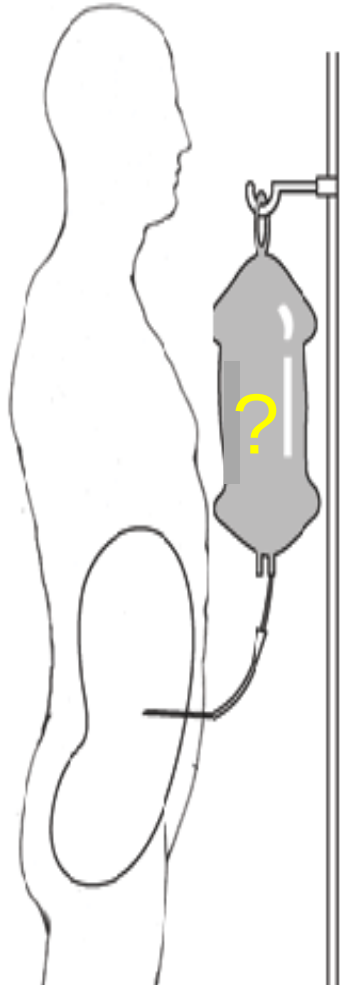
Biocompatible Peritoneal Dialysis Solutions: Have We Found One?



Jeffrey Perl MD SM FRCP(C)
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University of Toronto, Canada
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Friday April 4, 2014
Western Canada PD Days
Vancouver, British Columbia

St. Michael's
Inspired Care. Inspiring Science.

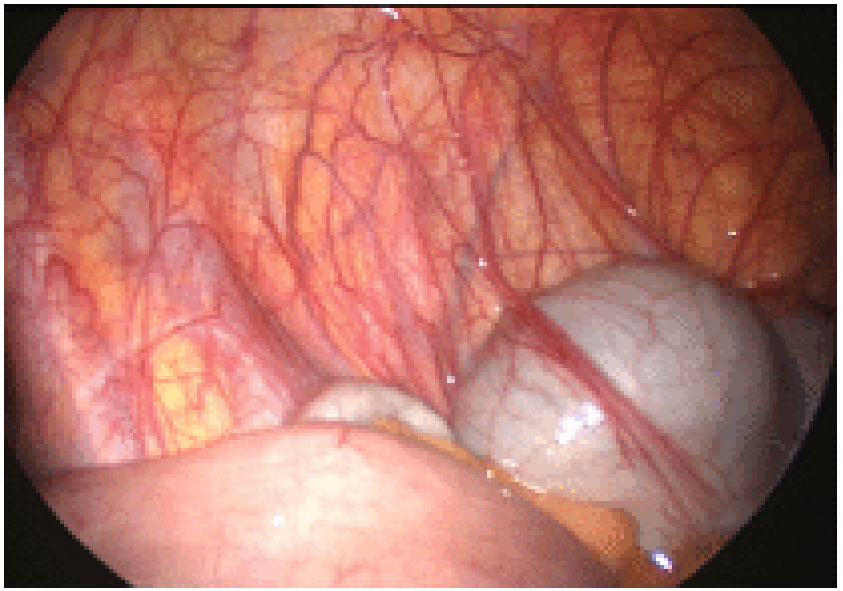
Disclosures

- Speaking Honoraria, Consultancy Fees:
  - Baxter Healthcare
  - DaVita Healthcare Partners
  - Amgen, Canada
  - Takeda Canada
  - Hemosphere USA
  - Shire Canada
- Unrestricted Educational Fellowship:
  - Baxter Healthcare Canada
- Salary Support:
  - Arbor Research Collaborative For Health

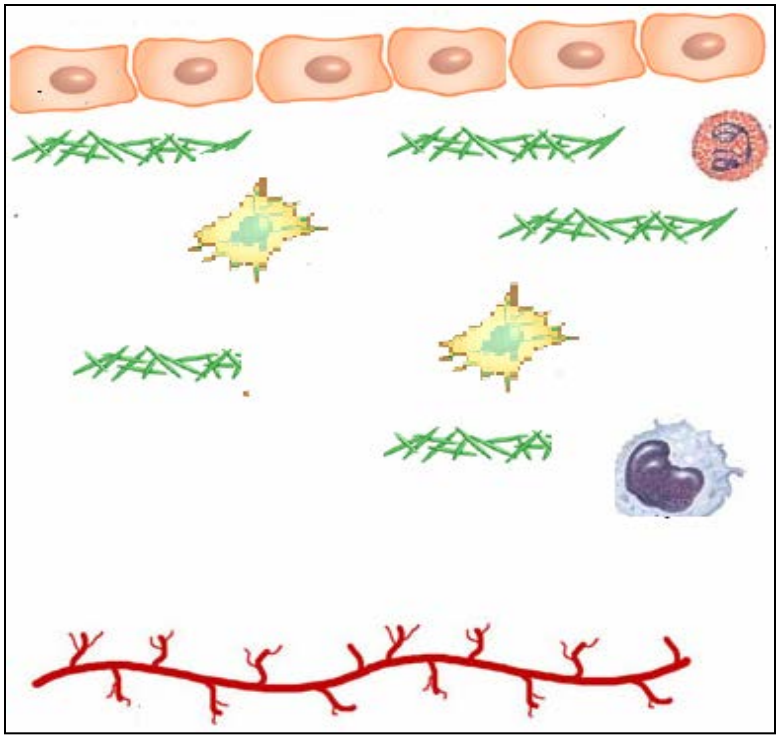
Objectives

- Peritoneal Membrane Structure and Function and Changes With Time
- What are ‘’Biocompatible’’ PD Solutions
- Impact on Markers of Peritoneal Membrane Integrity
- Impact on Preservation of Residual Kidney Function (RKF) and peritonitis risk
- The RKF/Transport Status/Peritoneal UF Paradox

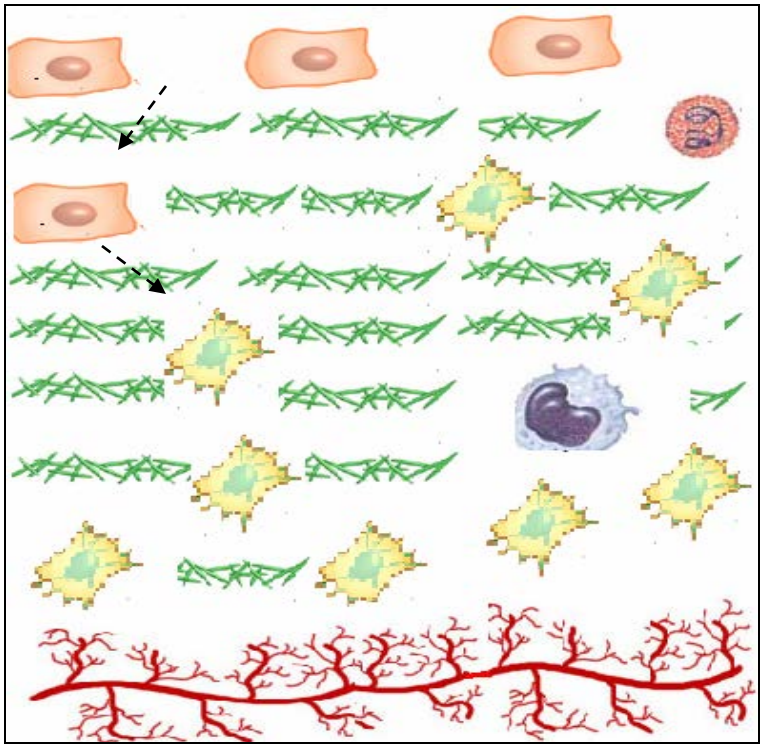
Peritoneal Dialysis: The Challenge



The Natural History of The Peritoneal Membrane: Structure



''Virgin'' peritoneum



Peritoneum: 7 years of PD

Nakayama, Perit. Dial. Int. 2005 25: S71-76S.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Peritoneal Dialysis and Epithelial-to-Mesenchymal Transition of Mesothelial Cells

María Yáñez-Mó, Ph.D., Enrique Lara-Pezzi, Ph.D., Rafael Selgas, Ph.D., M.D., Marta Ramírez-Huesca, B.S., Carmen Domínguez-Jiménez, Ph.D., José A. Jiménez-Heffernan, M.D., Abelardo Aguilera, M.D., José A. Sánchez-Tomero, Ph.D., M.D., M. Auxiliadora Bajo, Ph.D., M.D., Vincente Álvarez, Ph.D., M.D., M. Angeles Castro, Ph.D., Gloria del Peso, Ph.D., M.D., Antonio Cirujeda, M.D., Carlos Gamallo, Ph.D., M.D., Francisco Sánchez-Madrid, Ph.D., and Manuel López-Cabrera, Ph.D.

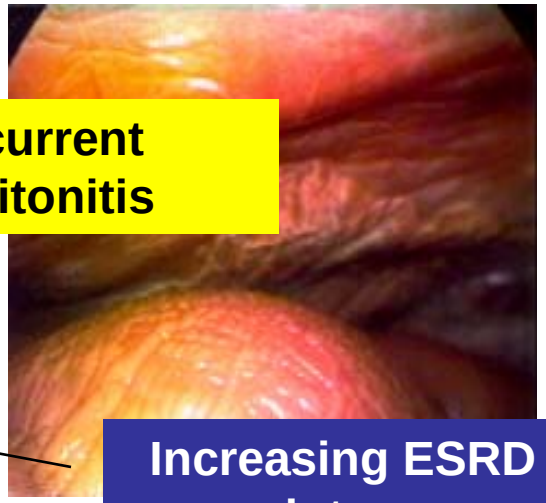
ABSTRACT

2003

The Natural History of The Peritoneal Membrane: Structure

''Virgin'' peritoneum

Peritoneum: 7 years of PD



acidic pH 5.2

Glucose

GDP

AGE

recurrent peritonitis

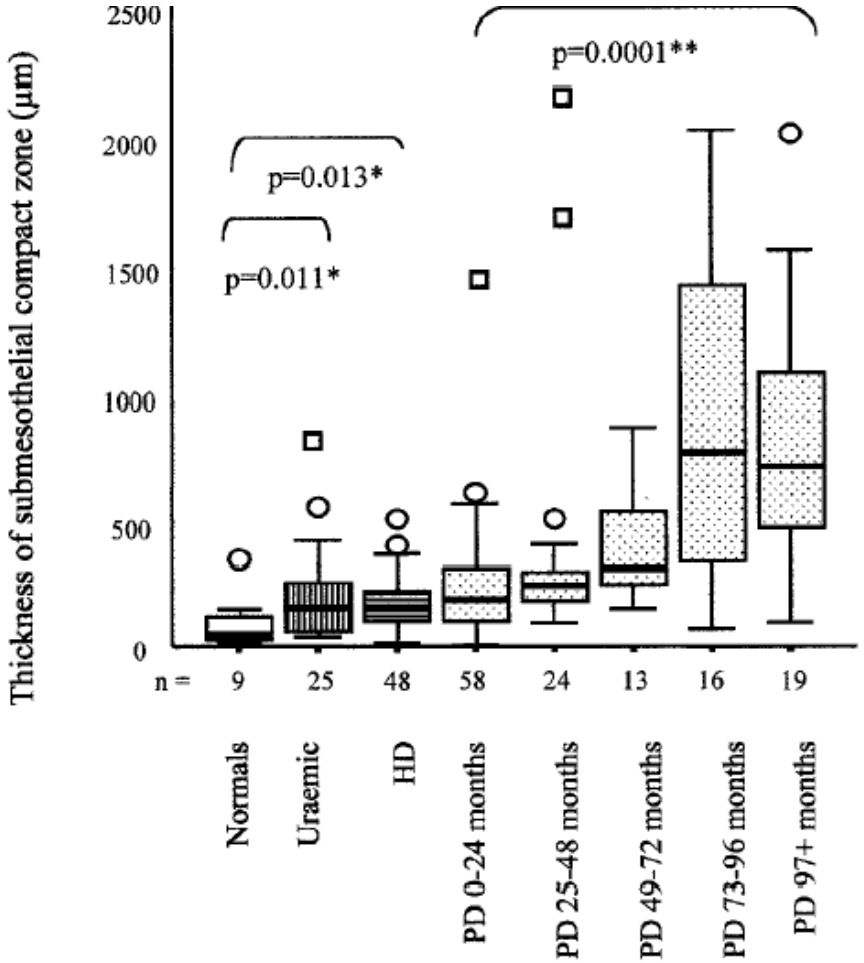
Increasing ESRD vintage

Loss of residual kidney function

Genetic variation

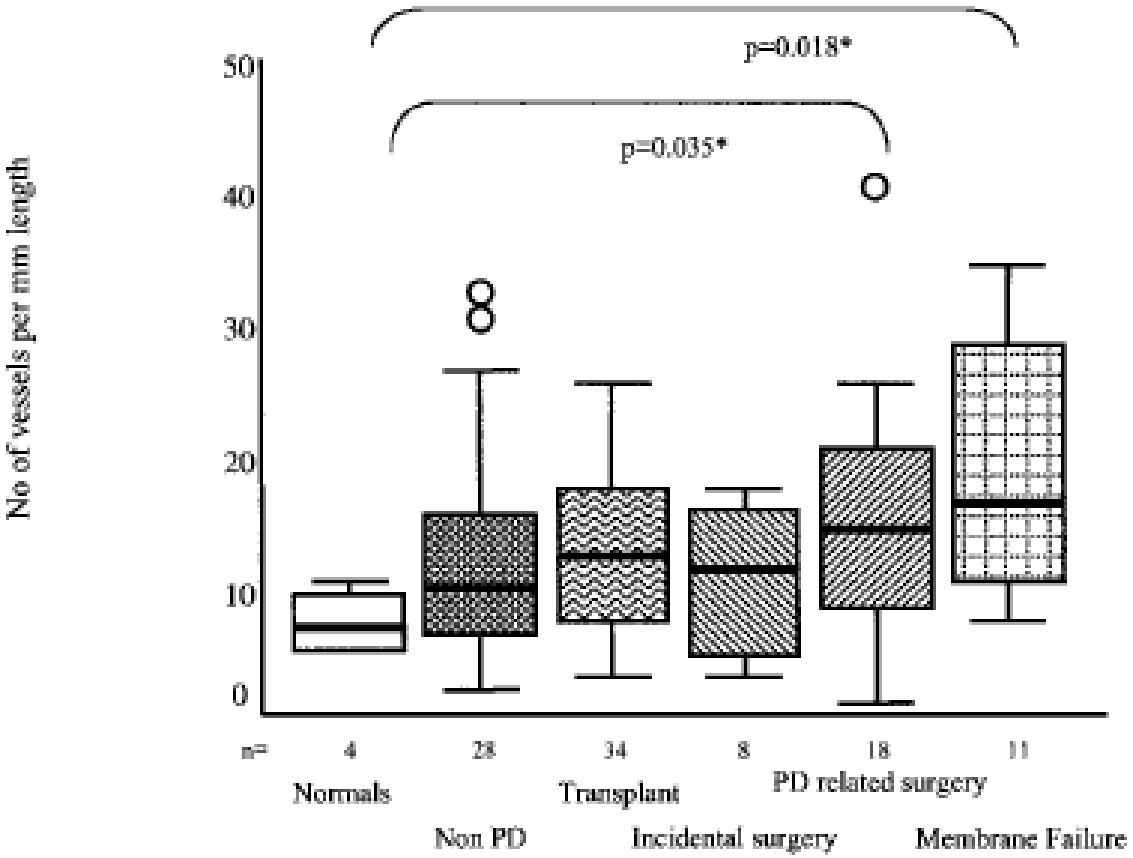
Nakayama, Perit. Dial. Int. 2005 25: S71-76S.

Peritoneal membrane morphology on long term PD: *fibrosis*



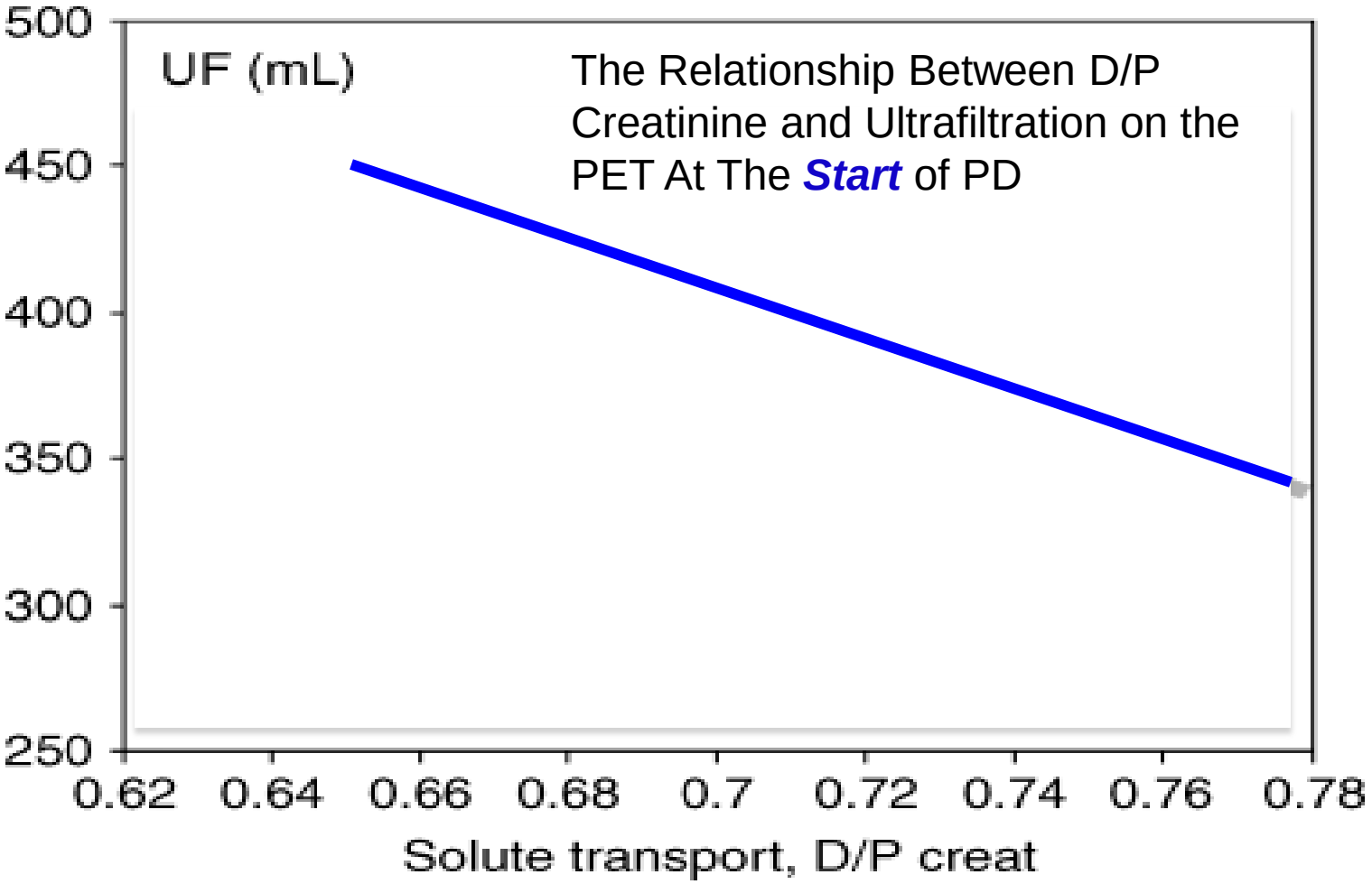
Williams et al, J Am Soc Nephrol 13: 470–479, 2002

Peritoneal membrane morphology on long term PD: *neovascularization*



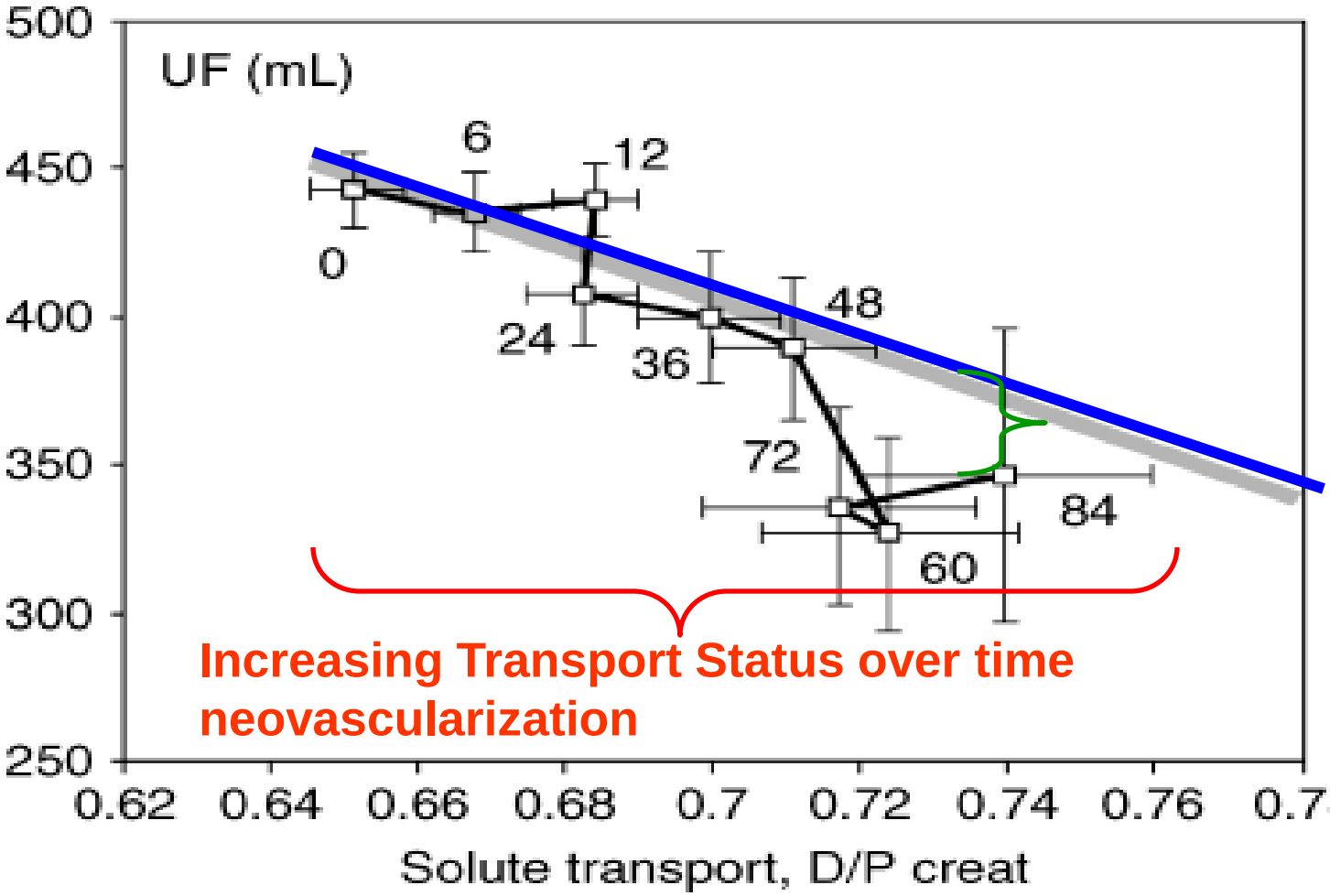
Williams et al, J Am Soc Nephrol 13: 470–479, 2002

The Peritoneal Membrane At The *Start* Of PD



Davies et al, *Kidney International* (2004) 66, 2437–2445

The Peritoneal Membrane Over Time On PD



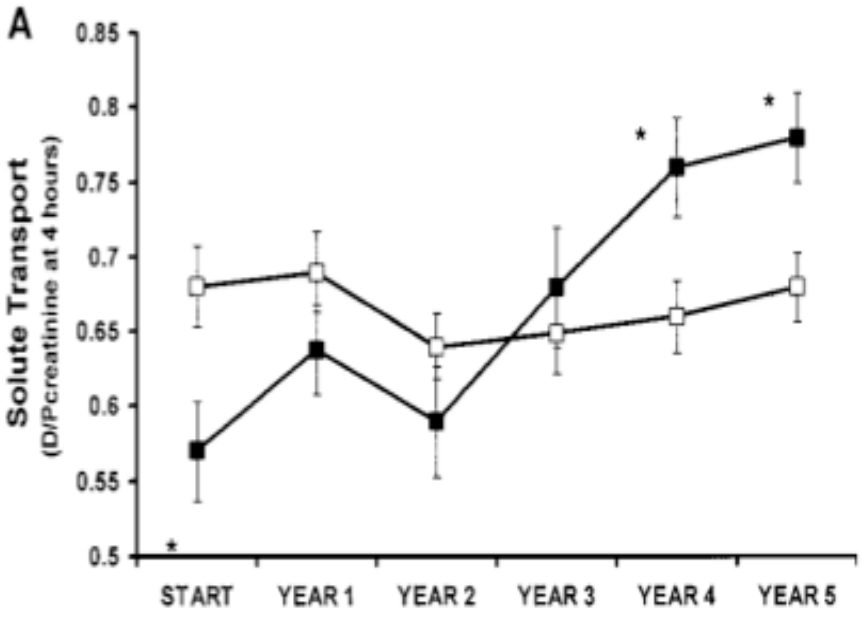
Fibrosis:

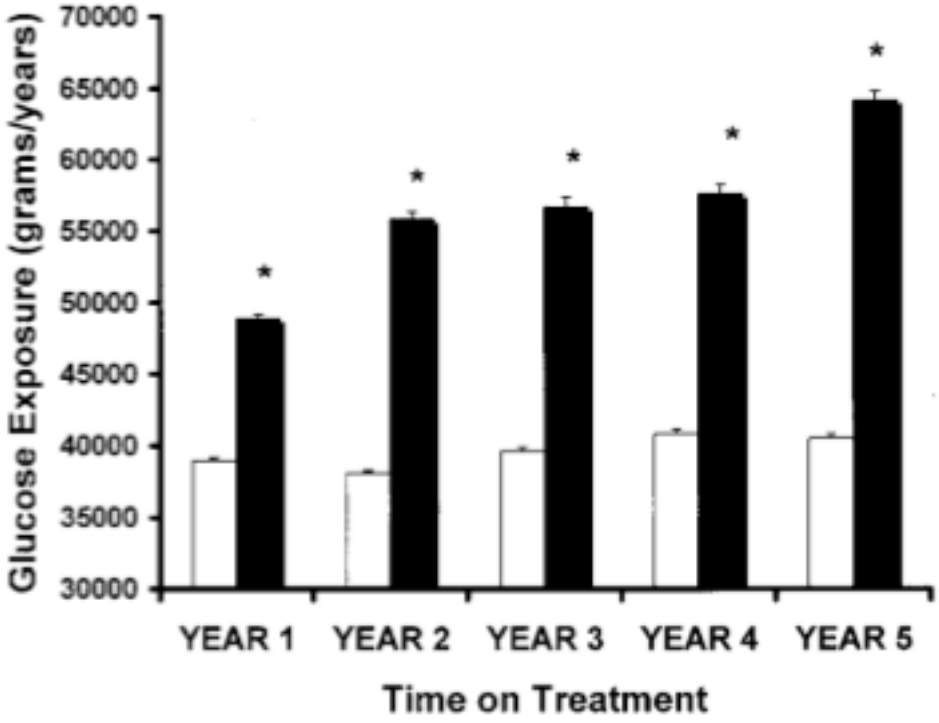
A given transport status over time leads to less UF:

reduced osmotic conductance to glucose

Davies et al, *Kidney International* (2004) 66, 2437–2445

Glucose and Peritoneal Membrane Transport Status Chicken or Egg?





Davies et al JASN 2001

Glucose Loading And Peritoneal Membrane Changes

Glucose

Membrane Changes

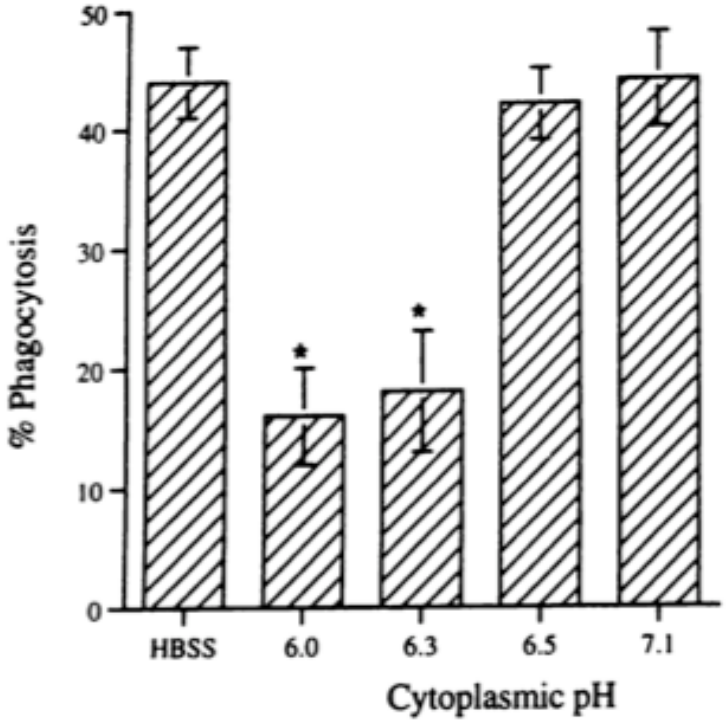
The Current State of Peritoneal Dialysis Solutions

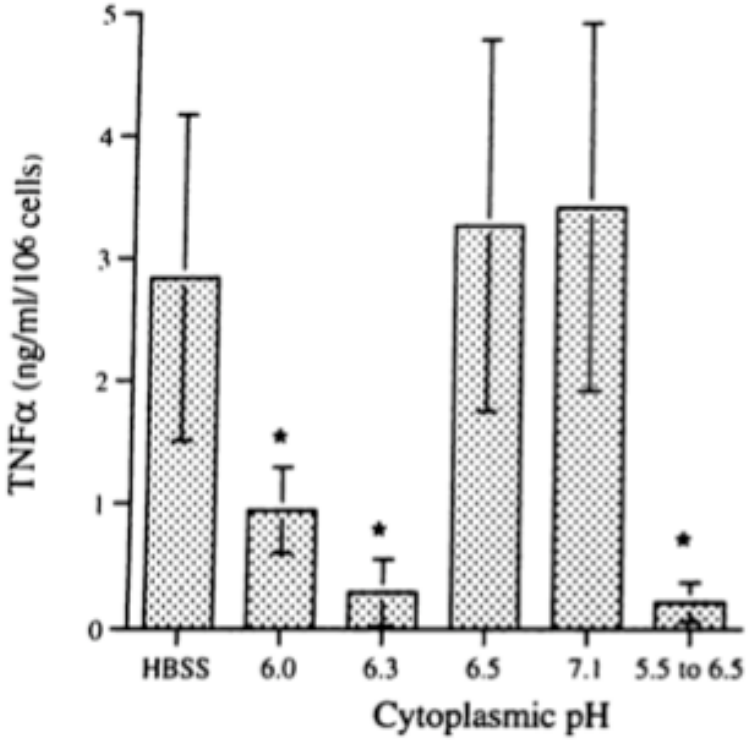
- Glucose based
- Heat sterilisation of glucose -> GDP
- GDP -> AGE
- Hyperosmolar (360-511 mosm/kg)
- Acidic pH (5.2)

Impact on Peritoneal Membrane Structure and Function?

Glucose: Friend or Foe ?

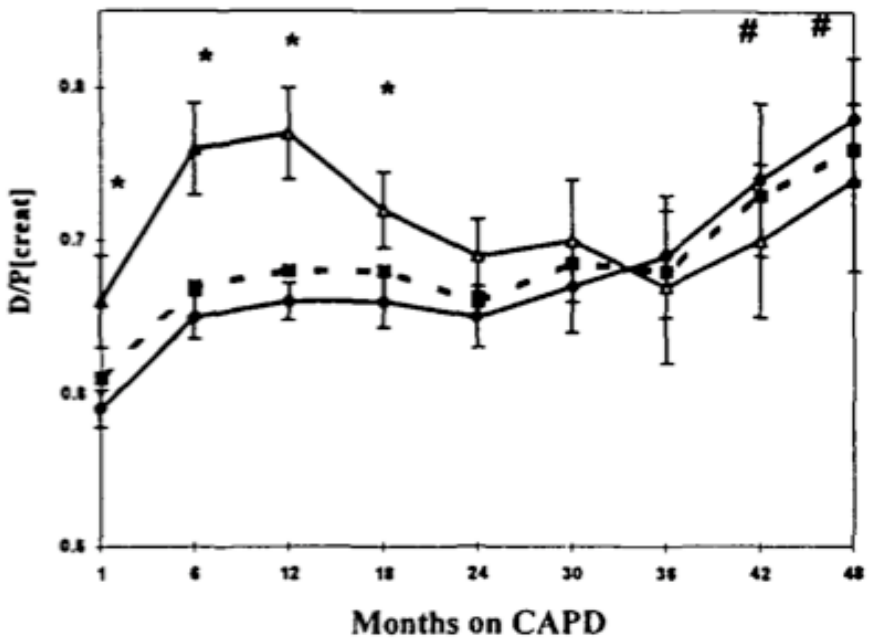
Influence of pH on peritoneal macrophage function

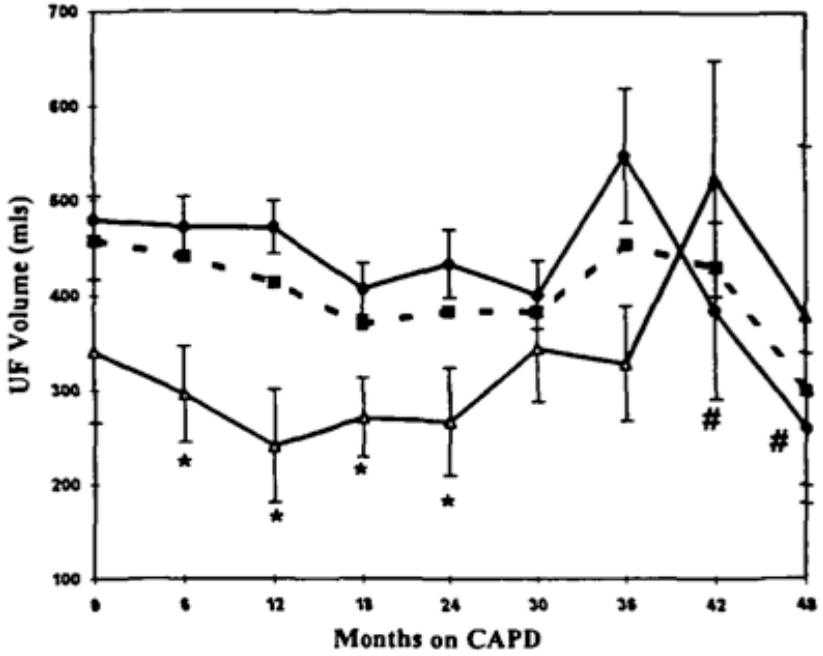




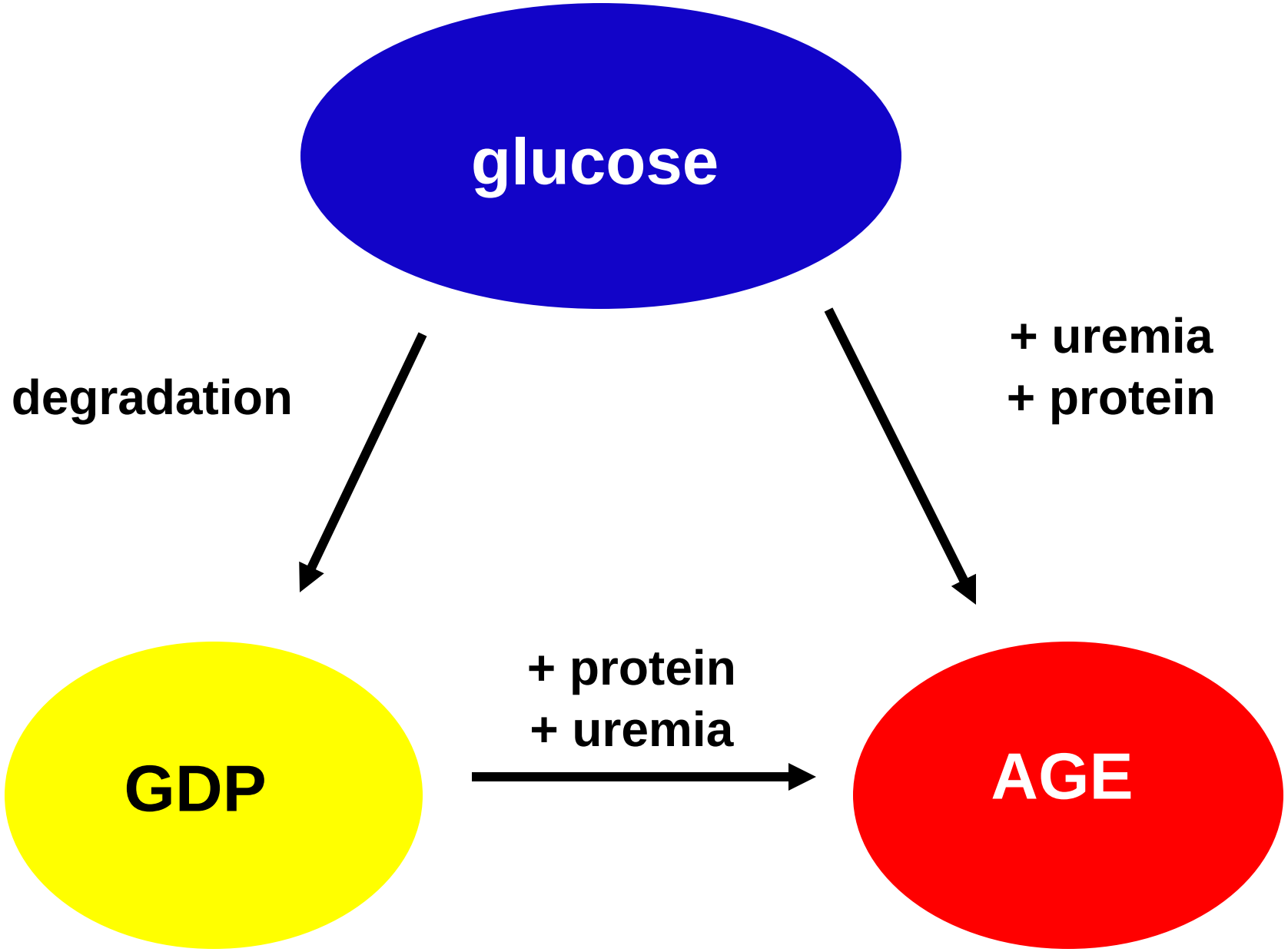
J. Am. Soc. Nephrol., Aug 1995; 6: 207 - 213.

Recurrent Peritonitis and peritoneal membrane function

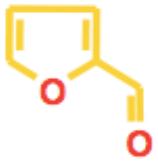
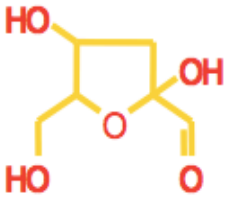
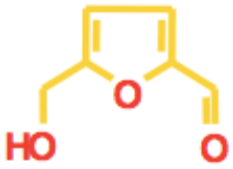
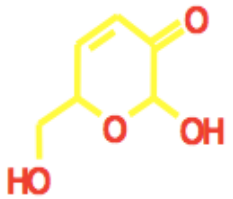




Davies et al Nephrol Dial Transplant (1996) 11: 498-506

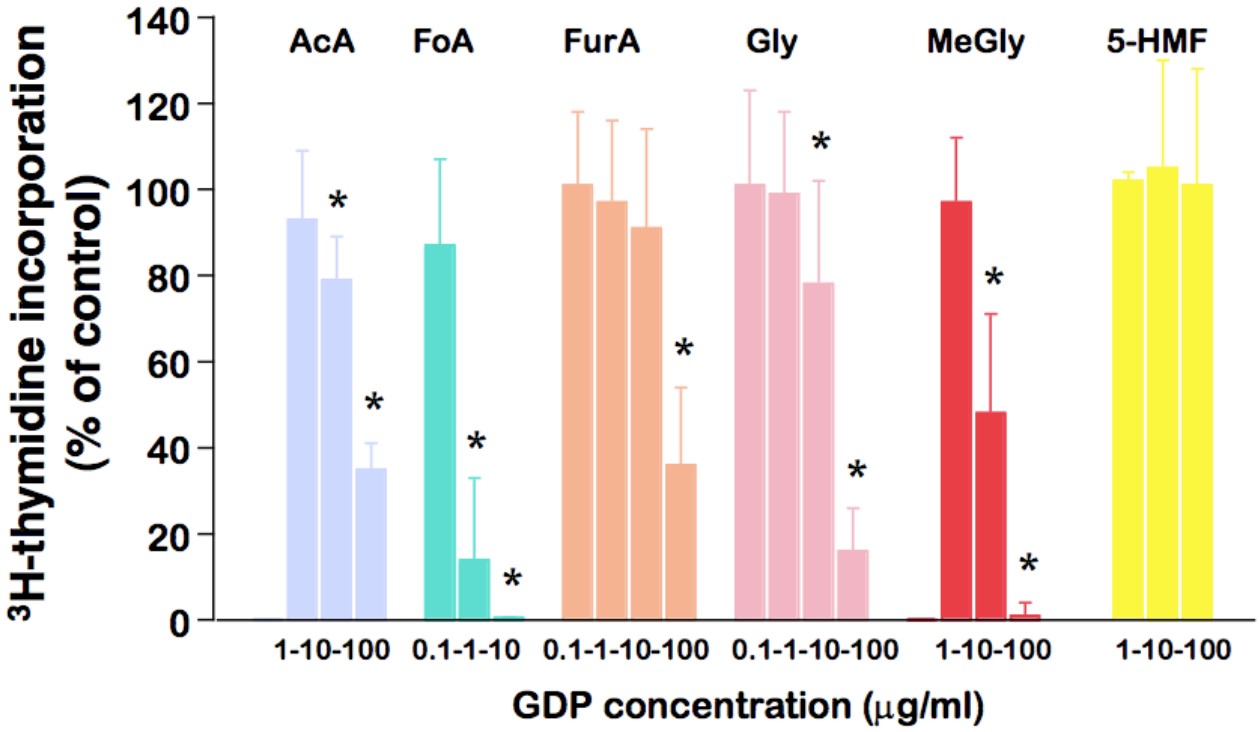

glucose
degradation
+ uremia
+ protein
GDP
+ protein
+ uremia
AGE

GDP's

Acetaldehyde	MW 44.05		Methyl-glyoxal	MW 72.06	
Formaldehyde	MW 30.03		Glyoxal	MW 58.04	
Furaldehyde	MW 96.08		3-Deoxy-glucosone	MW 162.14	
5-Hydroxy-methyl-furaldehyde	MW 126.11		3,4-Dideoxy-glucosone-3 - ene	MW 144.12	

Slide courtesy : Dr. A Jorres

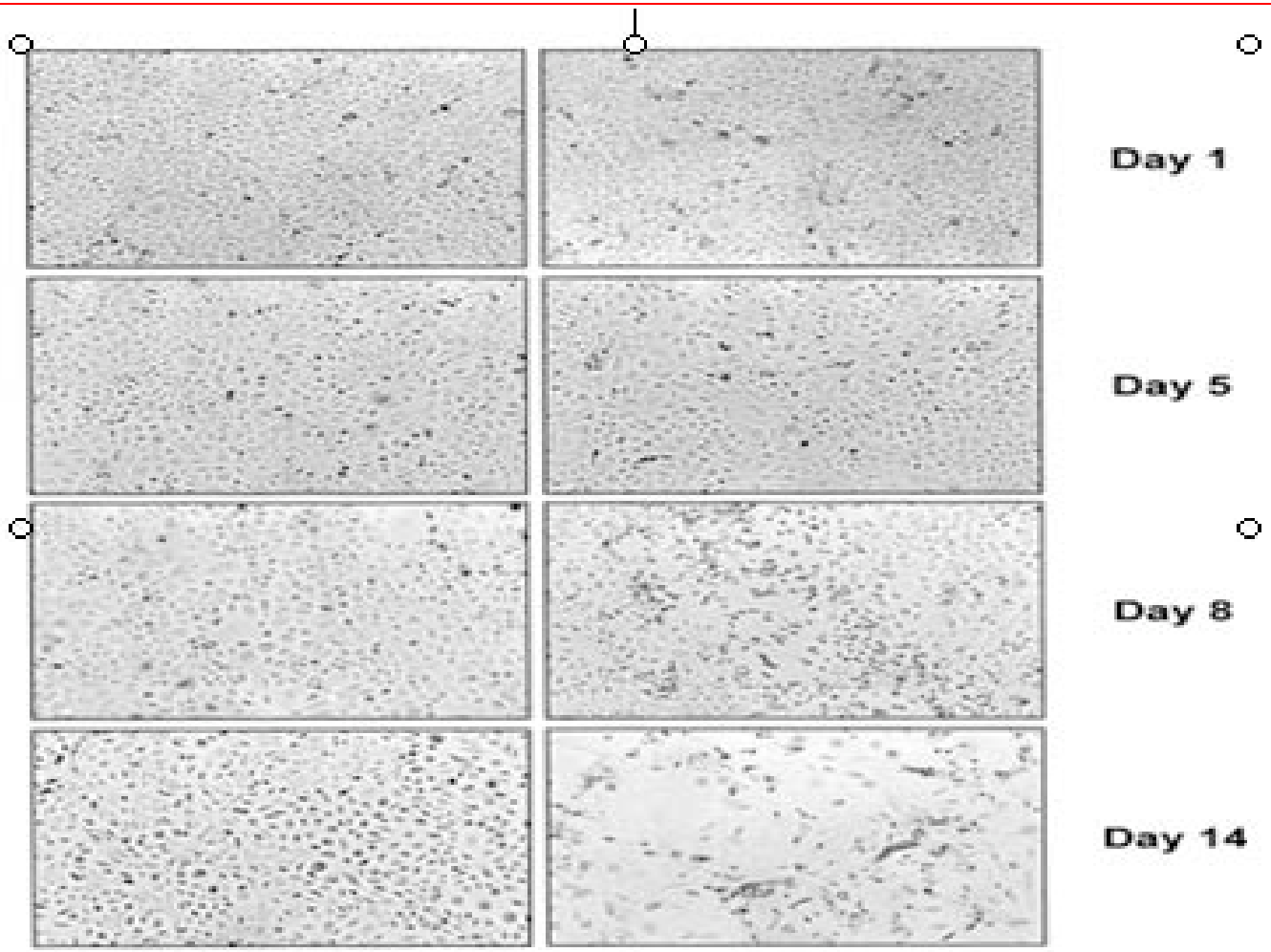
GDPs Inhibit Mesothelial Cell Proliferation



Witowski et al, J. Am Soc Nephrol. 2000 11:729-739

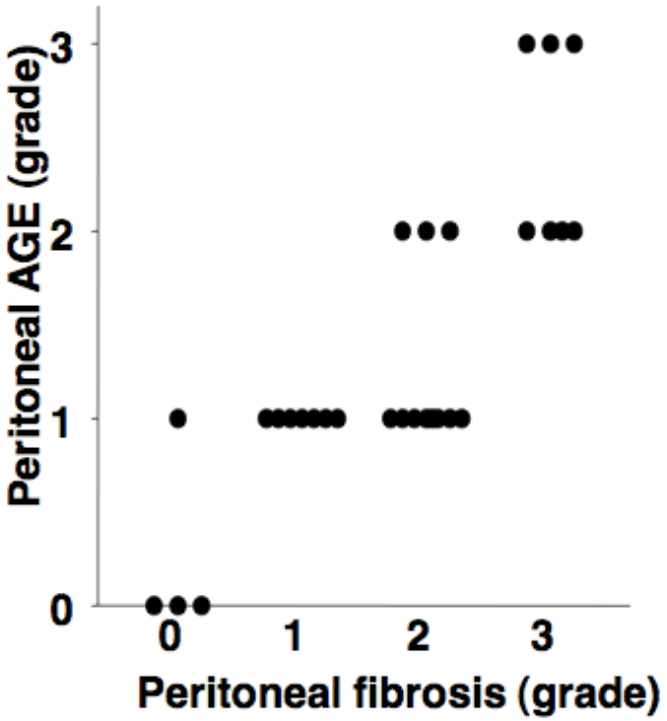
Slide courtesty Dr. A Jorres

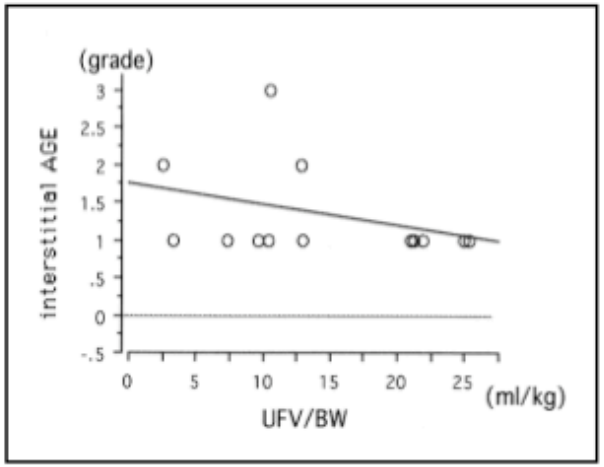
GDPs Inhibit Mesothelial Cell Proliferation

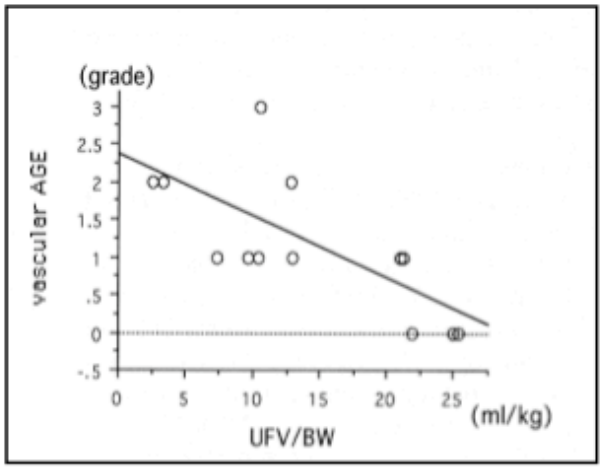


J Am Soc Nephrol 12:2434-2441, 2001

Peritoneal AGE deposition: Correlation with fibrosis and ultrafiltration failure

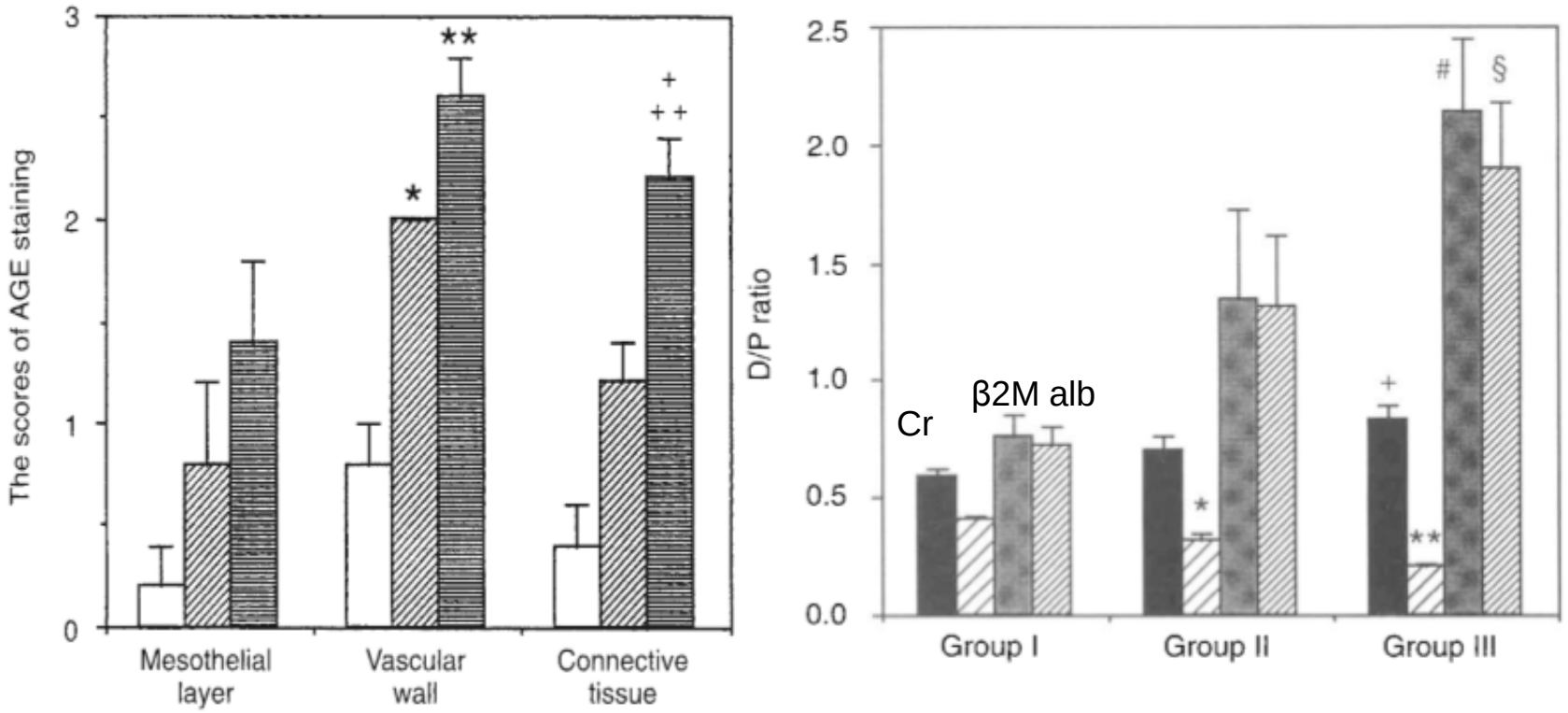






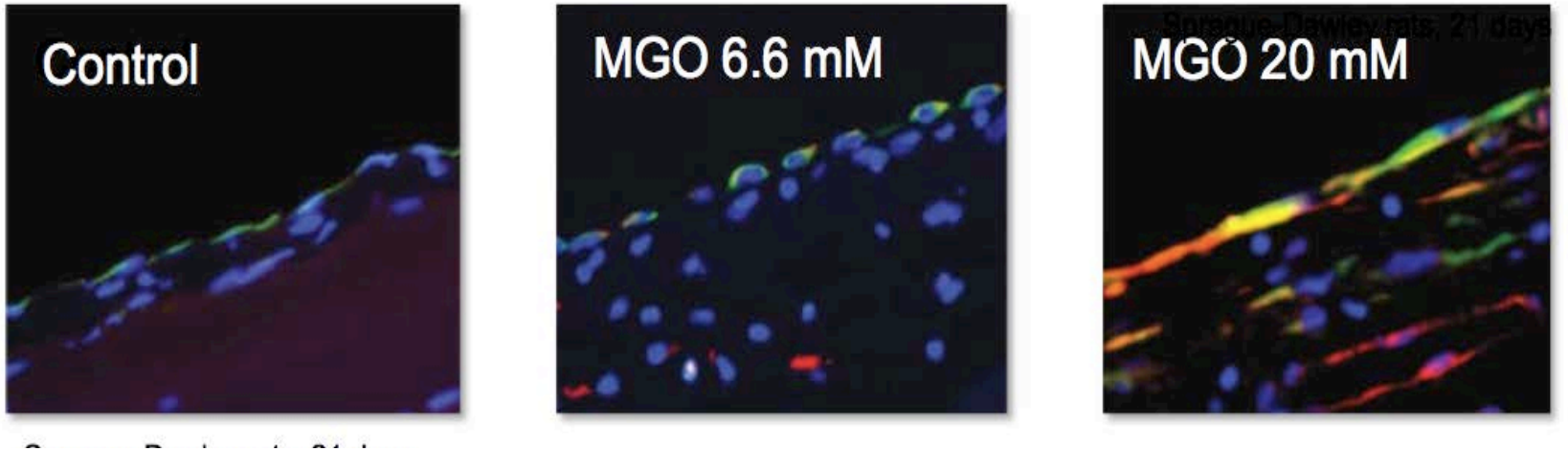
Honda et al, NDT 1999;14:1541-1549

Peritoneal AGE deposition: Association with solute transport



Nakayama et al, Kidney In. 1997;51: 182-186

GDP (methylglyoxal) stimulates EMT in rate mesothelial cell culture



cytokeratin

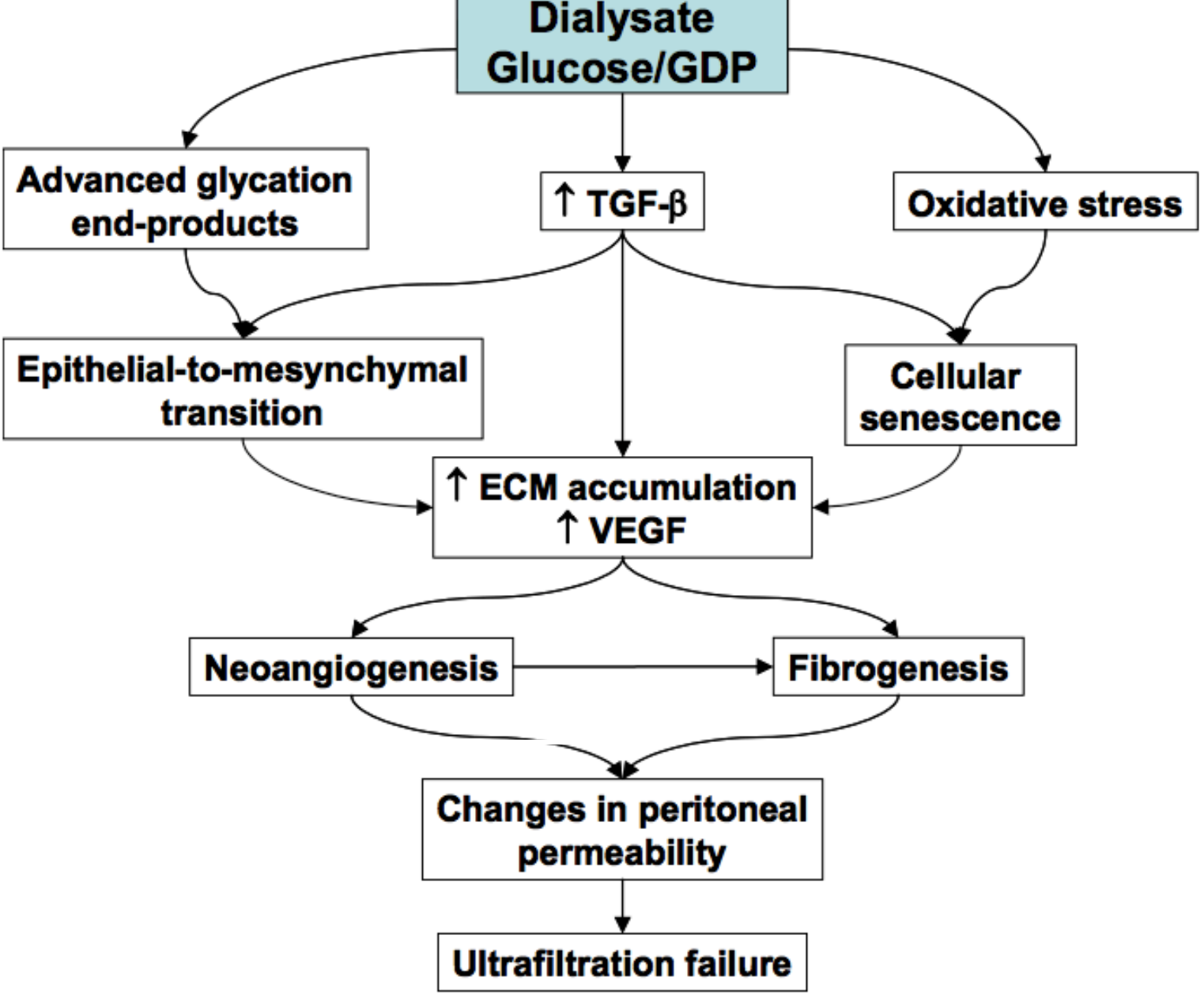
α-smooth muscle actin

DAPI **(dual positive cells)**

Methyl-glyoxal

MW 72.06

Nephrol Dial Transplant (2009) 24: 437–447



Witowski et al, *Nephron Exp Nephrol* 2008; 108: e69-e73

Options: Minimize glucose mediated toxicity

- Glucose minimization
- Icodextrin
- Amino acid based solutions

Options: Low GDP solutions

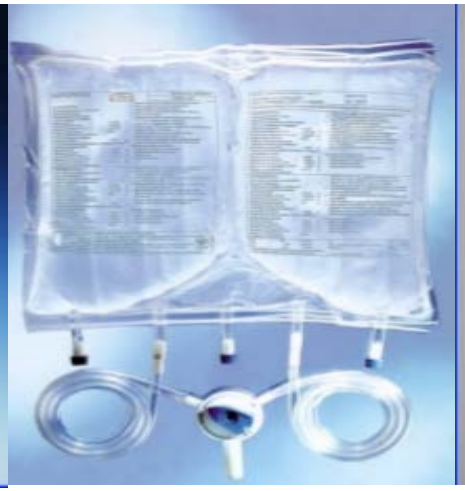
- Traditionally heat sterilization of fluids
- avoidance of caramalization of glucose at low pH
- GDPs produced
- Dual chamber separates glucose from catalyzing substances
- Lowers pH in glucose compartment (approximately 2.8)
- allows for reduced GDP in production and storage)

Low GDP Solutions

Staysafe

Bicavera

(FMC)



Staysafe

Balance

(FMC)

Gambrosol

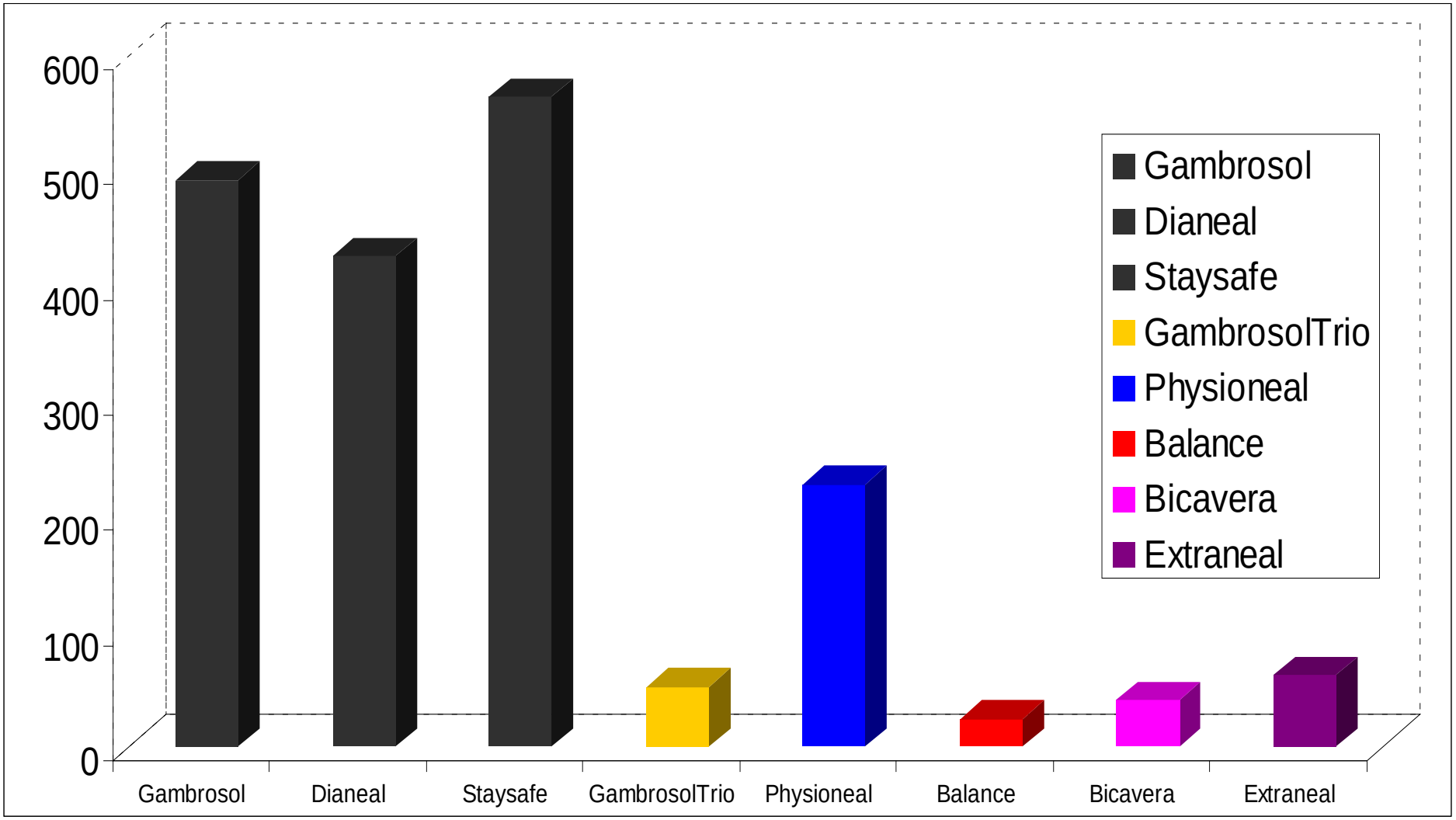
Trio /Saltrio

(Gambro)

Physioneal

(Baxter)

GDP content of PD solutions: Total



Erixon M, PDI 2006;26 490-497

WANTED

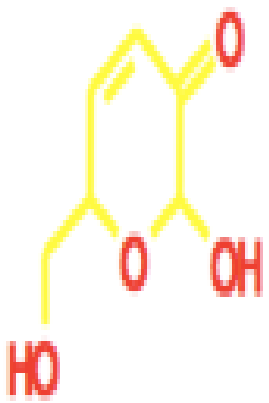
OFFICE OF THE SHERIFF
COUNTY OF BERGEN
SHERIFF
Joel Trella

FOR QUESTIONING CONCERNING THE OFFENSE OF

PERITONEAL AND RENAL TOXICITY

3,4-Dideoxy-glucosone-3 - ene

MW 144.12



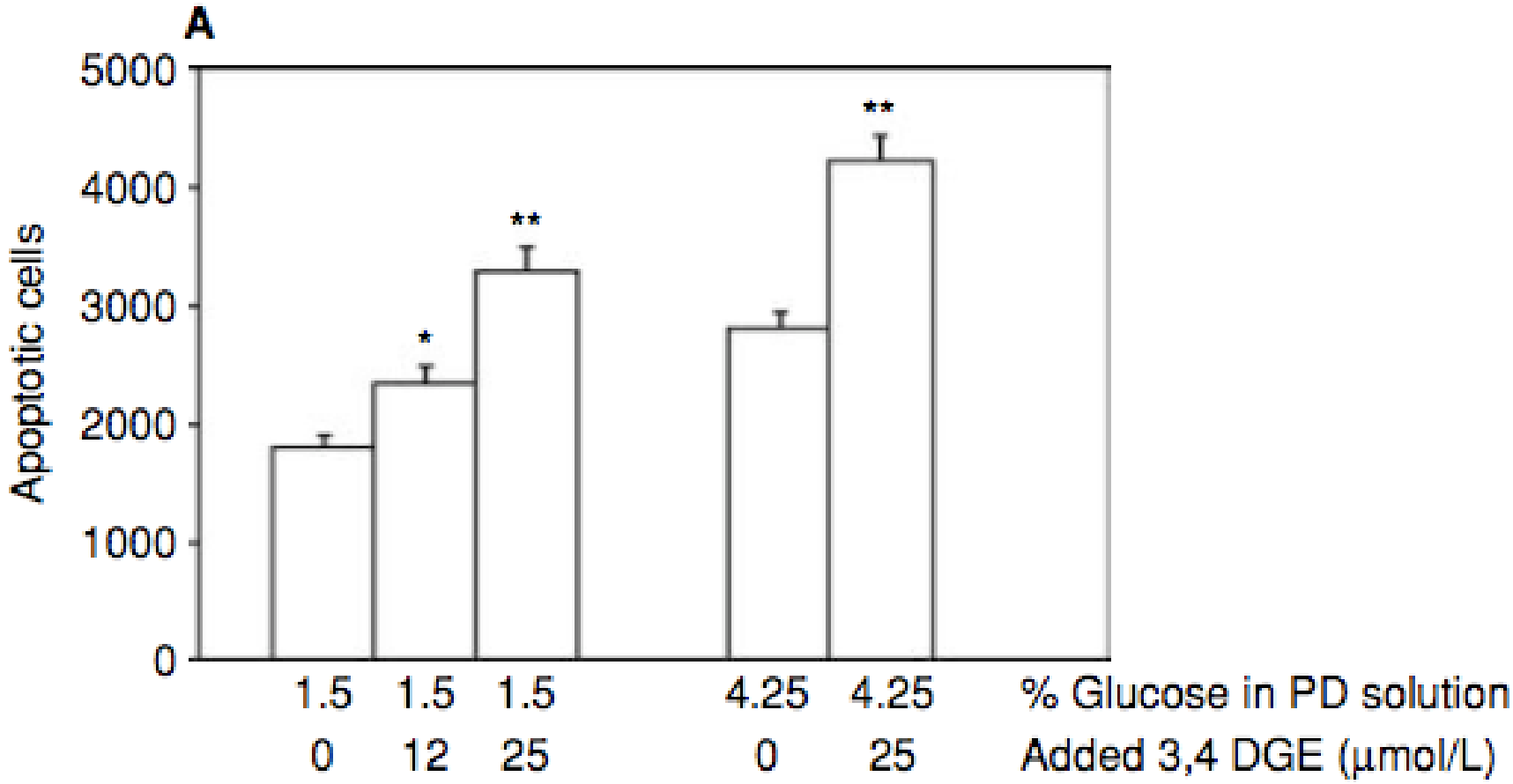
REMARKS : On August 08, 2003 at approximately 2215 hours a female victim was driving home from work, the victim stated that about two blocks from her home she noticed a large dark sport utility vehicle following her . She then pulled up to her house got out of her vehicle and was approaching her front door when the above described suspect came up from behind and grabbed her purse, the victim struggled with the suspect and was dragged her across her front lawn , the victim eventually let go of her purse and the suspect fled on foot.

ANY INFORMATION REGARDING THIS MATTER CONTACT

Elmwood Park Police Department

201– 796-0700

All GDP's are toxic but some more toxic than others



3,4-di-deoxyglucosone-3-ene promotes leukocyte apoptosis
Kidney International, Vol. 68 (2005), pp. 1303–1311

All GDP's are toxic but some more toxic than others

3,4-Dideoxyglucosone-3-ene Induces Apoptosis in Renal Tubular Epithelial Cells

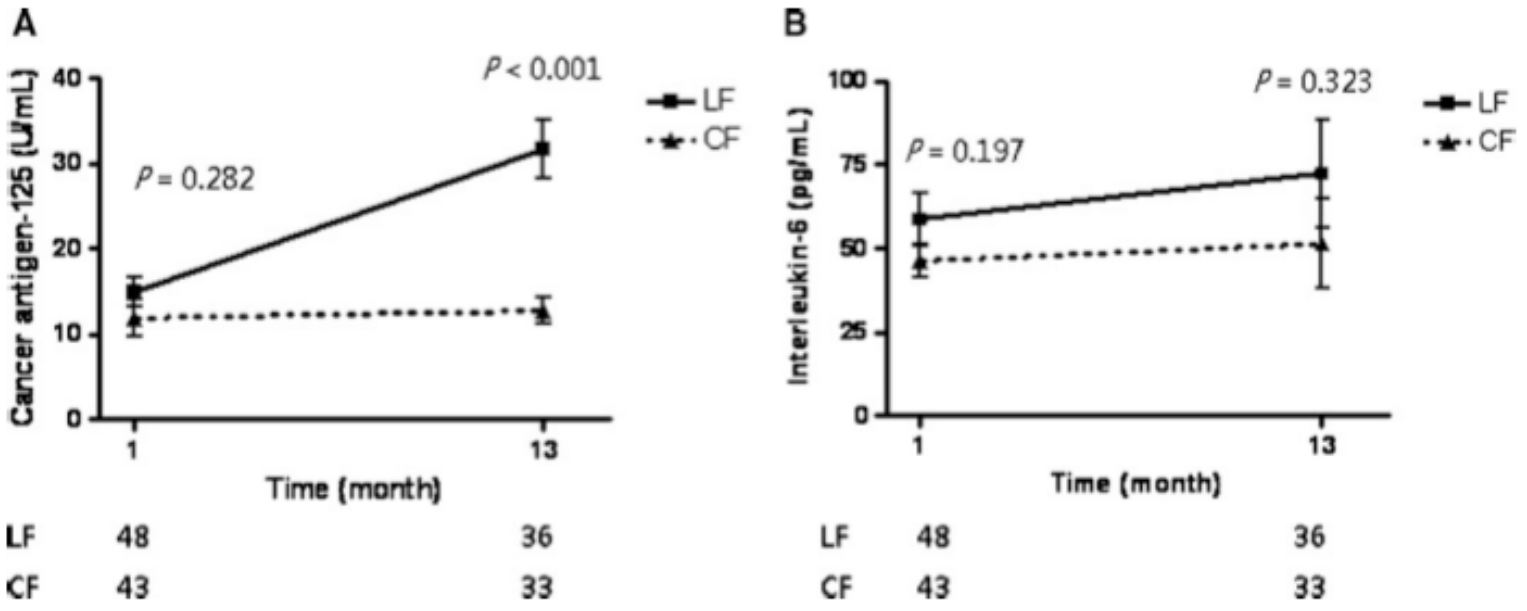
Pilar Justo,[1] Ana Belén Sanz,[1] Jesús Egido,[1,2,3] and Alberto Ortiz[1,2,3]

2005 Aug;54(8):2424-9.

Buffer and pH of low GDP solutions

	Lactate (mmol/L)	Bicarbonate (mmol/L)	pH
Physioneal ®	25	15	7-7.4
GambrosolTrio/ Saltrio (FMC)®	39-41	0	6.5
Balance®	40	0	6.8
Bicavera®	0	34	7.1

Increase in markers of mesothelial cell viability



Kim et al, Nephrol. Dial. Transplant. 2009 24: 2899-2908

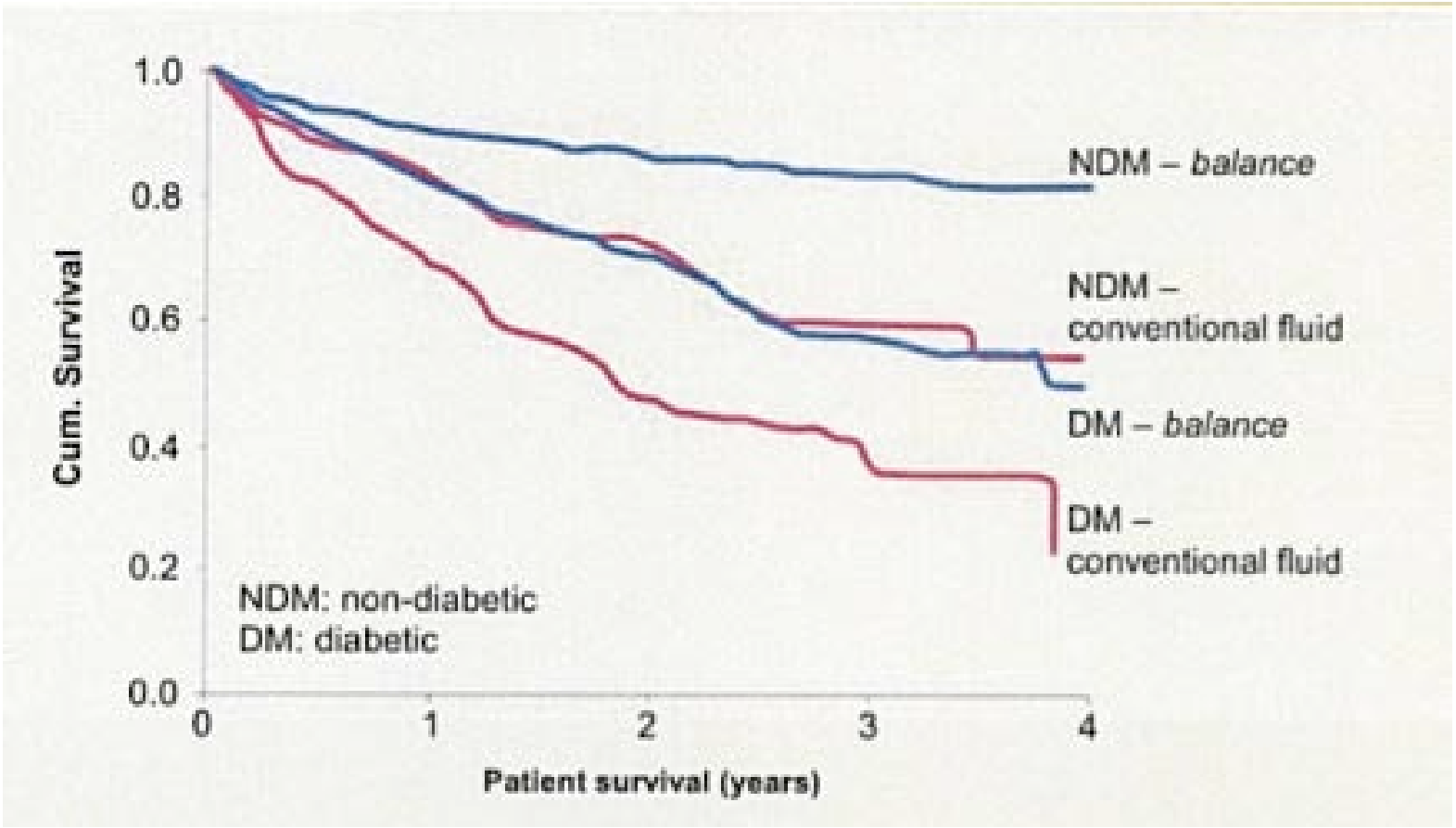
CA-125 increases with low GDP solutions:

- Fusshoeller NDT 2004;
- Jones et al KI, 2001
- Zeier KI 2004
- Rippe KI 2001
- Haas Jasn 2003
- Williams et al KI 2004
- Choi et al PDI 2008

Clinical Experience: Low GDP, neutral PH solutions

- ◊ survival
- ◊ residual kidney function
- ◊ peritonitis
- ◊ small solute transport characteristics
- ◊ peritoneal UF capacity

Low GDP solutions and survival



Lee, Nephrol Dial Transplant 2006; 21:2893-2899

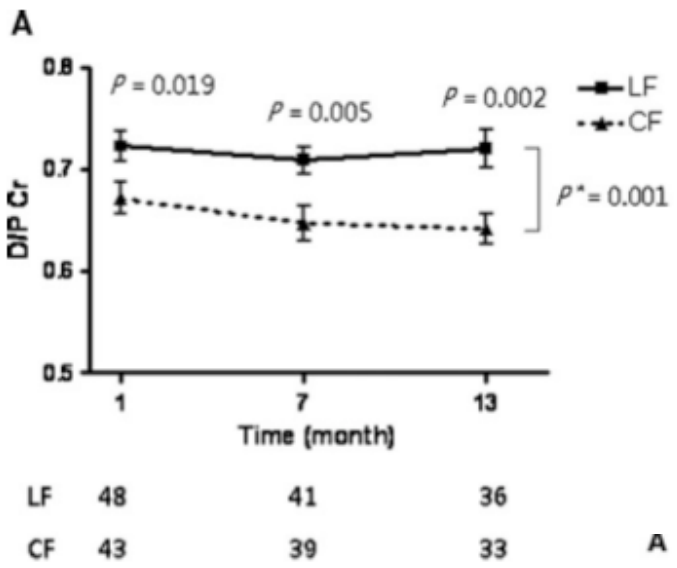
Clinical Experience with Low GDP solutions (Lee et al):

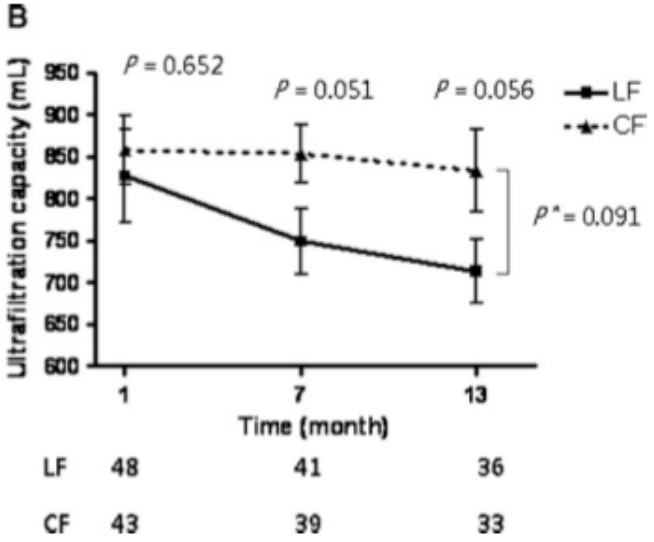
- Observational study (1909 patients)
- Balance solution
- Excluded patients from initial analysis (n=305) who switched solutions, had excellent survival

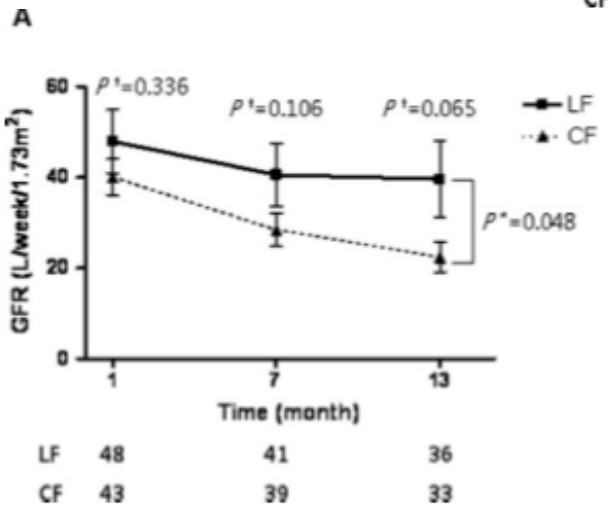
- Counfounding by indication
- younger patients and experienced centres most likely to receive novel solutions.
- Adjustment for diabetes and age
- no other comorbidity and biochemical paramaters

Study	N	Follow-up	Pop.	Design	Solution	RKF	UF	Solute Transport
Euro-Balance KI 2004	86	24-wks (12/12)	Prevalent	Multicentre Crossover RCT	Balance	↑	↓	↑
Fan et al KI 2007	93	1-year	Incident 59 APD	SingleCentre RCT	Physioneal/ Balance (free ico use)	↔	↔	↔
Choi et al PDI 2008	104	1-year	Prevalent CAPD 34 anuric	Single Centre RCT	Balance	↔	↑	↔
Montenegro Et al PDI 2006	36	1-year	Incident CAPD	Prospective Obs. study	Bicavera	↑	↓	↔
Szeto et al NDT 2007	50	1-year	Incident CAPD	SingleCentre RCT	Balance	↔	↔	↔
Kim et al NDT 2009	91	1-year	Incident CAPD	Multicentre RCT	Balance	↑	↓	↑

The relationship between RKF, Peritoneal UF, and small solute clearance

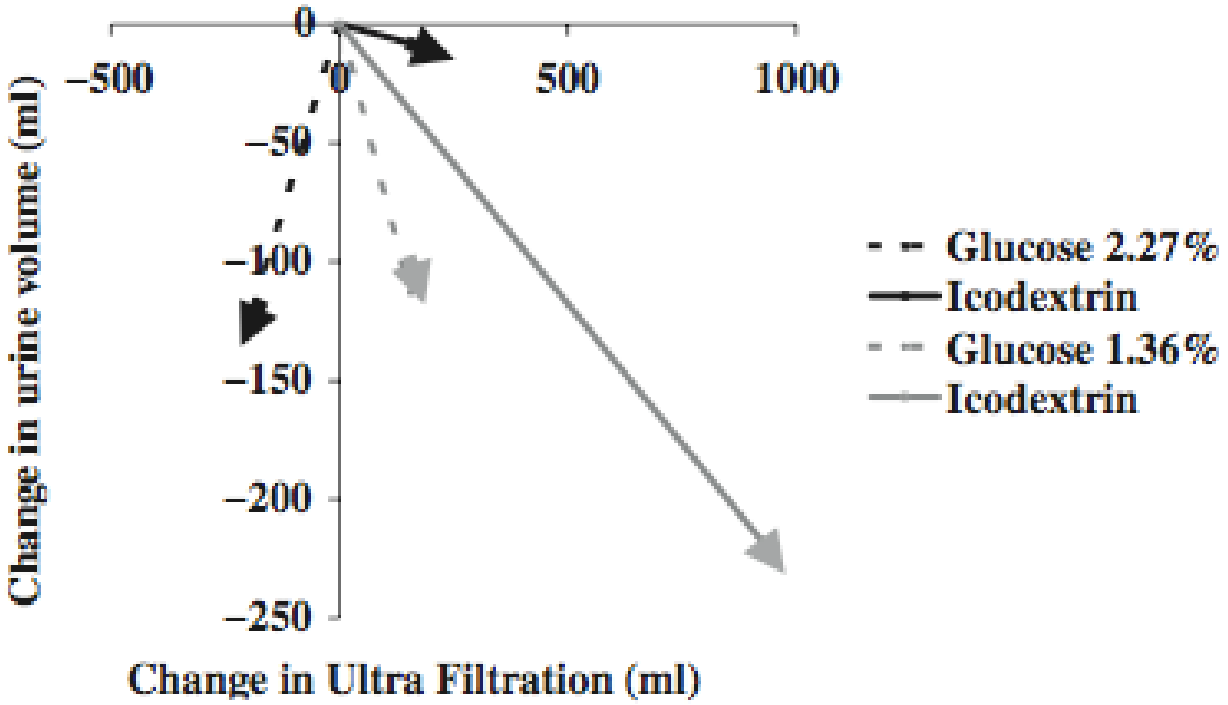






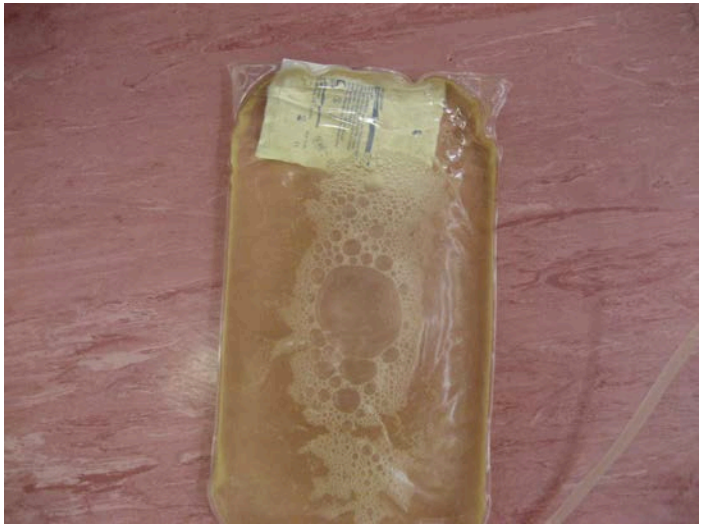
Kim et al Nephrol. Dial. Transplant. 2009 24: 2899-2908

Urine volume vs. Peritoneal UF



Nephrol Dial Transplant (2006) 21 [Suppl 2]: ii47–ii50

Urine volume vs. Peritoneal UF



CLINICAL RESEARCH www.jasn.org

Effects of Biocompatible versus Standard Fluid on Peritoneal Dialysis Outcomes

David W. Johnson,*† Fiona G. Brown,‡ Margaret Clarke,§ Neil Boudville,‖ Tony J. Elias,¶ Marjorie W.Y. Foo,** Bernard Jones,†† Hemant Kulkarni,‡‡ Robyn Langham,§§‖‖ Dwarakanathan Ranganathan,†¶¶ John Schollum,*** Michael Suranyi,††† Seng H. Tan,‡‡‡§§§‖‖‖ and David Voss,¶¶¶ on behalf of the balANZ Trial Investigators

JASN 2012

balANZ

- multicenter, open-label, parallel-group, randomized controlled trial in Aus and NZ
- Adult >18 years old, GFR > 5mL/min/1.73m^2
- 1:1 neutral pH, lactate-buffered low GDP Balance solutions vs. conventional standard lactate-buffered PD solutions (stay.safe)
- Free use of icodextrin in both groups
- CAPD until 2006 then APD patients included

balANZ

Primary outcome:

- slope of decline over time of residual renal function
  - arithmetic mean of 24-hour urinary urea and creatinine clearances
  - 0, 3, 6, 9, 12, 18, and 24 months

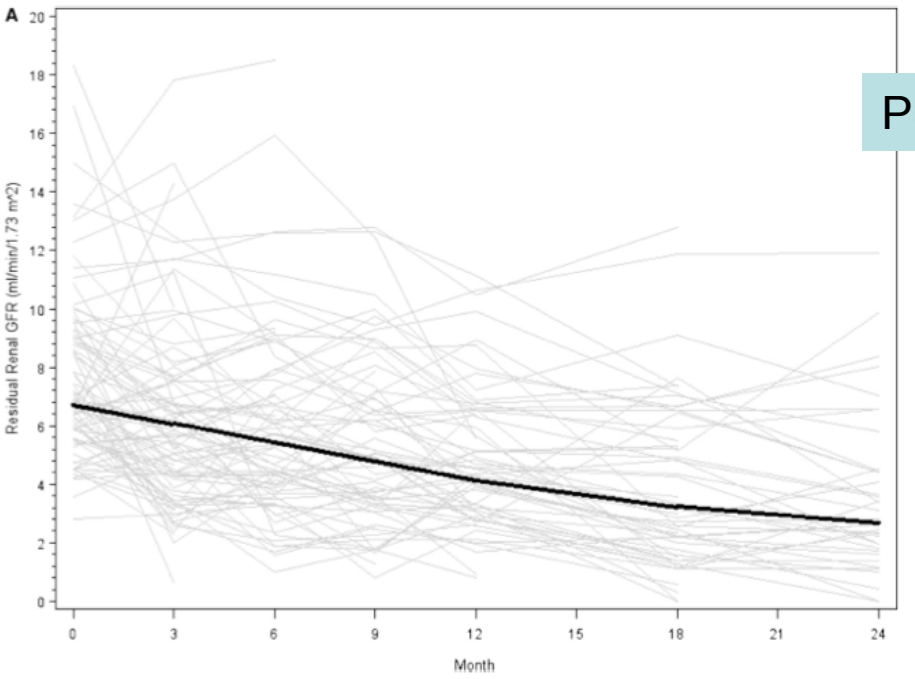
Secondary outcomes:

- time from randomization to occurrence of anuria (urine volume ,100 ml/d)
- weight, BP, urine volume, peritoneal ultrafiltration volume, serum albumin, hemoglobin
- peritonitis-free survival, technique survival, patient survival, and adverse events.

Characteristic	Biocompatible (*n*=91)	Control (*n*=91)
Age (yr)	59.3±14.20	57.9±14.72
Female	39 (42.9)	43 (47.3)
Ethnicity		
Caucasian	77 (85)	69 (76)
Aboriginal and Torres Strait Islander	0 (0)	2 (2)
Asian	10 (11)	13 (14)
Maori and Pacific Islander	4 (4)	7 (7)
Cardiovascular disease	70 (76.1)	71 (81.6)
Diabetic nephropathy	30 (33.0)	31 (34.1)
Medications		
angiotensin converting enzyme inhibitor	40 (44.0)	41 (45.1)
angiotensin receptor blocker	25 (27.5)	29 (31.9)
β-blocker	45 (49.5)	51 (56.0)
statin	67 (73.6)	61 (67.0)
aspirin	40 (44.0)	46 (50.5)
nonsteroidal anti-inflammatory drug	4 (4.4)	2 (2.2)
anticoagulants	16 (17.6)	18 (19.8)
diuretics	40 (44.0)	46 (50.5)
exit-site mupirocin	29 (31.9)	36 (39.6)
exit-site gentamicin	0 (0)	0 (0)
Body mass index (kg/m^2)	27.7±5.02	28.4±6.16
Systolic BP (mmHg)		
supine	139.8±21.4	138.9±21.8
standing	134.2±20.7	133.3±23.4
Diastolic BP (mmHg)		
supine	76.6±11.3	78.1±11.0
standing	76.7±11.9	78.0±12.7
Hemodialysis before PD	13 (14.3)	4 (4.4)
Initial PD modality		
continuous ambulatory PD	81 (89.0)	82 (90.1)
automated PD	10 (11.0)	9 (9.9)
Prescribed dialysate volume (L/d)	8 (2–10)	8 (2–8.7)
Dialysate glucose exposure (g/d)	122±35	124±36
GFR (ml/min per 1.73 m^2)	7 (3–18)	7 (3–18)
Urine volume (mL/d)	1495 (379–3525)	1365 (455–3359)
Weekly peritoneal urea clearance (L/wk per 1.73 m^2)	51.1±10.4	52.6±14.5
Weekly peritoneal creatinine clearance (L/wk per 1.73 m^2)	38.3±9.0	36.3±11.9
Peritoneal ultrafiltration (ml/d)	700 (−700 to 3500)	1090 (−400 to 2800)
Dialysate/plasma creatinine ratio at 4 hours (1 mo)	0.67±0.10	0.62±0.10
Normalized protein nitrogen appearance (g/kg/d)	1.05±0.25	1.06±0.26
Serum albumin (g/L)	37.9±4.8	36.9±5.7
Serum total calcium corrected (mmol/L)	2.4±0.2	2.4±0.3
Hemoglobin (g/L)	115±17	115±17

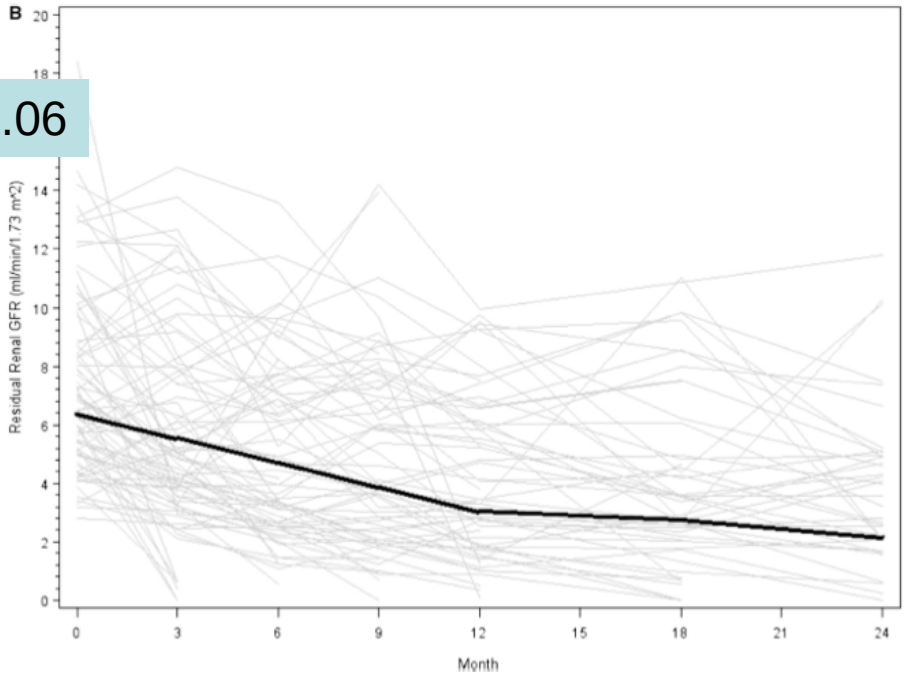
Results of Primary Outcome: Slope of GFR Decline

Standard Solution Group



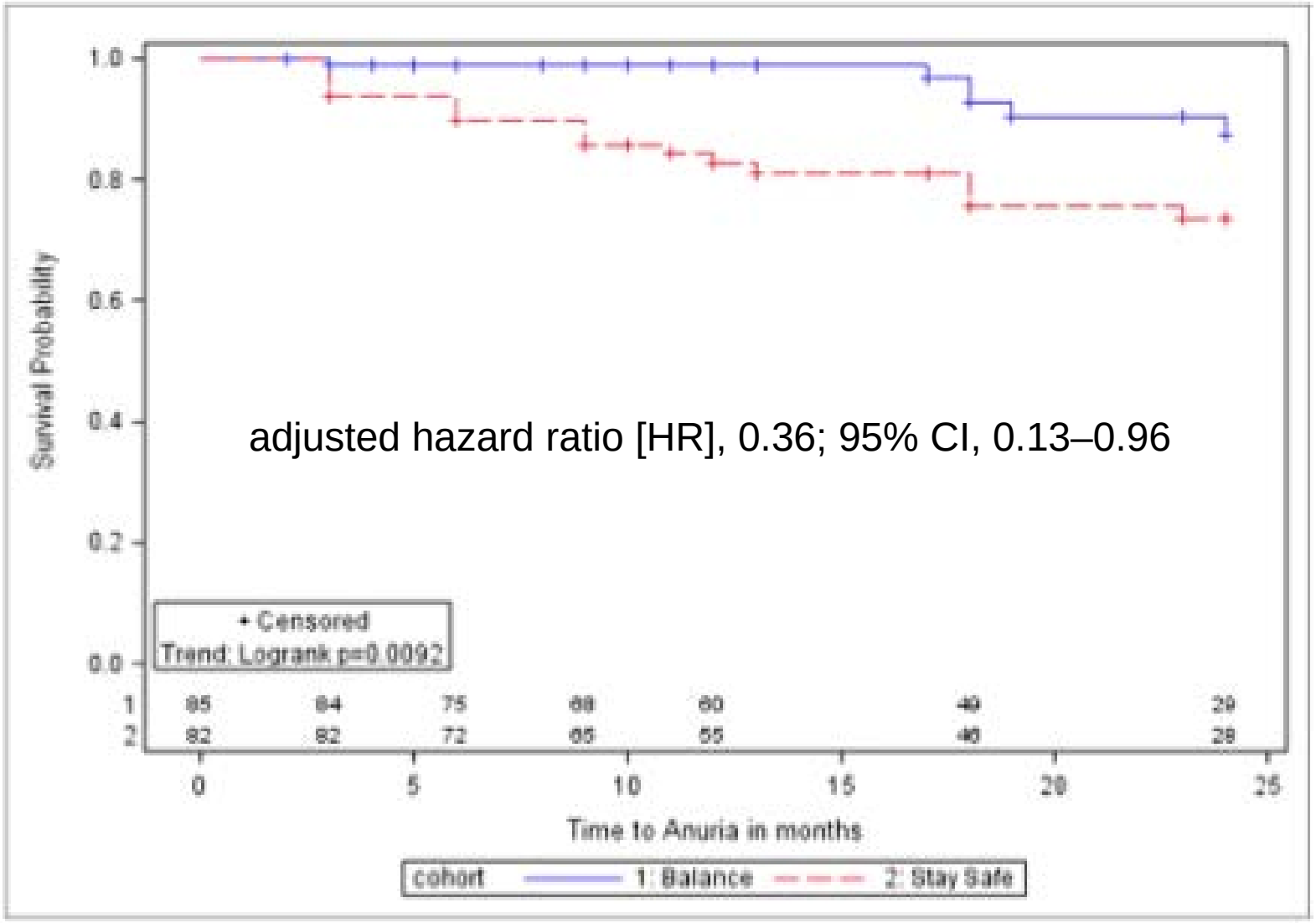
P=0.06

Low GDP Group

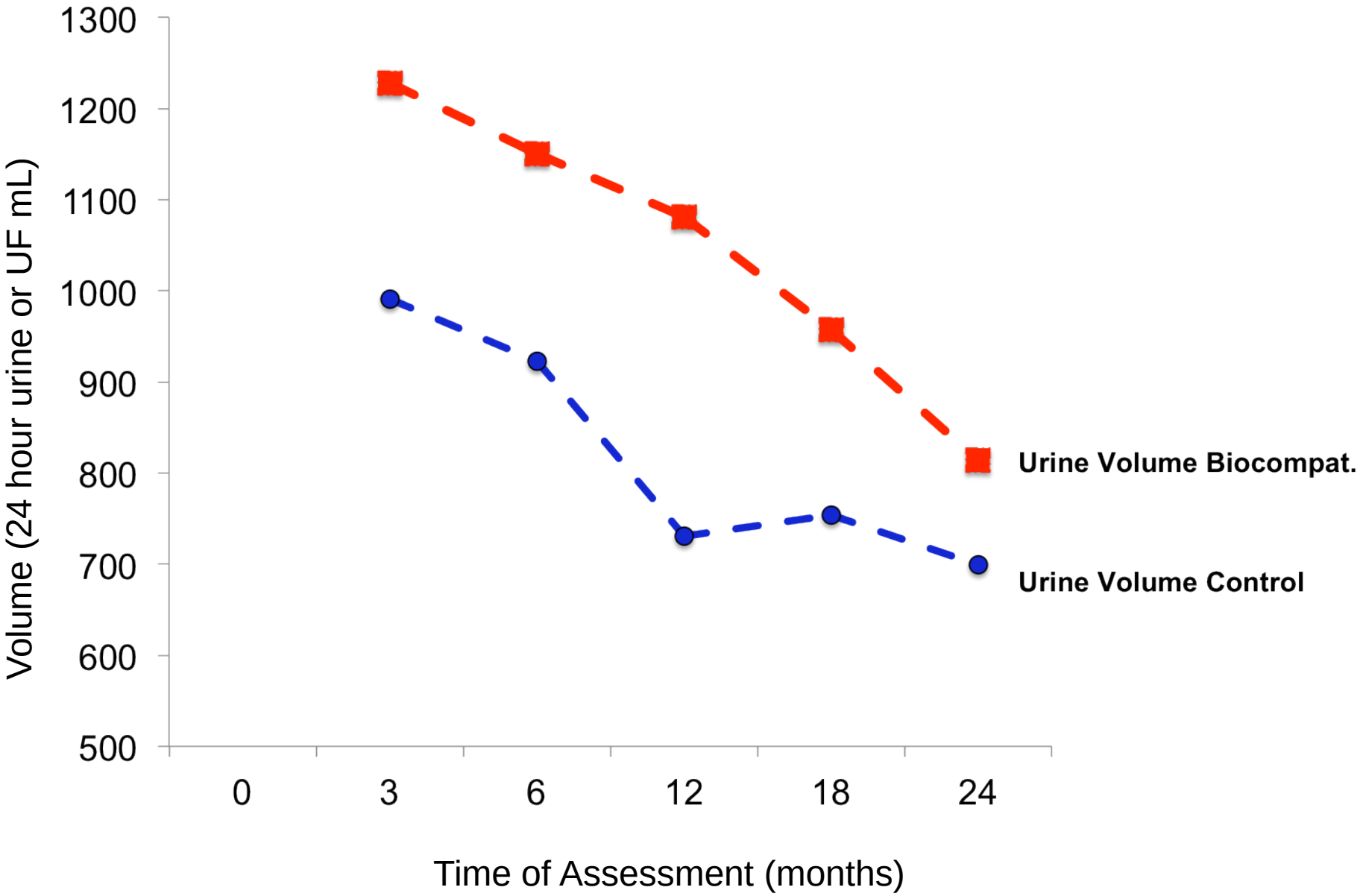


- Year 1 0.06 mL/min difference in GFR decline [95% CI], -0.05 to 0.17; P=0.17
- Year 2 0.01 mL/min difference in GFR decline [95% CI], -0.18 to 0.20; P=0.9.
- Across the two 12-month periods p=0.06;

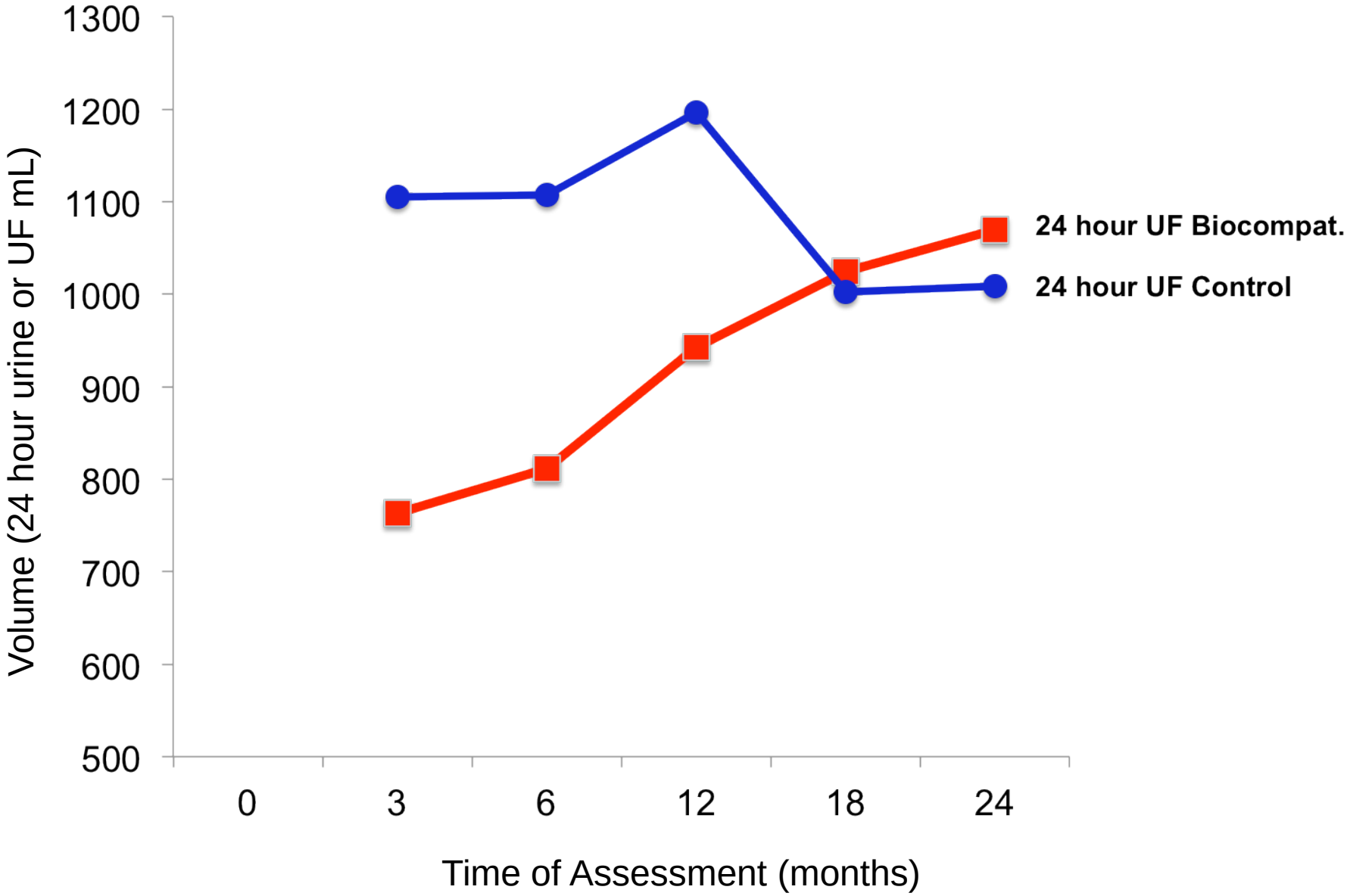
Secondary Outcome: Time To Anuria



Urine Volume Biocompatible Vs. Control

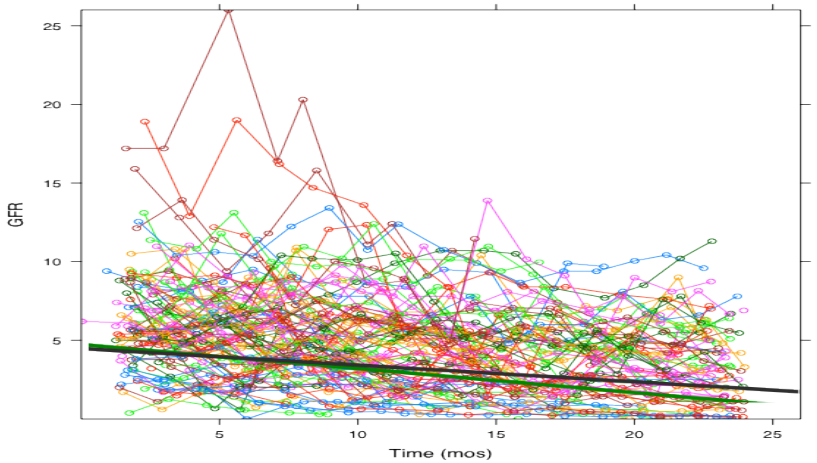


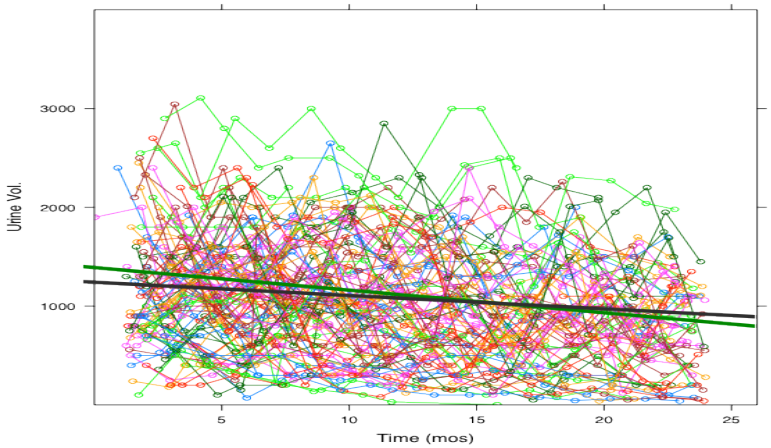
24 hour UF: Biocompatible Vs. Control



Preliminary Results From The TrioTrial

Gambrosol Trio ® -n=50 vs. Dianeal ® n=49





Glomerular filtration decline

Low GDP group: 0.1160(+/-0.024) mL/min/month

Standard Arm: 0.1678 (+/-0.023) m/min/month

Difference: 0.0518 mL/min/month p=0.1130.

Glomerular filtration decline

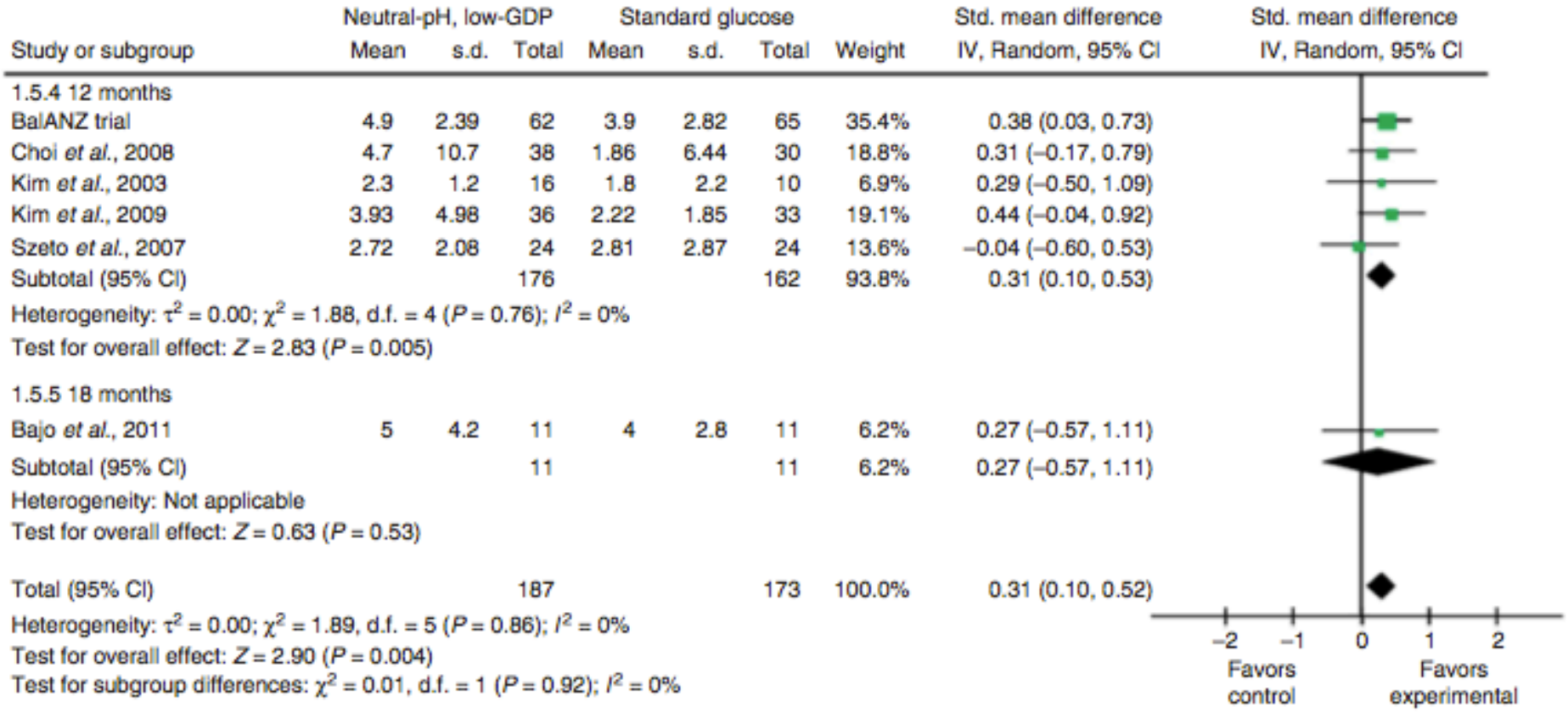
Low GDP group: 0.1160(+/-0.024) mL/min/month

Standard Arm: 0.1678 (+/-0.023) m/min/month

Difference: 0.0518 mL/min/month p=0.1130.

Sikaneta et al unpublished

Residual Kidney Function : Results of A Meta-Analysis



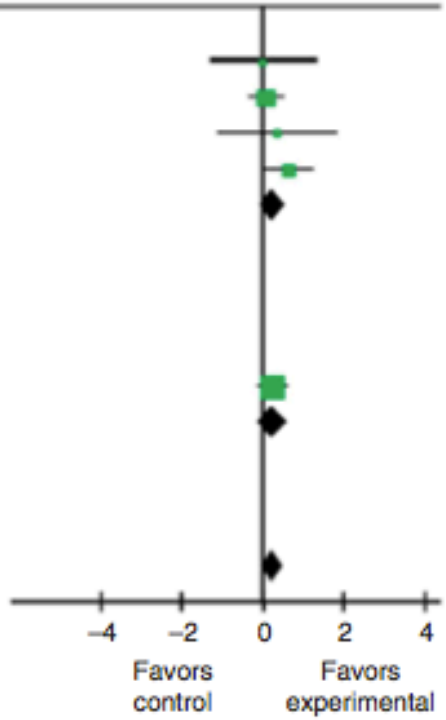
Study or subgroup	Neutral-pH, low-GDP Mean	s.d.	Total	Standard glucose Mean	s.d.	Total	Weight	Std. mean difference IV, Random, 95% CI
1.5.4 12 months								
BalANZ trial	4.9	2.39	62	3.9	2.82	65	35.4%	0.38 (0.03, 0.73)
Choi *et al.*, 2008	4.7	10.7	38	1.86	6.44	30	18.8%	0.31 (–0.17, 0.79)
Kim *et al.*, 2003	2.3	1.2	16	1.8	2.2	10	6.9%	0.29 (–0.50, 1.09)
Kim *et al.*, 2009	3.93	4.98	36	2.22	1.85	33	19.1%	0.44 (–0.04, 0.92)
Szeto *et al.*, 2007	2.72	2.08	24	2.81	2.87	24	13.6%	–0.04 (–0.60, 0.53)
Subtotal (95% CI)			176			162	93.8%	0.31 (0.10, 0.53)
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.88$, d.f. = 4 ($P = 0.76$); $I^2 = 0\%$								
Test for overall effect: $Z = 2.83$ ($P = 0.005$)								
1.5.5 18 months								
Bajo *et al.*, 2011	5	4.2	11	4	2.8	11	6.2%	0.27 (–0.57, 1.11)
Subtotal (95% CI)			11			11	6.2%	0.27 (–0.57, 1.11)
Heterogeneity: Not applicable								
Test for overall effect: $Z = 0.63$ ($P = 0.53$)								
Total (95% CI)			187			173	100.0%	0.31 (0.10, 0.52)
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.89$, d.f. = 5 ($P = 0.86$); $I^2 = 0\%$								
Test for overall effect: $Z = 2.90$ ($P = 0.004$)								
Test for subgroup differences: $\chi^2 = 0.01$, d.f. = 1 ($P = 0.92$); $I^2 = 0\%$								

With 12-24 months of follow-up

Cho et al KI 2013

Residual Kidney Function : Results of A Meta-Analysis

Study or subgroup	Neutral-pH, low-GDP Mean	s.d.	Total	Standard glucose Mean	s.d.	Total	Weight	Std. mean difference IV, Random, 95% CI
1.6.6 24 months								
Bajo *et al.*, 2011	4.2	2.6	9	4.2	4	3	3.3%	0.00 (–1.31, 1.31)
BalANZ trial	3.4	2.79	40	3.2	2.82	48	32.3%	0.07 (–0.35, 0.49)
Fernandez-Perpen *et al.*, 2012	6	4.4	5	4.2	4	3	2.7%	0.37 (–1.09, 1.82)
Kim *et al.*, 2009	3.5	3.4	25	1.65	1.97	21	16.0%	0.64 (0.04, 1.24)
Subtotal (95% CI)			79			75	54.3%	0.25 (–0.07, 0.57)
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.51$, d.f. = 3 ($P = 0.47$); $I^2 = 0\%$								
Test for overall effect: $Z = 1.51$ ($P = 0.13$)								
1.6.7 3 years +								
Lai *et al.*, 2012	2.3	2.74	58	1.69	2.29	67	45.7%	0.24 (–0.11, 0.59)
Subtotal (95% CI)			58			67	45.7%	0.24 (–0.11, 0.59)
Heterogeneity: Not applicable								
Test for overall effect: $Z = 1.34$ ($P = 0.18$)								
Total (95% CI)			137			142	100.0%	0.25 (0.01, 0.48)
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.51$, d.f. = 4 ($P = 0.64$); $I^2 = 0\%$								
Test for overall effect: $Z = 2.02$ ($P = 0.04$)								
Test for subgroup differences: $\chi^2 = 0.00$, d.f. = 1 ($P = 0.98$); $I^2 = 0\%$								



With 24 months or greater follow-up

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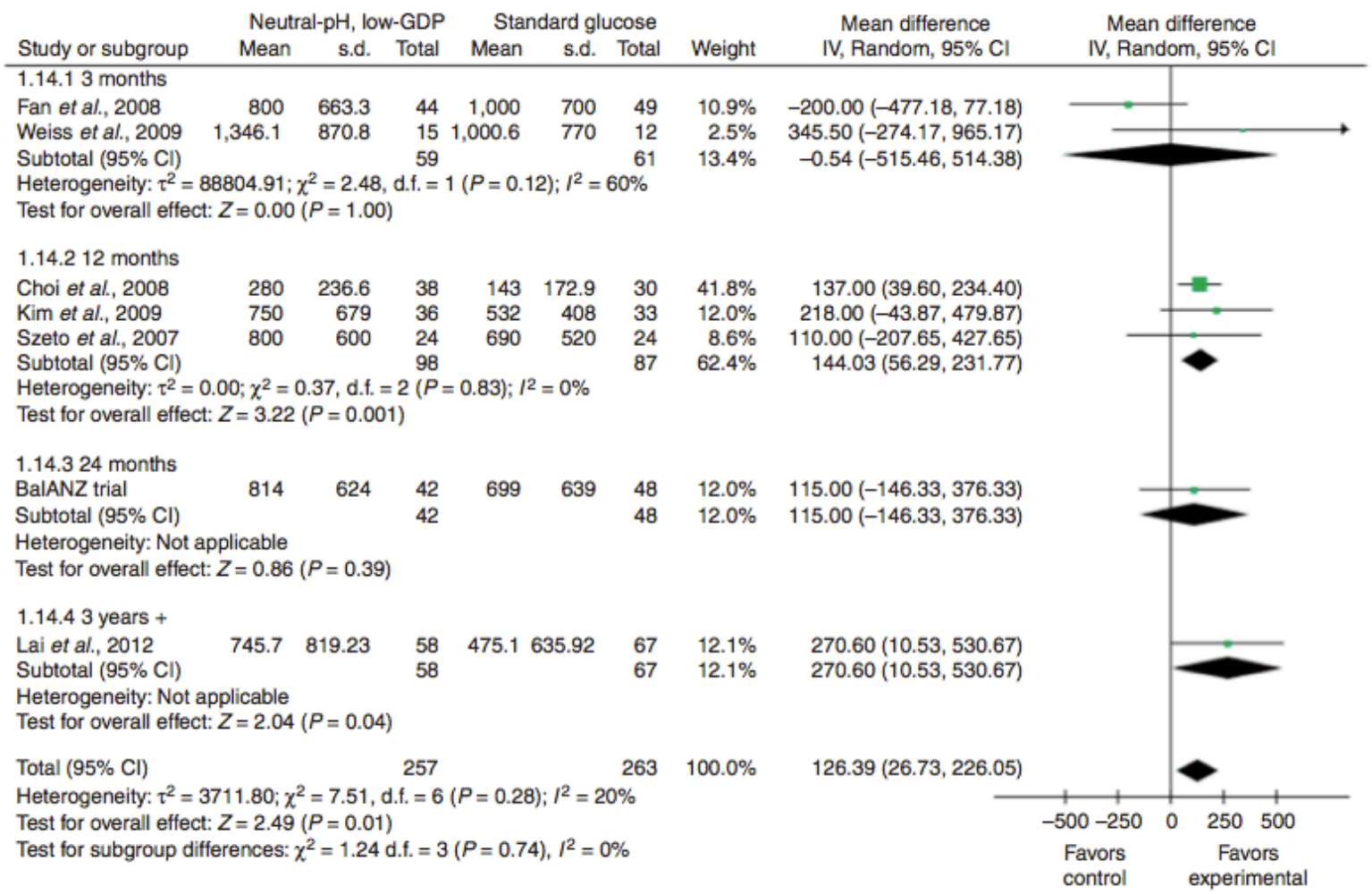
Urine Volume: Results of A Meta-Analysis



Study or subgroup	Neutral-pH, low-GDP Mean	s.d.	Total	Standard glucose Mean	s.d.	Total	Weight	Mean difference IV, Random, 95% CI
1.14.1 3 months								
Fan *et al.*, 2008	800	663.3	44	1,000	700	49	10.9%	–200.00 (–477.18, 77.18)
Weiss *et al.*, 2009	1,346.1	870.8	15	1,000.6	770	12	2.5%	345.50 (–274.17, 965.17)
Subtotal (95% CI)			59			61	13.4%	–0.54 (–515.46, 514.38)
Heterogeneity: $\tau^2 = 88804.91$; $\chi^2 = 2.48$, d.f. = 1 ($P = 0.12$); $I^2 = 60\%$								
Test for overall effect: $Z = 0.00$ ($P = 1.00$)								
1.14.2 12 months								
Choi *et al.*, 2008	280	236.6	38	143	172.9	30	41.8%	137.00 (39.60, 234.40)
Kim *et al.*, 2009	750	679	36	532	408	33	12.0%	218.00 (–43.87, 479.87)
Szeto *et al.*, 2007	800	600	24	690	520	24	8.6%	110.00 (–207.65, 427.65)
Subtotal (95% CI)			98			87	62.4%	144.03 (56.29, 231.77)
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.37$, d.f. = 2 ($P = 0.83$); $I^2 = 0\%$								
Test for overall effect: $Z = 3.22$ ($P = 0.001$)								
1.14.3 24 months								
BalANZ trial	814	624	42	699	639	48	12.0%	115.00 (–146.33, 376.33)
Subtotal (95% CI)			42			48	12.0%	115.00 (–146.33, 376.33)
Heterogeneity: Not applicable								
Test for overall effect: $Z = 0.86$ ($P = 0.39$)								
1.14.4 3 years +								
Lai *et al.*, 2012	745.7	819.23	58	475.1	635.92	67	12.1%	270.60 (10.53, 530.67)
Subtotal (95% CI)			58			67	12.1%	270.60 (10.53, 530.67)
Heterogeneity: Not applicable								
Test for overall effect: $Z = 2.04$ ($P = 0.04$)								
Total (95% CI)			257			263	100.0%	126.39 (26.73, 226.05)
Heterogeneity: $\tau^2 = 3711.80$; $\chi^2 = 7.51$, d.f. = 6 ($P = 0.28$); $I^2 = 20\%$								
Test for overall effect: $Z = 2.49$ ($P = 0.01$)								
Test for subgroup differences: $\chi^2 = 1.24$ d.f. = 3 ($P = 0.74$), $I^2 = 0\%$								

All Studies

Cho et al KI 2013

But Since Then ……

- three large trials (Cho K et al, Park et al and Lui et al), all of which were published after the Cho K et al meta-analysis
- added over 350 patients
- Two trials included that maybe shouldn't have been:
  - pediatric patients (Haas et al)
  - Less than ten patients in study included in their analysis of peritoneal UF (Coles et al) .
  - Randomized study conducted by Fan et al had challenges in interpreting final data .

1. Cho, K.H., et al., *The effect of low-GDP solution on ultrafiltration and solute transport in continuous ambulatory peritoneal dialysis patients.* Perit Dial Int, 2013. **33**(4): p. 382-90.
2. Park, S.H., et al., *Effects of neutral pH and low-glucose degradation product-containing peritoneal dialysis fluid on systemic markers of inflammation and endothelial dysfunction: a randomized controlled 1-year follow-up study.* Nephrol Dial Transplant, 2012. **27**(3): p. 1191-9.
3. Lui, S.L., et al., *A combination of biocompatible peritoneal dialysis solutions and residual renal function, peritoneal transport, and inflammation markers: a randomized clinical trial.* Am J Kidney Dis, 2012. **60**(6): p. 966-75.
4. Haas, S., et al., *Improved acidosis correction and recovery of mesothelial cell mass with neutral-pH bicarbonate dialysis solution among children undergoing automated peritoneal dialysis.* J Am Soc Nephrol, 2003. **14**(10): p. 2632-8.
5. Coles, G.A., et al., *A controlled trial of two bicarbonate-containing dialysis fluids for CAPD--final report.* Nephrol Dial Transplant, 1998. **13**(12): p. 3165-71.
6. Fan, S.L., et al., *Randomized controlled study of biocompatible peritoneal dialysis solutions: effect on residual renal function.* Kidney Int, 2008. **73**(2): p. 200-6.

Meta Analysis By Yohanna, Jain et al

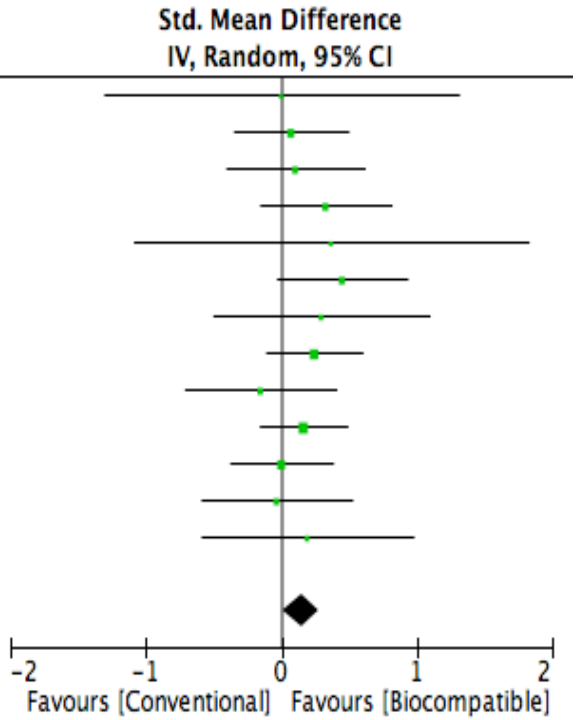
Impact on Residual Kidney Function

All Durations of follow-up

Study or Subgroup	Biocompatible Mean	SD	Total	Conventional Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bajo MA (2011)	4.2	2.6	9	4.2	4	3	1.1%	0.00 [-1.31, 1.31]
balANZ 2012	3.4	2.79	40	3.2	2.82	48	10.5%	0.07 [-0.35, 0.49]
Cho (2013)	2.4	1.72	32	2.2	2.14	28	7.2%	0.10 [-0.41, 0.61]
Choi HY (2008)	4.9	10.9	38	1.86	6.44	30	8.0%	0.33 [-0.16, 0.81]
Fernandez-Perpen (2012)	6	4.4	5	4.2	4	3	0.9%	0.37 [-1.09, 1.82]
Kim SG (2008)	3.9	4.9	36	2.2	1.8	33	8.1%	0.45 [-0.03, 0.93]
Kim YL (2003)	2.3	1.2	16	1.8	2.2	10	2.9%	0.29 [-0.50, 1.09]
Lai KN (2012)	2.3	2.74	58	1.69	2.29	67	14.9%	0.24 [-0.11, 0.59]
Le Poole (2005)	4.3	2.9	24	4.8	3.4	26	6.0%	-0.16 [-0.71, 0.40]
Lui SL (2012)	3.24	1.98	77	2.88	2.43	73	18.1%	0.16 [-0.16, 0.48]
Park (2012)	2.9	3.1	64	2.9	2.3	47	13.1%	0.00 [-0.38, 0.38]
Szeto (2007)	2.72	2.08	25	2.81	2.87	25	6.0%	-0.04 [-0.59, 0.52]
Weiss (2009)	4.77	3.78	15	4.1	2.8	11	3.1%	0.19 [-0.59, 0.97]
Total (95% CI)			**439**			**404**	**100.0%**	**0.15 [0.01, 0.29]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.91$, df = 12 (P = 0.96); $I^2 = 0\%$

Test for overall effect: Z = 2.14 (P = 0.03)



Yohanna…. Jain et al unpublished

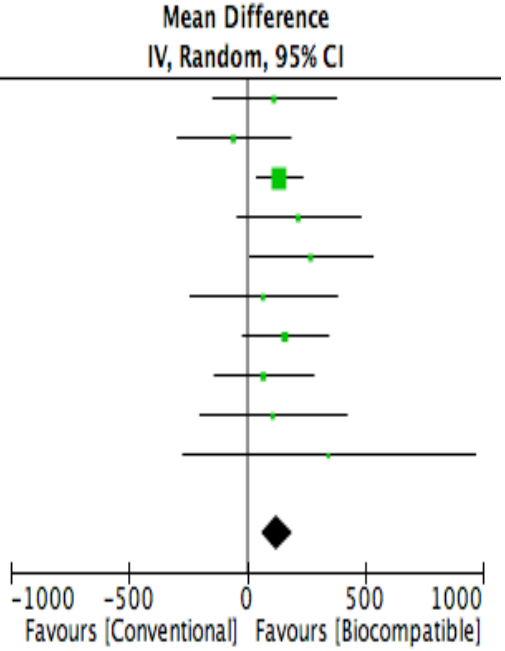
Impact on Urine Volume

All Durations of follow-up

Study or Subgroup	Biocompatible Mean	SD	Total	Conventional Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
balANZ 2012	814	624	42	699	639	48	6.0%	115.00 [-146.33, 376.33]
Cho (2013)	624.7	487.7	32	681.8	460.1	28	7.2%	-57.10 [-297.09, 182.89]
Choi HY (2008)	280	236.6	38	143.7	172.9	30	43.4%	136.30 [38.90, 233.70]
Kim SG (2008)	751	679	36	533	408	33	6.0%	218.00 [-43.87, 479.87]
Lai KN (2012)	745.7	819.2	58	475.1	636	67	6.1%	270.60 [10.52, 530.68]
Le Poole (2005)	846	536	28	777	649	28	4.2%	69.00 [-242.77, 380.77]
Lui SL (2012)	959	515	77	798	615	73	12.4%	161.00 [-21.03, 343.03]
Park (2012)	714	537	64	644	575	47	9.3%	70.00 [-140.55, 280.55]
Szeto (2007)	800	600	25	690	520	25	4.3%	110.00 [-201.23, 421.23]
Weiss (2009)	1,346.1	870.8	15	1,000.6	770	12	1.1%	345.50 [-274.17, 965.17]
Total (95% CI)			**415**			**391**	**100.0%**	**129.45 [65.27, 193.64]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.97$, df = 9 (P = 0.84); $I^2 = 0\%$

Test for overall effect: Z = 3.95 (P < 0.0001)

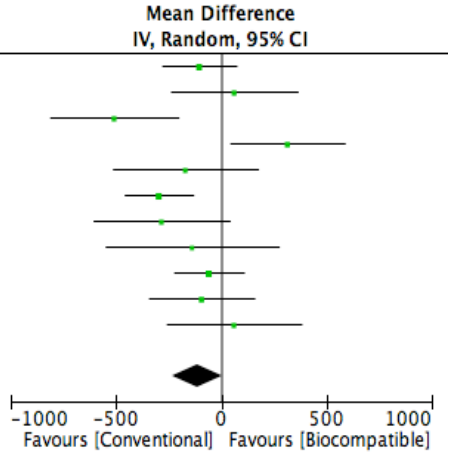


Yohanna…. Jain et al unpublished

Impact on Peritoneal Ultrafiltration

Study or Subgroup	Biocompatible Mean	SD	Total	Conventional Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bajo MA (2011)	720	195	9	825	106	3	12.1%	-105.00 [-279.98, 69.98]
balANZ 2012	1,070	689	42	1,009	762	48	8.1%	61.00 [-238.81, 360.81]
Cho (2013)	790.3	692.6	32	1,299.6	501.2	28	8.0%	-509.30 [-812.70, -205.90]
Choi HY (2008)	1,301	597.6	38	987.1	538.8	30	9.0%	313.90 [43.21, 584.59]
Fernandez-Perpen (2012)	654	367	5	825	106	3	7.0%	-171.00 [-514.32, 172.32]
Kim SG (2008)	750	350	36	1,047	334	33	12.6%	-297.00 [-458.42, -135.58]
Lai KN (2012)	540	820.4	58	824.3	1,015.8	67	7.6%	-284.30 [-606.39, 37.79]
Le Poole (2005)	1,126	817	24	1,265	645	26	5.7%	-139.00 [-549.25, 271.25]
Lui SL (2012)	336	483	77	395	542	73	12.5%	-59.00 [-223.61, 105.61]
Park (2012)	845	633	64	939	683	47	9.6%	-94.00 [-343.36, 155.36]
Szeto (2007)	830	560	25	770	590	25	7.6%	60.00 [-258.87, 378.87]
Total (95% CI)			**410**			**383**	**100.0%**	**-111.38 [-232.37, 9.60]**

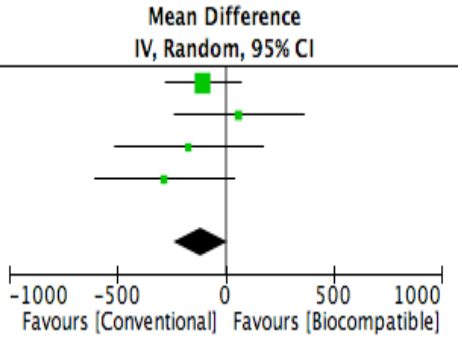
Heterogeneity: $Tau^2 = 23393.02$; $Chi^2 = 25.13$, df = 10 (P = 0.005); $I^2 = 60\%$
Test for overall effect: Z = 1.80 (P = 0.07)



All Durations

Study or Subgroup	Biocompatible Mean	SD	Total	Conventional Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bajo MA (2011)	720	195	9	825	106	3	52.8%	-105.00 [-279.98, 69.98]
balANZ 2012	1,070	689	42	1,009	762	48	18.0%	61.00 [-238.81, 360.81]
Fernandez-Perpen (2012)	654	367	5	825	106	3	13.7%	-171.00 [-514.32, 172.32]
Lai KN (2012)	540.7	824	58	824.3	1,015.8	67	15.5%	-283.60 [-606.29, 39.09]
Total (95% CI)			**114**			**121**	**100.0%**	**-111.92 [-239.05, 15.21]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.48$, df = 3 (P = 0.48); $I^2 = 0\%$
Test for overall effect: Z = 1.73 (P = 0.08)



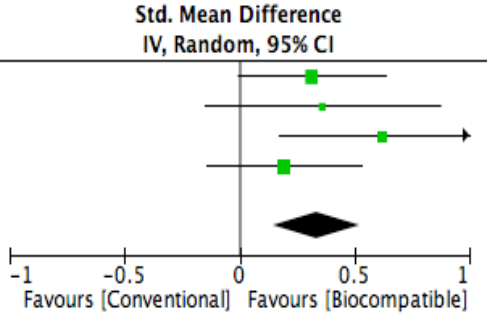
Greater than 12 months duration

Yohanna…. Jain et al unpublished

Impact on Transport Status (D/P cr)

Study or Subgroup	Biocompatible Mean	SD	Total	Conventional Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
balANZ 2012	0.67	0.1	76	0.64	0.09	75	35.7%	0.31 [-0.01, 0.63]
Cho (2013)	0.67	0.13	32	0.63	0.08	28	14.1%	0.36 [-0.15, 0.87]
Kim SG (2008)	0.71	0.08	41	0.65	0.11	39	18.2%	0.62 [0.17, 1.07]
Lui SL (2012)	0.75	0.18	72	0.72	0.12	63	32.0%	0.19 [-0.15, 0.53]
Total (95% CI)			**221**			**205**	**100.0%**	**0.34 [0.15, 0.53]**

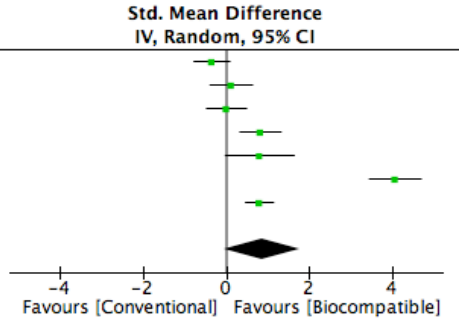
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.25$, df = 3 (P = 0.52); $I^2 = 0\%$
Test for overall effect: Z = 3.45 (P = 0.0006)



< 12 months Durations

Study or Subgroup	Biocompatible Mean	SD	Total	Conventional Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
balANZ 2012	0.67	0.09	37	0.7	0.08	50	14.6%	-0.35 [-0.78, 0.08]
Cho (2013)	0.67	0.09	32	0.66	0.08	28	14.4%	0.12 [-0.39, 0.62]
Choi HY (2008)	0.66	0.1	38	0.66	0.11	30	14.4%	0.00 [-0.48, 0.48]
Kim SG (2008)	0.72	0.11	36	0.64	0.08	33	14.4%	0.82 [0.32, 1.31]
Kim YL (2003)	0.66	0.02	16	0.64	0.03	10	13.4%	0.80 [-0.03, 1.62]
Lai KN (2012)	0.71	0.013	58	0.65	0.016	67	14.1%	4.06 [3.44, 4.68]
Lui SL (2012)	0.78	0.13	77	0.68	0.12	73	14.7%	0.79 [0.46, 1.13]
Total (95% CI)			**294**			**291**	**100.0%**	**0.88 [-0.04, 1.80]**

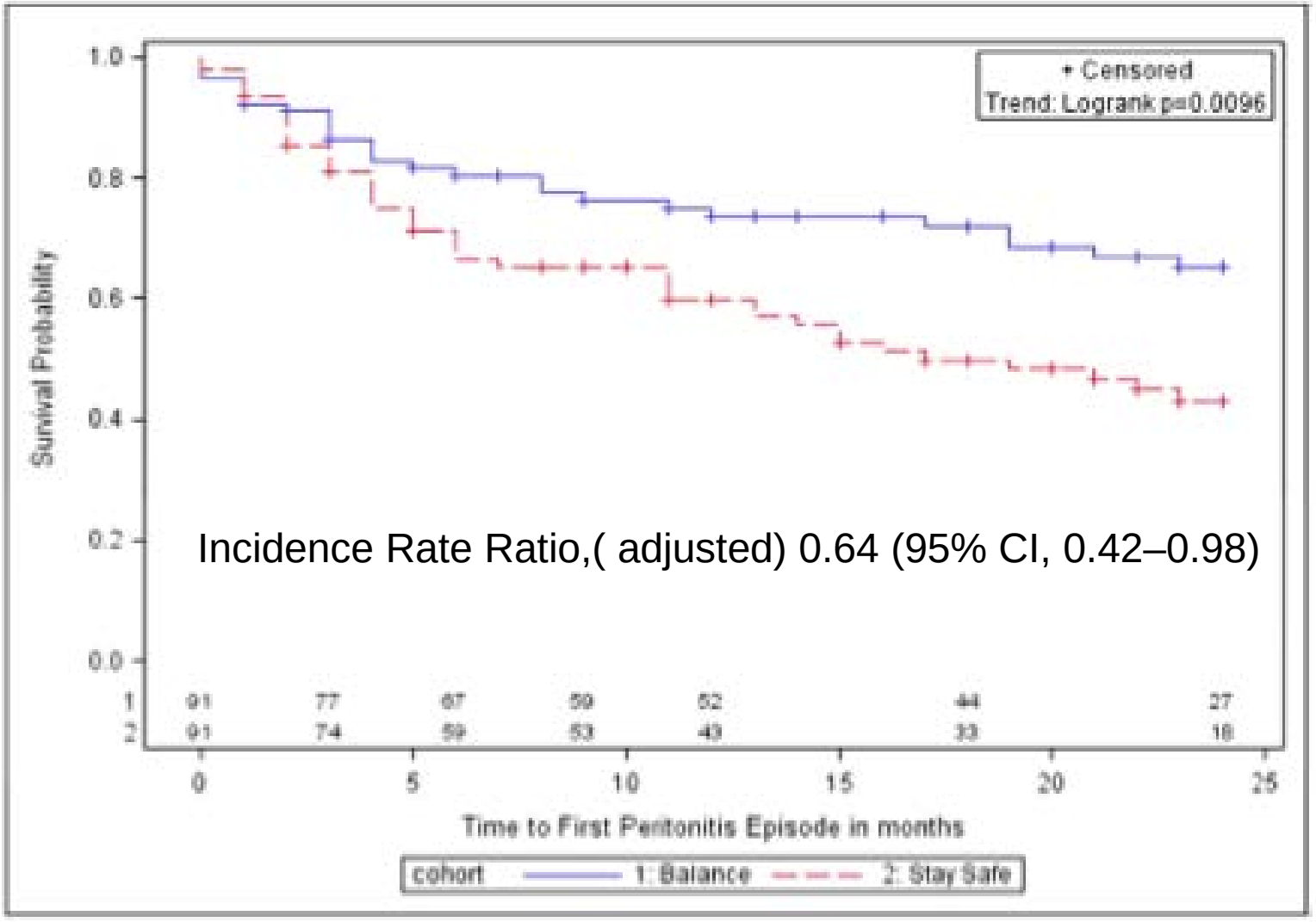
Heterogeneity: $Tau^2 = 1.47$; $Chi^2 = 149.61$, df = 6 (P < 0.00001); $I^2 = 96\%$
Test for overall effect: Z = 1.87 (P = 0.06)



>12 months duration

Yohanna…. Jain et al unpublished

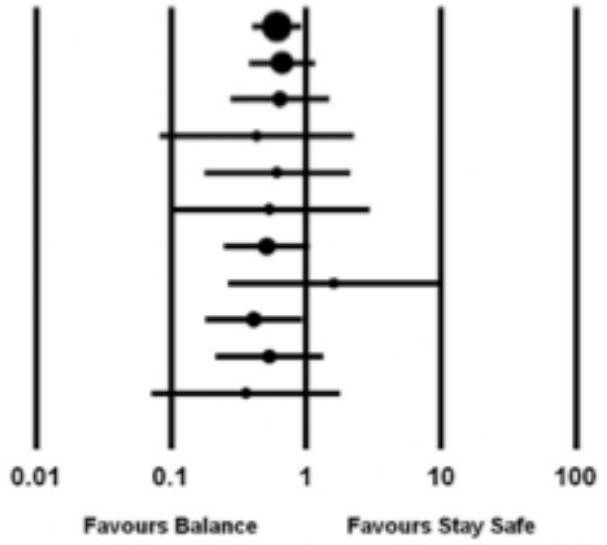
Secondary Outcome: Time To First Peritonitis



Incidence Rate Ratio,(adjusted) 0.64 (95% CI, 0.42–0.98)

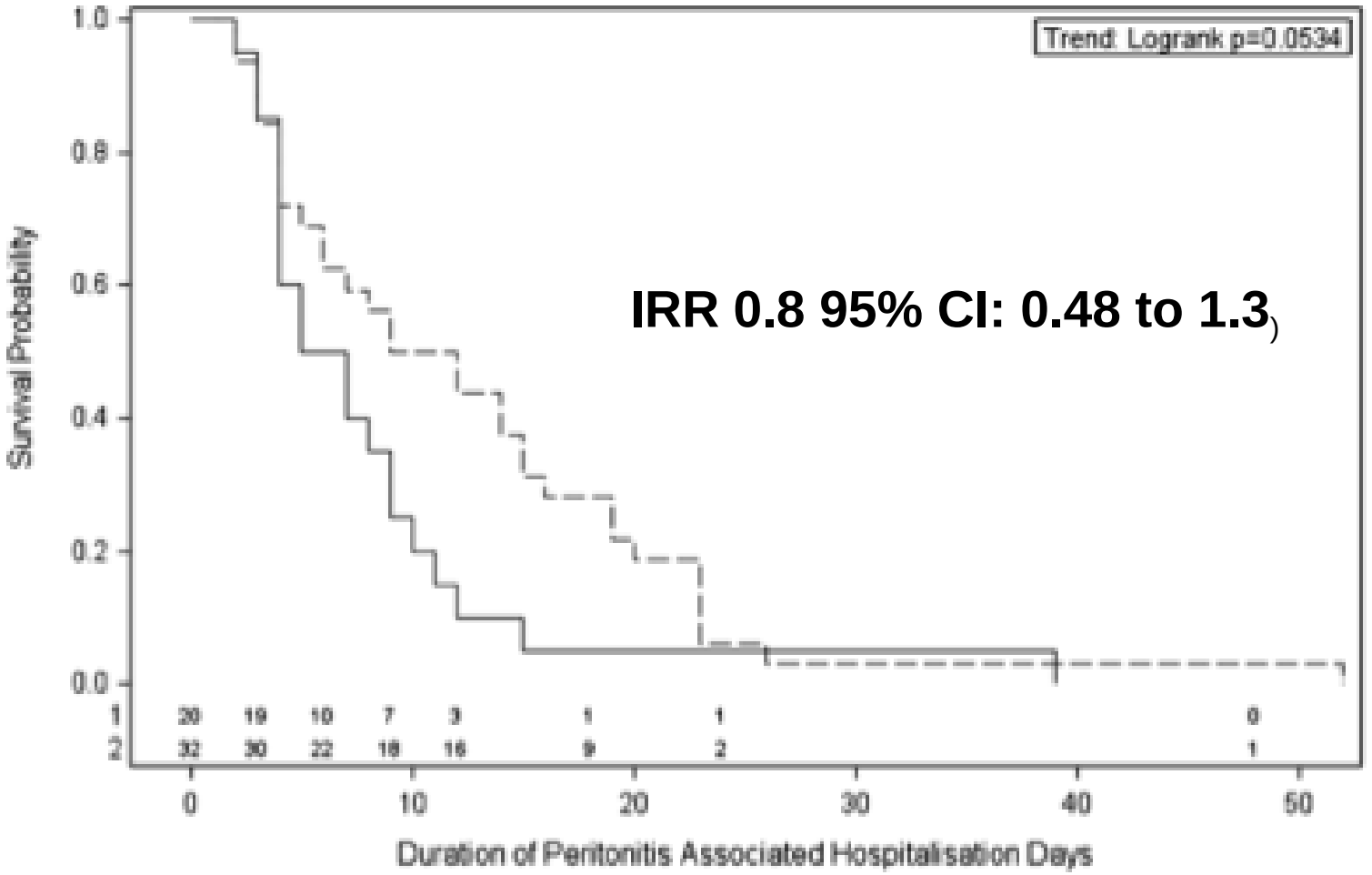
Peritonitis By Organism

Study name	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
All peritonitis	0.608	0.408	0.905	-2.453	0.014
Gram Positive: All	0.662	0.384	1.140	-1.488	0.137
Gram Positive: CNS	0.643	0.281	1.469	-1.048	0.295
Gram Positive: S.Aureus	0.429	0.083	2.209	-1.013	0.311
Gram Positive: Streptococcus	0.612	0.179	2.091	-0.783	0.434
Gram Positive: Other	0.536	0.098	2.924	-0.721	0.471
Gram Negative: All	0.512	0.250	1.051	-1.824	0.068
Gram Negative: Pseudomonas	1.607	0.269	9.617	0.520	0.603
Gram Negative: Non-psuedomonas	0.408	0.181	0.921	-2.157	0.031
Culture negative	0.536	0.216	1.327	-1.349	0.177
Polymicrobial	0.357	0.072	1.769	-1.261	0.207



Johnson et al PDI 2012

Peritonitis Severity



61% of peritonitis episodes hospitalized in each group!!!

Johnson et al PDI 2012

Peritonitis Severity

Rating of Peritonitis Severity By Clinician

	Biocompatible	Control
Mild	14	7
Moderate	17	52
Severe	7	8

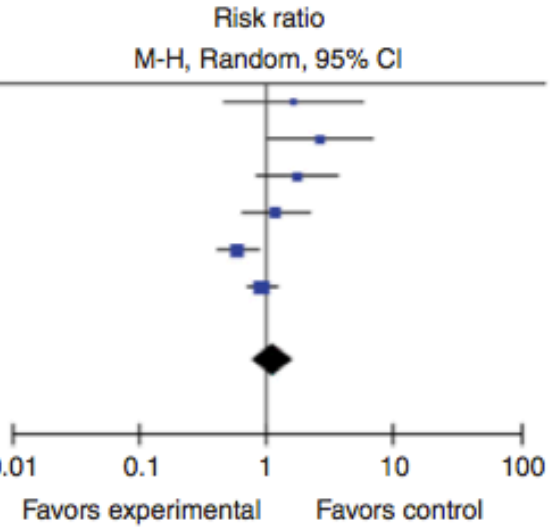
Johnson et al PDI 2012

Peritonitis: Results o A Meta-Analysis

Study or subgroup	Neutral-pH, low-GDP Events	Total	Standard glucose Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Coles *et al.*, 1998	10	109	3	54	7.2%	1.65 (0.47, 5.75)
Kim *et al.*, 2009	14	689	6	789	10.6%	2.67 (1.03, 6.92)
Bajo *et al.*, 2011	18	281	12	330	14.9%	1.76 (0.86, 3.59)
Rippe *et al.*, 2001	25	541	17	437	17.4%	1.19 (0.65, 2.17)
BalANZ trial	38	1528	67	1637	23.1%	0.61 (0.41, 0.90)
Fan *et al.*, 2008	117	3942	110	3465	26.8%	0.93 (0.72, 1.21)
Total (95% CI)		7090		6712	100.0%	1.13 (0.77, 1.66)
Total events	222		215			

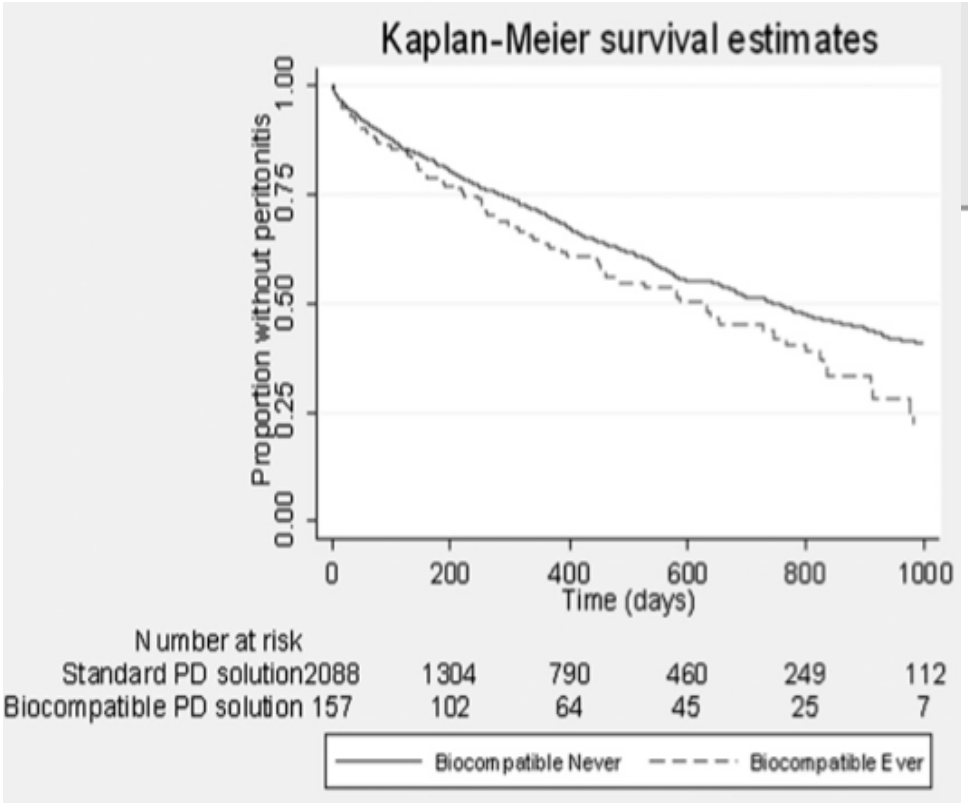
Heterogeneity: $\tau^2 = 0.13$; $\chi^2 = 13.71$, d.f. = 5 ($P = 0.02$); $I^2 = 64\%$

Test for overall effect: $Z = 0.62$ ($P = 0.54$)



Cho et al KI 2013

Peritonitis: Observational Data



Model	Time to First Peritonitis	
	HR (95% CI)	*P* Value
Unadjusted	1.33 (1.05 to 1.67)	0.02
Adjusted[a]	1.48 (1.17 to 1.87)	0.001
Unadjusted + PS	1.38 (1.09 to 1.74)	0.007
Unadjusted + PS in quintiles	1.37 (1.09 to 1.74)	0.007
Unadjusted in PS-matched cohorts (*n*=2242)	1.36 (1.09 to 1.71)	0.007
Unadjusted in 1:1 PS-matched cohorts (*n*=312)	1.38 (0.97 to 1.95)	0.07
Competing risk regression[a]	1.32[b] (1.06 to 1.65)	0.007

Cho et al CJASN 2013

Other Outcomes: Results of Meta-Analysis

Outcomes	No. of participants (no. of studies)	Relative effect (95% CI)	Quality of the evidence (GRADE)	Study limitations applicable to measured outcome (no. of studies)	Comments
Residual renal function (renal creatinine clearance, glomerular filtration rate)	564 (11)	SMD 0.16 (−0.01 to 0.32)	Moderate	Inadequate random sequence generation/allocation concealment (3) >20% loss to follow-up (8) Presence of other significant bias (4)	Benefit reached statistical significance once treatment duration exceeded 12 months.
Urine volume (ml/day)	520 (7)	MD 126.39 (26.73 to 226.05)	Moderate	Inadequate random sequence generation/allocation concealment (1) >20% loss to follow-up (4) Presence of other significant bias (2)	Benefit was greater with longer treatment duration (i.e., greater than 12 months)
Peritoneal ultrafiltration 4 h (ml per 4 h)	196 (6)	SMD −0.28 (−0.67 to 0.10)	Moderate	Inadequate random sequence generation/allocation concealment (2) >20% loss to follow-up (5) Presence of other significant bias (3)	
Daily peritoneal ultrafiltration (ml/day; ml/day/m^2)	451 (7)	SMD −0.23 (−0.62 to 0.16)	Very low	Inadequate random sequence generation/allocation concealment (1) >20% loss to follow-up (4) Presence of other significant bias (1)	Unclear disclosure on use of 7.5% icodextrin between groups and prescribed glucose load.
Body weight (kg)	252 (3)	MD −0.59 (−4.47 to 3.29)	Moderate	>20% loss to follow-up (2) Presence of other significant bias (1)	
Peritoneal solute transport rate (4 h dialysate: peritoneal creatinine)	363 (5)	MD 0.01 (−0.02 to 0.04)	Moderate	Inadequate random sequence generation/allocation concealment (1) >20% loss to follow-up (3)	
Peritoneal small-solute clearance					
a. Creatinine clearance (l/week per 1.73 m^2)	400 (6)	MD −0.25 (−2.05 to 1.55)	Moderate	Inadequate random sequence generation/allocation concealment (1) >20% loss to follow-up (4) Presence of other significant bias (1)	
b. Kt/V urea	312 (5)	MD 0.00 (−0.10 to 0.11)	Moderate	Inadequate random sequence generation/allocation concealment (1) >20% loss to follow-up (4) Presence of other significant bias (1)	
Peritonitis rate (no. of episodes/total patient-months)	13 802 months (6)	RR 1.13 (0.77 to 1.66)	Low	Inadequate random sequence generation/allocation concealment (1) >20% loss to follow-up (5) Presence of other significant bias (2)	High risk of attrition bias in the majority of trials included in analyses.
Inflow pain	58 (1)	RR 0.51 (0.24 to 1.08)	Low	Lack of blinding—participants/assessors (1) >20% loss to follow-up (1)	One double-blind trial[29] included in the review (but not meta-analyzed) observed less inflow pain with the use of neutral-pH, low-GDP PD solutions.
Hospitalization (no. of days)	230 (2)	MD 3 (−7.08 to 13.12)	Moderate		
Technique failure (death-censored)	968 (12)	RR 1.04 (0.60 to 1.78)	Very low	Inadequate random sequence generation/allocation concealment (3) >20% loss to follow-up (8) Presence of other significant bias (4)	None of the trials were adequately powered. Number after combining trials remained too small to accurately assess this outcome.
Patient survival	858 (11)	RR 0.78 (0.48 to 1.29)	Very low	Inadequate random sequence generation/allocation concealment (3) >20% loss to follow-up (7) Presence of other significant bias (4)	None of the trials were adequately powered. Number after combining trials remained too small to accurately assess this outcome.

J Am Soc Nephrol 14: 2948–2957, 2003

Survival of Functionally Anuric Patients on Automated Peritoneal Dialysis: The European APD Outcome Study

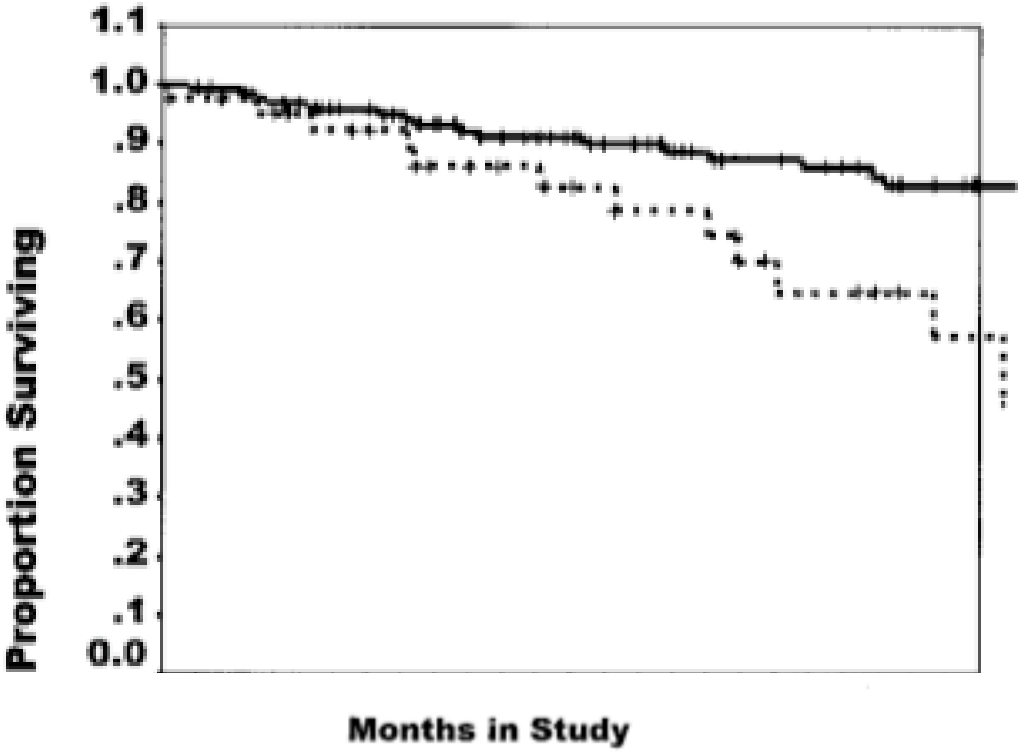


Figure 3. Kaplan Meier patient survival according to baseline UF of >750 ml/d (▤) and <750 ml/d (▪▪▪); $P = 0.0048$.

UF failure second most common cause of transfer to hemodialysis

No adverse metabolic consequences with absorption

No alteration of peritoneal host defences

What does "biocompatibility" mean to you

No long term alterations in peritoneal membrane function with use

If absorbed, may yield positive nutritional, metabolic effects

No induction of peritoneal and systemic inflammation

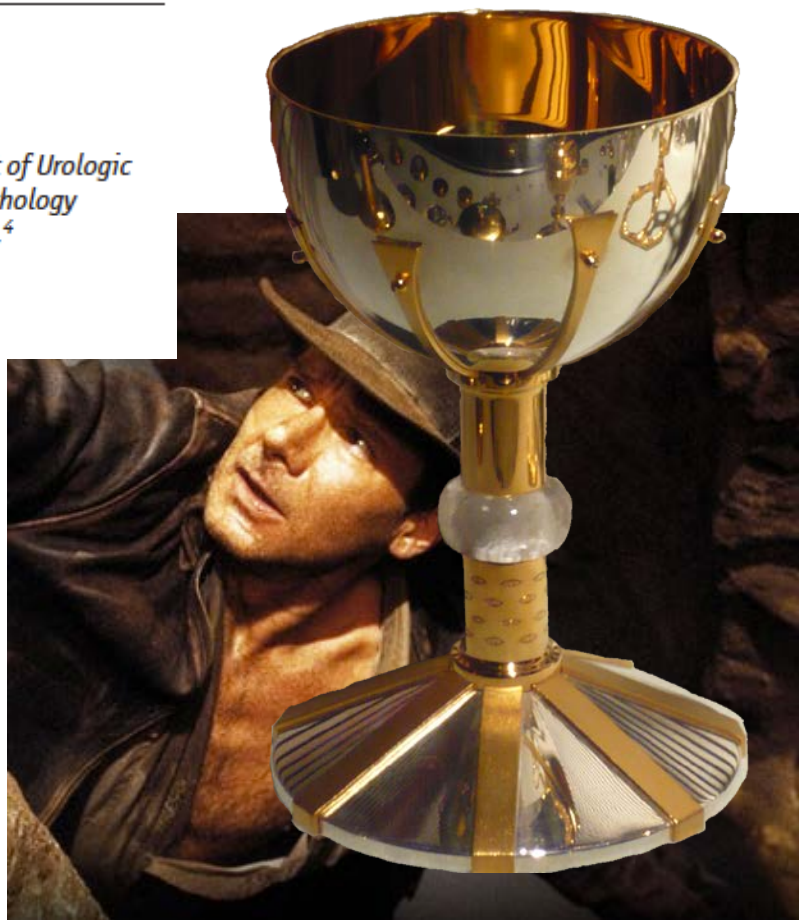
Delivers prolonged and sustained ultrafiltration sodium removal and solute clearance (middle and small molecules)

We Are Still Searching For The Holy Grail

HYPERBRANCHED POLYGLYCEROL IS AN EFFICACIOUS AND BIOCOMPATIBLE NOVEL OSMOTIC AGENT IN A RODENT MODEL OF PERITONEAL DIALYSIS

Asher A. Mendelson,[1] Qiunong Guan,[2] Irina Chafeeva,[3] Gerald A. da Roza,[1]
Jayachandran N. Kizhakkedathu,[3,4] and Caigan Du[2,5]

Division of Nephrology,[1] Department of Medicine, University of British Columbia; Department of Urologic Sciences,[2] University of British Columbia; Centre for Blood Research,[3] Department of Pathology and Laboratory Medicine, University of British Columbia; Department of Chemistry,[4] University of British Columbia; and Immunity and Infection Research Centre,[5] Vancouver Coastal Health Research Institute, Vancouver, British Columbia, Canada



Be Cautious of Unintended Consequences With New Technology: Thank you!