Universitair Ziekenhuis Gent

UNIVERSITEIT GENT

AN UPDATE ON UREMIC TOXINS

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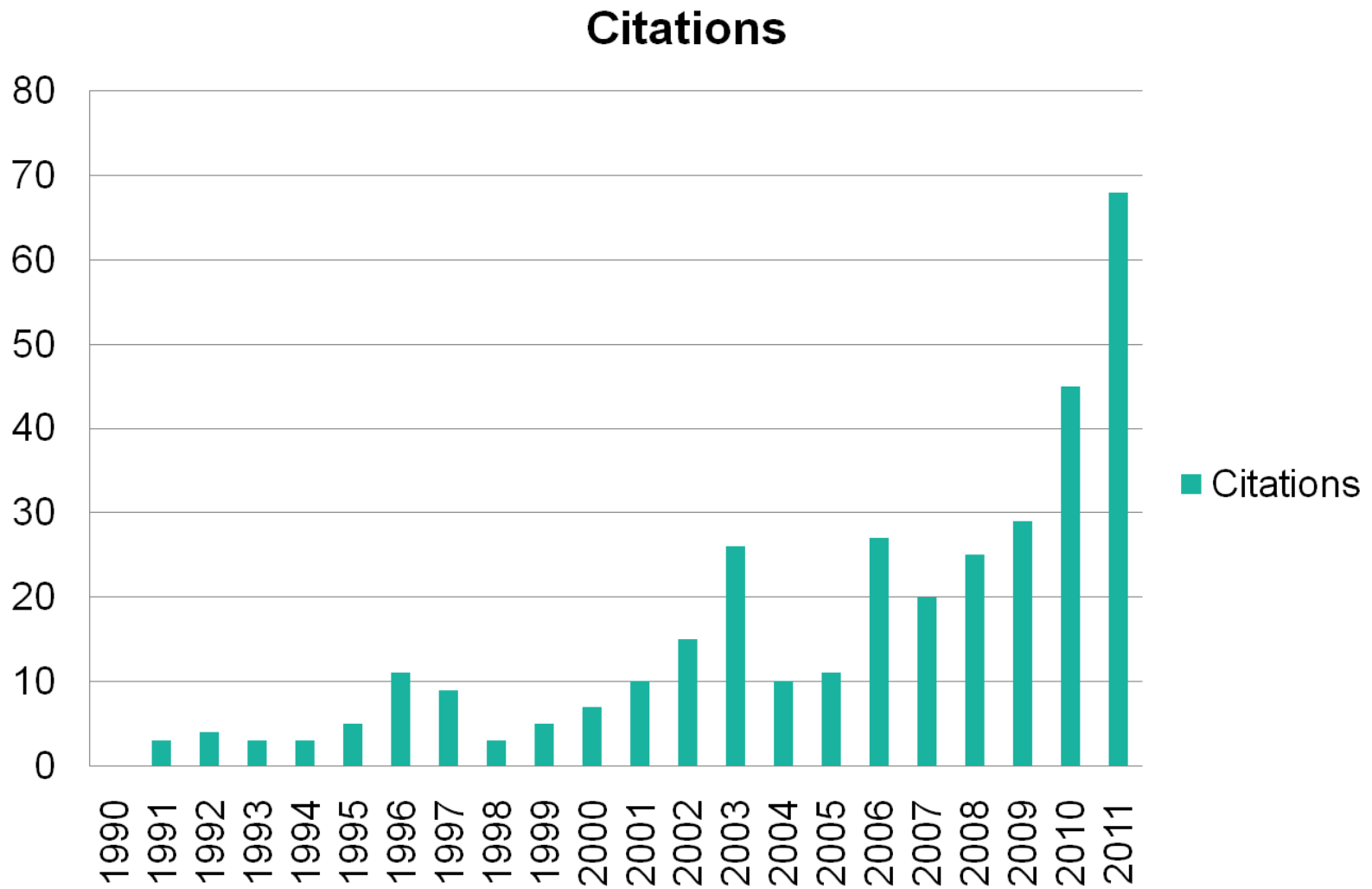
Indoxyl sulfate

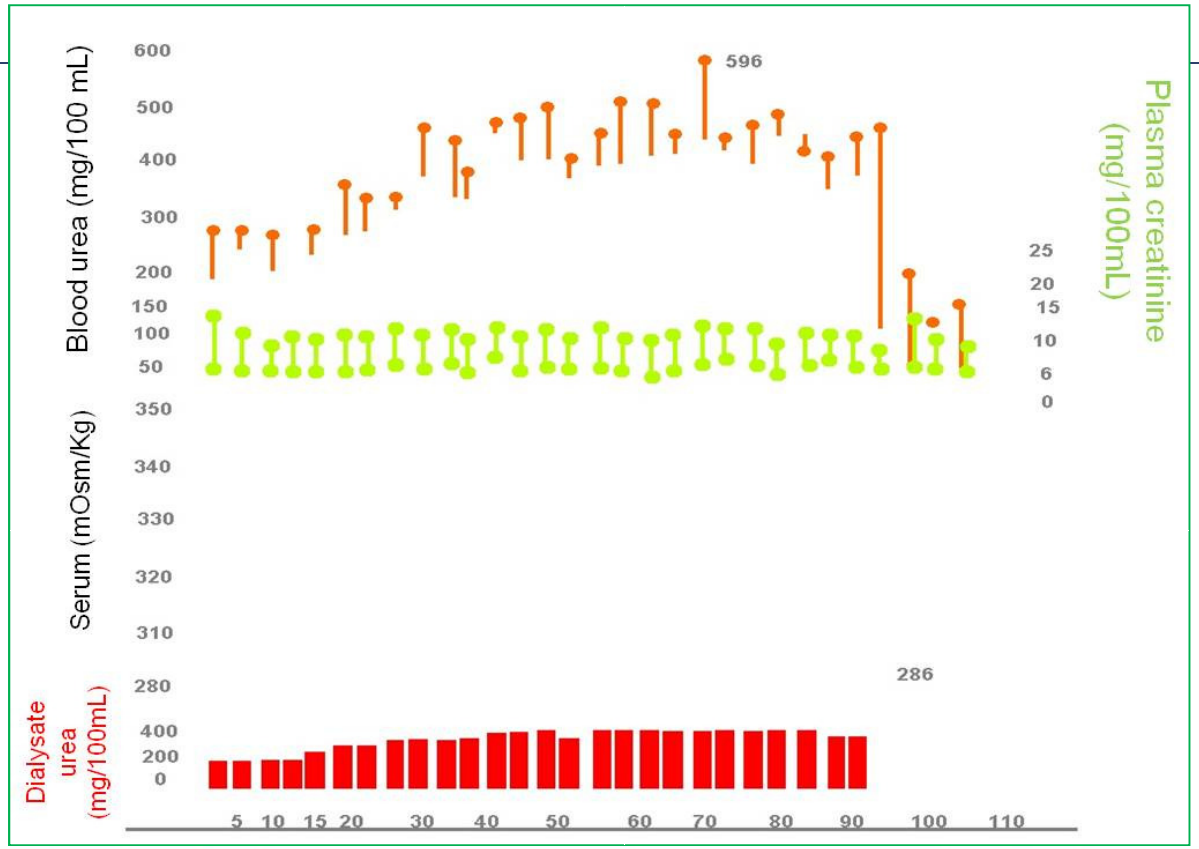


TOPICS

- The small water soluble compounds
- The middle molecules
- The protein-bound molecules

- In vitro studies
- In vivo studies
- Outcome studies

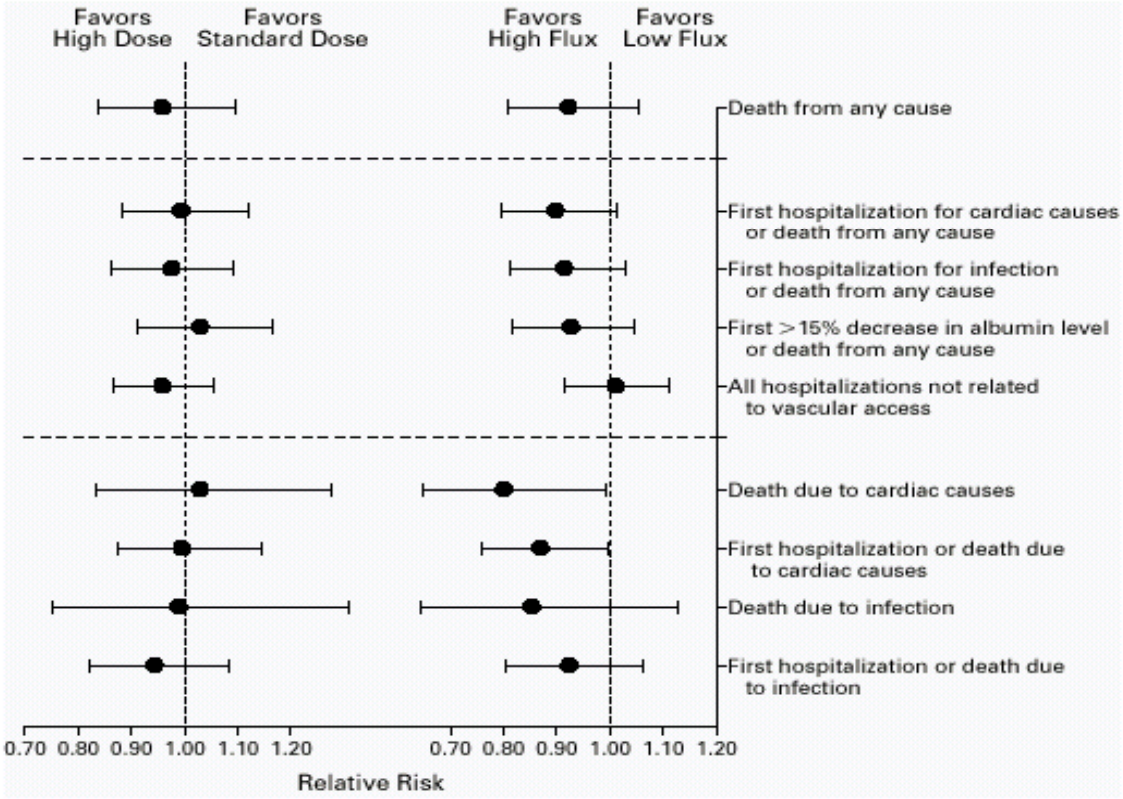
EFFECT OF INCREASING DIALYSATE UREA



Lethargy	+	+	0	0	0	0	0	0	+	+	+	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Headache	3+	3+	0	0	0	1+	1+	2+	0	1+	0	2+	0	0	2+	1+	1+	2+	1+	1+	1+	1+	1+	1+	0	3+	1+	1+	0	0
Emesis	0	0	0	0	1+	0	2+	1+	1+	1+	0	2+	0	0	2+	1+	2+	2+	2+	2+	2+	0	0	0	0	2+	2+	1+	0	0
Bleeding	0	2+	2+	2+	0	1+	1+	1+	1+	1+	2+	2+	1+	0	0	1+	1+	1+	1+	0	0	0	0	0	0	0	1+	0	0	0
Cramps	0	0	0	0	0	0	0	0	0	1+	0	0	0	0	0	0	0	1+	1+	1+	0	1+	0	0	0	0	0	0	0	0
Tremor	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2+	0	0	0

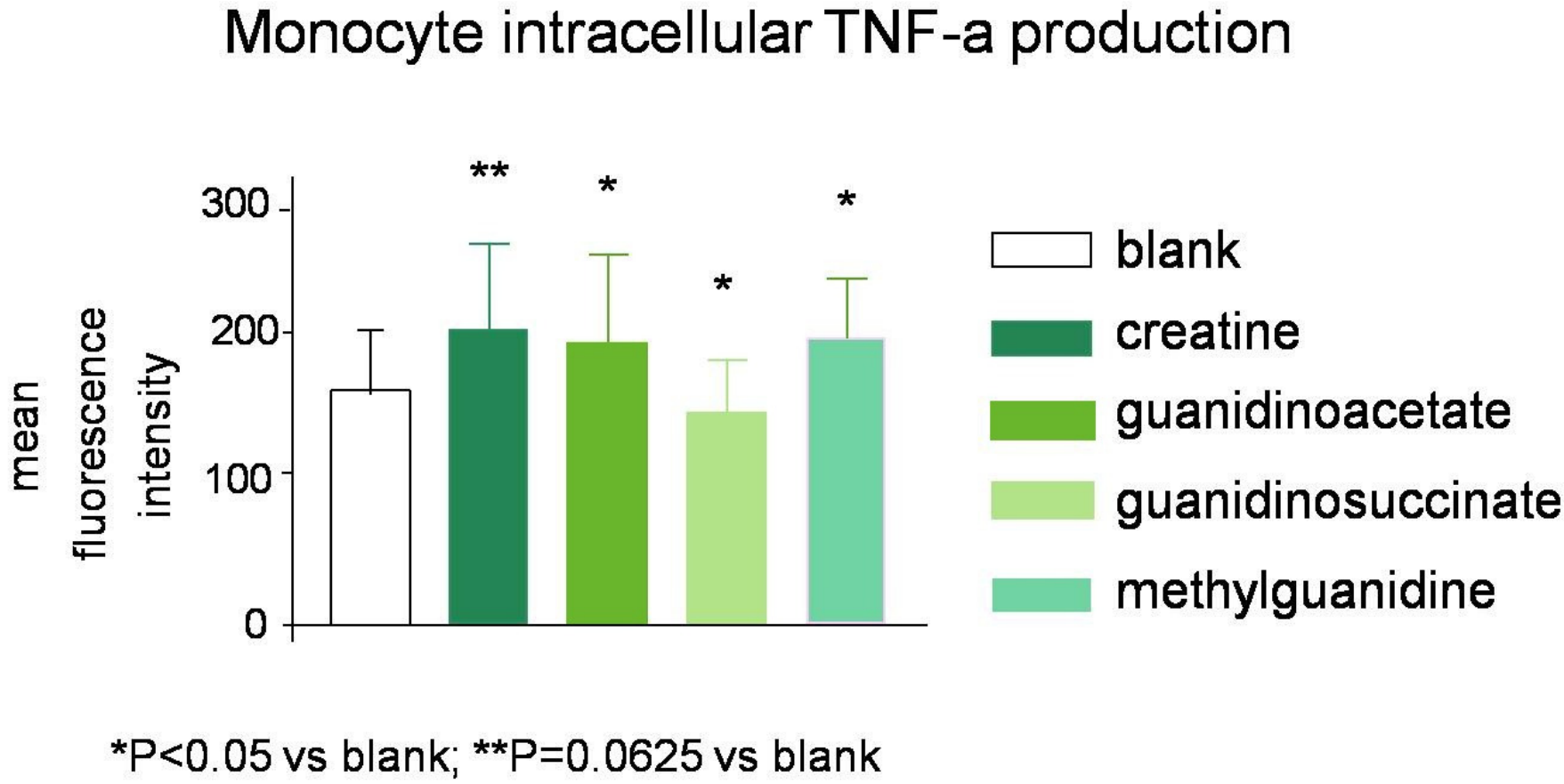
Johnson et al, Mayo Clin. Proc., 47: 21-29; 1972

HEMO-STUDY: PRIMARY AND SECONDARY OUTCOMES



Eknoyan et al, NEJM, 25: 2010-2019; 2002

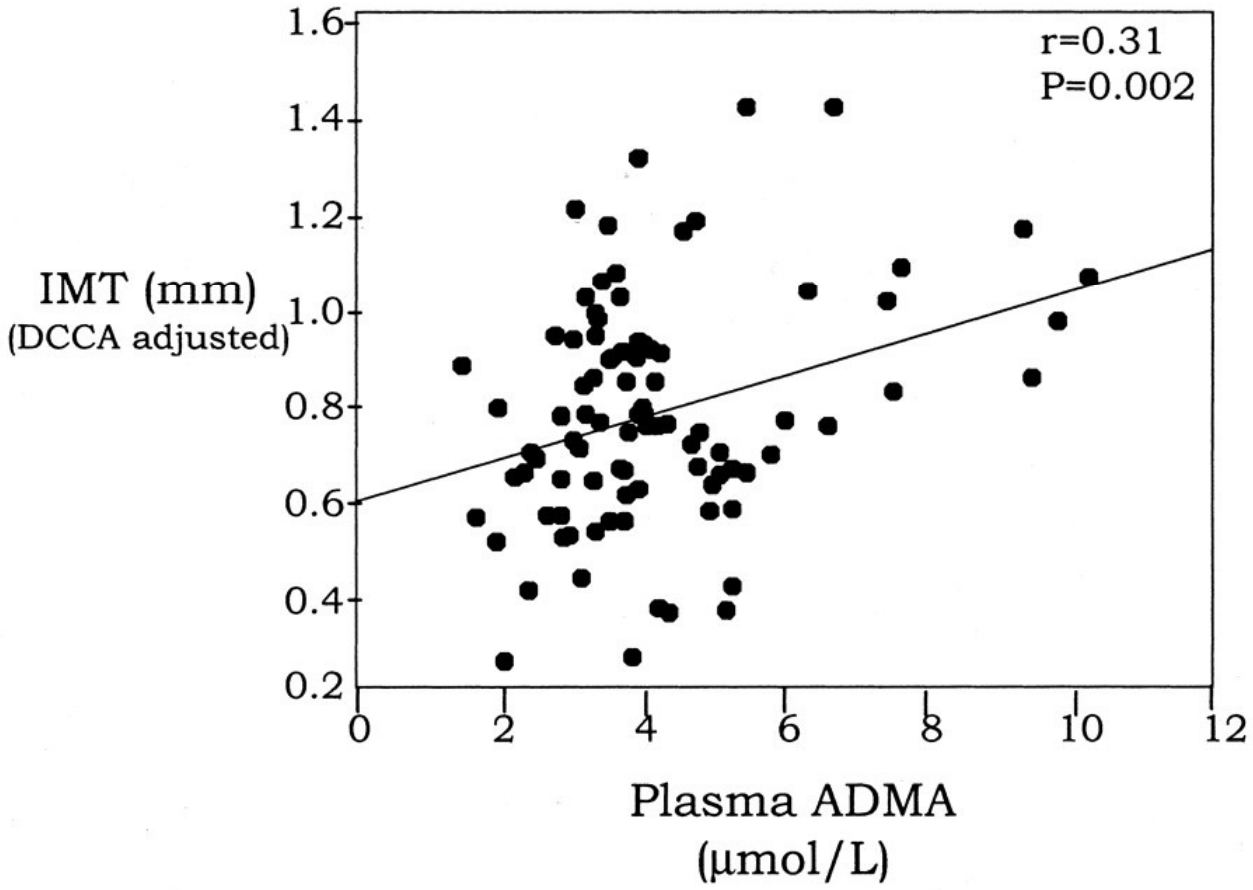
GUANIDINES AND LEUKOCYTE FUNCTION



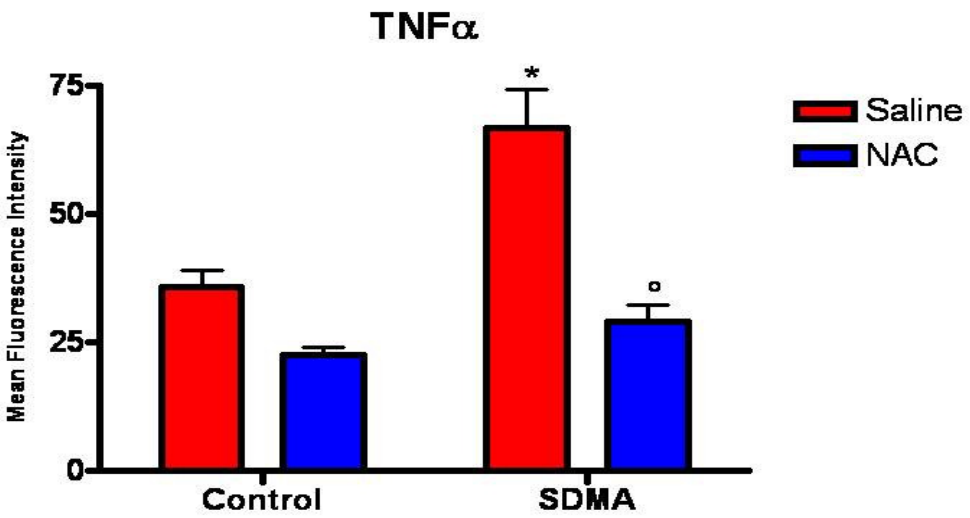
*P<0.05 vs blank; **P=0.0625 vs blank

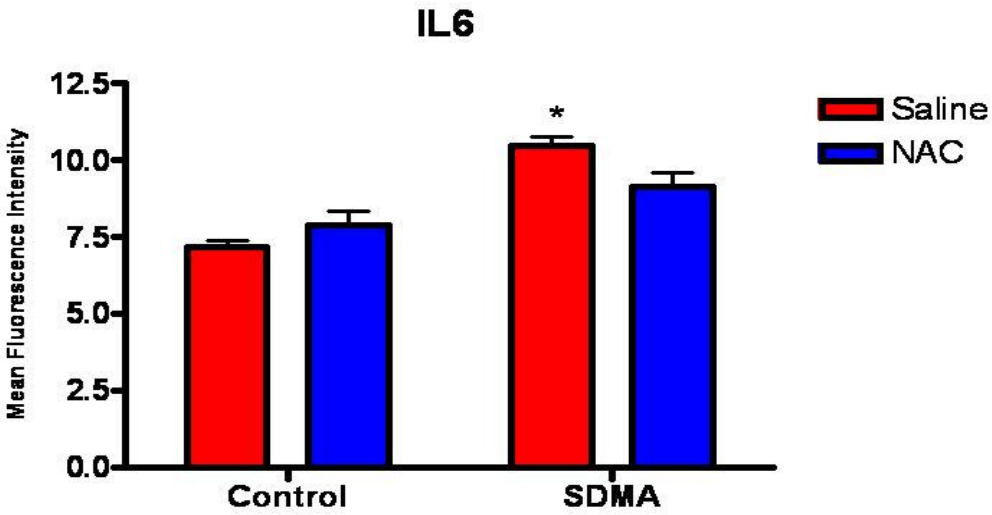
Glorieux et al, KI, 65: 2184-2192; 2004

ADMA AND INTIMA-MEDIA THICKNESS



Zoccali et al, JASN, 13 490-496, 2002





Schepers et al, cJASN, 6, 2374- 2383, 2011

Linear regression analysis – variables associated with the serum levels of SDMA and ADMA

	SDMA			ADMA		
	R^2	Difference (95%CI)	P	R^2	Difference (95%CI)	P
EPO use	0.35	0.35 (0.31-0.80)	<0.0001			
CKD Stage	0.32	0.52 (0.40 - 0.65)	<0.0001	0.11	0.06 (0.03 - 0.09)	<0.0001
Hemoglobin	0.11	-0.15 (-0.22 - -0.08)	<0.0001	0.04	-0.02 (-0.03- - 0.00)	0.02
Ln-normalized TNF-α	0.10	0.57 (0.28 - 0.87)	<0.0001	0.06	0.08 (0.02 - 0.14)	0.006
Ln-normalized IL-6	0.10	0.23 (0.11 - 0.36)	<0.0001	0.06	0.03 (0.01 - 0.06)	0.009
Phosphate	0.080	0.48 (0.21 - 0.75)	0.001	0.08	0.10 (0.04 - 0.15)	<0.0001
Albumin	0.07	-0.03 (-0.05 - -0.01)	0.001	0.03	-0.004 (-0.01 - 0.00)	0.03
Iron Use	0.06	0.23 (0.13 - 0.72)	0.005			
Body Mass Index	0.05	-0.03 (-0.05 - -0.01)	0.01			
Statin use	0.04	-0.30 (-0.56 - -0.04)	0.02	0.03	-0.06 (-0.11 - - 0.01)	0.03

Schepers et al, cJASN, 6, 2374- 2383, 2011

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Schepers et al, cJASN, 6, 2374- 2383, 2011

COMPARTMENTALISATION GUANIDINES

Compound	V	Eff Rem
Urea	42.7±6.0	67±4
Creatine	98.0±52.3*	42±16*
Creatinine	54.0±5.9*	58±6*
Guanidino acetic acid	123.8±66.9*	37±14*
Guanidine	89.7±21.4*	43±7*
Methylguanidine	102.6±33.9*	42±12*

*: $p<0.05$; V: distribution volume (L); Eff Rem: effective removal (%)

Eloot et al, KI, 67: 1566-1575; 2005

CONCLUSION / SMALL WATER SOLUBLE MOLECULES

- Uremia and the uremic syndrome are the consequence of the retention of more molecules than urea alone
- When analyzing and optimizing uremic retention solute removal, one should analyze and optimize more than urea removal alone

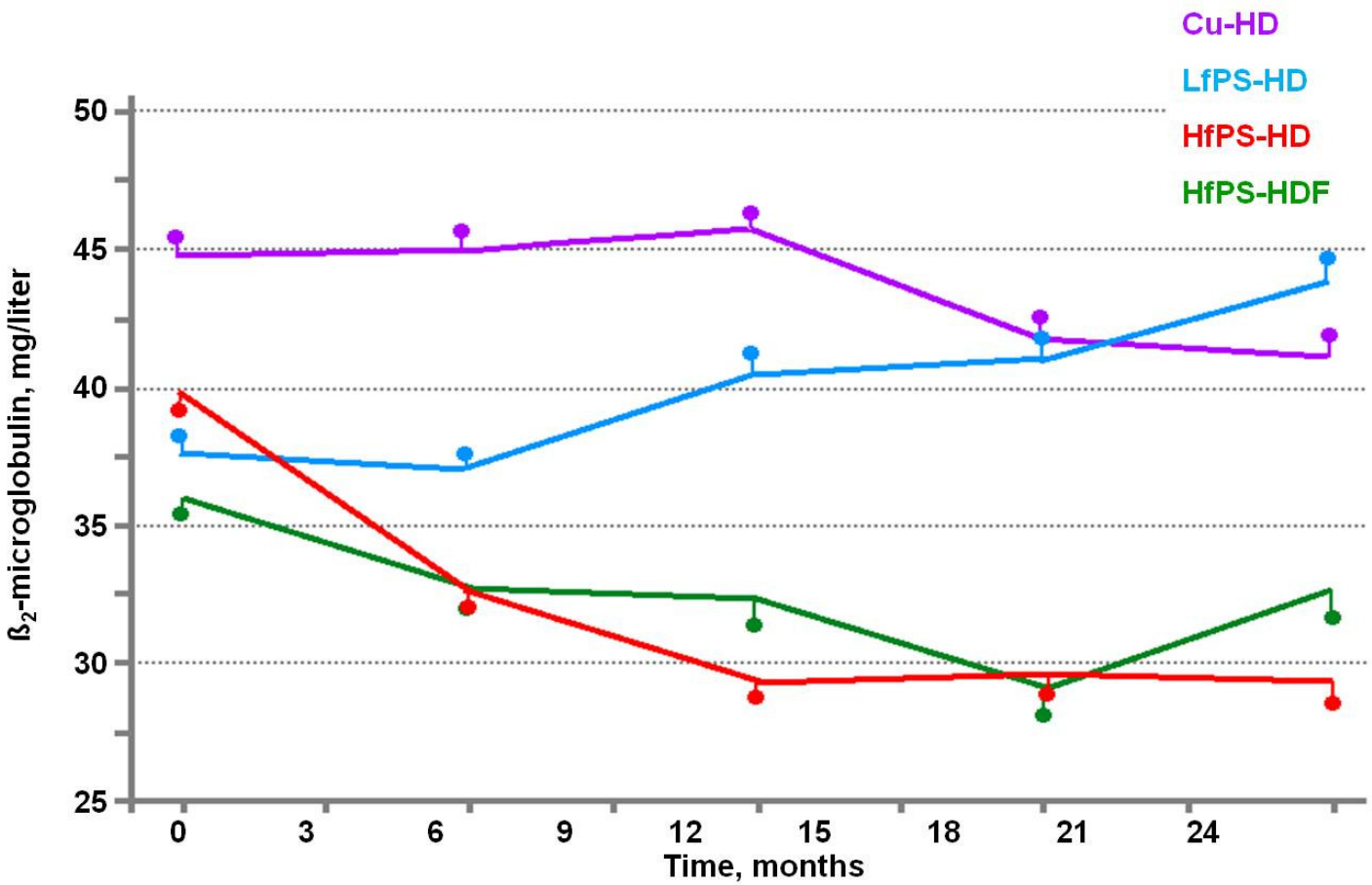
TOPICS

- The small water soluble compounds
- The middle molecules
- The protein-bound molecules

MM WITH BIOLOGICAL POTENTIAL

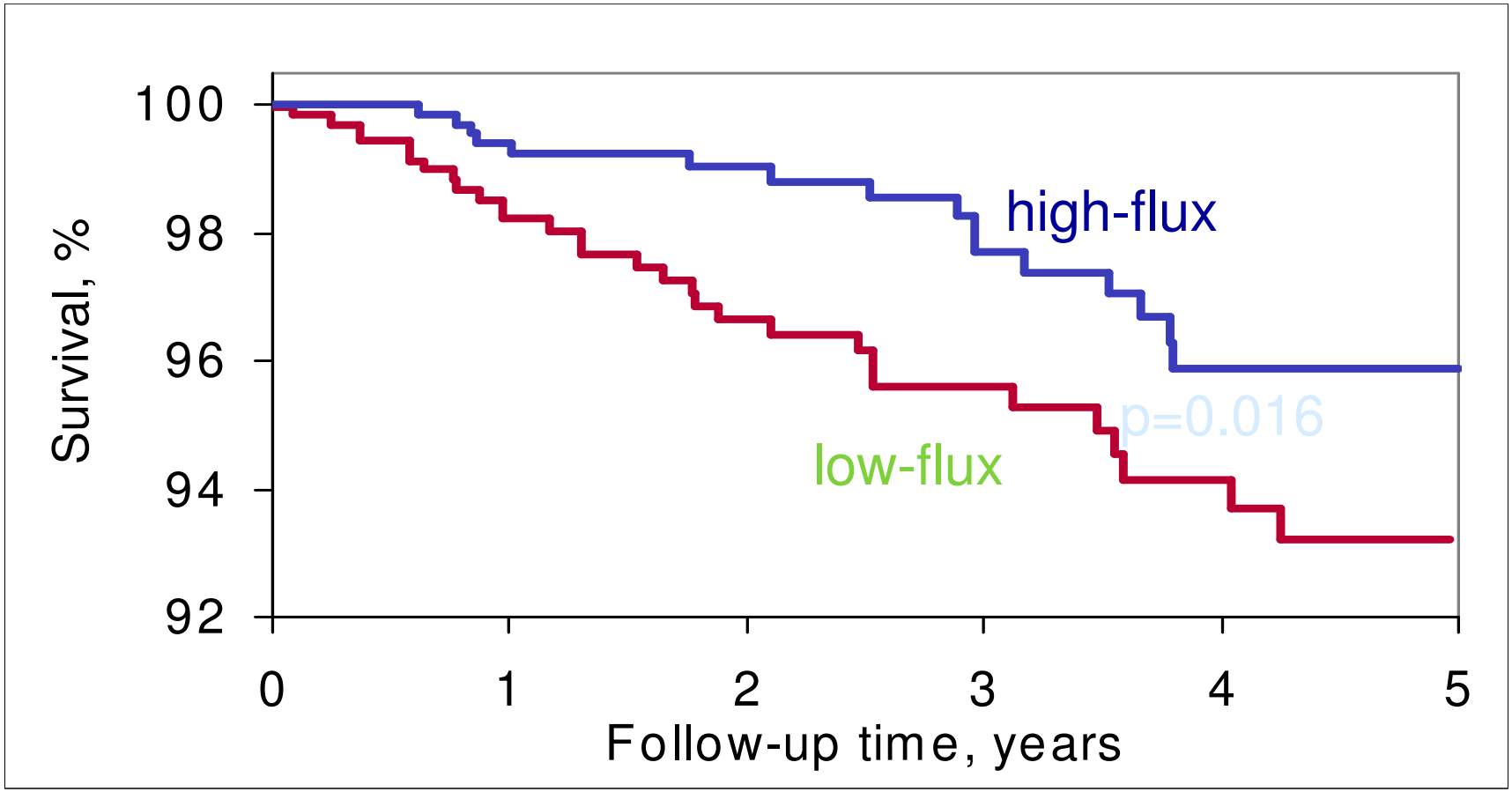
- Adrenomedullin
- AGE
- Angiogenin
- AOPP
- Atrial natriuretic peptide
- Cholecystokin
- Clara cell protein
- Complement factor D
- Cystatin C
- Cytokines
- Delta sleep inducing protein
- Endothelin
- β-Endorphin
- Ghrelin
- Glomerulopressin
- GIP I
- GIP II
- Leptin
- β-Lipotropin
- Macrophage-colony-stimulating factor
- Methionine-enkephalin
- β_2-Microglobulin
- Neuropeptide Y
- Orexin A
- Retinol binding protein

EVOLUTION OF β2-M OVER TIME



Locatelli et al, KI, 50: 1293-1302; 1996

DEATH FROM CEREBROVASCULAR DISEASE IN THE HEMO STUDY

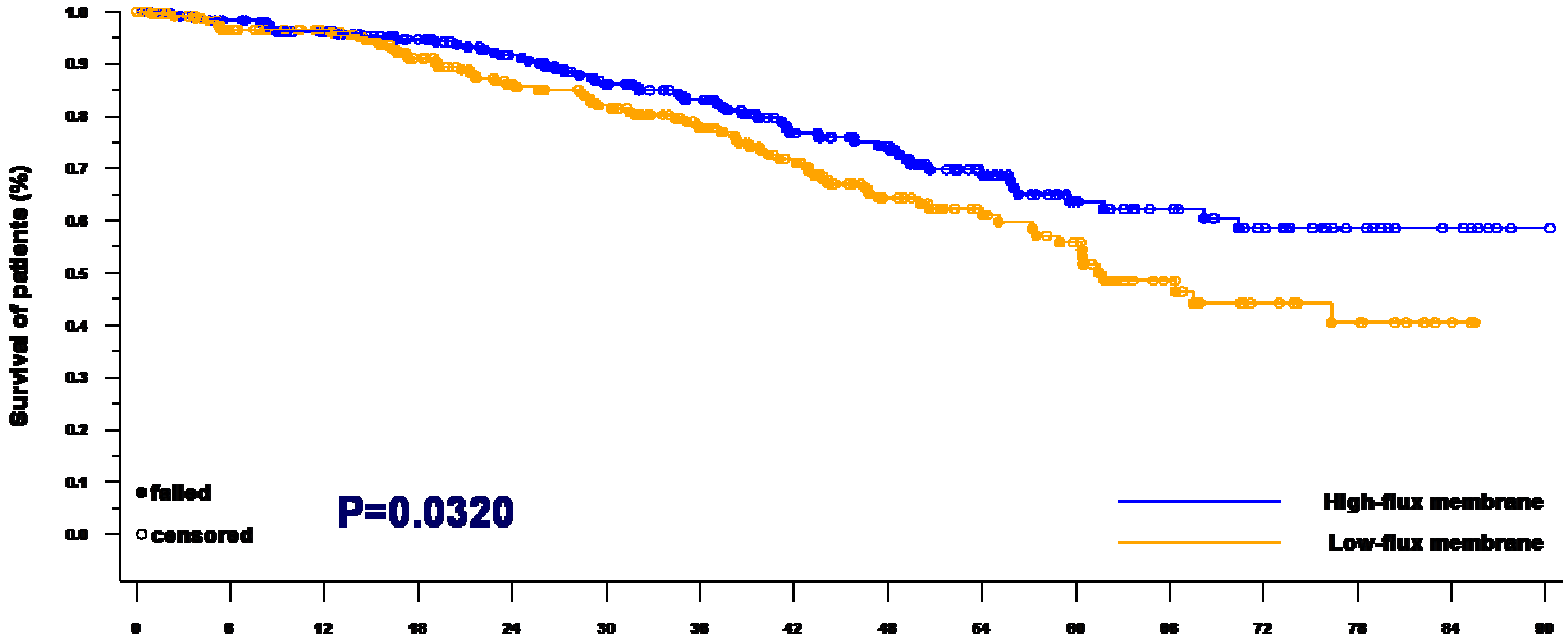


1486 patients without CBVD at baseline

Delmez et al, AJKD, 47: 131-138; 2006

KAPLAN-MEIER SURVIVAL ANALYSIS

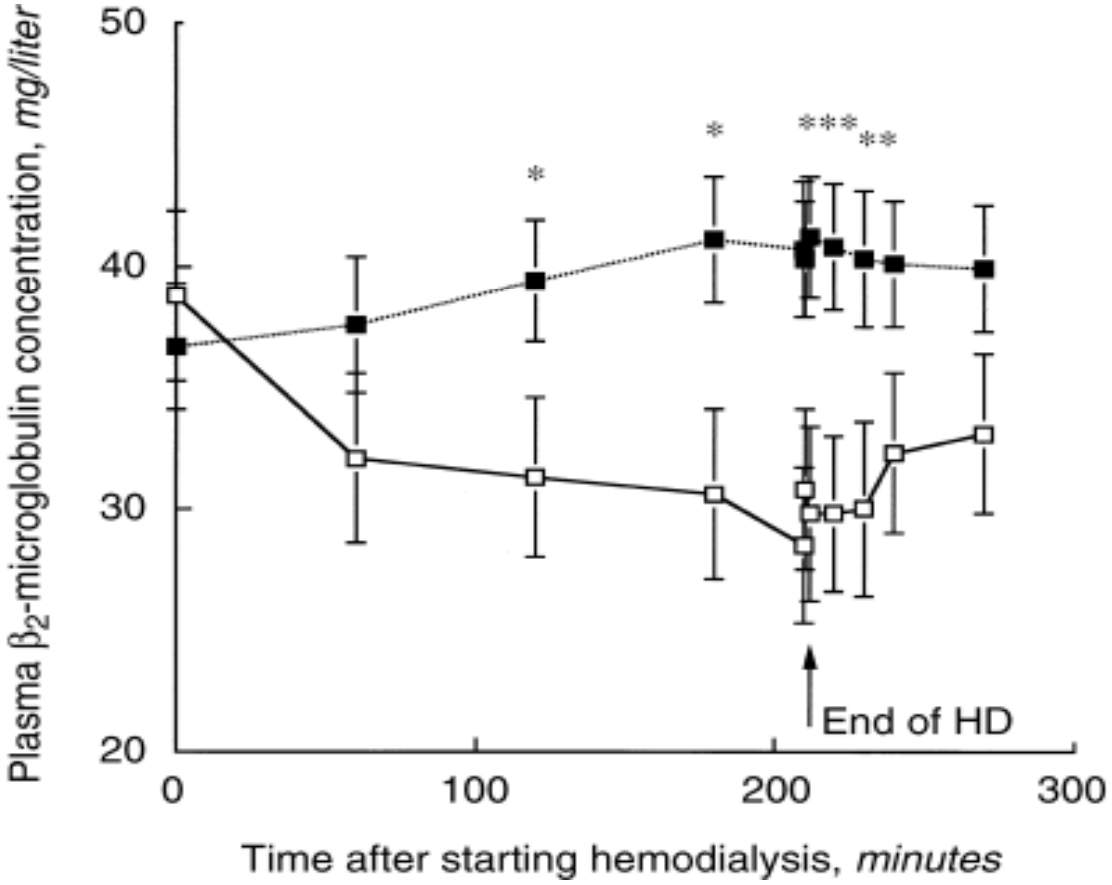
≤ 4g/dl Al



No. at risk								
High-flux	250	212	173	134	85	44	26	7
Low-flux	243	202	152	117	67	41	15	3

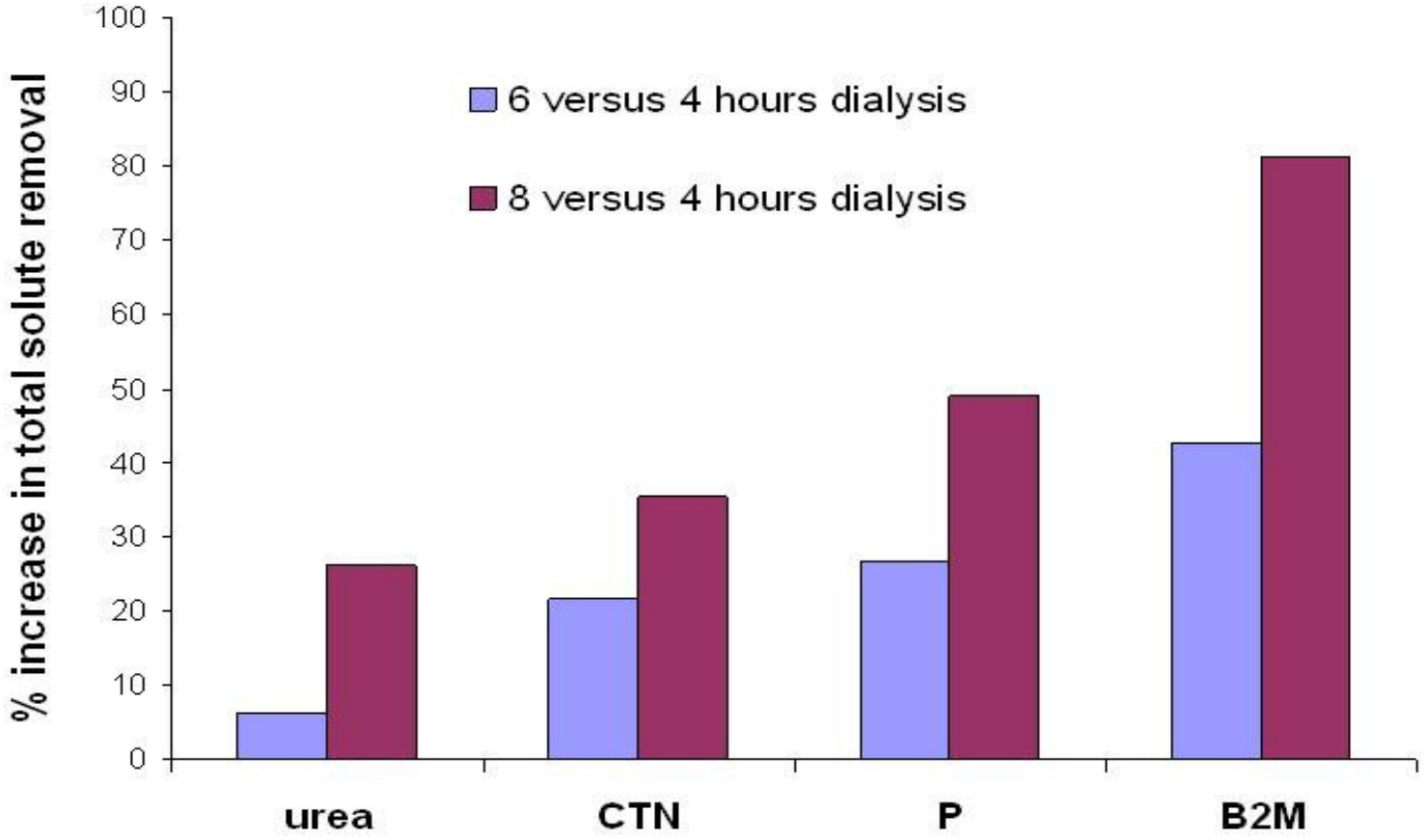
Locatelli et al, JASN, 20: 645-654; 2009

KINETICS MIDDLE MOLECULES



Leypoldt et al, KI, 56: 1571-1577; 1999

PERCENTAGE CHANGE VS. 4 HRS



Eloot et al, KI, 73: 765-770

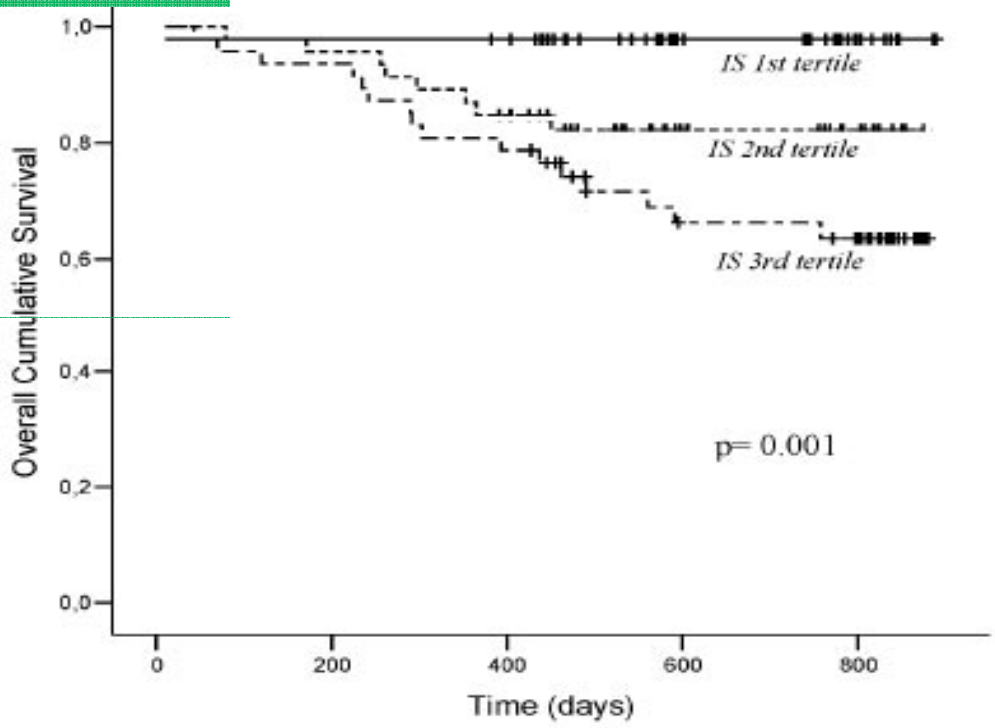
TOPICS

- The small water soluble compounds
- The middle molecules
- The protein-bound molecules

PROTEIN-BOUND COMPOUNDS: FUNCTIONAL IMPACT

- AGEs: inflammation, vascular disease
- CMPF: PB drugs, detoxification, neuropathy, anemia
- Cytokines: inflammation, malnutrition, anemia
- Dimethylguanidine: inhibition Ca^{2+} ATP-ase
- Hippuric acid: PB drugs, glucose intolerance
- Homocysteine: vessel disease, detoxification
- Indole-3-acetic acid: PB drugs, neuropathy, cytotoxicity
- Indoxyl sulfate: decline renal function, thyroid function, PB drugs, detoxification, endothelial function and repair
- Kinurenine: neuropathy
- Leptin: malnutrition
- Phenols: immune function, neuropathy
- Phenylacetic acid: nitric oxide synthesis
- Quinolinic acid: neuropathy

INDOXYL SULFATE AND SURVIVAL



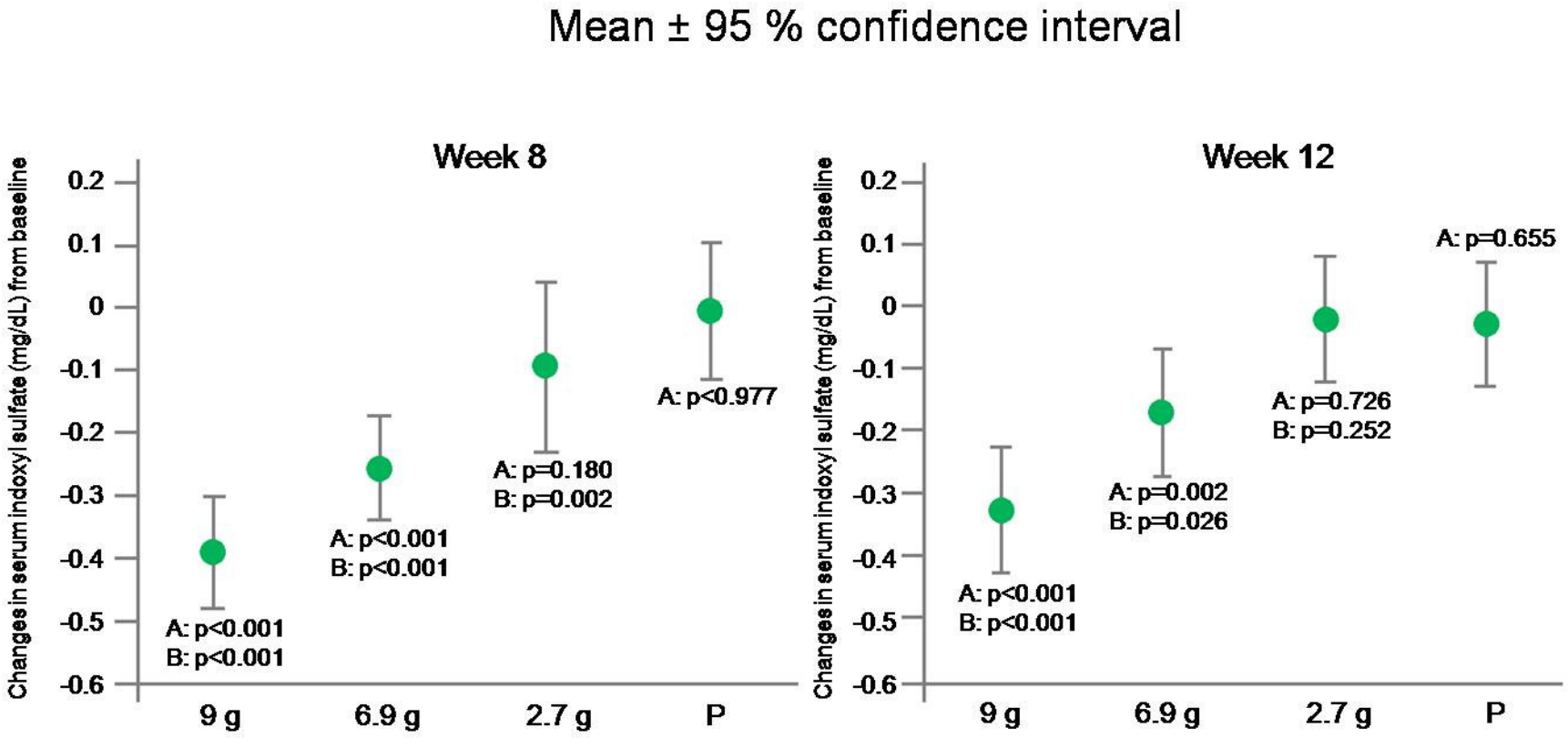
Kaplan-Meyer estimates of overall mortality for patients as a function of tertiles for serum IS levels

Number of patients at risk

	Days of Follow up				
	0	200	400	600	800
IS 1st tertile	46	45	44	23	8
IS 2nd tertile	46	44	38	17	9
IS 3rd tertile	47	44	37	24	21

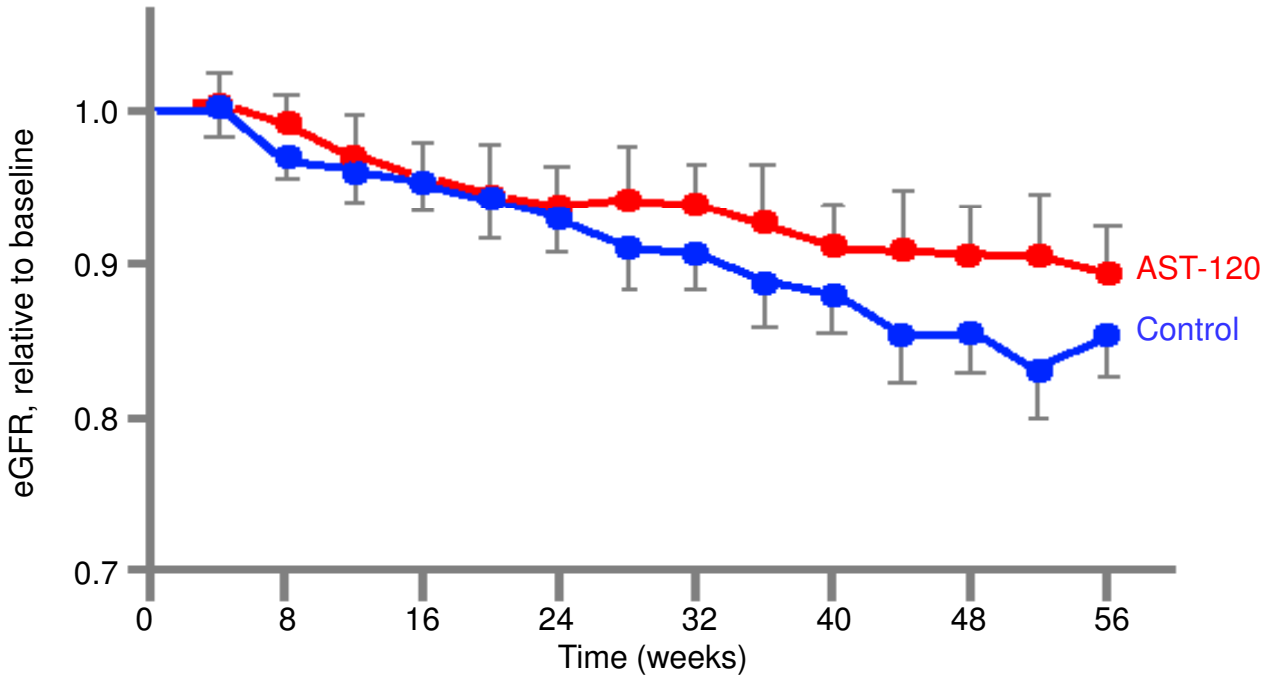
Barreto et al, CJASN, 4: 1551-1558; 2009

AST-120 AND SERUM INDOXYL SULFATE



Schulman G. et al, AJKD, 47: 565-577; 2006

ESTIMATED GLOMERULAR FILTRATION RATE



P<0.001

Akizawa T. et al, AJKD, 54: 459-467; 2009

CONCLUSIONS

- Uremic toxicity results from a complex retention pattern involving small water soluble compounds, protein bound compounds and middle molecules.
- Urea removal is not representative for that of most other molecules
- Enhancing middle molecule removal by increasing dialyzer pore size improves outcomes. Enhancing this process by convection might further improve outcomes
- Removal of protein bound compounds can be enhanced by intestinal adsorption which has a positive impact on the decline of residual renal function.
- Highly efficient convective strategies also improve removal of protein bound solutes