UniversityHospital Heidelberg

ERKNet
The European
Rare Kidney Disease
Reference Network

Optimizing PD in Children

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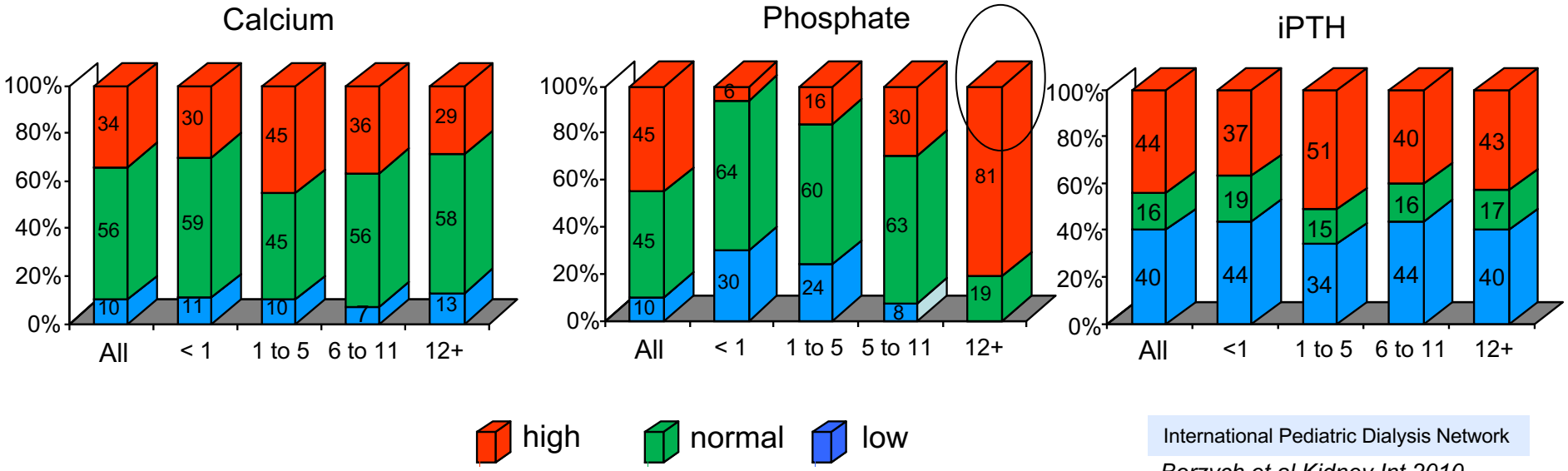
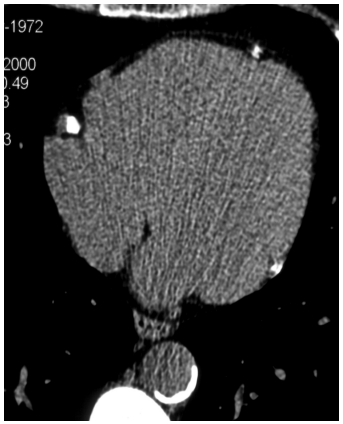
Inadequate control of CKD-MBD in Children on PD



International Pediatric Dialysis Network

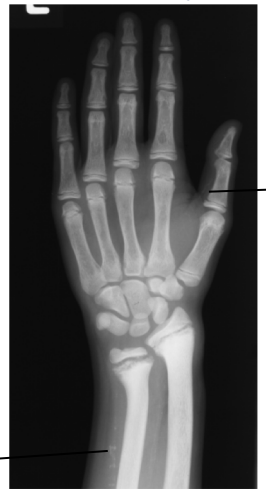
Borzych et al Kidney Int 2010

28 years
Juvenile onset of HD



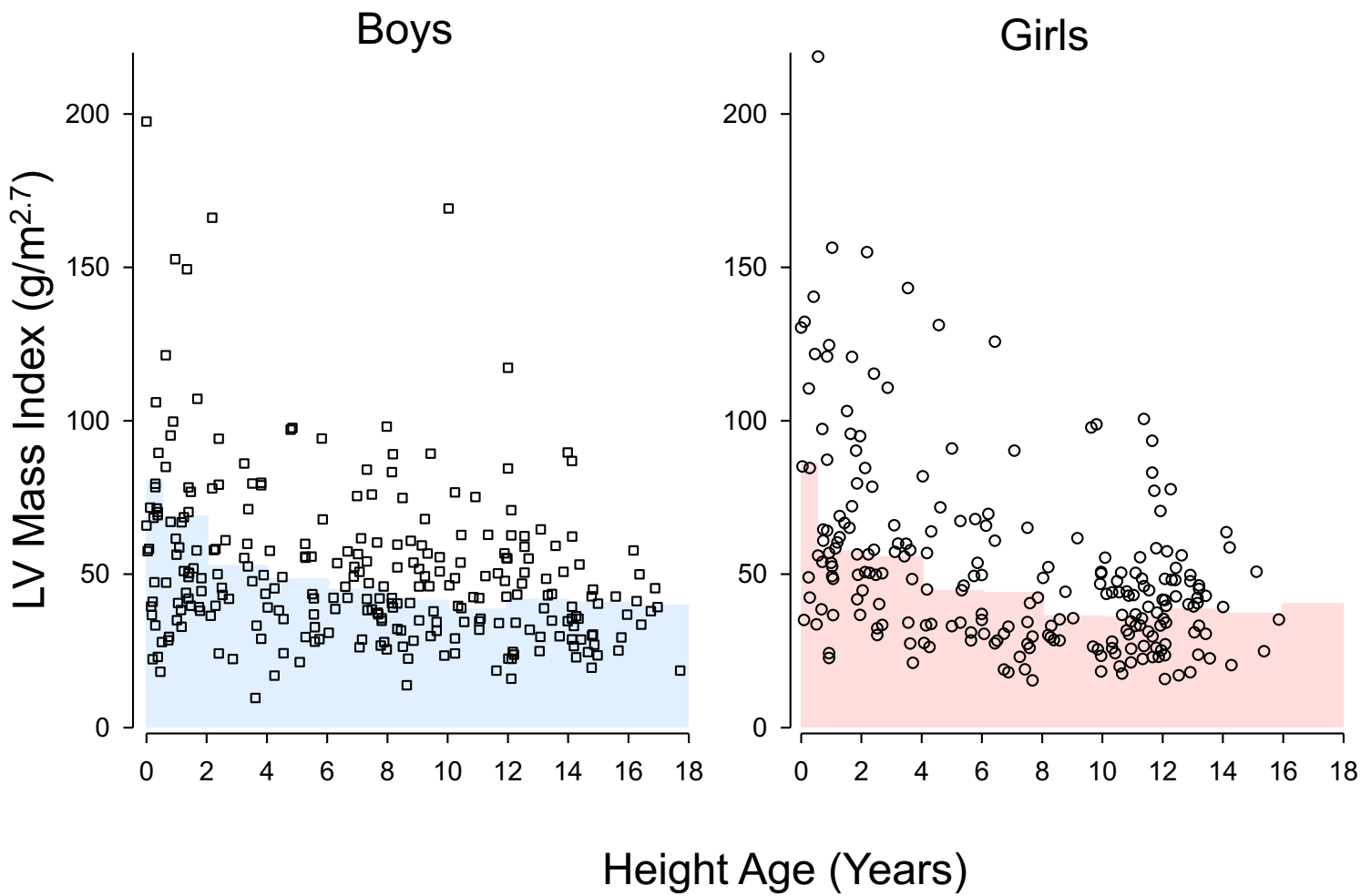
ECG-gated CT

16 years
HD since 4 years

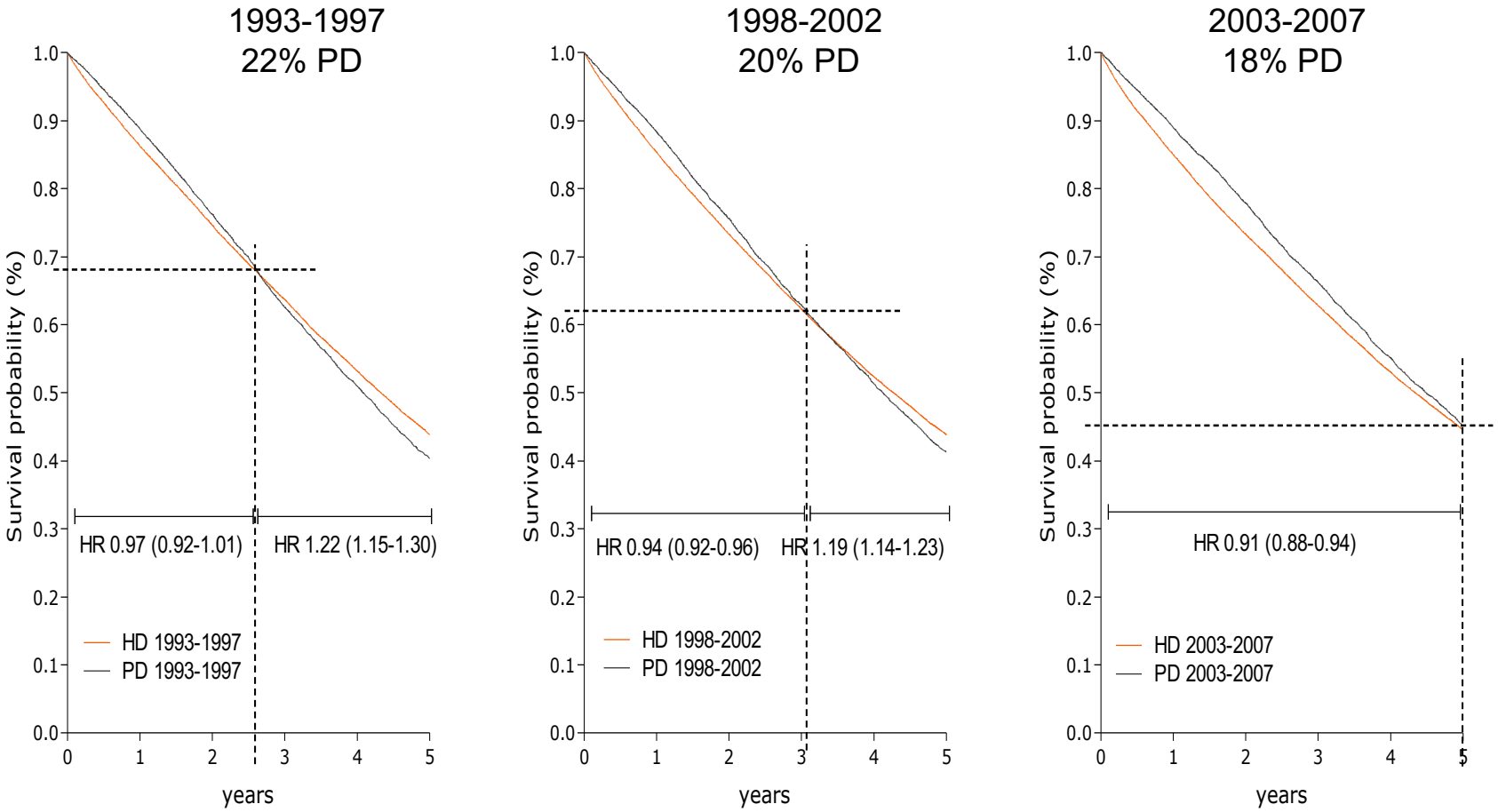


=> Early CVD due to uncontrolled CKD MBD in pediatric dialysis

Inadequate blood pressure, salt and water control in Pediatric PD: Increased Left Ventricular Mass

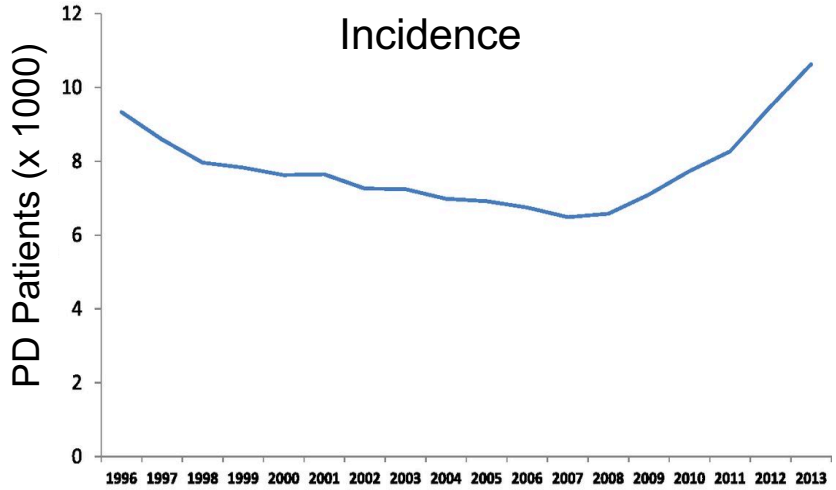


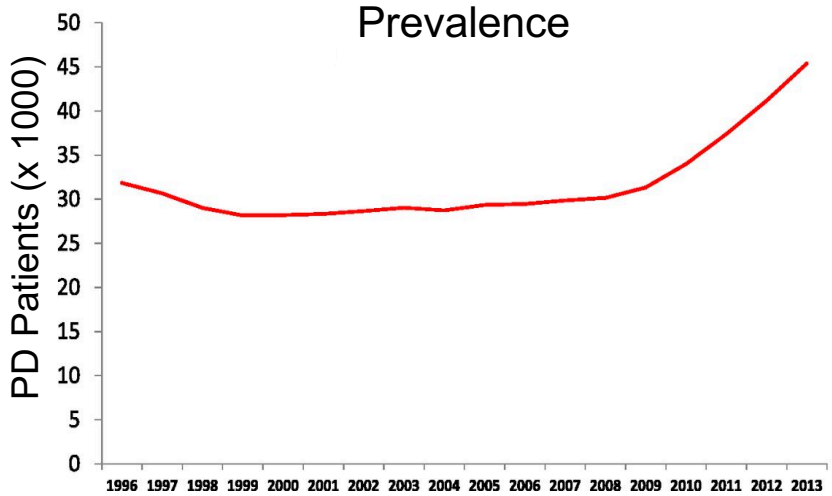
ERA-EDTA Registry
Superior 5 year survial with PD

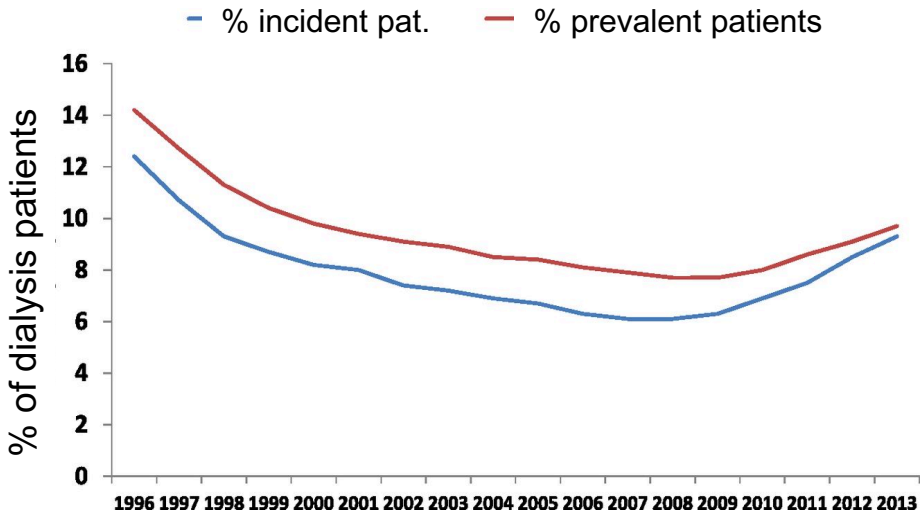


5 year patient survival for patients starting dialysis on HD and PD in 1993-1997, 1998-2002, and 2003-2007, adjusted for age, sex, primary renal disease, and country
(n= 29368 – 44726 HD, 8466-9998 PD)

Number of PD Patients, USA 1996 - 2013







Mehrotra R et al. JASN 2016

Advances in PD

- ⇒ *Increasing evidence on infection, hospitalizations…*
  (IPPN, some RCT …)
- ⇒ *New cycler with semi-automated connection, 'flush before fill'*
- ⇒ pH neutral, low GDP PDF, icodextrin, bicarbonate buffer
- ⇒ Adapted APD (?)
- ⇒ Telemetry / Remote Patient Monitoring
- ⇒ Ongoing research activities

PD Adequacy in Children

- Dialytic and renal creatinine clearance in APD
  > 63 l/1,73 m²/week, Kt/V > 2.1/week
  - no pediatric reference values
  - adult targets considered the lower limit of adequacy

- Optimal growth and weight gain

- Minimize cardiovascular risk:
  Normal blood pressure, hydration and sodium status
  Ca, phosphate, PTH in the target range
  ….

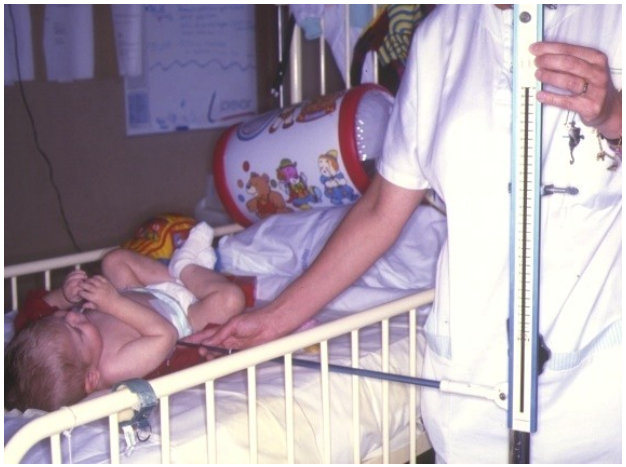
- Normal psychomotor development, schooling

Optimizing PD

- Define dwell volume
- Define dwell time
- Adapted APD
- RPM in PD
- Prevent peritoneal membrane transformation
- (Prevent PD related infections, see ISPD recommendations)

Dwell volume: IntraPeritoneal Pressure Measurement

- Back filtration with increased IPP: UF loss and toxin reabsorption via small pores and lymphatics
- Patients perception of IPP is mostly “incorrect”, objective numbers needed
- Individualize, optimize fill volume



Descirption of IPPM: Fischbach M et al, *Ped Nephrol* 2003

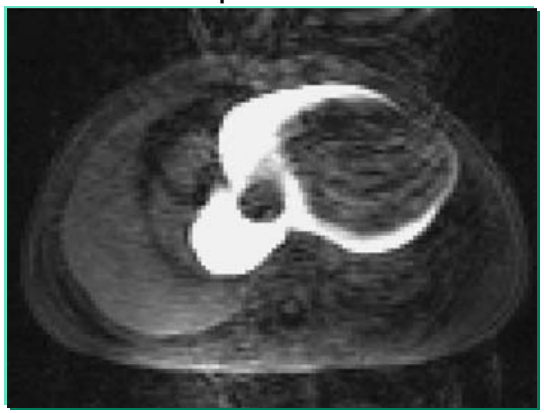
Increased risk of hernia/leakage with high intraperitoneal pressure?

- ~ 7% of children on PD develop <u>hernia/leakage</u> until Tx

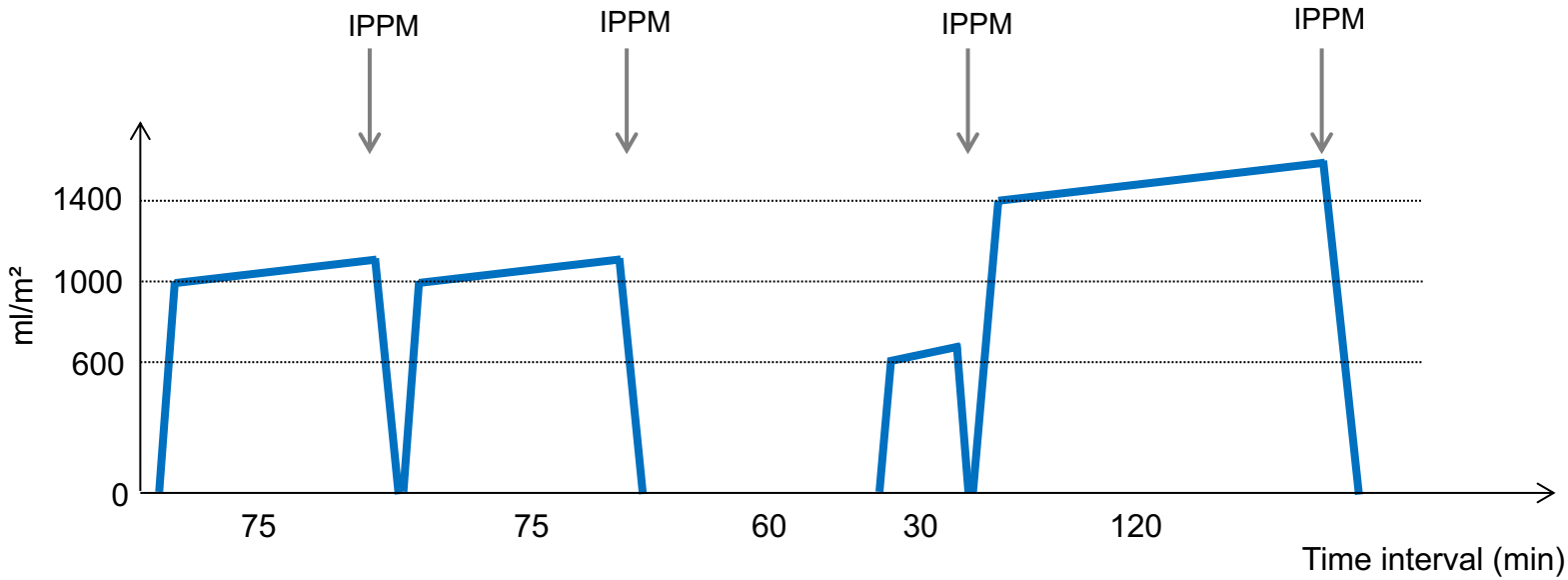
  Potential risk factors:
  - Organomegaly
  - Adhesions
  - Constipation
  - Malnutrition (vicious circle with low fill volume)
  - Surgery
  - Pain

- Higher incidence in infants

Peritoneal-pericardial fistula



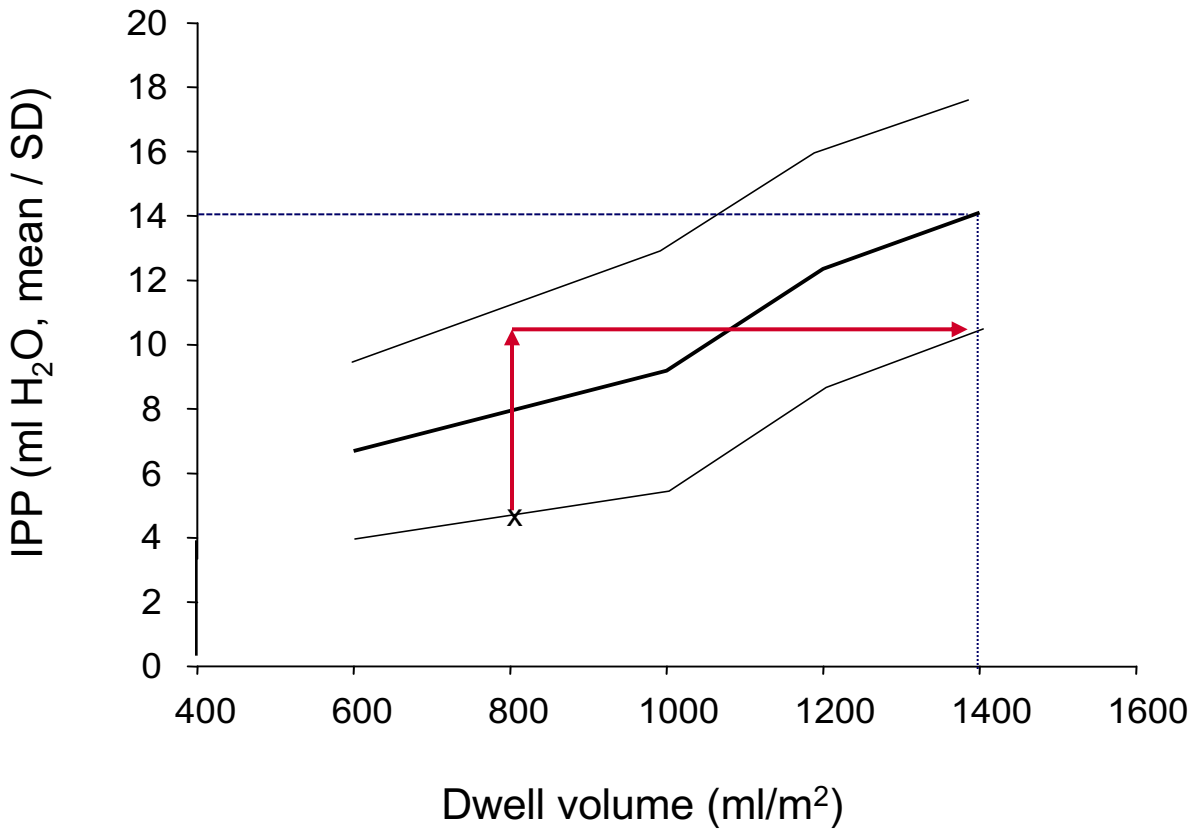
Intraperitoneal pressure: Double mini PET



Dwell time	75 min, I	75 min, II	30 min	120 min
IPP (cm H_2O)	12.2 ± 4.0	13.9 ± 3.1	11.4 ± 3.9	15.1±4.0
IPP/100 ml PDF	1.03 ± 0.42	1.16 ± 0.46	1.61 ± 0.66	0.89 ± 0.41

⇒ All patients were asymptomatic
⇒ Several IPPM outliers (included in analysis)
⇒ Intraindividual variation: IPP 75 min I-II: 0.13 ± 0,27cm/100ml

Dwell volume according to IPP



- < 2 years: < 8 -10 cm H_2O
- > 2 years: ≤ 14 cm H_2O

Increased risk of enteric peritonitis with IPP > 14 cm H_2O *(Dejardin et al, NDT 2007)*

IPPM Predictor of Outcome (HD-Switch/Death)?

54 adapted APD patients
IPP 18.8 ± 5.2cm H_2O
PD: 5.5 (2-19) months

3 Hydrothoraces
11 AW-Hernia
4 x GE reflux

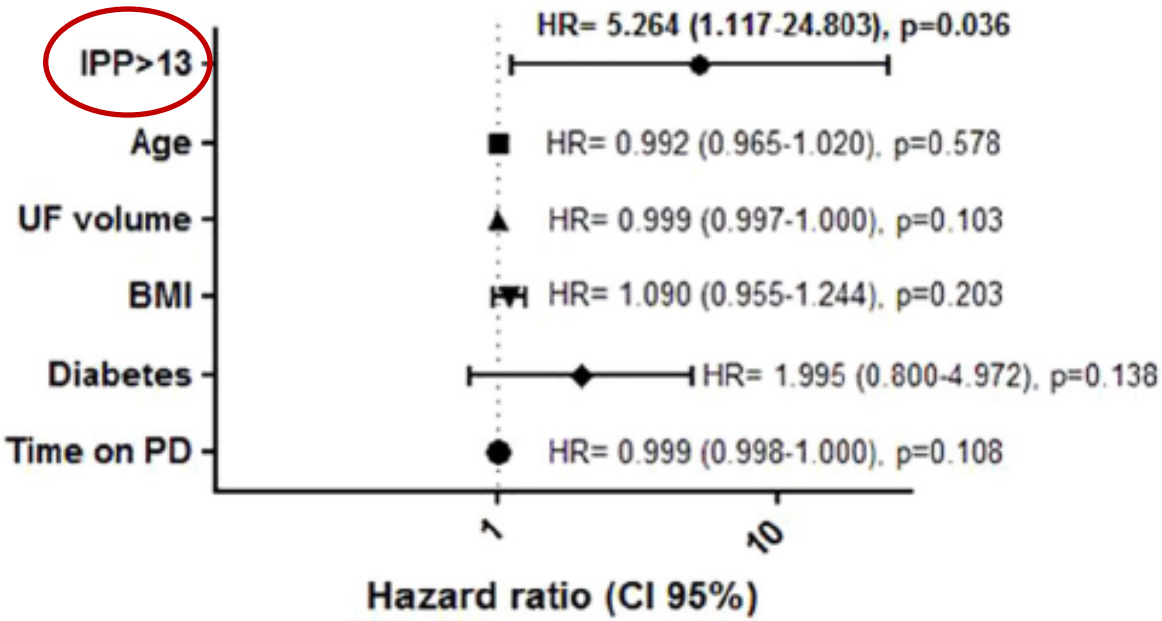


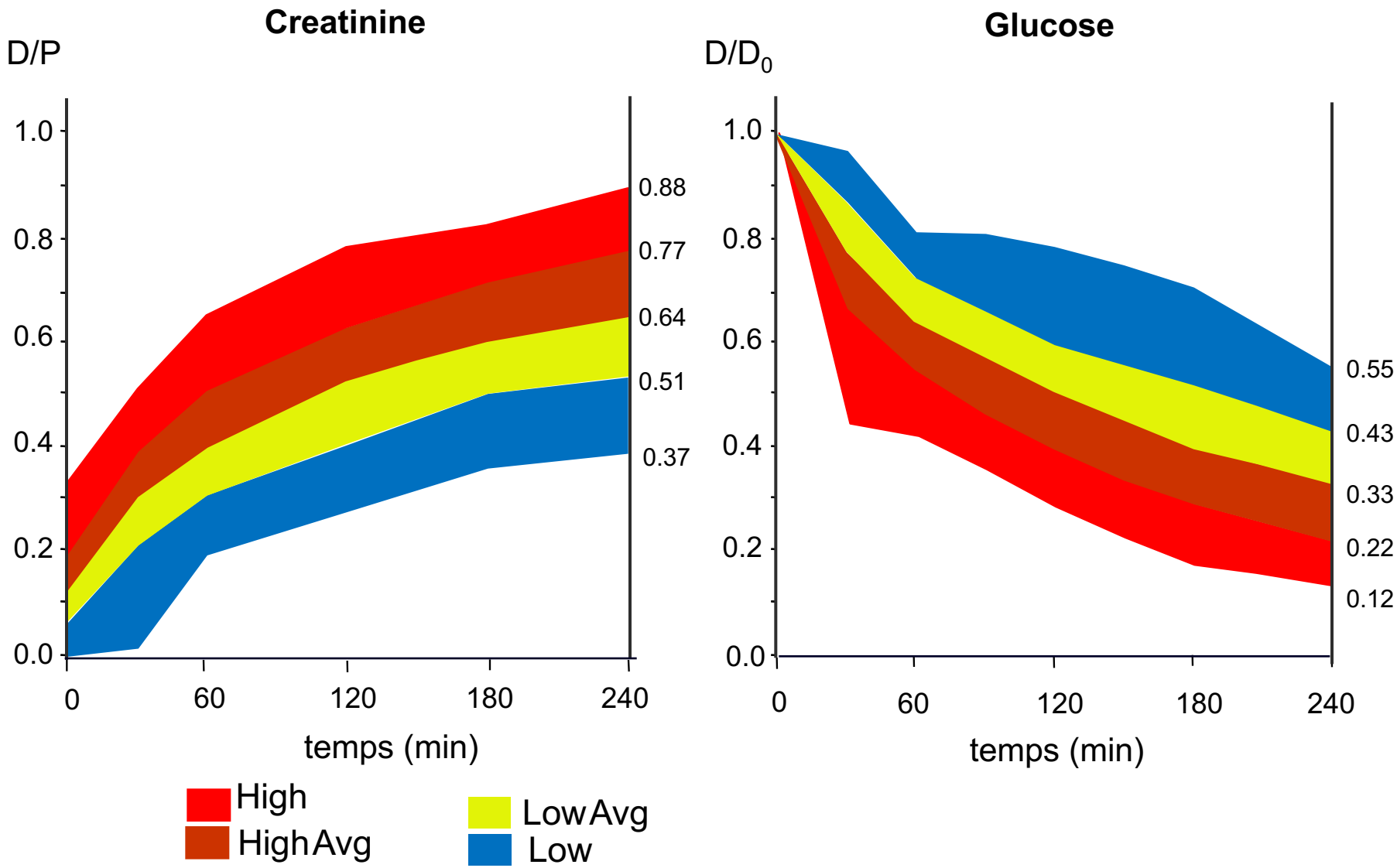
Figure 1 — Multivariate analysis of predictors of death or switch to hemodialysis. IPP = intraperitoneal pressure; UF = ultrafiltration; BMI = body mass index; PD = peritoneal dialysis; HR = hazard ratio; CI = confidence interval.

Outerelo et al PDI 2014

=> Convincing concept, but observational evidence only

Continuous IPP measurement in a child with ARPKD

Defining Dwell Time According to Peritoneal Equilibration Test

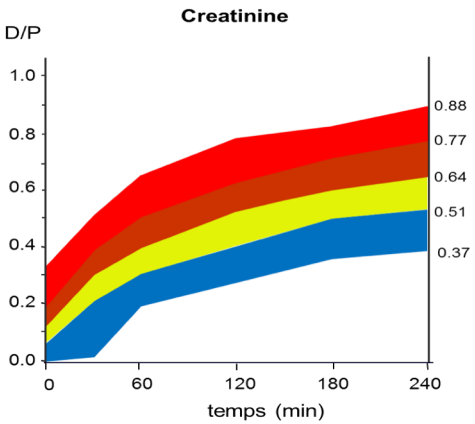


Warady et al., JASN, 1996

Peritoneal Transporter Type Characteristics

Patients (%)	Type	4-hours D/P creatinine	Characteristics
10%	High	> 0.78	Rapid solute transport Absorption of glucose: Reduced UF Loss of proteins? Serum albumin?
53%	High Average	0.65 - 0.77	Good solute transport Sufficient UF
31%	Low Average	0.52 - 0.64	Solute transport relatively slow Good UF
6%	Low	< 0.51	Slow solute transport Clearance targets difficult to achieve Very good UF

Information from Peritoneal Equilibration Test



⇒ <u>Low transporter:</u>
- longer dwell time, less cycles (less glucose exposure),
- long daily dialysis duration (+ day time dwell)

<u>High transporter</u>:
short dwell time, frequent cycles, icodextrin

⇒ Consider <u>sodium sieving</u> (selective water transport via AQP1):
- mainly with short dwells / high glucose
- good UF but insufficient sodium removal (BCM)
- if child hypertensive despite lowered BW increase dwell time and total dialysis time

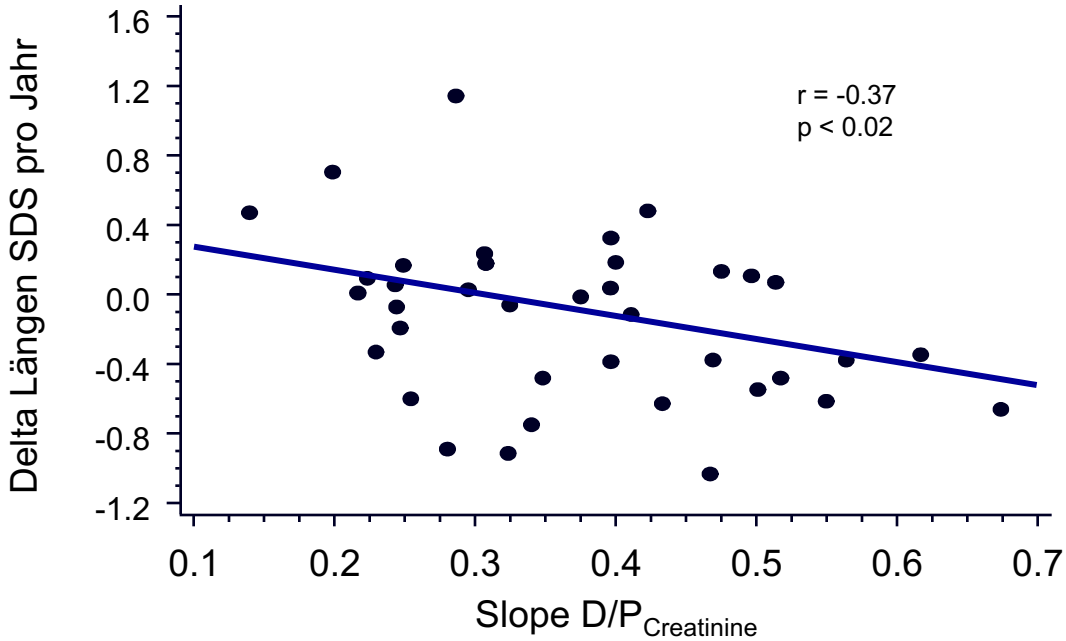
⇒ Repeated PET: <u>membrane transformation</u> over time?
(cave: EPS in long term PD)

⇒ Perform PET initially, yearly / in case of problems
Monitor residual renal function (e.g. every 6 months)

Transporter Status and Outcome

Membrane type	Death	Transfer to HD
L	1.00	1.00
LA	1.60	3.26
HA	2.30	4.04
H	1.94	5.82

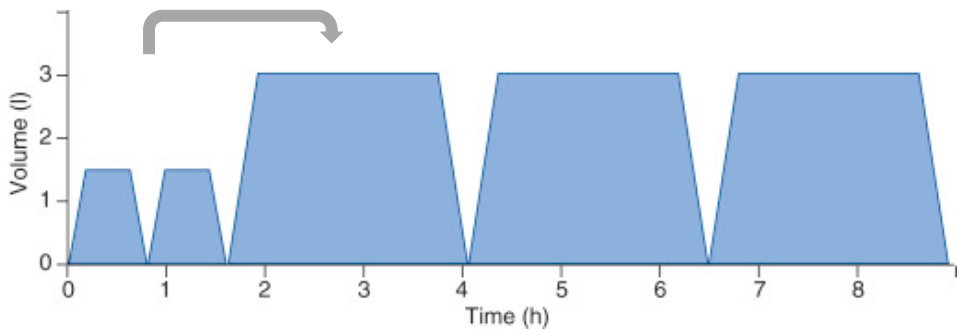
Churchill et al, JASN, 1998



Schaefer et al. JASN 1999

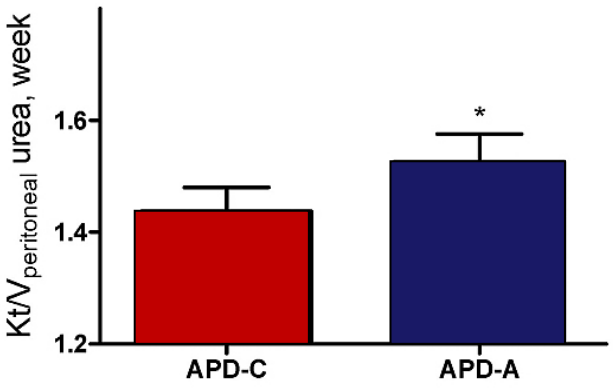
Concept of Adapted APD:

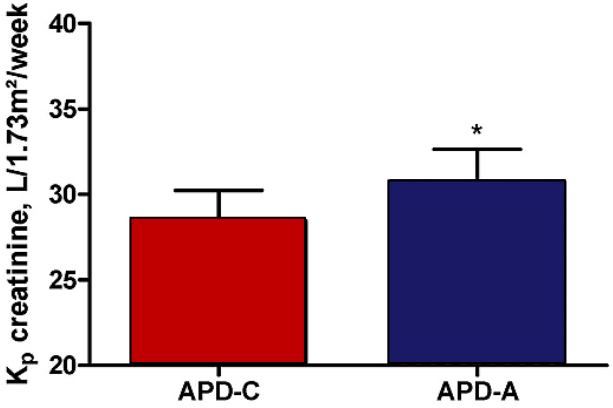
- Varying dwell volume and dwell time within one session
- Equal total dialysis time, dialysate volume, glucose exposure
- Positive carry over effects?

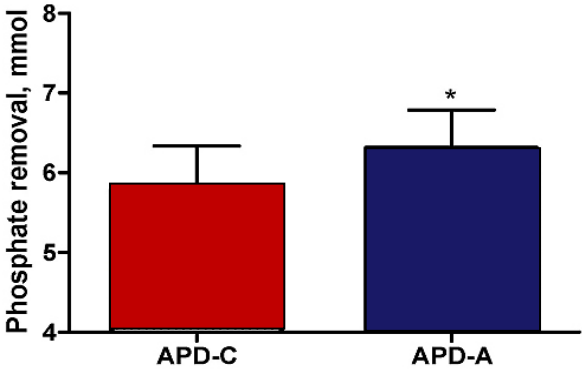


	Dwell time	Dwell volume	Supposed effects
Short dwell / small volume	30-40 min (APEX, ?)	~ 50% of large dwells	- Low IPP, UF↑ ↑ Free water transfer, ↑ solutes in blood , i.p.↓
Long dwell / large volume	~3 x short dwell	- IPP up to 14cm H_2O - up to 1400 ml/m^2 BSA (> 2 yrs of age)	- Perit. area (small pore) recruitment => ↑ solute / toxin removal

Fischbach M, Schmitt CP et al. Ped Neph 2013 / KI 2016







	Conv. APD	Adapted APD	P
Effluent sodium (mmol/l)	126.4±1.4	127.5±1.3	< 0.05
UF (ml/day)	656±275	743±358	< 0.01
MAP (mmHg)	105±15	100±14	< 0.01

Long term glucose saving?

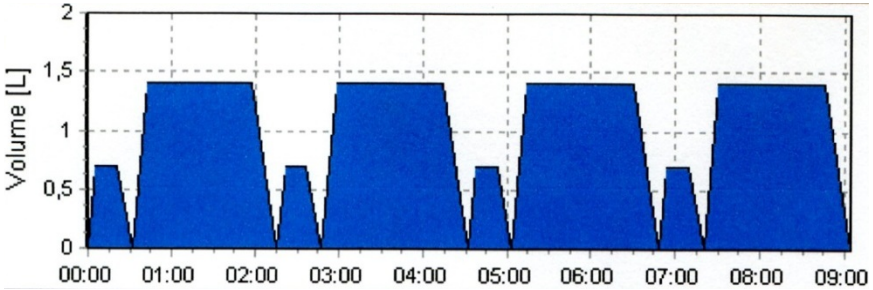
Fischbach M et al. PDI 2011

Adapted APD: Open issues

- Mathematical modeling: 10-15% higher sodium removal
  => Findings not explained by 3 pore model; experimental data?

- Hemoconcentration and dilution of residual dialysate with short, small dwells (by free water removal via AQP1)? Recruitment of peritoneal surface with long /large dwells?

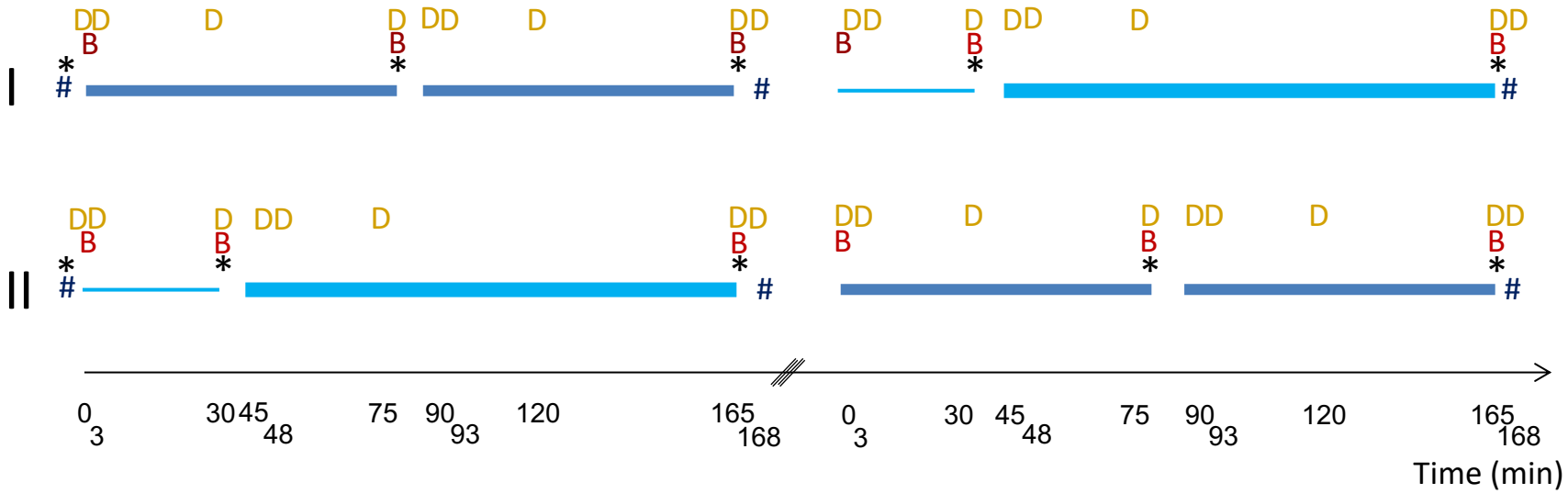
=>



?

- Defining individual regimen?

Proof of Concept Study



* = Intraperitoneal pressure measurement

B = Blood sampling

D = Dialysate sampling

= Body composition monitoring

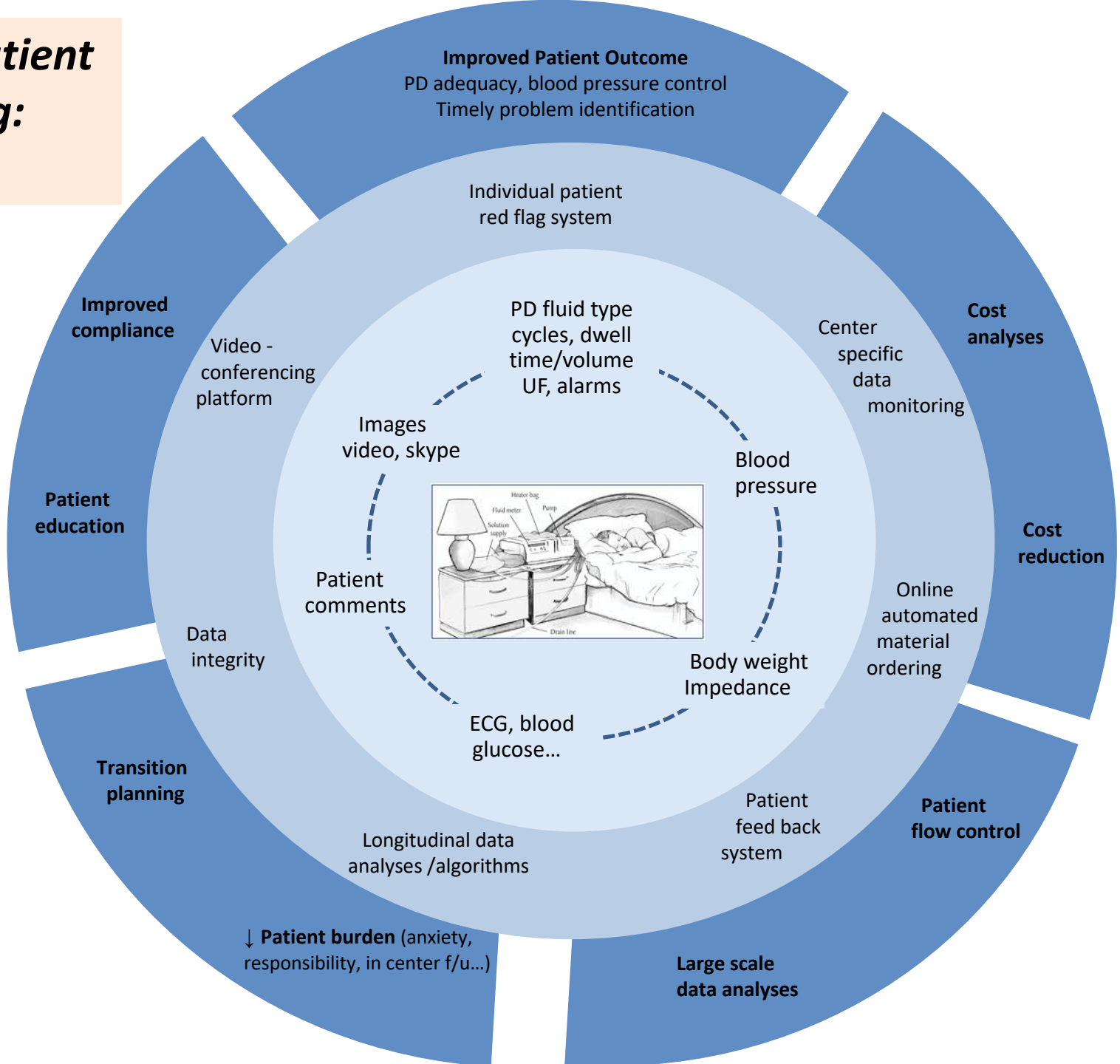
60 min interval between the two double mini PET

Balance®, 1.25 mmol/l calcium, 2.3% glucose

Ployuric patients excluded

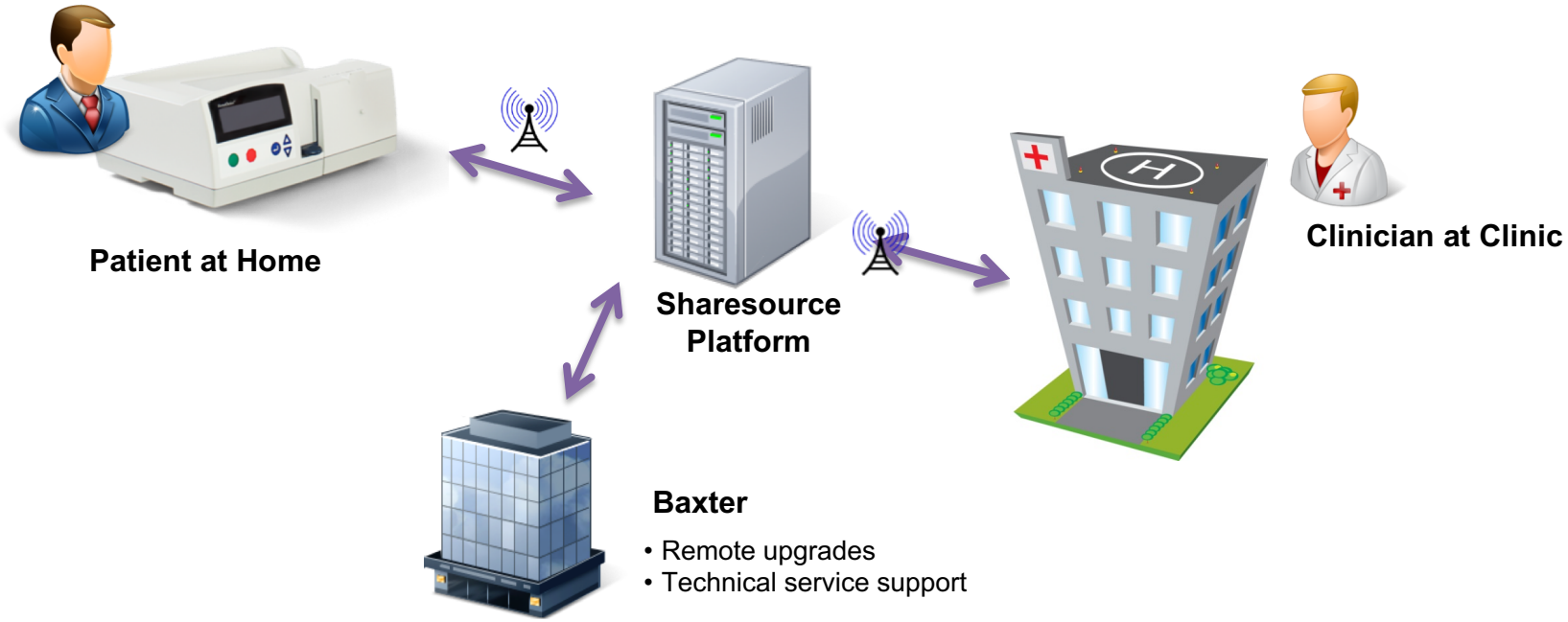
?

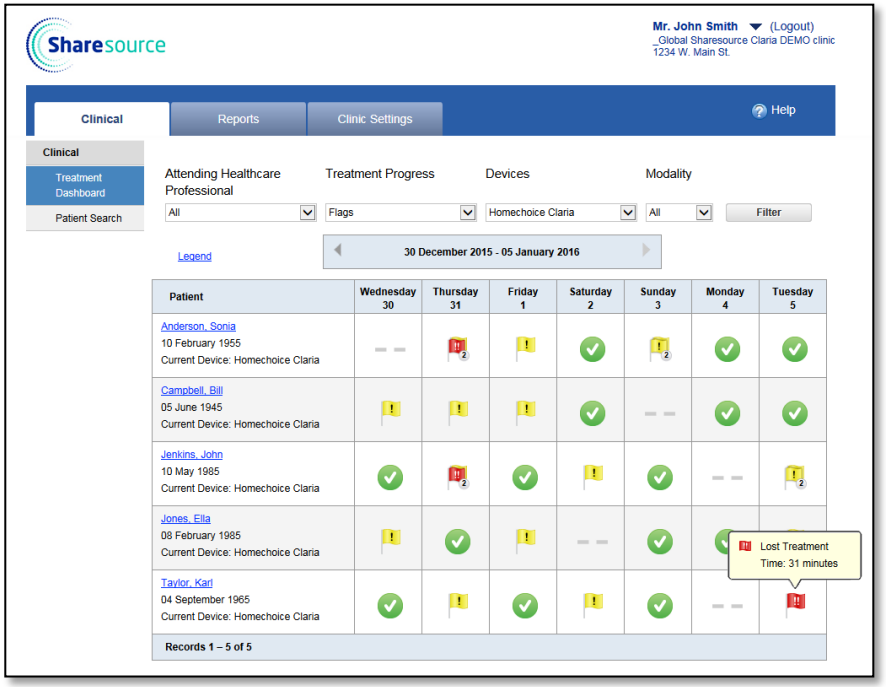
Remote patient Monitoring: The model



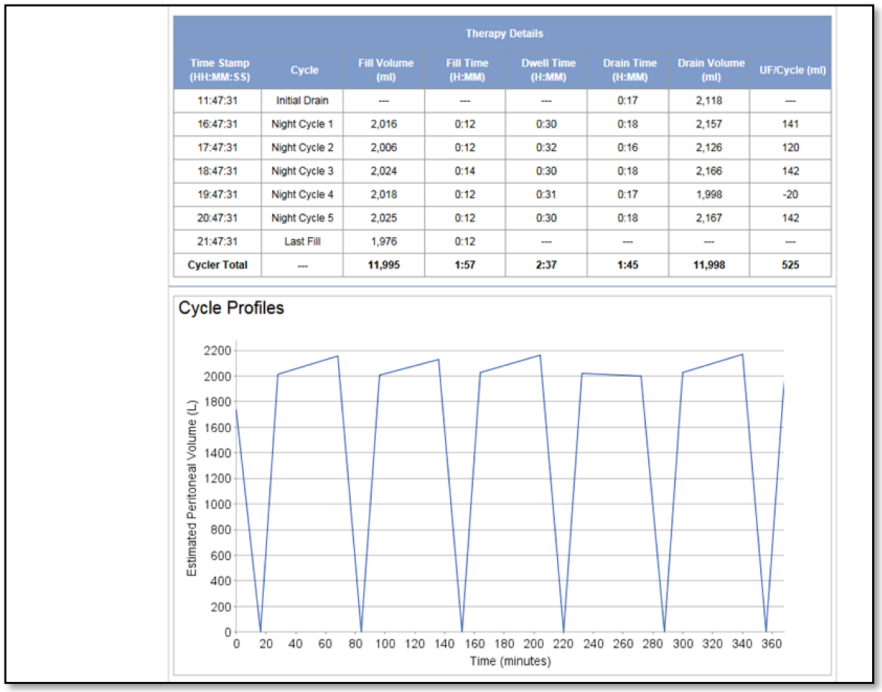
Homechoice Claria with Sharesource Clinical Portal

- Cloud based application – transparent to patient
- Clinicians view treatment data / alerted through programmable flags
- Clinicians can change settings to adjust next dialysis session





- Overview on daily dialysis outcomes of all patients
- Customized flags alerts e.g.:
  - Initial drain variance
  - Drain ended early
  - Lost treatment time
  - Lost dwell time
  - Events (alarms) during treatment



Therapy Details

Time Stamp (HH:MM:SS)	Cycle	Fill Volume (ml)	Fill Time (H:MM)	Dwell Time (H:MM)	Drain Time (H:MM)	Drain Volume (ml)	UF/Cycle (ml)
11:47:31	Initial Drain	---	---	---	0:17	2,118	---
16:47:31	Night Cycle 1	2,016	0:12	0:30	0:18	2,157	141
17:47:31	Night Cycle 2	2,006	0:12	0:32	0:16	2,126	120
18:47:31	Night Cycle 3	2,024	0:14	0:30	0:18	2,166	142
19:47:31	Night Cycle 4	2,018	0:12	0:31	0:17	1,998	-20
20:47:31	Night Cycle 5	2,025	0:12	0:30	0:18	2,167	142
21:47:31	Last Fill	1,976	0:12	---	---	---	---
Cycler Total	---	**11,995**	**1:57**	**2:37**	**1:45**	**11,998**	**525**

- Individual therapy session information and historical data available at a click

Overview on Systematic Reviews on RPM in Heart Failure

Table 5. Clinical outcomes reported by the systematic reviews.

Author	Clinical outcome[a]											
	1	2	3	4	5	6	7	8	9	10	11	12
Kotb et al [8]		Yes	Yes	Yes								
Inglis et al [9]	Yes			Yes		Yes				Yes		Yes
Nakamura et al [10]	Yes								Yes			
Pandor et al [11]	Yes		Yes	Yes		Yes				Yes		
Smith [12]			Yes								Yes	
Maric et al [24]												
Chaudhry et al [20]	Yes		Yes	Yes								
Clark et al [21]	Yes		Yes	Yes		Yes						Yes
Dang et al [22]	Yes		Yes	Yes	Yes	Yes				Yes	Yes	Yes
Hughes and Granger [23]						Yes					Yes	Yes
Martinez et al [25]	Yes					Yes				Yes		Yes
Schmidt et al [26]	Yes		Yes			Yes						

[a]Clinical outcomes: 1, all-cause mortality; 2, heart failure mortality; 3, all-cause hospitalizations; 4, heart failure–related hospitalizations; 5, emergency department visits; 6, quality of life; 7, knowledge; 8, self-care; 9, medication adherence or medication management; 10, length of stay; 11, readmission; 12, costs.

- RPM reduces hospitalisations and mortality in patients with heart failure (Grade 1A evidence)

- Impact of mobile phone-based monitoring and videoconferencing unclear

RCT on RPM in high-risk HD patients

	RPM N=19	**SoC N=25**	
	MEAN (SD)	MEAN (SD)	P
SF-36 (6–9 months)	60.76 (20.70)	59.50 (17.56)	0.417
Hospital days (per study day)	0.0082 (0.0225)	0.0355 (0.0555)	0.016[b]
Hospitalizations (per study day)	0.0018 (0.0029)	0.0056 (0.0062)	0.008[b]
ER visits (per study day)	0.0003 (0.0008)	0.0019 (0.0036)	0.035[b]
Hospital ER charges (per study day)	$114 (179.45)	$322 (336.53)	0.041[b]

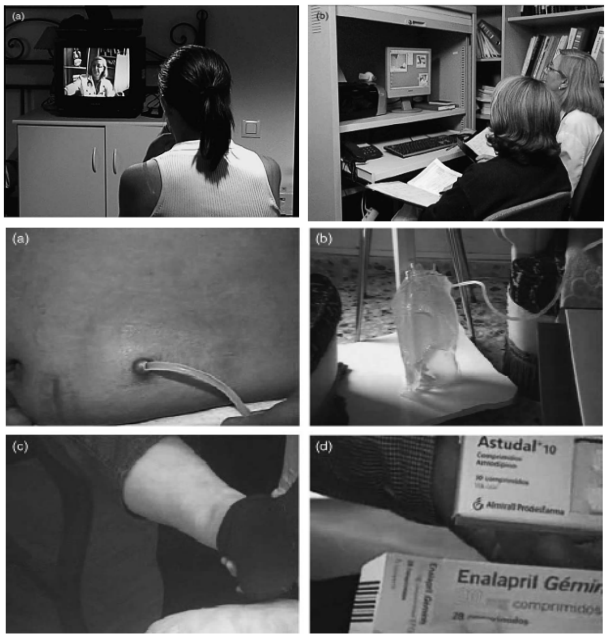
Berman SJ et al. Telemedicine and E Health 2011

Video conferencing in PD

25 patients (refusal of participation => control group)
~200 TM months, 172 teleconsultations

Patients	Age (years) Mean (SD)	Charlson's co-morbidity index Mean (SD)	Hospitalization (days/patient/year) Mean (SD)
Group A – with telemedicine (n=25)	48 (10)	3.2 (1.4)	2.2 (2.4)
Group B – without telemedicine (n=32)	45 (16)	3.4 (1.9)	5.7 (9.0)
	P=0.403	*P*=0.580	*P*=0.043

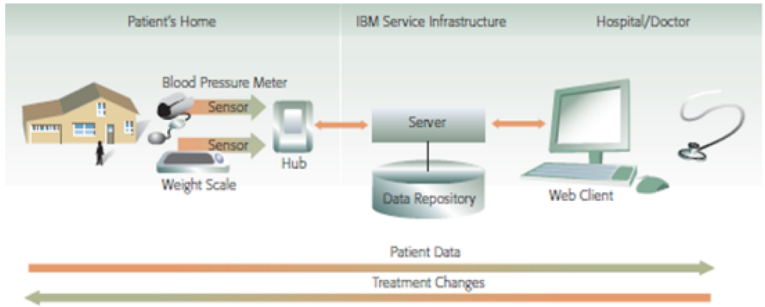
	Hospital visits (€)	Teleconsultations (€)
Staff	23.45	13.88
Pharmaceuticals	58.92	58.92
Hospital space	19.45	19.45
Consumables (e.g. antiseptics, gauze, latex gloves, clamps)	15.25	
Videoconference equipment		55.18
Videoconference call costs		50.95
Transportation	60.00	
Total	*177.07*	*198.40*



Gallar P et al. Telemed Telecare. 2007

Pediatric home dialysis RPM pilot study

- 20 patients, 6–18 years
- 14 APD, 5 center HD,
  1 home-HD
- 2–5 weeks TM/patient

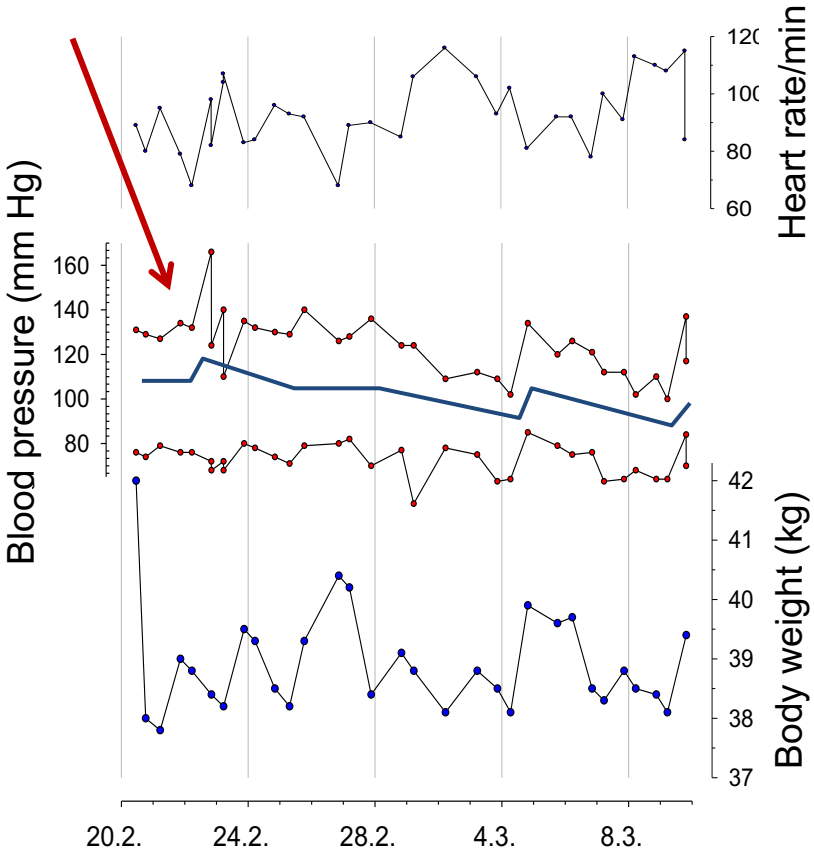


- **Body weight:** Digital balance
  730 measurements (1.7/patient/d)
- **Blood pressure:** Oscillometric devices

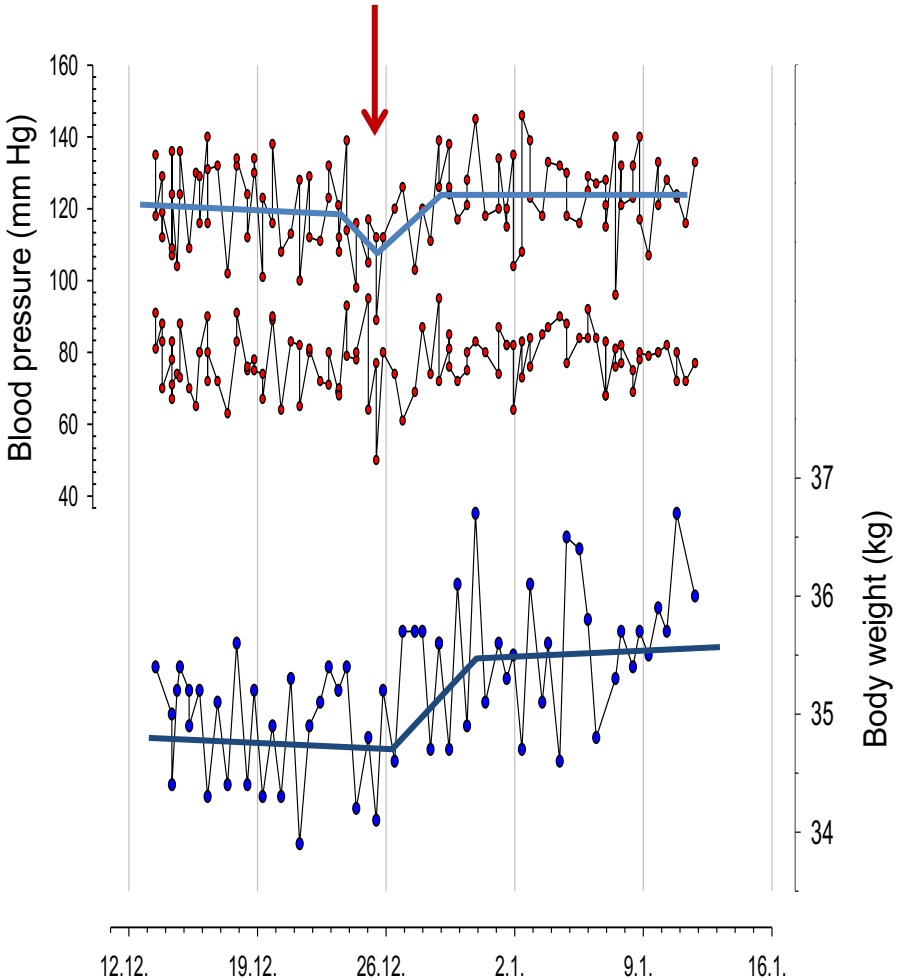
  997 blood pressure/HR measurements
- Once daily validation by the dialysis team

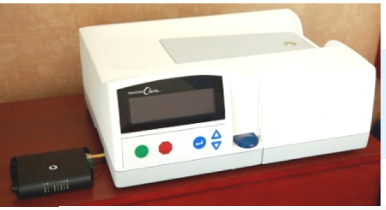
Kirschfink C et al. IBM SYSTEMS JOURNAL, 2007

Home HD Patient
(9 years)

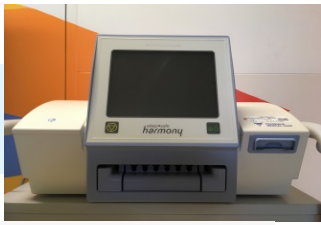


PD Patient
(11 years)





Prospective RPM Data Collection



International Pediatric Dialysis Network

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About IPDN

The International Pediatric Dialysis Network is a global consortium of pediatric nephrology centers dedicated to the care of children on chronic dialysis. The IPDN aims to

- **improve the quality of pediatric dialysis care worldwide**
- **collect basic information regarding pediatric dialysis practices and outcomes**
- **provide useful tools and management algorithms for daily dialysis practice**
- **provide global benchmarking of pediatric dialysis outcomes**
- **perform prospective observational studies on important clinical issues in pediatric dialysis**

IPDN entertains two registries:
The IPPN registry for children on chronic peritoneal dialysis, and the IPHN registry for children on hemodialysis.If you would like to join the IPDN, please fill out the registration form. IPDN membership is free of charge. We grant institutional and individual memberships: With your institutional membership you have access to all information pages of the website.

At present,
242 institutions participate in the network
and
558 individual members actively contribute data to the network.

To date,
3498 patients have been enrolled in the IPPN Registry at 124 contributing centers in 43 countries
and
817 patients have been enrolled in the IPHN Registry at 82 contributing centers in 36 countries.

Initial RPM questionnaire

- Mode of RPM data assessment (who, how, frequency of transferred data evaluation)
- Alert systems and criteria for (safety) margins
- Standards of health care provider RPM feedback to patients

6 month updates

- Number of (unscheduled) outpatient /EMR visits
- PD modalities, body weight/length, biochemistry, medication, blood pressure, echocardiography, 24 h ABPM …
- Access revisions, peritonitis, exit-site infections, hospitalizations …

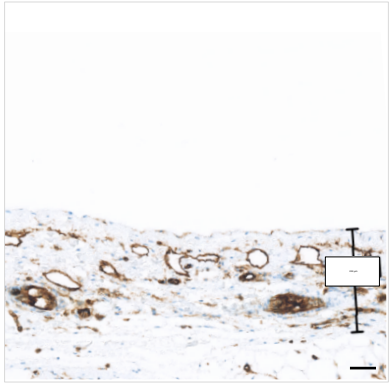
Annual RPM questionnaires

- Specific changes in center RPM settings
- Work load for doctors / nurses (semi-quantitatively)
- Acceptance by patients, parents, doctors and nurses (semi-quantitatively)
- Estimates on average changes in PD regime / medication performed based on RPM data and estimates on how often the modification proved to be beneficial

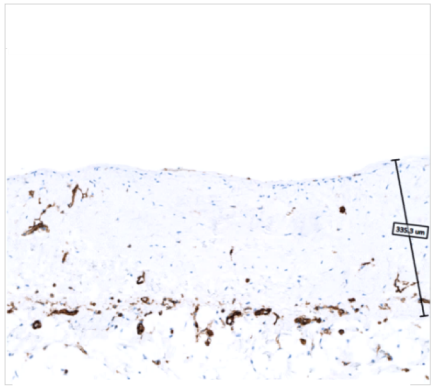
Discontinuation questionnaires

- Patient and center specific reasons

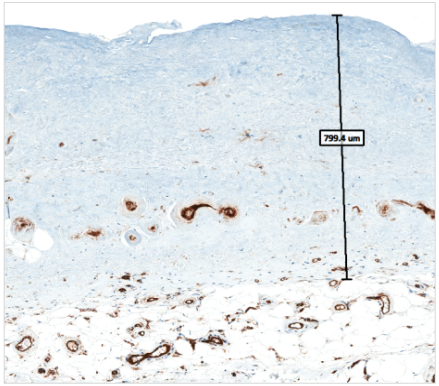
Peritoneal membrane preservation?



Hypervascularized
(early changes)



Average



Fibrotic
(late changes)

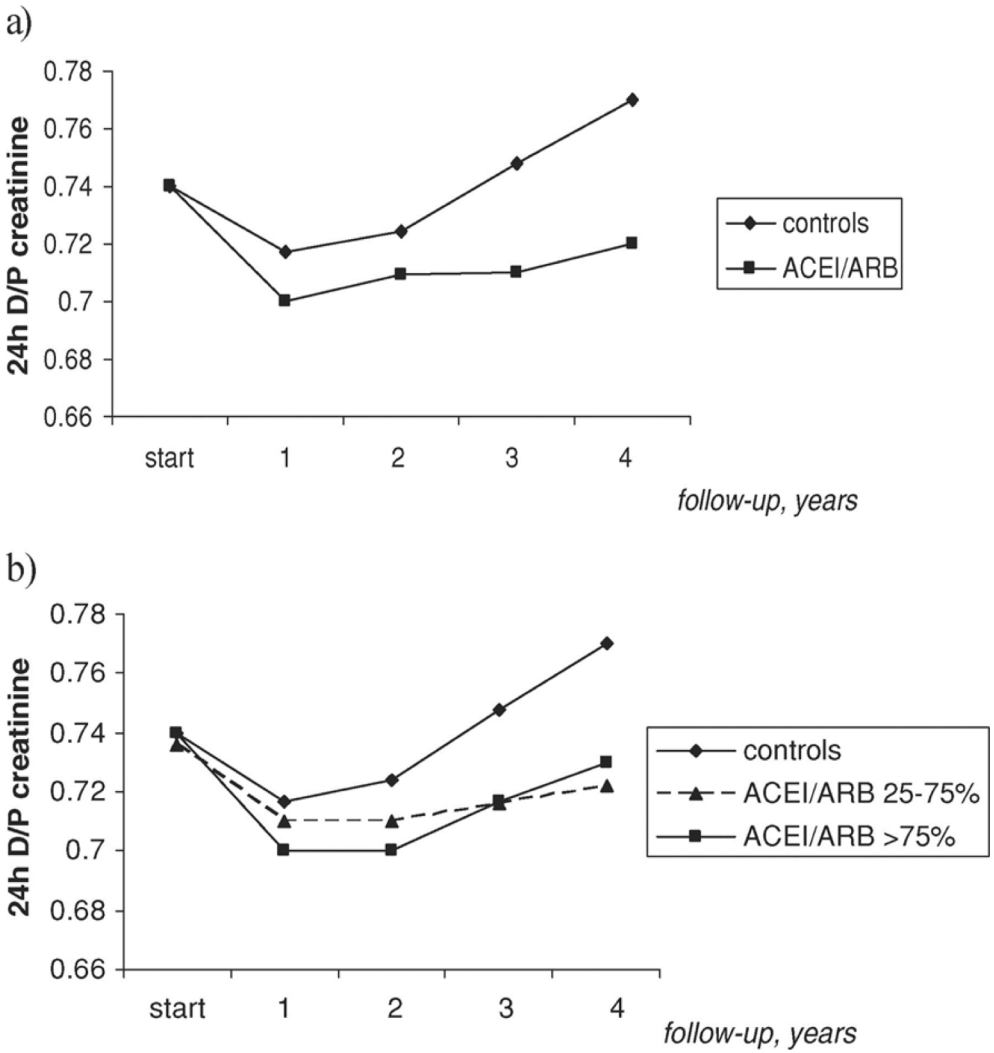
Preservation of Peritoneal Membrane Function with ACEI/ARB?

120 ACEI/ARB treated PD pts vs. 97 untreated controls

PD duration > 2 yrs

=> Small solute transport only increased in PD patients not on ACE-I/ARB treatment

=> No effect on RRF, technique and patient survival

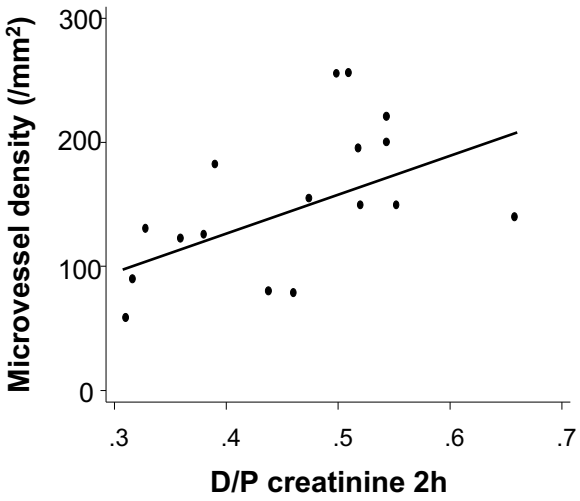


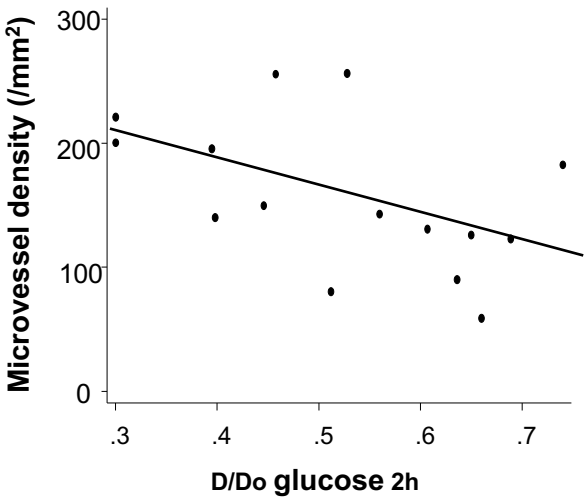
Kolesnyk et al. NDT 2009

Early PD membrane transformation with low GDP PD

	CKD5 n=90	PD <6 Mo n=13	PD 6-12 Mo n=19	PD 12-24 Mo n=21	PD 24-48 Mo n=16	PD ≥48 Mo n=13	p
PD duration (months)	0	**4.0 (2.3, 4.8)**	9.0 (7.3, 10.0)	15.7 (12.8, 19.0)	33.0 (27.3, 36.2)	72.3 (63.0, 85.2)	<0.001
Glucose exposure (g/m^2/day)	63 (27, 102)	104.7 (87.9, 131.3)	116.1 (85.4, 185.9)	100 (86, 123)	117 (57, 153)	131 (118, 154)	0.011
Mesothel coverage (0-6)	4 (3, 6)	2 (0, 6)	2 (0, 3)	1 (0, 3)	0, (0, 2.5)	0 (0, 2)	<0.001
Submesothelial thickness (µm)	268 (208, 380)	330 (304, 482)	424 (358, 525)	300 (237, 420)	373 (258, 511)	826 (328, 950)	<0.001
Microvessel density (/mm^2)	124 (78.4, 174.9)	179.1 (132.3, 274.3)	235.5 (124.9, 368.0)	161 (96.9, 384.9)	181 (112.3, 269.4)	169 (88.6, 236.6)	0.002
Submesothelial microvessels / mm	29.0 (20.3, 47.0)	57.1 (31.7, 138.3)	105.6 (69.4, 171.8)	57.5 (30.0, 95.5)	59.0 (26.0, 89.9)	69.8 (38.1, 185.1)	<0.001
Lymphatic vessel density (/mm^2)	28.1 (18.9, 49.6)	23.3 (16.2, 35.4)	32.9 (10.8, 46.3)	28.5 (21.8, 45.9)	39.5 (14.7, 55.0)	25.1 (16.5, 44.5)	0.9
Diffuse podoplanin staining	0%	15%	21%	21%	31%	36%	0.002
Blood vessel density (/mm^2)	**85.6 (46.7, 147.9)**	**180.0 (142.8, 251.0)**	**166.0 (73.7, 311.8)**	**120 (64.4, 286.4)**	**175.7 (96.0, 269.5)**	**131 (47.7, 202.8)**	**<0.001**
Endothelial surface area (µm^2/µm^3)	7.3 (4.1, 10.3)	10.0 (9.4, 15.4)	12.3 (7.7, 19.1)	9.0 (5.3, 17.3)	10.2 (7.8, 13.2)	9.0 (4.4, 11.3)	0.004
L/V ratio	0.5 (0.4, 0.6)	0.4 (0.4, 0.5)	0.4 (0.3, 0.4)	0.4 (0.3, 0.5)	0.3 (0.2, 0.5)	0.4 (0.2, 0.6)	0.008

Microvessel density predicts PD membrane function





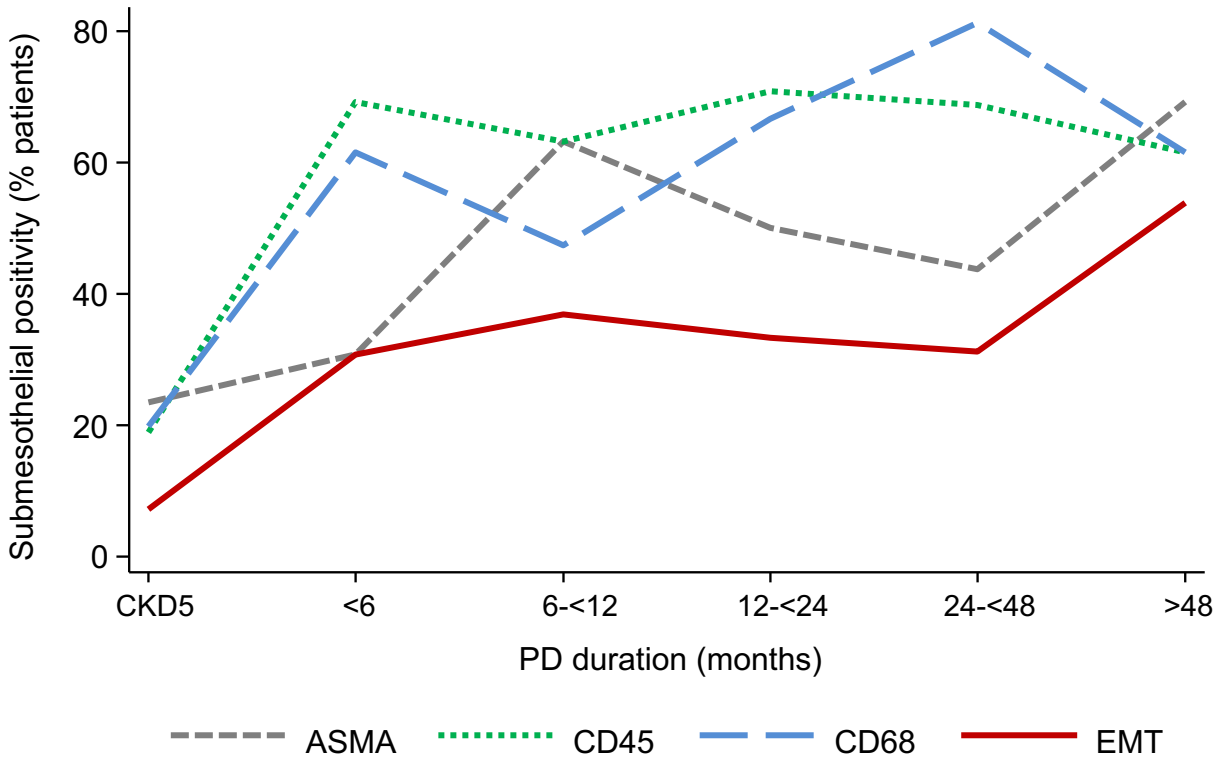
MVLR Analysis *2 hours D/P creatinine*

	Coeff.	lower CI95%	upper CI95%	p-value
Age (years)	0.007	-0.002	0.015	0.115
Glucose exposure (g/m²/day)	0.002	-0.000	0.003	0.059
Microvessel density (/mm²)	**0.166**	**0.069**	**0.264**	**0.004**
Submesothelial thickness (µm)	-0.000	-0.001	0.000	0.111

MVLR Analysis *2 hours D/D_0 glucose*

	Coeff.	lower CI95%	upper CI95%	p-value
Age (years)	-0.011	-0.027	0.005	0.142
Glucose exposure (g/m²/day)	-0.002	-0.005	0.001	0.147
Microvessel density (/mm²)	**-0.203**	**-0.404**	**-0.003**	**0.047**
Submesothelial thickness (µm)	0.001	-0.000	0.001	0.089

Inflammatory Cell Infiltration/EMT with low GDP PD

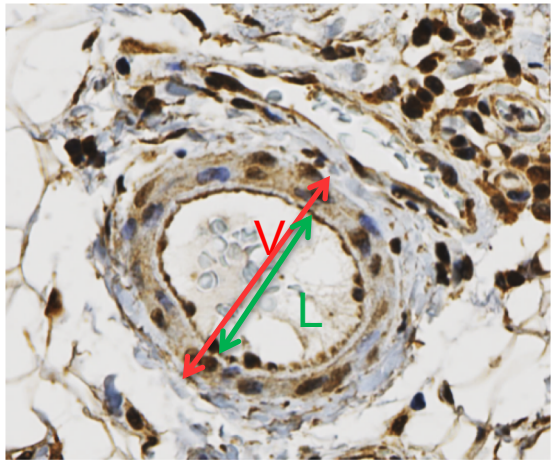


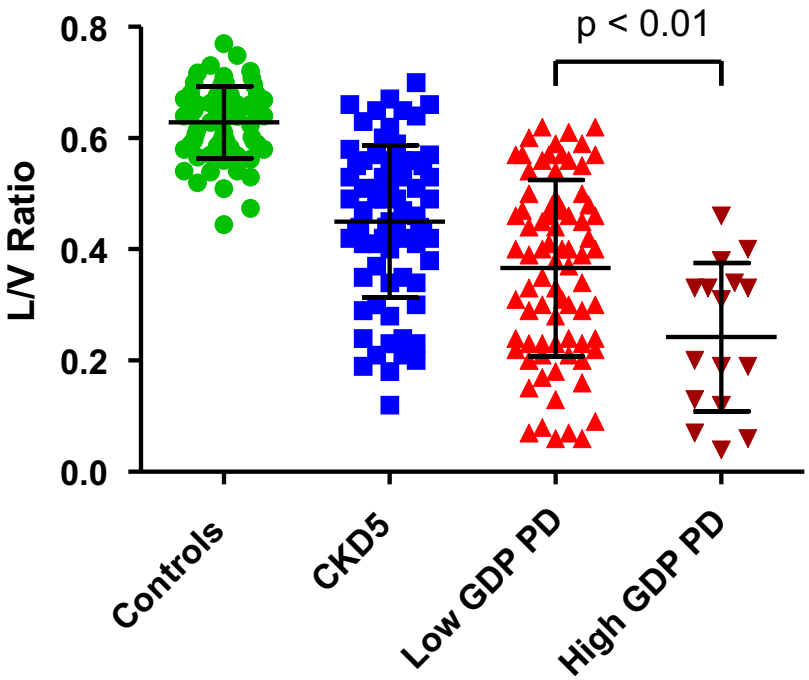
Low versus high GDP PD

(matched for age, dialytic glucose exposure and PD vintage)

	Low GDP PD	**High GDP PD**	**p-value**
	n = 15	n = 15	
PD duration (months)	15 (24.5)	10 (30)	0.65
Glucose exposure (g/m^2/day)	65.7 (28.5)	56.3 (19.5)	0.21
Mesothel absent	60 %	40 %	0.49
Mesothel score (0 - 6)	0.0 (2.0)	2.0 (3.0)	0.27
Submesothelial thickness (um)	294 (223)	470 (523)	<0.05
Microvessel density (/ mm^2)	163.1 (163.6)	182.4 (142.6)	0.66
Lymphatic vessel density (/ mm^2)*	33.0 (34.3)	16.8 (11.5)	n.a.*
Blood cap. vessel density (/ mm^2)	118.4 (163.9)	224.2 (234.8)	0.74
Total endothelial surface area (um^2/um^3)	9.4 (9.6)	10.3 (7.6)	0.90
Lym. Endothelial surface area (um^2/um^3)	2.5 (3)	1.3 (0.6)	n.a.*
Blood cap. End. Surface area (um^2/um^3)	5.7 (9.8)	8.6 (9.7)	0.61
L/V ratio	0.4 (0.2)	0.3 (0.2)	<0.05
ASMA negative	40 %	67 %	0.14
ASMA score (0 - 3)	1.0 (3.0)	0.0 (1.0)	0.11
CD45 negative	40 %	40 %	1.00
CD45 score (0 - 3)	1.0 (3.0)	1.0 (2.0)	0.83
CD68 negative	27 %	60 %	0.07
CD68 score (0 - 3)	1.0 (3.0)	0.0 (1.0)	0.07
Fibrine	33 %	27 %	0.69
Epithelial–Mesenchymal Transition	27 %	47 %	0.26
EMT (cells / mm^2)	42.9 (45.9)	15.0 (50.0)	0.34
Diffuse podoplanin staining	14 %	60 %	<0.05*

Less peritoneal vasculopathy with low GDP PD fluids

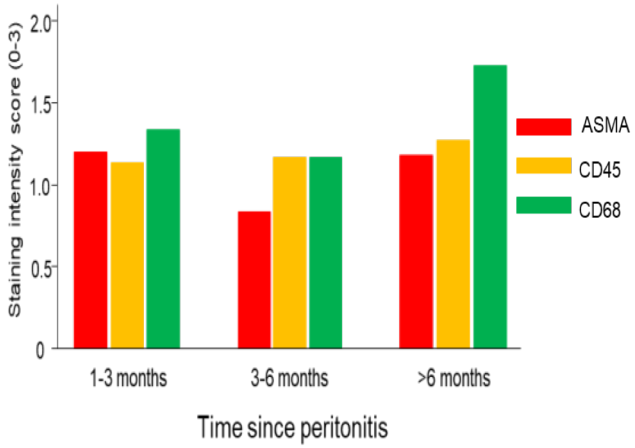




L/V: Lumen/Vessel Ratio
L: Luminal diameter
V: Vessel diameter

No major impact of peritonitis

	No peritonitis (n=24)	peritonitis (n=24)	p-value
MATCHING			
Age (years)	4.0 (1.8, 9.4)	3.3 (1.5, 10.1)	0.71
Female (%)	46%	58%	0.39
Body surface area (/m^2)	0.6 (0.4, 1.2)	0.6 (0.5, 1.0)	0.88
PD duration (months)	11.3 (8.5, 21.4)	12.0 (8.5, 22.4)	0.66
Glucose exposure (mg/day/bsa)	97 (89, 132)	100 (85, 108)	0.64
Absent mesothel layer	46%	38%	0.53
Mesothelial cell coverage (0-6)	0.5 (0.0, 3.5)	1.0 (0.0, 3.0)	0.91
Submesothelial thickness (um)	304 (200, 358)	413 (250, 500)	0.24
Microvessel density (/mm^2)	200 (107, 325)	170 (97, 318)	0.82
Microvessel number / mm	59 (32, 75)	82 (30, 116)	0.21
Lymphatic vessel density (/mm^2)	39 (23, 56)	33 (22, 46)	0.41
Blood cap. vessel density (/mm^2)	176 (71, 238)	139 (66, 362)	0.72
Total endothelial surface area (um^2/um^3)	10.0 (7.7, 19.0)	10.2 (5.9, 16.4)	0.82
Lym. endothelial surface area (um^2/um^3)	3.4 (1.8, 5.7)	2.6 (1.3, 4.4)	0.30
Blood cap. endothelial surface area (um^2/um^3)	8.0 (4.1, 12.8)	6.7 (3.3, 15.7)	0.89
L/V ratio	0.4 (0.2, 0.5)	0.4 (0.3, 0.5)	0.28
ASMA score (0-3)	1 (0, 1)	1 (0, 2)	0.55
CD45 score (0-3)	1 (1, 1.5)	1 (0, 2)	0.89
CD68 score (0-3)	1 (0, 1.5)	2 (1, 2)	0.11
Fibrine (% positive patients)	25%	25%	1.00
Epithelial–Mesenchymal Transition (% pos. Pat.)	46%	42%	0.77
EMT (cells/mm2)	49 (20, 198)	21 (8, 65)	0.34
Diffuse staining (% positive patients)	33%	23%	0.42
VEGF-A (% submesothelial area)	32 (19, 63)	35 (20, 51)	0.50
pSMAD2/3 (% submesothelial area)	18.1 (6.2, 29.1)	20.3 (7.3, 26.7)	0.65



Optimize PD

- Dwell volume: IPPM a useful tool, but evidence on effect on clincial outcome parameter scant

- Dwell time: PET provides significant information

- Adapted PD: Intriguing concept, benefits still uncertain
  Underlying mechanisms? Individual regime?

- Remote patient Monitoring: Promising
  Evidence from other diseases, that impact on outcome in adult CKD 5D
  - Who? How? When?
  - Privacy?
  - Automated surveillance algorithms?
  - Responsibility, legal aspects?
  - Cost-utility ratio (“Comprehensive but easy to use”)

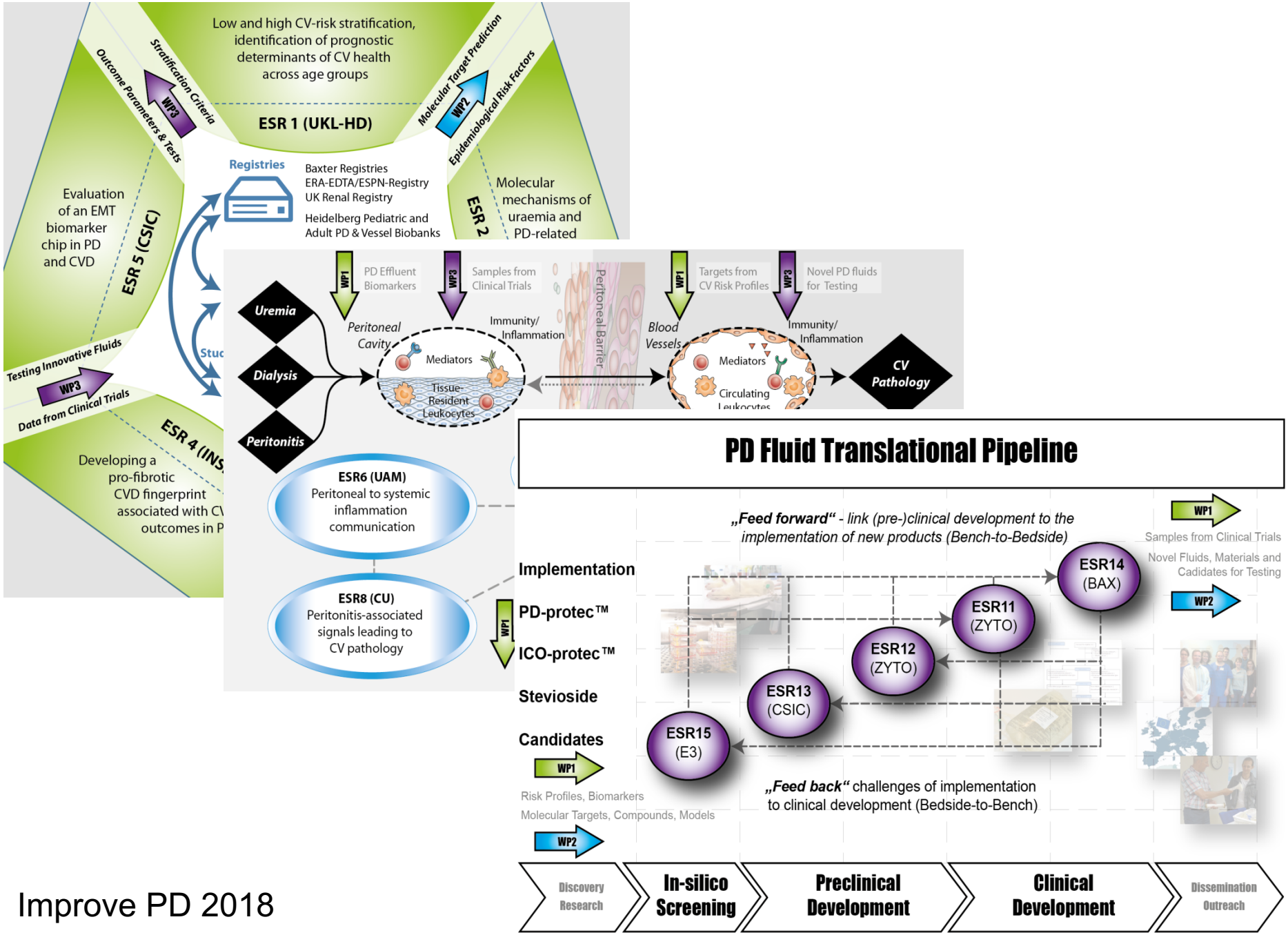
Optimize PD

- ACEI/ARB to preserve residual renal function and potentially peritoneal membrane transporter status (?)

- Small long term impact of bacterial peritonitis on peritoneal morphology, provided adequate treatment

- Low GDP fluids recommended in children:
  - preserve residual renal function
  - mitigate peritoneal vasculopathy
  - not short term membrane protection, but long term benefits (?)

  => alternative osmotic agents?
  => locally and systemically active additives (such as.alanyl-glutamine)?



Improve PD 2018

Next ERKNet Webinar:

September, 04

Max Liebau (Cologne)

A Primer to Cystic Kidney Diseases and Ciliopathies

Contact: claus.peter.schmitt@med.uni-heidelberg.de

Financial support: EU Grant, FP7, 287813
Fresenius Medical Care
Medical Faculty Heidelberg