Are the Apparent Survival Benefits of Hemodiafiltration Due to Changes in Extracorporeal Temperature?

Prof. Bernard Canaud

Montpellier University, School of Medicine, Montpellier-F
& Senior Medical Scientist, Global Medical Office FMC, Bad Homburg-G

Health Care

Annual Dialysis CONFERENCE
March 5-7, 2021

School of Medicine
University of Missouri Health

Are the Apparent Survival Benefits of **Hemodiafiltration** Due to **Different Thermal Energy Balance**?

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5. Any Role for Non-Thermal Factors?
6. Take home message: HDF has a Cardiac Protecting Effect

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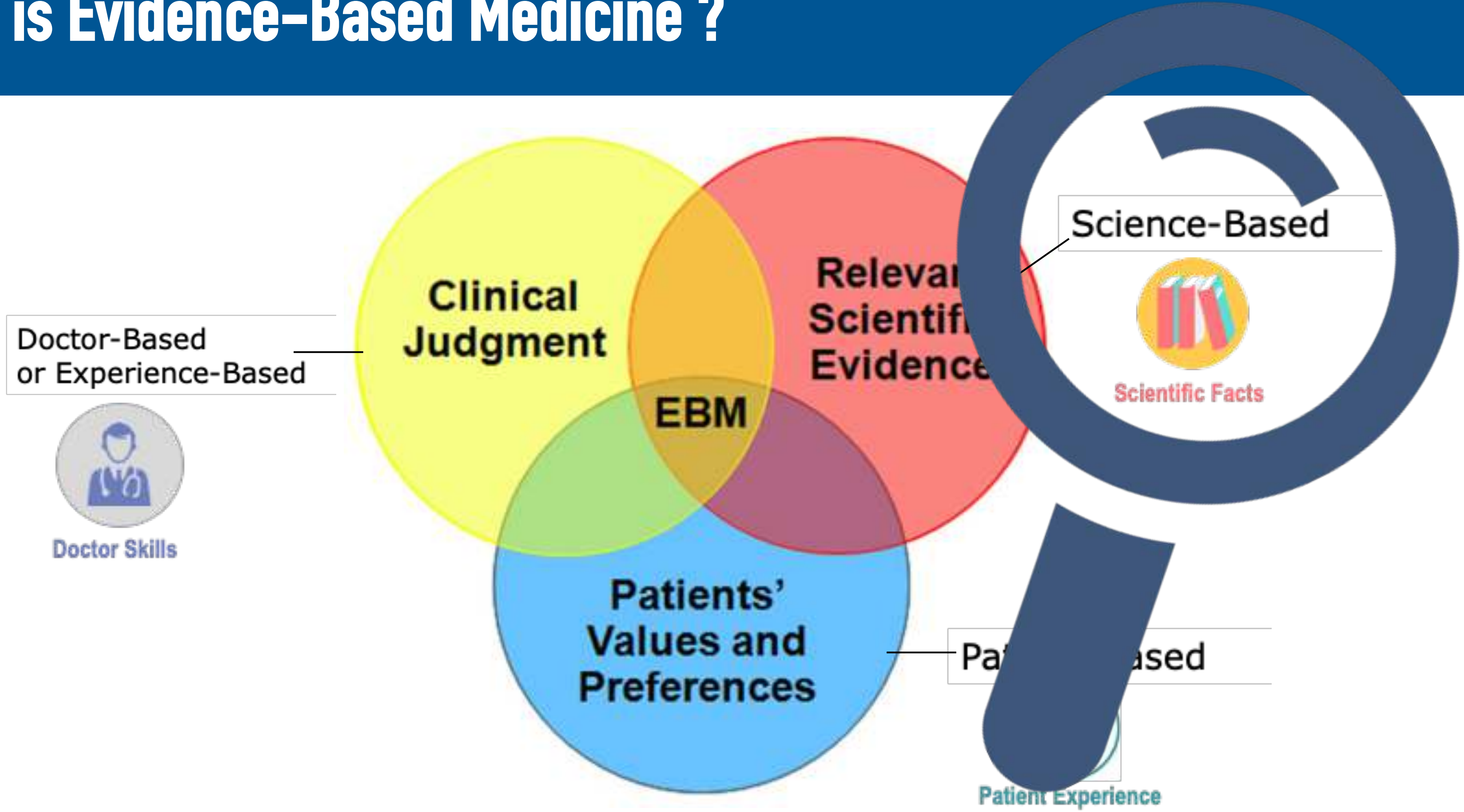
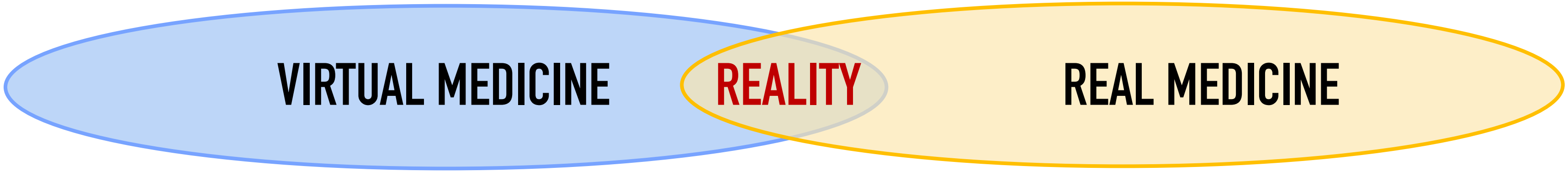
What is Evidence-Based Medicine ?

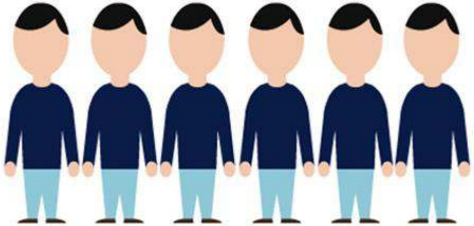


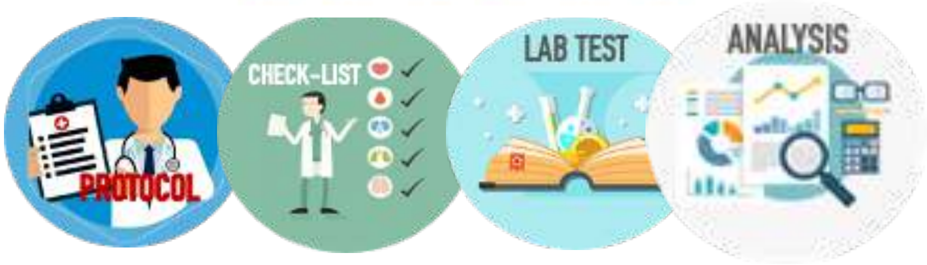
Sackett DF et al, *BMJ* 1996;312(7023):71-72

Science-Based EBM Applied to Hemodiafiltration



HIGHLY SELECTED POPULATION





RANDOMIZED CONTROLLED STUDIES

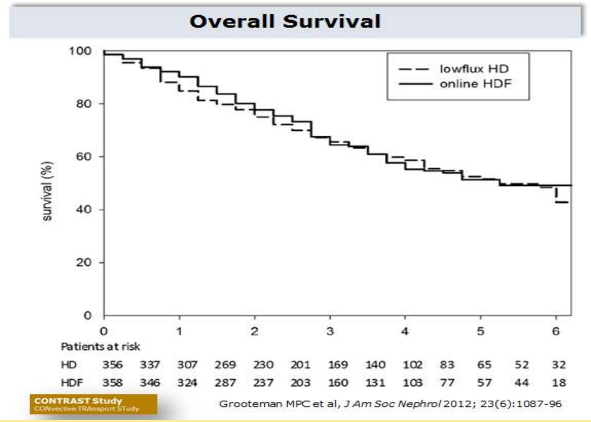
UNSELECTED POPULATION

POPULATION BASED STUDIES

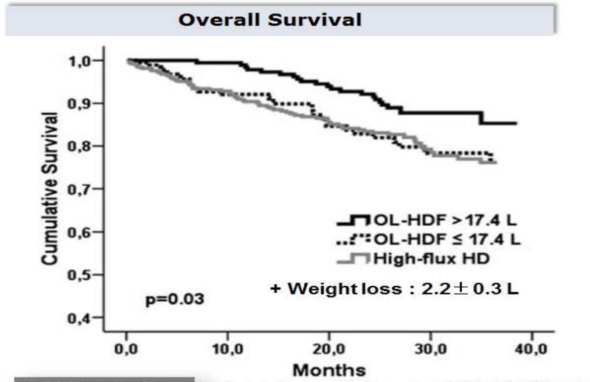
Primary Outcome HDF vs HD

Outcome is Improved When Right Dosage Is Delivered

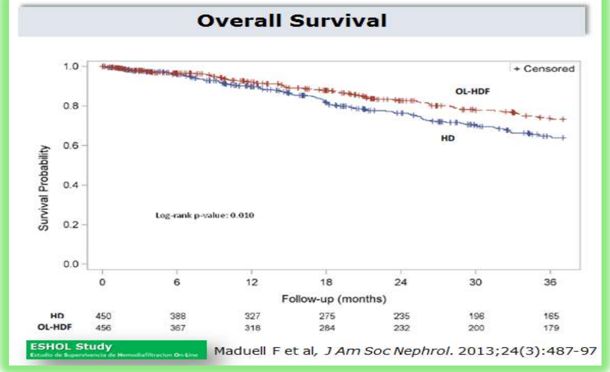
Randomized Controlled Trials



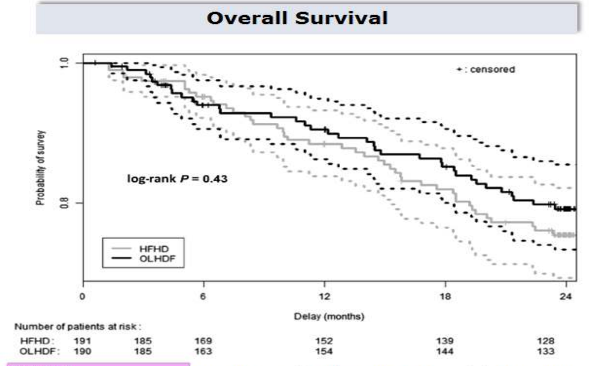
Grooteman MPC et al, *J Am Soc Nephrol* 2012; 23(6):1087-96



Ok E et al, *Nephrol Dial Transplant*. 2013;28(1):192-202



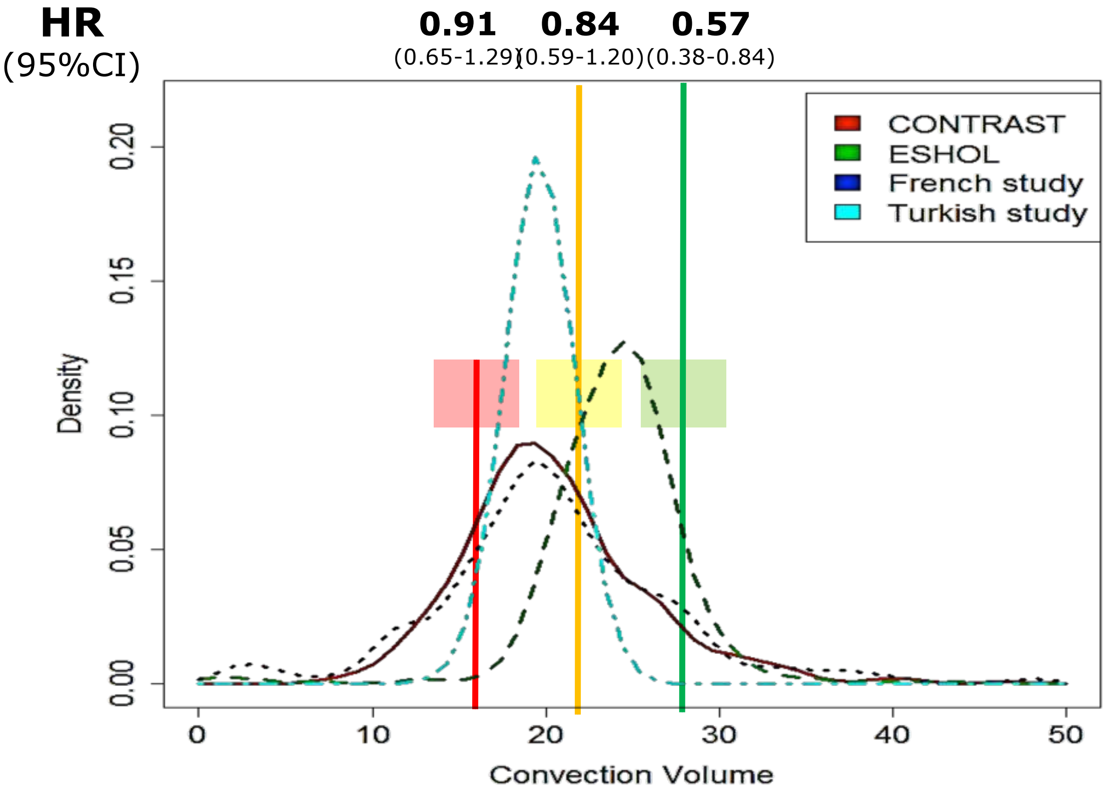
Maduell F et al, *J Am Soc Nephrol*. 2013;24(3):487-97



Morena M et al, *Kidney Int*. 2017;91(6):1495-1509.

Convective Dose Dependency CV Mortality

Total Ultrafiltered Volume Distribution Per Study



European Pooling Project

Peters SA et al, Nephrol Dial Transplant. 2016;31(6):978–984.

HDF European Pooling Project
Four Randomized Clinical Trials

Individual Patient Data Meta-Analysis

Dutch Trial	Turkish Trial	Catalonian Trial	French Trial
Open label RCT	Open label RCT	Open label RCT	Open label RCT
LF-HD vs HDF	HF-HD vs HDF	HF-HD vs HDF	HF-HD vs HDF > 65yo
358/356	220/228	450/456	200/200
JASN	NDT	JASN	KI
CONTRAST Study	Turkish HDF Study	ESHOL Study	French HDF Study

2708 prevalent ESKD pts

HD1393

HDF1315

mode	HD	Ol-HDF	Ol-HDF	Ol-HDF
Ol-HDF dose		Lowest	Middle	Highest
Convection volume (l)	NA	18.0 (16.0–18.8)	21.0 (20.2–22.0)	25.7 (24.4–27.4)
Number	1393	433	447	435
Body surface area (m^2)	1.77 (0.22)	1.72 (0.23)	1.77 (0.20)	1.80 (0.20)
BMI post dialysis (kg/m^2)	25.2 (4.6)	24.7 (5.0)	24.9 (4.6)	25.8 (4.8)
Weight (kg)	68.7 (15.4)	66.2 (14.6)	68.9 (13.7)	71.5 (14.5)
Total body water (l)	35.1 (6.5)	34.6 (6.7)	35.3 (6.2)	35.0 (6.2)

Pooled individual patient analysis of four prospective trials compared thirds of delivered convection volume with hemodialysis. Convection volumes were either not standardized or standardized to weight, body mass index, body surface area, and total body water. Data were analyzed by multivariable Cox proportional hazards modeling from 2793 patients.

Peters SAE et al, *Nephrol Dial Transplant* 2016;31(6):978-84.

Effects of Pooled Database on HR

HDF is Associated with a Significant Reduction of Mortality Risk

Individual Patient Data Meta-Analysis

A Pooled Meta-Analysis of Individual Participant Data* from four randomized controlled trials

2708 prevalent ESKD pts

- **HD1393**
- **HDF1315**

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)

↘14%

↘23%

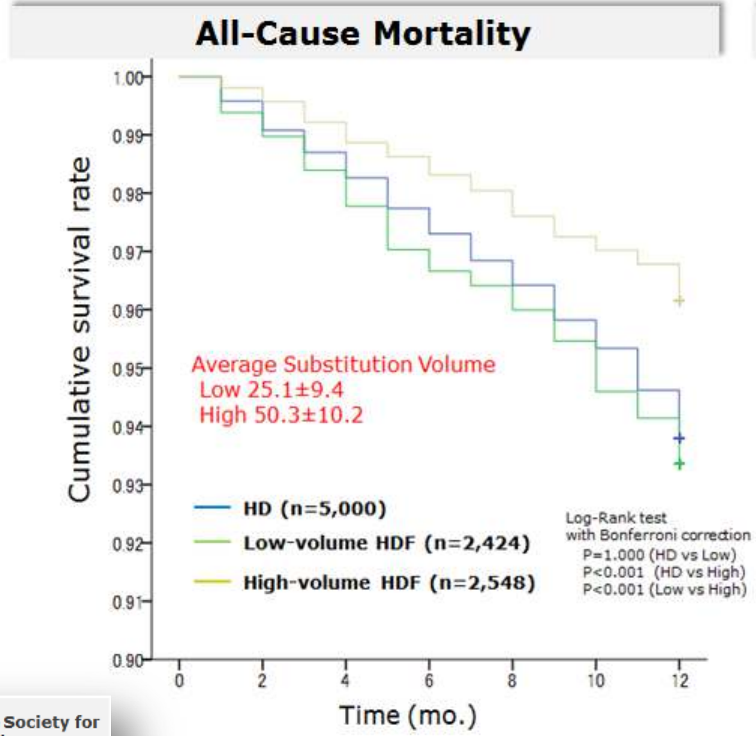
EUDIAL

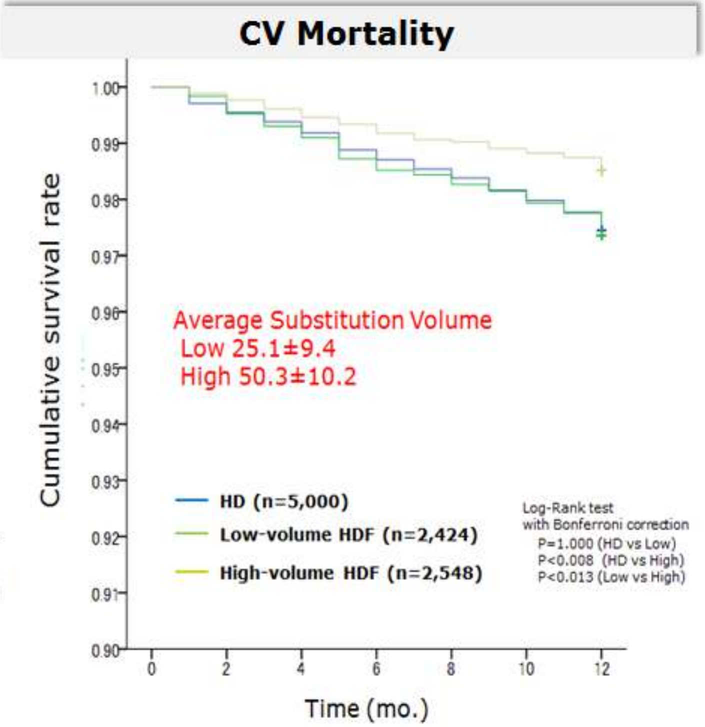
*Riley RD et al, *BMJ* 2010;340:c221

Peters SAE et al, *Nephrol Dial Transplant* 2016;31(6):978-84.

HDF is Associated With Better Outcome with High Volume Convection

Cohort Study
National Registry





The Japanese Society for Dialysis Therapy

Kikuchi K et al, *Kidney Int.* 2019 Feb 16. pii: S0085-2538(18)30897-4.

HDF is Associated with Better Outcome at Patient Level and at Facility Level

Cohort Study
National Registry

	All-Cause Mortality[a]	Cardiovascular Mortality[b]	Noncardiovascular Mortality[b]
Patient-level predictor analyses			
Sex-adjusted model, HDF	0.81 (0.74-0.89)	0.71 (0.59-0.86)	0.86 (0.78-0.95)
Fully adjusted model,[c] HDF	0.84 (0.77-0.91)	0.73 (0.61-0.88)	0.89 (0.81-0.97)
Fully adjusted model,[c] HDF exclusive vs never	0.77 (0.67-0.87)	0.66 (0.50-0.86)	0.82 (0.72-0.92)
Facility-level predictor analyses[d]			
Overall population	0.87 (0.77-0.99)	0.72 (0.54-0.96)	0.96 (0.84-1.09)
In-center and satellite facility patients	0.82 (0.72-0.94)	0.68 (0.51-0.93)	0.90 (0.78-1.04)

French Renal Epidemiology and Information Network Registry (REIN)

22,881 were not treated with HDF

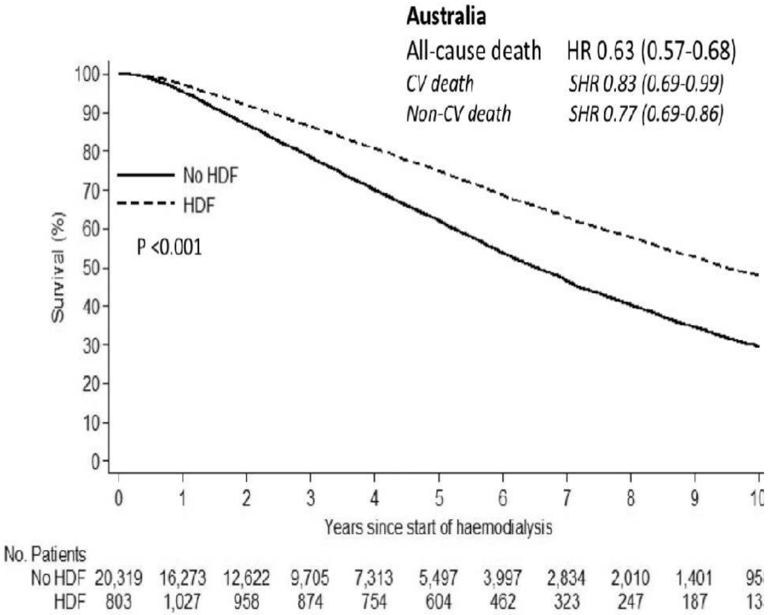
5,526 were treated at least once with HDF

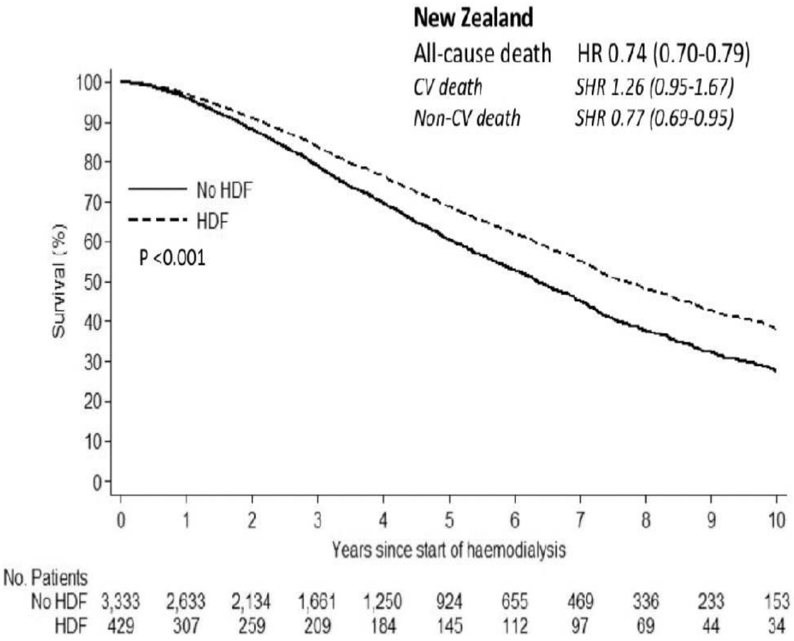
2,254 exclusively treated with HDF

Mercadal L et al, *Am J Kidney Dis.* 2016;68(2):247-255.

HDF is Associated with Better Outcome Over 10 Years Period both in Australia & New Zealand

Cohort Study
National Registry





4,110 were regularly treated with HDF

22,851 were regularly treated with HD

Lee E et al, *Nephrol Dial Transplant.* 2018; 33 (Sup.1): i332–i333

Outline – Are the Apparent Survival Benefits of HDF Due to Different Thermal Balance?

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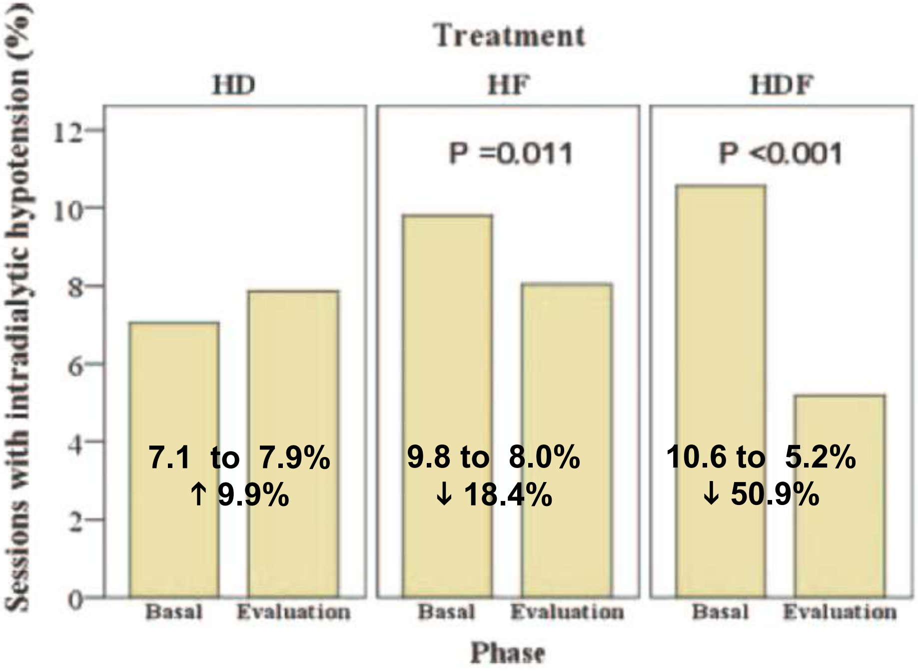
6 Take home message: HDF has a Cardiac Protecting Effect

Intra Dialytic Hypotension is Reduced in HDF

Total incidence of IDH 7.5% 28950 sessions



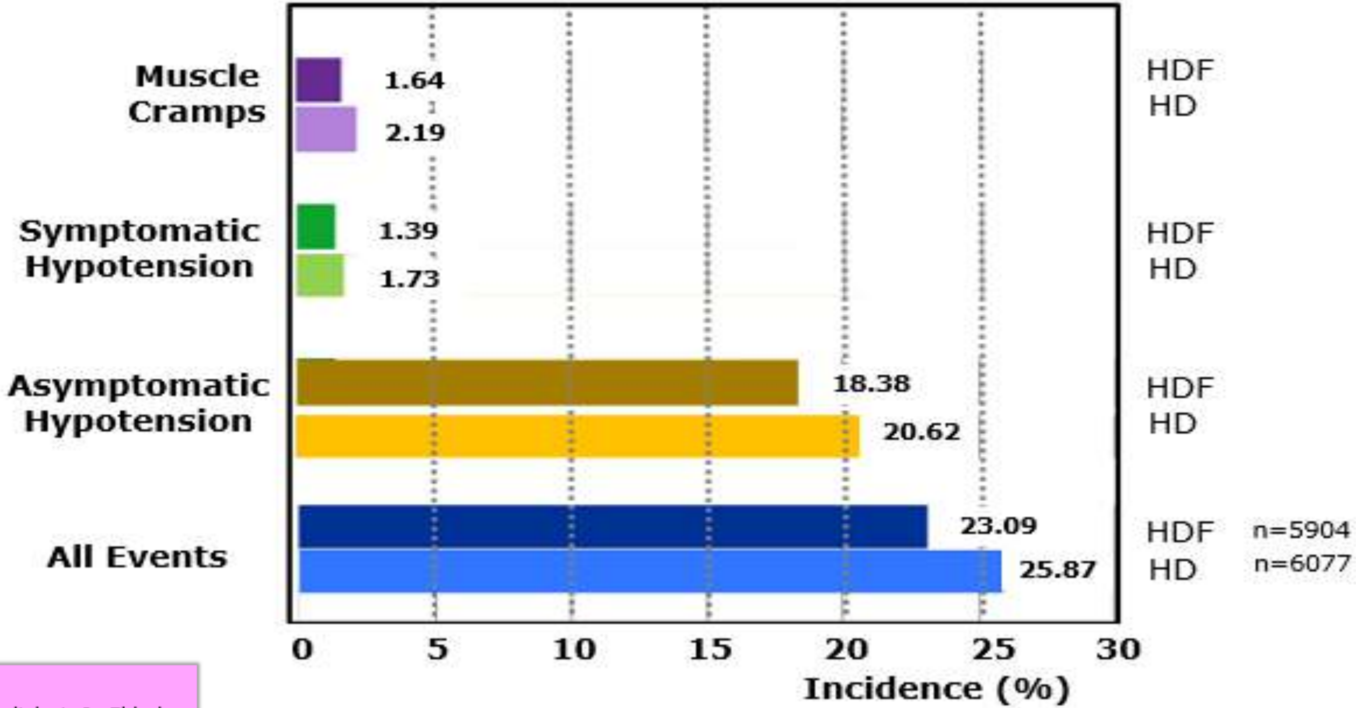
Italian C/D Study

Italian Multicenter Convective vs Diffusive Study

Locatelli F et al, *J Am Soc Nephrol* 2010; 21:1798-1807

Intradialytic Morbidity is Reduced in Elderly Patients with HDF

Reduced incidence of hypotensive episodes and cramps

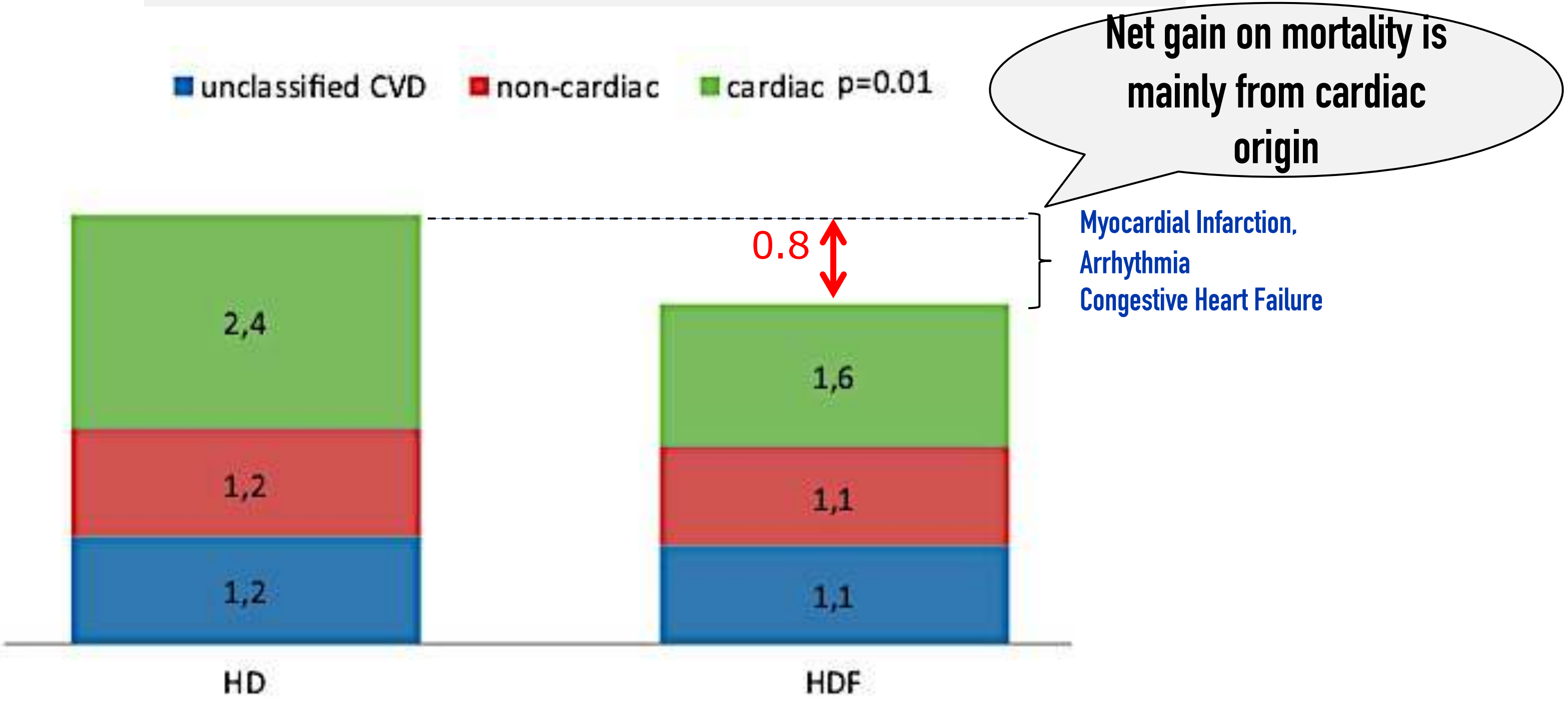


FRENCHIE
French Convective vs Hemodialysis In Elderly

Morena M et al, *Kidney Int.* 2017;91(6):1495-1509.

A Cause-Specific Analysis of HD/HDF Shows Cardiac Benefit Exclusively

Annualized CVD mortality per 100 patient-years in the HD and olHDF groups. The numbers in boxes represent fatal CVD



Nubé MJ et al. HDF Pooling Project investigators. *Nephrol Dial Transplant.* 2017;32(3):548-555.

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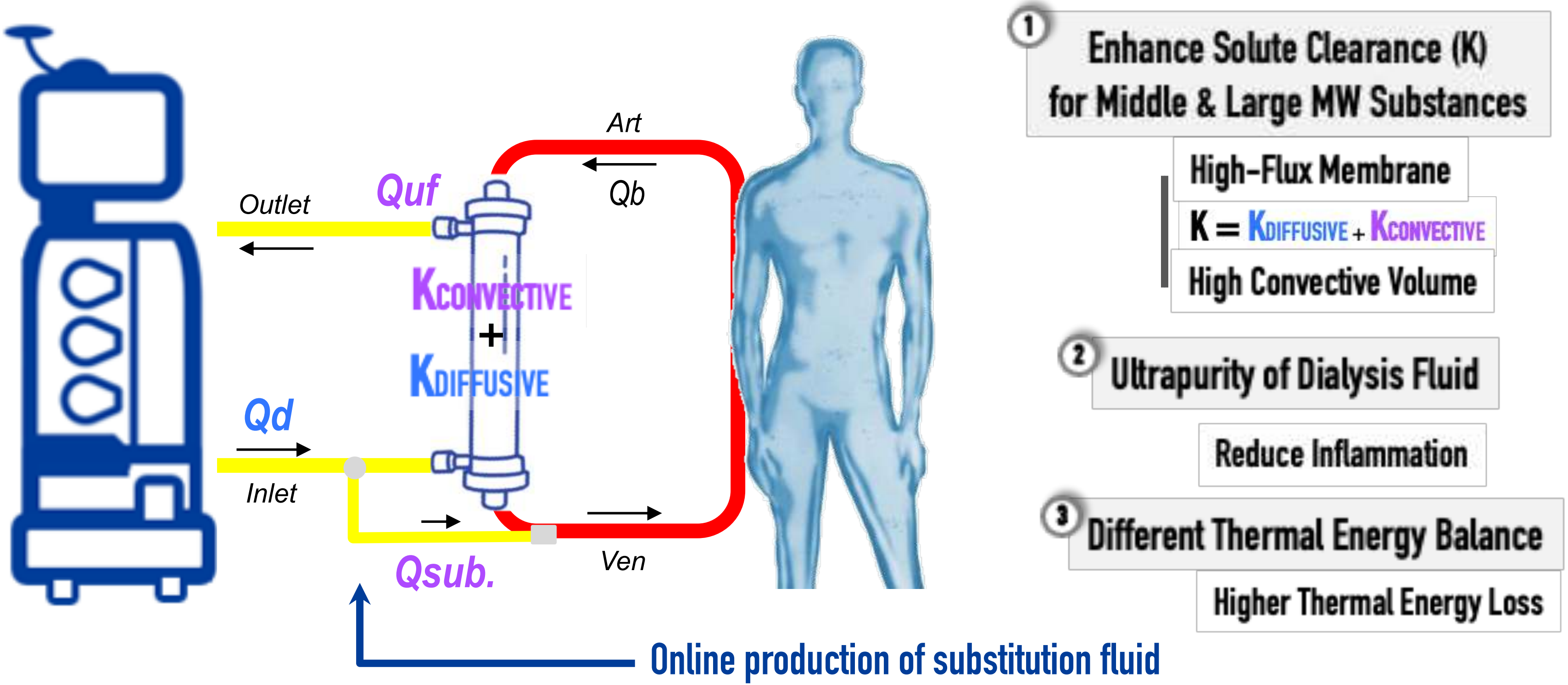
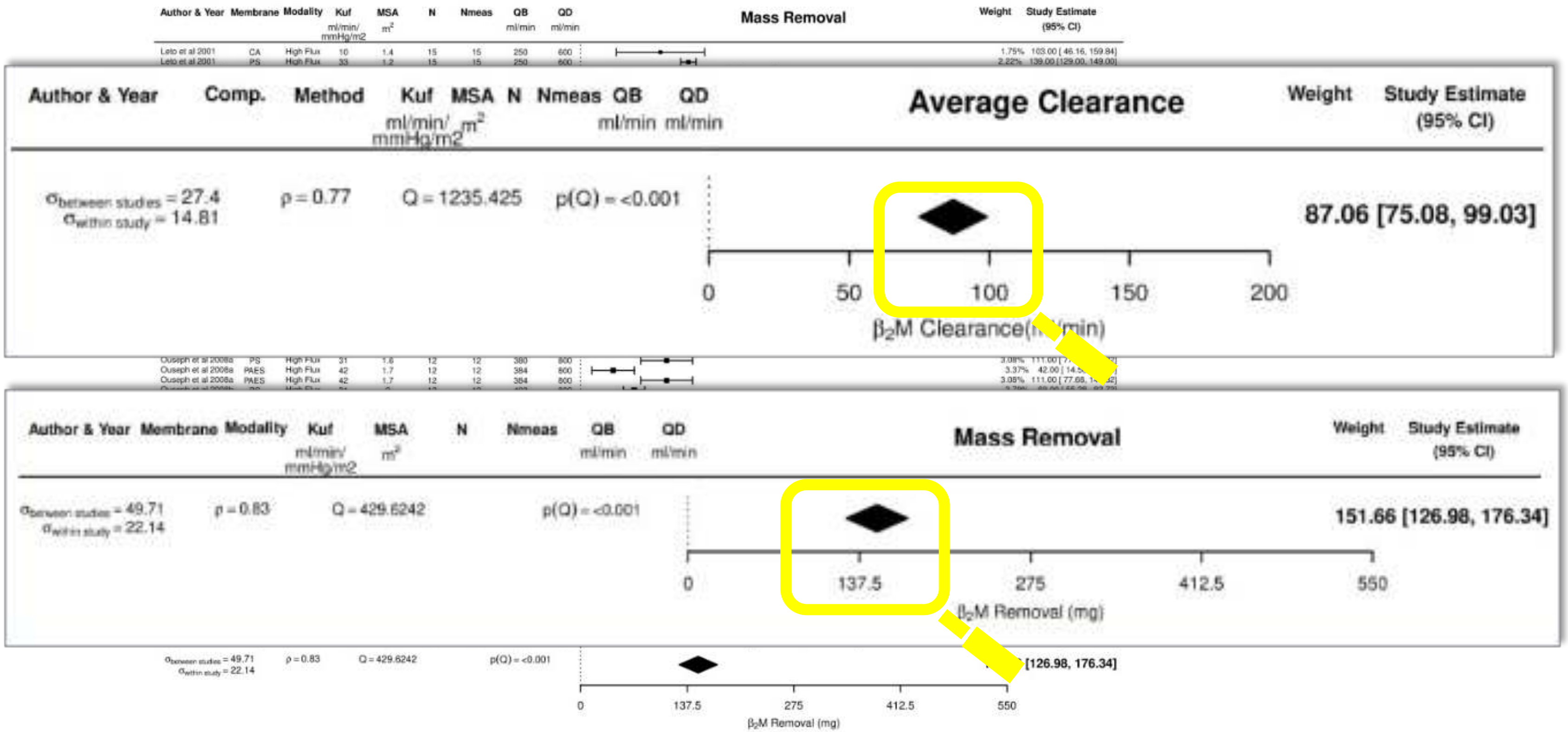
Online Hemodiafiltration Has Different Features and Biologic Actions



HDF Provides Significantly Higher ß2M Clearance & Mass Removal



Roumelioti ME et al, *Nephrol Dial Transplant* 2018; 33: 1025–1039

Inflammation, Oxidative Stress, Nutrition and Anemia Markers Are Improved with Ultrapure Dialysate and HDF

Outcome variables	No. studies	No. patients	Mean net change[a] (95% CI)	P-value
Inflammatory markers				
C-reactive protein, mg/L	9	414	−4.38 (−7.47, −1.29)	0.006
Interleukin-6, pg/mL	9	278	−11.61 (−17.74, −5.49)	<0.001
Interleukin-1 receptor antagonist, ng/mL	2	87	−0.06 (−0.17, 0.04)	0.243
Tumor necrosis factor-α, pg/mL	3	50	−5.50 (−12.86, 1.87)	0.144
Oxidative stress markers				
Oxidized LDL cholesterol, U/L	2	166	−14.04 (−21.26, −6.83)	<0.001
Nutritional markers				
Albumin, g/dL	4	176	0.25 (0.02, 0.48)	0.031
Anemia parameters				
Hemoglobin, g/dL	5	206	0.13 (0.00, 0.26)	0.049
Erythropoietin dose, units/week	5	206	−1188 (−2371, −4)	0.049

Susantitaphong P et al, *Nephrol Dial Transplant* 2013;28: 438–446

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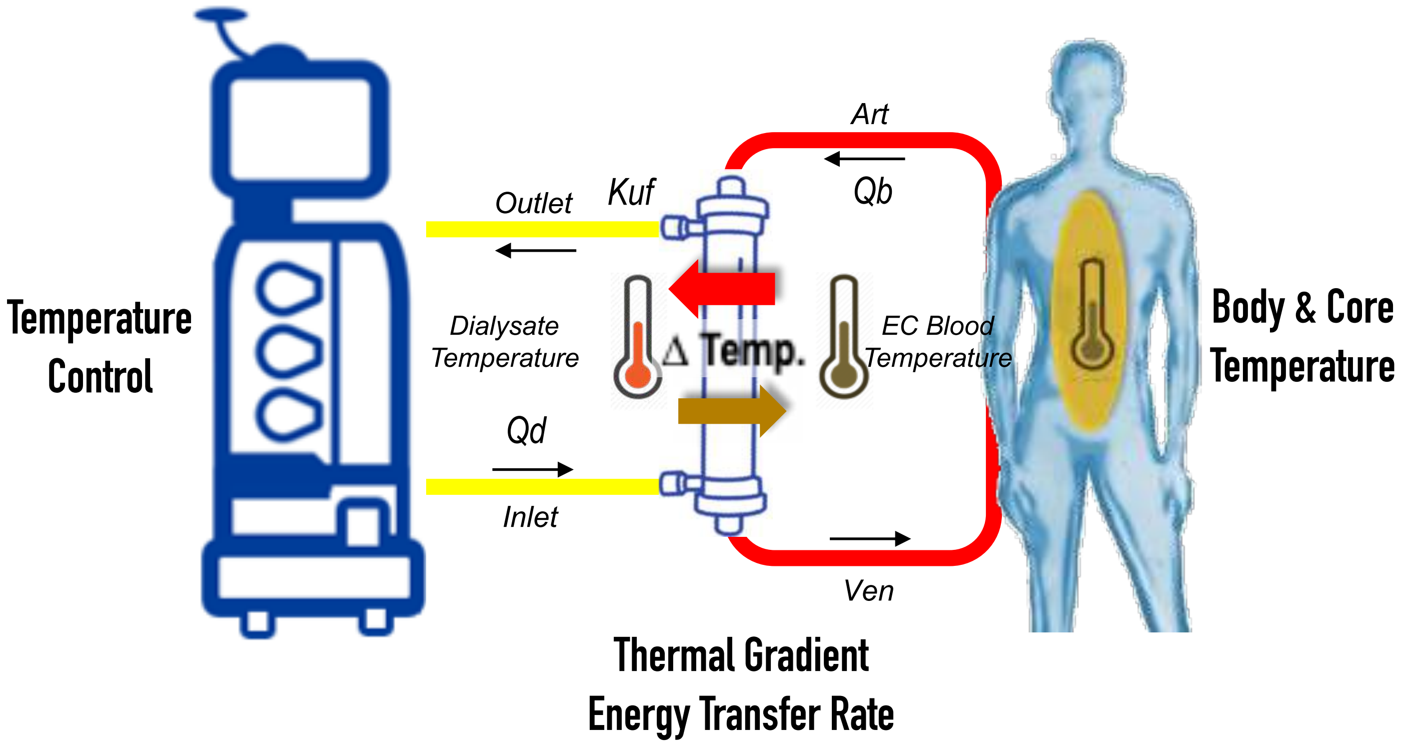
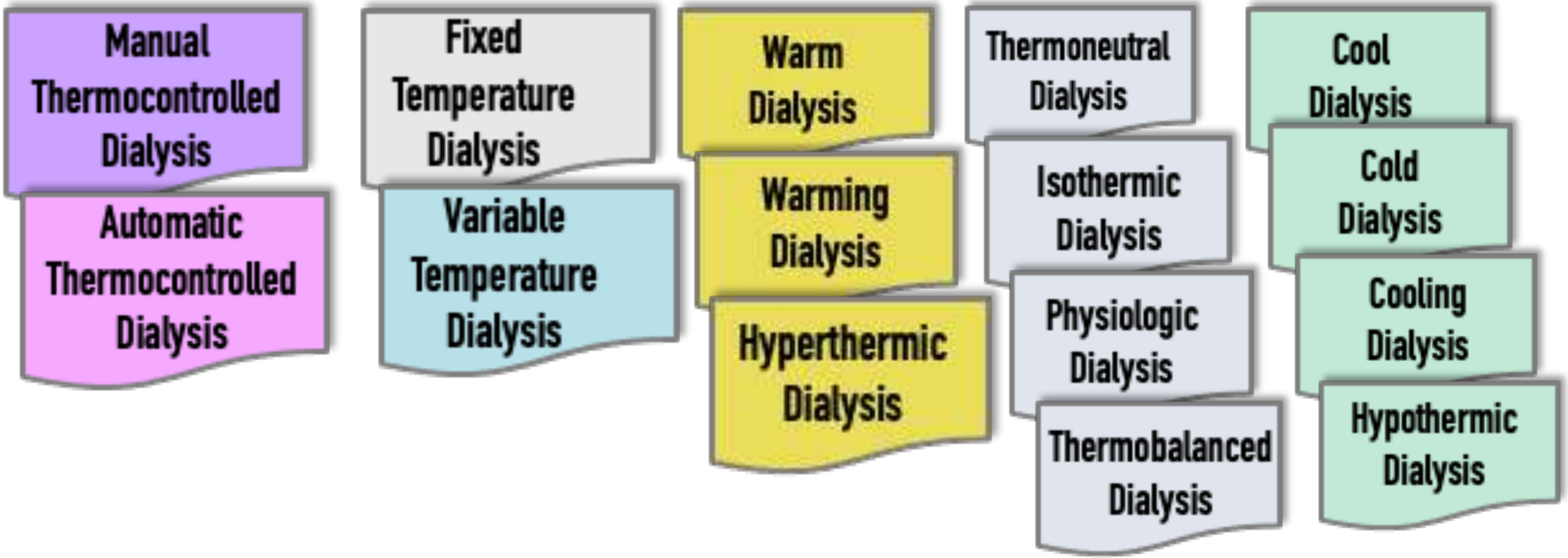
Hemodialysis as Heat Exchanger System



Schneditz D. *Semin Dial.* 2001;14(5):357-64.

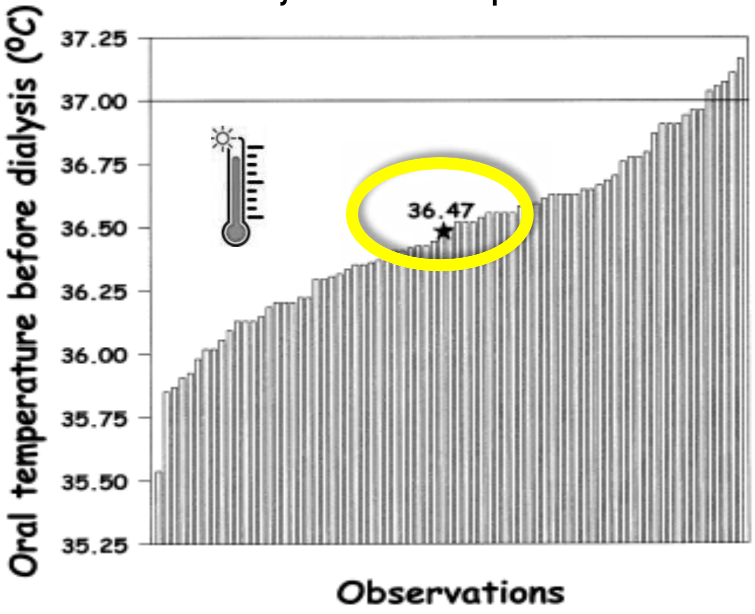
Terminology Used to Define Thermal Balance in HD is Confusing



Schneditz D. *Semin Dial.* 2001;14(5):357-64.

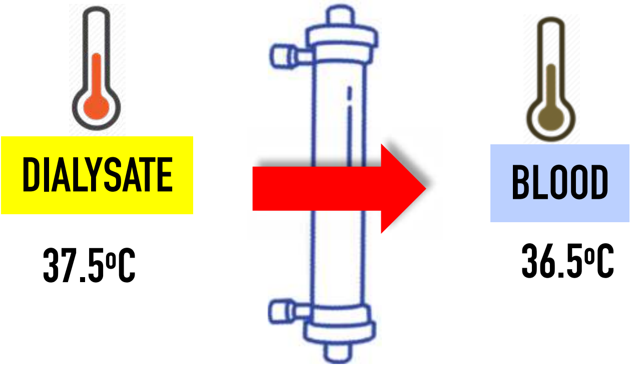
Thermal Energy Balance in Standard HD Treatment

Mean Predialysis Auricular Temperature is 36.5ºC



Prospective Study
75 Stable HD pts
One week x 3 ses.

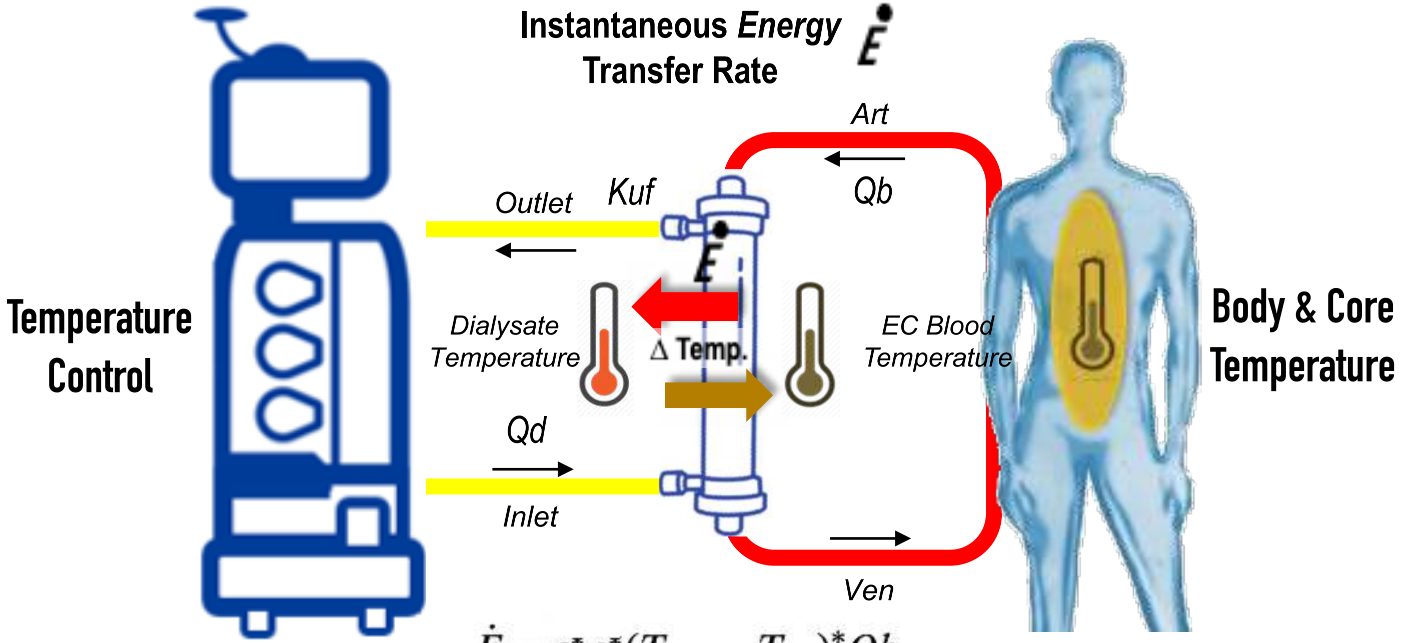
Standard Dialysate Temperature is Set at 37-37.5ºC



Heat Gain
Positive Energy Transfer Rate

Pergola et al. *Am J Kidney Dis* 2004;44:155-165

Heat Flow Transfer – Instantaneous Energy Transfer Rate



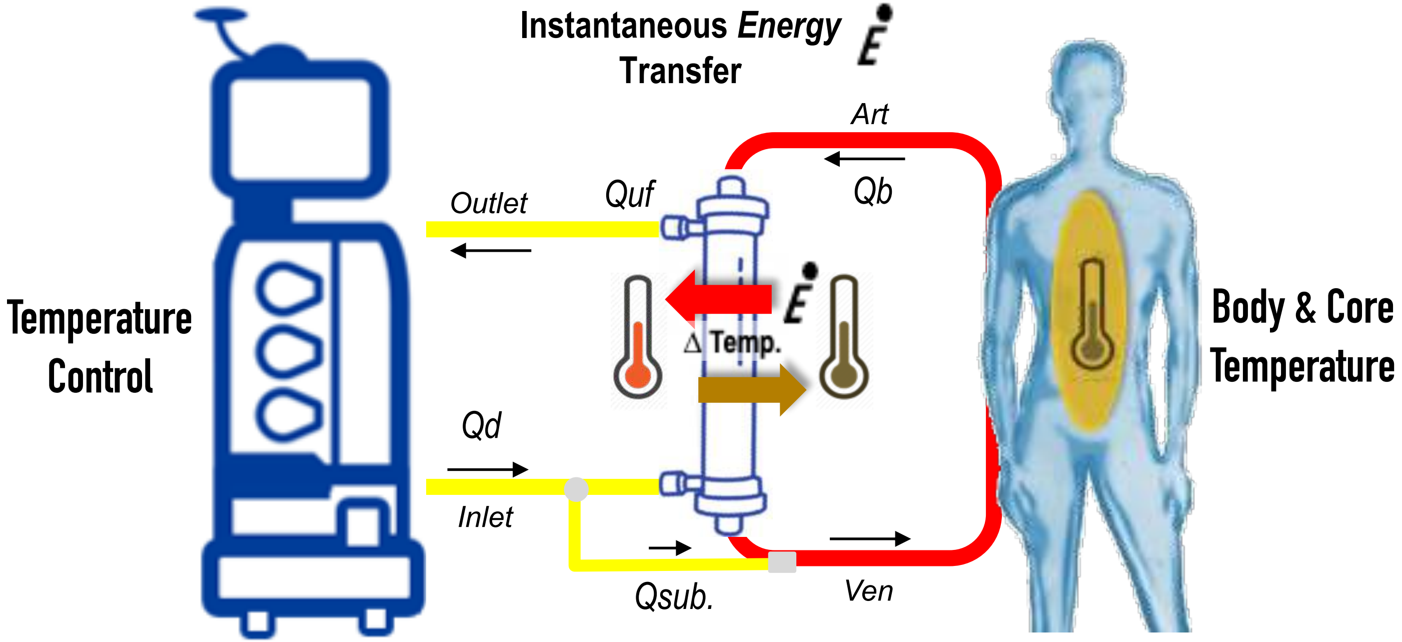
$$\dot{E} = c^{*}\rho^{*}(T_{ven} - T_{art})^{*}Qb$$

c : specific caloric capacity of blood
ρ: hematic density (hematocrit)
T_{ven} : temp. returning to patient
T_{art} : temp. leaving the patient

Schneditz D. *Semin Dial.* 2001;14(5):357-64.

Online HDF has an Additional Component to Heat Flow Transfer Equation

Substitution and Ultrafiltration Flow and Segments



$$\dot{E} = c^{*} \rho^{*} [(T_{ven} - T_{art})^{*} Qb + (Quf - Qsub.)]$$

Schneditz D. *Semin Dial.* 2001;14(5):357-64.

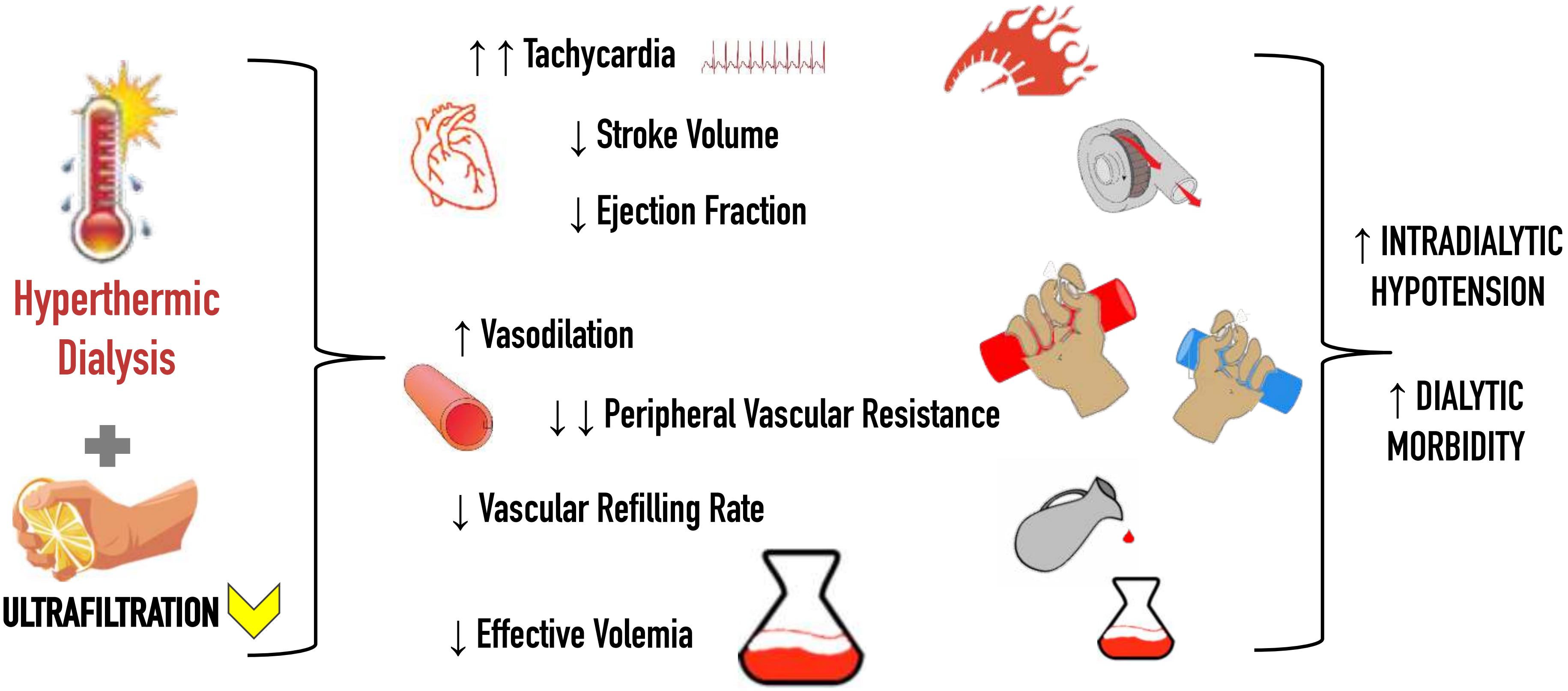
Thermal Energy Balance in HD Patient – Temperature Gradient

Thermal Energy Balance in HD Patient Results Mainly
from <u>Dialysate-Blood Temperature Gradient</u>

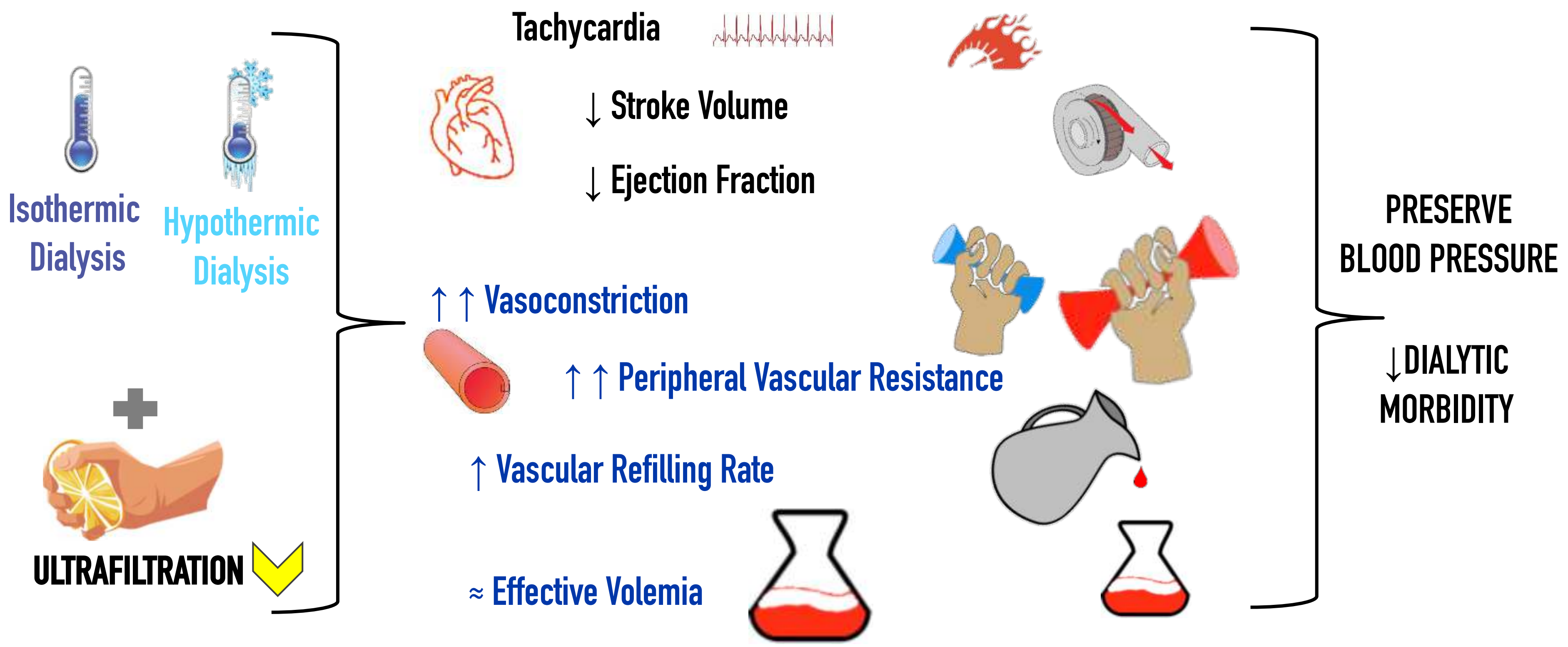
Temp. D > B	Temp. D = B	Temp. D < B
		
Hyperthermic Dialysis	Isothermic Dialysis	Hypothermic Dialysis
Patient Gain Thermal Energy (kJ/ses. or W/ses.)	**<u>No</u> Thermal Energy Gain/Loss (kJ/ses. or W/ses.)**	**Patient Loss Thermal Energy (kJ/ses. or W/ses.)**

Schneditz D. *Semin Dial.* 2001;14(5):357-64.

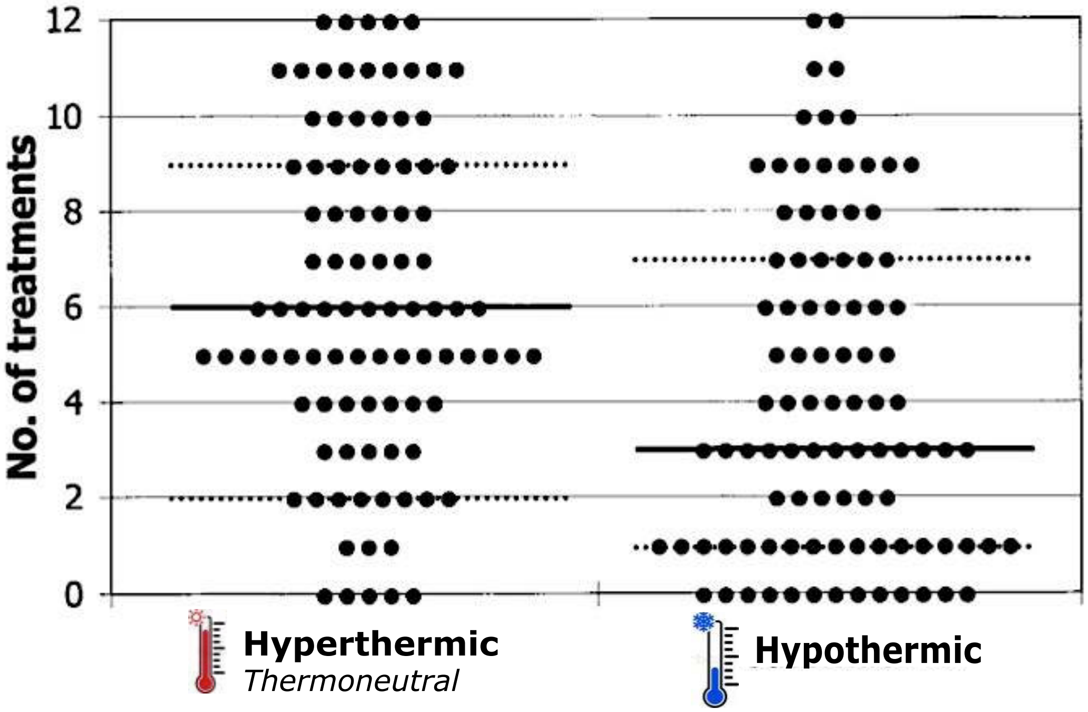
Hemodynamic Response to Ultrafiltration and Hyperthermic Dialysis



Hemodynamic Response to Ultrafiltration and Hypothermic Dialysis

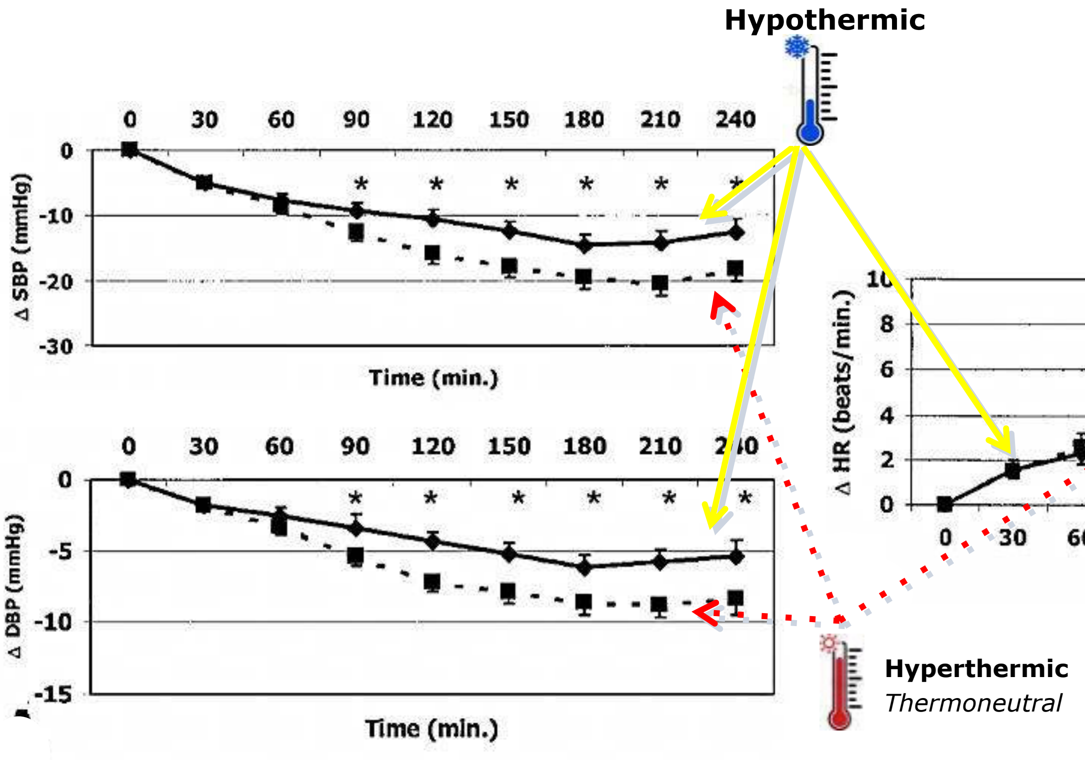


Hypothermic Dialysis Reduces Incidence of Intra-Dialytic Hypotensive Episodes



Maggiore Q et al, *Am J Kidney Dis.* 2002;40:280-290

Effect of Thermal Balance Regime on Hemodynamic Behavior (BP & HR)



Maggiore Q et al, *Am J Kidney Dis.* 2002;40:280-290

Hemodynamic Response to Thermal Energy Balance in HD/HDF Patients

Exploring Thermal Balance and Volume Effects: Different Design of Studies

Clinical Studies Exploring Effects of Thermal Balance HD vs. HDF

Dialysate-Blood Temperature Setting

Substitution Fluid is Maintained at Room Temperature

Manual Setting
Dialysate-Blood Temperature Gradient

HD Isothermic → VS. → ol-HDF *High UF Volume*

HD Hyperthermic / Hypothermic → VS. → HDF *Low UF Volume* / HDF *Medium UF Volume*

Automated Thermocontrolled
Blood Temperature Module (BTM)

Isothermic

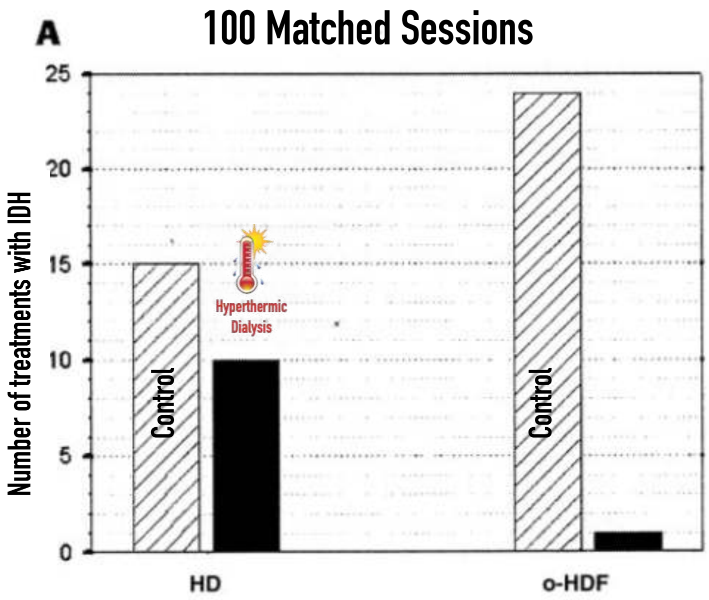
HD → VS. → ol-HDF *High UF Volume*

Hemodynamic Response to HD vs. HDF with Hyperthermic HD

Reduction of Intradialytic Hypotension with HDF and Hypothermic HD

Prospective Controlled Studies

Period A
17 Hypotensive prone pts
Period B
25 Stable HD pts
100 Paired consecutive HD/HDF treatments
Control phase 6 weeks – IDH prevalence
Active Intervention:
HD Hyperthermic / Hypothermic Controlled
Vs. Postdilution HDF



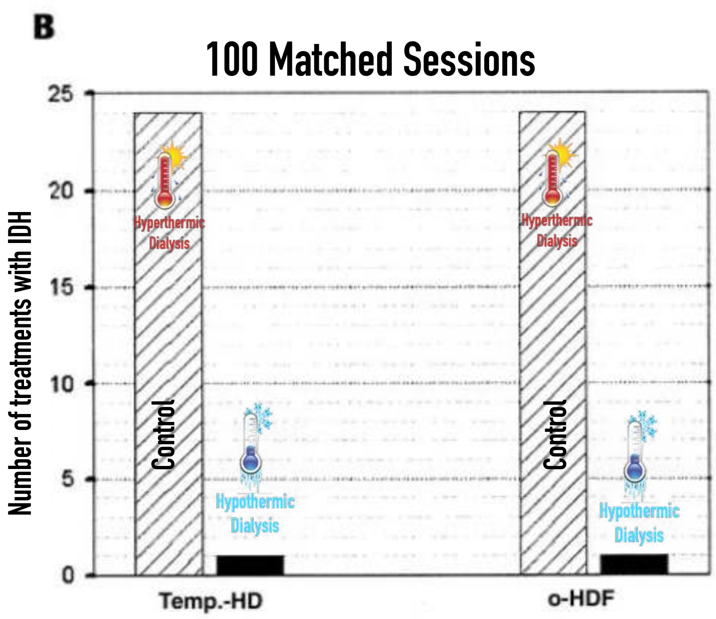
Donauer et al, *Nephrol Dial Transplant* 2003;18: 1616–1622

Hemodynamic Response to HDF vs. HD with Hypothermic HD

Significant Reduction of Intradialytic Hypotension Episodes with Hypothermic HD Matching HDF

Prospective Controlled Studies

Period A
17 Hypotensive prone pts
Period B
25 Stable HD pts
100 Paired consecutive HD/HDF treatments
Control phase 6 weeks – IDH prevalence
Active Intervention:
HD Hyperthermic / Hypothermic Controlled
Vs. Postdilution HDF



Donauer et al, *Nephrol Dial Transplant* 2003;18: 1616–1622

Hemodynamic Response to HDF vs. HD and Thermal Balance

Comparable Reduction of Intradialytic Hypotension Episodes with Hypothermic HD and HDF

HDF is associated with thermal loss equivalent to hypothermic HD

	Treatment modality	Treatments with hypotension/all treatments (%)	T_{art} 0 min (°C)	ΔT_{av} (°C)	Min BV (%)	ET (W)	Systolic blood pressure (mmHg)	
							Beginning	End
Study A	o-HDF	1/25 (4%)	36.4 ± 0.4	1.2 ± 0.3[c]	91.8 ± 3.1	−16.6 ± 4.0[e]	144.0 ± 17.9	141.2 ± 17.9
	HD	10/25[a] (40%)	36.5 ± 0.5	0.4 ± 0.4[c,b]	94.0 ± 3.2[d]	−5.4 ± 5.1[b,e]	142.1 ± 19.6	124.9 ± 17.5[c]
Study B	o-HDF	1/25 (4%)	36.5 ± 0.5	1.2 ± 0.3[c]	92.9 ± 4.0	−15.9 ± 1.9[e]	144.0 ± 27.3	131.8 ± 25.8
	Temp-HD	1/25[f] (4%)	36.5 ± 0.3	1.1 ± 0.1[c]	93.5 ± 3.8	−16.3 ± 4.2[e]	143.2 ± 28.1	135.8 ± 27.8

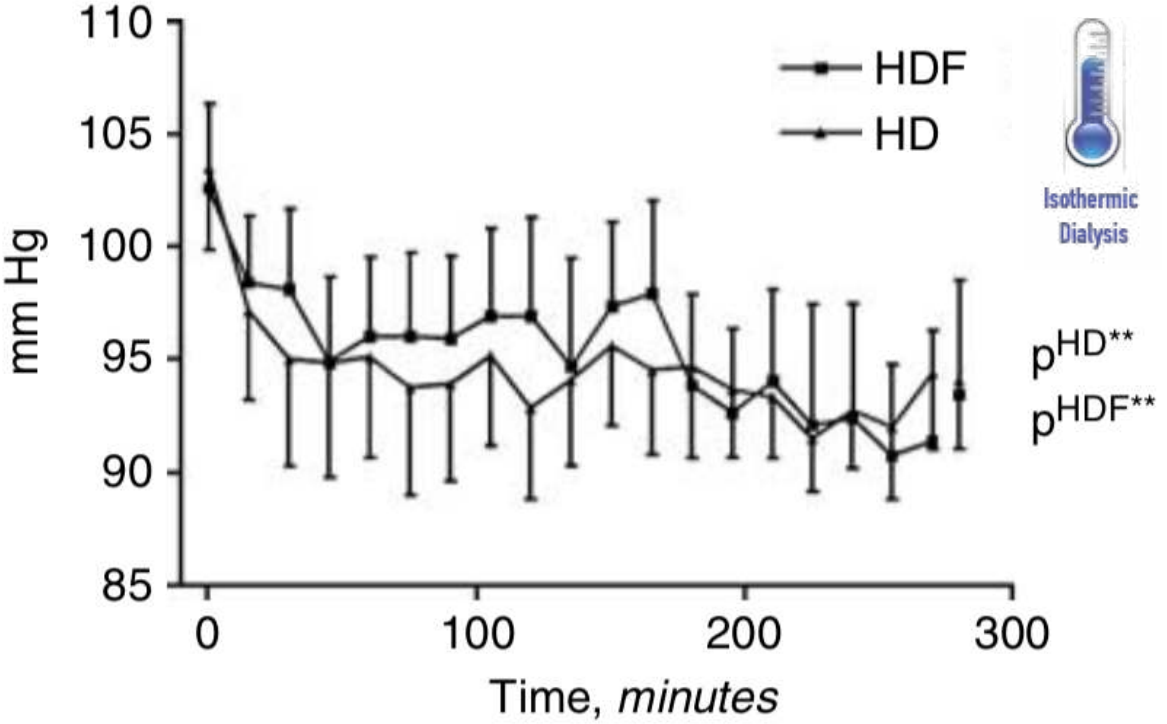
	Study A		Study B	
	o-HDF	HD	o-HDF	Temp-HD
Mean blood flow (ml/min)	222.7 ± 14.8	214.4 ± 20.3	215.8 ± 17.8	222.4 ± 27.2
Mean ultrafiltration volume (l)	2.6 ± 1.0	2.5 ± 0.9	2.1 ± 0.7	2.2 ± 0.8
Replacement fluid prescribed per treatment (ml/min)	50	–	50	–
Dialysate flow (ml/min)	500	500	500	500
Mean dialysate temperature	36.8 ± 0.4	36.8 ± 0.3	36.9 ± 0.3	35.6 ± 0.4

Donauer et al, *Nephrol Dial Transplant* 2003;18: 1616–1622

Intradialytic Hemodynamic HDF vs. HD with Isothermic Conditions

Mean Arterial Pressure Decline in Similar Way

	HD	HDF pre
Ultrafiltration *mL*	3066 ± 276	2992 ± 256
Relative blood volume%	90 ± 1.9	89 ± 1.1
Total energy transfer *kJ*	155 ± 42	135 ± 39



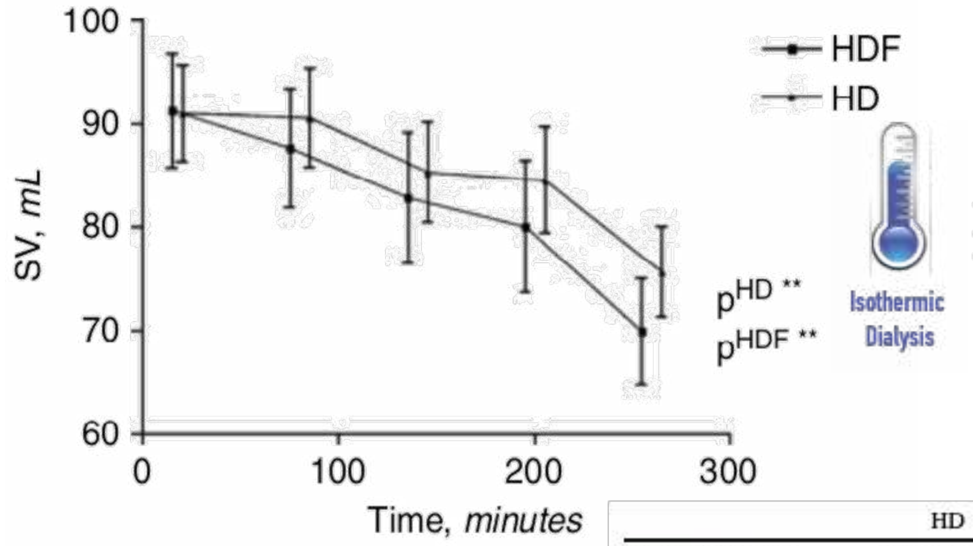
Prospective Crossover RC Study
12 HD pts - 4hrs x 3 wk
High Flux HD vs. HDF Predilution High Volume 85±15l/ses.
ISOTHERMIC CONTROLLED CONDITION (BTM)
Intradialytic Hemodynamic Monitoring – US Transonics

Karamperis N et al, *Kidney Int.* 2005;67:1601–1608

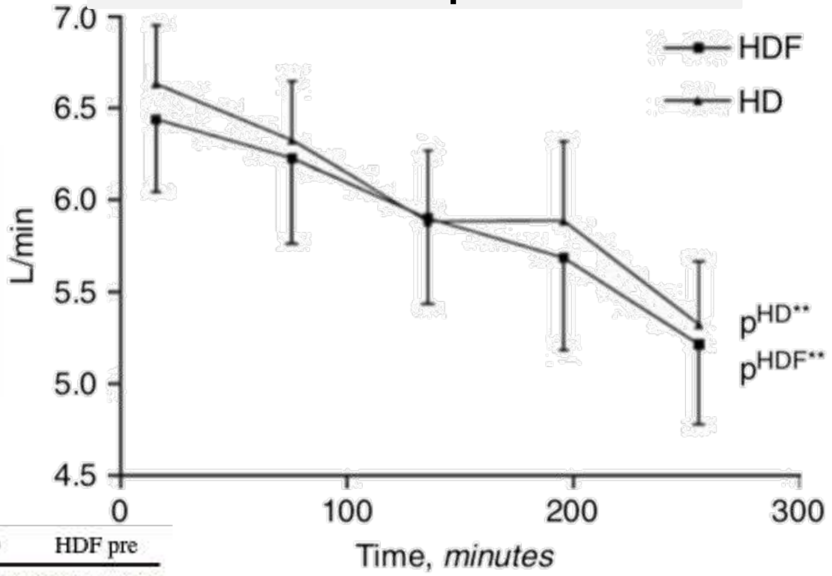
Intradialytic Hemodynamic of HDF vs. HD with Isothermic Conditions

Cardiac Performance Decline Follows Blood Volume Reduction

Stroke Volume



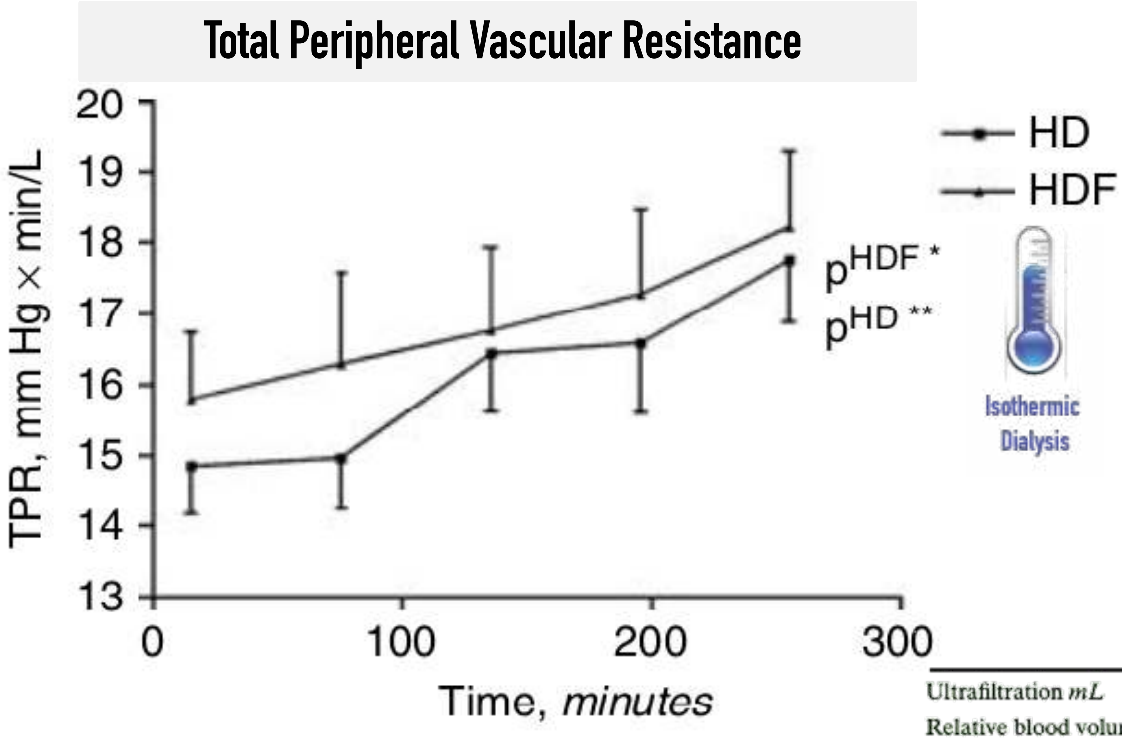
Cardiac Output



	HD	HDF pre
Ultrafiltration *mL*	3066 ± 276	2992 ± 256
Relative blood volume%	90 ± 1.9	89 ± 1.1
Total energy transfer *kJ*	155 ± 42	135 ± 39

Karamperis N et al, *Kidney Int.* 2005;67:1601–1608

Intradialytic Hemodynamic HDF vs. HD with Isothermic Conditions
Higher Increase in Total Peripheral Resistance with HDF



	HD	HDF pre
Ultrafiltration *mL*	3066 ± 276	2992 ± 256
Relative blood volume%	90 ± 1.9	89 ± 1.1
Total energy transfer *kJ*	155 ± 42	135 ± 39

Prospective Crossover RC Study
12 HD pts - 4hrs x 3 wk
High Flux HD vs. HDF Predilution High Volun
ISOTHERMIC CONTROLLED CONDITION (BTM)
Intradialytic Hemodynamic Monitoring – US Transonics

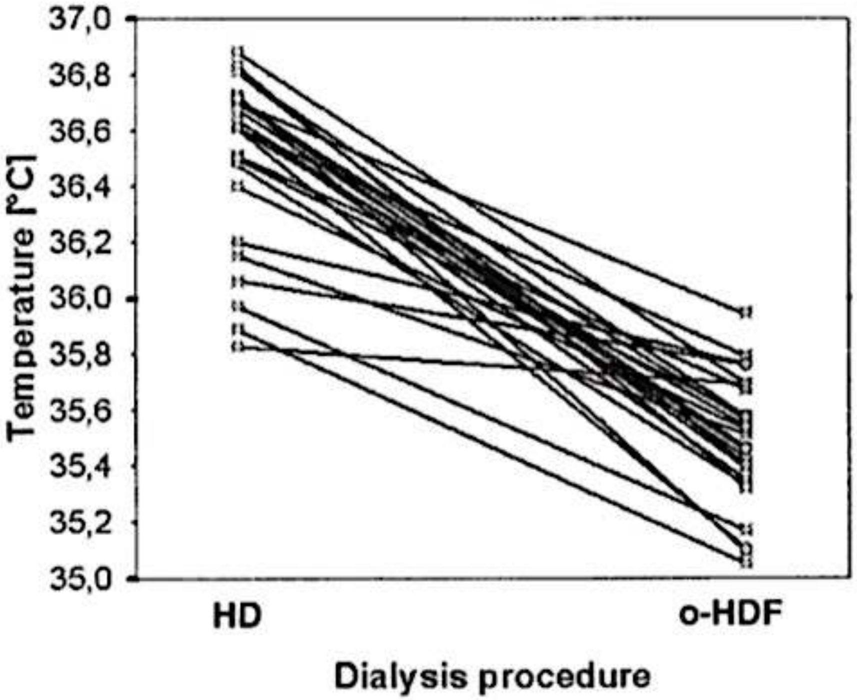
Karamperis N et al, *Kidney Int.* 2005;67:1601–1608

Thermal Balance and Temperature Change in HD vs. HDF

Cooling Effect of online HDF

Prospective Controlled Studies

Period A
17 Hypotensive prone pts
Period B
25 Stable HD pts
100 Paired consecutive HD/HDF treatments
Control phase 6 weeks – IDH prevalence
Active Intervention:
HD Hyperthermic / Hypothermic Controlled
Vs. Postdilution HDF



Donauer et al, *Nephrol Dial Transplant* 2003;18: 1616–1622

Effects of Thermal Balance and Substitution Volume on Hemodynamic during HDF vs. HD

Same treatment conditions
4hrs x 3wk – Qb 300 QD 500
Dialysate Electrolyte Composition
Dialyzer: Polyamide
Same day & Hours – UFR …

12 HD pats

2 x 2 Factorial Study

	HD 35.5°	**HDF 1L/h (6L/ses.)**	**HD 37.5°**	**HDF 2.5L/H (10L/ses.)**
WL (l/ses.)	2.2 ±0.6	2.3 ± 0.7	2.4 ± 0.7	2.3 ± 0.8 L
TVUF (l/ses.)	2.2 ±0.6	8.3 ± 1.7	2.4 ± 0.7	12.3 ± 1.8 L

Hemodynamic Monitoring: AP, MAP, HR…
Energy Transfer Rate – Blood volume control

*HDF substitution fluid bag, room temperature

Van Der Sande F et al, J Am Soc Nephrol 2001;12:1916 –1920

Thermal Effects on Hemodynamic during HDF & HD

Effect of Amount of Replacement Fluid and Dialysate Temperature

Total ultrafiltration volume is correlated with negative thermal energy balance

Modality	ΔCT (C)	ET (W)	ΔMAP (mmHg)	ΔBV (%)	UF (l/ses.)
$HD^{37.5}$	+0.38 ± 0.22	−3.53 ± 6.44	−25.6 ± 13.5	−7.3 ± 5.0	2.2 ±0.6
$HD^{35.5}$	+0.00 ± 0.29	−26.61 ± 5.33	−15.1 ± 13.8	−9.8 ± 4.8	2.3 ± 0.7
HDF^{1}	+0.29 ± 0.23	−15.88 ± 6.94	−23.0 ± 14.0	−9.1 ± 6.1	2.4 ± 0.7
$HDF^{2.5}$	−0.10 ± 0.40	−25.25 ± 7.91	−19.2 ± 17.7	−9.8 ± 6.5	2.3 ± 0.8

[a] Values are mean ± SD [range]. $HD^{37.5}$ and $HD^{35.5}$ are ultrafiltration combined with hemodialysis at a dialysate temperature of 37.5°C and 35.5°C, respectively; HDF^{1} and $HDF^{2.5}$ are postdilution hemodiafiltration with amount of replacement fluid at room temperature of 1 L/h and 2.5 L/h respectively. ET, energy transfer rate in W (watts); ΔCT, change in core temperature *versus* baseline in °C; ΔMAP, is maximum decrease in mean arterial blood pressure in mmHg; ΔBV, change in blood volume *versus* baseline in %.

[b] $P < 0.05$; changes *versus* baseline.

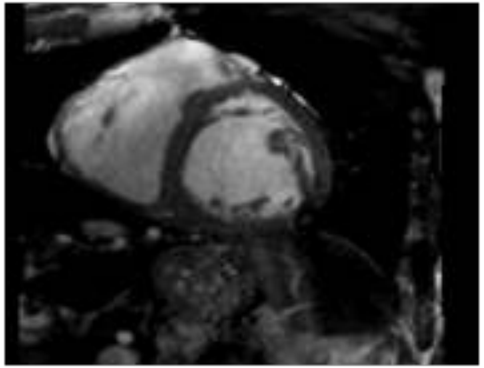
[c] $P < 0.05$; *versus* $HD^{37.5}$.

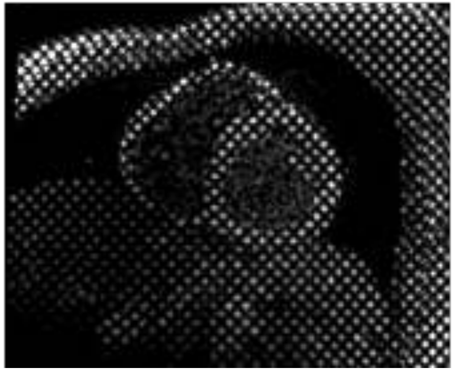
[d] $P < 0.05$; *versus* HDF^{1}.

Van Der Sande F et al, J Am Soc Nephrol 2001;12:1916 –1920

Intradialytic Hemodynamic under Thermocontrolled Conditions

Imaging by Cardiac MRI – Clinical Setting for in vivo Assessment

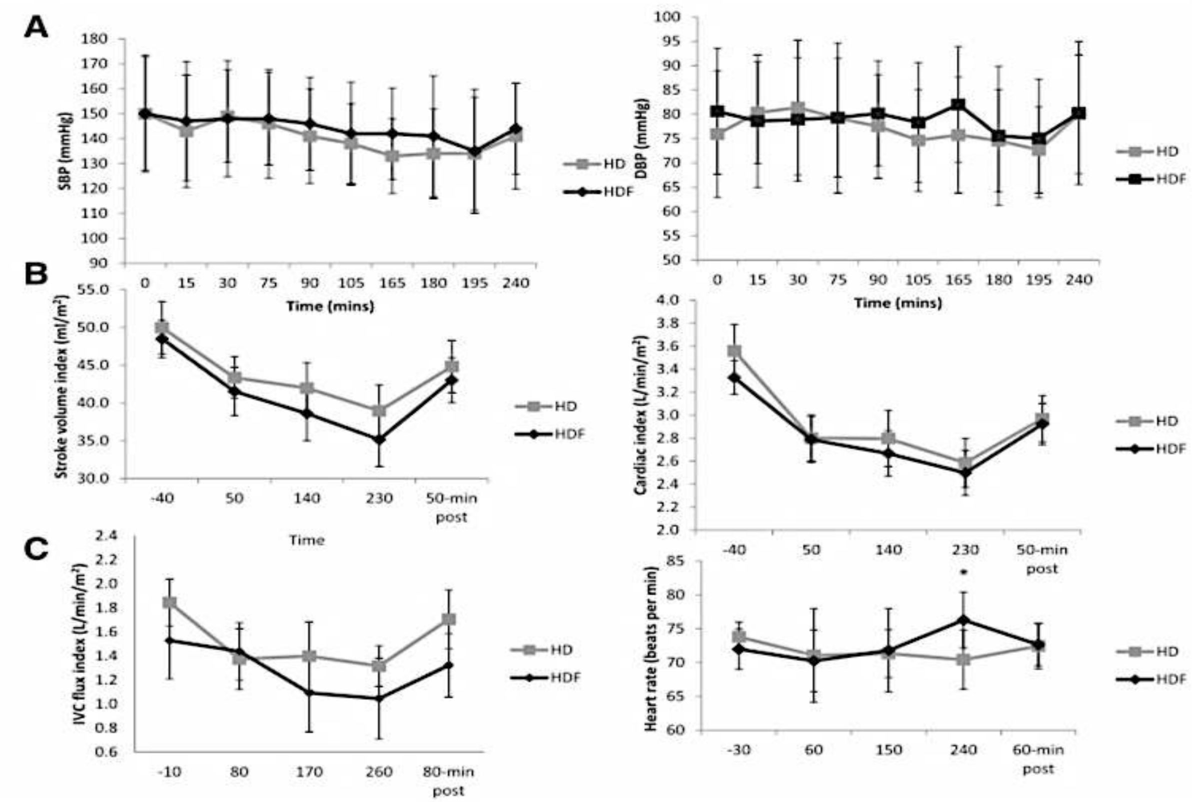




Hemodynamic Behavior of HD vs. HDF

No Significant Difference in Isothermic Controlled Conditions

Fits closely with intradialytic blood volume change →



Substitution volume, l	n/a	23.0±2.5
UF rate, ml/kg per h	3.8±2.9	4.4±2.5
UF volume, L	1.1±0.7	1.3±0.6

Prospective Crossover RC Study
12 HD patients - High Flux HD vs. HDF
ISOTHERMIC CONTROLLED BTM
Intradialytic Hemodynamic Assessment
Intradialytic Cardiac MRI

Buchanan Ch et al, *J Am Soc Nephrol* 2017;28: 1269–1277.

Outline – Are the Apparent Survival Benefits of HDF Due to Different Thermal Balance?

1 What are the Evidences?

2 What is the Main Organ Target?

3 Why Hemodiafiltration Acts Differently?

4 What Role for Thermal Energy Balance?

5 **Any Role for Non-Thermal Factors?**

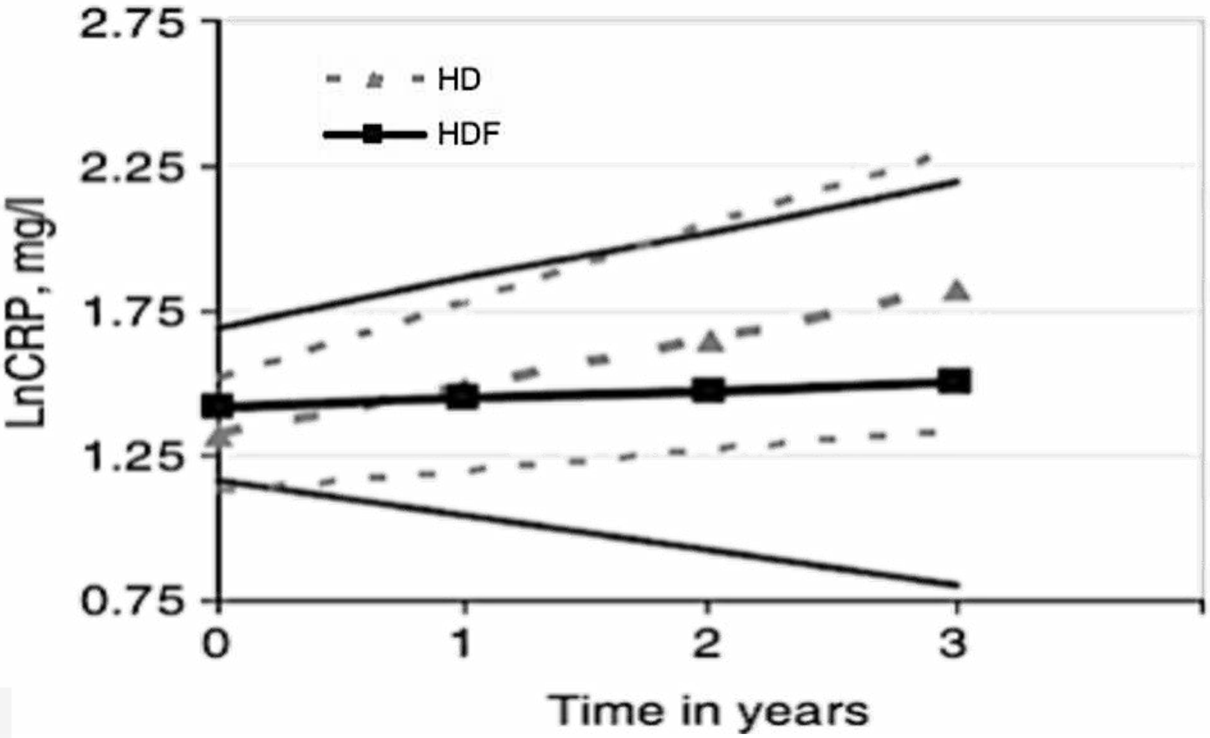
6 Take home message: HDF has a Cardiac Protecting Effect

Non-Thermal Factors Contributing to Hemodynamic Response

- Inflammation – Oxidative Stress
- Endothelial Dysfunction
- Pulse Wave Velocity
- Sympathetic Nerve Activity
- Cardiac Arrhythmogenic Activity

Time Behavior of CRP in Patients Treated with HD and HDF

CRP Remains stable in HDF and Increases in HD



CONTRAST
CONvective TRAnsport STudy

den Hoedt CH et al, *Kidney Int.* 2014;86(2):423-32.

Effects of HD/HDF on Endothelial Dysfunction

Correlate with Markers of Oxidative Stress, Inflammation & NO Pathway

Endothelial dysfunction is reduced with HDF

	Baseline		Change after 4 months		P value
	HD	HDF	HD	HDF	
Oxidative stress					
TBARs (μmol/L) Median (IQR)	0.24 (0.19–0.32)	0.22 (0.16–0.45)	0.02 (−0.1 to 0.2)	−3 (−0.2 to 0.2)	0.34
ROS (μmol/L) Median (IQR)	34.7 (29.5–50.0)	38.3 (30.0–49.5)	−3 (−11 to 2)	−3 (−13 to 19)	0.34
TAS (mmol/L) Median (IQR)	1.55 ± 0.22	1.58 ± 0.26	−0.16 ± 0.29	−0.18 ± 0.40	0.99
Inflammation					
hs-CRP (mg/L)	4.4 (1.8–16)	4.7 (2.1–13.5)	1 (−2 to 4)	−1 (−6 to 3)	0.40
TNFα mRNA to 18S rRNA ratio Median (IQR)	0.61 (0.56–0.88)	0.51 (0.42–1.12)	0.37 (0.30 to 1.02)	−0.16 (−0.24 to 0.10)	<0.001
NO pathway					
PKCβ_2 mRNA to 18S rRNA ratio Median (IQR)	0.59 (0.56–0.70)	0.48 (0.36–0.59)	0.12 (0.03 to 0.31)	−0.07 (−0.28 to 0.11)	<0.001
P85β mRNA to 18S rRNA ratio Median (IQR)	0.80 (0.58–1.12)	0.77 (0.60–1.00)	−0.04 (−0.27 to −0.0[illegible])	−0.11 (−0.40 to 0.34)	0.48

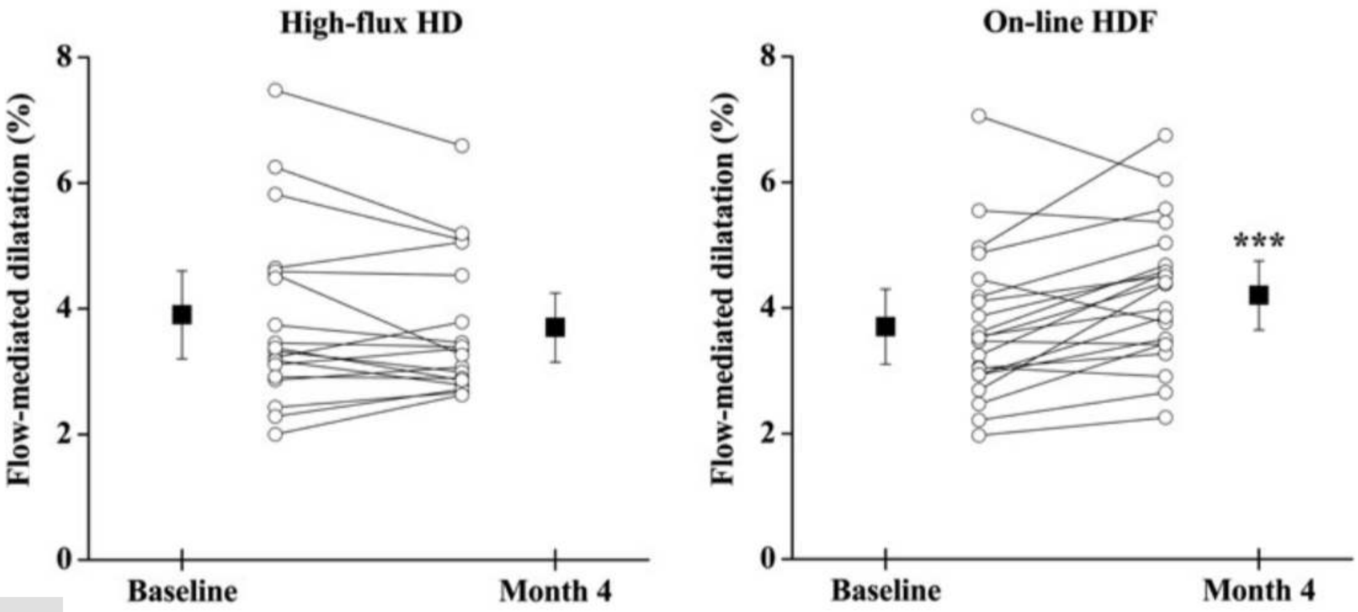
Prospective RC Trial
42 prevalent HD patients
High vol. HDF vs. HD – 4Mo FU
Hemodynamic monitoring
Inflammation – Oxidative Stress
Endothelial function monitoring

Bellien J et al, *Nephrol Dial Transplant* 2014;29: 414–422

Effects of HD/HDF on Endothelial Dysfunction

Flow Mediated Dilatation

Flow mediated dilatation is improved with HDF



Prospective RC Trial
42 prevalent HD patients
High vol. HDF vs. HD – 4Mo FU
Hemodynamic monitoring
Inflammation – Oxidative Stress
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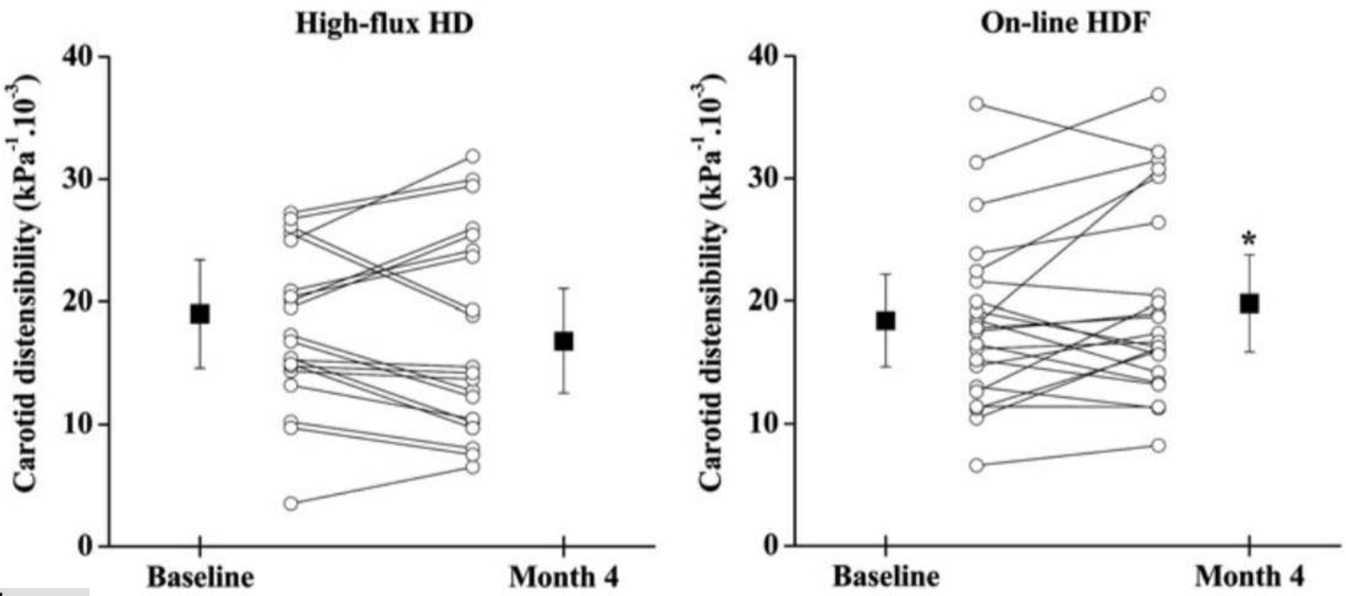
Bellien J et al, *Nephrol Dial Transplant* 2014;29: 414–422

Effects of HD/HDF on Endothelial Dysfunction
Carotid Distensibility

Carotid distensibility is improved with HDF



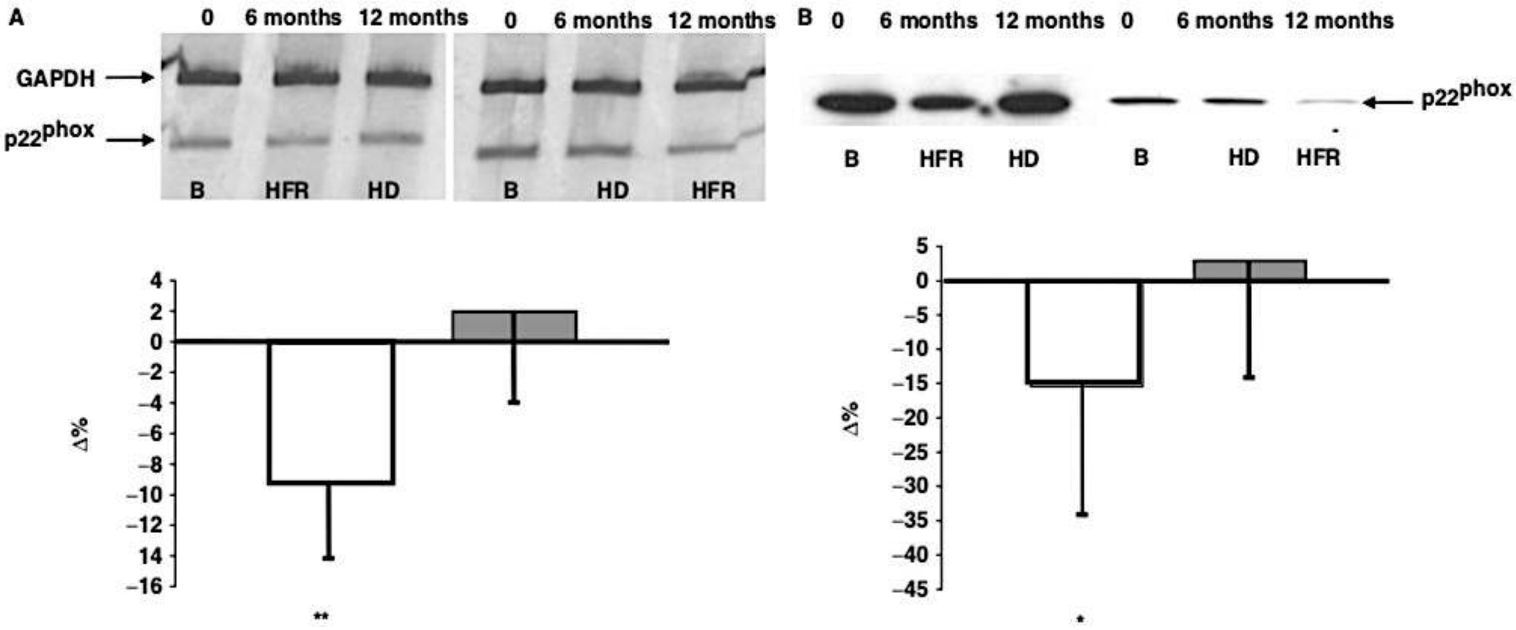
Prospective RC Trial
42 prevalent HD patients
High vol. HDF vs. HD – 4Mo FU
Hemodynamic monitoring
Inflammation – Oxidative Stress
Endothelial function monitoring

Bellien J et al, *Nephrol Dial Transplant* 2014;29: 414–422

Effects of HD/HDF (HFR) on Oxidative Stress

HDF Reduced Both Mononuclear Cell mRNA Expression and Protein Level of p22phox

p22phox* expression is reduced with HDF
*subunit of NADPH oxidase generating superoxide anion (O^{2-})

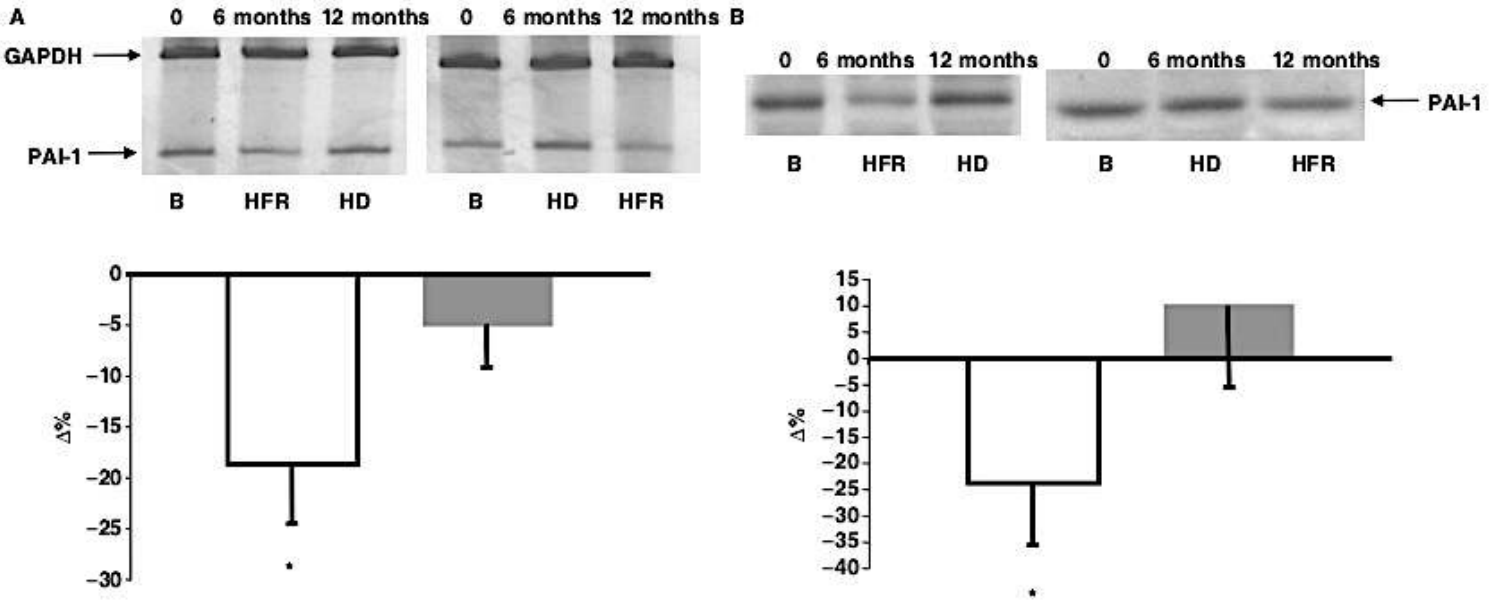


Calò LA et al, *Nephrol Dial Transplant.* 2007;22(5):1413-9.

Effects of HD/HDF (HFR) on Inflammatory Cytokines

HDF Reduced both Mononuclear Cell of RNA and Protein Level of Plasminogen Activator Inhibitor (PAI-1)

- PAI-1, Plasminogen Activator Inhibitor 1* expression is reduced
- Marker of oxidative stress-related response to inflammatory cytokines

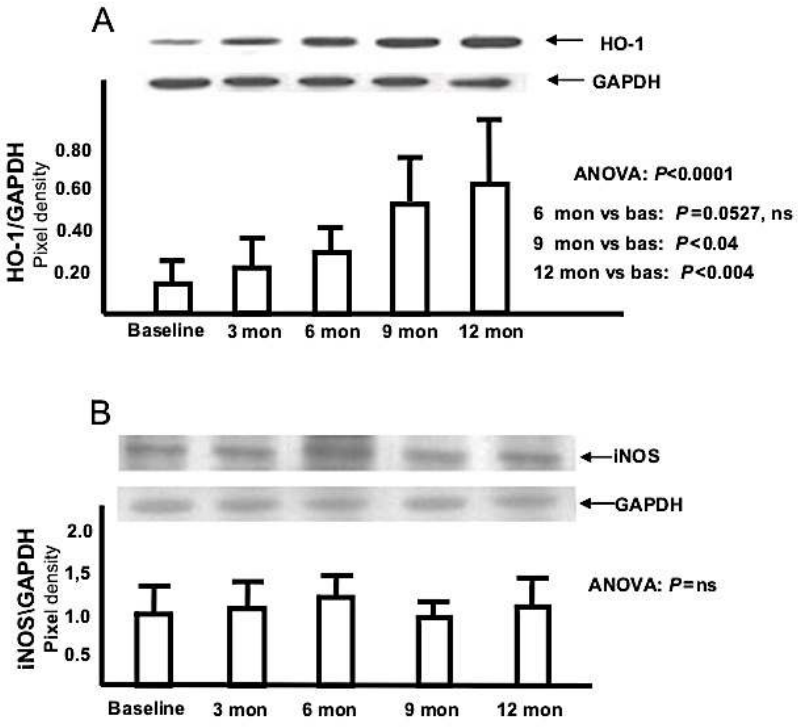


Calò LA et al, *Nephrol Dial Transplant.* 2007;22(5):1413-9.

Effects of HD/HDF (HFR) on Inflammatory Cytokines

HDF Increased the Protein Expression of Heme Oxygenase (HO-1)

HO-1: Antioxidant, anti-inflammatory, anti-proliferative & oxidized LDL



Calò LA et al. *Artif Organs*. 2011;35(2):183-7.

Effects of HDF vs. HD on Inflammation, OS and ED in ESKD Infants

3H Study Pediatric

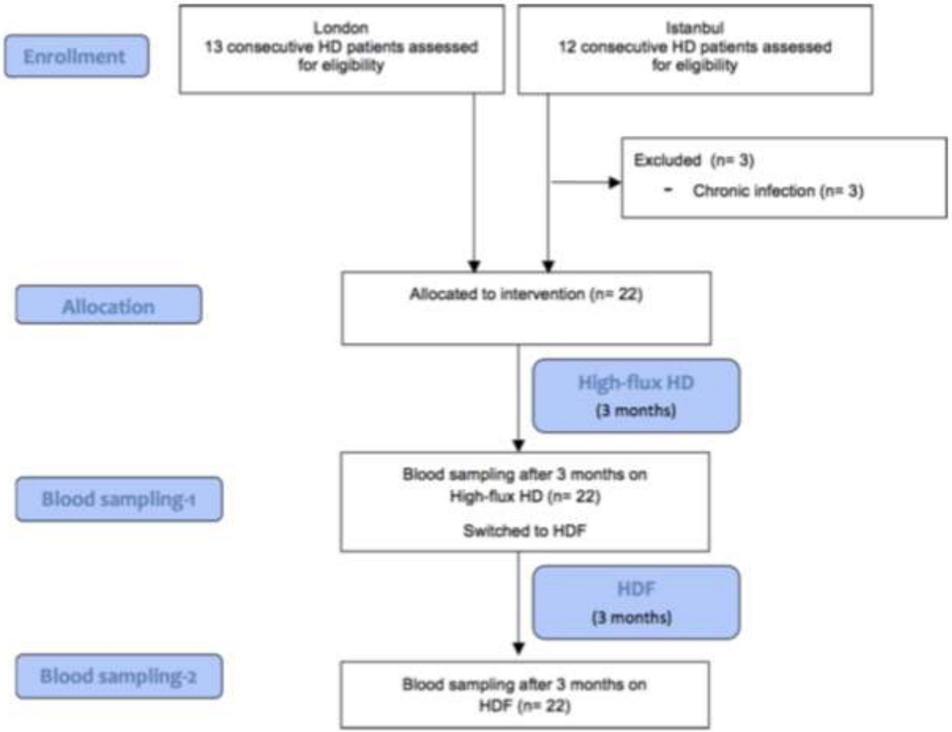
HDF, Heart & Height Study

Prospective interventional controlled multicentric study

Four Months FU

Effects of HDF vs HD

- Inflammation, Oxidative Stress, Endothelial Dysfunction
- CV & Height Outcomes



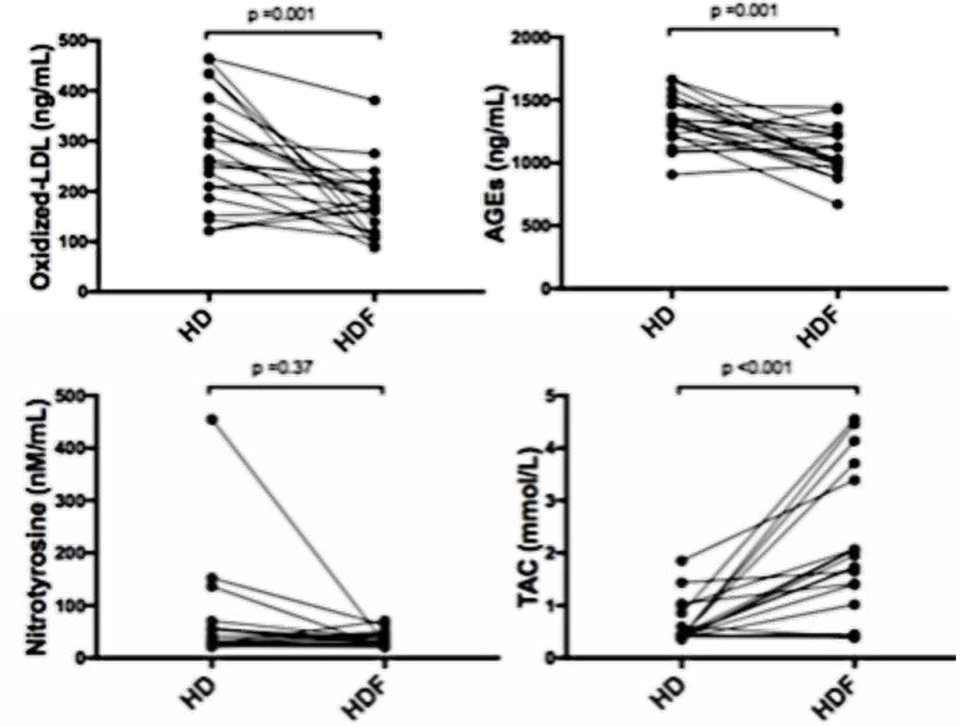
Ağbas A et al, *PLoS ONE* 2018;13(6): e0198320.

Effects of HDF vs. HD on Oxidative Stress

Markers of Oxidative Stress Are Significantly Reduced in HDF

Oxidative stress is reduced and total antioxidant capacity improved in HDF

3H Study Pediatric
HDF, Heart & Height Study
Prospective interventional controlled multicentric study
Four Months FU
Effects of HDF vs HD
- Inflammation, Oxidative Stress, Endothelial Dysfunction
- CV & Height Outcomes



Ağbas A et al, *PLoS ONE* 2018;13(6): e0198320.

Effects of HDF vs. HD on Inflammation

Inflammation Markers and B2M Are Reduced with HDF

Inflammation is reduced with HDF

3H Study Pediatric

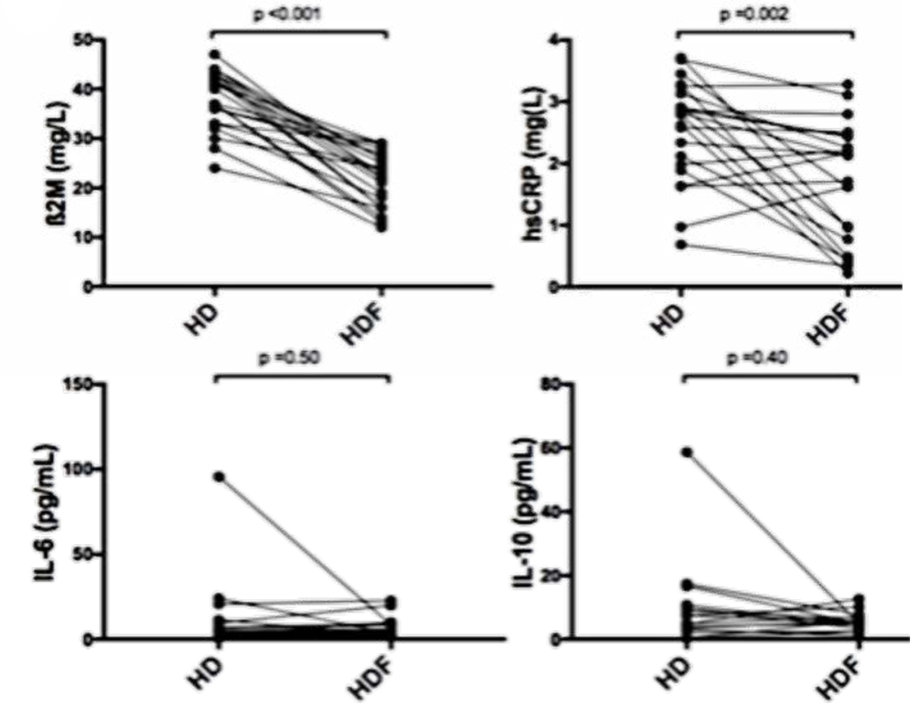
HDF, Heart & Height Study

Prospective interventional controlled multicentric study

Four Months FU

Effects of HDF vs HD

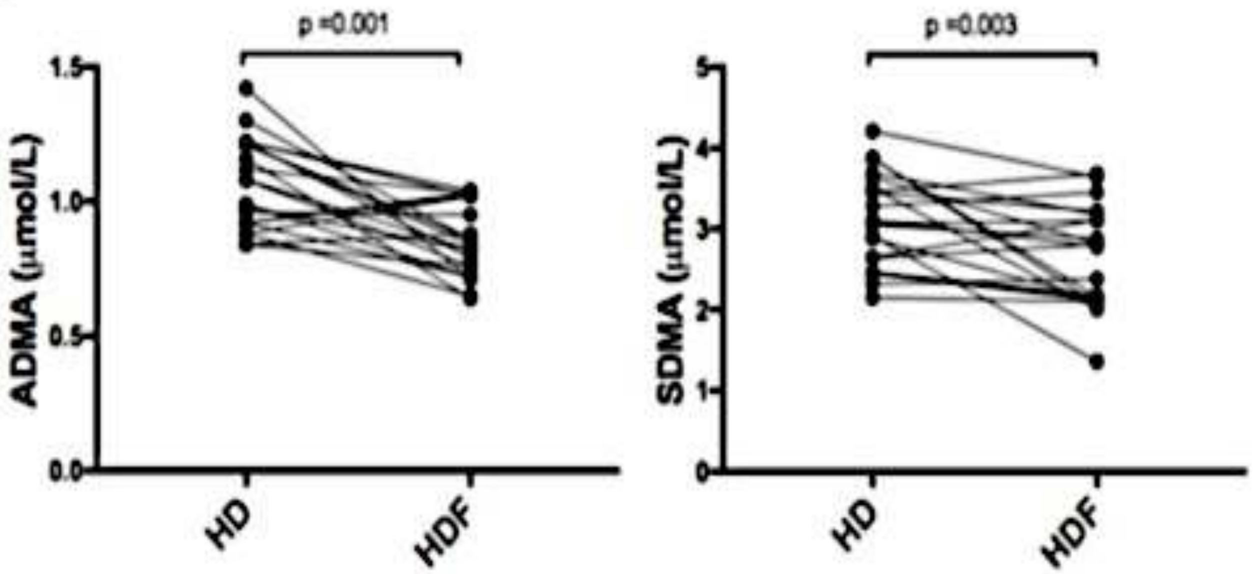
- Inflammation, Oxidative Stress, Endothelial Dysfunction
- CV & Height Outcomes



Ağbas A et al, *PLoS ONE* 2018;13(6): e0198320.

Effects of HDF vs. HD on Endothelial Dysfunction
Endothelial Function is Improved with HDF

ADMA concentrations are reduced in HDF



3H Study Pediatric
HDF, Heart & Height Study
Prospective interventional controlled multicentric study
Four Months FU
Effects of HDF vs HD
- Inflammation, Oxidative Stress, Endothelial Dysfunction
- CV & Height Outcomes

Effect of HDF vs. HD on Vascular Stiffness

Aortic Pulse Wave Velocity

Multicenter Prospective Parallel Comparative Study

289 prevalent HD patients: HD 69; 78 HD-HDF; 142 HDF

6 months Follow-Up - Hemodynamic monitoring - CV Event

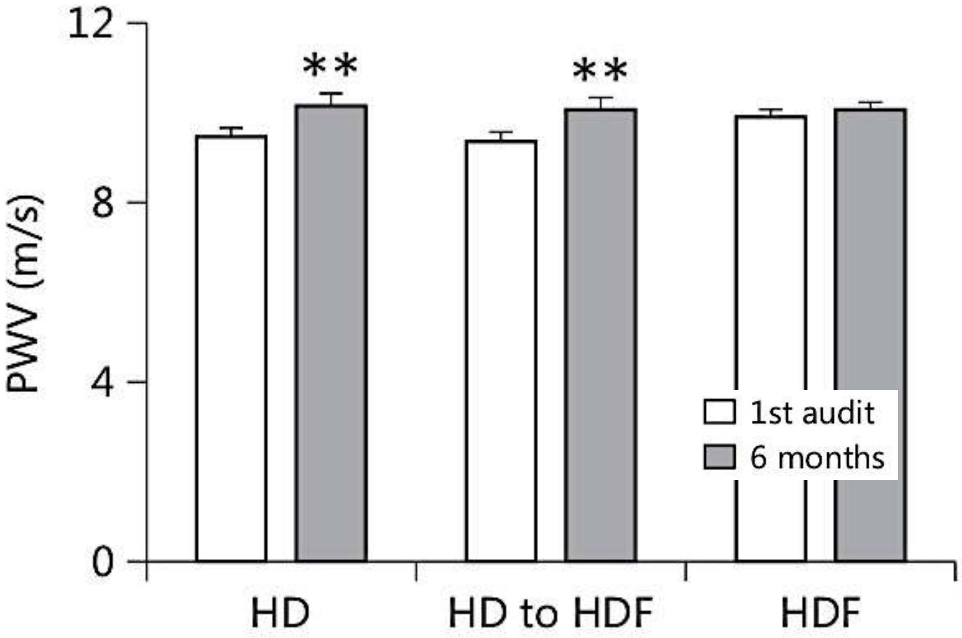
Blood Pressure - ECG - EchoCG -Pulse Wave Velocity

	HD	HD to HDF	HDF
Patients, n	69	78	142
Age, years	64.2±15.2	64.1±16.5	67.0±19.7
Males, %	65.2	59.0	62.6
Diabetics, %	44.9	56.4	44.4
Weight, kg	72.5±16.6	71.9±17.5	70.5±16.3
Body mass index	26.1±5.8	25.8±5.2	25.7±5.2
Dialysis vintage, months	24 (7–52)	28.5 (14–50)	39 (21–75)*
Dialysis session, h	3.92±0.36	3.93±0.42	3.99±0.37
Hypertension, %	72.2	66.7	85.9
IHD, %	20.3	32.1	31.7
PVD, %	14.5	14.1	23.9
CVD, %	8.7	12.8	19.7
Current smokers, %	14.5	13.7	3.5
Ex-smokers, %	29.0	27.5	24.6
ACEI/ARB, %	33.3	33.3	31.5
CCB, %	24.6	15.4	22.5
BB, %	42.0	12.8*	19.7*

Effect of HDF vs. HD on Vascular Stiffness
Aortic Pulse Wave Velocity

Multicenter Prospective Parallel Comparative Study
289 prevalent HD patients: HD 69; 78 HD-HDF; 142 HDF
6 months Follow-Up - Hemodynamic monitoring - CV Event
Blood Pressure - ECG - EchoCG -Pulse Wave Velocity

Aortic PWV is stabilized with HDF



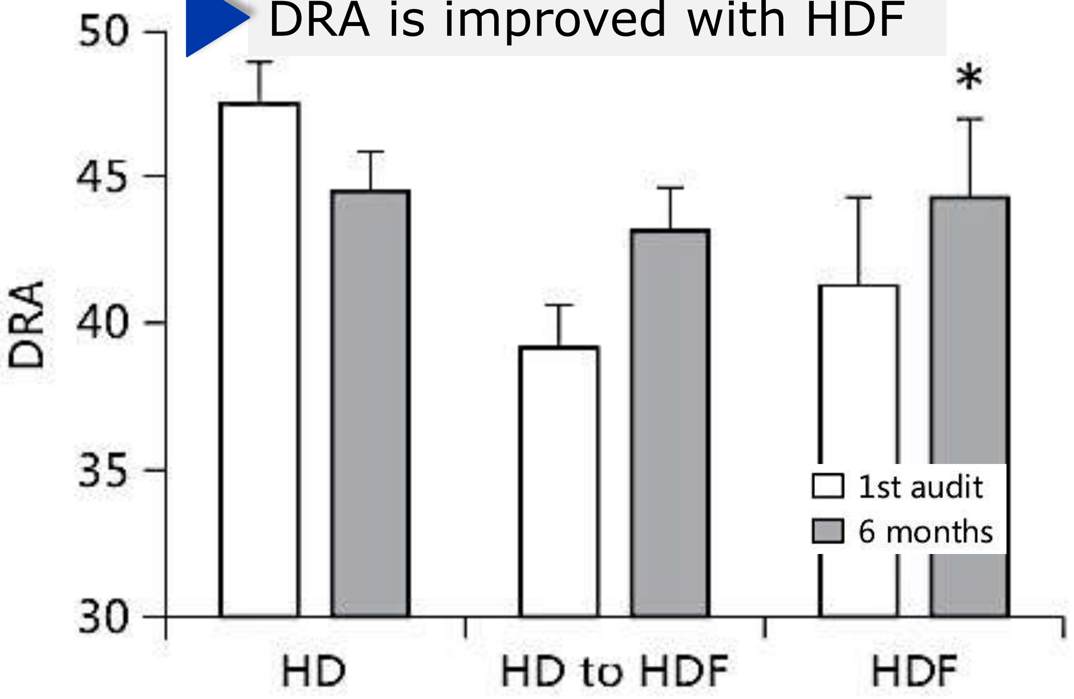
PWV: aortic pulse wave velocity

Charitaki E et al, *Nephron Clin Pract* 2014;128:185–191

Effect of HDF vs. HD on Diastolic Coronary Refilling Capacity
Diastolic Relaxation Area

Multicenter Prospective Parallel Comparative Study
289 prevalent HD patients: HD 69; 78 HD-HDF; 142 HDF
6 months Follow-Up - Hemodynamic monitoring - CV Event
Blood Pressure - ECG - EchoCG -Pulse Wave Velocity

DRA is improved with HDF

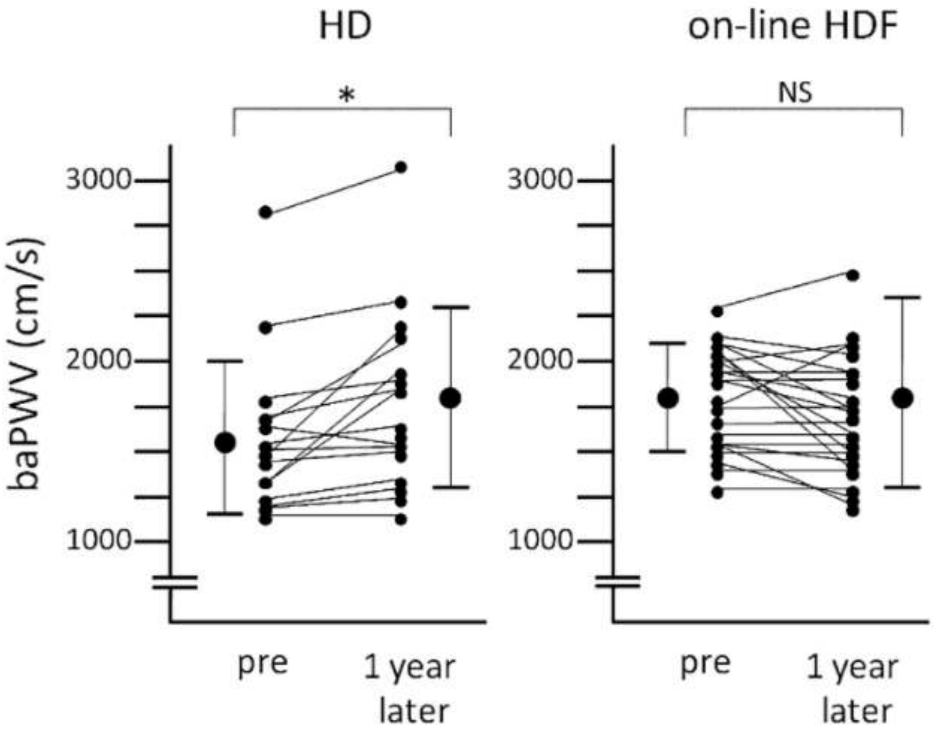


DRA: Diastolic relaxation area
a measure of diastolic refilling of the left coronary artery

Charitaki E et al, *Nephron Clin Pract* 2014;128:185–191

Effects of HDF vs. HD on Arterial Stiffness

Brachial Pulse Wave Velocity

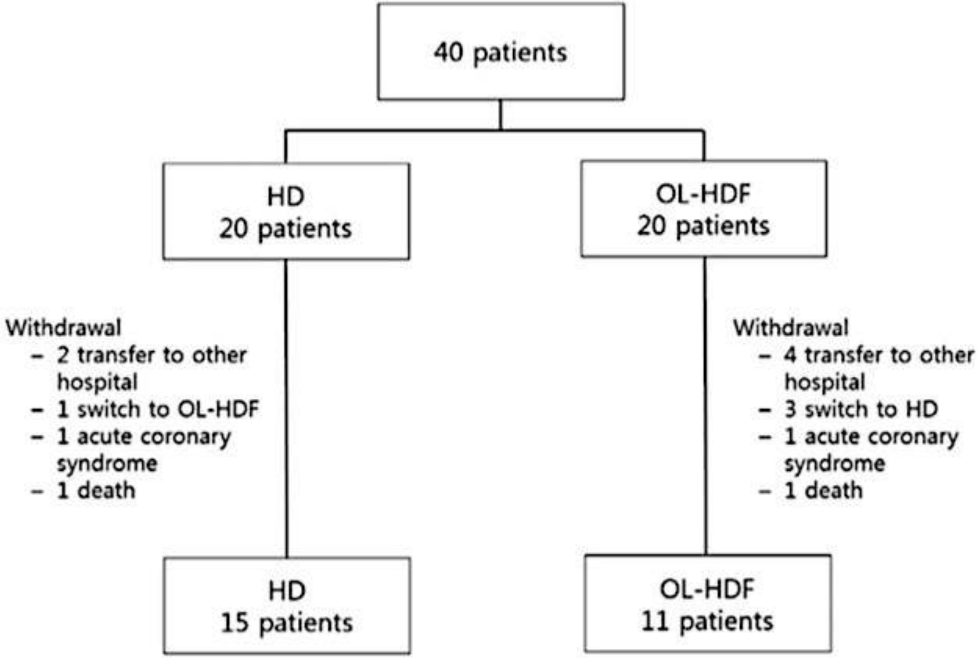


Prospective RCT Study
HDF(13) vs. Conv. HD(9)- 1 year FU
Surrogate markers: EchoCG-baPWV-IMT

Ohtake T et al, *Ther Apher Dial.* 2012; 16(2):181–188

Effects of HD vs. HDF on Autonomic Nervous System Dysfunction

Prospective RC Study
40 HD pts – 20HD vs.20 HDF
24hrs Holter ECG monitoring
Heart Rate Variability (HRV)
Time & frequency domain measures

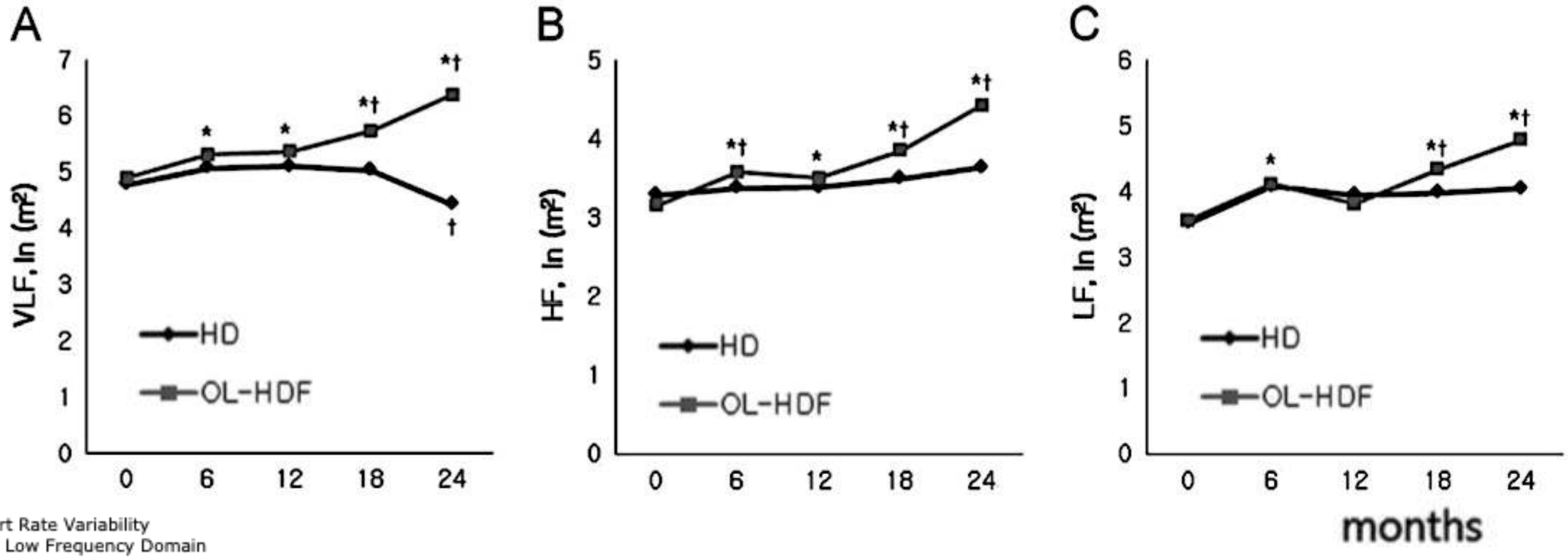


Park KW et al, *Kidney Res Clin Pract.* 2013;32(3):127-33.

Effects of HD/HDF on Autonomic Dysfunction

Heart Rate Variability (HRV) is Reduced with HDF

- Frequencies domain measures (VLF, HF & LF) increase significantly with HDF, translating an improvement in autonomic nervous system dysfunction



HRV, Heart Rate Variability
VLF, Very Low Frequency Domain
HF, high Frequency Domain
LF, Low Frequency Domain

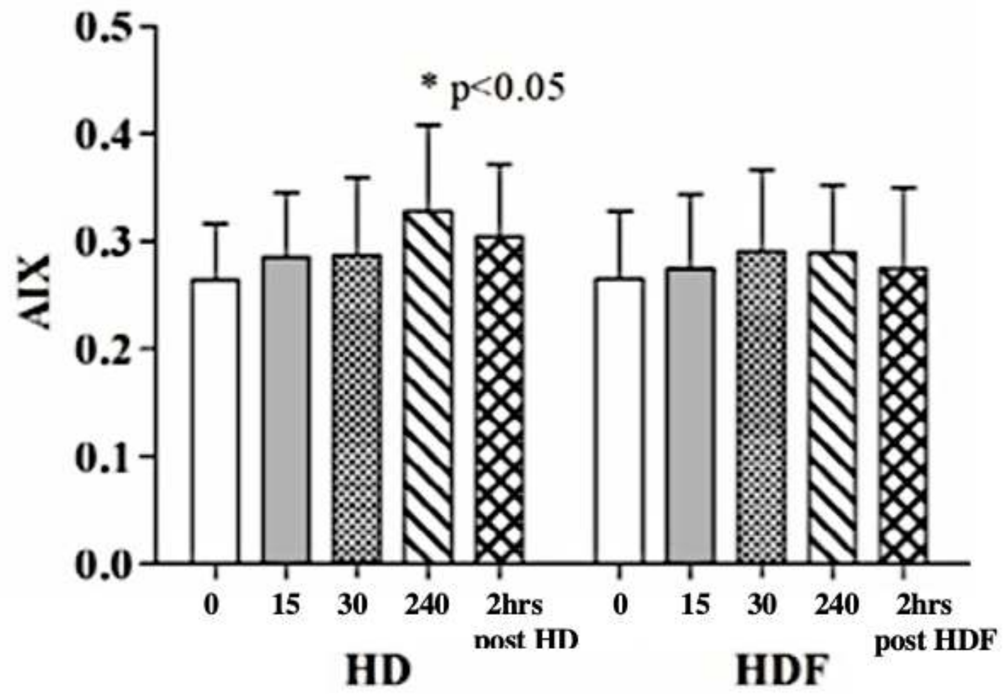
Park KW et al, *Kidney Res Clin Pract.* 2013;32(3):127-33.

Effects of HD/HDF on Intradialytic Cardiac Arrhythmogenicity

Changes In T Peak-end Interval (Tpe)

HDF is associated with a reduced Tpe value meaning less arrhythmic risk

Prospective Randomized Cross-sectional Study
30 HD pats - HD vs. HDF 3 Mo
4h x3 wk - Cardiac assessment
ECG Monitoring & precise analysis: rhythm
EchoCG - Doppler : Structure & Function



Páll A et al, *Trauma Emerg Care,* 2017;2(5):1-6

Outline – Are the Apparent Survival Benefits of HDF Due to Different Thermal Balance?

1. What are the Evidences?
2. What is the Main Organ Target?
3. Why Hemodiafiltration Acts Differently?
4. What Role for Thermal Energy Balance?
5. Any Role for Non-Thermal Factors?
6. **Take home message: HDF has a Cardiac Protecting Effect**

HDF is Associated with Negative Thermal Balance

and Intradialytic Hemodynamic Benefits

High Volume HDF

Negative Thermal Energy Balance
Correlated to Substitution/Ultrafiltration Volume

↑↑ Peripheral Vascular Resistance

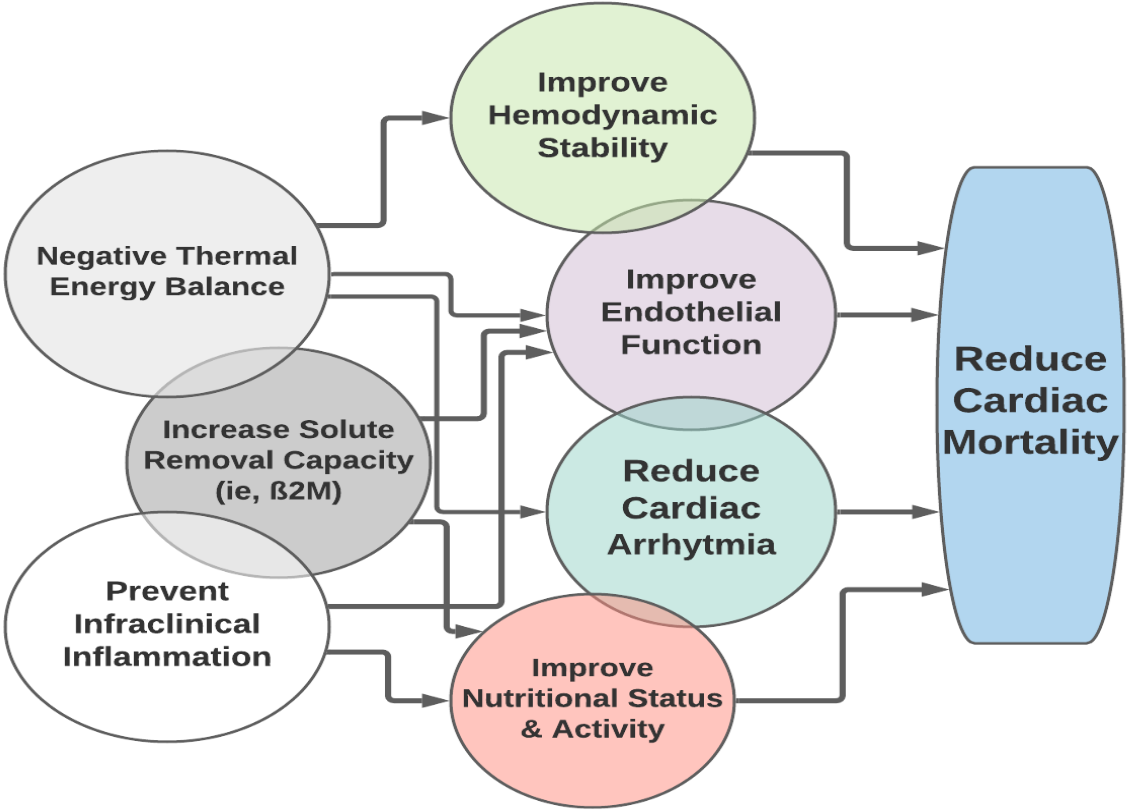
↑ ↑ Hemodynamic Response
to Ultrafiltration/Weigh Loss

↓↓ Intradialytic
Morbidity & Incidence IDH

↓↓ Hemodynamic Dialysis Induced

Beyond Thermal Balance HDF Has Additional CV Benefits

HEMODIAFILTRATION



Crush Injury and Beyond: Disaster Nephrology

Norbert Lameire, MD, PhD
Emeritus Professor of Medicine
University Hospital
Ghent, Belgium

With sincere thanks to Raymond Vanholder and Mehmet S Sever

Virtual Annual Dialysis Conference Meeting
March 7, 2021

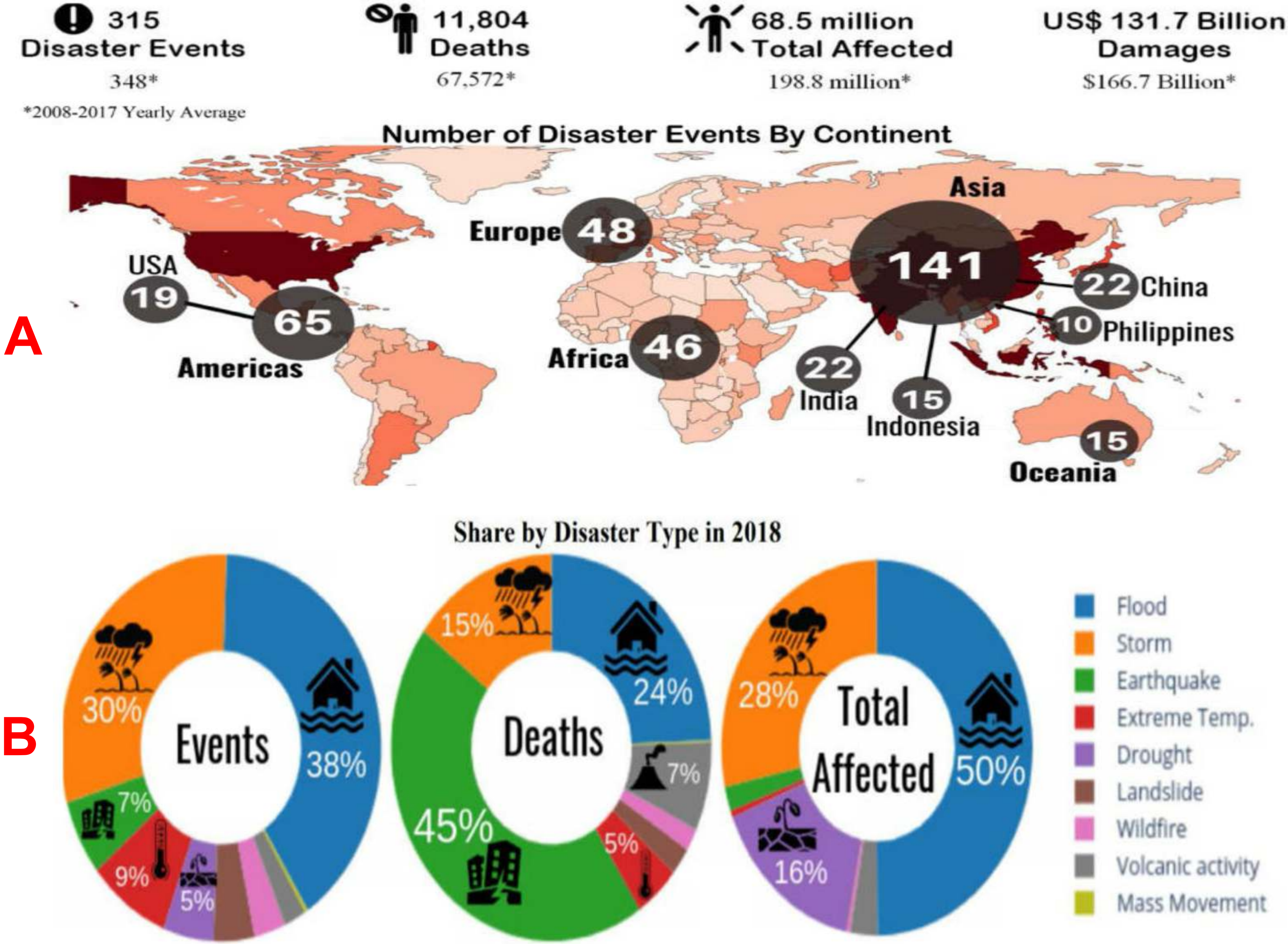
Disaster-WHO Definition

"an act of nature of such magnitude as to create a catastrophic situation in which the day-to-day patterns of life are suddenly disrupted and people are plunged into helplessness and suffering and as a result need food, clothing, shelter, medical and nursing care and other necessities of life, and protection against unfavorable environmental factors and conditions."

Sudden calamities producing extensive damage, loss and distress

- Natural
  - Earthquakes
  - Landslides
  - Avalanches
  - Hurricanes
  - Tornadoes
- Man-made
  - War
  - Mining
  - Tunnel collapse
  - Terrorism, torture

Lameire, et al. Semin Nephrol 40:393–407, 2020

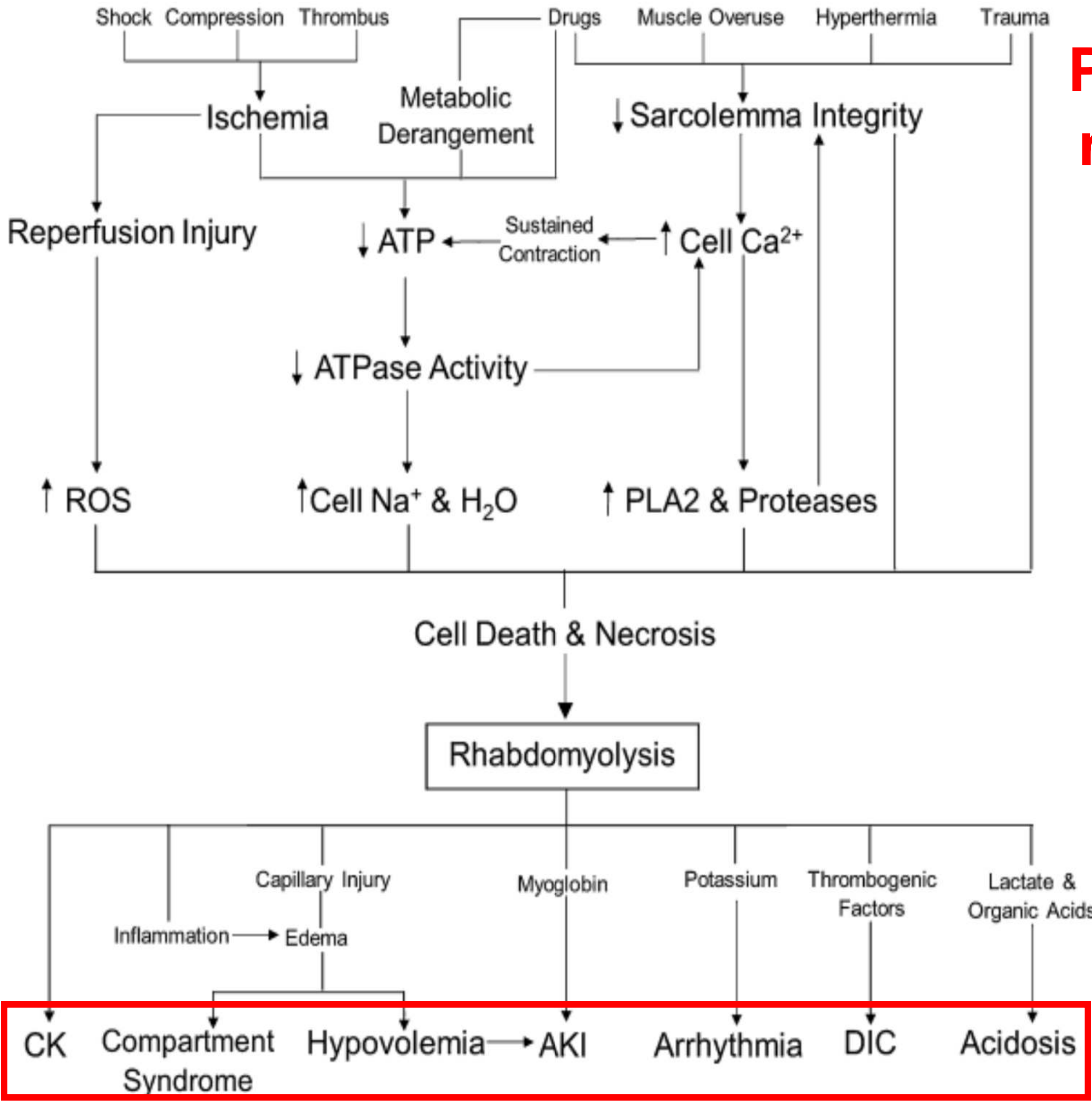


Centre for Research on the Epidemiology of Disasters (CRED)

Definitions

- *Rhabdomyolysis*: Damage to striated muscle resulting in the systemic release of intramuscular components
- *Crush injury*: Direct injury by collapsing material and debris causing muscle swelling and/or neurological disturbances in the affected parts of the body
- *Crush syndrome*: Crush injury combined with systemic manifestations, including AKI, sepsis, ARDS, DIC, bleeding, hypovolemic shock, cardiac failure, arrhythmias, electrolyte disturbances

Pathogenesis of rhabdomyolysis



Cote et al, J of Anesthesia (2020) 34:585–598

A. Clinical significance of the CPK level

Diagnosis	CK level	Clinical Significance	Treatment Needed
Normal CK level	~40-200 U/L		
Mild rhabdomyolysis	1,000-5,000 U/L	Low risk for kidney injury	Possible Depends on context
Moderate rhabdomyolysis	5,0000-15,000 U/L	Increased risk of renal injury	Yes
Severe rhabdomyolysis	>15,000 U/L	Increased risk of dialysis	Yes

Variable	Points	
Age, years	≤50	0
	51-70	1.5
	71-80	2.5
	>80	3
Sex	Male	0
	Female	1
Initial Creatinine	<1.4 mg/dL (<124 μmol/L)	0
	1.4-2.2 mg/dL (124-195 μmol/L)	1.5
	>2.2 mg/dL (>195 μmol/L)	3
Initial Calcium <7.5 mg/dL (1.88 mmol/L)	No	0
Initial CK > 40000 U/L	Yes	2
	No	0
	Yes	2
Rhabdo secondary to seizures, syncope, exercise, statins or myositis	Yes	0
	No	3
Initial Phosphate	<4.0 mg/dL (<1.0 mmol/L)	0
	<4.0-5.4 mg/dL (1.0-1.4 mmol/L)	1.5
	>5.4 mg/dL (>1.4 mmol/L)	3
Initial Bicarbonate <19 mEq/L (19 mmol/L)	No	0
	Yes	2

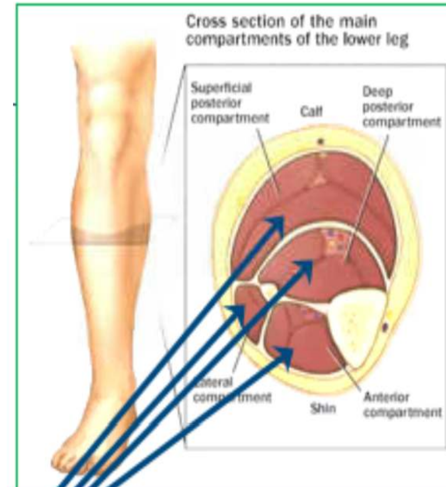
B. The McMahon Risk Score of RRT and/or mortality in Rhabdomyolysis

A low risk score predicted a favorable outcome: a score of < 5 identified patients with a 3% risk of t**he primary outcome,** while a score of > 10 was associated with a risk of 59.2%.

McMahon et al, JAMA Intern Med. 2013;173:1821-1828

The Compartment Syndrome

- **Compartment: space restricted by the rigid fasciae surrounding the muscles**



Compartment syndrome

- **increased pressure in the compartments due to traumatic tissue swelling**

Disrupts perfusion / hinders muscle function

FASCIOTOMIES in the Marmara E.

397 fasciotomies in 323 patients

Sepsis:	Fasc. (+): 25%
	Fasc. (-): 13%

Mortality	Sepsis (+): 27%
	Sepsis (-): 12%

Sever et al. NDT 2002

Fasciotomies ⇒ objective criteria

Better et al. KI 2003;63:1155-1157

FOLLOWING DISASTERS:

CRUSH SYNDROME

↓

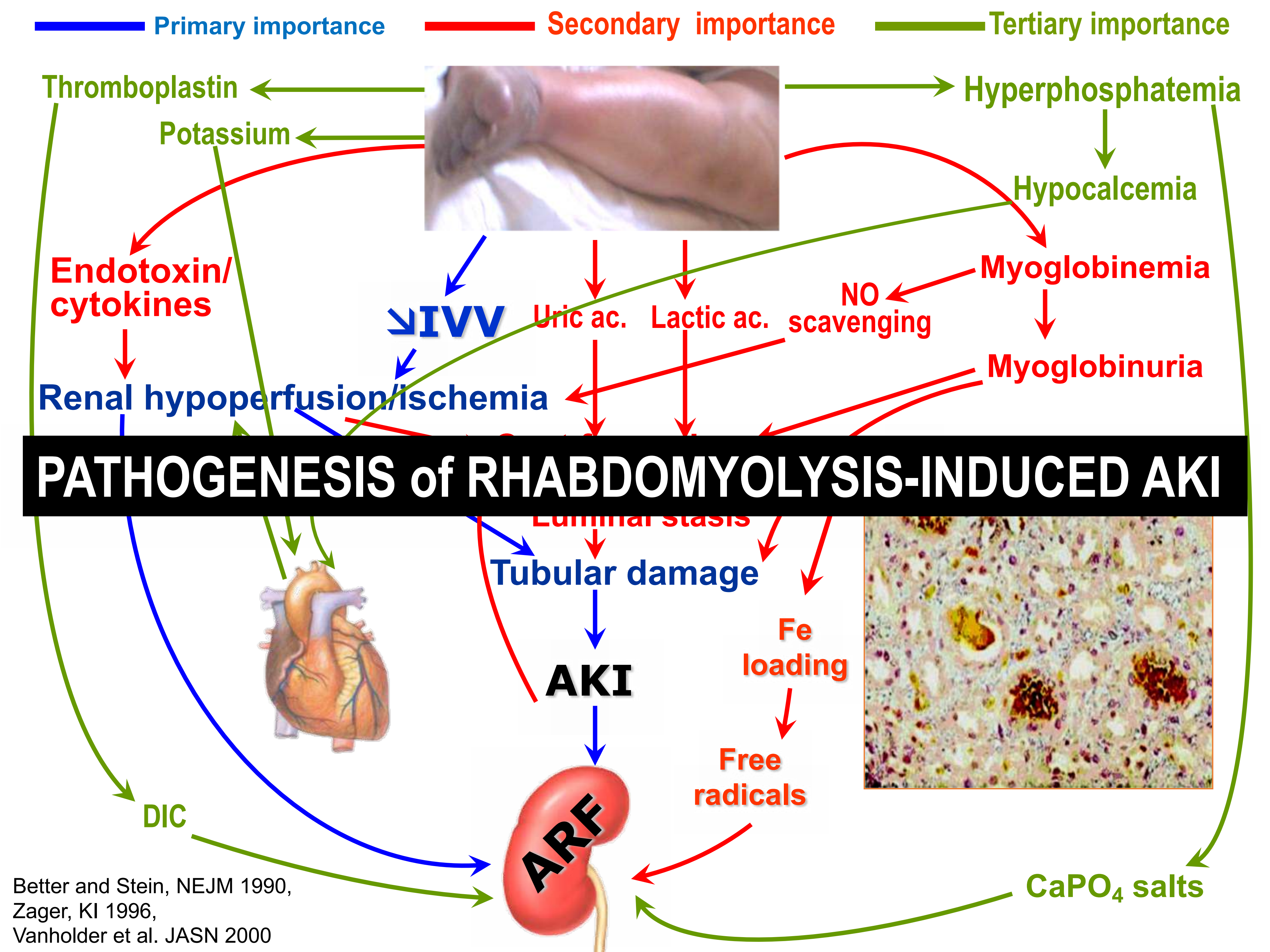
the second most frequent cause of death (following direct trauma) Ukai, Ren Fail,1997

↓

RENAL DISASTER

Solez et al. KI. 1993

PATHOGENESIS of RHABDOMYOLYSIS-INDUCED AKI



Crush Syndrome History

First described in the German literature in victims of Messina earthquake of 1909

WW I Germans noted traumatic rhabdomyolysis

A. Hackard "vasomotorische nephrose"

Minami in 1924 linked rhabdomyolysis and renal failure

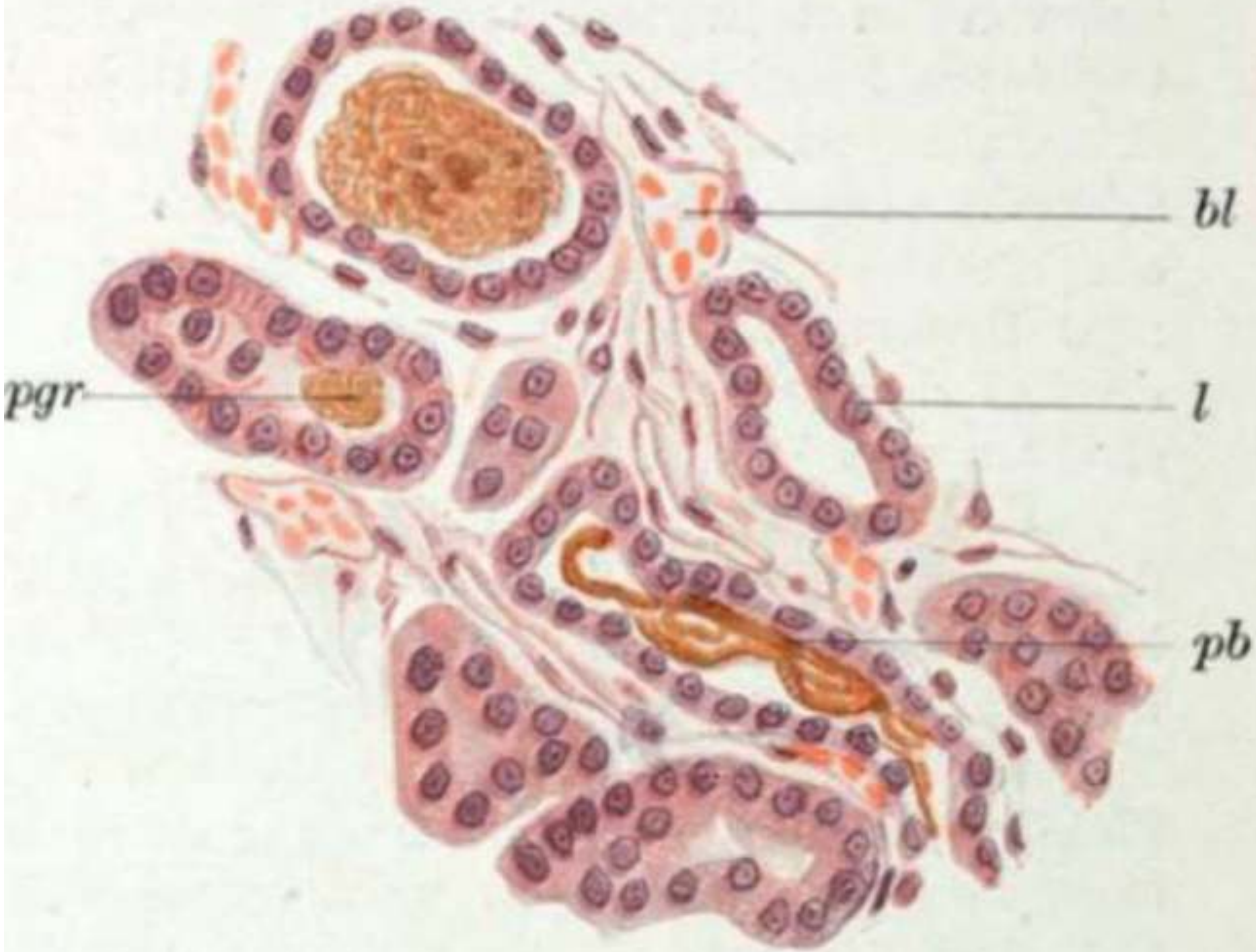


Abb. 3. Schnitt aus Nierenrinde (Fall 1159). Tod nach Verschüttung am 7. Tag. Hämalaunfärbung. Leitz, Oc. 1, Obj. 6, Tub. 155. *pgr* = Pigmentgranula in dichter Lagerung innerhalb von Tubuli contorti: *pb* = Pigmentstreifen und -bänder; *e* = Epithelien der Tubuli contorti; *bl* = geschrumpfte rote Blutkörperchen in Blutcapillaren.

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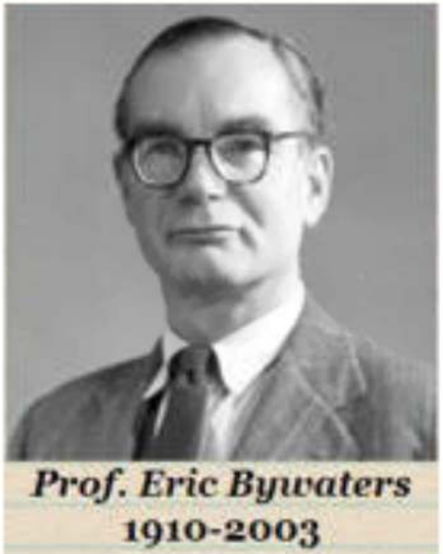
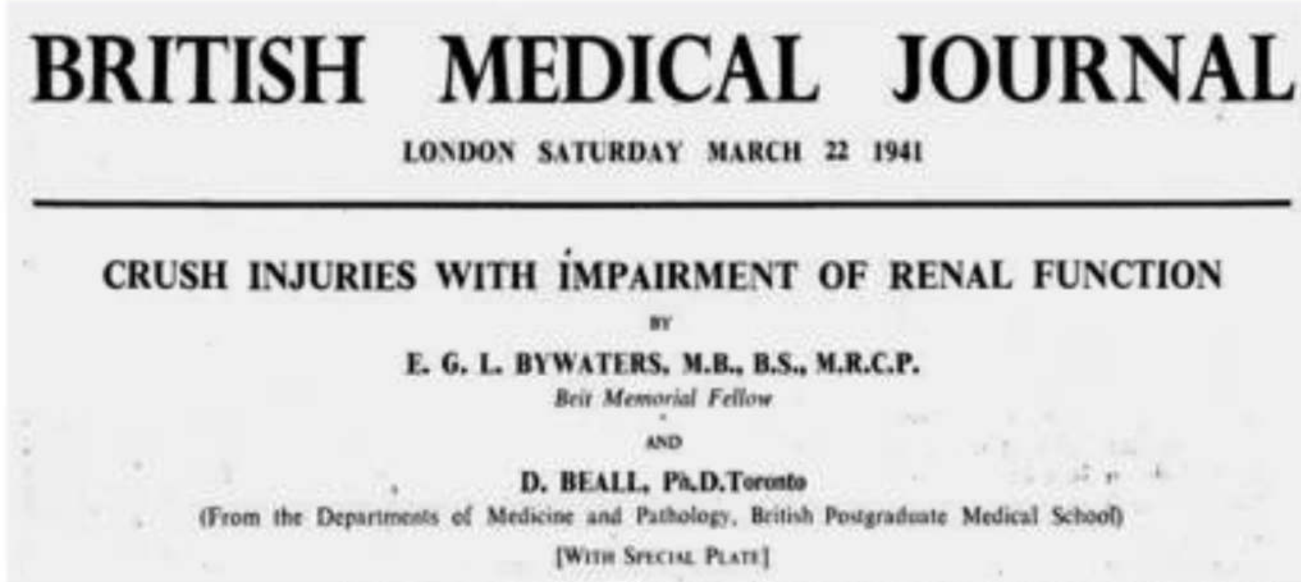




BRITISH MEDICAL JOURNAL

LONDON SATURDAY MARCH 22 1941

CRUSH INJURIES WITH IMPAIRMENT OF RENAL FUNCTION

BY

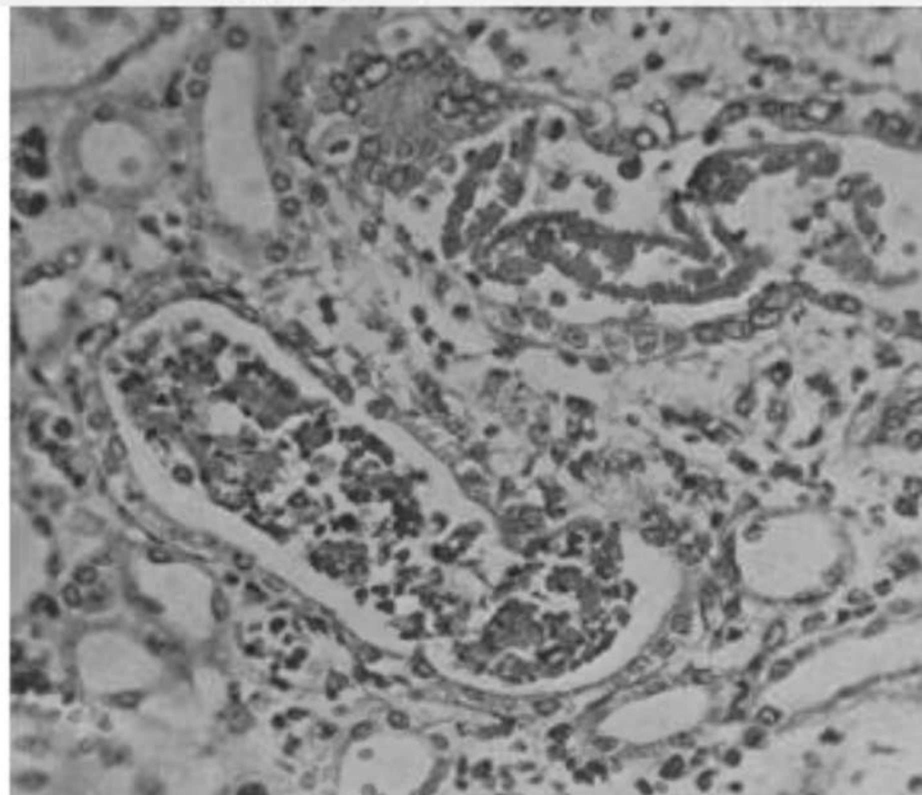
E. G. L. BYWATERS, M.B., B.S., M.R.C.P.
Beit Memorial Fellow

AND

D. BEALL, Ph.D.Toronto
(From the Departments of Medicine and Pathology, British Postgraduate Medical School)

[WITH SPECIAL PLATE]

- Four crushed cases
- Three oliguric
- Dark brownish urine color
- All died
- Autopsies were performed



1988: The Armenian Earthquake

- Death toll: 25,000 ?
- Crush cases: 600 ?
- Many crush pts. died due to lack of dialysis

No organized international support structure was available

Eknoyan G. Ren Fail 1992; 14: 241

Need for preplanned logistic organisation

RENAL DISASTER RELIEF TASK FORCE

Supplementation of MEDICAL MATERIAL and PERSONNEL

International relief ≠ functional help

- Guatemalan e.1976 ⇒ 90% drugs useless (unsorted) Seaman, Injury, 1990
- Armenian e.1978 ⇒ 70% useless (expired or damaged) Auiter, Lancet, 1990

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International personnel support ⇒ useful or harmful

Local / Global integrated responses are mandatory !

↓

RENAL DISASTER RELIEF TASK FORCE

Kidney International, Vol. 44 (1993), pp. 479–483

INVITED CONTRIBUTION

International dialysis aid in earthquakes and other disasters[1]

KIM SOLEZ, DAVID BIHARI, ALLAN J. COLLINS, GARABED EKNOYAN, HASKEL ELIAHOU, V.D. FEDOROV, CARL KJELLSTRAND, NORBERT LAMEIRE, JOSEPH LETTERI, ALLEN R. NISSENSON, ERIC K. NOJI,[2] J.P. WAUTERS, and YASUHIRO YAMAMOTO

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Conditions and advantages of cooperation with Médeçins sans Frontières

- MSF has over the years accumulated an enormous experience in disaster relief all over the world.
- MSF has permanent links and access to the Ministry of Foreign Affairs for quickly obtaining visa, solving a number of diplomatic and logistic problems. The organisation is known world-wide for its strict political neutrality and has therefore access to countries where other organisations could not have access (Nobel Prize for Peace 1999).
- They also dispose of very sophisticated communication systems
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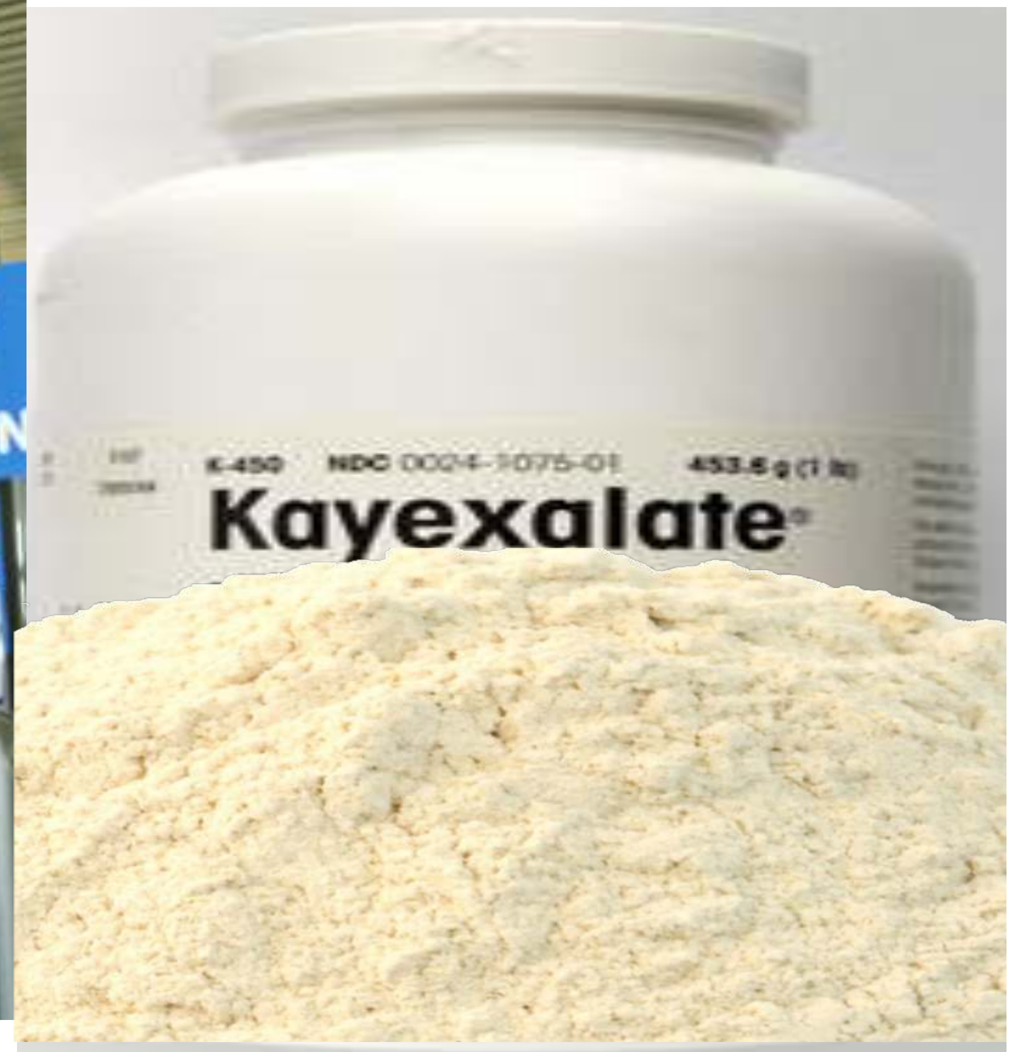
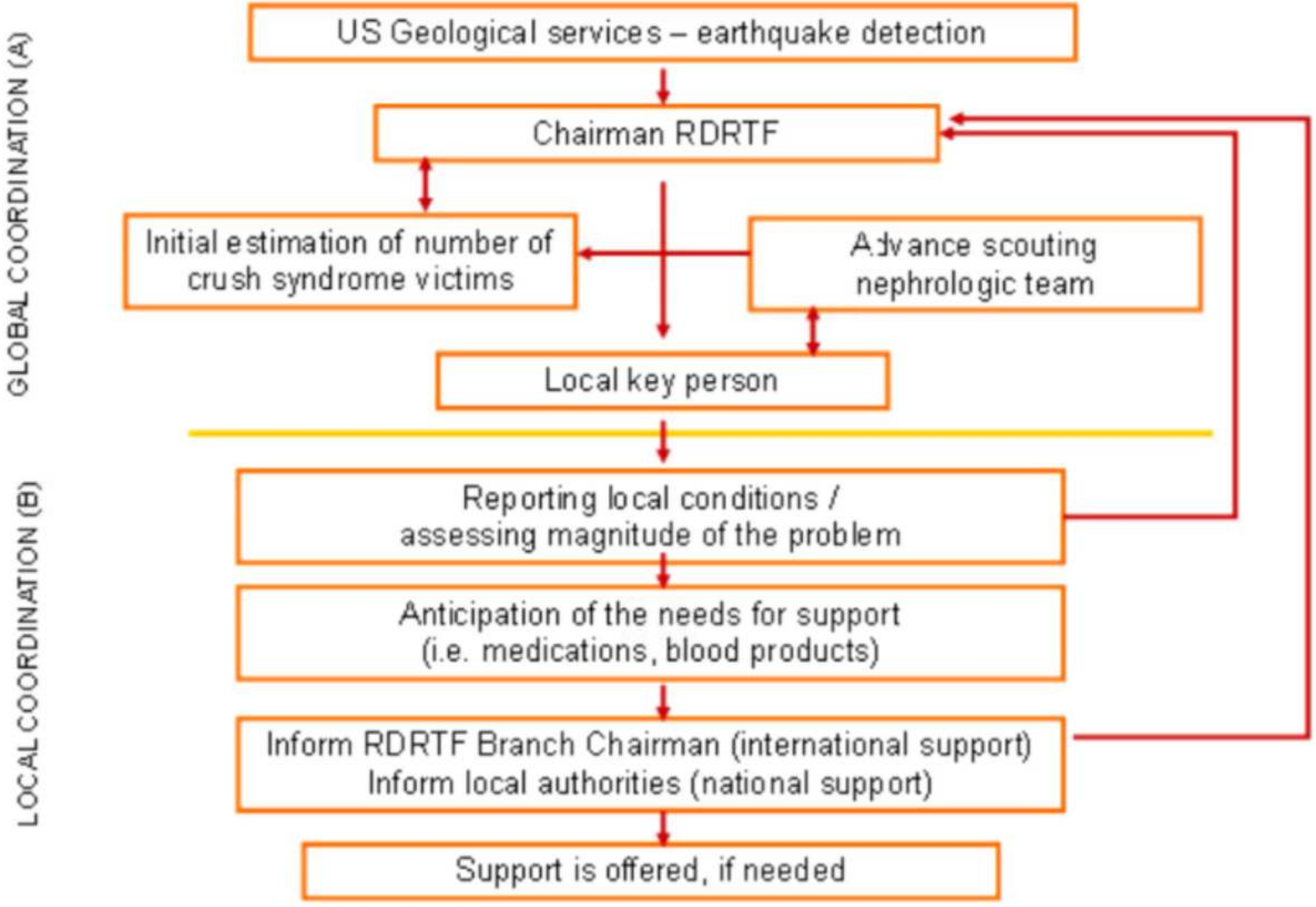
- MSF financially supports travel, accomodation, and insurance of all volunteers
- MSF finances all medical and dialysis equipment needed for the acute dialysis of the victims

“No! It’s not cocaïne, it’s kayexalate! I am on a humanitarian mission…!”



The Global and Local Organisation & Coordination of the RDRTF



Sever, Vanholder , Lameire. N Engl J Med, 354 (2006), 1052-1063

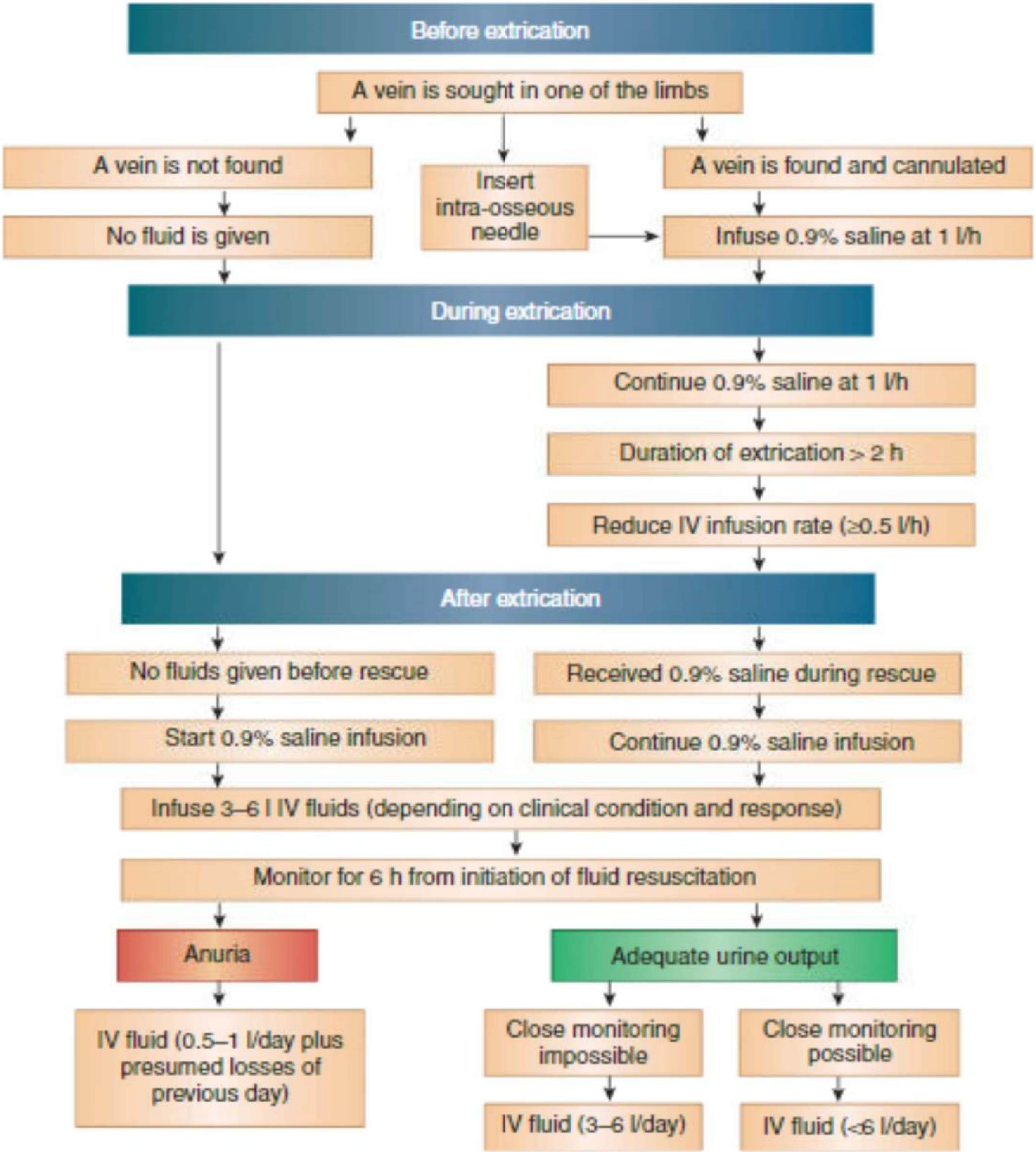
MEDICAL INTERVENTIONS AT THE DISASTER FIELD (FOR PROPHYLAXİS OF CRUSH SYNDROME)

EARLY FLUID ADMINISTRATION IS OF VITAL IMPORTANCE !

Better and Stein, NEJM, 1990

Vanholder et al, Kidney Int, 2000

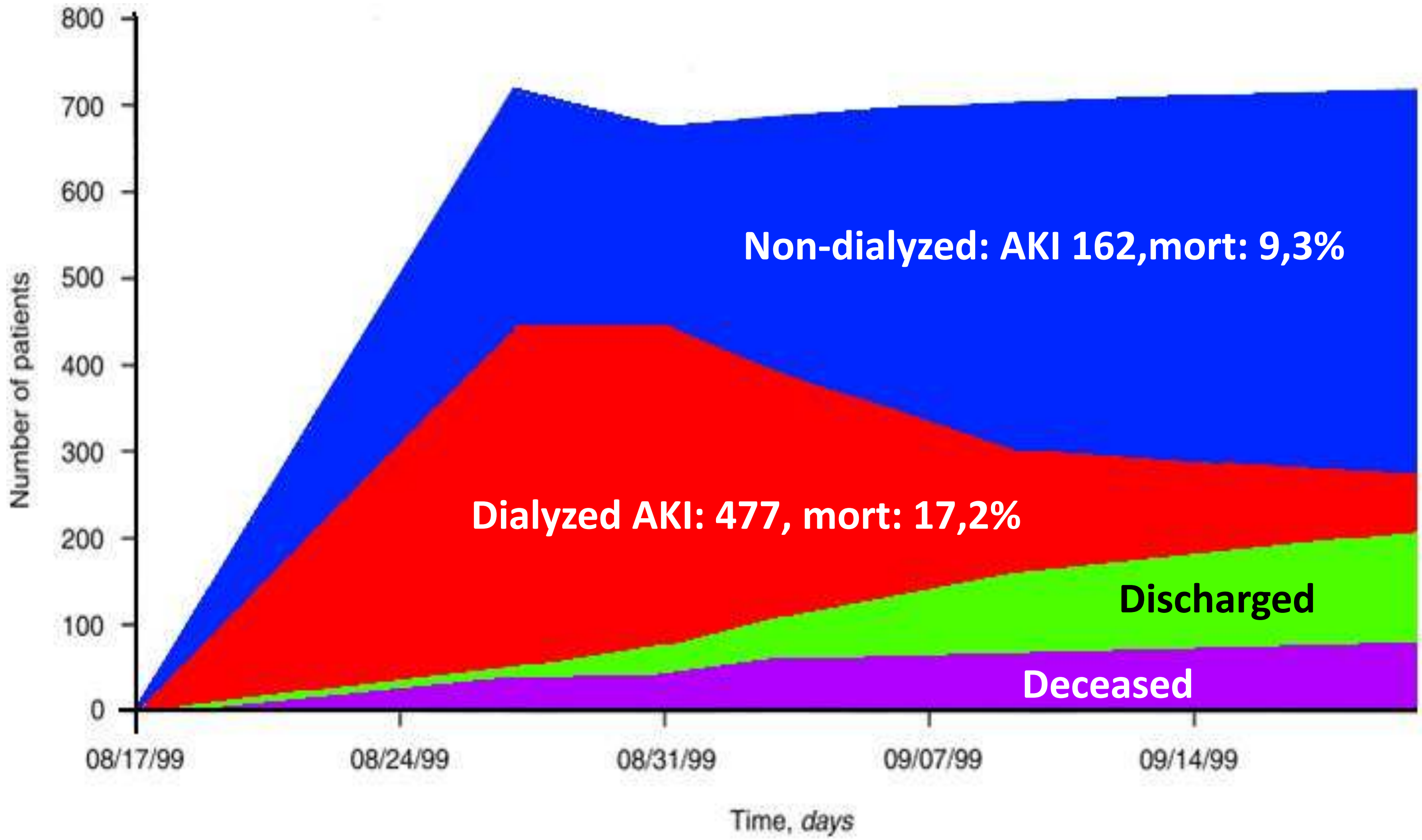
Fluid management in crush victims of mass disasters



Gibney et al Kidney Int (2014)85,1049–1057

Evolution of AKI population Marmara earthquake

(n: 639, overall mortality: 15,2%)



Erek et al, NDT, 2002, 17:33-40

Vanholder et al, KI, 59, 783-791, 2001

Interventions of the RDRTF

- Iran, March, 1997: Material support
- Macedonia, May, 1999: Evacuation chronic patients
- Macedonia/Kosova, July, 1999: Material support
- Turkey, August, 1999: Major intervention
- Kosova, February, 2000: Educational support
- India, January, 2001: Assessment
- Turkey, May, 2003: Material support
- Algeria, May, 2003: Assessment
- Iran, December, 2003: Major intervention
- Luisiana, August, 2005: Advisory role
- Pakistan, October 2005: Major intervention
- Indonesia, May, 2006: Assessment
- Lebanon, July, 2006: Material support
- Peru, August, 2007: Scouting
- China, May 2008, Major intervention
- Italy, April 2009, Advice
- Indonesia, September 2009, Assessment
- Haiti, January 2010, Major intervention
- Chile, February 2010, Advice
- Turkey, March 2010, Advice
- New Zealand 2010 & 2011, Advice
- Ivory coast, 2012, Material support
- Lybia, May 2012, Material support
- Phillipines, December 2013, Material support
- Syria, March-April 2014, Material support
- Nepal, April-May, 2015, Material support

ISSN 0931-0509 (Print) ISSN 1460-2385 (Online)
Volume 27 Supplement 1 April 2012

ndt

NEPHROLOGY DIALYSIS TRANSPLANTATION

Basic and clinical renal science

RECOMMENDATIONS FOR THE MANAGEMENT OF CRUSH VICTIMS IN MASS DISASTERS

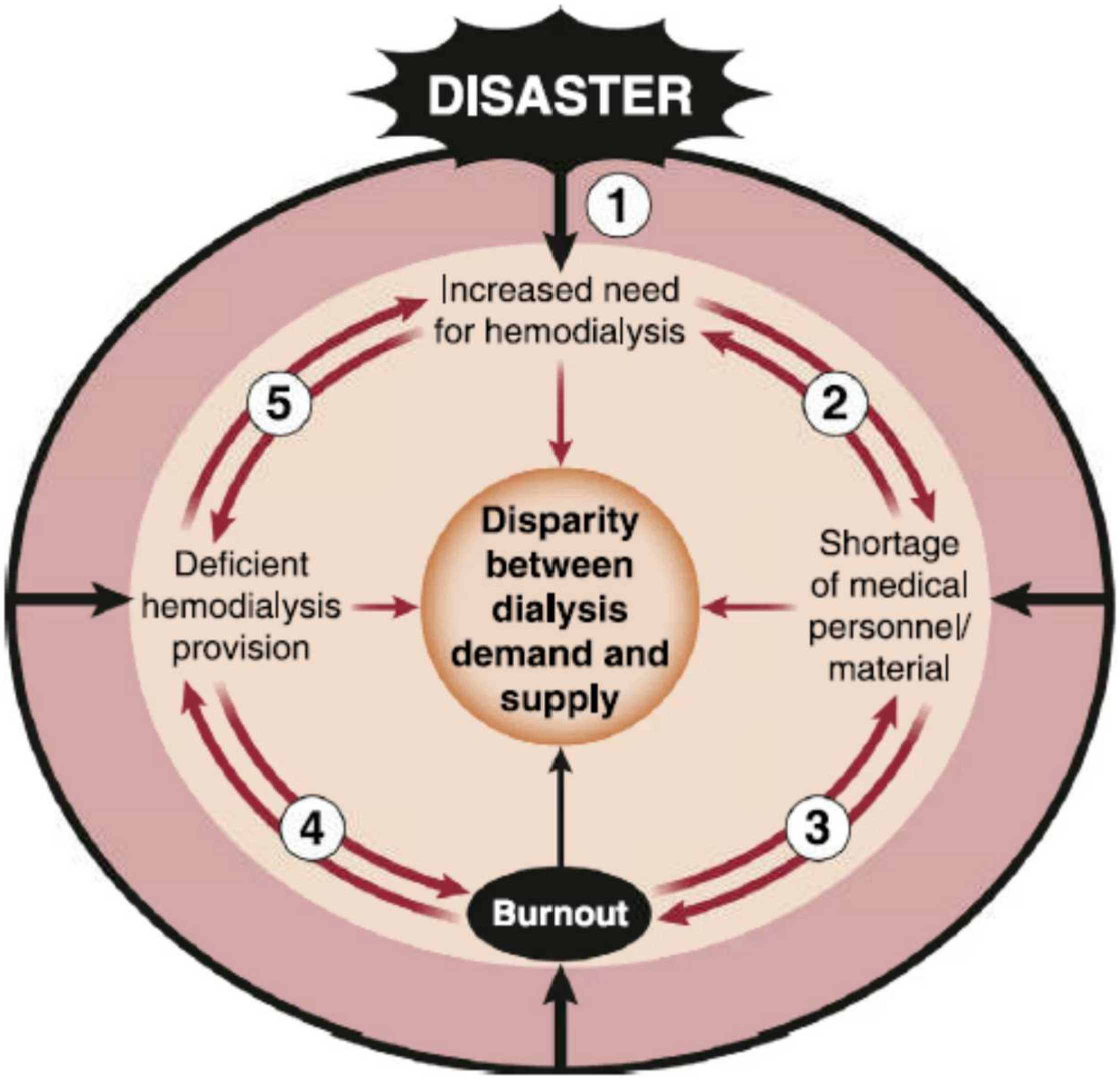
Workgroup Co-Chairs: Mehmet Sukru Sever and Raymond Vanholder

Lessons learned over the years of activity of the RDRTF 1998-2015

- *Nephrological impact of disasters*
  - Crush injury and AKI, pathogenesis, prevention by resuscitation, monitoring and dialysis
  - Acute compartment syndrome
- *Management of chronic dialysis and transplant patients in disaster area*
  - Advance planning
  - Post disaster response: logistics, communications,and supplies
  - Disengagement and debriefing
- *Psychological and mental support of intervention team*


a
b
c
d

Complex interaction between disasters and HD delivery



Sever et al CJASN 16: ccc–ccc, 2021

Achievements and reflections on the future

- There are some NEW **OPPORTUNITIES** for the RDRTF:
- start up of ISN regional chapters might help and assist in to providing local anchoring of RDRTF
- cooperation with industrial partners might expand both logistical and organisational support for RDRTF
- some nephrology societies (eg French) willing to be more involved and creating their own disaster preparedness renal group
- gradually most regions in the world provide some degree of chronic renal support, providing the necessary and indispensable background to the work of RDRTF.

- There are some **THREATS** for the RDRTF:
- The headquarters are localized in only one single center (Renal division of UH Ghent requiring complex organizational activities, necessitating full-time involvement of one medical coordinator and at least one secretarial assistant.
- In addition, keeping the program and volunteers up-to-date is cumbersome because of unpredictability of interventions
- escalating number of unsafe and war struck areas on a global level
- growing number of regions where dialysis is provided for the happy few, but not for all, creating ethical problems when bringing in acute dialysis opportunities during a short lived window.

Lameire N et al, Semin Nephrol 40:393−407, 2020

Crush Injury and Beyond: Disaster Nephrology

Norbert Lameire, MD, PhD
Emeritus Professor of Medicine
University Hospital
Ghent, Belgium

With sincere thanks to Raymond Vanholder and Mehmet S Sever

Virtual Annual Dialysis Conference Meeting
March 7, 2021

Thou shalt be visited by the Lord of hosts with thunder, and with earthquakes and great noise, with storm and tempest, and the flame of devouring fire.

Isaiah 29:6

Disaster

Sudden calamities producing extensive damage, loss and distress

- Natural
  - Earthquakes
  - Landslides
  - Avalanches
  - Hurricanes
  - Tornadoes
- Man-made
  - War
  - Mining
  - Tunnel collapse
  - Terrorism, torture

A

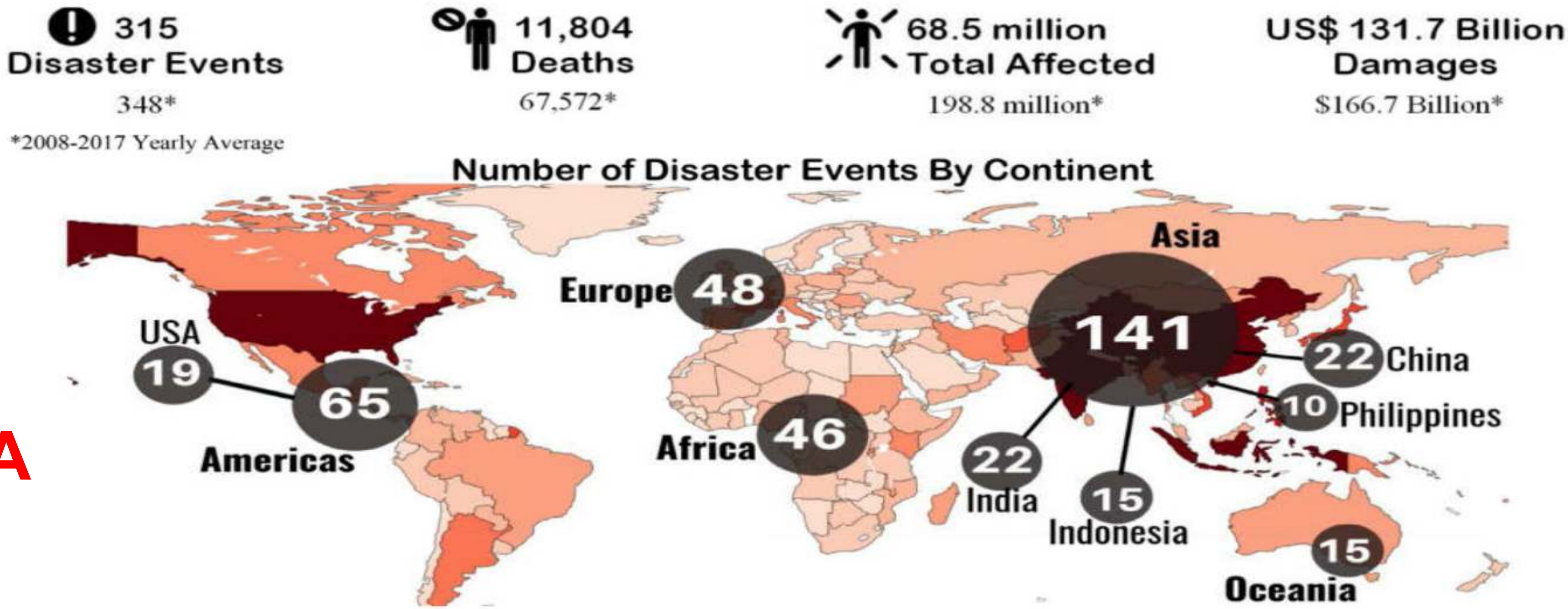


Figure 1. Global number of climate-related and geophysical disaster events by continent recorded in the International Disaster Database (EM-DAT) in 2018 and compared with the yearly average between 2008 and 2017.[7]

B

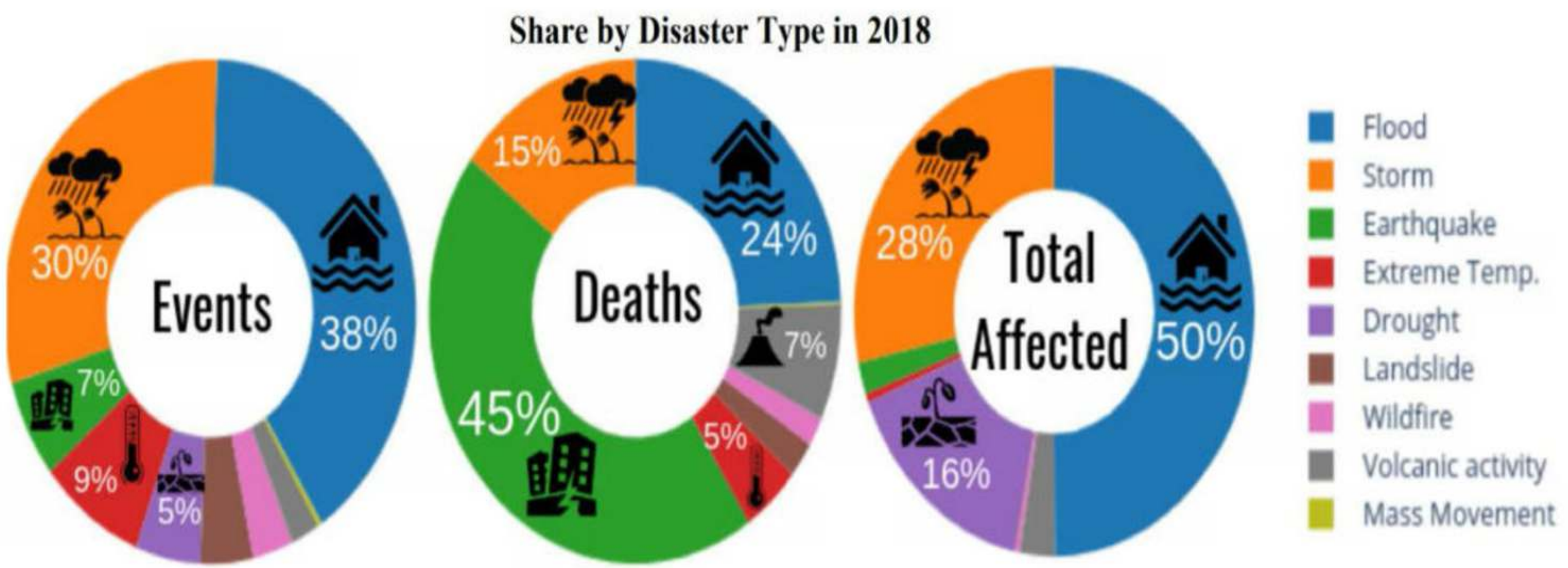
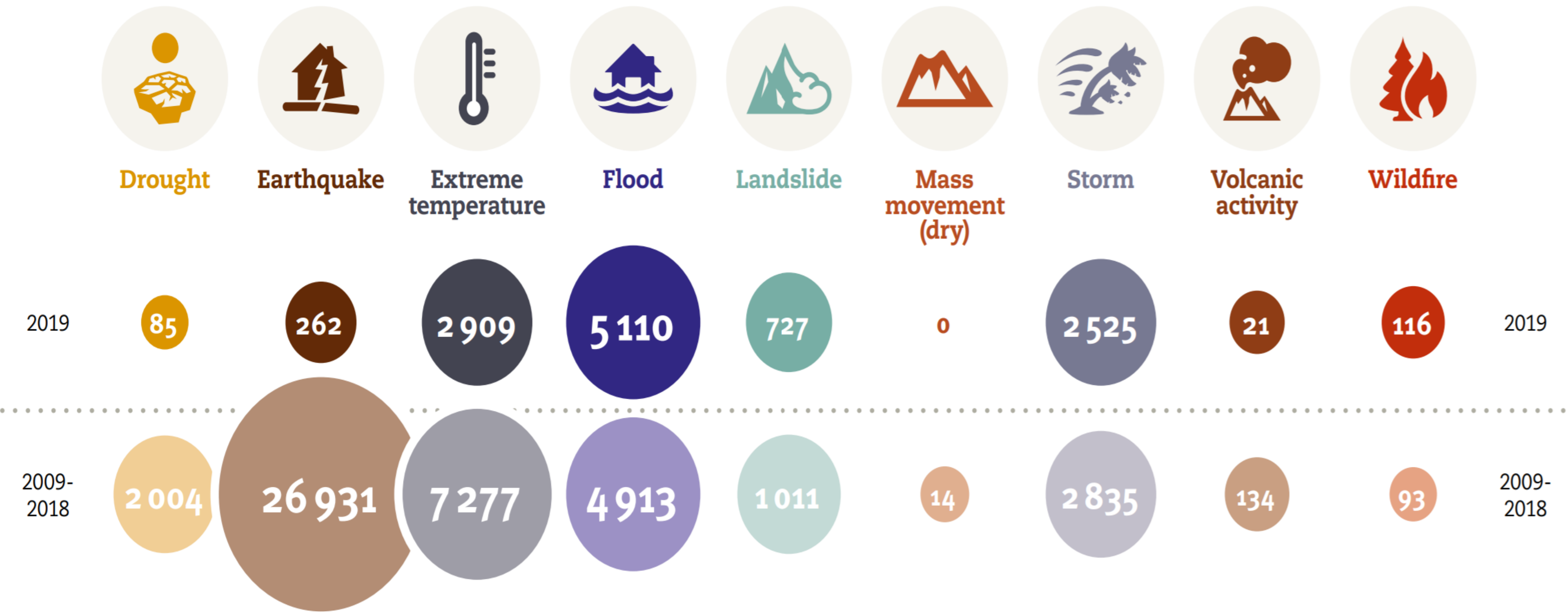


Figure 2. Illustration of the percentage of each disaster type registered in 2018.[7] Abbreviation: Temp, temperature.

Number of deaths by disaster type: 2019 compared to 2009-2018 annual average

45,212
2009 to 2018

11,755
in 2019

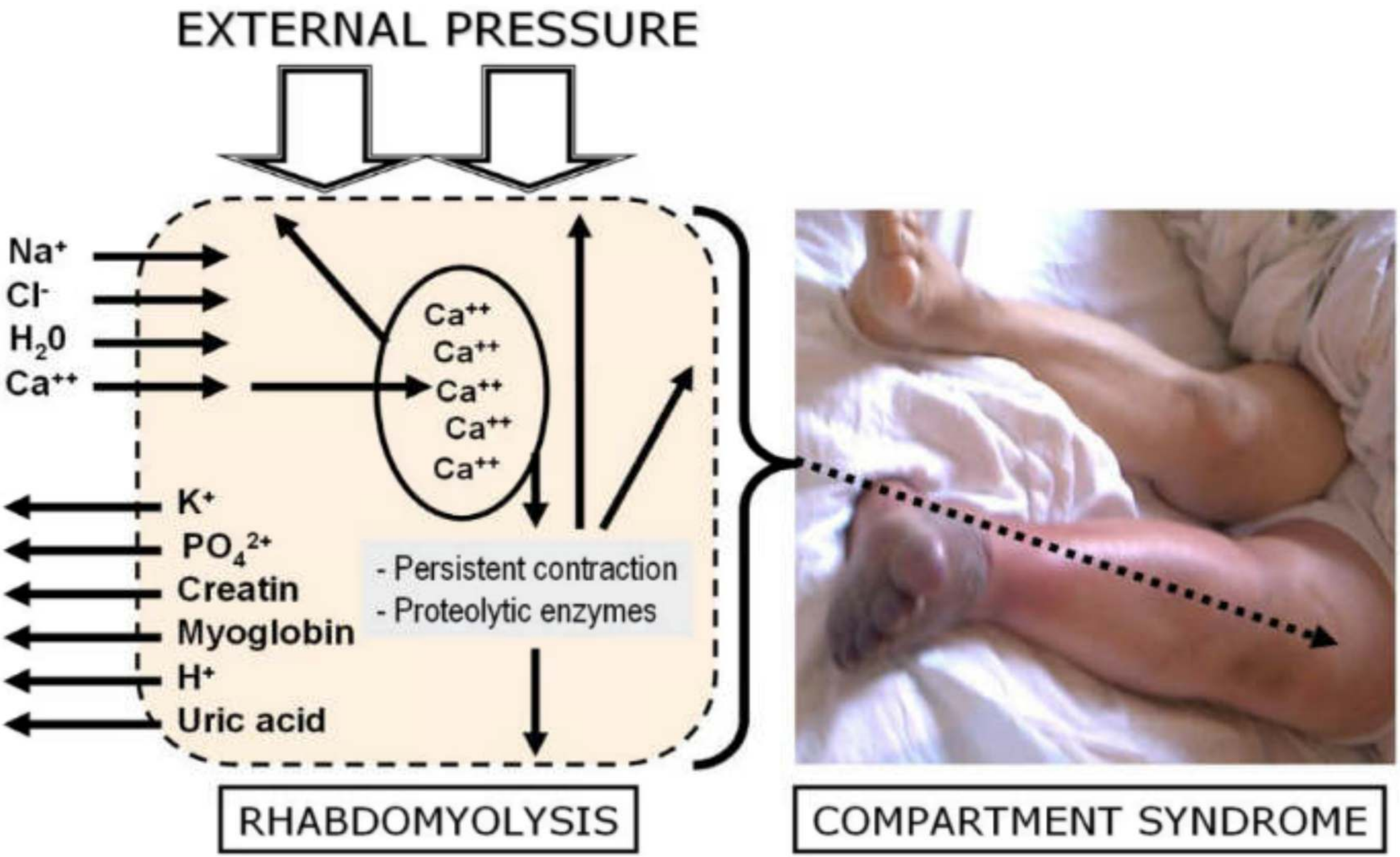


Centre for Research on the Epidemiology of Disasters (CRED)

Definitions

- *Rhabdomyolysis*: Damage to striated muscle resulting in the systemic release of intramuscular components
- *Crush injury*: Direct injury by collapsing material and debris causing muscle swelling and/or neurological disturbances in the affected parts of the body
- *Crush syndrome*: Crush injury combined with systemic manifestations, including AKI, sepsis, ARDS, DIC, bleeding, hypovolemic shock, cardiac failure, arrhythmias, electrolyte disturbances

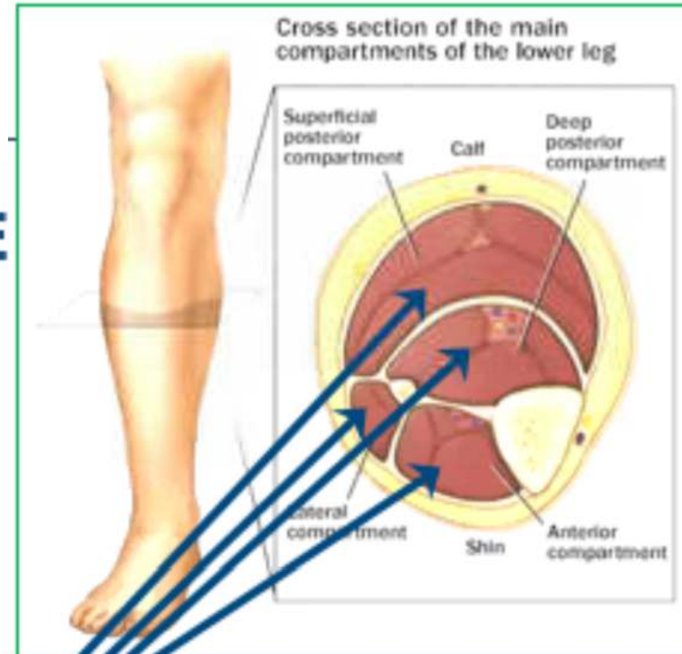
Pathophysiology of rhabdomyolysis induced by pressure on muscle cells



Sever MS et al, Semin Nephrol 40:341–353 2020

COMPARTMENT SYNDROME

- **Compartment: space restricted by the rigid fasciae surrounding the muscles**



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CRUSH SYNDROME

↓

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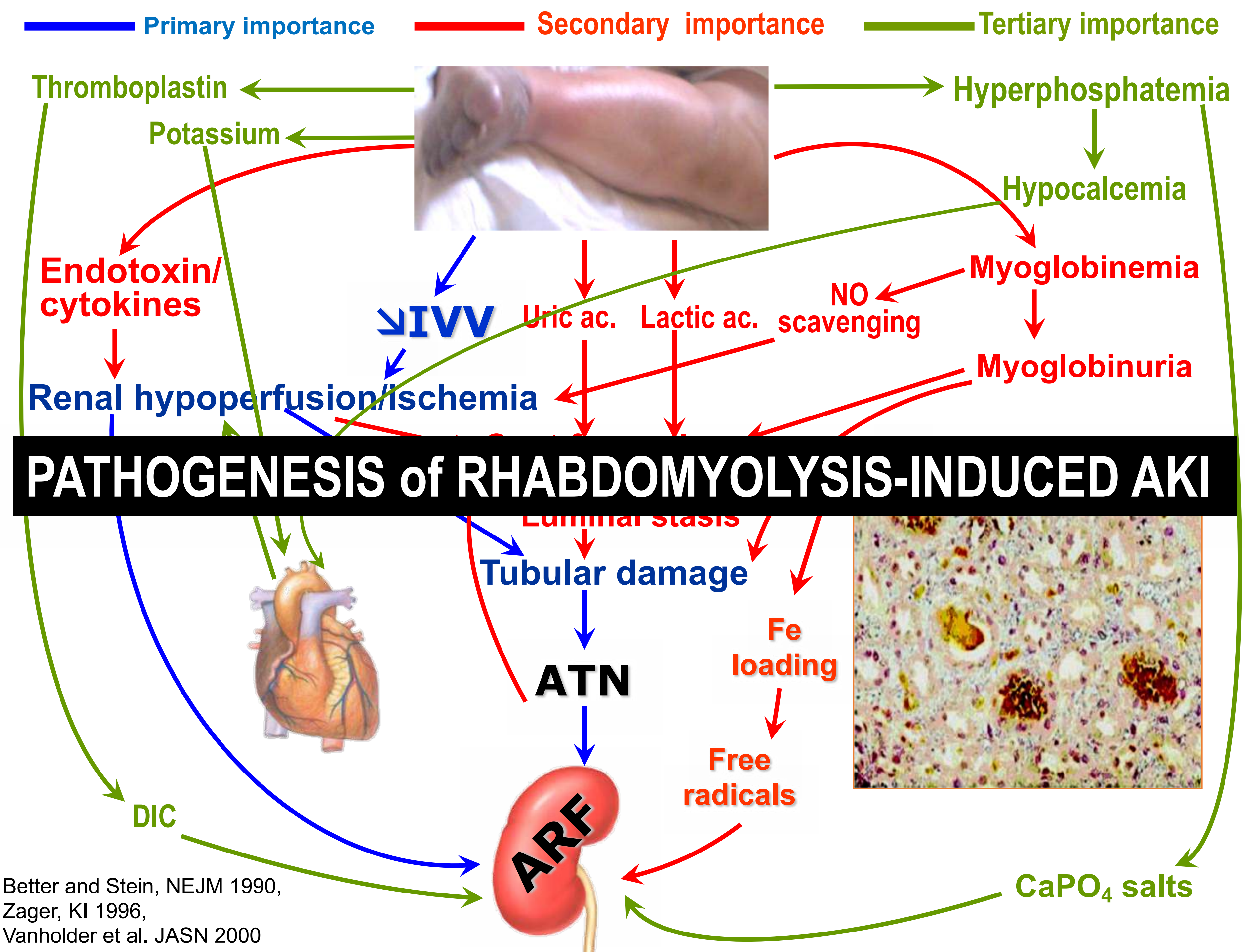
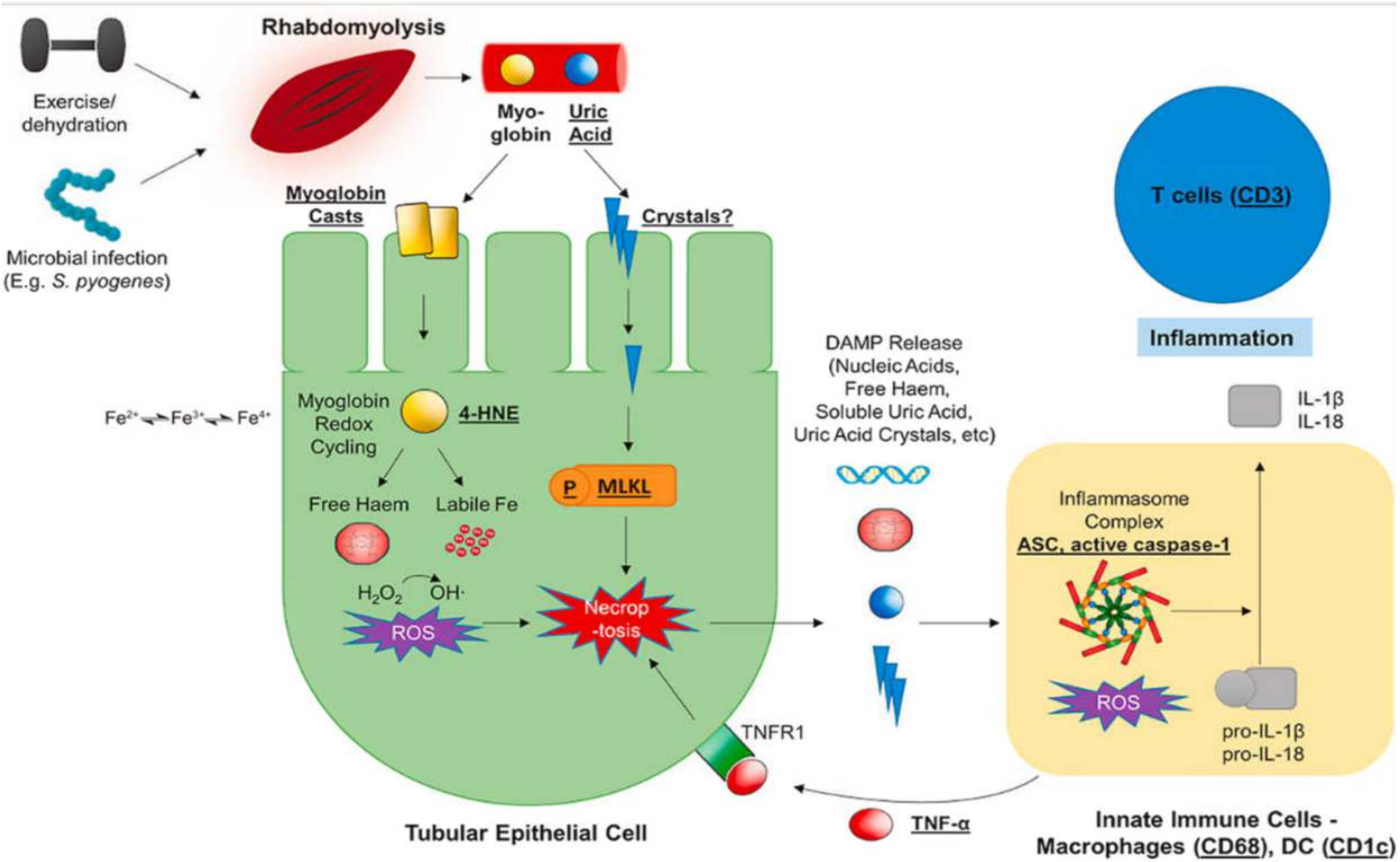


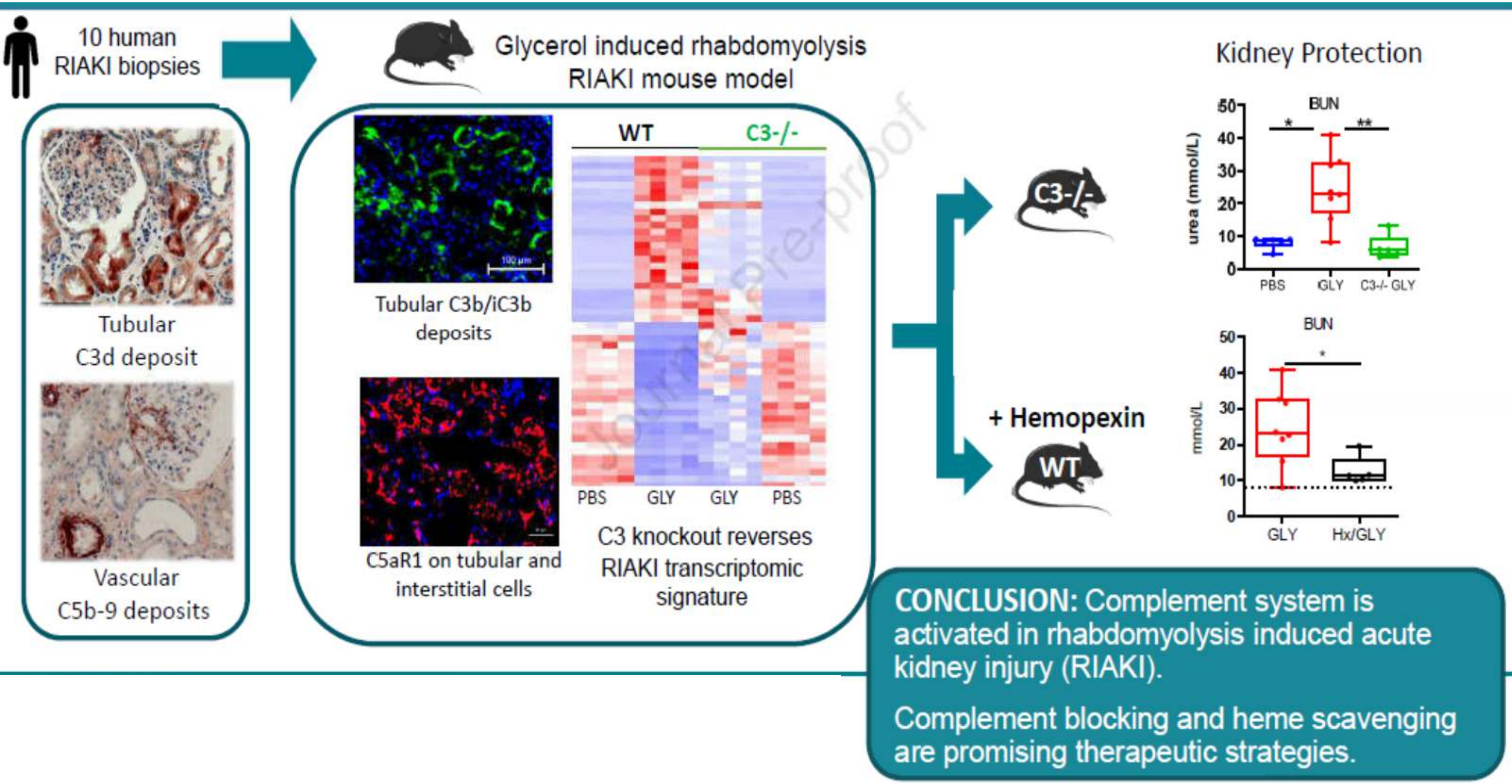
Better and Stein, NEJM 1990,
Zager, KI 1996,
Vanholder et al. JASN 2000

Oxidative stress and inflammasome activation in human rhabdomyolysis-induced AKI



Grivei et al Free Radical biology and Medicine 160, 2020,690-695

Complement activation is a crucial driver of AKI in rhabdomyolysis



Boudhabhay I et al, Kidney Int 2020 Oct 30;S0085-2538(20)31244-8.
doi: 10.1016/j.kint.2020.09.033. Online ahead of print.

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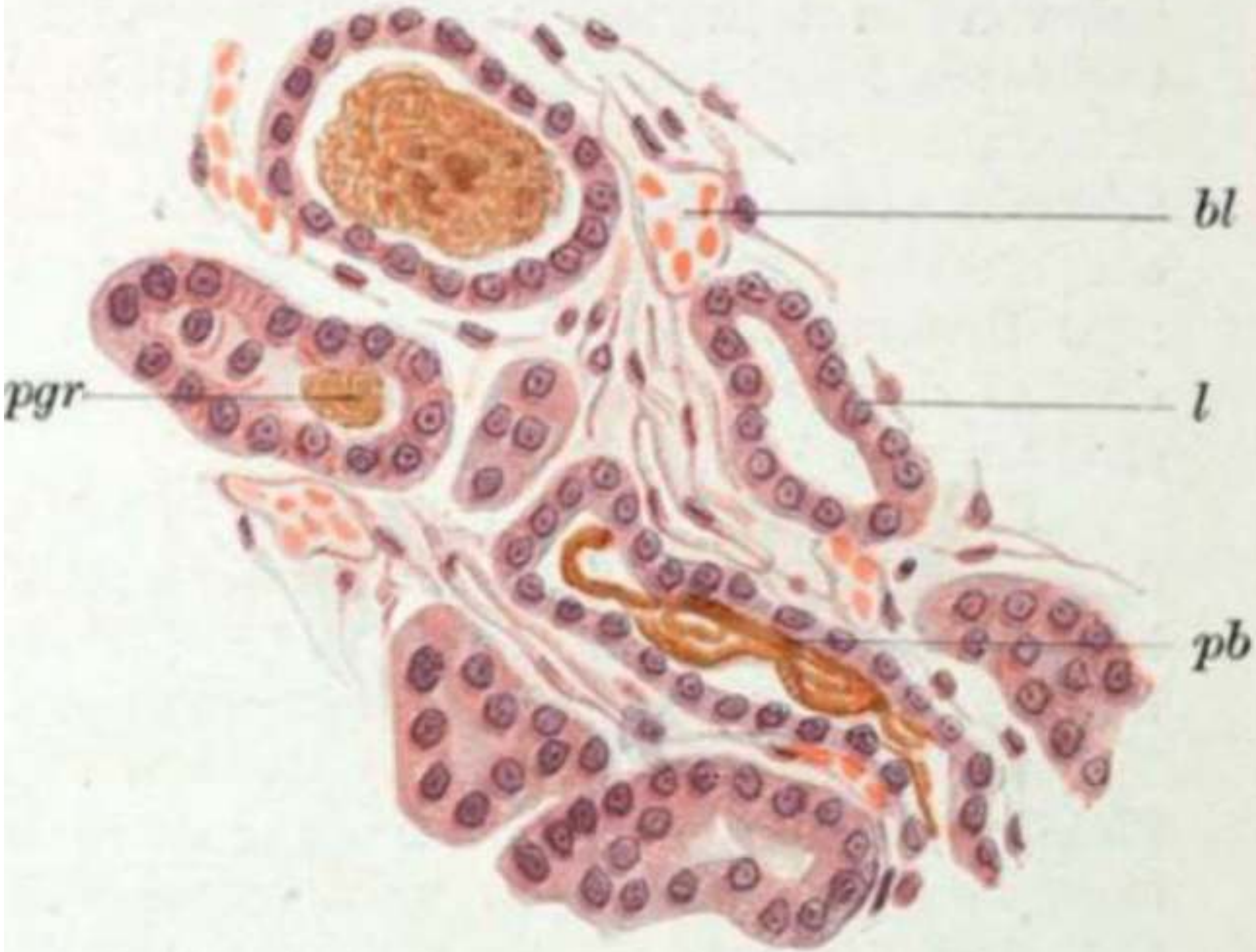

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Prof. Eric Bywaters
1910-2003

BRITISH MEDICAL JOURNAL

LONDON SATURDAY MARCH 22 1941

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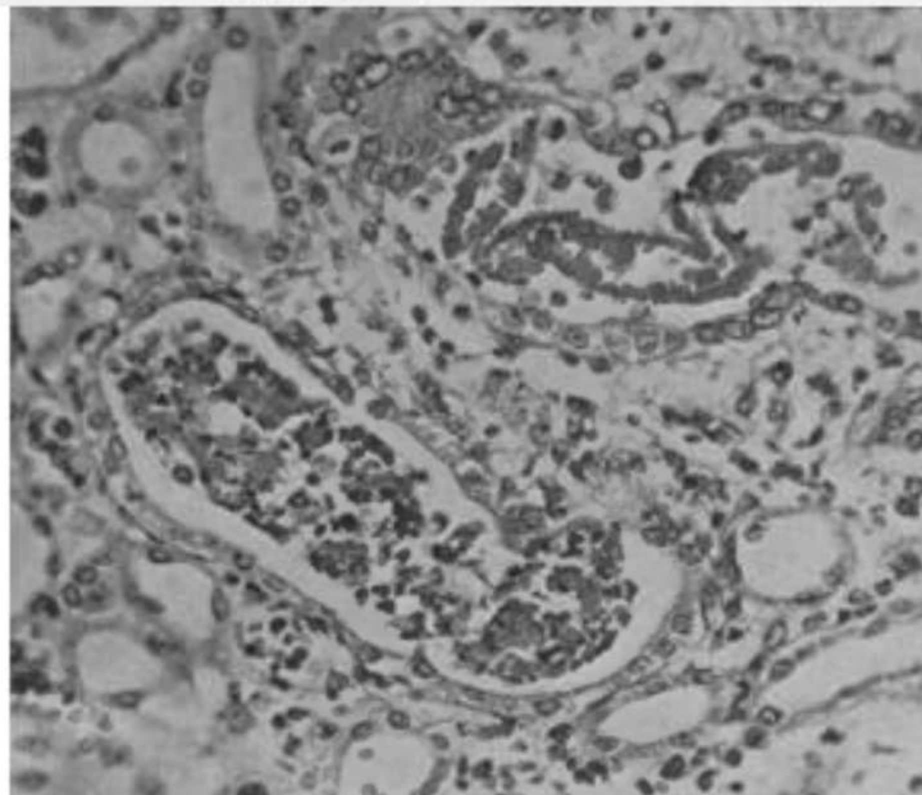

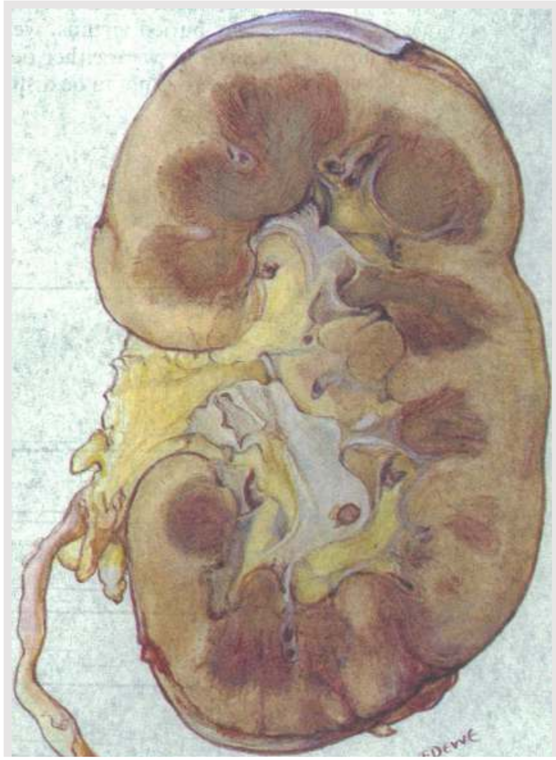

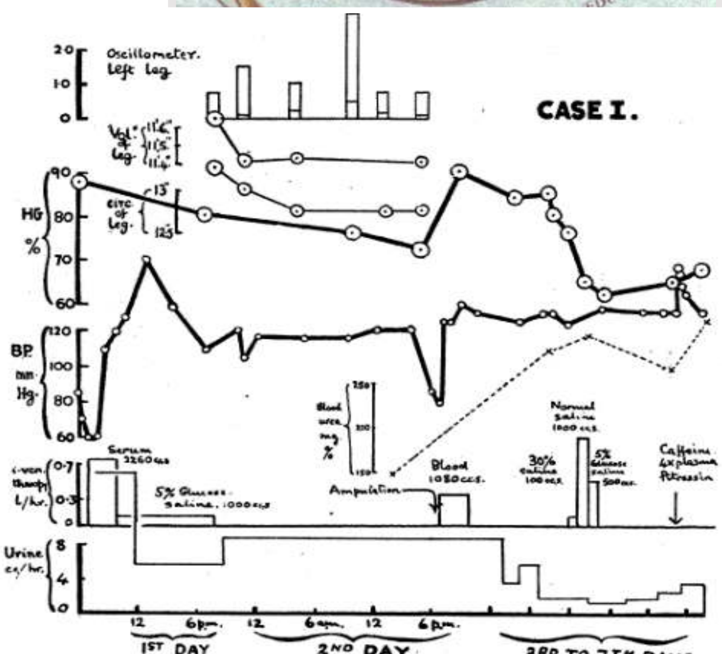

CHART I.—Case I.

Kidney of patient who died of uraemia nine days after release; gross swelling (weight 192 g) and pigmented casts

Bywaters** EGJ.* ***BMJ 1990;301:1412-1415

and hot bottles were applied to the loins. Despite these measures, directed towards restarting urine flow, the patient, whose blood pressure was maintained at 130/70, suddenly collapsed at 12:13 p.m. on the eighth day and died in three minutes. A systolic murmur at the

December 7th, 1988; Richter 6.8

20,-40,000 deaths?

600 crush patients?,

Timeline foreign dialysis help in Armenian earthquake Wednesday December 7th, 1988-6.8 Richter scale

7/12	8/12	9/12	10/12	11/12	12/12	13/12	14/12
Quake	Gorbachov UN speech NY		Visit disaster area Gorbachev	Opening ASN, Request for dialysis help- Arrival German team		British team assembled equipment	Arrival British team Yerevan

Based on Richards, Tattersall, et al, Br Med J 1989;298:443-445

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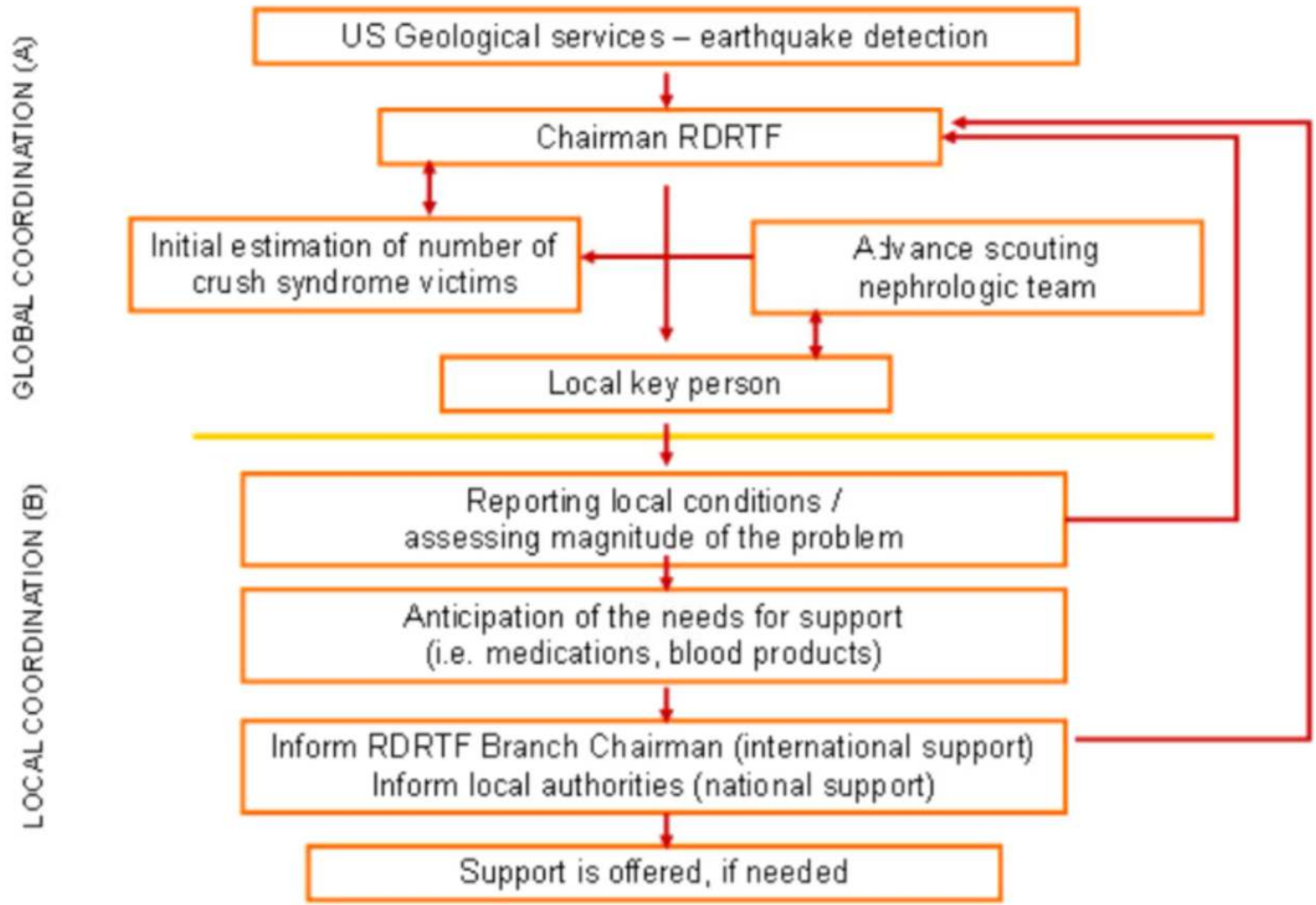
GLOBAL COORDINATION (A)
US Geological services – earthquake detection
Chairman RDRTF
Initial estimation of number of crush syndrome victims
Advance scouting nephrologic team
Local key person
LOCAL COORDINATION (B)
Reporting local conditions / assessing magnitude of the problem
Anticipation of the needs for support (i.e. medications, blood products)
Inform RDRTF Branch Chairman (international support)
Inform local authorities (national support)
Support is offered, if needed

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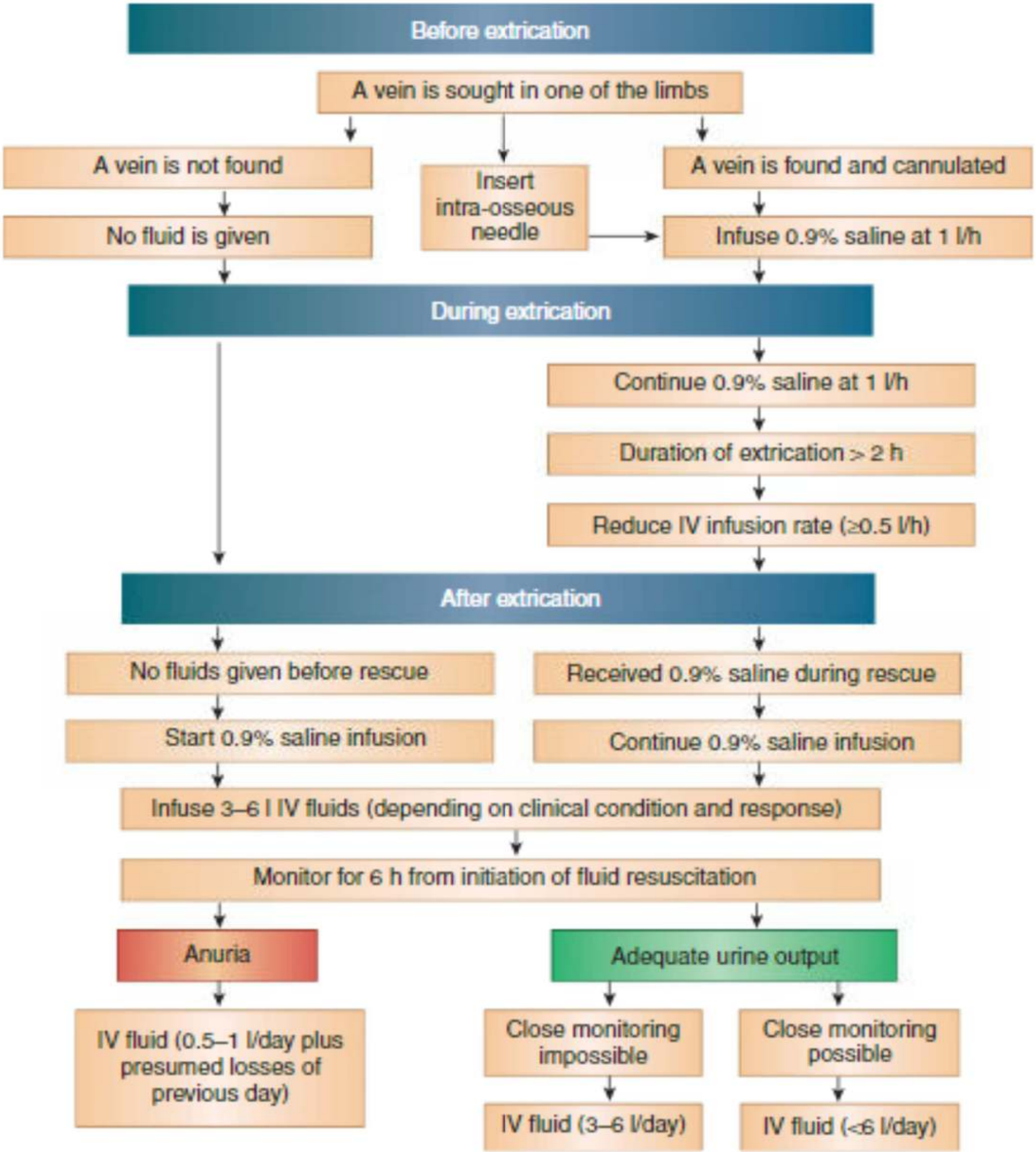
EARLY FLUID ADMINISTRATION IS OF VITAL IMPORTANCE !

Better and Stein, NEJM, 1990

Vanholder et al, Kidney Int, 2000

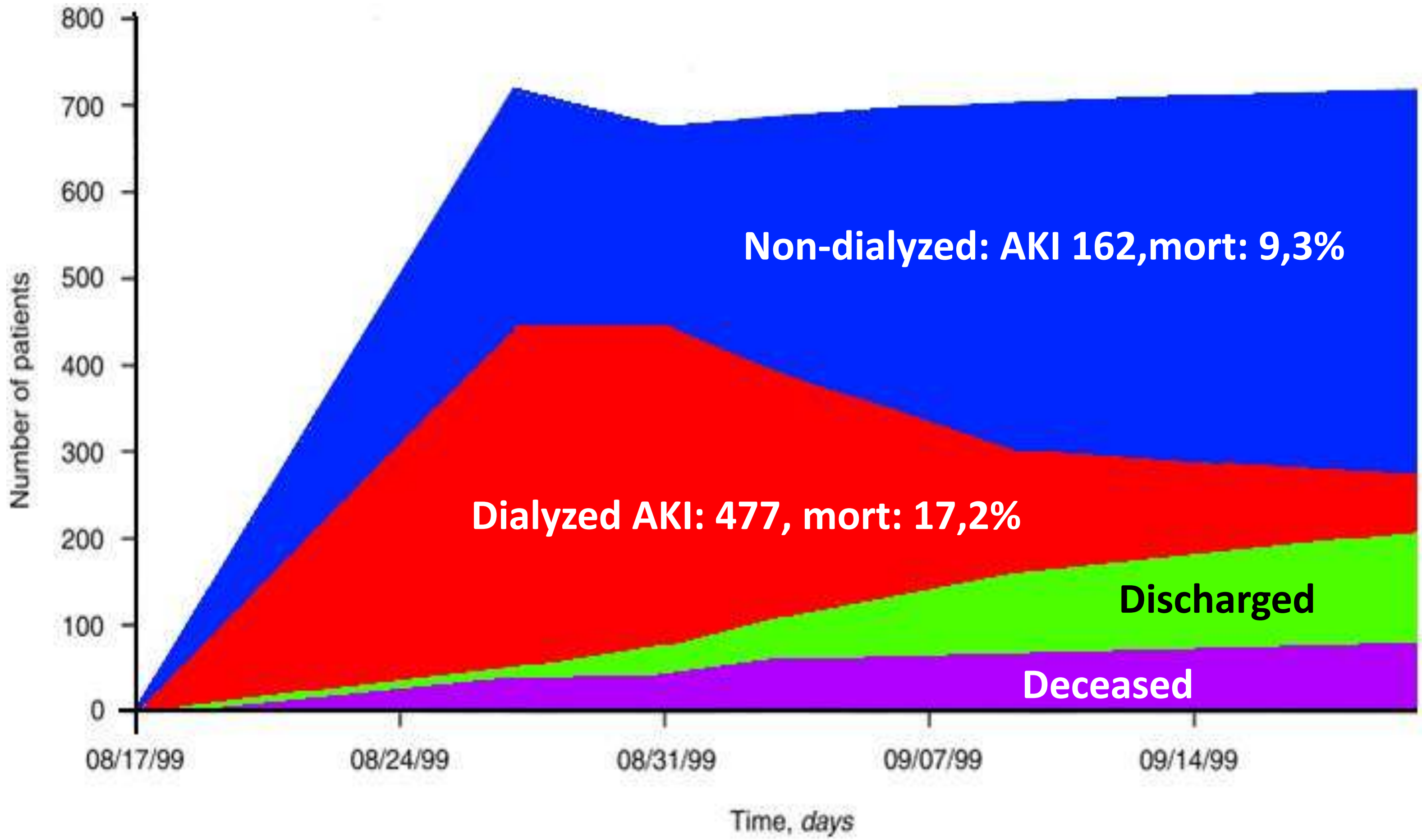
Fluid management in crush victims of mass disasters



Gibney et al Kidney Int (2014)85,1049–1057

Evolution of AKI population Marmara earthquake

(n: 639, overall mortality: 15,2%)



Erek et al, NDT, 2002, 17:33-40

Vanholder et al, KI, 59, 783-791, 2001

ISSN 0931-0509 (Print) ISSN 1460-2385 (Online)
Volume 27 Supplement 1 April 2012

ndt

NEPHROLOGY DIALYSIS TRANSPLANTATION

Basic and clinical renal science

RECOMMENDATIONS FOR THE MANAGEMENT OF CRUSH VICTIMS IN MASS DISASTERS

Workgroup Co-Chairs: Mehmet Sukru Sever and Raymond Vanholder

Interventions of the RDRTF

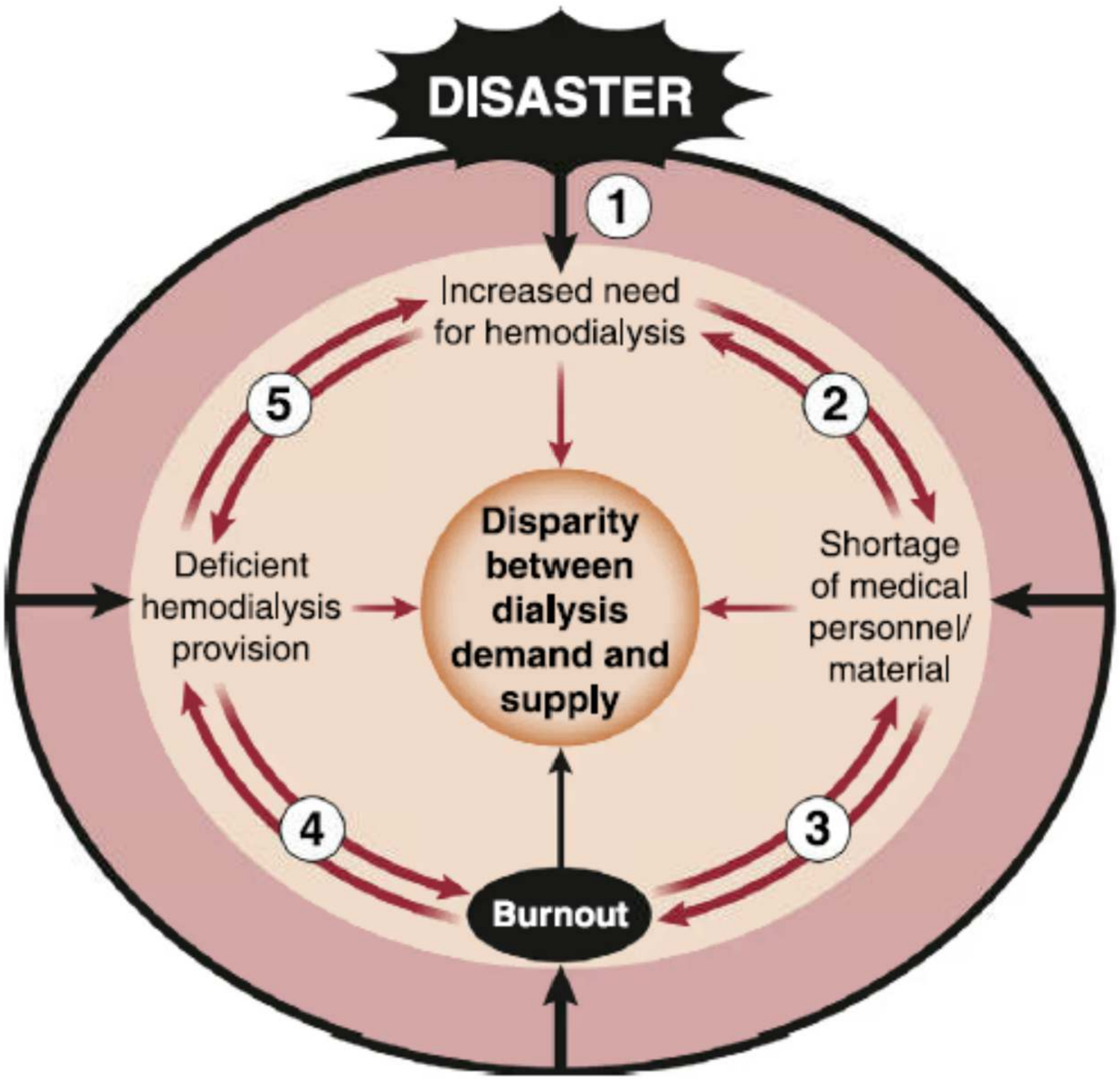
- Iran, March, 1997: Material support
- Macedonia, May, 1999: Evacuation chronic patients
- Macedonia/Kosova, July, 1999: Material support
- Turkey, August, 1999: Major intervention
- Kosova, February, 2000: Educational support
- India, January, 2001: Assessment
- Turkey, May, 2003: Material support
- Algeria, May, 2003: Assessment
- Iran, December, 2003: Major intervention
- Luisiana, August, 2005: Advisory role
- Pakistan, October 2005: Major intervention
- Indonesia, May, 2006: Assessment
- Lebanon, July, 2006: Material support
- Peru, August, 2007: Scouting
- China, May 2008, Major intervention
- Italy, April 2009, Advice
- Indonesia, September 2009, Assessment
- Haiti, January 2010, Major intervention
- Chile, February 2010, Advice
- Turkey, March 2010, Advice
- New Zealand 2010 & 2011, Advice
- Ivory coast, 2012, Material support
- Lybia, May 2012, Material support
- Phillipines, December 2013, Material support
- Syria, March-April 2014, Material support
- Nepal, April-May, 2015, Material support

Lessons learned over the years of activity of the RDRTF 1998-2015

- *Nephrological impact of disasters*
  - Crush injury and AKI, pathogenesis, prevention by resuscitation, monitoring and dialysis
  - Acute compartment syndrome
- *Management of chronic dialysis and transplant patients in disaster area*
  - Advance planning
  - Post disaster response: logistics, communications,and supplies
  - Disengagement and debriefing
- *Psychological and mental support of intervention team*


a
b
c
d

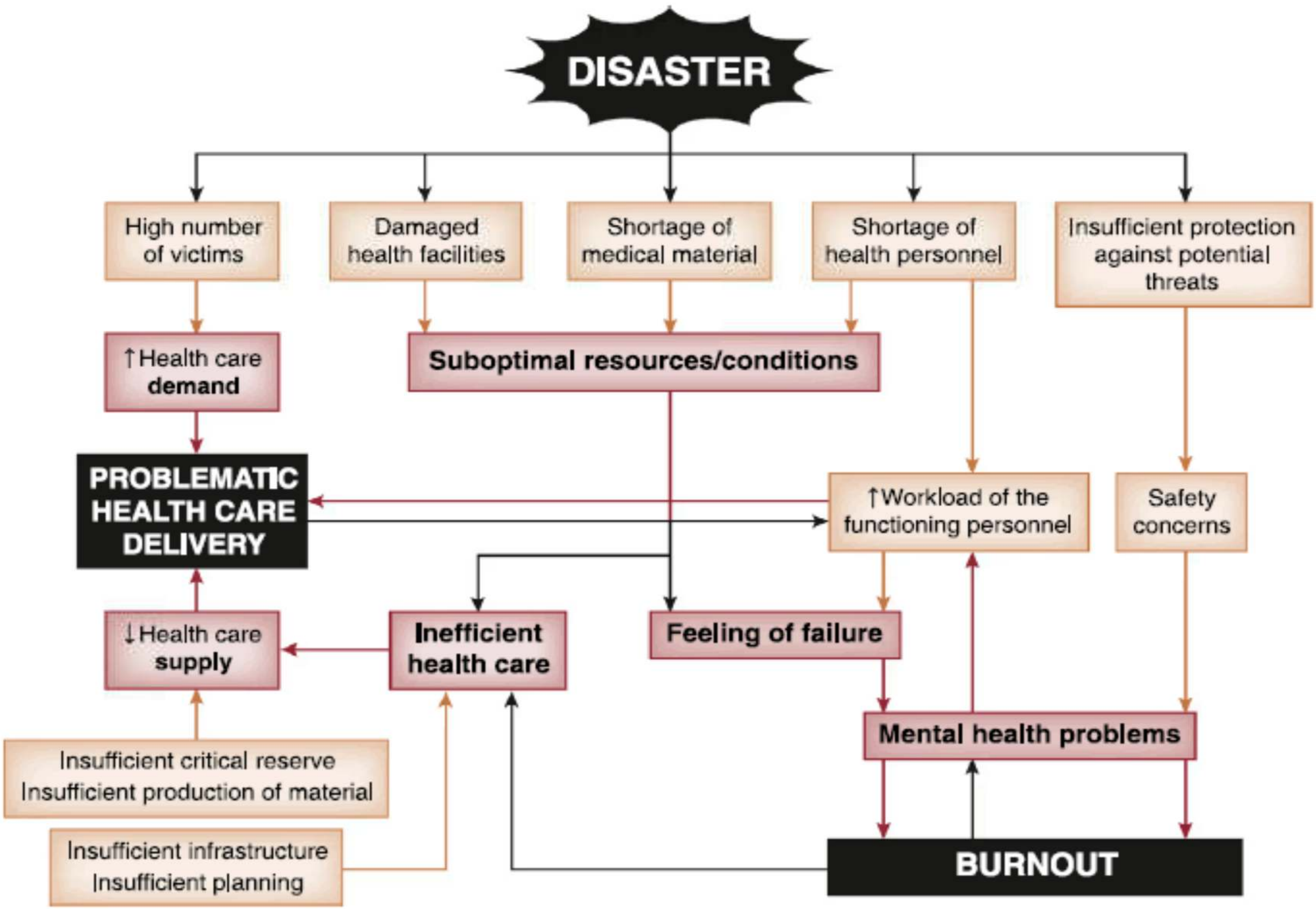
Complex interaction between disasters and HD delivery



Sever et al CJASN 16: ccc–ccc, 2021

"No! It's not cocaïne, it's kayexalate! I am on a humanitarian mission…!"

Role of burnout in health care provision after mass disasters



Sever et al CJASN 16: ccc–ccc, 2021

Achievements and reflections on the future

- There are some **OPPORTUNITIES** for the RDRTF:
- start up of ISN regional chapters might help and assist to provide local anchoring of RDRTF
- cooperation with industrial partners might expand both logistical and organisational support for RDRTF
- some nephrology societies (eg French) willing to be more involved and creating their own disaster preparedness renal group
- gradually most regions in the world provide some degree of chronic renal support, providing the necessary and indispensable background to the work of RDRTF.

- There are some **THREATS** for the RDRTF:
- The headquarters are localized in only one single center (Renal division of UH Ghent requiring complex organizational activities, necessitating full-time involvement of one medical coordinator and at least one secretarial assistant.
- In addition, keeping the program and volunteers up-to-date is cumbersome because of unpredictability of interventions
- escalating number of unsafe and war struck areas on a global level
- growing number of regions where dialysis is provided for the happy few, but not for all, creating ethical problems when bringing in acute dialysis opportunities during a short lived window.

Lameire N et al, Semin Nephrol 40:393–407, 2020

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UREMIC TOXINS: GUT-KIDNEY INTERACTION

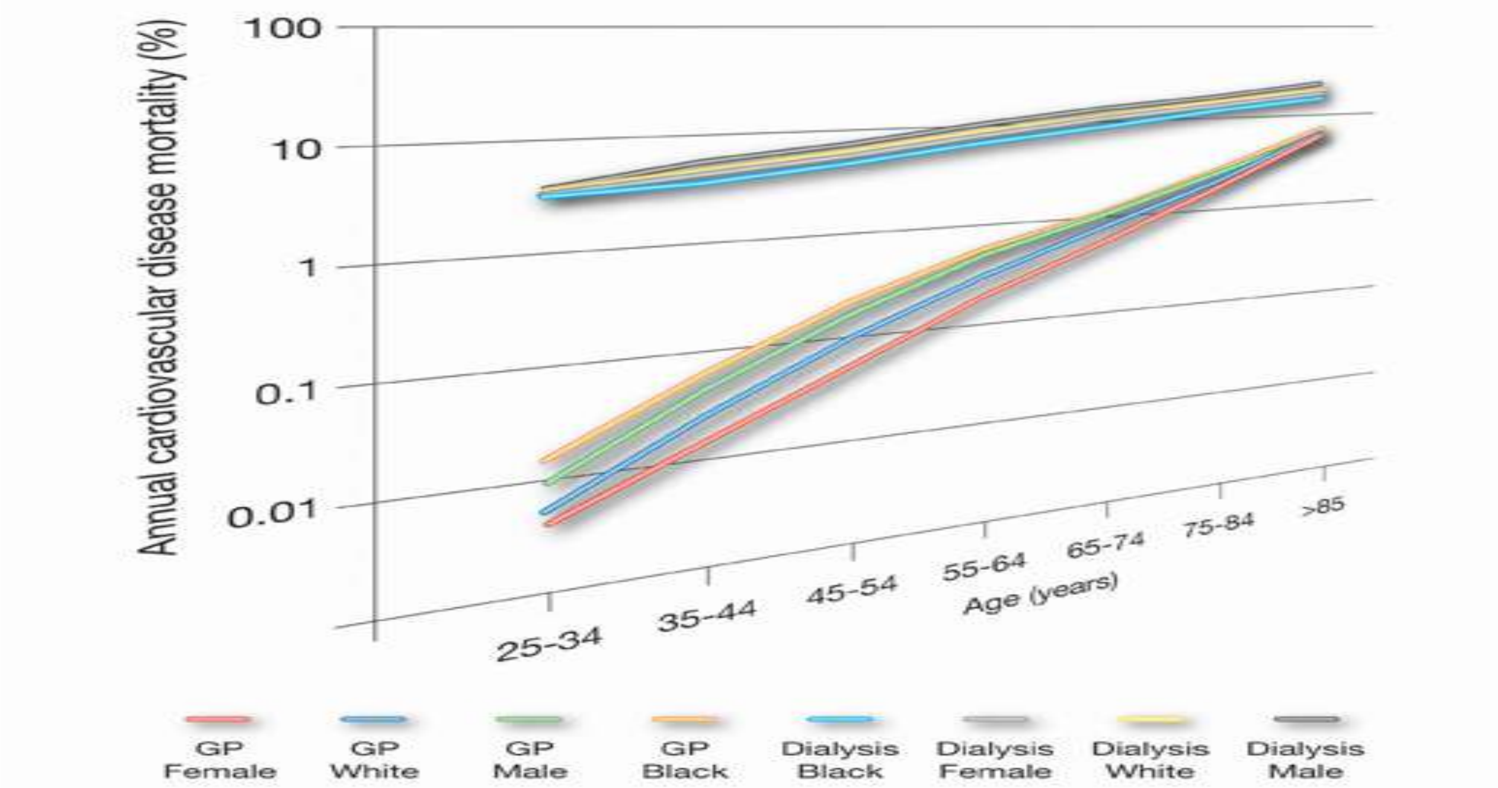
R Vanholder
University Hospital, Gent,
Belgium

SUMMARY

- **CKD: a devastating disease**
- **Role of the intestine in CKD morbidity**
  - Loss of intestinal integrity
  - Pro-inflammatory effect
  - Generation of uremic toxins
- **Potential impact of probiotics**
  - Anti-inflammatory effect
  - Decrease uremic toxin concentration

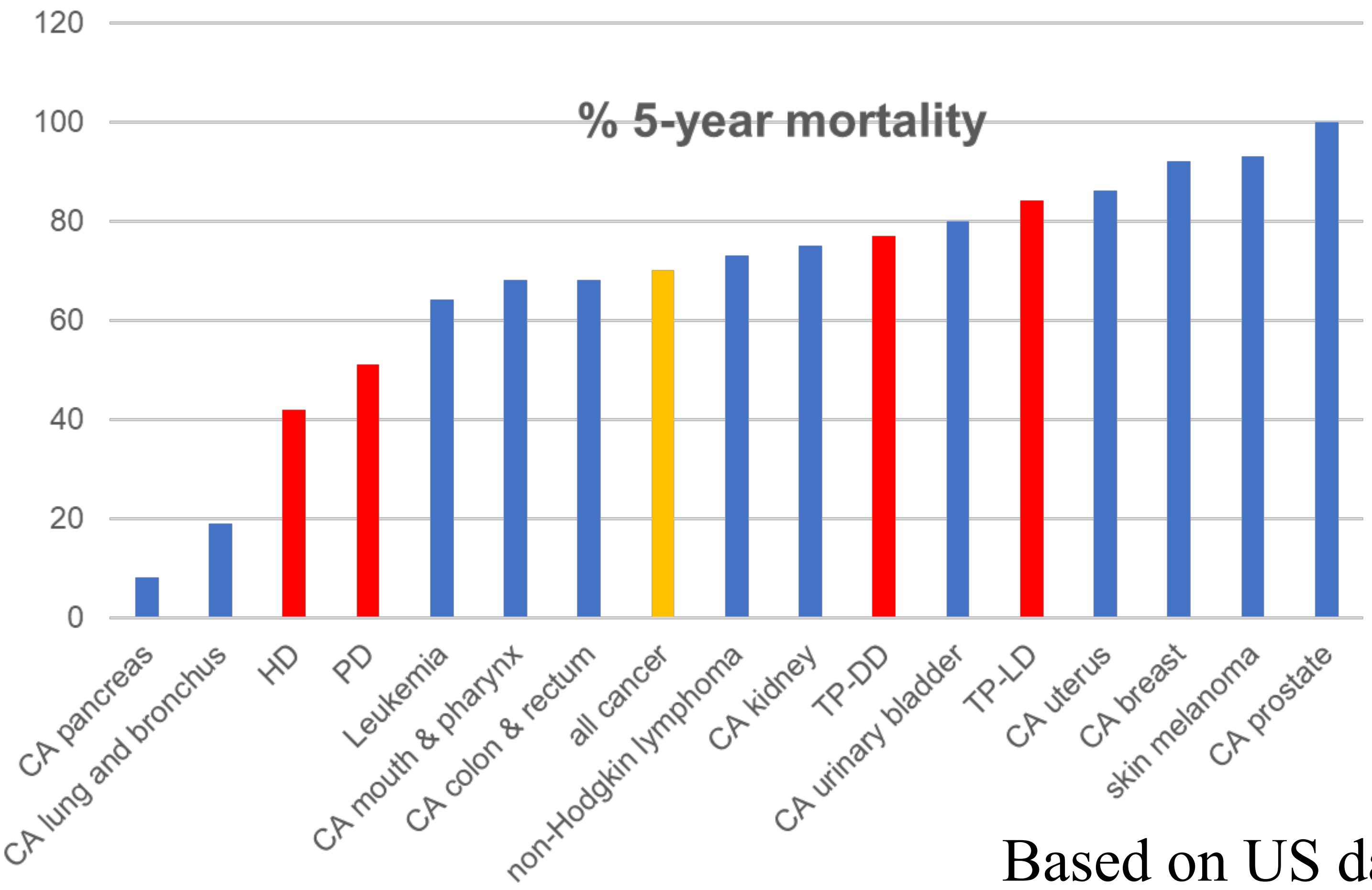
CKD IS A DEVASTATING DISEASE

CHRONIC KIDNEY DISEASE: THE MORTALITY CHALLENGE



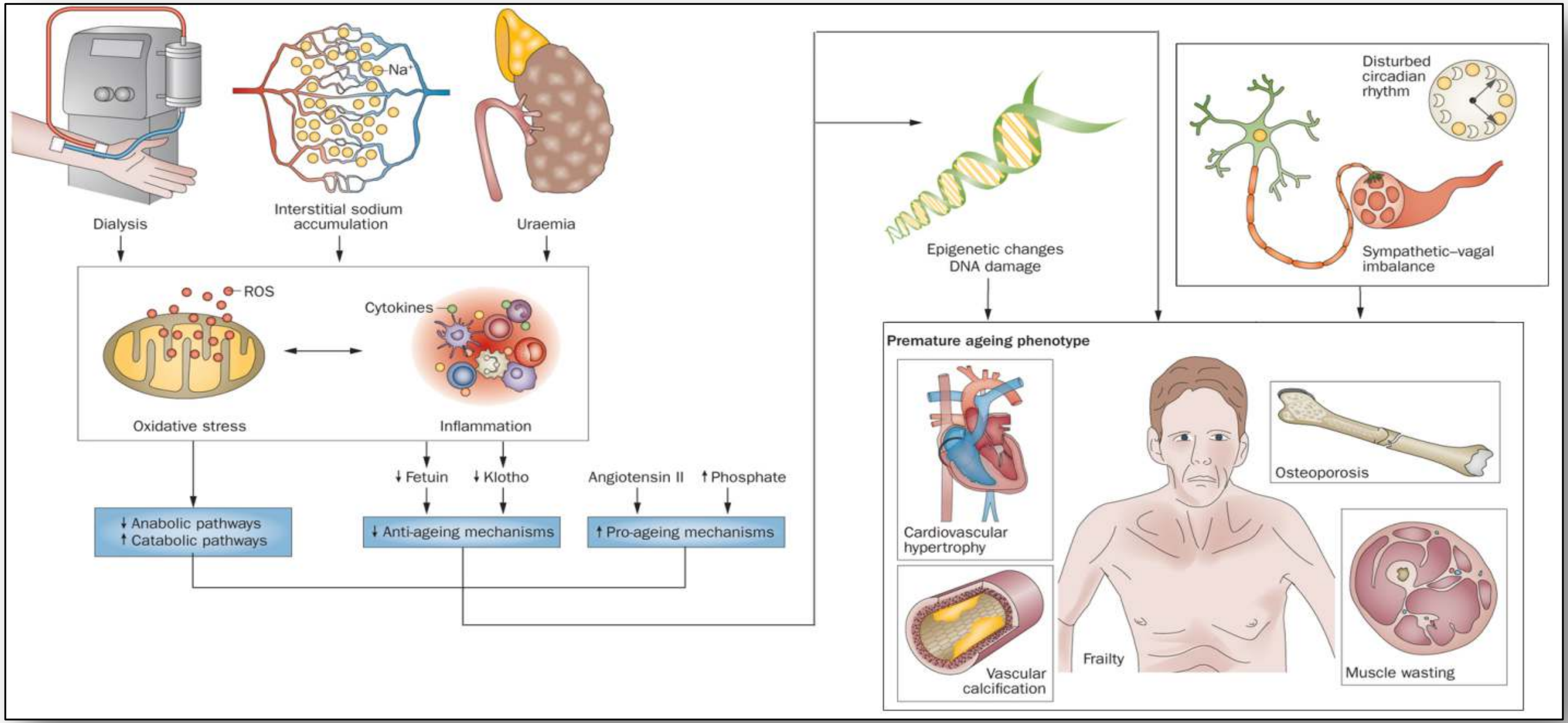
modified, Foley et al, AJKD, S3:S112-S119; 1998

MORTALITY DIALYSIS HIGHER THAN FOR CANCER

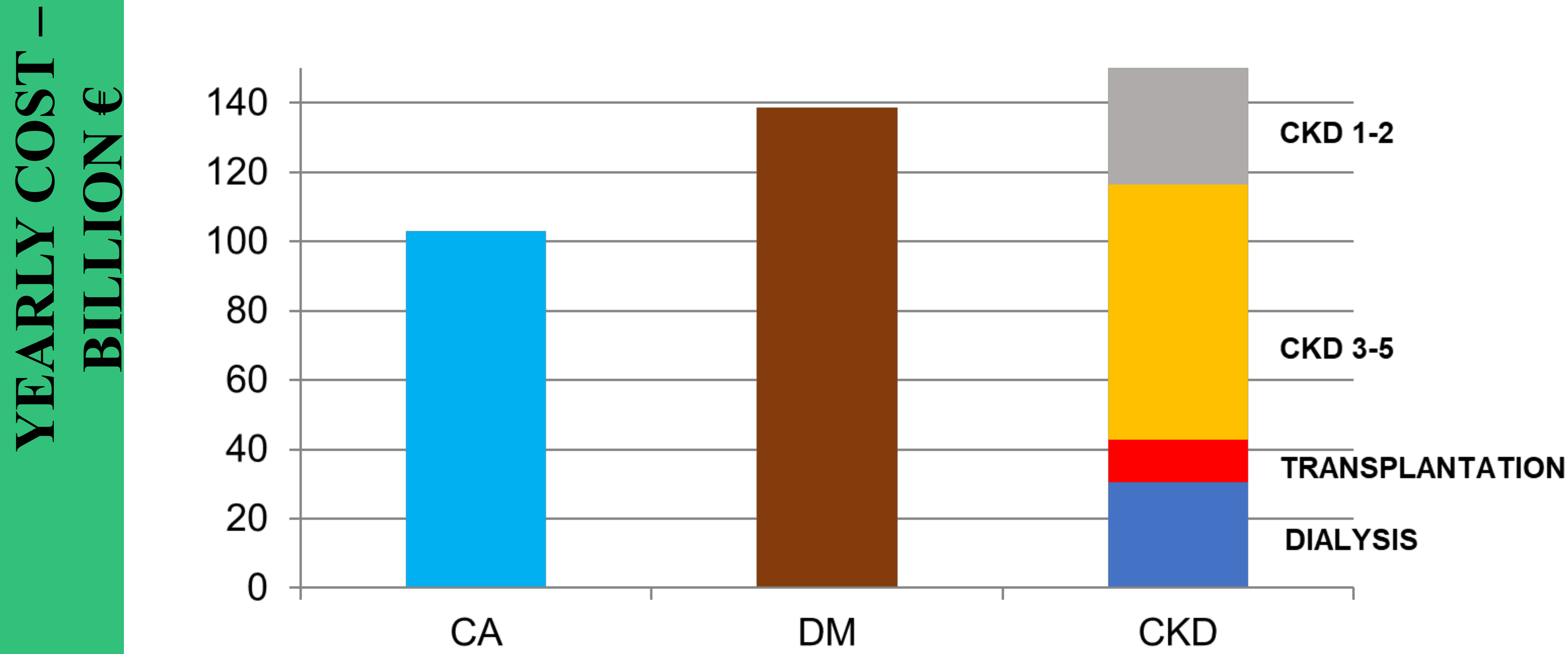


Based on US data

IN CKD VIRTUALLY ALL BIOCHEMICAL AND ORGANS SYSTEMS ARE AFFEECTED

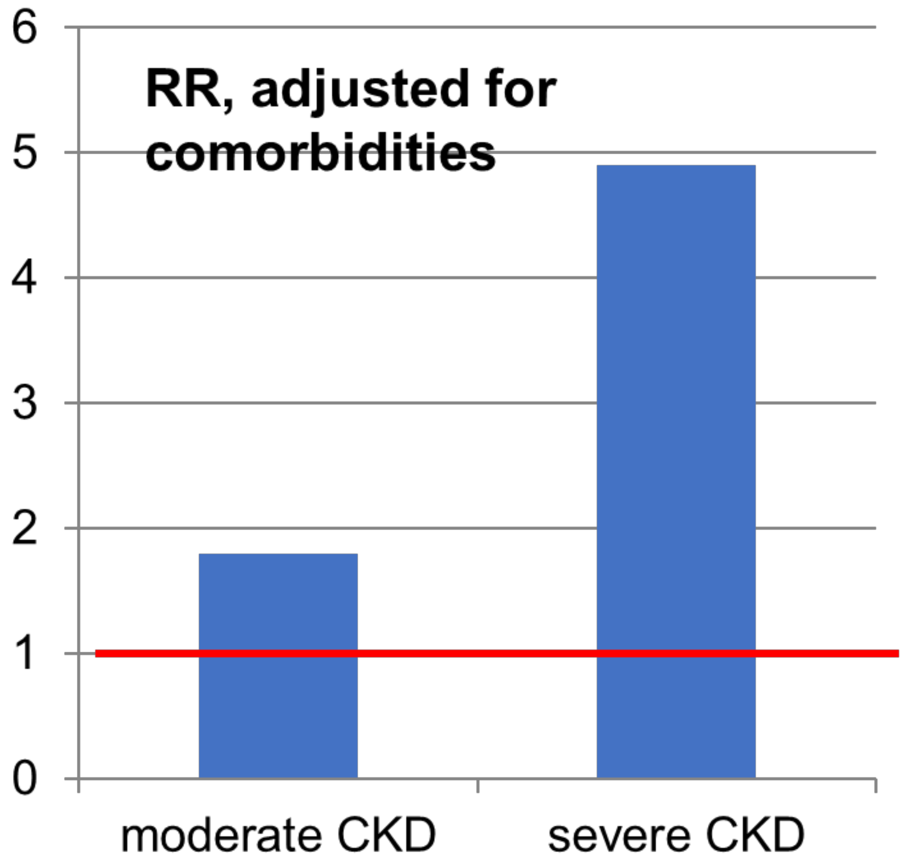


YEARLY AGGREGATED COST CKD ≥ CA/DM



Vanholder et al, unpublished

MORBIDITY AND MORTALITY ARE DUE TO CKD, NOT TO COMORBIDITIES



Fai Xan et al, JASN, 30, 1991-1999, 2019

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ROLE OF THE INTESTINE IN UREMIC MORBIDITY AND MORTALITY

CKD DISTURBS INTEGRITY OF THE INTESTINAL EPITHELIUM

Nephrol Dial Transplant (2012) 27: 2686–2693
doi: 10.1093/ndt/gfr624
Advance Access publication 29 November 2011

NDT Nephrology Dialysis Transplantation

Original Articles

Disintegration of colonic epithelial tight junction in uremia: a likely cause of CKD-associated inflammation

Nosratola D. Vaziri, Jun Yuan, Ardeshir Rahimi, Zhenmin Ni, Hyder Said and Veedamali S. Subramanian

Division of Nephrology and Hypertension, Department of Medicine, University of California, Irvine, CA, USA

Correspondence and offprint requests to: Nosratola D. Vaziri; E-mail: ndvaziri@uci.edu

Vaziri et al, NDT, 27, 2686-2693, 2011

CKD DISTURBS INTEGRITY OF THE INTESTINAL EPITHELIUM

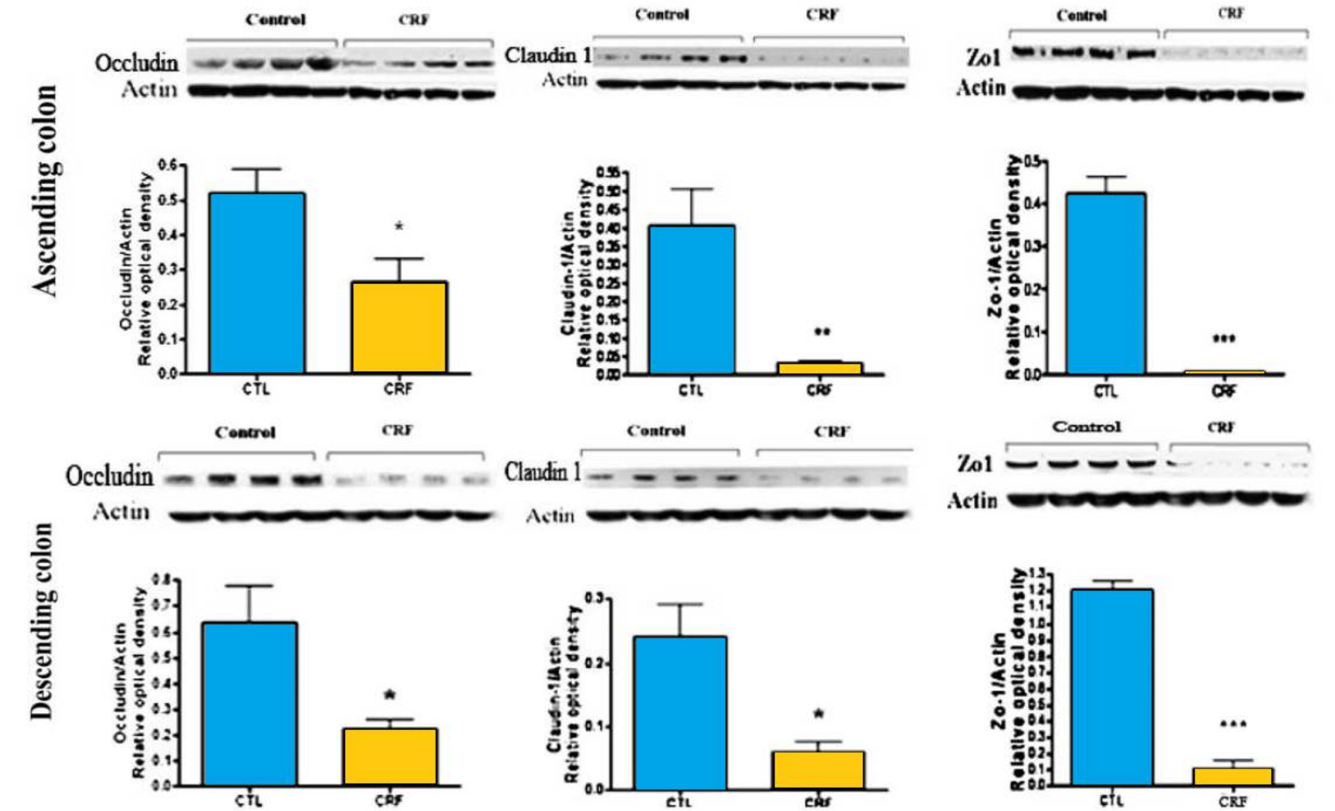


Fig. 2. Representative western blots and group data depicting protein abundance of occludin, claudin 1 and ZO-1 in the ascending and descending colonic tissues of the CKD and control (CTL) groups. *P < 0.05, **P < 0.001, ***P < 0.001, $N = 6$ animals in each group.

Vaziri et al, NDT, 27, 2686-2693, 2011

UREA DISRUPTS INTESTINAL WALL PROTECTIVE BARRIER

Original Report: Laboratory Investigation

American Journal of Nephrology

Am J Nephrol 2013;37:1–6
DOI: 10.1159/000345969

Received: October 22, 2012
Accepted: November 20, 2012
Published online: December 19, 2012

Role of Urea in Intestinal Barrier Dysfunction and Disruption of Epithelial Tight Junction in Chronic Kidney Disease

Nosratola D. Vaziri[a] Jun Yuan[a] Keith Norris[b]

[a]Division of Nephrology and Hypertension, University of California, Irvine, Calif., and [b]Department of Internal Medicine, Charles Drew University, Los Angeles, Calif., USA

Vaziri et al, Am J Nephrol, 37: 1-6; 2013

UREA DISRUPTS INTESTINAL WALL PROTECTIVE BARRIER

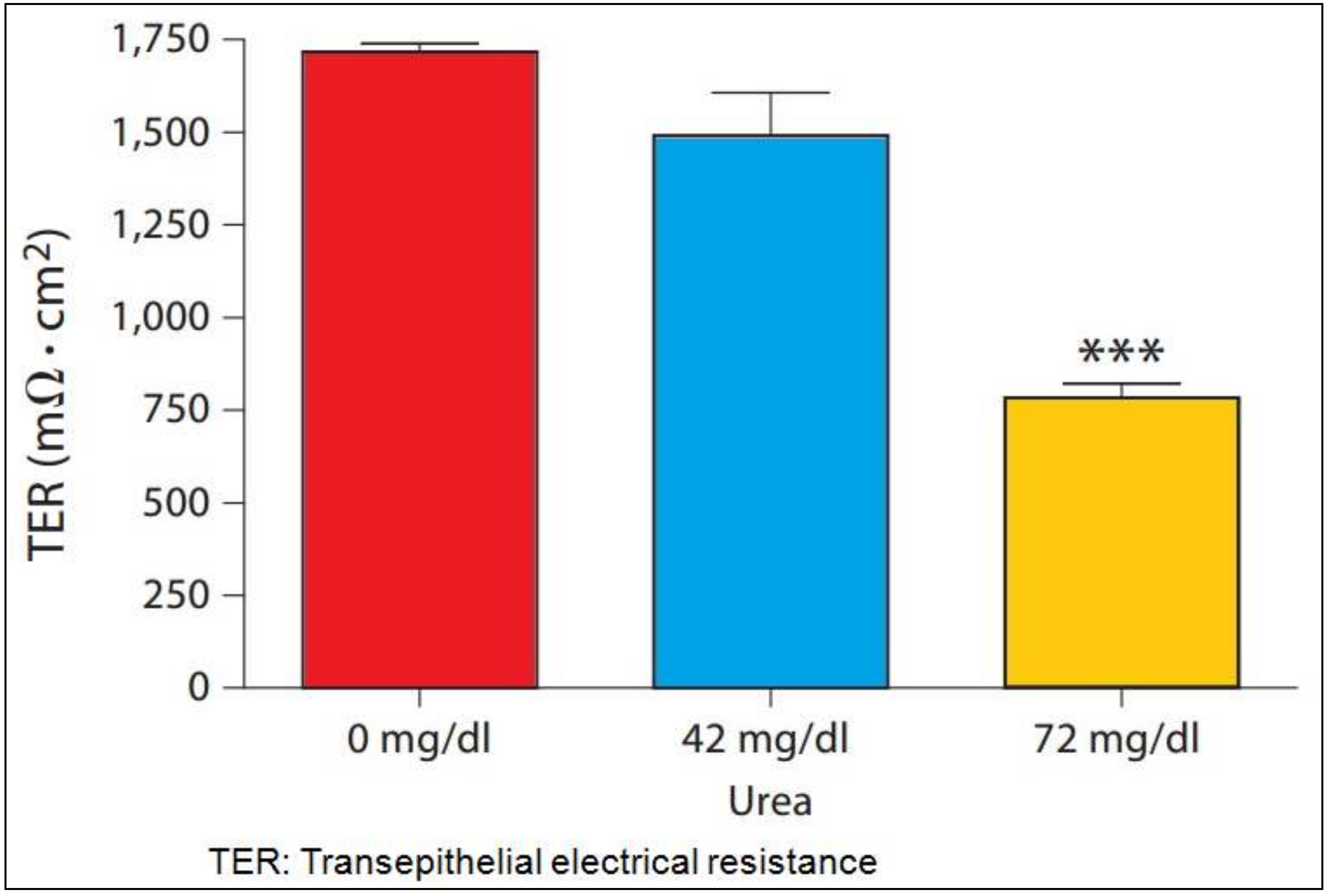


Figure 1
Bar graphs depicting the TER (transepithelial electrical resistance) in intestinal epithelial T84 cell monolayers incubated for 24 h in regular media and those incubated in media containing 42 or 72 mg/dl urea. *** $p < 0.001$.

Vaziri et al, Am J Nephrol, 37: 1-6; 2013

CKD IS ASSOCIATED WITH TRANSLOCATION OF GUT BACTERIAL DNA – GUT GENUS DETECTED IN BLOOD (% OF TOTAL GUT GENUS)

NEPHROLOGY

Nephrology 17 (2012) 733–738

Original Article

Gut bacterial translocation is associated with microinflammation in end-stage renal disease patients

FEIQIAN WANG,[1] HONGLI JIANG,[1] KEHUI SHI,[1] YI REN,[1] PAN ZHANG[1] and SHAOLI CHENG[2]

[1]Dialysis Department of Nephrology Center, First Affiliated Hospital of Medicine School, Xi'an Jiaotong University, [2]Morphological Experiment Centre, Medicine School of Xi'an Jiaotong University, Xi'an, Shaanxi, China

KEY WORDS:
bacteria translocation, end-stage renal disease, gut, microbiome dysbiosis, microinflammation.

Correspondence:
Dr Hongli Jiang, Dialysis Center of First Affiliated Hospital of Medicine School, Xi'an Jiaotong University, Xi'an, Shaanxi 710061, China. Email: j92106@sina.com

Accepted for publication 16 July 2012.
Accepted manuscript online 23 July 2012.

doi:10.1111/j.1440-1797.2012.01647.x

SUMMARY AT A GLANCE

Wang *et al*. evaluated the bacterial translocation in the intestinal tract in non-dialysed ESRD patients and its contribution to micoinflammation in the patient population.

ABSTRACT

Aim: To investigate whether gut bacteria translocation occurs in end-stage renal disease patients and contributes to microinflammation in end-stage renal disease (ESRD).

Methods: The subjects were divided into two groups: nondialysed ESRD patients (n = 30) and healthy controls (n = 10). Blood samples from all participants were subjected to bacterial 16S ribosomal DNA amplification and DNA pyrosequencing to determine the presence of bacteria, and the alteration of gut microbiomes were examined with the same methods. High-sensitive C-reactive protein and interleukin-6 were detected. Plasma D-lactate was tested for gut permeability.

Results: Bacterial DNAs were detected in the blood of 20% (6/30) of the ESRD patients. All the observed genera in blood (*Klebsiella* spp, *Proteus* spp, *Escherichia* spp, *Enterobacter* spp, and *Pseudomonas* spp) were overgrown in the guts of the ESRD patients. Plasma D-lactate, High-sensitive C-reactive protein, and interleukin-6 levels were significantly higher in patients with bacterial DNA than those without. The control group showed the same results as that of patients without bacterial DNA.

Conclusion: Bacterial translocation occurs in ESRD patients and is associated with microinflammation in end stage renal disease.

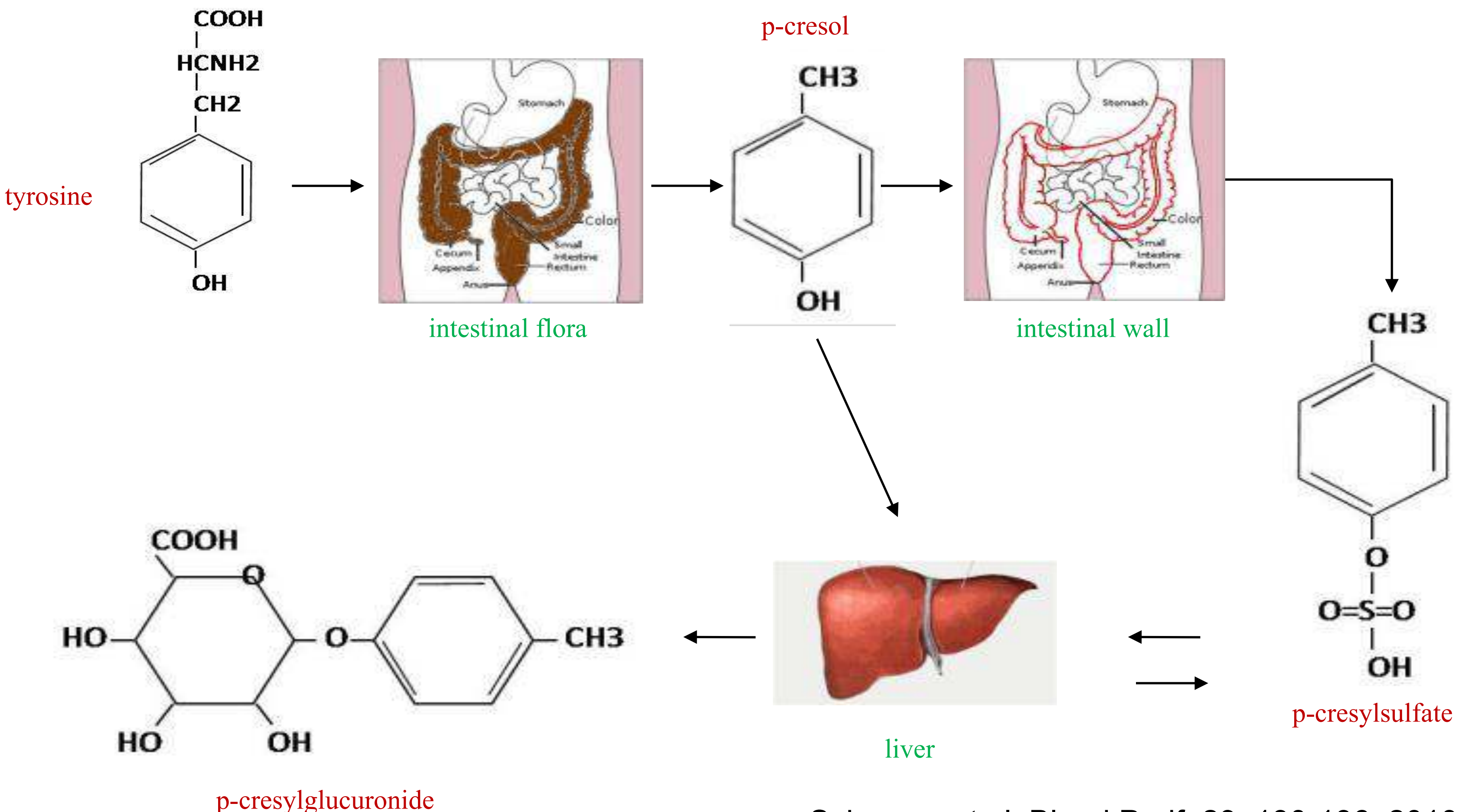
Wang et al, Nephrology, 17: 733-738; 2012

CKD IS ASSOCIATED WITH TRANSLOCATION OF GUT BACTERIAL DNA – GUT GENUS DETECTED IN BLOOD (% OF TOTAL GUT GENUS)

	Controls (n=10)	ESRD (n=30)	P
Klebsiella spp	0.60	1.93	0.037
Proteus spp	0.12	10.61	0.011
Escherichia spp	0.42	4.33	0.045
Enterobacter spp	0	0.42	0.001
Pseudomonas spp	0.04	0.23	0.014

Wang et al, Nephrology, 17: 733-736; 2012

ROLE INTESTINE IN GENERATION CRESOLS



Schepers et al, Blood Purif, 29: 130-136; 2010

BRIEF REVIEW www.jasn.org

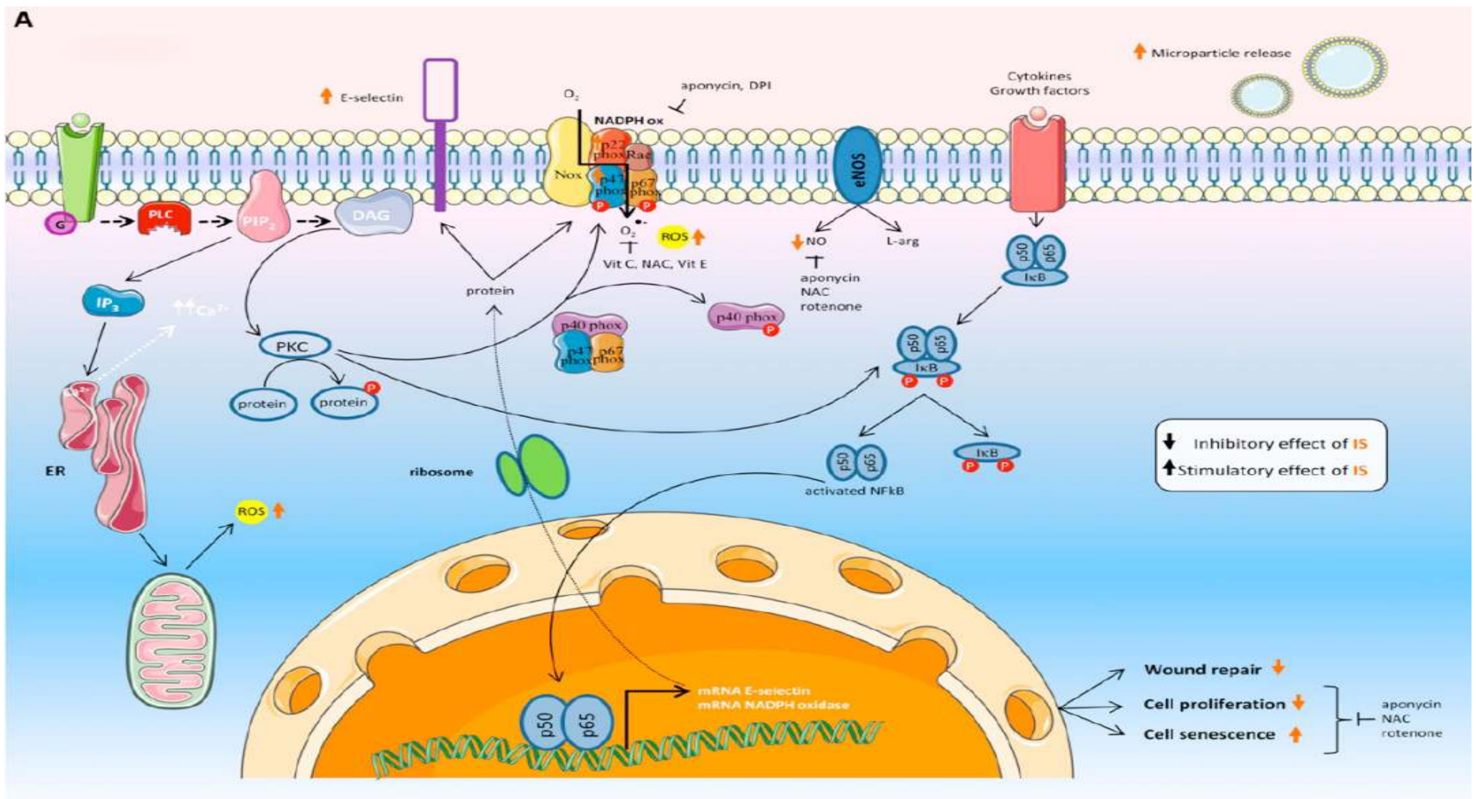
The Uremic Toxicity of Indoxyl Sulfate and p-Cresyl Sulfate: A Systematic Review

Raymond Vanholder, Eva Schepers, Anneleen Pletinck, Evi V. Nagler, and Griet Glorieux

Nephrology Section, Ghent University Hospital, Ghent, Belgium

Vanholder et al, JASN, 25:1897-1907; 2014

INDOXYLSULFATE AND P-CRESYLSULFATE HAVE BEEN LINKED TO A MYRIAD OF TOXIC EFFECTS:



Vanholder et al, JASN, 25, 1897-1907, 2014

TMAO ENHANCES ATHEROGENESIS

ARTICLE

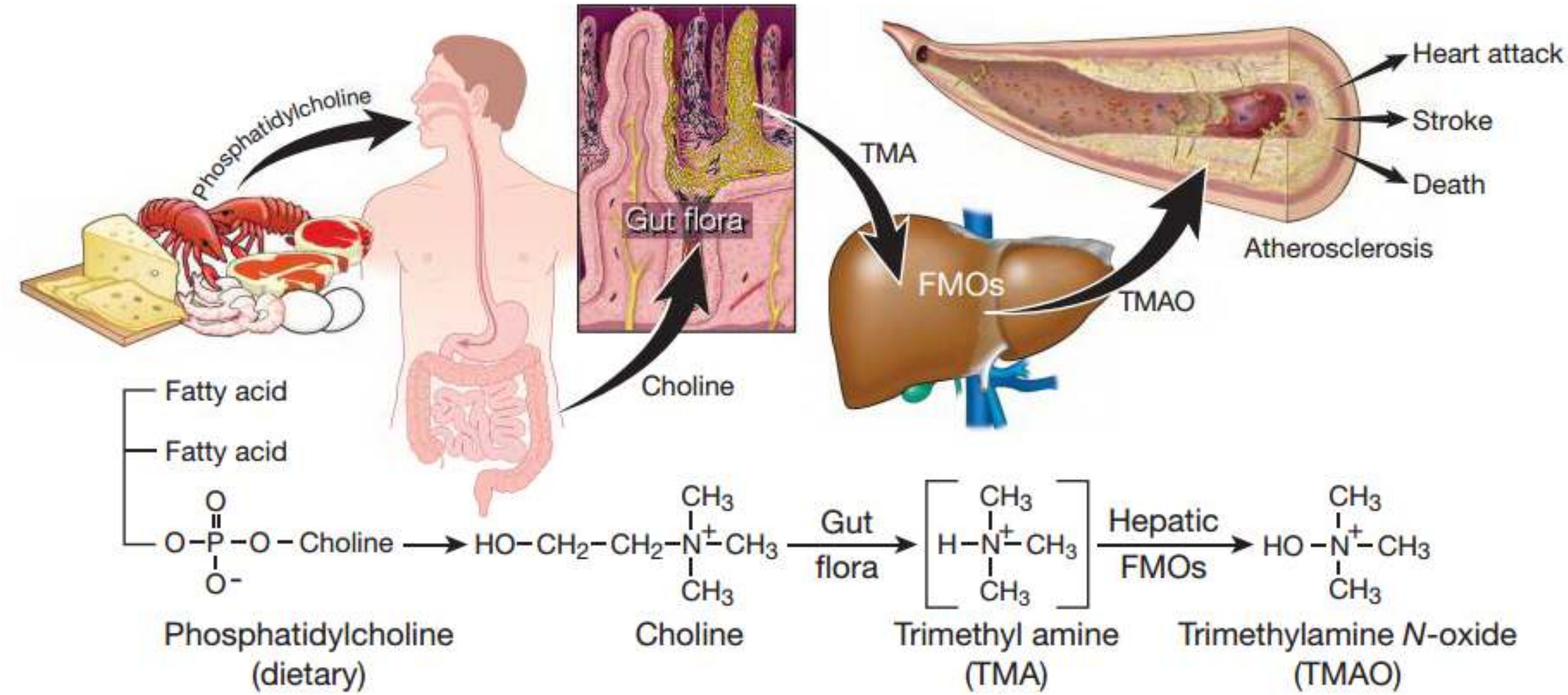
doi:10.1038/nature09922

Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease

Zeneng Wang[1,2], Elizabeth Klipfell[1,2], Brian J. Bennett[3], Robert Koeth[1], Bruce S. Levison[1,2], Brandon DuGar[1], Ariel E. Feldstein[1,2], Earl B. Britt[1,2], Xiaoming Fu[1,2], Yoon-Mi Chung[1,2], Yuping Wu[4], Phil Schauer[5], Jonathan D. Smith[1,6], Hooman Allayee[7], W. H. Wilson Tang[1,2,6], Joseph A. DiDonato[1,2], Aldons J. Lusis[3] & Stanley L. Hazen[1,2,6]

Wang et al, Nature, 472: 57-63; 2011

TMAO ENHANCES ATHEROGENESIS



Role of intestinal microbiota: effect precursors TMAO neutralized by antibiotics

Wang et al, Nature, 472: 57-63; 2011

International Journal of *Molecular Sciences*

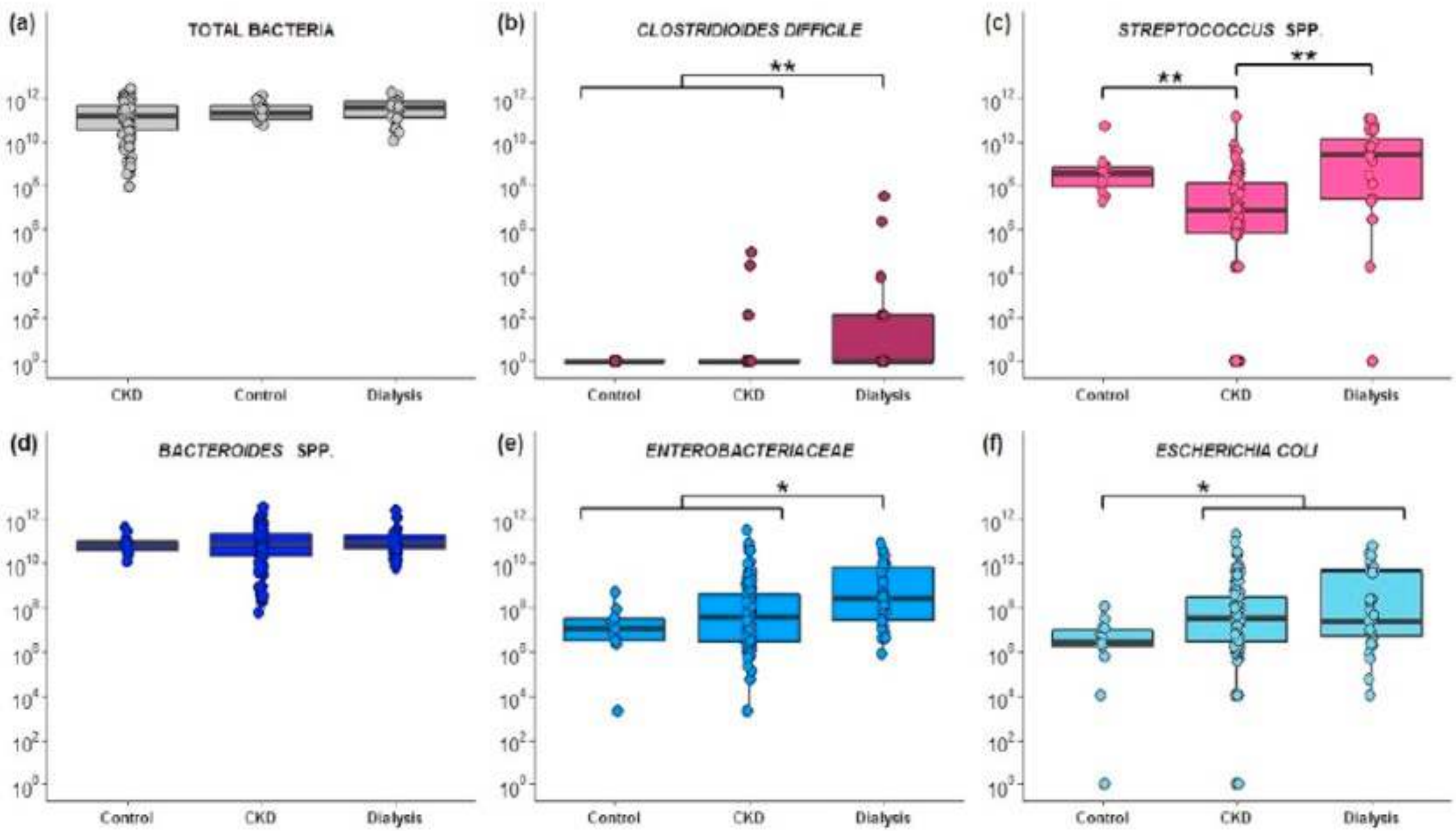
MDPI

Article

Isolation and Quantification of Uremic Toxin Precursor-Generating Gut Bacteria in Chronic Kidney Disease Patients

Tessa Gryp [1,2,3,*], Geert R.B. Huys [3], Marie Joossens [3], Wim Van Biesen [1], Griet Glorieux [1,†] and Mario Vaneechoutte [2,†]

INTESTINAL MICROBIOTA CHANGE IN CKD

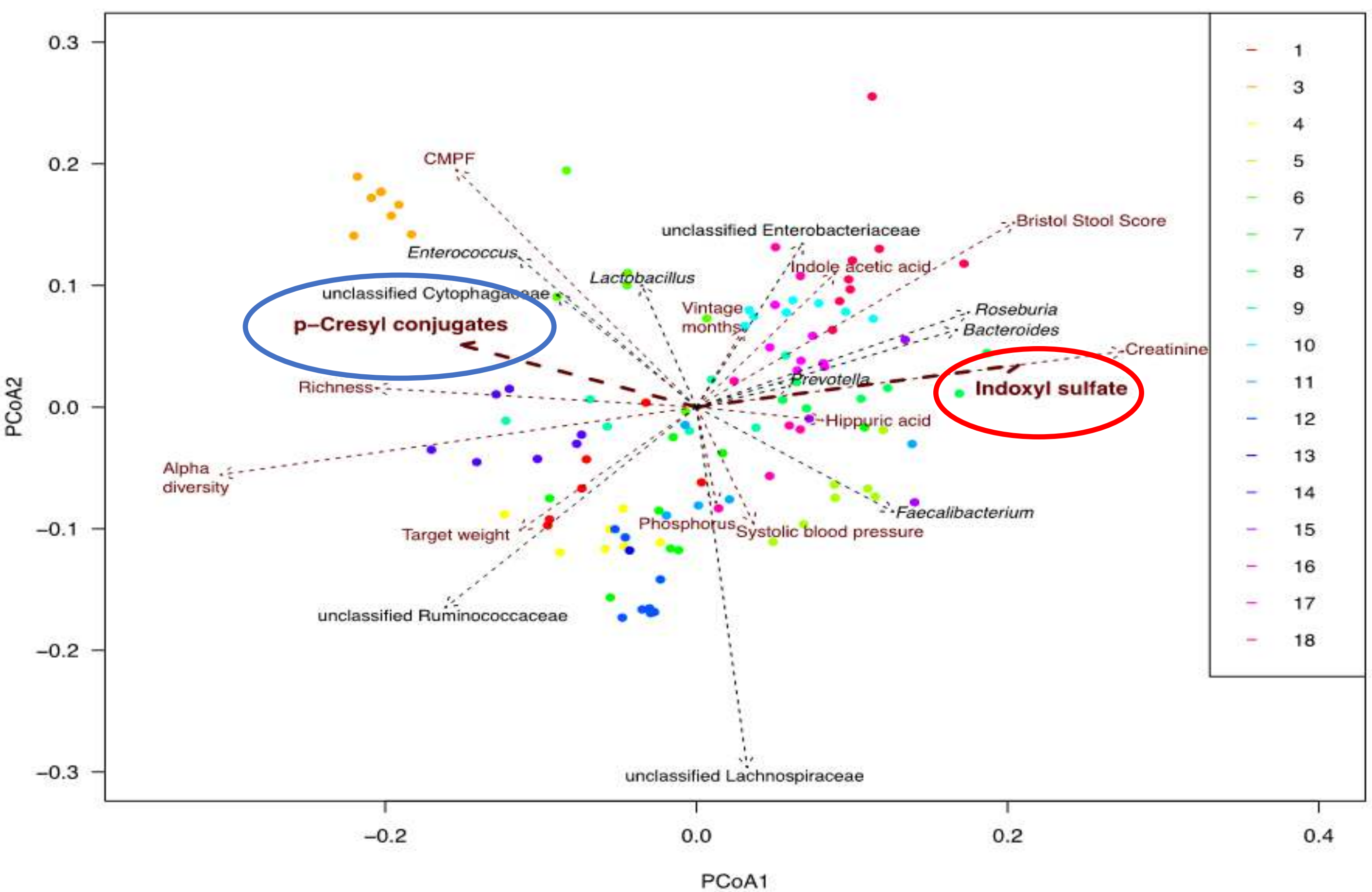


Gryp et al, Int J Mol Sci, 21, 1986, 2020

Gut microbiota dynamics and uraemic toxins: one size does not fit all

Marie Joossens,[1,2] Karoline Faust,[1]
Tessa Gryp,[1,3,4] Anh Thi Loan Nguyen,[5]
Jun Wang,[1,2,6] Sunny Eloot,[3] Eva Schepers,[3]
Annemieke Dhondt,[3] Anneleen Pletinck,[3]
Sara Vieira-Silva,[1,2] Gwen Falony,[1,2]
Mario Vaneechoutte,[4] Raymond Vanholder,[3]
Wim Van Biesen,[3] Geert Roger Bertrand Huys,[1,2]
Jeroen Raes,[1,2] Griet Glorieux[3]

TOXINS STEM FROM DIFFERENT MICROBIOTA



Joostens et al, Gut, 68, 2257-2260, 2019

NO INCREASE IN INTESTINAL GENERATION IN CKD

www.kidney-international.org clinical investigation

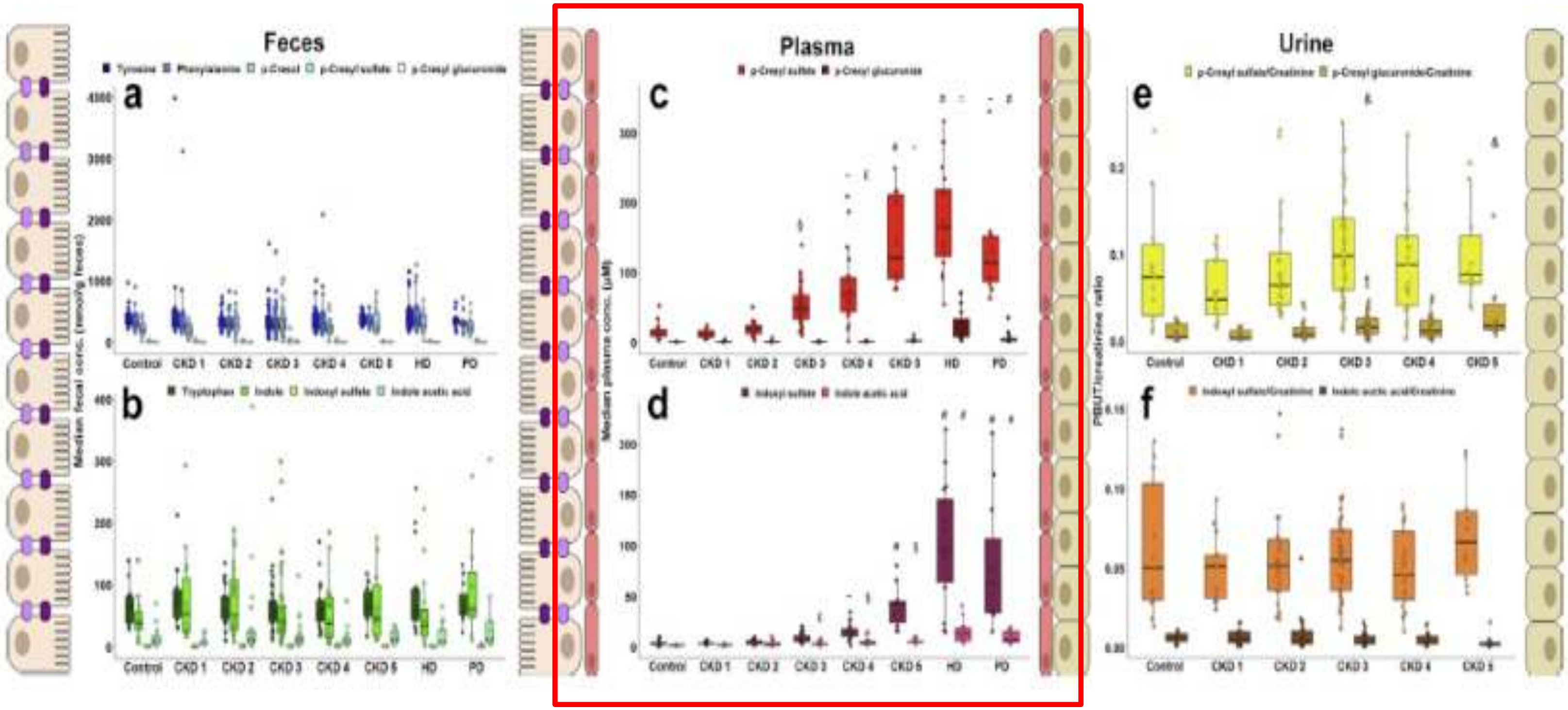
Gut microbiota generation of protein-bound uremic toxins and related metabolites is not altered at different stages of chronic kidney disease

OPEN

Tessa Gryp[1,2,3], Kim De Paepe[4], Raymond Vanholder[1], Frederiek-Maarten Kerckhof[4], Wim Van Biesen[1], Tom Van de Wiele[4], Francis Verbeke[1], Marijn Speeckaert[1], Marie Joossens[3], Marie Madeleine Couttenye[5], Mario Vaneechoutte[2] and Griet Glorieux[1]

Gryp et al, KI, 97, 1230-1242, 2020

NO INCREASE IN INTESTINAL GENERATION IN CKD



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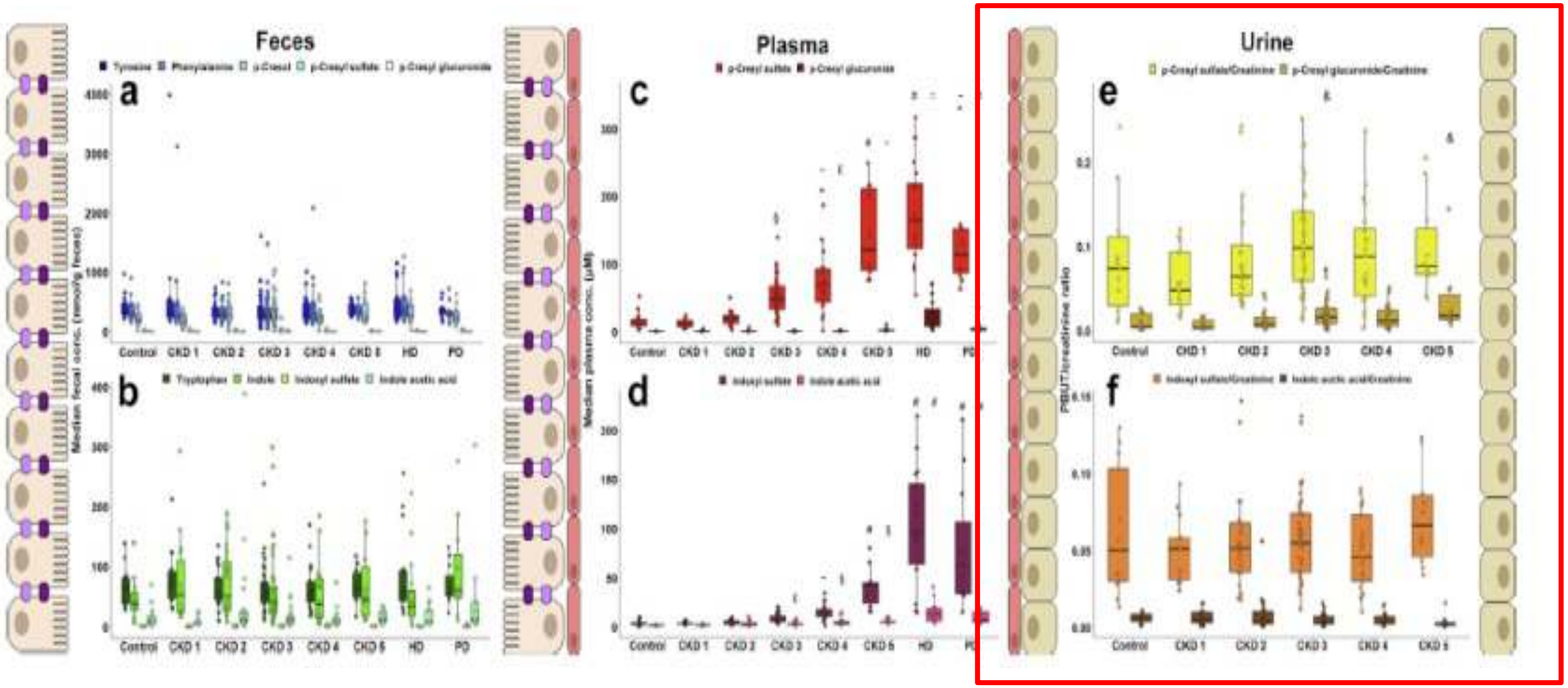
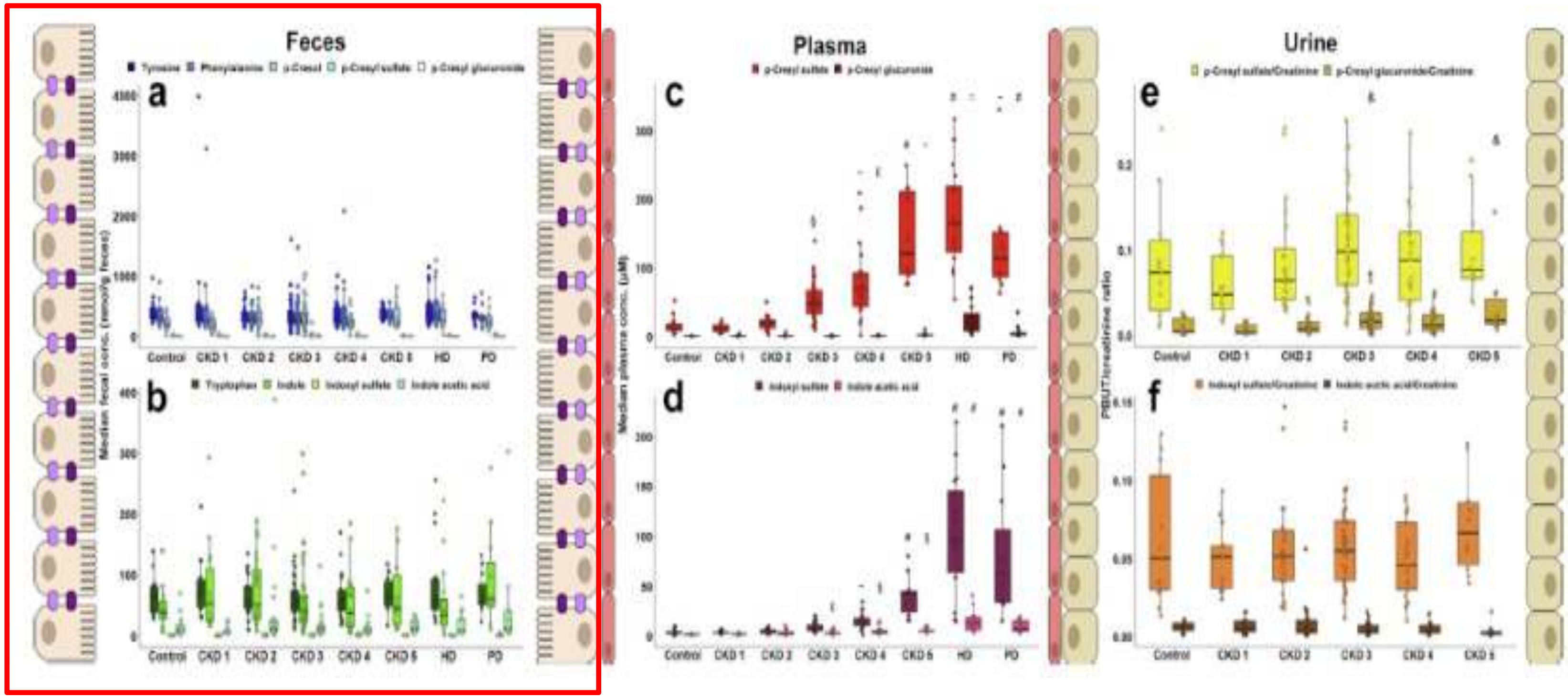
NO INCREASE IN INTESTINAL GENERATION IN CKD



Gryp et al, KI, 97, 1230-1242, 2020

NO INCREASE IN INTESTINAL GENERATION IN CKD



Gryp et al, KI, 97, 1230-1242, 2020

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THERAPEUTIC OPTIONS

THERAPEUTIC OPTIONS

- Diet
  - Cave malnutrition
- Prebiotics
  - Non-digestible compounds beneficially modifying composition and/or function of intestinal flora
- Probiotics
  - Bacteria adminstered as food components or supplements providing specific benefits themselves
- Synbiotics
  - Prebiotics + probiotics
- Sorbents

Schepers et al, Blood Purif, 29: 130-136; 2010

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Schepers et al, Blood Purif, 29: 130-136; 2010

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INFLAMMATION

ANTI-INFLAMMATORY EFFECT PROBIOTICS: DECREASE CRP – META-ANALYSIS

nutrients
MDPI

Review

Impact of Probiotic Administration on Serum C-Reactive Protein Concentrations: Systematic Review and Meta-Analysis of Randomized Control Trials

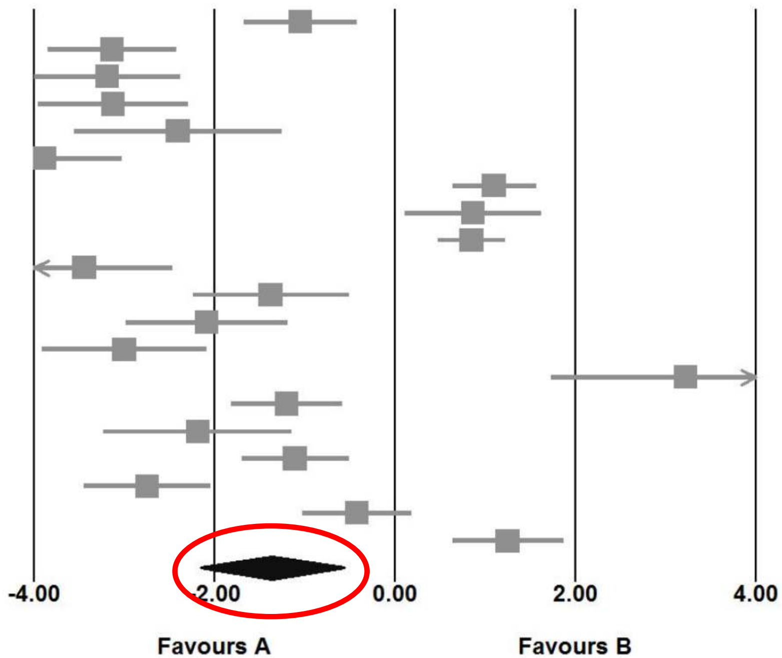
Mohsen Mazidi [1,2], Peyman Rezaie [3], Gordon A. Ferns [4] and Hassan Vatanparast [5,*]

Mazidi et al, Nutrients, 9:20; 2017

ANTI-INFLAMMATORY EFFECT PROBIOTICS: DECREASE CRP – META-ANALYSIS

Std diff in means and 95% CI

Study name	Variance
Alipour B,2014 [6]	0.099
Asemi Z,2011 [40]	0.127
Asemi Z,2012 [47]	0.168
Gøbel R,2012 [48]	0.178
Hatakka K,2003 [26]	0.339
jenks K,2010 [8]	0.186
Kajnder K,2008 [41]	0.054
Leber B,2012 [49]	0.146
McNaught C,2002 [50]	0.034
Natarajan R,2014 [45]	0.242
Ozkan T, 2007 [42]	0.188
Rajkumar H,2014 [51]	0.206
Rajkumar H,2014 [52]	0.212
Ranganathan N,2009 [53]	0.575
Sharma B,2011 [44]	0.095
Stiksrud B,2015 [54]	0.277
Tan M,2011 [46]	0.089
Valentini L,2015 [43]	0.125
Villar-García J,2015 [55]	0.093
Zarrati M,2014 [56]	0.096
	0.166



Mazidi et al, Nutrients, 9:20; 2017

SALT INTAKE, INFLAMMATION AND HYPERTENSION

ARTICLE

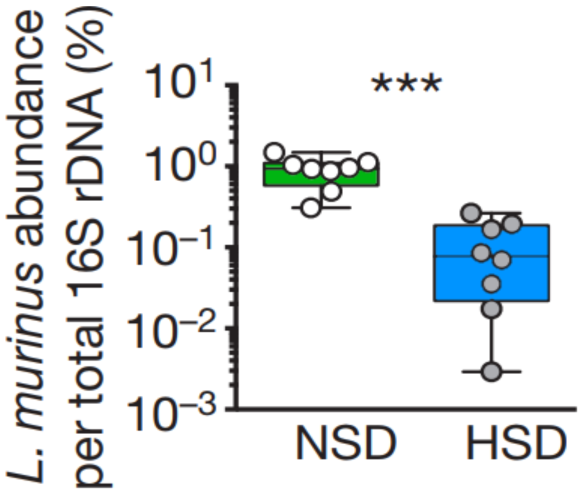
doi:10.1038/nature24628

Salt-responsive gut commensal modulates T_H17 axis and disease

Nicola Wilck[1,2,3,4,5], Mariana G. Matus[6,7], Sean M. Kearney[6], Scott W. Olesen[6], Kristoffer Forslund[8], Hendrik Bartolomaeus[1,2,3,4], Stefanie Haase[9], Anja Mähler[1,5], András Balogh[1,2,3,4,5], Lajos Markó[1,2,3,4,5], Olga Vvedenskaya[3,10,11], Friedrich H. Kleiner[1], Dmitry Tsvetkov[1,2], Lars Klug[1,5], Paul I. Costea[8], Shinichi Sunagawa[8,12], Lisa Maier[13], Natalia Rakova[1,9], Valentin Schatz[14], Patrick Neubert[14], Christian Frätzer[15], Alexander Krannich[5], Maik Gollasch[1,2,3], Diana A. Grohme[16], Beatriz F. Côrte-Real[17], Roman G. Gerlach[18], Marijana Basic[19], Athanasios Typas[13], Chuan Wu[20], Jens M. Titze[21], Jonathan Jantsch[14], Michael Boschmann[1,5], Ralf Dechend[1,2,5], Markus Kleinewietfeld[16,17,22], Stefan Kempa[3,5,10], Peer Bork[3,8,23,24], Ralf A. Linker[9]§, Eric J. Alm[6]§ & Dominik N. Müller[1,2,3,4,5]§

Wilck et al, Nature, 7682: 585-589; 2017

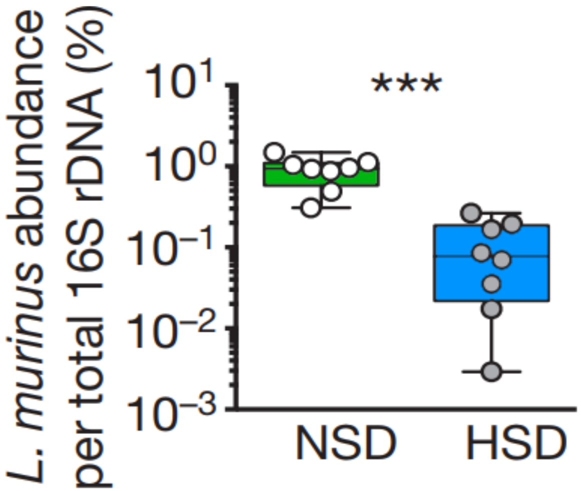
SALT INTAKE, INFLAMMATION AND HYPERTENSION

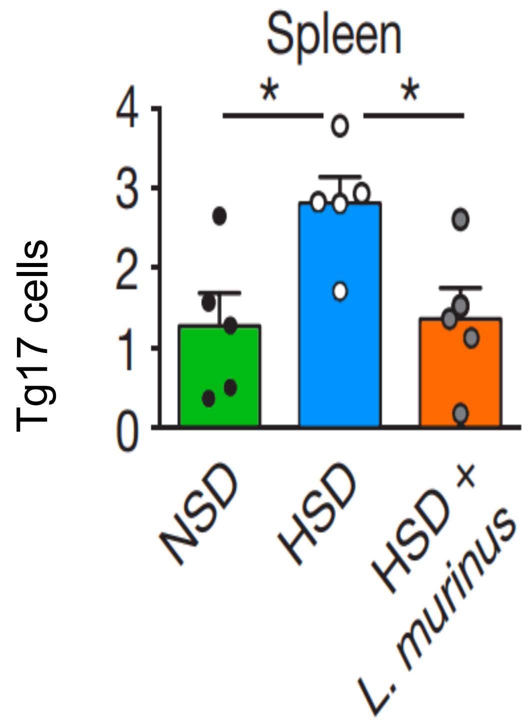


NSD: normal salt diet
HSD: high salt diet
L. murinus: Lactobacillus murinus

Wilck et al, Nature, 7682: 585-589; 2017

SALT INTAKE, INFLAMMATION AND HYPERTENSION





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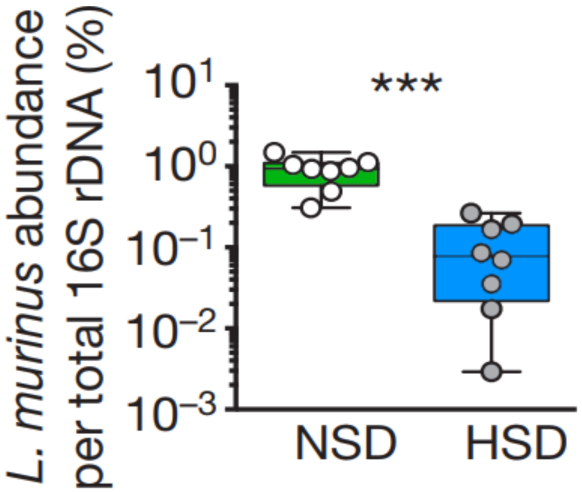
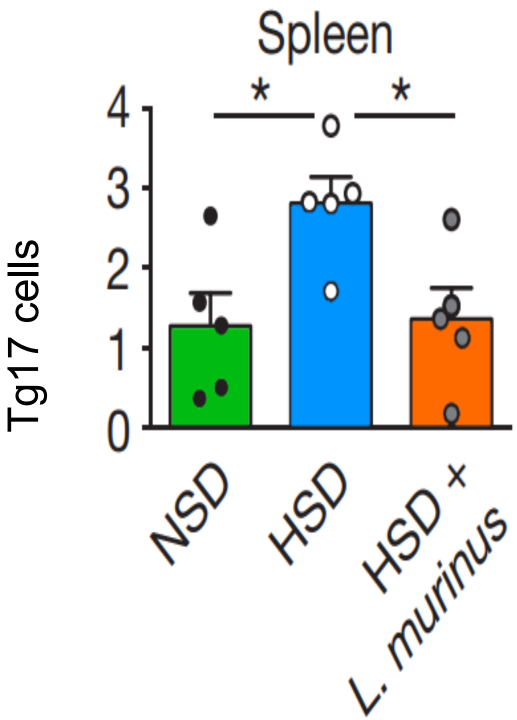
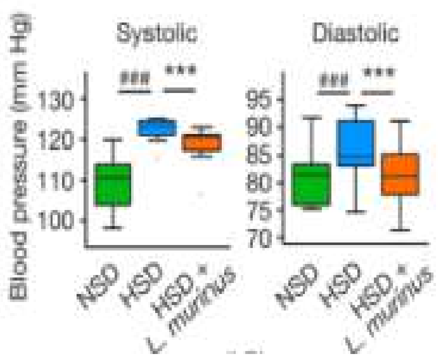
SALT INTAKE, INFLAMMATION AND HYPERTENSION







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UREMIC TOXIN CONCENTRATION

DECREASE UREMIC TOXINS WITH SYNBIOTICS: RCT

Article

Synbiotics Easing Renal Failure by Improving Gut Microbiology (SYNERGY): A Randomized Trial

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Rossi et al, cJASN, 11: 223-231; 2016

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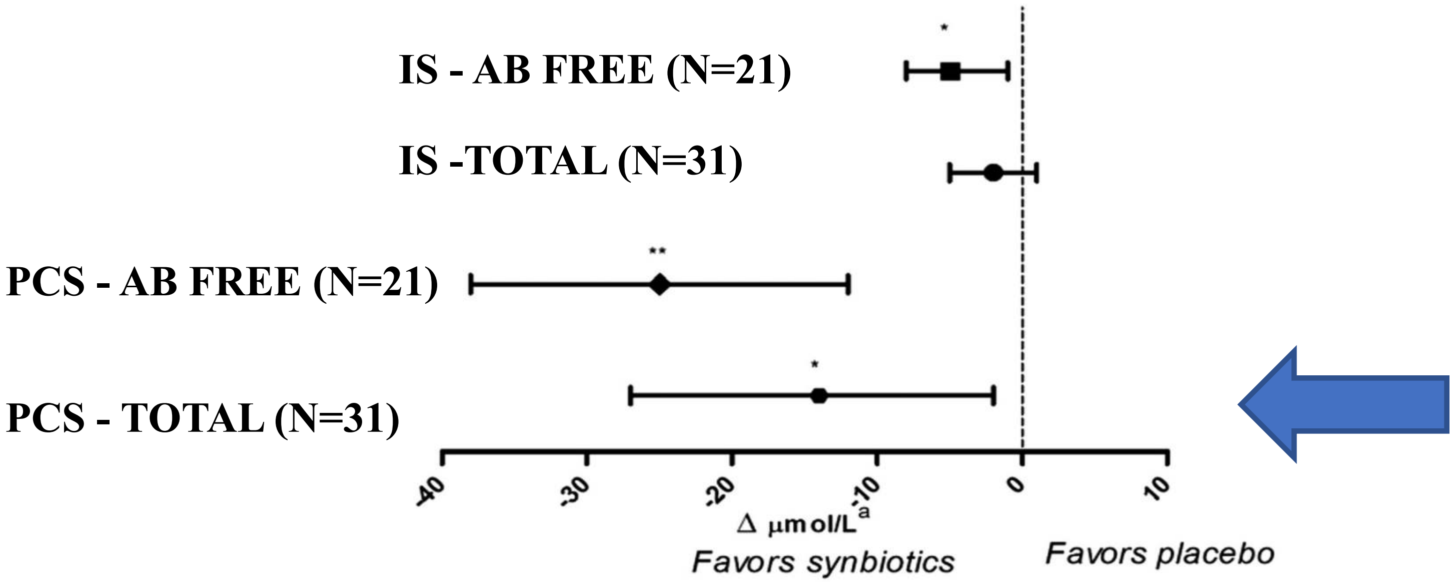

[a] Treatment effect (95% CI) derived from regression modelling accounting for period effect
* p=0.03
** p=0.001

Figure 3. Treatment effect of synbiotics on serum uremic toxins in all completing patients *(n=31) and patients who were antibiotic free (n=21).* [a]*Treatment effect (95% confidence interval) derived from regression modeling accounting for period effect. *P=0.03; **P=0.001.*

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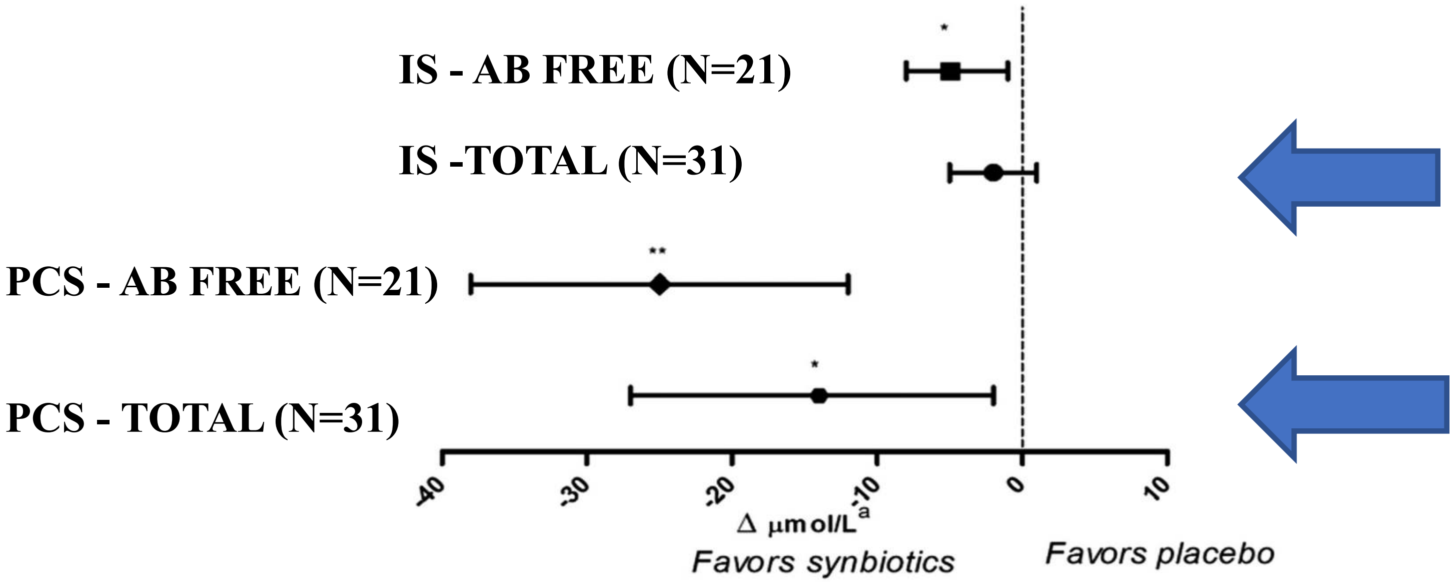

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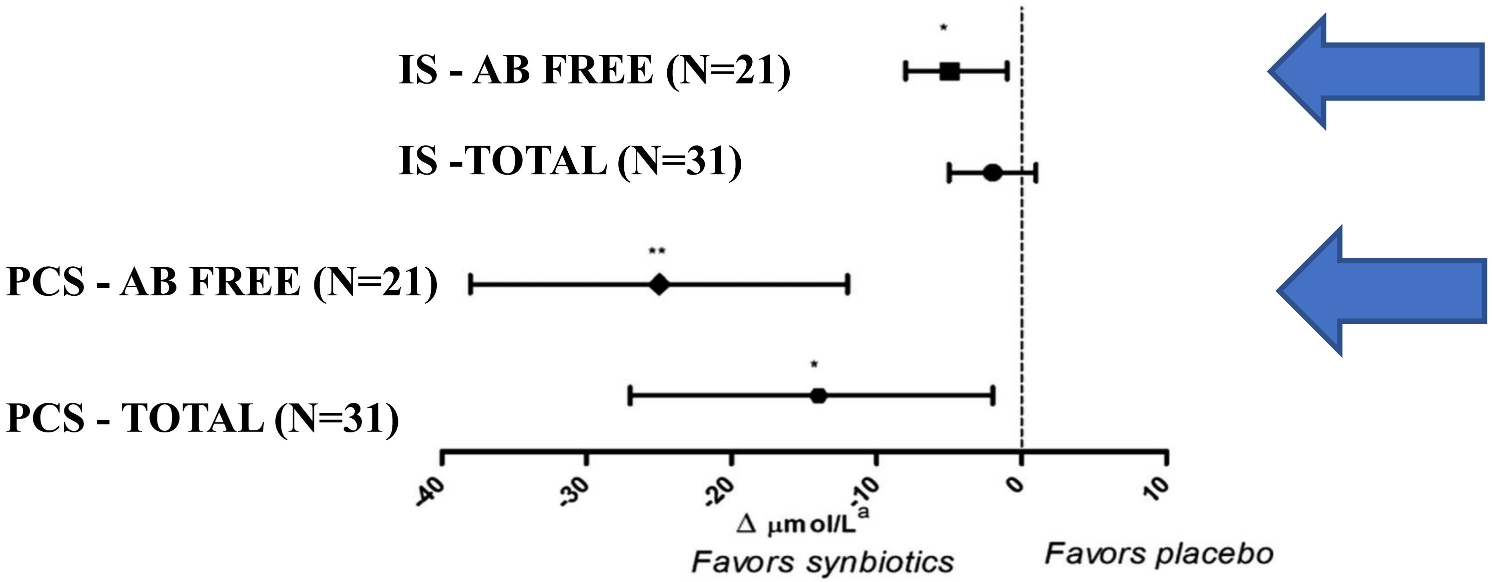

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Rossi et al, cJASN, 11: 223-231; 2016

PROBIOTICS DECREASE UREMIC TOXINS

Author	Reference	Toxin
Garcia-Arroyo et al	Plos One, 13, e0202901, 2018	Uric acid
Dunn et al	Int Dairy J, 8, 545-553, 1998	DMA, NDMA
Takayama et al	AJKD, 41 (Suppl 1), S142-S145, 2003	Indoxyl sulfate
Guida at al	Nutr Metab Cardiovasc Dis, 24, 1043-1049, 2014	P-cresol
Simeoni et al	Eur J Nutr, doi: 10.1007/s00394-018-1785-z	β2-M, PTH
Thongprayoon et al	Digest Dis Sci, doi: 10.1007/s10620-018-5243-9	PBUT
Firouzi et al	Nutrition, 51-52, 104-113, 2018	Urea
Saggi et al	Int J Probiot Prebiot, 12, 43-54, 2017	Urea
Deghani et al	Iran J kidney Dis, 10, 351-357, 2016	Urea
Ranganathan et al	Scientif World J, 5, 652-666, 2005	Urea

DMA: dimethylarginine, NDMA: nitrosodimethylarginine, β2-M: β2-microglobulin, PTH: parathyroid hormone; PBUT: protein bound uremic toxins

UREA IS NOT INERT

Nephrol Dial Transplant (2018) 33: 4–12
doi: 10.1093/ndt/gfx039
Advance Access publication 12 April 2017

ndt
Nephrology Dialysis Transplantation

Full Reviews

Urea and chronic kidney disease: the comeback of the century? (in uraemia research)

Raymond Vanholder[1], Tessa Gryp[2] and Griet Glorieux[2]

[1]Nephrology Section, Department of Internal Medicine, Ghent University Hospital, Ghent, Belgium and [2]Laboratory for Bacteriology Research, Department of Clinical Chemistry, Microbiology and Immunology, Ghent University, Ghent, Belgium

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Vanholder et al, NDT, 33:4-12; 2018

UREA INDUCES INSULIN RESISTANCE

JCI The Journal of Clinical Investigation

Amendment history:
- Addendum (October 2014)
- Erratum (March 2010)

Urea-induced ROS generation causes insulin resistance in mice with chronic renal failure

Maria D'Apolito, … , Michael Brownlee, Ida Giardino

J Clin Invest. 2010;120(1):203-213. https://doi.org/10.1172/JCI37672.

D'Apolito et al, J Clin Invest, 120:203-213; 2010

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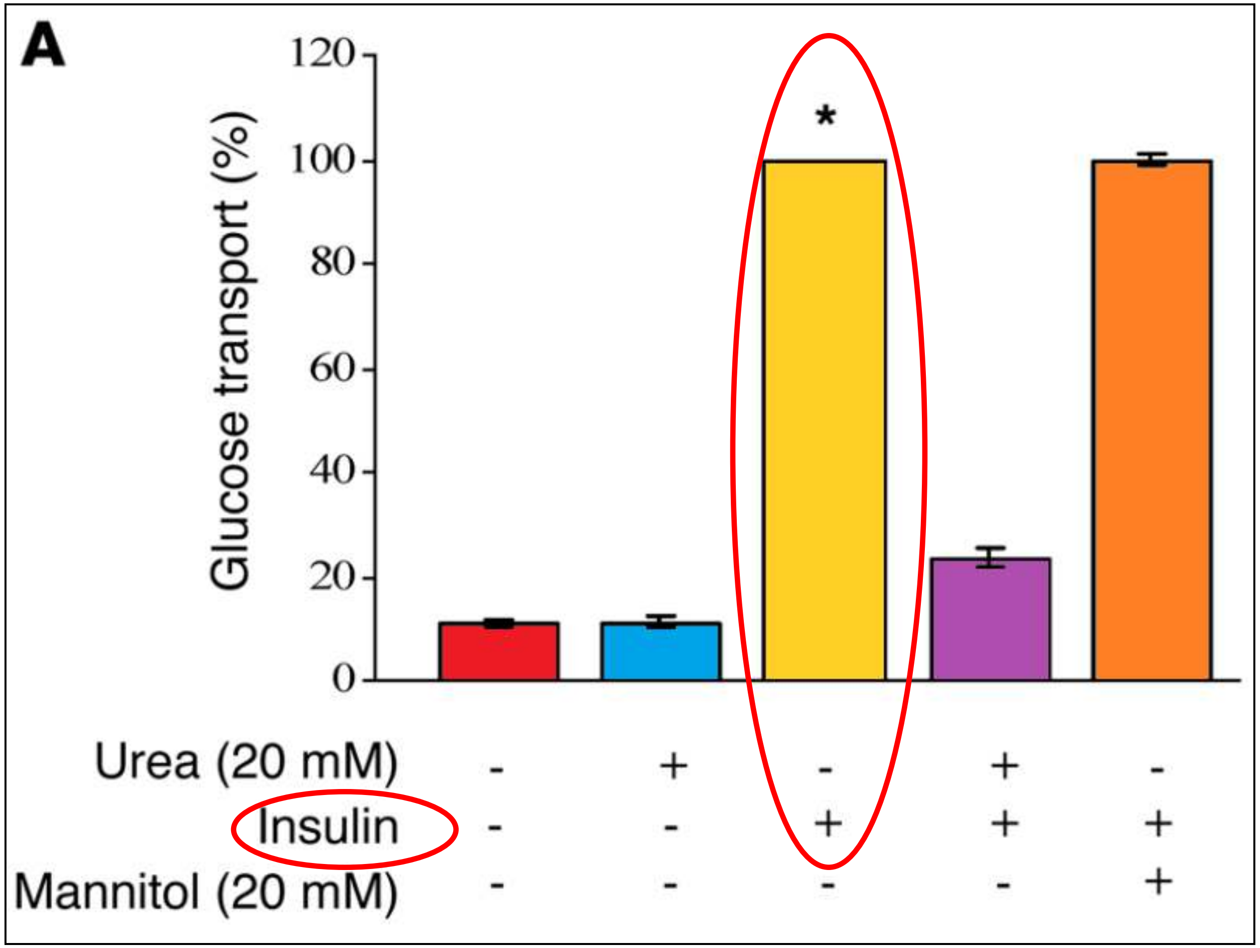

Figure 3
Urea causes decreased insulin sensitivity in differentiated 3T3L1 adipocytes. (A) Effect of urea on insulin-stimulated glucose uptake in differentiated 3T3L1 cells.

D'Apolito et al, J Clin Invest, 120:203-213; 2010

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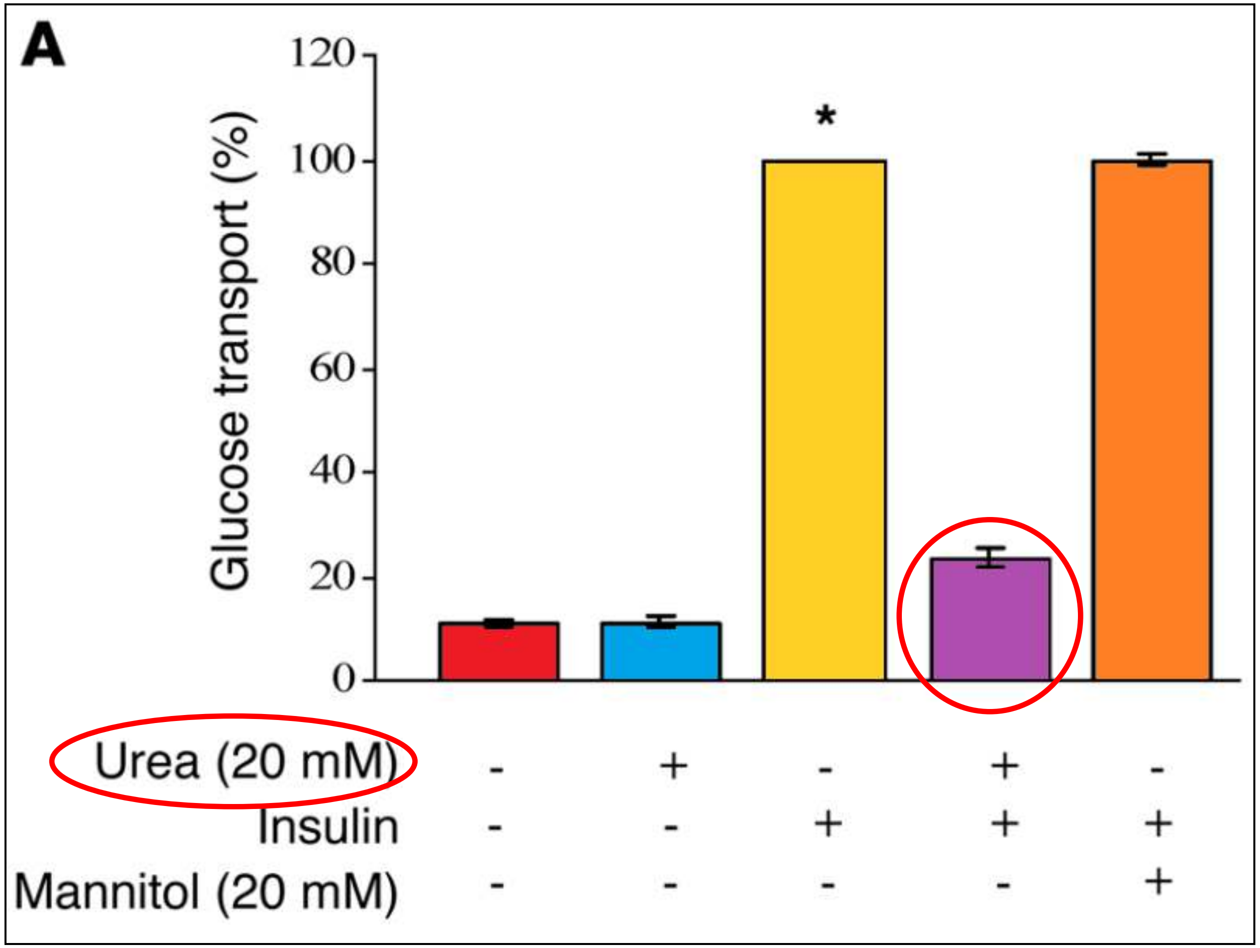

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D'Apolito et al, J Clin Invest, 120:203-213; 2010

UREA IS RELATED TO THE DEVELOPMENT OF DIABETES MELLITUS

www.kidney-international.org clinical investigation

Higher blood urea nitrogen is associated with increased risk of incident diabetes mellitus

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Yan Xie[1], Benjamin Bowe[1], Tingting Li[1,2], Hong Xian[1,3], Yan Yan[1,4] and Ziyad Al-Aly[1,2,5,6]

Xie et al, KI, 93: 741-752; 2018

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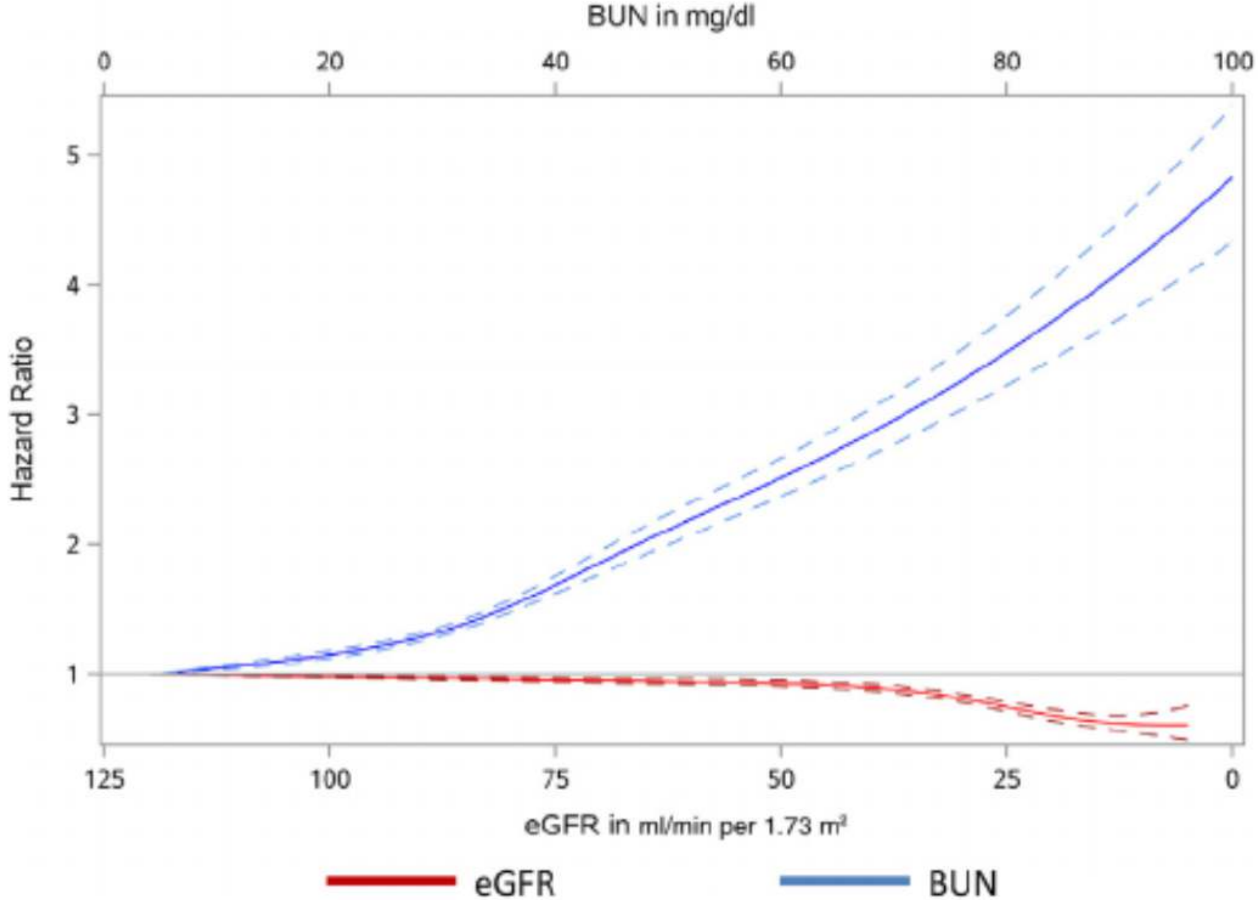

Xie et al, KI, 93: 741-752; 2018

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PROGRESSION CKD

PROBIOTICS REFRAIN PROGRESSION OF CKD

Minerva Urologica e Nefrologica 2016 April;68(2):222-6

ORIGINAL ARTICLE
NEPHROLOGY

Influence of prebiotic and probiotic supplementation on the progression of chronic kidney disease

Malleshappa PAVAN*

Pavan, Minerva Urol Nephrol, 68:222-226; 2016

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- **CKD is a devastating disease**
- **The gut plays a patho-physiologic role by inducing inflammation and generating uremic toxins**
- **Probiotics may alter this chain of events by:**
  - An anti-inflammatory effect
  - Reducing uremic toxins
- **Evidence on the impact of probiotics could be strengthened**