Sodium and Fluid Overload in CKD

Consequences of chronic overhydration

ECV expansion ~~→~~ increase of renal filtration

increased blood pressure

increased vascular stiffness

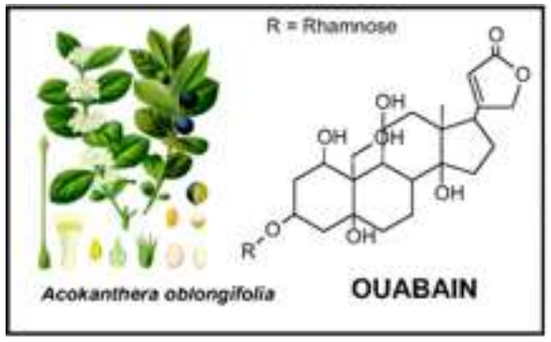
Left ventricular hypertrophy

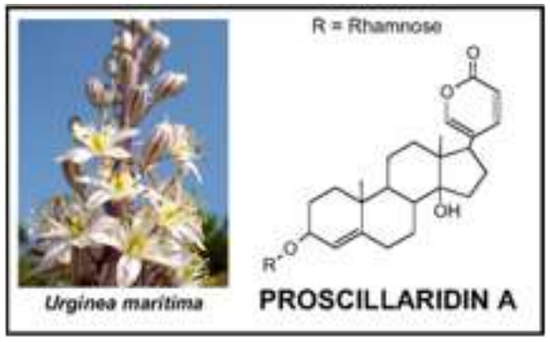
Sodium

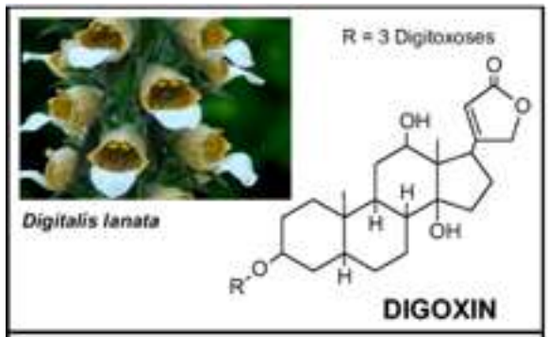
a) oxidative stress
b) Tumor growth factor-β
c) ratio α-2 to β-2 adrenoreceptors rises

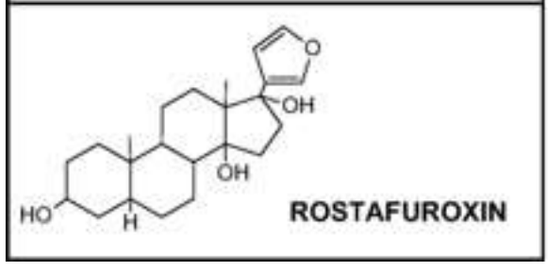
Ouabain
Marinobufagenin

Endogenous Cardiotonic Steroids









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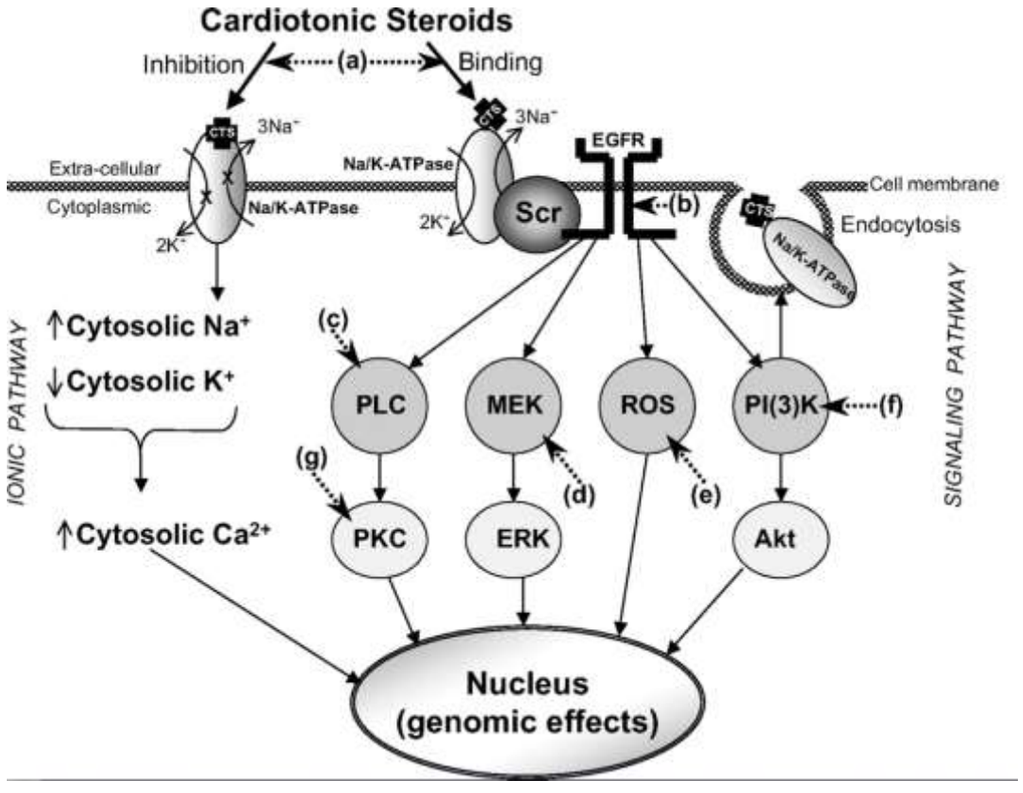
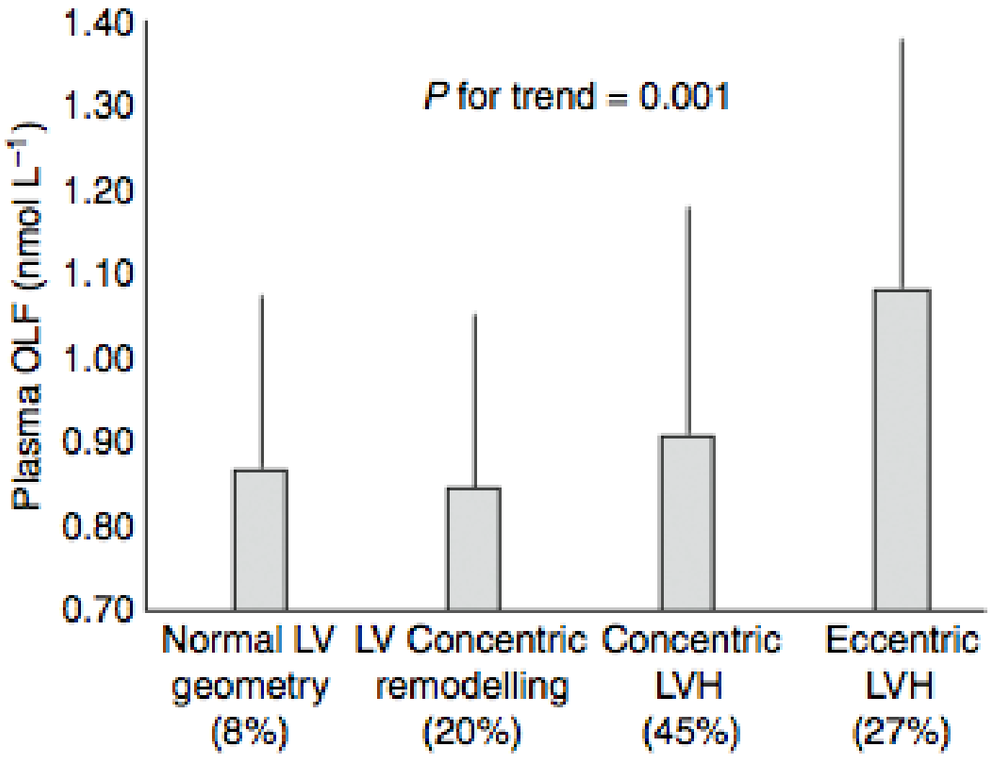
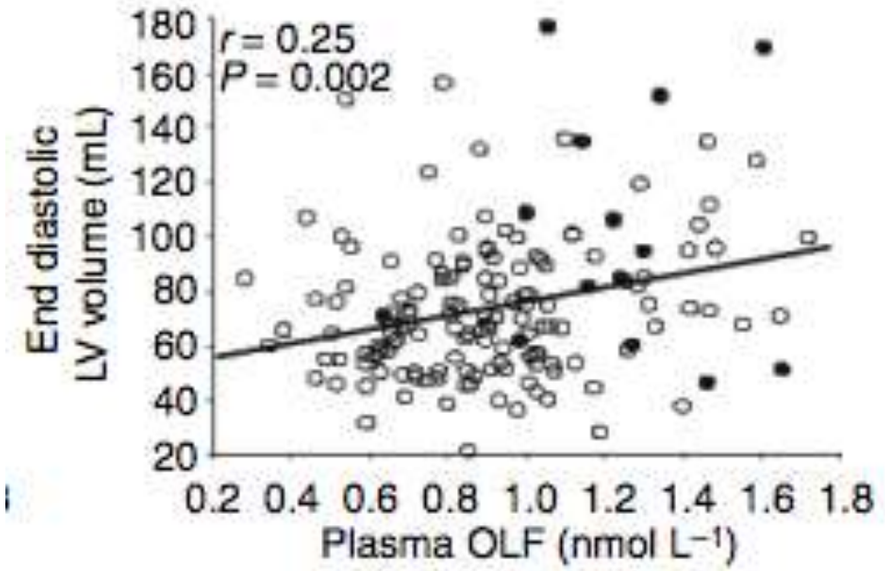


Bagrov AY, Shapiro JI, Fedorova OV. Endogenous cardiotonic steroids: physiology, pharmacology, and novel therapeutic targets. Pharmacol Rev. 2009;61(1): 9-38.

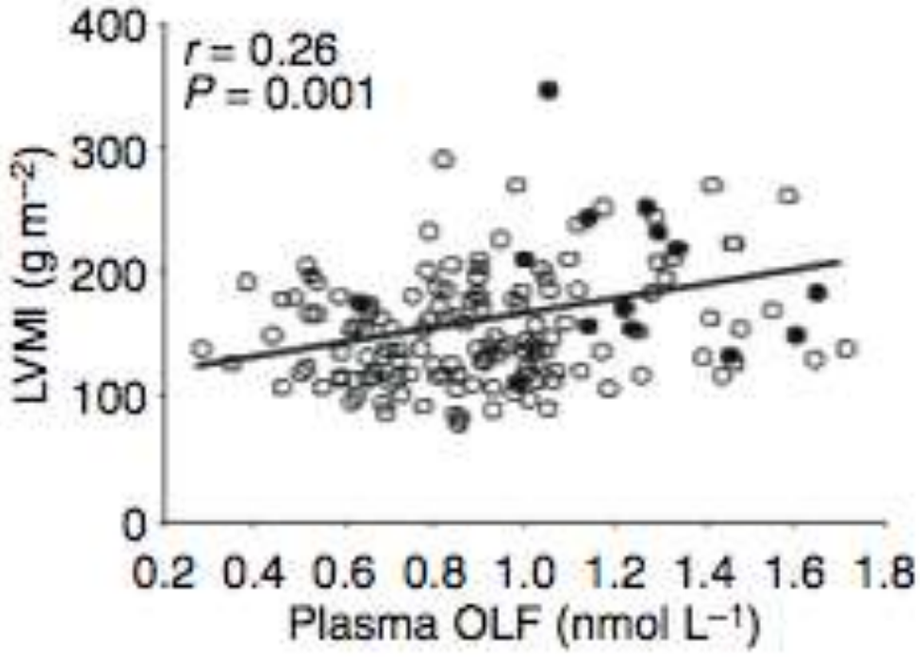
Endogenous Cardiotonic Steroids



Relationship of plasma ouabain and left ventricular geometry in HD pts



Relationship of plasma ouabain with end-diastolic left-ventricular volume.



Relationship of plasma ouabain with left-ventricular mass index (LVMI).

Stella P, et al. Endogenous ouabain and cardiomyopathy in dialysis patients. J Intern Med. 2007.

Nephrol Dial Transplant (2006) 21: 2052–2056

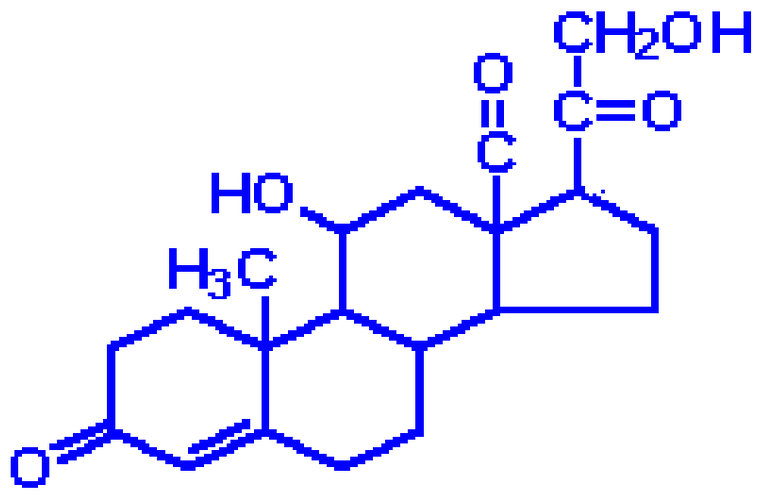
Salt—friend or foe?

Eberhard Ritz

Some physiology …

volume decrease

aldosterone rises



sodium reabsorbed

kidney

Salt – sodium chloride - NaCl

- Salt tax = Gabelle (introduced by Karl V. in the 13th century in France)
- 9 kg per person had to be purchased each year
- about 12 % of the income of a peasant family
- Gabelous = special Police in France to fight salt smuggling
- 3500 executions reported in 1788 for salt smuggling

❖ Roman kitchen: 25g/day (at the time of Caesar)

❖ Swedish kitchen: 100g/day (Vikings)

❖ French kitchen: 20g/day (Middle Ages)

Classical view

Aldosterone

↓

Kidney

↓

Salt retention

↓

Blood pressure

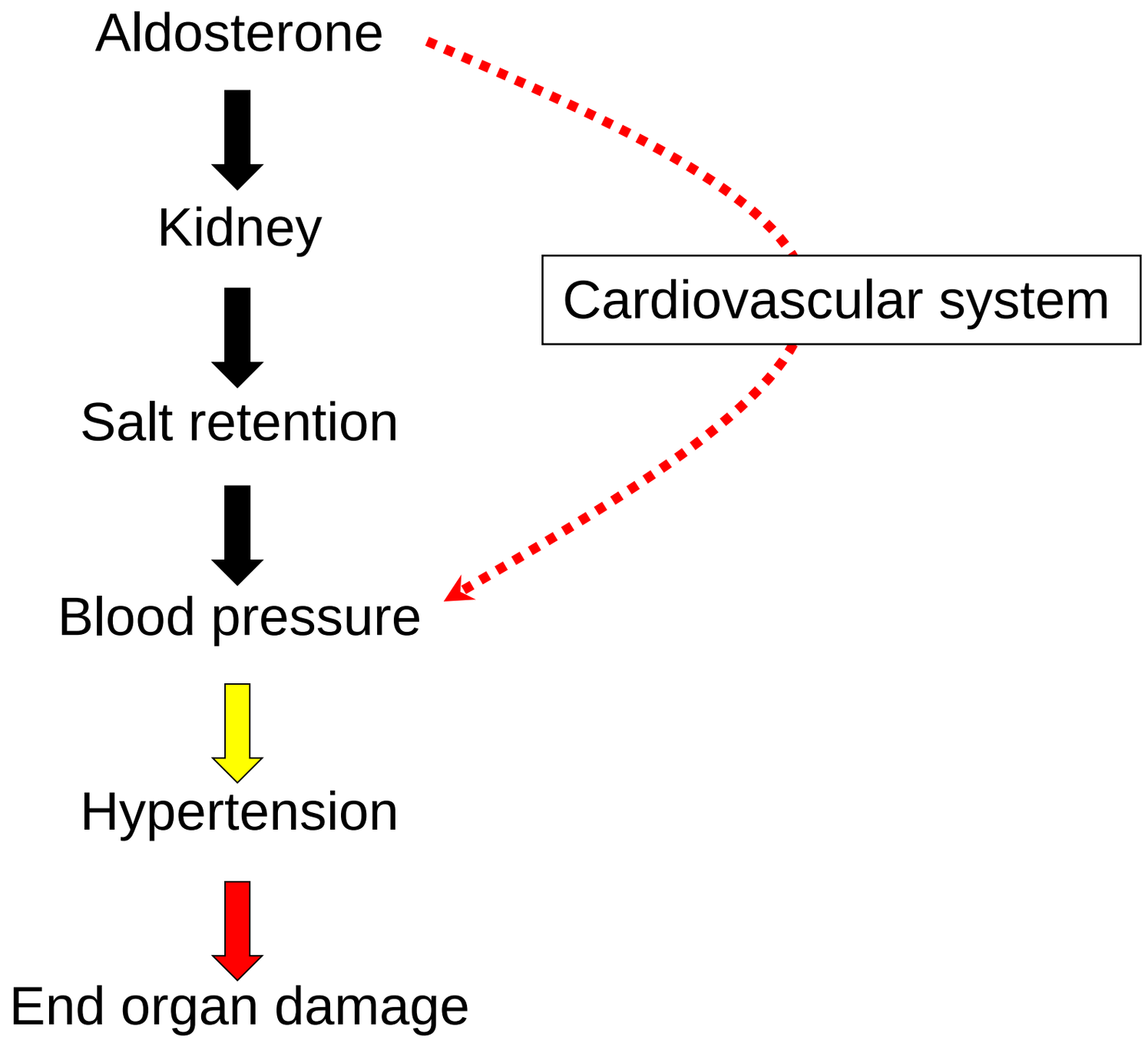
↓

Hypertension

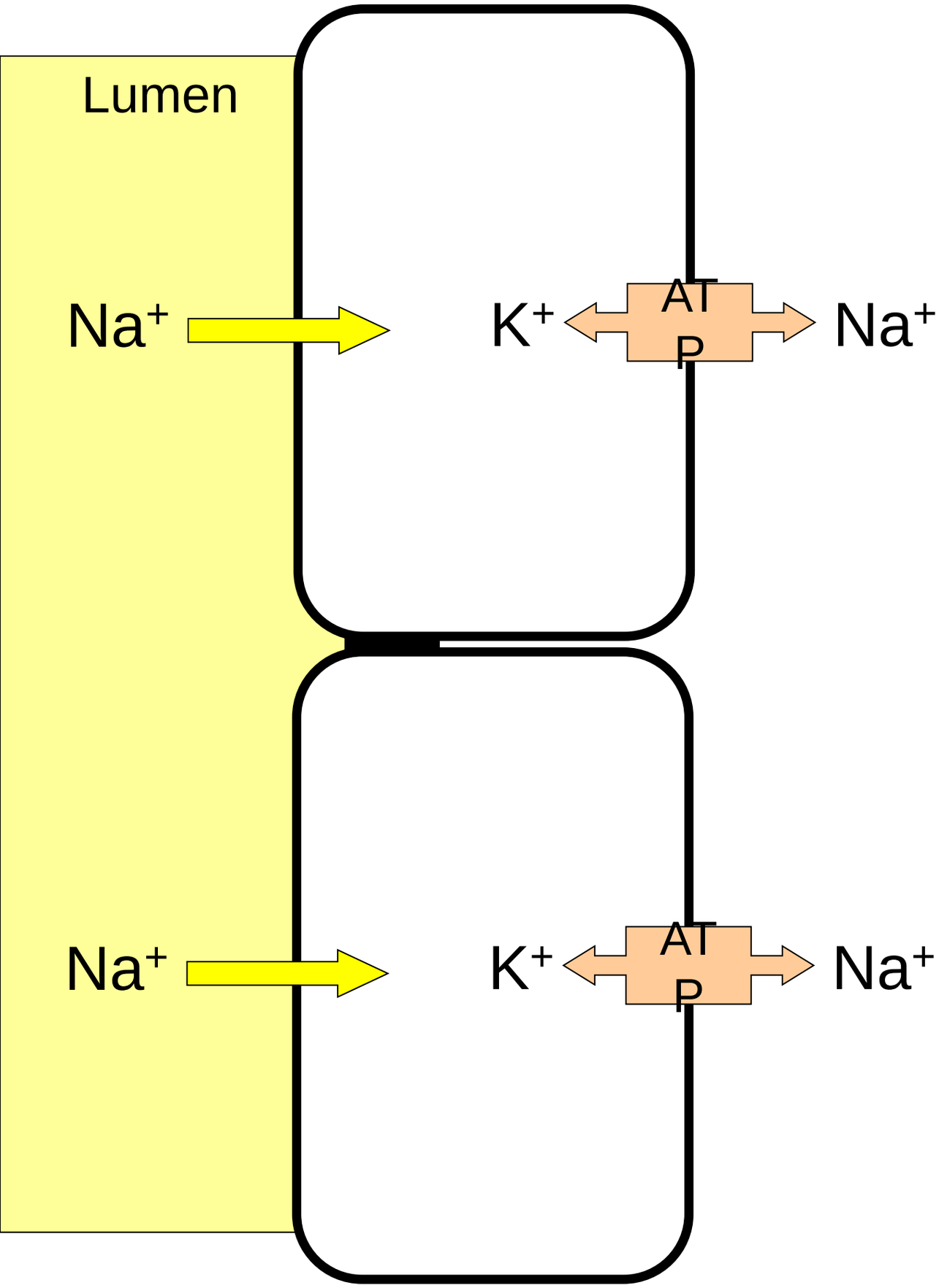
↓

End organ damage

Paradigm shift



Aldosterone acts on epithelium



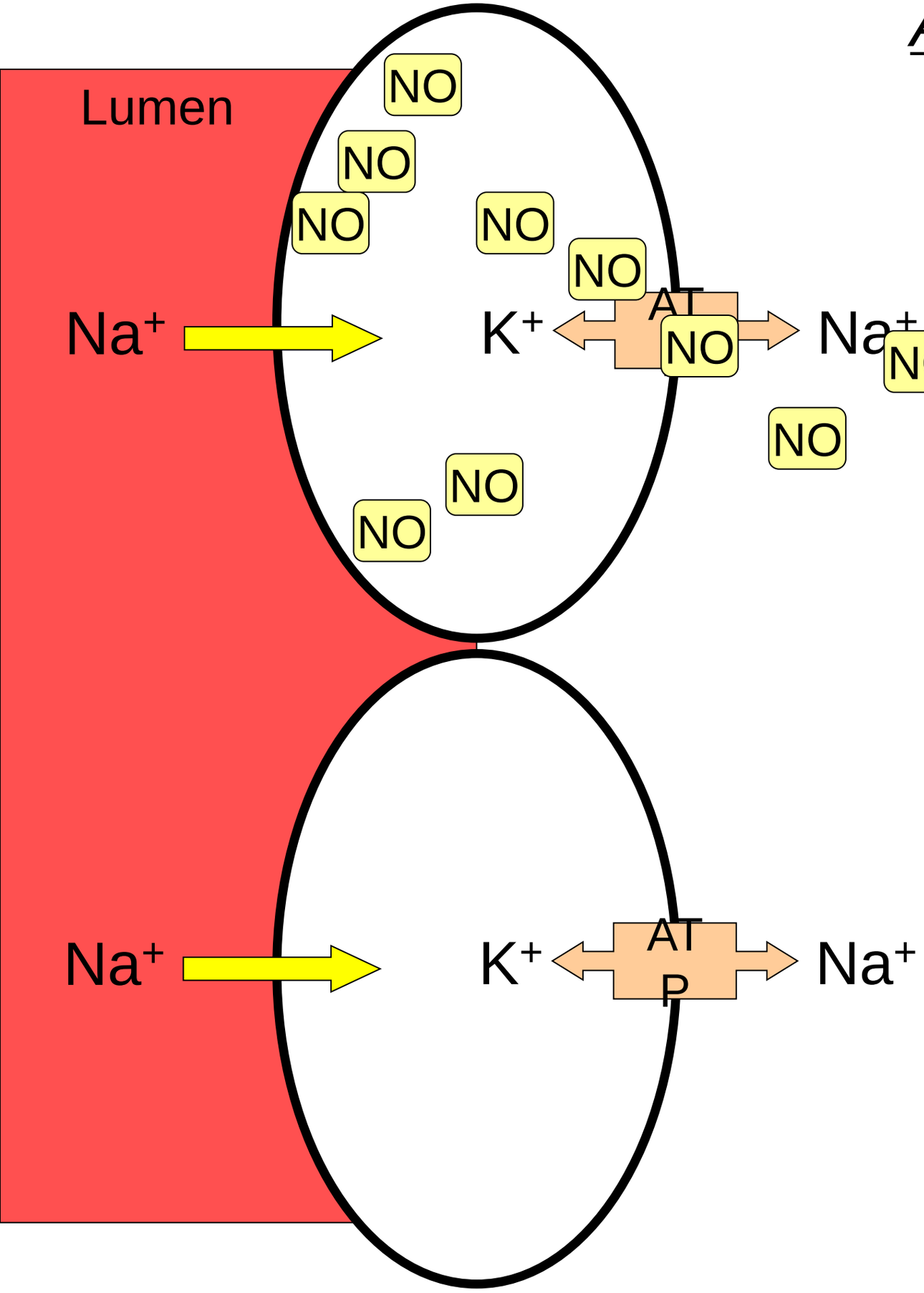
Ion Transport

↓

blood pressure

- classicial view -

<u>Aldosterone</u> acts on endothelium



<u>interacts</u> with nitric oxide release

blood pressure

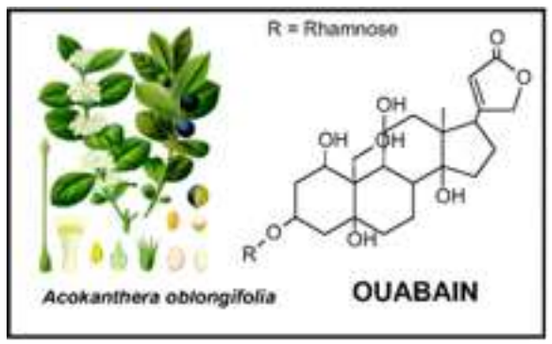
- new -

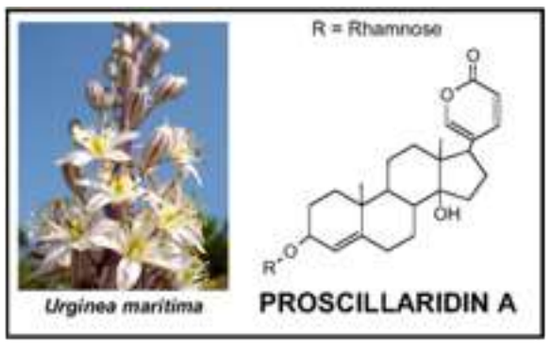
Aldosterone can have adverse effects on the cardiovascular system

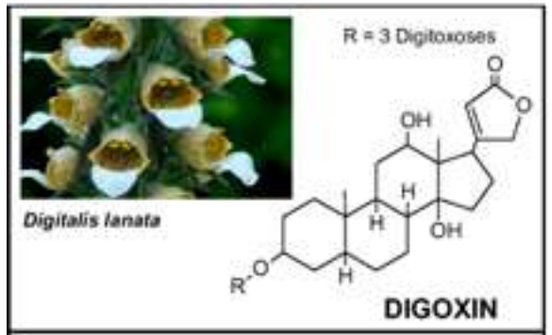
Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system	Weber and Brilla *Circulation 1991*
The effect of spironolactone on morbidity and mortality in patients with severe heart failure (RALES)	Pitt et al *NEJM 1999*
Aldosterone and vascular damage	*Duprez et al* *Curr Hypertens Rep 2000*
Aldosterone and vascular inflammation	Brown Hypertension 2008
Aldosterone, a vasculotoxic agent--novel functions for an old hormone.	Ritz and Tomaschitz *Nephrol Dial Transplant 2009*

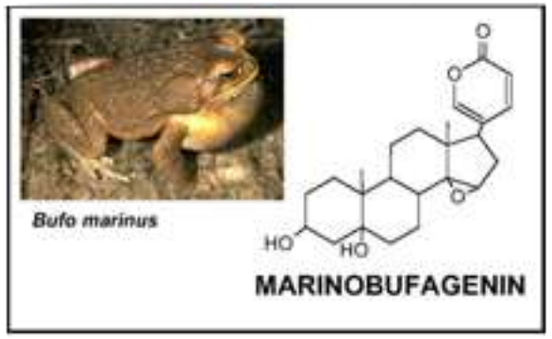
arbitrarily chosen publications

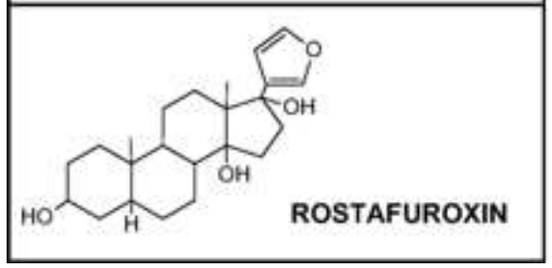
Endogenous Cardiotonic Steroids











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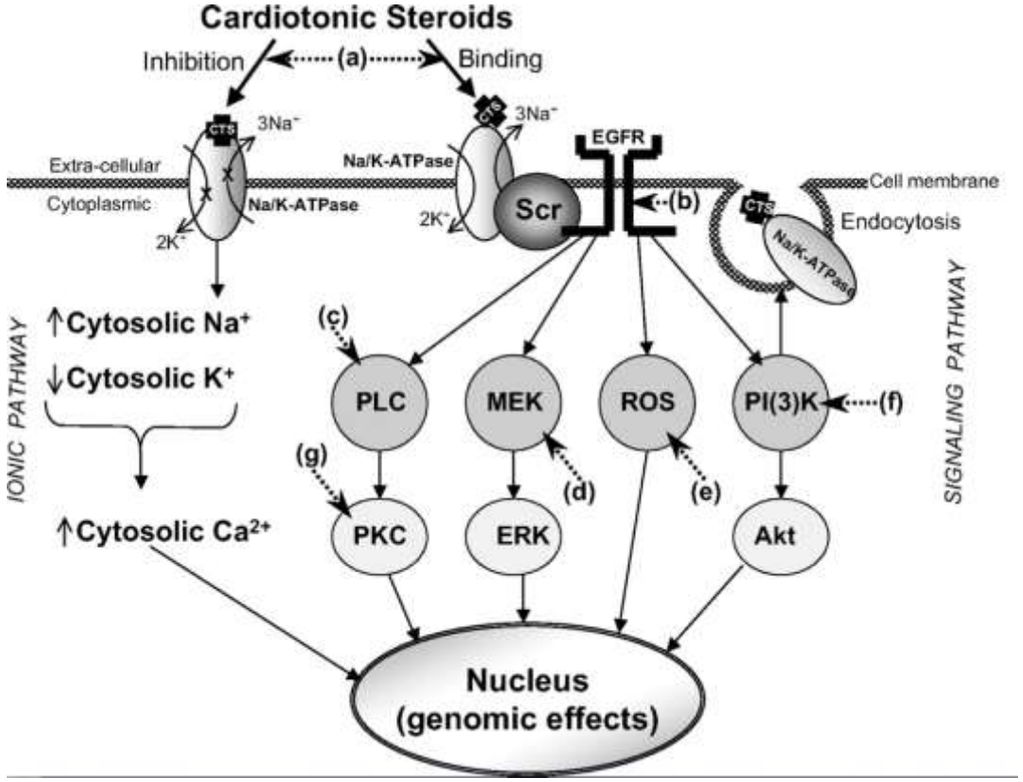
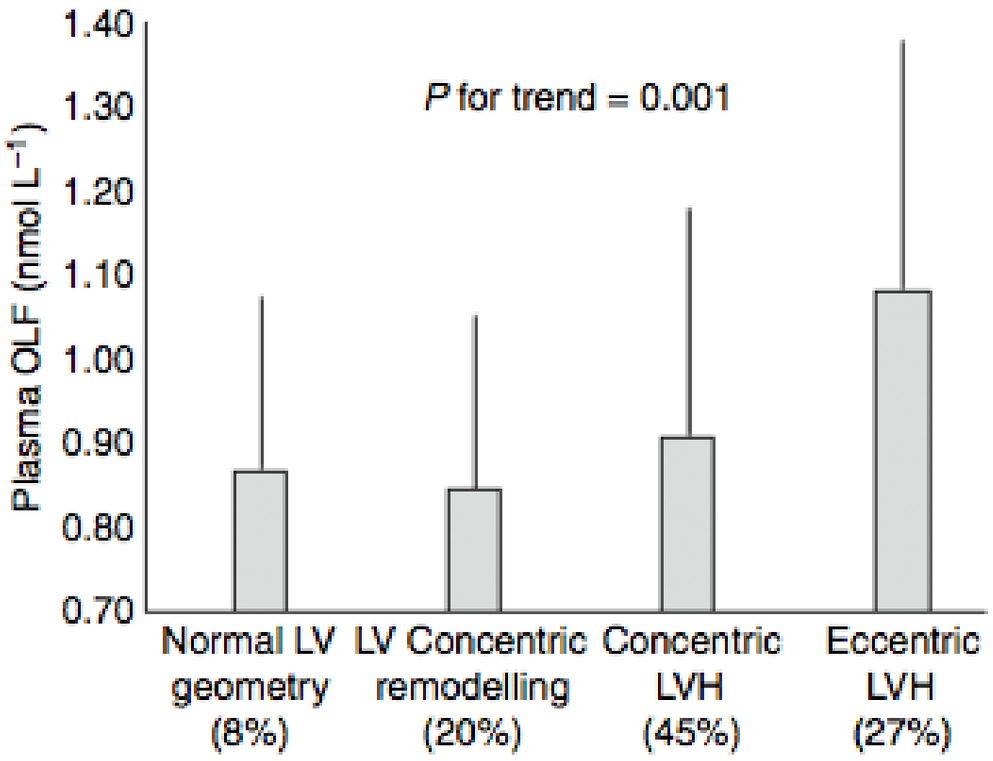
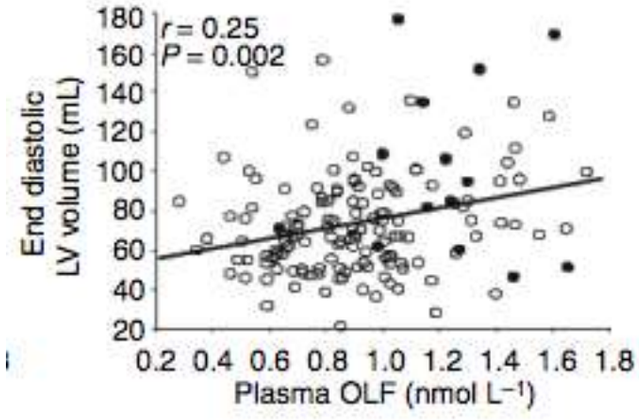


Bagrov AY, Shapiro JI, Fedorova OV. Endogenous cardiotonic steroids: physiology, pharmacology, and novel therapeutic targets. Pharmacol Rev. 2009;61(1): 9-38.

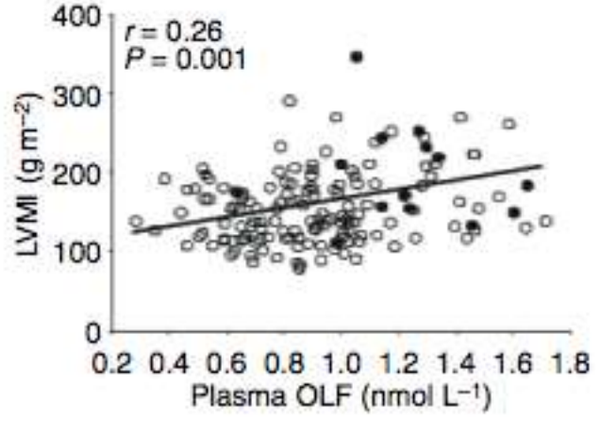
Endogenous Cardiotonic Steroids



Relationship of plasma ouabain and left ventricular geometric patterns amongst dialysis patients.



Relationship of plasma ouabain with left-ventricular mass index (LVMI).



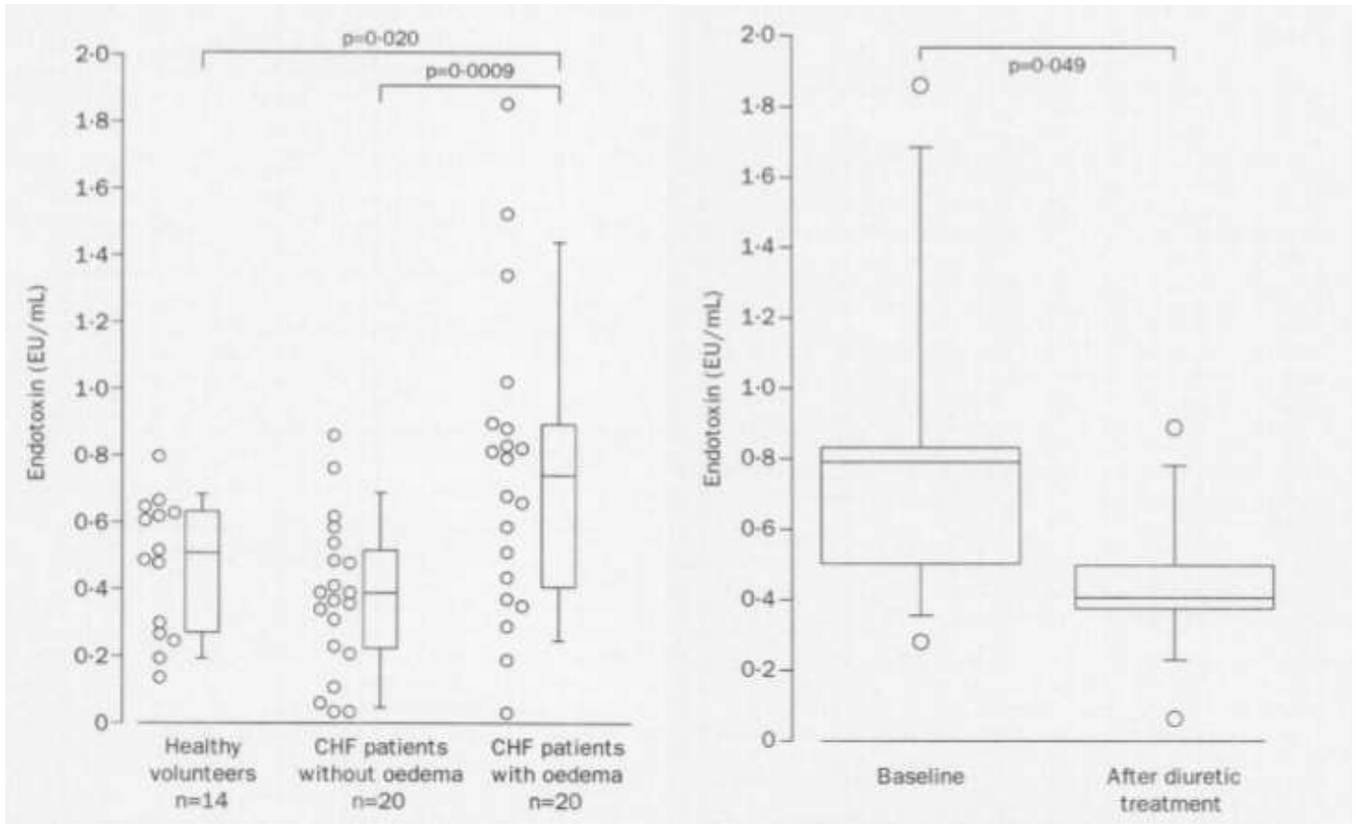
Relationship of plasma ouabain with end-diastolic left-ventricular volume.

Stella P, Manunta P, Mallamaci F, Melandri M, Spotti D, Tripepi G, et al. Endogenous ouabain and cardiomyopathy in dialysis patients. J Intern Med. 2007

Non-cardiovascular Consequences of overhydration

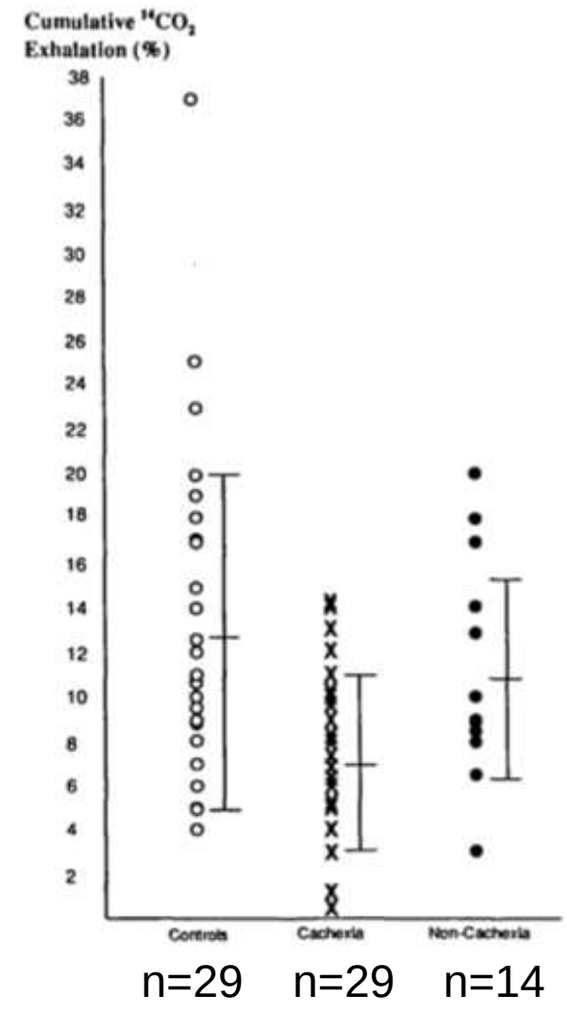
Bowel wall edema

Inflammation



Niebauer J, Volk HD, Kemp M, Dominguez M, Schumann RR, Rauchhaus M, et al. Endotoxin and immune activation in chronic heart failure: a prospective cohort study. Lancet. 1999;353(9167): 1838-1842.

Nutrition



King D, Smith ML, Chapman TJ, Stockdale HR, Lye M. Fat malabsorption in elderly patients with cardiac cachexia. Age Ageing. 1996;25(2): 144-149.

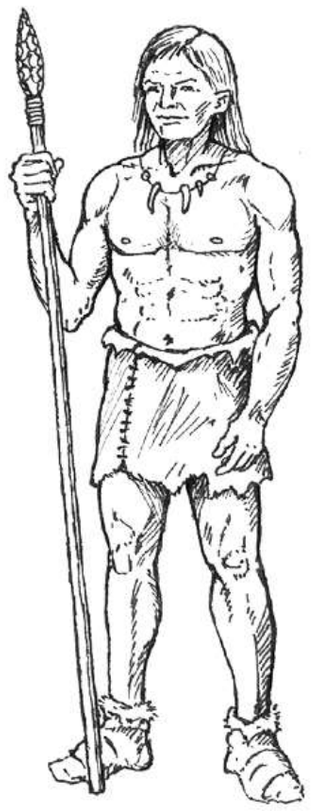
The human body has excellent mechanisms

to retain salt & water

but

has poor mechanisms to get rid of excessive salt

evolution



Salt toxicity in Dialysis

High intradialytic weight gain

High ultrafiltration volume frequently not removed (time constraints; CVD)

Thirst

Na Loading

High Na^+ diet

Dialysate Na^+ greater than serum Na^+

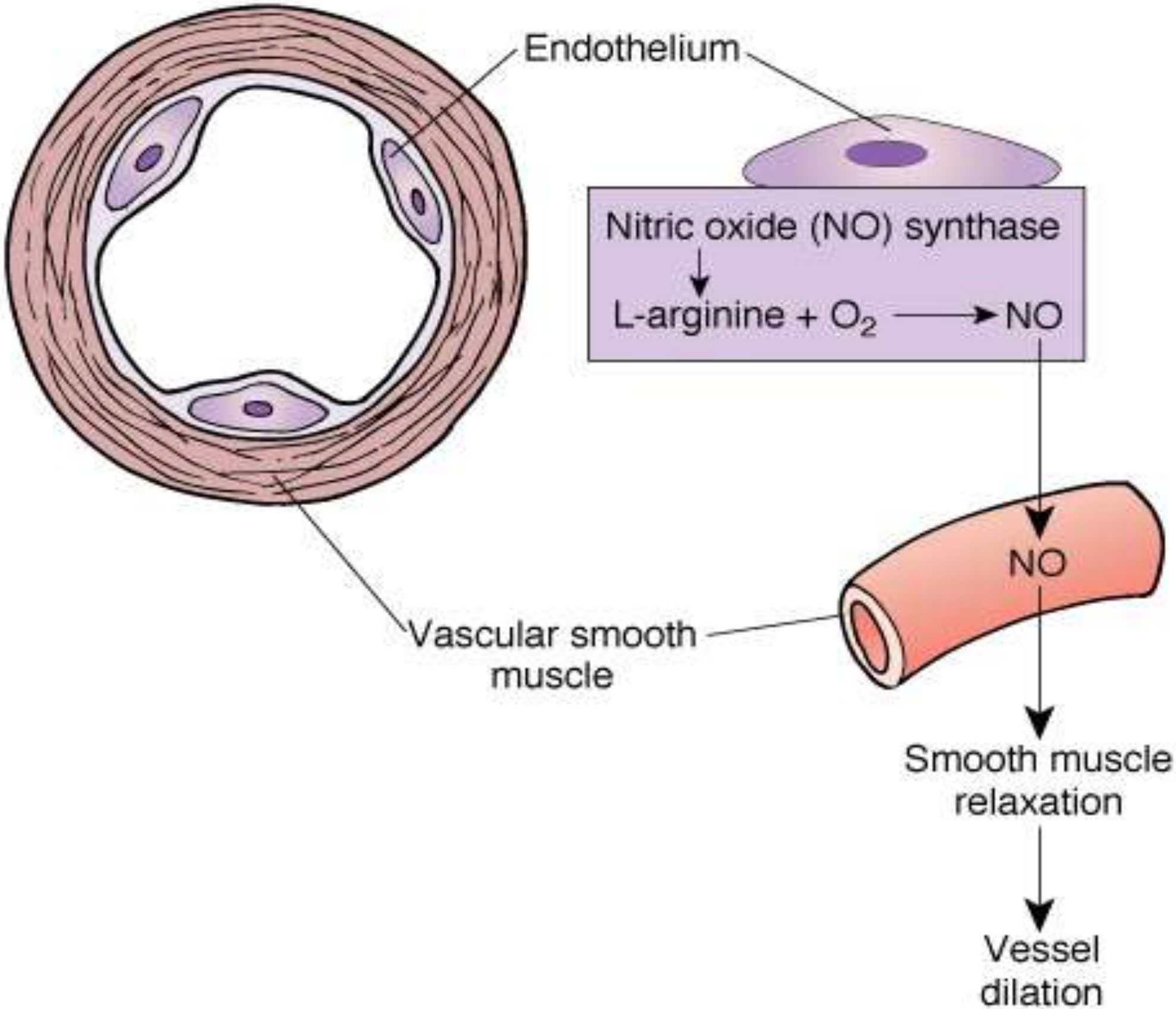
Congestive heart failure

Sensitivity to ultrafiltration

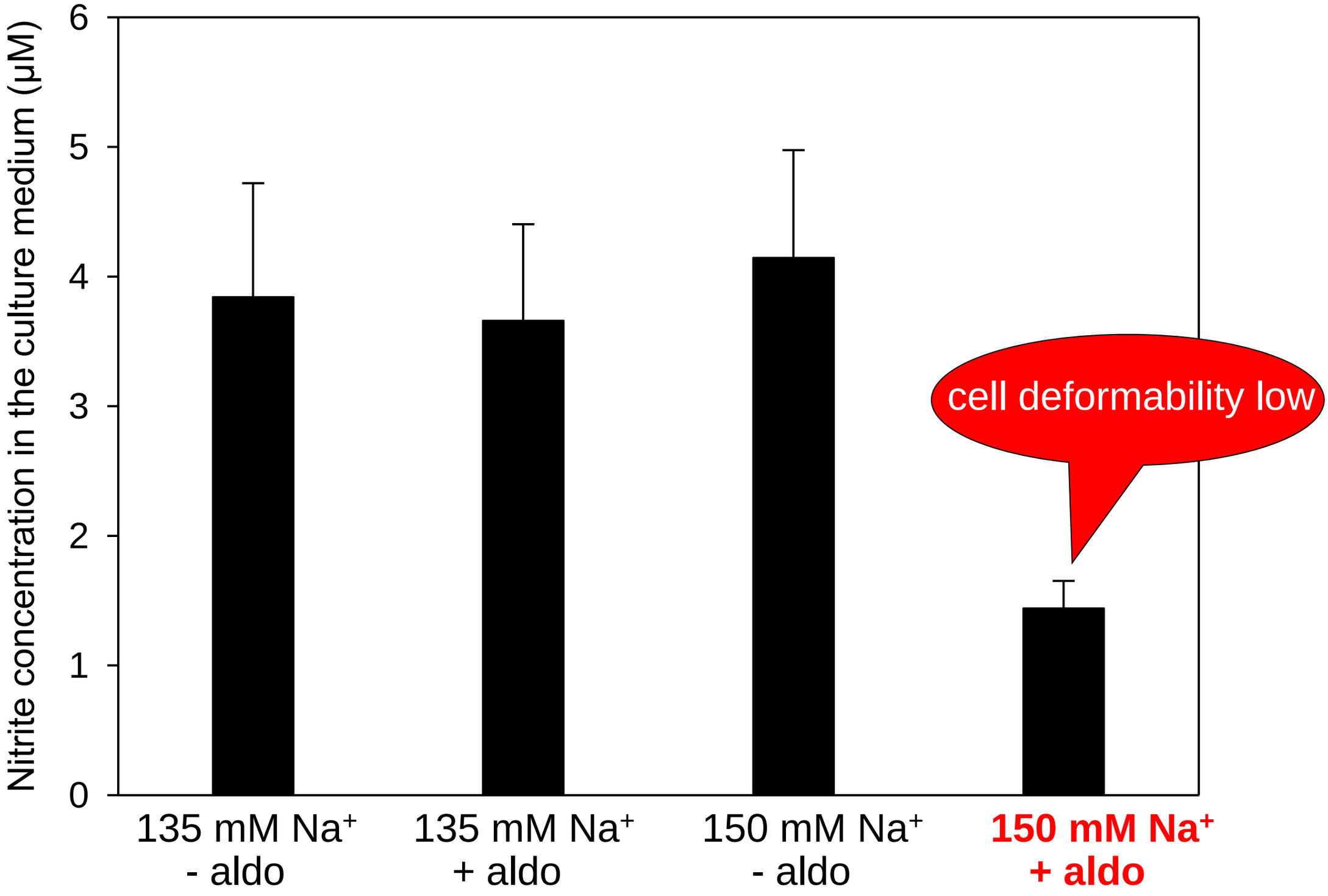
Inability to reach dry weight

Sea water comparison – *salt content in 1 g food vs 1 ml Atlantic water*

Smoked fish	190%
Sweet pickle	170%
Processed cheese	130%
Tomato Ketchup	110%
Cornflakes	100%
Lasagne	40%


Endothelium
Nitric oxide (NO) synthase
L-arginine + O_2 → NO
NO
Vascular smooth muscle
Smooth muscle relaxation
Vessel dilation

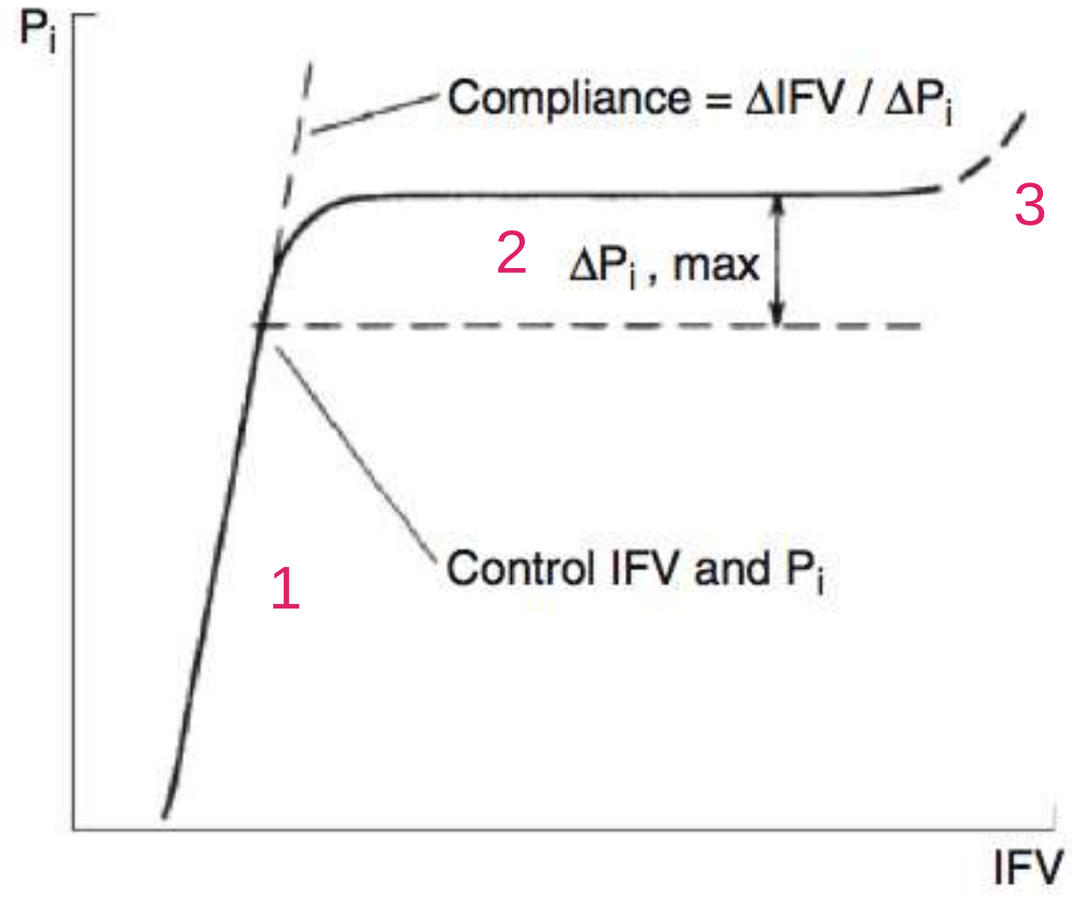
NO release



PNAS 2007

ECV expansion and the interstitial compartment

The interstitial compartment is a significant capacity to compensate ECV expansion.



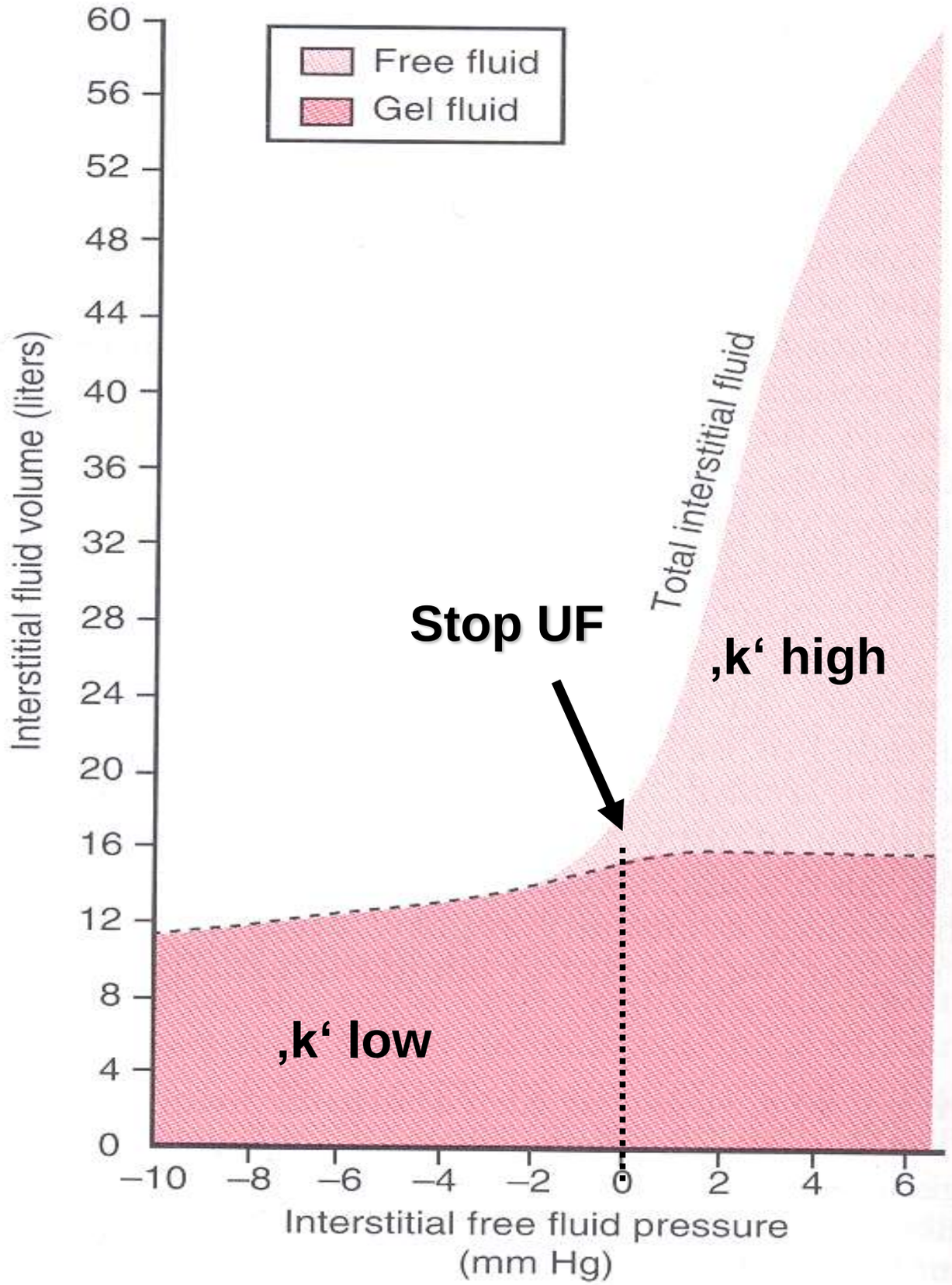
Aukland K, Reed RK, 1993

<u>The relationship between interstitial pressure (P_i) and interstitial fluid volume (IFV):</u>

1. Linear relationship in dehydration

2. Increased IFV accompanied by constant Pi (th implies infinite compliance)

3. At a certain IFV amount (equal to overhydration) the Pi increases again. Reduced compliance due to anatomical structures (e.g. fasciae)



The transport constant ‚k‘ for interstitial free fluid is higher than ‚k‘ for interstitial gel fluid.
Therefore, interstitial free fluid is easier removed during HD than interstitial gel fluid

(Guyton Textbook of Physiology)

Definition of dry weight

The body weight at physiological extracellular volume (ECV)

“... not merely the absence of edema, but the edge of hypovolemia which should be achieved at the end of the session, without becoming hypotensive.”

Thomson GE, Waterhouse K, McDonald HP, Jr., Friedman EA. Hemodialysis for chronic renal failure. Clinical observations. Arch Intern Med. 1967;120(2): 153-167.

“... the post-dialysis weight at which all or most excess body fluid has been removed, below which the patient, more often than not, will develop symptoms of hypotension.”

Daugirdas JT., Blake PG., Ing TS. Handbook of dialysis: Lippincott Williams &, 2007.

“... the post-dialysis weight at which the patient is and remains normotensive until the next dialysis in spite of fluid retention without antihypertensive medication.”

Charra B, Laurent G, Chazot C, Calemard E, Terrat JC, Vanel T, et al. Clinical assessment of dry weight. Nephrol Dial Transplant. 1996;11 Suppl 2: 16-19.

Assessment of Dry Weight

TABLE 1. Different techniques of estimating dry weight and their applications

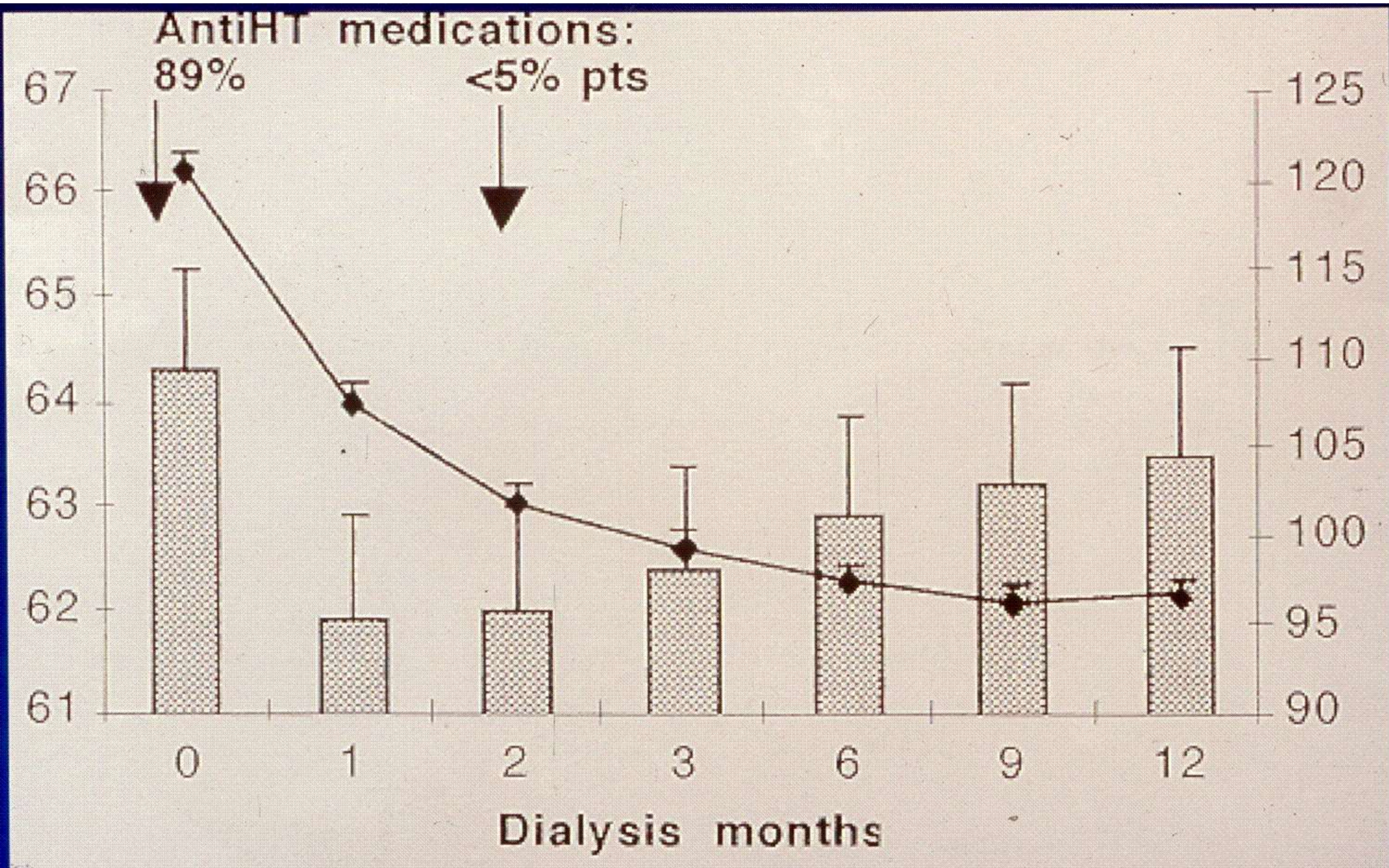
Technique	Advantages	Disadvantages
On-line blood volume monitoring	Accurate in measuring relative blood volume change	Determines rate of plasma refilling rather than actual interstitial fluid volume
Inferior vena cava diameter	Simple to perform	Operator dependent; inaccurate; needs to be measured long after end of hemodialysis
Biochemical measures (atrial natriuretic peptide, cGMP, BNP)	Blood tests	Large interindividual variability; values influenced by underlying cardiac dysfunction and nutritional status
Whole-body bioimpedance (WBIA)	Quantitative estimate of body hydration and extracellular fluid removal	Standard deviation too large; influenced by body composition
Segmental bioimpedance analysis (SBIA)	Quantitative estimate of body hydration; more accurate extracellular volume measurement (compared to WBIA); less influenced by body position; less standard deviation of estimate compared to WBIA	Needs special device, patient cooperation

BNP, brain natriuretic peptide; cGMP, cyclic guanosine monophosphate.

Sarkar, Kotanko, Levin. Sem Dialysis 2006

Four practical approaches to reduce sodium excess

1. **Dietary restriction (serious)**
2. Equating dialysate sodium with patient’s sodium
3. Avoidance of intradialytic saline infusion
4. Avoidance of “bad” sodium profiling



Charra B.: AJKD, 1998

The benefit of salt restriction in the treatment of end-stage renal disease by haemodialysis

NDT, 2009

Meral Kayikcioglu[1], Murat Tumuklu[2], Mehmet Ozkahya[3], Oner Ozdogan[4], Gulay Asci[3], Soner Duman[3], Huseyin Toz[3], Levent H. Can[1], Ali Basci[3,5] and Ercan Ok[3,5]

A–Salt restriction 5g/d

Table 2. Blood pressure characteristics of the patients treated in two centres

	Centre A ($n = 190$)	Centre B ($n = 204$)	P-value
Use of antihypertensive medication (n = %)	13 (7%)	86 (42%)	0.001
ACE-/I or ARB	8	27	
Calcium channel blocker	1	43	
Beta blocker	2	3	
Furosemide	1	1	
Combination of two medications	1	12	
Interdialytic weight gain (kg)	2.29 ± 0.83	3.31 ± 1.12	0.0001
Interdialytic weight gain (kg for 70 kg man)	2.61 ± 0.98	4.05 ± 1.52	0.0001
Systolic BP (mmHg)	126 ± 15	126 ± 21	ns
Diastolic BP (mmHg)	75 ± 12	76 ± 11	ns
Pulse pressure (mmHg)	51 ± 9	50 ± 12	ns
Systolic BP ≥140 (%)	18	37	0.001
Diastolic BP ≥90 (%)	12	8	ns
Patients with systolic BP ≥140 and/or diastolic BP ≥90 (%)			
At the time of starting the HD programme	78	83	ns
Current situation	19	37	0.001
Intradialytic hypotension (number of episode per 100 HD sessions)	11	27	0.009

Values are expressed as mean ± SD unless otherwise defined.
BP: blood pressure, ns: non-significant.

Table 3. Echocardiographical data of the centres

	Centre-A ($n = 190$)	Centre-B ($n = 204$)	P-value
LA indices			
LA index (cm/m^2)	2.40 ± 0.34	2.74 ± 0.53	0.0001
LA volume index (mL/m^2)	29.5 ± 10.0	36.7 ± 21.7	0.0001
LV measurements and indices			
LV diastolic index (cm/m^2)	2.61 ± 0.33	2.97 ± 0.64	0.0001
LV end-systolic index (cm/m^2)	1.60 ± 0.29	1.96 ± 0.47	0.0001
Interventricular septalindex (cm/m^2)	0.79 ± 0.13	0.83 ± 0.14	0.018
Posterior wall index (cm/m^2)	0.76 ± 0.11	0.83 ± 0.11	0.0001
LV ejection fraction (%)	68 ± 10	63 ± 09	0.0001
LV fractional shortening (%)	39 ± 8	35 ± 6	0.0001
LV mass indexed to height$^{2.7}$ (g/m$^{2.7}$)	59 ± 16	74 ± 27	0.0001
LV hypertrophy (%)[a]	124 (74%)	171 (88%)	0.001
Pulsed Doppler parameters			
Mitral-inflow E (cm/s)	73 ± 22	76 ± 27	ns
Mitral-inflow A (cm/s)	83 ± 18	82 ± 25	ns
Deceleration time (min/s)	0.23 ± 0.06	0.28 ± 0.07	0.0001
Isovolumic relaxation time (min/s)	0.08 ± 0.01	0.12 ± 0.02	0.0001
Mitral-inflow A-wave duration (min/s)	0.14 ± 0.02	0.16 ± 0.03	0.0001
E/A ratio	0.90 ± 0.31	0.96 ± 0.33	0.076
Mitral valve lateral annulus Ee/Ae (min/s)	0.99 ± 0.43	0.89 ± 0.41	0.034

Values are expressed as mean ± SD.
LA, left atrium; LV, left ventricular; ns, non-significant.
[a]LV hypertrophy was defined as the LV mass index >50 g/m$^{2.7}$ in males and >47 g/m$^{2.7}$ in females.

Conclusions from Studies on Low Sodium Diet:

- Low sodium diet associated with *reduced* interdialytic weight gain.
- Reduced fluid intake occurred *spontaneously*

What actually is overhydration(better known as fluid overload) And what does it have to do with “dry weight”?

Neutral Sodium Balance over the Entire Dialysis Cycle is Key to Therapy of Fluid Overload

Why Sodium Alignment?

- In the presence of a positive sodium gradient (DNa+ > SNa+) a substantial amount of Na+ may be transferred from the dialysate to the patient
- Hospitalization rates relate to Na+ gradient (observational RRI data)
- A large longitudinal FMCNA cohort study showed that lowering DNa+ from 140 to 137 mmol/L reduced hospitalization (ASN, 2011)
- Individualization of DNa+ based on the patients SNa+ may confer benefits beyond an “one size fits all” approach

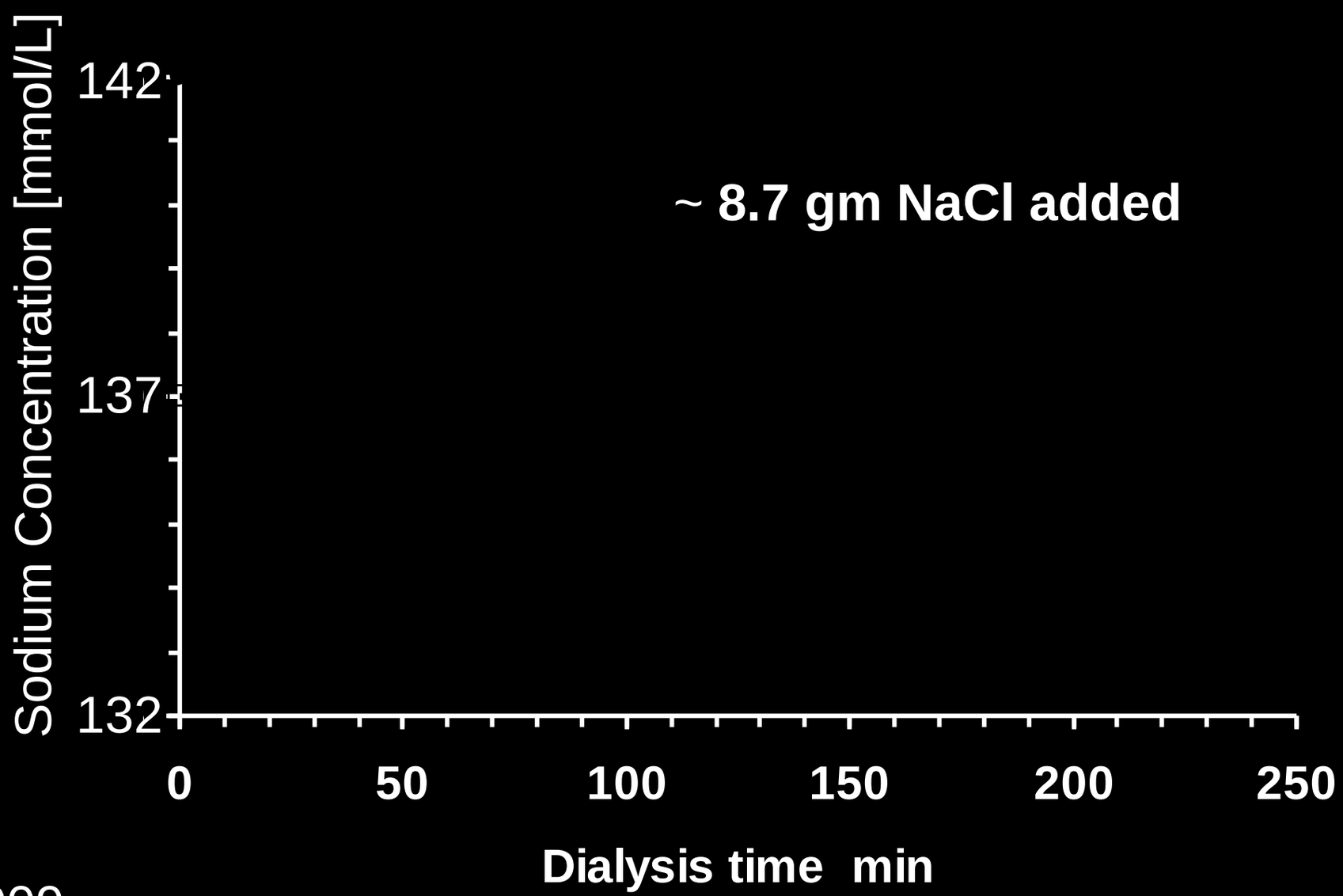
Sodium Flux during Hemodialysis

Example:

Serum sodium:
137 mmol/L

- Whenever dialysate Na+ exceeds serum Na+, sodium fluxes from the dialysate into the patient

Projected Sodium Transfer from Dialysate to Serum



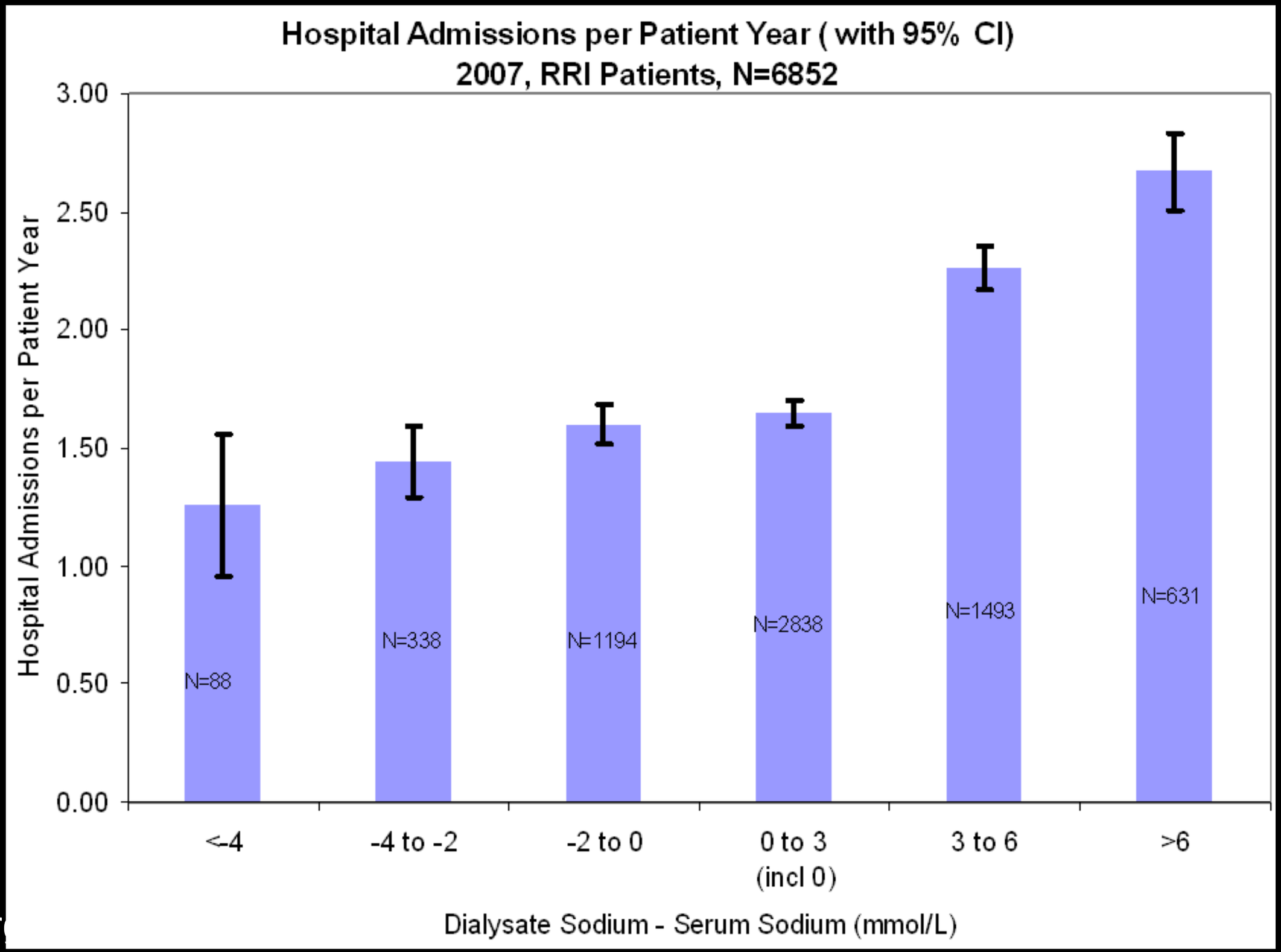
F Gotch, 2009

Na+ Gradient Hypothesis

↓ Dialysate Na+ → ↓ IDWG → ↓ Systolic BP → ↓ Hospitalizations due to Fluid Overload*

* **Fluid Overload Hospitalization** consisted of ICD-9 codes for heart failure, acute pulmonary edema, or fluid overload as the primary diagnosis or as a secondary diagnosis when a primary diagnosis was listed as shortness of breath

Observational RRI Data Associate Na+ Gradient with Hospitalization

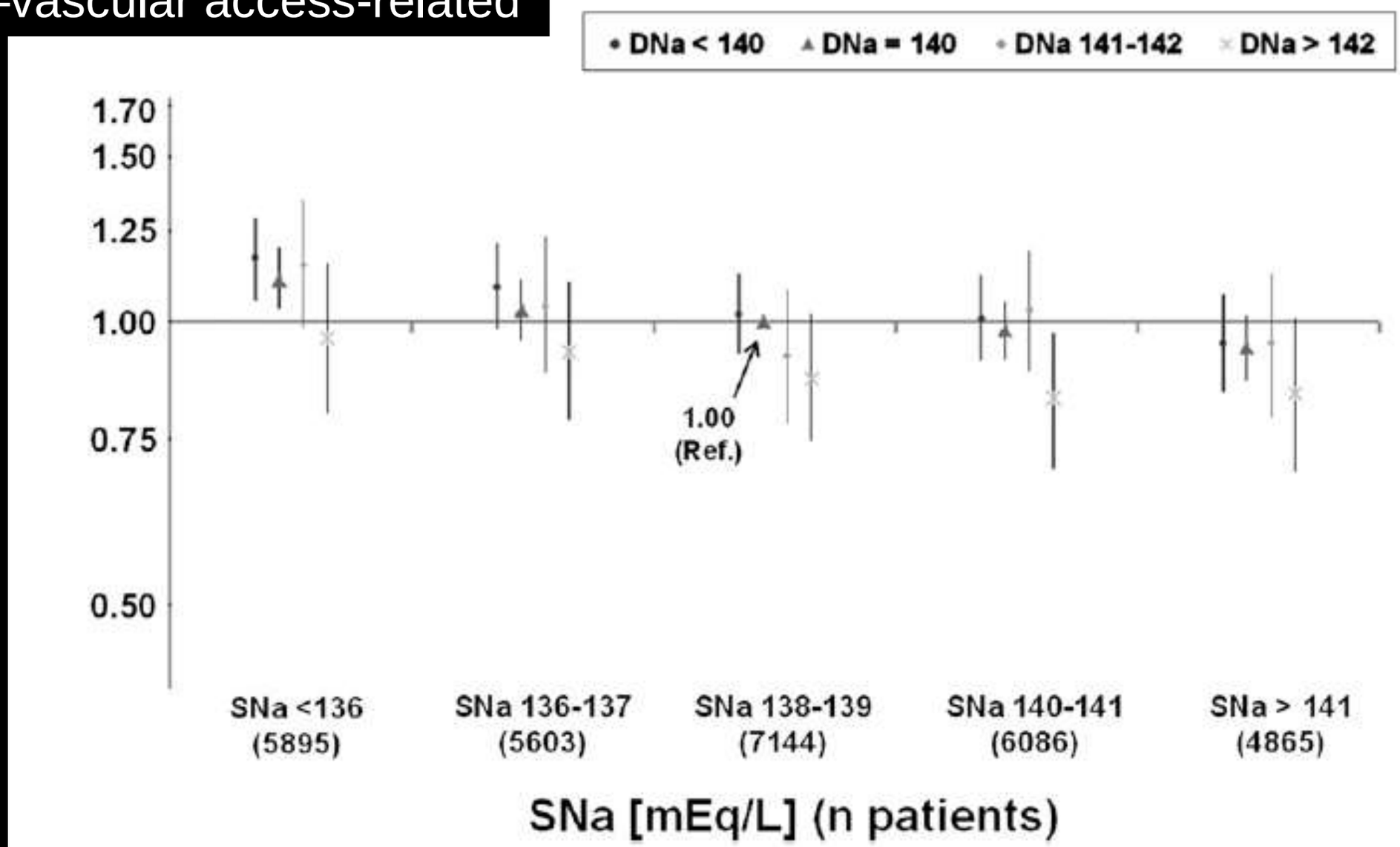


Ser

Dialysate Sodium Concentration and the Association with Interdialytic Weight Gain, Hospitalization, and Mortality

Manfred Hecking,[*†] *Angelo Karaboyas,*[*] *Rajiv Saran,*[‡] *Ananda Sen,*[§] *Masaaki Inaba,*[‖] *Hugh Rayner,*[¶] *Walter H. Hörl,*[†] *Ronald L. Pisoni,*[*] *Bruce M. Robinson,*[*] *Gere Sunder-Plassmann,*[†] *and Friedrich K. Port*[*]

Hospitalizations of all-cause but non–vascular access-related



CJASN 7: 92-

A Unique “Natural Experiment”

- Before January 2009, the predominant Na+ dialysate prescription in FMCNA was 140 mEq/L, consistent with the concentration in 9000 Series formulation

- During January 2009 – June 2009, the prescribed Na+ dialysate shifted to predominantly 137 mEq/L, coincident with the introduction of the 4000 Series formulation

- Physicians opted to either retain Na+ dialysate prescriptions or change to a lower dialysate Na+

  - We selected 581 “case facilities” (28,568 patients) based on the change in Na+ dialysate prescription from 140 to 137 mEq/L in essentially all patients

  - We selected 184 “control facilities” (11,525 patients) based on minimal change in all Na+ dialysate prescriptions despite the change in dialysate Na+ formulation

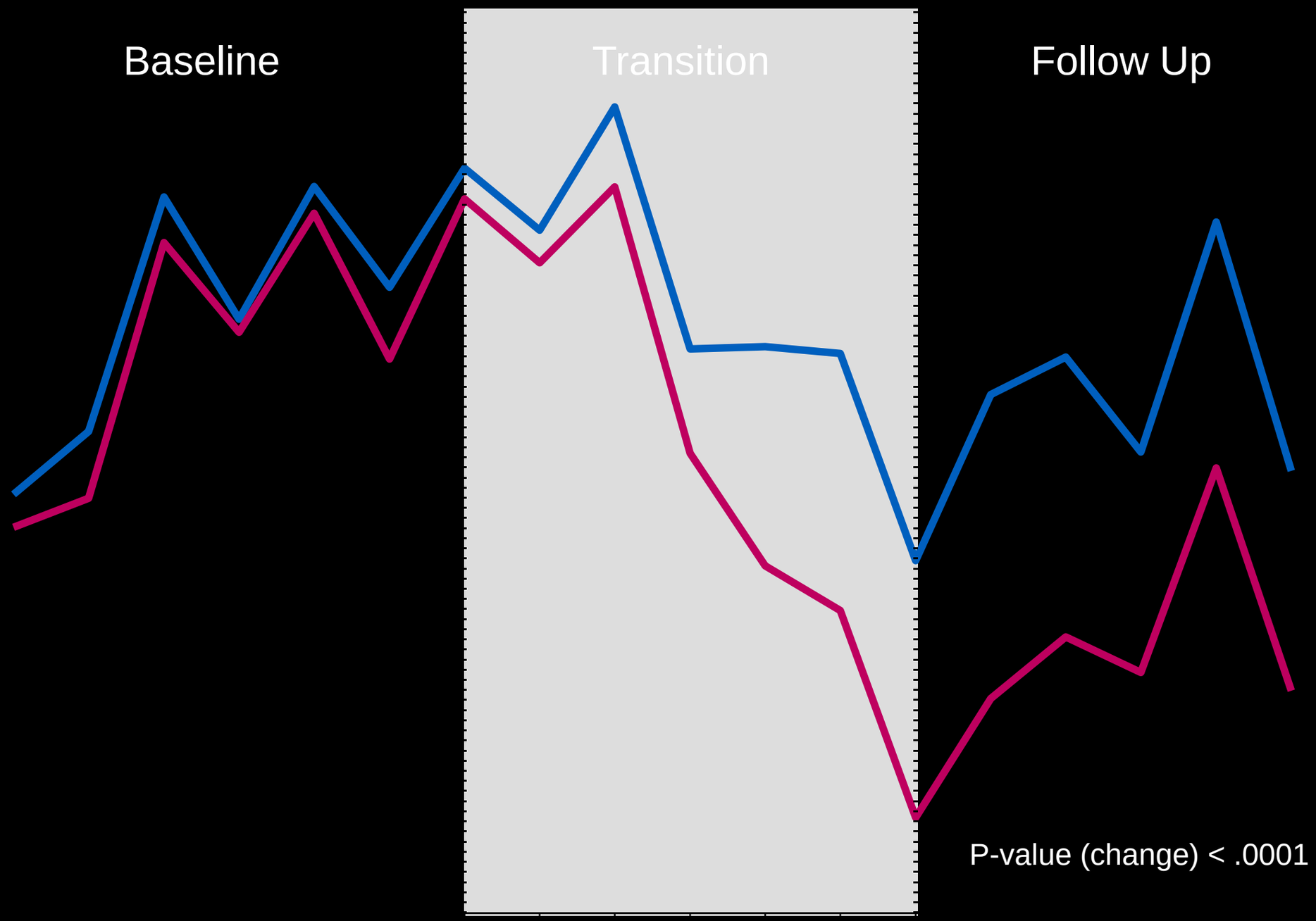
IDWG / SBP Analysis: The 18-month “survivor cohort”

- Identified adult (age >18) patients managed in IDWG clinics
- Restricted analysis to patients with data for all 18 months (July, 2008 – December, 2009) to determine longitudinal impact of changing the dialysate Na+ exposure in the same patients:

- **Baseline**: before dialysate Na+ conversion (Jun-Dec, 2008)

- **Transition**: roll-out of new dialysate formulation (Jan-Jun, 2009)

- **Follow Up**: after dialysate Na+ conversion (Jul-Dec,



Case Facilities (———) and Control Facilities (———)

Hospitalization Analysis: Hospitalization for Fluid Overload

- "Survivor cohort" not ideal for hospitalization analysis due to possible competing risk of death
- The "expanded study cohort" includes all prevalent patients at case/control facilities as of July 1, 2008
- Follow up extended to 36 months
- (= 24 months of follow-up post-transition)

All Cause Hospitalization Rates

N at baseline: Cases=23,727; Controls=9,506

% of patients hospitalized

Baseline

Transition

Follow-up

Fluid Overload Hospitalization Rates

N at baseline: Cases=23,727; Controls=9,506

% of patients hospitalized for fluid overload

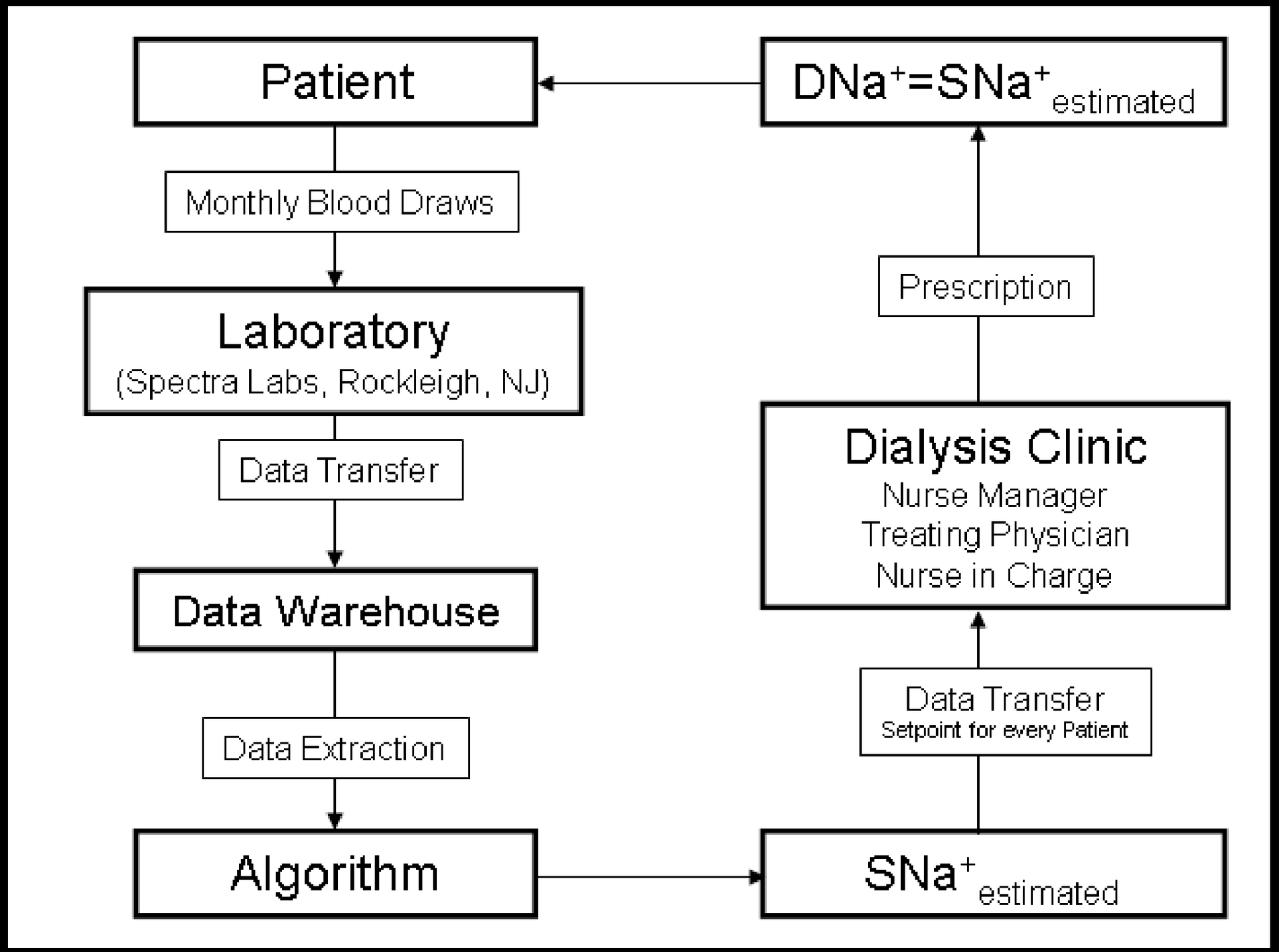
Baseline

Transition

Follow-up

Change from baseline to final 6 month period	**6.80 - 3.65 = 3.15**	**5.81 - 4.11 = 1.70**	**0.004**

Sodium Alignment – Practical Application



Raimann et al. Seminar Dial 2011; Utility filed at USPTO

Na+ Alignment: Results from NC RRI Unit

(Raimann et al., Seminar in Dialysis, 2011)

TABLE 1. Predialysis body weight (kg) before and after implementation of a sodium alignment algorithm

	Before alignment (mean ± SD)	After alignment (mean ± SD)	Difference (95% CI)	Treatment effect (95% CI)
Alignment (n = 20) (kg)	81.1 ± 25.5	78.8 ± 24.5	−2.2 (−4.6 to 0.08)	−1.6 (−4.0 to 0.8)
No Alignment (n = 108) (kg)	82.7 ± 25.0	82.0 ± 25.3	−0.6 (−1.3 to 0.02)	

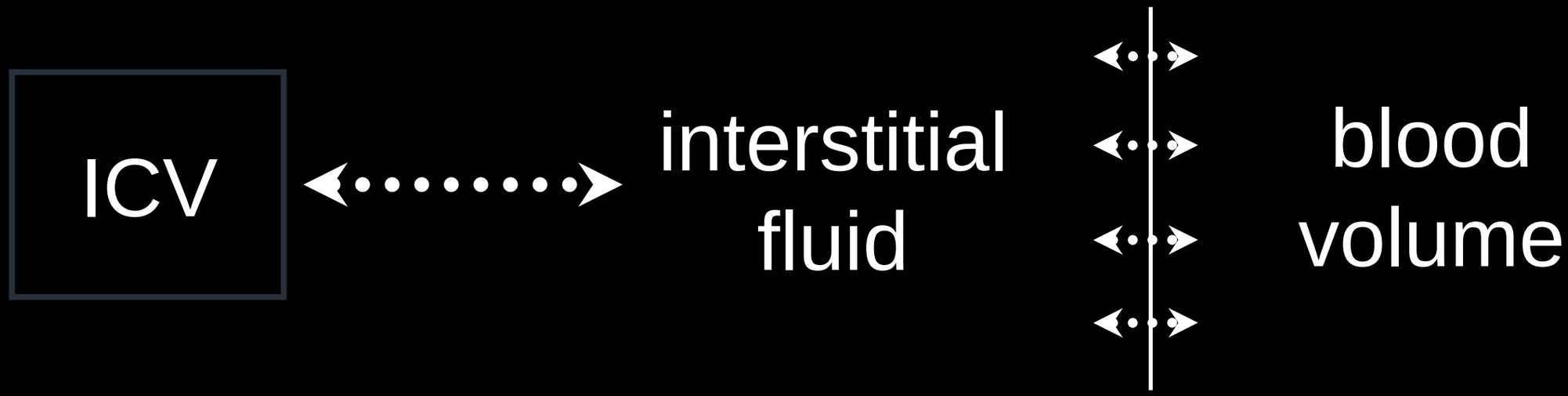
No significant differences found..

TABLE 2. Predialysis systolic blood pressure (mmHg) before and after implementation of a sodium alignment algorithm

	Before alignment (mean ± SD)	After alignment (mean ± SD)	Difference (95% CI)	Treatment effect (95% CI)
Alignment (n = 20) (mmHg)	154.3 ± 18.4	146.7 ± 20.7	−7.6 (−13.9 to −1.3)*	−4.8 (−12.6 to 2.9)
No alignment (n = 108) (mmHg)	154.6 ± 18.1	151.8 ± 19.6	−2.8 (−5.9 to 0.4)	

*$p < 0.05$.

Fluid compartments ...

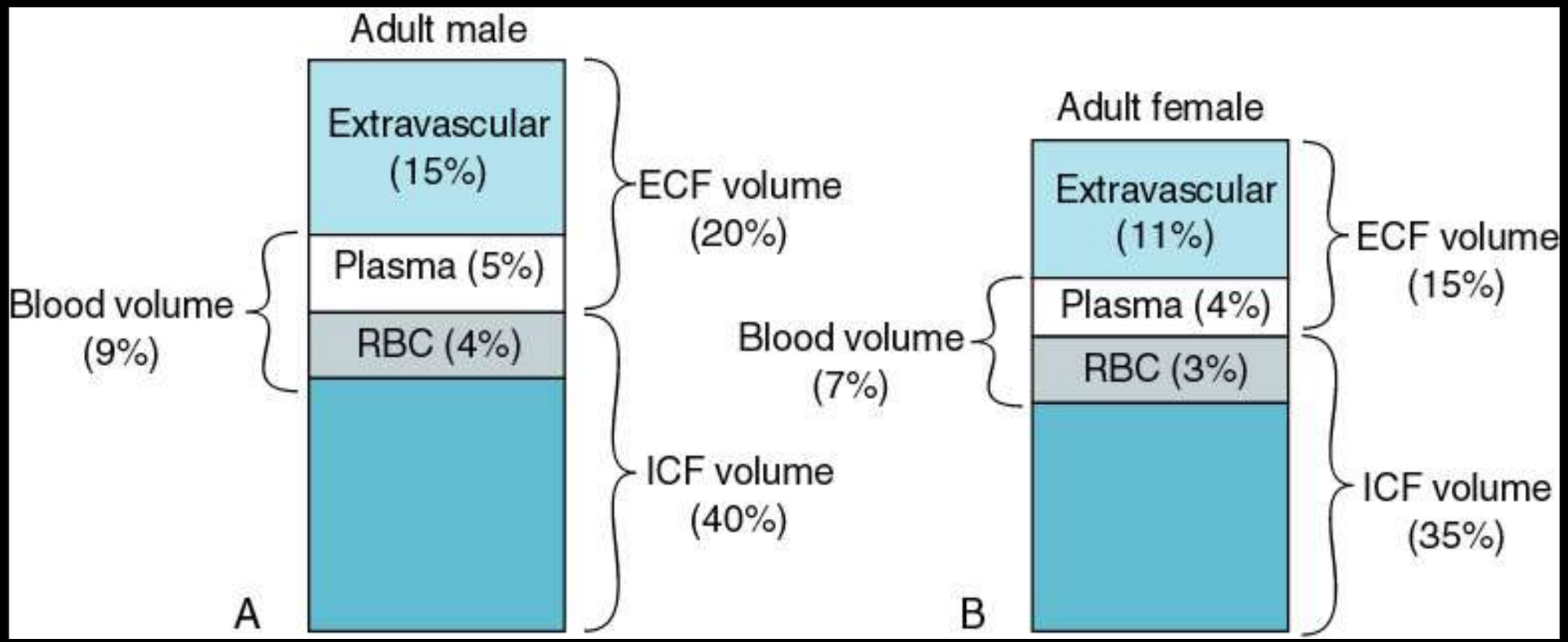


Distribution of fluid between interstitial and intravascular compartment is determined by the Starling Forces:

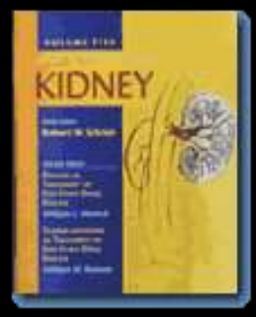
$$J_v/A = L_P[P_c - P_i) - \sigma_m(COP_p - COP_i)],$$

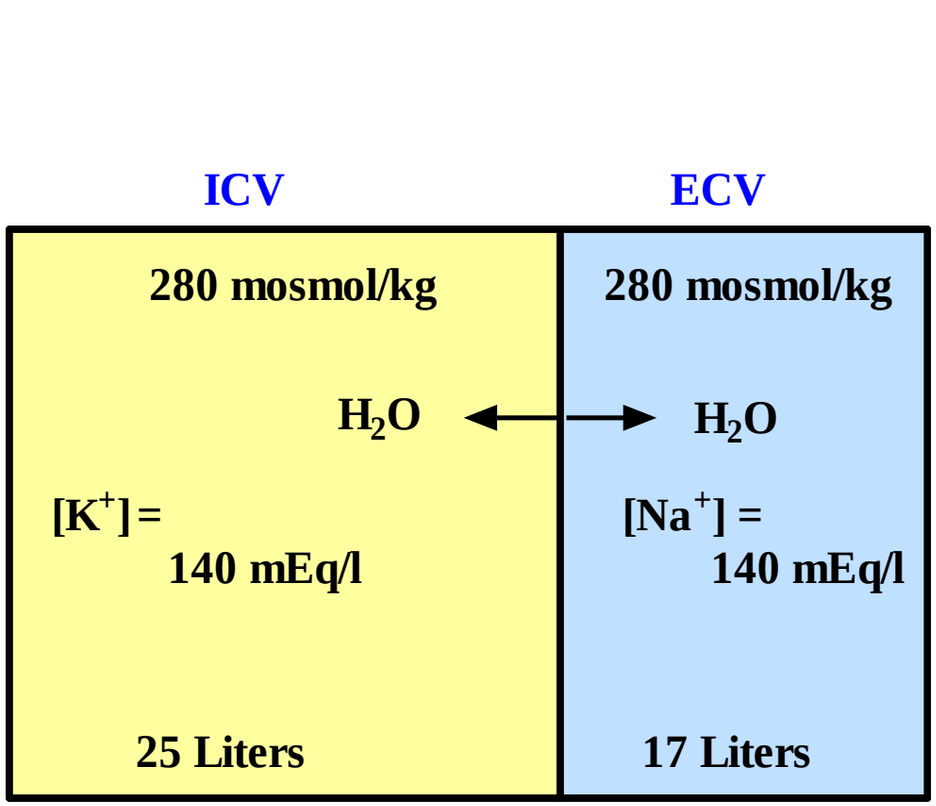
J_v = rate of fluid flow [mL/min]
L_P = hydraulic permeability coefficient of the membrane [µL/s/mm Hg]
P_c = capillary hydrostatic pressure [mm Hg]
P_i = interstitial hydrostatic pressure [mm Hg]
σ_m = mean reflection coefficient of macromolecules at the membrane
COP_p = oncotic pressure in the capillaries [mm Hg]
COP_i = oncotic pressure in the interstitium [mm Hg]

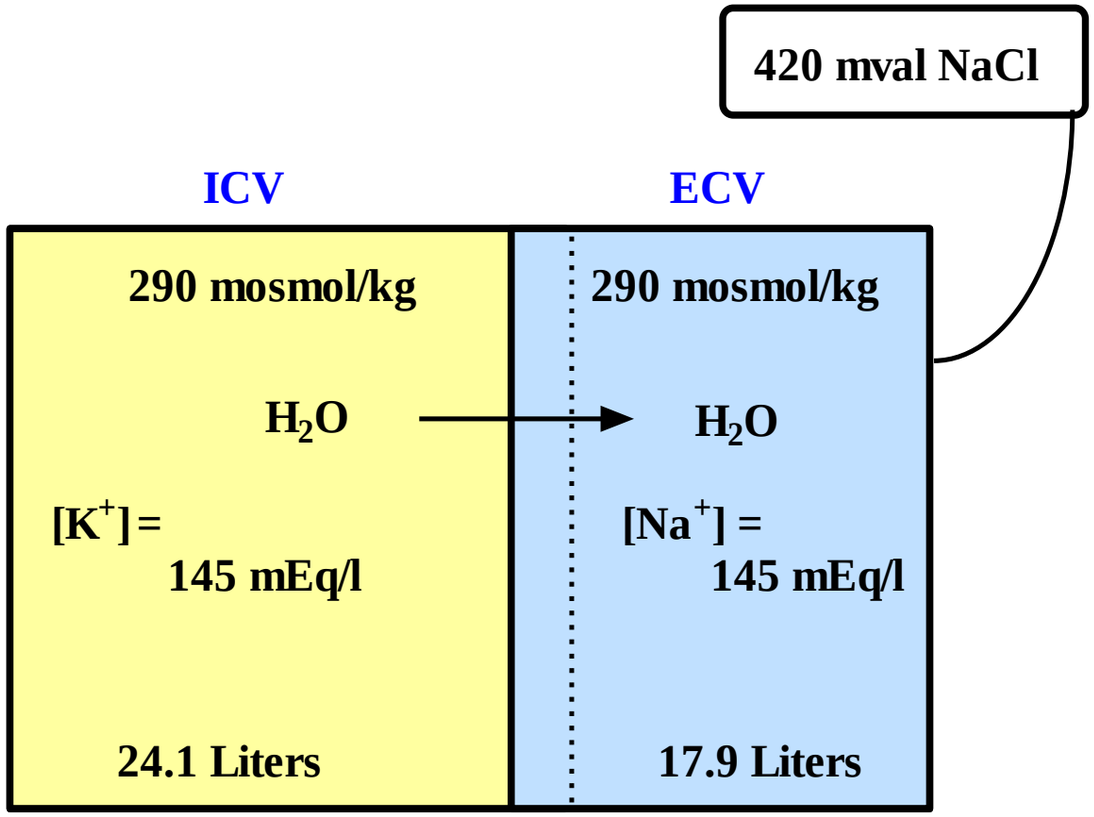
Distribution of Body Water

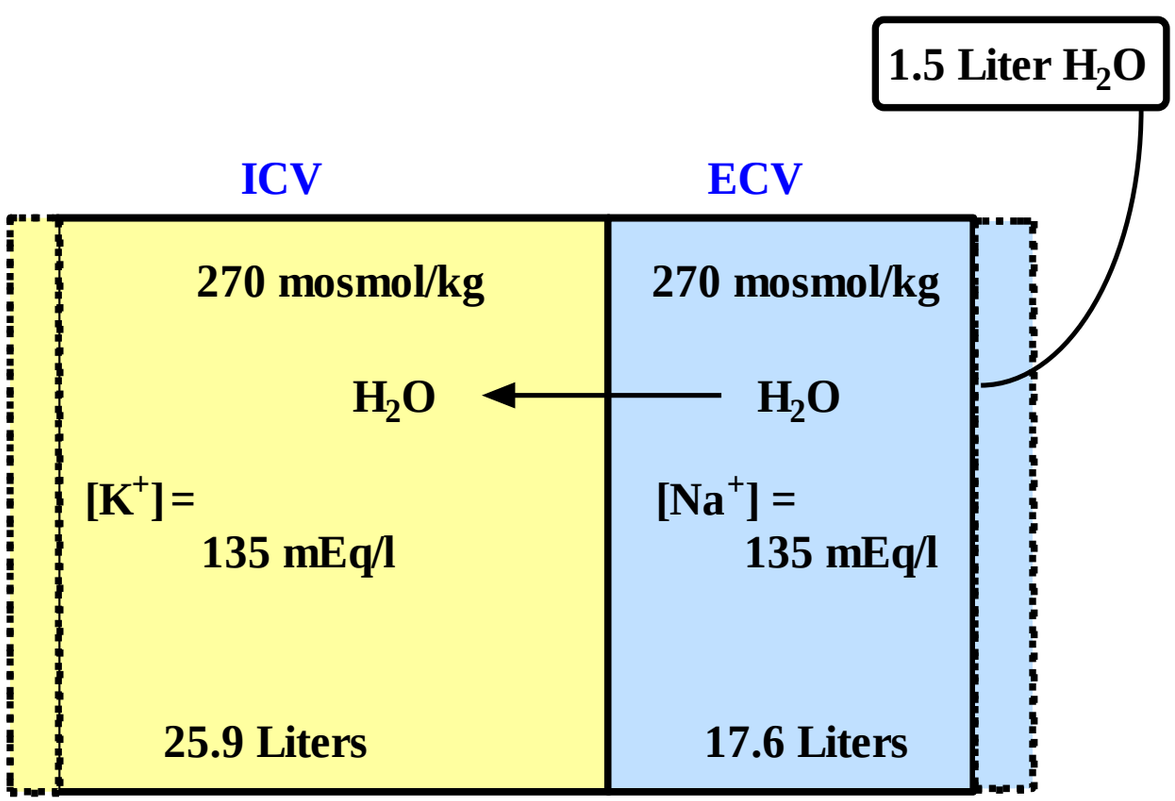


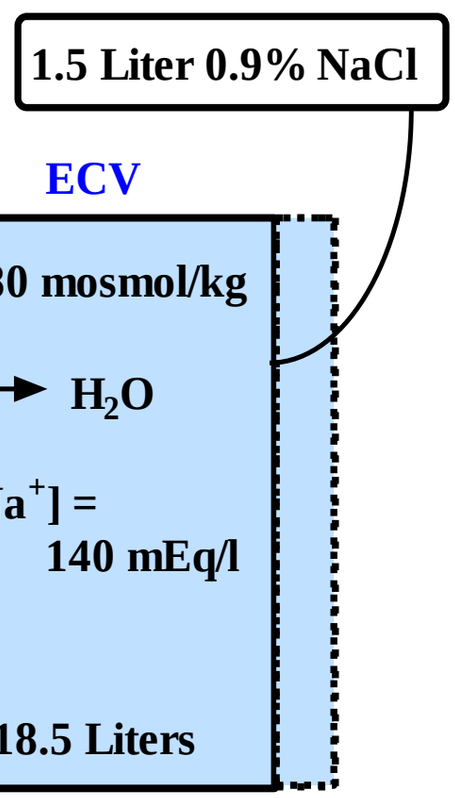
Total body water is about 60% of body weight



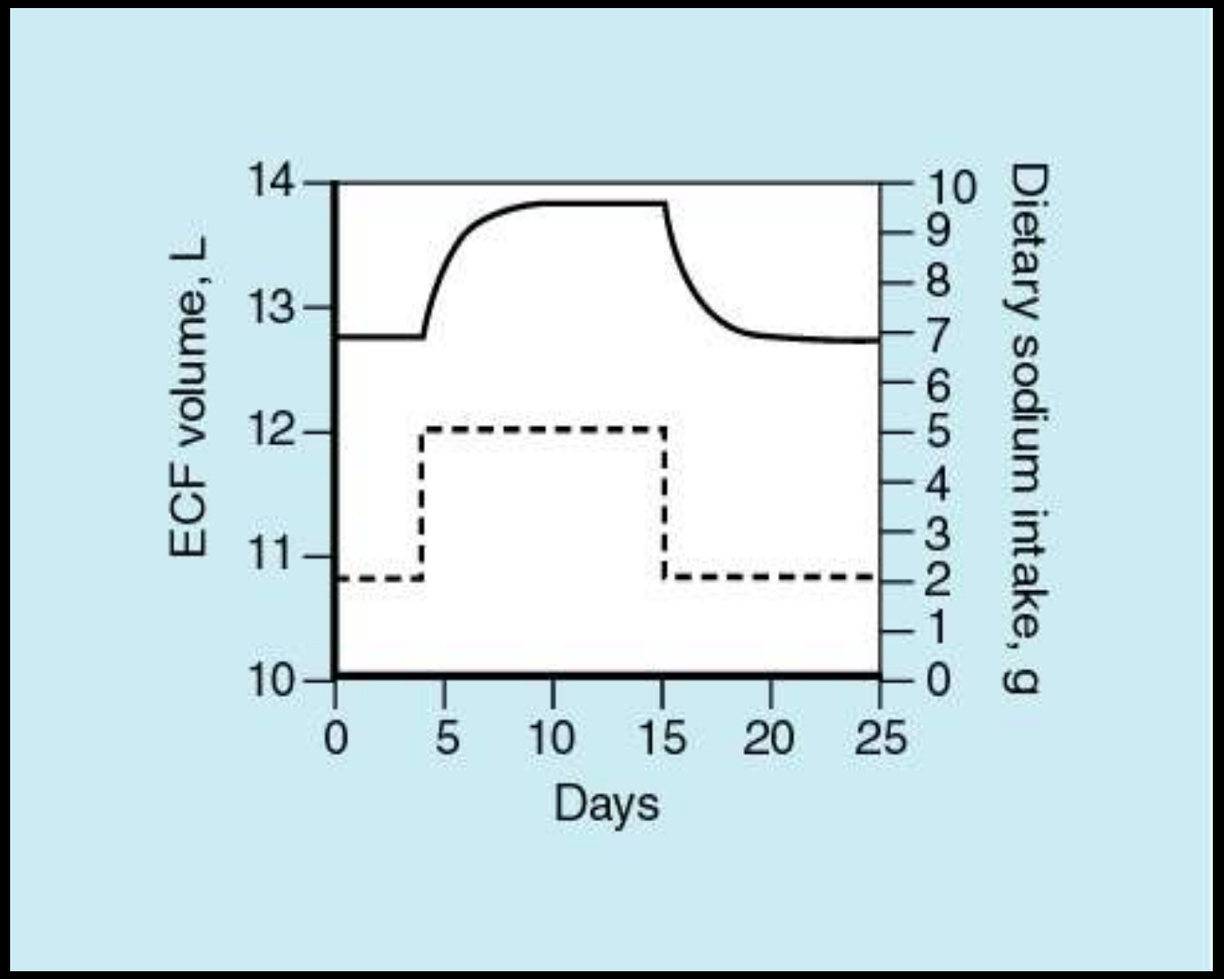

ICV
ECV
280 mosmol/kg
280 mosmol/kg
H_2O
H_2O
$[K^+]$ =
140 mEq/l
$[Na^+]$ =
140 mEq/l
25 Liters
17 Liters

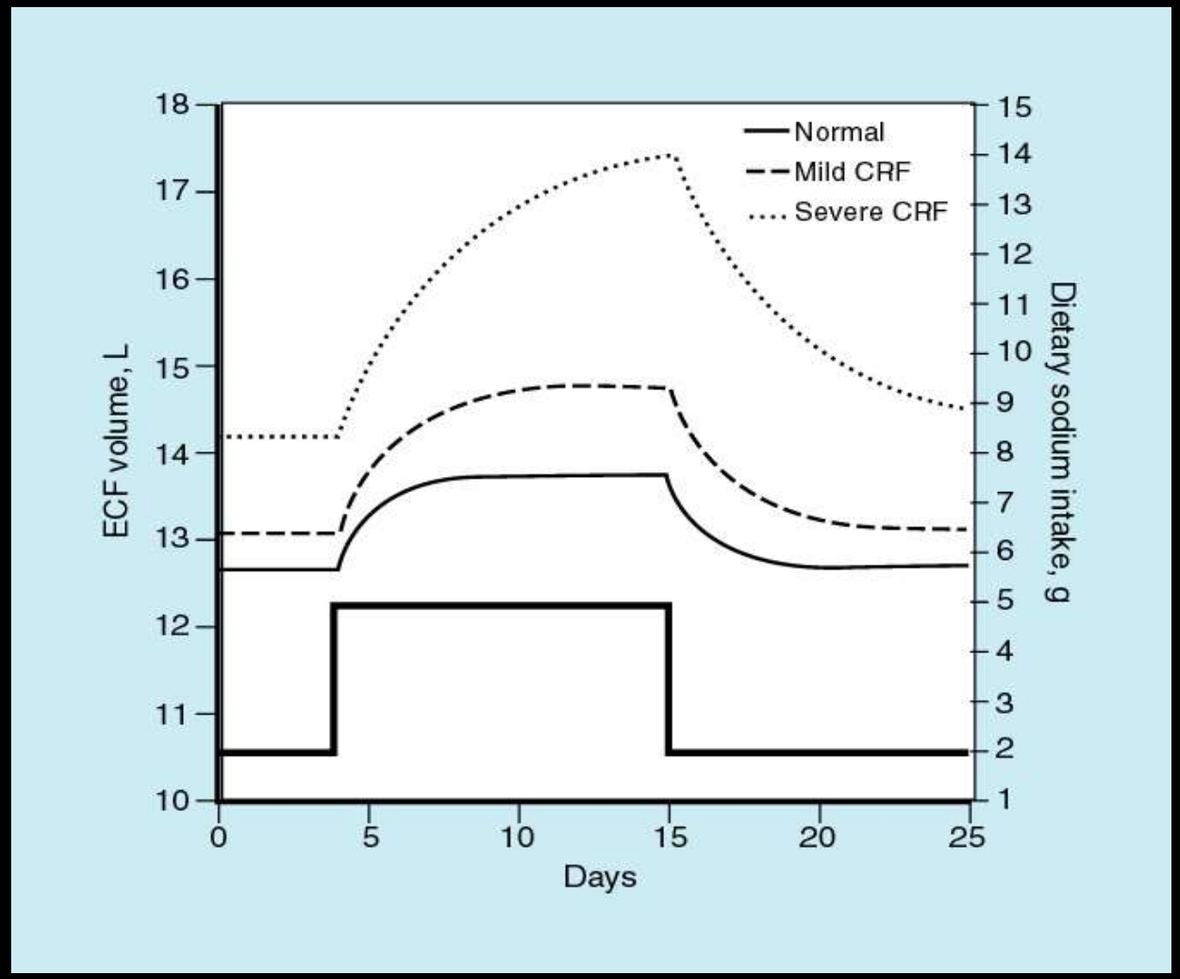

420 mval NaCl
ICV
ECV
290 mosmol/kg
290 mosmol/kg
H_2O
H_2O
$[K^+]$ =
145 mEq/l
$[Na^+]$ =
145 mEq/l
24.1 Liters
17.9 Liters


1.5 Liter H_2O
ICV
ECV
270 mosmol/kg
270 mosmol/kg
H_2O
H_2O
$[K^+]$ =
135 mEq/l
$[Na^+]$ =
135 mEq/l
25.9 Liters
17.6 Liters


1.5 Liter 0.9% NaCl
ICV
ECV
280 mosmol/kg
280 mosmol/kg
H_2O
H_2O
$[K^+]$ =
140 mEq/l
$[Na^+]$ =
140 mEq/l
25 Liters
18.5 Liters

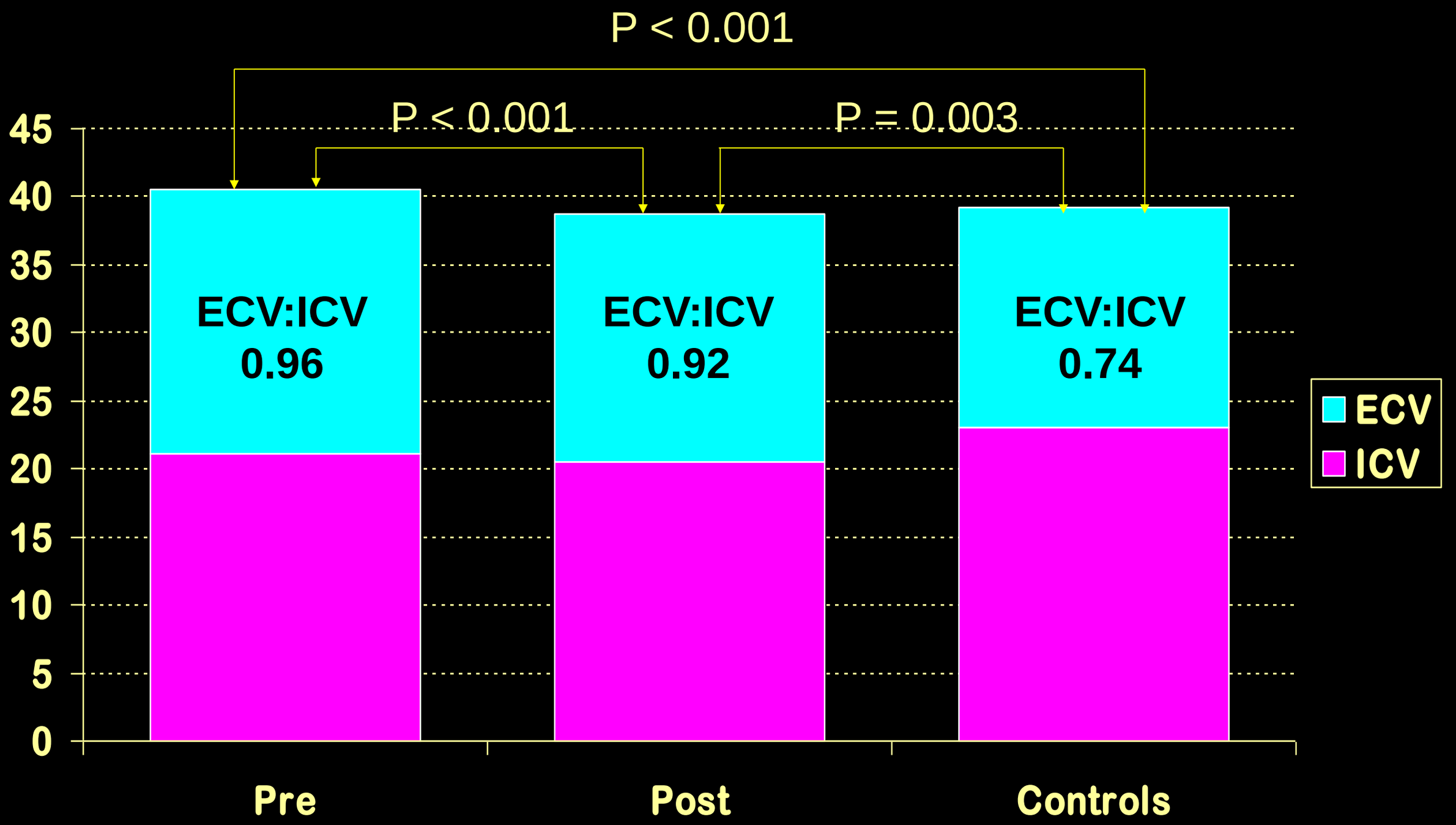
Effect of Dietary Na^+-Intake on ECV





ECV-Expansion in 21 Chronic Hemodialysis Patients as Determined by BIS

Lindsay RM et al. HDI 2003



What is the relationship between ECV and blood volume?

Capillary barrier

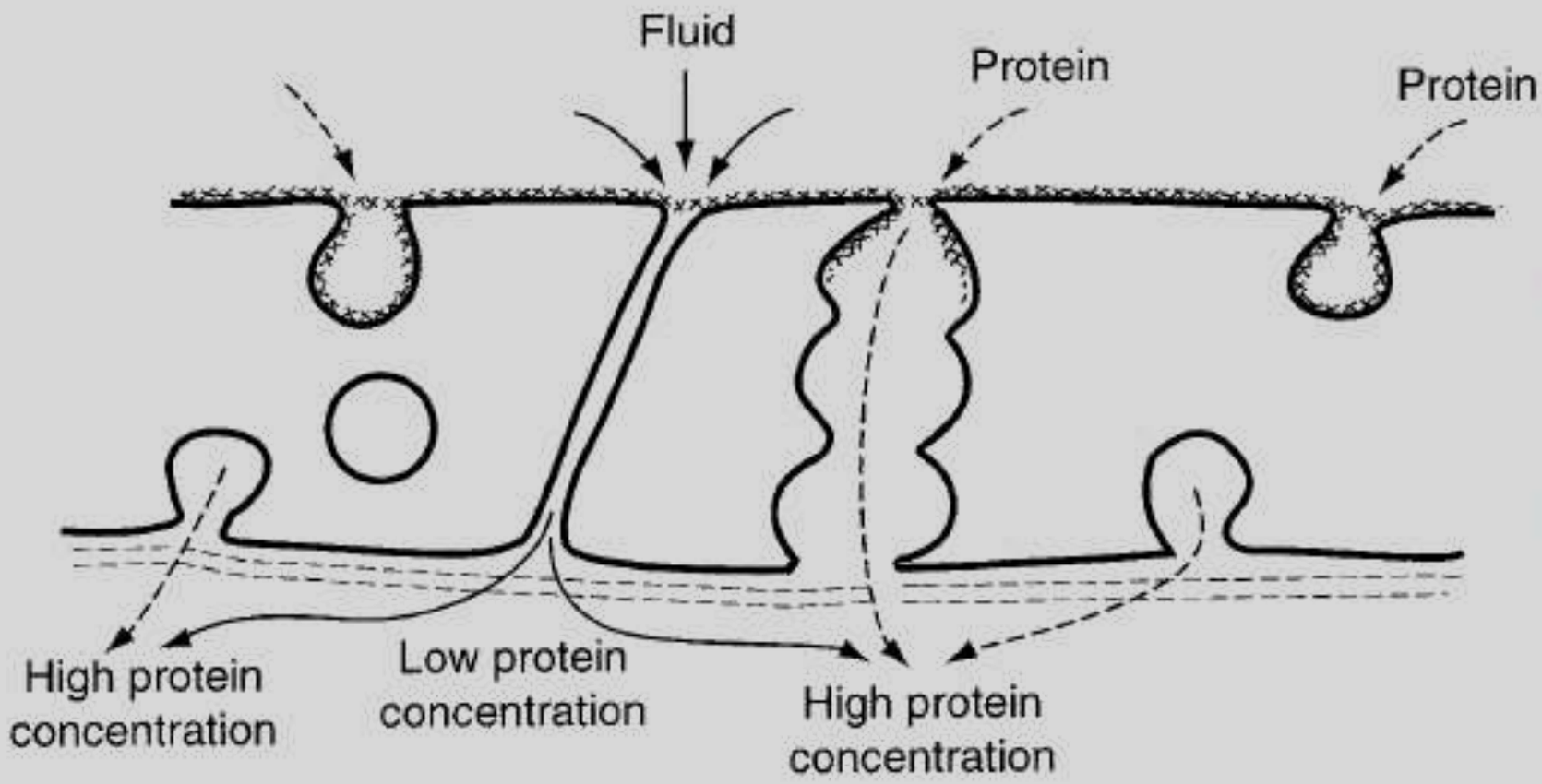


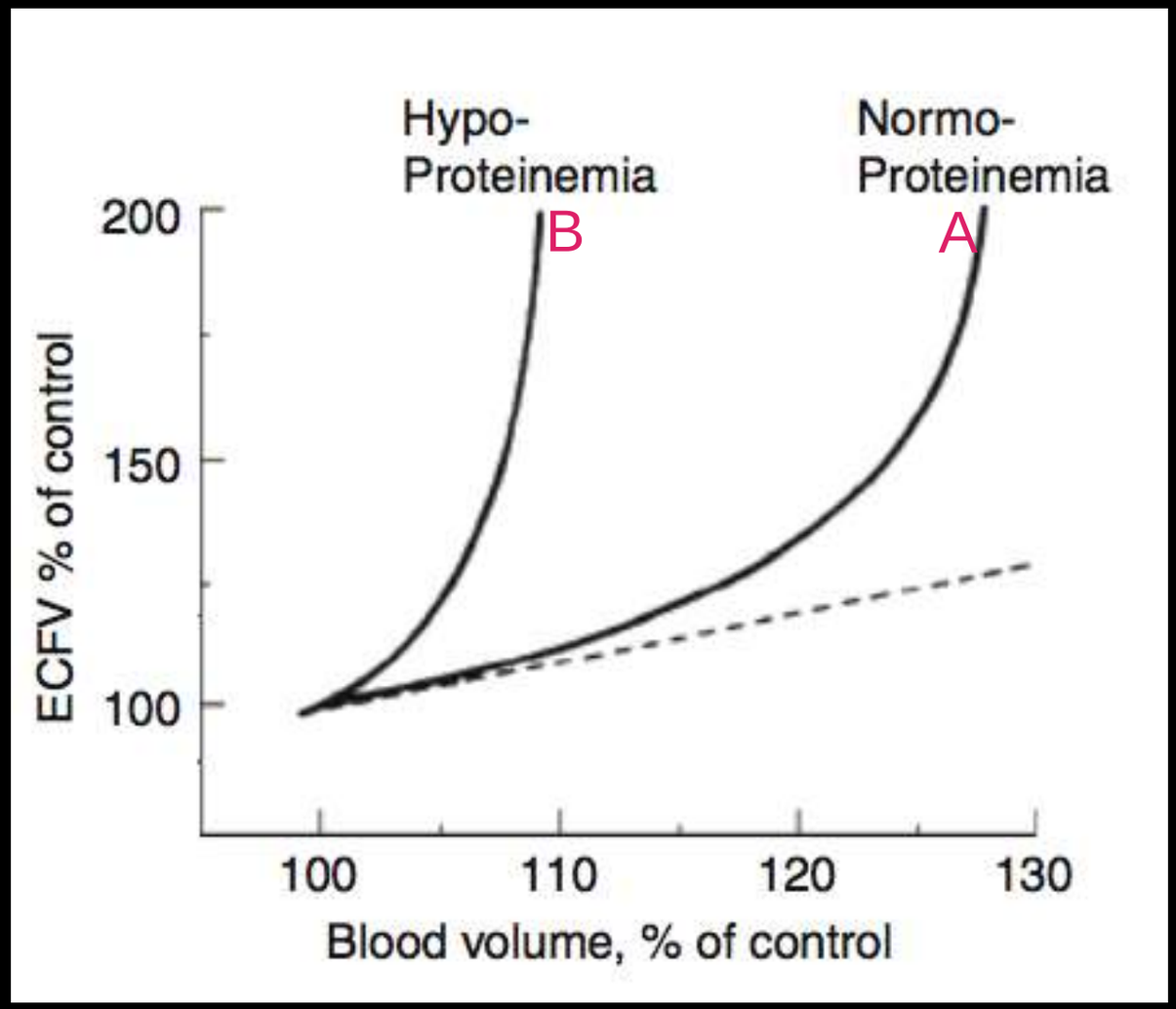
FIG. 10. Diagram of microvascular endothelium to show how separate pathways for fluid (through intercellular cleft containing a fiber matrix at luminal entrance) and protein (through vesicular system) can lead to differences between mean osmotic pressure between plasma and interstitium (and lymph) and plasma and fluid in intercellular cleft downstream from sieving matrix. [From Michel (188).]

Microvascular Permeability

C. C. MICHEL AND F. E. CURRY

Starling's equation

$$J_V/A = L_P[P_c - P_i) - \sigma_m(COP_p - COP_i)]$$



Aukland K, Reed RK, 1993

Subjects during varying dietary salt intake

A: normal plasma protein concentration
B: hypoproteinemia (nephrotic syndrome)

	ECV	BV
9 healthy subjects	+20%	+11%
21 nephrotic pts	+60%	+4 to +11%
14 HD pts & 29 CKD 1-5	68%	19%

Do other components of the Starling forces matter?

Relationship between Filtration Coefficients of Microvasculature and Levels of Atrial Natriuretic Peptide or Echocardiographic Measurements

M. Yashiro[a] H. Watanabe[a] M. Tomita[a] N. Yamadori[a] E. Muso[b]

[a]Division of Nephrology, Kyoto City Hospital, Kyoto, and [b]Division of Nephrology, Kitano Hospital of Medical Institute, Osaka, Japan

Blood Purification, 2005

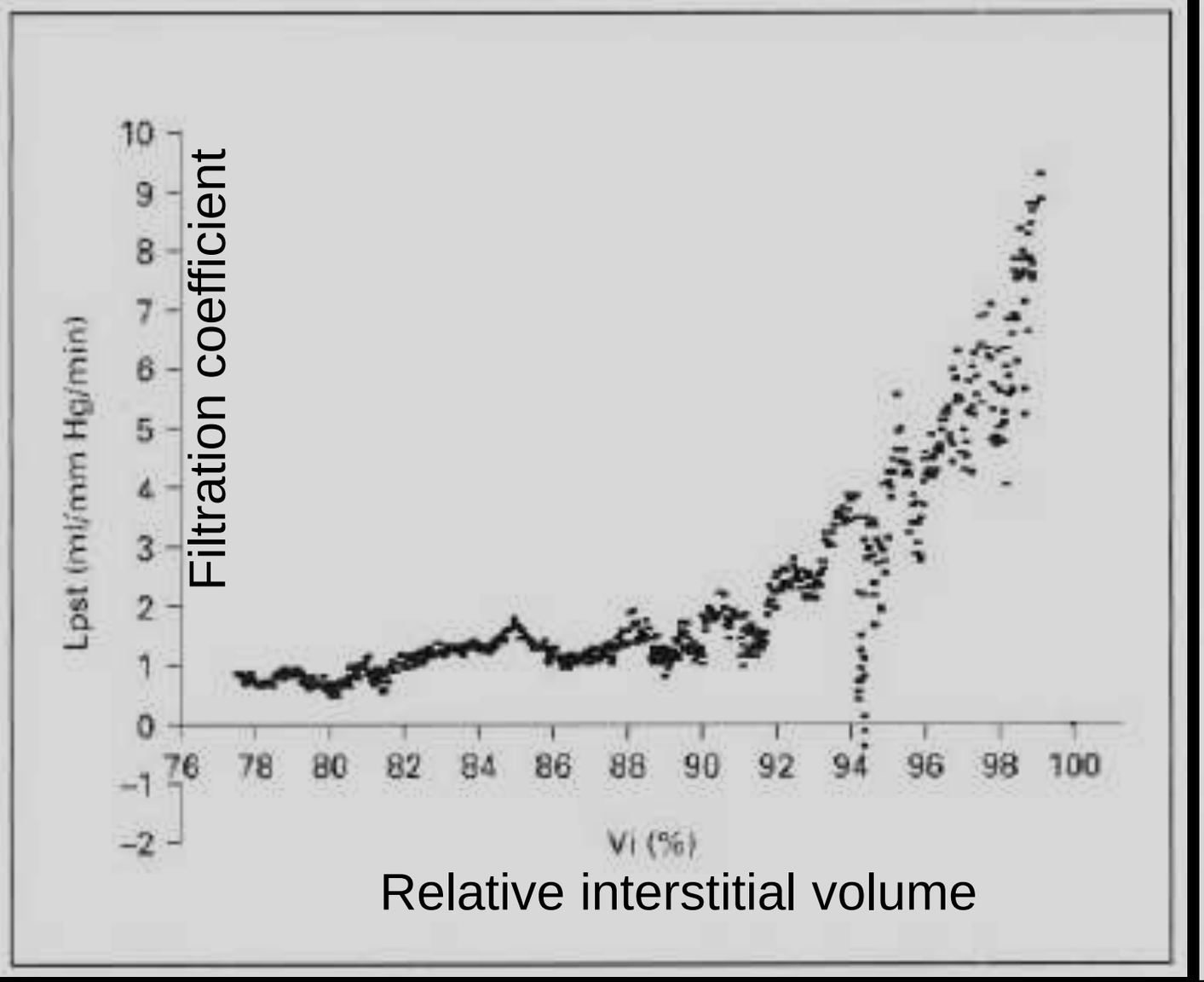
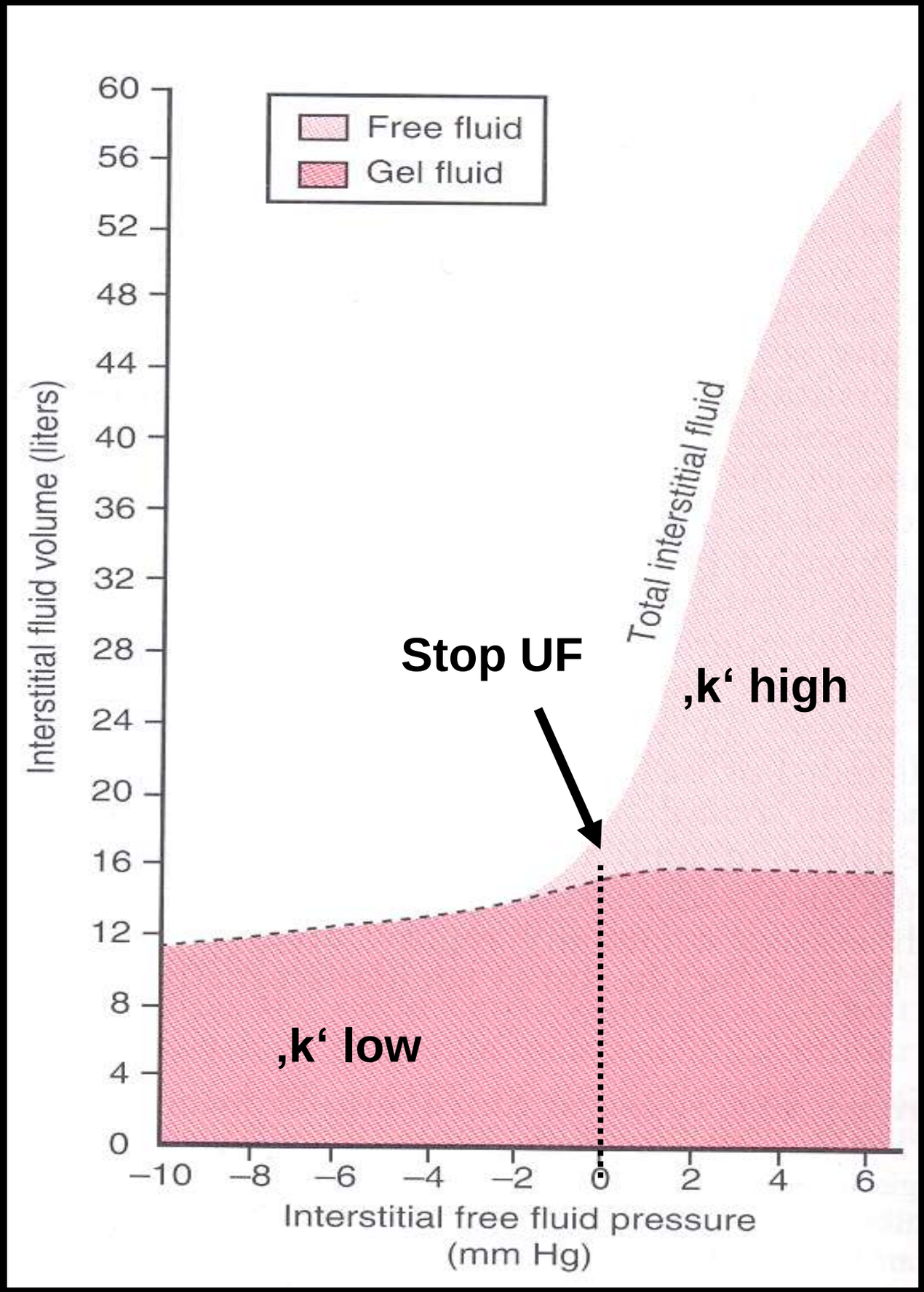


Table 2. Correlation coefficients between Lpst and other parameters

	Lpst (ml/mm Hg/min)	p
ANP, pg/ml	0.613*	<0.001
TUF/DW, l/kg	−0.230	0.101
UFR/DW, l/h/kg	−0.073	0.608
Age, years	−0.069	0.625
CTR, %	0.046	0.745
LVd, cm	0.340*	0.014
LVs, cm	0.309*	0.026
LA, cm	0.496*	<0.001
IVCe, cm	0.630*	<0.001
IVCi, cm	0.685*	<0.001
CI	−0.308*	0.027

* Statistically significant.

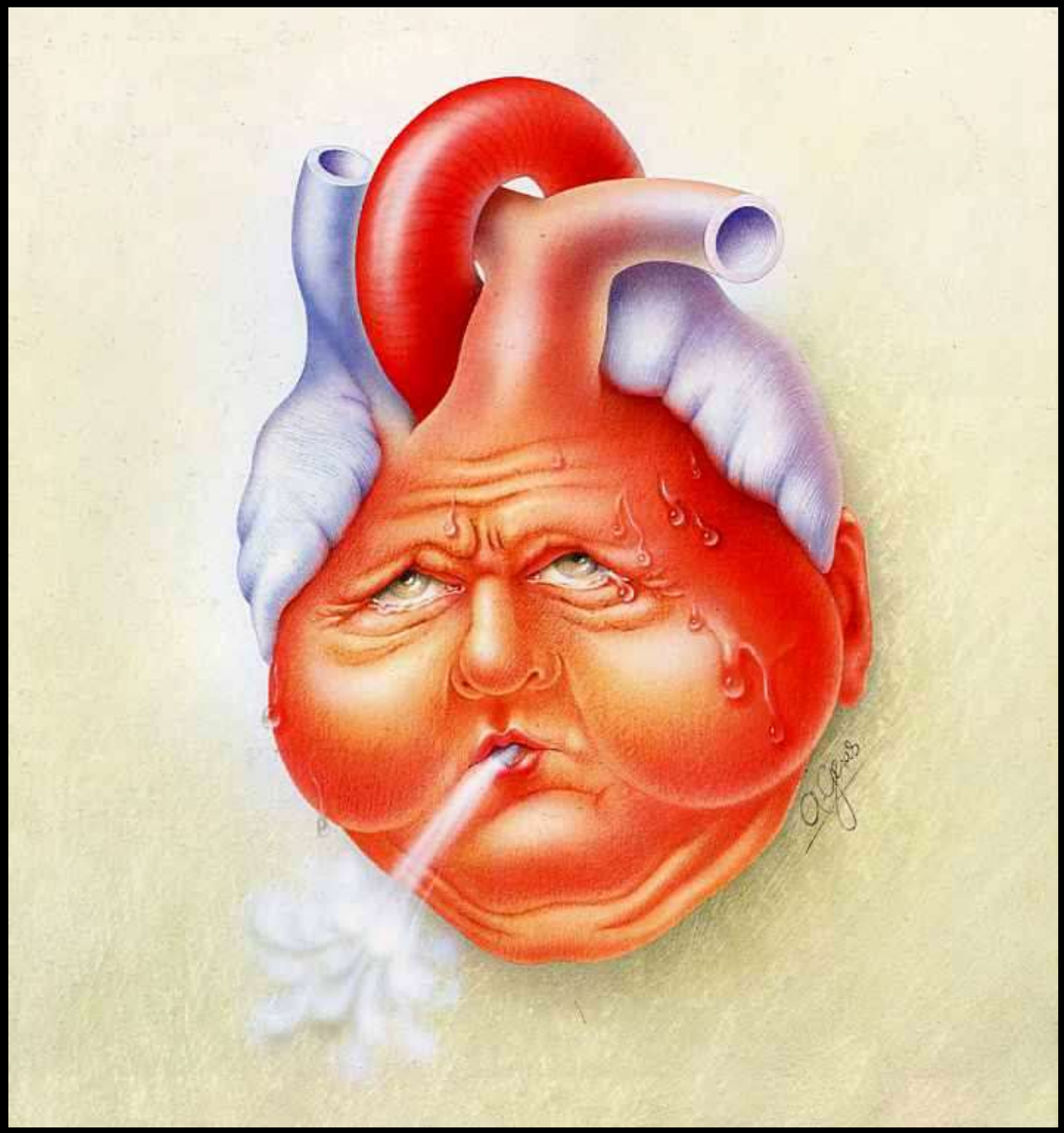
TUF/DW = Total ultrafiltration volume (l)/dry weight (kg) × 100; UFR/DW = ultrafiltration rate (l/h)/dry weight (kg) × 100; CTR = cardiothoracic ratio; LVd = left ventricular diastolic diameters; LVs = left ventricular systolic diameters; LA = left atrial diameters; IVCe = inferior vena cava diameters in quiet expiration; IVCi = inferior vena cava diameters in quiet inspiration; CI = collapsibility index (IVCe – IVCi)/IVCe.



(Guyton Textbook of Physiology)

- ***<u>The new concept:</u>***
- **Continuously monitor changes in ECV during HD**
- **Stop UF when all excess ECV has been removed**
- **Bioimpedance spectroscopy is used for continuous ECV monitoring**

Long-term Effects of ECV-Expansion: LVH and Congestive Heart Failure



Interdialytic Weight Gain: Dependent on Na^+-Intake, Not on Fluid Restriction.

Procedure: **Patients randomized to either standard or low Na^+ diet (< 1g/day) without fluid restriction.**

Results: **Despite no fluid restriction interdialytic weight gain *dropped* from *2.8±0.2 kg* to *1.9±0.2 kg* (p=0.007).**

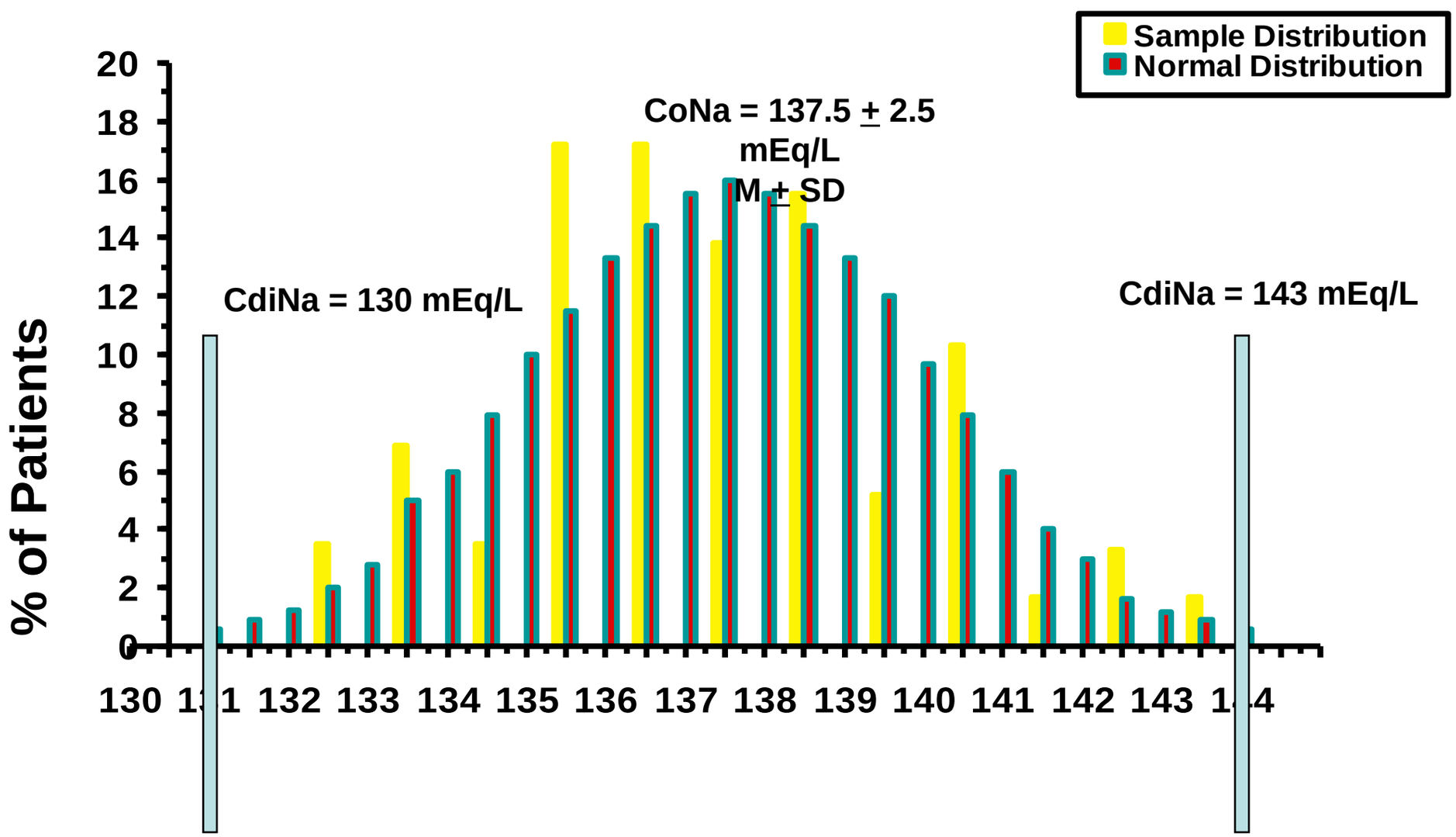
n = 28 HD-pts, 3 outpatient units
prospective randomized cross-over study

A. Rigby-Mathews et al,
J ASN, 10:267A (1999)

Four practical approaches to reduce sodium excess

1. Dietary restriction (serious)
2. **Equating dialysate sodium with patient's sodium**
3. Avoidance of intradialytic saline infusion
4. Avoidance of "bad" sodium profiling

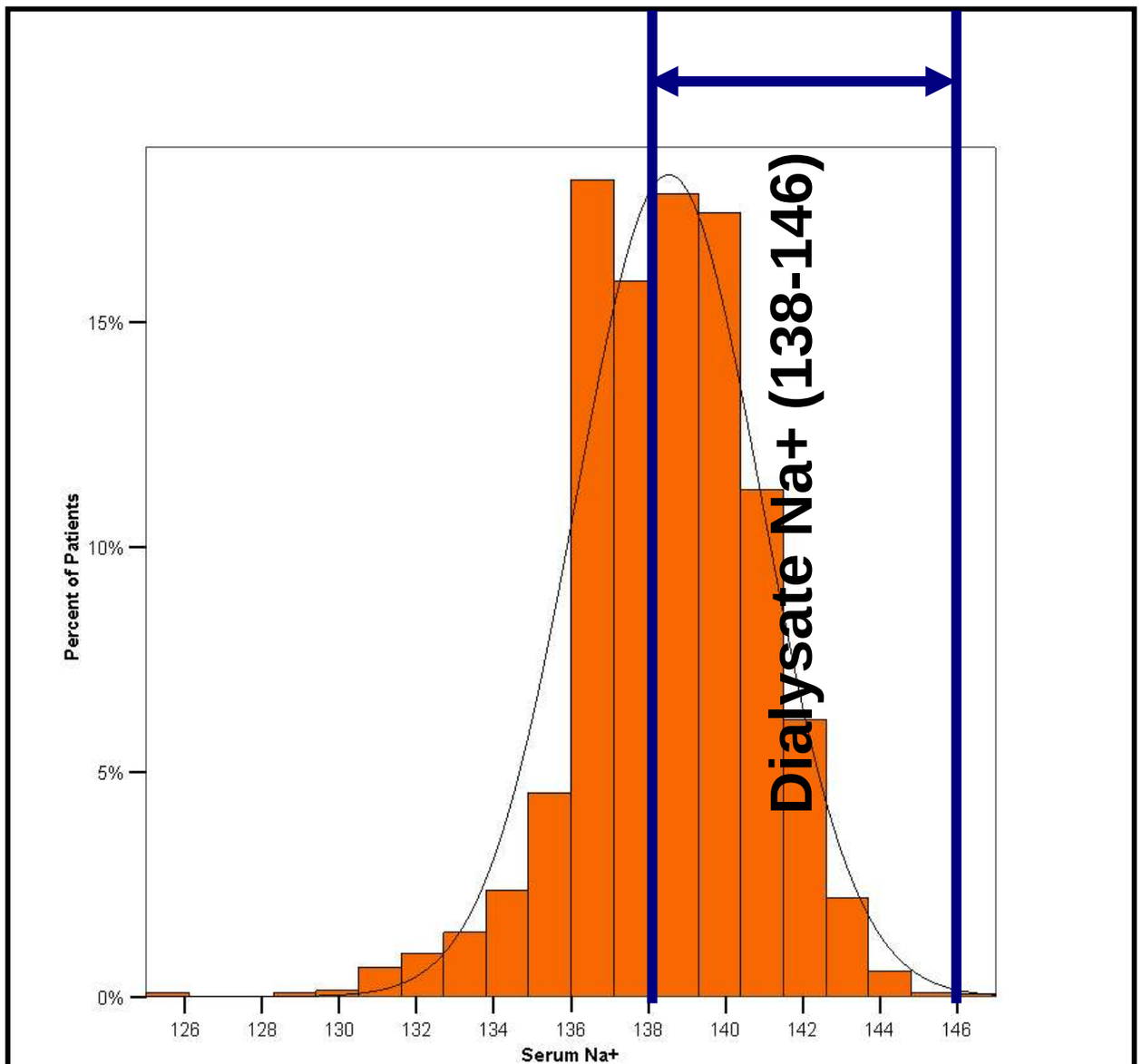
DISTRIBUTION OF MEAN PREDIALYSIS Na^+ CONCENTRATIONS (CpNa)



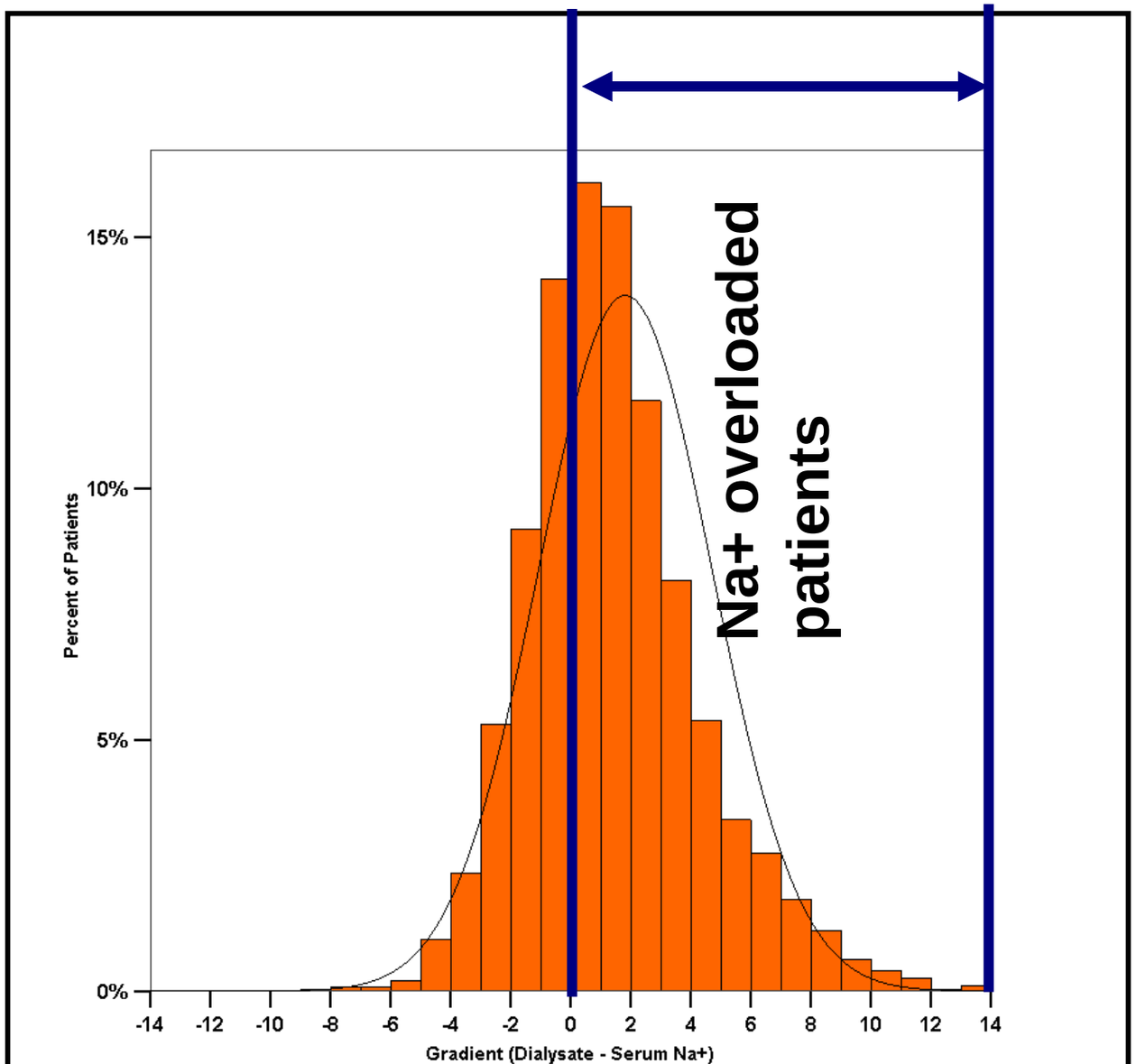
M. Keen

Na+ Gradient = Dialysate Na+ minus Serum Na+

Serum Na+



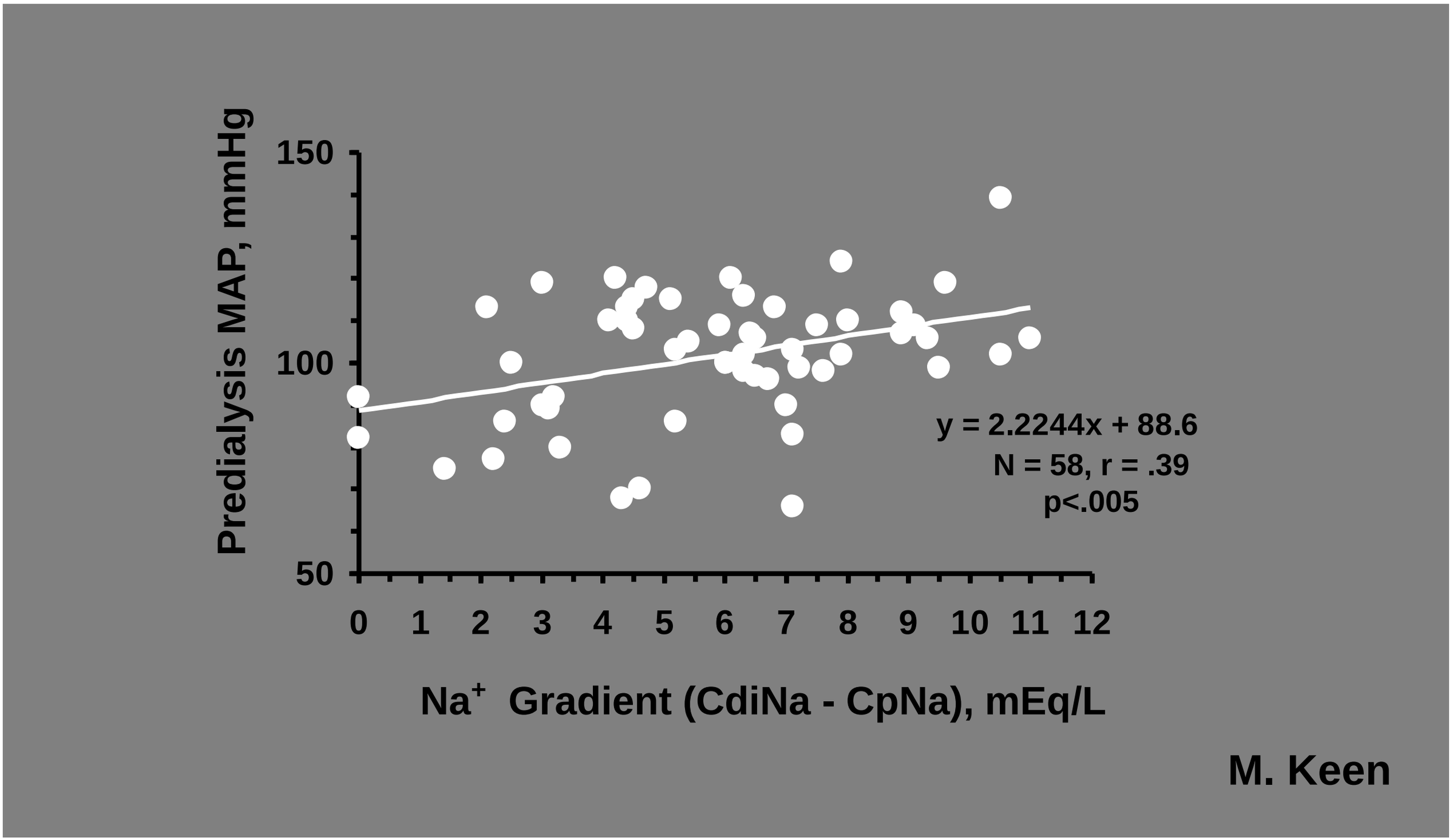
Na+ Gradient



- In 70% of patients dialysate Na+ exceeds serum Na+ plasma
  → a POSITIVE Na+ gradient

Sergeyeva, 2008

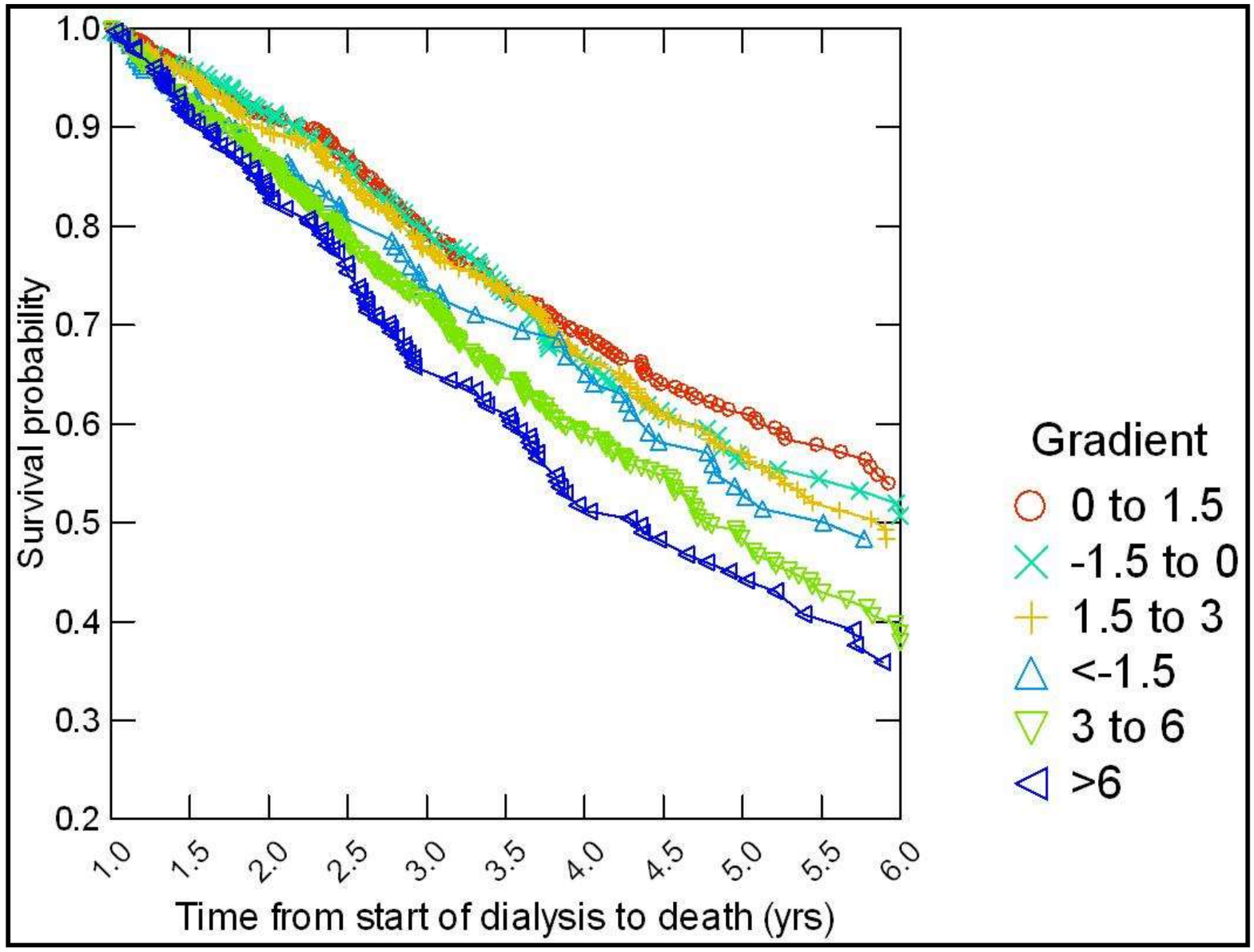
RELATIONSHIP OF PREDIALYSIS MAP TO PREDIALYSIS Na^+ GRADIENT (CdiNa - CpNa)



M. Keen

Survival based on Na+ Gradient

- Mean survival time (years) per Na+ gradient (mmol/L)
  - below -1.5: 5.3 yrs
  - -1.5 to 0: 5.4 yrs
  - 0 to 1.5: 5.6 yrs
  - 1.5 to 3: 5.4 yrs
  - 3 to 6: 4.8 yrs
  - Greater 6: 4.6 yrs



Sergeyeva, 2008

Hospital Admissions per Pt Yr Based on Na+ Gradient

Na+ Gradient (mmol/L)	CVD	Fluid overload	Infections	Other	Total Admissions
< 0	0.18	0.09	0.18	1.05	**1.5**
0 - 3	0.18	0.09	0.2	1.16	**1.62**
3 - 6	0.21	0.13	0.23	1.49	**2.07**
> 6	0.24	0.16	0.25	1.72	**2.37**

What can we do about the positive Na+ gradient ?

Sequential sodium therapy allows correction of sodium-volume balance and reduces morbidity

A. Murisasco[1], G. France[1], G. Leblond[1], C. Durand[1], M. El Mehdi[1], A. Crevat[1], R. Elsen[2], Y. Boobes and M. Baz

[1]*Hôpital Sainte-Marguerite, 270, Bd de Ste-Marguerite 13277 Marseille Cedex 9, France*
[2]*Cordis-Dow Research, Brussels, Belgium*

Clin Nephrol, 1985

extracellular volume (ECV). Since the initial development of chronic hemodialysis, various levels of Na^+ dialysate concentrations (Na^+_{Di}) have been proposed. In particular, in addition to isotonic dialysate solutions, hypotonic baths have been advised to correct certain types of arterial hypertension and hypertonic baths to avoid hypotension during dialysis. Since 1965, we have individually adapted Na^+_{Di} in our unit, taking into account the plasma Na^+ level of each patient. In the present study, we examined the effect

Adaptive Phase

Group 1 (Figure 4). The results of the retrospective and the exploratory phases allowed us to identify for all 65 patients belonging to Group 1 an equilibrium point as defined in the previous section. The distribution of the equilibrium points over the patient population was as follows:

140 ± 1 mEq/l	22 patients
137 ± 1 mEq/l	23 patients
134 ± 1 mEq/l	20 patients.

"Equilibrium points"

From the start of the adaptive phase, patients were dialyzed against a dialysate with $Na^+_{D_i}$ designed to maintain patients' Na^+_o and Na^+_p at the equilibrium level.

Improvements in intradialytic morbidity. Intradialytic symptomatology disappeared almost completely after the patient had been stabilized at the equilibrium point.

Improvements in interdialytic hypertension (Figure 5). Before the start of the adaptive phase, i.e., before $Na^+_{D_i}$ was adjusted to their individual equilibrium levels, 19 out of 65 patients were hypertensive and were treated with anti-hypertensive drugs. Adaptation of $Na^+_{D_i}$ at the individual equilibrium level reduced the incidence of hypertension to 6 out of 65. The distribution of the 19 initially hypertensive patients with respect to their $Na^+_{D_i}$ equilibrium level before the adaptative phase had been implemented was as follows:

Equilibrium level	Number of hypertensive patients
140 mEq/l	3
137 mEq/l	7
134 mEq/l	9

The negative correlation of the incidence of hypertension with the level of the equilibrium point indicates that the patients with the lower equilibrium level had been dialyzed against a dialysate which was not adapted to their condition and was actually too high in Na^+. This reinforces the concept of the equilibrium point and the importance of adapting $Na^+_{D_i}$ to match the patient's individual equilibrium point.

Murisasco, 1985

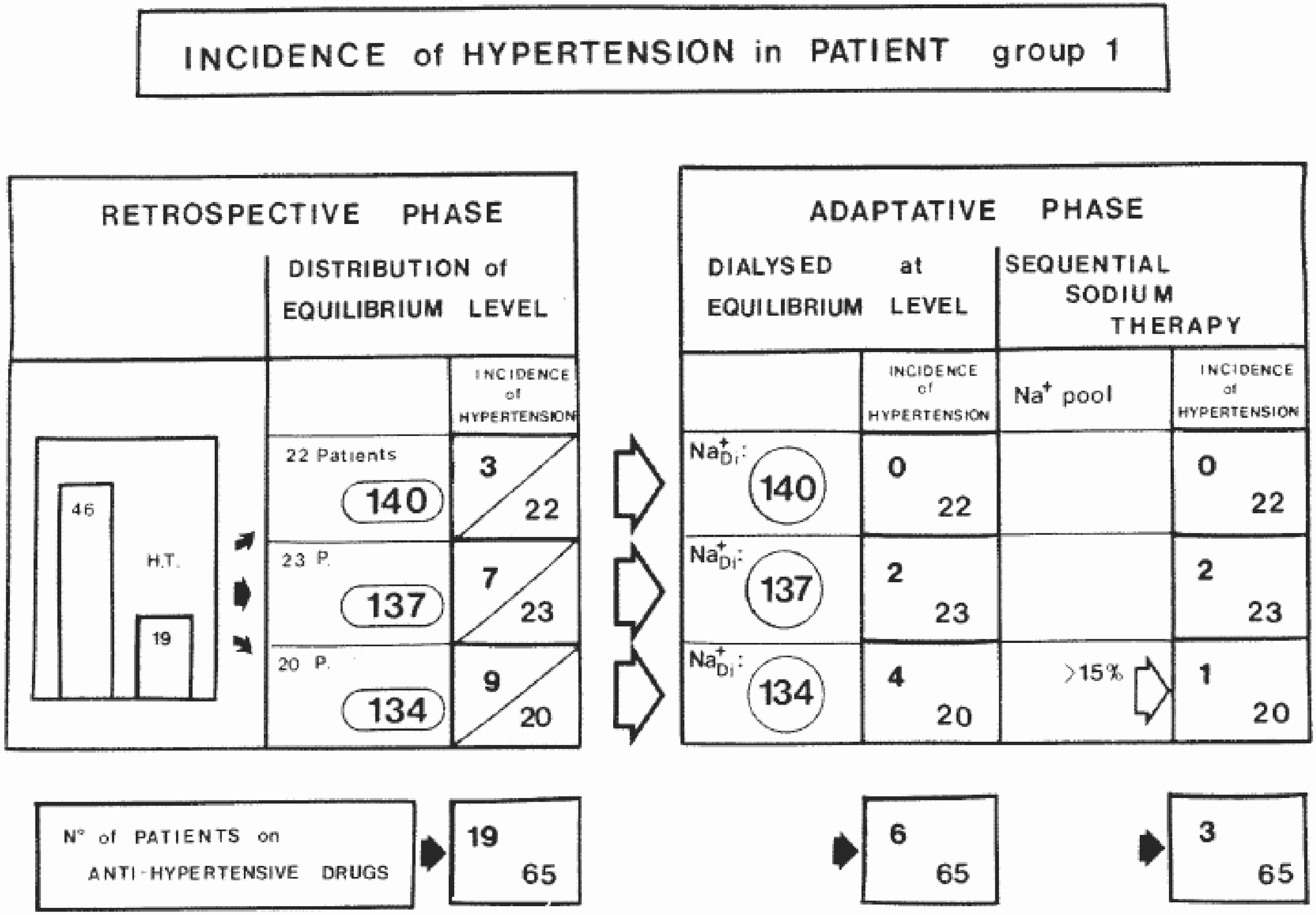


Fig. 5 Incidence of hypertension in patient group 1 (H.T. = arterial hypertension).

Murisasco, 1985

SST = DNa [131 (30min) / 134 (90 min)] x 3

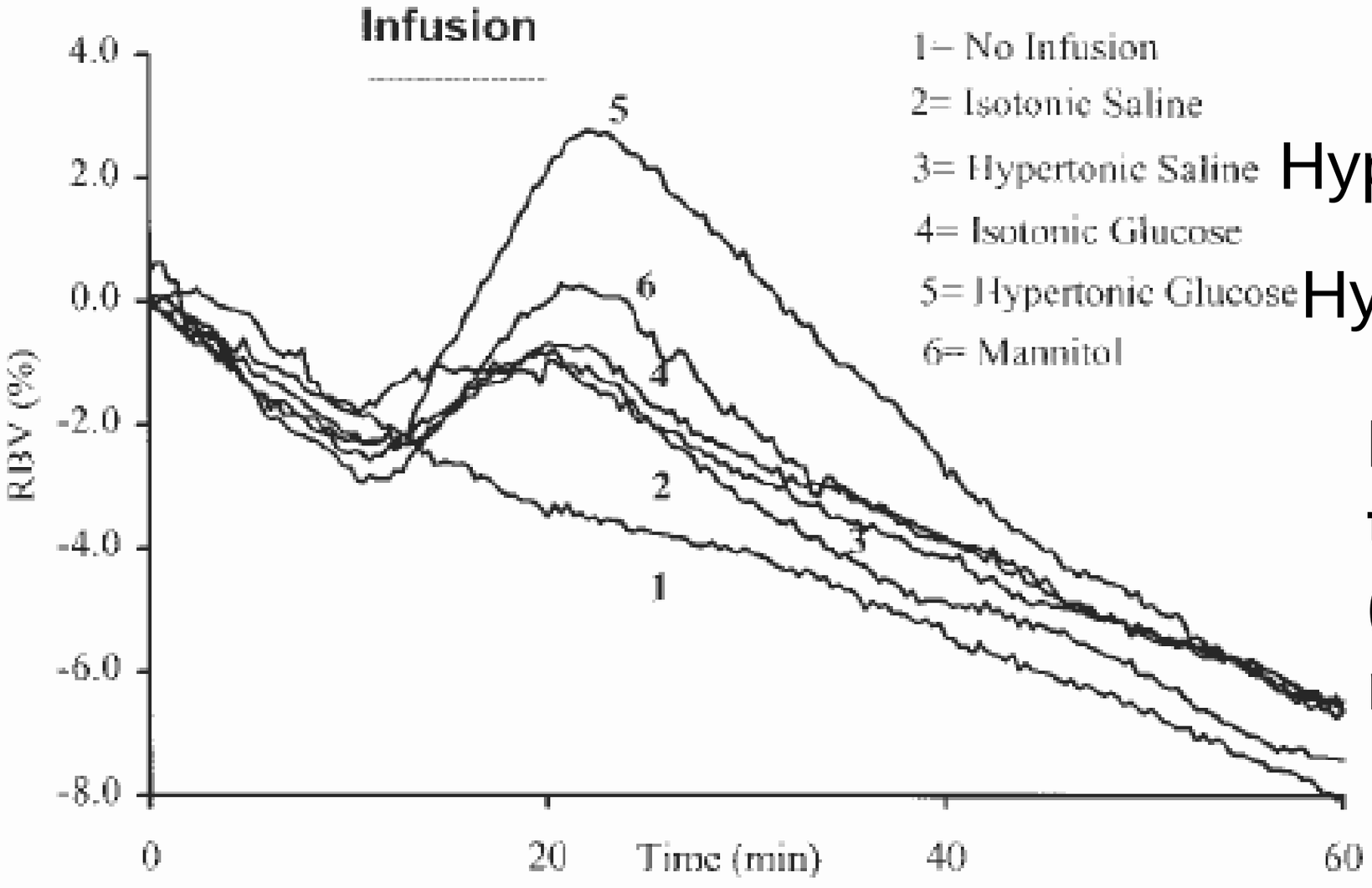
Four practical approaches to reduce sodium excess

1. Dietary restriction (serious)
2. Equating dialysate sodium with patient's sodium
3. **Avoidance of intradialytic saline infusion**
4. Avoidance of "bad" sodium profiling

Specific effect of the infusion of glucose on blood volume during haemodialysis

NDT, 2002

Robert W. Nette, Harmen P. Krepel, Anton H. van den Meiracker, Willem Weimar and Robert Zietse



Hypertonic saline 3%

Hypertonic glucose 20%

Fluids were given at the same rate as UF (20 mL/kg/hr over 10 min)

Fig. 1. Mean changes in relative blood volume (%) for all patients during combined dialysis and ultrafiltration (20 ml/kg/h) following the infusion of different solutions. The increase in RBV is significantly greater during infusion of hypertonic glucose (5).

Suggested practical approach

- 20 mL of glucose 50% in the event of muscle cramps or intradialytic hypotension followed by a second bolus after 5 min if needed

Four practical approaches to reduce sodium excess

1. Dietary restriction (serious)
2. Equating dialysate sodium with patient's sodium
3. Avoidance of intradialytic saline infusion
4. **Avoidance of "bad" sodium profiling**

Sodium profiling

- A a positive intradialytic Na+ balance occurs when the amount of sodium added to the patients exceeds the amount of sodium removed
- Careful adjustment of dialysate Na+ levels necessary during Na+ profiling

In a nutshell -

- Fluid overload results in cardiovascular disease, most prominently LVH and hypertension.
- Salt management results in regression of LVH
- Neutral sodium balance over the whole dialysis cycle is key to avoid fluid overload
  - Serious diet: 5 g salt per day
  - Alignment of dialysate and serum Na+

Na+ “SET POINT” Hypothesis

Whenever serum Na+ is above one's individual serum Na+ " set point", thirst occurs and fluid is consumed until this "set point" is reached.
Knowledge of the individual “set point” allows adjustment of dialysate Na+

M. Keen

DOPPS Symposium

EDTNA/ERCA Congress
Ljubljana, Slovenia
September 12, 2011

Chairs:
Nathan Levin and Alessandra

Dialysate composition: Associations with patient outcomes

Nathan Levin

Renal Research Institute

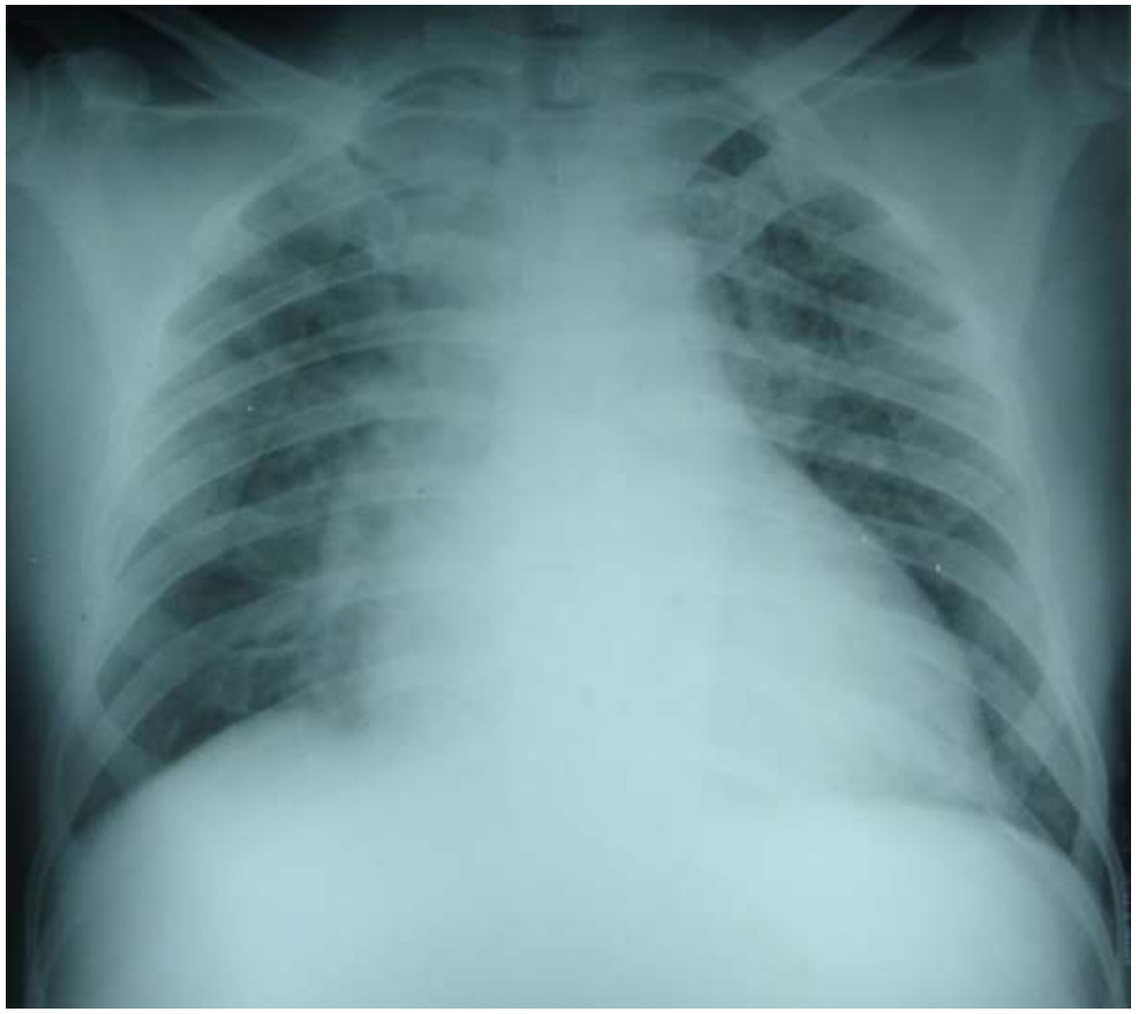
New York, NY

Back to haemodialysis basics

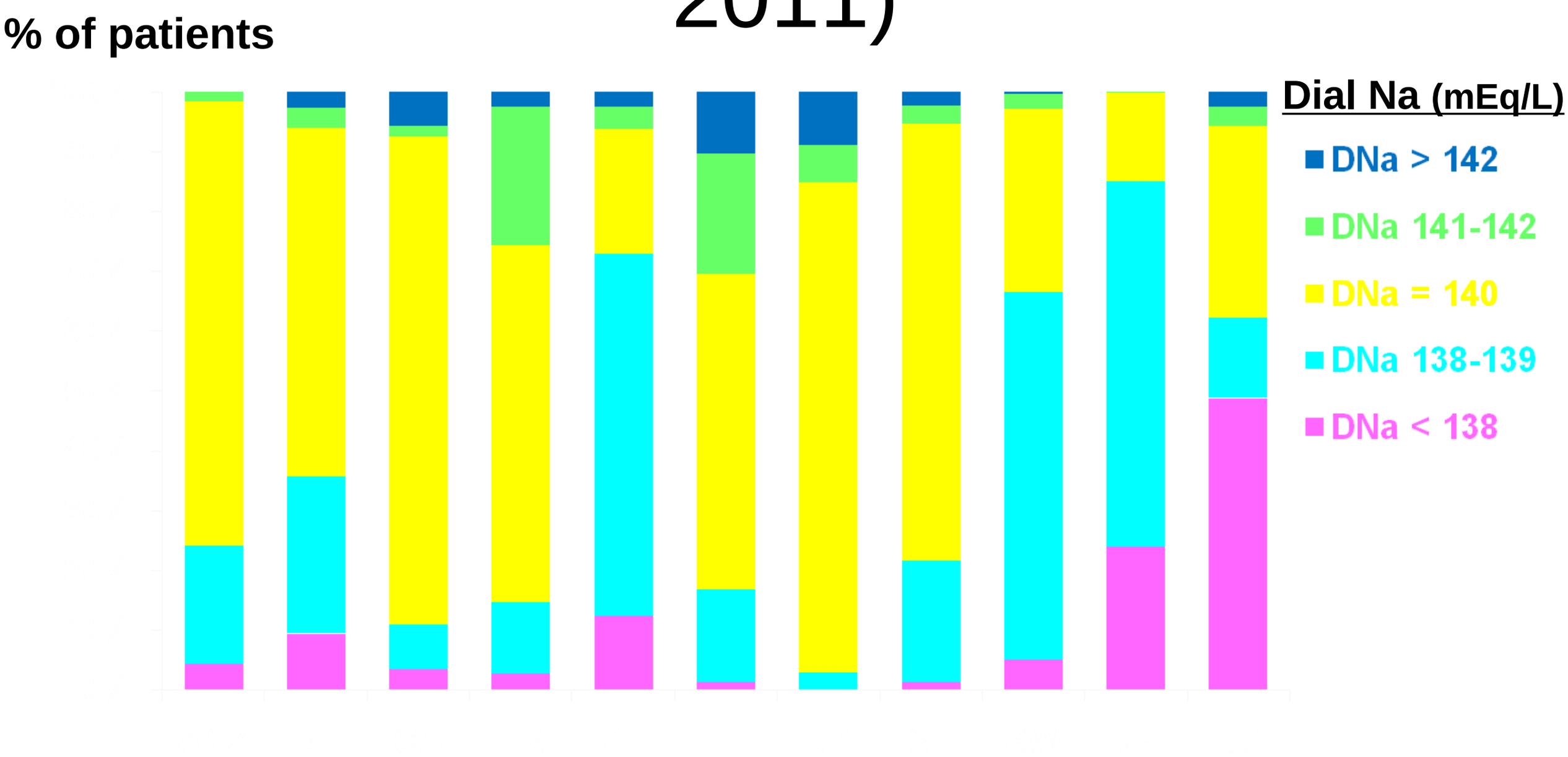
- **Dialysis fluid is a fundamental aspect of hemodialysis that can easily be modified**
- **Only one randomized trial published so far, acetate vs. bicarbonate (Uldall**

Dialysate Sodium

- **Dialysate sodium concentrations originally were low to achieve a negative sodium balance during HD**
- **Dialysate sodium concentrations increased after the introduction of volume controlled ultrafiltration**



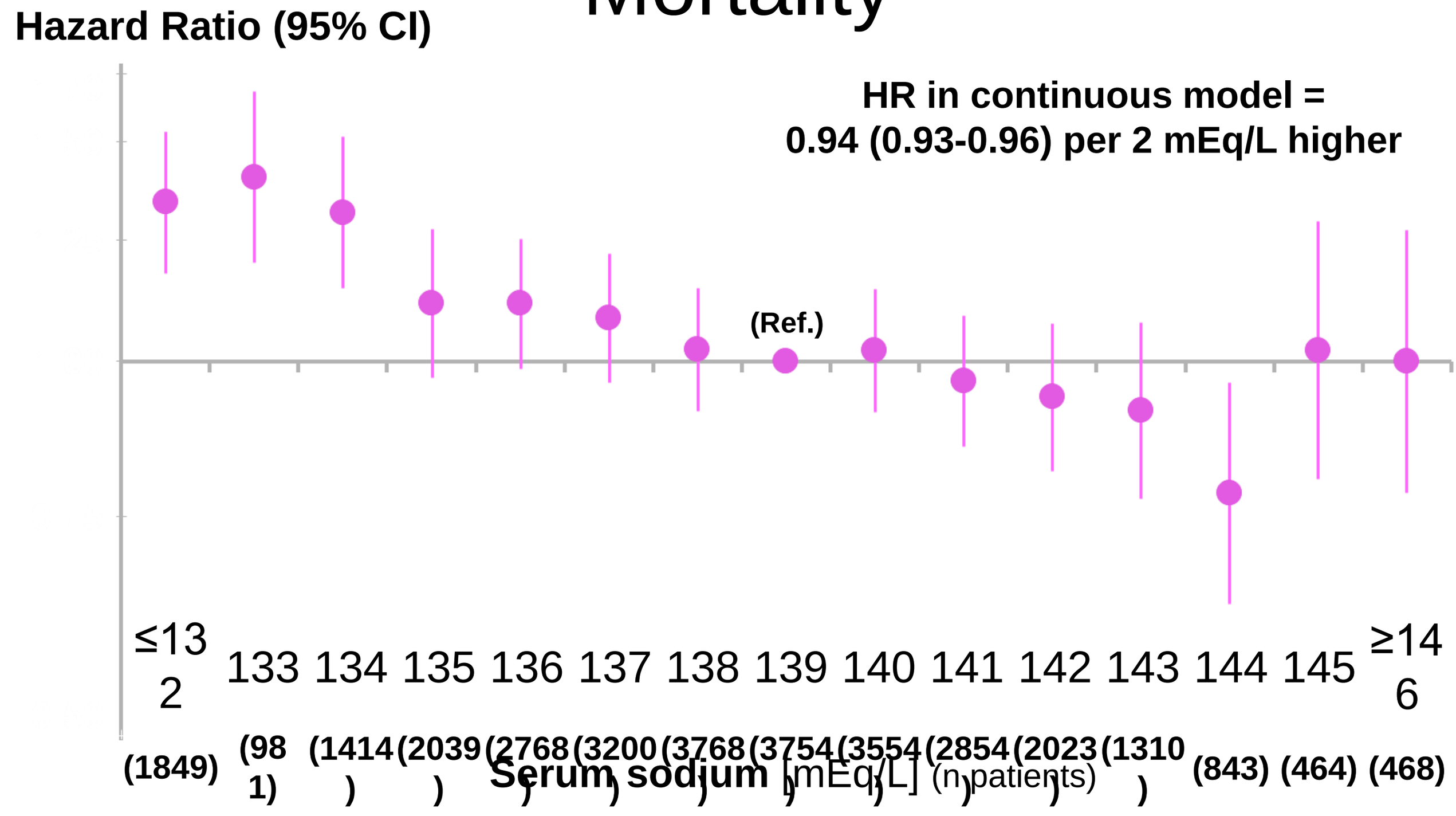
Dialysate Na by Country (2009-2011)



N patients	**518**	**565**	**296**	**510**	**729**	**725**	**1873**	**842**	**577**	**422**	**3256**
Mean DNa	139.4	139.3	140.0	140.2	138.5	140.4	140.4	139.7	138.6	137.9	138.4
Single	71%	39%	47%	36%	29%	35%	91%	50%	29%	75%	56%

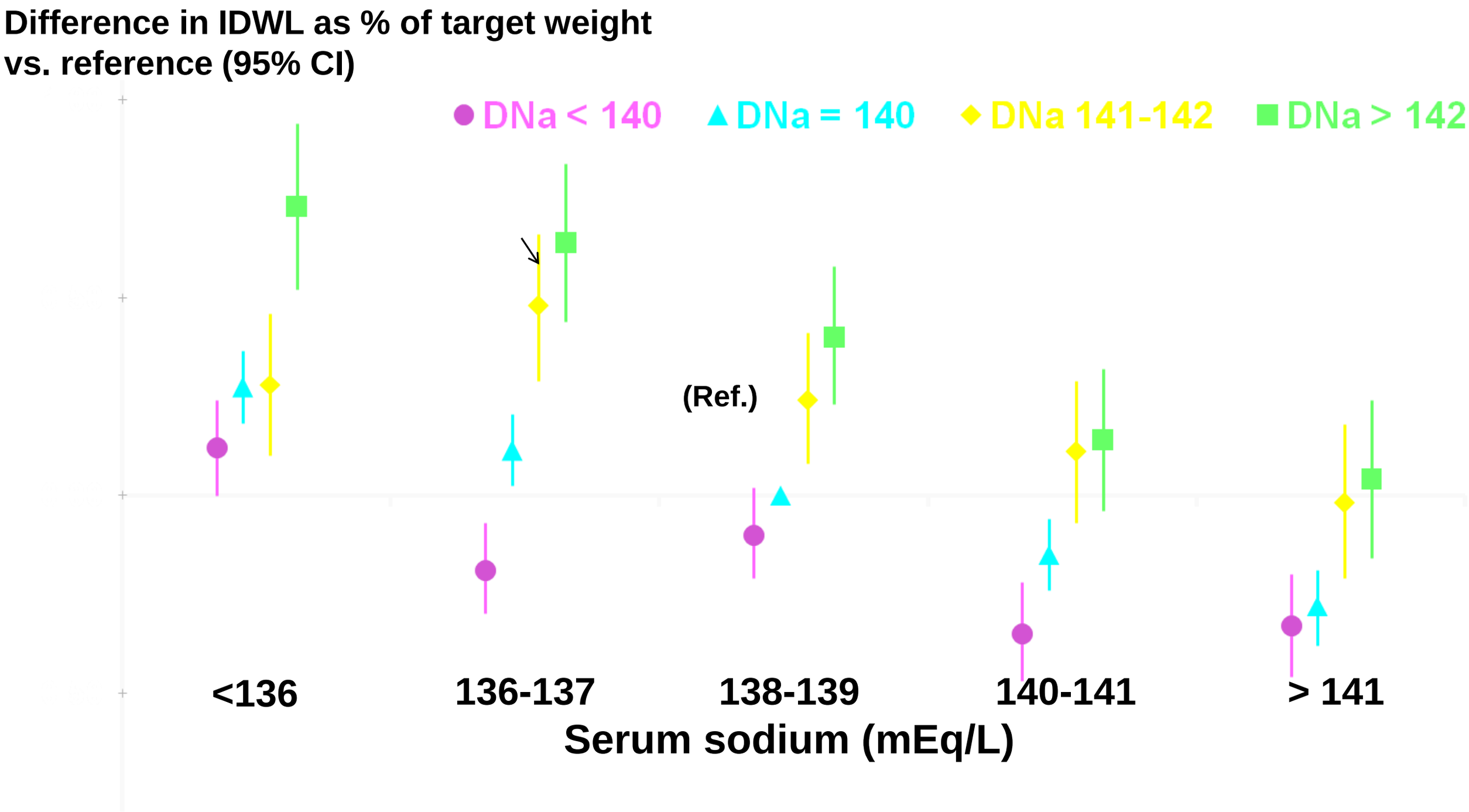
* % of facilities where ≥ 90% of patients use a single DNa concentration
Na modeling patients excluded

Pre-HD Serum Na and All-Cause Mortality



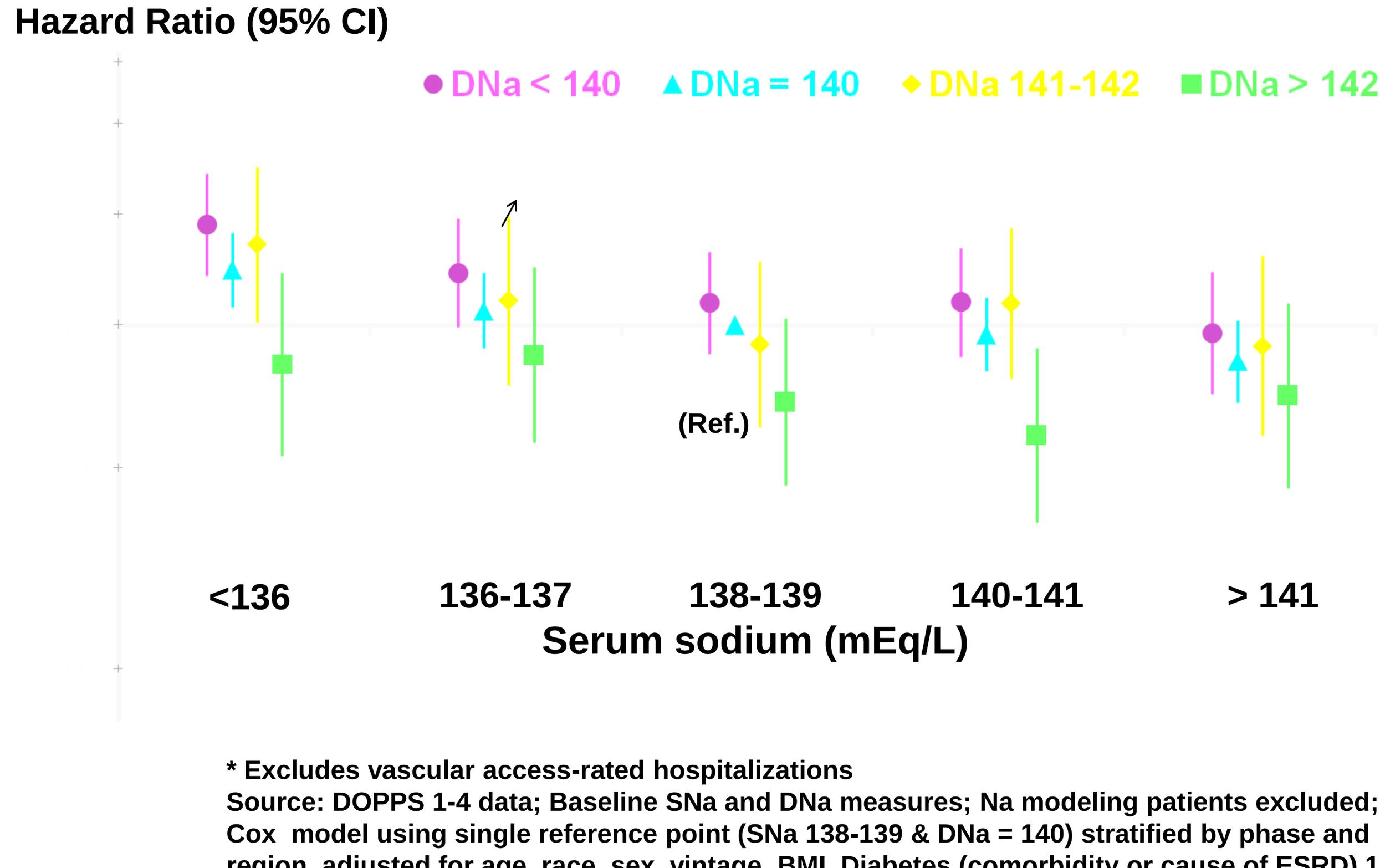
Source: DOPPS 1-4 data; Baseline SNa measures; Na modeling patients excluded;
Cox Model: Stratified by phase and country, adjusted for age, gender, black race, vintage, BMI, intradialytic weight loss, DNa, residual renal function, vascular access, albumin, Hgb, creatinine, ferritin, white blood cell count, 14 comorbidities, and facility clustering effects

Intradialytic Weight Loss Increases with Lower Serum Na and Higher Dialysate Na



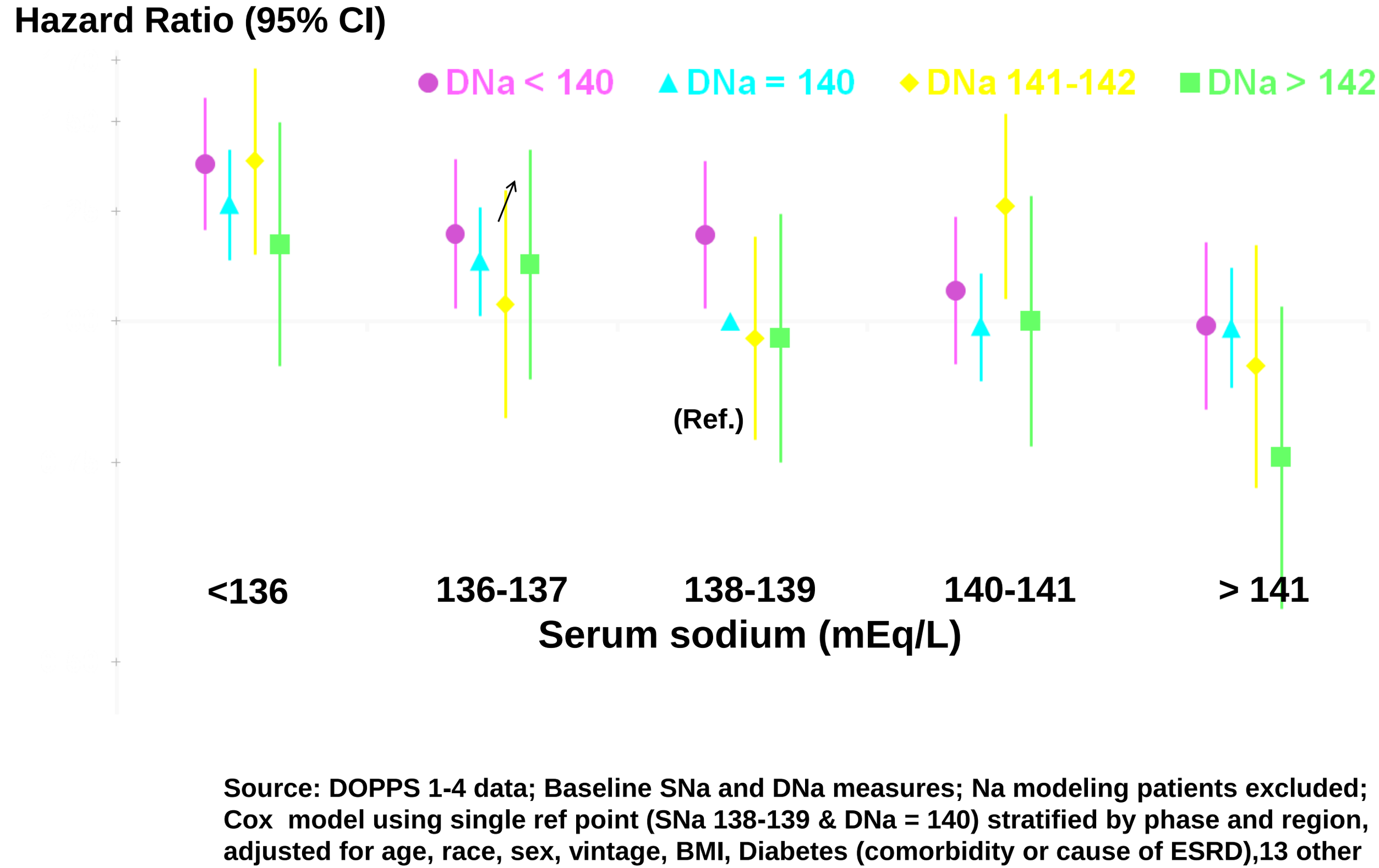
Source: DOPPS 1-4 data; Baseline SNa and DNa measures; Na modeling patients excluded; Linear regression model using single reference point (SNa 138-139 & DNa = 140) and adjusted for DOPPS phase, country, age, sex, BMI, Diabetes, and 13 other comorbid condidtions. Test

Hospitalization Risk Increases with Lower Serum Na and Lower Dialysate Na



*** Excludes vascular access-rated hospitalizations**
Source: DOPPS 1-4 data; Baseline SNa and DNa measures; Na modeling patients excluded; Cox model using single reference point (SNa 138-139 & DNa = 140) stratified by phase and region, adjusted for age, race, sex, vintage, BMI, Diabetes (comorbidity or cause of ESRD),13

All-Cause Mortality Risk Increases with Lower Serum Na



Source: DOPPS 1-4 data; Baseline SNa and DNa measures; Na modeling patients excluded; Cox model using single ref point (SNa 138-139 & DNa = 140) stratified by phase and region, adjusted for age, race, sex, vintage, BMI, Diabetes (comorbidity or cause of ESRD),13 other

Sodium: Summary

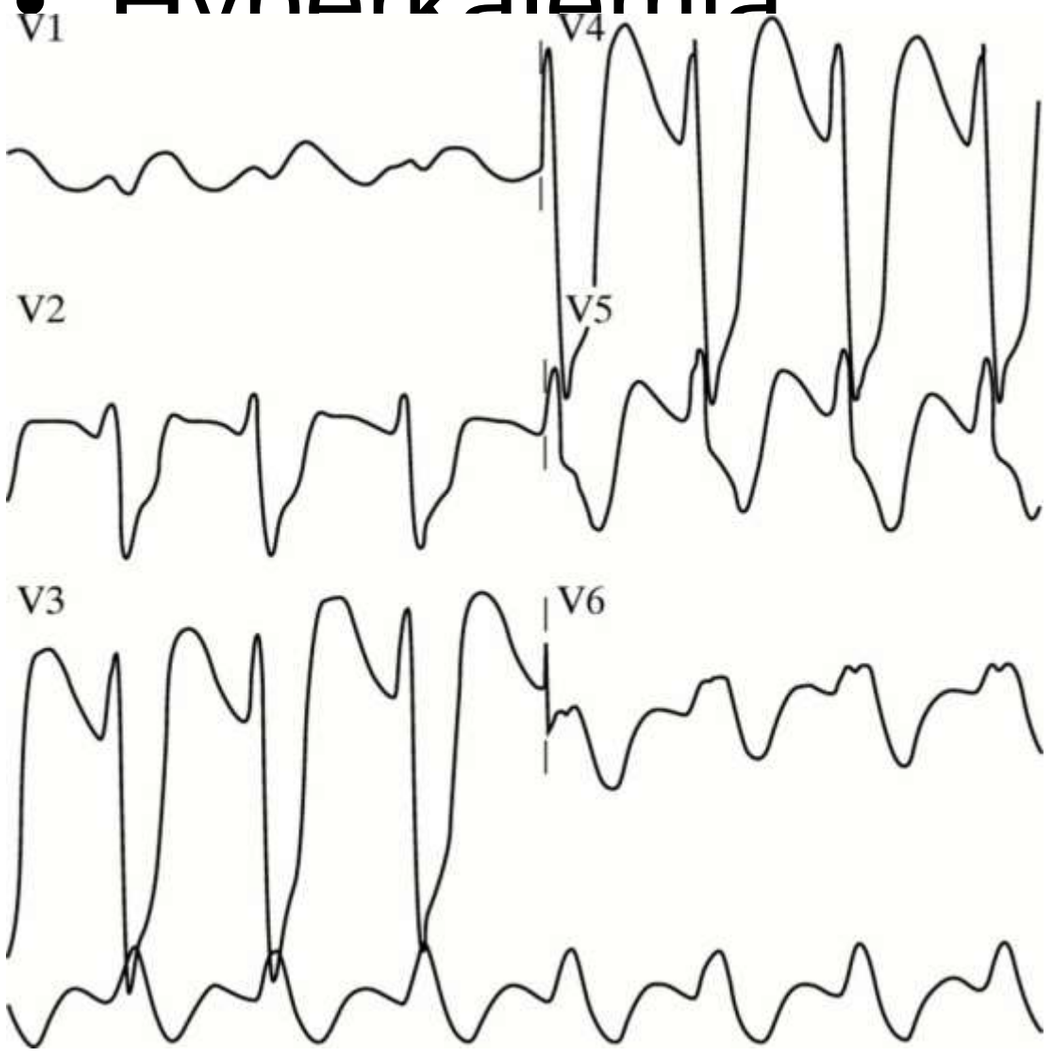
- **Prescribed dialysate Na concentration varies widely across DOPPS countries**

- **Lower serum Na associated with higher risk of hospitalization and mortality**

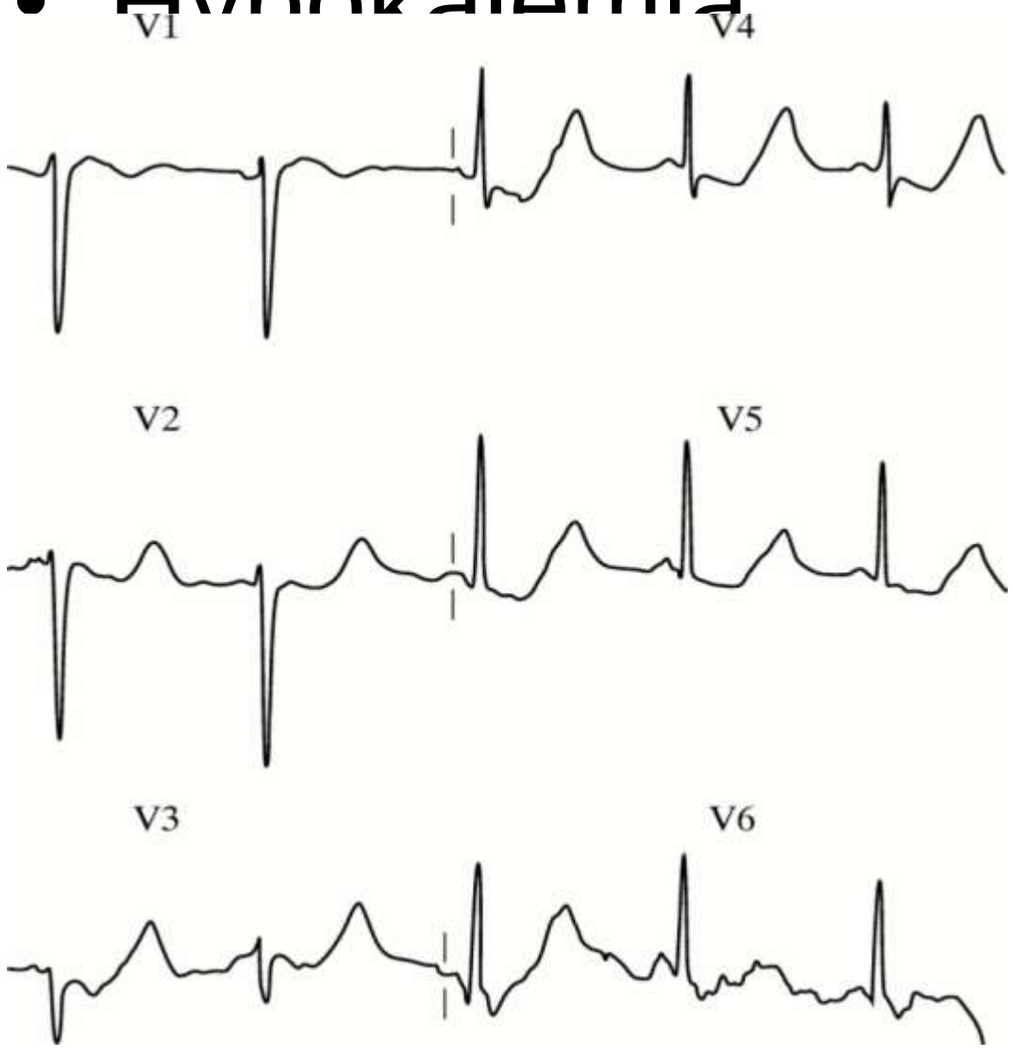
- **Higher dialysate Na concentration associated with higher ultrafiltration volumes, independent of serum Na**

Potassium
double jeopardy

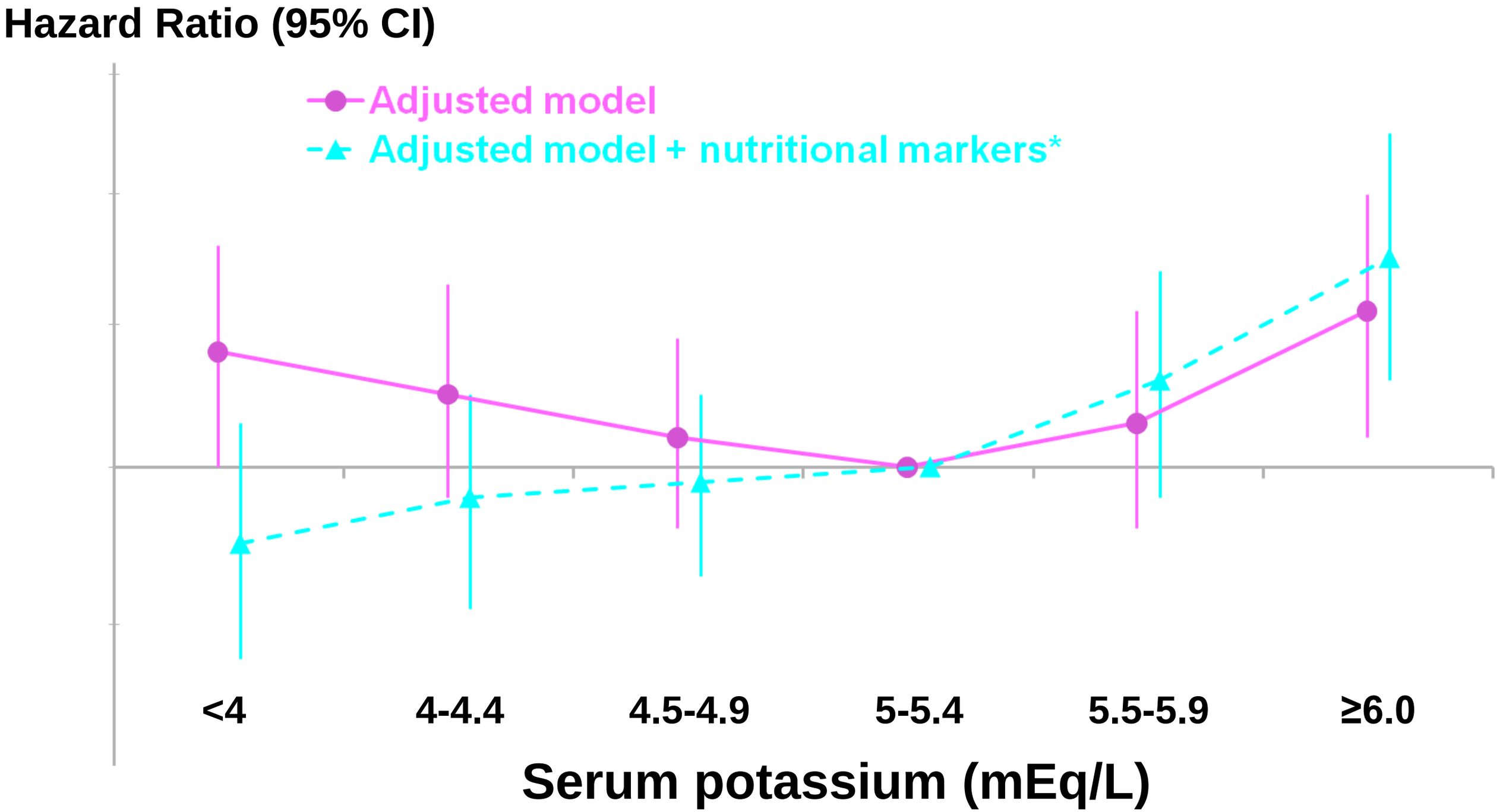
- Hyperkalemia



- Hypokalemia



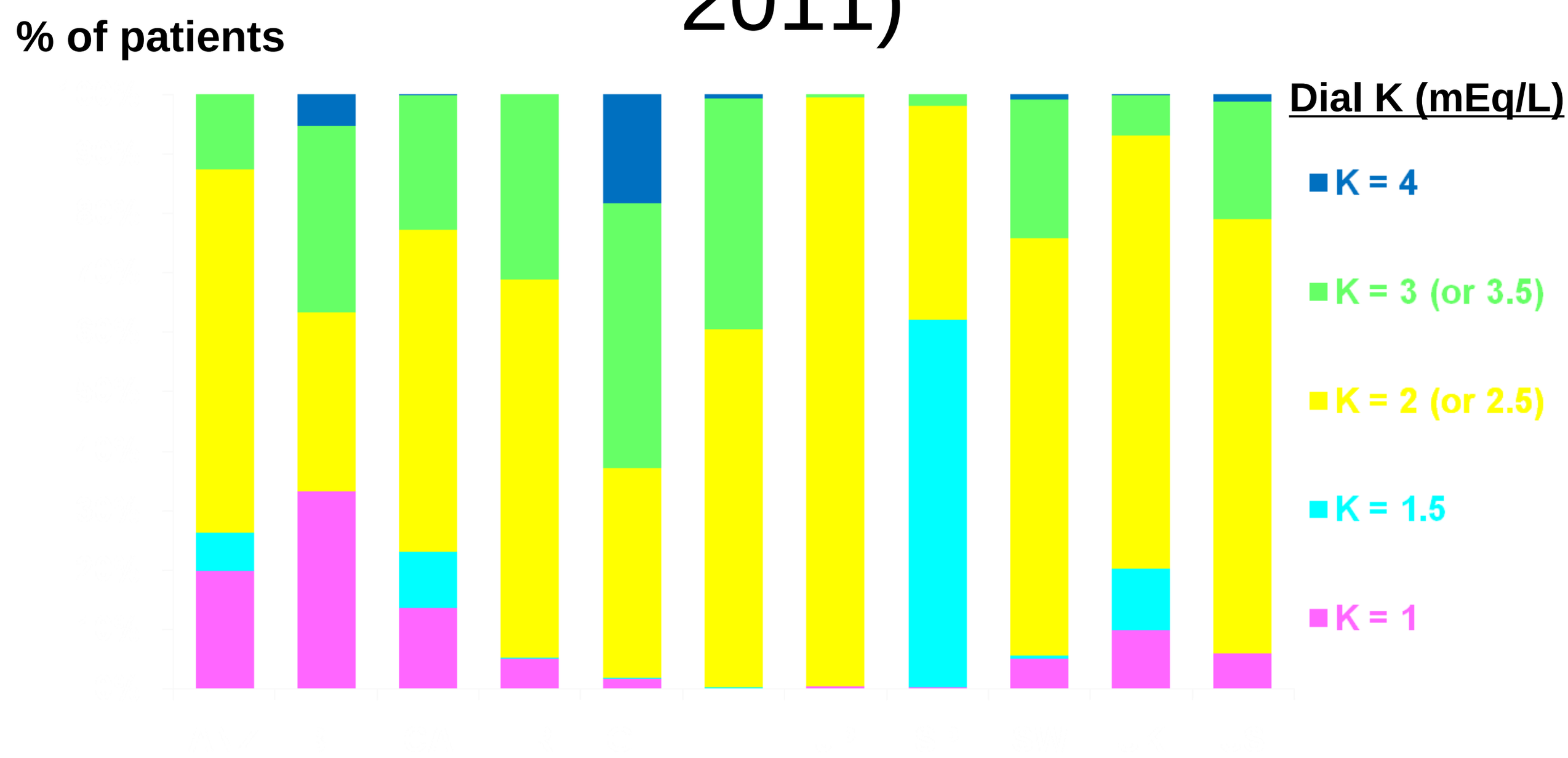
Mortality Risk is Higher at Low and High Serum Potassium Levels



N=37,967 patients; model stratified by country and study phase, accounted for facility level clustering, and adjusted for age, sex, race, vintage, 13 comorbidities, smoking, prior TX, catheter use, employment status, education level, living status and marriage status, skipped ≥1 hemodialysis session in past 30 days, shortened ≥1 hemodialysis session by ≥10 minutes in past 30 days, IDWG >5.7% of dry weight, PO4 >7.5 mg/dL, spKt/V, and hemoglobin at study enrollment

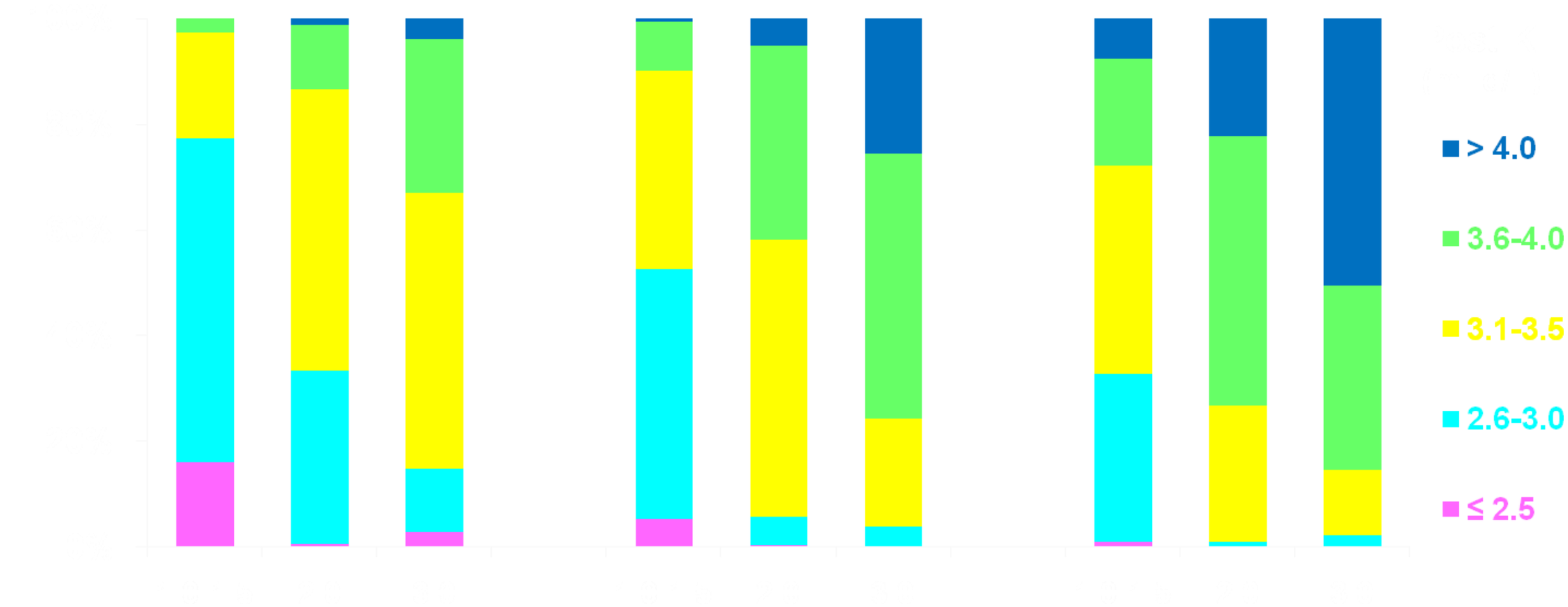
*Model also adjusted for BMI, albumin, creatinine and normalized PCR at study enrollment

Dialysate K by Country (2009-2011)



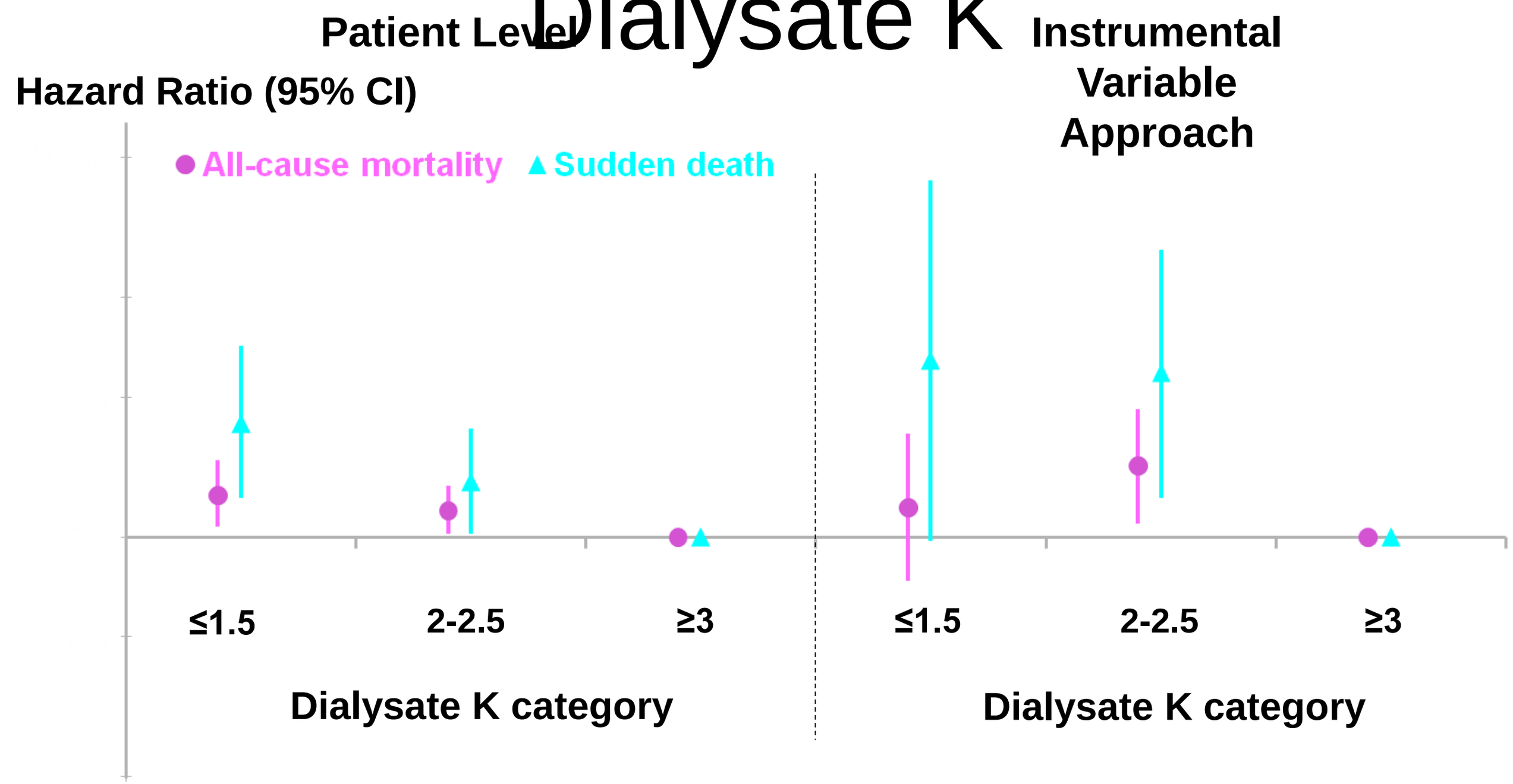
N patients	**518**	**630**	**460**	**541**	**781**	**754**	**1903**	**866**	**588**	**501**	**4102**
Mean D. K	1.9	2.1	2.1	2.3	2.8	2.4	2.0	1.7	2.2	1.9	2.2
Single	* % of facilities where ≥ 90% of patients use a single dialysate K concentration										
	12%	6%	7%	26%	10%	55%	98%	85%	18%	56%	18%

Distribution of Post-HD Serum K, by Pre-HD Serum K and Dialysate K



Source: DOPPS 4 (2009-2011)

Higher Mortality at Low Dialysate K



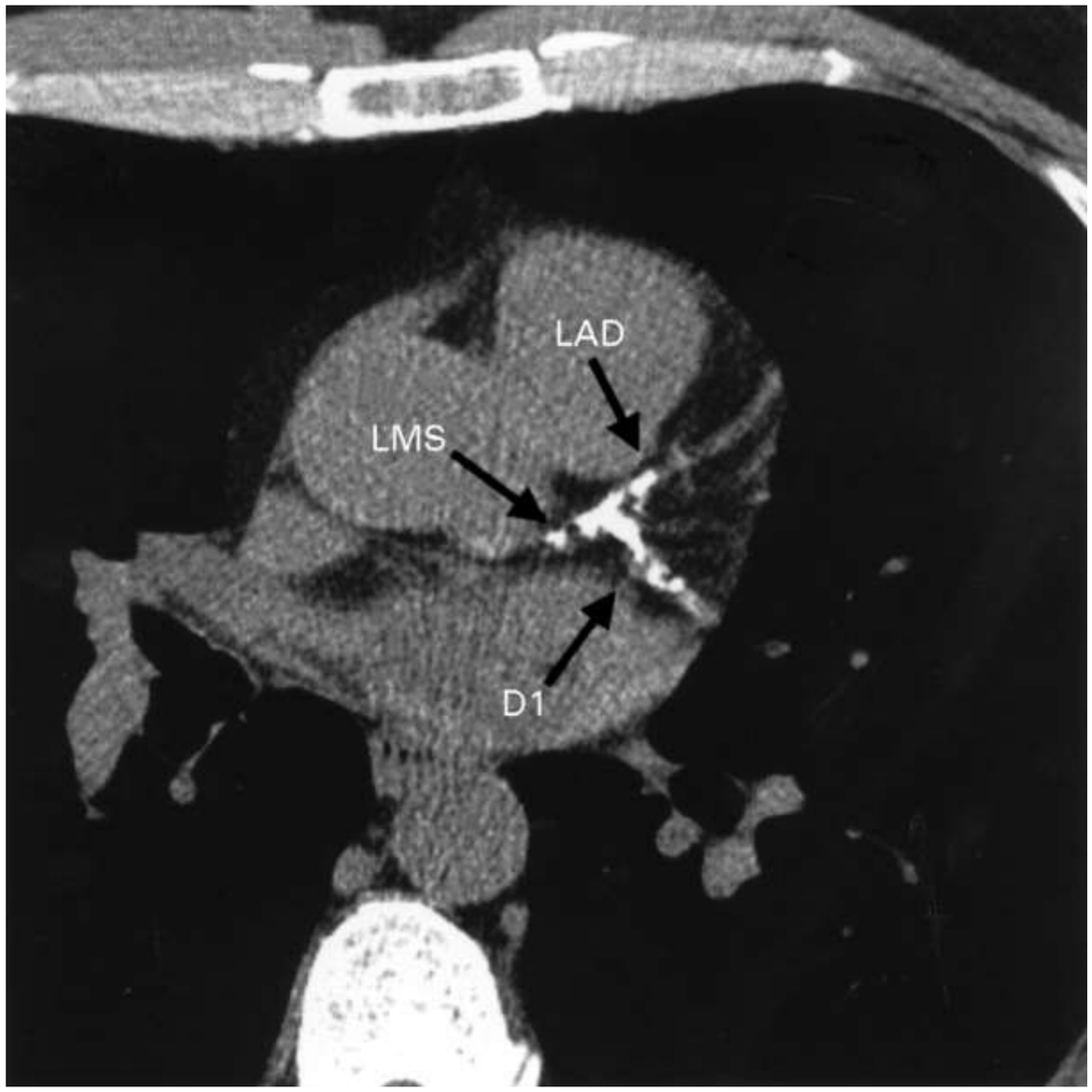
Sudden Death = death due to cardiac arrest, arrhythmia, or hyperkalemia (exclusion of hyperkalemia did not substantially alter findings);
IV approach – use predicted dialysate K as predictor;
All models are adjusted for age, race, gender, BMI, vintage, 14 comorbid classes, serum albumin, phosphorus, PTH, Hgb, creatinine, ferritin, WBC count, Kt/V, catheter use, serum K, facility % of patients with alb <3.5 g/dL, PO4 >5.5 mg/dL, Hgb <11 g/dL, Kt/V <1.2, and % with catheter; stratified by phase and country; and accounted for facility clustering

Potassium: Summary

- **Use of dialysate K<3 mEq/L is common in some countries and leads to low post-HD K levels**
- **Risk of sudden death is higher for patients in HD units where more patients have dialysate K<3 mEq/L**
- **Higher risk is especially clear for patients with pre-HD serum K<5 mEq/L**

Calcium

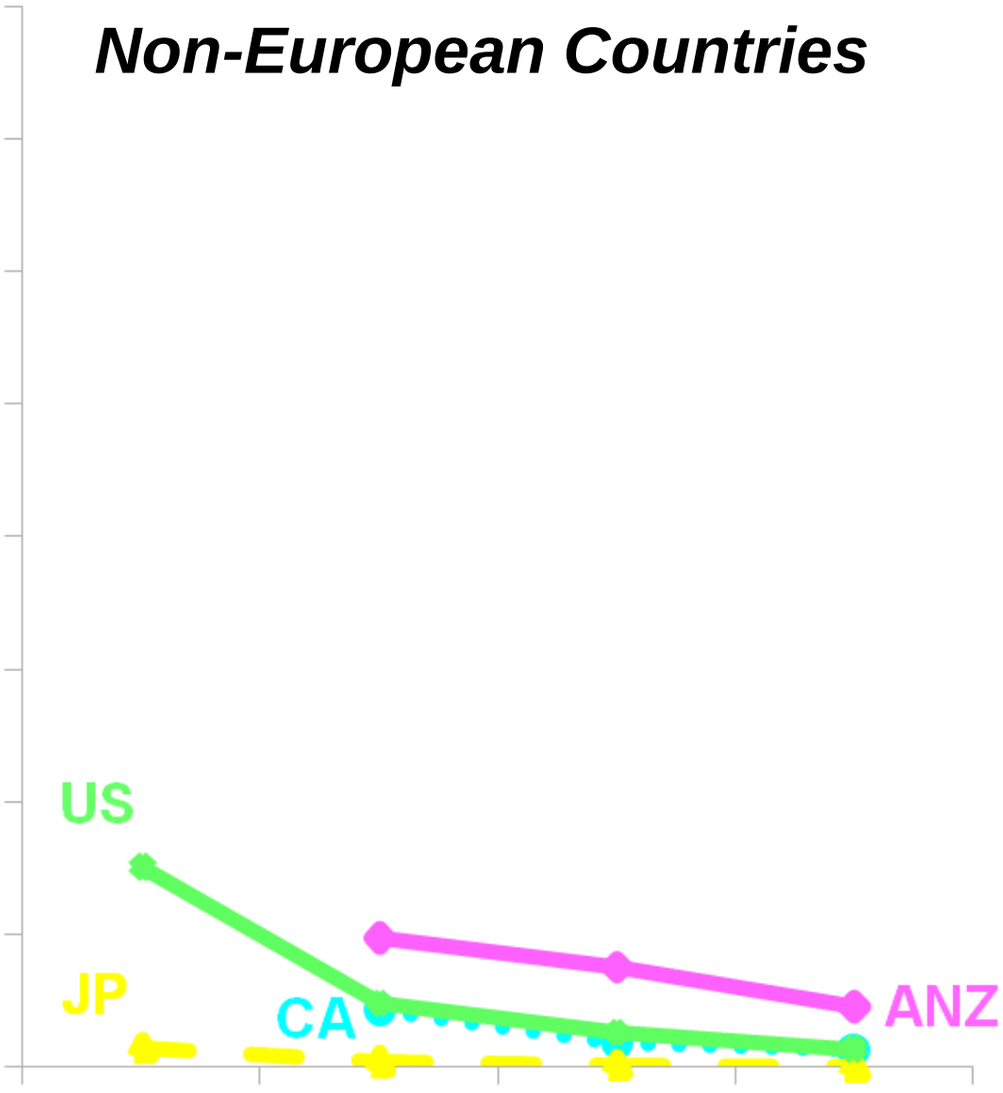
- **Exposure to exogenous calcium in the dialysate or from phosphate binders may contribute to vascular calcification**
- **Prolonged**



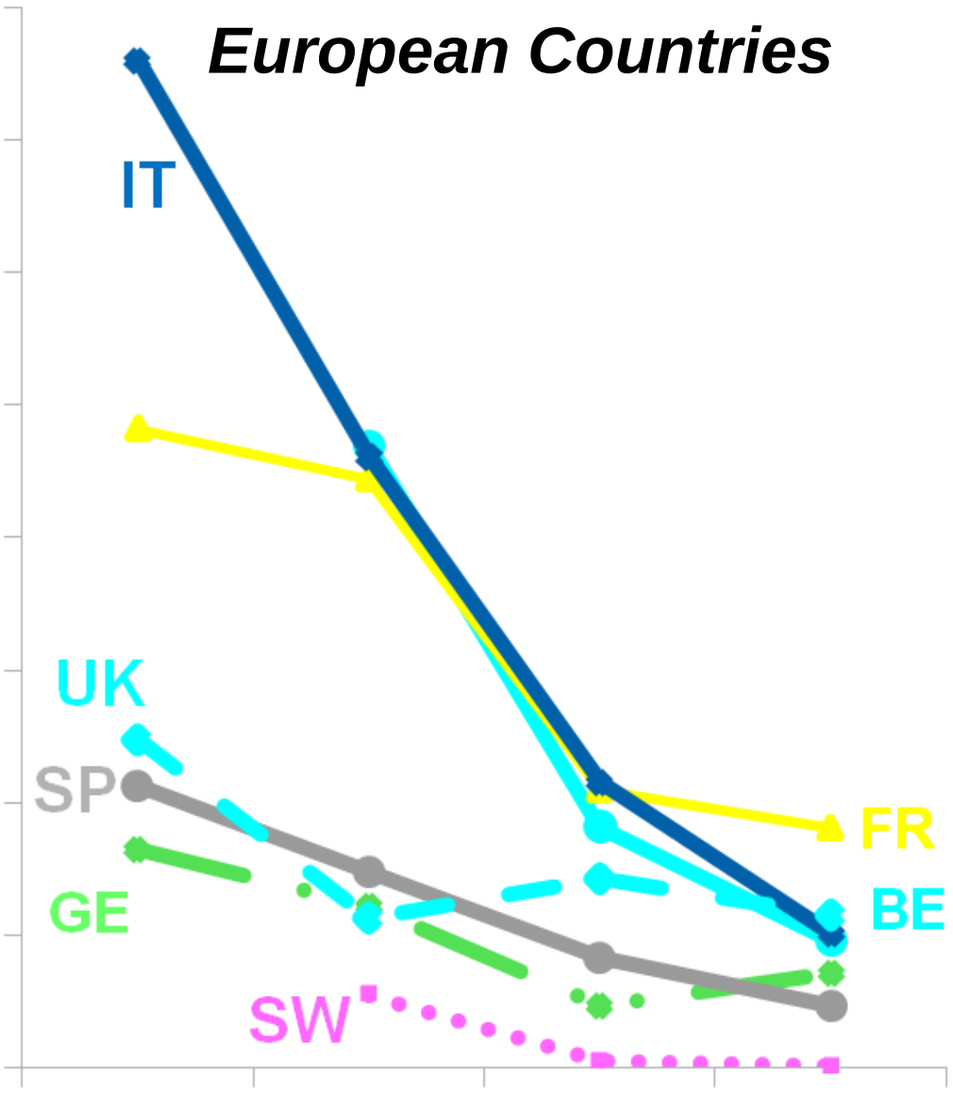
Use of Dialysate Ca = 3.5 mEq/L by Country (1996-2011)

% of patients

Non-European Countries

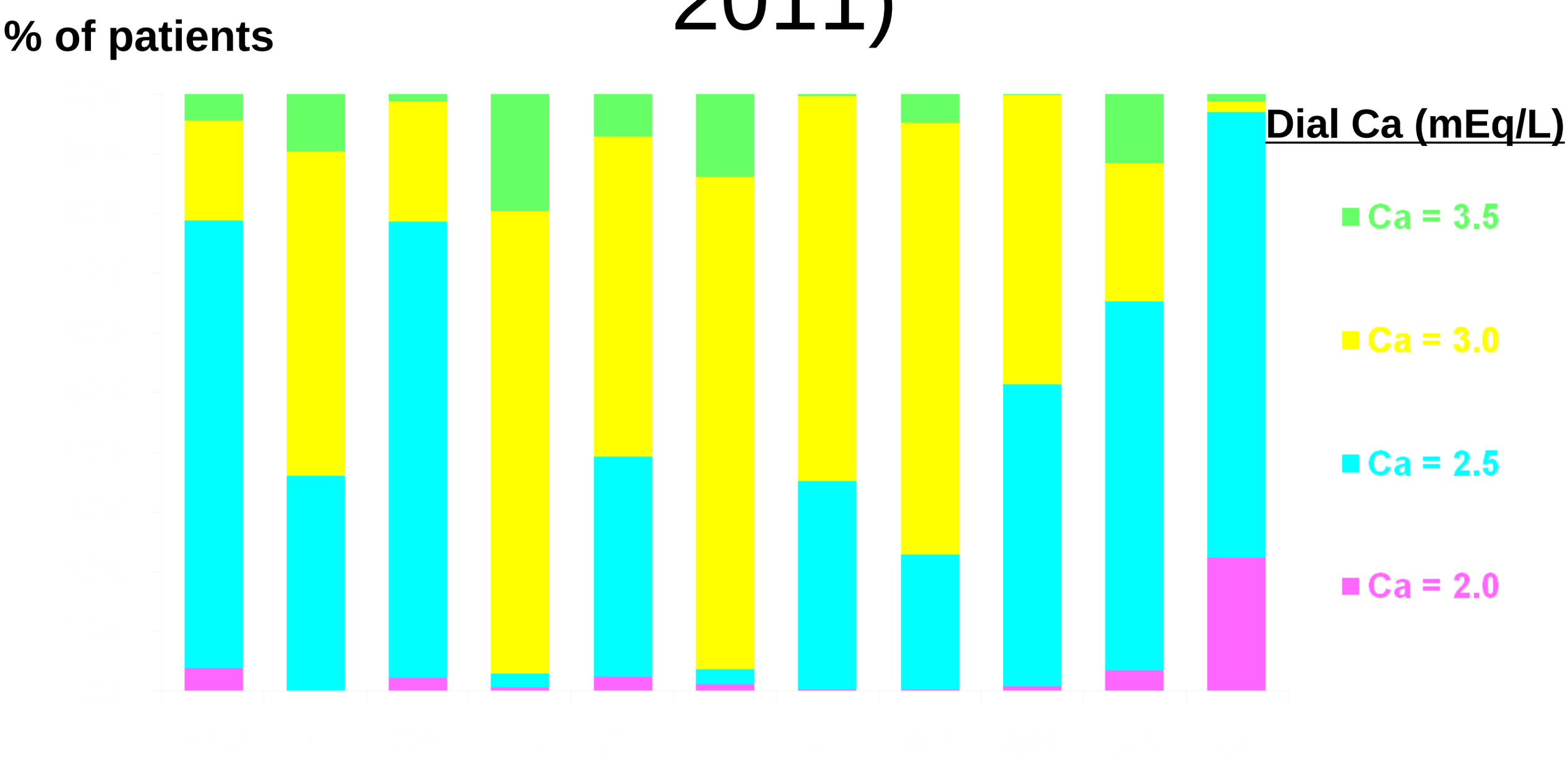


European Countries



Source: DOPPS 1 (1996-2001), DOPPS 2 (2002-2004), DOPPS 3 (2005-2008), DOPPS 4 (2009-2011)

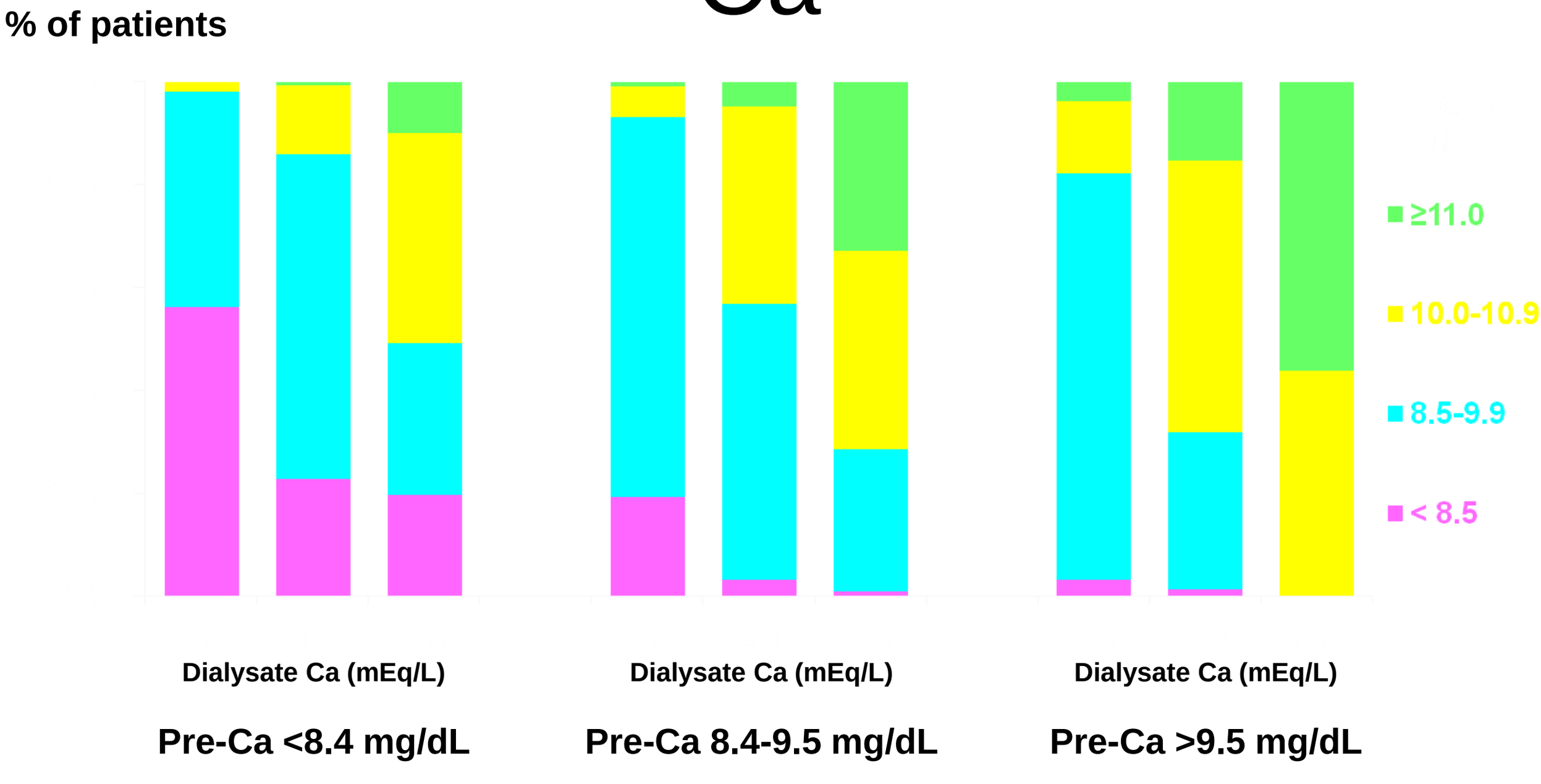
Dialysate Ca by Country (2009-2011)



N patients	**509**	**631**	**461**	**540**	**794**	**753**	**1865**	**862**	**591**	**494**	**4079**
Mean D. Ca	2.7	2.9	2.6	3.1	2.8	3.0	2.8	2.9	2.7	2.7	2.4
Single D. Ca*	59%	44%	33%	57%	29%	55%	86%	55%	59%	44%	70%

* % of facilities where ≥ 90% of patients use a single dialysate Ca concentration

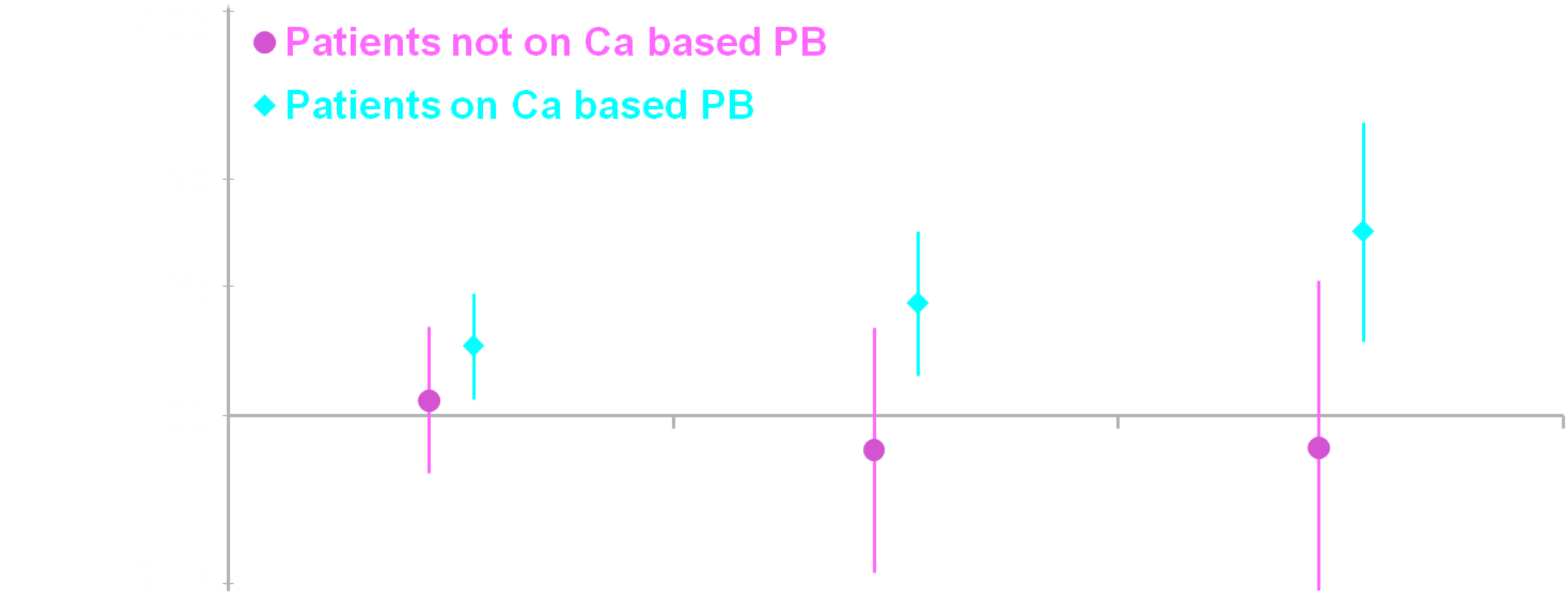
Distribution of Post-HD Serum Ca, by Pre-HD Serum Ca and Dialysate Ca



Source: DOPPS 4 (2009-2011)

Mortality Risk Higher with Dialysate Ca = 3.5 mEq/L on Ca-based Phosphate Binder

Hazard ratio (95% CI) - patients with Dial Ca=3.5 vs. <3.5 mEq/L



	All-causes	Cardiovascular death	Sudden death
Interaction Dial Ca x Ca-based PB	p=0.19	p=0.02	p=0.02

* n=34,575 patients (869 facilities) in DOPPS 1-3 (1996-2008). Cox regression was stratified by region and phase, adjusted for patient characteristics + Ca based PB, interaction term of ca based PB and dial Ca, accounting for facility clustering effects.

Calcium: Summary

- **Use of dialysate Ca = 3.5mEq/L has declined over time**

- **Use of dialysate Ca = 3.5mEq/L leads to a significant rise in serum Ca during dialysis**

- **Risks of cardiovascular death and sudden death are significantly greater in patients dialysed with dialysate Ca = 3.5mEq/L who are taking a Ca-based**

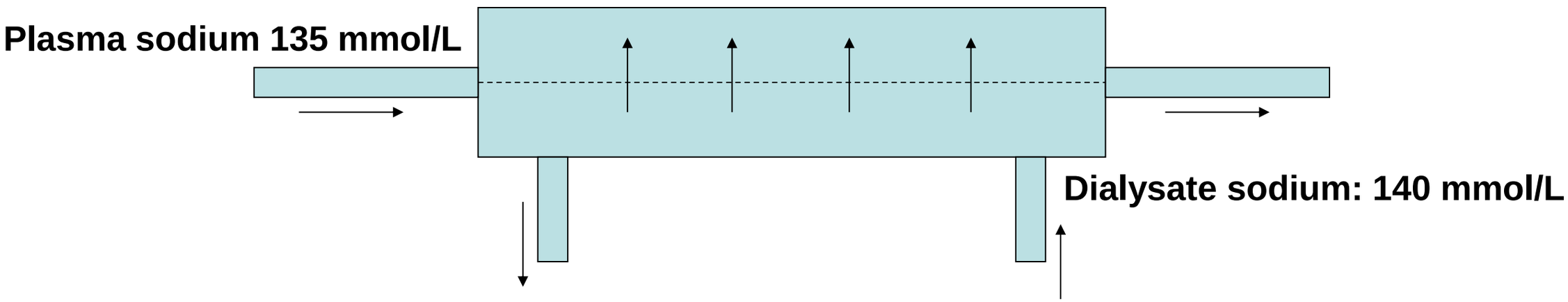
Conclusions

- **We have demonstrated significant associations between serum and dialysate electrolyte concentrations and patient outcomes that have plausible causal interpretations**

- **Modification of dialysate composition warrants closer attention as a way of reducing patient mortality**

Why should sodium be aligned?

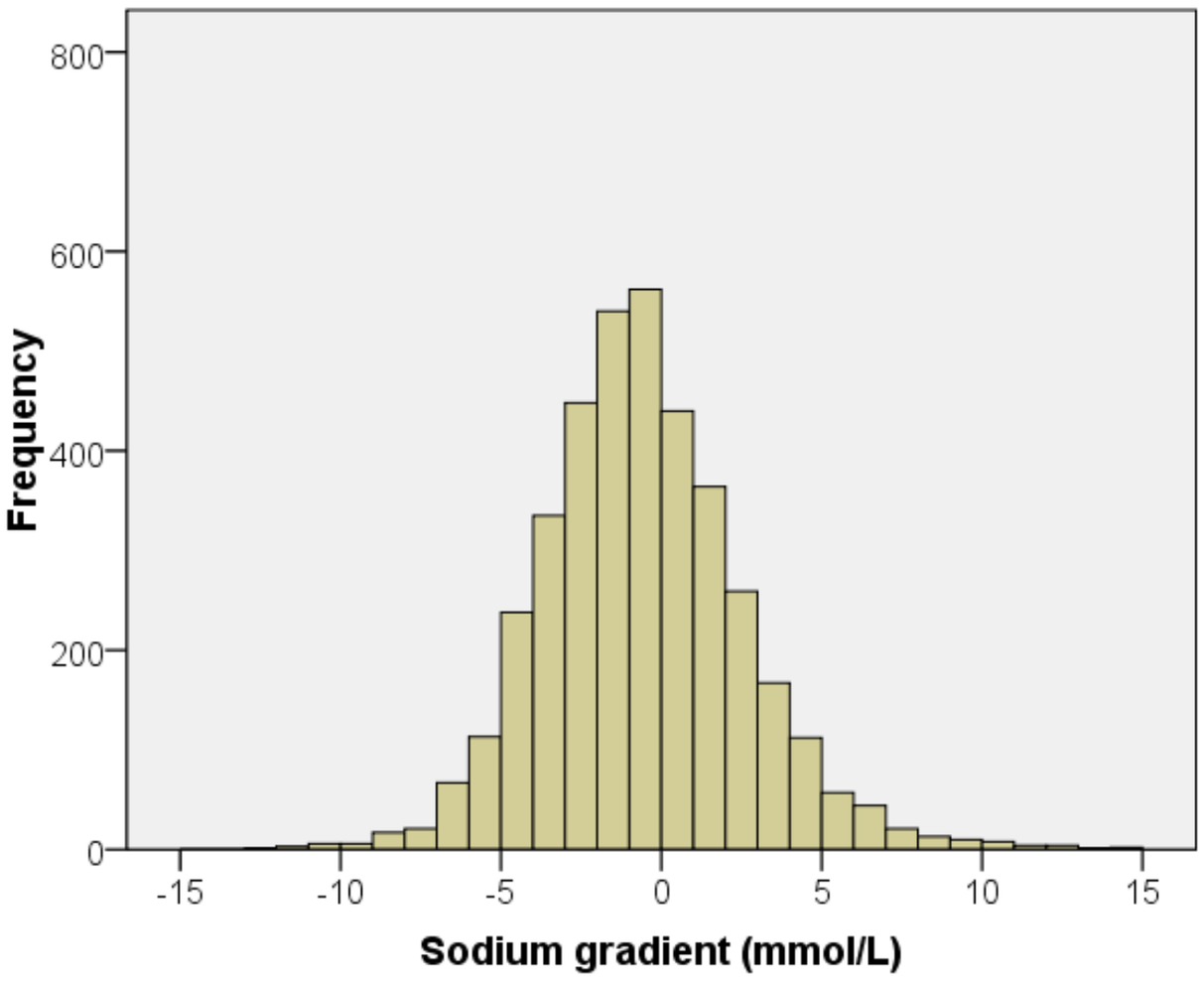
Example:



- Sodium loading: fluid overload, hypertension
- Positive sodium balance:
  - Adverse outcome (mortality, hospitalization)

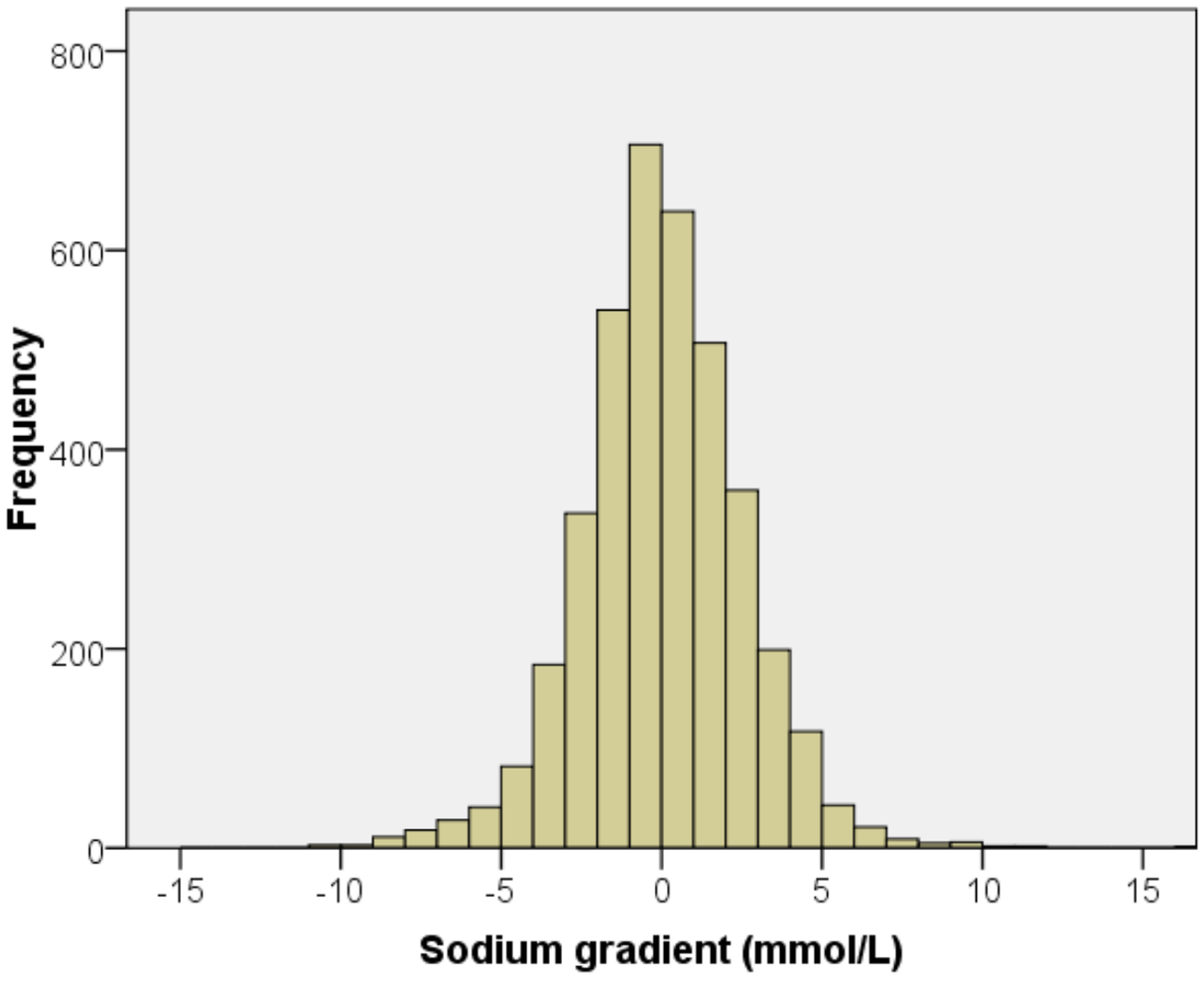
Sodium gradient

Fixed dialysate sodium of 138 mmol/L



gradient >5 or <-5 in 15% of patients

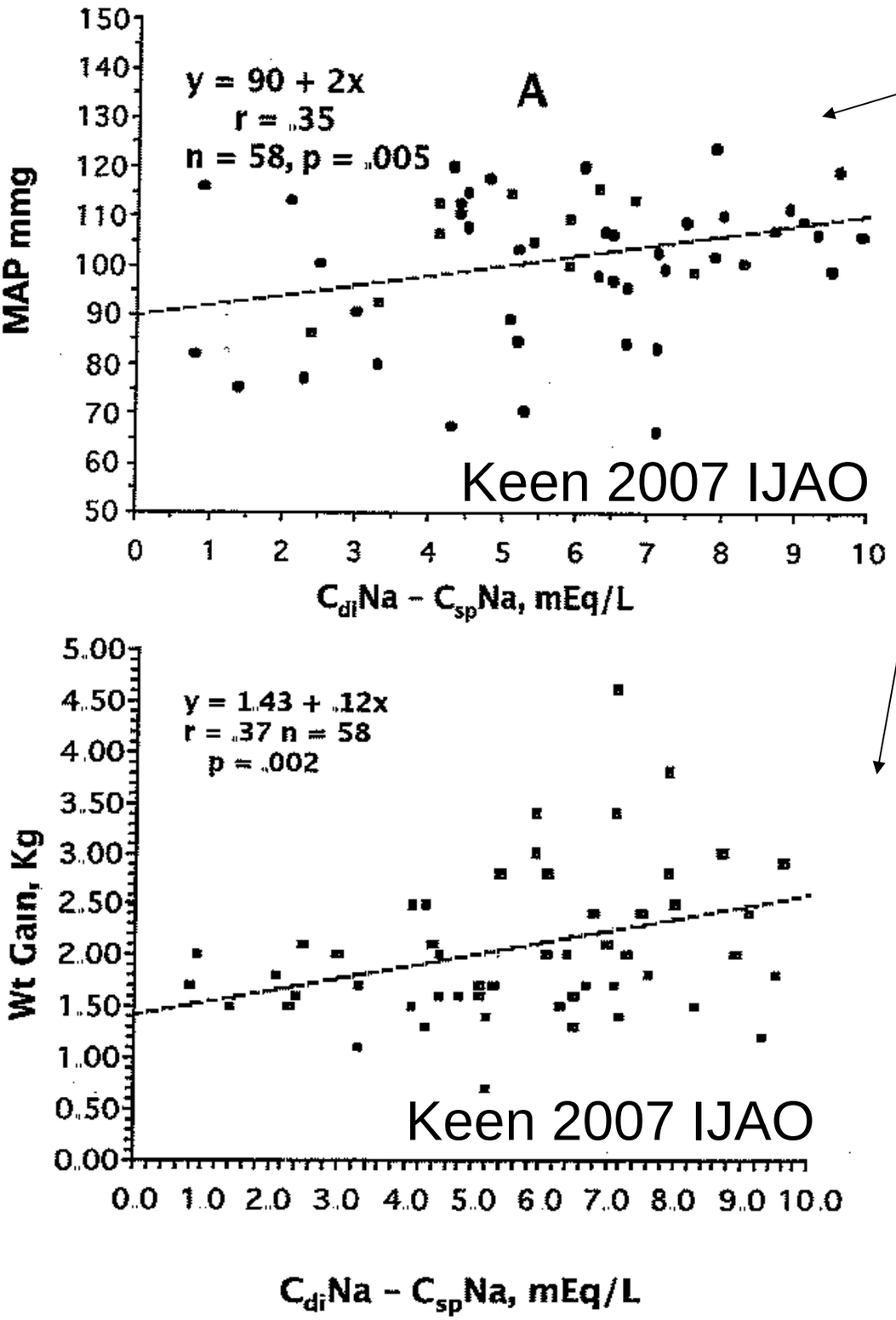
Aligned dialysate sodium, using average sNa+ of previous 4 months



gradient >5 or <-5 in 5% of patients

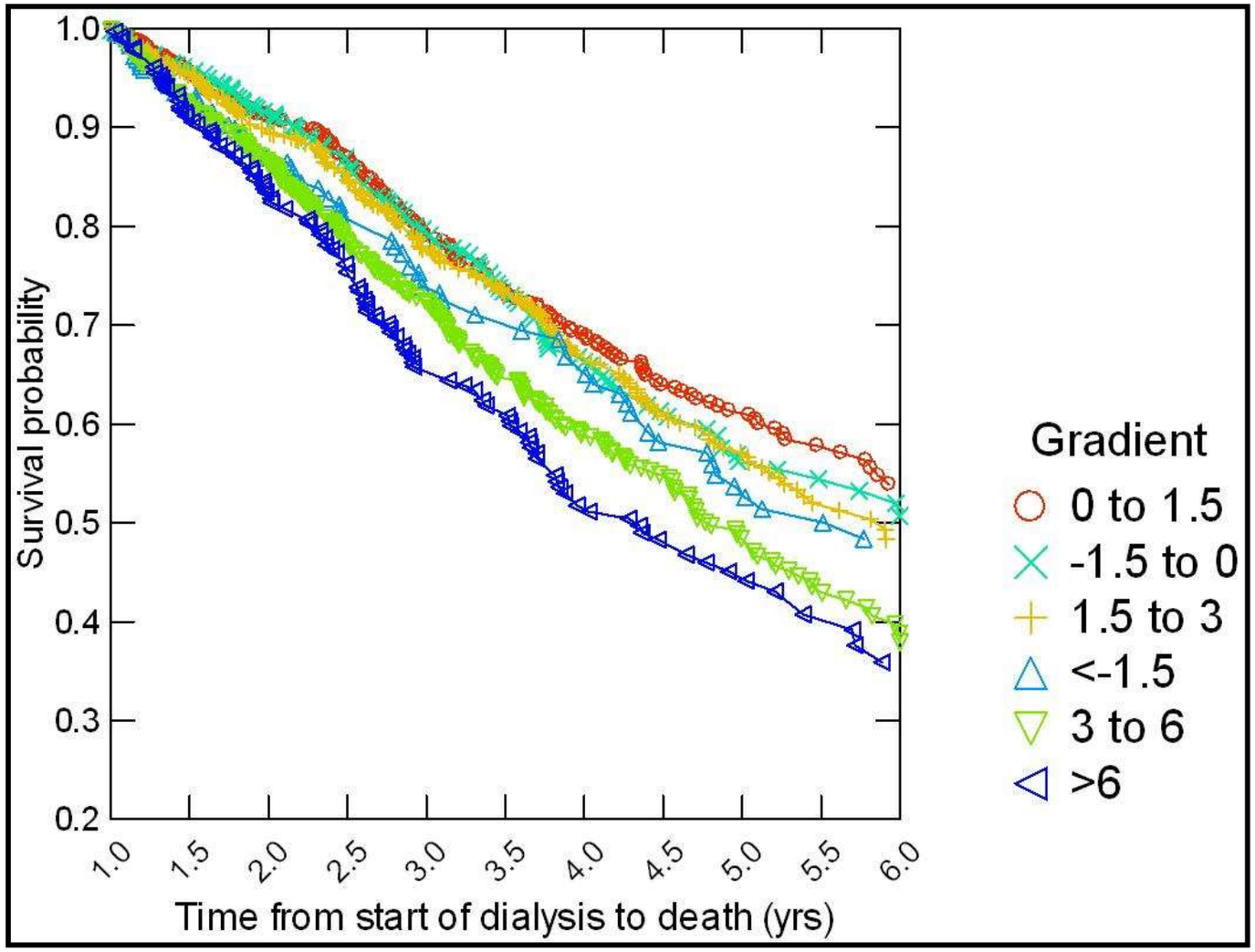
- *Excluding patients with incomplete data (n=692) do not change the results*
- *Data from August 2009*

Sodium gradient and outcome



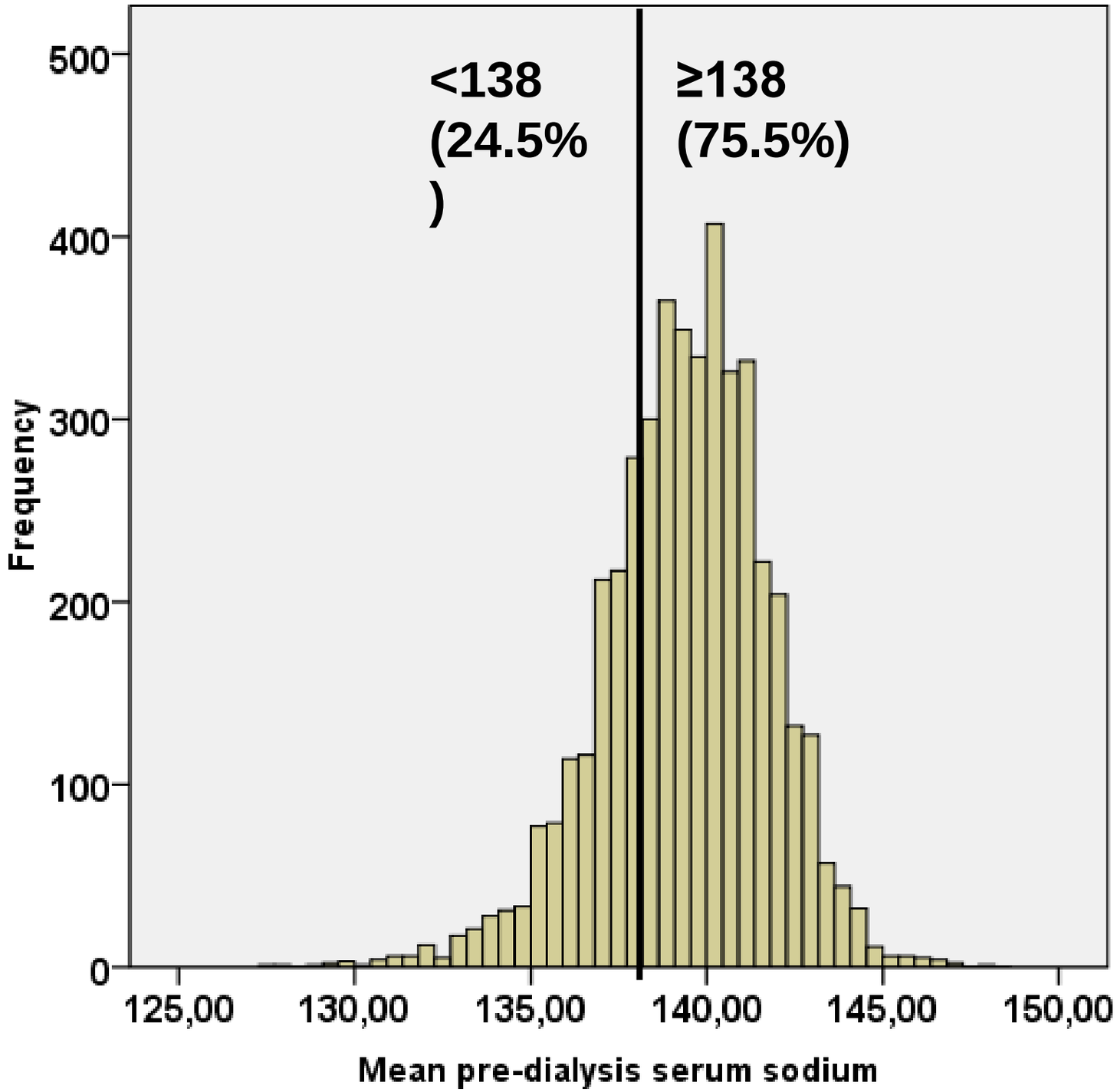
Sodium gradient is related with blood pressure and weight gain

High positive gradient is related with mortality



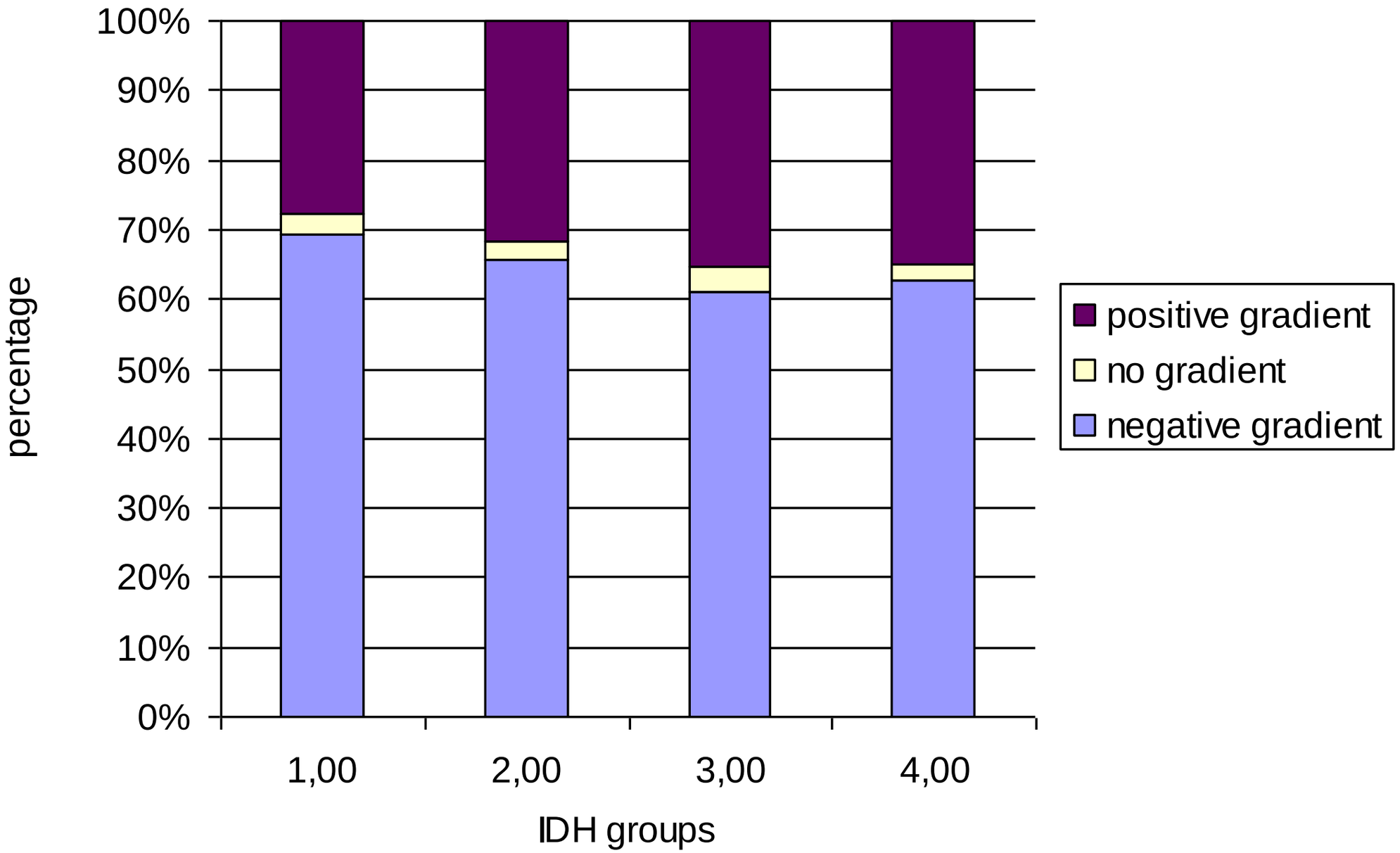
Sergeyeva 2008

Pre-dialysis serum sodium in chronic hemodialysis patients



N=4532
Mean = 139.4 mmol/L
Period: Jan-Dec 2009

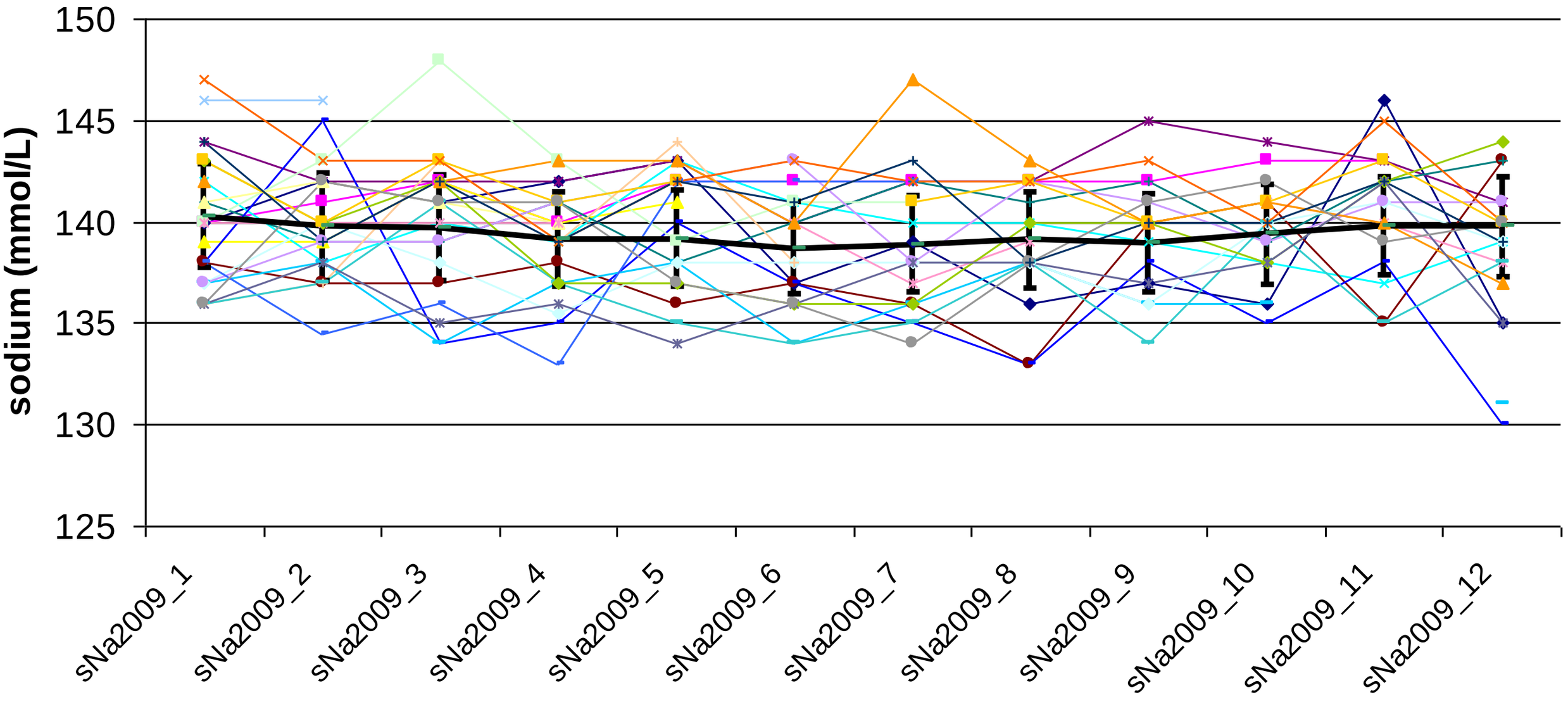
Intradialytic events vs gradient



What is the ideal dialysate sodium?

Gradient	Intradialytic hypotensive episodes: +	Intradialytic hypotensive episodes: -
+		reduce dNA
-	increase dNA	

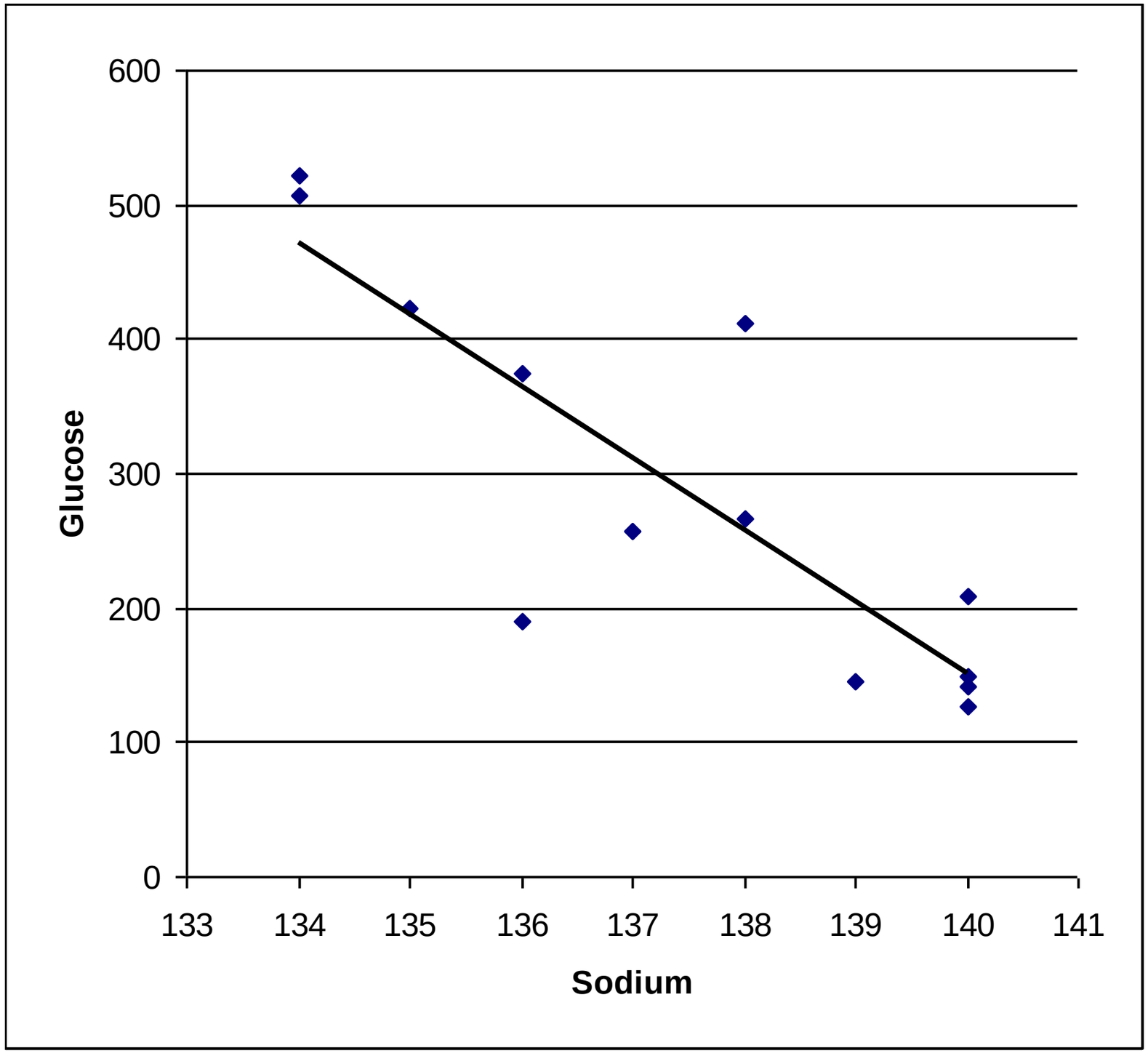
Mean serum sodium in time



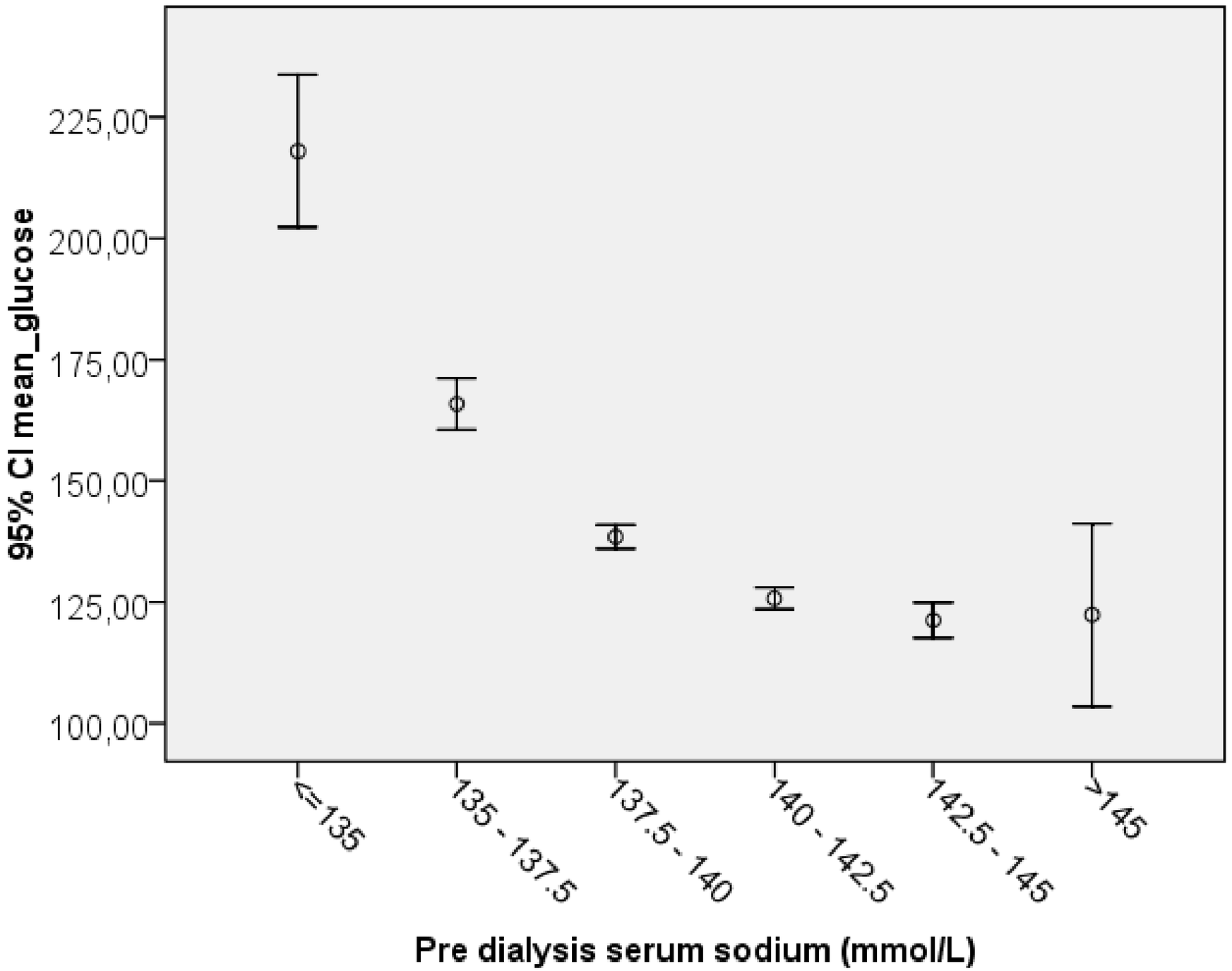
Black line represents population mean of sNa (± SD)
Colored lines represent examples of individual patients

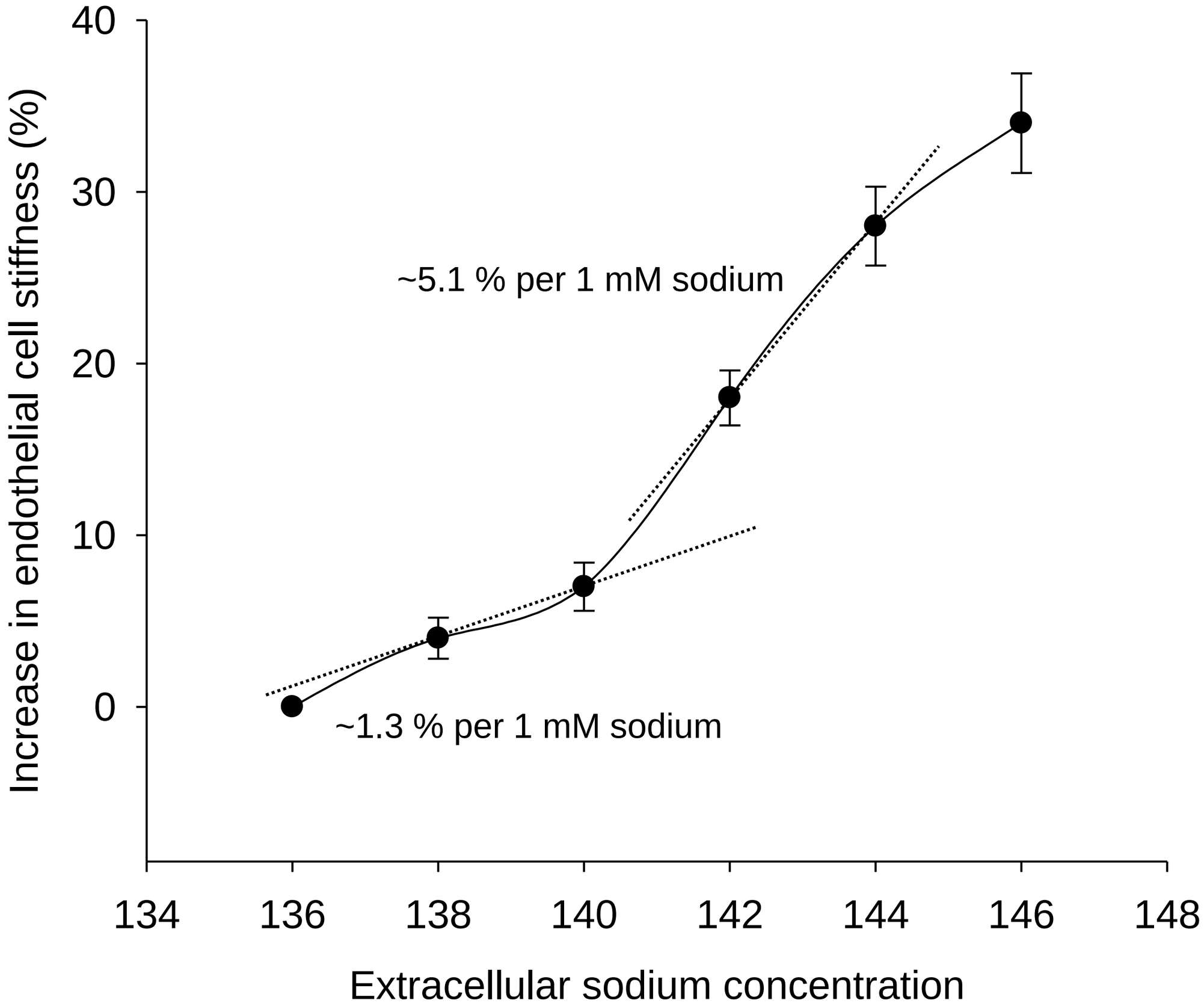
Period: Jan-Dec 2009
N= 4487
Mean sNA = 139.4 mmol/L

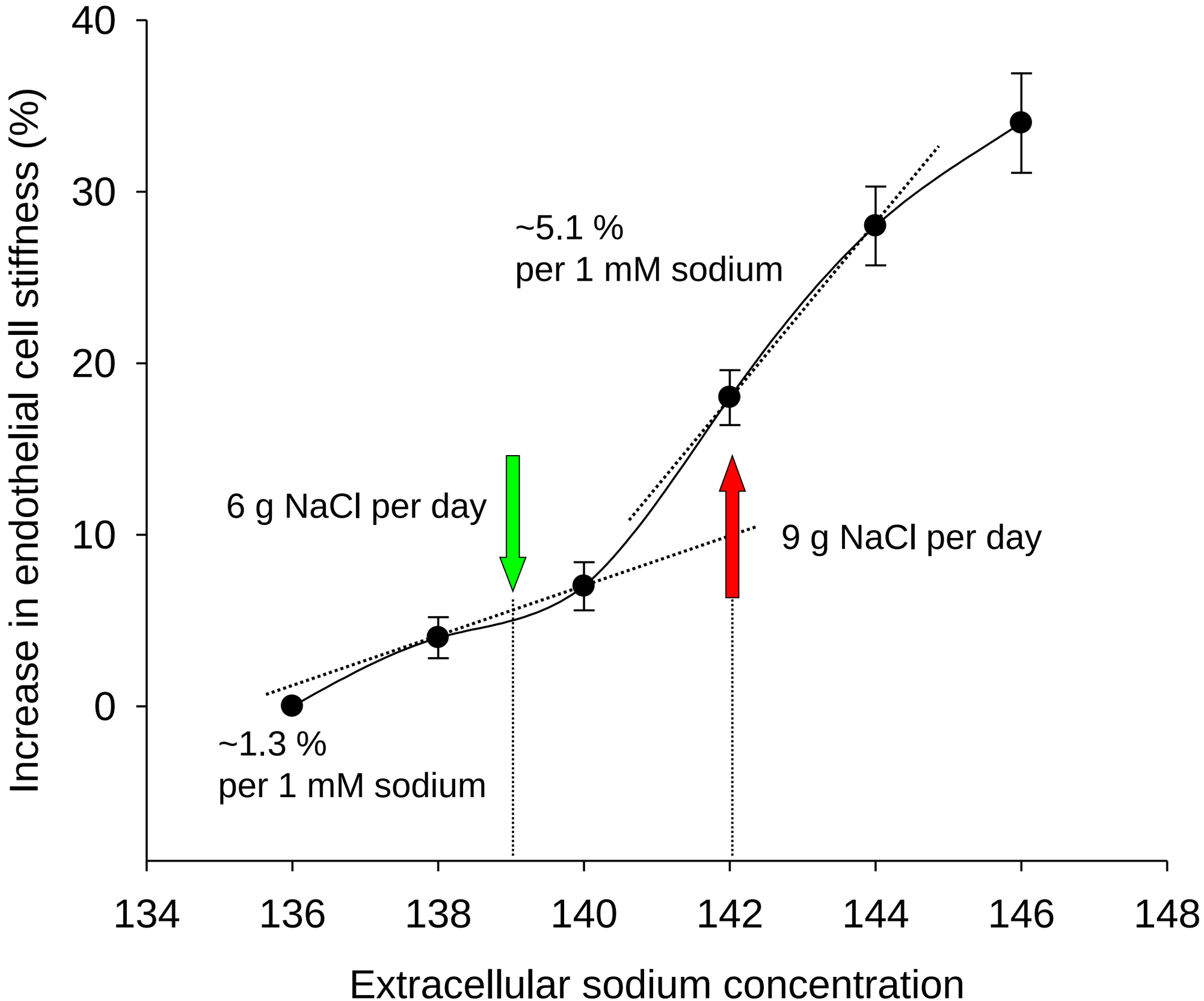
Relation between sodium and glucose in an incompliant patient



Relation between serum sodium level and mean glucose




Increase in endothelial cell stiffness (%)
40
30
20
10
0
~5.1 % per 1 mM sodium
~1.3 % per 1 mM sodium
134
136
138
140
142
144
146
148
Extracellular sodium concentration

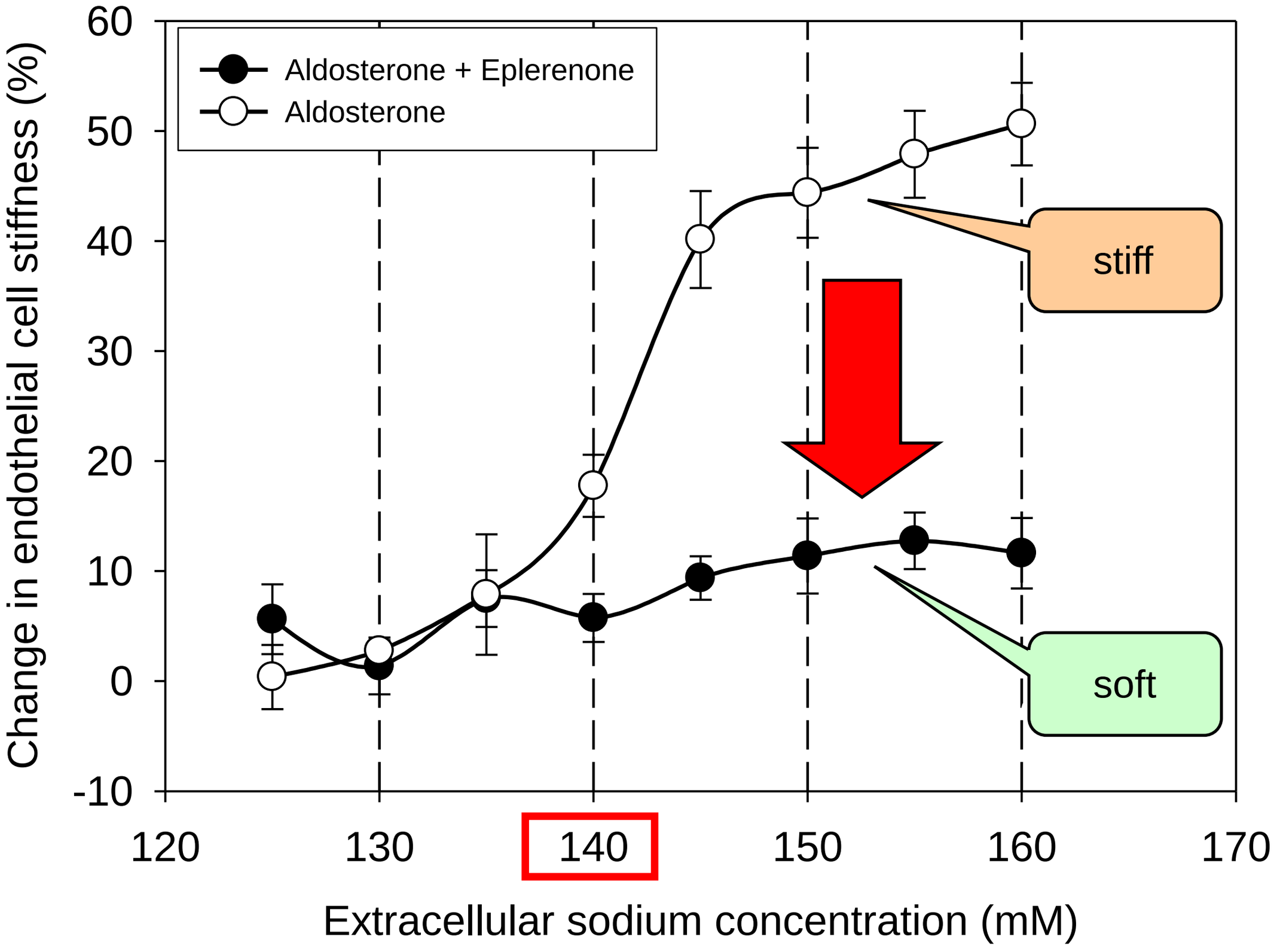

Increase in endothelial cell stiffness (%)
40
30
20
10
0
134
136
138
140
142
144
146
148
Extracellular sodium concentration
~5.1 %
per 1 mM sodium
~1.3 %
per 1 mM sodium
6 g NaCl per day
9 g NaCl per day

Actually,we have two choices:

We reduce salt intake

or

we take aldosterone receptor blockers

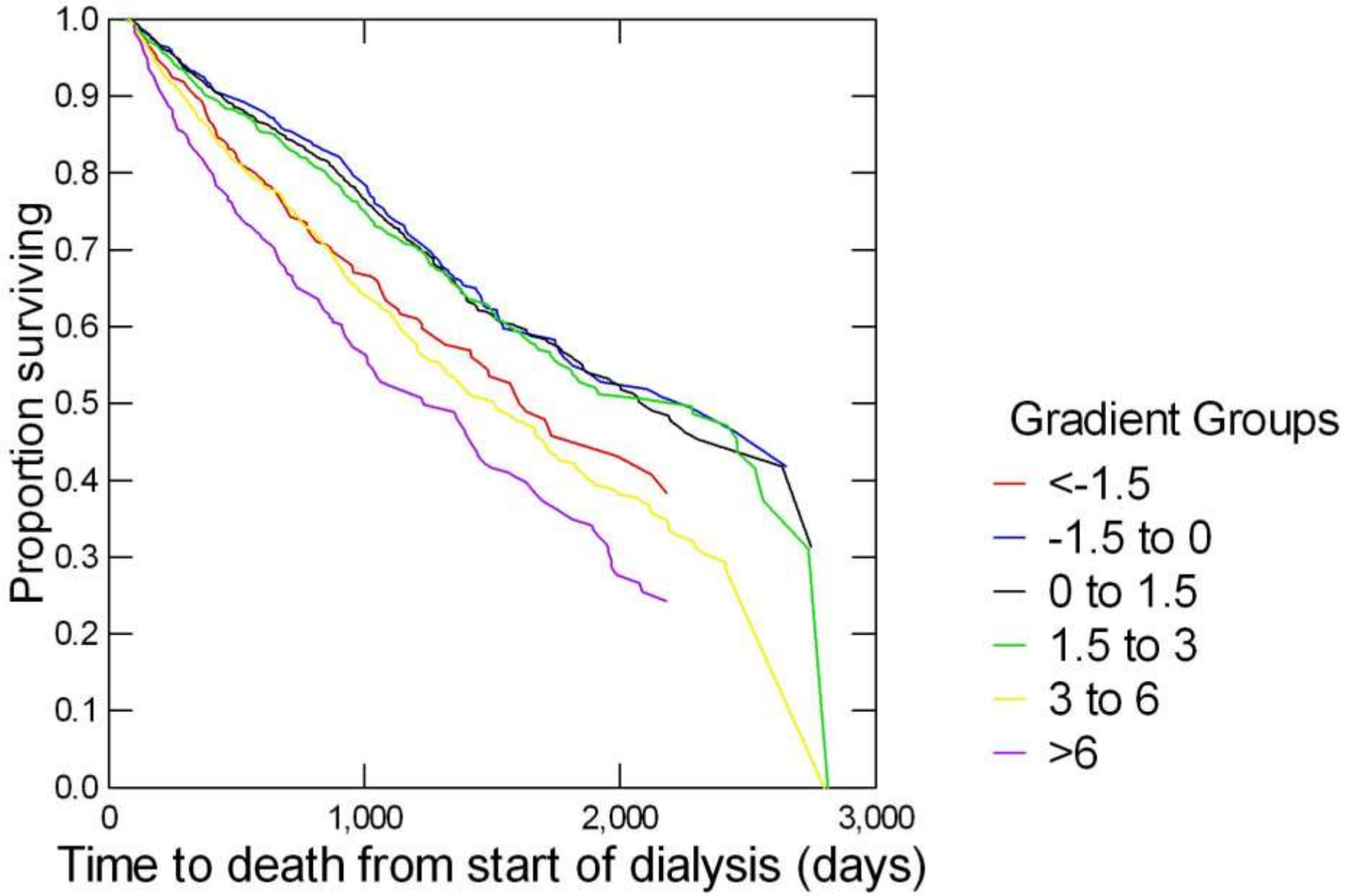

Aldosterone + Eplerenone
Aldosterone
stiff
soft
Change in endothelial cell stiffness (%)
60
50
40
30
20
10
0
-10
120
130
140
150
160
170
Extracellular sodium concentration (mM)

PNAS 2007

Na+

Survival based on Na+ Gradient

- Mean survival time
- (p<0.001):
  - <-1.5: 4.6 yrs
  - 1.5-0: 5.3 yrs
  - 0-1.5: 5.1 yrs
  - 1.5-3: 5.1 yrs
  - 3-6: 4.3 yrs
  - >6: 3.8 yrs

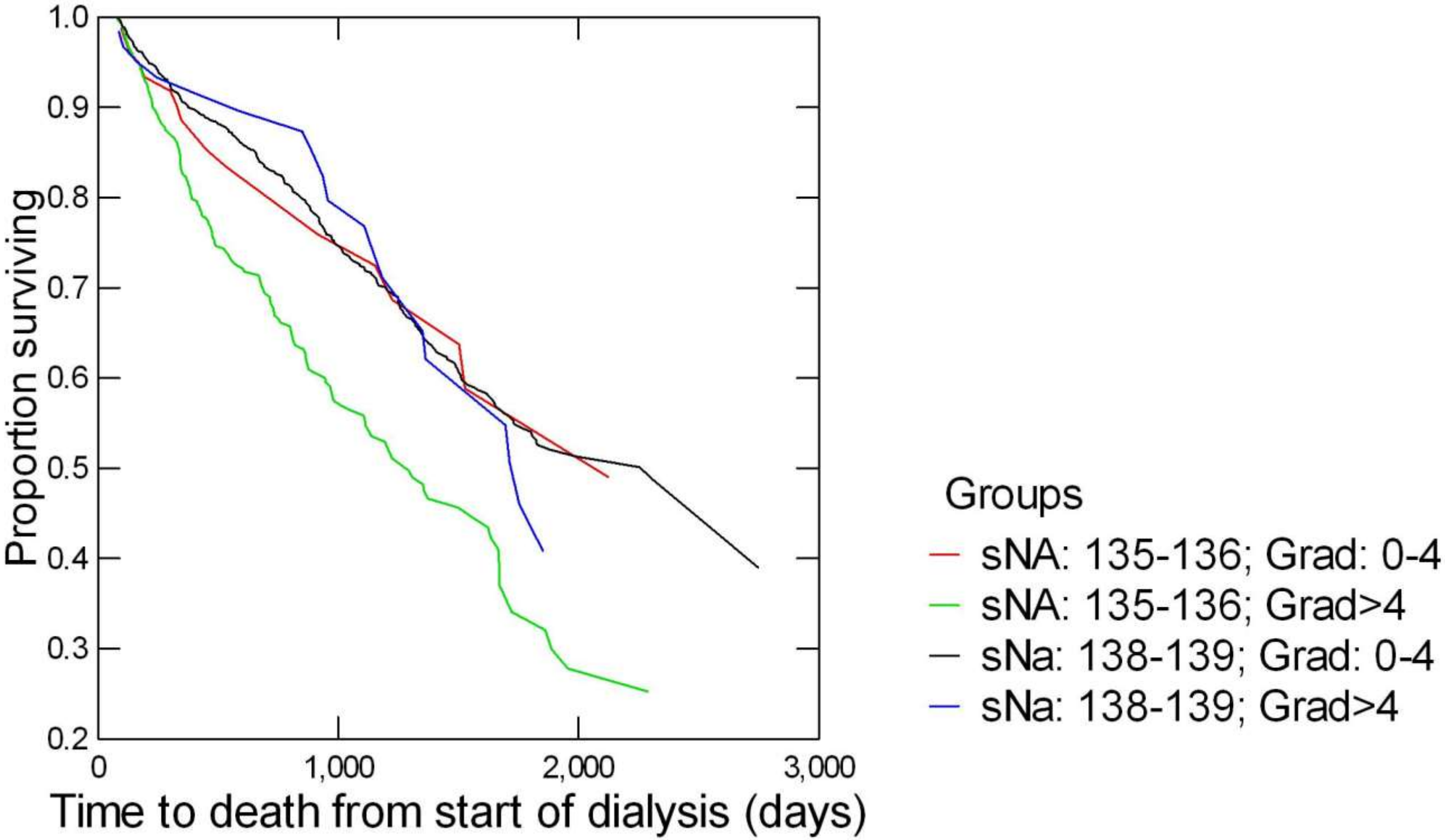


Hospital Admissions Hazard Ratios Based on Na+ Gradient

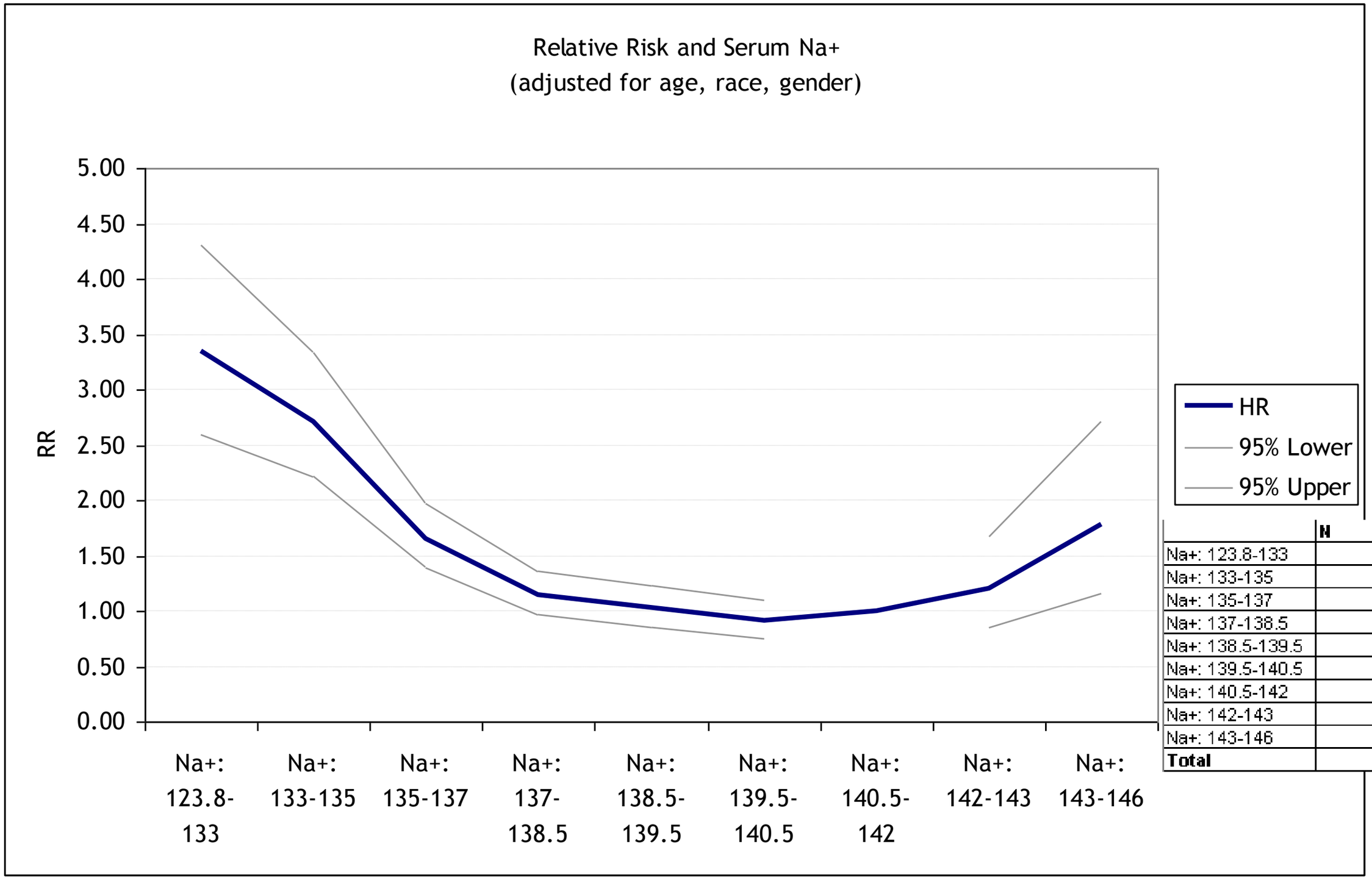
Gradient Groups	CVD	Fluid overload	Infections	Other	Total Hospital Admissions
<0 *	1.00	1.00	1.00	1.00	**1.00**
0-3	1.00	1.00	1.11	1.10	**1.08**
3-6	1.17	1.44	1.28	1.42	**1.38**
>6	1.33	1.78	1.39	1.64	**1.58**

*Gradient<0 is the reference group

Serum Na+ or Gradient?

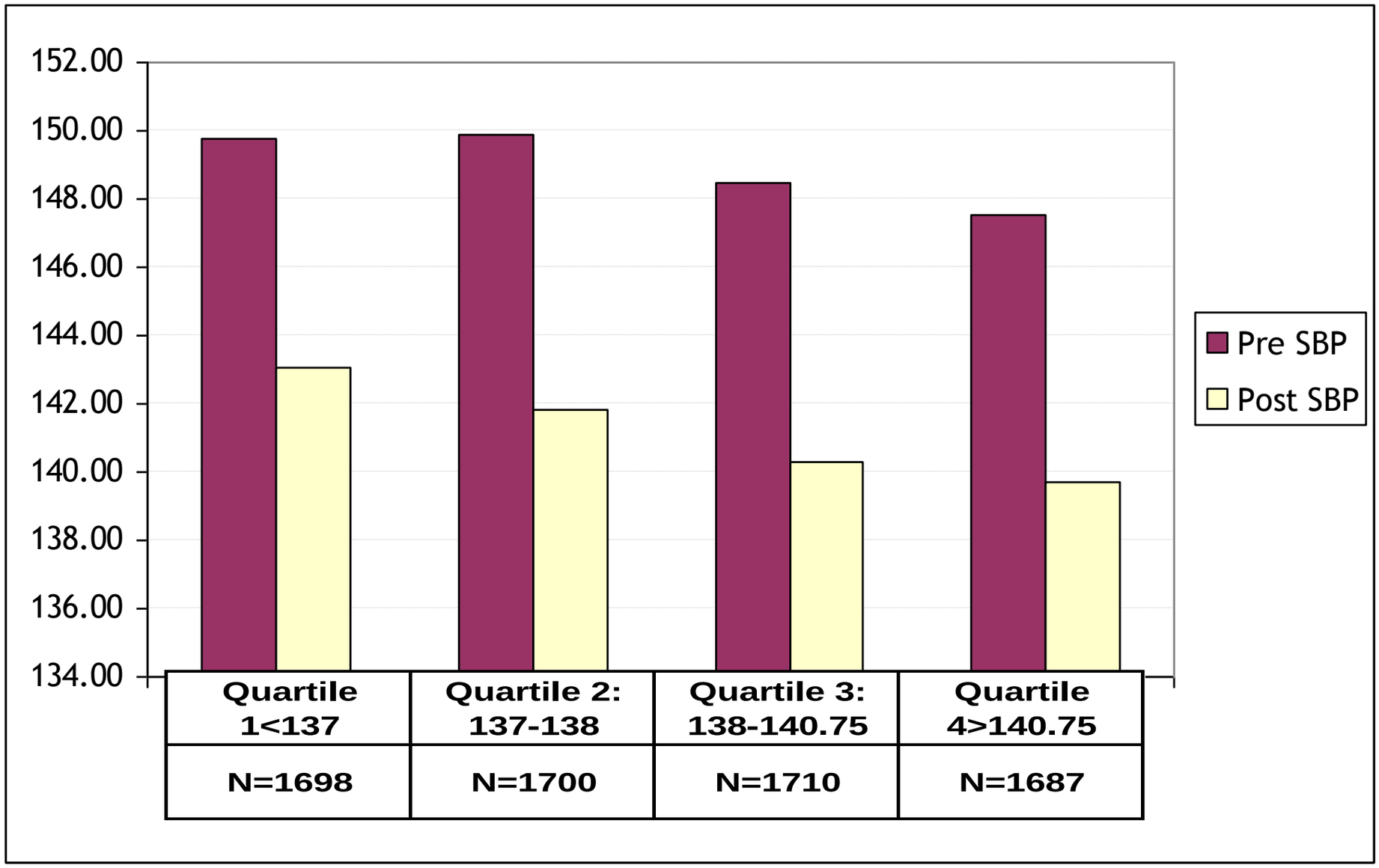


Serum Na+ and Survival

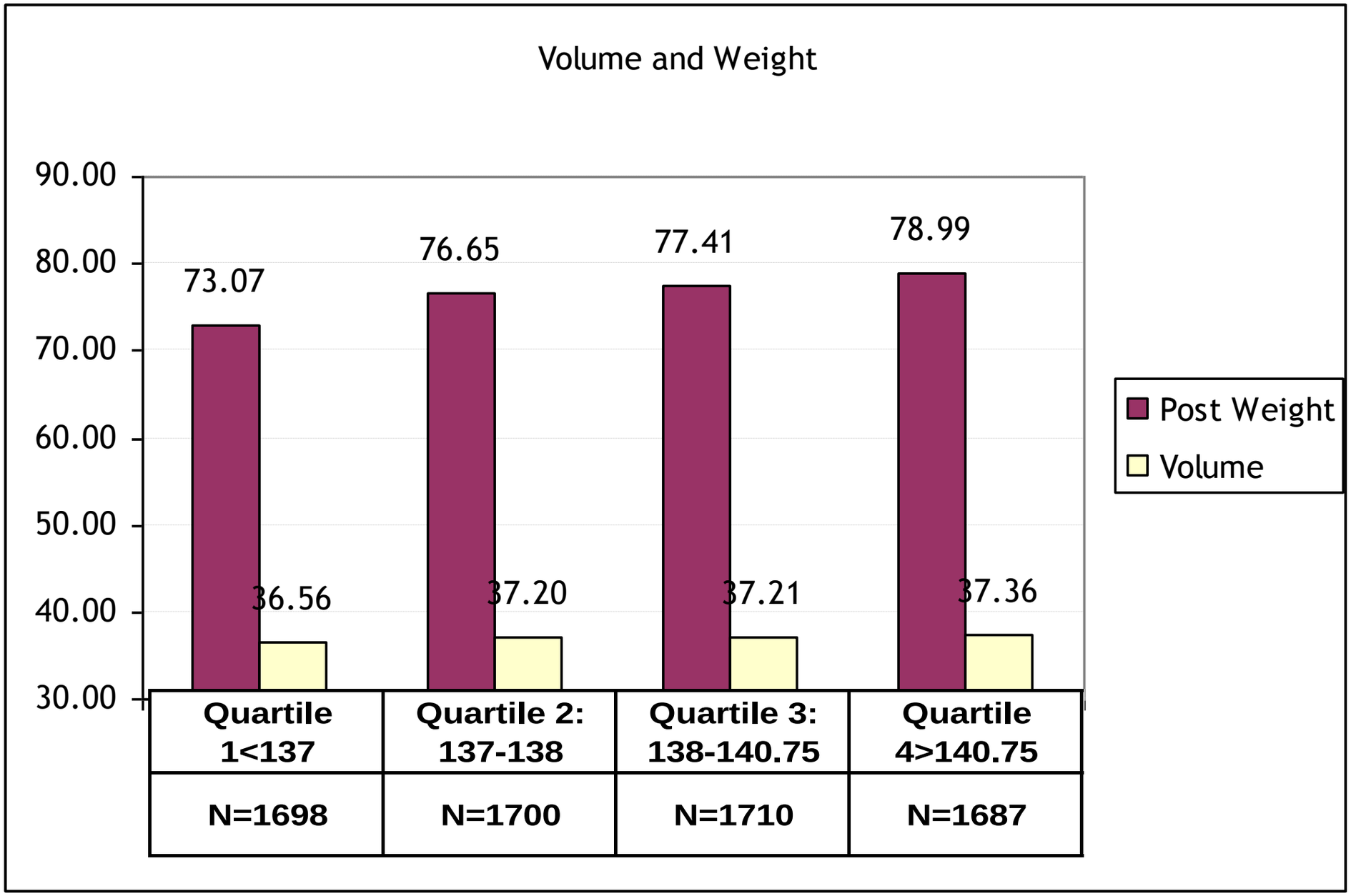


	N
Na+: 123.8-133	196
Na+: 133-135	473
Na+: 135-137	1361
Na+: 137-138.5	1655
Na+: 138.5-139.5	1254
Na+: 139.5-140.5	1012
Na+: 140.5-142	838
Na+: 142-143	169
Na+: 143-146	72
Total	**7030**

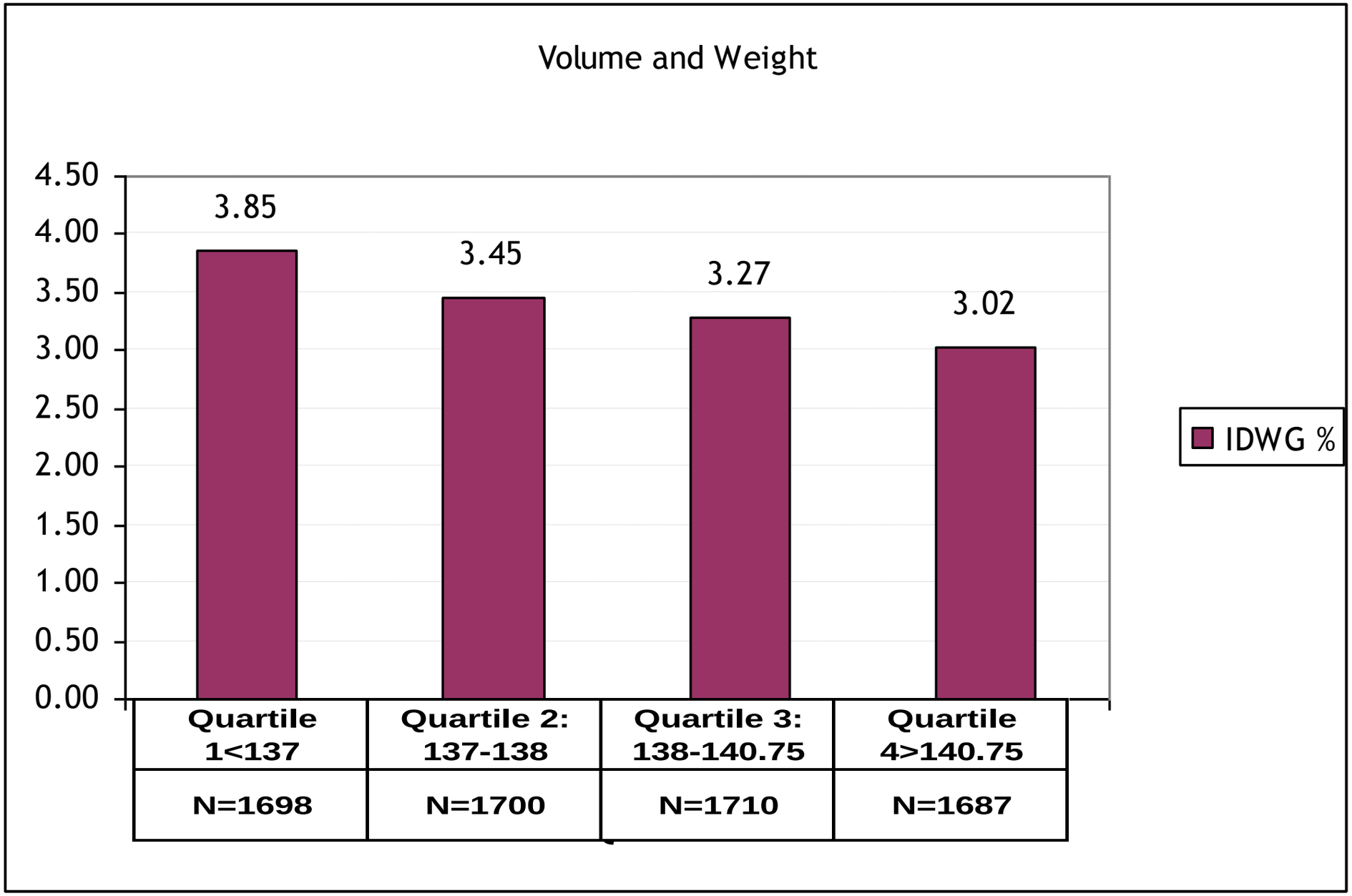
Na+ Quartile and Blood Pressure



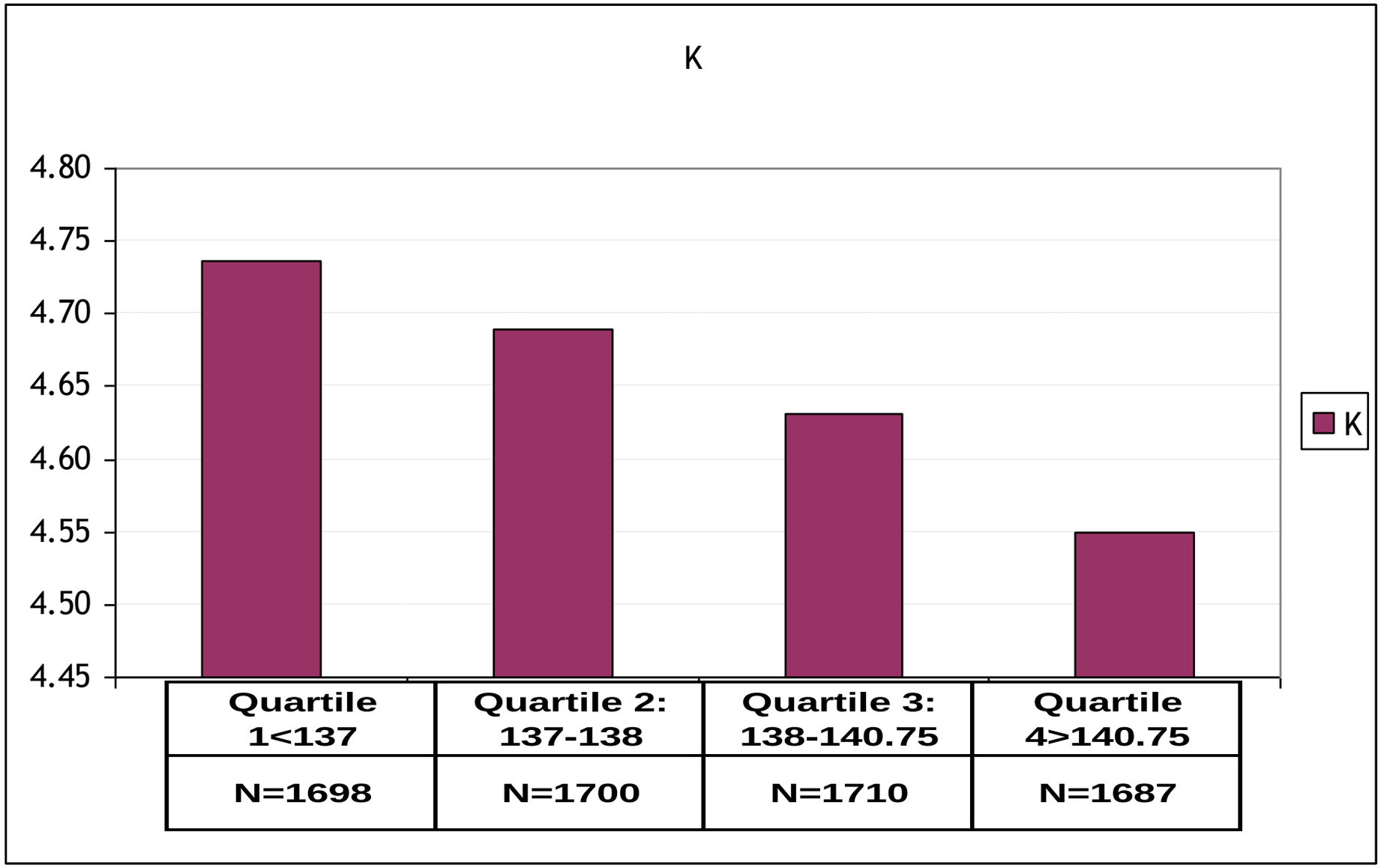
Na+ Quartile and Body Size



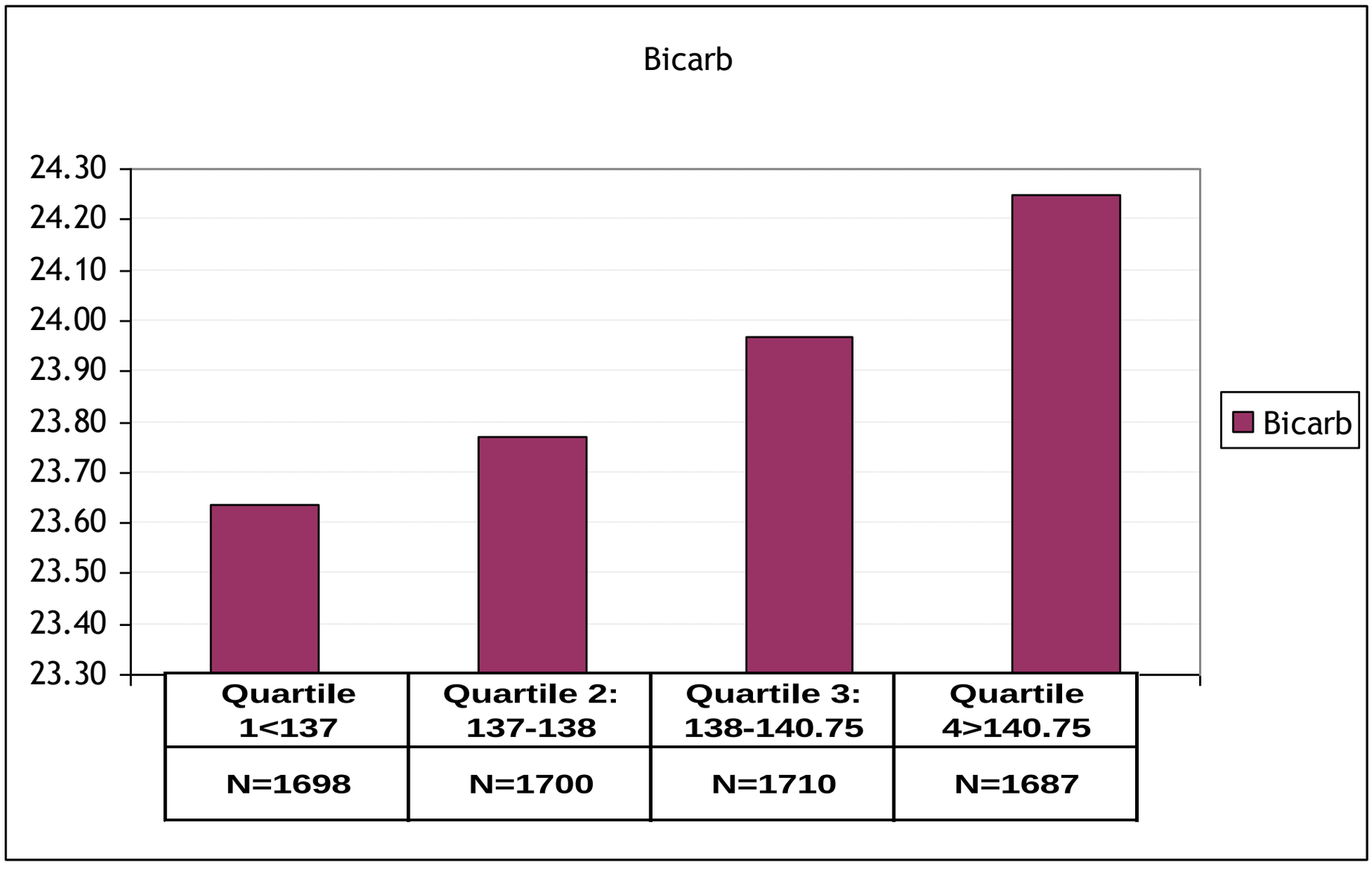
Na+ Quartile and IDWG%



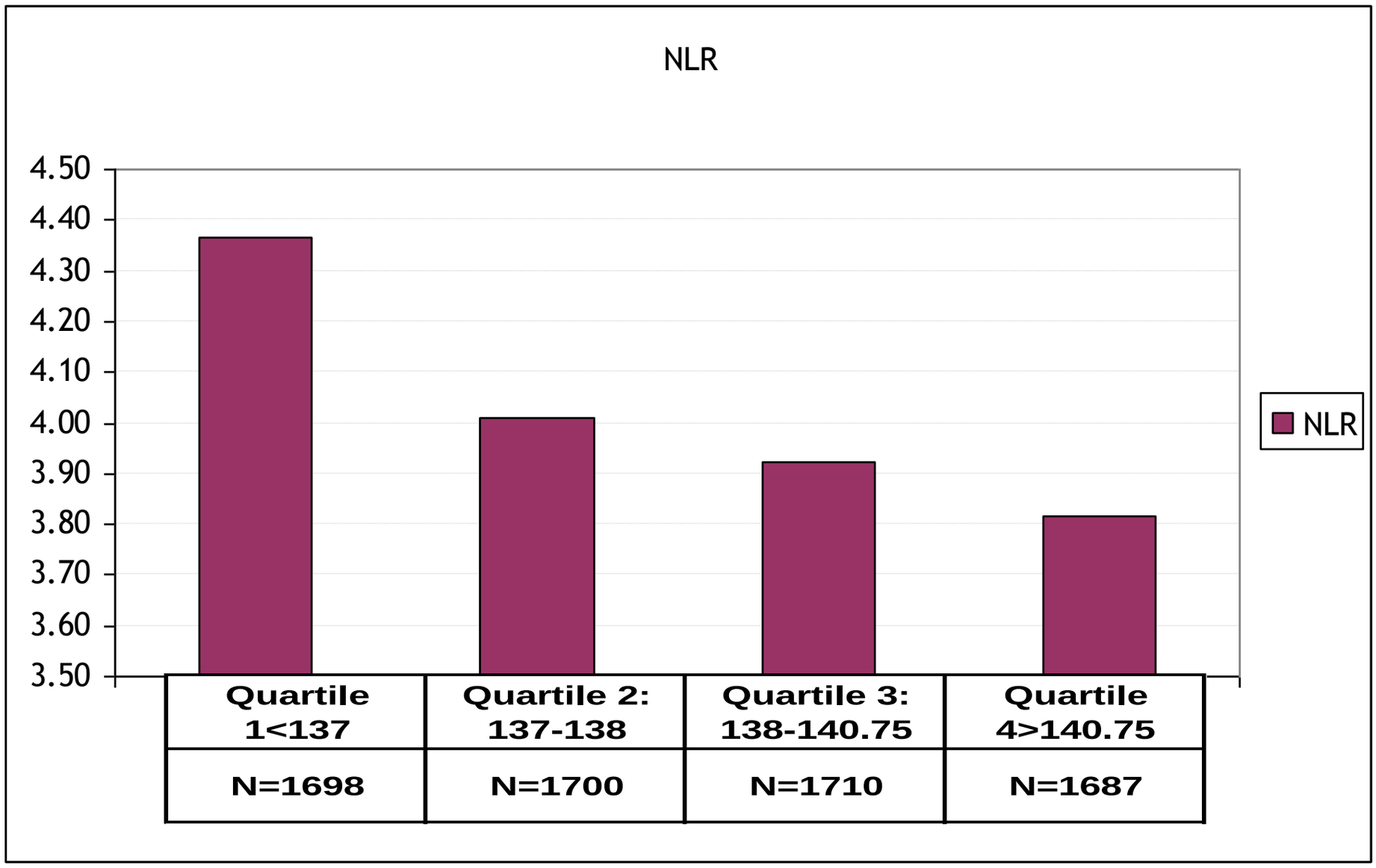
Na+ Quartile and Potassium



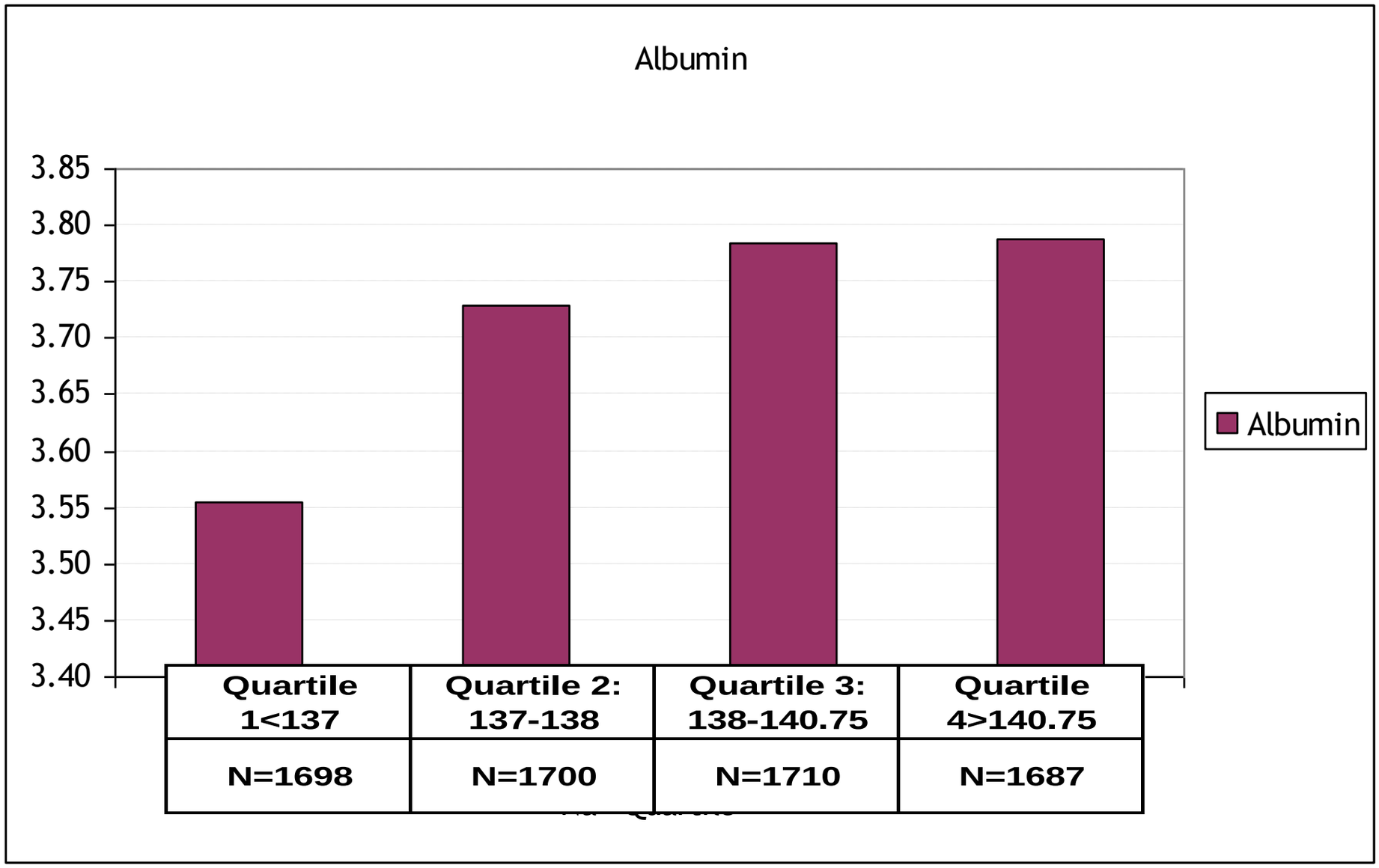
Na+ Quartile and Bicarb



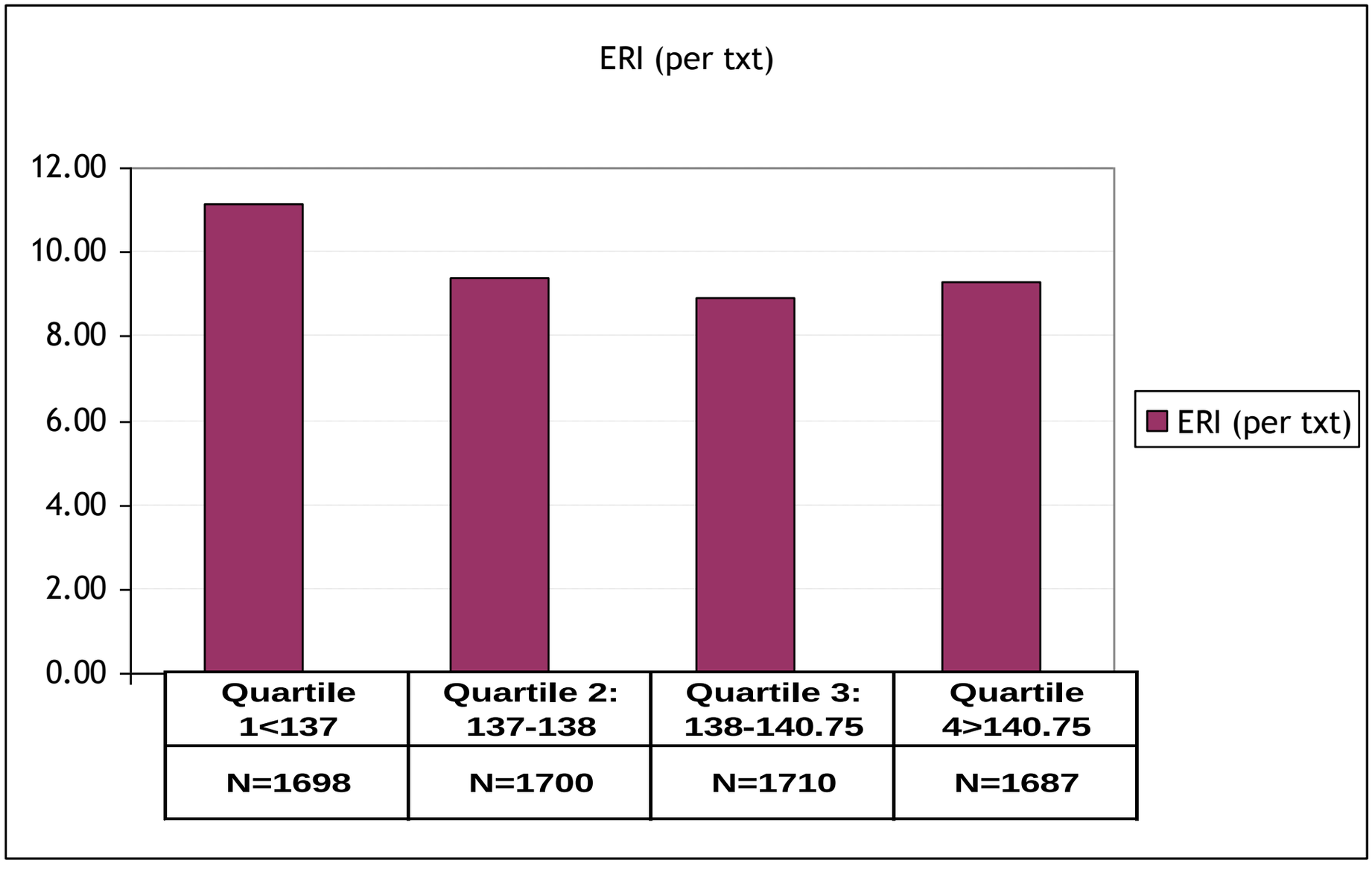
Na+ Quartile and NLR



Na+ Quartile and Albumin



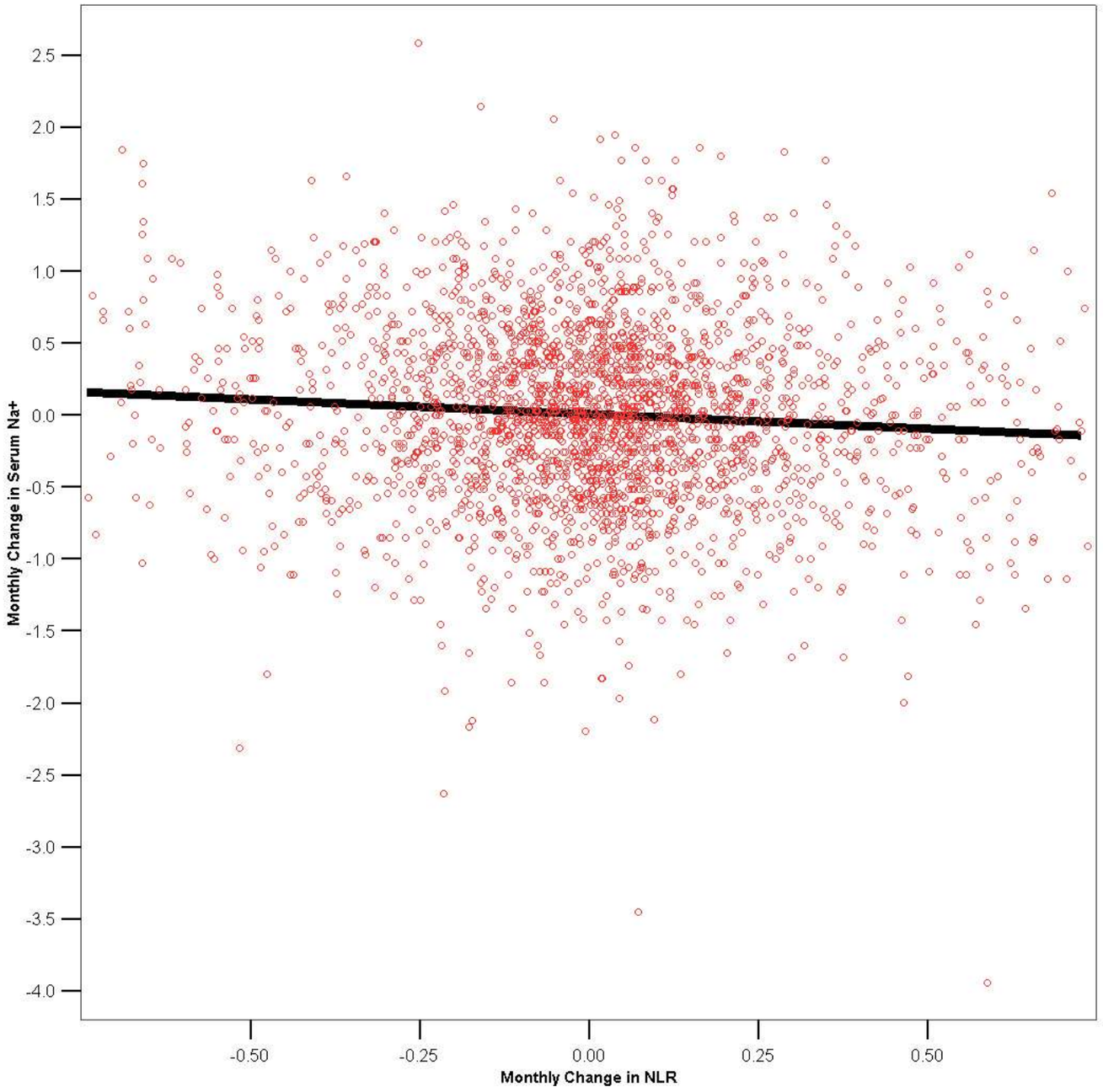
Na+ Quartile and ERI



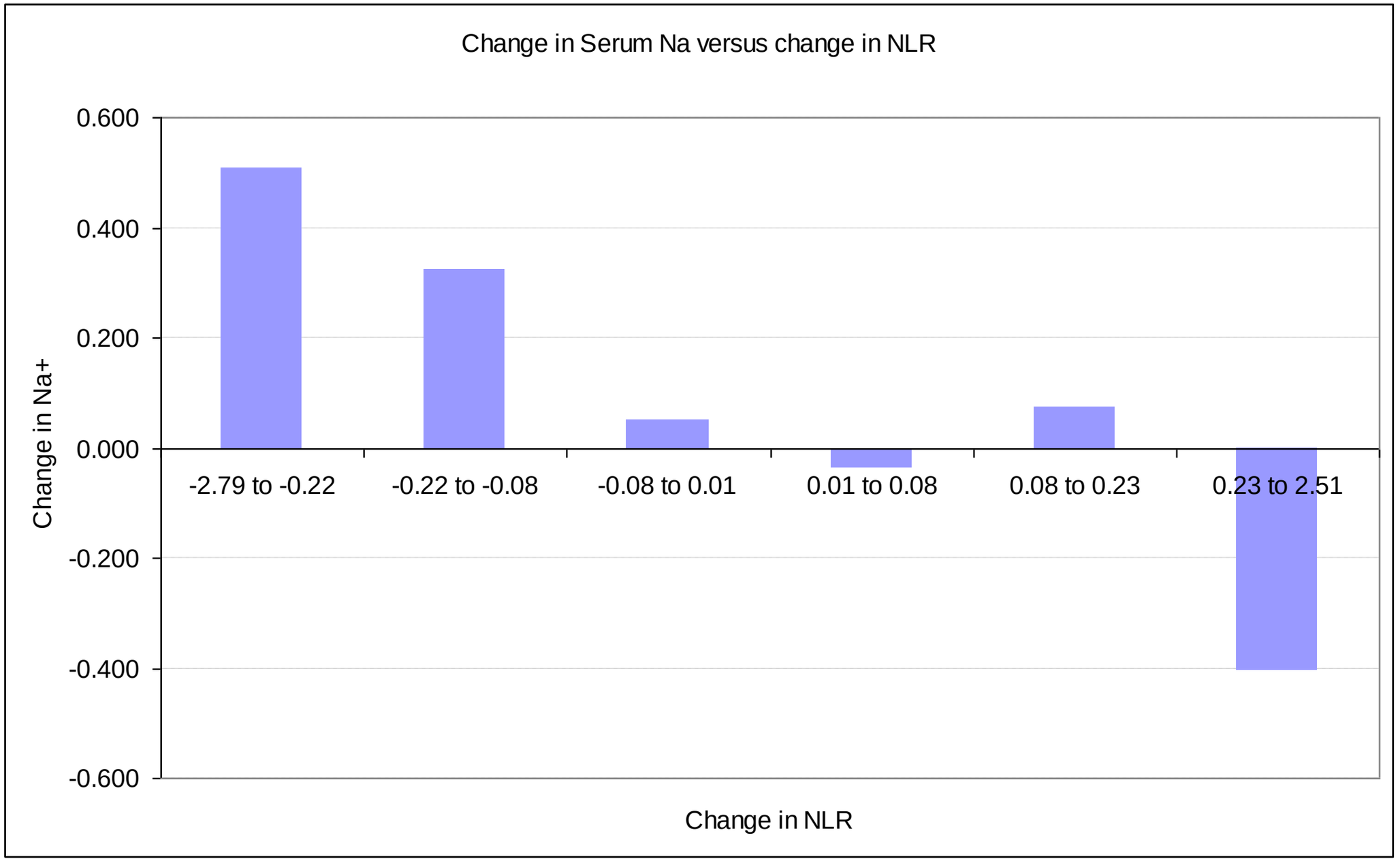
Change in NLR versus Na+ (over six month period)

NLR Monthly Change	Mean NLR at Start	Mean NLR at End	N	Mean Na at Start	Mean Na at End
-2.79 to -0.22	5.8	3.3	463	137.6	138.1
-0.22 to -0.08	3.4	2.8	462	138.0	138.4
-0.08 to 0.01	2.7	2.6	462	138.4	138.5
0.01 to 0.08	2.6	2.8	462	138.4	138.3
0.08 to 0.23	2.7	3.4	462	138.1	138.2
0.23 to 2.51	3.4	5.9	463	138.1	137.7

Change in NLR versus Na+



Change in NLR versus Na+



p<0.001 using ANOVA

Change in Albumin versus Na+ (over six month period)

Albumin Monthly Change	Mean Albumin at Start	Mean Albumin at End	N	Mean Na at Start	Mean Na at End
-0.37 to -0.04	3.94	3.56	476	138.5	138.5
-0.04 to -0.01	3.88	3.78	460	138.1	138.3
-0.01 to 0.02	3.87	3.91	474	138.3	138.4
0.02 to 0.04	3.75	3.90	441	137.8	138.0
0.04 to 0.07	3.70	3.97	461	138.0	138.1
0.07 to 0.39	3.39	3.96	461	137.9	137.7

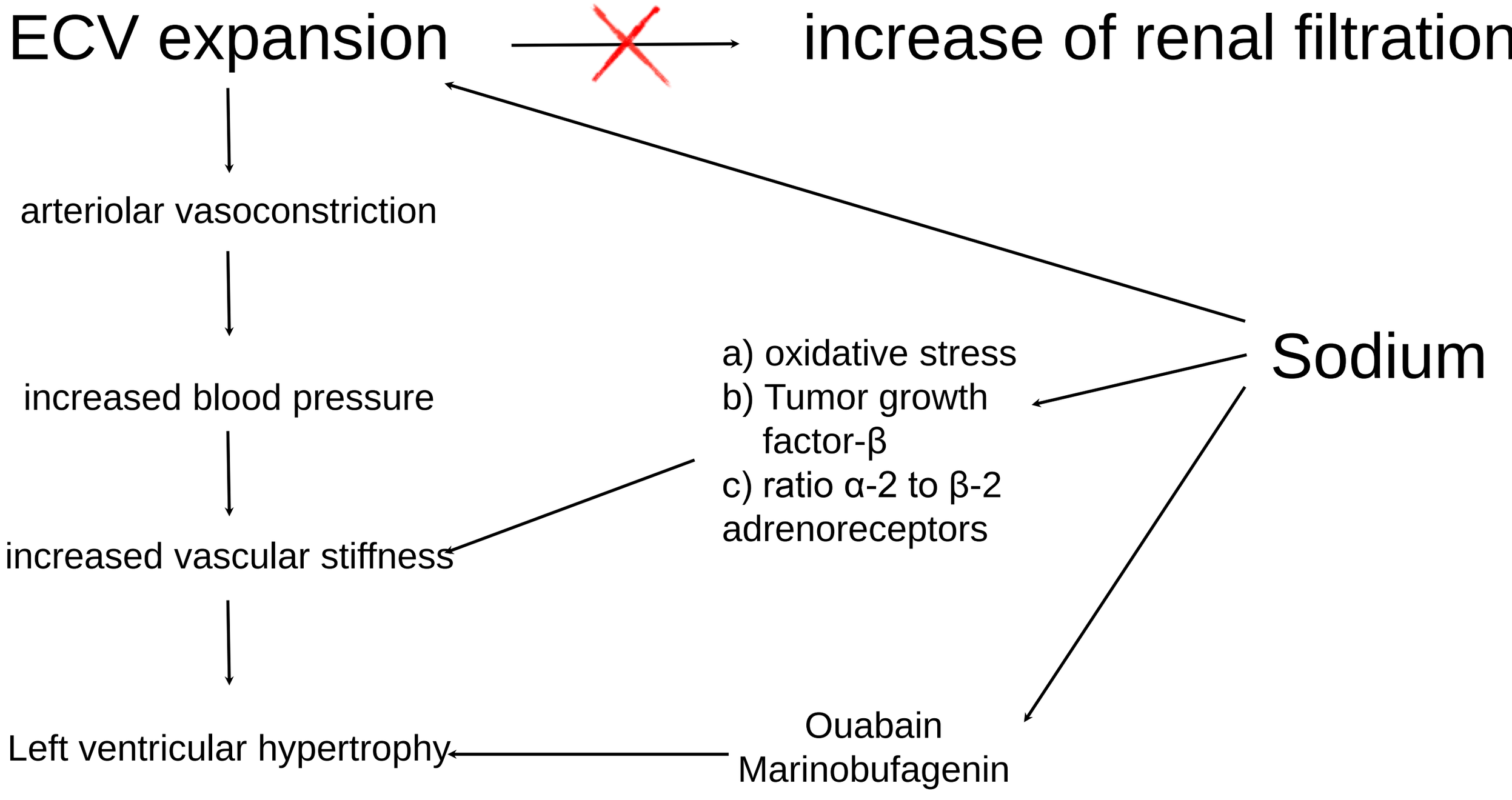
A fresh look at dry weight

Jochen Raimann[1,2], Li Liu[1,2], Sudhi Tyagi[1],
Nathan W. Levin[1], Peter Kotanko[1]

1 Renal Research Institute, New York City
2 Beth Israel Medical Center, New York City

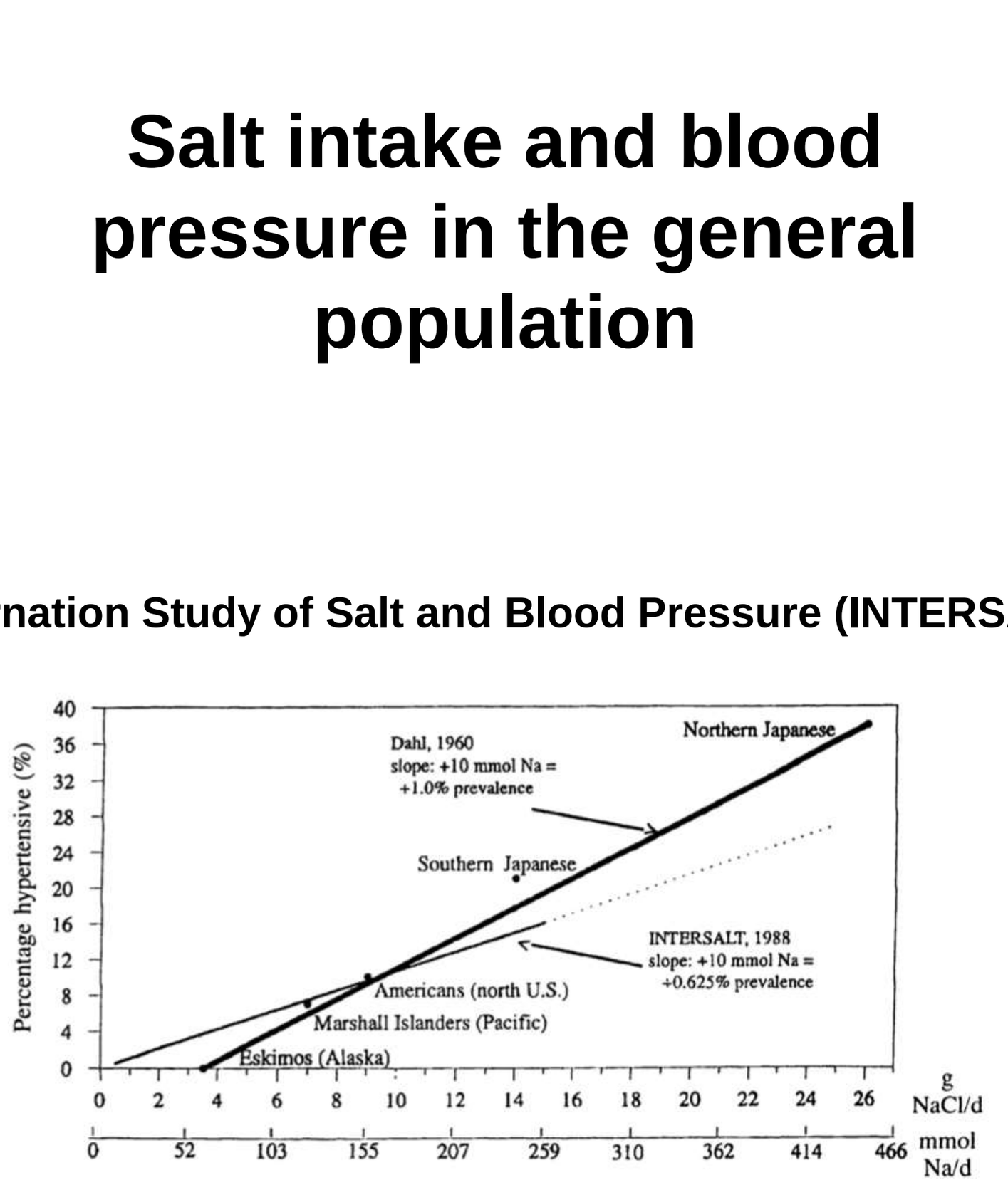
Hemodialysis International 2008; **12**:395-405

Consequences of chronic overhydration



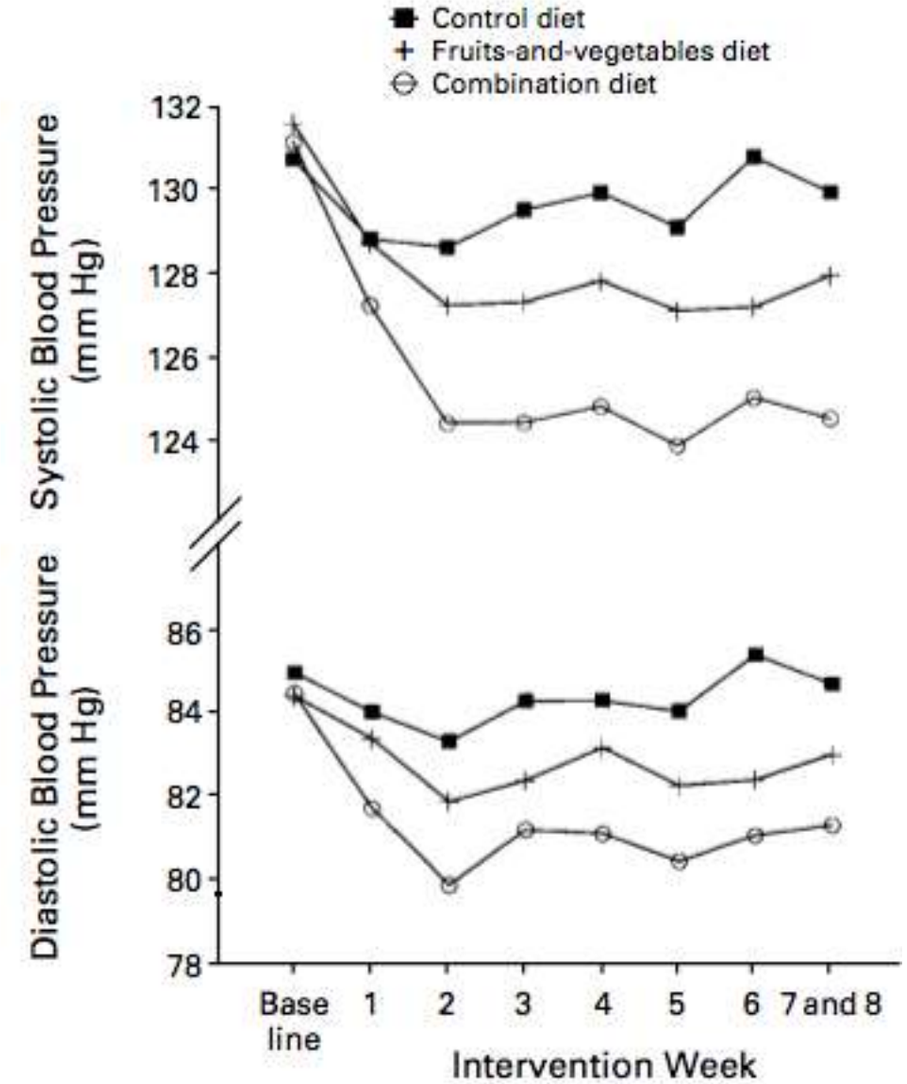
Salt intake and blood pressure in the general population

ernation Study of Salt and Blood Pressure (INTERSALT)



Stamler J. The INTERSALT Study: background, methods, findings, and implications. Am J Clin Nutr. 1997;65(2 Suppl): 626S-642S.

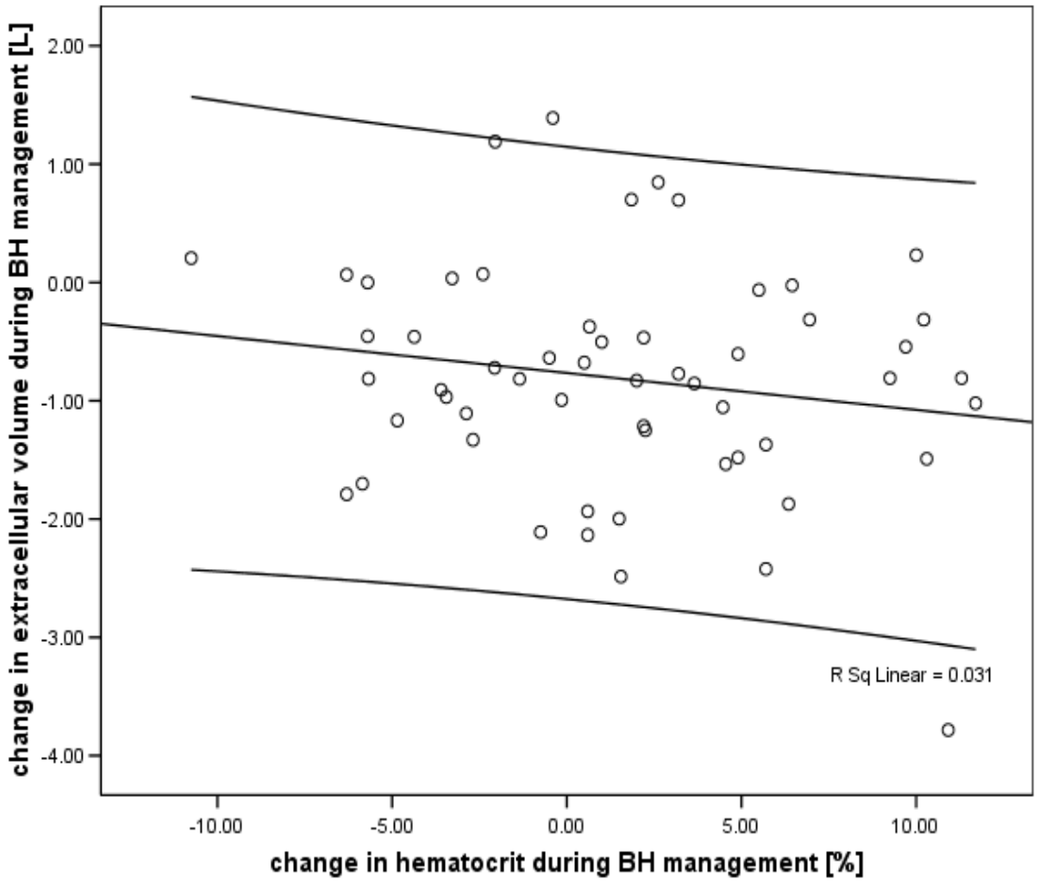
Dietary Approach to Stop Hypertension (DASH)



Moore TJ, Vollmer WM, Appel LJ, Sacks FM, Svetkey LP, Vogt TM, et al. Effect of dietary patterns on ambulatory blood pressure : results from the Dietary Approaches to Stop Hypertension (DASH) Trial. DASH Collaborative Research Group. Hypertension. 1999;34(3): 472-477.

Non-cardiovascular Consequences of overhydration

Anemia management



	Pre HD weight [kg]	ECV [L]	nRho [Ωm³/kg]	Hct [%]	Hgb [mg/dL]	ERI [units/kg/week /g of Hgb]
Beginning of BH management	79.14±21.9	18.14±0.62	13.69±2.9	36.93±4.23	11.94±1.29	25.48±21.23
End of BH management	77.64±21.56	17.34±4.57	14.77±2.61	38.49±3.88	12.32±1.16	23.3±19.47
Difference	**-1.5 (-1.93 to -1.07) ***	**-0.8 (-1.04 to -0.55) ***	1.08 (0.71 to 1.46)	**1.56 (0.13 to 2.99) ***	0.39 (0.83 to -0.06)	-2.18 (-5.98 to 1.61)

P<0.05 P<0.05 P<0.05 P=0.087

Calf bioimpedance guided “body hydration” management

n=58 patients

13 ± 12 HD treatments

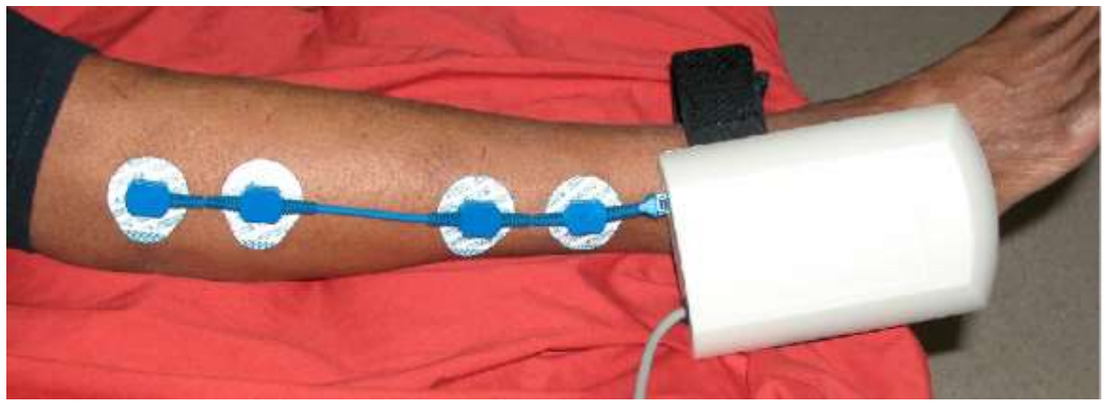
Raimann J., Liu L., Sipahioglu M., Usvyat L., Bomback A., Klemmer A., Zhu F., Kotanko P., Levin N. W.. Decrease in extracellular volume - results and its possible impacts on anemia management. Accepted for poster presentation at the “Renal weeks 2009” of the Amercian Society of Nephrology in San Diego, CA.

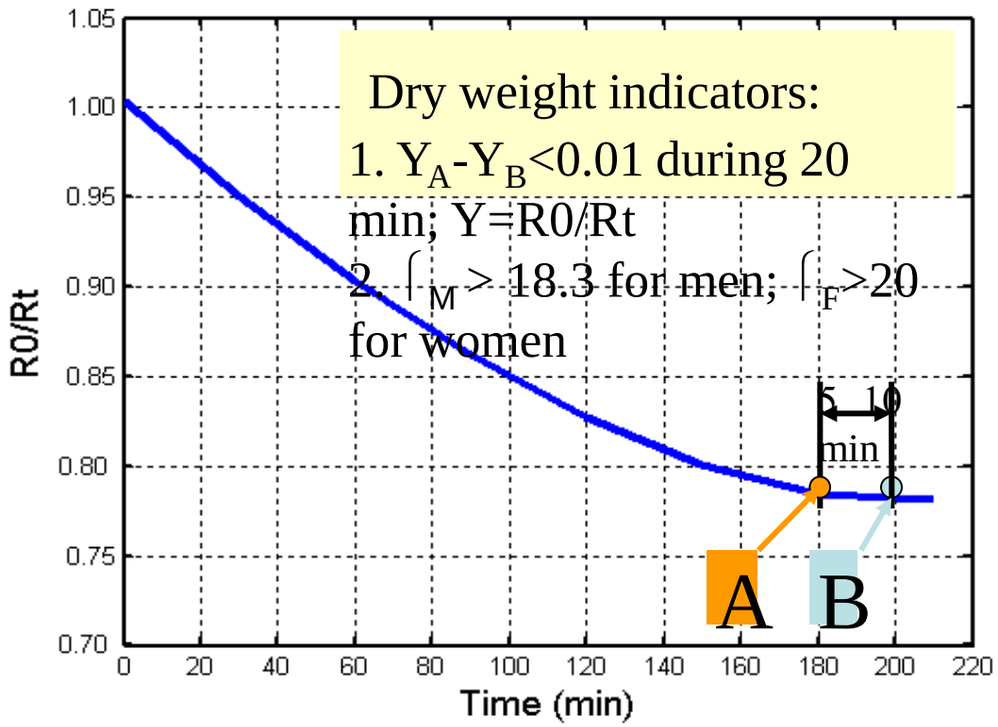
Assessment of dry weight

Calf Bioimpedance Spectroscopy (cBIS)

monitors changes in calf resistance continuously over the whole dialysis session

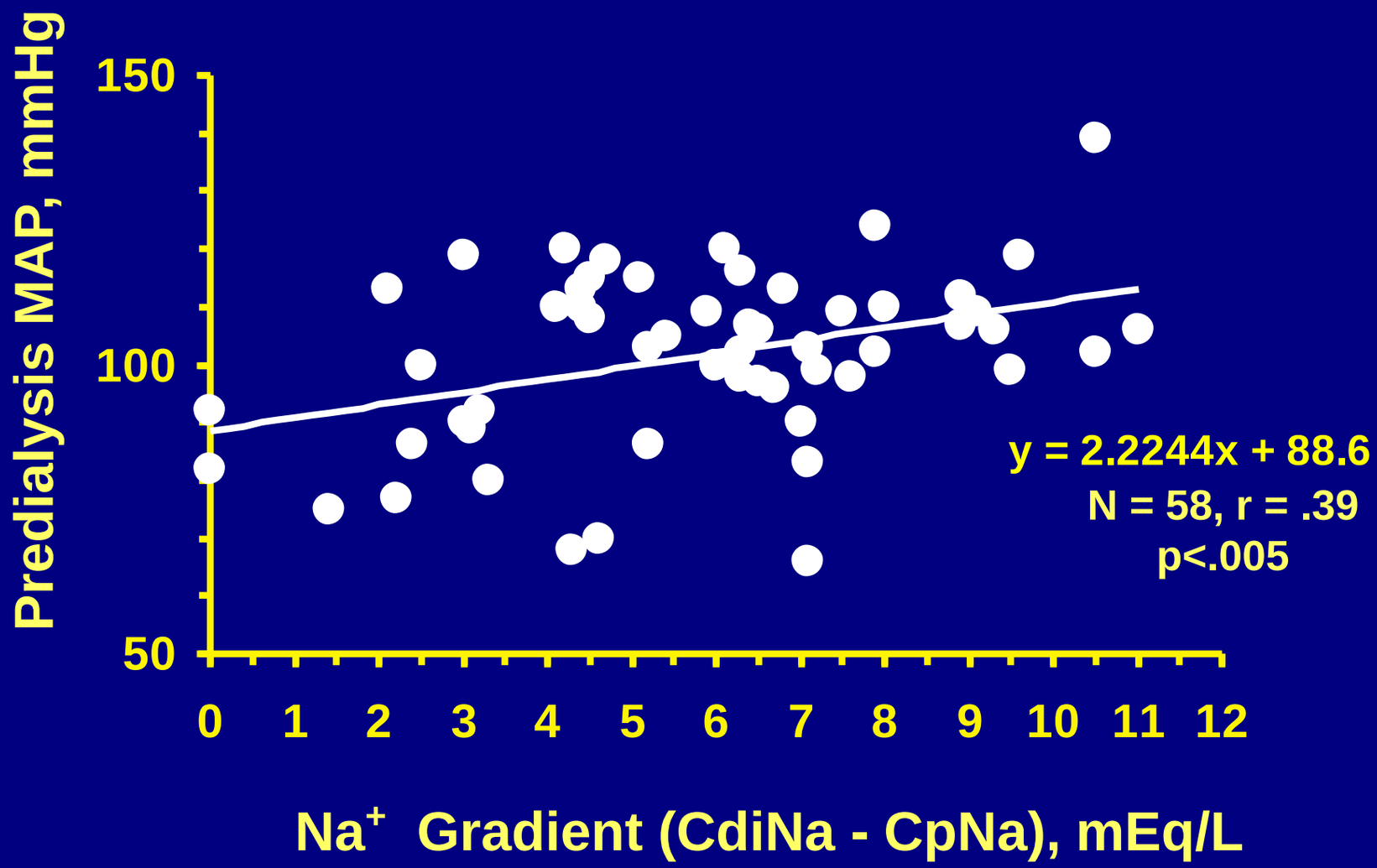
patient serves thereby as his own control





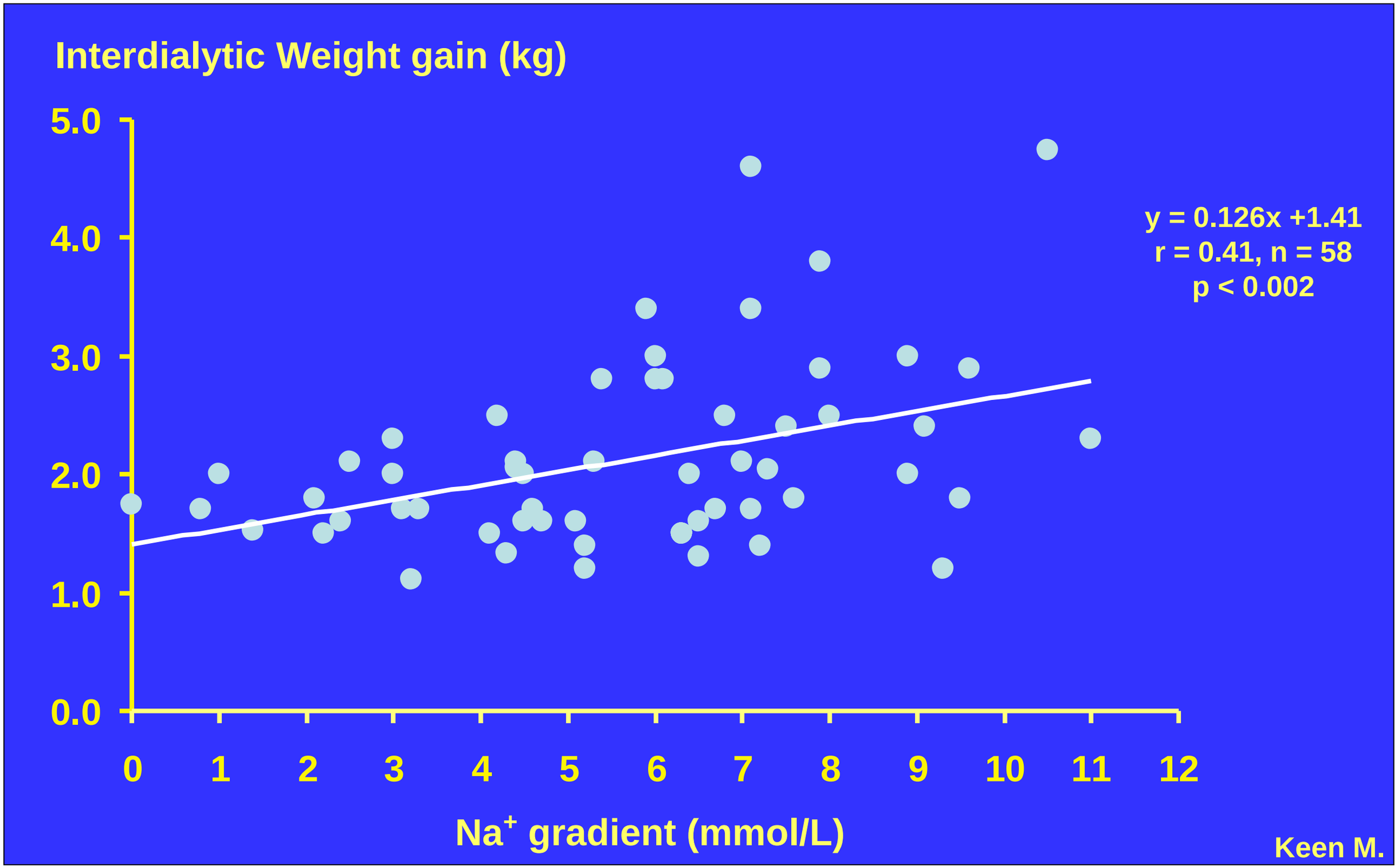
Zhu F, Kuhlmann MK, Kotanko P, Seibert E, Leonard EF, Levin NW. A method for the estimation of hydration state during hemodialysis using a calf bioimpedance technique. Physiol Meas. 2008;29(6): S503-516.

RELATIONSHIP OF PREDIALYSIS MAP TO PREDIALYSIS Na^+ GRADIENT (CdiNa - CpNa)

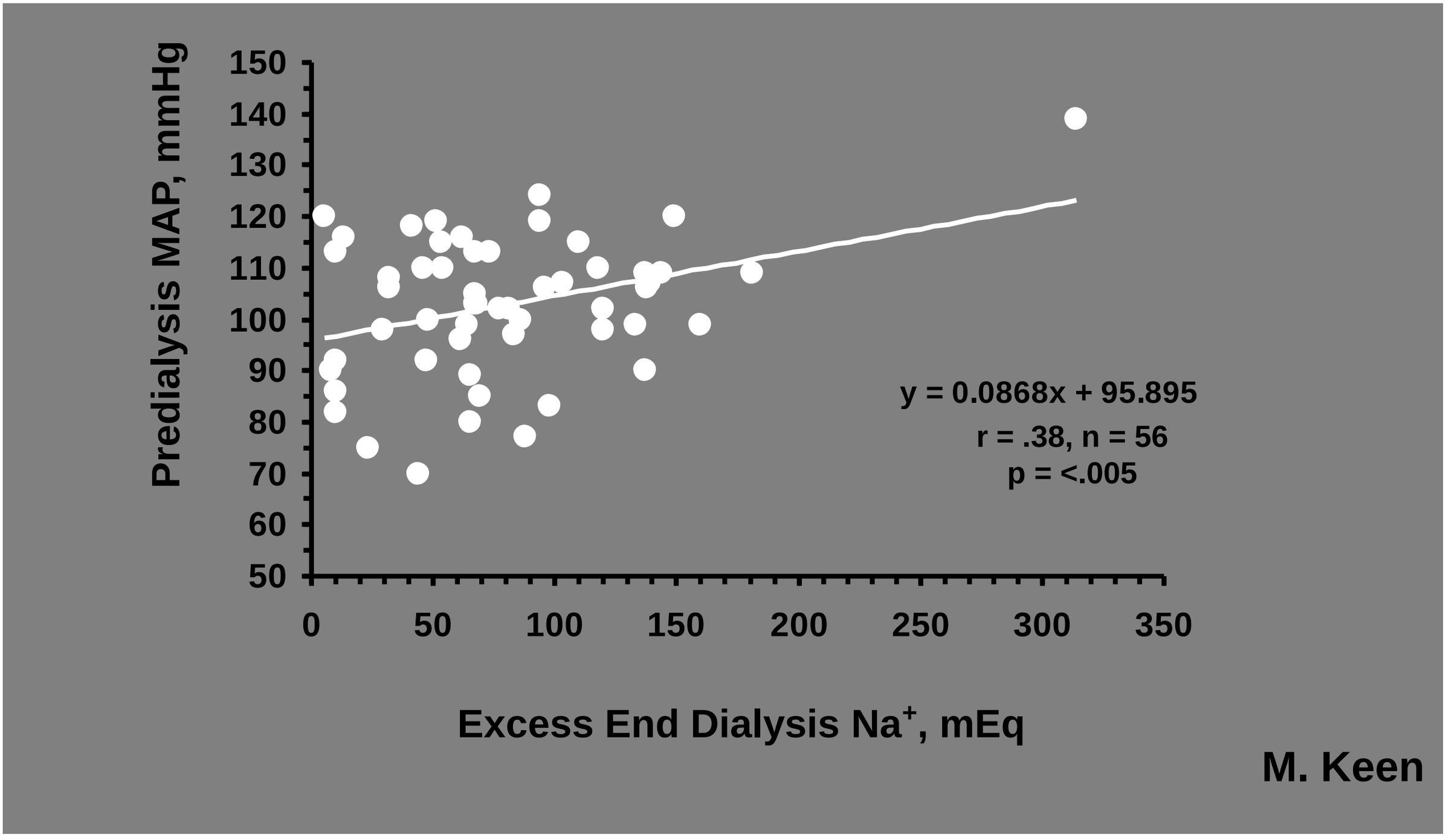


M. Keen

Correlation of Interdialytic Weight Gain and Pre-HD Dialysate-to-Blood Na^+ Gradient



CORRELATION OF PREDIALYSIS MEAN ARTERIAL PRESSURE TO CALCULATED EXCESS END-DIALYSIS BODY Na^+ CONTENT



M. Keen