IPERURICEMIA E PROGRESSIONE DEL DANNO RENALE

Gherardo Buccianti

ASPREMARE - FONDAZIONE BUCCIANTI

Ospedale Metropolitano Niguarda - Milano

Ivano Baragetti

DIVISIONE DI NEFROLOGIA E DIALISI

Ospedale Bassini - ASST NORD Milano

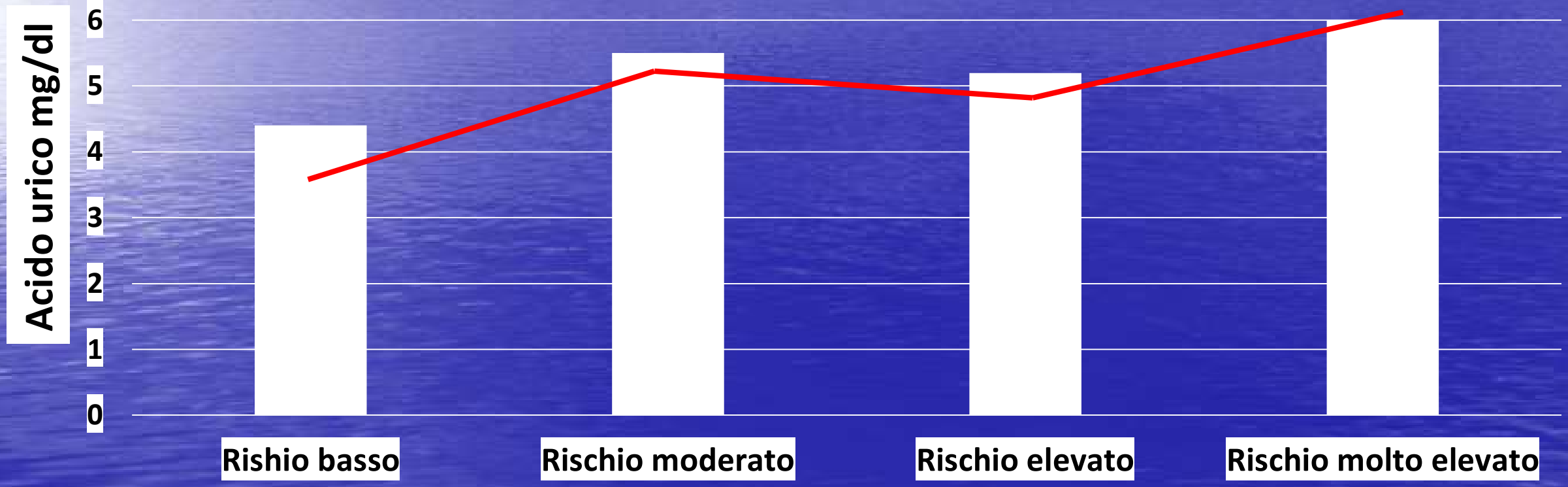
ASPREMARE - FONDAZIONE BUCCIANTI

Ospedale Metropolitano Niguarda - Milano

Milano 02-12-2016

Grassi G et al. Blood pressure control and cardiovascular risk profile in hypertensive patients from central and eastern european countries: results from the BP-CARE study. Eur Jeart J 2011.

Ipertensione arteriosa, Eventi cardiovascolari, Diabete, Sindrome metabolica, Dislipidemia, Fumo, Insufficienza renale cronica, Danno d'organo subclinico, IVS, Fibrillazione atriale, scompenso cardiaco, eventi cerebrovascolari



In base alla stratificazione del rischio CV delle ESH e ESC (Mancia G et al. J Hypertens 2007)

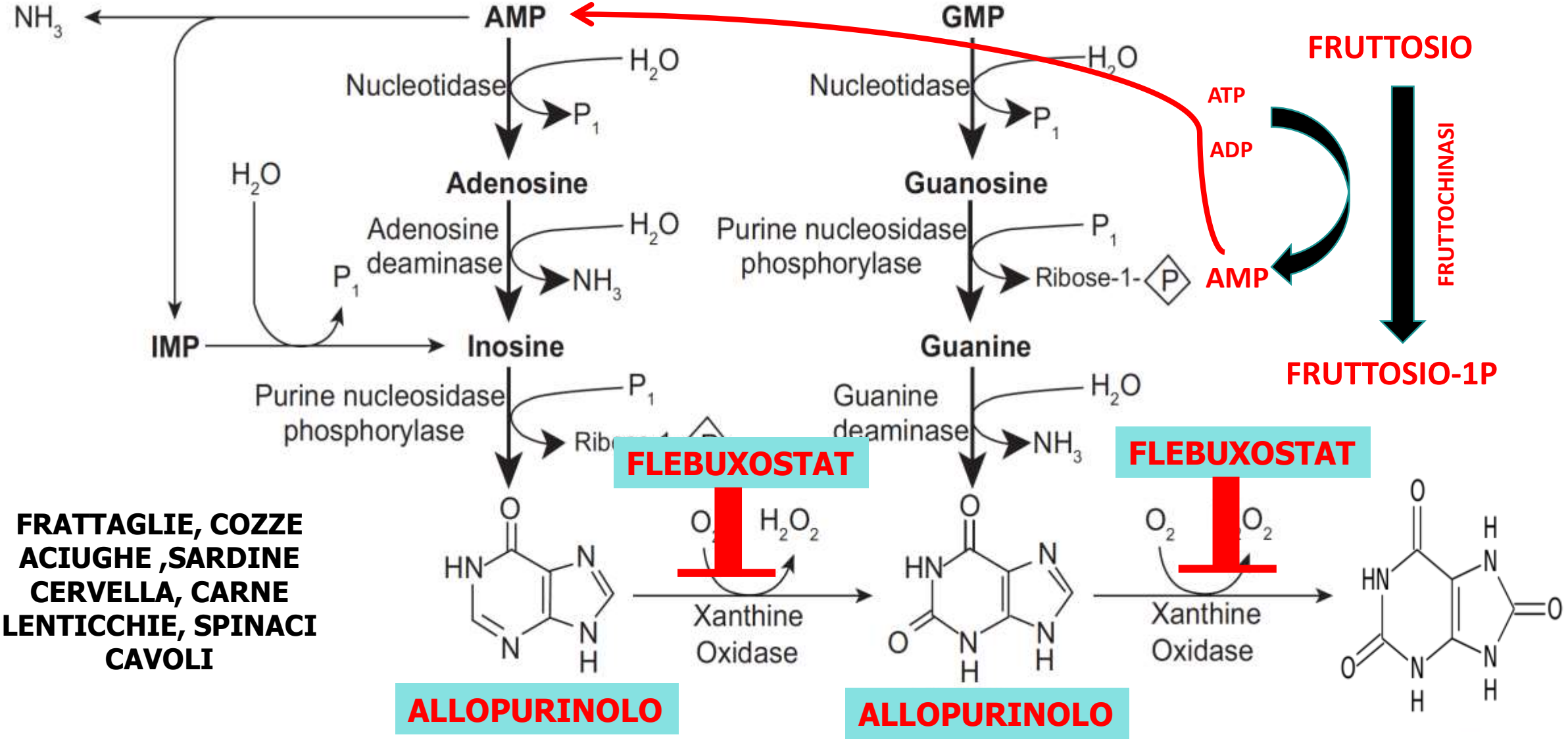
- **Ha un ruolo causale sul rischiocardiovascolare globale e sulla disfunzione renale?**

- **Con quali meccanismi?**

METABOLISMO DELL'ACIDO URICO

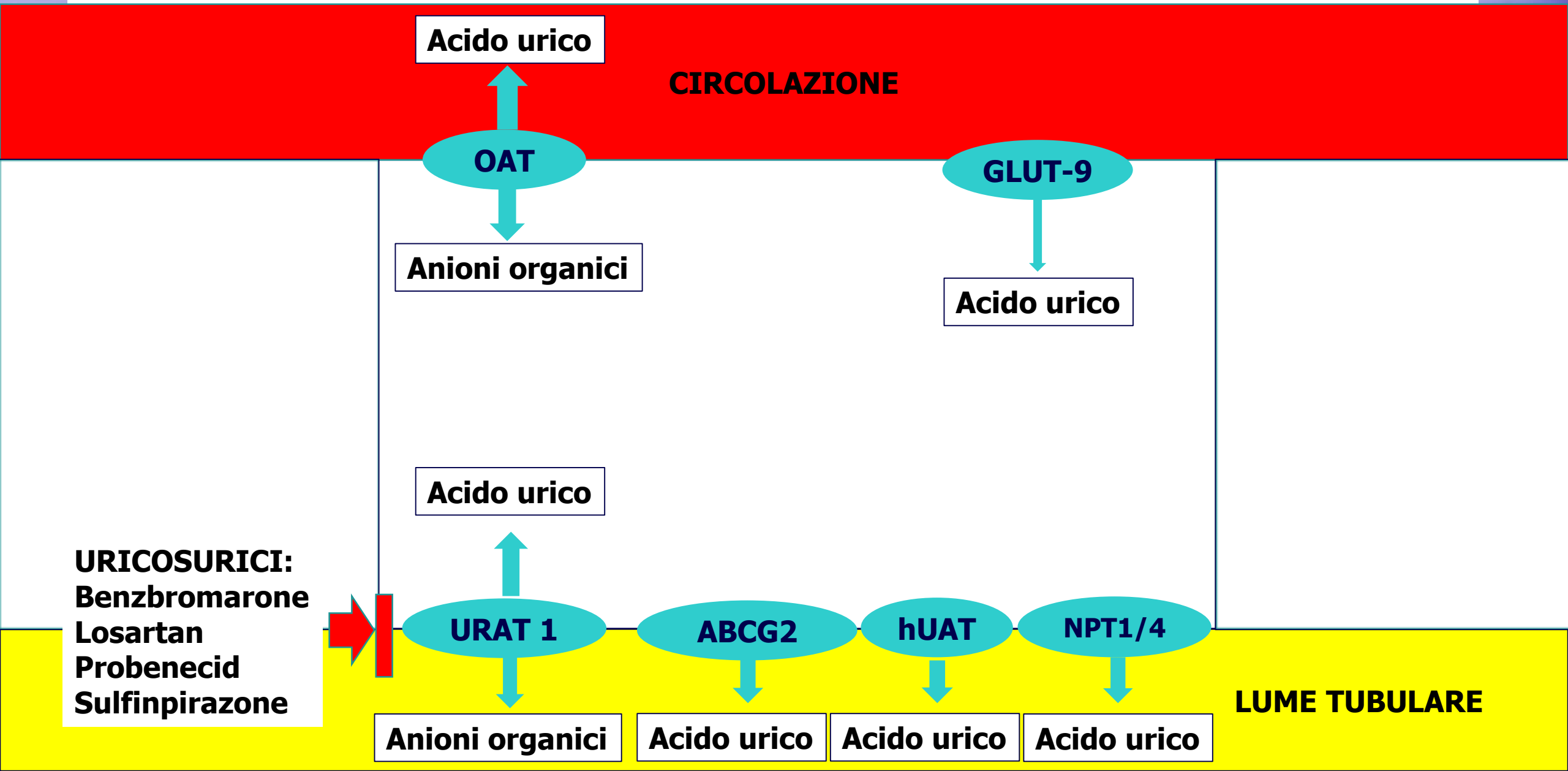
ZUCCHERO, BIBITE
FRUTTA, MIELE
UVA PASSA
DATTERI
FICHI SECCHI

ALCOLICI, BIRRA



FRATTAGLIE, COZZE
ACIUGHE ,SARDINE
CERVELLA, CARNE
LENTICCHIE, SPINACI
CAVOLI

Handling tubulare dell'acido urico



URICEMIA E SINDROME METABOLICA

Johnson et al. Sugar, uric acid, and the etiology of diabetes and obesity. Diabetes 2013

-Stimolo della fruttochinasi

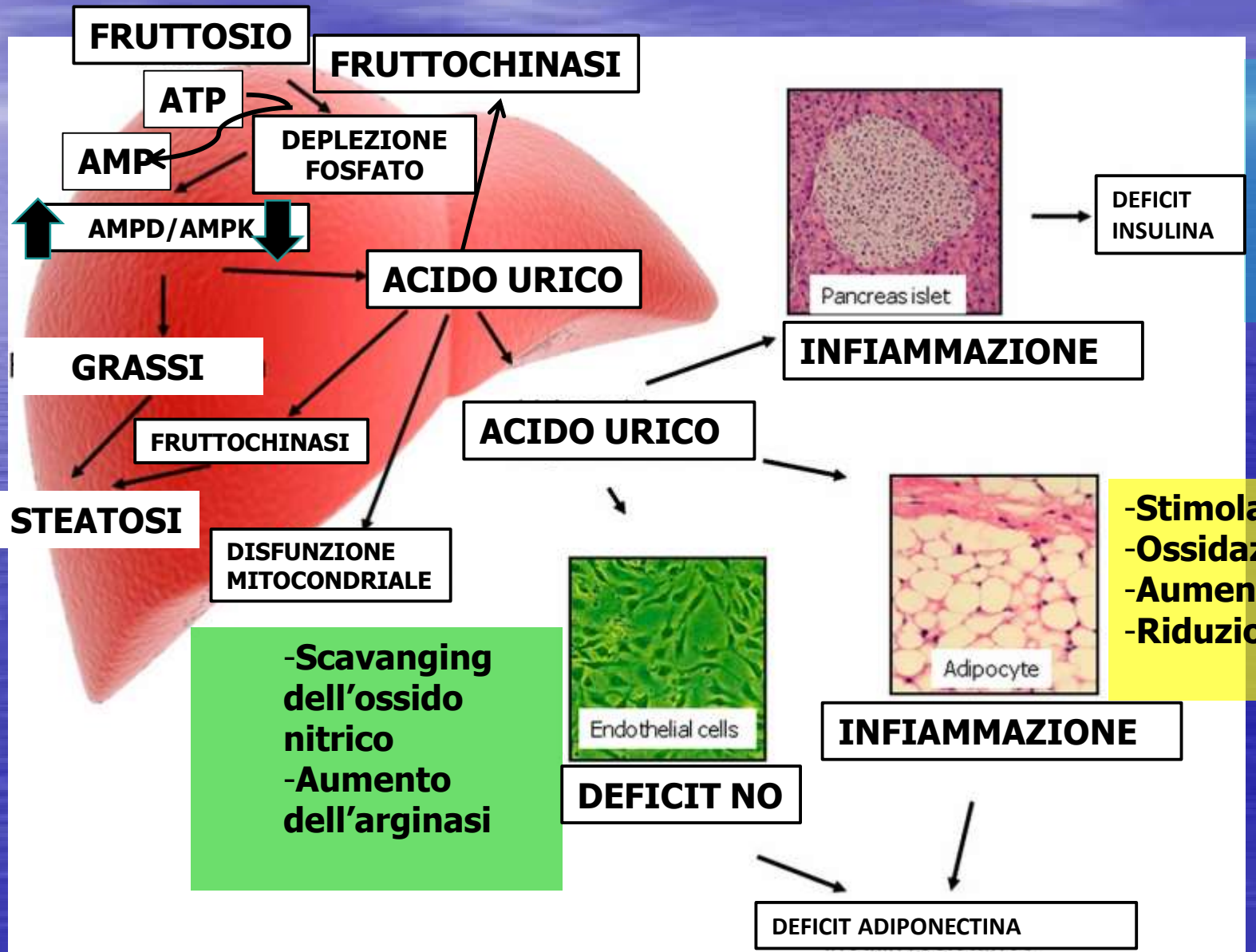
-Stimola la NADPH ossidasi, stress ossidativo

-Aumento NF-kB ed MCP-1

-Riduzione mitocondriale dell'aconitasi-2

-Accumulo di citrato

-Accumulo di trigliceridi



- Stress Ossidativo
-Aumento NF-Kb e dell'MCP-1
-Riduzione produzione di insulina

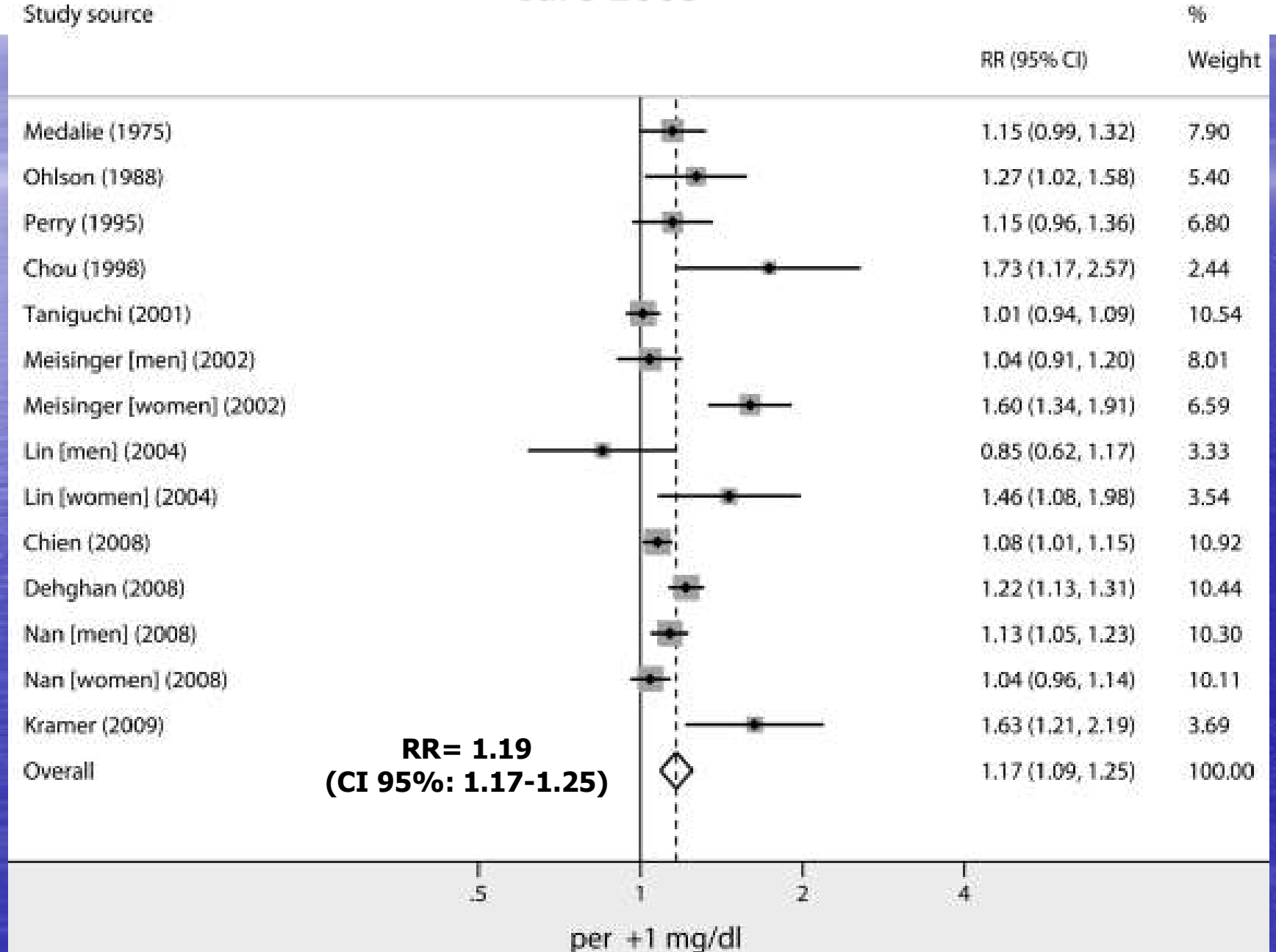
-Stimola la NADPH ossidasi
-Ossidazione lipidica
-Aumento dell'MCP-1 e NF-kB
-Riduzione dell'adiponectina

Kodama S. Association between serum uric acid and development of type 2 diabetes. Diabetes Care 2009

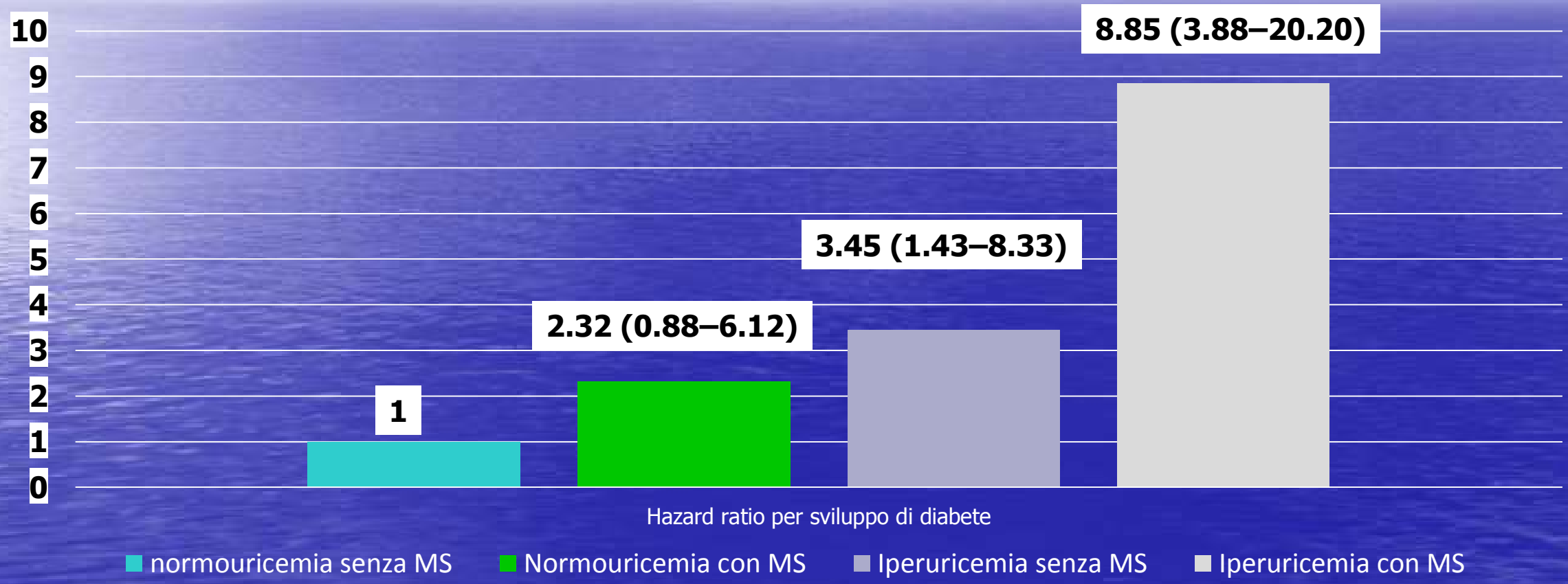
Follow-up: 2- 13,5 anni

N° soggetti: 161- 8.688 TOT= 43.834

Casi incidenti di diabete: 3.305

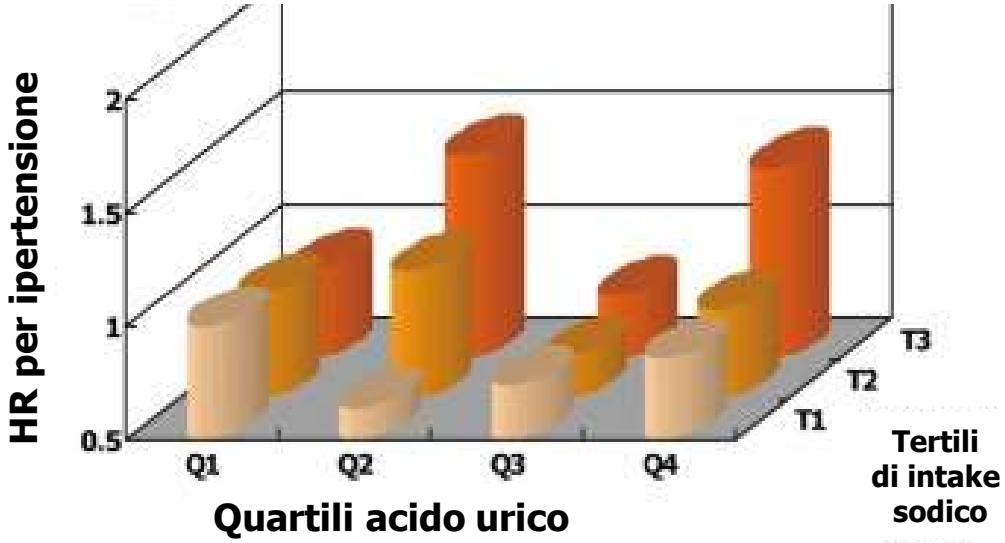


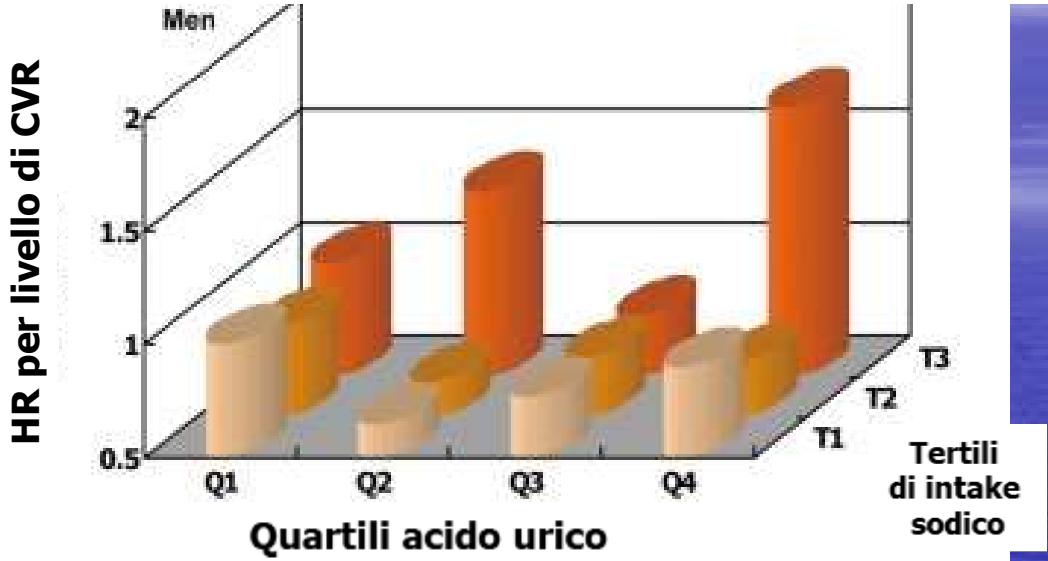
Viazzi F et al. Serum Uric Acid Levels Predict New-Onset Type 2 Diabetes in Hospitalized Patients With Primary Hypertension: The MAGIC Study. Diabetes Care 2011



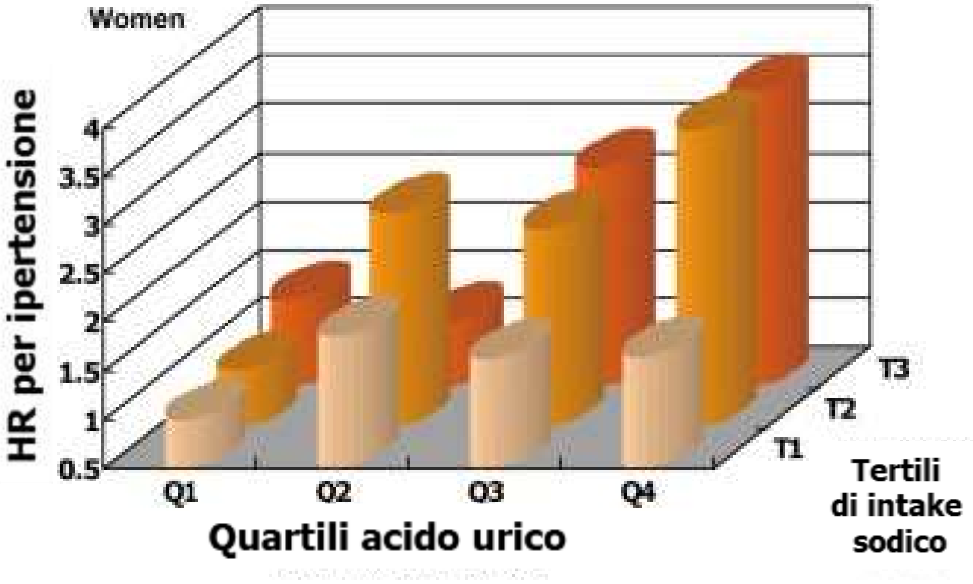
758 Pazienti ipertesi non trattati, follow up 11 anni

Hou L. et al. Influence of Salt Intake on Association of Blood Uric Acid with Hypertension and Related Cardiovascular Risk. Plos One 2016

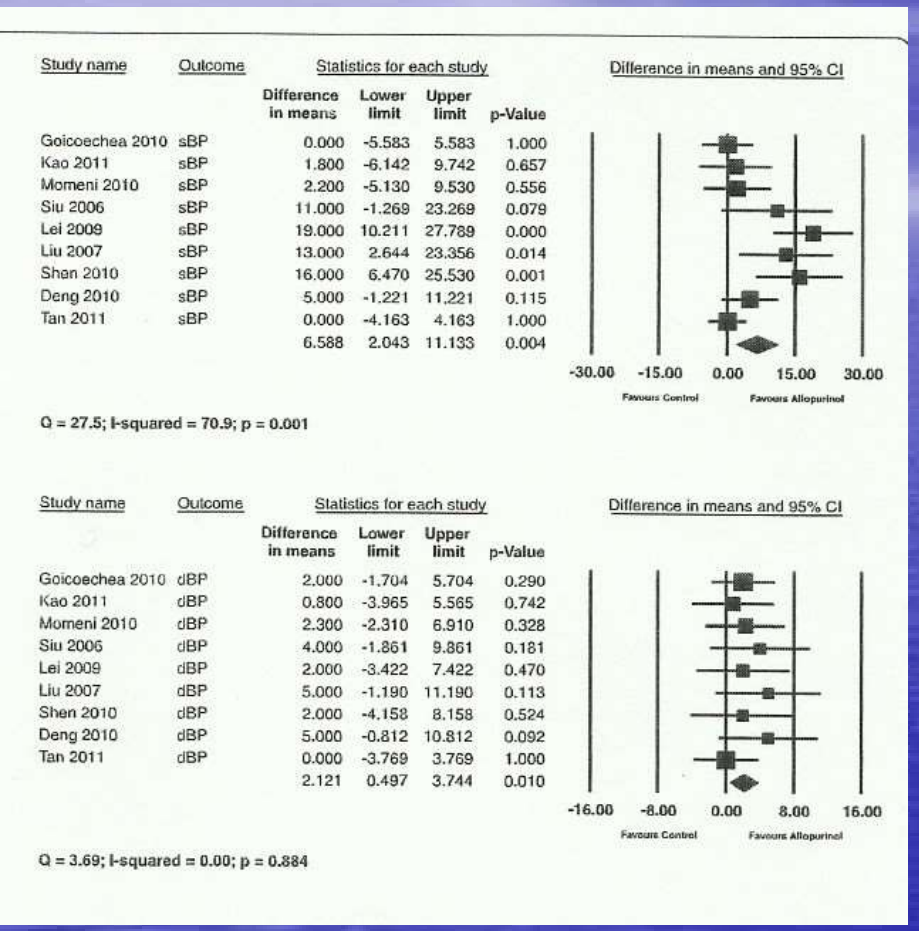




1805 soggetti, studio trasversale



Kanji T etal. Urate lowering therapy to improve renal outcomes in patients with chronic kidney disease: systematic review and meta-analysis. BMC Nephrology 2015.



Study name	Outcome	Difference in means	Lower limit	Upper limit	p-Value
Goicoechea 2010	sBP	0.000	-5.583	5.583	1.000
Kao 2011	sBP	1.800	-6.142	9.742	0.657
Momeni 2010	sBP	2.200	-5.130	9.530	0.556
Siu 2006	sBP	11.000	-1.269	23.269	0.079
Lei 2009	sBP	19.000	10.211	27.789	0.000
Liu 2007	sBP	13.000	2.644	23.356	0.014
Shen 2010	sBP	16.000	6.470	25.530	0.001
Deng 2010	sBP	5.000	-1.221	11.221	0.115
Tan 2011	sBP	0.000	-4.163	4.163	1.000
		6.588	2.043	11.133	0.004

Difference in means and 95% CI

-30.00 -15.00 0.00 15.00 30.00

Favours Control Favours Allopurinol

Q = 27.5; I-squared = 70.9; p = 0.001

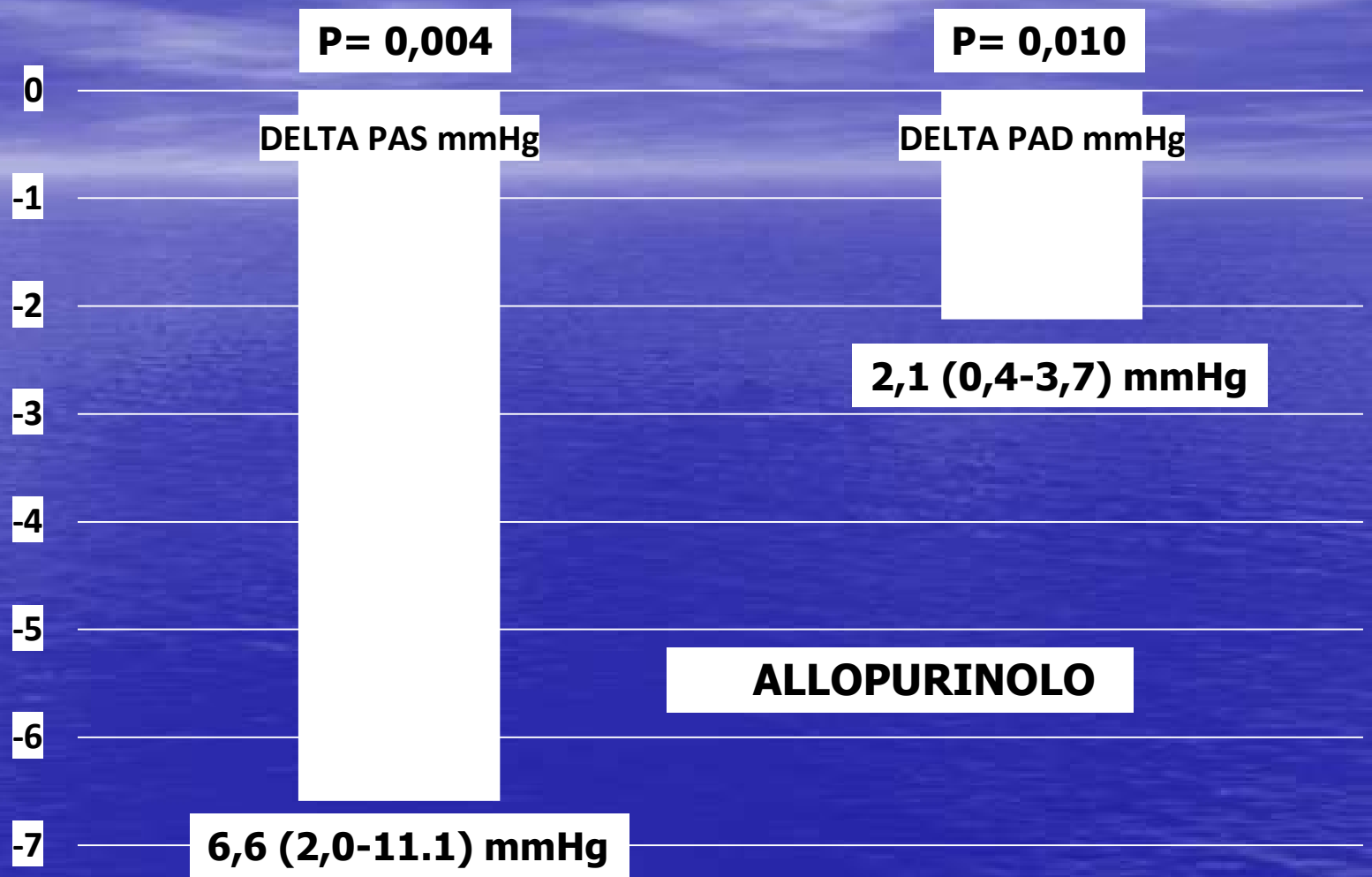
Study name	Outcome	Difference in means	Lower limit	Upper limit	p-Value
Goicoechea 2010	dBP	2.000	-1.704	5.704	0.290
Kao 2011	dBP	0.800	-3.965	5.565	0.742
Momeni 2010	dBP	2.300	-2.310	6.910	0.328
Siu 2006	dBP	4.000	-1.861	9.861	0.181
Lei 2009	dBP	2.000	-3.422	7.422	0.470
Liu 2007	dBP	5.000	-1.190	11.190	0.113
Shen 2010	dBP	2.000	-4.158	8.158	0.524
Deng 2010	dBP	5.000	-0.812	10.812	0.092
Tan 2011	dBP	0.000	-3.769	3.769	1.000
		2.121	0.497	3.744	0.010

Difference in means and 95% CI

-16.00 -8.00 0.00 8.00 16.00

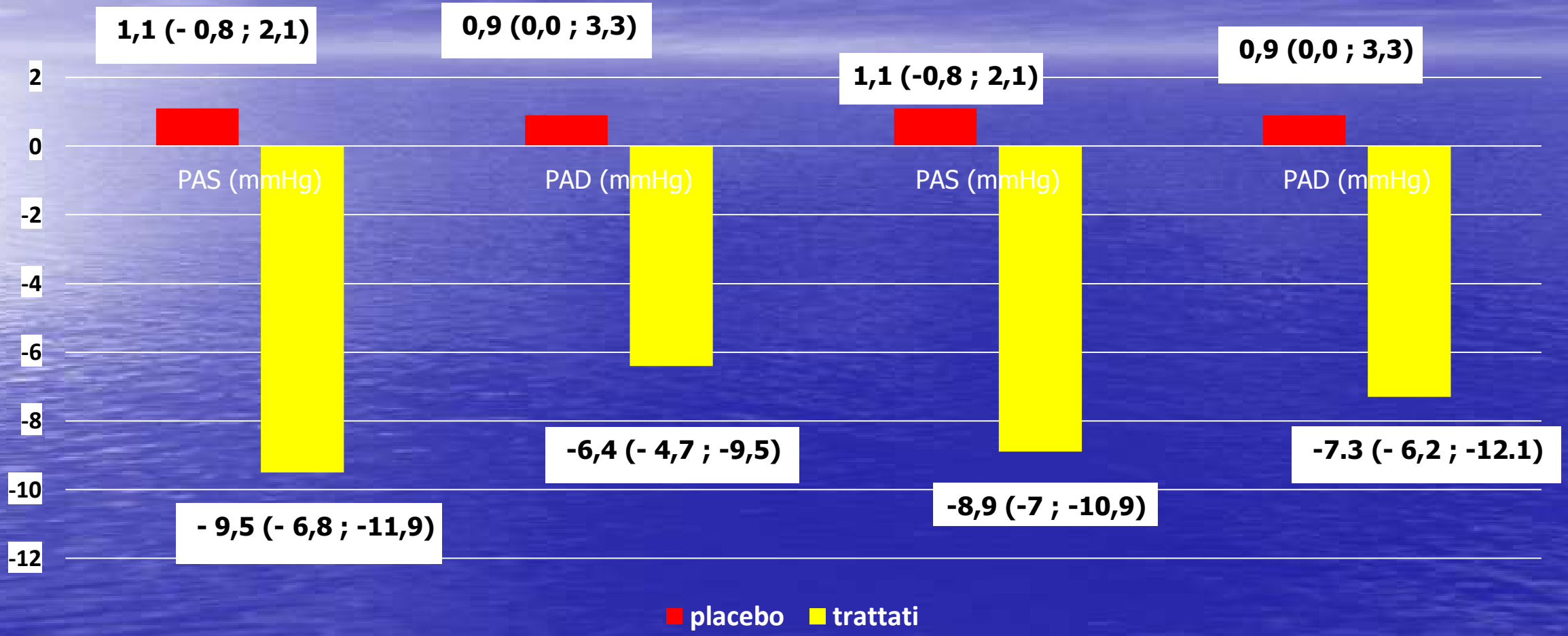
Favours Control Favours Allopurinol

Q = 3.69; I-squared = 0.00; p = 0.884



19 studi pubblicati tra il 1998 e il 2012, 992 pazienti, follow-up > 3 mesi, 16 controllati e 3 in cross-over
Trattamento con Allopurinolo, Flebuxostat, Benzbromarone, Probenecid e sulfinpirazone

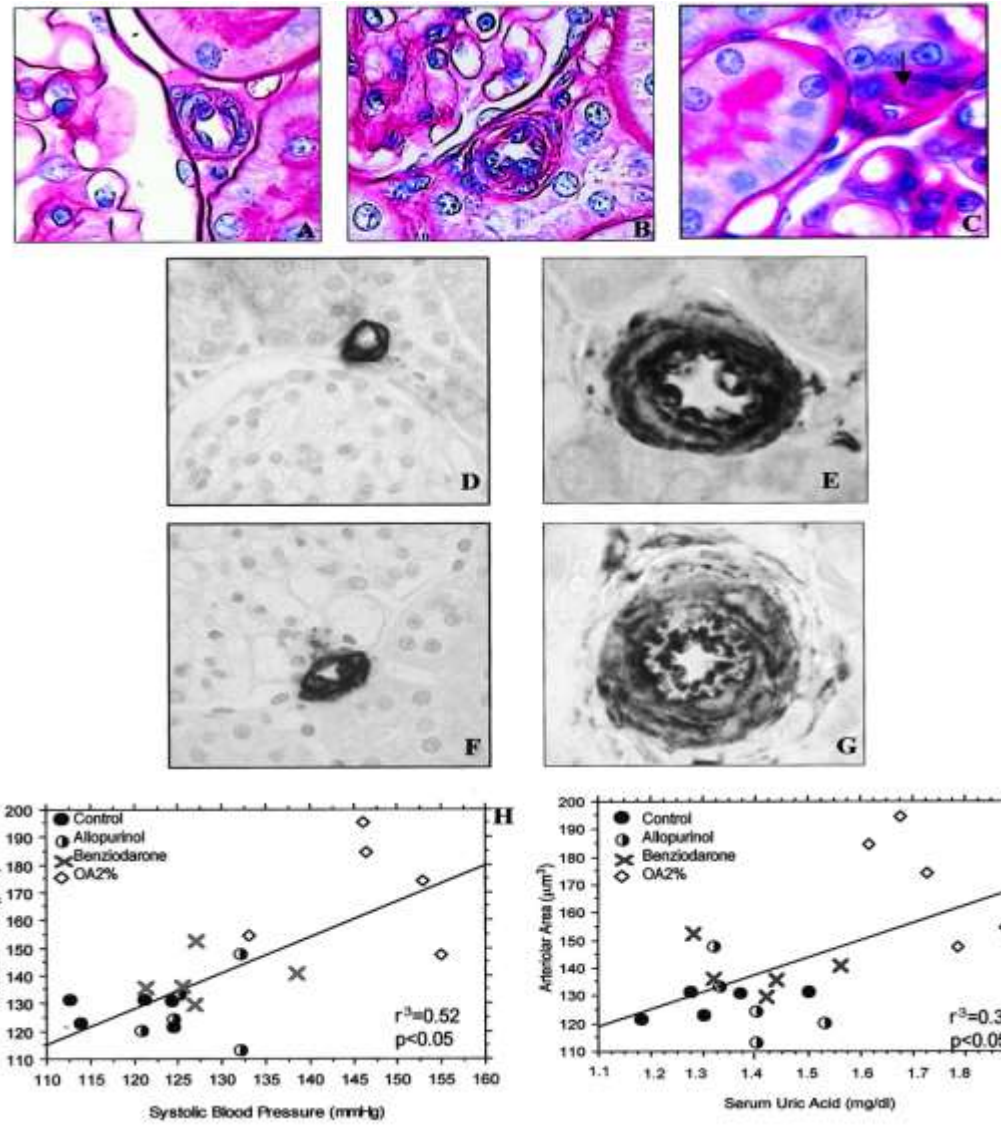
Soletsky B et al. Uric acid reduction rectifies pre-hypertension in obese adolescents. Hypertension 2012.

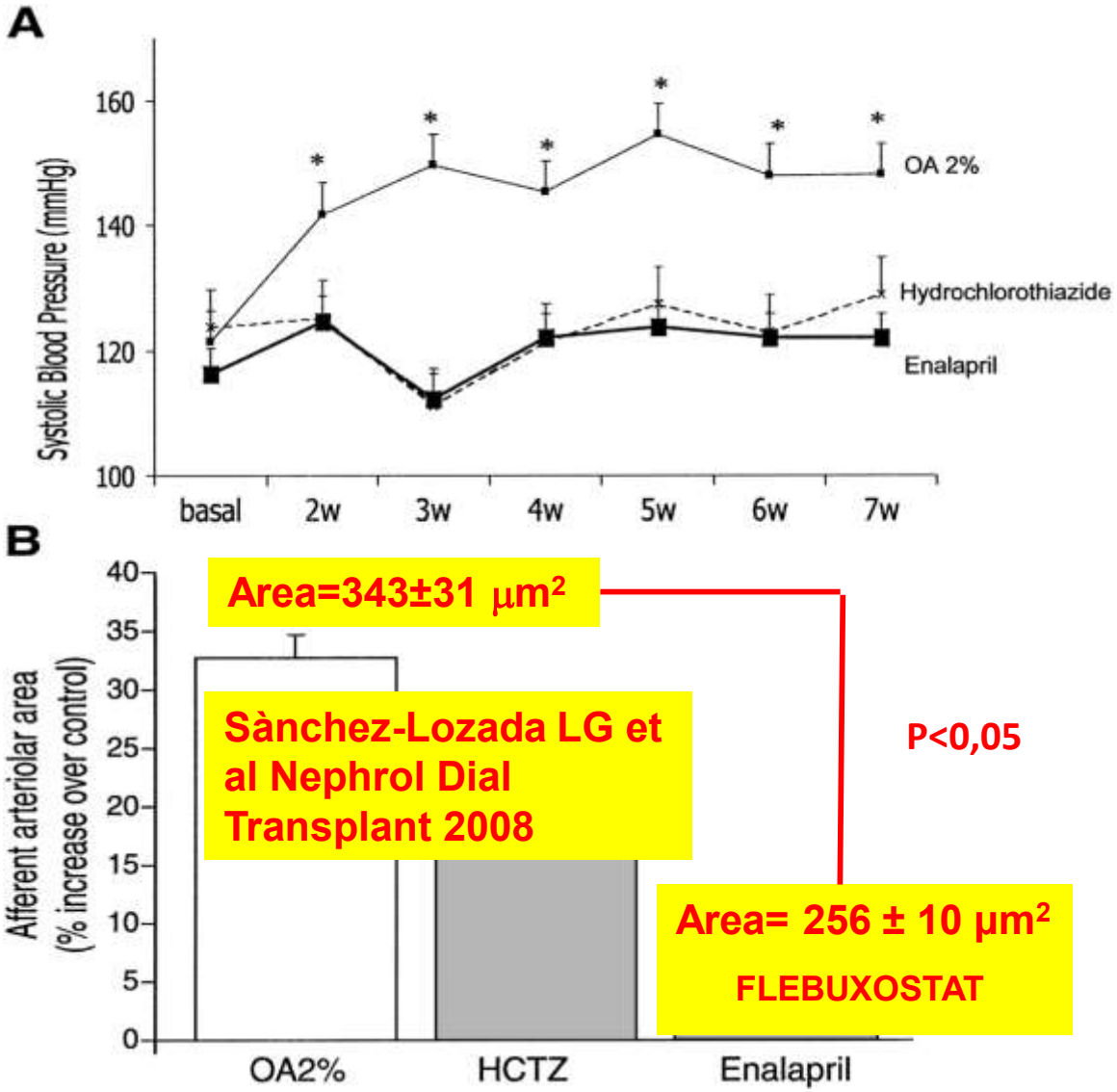


60 pazienti (età media 14,3 anni, obesi e pre-ipertesi): 20 placebo, 20 in allopurinolo e 20 in Probenecid

Mazzali M.et al. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol 2002.

Perdita dell'autoregolazione, ipertensione glomerulare, albuminuria

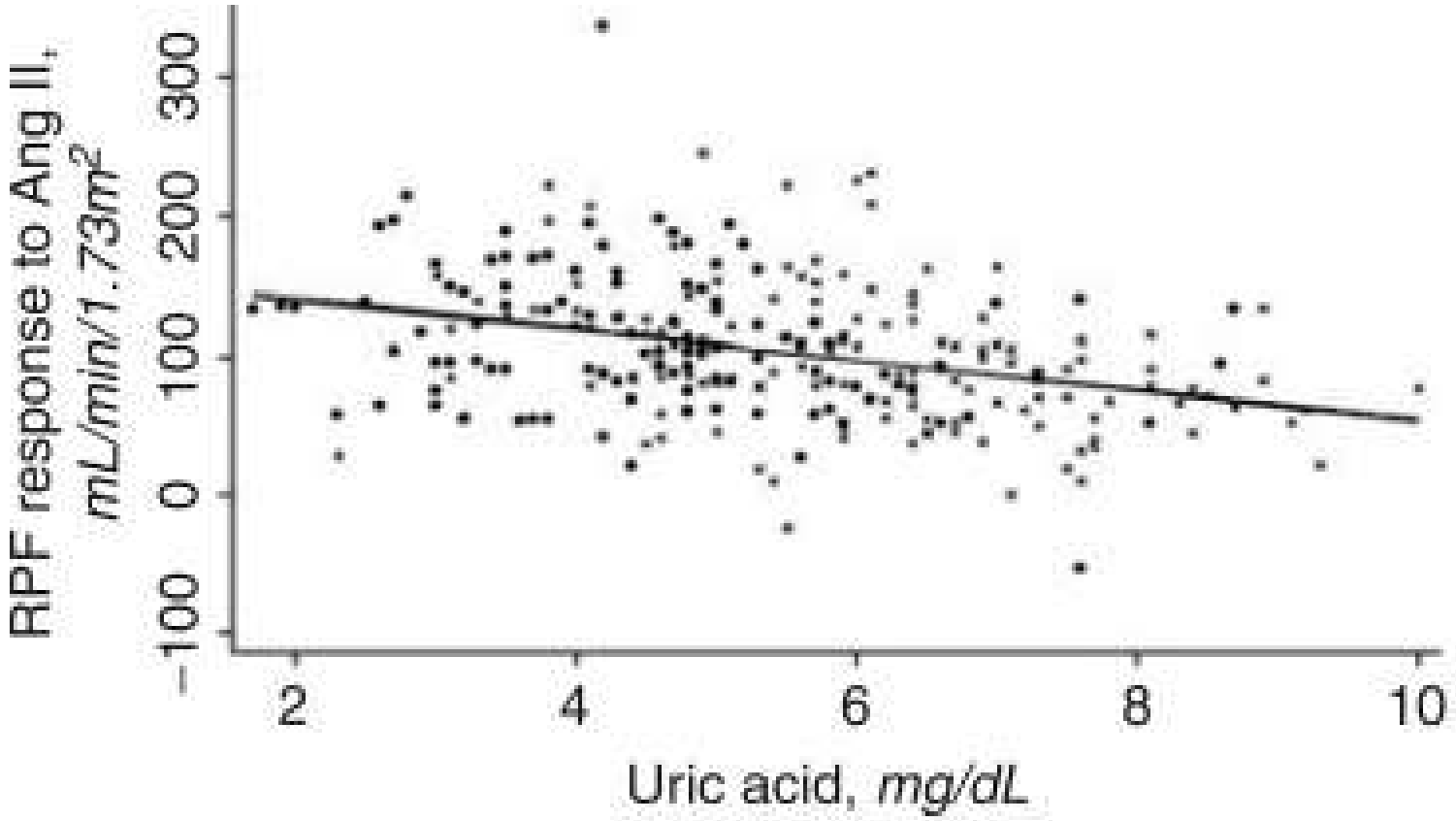




Pelskein TS et al. Uric acid and the state of the intrarenal renin-angiotensin system in humans. Kidney Int 2004

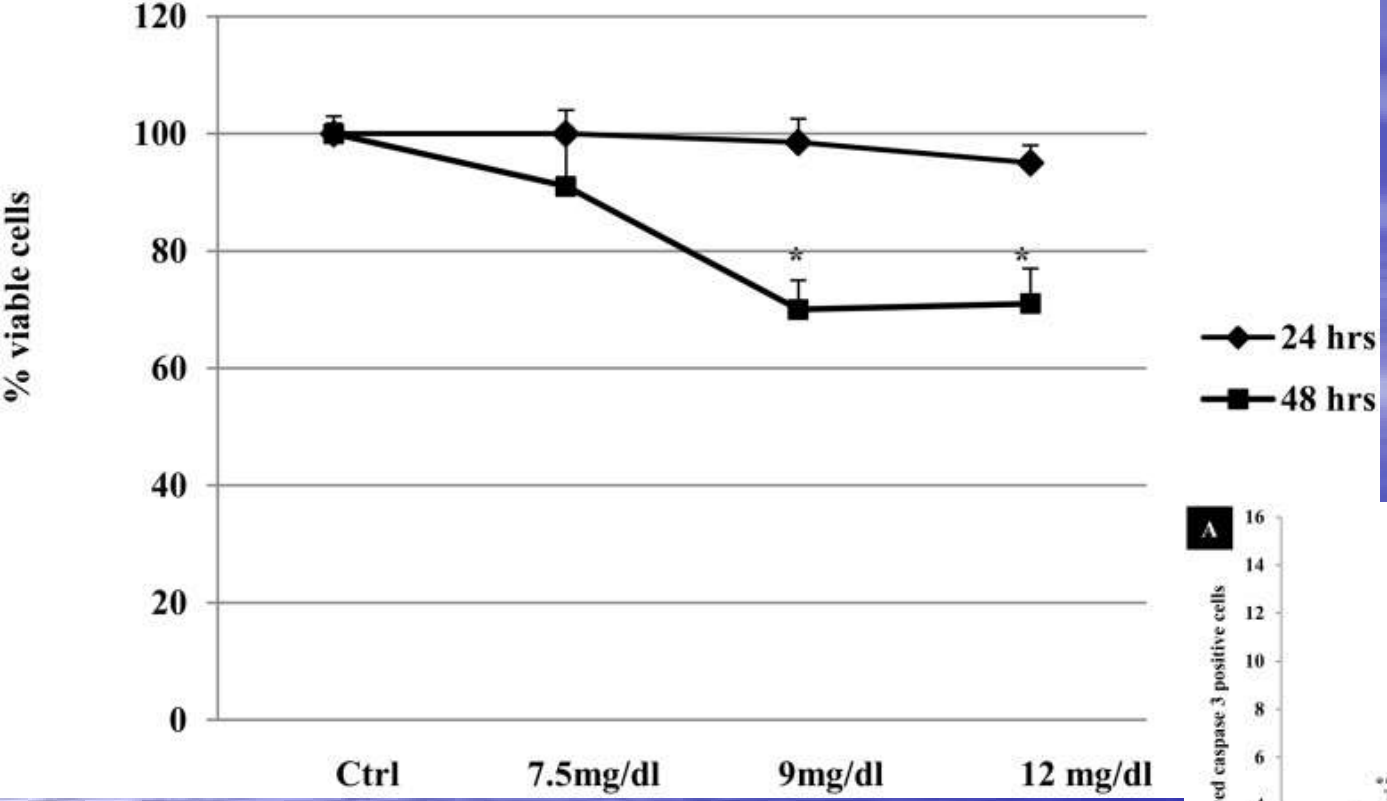
249 soggetti a dieta ipersodica. Correlazione inversa tra uricemia e variazione del flusso plasmatico renale pre e post infusione di Agiotensina II.

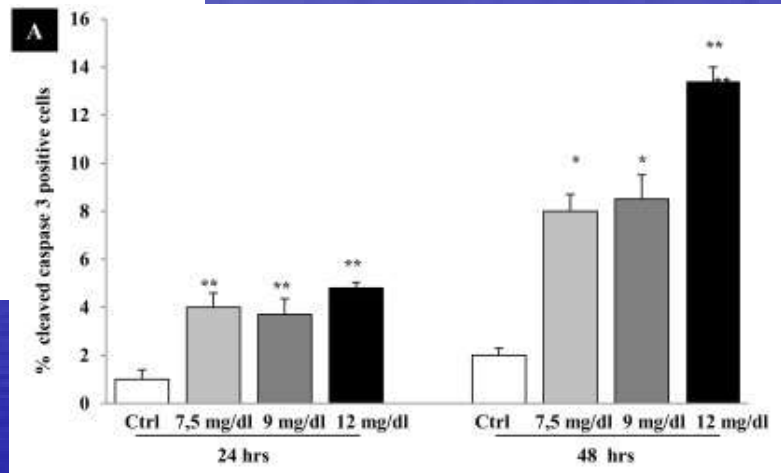
Δ pre e post infusione di Angiotensina 2

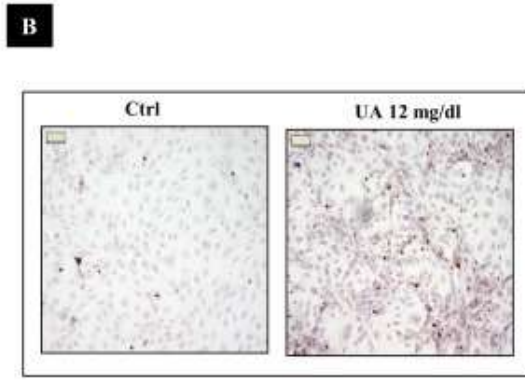


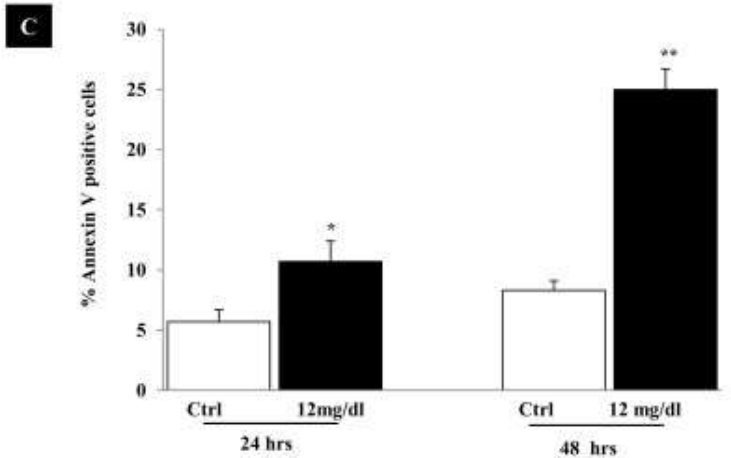
(*r*=-0.26, *P* < 0.01)

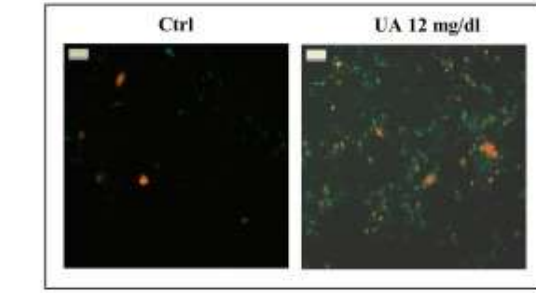
ACIDO URICO E DANNO TUBULO INTERSTIZIALE











Verzola et al.

Uric acid promotes apoptosis in human proximal tubule cells by oxidative stress and the activation of NADPH oxidase NOX 4.

Plos One 2014

Verzola et al.

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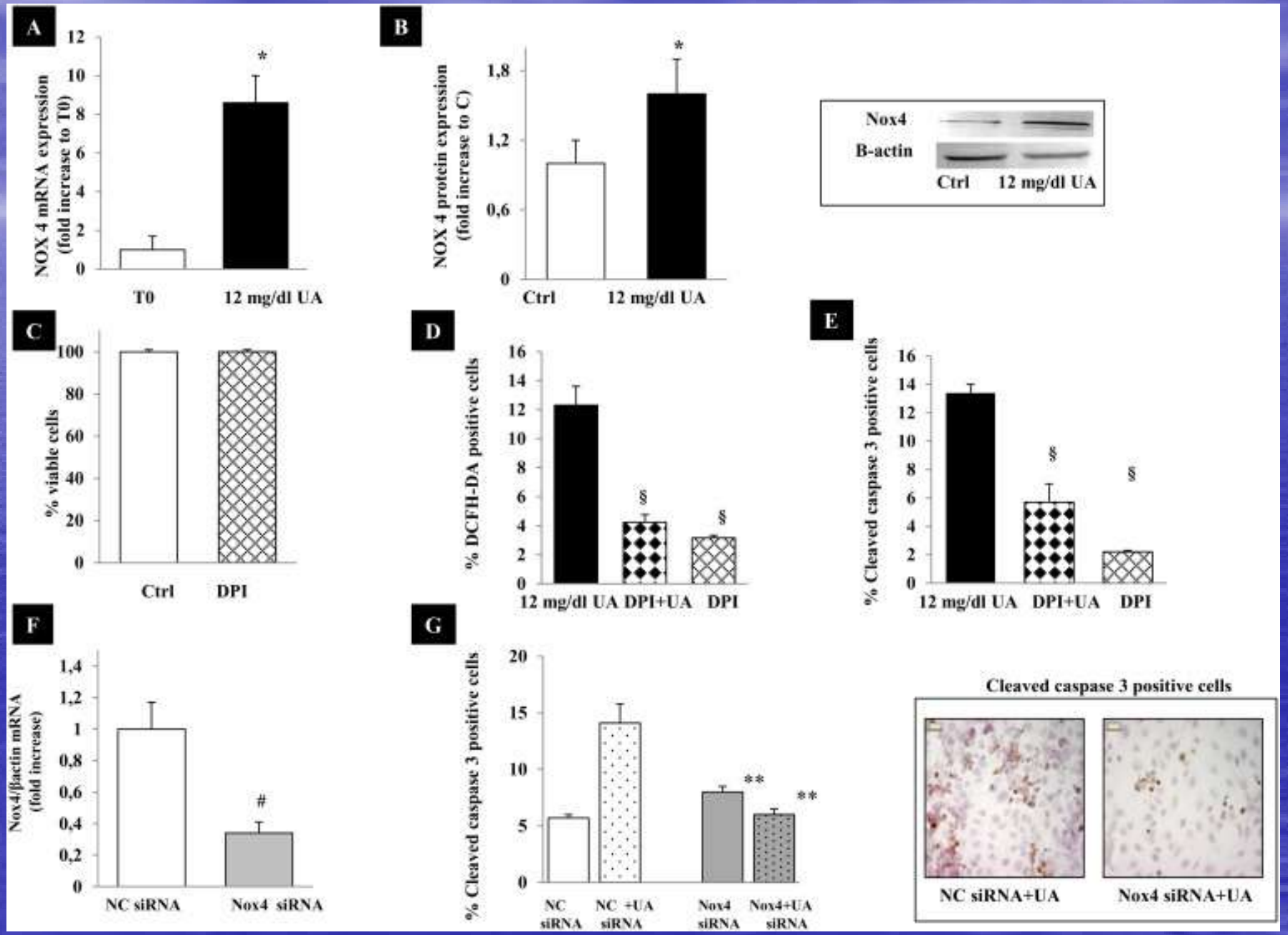
Plos One 2014

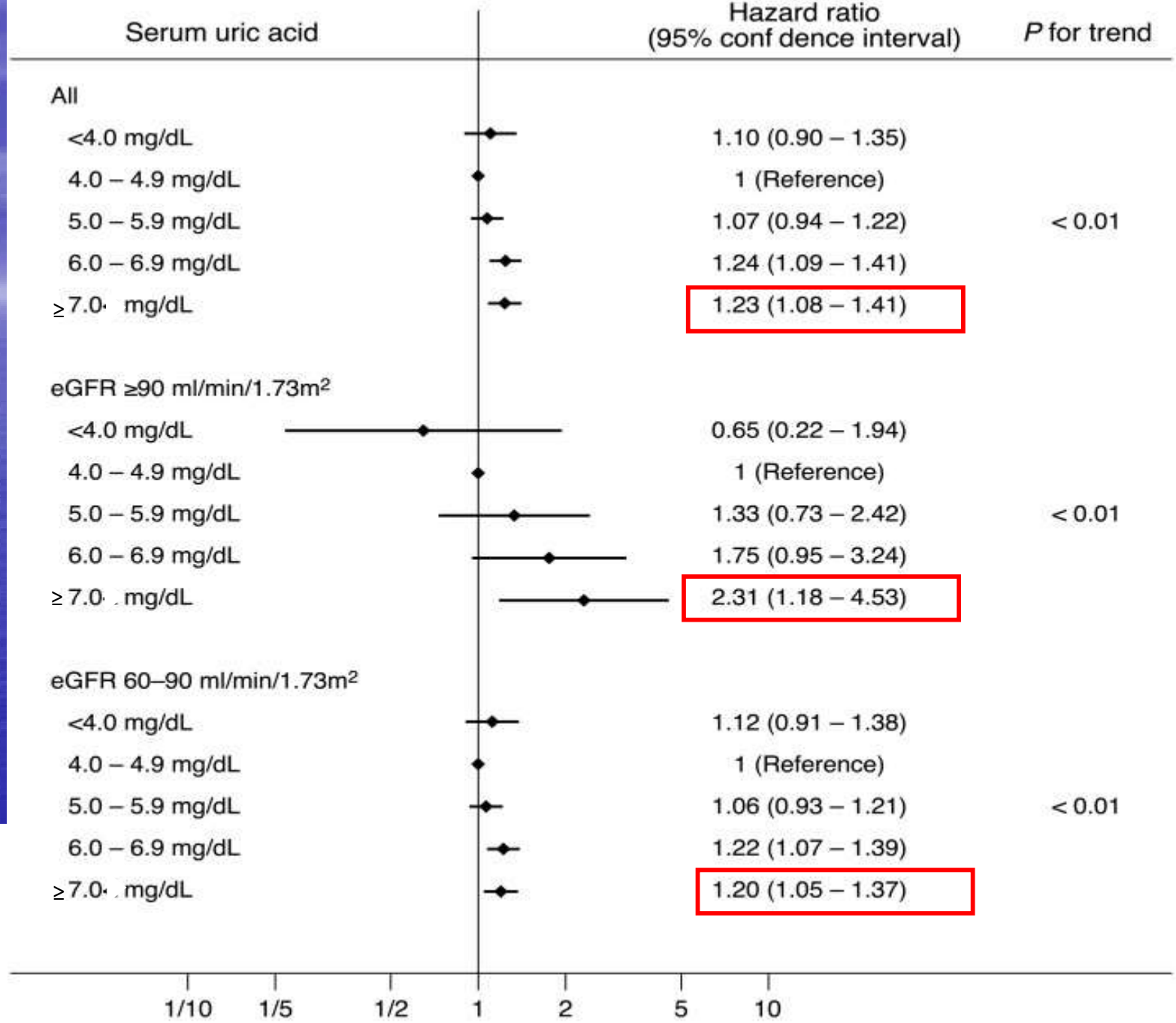


Toyama T et al.

Relationship between Serum Uric Acid Levels and Chronic Kidney Disease in a Japanese Cohort with Normal or Mildly Reduced Kidney Function.

Plos One 2015

41632 soggetti dal 1998 al 2007
Età media 45,4 anni
Follow-up medio 4 anni
CKD in 3186 casi (7,6%)



END POINT: GFR < 60 ml/min

Shunya U. et al. Targeting uric acid and the inhibition of progression to end stage renal disease-a propensity score analysis. Plos One, Dec 2015

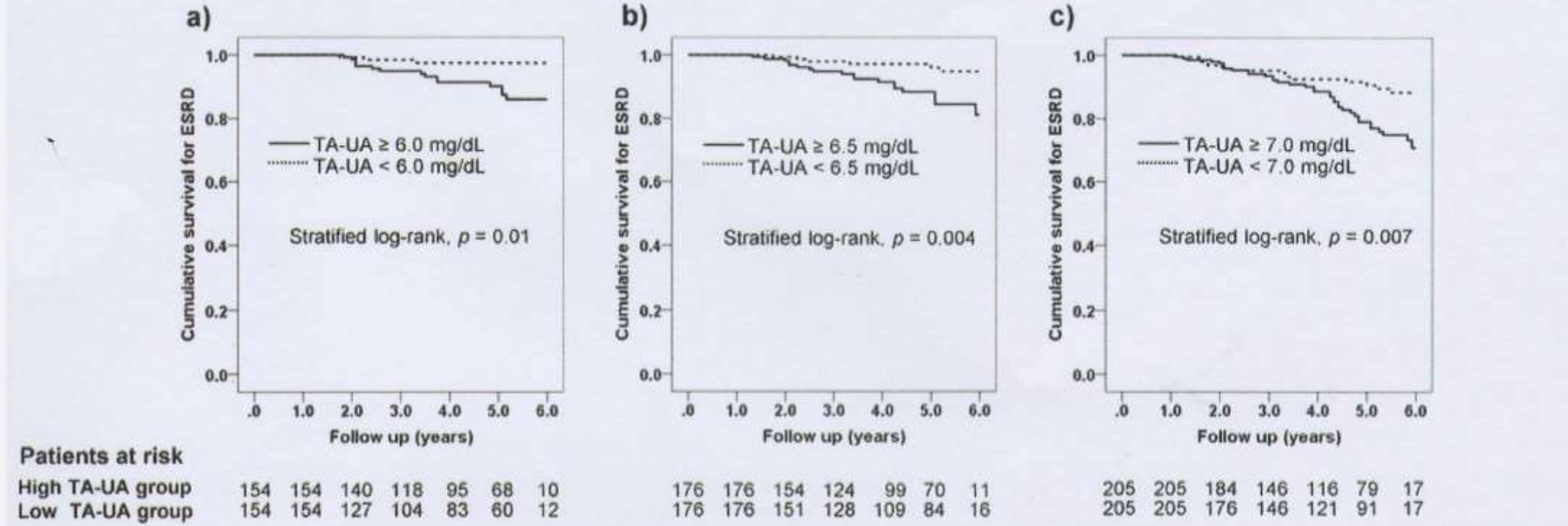


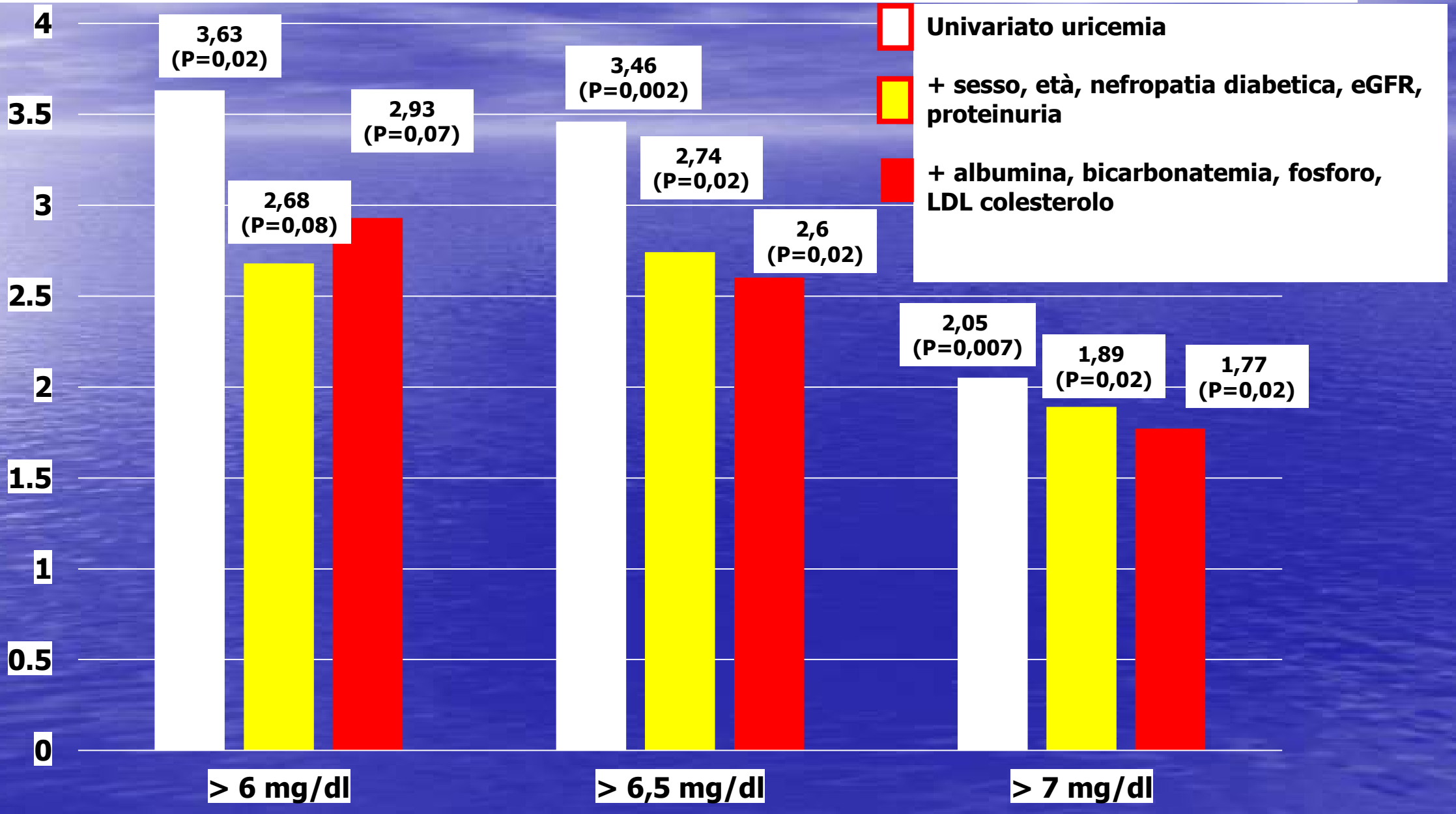
Fig 3. Kaplan-Meier plots after the propensity score matching. a) Time-averaged uric acid of 6.0 mg/dL, b) Time-averaged uric acid of 6.5 mg/dL, c) Time-averaged uric acid of 7.0 mg/dL. The patients at risk are shown below and *p* values are computed by stratified log-rank test.

doi:10.1371/journal.pone.0145506.g003

803 pazienti con CKD in stadio 3-4 seguiti per 6 anni (GFR medio di partenza= 46±11 ml/min; TA-UA: time average uric acid).

End point primario: ESRD

Shunya U. et al. Targeting uric acid and the inhibition of progression to end stage renal disease-a propensity score analysis. Plos One, Dec 2015



Goicoechea M et al.

Effect of Allopurinol i chronic Kidney Disease Progression and Cardiovascular Risk.

JASN 2010

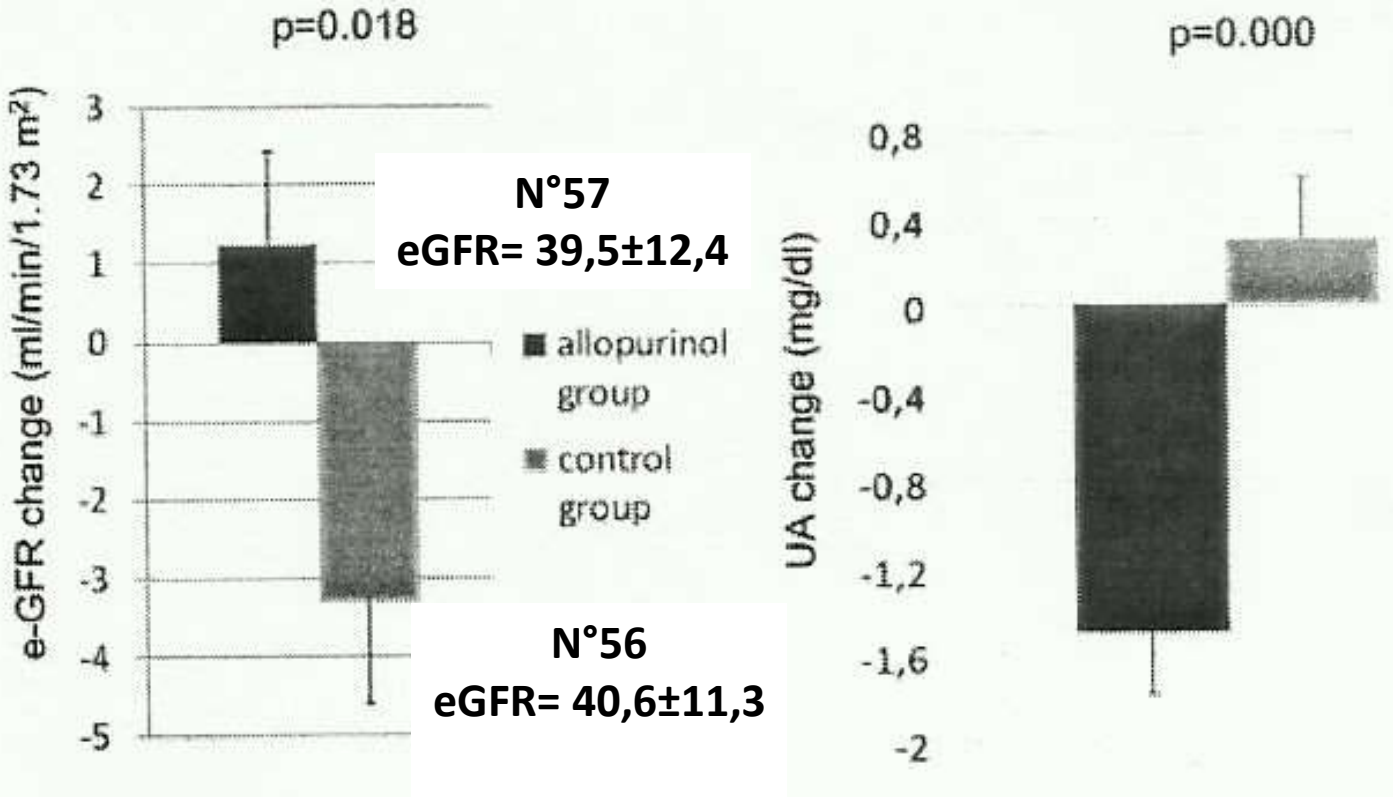


Figure 2. Change in UA levels and change in eGFR at the end of study. Values are expressed as mean ± SEM.

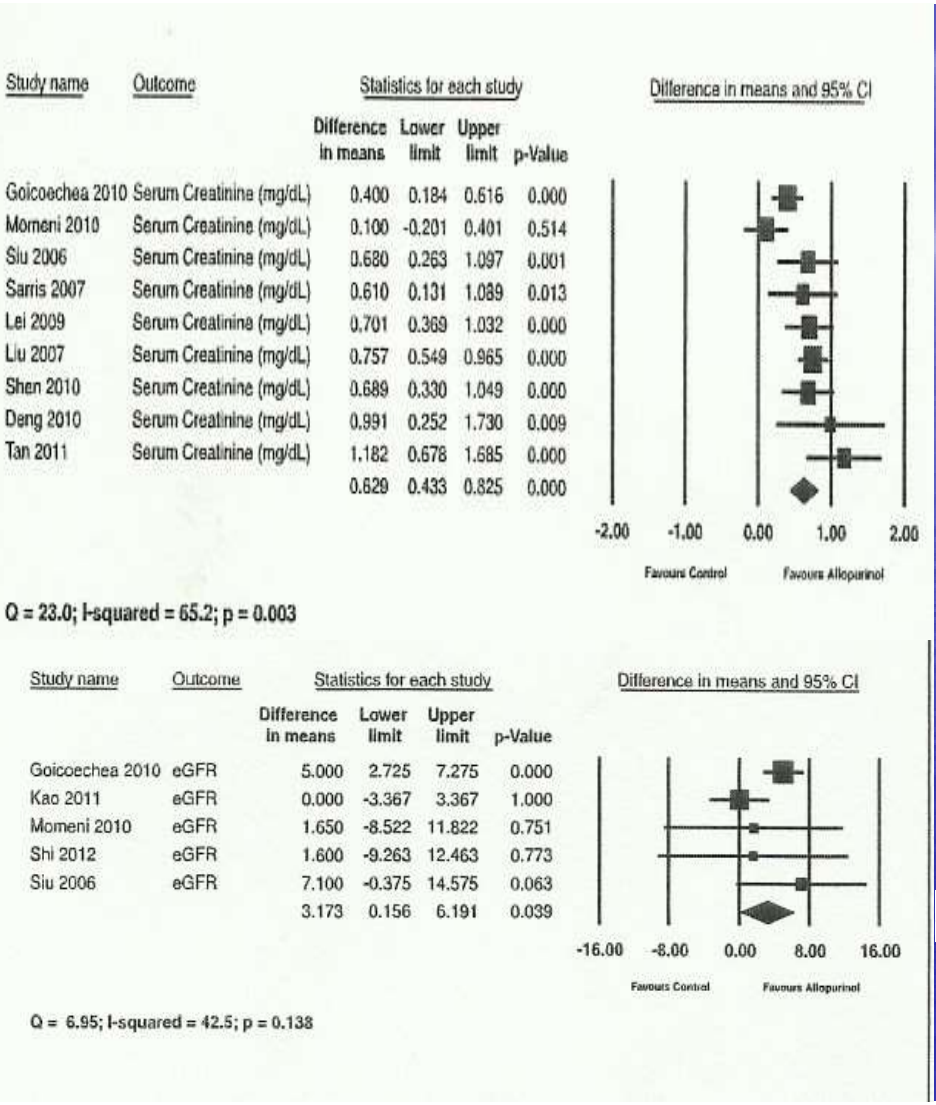
113 paziente con eGFR < 60 ml/min

Δ GFR trattati= + 1,3± 1,3 ml/min

Δ GFR controlli= - 3,3± 1,2 ml/min

Follow-up: 1 anno

Kanji T etal. Urate lowering therapy to improve renal outcomes in patients with chronic kidney disease: systematic review and meta-analysis. BMC Nephrology 2015.

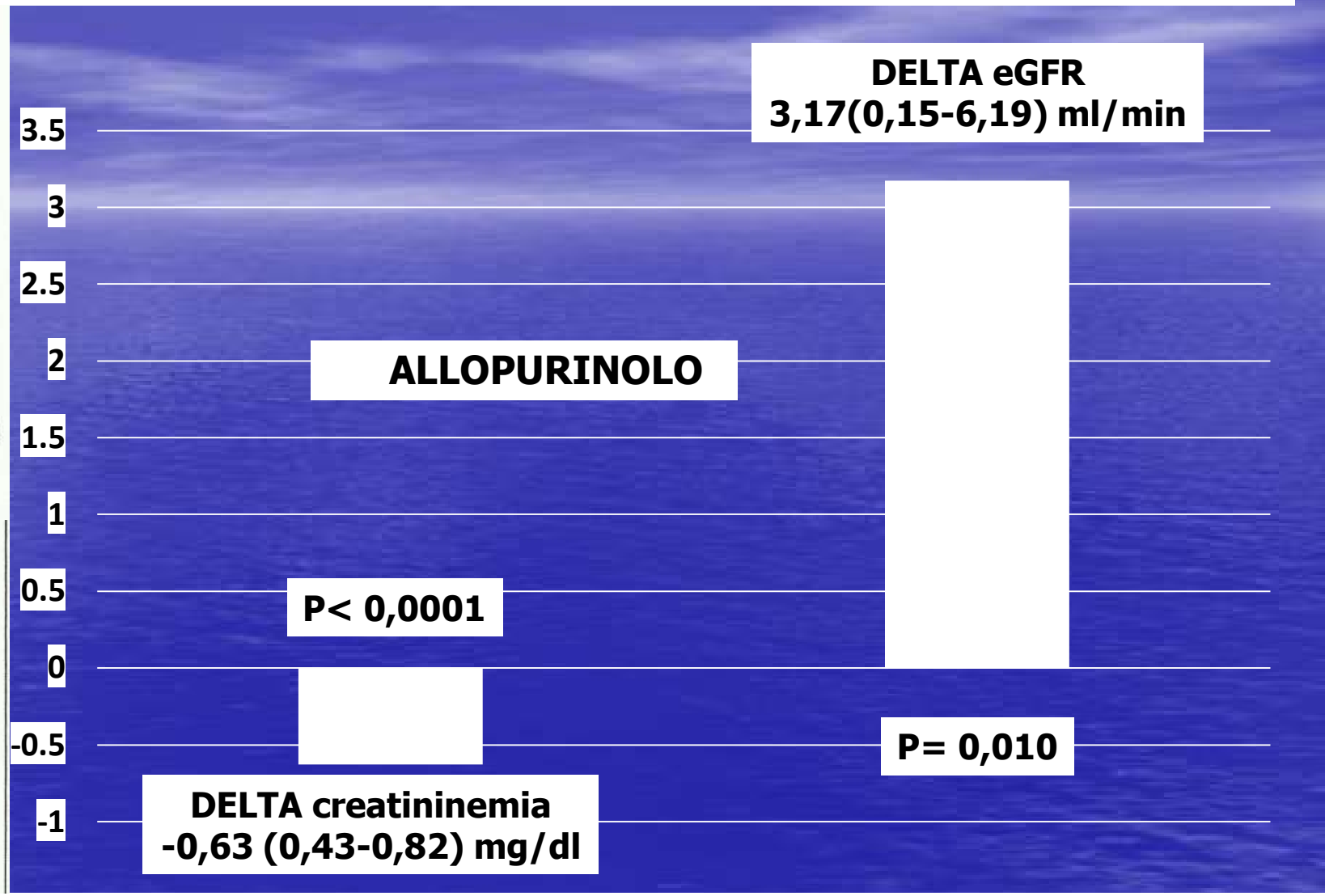


Study name	Outcome	Difference in means	Lower limit	Upper limit	p-Value
Goicoechea 2010	Serum Creatinine (mg/dL)	0.400	0.184	0.616	0.000
Momeni 2010	Serum Creatinine (mg/dL)	0.100	-0.201	0.401	0.514
Siu 2006	Serum Creatinine (mg/dL)	0.680	0.263	1.097	0.001
Sarris 2007	Serum Creatinine (mg/dL)	0.610	0.131	1.089	0.013
Lei 2009	Serum Creatinine (mg/dL)	0.701	0.369	1.032	0.000
Liu 2007	Serum Creatinine (mg/dL)	0.757	0.549	0.965	0.000
Shen 2010	Serum Creatinine (mg/dL)	0.689	0.330	1.049	0.000
Deng 2010	Serum Creatinine (mg/dL)	0.991	0.252	1.730	0.009
Tan 2011	Serum Creatinine (mg/dL)	1.182	0.678	1.685	0.000
		0.629	0.433	0.825	0.000

Q = 23.0; I-squared = 65.2; p = 0.003

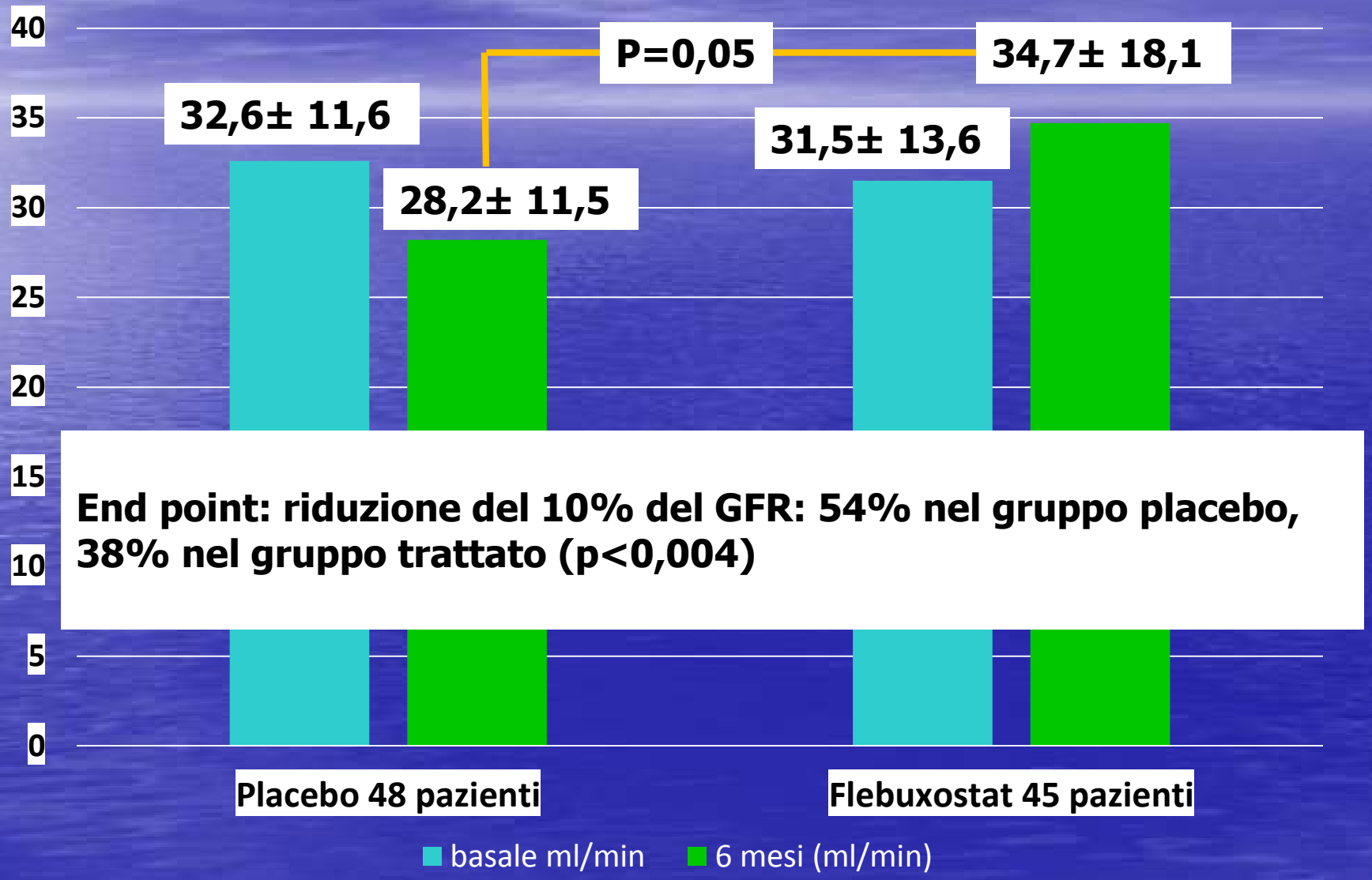
Study name	Outcome	Difference in means	Lower limit	Upper limit	p-Value
Goicoechea 2010	eGFR	5.000	2.725	7.275	0.000
Kao 2011	eGFR	0.000	-3.367	3.367	1.000
Momeni 2010	eGFR	1.650	-8.522	11.822	0.751
Shi 2012	eGFR	1.600	-9.263	12.463	0.773
Siu 2006	eGFR	7.100	-0.375	14.575	0.063
		3.173	0.156	6.191	0.039

Q = 6.95; I-squared = 42.5; p = 0.138



19 studi pubblicati tra il 1998 e il 2012, 992 pazienti, follow-up > 3 mesi, 16 controllati e 3 in cross-over
Trattamento con Allopurinolo, Flebuxostat, Benzbromarone, Probenecid e sulfinpirazone

Sircar D et al. Efficacy of Flebuxostat fro slowing the GFR decline in patients wih CKD and asymptomatic hyperuricemia: a 6-months, double blind,randomized, placebo-controlled trial. Am J Kidney Dis 2015



End point: riduzione del 10% del GFR: 54% nel gruppo placebo, 38% nel gruppo trattato (p<0,004)

I DATI CLINICI SONO ALLO STATO EMBRIONALE……
SPORADICI….ANCHE SE INCORAGGIANTI
MANCANO GLI HARD END POINTS……

?!

….IL TRATTAMENTO NON PARE AVERE UN EFFETTO DELETERIO SUL RENE……

…NON RIMANE CHE TRATTARE L'IPERURICEMIA……..

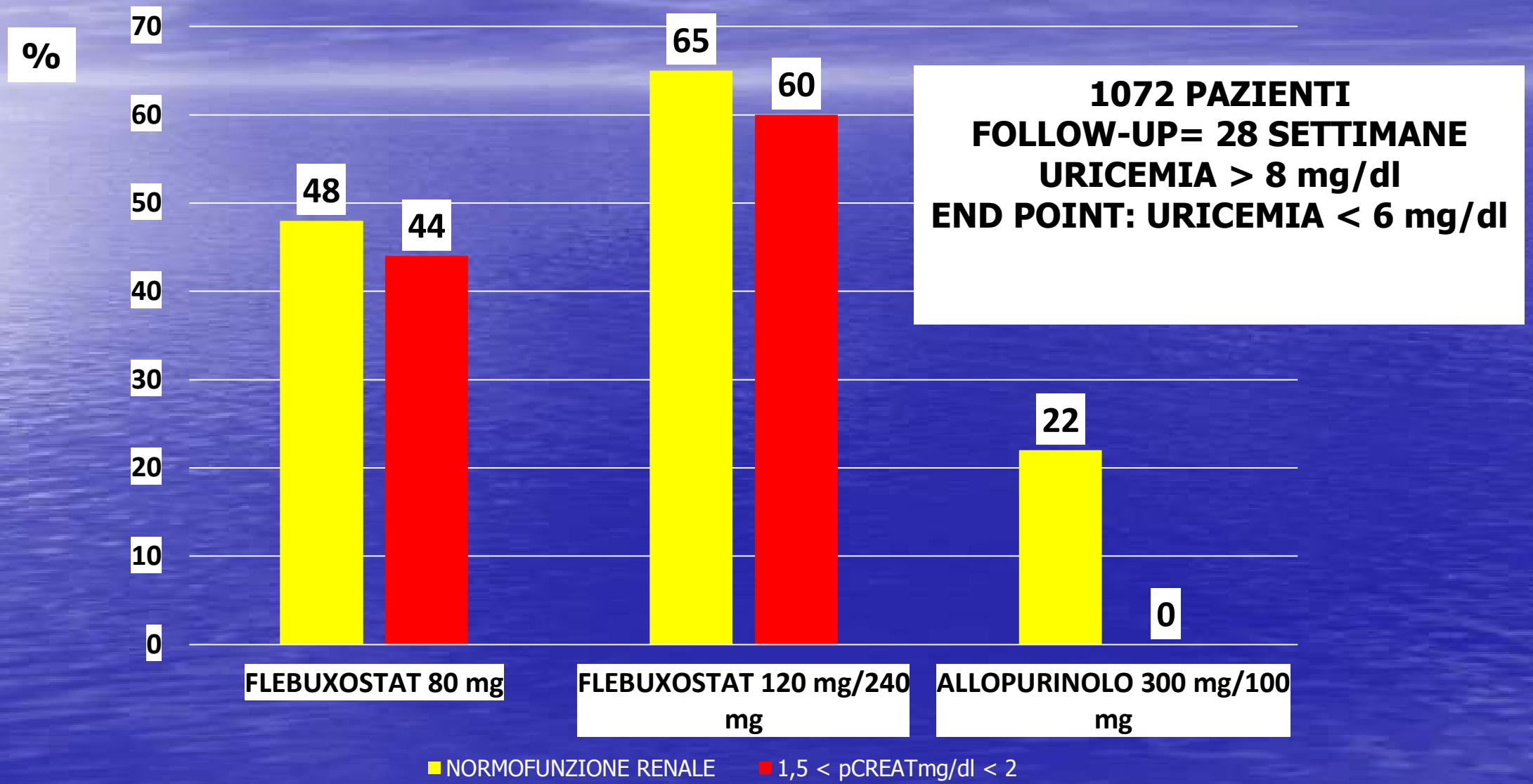
URICEMIA E RENE:
E' ORA DI CONSIDERARE L'URICEMIA?

Modificato da classificazione NFK-K/DOQI, 2002

Stadio I	**Stadio II**	**Stadio III**	**Stadio IV**	**Stadio V**
GFR > 90	60<GFR<90	30<GFR<60	15<GFR<30	GFR<15
Presenza d:i microalbuminuria, microematuria, proteinuria, alterazioni morfologiche ecografiche		3a: 60<GFR<45 3b: 45<GFR<30		Necessità di terapie Sostitutive: PREDIALISI
PA < 140/80 mmHg **Colesterolo LDL < 135 mg/dl** **HbA1c< 7%** **Controllo funzione renale** **Dieta iposodica** **Imaging** **Uricemia**	**PA < 140/80 mmHg** **Colesterolo LDL < 135 mg/dl** **HbA1c< 7%** **Dieta iposodica** **Controllo funzione renale** **Uricemia**	**PA < 140/80 mmHg** **Colesterolo LDL < 135 mg/dl** **HbA1c< 7%** **Controllo funzione renale** **Controllo anemia** **Controllo calcio-fosforo** **Dieta iposodica** **Proteine 0.8-1 g/Kg** **Uricemia**	**PA < 140/80 mmHg** **Colesterolo LDL < 135 mg/dl** **HbA1c< 7%** **Controllo funzione renale** **Controllo anemia** **Controllo calcio-fosforo** **Dieta iposodica** **Proteine 0.6 g/Kg** **Uricemia**	

Febuxostat vs allopurinolo: Studio APEX

Becker MA et al. NEJM 2005



1072 PAZIENTI
FOLLOW-UP= 28 SETTIMANE
URICEMIA > 8 mg/dl
END POINT: URICEMIA < 6 mg/dl

- **ALLOPURINOLO:**
  - **partire con 100 mg/die**
  - **Aumentare di 100 mg ogni 2-4 settimane sino ad uricemia < 6mg/dl**
  - **Dose massima consentita 800 mg/die**
  - **Attenzione ad Azatioprina e 6-mercaptopurina**
  - **Scarsa maneggevolezza in corso di disfunzione renale (riduzione dose)**

- **FLEBUXOSTAT**
  - **10-30 volte più potente**
  - **Biodisponibilità 84%**
  - **Eliminazione epatica e renale: maneggevole in caso di disfunzione renale o epatica**
  - **Dose massima raccomandata 120 mg/die**
  - **Attenzione ad Azatioprina e 6-mercaptopurina**

GRAZIE