

Clinical Experience with Combined PD and HD for Long-Term PD Patients

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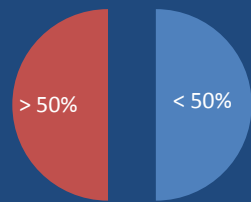
Presentation Outline

- Challenges in the management of long-term PD patients:
 - Loss of residual renal function and its effect on solute clearances and volume management
 - Loss of peritoneal ultrafiltration capacity
 - Encapsulating peritoneal sclerosis
- Can combination HD/PD therapy mitigate these challenges?
 - Dialysis prescription
 - Effect on solute clearances and volume management
 - Effect on quality of life
 - Long term effects on morbidity and mortality
- Clinical Perspectives
 - Is HD a superior therapy for anuric patients?
 - Who should we use the combination therapy for?

CHALLENGES IN THE MANAGEMENT OF LONG-TERM PD PATIENTS

Solute Removal in Anuric PD Patients Urea - Hong Kong

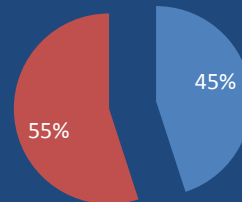
■ Kt/V < 1.7 ■ Kt/V ≥ 1.7



140 CAPD pts.; mean Kt/V 1.72 ± 0.31
Mean Exchange Volume, 7.4 ± 1.4 L
6 L/d, 42%; 8 L/d, 45%; 10 L/d, 13%

Szeto et al, J Am Soc Nephrol 2001; 12: 355-60

■ Kt/V < 1.7 ■ Kt/V ≥ 1.7

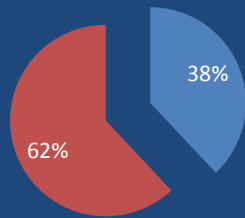


150 PD pts.; 149 CAPD
Mean Kt/V 1.74 ± 0.29
Mean Exchange Volume, 6.7 L/d

Lo et al, Kidney Int 2005; 27: 2032-8

Solute Removal in Anuric PD Patients Urea – Europe/USA

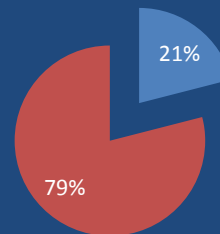
■ Kt/V < 1.7 ■ Kt/V ≥ 1.7



130 PD pts. – 102 CAPD, 28 APD
mean Kt/V 1.8 ± 0.3
No data on PD prescription

Jansen et al, Kidney Int 2005; 68: 1199-1205

■ Kt/V < 1.7 ■ Kt/V ≥ 1.7



1,432 PD pts

Fried et al, Am J Kidney Dis 2008; 52: 1122-30

Solute Removal in Anuric PD Patients Urea

- Current small solute clearance targets for PD are evidence-based:
 - Supported by two randomized, controlled clinical trials
- Studies that show difficulties in reaching small solute clearance targets don't seem to leverage the range of prescriptions possible with PD:
 - APD used for a small minority of patients
 - Total daily exchange volume in anuric Hong Kong patients substantially lower than is conventionally used in many other parts of the world
- PD prescription can be readily leveraged for achieving small solute clearance targets for virtually all anuric patients:
 - Large body size is NOT an impediment in achieving small solute clearance targets even in anuric PD patients

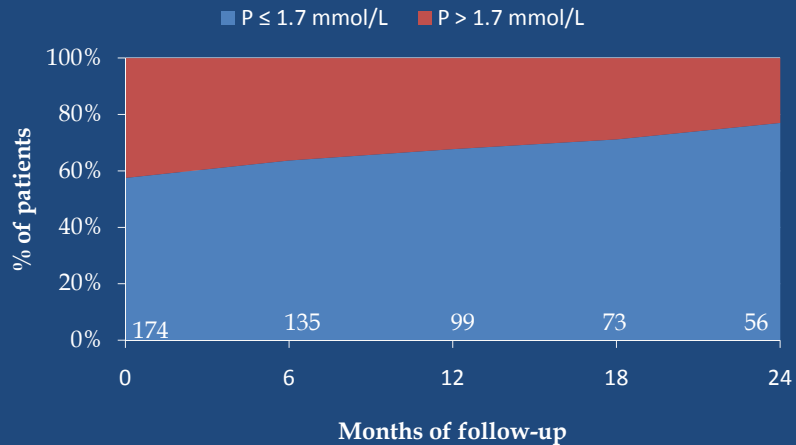
But it isn't all about urea!!

	N	Serum P	Total P clearance* (ml/min/1.73 m ²)	Daily P excretion (mg/d)
With RRF	18	5.13 ± 1.41	6.74 ± 2.95	471.6 ± 216.3
Anuric	38	5.27 ± 1.54	5.25 ± 1.14	399.9 ± 141.8

Mean P Intake – 906 ± 276 mg/d

Sedlacek et al, Am J Kidney Dis, 2000; 36: 1020-1024

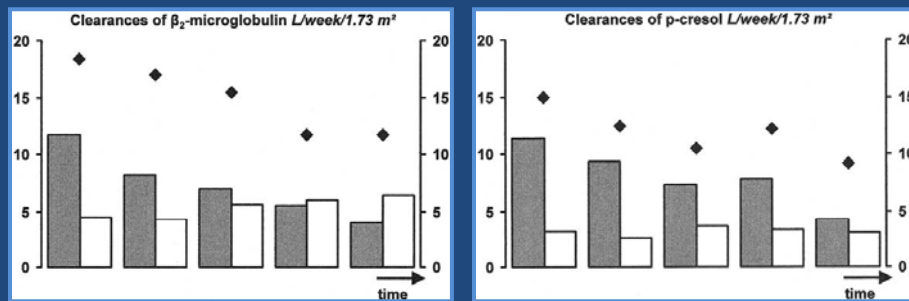
Leveraging PD prescription can achieve P control in anuric PD patients



European APD Outcome Study – functionally anuric PD patients

Brown et al, J Am Soc Nephrol 2003; 14: 2948-57

The problem is with middle molecules and protein-bound solutes



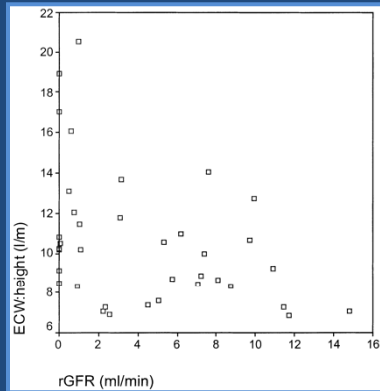
N = 24; FU time, 7 months
On FU, 22 used APD, 15 used icodextrin

Bammens et al, Am J Kidney Dis 2005; 46: 512-9

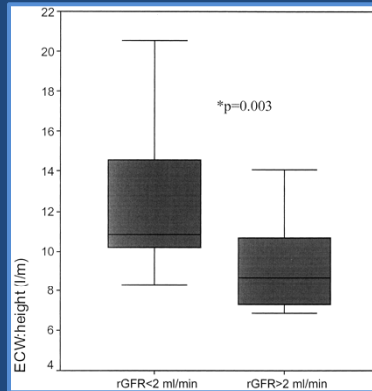
Anuric PD patients and solute clearances

- In anuric PD patients, using the full range of PD prescription allows for:
 - Achieving small solute clearance targets for virtually all patients
 - Serum P targets in most
- Peritoneal clearances are generally insufficient to compensate for renal clearances of middle molecules and protein-bound solutes:
 - Clinical relevance, however, uncertain

Loss of RRF associated with hypervolemia in PD patients



37 CAPD patients
 $r = -0.40$, $p = 0.016$

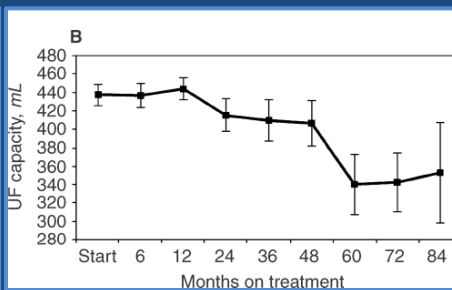
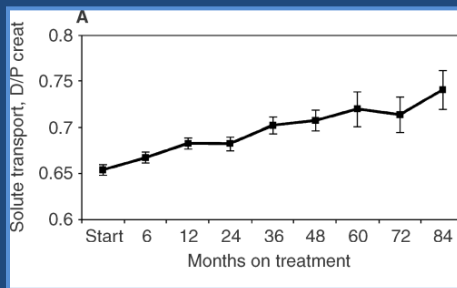


Residual Diuresis: 270 vs 1438 ml
 Peritoneal UF: 1856 ml vs 658 ml
 Peritoneal Glucose prescript: 216 vs 156 g/day

Konings, *Nephrol Dial Transplant* 2003; 18: 797-803

Problem compounded by changes in peritoneal membrane

↑ capillary density → ↑ effective peritoneal surface area → ↑ peritoneal solute transfer rate

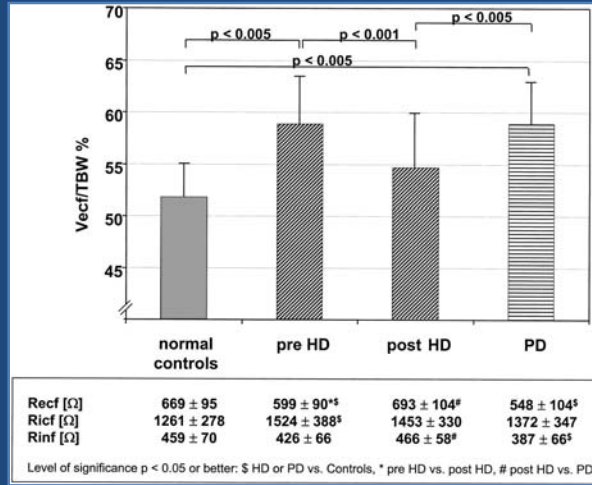


Baseline: 574 subjects
 One-year: 299
 Seven-year: 27

Davies, *Kidney Int* 2004; 66: 2437-2445

CPD patients and Volume Overload

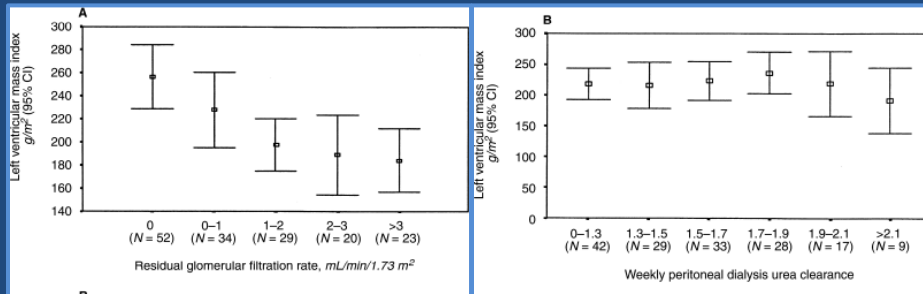
Dialysis Vintage
 HD, 36 mo
 PD, 23 mo



No details on use of APD or other information on PD prescription

Plum et al, *Nephrol Dial Transplant* 2001; 16: 2378-85

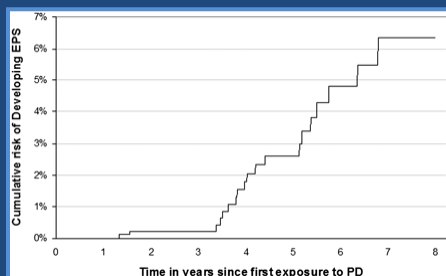
Residual Renal Function and LVH



158 non-diabetic CAPD patients

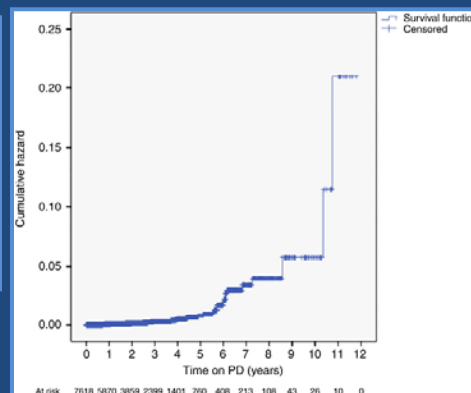
Wang et al, *Kidney Int* 2002; 62: 639-47

And then there is concern for EPS



SCOTLAND
1238 pts (1/1/2000-12/31/2007)
46 cases
8-year cumulative incidence, 8.1%

Brown et al, Clin J Am Soc Nephrol 2009; 4: 1222-9
Johnson et al, Kidney Int 2010; 77: 904-12



Australia and New Zealand
7618 pts (1/1/1995-12/31/2007)
33 cases
8-year cumulative incidence, 3.9%

Challenges in management of long-term PD patients

- Maintaining clearances of middle molecules and protein-bound uremic solutes
- Maintaining euvolemia
- Encapsulating peritoneal sclerosis
- However, many of studies that describe the challenges with long-term PD patients have not leveraged the entire range of PD prescriptions

CAN COMBINATION THERAPY MITIGATE THESE CHALLENGES?

Patterns of combination of PD and HD

- Temporary of HD in PD patients:
 - Insufficient UF
 - Peritonitis necessitating catheter removal
 - Initiation period of HD
- Periodic combination therapy (*true combination therapy*)
- Other:
 - Peritoneal lavage after shifting to HD

PD + HD for long-term PD patients Published Experience in English

	Author	Site	Patient Number
Japan	Hashimoto, '00	Shizuoka	6
	Hoshi, '06	Saitama	9
	Kawanishi, '06	4 centers	52
	Matsuo, '10	Jikei, Tokyo	53
United States	Agarwal, '03	US and Canada	31 (4 local)

About 150 patients total - not include McIntyre's experience with incident patients

Estimates suggest that 20% of PD patients in Japan are treated with combination therapy
Japanese payors don't reimburse for the additional HD treatment; providers absorb the cost
Larger published experience in Japanese language - not readily available

PD + HD for long-term PD patients Published Experience in English

- Hashimoto and Matsubara. Adv Perit Dial 2000; 16: 108-112
- Agarwal et al, Perit Dial Int 2003; 23: 157-161
- Hoshi et al, Adv Perit Dial 2006; 22: 136-140
- Kawanishi et al, Perit Dial Int 2006; 26: 150-4
- Mastuo et al, Clin Nephrol 2010; 74: 209-16

PD + HD: Prescription Management

PD PD PD PD PD HD Holiday

PD PD PD PD PD HD PD

PD + HD: Prescriptions Used

Author	CAPD/APD	Daily fill Volume/Prescription
Hashimoto, '00	6/0	4 exch/d (possibly 6.0-8.0 L/d)
Agarwal, '03	11/20	4.0 - 24.0 L/d
Hoshi, '06	9/0	6.0 - 8.0 L/d
Kawanishi, '06	52/0	Unknown (possibly 6.0-8.0 L/d)
Matsuo, '10	Unknown	8.8 ± 2.0 L/d

Generally one 4-hour HD treatment with high-flux dialyzers/ wk

Combination therapy increase small solute clearances

PD Kt/V	Month 1 total Kt/V	Month 3 total Kt/V	Month 6 total Kt/V
1.73 ± 0.23	2.04 ± 0.38	1.81 ± 0.38	1.67 ± 0.36

Agarwal et al, Perit Dial Int 2003; 23: 157-161

- Using calculated equivalent renal clearances:
 - Kt/V_{ef} increased from 1.55 ± 0.40 to 2.27 ± 0.43
 - Creat clear increased from 42.0 ± 7.7 to 60.3 ± 9.2 L/wk/1.73 m²
 - nPNA increased from 0.77 ± 0.14 to 0.93 ± 0.16 g/kg/d

Kawanishi et al, Adv Perit Dial 2007; 23: 135-9

Combination Therapy Effect on Serum Solute Concentrations

	T0	Year One	Year Two	Year Three
BUN, mg/dl	76.4 ± 7.8	70.7 ± 3.0	63.8 ± 4.5	67.6 ± 2.8
S. Ca, mg/dl	8.5 ± 0.5	9.1 ± 0.6	9.7 ± 0.3	8.8 ± 0.5
S. P, mg/dl	7.2 ± 0.7	7.6 ± 0.6	6.5 ± 0.7	7.5 ± 0.7
Serum K, meq/L	4.8 ± 0.3	4.7 ± 0.3	4.3 ± 0.2	4.5 ± 0.3
S. albumin, g/dl	3.7 ± 0.3	3.8 ± 0.3	4.1 ± 0.2*	4.0 ± 0.2*

N=9

Hoshi et al, Adv Perit Dial 2006; 22: 136-40

Combination Therapy Effect on Serum Solute Concentrations

	T0	3 mo	6 mo	12 mo	18 mo	24 mo
n (1/2 HD)	0/0	52/0	25/9	19/8	17/10	9/7
BUN, mg/dl	63.0 ± 18.2	58.1 ± 15.4*	55.9 ± 18.1*	64.1 ± 12.5	63.3 ± 14.8	57.6 ± 16.8
S. creat, mg/dl	13.1 ± 3.3	12.5 ± 2.6	12.5 ± 2.8*	12.4 ± 3.6	12.8 ± 3.3	12.2 ± 3.2
S. P, mg/dl	5.7 ± 1.6	6.1 ± 1.6	6.0 ± 1.5	6.0 ± 1.6	6.2 ± 1.8±*	5.7 ± 2.2
Serum β2 microglobulin	35.8 ± 14.3	37.4 ± 10.4	37.5 ± 17.7	31.5 ± 8.9*	33.2 ± 8.9	33.2 ± 7.9*
S. albumin, g/dl	3.3 ± 0.6	3.5 ± 0.5*	3.5 ± 0.4	3.5 ± 0.3	3.5 ± 0.5	3.6 ± 0.5

Kawanishi et al, Perit Dial Int 2006; 26: 150-4

Combination Therapy Effect on Serum Solute Concentrations

	T0	1 year	P-value
BUN, mg/dl	61 ± 16	59 ± 13	0.11
S. creat, mg/dl	13.5 ± 3.6	12.7 ± 3.1	< 0.01
S. P, mg/dl	5.9 ± 1.7	5.5 ± 1.3	0.37
Serum β2 microglobulin	35.9 ± 7.5	33.1 ± 7.9	0.18
S. albumin, g/dl	3.5 ± 0.4	3.6 ± 0.6	0.18

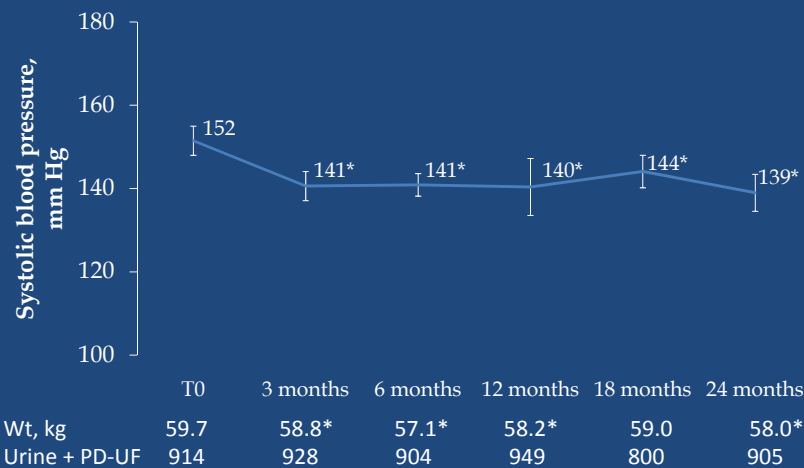
N=53

Matsuo et al, Clin Nephrol 2010; 74: 209-16

Effect of combination PD and HD on solute removal

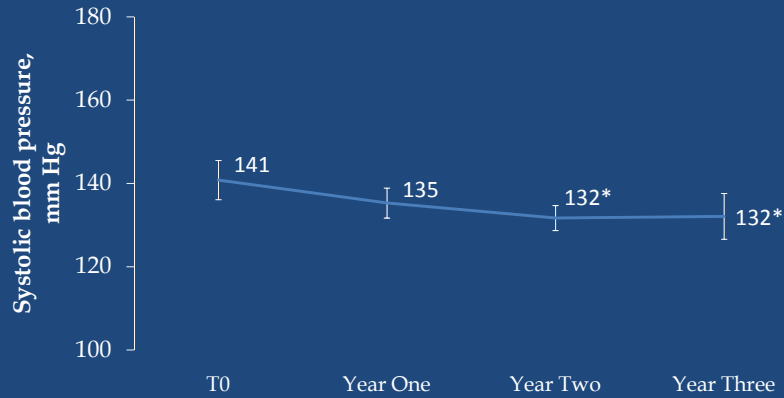
- Urea, creatinine, and β 2microglobulin removal higher
 - Difficult to interpret serum solute levels:
 - BUN - affected by dietary protein intake
 - Creatinine - affected by muscle mass
- Phosphorus:
 - additional determinants include dietary intake, P-binder and vitamin D use, and PTH levels
 - Nevertheless, increase in clearance insufficient to have a meaningful or sustained effect on serum P levels
- Clinical implications of higher solute clearances unclear

Combined PD and HD Hemodynamic Effect



Kawanishi et al, Perit Dial Int 2006; 26: 150-4

Combined PD and HD Hemodynamic Effect



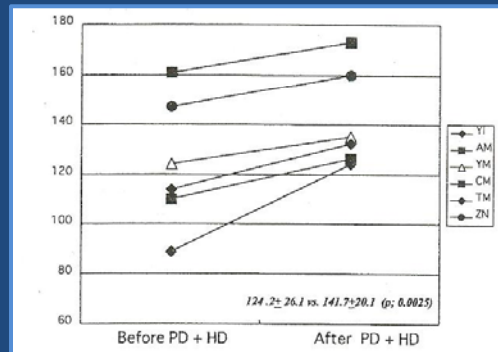
Hoshi et al, Adv Perit Dial 2006; 22: 136-40

Combined PD and HD Hemodynamic Effect

	At study start	After 1 year	p-value
Body weigh, kg	62.6 ± 11.3	61.1 ± 12.9	< 0.01
Systolic BP	145 ± 22	138 ± 17	0.03
Diastolic BP	84 ± 17	78 ± 11	0.12
Anti-HTN meds, no.	2.6 ± 1.4	2.1 ± 1.4	< 0.01
ANP, pg/ml	123 ± 104	60 ± 50	< 0.01
Urine volume, ml/d	253 ± 405	123 ± 331	< 0.01
PD UF, ml/d	907 ± 579	1,008 ± 383	0.17

Matsuo et al, Clin Nephrol 2010; 74: 209-16

PD + HD: Effect on QOL



Six CAPD patients; QOL assessed using Kidney Disease Questionnaire by Laupacis
Improvement in dimensions of fatigue, depression, relation with others; and frustration. No change in physical symptoms

Hashimoto et al, Adv Perit Dial 2000; 16: 108-112

Status upon follow-up

	FU period, months	Death	HD only	PD only	PD + HD	Tx
Kawanishi' 06 (n=52)	25 mo	3 (6%)	14 (27%)	0	33 (63%)	2 (4%)
Matsuo, '10 (n=53)	26 mo	2 (4%)	21 (40%)	0	28 (53%)	2 (4%)
TOTAL (n=105)		5 (5%)	35 (33%)	0	61 (58%)	4 (4%)

Kawanishi et al, Perit Dial Int 2006; 26: 150-4
Matsuo et al, Clin Nephrol 2010; 74: 209-16

Other Effects

- Addition of 1-2 weekly HD treatments improves volume management and blood pressure control:
 - Effect on LV mass index unknown
- Improvement in Epo responsiveness
- Reduction in inflammatory markers
- Word of caution:
 - Only a handful of patients in these studies treated with APD and limited, if any, use of icodextrin
 - Unclear if a single HD treatment in a long-term PD patient is superior to use of APD with icodextrin for day dwell

CLINICAL PERSPECTIVES

How Well Do Anuric PD patients Do?

Region	Author	N	Mean Age	% diabetics	CAPD/APD	Two-year Survival
Hong Kong	Szeto, '01	140	53 y	26%	140/0	69%
	Lo, '05	150	58 y	28%	149/1	89%
				27%	289/1	79%
Europe	Brown, '03	177	54 y	42%	0/177	78%
	Jansen, '05	130	53 Y	12%	102/28	67%
				29%	102/205	73%
United States	Fried, '08	1428	54 y	42%	?	60%

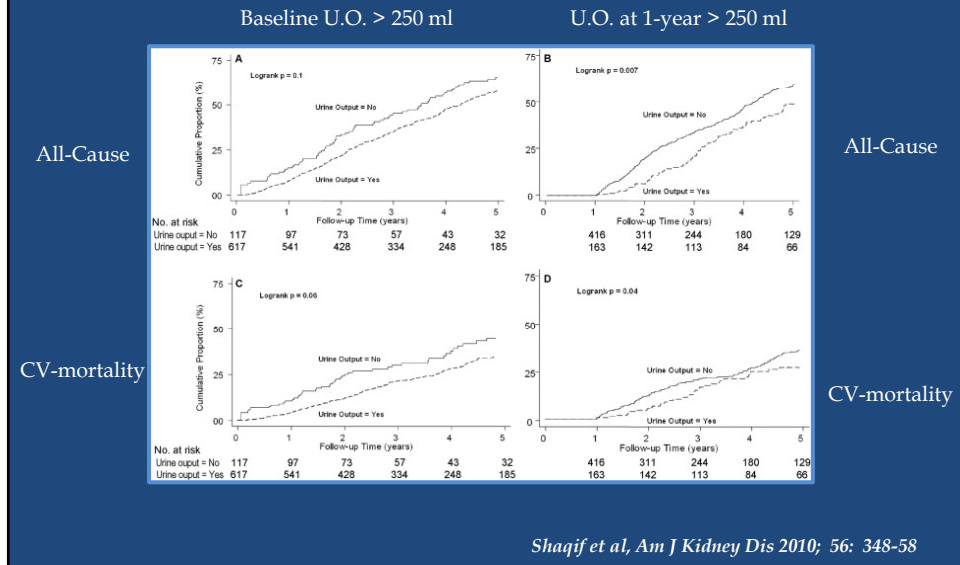
Only somewhat worse than PD patients with residual renal function

RRF Important for HD

	Relative Risk	95% CI
Age, per year	1.03	1.02-1.05
Male Gender	0.84	0.64-1.10
Co-morbidity score		
High	4.74	3.04-7.40
Intermediate	2.35	1.63-3.39
Primary kidney disease		
Diabetes	1.43	0.98-2.09
HTN	0.67	0.38-1.20
Renal Vascular Dis	1.18	0.86-1.62
Albumin, per 0.1 g/dl increase	0.98	0.95-1.01
SGA (scale 1-7)	0.89	0.80-0.99
BMI (kg/m ²)	0.96	0.93-0.99
Residual rKt/V _{urea} (/wk) - time varying	0.44	0.30-0.65
Dialysis Kt/V _{urea} (/wk) - time varying	0.76	0.64-0.92

Termorshuizen et al, J Am Soc Nephrol 2004; 15: 1061-70

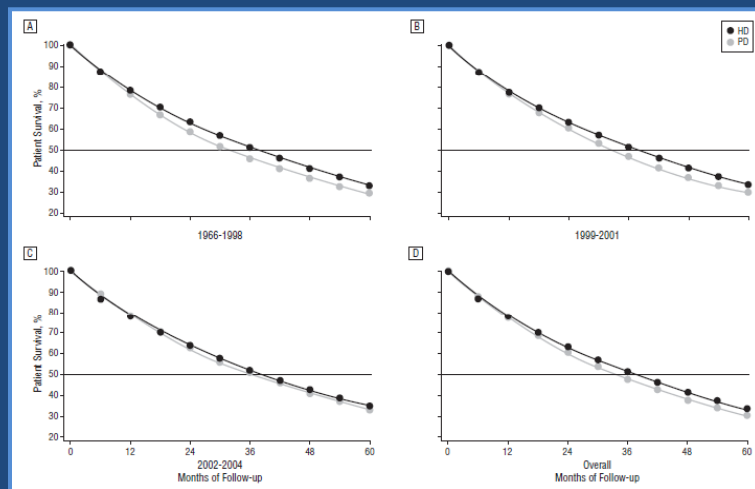
RRF Important for HD



How do the survival of anuric HD and PD patients compare?

- Not aware of direct comparisons of survival of anuric HD and PD patients
- PD (*Fried et al, Am J Kidney Dis 2008; 52: 1122-30*):
 - Mean age, 54 years; 42% diabetics
 - 60% two-year survival
 - 20% annual mortality
- HD (*Shaqif et al, Am J Kidney Dis 2010; 56: 348-58*):
 - Mean age, 60 years; 44% diabetics
 - 227 deaths per 1000 patient-years
 - 22% annual mortality

These findings are consistent with recent reports of equivalent five-year survival

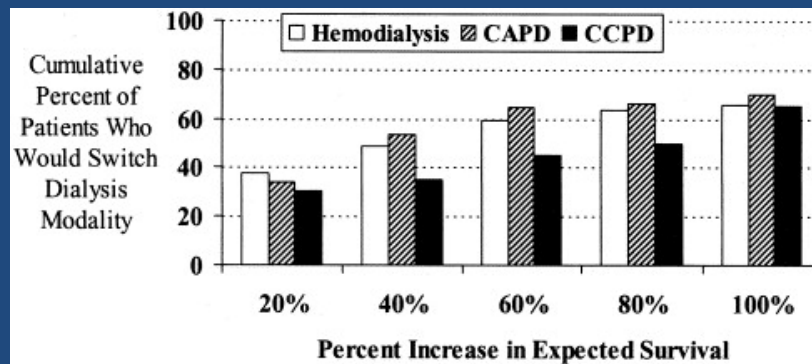


Mehrotra et al, Arch Intern Med 2010; Sep 27 epub

Conclusions

- Residual renal function is important for both PD and HD patients:
 - Anuria makes management with either one dialysis modality more challenging
- Combination therapy enhances solute removal and improves hypervolemia
- However, all these measures are surrogate measures:
 - Effect on long-term outcomes unknown

However, long-term PD patients who are not achieving optimal control, may accept a single HD treatment over abandoning PD altogether



Bass et al, *Am J Kidney Dis* 2004; 44: 695-705

Indications for Combination Therapy

Kawanishi et al

- Patients in whom increased PD dose is not compatible with patient's lifestyle or subjective tolerance of increased fill volume, with:
 - Insufficient small solute clearance
 - Fluid overload
- Medical reasons for not increasing dialysate volume e.g., limited peritoneal capacity, hernia, hydrothorax
- Severe mental stress due to PD; PD holiday
- Peritoneal rest (with the expectation of improved peritoneal function/postponement of membrane deterioration)
- Prevention of complications related to the intermittent nature of HD, e.g., loss of residual renal function
- HD patients with cardiovascular instability

Kawanishi et al, Perit Dial Int 2006; 26: 150-4