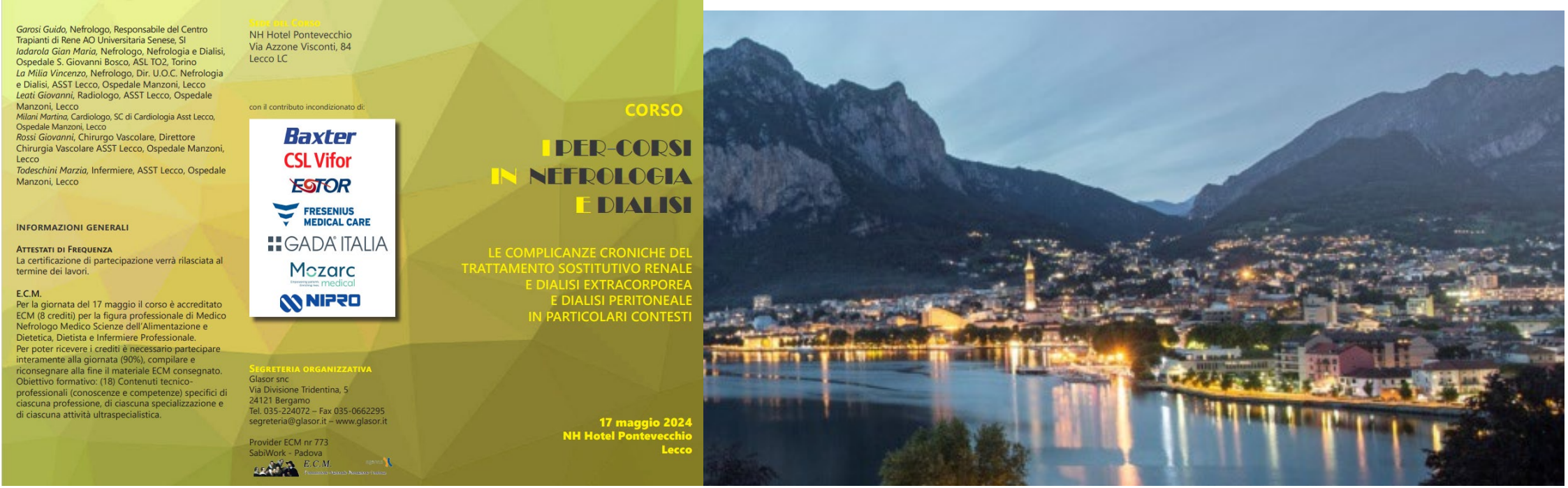


Il deficit di ultrafiltrazione in dialisi peritoneale

Vincenzo La Milia

Nefrologia e Dialisi

Ospedale A. Manzoni, Lecco

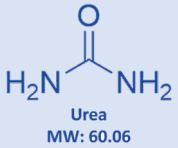
Peritoneal dialysis offers several advantages for the treatment of kidney failure

- Highly effective and safe
- Main home-based dialysis modality
- Promotes patients' empowerment

- Also: helps preserving residual kidney function, reduces exposure to SARS-CoV-2, less expensive than in-center HD, reduced use of water as compared to HD

High-quality PD prescription
ISPD guidelines

PERITONEAL DIALYSIS INTERNATIONAL

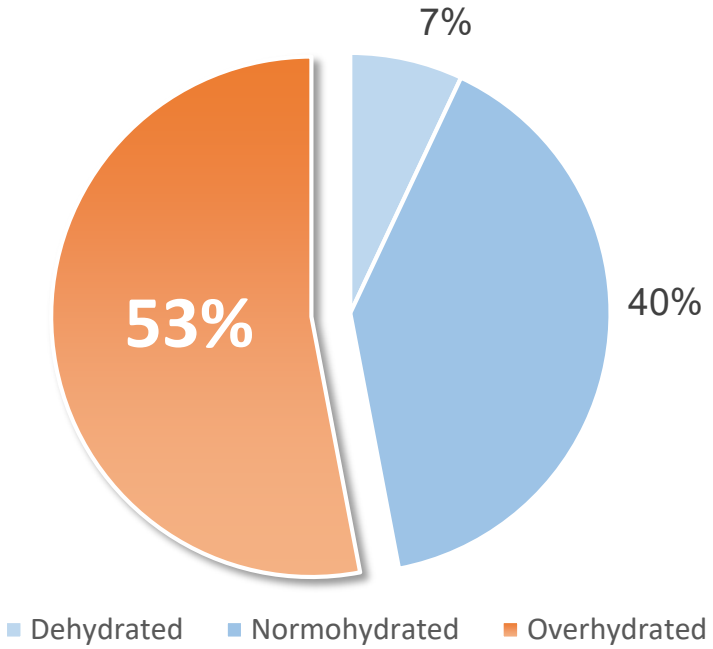
Targets		
✗	‘Numbers’ for small solutes removal: *i.e.* specific value of Kt/V urea or Clcreat	
✓	**Patient well-being** - disease symptoms, impact of dialysis, mental health, social circumstances	
✓	**Adequate nutritional status** - appetite, body weight, clinical examination, blood tests	
✓	**Optimal fluid balance** – both urine output and fluid removed by dialysis contribute	

Brown et al, *Perit Dial Int* 2020

Fluid overload in PD patients

>50% of prevalent PD patients are fluid overloaded

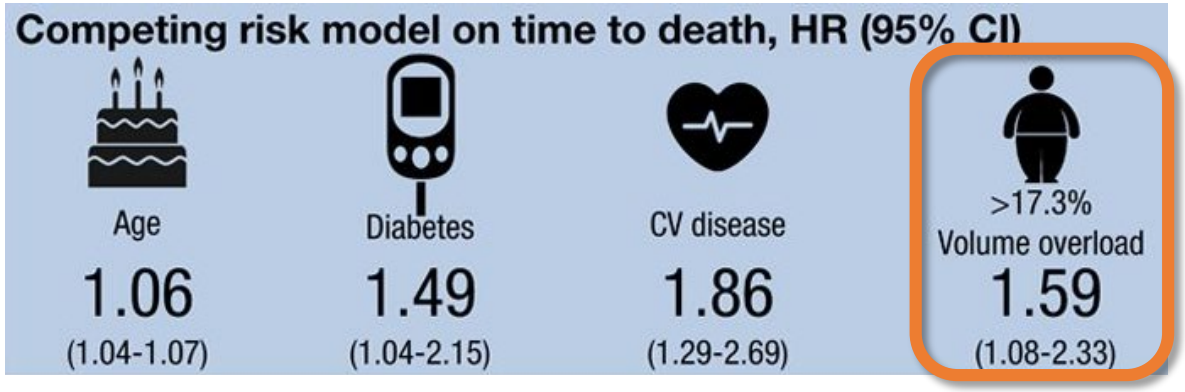
639 prevalent PD patients
28 centres, 6 countries, bioimpedance



Van Biesen et al, *PLOS* 2011

Fluid overload associates with mortality

1054 incident PD patients - 135 centers, 28 countries, bioimpedance spectroscopy
Relationship of fluid overload with mortality



IPOD-PD study

Van Biesen et al, *CJASN* 2019; Zoccali et al, *JASN* 2017; Tabinor et al, *Sci Rep* 2018

Ultrafiltrazione e sopravvivenza in dialisi peritoneale

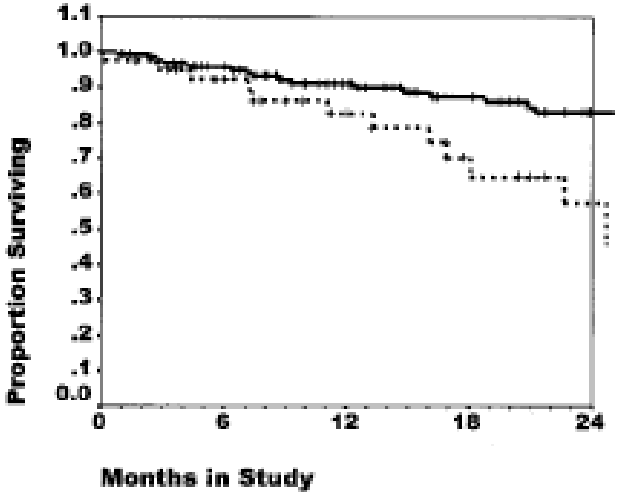


Figure 3. Kaplan Meier patient survival according to baseline UF of >750 ml/d (▥) and <750 ml/d (- - -); $P = 0.0048$.

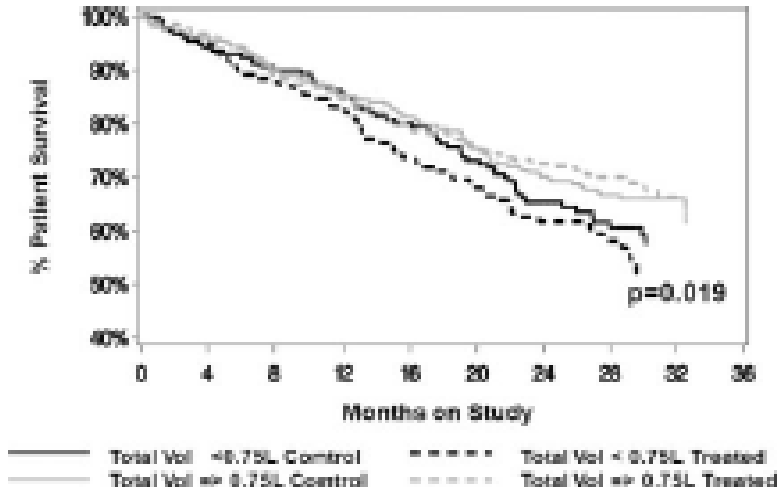


Figure 4. Patient overall survival (all cause mortality) by total fluid removal (urinary and peritoneal) and treatment assignment. Groups were divided based on a value of fluid removal

Un valore cut-off di escrezione totale d'acqua <750 mL/die in una popolazione di pazienti anurici in dialisi peritoneale (Fig. 3) [1] e in quella dello studio ADEMEX (Fig. 4) [2] è risultato influenzare la loro sopravvivenza in modo significativo.

1. Brown EA, et al. Survival of functionally anuric patients on Automated Peritoneal Dialysis: the European APD Outcome Study. J Am Soc Nephrol 2003, 14:2948-57.
2. Paniagua R, et al. Predictive value of Brain Natriuretic Peptides in patients on peritoneal dialysis: results from the ADEMEX trial. Clin J Am Soc Nephrol 2008; 3:407-415.

Ultrafiltrazione e sopravvivenza in dialisi peritoneale

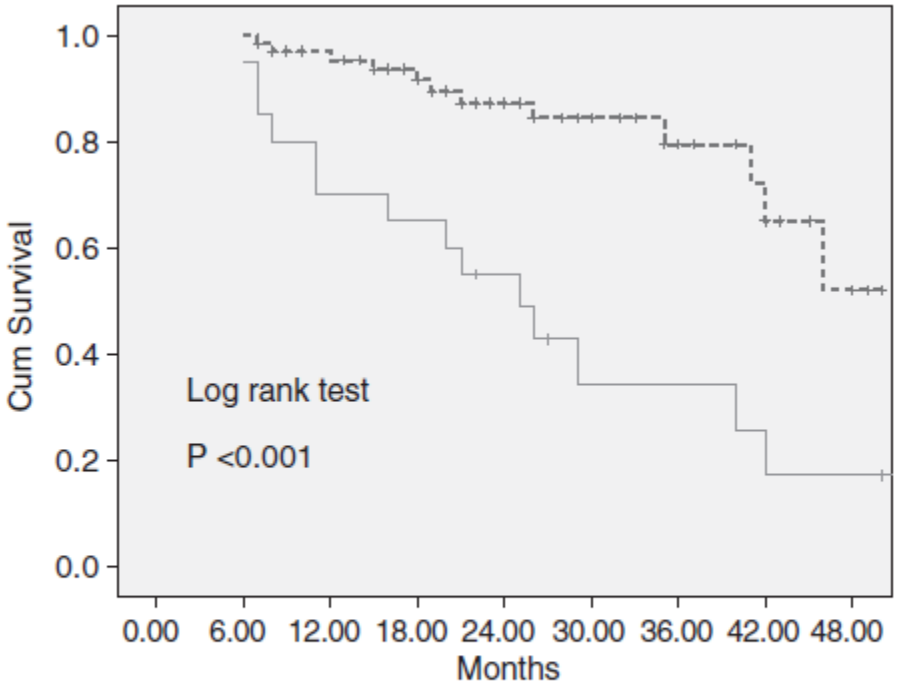


Fig. 1. Kaplan–Meier survival curves for all-cause mortality in 86 anuric PD patients grouped according to baseline UF of ≥1 L/24 h (dashed) and <1 L/24 h (solid); $P < 0.001$.

Ultrafiltrazione > 1 L/24 ore vs < 1 L/24 ore

Lin X, et al. Daily peritoneal ultrafiltration predicts patient and technique survival in anuric peritoneal dialysis patients. Nephrol Dial Transplant 2010; 25:2322-27.

Causes of fluid overload in PD patients

Fluid overload in PD

- Excessive salt and water intake
- Loss of residual diuresis
- Inadequate peritoneal UF
  - Catheter dysfunction
  - Mechanical problems, fluid sequestration or excessive absorption
  - Inadequate prescription
  - Membrane dysfunction

Fluid overload = imbalance between…

what goes in *what goes out*

of the organism in terms of water and sodium

Optimizing ultrafiltration

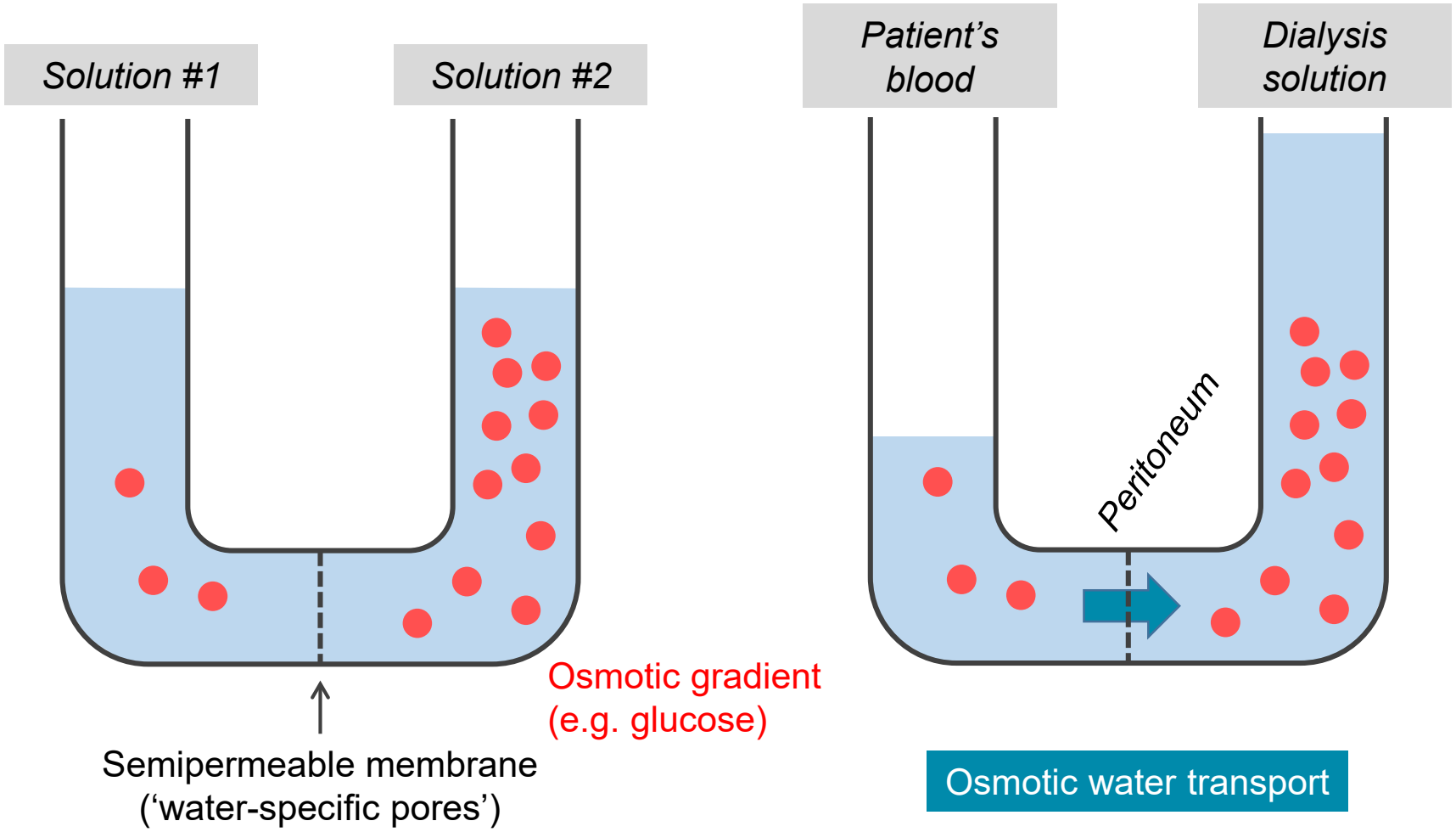
Key to restore fluid balance and to the efficiency of PD

Relies on a functional peritoneal membrane and personalized PD prescription

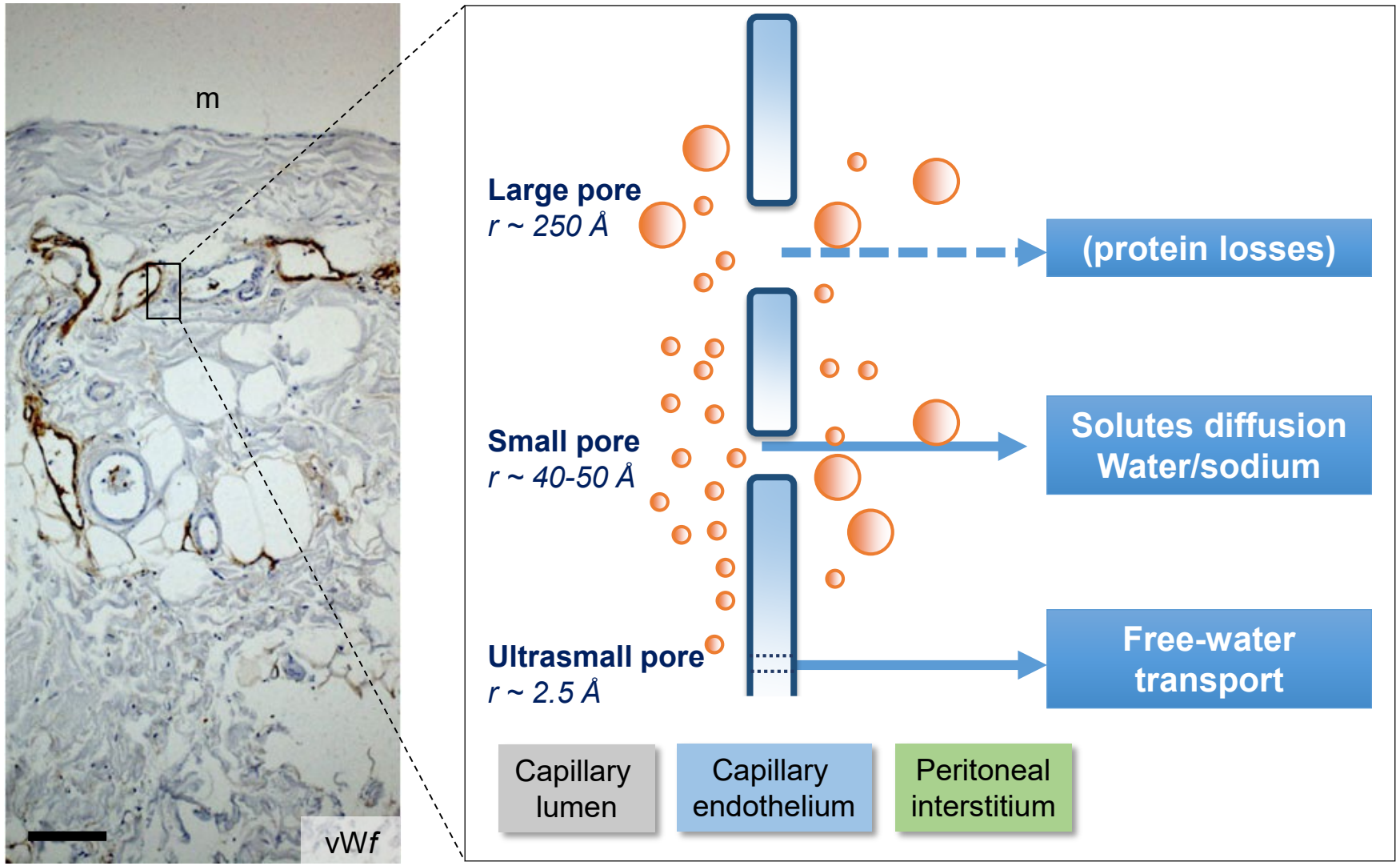
Learning objectives

- To understand the mechanisms of osmosis across the peritoneal membrane and the role of water channels in PD
- To identify membrane dysfunction and its underlying mechanisms
- To explain how a common variant in the *AQP1* gene influences water transport and outcomes in PD

To drive ultrafiltration, PD applies the principle of osmosis

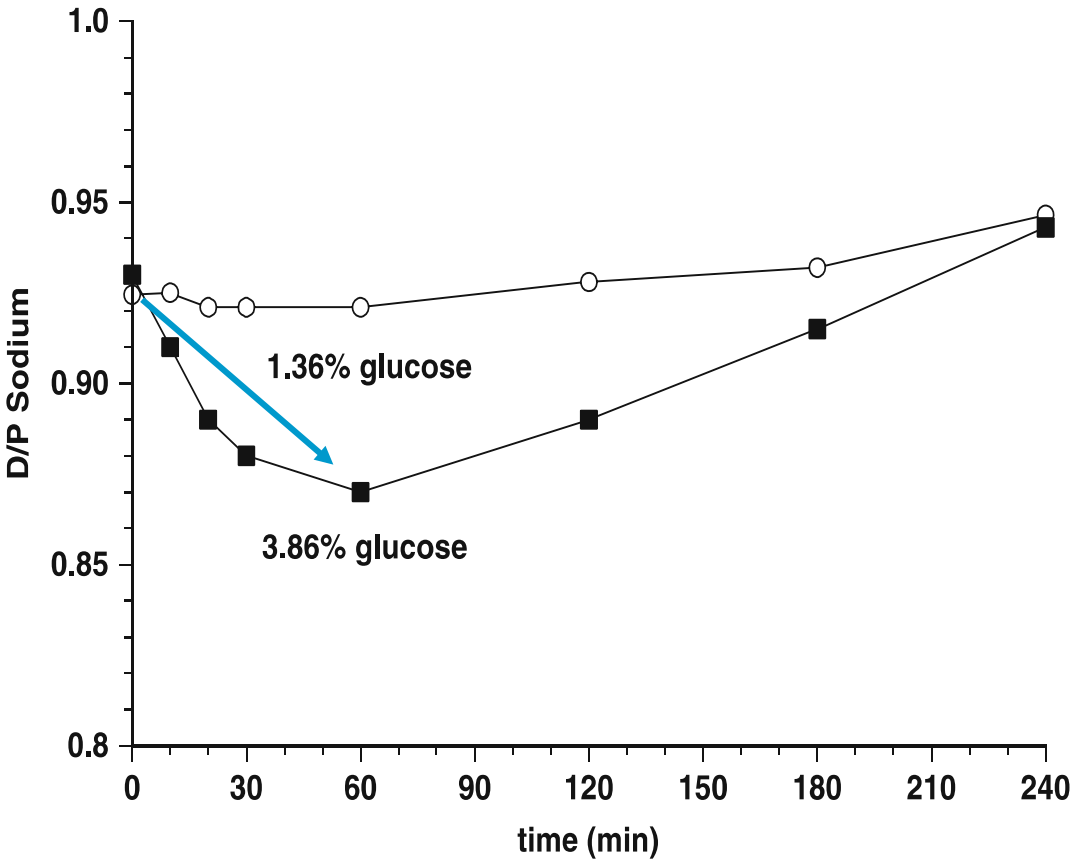


The peritoneal membrane and the 3-pore model



Rippe et al, *Kidney Int* 1991

Free-water transport across the ultrasmall pores explains the sodium sieving or sodium dip

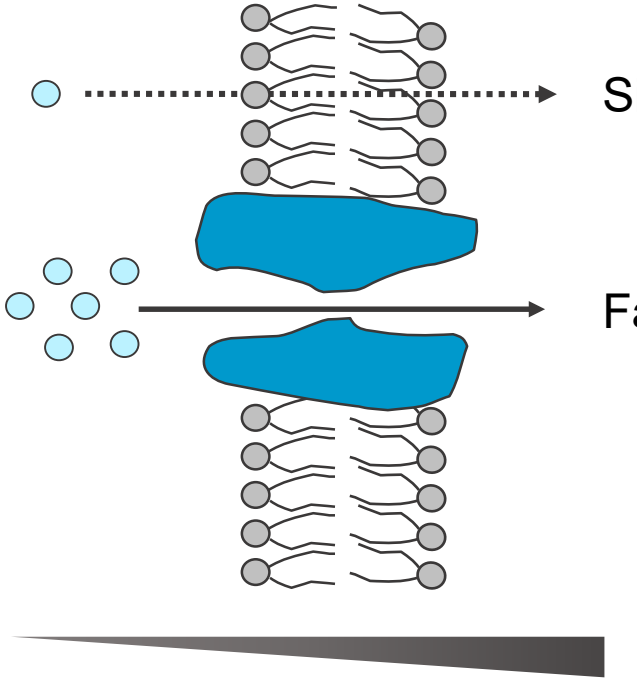


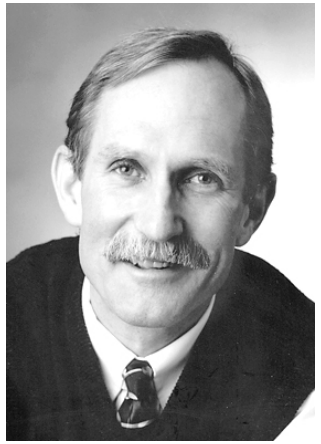
- Rapid decrease in dialysate sodium concentration
  - during the first part (60 min)
  - of a dwell with hypertonic glucose
- Dilution of sodium in the peritoneal fluid by free-water transport across
  - the ultrasmall pores and
  - the ‘whole’ peritoneal membrane

Identity of ‘water-specific channels’

Appearance of Water Channels in *Xenopus* Oocytes Expressing Red Cell CHIP28 Protein

Gregory M. Preston, Tiziana Piazza Carroll, William B. Guggino, Peter Agre*



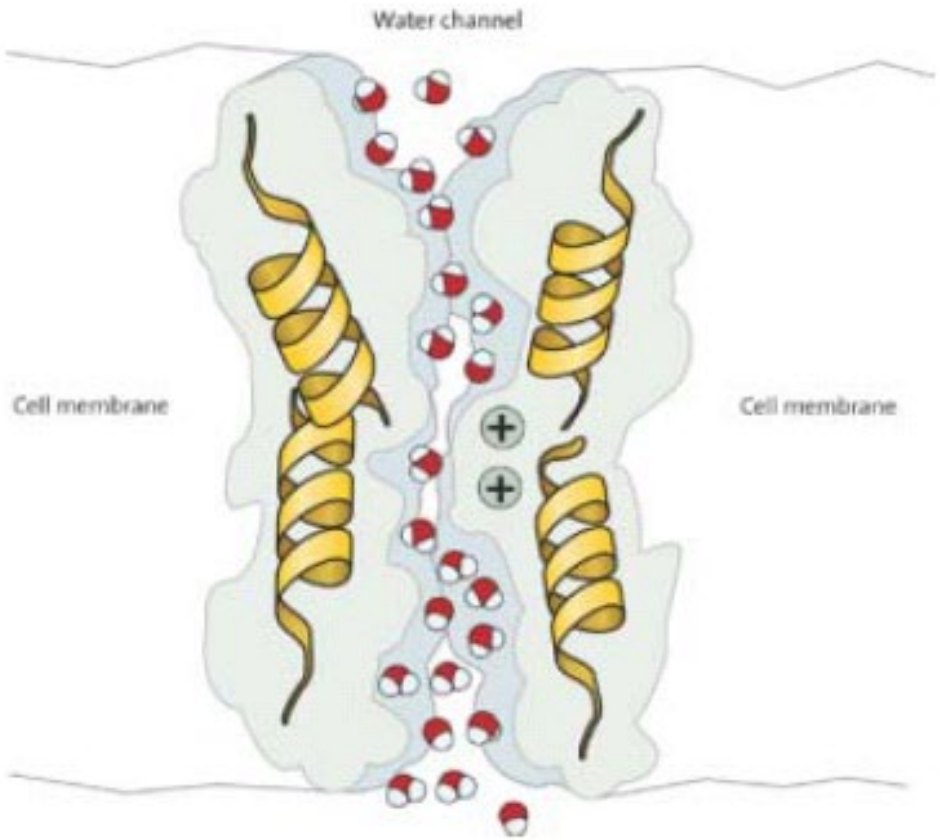


Peter Agre
Nobel Prize in Chemistry, 2003

- Small proteins with properties of water channels
- Facilitate the diffusion of water molecules across biological membranes - called *aquaporins*
- Expressed in RBC and in kidney tubules

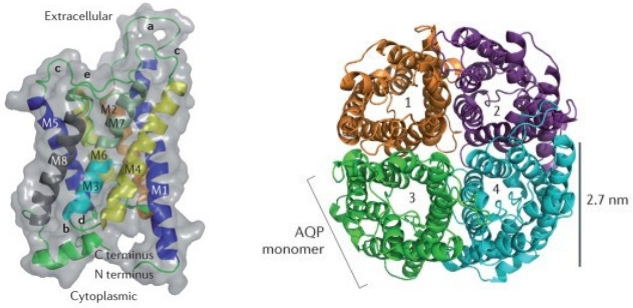
SCIENCE • VOL. 256 • 17 APRIL 1992

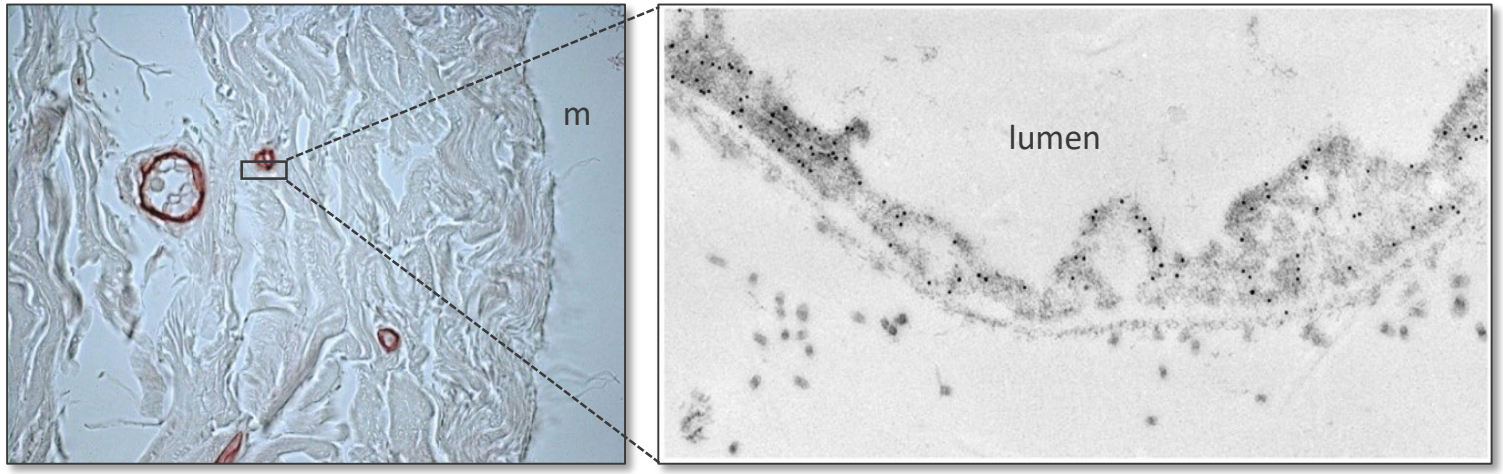
Aquaporin-1 :
The ultrasmall pore

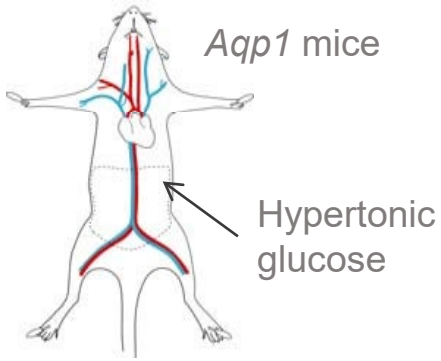


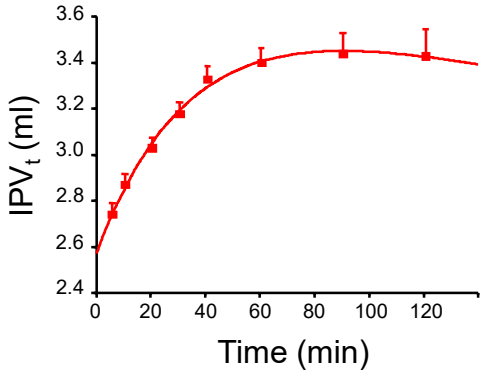
Aquaporin-1 Water Channels in PD

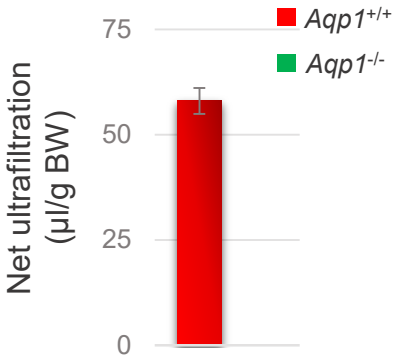
Aquaporin water channels

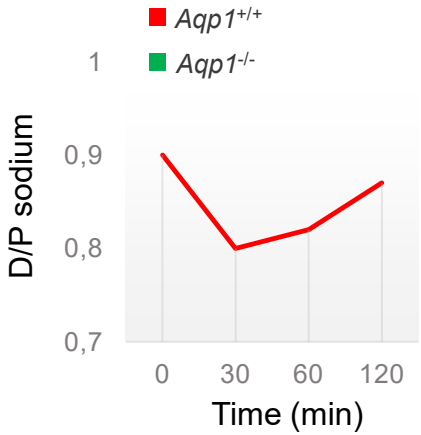








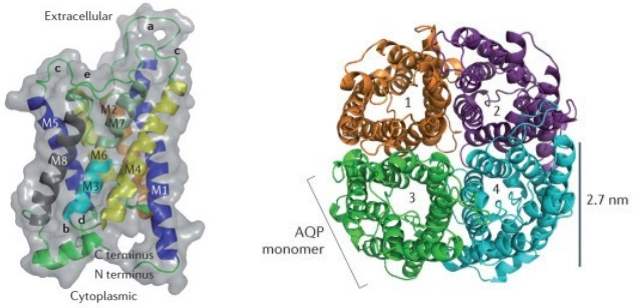


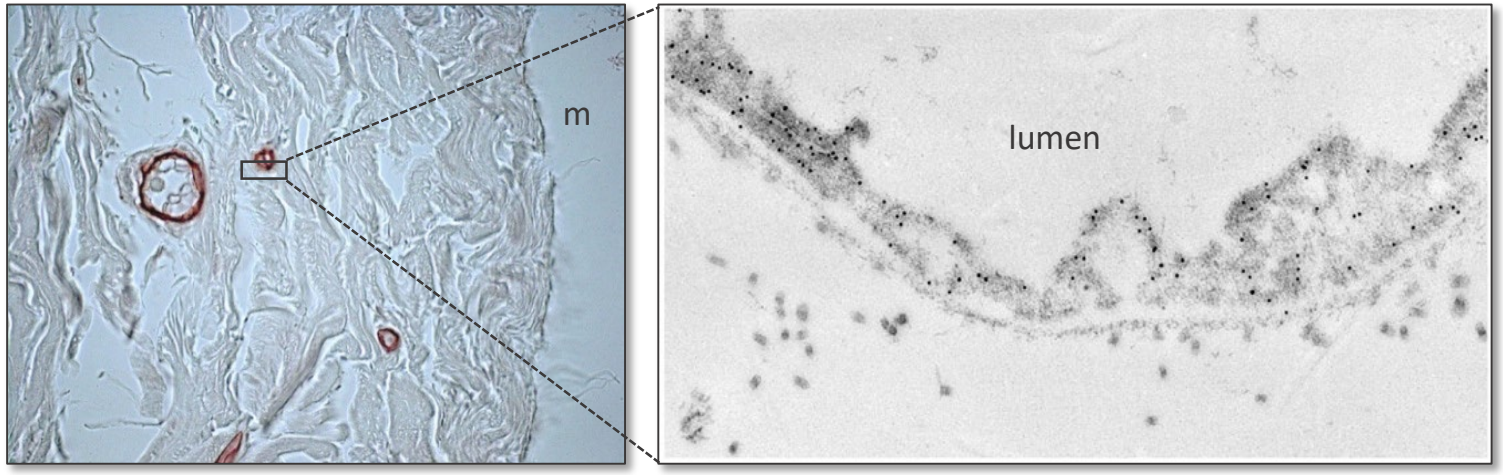


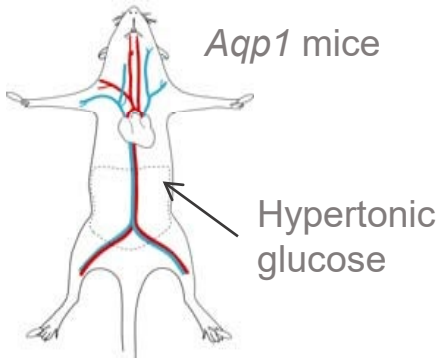
Devuyst et al, *Am J Physiol* 1998 ; Ni et al, *Kidney Int* 2006; Morelle et al, *Am J Physiol Renal Physiol* 2014

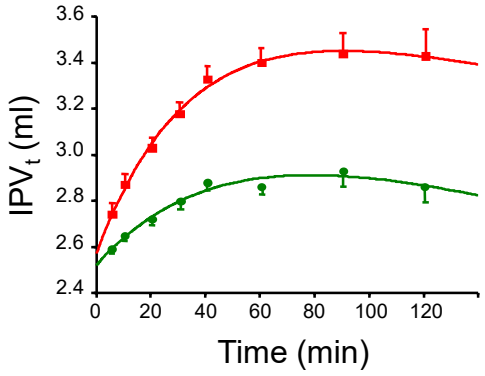
Aquaporin-1 Water Channels in PD

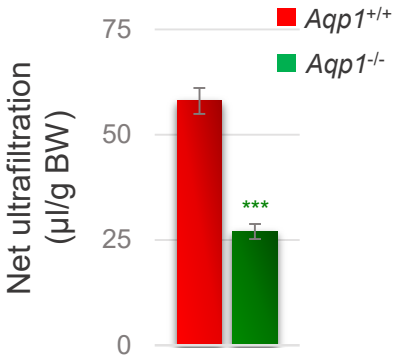
Aquaporin water channels

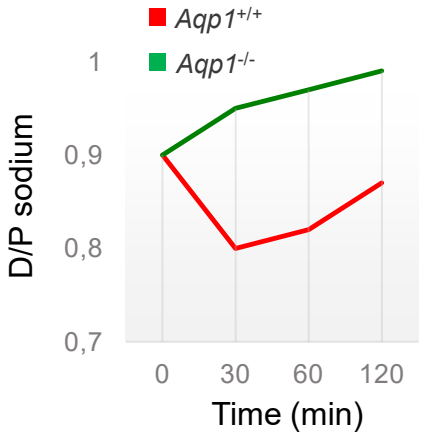












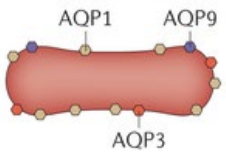
Endothelial AQP1 → 40-50% UF and sodium sieving (glucose)

Devuyst et al, *Am J Physiol* 1998 ; Ni et al, *Kidney Int* 2006; Morelle et al, *Am J Physiol Renal Physiol* 2014

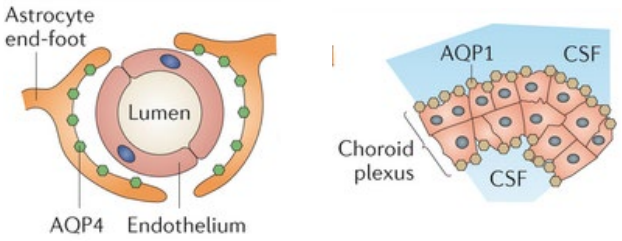
Tissue distribution of mammalian aquaporins

13 AQPs in mammals
AQP0-AQP12

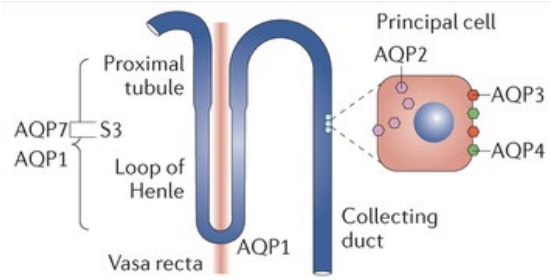
Red blood cells



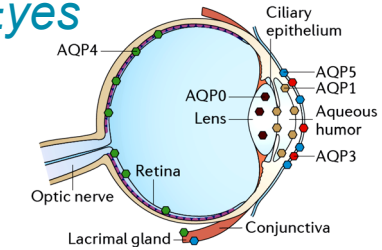
Central nervous system



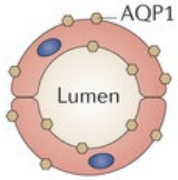
Renal tubule epithelia



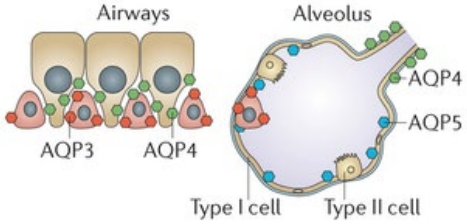
Eyes



Endothelial cells



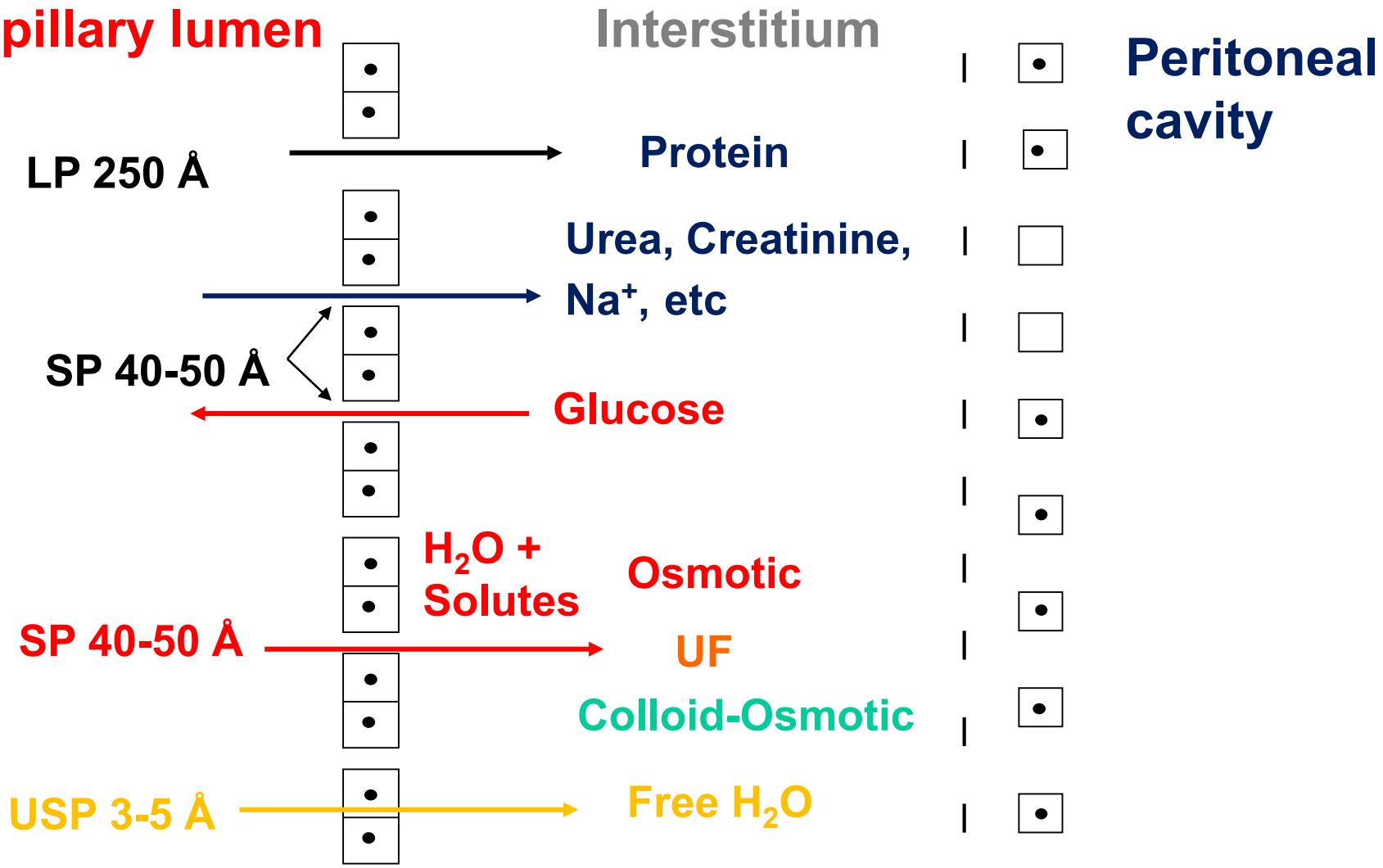
Lungs



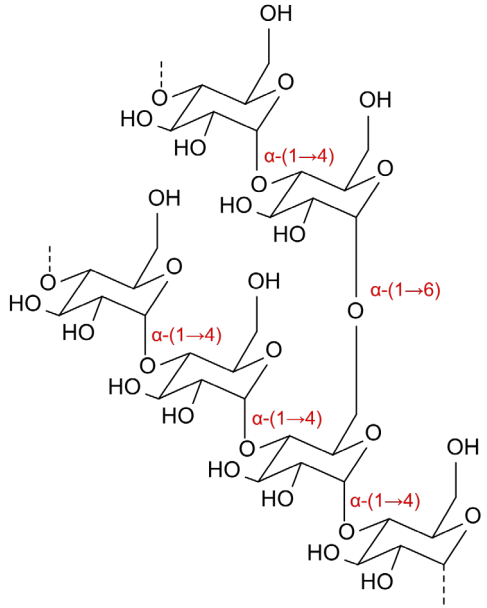
…but also in adipocytes, salivary glands, intestine, skeletal muscle, epidermis

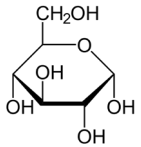
Verkman et al, *Nat Rev Drug Discov* 2014

The three-pore model of peritoneal membrane



Mechanisms of Crystalloid versus Colloid Osmosis across the Peritoneal Membrane





Glucose

- **Critical role for AQP1**
- Small molecule (MW 180 Da, R_H 0.37 nm)
- Diffuses rapidly across membranes, transient effect on UF

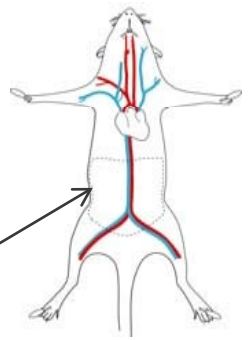
Icodextrin

- Mixture of glucose polymers
- Variable size, incl. large (colloidal) molecules
- Slowly absorbed, long-dwells
- **Role of AQP1?**

Morelle et al, *J Am Soc Nephrol* 2018

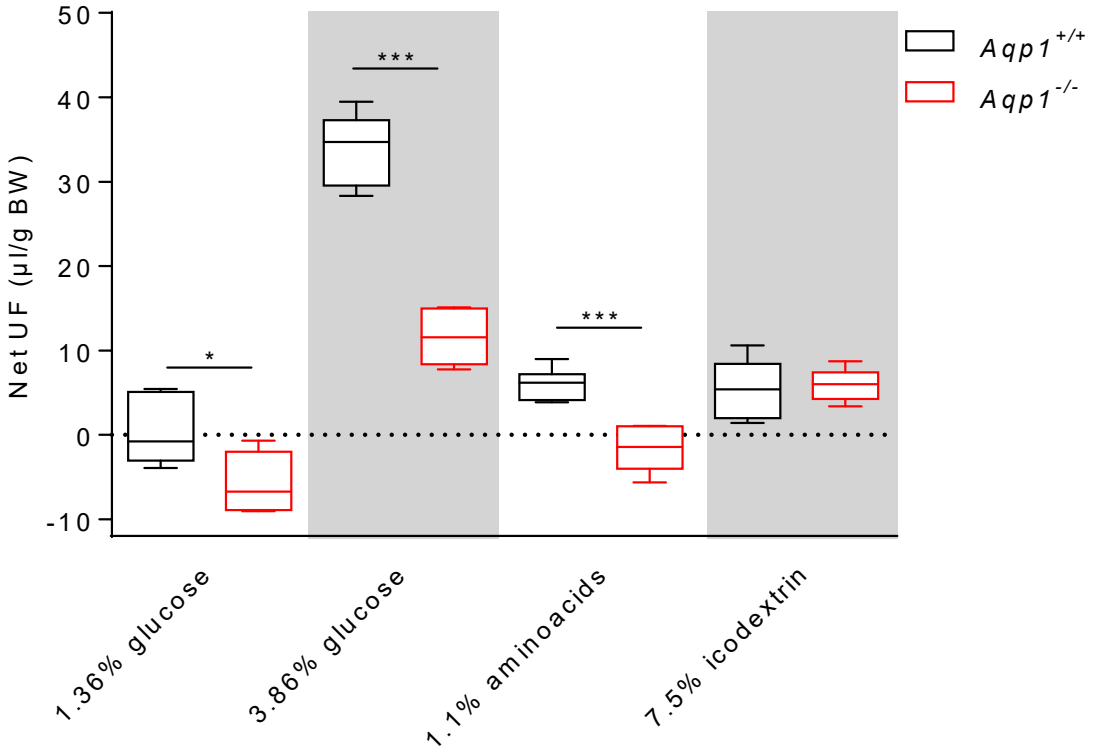
Pathways and mechanisms of icodextrin-induced water flow?

Mouse model of PD



Icodextrin vs. glucose or aminoacids

Aqp1 mice
2-h dwells

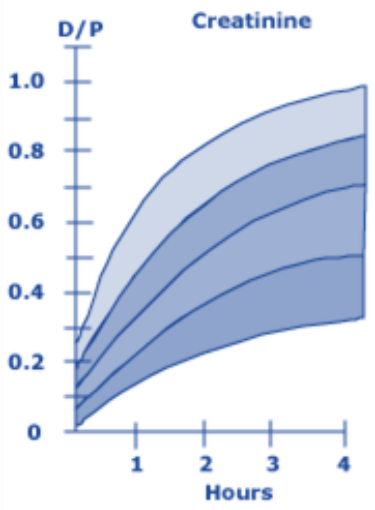


Icodextrin induces water transport independently of water channels, exclusively across small pores (enhanced water and sodium removal)

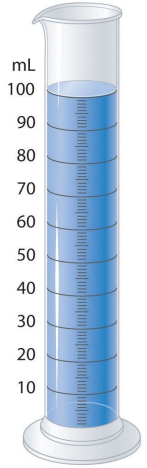
Morelle et al, *J Am Soc Nephrol* 2018

Back to the patient: peritoneal transport testing and expectations from clinicans

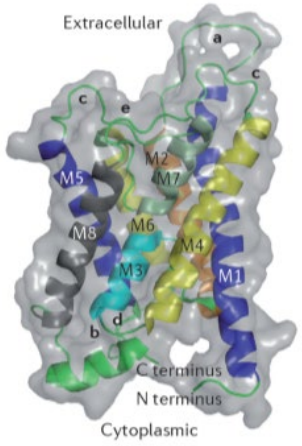
Diffusion rate of small solutes



Water transport (‘ultrafiltration’)



AQP-mediated water transport

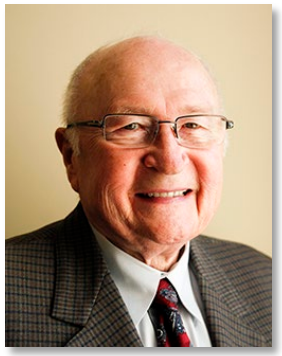


→ Individual transport characteristics of the peritoneal membrane

Morelle et al, *Perit Dial Int* 2021

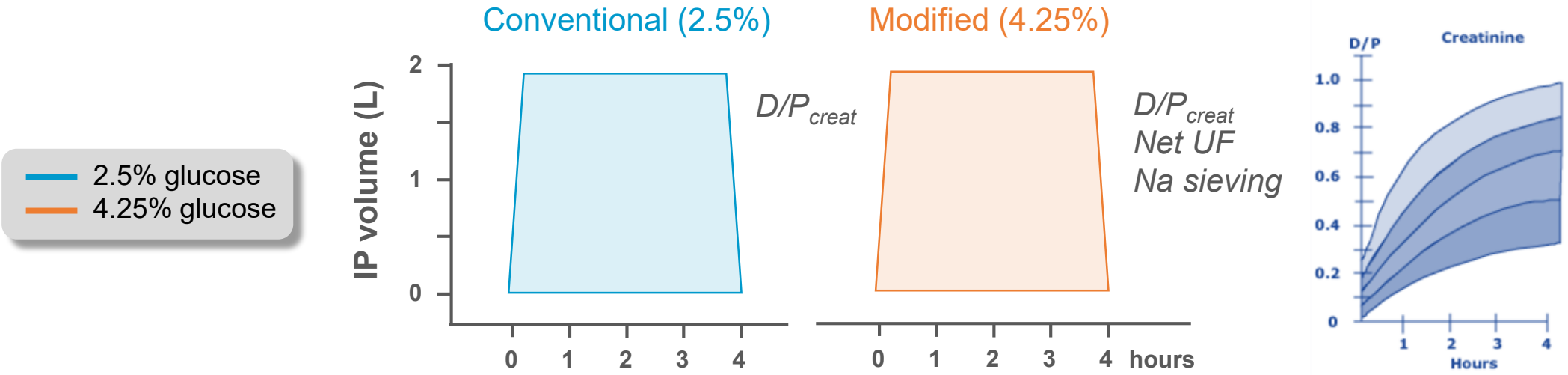
Peritoneal equilibration test (PET)

Dr. Verger
France



Dr. Twardowski
USA

- Standardized 4-h dwell, using 2.5% or 4.25% glucose
- Quantification of the equilibration rate of small solutes across the membrane (D/P_{creat} 4h)
  + net UF and sodium sieving (using hypertonic glucose)
- Safe, easy, accurate, highly reproducible



Verger et al, et al, *Front Perit Dial* 1986; Twardowski et al, *Perit Dial Bull*, 1987

GdP Dialisi Peritonale

sin reni Società Italiana Nefrologia

Dr. Vincenzo La Milia

THOROUGH CRITICAL APPRAISAL

JNEPHROL 2010; 23(06): 633-647

www.sin-italy.org/jnonline – www.jnephrol.com

Peritoneal transport testing

Vincenzo La Milia

Nephrology and Dialysis Department, A. Manzoni Hospital, Lecco - Italy

BEST PRACTICE

JNEPHROL 2013; 26(Suppl 21): S120-S139

DOI: 10.5301/JN.2013.11637

Functional assessment of the peritoneal membrane

Vincenzo La Milia[1]

Reviewers: Giovambattista Virga[2]**, Giampaolo Amici**[3]**, Silvio Bertoli**[4]**, Giovanni Cancarini**[5]

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PERITONEAL EQUILIBRATION TEST REFERENCE VALUES USING A 3.86% GLUCOSE SOLUTION DURING THE FIRST YEAR OF PERITONEAL DIALYSIS: RESULTS OF A MULTICENTER STUDY OF A LARGE PATIENT POPULATION

Vincenzo La Milia,[1] Gianfranca Cabiddu,[2] Giovambattista Virga,[3] Valerio Vizzardi,[4] Anna Giuliani,[5] Viviana Finato,[6] Mariano Feriani,[7] Armando Filippini,[8] Loris Neri,[9] Lucia Lisi,[10] on behalf of the Ultrafiltration Failure Assessment (UFFA) Study* of the Italian Society of Nephrology Peritoneal Dialysis Study Group

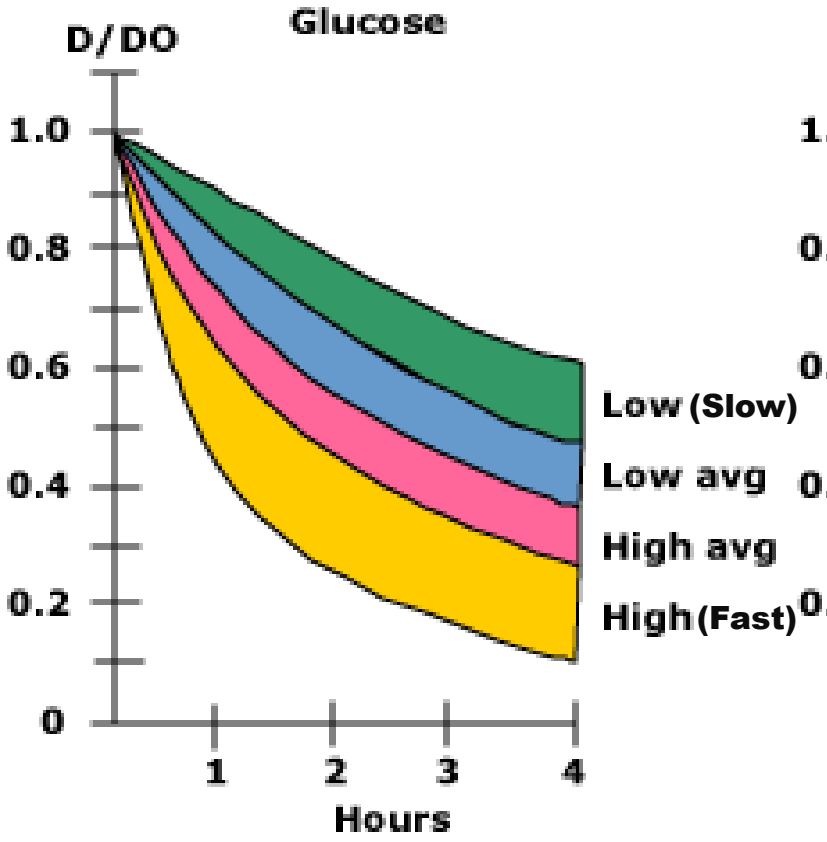
Classification of PD Patients into Transport Classes Based on D/P_{Creat} Values

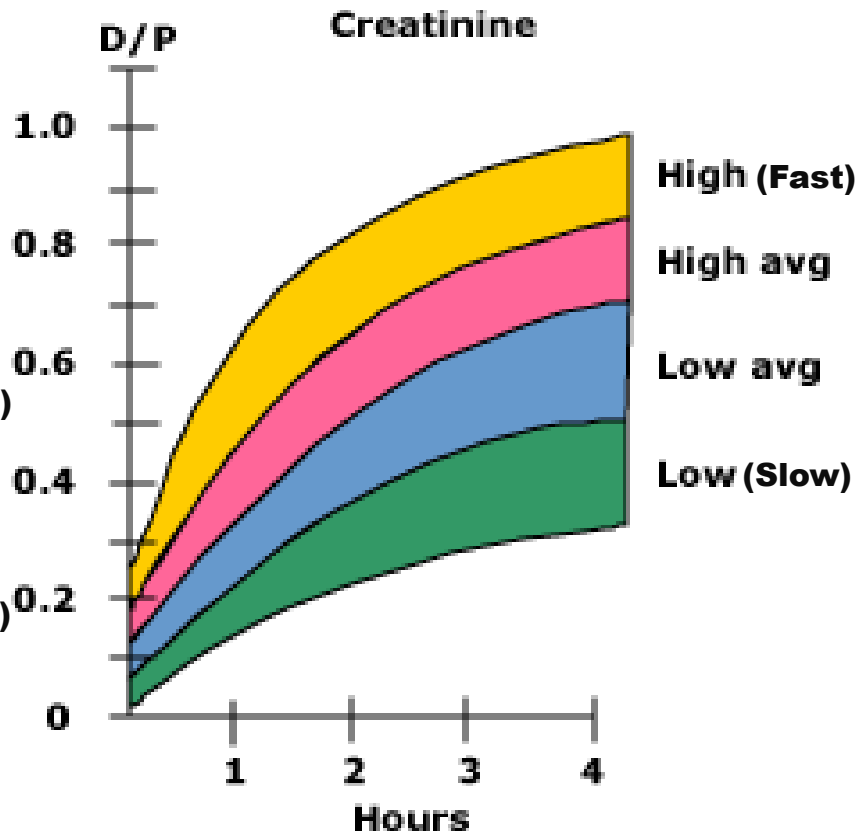
Transport class	D/P_{Creat}	Number of patients
Fast	>0.84	107
Average	0.62–0.84	523
Slow	<0.62	115
Overall	—	745

Fast = D/P_{Creat}>mean +1 SD; Average = D/P_{Creat} between the mean −1 SD and the mean +1 SD; Slow = D/P_{Creat}<mean −1 SD. PD = peritoneal dialysis; D/P_{Creat} = ratio of dialysate to plasma creatinine; SD = standard deviation.

The standard PET

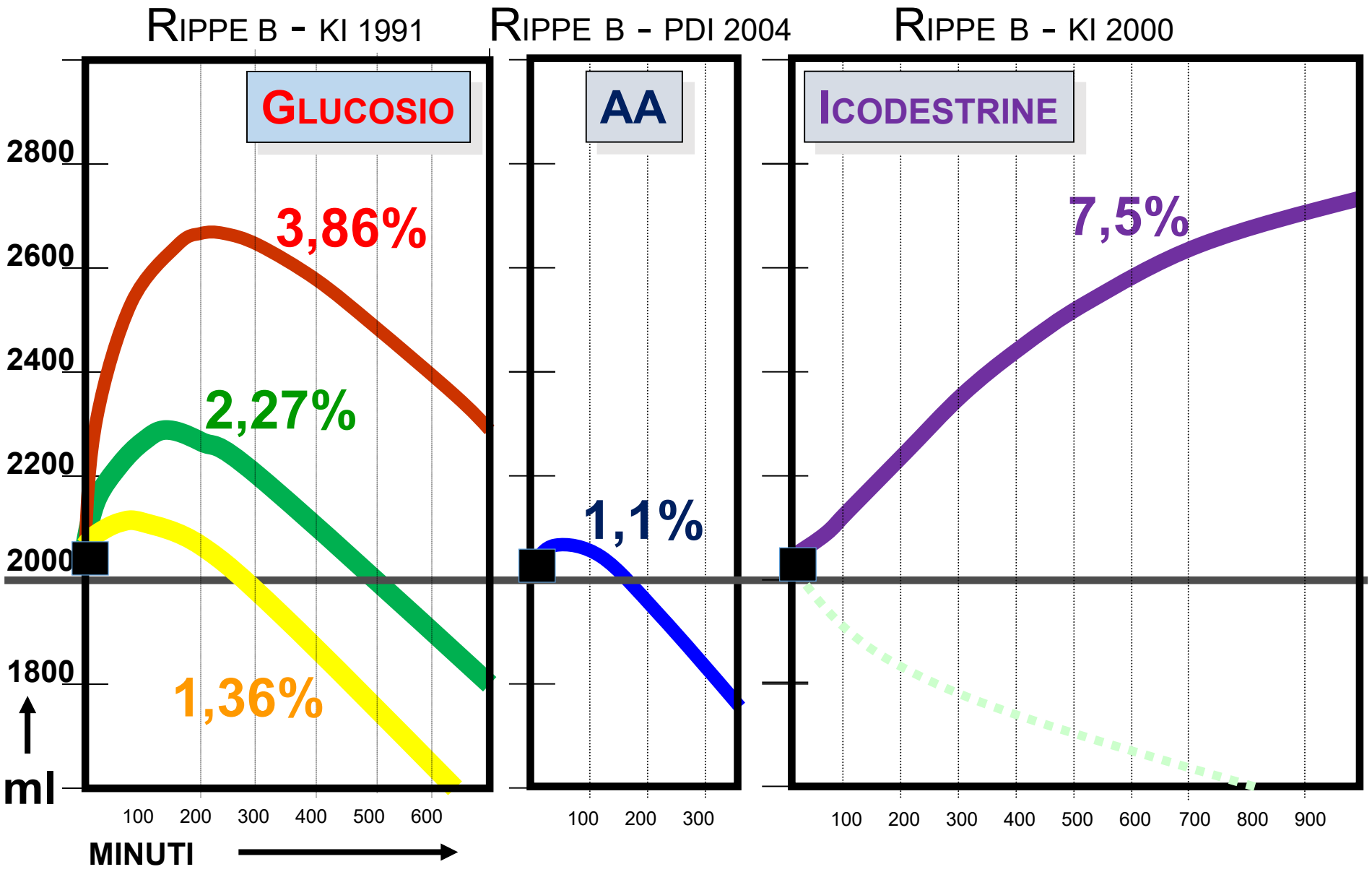
Classification of transport status



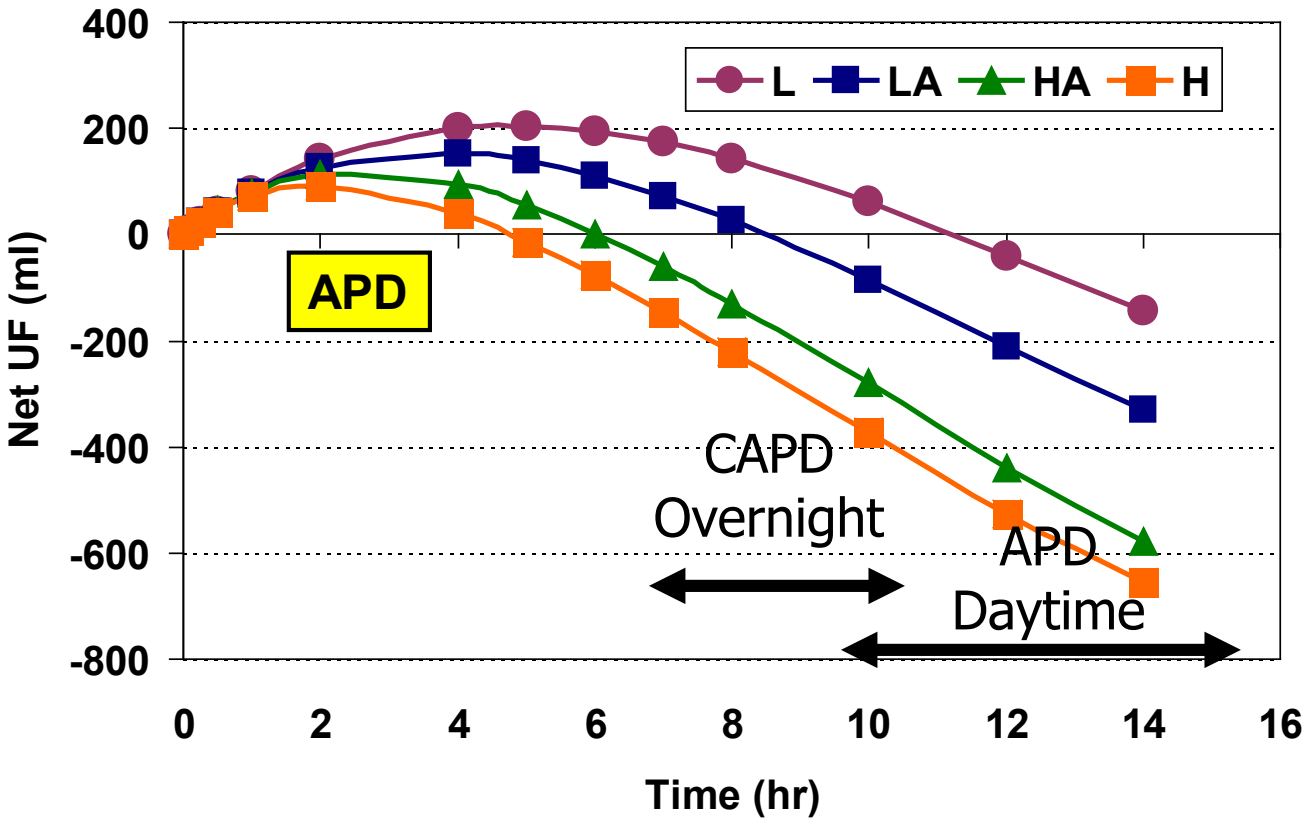


(Twardowski ZJ, et al. Blood Purif 1989)

DURATA DELLA SOSTA - CONCENTRAZIONI



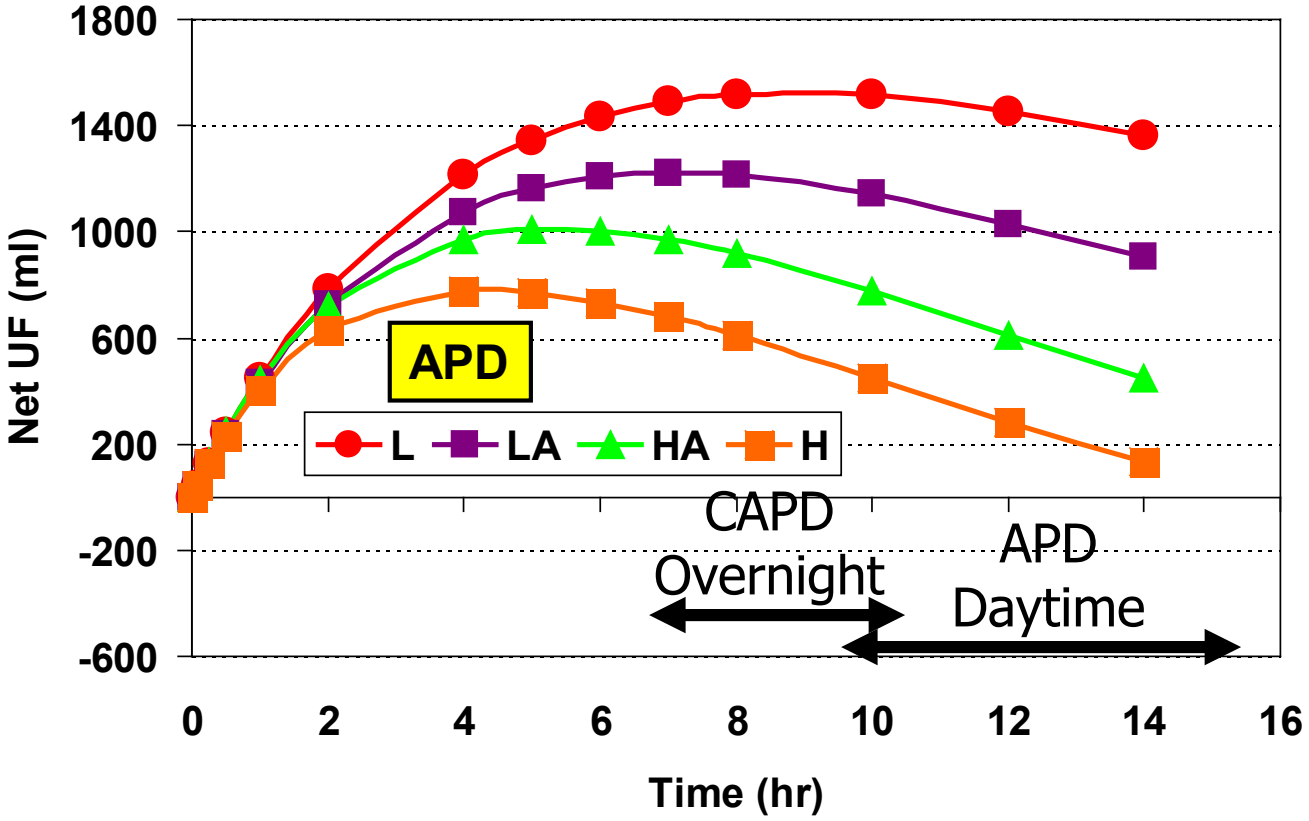
UF Profile with *1.5%* dextrose



Mujais S, et al. *Kidney Int*. Volume 62: s81, S17-S22, 2002

rr

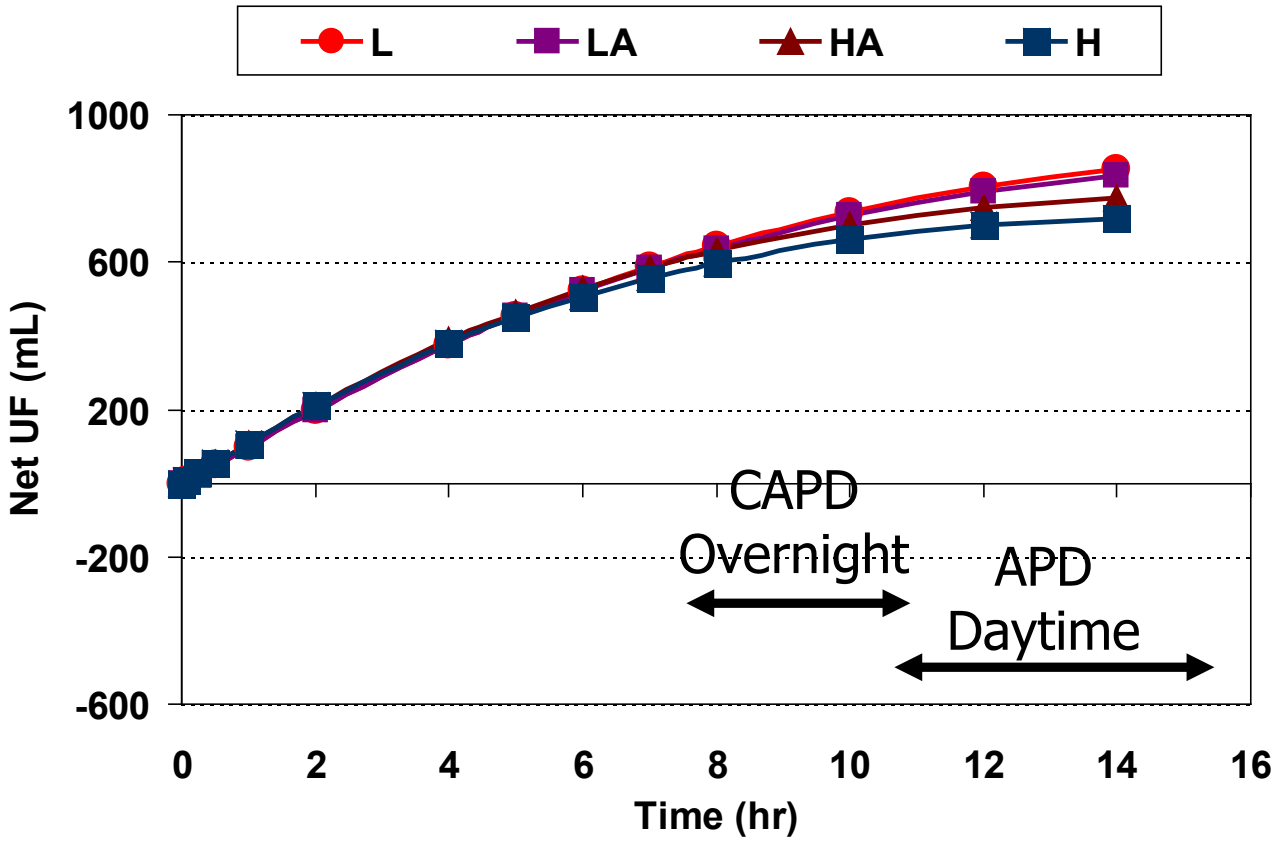
UF Profile with *4.25%* dextrose



Mujais S, et al. *Kidney Int*. Volume 62: s81, S17-S22, 2002

rr

UF Profile with Icodextrin



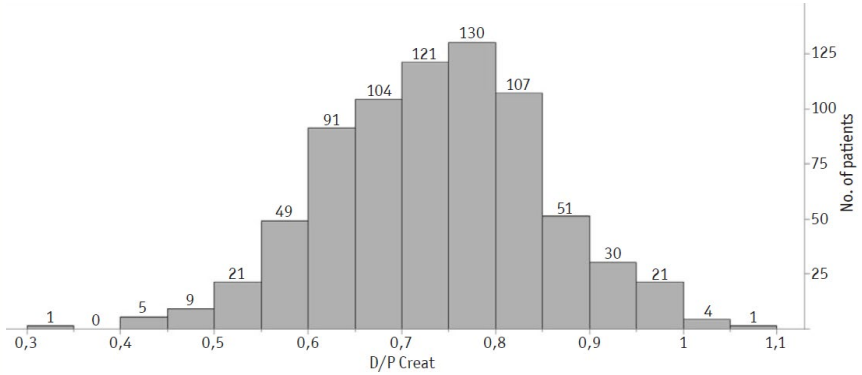
Mujais S, et al. *Kidney Int*. Volume 62: s81, S17-S22, 2002

rr

Why evaluation of membrane function matters

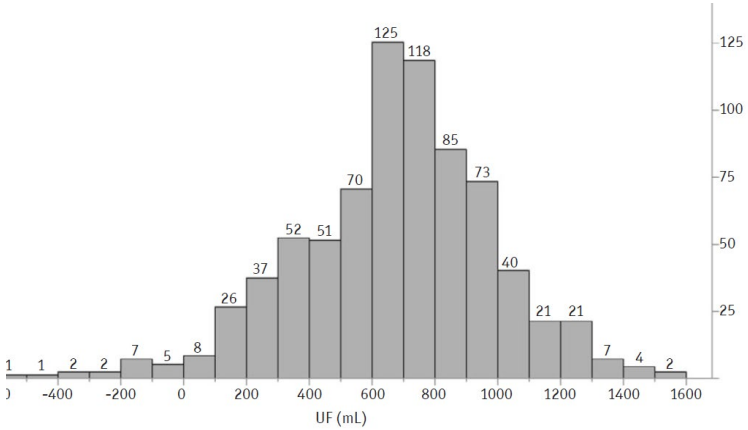
758 incident PD patients with 4.25% dextrose-based 4-h PET at PD start, Italy

PSTR



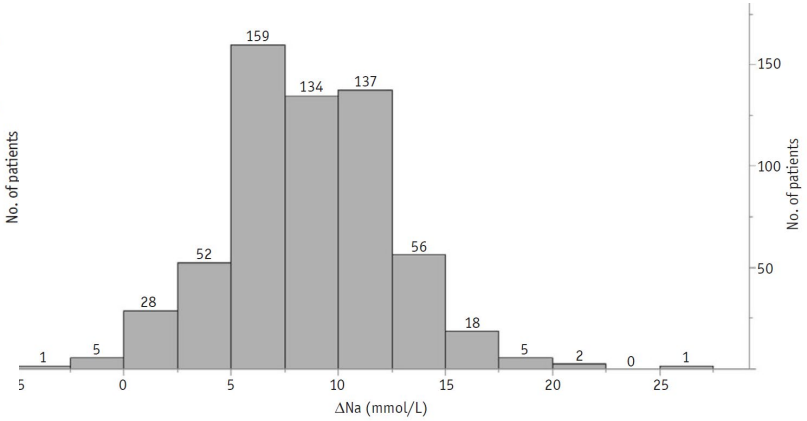
0.3 to >0.9

Net UF



-600 to +1500 ml

Dip Na



-3 to +20 mEq/l

Significant variability in membrane characteristics between individuals, already at PD initiation

- Associated with outcome
- Clinical impact on fluid removal and dialysis prescription

La Milia et al, *Perit Dial Int* 2017

PERITONEAL DIALYSIS INTERNATIONAL

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ISPD recommendations for the evaluation of peritoneal membrane dysfunction in adults: Classification, measurement, interpretation and rationale for intervention

Johann Morelle[1], Joanna Stachowska-Pietka[2], Carl Öberg[3], Liliana Gadola[4], Vincenzo La Milia[5], Zanzhe Yu[6], Mark Lambie[7], Rajnish Mehrotra[8], Javier de Arteaga[9] and Simon Davies[7]

https://journals.sagepub.com/doi/pdf/10.1177/0896860820982218

Membrane dysfunction: definition

Importance of UF/fluid balance

Membrane that fails to achieve sufficient UF
to maintain adequate fluid status
and/or

Low UF capacity: net UF from a 4-h PET <400 ml (3.86% glucose)
or <100 ml (2.27% glucose) (GRADE 1B)

! Rule out catheter dysfunction and other mechanical problems

Membrane dysfunction: classification

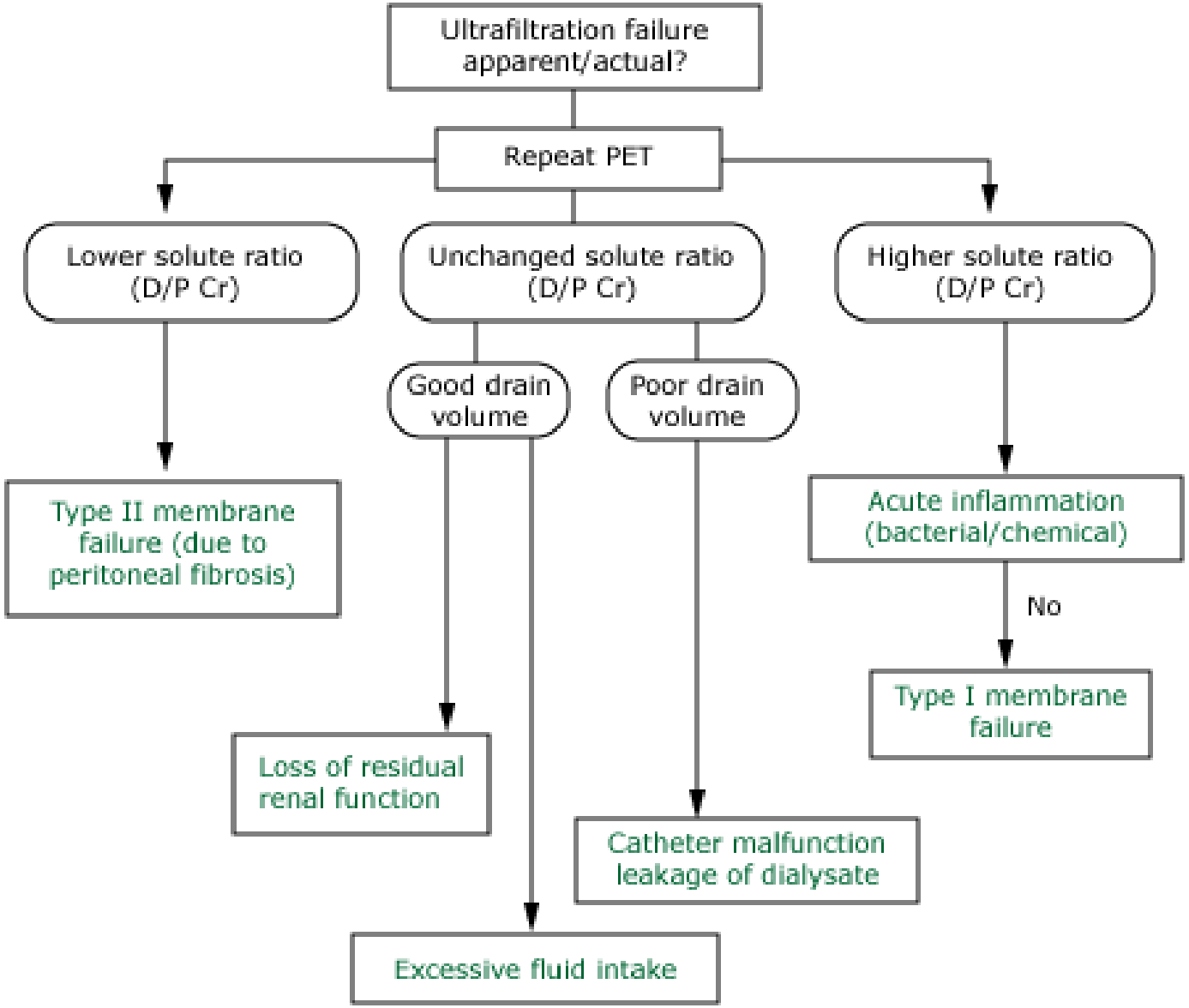
Insufficient UF to maintain fluid balance

1. **Fast peritoneal solute transfer rate (PSTR)**
   Rapid diffusion of small solutes

2. **Acquired membrane insufficiency**
   Membrane becomes less effective over time

3. **Poor intrinsic ultrafiltration**
   Low UF capacity from the start of PD

Pathophysiology – Risk evaluation – Management



(Twardowski ZJ, et al ASAIO Trans 1990)

Prescrizione della tecnica in base al PET

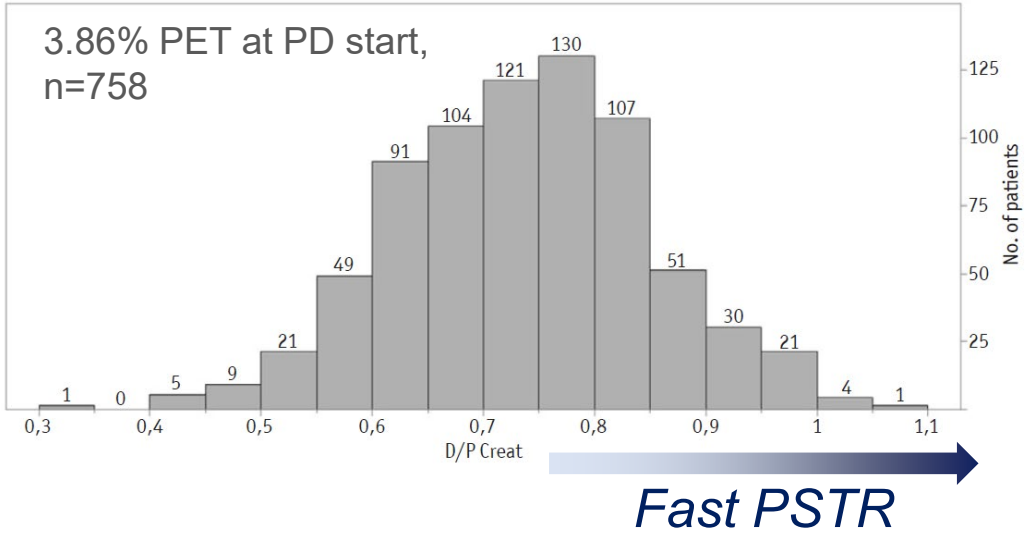
Rapidi (H) Trasportatori → APD

Medio Rapidi Trasportatori (H-A) → CAPD o CCPD1

Medio Lenti (L-A) Trasportatori → CAPD o CCPD2

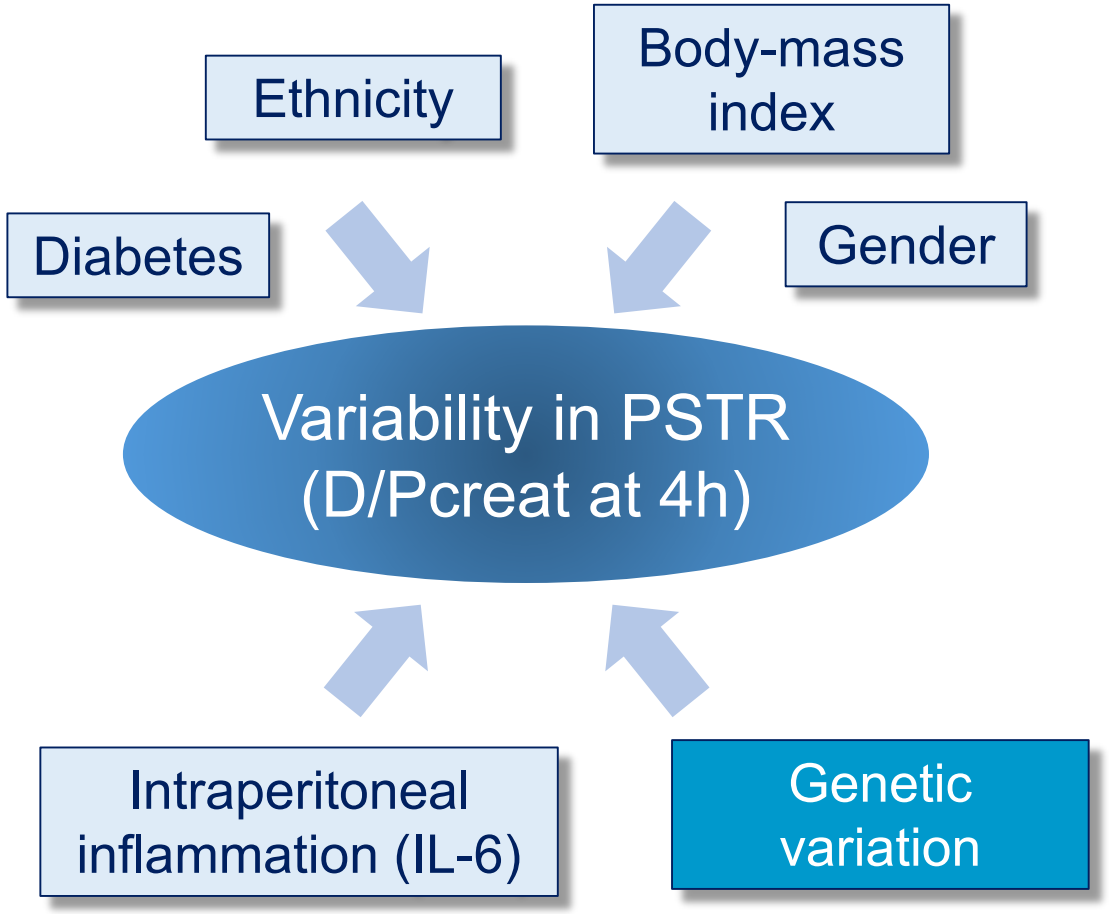
Lenti (L) Trasporatori → high-dose CAPD (HD)

1. Fast peritoneal solute transfer rate (PSTR)



Fast PSTR (high D/Pcreat at 4h)

- Rapid absorption of glucose
- Early dissipation of osmotic gradient and low UF with glucose
- At risk for fluid overload



La Milia et al, *Perit Dial Int* 2017; Lambie et al, *J Am Soc Nephrol* 2013; Gillerot et al, Kidney Int 2005; Siddique et al, *Perit Dial Int* 2015

Bio-PD Study:

First genome-wide association study in PD patients → Gene variants associated with peritoneal transport?

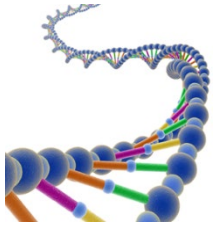
Genowide association study

- Looked for potential associations between gene variants along the entire genome and baseline D/Pcreat at 4h
- 2850 patients, 69 centers, 6 countries

Principal investigator: R. Mehrotra,
University of Washington, Seattle, USA

NIH

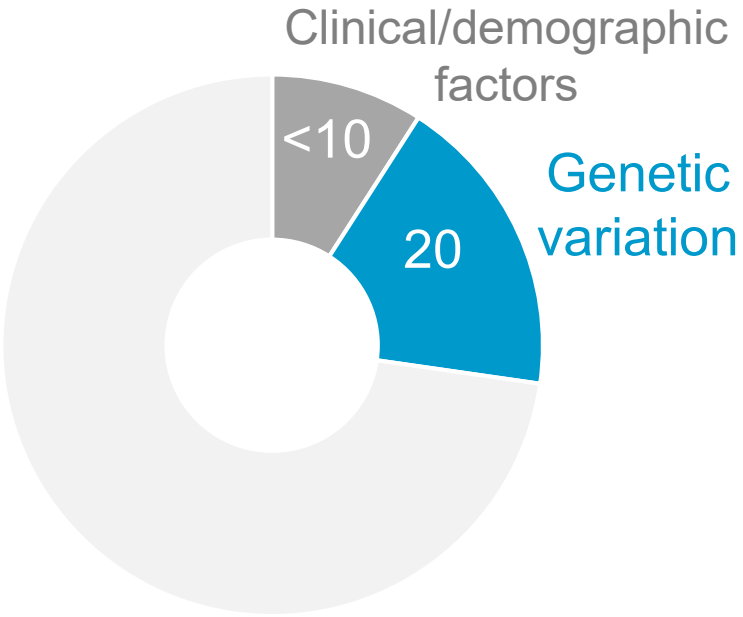
PDOPPS
Peritoneal Dialysis Outcomes and Practice Patterns Study



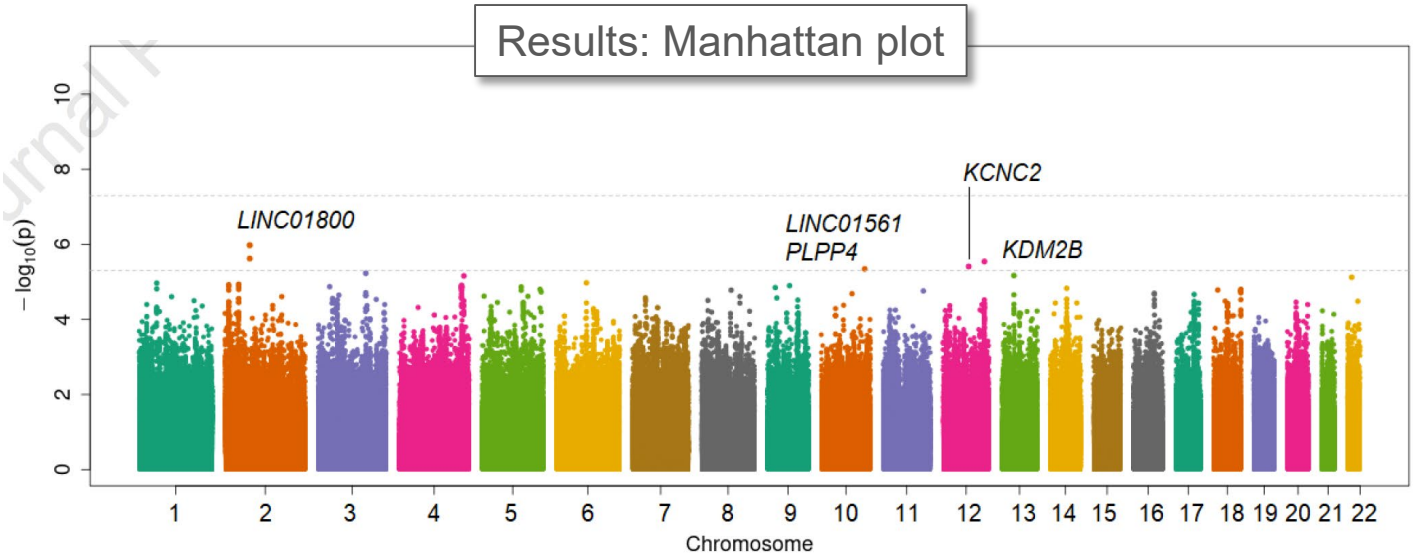
Mehrotra et al, *Kidney Int* 2021

Bio-PD study: main results

Heritability of PSTR ~20%



Loci with suggestive associations with PSTR



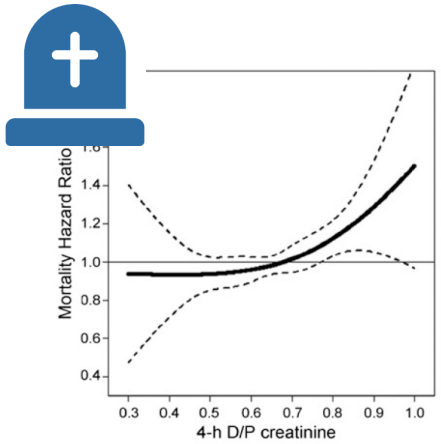
→ *Strong influence of genetic variation on peritoneal solute transfer*

Mehrotra et al, *Kidney Int* 2021

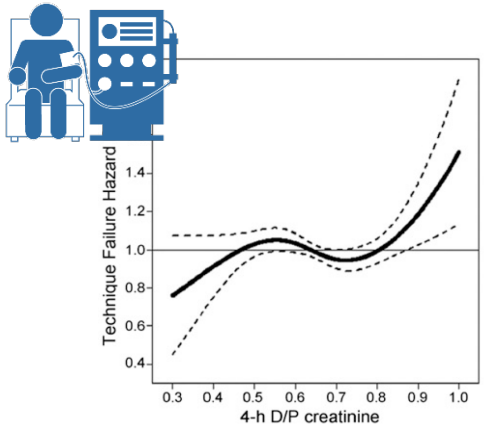
Peritoneal Equilibration Test and Patient Outcomes

Contemporary cohort 2007-2011
10,142 patients on PD from 764 facilities in the USA
Data adjusted for multiple confounders

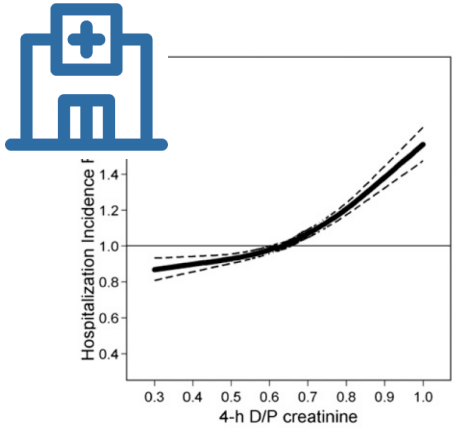
All-cause mortality



Technique failure



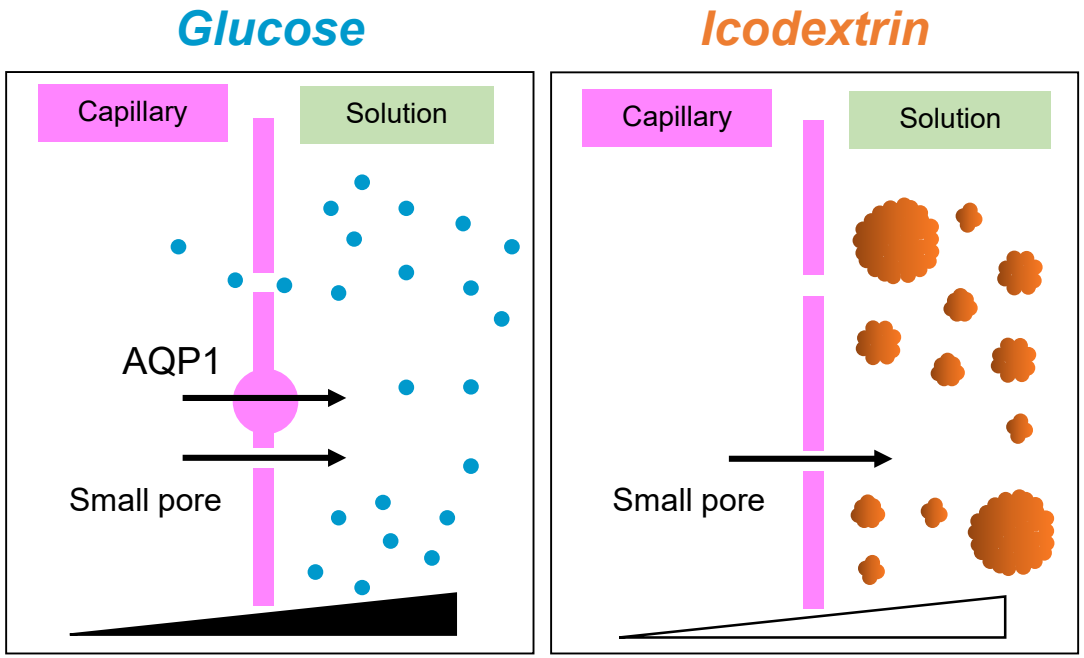
Hospitalization

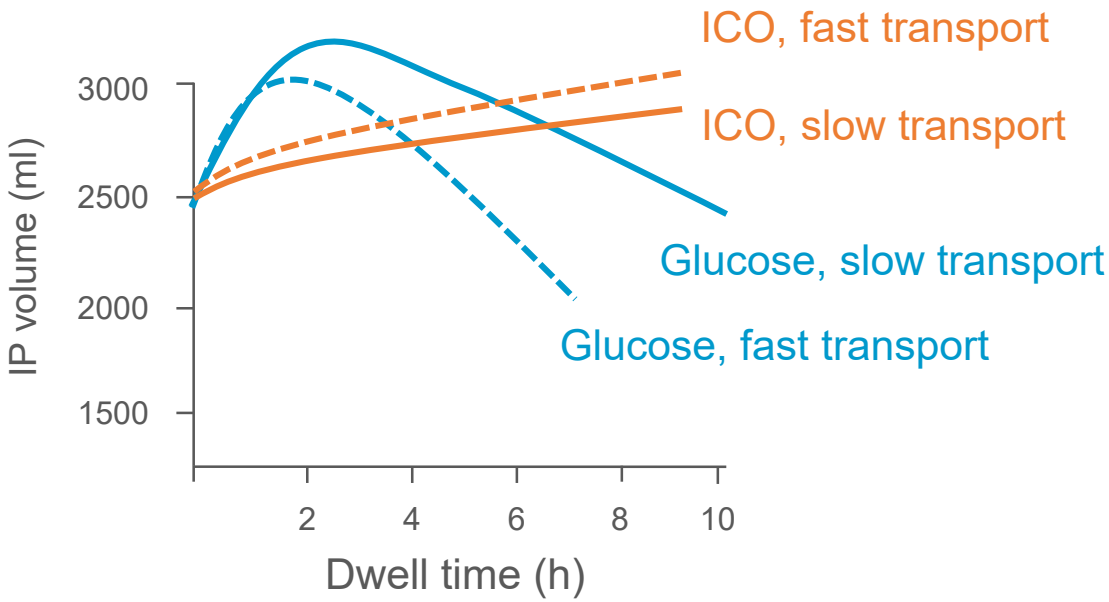


Strong and continuous association between PSTR (D/P_{creat} at 4h) and outcome

Mehrotra et al, *Clin J Am Soc Nephrol* 2015

Glucose *vs.* icodextrin in patients with fast PSTR





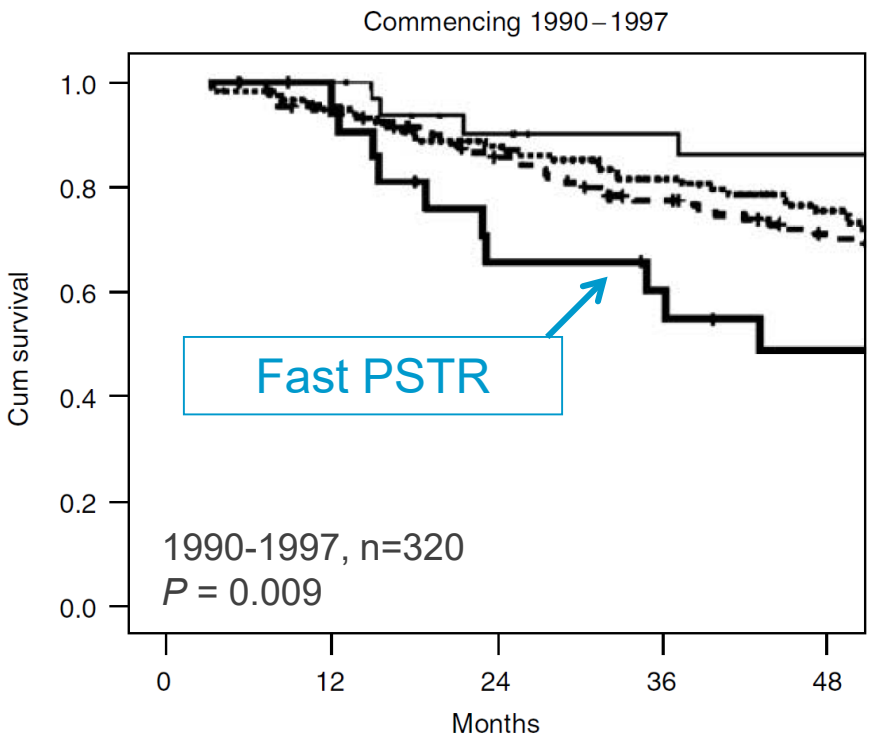
Glucose → transient effect on UF, especially in patients with fast PSTR

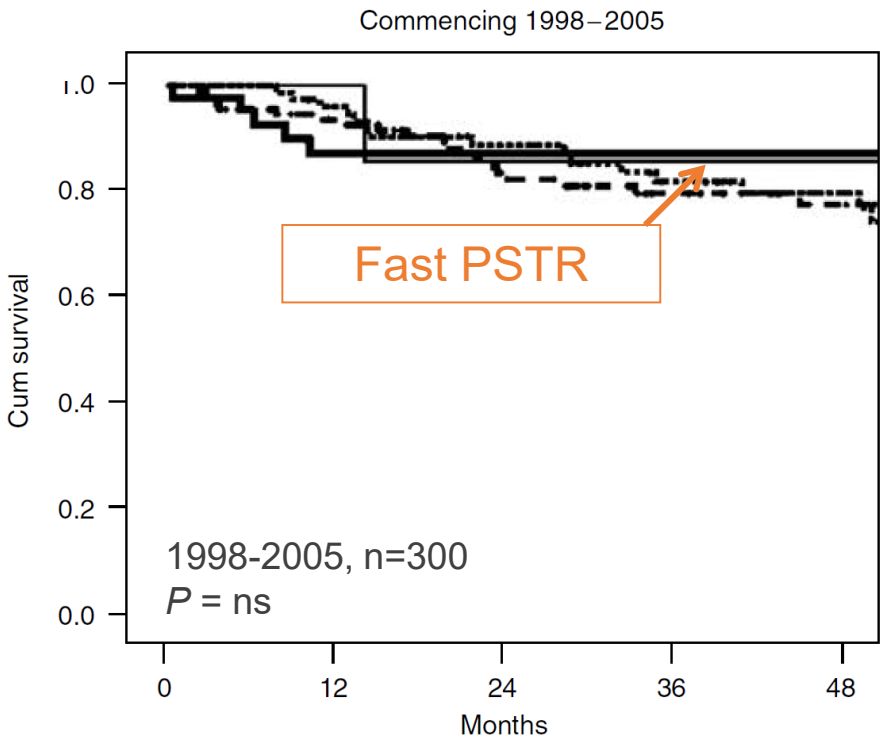
Icodextrin → slower but sustained UF, very convenient to avoid absorption, i.e. in fast PSTR

Wilkie, *Clin J Am Soc Nephrol* 2016; Davies et al, *J Am Soc Nephrol* 2003; Paniagua et al, *Perit Dial Int* 2009; Cho et al, Nephrol Dial Transplant 2013; Cho et al, *Cochrane* 2014; Htay, Johnson…Cho, Cochrane 2018; Morelle et al, *J Am Soc Nephrol* 2018

Strategies to manage patients with fast PSTR

Survival on PD according to transport category at the start of treatment (Stoke experience)





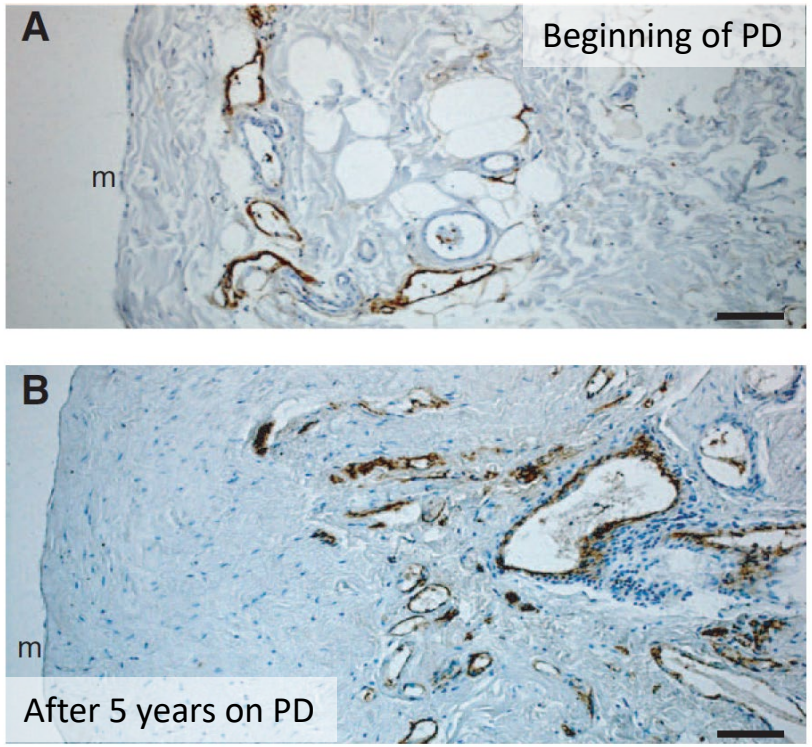
CAPD only
Glucose as the only osmotic agent

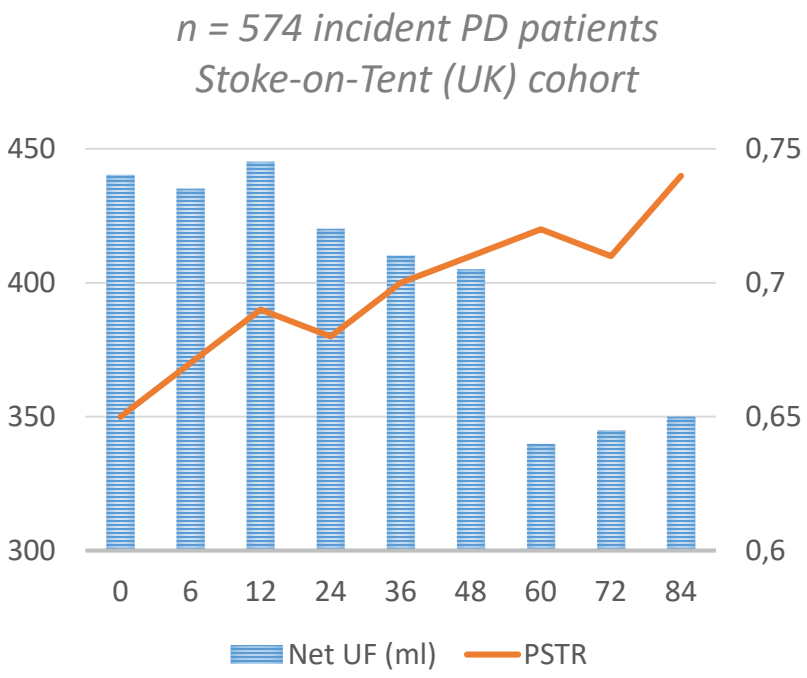
Short glucose dwells (i.e. APD)
Use of **icodextrin**

Davies, *Kidney Int* 2006

2. Acquired membrane insufficiency

Structural and functional alterations over time on PD

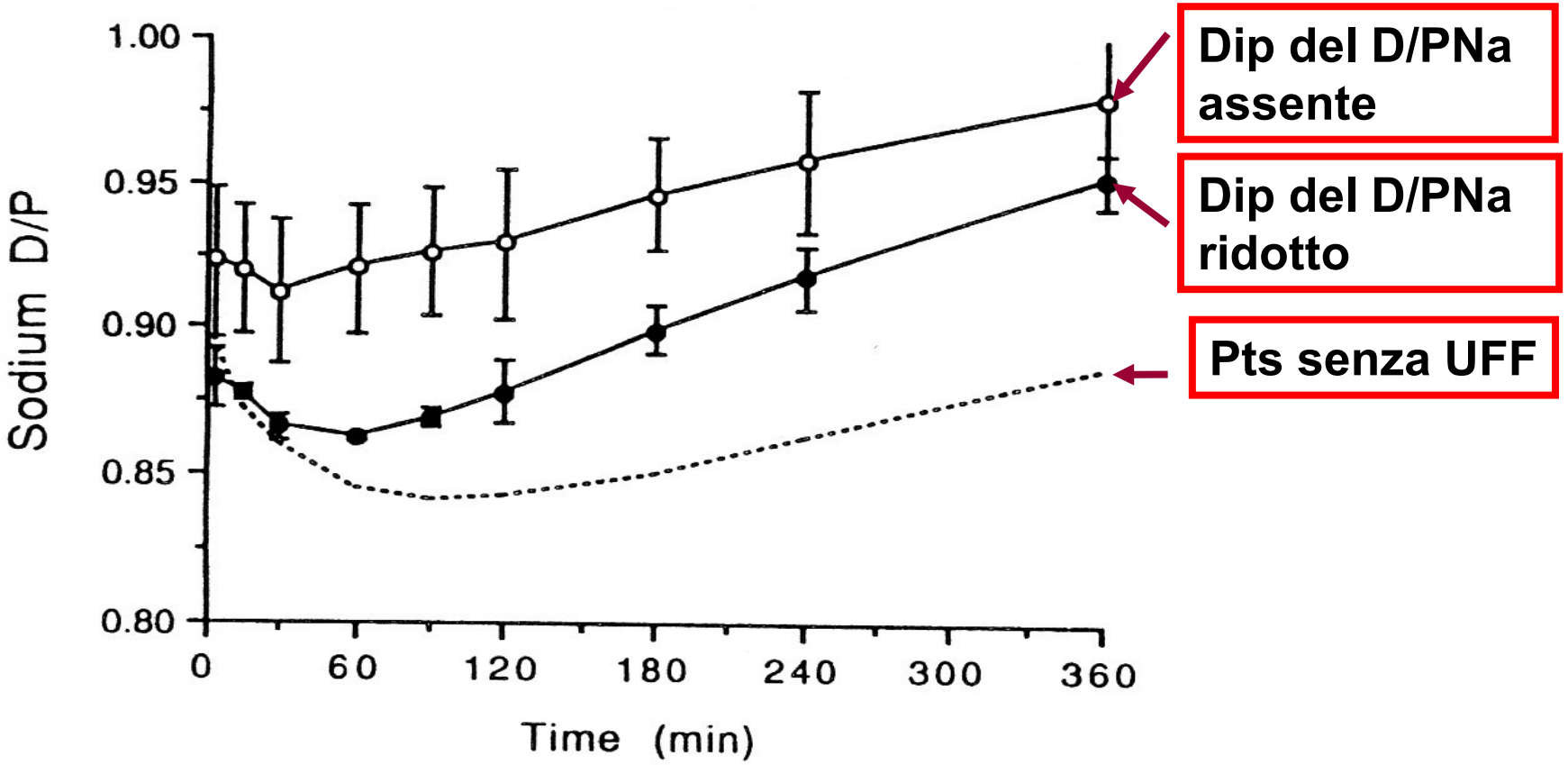




Progressive increase in PSTR
Loss of UF capacity

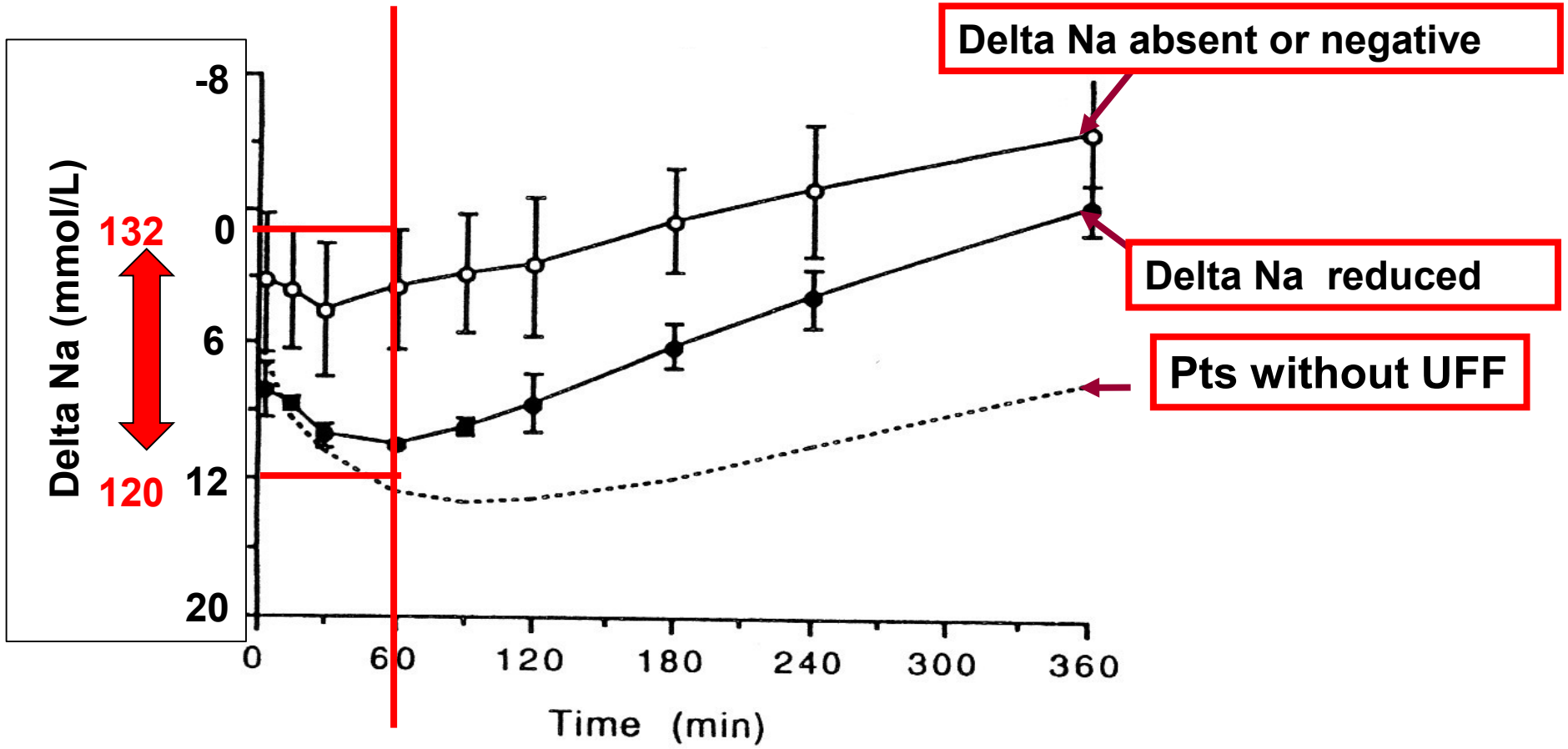
Devuyst, *J Am Soc Nephrol* 2010; Davies, *J Am Soc Nephrol* 2004

D/P Na in pazienti con deficit di ultrafiltrazione

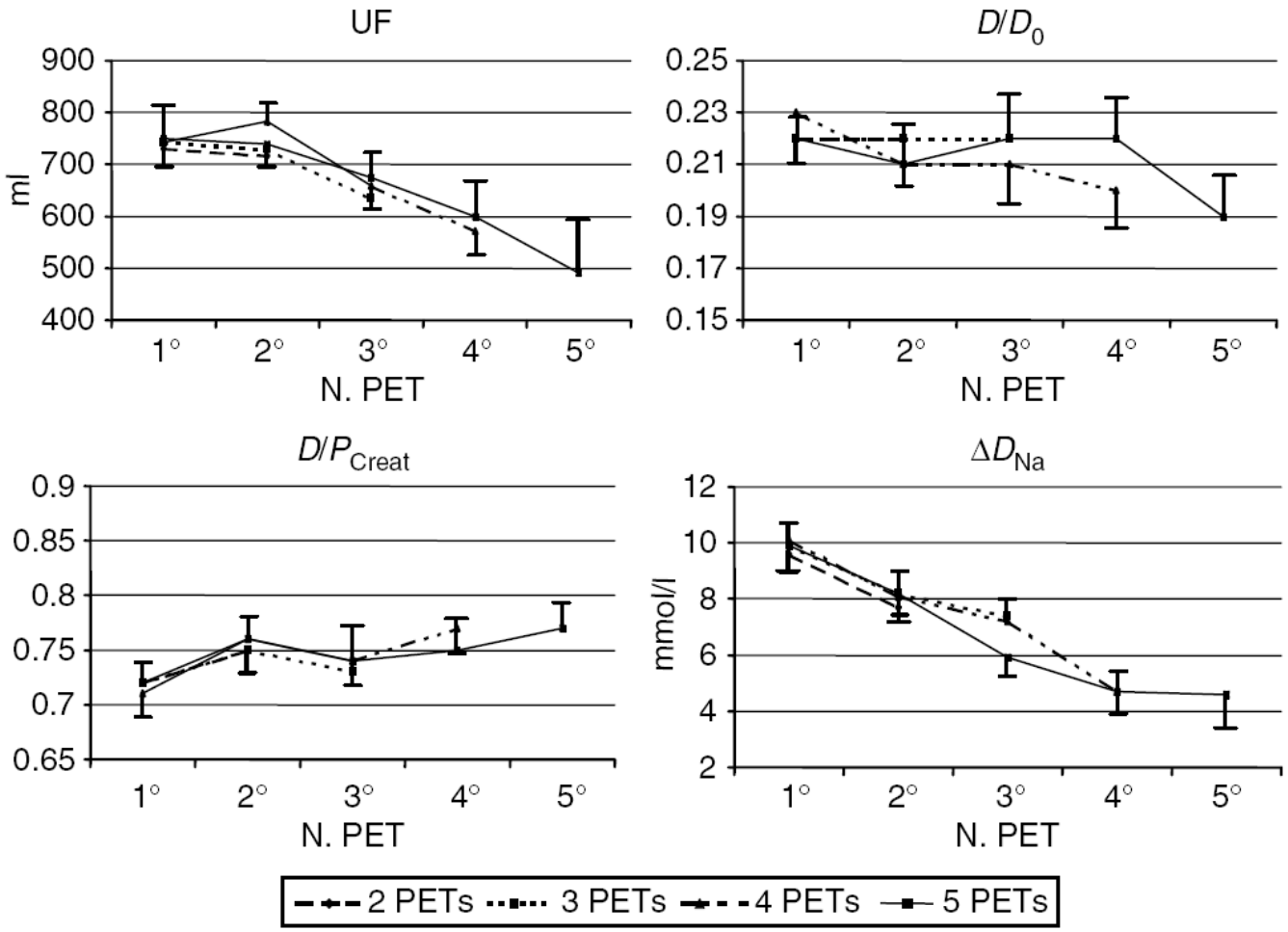


Heimbürger O et al Nephrol Dial Transplant 1994

Delta Sodium in patients with ultrafiltration failure

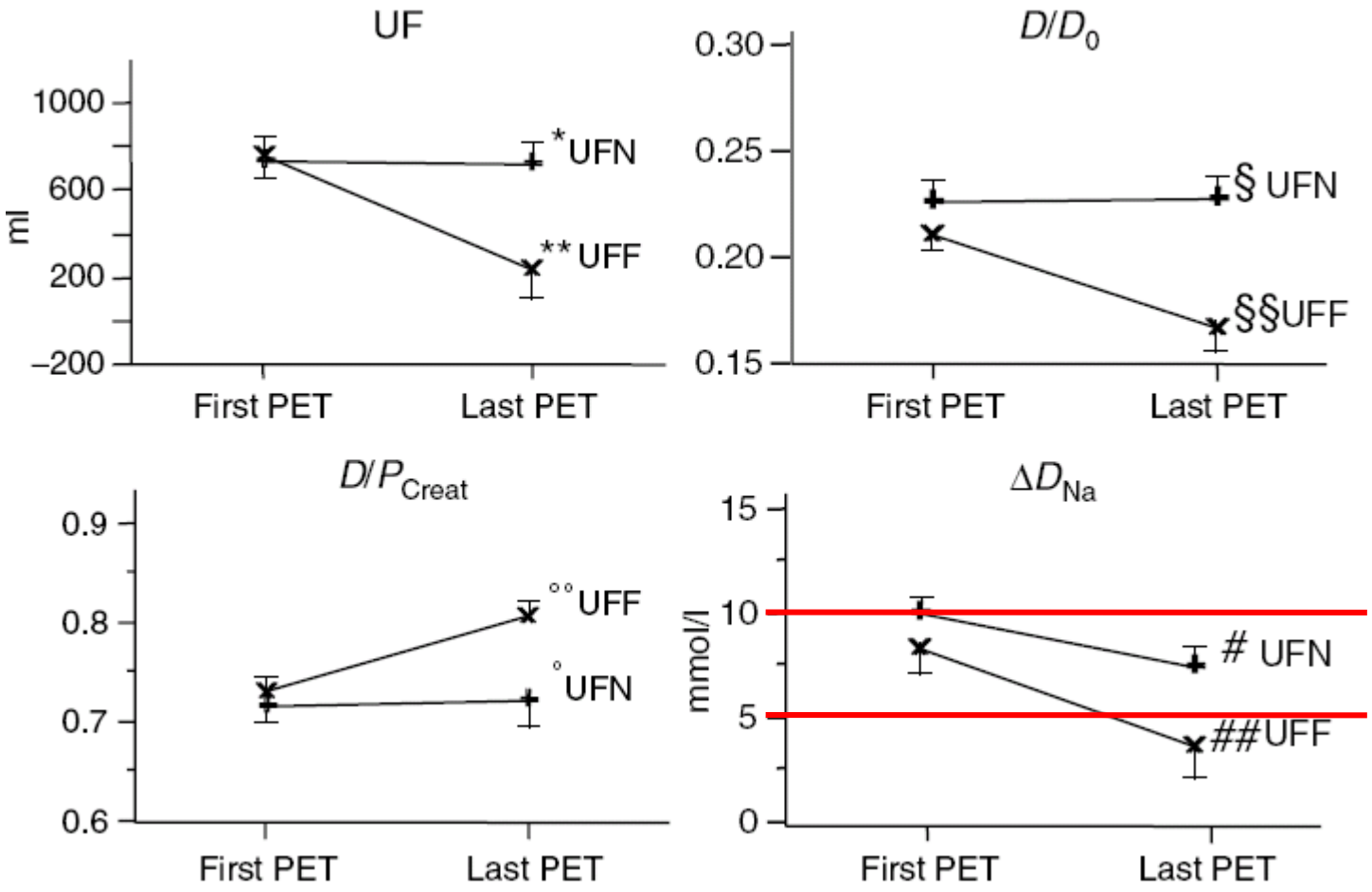


Δ Dialisato Na nei pazienti in dialisi peritoneale



La Milia V et al Kidney Int 2006

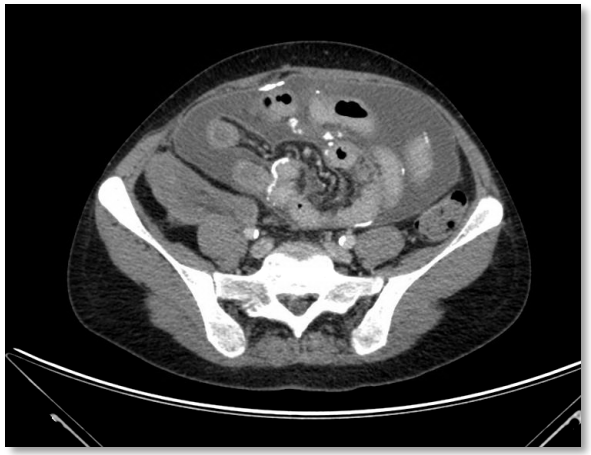
Δ Dialisato Na nei pazienti in dialisi peritoneale

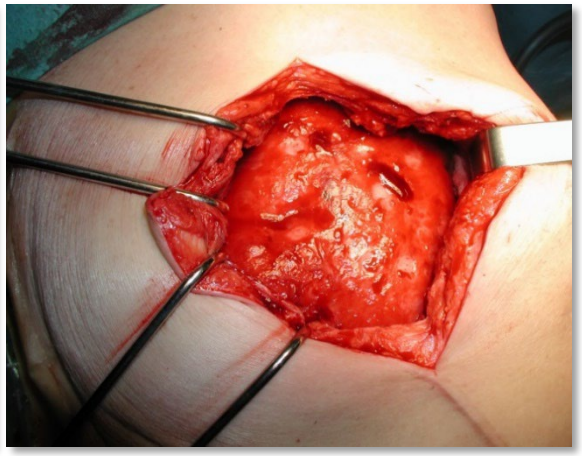


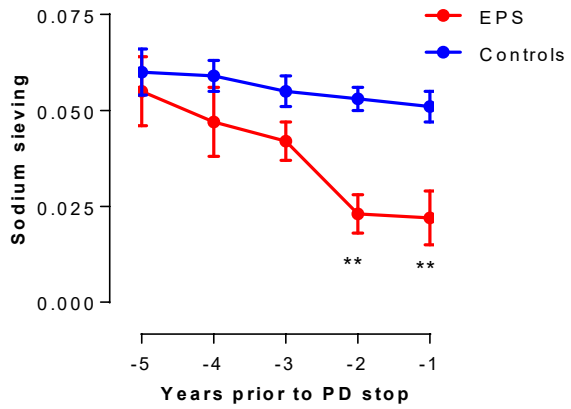
La Milia V et al Kidney Int 2006

Encapsulating peritoneal sclerosis (EPS)

Very rare – dramatic complication of long-term PD - excessive fibrogenic response that ultimately encapsulates the bowel, leading to intestinal obstruction







Registry and cohort studies have consistently observed that peritoneal transport defects, i.e. acquired and progressive loss of UF capacity and sodium sieving, precede and predict the development of overt EPS (link with interstitial fibrosis)

Lambie…Davies, *Kidney Int* 2010; Sampinon…Krediet, *Nephrol Dial Transplant* 2011; Morelle…Devuyst, Goffin, *J Am Soc Nephrol* 2015; La Milia et al, *J Nephrol* 2018

ISPD statement

Length of Time on Peritoneal Dialysis and Encapsulating Peritoneal Sclerosis: Position Paper for ISPD – Update 2017

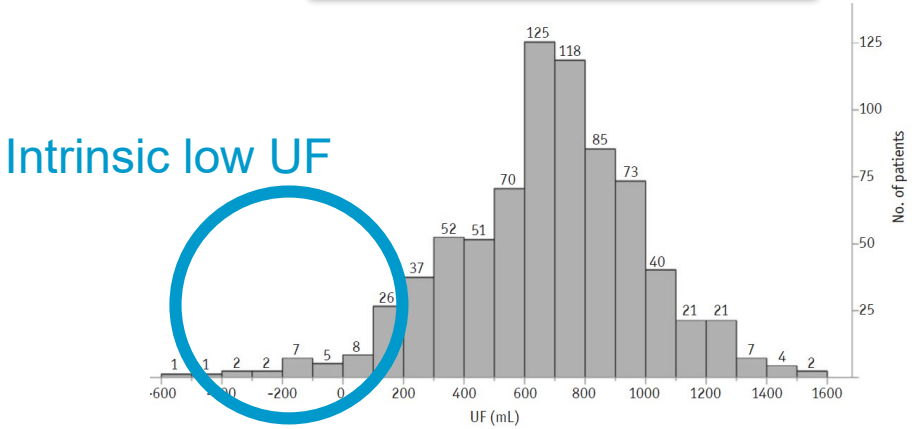
7. There are no specific predictors for the development of EPS:
   b. There is no evidence that CT scanning has any value
   c. Progressive loss of OCG (uncoupling between water and solute transport, altered sodium sieving, decreased FWT) may reflect the development of peritoneal interstitial fibrosis and may help identifying patients at risk of EPS

Monitoring OCG → early detection of patients at risk for EPS

Brown et al, *Peritoneal Dialysis International* 2017

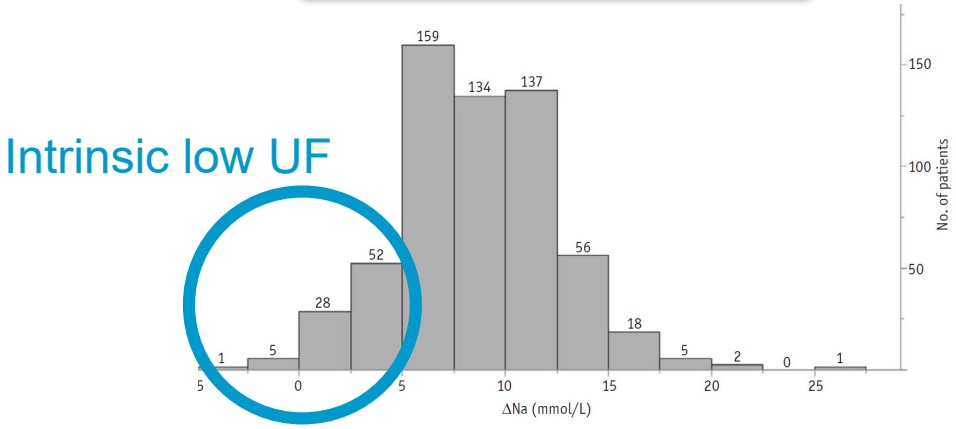
3. Low intrinsic ultrafiltration

Net ultrafiltration



-600 to +1500 ml

Sodium sieving



-3 to +20 mEq/l

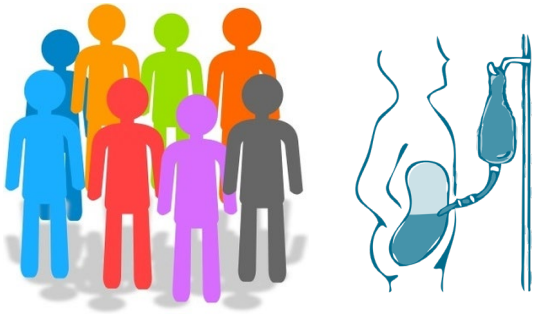
- Huge variability between patients - mechanisms unknown
- Low intrinsic UF: low UF capacity and low sodium sieving, from the start of PD - more glucose to achieve same UF, potential impact on outcome

La Milia et al, Kidney Int 2006; La Milia et al, *Perit Dial Int* 2017

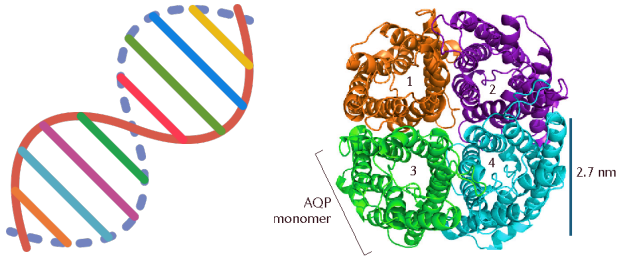
- The huge variability in water transport remains poorly understood
- Aquaporin water channels mediate half the ultrafiltration in PD with glucose

Role for genetic variation in *AQP1*, the gene encoding water channels?

Association between *AQP1* variants and peritoneal water transport?



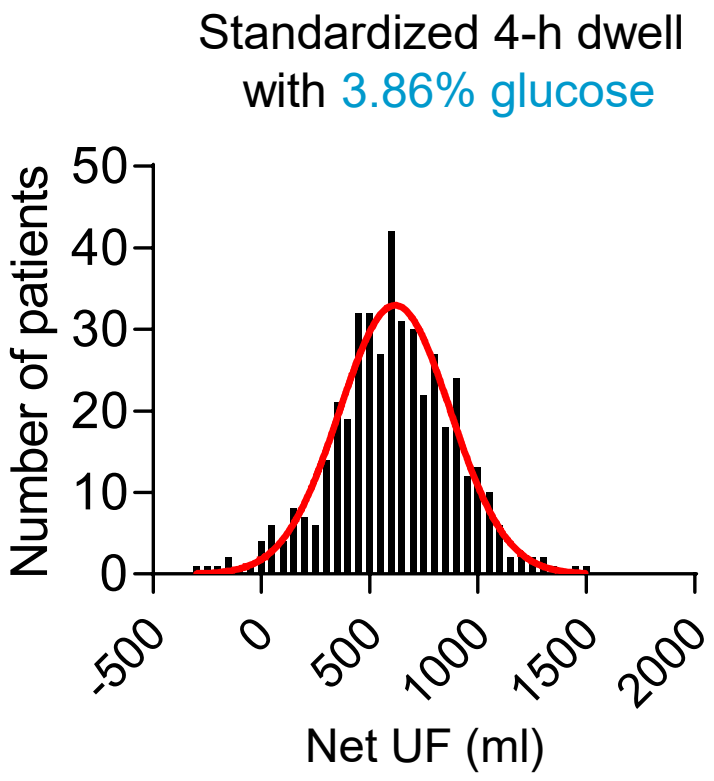
- 1851 patients with kidney failure treated by PD
  - From 7 cohorts in Belgium, the Netherlands (Amsterdam and NECOSAD), Spain, UK (Stoke-on-Trent and PD-CRAFT) and China
  - Mean age (±SD): 54 years (±16); 38% women; European (75%) or Asian (23%) descent

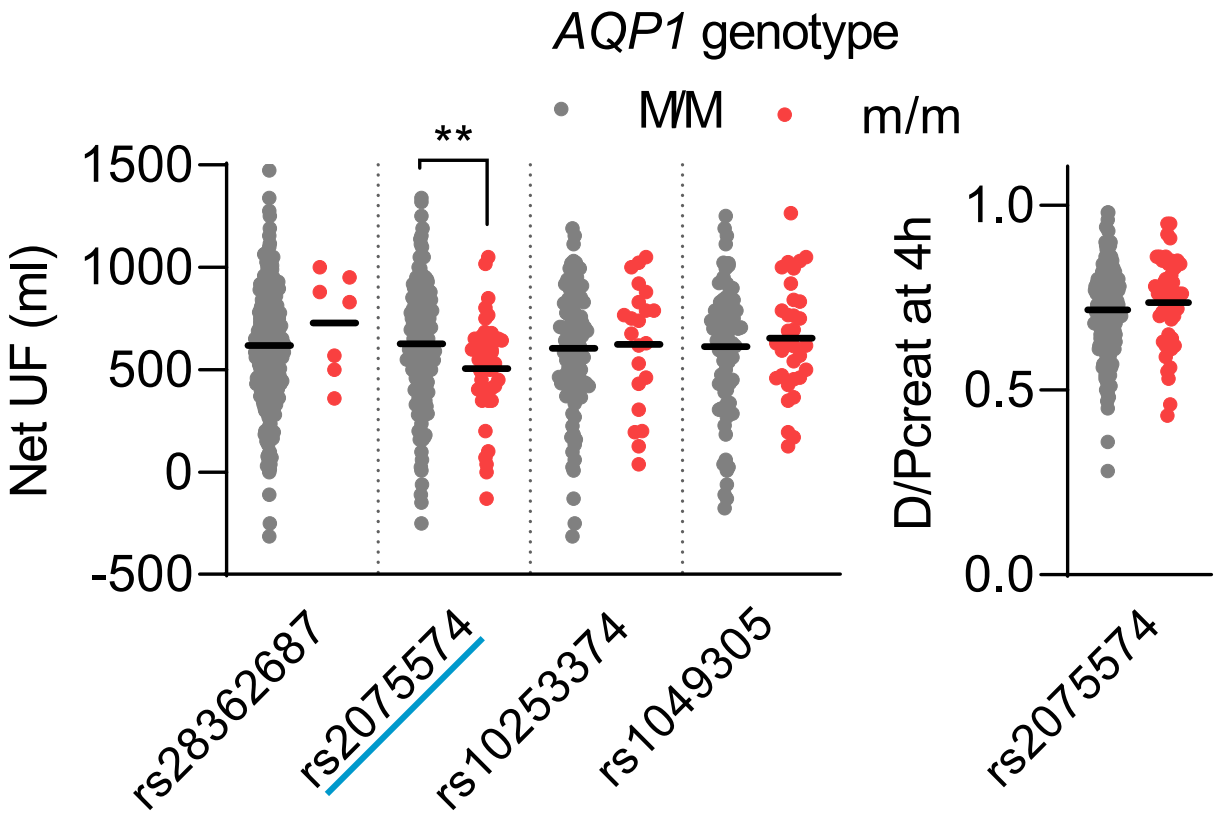


- Genotyping of common variants in the *AQP1* gene
  - MAF >10%
  - rs28362687, rs2075574, rs10253374, rs1049305
  - Covering the major LD blocks over *AQP1*

Morelle et al, *N Engl J Med* 2021

Discovery phase : net UF achieved during baseline PET (n=433)





Significant inter-individual variability in net UF and sodium sieving at initiation of PD

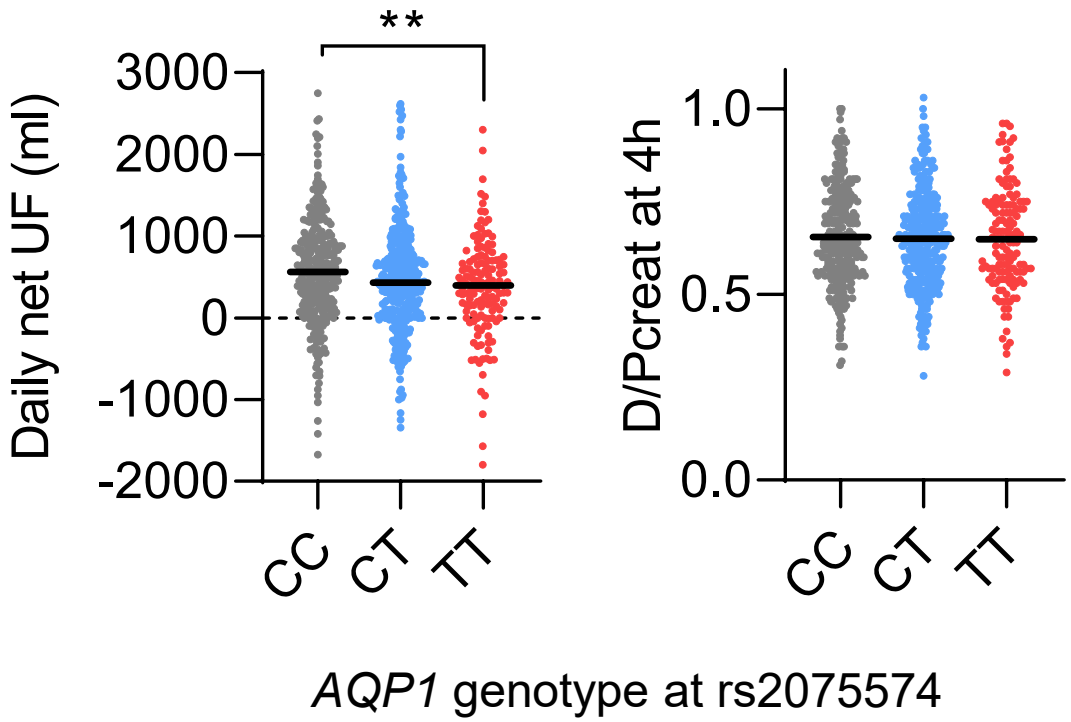
rs2075574 (c.-781C>T) associates with water transport
Patients with TT genotype (14% of patients)
→ lower net UF and Na sieving (vs. CC) - similar PSTR

Morelle et al, *N Engl J Med* 2021

Validation phase: daily net UF (n=985)

Daily net UF

- Total amount of UF achieved over 24h
- High clinical relevance



TT genotype associated with lower daily net UF

as compared to those with the CC genotype (368±603 ml vs. 563±641 ml, P=0.003)

- independently from other characteristics, including PSTR

Morelle et al, *N Engl J Med* 2021

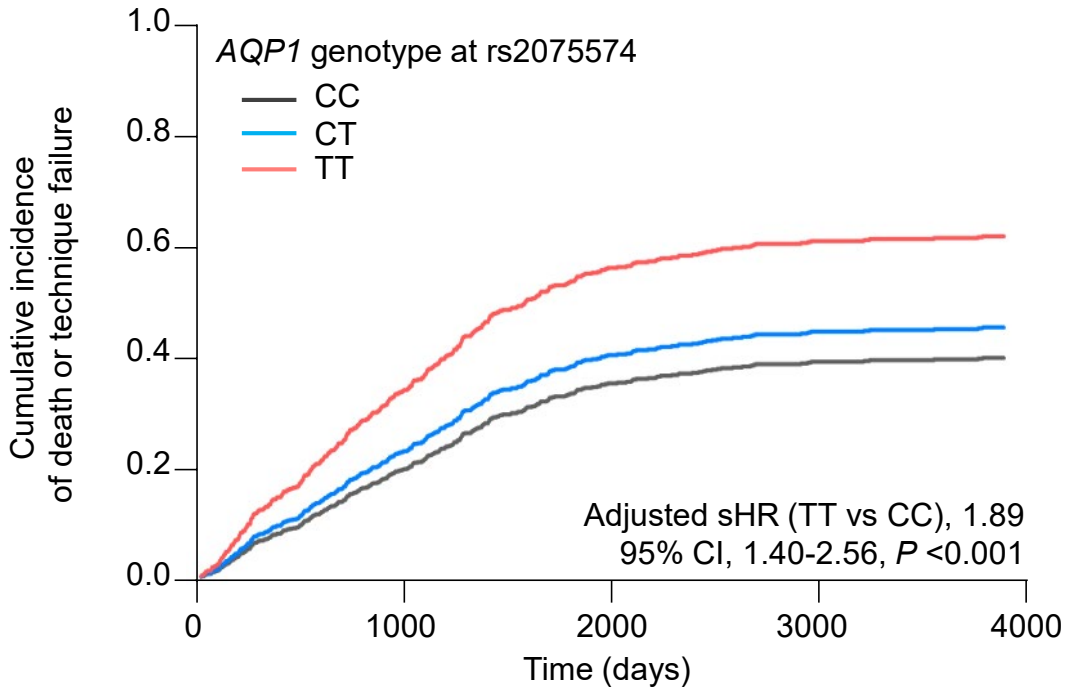
Common variant in the *AQP1* gene with functional relevance

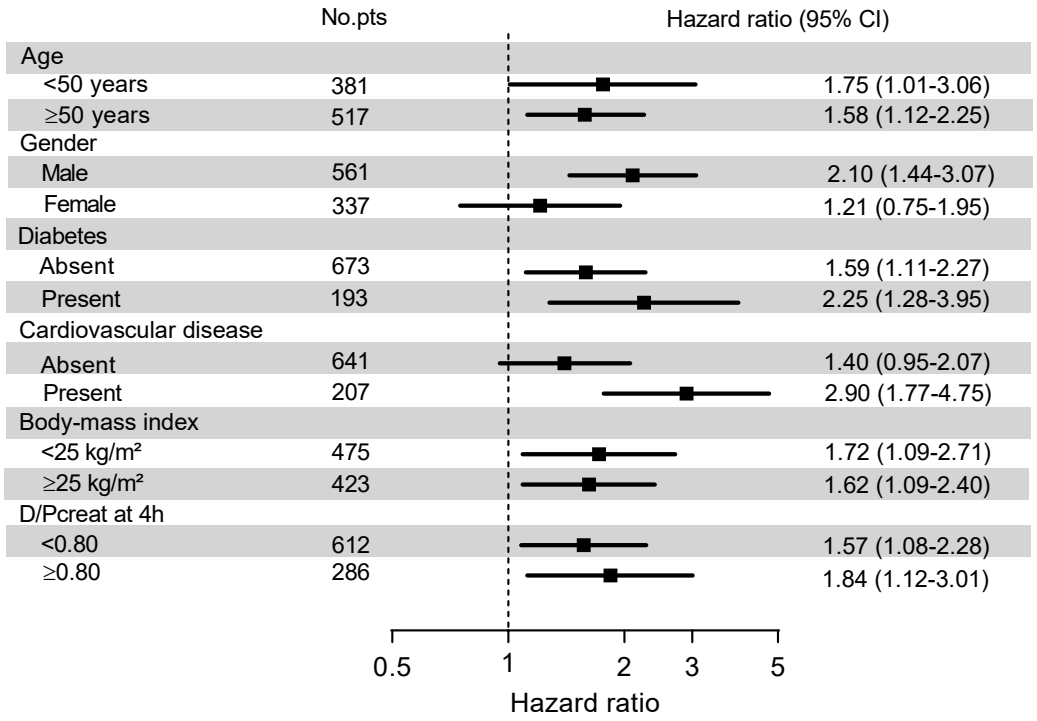
Association with defective water transport across the peritoneal membrane

Water transport is a critical parameter of PD efficiency and outcome

→ Does the variant associate with outcome in incident PD patients?

AQP1 promoter risk variant and outcome in PD patients





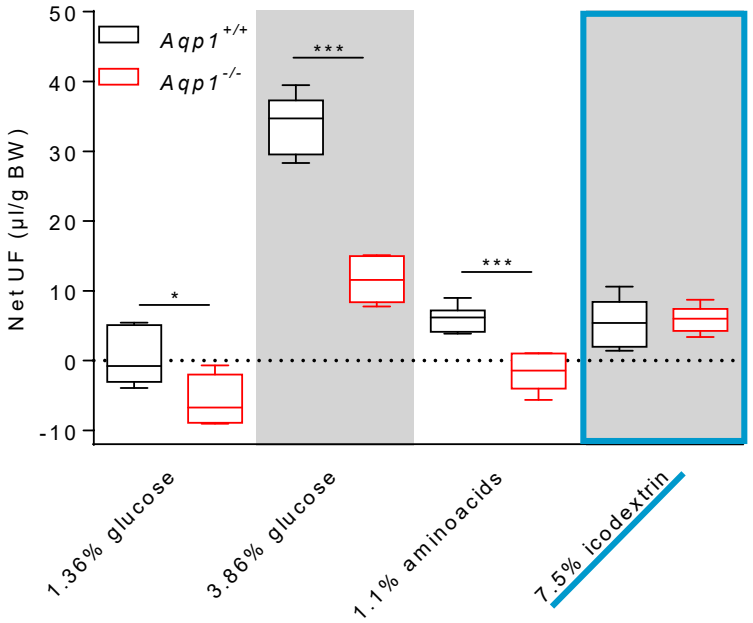
Outcome	Overall n=898	CC n=384	CT n=400	TT n=114	*P*
Composite – no. (%)	419 (47)	162 (42)	191 (48)	66 (58)	0.01
Technique failure – no. (%)	280 (31)	105 (27)	136 (34)	39 (34)	0.10
All-cause death – no. (%)	139 (15)	57 (15)	55 (14)	27 (24)	0.03

Morelle et al, *N Engl J Med* 2021

Is it possible to mitigate poor outcomes associated with the *AQP1* risk variant?

Colloid osmosis to mitigate deleterious effects of the *AQP1* variant?

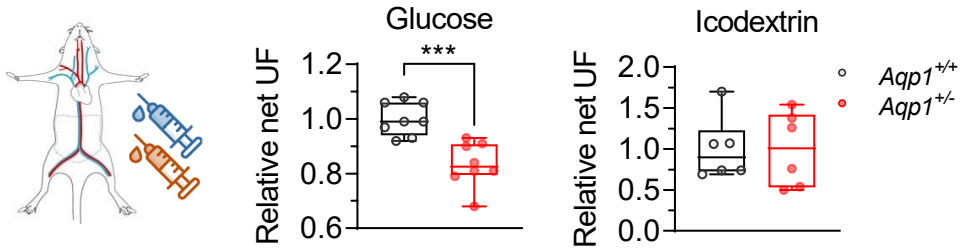
Aqp1 null mice, biophysical studies and modelling



Icodextrin → water transport independent from AQPs

Morelle…Rippe, Oberg*, Devuyst*, *J Am Soc Nephrol* 2018

Heterozygous *Aqp1* mice (50% reduction AQP1)



Icodextrin → water transport unchanged

Subgroup of 144 incident PD patients (11% TT)

UF generated with icodextrin:
no association with the variant

Morelle et al, *N Engl J Med* 2021

Influence of genetic factors on PD efficiency

Combined genetic, translational, and clinical data

- *AQP1* promoter variant rs2075574
  - Influences osmotic water transport and ultrafiltration
  - Independently associated with an increased risk of the composite of death or technique failure (driven by a significantly higher risk of death)
- Biological relevance: the rs2075574 variant influenced
  - Activity of the *AQP1* promoter
  - Expression of water channels in peritoneal microvessels
- Colloid osmotic agents may mitigate the risk associated with the variant

→ « Precision medicine » in dialysis

‘Precision Medicine’ in Dialysis

Taking variability into account
to individualize prescription/management,
and ultimately improve patients’ outcome

Jameson et al, *N Engl J Med* 2015

Should pre-dialysis patients be screened for the variant and those carrying two risk variants (TT genotype) be advised to start hemodialysis and not PD?

- No, definitely!
- PD offers many advantages and, as for many complex traits, the relative contribution of genotype to UF is low (few %) and there is a significant overlap in net UF between genotypes
- When urine volume remains significant and no or moderate peritoneal UF is required to achieve fluid balance, the impact of the variant is likely limited

Should PD patients be screened for the *AQP1* variant?

- Screening might be useful for risk stratification and mitigation, especially if fluid intake is excessive or if urine volume is low
- In patients carrying two risk variants, the use of icodextrin, careful monitoring of fluid status, and diuretic use, may potentially help improving fluid balance and outcome (yet to be confirmed)

- Another (albeit indirect) message suggested by the study: fluid balance is important in (all) PD patients!

Take-home messages

- Restoring/maintaining fluid balance is critical for the success of PD
- Understanding how the peritoneum works as a dialysis membrane is key to individualize prescription and improve clinical outcome - major role of water channels in peritoneal ultrafiltration
- Identifying membrane dysfunction and the underlying mechanism may help tailoring the PD prescription/management
- *AQP1* gene variant influences water transport and outcome in PD

Thank you for your attention!

Questions and discussion