



Hypertension in Chronic Kidney Disease

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Scope of Talk

- Relevance of cardiovascular disease
- Prevalence of hypertension
- Association with primary disease and pathophysiology
- Effect of hypertension on progression of CKD
- Hypertension as a cardiovascular risk factor
- Complications of hypertension in CKD
- Clinical implications

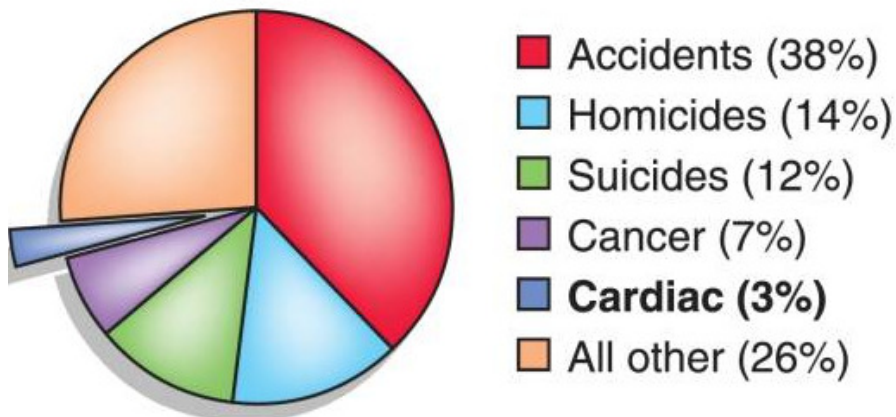
Why does it matter?

There is an increased rate of cardiovascular mortality in **children** and **young adults** [with *childhood onset* chronic kidney disease (CKD)] on renal replacement therapy

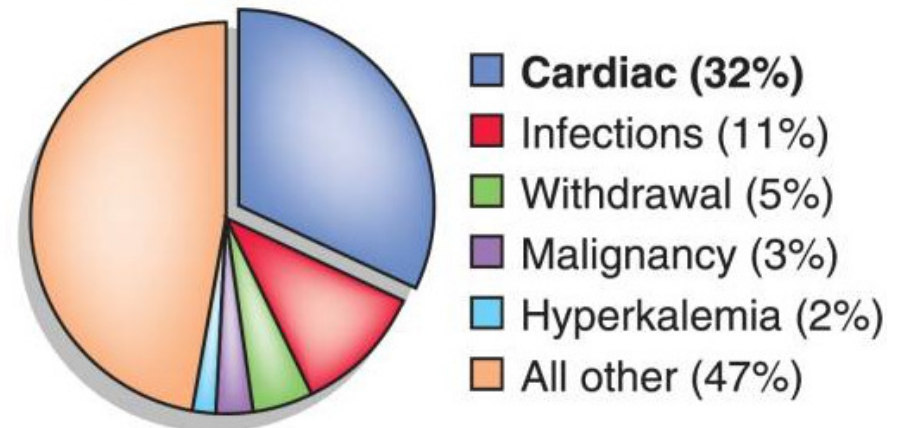
In young adults *with childhood onset* CKD **40% - 45% mortality** is cardiac

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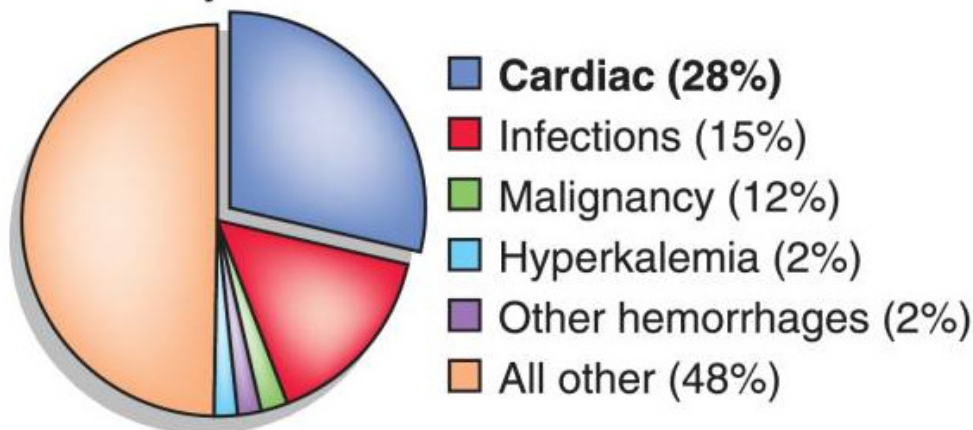
General population 1–24 years



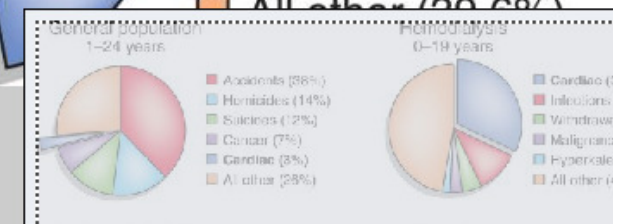
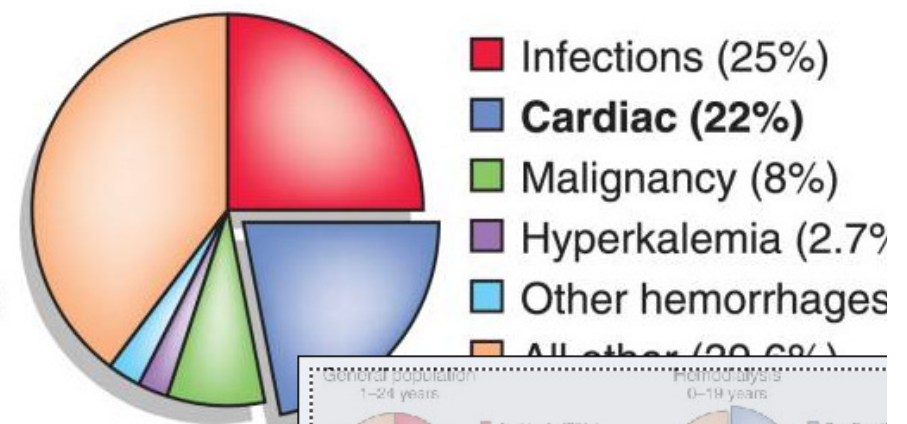
Hemodialysis 0–19 years

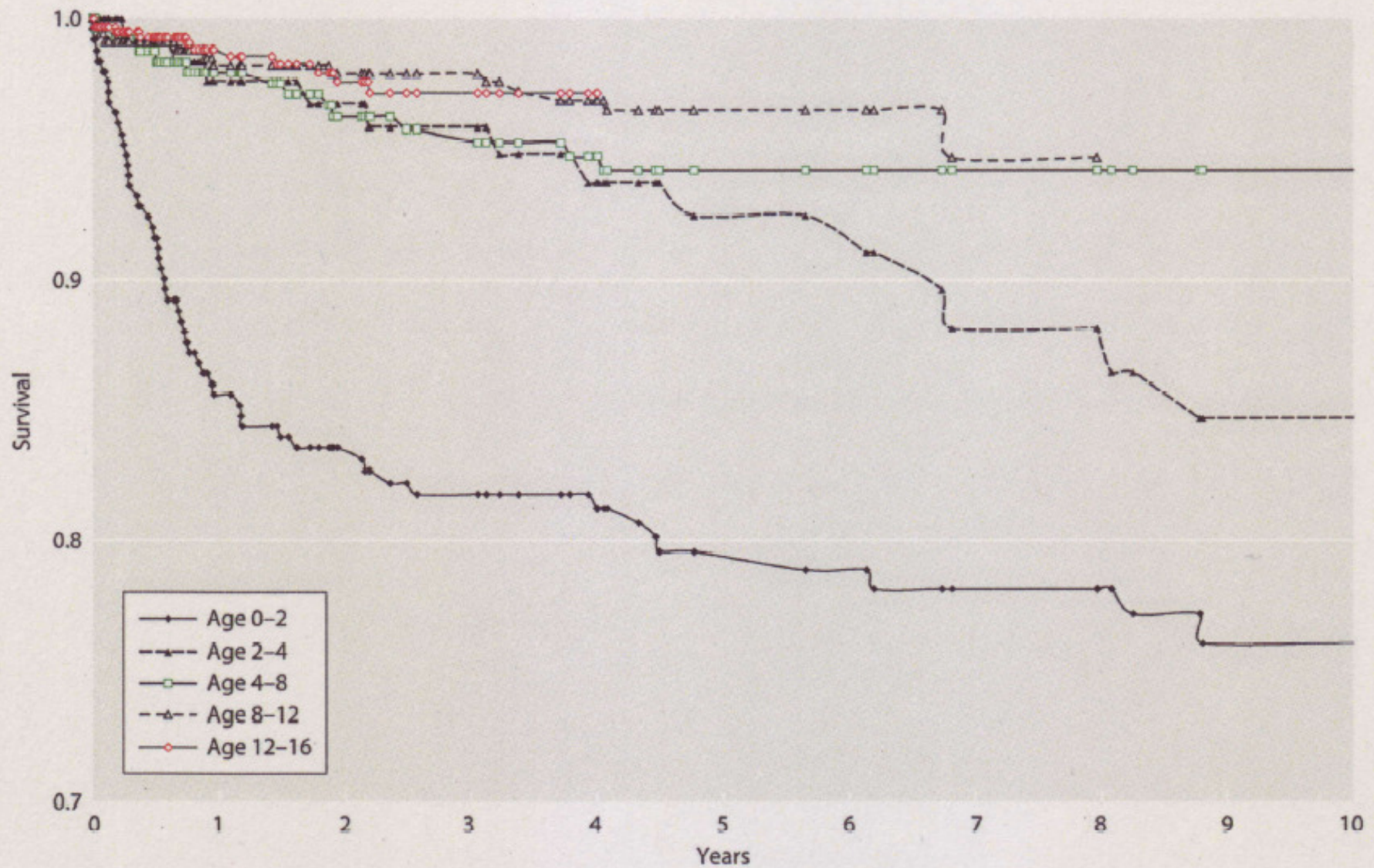


Peritoneal dialysis 0–19 years



Transplant 0–19 years





.5. Unadjusted KM in paediatric patients starting RRT between 1997 and 2010, by age at start

Pruthi R et al. Chapter 4. UK Renal Registry Report _2013.

Pre-dialysis CKD during childhood?

- Over the past 8 years, two large multi-centre cohorts established for observational studies
- North American cohort : **CKiD Study**
 - Prospective cohort study; GFR 30-90ml/min/1.73m²
 - N=586; aged 1-16 year olds
- European study: **4C study**
 - Prospective cohort study; GFR 10-45ml/min/1.73m²
 - n>600 ; aged 6-17 year olds
 - No data published so far but plenty coming...

Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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

Joseph T. Flynn, Mark Mitsnefes, Christopher Pierce, Steven R. Cole, Rulan S. Parekh, Susan L. Furth and Bradley A. Warady

Hypertension. 2008;52:631-637; originally published online August 25, 2008;

doi: 10.1161/HYPERTENSIONAHA.108.110635

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0194-911X. Online ISSN: 1524-4563



Reviews

Microsoft PowerPoint ...

Prevalence and Corre...

Hypertension-2008-Fl...



CKiD study blood pressure report

Flynn et al Hypertension 2008

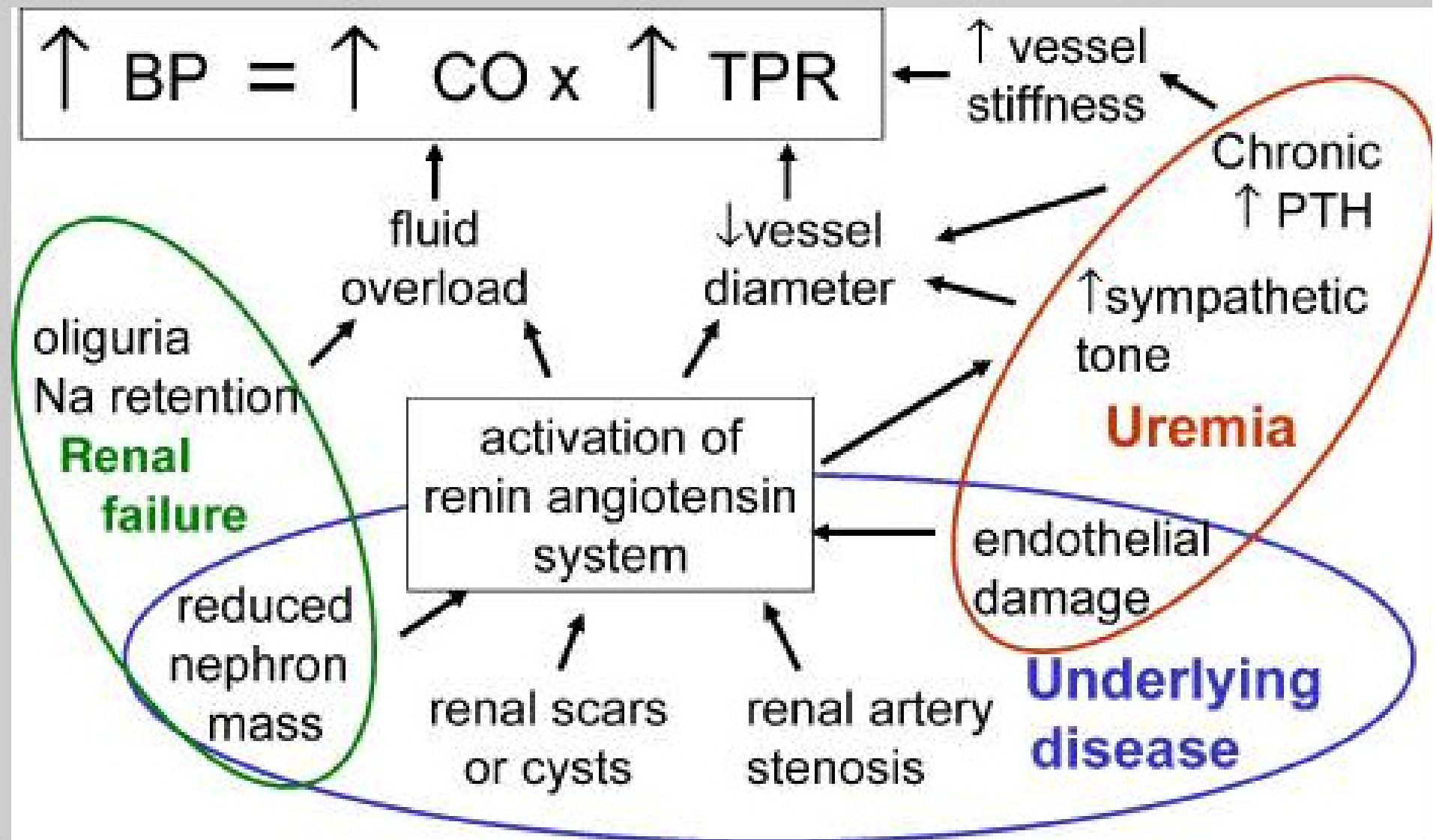
- CKiD study (n=432)
 - Hypertensive/on treatment of hypertension in 54%
 - Despite treatment 48% remained hypertensive
 - Of those with elevated BP 39% were not receiving any treatment
- Findings similar to that reported in the NAPRTCS report in 2003 [Mitsnefes JASN 2003]
 - Prevalence of hypertension at 48% and similar level of BP!

Association of primary renal disease and hypertension

- Hypertension is extremely common in all forms of **glomerulonephritides**
 - acute GN: PIGN, HSP: mostly reversible but persists in HUS, lupus
 - Chronic GN: mostly seen in SRNS,
- Hypertension commonly also seen with **non-glomerular disorders**
 - CAKUT and PKD; and in Reflux nephropathy
- Reno-vascular disease
- Generally observed that children with GN or PKD tend to have higher blood pressure levels than those with CAKUT for any level of GFR

Patho-physiological mechanisms

- Activation of the Renin-Angiotensin-Aldosterone system
- Sodium and Water Retention
- Activation of the Sympathetic nervous system
- Nitric oxide
- CKD-MBD
- Intrauterine programming



Recent pubmed search

“more of the same”?

- Improved data now including pre-dialysis CKD
 - Small -> larger datasets
 - retrospective -> prospective
 - cross-sectional -> multiple cross sectional -> longitudinal
 - most display poor achievement of standards... the cynic in me “more of the same”
 - **few data showing causation...**
 - **few exploring ways of reducing these risk factors...**
 - **few clinical trials in children**

Summary-1

- Hypertension is an inevitable consequence of CKD
- Worst BP levels with more severe CKD → ERF
- Asymptomatic, hence need to measure BP surveillance BUT accurately
- Plenty of room for improvement

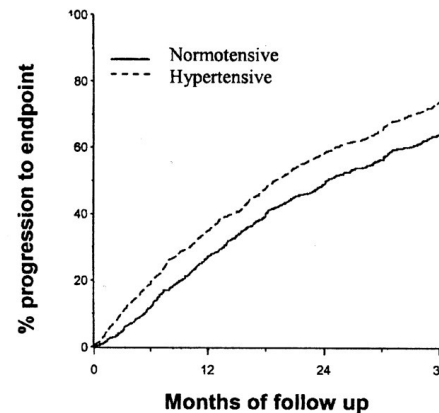
What progress have we made
regarding hypertension in children
with CKD over the past 10-15 years?

Effect of hypertension on progression of CKD - adults

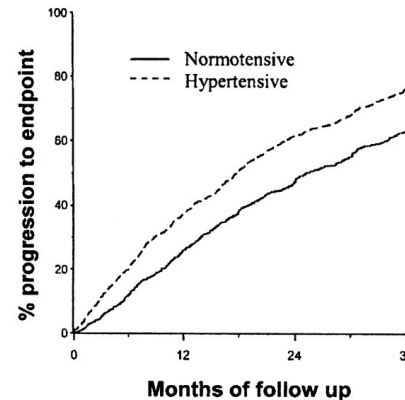
- Substantial evidence in adults that **hypertension** is a significant **risk factor for progressive renal disease**
- Additionally, presence of **proteinuria** in adults is **associated with progressive renal disease** in both diabetic and non-diabetics
- Numerous **intervention trials** have provided evidence that **renal function is preserved by controlling BP** in hypertensives (DM & non-DM)

Effect of hypertension on progression of CKD - children

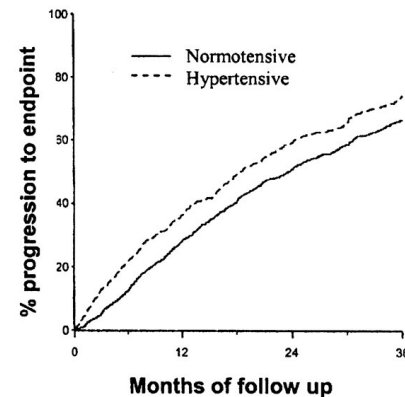
- Initial observations from restricted protein intake study in children with CKD
 - Suggested those with SBP >120 did worse and proteinuria >50mg/m²/day
 - Lancet 1997; 349: 1117-1123
- Observational data from NAPRTCS highlighted role of BP – 58% vs 49%
 - systolic HTN following multivariate analyses
 - JASN 2003; 14: 2618-2622



Systolic and diastolic hypertension ($p < 0.0001$)



Systolic hypertension only ($p < 0.0001$)



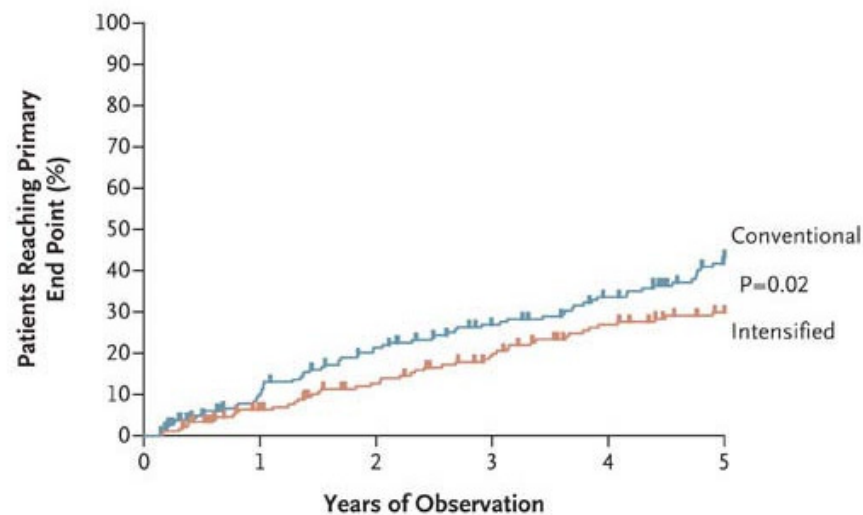
Diastolic hypertension only ($p < 0.0001$)

Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF [chronic renal failure] in Pediatric Patients (ESCAPE) Trial Group

NEJM 2009

- Assessed the long-term reno-protective effect of intensified blood-pressure control among children receiving a fixed high-dose of an ACEi
 - 385 children, aged 3-18 years with eGFR 15-80 ml/min/1.73m²
 - Ramipril 6mg/m² following 6-month run-in period
 - Intensive arm (24-hour MAP <50th percentile) and conventional arm (MAP 50th-95th percentile)
- Primary outcome was the time to a 50% loss of GFR or ERF
- Primary outcome observed in 29.9% of intervention arm versus 41.7% in the control group (p=0.02)

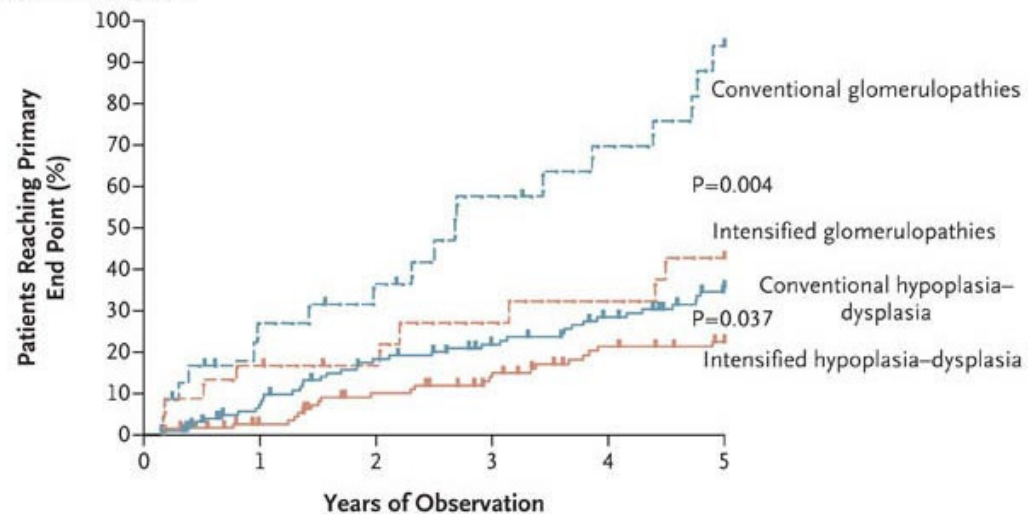
A All Patients



No. at Risk

Intensified	182	167	152	142	135	126	119	110	102	97	90
Conventional	190	168	154	142	131	122	112	107	97	86	75

B Glomerulopathies or Hypoplasia–Dysplasia



No. at Risk

Intensified glomerulopathies	28	21	19	18	17	15	15	14	14	12	12
Conventional glomerulopathies	24	20	16	15	13	11	8	6	5	4	1
Intensified hypoplasia–dysplasia	125	118	112	102	97	93	88	81	76	74	71
Conventional hypoplasia–dysplasia	139	127	116	108	101	98	91	88	78	70	63

...‘cardiovascular risk’

In young adults with ‘*childhood-onset CKD*’, it is likely that cardiovascular pathology develops during childhood

CV risk factors in adults

Traditional

- Age, white race and male
- **Hypertension**
- **Dyslipidaemia**
- **Diabetes mellitus**
- Tobacco use
- Physical inactivity
- LVH
- **Obesity**

CKD-related

- Malnutrition
- Decreased GFR
- ↑Proteinuria
- peripheral RAA activity
- Abnormal Ca-P
- Hypoalbuminaemia
- Anaemia and fluid overload
- Hyperhomocystinaemia
- Chronic inflammation
- Dyslipidaemia
- Oxidative stress

Prevalence and Correlates of Multiple Cardiovascular Risk Factors in Children with Chronic Kidney Disease

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Amy C. Wilson^{*}, Michael F. Schneider[†], Christopher Cox[†],
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Abstract

This Article

Published online before
print October 2011,
doi: 10.2215/
CJN.03010311

CJASN December 2011
vol. 6 no. 12 2759-2765

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CKiD study: cardiovascular risk factors

Wilson et al CJASN 2011

- CKiD study (n=250)
 - Investigated CV risk factors including hypertension, dyslipidaemia, obesity and abnormal glucose metabolism
 - 26% only with no risk factors
 - **Hypertension** - SINGLE most prevalent risk factor seen in 46%
 - It remained the most prevalent risk factor alone or in combination

Summary-2

- Improved control of blood pressure and proteinuria in children with CKD will delay progression
- Hypertension is one of the most prevalent CV risk factors in CKD
- What about hard end points?
- What evidence do we have that hypertension affects the heart and blood vessels?

Well there are no hard end points...

So, in children with pre-dialysis stages of CKD in the absence of hard end-points--- **surrogate markers** of CV disease

Spectrum of surrogate markers

- Cardiac disease:
 - **m-mode to measure LV mass** (other methods include 3D echo and CMRI), tissue doppler imaging
- Arterial disease:
 - Structural: **cIMT** and coronary artery calcification score
 - Functional: **PWV**, PWA, arterial distensibility, heart rate variability and flow-mediated dilatation

Relation of blood pressure with LVH

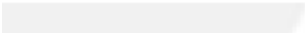
- In children with pre-dialysis CKD the evidence for the **relationship of BP with LVH** controversial
- *ESCAPE* study –**NO** : n=156 children from 20 centres across Europe
 - recent follow up data in a cohort of n=84 over 1-2 years
 - In multivariate analysis, improvement in myocardial function was associated with reduction in BP ($r=20.4$; $P<0.05$), independently of LVMI reduction
- *CKiD* study – **YES**: n=198 children from 46 centres across USA
 - recent follow up data over 4-years confirms this

Blood Pressure Control and Left Ventricular Mass in Children with Chronic Kidney Disease

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Charles Turner,[§] R. Neil Dalton,[§] Christopher J.D. Reid,^{*} Susan P.A. Rigden,^{*}
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Clin J Am Soc Nephrol 6: ●●●–●●●, 2011. doi: 10.2215/CJN.04690510



Aims

Our aims after adjustment for confounders were to

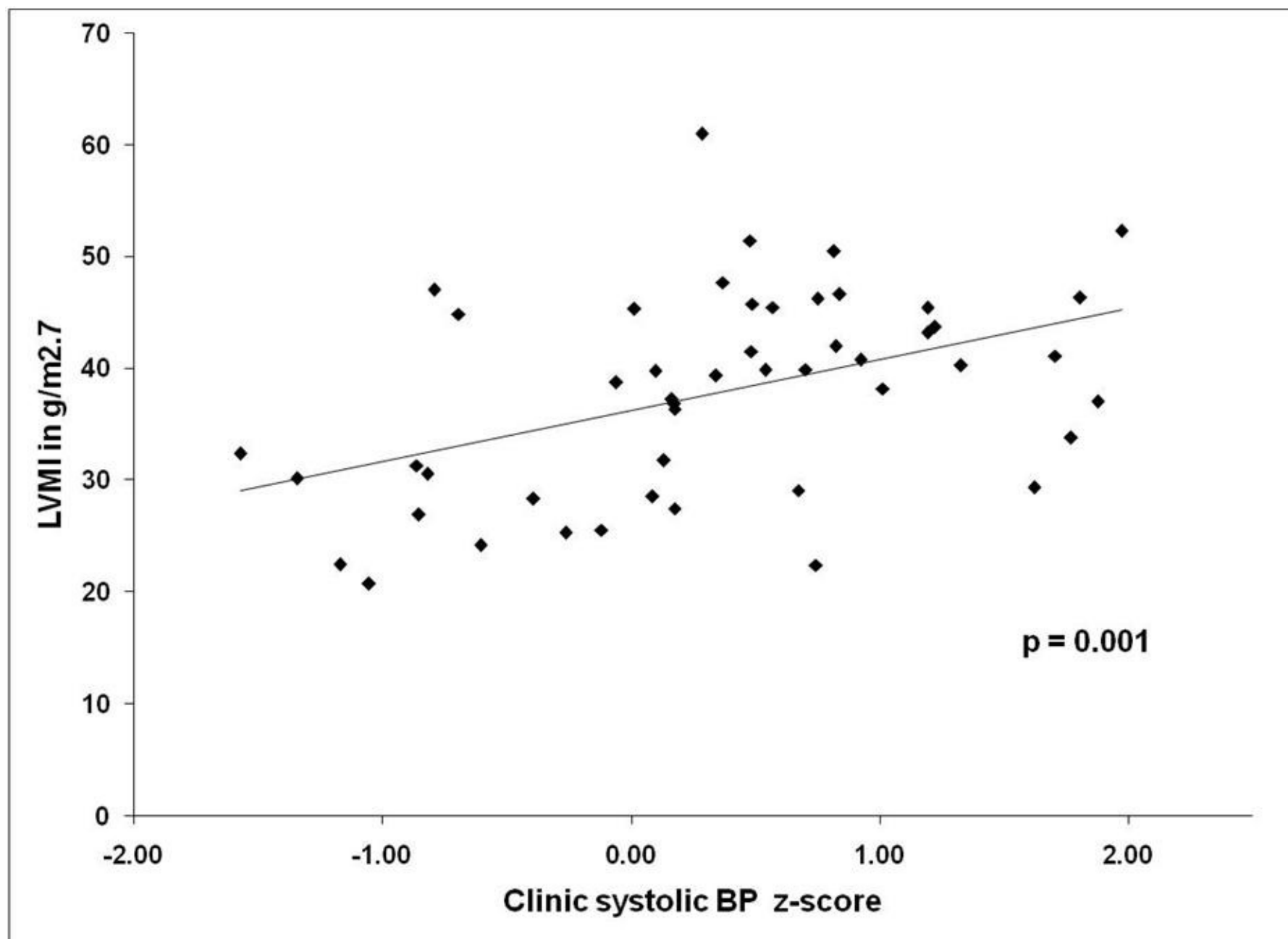
- (i) evaluate whether there is a relationship between LVH and BP in *normotensive* children with CKD and
- (ii) whether current targets for BP control are appropriate

Table 1. Patient demographics on the day of study

Demographics	All Patients (<i>n</i> = 49)	No LVH (<i>n</i> = 25)	LVH (<i>n</i> = 24)	<i>P</i>
Age (years)	12.6 ± 3.0	13.0 ± 3.0	12.3 ± 3.1	0.41
Male gender, <i>n</i> (%)	29 (59.2%)	13 (52%)	16 (66.7%)	0.39
Primary diagnosis structural disease, <i>n</i> (%)	38 (77.6%)	21 (84%)	17 (70.8%)	0.32
Height z-score	−0.65 ± 1.28	−0.69 ± 1.34	−0.62 ± 1.23	0.84
Weight z-score	0.03 ± 1.26	−0.25 ± 1.21	0.33 ± 1.27	0.10
BMI z-score	0.53 ± 1.29	0.18 ± 1.33	0.89 ± 1.17	0.05
Antihypertensive medications, <i>n</i> (%)	27 (55.1%)	13 (52%)	14 (58.3%)	0.78
ACEI ± ARB or combination with ACEI ± ARB, <i>n</i>	24	13	11	
CKD stage 3; stage 4; stage 5, <i>n</i>	19; 22; 8	11; 11; 3	8; 11; 5	0.64
Hydroxylated vitamin D3, <i>n</i>	35	16	19	0.61
Hydroxylated vitamin D3 dose, µg/d	0.41 ± 0.23	0.39 ± 0.22	0.43 ± 0.25	

Data shown as mean ± SD unless stated otherwise. LVH was defined using age-specific reference intervals for normal children (19). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

- 19 children under paediatric nephrology care since birth
- The duration of median (IQR) follow-up with us was 7.2 (1.9, 11.0) years



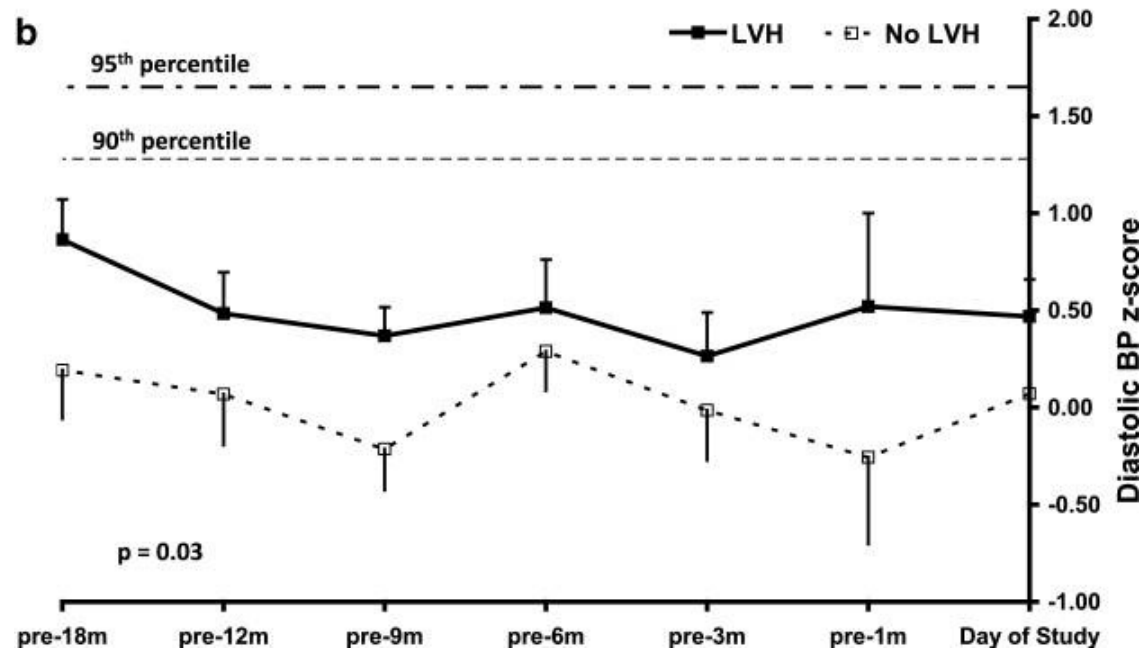
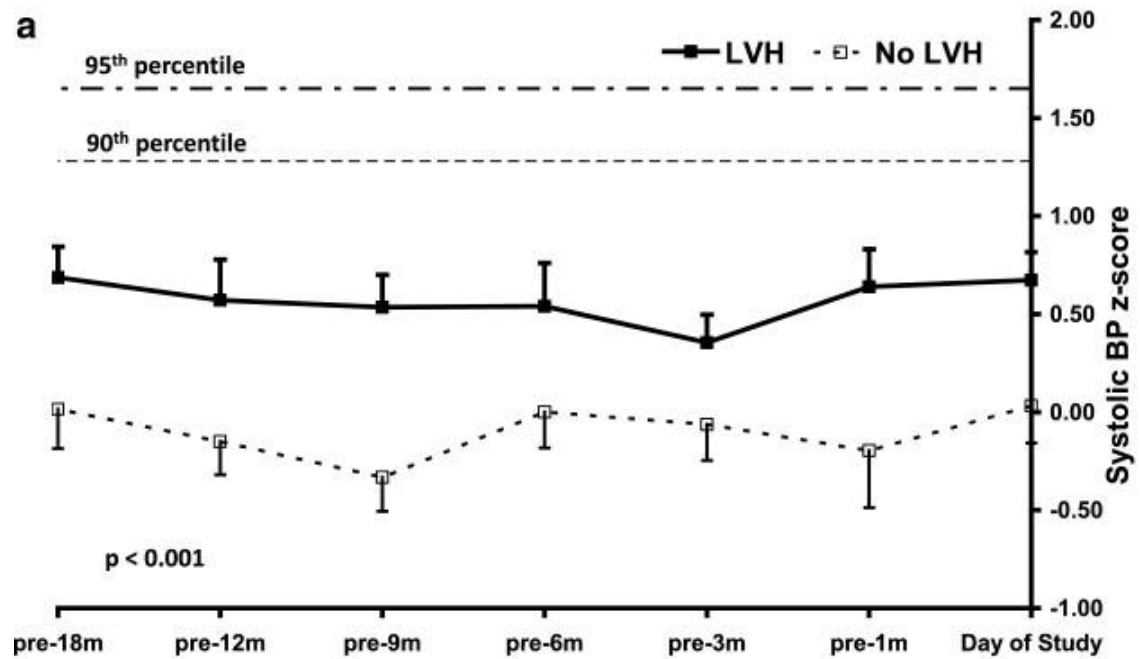


Table 4. Quantification of the relationship between BP (independent variable) and LVMI (dependent variable) expressed in $\text{g}/\text{m}^{2.7}$ via multiple linear regression

Variable	Model A, Clinic SBP z-Score		$r^2 = 0.40$, adjusted $r^2 = 0.29$	
	Coefficient	SEM	<i>P</i>	Variance Inflation Factor
Clinic SBP z-score ^a	3.94	1.41	0.008	1.41
BMI	0.12	0.28	0.67	1.06
eGFR	-0.09	0.10	0.37	1.58
Antihypertensive medication	-0.65	2.22	0.77	1.13
Time-averaged log iPTH	-0.28	1.59	0.86	1.38
Time-averaged serum Ca	13.17	15.26	0.39	1.44
Elemental Ca intake	2.99	1.32	0.03	1.27

A separate model was constructed for each of the BP methods with adjustment for the same confounders throughout.

Discussion

- Significant association between BP and indexed LVM in children with CKD stages 3-5
- Despite having BP measurements consistently within the currently accepted normal range
- 49% had LVH as defined by age specific reference intervals, related to systolic BP values measured both in clinic and by ambulatory BP monitoring
- Thus, even for children with apparently “normal” BP, the level of BP would appear to be an important determinant of LVH

Conclusions

LVH was significantly associated with SBP even in children with BP below the 90th percentile: findings have implications for the degree of control of BP which is sought in this patient group

**The Hypertension Optimal Treatment in
Children with Chronic Kidney Disease study:
The H^OT-KID study- A randomised trial to
compare effects of aggressive versus
standard targets in blood pressure on target
organ damage in children with CKD**

UK-wide multi-centre RCT

UKCRN ID: 12925

MREC: 10/H0802/13

ISRCTN: 25006406



University of London



Hypotheses

1. Elevated blood pressure is the major determinant of left ventricular hypertrophy (LVH), arterial function and structure in paediatric patients with chronic kidney disease.
2. Optimal control of **clinic systolic** blood pressure (below the 40th percentile) as opposed to standard care (maintaining blood pressure between 50th-75th percentile) will result in (i) normalising left ventricular hypertrophy and (ii) arterial function and structure

Purpose of clinical trial

This study will determine whether controlling blood pressure to a lower level than is currently recommended will prevent damage to the heart and arteries in children with pre-dialysis CKD

??????????

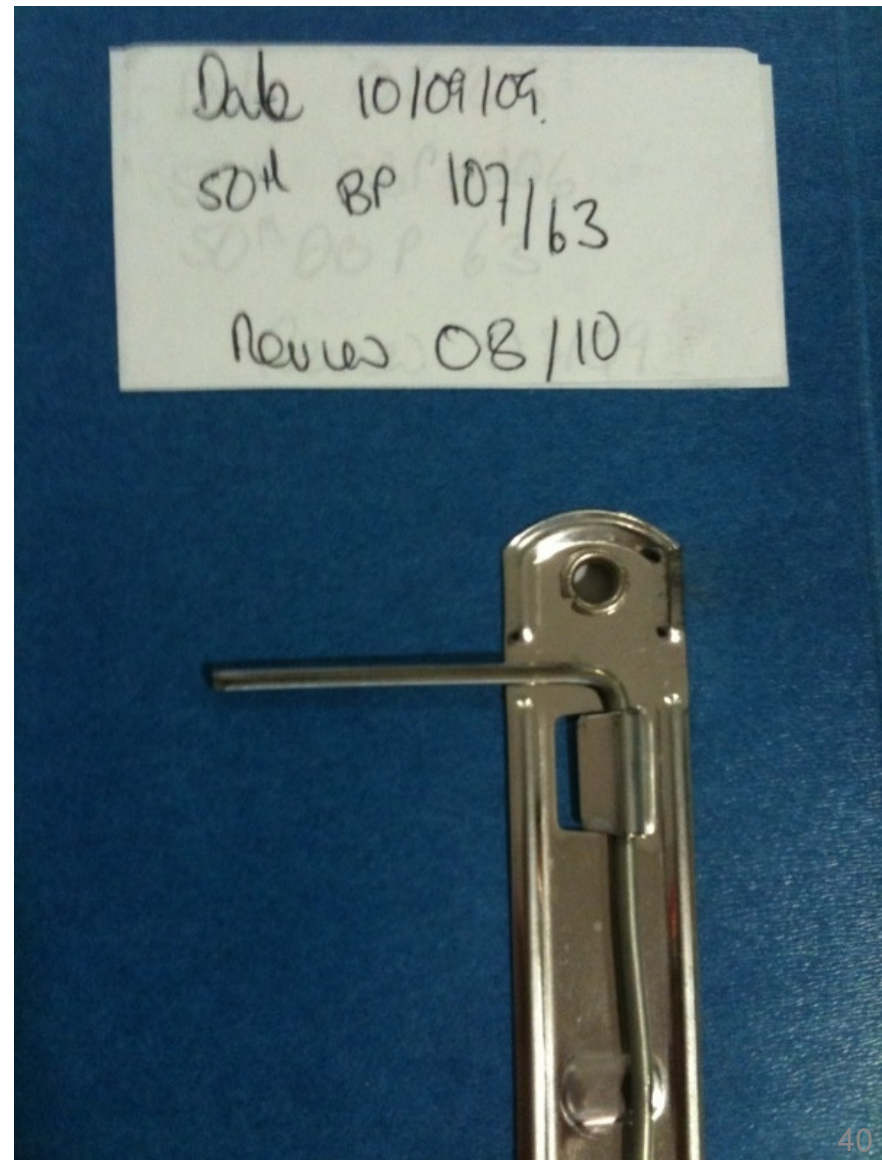
**All that is very well but what can I do
now to improve blood pressure
control in my clinic?**

Clinical targets to reduce hypertension related CV disease

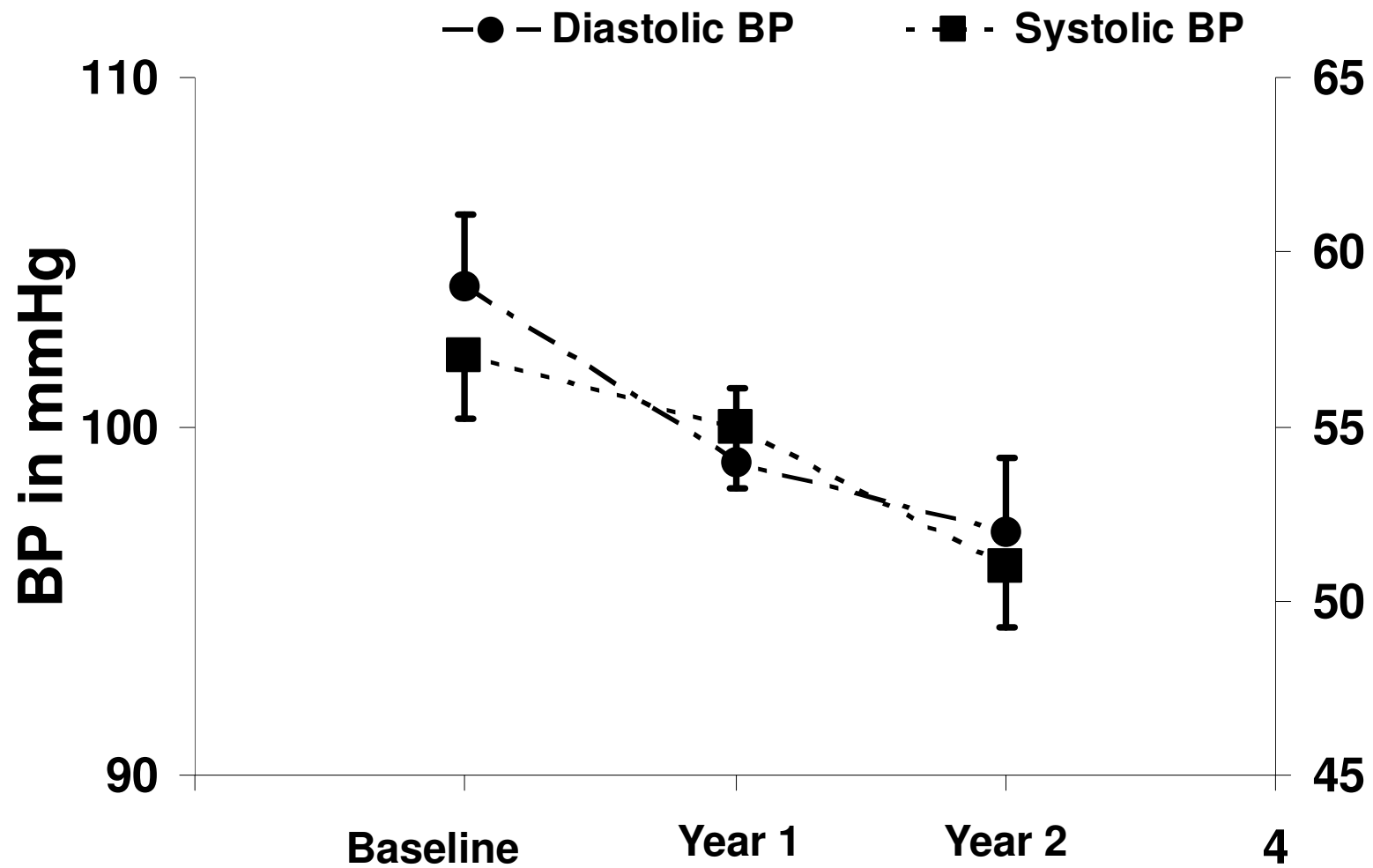
- **Blood pressure: Aim for SBP <75th percentile**
- **Use of an accurate technique to measure BP**
- **Use of ACEi**
- **Out of office assessment of blood pressure profile**
 - **ABPM and home BP assessment**

How we improved this in our CKD clinic

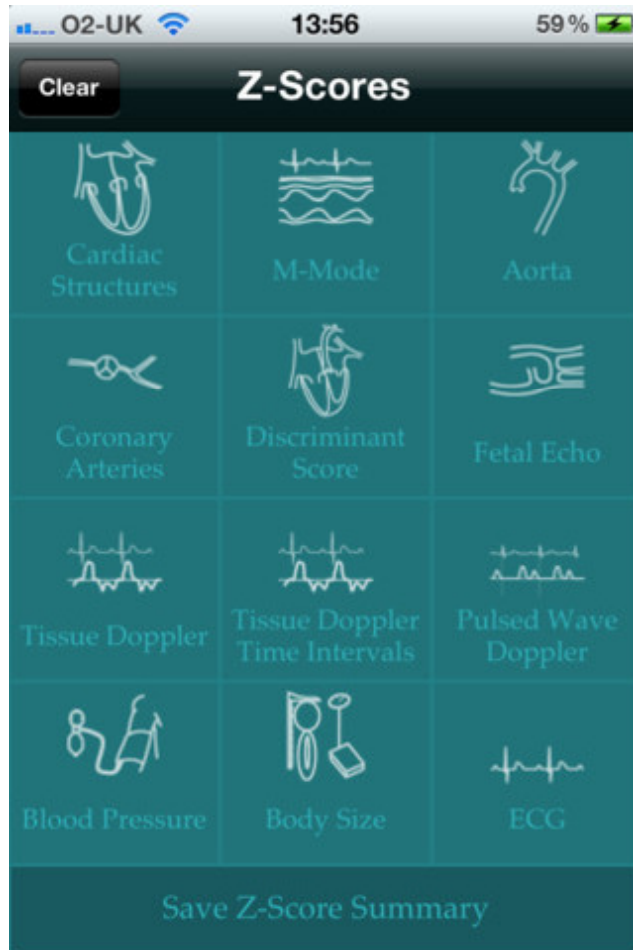
- All patients in clinic grouped by birthday months
- At the end of the month latest height and BP related data collected
- Updated 'target BP' label in notes



Clinic BP in CKD 3-5



'Cardio Z' iphone app from ECH



- allows calculation of z-scores of:
 - Height, weight, BMI and head circumference
 - Clinic blood pressure, with calculation of a user-defined 'target centile' blood pressure
- <http://www.ubqo.com/cardioz>

Clinical targets to reduce hypertension related CV disease

- **Blood pressure: Aim for SBP <75th percentile; ACEi; out of office**
- Pre-emptive transplantation
 - remember transplantation reduces but does not eliminate risk factors
- **Obesity (and dyslipidaemia)**
- Anaemia: Hb: 9.5-11.5 in <2years; 10-12g/dl >2years
- CKD-MBD: maintain serum calcium and phosphate in normal range; preferably target PO4 levels <50th percentile; PTH<2X ULN; renal dietician
- Longer and more frequent dialysis and screening for LVH
- Pre-clinic meeting to discuss and plan management of these patients

Thank You

Acknowledgments

- Kings College London
- Guy's & St Thomas' Charity
- British Heart Foundation