KDIGO - Controversies Conference
Cardiovascular Disease in CKD: What is it and What can we do about it?
29-31 October, 2010
London, England

Salt and Fluid Balance in CKD Stage 5

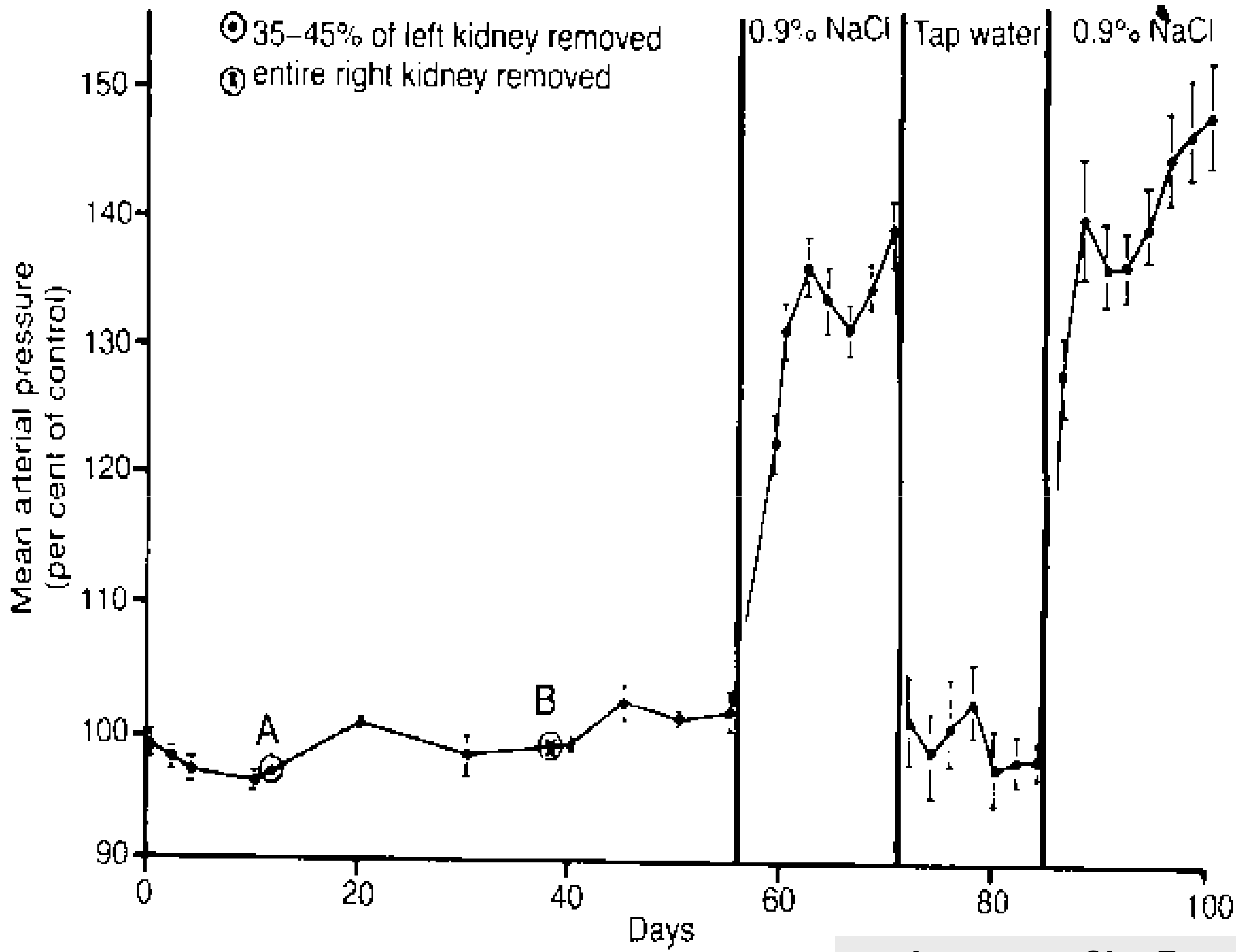
Charles Chazot
NephroCare Tassin
France

Physiological paradigms

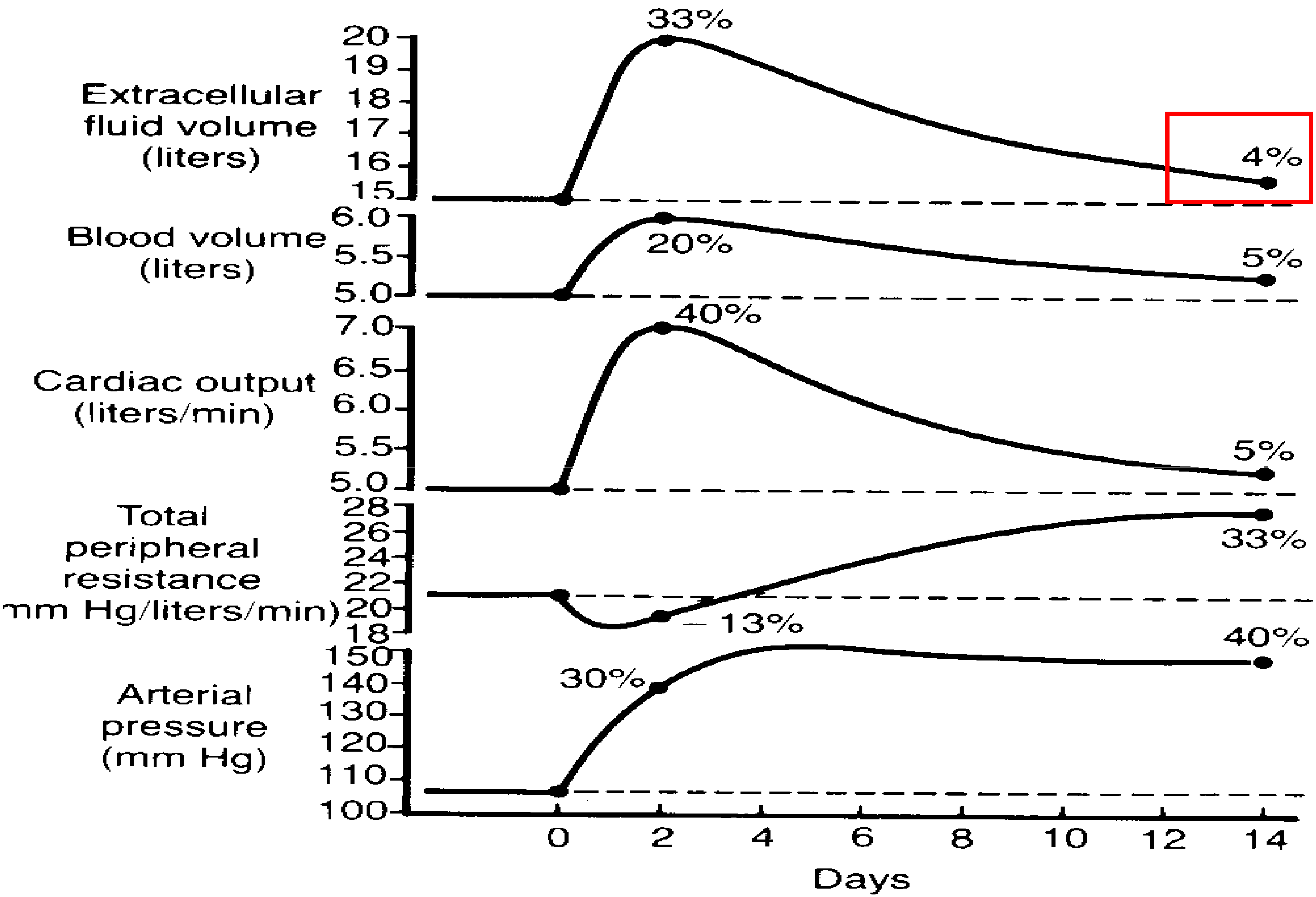
- The sodium is the « backbone » of extra-cellular volume

- The kidney is the key organ of extracellular fluid balance

CKD and sodium and fluid imbalance



Langstan, Circ Res 1963



GFR:30% of normal + Na intake x 6

Guyton, Hypertension 1992

From dog to human being…

Koomans, Hypertension, 1985

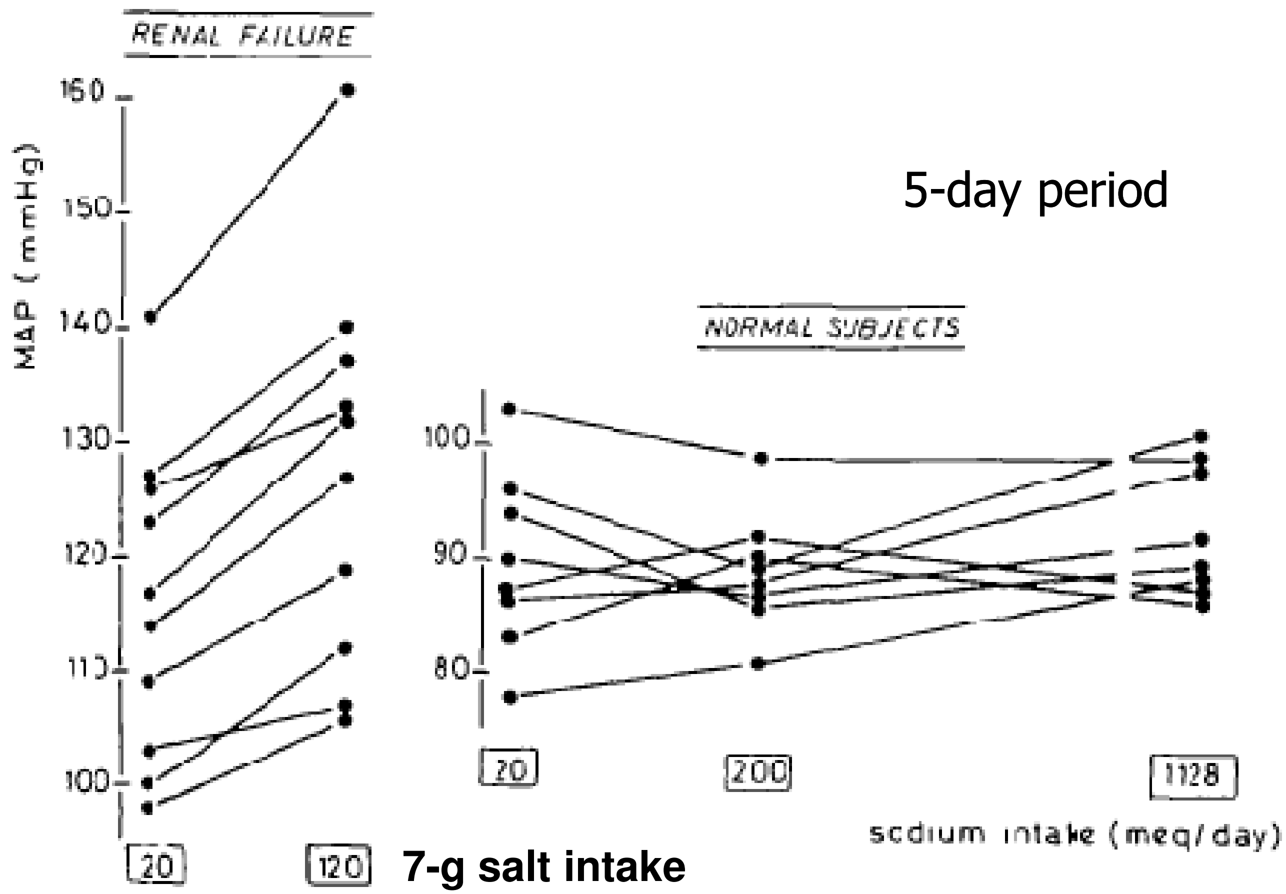


FIGURE 3. *Individual values of mean arterial pressure (MAP) in 10 patients with renal failure and eight normal volunteers at various sodium intakes*

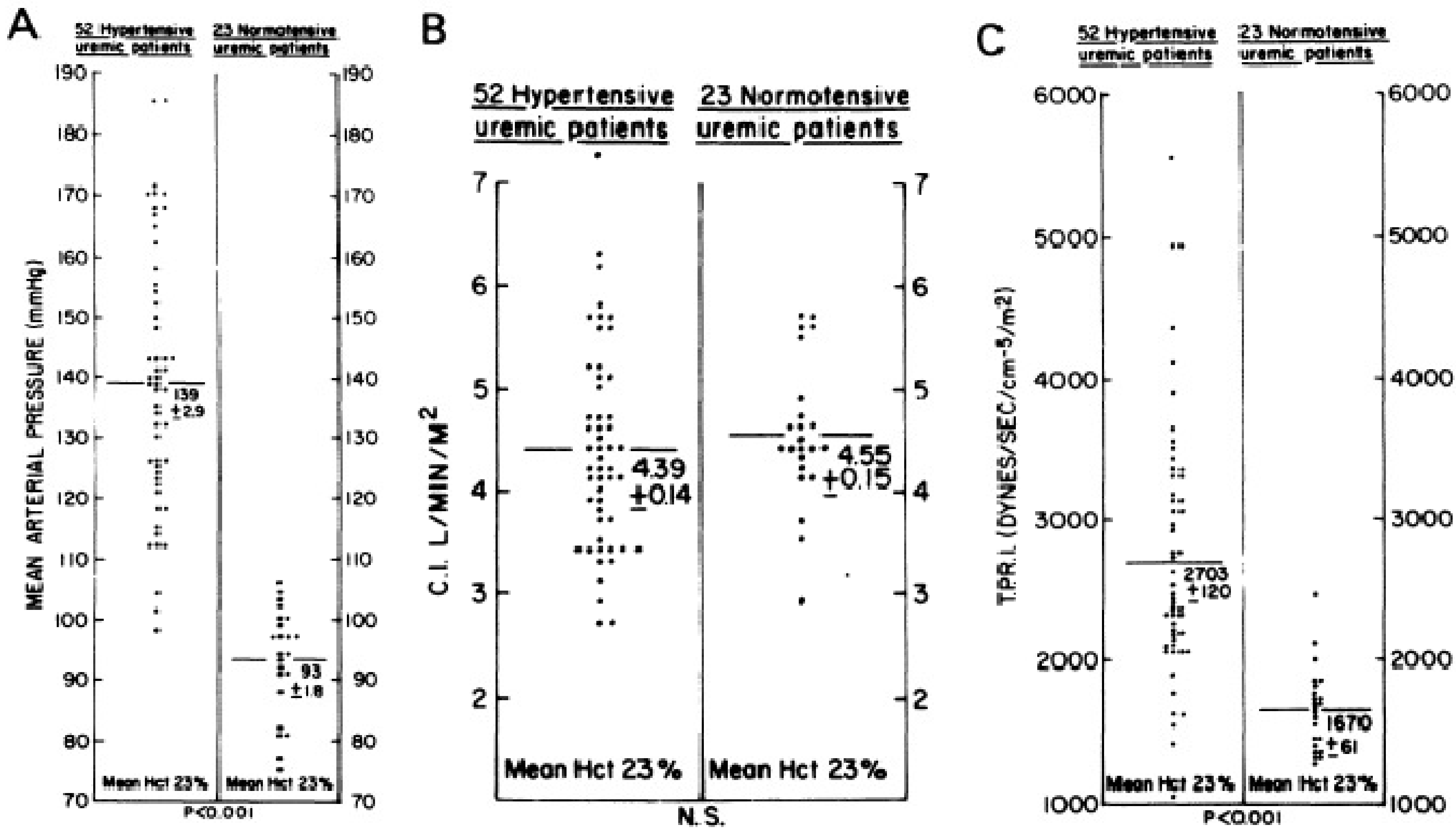


Figure 2

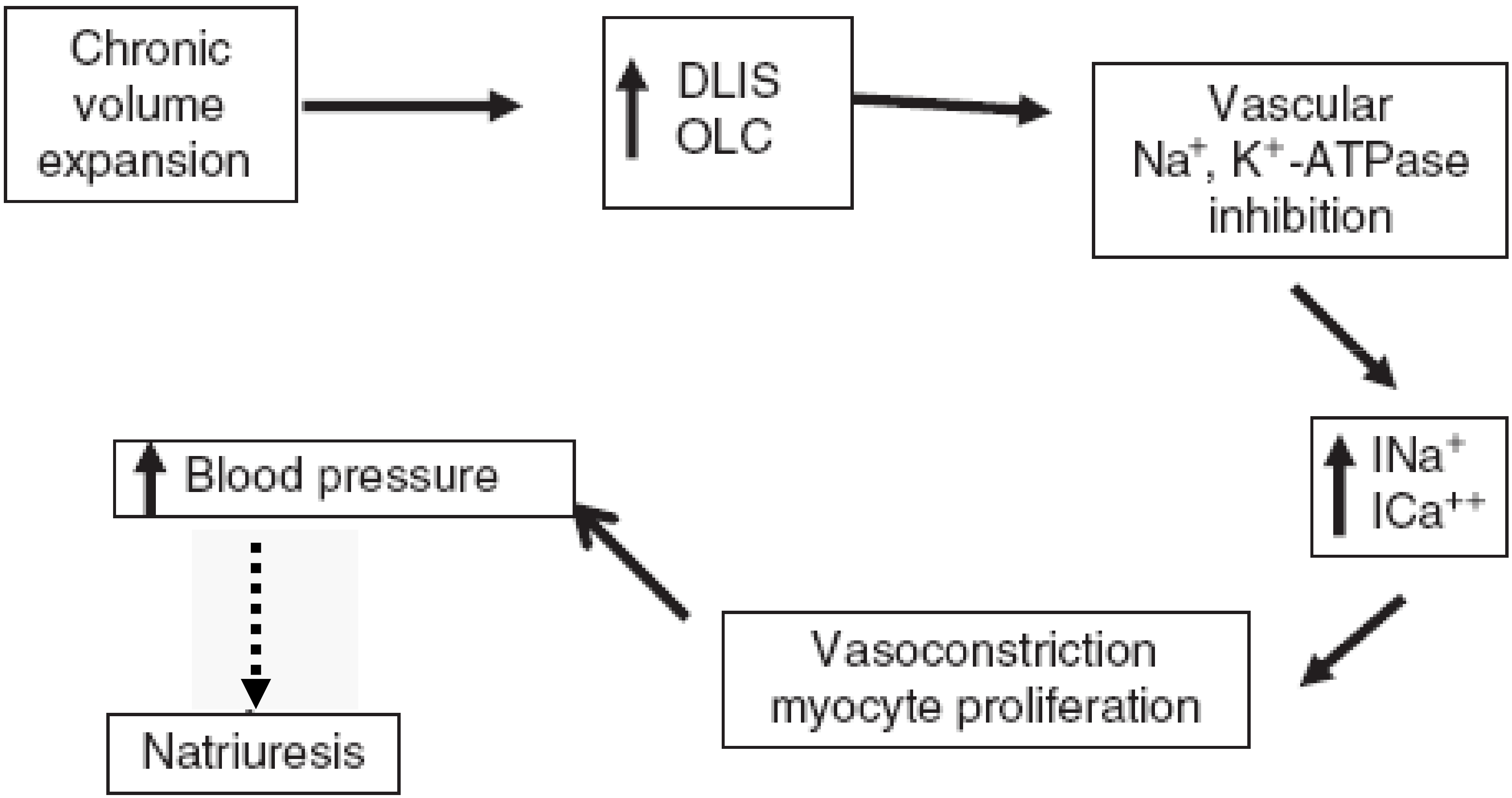
Comparison of mean arterial pressure (A), cardiac index (B), and total peripheral resistance index (C) of 52 hypertensive and 23 normotensive patients with end-stage renal disease.

Kim et al, Circulation 1972;46:456

Mechanisms of vascular remodeling

- Na+/K+ inhibitors
- NO/ADMA imbalance
- Non osmotically-active sodium stores

Role of inhibitors of Na^+/K^+ pumps

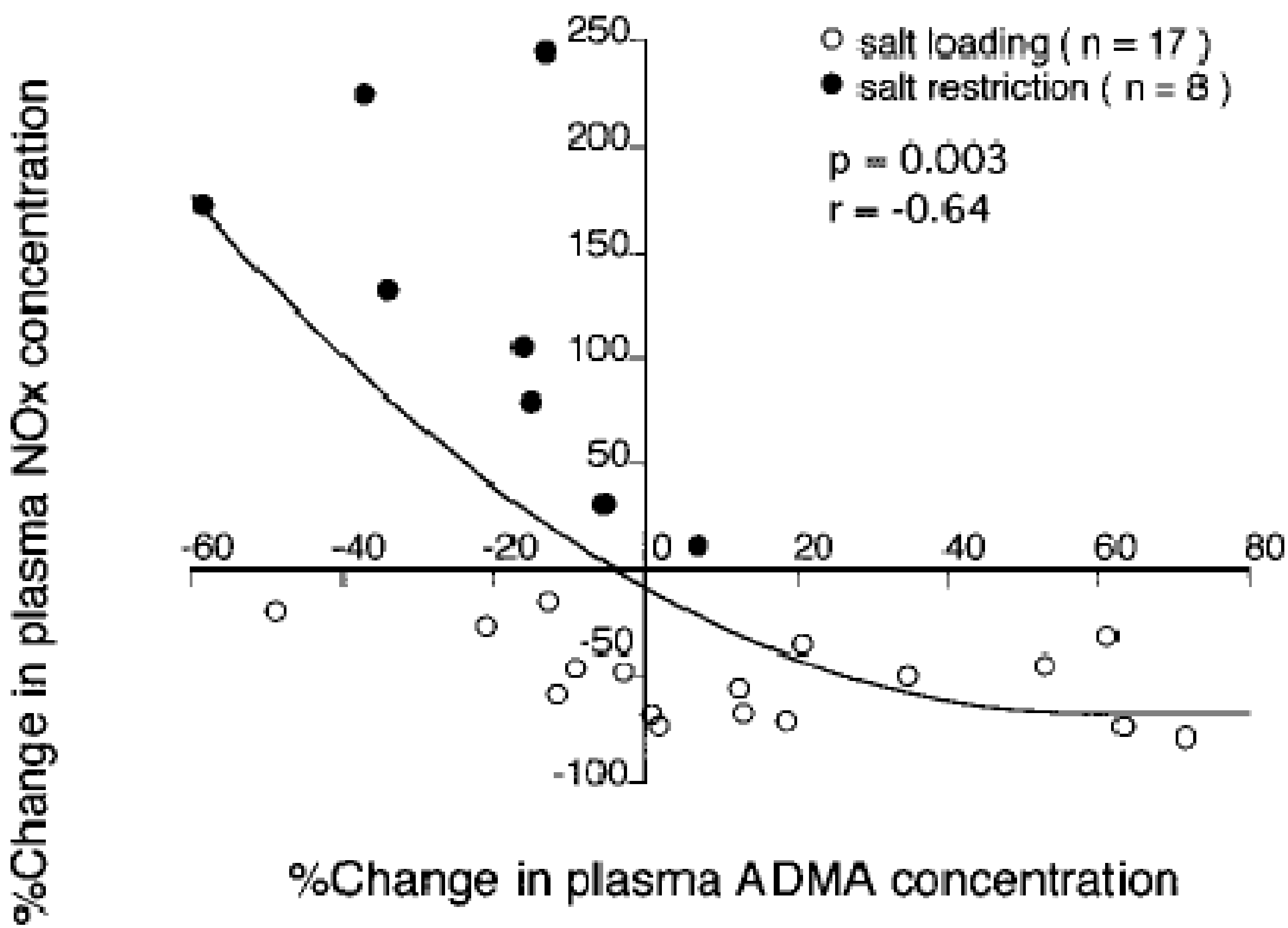


Twardowski HD Int 2008

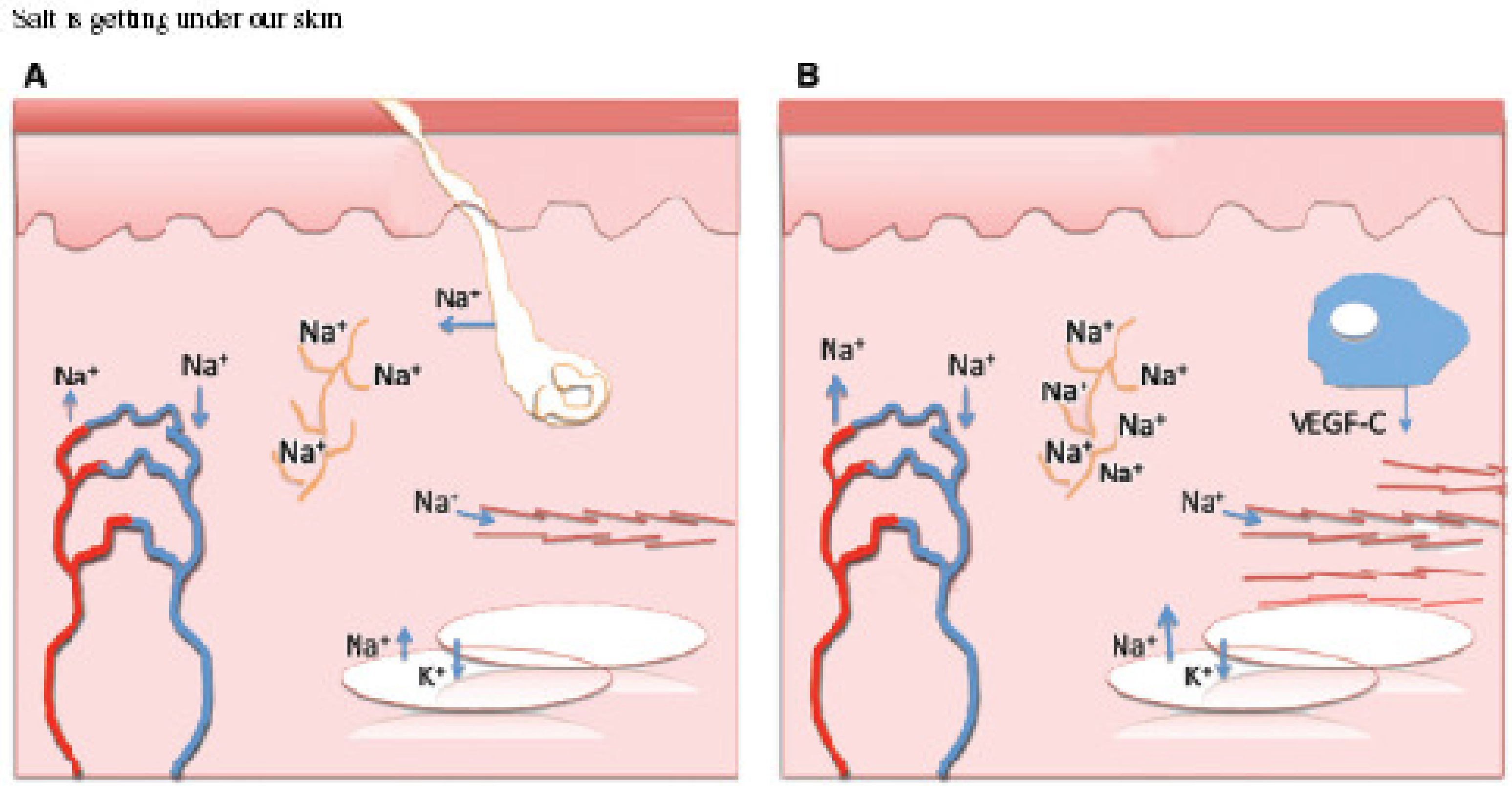
Sodium and NO metabolism

Fujiwara, Circulation 2000

Essential hypertension patients



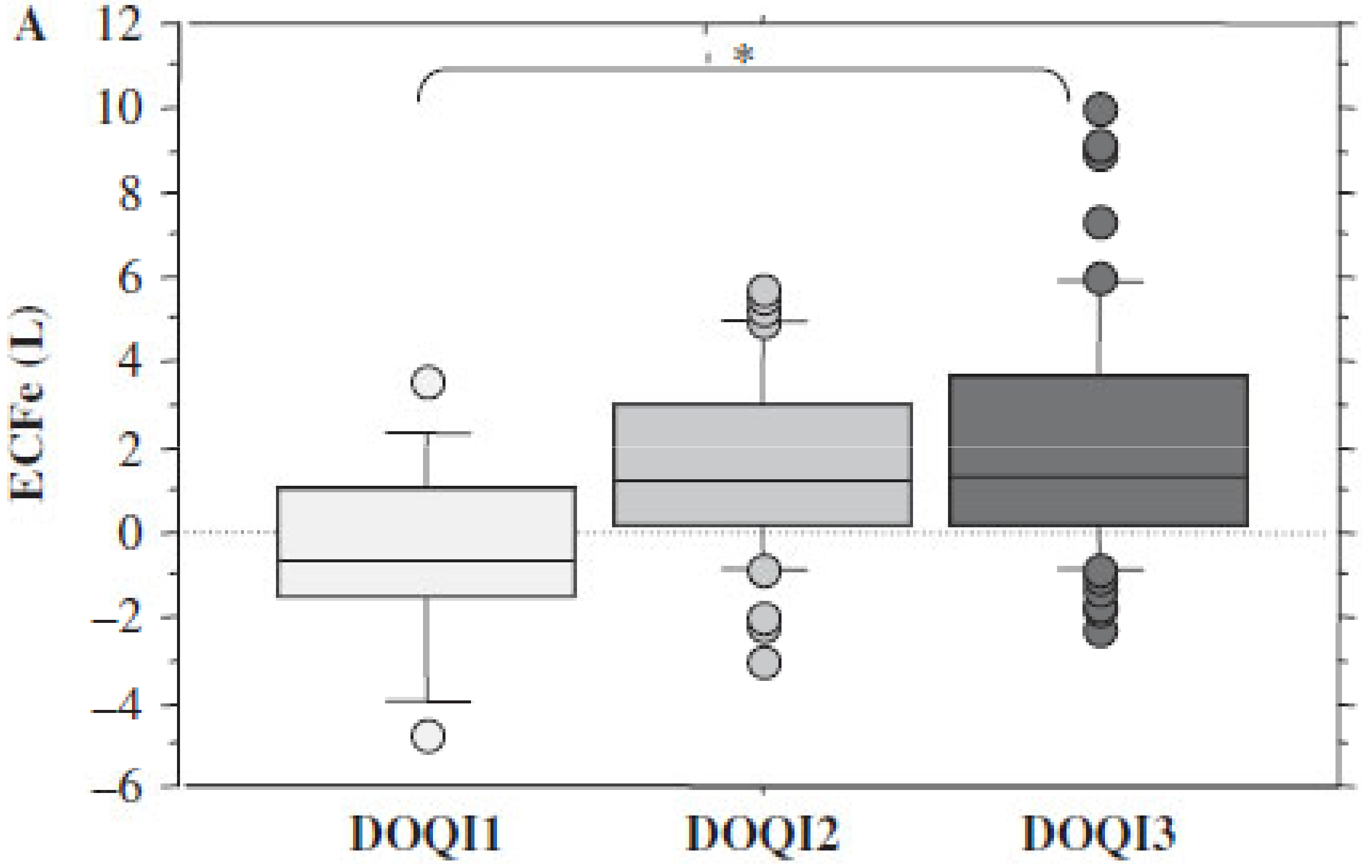
The hidden sodium



Rabelink&Rotmans, NDT 2009
Titze Semin Dial 2009

- Non renal-regulated sodium pool
- Sodium accumulation in tissues like skin acting as a reservoir
- Role of polyanionic glycosamino-glycans of extracellular matrix
- Non osmotically active: water-free sodium pool
- Decreased by low sodium diet in animals (↓ 40%) without water losses
- Associated with osmo-dependent lympangiogenesis (contribution to ↑ ECF?)

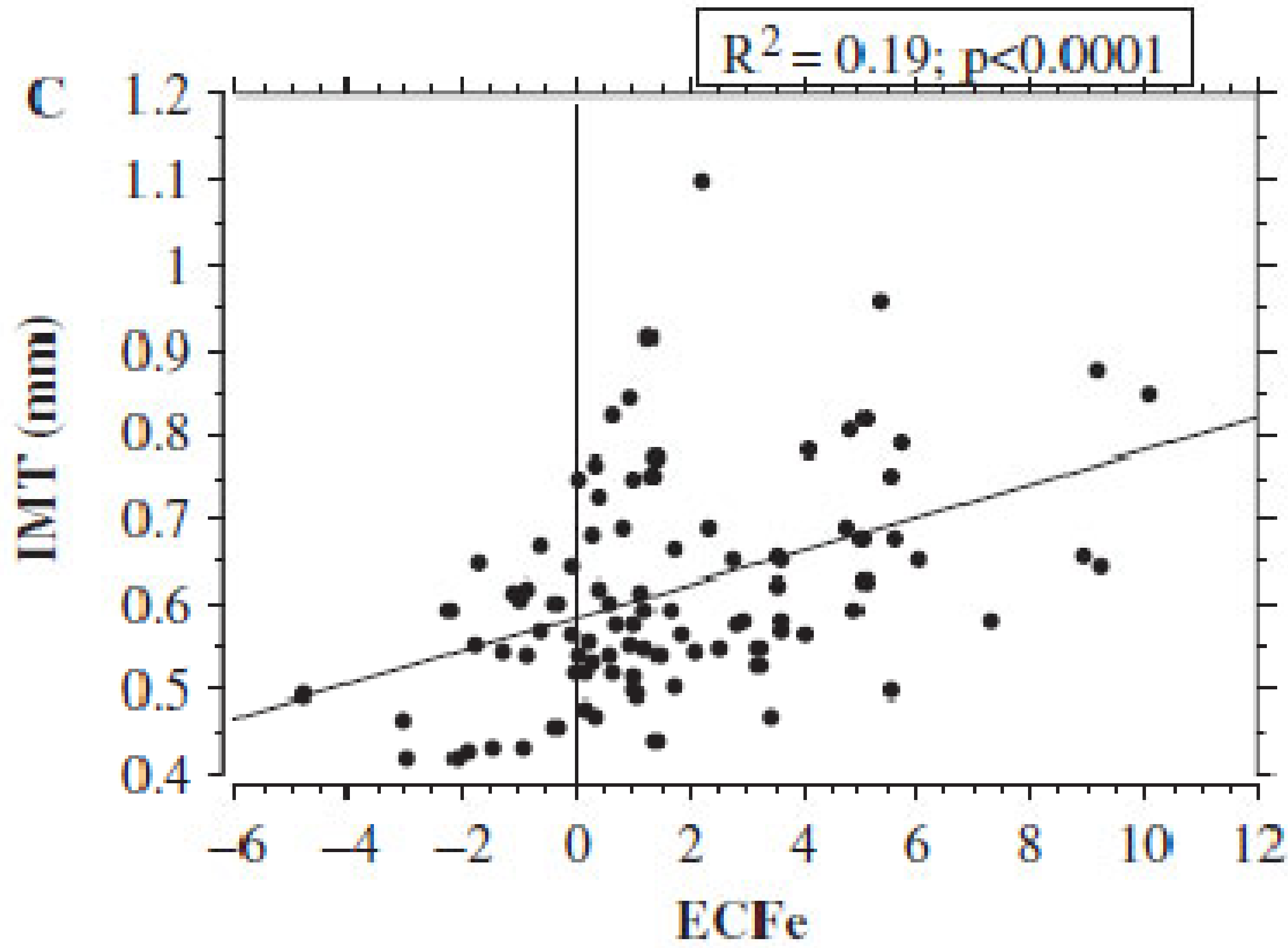
Fluid accumulation in early CKD (1)



CKD-1 **CKD-2** **CKD-3**

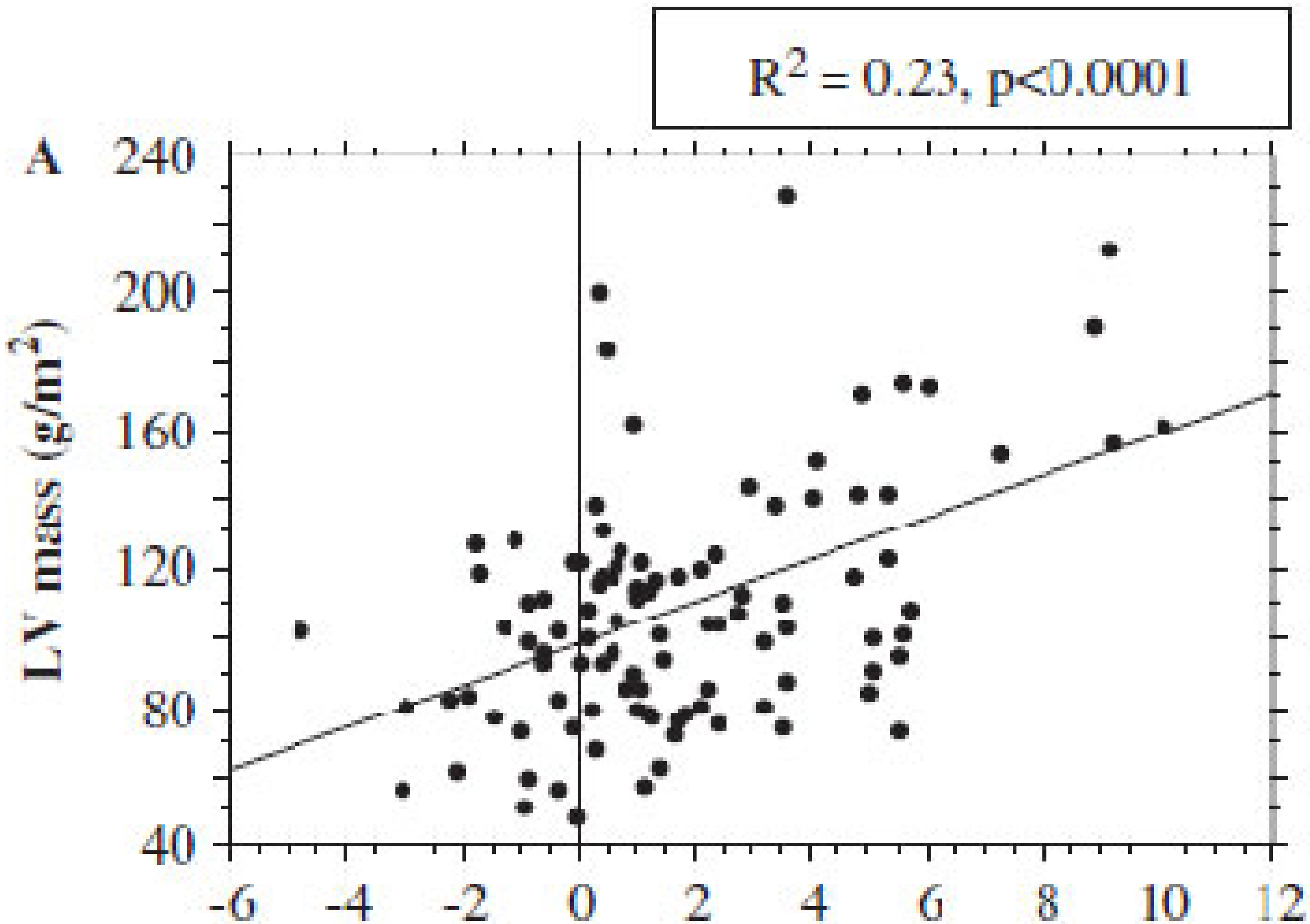
Essig, NDT 2008

Fluid accumulation in early CKD (2)



Essig, NDT 2008

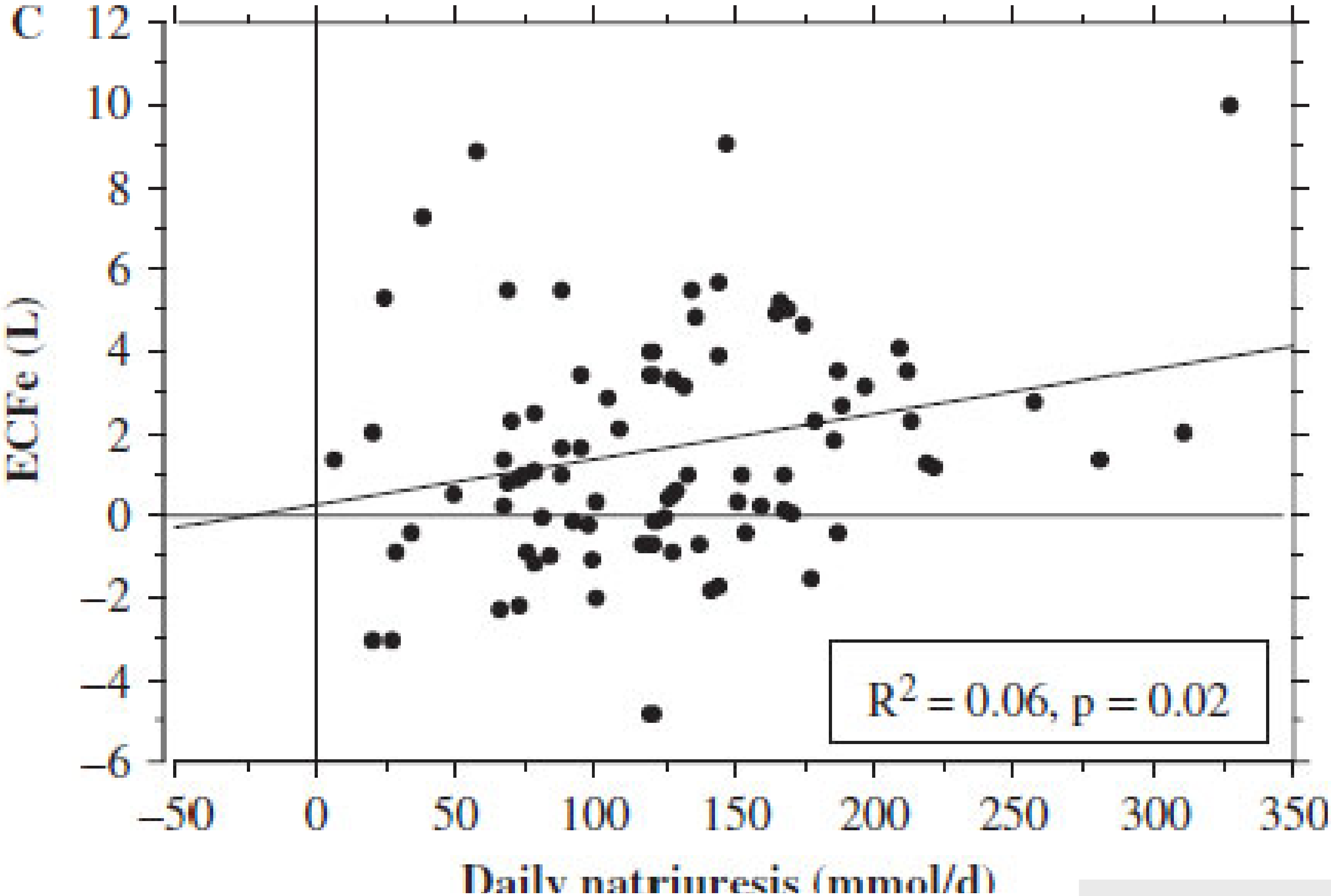
Fluid accumulation in early CKD (3)



ECF (L)

Essig, NDT 2008

Fluid accumulation in early CKD (4)



Essig, NDT 2008

Summary #1

Sodium is one of the most dangerous uremic toxin

Sodium imbalance is responsible for fluid accumulation early in CKD evolution

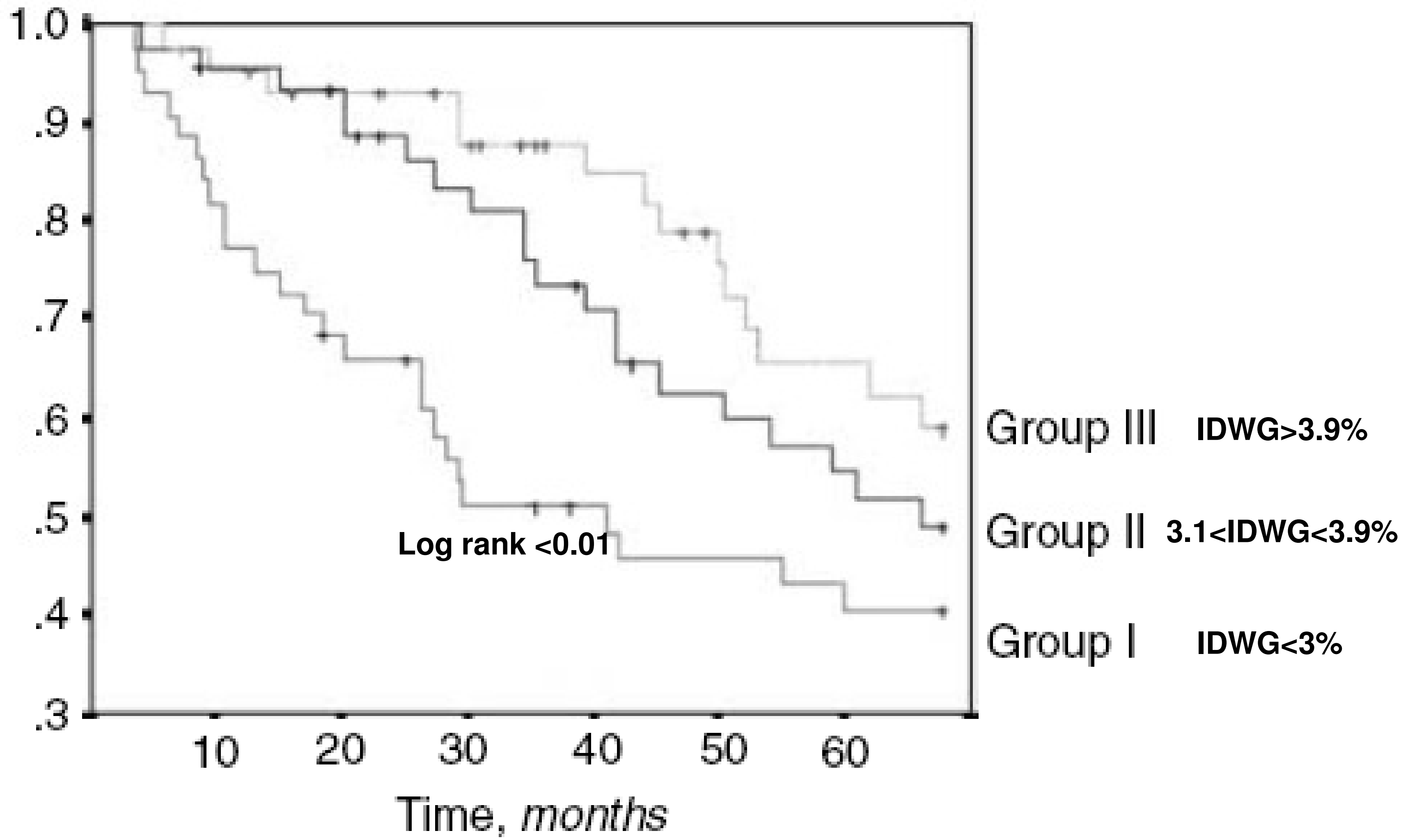
Fluid accumulation in CKD leads to vascular remodeling and hypertension

What is fluid retention in HD patients?
How does it influence patient outcomes?

Sequential fluid retention in HD patients:

Related to interdialytic weight gain (IDWG)
Treated by sequential UF
Measured with a scale

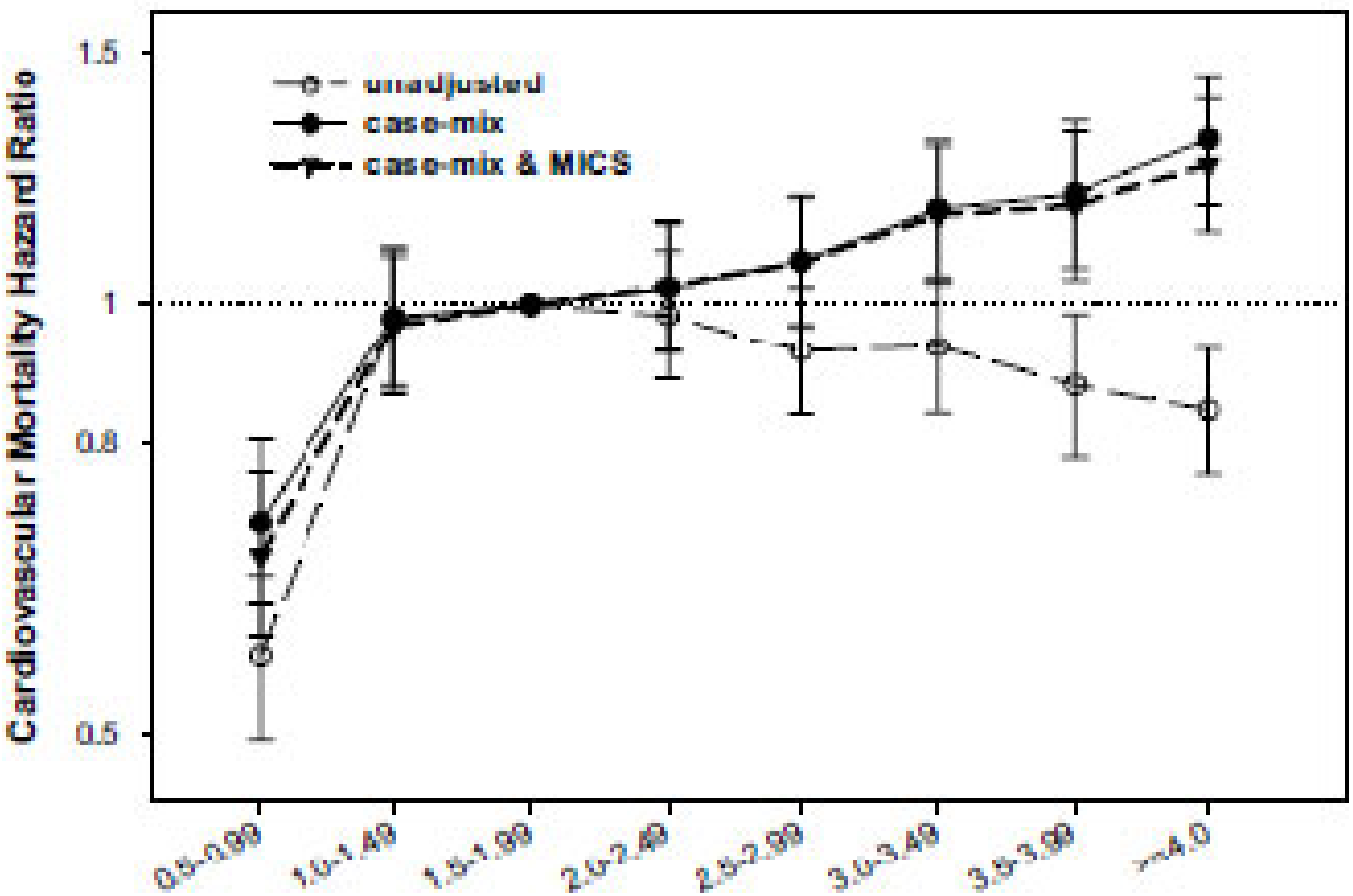
Sequential fluid retention and mortality (1)



IDWG correlated with nutritional markers and predialysis blood pressure.
No multivariate analysis

Lopez-Gomez KI 2005

Sequential fluid retention and mortality (2)



Kalantar-Z. Circulation 2009

Sequential fluid retention and mortality (3)

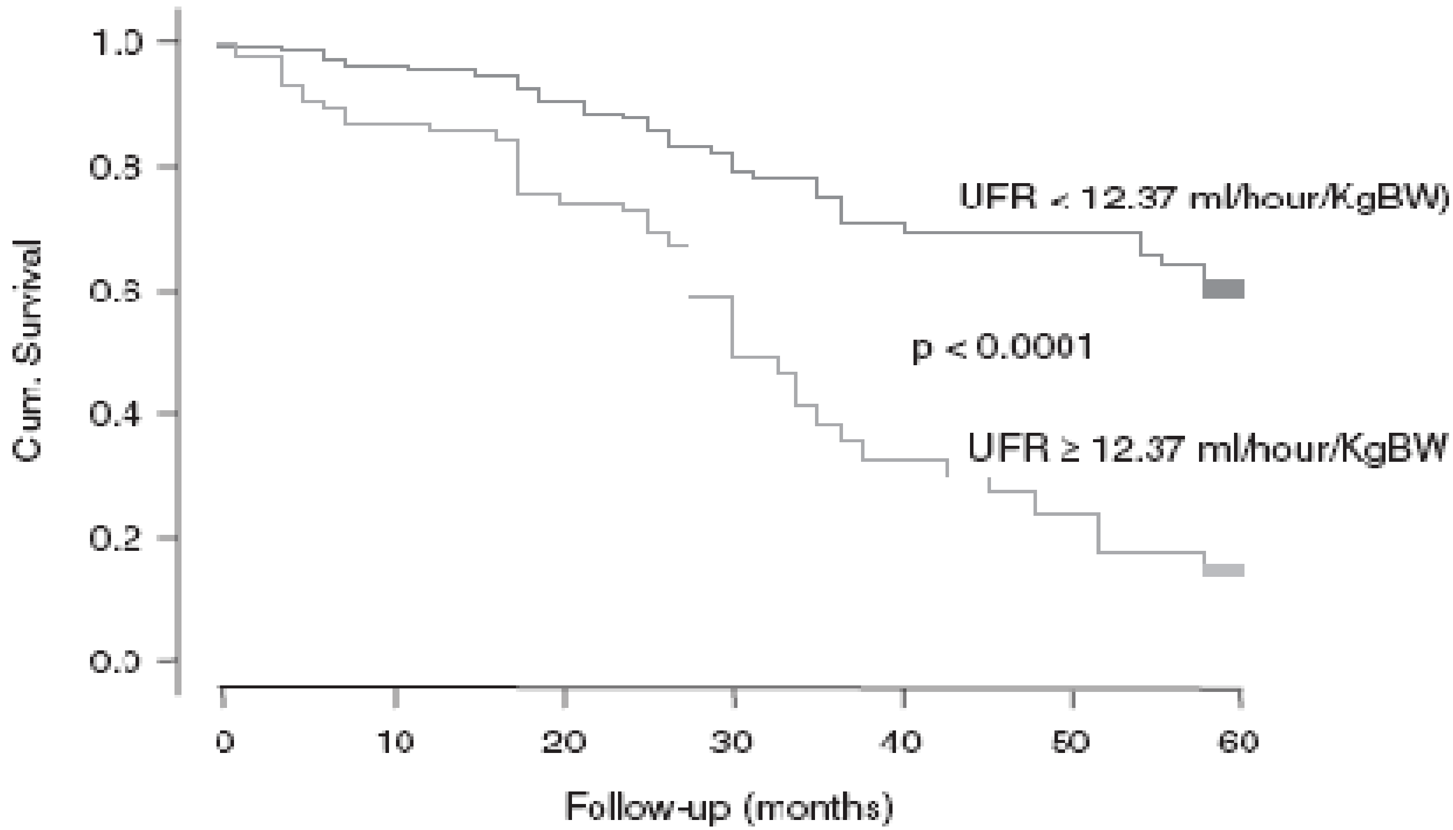


Fig. 3. Survival curves adjusted for significant predictors at Cox regression analysis by using UFR as categorical variable defined according to the receiver operating characteristic (ROC) derived UFR threshold of 12.37 ml/h/kg BW.

Movili, NDT 2007

Sequential fluid retention and mortality (4)

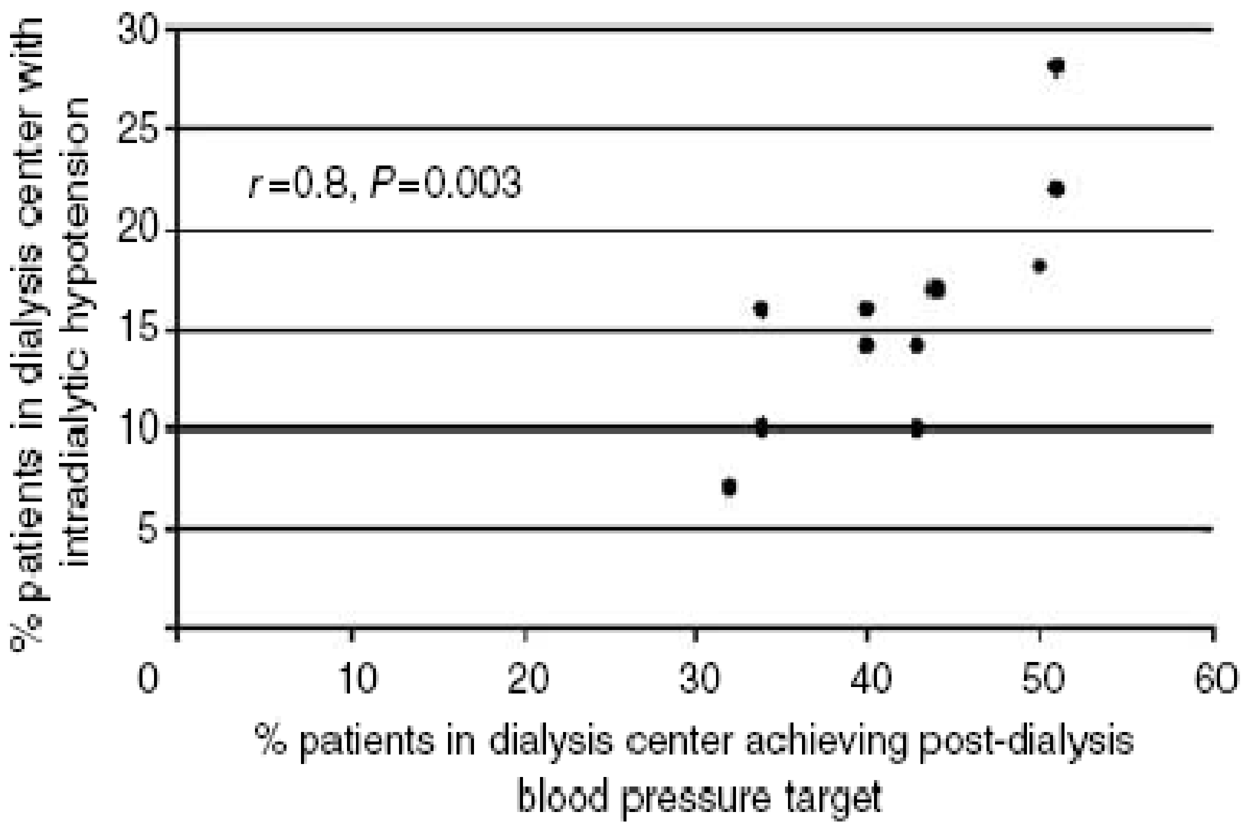
A high UF rate is associated with all-cause mortality in DOPPS

Outcome	RR	p value
Adjusted all-cause mortality	1,09	0,02
Adjusted cardiopulmonary mortality	1,04	0,41

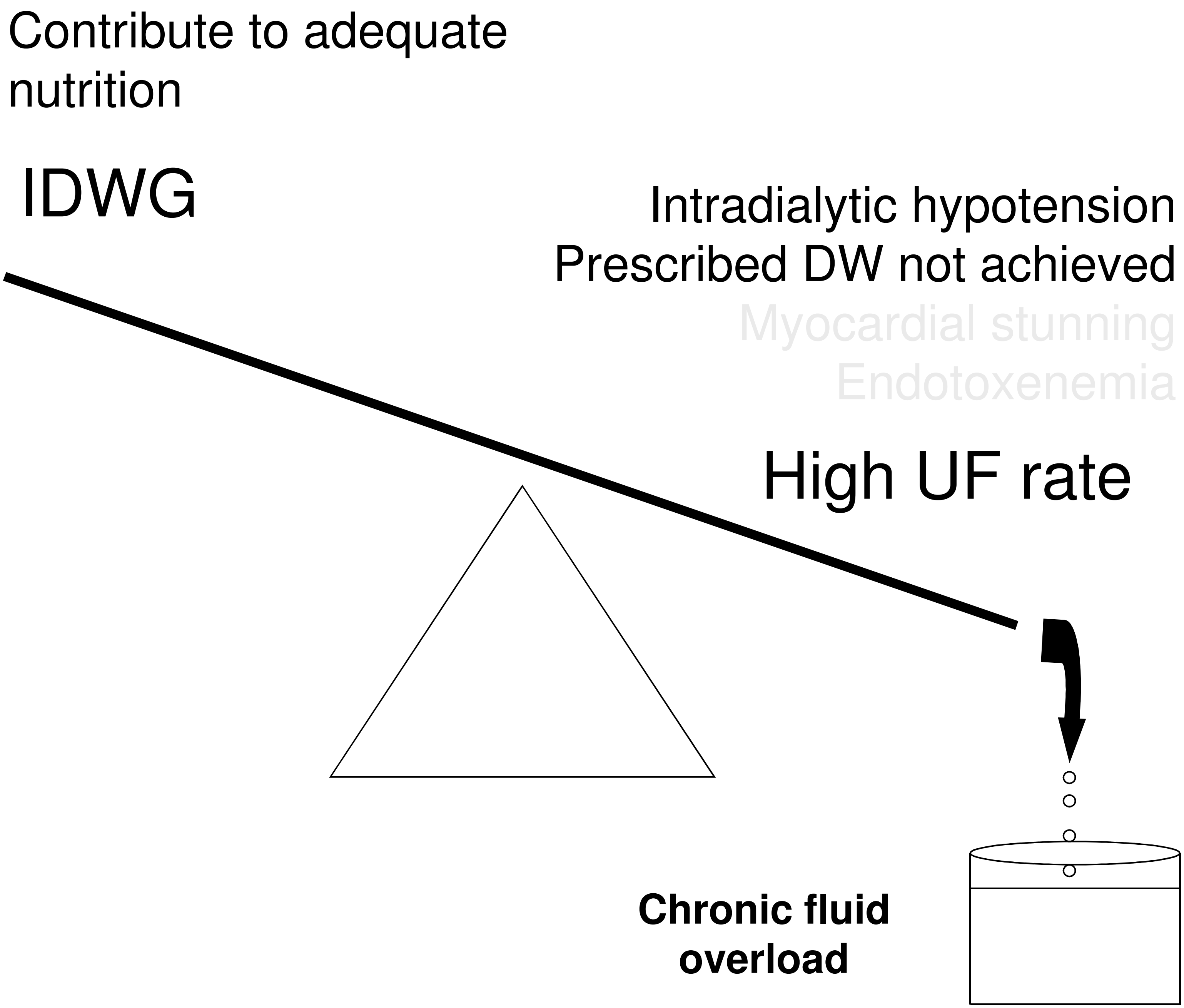
Cut-off : 10 ml/kg/hour

Saran, Kidney Int 2006

The dry weight method is demanding with standard dialysis because of hemodynamic effect of high UF rates

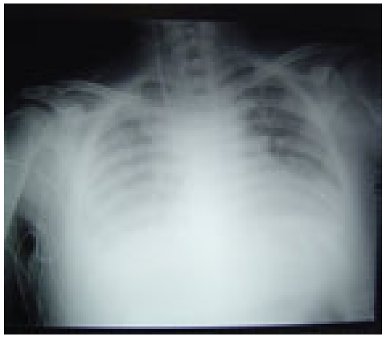


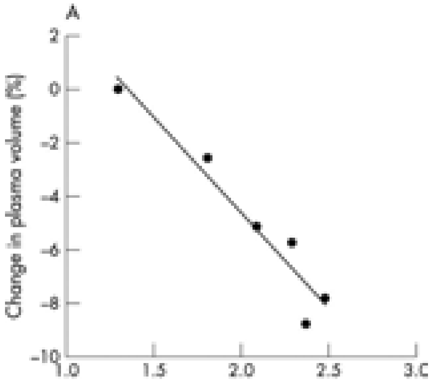
Davenport, KI 2008


Contribute to adequate nutrition
IDWG
Intradialytic hypotension
Prescribed DW not achieved
Myocardial stunning
Endotoxenemia
High UF rate
Chronic fluid overload

Chronic fluid retention in HD patients:

Permanent extracellular volume accumulation beyond IDWG remaining between dialysis Measured with chest X-ray, BIA, plasma volume monitoring





Chronic fluid retention and mortality (1)

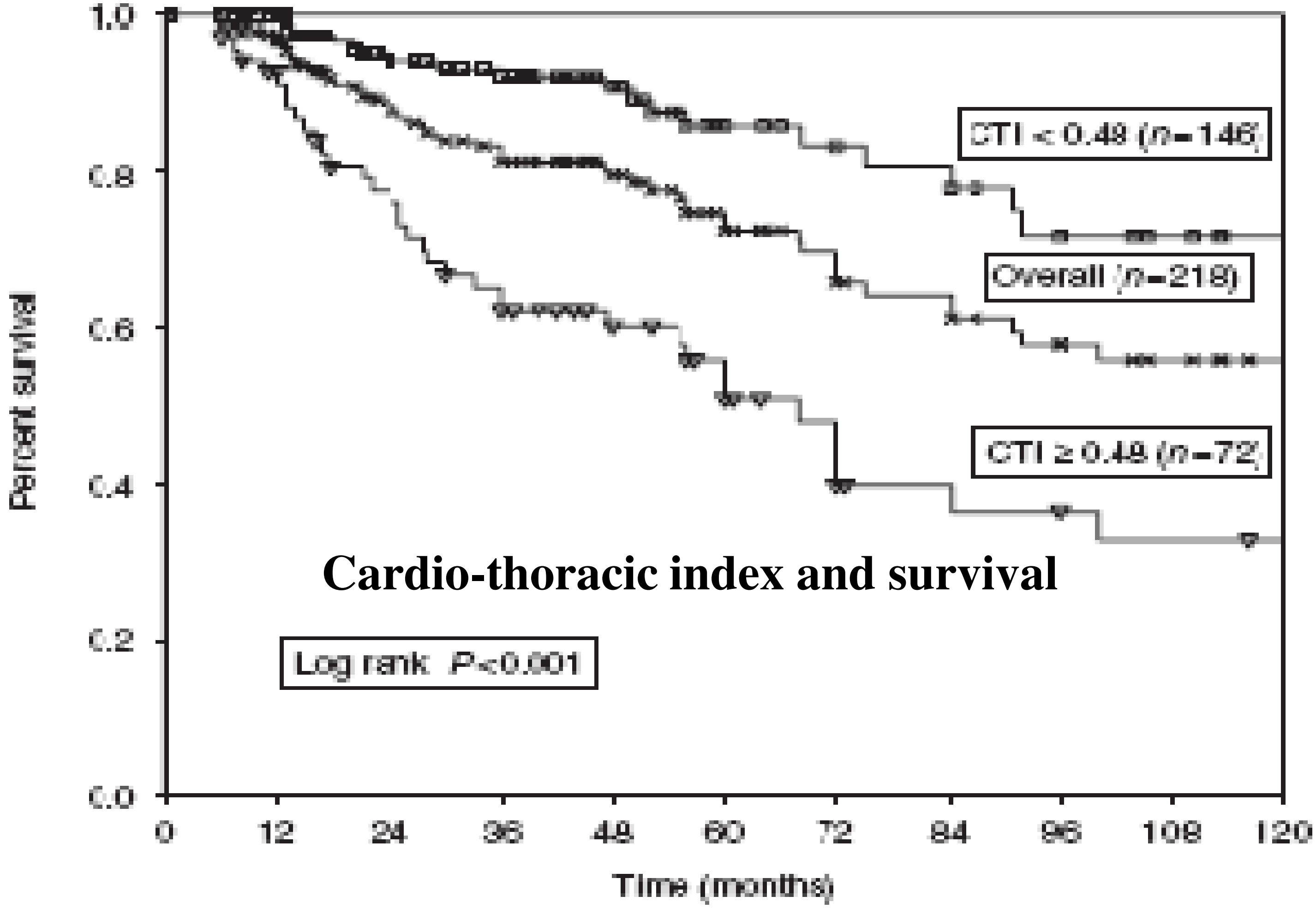
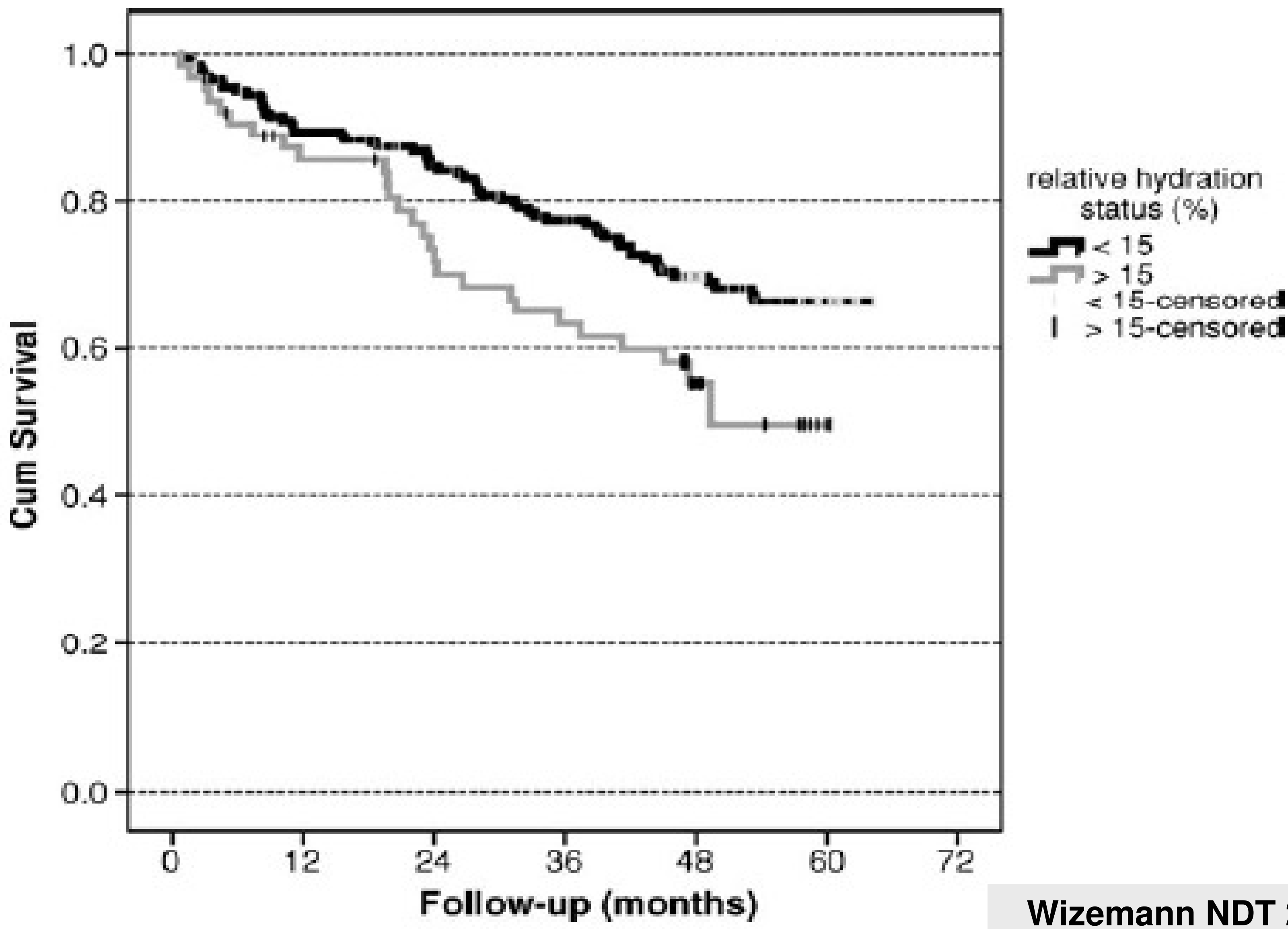


Fig. 3. The Kaplan–Meier survival data of all patients according to CTI (CTI <0.48 *vs* CTI ≥ 0.48, log-rank $P < 0.001$).

Ozkahya NDT 2006,21:3506

Chronic fluid retention and mortality (2)

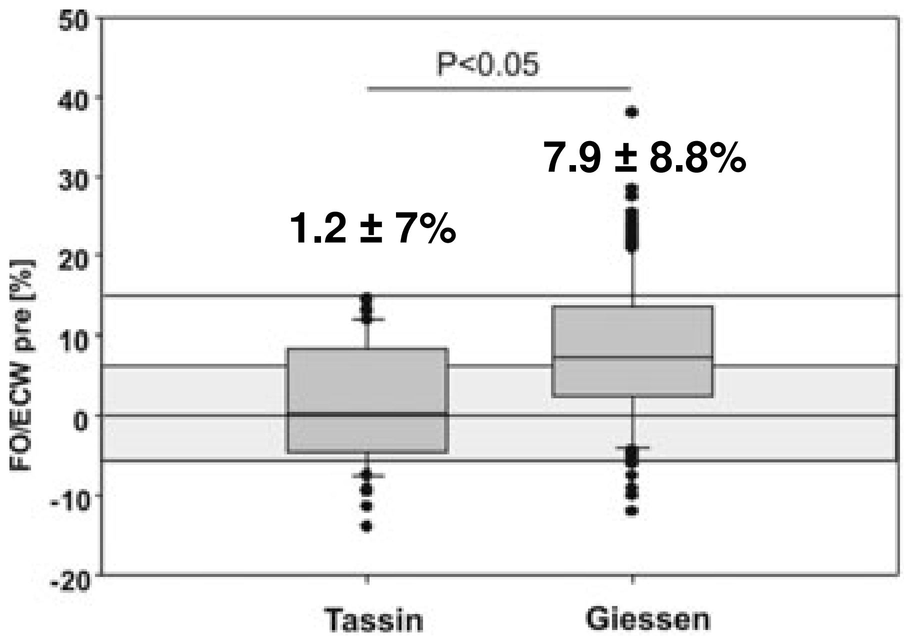


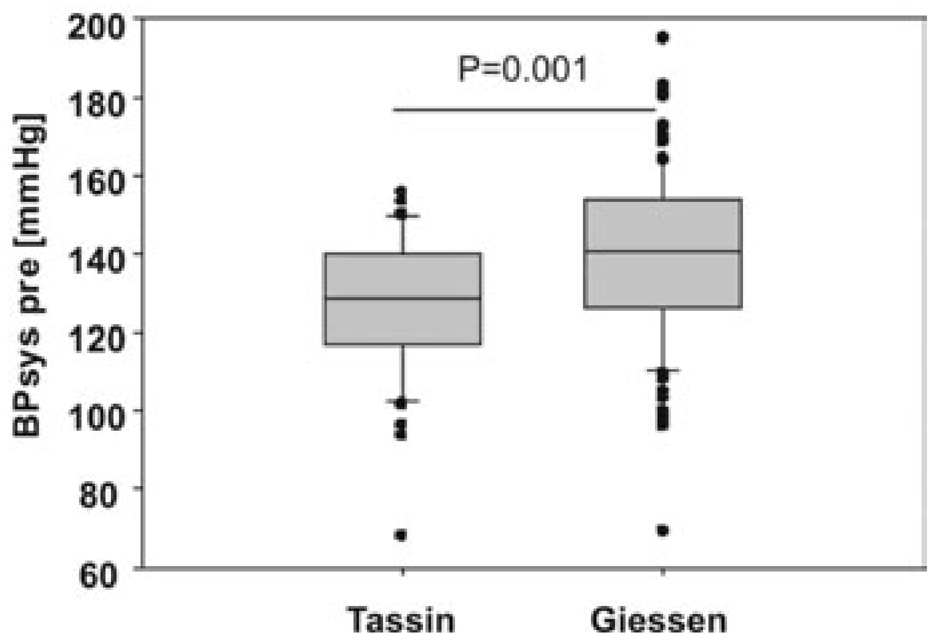
Wizemann NDT 2009

Tassin: 51 HD patients clinically at dry weight (Dr Charra)

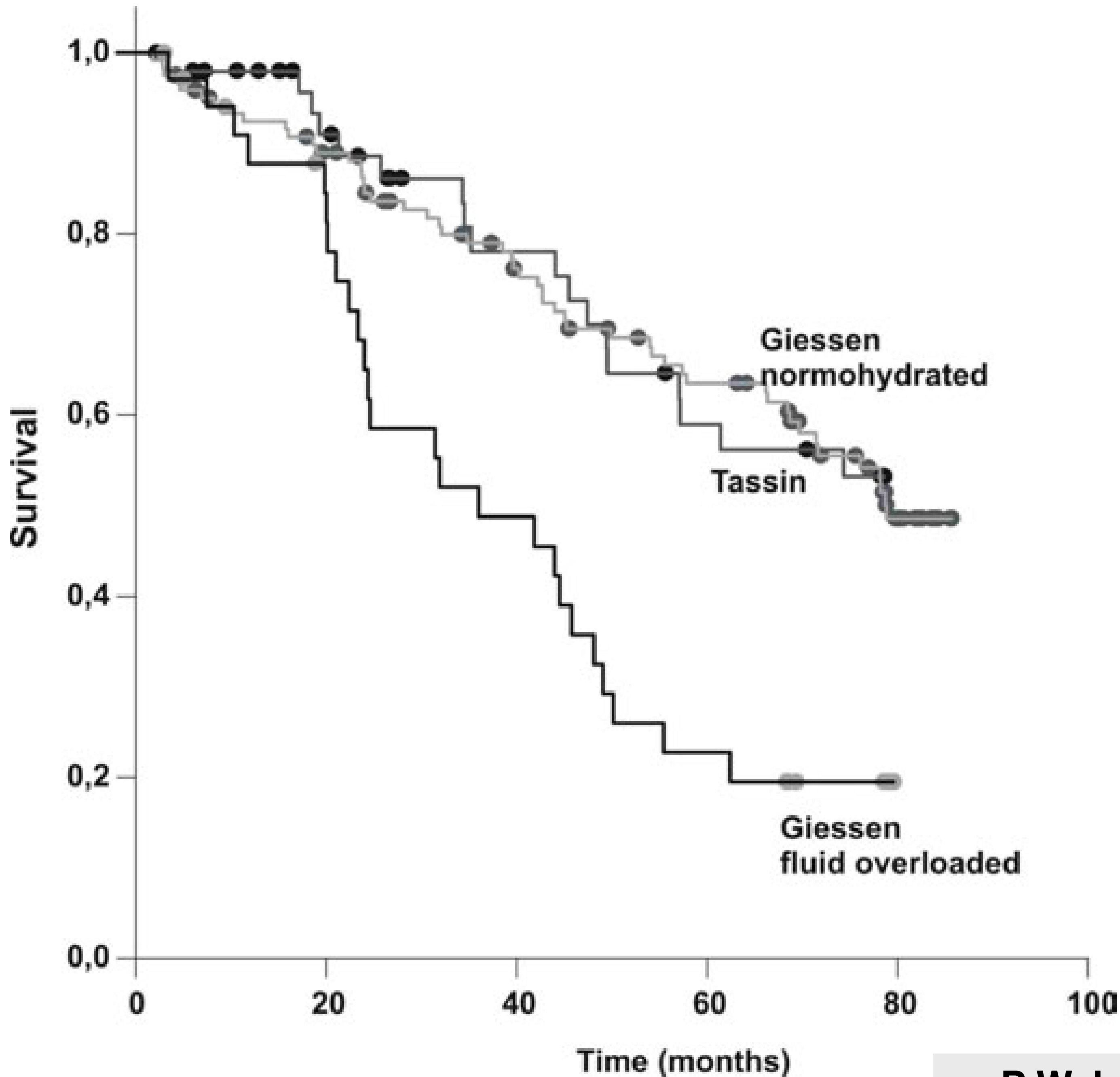
Giessen: 180 non selected HD patients

Overhydration (%): Fluid excess/ECW >15%





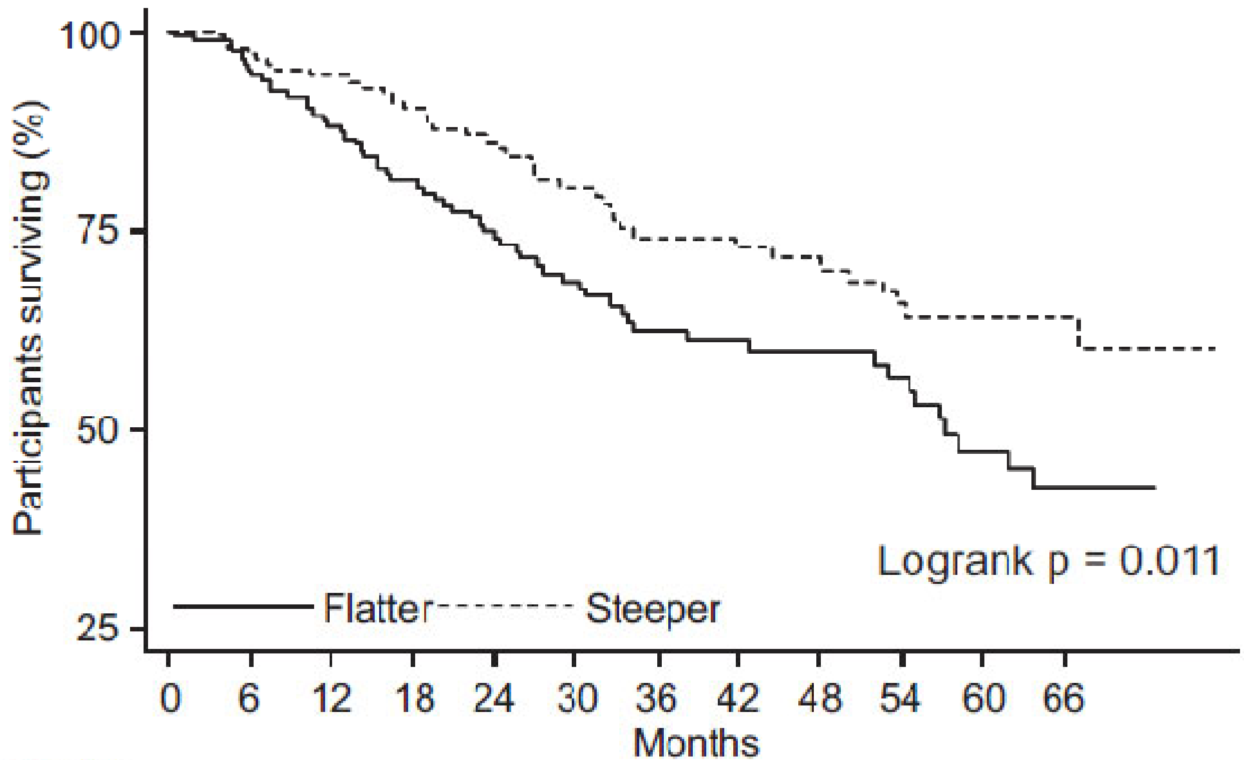
P Wabel courtesy



P Wabel courtesy

Chronic fluid retention and mortality (3)

Relative Plasma Monitoring – Refilling status



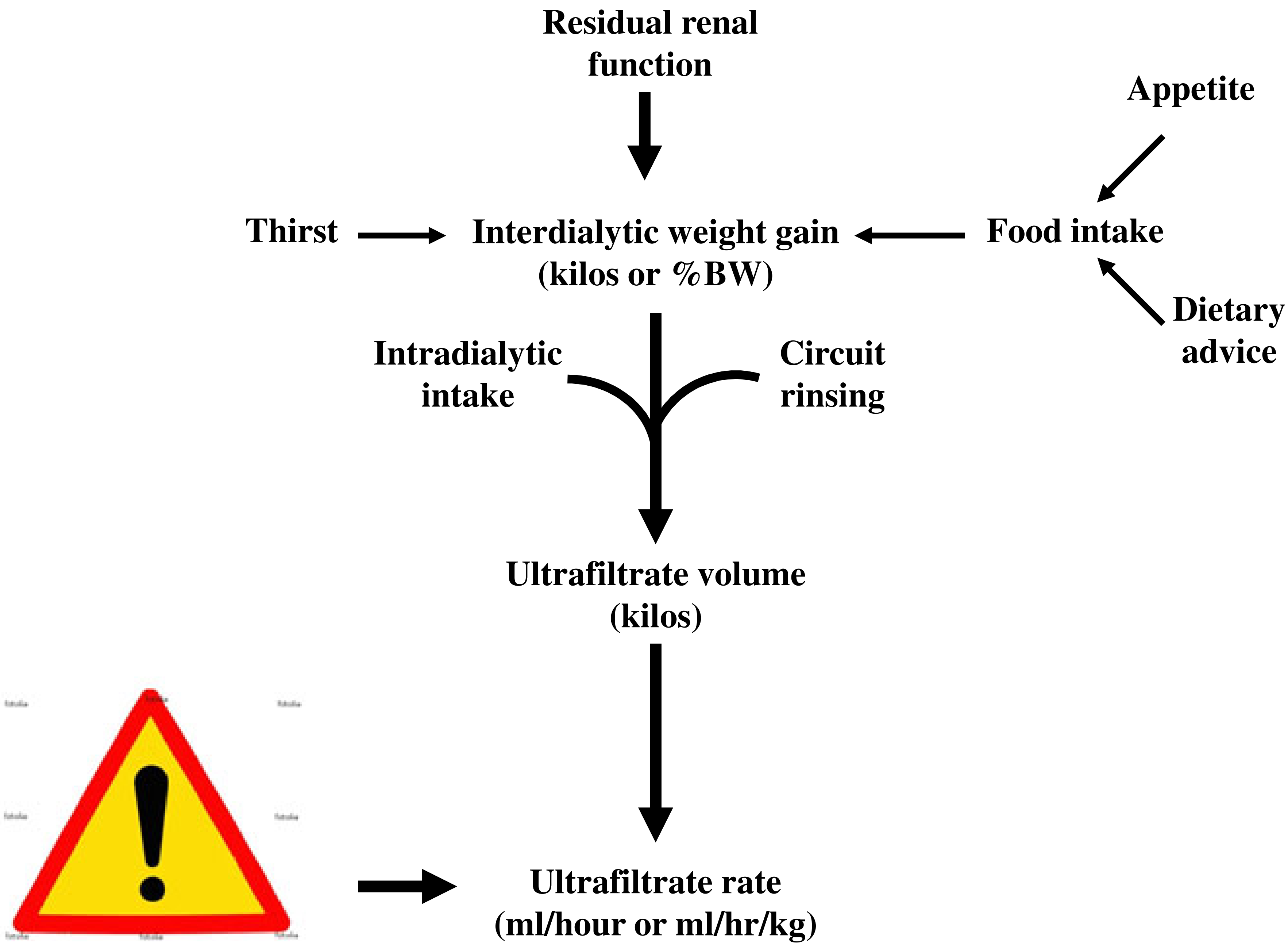
Number at risk

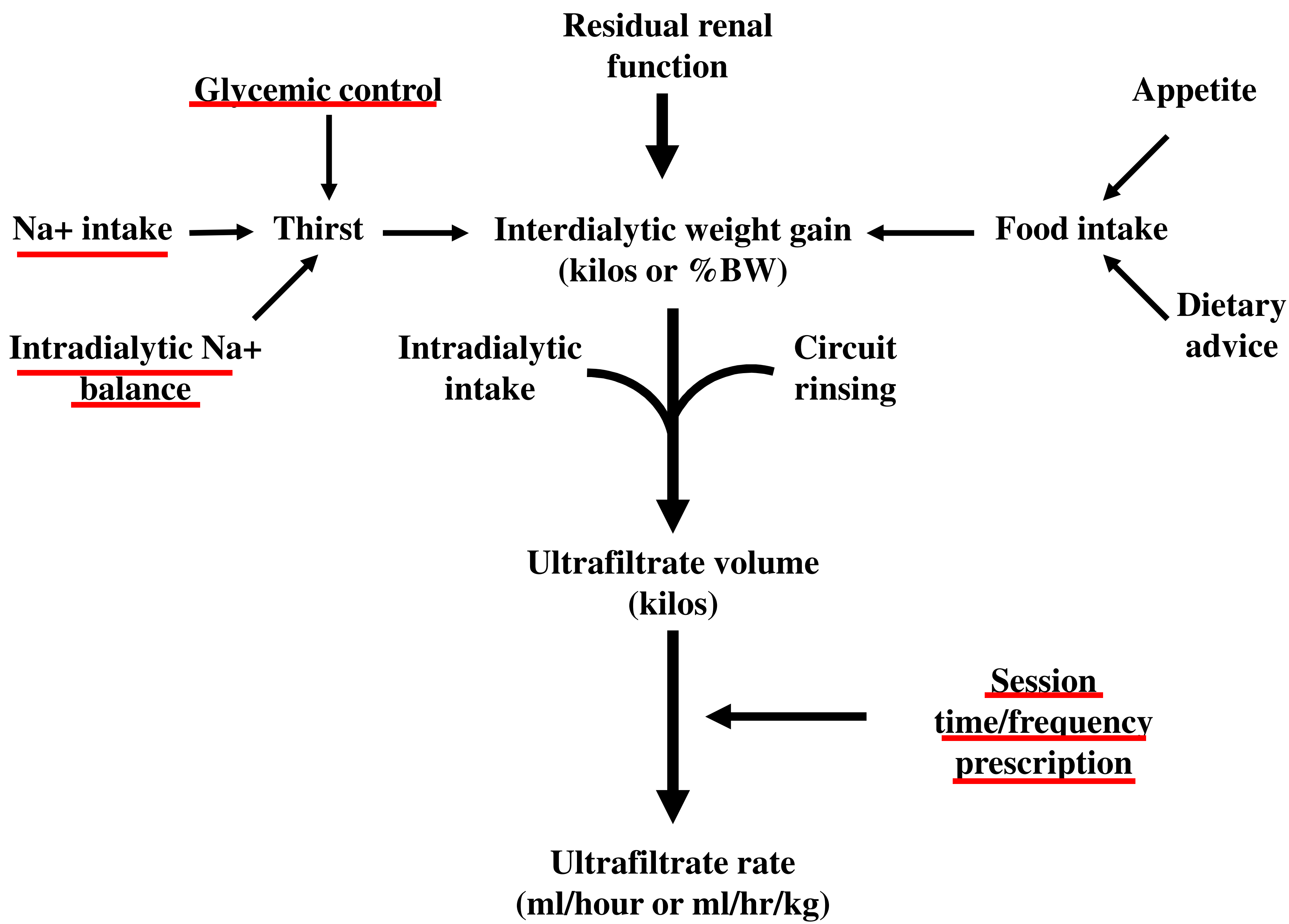
Flatter slope	155	136	121	103	87	73	52	44	39	34	22	15
Steeper slope	154	138	123	111	97	80	66	55	51	43	29	18

Agarwal Hypertension 2010

Summary #2

- High UF rates (↔ high IDWG) is associated with decreased survival when adjusted for comorbidities
- High UF rate leads to intradialytic side effects
- Prescribed dry weight is not achieved with chronic fluid overload in a significant number of patients
- Chronic fluid overload is related with ↑ mortality


Residual renal function
Appetite
Thirst
Interdialytic weight gain (kilos or %BW)
Food intake
Dietary advice
Intradialytic intake
Circuit rinsing
Ultrafiltrate volume (kilos)
Ultrafiltrate rate (ml/hour or ml/hr/kg)

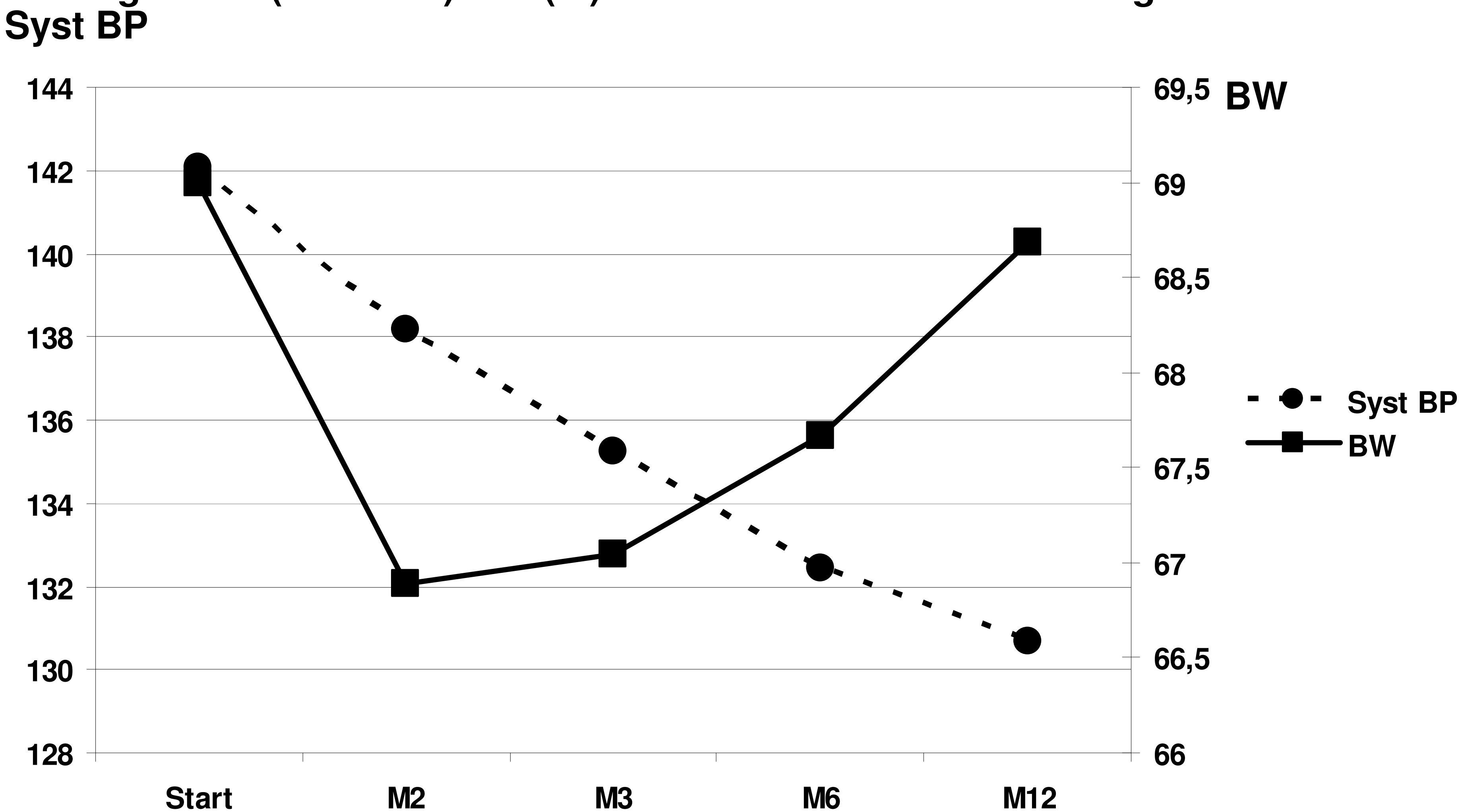


Residual renal function
Glycemic control
Appetite
Na+ intake
Thirst
Interdialytic weight gain (kilos or %BW)
Food intake
Dietary advice
Intradialytic Na+ balance
Intradialytic intake
Circuit rinsing
Ultrafiltrate volume (kilos)
Session time/frequency prescription
Ultrafiltrate rate (ml/hour or ml/hr/kg)

Clinical effects of strict UF policy and low salt diet

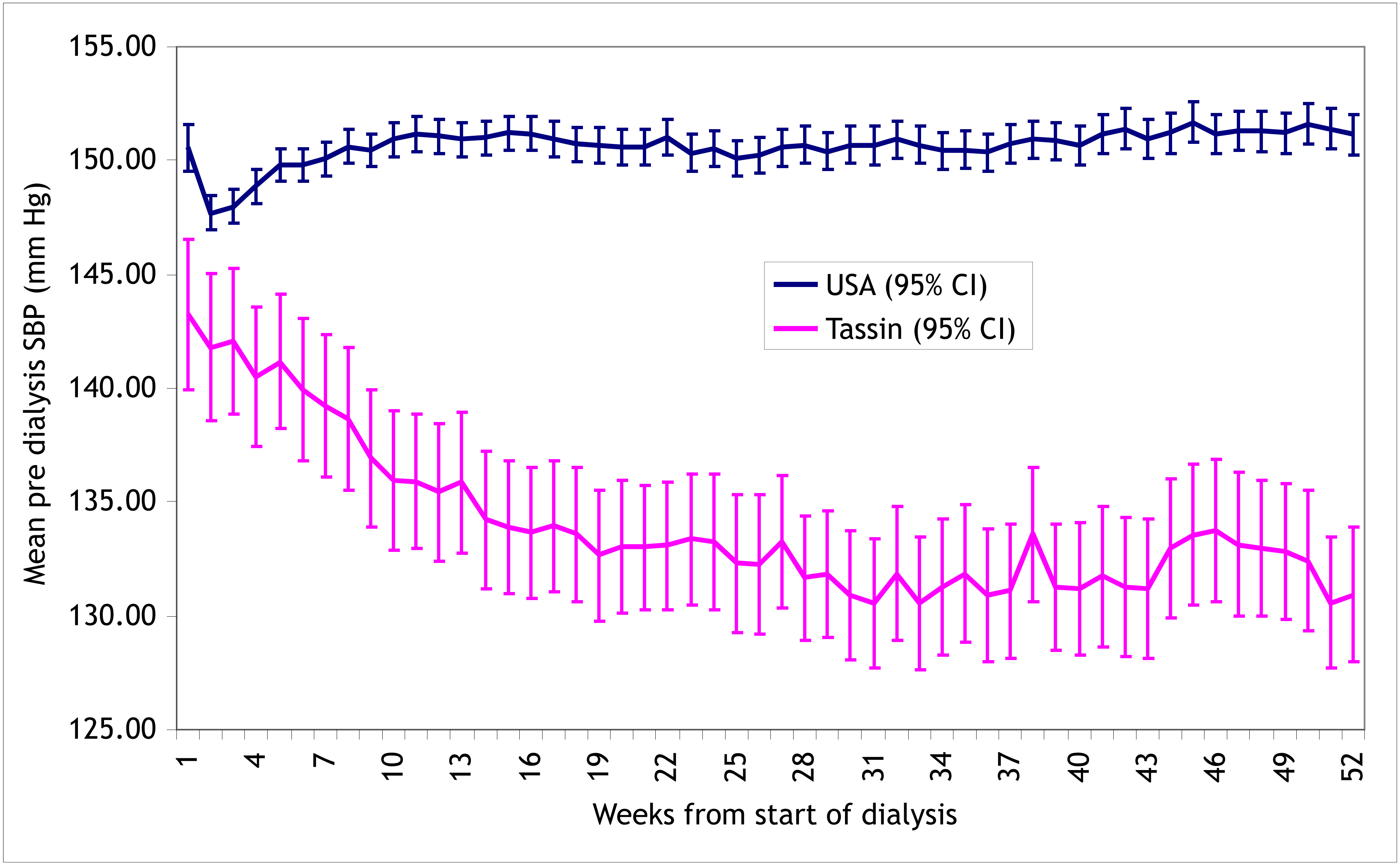
Dry weight method applied in 308 incident patients between 2000-2008

Age=65.8 (20.5-95.7) F/M (%)=37/63 Diabetes=36.4% Average TT:6.6 hours



AntiHTA drugs	2.38		0.51	0.44	0.35

Personal data



Sipahioglu, ASN San Diego 2009

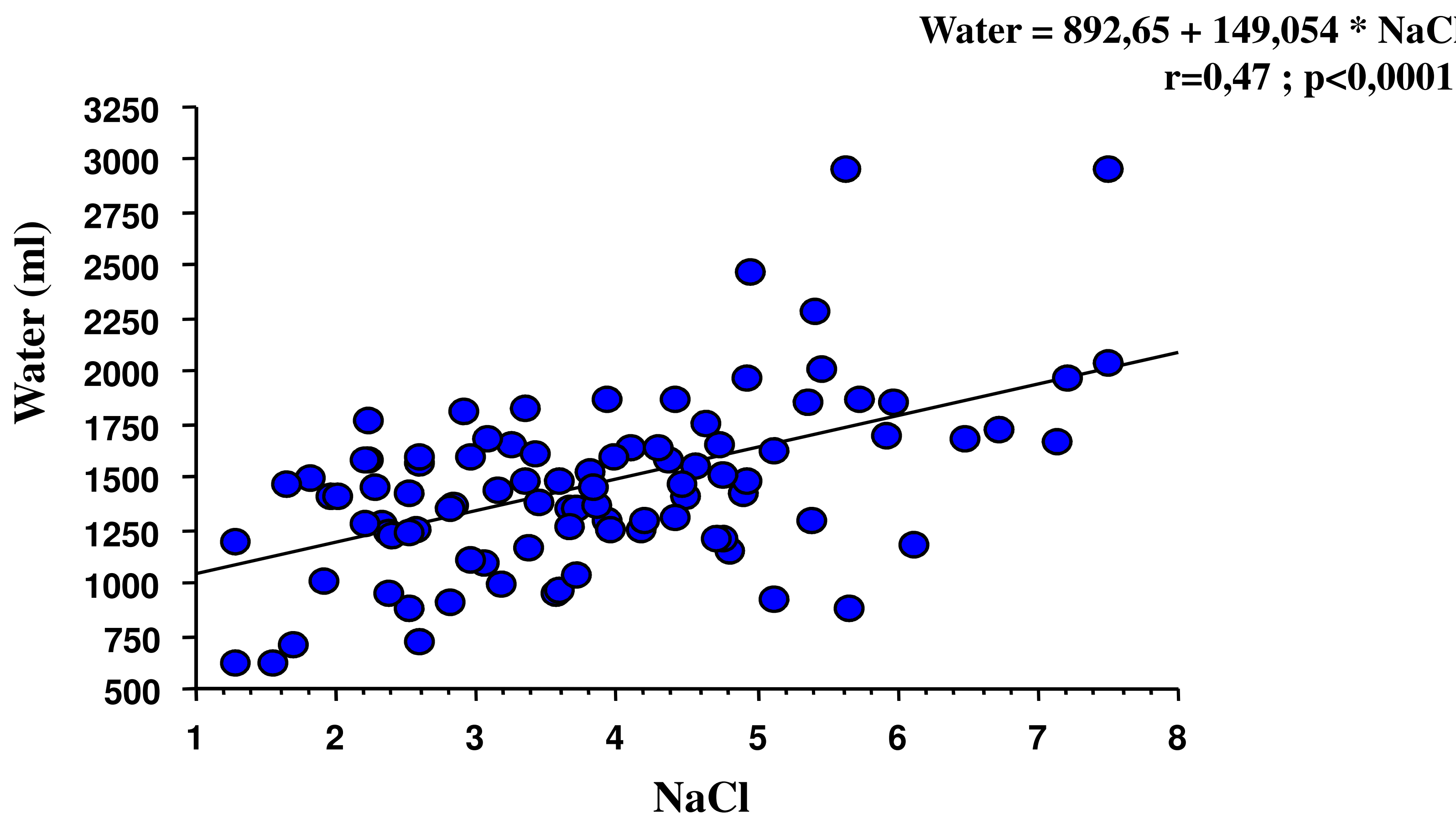
Correction of HTN with standard dialysis and DW method

3x4 hours/week in prevalent patients
Strict UF policy, low salt diet, extra UF sessions
36 months of follow-up

	Start	6	12	24	36	>36
n Patients	67	67	60	43	22	19
BW (kg)	64.5±13	63.5±14	65.0±11	67±9	66±12	67±13
IDWG (kg)	2.9±1.3	1.7±0.9	1.8±1.0	1.8±1.1	1.9±1.2	1.8±1.2
CTI (%)	52±4	47±3	45±3	43±3	42±4	42±5
Syst BP (mmHg)	173±17	139±16	131±17	122±11	118±12	114±10
Dia BP (mmHg)	102±9	86±11	81±9	76±6	73±6	71±7

Ozkahya, Am J Kid Dis 1999,34:218-221

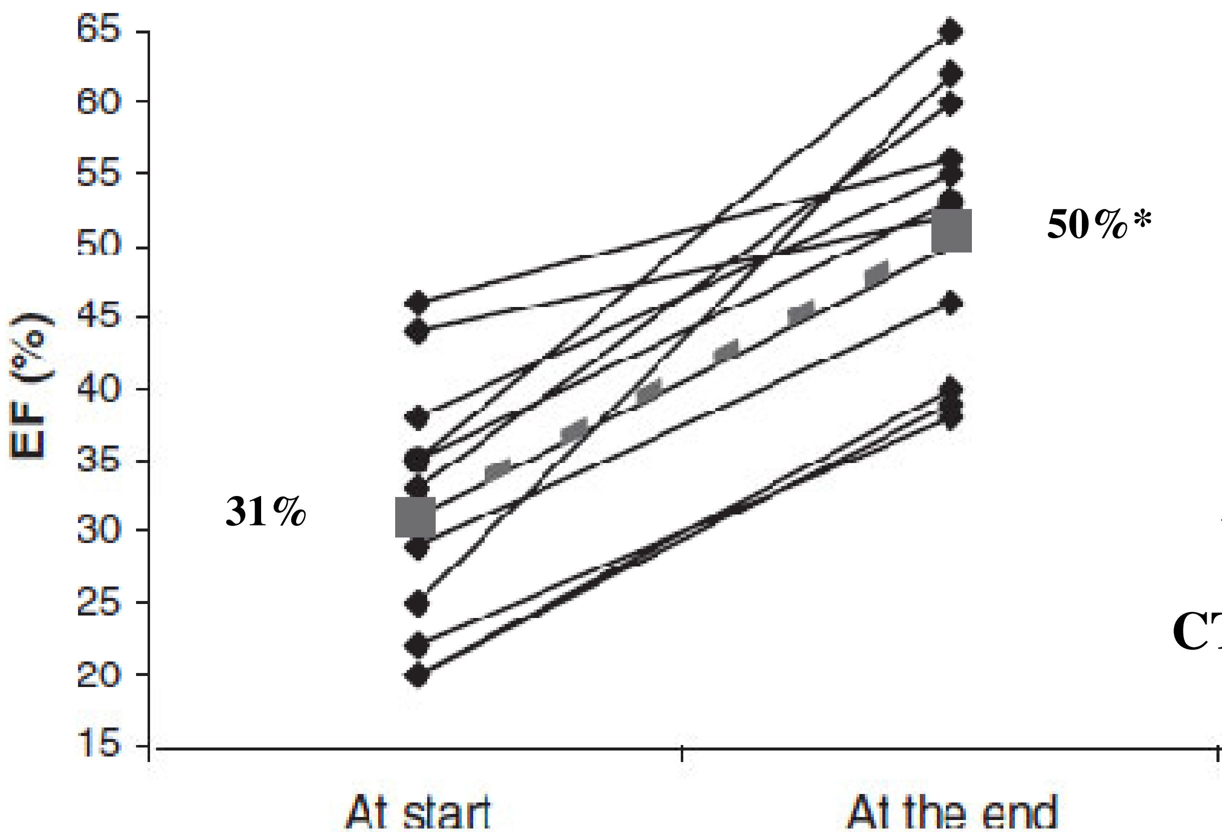
Relationship between salt and water intakes



Chazot Sem Dial 2009

Ejection fraction and long-slow Ultrafiltration

Uremic cardiomyopathy



12 pts
20 to 120 days
-12±10 kgs
CTI:0.59 to 0.47

Toz, HD Int 2007

Interventional studies on salt restriction

TABLE 1. Interventional studies of salt restriction in dialysis patients

Reference	Year	Patients and method	Daily salt prescription (g/j)	Follow-up	Control group (yes/no)	Salt intake assessment (yes/no)	Dialysate Na^+ decrease	DW decrease	↓ IDWG (yes/no)	↓BP (yes/no)	↓Anti-HTN drugs (yes/no)
Krautzig (35)	1998	8 HD	6 g	Unknown	No	No	Yes 140 → 135	No	Yes[a]	Yes	Yes
Ang (36)	1999	5 HD	6–8 g	??	No	No	Yes 142 → 135	No	NA	Yes	NA
Ozakhya (31)	1999	67 HD	6 g	36 months	No	No	NA	Yes	Yes	Yes	Yes
Rigby-Mattews (22)	2000	28 HD	1 g	44 hours	Yes[b]	No	No	No	Yes	NA	NA
Maduell (21)	2000	15 HD	7 g	2 weeks	Yes[a]	Yes[c]	No	No	Yes	Yes	NA
Gunal (19)	2001	47 DP	6 g	4 weeks	No	No	No	No	NA	Yes[d]	Yes
Al-Hilali (37)	2006	105 HD	NA	??	No	No	No	Yes	NA	Yes	NA
Kayikcioglu (20)	2009	394 HD	5 g	Cross-sectional	No	No	No	Yes	Yes	Yes	Yes

NA, no available; BP, blood pressure; IDWG, interdialytic weight gain; HTN, hypertension.
[a]In 50% of the patients; [b]cross-over study; [c]sodium mass transfer; [d]in 20/47 patients.

Chazot, Sem Dial 2009

Effect of strict UF control + salt-restricted diet

Ozkahya NDT 1998

	BW (kg)	CTI (%)	Pre-dialysis SBP (mmHg)	Pre-dialysis DBP (mmHg)
At start of HD	55.7 ± 13.1	54 ± 3	191 ± 20	109 ± 7
At first echo	53.2 ± 13.2	48 ± 2	139 ± 20	83 ± 11
$P^a <$	NS	0.001	0.001	0.001
In between ($n = 9$)*	53.3 ± 12.5	45 ± 3	129 ± 16	80 ± 10
$P^b <$	NS	0.01	NS	NS
At end of observation	55 ± 12	43 ± 4	116 ± 12	73 ± 7
$P^c <$	NS	0.001	0.001	0.001

Left Ventricular Mass Index: 175±60 → 105±39 gm^2

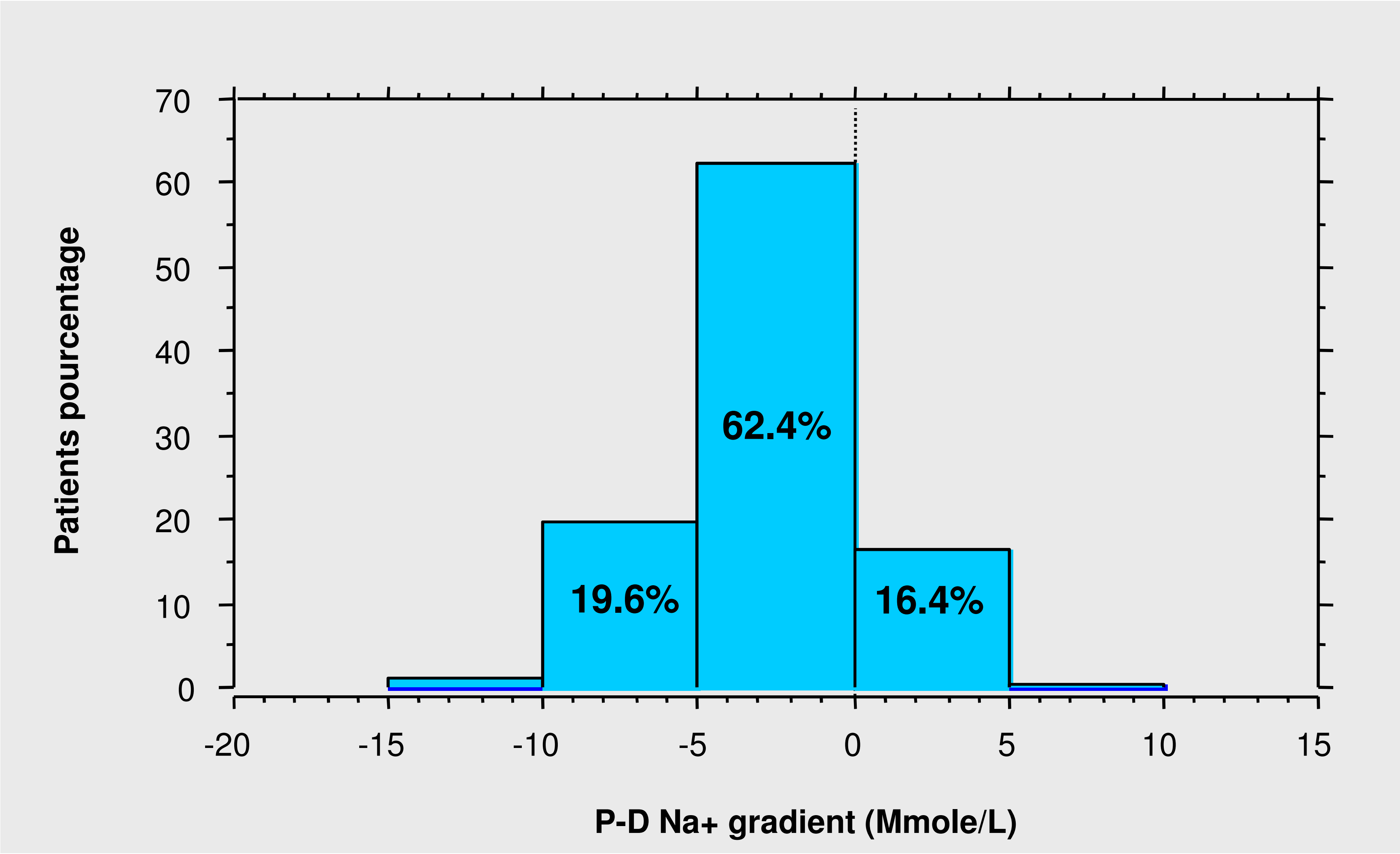
15 patients during 37±11 months

Effect of salt restriction
Retrospective cross-sectional study
Kayikcioglu, NDT 2009

	Centre A Salt restriction strict UF policy	Centre B Standard Loose DW policy
n	**190**	**204**
HTN history (%)	**78**	**83**
Anti-HTN drugs	**7%**	**42%****
IDWG	**2.29 kilos**	**3.31 kilos****
Predial BP	**126/75**	**126/75**
% SBP>140	**18%**	**37%***
BP drops	**11%**	**27%***
LV hypertrophy	**74%**	**88%***

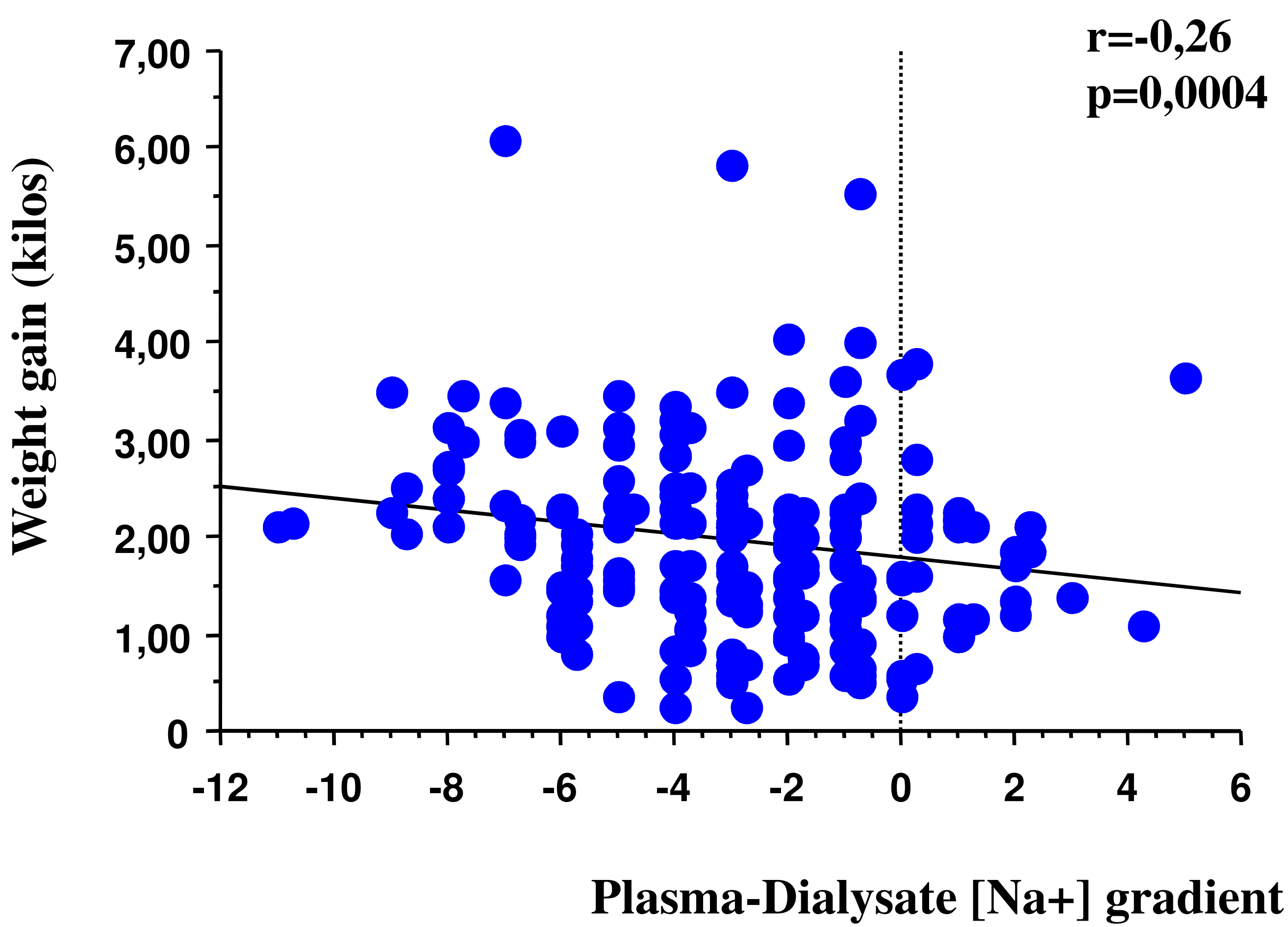
Do not forget dialysate [Na]…

Cross-sectional study among 189 HD patients with Na+ dialysate concentration at 138 mmoles/l



ISBP meeting
Rotterdam 2005

Weight gain Δ versus P-D Na+ gradient



ISBP meeting
Rotterdam 2005

Sodium dialysate individualization

De Paula, Kidney Int 2004,66:1232

27 stable HD patients studied 6 weeks

Cross-over study :

Na dialysate=138 mmoles/l vs Na dialysate = 0,95 x Plasma Na

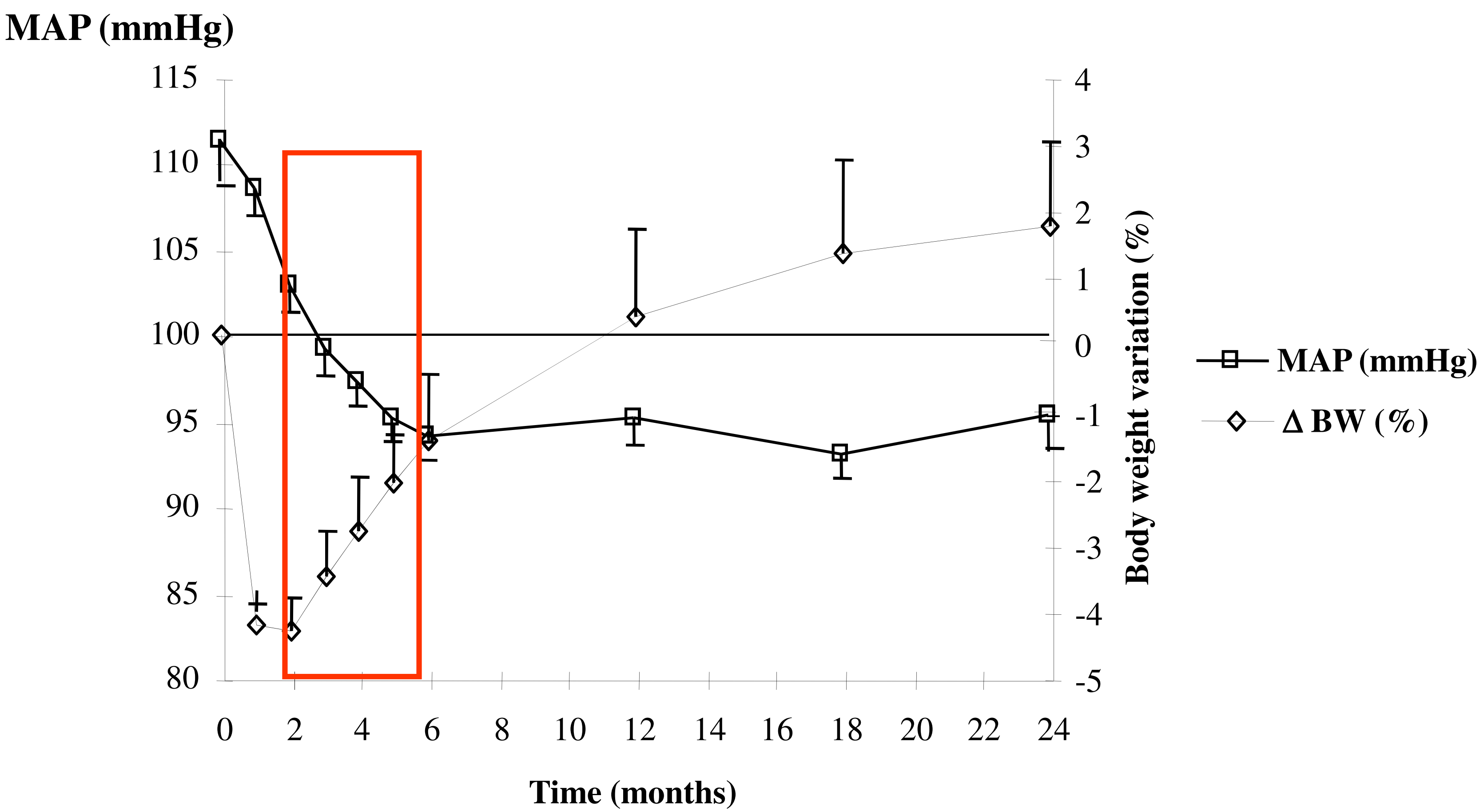
(average= 134 mmoles/l)

- ↓Thirst ↓ IDWG ↓ HD-related symptoms
- ↓ pre-HD BP (in patients with uncontrolled BP at baseline)

Correction of vascular remodeling or the lag phenomenon

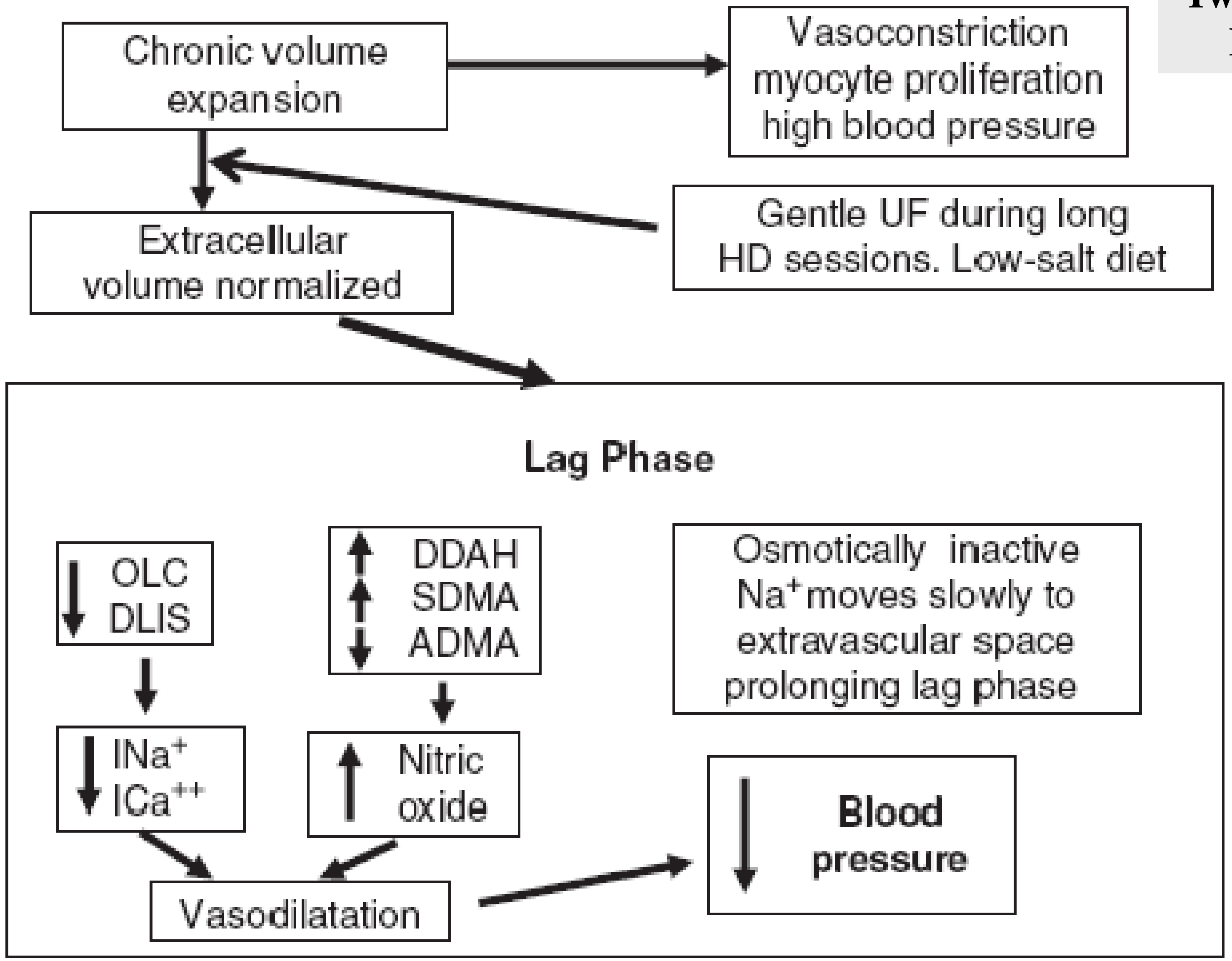
The lag phenomenon

Charra et al, AJKD 1998



Chazot, NDT 1999

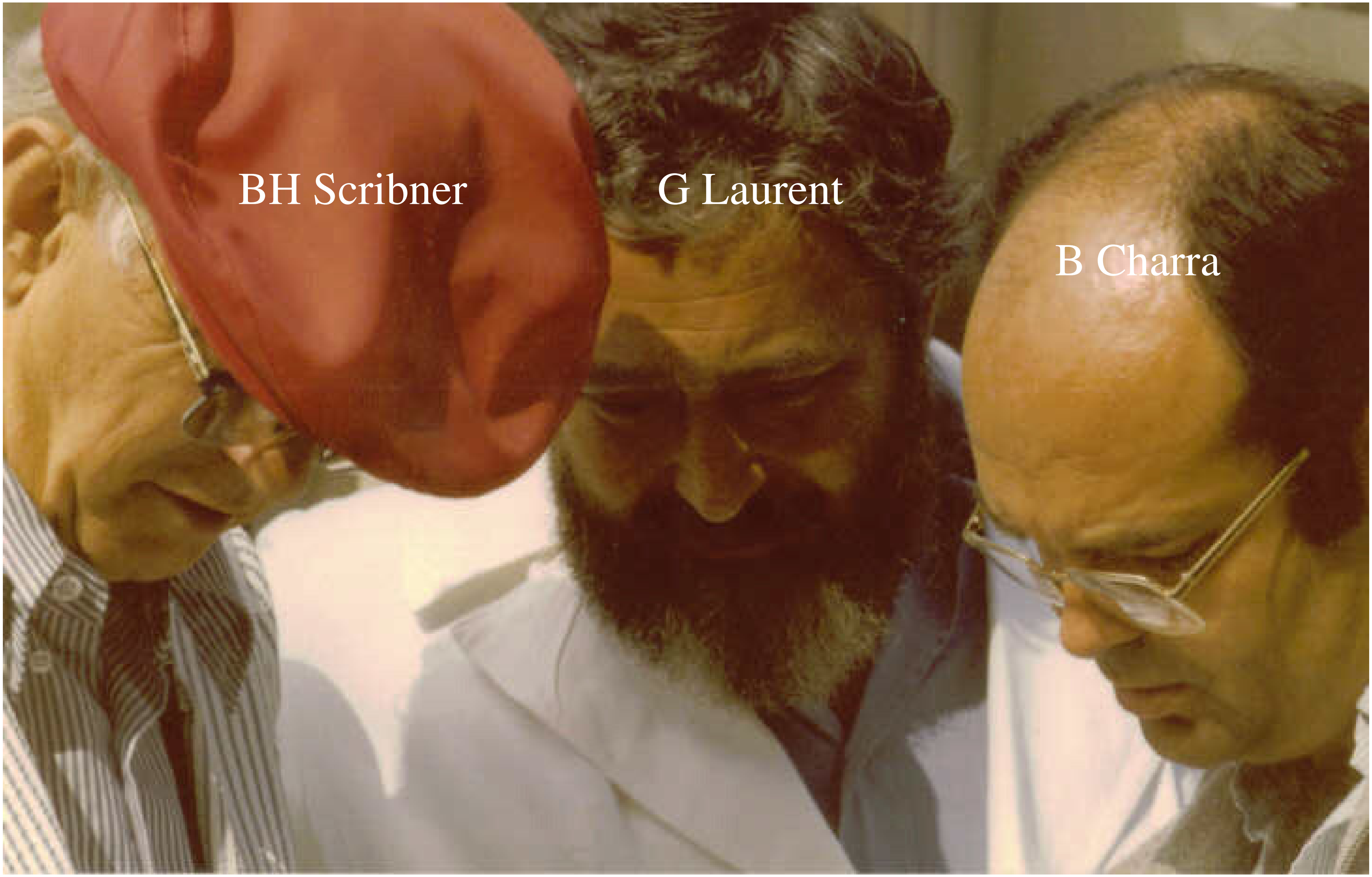
Twardowski
HDI 2008



Shown with nocturnal daily HD (Chan Hypertension 2003)

Conclusions

- Sodium: a true uremic toxin, the main factor responsible for fluid accumulation in CKD, hypertension and vascular remodeling
- Correction of EC fluid excess by the dry weight method + salt restricted diet lowers BP and may correct CV remodeling
- High UF rates: the enemy to apply dry weight method because of intradialytic side-effects, especially hypotension leading to chronic fluid overload
- High UF volumes and chronic fluid excess are associated with decreased patient survival and ↑ CV mortality
- Salt restriction is the main and only tool to limit the UF rate when session time/frequency increase is not possible. Patient education is the key


BH Scribner
G Laurent
B Charra