VOLUME MANAGEMENT IN PERITONEAL DIALYSIS

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Presentation Plan

Volume Status in PD

Physiology of Ultrafiltration

Volume Management: Prescription Design

- Short Dwell
- Long Dwell

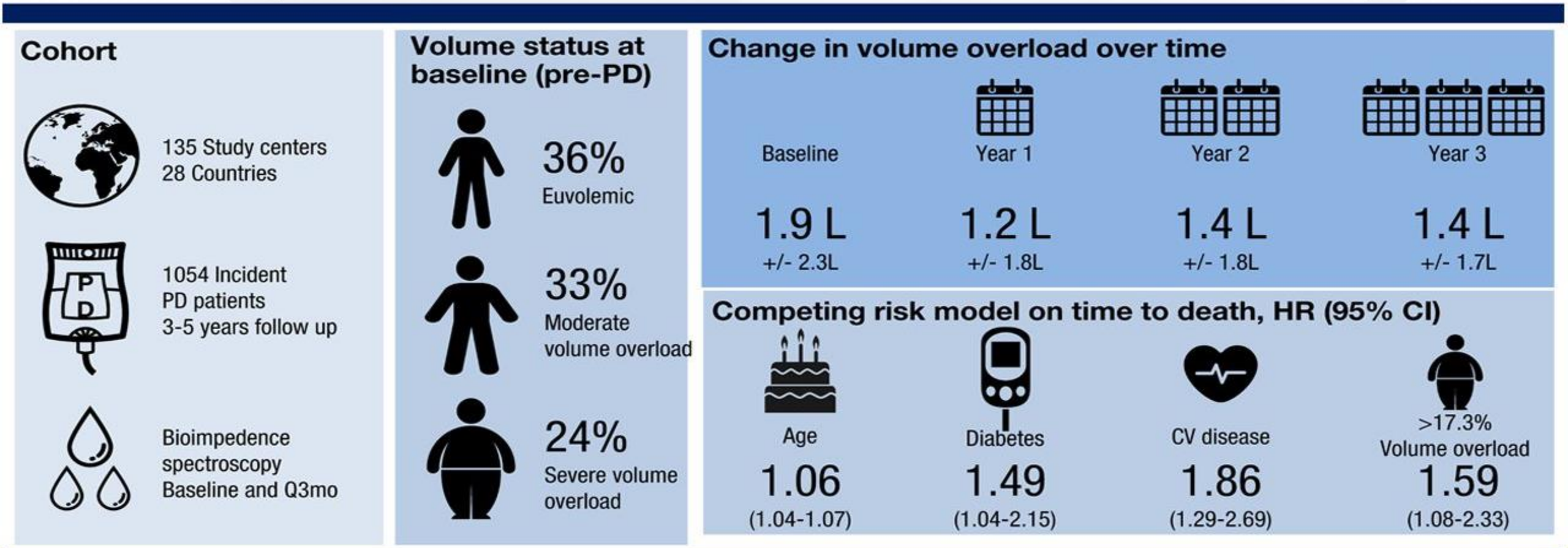
Volume Management: Beyond Glucose

Volume Overload

- Diagnosis
- Management

Volume Status in PD Patients

CJASN
CLINICAL JOURNAL OF AMERICAN SOCIETY OF NEPHROLOGY

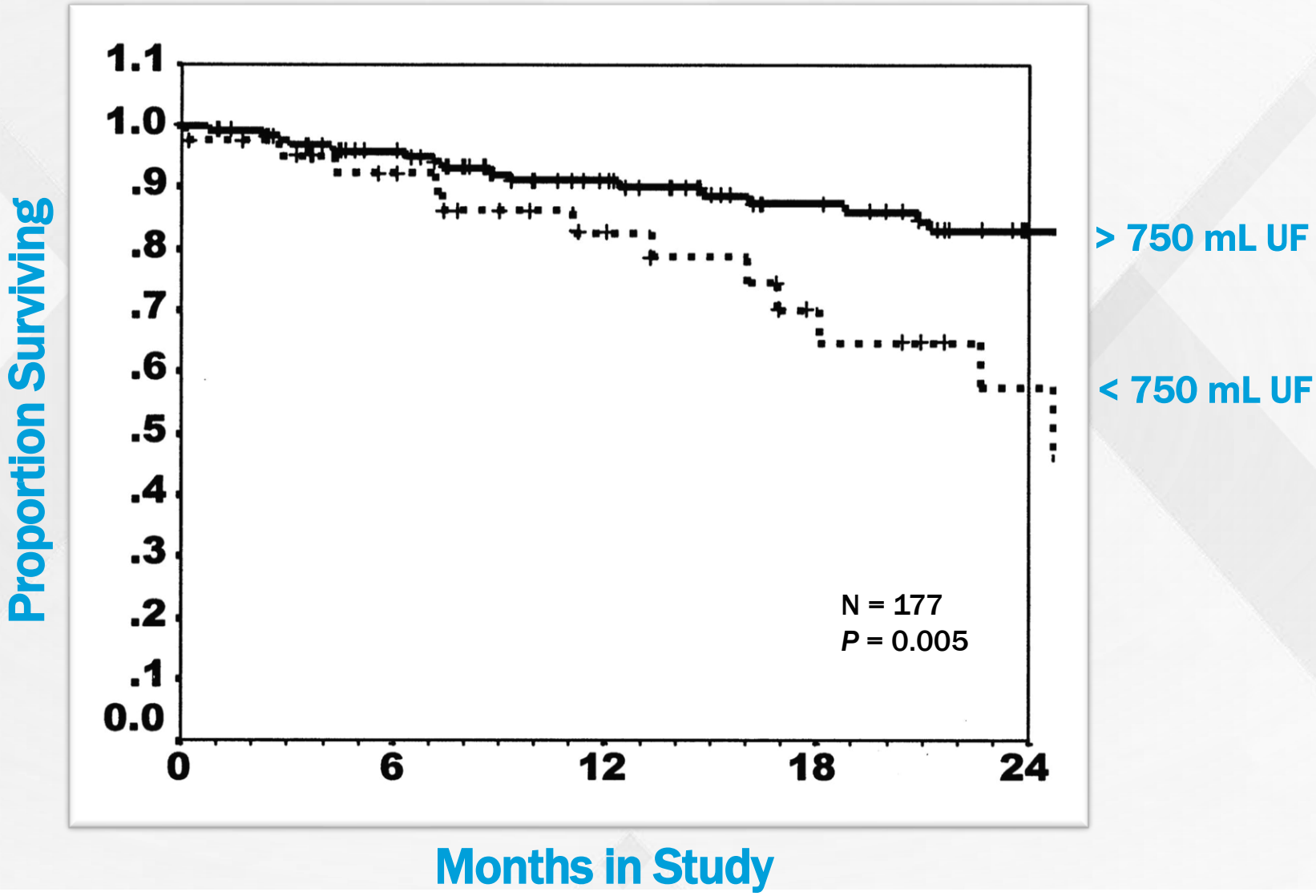


Conclusions In this cohort of incident patients on PD, we found substantial volume overload at start of dialysis. Volume overload improved over time, and associated with survival.

Wim Van Biesen, Christian Verger, James Heaf, François Vrtovsnik, et al. Evolution Over Time of Hydration Status and PD Related Practice Patterns in an Incident Peritoneal Dialysis Patient Cohort. CJASN doi: 10.2215/CJN.11590918
Visual Abstract by Michelle Rheault, MD

Van Biesen W. et al. *Clin J Am Soc Nephrol.* 2019; 14: 882-893.

Survival and Fluid Removal: Anuric Patients



Brown EA, et al. *J Am Soc Nephrol*. 2003;14:2948-2957.

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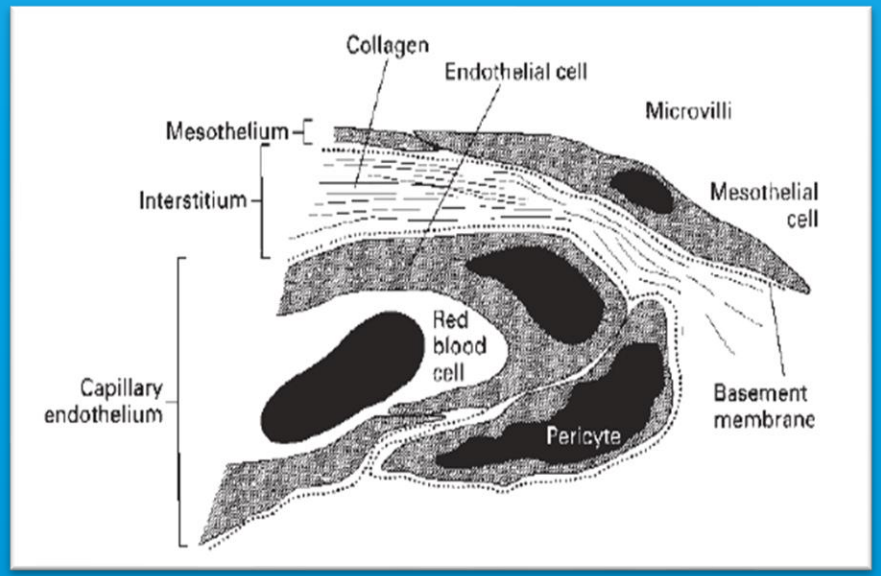
Peritoneal System

TWO TRANSPORT PATHWAYS

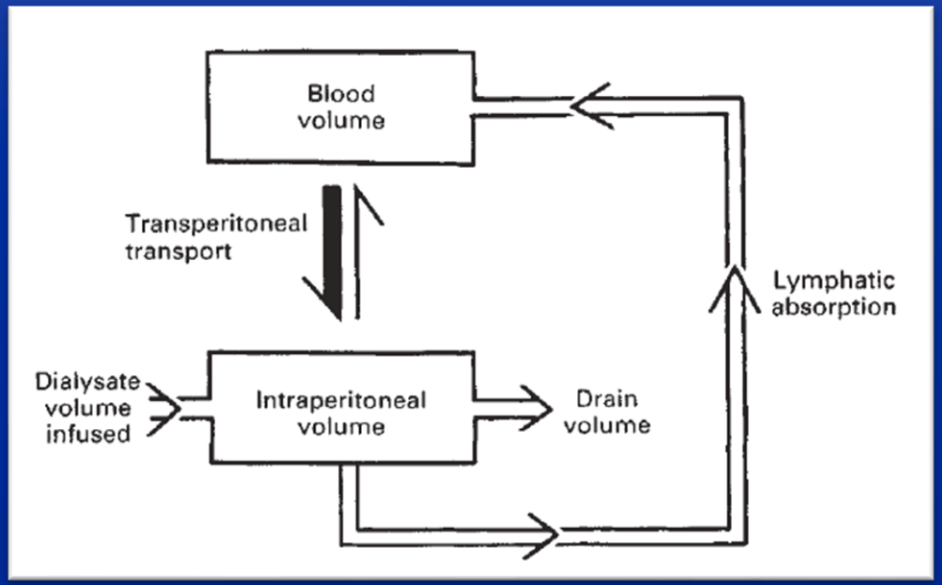
Peritoneal Membrane: Three layers[1]

- Mesothelium
- Interstitium
- Endothelial cell/capillary wall



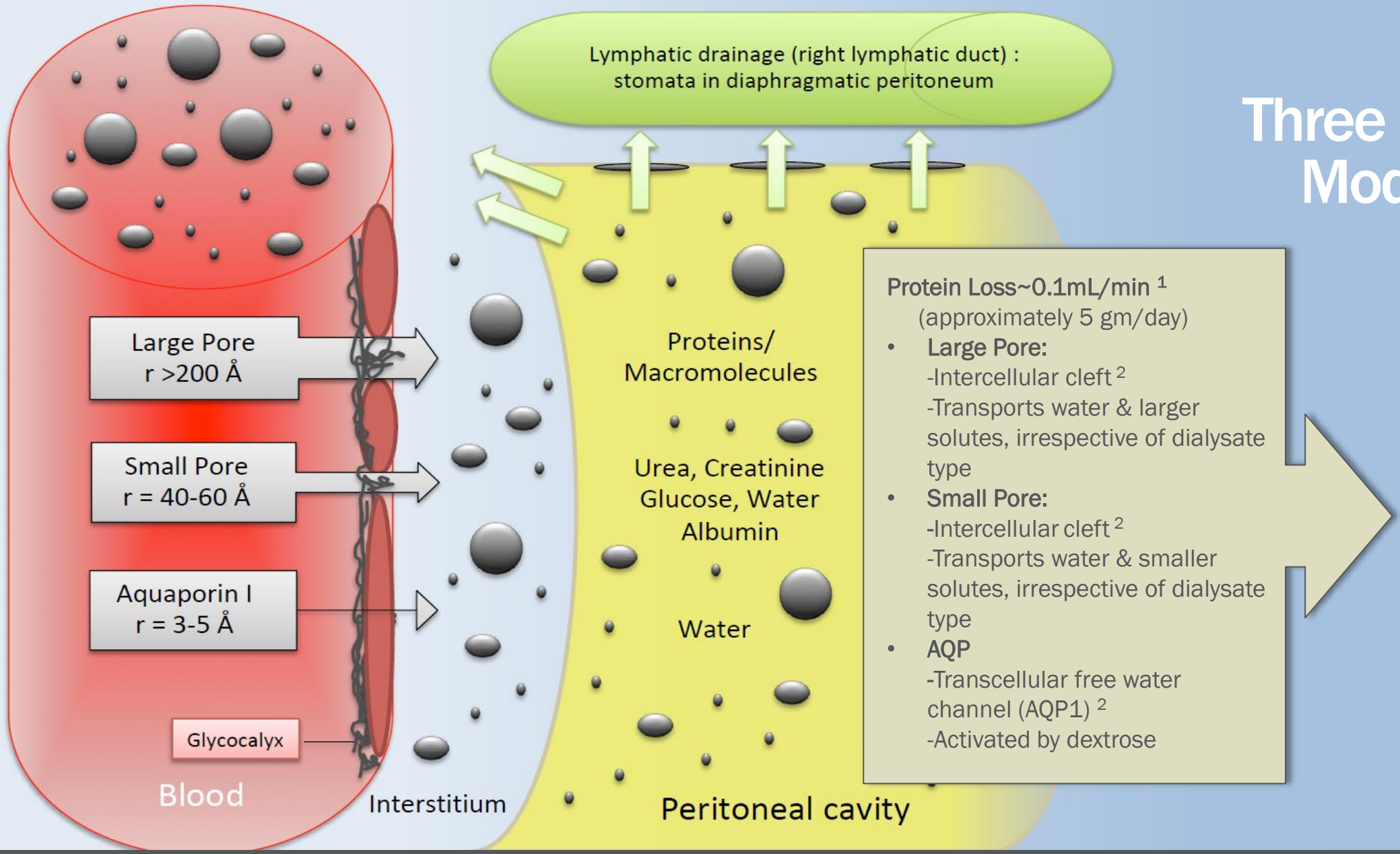
Lymphatic System[1, 2]

- 1.0-1.5 mL/min;
  1.5 - 2.1 L/day[1]



1. Krediet RT. The physiology of peritoneal solute, water and lymphatic transport. In: Khanna R and Krediet RT, eds. *Nolph and Gokal's Textbook of peritoneal dialysis*. 3rd ed. NeYork: Springer Science+Business Media; 2009:137-172.
2. Mactier RA, Khanna R, Twardowski ZJ, Nolph KD. Role of peritoneal cavity lymphatic absorption in peritoneal dialysis. Kidney Int. 1987;32:165-172.

Three Pore Model



Protein Loss~0.1mL/min [1]
(approximately 5 gm/day)

- **Large Pore:**
  -Intercellular cleft [2]
  -Transports water & larger solutes, irrespective of dialysate type
- **Small Pore:**
  -Intercellular cleft [2]
  -Transports water & smaller solutes, irrespective of dialysate type
- **AQP**
  -Transcellular free water channel (AQP1) [2]
  -Activated by dextrose

1. *Figure adapted from Guedes AM. Perit Dial Int. 2019; 39:201-209.*
2. *Rippe B and Stelin G. Kidney Int. 1989; 35:1234-1244.*

Volume Management: ISPD Recommendations 2020

01

Initial PET 6-12 weeks post training; repeat as clinically indicated. [1,2]

Routine monitoring: PET , volume status, BP & clinical exam[3]

02

Icodextrin to improve UF independent of transport type[4]

"Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload"[2]

03

Dietary counseling of appropriate salt / water intake[1]

04

Protection of RRF[5]**; Loop diuretics if RRF present**[1]

Furosemide 160-480 mg/day (split-2 doses)[6]

Metolazone 5-10 mg/day[6]

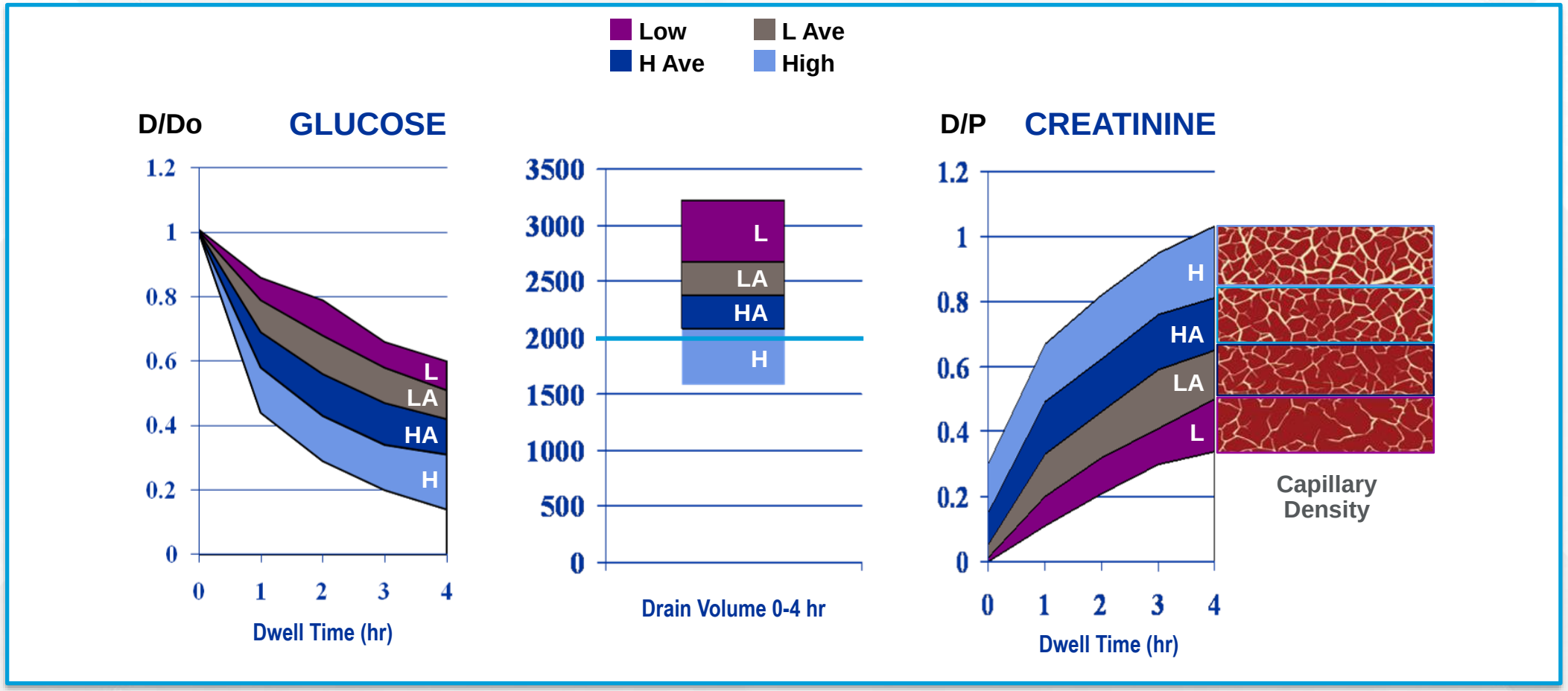
05

Preservation of peritoneal membrane function[1]

Avoid peritonitis & hypertonic glucose solutions

1. Mujais S, et al. *Perit Dial Int*. 2000; 20(suppl 4):S5-S21.
2. Morelle J, et al. ISPD Guidelines. (Evaluation of Membrane Dysfunction) *Perit Dial Int.* 2021; 41: 352-372.
3. Wang A, et. ISPD Guidelines. (Volume Management) *Perit Dial Int.* 2020; 40: 282-292.
4. Boudeville N, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 254-260.
5. Brown E, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 244-253.
6. Chen H, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 274-281.

Peritoneal Equilibration Test: Solute Transport



[1]

Fast transport rate is associated with lower survival;
APD and icodextrin may mitigate this mortality risk (grade 1A evidence).[2]

1. Twardowski Z, et al. *PDB*, 1987.
2. Morelle J, et al. ISPD Guidelines. (Evaluation of Membrane Dysfunction) *Perit Dial Int.* 2021;41:352-372.

ISPD Clinical Practice Guidelines

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

Guideline 2b: *Clinical implications and mitigation of fast solute transfer:* A faster peritoneal solute transport rate (PSTR) is associated with lower survival on PD. (**GRADE 1A**) This risk is in part due to the lower ultrafiltration (UF) and increased net fluid reabsorption that occurs when the PSTR is above the average value. The resulting lower net UF can be avoided by shortening glucose-based exchanges, using a polyglucose solution (icodextrin), and/or prescribing higher glucose concentrations. (**GRADE 1A**)

Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload.(**GRADE 1A)**

Use of automated PD and icodextrin may mitigate the mortality risk associated with fast PSTR. (**practice point**)

Morrelle, J,et al. ISPD Guidelines. (Evaluation of Membrane Dysfunction) *Perit Dial Int.* 2021;41:352-372.

Volume Management

MECHANISMS OF ULTRAFILTRATION

- In Hemodialysis – **hydraulic** trans-membrane pressure
- In Peritoneal Dialysis - **dialysate dependent**
  - Crystalloid (dextrose) – **osmotic** pressure
    UF : AQP ~50% (free water), small/large pores~50%
  - Colloid (icodextrin)– **oncotic** pressure
    UF : all small/large pores~100%
- Results of Ultrafiltration:
  - Fluid removal
  - Convective removal of solutes (key for LMW solutes)

Composition of PD Fluids

	Crystalloid PD Solution[1]	Colloid PD Solution[2]
Dextrose (g/dL)	1.5, 2.5, 4.25	—
Icodextrin (g/dL)	—	7.5
Sodium (mEq/L)	132	132
Chloride (mEq/L)	96	96
Calcium (mEq/L)	3.5/2.5	3.5
Magnesium (mEq/L)	0.5	0.5
Lactate (mEq/L)	40	40
Osmolarity (mOsm/L)	346-485	282
pH	4.0-6.5	5.0-6.0

1. Data on File
2. Data on File

Glucose Concentration: PD Fluids

Fluid	Glucose Concentration	Osmolality
1.5%	1360 mg/dl	347 mOsm/L[1]
2.5%	2260 mg/dl	397 mOsm/L[1]
4.25%	3860 mg/dl	485 mOsm/L[1]
Icodextrin-7.5%	0 mg/dl	282 mOsm/L[2]
Blood	65-99[3]	280-295 mOsm/L

Prescription Considerations:

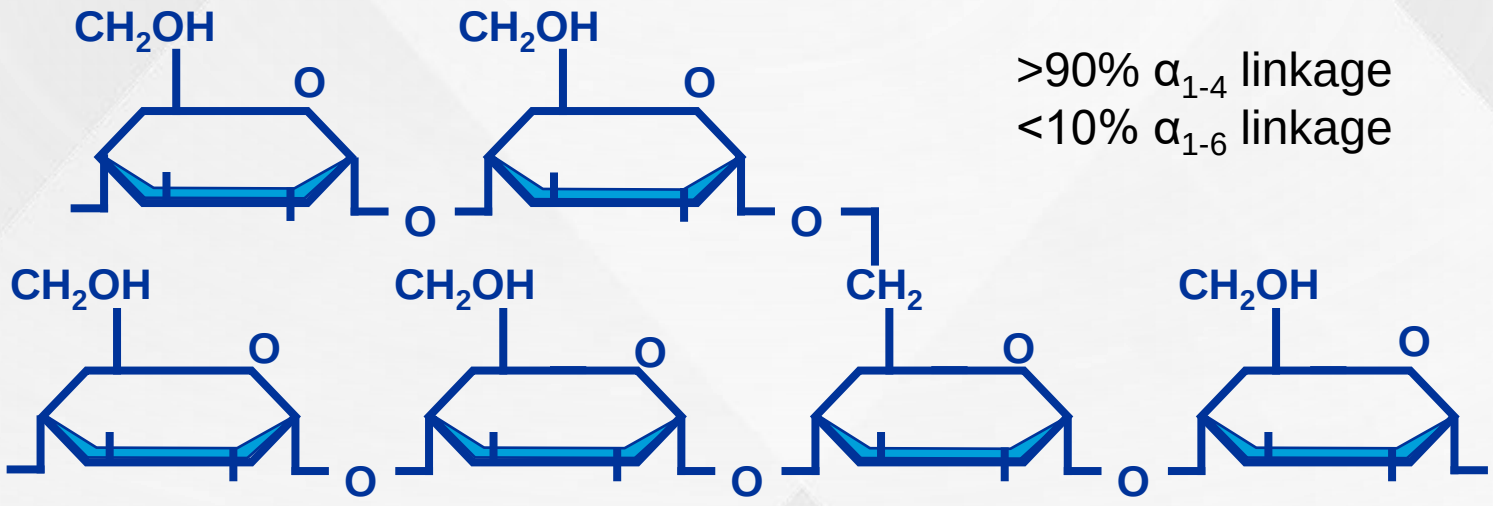
- Glucose Load: Always use lowest concentration needed to achieve UF targets[4]
- ISPD: "Icodextrin can translate into improved fluid status and fewer episodes of fluid overload.[6]
- ISPD recommends icodextrin to improve UF independent of transport type [5]
- Diabetics: Keep blood sugar well controlled[4]

1. Data on File
2. Data on File
3. https://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=483&fromFlyOut=true accessed 1/9/15.
4. NKF-KDOQI Guidelines. *Am J of Kidney Dis*, 2006; 48, Suppl 1:S143-S145.
5. Boudeville N Et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40 254-260.

Colloidal Peritoneal Dialysis Solution (icodextrin)

- Starch-derived polymer: **weight**-average molecular weight 13,000-19,000 daltons (structurally similar to glycogen)

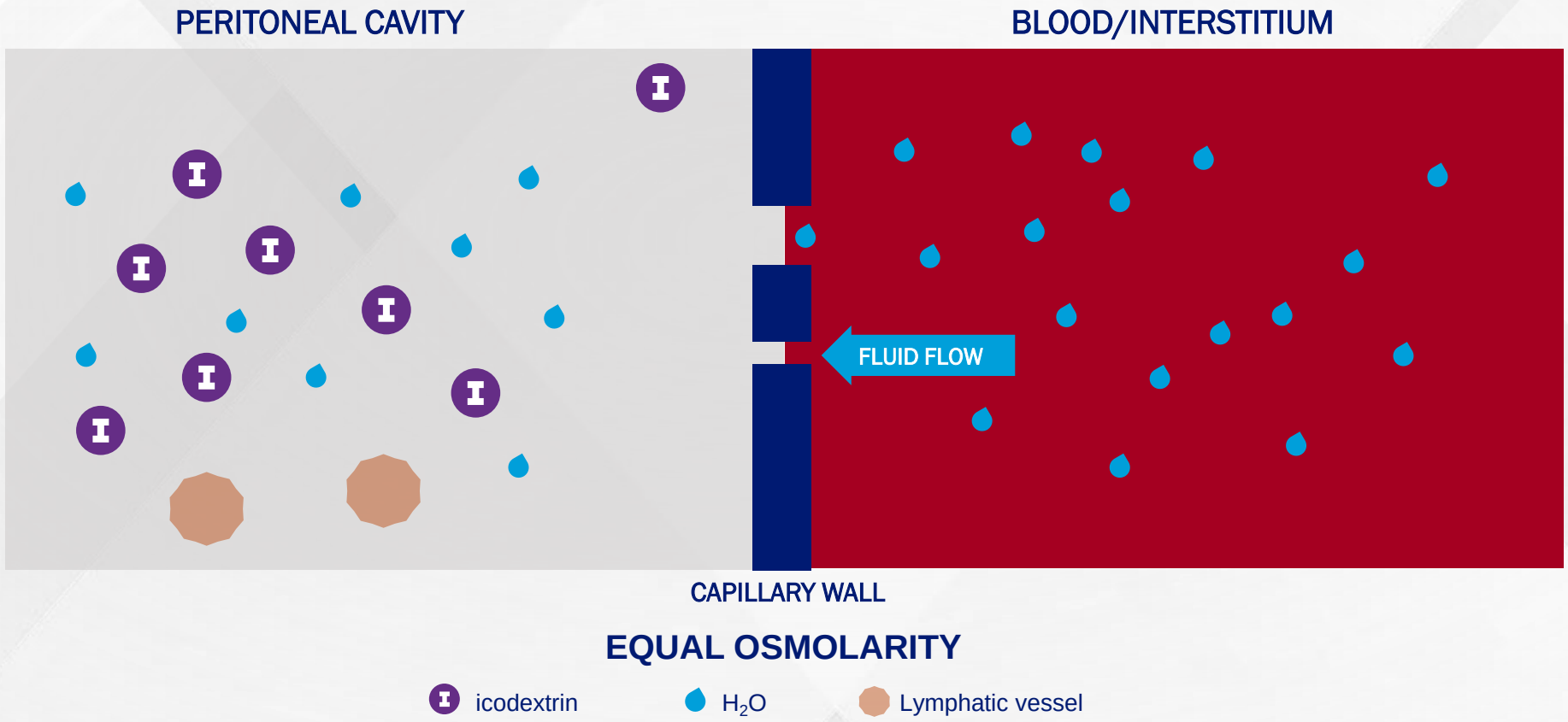
- Induces ultrafiltration via colloid osmosis
  - Water transport across small intercellular pores of peritoneal capillary endothelium
  - Maintains colloid osmotic pressure gradient for the duration of the long dwell due to slow rate of absorption via the lymphatics



Please see important safety information at the end of this presentation.

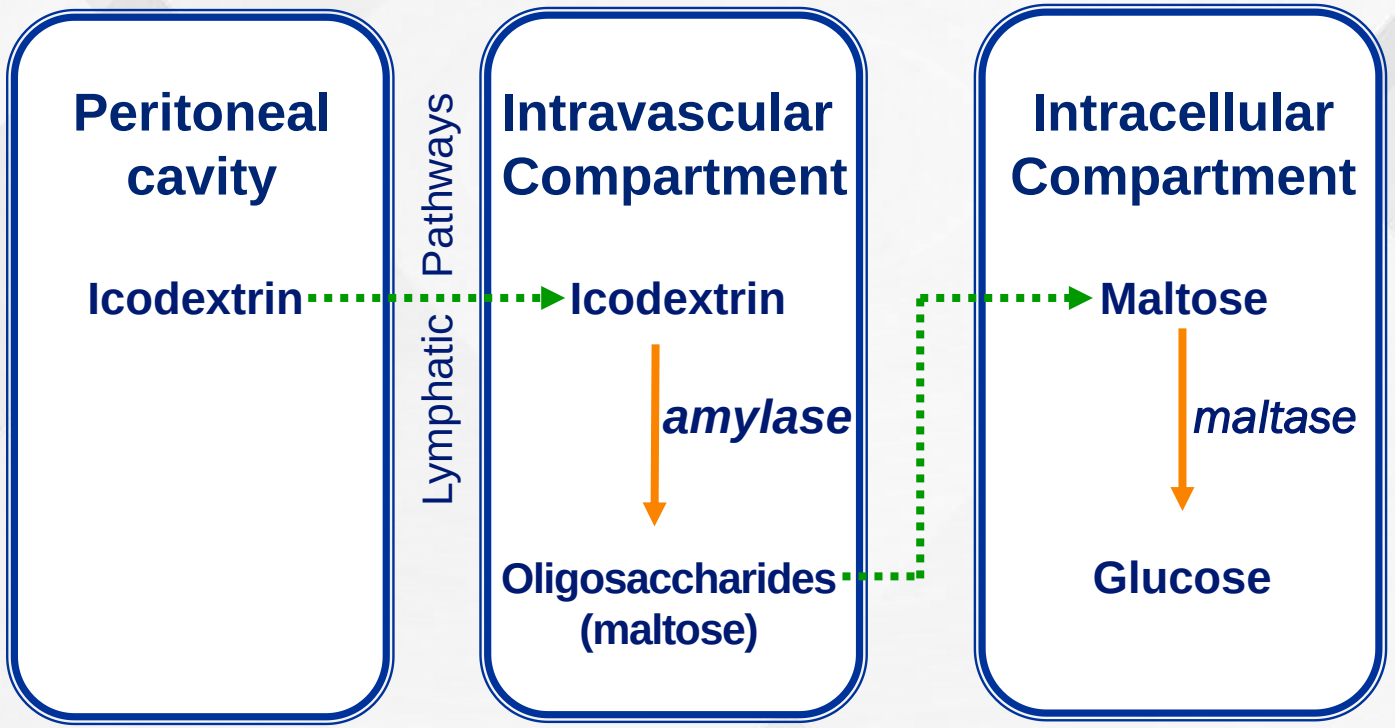
Icodextrin Mechanism of Action: Colloidal Osmosis

HIGH REFLECTION COEFFICIENT (SIZE) OF ICODEXTRIN UNDERLIES COLLOID EFFECTS AND SUSTAINS UF DURING LONG DWELLS

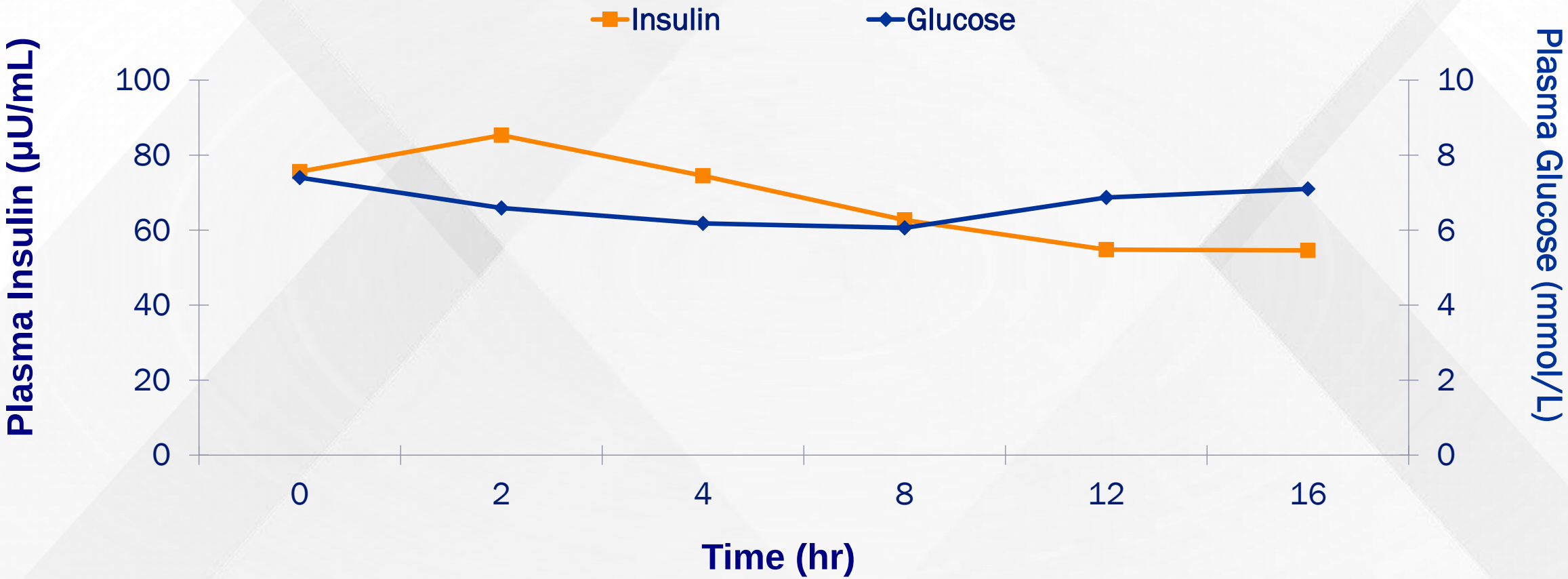


Reduced Membrane Glucose Exposure

- Icodextrin is a glucose-free osmotic agent
- Metabolism of icodextrin to glucose occurs predominantly after absorption from the peritoneal cavity via lymphatic pathways



Effects of icodextrin: Glucose / Insulin



Gokal, et al. *Kidney Int*. 2002;62(suppl 81):S62-S71.

Metabolic and Laboratory Effects of Icodextrin

Serum Sodium

- Predominantly due to dilutional effect of icodextrin metabolites (osmotic effect)
- Similar to hyponatremia related to hyperglycemia or mannitol-like solutes in blood

Amylase Assay

- Serum amylase may be low due to interference of icodextrin metabolites with the enzymatic-based amylase assay
- Serum lipase does not appear affected by icodextrin; may be adequate method to diagnose pancreatitis

Alk Phosphatase

- Increases observed in clinical studies
- Increased levels not associated with increases in liver function tests
- No evidence of progressive increase in serum levels seen over 12-month study period
- Levels returned to normal about two weeks after icodextrin was discontinued

1. Data on File
2. Gokal R, Moberly J, Lindholm B, Mujais S. Metabolic and laboratory effects of icodextrin. *Kidney Int*. 2002; 62 (suppl 81):S62-S71.

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Prescription Elements: Transport Type

DETERMINED BY THE PET

High (H) /High Average (HA)
(0.65 to 1.03)

- Higher D/P creatinine
- Greater vascular surface area
- Equilibrate rapidly
- **Rapid absorption of glucose → results in diminished UF**
- Need **shorter dwells** to minimize reabsorption and maximize UF

Low (L) /Low Average (LA)
(0.34 to 0.64)

- Lower D/P creatinine
- Less vascular surface area
- Equilibrate slowly
- **Slow absorption of glucose → results in optimal UF**
- Need **longer dwells** to enhance solute clearance

1. Twardowski Z. *Blood Purif.* 1989; 7:95-108.

Prescription Elements: Dwell Time

SHORT DWELL VS. LONG DWELL FUNCTION

SHORT DWELL

- Provides UF and diffusive clearance of small solutes
- CAPD-day time exchanges
  - 4 - 6 hours based on lifestyle
- APD-night time exchanges
  - 1.5 - 3 hours based on transport type
- Potential clinical problem: sodium sieving (short dwell too short; APD)

LONG DWELL

- Provides convective clearance of larger solutes
- Optimizes sodium removal
- Potential clinical problem: reabsorption of fluid, especially for H & HA (when using dextrose)
- APD-day time dwell management
  - exchanges dependent upon transport status and fluid selection
  - **Required in anuric pts per KDOQI[1]**

Dwell time and number of exchanges should be determined by transport type and clearance goal.

NKF-KDOQI Clinical practice recommendations for peritoneal dialysis adequacy. *Am J of Kidney Dis*. 2006;48, Suppl 1: S130-S158.

Ultrafiltration in PD: Dwell Time Matters

ULTRAFILTRATION PROFILE DURING DEXTROSE EXCHANGE

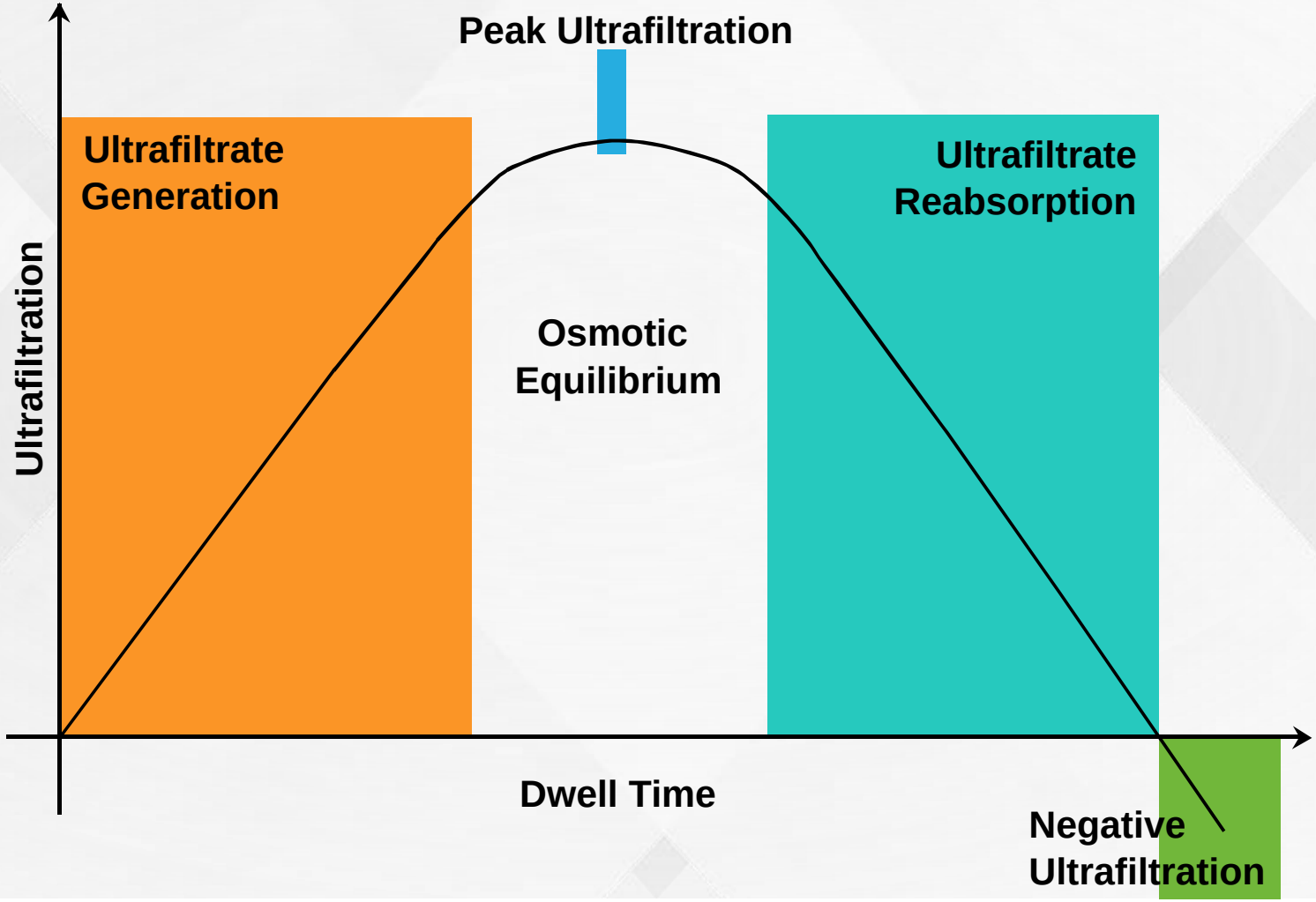
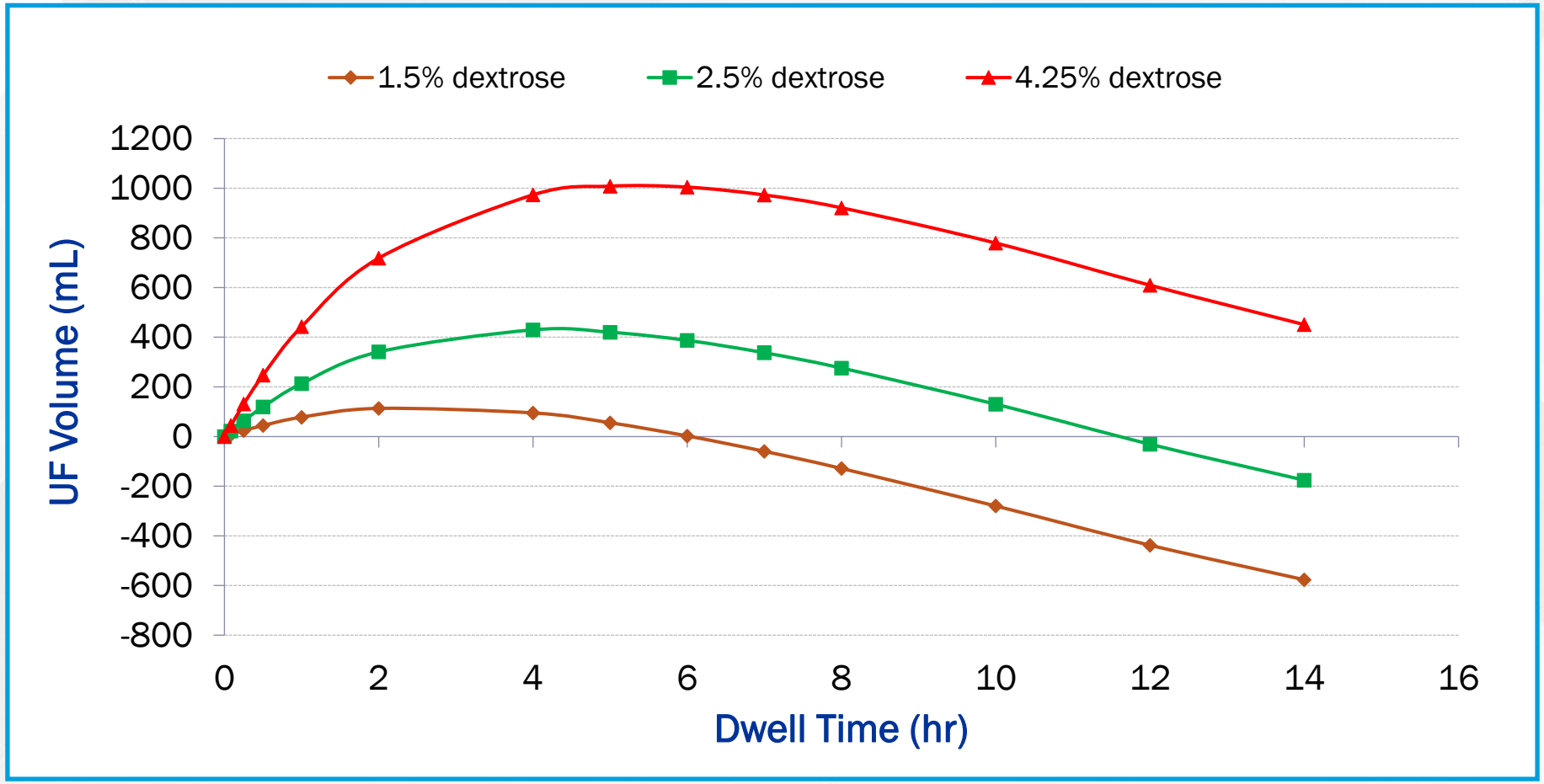


Image courtesy of S. Guest MD

Peak UF with Different Strengths of Dextrose

High Average Transporter

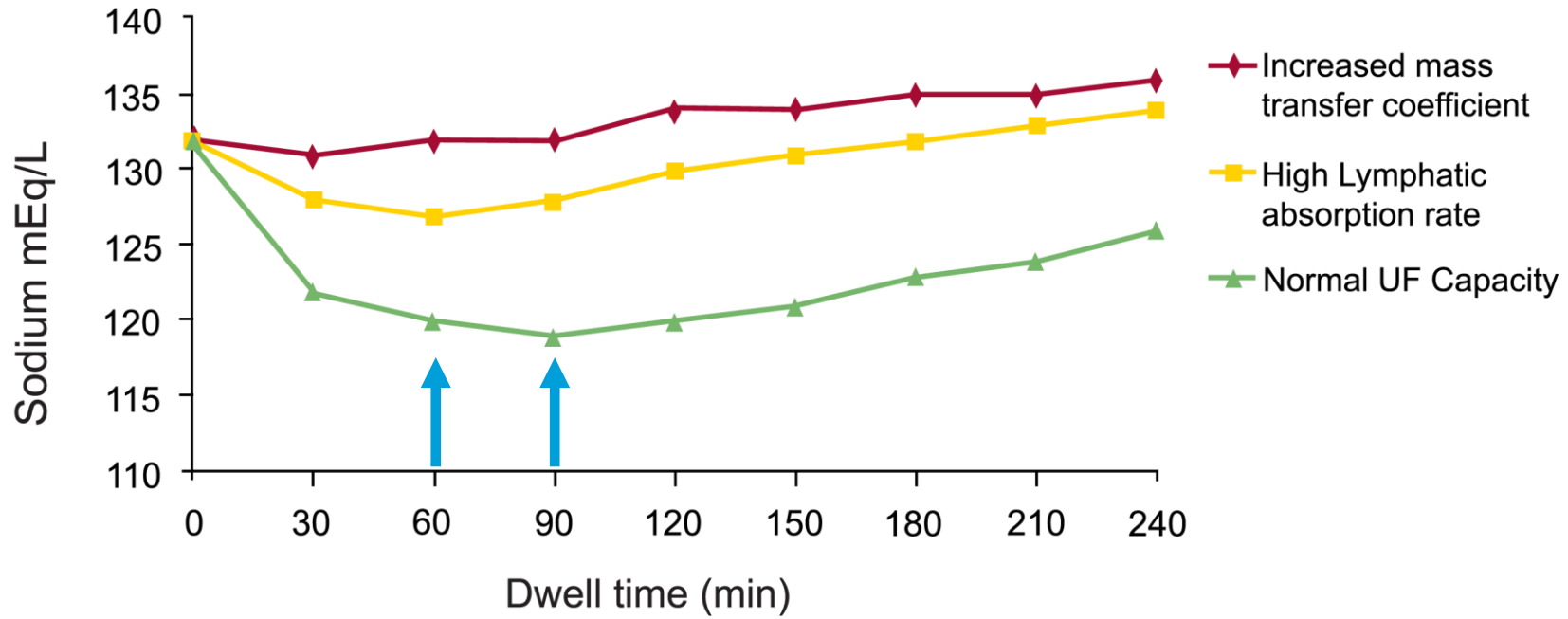


Mujais S, Vonesh E. *Kidney Int.* 2002; 62:S17-S22.

THE SHORT DWELL: SODIUM SIEVING

Sodium Removal: When is Sodium Removed?

Dialysate sodium concentration vs. time over 6-hour dwell with 3.86% glucose[1]



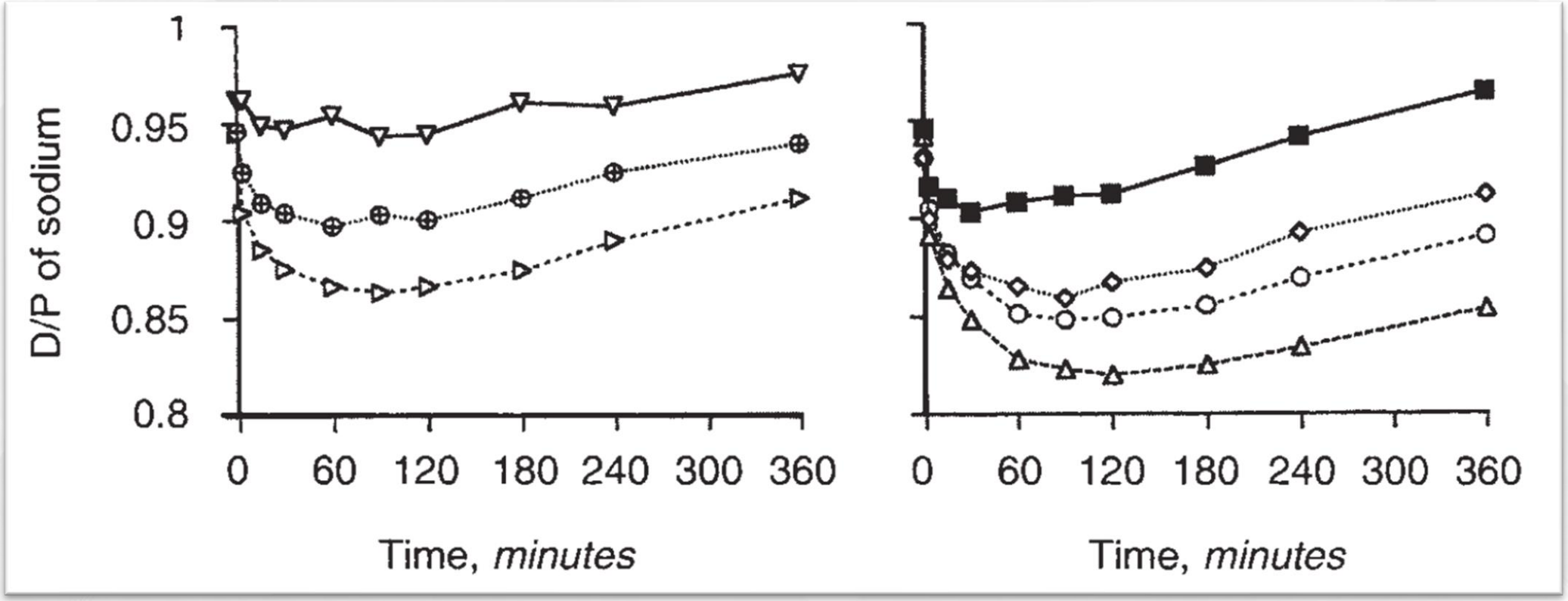
- High rates of UF (water via AQP1) in the early dwell period
- Ultrafiltrate is virtually DEVOID of Sodium
- Solutes (i.e. Na+) diffuse more slowly, across the small pores

A dialysate sodium dip ≤ 5 meq/L at 1 hr indicates UF insufficiency[2]

1. Heimbürger O, Waniewski J, et al. *Kidney Int.* 1990;38:495-506.
2. Morelle J, et al. ISPD Guidelines. (Evaluation of Membrane Dysfunction) *Perit Dial Int.* 2021; 41:352-372.

When is Sodium Removed?

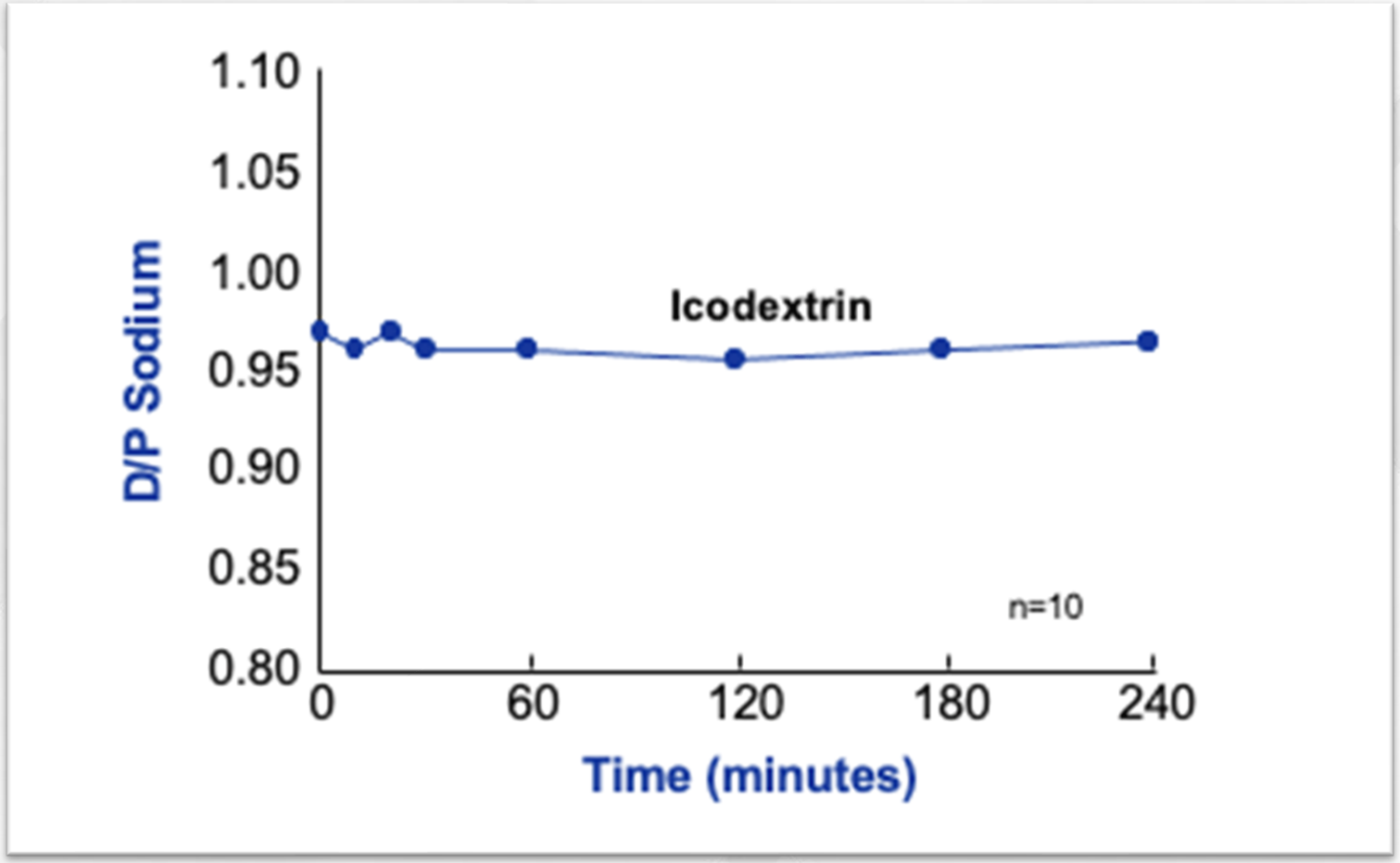
MINIMAL SODIUM SIEVING WITH 1.36% DEXTROSE AND IN HIGH TRANSPORTERS



Wang T, et al. *Kidney Int*. 1997;52:1609-1616.

Sodium Sieving & Icodextrin

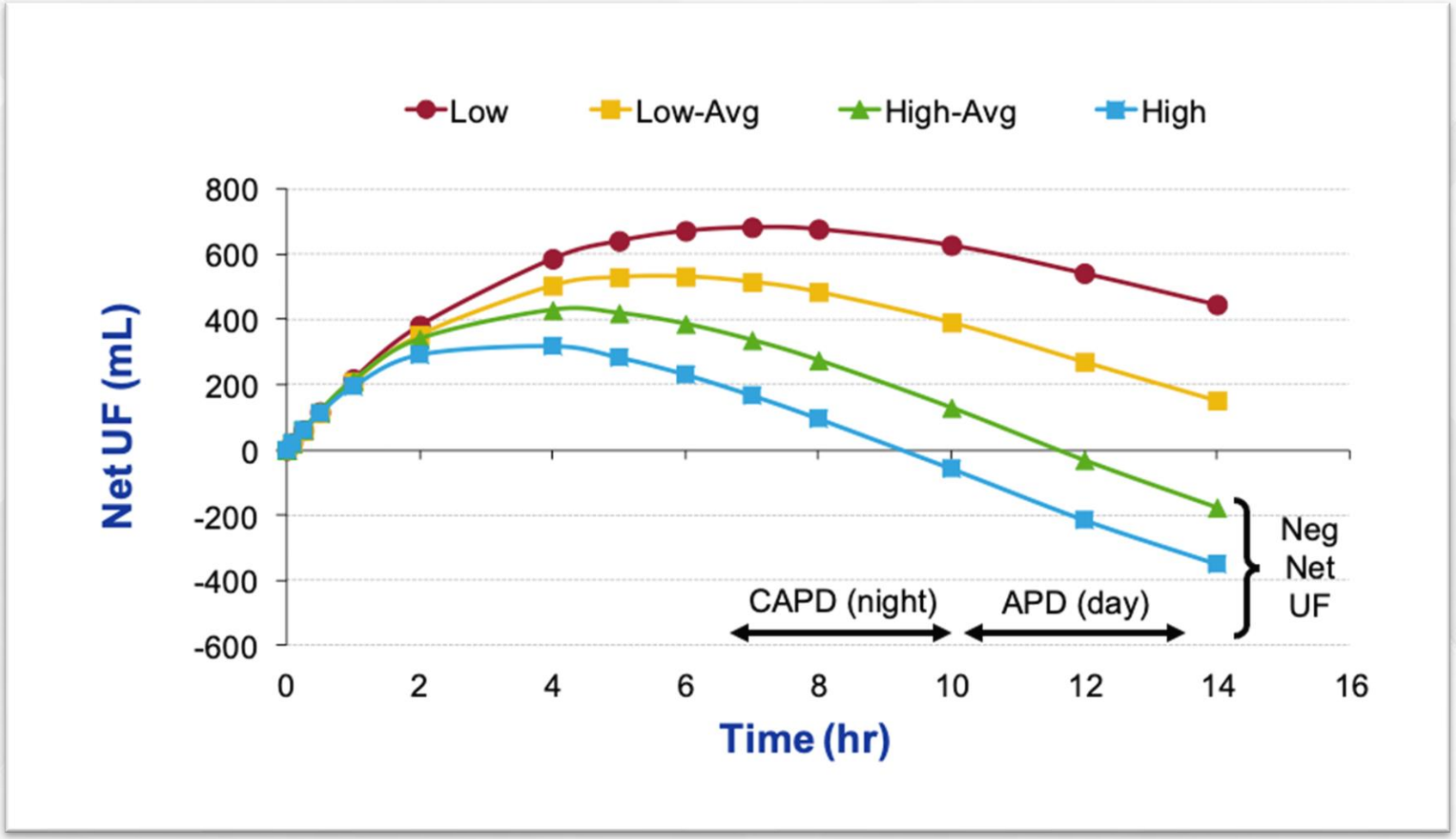
LACK OF NA SIEVING WITH ICODEXTRIN IMPLIES UF THROUGH NA PERMEABLE “PORE”, NOT AQUAPORIN PORE



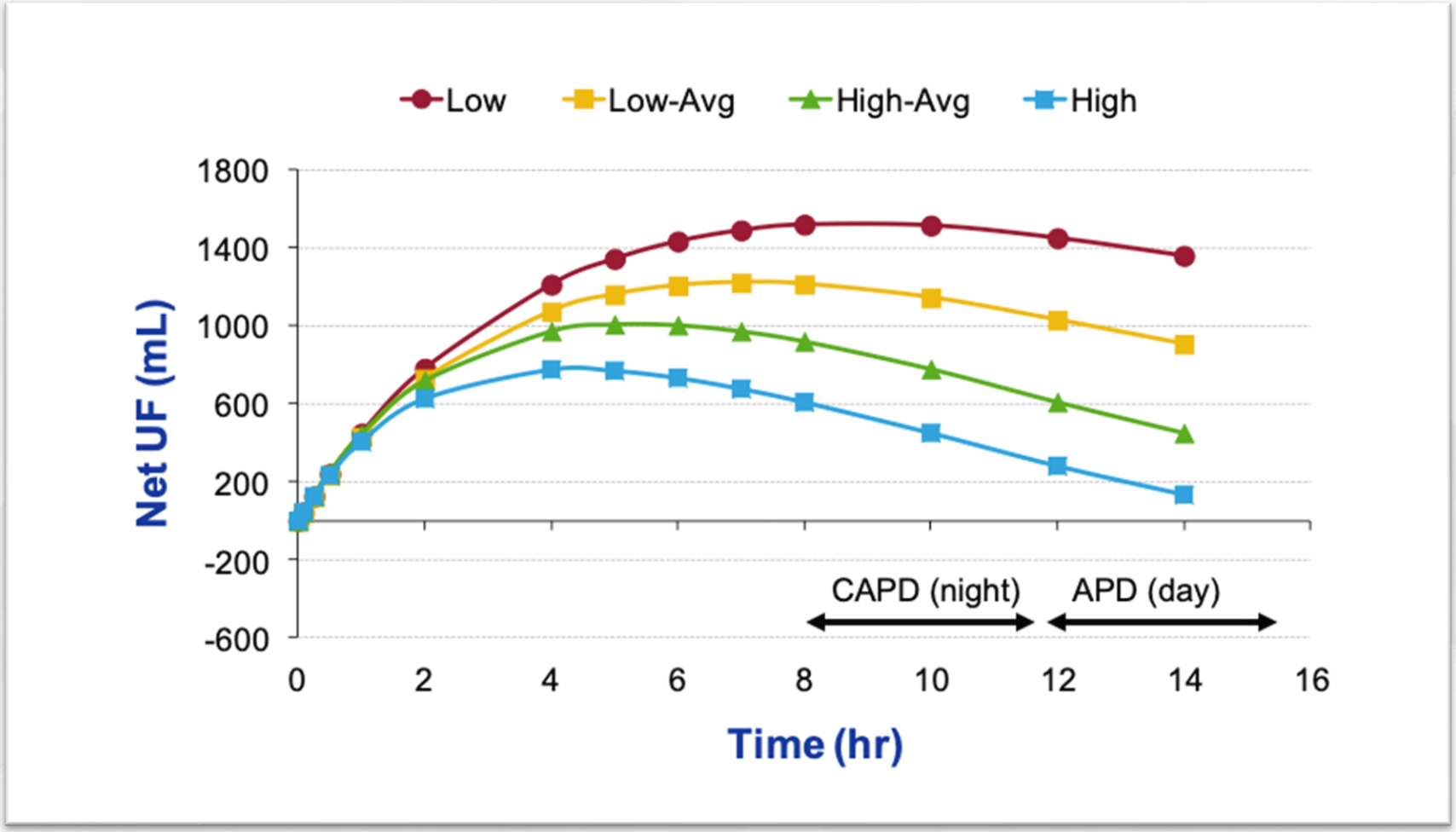
Ho-dac-Pannekeet, et al, *Kidney Int,* 50: 979-986, 1996.

THE LONG DWELL: REABSORPTION

Long-dwell UF Potential: 2.5% Dextrose



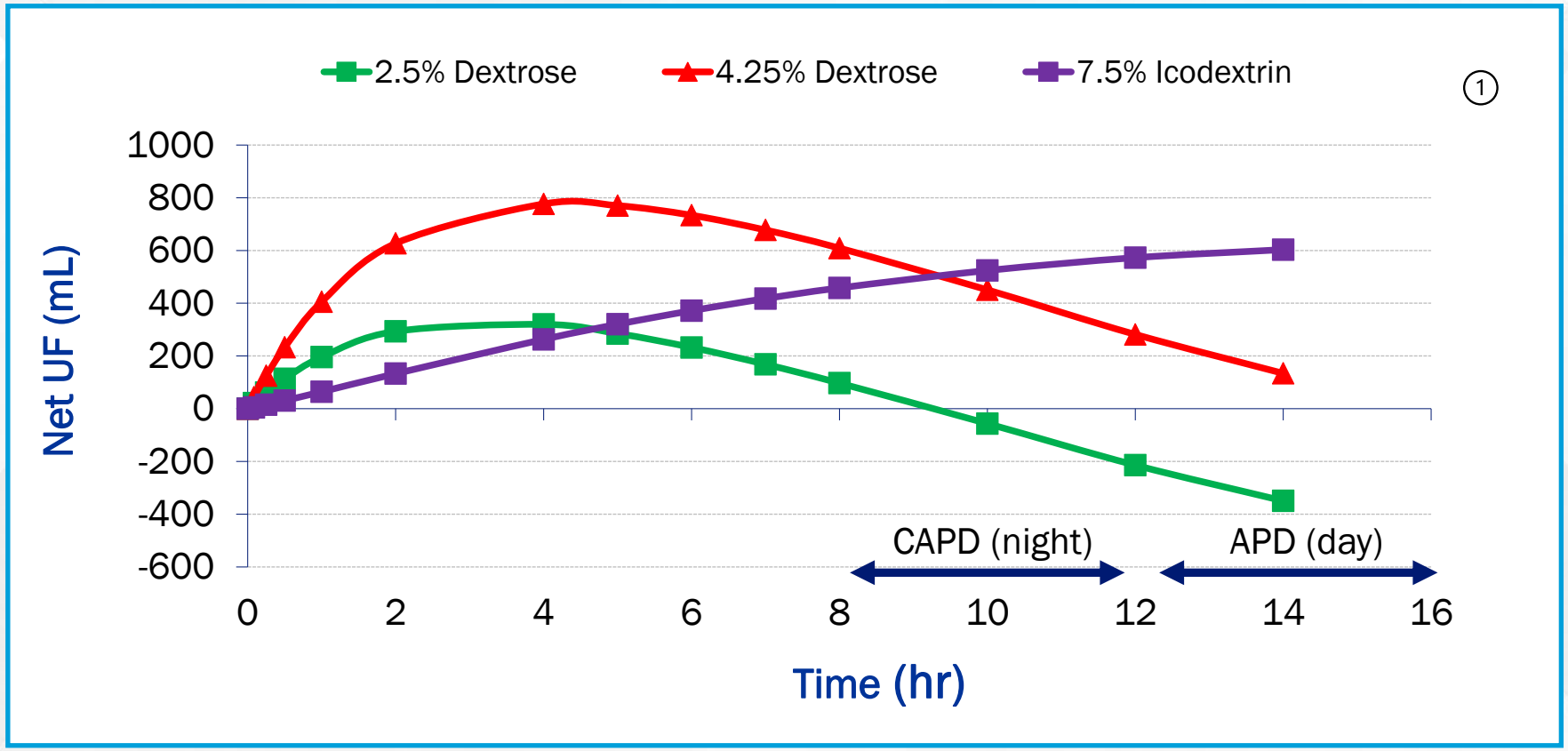
Long-dwell UF Potential: 4.25% Dextrose



Reprinted by permission from MacMillan Publishers Ltd: Mujais S, Vonesh E. *Kidney Int*. 2002;62(suppl 81):S17-S22, copyright 2002.

UF Profile in High Transporters

DEXTROSE VS. ICODEXTRIN



"Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload"[2]

1. Mujais S, Vonesh E. *Kidney Int.* 2002;62(suppl 81):S17-S22; Data on file, Baxter Healthcare Corporation.
2. Morelle J, et al. ISPD Guidelines. (Evaluation of Membrane Dysfunction) *Perit Dial Int.* 2021; 41: 352-372.

Volume Management: ISPD Recommendations 2020

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Preservation of peritoneal membrane function[1]

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1. Mujais S, et al. *Perit Dial Int*. 2000; 20(suppl 4):S5-S21.
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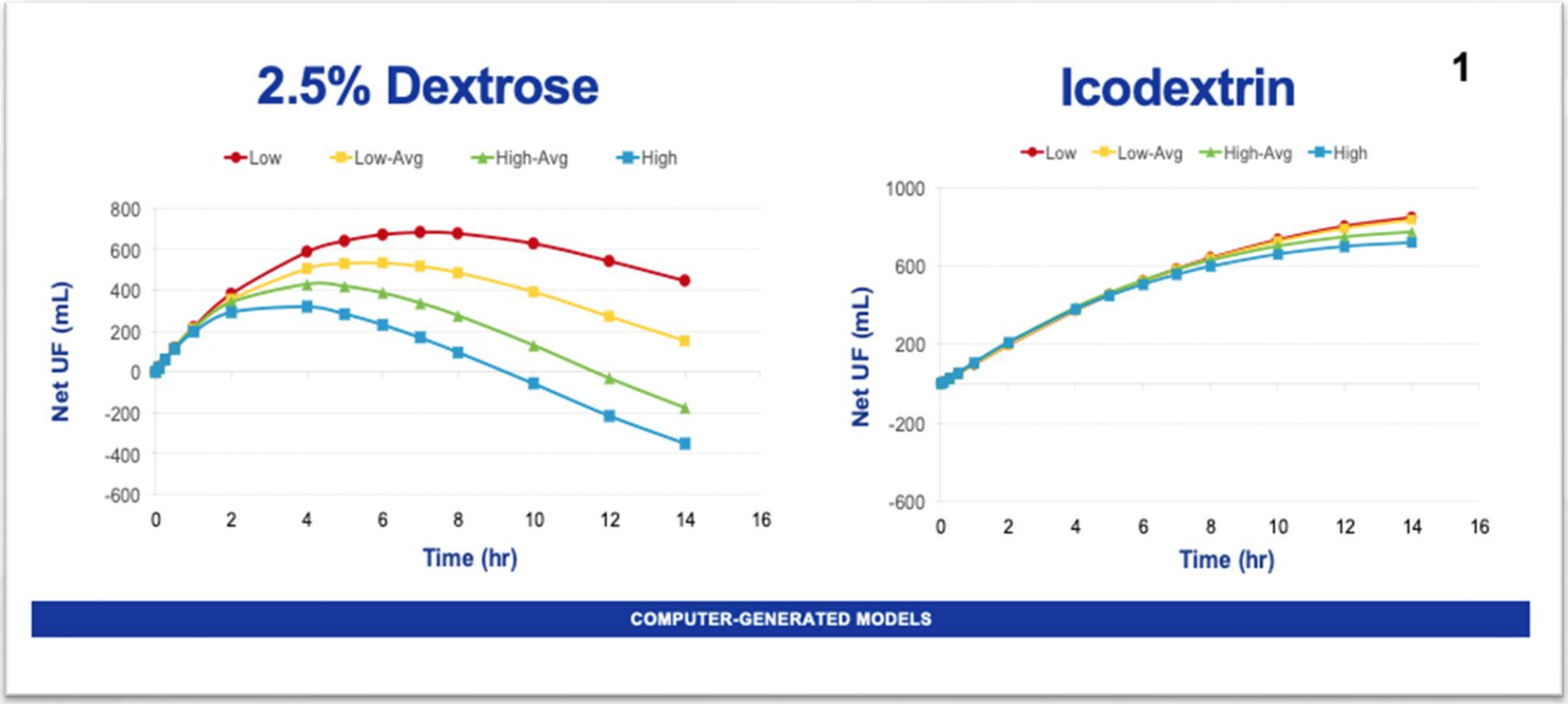
5. Brown E, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 244-253.
6. Chen H, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 274-281.

Icodextrin Functions Irrespective of Transport Type



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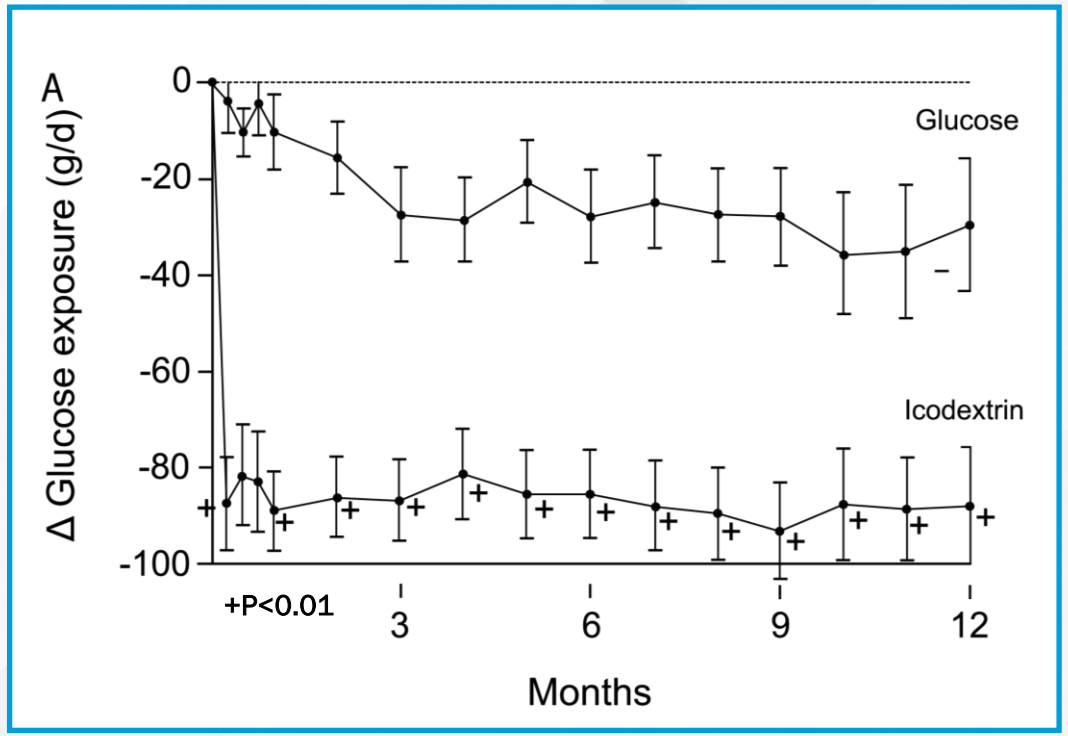
2. Morelle J, et al. ISPD Guidelines. (Evaluation of Membrane Dysfunction) *Perit Dial Int.* 2021; 41: 352-372.

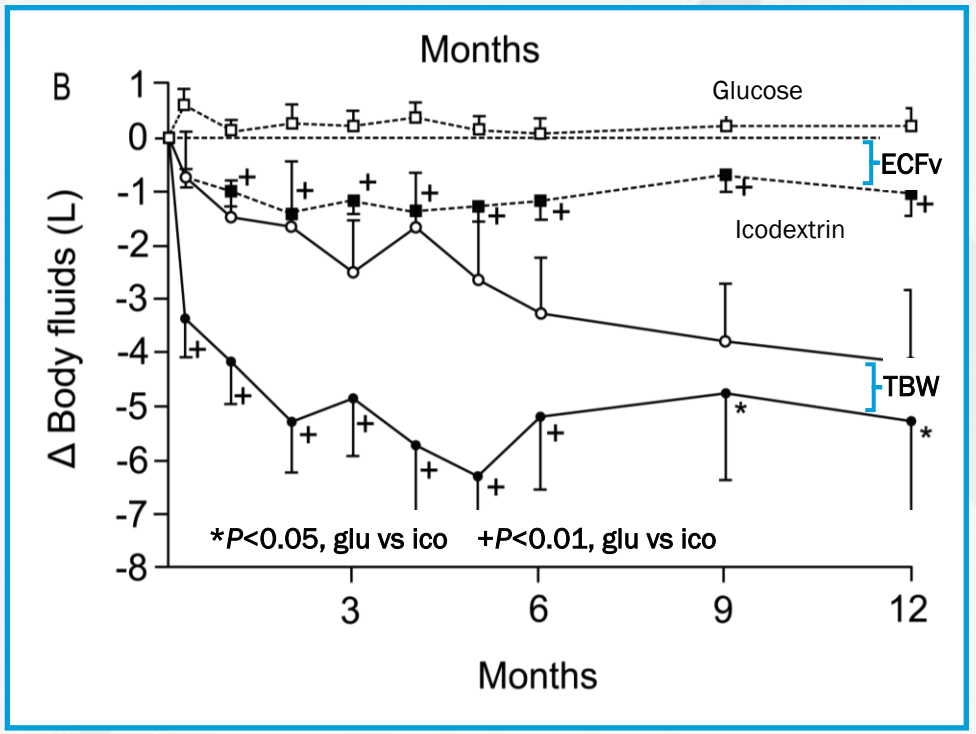
Icodextrin: Clinical Outcomes

RCT 59 HA/H TRANSPORTERS ALL DM ON CAPD OVER 12 MONTHS RANDOMIZED TO ALL GLUCOSE OR ICODEXTRIN FOR LONG DWELL

Mean UF difference icodextrin vs glucose was 197 mL/day (p<0.006)

Decreased glucose exposure in icodextrin group (p<0.01)

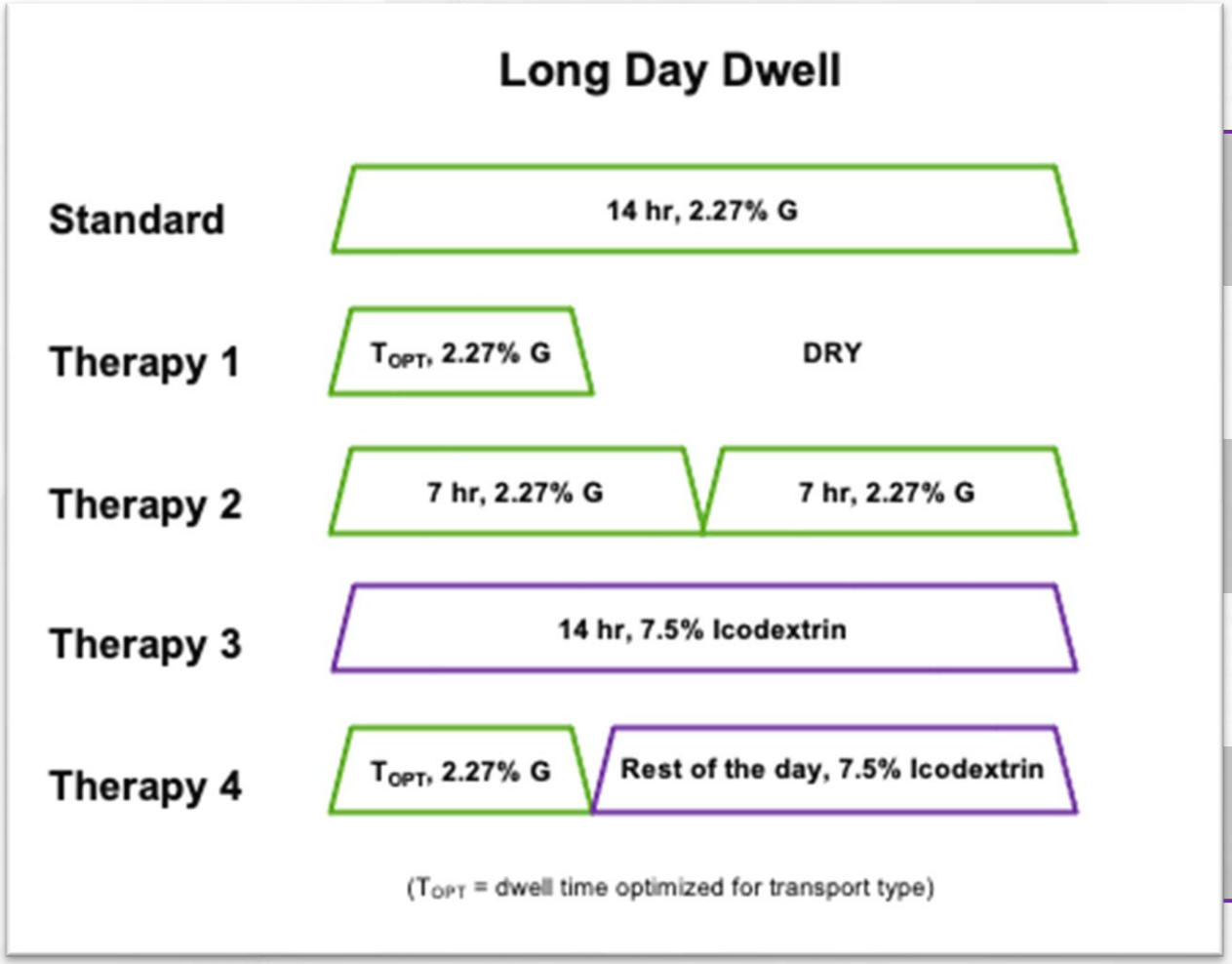




Paniagua R et al. *Perit Dial Int.* 2009; 29:422-432.

Management of Day Dwell in APD

COMPUTER MODELING CLEARANCE STUDY: DAYTIME PRESCRIPTIONS IN H, HA & LA ANURIC PTS



Therapy Type	UF	Na^+ Removal	Kt/V	B2M Clearance mL/min
Std	-230	-26	0.30	0.33
1	183	18	0.34	0.18
2	210	22	0.70	0.57
3	476	71	0.42	0.51
4	574	77	0.74	0.56

Akonur A et al. *Perit Dial Int.* 2013; 33: 646-654.

PDOPPS: Current Practice Patterns

Number of Patients	A/NZ 324	Japan 532	Canada 376	UK 221	US 2657
Total Kt/V urea	2.13 (0.82)	1.89 (0.71)	1.89 (0.93)	2.26 (0.66)	2.30 (0.63)
Residual Kt/V urea	0.87 (0.79)	0.78 (0.76)	0.67 (0.69)	1.04 (0.73)	0.77 (0.80)
Peritoneal Kt/V urea	1.25 (0.52)	1.14 (0.46)	1.21 (0.58)	1.22 (0.54)	1.54 (0.51)
24-hour urine volume, L	0.87 (0.69)	0.80 (0.63)	0.85 (0.65)	1.19 (0.79)	0.75 (0.75)
24-hour urine volume per BSA, L/1.73 m^2	0.79 (0.64)	0.86 (0.65)	0.78 (0.60)	1.01 (0.69)	0.67 (0.66)
Anuric[a]	9%/19%	7%/37%	15%/25%	6%/30%	23%/24%
PD solution type[b]					
Icodextrin	47%	43%	58%	58%	23%
PD solution glucose concentration[b]					
Without any 2.5%or 4.25% use	17%	68%	22%	52%	4%
Use of 2.5% but not 4.25%	77%	32%	66%	47%	51%
Use of any 4.25%	6%	0%	12%	1%	45%

a. The first number assumes the anuric status of patients missing urine volume data is unknown and excludes these patients from the anuric % / Second number assumes patients missing urine volume data are anuric in order to account for the potential practice in some countries/facilities whereby urine volume is not reported for patients known to be anuric.
b. PD solution type only provided by non-LDOs in the US.
Abbreviations: BSA, body surface area; Kt/V, urea clearance; PD, peritoneal dialysis; UK, United Kingdom; US, United States

The US is hyper focused on solute clearance at the expense of optimal volume management

Adapted from: Wang A, et al. *Perit Dial Int. 2020;* 40:282-292. Supplemental materials for International comparison of peritoneal dialysis prescriptions from the PDOPP study.

Presentation Plan

Volume Status in PD

Physiology of Ultrafiltration

Volume Management: Prescription Design

- Short Dwell
- Long Dwell

Volume Management: Beyond Glucose

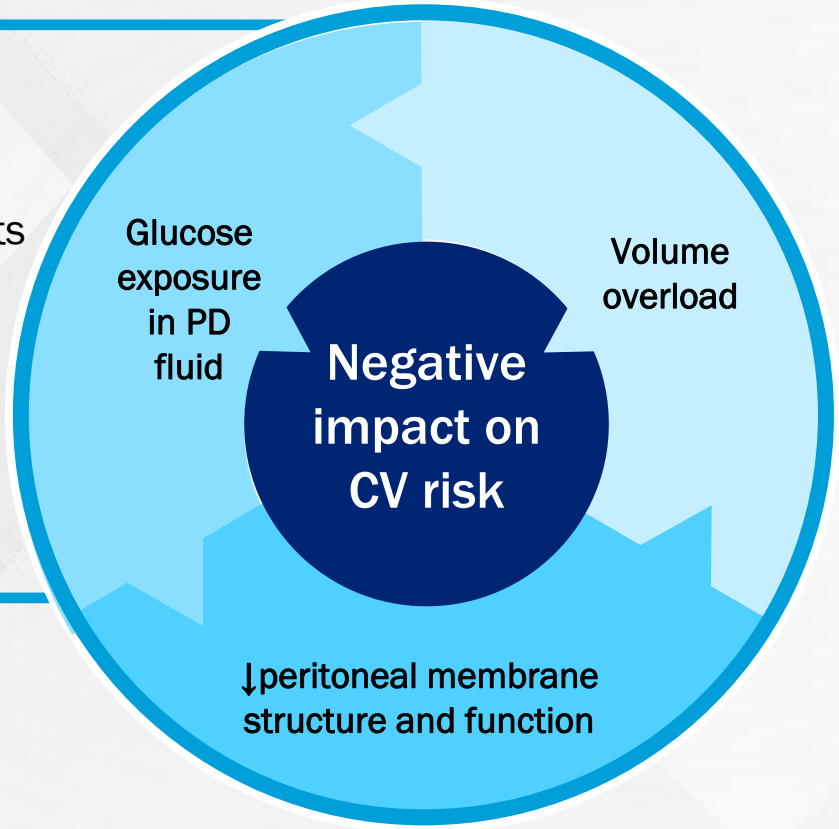
Volume Overload

- Diagnosis
- Management

Minimizing Glucose Exposure

PDOPPS: IN US 45% USE SOME 4.25%; 23% USE ICODEXTRIN[1]

Glycemic control
Dyslipidemia
Acute hemodynamic effects
Insulin resistance
Vascular calcification
Truncal fat mass



Techniques to Minimize Glucose Exposure

- Incremental start[2]
  - Dry periods with compensating RRF
- Diuretic use UO >100 mL/day[3]
- 2 gm Na+ diet[4,5]
- Fluid restriction[5]
- Icodextrin use[6]
  - glucose free solution

1. Adapted from: Wang A, et al. *Perit Dial Int.* 2020; 40:282-292. Supplemental materials for International comparison of peritoneal dialysis prescriptions from the PDOPP study.
2. Auguste BL & Bargman. *JM Sem Dial.* 2018;31:445-448.
3. Blake PG, et al. *Perit Dial Int.* 2011; 31:218-239.
4. Günal AI, et al. *Am J Kid Dis.* 2001; 37:588-593.
5. NKF-KDOQI Guidelines. *Am J of Kidney Dis.* 2006; 48, (Suppl 1):S98-129.
6. Woodrow G et al. *BMC Nephrol.* 2017; 18:333.

Incremental Start:
Initiation with Full Dose PD Often not Required

- RKF CONTRIBUTES TO TOTAL Kt/V
- WHAT GFR GIVES A Kt/V OF 1.7 WITHOUT DIALYSIS?

9.7 mL/min/1.73 m²

(computer modeled from 1200 patients)[1]

GFR at dialysis initiation[2]

GFR >15	10.6%
GFR 10-14	27.3%
GFR 5-9	47.9%
GFR < 5	14.2%

As RKF declines the dose of dialysis must increase.

1. Guest S, et al. *Perit Dial Int.* 2012; 32:142-148.
2. USRDS 2019 Vol 2 fig 1.19

Volume Management: ISPD Recommendations 2020

01

Initial PET 6-12 weeks post training; repeat as clinically indicated. [1,2]

Routine monitoring: PET , volume status, BP & clinical exam[3]

02

Icodextrin to improve UF independent of transport type[4]

"Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload"[2]

03

Dietary counseling of appropriate salt / water intake[1]

04

Protection of RRF[5]**; Loop diuretics if RRF present**[1]

Furosemide 160-480 mg/day (split-2 doses)[6]

Metolazone 5-10 mg/day[6]

05

Preservation of peritoneal membrane function[1]

Avoid peritonitis & hypertonic glucose solutions

1. Mujais S, et al. *Perit Dial Int*. 2000; 20(suppl 4):S5-S21.
2. Morelle J, et al. ISPD Guidelines. (Evaluation of Membrane Dysfunction) *Perit Dial Int.* 2021; 41: 352-372.
3. Wang A, et. ISPD Guidelines. (Volume Management) *Perit Dial Int.* 2020; 40: 282-292.
4. Boudeville N, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 254-260.
5. Brown E, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 244-253.
6. Chen H, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 274-281.

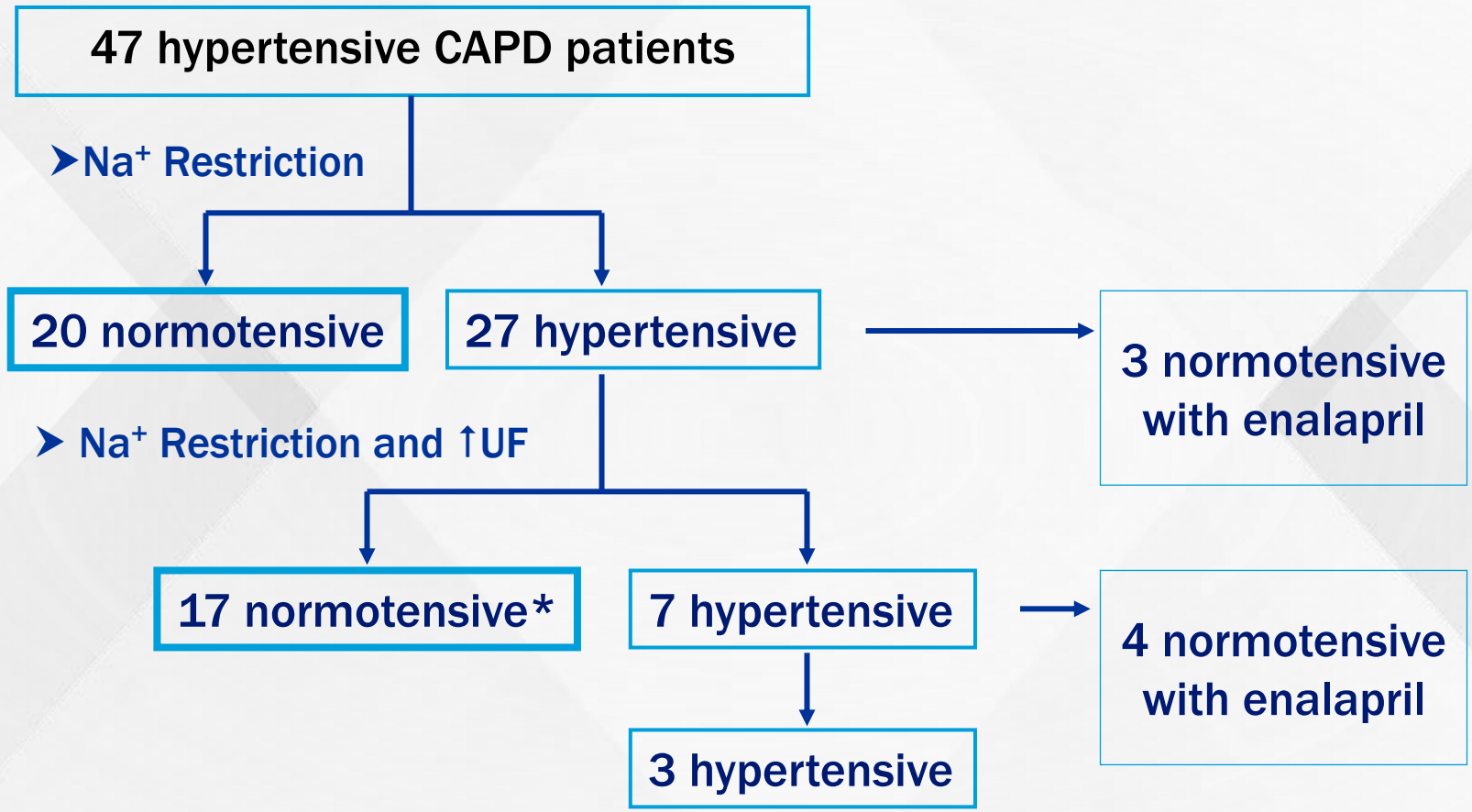
Volume Management

CANADIAN SOCIETY OF NEPHROLOGY GUIDELINES 2011

- Treatment of hypervolemia
  - **3.2.1 Sodium intake should be restricted to 65 mmol (1500 mg) or less daily in pts with hypervolemia**
  - 3.2.2 In patients with RRF, high-dose diuretics (furosemide 250 mg with or without metolazone 5 mg po QD) increase sodium excretion and urine volume
  - 3.2.3 Hypertonic 4.25% dextrose solution may be required to achieve euvolemia: however, sustained use of such solution is not desirable
  - 3.2.4 Icodextrin solution is preferred over glucose-based dialysate for long-duration (>8 hour) dwells

Blake P, et al. *Perit Dial Int*. 2011;31:218-239.

Fluid Management in PD



*37 (79%) patients normotensive by volume control alone

Günal AI, et al. *Am J Kid Dis*. 2001; 37:588-593.

Strict Volume Control Normalizes BP

- Aggressive dietary approach, followed by UF approach, lowered the body wt 2.8 kg in 47 hypertensive PD pts
- BP 158/96 dropped to 120/78
- In 19 pts with RRF, daily urine volume dropped to 28% of pre-treatment
- Kt/V dropped from 2.06 to 1.85 with loss of RRF

ISPD 2020:

High-quality PD should achieve and maintain clinical euvolemia while accounting for RKF and its preservation. Avoid RKF compromise by considering both peritoneal UF and UO in patient management.

Günal AI, et al. *Am J Kid Dis*. 2001; 37:588-593.
ISPD 2020. Wang A, et al. ISPD Guidelines. (volume management) *Perit Dial Int.* 2020; 40: 282-292

Does Attainment of Euvolemia Necessarily Affect RKF Adversely?

- Multicenter, double blind, RCT of icodextrin vs. 2.5% dextrose for long dwell
- N=50, high transporters with UO <750 mL/day
- Icodextrin group lost weight, total body water and salt, dextrose group gained all three ($p<0.05$)
- BP control not different
- Urine volume better maintained in icodextrin group
  - Difference: 89 mL/d ($p<0.04$)

Davies SJ, et al. *J Am Soc Nephrol*. 2003; 14:2338-2344.

Volume Management: ISPD Recommendations 2020

01 **Initial PET 6-12 weeks post training; repeat as clinically indicated.** [1,2]

Routine monitoring: PET , volume status, BP & clinical exam[3]

02 **Icodextrin to improve UF independent of transport type**[4]

"Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload"[2]

03 **Dietary counseling of appropriate salt / water intake**[1]

04 **Protection of RRF**[5]**; Loop diuretics if RRF present**[1]

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Metolazone 5-10 mg/day[6]

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Avoid peritonitis & hypertonic glucose solutions

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3. Wang A, et. ISPD Guidelines. (Volume Management) *Perit Dial Int.* 2020; 40: 282-292.
4. Boudeville N, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 254-260.
5. Brown E, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 244-253.
6. Chen H, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 274-281.

CANUSA Study: Effect of Residual Renal Function and Urine Volume on Mortality

Table 2: Cox model of relative risk of death with time-dependent CCr divided into peritoneal clearance and GFR and entered as time-dependent covariates

Variable	Relative Risk	95% Confidence Limit
Age	1.02	1.005-1.044
CVD	2.42	1.499-3.904
Diabetes mellitus	1.25	0.769-2.036
Serum albumin	0.96	0.912-1.000
LA transport	1.66	0.379-7.218
HA transport	2.33	0.554-9.801
H transport	2.01	0.430-9.357
SGA	0.74	0.647-0.842
Ccrp (5 L/wk per 1.73m^2 greater)	1.00	0.898-1.105
GFR (5 L/wk per 1.73m^2 greater)	**0.88**	0.829-0.943

Table 3: Cox model of relative risk for death with urine volume forced in as a time-dependent covariate

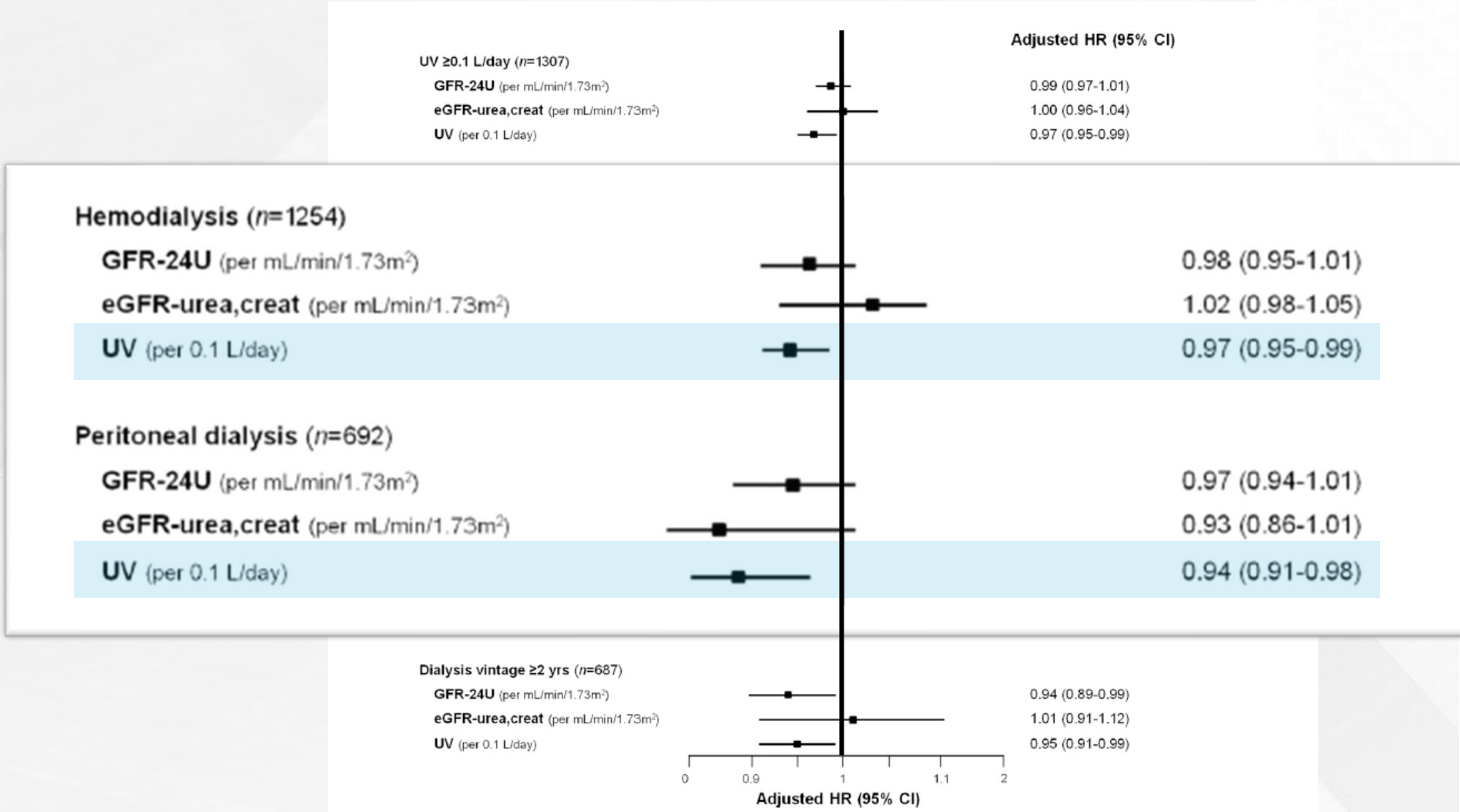
Variable	Relative Risk	95% Confidence Limit
Age (1 yr older)	1.02	1.002-1.041
CVD	2.37	1.465-3.821
Diabetes mellitus	1.31	0.807-2.134
Serum albumin (1 g/L increase)	0.96	0.914-1.003
LA transport	1.84	0.418-8.075
HA transport	2.71	0.631-11.623
H transport	2.46	0.523-11.590
SGA (1 unit greater)	0.78	0.672-0.876
Ccrp (5 L/wk per 1.73m^2 greater)	0.93	0.795-1.079
GFR (5 L/wk per 1.73m^2 greater)	0.99	0.943-1.044
Urine vol (250 ml daily greater)	**0.64**	0.508-0.800

Bargman J, et al. *J Am Soc Nephrol*. 2001;12:2158-2

Prognostic Value of Urine Volume

Prospective cohort study N=1946, 36 Korean clinics 8/2008-12/2014. FU mean-42 months

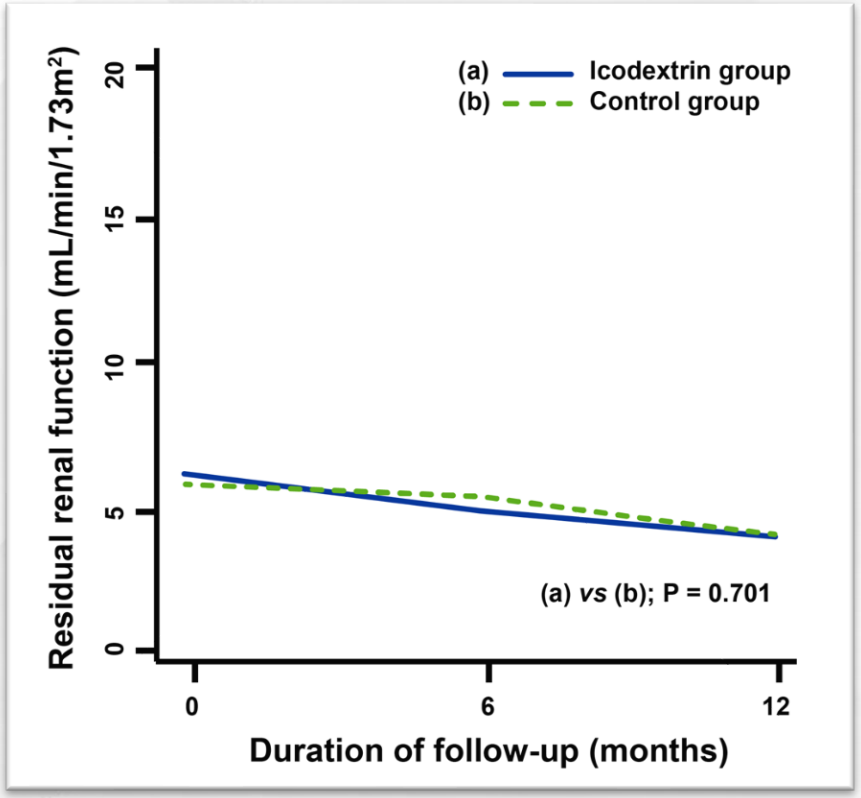
- **Higher residual urine volume** was significantly associated with a **lower risk of death** and exhibited a stronger association with mortality than GFR calculated using 24-hour urine collection and eGFR-urea, creatinine.
- **Monitoring residual urine** volume may be beneficial to predict **survival of dialysis pts.**

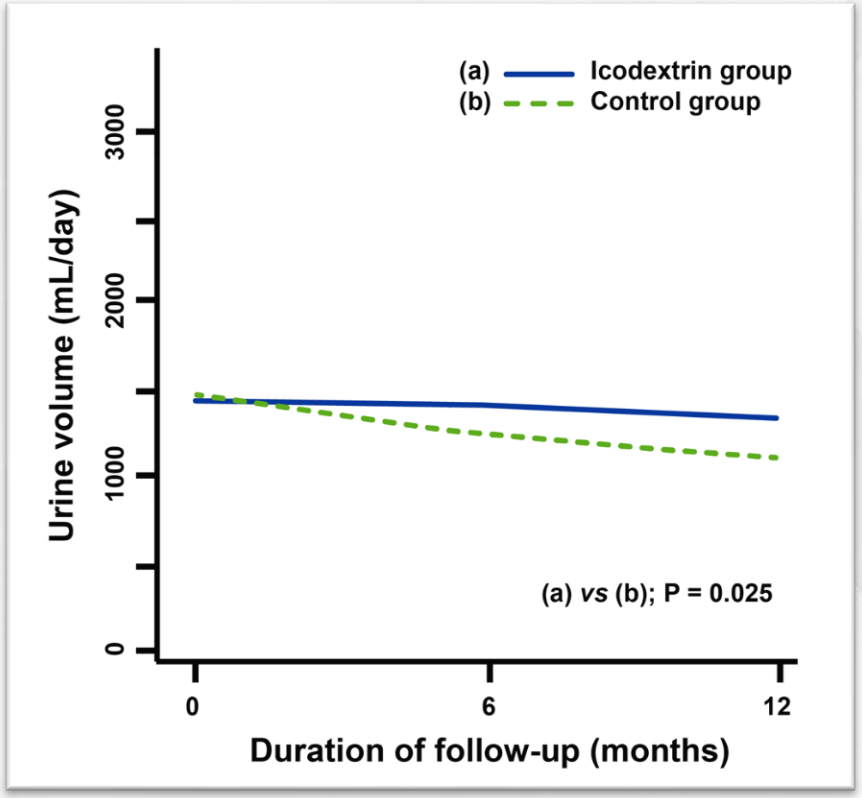


Lee MJ, et al. *Clin J Am Soc Nephrol*. 2017; 12:426-434.

Icodextrin: Urine Output

MULTI-CENTER PROSPECTIVE RCT: N=100 CAPD; UO ≥ 750CC/DAY RANDOMIZED TO ICODEXTRIN VS. 1.5% / 2.5% DEXTROSE-BIOCOMPATIBLE SOLUTIONS.





No difference in GFR; better preservation of urine output

Chang TI, et al. *Medicine*. 2016; 95:e2991.

Canadian Clinical Practice Guidelines

1.2 USE OF DIURETICS TO PRESERVE RRF

Recommendations:

- 1.2.3 Strong consideration should be given to the use of high-dose oral furosemide (**up to 250 mg daily**) and oral metolazone (up to 5 mg daily) in all PD patients with significant (>100 mL daily) urine output, *provided that this is not associated with signs and symptoms of postural hypotension or volume depletion* (grade B).

Blake PG, et al *Perit Dial Int*. 2011; 31:218-239.

Why such high diuretic doses?

FUROSEMIDE 160-480 MG/DAY (SPLIT-2 DOSES) & METOLAZONE 5-10 MG/DAY[1]

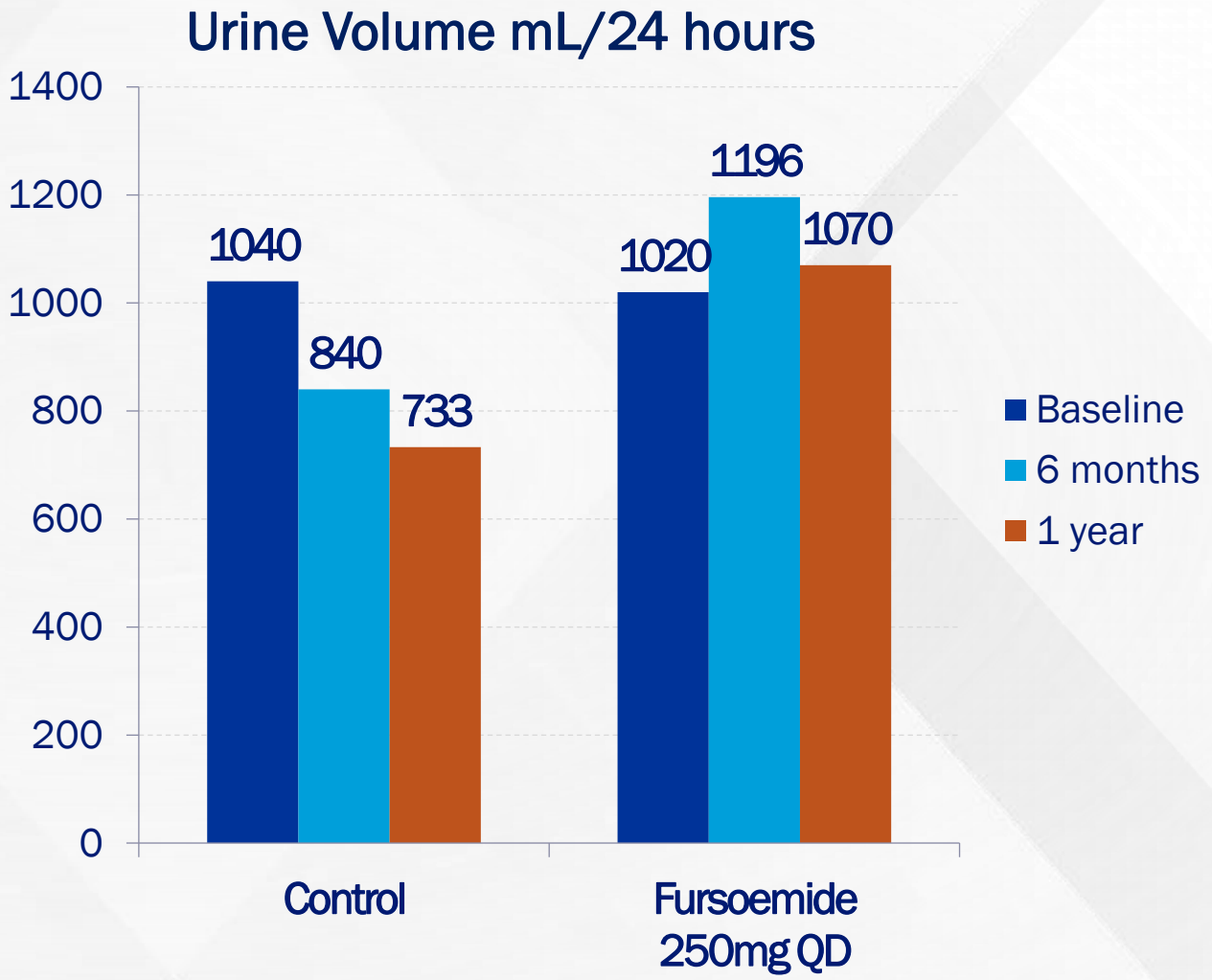
Per Dr George Arnoff's book: *Drug Prescribing in Renal Failure:*[2]

- Furosemide, bumetanide, & ethacrynic acid are organic acids which must reach the tubular lumen to be active.
- "In patients with impaired renal function, endogenous organic acids accumulate and compete with diuretics for secretion into the tubular lumen."
- "Consequently, as renal function decreases, larger doses of diuretics are required."

1. Chen H, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 274-281.
2. Arnoff GR et al. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults. 4th ed.; Philadelphia: American College of Physicians. pg 22.

Diuretics Increase Urine Volume

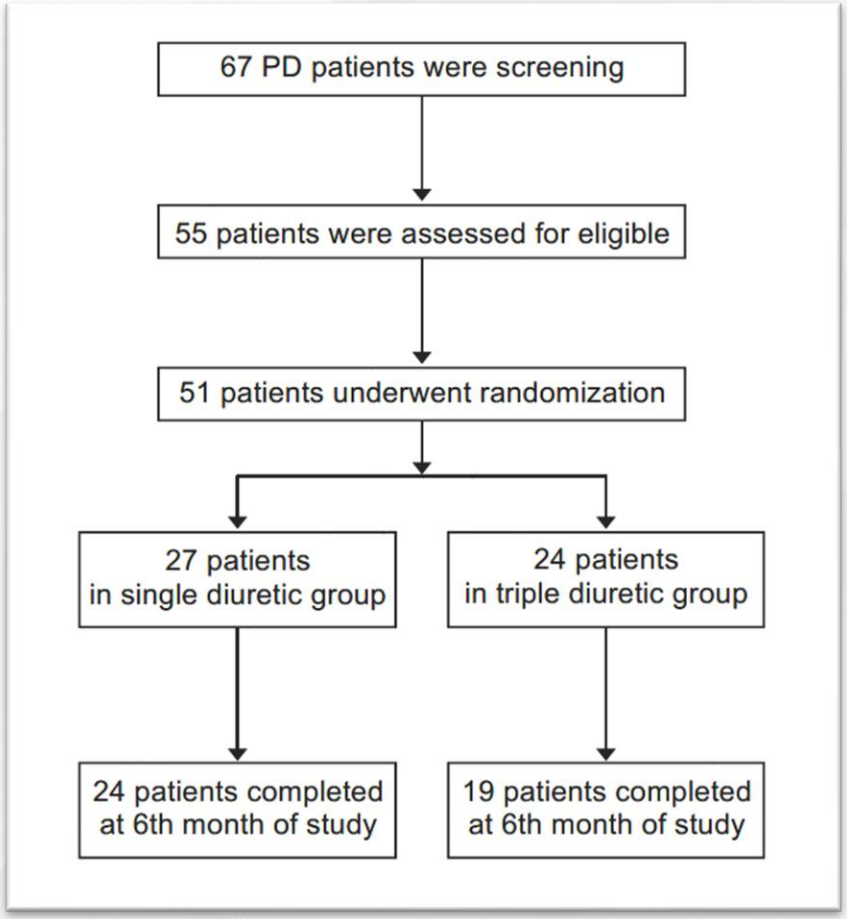
- 61 CAPD patients new to dialysis randomized to furosemide 250 mg/day or control
- Change in urine volume: +6.47 vs.
  -23.3 mL/mo
  (P = 0.047)
- No effect on rate of decline of urinary solute clearances



Medcalf JF, et al. *Kidney Int*. 2001;59:1128-1133.

Triple Diuretic Treatment: CAPD

TWO PHASE PROSPECTIVE, DOUBLE BLIND RCT (6 MONTH)

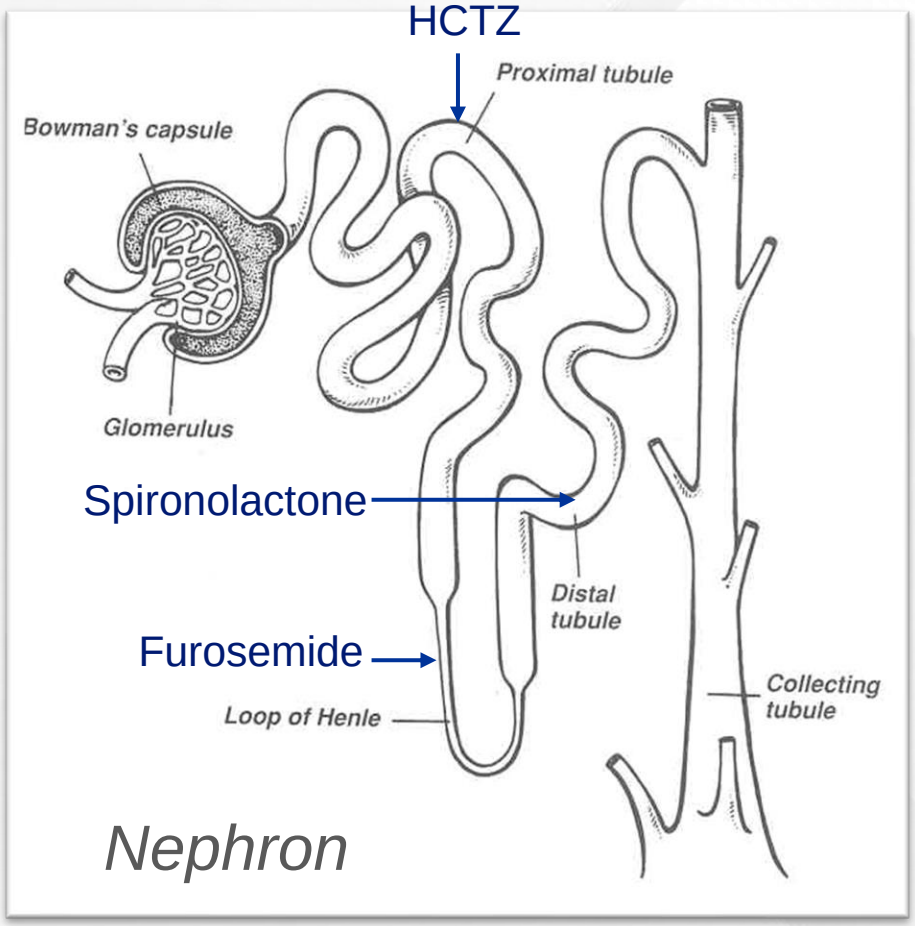


SINGLE DRUG ARM

- Furosemide: 1,000 mg/day

TRIPLE DRUG ARM

- Furosemide: 1,000 mg/day
- HCTZ: 100mg/day
- Spironolactone: 50 mg/day



Triple diuretic therapy blocks Na+ through whole nephron

Witoon R, et al. *Kidney Res Clin Pract.* 2019; 38: 108-115.

Triple Diuretic Treatment: CAPD

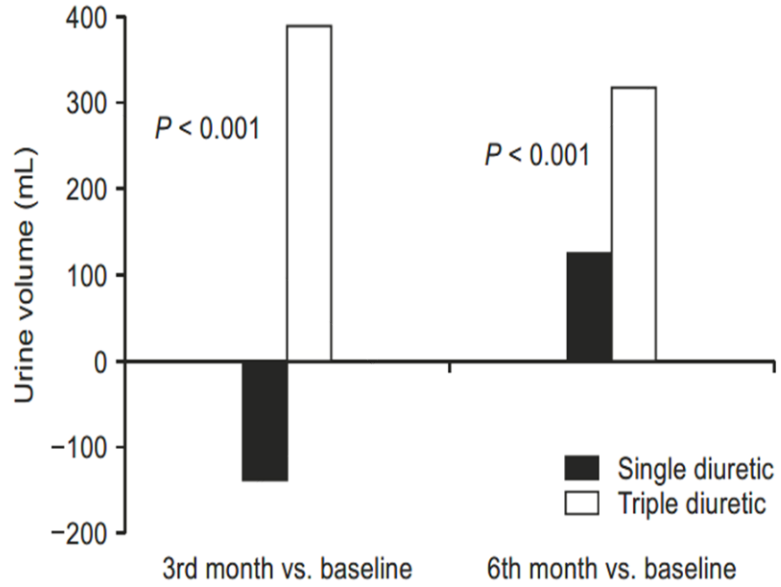


Figure 2. Mean differences in urine volume at baseline vs. 3rd month and baseline vs. 6th month of study for single diuretic-treated group and triple diuretic-treated group.

Table 2. Overhydration measured by BIS in the single diuretic group and the triple diuretic group at baseline, 3rd month, and 6th month of study

	Single diuretic	Triple diuretics	*P* value
OH (L)			
Baseline	2.27 ± 2.35	2.94 ± 2.08	0.34
3rd month	2.03 ± 1.80	1.03 ± 0.68	0.01
6th month	2.78 ± 2.42	1.39 ± 1.64	0.06

Table 4. Adverse event profiles

Adverse events	Single diuretic	Triple diuretics
Hyponatremia[a]	4 (14.8)	5 (20.8)
Hypokalemia[b]	7 (25.9)	6 (25.0)
Hyperkalemia[c]	1 (3.7)	1 (4.2)
Dizziness	1 (3.7)	1 (4.2)
Hypotension	1 (3.7)	1 (4.2)

Data are presented as number (%).

[a]Serum sodium < 135 mmol/L, [b]serum potassium (K) < 3.5 mmol/L, [c]K > 5.5 mmol/L.

"There was no serious adverse event in this study."

Witoon R, et al. *Kidney Res Clin Pract.* 2019; 38: 108-115.

Long Term Diuretics in HD Patients

N=13 HD patients
studied over 1 year

(10 completed full year)

Furosemide doses:
3 = 250 mg/d

3 = 500 mg/d (in 2 doses)

1 = 750 mg/d (in 2 doses)

6 = 1000 mg/d (in 2 doses)

- ***Furosemide levels < 40 ug/ml (ototoxic level 85 ug/ml)***
- Audiometry at baseline and
  Q 3 months – no change in normal hearing range
- Bullous Dermatitis – in 2 of 10 (sunlight induced)

*p<0.005 **p<0.02

URINE	MONTHS	MEDIAN	RANGE
Volume	0	750	120-1,290
ml/day	3	1,250*	200-1,840
	6	960*	180-1,580
	9	625	140-1,580
	12	710	180-1,820
Na*	0	37	6-68
mmol/day	3	75*	16-115
	6	54*	12-142
	9	40	9-155
	12	41	9-153
Cl^-	0	14	2-49
mmol/day	3	69*	16-103
	6	52*	12-118
	9	40**	9-135
	12	42**	10-144
K^+	0	21	1-45
mmol/day	3	28*	2-55
	6	27**	3-49
	9	16	2-56
	12	28**	9-50
Ca^{2+}	0	0.40	0.12-1.35
	3	1.04**	0.35-2.30
	6	1.05**	0.26-2.36
	9	0.62	0.21-2.18
	12	0.69	0.19-2.19
Osmolality	0	296	212-445
mosm/kg	3	287	223-323
	6	275	207-328
	9	284	182-332
	12	280	229-359
F, mg/day	3	11.9	2.1-33.4
(Furosemide excretion)	6	8.9**	1.9-26.8
	9	7.9*	1.4-26.6
	12	7.5*	1.1-27.2
ECC	0	5.6	0.7-6.8
ml/min/1.73 m^2	3	4.5**	0.6-6.4
(Endogenous Creatinine Clearance)	6	4.3**	0.6-6.3
	9	3.2**	0.5-6.0
	12	1.9**	0.5-5.9

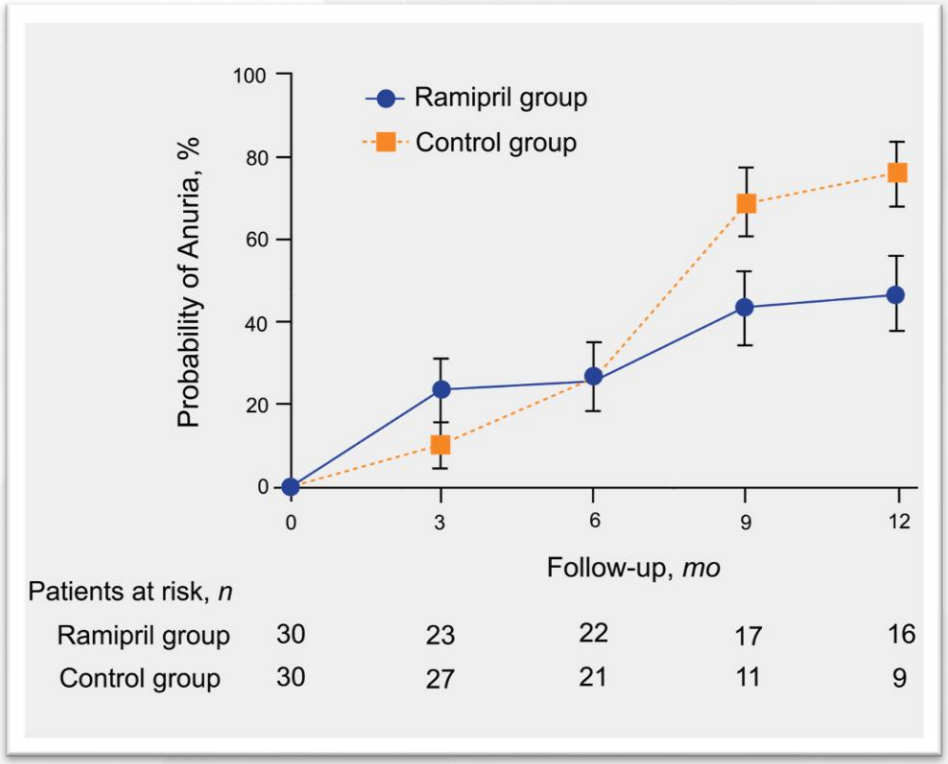
Van Olden RW, et al. *Am J Nephrol*, 1992;12:351-356.

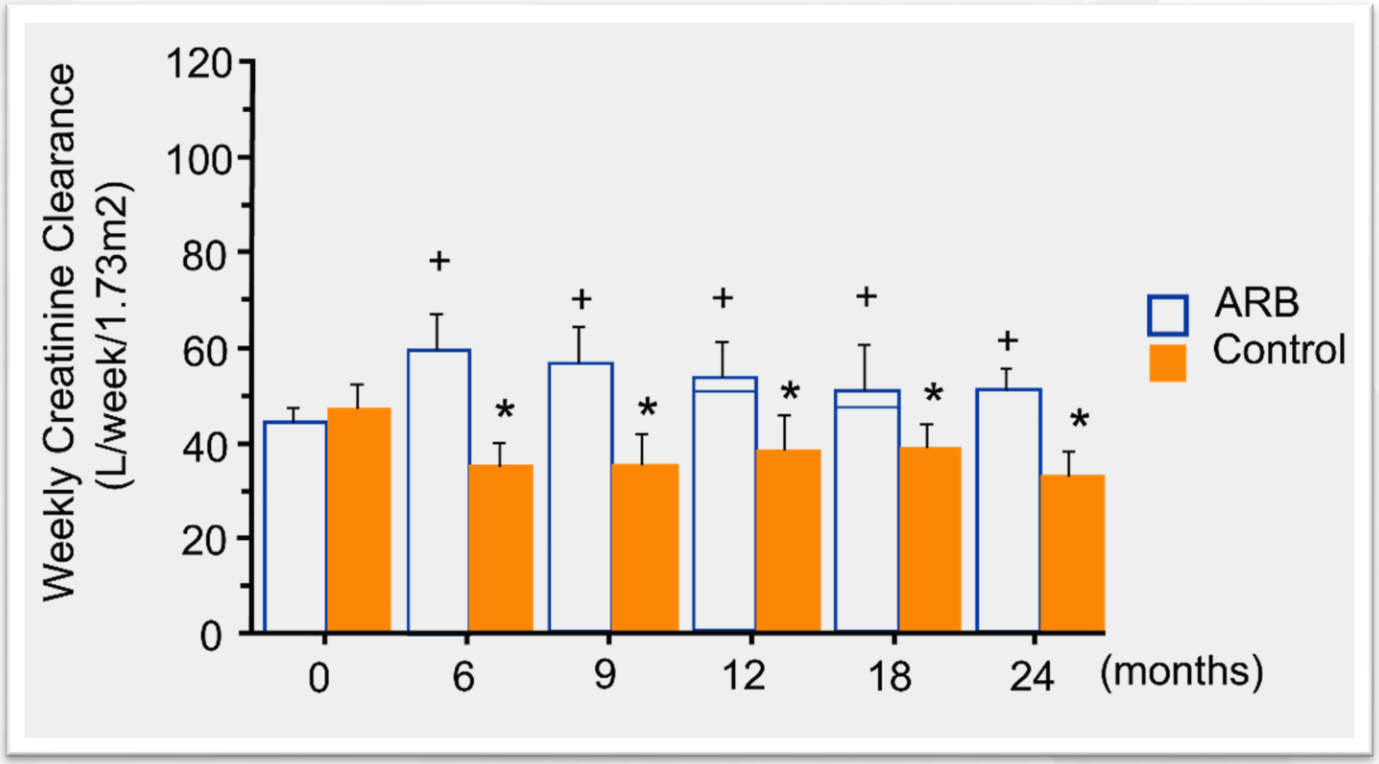
Preservation of RRF

CANADIAN SOCIETY OF NEPHROLOGY GUIDELINES 2011

- **1.2.2 Angiotensin converting-enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) should be strongly considered, unless contraindicated, in all PD patients with significant (>100 mL daily) urine output.**
- 1.2.3 Strong consideration should be given to the use of high-dose oral furosemide (up to 250 mg daily) and oral metolazone (up to 5 mg daily) in all PD patients with significant (>100 mL daily) urine output, provided that this is not associated with signs and symptoms of postural hypotension or volume depletion.

Effect of ACE-I & ARB on RRF in PD: 2 RCTs





Multivariate analysis, Ramipril 5 mg/day vs. placebo:

RKF loss at 12 mo:

- 2.07 ml/min Ramipril
- 3.00 ml/min control (p=0.03)

- Valsartan 40-80 mg/day vs. placebo. p<0.01 increased residual CrCl by 2-3 ml, residual diuresis by 200-300 ml/day and weekly total clearance

1. Li P, et al. *Ann Intern Med*. 2003; 139:105-112.
2. Suzuki H, et al. *Am J Kidney Dis*. 2004; 43:1056-1064.

Risk Factors for Loss of RKF

- Radiocontrast dye
- Aminoglycoside antibiotics
- NSAIDS, including cox-2 inhibitors
- ECF volume depletion
- Urinary tract obstruction
- Hypercalcemia
- Withdrawal of immunosuppressive therapy from transplanted kidney

NKF-KDOQI Guidelines. *Am J of Kidney Dis*, Vol 48, No 1, Suppl 1 (July), 2006:S117-S126.

Volume Management: ISPD Recommendations 2020

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Routine monitoring: PET , volume status, BP & clinical exam[3]

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"Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload"[2]

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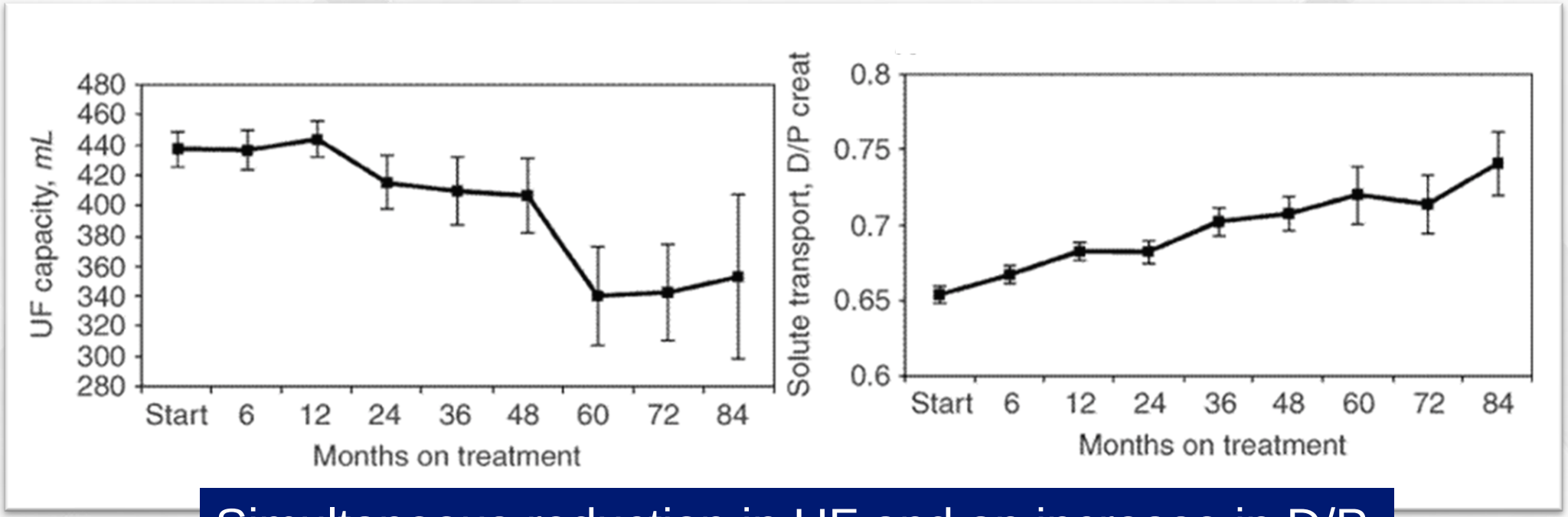
6. Chen H, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 274-281.

Longitudinal Relationship Between Solute Transport and Ultrafiltration Capacity in Peritoneal Dialysis Patients

- Single center retrospective observational study
- Cohort: All patients from 1990-2003
- 574 new patients available for study with annual PET data

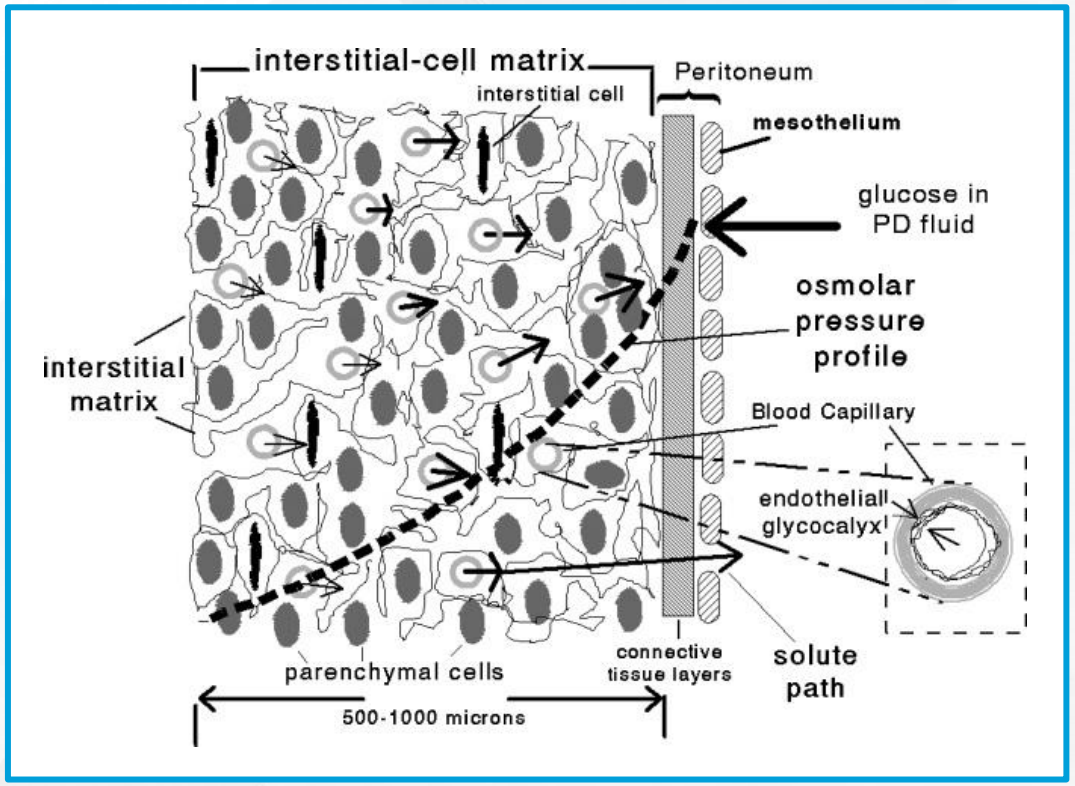


Simultaneous reduction in UF and an increase in D/P

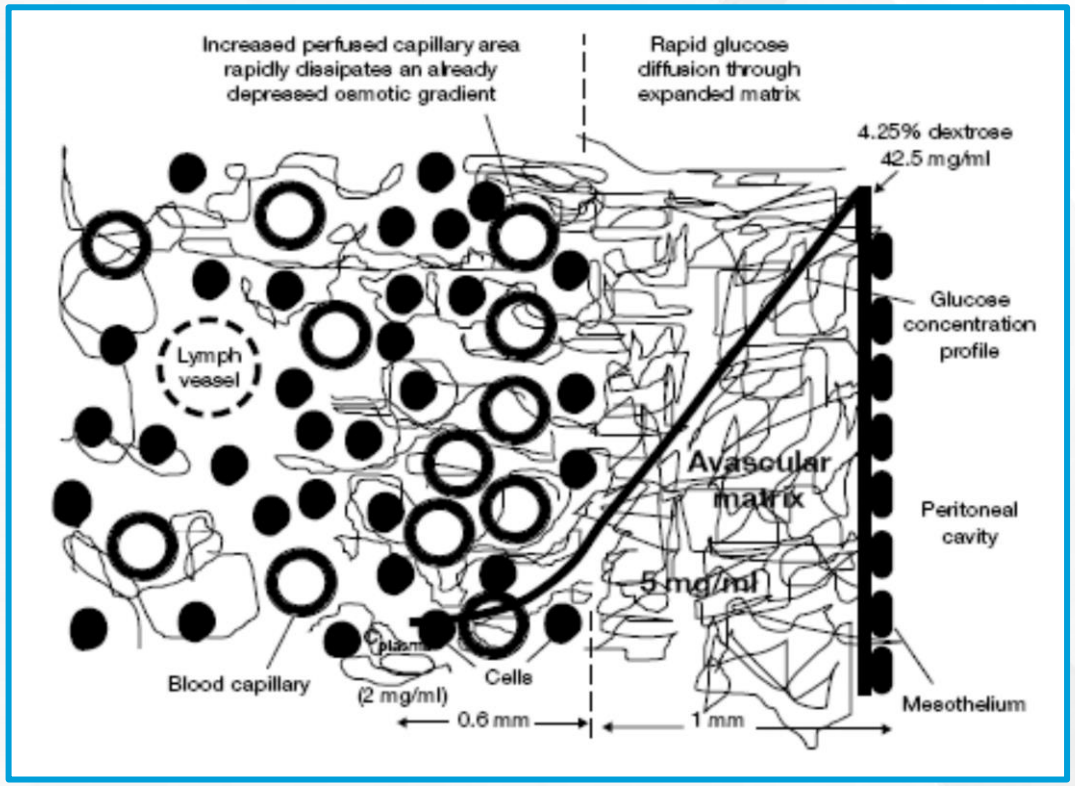
Davies SJ, et al. *Kidney Int*. 2004;66:2437-2445.

Long-term Functional Effects on the Peritoneal Membrane

MEMBRANE AT PD INITIATION[1]

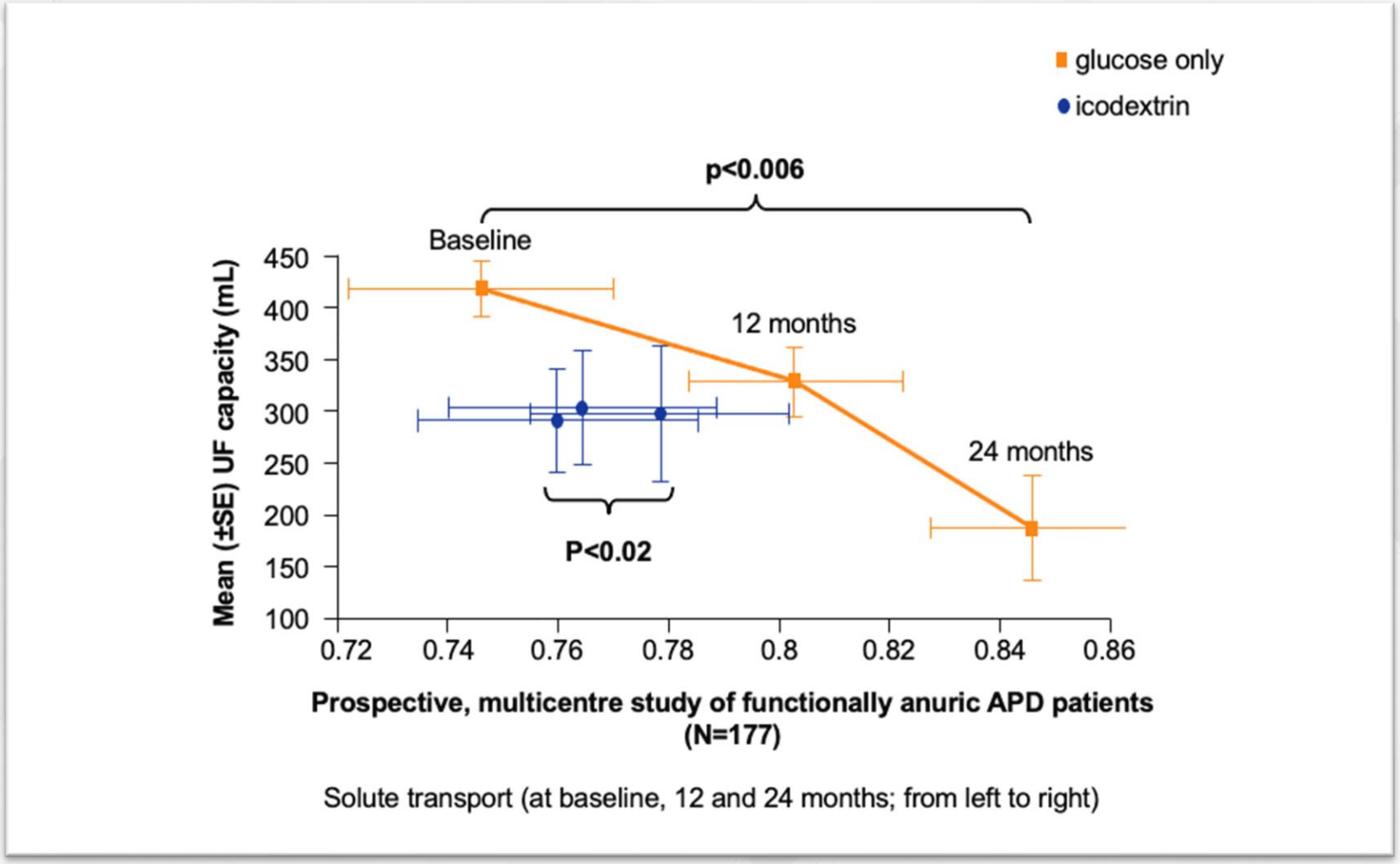


MEMBRANE OVER TIME ON PD: ↑ FIBROSIS AND ANGIOGENESIS[2]



1. Flessner MF. *Nephrol Dial Transplant*. 2008;23:2142-2146.
2. Flessner MF. *Contrib to Nephrol*. 2006; 150:174-180.

Low Glucose Therapy May Stabilize Peritoneal Membrane Function



Davies SJ, et al. *Kidney Int*. 2005;67:1609–1615.

UK Renal Association: Minimizing Glucose Exposure

Avoid use of 4.25% & 2.5% as much as possible due to systemic effects:[1]

- Poor DM control and Hyperinsulinemia
- Weight gain

Minimize hypertonic solution use:

- Diuretics to maximize residual diuresis
  - furosemide 250mg QD
- Substitute icodextrin for glucose during long dwell

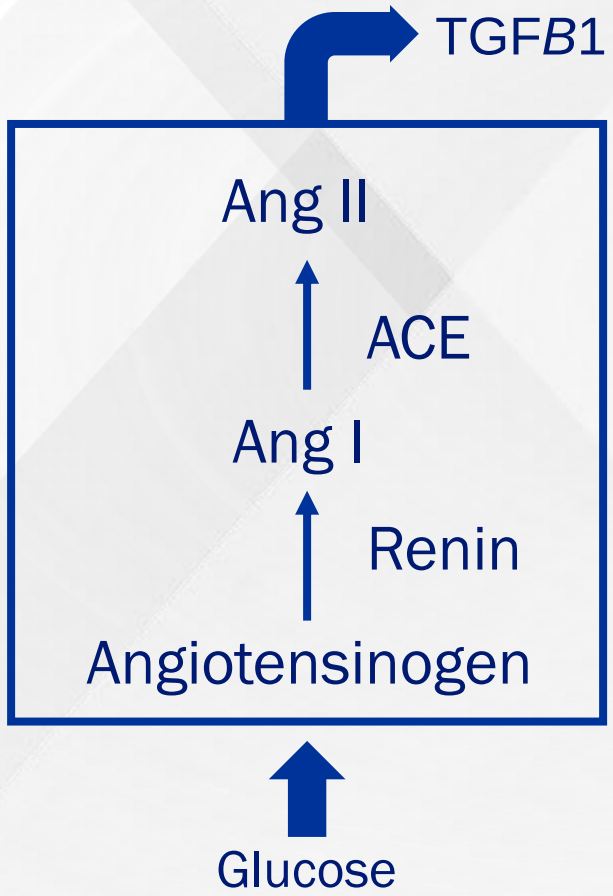
Optimal way to prescribe PD to minimize glucose exposure[1]

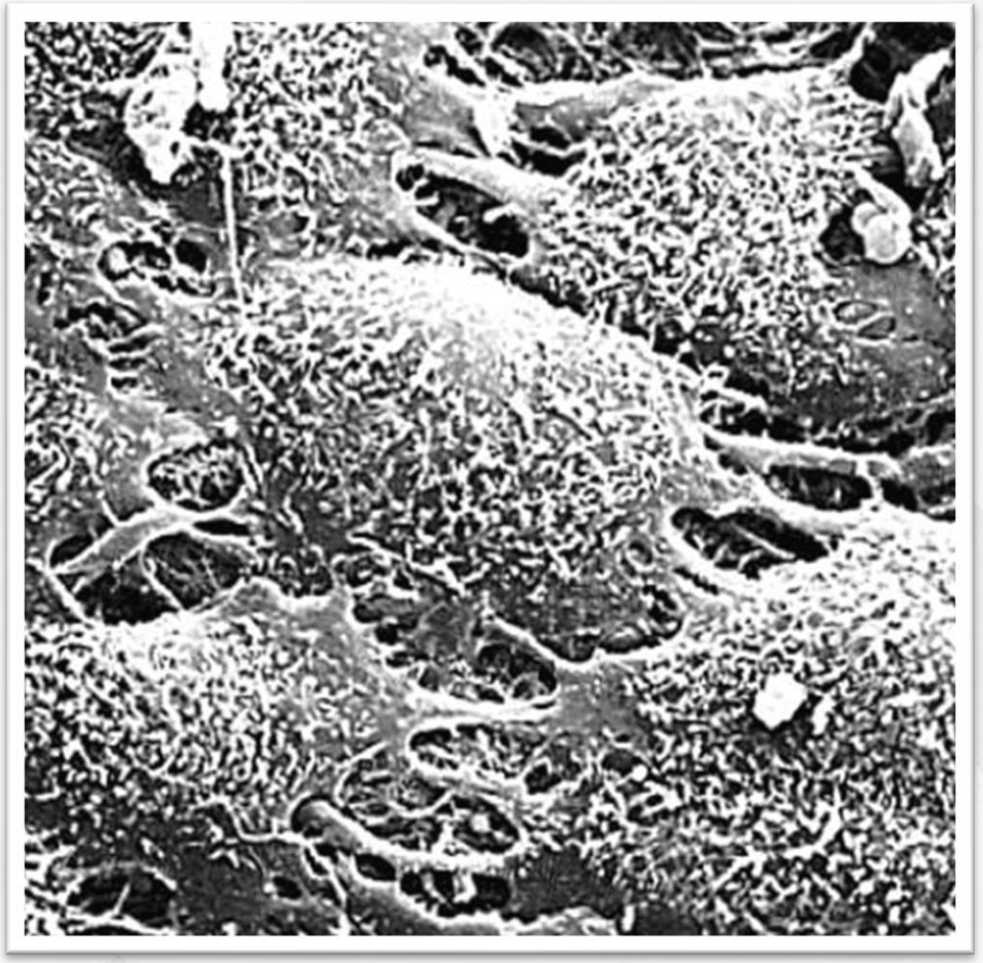
ISPD: Both loop diuretics and icodextrin help maintain fluid balance in PD patients[2]

1. Woodrow G, et al. *BMC Nephrol*. 2017; 18: 333.
2. Chen H et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40:274-281.

Possible Membrane Preservation

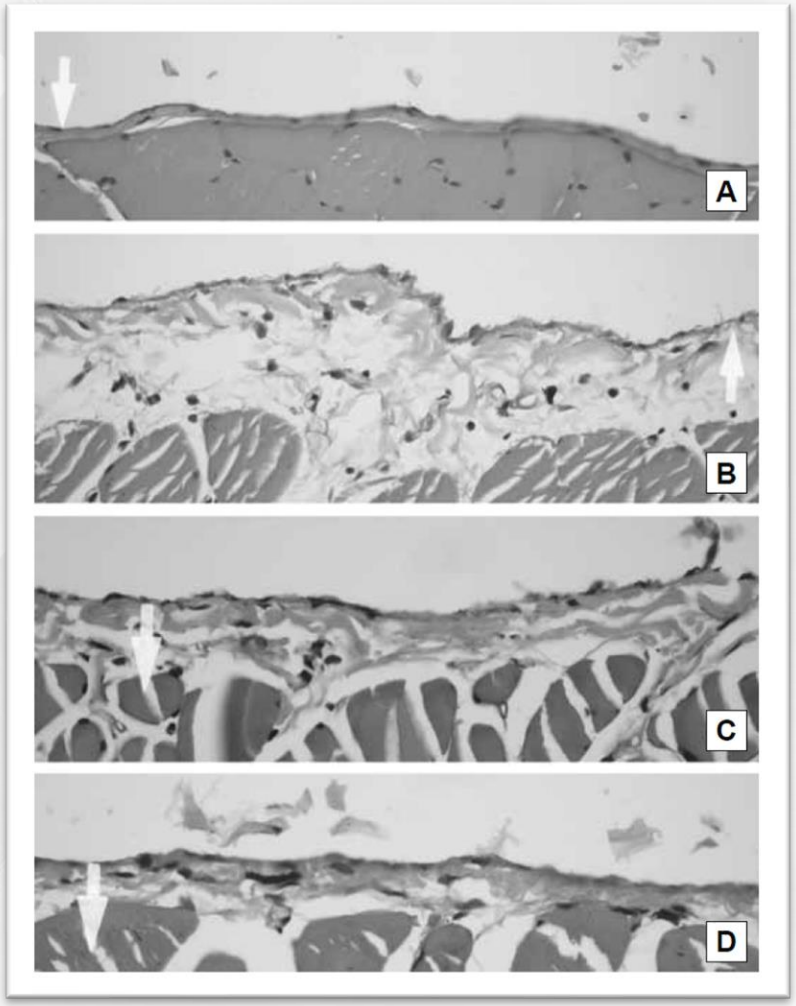
MESOTHELIAL RAAS SYSTEM





Slide adapted from Duman S, et al. *Int J Artif Org*. 2005,28:156-163.

Effect of Valsartan vs. Lisinopril on Peritoneal Sclerosis in Rats



A. Normal-Sham Rats

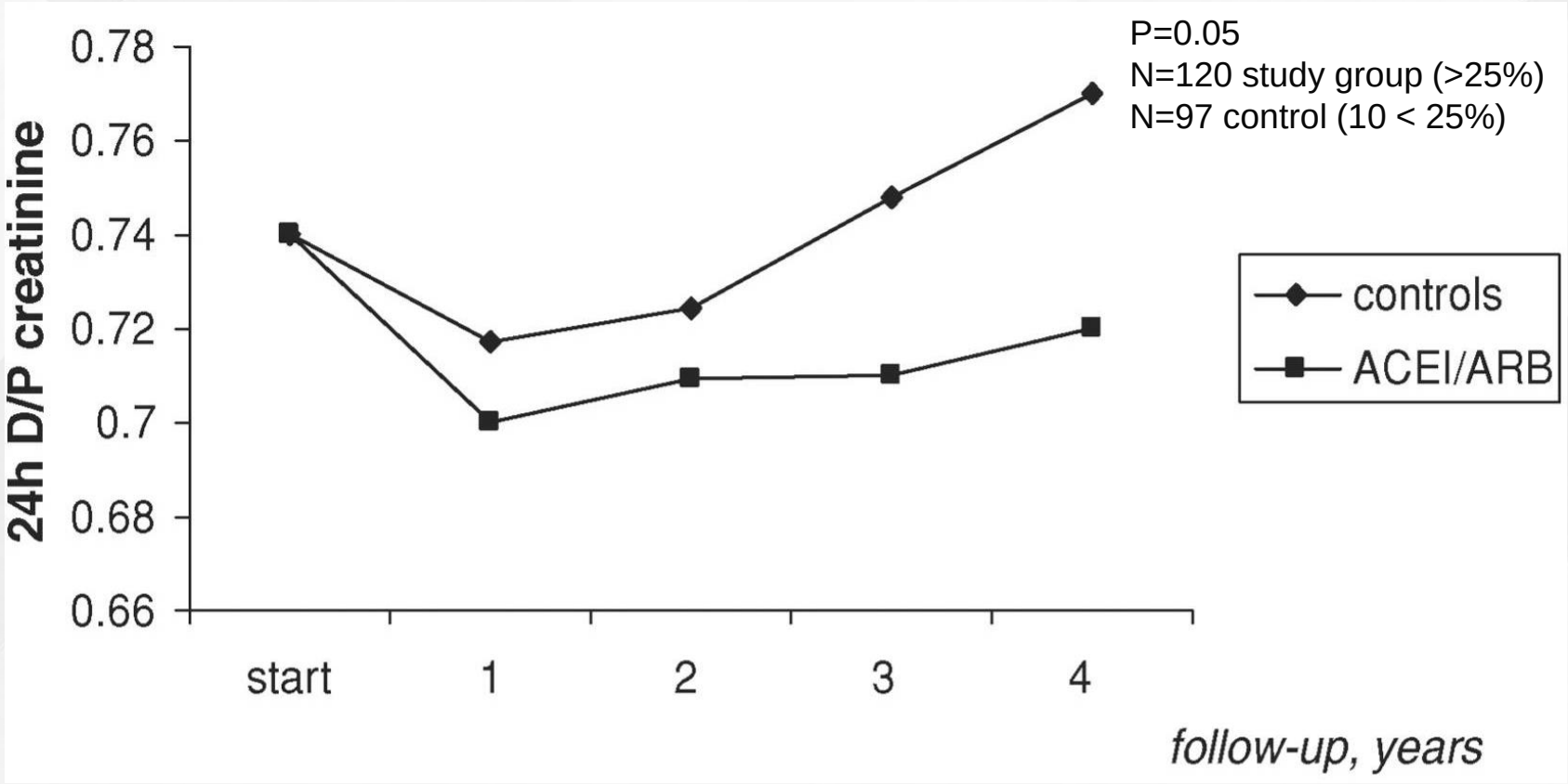
B. PD Solution (3.86%) only

C. 3.86% + Valsartan
(10-15 mg/day)

D. 3.86% + Lisinopril
(2-2.5 mg/day)

Duman S, et al. *Int J Artif Organs.* 2005;28:156-163.

ACEI Effect on Peritoneal Membrane Function PD Patients



Kolesnyk I, et al. *Nephrol Dial Transplant.* 2009;24:272-277.

Presentation Plan

Volume Status in PD

Physiology of Ultrafiltration

Volume Management: Prescription Design

- Short Dwell
- Long Dwell

Volume Management: Beyond Glucose

Volume Overload

- Diagnosis
- Management

Fluid Overload vs. UF Insufficiency

Fluid overload is a clinical syndrome with multiple components and etiologies

Ultrafiltration insufficiency is a pathophysiologic characterization of **one** of the causes of the clinical syndrome

Distinction between syndrome and causation determines further intervention

Volume overload is not always UF insufficiency!

Essential Clinical Evaluation of Volume Overload

Residual Renal Function	Reversible Issues			Membrane Evaluation
	Appropriate Prescription	Dietary Indiscretion, Compliance	Mechanical Issues	Modified PET
	Dwell time	Deficient education	Malposition	
	Dialysate tonicity	Complex regimen	Obstructions	
		Burn-out	Leaks	
			Entrapment	

Work-up

1. History & physical exam
2. Observe a 2-liter rapid in and out exchange to assess flow mechanics
3. Perform a 2-liter 4.25% dextrose PET

Adapted from Mujais S, et al. Perit Dial Int. 2000;20:Suppl4:S5-S21.

Evaluation of UF Insufficiency

MODIFIED PET: RULE OF FOURS[1]

- 2 L of 4.25% dextrose (rather than 2.5%)
- Do an additional measure of dialysate sodium at 60 min
- Abnormal findings indicating possible UF Insufficiency
  - Ultrafiltration < 400 mL
  - Dialysate sodium dip ≤ 5 meq/L at 60 min indicates UF insufficiency [2]

Ultrafiltration Insufficiency
2 L of **4.25%** dwell **4 hours** see **< 400 mL UF**

1. Mujais S, et al. *Perit Dial Int*. 2000; 20(Suppl 4):S5-S21.
2. Morelle J, et al. ISPD Guidelines. (Evaluation of Membrane Dysfunction) *Perit Dial Int.* 2021; in press. 1.

Membrane Evaluation

Low UF capacity identified
Net UF at 4 hours <400 ml using 4.25%

2 patients with 300 ml UF at 4 hours
Pt 1
Dialysate Na+ 125 mEq/L at 60 min
Pt 2
Dialysate Na+ 129 mEq/L at 60 min

Rule out mechanical problems/leaks

Fast Peritoneal Solute Transfer Rate
Local inflammation
(interstitial thickening & peritoneal membrane capillary proliferation)

- Inherent fast transfer rate
  -variability present at baseline
- Acquired membrane injury
  -Long-term PD/Peritonitis

Low osmotic conductance to glucose
Reduced free water transport
(decreased AQP1 function)

- Intrinsic low UF
  -variability present at baseline
- Acquired membrane injury
  -Progressive fibrosis/vasculopathy
  -At risk for Encapsulating Peritoneal Sclerosis

Adapted from Morelle J, et al. ISPD Guidelines. (Evaluation of Membrane Dysfunction) *Perit Dial Int.* 2021;41:352-372.

Summary

VOLUME MANAGEMENT: ISPD RECOMMENDATIONS 2020

01 **Routine monitoring: PET[1], volume status, BP & clinical exam[2]**

02 **Icodextrin to improve UF independent of transport type[3]**

03 **Dietary counseling of appropriate salt / water intake[1]**

04 **Protection of RRF[4]; Loop diuretics if RRF present[1]**

- Furosemide 160-480 mg/day (split-2 doses)[5]
- Metolazone 5-10 mg/day[5]

05 **Preservation of peritoneal membrane function[1]**

- Avoid peritonitis & hypertonic glucose solutions

1. Mujais S, et al. *Perit Dial Int*. 2000; 20(suppl 4):S5-S21.
2. Wang A, et. ISPD Guidelines. (Volume Management) *Perit Dial Int.* 2020; 40: 282-292.
3. Boudeville N, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 254-260.
4. Brown E, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 244-253.
5. Chen H, et al. ISPD Guidelines. *Perit Dial Int.* 2020; 40: 274-281.

QUESTIONS?

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SUPPLEMENTAL SLIDES

Management of Fluid Overload in APD

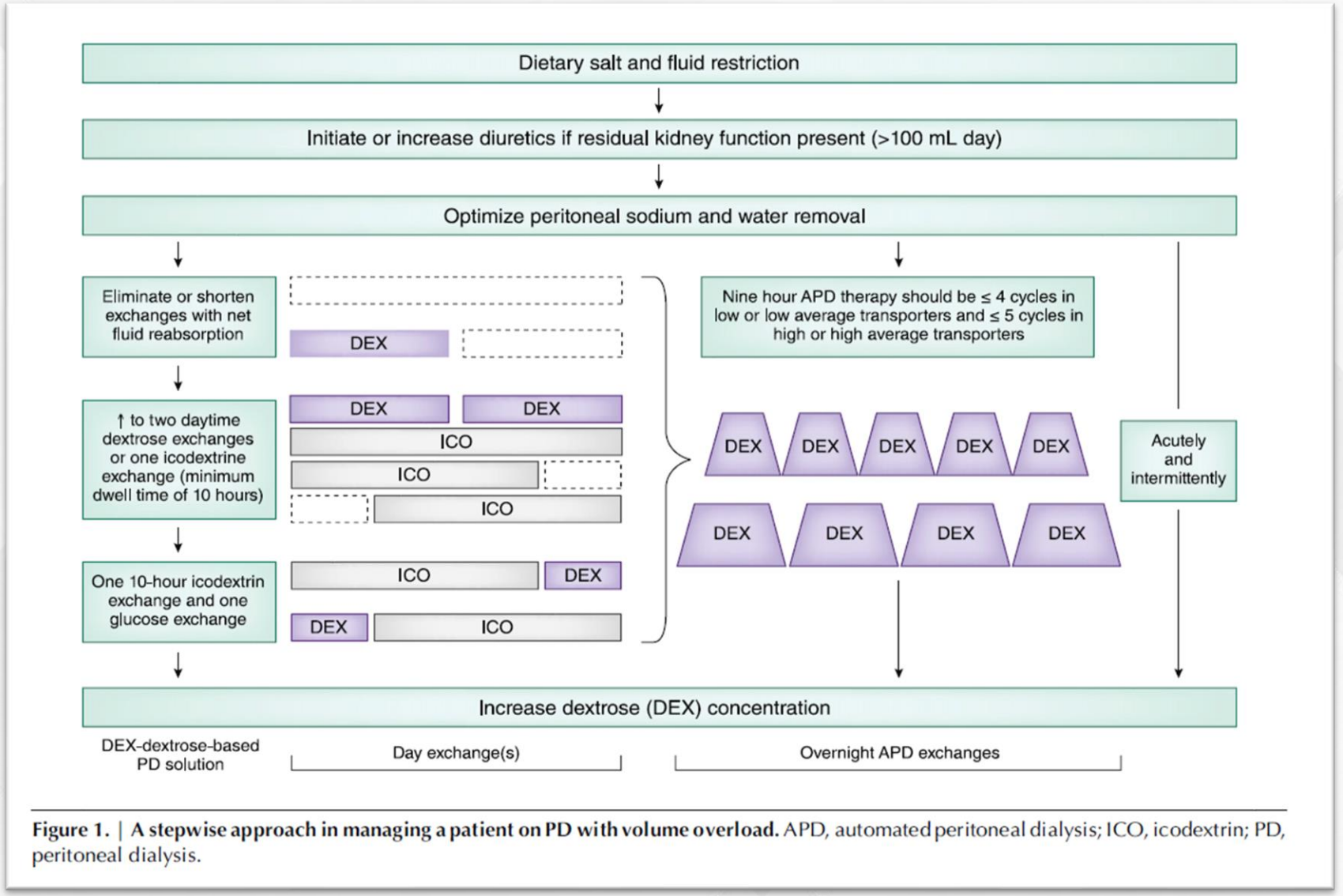

Figure 1. | A stepwise approach in managing a patient on PD with volume overload. APD, automated peritoneal dialysis; ICO, icodextrin; PD, peritoneal dialysis.

Trinh E & Perl J. *Clin J Am Soc Nephrol.* 2018; 13: 1732-1734

Membrane Dysfunction Classifications

Fast Peritoneal Solute Transfer Rate

Local inflammation

- Inherent fast transfer rate
  -variability present at baseline
- Acquired membrane injury
  -Long-term PD/Peritonitis

Definition

- D/P creatinine ratio above the population mean value at the end of a 4-hr PET using either 2.27/2.5% or 3.86/4.25% glucose/dextrose-based solutions. While most studies report that PSTR is normally distributed, with a typical average value of 0.65, multicenter studies show a significant center effect.
- Can be present at the start of PD and/or develop or resolve over time

Pathophysiology

- Membrane inflammation causing a large effective vascular surface area
- Neovascularization
- Both the above may potentially be, in part, genetically determined

Low osmotic conductance to glucose

Reduced free water transport

- Intrinsic low UF
  -variability present at baseline
- Acquired membrane injury
  -Progressive fibrosis/vasculopathy
  -most serious outcome is EPS

Definition

- Sodium dip at 60 min ≤5 mmol/l or sodium sieving ratio<0.07 with a 3.86% glucose/4.25% dextrose PET

Pathophysiology 1

- Explanations largely not understood
- Potential influence of genetic determinants (e.g. aquaporin expression)
- Note: a low ΔD_{Na} 0-60 min can also be observed in patients with very fast PSTR due to early dissipation of the osmotic gradient

Pathophysiology 2

- Structural alterations in the peritoneal interstitium in keeping with progressive fibrosis
- Usually associated with fast PSTR

Adapted from Morelle J, Stachowska-Pietka J, Öberg C, Gadola L, La Milia V, Yu Z, Lambie M, Mehrotra R, de Arteaga J, Davies S. ISPD recommendations for the evaluation of peritoneal membrane dysfunction in adults: Classification, measurement, interpretation and rationale for intervention. Perit Dial Int. 2021 Jul;41(4):352-372.