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The Effect of Antihypertensive Dosing on Hypertension in Children with Chronic Kidney Disease

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Background

- Hypertension (HTN) is a highly prevalent and major risk factor for poor cardiovascular and renal outcomes in chronic kidney disease (CKD).
- Previous research suggests that HTN is underdiagnosed and undertreated in children with CKD (*Hypertension* 2018;71:1-7).
- To our knowledge no studies have investigated the effect of antihypertensive dose on blood pressure control in this population.

Objective

- To determine the effect of antihypertensive dose on HTN status in children with CKD.
- Hypothesis: Uncontrolled HTN is associated with lower antihypertensive dose.

Methods

Study population: 255 participants studied in the Chronic Kidney Disease in Children (CKiD) study at their third visit.

Inclusion criteria: Age 1-16 years with estimated GFR 30-90 mL/min/1.73m^2, taking at least one antihypertensive medication, successful 24h ABPM study.

Exclusion: White-coat hypertension (n=5).

Study variables:

•**Cumulative Drug Dose Index (cDDI):** We developed a new quantitative tool, Drug Dose Index (DDI, Fig 1) 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. cDDI is the sum DDI for all antihypertensive agents taken by the subject.

•**Primary outcome:** HTN status classified into controlled HTN (cHTN) or uncontrolled HTN (uHTN = masked HTN or ambulatory HTN) based on 2017 AAP guidelines and 24h ABPM study (see Fig 3).

•**Secondary outcome:** Left ventricular hypertrophy (LVH = LVMI>38g/m^2).

Statistical analysis:

Univariate analysis: t-test and ANOVA (continuous variables) and chi-square test (categorical variables) used to compare cDDI between the outcome groups (Fig 4): a) cHTN vs. uHTN, b) cHTN, MH vs. AH, and c) LVH vs. no LVH.

Multivariate Logistic Regression Analysis:

•Two outcomes: Table 2) uHTN and Table 3) LVH.

Results

Figure 1

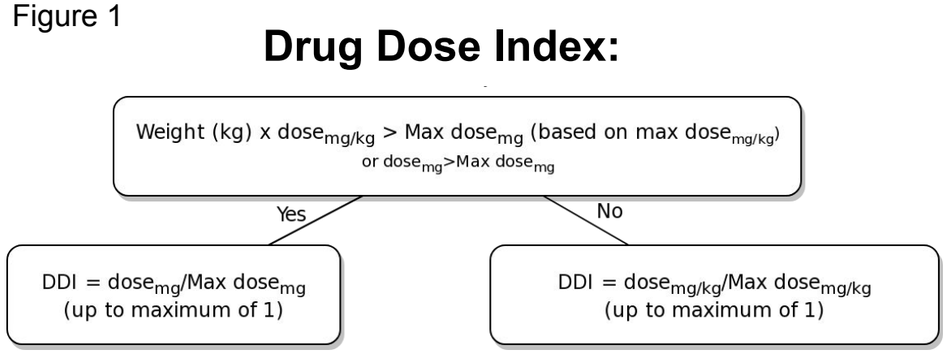


Figure 2

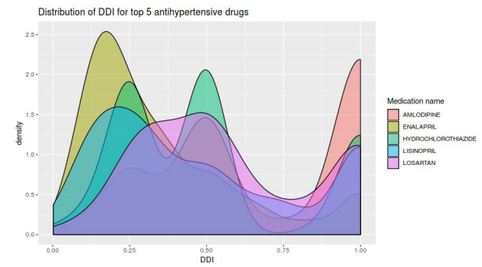


Table 1

Summary of Sociodemographic, clinical and pharmacological factors

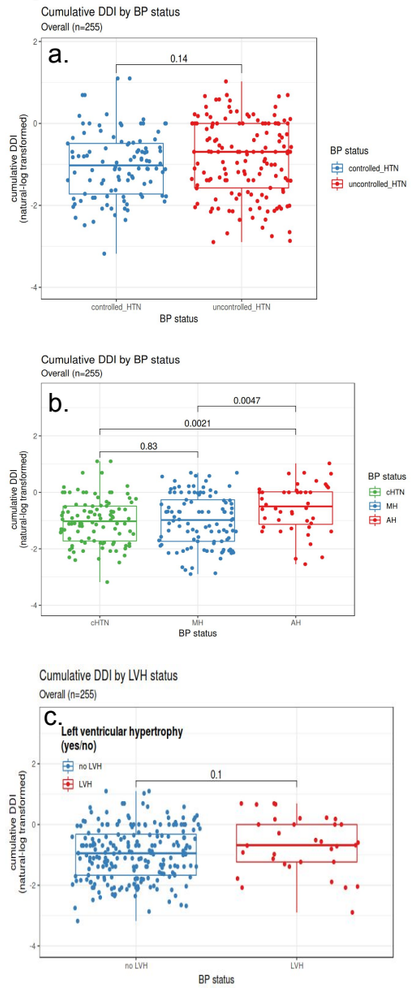
Summary Statistics	Overall (n=255)	Controlled hypertension (n=105)	Uncontrolled hypertension (n=155)	P-value
Age (years)				
◦	12.85 ± 3.68	12.79 ± 3.40	12.89 ± 3.88	0.83
Gender				
Male gender	150 (59%)	60 (57%)	90 (60%)	0.74
Race				
Caucasian race	176 (69%)	81 (77%)	95 (63%)	0.027
Maternal education				
High school or less	102 (40%)	37 (35%)	65 (43%)	0.53
Some college	63 (25%)	27 (26%)	36 (24%)	
College graduate	79 (31%)	37 (35%)	42 (28%)	
Unknown	11 (4%)	4 (4%)	7 (5%)	
CKD onset (years before study entry)*				
◦	250; -8.28 ± 4.84	104; -8.44 ± 4.71	146; -8.17 ± 4.94	0.66
CKD diagnosis				
Non-glomerular	164 (64%)	64 (61%)	100 (67%)	0.42
Glomerular	91 (36%)	41 (39%)	50 (33%)	
Urine protein:creatinine ratio				
◦	0.94 ± 1.44	0.88 ± 1.67	0.99 ± 1.26	0.14
BMI z-score				
◦	0.41 ± 1.14	0.40 ± 1.13	0.42 ± 1.15	0.91
estimated GFR				
◦	51.52 ± 20.90	51.29 ± 21.02	51.69 ± 20.89	0.88
CKD stage				
1	1 (0%)	0 (0%)	1 (1%)	0.76
2	35 (14%)	13 (12%)	22 (15%)	
3	143 (56%)	60 (57%)	83 (55%)	
4	63 (25%)	25 (24%)	38 (25%)	
5	13 (5%)	7 (7%)	6 (4%)	
Family history of hypertension				
Yes	98 (43%)	40 (41%)	58 (44%)	0.78
Number of antihypertensive agents				
1	203 (80%)	92 (88%)	111 (74%)	0.048
2	42 (16%)	11 (10%)	31 (21%)	
3	7 (3%)	2 (2%)	5 (3%)	
4	3 (1%)	0 (0%)	3 (2%)	
Cumulative Drug Dose Index				
◦	0.57 ± 0.52	0.50 ± 0.50	0.61 ± 0.52	0.19
Steroids use				
Currently Taking	19 (7%)	6 (6%)	13 (9%)	0.52
Antihypertensive drug class				
RAASi	220 (86%)	103 (98%)	117 (78%)	<0.001
CCB	48 (19%)	5 (5%)	43 (29%)	<0.001
Diuretic	19 (7%)	7 (7%)	12 (8%)	0.88
Beta-blocker	14 (5%)	0 (0%)	14 (9%)	0.0033
Other	9 (4%)	0 (0%)	9 (6%)	

*Missing data: 5 patients with unknown CKD onset

Figure 3

AAP 2017	NL	WCH	MH	AH	Sum
	4th Report				
NL	100	5	0	0	105
WCH	5	0	0	0	5
MH	0	0	97	8	105
AH	0	0	45	0	45
Sum	105	5	142	8	260

Figure 4



Tables 2 and 3 **Logistic Regression Analysis**

Model 1: Predictors of Uncontrolled Hypertension

Predictors of uHTN	Odds ratio	95% CI	P-value
age (yrs)	1.03	0.908 - 1.161	0.67831
gender (M)	1.26	0.672 - 2.369	0.47015
race (Caucasian)	0.47	0.228 - 0.956	0.03727
maternal education	0.96	0.840 - 1.100	0.56658
CKD onset (yrs)	1.04	0.928 - 1.160	0.51617
BMI z-score	0.97	0.736 - 1.291	0.85848
CKD diagnosis (glomerular)	0.38	0.135 - 1.070	0.06708
proteinuria (Up:c)	1.28	0.990 - 1.667	0.05945
eGFR	1.01	0.995 - 1.032	0.14712
FHx HTN (+)	0.80	0.428 - 1.490	0.48030
number of antiHTN agents	4.01	1.259 - 12.751	0.01880
log(cumulative DDI)	0.91	0.593 - 1.385	0.65011
steroids (+)	1.36	0.345 - 5.337	0.66159
RAASi+	0.05	0.006 - 0.347	0.00290
CCB+	1.73	0.368 - 8.100	0.48808
diuretic+	0.12	0.018 - 0.768	0.02531

Model 2: Predictors of LVH

Predictors of LVH	Odds ratio	95% CI	P-value
age (yrs)	0.89174	0.741 - 1.073	0.22529
gender (M)	0.27175	0.095 - 0.775	0.01481
race (Caucasian)	0.72129	0.232 - 2.240	0.57199
maternal education	1.00098	0.823 - 1.217	0.99219
CKD onset (yrs)	1.05476	0.888 - 1.252	0.54259
BMI z-score	2.12426	1.224 - 3.686	0.00737
CKD diagnosis (glomerular)	1.83839	0.367 - 9.206	0.45881
proteinuria (Up:c)	0.91758	0.610 - 1.380	0.67946
BP class (cHTN/uHTN)	1.40202	0.434 - 4.528	0.57210
eGFR	0.95876	0.926 - 0.992	0.01695
FHx HTN (+)	1.50909	0.540 - 4.215	0.43231
number of antiHTN agents	4.26300	1.301 - 13.968	0.01664
log(cumulative DDI)	0.49353	0.239 - 1.021	0.05680
steroids (+)	0.51147	0.072 - 3.611	0.50134
RAASi+	0.31266	0.060 - 1.641	0.16929
CCB+	2.13735	0.410 - 11.147	0.36739
diuretic+	0.85261	0.103 - 7.072	0.88256

Discussion

- This was the first quantitative analysis of antihypertensive dose expressed as a newly developed measure, cDDI, and its relationship with hypertension status in children with CKD.
- No differences in cDDI between uHTN vs. cHTN, or LVH vs. no LVH, but higher cDDI was associated with AH on univariate analysis.
- RAASi and diuretic use were associated with lower odds of uHTN.
- Non-Caucasian race, absence of RAASi and diuretic agents, and higher number of agents were associated with greater odds of uHTN.
- Female gender, higher BMI z-score, lower eGFR, higher number of agents and lower cDDI were associated with greater odds of LVH.

Conclusions

- Lower dose (cDDI) is not a significant predictor of uHTN, however it may be associated with LVH.
- Further research is needed to validate the use of cDDI and the the roles of medication class and dose on blood pressure control in children with CKD.