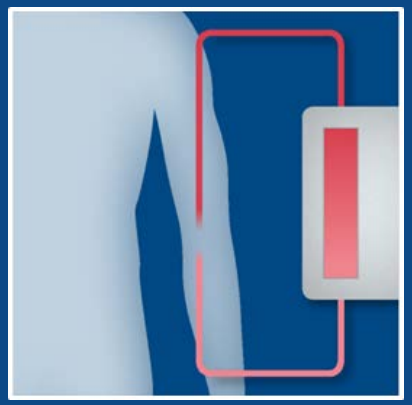
Nephro Update Europe 2017

6-7 October, Vienna

Hemodialysis



Denis Fouque, France

Foreword:
Evidence base data

A general comment on the source of Evidence

- Most reported data in hemodialysis come from retrospective or propsective non-controlled studies
- There are very few methodologically adequate studies (untrue in transplantation)
- Many biases are present, and therapeutic evidence should not be deducted
- At last, ideas, size of trials, outcome criteria can be derived from these studies, including this lecture!

- Hemodiafiltration
- Mineral bone disease
- Nutrition
- Blood pressure

Hemodiafiltration

State of the Art

HDF is growing (European countries at least)

- Almost 50% pts in France
- Still doubts about survival
- Current questions:
  - Which convection volume
  - Which efficiency parameters
  - Which population selection
  - ...

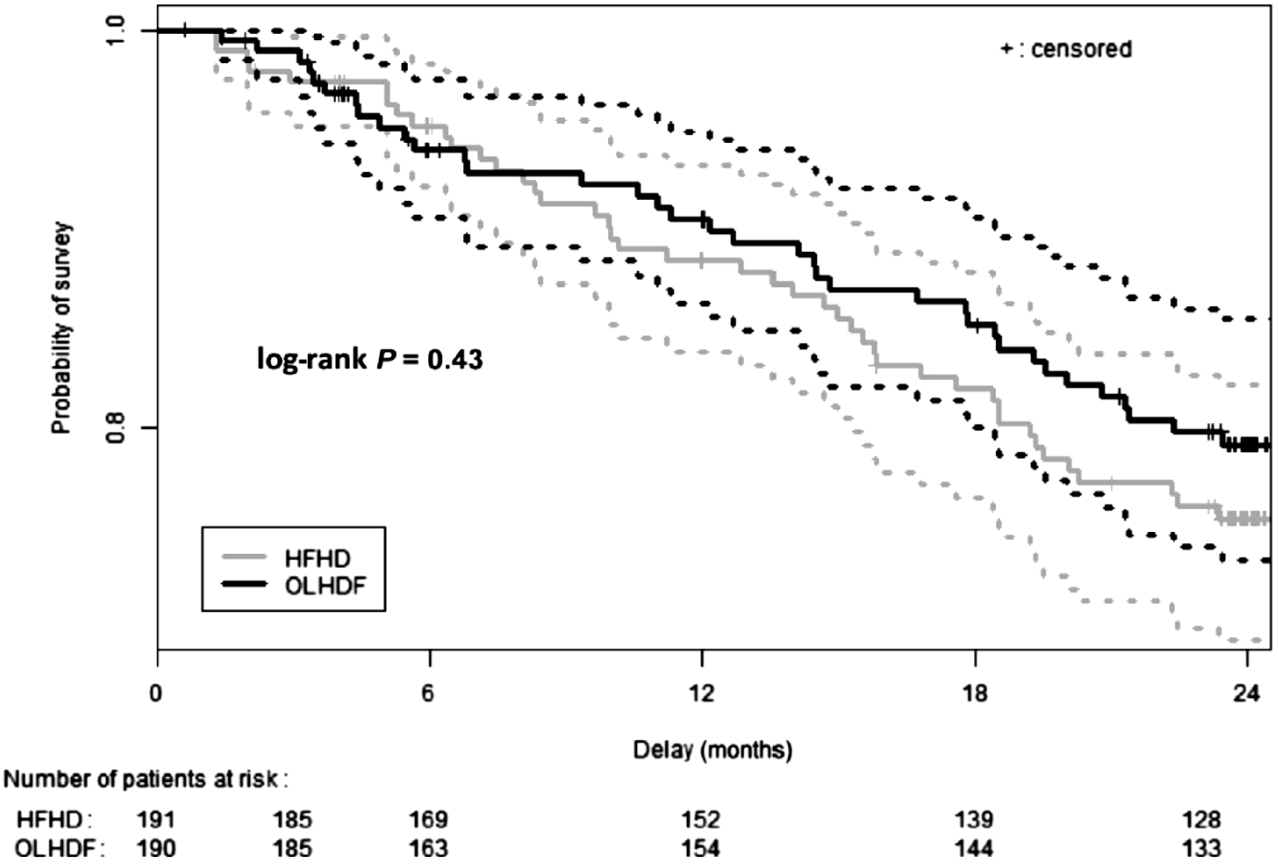
Treatment tolerance and patient-reported outcomes favor online hemodiafiltration compared to high-flux hemodialysis in the elderly

Marion Morena[1,2,3], Audrey Jaussent[4], Lotfi Chalabi[5], Hélène Leray-Moragues[6], Leila Chenine[6], Alain Debure[7], Damien Thibaudin[8], Lynda Azzouz[9], Laure Patrier[10], Francois Maurice[11], Philippe Nicoud[12], Claude Durand[13], Bruno Seigneuric[14], Anne-Marie Dupuy[1], Marie-Christine Picot[4], Jean-Paul Cristol[1,2,3] and Bernard Canaud[2,15]; for the FRENCHIE Study Investigators[16]

- Elderly MHD pts 76 yr old
- RCT 2 yr fup, 2005-2011
- 191 HDF – 190 HD
- Intolerance, QoL,
- Mean convection volume 19.3 (Bl) 22.5 L (end)

Morena, M, et al., Kidney Int, 2017, 91.6: 1495-509

Survival

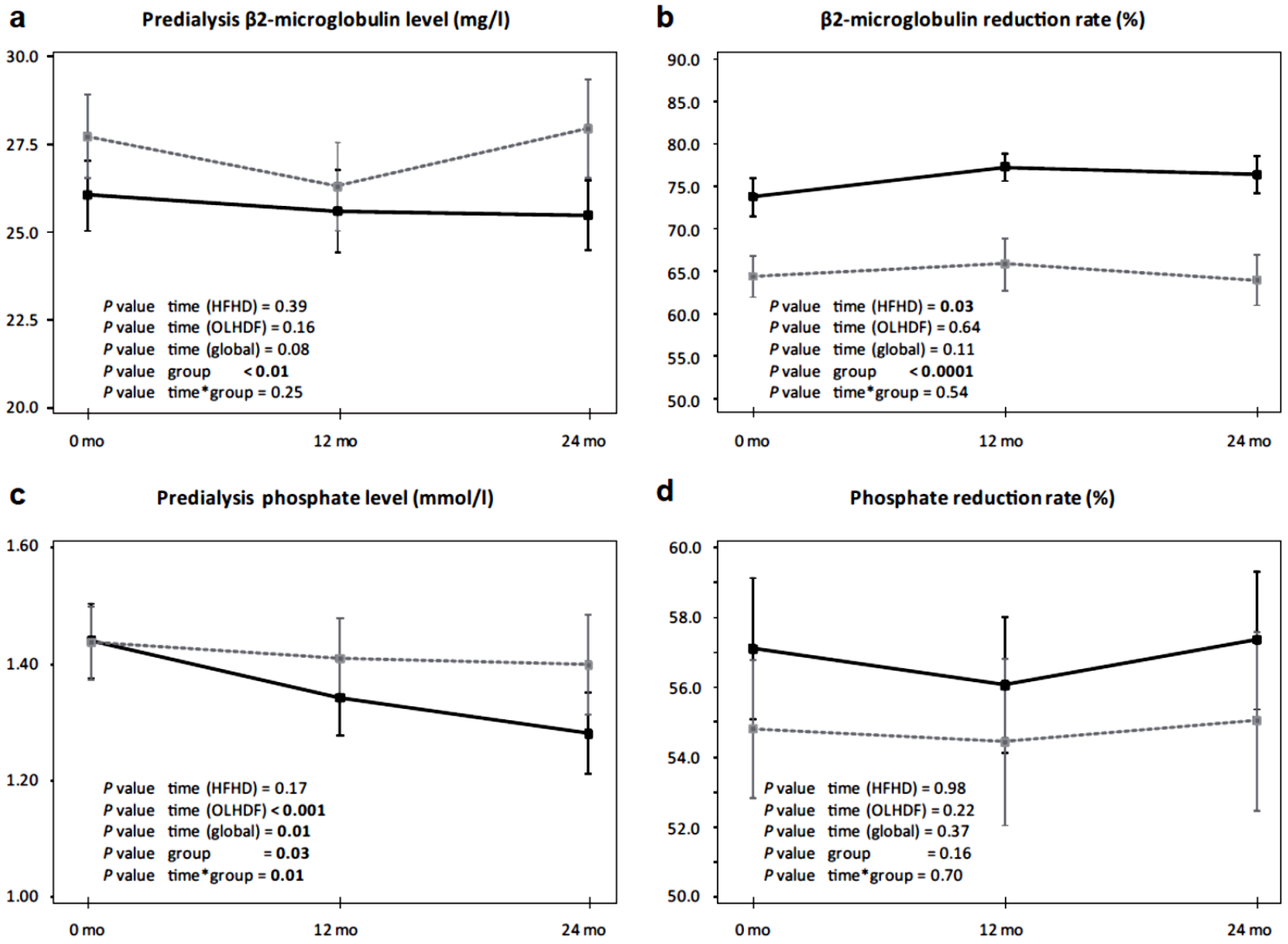


Number of patients at risk :

HFHD :	191	185	169	152	139	128
OLHDF :	190	185	163	154	144	133

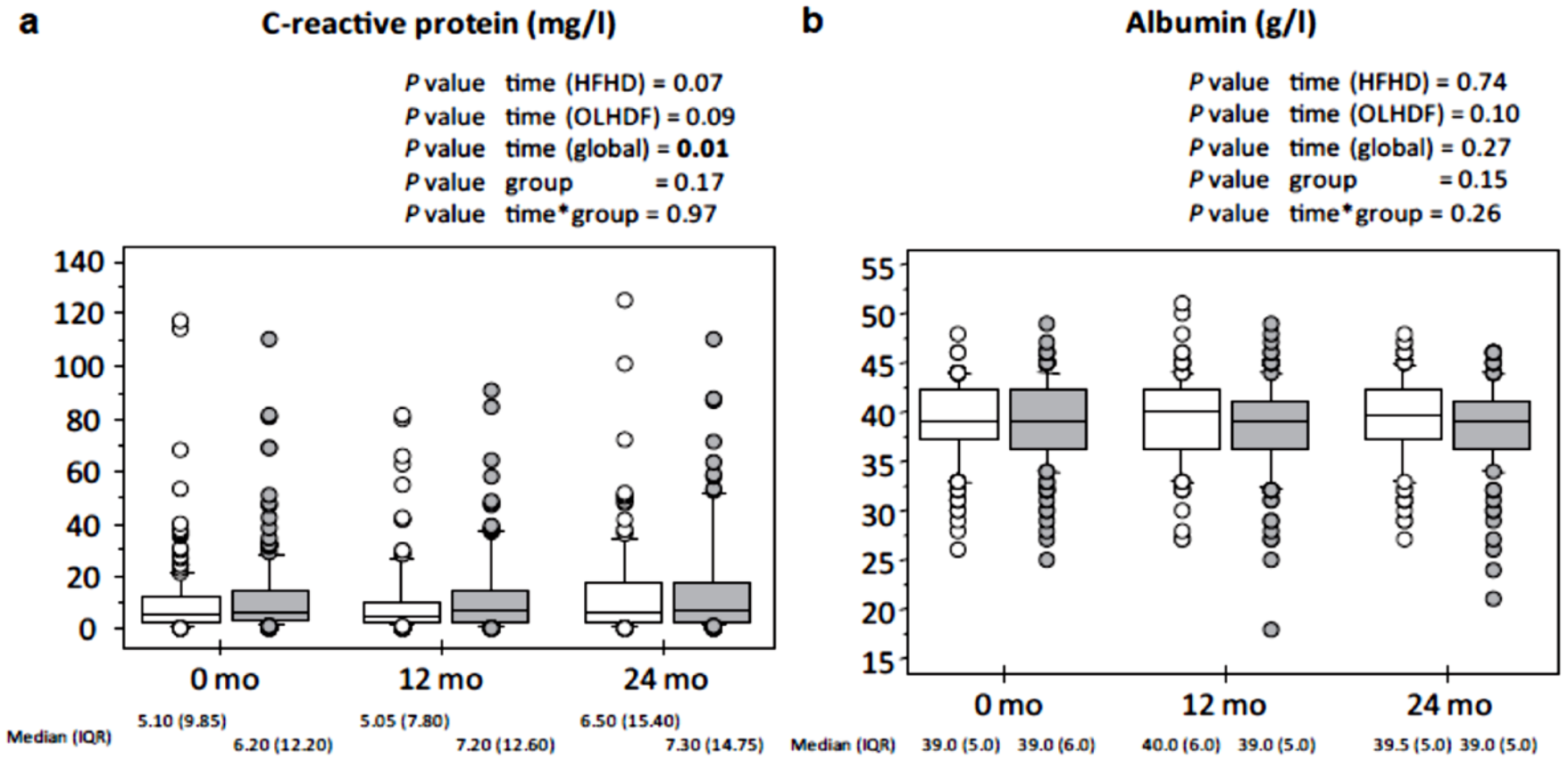
Morena, M, et al., Kidney Int, 2017, 91.6: 1495-509

Metabolic control



Morena, M, et al., Kidney Int, 2017, 91.6: 1495-509

Inflammation and nutrition



Morena, M, et al., Kidney Int, 2017, 91.6: 1495-509

Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials

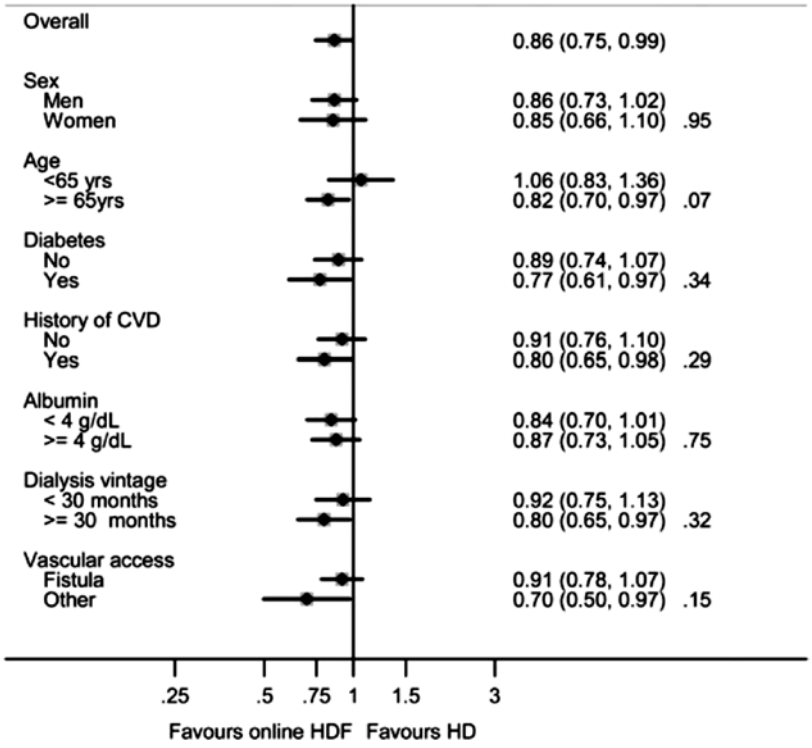
Sanne A.E. Peters[1,2], Michiel L. Bots[2], Bernard Canaud[3,4], Andrew Davenport[5], Muriel P.C. Grooteman[6], Fatih Kircelli[7], Francesco Locatelli[8], Francisco Maduell[9], Marion Morena[4,10,11], Menso J. Nubé[6], Ercan Ok[7], Ferran Torres[12,13], Mark Woodward[1,14,15] and Peter J. Blankestijn[16] on behalf of the HDF Pooling Project Investigators

- Contrast (-)
- ESHOL (+)
- Frenchie (-)
- Turkish (-)
- Total 2793 pts; 50% HDF/HD

Nephrol Dial Transplant (2016) 31: 978–984

Hazard ratios

Cause	HD			HDF			HR (95% CI) for HDF versus HD
	n	Events	Events/100 PY	*n*	Events	Events/100 PY	
All-causes	1369	410	12.10	1367	359	10.45	0.86 (0.75; 0.99)
Cardiovascular disease	1302	164	4.84	1289	128	3.73	0.77 (0.61; 0.97)
Infections	1302	77	2.27	1289	73	2.13	0.94 (0.68; 1.30)
Sudden death	1302	56	1.65	1289	56	1.63	0.99 (0.68; 1.43)



Improvement in survival:

- **Overall mortality (-14%)**
- **In elderly >65 yr**
- **Diabetic pts**
- **History CVD**
- **Vintage > 30 months**

Peters et al, NDT(2016) 31: 978–984

The role of convection volume

- However improvement was only observed if:

Cause	Online HDF: BSA-adjusted convection volume (L/session)		
	<19	19–23	>23
All-causes			
Unadjusted	0.91 (0.74; 1.13)	0.88 (0.72; 1.09)	0.73 (0.59; 0.91)
Adjusted	0.83 (0.66; 1.03)	0.93 (0.75; 1.16)	0.78 (0.62; 0.98)
Cardiovascular			
Unadjusted	1.00 (0.71; 1.40)	0.71 (0.50; 1.01)	0.69 (0.48; 0.98)
Adjusted	0.92 (0.65; 1.30)	0.71 (0.49; 1.03)	0.69 (0.47; 1.00)
Infections			
Unadjusted	1.50 (0.93; 2.41)	0.96 (0.56; 1.65)	0.56 (0.30; 1.08)
Adjusted	1.50 (0.92; 2.46)	0.97 (0.54; 1.74)	0.62 (0.32; 1.19)
Sudden death			
Unadjusted	1.24 (0.80; 1.91)	0.91 (0.57; 1.47)	0.60 (0.35; 1.03)
Adjusted	1.09 (0.69; 1.74)	1.04 (0.63; 1.70)	0.69 (0.39; 1.20)

Improvement in survival:
- ***Overall mortality (-14%)***
- ***In elderly >65 yr***
- ***Diabetic pts***
- ***History CVD***
- ***Vintage > 30 months***

Adjusted for age, gender, albumin, creatinine, diabetes and CVD

Peters et al, NDT(2016) 31: 978–984

Original Investigation

Convective Versus Diffusive Dialysis Therapies for Chronic Kidney Failure: An Updated Systematic Review of Randomized Controlled Trials

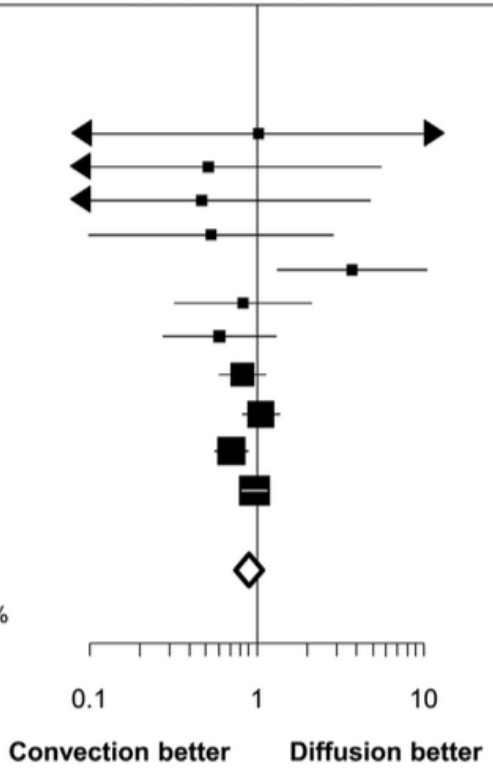
Ionut Nistor, MD,[1,2,] Suetonia C. Palmer, MBChB, PhD,[3,*] Jonathan C. Craig, MBChB, DCH, MM, PhD,[4] Valeria Saglimbene, MSc,[5] Mariacristina Vecchio, MSc,[6] Adrian Covic, MD, PhD,[1] and Giovanni F.M. Strippoli, MD, PhD, MM, MPH[4,5,6]*

Am J Kidney Dis. 2014;63(6):954-967

Overall survival

	No. of events/ No. of participants		Relative risk (95% CI) Random effects model	Weight
	Convection	Diffusion		
All-cause mortality				
Beerenhout et al, 2005	1/20	1/20	1.00 (0.07 to 14.9)	0.47%
Schiffl, 2007	1/38	2/38	0.50 (0.05 to 5.28)	0.62%
Wizemann et al, 2000	1/23	2/21	0.46 (0.04 to 4.68)	0.63%
PROFIL study, 2011	2/27	3/21	0.52 (0.10 to 2.83)	1.17%
Locatelli et al, 1996	7/50	6/155	3.62 (1.27 to 10.26)	2.94%
Locatelli et al, 2010	7/76	8/70	0.81 (0.31 to 2.11)	3.41%
Santoro et al, 2008	7/32	12/32	0.58 (0.26 to 1.29)	4.80%
TURKISH OL-HDF study, 2013	52/391	65/391	0.80 (0.57 to 1.12)	16.62%
Tessitore et al, 2012	65/177	69/194	1.03 (0.79 to 1.35)	20.56%
ESHOL study, 2013	85/456	122/450	0.69 (0.54 to 0.88)	22.34%
CONTRAST study, 2012	131/358	138/356	0.94 (0.78 to 1.14)	26.43%
Total	**359/1648**	**428/1748**	**0.87 (0.70 to 1.07)**	**100.0%**

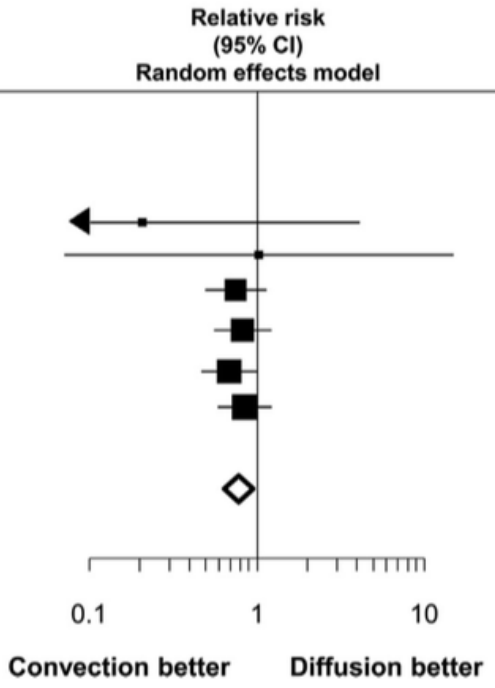
Heterogeneity: χ^2_{10}= 15.1; P = 0.1; I^2 = 34%



No difference between treatments

CV mortality

	No. of events/ No. of participants		Relative risk (95% CI) Random effects model	Weight
	Convection	Diffusion		
Cardiovascular mortality				
Schiffl, 2007	0/38	2/38	0.20 (0.01 to 4.03)	0.45%
Beerenhout et al, 2005	1/20	1/20	1.00 (0.07 to 14.9)	0.55%
TURKISH OL-HDF study, 2013	32/391	44/391	0.73 (0.47 to 1.12)	21.42%
CONTRAST study, 2012	37/358	46/356	0.80 (0.53 to 1.20)	27.68%
ESHOL study, 2013	37/456	55/450	0.66 (0.45 to 0.99)	25.66%
Tessitore et al, 2012	36/177	48/194	0.82 (0.56 to 1.20)	24.25%
Total	**143/1440**	**196/1449**	**0.75 (0.58 to 0.97)**	**100.0%**
			Heterogeneity: χ^2_5= 1.49; P = 0.9; I^2 = 0%	



Reduction in CV mortality

Take-Home Message

Still uncertainty on robust outcomes

Possible insufficient power

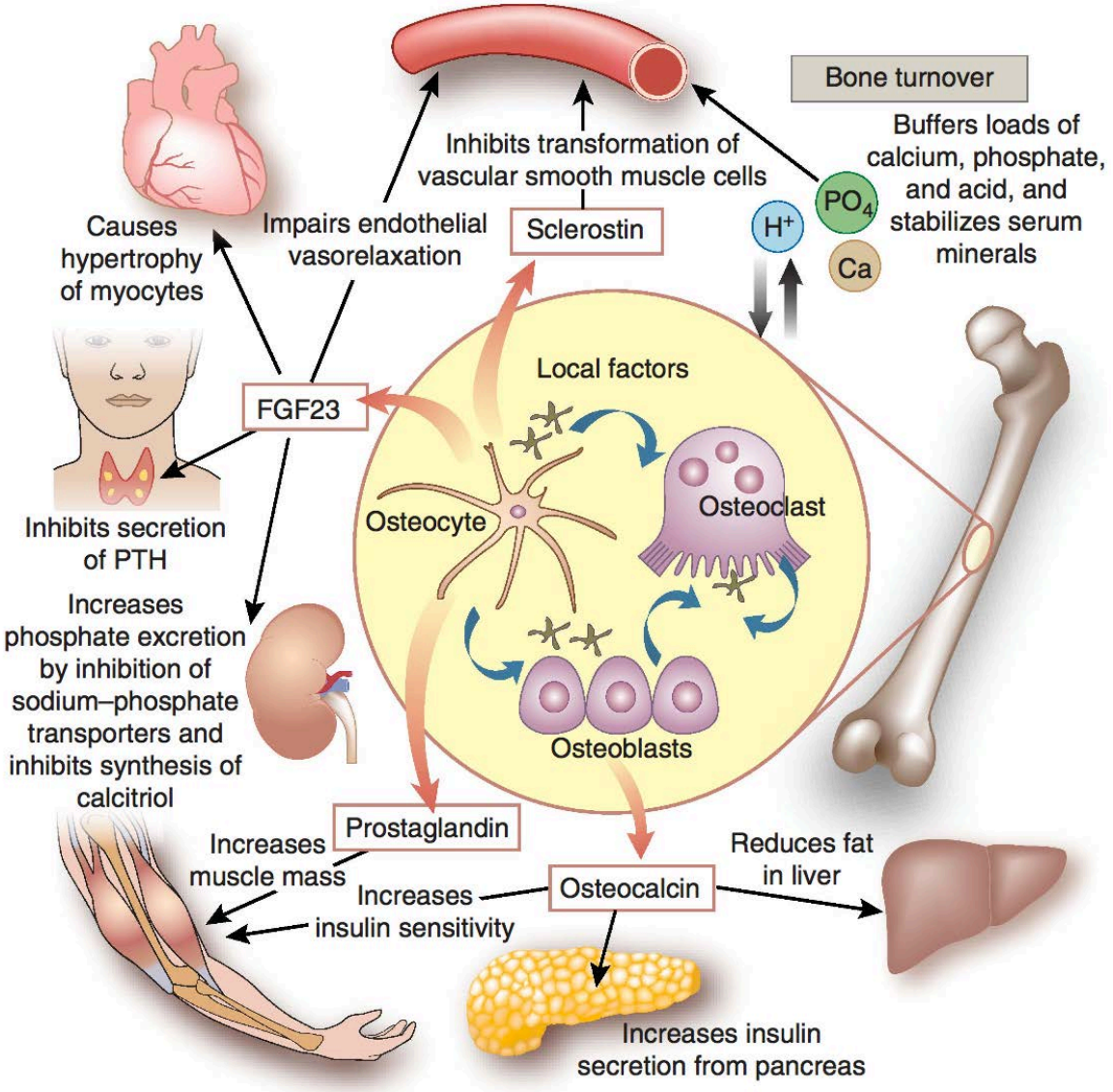
Improvement in surrogates

Better definition of:

- target population
- convection volume

Mineral Metabolism and Cardiovascular Events

A bone-vascular interaction



Ott Kidney Int 2015;87(3):499-501

Phosphate metabolism: Klotho/FGF interaction

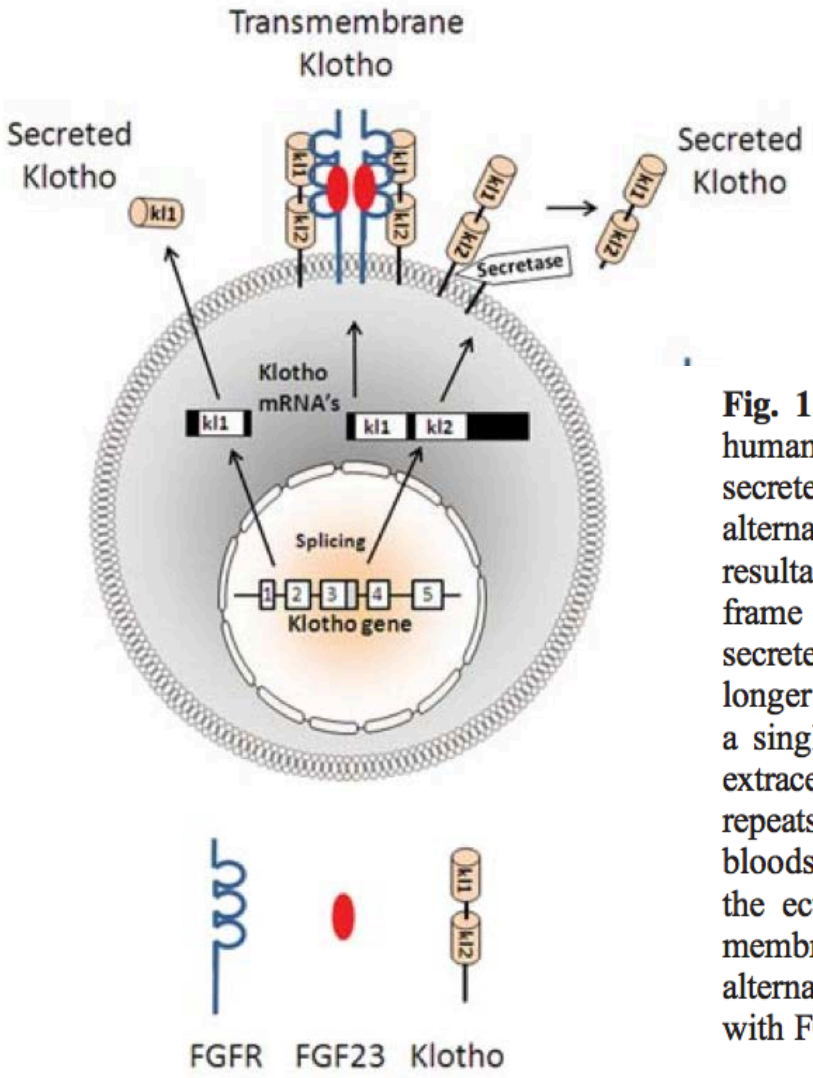
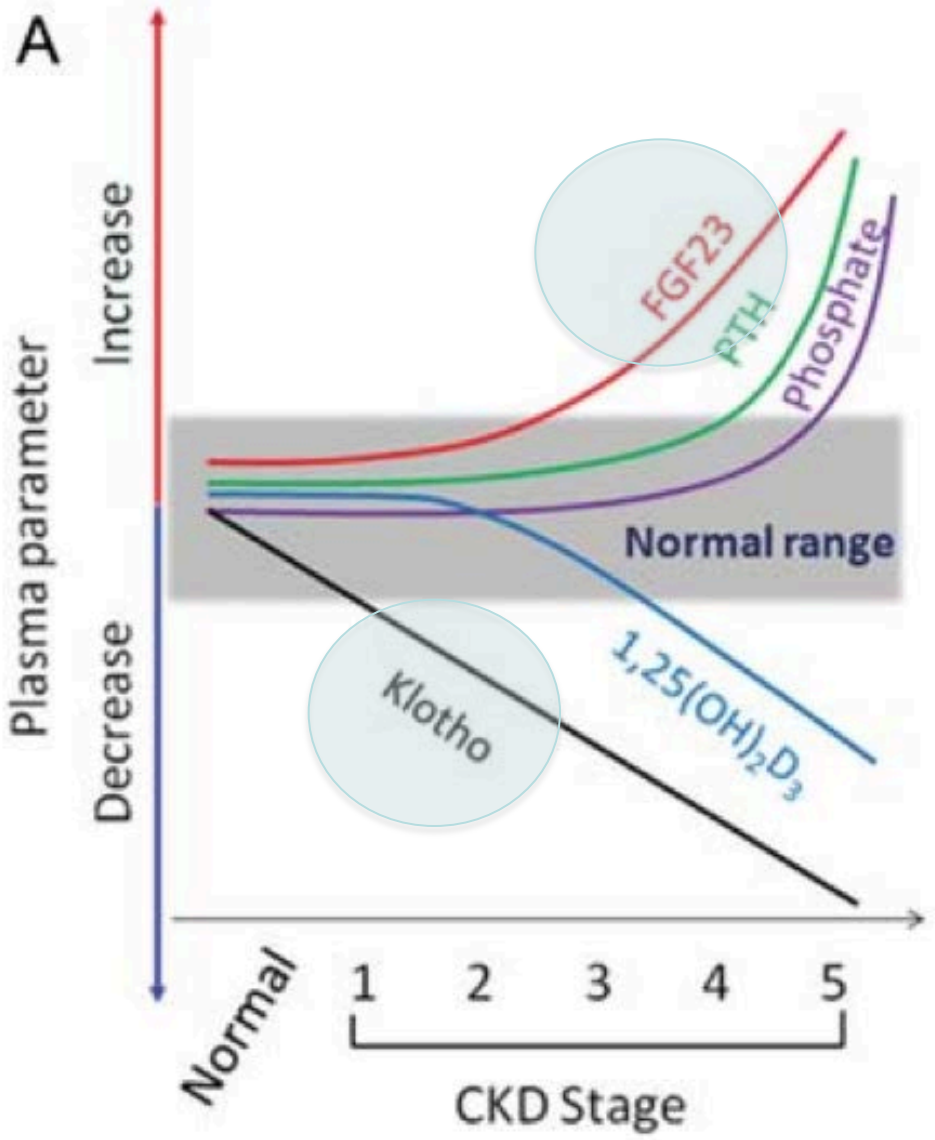


Fig. 1. Schema for Klotho gene, transcripts and proteins. Rodent and human *Klotho* spans 50 kb and consists of five exons. Two transcripts, secreted and membrane forms of Klotho, are generated through alternative RNA splicing. The internal splice donor site is in exon 3. The resultant alternatively spliced transcript after exon 3 (grey) with an in-frame translation stop codon is introduced. The short protein product, secreted Klotho, contains only Kl1 and is released from the cell. The longer Klotho encoded by the membrane form of the Klotho transcript is a single-pass transmembrane protein anchored in the cell surface. The extracellular domain of membrane Klotho containing Kl1 and Kl2 repeats is shed and cleaved by ADAM10/17, and released into bloodstream. Thus, the circulation harbors two forms of Klotho—one is the ectodomain derived from cleavage of the extracellular domain of membrane Klotho and another is the secreted protein derived from an alternatively spliced Klotho transcript. Transmembrane Klotho works with FGFRs as co-receptor for FGF23 signal transduction.

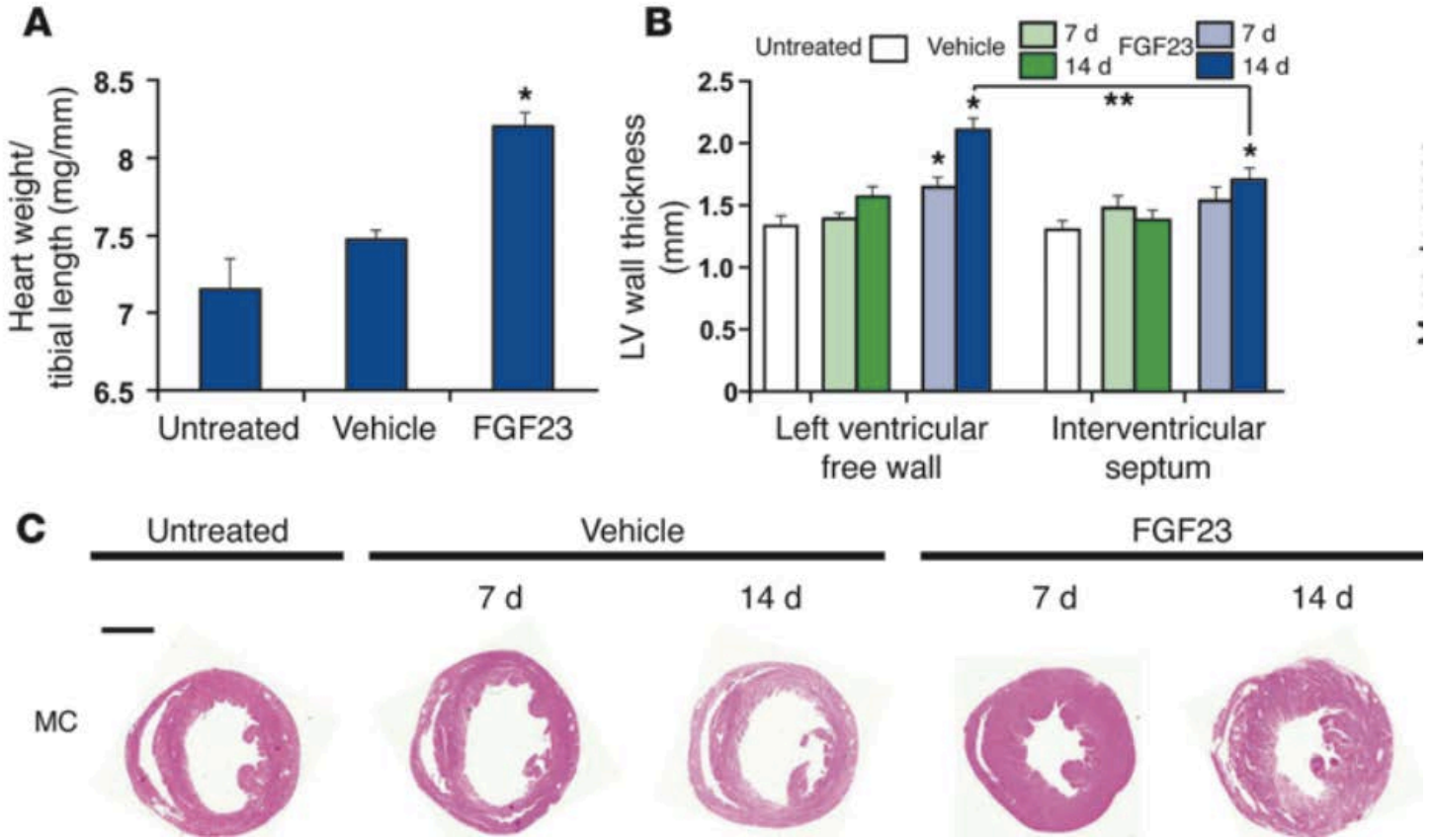
Hu et al, NDT 2012; 27:2650

Klotho, FGF23, PTH and phosphorus



Hu et al, NDT 2012; 27:2650

FGF23 is directly toxic on myocardium and induces LVH independent from Klotho

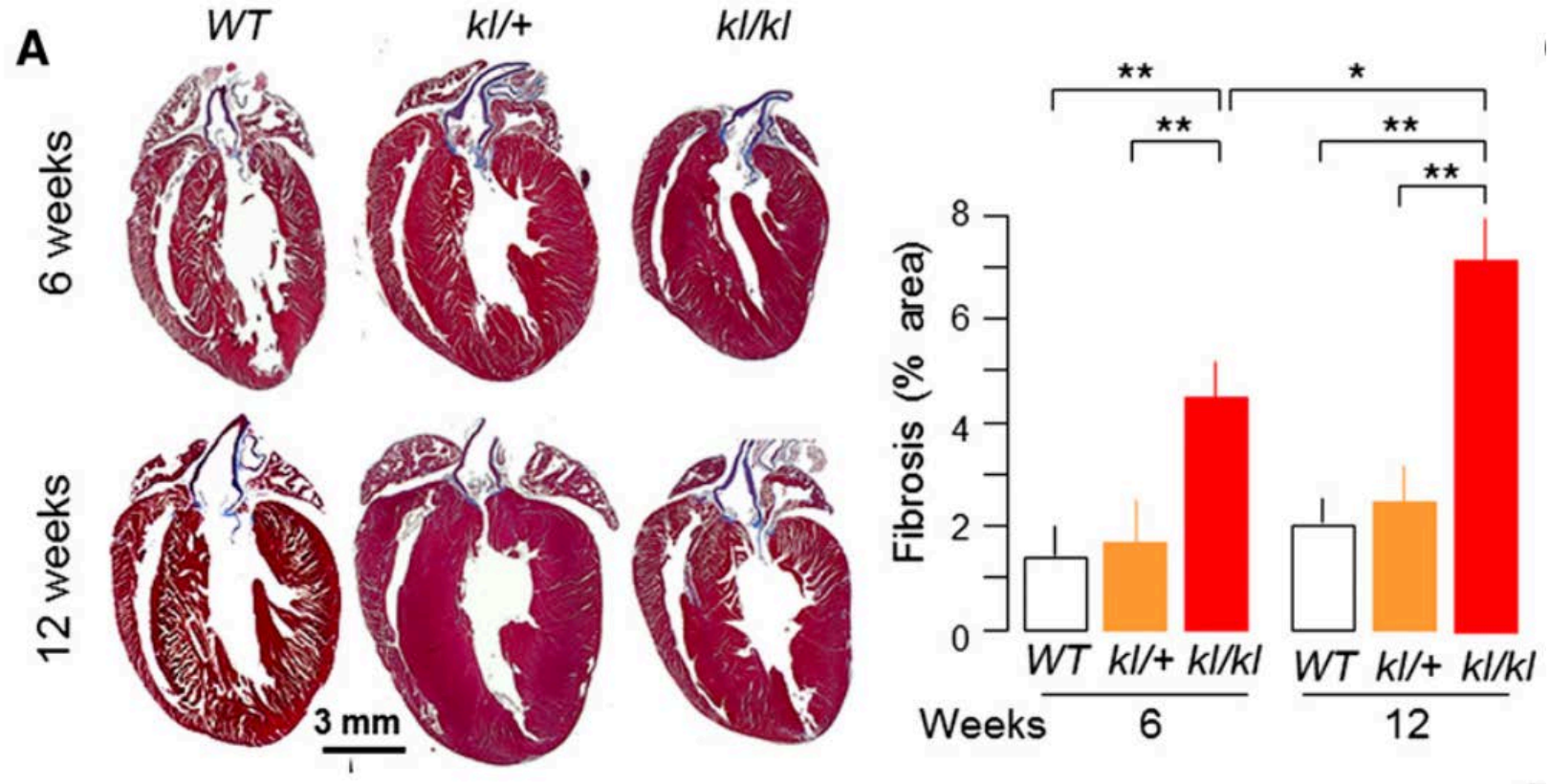


Direct FGF23 intracardiac injection

Faul et al, J Clin Invest. 2011;11:4393-4408

Klotho and Phosphate Are Modulators of Pathologic Uremic Cardiac Remodeling

Ming Chang Hu,*† Mingjun Shi,* Han Jun Cho,* Beverley Adams-Huet,*†‡ Jean Paek,* Kathy Hill,* John Shelton,§ Ansel P. Amaral,‖¶ Christian Faul,‖¶ Masatomo Taniguchi,*‡ Myles Wolf,‖ Markus Brand,** Masaya Takahashi,†† Makoto Kuro-o,*§ Joseph A. Hill,†‡‡ and Orson W. Moe*†§§



 Hu et al J Am Soc Nephrol 2015; 26:1290-302

Serum Klotho protects MHD patients from cardiovascular events

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Circulating Klotho associates with cardiovascular morbidity and mortality during hemodialysis.

Christophe Marçais (PharmD), Delphine Maucort-Boulch (MD, PhD), Jocelyne Drai (PharmD), Emmanuelle Dantony (MEng), Marie-Christine Carlier (PharmD), Emilie Blond (PharmD, PhD), Leslie Genet, François Kuentz (MD), Dominique Lataillade (MD), Eric Legrand (MD), Xavier Moreau-Gaudry (MD), Guillaume Jean (MD) and Denis Fouque (MD, PhD) for the ARNOGENE project

Marcais et al, J Clin Endocrinol Metab. 2017 Sep 1;102(9):3154-3161.

2-yr CV events in 769 MHD patients

Variables	OR 95%CI	P-value*
Serum Klotho ≥280ng/L	0.86 [0.76 ;0.99]	0.030
Age (+1yr)	1.00 [1.00 ; 1.01]	0.244
Dialysis vintage (+1yr)	1.00 [0.99 ; 1.01]	0.656
Hemoglobin (+1g/dL)	0.98 [0.93 ; 1.03]	0.449
Serum FGF-23 (+1 logRU/mL)	1.07 [1.02 ; 1.13]	0.005
Gender (M/F)	0.89 [0.79 ; 1.00]	0.054
Diabetes (Y/N)	1.11 [0.98 ; 1.26]	0.103
Cardiac insufficiency (Y/N)	1.17 [1.03 ; 1.33]	0.020
Serum albumin (per 1g/L)	1.00 [0.98 ; 1.01]	0.793
Serum calcium (+1 mmol/L)	0.78 [0.56 ; 1.10]	0.157
Serum phosphate (+1 mmol/L)	0.94 [0.85 ; 1.04]	0.254

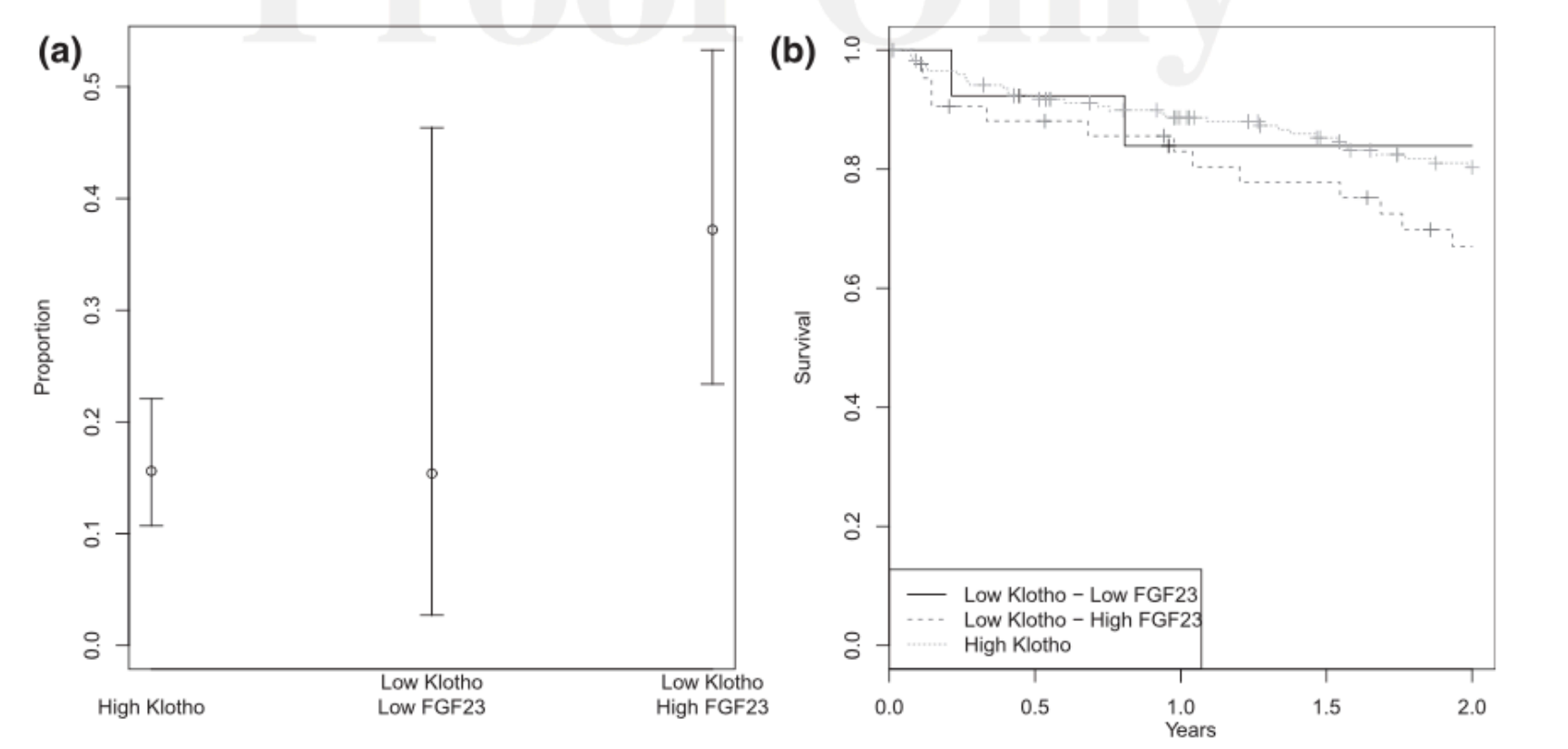
CI Confidence Interval

*P-value obtained from a Wald test

Multivariate analysis

Marcais et al, J Clin Endocrinol Metab. 2017 Sep 1;102(9):3154-3161.

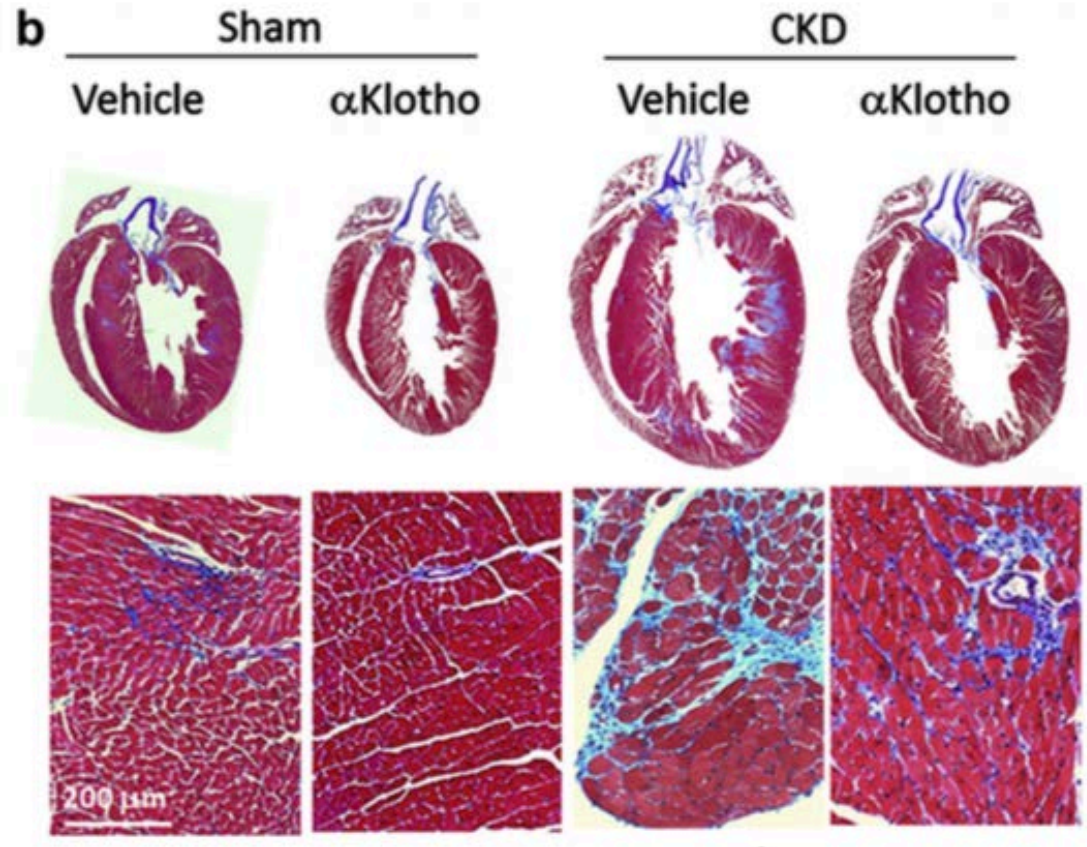
CV events according to quartiles of S klotho and FGF23



Marcais et al, J Clin Endocrinol Metab. 2017 Sep 1;102(9):3154-3161.

Recombinant α-Klotho may be prophylactic and therapeutic for acute to chronic kidney disease progression and uremic cardiomyopathy

Ming Chang Hu[1,2], Mingjun Shi[2], Nancy Gillings[2], Brianna Flores[2], Masaya Takahashi[3,4], Makoto Kuro-o[2,5] and Orson W. Moe[1,2,6]



Hu et al, Kidney Int. 2017 May;91(5):1104-1114

Take-Home Message

Altered phosphate metabolism:

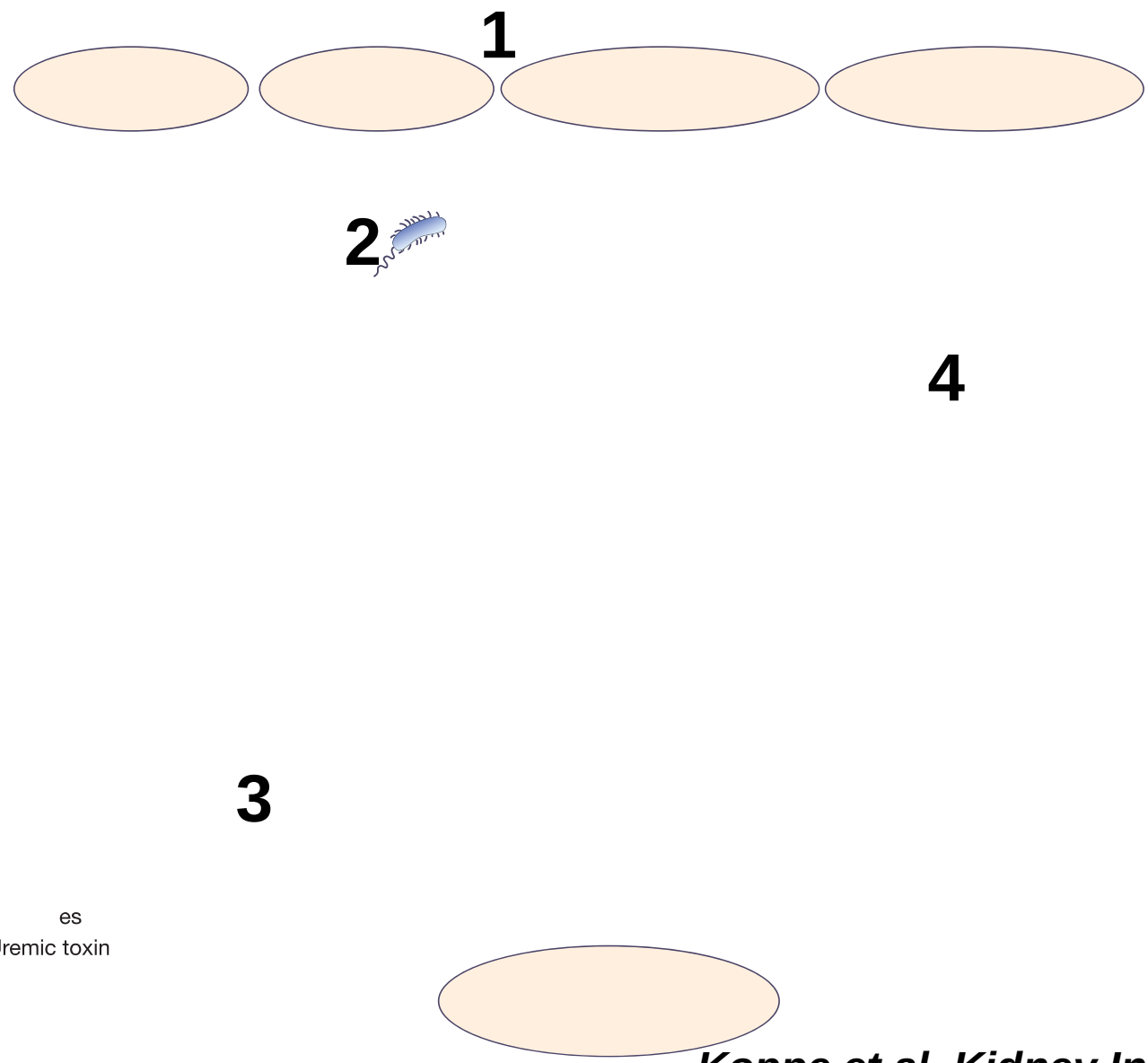
- Low Klotho (reason unknown yet)
- Elevated FGF23 in response to phosphate load
- Cardiac toxicity of FGF23
- No treatment to decrease FGF23
- Lack of cardiac protection by Klotho
- Possible benefits of Klotho supplementation

Nutrition

Many microbiotae

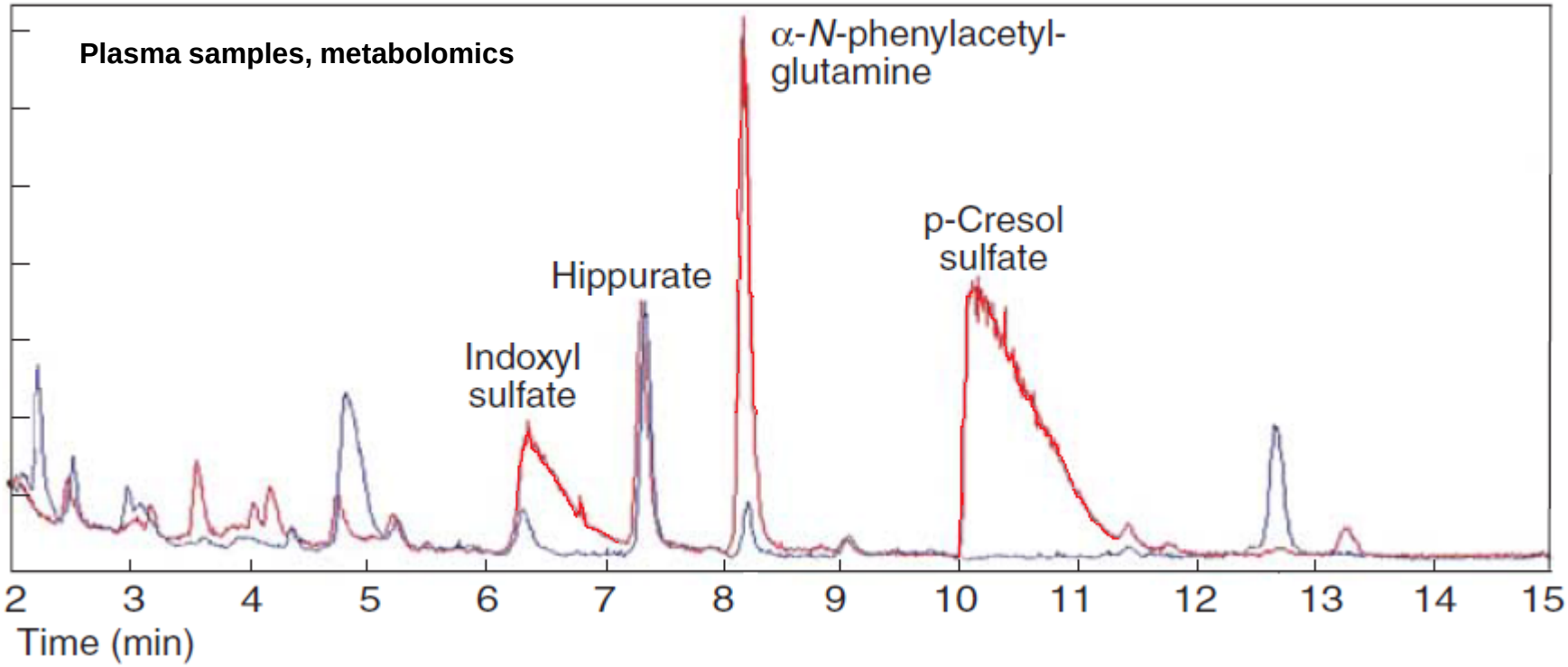
- 10^{14} cells (= 100x cell number of the human body)
- Mostly anaerobic; total 2 kg
- 500-1000 species/ individual
- 5 millions genes (20 000 in the human genome)
- Metabolic activity equivalent to that of the liver

There is a dysbiosis during chronic kidney disease



Koppe et al, Kidney Int 2015;88:958-66

Uremic toxins profile : intact colon vs colectomy in MD patients



HD with intact colon vs. **HD with colectomy**

Courtesy P.Envenepoel

Meyer et al. Kidney Int. 2012;81:949-54

Aronov et al. J Am Soc Nephrol. 2011;22:1769-76

Effect of a Symbiotic Gel (*Lactobacillus acidophilus* + *Bifidobacterium lactis* + Inulin) on Presence and Severity of Gastrointestinal Symptoms in Hemodialysis Patients

Daniela Viramontes-Hörner, BSc, Fabiola Márq*
Barbara Vizmanos-Lamotte, MD, PhD,† Ana S
Juan Armendáriz-Borunda, MD, PhD,‡ Héctor
and Guillermo García-García, MD¶

RCT, 42 pts, 2 months treatment with symbiotics

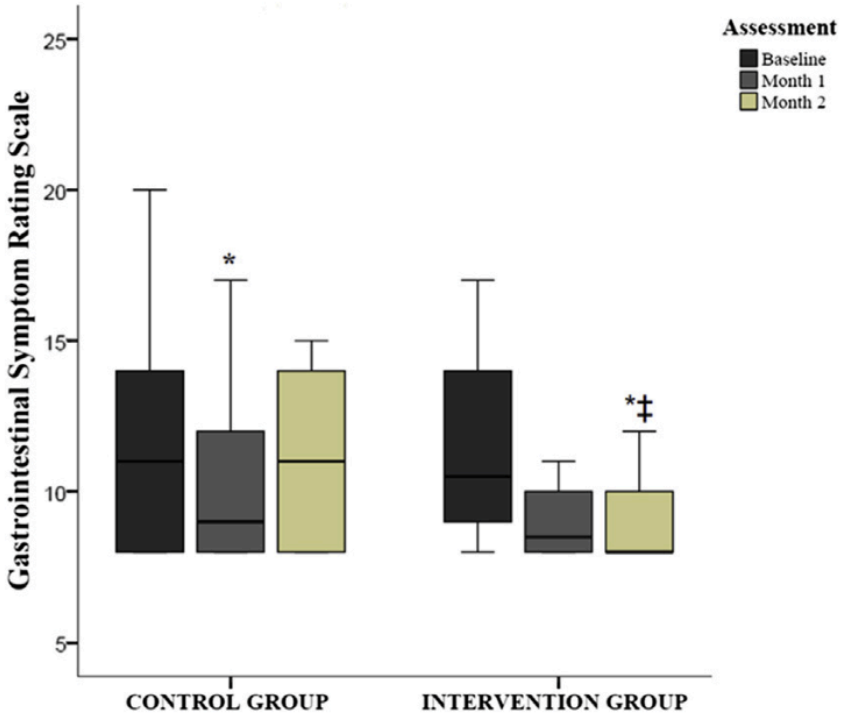
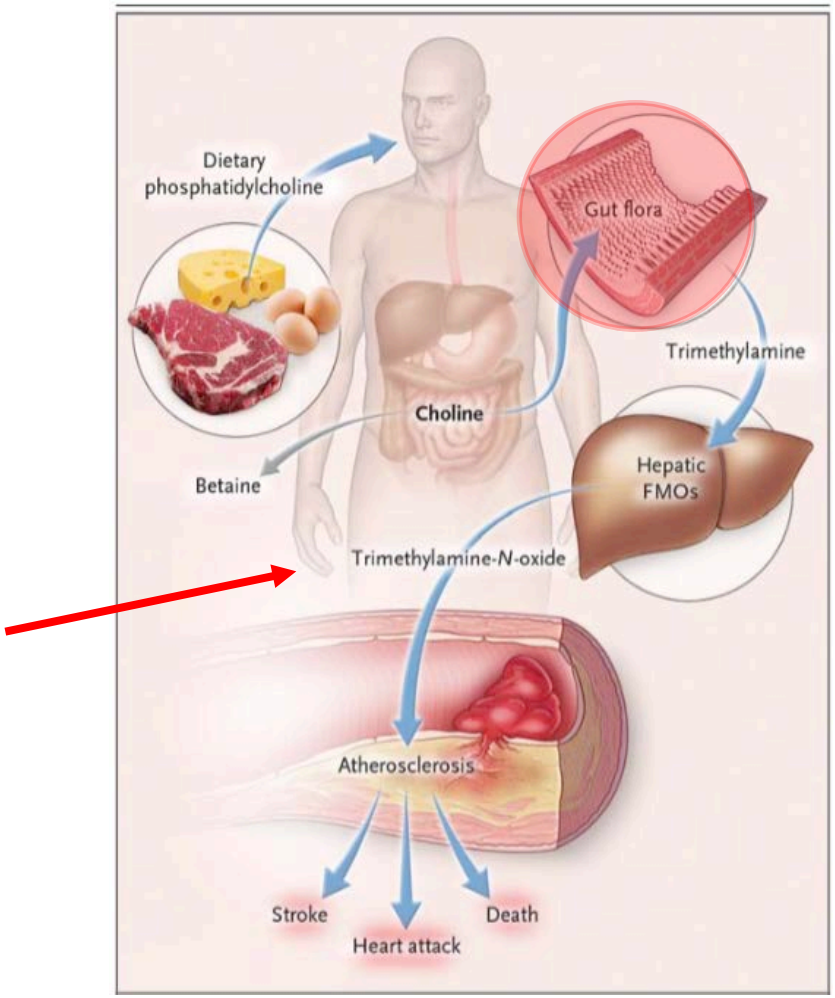


Figure 2. Gastrointestinal symptom rating scale during the study. *$P \leq .05$ versus baseline; ‡$P \leq .05$ versus control.

Journal of Renal Nutrition 25; 2015: 284-291

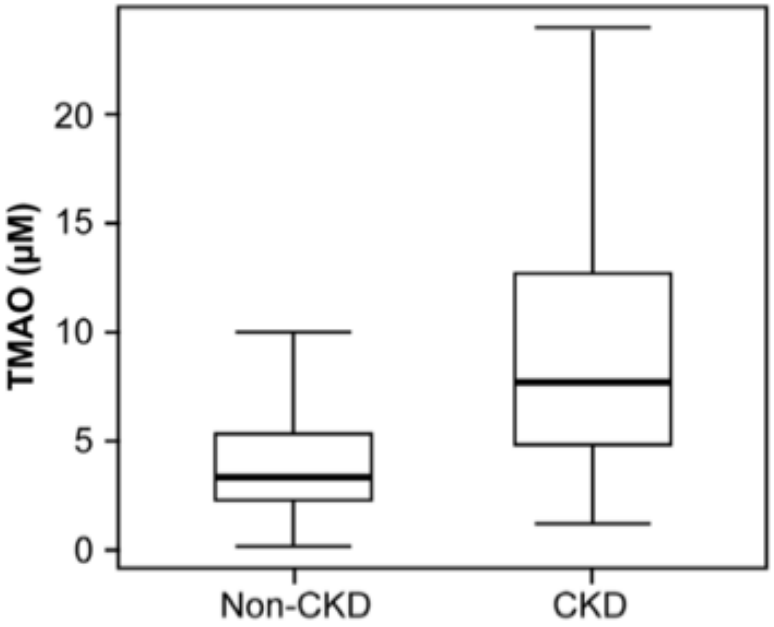
Trimethylamine oxide (TMAO) and CV risk

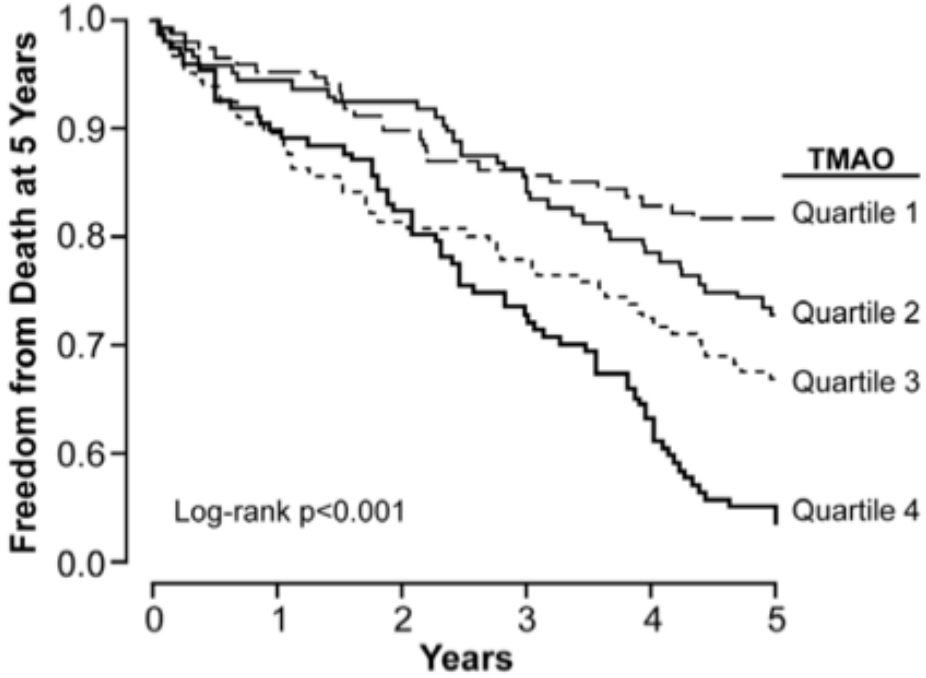


Tang WH et al, N Engl J Med. 2013 Apr 25;368(17):1575-84.

Gut Microbiota-Dependent Trimethylamine *N*-Oxide (TMAO) Pathway Contributes to Both Development of Renal Insufficiency and Mortality Risk in Chronic Kidney Disease

W.H. Wilson Tang, Zeneng Wang, David J. Kennedy, Yuping Wu, Jennifer A. Buffa, Brendan Agatisa-Boyle, Xinmin S. Li, Bruce S. Levison, Stanley L. Hazen





Cleveland, USA,5 yr follow-up

Circ Res. 2015;116:448-455.

Trimethylamine *N*-Oxide and Cardiovascular Events in Hemodialysis Patients

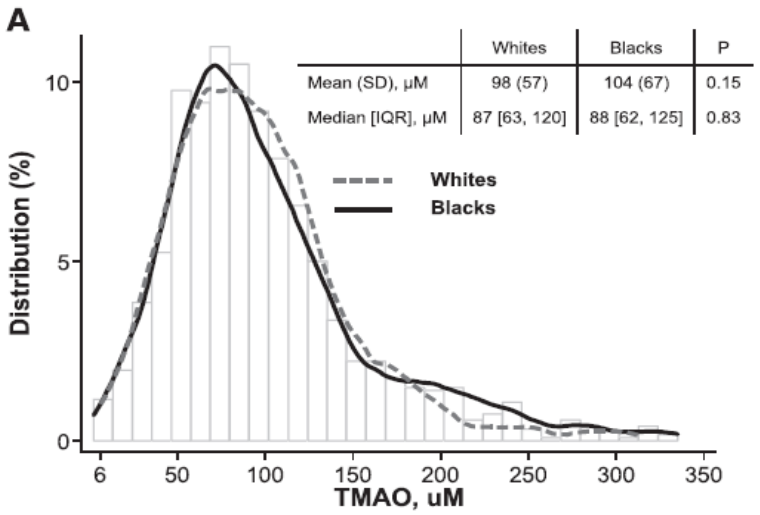
Tariq Shafi,*† Neil R. Powe,‡ Timothy W. Meyer,§ Seungyoung Hwang,* Xin Hai,‖ Michal L. Melamed,¶ Tanushree Banerjee,‡ Josef Coresh,*†** and Thomas H. Hostetter‖

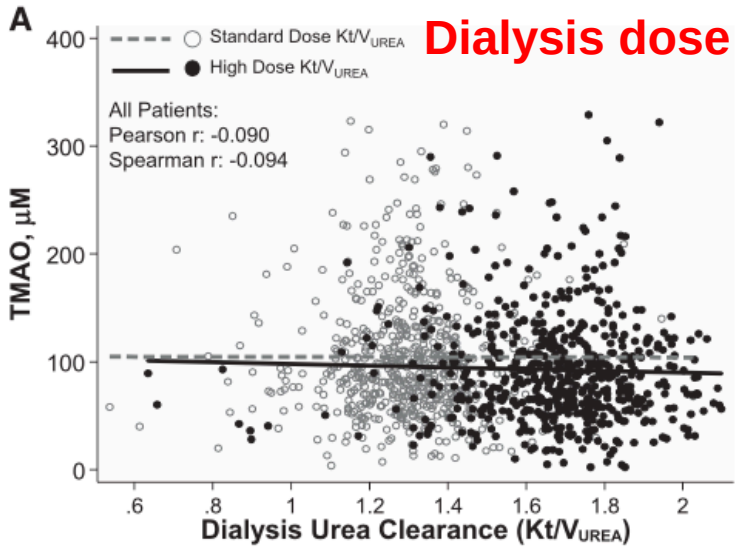
*Department of Medicine and †Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, Maryland; ‡Department of Medicine, University of California, San Francisco, California; §Department of Medicine, Palo Alto Veterans Affairs Health Care System and Stanford University, Palo Alto, California; ‖Department of Medicine, Case Western University School of Medicine, Cleveland, Ohio; ¶Departments of Medicine and Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, New York; and **Departments of Epidemiology and Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

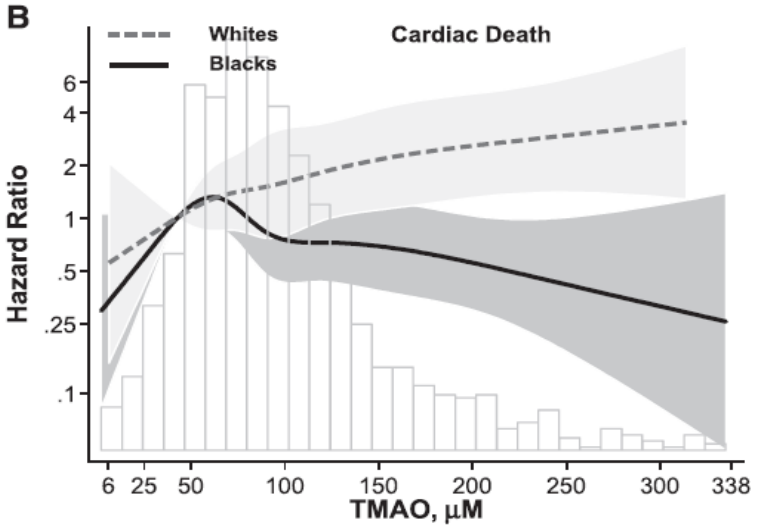
- HEMO study (quite old now)
- 1800 MHD pts
- Survival based on TMAO levels

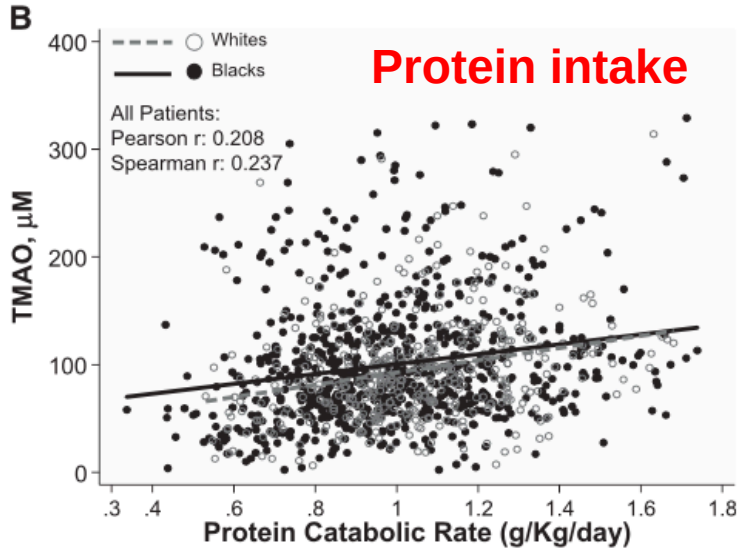
Shafi, T, et al., J Am Soc Nephrol, 2017;28:321-331.

Trimethylamine *N*-Oxide and Cardiovascular Events in Hemodialysis Patients









Shafi, T, et al., J Am Soc Nephrol, 2017;28:321-331.

Results of the HEMO Study suggest that p-cresol sulfate and indoxyl sulfate are not associated with cardiovascular outcomes

Tariq Shafi[1,2,3], Tammy L. Sirich[4], Timothy W. Meyer[4], Thomas H. Hostetter[5], Natalie S. Plummer[4], Seungyoung Hwang[1], Michal L. Melamed[6,7], Tanushree Banerjee[8], Josef Coresh[1,2,3] and Neil R. Powe[8]

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		Cardiac death	Sudden cardiac death	First CV event	Any-cause death
Events, *n*		221	127	641	563
Event probability, %		17.4	10.0	54.2	44.2
Solutes	**SD**	**HR**	**HR**	**HR**	**HR**
PCS	1.351	1.19	1.25	1.14	1.11
IS	0.930	1.29	1.40	1.22	1.17
HIPP	1.369	1.19	1.26	1.15	1.12
PAG	1.031	1.26	1.35	1.20	1.15

ABW, adjusted body weight; CV, cardiovascular; HIPP, hippurate; HR, hazard ratio; ICED, Index of Coexistent Disease; IS, indoxyl sulfate; nPCR, normalized protein catabolic rate; PAG, phenylacetylglutamine; PCS, p-cresol sulfate.

The minimum detectable HR per 2-fold increase in solute was calculated assuming 90% power and alpha = 0.05. Observed SD of the solutes and R^2 from the linear regression of solutes on predictors in the fully adjusted model (model 4 in Table 2) were calculated from the data.

Shafi, T, et al., Kidney Int, 2017, In Press.

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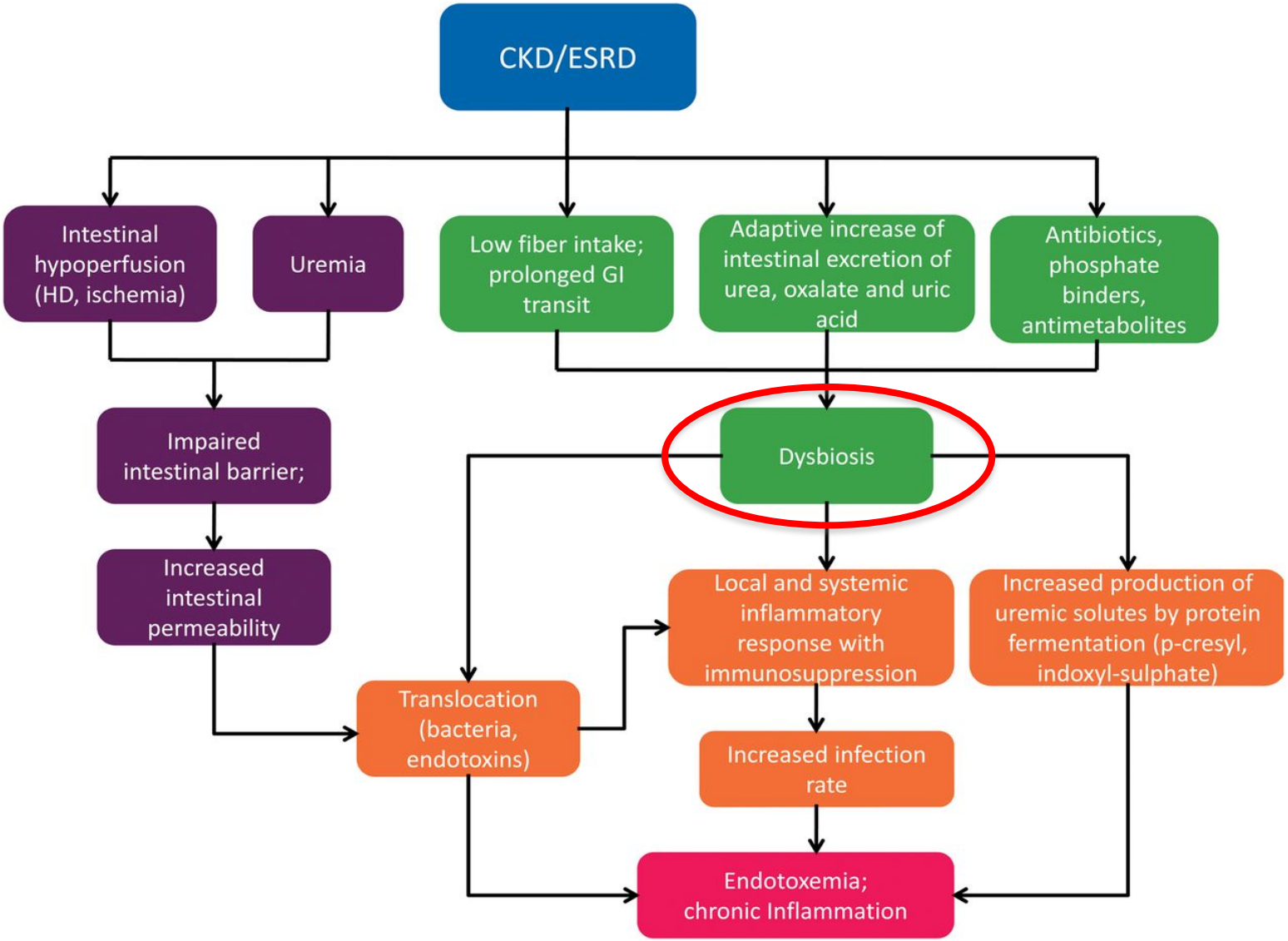
- No change in P-cresol and indoxyl-sulfate despite 30% increase in dialysis dose

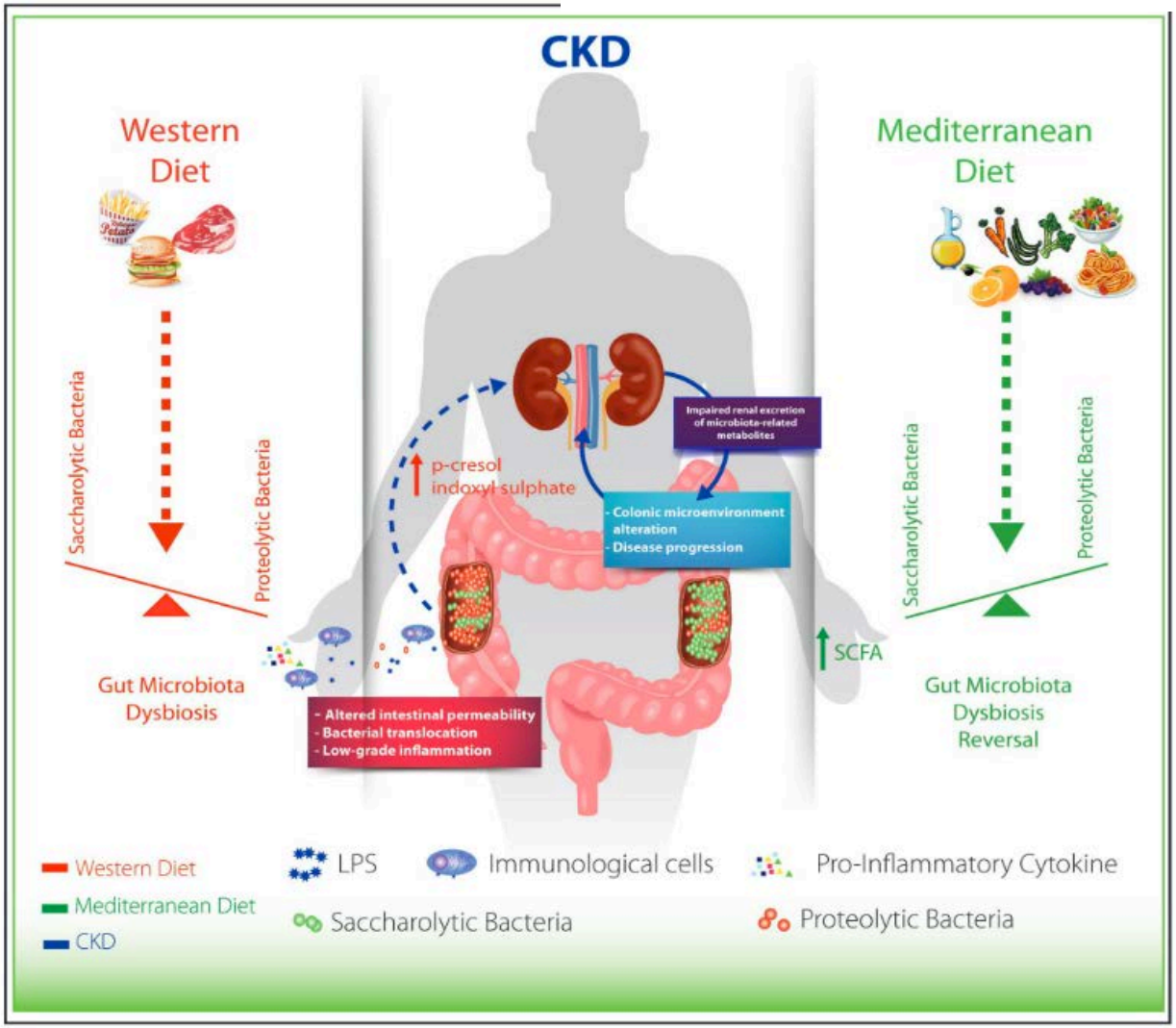
Shafi, T, et al., Kidney Int, 2017, In Press.

Negative effects of CKD/ESRD on intestinal barrier and microbiota



Sabatino et al. NDT 2015;30:924-933

Fig. 1. The social network between diet, gut microbiota and kidney in CKD. In CKD, gut microbiota dysbiosis is present, leading to a prevalence of proteolytic species and to an increase in microbial uremic toxins (p-cresol and indoxyl sulphate). The impaired renal function, in turn, worsens the dysbiosis status and leads to an altered intestinal permeability and to low-grade inflammation. All this factors contribute to disease progression. In this context, a Western-style Diet contributes to the worsening of the dysbiosis, promoting the selective proliferation of proteolytic species. The Mediterranean Diet, by leading gut microbial metabolism towards a saccharolytic profile, can restore gut microbiota balance, ameliorating CKD conditions and slowing down disease progression.



 Montemurno et al, Kidney Blood Press Res. 2014;39(2-3):114-23.

Take-Home Message

Evidence for altered microbiota in CKD: relationship with:

- the type of food intake
- the severity of CKD
- the concentration of serum toxins
- patients survival

- In 2017 uremic toxins still not improved by dialysis

Blood Pressure Control

State-of-the-Art

- NKF-KDOQI guidelines (2005): In hemodialysis patients, it is reasonable to keep BP below 140/90 mmHg

- KDIGO did not want to adress HD in their 2012 BP guideline because of lack of data
- Consensus papers 2012-2014 with weak evidence

Which level of blood pressure?

Multiphasic effects of blood pressure on survival in hemodialysis patients

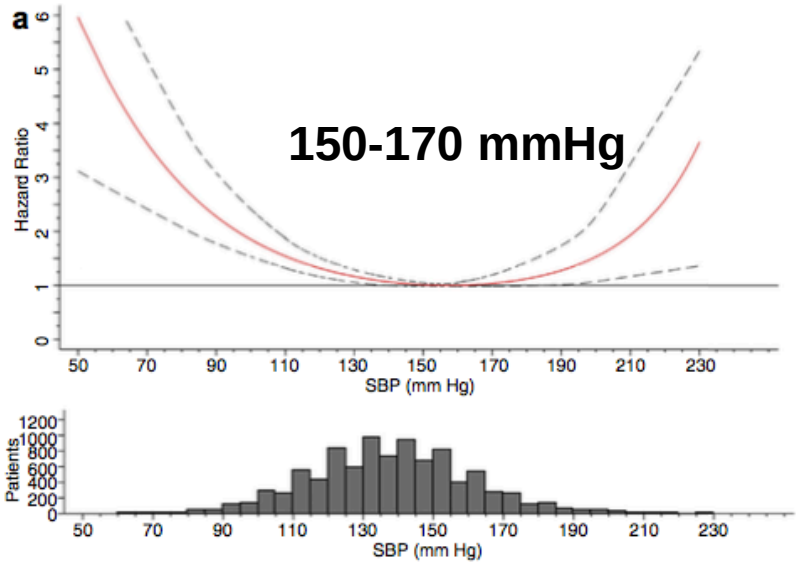
Thierry Hannedouche[1], Hubert Roth[2], Thierry Krummel[1], Gérard M. London[3], Guillaume Jean[4], Jean-Louis Bouchet[5], Tilman B. Drüeke[6] and Denis Fouque[7]; on behalf of the French Observatory[8]

[1]Service de Néphrologie, Hôpitaux Universitaires de Strasbourg, Faculté de Médecine, Strasbourg, France; [2]Centre de Recherche en Nutrition Humaine Rhône-Alpes, Pôle Recherche CHU-Grenoble, Inserm U1055-Bioénergétique, Université Grenoble-Alpes, France; [3]Hôpital Manhes, Fleury-Mérogis, France; [4]Centre de Rein Artificiel, Tassin-La-Demi-Lune, France; [5]Centre de Traitement des Maladies Rénales Saint-Augustin, Bordeaux, France; [6]Inserm U1018, Centre de recherche en Epidémiologie et Santé des Populations, Universitaire Paris-Saclay, Universitaire Paris-Sud, Université de Versailles Saint-Quentin-en-Yvelines, Villejuif, France; and [7]Department of Nephrology, Hôpital Lyon Sud, Université de Lyon, Centre Européen de Nutrition pour la Santé, Lyon, France

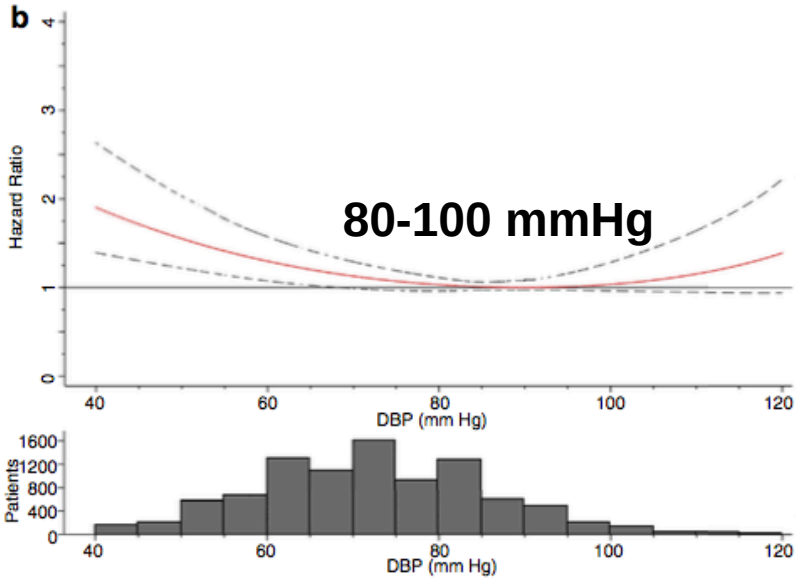
Hannedouche et al, Kidney International (2016) 90, 674–684

2-yr cardiovascular mortality

SBP



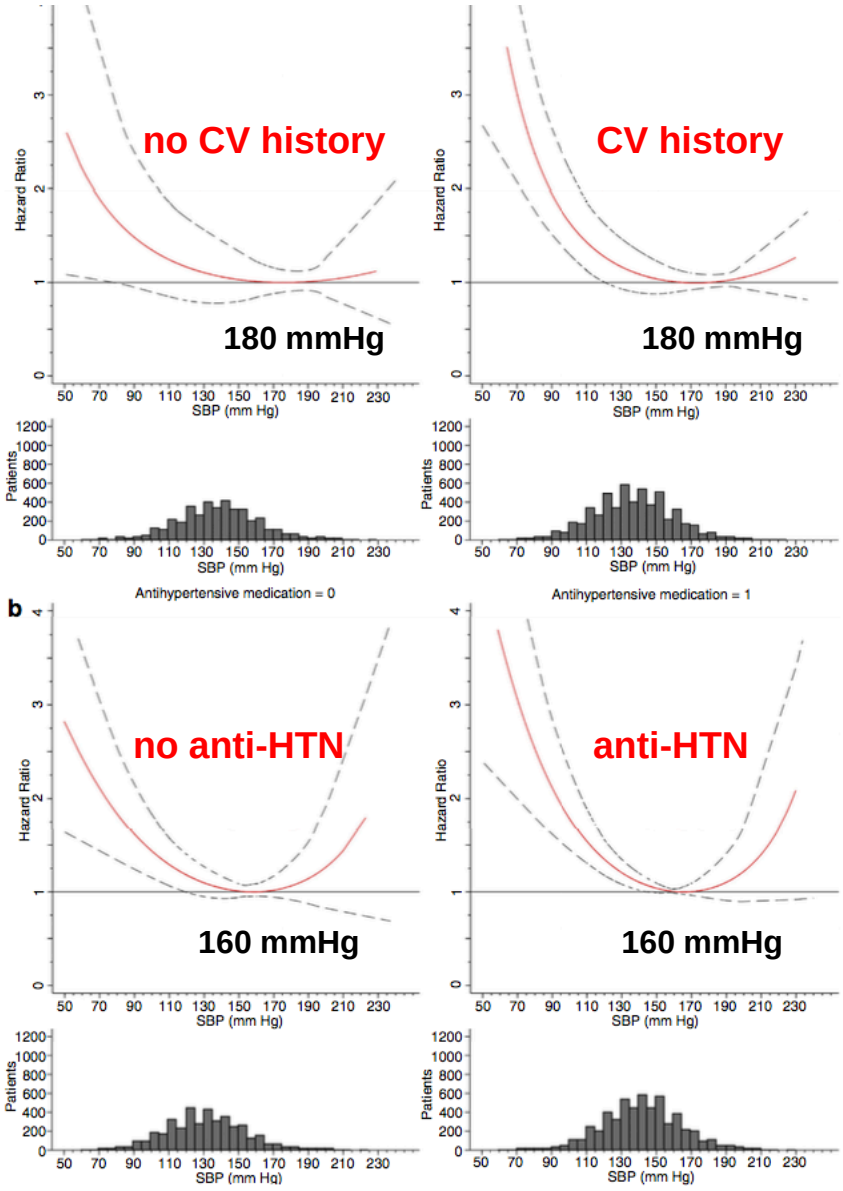
DBP



Adjusted fractional polynomials

Hannedouche et al, Kidney International (2016) 90, 674–684

By subgroups



Hannedouche et al, Kidney International (2016) 90, 674–684

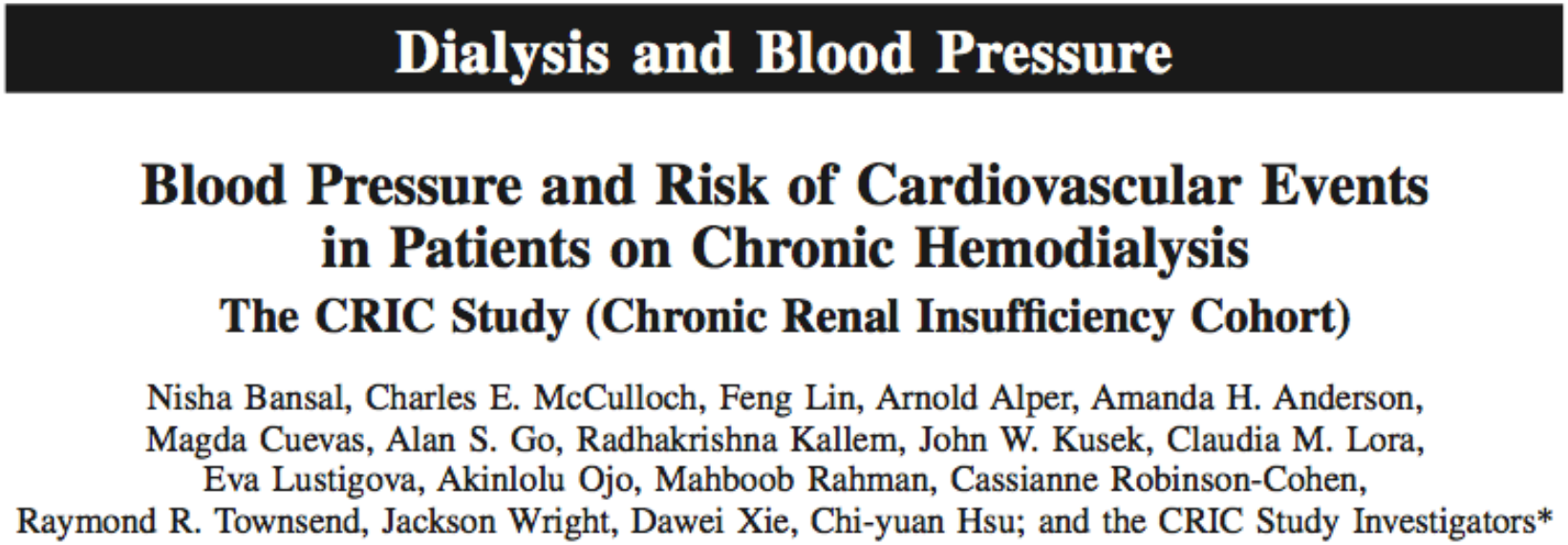
When to measure blood pressure?

Managing hypertension using home blood pressure monitoring among hemodialysis patients – a call to action

Agarwal, Nephrology Dialysis Transplantation. 2010:25(6) 1766-1771

Already in 2010

Which blood pressure?



Dialysis and Blood Pressure

Blood Pressure and Risk of Cardiovascular Events in Patients on Chronic Hemodialysis

The CRIC Study (Chronic Renal Insufficiency Cohort)

Nisha Bansal, Charles E. McCulloch, Feng Lin, Arnold Alper, Amanda H. Anderson, Magda Cuevas, Alan S. Go, Radhakrishna Kallem, John W. Kusek, Claudia M. Lora, Eva Lustigova, Akinlolu Ojo, Mahboob Rahman, Cassianne Robinson-Cohen, Raymond R. Townsend, Jackson Wright, Dawei Xie, Chi-yuan Hsu; and the CRIC Study Investigators*

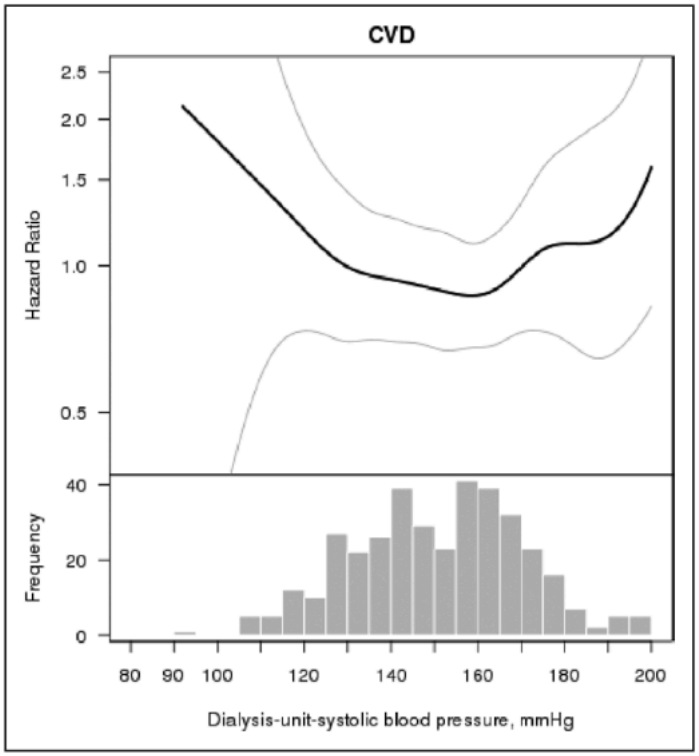
Either per dialysis session (pre-dialysis) or out of dialysis unit (other day)

383 MHD pts, CRIC study USA

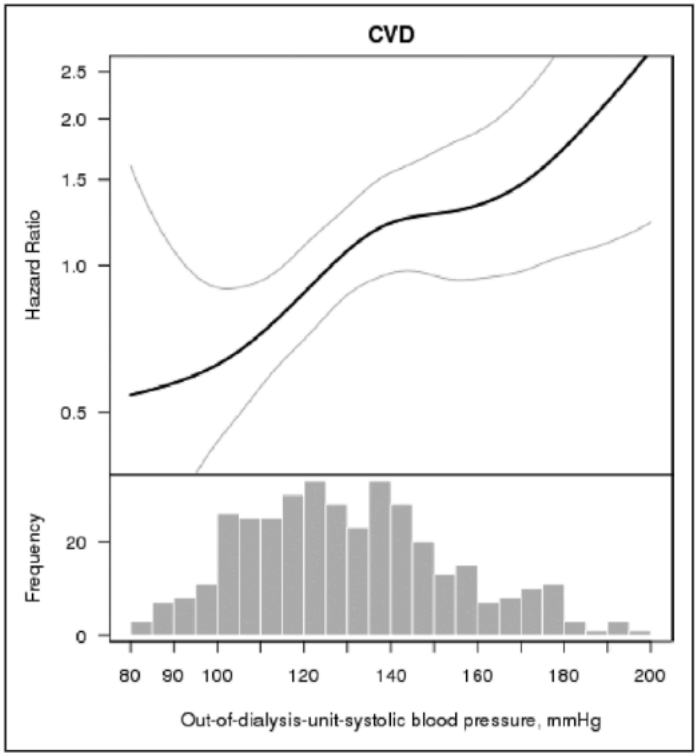
Bansal et al, Hypertension. 2017;70:435-443.

Pre-dialysis vs out of dialysis SBP and CV events

Per Dialysis



Out of Dialysis



Mean Follow-up 2.4 yr

Bansal et al, Hypertension. 2017;70:435-443.

CRIC limitations

- Age in cohorts (60 yr)
- BP measurement method (Sprint)
- Small sample (350 pts)
- Long interval between BP taken during session and taken out-of-dialysis (mean 100 d, up to 200 d)
- Worth to be explored

Bansal et al, Hypertension. 2017;70:435-443.

Which BP treatment class in dialysis?

Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial

- Rajiv Agarwal et al

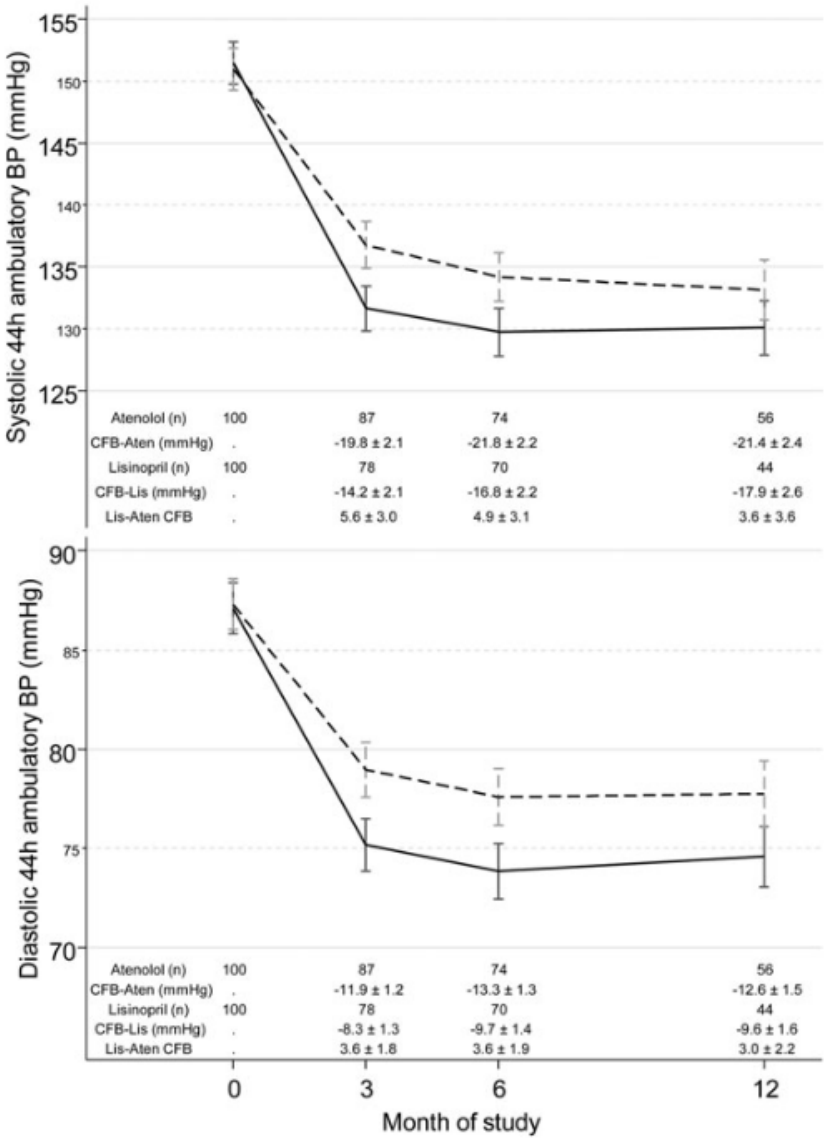
Nephrol Dial Transplant 2014;29:672-681

44-hr ambulatory blood pressure

SBP

DBP

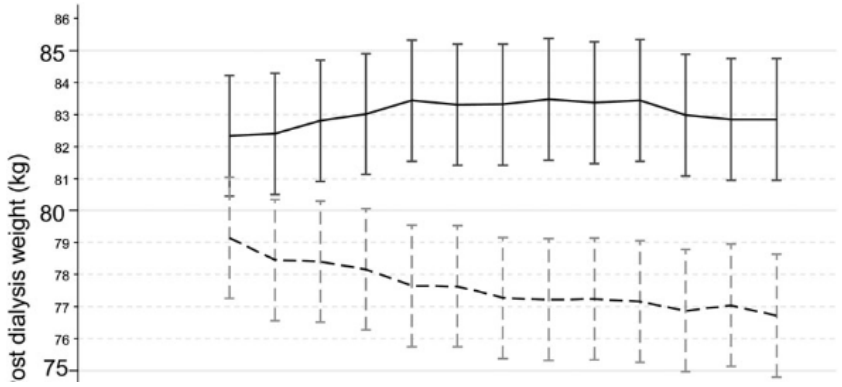
- **Lisinopril --------**
- **Atenolol _____**



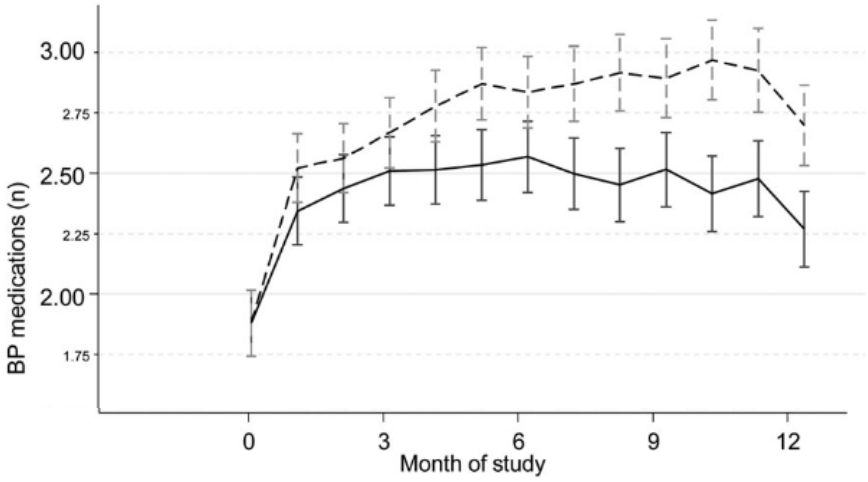
Rajiv Agarwal et al, Nephrol Dial Transplant 2014;29:672-681

Dry weight and number of drugs

Post dialysis weight



Number of medications

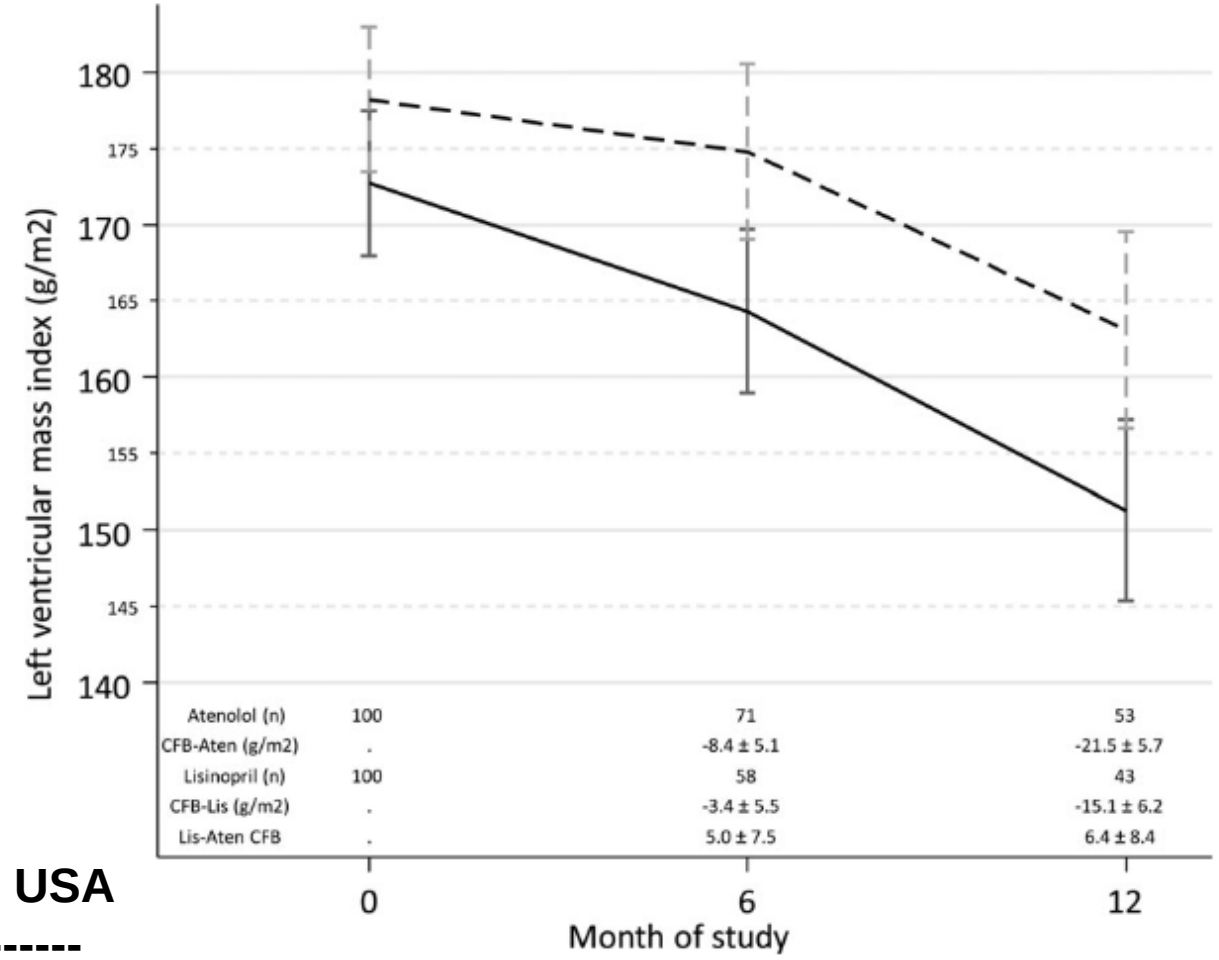


RCT, 200 MHD, USA

- **Lisinopril --------**
- **Atenolol _____**

Rajiv Agarwal et al, Nephrol Dial Transplant 2014;29:672-681

Improvement in cardiac hypertrophy



RCT, 200 MHD, USA

- **Lisinopril --------**
- **Atenolol _____**

Rajiv Agarwal et al, Nephrol Dial Transplant 2014;29:672-681

Take-Home Message

No valid data to recommend target BP

- Like diabetes, probably less stringent control in the future
- Best measure time to be confirmed
- RCTs eagerly needed
- B-blockers preferred

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