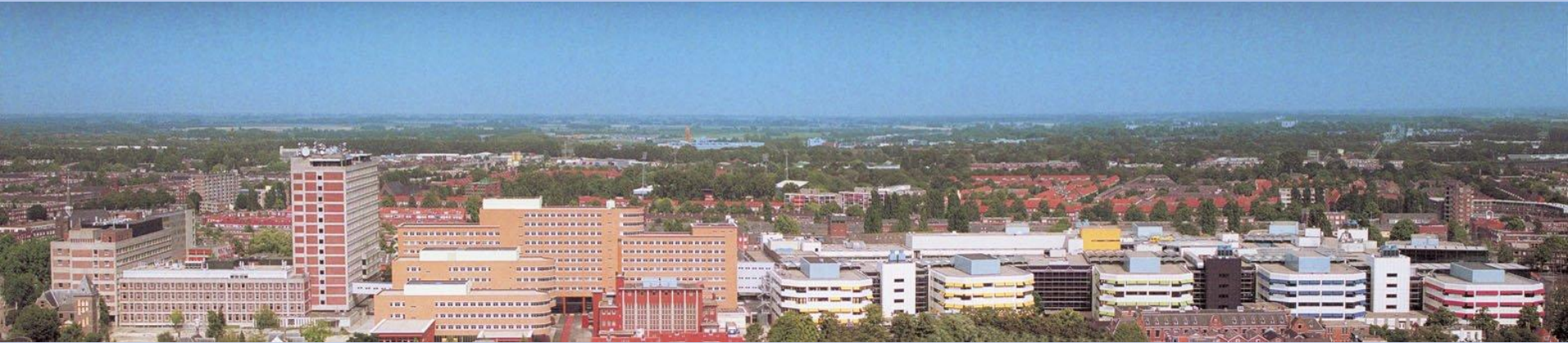


Beneficial effects of sodium restriction on outcome of renoprotective therapy in CKD



Gerjan Navis

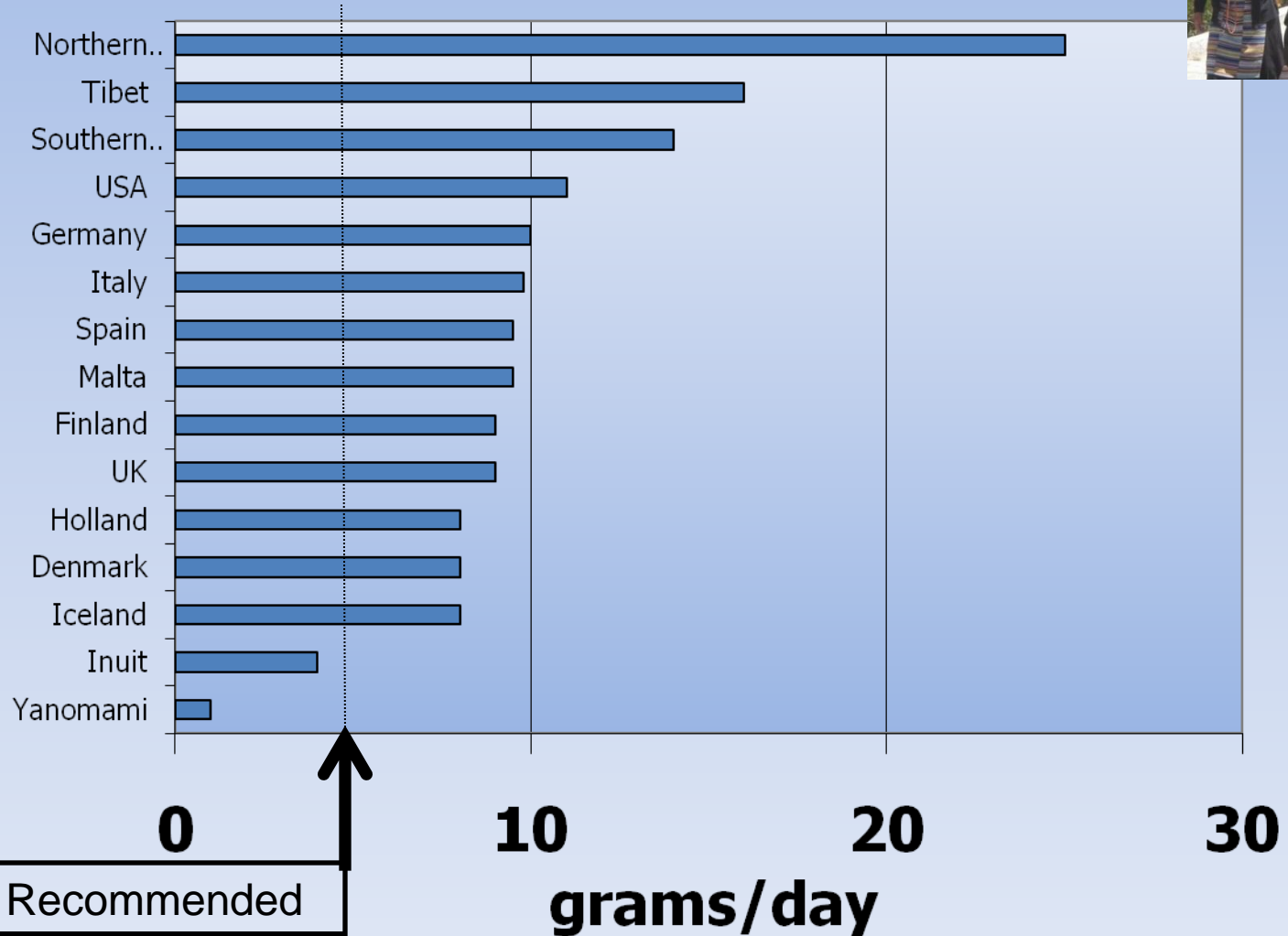
UMCG

Groningen

The Netherlands

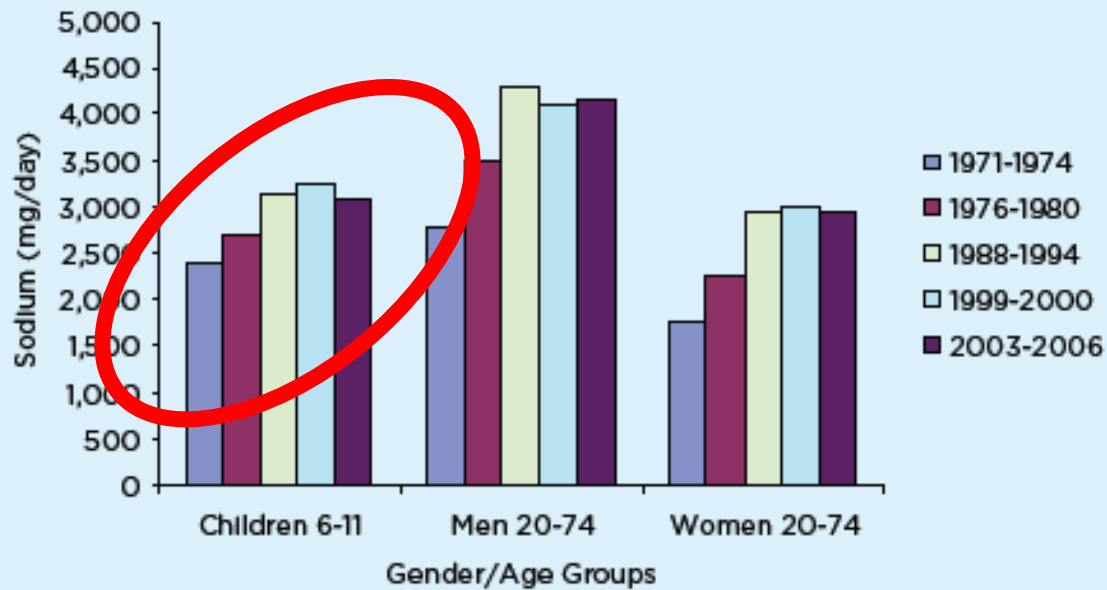


Saltintake around the world



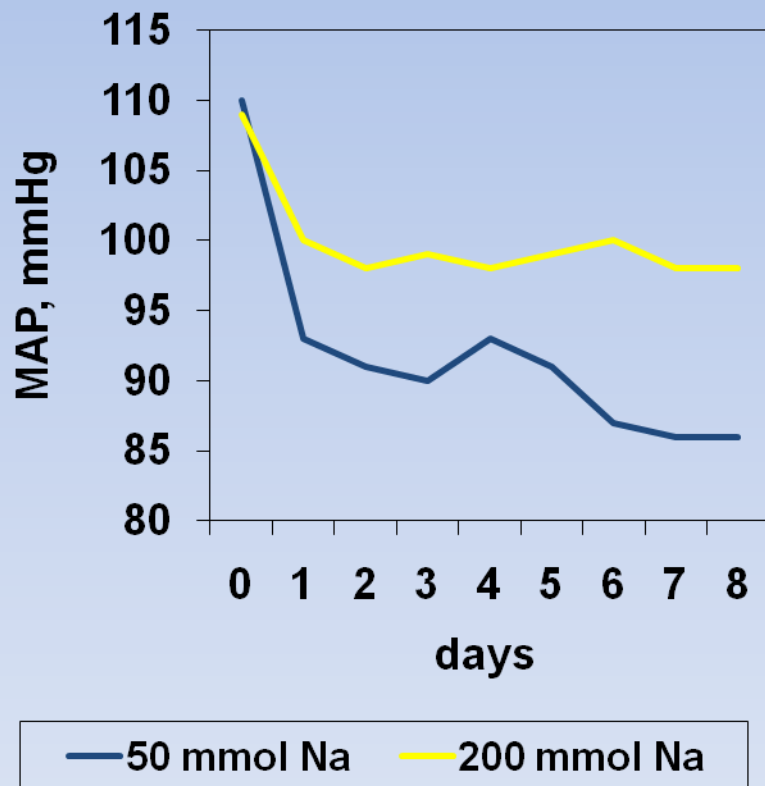
Sodium intake over time

Figure 1: Trends In Mean Sodium Intake from Food for Three Gender/Age Groups, 1971-1974 to 2003-2006



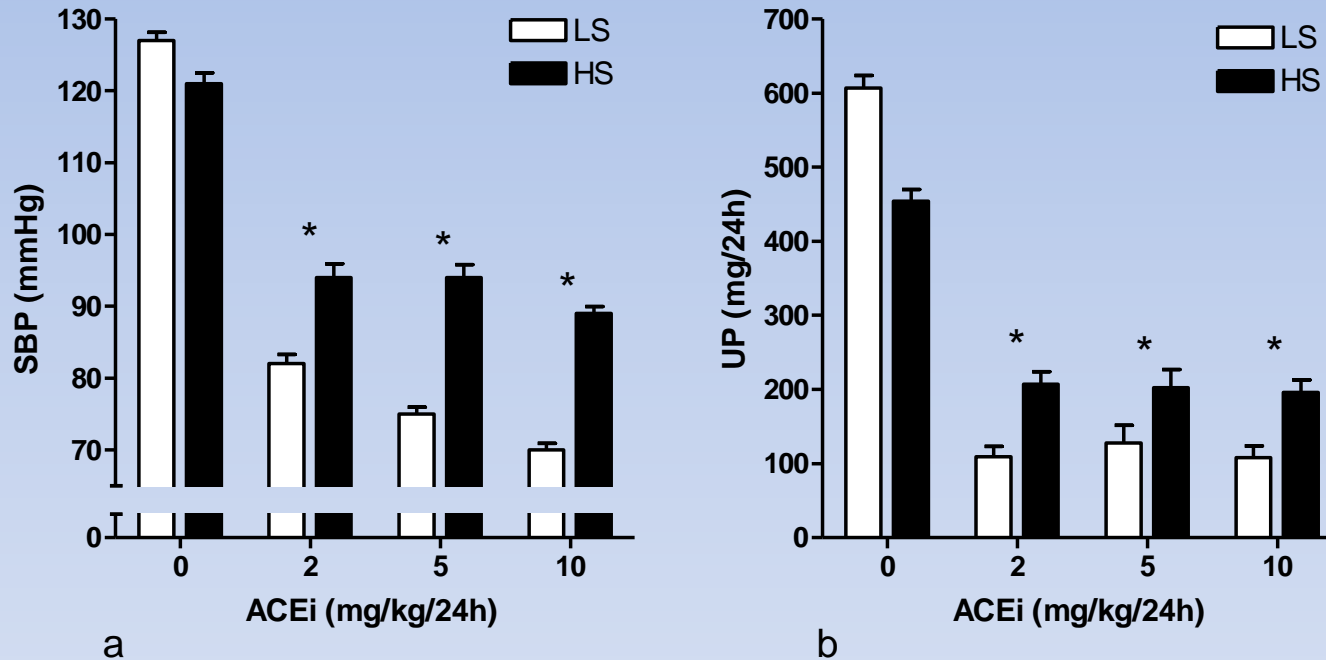
Source: Briefel and Johnson (2004) and NHANES (2003-2006)

Sodium restriction and ACEi in essential hypertension



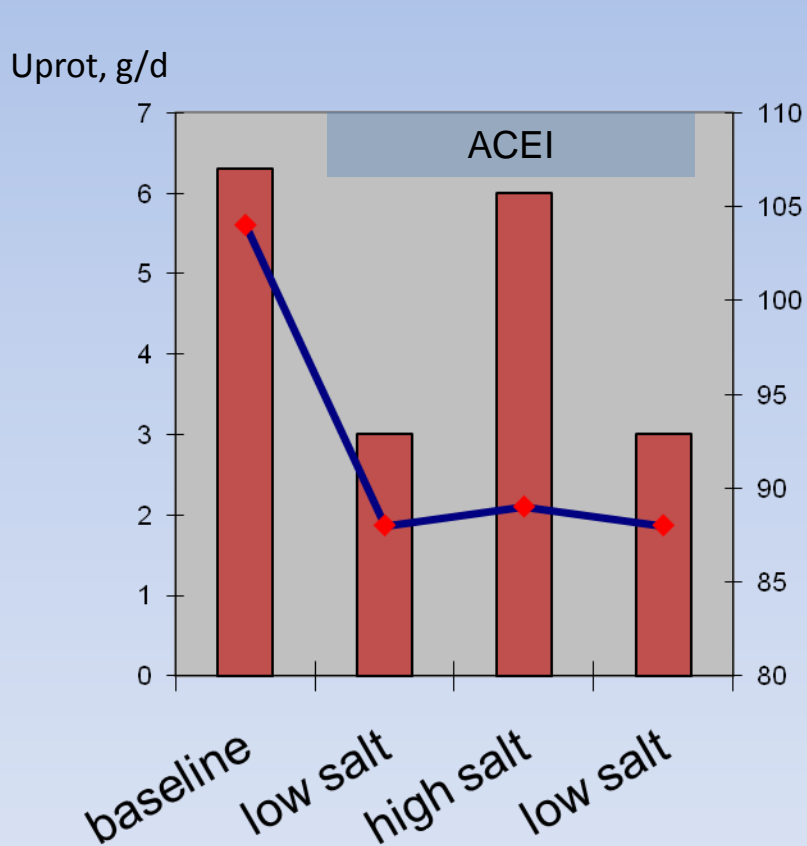
- RAAS-blockade potentiates effect of low Na⁺ diet
- RAAS-blockade makes blood pressure sodium sensitive in all patients!

Low sodium diet increases top of dose-response for ACEi on blood pressure and proteinuria

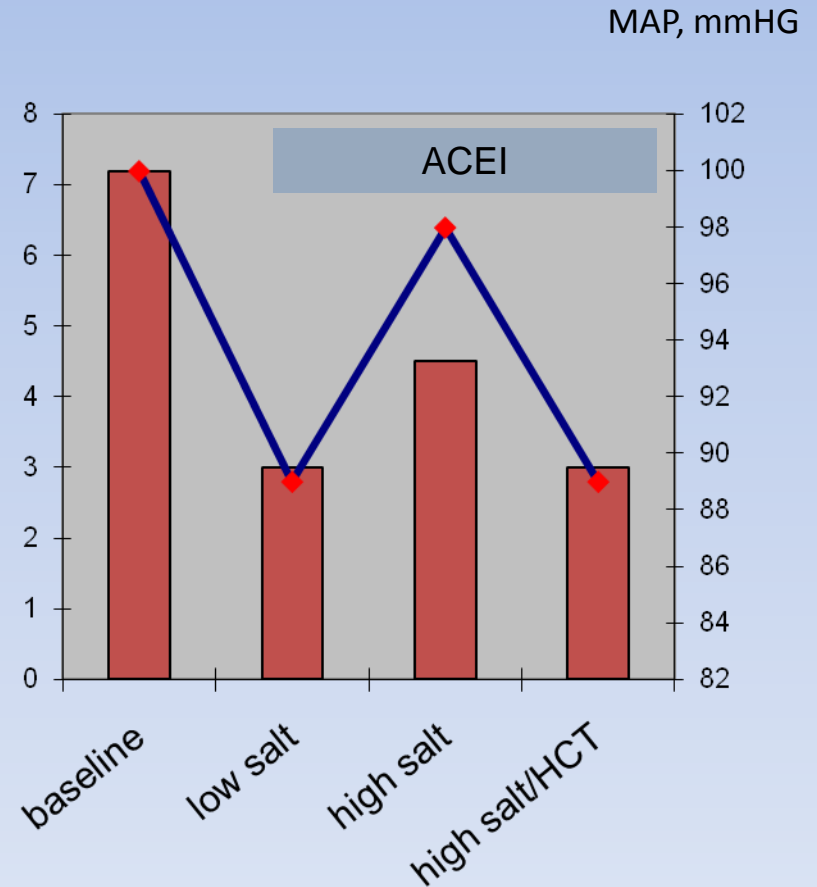


Experimental nephrotic syndrome

Control of sodium excess improves therapy response in CKD

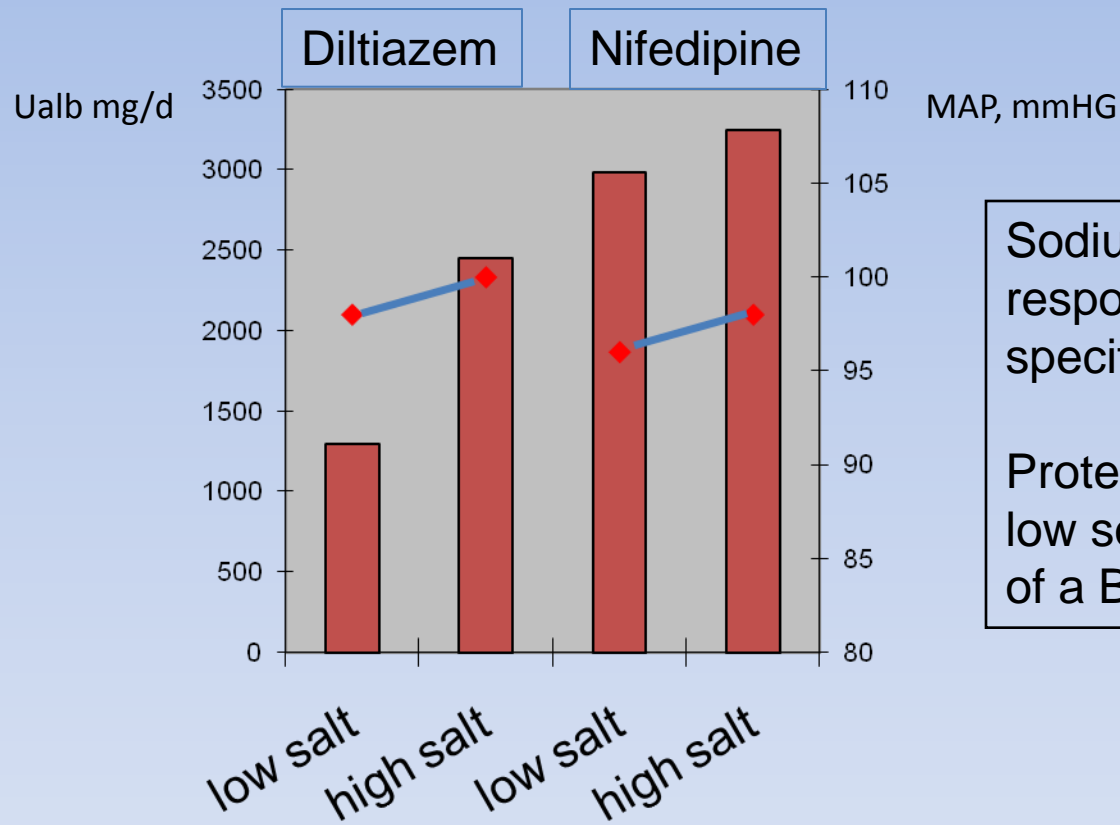


Heeg, Kidney Int 1989; 36,272



Buter, NDT 1998: 13: 1682

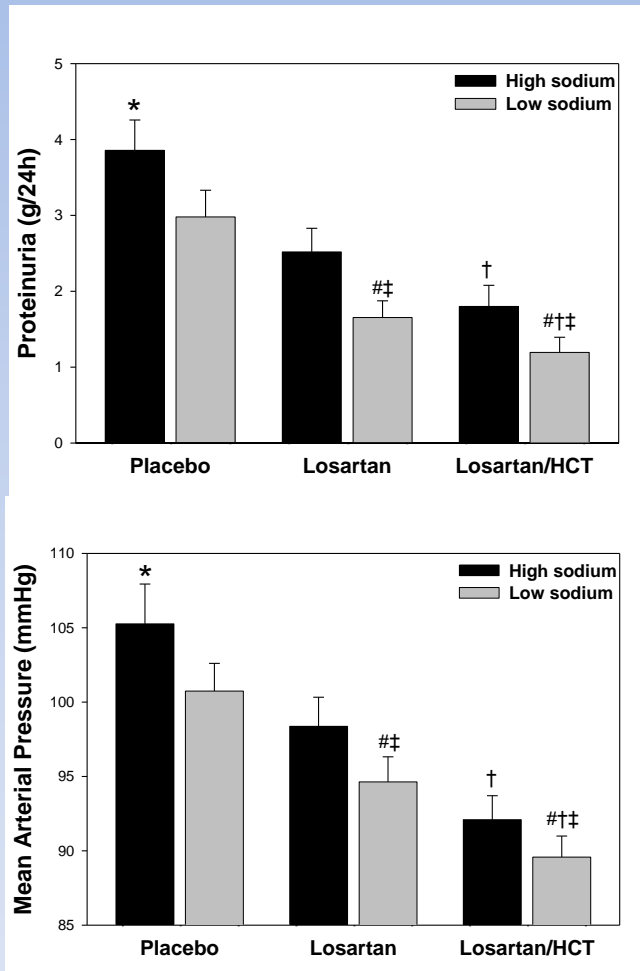
Effect of sodium status on therapy response to CCB in diabetic nephropathy



Sodium-dependency of Rx-response may depend on specific drug characteristics

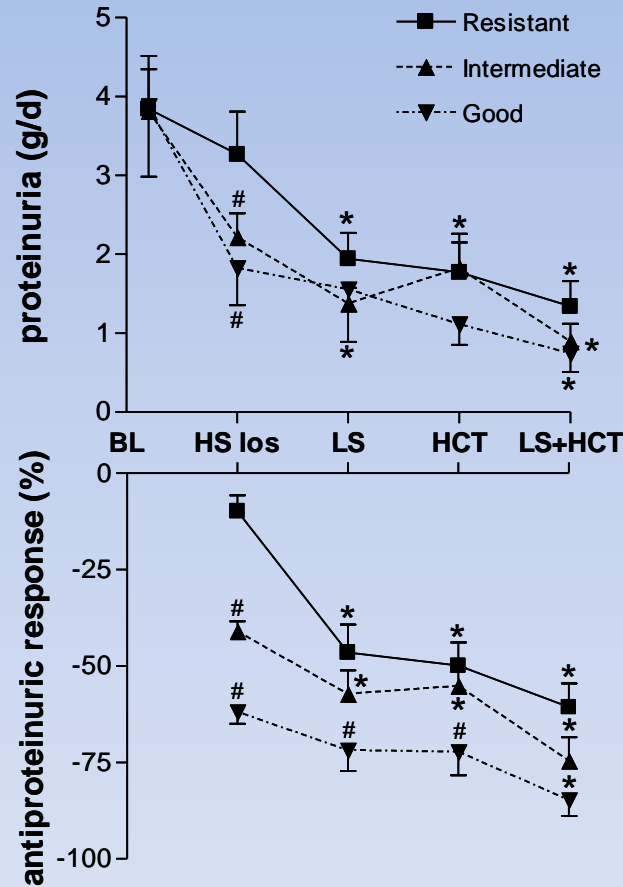
Proteinuria can respond to low sodium in the absence of a BP response

Excess sodium blunts the effects of RAAS-blockade, even during diuretic therapy

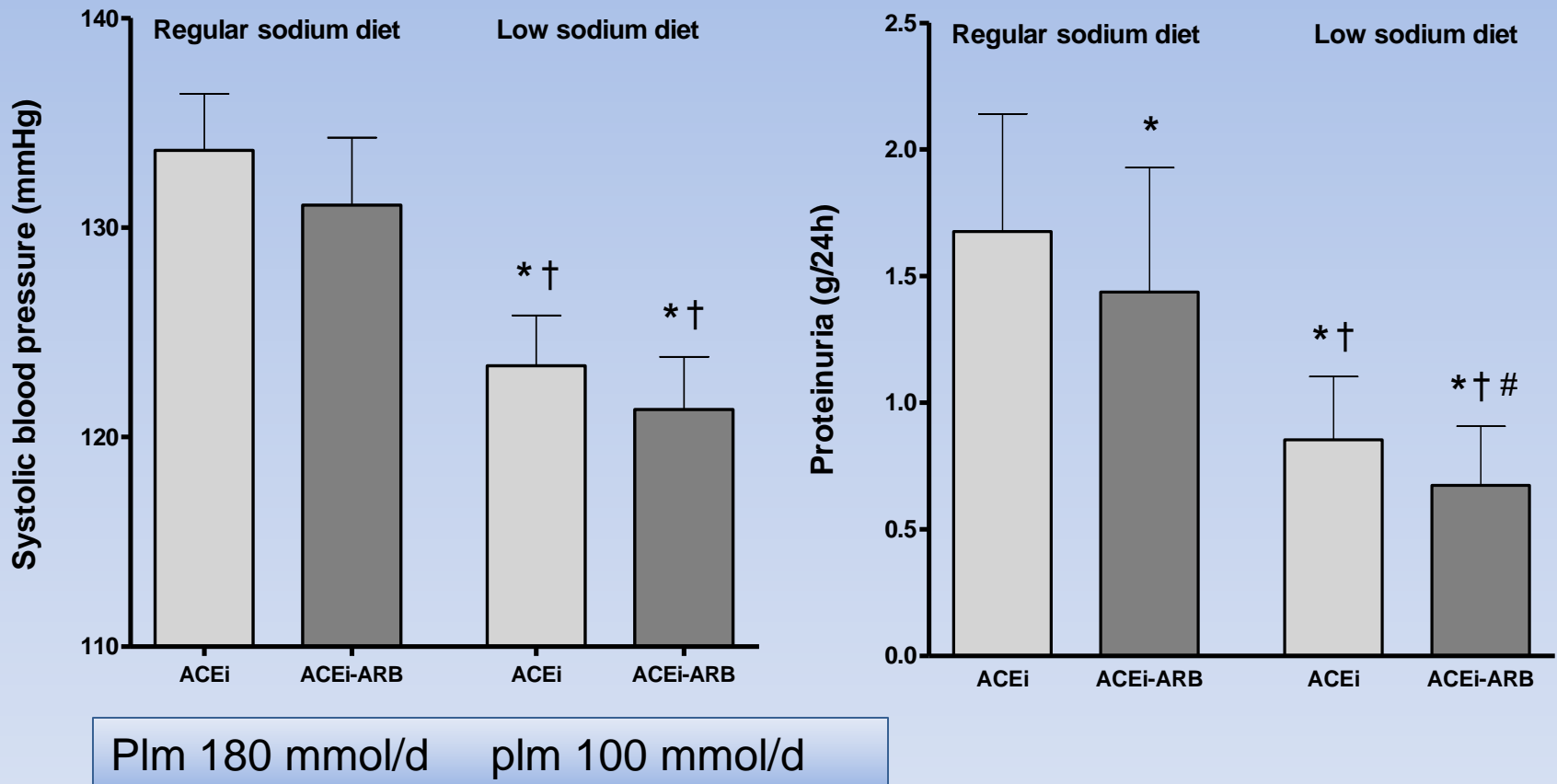


- Low sodium diet reduces blood pressure and proteinuria
- Low sodium diet potentiates effect AT1RA on blood pressure and proteinuria, plm equivalent to diuretic
- Lowest blood pressure and proteinuria during combination low sodium/diuretic
- NB: target LS: 50 mmol/d
- Obtained: 90-100 mmol/d !

Low sodium specifically potentiates responses in subjects with poor response to RAAS-blockade



Sodium restriction more effectively potentiates ACEi than dual blockade



Slagman et al, BMJ 2011, in press

Table 2. Clinical parameters during the four treatment regimens

	Regular sodium diet		Low sodium diet	
	ACEi	ACEi-ARB	ACEi	ACEi-ARB
Plasma:				
Sodium – mmol/L	140.7±0.4	140.8±0.4	139.5±0.4 * †	139.1±0.4 * †
Potassium – mmol/L	4.6±0.1	4.6±0.1	4.7±0.1	5.0±0.1 * † #
Creatinine – umol/L	137±8	137±8	149±9 *	157±9 * †
Urea – mmol/L	9.8±0.7	10.2±0.7	11.8±0.8 * †	12.9±0.8 * †
Albumin – g/L	38±1	39±1	40±1 * †	40±1 * †
Total protein – g/L	68±1	69±1	71±1 *	72±1 * †
Total cholesterol – mmol/L	5.1±0.2	5.0±0.2	4.8±0.1	4.9±0.2
Urine:				
Creatinine – mmol/24h	13.8±0.6	14.0±0.5	13.5±0.6	13.4±0.6
Sodium – mmol/24h	189±8	180±9	106±7 * †	105±8 * †
Urea – mmol/24h	395±18	403±19	359±17 * †	352±19 * †
Potassium – mmol/24h	78±3	76±4	76±4	73±3
Creatinine clearance – mL/min	72 [62-84]	74 [65-84]	66 [57-76] * †	61 [53-70] * †
Protein/creatinine ratio – mg/mg	1.2 [0.9-1.5]	0.9 [0.7-1.3] *	0.6 [0.4-0.8] * †	0.5 [0.3-0.7] * † #
Other:				
Body weight – kg	89±3	89±2	87±2 * †	87±2 * †
Edema – no. (%)	35±8	38±8	15±6 †	8±4 * †

REIN trial by mean salt excretion/2 yrs

LSD: plm 5-7 g/d

MSD: plm 10-12 g/d

HSD: plm 15 g/d

(

Short-term BP response:

LSD: -6.9 mmHg

MSD: -7.5 mmHg (NS)

HSD: -5.0 mmHg (NS)

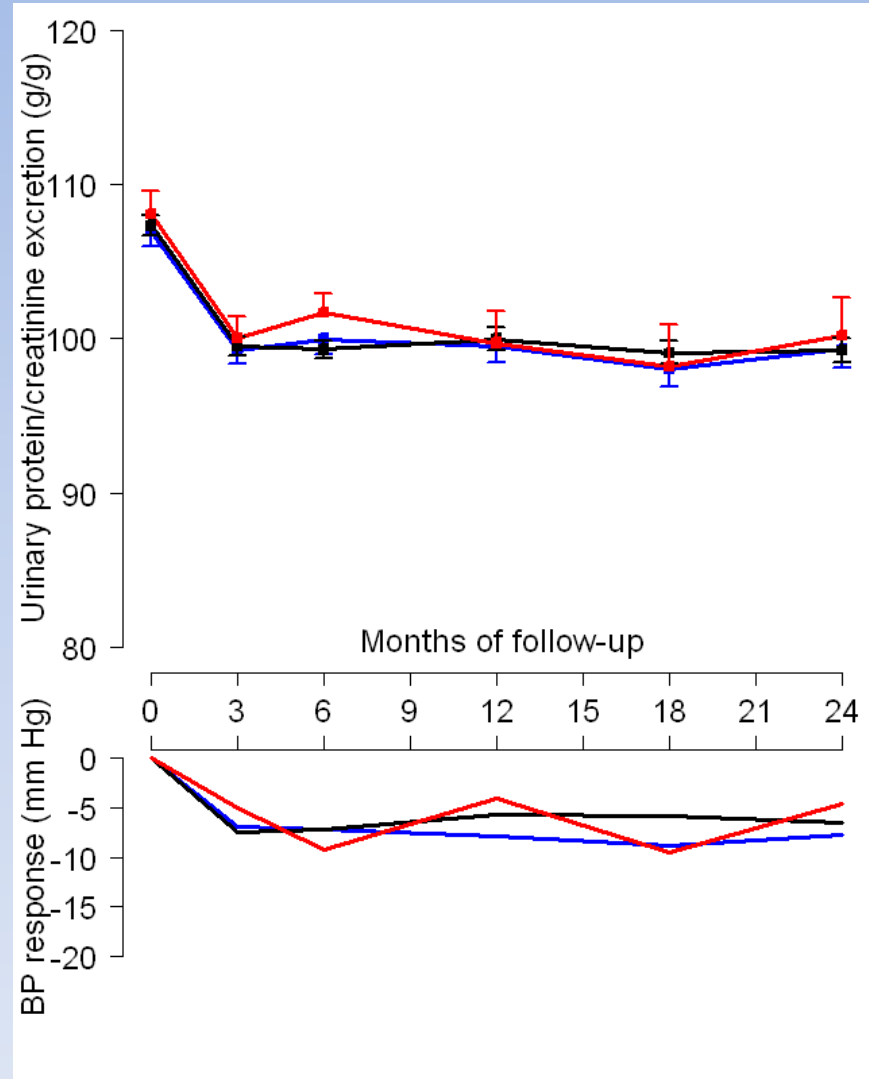
(Wilcoxon rank sum test)

Long-term response:

No changes (NS)

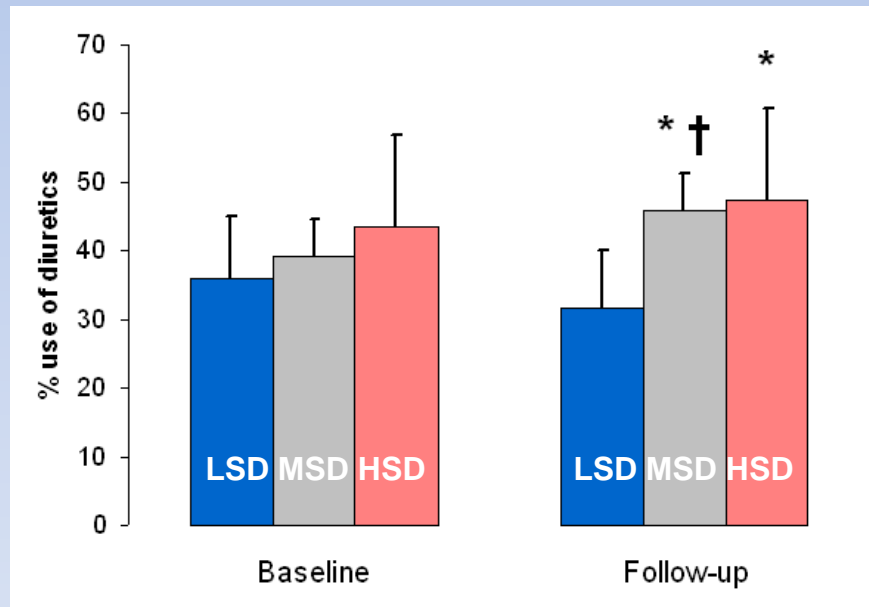
No difference between groups (NS)

(Joint modelling, *J Stat Soft* 2010; 35:1-33)



REIN trial: need for diuretics

- BP *control* was independent of sodium intake
- However, MSD and HSD required more diuretics than LSD



Results - proteinuria

At inclusion (before ACEi):

LSD: 2.0 g/g

MSD: 2.1 g/g (P=0.014)

HSD: 2.6 g/g (P=0.011)

(Wilcoxon rank sum test)

Short-term response:

LSD: -31%

MSD: -25% (P=0.034)

HSD: -20% (P=0.031)

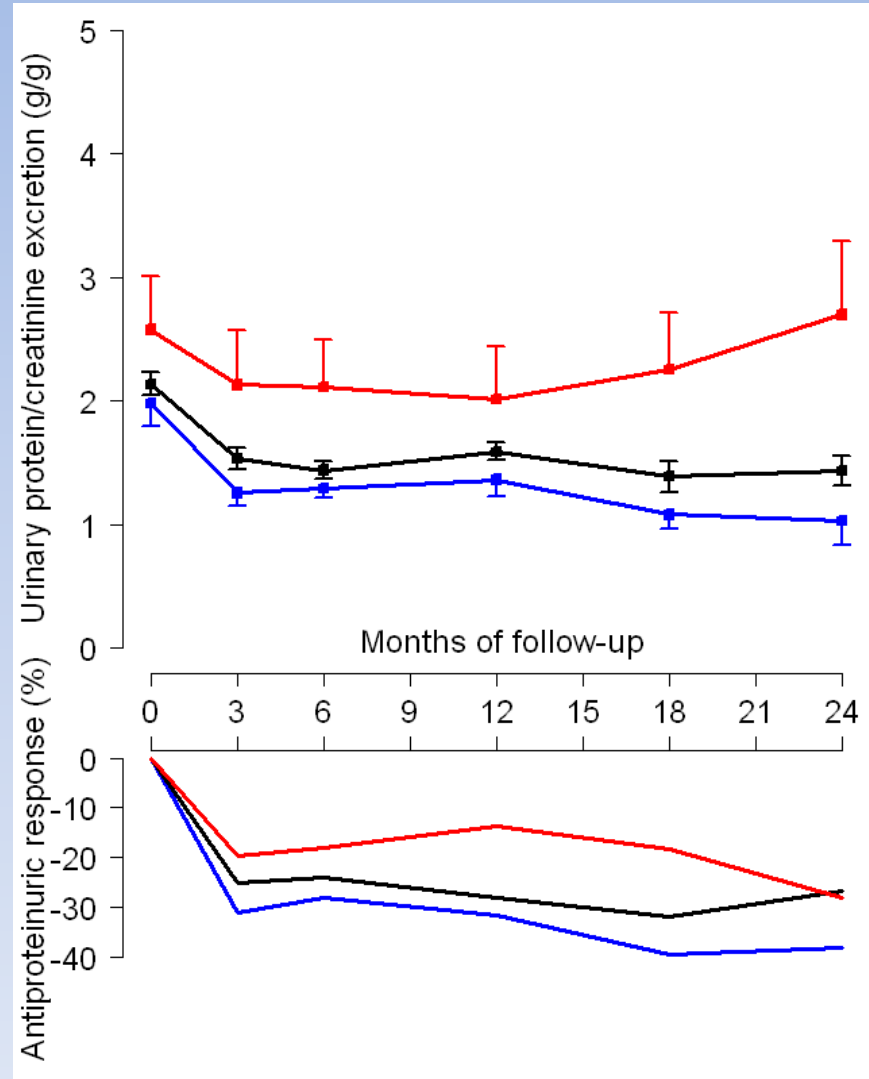
(Wilcoxon rank sum test)

Long-term response:

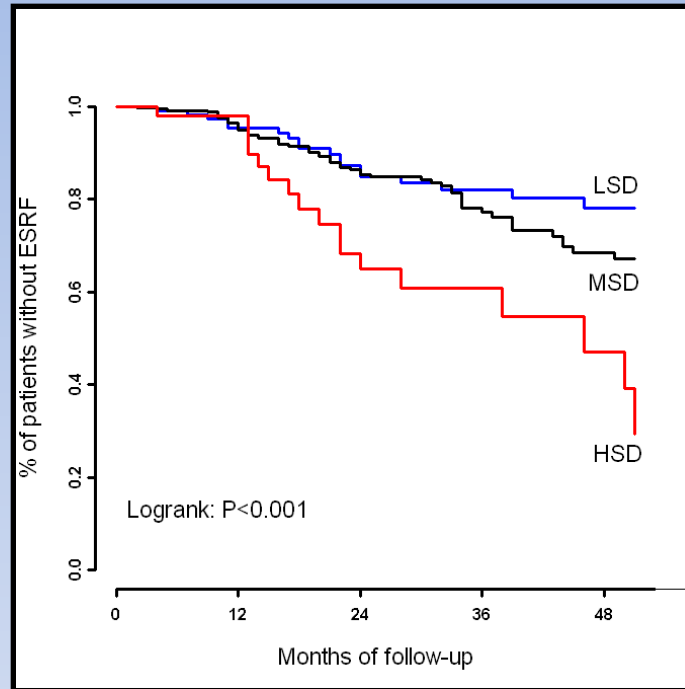
-0.66% per month (P=0.039)

No difference between groups (NS)

(Joint modelling, *J Stat Soft* 2010; 35:1-33)

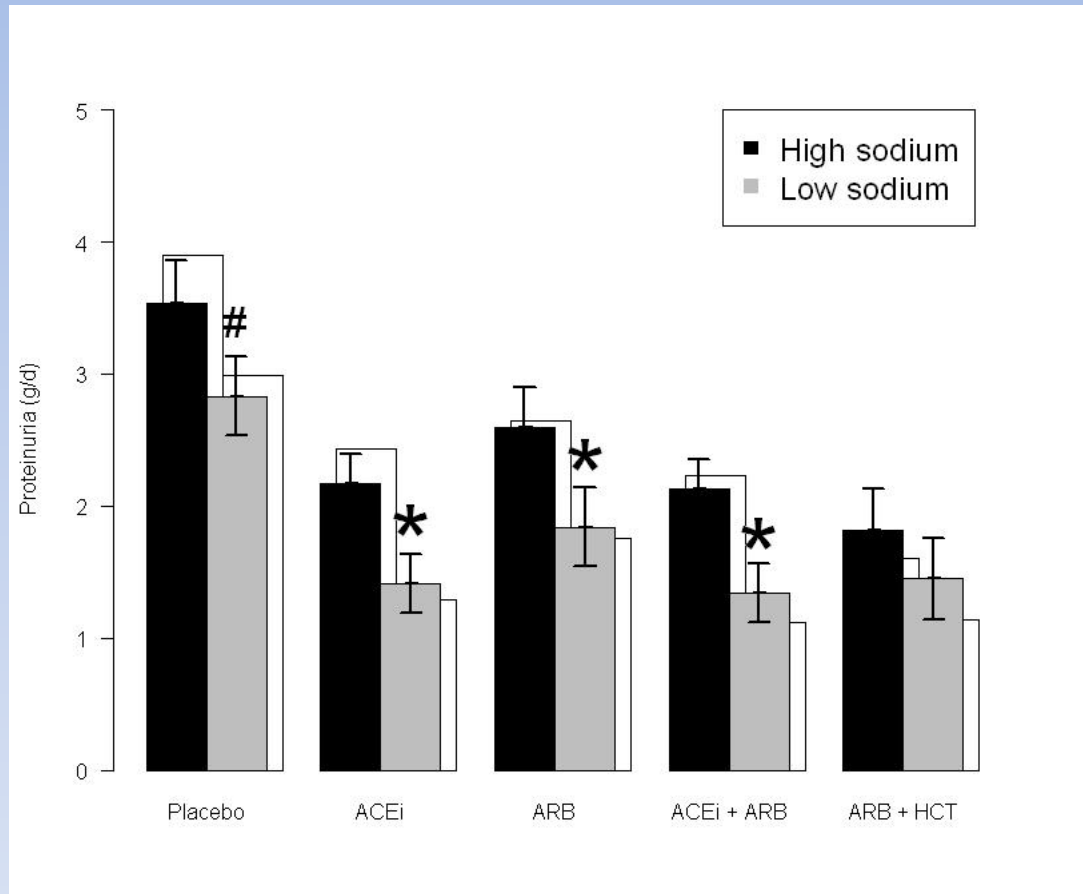


REIN TRIAL: hard renal end points by salt intake

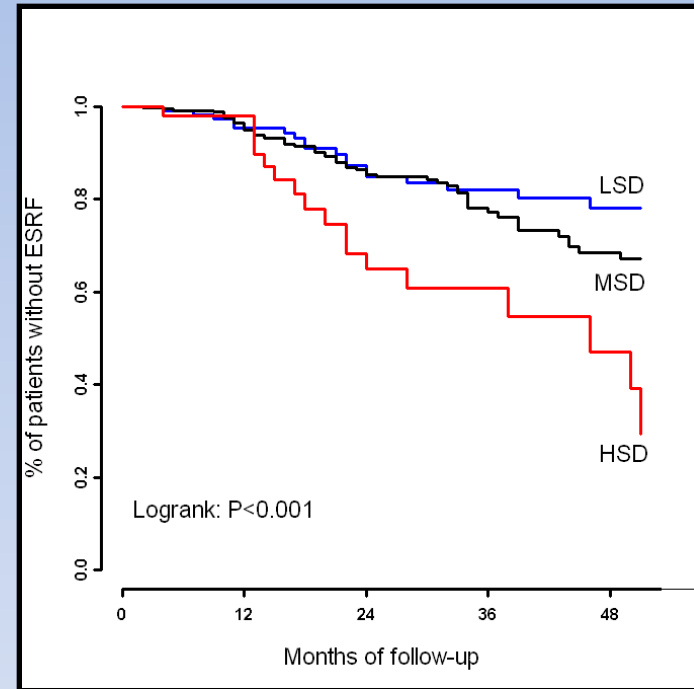
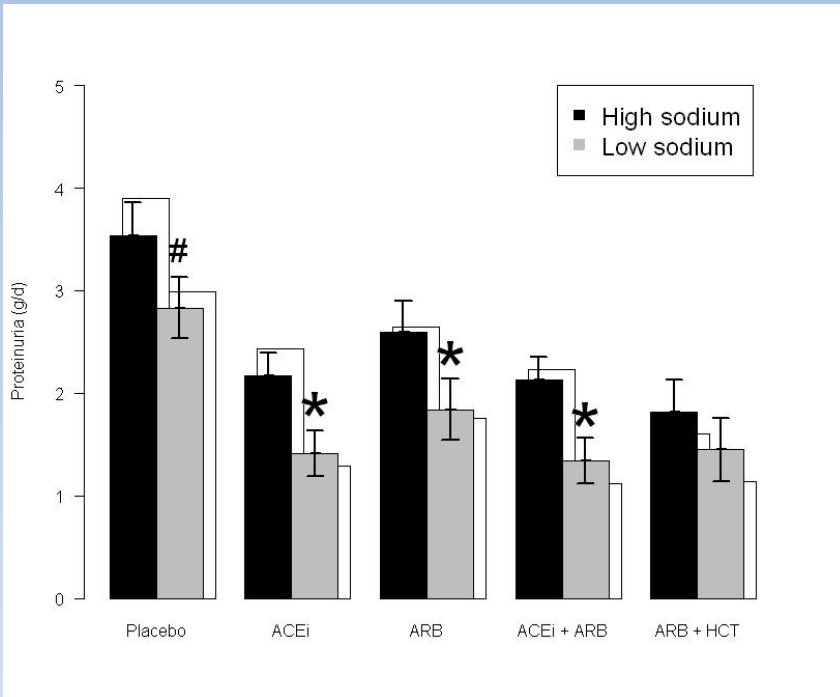


Excessive salt intake is associated with worse renal outcome, **DESPITE** well-controlled blood pressure !

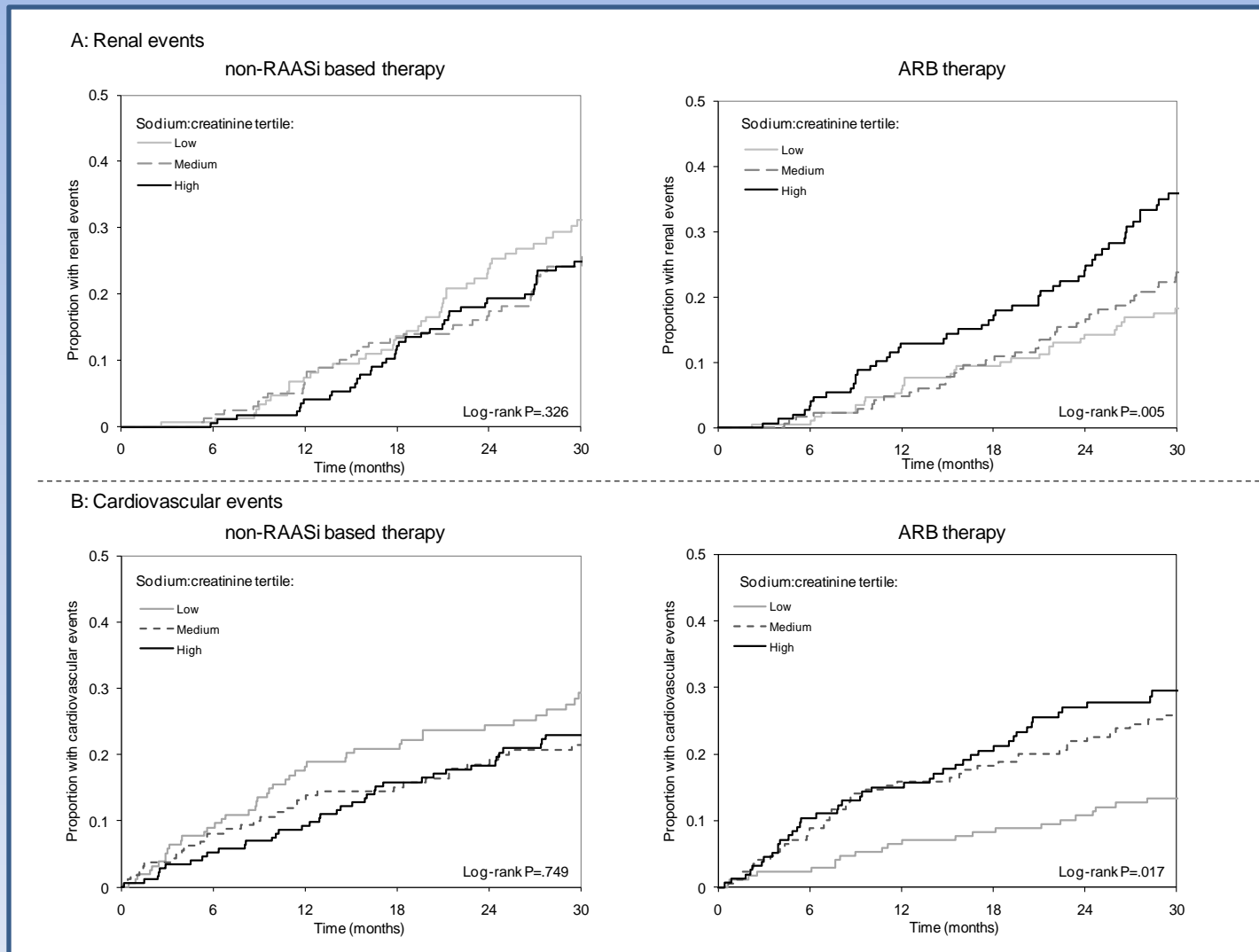
Reduction in proteinuria by moderate salt restriction is partly independent of BP !



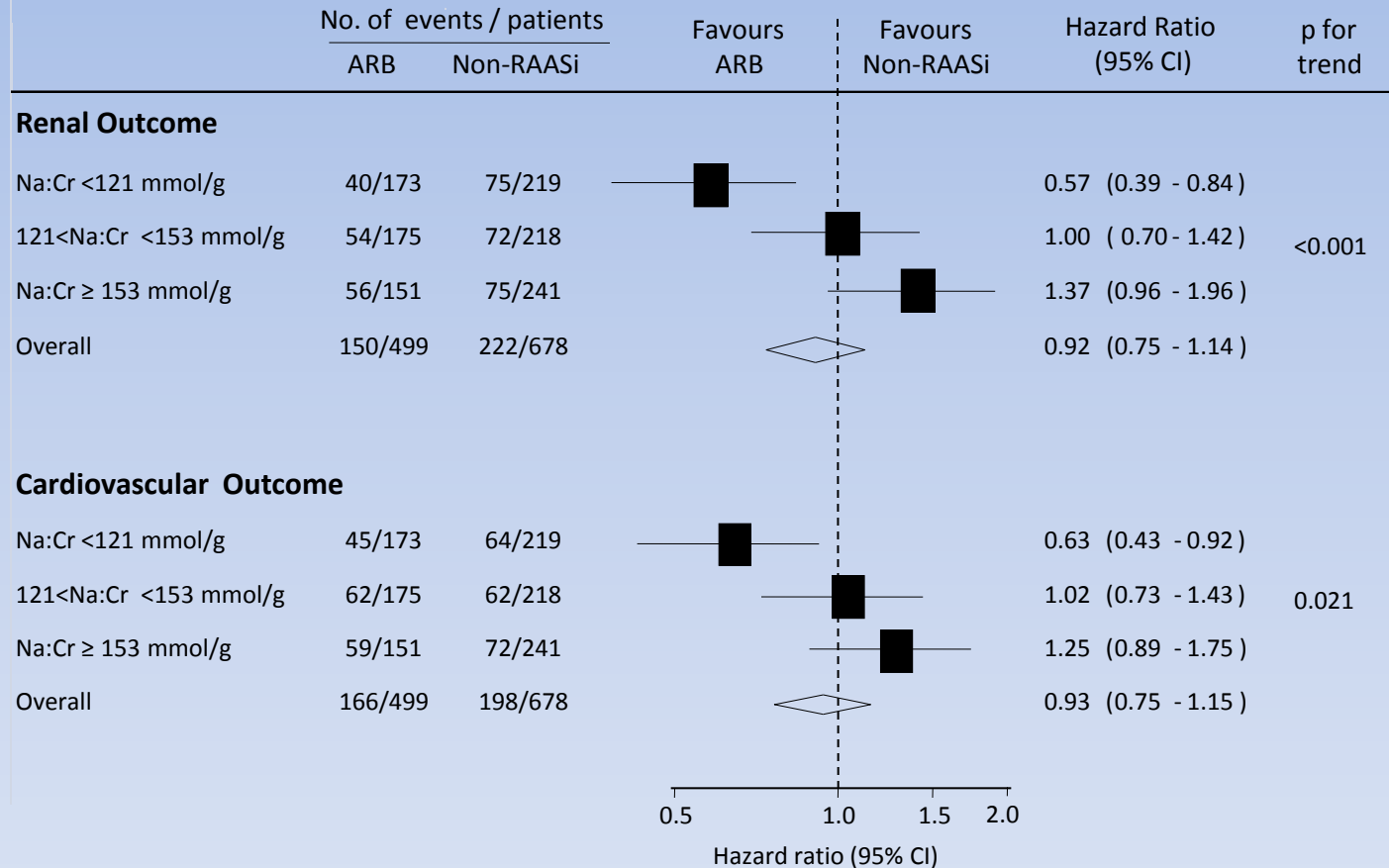
Dietary sodium restriction provides renoprotection beyond blood pressure control !



RENAAL-IDNT: Effect of sodium status on outcome

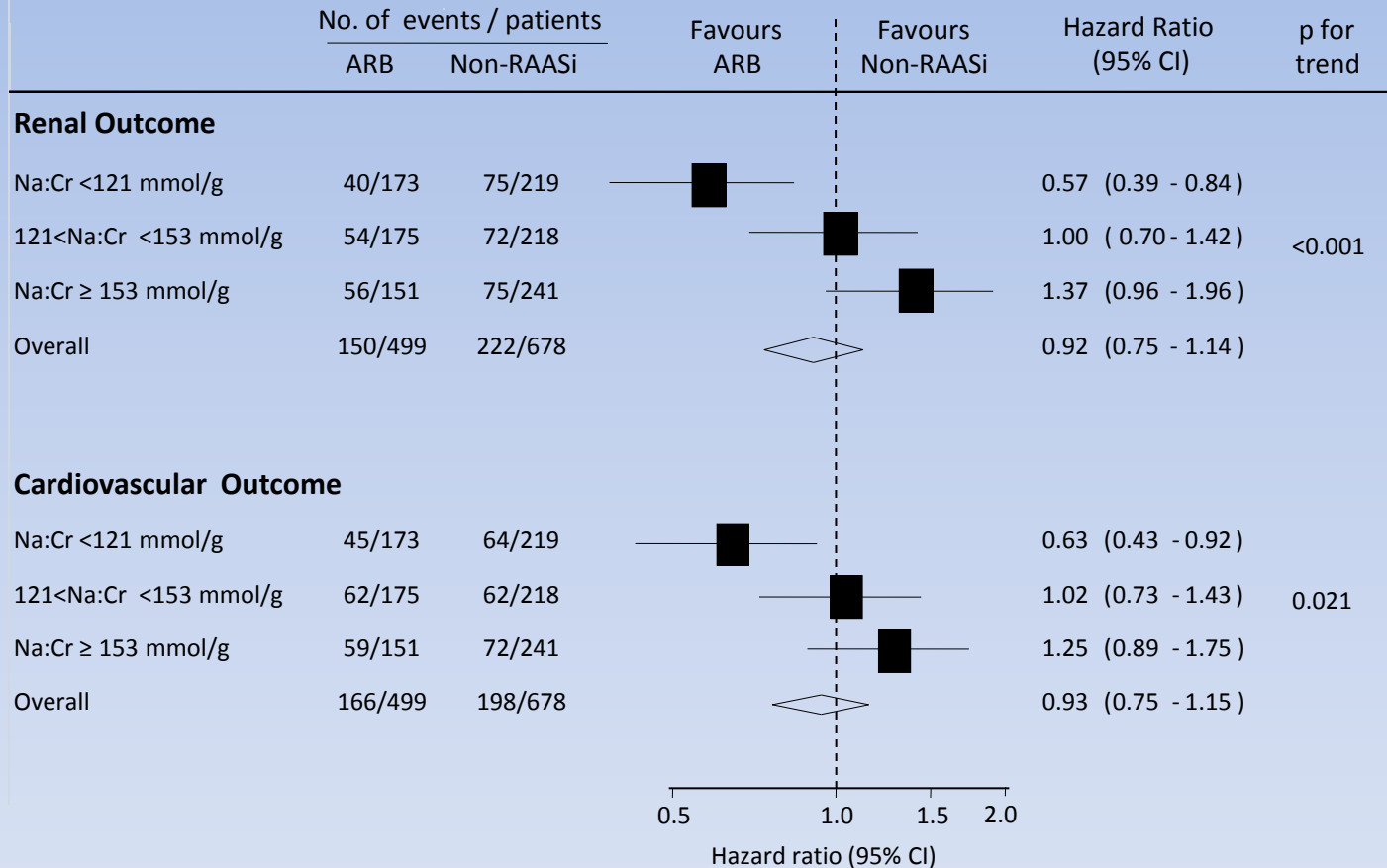


RENAAL-IDNT: salt excess annihilates renal and CV protection by ARB



RENAAL-IDNT: salt excess annihilates renal and CV protection by ARB

UNaV
152/d
179/d
209/d



Resume

The NEW ENGLAND JOURNAL of MEDICINE

Compelling Evidence for Public Health Action to Reduce Salt Intake

Lawrence J. Appel, M.D., M.P.H., and Cheryl A.M. Anderson, Ph.D., M.P.H.

- Modest reduction of dietary salt, towards targets recommended for the general population is associated with substantial benefits in renal patients
- Modest dietary sodium restriction provides renoprotection beyond blood pressure control !
- Use of diuretics does NOT overcome effect of salt excess on hard renal end points
- The beneficial effect of avoiding sodium excess also present in diabetic patients

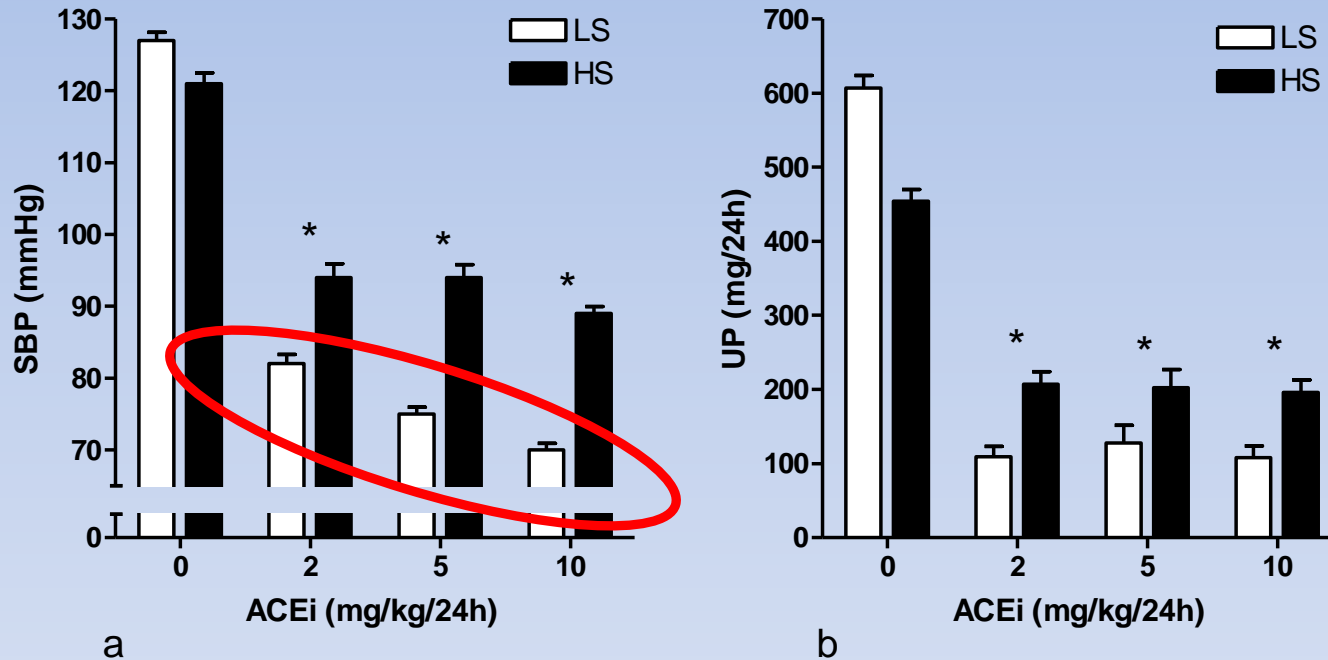
Compelling Evidence for Public Health Action
to Reduce Salt Intake

Lawrence J. Appel, M.D., M.P.H., and Cheryl A.M. Anderson, Ph.D., M.P.H.

Issues to consider

- How low should we go? Can we go *too* low?
- Short term renal function decline : a reason for concern?
- Recent studies claiming that high salt is beneficial
- Feasibility

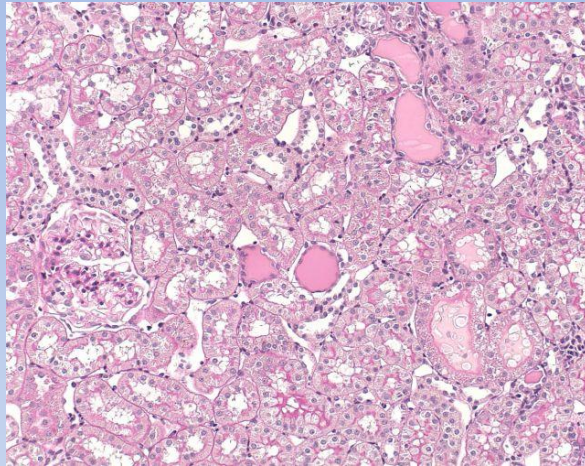
Low sodium diet increases top of dose-response for effects of ACEi on blood pressure and proteinuria



Experimental nephrotic syndrome: lower BP and UP did not translate into better protection against FGS

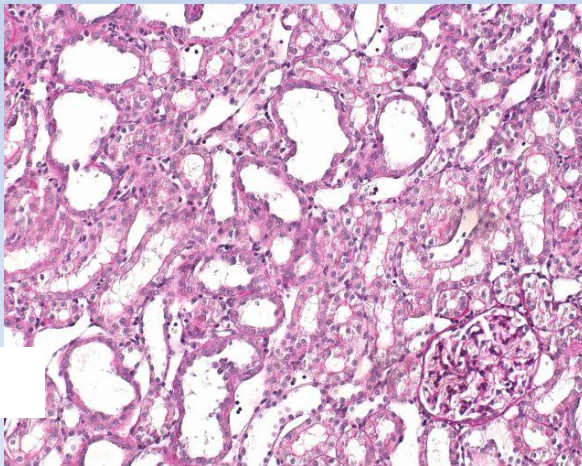
Dissociation of BP & proteinuria from interstitial fibrosis during ACEi-low salt: adriamycin nephrosis

ACEi



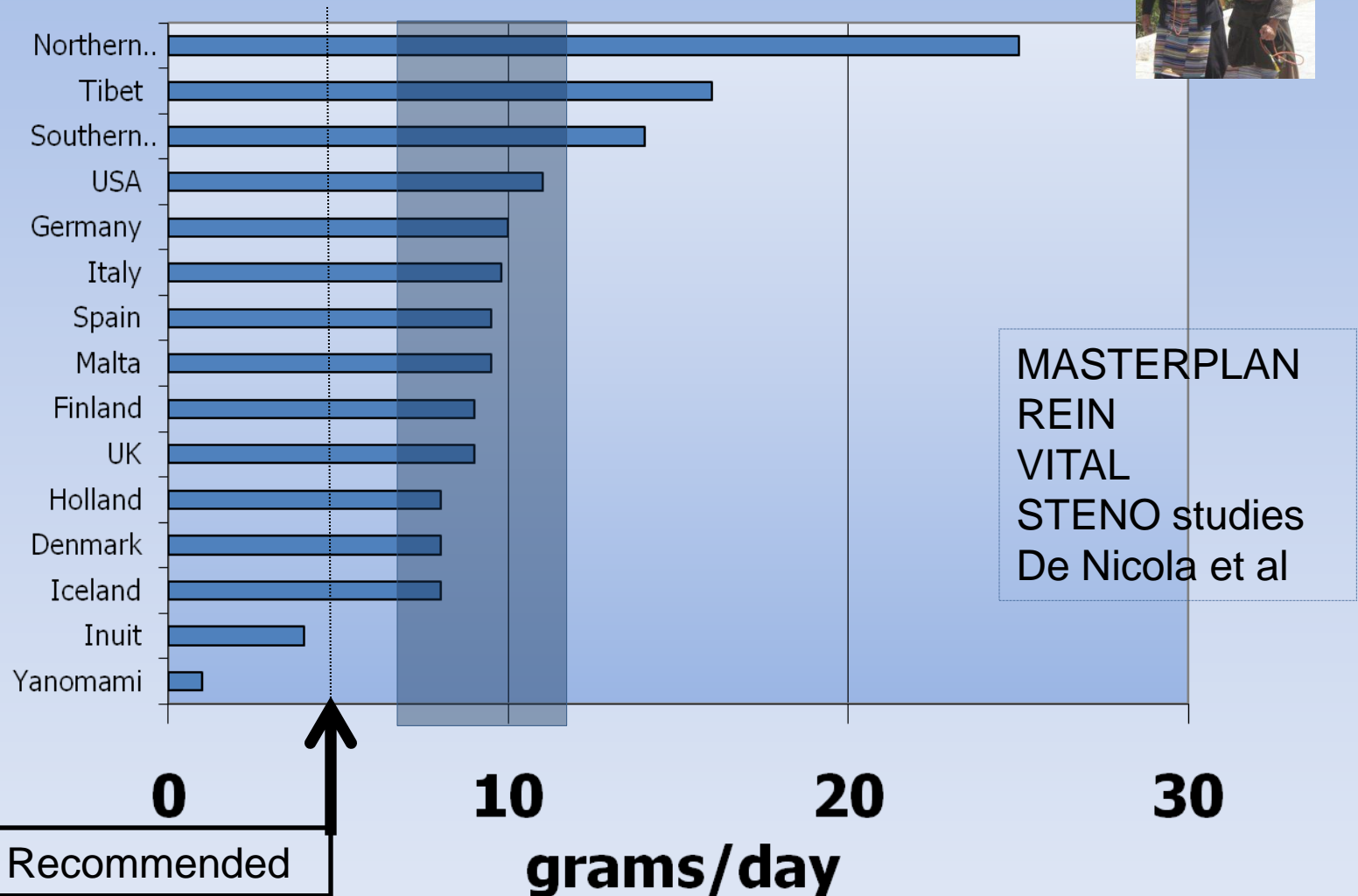
SBP: 111 ± 19 mmHg
UP 350 ± 239 mg/24h
Pcr 4.6 ± 1.3 mg/L
FGS: moderate/severe
IF: moderate

ACEi: low salt

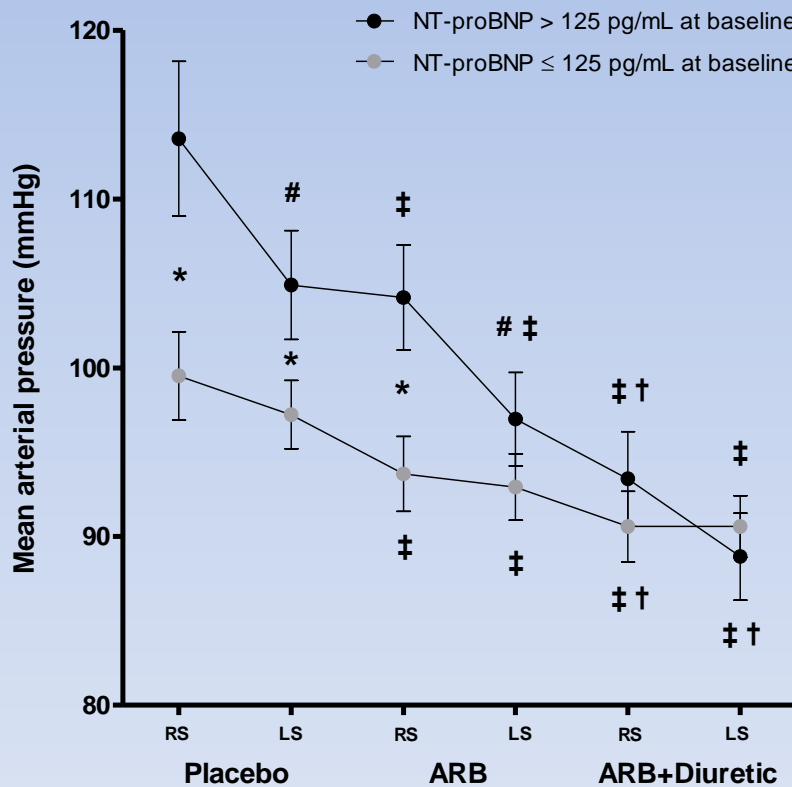


SBP: 102 ± 19 mmHg
UP 48 ± 17 mg/24h
Pcr 4.6 ± 1.4 mg/L
FGS: mild/absent
IF: severe !!!!!

Saltintake from UNaV in CKD cohorts



Volume titration for individual patients: elevated NT-proBNP indicates volume dependency of blood pressure & proteinuria



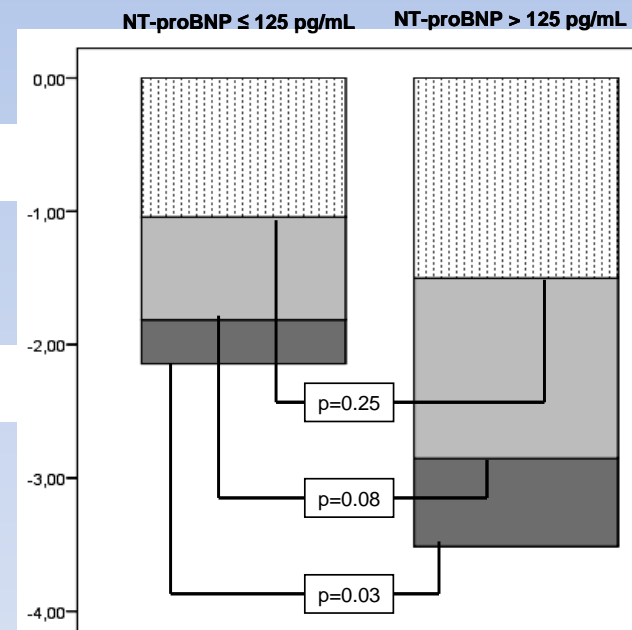
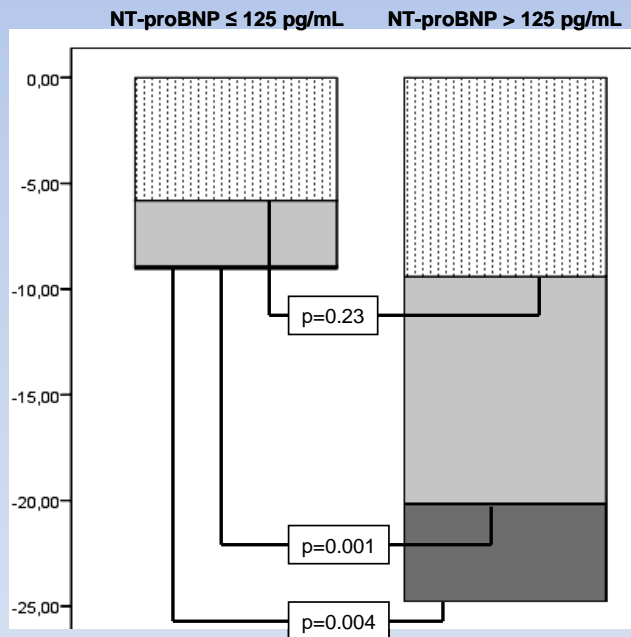
- NT-proBNP above normal predicts benefit of volume intervention in proteinuric CKD


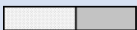
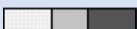
At each titration step elevated NT-proBNP predicts efficacy of volume intervention

Baseline

Mean arterial pressure

Proteinuria



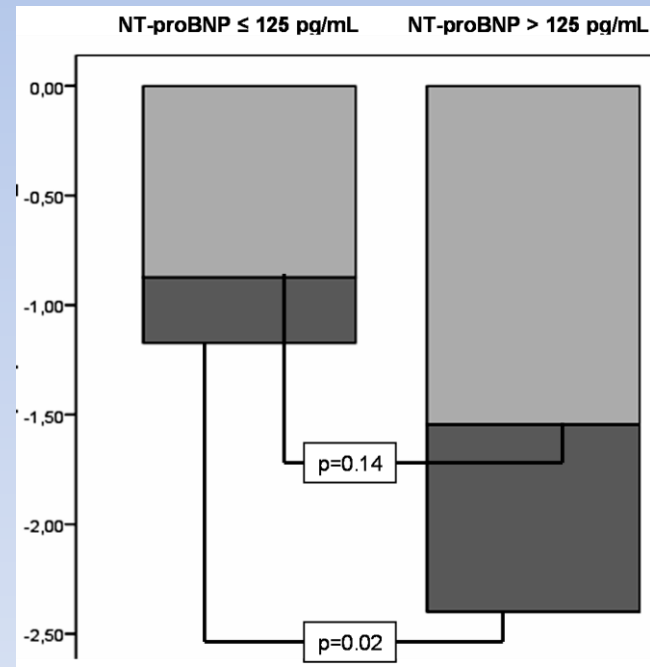
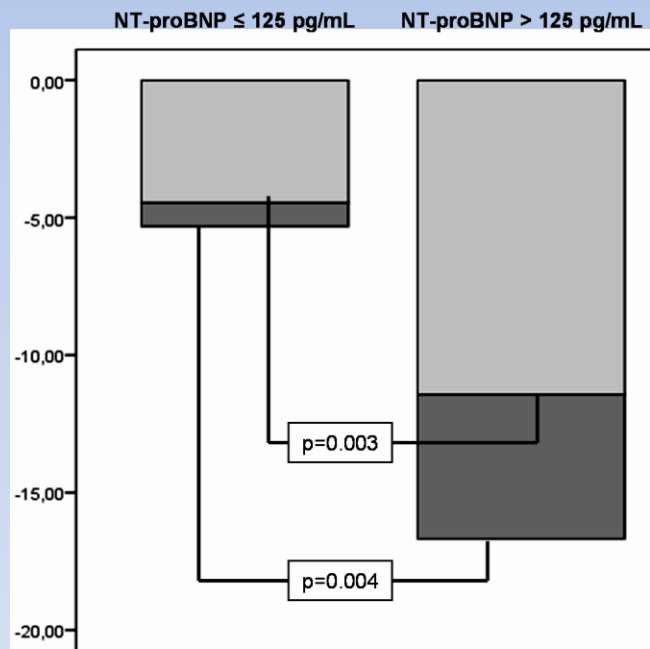
 Change from baseline: effect of ARB
 Change from baseline: effect of ARB + diuretics
 Change from baseline: effect of ARB + diuretics + LS

At each titration step elevated NT-proBNP predicts efficacy of volume intervention

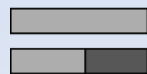
ARB

Mean arterial pressure

Proteinuria



Slagman, NDT, in press



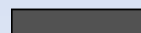
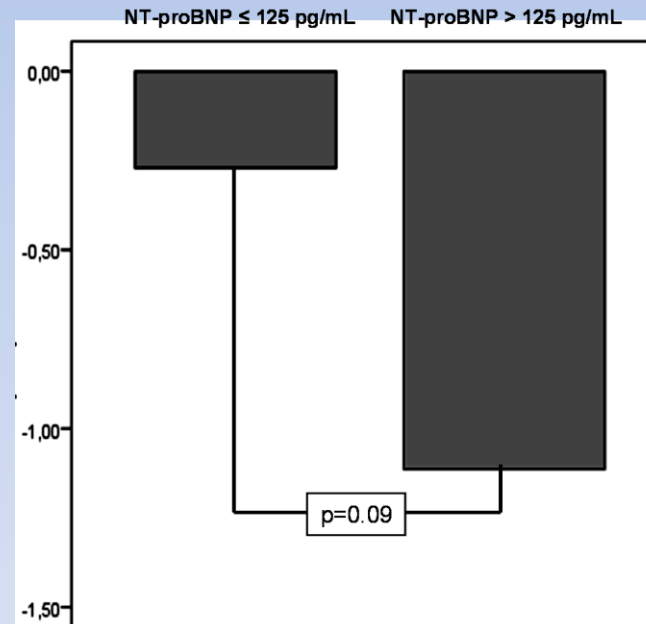
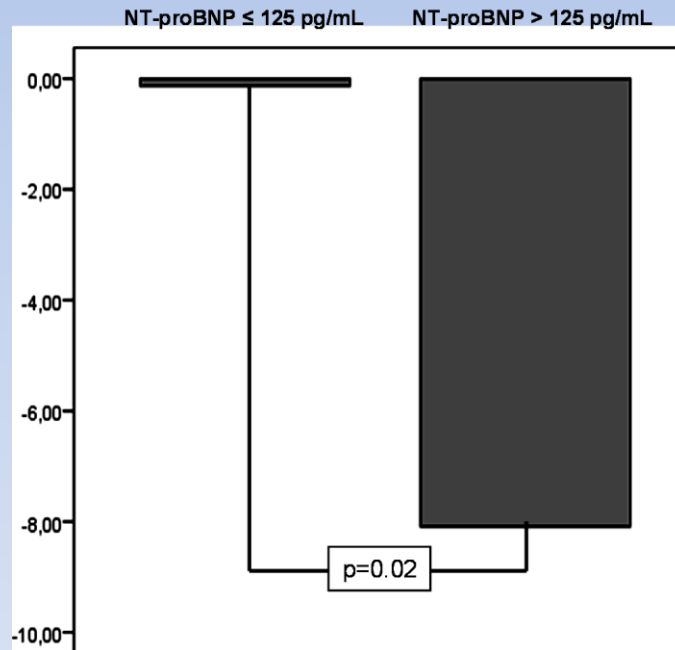
Change from ARB: effect of diuretics
Change from ARB: effect of diuretics + LS

At each titration step elevated NT-proBNP predicts efficacy of volume intervention

ARB + HCT

Mean arterial pressure

Proteinuria



Change from ARB + diuretics: effect of LS

Issues to consider

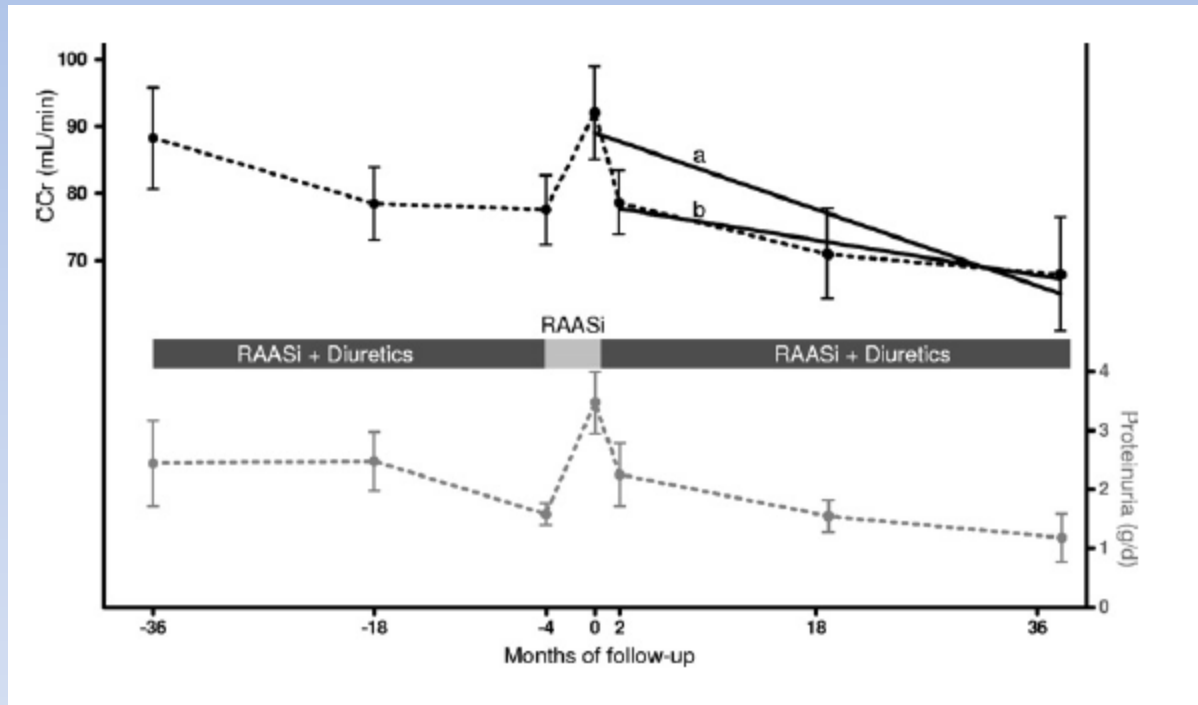
The NEW ENGLAND JOURNAL of MEDICINE

Compelling Evidence for Public Health Action to Reduce Salt Intake

Lawrence J. Appel, M.D., M.P.H., and Cheryl A.M. Anderson, Ph.D., M.P.H.

- How low should we go? Can we go *too* low?
- Short term renal function decline : a reason for concern?
- Recent studies claiming that high salt is beneficial
- Feasibility

Short-term renal function decline by diuretic added to RAASi: reversible and probably protective



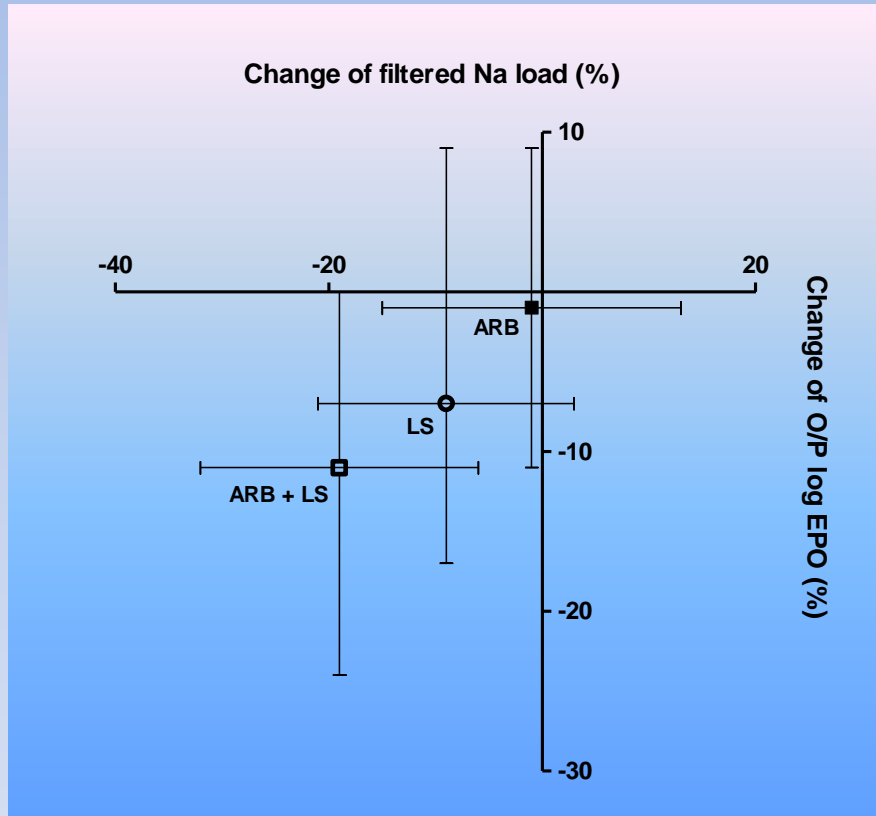
Short term decline GFR at
onset of treatment predicts
long term renoprotection

(apperloo, hansen)

This is interpreted as
alleviation of glomerular
hypertension

Sodium restriction on top of RAASi lowers EPO level in CKD

Marker of alleviated tubular work-load?



Short term decline GFR at onset of treatment predicts long term renoprotection
(*apperloo, hansen*)

This is interpreted as alleviation of glomerular hypertension

Of note, it also results in reduction of tubular work-load and improved renal oxygen status !

Issues to consider

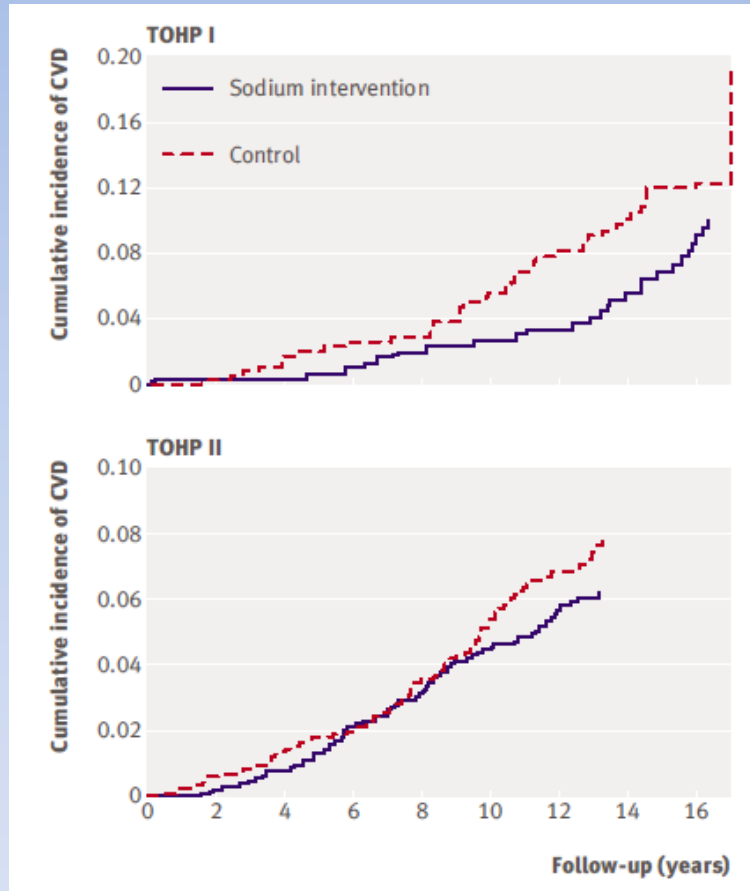
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Compelling Evidence for Public Health Action to Reduce Salt Intake

Lawrence J. Appel, M.D., M.P.H., and Cheryl A.M. Anderson, Ph.D., M.P.H.

- How low should we go? Can we go *too* low?
- Short-term renal function decline – a reason for concern?
- Recent studies claiming that high salt is beneficial
- Confounding by “indication”
- Do not consider therapy effects
- Should NOT be extrapolated to renal patients

Effect reduction in salt intake on hard end points:



TOHP I and TOHP II
744 and 2382 pre-hypertensives
Counseling for salt restriction
(18 & 36-48 mo)

Reduction UNaV by 44 and 33
mmol/day, from baseline 155 and
182

BMI: 27,1 and 30.9
(90% > 25)

25 % reduction long time CV
events.

Issues to consider

The NEW ENGLAND JOURNAL of MEDICINE

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- How low should we go? Can we go *too* low?
- Short term renal function decline – a reason for concern?
- Recent studies claiming that high salt is beneficial
- **Feasibility**
 - Has been proven in TOPH in primary care settings
 - Has been proven in outpatient nephrology settings
 - 24h urine provides unbiased measure of sodium intake: this helps to improve dietary habits (and overcome poor food labelling)
 - Should never be an excuse !

Compelling Evidence for Public Health Action to Reduce Salt Intake

Lawrence J. Appel, M.D., M.P.H., and Cheryl A.M. Anderson, Ph.D., M.P.H.

Projected Effect of Dietary Salt Reductions on Future Cardiovascular Disease

Kirsten Bibbins-Domingo, Ph.D., M.D., Glenn M. Chertow, M.D., M.P.H.,
Pamela G. Coxson, Ph.D., Andrew Moran, M.D., James M. Lightwood, Ph.D.,
Mark J. Pletcher, M.D., M.P.H., and Lee Goldman, M.D., M.P.H.

Annals of Internal Medicine

ARTICLE

Population Strategies to Decrease Sodium Intake and the Burden of Cardiovascular Disease

A Cost-Effectiveness Analysis

Crystal M. Smith-Spangler, MD; Jessie L. Jusuola, MS; Eva A. Enns, MS; Douglas K. Owens, MD, MS; and Alan M. Garber, MD, PhD

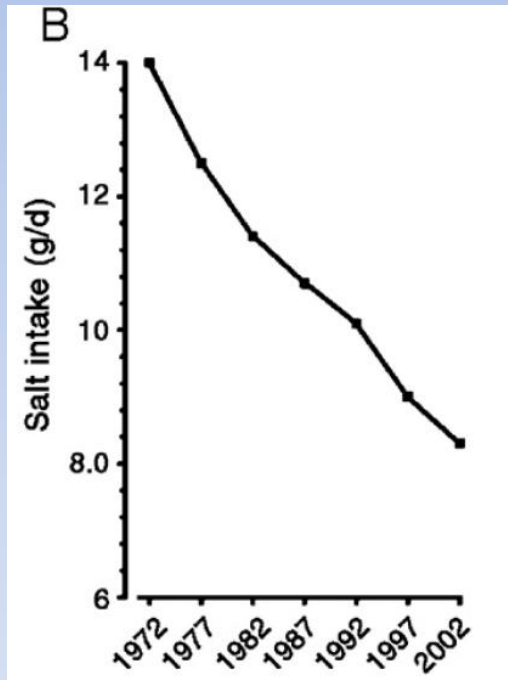
Reducing Dietary Sodium The Case for Caution

Michael H. Alderman, MD

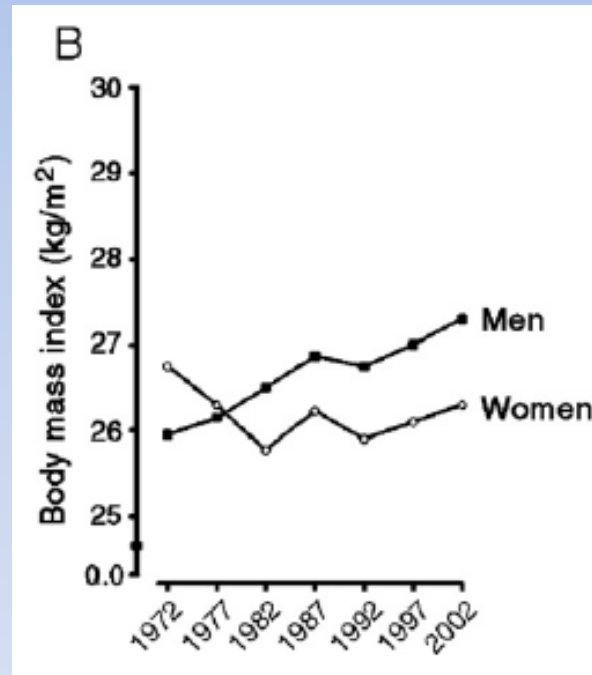
though applica
relevance. How

Global lifestyle improvement the Finnish Experience

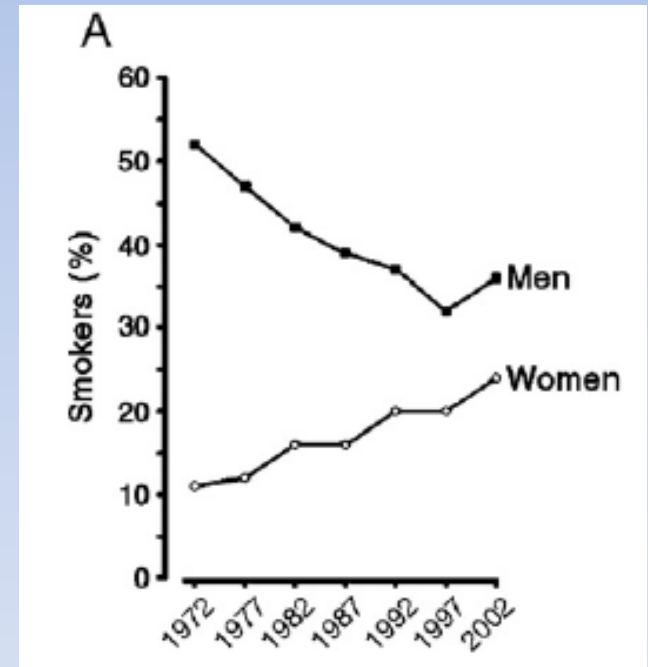
Salt



BMI

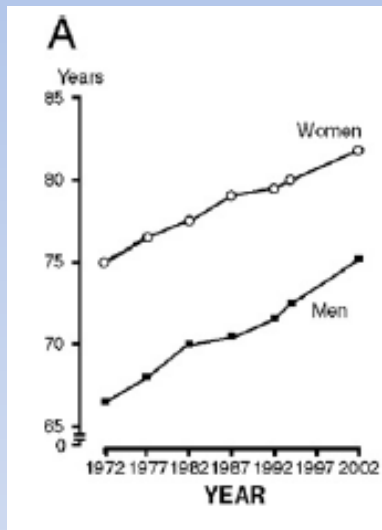


Smoking

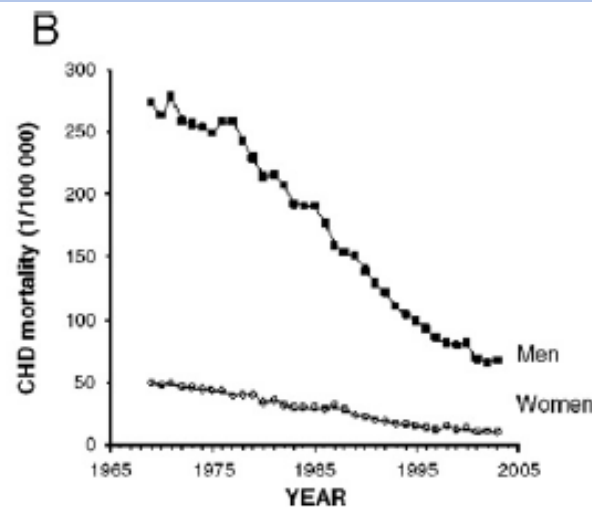


Global lifestyle improvement the Finnish Experience

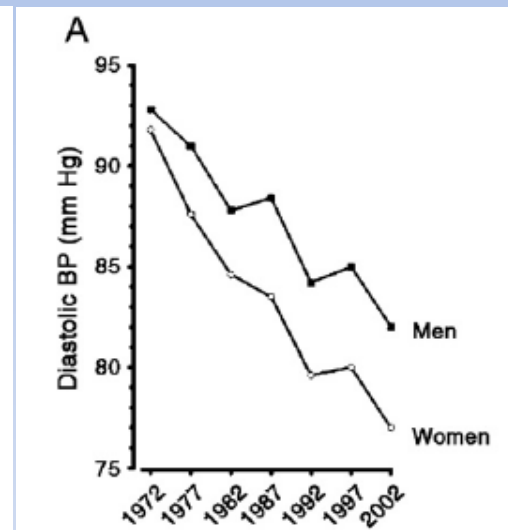
Life expectancy



CHD mortality



Blood pressure



HEALTH BENEFITS

Call for action !

- Better salt awareness is a must !
- Modest reduction dietary salt is already associated with substantial benefits in renal patients, including diabetics
- Nephrologists should take a lead in the combat against salt excess!
- Counsel & support individual patients
- Target government and industry
- Conduct hard end point trials!

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