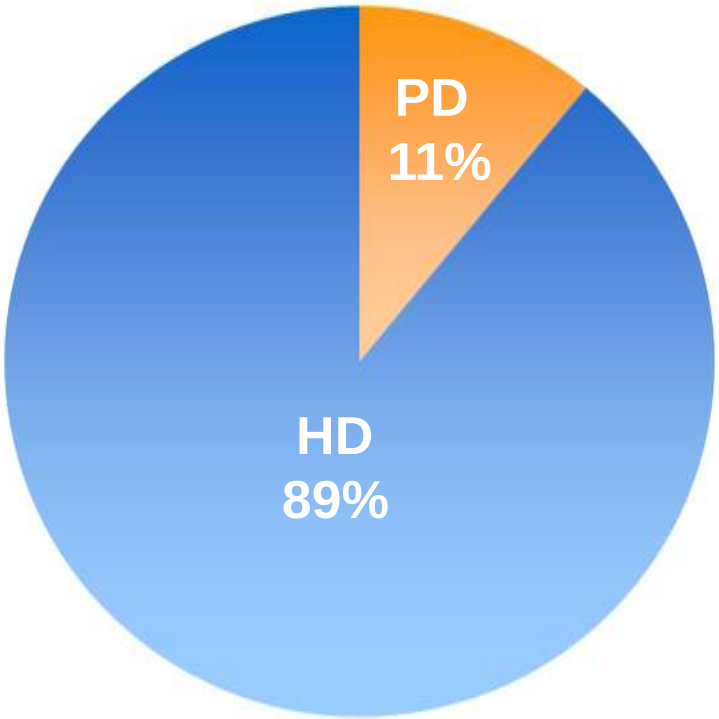
The Present and Future of Peritoneal Dialysis

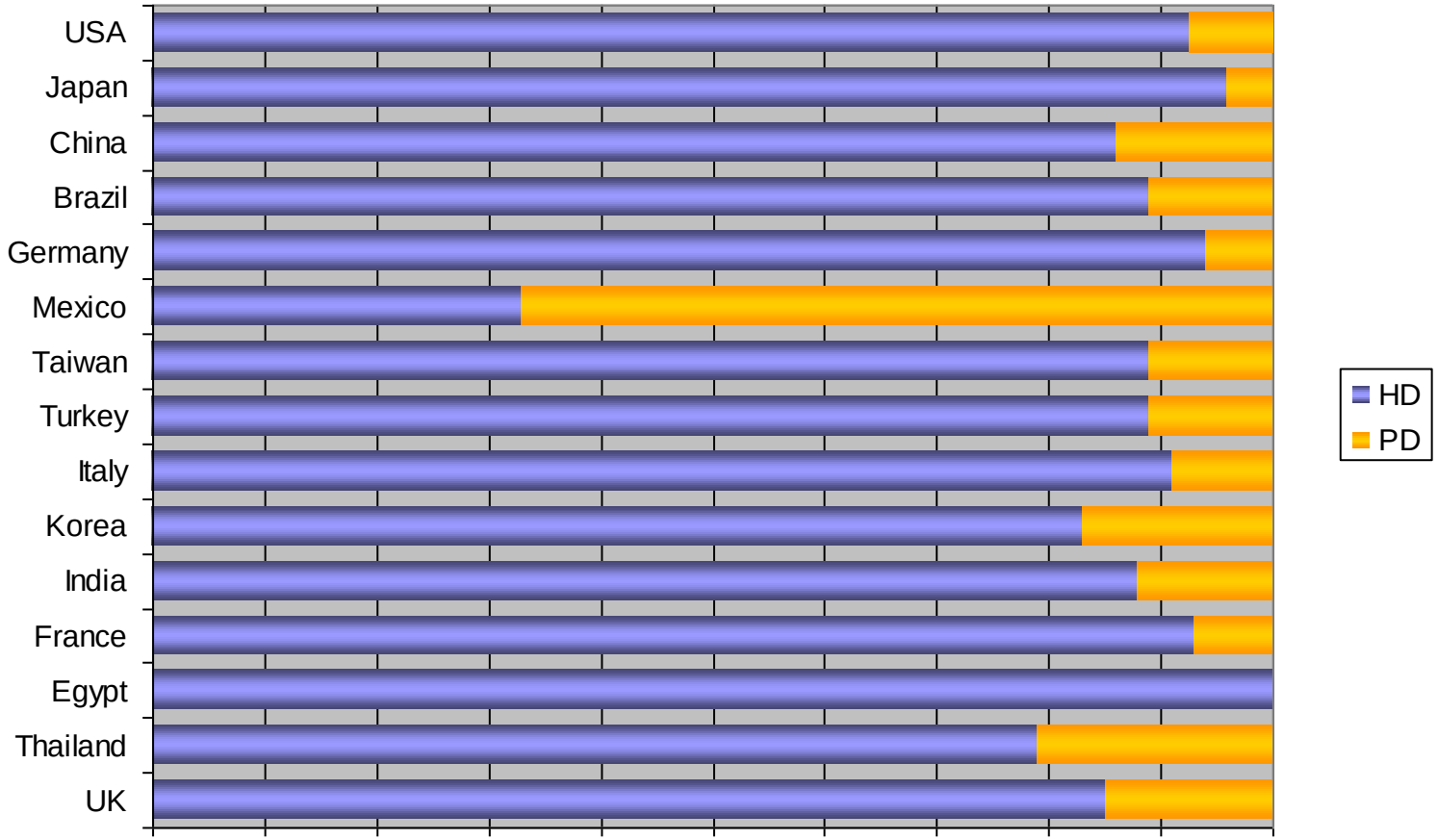
Ágnes Haris MD, PhD
Budapest

Dialysis patient population split by treatment modality



Global: 2,029,000 dialysis patients

HD-PD split in the 15 largest countries ranked by dialysis patient population



Advantages of PD

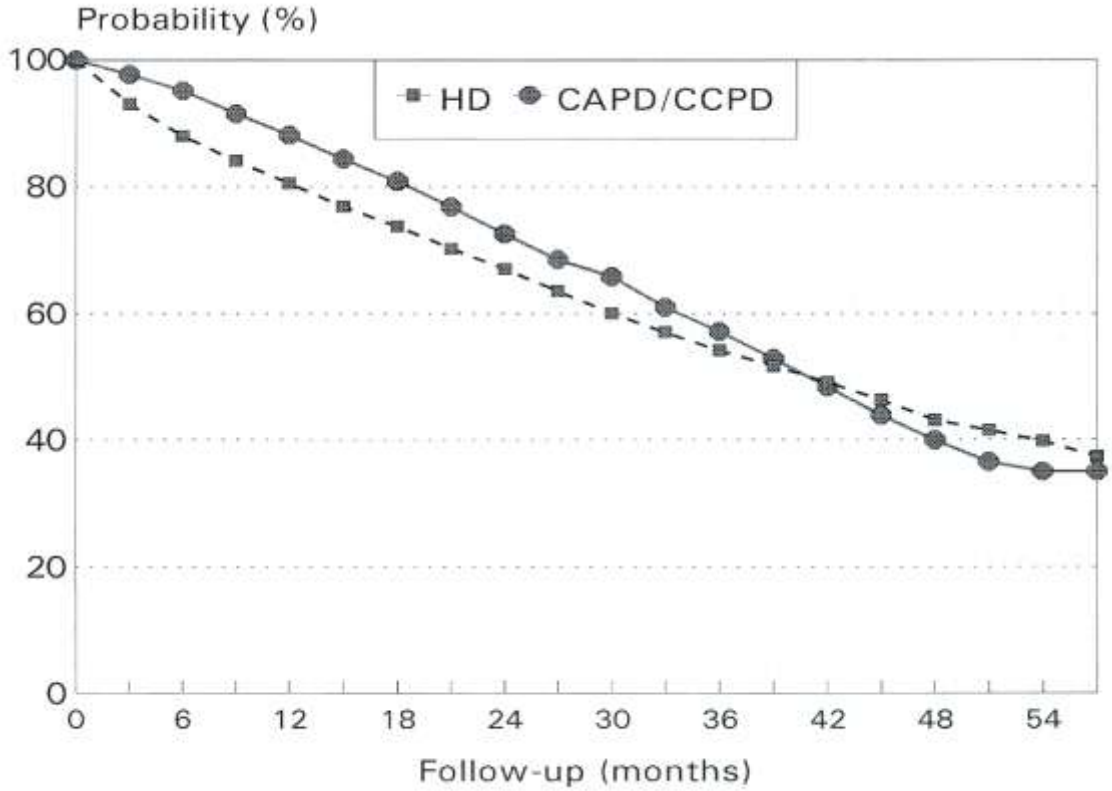
- PD is an efficient home treatment
  - less expensive than HD
  - can be tailored to the individual patient's clinical and social requirements
  - permits a high degree of social rehabilitation and physical freedom
  - high degree of patient satisfaction
- PD patients are more satisfied and rate their care 1,46 times higher then HD patients

„Integrated care" approach to ESRD

- PD, HD and Tx should be offered to the patients in an unbiased way
- For many patients PD is the best choice for initial RRT

- The question has to be:
  „Which treatment sequence is the best?"
  rather than
  „Which treatment is the best?"

Dialysis modality and mortality



Fenton et al. Am J Kidney Dis, 1997

EDTA Registry Data 1997 -2001 and 2002-2006

Survival type	Cohort	1 year Survival (95%CI)	2 year Survival (95%CI)	5 year Survival (95%CI)	Crude HR (95%CI)	Adjusted HR (95%CI)[a]
Patient survival on RRT	1997–2001	81.3 (81.1–81.6)	69.8 (69.6–70.1)	46.3 (46.2–46.5)	1 (ref)	1 (ref)
	2002–2006	81.3 (81.1–81.5)	70.0 (69.8–70.2)		0.98 (0.97–1.00)	0.88 (0.86–0.89)
Patient survival on dialysis	1997–2001	80.7 (80.4–80.9)	67.7 (67.5–68.0)	37.2 (37.1–37.4)	1 (ref)	1 (ref)
	2002–2006	80.6 (80.4–80.8)	68.1 (67.9–68.3)		0.97 (0.95–0.98)	0.89 (0.88–0.91)
Haemodialysis	1997–2001	**78.8** (78.5–79.1)	**65.8** (65.5–66.0)	**35.9** (35.7–36.0)	1 (ref)	**1 (ref)**
	2002–2006	**78.7** (78.4–78.9)	**65.8** (65.5–66.0)		0.98 (0.96–0.99)	**0.90** (0.89–0.92)
Peritoneal dialysis	1997–2001	**88.4** (87.9–88.9)	**75.9** (75.3–76.5)	**43.1** (42.7–43.6)	1 (ref)	**1 (ref)**
	2002–2006	**89.7** (89.3–90.2)	**79.4** (78.8–80.0)		0.87 (0.83–0.90)	**0.81** (0.78–0.85)

Propensity-matched mortality comparison of incident HD and PD patients

Weinhandl et al. JASN 2010

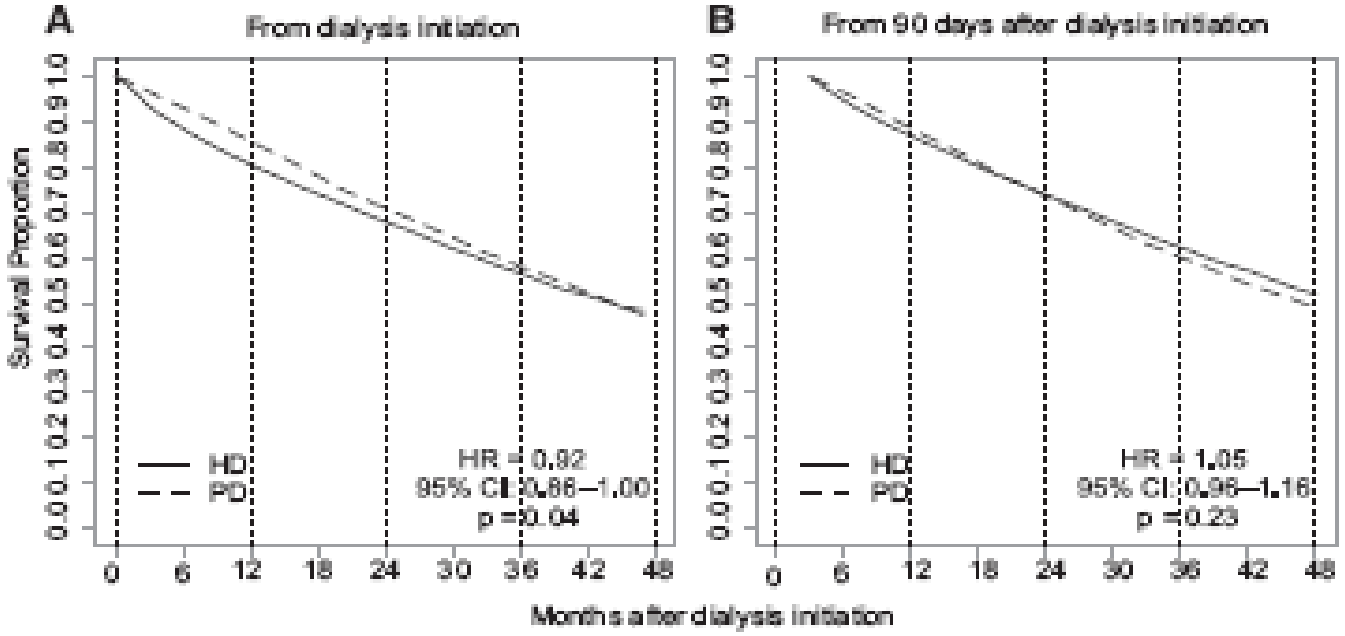
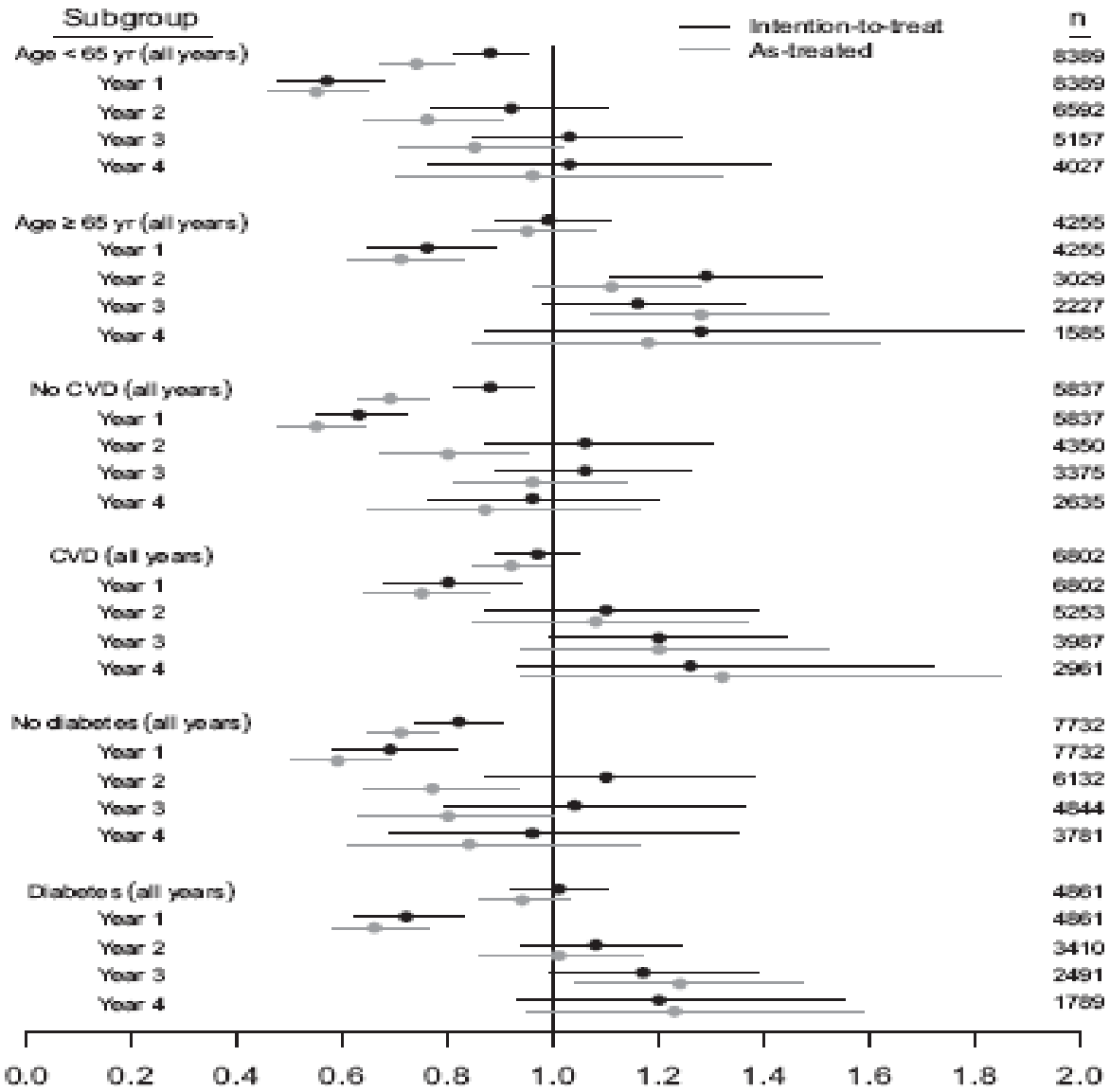
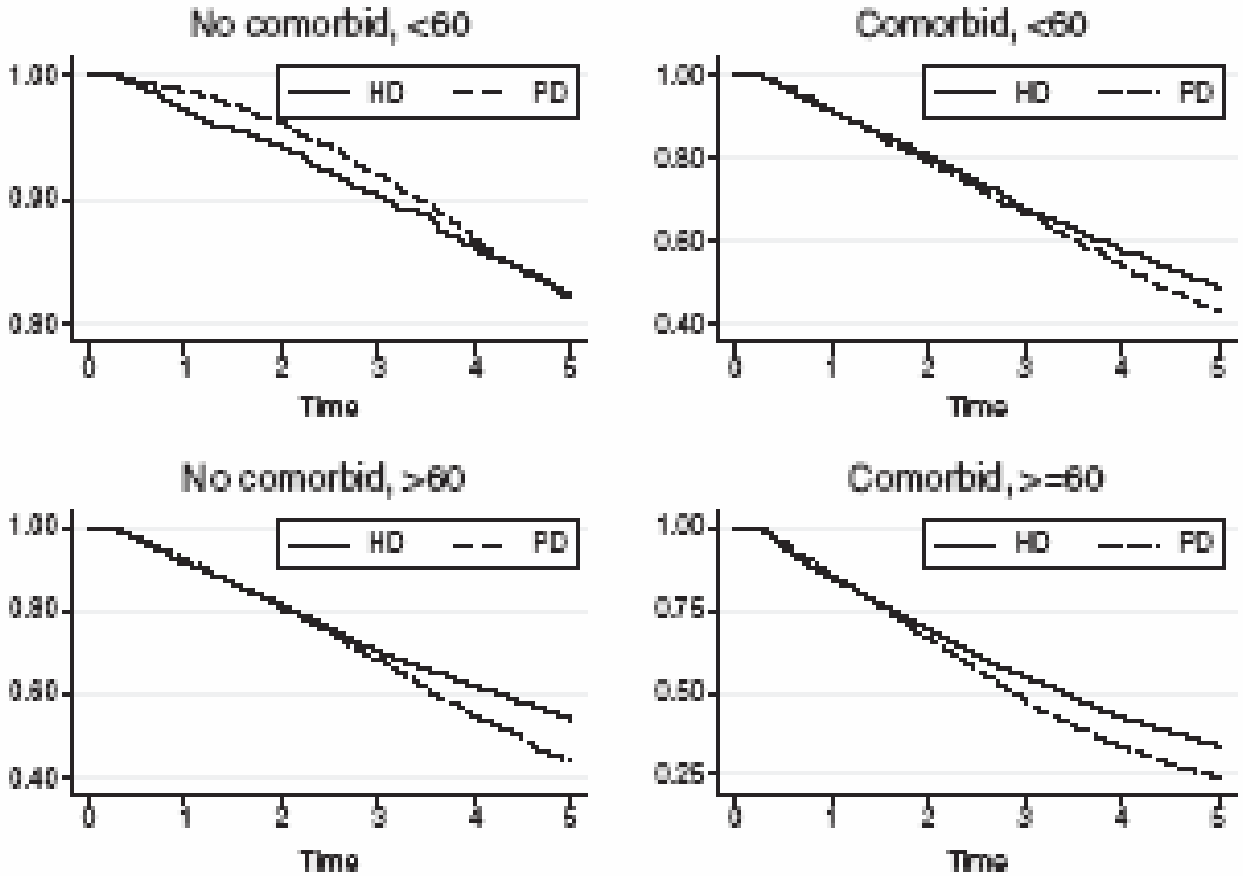


Figure 1. Intention-to-treat in the matched cohort showed lower death risk in PD when follow up began at initiation of dialysis. Risks were similar when follow-up began at day 90. HD, hemodialysis; PD, peritoneal dialysis.


Subgroup
Intention-to-treat
As-treated
n
Age < 65 yr (all years) 8389
Year 1 8389
Year 2 6592
Year 3 5157
Year 4 4027
Age ≥ 65 yr (all years) 4255
Year 1 4255
Year 2 3029
Year 3 2227
Year 4 1585
No CVD (all years) 5837
Year 1 5837
Year 2 4350
Year 3 3375
Year 4 2635
CVD (all years) 6802
Year 1 6802
Year 2 5253
Year 3 3987
Year 4 2961
No diabetes (all years) 7732
Year 1 7732
Year 2 6132
Year 3 4544
Year 4 3781
Diabetes (all years) 4861
Year 1 4861
Year 2 3410
Year 3 2491
Year 4 1789
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0

Relationship of modality with mortality

ANZDATA registry (1991-2005)

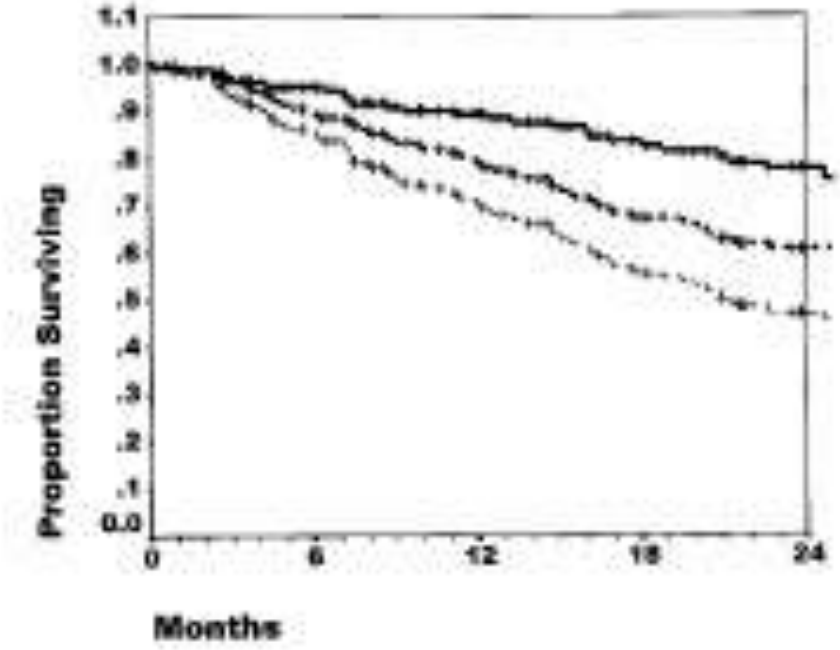


14 733 HD pts, 10 554 PD pts

McDonald et al. JASN 2009

Survival of anuric patients on APD – EAPOS study

Brown et al. JASN 2003



2-yr Patient survival - 78%

2-yr pure technique survival - 62%

2-yr combined patient and technique survival - 49%

Prospective, multicenter, study, 177 prevalent patients
Targets: Creat. clearance > 60 l/week, UF > 750 ml/day

Clinical outcomes of elderly patients on PD versus HD

North Thames Dialysis Study

Clinical Outcomes in Peritoneal Dialysis (PD) and Hemodialysis (HD) Patients

Outcome	At risk (*n*)	Events [*n* (%)]	Unadjusted $RR_{PD/HD}$ (95% CI)	Adjusted $RR_{PD/HD}$[a] (95% CI)
Death				
PD	76	18 (24)	0.99 (0.53–1.84)	1.13 (0.60–2.11)
HD	95	22 (23)	1.00	1.00
Hospitalization				
PD	76	52 (68)	0.93 (0.74–1.17)	0.97 (0.77–1.22)
HD	95	63 (66)	1.00	1.00

[a] Adjusted for study cohort, time on dialysis, age, sex, and comorbidity.

Harris et al. PDI 2002

Why is PD underutilized?

- The benefit of PD is apparent in the first 3-4 years on RRT
- Why don't we use PD more?
  - education of the nephrologists
  - education of the patients
  - reimbursement
- What are the reasons of technique failure in PD?
  (7-11 %/year)
  - recurrent episodes of peritonitis
  - loss of residual renal function
  - loss of peritoneal membrane function - UF failure

Update on PD peritonitis

PD peritonitis

UK Audit, Davenport, PDI 2009

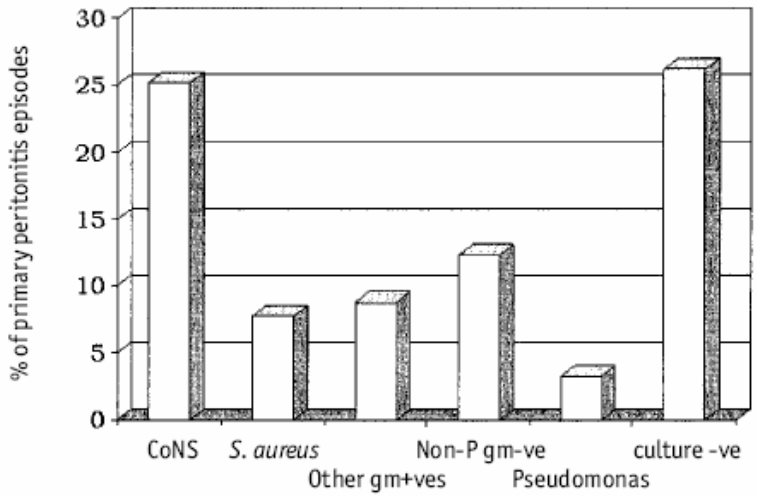


Figure 2 — Causes of primary peritoneal infections as percentages of total episodes of peritonitis. CoNS = coagulase-negative staphylococci; *S. aureus* = *Staphylococcus aureus*; gm+ves = gram positives; Non-P gm-ve = non-pseudomonas gram-negative micro-organisms; -ve = negative.

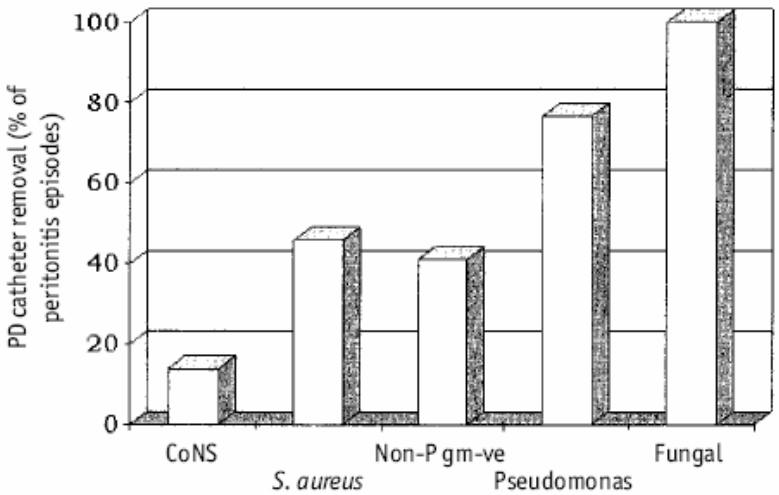


Figure 3 — Peritoneal dialysis (PD) catheter loss and bacterial infection. CoNS = coagulase-negative staphylococci; *S. aureus* = *Staphylococcus aureus*; Non-P gm-ve = non-pseudomonas gram-negative micro-organisms.

2002-2003, 12 PD units, 635 pts on CAPD, 445 on APD

Peritonitis related mortality

Fontán et al PDI 2005

Etiologic Agents of Peritonitis. Values expressed as [*n* (%)].

Micro-organism	Episodes	Mortality
Staphylococcus aureus[a]	46 (6.6)	7[c] (15.2)
Coagulase-negative staphylococcus	206 (29.7)	1 (0.5)
Enterococcus spp[a]	22 (3.2)	1 (4.5)
Streptococcus spp	113 (16.3)	5[d] (4.4)
Other gram-positive bacteria	23 (3.3)	0 (0)
Enterobacteriaceae	85 (12.3)	4 (4.7)
Pseudomonas aeruginosa and related gram-negative bacteria	9 (1.3)	1 (11.1)
Other gram-negative bacteria	11 (1.6)	0 (0)
Polymicrobial non-enteric	26 (3.8)	1[c] (3.8)
Enteric	62 (8.9)	12 (19.4)
Fungal (primary)[b]	22 (3.2)	6 (27.3)
Tuberculosis	3 (0.4)	2 (66.7)
Negative culture	65 (9.4)	1 (1.5)
Total	693 (100)	41 (5.9)

Local application of gentamycin versus mupirocin in the prevention of ESI and PTIS

Chu et al, PDI 2008

Exit-Site Infection

	Gentamicin (*n*)	Gentamicin Rate[a]	Mupirocin (*n*)	Mupirocin Rate[a]	*p* Value
Total	15	0.38	9	0.20	0.36
Gram positive	7	0.18	0	0	NA
SA	2	0.05	0	0	
MRSA	3	0.08	0	0	
CoNS	0	0	0	0	
Streptococcus spp	0	0	0	0	
Diphtheroids	1	0.03	0	0	
Corynebacterium sp	1	0.03	0	0	
Gram negative	8	0.20	9	0.20	0.62
PA	7	0.18	6	0.13	
Mixed	1	0.03	3	0.07	

SA = *Staphylococcus aureus*; MRSA = methicillin-resistant SA; CoNS = coagulase-negative staphylococcus; PA = *Pseudomonas aeruginosa*, NA = not available.

[a] Rate expressed as episodes/patient-year.

Peritonitis

	Gentamicin (*n*)	Gentamicin Rate[a]	Mupirocin (*n*)	Mupirocin Rate[a]	*p* Value
Total	13	0.33	12	0.27	0.91
Gram positive	6	0.15	8	0.18	0.45
Streptococcus spp	5	0.13	2	0.04	
SA	0	0	1	0.02	
MRSA	1	0.03	0	0	
CoNS	0	0	4	0.09	
Mixed	0	0	1	0.03	
Gram negative	7	0.18	4	0.09	0.49
PA	2	0.05	1	0.02	
Campylobacter sp	1	0.03	0	0	
Plesiomonas sp	1	0.03	0	0	
Escherichia coli	2	0.06	2	0.04	
Klebsiella sp	1	0.03	1	0.02	

SA = *Staphylococcus aureus*; MRSA = methicillin-resistant SA; CoNS = coagulase-negative staphylococcus; PA = *Pseudomonas aeruginosa*.

[a] Rates expressed as episodes/patient-year.

81 patients, approx. 500 patient-months for each group

The Achilles'heel of PD - Peritonitis

- **Peritonitis**
  - major cause of transfer from PD to HD (40-45%)
  - cause of mortality in 1-6 %
  - no difference in PTIS rates between CAPD and APD
- **ISPD recommendations**:
  - PTIS rate < 1/18 months
  - ES care: mupirocin/gentamcin cream may be applied daily to prevent ES infections
  - training and retraining
  - prophylaxis (antibiotic before procedures; nystatin, fluconazole during prolonged antibiotic therapy in programs with high rates of fungal PTIS)

Update on preserving RRF

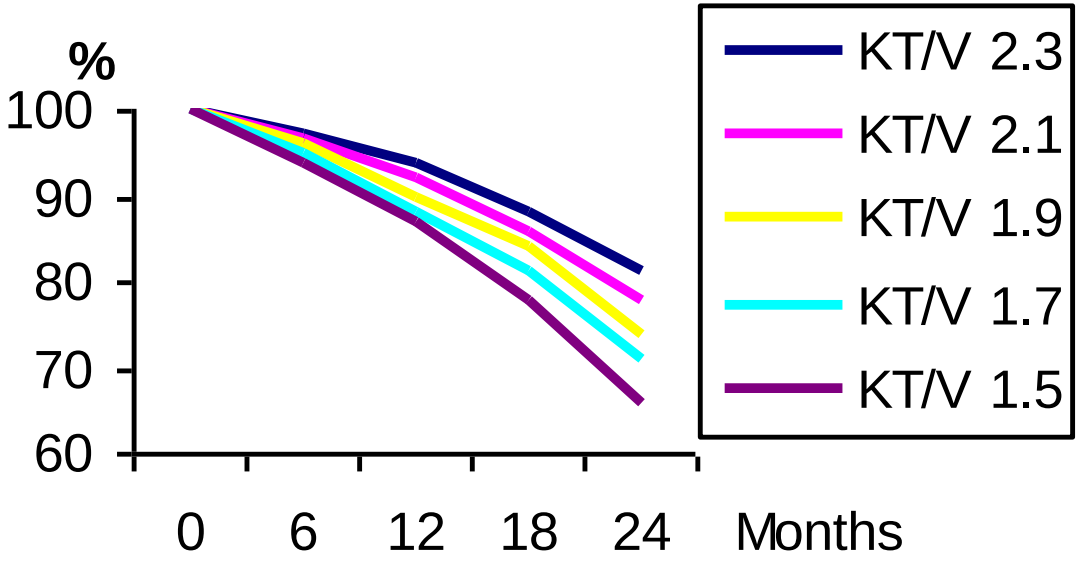
The importance of residual renal function in dialyzed patients

- RRF helps in
  - fluid balance
  - normalization of blood pressure
  - phosphate excretion
- In anuric patients
  ↑ EPO requirements, ↑ inflammation, ↑ CaxP, ↑ LVH
  ↑ BP, ↓ nutrition, ↑ total and cardiovascular mortality
- Each 250 ml daily residual urine output decreases the risk of mortality by 36%

CANUSA study

- 14 dialysis centers in USA and Canada
- 680 incident peritoneal dialysis patients followed for 3,3 years
- Total Kt/Vurea (peritoneal+renal) at the initiation of PD was 2,38
- After 2 years it decreased to 1.99

Survival data according to Kt/Vurea



Risk of mortality decreased 6% by each 0.1 higher value of Kt/Vurea

Changes of Kt/V urea during the 24 months observation period

Months	0	6	12	18	24
Kt/V urea	2.38	2.25	2.1	2.0	1.99
Peritoneal Kt/V	1.67	1.67	1.68	1.66	1.7
RRF Kt/V	0.71	0.58	0.41	0.39	0.28

Significance of the residual renal function

Reanalysis of the CANUSA study (B*argman et al. JASN 2001*)

- It is the *residual renal function*, not the peritoneal clearance, which determines survival data

ADEMEX study – CAPD *(Paniagua et al. JASN 2002)*

- Residual renal function predicts survival

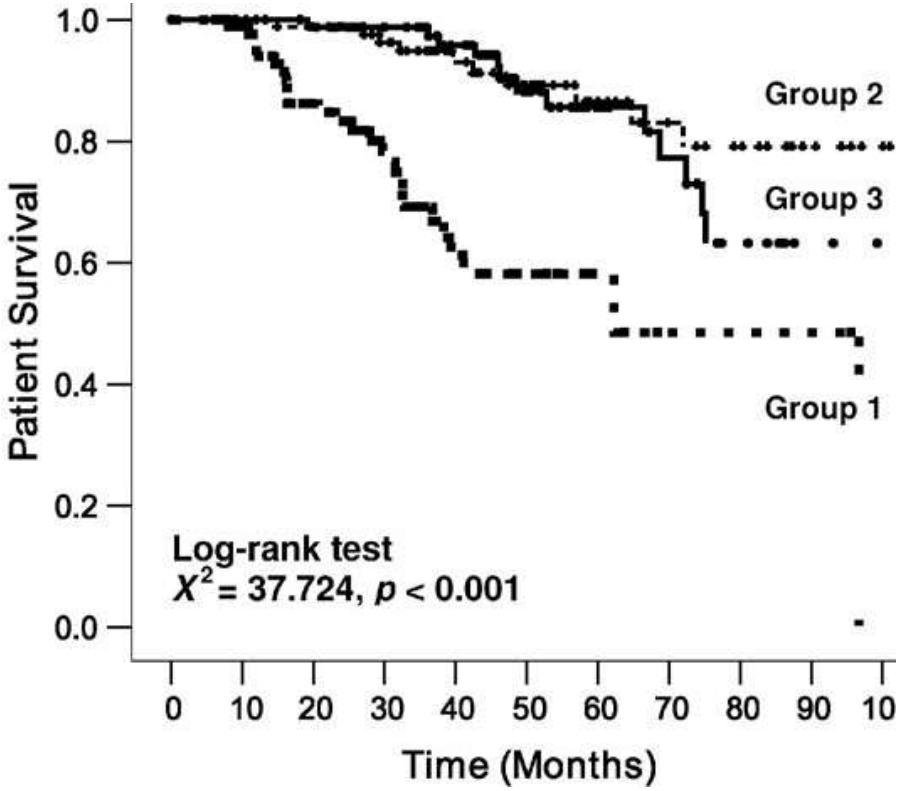
NECOSAD study – HD *(Termorshuizen et al. JASN 2004)*

- The higher residual renal Kt/V is an independent, significant predictor of survival

Association between the rate of decline of residual renal function and survival

Liao et al. NDT 2009.

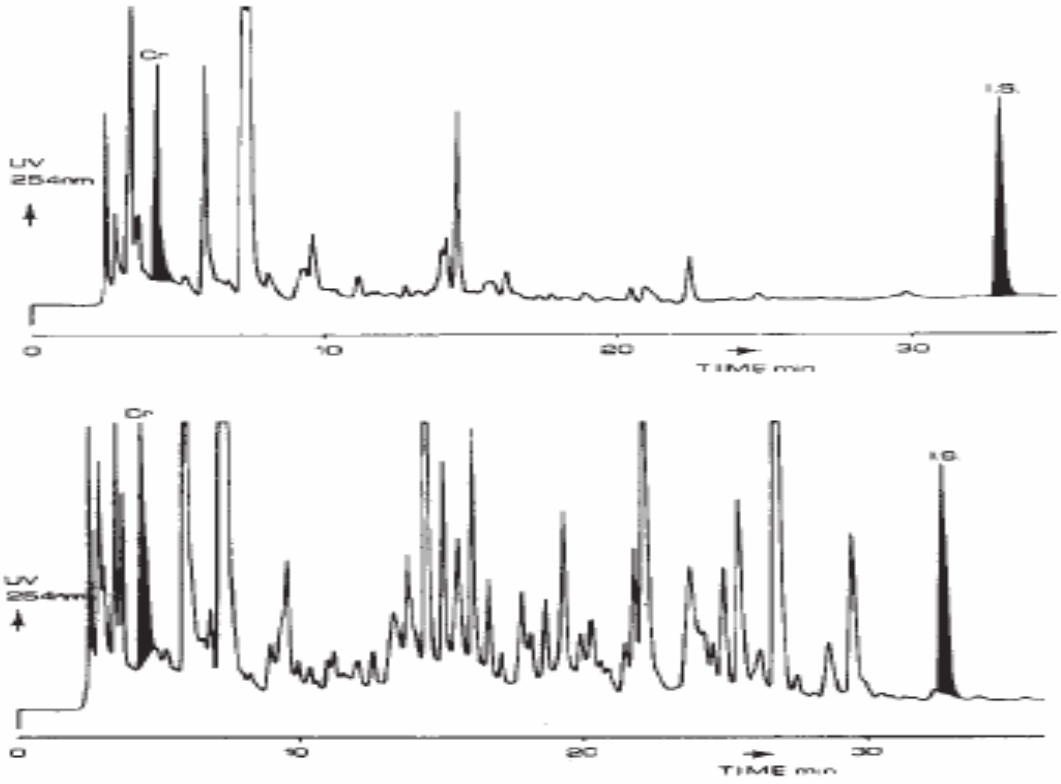
- 270 PD patients
- 1 group: quick RRF ↓
- 2 group: moderate RRF ↓
- 3 group: slow RRF ↓



Role of the residual renal function in the clearance of uremic toxins

Dialysed patient with RRF

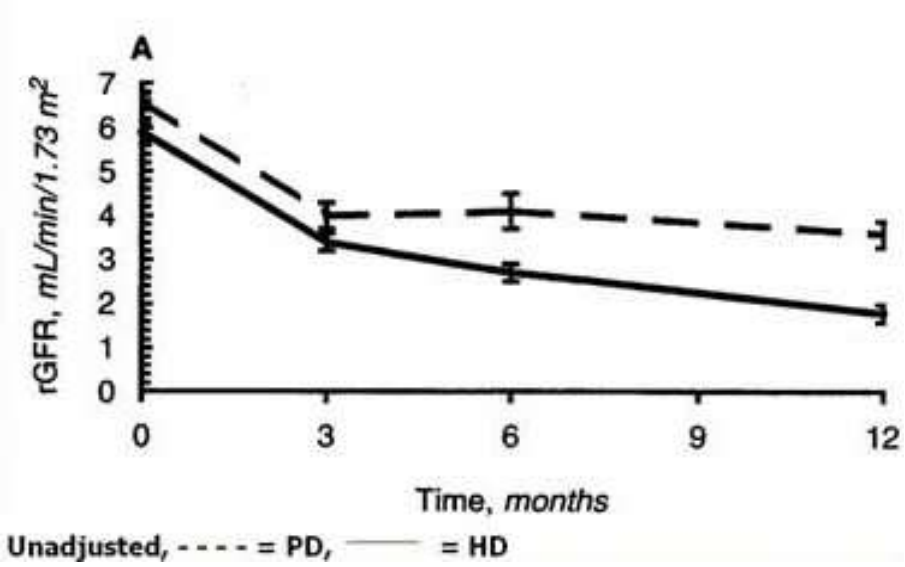
Dialysed anuric patient



Chromatograpy of the uremic plasma *(Krediet, NDT 2006)*

Role of dialysis modality in preserving residual renal function

- Volume homeostasis ↓↑
- Osmotic homeostasis ↓↑
- Ischaemic episodes ↑
- HD capillar → IL-1 ↑
- HD dialysis solution's bioincompatibility



From: Jansen MAM et al. Kidney Int, 2002

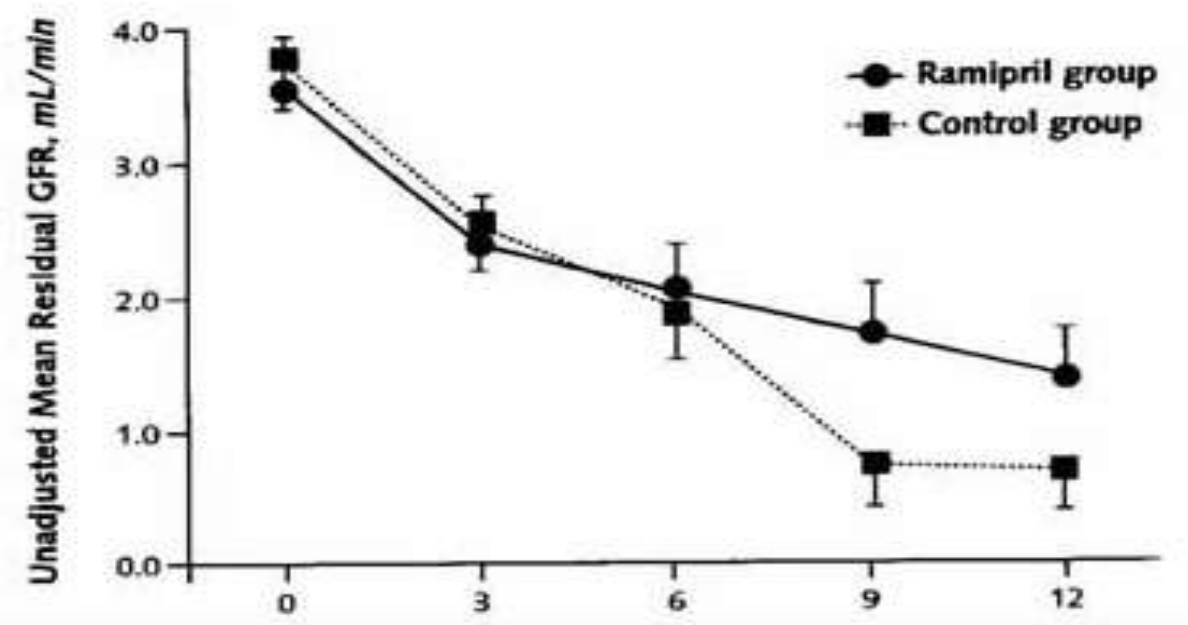
Factors associated with higher rate of decline of RRF

- 242 incident PD patients between 1994-1997
- RRF measured every 3-4 months, followed until anuria developed (<100 ml/day), or until December 1998
- 40% of patients got anuric in an average of 20 months
- Rate of decline was faster:
  - males, higher BMI
  - in diabetics
  - in proteinuric pts
  - in pts with CHF
  - in pts with multiple PTIS
  - use of aminoglycoside

Singhal, Bhaskaran, Vidgen, Bargman, Vas, Oreopoulos, PDI 2000.

Effect of ACE inhibitor on the preservation of residual renal function

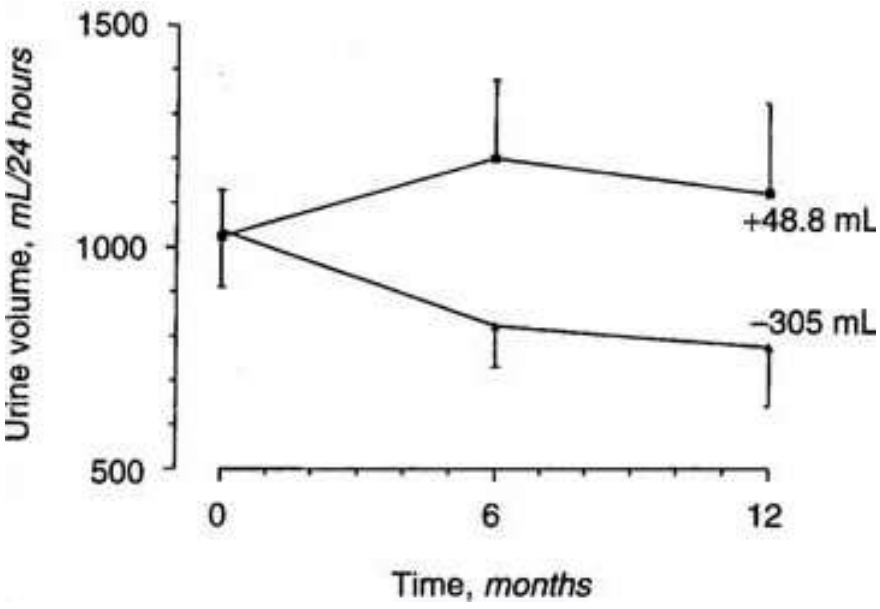
rGFR in PD patients randomized for ramipril or placebo



From: Li Ph-T et al. Ann Int Med, 2003

Role of diuretics in the preservation of residual renal function in patients on CAPD

- Loop diuretics: Increased excretion of Na, K and water, stable GFR
- Don't influence of the natural course of RRF



From: Metcalf JF et al. Kidney Int, 2001

61 patients, CAPD, 250 mg/day furosemid (+thiazid)

Suggested strategies to preserve RRF

- Choose PD as first dialysis modality!
- Avoid hypovolaemia
- Reach blood pressure target
- Administer ACE inhibitor or ARB
- Administer furosemide to increase urine output
- Avoid nephrotoxic drugs (aminoglycosides, NSAIDs, radiocontrast agents, cyclosporin, tacrolimus)
- Biocompatible dialysis solutions (?)

Update on the preservation of peritoneal membrane function

Causes of changes of membrane structure and function - bioincompatibility of PD solutions

- Low pH - high levels of lactate
- High glucose concentration
  - hyperosmolarity
  - glucose degradation products (GDPs):
    produced from glucose during heat sterilization
    (most important: 3,4-dideoxyglucosone-3-ene, 3,4-DGE);
  - advanced glycation end products
    (AGEs, most important ligand, N-carboxymethy-lysin, for receptor for AGEs /RAGE/)
- GDPs and AGEs → mesothelial cell activation

UF failure due to the „peritoneal fibrosing syndrome"

- TGF-ß

  (stimulated by GDPs, uremic toxins, AGEs and leptin)

  → epithelial-mesenchymal transition

  (mesothelial cells transform into myofibroblasts or smooth muscle cells)

- EMT

  → fibrogenic activity: collagen, fibronectin, VEGF

  - fibrosis of the peritoneum
  - angiogenesis - VEGF
  - vasculopathy

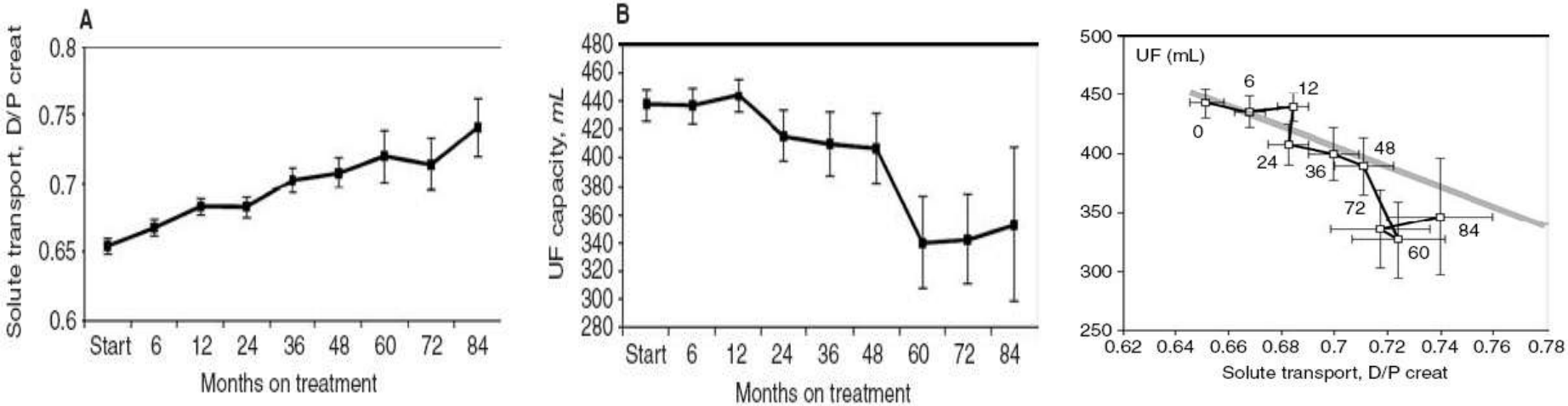
- ↑ small solute diffusion <u>but</u> ↓fluid transport

  (dysfunction of AQP1 in peritoneal endothelial cells)

In vivo study of the relationship between solute transport and UF capacity in long term PD patients

S.J. Davies, KI 2004.

- 574 new pts commencing PD between 1990-2003, followed for 7 yrs



- Pts who used higher glucose concentration, had more rapid increase in solute transport and a disproportionate fall in the UF capacity
- These pts were older, had more comorbidities, and less RRF

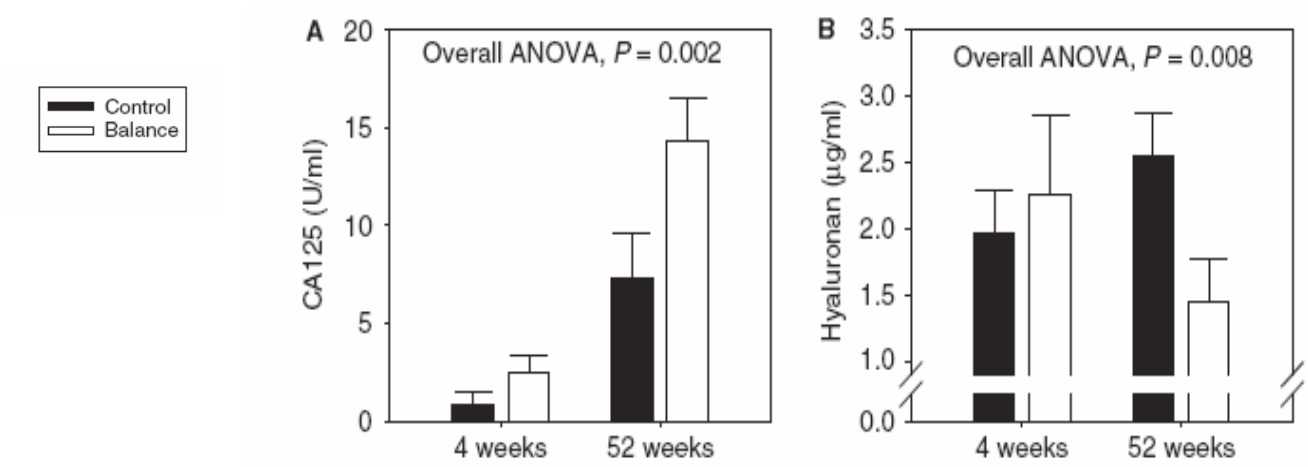
Composition of Peritoneal Dialysis Fluids

	Conventional	Icodextrin	Bicarbonate
Dextrose (g/dL)	1.5, 2.5, 4.25	0	1.5, 2.5, 4.25
Icodextrin (g/dL)	0	7.5	0
Sodium (mmol/L)	132.0	132.0	132.0
Chloride (mmol/L)	102.0	96.0	95.0
Calcium (mEq/L)	2.5-3.5	3.5	2.5
Magnesium (mEq/L)	0.5-1.5	0.5	0.5
Lactate (mEq/L)	40.0	40.0	0-15
Bicarbonate (mmol/L)	0	0	25-40
Osmolality (mOsm/Kg)	346-485	282-286	346-485
pH	5.2	5.2	7.4

	Glucose 15 g/L			Glucose 42.5 g/L		
	bicaVera	Balance	stay·safe	bicaVera	Balance	stay·safe
Lactate (mmol/L)	0	35	35	0	35	35
Bicarbonate (mmol/L)	34	2.5	0	34	2.5	0
Osmolality (mOsm/L)	358	358	358	511	511	511
pH	7.4	7.0	5.5	7.4	7.0	5.5
Glucose degradation products (μmol/L)						
3-deoxyglucosone	34±5	42±5	172±19	49±5	60±4	324±23
Methylglyoxal	<1	<1	5.8±0.4	<1	<1	9.9±0.5
Acetaldehyde	<2	<2	97±9	<2	<2	138±7
Formaldehyde	<3	<3	<3	<3	<3	4.3±0.3

PD effluent biomarkers of biocompatibility

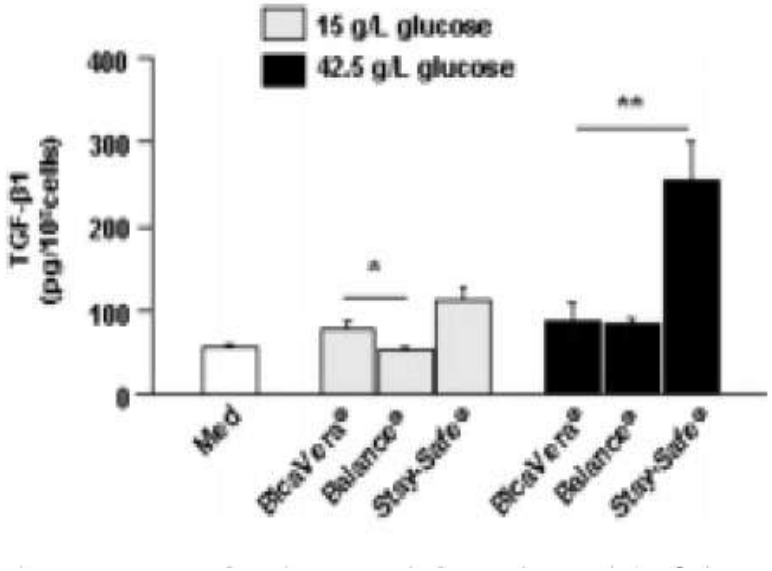
- Balance – lactate based pH neutral, low GDP solution
- Stay Safe - conventional glucose solution
- 50 new PD pts randomized to one of the two solutions, CAPD for 1 yr
- Effluent CA125 and hyaluronan levels

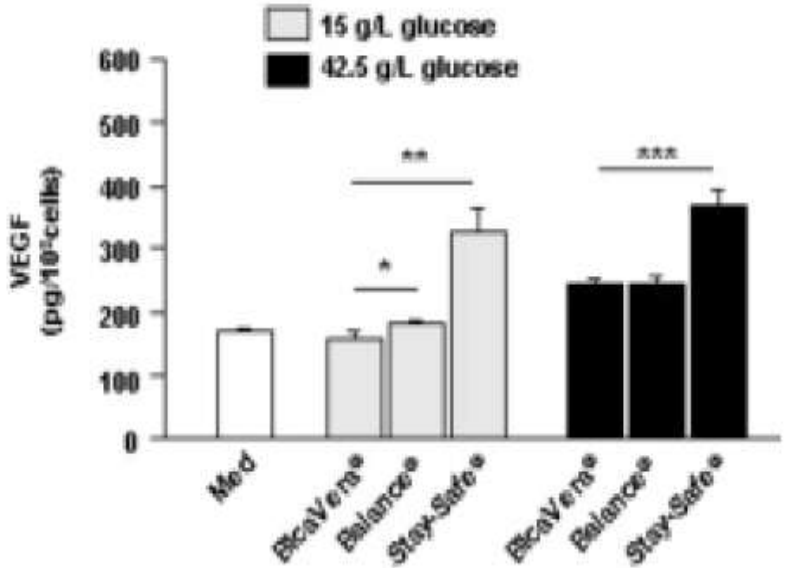


Szeto et al. NDT 2007

Growth factor production by human peritoneal mesenchymal cells

- In vitro cell cultures from healty people who had undergone elective abdominal surgery
- TGF-ß and VEGF measured in the cell culture supernatants





Grossin et al PDI 2006

Survival advantage of biocompatible PD solution – and its criticism

Lee et al. NDT 2006 – Bargman J NDT 2006

- *Balance* - Retrospective observational study, comparing survival of pts treated with conventional and low GDP, neutral pH solutions
- Superior survival of pts treated with Balance was found, compared to conventional solution

<u>BUT</u>

- No difference in technique survival, PTIS rate
- Older pts, more diabetics in the conventional group
- Pts were not randomized – The „centre effect”

Can low GDP solutions preserve RRF?
Kim et al. PDI 2008 – Bargman J. NDT 2010

- *Balnet* study – 91 new PD pts randomized for 1 yr
- Results:
  -rGFR was better preserved by biocomp. solution
  -no difference in patient or technique survival, PTIS rate

<u>BUT</u>

- Reduction in ultrafiltration with the biocompatible solution kept the patients more subclinically fluid overloaded
- However, healthier, less-inflamed pts may maintained their RRF longer. This may result in survival benefit.

Icodextrin

- 7,5 % glucose-polymer, molecular weight 16800 Da
- Similar UF as 3.86% glucose solution
- For the long dwell
- Increases UF in pts with inadequate ultrafiltration
  -in high transporters,
  -during peritonitis,
  -without excessive glucose absorption
- More biocompatible than glucose

Icodextrin

- Only 10-20% is reabsorbed by the lymphatics, but not via peritoneum
- Does not affect low molecular weight solute clearance, but increases $ß_2$-microglobulin clearance by convection
- Some unique features:
  - some maltose accumulation in the blood
  - pseudohyponatraemia by 2 mmol/l
  - spurious blood sugar levels if measured by glucose dehydrogenase determination
  - spuriously low serum amylase
- Potential side effects: rarely skin rashes and sterile peritonitis (peptidoglycan)

Metabolic and fluid management by icodextrin or glucose PD solutions

Paniagua et al. PDI 2009

- RCT for 12 months
- 59 pts with DM
- High- or high-average transporters

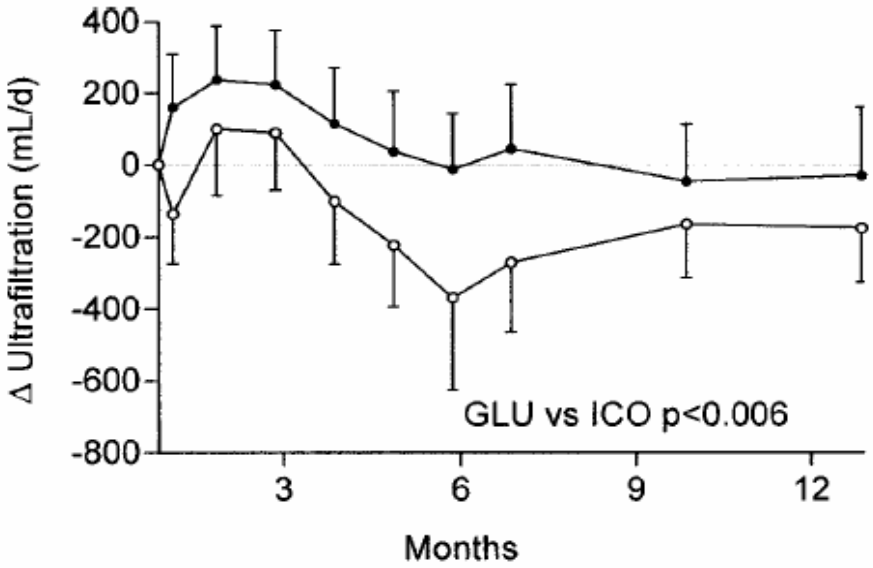
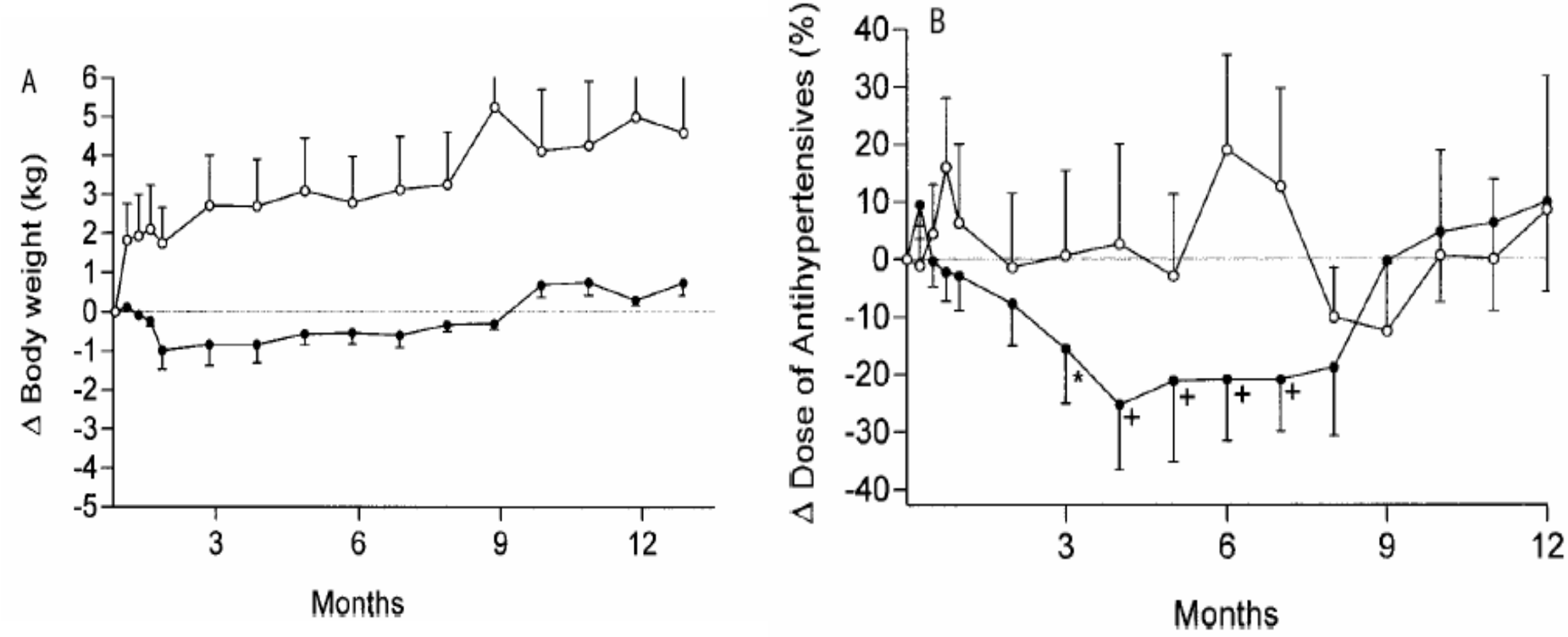


Figure 2 — Ultrafiltration was higher in patients using icodextrin-based dialysis solutions for the long dwell (ICO group; closed circles) than in patients using glucose-based dialysis solutions (GLU group; open circles), even with more frequent use of solutions with glucose concentration higher than 1.5% in the latter group. Mean difference between groups over time was 197 mL/day ($p < 0.006$).

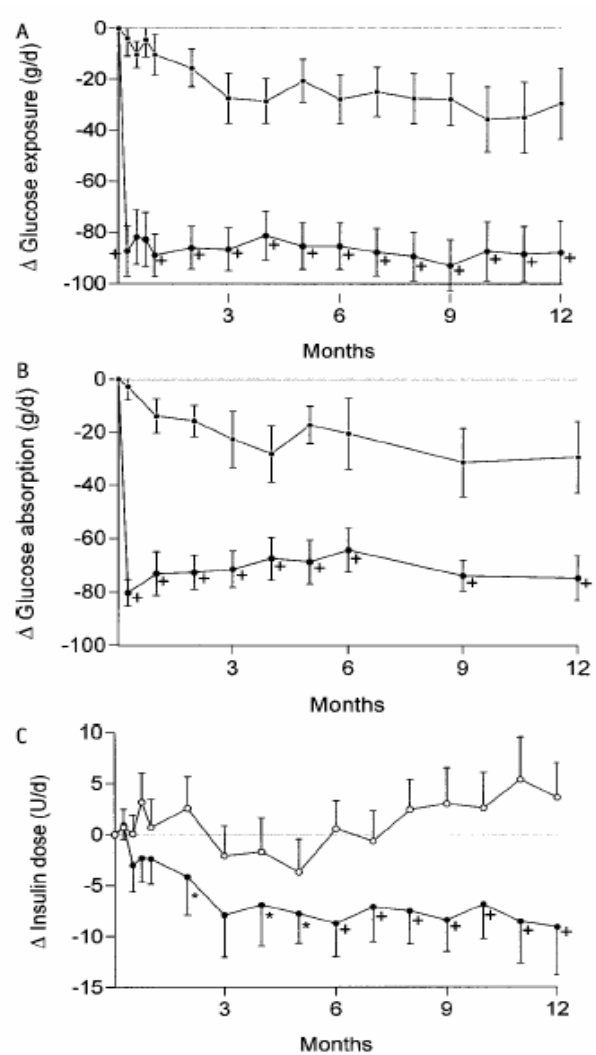
Changes of body weight and doses of the antihypertensive medications

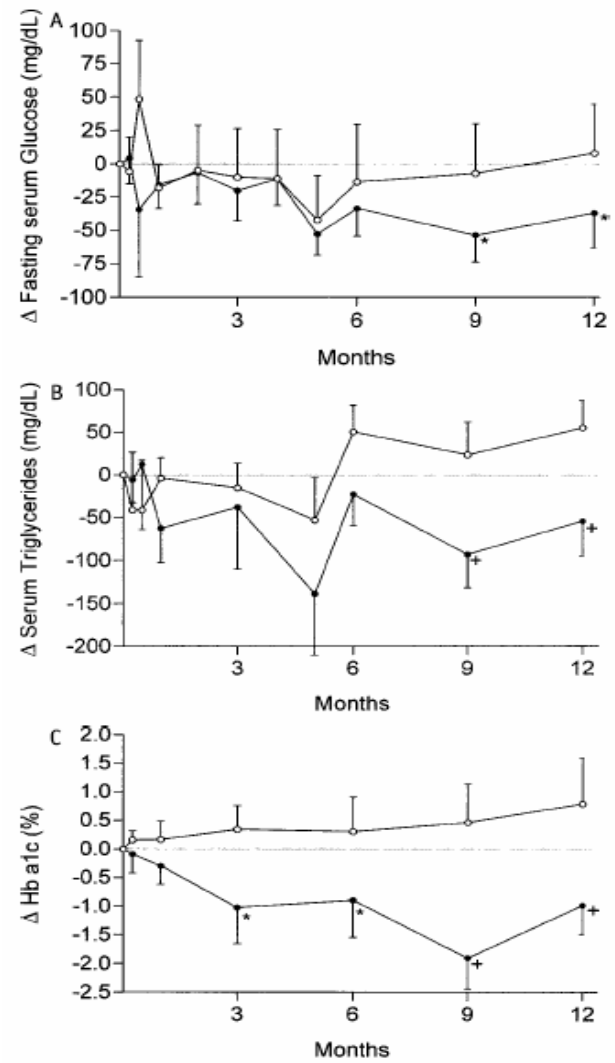
Paniagua et al. PDI 2009



Changes of glucose exposure, glucose absorption, insulin dose, serum glucose triglicerydes and Hb a1c

Paniagua et al. PDI 2009





Encapsulating peritoneal sclerosis - EPS

- Incidence: likely between 2-8% after 5-8 yrs on PD, rarely reported before 3 yrs on PD
- Etiology is not known, however the amount of glucose exposure, episodes of severe peritonitis, race, genetic factors may play roles
- Diagnosis - abdominal CT: bowel thickening, dilatation, peritoneal calcification
- Associated with bowel obstuction and high morbidity (around 50%)
- May develop or progress after discontinuation of PD
- Rx: nutrition, steroid/tamoxifen/immunosuppression, surgery

Summary

- Pay attention to modality selection – PD has several advantage and provides good outcome for most of our pts with ESRD
- PD has been underutilized
- Most important tasks
  - prevent PD peritonitis as much as possible
  - preserve residual renal function
  - use icodextrin for patients with UF problems
  - consider more biocompatible PD solutions