Revisiting Sodium As the Uremic Toxin

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Health Care

Annual Dialysis CONFERENCE

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School of Medicine
University of Missouri Health

Outline – Revisiting Sodium as the Uremic Toxin

1 Uremic Toxins, How to Define?

- ☐ Basic Considerations

2 Sodium, What's New?

- ☐ From 2 to 3 Compartments Model
- ☐ Clinical Implications

3 Sodium Toxicity, What are the facts?

- ☐ Water-Bound Sodium: Osmotic Active
- ☐ Water-Free Sodium: Metabolically Active

4 Sodium Management, How to Act?

- ☐ Monitoring
- ☐ Controlling

5 Take home message: Sodium-First Policy Approach

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Definition of a Uremic Toxin

Specific Conditions Required

1. The toxin must be chemically identified and characterized.
2. Quantitative analysis of the toxin in biological fluids should be possible.
3. The level of the toxin in biological fluids must be elevated in uremia.
4. A relationship between the level of the toxin in biological fluids and one or more of the manifestations of uremia must be present.
5. A reduction in the level of the toxin in biological fluids must result in the amelioration of the uremic manifestation.
6. Administration of the toxin to achieve levels similar to those observed in uremia must reproduce the uremic manifestation in otherwise normal animals or man (in vitro demonstration of cellular toxicity alone is insufficient to fulfill this criterion).
7. A plausible pathobiological mechanism should be demonstrated to explain the linkage between the toxin and the uremic manifestation.

Chmielewski M et al, *Uremic Toxicity*, in Nutritional Management of Renal Disease, 2013,4:49-77

Uremic Toxicity

Result from a Multifactorial Combination

Uremic Toxins

Inorganic Compounds	Organic Compounds	Concentration Circulating/Tissular	Exposure Time Acute/Chronic
Interaction	Metabolic Modification	Pharmacokinetic Pharmacodynamic	Individual Susceptibility

Clinical Research is Currently Focused on Toxicity of Organic Compounds

Small Molecules (Water Soluble) < 500 Da	Protein-Bound Molecules 500 - 22000 Da	Middle → Large Molecules > 500 Da to >25K Da
Asymmetric dimethylarginine	3-Deoxyglucosone	Adrenomedullin
Benzylalcohol	Carboxy-Methyl-Propyl-Furanpropionic Acid	Atrial natriuretic peptide
ß-Guanidinopropionic acid	Fructoselysine	ß2-Microglobulin
ß-Lipotropin	Glyoxal	ß-Endorphin
Creatini	ippuric acid	ystokinin
Cytidin	omocysteine	ell protein
Guanid	ydroquinone	ment factor D
Guanidi	ndole-3-acetic acid	n C
Guanidi	ndoxyl sulfate	Degranulation inhibitin
Hypoxanthine	Kinurenine	Delta-sleep-inducing peptide
Malondialdehyde	Kynurenic acid	Endothelin
Methylguanidine	Me ylglyoxal	Hyaluronic acid
Myoinositol	N-carboxymethyllysine	Interleukin 1ß
Orotic acid	P-cresol	Interleukin 6
Orotidine	Pentosidine	Kappa-Ig light chain
Oxalate	Phenol	Lambda-Ig light chain
Pseudouridine	P-OH Hippuric Acid	Leptin
Symmetric dimethylarginine	Quinolinic acid	Methionine-Enkephalin
Urea	Spermidine	Neuropeptide Y
Uric acid	Spermine	Parathyroid hormone
Xanthine		Retinol Binding Protein
		Tumor Necrosis Factor Alpha

Gut Microbiota
Indoxyl Sulfate
Para Cresyl Sulfate

Inflammation Mediators
IL1, IL6

Specific Compounds
ß2-M, ANP, BNP

Ig Light Chain
Kappa-Ig
Lambda-Ig

European Uremic Toxin Work Group of the ESAO

Vanholder R. et al New insights in uremic toxins. *Kidney Int*, 2003, 63; 84: S6–S10

But Inorganic Compounds Should Be Considered More Carefully...

Inorganic Compounds

Na^{+}, H_2O

K^{+}, H^{+}, HCO_3^{2-}

PO_4^{2-}, Ca^{2+}, Mg^{2+}

...

Salt, the Neglected Silent Killer

Stanley Shaldon* and Joerg Vienken†

Sem Dialysis 2009; 22(3):264-26

Hyperphosphataemia : a silent killer of patients with renal failure?

Kerstin Amann, Marie-Luise Gross, Gérard M. London, Eberhard Ritz

Nephrol Dial Transplant 1999;14(9):2085-2087

Hyperkalemia: A Potential Silent Killer

I. DAVID WEINER and CHARLES S. WINGO

J Am Soc Nephrol 9: 1535–1543, 1998

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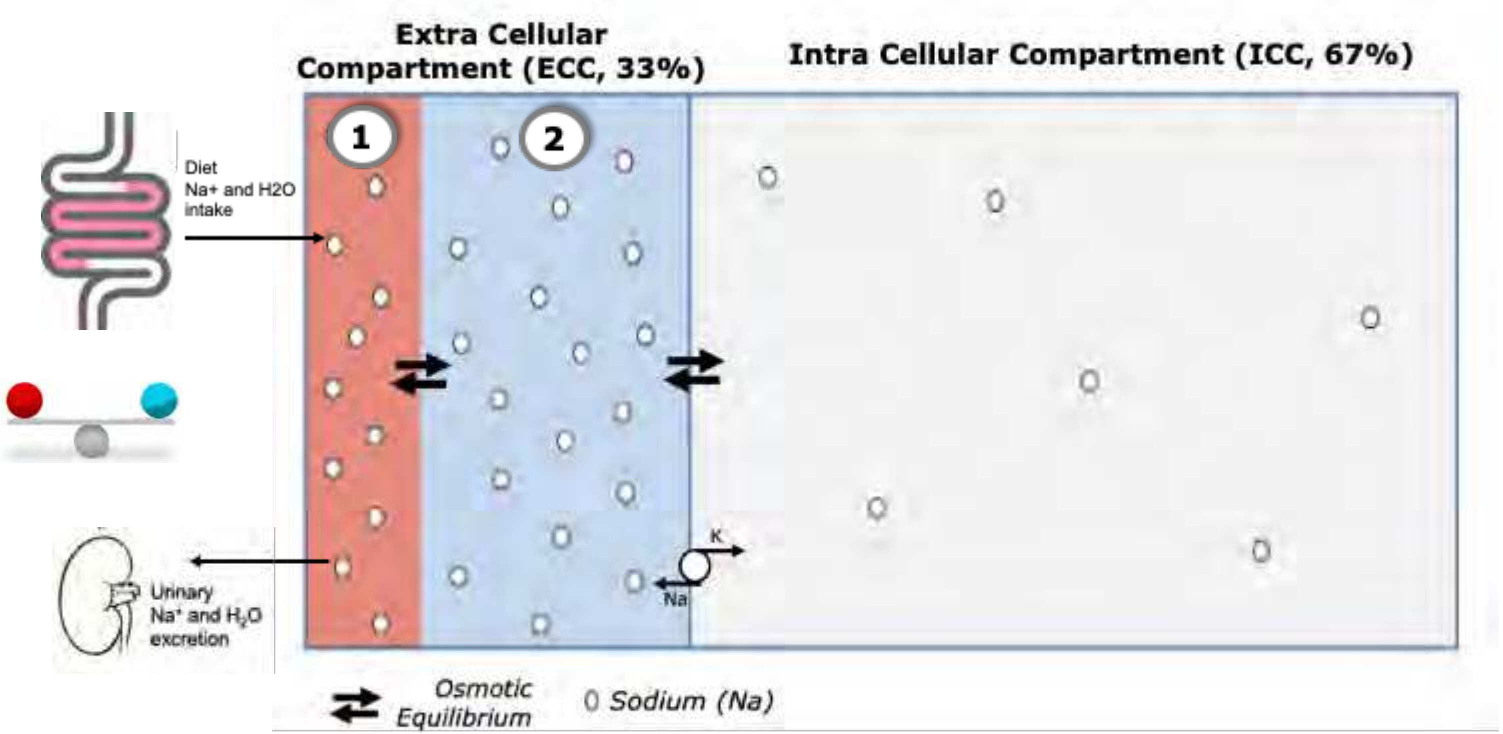
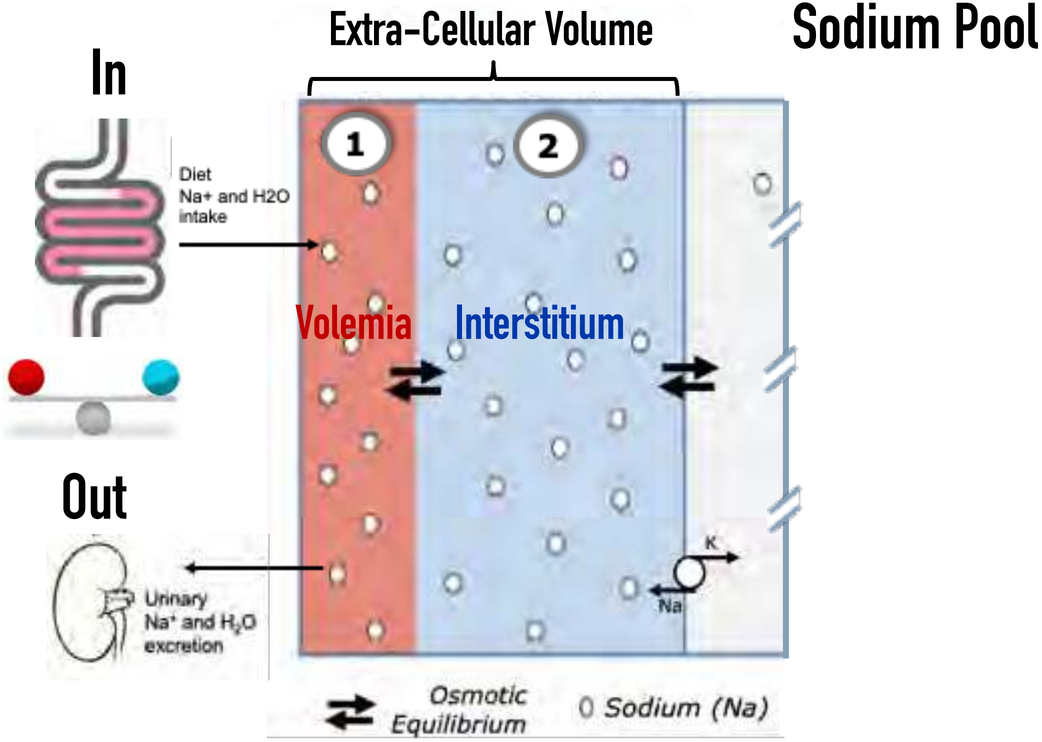
Internal Milieu Homeostasis – Cl. Bernard Model

Traditional Concept of Body Sodium & Fluid Volume Balance



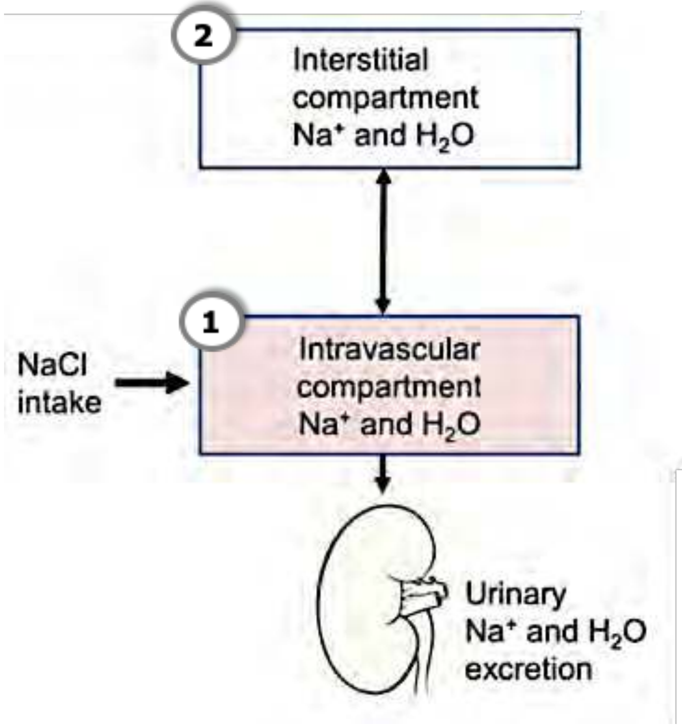
Sodium Physiology: Two Compartments Model

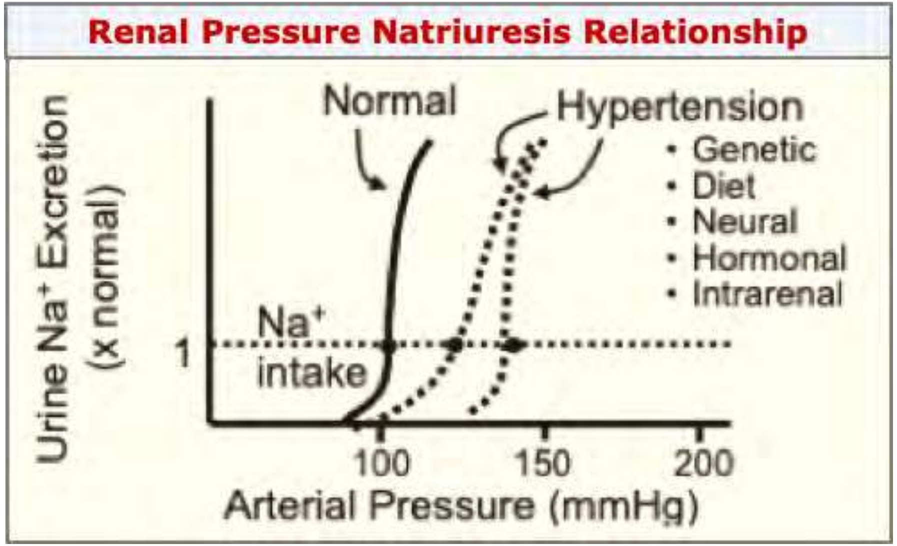
Sodium Balance - Homeostasis



Sodium Physiology: Two Compartments Model

'Kidney Centric Model' from Guyton

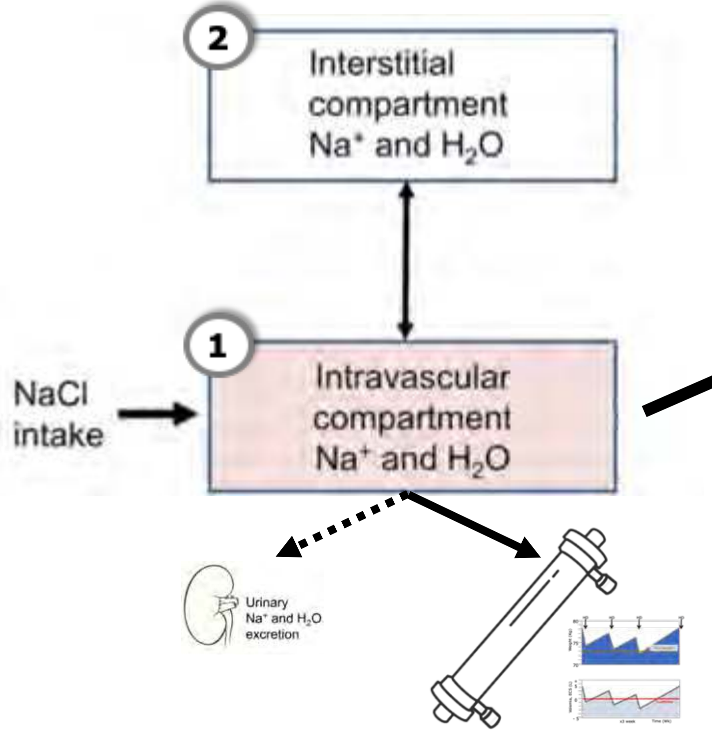


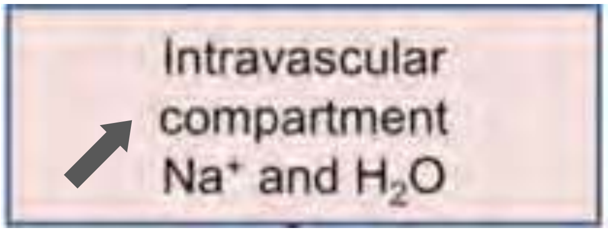


Guyton AC et al, Am J Med 1972; 52(5): 584-94.
Guyton AC et al, *Science* 1991; 252(5014): 1813-6.
Hall JE. *Circulation*. 2016;133(9):894–906

CKD5 Dialysis Patient – Worst Scenario for Na Imbalance

Sodium Excess, Fluid Volume Overload and Hypertension: End Organ Damage





Osmotic & Hemodynamic Action

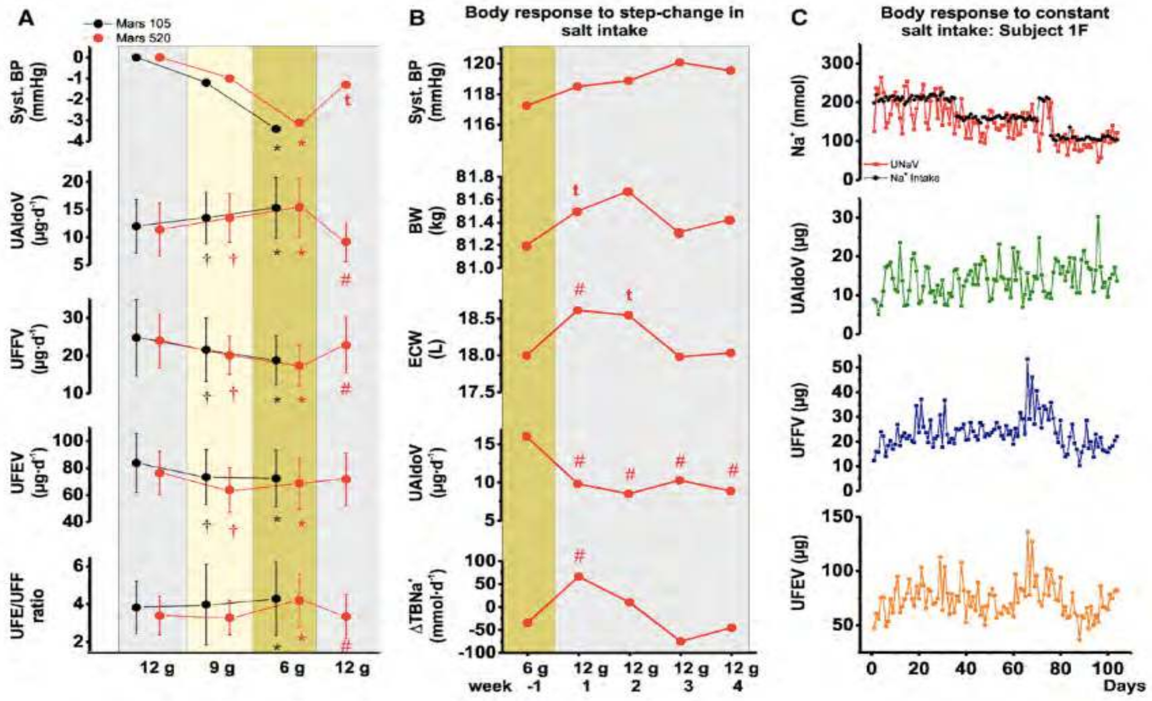
Hypertension

Clinical	Mechanical	Biological
Congestion Hypertension	Cardiac & Vascular & End Organ Damage	Inflammation & Metabolic

CV Outcome

Body Response to Salt Intake Changes in Confined Environment Suggests that Na Accumulated in Another Compartment (Sodium Imbalance)

Total-body Na^+ content exceeded weight gain, suggesting that sodium had accumulated in another compartment without being osmotically active

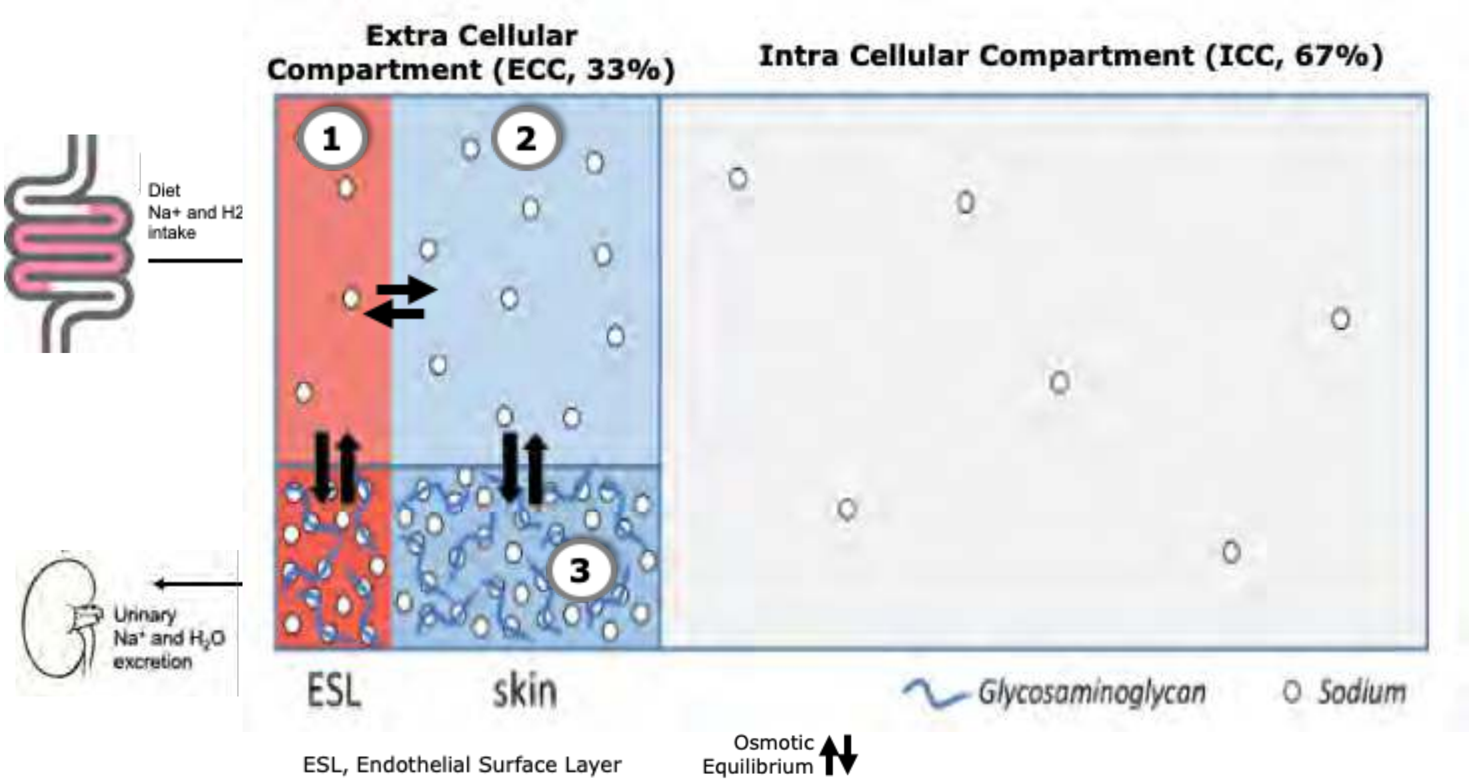


MARS (105 -520) Mission

Rakova N et al, *Cell Metab.* 2013;17(1):125–131.

Three Compartments Model

Tissue Sodium Storage – Skin & Muscle



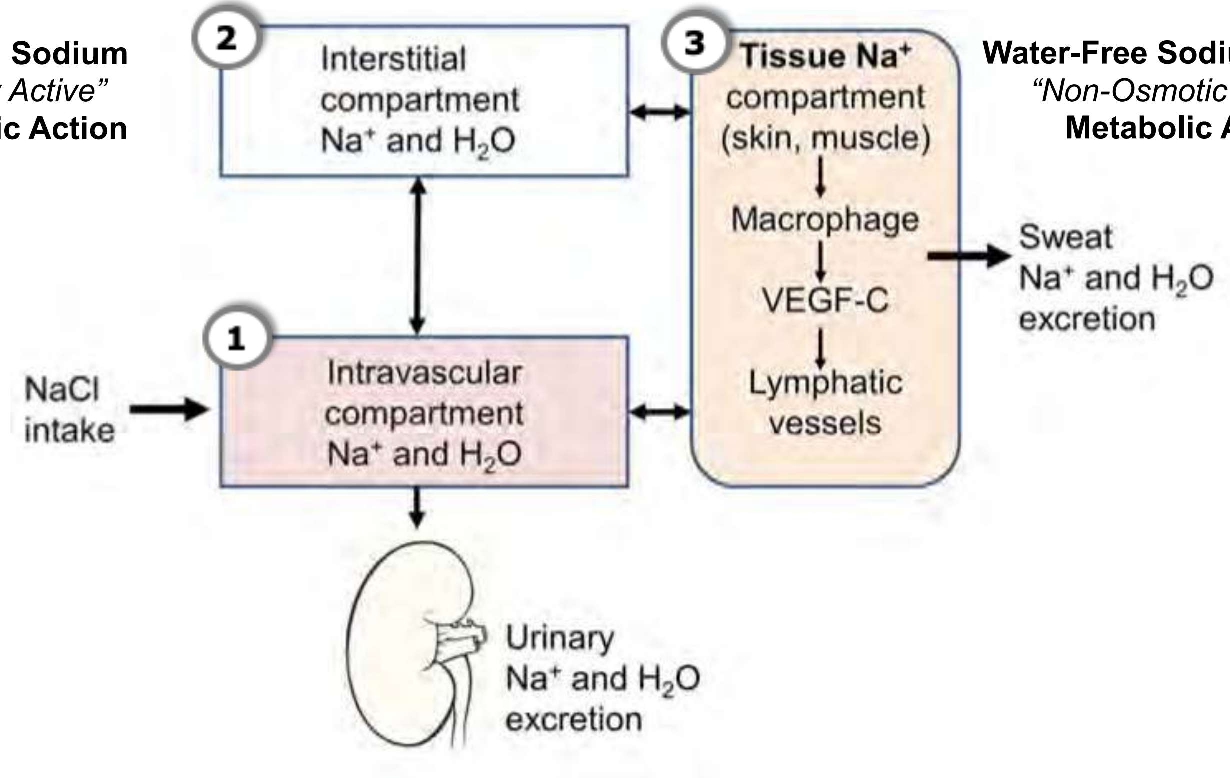
Olde Engberink RHG et al. Pediatr Nephrol. 2019;10.1007/s00467-019-04305-8.

Three Compartment Model

Sodium and Fluid Homeostasis in Normal Subject

Water-Bound Sodium
"Osmotically Active"
Hemodynamic Action

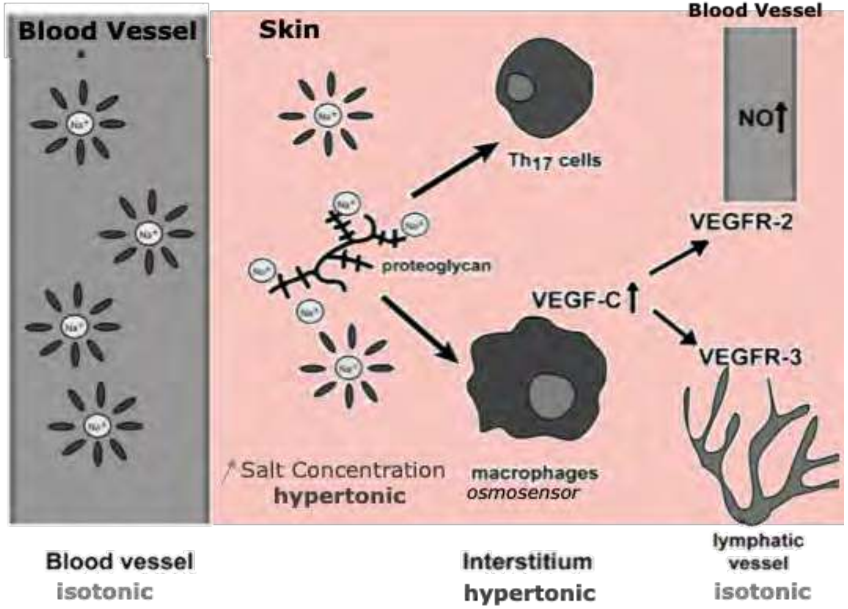
Water-Free Sodium Storage
"Non-Osmotic Sodium"
Metabolic Action

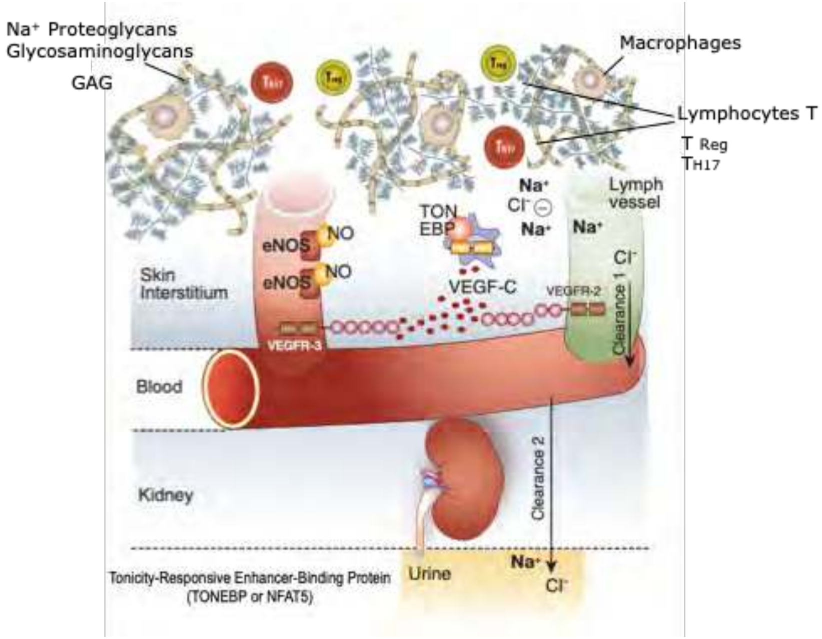


Polychronopoulou E et al *Front Cardiovasc Med.* 2019;6:136.

Role of Skin in Sodium & Water Homeostasis and Beyond

Immune and Vascular Angiogenesis (Lymphangiogenesis & NO Release)



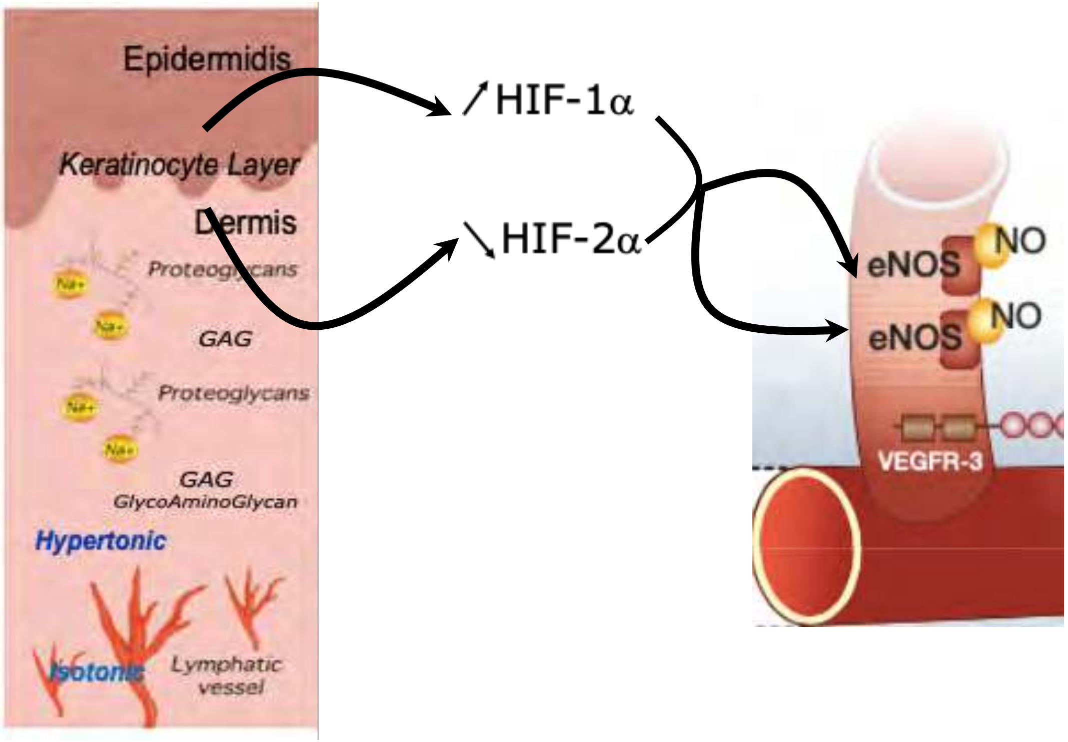


Rakova N et al, *J Reprod Immunol.* 2014;101-102:135–139.

Titze J et al, *Kidney Int.* 2017;91(6):1324–1335.

Skin Acts on Systemic Arterial Pressure

Imbalance Isoform HIF-1α/HIF-2α



Vasomotricity

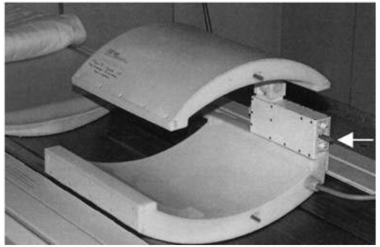
Hypertension

Cowburn AS et al, *Proc Natl Acad Sci USA.* 2013;110(43):17570–17575.

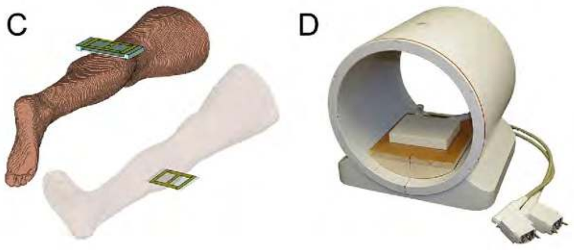
Skin Sodium Content Measured with ^{23}Na MRI at 7.0 T.

MRI Coil

Whole Body MRI

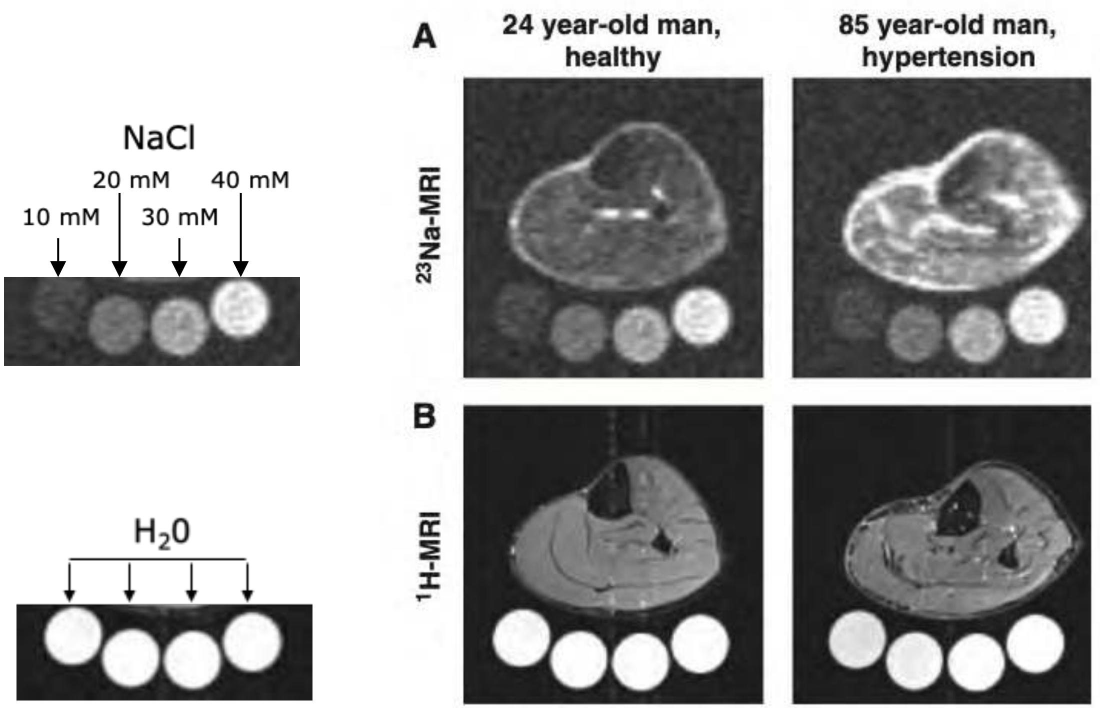


Segmental MRI



Linz P et al. NMR Biomed. 2015;28(1):54–62.
Francis S et al. Curr Opin Nephrol Hypertens. 2017;26(6):435–441.

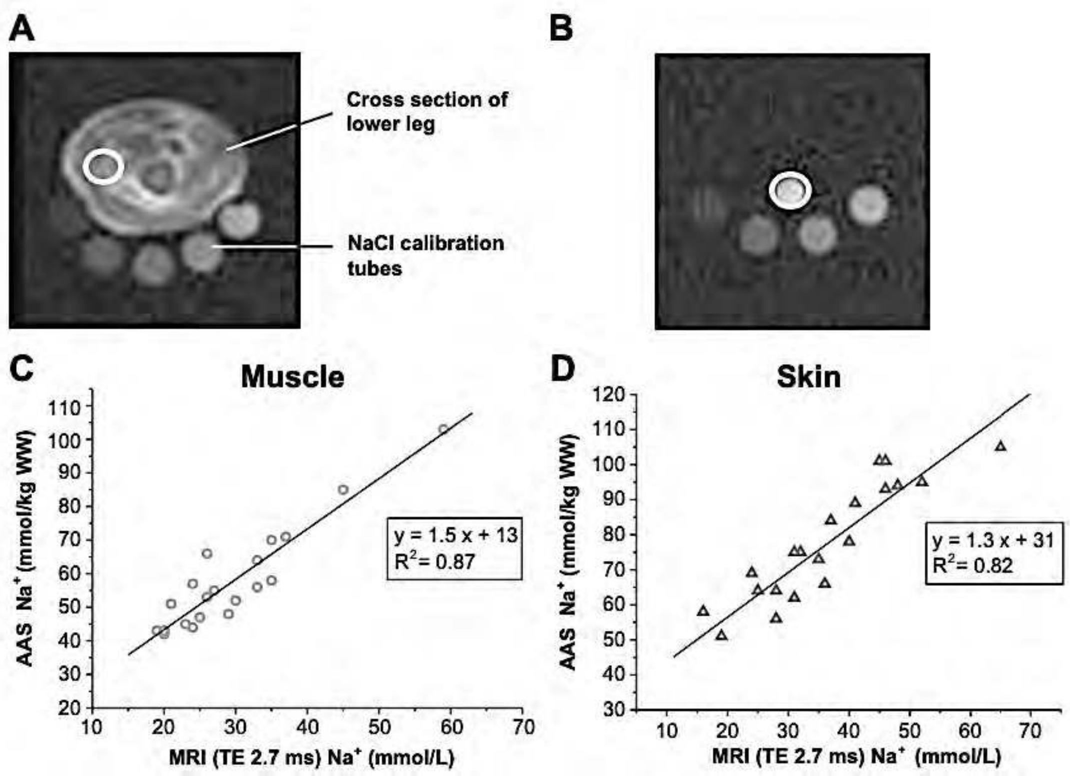
^{23}Na Magnetic Resonance Imaging (^{23}Na MRI) of Tissue Content



Kopp C et al, *Hypertension*. 2013;61(3):635–640.

^{23}Na MRI Tissue Content in Human

Imaging and Quantifying Na Tissue Content



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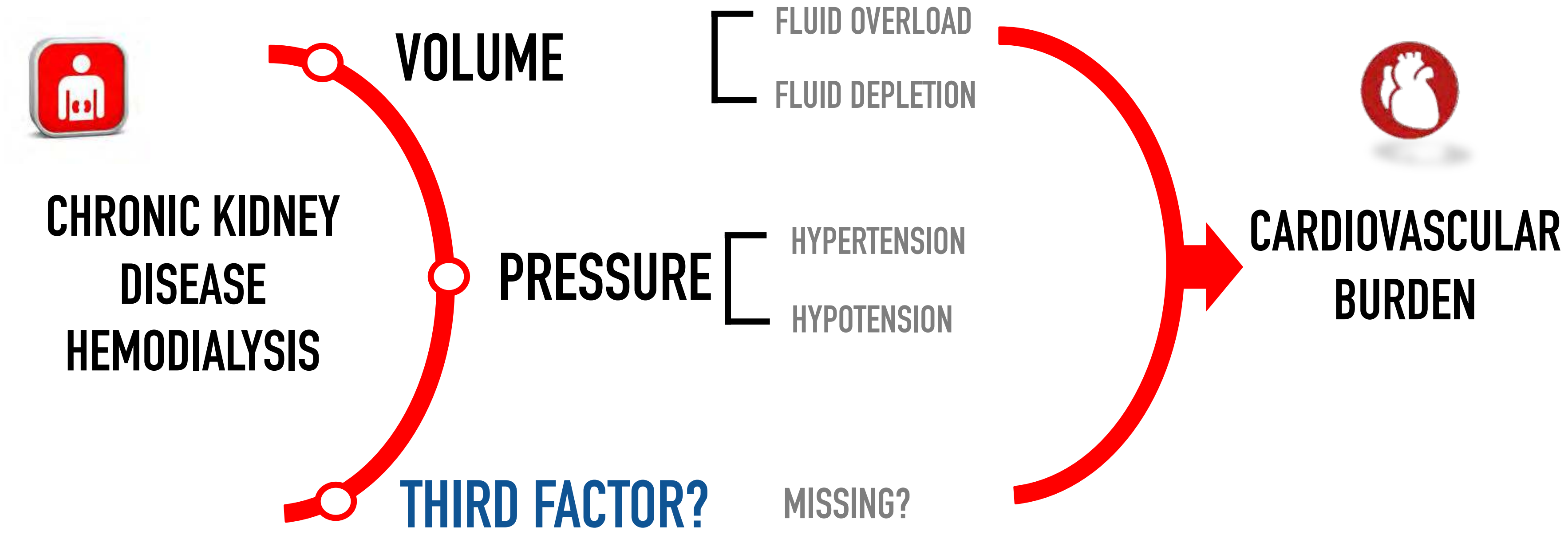
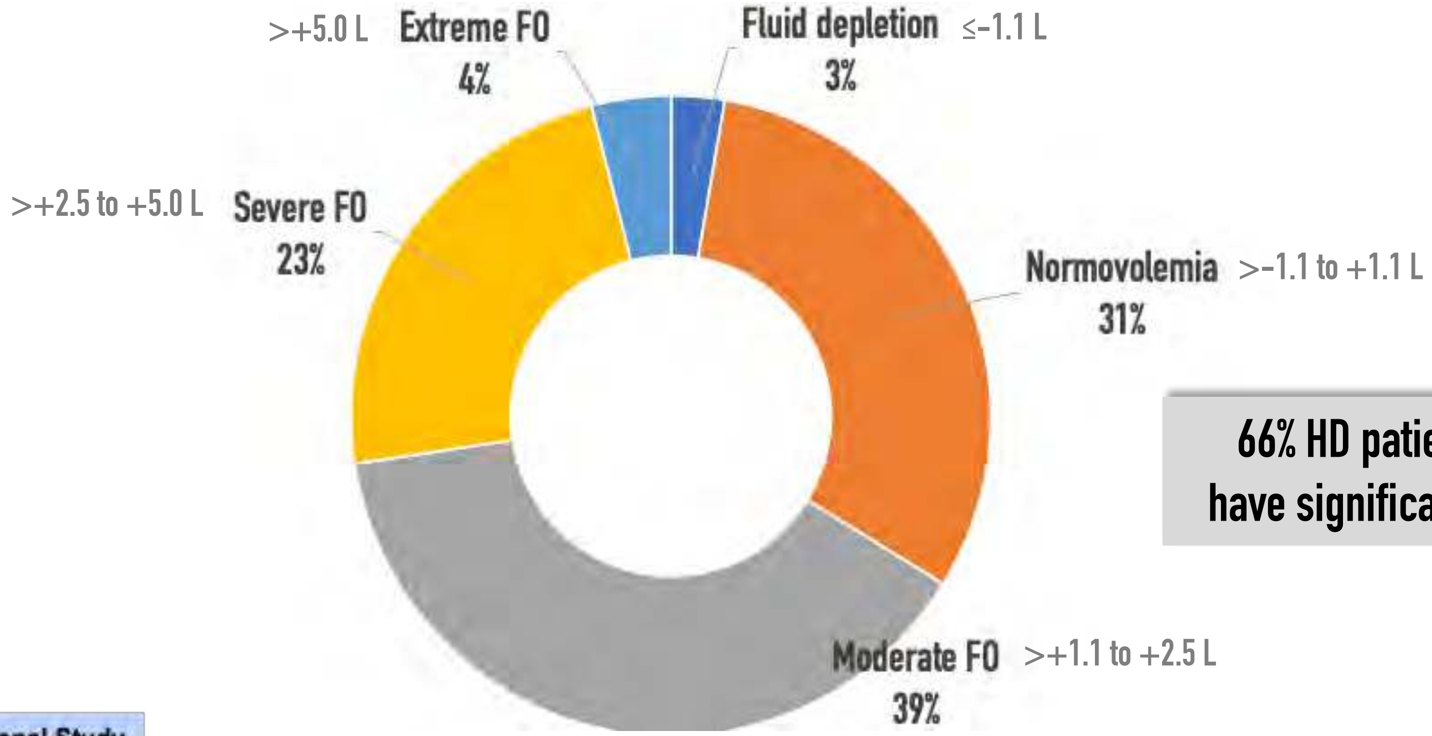
Mechanistic Approach – Traditional Concept of CVD Burden



Fluid Overload is Common in HD Patients



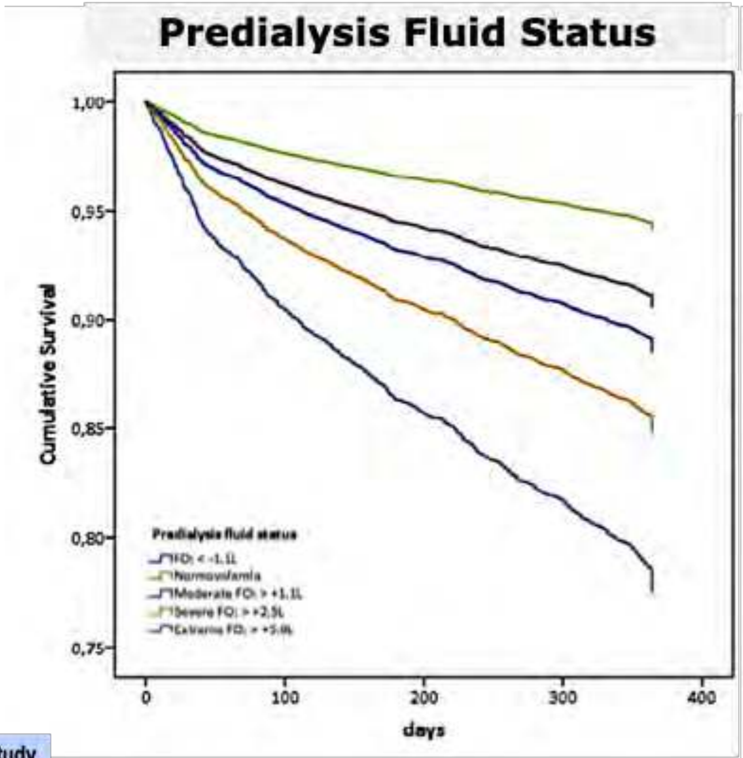
66% HD patients have significant FO

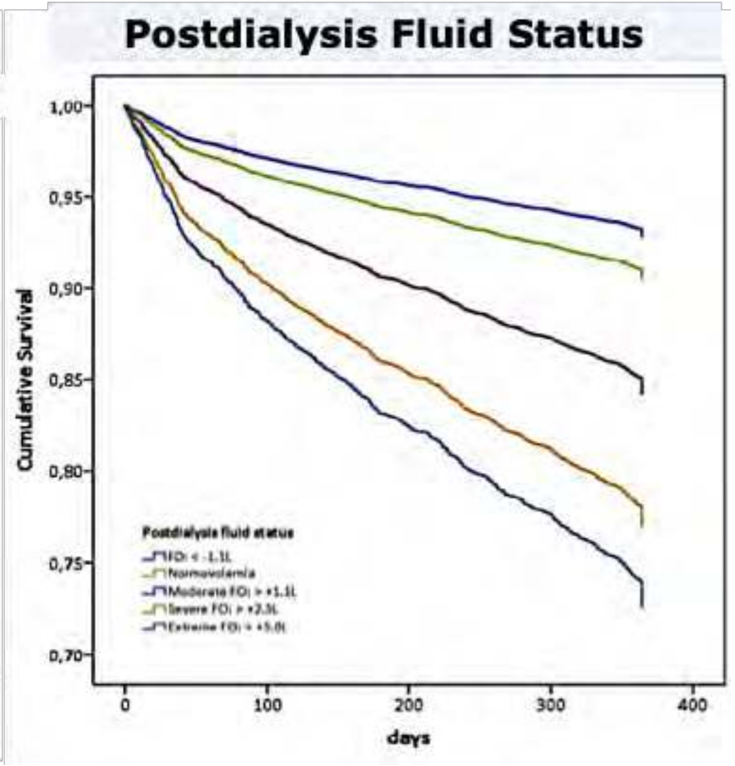
MONDO

European Cross-Sectional Study
3 mo. – 8883 prevalent HD pts
Fluid Status assessed by MF-BIA

Dekker MJ et al; *Kidney Int.* 2017;91(5):1214-1223.

Fluid Overload is Associated with Poor Outcome





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3 mo. – 8883 prevalent HD pts
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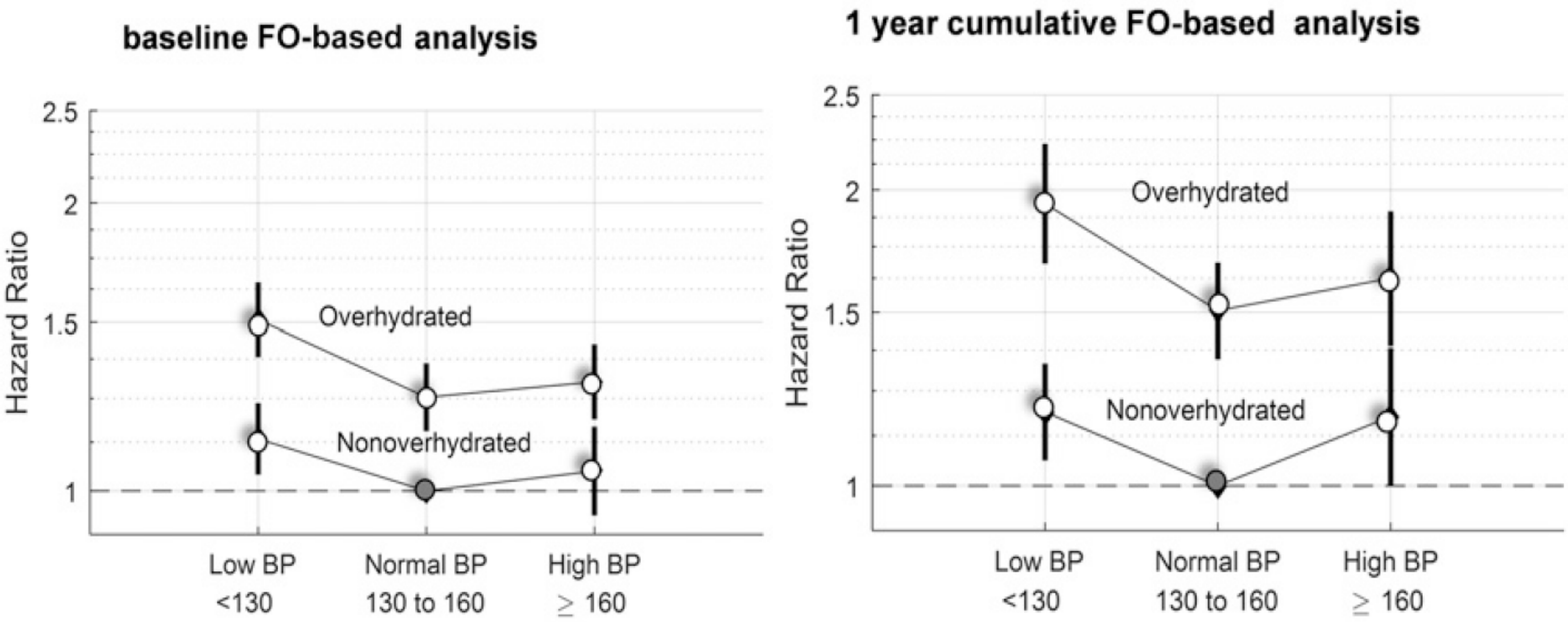
Dekker MJ et al, *Kidney Int.* 2017;91(5):1214–1223.

Chronic EC Fluid Overload is an Additive CV Risk Factor to Hypertension



Retrospective Cohort Study
39566 incident HD pts
26 countries – 1 year follow-up
BP – Fluid status - **Mortality**
Fluid Status: **BIA spectroscopy**

Zoccali C et al, *J Am Soc Nephrol.* 2017;28(8):2491-2497.

Fluid Volume Overload is an Independent CV Risk Factor

Retrospective Observational International Database Study MONDO Initiative

↓

8883 HD Prevalent Pts

1 Year FU

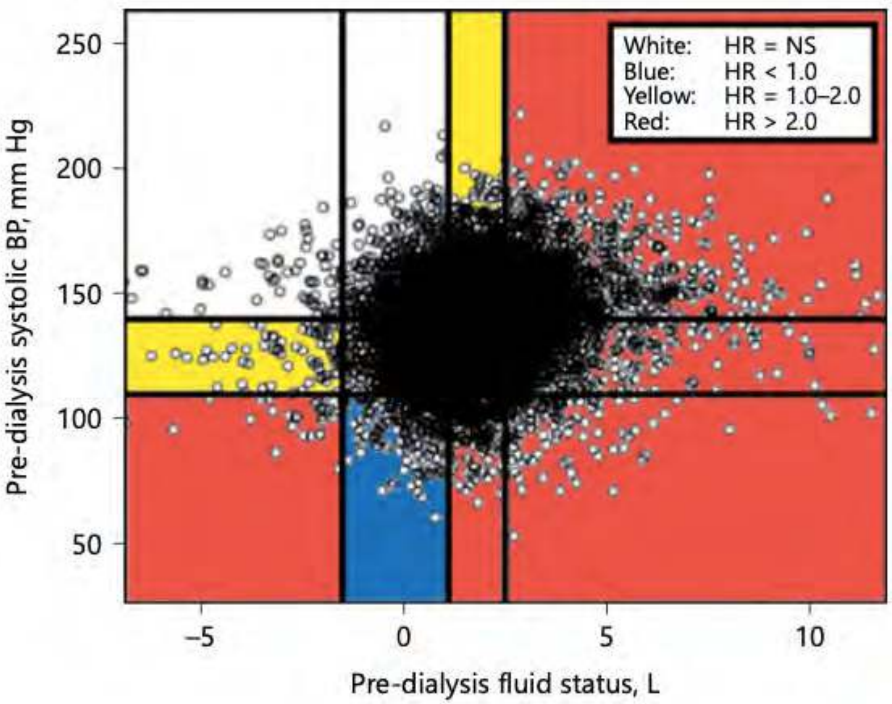
Assessment Blood Pressure Fluid Status (BIS)

↓

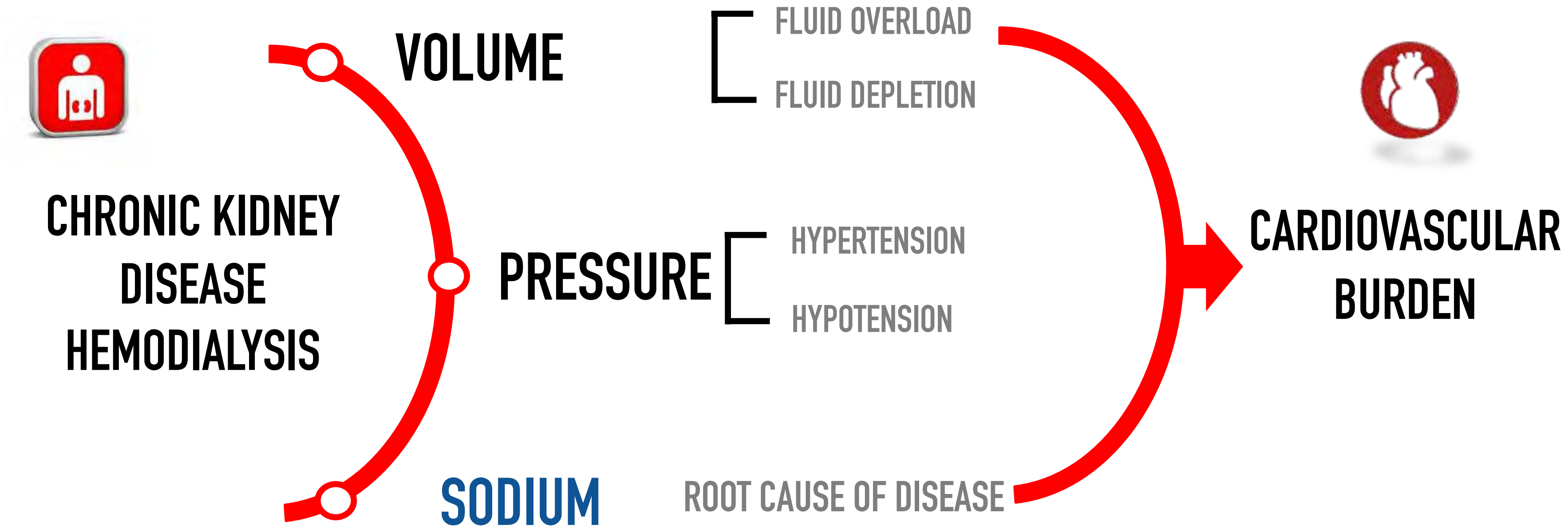
Extended Cox Regression Multivariate Analysis

↓

Outcomes Mortality (All-Cause, CV)

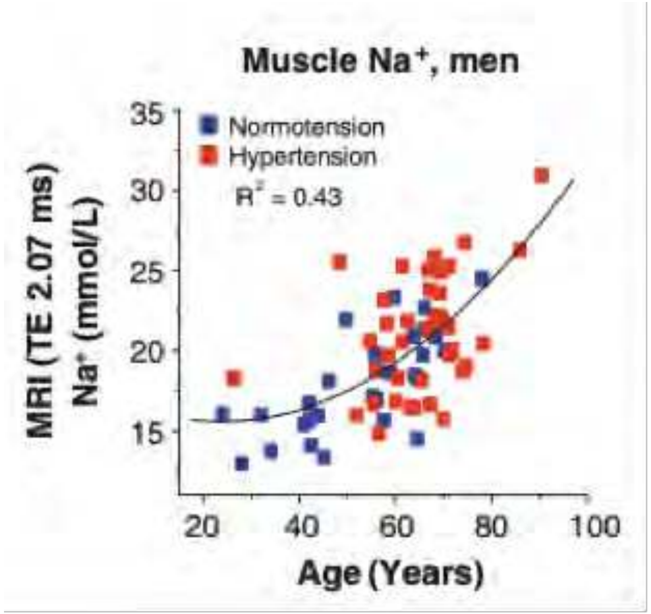


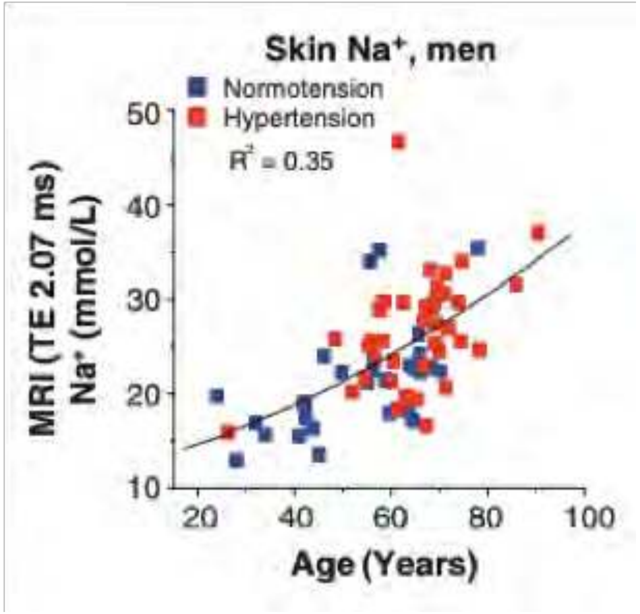
Mechanistic Approach – Sodium is the Root Cause of CVD



Tissue Na Content (Muscle–Skin) Increases with Age

Effects of Gender: Steeper in Men

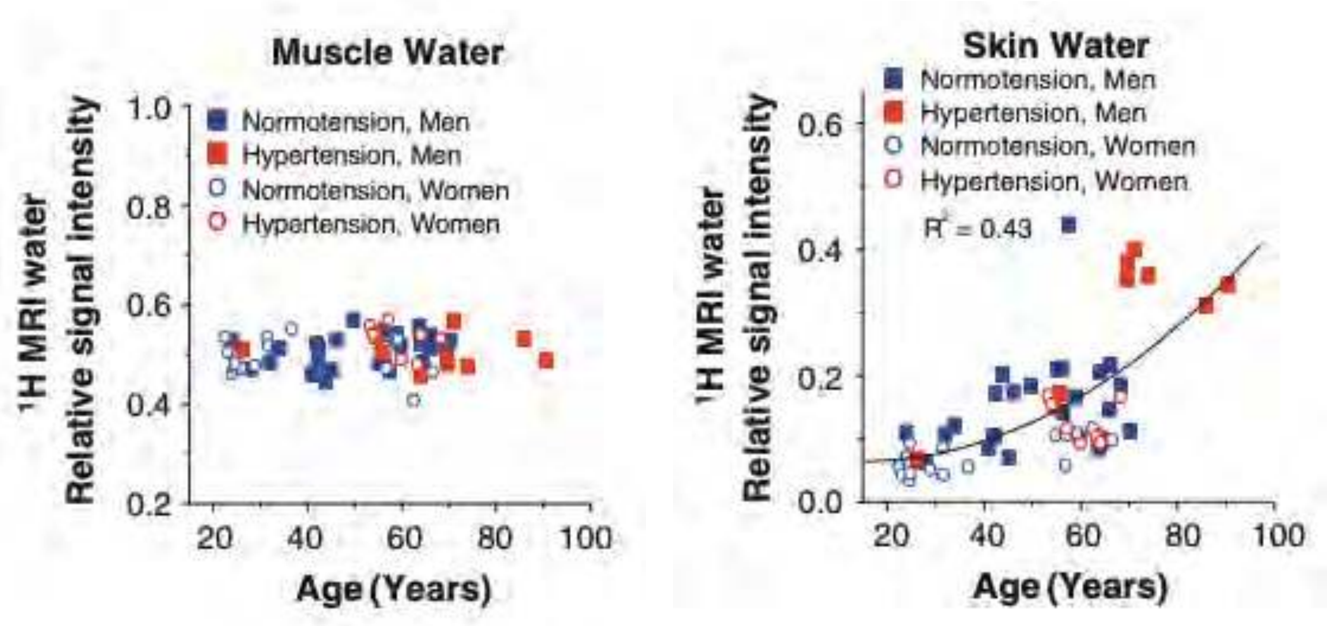




Kopp C et al, *Hypertension*. 2013;61(3):635–640.

Tissue Water Content (Muscle–Skin) in Hypertensive Patients:

Effects of Age and Gender



Kopp C et al, *Hypertension*. 2013;61(3):635–640.

Tissue Sodium Accumulation Starts Early in CKD

Poorly Correlated with Fluid Overload Assessed by MF-BIA

Parameter	OH: <−0.8 L, *n*=29	OH: −0.8 to +0.1 L, *n*=34	OH: >0.1 L, *n*=35	P Value
Age, yr, median (range)	63 (39–76)	61 (25–78)	69 (23–75)	0.26
Sex, men/women	16/13	15/19	26/9	0.04
Weight, kg, mean (95% CI)	86 (81 to 92)	82 (75 to 89)	88 (82 to 93)	0.34
Height, cm, mean (95% CI)	170 (166 to 175)	170 (167 to 174)	174 (172 to 176)	0.15
Body mass index, kg/m^2, median (range)	28 (24–41)	28 (18–39)	28 (20–39)	0.30
Office SBP, mmHg, mean (95% CI)	133 (127 to 140)	131 (126 to 135)	135 (130 to 140)	0.58
Office DBP, mmHg, mean (95% CI)	82 (78 to 86)	80 (77 to 83)	80 (76 to 83)	0.60
24-h SBP, mmHg, mean (95% CI)	124 (120 to 129)	123 (120 to 127)	129 (124 to 133)	0.12
24-h DBP, mmHg, mean (95% CI)	76 (72 to 79)	76 (74 to 79)	78 (75 to 81)	0.51
Hypertension, %	90	94	91	0.81
Treatment resistant hypertension, %	10	15	17	0.74
Number of BP medications, median (range)	2 (0–4)	3 (0–5)	2 (0–6)	0.24

CARVIDA Study

CKD3-4 (n=99)
FO-BIS, BP, 24hBP,
Skin Na-MRI, Cardiac MRI

Schneider MP et al, *J Am Soc Nephrol 2017;* 28: 1867–1876

Tissue Sodium Accumulation Starts Early in CKD

Poorly Correlated with Hemodynamic Parameters

Parameter	Skin Sodium <16.8 mmol/L, *n*=30	Skin Sodium 16.8–22.2 mmol/L, *n*=31	Skin Sodium >22.2 mmol/L, *n*=32	P Value
Age, yr, median (range)	54 (23–76)	67 (46–75)	70 (47–78)	<0.001
Sex, men/women	9/21	19/12	24/7	0.001
Weight, kg, mean (95% CI)	79 (73 to 86)	85 (80 to 91)	93 (87 to 99)	0.005
Height, cm, mean (95% CI)	170 (167 to 173)	172 (168 to 176)	173 (170 to 176)	0.40
Body mass index, kg/m^2, median (range)	27 (18–37)	28 (23–41)	30 (23–39)	0.02
Office SBP, mmHg, mean (95% CI)	129(123 to 135)	133 (127 to 139)	135 (131 to 140)	0.22
Office DBP, mmHg, mean (95% CI)	81 (77 to 85)	82 (79 to 86)	78 (73 to 82)	0.18
24 h-SBP, mmHg, mean (95% CI)	122 (118 to 126)	124 (121 to 127)	132 (127 to 137)	0.002
24 h-DBP, mmHg, mean (95% CI)	78 (75 to 81)	76 (74 to 79)	77 (72 to 81)	0.64
Hypertension, %	83	90	100	0.07
Treatment resistant hypertension, %	10	10	23	0.25
Number of BP medications, median (range)	1 (0–4)	1 (0–5)	3 (0–6)	<0.001

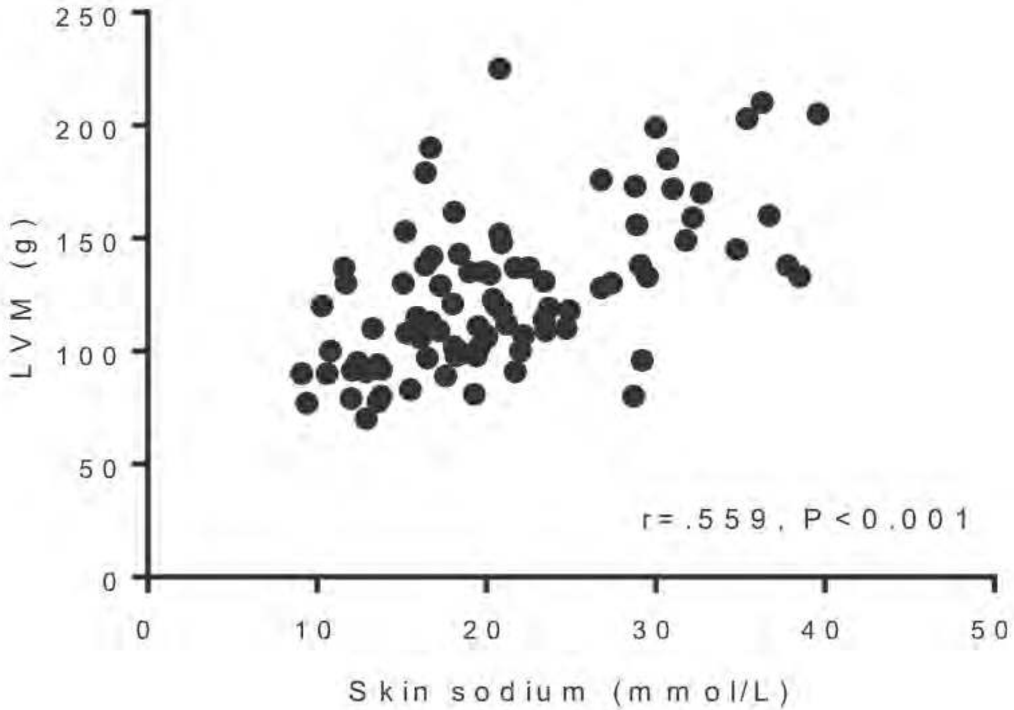
CARVIDA Study

CKD3-4 (n=99)
FO-BIS, BP, 24hBP,
Skin Na-MRI, Cardiac MRI

Schneider MP et al, *J Am Soc Nephrol 2017;* 28: 1867–1876

Tissue Sodium Accumulation Starts Early in CKD

Strongly Correlated with Left Ventricular Mass



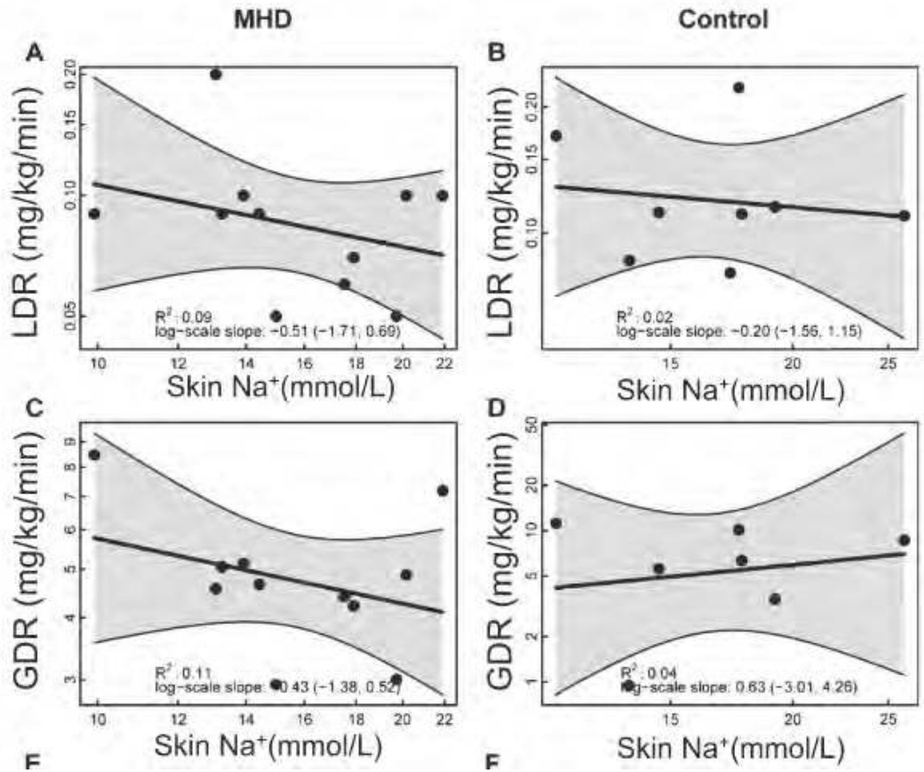
CARVIDA Study

CKD3-4 (n=99)
FO-BIS, BP, 24hBP,
Skin Na-MRI, Cardiac MRI

Schneider MP et al, *J Am Soc Nephrol 2017;* 28: 1867–1876

Tissue Sodium Accumulation in HD Patients

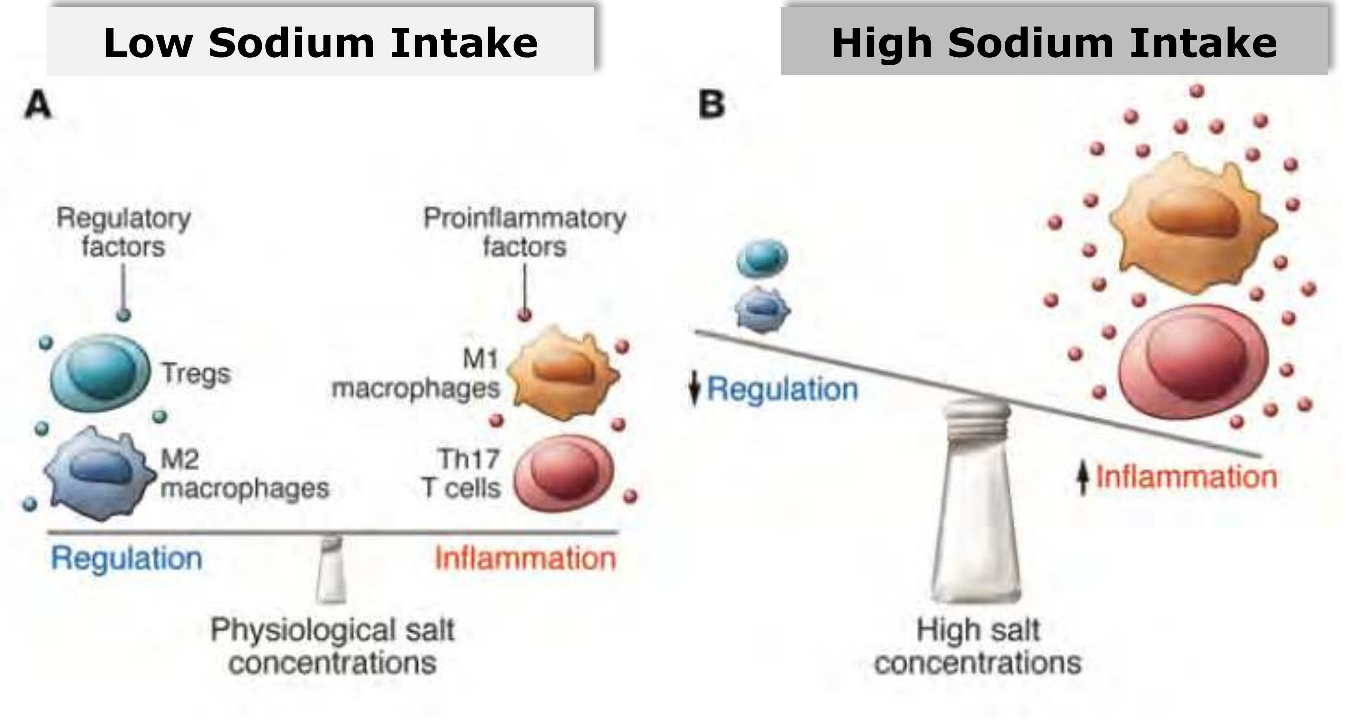
Peripheral Insulin Resistance



Prospective Study
11 MHD pts vs. 8 controls
Hyperinsulinemic– euglycemic euaminoacidemic clamp studies
Measure Glucose Disposal Rate (GDR)
Leucine Disposal Rate (LDR)
Lower left leg 23Na MRI to measure Na+ concentration in muscle skin tissue.

Deger SM et al. *J Cachexia Sarcopenia Muscle.* 2017;8(3):500–507.

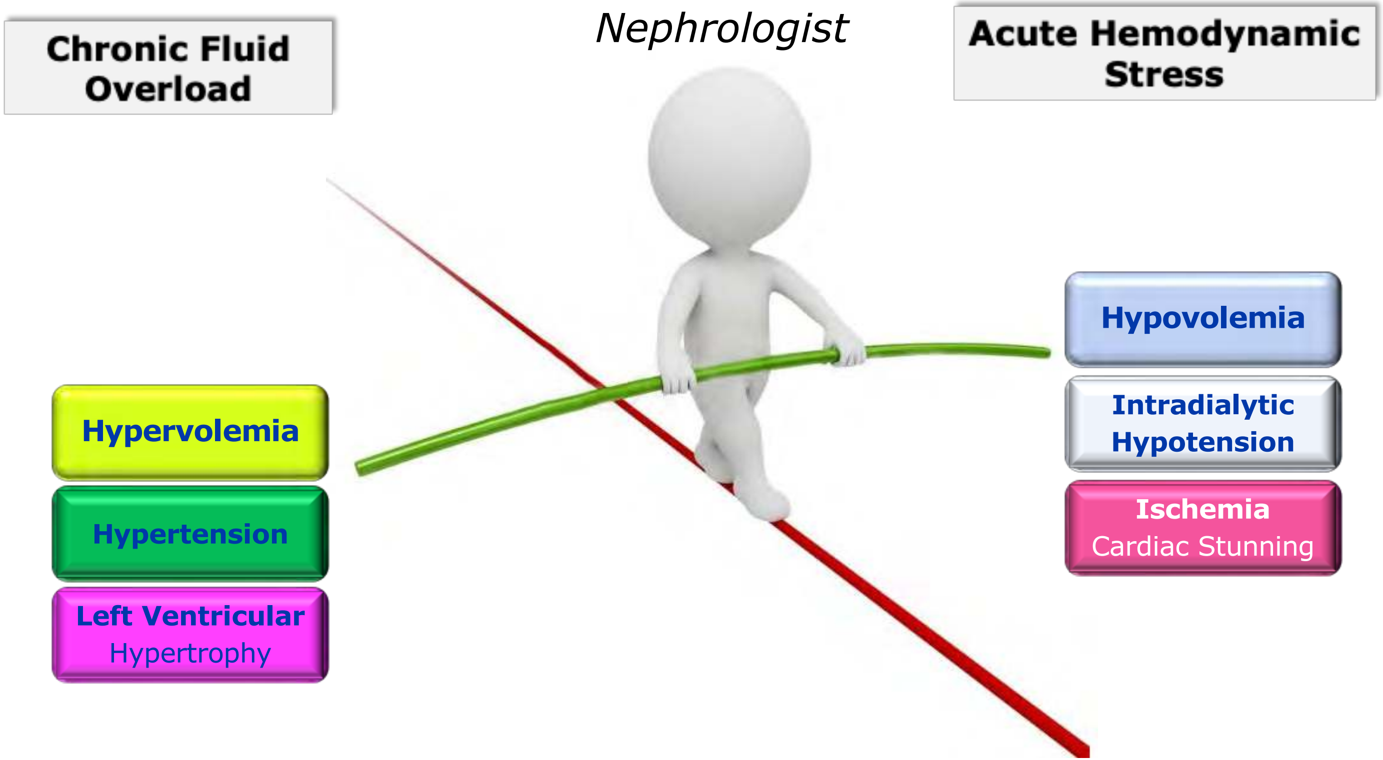
High Salt Intake Induces Inflammation and Immune Imbalance



Min B et al. *J Clin Invest.* 2015;125(11):4002–4004.

Volume and Pressure Management in HD Patients

Challenging Situation & Risk HD-Induced Hemodynamic Stress

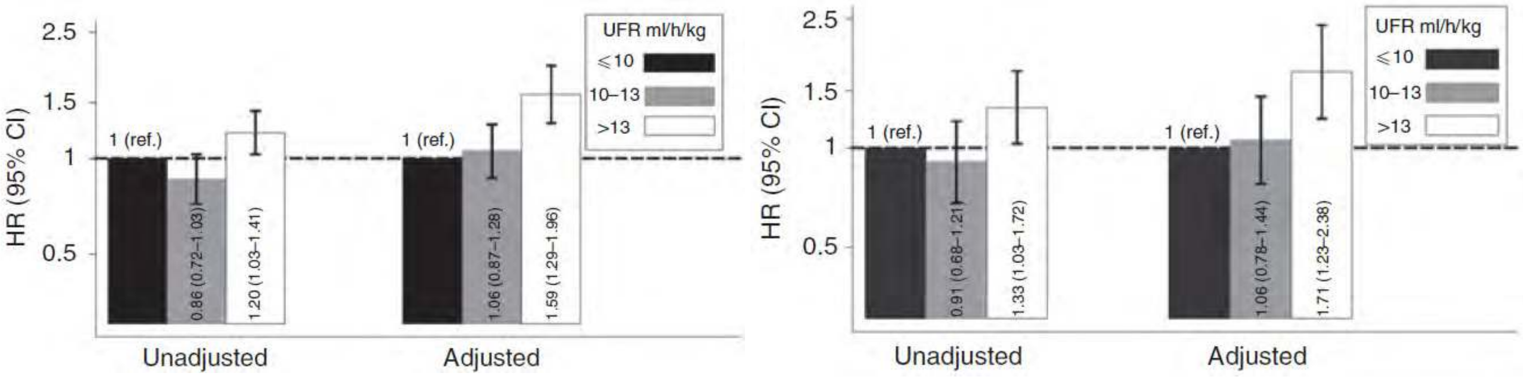


Fluid Depletion as Ultrafiltration Rate and Mortality

Rapid Fluid Depletion is Associated with CV Mortality

Association between UFR and all-cause mortality

Association between UFR and CV mortality



Based on data of the Hemodialysis Study, an almost-7-year randomized clinical trial of 1846 patients receiving thrice weekly chronic dialysis. The ultrafiltration rates were divided into three categories: up to 10 ml/h/kg, 10–13ml/h/kg, and over 13 ml/h/kg.

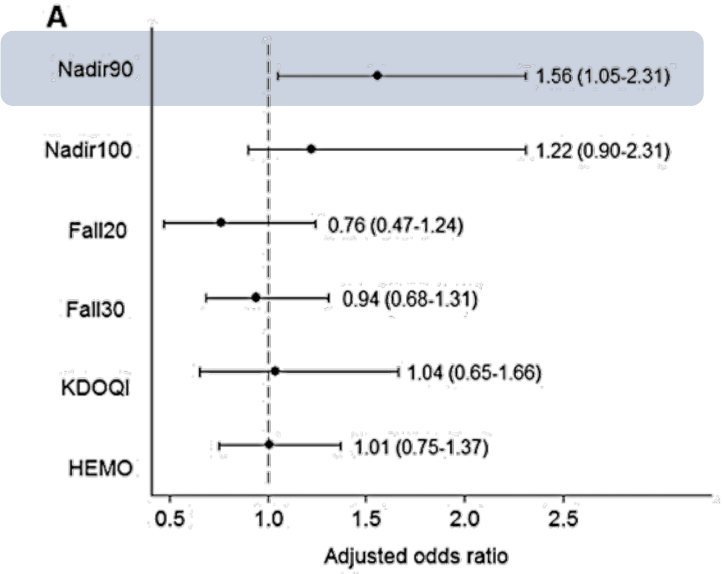
Flythe J et al, *Kidney Int.* 2011; 79, 250–257

Intra-Dialytic Hypotension and Mortality

Intensity and Frequency of IDH >90 mmHg are Associated with Poor Outcome

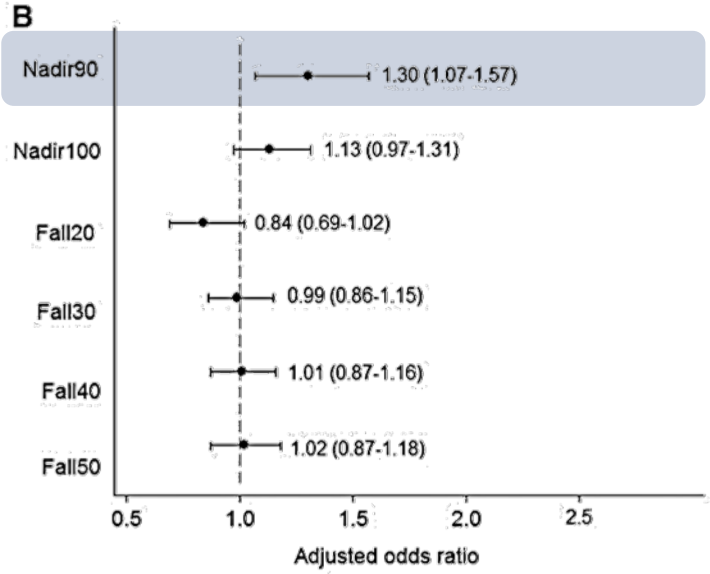
HEMO Cohort

1409 patients
12 561 treatments



LDO Cohort

10 392 patients
136 754 treatments



Flythe J et al, *J Am Soc Nephrol* 2015; 26: 724–734

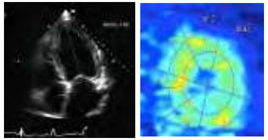
Multi-Organ Stress Dialysis-Induced

End Organ Damage and Outcome

Intra-Dialytic Hypotension

Repetitive Ischemic Insults

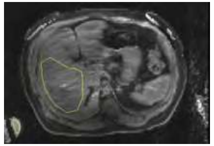
Cardiac Stunning | **Leukoaraiosis** | **Gut Translocation** | **Liver Dysfunction** | **Distal Necrosis** | **Inflammation** | **Residual Kidney Function**



Burton JO et al.
CJASN 2009

McIntyre CW et al.
JASN 2014

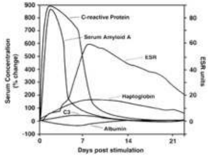
Jefferies HJ et al
Nephron Clin Pract. 2014



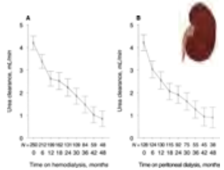
Grant CI et al
BMC Nephrol. 2018

Games FL et al,
Nephron Clin Pract. 2013

Stenvinkel P et al.
NDT 2002



McIntyre CW et al.
CJASN 2011



McKane W et al,
Kidney Int. 2002

Poor Outcome

Skin Sodium Content is Closely Linked to Left Ventricular Mass in Patients With CKD

Prospective Clinical Study

↓

99 Pts CKD2-3A

42F Age 65[23-78]

↓

Fluid Status (BIS)

BP (Office, 24hABPM)

Skin Na (23Na-MRI)

Echocardiography

Medications

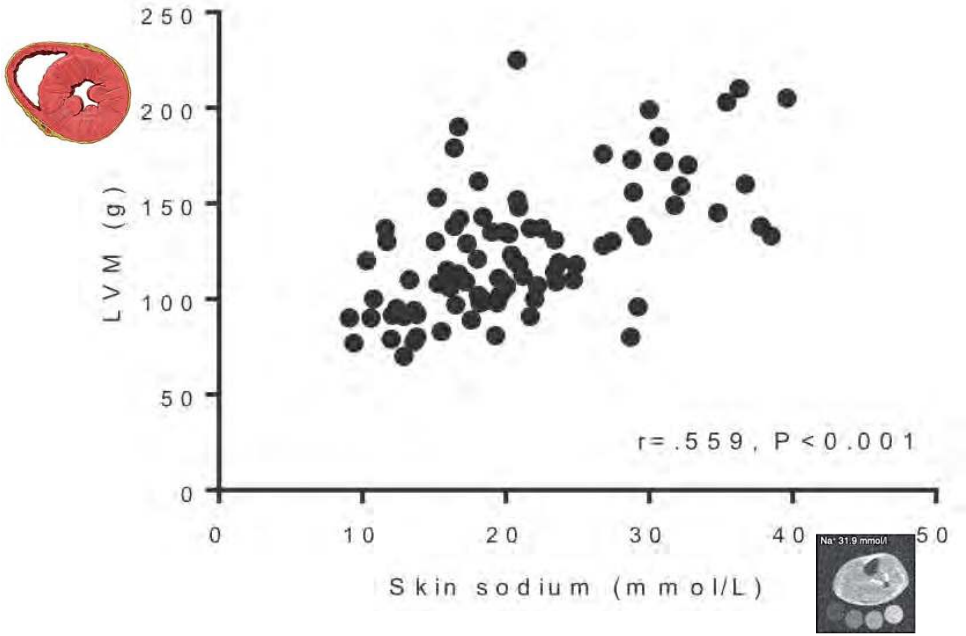
↓

Outcomes

Skin Na – 24hr-BP

Fluid Overload

Echocardiography



Schneider MP et al. *J Am Soc Nephrol.* 2017;28(6):1867-1876.

Skin Sodium Content is Poorly Linked to Hypertension and FO in Patients with Advanced CKD

Parameter	Skin Sodium <16.8 mmol/L, *n*=30	Skin Sodium 16.8–22.2 mmol/L, *n*=31	Skin Sodium >22.2 mmol/L, *n*=32	*P* Value
Office SBP, mmHg, mean (95% CI)	129(123 to 135)	133 (127 to 139)	135 (131 to 140)	0.22
Office DBP, mmHg, mean (95% CI)	81 (77 to 85)	82 (79 to 86)	78 (73 to 82)	0.18
24 h-SBP, mmHg, mean (95% CI)	122 (118 to 126)	124 (121 to 127)	132 (127 to 137)	0.002
24 h-DBP, mmHg, mean (95% CI)	78 (75 to 81)	76 (74 to 79)	77 (72 to 81)	0.64
Hypertension, %	83	90	100	0.07

Schneider MP et al. *J Am Soc Nephrol.* 2017;28(6):1867-1876.

Outline – Revisiting Sodium as the Uremic Toxin

1 Uremic Toxins, How to Define?
- ☐ Basic Considerations

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- ☐ From 2 to 3 Compartments Model
- ☐ Clinical Implications

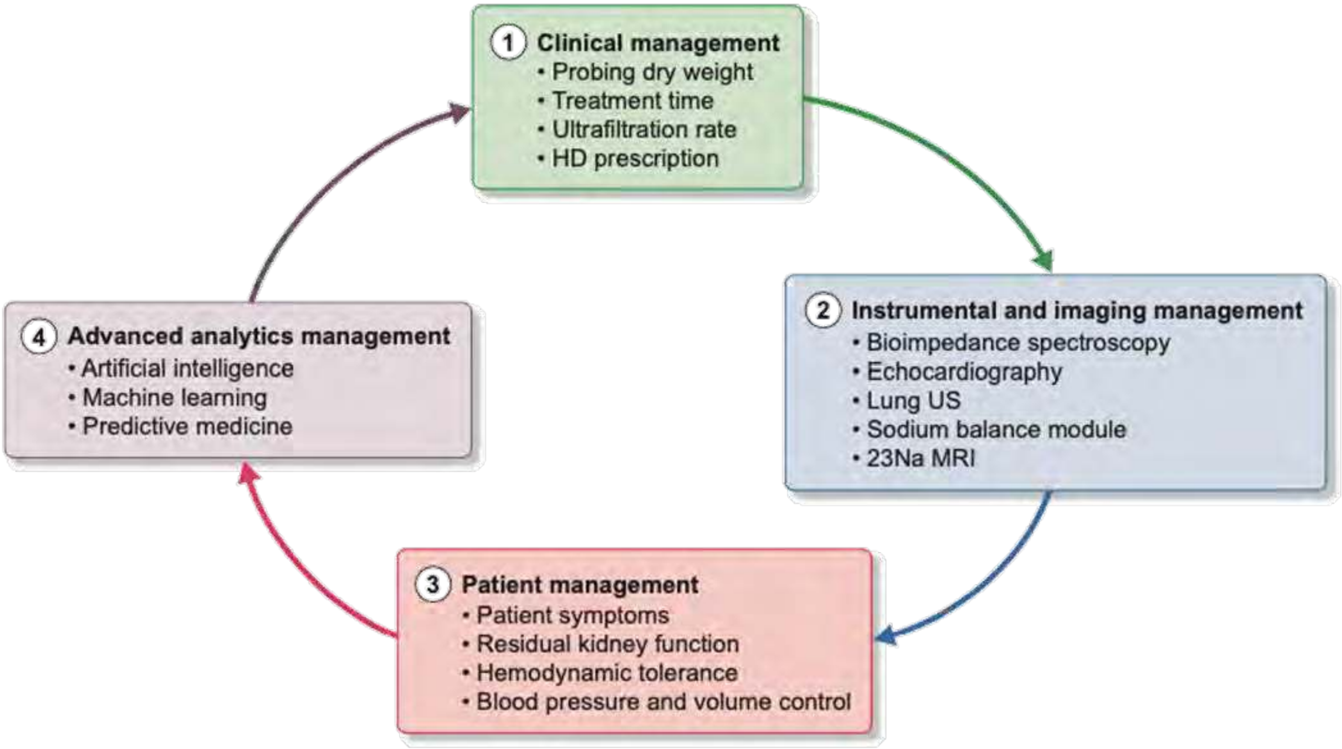
3 Sodium Toxicity, What are the facts?
- ☐ Water-Bound Sodium: Osmotic Active
- ☐ Water-Free Sodium: Metabolically Active

4 **Sodium Management, How to Act?**
- ☐ Monitoring
- ☐ Controlling

5 Take home message: Sodium-First Policy Approach

Volume and Pressure Management In HD Requires a New Vision

Comprehensive Assessment and Support of New Tools is Needed



Pinter J et al. *Nephrol Dial Transplant.* 2020;35(Suppl 2):ii23-ii30.

Effect of Active Dry Weight Reduction Guided by MF-BIA on Blood Pressure Control?

CKD5D Patients
(n = 55)

Dehydrated (n= 12)	Normovolemic (n= 26)	Overloaded (n=17)
TAFO≤0.25L	TAFO 0.25-1.25L	TAFO >1.25L
	Active Dry Weight Reduction Guided BCM Weekly	
3 Months FU		3 Months FU

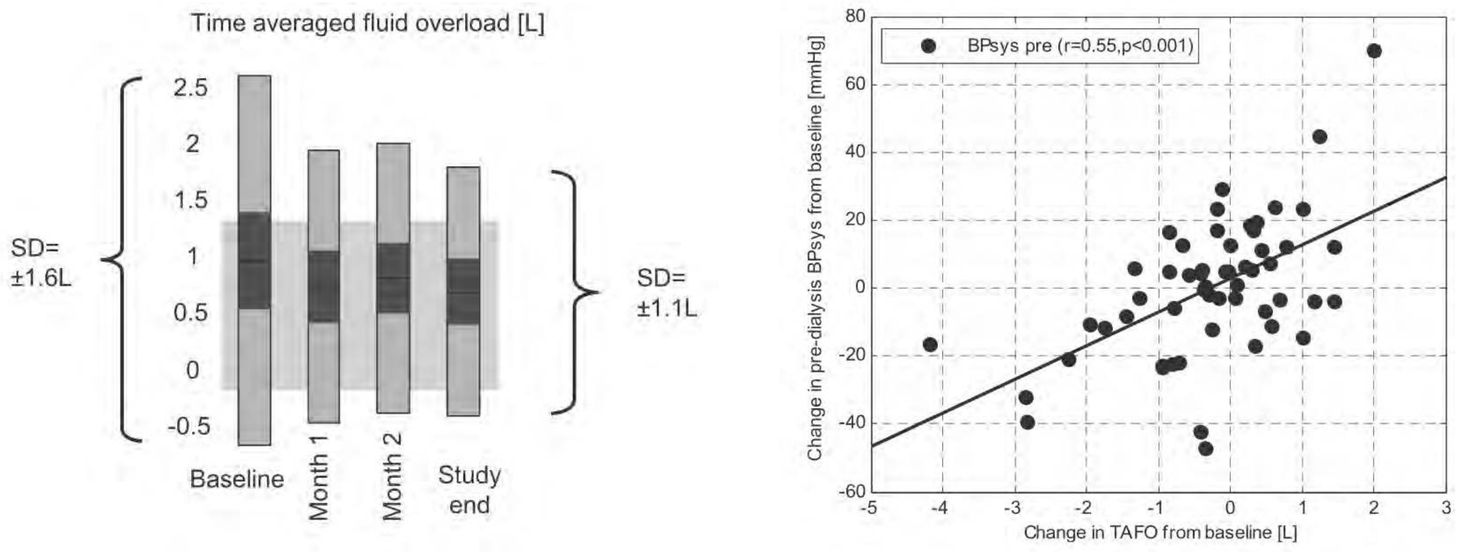
Outcomes

FO pre/post
BP pre/post
Weight pre/post
BNP
AHT

Moissl U et al. *Clin J Am Soc Nephrol.* 2013;8(9):1575-82.

Time Change of Fluid Overload (TAFO) and Blood Pressure

Overloaded Group



Moissl U et al. *Clin J Am Soc Nephrol.* 2013;8(9):1575-82.

Effect of Active Dry Weight Reduction Guided by Lung US on Blood Pressure Control?

CKD5D Patients
Hypertensive clinically euvolemic
(n = 71)


B-Lines

Intervention Group (n= 35)

Active Dry Weight Reduction Guided Lung US

Control Group (n=36)

Standard of Care


Standard of Care

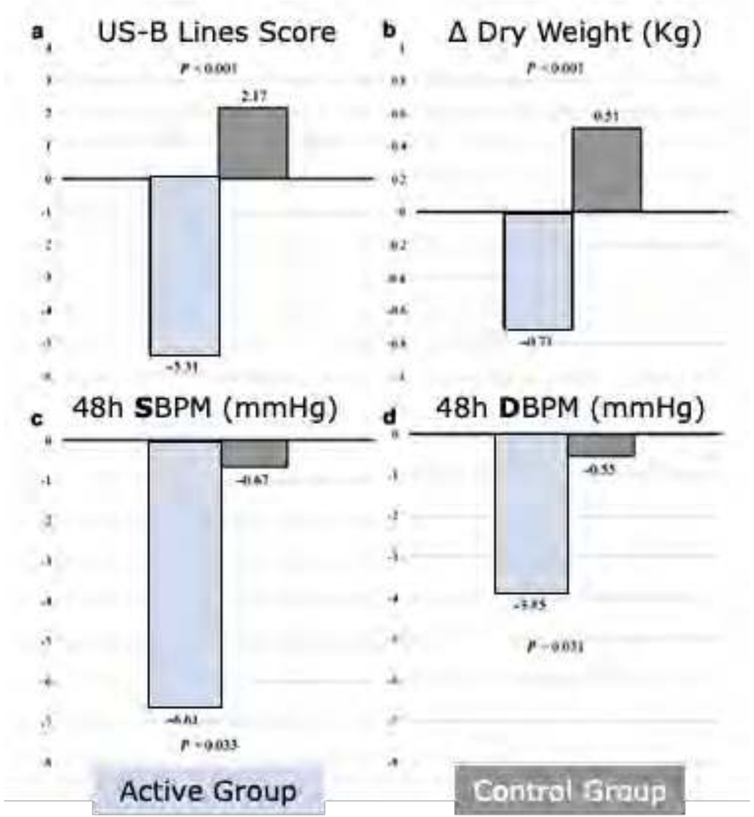
	Intervention Group	Control Group
Baseline	*48h-ABPM*	*48h-ABPM*
8 Week FU	*48h-ABPM*	*48h-ABPM*

Prospective RCT Study
Dry Weight reduction guided Lung US
Effect on ABPM

Loutradis C et al, *Kidney Int.* 2019; 95, 1505-1513

Active Intervention Guided by Lung US

Significant Reduction of DW and ABPM Values

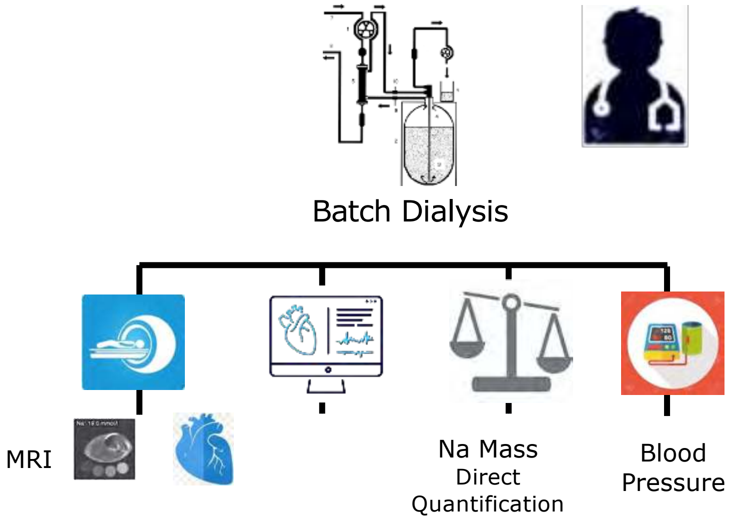


Prospective RCT Study
Dry Weight reduction guided Lung US
Effect on ABPM

Loutradis C et al, *Kidney Int.* 2019; 95, 1505-1513

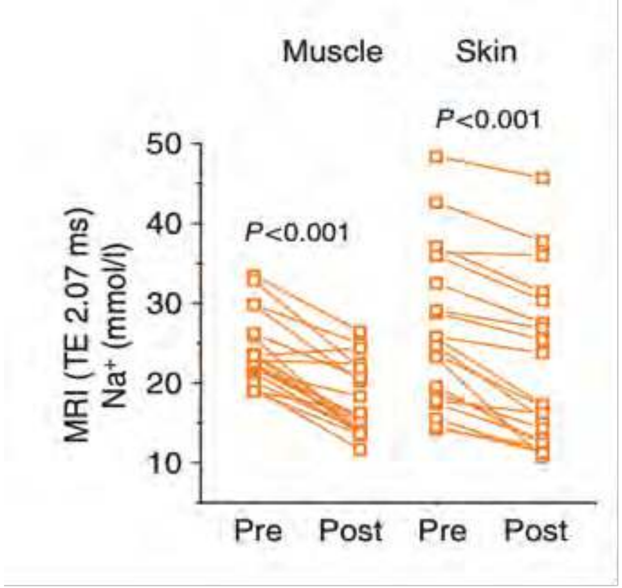
Is Tissue Sodium Mobilizable by Hemodialysis?

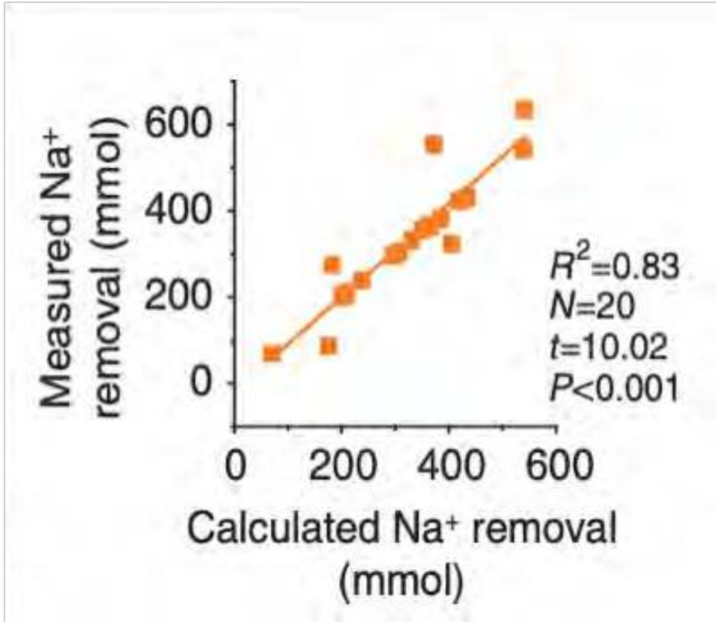
CKD5D Patients
(n = 20)



Tissue Sodium (Skin, Muscle) Mobilized by Dialysis

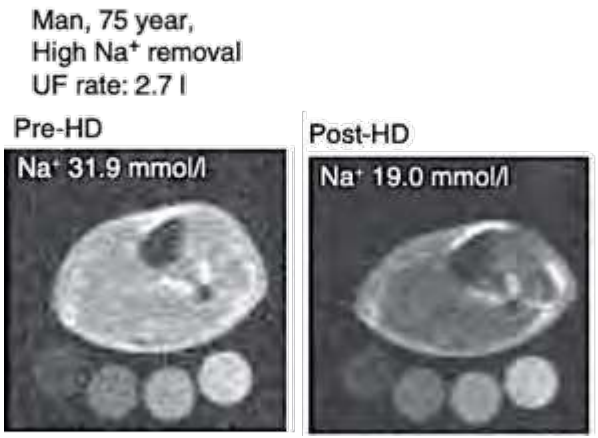
Correlated with Sodium Mass Removed

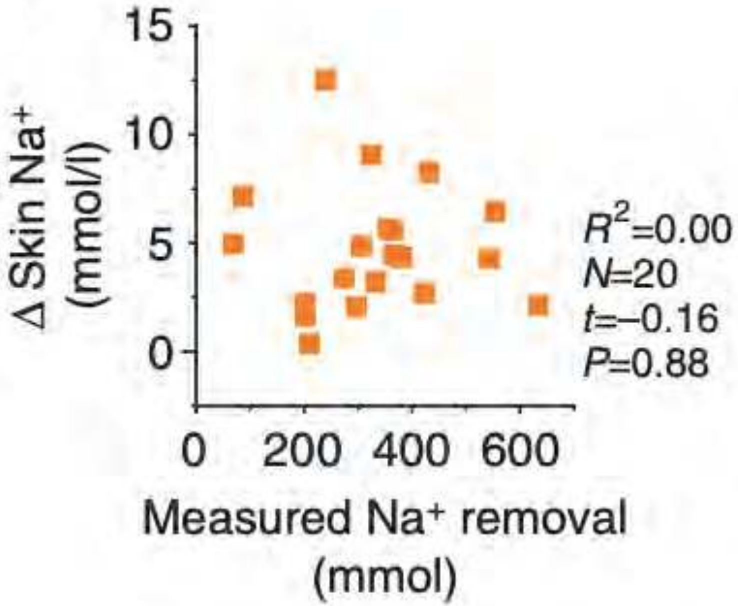




Dahlmann A et al, *Kidney Int.* 2015;87, 434–441

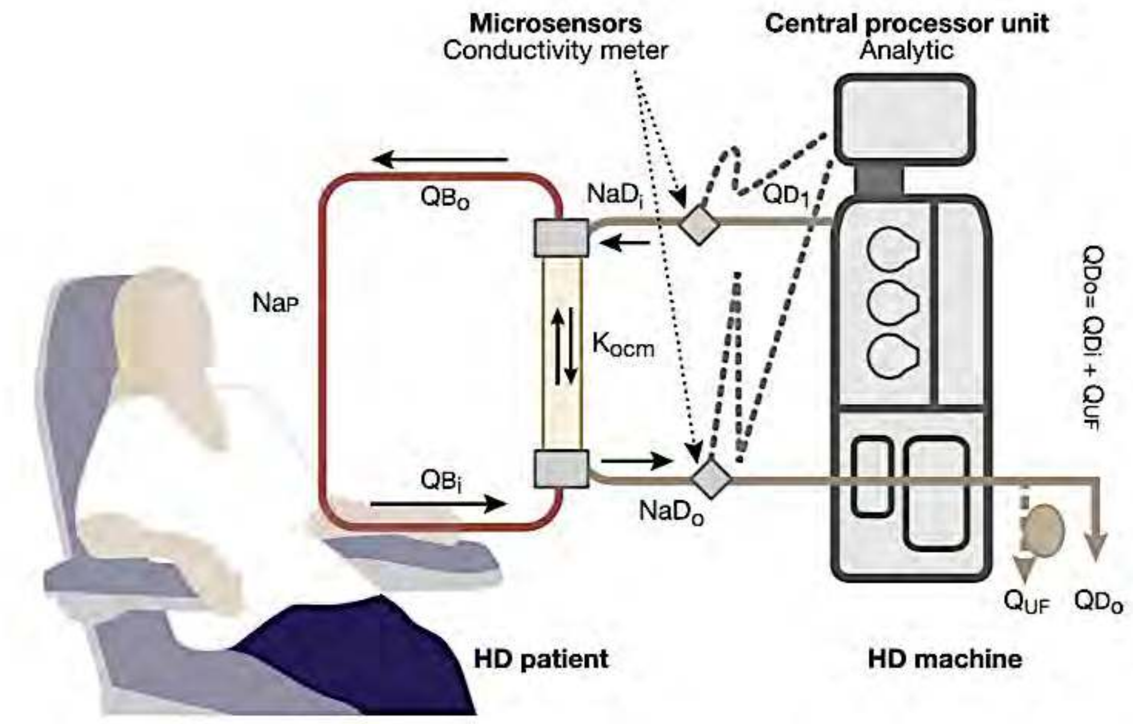
Tissue Sodium (Skin, Muscle) Mobilized in Dialysis by the Picture





Sodium Control Modul* Algorithm Implemented on HD Machine

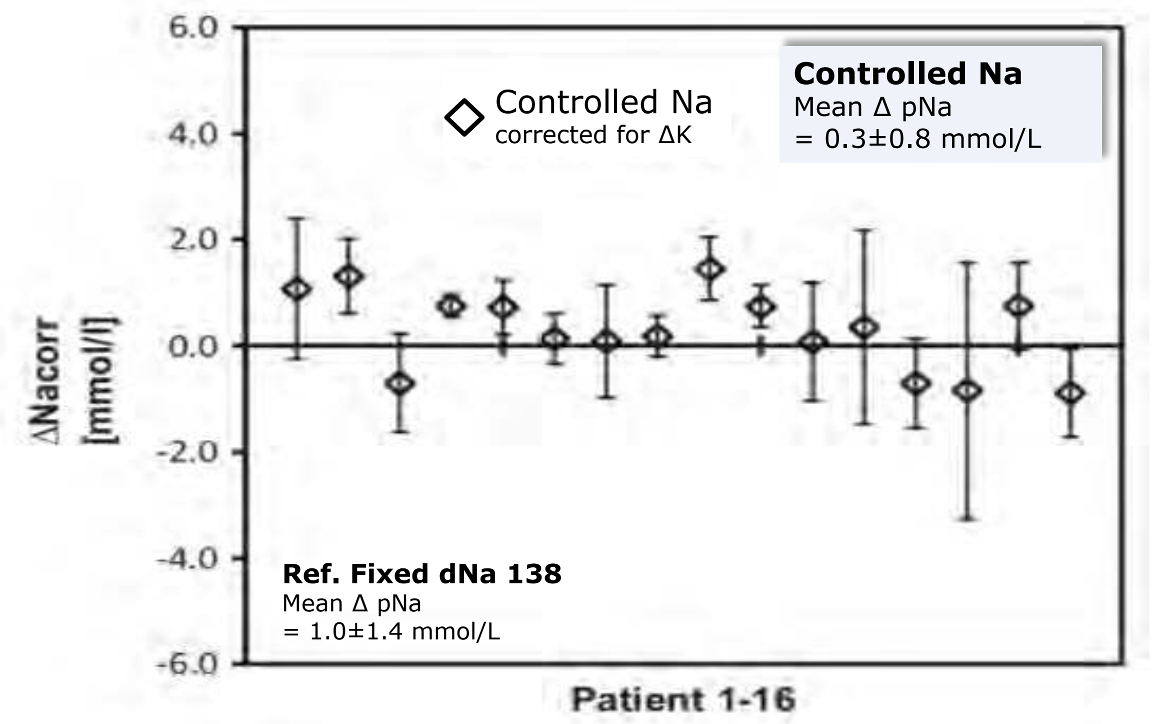
Automated Feedback Control



*Note that this Technical Option is Not Available in US

Canaud B et al, *Kidney Int.* 2019;95: 296–309

Plasma Sodium Changes during *'Zero Diffusive Na'* (ISONATREMIC) Condition

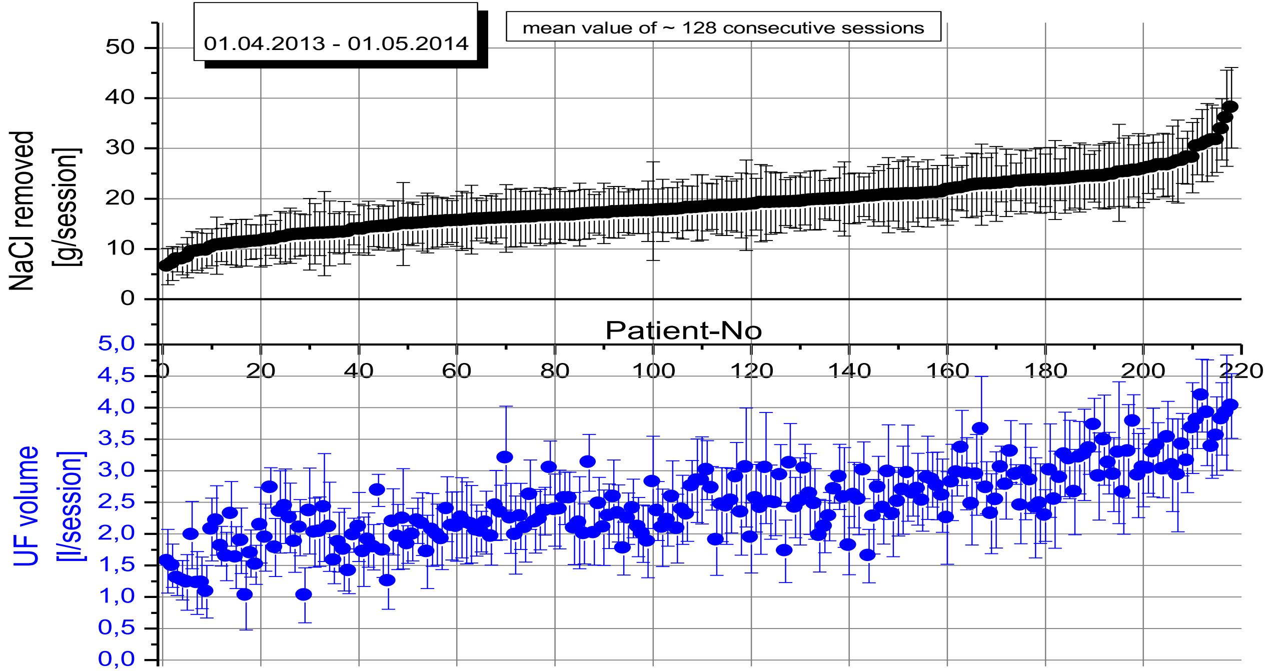


Kuhlmann U et al, *Artif Organs.* 2019;43(2):150-158

Quantification of Salt Mass Removed/Intake

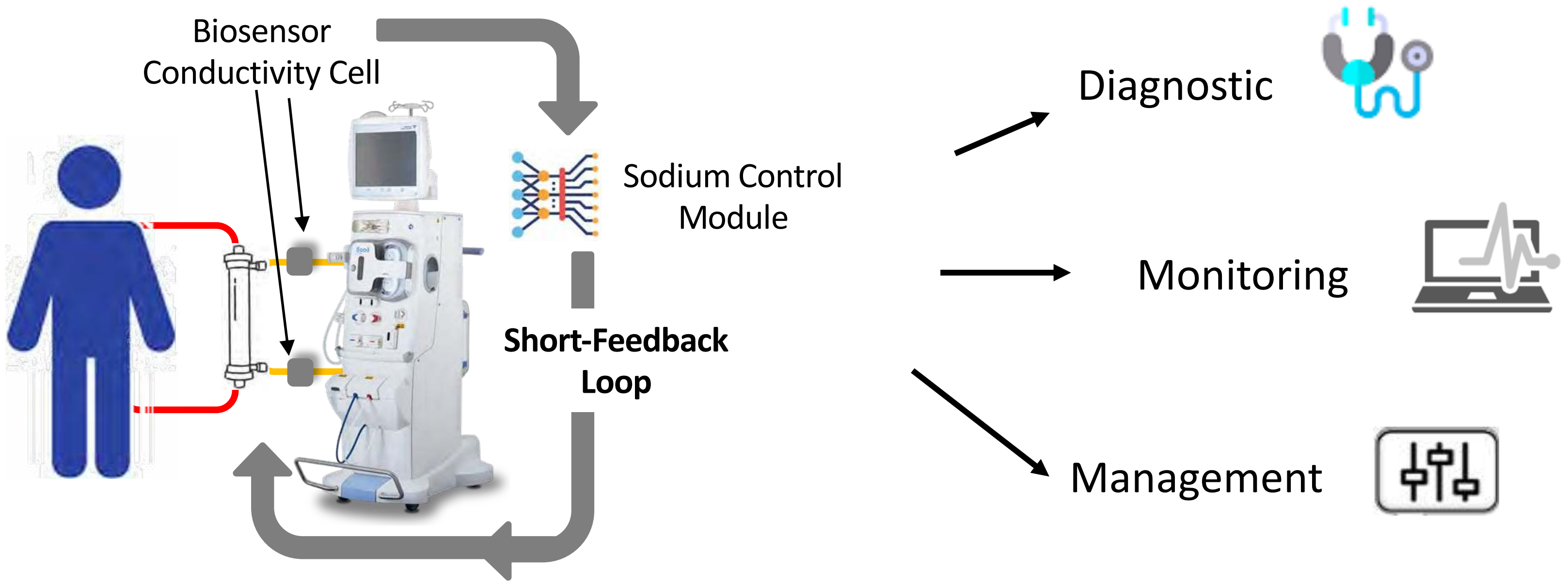
Individual Salt Mass Removed (g/session)

Mean Value over 126 Sessions in 220 Patients



Hemodialysis Machine with Automated Sodium Control Module*

Beyond Dialysis, a Diagnostic, Monitoring & Therapeutic Tool to Improve Care

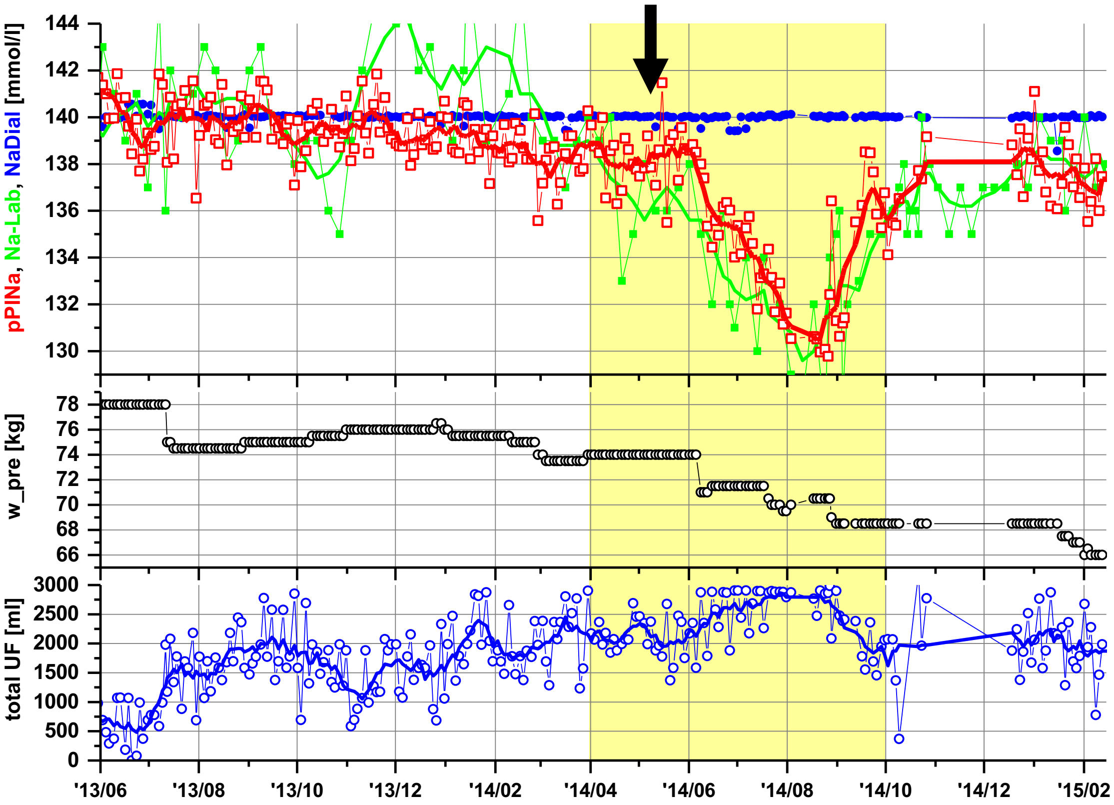


*Note that this Technical Option is Not Available in US

Canaud B et al, *Kidney Int.* 2019;95: 296–309

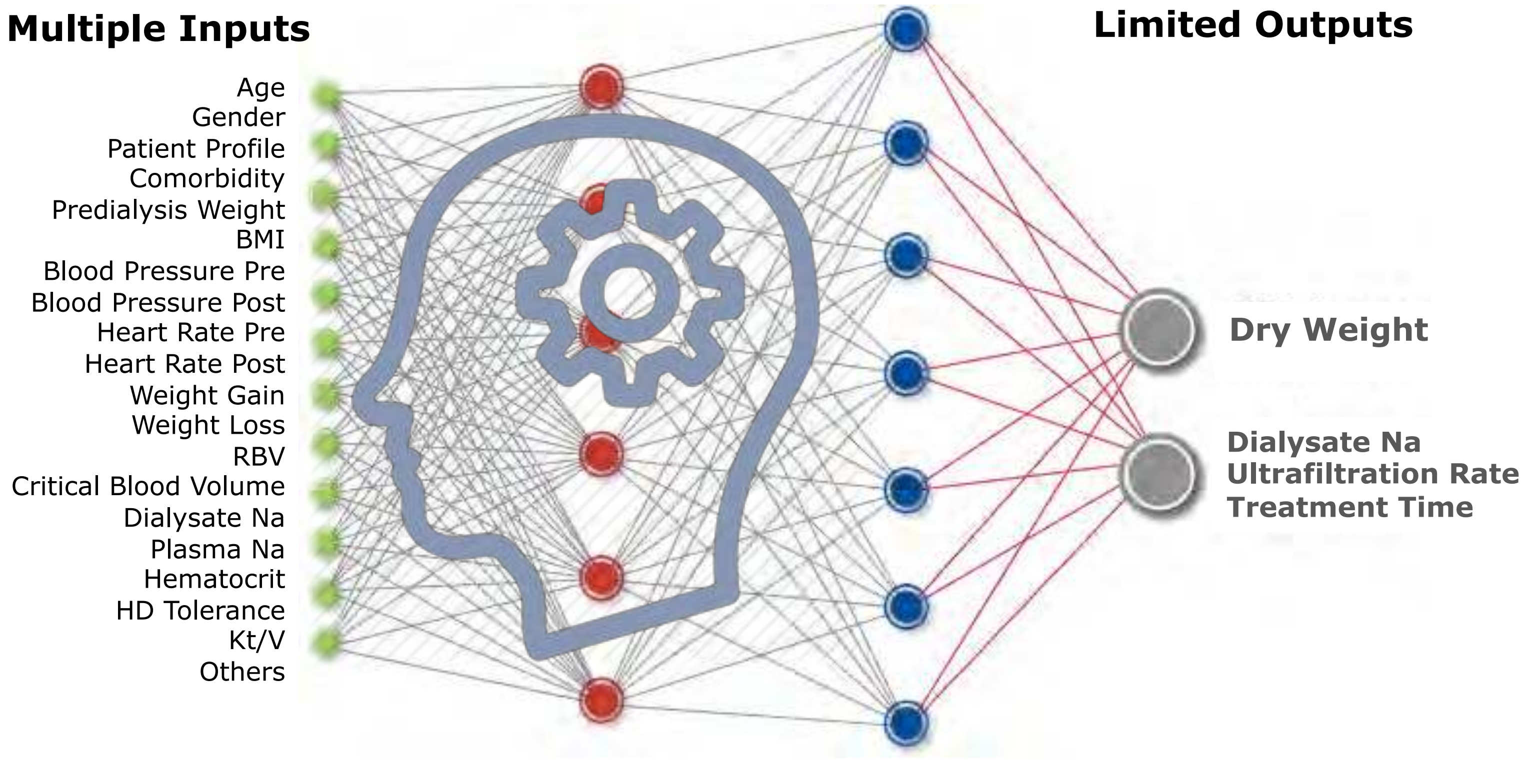
Early Detection of Hypotonic Hyponatremia with Sodium Controlled Module

Clinical Case#1: Detection of Congestive Heart Failure Treated by Intensive Ultrafiltration



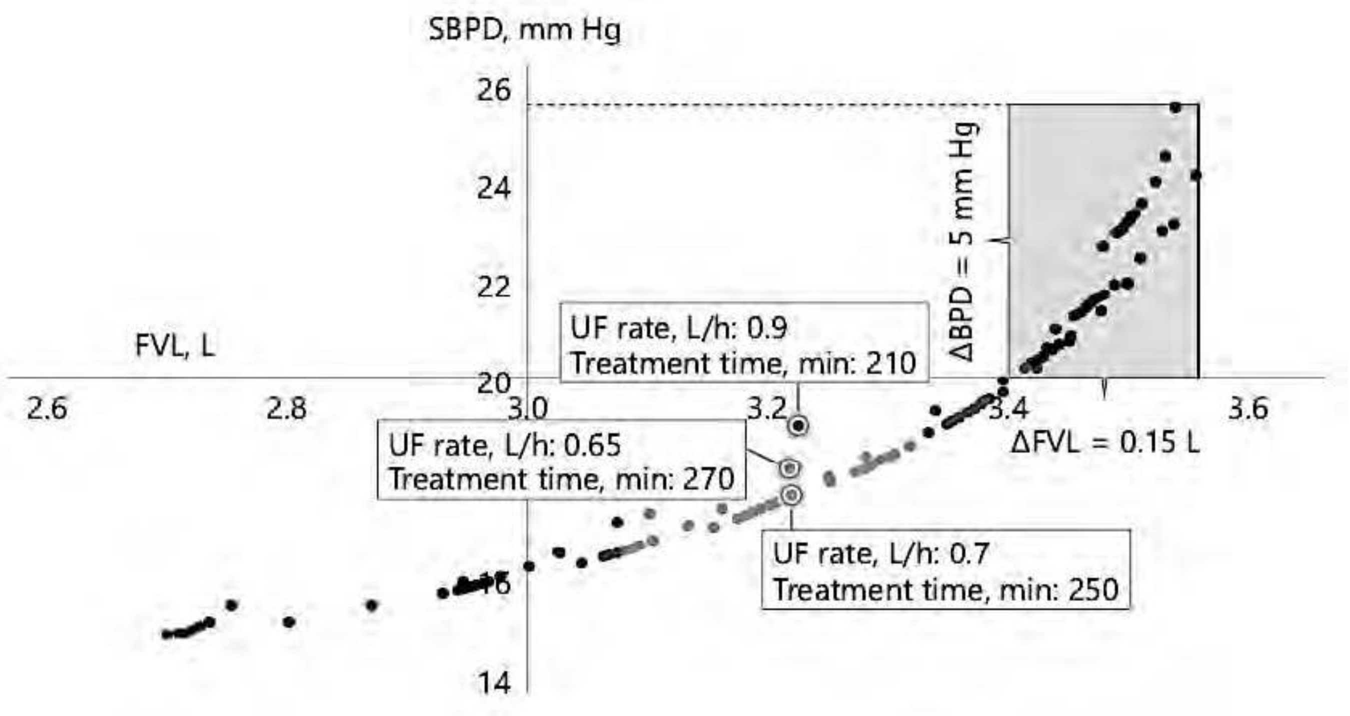
Harlos J et al. *Nephrol Dial Transplant.* 2020;35(S35):1067 (Abstract ERA-EDTA 2020)

Artificial Intelligence to Support Sodium, Water and Hemodynamic Management in Dialysis Patient



AI to Guide Fluid and Hemodynamic Mgt in HD Patient

UF Prescription and Simulated SBP Change in 2 Patients



Barbieri C et al, *Kidney Dis* 2019;5:28–33

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- ☐ Controlling

5 **Take home message: Sodium-First Approach**

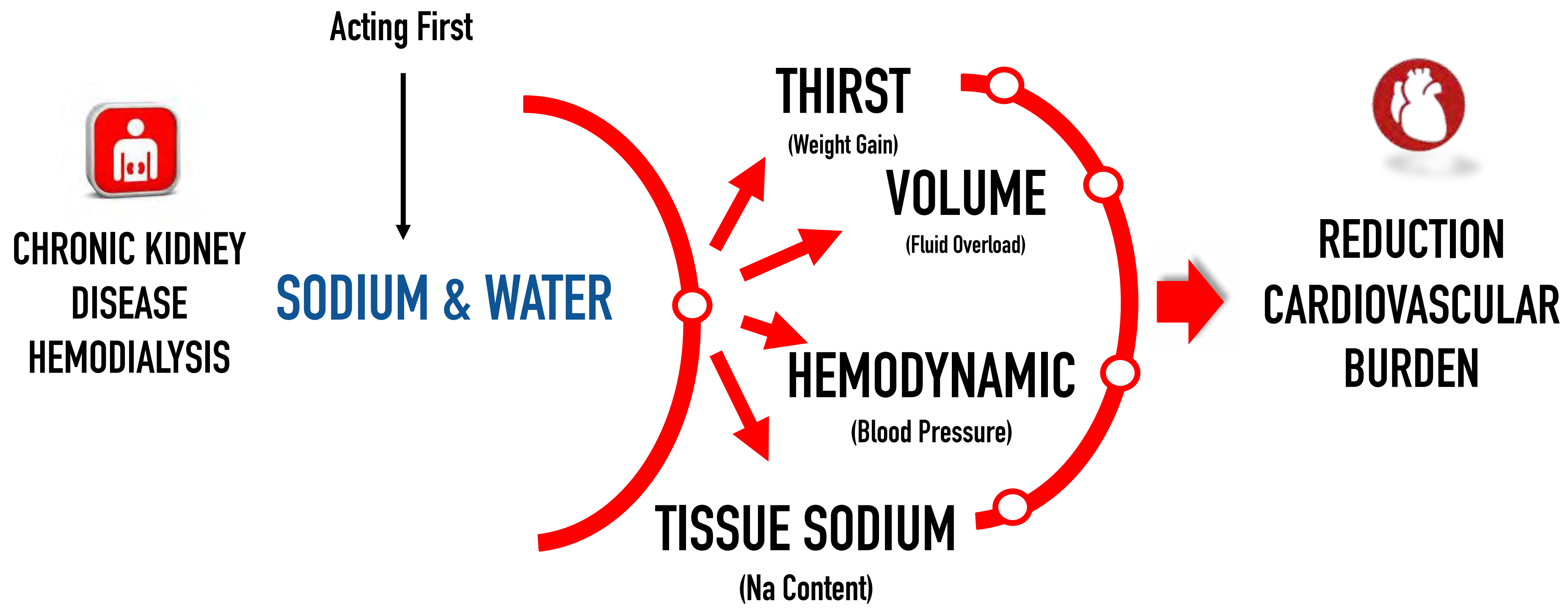
Sodium is a Premium Uremic Toxin . . . at our Reach

- ✓ Sodium is chemically identified and characterized.
- ✓ Quantitative measurement of Sodium in biological fluids and body is possible.
- ✓ The level of Sodium in biological fluids and body is elevated in uremia.
- ✓ A relationship between the amount of Sodium in biological fluids and body is responsible for most of CVD manifestations in uremia.
- ✓ A reduction in the amount of Sodium in body will result in the amelioration of the uremic manifestation.
- ✓ Excessive intake of Sodium reproduces major part of the uremic manifestations
- ✓ Pathobiological mechanism linkage between Sodium amount and the uremic manifestation is obvious.

Chmielewski M et al, *Uremic Toxicity*, in Nutritional Management of Renal Disease, 2013,4:49-77

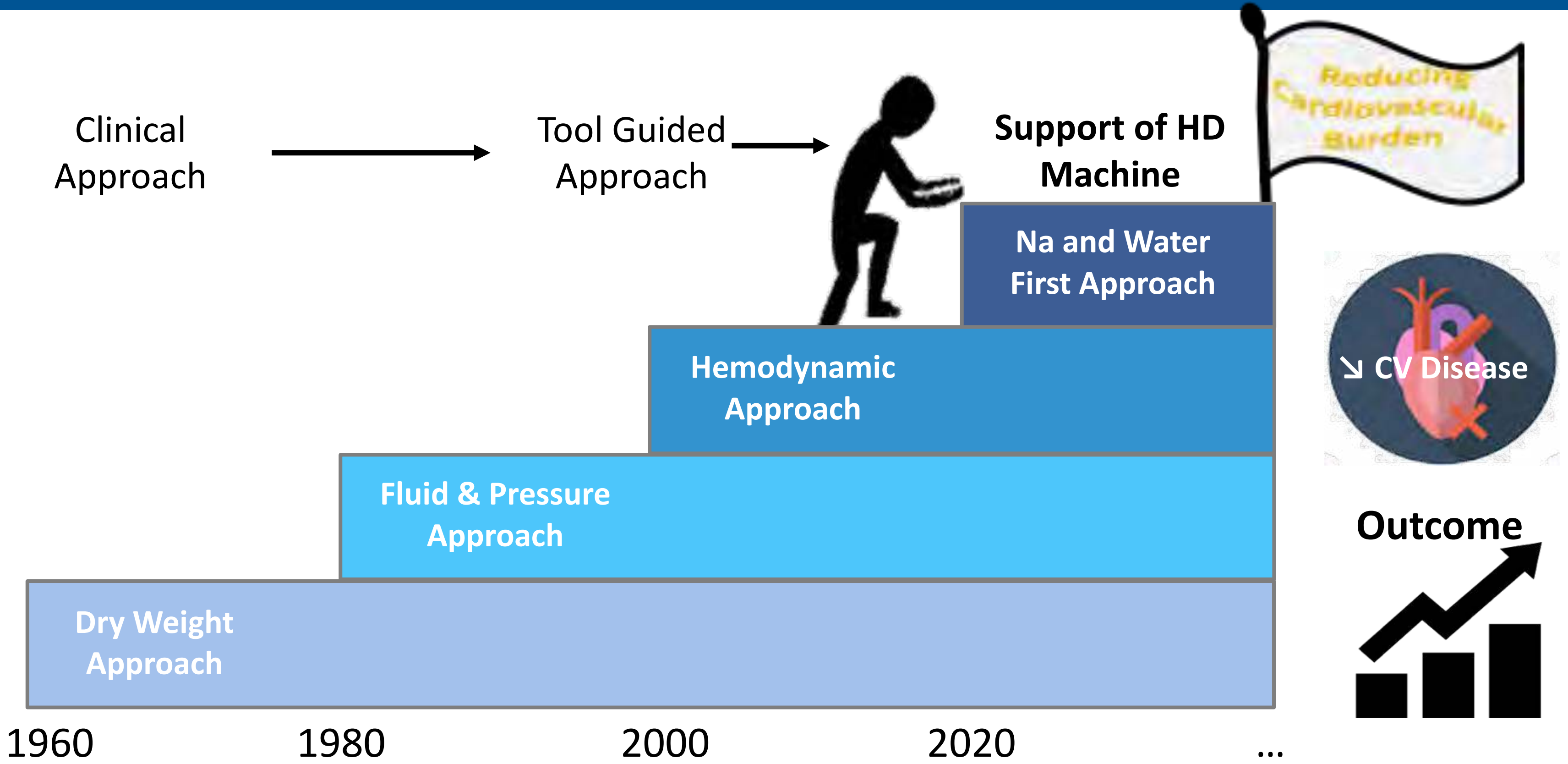
Acting First on Sodium and Water: Root Cause of CVD

Sodium First Approach



Acting on Na and Water to Tackle the Main Root of CV Disease in HD Patient

Integrated Tool Support Approach – A Step Further



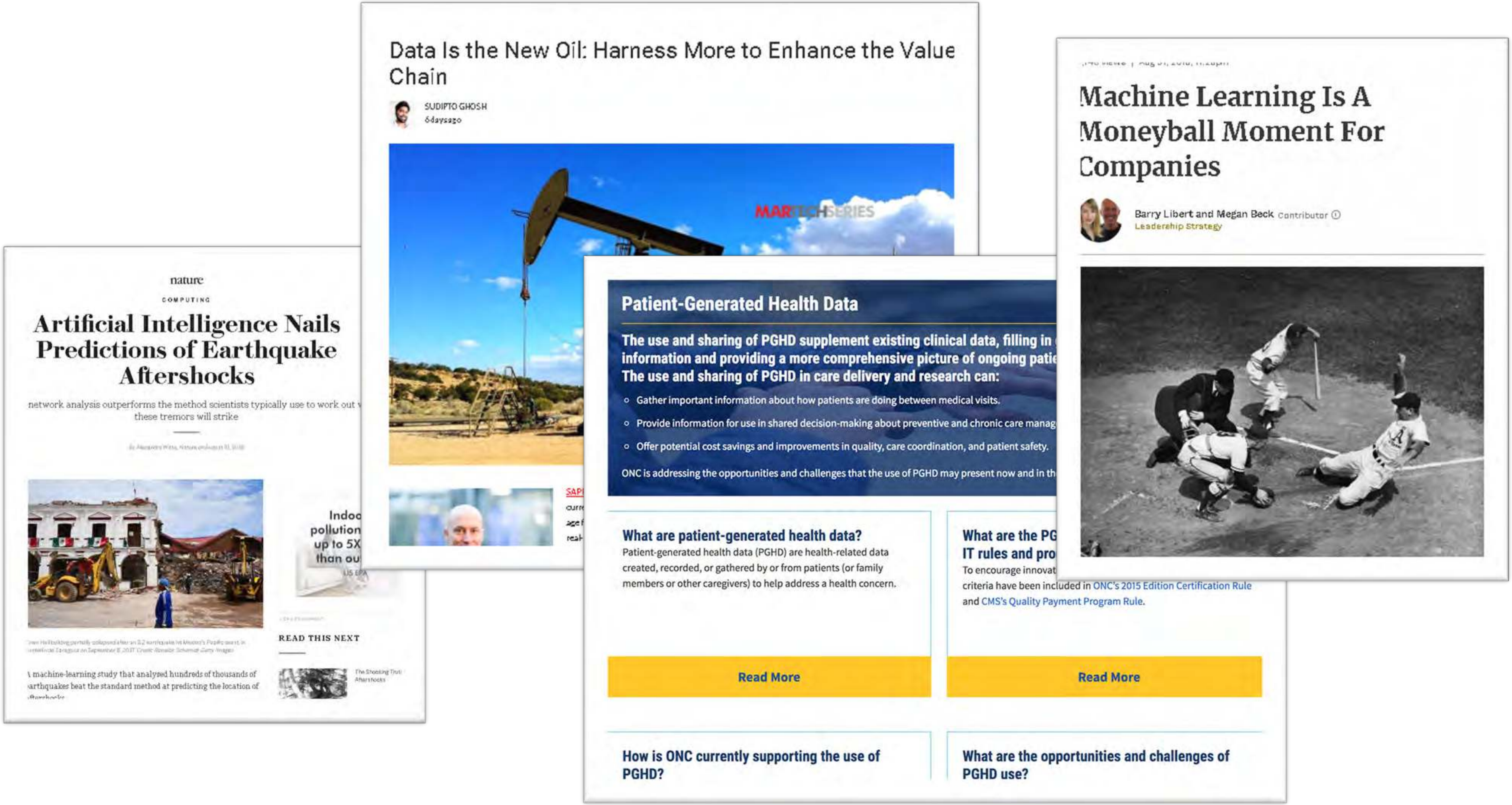
Annual Dialysis Conference

Artificial Intelligence in Kidney Care: Prospects and Challenges

Peter Kotanko, MD, FASN
Renal Research Institute
New York, NY

Disclosures

- I am an employee of the Renal Research Institute, New York, NY, a wholly owned subsidiary of Fresenius Medical Care (FMC)
- I hold stock in FMC
- I receive author royalties from UpToDate



nature

COMPUTING

Artificial Intelligence Nails Predictions of Earthquake Aftershocks

network analysis outperforms the method scientists typically use to work out w… these tremors will strike

READ THIS NEXT

Data Is the New Oil: Harness More to Enhance the Value Chain

SUDIPTO GHOSH
6daysago

MARTECHSERIES

Patient-Generated Health Data

The use and sharing of PGHD supplement existing clinical data, filling in … information and providing a more comprehensive picture of ongoing patie… The use and sharing of PGHD in care delivery and research can:

- Gather important information about how patients are doing between medical visits.
- Provide information for use in shared decision-making about preventive and chronic care manag…
- Offer potential cost savings and improvements in quality, care coordination, and patient safety.

ONC is addressing the opportunities and challenges that the use of PGHD may present now and in th…

What are patient-generated health data?

Patient-generated health data (PGHD) are health-related data created, recorded, or gathered by or from patients (or family members or other caregivers) to help address a health concern.

Read More

What are the PG… IT rules and pro…

To encourage innovat… criteria have been included in ONC's 2015 Edition Certification Rule and CMS's Quality Payment Program Rule.

Read More

How is ONC currently supporting the use of PGHD?

What are the opportunities and challenges of PGHD use?

Machine Learning Is A Moneyball Moment For Companies

Barry Libert and Megan Beck Contributor
Leadership Strategy

C.David Naylor

JAMA Published online August 30, 2018

VIEWPOINT

On the Prospects for a (Deep) Learning Health Care System

JACC REVIEW TOPIC OF THE WEEK

Artificial Intelligence in Cardiology

Kipp W. Johnson, BS,[a,b] Jessica Torres Soto, MS,[c,d,e] Benjamin S. Glicksberg, PhD,[a,b,f] Khader Shameer, PhD,[g] Riccardo Miotto, PhD,[a,b] Mohsin Ali, MPhil,[a,b] Euan Ashley, MBChB, DPhil,[c,d,e] Joel T. Dudley, PhD[a,b]

EDITORIAL

Clinical Implications and Challenges of Artificial Intelligence and Deep Learning

William W. Stead, MD

nature biomedical engineering

REVIEW ARTICLE

https://doi.org/10.1038/s41551-018-0305-z

Artificial intelligence in healthcare

Kun-Hsing Yu[1], Andrew L. Beam[1] and Isaac S. Kohane[1,2*]

www.kidney-international.org
review

Big science and big data in nephrology

OPEN

Julio Saez-Rodriguez[1,2,3], Markus M. Rinschen[4,5], Jürgen Floege[6] and Rafael Kramann[6,7]

Machine Learning Comes to Nephrology

Kevin V. Lemley
Division of Nephrology, Children's Hospital Los Angeles, Los Angeles, California; and Department of Pediatrics, Keck School of Medicine of the University of Southern California, Los Angeles, California

JASN 30: ●●●–●●●, 2019.
doi: https://doi.org/10.1681/ASN.2019070664

Computational Segmentation and Classification of Diabetic Glomerulosclerosis

Brandon Ginley,[1] Brendon Lutnick,[1] Kuang-Yu Jen,[2] Agnes B. Fogo,[3] Sanjay Jain,[4] Avi Rosenberg,[5] Vighnesh Walavalkar,[6] Gregory Wilding,[7] John E. Tomaszewski,[1,8] Rabi Yacoub,[9] Giovanni Maria Rossi,[5,10] and Pinaki Sarder[1,7,11]

September 2019 | ASN Kidney News |

CLINICAL RESEARCH www.jasn.org

With PEAK Program, Artificial Intelligence Helps Build Smooth Transition to Dialysis, Encouraging Home Modalities

By Ollie Fielding

Deep Learning–Based Histopathologic Assessment of Kidney Tissue

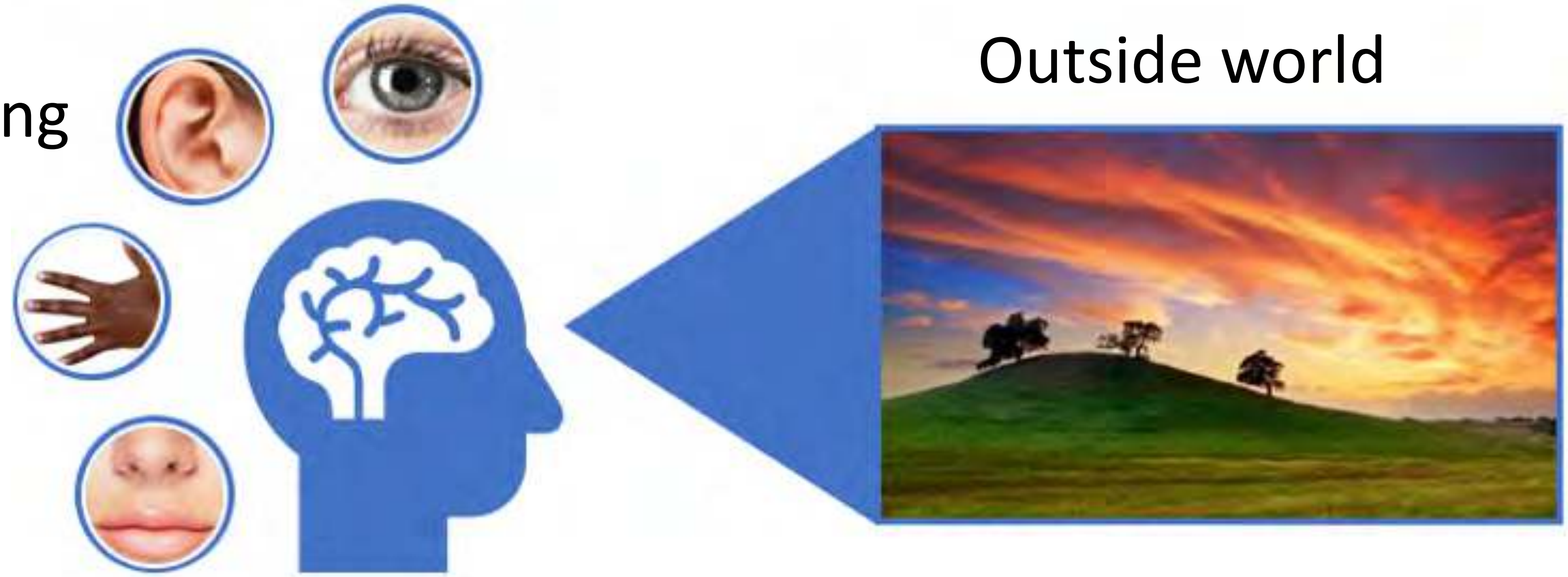
Meyke Hermsen,[1] Thomas de Bel,[1] Marjolijn den Boer,[1] Eric J. Steenbergen,[1] Jesper Kers,[2,3,4] Sandrine Florquin,[2] Joris J. T. H. Roelofs,[2] Mark D. Stegall,[5,6] Mariam P. Alexander,[6,7] Byron H. Smith,[6,8] Bart Smeets,[1] Luuk B. Hilbrands,[9] and

Perspective
AJKD

Artificial Intelligence in Nephrology: Core Concepts, Clinical Applications, and Perspectives

Olivier Niel and Paul Bastard

We are dealing with an old problem …
How to make sense of the many inputs we receive



The amount of data has grown exponentially over the past years, also in medicine. How to make sense of them?

One way (I am not saying the only one!) is to use
“Artificial Intelligence (AI)” tools.
AI applications love (and require) huge data sets

A Brief History of AI – The Dartmouth Summer Research Project (1956)

- A group of avant-garde experts from different areas, among them Claude Shannon, decided to organize a summer research project on AI.
- The primary purpose of the research project was to tackle "**every aspect of learning or any other feature of intelligence that can in principle be so precisely described, that a machine can be made to simulate it**."
- It led to the idea that intelligent computers can be created.
- A new era began - **Artificial intelligence.**

- There is no universal definition of AI in the literature, but central to most definitions is the **ability of a machine system to learn**.
- Machine learning (ML), a sub-discipline of AI, is the scientific study of algorithms and statistical methods that **use patterns and inference to learn from training examples how to perform a specific task without using explicit instructions**.
- Deep Learning (DL) is a subfield of ML that uses **highly complex artificial neural networks** to learn.

What are AI, Machine Learning, Deep Learning?

Artificial Intelligence

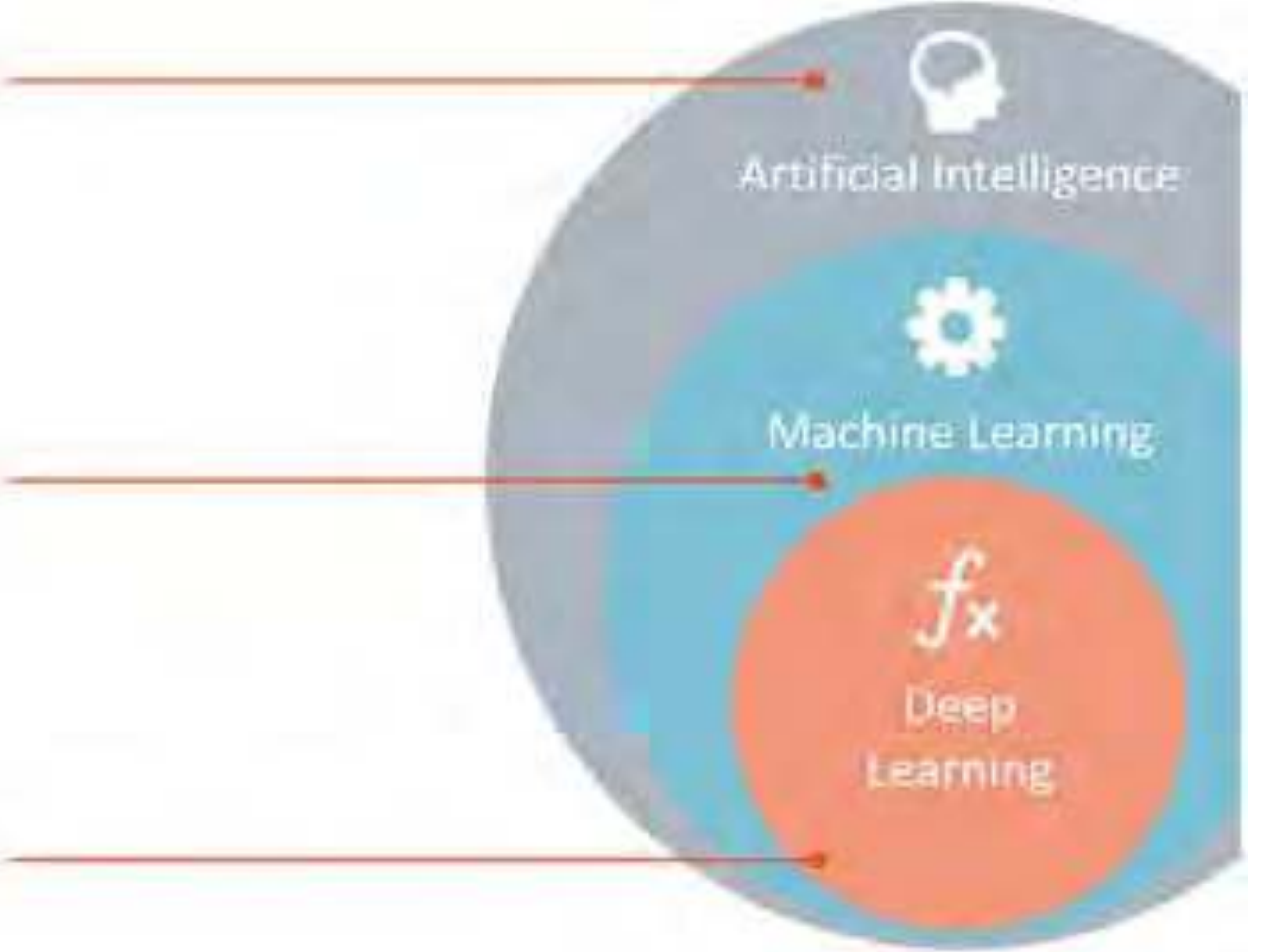
Any technique which enables computers to mimic human behavior.

Machine Learning

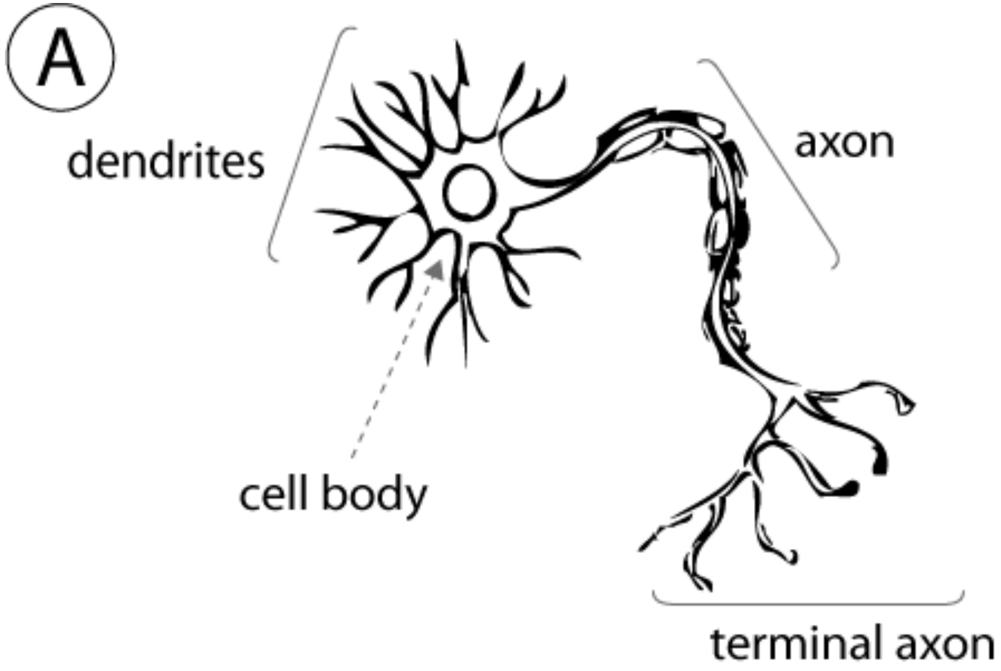
Subset of AI techniques which use statistical methods to enable machines to improve with experiences.

Deep Learning

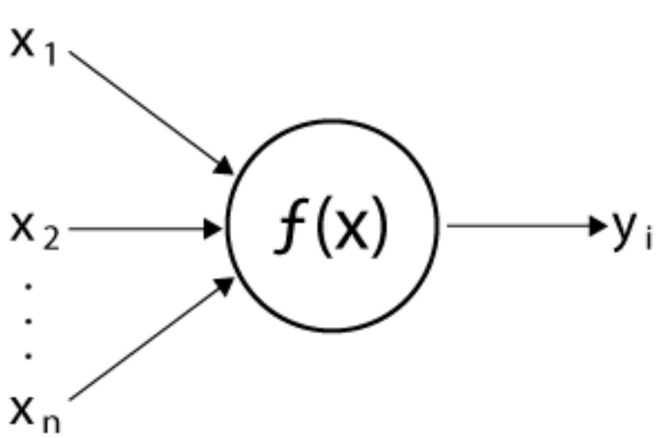
Subset of ML which make the computation of multi-layer neural networks feasible.

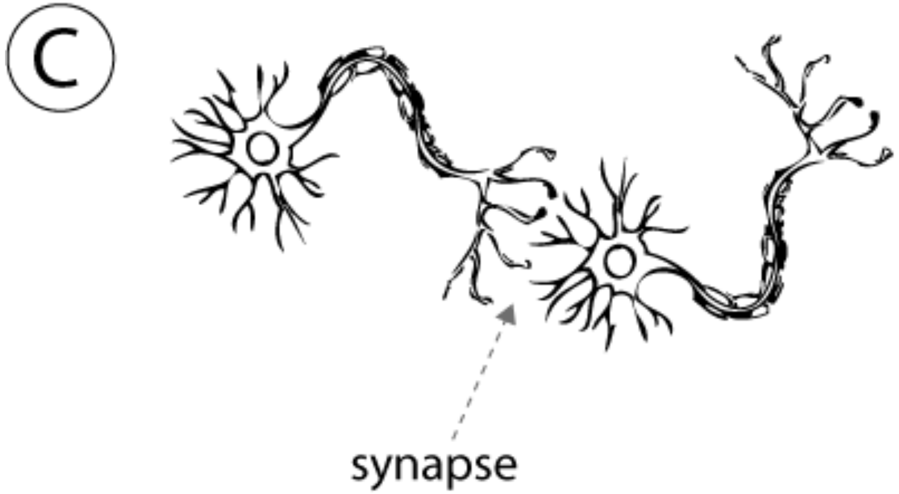


Artificial neural network – a quintessential AI methods

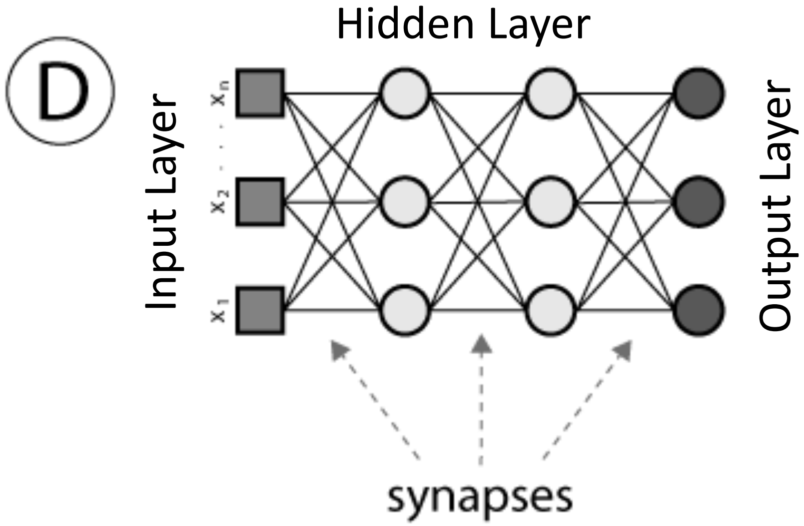


B **Artificial "neuron"**





Artificial neural network



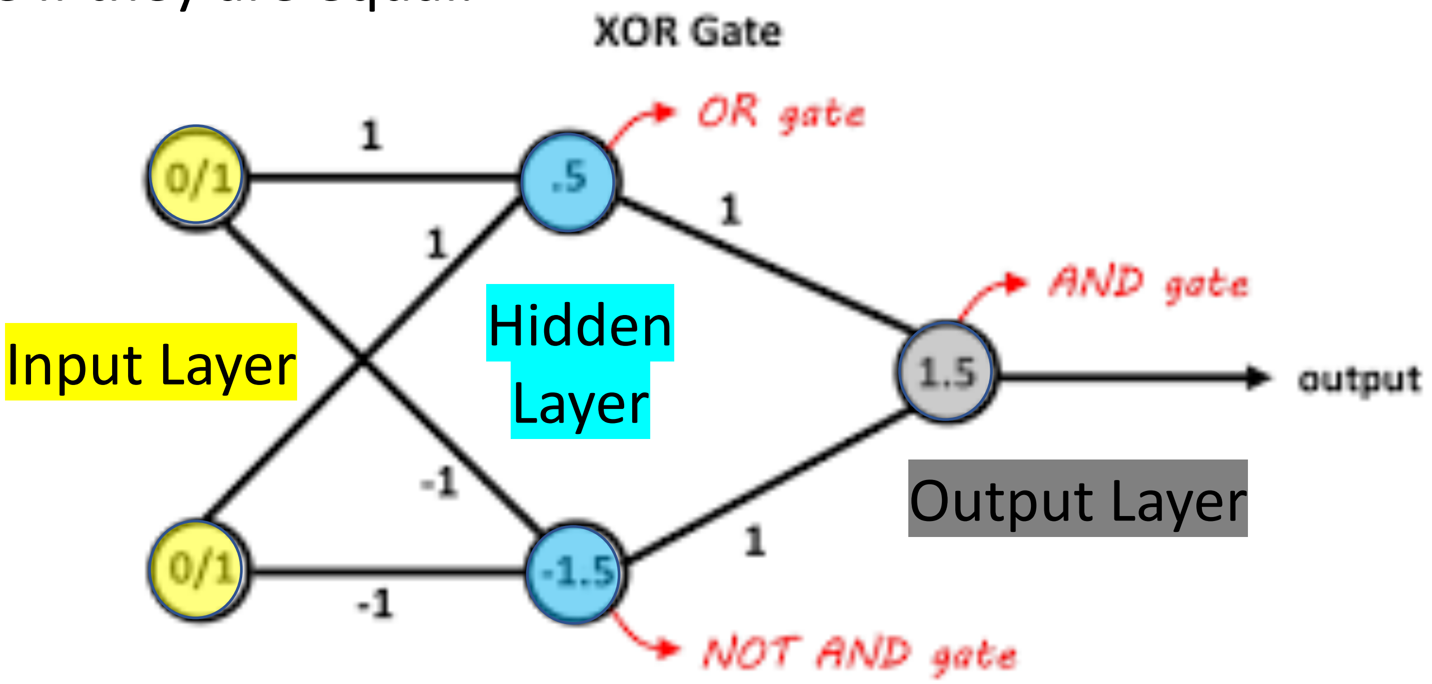
The XOR Problem Breakthrough: A Fundamentally Important Step for Pattern Recognition

The **XOR (“**exclusive or”**) problem** is a **classic problem in artificial neural network (ANN) research**. It is the problem of using an ANN to predict the outputs of XOR logic gates given two binary inputs.

An XOR function (see XOR truth table below) should return a true value if the two inputs are not equal and a false value if they are equal.

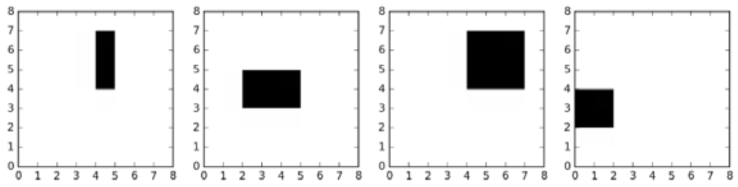
XOR Truth Table

Inputs		Outputs
X	Y	Z
0	0	0
0	1	1
1	0	1
1	1	0

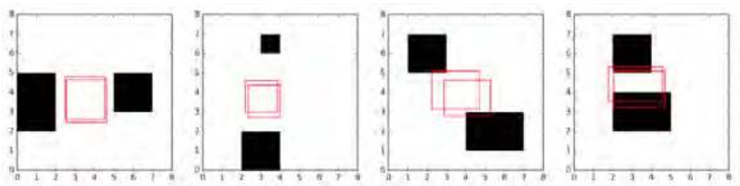


Solving the XOR Problem Led to Rapid Evolution of Image Recognition Using ANN with 1 to 3 Hidden Layers

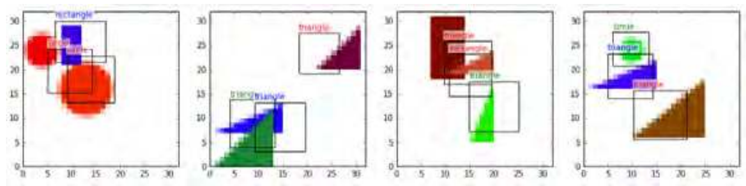
Single Object



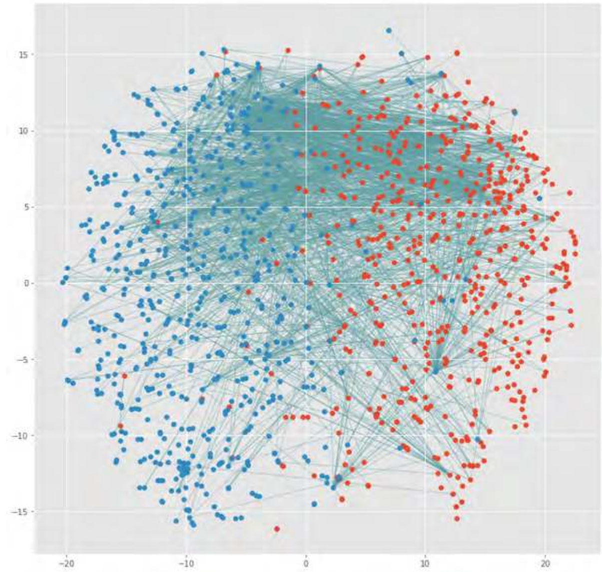
Multiple Objects



Complex Objects



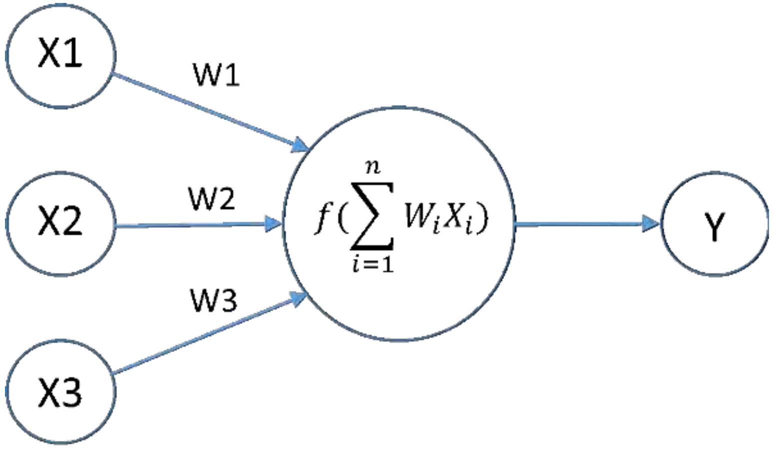
These Insights are the Foundation to the Creation of Complex AI Models

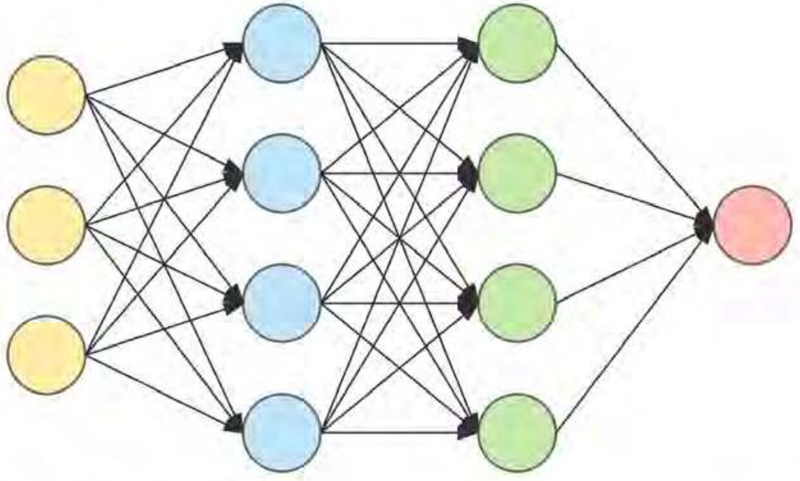


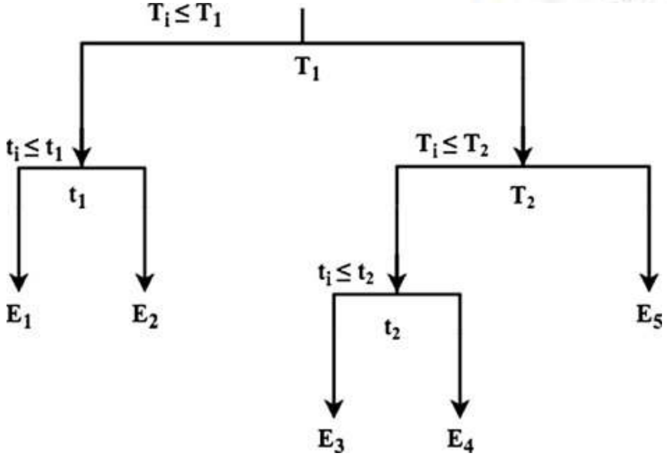
1. Initialize model with a constant value:

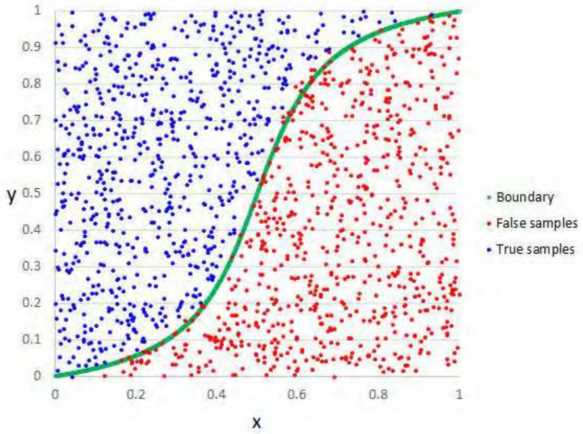
$$F_0(x) = \arg\min_{\gamma} \sum_{i=1}^{n} L(y_i, \gamma).$$

2. For $m = 1$ to M:
   1. Compute so-called *pseudo-residuals*:
   $$r_{im} = -\left[\frac{\partial L(y_i, F(x_i))}{\partial F(x_i)}\right]_{F(x)=F_{m-1}(x)} \quad \text{for } i = 1, \ldots, n.$$
   2. Fit a base learner $h_m(x)$ to pseudo-residuals, i.e. train it using the training set $\{(x_i, r_{im})\}_{i=1}^{n}$.
   3. Compute multiplier γ_m by solving the following one-dimensional optimization problem:
   $$\gamma_m = \arg\min_{\gamma} \sum_{i=1}^{n} L(y_i, F_{m-1}(x_i) + \gamma h_m(x_i)).$$
   4. Update the model:
   $$F_m(x) = F_{m-1}(x) + \gamma_m h_m(x).$$
3. Output $F_M(x)$.

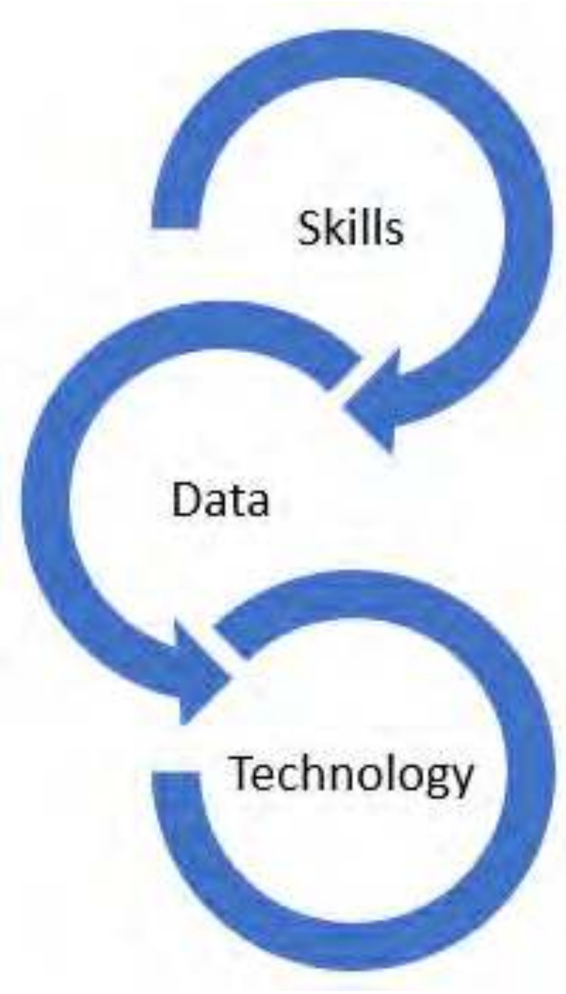








Who does What in AI?



Domain Expert (e.g. physician)

Domain Expert defines the goal, helps other team members to grasp the relevance of real-life questions

Data Scientist

Data Scientists use analytical and technical capabilities to extract meaningful insights from data

Data Engineer

Data Engineers ensure uninterrupted flow of data between servers and applications. They are responsible for data architecture

Statistician

Statisticians use theoretical expertise in statistics and apply them to real life problems

Mathematician

Mathematicians use mathematical modeling and computational methods to solve practical problems

nature biomedical engineering
REVIEW ARTICLE
https://doi.org/10.1038/s41551-018-0305-z

The (Exaggerated?) Promise of AI for Healthcare

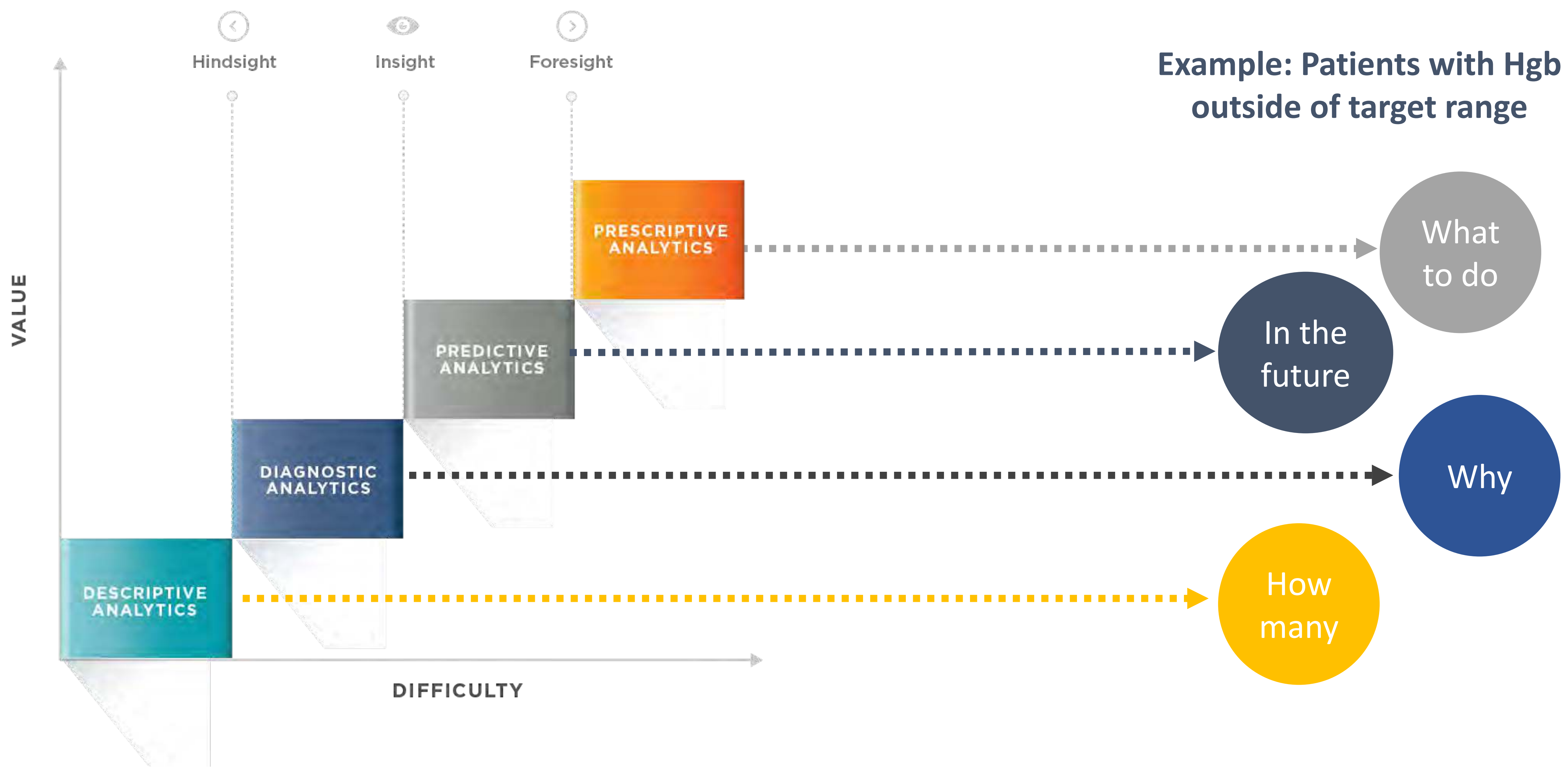
Artificial intelligence in healthcare

Kun-Hsing Yu[1], Andrew L. Beam[1] and Isaac S. Kohane[1,2*]

Table 1 | A non-exhaustive list of current and potential AI applications in medicine

Basic biomedical research	Translational research	Clinical practice
Automated experiments	Biomarker discovery	Disease diagnosis
Automated data collection	Drug–target prioritization	Interpretation of patient genomes
Gene function annotation	Drug discovery	Treatment selection
Prediction of transcription factor binding sites	Drug repurposing	Automated surgery
Simulation of molecular dynamics	Prediction of chemical toxicity	Patient monitoring
Literature mining	Genetic variant annotation	Patient risk stratification for primary prevention

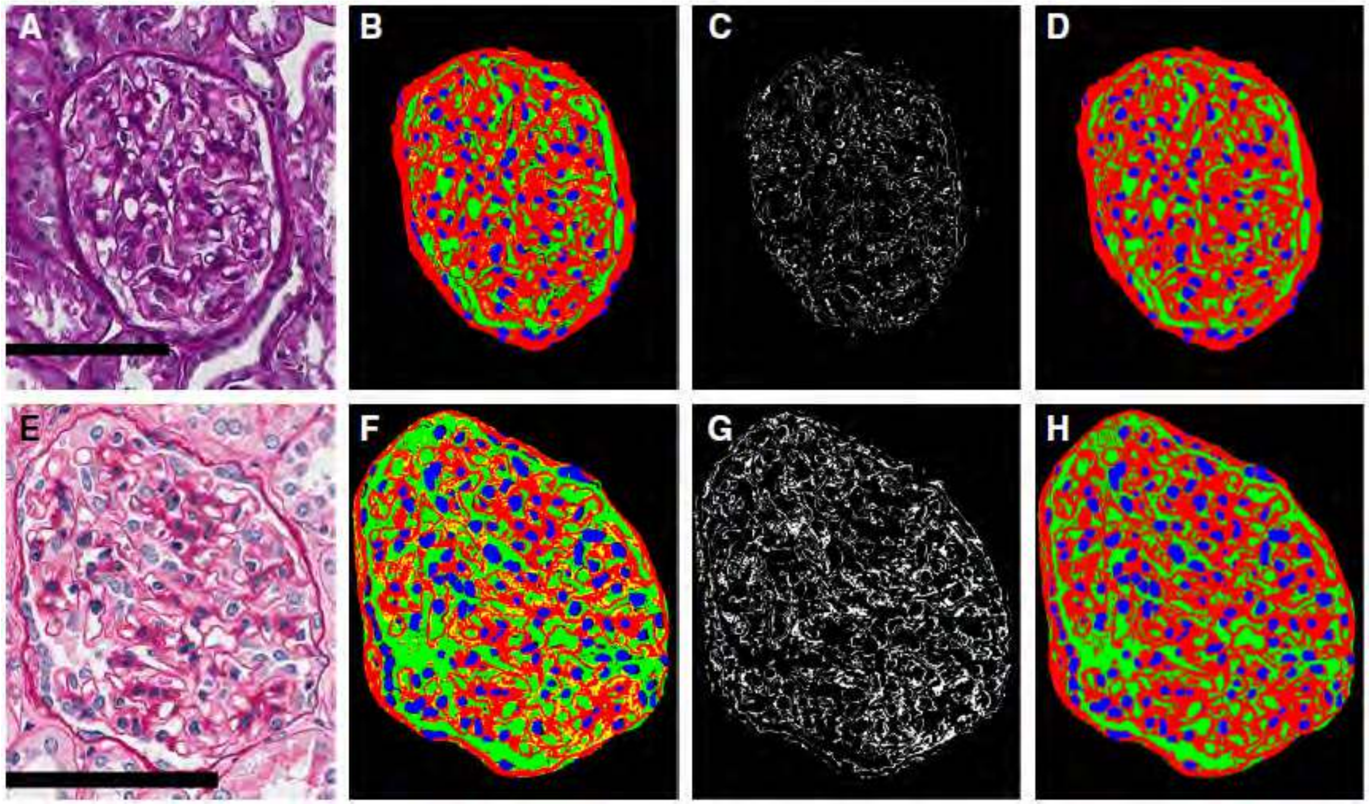
Evolution of Data Analytics



What are current AI applications in Nephrology?

- Image analysis
- Pattern recognition
- Prediction: e.g. AKI, hospitalization
- Natural language processing: interpretation of unstructured data, e.g. nurses’ notes

Use Cases in AI-Supported Image Recognition



Histopathology

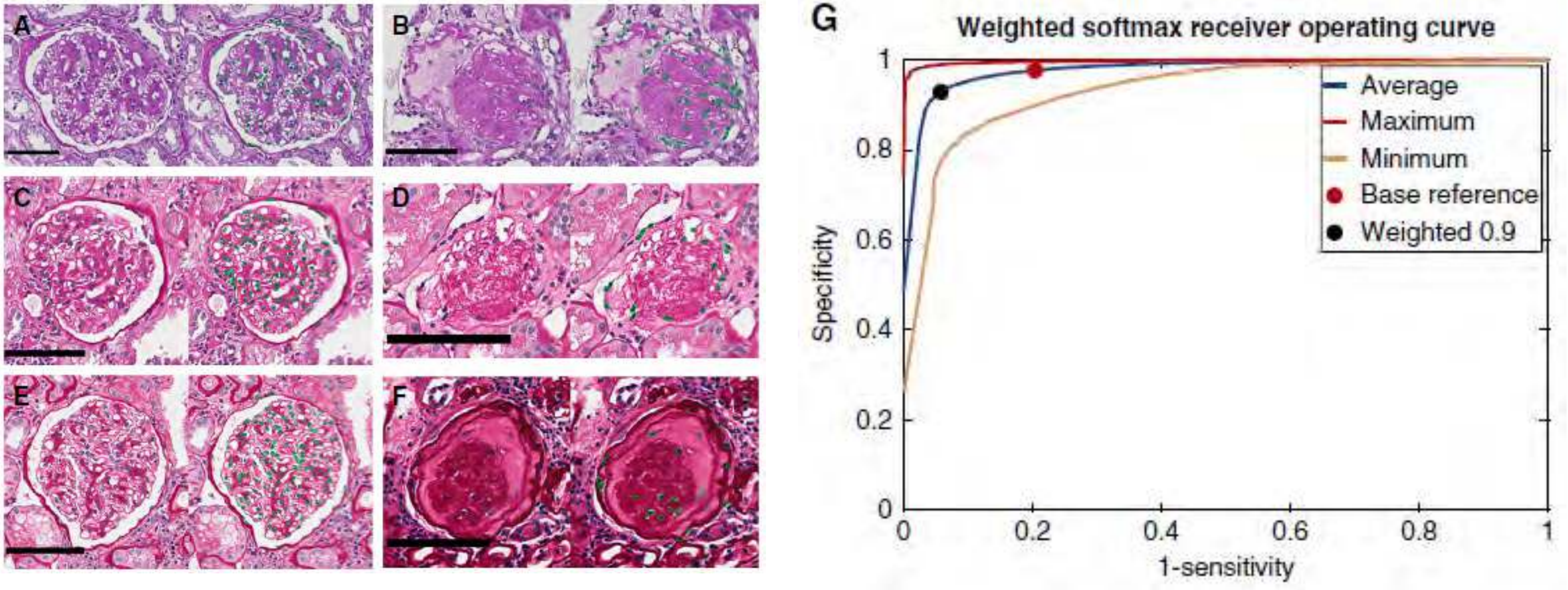
Aneurysm Diagnostics

JASN
Journal of the American Society of Nephrology

Computational Segmentation and Classification of Diabetic Glomerulosclerosis

Brandon Ginley,[1] Brendon Lutnick,[1] Kuang-Yu Jen,[2] Agnes B. Fogo,[3] Sanjay Jain,[4] Avi Rosenberg,[5] Vighnesh Walavalkar,[6] Gregory Wilding,[7] John E. Tomaszewski,[1,8] Rabi Yacoub,[9] Giovanni Maria Rossi,[5,10] and Pinaki Sarder[1,7,11]

JASN 30: ccc–ccc, 2019. doi: https://doi.org/10.1681/ASN.2018121259



Use of image analysis and machine learning algorithms to digitally classify biopsy samples from 54 patients with diabetic nephropathy. They found substantial agreement between digital classifications and those by three different pathologists.

JASN Journal of the American Society of Nephrology

JASN 30: ccc–ccc, 2019. doi: https://doi.org/10.1681/ASN.2019020144

Deep Learning–Based Histopathologic Assessment of Kidney Tissue

Meyke Hermsen,[1] Thomas de Bel,[1] Marjolijn den Boer,[1] Eric J. Steenbergen,[1] Jesper Kers,[2,3,4] Sandrine Florquin,[2] Joris J. T. H. Roelofs,[2] Mark D. Stegall,[5,6] Mariam P. Alexander,[6,7] Byron H. Smith,[6,8] Bart Smeets,[1] Luuk B. Hilbrands,[9] and Jeroen A. W. M. van der Laak[1,10]

Ground truth

	Interstitium	Arteries	Capsule	Atrophic tubuli	Distal tubuli	Proximal tubuli	Undefined tubuli	Glomeruli	Sclerotic glomeruli	pty Bowman's capsule	Border
Interstitium	0.83	0.01	0.03				0.02	0.01			0.09
Arteries	0.04	0.80	0.05	0.01				0.10			
Capsule	0.02		0.98								
Atrophic tubuli	0.05			0.48	0.13	0.04	0.16				0.14
Distal tubuli.	0.01		0.01	0.03	0.85	0.01	0.04				0.04
Proximal tubuli	0.01			0.04	0.02	0.82	0.07				0.04
Undefined tubuli	0.11		0.05	0.09	0.20	0.13	0.30		0.03	0.01	0.08
Glomeruli	0.01							0.98			0.01
Sclerotic glomeruli	0.14	0.23							0.62		0.01
Empty Bowman's capsule	0.14						0.52			0.28	0.06
Border	0.13	0.01	0.01	0.02	0.02	0.02	0.02	0.02			0.75

Predicted by the CNN

The ground truth labels are given vertically and the predicted labels by the CNN are written on the horizontal axis.

Here can be seen that, e.g., 98% of all pixels with ground truth label glomeruli, were classified as glomeruli by the convolutional neural networks (CNN) ensemble.

Which of these aneurysms is most worrisome?





Aneurysm Stages

STAGE 0
Fistula with normal skin

No Action Required

STAGE 1
Enlarged fistula with shiny skin

Monitor

STAGE 2
Enlarged fistula with hypopigmented skin

Refer to Vascular Access Team

STAGE 3
Enlarged fistula with open ulcer

Urgent Referral

Automatic Aneurysm Classification: The Process

Vascular Experts Adjudicate Images & Diagnose Aneurysm Stages

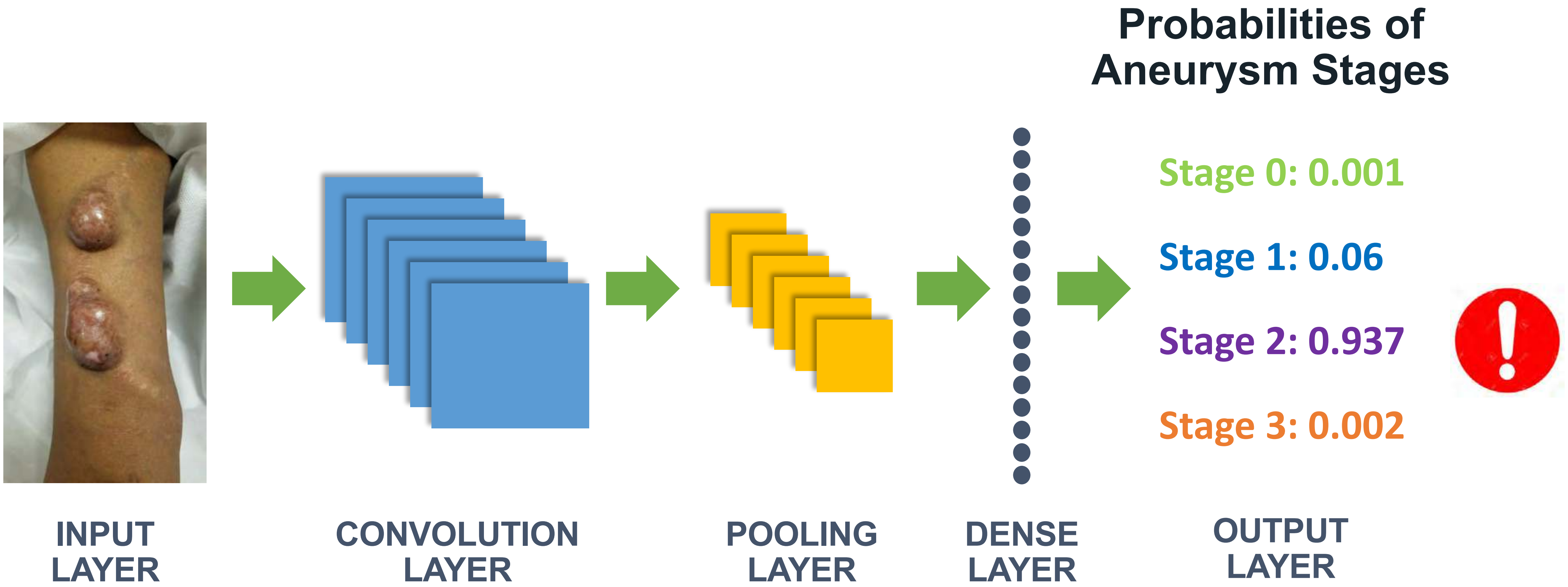
Image Pre-Processing for Input Into AI Tool

Collect Images

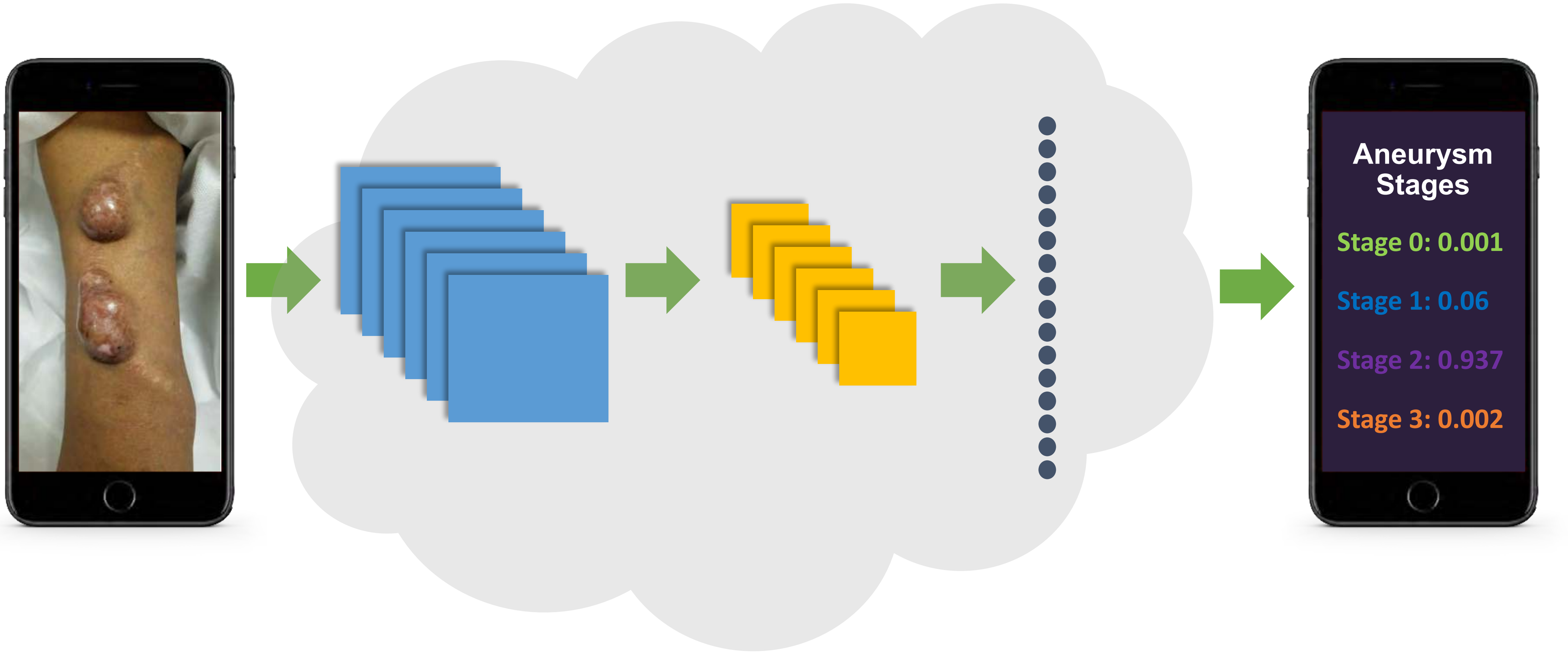
Randomize Images Into Training & Validation Samples

Employ AI: Convolutional Neural Networks

Aneurysm Classification with Convolutional Neural Network



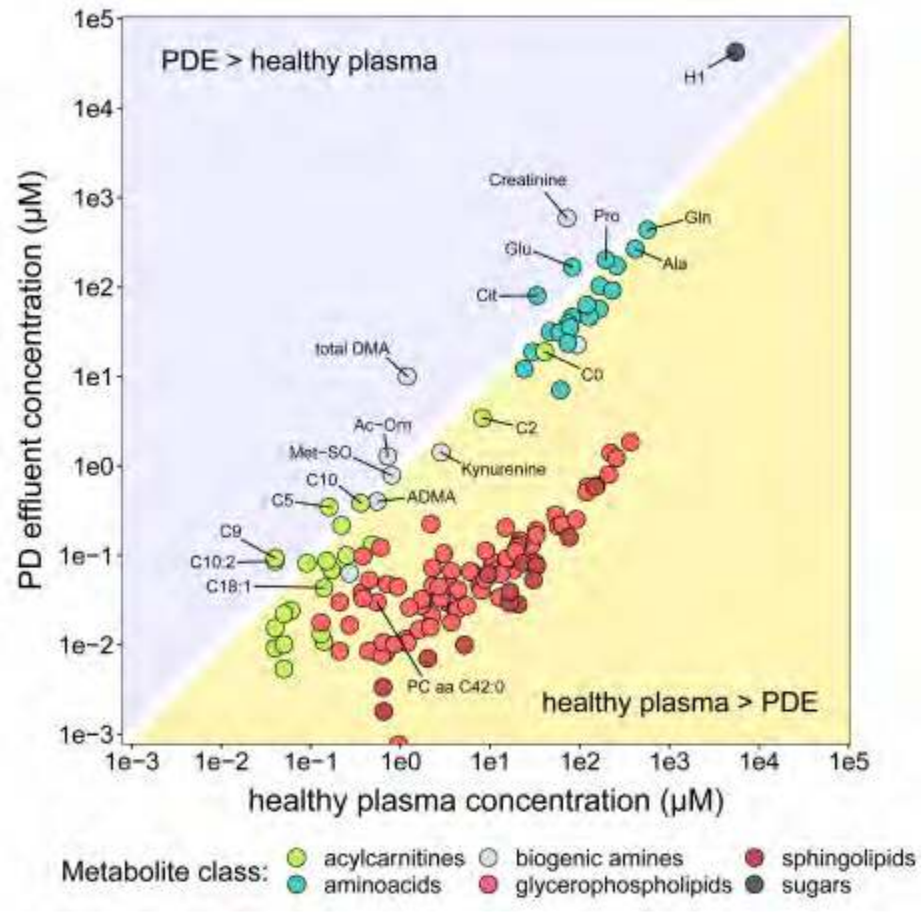
Smartphone App

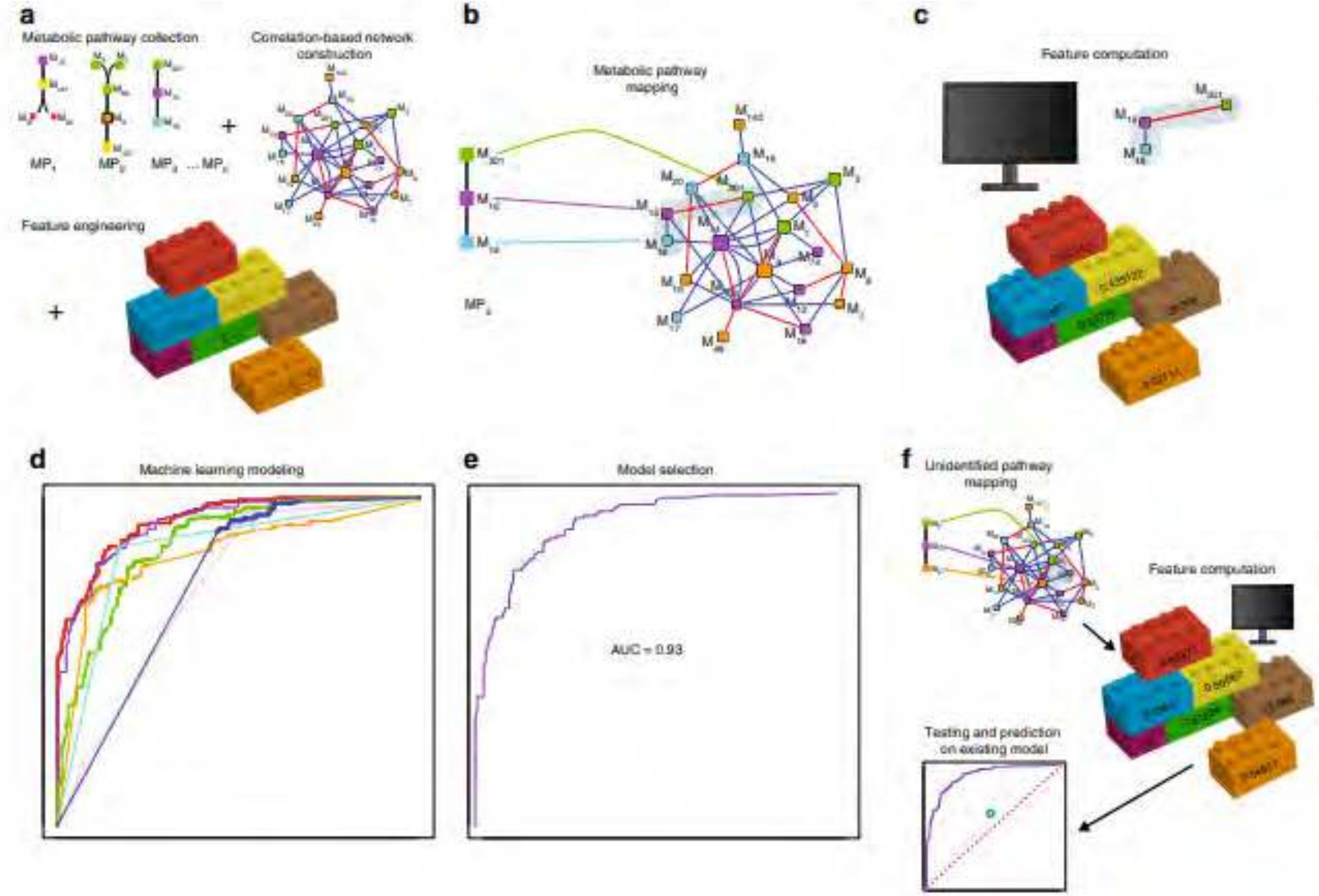


A rapidly evolving area: analysis of metabolomics data using machine learning & network analysis

COMMUNICATIONS BIOLOGY

Article | Open Access | Published: 18 June 2019





Wiesenhofer *et al.* (Frontiers in Physiology, 2019)

AI-Supported Prediction of the Patients' Future

Mortality Prediction in Hemodialysis Patients

Background and Goals

- Dialysis patients have a high mortality rate
- The last months before death are characterized by very high hospitalization rates
- Aim is to identify patients at an increased risk of death to
  - Prepare for supportive / palliative care
  - Initiate timely diagnostic and therapeutic interventions

Supportive Care: Time to Change Our Prognostic Tools and Their Use in CKD

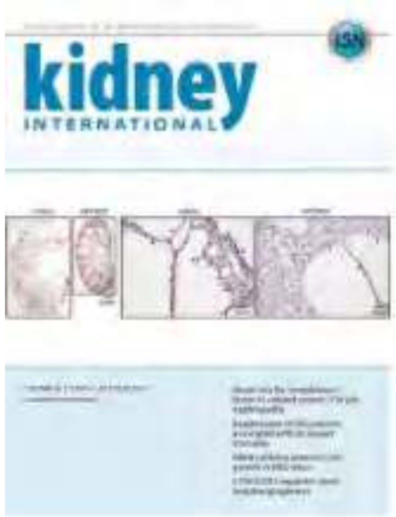
Cécile Couchoud,* Brenda Hemmelgarn,†‡ Peter Kotanko,§‖ Michael J. Germain,¶ Olivier Moranne,**†† and Sara N. Davison‡‡

(2016)

Table 2. Potential new predictors to be integrated in prognostic scores because of their dynamics in the terminal months

Parameter	Population Studied	Dynamics in Terminal Months before Death	References
Body composition			
Body weight (post-HD)	Women and men from the United States (blacks, whites, and Hispanics)	Decline at a rate of ≤3.2 kg per quarter	Kotanko *et al.* (40,45)
Body mass index	Women and men patients on PD from Brazil	Decline at a rate of ≤0.23 kg/m² per quarter	Calice-Silva, *et al.*, unpublished data
Fat mass	Women and men from Europe, South America, and Asia	Decline by 1.4 kg from months 9–12 to months 1–3 before death	A. Guinsburg, *et al.*, unpublished data
Fluid overload, L	Women and men from Europe, South America, and Asia	Increase by 0.3 L from months 9–12 to months 1–3 before death	A. Guinsburg, *et al.*, unpublished data
Fluid overload, % of lean tissue and fat mass	Women and men from Europe, South America, and Asia	Increase by 0.8% points from months 9–12 to months 1–3 before death	A. Guinsburg, *et al.*, unpublished data
Lean body mass	Women and men from Europe, South America, and Asia	Decline by 0.8 kg from months 9–12 to months 1–3 before death	A. Guinsburg, *et al.*, unpublished data
Clinical indicator			
BP (pre–HD systolic BP)	Women and men from the Americas (blacks, whites, and Hispanics), Europe, and Asia	Decline at a rate of ≤8 mmHg per quarter	Usvyat *et al.* (41)
Hospitalization	Women and men from the United States (blacks, whites, and Hispanics)	Increase from 0.32 ppm 4 mo before death to 1.85 ppm in month of death	Usvyat *et al.* (39)
IDWG, kg	Women and men from the Americas (blacks, whites, and Hispanics), Europe, and Asia	Decline at a rate of ≤0.15 kg per quarter	Usvyat *et al.* (43)
IDWG, % of post-HD weight	Women and men from the Americas (blacks, whites, and Hispanics), Europe, and Asia	Decline at a rate of ≤0.3% per quarter	Usvyat *et al.* (41)
Temperature (pre-HD)	Women and men from the United States (blacks, whites, and Hispanics)	Decline at a rate of ≤0.19°C per quarter	Usvyat *et al.* (42)
Laboratory indicator			
Albumin	Women and men from the Americas (blacks, whites, and Hispanics), Europe, and Asia	Decline at a rate of ≥0.5 g/dl per quarter	Kotanko *et al.* (40), Usvyat *et al.* (41)
C-reactive protein	Women and men from Europe	Increase at a rate of ≥20 mg/L per quarter	Usvyat *et al.* (41)
Glucose	Women and men patients on PD from Brazil	Increase at a rate of ≥5 mg/dl per quarter	Calice-Silva *et al.*, unpublished data
Neutrophil-to-lymphocyte ratio	Women and men from the Americas (blacks, whites, and Hispanics), Europe, Asia	Increase at a rate of ≥2.0 U per quarter	Usvyat *et al.* (43)
Nutritional score (composite of albumin, phosphate, creatinine, enPCR, and IDWG)	Women and men from the United States (blacks, whites, and Hispanics)	Decline at a rate of ≥3.0 percentile points per quarter	Thijssen *et al.* (44)
Potassium	Women and men patients on PD from Brazil	Decline at a rate of ≥0.05 mmol/L per quarter	Calice-Silva *et al.* (76)
Phosphorus	Women and men from the Americas (blacks, whites, and Hispanics), Europe, and Asia	Decline at a rate of ≥0.2 mg/dl per quarter	Usvyat *et al.* (43)
Quality of life			
SF-36 Physical Component Score	Women and men from the United States (blacks, whites, and Hispanics)	Decline at a rate of ≥0.29 points per quarter	S. Johnstone, *et al.*, unpublished data
SF-36 Mental Component Score	Women and men from the United States (blacks, whites, and Hispanics)	Decline at a rate of ≥0.49 points per quarter	S. Johnstone, *et al.*, unpublished data
Karnofsky Index	Women and men patients on PD from Brazil	Decline at a rate of ≥5.9 points per quarter	A. Modesto, *et al.*, unpublished data

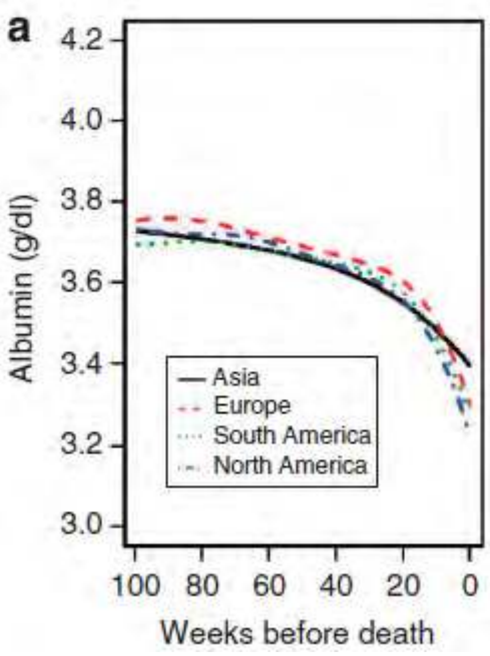
HD, hemodialysis; PD, peritoneal dialysis; ppm, per patient-month; IWDG, interdialytic weight gain; enPCR, equilibrated normalized protein catabolic rate; SF-36, Short Form (36) Health Survey.

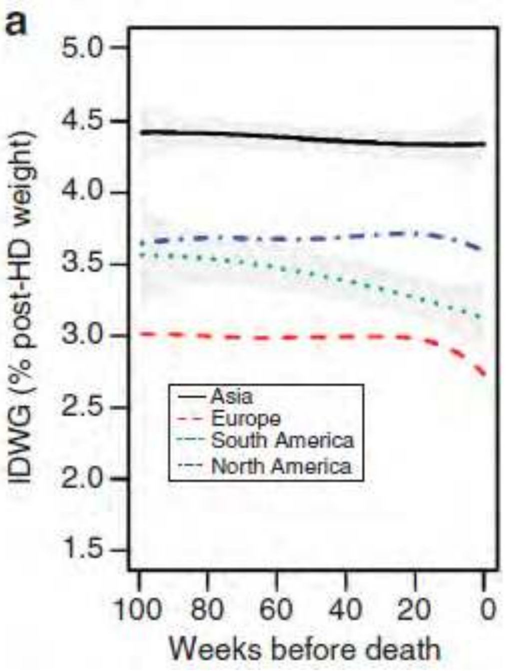


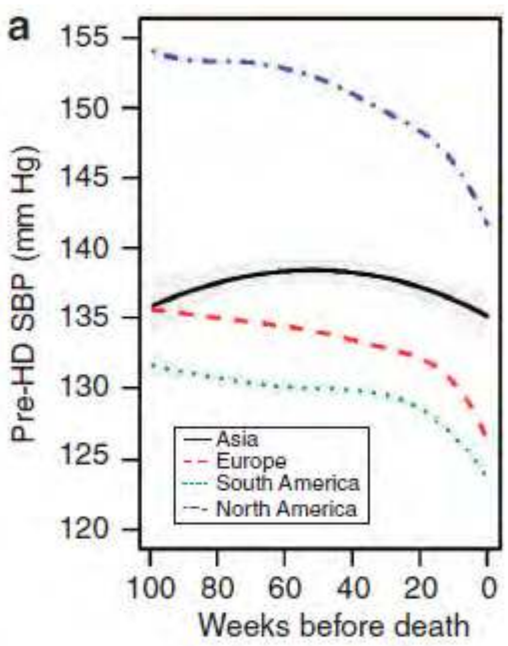
Interdialytic weight gain, systolic blood pressure, serum albumin, and C-reactive protein levels change in chronic dialysis patients prior to death

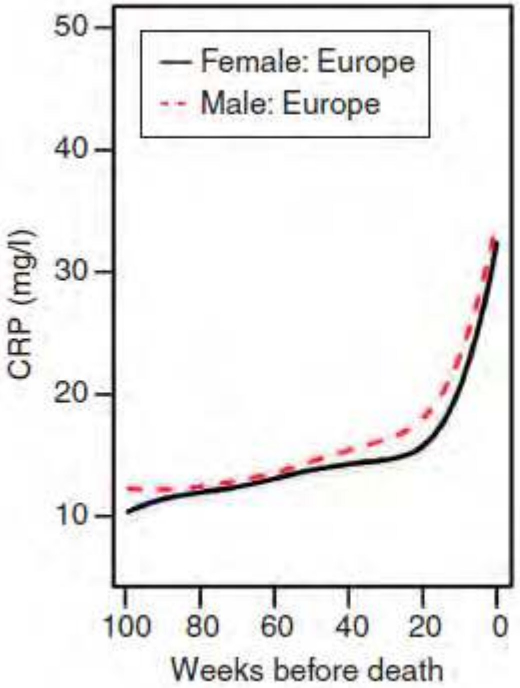
Len A. Usvyat[1], Claudia Barth[2], Inga Bayh[3], Michael Etter[4], Gero D. von Gersdorff[5], Aileen Grassmann[3], Adrian M. Guinsburg[6], Maggie Lam[4], Daniele Marcelli[3], Cristina Marelli[6], Laura Scatizzi[3], Mathias Schaller[5], Adam Tashman[7], Ted Toffelmire[8,9], Stephan Thijssen[1], Jeroen P. Kooman[10], Frank M. van der Sande[10], Nathan W. Levin[1], Yuedong Wang[7] and Peter Kotanko[1]

Parameter Dynamics in the 104 Weeks Before Death (N=41,903)





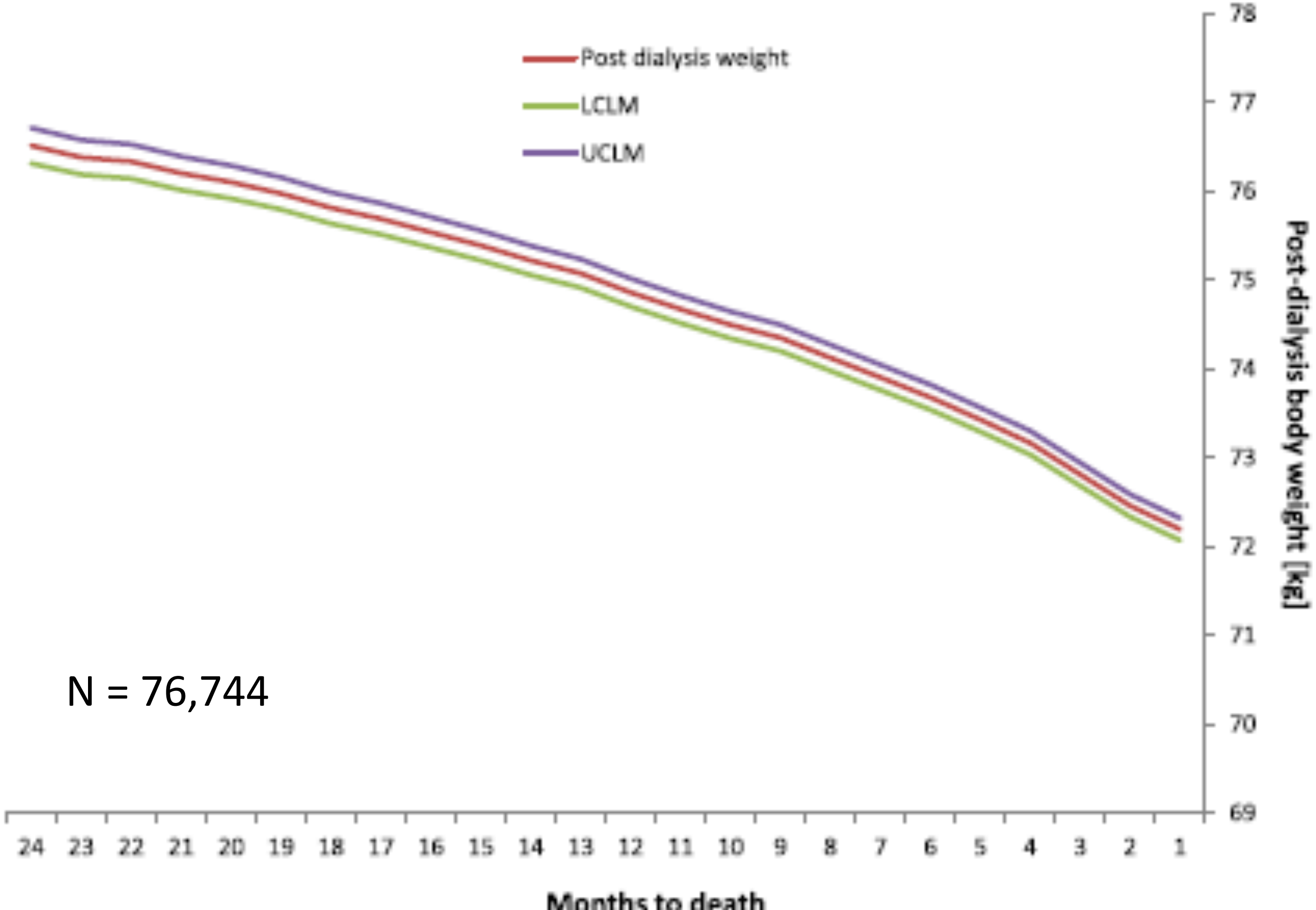




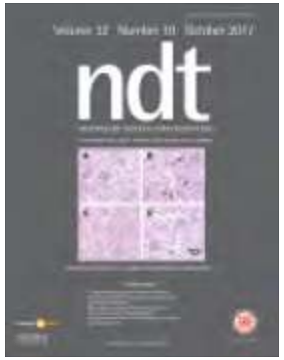
J Ren Nutr. 2014 Nov;24(6):357-63. doi: 10.1053/j.jrn.2014.06.011. Epub 2014 Sep 3.

Accelerated or out of control: the final months on dialysis.

Kotanko P[1], Kooman J[2], van der Sande F[2], Kappel F[3], Usvyat L[4].



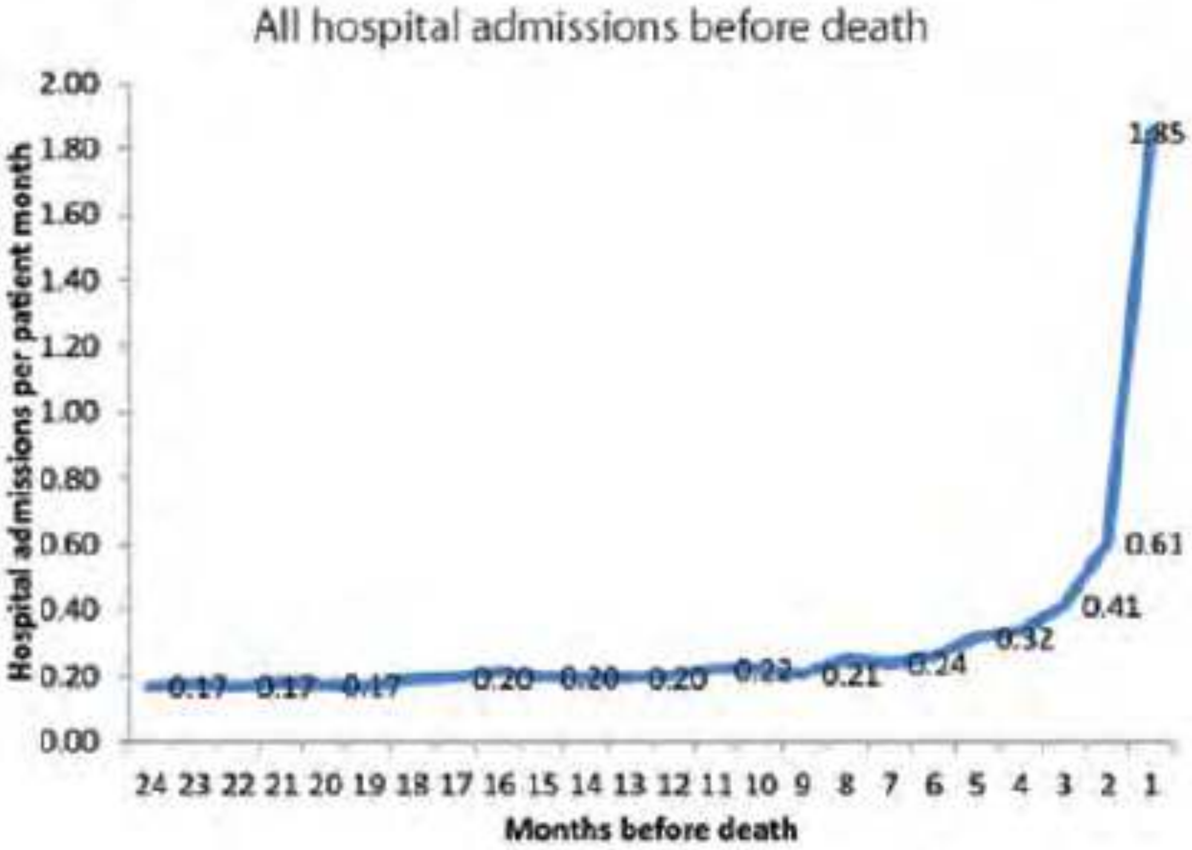
N = 76,744

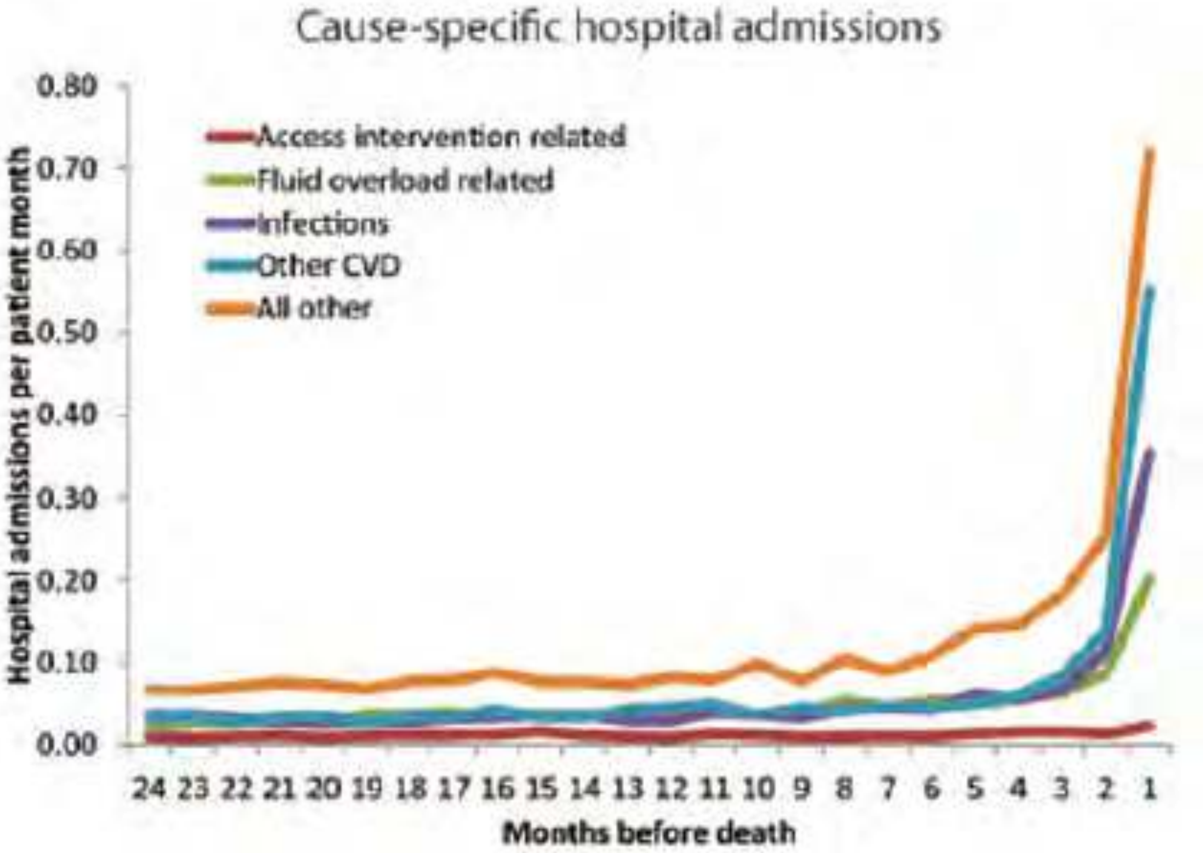


Dynamics of hospitalizations in hemodialysis patients: results from a large US provider

Len A. Usvyat[1,2], Jeroen P. Kooman[3], Frank M. van der Sande[3], Yuedong Wang[4], Franklin W. Maddux[2], Nathan W. Levin[1] and Peter Kotanko[1]

Hospital admission rates before death (Usvyat et al.)





RENAL RESEARCH INSTITUTE

How good are we in predicting mortality?

(2018)

Head-to-Head Comparison of Mortality Predictions by Physicians and Statistical Models

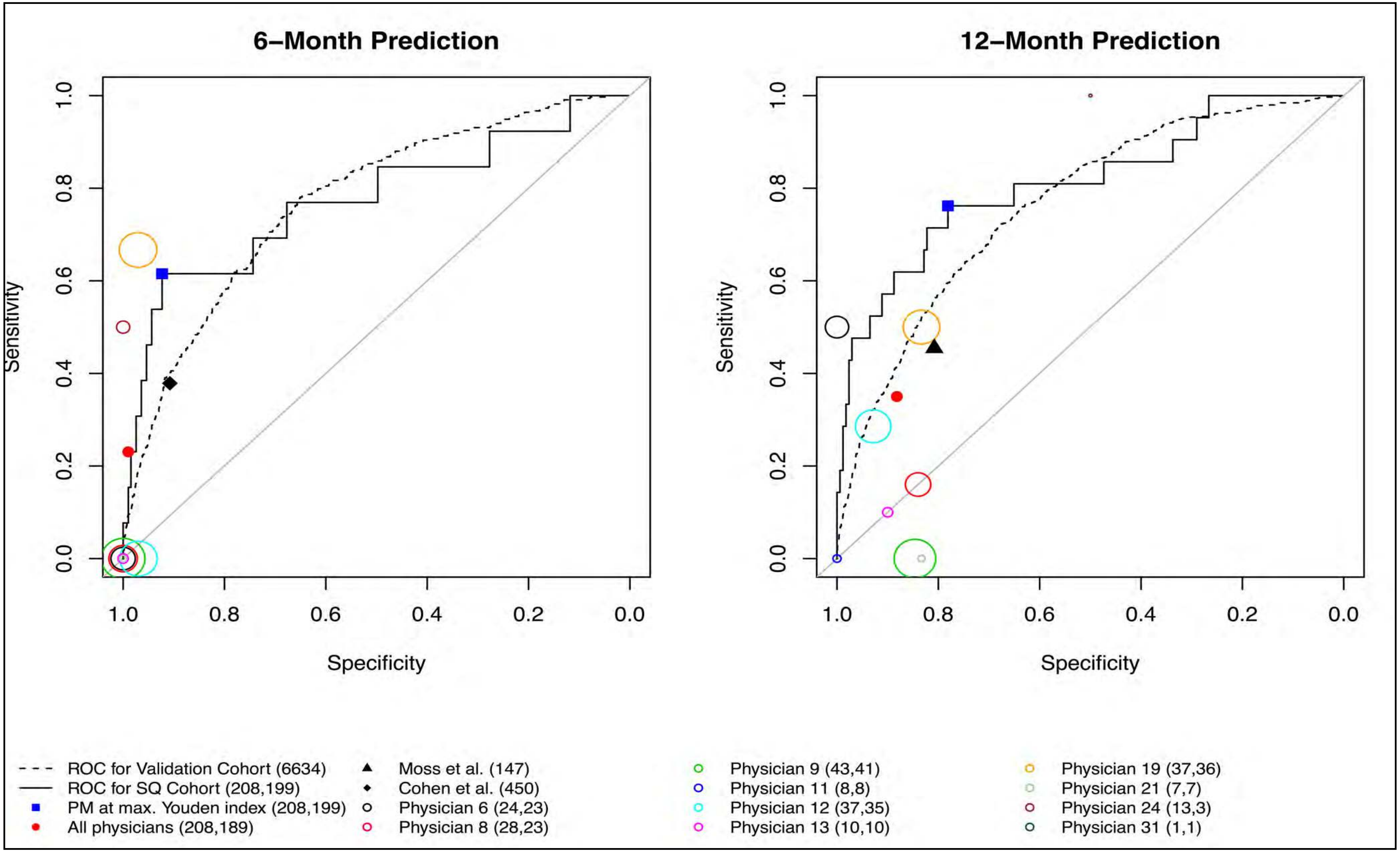
<u>Prediction Model</u>: Demographic, clinical, laboratory, and dialysis treatment indicators were used to model 6- and 12-month mortality probability in a hemodialysis patients training cohort (n=6,633).

<u>Physicians</u>: Ten nephrologists from 5 RRI hemodialysis clinics responded to the surprise question ("*Would you be surprised if your patient is still alive in 6 (12) months?*") in 215 patients who were then followed prospectively for 12 months.

<u>Evaluation</u>: The performance of prediction model was evaluated by ROC analysis. We compared sensitivities and specificities of prediction models and surprise question.

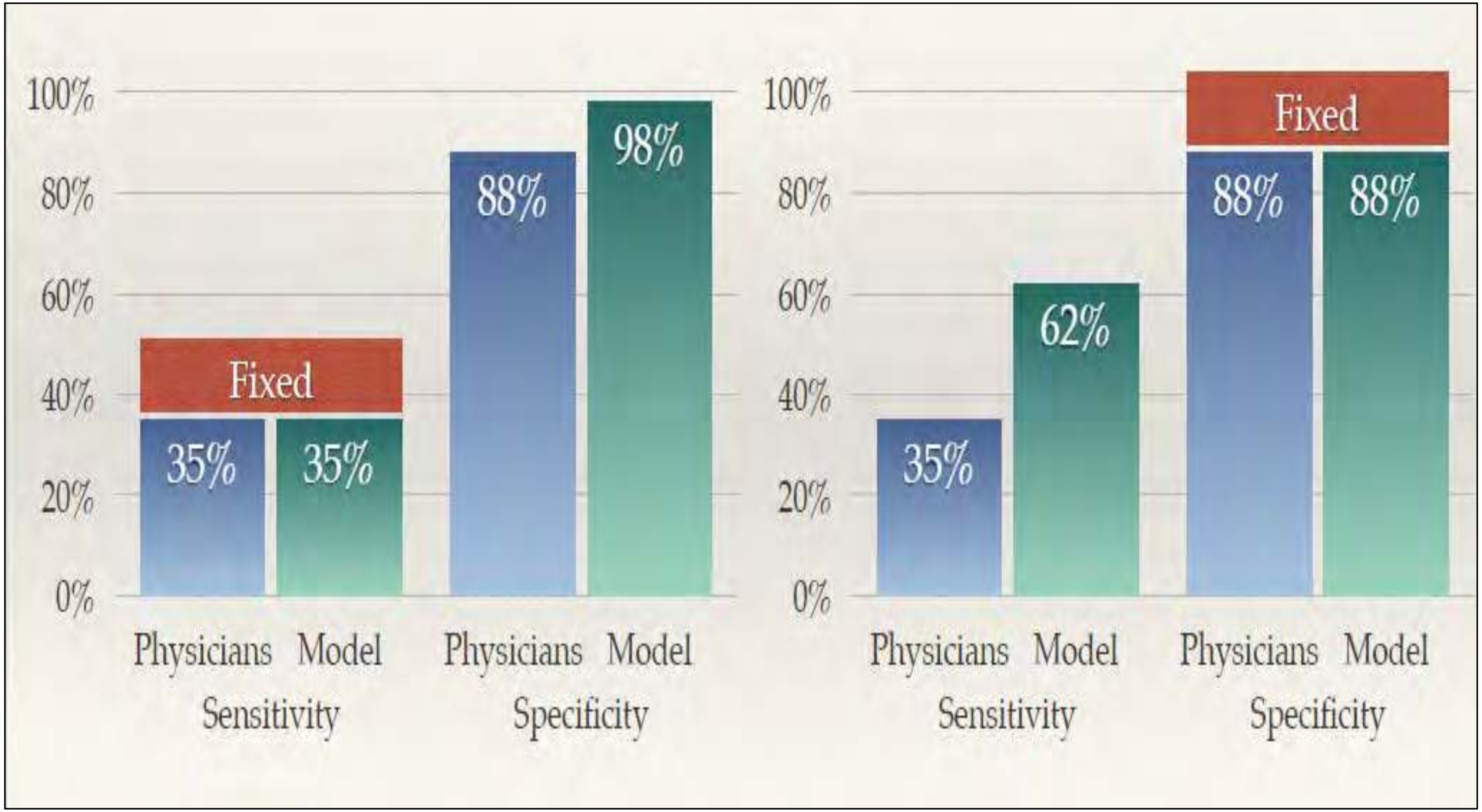

American Journal of
Nephrology
Highlights in this issue:

(2018)


6–Month Prediction
12–Month Prediction
Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0.0
ROC for Validation Cohort (6634)
ROC for SQ Cohort (208,199)
PM at max. Youden index (208,199)
All physicians (208,189)
Moss et al. (147)
Cohen et al. (450)
Physician 6 (24,23)
Physician 8 (28,23)
Physician 9 (43,41)
Physician 11 (8,8)
Physician 12 (37,35)
Physician 13 (10,10)
Physician 19 (37,36)
Physician 21 (7,7)
Physician 24 (13,3)
Physician 31 (1,1)


American Journal of
Nephrology
Highlights in this issue:
Effect of Exercise on Cardiac Tissue Oxidative and Inflammatory Mediators in Chronic Kidney Disease
Evaluation of Genetic Association and Expression Reduction of TRPC1 in the Development of Diabetic Nephropathy
Elevated Osteoprotegerin Levels Predict Cardiovascular Events in New Hemodialysis Patients

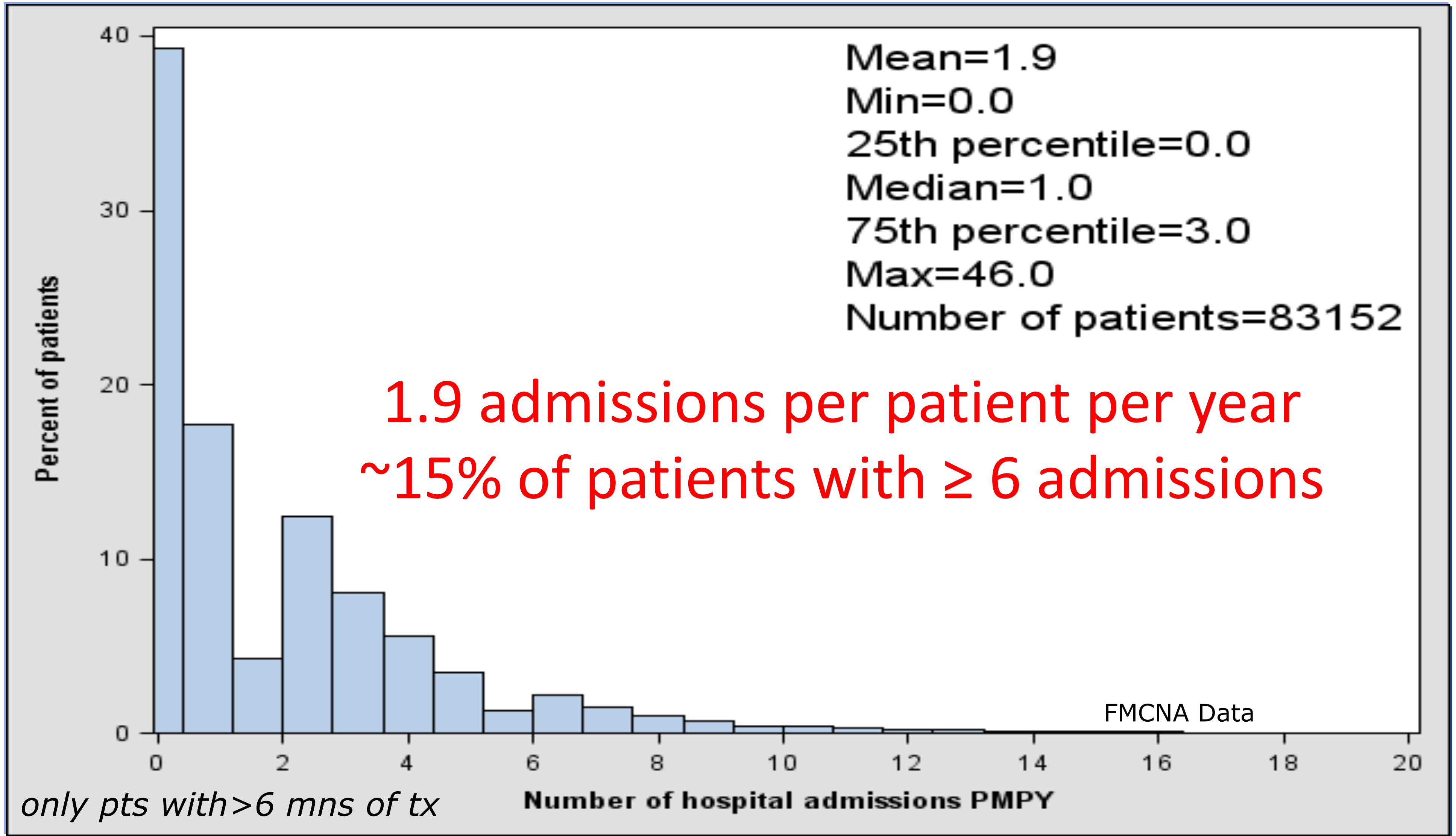
(2018)


100%
80%
60%
40%
20%
0%
Fixed
35%
35%
88%
98%
Physicians
Model
Physicians
Model
Sensitivity
Specificity
100%
80%
60%
40%
20%
0%
35%
62%
Fixed
88%
88%
Physicians
Model
Physicians
Model
Sensitivity
Specificity

Are predictions actionable?

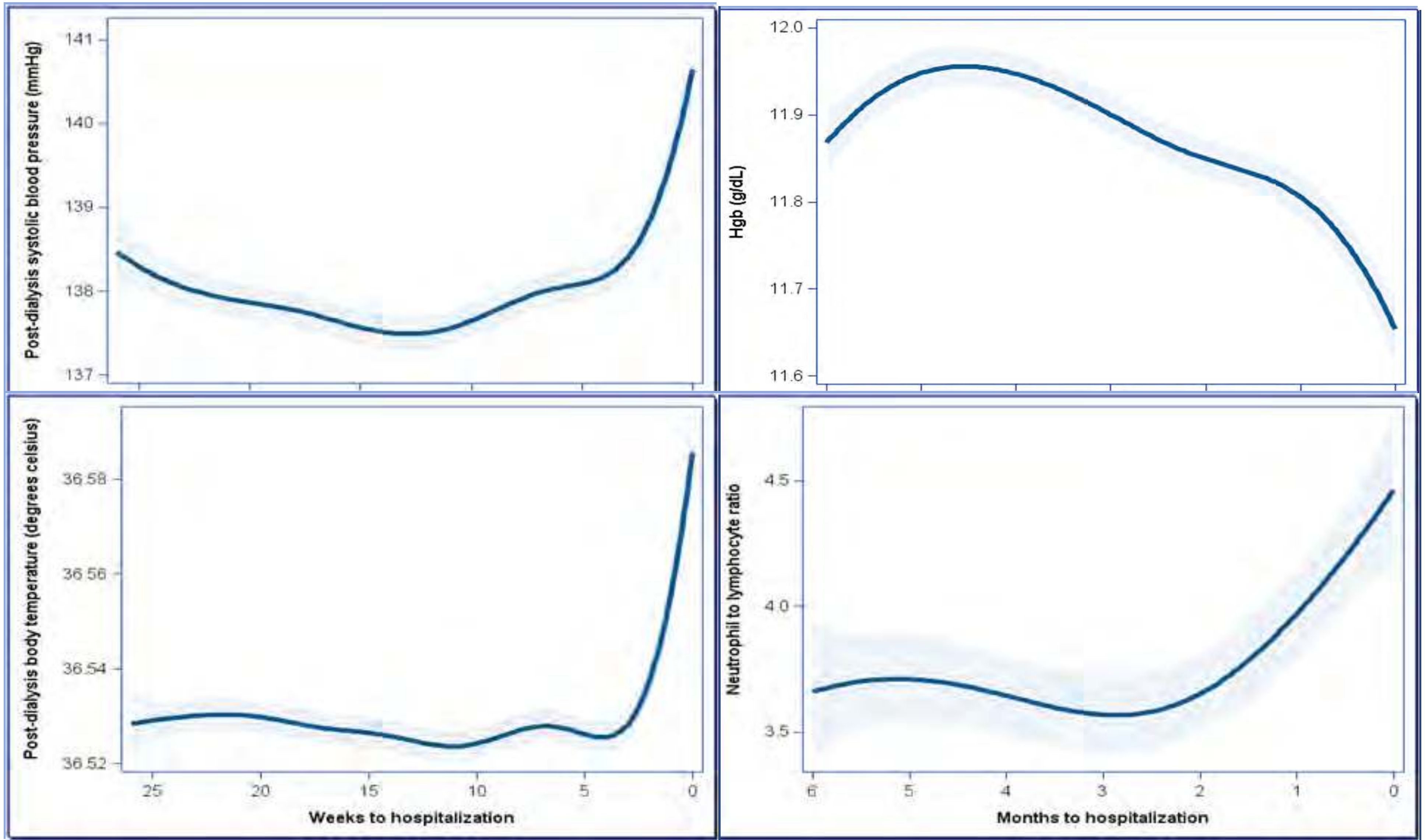
Predicting Hospitalizations in Hemodialysis Patients

How frequently are HD patients hospitalized?

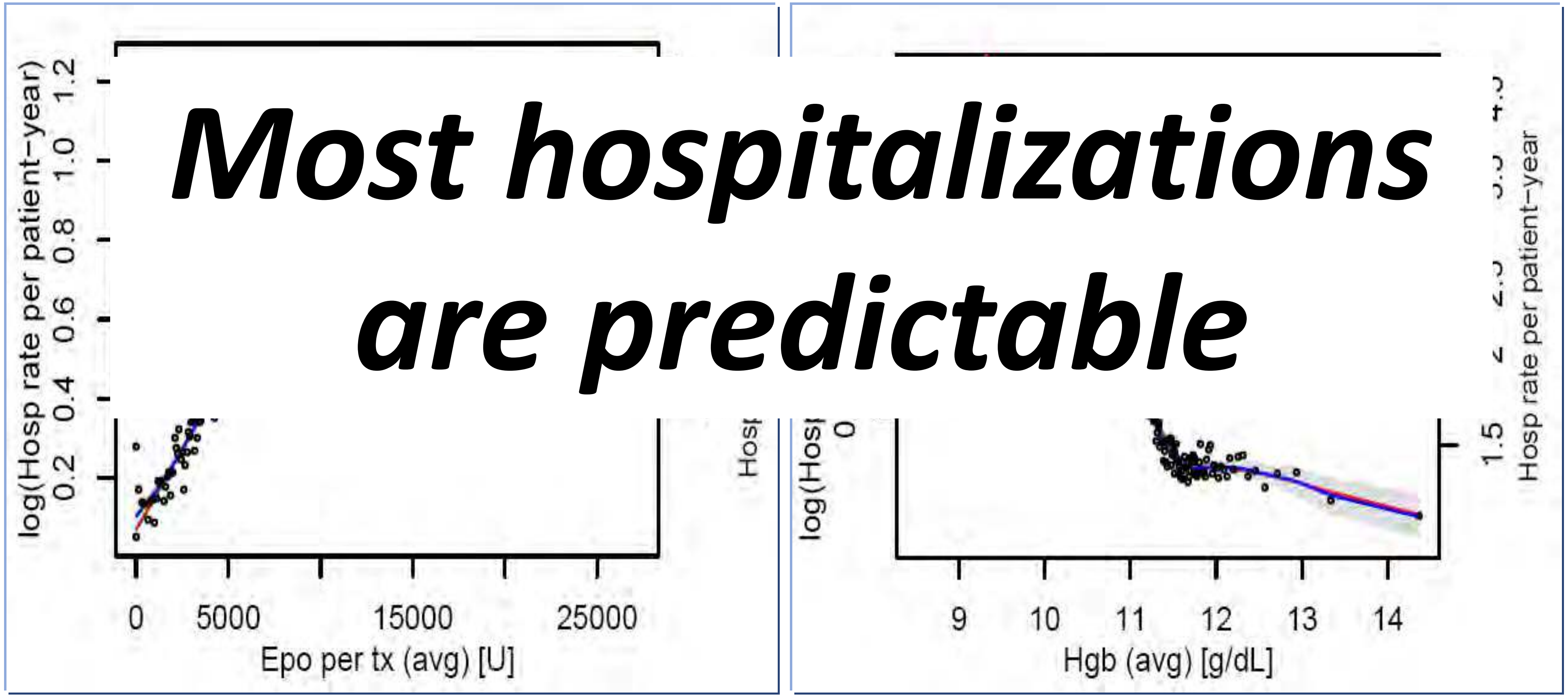


Indicators change before hospitalization
➔ *hospitalization is predictable*

Usvyat et al, 2012

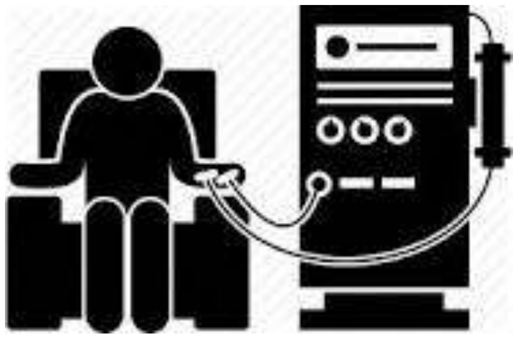


Individual parameters are associated with hospitalization



Most hospitalizations are predictable

Model setup



Data from ***142,360*** in-center hemodialysis patients

Number of initially explored variables: ***96***

Examples:

- ***Traditional***: blood pressure, Hgb, albumin, …
- ***Novel***: parameter variability and rate of change

Outcome: ***hospitalizations in the following year***

Model: several **traditional and machine learning techniques**

Predicting high risk patient

High risk patient = binomial variable (yes/no)

AUC = are

Best model:

AUC = 0.90

Sensitivity	.522	.535	.743	.717	.813
Specificity	.914	.901	.664	.759	.701
Youden index	.436	.436	.408	.476	.514

How to use predictions operationally?

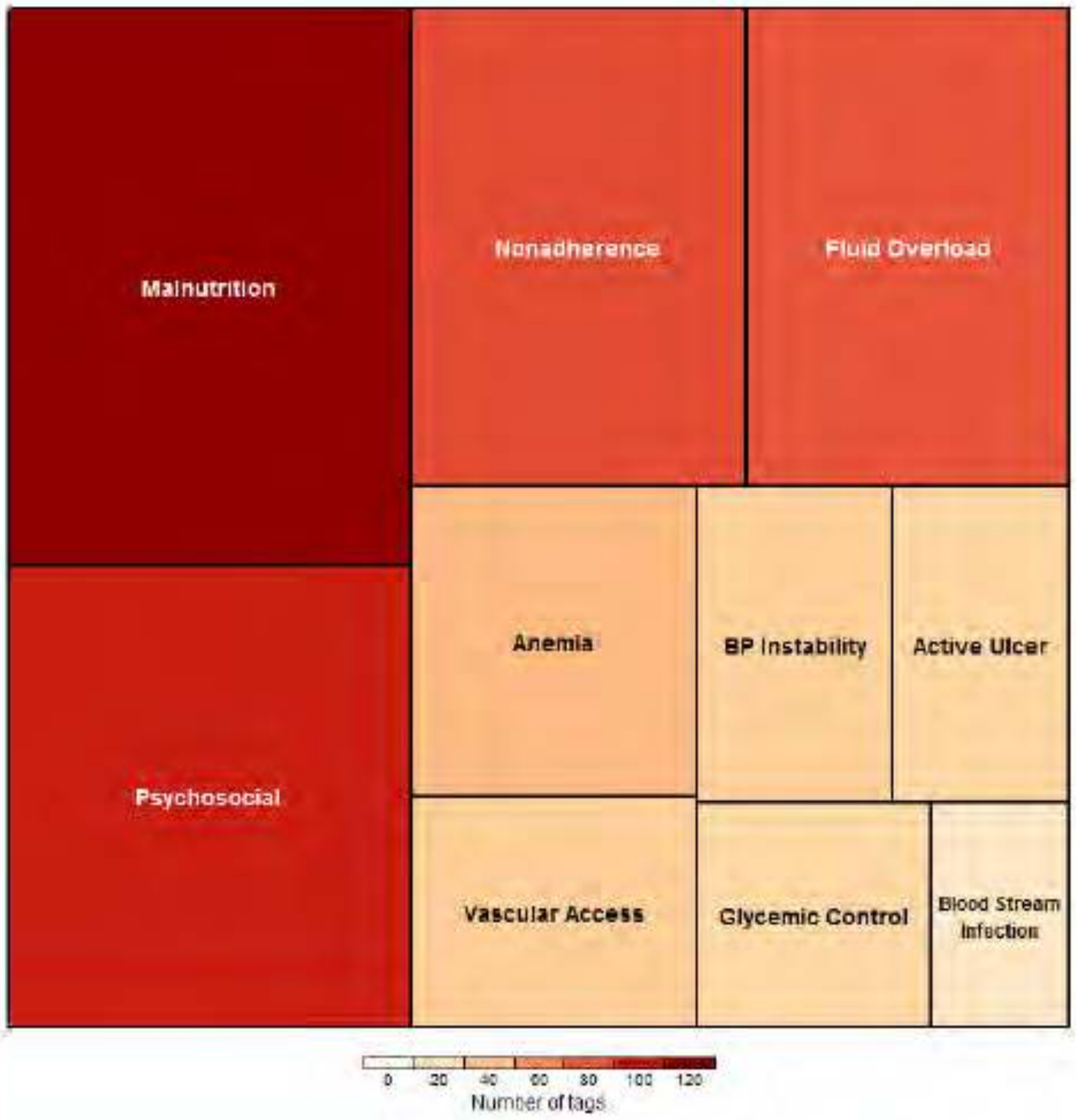
Data & Pre-dictions → Care co-ordination units → Clinic → Inter-vention

Most common tags

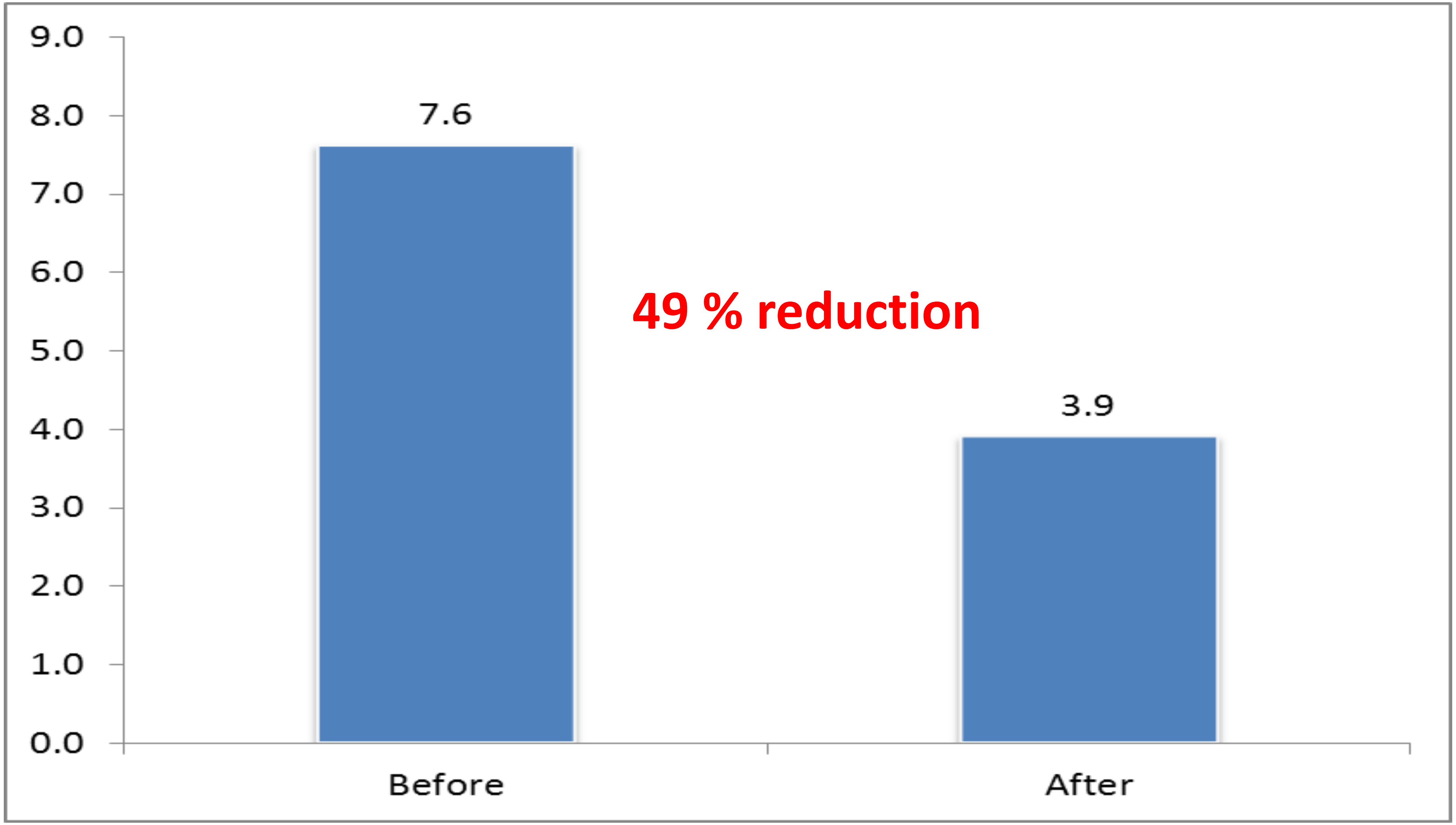
– 559 intervention tags

Leading problems related to

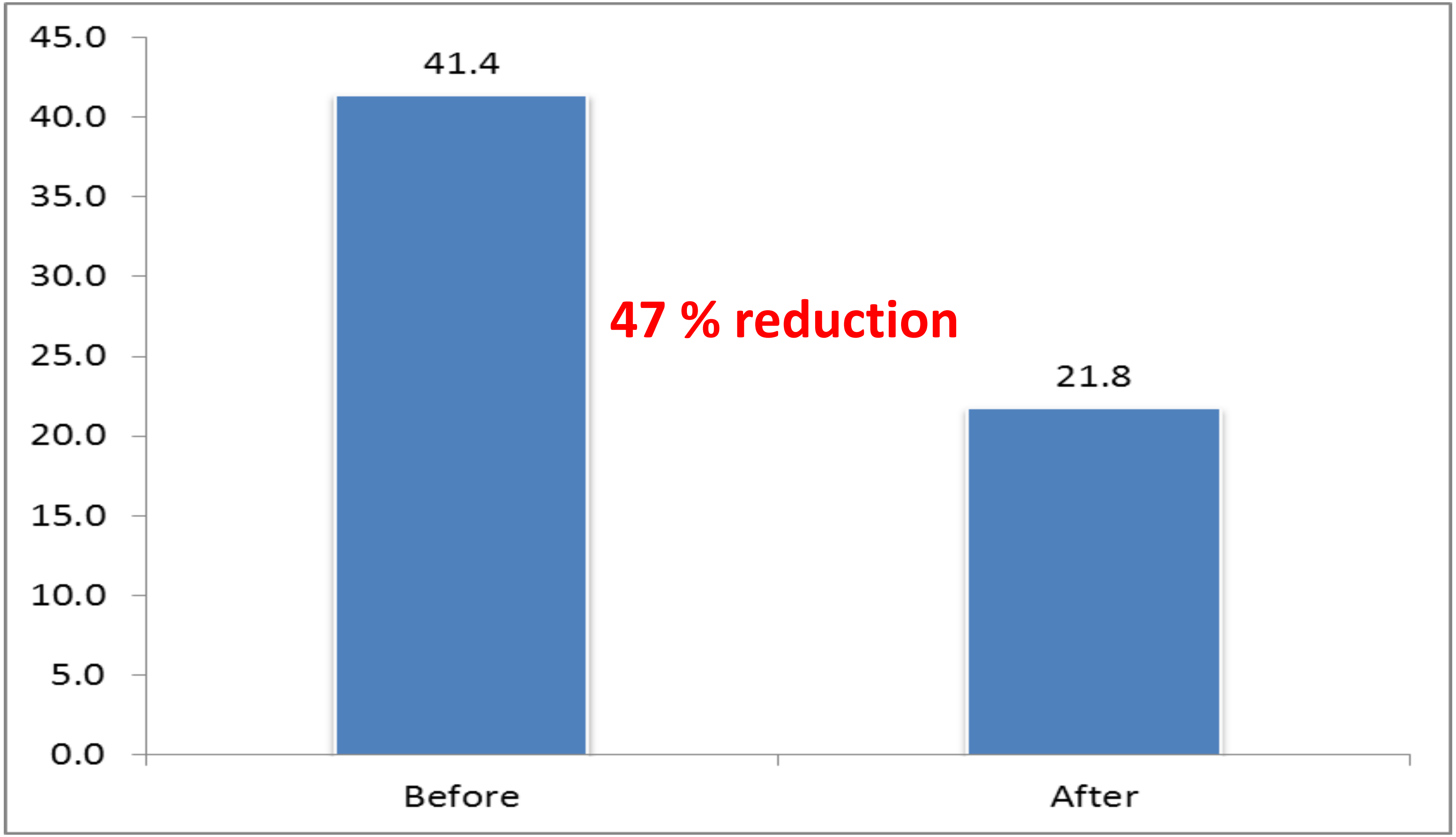
- Malnutrition
- Psychosocial issues
- Non-adherence
- Fluid overload



Comparison of annual hospital admission rates in patients with ≥ 6 hospitalization (data from 5 RRI clinics)



Comparison of annual hospital days in patients with ≥ 6 hospitalization (data from 5 RRI clinics)



Ethical and Societal Questions Raised by the Emergence of AI in Healthcare


AI IN HEALTHCARE
Treatment design
Assisting in monotonous tasks
AI Chatbots
Mining medical records
Virtual Healthcare Assistants

Common AI criticisms

- “Black box”: Impossible (at least very difficult) to discern AI’s decision-making process. This results in a host of regulatory, legal, and ethical issues.
- To date, AI is (in most cases) unable to identify causal links between input and output; the AI “insights” are primarily correlational
- Lack of inherent creativity (although, it is difficult to define “creativity”)
- Most use cases require large data sets (training and validation data)
- Problems to adapt to previously unknown input data

THE LANCET
Digital Health

Walking the tightrope of artificial intelligence guidelines in clinical practice

www.thelancet.com/digital-health **Vol 1 July 2019**

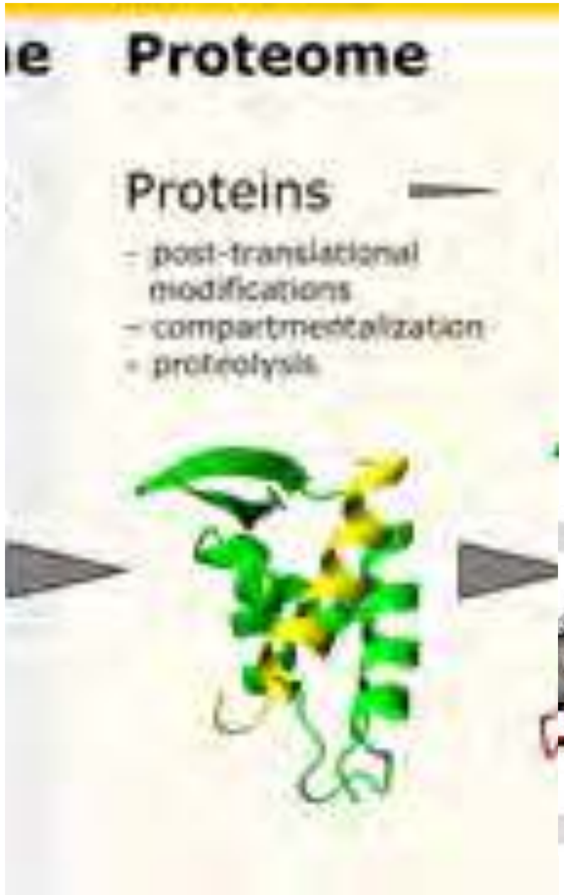
- AI approaches in medical practice need to be lawful, ethical, and robust.
- **EU guidelines** for trustworthy AI call for seven key requirements for ethical AI:
  - human agency and oversight;
  - technical robustness and safety;
  - privacy and data governance;
  - transparency;
  - diversity,
  - non-discrimination, and fairness;
  - societal and environmental wellbeing; and accountability.

Guidelines to address AI in health care are rapidly evolving

- **NHSX policy guidance announcement** https://www.publictechnology.net/articles/news/nhsx-createpolicy-guide-use-ai-healthcare
- **Public Health England guidance for the use of AI in screening** https://phescreening.blog.gov.uk/2019/03/14/new-guidancefor-ai-in-screening
- **EU ethics guidelines for trustworthy AI** https://ec.europa.eu/digital-single-market/en/news/ethics-guidelinestrustworthy-ai
- **NHS code of conduct** https://www.gov.uk/government/publications/codeof-conduct-for-data-drivenhealth-and-care-technology/initial-code-of-conduct-fordata-driven-health-and-caretechnology
- **NICE's guidelines for digital health interventions** https://www.nice.org.uk/Media/Default/About/what-we-do/ourprogrammes/evidencestandards-framework/digital-evidence-standardsframework.pdf
- **FDA whitepaper for modifications to software using machine learning models** https://www.regulations.gov/document?D=FDA-2019-N-1185-0001

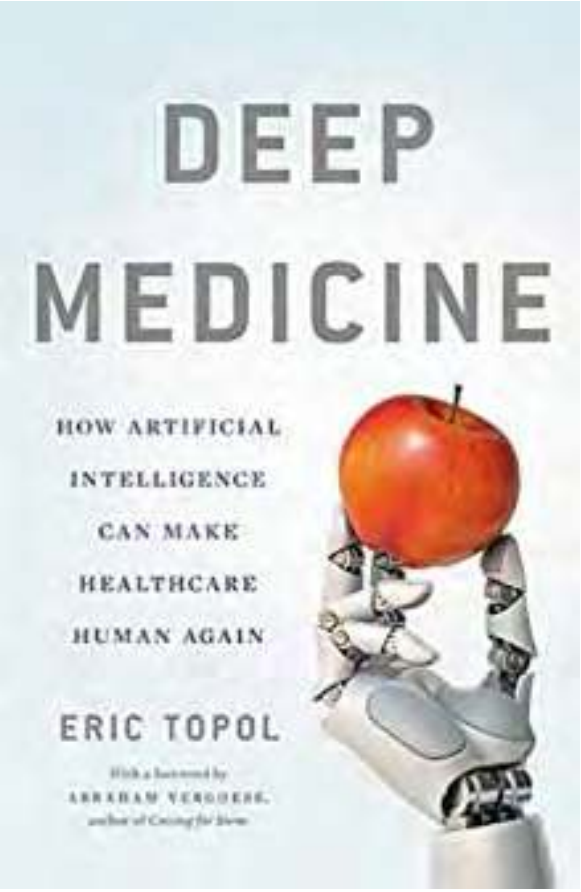
A 21st Century Trend: Convergence of Artificial Inteligence, Pervasive Sensing & Data Recording, and Precision Medicine

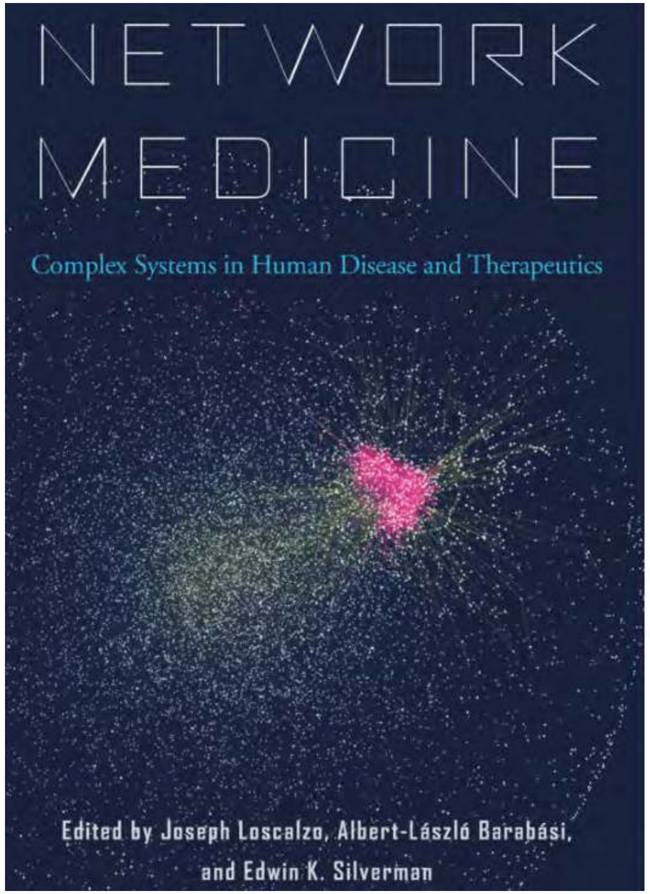
- Advanced AI and mathematics, network analysis, cloud computing
- Precision medicine (e.g. -omics)
- Electronic health records
- Socio-economic data
- Lifestyle data (e.g. from social media
- Pervasive sensing (e.g. Fitbit, Apple watch)



What is the role of us physicians?

- Maintain a patient-centered perspective
- Serve as the intermediary between our patients and AI experts
- This requires a basic understanding of fields such as AI, network medicine, statistics, and mathematics
- Protect our patients' privacy
- Communicate the meaning of AI output to our patients in clear terms and foster their ability to make informed decisions



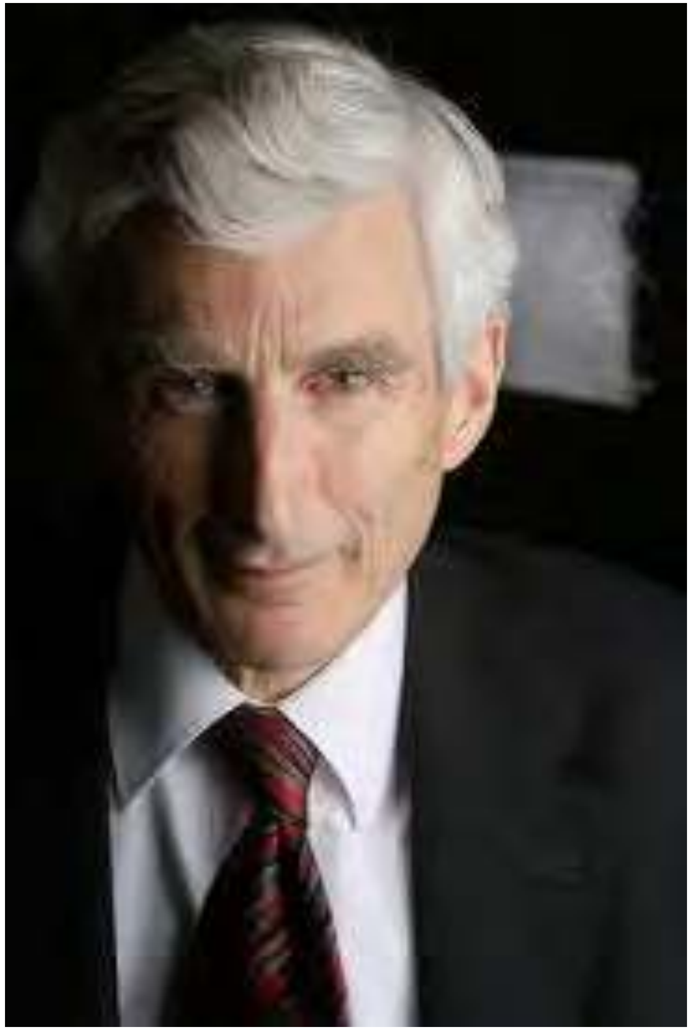


Finally, Martin Rees, acclaimed astrophysicist and Royal Astronomer to the Queen, takes a long view …

The Economist
7 Std. ·

"I think artificial intelligence will, for decades to come, be less of a worry than real stupidity", Martin Rees tells The Economist #OpenFuture

Übersetzung anzeigen



Herzlichen Dank!

Peter.Kotanko@rriny.com

www.renalresearch.com

Dialysis Induced Systemic Stress: How Future Management Will Look Like?

Chris McIntyre

Professor of Medicine, Medical Biophysics and Paediatrics

Robert Lindsay Chair of Dialysis Research and Innovation
University of Western Ontario

Director of the Lilibeth Caberto Kidney Clinical Research Unit

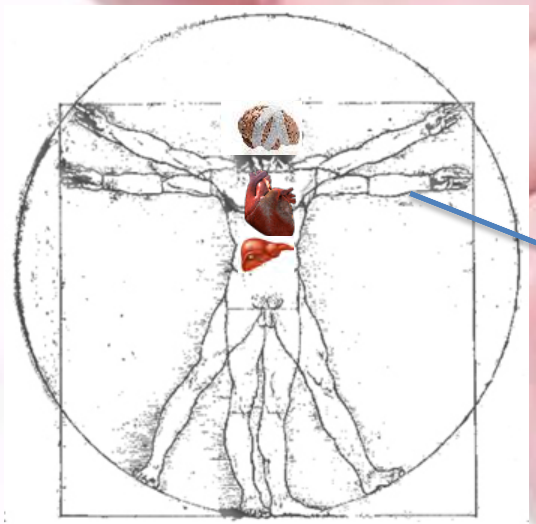
Outline- Scanning for solutions

- The horror of hemodialysis
- Mitigation of those horrors
  - Intradialytic
  - Interdialytic
- Where does it all go wrong?
  - Salt and water
- How to take out some of the guesswork

Dying to Feel Better: The Central Role of Dialysis–Induced Tissue Hypoxia

Christopher McIntyre and Lisa Crowley

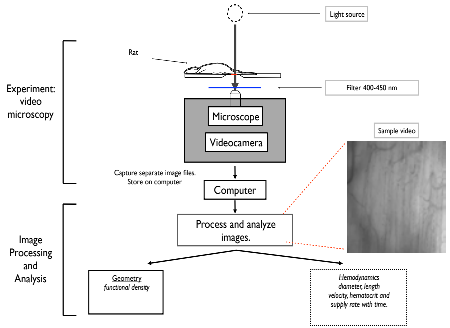
Clin J Am Soc Nephrol 11: ●●●–●●●, 2016. doi: 10.2215/CJN.01380216

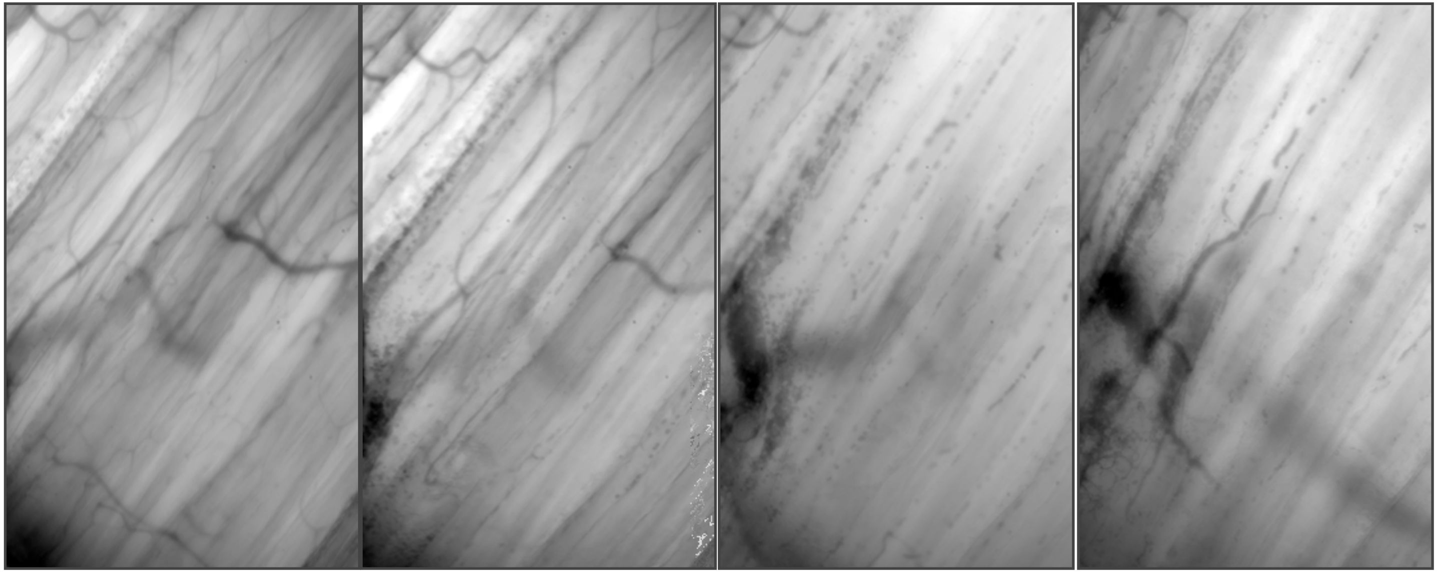


Just how much cardiovascular stress is dialysis?

Jannssen B, Zhang Y, McIntyre CW. Submitted 2020

Intravital microscopy- directly observed microcirculation





Control/Baseline 1hour dialysis 2hour dialysis 3hour dialysis

Jannssen B, Zhang Y, McIntyre CW. Submitted 2020

HD results in cardiac ischemia- Intradialytic PET and MRI

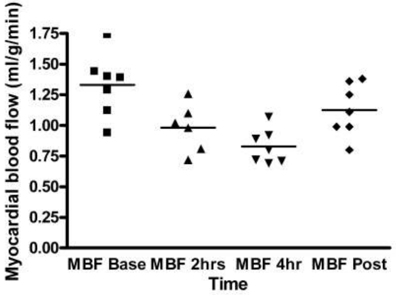
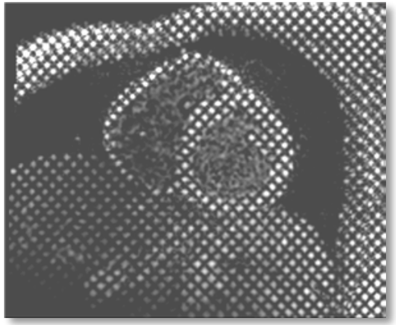
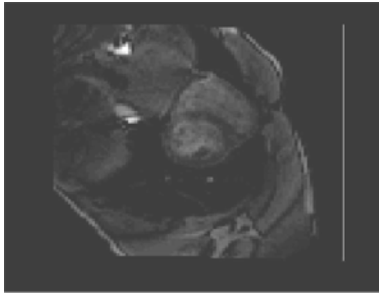


Figure 1. Mean global myocardial blood flow (MBF) reduced significantly during dialysis from baseline with partial restoration in the recovery period.



Myocardial perfusion

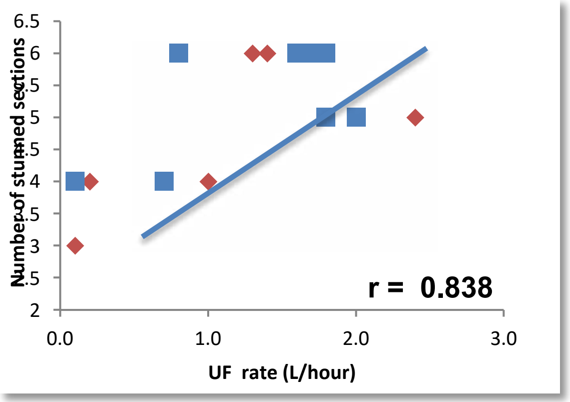


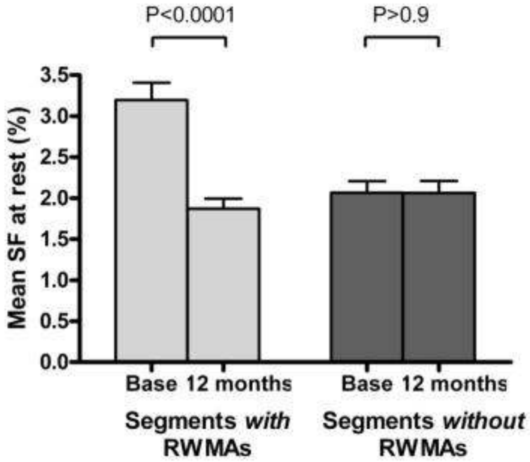
McIntyre CW et al. Clin J Am Soc Nephrol. 2008 Jan;3(1):19-26
McIntyre CW. Acute cardiac effects of haemodialysis. Kidney Int 2009

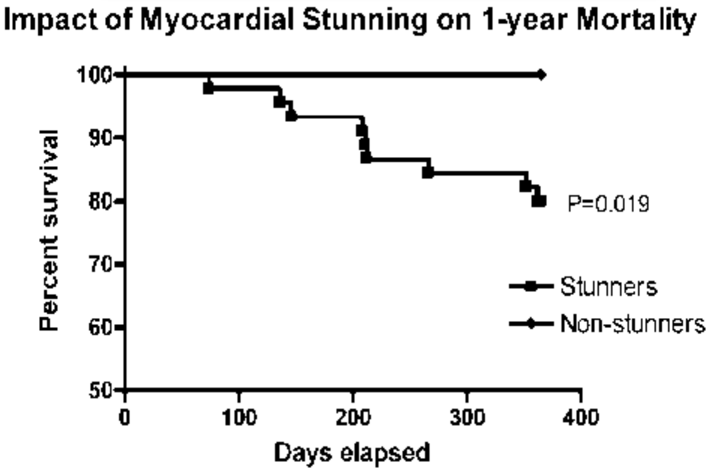
Buchanan C, Mohammed A, Taal MW, Selby NM, McIntyre CW. J Am Soc Nephrol. 2017

Longer term effects of recurrent cardiac injury- Heart failure

Factor associated with development of myocardial stunning	*OR*	*P value*
UF volume during HD of 1L	5.1	0.007
UF volume during HD of 1.5L	11.6	
UF volume during HD of 2L	26.2	
Max SBP reduction during HD of 10 mmHg	1.8	0.002
Max SBP reduction during HD of 20 mmHg	3.3	
Max SBP reduction during HD of 30 mmHg	6.0	



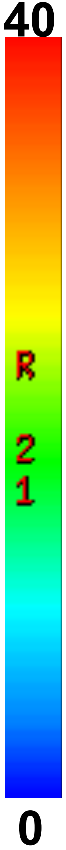


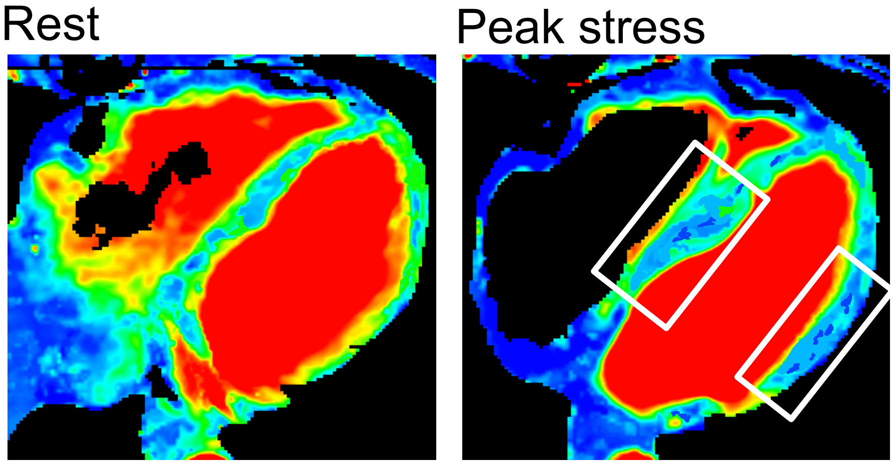


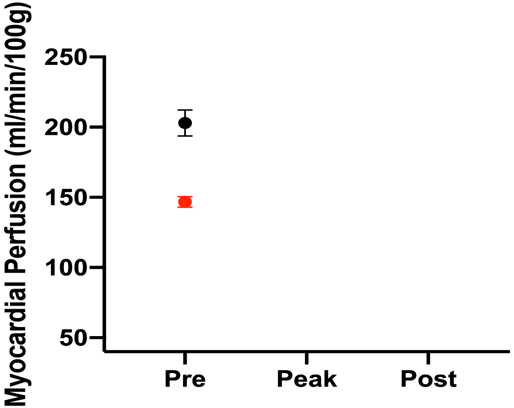
Burton JO, Korsheed S, McIntyre CW. Clin J Am Soc Nephrol. 2009 May;4(5):914-20

Burton JO, Jefferies HJ, *McIntyre CW* . Clin J Am Soc Nephrol. 2009 Dec;4(12):1925-31

256 slice CT- high resolution myocardial blood flow
Time to call cardiology?

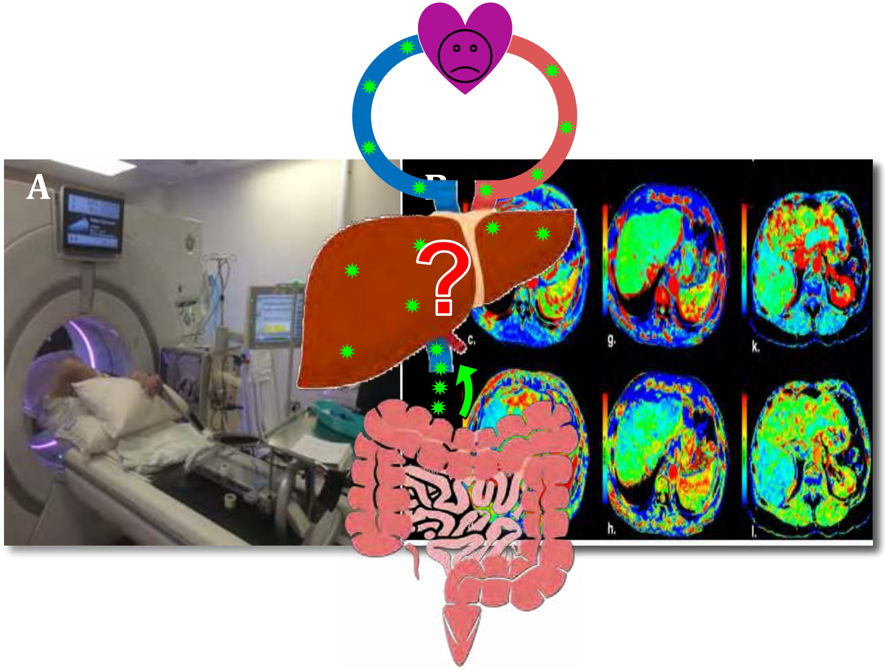


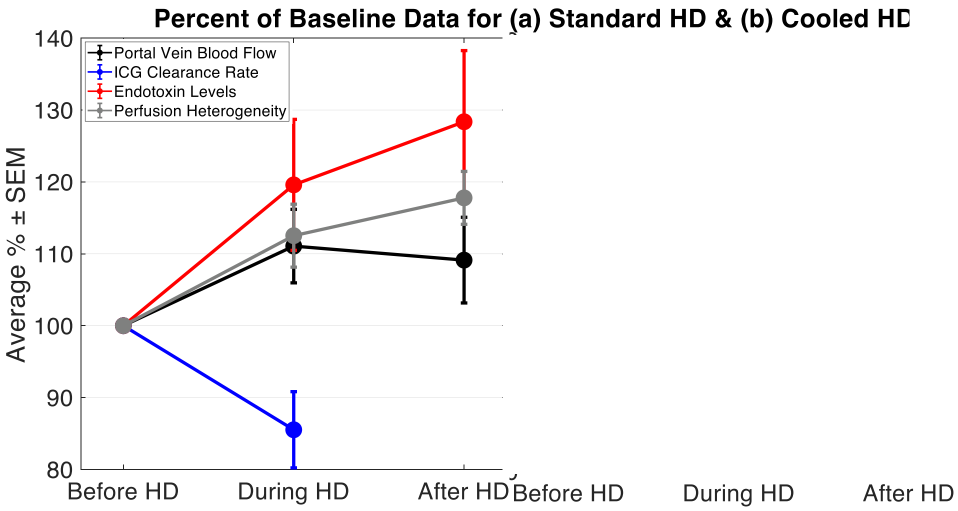




Hur L, So A, McIntyre CW. Current Opinions Hypertension and Nephrology 2020

Gut derived endotoxin in CKD

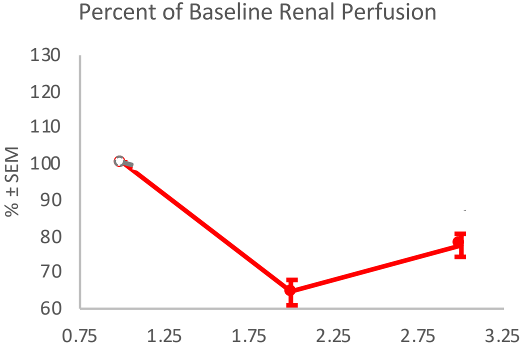


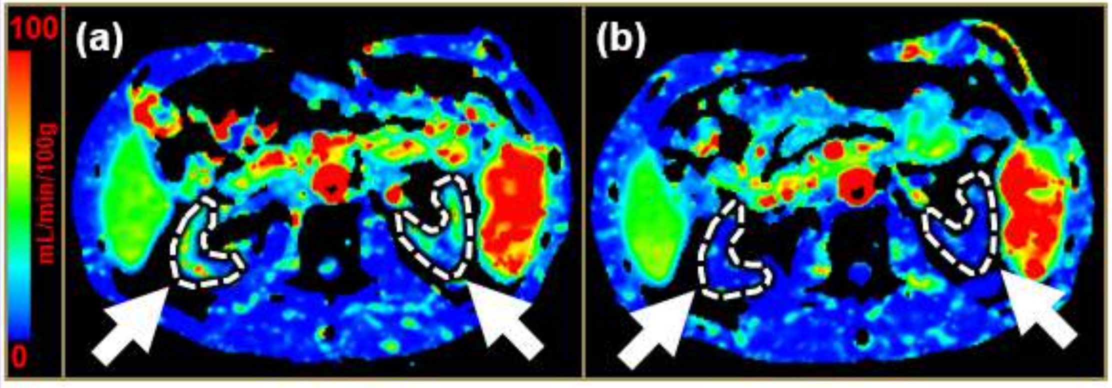


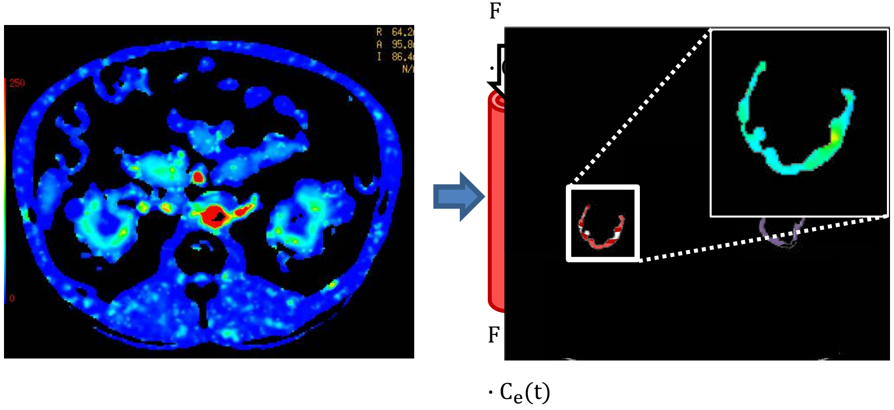
Grant CA, McIntyre CW. Seminars in Dialysis 2019

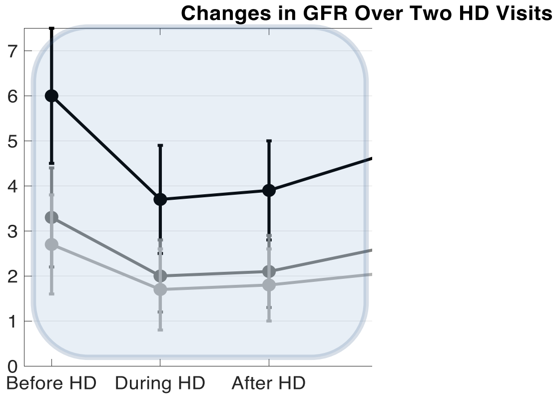
McIntyre CW, Harrison LE, Eldehni MT et al. Clin J Am Soc Nephrol. 2011 Jan;6(1):133-41
Harrison LEA, McIntyre CW. Nephron 2014

‘Kidney stunning’- recurrent dialysis induced AKI









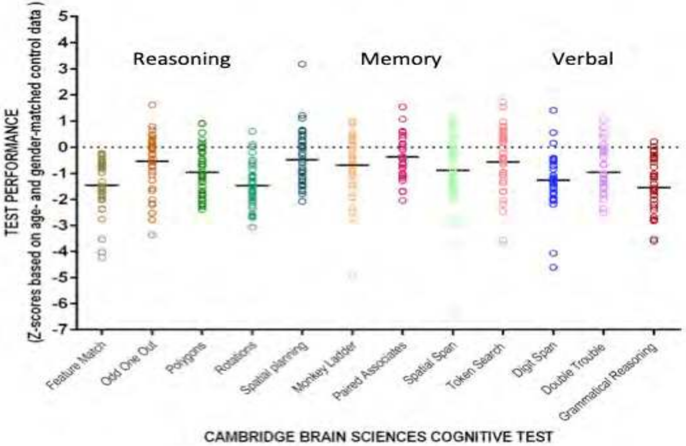
Marants R, Grant CA, Lee T, McIntyre CW. JASN 2019

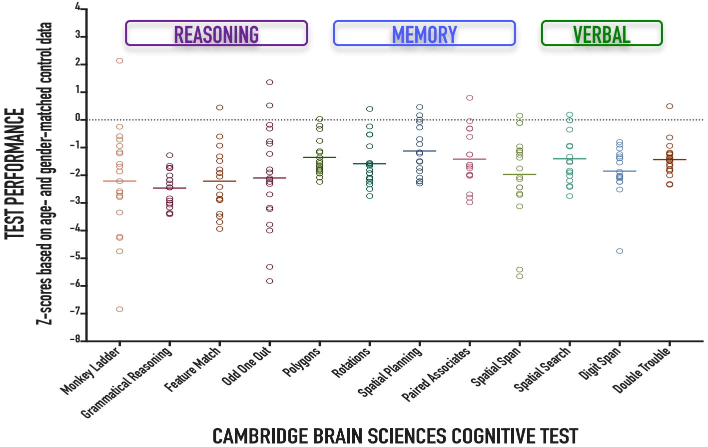
HD- associated brain injury

- Universal
- Progressive
- Directly proportional to white matter changes
- Independently associated to hemodynamic instability

McIntyre CW, Goldsmith DJ. Kidney Int. 2015 Jun;87(6):1109-15
Eldehni MT, Odudu A, McIntyre CW. J Am Soc Nephrol. 2015 Apr;26(4):957-65
Eldehni MT, McIntyre CW. Semin Dial. 2012 May;25(3):253-6
Eldehni MT, Odudu A, McIntyre CW. HDI 2019

Functional significance- CBS testing





POLYGONS

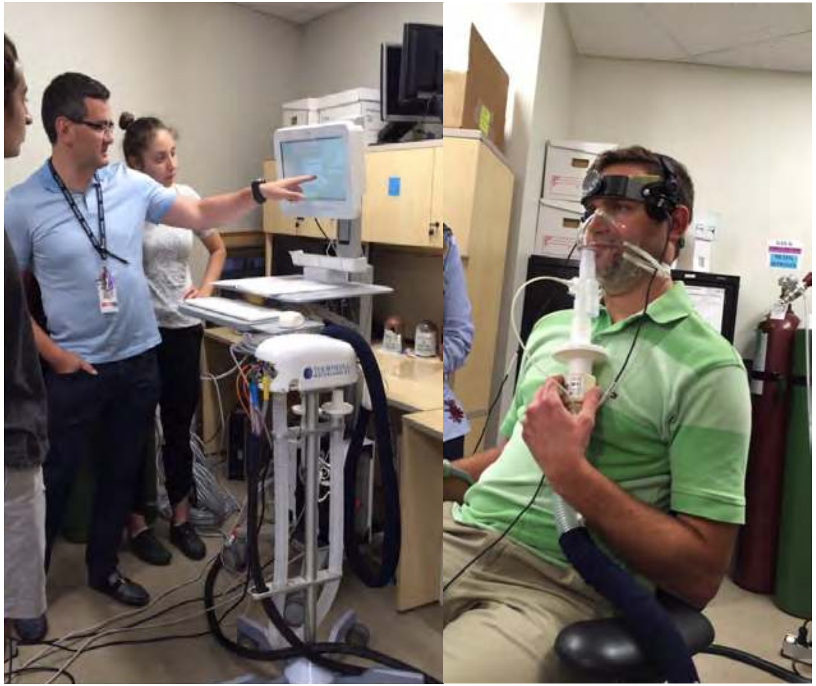
A visuospatial processing task.

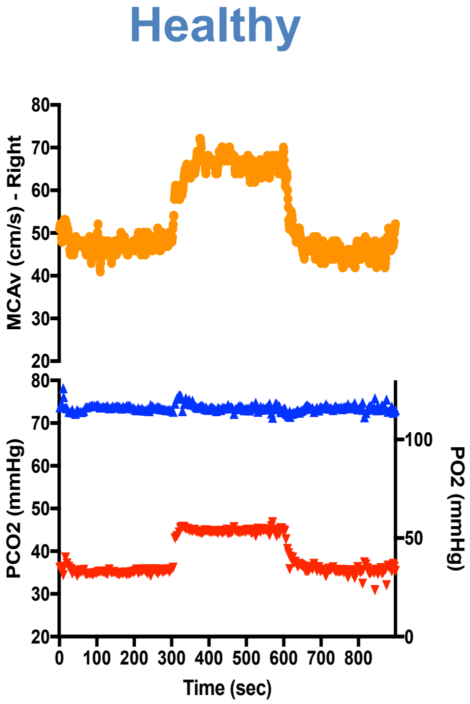
FEATURE MATCH

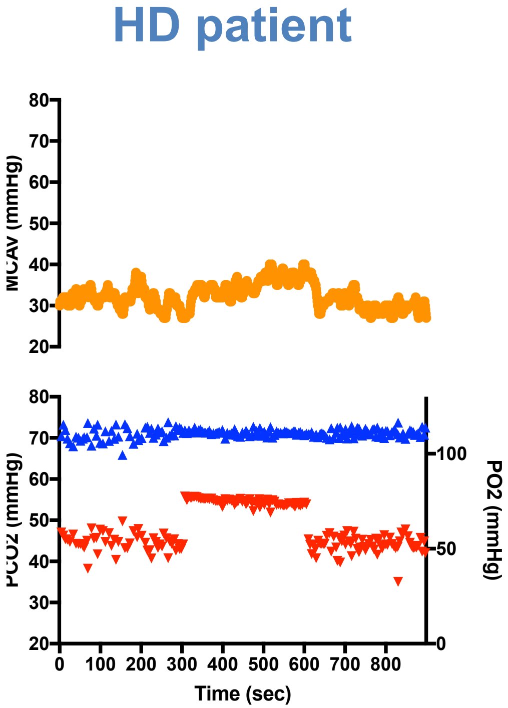
An attention task.

Honarmand K, McIntyre CW, Slessarev M. PlosOne 2019

Is autoregulation defective in dialysis patients?





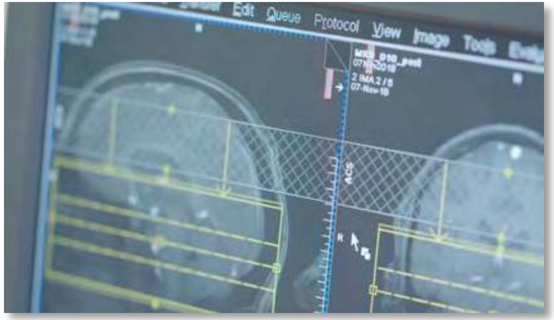


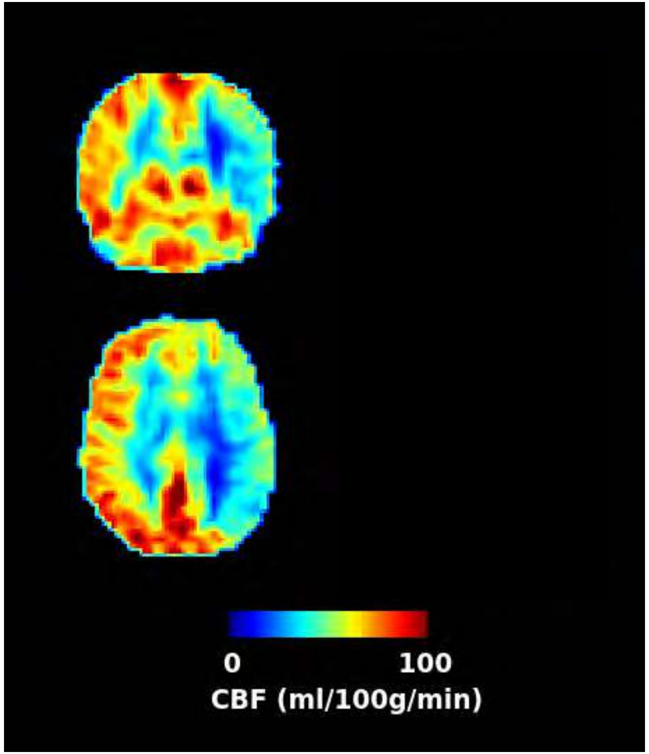
MCAv (cm/s) PO2 (mmHg) PCO2 (mmHg)

Slesarev M, McIntyre CW. Submitted 2020

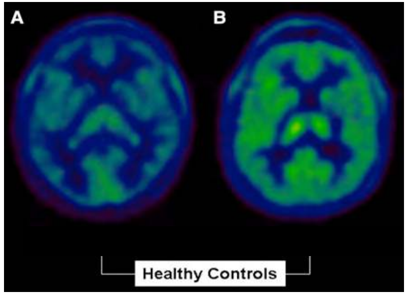
Acute effects of HD on brain- Ischemia and inflammation

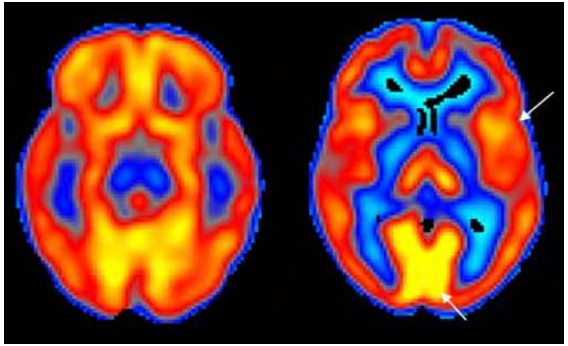
Blood flow- MRI ASL





Inflammation- ^{18}FEPPA PET





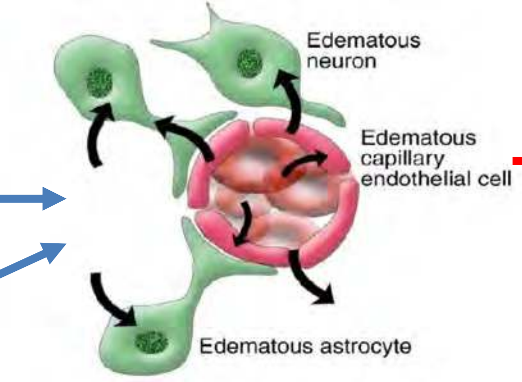
ClinicalTrials.gov Identifier: NCT03342183

Does acute reduction in CBF cause acute injury?

Ischemia → ATP depletion → Na/K pump malfunction → CYTOTOXIC EDEMA

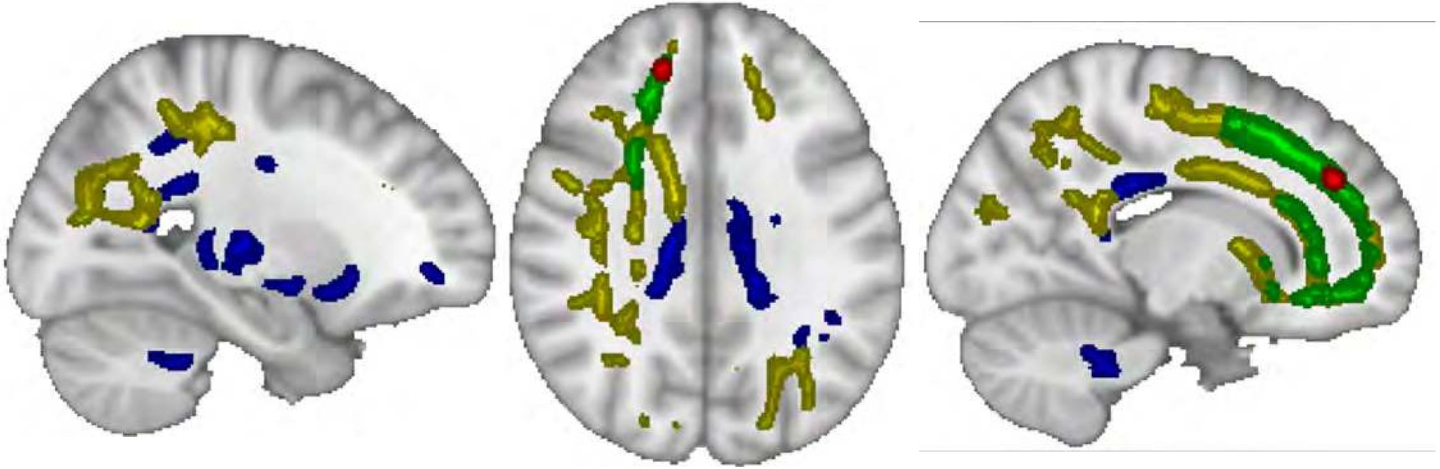
Inflammation → Glutamate

Oncotic stress



Leukoariarosis

Hemodialysis session causes acute brain injury



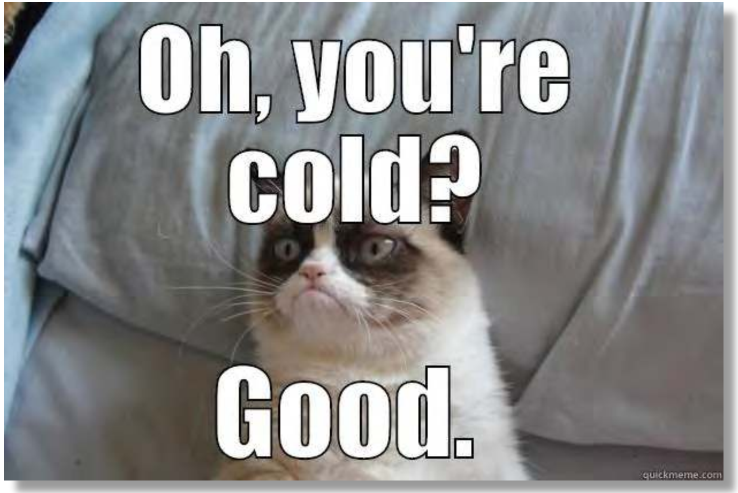
Regions where fractional anisotropy (blue), axial (yellow), radial (red), and mean (green) diffusivity increase at peak stress during hemodialysis

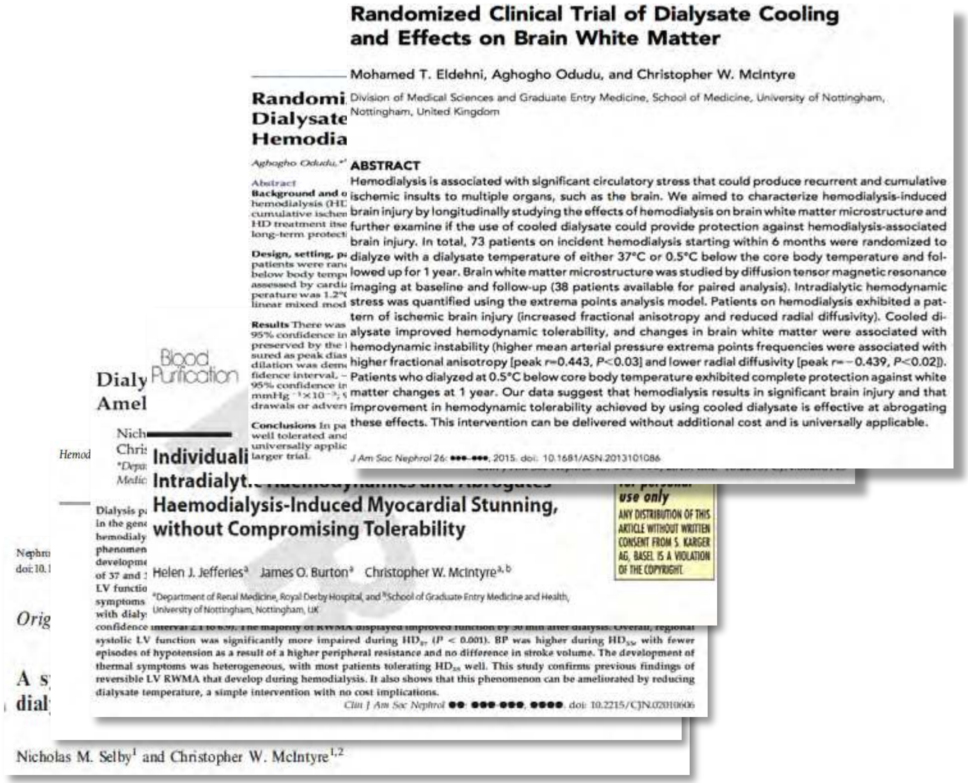
Significant (*P*<0.05) by tract-based spatial statistics with threshold-free contrast enhancement

Darcey M, Anazado U, McIntyre CW. ASN 2019

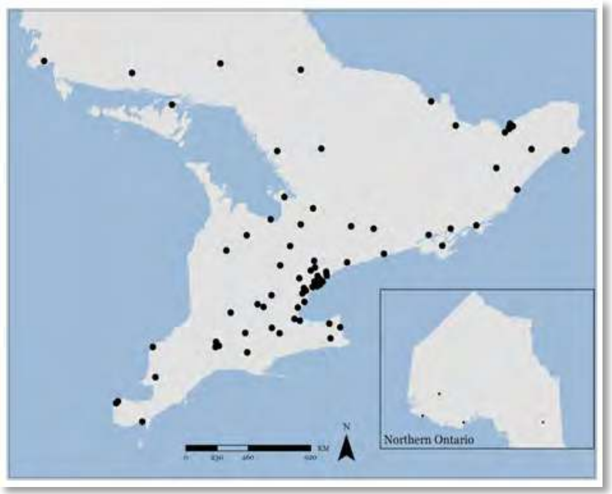
Intradialytic approaches

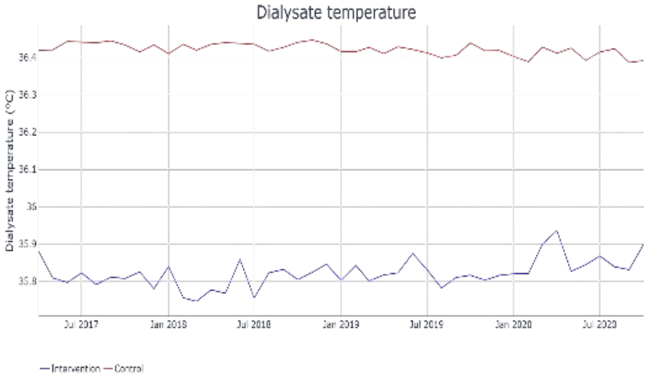
Reducing hypotension- Cooling

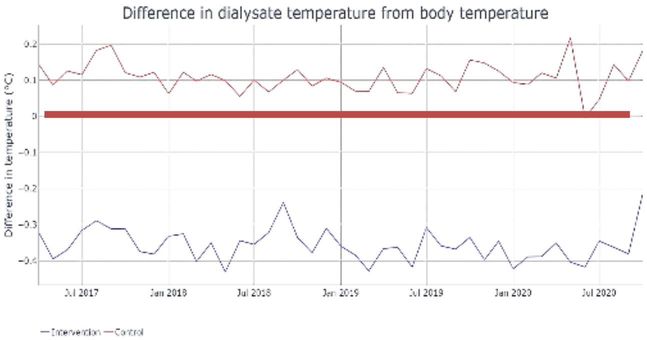




MY TEMP Trial- cluster RCT

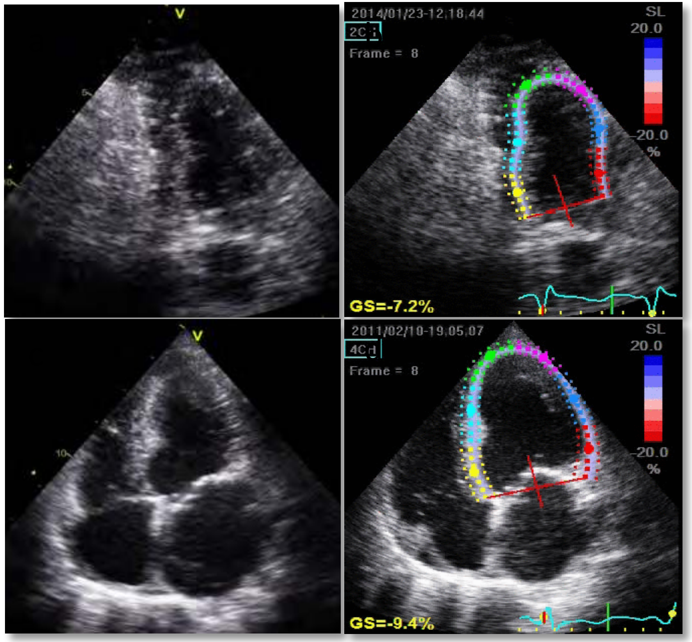


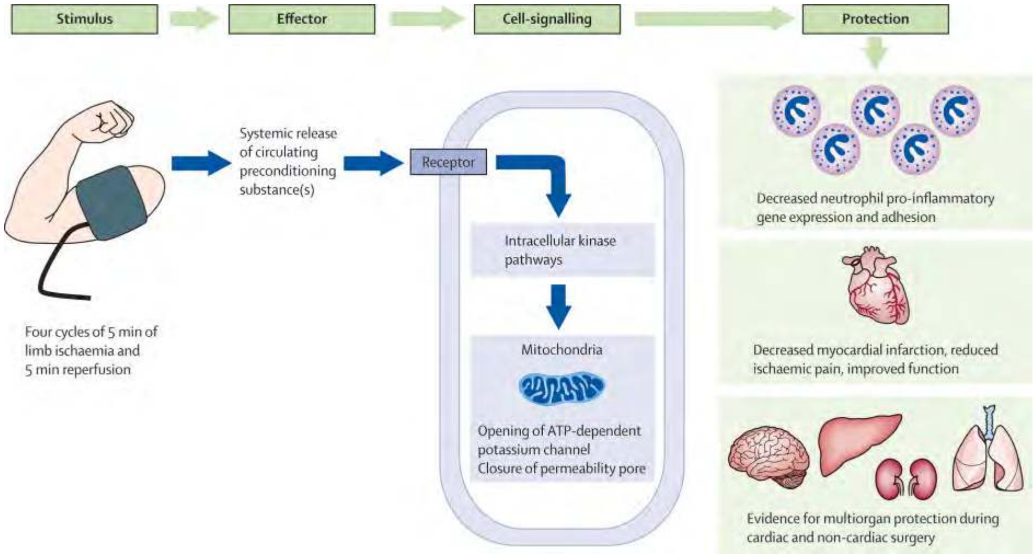




Can J Kidney Health Dis. 2020

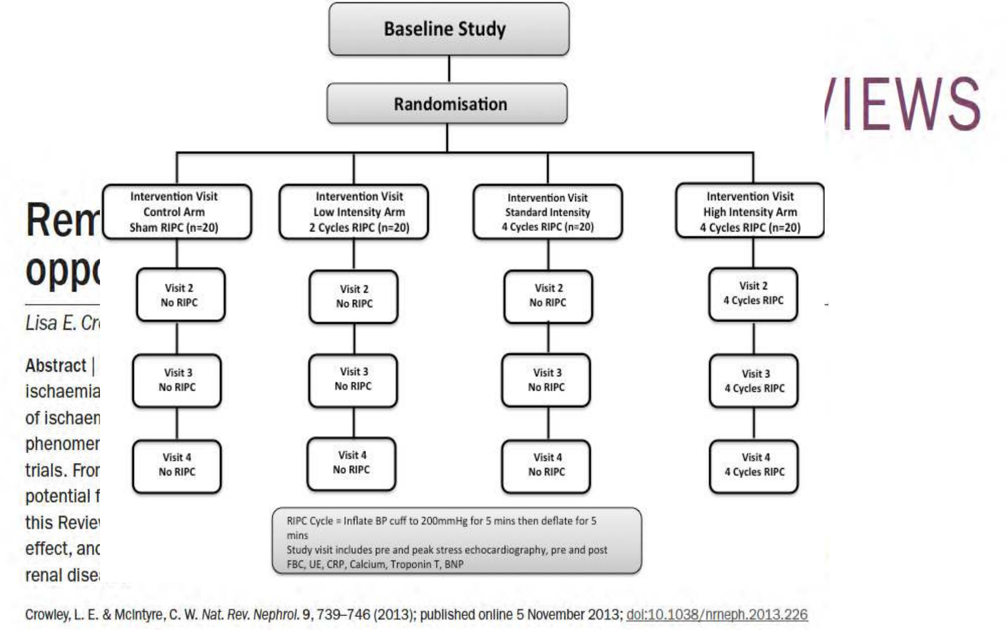
Protecting tissues from ischemic injoury- Remote ischemic preconditioning (RIPC)





Kharbanda KR et al. The Lancet 2009.

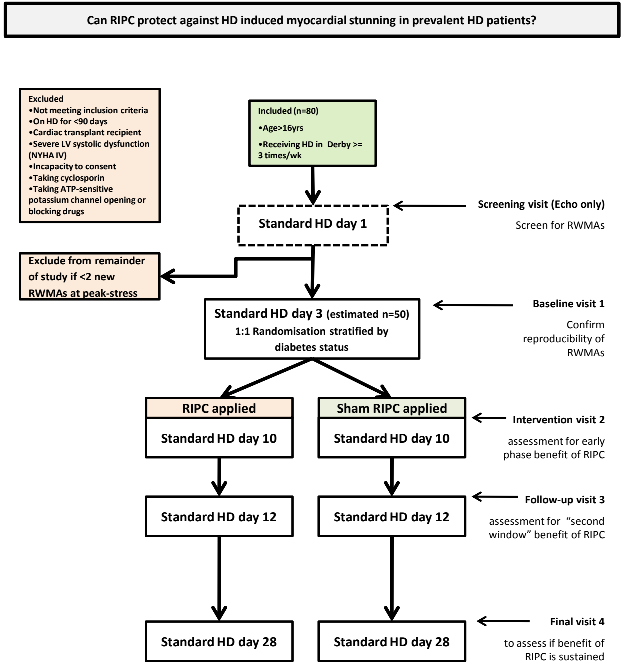
RIPC effect on dialysis induced cardiac injury



Salerno F, Tommassi T Penny J, McIntyre CW. SA-P0858 ASN 2018

Crowley L, Odudu A. McIntyre CW. ASN 2014

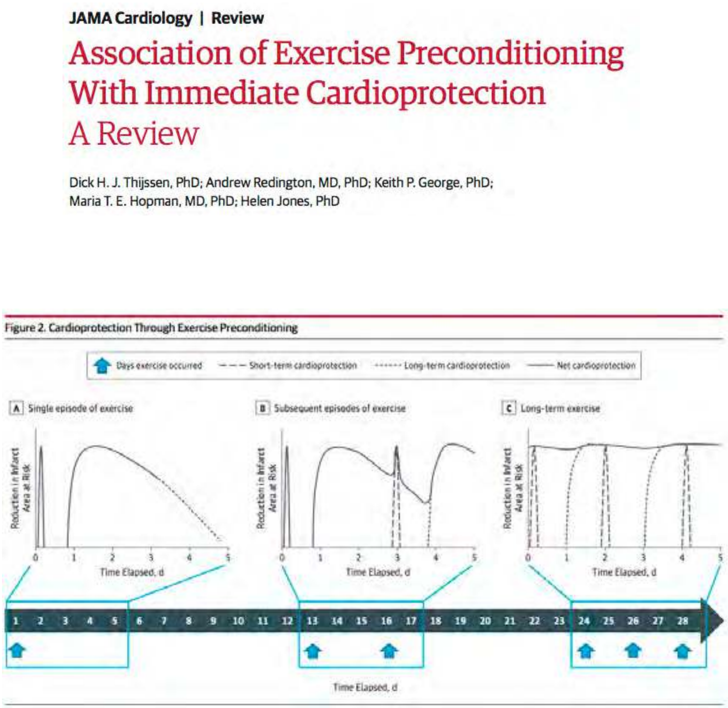
Figure 1



•**Dialysate conductivity and temperature** are fixed at 13.6mS/cm and 37.0`C.
•**RIPC at day 10** consists of 4x5 minute cuff inflations to 200mmHg, with 5 minute intervals of deflation. **Sham-RIPC** uses 4x5 minute cuff inflations to 40mmHg, with 5 minute intervals of deflation.
•**Cardiovascular assessment at day 3, 10, 12 and 28** comprises serial echocardiography, Bioreactance monitoring, pre-dialysis bioimpedance, Pulse wave velocity using Vicorder and digital-blood pressure monitoring with the Finometer.
•**Blood tests taken at day 3,10,12, and 28** pre & post dialysis include high-sensitivity troponin-T, Pre-dialysis BNP, IL-6 and hsCRP

Primary outcome
Percentage change in number of new stress-RWMAs across all participants at day 10

Exercise pre-conditioning to protect against HD-induced cardiac injury



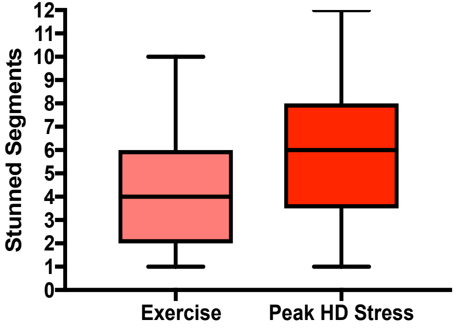
JAMA Cardiology | Review

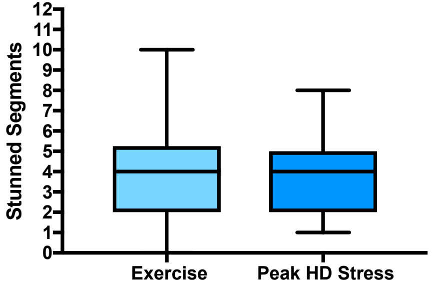
Association of Exercise Preconditioning With Immediate Cardioprotection

A Review

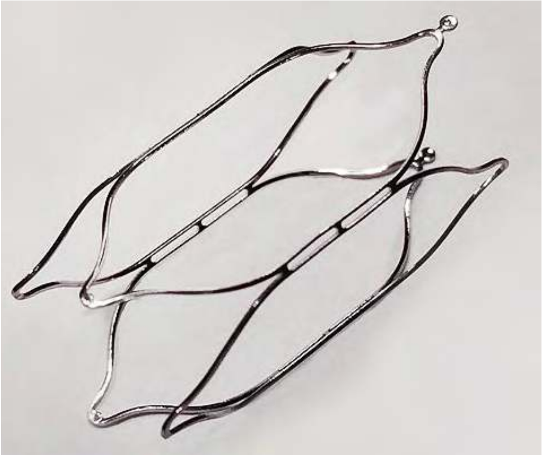
Dick H. J. Thijssen, PhD; Andrew Redington, MD, PhD; Keith P. George, PhD; Maria T. E. Hopman, MD, PhD; Helen Jones, PhD

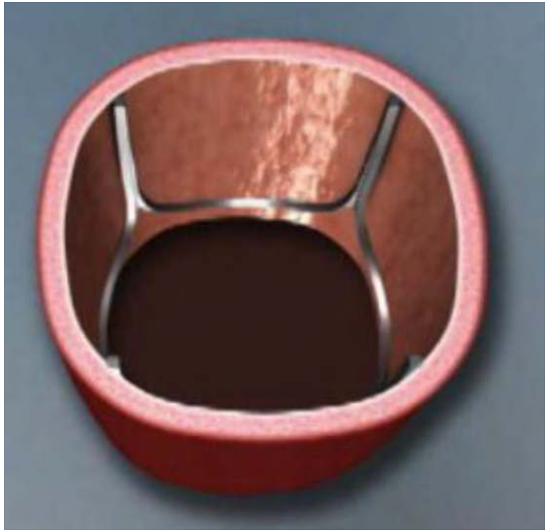
Figure 2. Cardioprotection Through Exercise Preconditioning

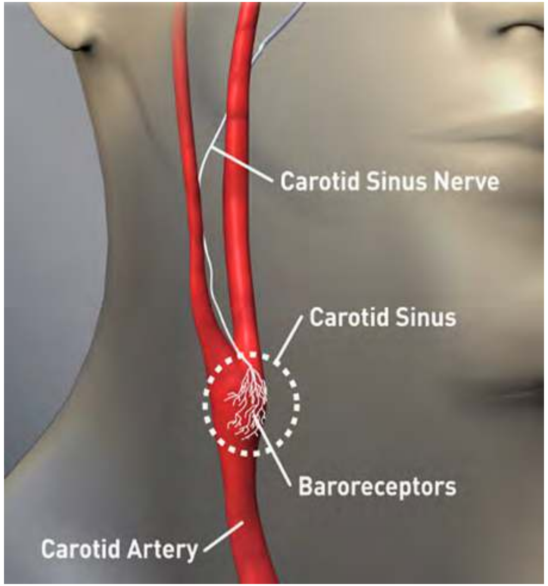




Penny J, McIntyre CW, Bohm C. Nephrol Dialysis and Transplant 2019



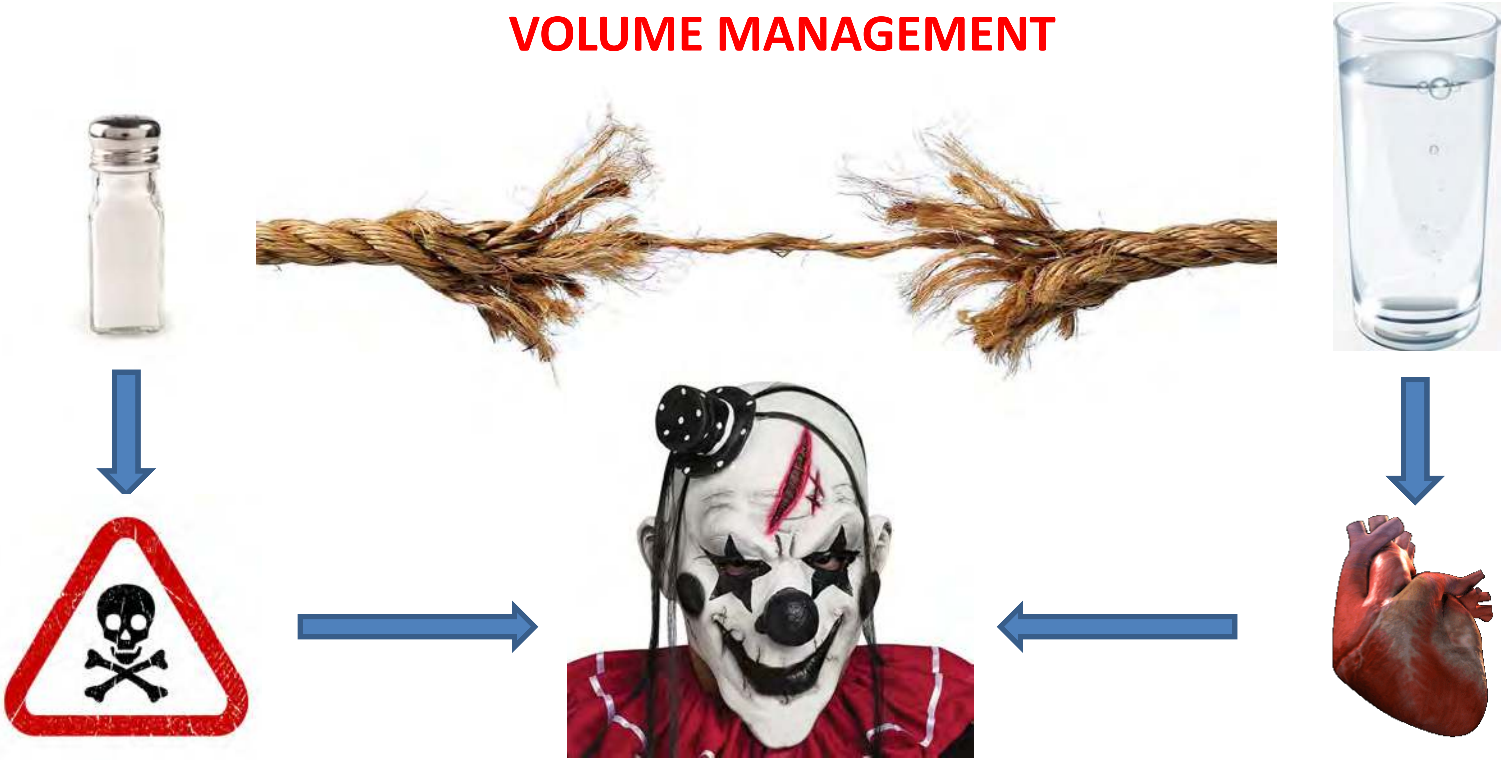




Improving vasomotor control- Baroreflex augmentation

Interdialytic approaches

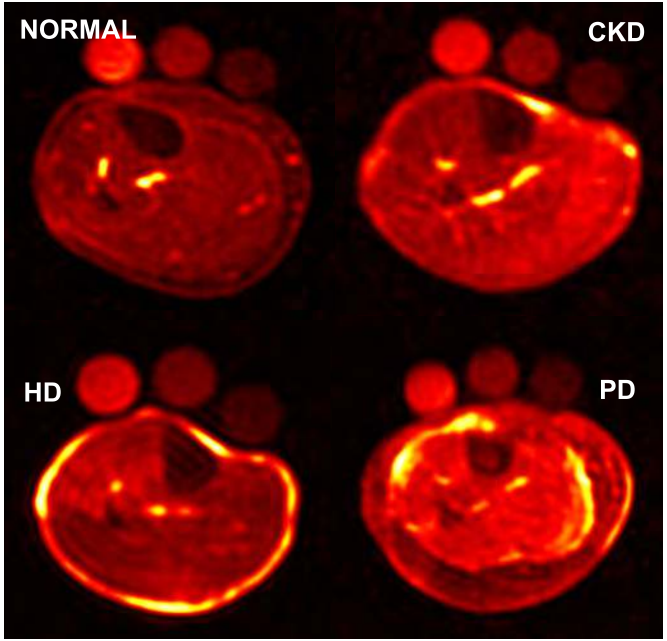
‘Elemental’ view of dialysis- salt vs. water

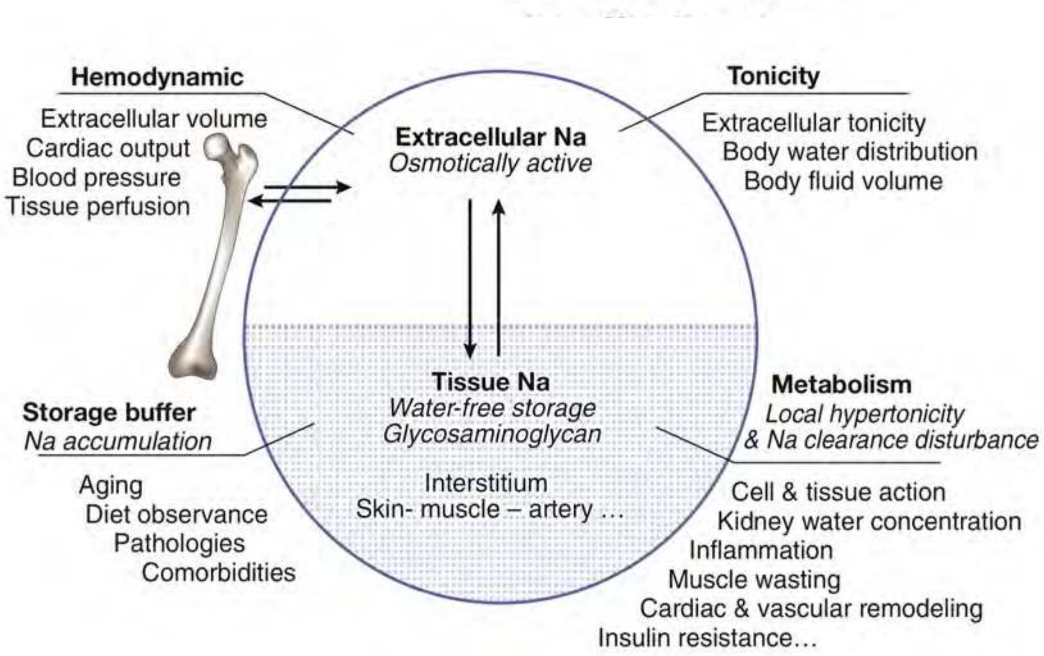


Salt- the uremic toxin at the heart of the matter

Sodium storage in CKD- no need for water!

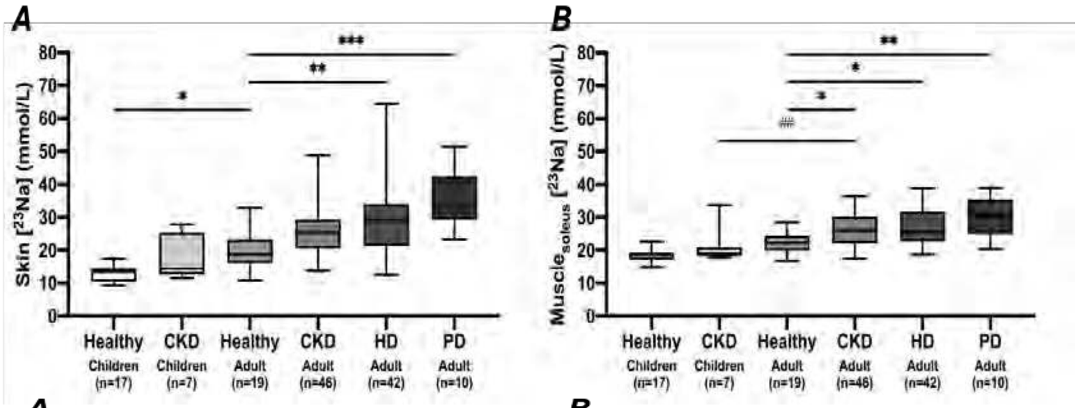
Canaud B et al. Kidney Int 2019

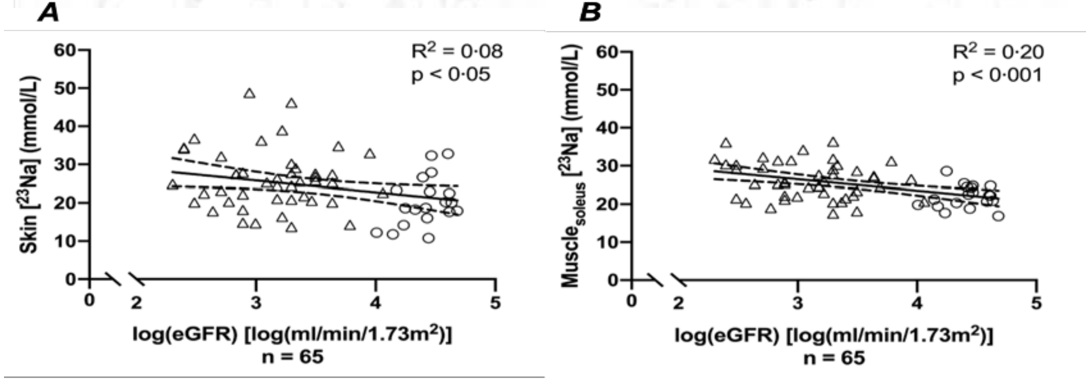


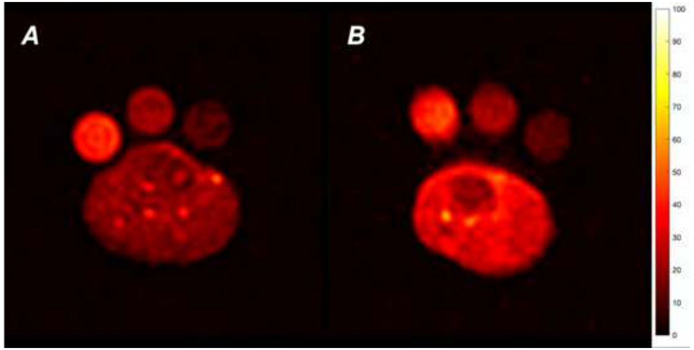


Salerno F, Qirjazi E, Akbari A, McIntyre CW. NDT 2020
Salerno F, Akbari A, Lemoine S, McIntyre CW. Submitted 2020

Determinants of Na deposition



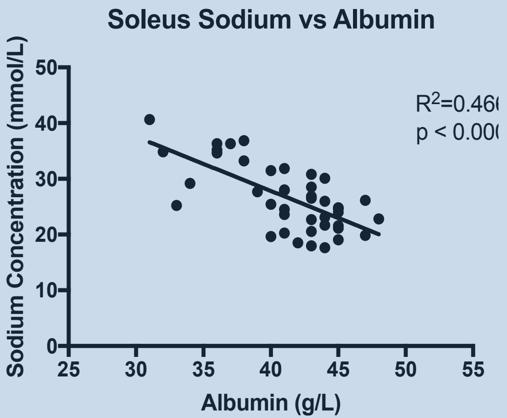


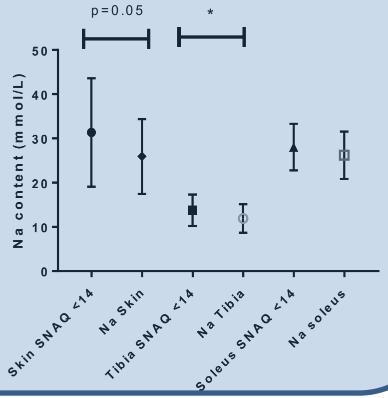


Salerno F, Akbari A, Lemoine S, McIntyre CW. Submitted 2020

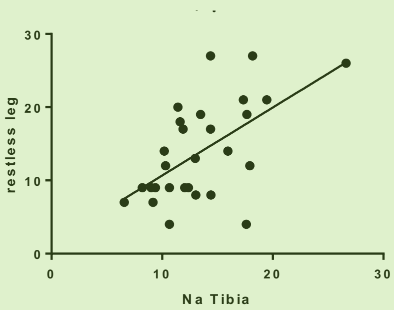
Stored Na drives CKD- associated badness

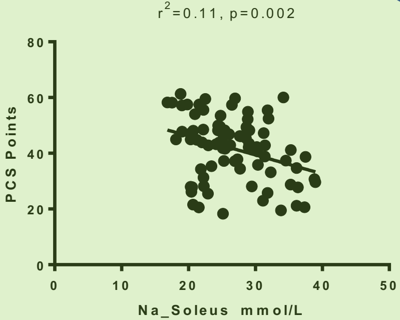
Inflammation and malnutrition



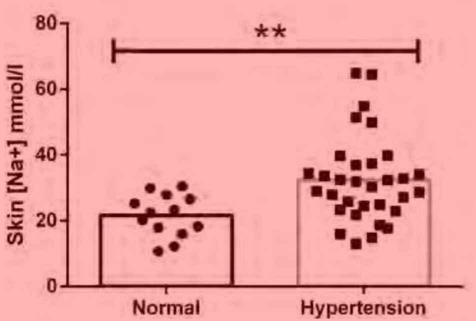


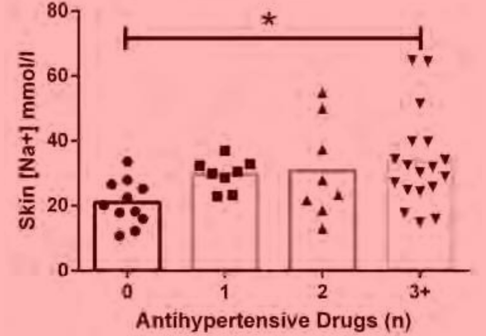
QOL and symptoms





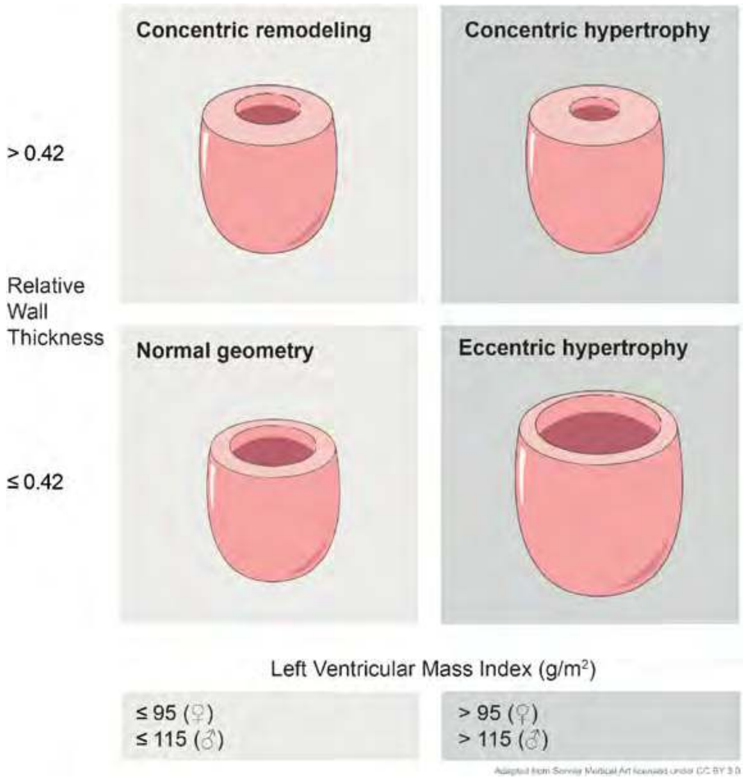
Hypertension

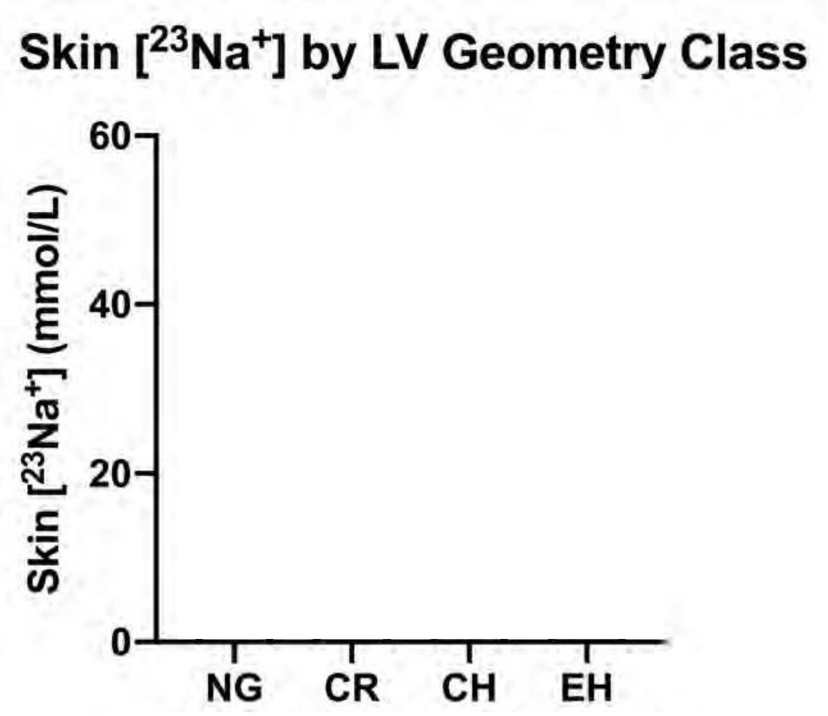




Salerno F, Akbari A, McIntyre CW. Nephrol Dialysis Transpl 2020

Tissue Na determines LV morphology

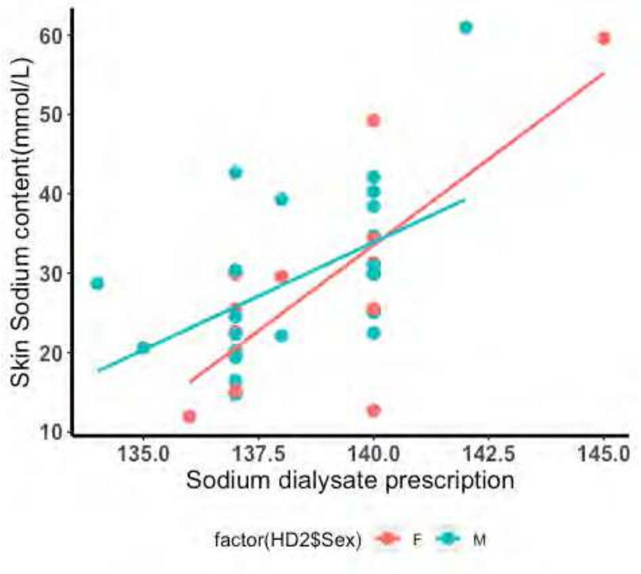


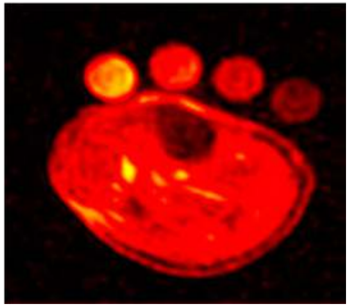


Salerno F, Akbhari A, McIntyre CW. In press NDT 2021

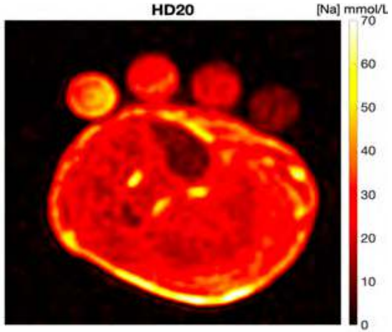
Lower dialysate [Na] removes tissue Na in HD

Association



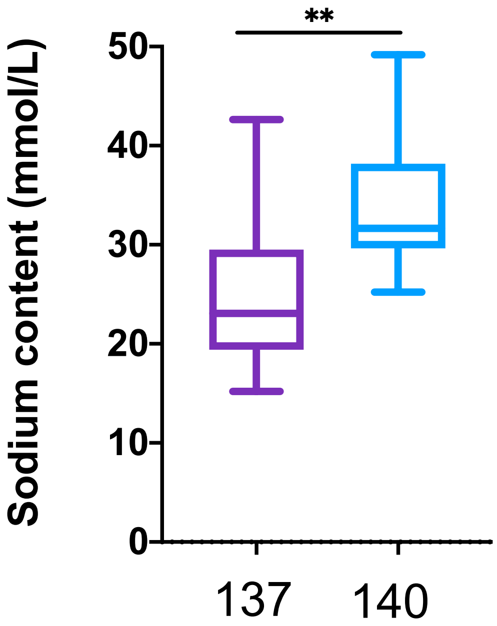


[137]D



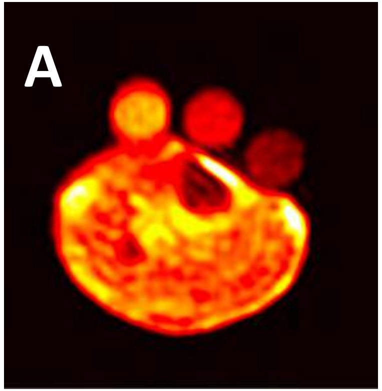
[140]D

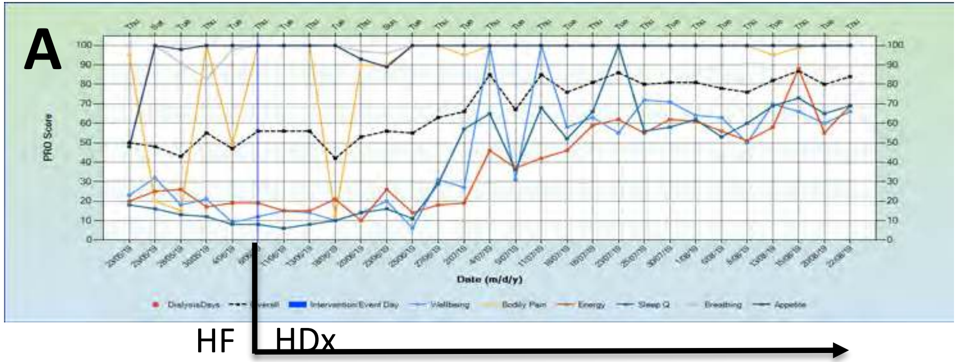
RCT- 12 months exposure

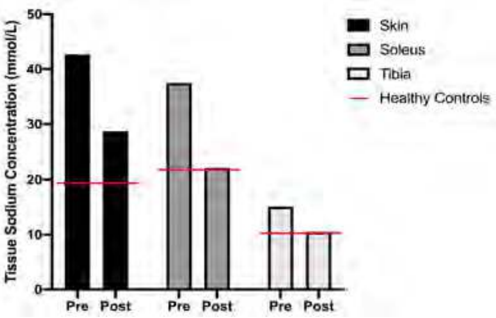


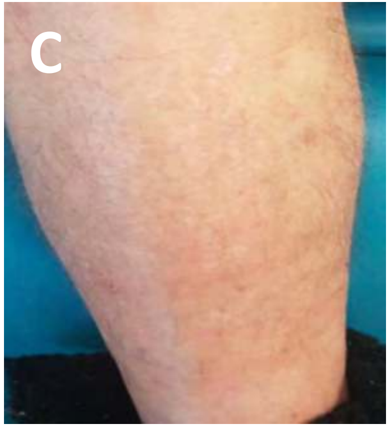
Salerno F, Akbari A, Lemoine S, McIntyre CW. AJKD epub 2021

MCO effect on tissue sodium and QOL- without use of low Na dialysate



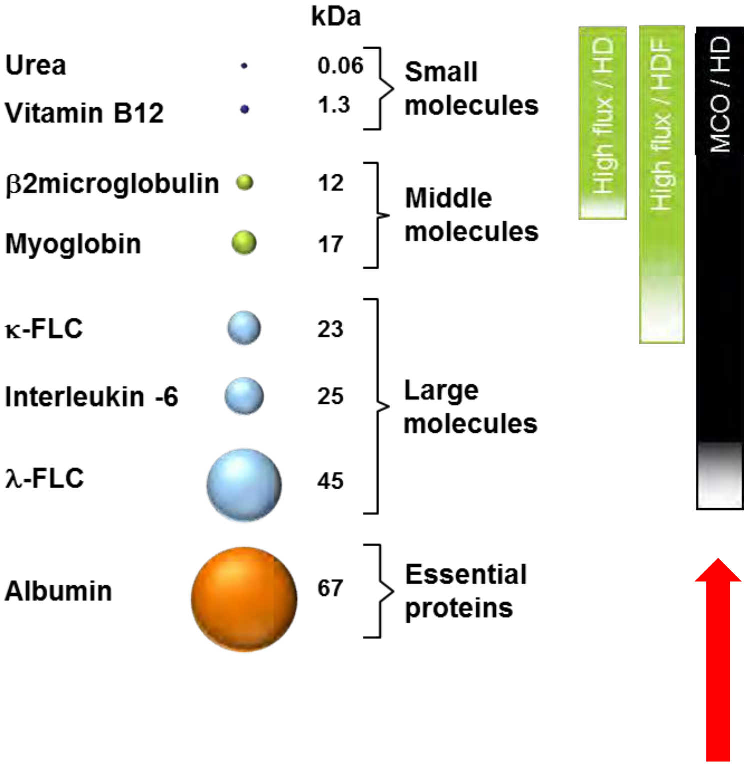




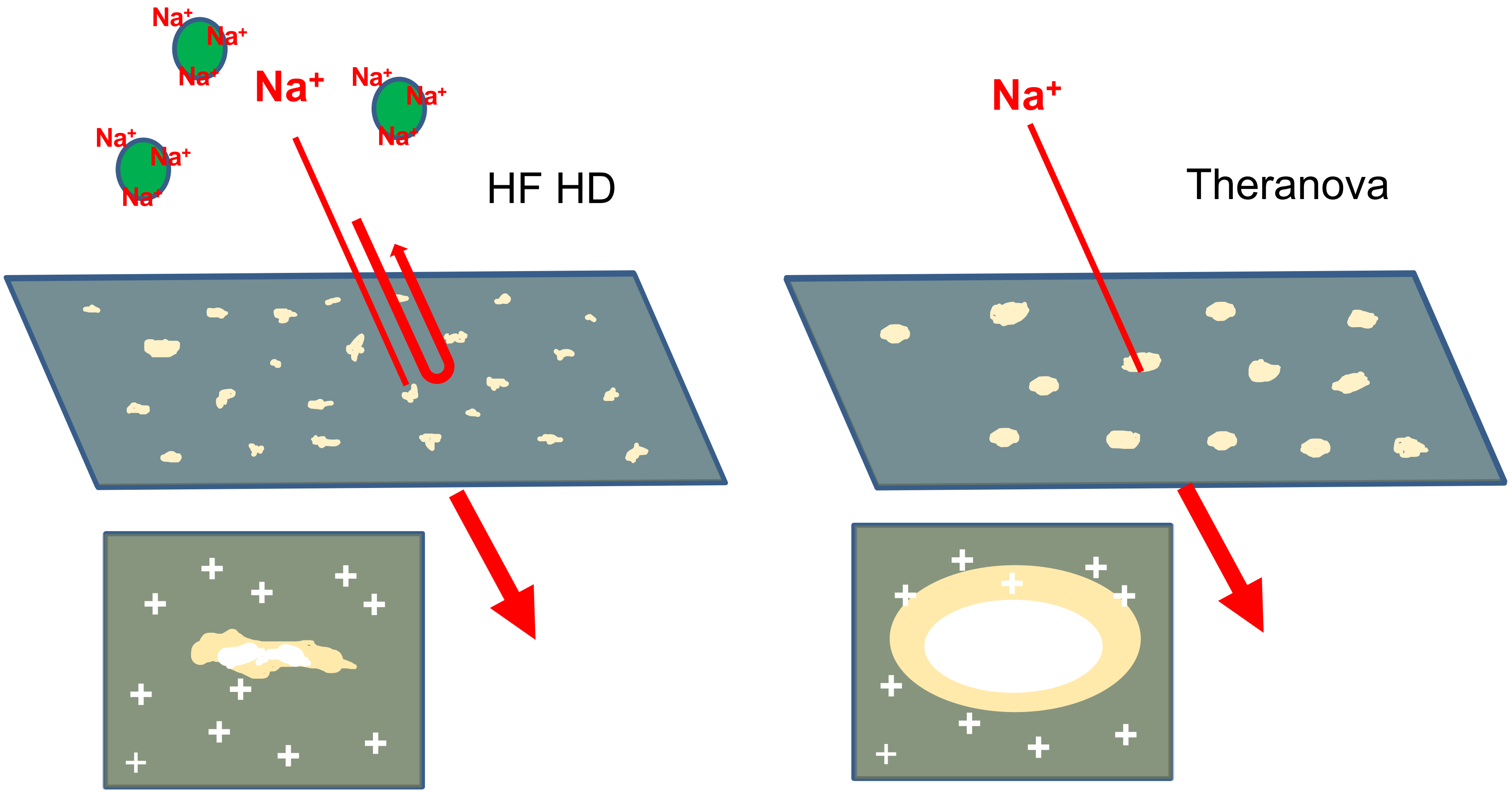


Penny J, Salerno R, McIntyre CW. HDI 2020

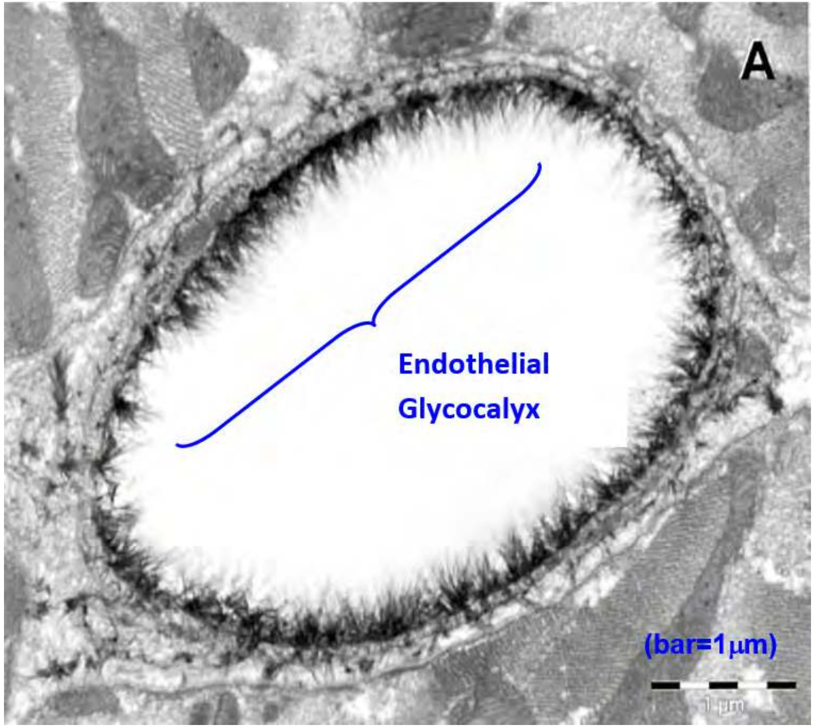
What are we actually removing from the molecular soup?



How might MCO be more permissive to Na?



Salt sensitive glycocalyx- endothelial dysfunction

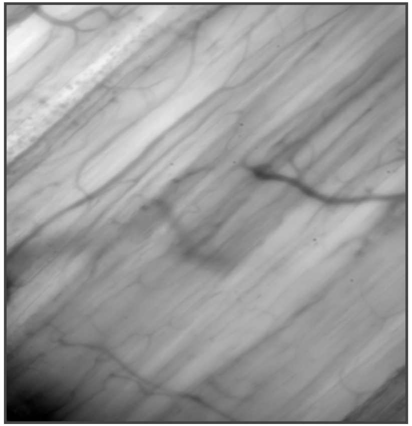


Am J Physiol Renal Physiol 319: F171–F177, 2020.
First published June 15, 2020; doi:10.1152/ajprenal.00005.2020.

RESEARCH ARTICLE

An acute rise of plasma Na^+ concentration associates with syndecan-1 shedding during hemodialysis

Josephine Koch,* Nienke M. A. Idzerda,* Esmée M. Ettema, Johanna Kuipers, Wendy Dam, Jacob van den Born, and Casper F. M. Franssen

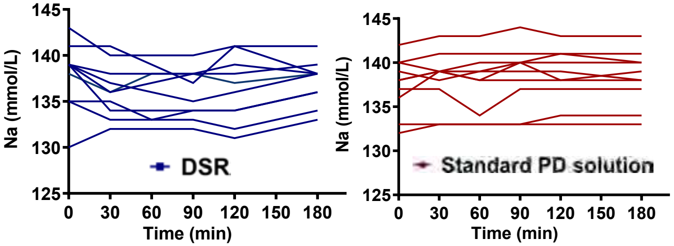


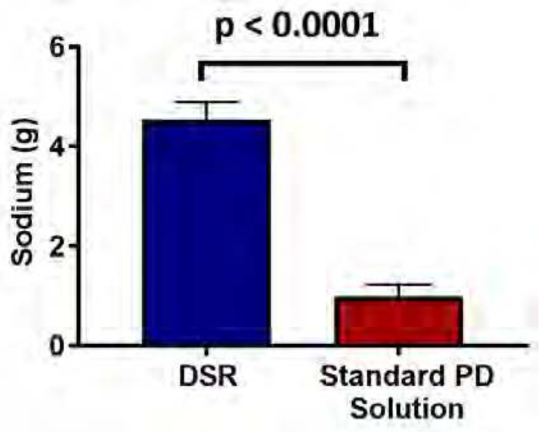
Direct Sodium Removal (DSR)

http://www.kidney-international.org

Complementary use of peritoneal and hemodialysis: Therapeutic synergies in the treatment of end-stage renal failure patients

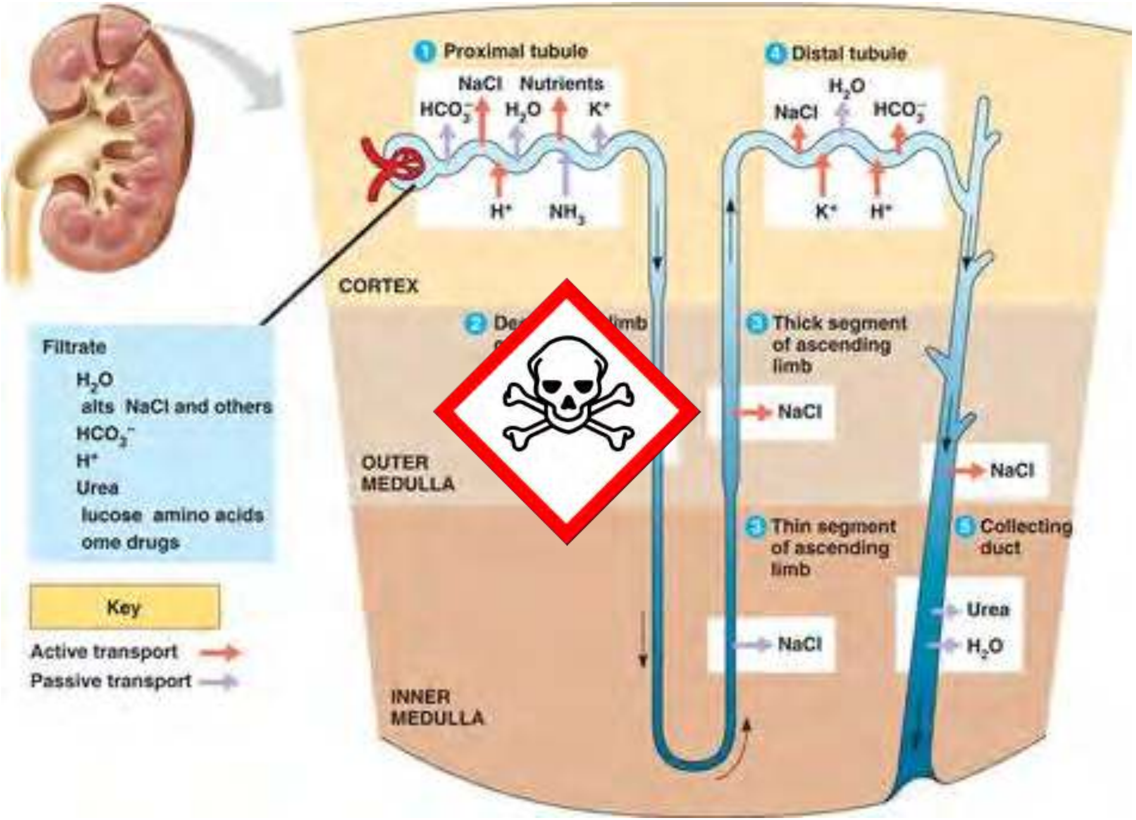
H Kawanishi[1] and C McIntyre[2,3]



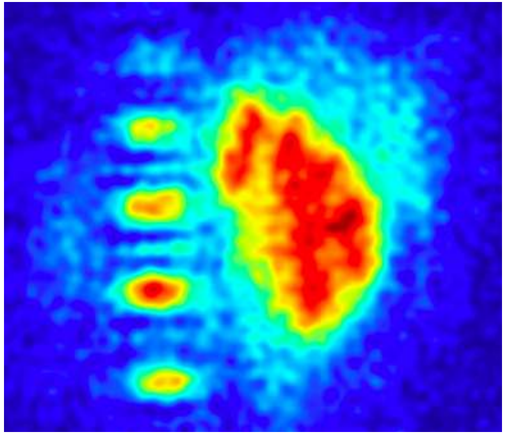


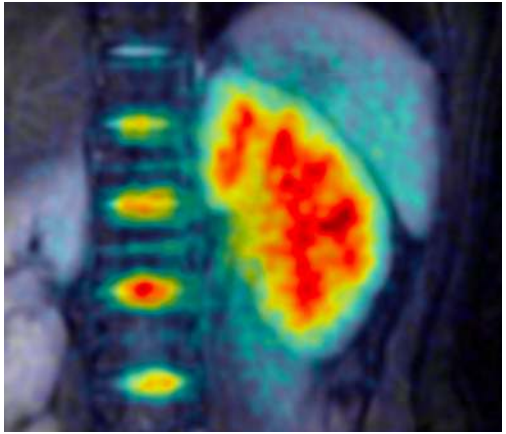
Rao V et al. Circulation 2020

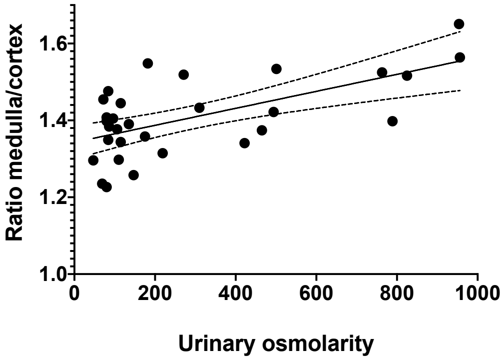
How do diuretics get rid of the extra fluid?



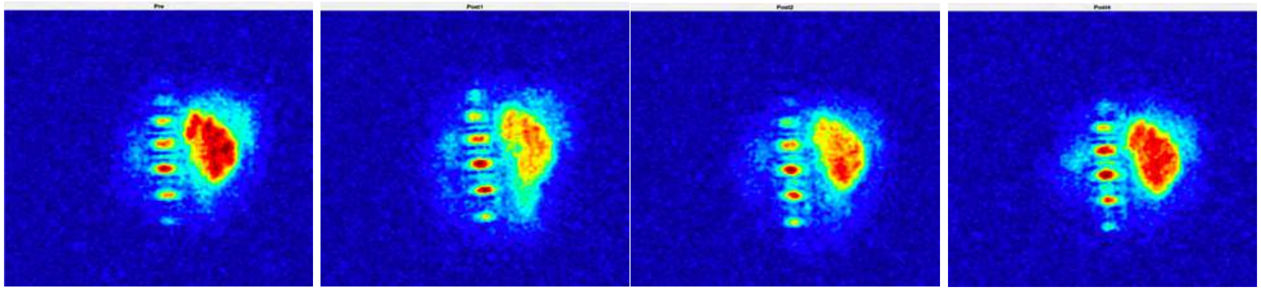
Sodium- Functional MRI for the kidney







Fluid restricted	Fluid challenge	15 min	45 min



Urine Osm			
956	47	175	501

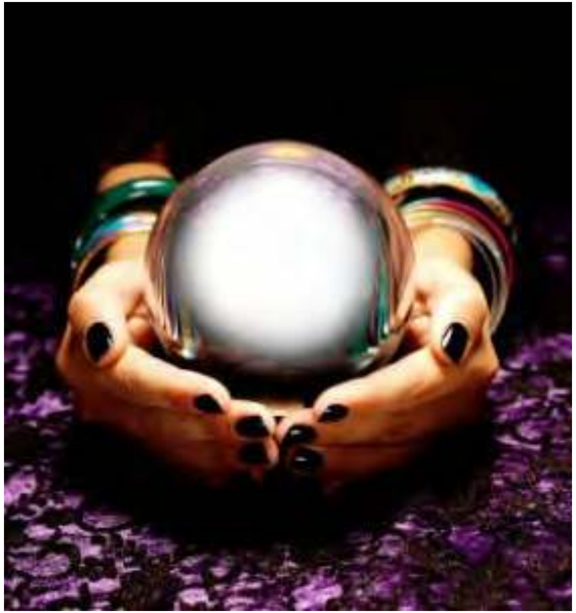
Lemoines S, Salerno F, Akbhari A, McIntyre CW. Under review JASN 2020

Interdialytic wearable solutions

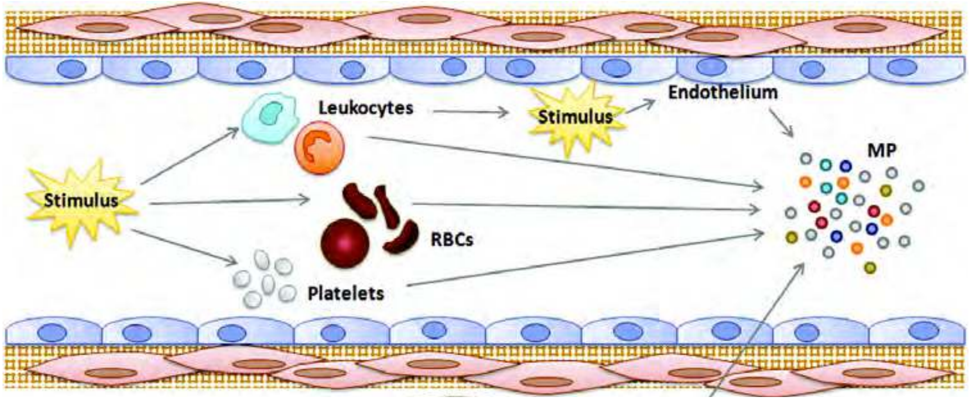
Taking out the guess work-

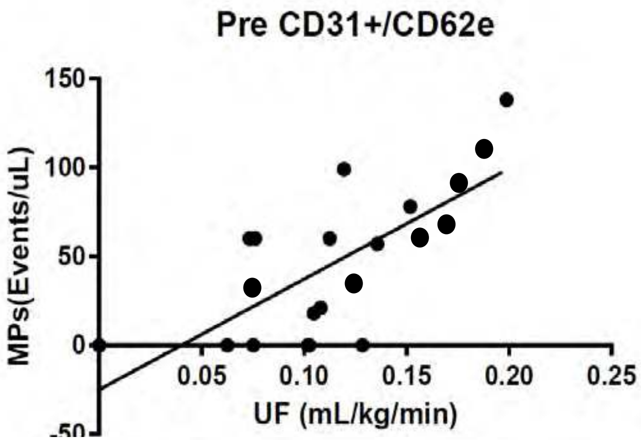
testing, monitoring and predicting response to treatment

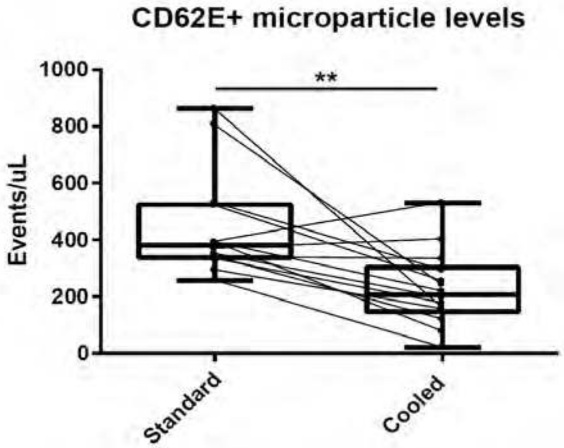
What do we want to do?



Blood test for all of this- Extracellular vesicles

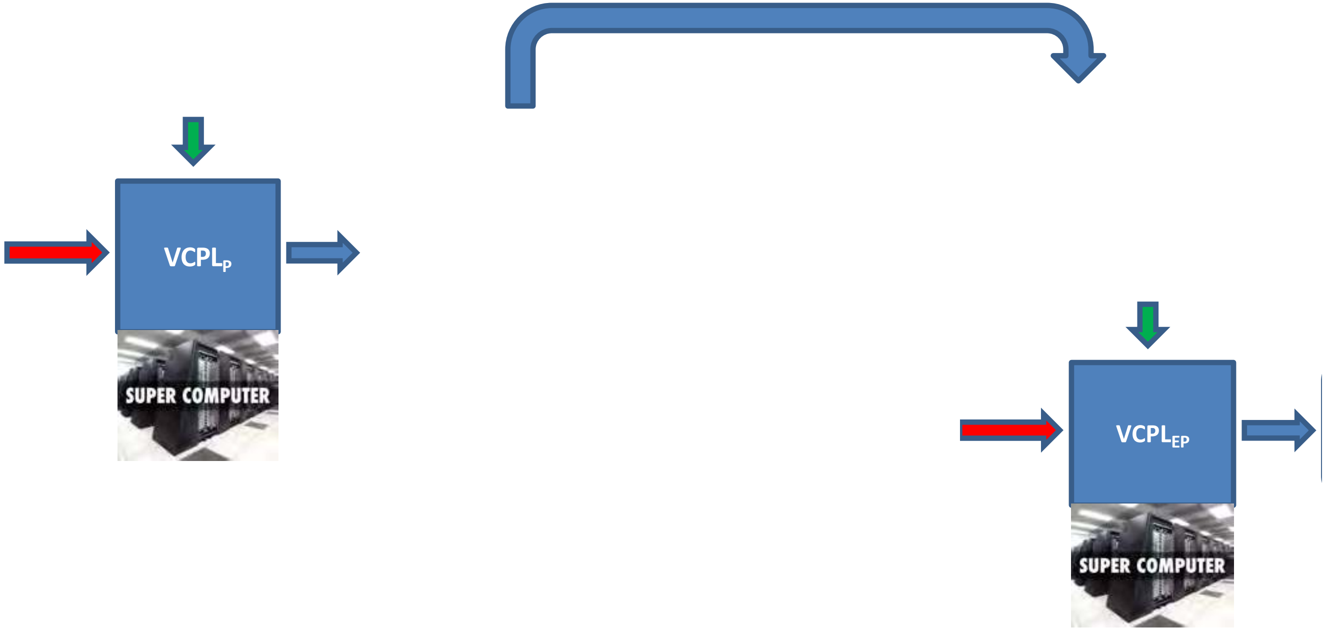






Gomes J, Qirjazi E, Leong H, McIntyre CW. FR-PO750 ASN 2018
Gomes J, Lucien F, McIntyre CW, Leong HS. Thromb Haemost. 2018 Sep;118(9):1612-1624

Virtual cardiac physiology laboratory- VCPL

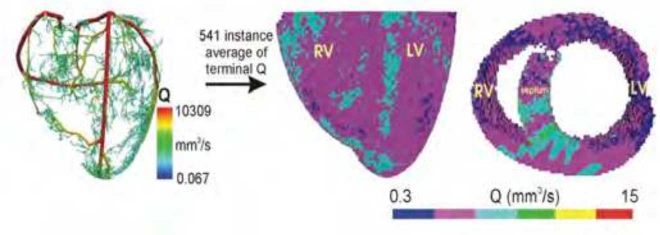


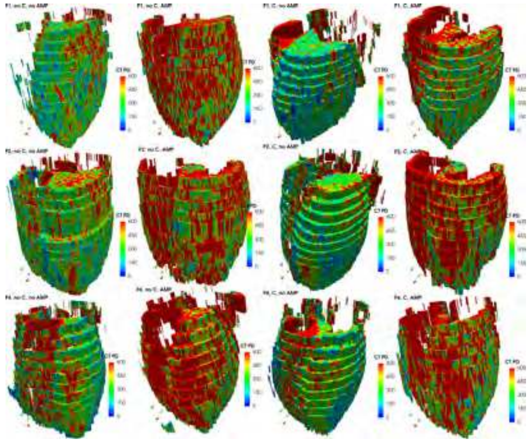
MYOCARDIAL PERFUSION

EP ACTIVITY

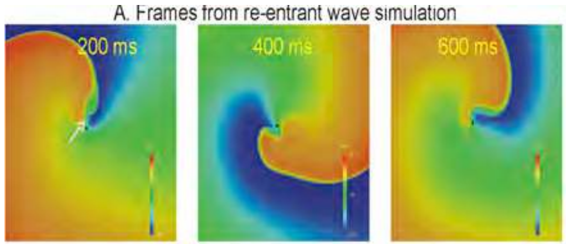
Virtual cardiac physiology laboratory- Patient specific simulation of uremic heart

$VCPL_P$

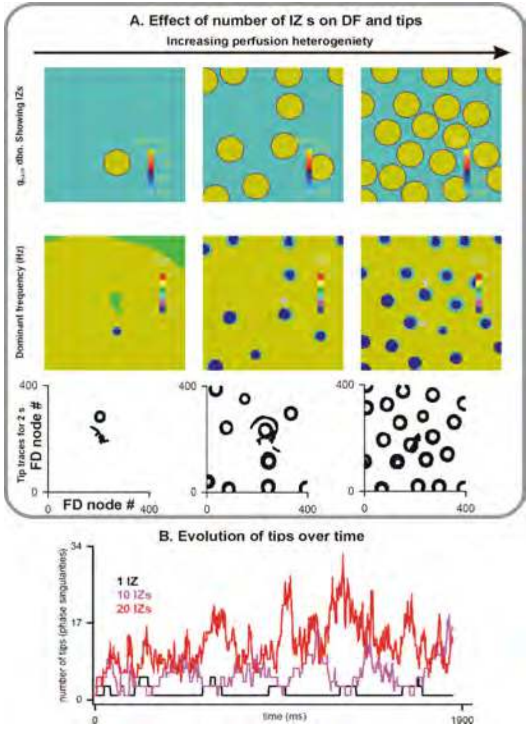




Patient specific data



$VCPL_{EP}$

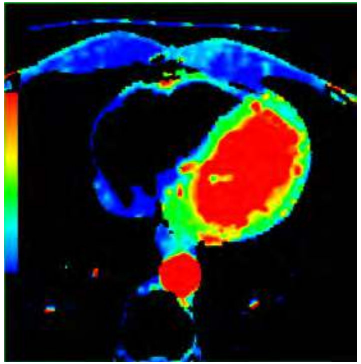


Kharche S, McIntyre CW. Frontiers in Physiol. 2018

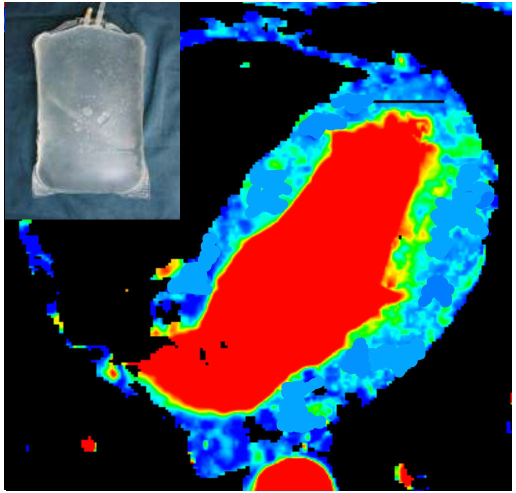
Kharche SR et al. PLOS ONE 2017

Myocardial quality- PD ahead again

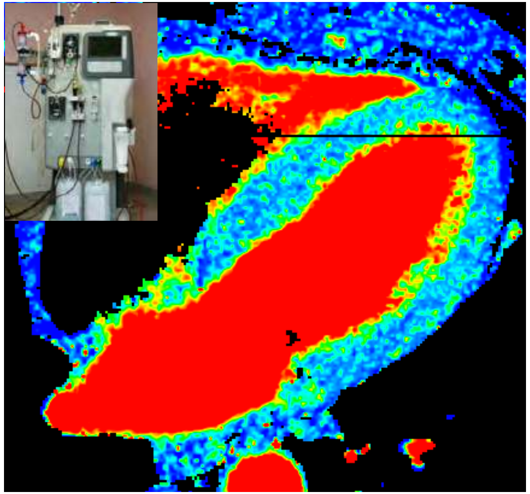
Normal

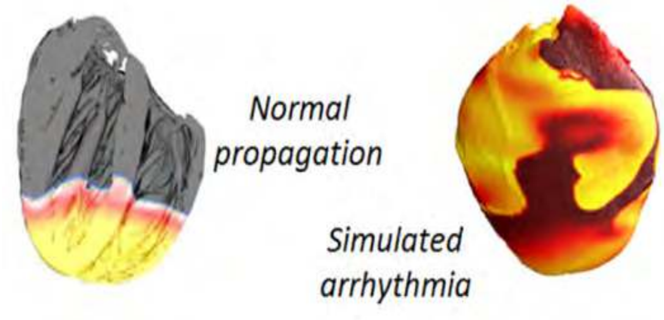


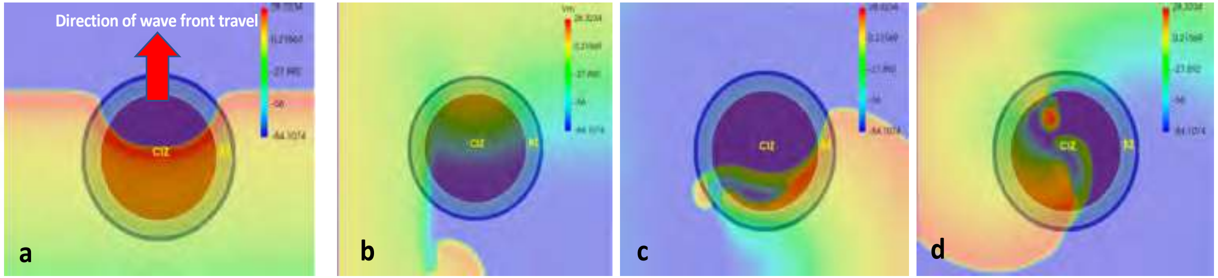
PD



HD







Kharche S, McIntyre CW. Annu Int Conf IEEE Eng Med Biol Soc. 2020

Kharche S, McIntyre CW. Frontiers in Physiol. 2018

Kharche SR et al. PLOS ONE 2017

So what does this all actually look like?

Current VCPL validation

Patient recruitment → Cardiac CT during HD → Non invasive EP mapping → Insertion of implantable loop recorder → Continuous monitoring of ILR (12 months)

Perfusion simulation → Cardiac CT during HD

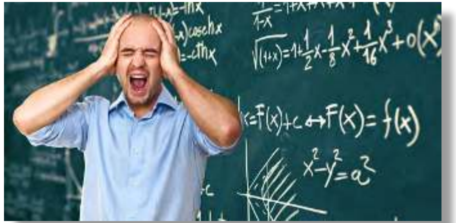
EP simulation → Non invasive EP mapping

Iterative EP simulations → Continuous monitoring of ILR (12 months)

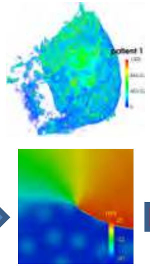
OPTIMIZED TREATMENT

Patient Specific data

VCPL

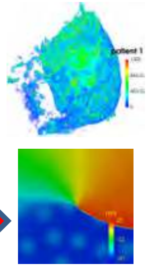


Simulated CV HD response



MODIFY VIRTUAL TREATMENT

Simulated CV HD response



"The best way to predict the future is to create it."

Abraham Lincoln