higher chance of having either masked or ambulatory hypertension (p=0.0018). The average number of agents in the controlled hypertension group was only 1.16 ± 0.44 compared with 1.60 ± 0.91 in subjects with ambulatory hypertension.

5. Cumulative RDI: There was a disproportionately high number (52%) of subjects in the third (higher dose) tertile with ambulatory hypertension compared to those in the first tertile (14%), with a p-value for one-way ANOVA of 0.0039. A boxplot comparing cRDI between controlled, masked and ambulatory hypertension demonstrates an increasing trend of cRDI for masked and ambulatory hypertension, and is shown in Figure 13.

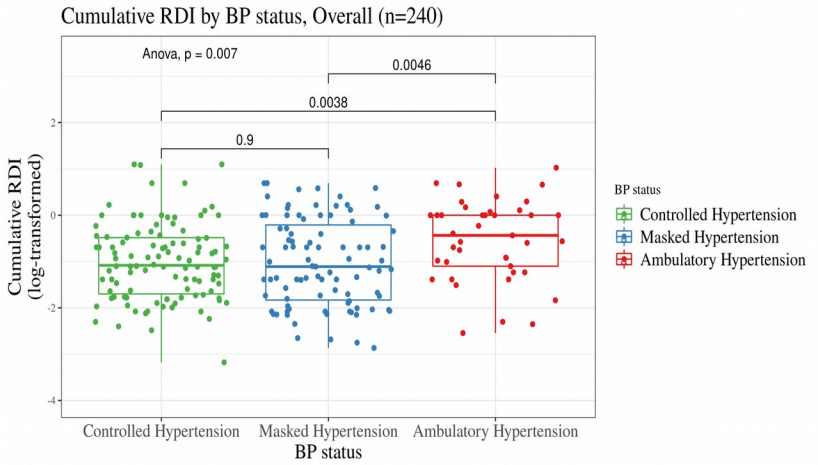

Figure 13: Comparison of cumulative relative dose index by blood pressure status (controlled vs. masked vs. ambulatory hypertension)
cRDI was log-transformed and comparison made with one-way ANOVA and between each pair of outcomes using independent two-sample t-test.

6. Antihypertensive class: Whereas subjects taking RAASi had a higher chance of having controlled hypertension ($p<0.001$), those taking CCB or BB had higher chance of having masked or ambulatory hypertension ($p<0.001$). Subjects taking diuretics did not have a significantly higher chance of having masked or ambulatory

hypertension vs. controlled hypertension (χ^2=0.07, p=0.78; χ^2=1.9, p=0.17, respectively).

Table 7 provides a summary of the overall study population and a comparison between controlled vs. uncontrolled hypertension with respect to the selected covariates which had corresponding p-values <0.05.

Table 7:Descriptive summary: controlled vs. masked vs. ambulatory hypertension

Descriptive Statistics	Overall (N = 240)	Controlled Hypertension (n = 107)	Masked Hypertension (n = 91)	Ambulatory Hypertension (n = 42)	P-value*
Race, n (%)					
Caucasian	164 (68%)	84 (79%)	52 (57%)	28 (67%)	0.012
African American	25 (10%)	6 (6%)	12 (13%)	7 (17%)	
Other	51 (21%)	17 (16%)	27 (30%)	7 (17%)	
Proteinuria (Urine protein:creatinine ratio)					
Normal-Mild (<1.0)	166 (69%)	81 (76%)	62 (68%)	23 (55%)	0.044
Moderate-Severe (>1.0)	74 (31%)	26 (24%)	29 (32%)	19 (45%)	
Estimated GFR					
mean ± sd	51.81 ± 21.11	51.61 ± 21.07	55.01 ± 19.09	45.38 ± 24.19	0.011
CKD stage					
1	1 (0%)	0 (0%)	0 (0%)	1 (2%)	0.017
2	32 (13%)	13 (12%)	7 (8%)	12 (29%)	
3	135 (56%)	60 (56%)	54 (59%)	21 (50%)	
4	59 (25%)	27 (25%)	27 (30%)	5 (12%)	
5	13 (5%)	7 (7%)	3 (3%)	3 (7%)	
Number of antihypertensive agents					
1	190 (79%)	93 (87%)	71 (78%)	26 (62%)	0.0018
2	39 (16%)	11 (10%)	18 (20%)	10 (24%)	
3	8 (3%)	3 (3%)	2 (2%)	3 (7%)	
4	3 (1%)	0 (0%)	0 (0%)	3 (7%)	
mean ± sd	1.27 ± 0.58	1.16 ± 0.44	1.24 ± 0.48	1.60 ± 0.91	0.0018
Cumulative Relative Dose Index (tertiles & mean)					
1st tertile (low dose)	80 (33%)	39 (36%)	35 (38%)	6 (14%)	0.0039
2nd tertile (moderate dose)	80 (33%)	39 (36%)	27 (30%)	14 (33%)	
3rd tertile (high dose)	80 (33%)	29 (27%)	29 (32%)	22 (52%)	
Antihypertensive Drug Class Use, n (%)					
Renin-Angiotensin System Inhibitor	209 (87%)	105 (98%)	78 (86%)	26 (62%)	<0.001
Calcium Channel Blocker	44 (18%)	6 (6%)	17 (19%)	21 (50%)	<0.001
Diuretic	20 (8%)	8 (7%)	5 (5%)	7 (17%)	0.087
Beta-blocker	12 (5%)	0 (0%)	5 (5%)	7 (17%)	<0.001
Other	9 (4%)	0 (0%)	5 (5%)	4 (10%)	

* P-values based on $\chi 2$ goodness-of-fit test for categorical and binary covariates. Kruskal-Wallis one-way ANOVA for continuous and ordinal covariates

Absence vs. presence of left ventricular hypertrophy

Unadjusted odds ratios of having left ventricular hypertrophy are shown in Figure 14 for covariates with p-values <0.2. Of the covariates examined, the risk factors that were associated with increased odds of having left ventricular hypertrophy in descending order included (OR [95% CI]):

1. Number of antihypertensive agents: There was a strong positive association between the number of antihypertensive agents taken by subjects and their odds of having left ventricular hypertrophy. Odds ratios for 4, 3 and 2 antihypertensive agents were 18.00 [1.56,207.92], 5.40 [1.20,24.39] and 3.10 [1.31,7.34], respectively compared to those taking only one agent. The average number of agents in the LVH group was significantly higher than in the group without LVH (1.65 ± 0.88 vs 1.20 ± 0.49, $p<0.001$).
2. Antihypertensive drug class: Taking a diuretic, beta blocker or calcium channel blocker was associated with higher odds of having LVH (4.97 [1.86,13.30], 4.90 [1.46,16.47], 3.49 [1.59,7.70], respectively. In contrast, those taking a renin-angiotensin-aldosterone system inhibitor had significantly lower odds of having LVH (0.27 [0.11,0.65]).
3. Race: African Americans had higher odds of having LVH compared with Caucasians (3.45 [1.36,8.72]).
4. eGFR: Kidney function was significantly lower in subjects with LVH compared to those without LVH (eGFR 43.87 ± 20.28 vs. 53.12 ± 21.01, $p = 0.02$; t-test).

5. Time of chronic kidney disease (CKD) onset: Onset of CKD before study entry was significantly earlier in those without LVH compared to those with LVH (-8.56 years ± 4.85 years vs -6.50 years ± 4.02 years, p = 0.021, t-test).

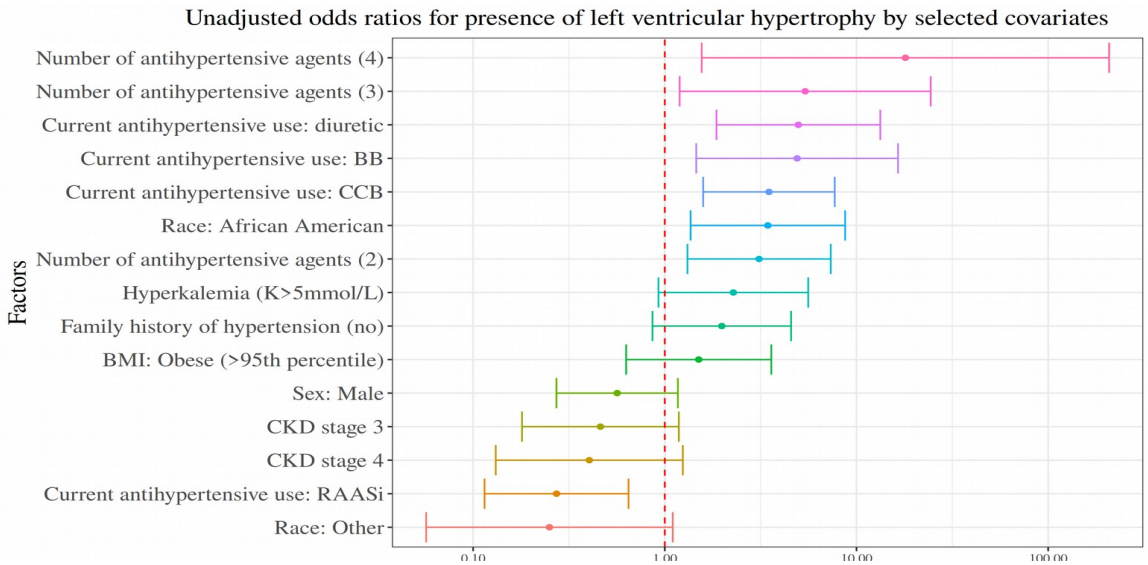

Figure 14: Unadjusted odds ratios of left ventricular hypertrophy for selected covariates
Error bars represent 95% confidence intervals. Covariates with p-values <0.2 in Table B3 on univariate analysis are shown.

Reference values for each categorical outcome in parentheses: Race (Caucasian), CKD stage (1), Number of agents (1), Sex (Female), Hyperkalemia (K<5 mmol/L), Current antihypertensive use (not using)

Abbreviations: RAASi renin-angiotensin-aldosterone system inhibitor, CCB calcium channel blocker, BB beta-blocker, CKD chronic kidney disease, K potassium, BMI body mass index

6. Cumulative RDI: There was no significant association with left ventricular hypertrophy (unadjusted OR for being in the second and third tertiles compared to the first tertile was 1.75 [0.68, 4.48]). A boxplot comparing cRDI between subjects without vs with left ventricular hypertrophy did not show any significant differences in cRDI, and is shown in Figure 15.

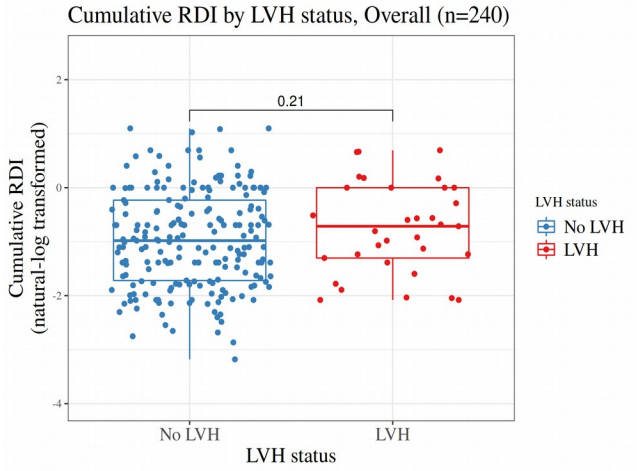

Figure 15: Comparison of cumulative relative dose index by left ventricular hypertrophy status (absent vs. present)
cRDI was log-transformed and compared using two-sided t-test (p-value = 0.21).

Table 8 provides a summary of the overall study population and a comparison between controlled vs. uncontrolled hypertension with respect to the selected covariates which had corresponding p-values <0.05.

Table 8: Descriptive summary: absence vs. presence of left ventricular hypertrophy:

Descriptive Statistics	Overall (N = 240)	LVH absent (n = 206)	LVH present (n = 34)	P-value*	OR [95% CI]**
Race, n (%)					
Caucasian	164 (68%)	141 (68%)	23 (68%)	<0.001	
African American	25 (10%)	16 (8%)	9 (26%)		3.45 [1.36,8.72]
Other	51 (21%)	49 (24%)	2 (6%)		0.25 [0.06,1.10]
CKD onset* (years before study entry)					
n, mean ± sd	235; -8.28 ± 4.79	203; -8.56 ± 4.85	32; -6.50 ± 4.02	0.021	
Estimated GFR					
mean ± sd	51.81 ± 21.11	53.12 ± 21.01	43.87 ± 20.28	0.02	
Number of antihypertensive agents					
1	190 (79%)	171 (83%)	19 (56%)	<0.001	
2	39 (16%)	29 (14%)	10 (29%)		3.10 [1.31,7.34]
3	8 (3%)	5 (2%)	3 (9%)		5.40 [1.20,24.39]
4	3 (1%)	1 (0%)	2 (6%)		18.00 [1.56,207.92]
mean ± sd	1.27 ± 0.58	1.20 ± 0.49	1.65 ± 0.88	<0.001	
Cumulative Relative Dose Index (tertiles)					
1st tertile (low dose)	80 (33%)	72 (35%)	8 (24%)	0.26	
2nd tertile (moderate dose)	80 (33%)	67 (33%)	13 (38%)		1.75 [0.68,4.48]
3rd tertile (high dose)	80 (33%)	67 (33%)	13 (38%)		1.75 [0.68,4.48]
Antihypertensive Drug Class Use, n (%)					
Renin-Angiotensin System Inhibitor	209 (87%)	185 (90%)	24 (71%)	0.0048	0.27 [0.11,0.65]
Calcium Channel Blocker	44 (18%)	31 (15%)	13 (38%)	0.0027	3.49 [1.59,7.70]
Diuretic	20 (8%)	12 (6%)	8 (24%)	0.0018	4.97 [1.86,13.30]
Beta-blocker	12 (5%)	7 (3%)	5 (15%)	0.017	4.90 [1.46,16.47]

* P-values based on $\chi 2$ goodness-of-fit test for categorical and ordinal covariates. Mann-Whitney U test for continuous and ordinal covariates.

** Unadjusted odds ratios [with 95% confidence intervals] calculated for selected factors with p-values <0.2

Subgroup analysis of cumulative relative dose index

Although cumulative relative dose index (cRDI) was not found in the preliminary analysis to be significantly associated with blood pressure status (cHTN/uHTN) and LVH, when uHTN was subdivided into masked and ambulatory hypertension, there was a positive association between cRDI and blood pressure status (Figure 13). Also, the cumulative relative dose index (cRDI) is defined as the sum RDI for all antihypertensive agents taken concurrently, and therefore number of antihypertensive agents would be expected to be an influencing factor on cRDI. Whereas cRDI gives information about the total cumulative dose of all antihypertensive agents, mean RDI gives information about the average dose of each antihypertensive agent. For example, two hypothetical subjects taking two and three antihypertensive agents, respectively with the same cRDI of 1, would have a mean RDI of 0.5 and 0.33 respectively. Although their cRDI is identical, the lower mean RDI in the latter subject would suggest a lower utilization of antihypertensive agents compared with the maximum potential dose. Tables 8 and 9 provide an overview of this interaction based on blood pressure and left ventricular hypertrophy status, respectively.

Table 9: Cumulative and mean relative dose index stratified by number of agents and grouped by blood pressure status

Number of antihypertensive agents		Controlled Hypertension (N=107)	Uncontrolled Hypertension (N=133)	Total (N=240)	p value*
1	cumulative RDI				0.44
	Mean (SD)	0.393 (0.268)	0.393 (0.307)	0.393 (0.288)	
	N	93	97	190	
	mean RDI				0.44
	Mean (SD)	0.393 (0.268)	0.393 (0.307)	0.393 (0.288)	
	N	93	97	190	
2	cumulative RDI				0.179
	Mean (SD)	0.914 (0.659)	1.178 (0.522)	1.104 (0.568)	
	N	11	28	39	
	mean RDI				0.179
	Mean (SD)	0.457 (0.329)	0.589 (0.261)	0.552 (0.284)	
	N	11	28	39	
3	cumulative RDI				0.024
	Mean (SD)	2.986 (0.024)	0.903 (0.318)	1.684 (1.104)	
	N	3	5	8	
	mean RDI				0.024
	Mean (SD)	0.995 (0.008)	0.301 (0.106)	0.561 (0.368)	
	N	3	5	8	
4	cumulative RDI				
	Mean (SD)	n/a	2.224 (0.489)	2.224 (0.489)	
	N	0	3	3	
	mean RDI				
	Mean (SD)	n/a	0.556 (0.122)	0.556 (0.122)	
	N	0	3	3	

*P-value obtained using Kruskal-Wallis tests comparing controlled vs. uncontrolled hypertension.

Table 10: Summary of cumulative and mean relative dose index stratified by number of antihypertensive agents grouped by left ventricular hypertrophy status

Number of antihypertensive agents		No LVH (N=206)	LVH (N=34)	Total (N=240)	p value*
1	cumulative RDI				0.74
	Mean (SD)	0.389 (0.282)	0.431 (0.340)	0.393 (0.288)	
	N	171	19	190	
	mean RDI				0.74
	Mean (SD)	0.389 (0.282)	0.431 (0.340)	0.393 (0.288)	
	N	171	19	190	
2	cumulative RDI				0.004
	Mean (SD)	1.259 (0.489)	0.654 (0.562)	1.104 (0.568)	
	N	29	10	39	
	mean RDI				0.004
	Mean (SD)	0.629 (0.244)	0.327 (0.281)	0.552 (0.284)	
	N	29	10	39	
3	cumulative RDI				0.453
	Mean (SD)	2.104 (1.218)	0.985 (0.359)	1.684 (1.104)	
	N	5	3	8	
	mean RDI				0.453
	Mean (SD)	0.701 (0.406)	0.328 (0.120)	0.561 (0.368)	
	N	5	3	8	
4	cumulative RDI				0.221
	Mean (SD)	2.789 (n/a)	1.942 (0.009)	2.224 (0.489)	
	N	1	2	3	
	mean RDI				0.221
	Mean (SD)	0.697 (n/a)	0.485 (0.002)	0.556 (0.122)	
	N	1	2	3	

*P-value obtained using Kruskal-Wallis tests comparing left ventricular hypertrophy absent vs. present.

From Tables 8 and 9, as expected, cRDI tends to increase with increasing number of agents. Mean RDI on the other hand did not show a consistent trend, and ranged from 0.3 to 0.7 for most subjects, suggesting that when taking multiple medications, patients had at least one agent that was not being taken at maximum dose. Among children taking 3 antihypertensive agents, both cRDI and mean RDI were significantly higher in the controlled hypertension group vs. uncontrolled hypertension (cRDI: 2.9 vs 0.9 and mean RDI: 0.95 vs. 0.3, p=0.02, respectively), however there were only 8 subjects in this stratum. Among the subjects taking 2 agents, cRDI and mean RDI were both significantly higher in those without

vs. with left ventricular hypertrophy (1.26 vs 0.65 and 0.63 vs. 0.33, $p<0.01$, respectively; n=39). Together, these suggest that looking within strata by number of agents, higher dose may be associated with controlled hypertension and absence of left ventricular hypertrophy.

These sub-analyses of cRDI among controlled vs masked vs ambulatory hypertension, on one hand and by number of agents on the other hand, raised the possibility of interaction between cRDI and other covariates in the analysis, potentially confounding the relationship between hypertension and cRDI. Subgroup analysis of cRDI was expanded to all categorical covariates comparing controlled vs. uncontrolled HTN and LVH vs no LVH.

Subgroup analysis: controlled vs. uncontrolled HTN

The only significant differences in cRDI between controlled and uncontrolled hypertension were in the subgroups for primary CKD diagnosis (glomerular vs non-glomerular) and current steroid use (Figure 16). In the glomerular and steroid-taking groups, cRDI was significantly higher among those with uncontrolled HTN, compared to those with controlled HTN (t-test, p=0.038 and 0.017, respectively).

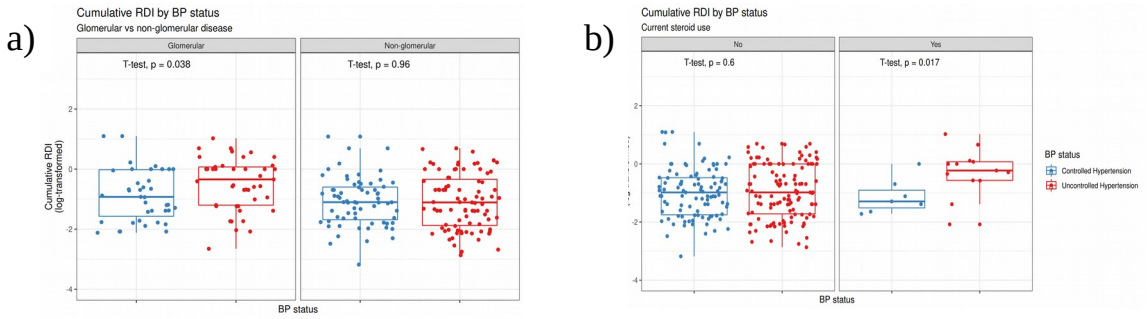

Figure 16: Subroups with significant interaction with cRDI: controlled vs. uncontrolled hypertension.
Boxplots of cRDI in subgroups: a) Primary CKD diagnosis (glomerular vs. non-glomerular), b) Current steroid use (no vs. yes)
Note: T-test of log-transformed cRDI used for statistical comparisons.

Subgroup analysis: left ventricular hypertrophy absent vs. present

Significant differences were noted for the subgroup analysis of number of antihypertensive agents (Figure 17). In this comparison, the cRDI was significantly higher in the group with no LVH among those taking two antihypertensive agents, whereas there were no differences in cRDI between those taking one or three agents.

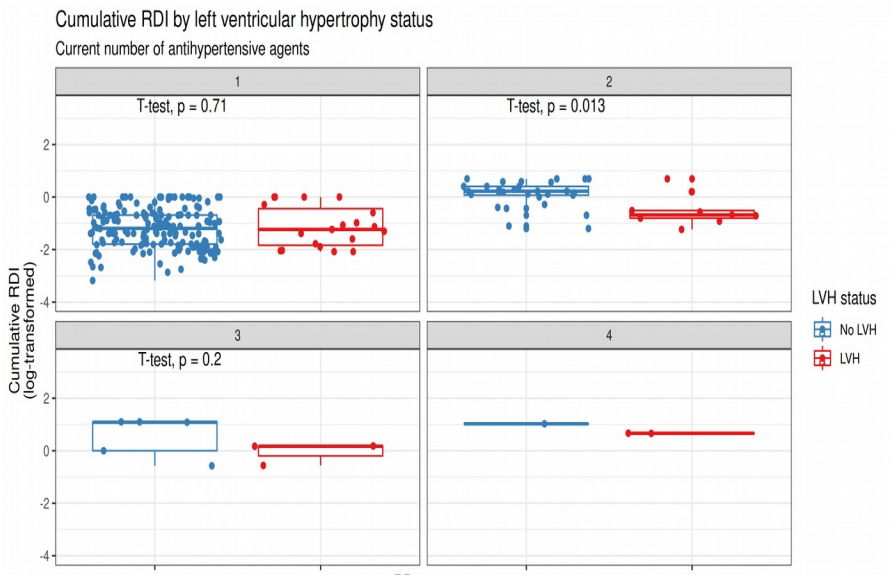

Figure 17: Subgroups with significant interaction with cRDI: left ventricular hypertrophy
Boxplots comparing cRDI between subjects with and without left ventricular hypertrophy, in subgroups for number of antihypertensive agents. T-test of log-transformed cRDI used for statistical comparisons.

Multivariate analysis with logistic regression

The final step in analysis was a multivariate logistic regression model in order to adjust for the influence of multiple covariates. For two outcome groups (controlled vs. uncontrolled HTN, and LVH absent vs. present) all the covariates were included in the model as they were considered clinically relevant factors which may have influence on the blood pressure status of the study population. A generalized linear model was used for the logistic regression. Proteinuria was categorized as either normal-mild or moderate-severe (urine protein:creatinine ratio <1 or ≥1, respectively). Tables for all models are found in Appendix C. An odds ratio plot was created from the resulting model to more conveniently identify significant covariates.

In the first model of uHTN (Figure 18), the only factor significantly associated with higher odds of uHTN was race (other), with OR 3.2 [95% CI 1.2-8.0, p=0.01]. Current use of diuretics and RAASi was associated with significantly lower odds of uHTN, with OR 0.12 [95% CI: 0.015-0.712, p=0.03], and OR 0.05 [95% CI: 0.04-0.32, p<0.01]. All other covariates were not found to be associated with uHTN. Regarding cRDI, with each increase in tertile, the odds of having uHTN increased by 1.2 times (95% CI: 0.75-1.9, p=0.45).

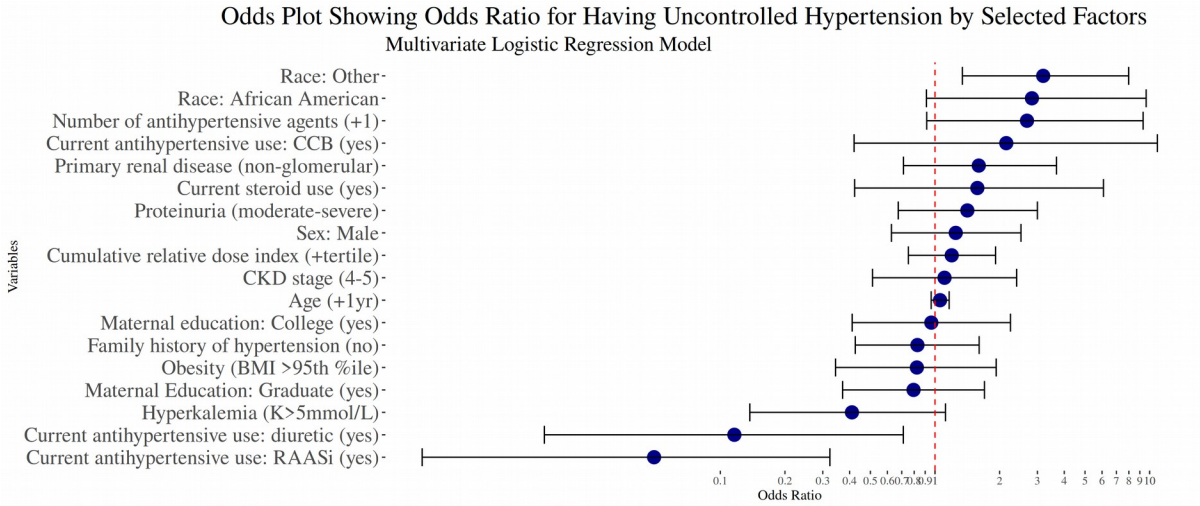

Figure 18: Odds ratio plot from multivariate logistic regression model of uncontrolled hypertension Error bars denote 95% confidence intervals for odds ratio. Reference categories for variables: Race – Caucasian, Current antihypertensive use – non-use, Primary renal disease - glomerular, Current steroid use – no, Proteinuria – normal-mild (urine protein:creatinine <1), Sex – female, CKD stage – stage 1-3, Family history of hypertension – yes, Obesity – non-obese, Hyperkalemia – no; For numeric variables (ie, number of antihypertensive agents, cumulative relative dose index tertile, age), the unit of increment is in parentheses.

For left ventricular hypertrophy (LVH), in the multivariate logistic regression model (Figure 19), odds of having LVH were significantly higher among African Americans (OR 4.06, 95% CI: 1.0-16.0, p=0.04). Male sex was associated with significantly lower odds of LVH (OR 0.22, 95% CI: 0.07-0.67, p=0.01). Having non-African American and non-

Caucasian race was also marginally associated with lower odds of LVH (OR 0.17, 95% CI: 0.01-0.99, p=0.1). The other covariates in the model were not significantly associated with LVH.

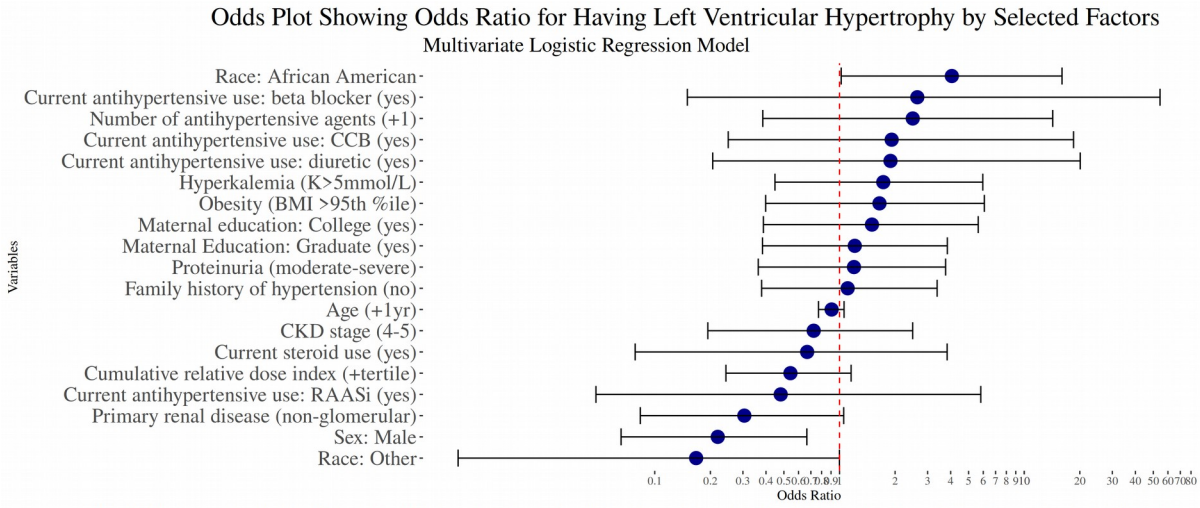

Figure 19: Odds plot for multivariate logistic regression of left ventricular hypertrophy. Error bars represent 95% confidence intervals for odds ratio. Refer to figure 18 for reference categories and increments used

Since number of agents was found to have a VIF above the cutoff in models for the left ventricular hypertrophy model (6.3), and was close to the cutoff for uncontrolled hypertension model (3.6) updated models were created for all dichotomous outcomes excluding number of agents. Therefore as part of a sensitivity analysis, the model was recreated with the exclusion of number of agents (Figure 20). In the updated model (Figure 14), in addition to the same factors previously noted, current use of diuretics (OR 4.6, 95% CI:1.1-21), CCB (OR 4.4, 95% CI: 1.1-20) and BB (OR 8.0 , 95% CI: 1.1-62) were found to be significantly associated with higher odds of LVH ($p<0.05$ for all OR). Regarding cRDI,

for every increase in tertile, the odds of LVH decreased by 0.59 times (95% CI: 0.07-3.2, p=0.17).

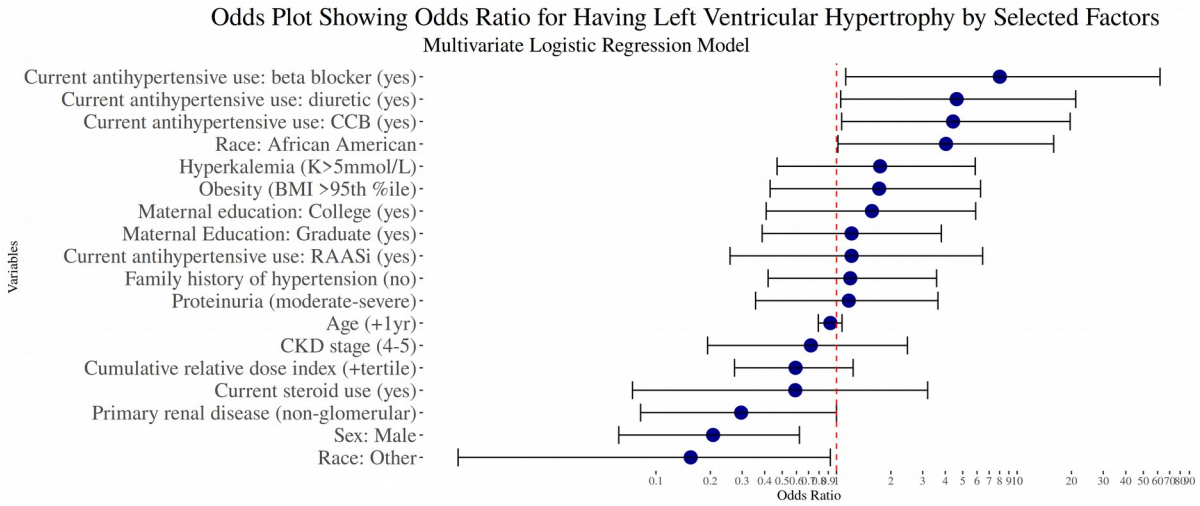

Figure 20: Logistic regression adjusted odds ratios for left ventricular hypertrophy after removing number of antihypertensive agents due to multicollinearity
Error bars represent 95% confidence intervals for odds ratios. Refer to figure 18 for reference categories and increments.

CHAPTER 5

DISCUSSION

Impact of updated BP classification on hypertension diagnosis and treatment

This is the first study of the CKiD cohort using updated blood pressure percentiles and classification scheme from the 2017 American Academy of Pediatrics guidelines. As seen in Figure 9, while the majority of children retained their classification with the new guidelines, there were significant proportions of subjects who received a more severe classification. For example, of 11 children classified with stage 2 hypertension based on AAP 2017 guidelines, 4 of these would be classified as stage 1 hypertension using Fourth Report guidelines. This pattern of increased severity of classification was apparent for both casual BP classification and ABPM classification. At this time, it is difficult to predict the impact this will have on long-term kidney and cardiovascular outcomes, however the use of the updated hypertension classification is likely to result in improved identification of hypertensive children and therefore may potentially reduce undertreatment.

Results of this study in context with previous research

In both the univariate and multivariate analyses, RAASi use was found to be associated with lower odds of uncontrolled hypertension (uHTN). African American race was

also found to be associated with higher odds of uHTN (univariate analysis) as well as LVH. The findings regarding hypertension are consistent with Flynn et al (2008)[44], and given the known benefits of RAASi in delaying CKD progression and reducing proteinuria, as well as the evidence supporting their ability to promote cardiac remodeling in both animal models and clinical studies[68], these findings would support their continued use in treating hypertension, and potentially reducing the risk of LVH in children with CKD. Due to their increased risk for CKD progression[3], African Americans with CKD and hypertension are particularly vulnerable for poor cardiovascular and renal outcomes and as such, Flynn et al. (2008) have identified this particular subpopulation as a "top priority of CKD care providers [worthy of] aggressive BP control"[44].

In addition to these factors, taking more than one antihypertensive agent was found to be a risk factor for uHTN as well as LVH (univariate analysis). In Flynn et al (2008), the use of 2 or more antihypertensive agents tended to be associated with uncontrolled HTN, however did not reach statistical significance. One explanation is that the number of antihypertensive agents is potentially a marker of disease severity, and considering that RAASi could potentially be used in non-hypertensive proteinuric kidney disease, as a means of delaying CKD progression, the use of additional antihypertensive agents could be a more sensitive marker for hypertension than use of RAASi alone. This may also explain why non-RAASi classes of antihypertensive medications (CCB) were associated with higher unadjusted odds of uHTN as well as LVH (CCB, BB and diuretics). It is also consistent with

Kupferman et al (2014) who found that other antihypertensive classes (non-RAASi) were associated with LVH in this population.

The use of diuretics was associated with lower adjusted odds of uncontrolled HTN. This is in contrast to their association, along with BB and CCBs, with higher odds of LVH, and which has not been previously reported. The significance of this finding is unclear, although may be worth considering as combining ACE-inhibitors with diuretics in adults patients with diabetic nephropathy showed a particular benefit in reducing proteinuria than with other medication combinations[69].

Also regarding race, whereas African Americans were at higher risk for uHTN and LVH, other non-Caucasian races (Asian, American Indian and Native Hawaiian, multiracial) were at higher risk of uHTN but *lower risk* of LVH when compared with Caucasians. The significance of this relationship is also unclear.

Regarding LVH and consistent with previous findings in this pediatric CKD population, females were at higher risk of LVH when adjusted for other covariates in the model (Figure 19).

Effect of cumulative relative dose index

The major significance of this study is in the novelty of the cRDI as a tool in the quantitative analysis of dose and its effect on blood pressure control and left ventricular hypertrophy in the pediatric CKD population. Our hypothesis that antihypertensive dose would be positively associated with controlled hypertension and absence of LVH was not

confirmed in this study. cRDI was not significantly associated with either outcome in both the primary and secondary analysis, even when number of agents was removed from the multivariate model in a sensitivity analysis (Figure 20). When uncontrolled hypertension was subdivided into masked and ambulatory hypertension, however, there was a significant rising trend in dose (expressed as log-transformed cRDI) with masked and ambulatory hypertension, respectively, compared with controlled hypertension (Figure 13).

Furthermore, from Tables 7 and 8, higher doses were associated with uncontrolled HTN and LVH when looking only at subjects with 3 and 2 antihypertensive agents in isolation. Although the low number of subjects in the strata limits the overall impact of these results, they were in the opposite direction from our hypothesis and could suggest that as with number of antihypertensive agents, cRDI may be considered a marker of disease severity. In other words, with hypertension, patients may be more likely to take higher doses of medication. In light of the distribution of cRDI in the study population, which demonstrates that most subjects were taking considerably less than their maximum potential dose (Figure 10), we therefore cannot exclude the possibility that with higher doses, subjects would have improved blood pressure control.

Differences between DDD defined by WHO and RDI

The RDI measure differs from the defined daily dose (DDD) as defined by the WHO in several ways. Firstly, unlike the DDD which uses a standard dose for the entire population, cRDI was developed specifically for children where individualized weight-based dosing is

often used to prescribe doses. Secondly, the DDD was designed to evaluate drug utilization among a population over time in epidemiological studies, whereas the cRDI is designed to quantify drug dose in terms of effect, by using maximum dose as the denominator. Finally, renal dose adjustments are accounted for in the cRDI by adjusting the maximum dose according to each individual child's eGFR and specific medications which require adjustments based on GFR. For these reasons, cRDI is a new concept that has not previously been applied, and results from this study will require validation in future studies. If validated, cRDI may have potential use in other fields of research as a means of performing a quantitative analysis of drug dose when multiple drug classes or medications are used to treat a single condition.

Study limitations

There were several limitations in this study:

1. Study population size – Firstly, the statistical power of the analysis was limited by the study size of 240 eligible participants, with a relatively large number of potential covariates. At the time of obtaining access to the CKiD data from the NIDDK central data repository, 651 subjects were present at the third visit. The current data is likely to include a larger number of participants which could increase the statistical power of the study. The exclusion criteria were necessary to maintain validity of the data and answer the research question. Subjects required an ABPM in order to classify their blood pressure status, drug doses were needed to calculate RDI, etc.

2. Retrospective cross-sectional study design – Since the study design was a retrospective cross-sectional analysis at one time point in the CKiD cohort, association rather than cause-and-effect are being analyzed. Data that was collected at time points beyond a 3-month time span could compromise the validity of the analysis. One way to include more data and increase statistical power would be to extend the study to follow participants over multiple visits using a mixed effects generalized linear model. A longitudinal analysis was beyond the scope of this research project, however the current dataset does include data from up to 10 visits or 9 years of follow-up, leaving an opportunity for future investigation open.
3. Definition of hypertension – The definition of hypertension in this study was limited to a single casual BP measurement, whereas clinical guidelines recommend repeated measurements taken over several weeks in order to confirm the diagnosis of hypertension[39]. In addition, we did not focus on subjects who were not taking antihypertensive medications. In Table 3, we summarized the blood pressure status and left ventricular hypertrophy status of these patients not taking antihypertensive agents at the third visit, and found that a significant portion of these subjects are indeed hypertensive (63%) and had LVH (20%). Although Mitsnefes et al (2003) found lower proportions of children with CKD and untreated hypertension in the NAPRTCS database, their group did not have ABPM studies available and therefore did not take into consideration those with masked hypertension. Regardless, these findings point towards a clinical need to diagnose and treat these particularly high-

risk children in order to reduce their increased rate of CKD progression and higher risk of cardiovascular comorbidities.

4. Reported medication use – Since the medication history was obtained from self-reported or parent-reported questionnaires with the help of a trained interviewer, the possibility of medication non-adherence as well as incorrect dose reporting is a potential limitation. About 86% of participants did not answer the question about frequency of antihypertensive medication non-adherence at the third visit. Of those who did, about 83% did report some degree of non-adherence or missed medications per week. As a result, while acknowledging this factor as a potential limitation that could impact our results, we did not consider it further in analysis.
5. Standard dose references – The relative dose index is based on dose references from articles related to treatment of hypertension in children published in peer-reviewed journals and a commonly used clinical medication reference tool, Lexicomp[17,66,67]. Dosing guidelines for antihypertensive medications in children is limited due to the low rate of FDA-approval of drugs in pediatric hypertension. Although the number of clinical drug trials is increasing over time, between 2000 and 2010, only 11 antihypertensive medications received FDA approval for children. Although there is a possibility of prescribers using dose references that do not match the ones used in this study, this would not be expected to change the underlying effect of that dose, whatever it may be, on blood pressure. Secondly, we used dose references that would

be expected to be widely followed by prescribers, in order to minimize the influence of this factor on the analysis.

APPENDIX

A. Dose reference table used for calculation of relative dose index

Drug	Class	max (mg/kg)	max (mg)	Renal dose adjustment **	Source
Lisinopril	ACEi	0.6	40	50% if GFR 10-50 25% if GFR<10	Chu PY et al.
Benazepril	ACEi	0.6	40		Chu PY et al.
Enalapril	ACEi	0.58	40	75% if GFR 10-50 50% if GFR<10	Chu PY et al.
Fosinopril	ACEi	0.6	40		Chu PY et al.
Ramipril	ACEi	*	20		Lexicomp
Captopril	ACEi	6	450	75% if GFR 10-50 50% if GFR<10	Lexicomp
Terazosin	alpha-1 blocker	*	20		Lexicomp
Clonidine	alpha-2 agonist	*	2.4		
Guanfacine	alpha-2 agonist	*	2		Lexicomp
Candesartan	ARB	0.4	32		Chu PY et al.
Losartan	ARB	1.4	100		Chu PY et al.
Valsartan	ARB	2.7	160		Chu PY et al.
Olmesartan	ARB	†	40		Lexicomp
Atenolol	BB	2	100		Chu PY et al.
Propranolol	BB	4	640		Chu PY et al.
Labetalol	BB	12	1200		Lexicomp
Metoprolol	BB	6	200		Misurac et al.
Amlodipine	CCB	0.6	10		Chu PY et al.
Nifedipine	CCB	3	120		Chu PY et al.
Diltiazem	CCB	6	360		Lexicomp
Felodipine	CCB	*	10		Lexicomp
Furosemide	diuretic	18	80		Lexicomp
Hydrochlorothiazide	diuretic	3	50		Chu PY et al.
Chlorothiazide	diuretic	40	2000		Misurac et al.
Amiloride	Na-channel blocker	0.625	20		Lexicomp
Hydralazine	vasodilator	7.5	200		Misurac et al.

* Maximum dose in mg/kg unavailable

**GFR expressed in units mL/min/1.73m^2

† Weight-based dosing for olmesartan: 5-20kg: max = 0.6mg/kg/day, 20-35kg: max=20mg/day, >35kg: max=40mg/day.

Abbreviations: ACEi angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker (ACEi and ARB are collectively referred to as renin-angiotensin-aldosterone system inhibitors, RAASi), BB beta-blocker, CCB calcium channel blocker.

B. Descriptive summary of study population by outcomes

Table B1: Controlled vs. uncontrolled hypertension

Descriptive Statistics	Overall (N = 240)	Controlled Hypertension (n = 107)	Uncontrolled Hypertension (n = 133)	P-value†	OR** [95% CI]
Age (years)					
mean ± sd	12.80 ± 3.68	12.54 ± 3.48	13.01 ± 3.83	0.23	
Sex, n (%)					
Male	142 (59%)	61 (57%)	81 (61%)	0.63	
Female	98 (41%)	46 (43%)	52 (39%)		
Race, n (%)					
Caucasian	164 (68%)	84 (79%)	80 (60%)	0.0074	
African American	25 (10%)	6 (6%)	19 (14%)		3.33 [1.26,8.75]
Other	51 (21%)	17 (16%)	34 (26%)		2.10 [1.09,4.05]
Maternal education*, n (%)					
High school or less	95 (41%)	38 (37%)	57 (45%)	0.33	
Some college	58 (25%)	26 (25%)	32 (25%)		
College graduate	78/231 (34%)	40/104 (38%)	38/127 (30%)		
CKD onset* (years before study entry)					
n, mean ± sd	235; -8.28 ± 4.79	106; -8.35 ± 4.57	129; -8.22 ± 4.98	0.75	
CKD diagnosis, n (%)					
Non-glomerular	154 (64%)	67 (63%)	87 (65%)	0.75	
Glomerular	86 (36%)	40 (37%)	46 (35%)		
Proteinuria (Urine protein:creatinine ratio)					
Normal (<0.5)	132 (55%)	65 (61%)	67 (50%)	0.041	
Mild [0.5-1.0)	34 (14%)	16 (15%)	18 (14%)		1.09 [0.51,2.32]
Moderate [1.0-2.0)	46 (19%)	19 (18%)	27 (20%)		1.38 [0.70,2.72]
Severe (>2.0)	28 (12%)	7 (7%)	21 (16%)		2.91 [1.16,7.31]
Normal-Mild (<1.0)	166 (69%)	81 (76%)	85 (64%)	0.05	
Moderate-Severe (>1.0)	74 (31%)	26 (24%)	48 (36%)		1.76 [1.00,3.10]
mean ± sd	0.96 ± 1.48	0.87 ± 1.66	1.03 ± 1.32	0.09	
BMI z-score					
<95th %-ile (non-obese)	197 (82%)	88 (82%)	109 (82%)	0.57	
>= 95th %-ile (obese)	43 (18%)	19 (18%)	24 (18%)		
mean ± sd	0.43 ± 1.15	0.37 ± 1.15	0.48 ± 1.15	1	
Estimated GFR					
mean ± sd	51.81 ± 21.11	51.61 ± 21.07	51.97 ± 21.23	0.82	
CKD stage					
1	1 (0%)	0 (0%)	1 (1%)	0.43	
2	32 (13%)	13 (12%)	19 (14%)		
3	135 (56%)	60 (56%)	75 (56%)		

Table B1 (continued)

Descriptive Statistics	Overall (N = 240)	Controlled Hypertension (n = 107)	Uncontrolled Hypertension (n = 133)	P-value†	OR** [95% CI]
4	59 (25%)	27 (25%)	32 (24%)		
5	13 (5%)	7 (7%)	6 (5%)		
Hyperkalemia* (K+ > 5 mmol/L), n (%)					
No	203 (86%)	86 (82%)	117 (89%)	0.15	
Yes	33/236 (14%)	19/105 (18%)	14/131 (11%)		0.54 [0.26,1.14]
Family history of hypertension*, n (%)					
Yes	94 (44%)	43 (43%)	51 (44%)	1	
No	121/215 (56%)	56/99 (57%)	65/116 (56%)		
Number of antihypertensive agents					
1	190 (79%)	93 (87%)	97 (73%)	0.0081	
2	39 (16%)	11 (10%)	28 (21%)		2.44 [1.15,5.18]
3	8 (3%)	3 (3%)	5 (4%)		1.60 [0.37,6.88]
4	3 (1%)	0 (0%)	3 (2%)		+
mean ± sd	1.27 ± 0.58	1.16 ± 0.44	1.35 ± 0.67	0.0081	
Cumulative Relative Dose Index (tertiles & mean)					
1st tertile (low dose)	80 (33%)	39 (36%)	41 (31%)	0.11	
2nd tertile (moderate dose)	80 (33%)	39 (36%)	41 (31%)		1.00 [0.54,1.86]
3rd tertile (high dose)	80 (33%)	29 (27%)	51 (38%)		1.67 [0.89,3.15]
mean ± sd	0.57 ± 0.55	0.52 ± 0.55	0.62 ± 0.54	0.2	
Mean Relative Dose Index					
mean ± sd	0.43 ± 0.29	0.42 ± 0.29	0.43 ± 0.30	0.82	
Current Steroids Use, n (%)					
No	220 (92%)	100 (93%)	120 (90%)	0.51	
Yes	20 (8%)	7 (7%)	13 (10%)		
Antihypertensive Drug Class Use, n (%)					
Renin-Angiotensin System Inhibitor	209 (87%)	105 (98%)	104 (78%)	<0.001	0.07 [0.02,0.29]
Calcium Channel Blocker	44 (18%)	6 (6%)	38 (29%)	<0.001	6.73 [2.72,16.65]
Diuretic	20 (8%)	8 (7%)	12 (9%)	0.84	
Beta-blocker	12 (5%)	0 (0%)	12 (9%)	0.0039	+
Other	9 (4%)	0 (0%)	9 (7%)		

* denotes missing values; please refer to denominator referring to total of known values

† P-values based on Chi-squared goodness-of-fit test for categorical factors (ie, sex, race, CKD diagnosis, obesity, hyperkalemia, family history of hypertension, steroid use, antihypertensive drug class use), Mann-Whitney U test for numerical or ordered factors (ie, age, maternal education, CKD onset, proteinuria, BMI z-score, estimated GFR, CKD stage, number of antihypertensive agents, cumulative relative dose index tertile, mean relative dose index)

** Unadjusted odds ratios calculated for selected factors with p-values <0.2, + symbol denotes invalid odds ratio due to occurrence of zero values

Table B2: Controlled vs. masked vs. ambulatory hypertension

Descriptive Statistics	Overall (N = 240)	Controlled Hypertension (n = 107)	Masked Hypertension (n = 91)	Ambulatory Hypertension (n = 42)	P-value†
Age (years)					
mean ± sd	12.80 ± 3.68	12.54 ± 3.48	13.13 ± 3.70	12.76 ± 4.14	0.44
Sex, n (%)					
Male	142 (59%)	61 (57%)	56 (62%)	25 (60%)	0.81
Female	98 (41%)	46 (43%)	35 (38%)	17 (40%)	
Race, n (%)					
Caucasian	164 (68%)	84 (79%)	52 (57%)	28 (67%)	0.012
African American	25 (10%)	6 (6%)	12 (13%)	7 (17%)	
Other	51 (21%)	17 (16%)	27 (30%)	7 (17%)	
Maternal education*, n (%)					
High school or less	95 (41%)	38 (37%)	38 (44%)	19 (48%)	0.58
Some college	58 (25%)	26 (25%)	21 (24%)	11 (28%)	
College graduate	78/231 (34%)	40/104 (38%)	28/87 (32%)	10/40 (25%)	
CKD onset* (years before study entry)					
n, mean ± sd	235; -8.28 ± 4.79	106; -8.35 ± 4.57	88; -8.15 ± 5.00	41; -8.38 ± 4.99	0.93
CKD diagnosis, n (%)					
Non-glomerular	154 (64%)	67 (63%)	62 (68%)	25 (60%)	0.57
Glomerular	86 (36%)	40 (37%)	29 (32%)	17 (40%)	
Proteinuria (Urine protein:creatinine ratio)					
Normal (<0.5)	132 (55%)	65 (61%)	48 (53%)	19 (45%)	0.056
Mild [0.5-1.0)	34 (14%)	16 (15%)	14 (15%)	4 (10%)	
Moderate [1.0-2.0)	46 (19%)	19 (18%)	17 (19%)	10 (24%)	
Severe (>2.0)	28 (12%)	7 (7%)	12 (13%)	9 (21%)	
Normal-Mild (<1.0)	166 (69%)	81 (76%)	62 (68%)	23 (55%)	0.044
Moderate-Severe (>1.0)	74 (31%)	26 (24%)	29 (32%)	19 (45%)	
mean ± sd	0.96 ± 1.48	0.87 ± 1.66	0.84 ± 0.96	1.45 ± 1.81	0.12
BMI z-score					
<95th %-ile (non-obese)	197 (82%)	88 (82%)	74 (81%)	35 (83%)	0.47
>= 95th %-ile (obese)	43 (18%)	19 (18%)	17 (19%)	7 (17%)	
mean ± sd	0.43 ± 1.15	0.37 ± 1.15	0.55 ± 1.17	0.33 ± 1.13	0.96
Estimated GFR					
mean ± sd	51.81 ± 21.11	51.61 ± 21.07	55.01 ± 19.09	45.38 ± 24.19	0.011
CKD stage					
1	1 (0%)	0 (0%)	0 (0%)	1 (2%)	0.017
2	32 (13%)	13 (12%)	7 (8%)	12 (29%)	

Table B2 (continued)

Descriptive Statistics	Overall (N = 240)	Controlled Hypertension (n = 107)	Masked Hypertension (n = 91)	Ambulatory Hypertension (n = 42)	P-value†
3	135 (56%)	60 (56%)	54 (59%)	21 (50%)	
4	59 (25%)	27 (25%)	27 (30%)	5 (12%)	
5	13 (5%)	7 (7%)	3 (3%)	3 (7%)	
Hyperkalemia* (K+ > 5 mmol/L), n (%)					
No	203 (86%)	86 (82%)	81 (90%)	36 (88%)	0.25
Yes	33/236 (14%)	19/105 (18%)	9/90 (10%)	5/41 (12%)	
Family history of hypertension*, n (%)					
Yes	94 (44%)	43 (43%)	39 (49%)	12 (33%)	0.3
No	121/215 (56%)	56/99 (57%)	41/80 (51%)	24/36 (67%)	
Number of antihypertensive agents					
1	190 (79%)	93 (87%)	71 (78%)	26 (62%)	0.0018
2	39 (16%)	11 (10%)	18 (20%)	10 (24%)	
3	8 (3%)	3 (3%)	2 (2%)	3 (7%)	
4	3 (1%)	0 (0%)	0 (0%)	3 (7%)	
mean ± sd	1.27 ± 0.58	1.16 ± 0.44	1.24 ± 0.48	1.60 ± 0.91	0.0018
Cumulative Relative Dose Index (tertiles & mean)					
1st tertile (low dose)	80 (33%)	39 (36%)	35 (38%)	6 (14%)	0.0039
2nd tertile (moderate dose)	80 (33%)	39 (36%)	27 (30%)	14 (33%)	
3rd tertile (high dose)	80 (33%)	29 (27%)	29 (32%)	22 (52%)	
mean ± sd	0.57 ± 0.55	0.52 ± 0.55	0.54 ± 0.50	0.78 ± 0.61	0.013
Mean Relative Dose Index					
mean ± sd	0.43 ± 0.29	0.42 ± 0.29	0.40 ± 0.28	0.51 ± 0.32	0.16
Current Steroids Use, n (%)					
No	220 (92%)	100 (93%)	85 (93%)	35 (83%)	0.099
Yes	20 (8%)	7 (7%)	6 (7%)	7 (17%)	
Antihypertensive Drug Class Use, n (%)					
Renin-Angiotensin System Inhibitor	209 (87%)	105 (98%)	78 (86%)	26 (62%)	<0.001
Calcium Channel Blocker	44 (18%)	6 (6%)	17 (19%)	21 (50%)	<0.001
Diuretic	20 (8%)	8 (7%)	5 (5%)	7 (17%)	0.087
Beta-blocker	12 (5%)	0 (0%)	5 (5%)	7 (17%)	<0.001
Other	9 (4%)	0 (0%)	5 (5%)	4 (10%)	

* denotes missing values; please refer to denominator referring to total of known values

† P-values based on Chi-squared goodness-of-fit test for categorical factors (ie, sex, race, CKD diagnosis, obesity, hyperkalemia, family history of hypertension, steroid use, antihypertensive drug class use), Kruskal-Wallis one-way ANOVA for numerical or ordered factors (ie, age, maternal education, CKD onset, proteinuria, BMI z-score, estimated GFR, CKD stage, number of antihypertensive agents, cumulative relative dose index tertile, mean relative dose index)

Table B3: Left ventricular hypertrophy absent vs. present

Descriptive Statistics	Overall (N = 240)	No LVH (n = 206)	LVH (n = 34)	P-value*	OR [95% CI]**
Age (years)					
mean ± sd	12.80 ± 3.68	12.93 ± 3.63	12.05 ± 3.91	0.23	
Sex, n (%)					
Male	142 (59%)	126 (61%)	16 (47%)	0.17	0.56 [0.27,1.17]
Female	98 (41%)	80 (39%)	18 (53%)		
Race, n (%)					
Caucasian	164 (68%)	141 (68%)	23 (68%)	<0.001	
African American	25 (10%)	16 (8%)	9 (26%)		3.45 [1.36,8.72]
Other	51 (21%)	49 (24%)	2 (6%)		0.25 [0.06,1.10]
Maternal education*, n (%)					
High school or less	95 (41%)	82 (41%)	13 (41%)	1	
Some college	58 (25%)	50 (25%)	8 (25%)		
College graduate	78/231 (34%)	67/199 (34%)	11/32 (34%)		
CKD onset* (years before study entry)					
n, mean ± sd	235; -8.28 ± 4.79	203; -8.56 ± 4.85	32; -6.50 ± 4.02	0.021	
CKD diagnosis, n (%)					
Non-glomerular	154 (64%)	135 (66%)	19 (56%)	0.37	
Glomerular	86 (36%)	71 (34%)	15 (44%)		
Proteinuria (Urine protein:creatinine ratio)					
Normal (<0.5)	132 (55%)	113 (55%)	19 (56%)	0.66	
Mild [0.5-1.0)	34 (14%)	31 (15%)	3 (9%)		
Moderate [1.0-2.0)	46 (19%)	41 (20%)	5 (15%)		
Severe (>2.0)	28 (12%)	21 (10%)	7 (21%)		
Normal-Mild (<1.0)	166 (69%)	144 (70%)	22 (65%)	0.55	
Moderate-Severe (>1.0)	74 (31%)	62 (30%)	12 (35%)		
mean ± sd	0.96 ± 1.48	0.93 ± 1.44	1.15 ± 1.72	0.82	
BMI z-score					
<95th %-ile (non-obese)	197 (82%)	171 (83%)	26 (76%)	0.12	
>= 95th %-ile (obese)	43 (18%)	35 (17%)	8 (24%)		1.50 [0.63,3.59]
mean ± sd	0.43 ± 1.15	0.38 ± 1.13	0.74 ± 1.25	0.5	
Estimated GFR					
mean ± sd	51.81 ± 21.11	53.12 ± 21.01	43.87 ± 20.28	0.02	
CKD stage					
1	1 (0%)	0 (0%)	1 (3%)	0.025	

Table B3 (continued)

Descriptive Statistics	Overall (N = 240)	No LVH (n = 206)	LVH (n = 34)	P-value*	OR [95% CI]**
2	32 (13%)	24 (12%)	8 (24%)		
3	135 (56%)	117 (57%)	18 (53%)		0.46 [0.18,1.18]
4	59 (25%)	52 (25%)	7 (21%)		0.40 [0.13,1.24]
5	13 (5%)	13 (6%)	0 (0%)		
Hyperkalemia* (K+ > 5 mmol/L), n (%)					
No	203 (86%)	178 (88%)	25 (76%)	0.12	
Yes	33/236 (14%)	25/203 (12%)	8/33 (24%)		2.28 [0.93,5.60]
Family history of hypertension*, n (%)					
Yes	94 (44%)	85 (46%)	9 (30%)	0.15	1.98 [0.86,4.56]
No	121/215 (56%)	100/185 (54%)	21/30 (70%)		
Number of antihypertensive agents					
1	190 (79%)	171 (83%)	19 (56%)	<0.001	
2	39 (16%)	29 (14%)	10 (29%)		3.10 [1.31,7.34]
3	8 (3%)	5 (2%)	3 (9%)		5.40 [1.20,24.39]
4	3 (1%)	1 (0%)	2 (6%)		18.00 [1.56,207.92]
mean ± sd	1.27 ± 0.58	1.20 ± 0.49	1.65 ± 0.88	<0.001	
Cumulative Relative Dose Index (tertiles & mean)					
1st tertile (low dose)	80 (33%)	72 (35%)	8 (24%)	0.26	
2nd tertile (moderate dose)	80 (33%)	67 (33%)	13 (38%)		
3rd tertile (high dose)	80 (33%)	67 (33%)	13 (38%)		
mean ± sd	0.57 ± 0.55	0.56 ± 0.55	0.63 ± 0.54	0.32	
Mean Relative Dose Index					
mean ± sd	0.43 ± 0.29	0.43 ± 0.29	0.39 ± 0.30	0.53	
Current Steroids Use, n (%)					
No	220 (92%)	190 (92%)	30 (88%)	0.66	
Yes	20 (8%)	16 (8%)	4 (12%)		
Antihypertensive Drug Class Use, n (%)					
Renin-Angiotensin System Inhibitor	209 (87%)	185 (90%)	24 (71%)	0.0048	0.27 [0.11,0.65]
Calcium Channel Blocker	44 (18%)	31 (15%)	13 (38%)	0.0027	3.49 [1.59,7.70]
Diuretic	20 (8%)	12 (6%)	8 (24%)	0.0018	4.97 [1.86,13.30]
Beta-blocker	12 (5%)	7 (3%)	5 (15%)	0.017	4.90 [1.46,16.47]
Other	9 (4%)	6 (3%)	3 (9%)		

† P-values based on Chi-squared goodness-of-fit test for categorical factors (ie, sex, race, CKD diagnosis, obesity, hyperkalemia, family history of hypertension, steroid use, antihypertensive drug class use), Mann-Whitney U test for numerical or ordered factors (ie, age, maternal education, CKD onset, proteinuria, BMI z-score, estimated GFR, CKD stage, number of antihypertensive agents, cumulative relative dose index tertile, mean relative dose index)

** Unadjusted odds ratios [with 95% confidence intervals] calculated for selected factors with p-values <0.2, + symbol denotes invalid odds ratio due to occurrence of zero values

C. Multivariate logistic regression model tables

Uncontrolled hypertension vs. Controlled hypertension	Model including number of antihypertensive agents 95% confidence interval					Model excluding number of antihypertensive agents 95% confidence interval				
Variables	Odds Ratio	lower	upper	P-value	VIF	Odds Ratio	lower	upper	P-value	VIF
Age (+1yr)	1.056	0.96	1.164	0.27	1.267	1.061	0.966	1.168	0.218	1.264
Sex: Male	1.249	0.627	2.515	0.529	1.167	1.223	0.619	2.438	0.563	1.159
Race: African American	2.829	0.912	9.63	0.08	1.12	2.718	0.888	9.157	0.089	1.119
Race: Other	3.192	1.342	7.983	0.01	1.13	3.049	1.286	7.609	0.013	1.125
Maternal education: College (yes)	0.961	0.411	2.247	0.927	1.387	1.001	0.432	2.32	0.997	1.392
Maternal Education: Graduate (yes)	0.795	0.371	1.7	0.552	1.327	0.763	0.359	1.62	0.481	1.324
Primary renal disease (non-glomerular)	1.599	0.713	3.681	0.26	1.557	1.514	0.68	3.446	0.314	1.551
Proteinuria (moderate-severe)	1.415	0.674	3	0.36	1.148	1.341	0.646	2.804	0.432	1.127
Obesity (BMI >95th %ile)	0.823	0.344	1.928	0.656	1.108	0.841	0.356	1.954	0.689	1.109
CKD stage (4-5)	1.107	0.511	2.401	0.795	1.336	1.079	0.5	2.33	0.846	1.336
Hyperkalemia (K>5mmol/L)	0.41	0.137	1.119	0.092	1.151	0.401	0.137	1.072	0.078	1.165
Family history of hypertension (no)	0.828	0.425	1.605	0.577	1.103	0.882	0.458	1.693	0.705	1.086
Number of antihypertensive agents (+1)	2.682	0.915	9.323	0.09	3.628					
Cumulative relative dose index (+tertile)	1.196	0.751	1.915	0.451	1.494	1.368	0.884	2.139	0.163	1.364
Current steroid use (yes)	1.575	0.422	6.092	0.499	1.143	1.377	0.374	5.273	0.631	1.123
Current antihypertensive use: RAASi (yes)	0.049	0.004	0.324	0.006	1.613	0.106	0.013	0.519	0.014	1.236
Current antihypertensive use: CCB (yes)	2.148	0.42	10.862	0.349	2.528	5.281	1.63	19.441	0.008	1.473
Current antihypertensive use: diuretic (yes)	0.116	0.015	0.712	0.026	2.14	0.32	0.069	1.309	0.121	1.302

Left ventricular hypertrophy present vs. Absent	Model including number of antihypertensive agents 95% confidence interval					Model excluding number of antihypertensive agents 95% confidence interval				
Variables	Odds Ratio	lower	upper	P-value	VIF	Odds Ratio	lower	upper	P-value	VIF
Age (+1yr)	0.906	0.77	1.058	0.222	1.729	0.924	0.793	1.073	0.304	1.57
Sex: Male	0.219	0.066	0.666	0.009	1.454	0.207	0.062	0.623	0.007	1.455
Race: African American	4.057	1.021	16.021	0.043	1.36	4.038	1.018	15.952	0.044	1.369
Race: Other	0.167	0.009	0.999	0.105	1.084	0.156	0.008	0.924	0.091	1.08
Maternal education: College (yes)	1.499	0.387	5.637	0.548	1.445	1.57	0.408	5.896	0.502	1.451
Maternal Education: Graduate (yes)	1.21	0.383	3.835	0.743	1.359	1.212	0.387	3.805	0.739	1.356
Primary renal disease (non-glomerular)	0.305	0.084	1.054	0.063	1.736	0.296	0.082	1	0.053	1.712
Proteinuria (moderate-severe)	1.198	0.363	3.754	0.759	1.276	1.169	0.356	3.645	0.789	1.284
Obesity (BMI >95th %ile)	1.646	0.398	6.084	0.467	1.29	1.724	0.429	6.277	0.42	1.287
CKD stage (4-5)	0.725	0.194	2.491	0.616	1.39	0.721	0.193	2.47	0.61	1.405
Hyperkalemia (K>5mmol/L)	1.726	0.447	5.968	0.402	1.206	1.743	0.468	5.864	0.382	1.203
Family history of hypertension (no)	1.107	0.379	3.377	0.853	1.195	1.192	0.418	3.582	0.746	1.162
Number of antihypertensive agents (+1)	2.492	0.384	14.267	0.313	6.314					
Cumulative relative dose index (+tertile)	0.543	0.243	1.156	0.121	1.965	0.593	0.272	1.235	0.171	1.863
Current steroid use (yes)	0.668	0.078	3.826	0.677	1.221	0.591	0.074	3.197	0.575	1.227
Current antihypertensive use: RAASi (yes)	0.481	0.048	5.821	0.546	4.01	1.211	0.257	6.445	0.814	1.839
Current antihypertensive use: CCB (yes)	1.916	0.25	18.497	0.548	4.336	4.419	1.068	19.665	0.043	2.053
Current antihypertensive use: diuretic (yes)	1.888	0.206	20.104	0.581	2.701	4.627	1.055	21.119	0.042	1.166
Current antihypertensive use: beta blocker (yes)	2.638	0.15	54.361	0.512	2.863	8.021	1.124	61.874	0.038	1.406

Note: For binary variables, reference values for odds ratios are opposite from values in parenthesesFor continuous and ordinal variables value in parentheses refers to increment for corresponding odds ratio

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VITA

Benjamin Alexander Matta was born on June 25, 1980 in Toronto, Canada. He is the eldest son of Jerry and Florence Matta, and brother of Sherri and Allyson. He attended Associated Hebrew Day Schools of Toronto from kindergarten through eighth grade and the Community Hebrew Academy of Toronto for high school. He received his Honours Bachelor of Science Degree in human biology and physiology, graduating with high distinction at the University of Toronto in 2001. During his undergraduate studies, he participated in a one-year pre-medical program at the Hebrew University of Jerusalem from 2000-2001 where he completed an independent research project on the chemical properties of protein-silicate complexes in the biotechnology laboratory under the supervisorship of Dr. Sergei Braun. Benjamin continued his studies in the field of neurosciences at the Hebrew University of Jerusalem in Israel where he performed research on mapping neuronal connectivity in Parkinson's disease in an *in vivo* rat model at the MRI laboratory using a novel intraneuronal trans-synaptic contrast agent. Ultimately his interest in medicine brought him to Haifa, Israel where he studied medicine at the Technion Israel Institute of Technology, graduating with distinction in 2011. During his medical education, he completed an independent research thesis on the effect of growth hormone on body mass index in children with idiopathic growth hormone deficiency, under the supervisorship of Dr. Yardena Tenenbaum-Rakover,

presenting his work at the national meeting of the Israel Society of Clinical Pediatrics in 2012.

In 2013, Benjamin started his pediatric residency training at Staten Island University Hospital in New York, and graduated in 2016. Following his residency, he pursued further post-graduate training as a pediatric nephrology fellow at Children's Mercy Hospital in Kansas City. He began his masters studies in bioinformatics at University of Missouri – Kansas City in 2017. Benjamin met Orit Kadosh during his time as a student in the Hebrew University of Jerusalem. They eventually got married in 2007, and they are now proud parents of 4 children, Aviya Halel, Noya Chava, Shalev Nisan and Yarden Geula.