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The Effect of Antihypertensive Dose on Blood Pressure Control in Children with Chronic Kidney Disease

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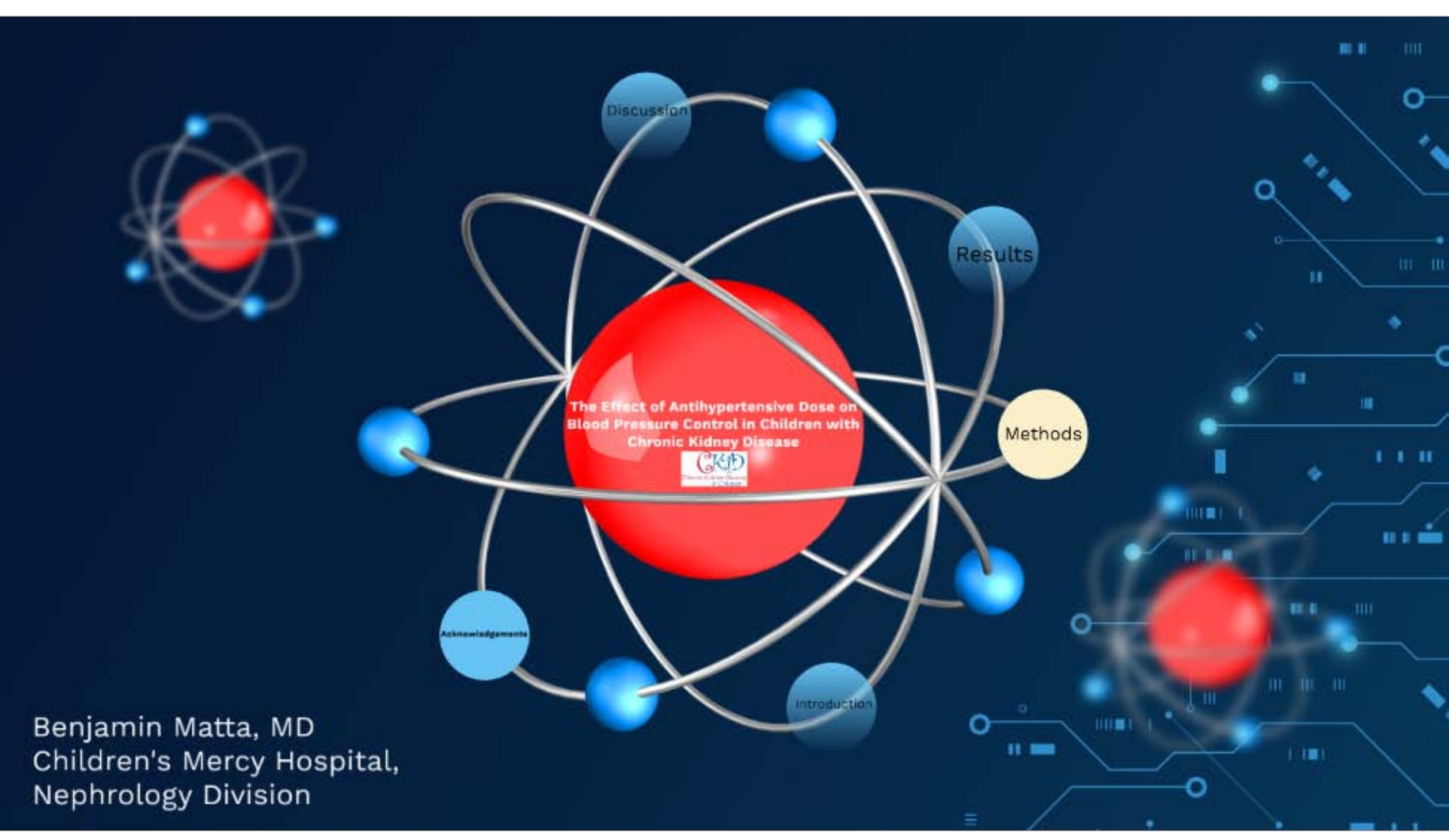

Benjamin Matta, MD
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Nephrology Division

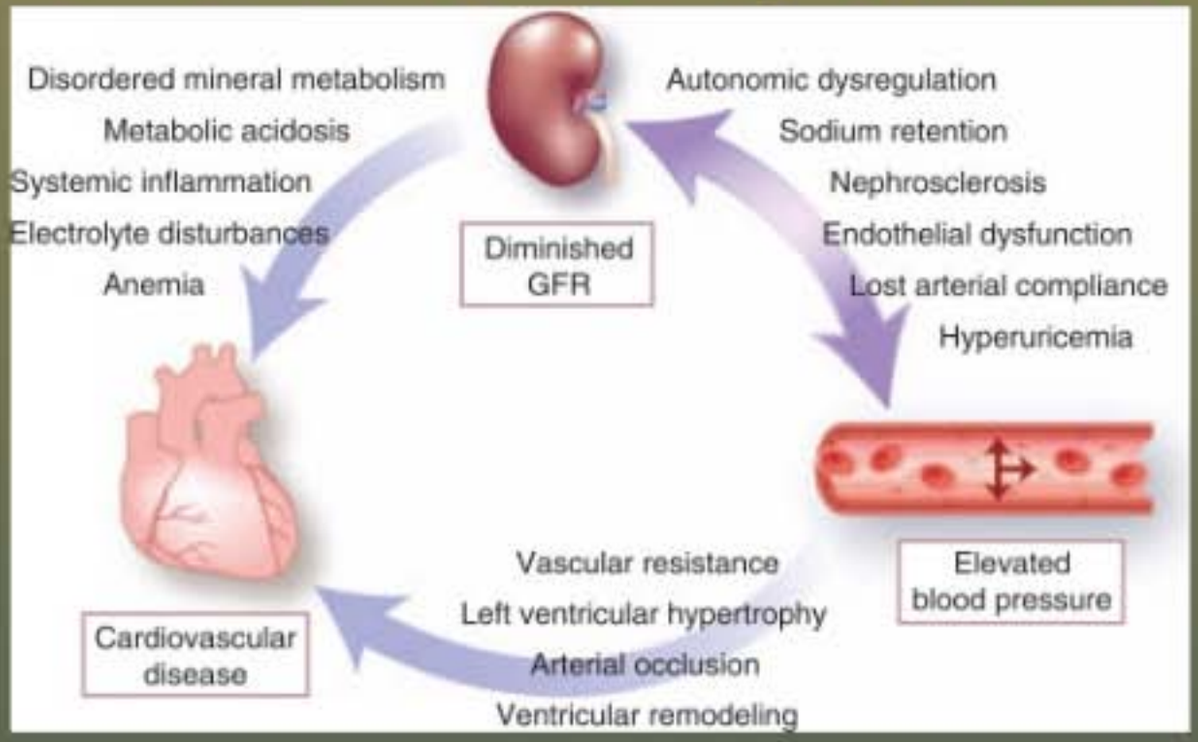
The Effect of Antihypertensive Dose on Blood Pressure Control in Children with Chronic Kidney Disease

Introduction

Hypertension in chronic kidney disease

Clinical significance of hypertension in CKD

- Highly prevalent and strong risk factor for poor cardiovascular and renal outcomes in adults and children with chronic kidney disease (CKD)



Middleton JP, Pun PH: Kidney International 77: 753–755, 2010

Opportunity for Improvement

Despite advances in understanding, challenges remain

- Barletta et al (2017): Period analysis of CKiD cohort to determine trends in hypertension over time
  - Prevalence of hypertension (63% vs 51%), especially masked hypertension increased (49% vs 36%)

Conclusion:
Hypertension may be **undertreated** in children with chronic kidney disease

CKiD
Chronic Kidney Disease in Children

- NIH-funded multicenter North American prospective cohort study

Enrollment criteria:
- age 1-16yrs
- eGFR 30-90mL/min/1.73m2

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Conclusion:

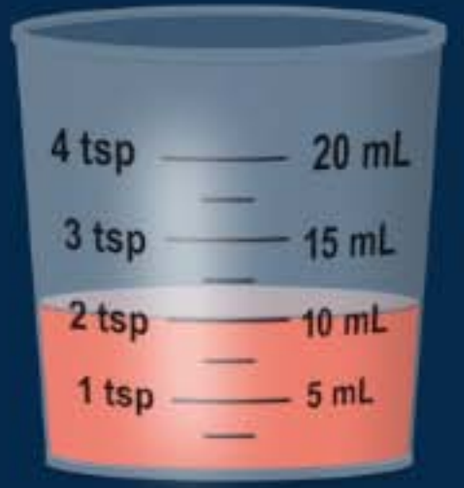
Hypertension may be **undertreated** in children with chronic kidney disease

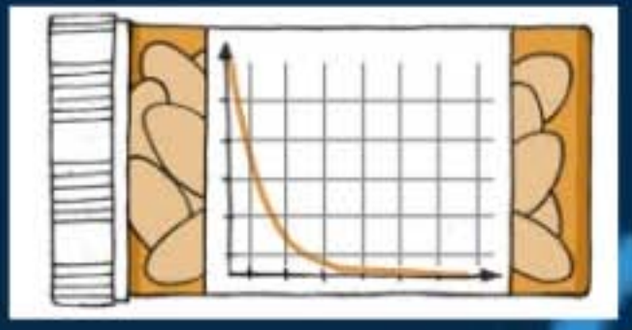
Objective: To determine the effect of antihypertensive dosing on blood pressure control in children with chronic kidney disease

Hypothesis: Children with **uncontrolled hypertension** are more likely to be on **lower doses** of medication compared to those with controlled hypertension

Challenges in quantitative analysis of dose

- Several medications are used to treat hypertension in children
- Medication dosing in children is complicated
- Renal dosing in ACEi/ARBs
- Many children require more than one antihypertensive medication





Drug Dose Index:
A quantitative tool to analyze drug dosing

Medication dose as a proportion of maximum potential dose:

$$\textbf{Drug Dose Index (max of 1)} = \frac{\textbf{Current dose (mg or mg/kg)}}{\textbf{Maximum dose}}$$

DDI Example

Cumulative DDI (cDDI) is the sum of DDI for each antihypertensive medicaiton

Example DDI calculations

Child A (30kg)

5mg amlodipine qD
(max daily dose: 10mg)

Child B (40kg)

20 mg lisinopril qD
(max daily dose: 40mg)

DDI = 0.5

Methods

Study design: Observational cross-sectional analysis at third visit

CKiD
Chronic Kidney Disease in Children

CKiD enrollment criteria:
- eGFR 30-90mL/min/1.73m2
- Ages 1-16yrs at time of enrollment

Ethics:
- Public access request via NIDDK application process
- IRB approval (ID: 18010022)
- no conflict of interest

Outcomes

Study population

Study variables

Primary Outcome

Classification of hypertension

24-hour ambulatory blood pressure monitoring study

24h ABPM study

clinic BP		Normal	Elevated
	Normal	Normotension (NL)	Masked hypertension (MH)
	Elevated	White-coat hypertension	Ambulatory hypertension (AH)

Controlled hypertension = NL
Uncontrolled hypertension = MH and AH

Secondary outcome

Secondary Outcome

Left ventricular hypertrophy (LVH)

- LVMI > 38g/m2 on echocardiogram

Study population

Inclusion criteria

- Enrolled in CKiD study:
  - eGFR 30-90mL/min/1.73m2
  - ages 1-16yrs at time of enrollment
- Taking at least one antihypertensive medication (hypertensive) (65%)
- Successful 24h ABPM (69%)
- Echocardiogram (100%)

N=255

Predictors included in analysis

Sociodemographic factors

- Age (years)
- Gender (Male/female)
- Race (Caucasian/non-Caucasian)
- Maternal education

Clinical factors

- Underlying CKD diagnosis (glomerular/non-glomerular)
- Time of CKD onset (years)
- Proteinuria severity (urine Pro:Cr ratio)
- estimated GFR
- BMI z-score

Pharmacological factors

- Currently taking steroids (yes/no)
- Number of antihypertensive drugs
- Antihypertensive drug class (RAASi/ CCB/Diuretic/Beta-blocker/other)
- **Cumulative Drug Dose Index**

Results
Primary Outcome
Secondary Outcome
Cumulative DDI
Multivariate Analysis

Primary outcome

Factors associated with uncontrolled hypertension

Predictor	P-value *
Non-Caucasian race	0.027
Higher number of antihypertensive agents	0.048
Drug class	
Absence of RAASi	<0.0001
Taking CCB	<0.0001
Taking BB	0.003
Cumulative DDI	0.14

* categorical variables: chi-square test
continuous variables: t-test

Secondary outcome

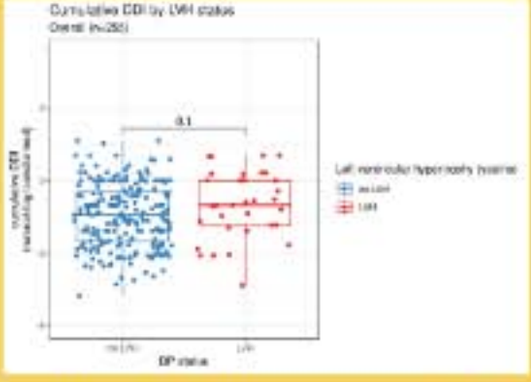
Factors associated with left ventricular hypertrophy

Predictor	P-value *
Longer CKD duration (yrs)	0.027
Lower estimated GFR (mL/min/1.73m2)	0.006
Higher number of antihypertensive agents	<0.0001
Drug class	
Absence of RAASi	0.01
Taking CCB	0.001
Taking diuretic	0.005
Taking BB	0.003
Cumulative DDI	0.23

* categorical variables: chi-square test
continuous variables: t-test

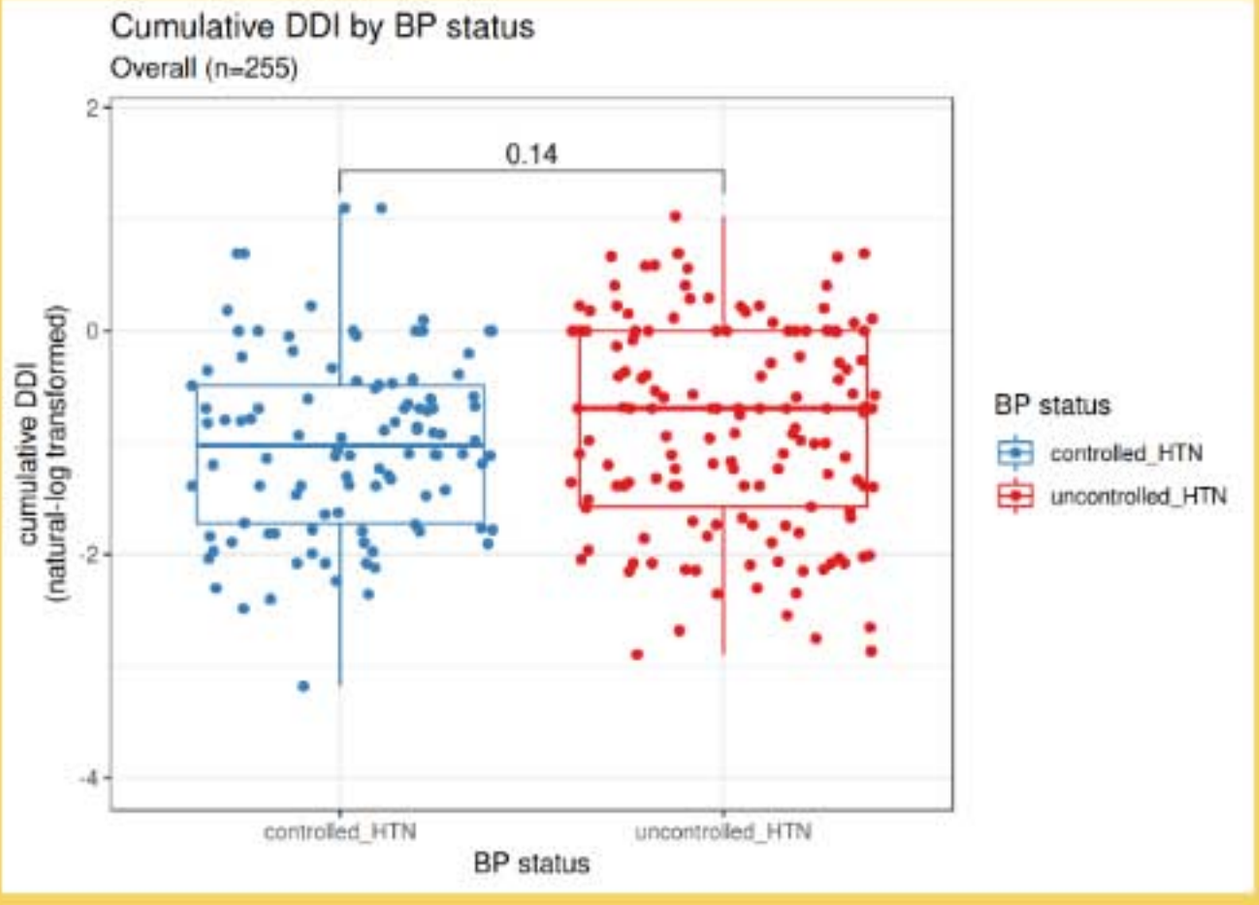
Relationship between blood pressure control and dose (cDDI)

Relationship between left ventricular hypertrophy and dose (cDDI)

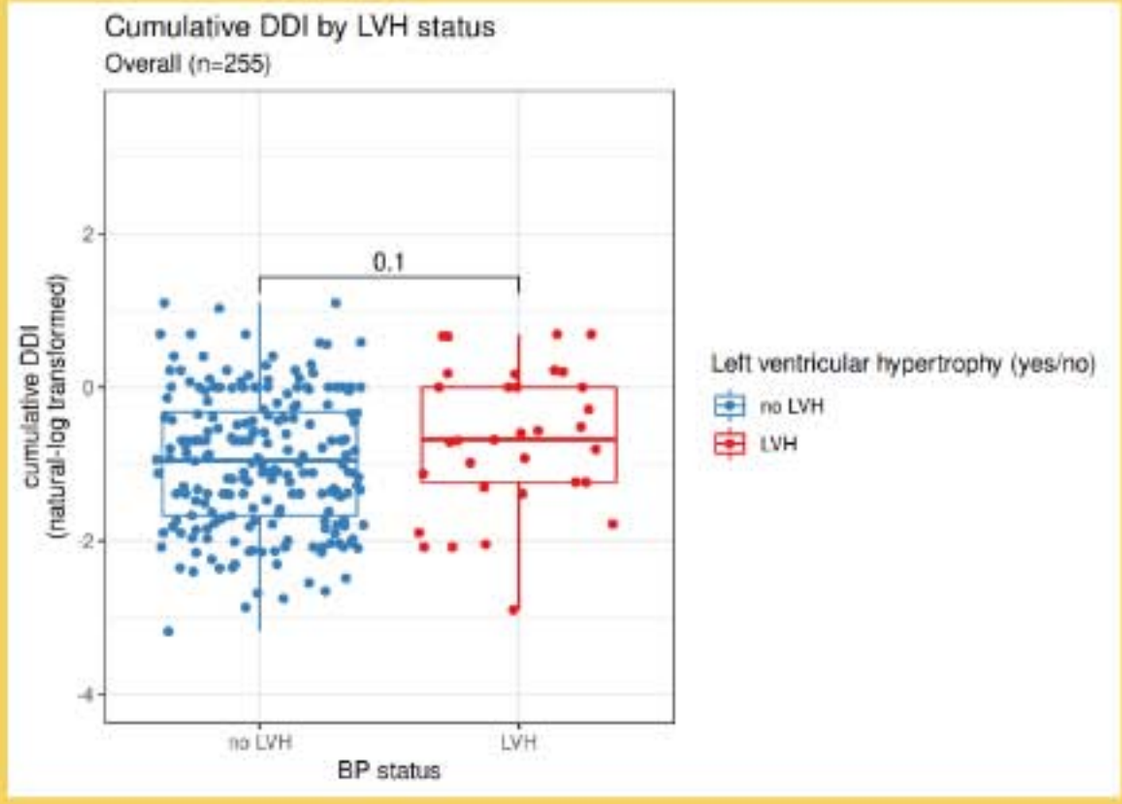


No significant differences in cDDI for other outcomes (LVH and uHTN)

Relationship between blood pressure control and dose (cDDI)



Relationship between left ventricular hypertrophy and dose (cDDI)



No significant differences in cDDI for other outcomes (LVH and uHTN)

Logistic Regression Analysis

Model 1: Predictors of Uncontrolled Hypertension

Predictor	Odds Ratio	P-value
Non-Caucasian race	2.1	0.04
Higher number of antihypertensive agents	4	0.02
Drug class		
Absence of RAASi	20	0.003
Absence of diuretic	8.3	0.03
Cumulative DDI (lower)	1.1	0.65

Model 2: LVH

Logistic Regression Analysis

Model 2: Predictors of Left Ventricular Hypertrophy

Predictor	Odds Ratio	P-value
Female gender	3.7	0.01
Higher BMI z-score	2.1	0.007
Higher number of antihypertensive agents	4.3	0.02
Lower estimated GFR	1.04	0.02
Cumulative DDI (lower)	2.02	0.06

Conclusion
Significance
Discussion

Conclusion

- Lower cumulative DDI was not associated with uncontrolled hypertension
- Trend of lower cumulative DDI associated with LVH

Significance of this study

- First quantitative analysis of antihypertensive dosing in children with chronic kidney disease
  - Implications for this study
  - Future step: Longitudinal analysis of cDDI and
    - BP control
    - LVH
    - CKD progression

- Potential uses for cDDI as analytical tool in other research:
  - hypertension, in general (adults + children)
  - any condition where multiple medications with different doses ranges are used (eg, antidepressants; antibiotics)

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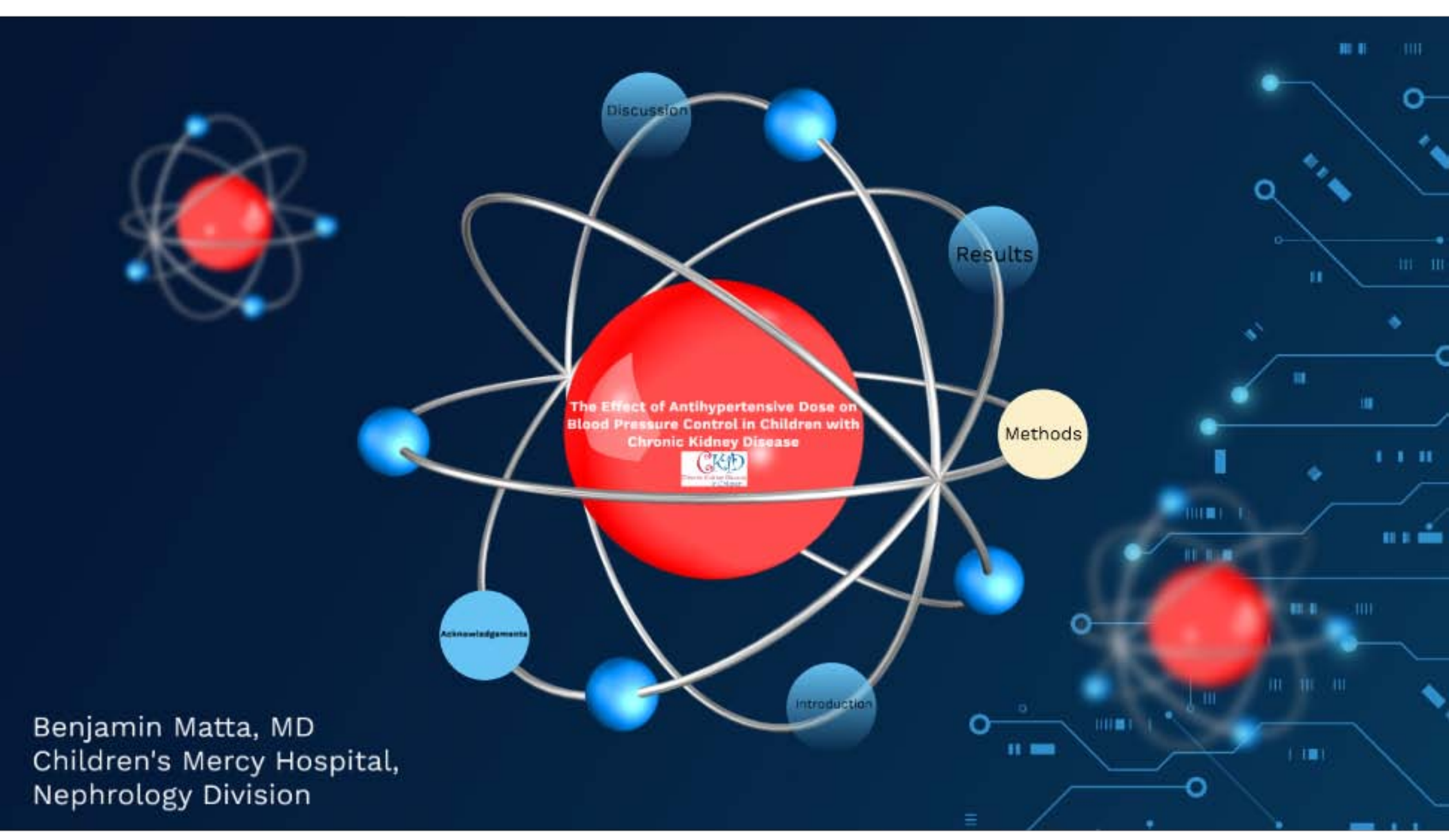

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