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Blood Pressure and Chronic Kidney Disease in Children and Adolescents

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Disclosure of Financial Relationships

Joseph T. Flynn, MD, MS

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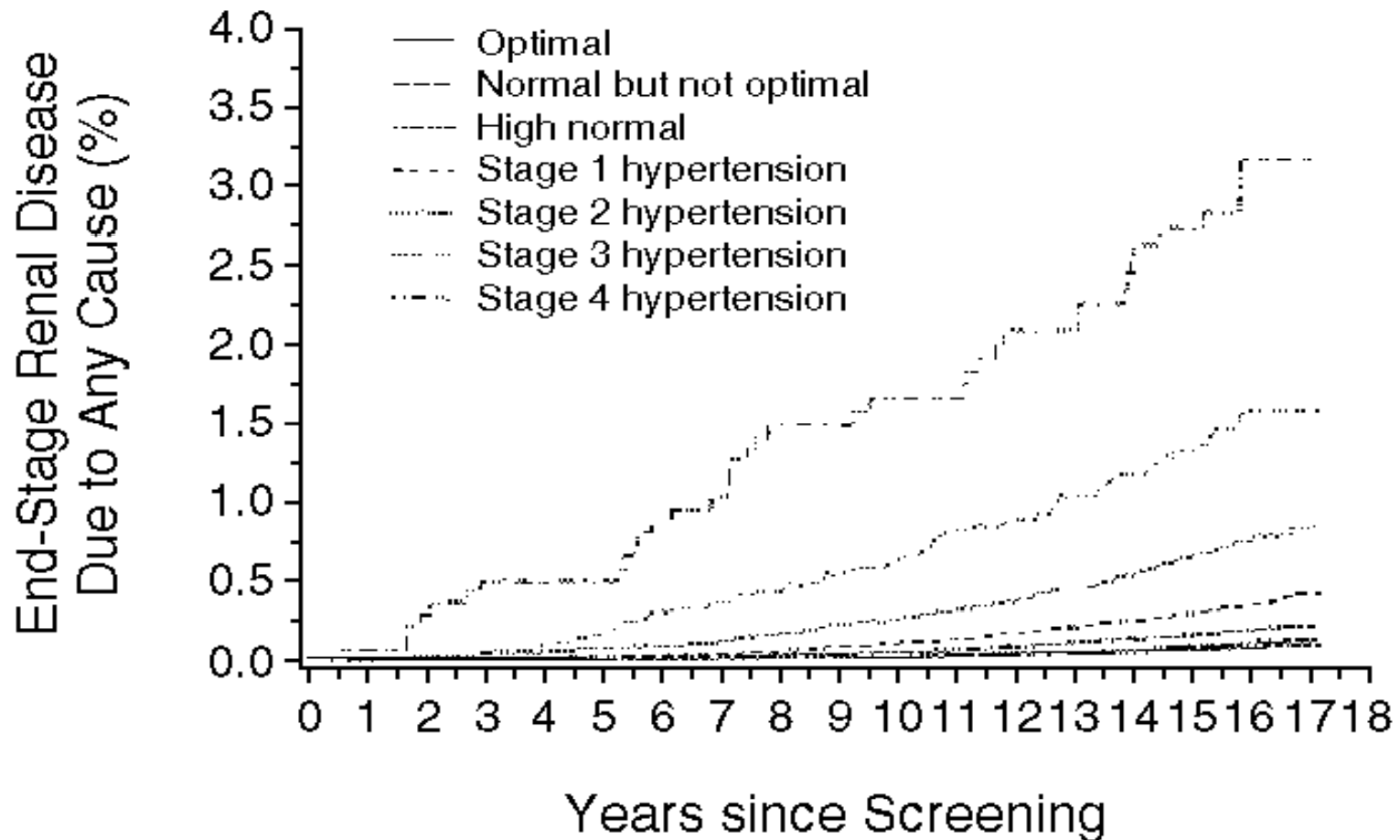
Outline

- Hypertension as a cause of chronic kidney disease
- Prevalence of hypertension in children and adolescents with CKD
- Role of hypertension in progression of CKD

HTN and Development of CKD

- Numerous studies in adults have demonstrated a strong relationship between hypertension and the development of renal disease
- Hypertension accounts for a significant percentage of ESRD in adults

MRFIT: BP & Development of ESRD



Klag et al, N Engl J Med 1996; 334:13

MRFIT: BP & Development of ESRD

Table 4. Adjusted Relative Risk of End-Stage Renal Disease Due to Any Cause According to Quintile of Blood Pressure in 332,544 Men Screened for MRFIT.

BLOOD-PRESSURE QUINTILE	SYSTOLIC			DIASTOLIC		
	RANGE	MEAN	ADJUSTED RELATIVE RISK (95% CI)*	RANGE	MEAN	ADJUSTED RELATIVE RISK (95% CI)*
	<i>mm Hg</i>			<i>mm Hg</i>		
Lowest	<117	110.2	1.0	<75	69.4	1.0
Second	117–123	120.1	1.0 (0.7–1.4)	75–79	77.2	1.3 (0.9–1.8)
Third	124–130	127.2	1.5 (1.1–2.2)†	80–85	82.2	1.4 (1.1–1.9)‡
Fourth	131–140	135.4	2.2 (1.6–3.1)§	86–91	88.4	2.0 (1.5–2.7)§
Highest	>140	153.2	5.0 (3.7–6.7)§	>91	98.9	4.0 (3.0–5.2)§

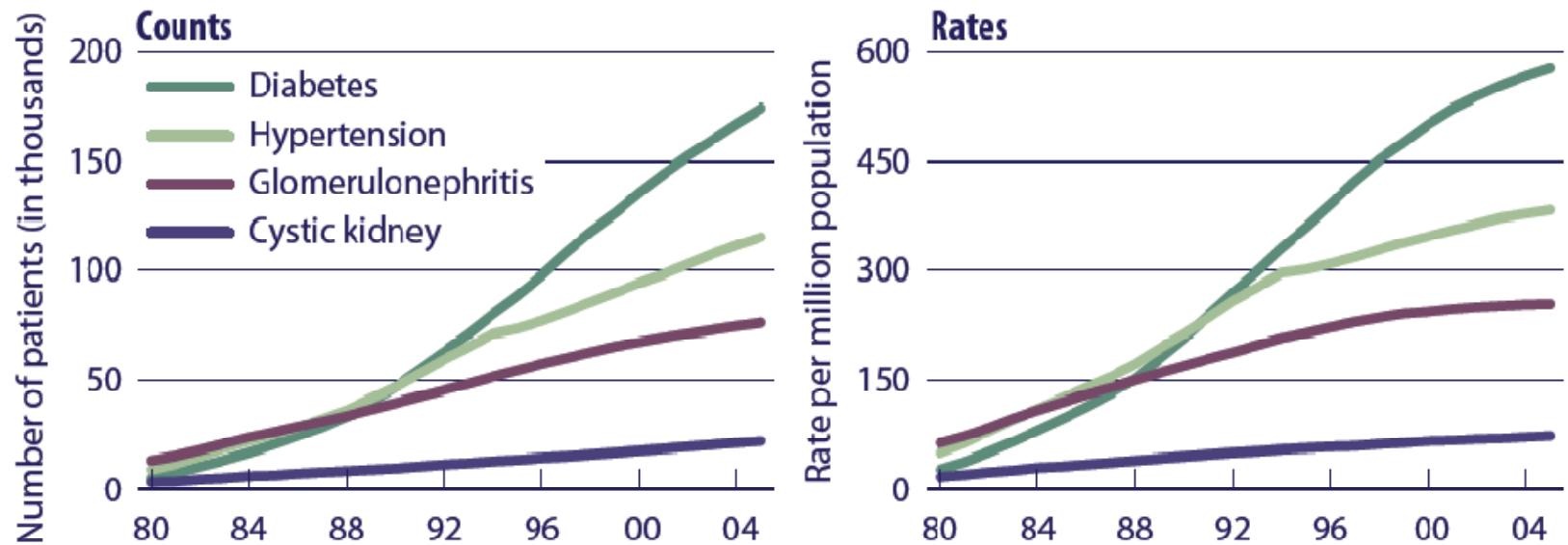
*Relative risks, with men in the lowest quintile as the reference category, were estimated with use of a proportional-hazards regression model, with stratification according to clinic and adjustment for age, race, income, serum cholesterol concentration, number of cigarettes smoked per day, use of medication for diabetes mellitus, and previous myocardial infarction. CI denotes confidence interval.

†P = 0.009.

‡P = 0.02.

§P < 0.001.

Causes of ESRD in Adults



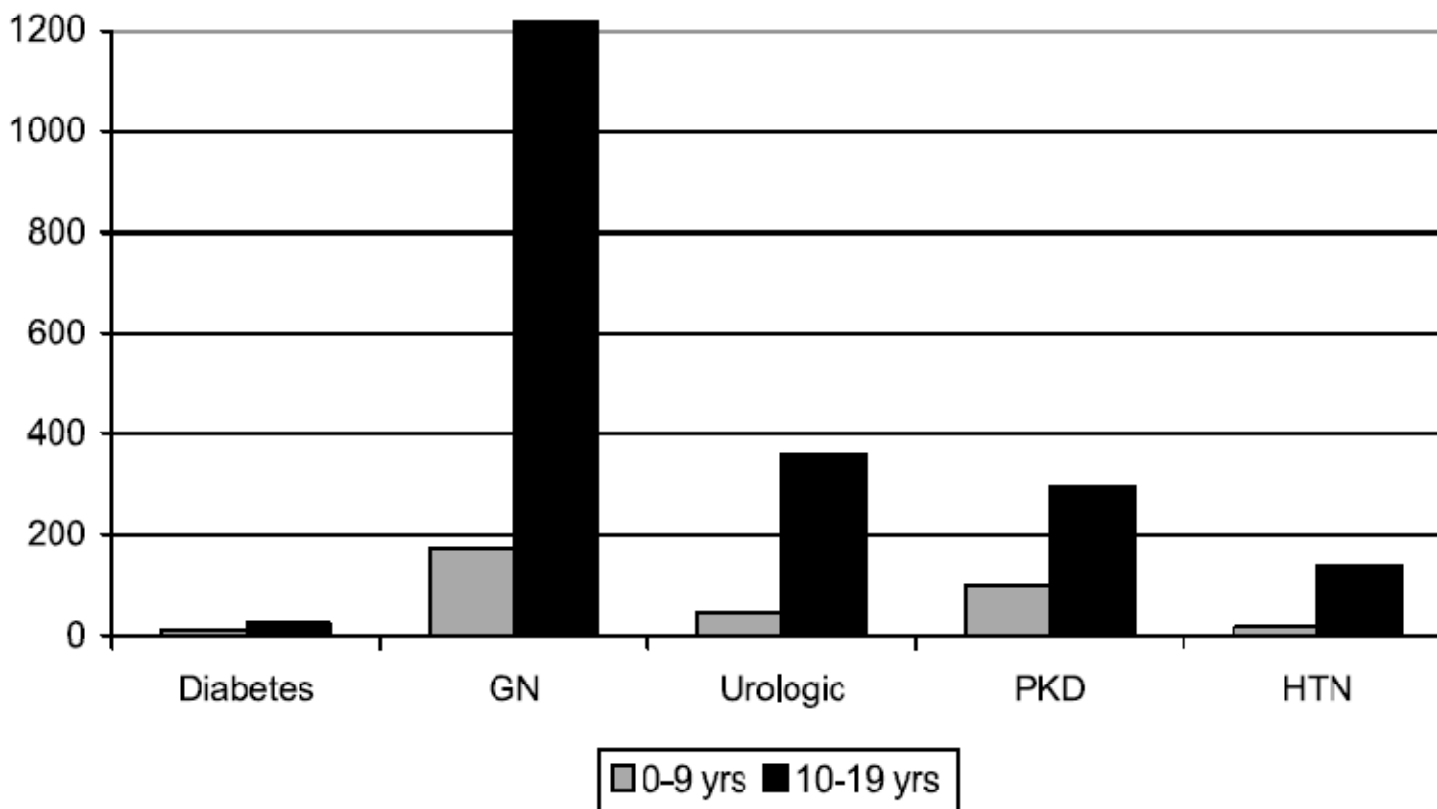
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Prevalent counts & adjusted rates, by primary diagnosis December 31 point prevalent patients

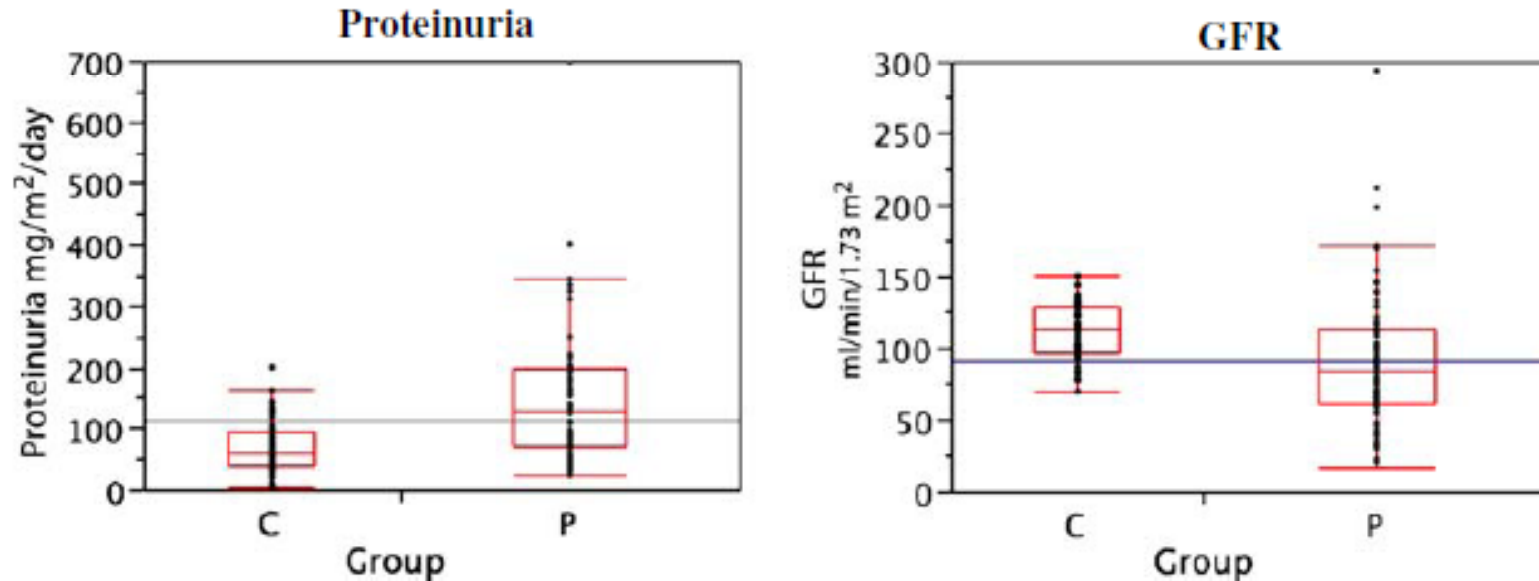
Does HTN Cause ESRD in Children?

- Percentage of pediatric dialysis or transplant pts reported to NAPRTCS with HTN as primary diagnosis = **0**
(2008 NAPRTCS report)
- Per USRDS data, HTN comprises between 3-10% of pediatric ESRD
- Mildly elevated BP in children has been related to proteinuria & decreased GFR

Selected Causes of ESRD in Children



Proteinuria & GFR in Children with Pre-hypertension



One Sample t Test

GFR	Prob	M _{GFR} > 90	M _{GFR} < 90	Proteinuria	Prob	M _{Prot} > 100	M _{Prot} < 100
Group	C	p < 0.001	p NS	Group	C	p NS	p < 0.001
	P	p NS	p NS		P	p NS	p NS

Prob = Probability

M_{GFR} = Mean GFR

M_{Prot} = Mean Proteinuria

Hypertension and Pediatric CKD

- Whether or not hypertension alone is a significant cause of pediatric CKD is debatable
- Hypertension clearly plays a role in the progression of renal failure in children with other forms of renal disease

Hypertension in Pediatric CKD

- Many childhood renal diseases are associated with hypertension
 - Acquired diseases > congenital/structural
- However the true prevalence of HTN among children with CKD is difficult to determine
- NAPRTCS: % of patients receiving antihypertensives
 - CRI database: 38%; Dialysis database: 47% of PD patients and 55% of HD patients

Hypertension in Pediatric CKD

Renal Disease	Percent with hypertension
Polycystic Kidney Disease	83
Glomerulonephritis	71
Hemolytic Uremic Syndrome	59
Pyelonephritis/Interstitial Nephritis	40
Renal Infarction	23
Structural Renal Disease	19
Other	35

Fivish et al, Ped Nephrol 12:328, 1998

Hypertension in Pediatric CKD

- Mitsnefes et al, JASN 2003
- Cross-sectional study of 3834 children in the NAPRTCS chronic renal insufficiency registry
- Systolic HTN, diastolic HTN, or both was present at baseline in 1847 patients (48%).

Systolic HTN only was present in 41%, diastolic HTN only in 28%, and both systolic & diastolic HTN in 34%

There were more African Americans ($P = 0.02$), obese patients ($P < 0.001$), and those with acquired kidney disease ($P < 0.001$) in the hypertensive group than in the group of children with normal BP.

One-third of normotensive children and one-half of hypertensive children were receiving antihypertensive medications at baseline.

Hypertension in Pediatric CKD

- Prior data derived from NAPRTCS registry
- Accuracy of prevalence information unknown
 - Self-report of receipt of antihypertensive medications (Fivush)
 - Single BP measurement obtained at unknown time point by unknown method (Mitsnefes)
- Need for prospective data

CKiD Study – Study Design

- **Observational Cohort Study**
5 year study, 4 year follow-up, annual visits
Funded 2003, recruitment began April 2005
- **Enrollment - 590 Children**
1-16 years of age
Mild to moderately impaired kidney function, estimated
GFR 30-75 ml/min/1.73m²
- **Multiple Pediatric Nephrology Centers involved**
Johns Hopkins Univ, Children's Mercy Hospital
Johns Hopkins School of Public Health

C-KID Study – CVD

- **SPECIFIC AIMS:**
 - I. To determine the relationship between blood pressure (BP) and GFR as well as other markers of CKD progression.**
 - II. To describe the prevalence of hypertension-induced cardiovascular target-organ damage.
 - III. To characterize the dyslipidemia present in children with CKD and determine the relationship between dyslipidemia and GFR.
 - IV. To characterize other metabolic abnormalities in children with CKD, including insulin resistance, hyperhomocysteinemia, and markers of inflammation

Blood Pressure in Children With Chronic Kidney Disease: A Report From the CKiD Study

- Flynn et al, Hypertension 2008; 52:631
- Cross-sectional analysis performed to:
 1. Describe the distribution of BP, hypertension, and antihypertensive medication use in a large cohort of children with CKD;
 2. Identify demographic and clinical characteristics associated with elevated BP or uncontrolled BP in this population.

Study Procedures

- Three BP's measured by trained examiner using aneroid sphygmomanometer
- GFR measured by iohexol disappearance
- Collection of demographic & anthropometric data; medication use

BP Classification

- BP classified according to NHBPEP Fourth Report:
 - Hypertension: $BP \geq 95^{\text{th}}$ percentile
 - Pre-hypertension: $BP \geq 90^{\text{th}}$ and $< 95^{\text{th}}$ percentiles
 - Normal BP: $BP < 90^{\text{th}}$ percentile

Definitions

- Hypertension (HTN) was defined as BP \geq 95th percentile or as self-report of HTN plus current treatment with antihypertensive medications.
- Elevated BP – hypertensive or pre-hypertensive range BP
- Controlled BP: medication use plus BP $<$ 90th percentile
- Uncontrolled BP: medication use plus BP $>$ 90th percentile

Table 1. Demographic, Anthropometric, and Clinical Characteristics of CKiD Study Participants at Baseline (N=432)

Characteristic	Mean±SD or % (n)
Age, years	11±4
Male	60% (260)
Race	
White	69% (298)
Black	16% (67)
Other	15% (66)
Hispanic ethnicity	14% (59)
Weight percentile	47±33
Height percentile	32±29
BMI percentile	60±30
Percent obese, BMI >95th percentile	17% (72)
Low birth weight, <2500 g	20% (83)
Premature birth, <36 weeks	24% (100)
Iohexol GFR, mL/min per 1.73 m ²	44±15
Glomerular CKD	22% (93)
Duration of CKD, years	7±5

Flynn et al, Hypertension 52:631, 2008

Blood Pressure Status

Table 2. BP Status of CKiD Study Participants (N=432)

Characteristic	Mean±SD or % (n)
SBP, mm Hg	107±13
SBP status	
SBP <90th percentile	75% (322)
SBP ≥90th to <95th percentile	11% (49)
SBP ≥95th percentile	14% (61)
Diastolic BP, mm Hg	66±11
Diastolic BP status	
DBP <90th percentile	77% (332)
DBP ≥90th to <95th percentile	9% (41)
DBP ≥95th percentile	14% (59)
Current use of antihypertensive medication	64% (275)
Among children with SBP >90th percentile	68%
Among children with DBP >90th percentile	53%
Self-reported hypertension	47% (201)
Parental history of hypertension	28% (122)

Flynn et al, Hypertension 52:631, 2008

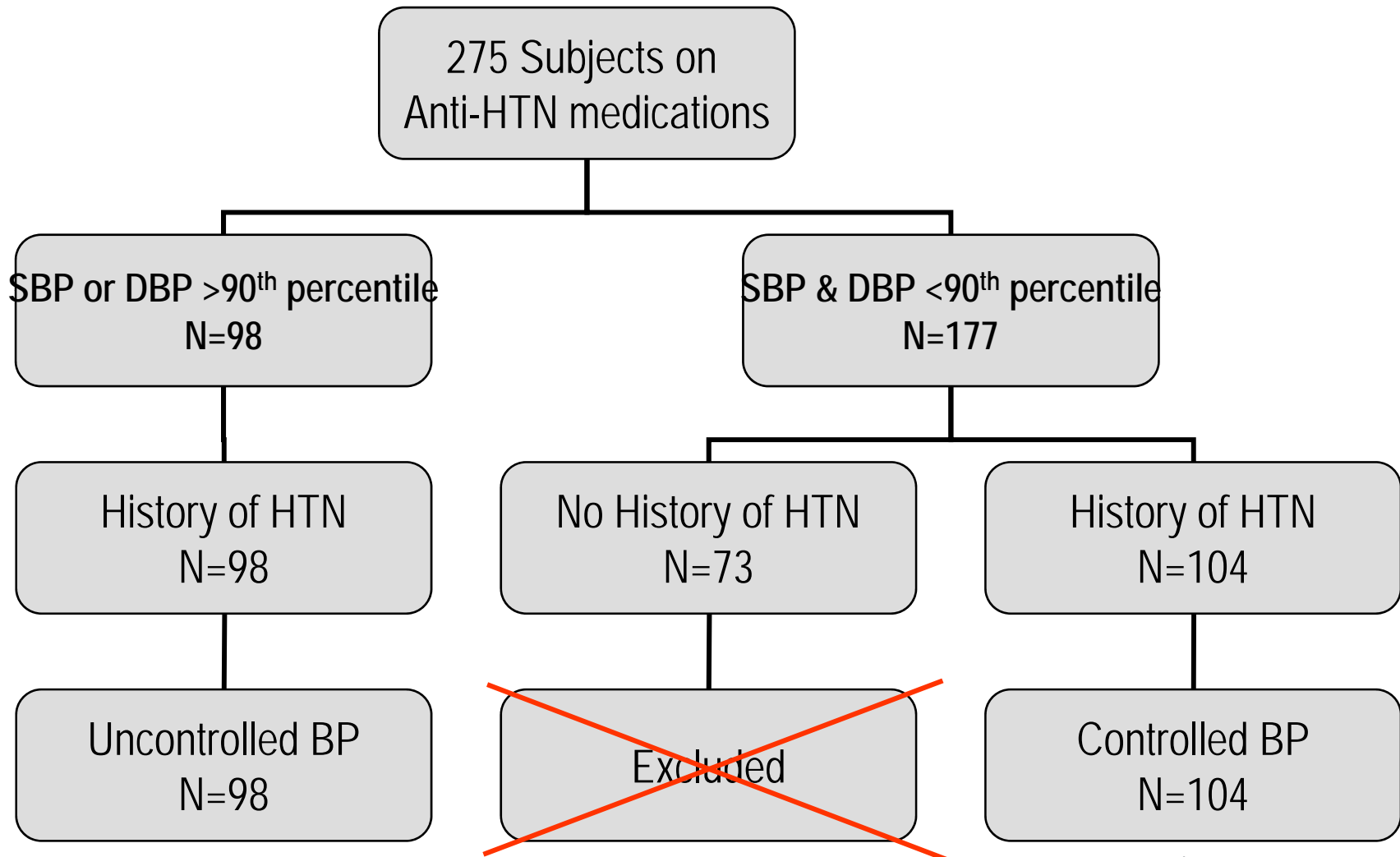
Characteristics Associated with Elevated BP – Unadjusted Analysis

- Black race, glomerular CKD, shorter duration of CKD, obesity, self-reported history of hypertension and elevated serum potassium were significantly associated with elevated SBP
Nephrotic-range proteinuria demonstrated a weaker association with elevated SBP (P=0.06)
- Younger age, black race, shorter duration of CKD and nephrotic-range proteinuria were significantly associated with elevated DBP

Characteristics Associated with Elevated BP – Adjusted Analysis

- **Black children** were 63% **more likely** (PR: 1.63 95% CI 1.13-2.37) to have elevated SBP and 79% more likely (PR: 1.79, 95% CI 1.21-2.63) to have elevated DBP compared to non-black children.
- Elevated serum potassium was independently associated with elevated SBP (PR: 1.07, 95% 1.01-1.14 per 0.2 mmol/L increase in serum potassium).
- **Longer duration of CKD** (PR: 0.85, 95% CI 0.74-0.99, per 3 year increase) and **current antihypertensive medication use** (PR: 0.63, 95% 0.42-0.93) were both independently associated with a **decreased prevalence** of elevated DBP.

Controlled vs. Uncontrolled BP



Flynn et al, Hypertension 52:631, 2008

Controlled vs. Uncontrolled BP

- Those with uncontrolled BP were more likely to be **male, black**, had a **shorter mean duration of CKD**, and were **less likely to be receiving an ACEi or ARB** compared to those with controlled BP.
- A higher percentage of those with uncontrolled BP were obese and were being treated with either CCB's or another non-ACEi/ARB antihypertensive.

Table 4. Demographic and Clinical Characteristics of Participants Receiving Antihypertensive Medications With Controlled and Uncontrolled Blood Pressure (N=202)*

Characteristic†	BP Status		P(χ ²)
	Uncontrolled BP (N=98)	Controlled BP (N=104)	
Age, years	11 ± 4	11 ± 3	0.72
Male	68% (67)	51% (53)	0.01
Black race	22% (22)	10% (10)	0.02
Hispanic ethnicity	19% (18)	12% (12)	0.16
Obese, BMI ≥95th percentile	28% (27)	17% (17)	0.06
Glomerular CKD	34% (33)	26% (27)	0.23
Iohexol GFR, mL/min per 1.73 m ²	44 ± 16	44 ± 16	0.99
CKD duration, years	6 ± 4	8 ± 4	<0.01
Premature birth, gestational age <36 weeks	24% (23)	31% (31)	0.29
Low birth weight, <2500 g	18% (17)	27% (26)	0.17
Proteinuria			0.33
Significant, 0.2 ≤Up/c <2.0	59% (55)	56% (54)	
Nephrotic, Up/c ≥2.0	19% (18)	16% (16)	
Parental history of hypertension	31% (30)	29% (30)	0.78
Antihypertensive use			
ACEi/ARB	76% (74)	88% (92)	0.02
Calcium channel blockers	33% (32)	16% (17)	<0.01
Other	35% (34)	21% (22)	0.03
≥2 Antihypertensive medications	44% (43)	33% (34)	0.10

Flynn et al, Hypertension 52:631, 2008

Controlled vs. Uncontrolled BP

Table 4. Demographic and Clinical Characteristics of Participants Receiving Antihypertensive Medications With Controlled and Uncontrolled Blood Pressure (N=202)*

Characteristic†	BP Status		P(χ^2)
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Antihypertensive use			
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Calcium channel blockers	33% (32)	16% (17)	<0.01
Other	35% (34)	21% (22)	0.03

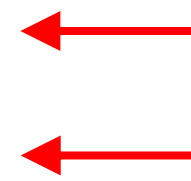
Flynn et al, Hypertension 52:631, 2008

Controlled vs. Uncontrolled BP

Table 5. Prevalence Ratios of Uncontrolled BP Among Those Receiving Antihypertensive Medications for Select Demographic and Clinical Characteristics (N=202)

Characteristic	PR [95% CI] of Uncontrolled BP	
	Unadjusted	Adjusted*
Age, per 4 years	0.97 [0.84–1.13]	1.00 [0.87–1.15]
Male	1.48 [1.07–2.03]	1.54 [1.14–2.08]
Race, black vs nonblack	1.54 [1.15–2.05]	1.15 [0.84–1.58]
Obese, BMI \geq 95th percentile	1.36 [1.01–1.82]	1.26 [0.93–1.72]
Iohexol GFR, per 10% decrease	1.00 [0.96–1.04]	1.01 [0.96–1.05]
Glomerular CKD	1.20 [0.90–1.61]	1.03 [0.74–1.42]
Duration of CKD, per 3 years	0.87 [0.78–0.97]	0.88 [0.78–0.98]
Nephrotic proteinuria, Up/c \geq 2.0	1.11 [0.78–1.58]	1.00 [0.69–1.44]
ACEi/ARB use	0.67 [0.50–0.89]	0.72 [0.52–0.99]

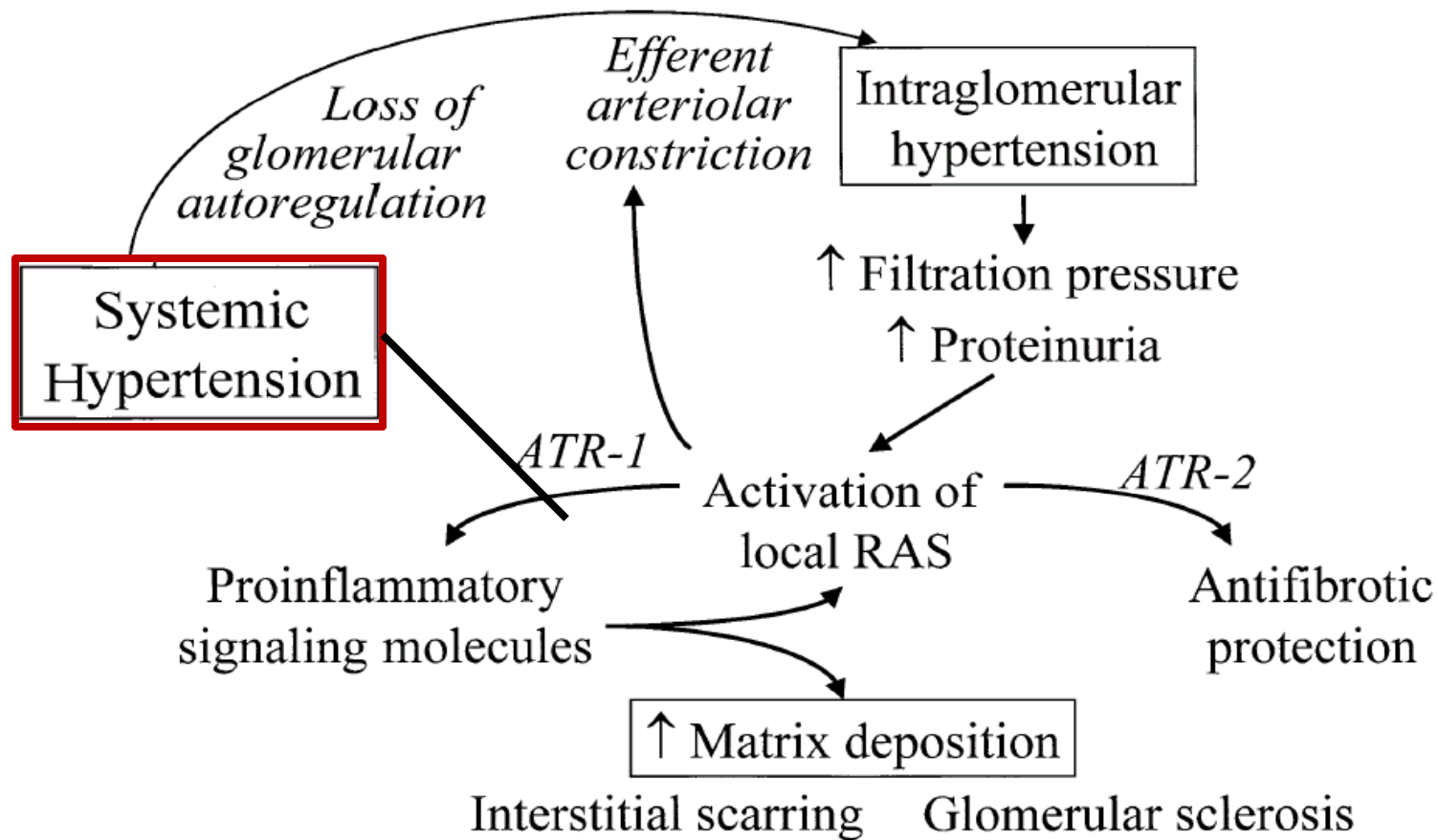
*Adjusted for all variables listed in the table.



Summary – CKiD Data

- A significant proportion of children enrolled in the CKiD study suffer from elevated BP.
37% had either elevated SBP or DBP
- 39% of those with elevated BP were not receiving antihypertensive meds, indicating that HTN is frequently under- or even untreated in pediatric CKD
- ACEi/ARB treatment was associated with improved BP control

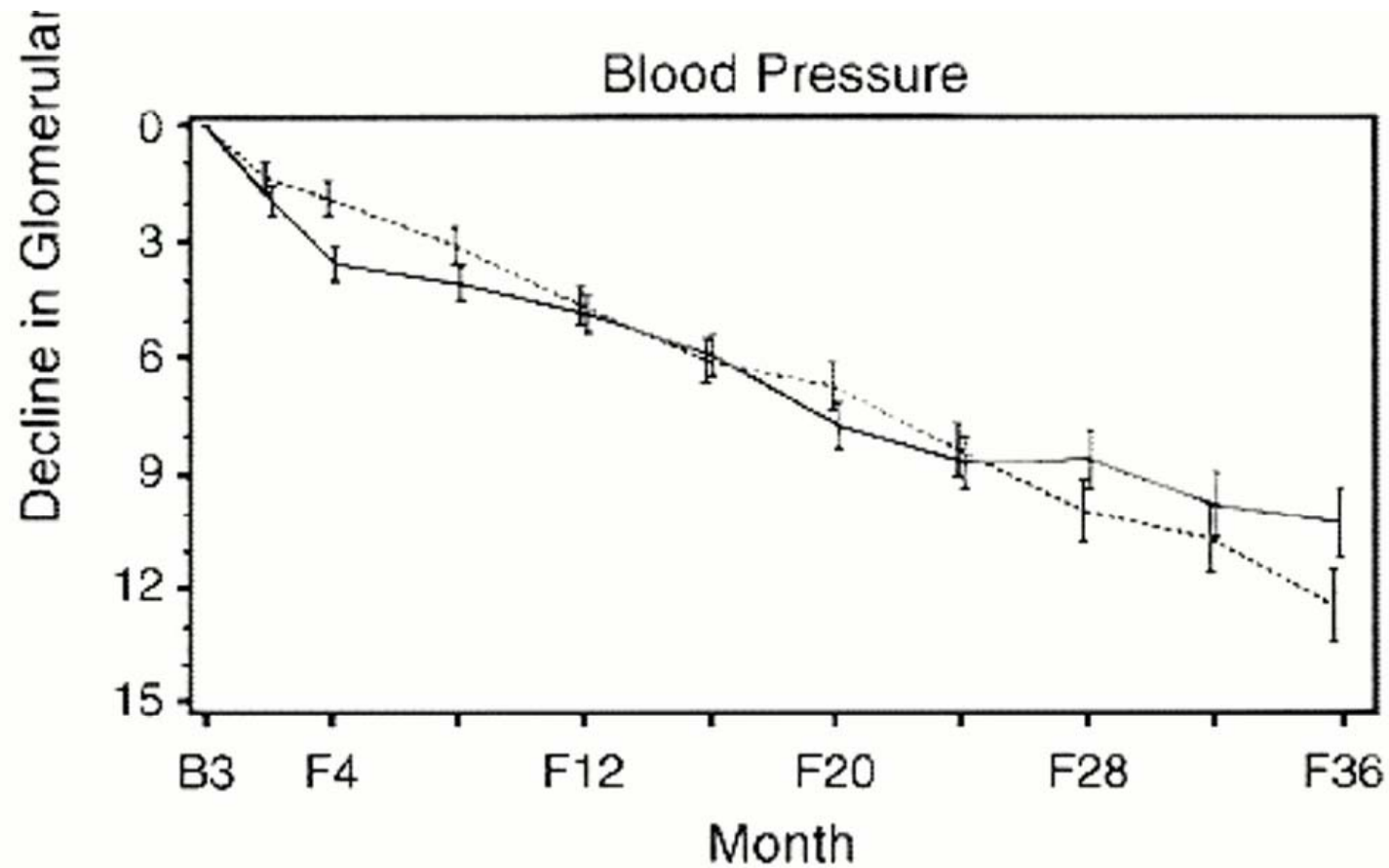
Role of Hypertension in Progression of Chronic Kidney Disease



Role of Hypertension in Progression of Chronic Kidney Disease

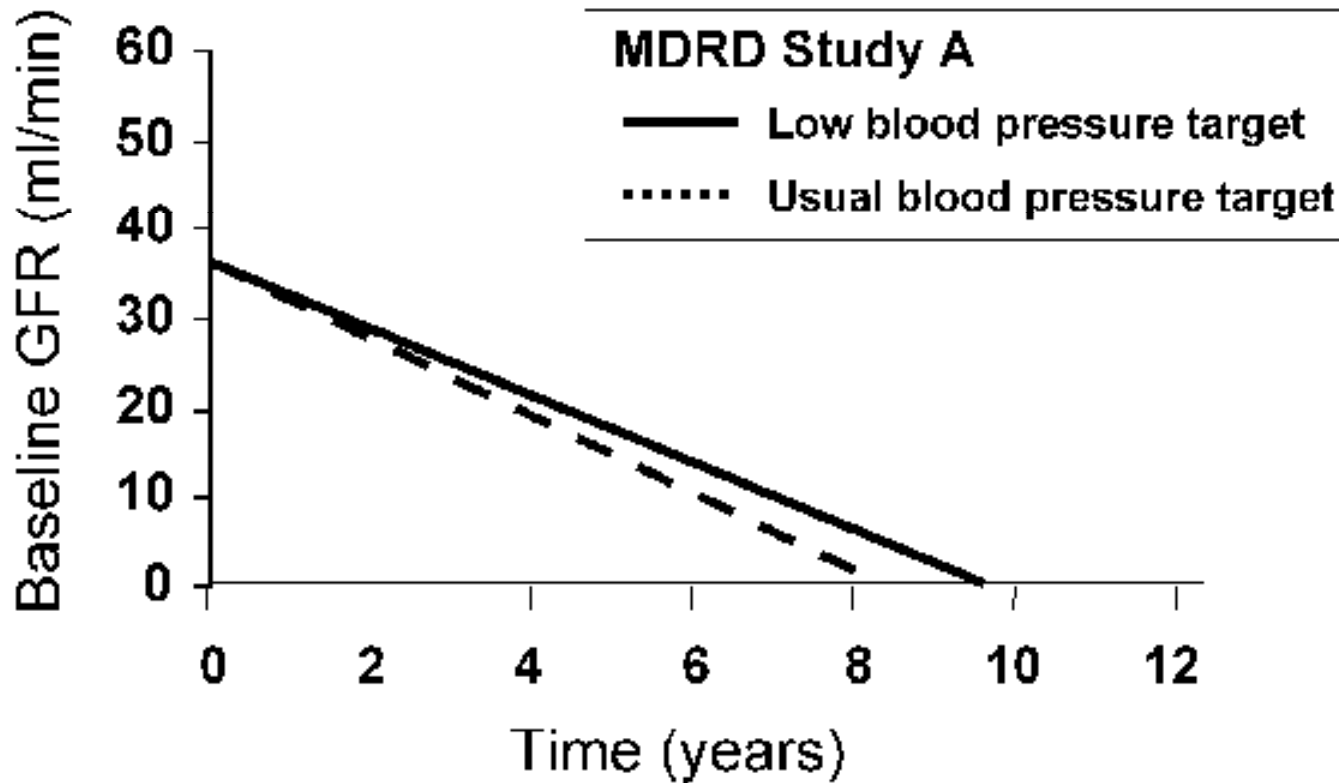
- Data in adults indicates that control of BP may slow progression of CKD
- One prior study of dietary protein restriction in children with CKD (Wingen et al) showed no effect of protein restriction but slower rate of progression in those with lower SBP
- Analysis of NAPRTC database suggests that BP has important role in pediatric CKD progression
- ESCAPE trial demonstrates benefit of lower BP target in children with CKD

MDRD Study: Effect of BP Control on Progression



Klahr S et al. NEJM 1994;330:877

MDRD Study: Effect of BP Control on Progression



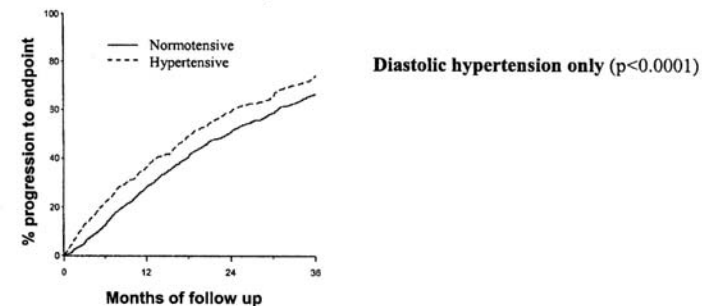
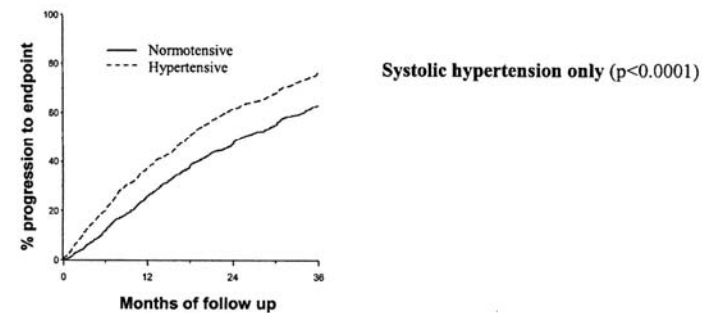
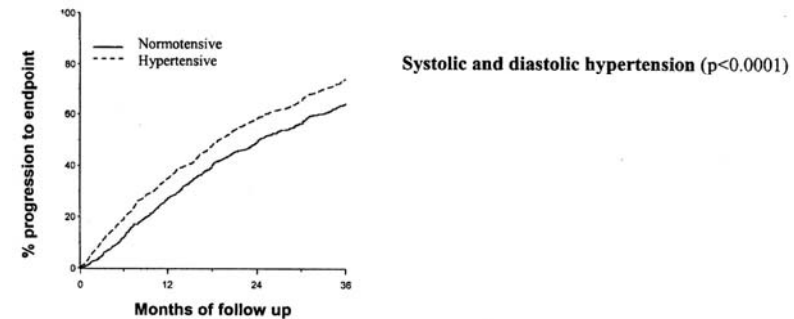
HTN and Progression of CKD in Children: NAPRTCS

- Cohort study of 3800 children enrolled in NAPRTCS chronic renal insufficiency database
All had CrCl < 75ml/min/1.73m² at enrollment
- Divided into those with HTN and those without
HTN defined as either systolic or diastolic BP at baseline (time of enrollment) > 95th % for sex, age and height
48% of the study patients had HTN at baseline
- Followed from enrollment in database to development of ESRD or 10ml/min/1.73m² drop from baseline CrCl

Mitsnemes et al, JASN, 14:2618, 2003

HTN and Progression of CKD in Children: NAPRTCS

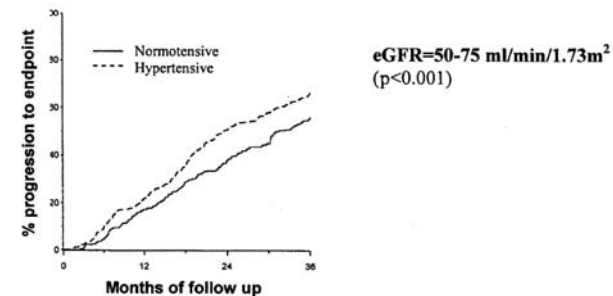
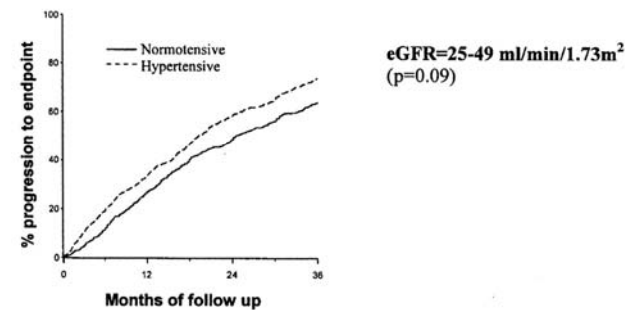
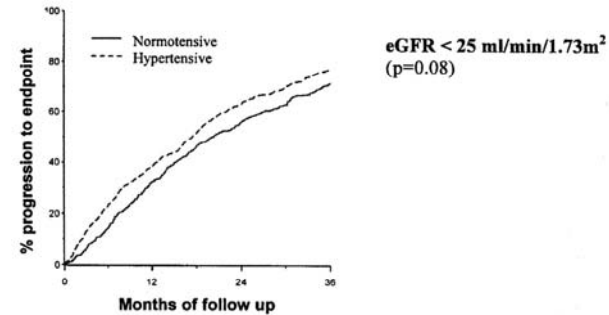
- At 24 months, children with HTN reached endpoints significantly faster than those with normal BP (58% vs. 49%, $p < 0.001$).



Mitsnefes et al, JASN, 14:2618, 2003

HTN and Progression of CKD in Children: NAPRTCS

- The presence of HTN resulted in a more rapid progression of CKD at all levels of calculated GFR



Mitsnemes et al, JASN, 14:2618, 2003

HTN and Progression of CKD in Children: NAPRTCS

- HTN was a significant predictor of progression of CrI ($p=0.0015$) with adjusted RR of 1.16 .
Other significant predictors of CrI progression were older age ($p<0.001$), African-American ethnicity ($p=0.03$), obesity ($p=0.03$), acquired renal disease ($p<0.001$) and baseline CrCl < 50 ml/min/1.73m² ($p<0.001$).
- Conclusion: HTN is a strong independent risk factor for progression of chronic kidney disease in pediatric patients.

HTN and Progression of CKD in Children: ESCAPE

- Prospective study of 385 children with CKD, conducted at 33 centers in Europe
- All children treated with fixed dose of ramipril, randomized to conventional vs. intensified BP control based upon ABPM
 - Conventional: 24-hr MAP 50-95th percentiles
 - Intensified: 24-hr MAP <50th percentile
- End-point: 50% decline in GFR or progression to ESRD
- 5-year follow-up

ESCAPE Study Group, NEJM 2009; 361:17

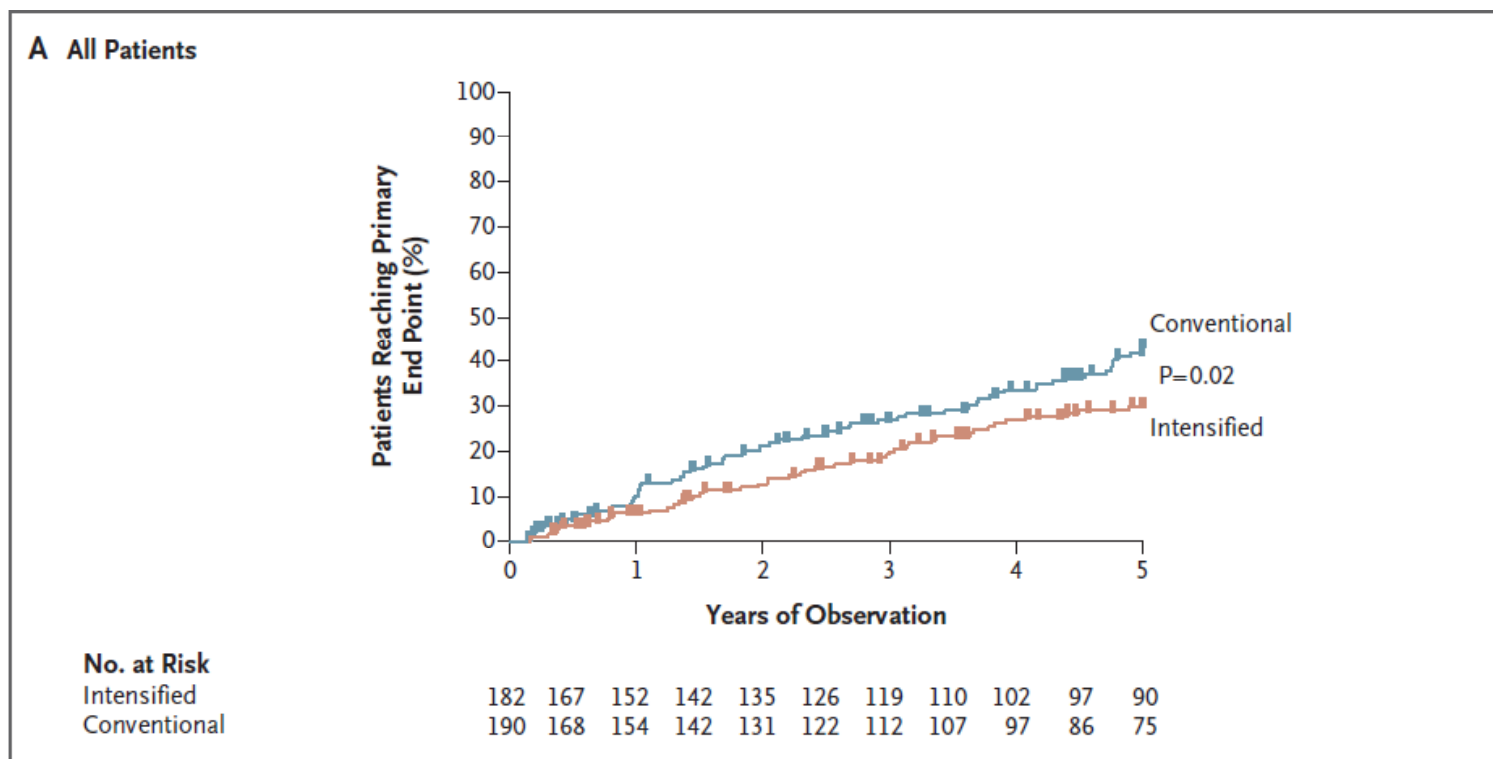
Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Intensified Blood-Pressure Control (N= 189)	Conventional Blood-Pressure Control (N= 196)	P Value
Age (yr)	11.5±4.1	11.5±4.0	0.91
Male sex (%)	56.6	62.2	0.20
Underlying renal disorder (% of patients)			0.71
Glomerulopathies	14	12	
Hypoplasia–dysplasia	66	71	
Other	20	17	
Duration of chronic kidney disease (yr)	6.4±4.4	6.7±4.5	0.69
24-hour mean arterial pressure			
mm Hg	89.5±10.3	89.5±9.5	0.46
Standard-deviation score	1.53±2.15	1.45±1.61	0.93
>95th percentile of mean arterial pressure (%)	37.6	40.8	0.47
ACE-inhibitor washout required (%)	32.8	35.5	0.63
Antihypertensive treatment other than ramipril (% of patients)			
No. of medications			0.21
None	67	67	
1	19	23	
≥2	14	10	
Type of medication			0.65
Diuretic	9	11	
Calcium-channel blocker	18	15	
Beta-blocker	24	21	
Estimated GFR (ml/min/1.73 m ²)	46.4±19.1	45.4±19.9	0.57
Median change in GFR (ml/min/1.73 m ² /yr)	-3.8	-4.5	0.50
GFR reduction >3 ml/yr (%)	48.7	52.0	0.47
24-Hr urinary protein excretion (mg/m ² /day)	978±1603	804±1250	0.33

ESCAPE Study Group, NEJM 2009; 361:17

HTN and Progression of CKD in Children: ESCAPE

- Intensified BP control group had slower rate of reaching end-point than conventional control group



ESCAPE Study Group, NEJM 2009; 361:17

Conclusions

- Hypertension is frequent in pediatric CKD and is often under-treated or untreated
- Ample data demonstrate the significant role of HTN in pediatric CKD progression
- Lower BP targets in children with CKD may slow the rate of CKD progression
Role of drug class, routine ABPM need further exploration

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Questions?

