Dialysis Dosing: Kinetics Versus Physiology

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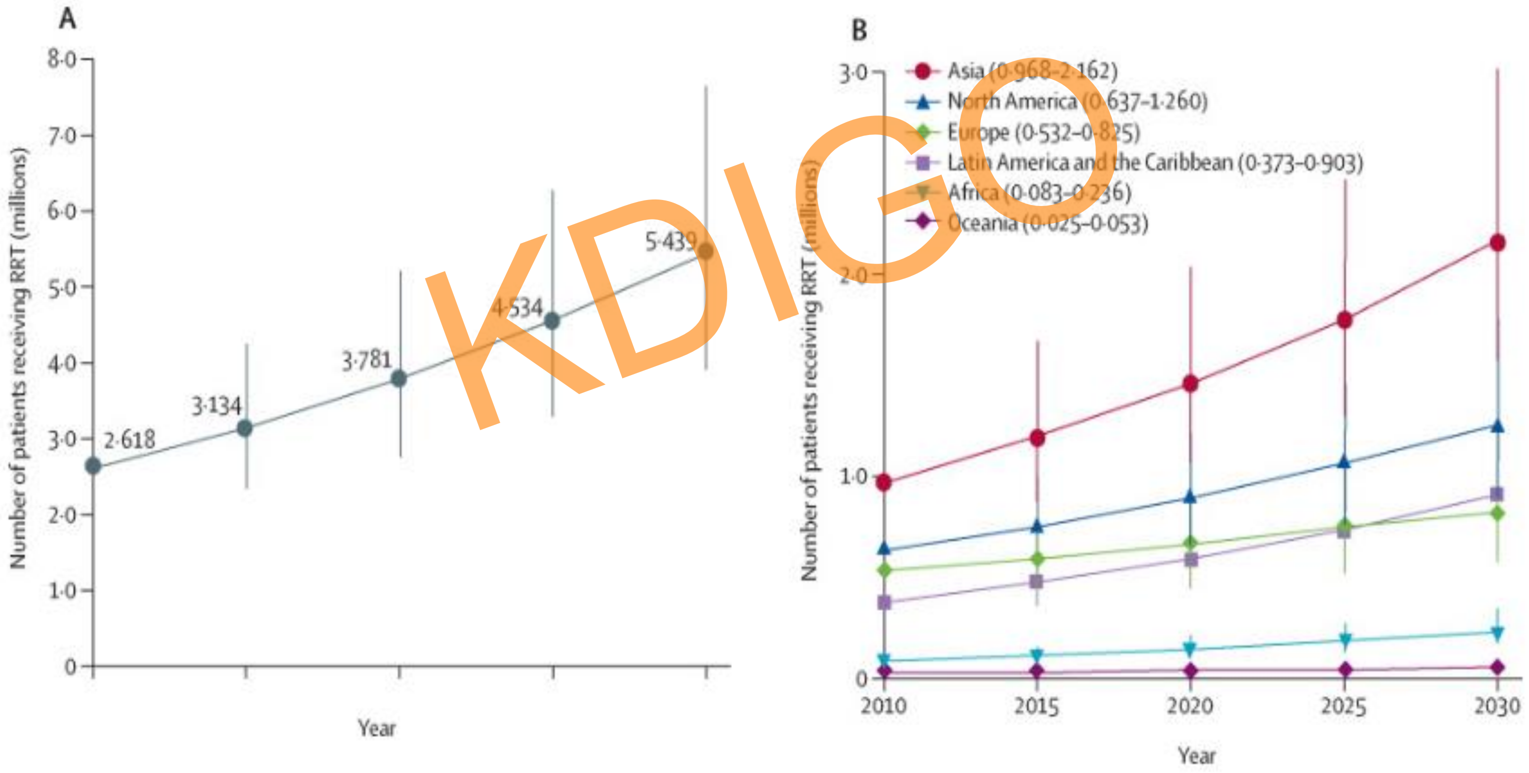
Navarra, Spain

Disclosure of Interests

- NxStage European Medical Advisory Board

Epidemiology

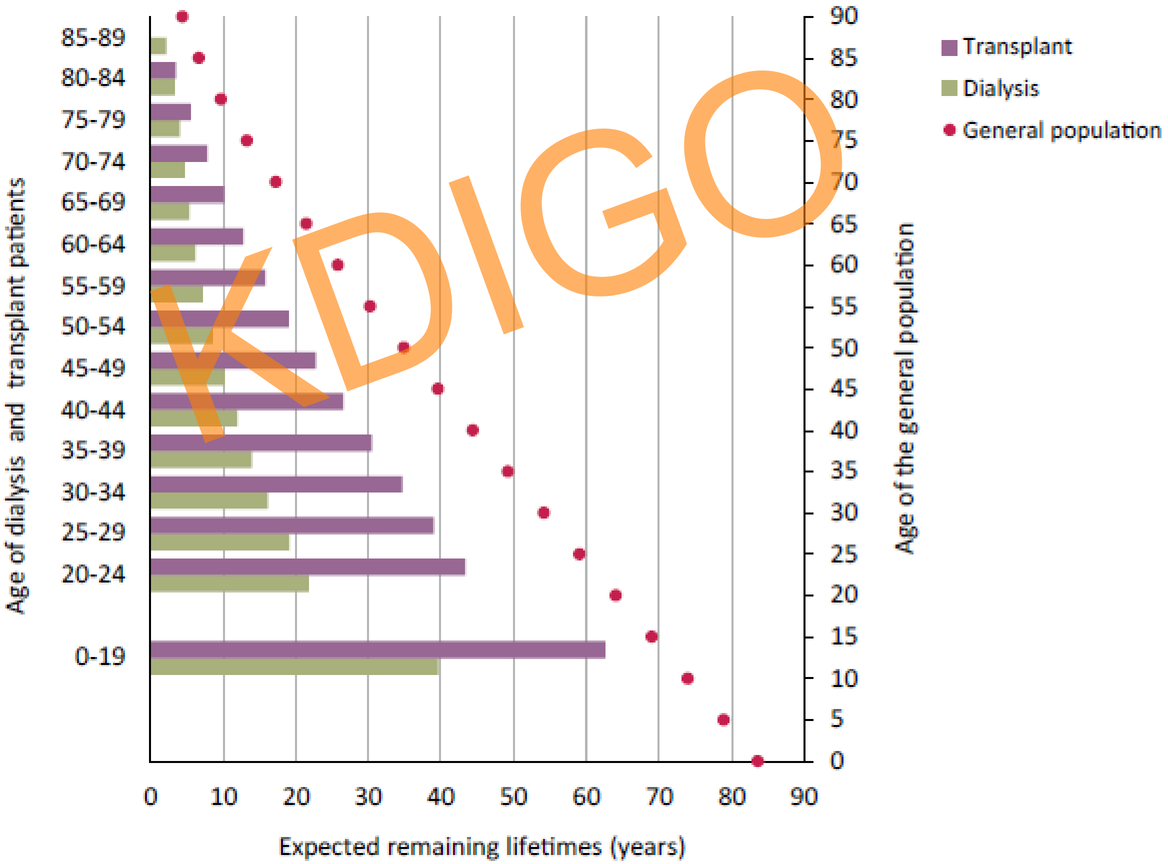
Estimated number of patients undergoing RRT from 2010 to 2030 **worldwide (A)** and by **region (B)**



Liyanage T, et al. Lancet 2015

Epidemiology

Expected remaining lifetime (years) of the **general population** (cohort 2011-2015) and of prevalent **dialysis and transplant patients** (cohort 2011-2015)

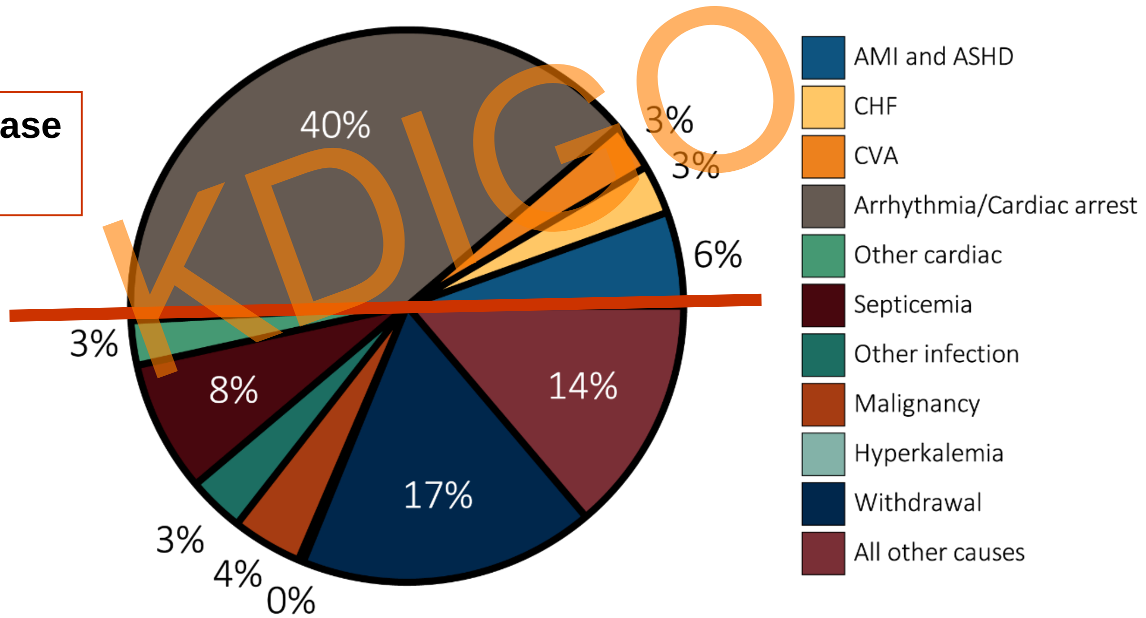


ERA-EDTA Registry Annual Report 2015

Epidemiology

Unadjusted percentages of deaths in 2014 by cause, excludes missing/unknown causes of death data among **dialysis patients**

Cardiovascular disease
> 50%



Abbreviations: ASHD, atherosclerotic heart disease; AMI, acute myocardial infarction; CHF, congestive heart failure; CVA, cerebrovascular accident.

USRDS Annual Data Report 2017

Dialysis Therapy

SOLUTES CLEARANCE

Uremic Toxins

Electrolites Regulation

Acid–base Balance

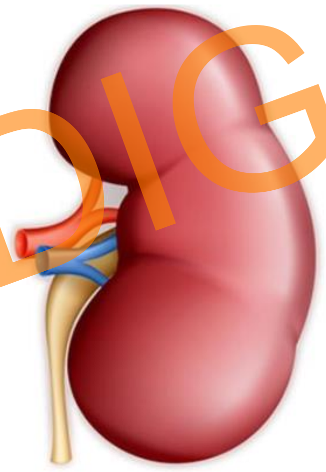
Calcium–phosphate control

HORMONE PRODUCTION

Red blood cell mass regulation

Vitamin D regulation

Others



VOLUME HOMEOSTASIS

Fluid Overload

Blood pressure control

Dialysis Therapy

SOLUTES CLEARANCE

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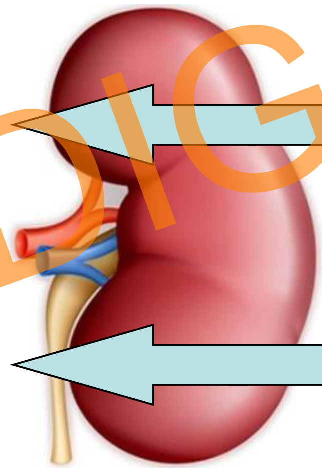


Convetional Hemodialysis

Peritoneal dialysis

Hemodiafiltration technologies

Intensive Hemodialysis

Ability for **solute clearance, frequency** and **therapy duration**

Adequacy Dialysis Dose

"From an **idealistic** clinical perspective, an **adequately** treated **dialysis patient** is **physically active,** well **nourished**, **euvolemic** and **normotensive**, with a maintained good **quality** of **life** and a **life expectancy** that is **not inferior** to that of **healthy** patients"[1]

1. Floege J et al. Comprehensive Clinical Nephrology, 2015

Adequacy Dialysis Dose

- The **marker** of **dialysis adequacy** has been typically determined **just** by measuring **small solute clearance,** based on **urea removal**

- **Urea kinetics modeling** has been taken as a **paradigm** of **all uremic toxins**; but now **it is clear**, that urea removal **is not very similar** to **kinetics** of **other** retention solutes

- **Calculation** of the **index of urea clearance** (**Kt/Vurea**) has been the **principal tool** to estimate **dialysis dose**, correlated with **clinical outcomes** for more than **30 years**

Dialysis Adequacy

Relevant studies have changed dialysis adequacy over the years

Dialysis sessions were long procedures **20-40 h/week**

Time was a "**prime measure**" in the concept **of dialysis adequacy**

Financial and **logistical pressures created** an incentive **to shorten dialysis time**

RRF and total UF important factors in **PD adequacy**

Adequacy HD target **spKt/v 1,4 until now!!!**

More attention has turned to **alternative dialysis schedules**

1951 – **First serious approach to quantify dialysis** Wolf et al

1971 – **Hypothesis "Square meter hour"** Babb et al

1973 – MEDICARE ESRD

1990s – **Equilibrated Kt/v** by Daugirdas; **URR** by Lowrie

1996 – **CANUSA** Study

2002 – **HEMO** Study

2003 – **NECOSAD** **EAPOS** Study

2007 – **Alberta Nocturnal Trial**

2010- 2011 – **FHN Trials**

2013 – **ESHOL**; **Turkish HDF**

2015 – **Last Guidelines**

1949 – **First HD** in North America Performed by Murray

1983 – **NCDS** Study

2002 – **ADEMEX** Trial

2003 – **Hong Kong Study** (Lo et al)

2008 – **MPO** Study

2012 – **CONTRAST**

2018

Time on dialysis **was less important**, as long as **urea clearance reached the target**

Urea clearance index (**Kt/Vurea**) became the **marker of dialysis adequacy** until today!

Adequacy **PD target weekly Kt/v 1,7 until now!!!**

Technological improvements **New convective modalities**

Adequacy Guidelines

Kt/Vurea

NEPHROLOGY

Nephrology 18 (2013) 485–488

KIDNEY HEALTH AUSTRALIA CARI GUIDELINES

PD 2005 **HD** 2005- 2013

Original Article

KHA-CARI guideline: Dialysis adequacy (haemodialysis): Dialysis membranes

PETER G KERR[1,4] and NIGEL D TOUSSAINT[2,3]

Nephrol Dial Transplant (2007) 22 [Suppl 2]: ii5–ii21
doi:10.1093/ndt/gfm022

NDT Nephrology Dialysis Transplantation

PD 2005 - **HD** 2007

EBPG guideline on dialysis strategies

Therapeutic Apheresis and Dialysis

HD 2015

Japanese Society for Dialysis Ther...
"Maintenance Hemodialysis: Her...

Therapeutic Apheresis and Dialysis

PD 2009

2009 Japanese Society for Dialysis Therapy Guidelines for Peritoneal Dialysis

KDIGO

National Kidney Foundation

2006 Updates Clinical Practice Guidelines and Recommendations

PD 2006

- Hemodialysis Adequacy
- Peritoneal Dialysis Adequacy
- Vascular Access

National Kidney Foundation® | KDOQI® Kidney Disease Outcomes Quality Initiative

HD 2015

KDOQI CLINICAL PRACTICE GUIDELINE FOR HEMODIALYSIS ADEQUACY: 2015 UPDATE

International Society for Peritoneal Dialysis ISPD

ISPD GUIDELINES/RECOMMENDATIONS

PD 2011

CLINICAL PRACTICE GUIDELINES AND RECOMMENDATIONS ON PERITONEAL DIALYSIS ADEQUACY 2011

SUMMARY OF CLINICAL PRACTICE GUIDELINES

THE RENAL ASSOCIATION founded 1950

HD 2009 **PD** 2017

Peritoneal Dialysis International, Vol. 31, pp. 218–239
doi:10.3747/pdi.2011.00026

PD 2011

CANADIAN SOCIETY OF NEPHROLOGY GUIDELINES/RECOMMENDATIONS

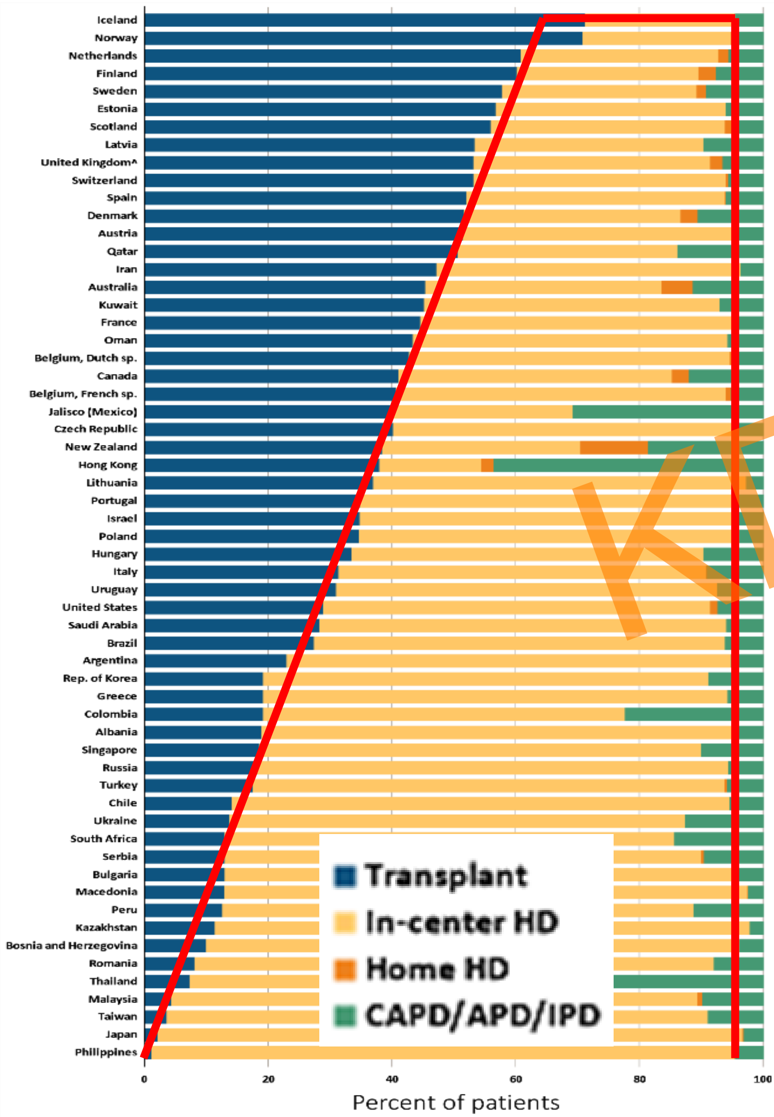
CLINICAL PRACTICE GUIDELINES AND RECOMMENDATIONS ON PERITONEAL DIALYSIS ADEQUACY 2011

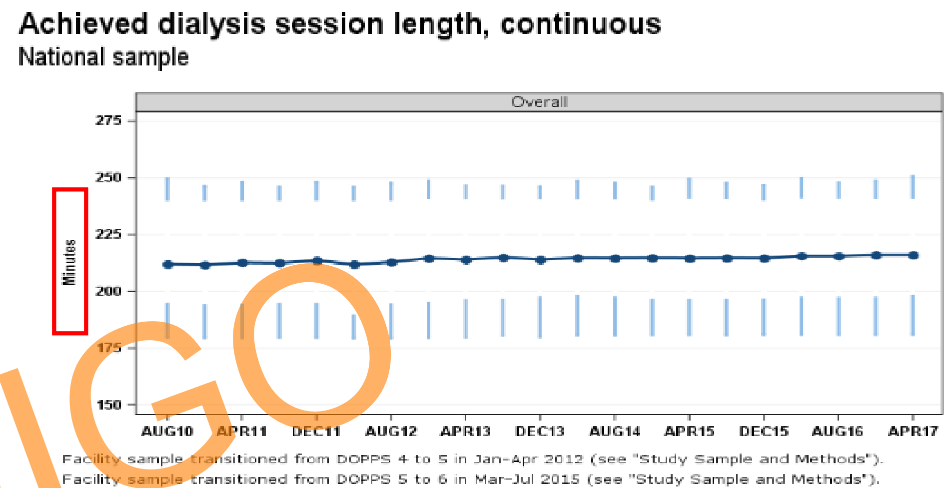
Dialysis Adequacy

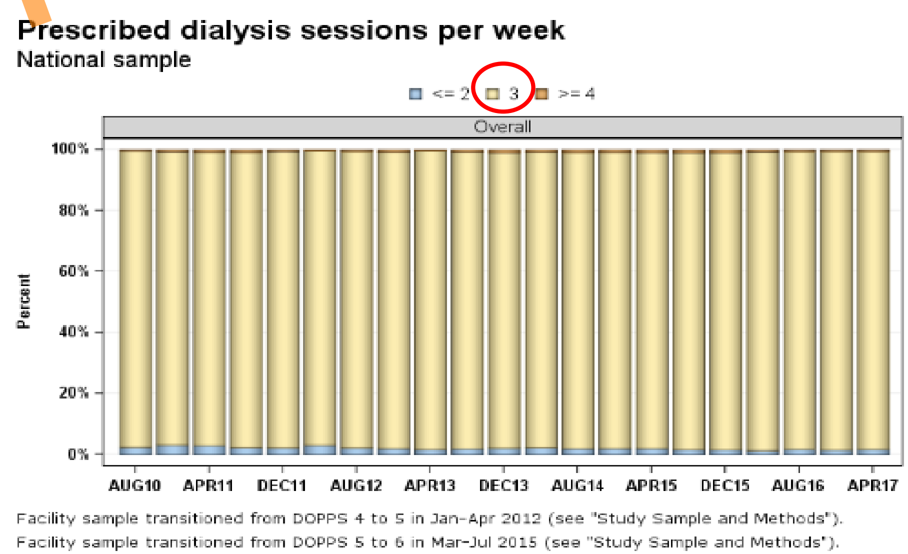
Where are we

Now ?

Prescription - **Actual Situation**



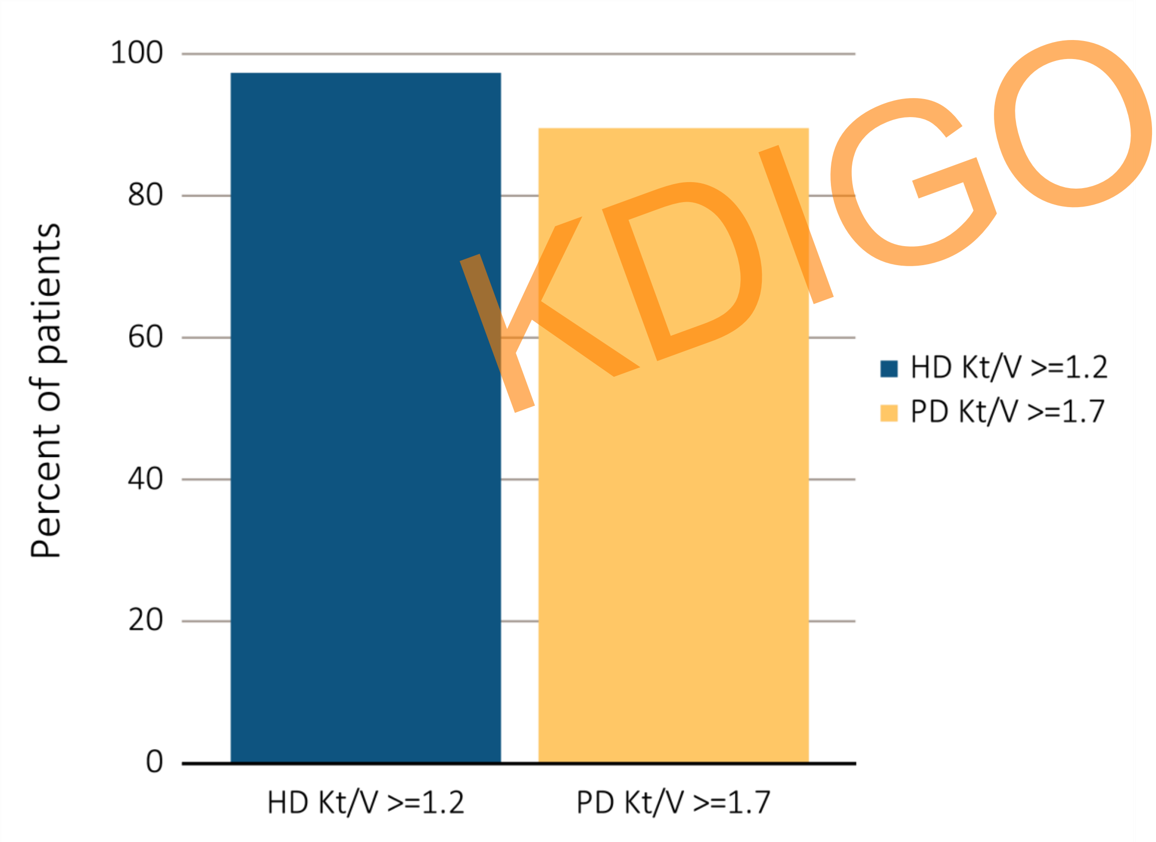




USRDS Annual Data Report 2017
US-DOPPS Practice Monitor, August 2017; http://www.dopps.org

Adequacy - **Actual Situation**

Percentage of prevalent hemodialysis and peritoneal dialysis patients meeting clinical care guidelines for **dialysis adequacy, by modality**



> 80% achived adequacy target

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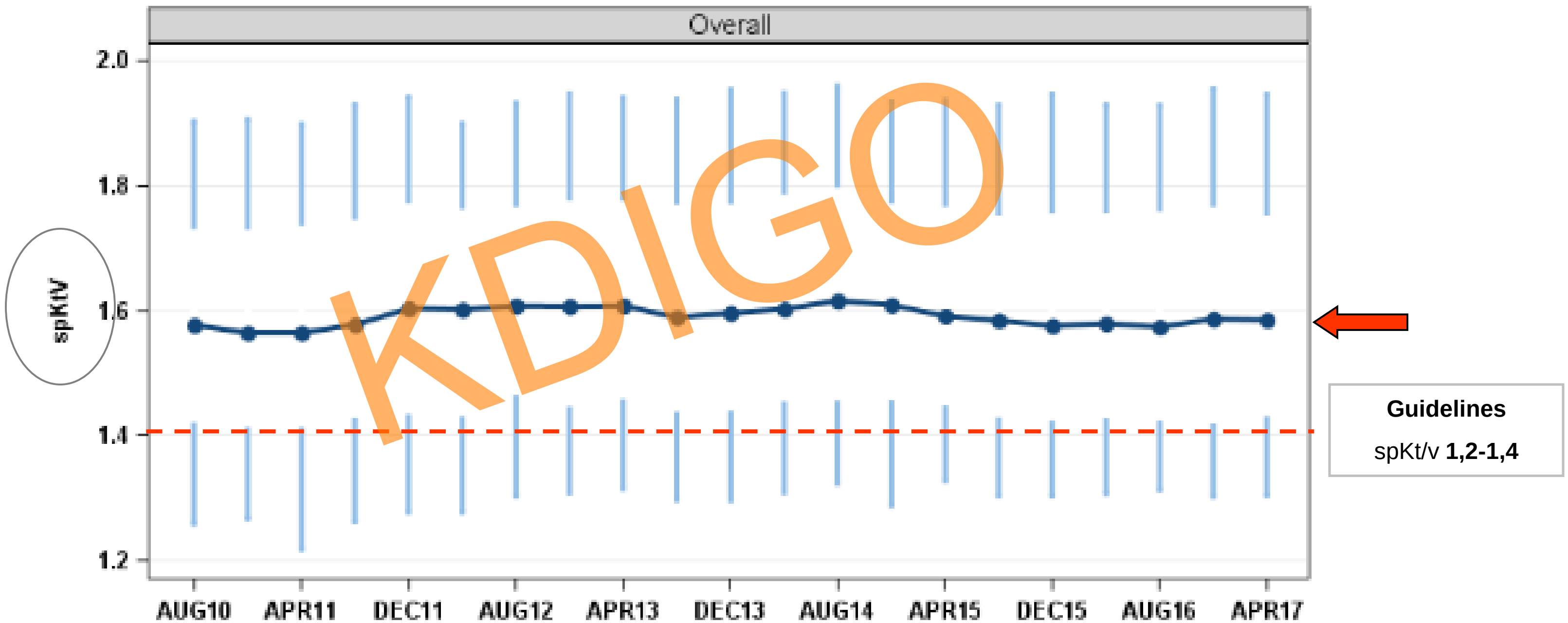
USRDS Annual Data Report 2017

Adequacy - **Actual Situation**

Single-pool Kt/V, continuous
National sample



Among patients with >365 days on dialysis

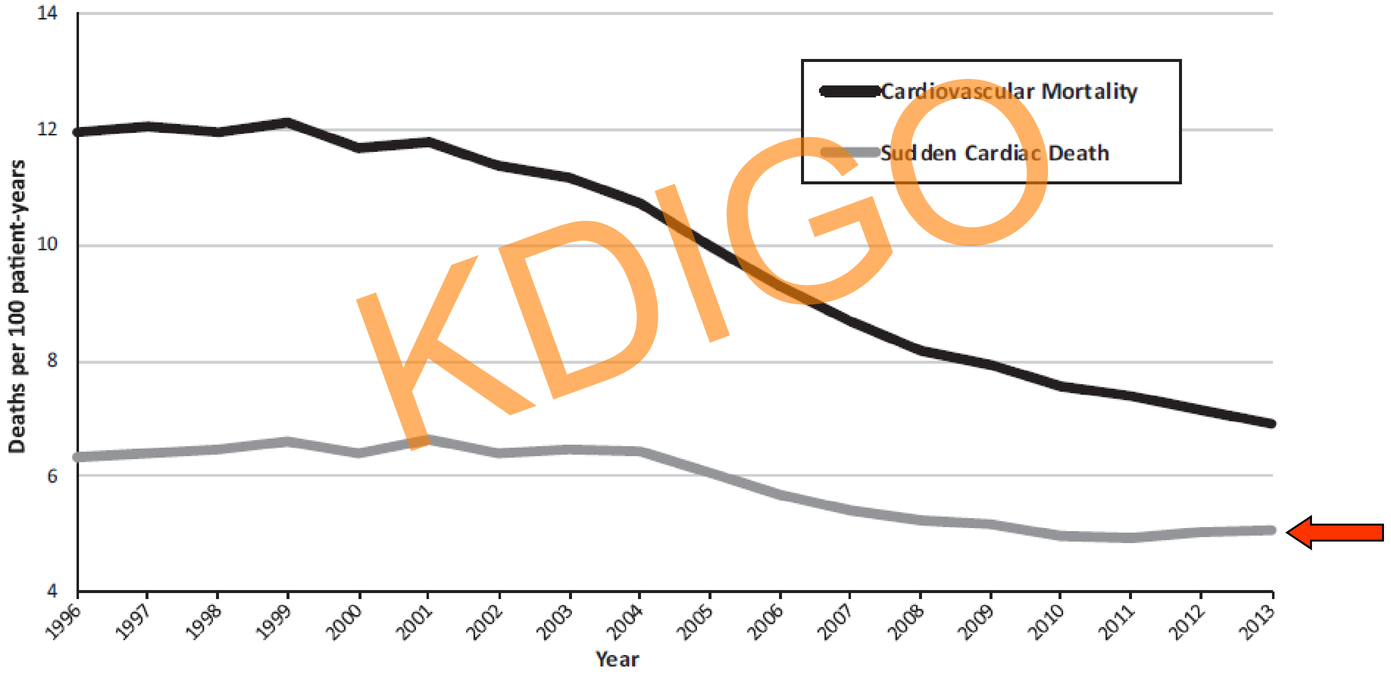
Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods").

Facility sample transitioned from DOPPS 5 to 6 in Mar-Jul 2015 (see "Study Sample and Methods").

US-DOPPS Practice Monitor, August 2017; http://www.dopps.org

Sudden Cardiac Death - **Actual Situation**

From the 2016 Peer Kidney Care Initiative Report

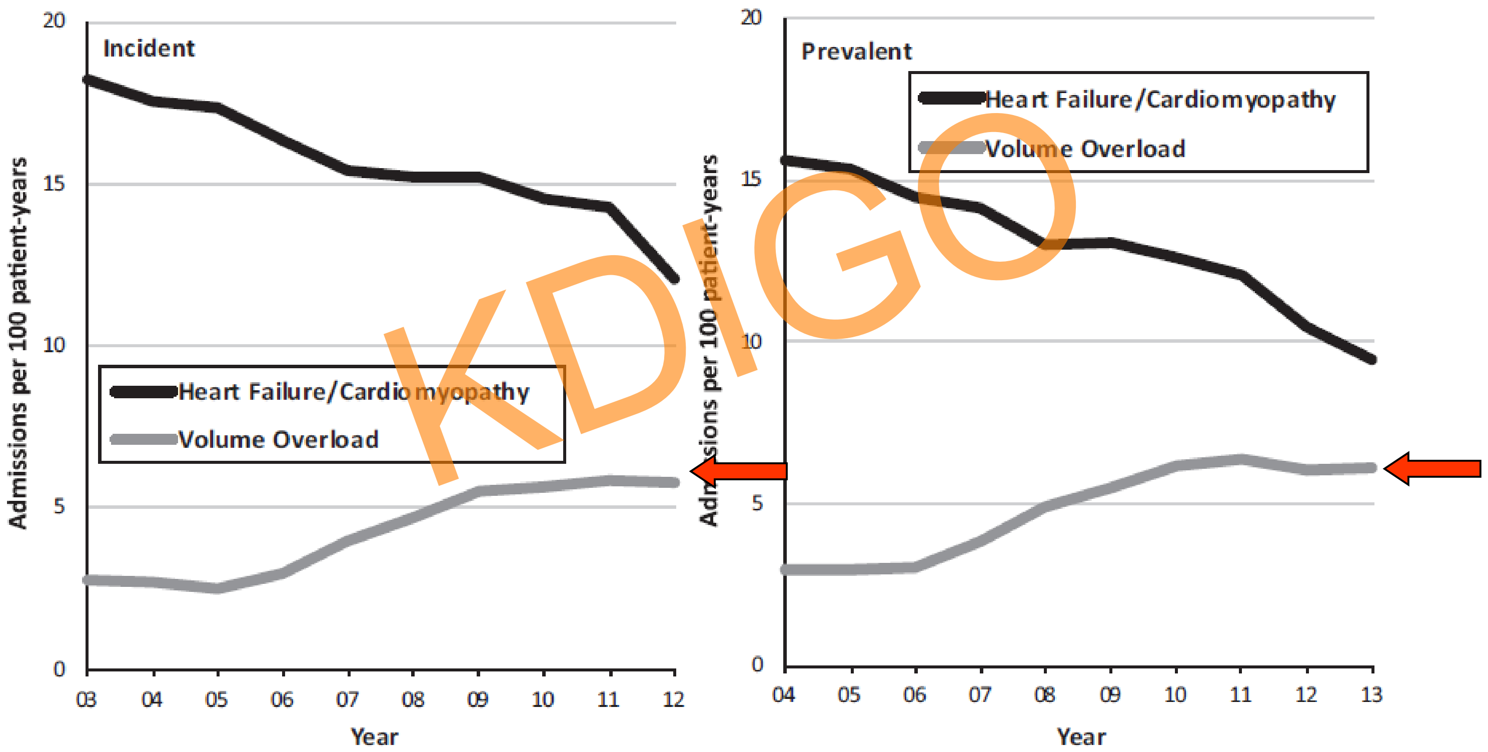


Annual rates of all-cause cardiovascular mortality and sudden cardiac death in maintenance dialysis patients.

Wetmore J et al. Am J Kidney Dis. 2018

Volume Overload - **Actual Situation**

From the 2016 Peer Kidney Care Initiative Report

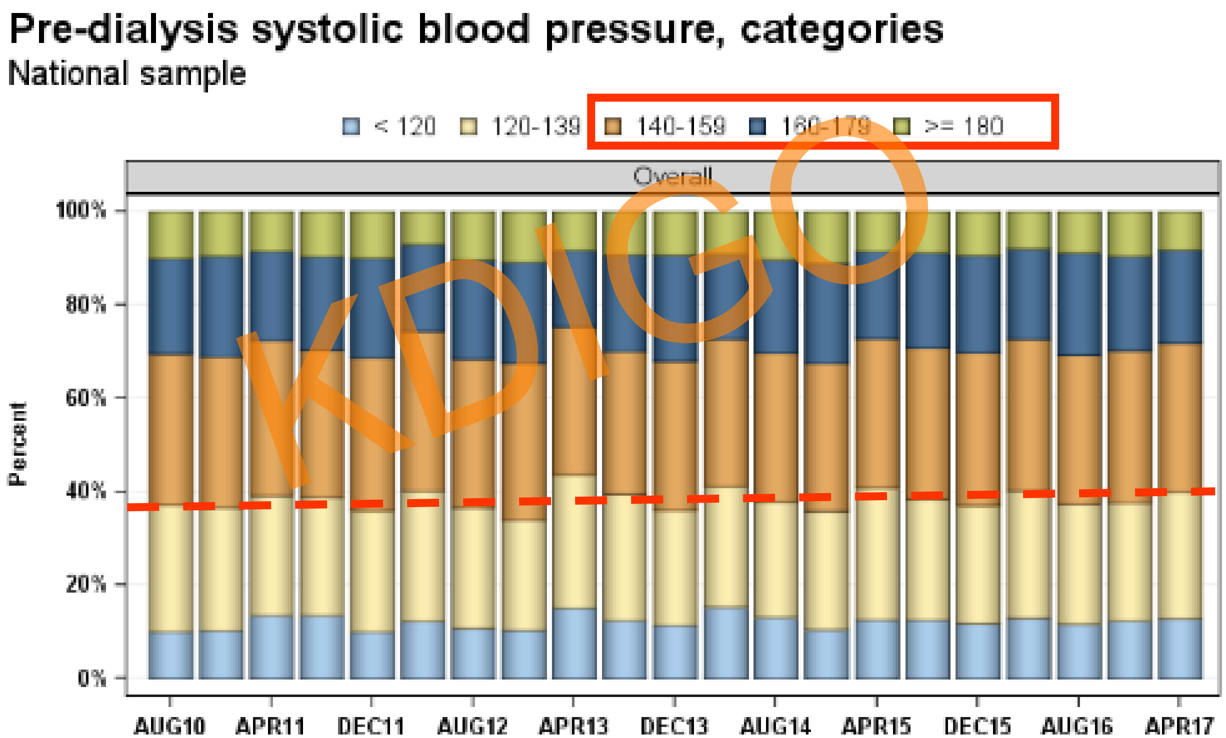


Annual rates of hospitalizations with primary discharge diagnosis of heart failure/cardiomyopathy or fluid overload for incident and prevalent maintenance dialysis patients.

Wetmore J et al. Am J Kidney Dis. 2018

Blood Pressure Control - **Actual Situation**

Pre-dialysis systolic blood pressure, remained relatively unchanged from 2010 to 2017

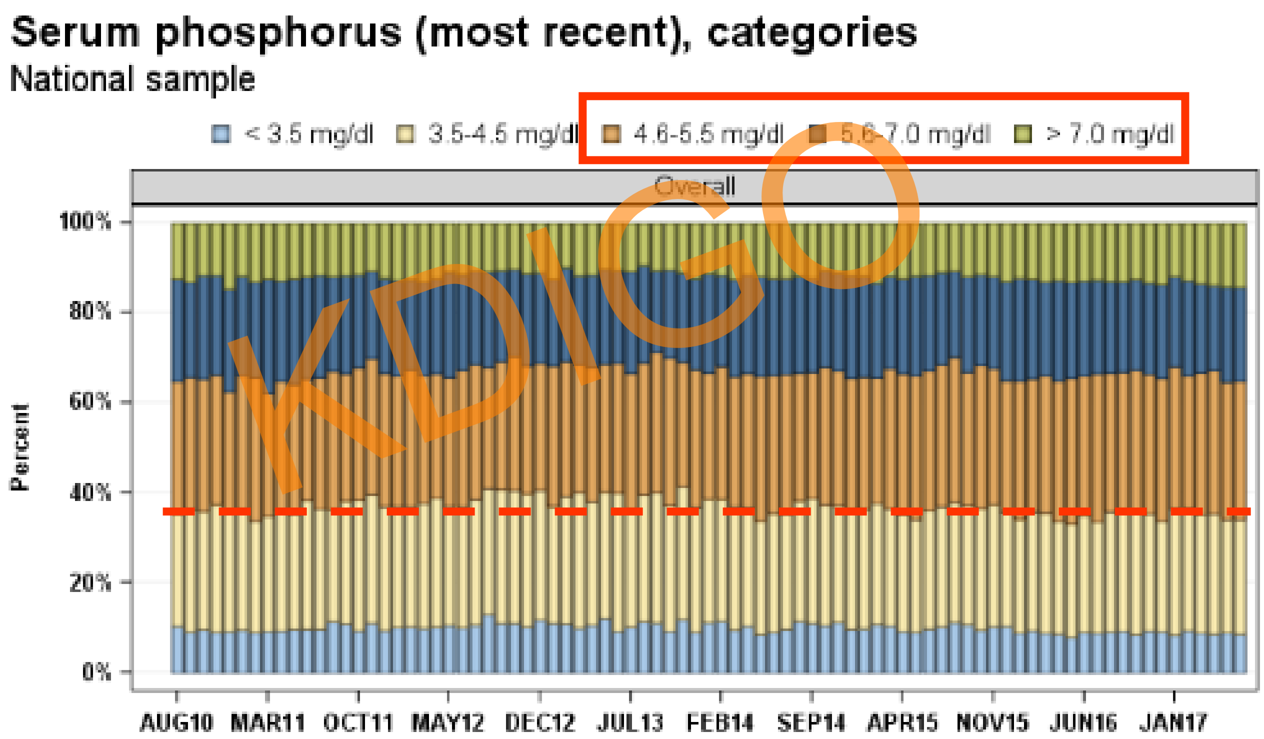


Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods").
Facility sample transitioned from DOPPS 5 to 6 in Mar-Jul 2015 (see "Study Sample and Methods").

US-DOPPS Practice Monitor, August 2017; http://www.dopps.org

Serum Phosphate - **Actual Situation**

Serum phosphate levels remained relatively unchanged from 2010 to 2017



Most recent (single) monthly value

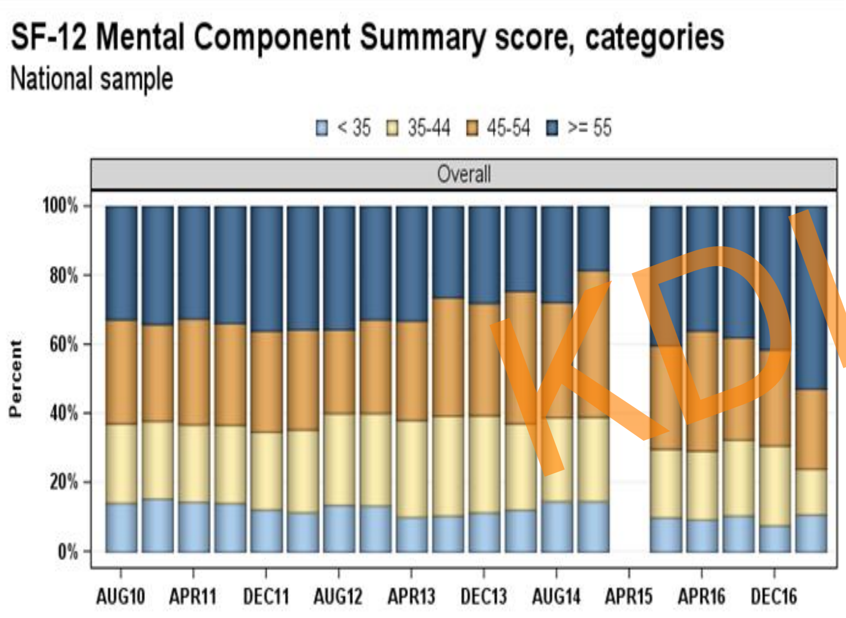
Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods").

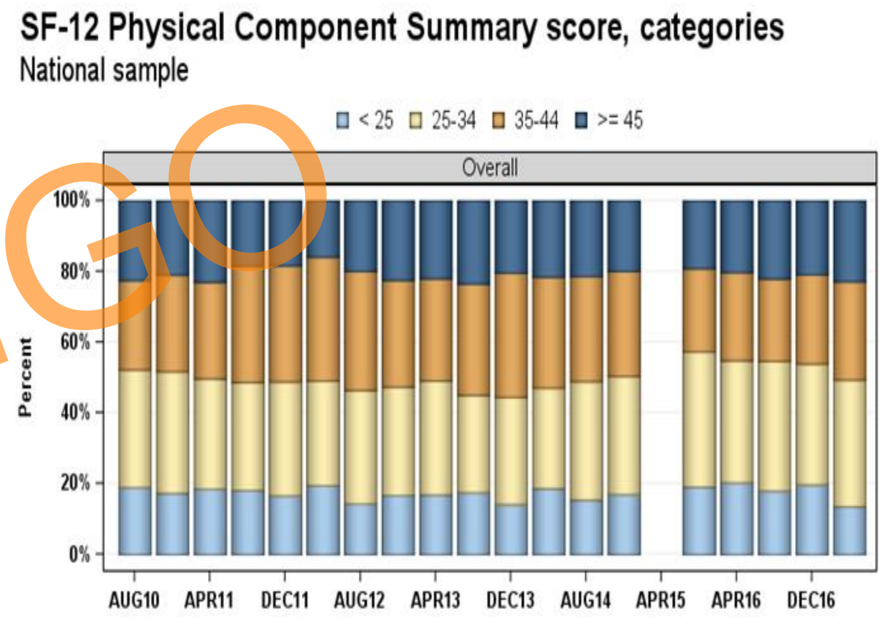
Facility sample transitioned from DOPPS 5 to 6 in Mar-Jul 2015 (see "Study Sample and Methods").

US-DOPPS Practice Monitor, August 2017; http://www.dopps.org

Health-related Quality of life – **Actual Situation**

No significant improvements in Mental and Physical Component of HRQL.





All DOPPS participants are asked to complete a questionnaire once a year. Participants who complete the questionnaire tend to be somewhat younger and healthier compared to non-respondents. Therefore results may not be representative of the US hemodialysis population overall.

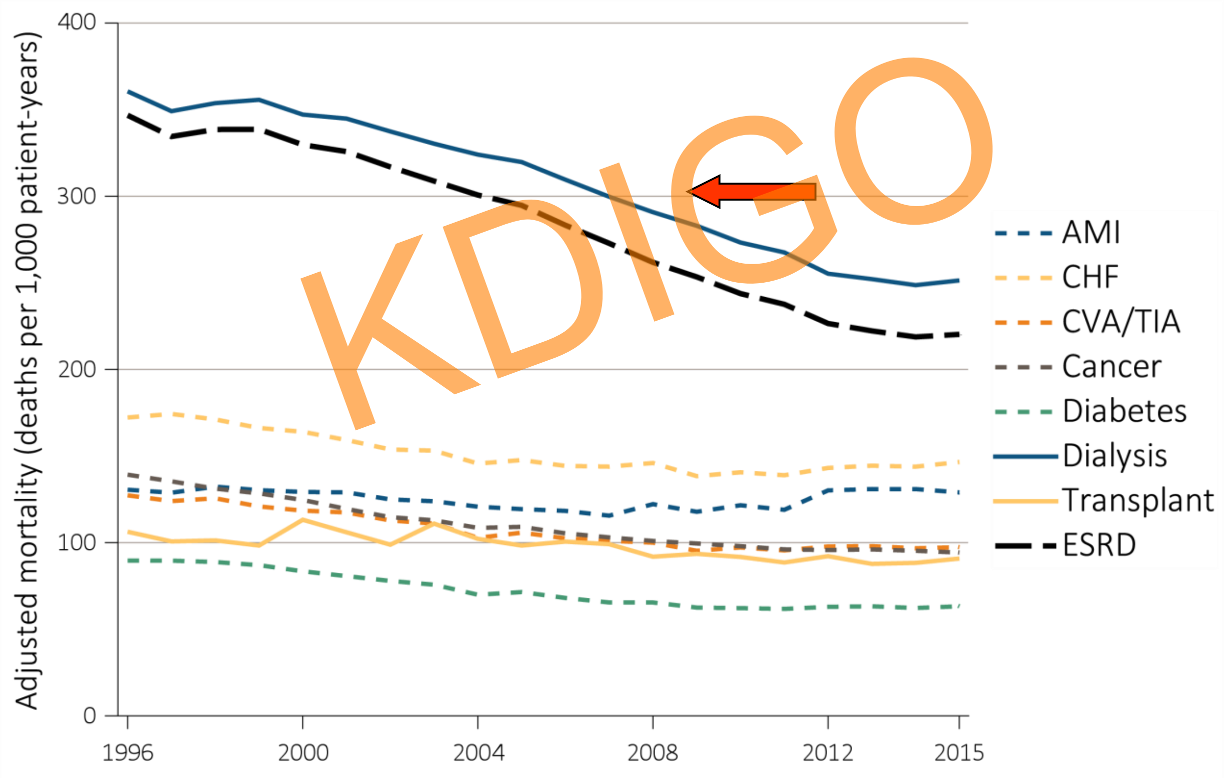
Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods").

Facility sample transitioned from DOPPS 5 to 6 in Mar-Jul 2015 (see "Study Sample and Methods").

US-DOPPS Practice Monitor, August 2017; http://www.dopps.org

Mortality – **Actual Situation**

Adjusted mortality (deaths per 1,000 patient-years) by calendar year, treatment modality, and comorbidity among ESRD patients and comorbidity-specific Medicare populations aged 65 & older, 1996-2015



USRDS Annual Data Report 2017

Is Kt/V_{urea} an **adequate** marker of **dialysis adequacy**?

Evidence

Kt/Vurea alone **is not enough!!**

A **broader concept** of adequacy **is required!!**

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http://www.kidney-international.org

2015

Once upon a time in dialysis: the last days of Kt/V?

Raymond Vanholder[1], Griet Glorieux[1] and Sunny Eloot[1]

[1]Nephrology Section, Department of Internal Medicine, Ghent University Hospital, Ghent, Belgium

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Hemodialysis International 2015; ••:••–••

Personal viewpoint: Limiting maximum ultrafiltration rate as a potential new measure of dialysis adequacy

John W M AGAR

Department of Renal Medicine Barwon Health, University Hospital, Geelong, Victoria, Australia

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Does the Adequacy Parameter Kt/V_{urea} Reflect Uremic Toxin Concentrations in Hemodialysis Patients?

Sunny Eloot*, Wim Van Biesen, Griet Glorieux, Nathalie Neirynck, Annemieke Dhondt, Raymond Vanholder

Nephrology Section, Department of Internal Medicine, Ghent University Hospital, Gent, Belgium

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Clinical Kidney Journal

Clinical Kidney Journal Advance Access published June 1, 2015

ckj

OXFORD

ERA EDTA Leading European Nephrology

Clinical Kidney Journal, 2015, 1–10

doi: 10.1093/ckj/sfv034

CKJ Review

CKJ REVIEW

Uraemic toxins and new methods to control their accumulation: game changers for the concept of dialysis adequacy

Griet Glorieux[1] and James Tattersall[2]

2016

Seminars in Dialysis

MAKING DIALYSIS ADEQUATE – ADDRESSING ITS LIMITATIONS

Effect of Treatment Duration and Frequency on Uremic Solute Kinetics, Clearances and Concentrations

John K. Leypoldt* and Björn K. I. Meijers†

*Renal Therapeutic Area and Medical Affairs, Baxter Healthcare Corporation, Deerfield, Illinois, and †Division of Nephrology, Department of Microbiology and Immunology, University Hospitals Leuven, Leuven, Belgium

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REVIEW

Clin J Am Soc Nephrol 2017

The Use of a Multidimensional Measure of Dialysis Adequacy—Moving beyond Small Solute Kinetics

Jeffrey Perl, Laura M. Dember, Joanne M. Bargman, Teri Browne, David M. Charytan, Jennifer E. Flythe, LaTonya J. Hickson, Adriana M. Hung, Michel Jadoul, Timmy Chang Lee, Klemens B. Meyer, Hamid Moradi, Tariq Shafi, Isaac Teitelbaum, Leslie P. Wong, and Christopher T. Chan, and on behalf of the American Society of Nephrology Dialysis Advisory Group

Evidence

Kt/Vurea alone
is not enough!!

A **broader concept** of adequacy **is required!!**

Seminars in Dialysis

2012

A Sad but Forgotten Truth: The Story of Slow-Moving Solutes in Fast Hemodialysis

Sunny Eloot, Wim Van Biesen, and Raymond Vanholder
Nephrology Section, Department of Internal Medicine, Ghent University Hospital, Gent, Belgium

PROGRESS IN DIALYSIS PRACTICE

Dialysis Dosing for Chronic Hemodialysis: Beyond *Kt/V*

John T. Daugirdas
Department of Medicine, University of Illinois, Chicago, Illinois

The International Journal of Artificial Organs / Vol. 27 / no. 6, 2004 / pp. 452-466

Review

2004

Short, thrice-weekly hemodialysis is inadequate regardless of small molecule clearance

Z.J. TWARDOWSKI

Division of Nephrology, Department of Medicine, University of Missouri, Columbia, Missouri - USA

Kt/V_{urea} should be abandoned as a measure of dialysis quality

Kidney International, Vol. 41 (1992), pp. 1286–1291

1992

Survival as an index of adequacy of dialysis

BERNARD CHARRA, EDOUARD CALEMARD, MARTIAL RUFFET, CHARLES CHAZOT, JEAN-CLAUDE TERRAT, THIERRY VANEL, and GUY LAURENT

Centre de rein artificiel, Tassin, France

Dialysis Therapy

SOLUTES CLEARANCE

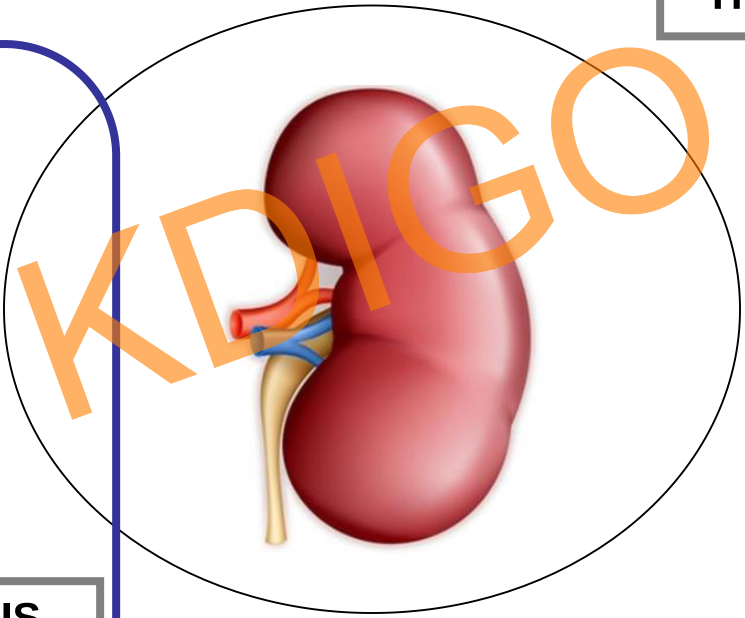
Kt/Vurea

Uremic Toxins

Electrolyte Regulation

Acid–base Balance

Calcium–phosphorus control



HORMONE PRODUCTION

Red blood cell mass regulation

Vitamin D regulation

Others

VOLUME HOMEOSTASIS

Fluid Overload

Blood pressure control

Major Unmet Clinical Needs

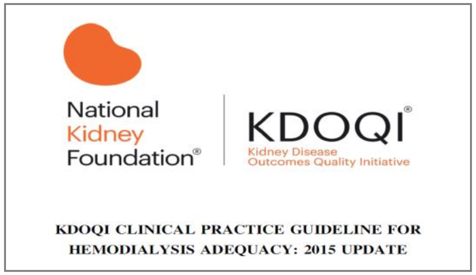
1. High risk of **cardiovascular morbidity and mortality**
   - Persistent hyperphosphatemia
   - Left ventricular hypertrophy and heart failure
   - Persistent hypertension
   - Limited tolerability of conventional hemodialysis treatment
   - Arrhythmias & Sudden Death

2. Diminished **quality of life**

More uremic toxins than urea

Persistent volume overload

Persistence Long Interdialytic Interval


National Kidney Foundation®
KDOQI®
Kidney Disease Outcomes Quality Initiative
KDOQI CLINICAL PRACTICE GUIDELINE FOR HEMODIALYSIS ADEQUACY: 2015 UPDATE

"It is important to distinguish ***adequacy of the dialysis*** *from* ***adequacy of patient*** *care".*[1]

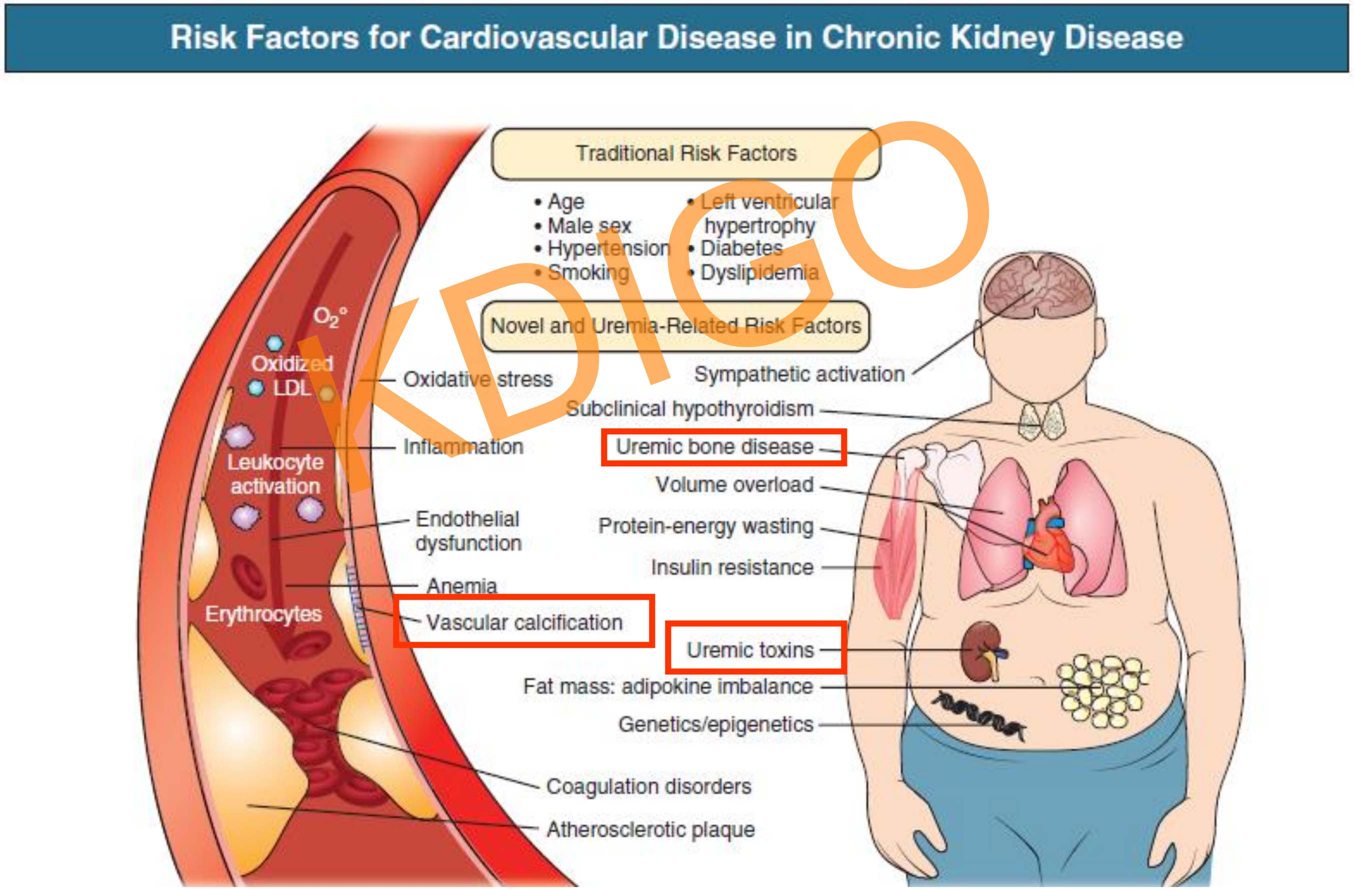
We **should focus** on the **patient**, and **focus on other dialysis parameters**, if we **want to increase** dialysis adequacy and **improve** our patients' **outcomes**

1. KDOQI. Am J Kidney Dis. 2015

Which **other parameters**
could be **important**
to **measure dialysis adequacy**
in order to **improve**
our patients' **outcomes**?

Cardiovascular Morbidity

The high incidence of **cardiovascular morbidity and mortality** in dialysis patients is **multifactorial**



Perl J et al. Clin J Am Soc Nephrol, 2017
Floege J et al. Comprehensive Clinical Nephrology, 2015

Uremic Toxins

The **uremic syndrome** is the consequence of the retention of **more molecules than urea** alone.

Retention solutes of **middle molecular** size, play an **important role** in the **pathogenesis** of the **uremic state** which contributes to the **high mortality** of dialysis patients

Organic Uremic Solutes

Free Water-Soluble Low-Molecular-Weight Solutes	MW
Guanidines	
ADMA	202
Argininic acid	175
Creatinine	113
Guanidine	59
Methylguanidine	73
Peptide	
β-Lipotropin	461
Polyols	
Erythritol	122
Myoinositol	180
Sorbitol	182
Threitol	122
Purines	
Cytidine	234
Hypoxanthine	136
Uracil	112
Uric acid	168
Xanthine	
Pyrimidines	
Orotic acid	
Thymine	
Uridine	
Ribonucleosides	
1-Methyladenosine	
Pseudouridine	
Xanthosine	
Others	
Malondialdehyde	
Oxalate	
Urea	

Protein-Bound Solutes	MW
AGEs	
3-Deoxyglucosone	162
Fructoselysine	308
Glyoxal	58
Pentosidine	342
Hippurate	
Hippuric acid	179
Indoles	
Indoxyl sulfate	251
Melatonin	126
Quinolinic acid	167
Phenols	
Hydroquinone	110
p-Cresol	108
Phenol	94
Polyamines	
Putrescine	88
Spermidine	145

Middle Molecules	MW
Cytokines	
Interleukin-1β	32,000
Interleukin-6	24,500
Tumor necrosis factor α	26,000
Peptides	
Adrenomedullin	5729
ANP	3080
β_2-Microglobulin	11,818
β-Endorphin	3465
Cholecystokinin	3866
Cystatin C	13,300
Delta sleep-inducing peptide	848
Hyaluronic acid	25,000
Leptin	16,000
Neuropeptide Y	4572
PTH	9225
Retinol-binding protein	21,200
Other	
[illegible]nt factor D	23,750

- **High-flux** membranes
- **Convection therapies**
- **Increasing** dialysis duration

Leypoldt JK et al. Seminars in Dialysis 2016
Ronco C. Expanded Hemodialysis. Basel, Karger, 2017
Floege J et al. Comprehensive Clinical Nephrology, 2015

Uremic Toxins

The **uremic syndrome** is the consequence of the retention of **more molecules than urea** alone.

Retention solutes of **middle molecular** size, play an **important role** in the **pathogenesis** of the **uremic state** which contributes to the **high mortality** of dialysis patients

Organic Uremic Solutes

Free Water-Soluble Low-Molecular-Weight Solutes	MW	Protein-Bound Solutes	MW	Middle Molecules	MW
Guanidines				**Cytokines**	
ADMA				Interleukin-1β	32,000
Argininic acid				Interleukin-6	24,500
Creatinine				Tumor necrosis factor α	26,000
Guanidine				**Peptides**	
Methylguanidine				Adrenomedullin	5729
Peptide				ANP	3080
β-Lipotropin				β_2-Microglobulin	11,818
Polyols				β-Endorphin	3465
Erythritol				Cholecystokinin	3866
Myoinositol				Cystatin C	13,300
Sorbitol				Delta sleep-inducing peptide	848
Threitol				Hyaluronic acid	25,000
Purines				Leptin	16,000
Cytidine				Neuropeptide Y	4572
Hypoxanthine				PTH	9225
Uracil				Retinol-binding protein	21,200
Uric acid				**Other**	
Xanthine				Complement factor D	23,750
Pyrimidines					
Orotic acid					
Thymine					
Uridine					
Ribonucleosides					
1-Methyladenosine					
Pseudouridine					
Xanthosine					
Others					
Malondialdehyde					
Oxalate					
Urea					

Kt/Vurea as adequacy target

↓

We are not measuring other Uremic Toxins

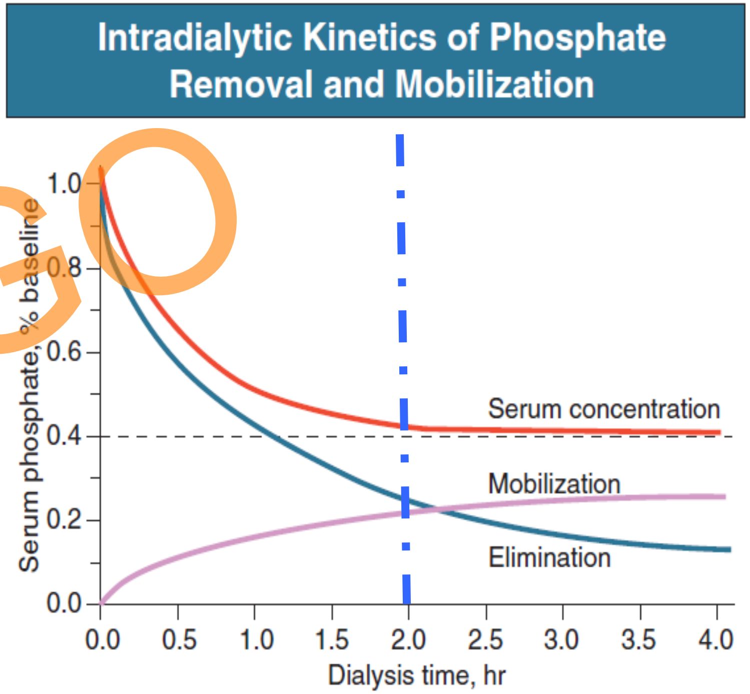
Leypoldt JK et al. Seminars in Dialysis 2016
Ronco C. Expanded Hemodialysis. Basel, Karger, 2017
Floege J et al. Comprehensive Clinical Nephrology, 2015

Phosphate Removal

The **kinetics** of intradialytic **phosphate** removal, **differ significantly** from classic **urea kinetics.**

- Despite **low molecular weight,** its elimination is **similar** to a **middle molecule**:
  - **Large distribution space**, and its **difficulty moving** from the **intracellular space**

- At the **beginning** of dialysis session there is a **decrease** in serum levels; but then because of **mobilization** of **phosphate** from the **intracelullar space, serum** phosphate reaches a **constant level**



Phosphate **needs more time** than urea to **decrease in serum levels** and **its removal** is **directly** related to **dialysis duration** and **frequency**

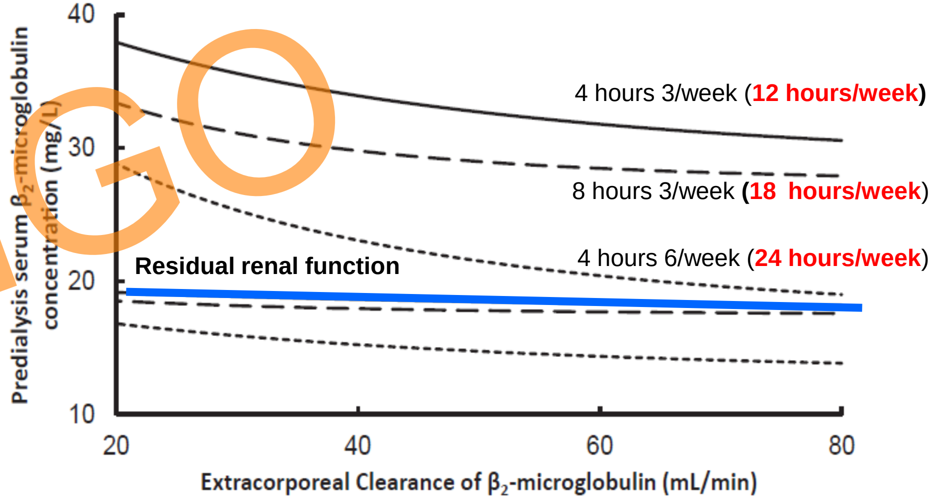
Kuhlmann M. Blood Purif 2010.
Daugirdas J.T, Seminars in Dialysis, 2015
Gutzwiller, JP et al.. Nephrol Dial Transplant 2017
Floege J et al. Comprehensive Clinical Nephrology, 2015

B2- microglobulin Removal

The **kinetics** of intradialytic **Beta-2-microgobulin** removal **differ significantly** from **urea kinetics,** and is the **general marker** for **middle molecules**

- Middle molecules **removal** is limited in **short sessions,** because of their **slower inter-compartmental equilibration rates**

- **Residual renal function** is the most important factor that **increases its elimination**

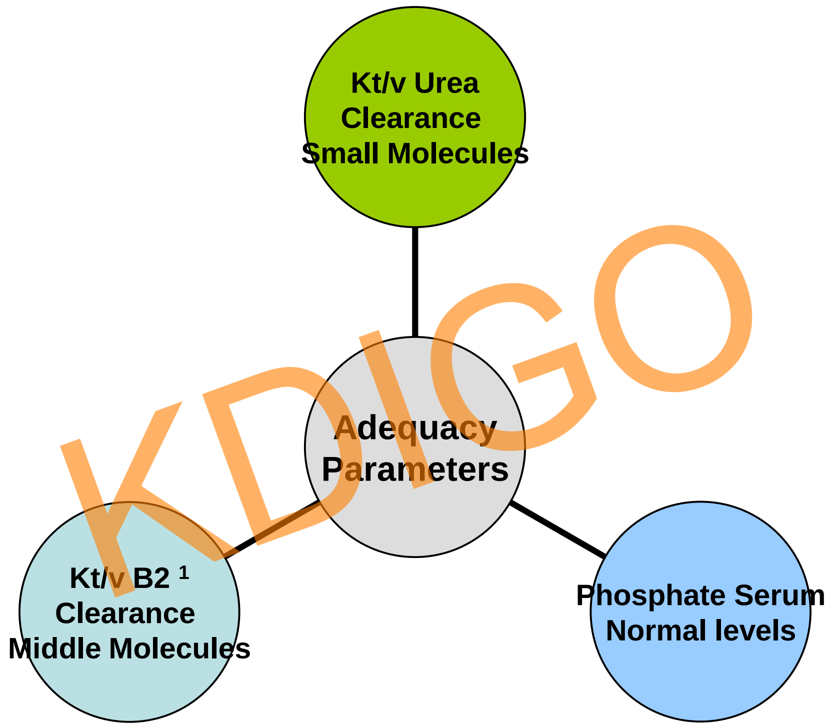


In **anuric** patientes:

The **dialyzer clearance** and the **weekly treatment duration** are the most important factors related **to its removal**

Leypoldt JK et al. Seminars in Dialysis 2016
Roumelioti et al. Nephrol Dial Transplant 2017
Tangvoraphonkchai K, et al. Seminars in Dialysis 2017

Dialysis Adequacy

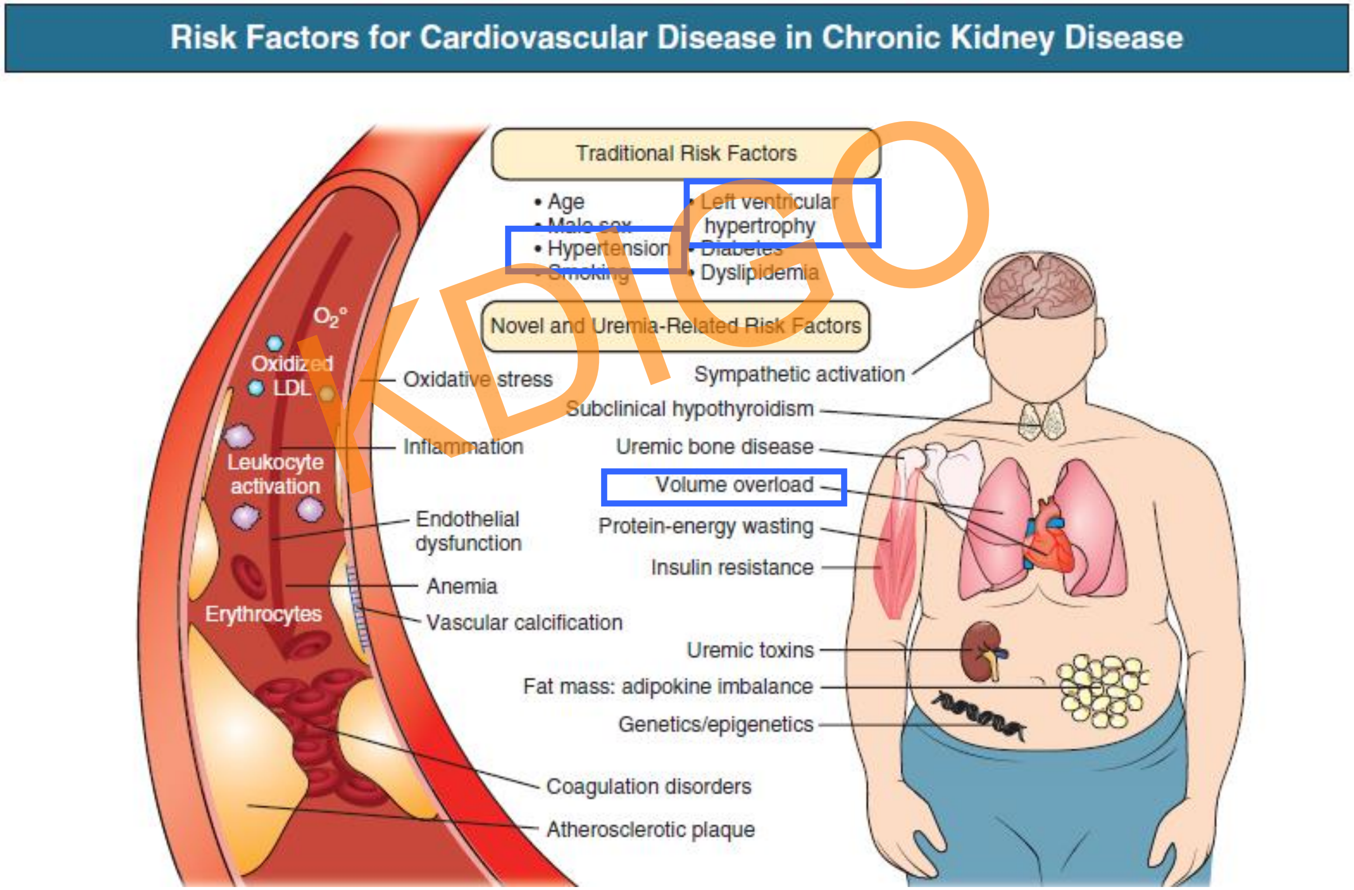


Surrogate parameters of middle molecules clearance

1. Casino F et al. Nephrology Dialysis Transplantation, 2015

Cardiovascular Morbidity

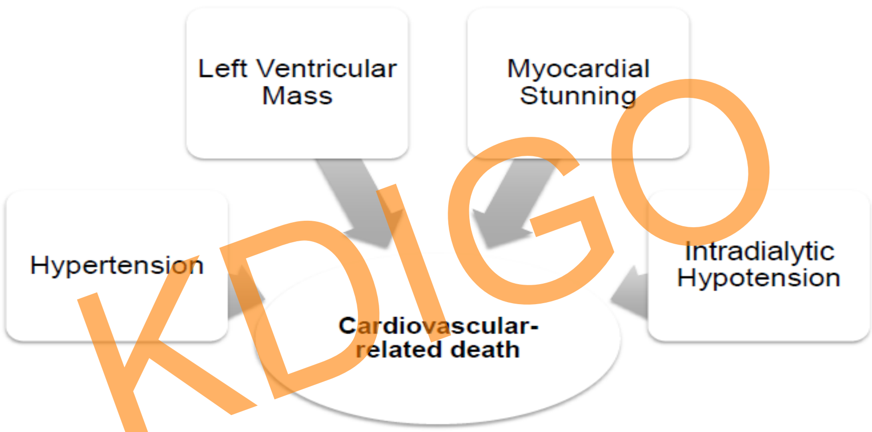
The high incidence of **cardiovascular morbidity and mortality** in dialysis patients is **multifactorial**



Perl J et al. Clin J Am Soc Nephrol, 2017
Floege J et al. Comprehensive Clinical Nephrology, 2015

Volume Overload

Fluid overload is a **major cause** of **morbidity** and **mortality** in ESRD population.



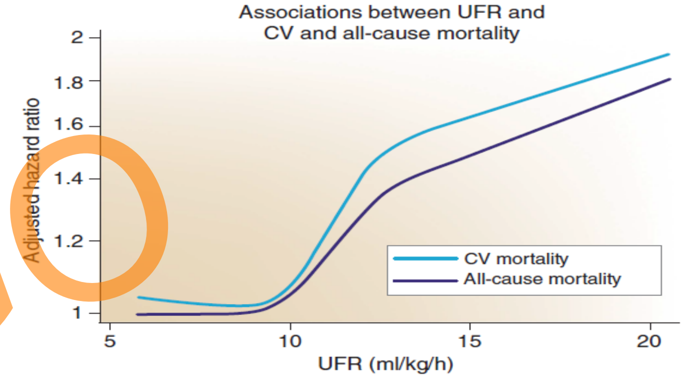
Volume has been **largely ignored,** because **solute clearance** has been the **major issue** in **dialysis adequacy goals**

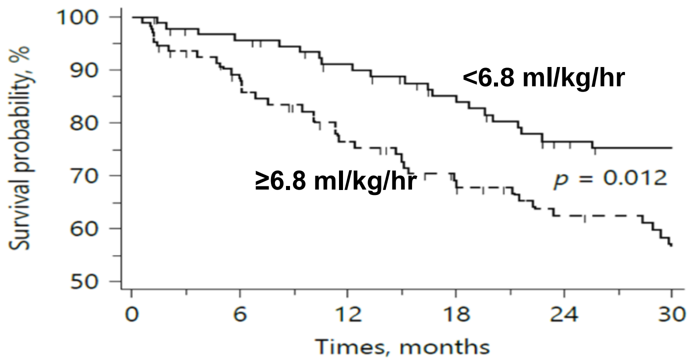
John W M AGAR. Hemodialysis International 2015
Hakim RM, Saha S:. Kidney Int 2014
Zoccali C et al. J Am Soc Nephrol, 2017

Intradialytic Hypotension

How do we **remove all that volume?**

- **Inadequate** response to **decreased intravascular** volume, when **ultrafiltration rate** exceeds **plasma refilling rate**
- There is an **association** between **rapid ultrafiltration** and **increased mortality**
- The **safety and tolerability** of the dialysis procedure **is related to** the **ultrafiltration rate**, which is determined by the **interdialytic weight gain** and **length** of each session



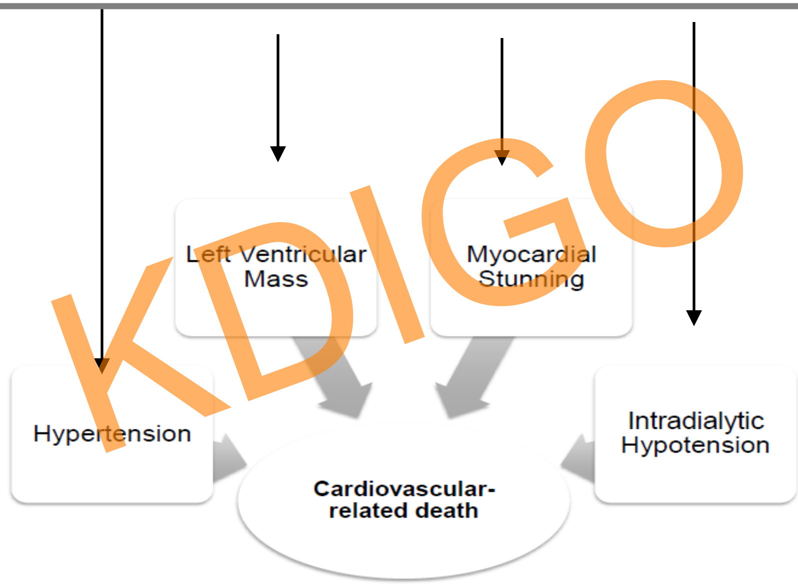


Dialysis **duration** and **ultrafiltration rate** are **tightly related**

Davenport A, Hemodialysis International 2011
Hakim RM, Saha S:. Kidney Int 2014
Chazot et al; Blood Purification 2017

Volume Overload

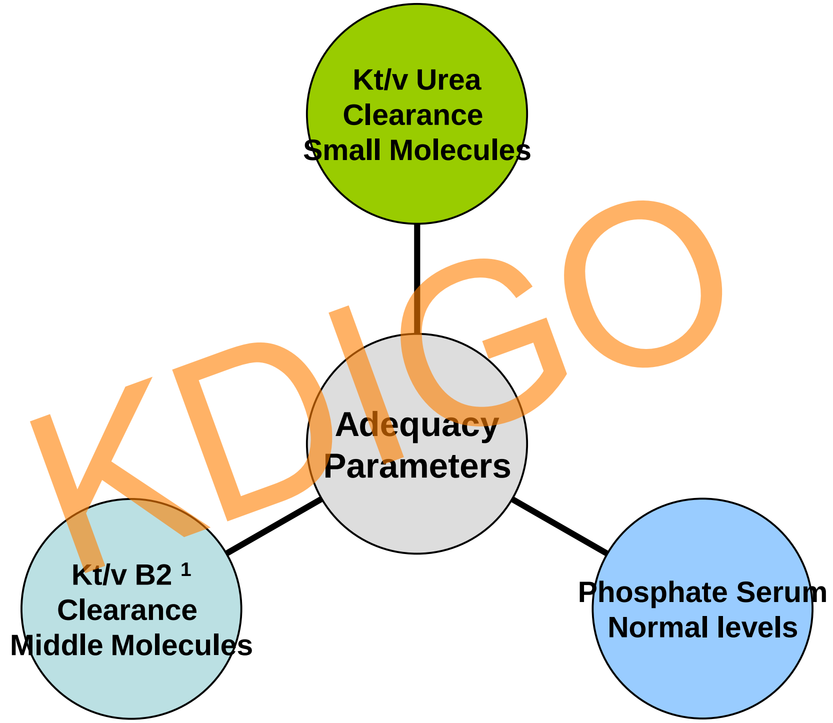
"**Volume First Initiative**" materializes the next best chance to **improve patients' outcomes**



Extending **treatment time** or **frequency** is an effective way **to address volume control** and **tolerance** of dialysis sessions**,** with **less** dialysis-related **morbidity and mortality**

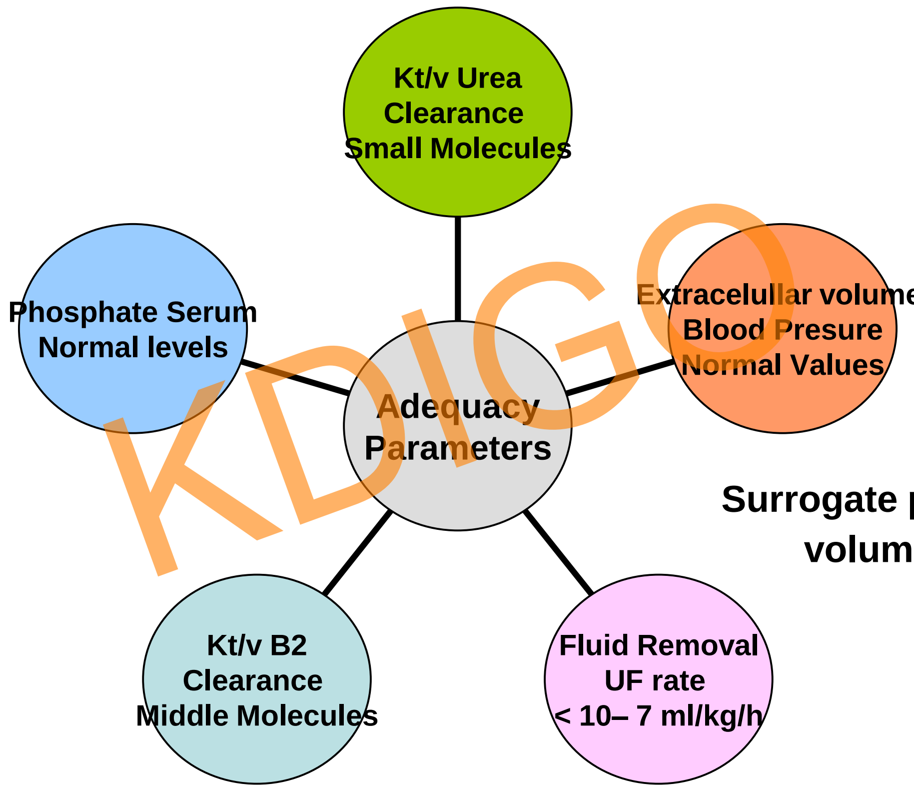
Weiner D, et al. Am J Kidney Dis, 2014
John W M AGAR. Hemodialysis International 2015

Dialysis Adequacy



Surrogate parameters of middle molecules clearance

Dialysis Adequacy

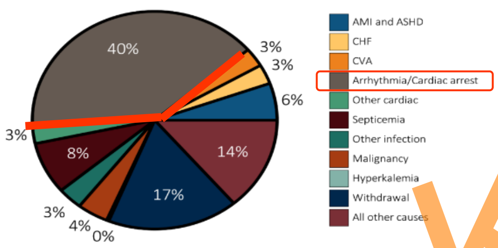


Surrogate parameters of volume control

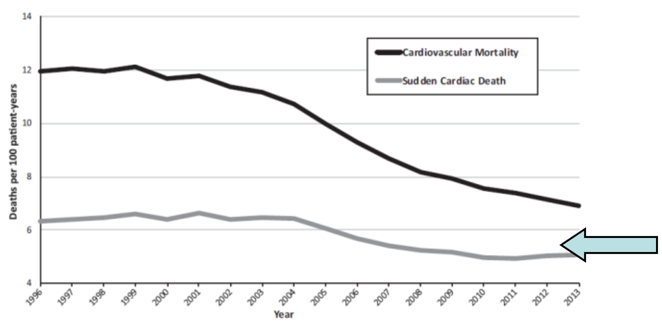
Sudden Cardiac Death

Leading cause of death in patients on **maintenance** dialysis, **mainly** related to **volume shifts and electrolyte** disorders.

Unadjusted percentages of deaths in 2014 by cause, excludes missing/unknown causes of death data among **dialysis patients.** [1]

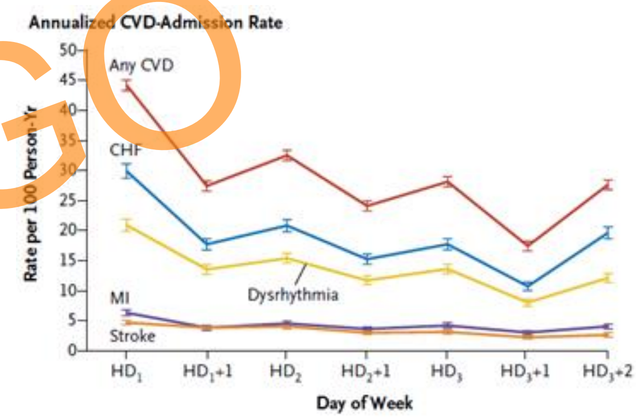


From the 2016 Peer Kidney Care Initiative Report [2]



Annual rates of all-cause cardiovascular mortality and sudden cardiac death in maintenance dialysis patients.

Long Interdialytic interval is an important **risk factor** for sudden Cardiac Death



Has not been **addressed with Conventional HD prescription**

1. USRDS Annual Data Report 2017
2. Wetmore J et al. Am J Kidney Dis. 2018
3. Basile C et al. J Nephrol 2017
4. Foley RN et al. N Engl J Med 2011

Sudden Cardiac Death

Modifiable risk factors for Sudden Cardiac Death in **dialysis patients,** related to **dialysis procedure**

Summary of Procedures and Techniques to Reduce Risk of Sudden Cardiac Death in the Hemodialysis Population

	Recommendations	References
1	Dietary counseling for potassium and fluid gain	
2	Individualize and adjust potassium bath at least monthly for each patient; consider point-of-care devices to measure potassium on a more regular basis	Bleyer et al[5]
3	Do not use dialysate potassium concentration < 2 mEq/L, particularly if predialysis potassium < 5 mEq/L; if patients present with high serum potassium level, consider extending the dialysis time, but do not lower dialysate potassium concentration to <2 mEq/L	Karnik et al,[15] Pun et al,[14] Kovesdy et al,[13] Jadoul et al[12]
4	Consider the use of dialysate potassium profiling (ie, start with dialysate concentration of 4 mEq/L and gradually reduce it during the treatment to 2 mEq/L) when predialysis potassium level is ≥ 6.5 mEq/L	Redaelli et al[23]
5	Adjust dialysate bicarbonate concentration (to achieve a target predialysis bicarbonate of 20-22 mEq/L) and reduce the risk of severe intradialytic alkalosis	Heguilen et al[22]
6	Reduce the risk of high ultrafiltration rate (>10 mL/kg/h) by sustaining dialysis time > 4 h	Flythe et al,[32] McIntyre et al,[30] Burton et al[31]
7	Measure magnesium monthly and supplement magnesium if needed	Sakaguchi et al[28]
8	Do not use dialysate calcium concentration < 2.25 mEq/L (and preferably maintain at 2.5 mEq/L), particularly in combination with a low potassium bath in patients at high risk of arrhythmias	Genovesi et al,[10] Pun et al[29]
9	Avoid the use of digoxin for heart failure or control of atrial fibrillation in hemodialysis patients, and if unavoidable, consider using a higher potassium bath	Chan[33]
10	Be aware of medications that prolong QTc interval, which may be prolonged further by rapid shift in potassium, calcium, and magnesium concentrations	Data from the general population[34-36]

Hung A et al. Am J Kidney Dis. 2015

Sudden Cardiac Death

Modifiable risk factors for Sudden Cardiac Death in **dialysis patients,** related to **dialysis procedure**

Summary of Procedures and Techniques to Reduce Risk of Sudden Cardiac Death in the Hemodialysis Population

s

1 Dietary counseli
2 Individualize and
point-of-care c
3 Do not use dialy l,[14]
potassium < 5 oul et al[12]
consider exter
concentration
4 Consider the use
of 4 mEq/L an
predialysis pot
5 Adjust dialysate
of 20-22 mEq/
6 Reduce the risk et al,[30]
7 Measure magne
8 Do not use dialy et al[29]
at 2.5 mEq/L),
high risk of ar
9 Avoid the use of
patients, and i
10 Be aware of medications that prolong QTc interval, which may be prolonged further Data from the general population[34-36]
by rapid shift in potassium, calcium, and magnesium concentrations

Avoid rapid electrolyte and **volume shifts** during **dialysis sessions**

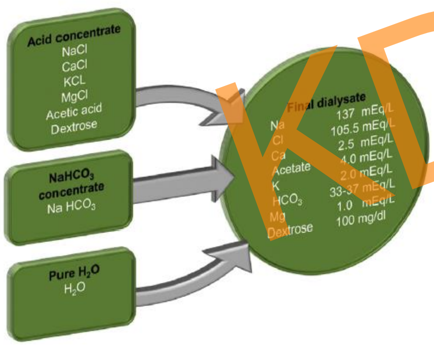
1. **Adjust** dialysate composition
2. **Adjust** ultrafiltration rate

Hung A et al. Am J Kidney Dis. 2015

Dialysate Composition

Dialysate composition is a **critical aspect** of the **dialysis prescription,** if we want to **avoid rapid electrolyte shifts** [1]

Often, the concentrations of **key components** may be determined **by default,** based on **dialysate manufacturer specifications** or hemodialysis **facility practices**. [2]



Composition of Dialysates for Bicarbonate Dialysis

	Concentration	
Component	**Range**	**Typical**
Electrolytes (mmol/l)		
Sodium	135-145	140
Potassium	0-4.0	2.0
Calcium	0-2.0	1.25
Magnesium	0.5-1.0	0.75
Chloride	87-124	105
Buffers (mmol/l)		
Acetate	2-4	3
Bicarbonate	20-40	35
pH	7.1-7.3	7.2
P_{CO_2} (mm Hg)	40-100	
Glucose	0-11 (0-200 mg/dl)	5.5 (100 mg/dl)

Dialysate **should be** considered “**as a drug to be adjusted”** to the individual **patient’s needs**

1. Am J Kidney Dis. 2015
2. McGill, Semin Dial. 2017
3. Floege J et al. Comprehensive Clinical Nephrology, 2015

Dialysate Composition

The **electrolyte** composition **of dialysate** is important for **fluid management, hemodynamic tolerance** and prevention **of arrhythmias**

Electrolyte	Impo	Recomendation
Dialysate sodium concentration	Related with: • Manageme control • Hemodinam	fits-all approach is likely not te prescribed in the range of 134- L, with deviations based on patient circumstances itive sodium balance
Dialysate potassium concentration	Arrhythmias cardiac death	ze concentration to avoid high K mun concentration 2-3 mEq/L. centration < 2 mEq/L. dialysis should be 3 mEq/L.
Dialysate bicarbonate concentration	Related with: • Manageme control •Hemodinam	d pre-HD bicarbonate serun ne range of 22 to 26 mmol/l
Dialysate calcium concentration	Related with • Intradialytic • Vascular ca	ze concentration. itive calcium balance mun concentration 2,5 -3 centration < 2 mEq/L. dialysis should be 3 mEq/L.
Dialysate magnesium concentration	Arrhythmias cardiac death	centration < 1 mEq/L.

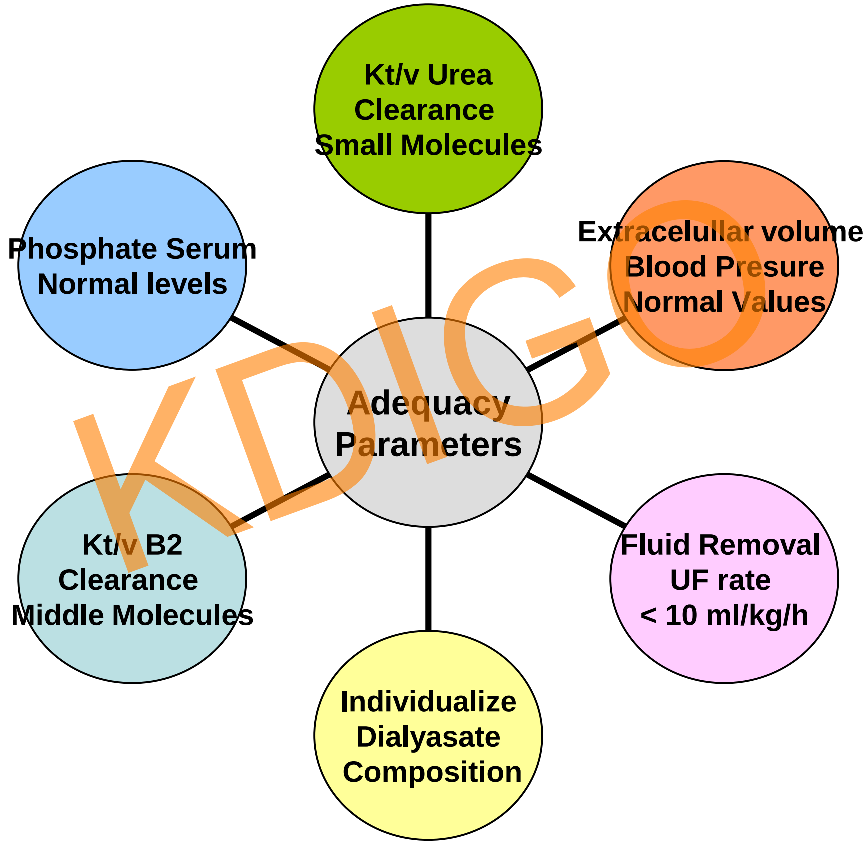
One-size-fits-all approach is **not appropriate!**

KDIGO

1. Avoid **positive sodium** balance
2. Avoid **positive calcium** balance
3. Avoid **high potassium** gradient
4. Avoid **low** concentration:
   Magnesium < 1mEq/L
   Calcium < 2 mEq/L
   Potassium < 2 mEq/L
5. Normalized **pre-HD bicarbonate serum** levels in range of **> 22 < 26 mmol/l**
6. Adjust **Potassium, Calcium** and **Phosphate** concentration **in nocturnal regimens**

Karaboyas et al. Am J Kidney Dis, 2017   McGill, Semin Dial, 2017   Flythe J. Seminars In Dialysis, 2017

Dialysis Adequacy



Surrogate parameter of electrolyte balance

Residual Renal Function

Preservation of **RRF** has been considered **an important aspect** of **peritoneal dialysis adequacy,** and **should be** considered **in hemodialysis** practice too.

Sustaining **RRF** is **important** for the **dialysis** patient because:

- Increases **clearances** of **middle molecule** and **protein bound** toxins
- Reduces **inter-dialytic weight gains**
- Increases **blood pressure** control
- Reduces **inflammatory markers**
- Is associated with better **nutrition status**
- Is associated with better **quality of life**

Beneficial effects extend to **very low levels**

RRF is strongly associated with improvement in **survival**

- **Novel markers** of renal function may provide alternative **methods of estimating RRF**, which **may simplify** its **measurement**

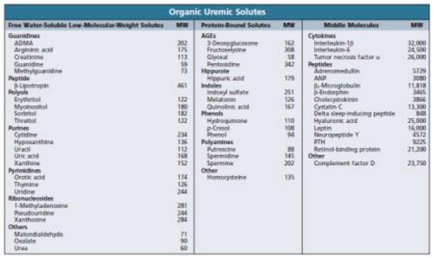
We **cannot underestimate** the maintenance of **residual renal function in HD patients**

We must try to **preserve it!**
We should **measure it!**

Shafi et al. Kidney Int. 2017
Davenport A. Hemodialysis International 2017
Tangvoraphonkchai et al.Seminars in Dialysis 2017

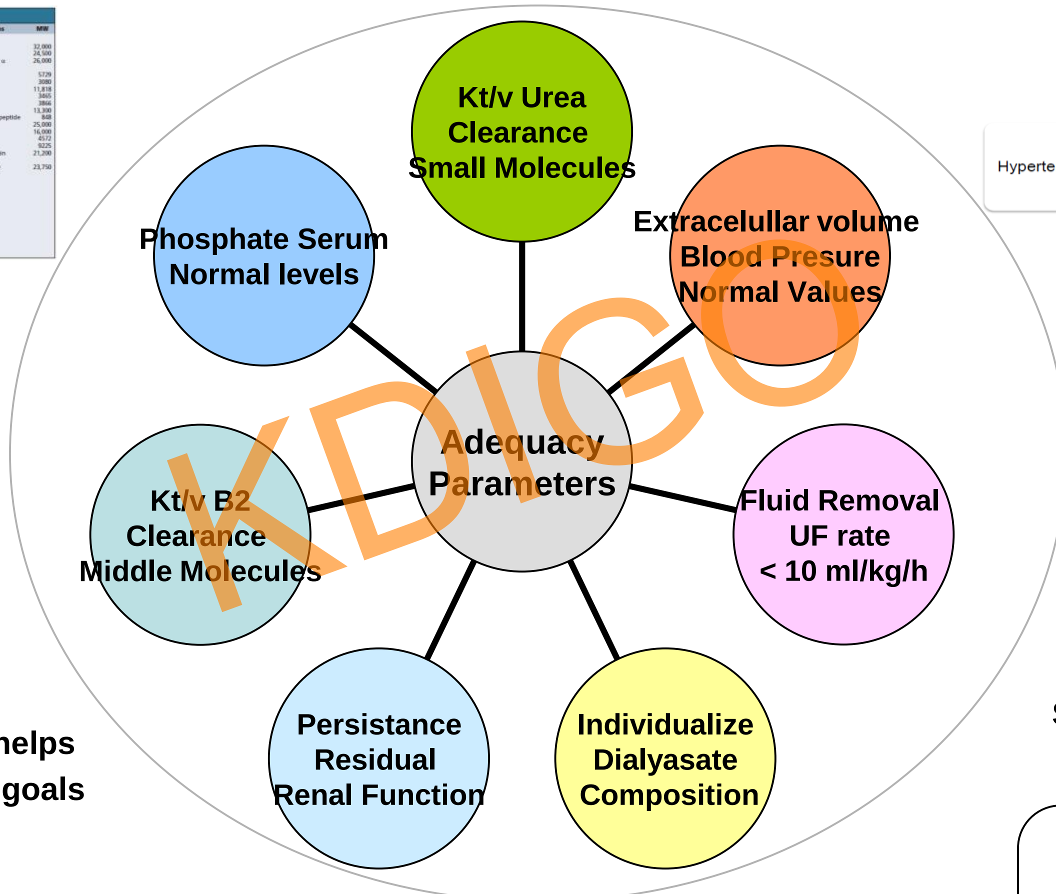
KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES KDIGO

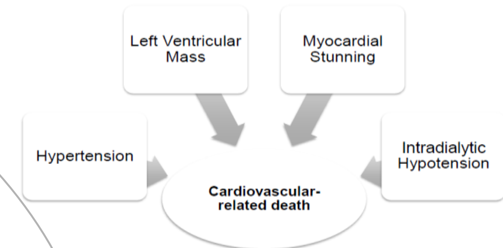
Dialysis Adequacy



Organic Uremic Solutes					
Free Water-Soluble Low-Molecular-Weight Solutes	**MW**	**Protein-Bound Solutes**	**MW**	**Middle Molecules**	**MW**
Guanidines		**AGEs**		**Cytokines**	
ADMA	202	3-Deoxyglucosone	162	Interleukin-1β	32,000
Argininic acid	175	Fructoselysine	308	Interleukin-6	24,500
Creatinine	113	Glyoxal	58	Tumor necrosis factor α	26,000
Guanidine	59	Pentosidine	342	**Peptides**	
Methylguanidine	73	**Hippurate**		Adrenomedullin	5729
Peptide		Hippuric acid	179	ANP	3080
β-Lipotropin	461	**Indoles**		β_2-Microglobulin	11,818
Polyols		Indoxyl sulfate	251	β-Endorphin	3465
Erythritol	122	Melatonin	126	Cholecystokinin	3866
Myoinositol	180	Quinolinic acid	167	Cystatin C	13,300
Sorbitol	182	**Phenols**		Delta sleep-inducing peptide	848
Threitol	122	Hydroquinone	110	Hyaluronic acid	25,000
Purines		p-Cresol	108	Leptin	16,000
Cytidine	234	Phenol	94	Neuropeptide Y	4572
Hypoxanthine	136	**Polyamines**		PTH	9225
Uracil	112	Putrescine	88	Retinol-binding protein	21,200
Uric acid	168	Spermidine	145	**Other**	
Xanthine	152	Spermine	202	Complement factor D	23,750
Pyrimidines		**Other**			
Orotic acid	174	Homocysteine	135		
Thymine	126				
Uridine	244				
Ribonucleosides					
1-Methyladenosine	281				
Pseudouridine	244				
Xanthosine	284				
Others					
Malondialdehyde	71				
Oxalate	90				
Urea	60				

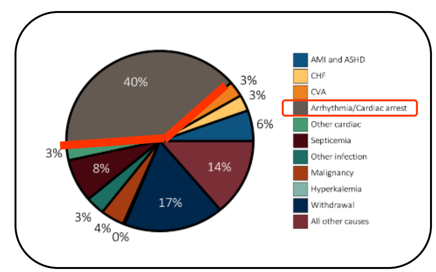
Surrogate parameters small and middle molecules clearance



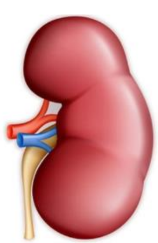


Surrogate parameters volume control

Surrogate parameters electrolyte shift



Determinant factor helps achieving adequacy goals



Broader Concept of Dialysis Adequacy

Dialysis Adequacy

Organic Uremic Solutes					
Free Water-Soluble Low-Molecular-Weight Solutes	MW	Protein-Bound Solutes	MW	Middle Molecules	MW
Guanidines		AGEs		Cytokines	
ADMA	202	3-Deoxyglucosone	162	Interleukin-1β	32,000
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Hypoxanthine	136	Polyamines		PTH	9225
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Xanthine	152	Spermine	202	Complement factor D	23,750
Pyrimidines		Other			
Orotic acid	174	Homocysteine	135		
Thymine	126				
Uridine	244				
Ribonucleosides					
1-Methyladenosine	281				
Pseudouridine	244				
Xanthosine	284				
Others					
Malondialdehyde	71				
Oxalate	90				
Urea	60				

Surrogate parameters small and middle molecules clearance

Kt/v Urea Clearance Small Molecules

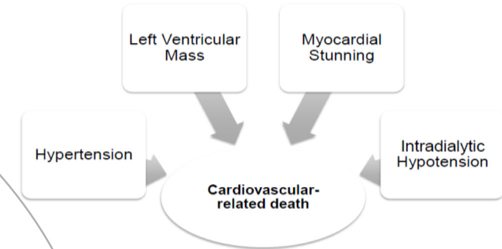
Phosphate Serum Normal levels

Extracelullar volume Blood Presure Normal Values

Dialysis adequacy cannot be a concept of clerance of **small solutes alone,**
but a concept that **concerns other factors** related to patient **survival**

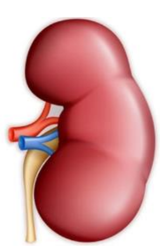
Persistance Residual Renal Function

Individualize Dialysate Composition



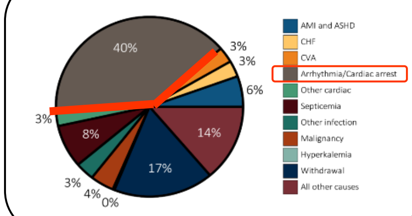
Surrogate parameters volume control

Determinant factor helps achieving adequacy goals



Broader concept of Dialysis Adequacy

Surrogate parameters electrolyte shift



How do **we achieve this broader concept** of adequacy?

"**We must** change, not only **what** we are going **to measure** related to dialysis parameters, **but also** the **way** we are **going to prescribe** dialysis"

"**Adequate dialysis schedule**"

How do **we achieve this broader concept** of adequacy?

Short

3 session/week

Conventional HD prescription

Is not adequate!!

This prescription **is the minimum treatment necessary to maintain life**, but it is **inadequate** in preventing **dialysis-related complications** and in **improving outcomes** [1]

1. Y Watanabe et al.Ther Apher Dial, 2015

Review

The International Journal of Artificial Organs / Vol. 27 / no. 6, 2004 / pp. 452-466

Short, thrice-weekly hemodialysis is inadequate regardless of small molecule clearance

Z.J. TWARDOWSKI

Division of Nephrology, Department of Medicine, Univer

This way of thinking is not new!

Advantages of long dialysis

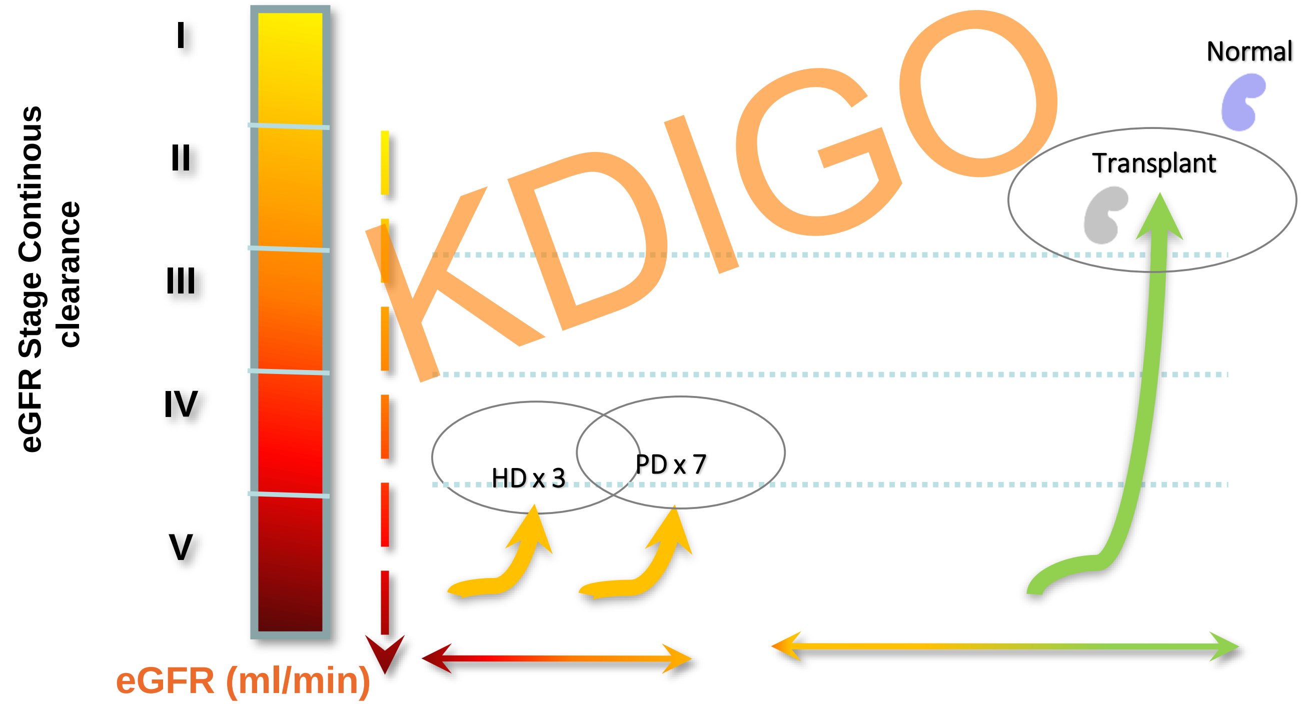
From the above discussion, the advantages of long dialysis to the patients are obvious: better tolerance of dialysis, better control of blood pressure, better removal of middle molecules, better rehabilitation, and longer survival.

Twarrdowski ZJ. Kidney International, 2004

Dialysis Dosing: Kinetics vs Physiology

The **goal of dialysis** is to **restore the body's** intracelullar and extracelullar **fluid environment toward** that of **healthy individuals** with functioning kidneys to the **greatest extent possible.**[1]

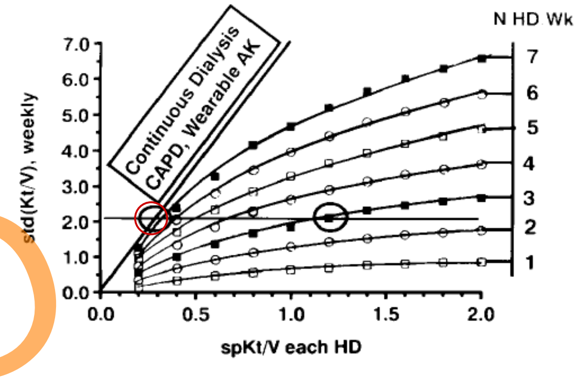
Conventional HD is far from
fluid and solute removal performed by **healthy kidneys**



1. Brenner and Rector's The Kidney, 2011
2. www.AdvancingDialysis.org

Dialysis Dosing: Kinetics vs Physiology

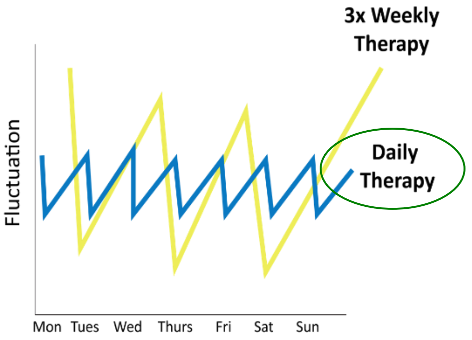
PD provides **similar** dialysis dose (standardized **weekly Kt/V**) to that of **thrice-weekly HD** prescription, **despite less** efficient small-solute clearance



Because it is a **continuous** and **frequent treatment,** (compared with conventional HD), PD **provides:**

- More **physiological clearance of solutes and water**, with **less fluid** and **eletrolyte shifts**
- Less **interdialytic oscillations**
- More clerance of **middle molecules**
- **Better preservation** of residual renal function

The peak concentration hypothesis



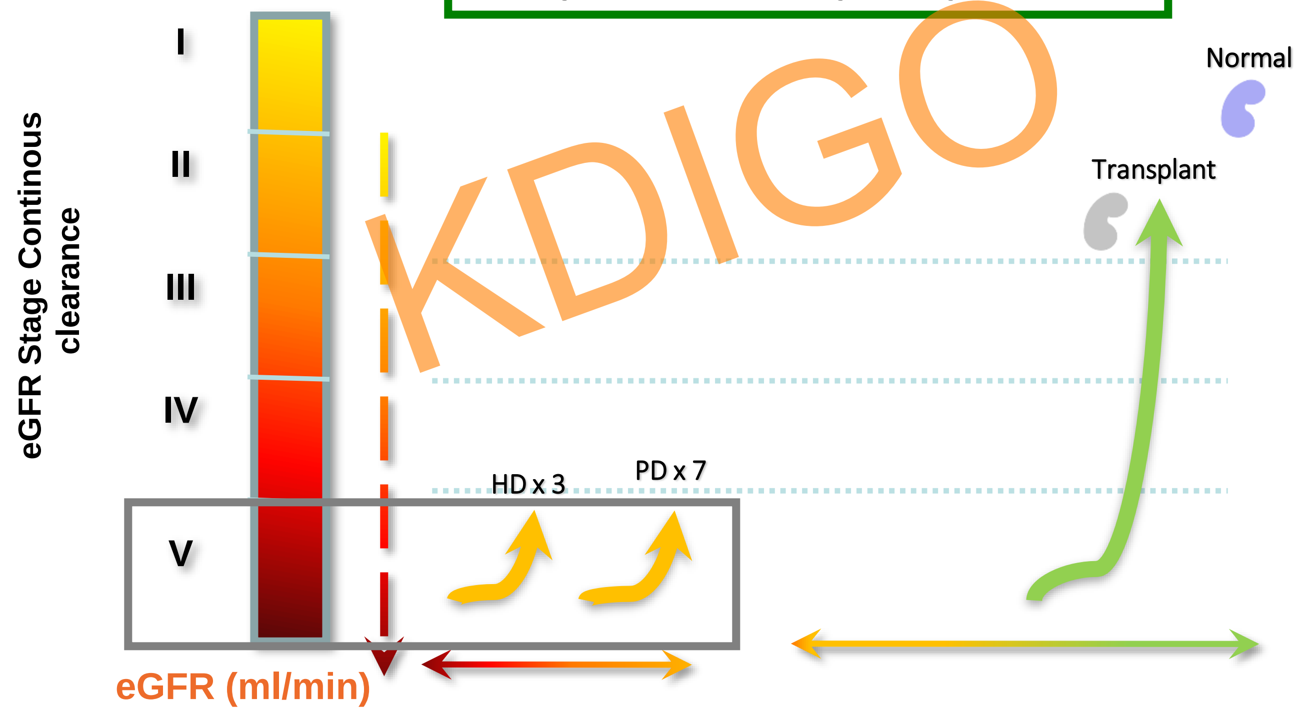
PD could offer a **number** of **advantages over conventional HD,** at least during the **first** 2-3 **years** when patients maintain **residual renal function**

1. Locatelli F et al. Nephrol Dial Transplant. 2005
2. Gotch FA. Nephrol Dial Transplant, 1998
3. Floege J et al. Comprehensive Clinical Nephrology, 2015

Dialysis Dosing: Kinetics vs Physiology

The **goal of dialysis** is to **restore the body's** intracelullar and extracelullar **fluid environment toward** that of **healthy individuals** with functioning kidneys to the **greatest extent possible.**[1]

Do we think that it **is enough** to replace **only 10-15%** of **healthy kidney** function?



1. Brenner and Rector's The Kidney, 2011
2. www.AdvancingDialysis.org

What else **should** we do**,**

if we want to **increase**

dialysis dose?

Dialysis Dosing: Kinetics vs Physiology

1. **More solute removal**

We still **don't know** which solutes **we SHOULD** remove,

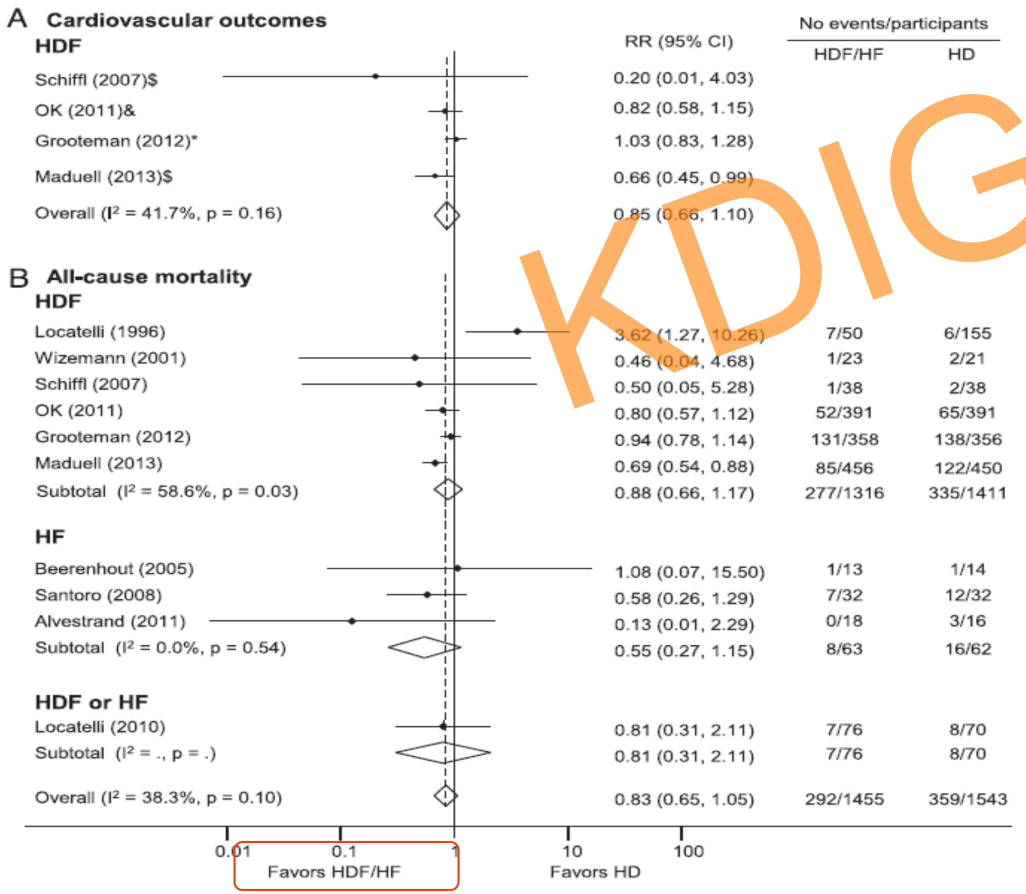
As well as

we still **don't know**, which solutes we **SHOULD NOT** remove!!

More Solute Removal

AJKD
Original Investigation

Effect of Hemodiafiltration or Hemofiltration Compared With Hemodialysis on Mortality and Cardiovascular Disease in Chronic Kidney Failure: A Systematic Review and Meta-analysis of Randomized Trials



Convective therapies provide:

- Better **middle molecule clearance**
- Increase **removal of inflammatory mediators**
- More **hemodynamic stability**
- Possibly **better cardiovascular outcome** with high sustitution volumen (**> 20 L** per sesión)

Wang A et al. Am J Kidney Dis. 2014

More Solute Removal

Cochrane Library

Cochrane Database of Systematic Reviews

Haemodiafiltration, haemofiltration and haemodialysis for end-stage kidney disease (Review)

Nistor I, Palmer SC, Craig JC, Saglimbene V, Vecchio M, Covic A, Strippoli GFM

2015 review update

Studies included: 40 (125 reports; 4150 participants)

Ongoing studies: 5 (5 reports)

Studies excluded: 133 (149 reports)

Studies awaiting assessment: 7 (8 reports)

Authors' conclusions

Convective dialysis may reduce cardiovascular but not all-cause mortality and effects on nonfatal cardiovascular events and hospitalisation are inconclusive. However, any treatment benefits of convective dialysis on all patient outcomes including cardiovascular death are unreliable due to limitations in study methods and reporting. Future studies which assess treatment effects of convection dose on patient outcomes including mortality and cardiovascular events would be informative.

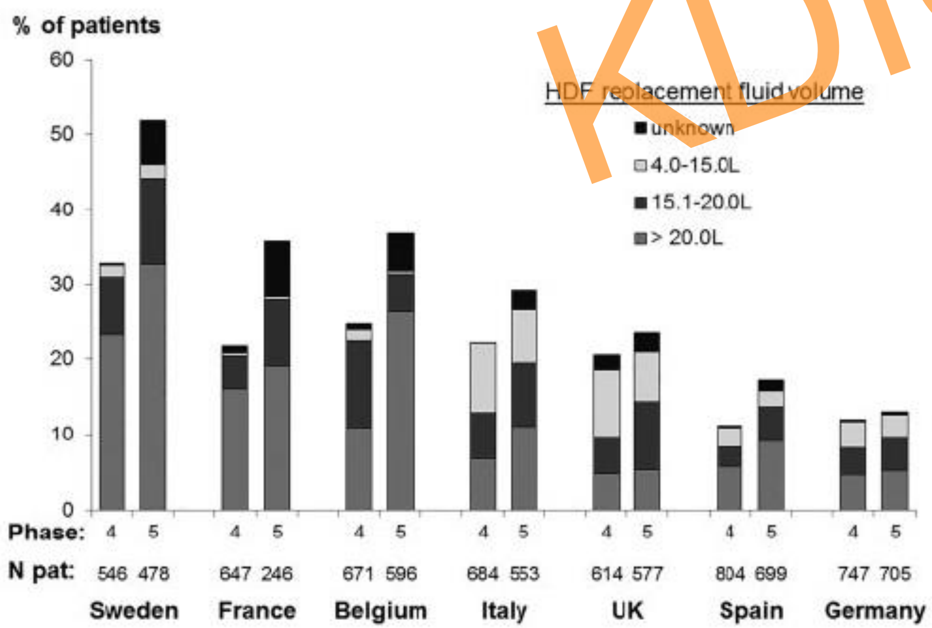
Nistor I et al. Cochrane Database of Systematic Reviews 2015

More Solute Removal

ndt
Nephrology Dialysis Transplantation
Nephrol Dial Transplant (2017) 1–7
doi: 10.1093/ndt/gfx277

Mortality risk in patients on hemodiafiltration versus hemodialysis: a 'real-world' comparison from the DOPPS

In this analysis, data from participants **in seven European countries** (Belgium, France, Germany, Italy, Spain, Sweden and the UK) **in DOPPS Phase 4 (2009–11) and Phase 5 (2012–15) were used.**



Conclusions. Our results do not support the notion that HDF provides superior patient survival. Further trials designed to test the effect of high-volume HDF (versus lower volume HDF versus HD) on clinical outcomes are needed to adequately inform clinical practices.

Locatelli F et al. Nephrol Dial Transplant 2017

What should we do?

1. More **solute removal**

2. More **volume control**

More frequent and/or longer sessions

More Weekly Treatment Time!

Longer sessions

Survival as an index of adequac

Bernard Charra, Edouard Calemard, Martial R
Jean-Claude Terrat, Thierry Vanel, an

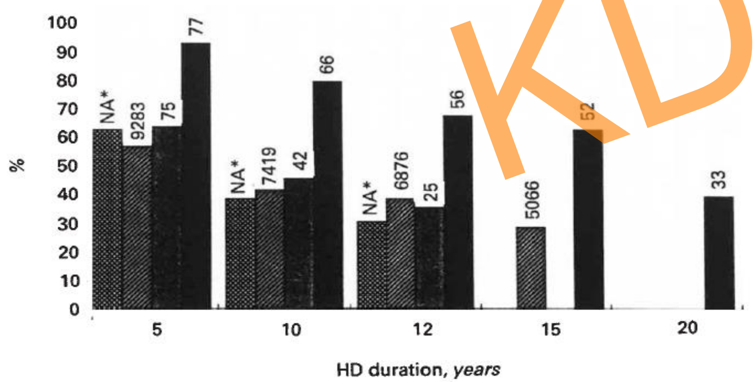
Centre de rein artificiel, Tassin, France

Kidney International, Vol. 41 (1992), pp. 1286–1291

This evidence is not new!

Tassin's artificial kidney center's experience

This group reported **one of the best dialysis survival estimates of any program or registry**



Long-term survival (%) of patients in four series: USRDS, EDTA; Japan and Tassin

it takes anywhere near eight hours of dialysis to achieve sufficient ultrafiltration to control blood pressure. What we do believe though, is that sometimes it takes longer to remove enough fluid to control blood pressure than it does to provide an adequate dose of dialysis.

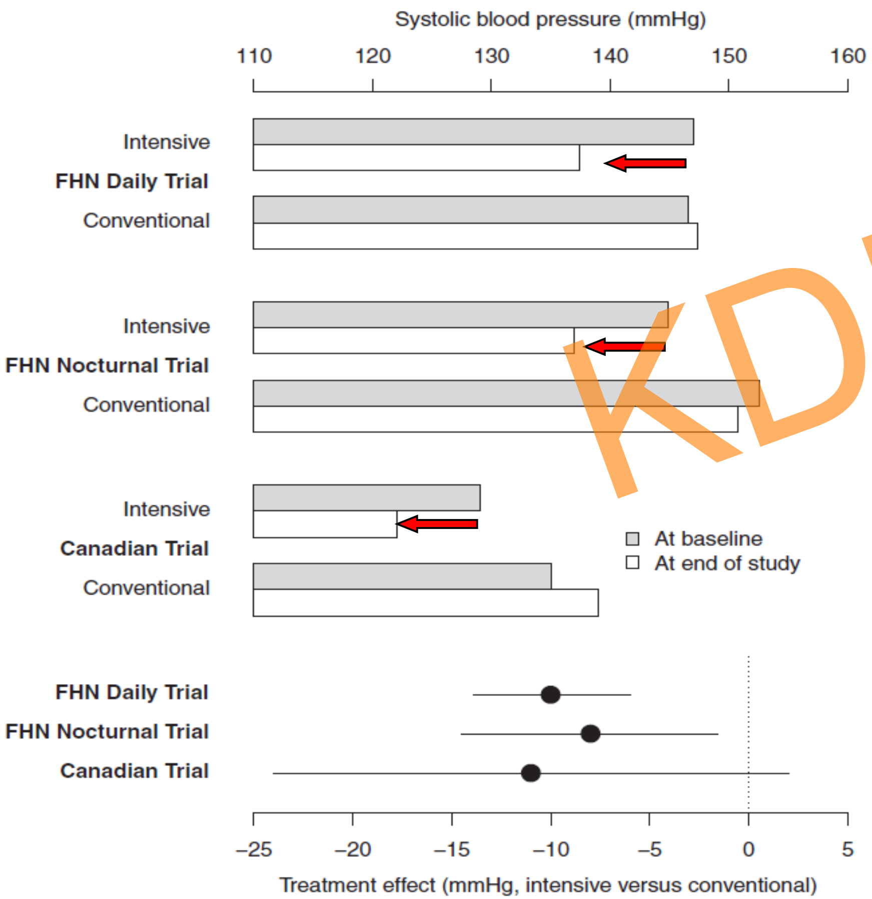
survival. Beyond that, it provides more than enough time for ultrafiltration to maintain dry weight and control blood pressure so effectively that antihypertensive medications are very seldom needed. This feature of our program is perhaps the most important factor contributing to our survival results.

Eight hours of dialysis three times/week (24 hours/week) (*Kt/V* of 1.67)

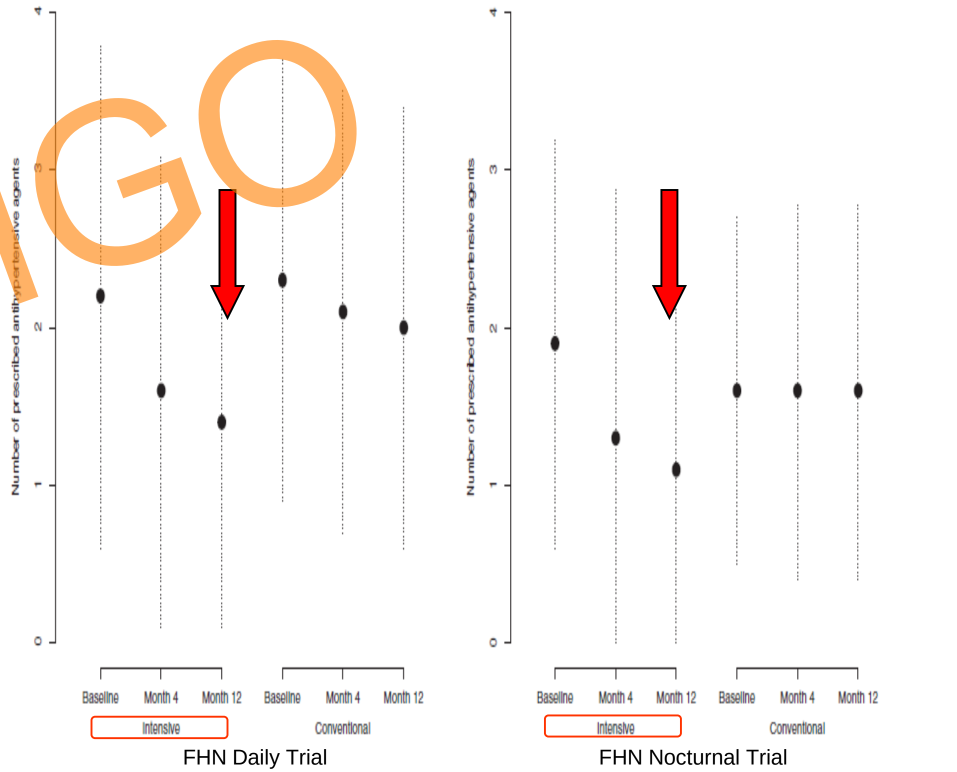
Charra et al. Kidney International, 1992

Blood Pressure Control

Effects of **Intensive HD vs conventional HD** on **predialysis systolic blood pressure** in FHN Daily Trial, FHN Nocturnal Trial, and Canadian Nocturnal Trial.



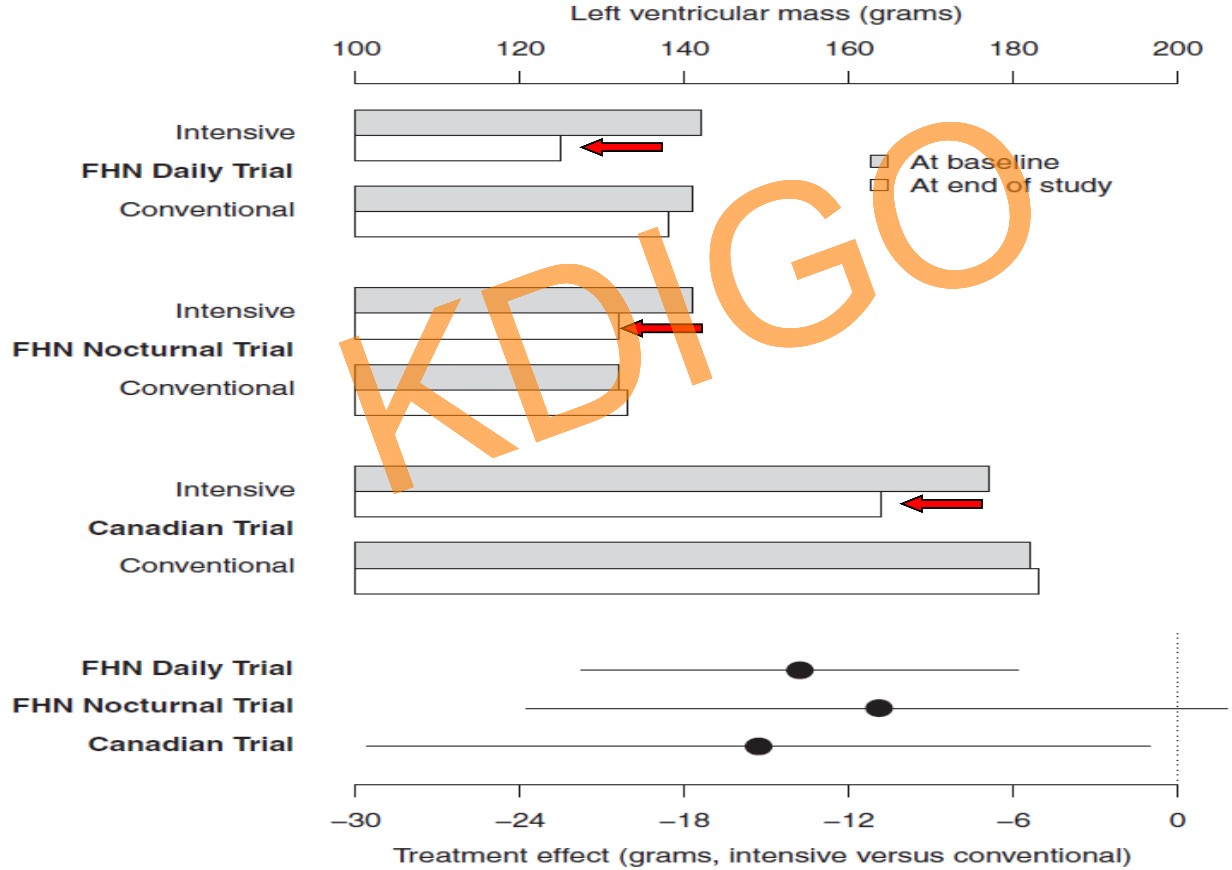
Mean number of prescribed antihypertensive



Bakris et al. Am J Kidney Dis. 2016

Left Ventricular Hypertrophy

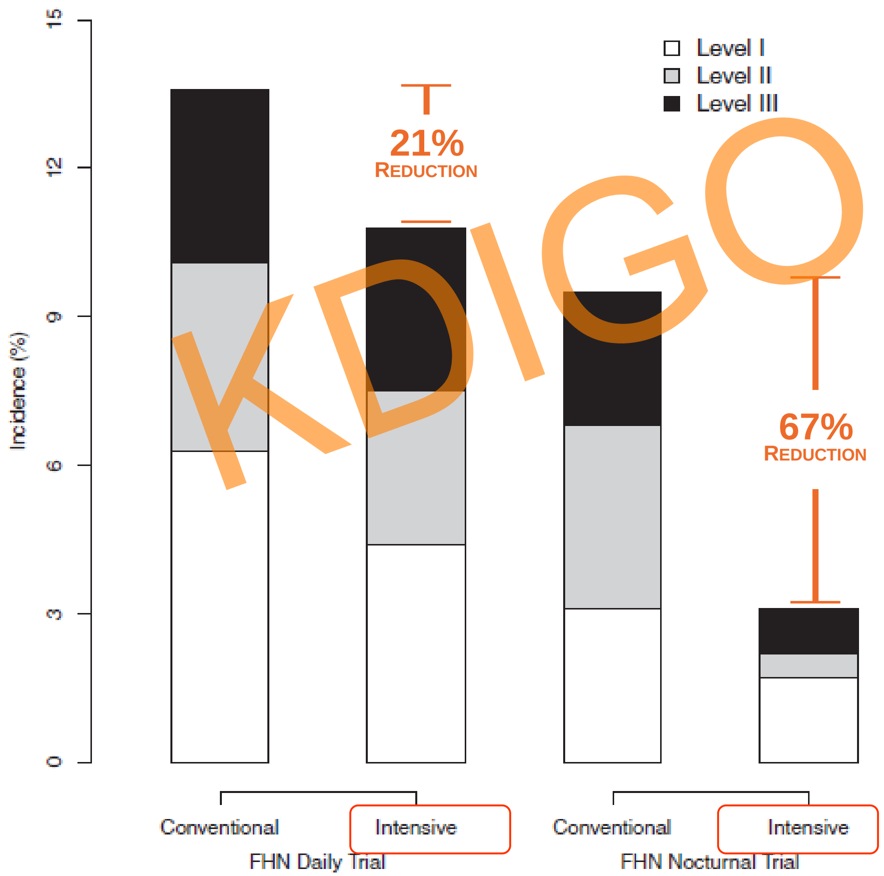
Effects of **Intensive HD vs conventional HD** on **regression of left ventricular mass** in FHN Daily Trial, FHN Nocturnal Trial, and Canadian Nocturnal Trial.



McCullough et al. Am J Kidney Dis. 2016

Intradialytic Hypotension

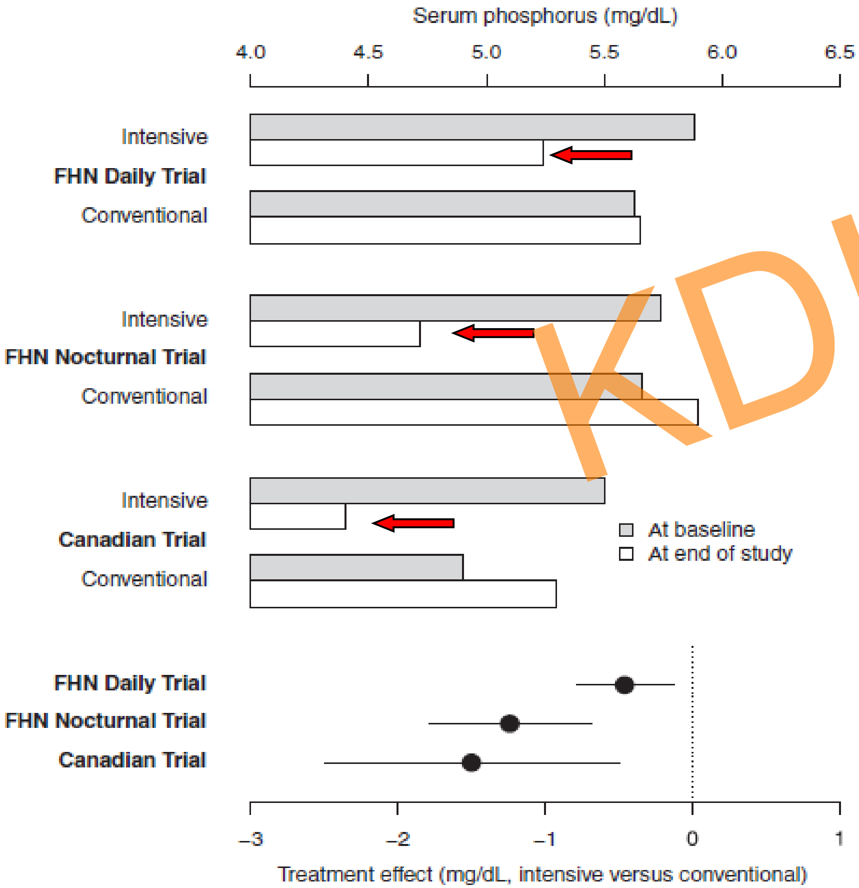
Incidences of levels I, II, and III **intradialytic hypotension** for **Intensive HD** versus **conventional HD** in the FHN Daily Trial and the FHN Nocturnal Trial.



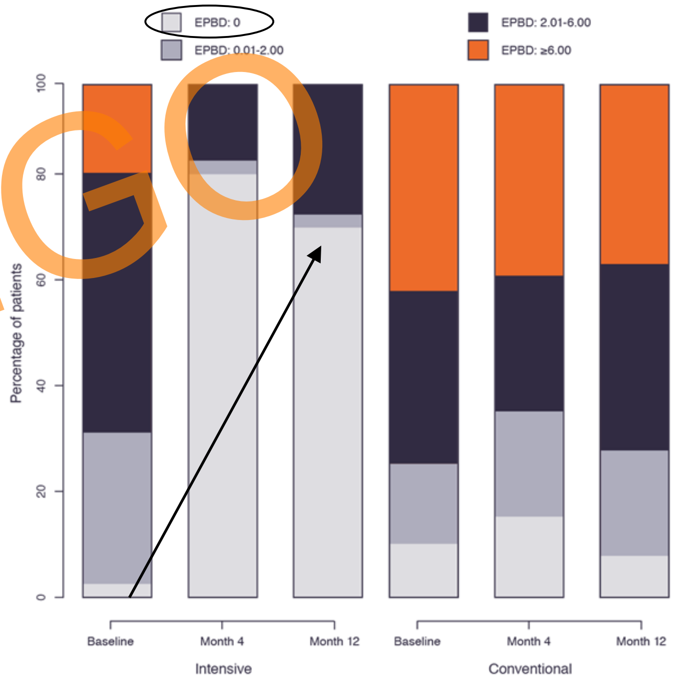
1. Morfin et al. Am J Kidney Dis. 2016
2. www.AdvancingDialysis.org

Phosphate Removal

Effects of **Intensive HD** vs **conventional HD** on **serum phosphote levels** in FHN Daily Trial, FHN Nocturnal Trial, and Canadian Nocturnal Trial.



Distribution of equivalent phosphorus binding dose for intensive versus conventional [2]

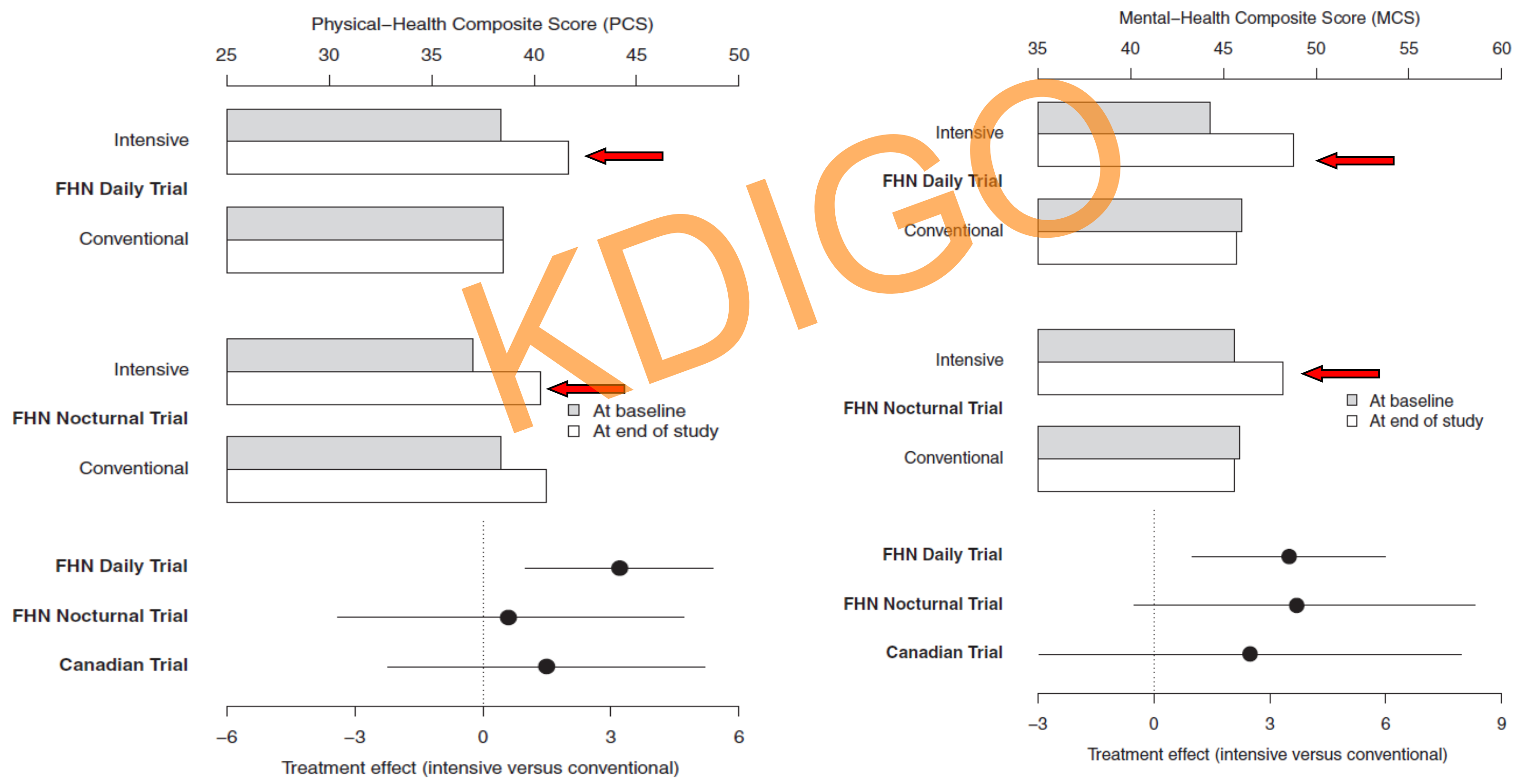


FHN Nocturnal Trial

1. Copland et al. Am J Kidney Dis. 2016
2. AdvancingDialysis.org

Health-related quality of life

Effects of **Intensive HD** vs **conventional HD on the physical and mental health composite score** in FHN Daily Trial, FHN Nocturnal Trial, and Canadian Nocturnal Trial.



Kraus et al. Am J Kidney Dis. 2016

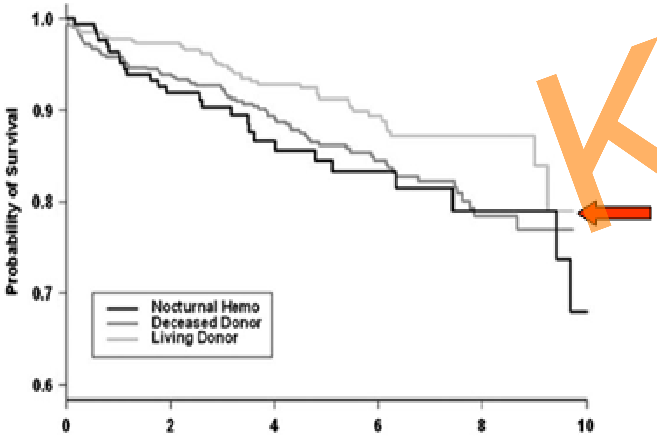
Intensive HD

NDT

Survival among nocturnal home haemodialysis patients compared to kidney transplant recipients

Robert P. Pauly[1], John S. Gill[2], Caren L. Rose[2], Reem A. Asad[3], Anne Chery[4], Andreas Pierratos[5] and Christopher T. Chan[3]

Using data from two regional Noctunal HD programmes from Canada and the USRDS from 1994 to 2006, performed a **matched cohort** study comparing survival **between NHD and deceased and living donor kidney transplantation**



N						
NHD	177	134	85	48	28	10
DTX	531	463	302	198	90	0
LTX	531	458	282	170	60	0

Time From Modality Start (Years)

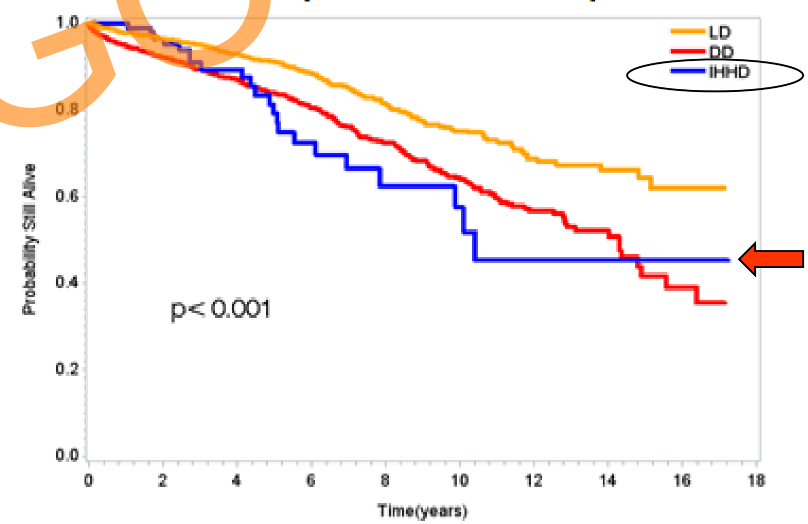
Intensive Home Hemodialysis Survival is Comparable to Deceased Donor Kidney Transplant

Angie Nishio Lucar MD[1], Genevieve R. Lyons MSPH[1], Subhasish Bose MD[2], Robert S. Lockridge MD[2]
[1]University of Virginia Medical Center, Charlottesville, VA and [2]Lynchburg Nephrology Physicians Lynchburg, VA

ASN

Study compared the **survival** of patients who receive a **kidney transplant or started IHHD** between October 1st 1997 and June 30th 2014 in the same Virginia region in the U.S.A

Survival by treatment modality



IHHD was defined as ≥ 4 dialysis/week or ≥20 hours per week

Pauly r et al. NephrolDial Transplant. 2009

Nishio Lucar et al. ASN Kidney Week. New Orleans 2017

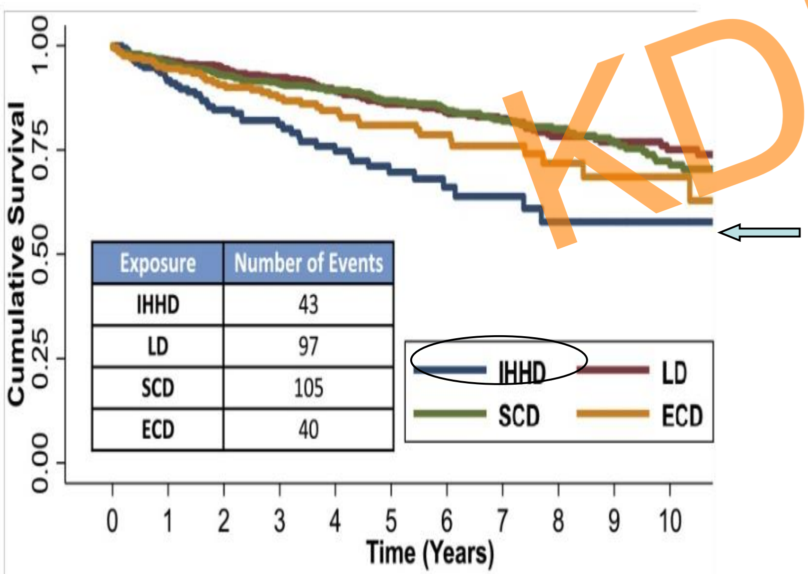
JASN

J Am Soc Nephrol. 2014 Sep; 25(9): 2113–2120.

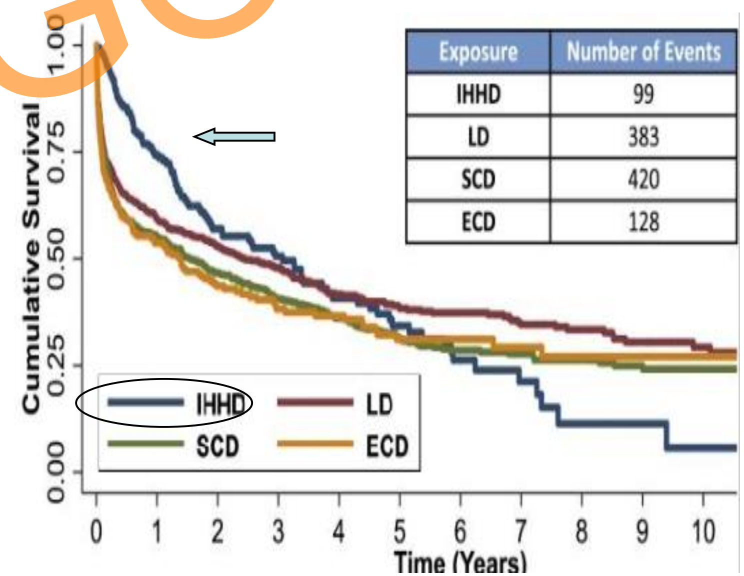
Survival and Hospitalization for Intensive Home Hemodialysis Compared with Kidney Transplantation

Canadian patients receiving **intensive home hemodialysis** (**IHHD; ≥16 hours per week**) vs **kidney transplant**

Time-to-death or treatment failure comparing IHHD patients and kidney transplant recipient subtypes



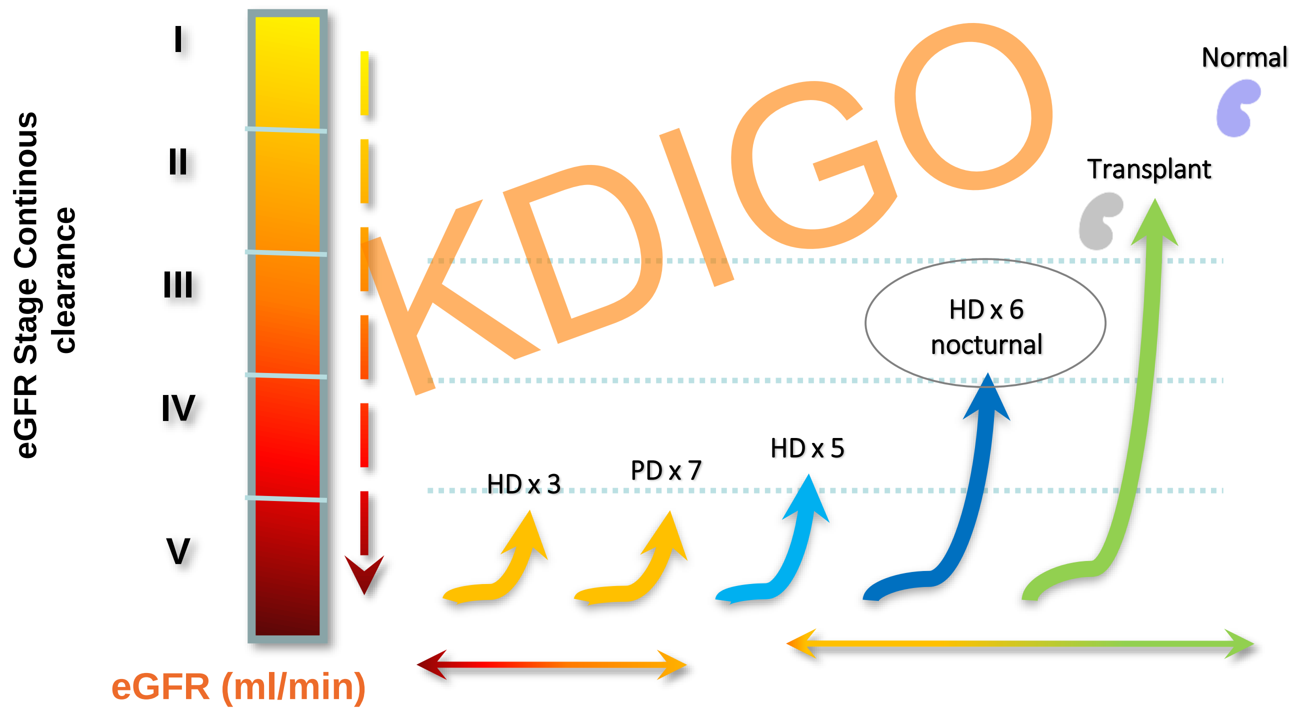
Time to first hospitalization comparing IHHD patients and kidney transplant recipient subtypes



Tennankore et al. J Am Soc Nephrol 2014

Dialysis Dosing: Kinetics vs Physiology

More frequent and **longer** dialysis prescription is the **dialysis** option that **more closely mimics** the **kidney`s function**



1. Brenner and Rector's The Kidney, 2011
2. www.AdvancingDialysis.org
3. Locatelli et al. Blood Purif 2015

Why do we

continue prescribing

Short 3 sessions/week

for the **majority** of our patients**?**

This is not the result of **demonstrated clinical superiority** of **the prescription**
but it is the result of
Increasing **financial and logistical pressures**[1]

Policy makers must work **with the renal professional,** to ensure that **financing approaches** to control costs, **do not adversely impact** the **quality** of **care** [2]

1. Collins AJ. Am J Kidney Dis. 2016
2. Swaminathan et al. Health Aff (Millwood). 2012

Is it time
to change?

Dialysis Adequacy

Relevant studies that have changed dialysis adequacy over years.

Conventional HD
Short thrice-weekly
Is **not enough!!**

Kt/v urea as the **only adequacy** parameter
Is **not enough!!**

1949 – **First HD** in North America Performed by Murray

1951 – **First serious approach to quantifying dialysis** Wolf et al

1971 – **Hypothesis "Square meter hour"** Babb et al

1983 – **NCDS** Study

1990s – **Equilibrated Kt/v** Daugirdas; **URR** by Lowrie

1996 – **CANUSA** Study

2002 – **HEMO** Study

2002 – **ADEMEX** trial

2003 – **NECOSAD EAPOS** Study

2003 – **Hong Kong Study** (Lo et al)

2007 – **Alberta Nocturnal Trial**

2008 – **MPO** Study

2010- 2011 – **FHN Trials**

2012 – **CONTRAST**

2013 – **ESHOL**; **Turkish HDF**

2015 – **Last Guidelines**

2018

Dialysis Adequacy

Relevant studies that have changed dialysis adequacy over years

TIME TO MOVE FORWARD

If we **really want to change** our patient's outcomes

- **1949** — **First HD** in North America Performed by Murray
- **1951** — **First serious approach to quantifying dialysis** Wolf et al
- **1971** — **Hypothesis "Square meter hour"** Babb et al
- **1983** — **NCDS** Study
- **1990s** — **Equilibrated Kt/v** Daugirdas; **URR** by Lowrie
- **1996** — **CANUSA** Study
- **2002** — **HEMO** Study
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- **2003** — **NECOSAD EAPOS** Study
- **2003** — **Hong Kong Study** (Lo et al)
- **2007** — **Alberta Nocturnal Trial**
- **2008** — **MPO** Study
- **2010- 2011** — **FHN Trials**
- **2012** — **CONTRAST**
- **2013** — **ESHOL**; **Turkish HDF**
- **2015** — **Last Guidelines**
- **2018**

Conclusions

1. After **3 decades** of focusing on **adequacy prescription** defined by **Kt/Vurea**, we **must change** our approach.

2. The **unmet clinical needs** derived from **conventional hemodialysis** have **prompted questions** about the **validity** of the current **adequacy goal,** and have generated **interest** in **other** clinical **parameters** for patient's **outcomes** that may be more important **than solute removal.**

3. **Weekly treatment time** is the **one factor** with the **potentially highest impact** on **dialysis dose,** that can **help** achieve **more solute clearance** as well as more **volume control.**

Conclusions

4. We **need** to think whether, instead of prescribing conventional HD for the **majority** of patients, we can turn to **alternative dialysis prescriptions** probably starting with patients who have **a longer life expectancy,** and with **those** that **can specifically benefit** from alternative **dialysis schedules**.

5. **Home dialysis** is an **attractive** and **cost-effective modality** to **increase time and frequency** due to **favorable logistics;** and also **offers** more **freedom** and **quality of life.**

6. When **home** dialysis **is not possible,** we need to think of different possibilities **to increase time and frequency, but** in an **in-center setting,** such as:
   - More **nocturnal** dialysis
   - **4 times/week** sessions
   - **Alternate-day** sessions

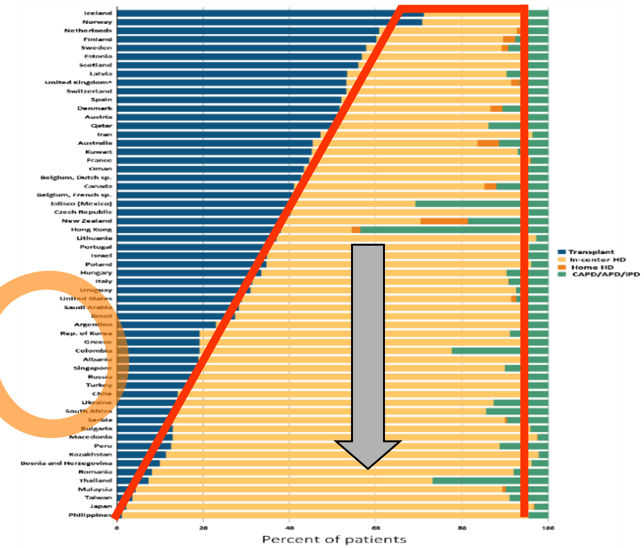
7. **Further** studies are required to compared **different dialysis prescriptions**

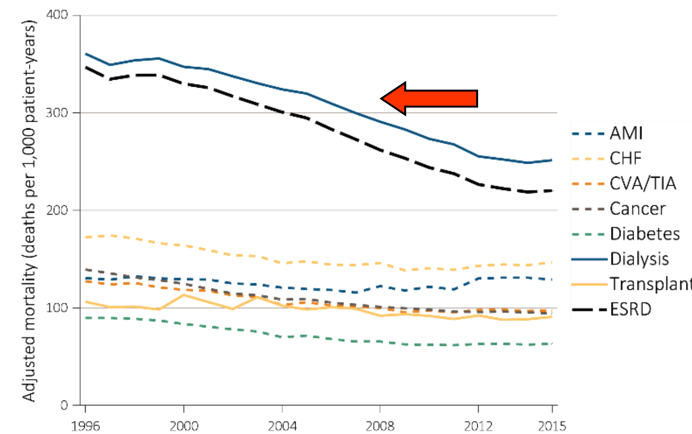
Conclusions

In the near future, we can have
a **different** picture of **RRT worldwide**,

with an **improvement** of patient's **outcomes,** because of a **change** in

Nephrologists' way of thinking!!





The FUTURE is in our HANDS!!

USRDS Annual Data Report 2017


Bedankt Merci 謝謝 Gracias ありがとう MERCI
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