



# Cardiovascular Involvement in Paediatric ESRD

***Tim Ulinski***

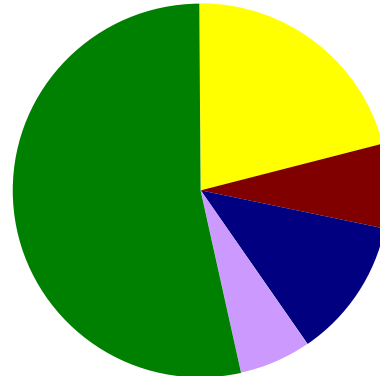
Pediatric Nephrology  
Trousseau Hospital & University Pierre et Marie Curie, Paris

*CME Course, Istanbul, 2011*

# Distribution (%) of causes of death for all dialysis patients by age (1994–96)

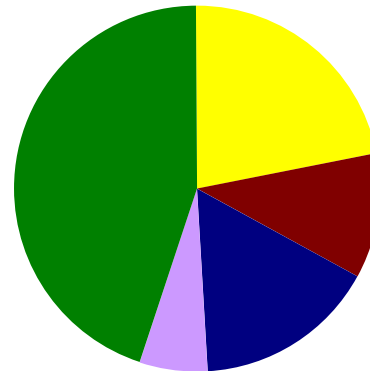
20–44 years

Rate: 95 deaths/10<sup>3</sup> patient years



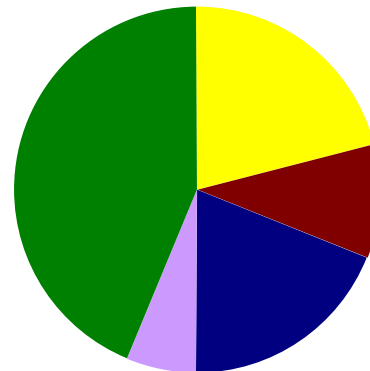
45–64 years

Rate: 173 deaths/10<sup>3</sup> patient years



+65 years

Rate: 341 deaths/10<sup>3</sup> patient years



♥ - vascular disease

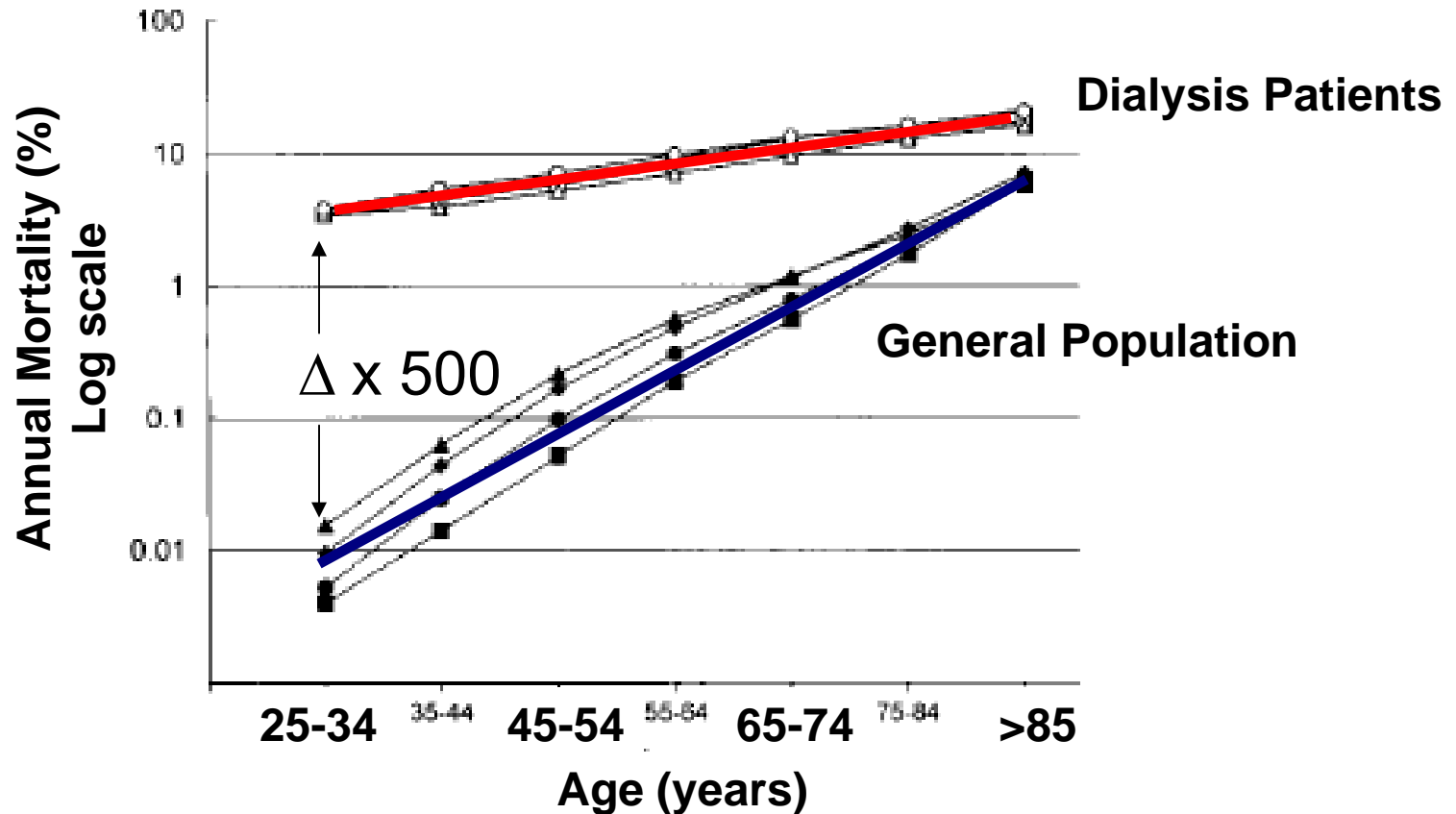
- Cardiac arrest
- Acute MI
- Other cardiac
- Cerebrovascular
- Non-cardiac

# Approximate prevalence of CVD by target population in adults

	<b>Coronary artery disease(%)</b>	<b>Left ventricular hypertrophy (%)</b>
<b>General population</b>	<b>5–12</b>	<b>20</b>
<b>Chronic renal failure</b>	<b>N/a</b>	<b>25–50</b>
<b>Hemodialysis (HD)</b>	<b>40</b>	<b>75</b>
<b>Peritoneal dialysis (PD)</b>	<b>40</b>	<b>75</b>
<b>Renal transplant recipients</b>	<b>15</b>	<b>50</b>

# Cardiovascular Disease Mortality General Population vs. ESRD Dialysis Patients

Cardiovascular mortality in young adults on dialysis  
Is ~ 500 fold increased compared to general population

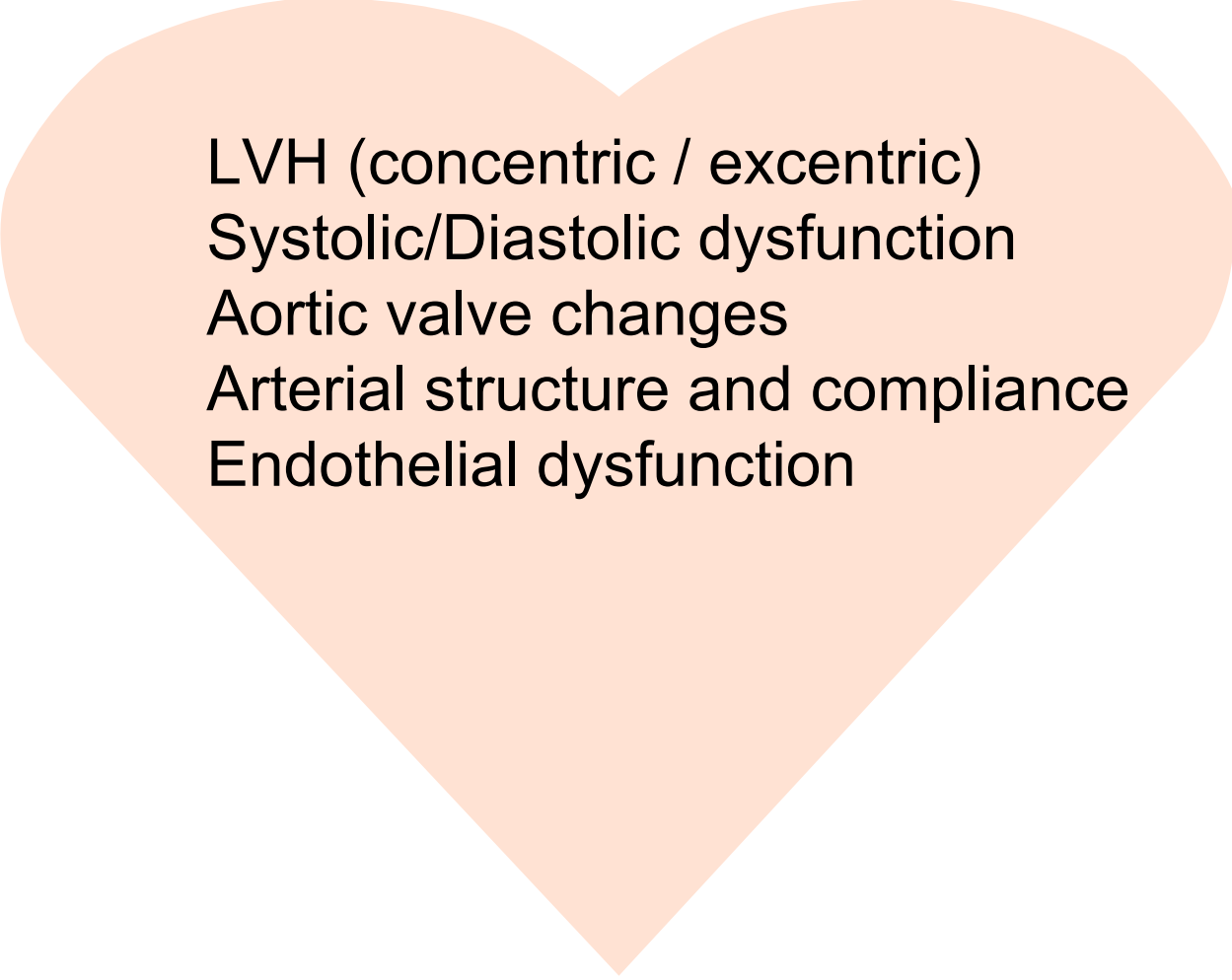




# What ♥-vascular involvement in pediatric ESRD ?



# Cardiovascular Pathology in ESRD Children



LVH (concentric / excentric)  
Systolic/Diastolic dysfunction  
Aortic valve changes  
Arterial structure and compliance  
Endothelial dysfunction



# Prevalence of CVI in pediatric PD and HD patients



# Prevalence of cardiovascular risk factors in children

Risk factor	CRI	HD/PD	Transplant
Hypertension	48%	52-75%	63-81%
Dyslipidemia	25-53%	33-87%	55-84%
Anemia	48%	40-67%	32-64%
Hyper-PTH	33-44%	58%	-
Hyperhomocyst.		87-92%	25-100%
↑CRP		76%	16%
Albumin↓		40-60%	-

**Cardiovascular risk factors persist post transplant**

*Adapted from Mitsnefes, Ped Nephrol, 2008*



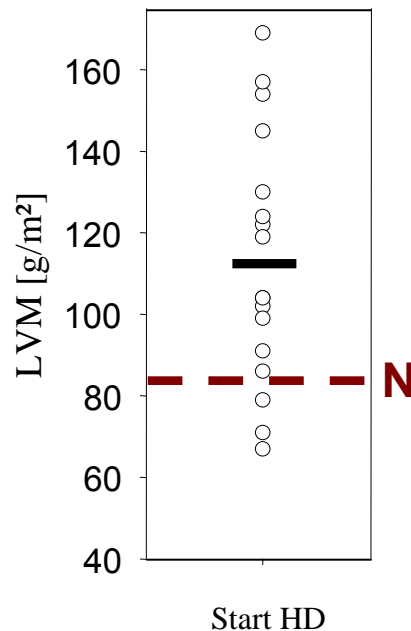


# Left Ventricular Hypertrophie in HD Children

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LVH at start of renal replacement therapy : 52 – 83%

*(Becker-Cohen 2008, Mitsnefes 2006, Ulinski 2006)*



- Dialysis start too late
- Blood pressure treatment insufficient



# Prevalence of LVH in PD & HD

Ten Harkel *NDT 2009*

LVH = 57% in PD patients

Bakkaloglu *NDT 2009*

LVH = 68% in PD patients

Mitsnefes *Ped Nephrol 2000*

LVH = 68% in PD

LVH = 85% in HD

PD eccentric 1/3

concentric 2/3

HD eccentric 2/3

concentric 1/3



# HD *versus* PD

- LVM not significantly different in children on HD vs. PD
- Aortic stiffness higher in HD vs. PD
- No relation between aortic stiffness + LVM (in HD or PD)

*Robinson et al, Ped Nephrol, 2005*



# Arterial Stiffness in Children on Dialysis

	<b>Dialysis (mean±SD)</b>	<b>Controls (mean±SD)</b>
Augmentation Index	29.7 ± 15.4	8.3 ± 8
Pulse Wave Velocity	6.6 ± 1.0	5.4 ± 0.6



# Increased Intima Media Thickness in ESRD

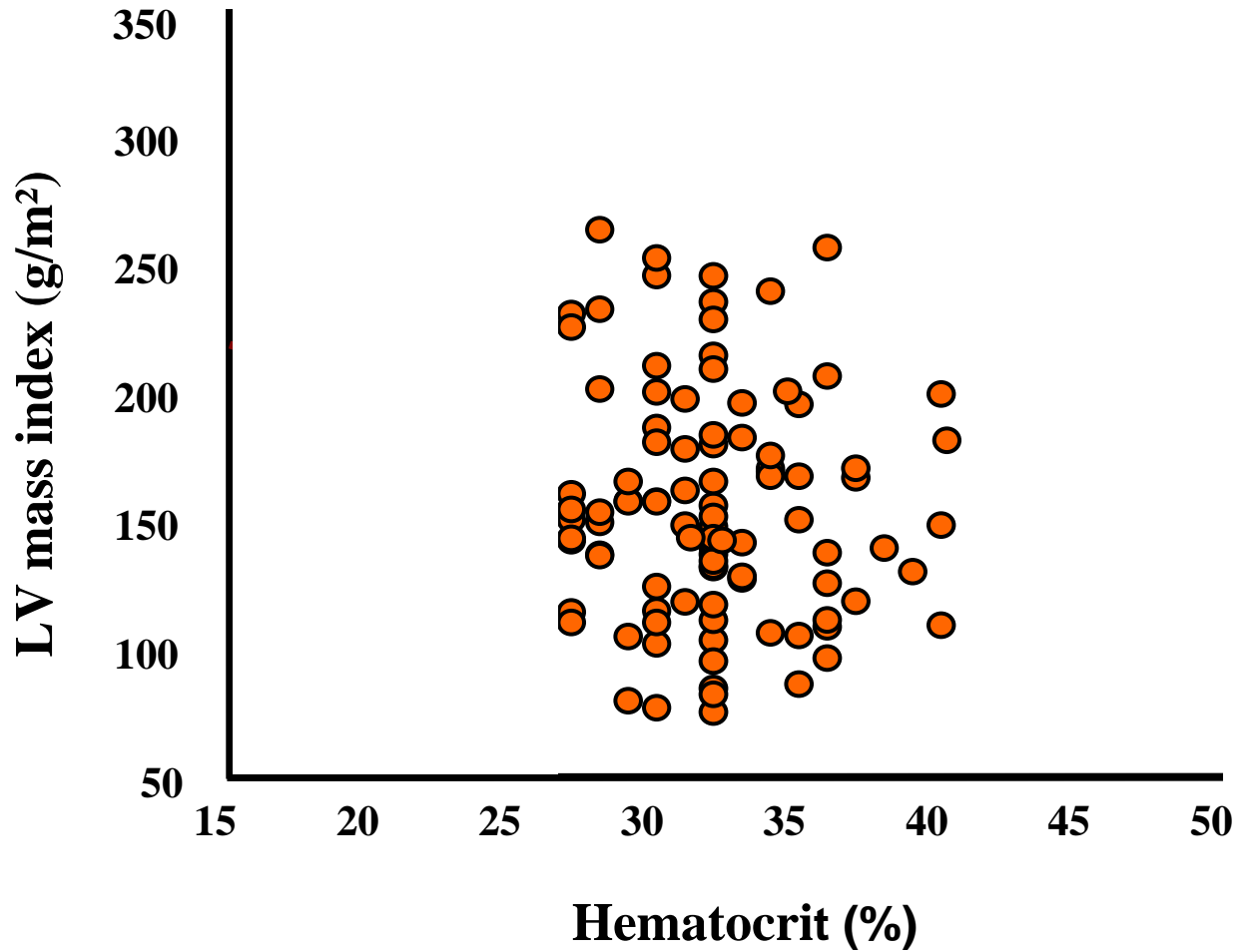




# Pathomechanisms – Risk factors

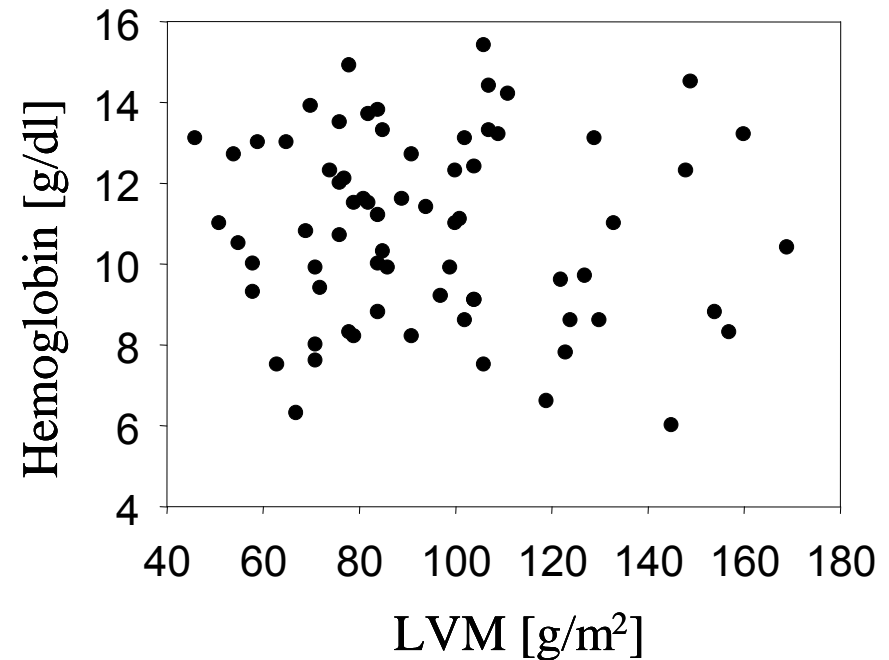
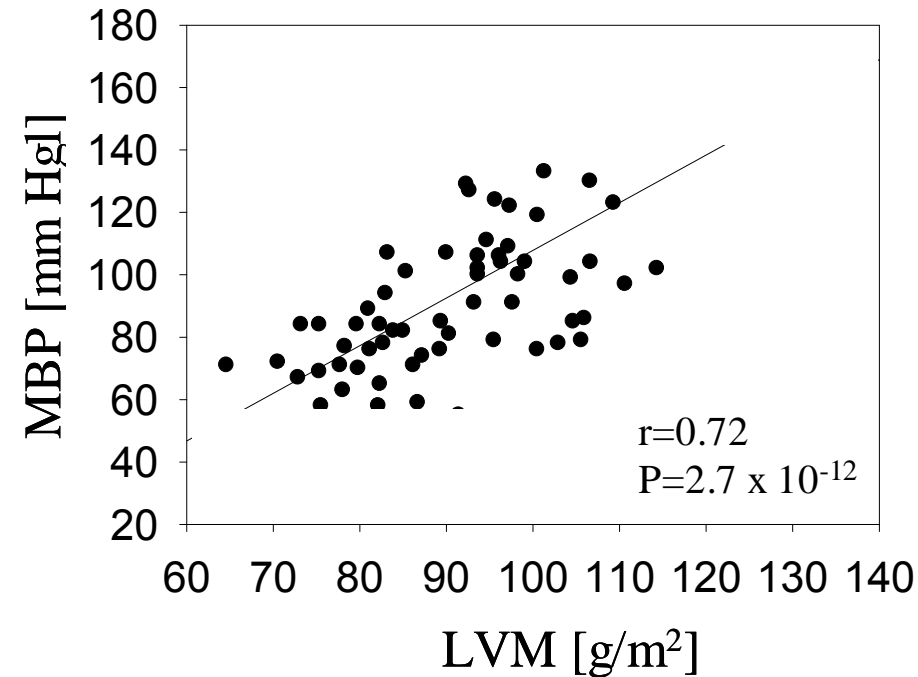


# Correlation between hematocrit and LVM index in ESRD adult patients



*London et al Kidney Int 1987*

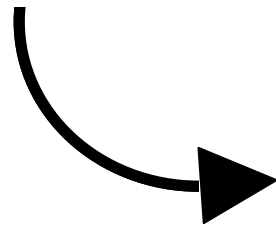
# LVM is correlated with blood pressure but not with hemoglobine level





## LVM in Pediatric HD + PD

LVM index	<i>n</i> (%)	Male	Female	White	Black	HD	PD
<90th	13 (20)	8	5	12	2	4	9
90th–95th	3 (5)	1	2	2	1	–	3
95th–99th	11 (17)	6	5	6	5	4	7
99th–51 g/m <sup>2.7</sup>	11 (17)	4	7	9	2	4	7
>51 g/m <sup>2.7</sup>	26 (41)	13	13	18	8	14	12
Total	64 (100)	32	32	46	18	26	38

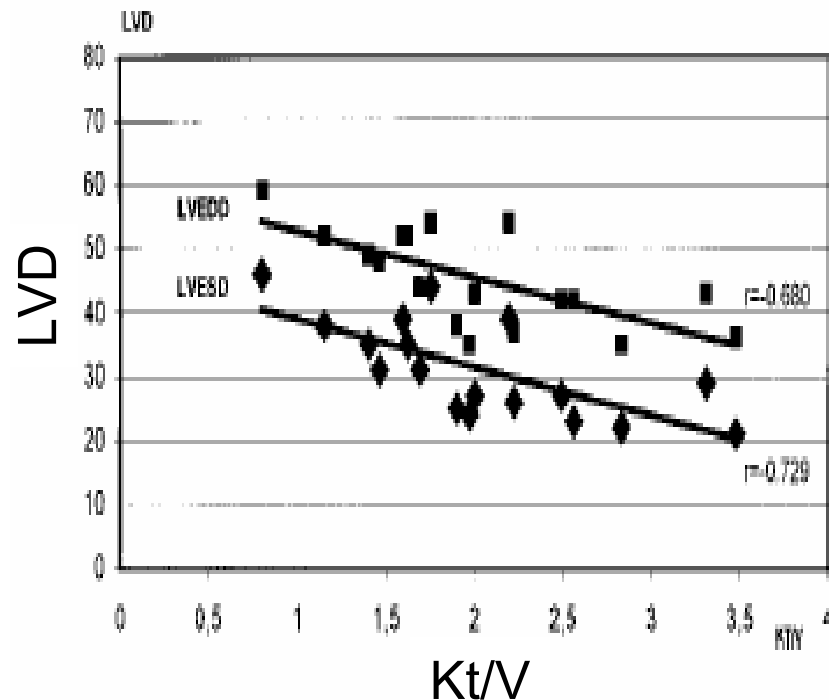
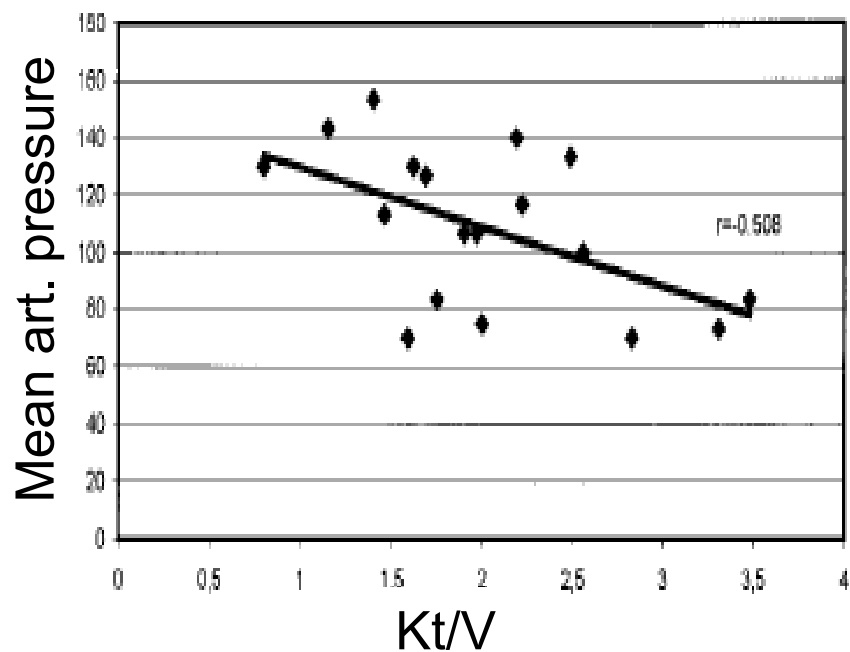


### Greatest risk factors:

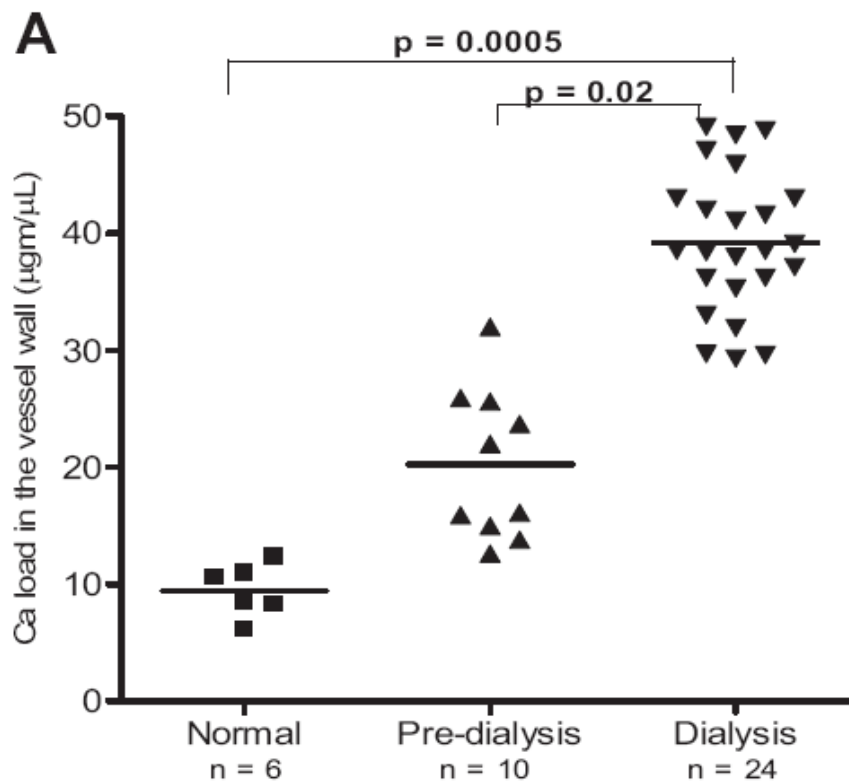
- African American origin
- HD



# Left ventricular architecture is related to dialysis dose in PD children



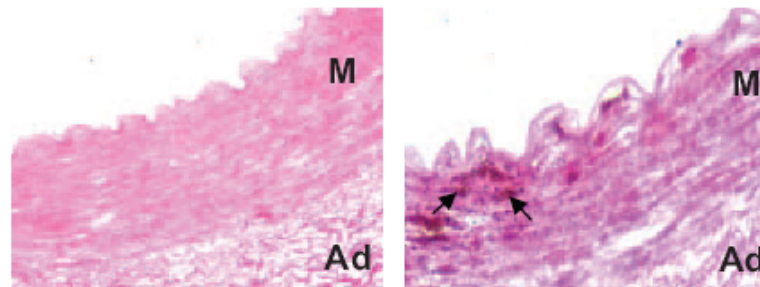
# Calcium Load in Vessel Wall is increased in CRF and ESRD Children



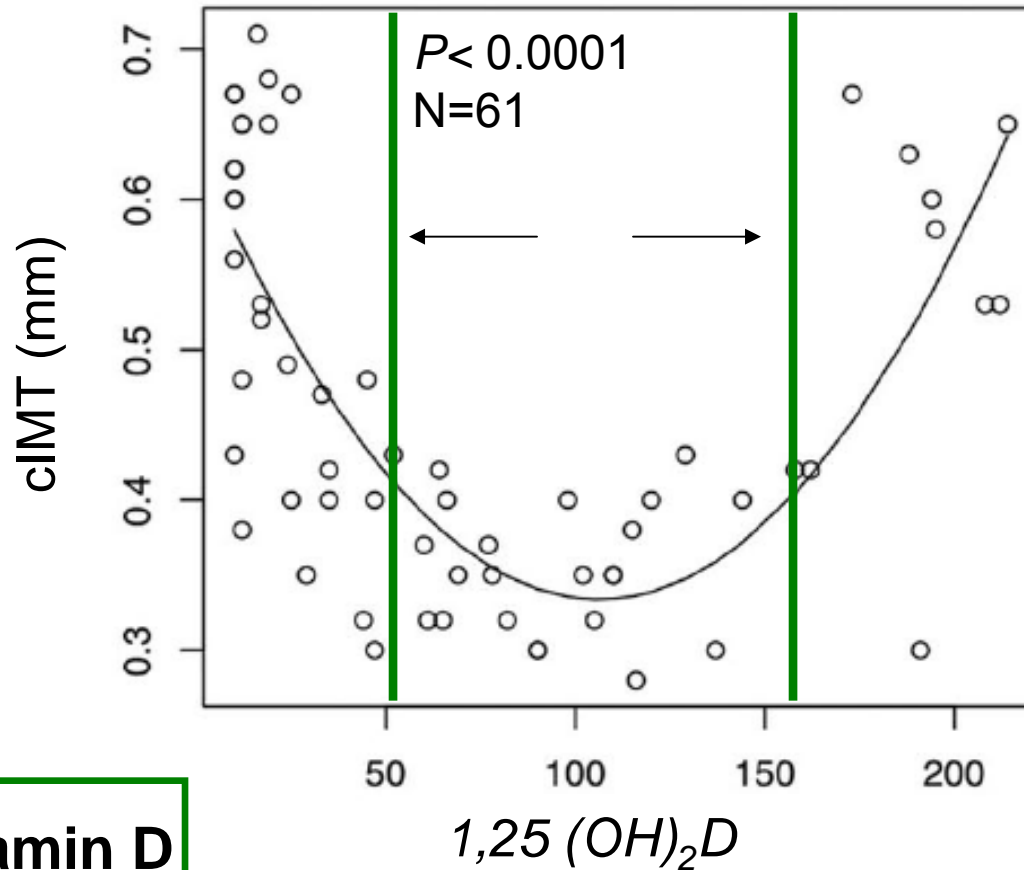
*Shroff et al*  
*Circulation 2008*

## **B** Control Patient      Dialysis Patient

Diffuse speckled calcification in the media and along the internal elastic lamina in 25% of dialysis vessels (von Kossa staining)



# cIMT shows a significant quadratic relationship with $1,25(\text{OH})_2\text{D}$ levels in Dialysis Children

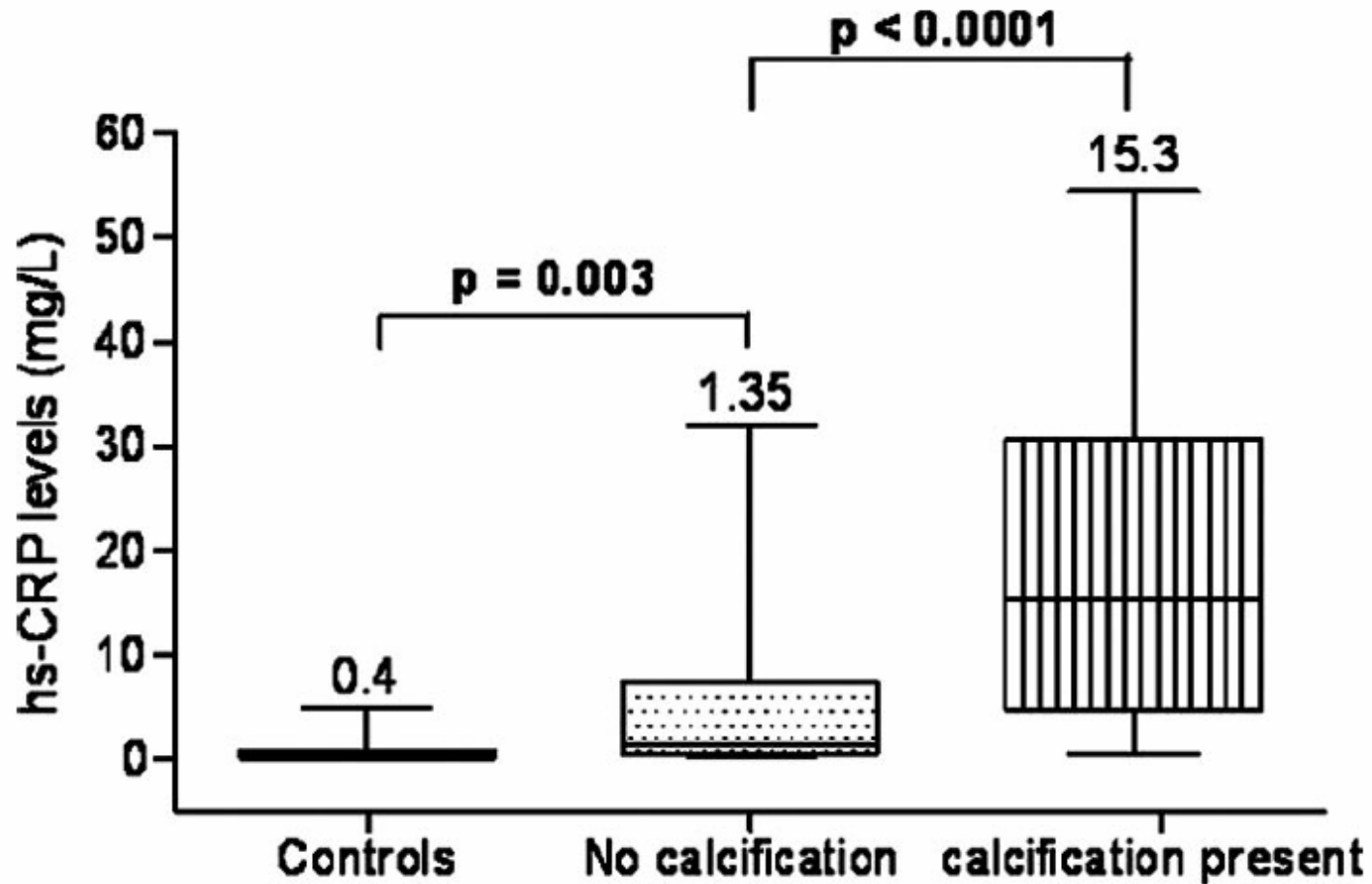


→  
**1,25 Vitamin D  
&  
Calcimimetics**

*Shroff, JASN 2008*



# HS-CRP is higher in patients with calcification

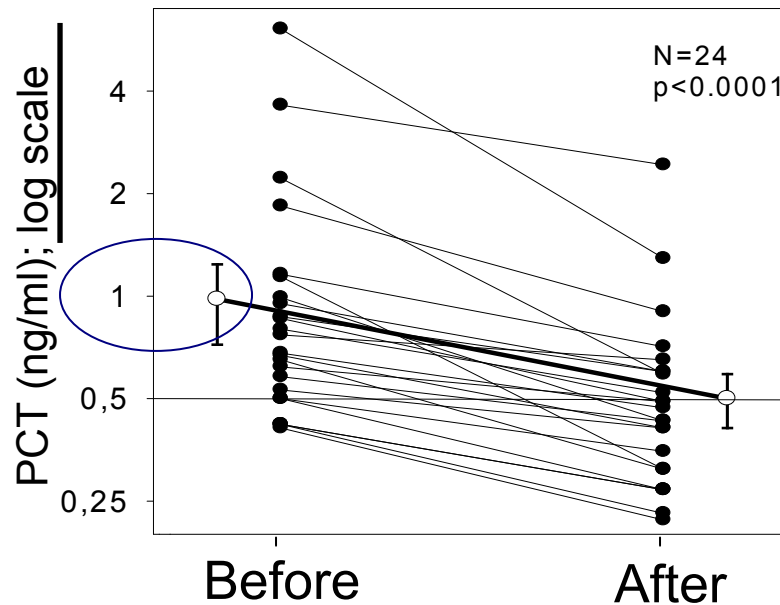


Shroff, JASN 2008

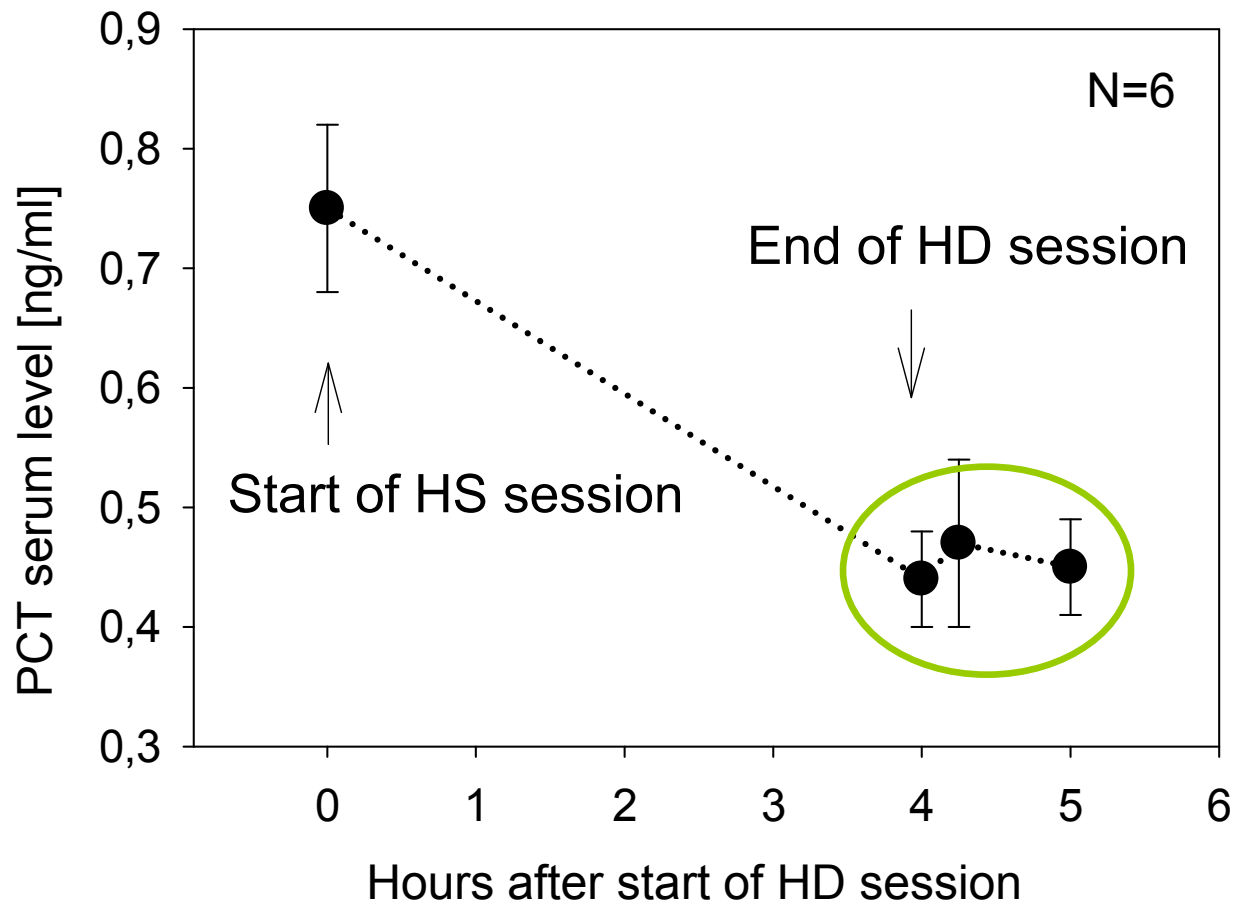


# PCT in Pediatric HD

- Marker for micro-inflammation in ESRD
- Micro-inflammation → ♥-vascular risk factor
- PCT serum levels ? dialysable (13 kDa) ?



# Hemodialysis ~~→~~ PCT synthesis



# Physiological inhibitors of calcification

## Fetuin-A + osteoprotegerin

Fetuin A



Neg correlation with PWV, arterial calcification

Osteoprotegerin



Pos correlation with PWV, arterial calcification

*Shroff et al., NDT 2008*





# ESRD

Intima calcification

Media calcification

« Classic » risk factors for atherosclerosis

More ESRD-specific

Age  
Diabetes  
Smoking  
LDL cholesterol  
Inflammation

*Sonography*

Hypertension  
Duration of dialysis  
Calcium containing P-binders

*PWV*  
*cIMT*

**Vascular smooth  
muscle cells**

Phosphate

↓ +

↑ +  
Uremia

**Osteoblast-like cells  
(expression of osteopontin+AP)**



Anemia      Hypertension      Hypercirculation      Arterial Stiffness

• AT-II   • Sympathic activity   • Inflammation



Interstitial Fibrosis

Myocardila capillary density ↓

LVH

*Eccentric*  
Vol. overload + Anemia

*Concentric*  
SBP + Art. Stiffness

**Arrhythmias**

**Death**





**What improvement is possible on RRT ?**



# Dry Weight Management

## Definition:

« The lowest weight a patient can tolerate without the development of symptoms or hypotension »

## Particular difficulties in pediatric patients: Quick changes

Bioimpedance

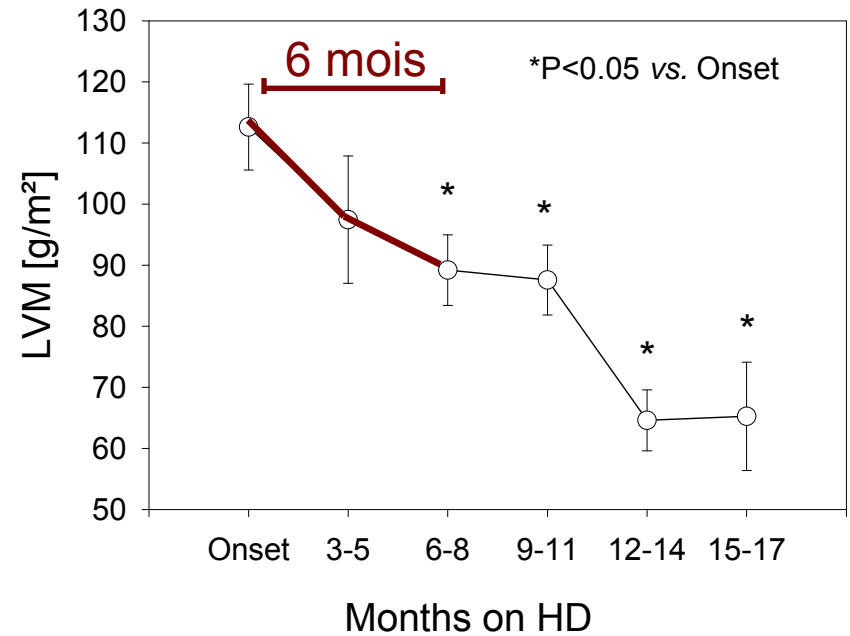
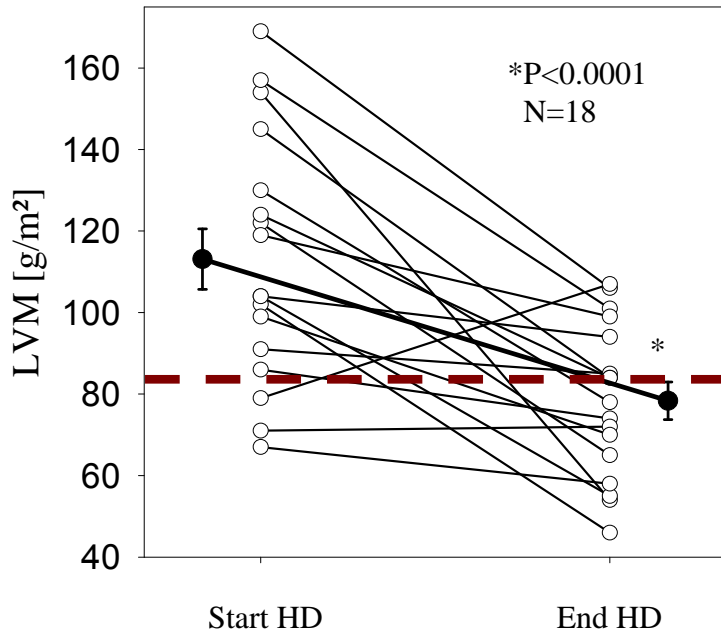
Vena cava diameter

ANP

Hematocrit monitoring



# Left Ventricular Hypertrophie in HD Children



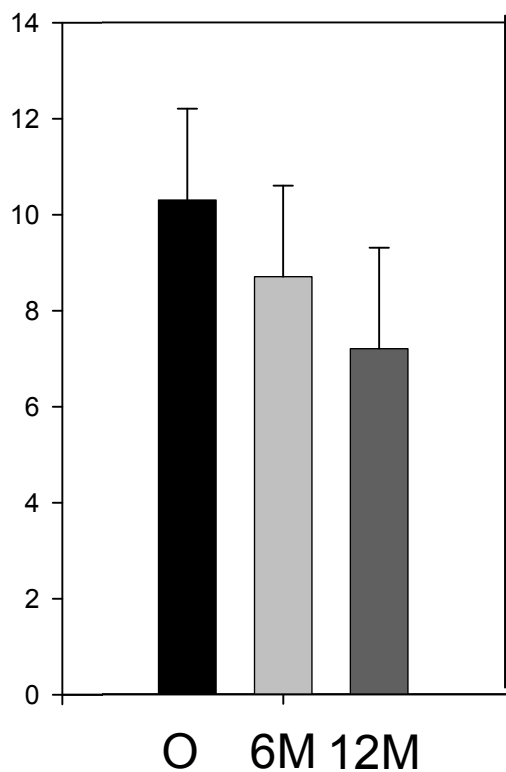
Weekly dry-weight adaptation  
Normalisation of blood pressure



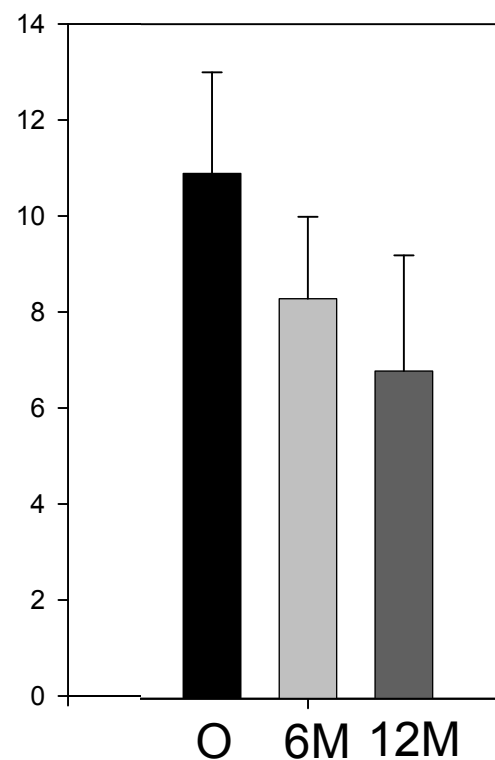


# Switch from HDF (3 times/week) to daily HDF

## Posterior Wall thickness



## Interventricul. Septum



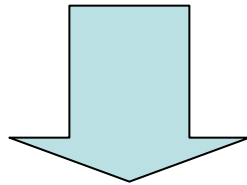
# Intensified dialysis regimen

Daily online hemodiafiltration

*Fischbach et al; NDT 2004*

Nocturnal hemodialysis

*Muller et al; PN 2008*



**LVM normalisation**

PTH  
HDL Cholesterol  
ADMA  
Phosphate  
Blood pressure

For children who  
can not be transplanted rapidly





# Changes after Transplantation





# Post Transplant Changes

Prevalence of LVH 54% → 8% ✓ *Becker-Cohen et al, 2008*

Young men (20-40 yrs)  
with juvenile ESRD

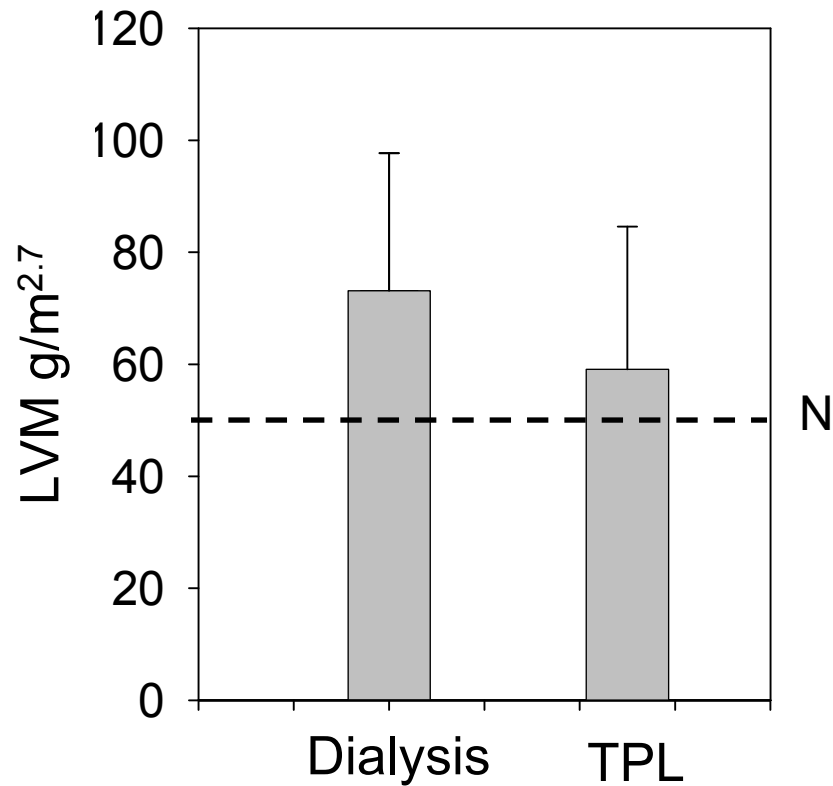
↳ 75% had functioning graft

↳ 50% LVH  
related to high BP



*Gruppen et al, 2003*

## Changes of LVMI after renal TPL



# Post Transplant Changes

- Uremia
- Anemia
- Volume overload
- Art.-ven. fistula



- Hypertension
- Ischemic cardiovascular disease
- Immunosuppressive therapy
- Genetic factors

=

**Present in TPL**

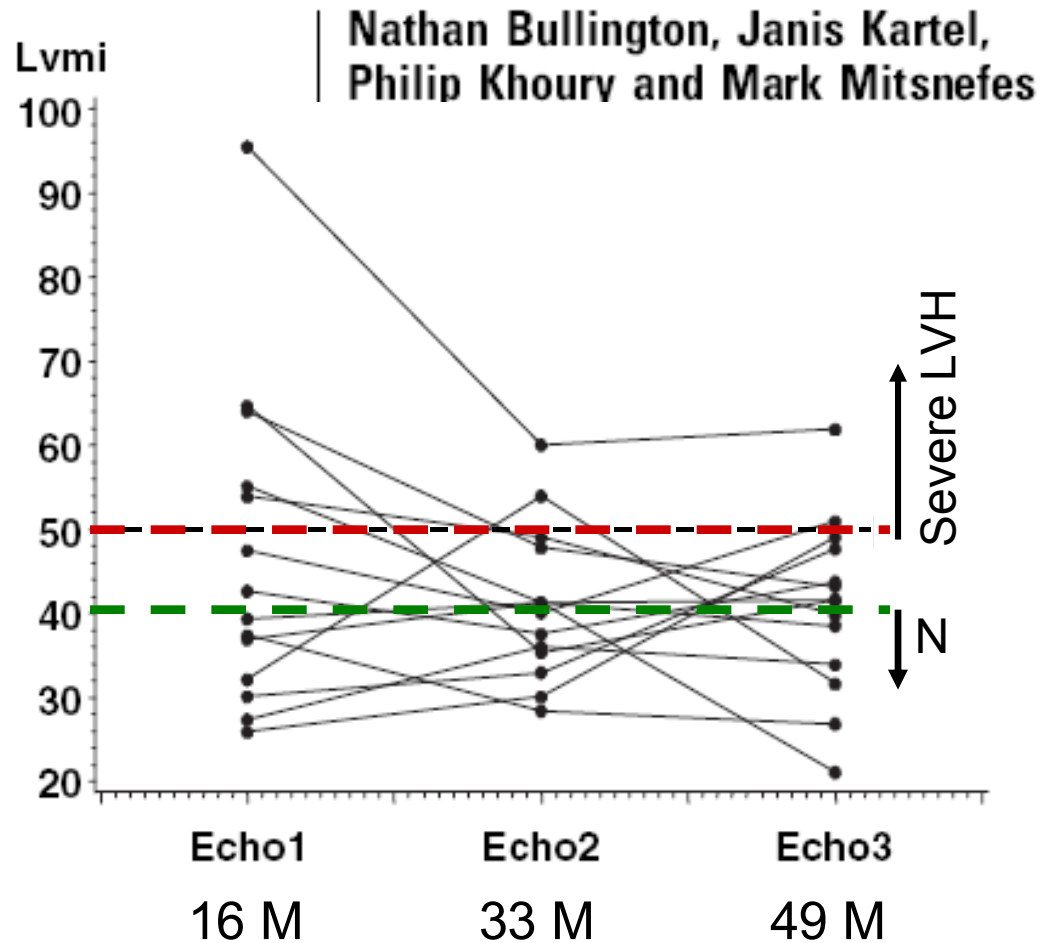
**Sympathic activity**



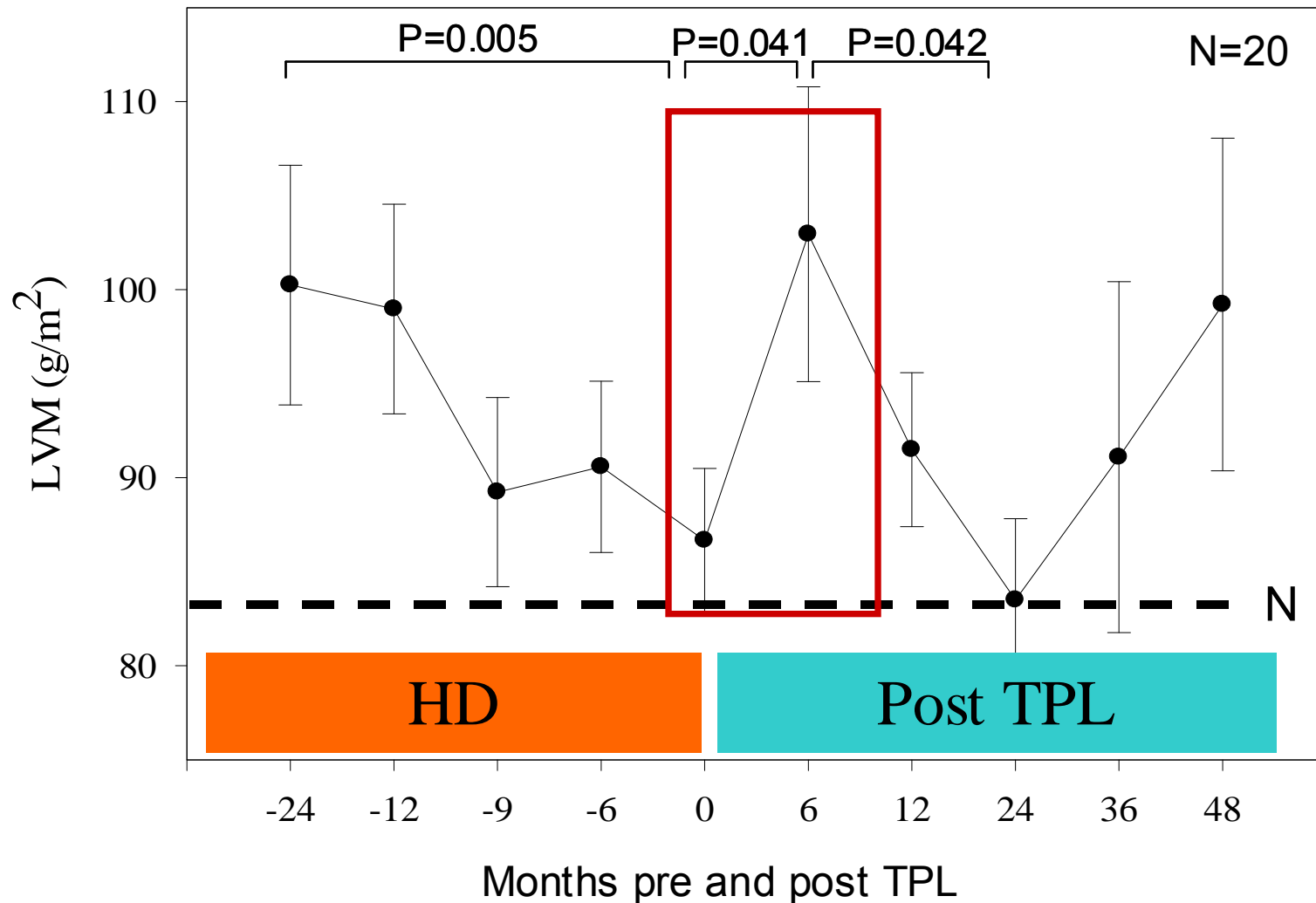
→ **Related to CyA dose and obesity**



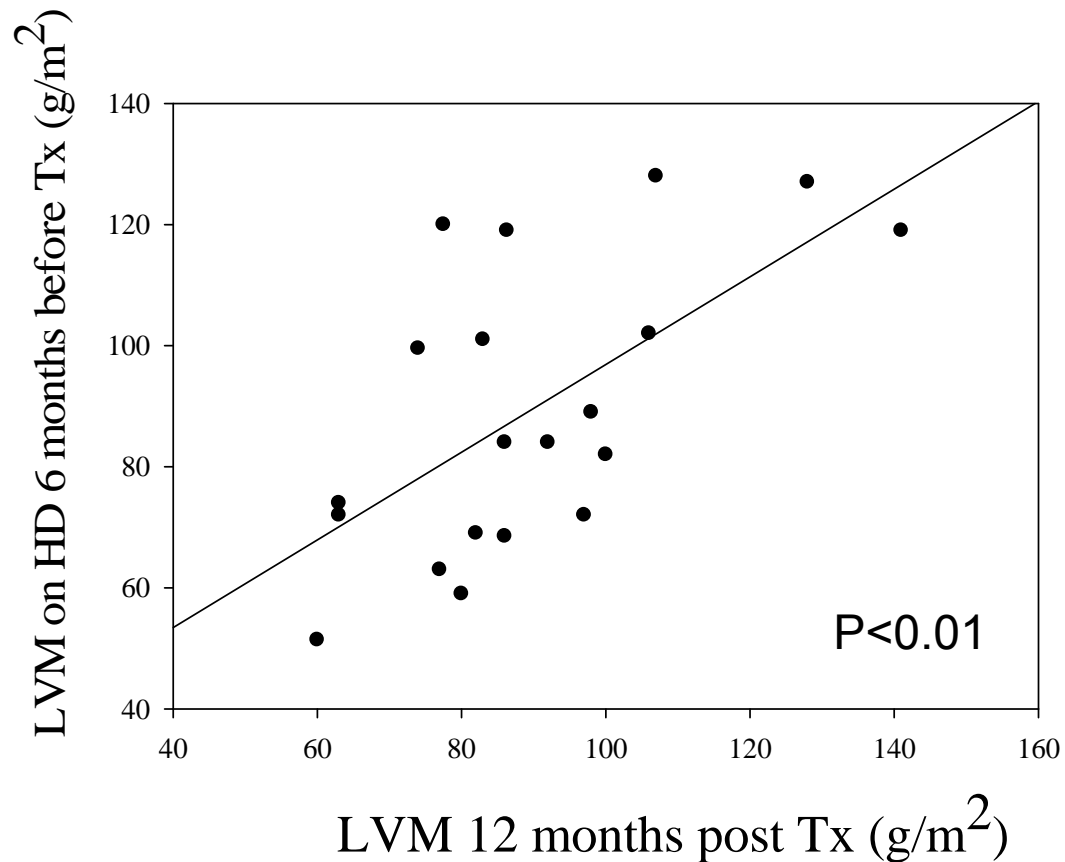
# Left ventricular hypertrophy in pediatric kidney transplant recipients: Long-term follow-up study



# Changes of LVM pre and post transplant



# Does LVH before TPL mean LVH post TPL ?



- Genetic factors
  - Acquired disease/susceptibility
- ?

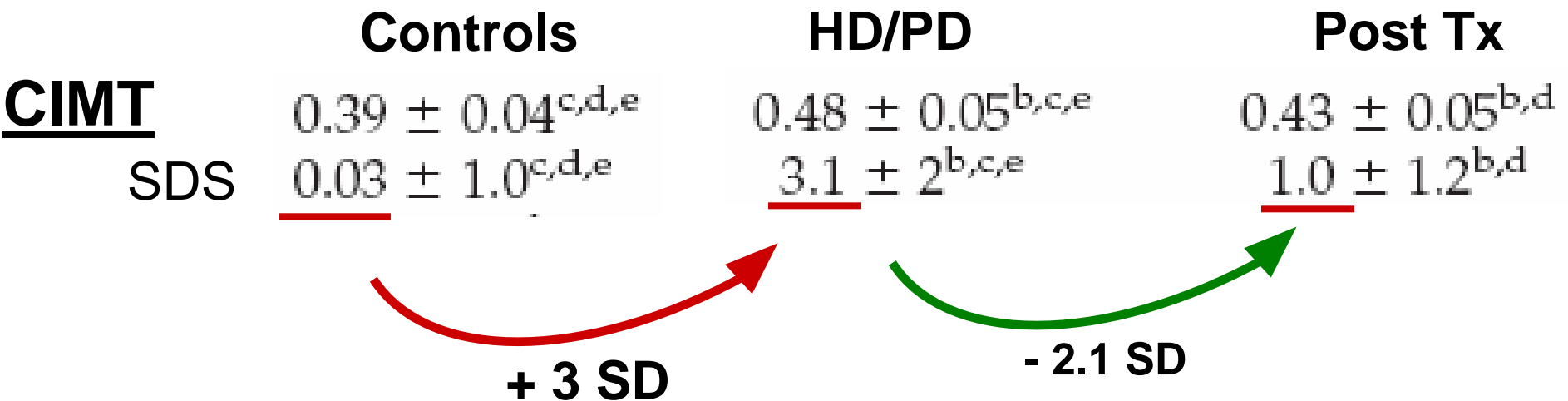
# Regressors $\neq$ Non-regressors

	$p$
- <u>Living donor grafts</u>	0.01
-Low sympathetic activity ( $\Delta$ LF/HF)	0.05
-Greater reduction of SBP at 6 months post TPL	0.003
-Higher basal LVM	0.08

*Guizar-Mendoza, Ped Nephrol, 2006*



# Decrease of Intima Media Thickness post TPL





## PWV and cIMT In dialysis children

**NORMAL if**

-Normal PTH  
-Well controlled Phosphate

**ANORMAL if**

-Elevated PTH  
-Phosphate > 2.1 mmol/l

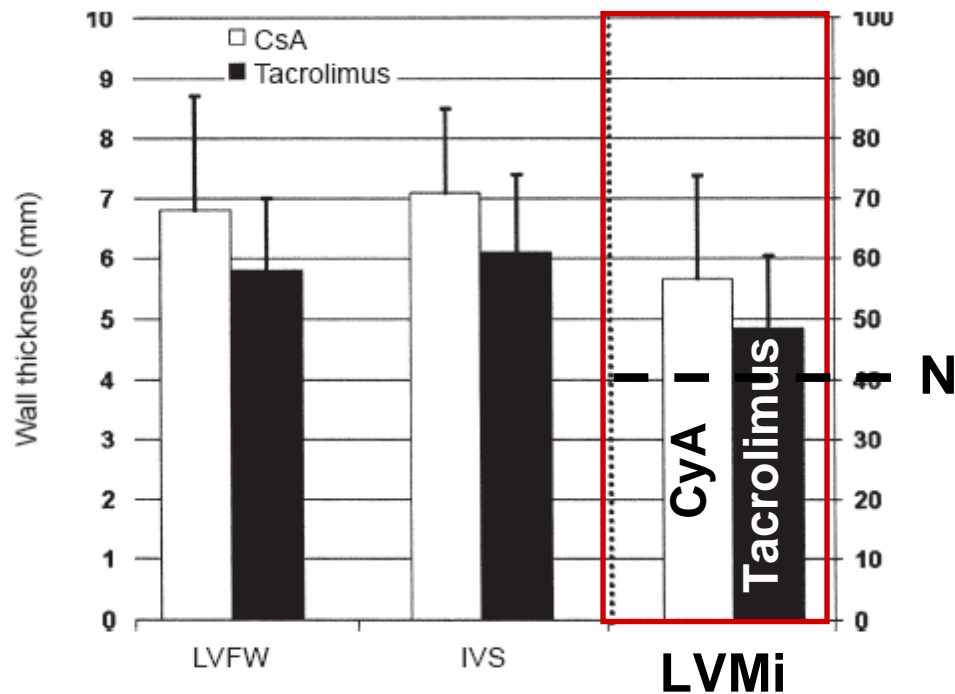
Shroff *et al*, JASN, 2007

**cIMT increases during dialysis and decreases after TPL**



# Echocardiographic findings of hypertrophic cardiomyopathy in children after orthotopic liver transplantation

Chang et al.  Role of steroids + immunosuppressive drugs





# Arterial Stiffness post Transplant

- Remains increased vs. matched controls ( $p < 0.01$ )
- Higher in ESRD than post TPL if  $\text{CrCl} > 90 \text{ ml/min/1.73m}^2$
- The longer the time on RRT the higher stiffness post TPL

## Pulse Wave Velocity

SBP ]  
DBP ]  $P < 0.05$

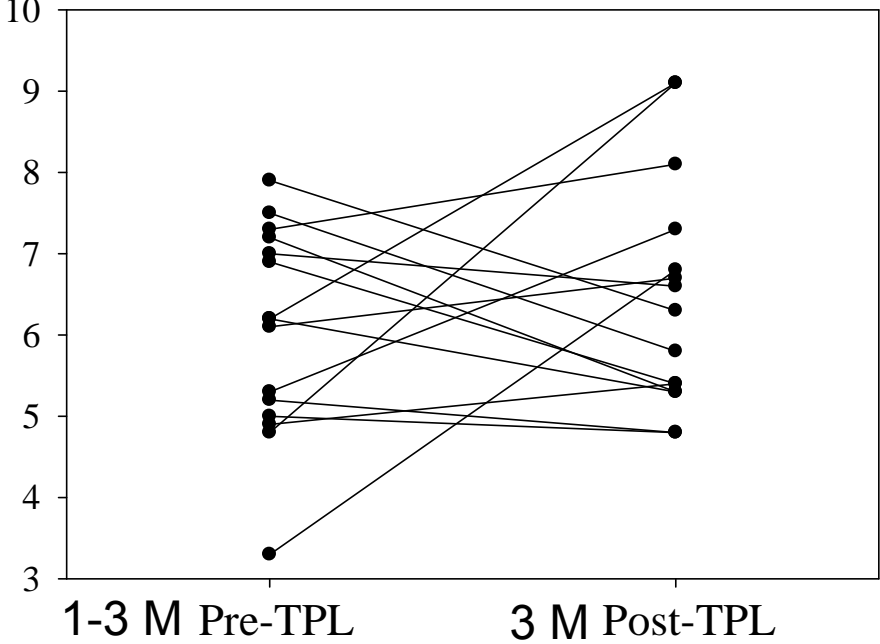
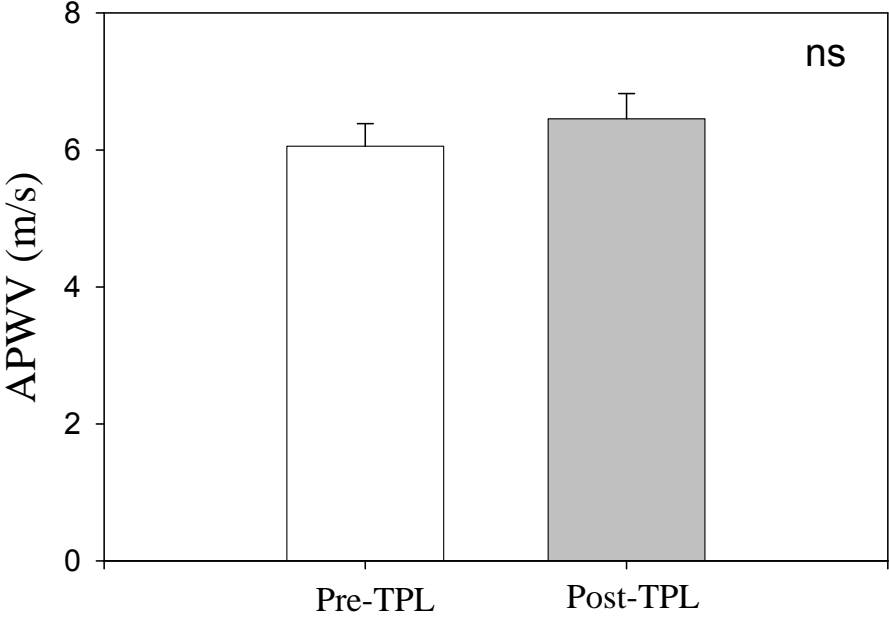
## Augmentation Index

SBP ]  
Ca x Ph ]  $P < 0.05$   
Sirolimus ]

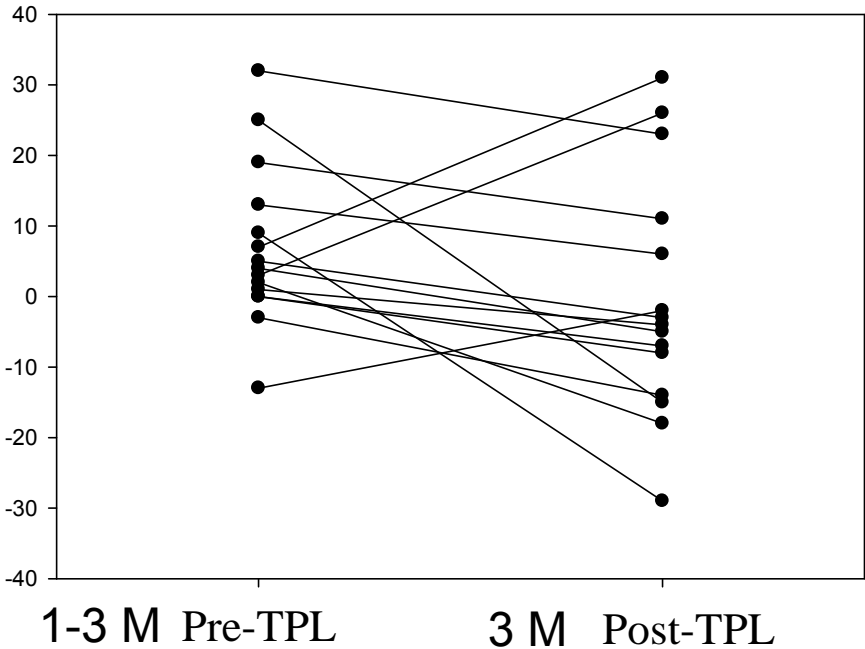
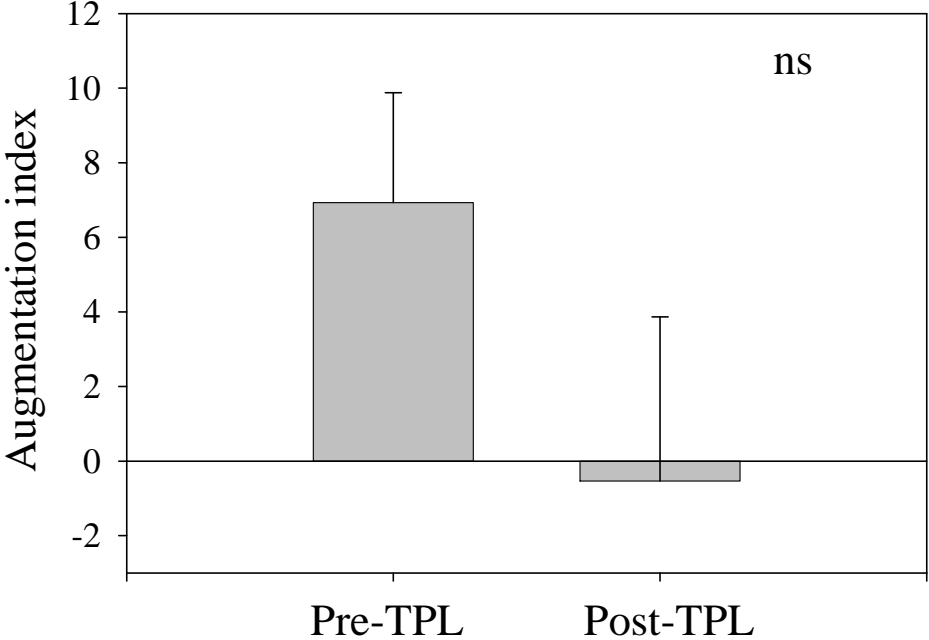
*Briese et al, Ped Nephrol, 2008*



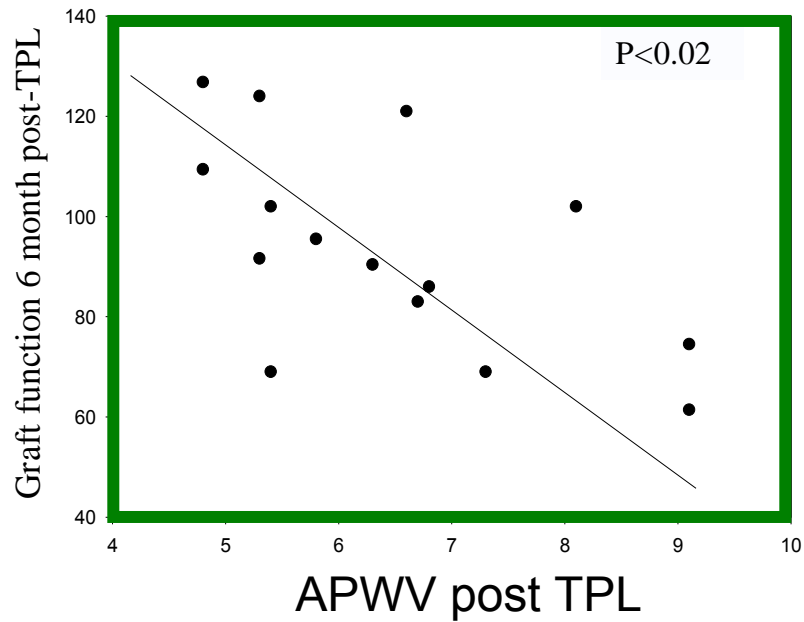
# Aortic Pulse Wave Velocity Pre and Post Transplant



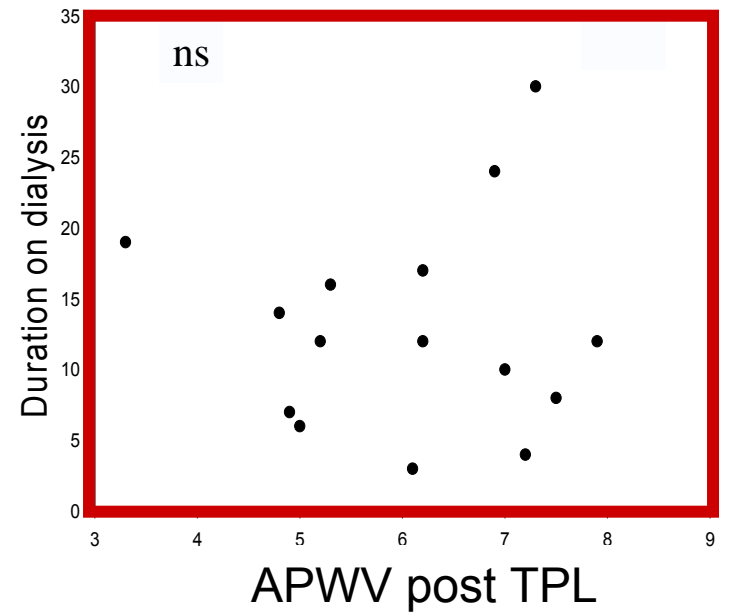
# Augmentation Index Pre and Post Transplant



## APWV and Graft Function



## APWV Post-TPL and HD Duration





# Outcome





**Children with ESRF**

Dialysis lifespan **40** years less

Transplantation lifespan **20** years less

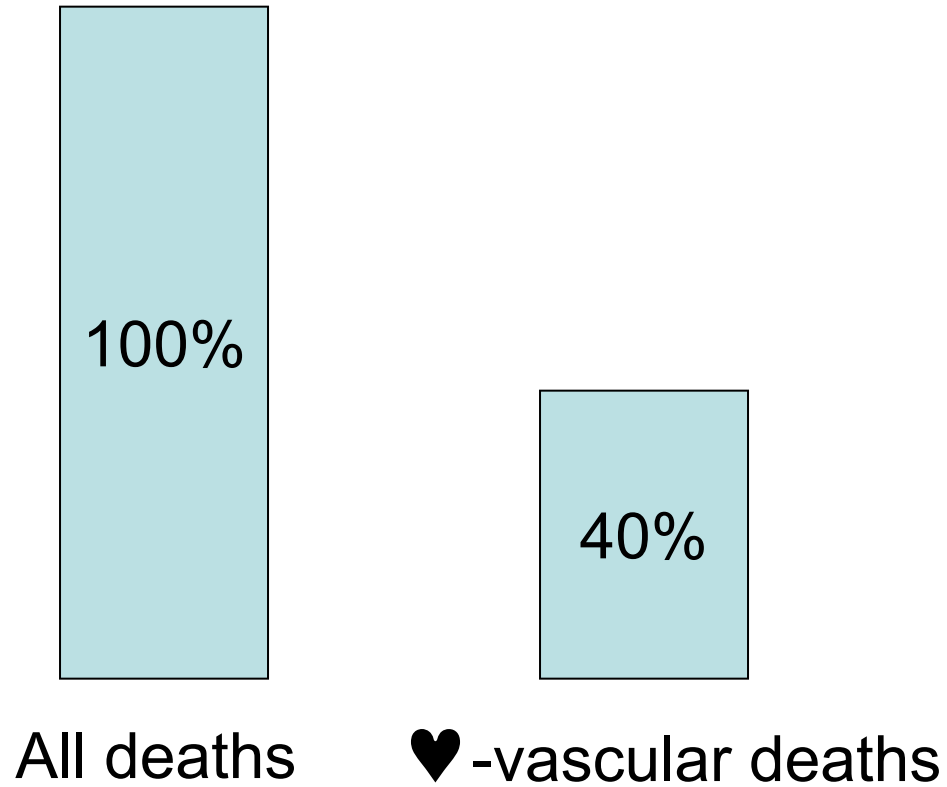
LERIC study: 381 patients started RRT in childhood (1972-1992).  
85 died.

**41% for cardiovascular disease**

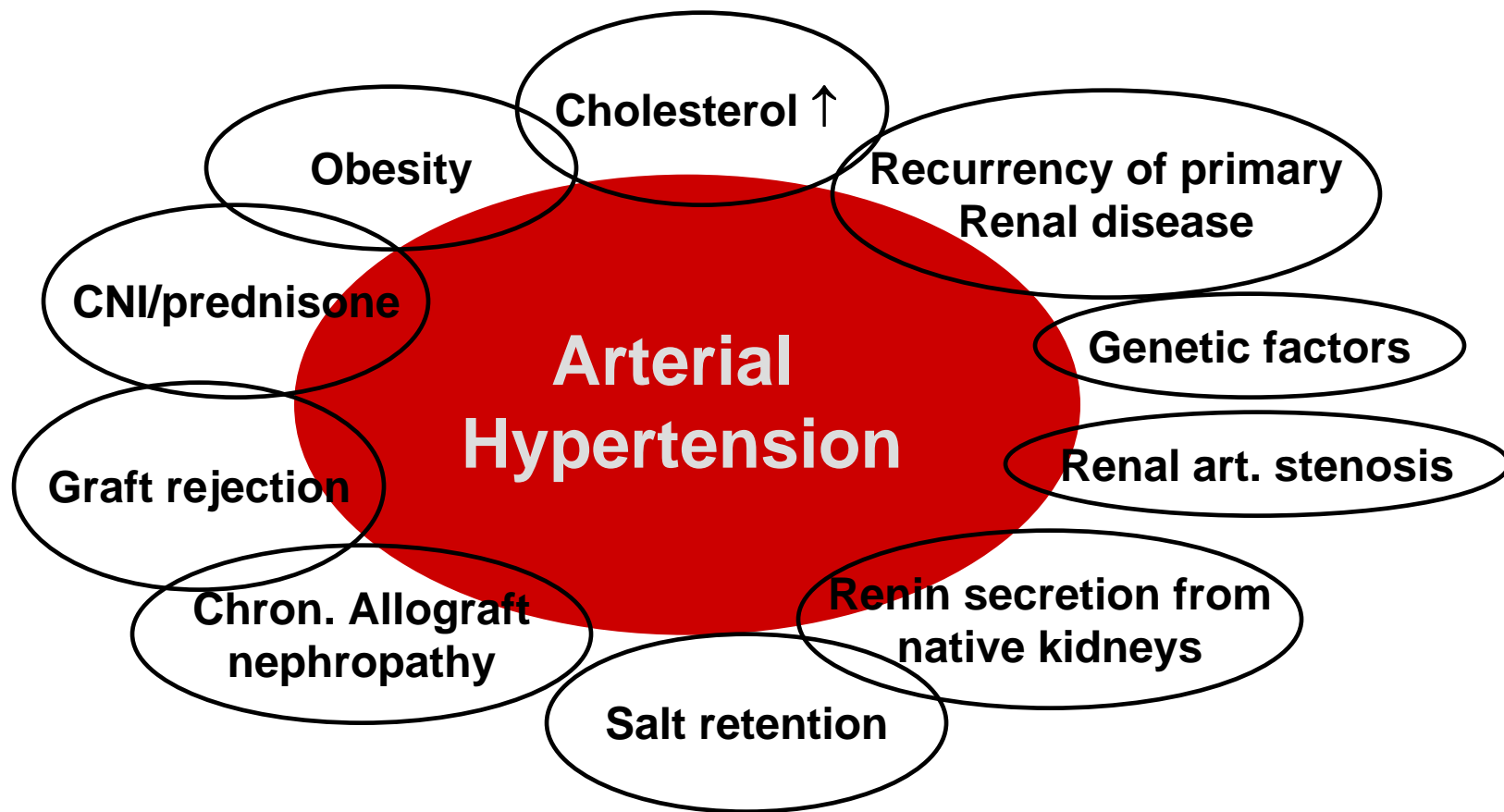




# Deaths in Pediatric ESRD Patients



# Interaction of Risk Factors for Arterial Hypertension post Transplant



*reproduced from Mitsnefes et al.*



# Conclusion

Dialysis	As intensive as possible As often as possible
Dry weight and Ca/Phosphorus adjustment	At least <u>weekly</u>
Blood Pressure Control	Target = <u>50th Percentile</u>
Immunosuppression post TPL	<b><i>A long way to go .....</i></b>

