



SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA



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Università degli Studi dell'Aquila



60° CONGRESSO NAZIONALE

NAPOLI 25-28 Novembre 2015

16° CORSO INFERMIERI

NAPOLI 26-27 Novembre 2015



Simposio:

***Dismetabolismo dell'acido urico:
quali novità per il geriatra?***

***La gestione dell'iperuricemia
cronica con e senza deposito di
urato nell'anziano tra clinica e
farmacoeconomia***

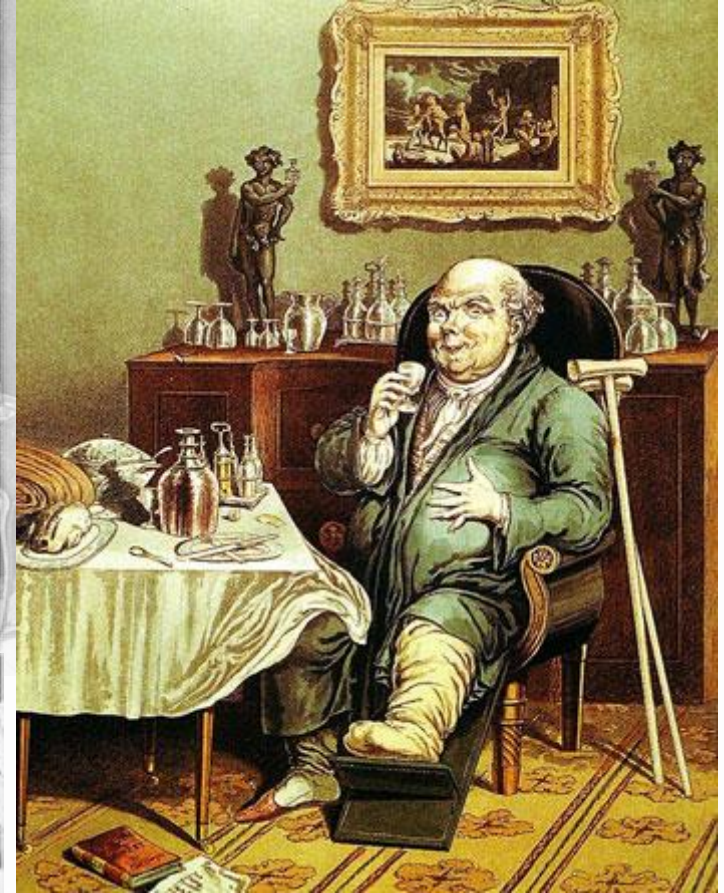
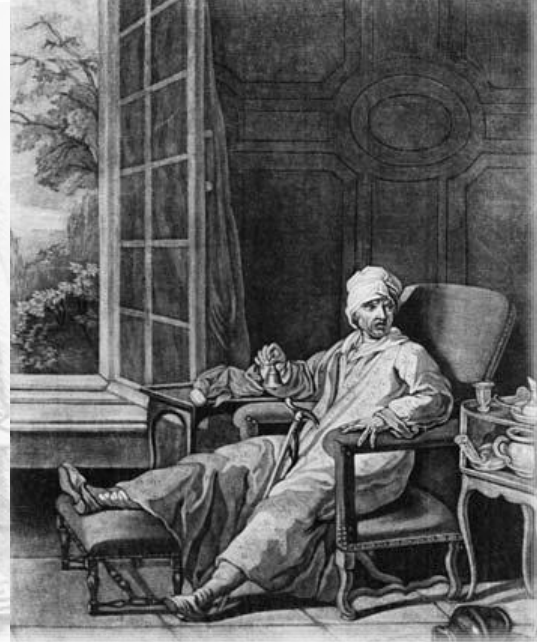
The therapeutical management of chronic hyperuricemia in the third millennium

- What we would like to treat/prevent by urate lowering treatment?
 - Flares, tophi, nephrolithiasis and ... subclinical damage?
 - Cardio-nephro-metabolic protection (?)
- How we can reduce serum uric acid?
 - Lifestyle
 - Drugs

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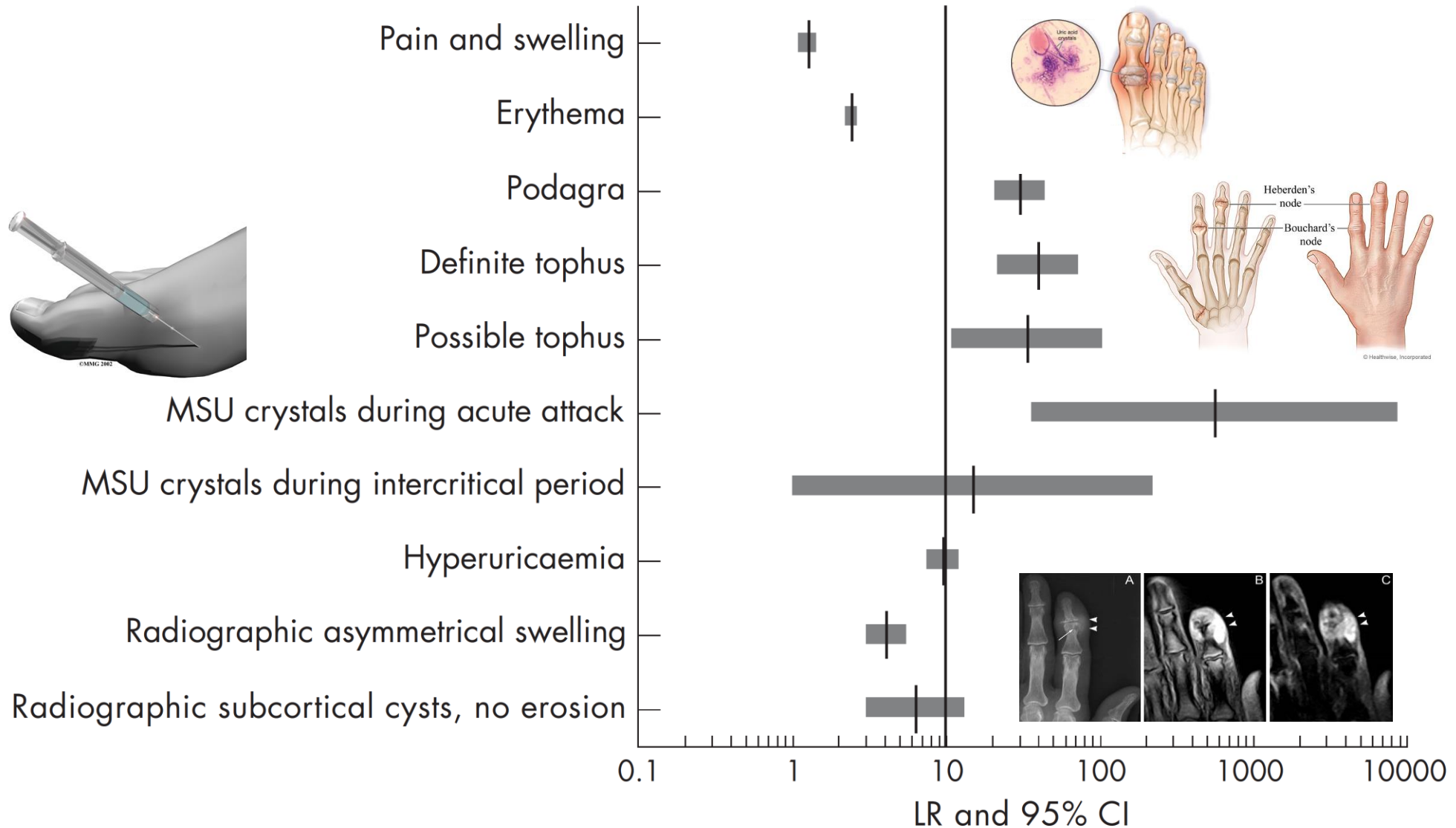
Gout: The Fashionable Disease



"the disease of kings"

"rich man's disease"

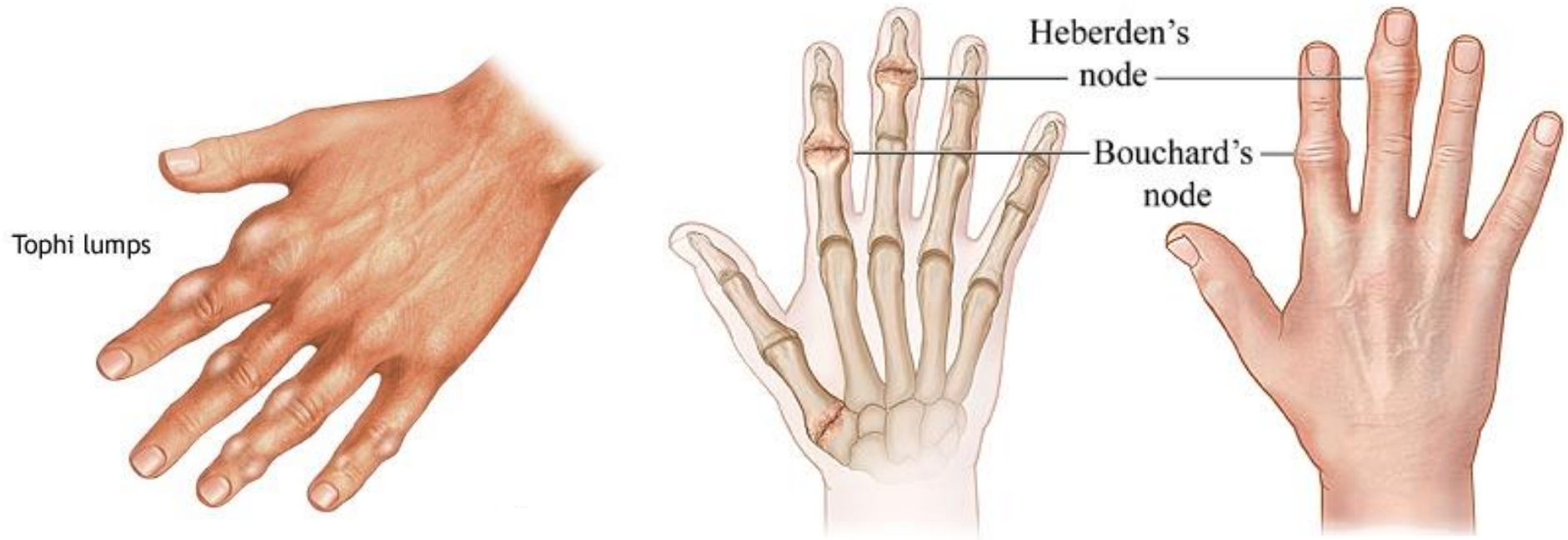
Likelihood ratio for various features in the diagnosis of gout - EULAR



Gout in the elderly: (a)typical features

- Gout is one of the most painful type of arthritis
- However, gout in the elderly tend to be more indolent while gout flares tend to be more polyarticular
- Given the chronicity of gout, elderly patients tend to have an increased incidence of tophi, especially of the elbows and hands

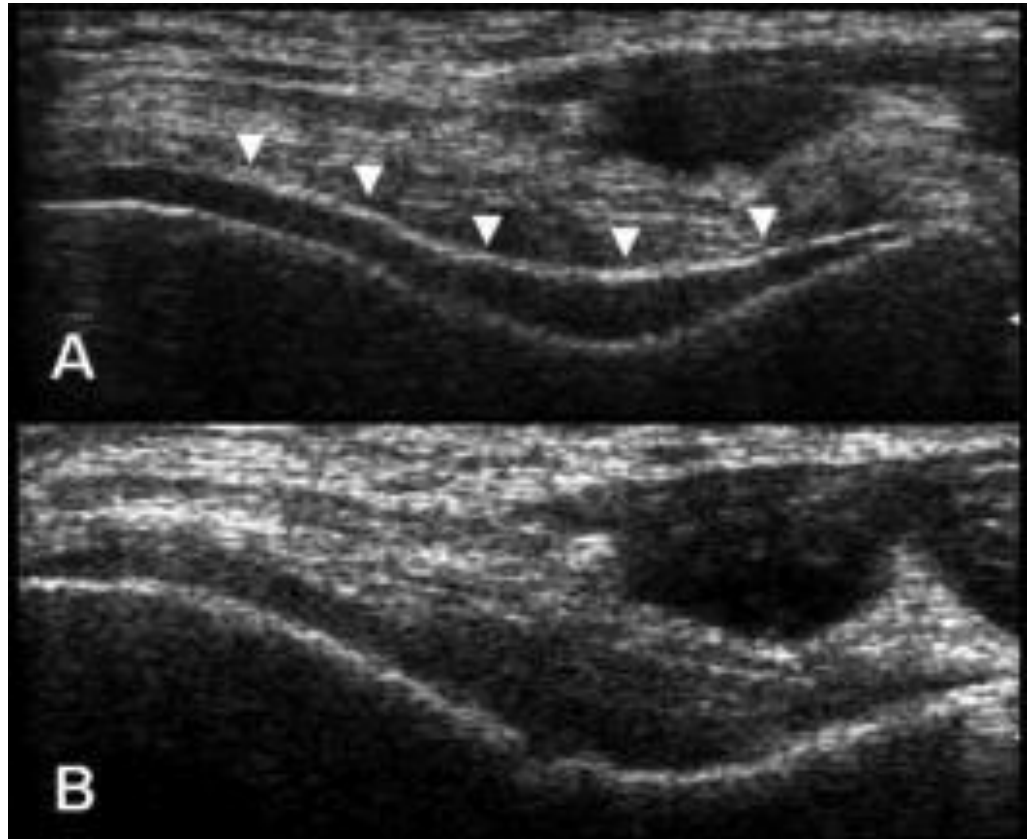
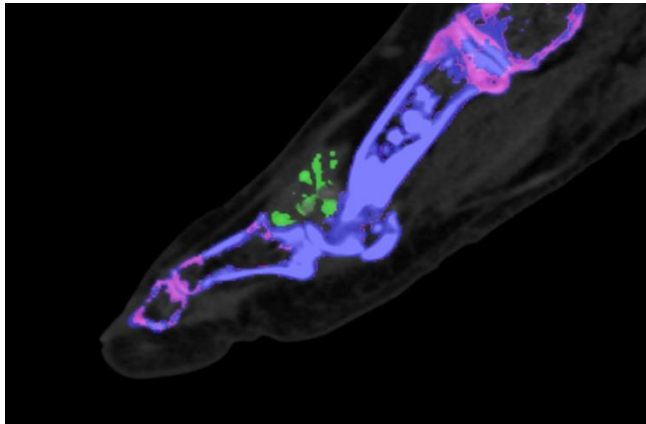
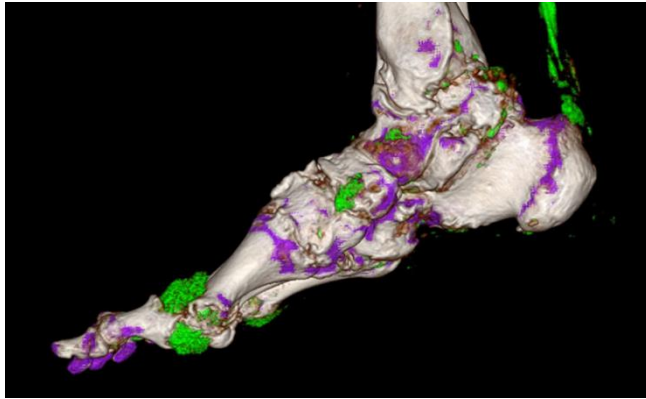
Gout in the Elderly can be mistaken for changes that are usually attributed to OA or RA



The presence of tophi in the hands and the upper extremities can be mistaken for rheumatoid nodules.

Tophi can supervene on Heberden's and Bouchard's nodes.

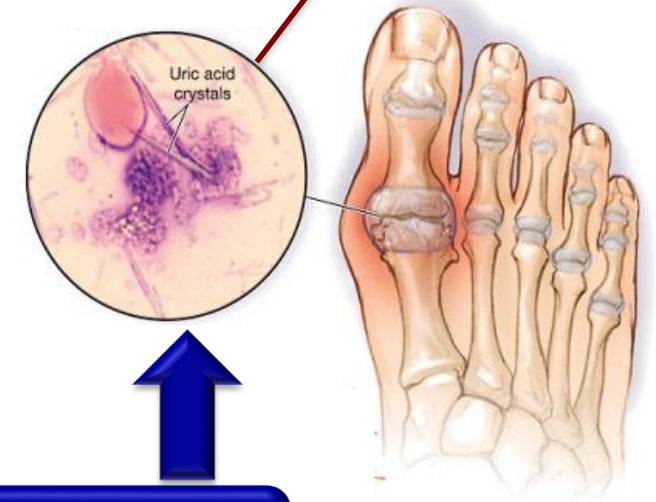
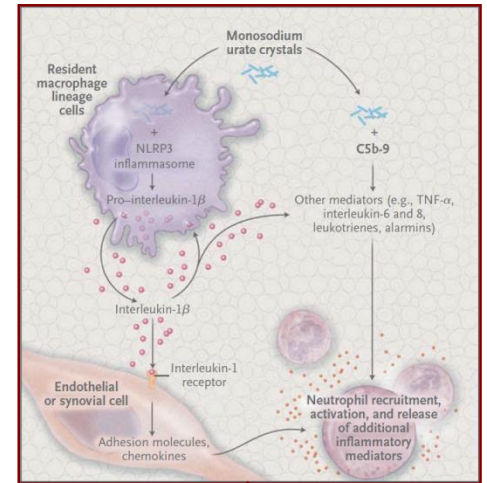
Asymptomatic articular damage in hyperuricemia



Musculoskeletal US can be able to visualize intraarticular crystal deposits with a characteristic hyperechoic enhancement of the outer surface of the hyaline cartilage, known as the “double contour sign.”

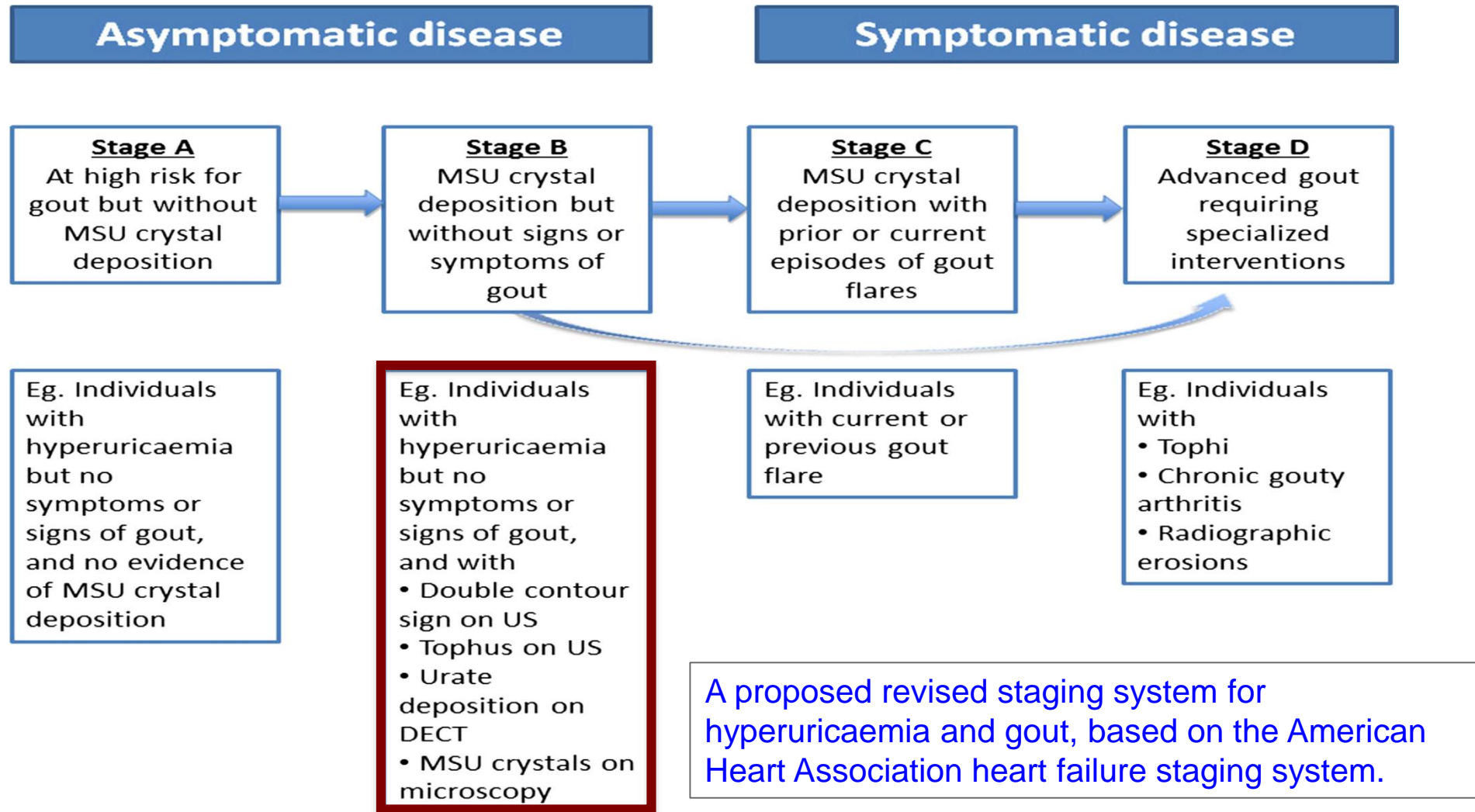
Asymptomatic articular damage in hyperuricemia

Anatomical site and US findings	Hyperuricemic (n = 100 joints)	Normouricemic (n = 104 joints)	P value
First MTP joint, n (%)			
Double contour sign	25 (25%)	0	<0.0001
Joint cavity widening (synovial fluid/ hypertrophy)	52 (52%)	25 (24%)	<0.0001
Power Doppler signal	0	0	NS
Bone erosion	12 (12%)	6 (5.7%)	NS
Knee, n (%)			
Double contour sign (femoral hyaline cartilage)	17 (17%)	0	<0.0001
Joint cavity widening (synovial fluid/ hypertrophy)	7 (7%)	2 (1.9%)	NS



High Serum Uric Acid

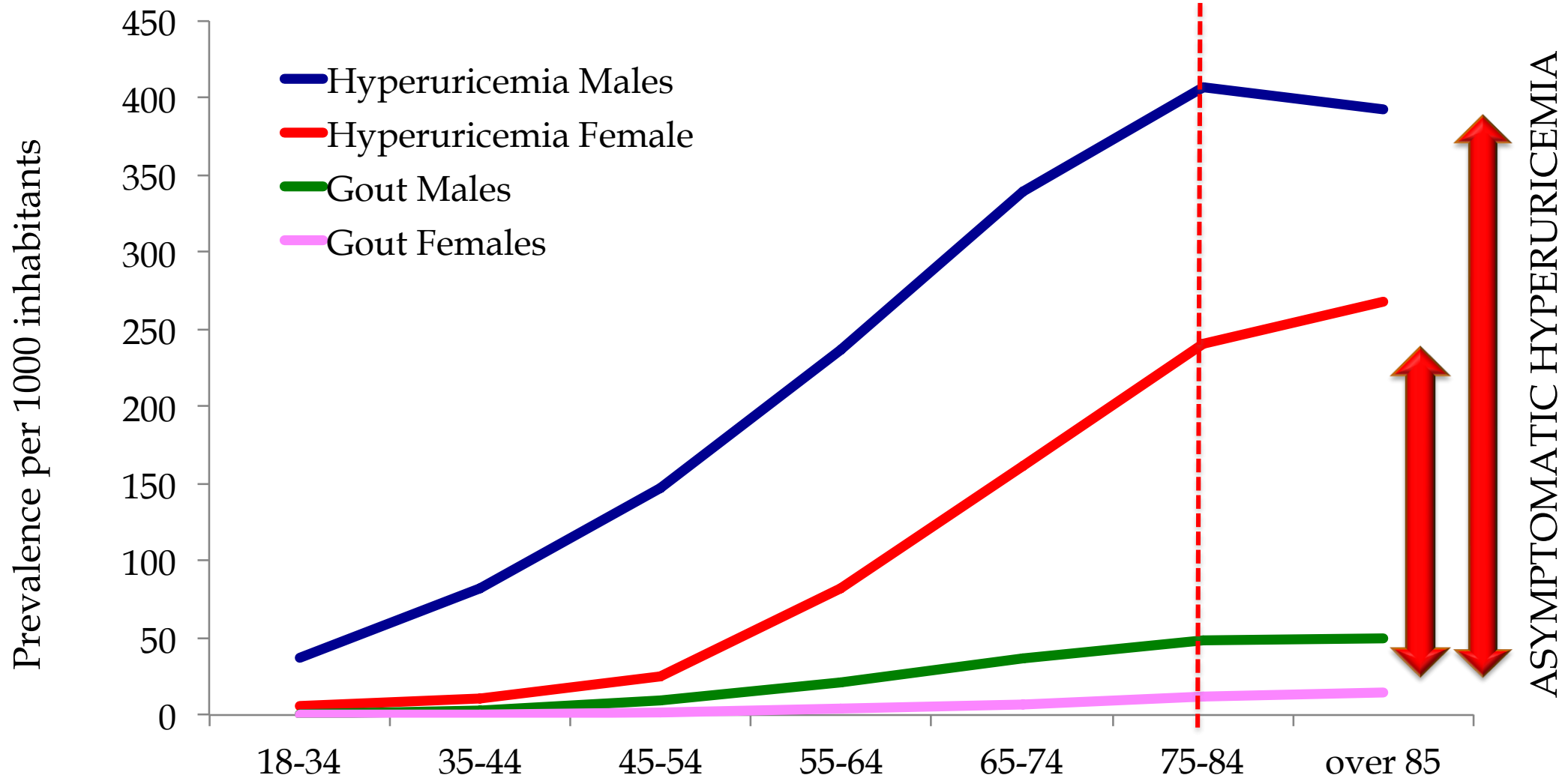
Hyperuricemia and gout: time for a new staging system?



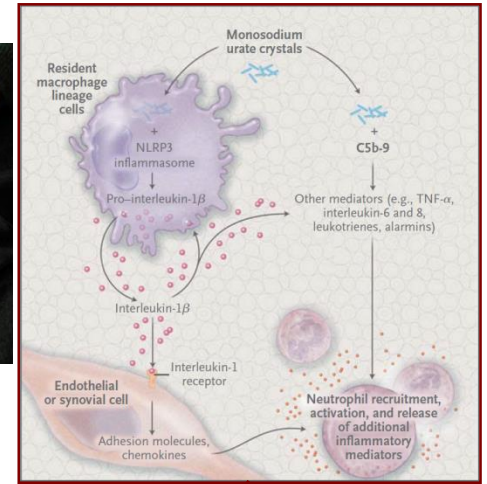
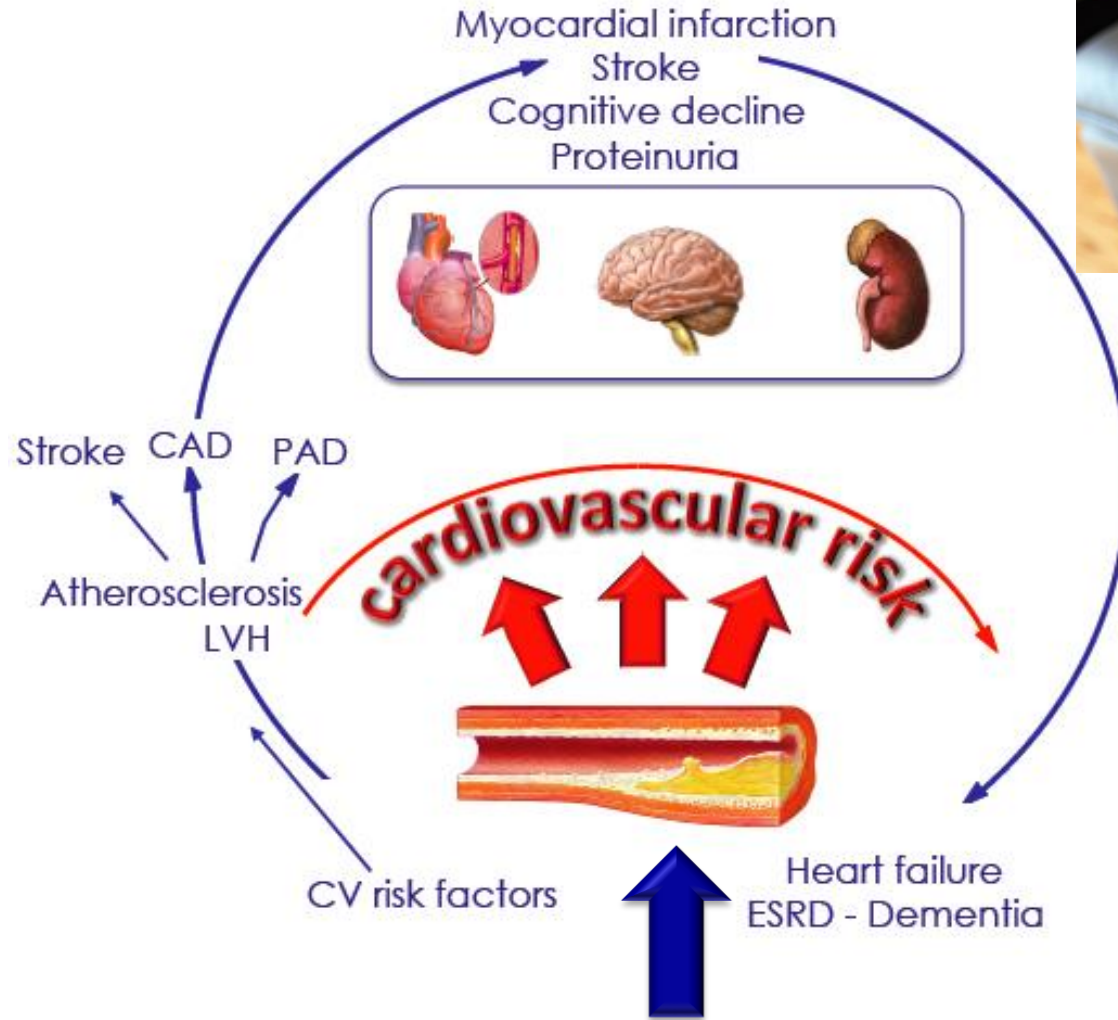
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Epidemiology of gout and hyperuricaemia (SUA >6 mg/dL) in Italy during the years 2005–2009



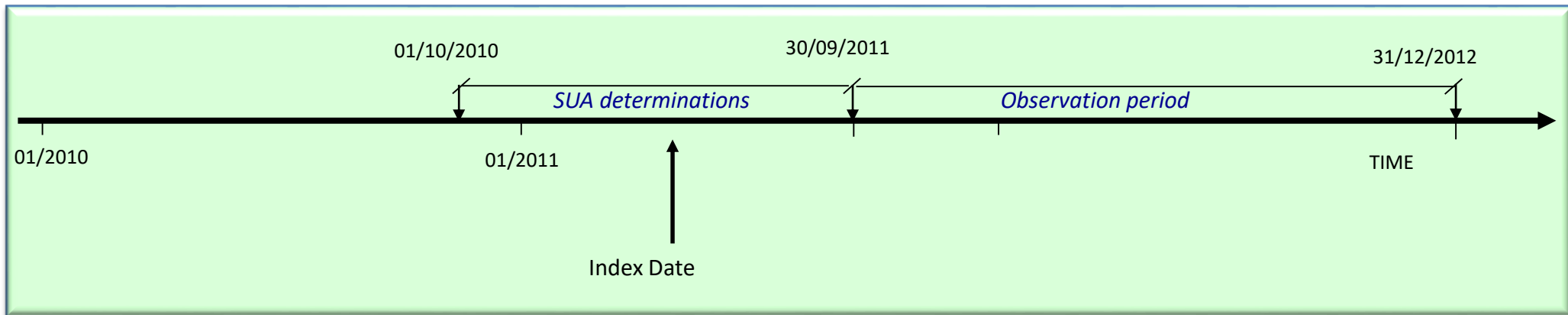
Hyperuricemia and CV disease



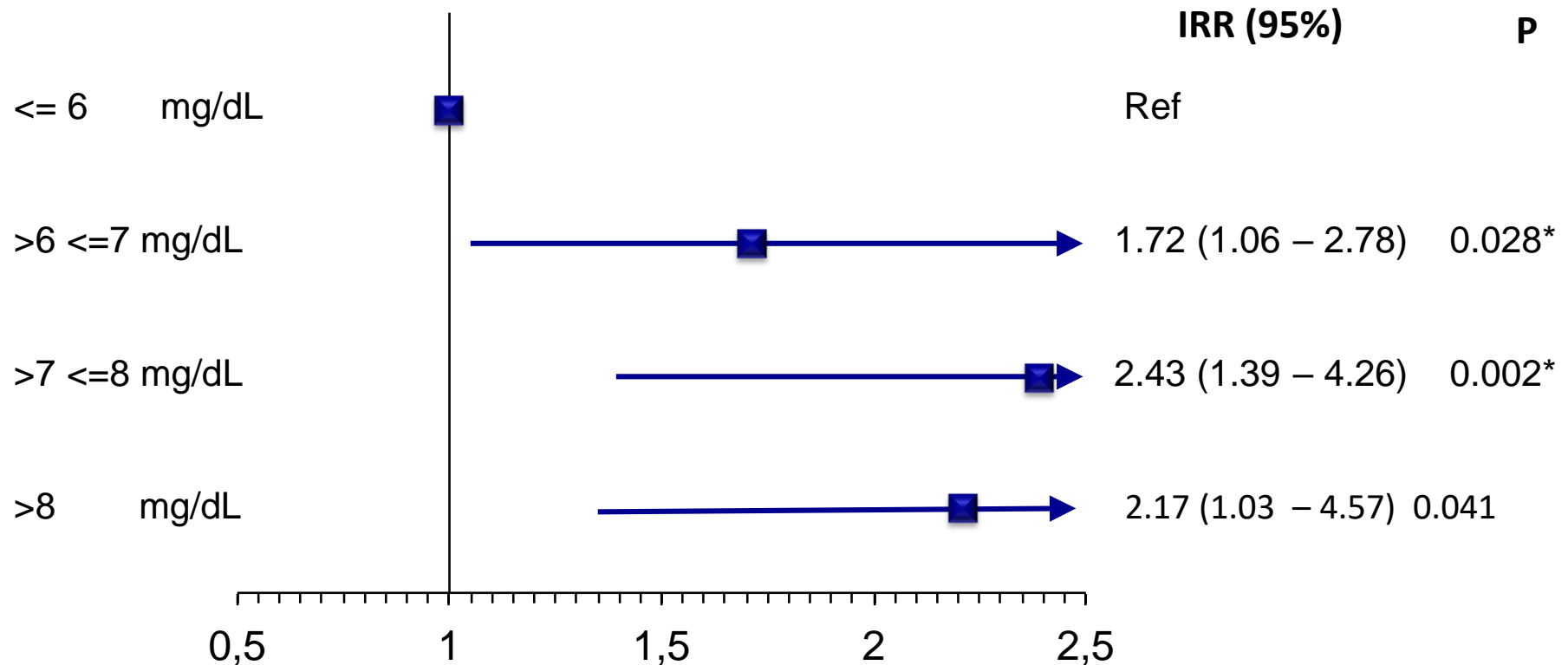
High Serum Uric Acid

Impact of high serum uric acid levels on hospitalization and healthcare costs in Italy – **Cohort Definition**

- Retrospective cohort study based on administrative databases in Italy
- 112170 subjects aged 18 years or older (mean age 65.1 ± 16.3 years) , living in the area of the LHUs, with ≥ 1 acid uric test between October 1, 2010 and September 30, 2011.
- The date of the first uric acid measurement in the period was considered as the beginning of observation for each individual (index-date). Outcomes were evaluated from the index date until Dec. 2012.

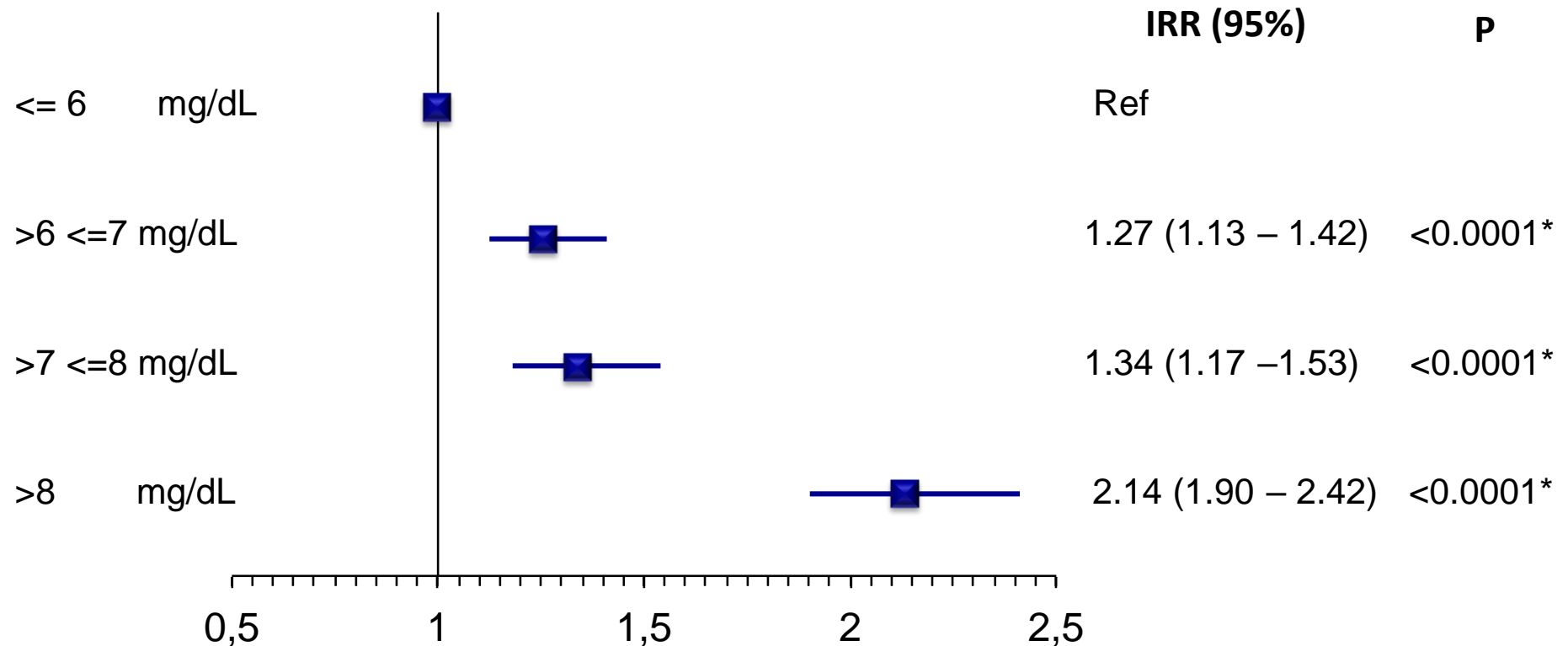


Forest plot of SUA level effect on hyperuricemia-related hospitalizations



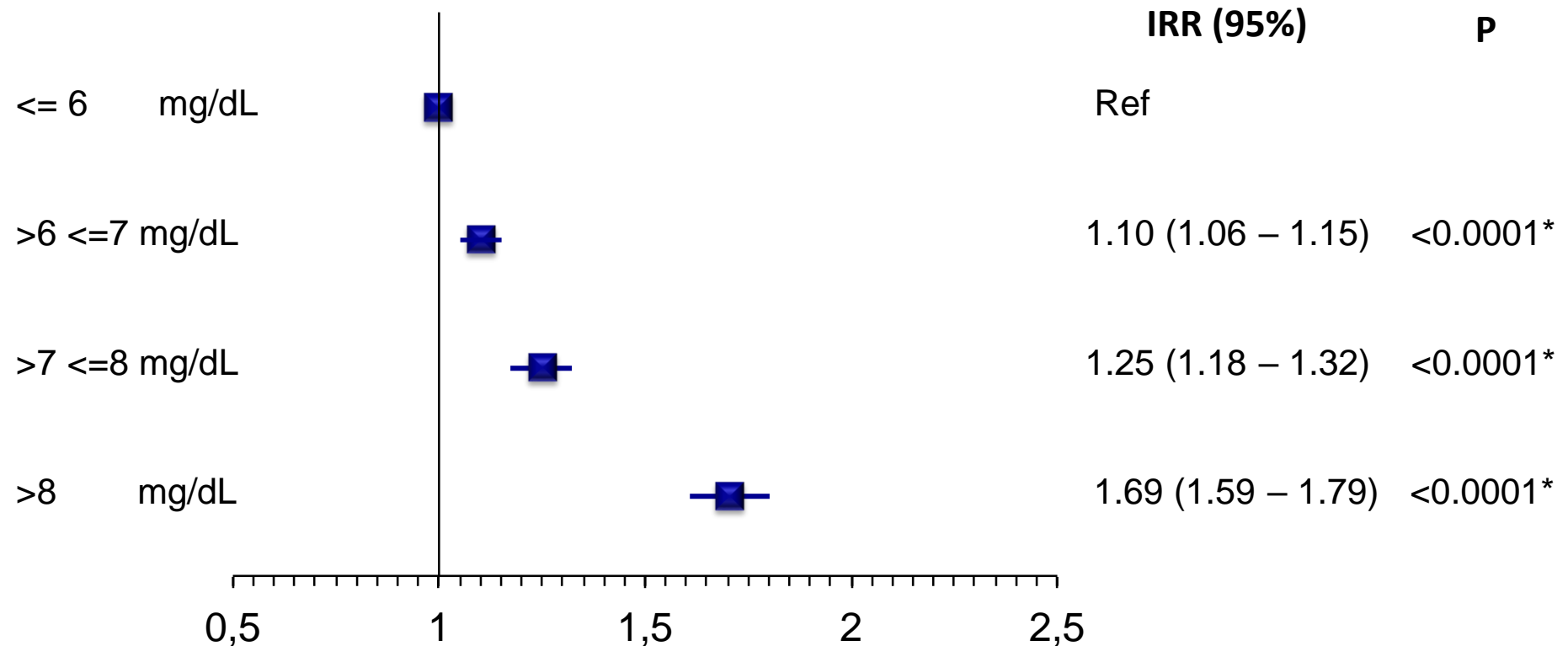
*: adjusted for age, gender, the use of antihypertensives, lipid-lowering drugs, platelet aggregation inhibitors and antidiabetic drugs, the presence of previous CV hospitalizations, TC, TG, LDL-C, CKD stage, the use of hyperuricemia treatment at baselines and during the observation period.

Forest plot of SUA level effect on **kidney-disease hospitalizations**



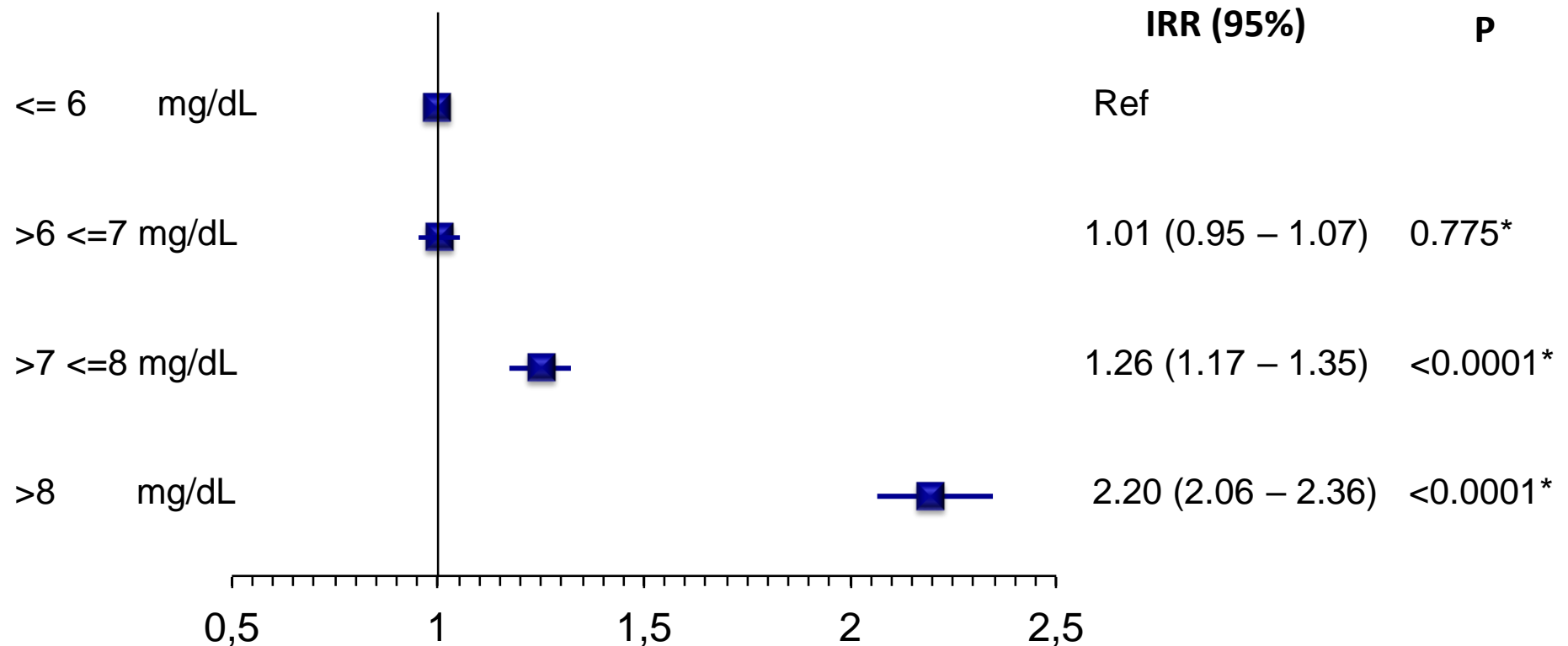
Multivariate analysis: *adjusted for age, gender, the use of antihypertensives, lipid-lowering drugs, platelet aggregation inhibitors and antidiabetic drugs, the presence of previous CV hospitalizations, TC, TG, LDL-C, CKD stage, the use of hyperuricemia treatment at baselines and during the observation period.*

Forest plot of SUA level effect on **CVD hospitalizations**



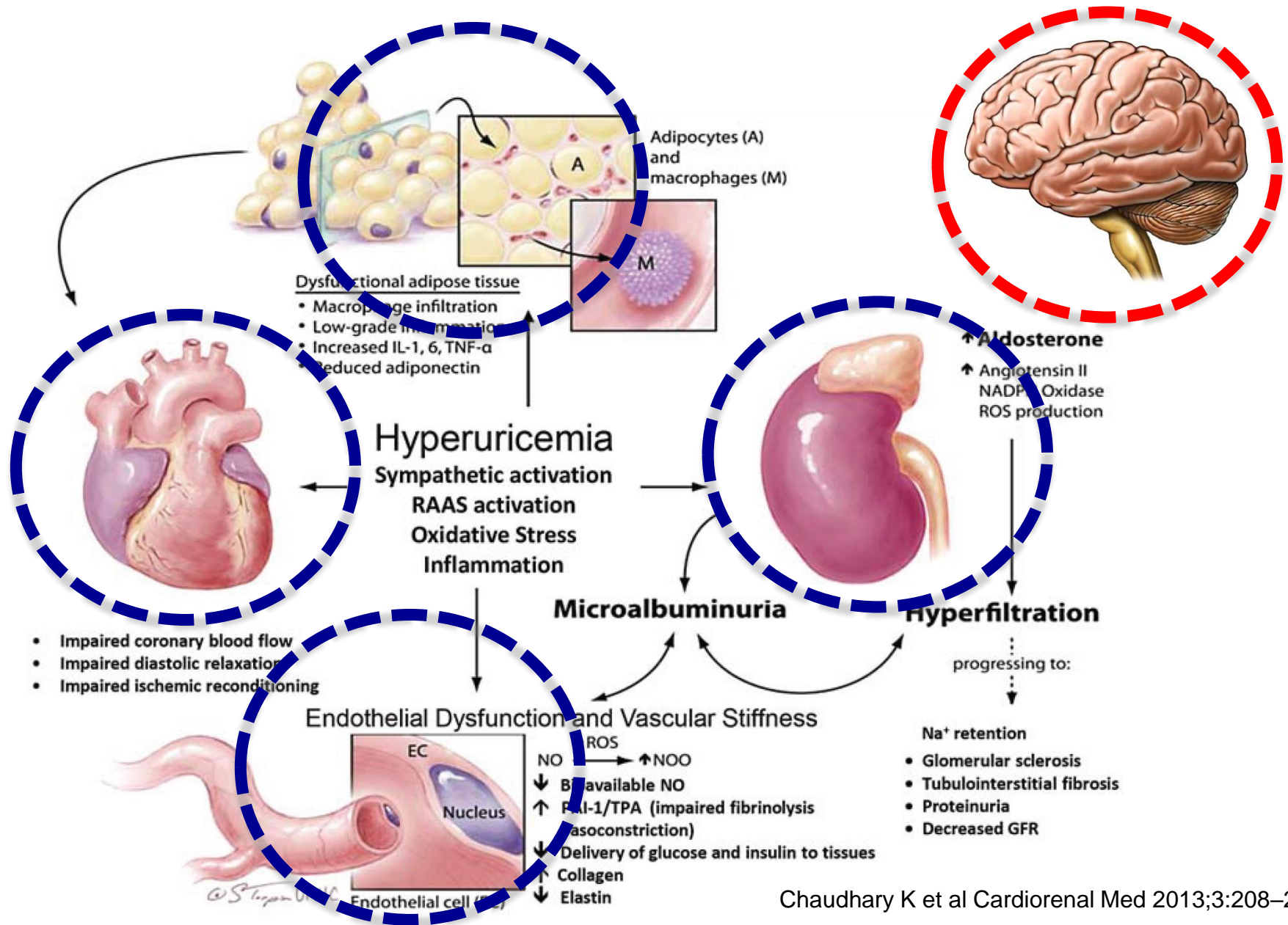
Multivariate analysis: *adjusted for age, gender, the use of antihypertensives, lipid-lowering drugs, platelet aggregation inhibitors and antidiabetic drugs, the presence of previous CV hospitalizations, TC, TG, LDL-C, CKD stage, the use of hyperuricemia treatment at baselines and during the observation period.*

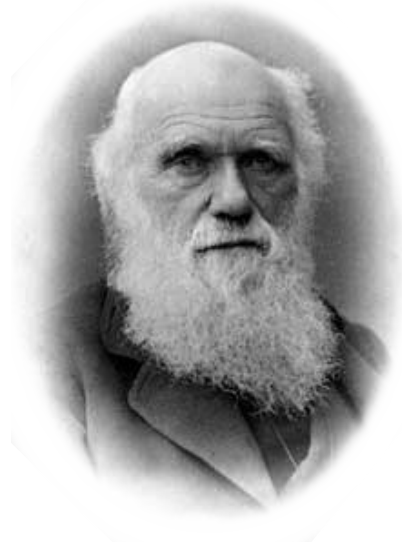
Forest plot of SUA level effect on **total mortality**



Multivariate analysis: *adjusted for age, gender, the use of antihypertensives, lipid-lowering drugs, platelet aggregation inhibitors and antidiabetic drugs, the presence of previous CV hospitalizations, TC, TG, LDL-C, CKD stage, the use of hyperuricemia treatment at baselines and during the observation period.*

Hyperuricemia and Cardiorenal Metabolic Syndrome





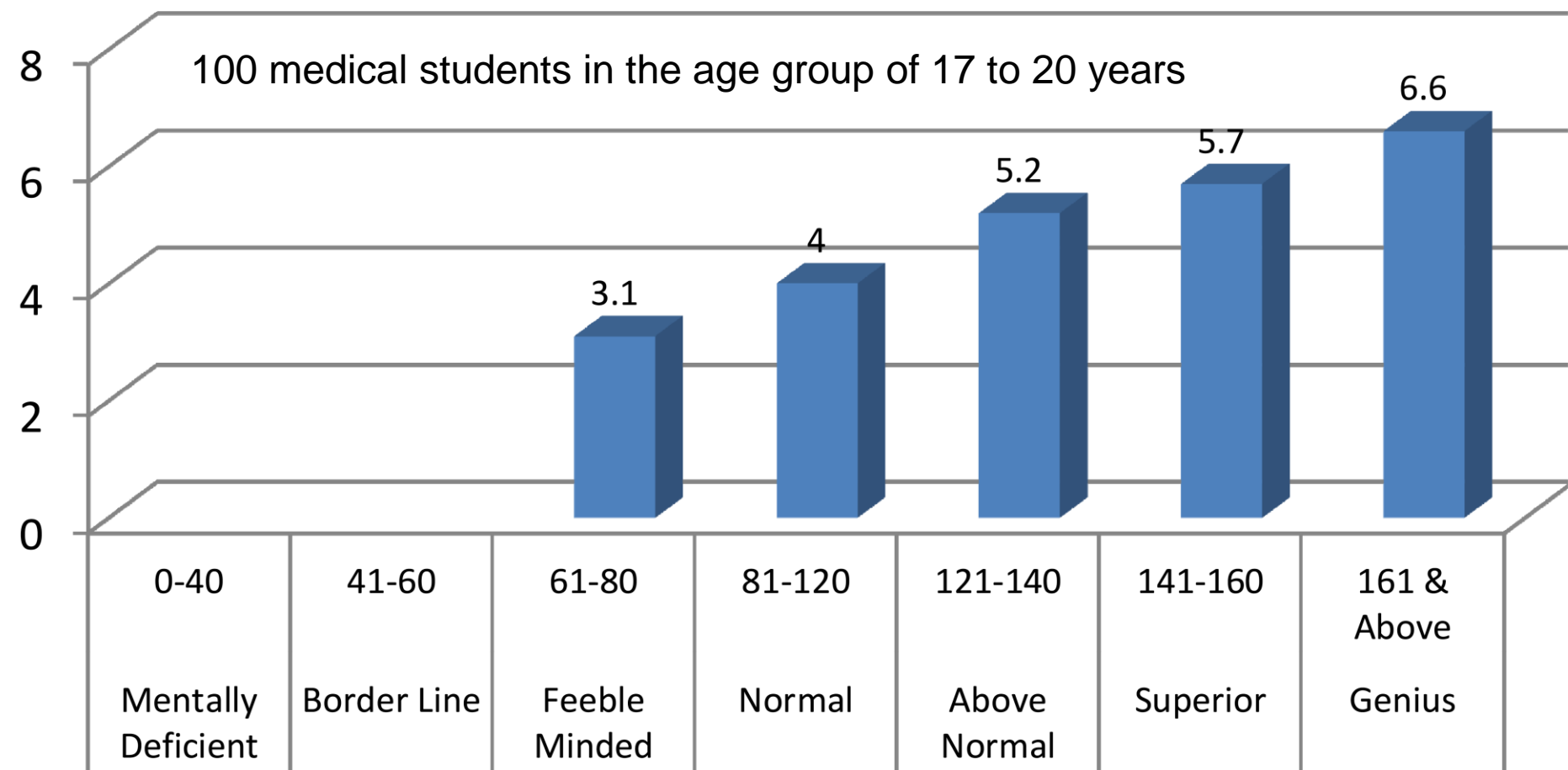
Alexander the great, Darwin,
Harvey, Newton, Sydenham,

This association cannot be mere
co-incidence....



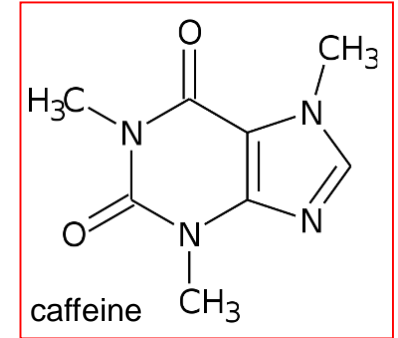
Study of Serum Uric Acid and its Correlation with Intelligence Quotient and Other Parameters in Normal Healthy Adults

Mean Serum Uric Acid Level - In Relation to IQ



Lessons from comparative physiology: could uric acid represent a physiologic alarm signal gone awry in western society?

- Uric acid having similar structure to that of caffeine and theobromine acts as a cerebral stimulant and thought to be responsible for better development of brain and more intelligence¹.
- Uric acid can increase locomotor activity in rats²
- Uric acid increases with emotional or physical stress³

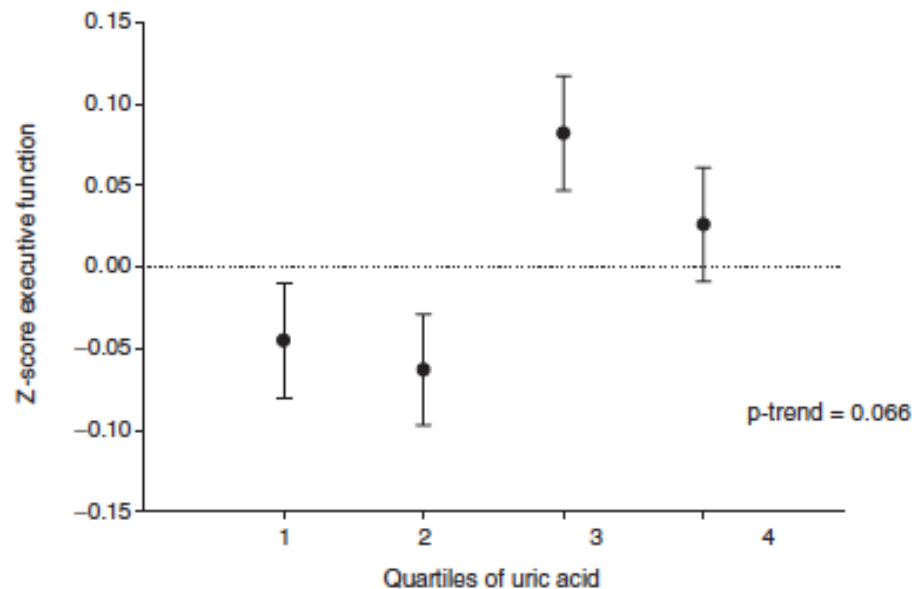
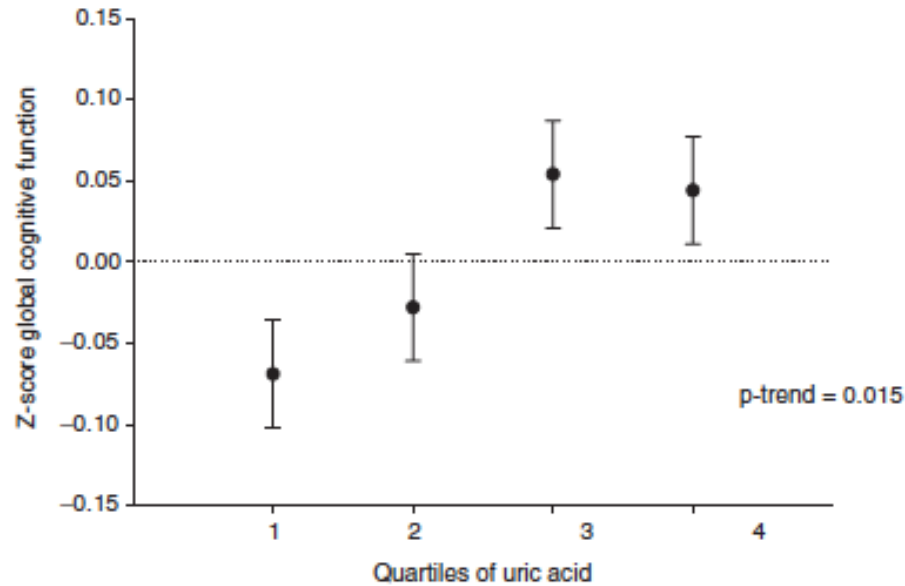


¹ Orowan E. Nature 1955;175:683–684.

² Barrea CM et al. Pharmacol Biochem Behav 1989;33:367–369.

³ Rahe RH et al. Psychosom Med 1974;36:258–268.

SUA and cognitive function and dementia



Uric acid and the risk of dementia

Uric acid	Model 1 ^a (457 cases)	Model 2 ^b (457 cases)
Per SD increase uric acid	0.93 (0.84–1.03)	0.89 (0.80–0.99)*
1 st Quartile	1 (reference)	1 (reference)
2 nd Quartile	0.97 (0.75–1.26)	0.95 (0.73–1.23)
3 rd Quartile	0.94 (0.73–1.22)	0.90 (0.69–1.18)
4 th Quartile	0.81 (0.62–1.05)	0.73 (0.55–0.97)*
P-trend	0.114	0.030

Estimates indicate hazard ratios with corresponding 95%.

^a Adjusted for age, sex and level of education. ^b Adjusted for age, sex, level of education serum creatinine levels, systolic blood pressure, ever smoking, total cholesterol and HDL-cholesterol levels, diabetes mellitus, waist/hip ratio, cardiovascular disease, all at baseline.

* $P < 0.05$.

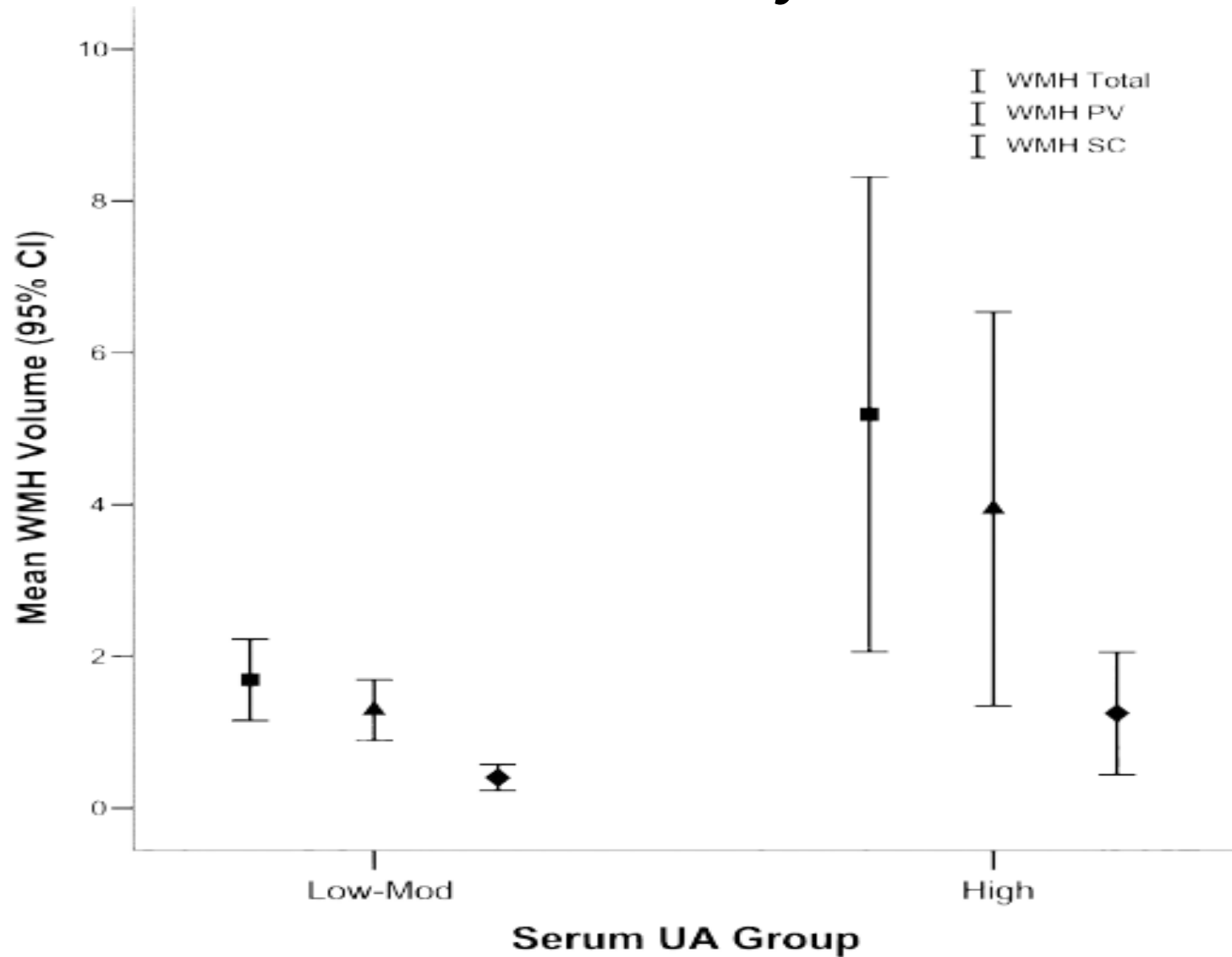
The mean age of the total sample of 4618 participants was 69.4 years, 61% were female and **the mean serum level of uric acid was 322.3 mmol/l.**

Uric Acid and Dementia in Community-Dwelling Older Persons: The InChianti Study

1.016 elderly subjects (age 74.38 ± 7.58 years)

Adjusted for	UA tertile	OR	p
age, sex, BMI, education	1) 3.82 ± 0.53 mg/dL 2) 5.05 ± 0.27 mg/dL 3) 6.72 ± 1.24 mg/dL	1 (reference) 2.34 (0.87–6.24) 3.06 (1.10–8.52)	- 0.0895 0.0323
+ alcohol, energy intake, smoking, chol, plasma vit. E	1) 3.82 ± 0.53 mg/dL 2) 5.05 ± 0.27 mg/dL 3) 6.72 ± 1.24 mg/dL	1 (reference) 2.73 (0.96–7.75) 3.63 (1.22–10.77)	- 0.0585 0.0199
+ renal function, hypertension, CVD, CBVD	1) 3.82 ± 0.53 mg/dL 2) 5.05 ± 0.27 mg/dL 3) 6.72 ± 1.24 mg/dL	1 (reference) 2.62 (0.91–7.52) 3.32 (1.06–10.42)	- 0.1465 0.0262
+ MMSE basal score	1) 3.82 ± 0.53 mg/dL 2) 5.05 ± 0.27 mg/dL 3) 6.72 ± 1.24 mg/dL	1 (reference) 11.02 (1.69–72.00) 18.89 (2.04–174.67)	- 0.0122 0.0096

Serum uric acid and brain ischemia in normal elderly adults



Cerebral Ischemia Mediates the Effect of Serum Uric Acid on Cognitive Function

Mean age, 59.9±18.9 mg/dL
Serum UA, 4.5±1.4 mg/dL

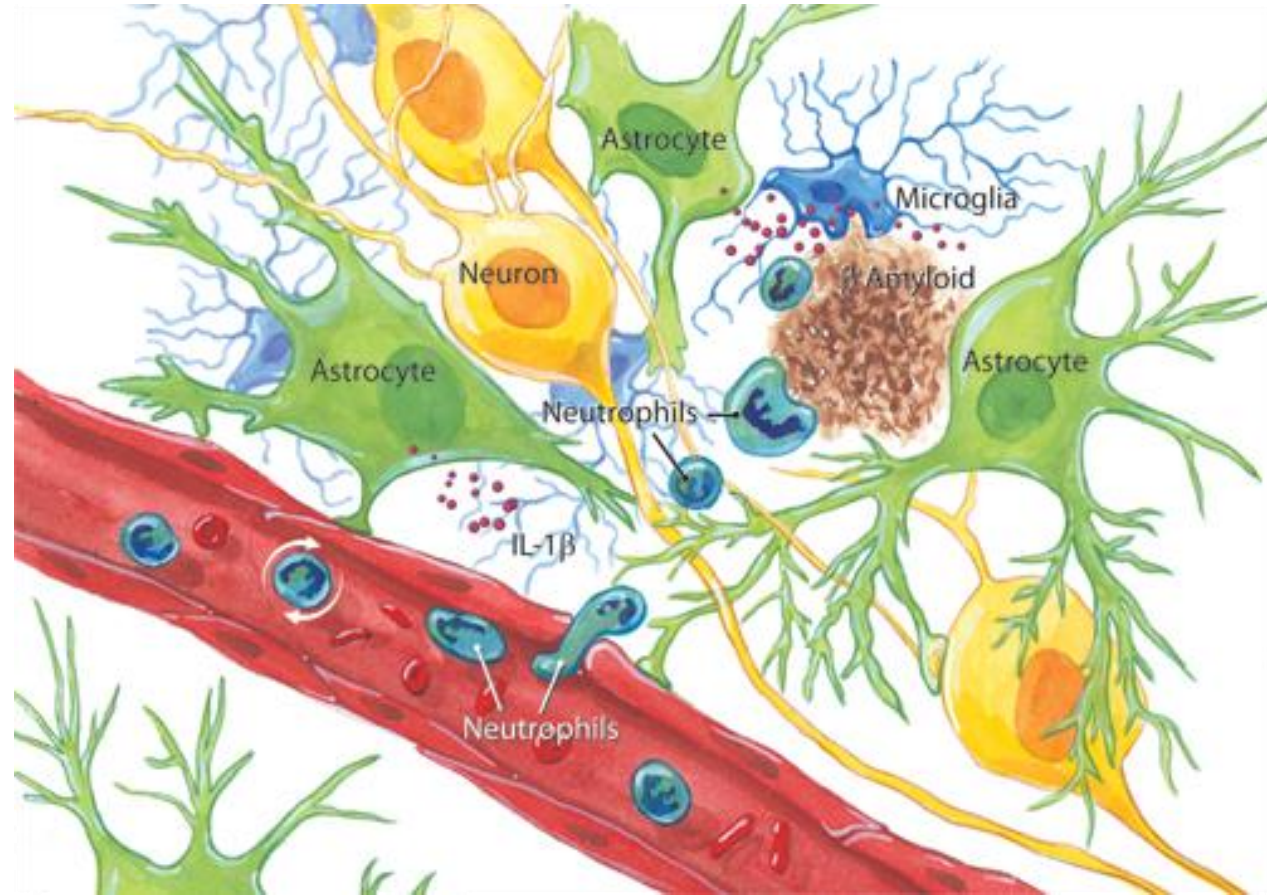
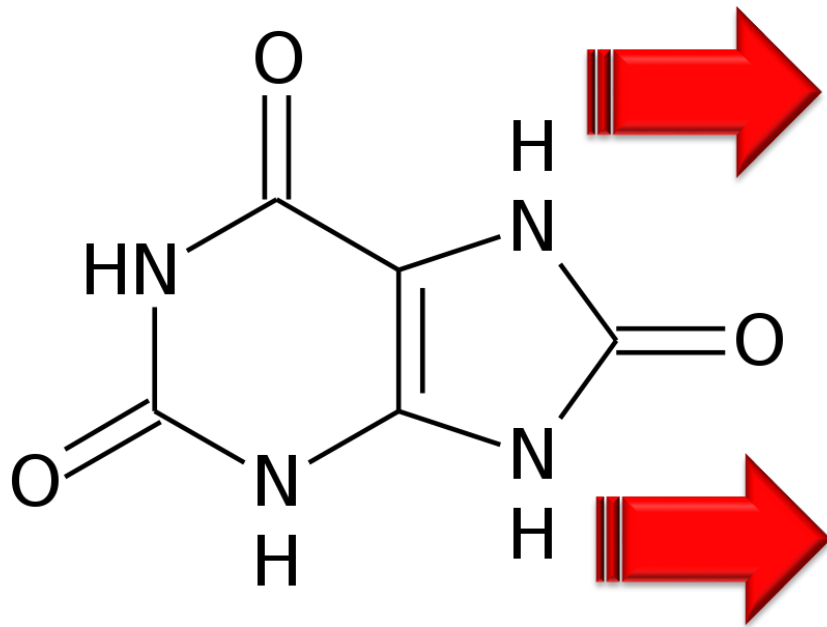
108 community-dwelling adults aged 20 to 96 years

	Serum UA	P	WMH Volume	P
Serum UA
WMH volume*	0.232	0.002
Working memory†	−0.245	0.001	−0.367	<0.001
Processing speed†	−0.118	0.011	−0.409	<0.001
Ideational fluency†	−0.204	0.006	−0.353	<0.001
Crystallized intelligence†	−0.060	0.427	−0.073	0.333
Fluid intelligence†	−0.128	0.087	−0.348	<0.001
Verbal learning/memory†	−0.257	<0.001	−0.307	<0.001
Visual learning/memory†	−0.118	0.115	−0.367	<0.001
Executive functioning‡	−0.047	0.533	−0.190	0.011

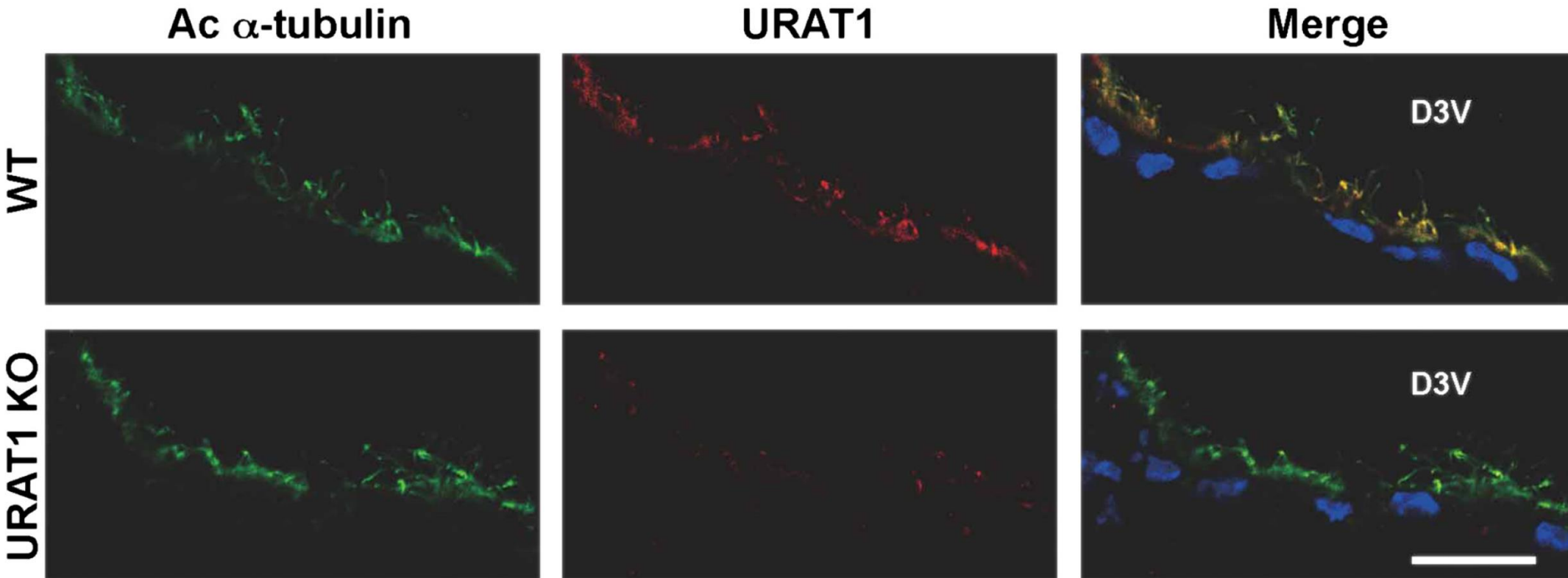
*P<0.05.
†P<0.01.
‡P=0.05.

Model 1	WM	PS	IF	VeM	Model 2	WM	PS	IF	VeM
Step 1 demographics and health	0.39†	0.60†	0.37†	0.32†	Step 1 demographics and health	0.39†	0.60†	0.37†	0.32†
Step 2 serum UA	0.03†	0.01‡	0.02*	0.03*	Step 2 WMH volume	0.05†	0.03†	0.05†	0.02*
Step 3 WMH volume	0.03†	0.02†	0.04†	0.01	Step 3 serum UA	0.01	0.00	0.00	0.01

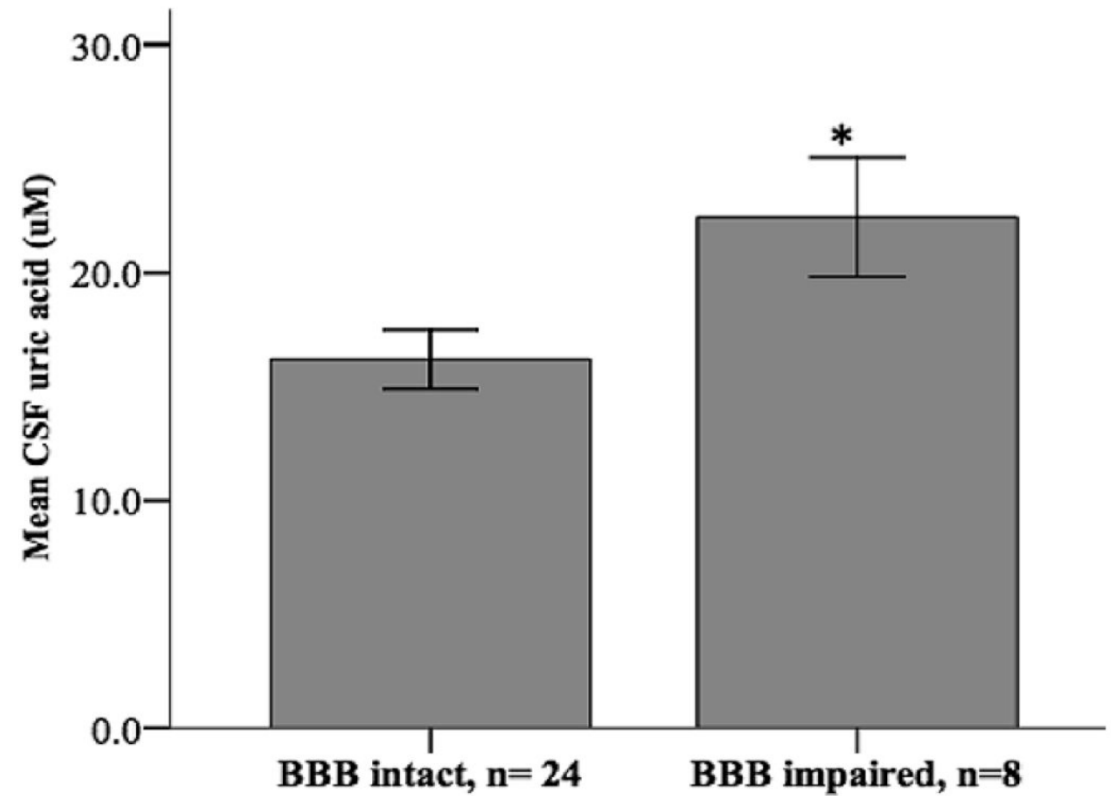
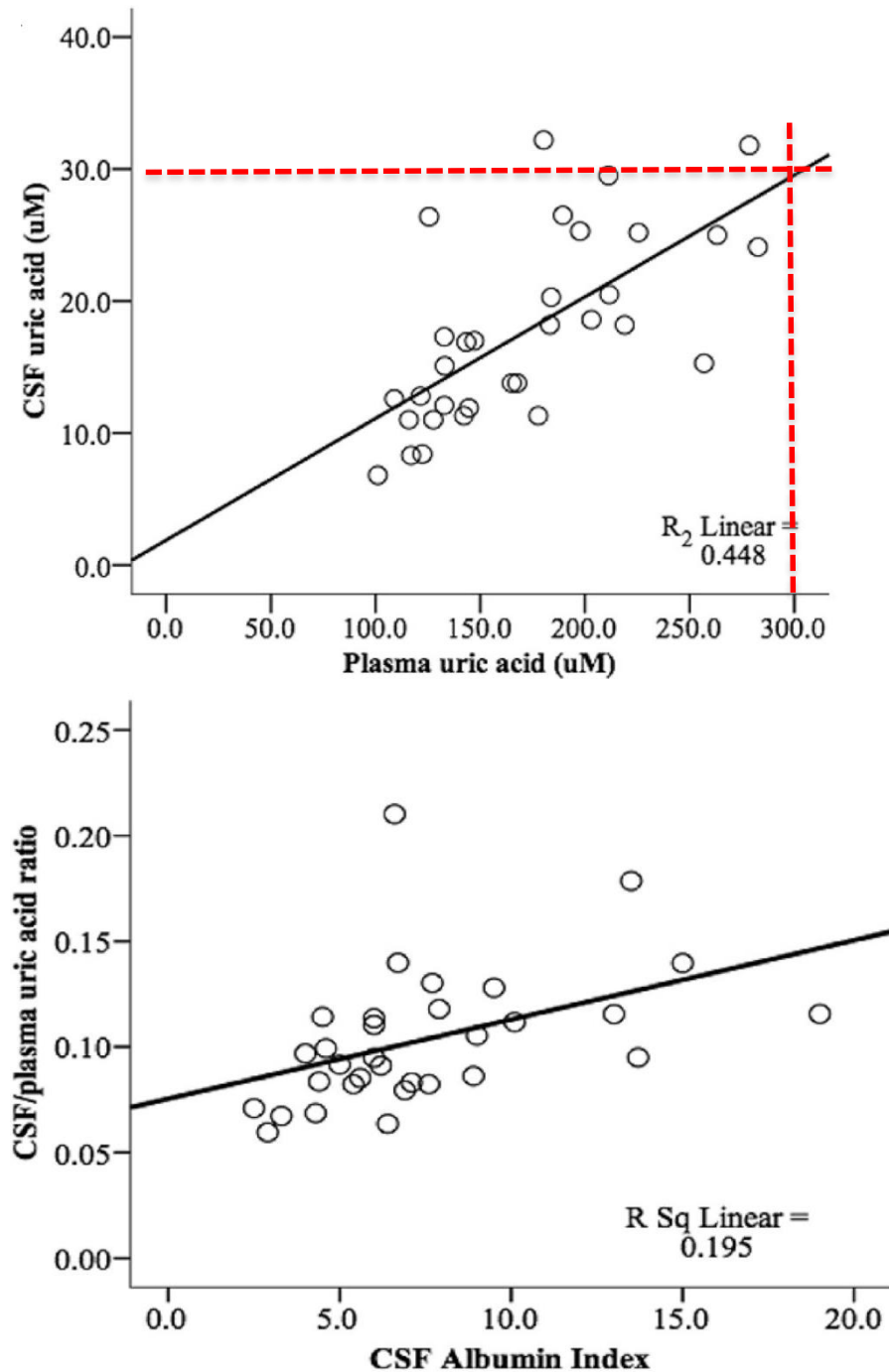
Could uric acid directly promote neuronal dysfunction and/or damage?



Ependymal cells of the mouse brain express urate transporter 1 (URAT1)



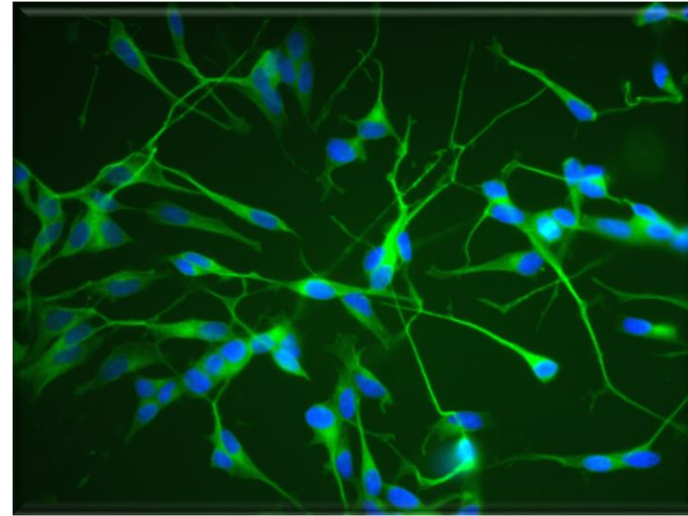
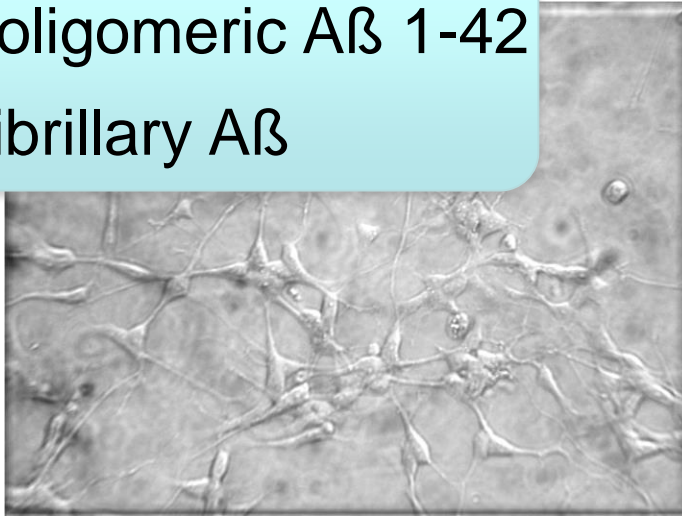
Association between plasma uric acid and blood-brain barrier integrity in AD



Differentiated SHSY5Y neuroblastoma were used to reproduce an in vitro model of early and late AD

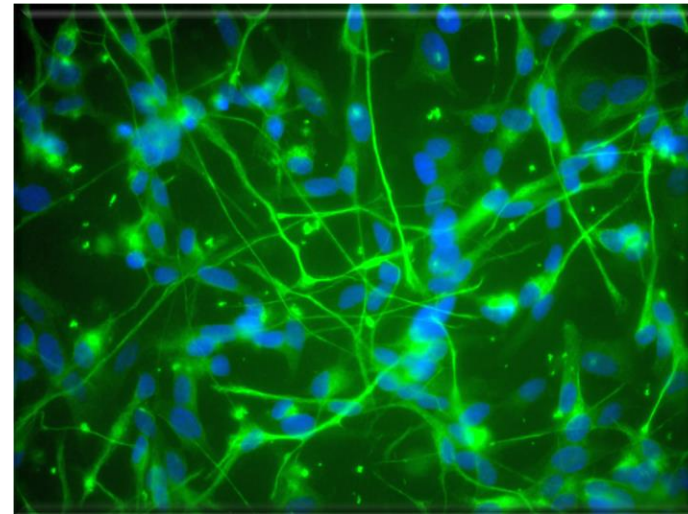
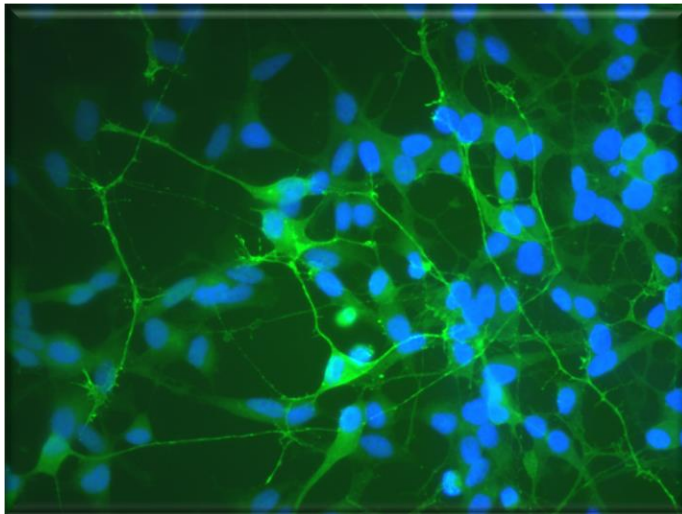
Early AD: oligomeric A β 1-42

Late AD: fibrillary A β



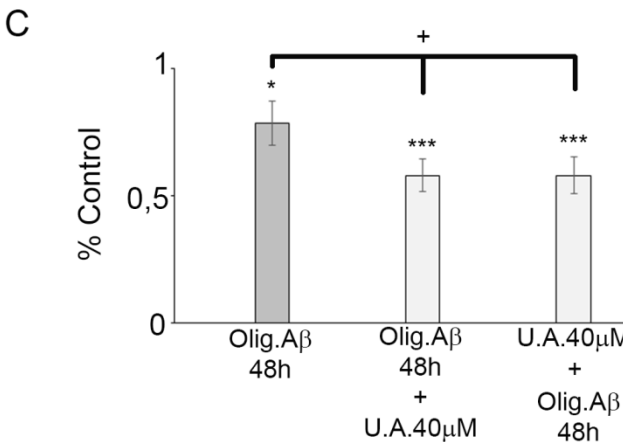
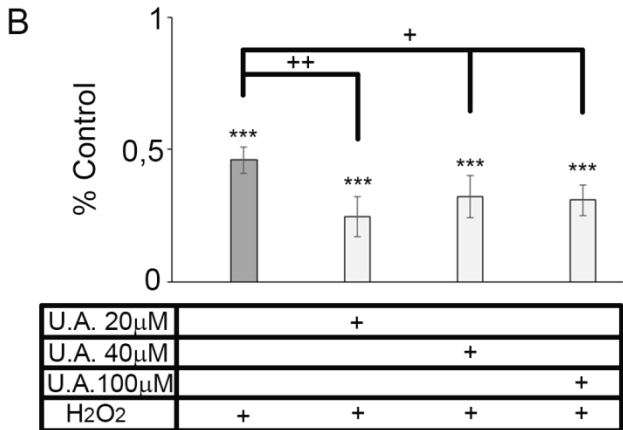
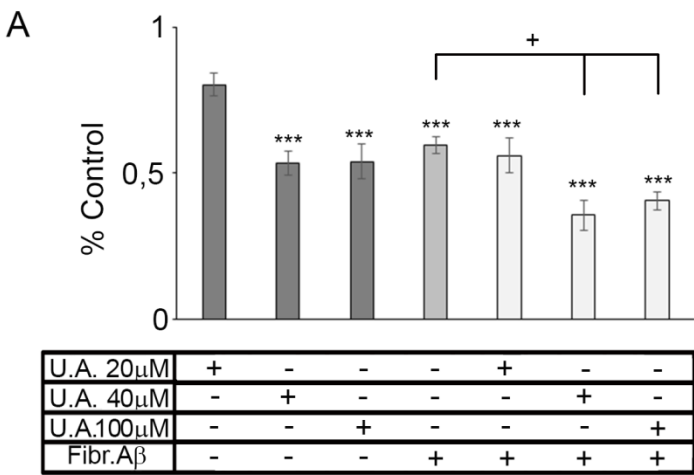
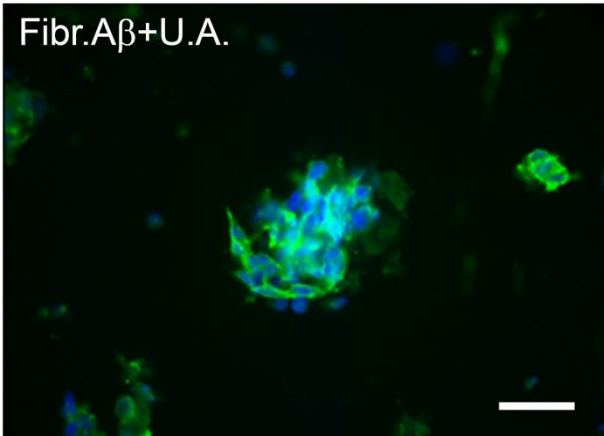
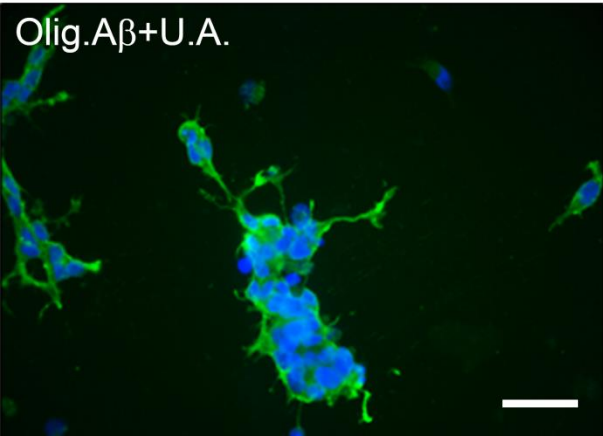
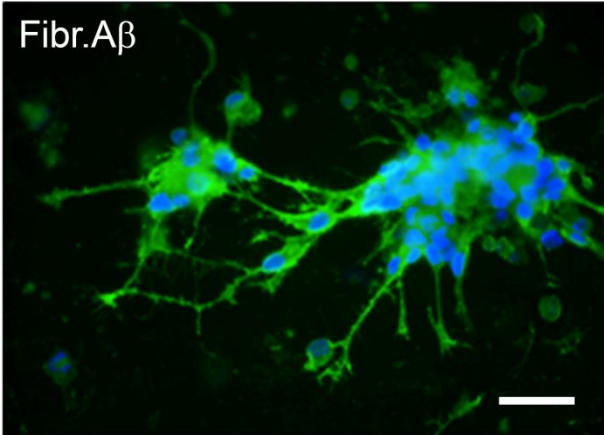
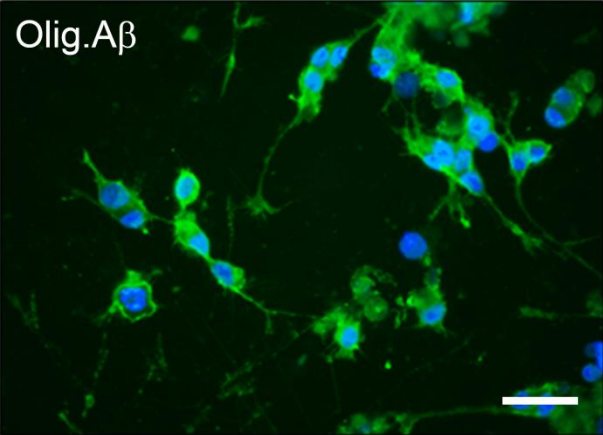
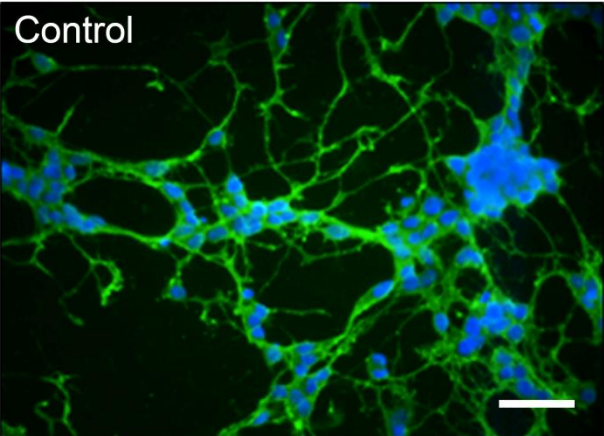
β tubulin III

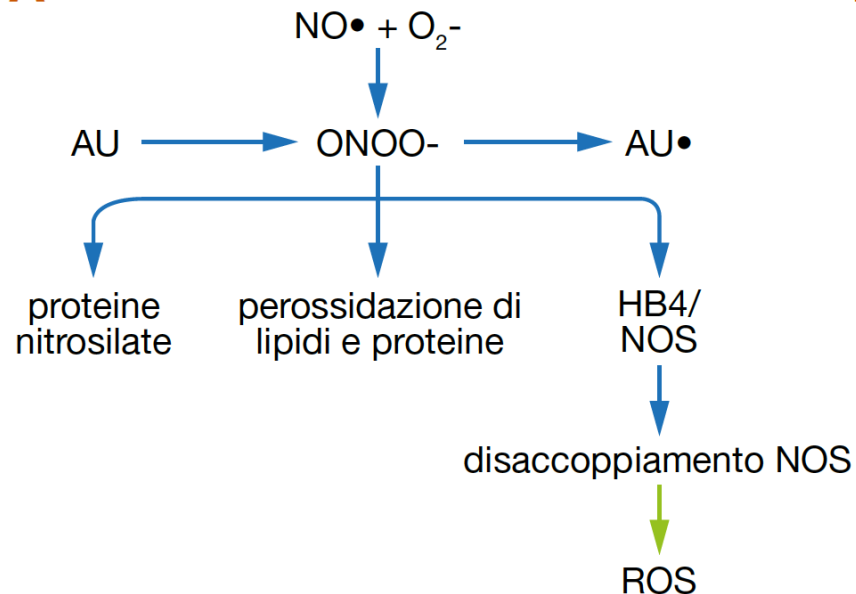
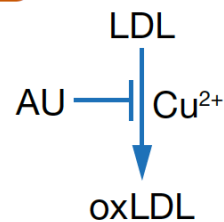
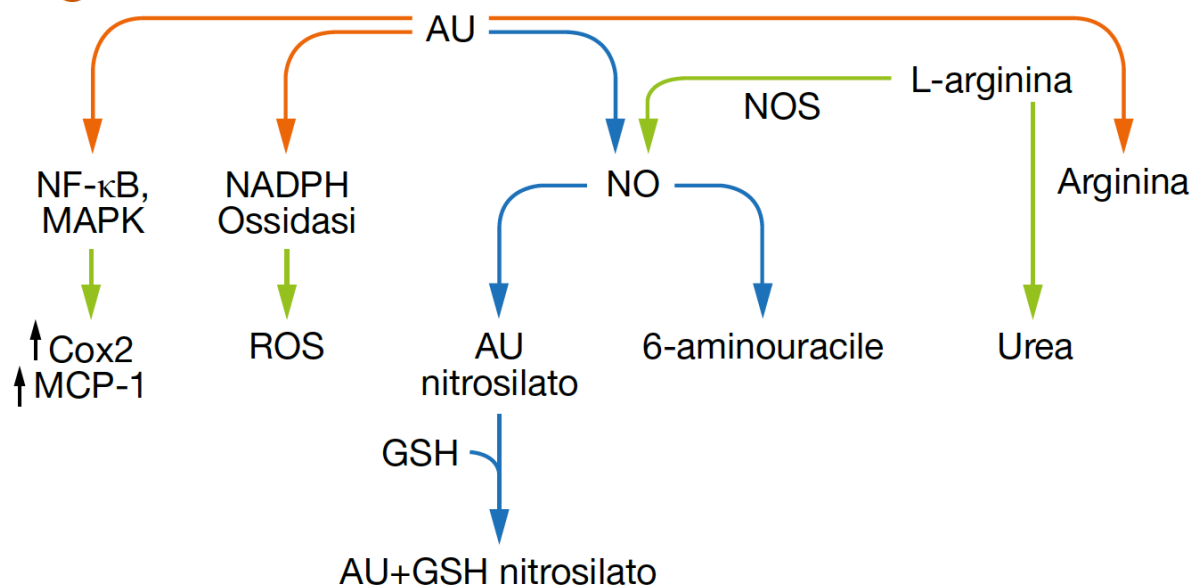
GAP-43



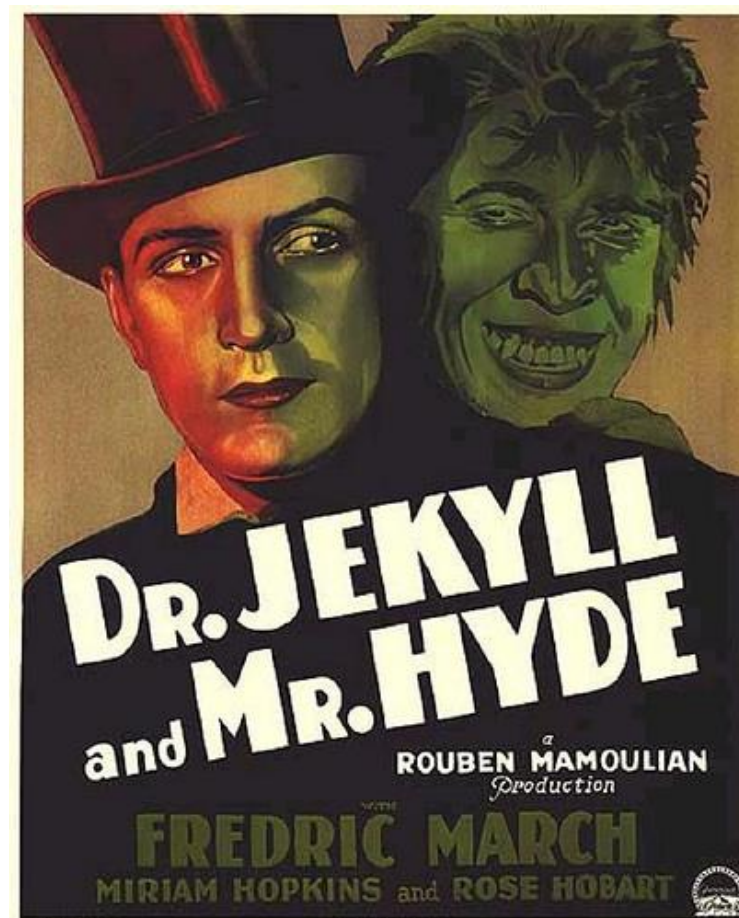
NF 200

GAP-43

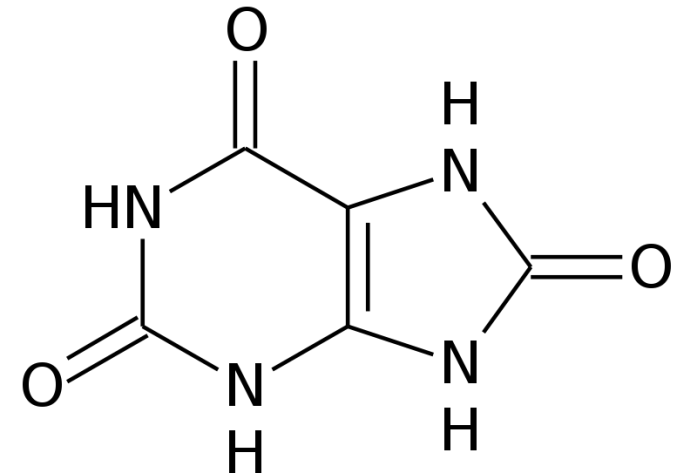


A**B****C**

Ambivalenza
biologica
dell'acido urico



Thus, uric acid could be really dangerous for the brain...



Hypertension

Diabetes

Insulin resistance

Metabolic syndrome

Endothelial dysfunction

Atherosclerosis

Atrial fibrillation

Oxidative stress

Neurotoxic effect



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- How we can reduce serum uric acid?
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 - **Drugs**

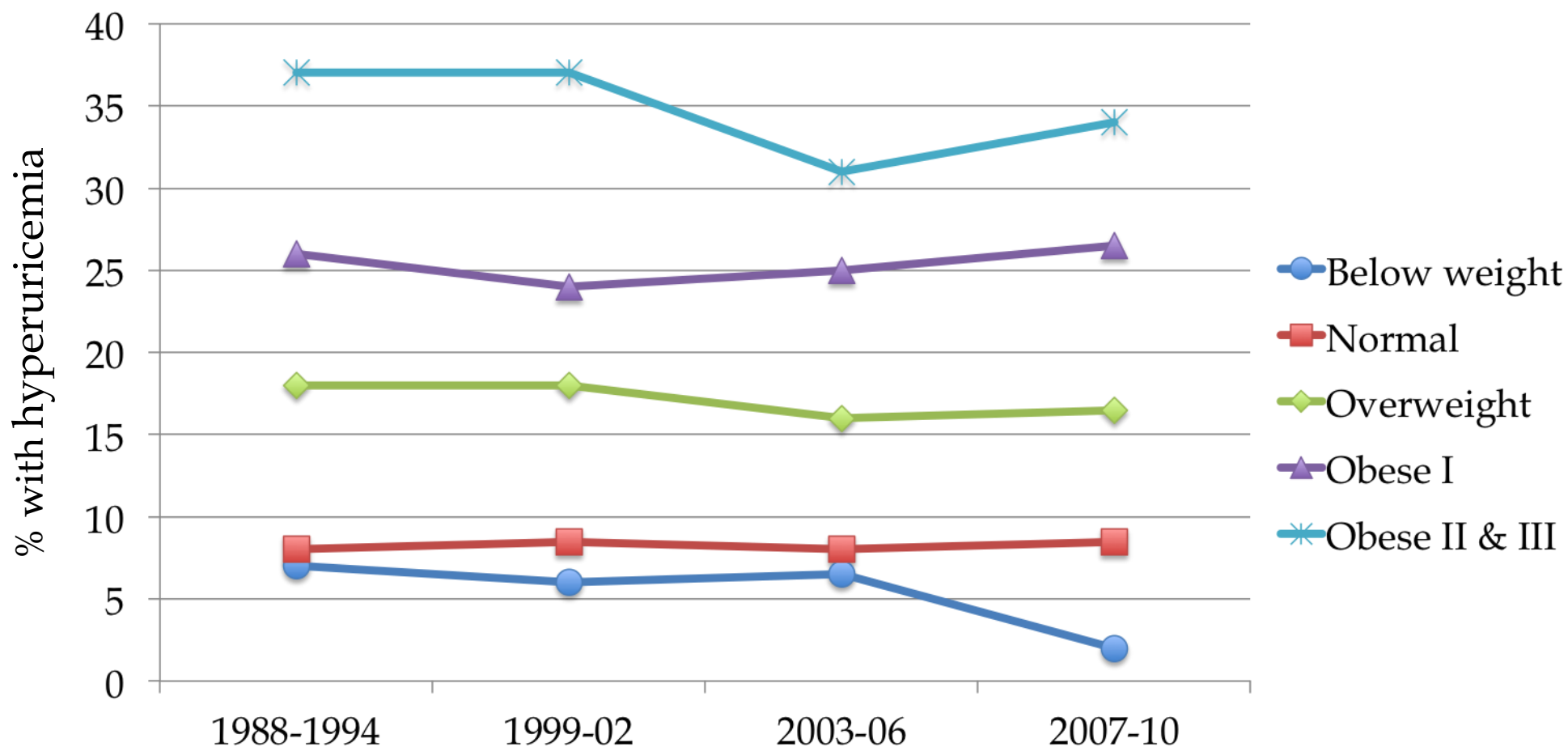
Patient education and appropriate lifestyle advice (healthy diet and reduced consumption of beverages containing fructose and alcohol, beer especially) are core aspects of management. Strength of recommendation (95% CI): 83 (75, 91)



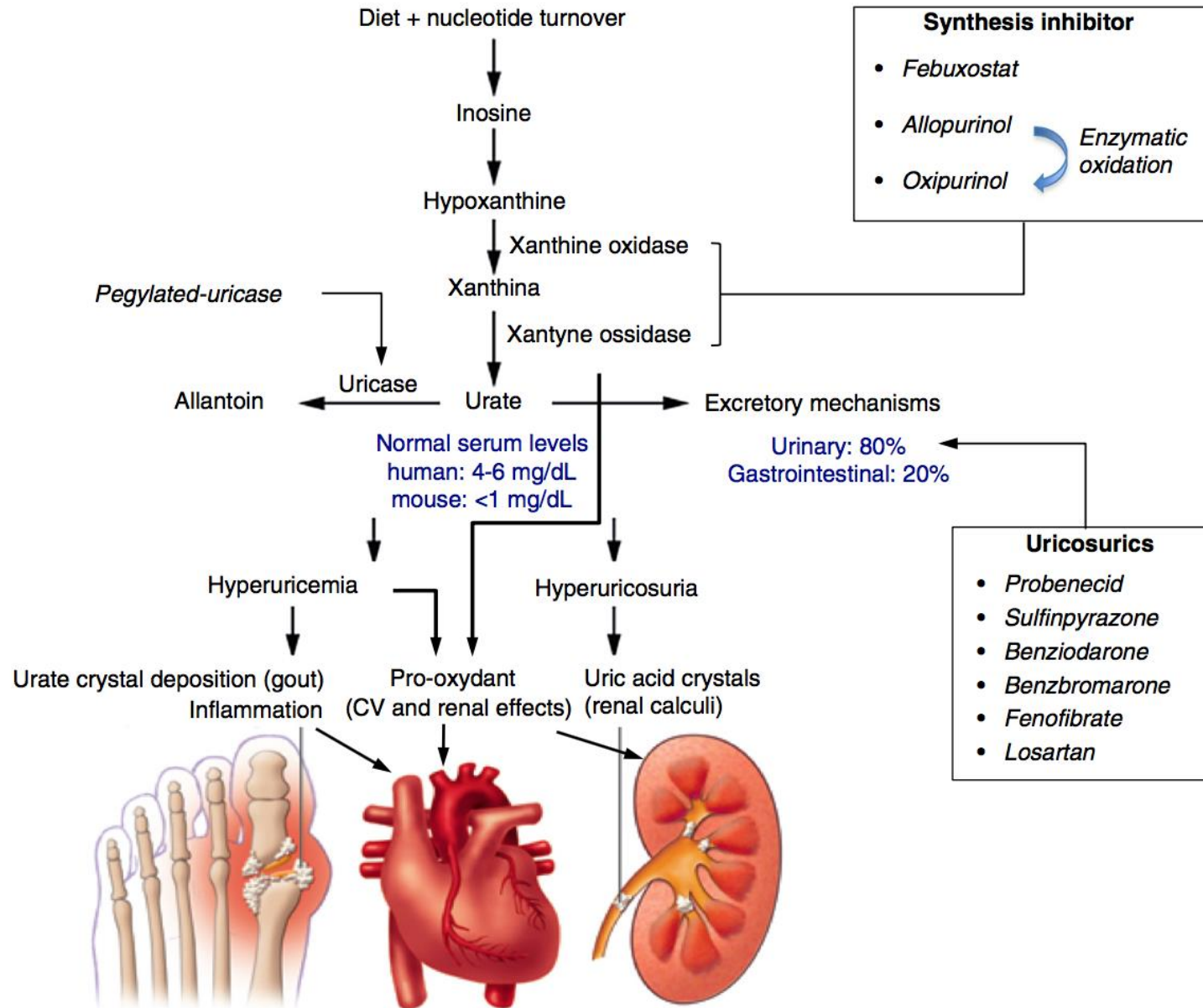
Charles Dickens wrote about gout in both Bleak House and The Pickwick Papers.

In The Pickwick Papers, the character Sam Weller warns his father that drinking will lead to gout.

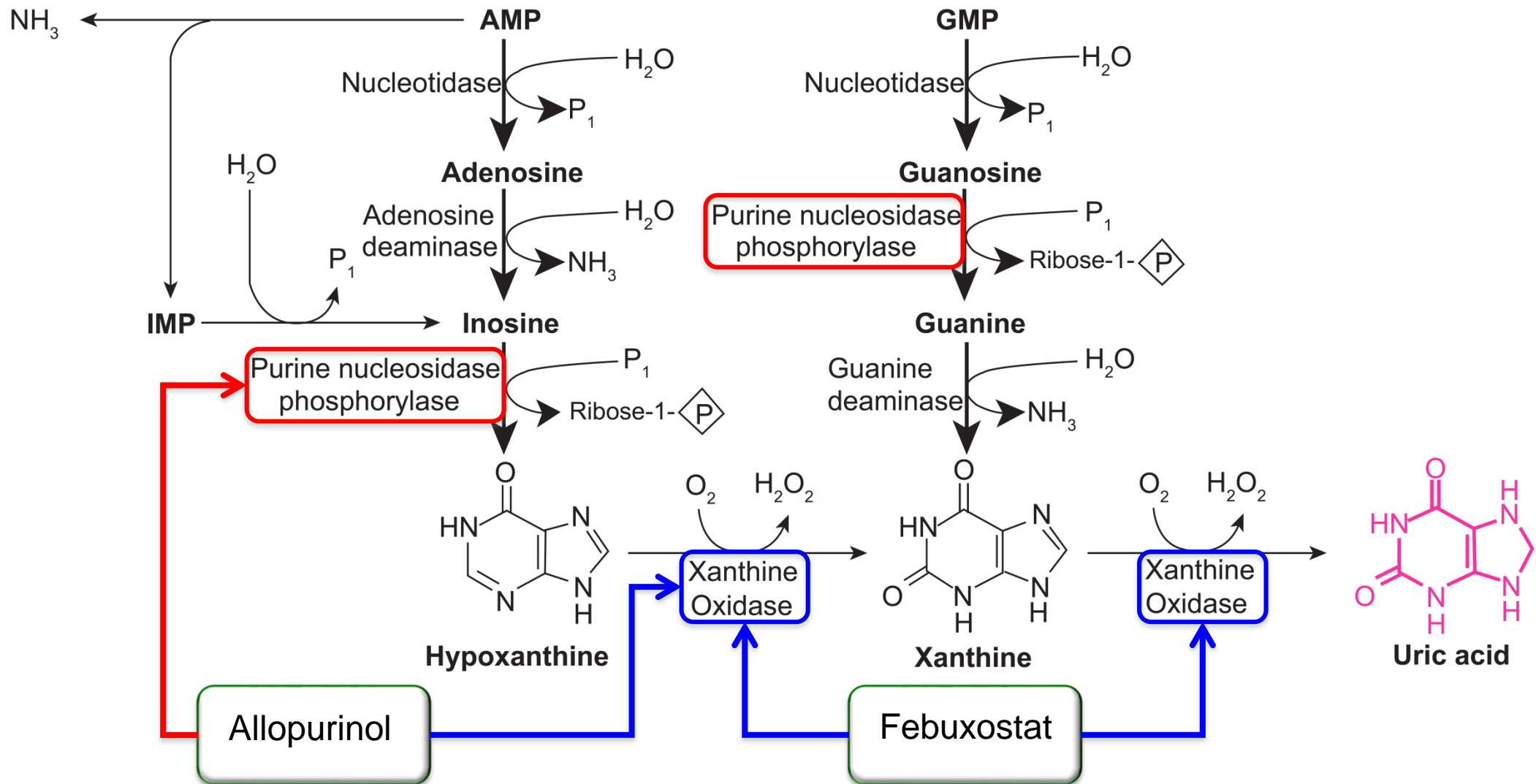
The prevalence of hyperuricemia stratified by degree of Body Mass Index



Therapeutic Approaches to Chronic Hyperuricemia and Gout



The purine degradation pathway



RCT meta-analysis comparing efficacy and safety of febuxostat and allopurinol in patients with gout.

Outcome	Association measure	Febuxostat			
		40mg	80mg	120mg	240mg
Target <6mg/dl	NNT (95%IC) [§]	20 [¶] (11.1, ∞) [§]	3.2 [¶] (2.9, 3.6) [§]	2.3 [¶] (2.1, 2.6) [§]	1.9 [¶] (1.6, 2.2) [§]
Flare up	RR (95%IC)	-	1.06 [¶] (0.93, 1.21) [§]	1.29 [¶] (0.87, 1.91) [#]	2.26 [¶] (1.72, 2.98) [§]
Serious Adverse Effects	RR (95%IC)	0.65 [¶] (0.41, 1.03) [§]	0.74 [¶] (0.51, 1.06) [§]	1.11 [¶] (0.61, 2.02) [§]	-
		Combined RR for all combined doses: 0.76 (0.59, 0.98)			

[§] fixed model, [#] random effect model; NNT: number needed to treat; RR: risk ratio; IC: interval di confidenza

¶

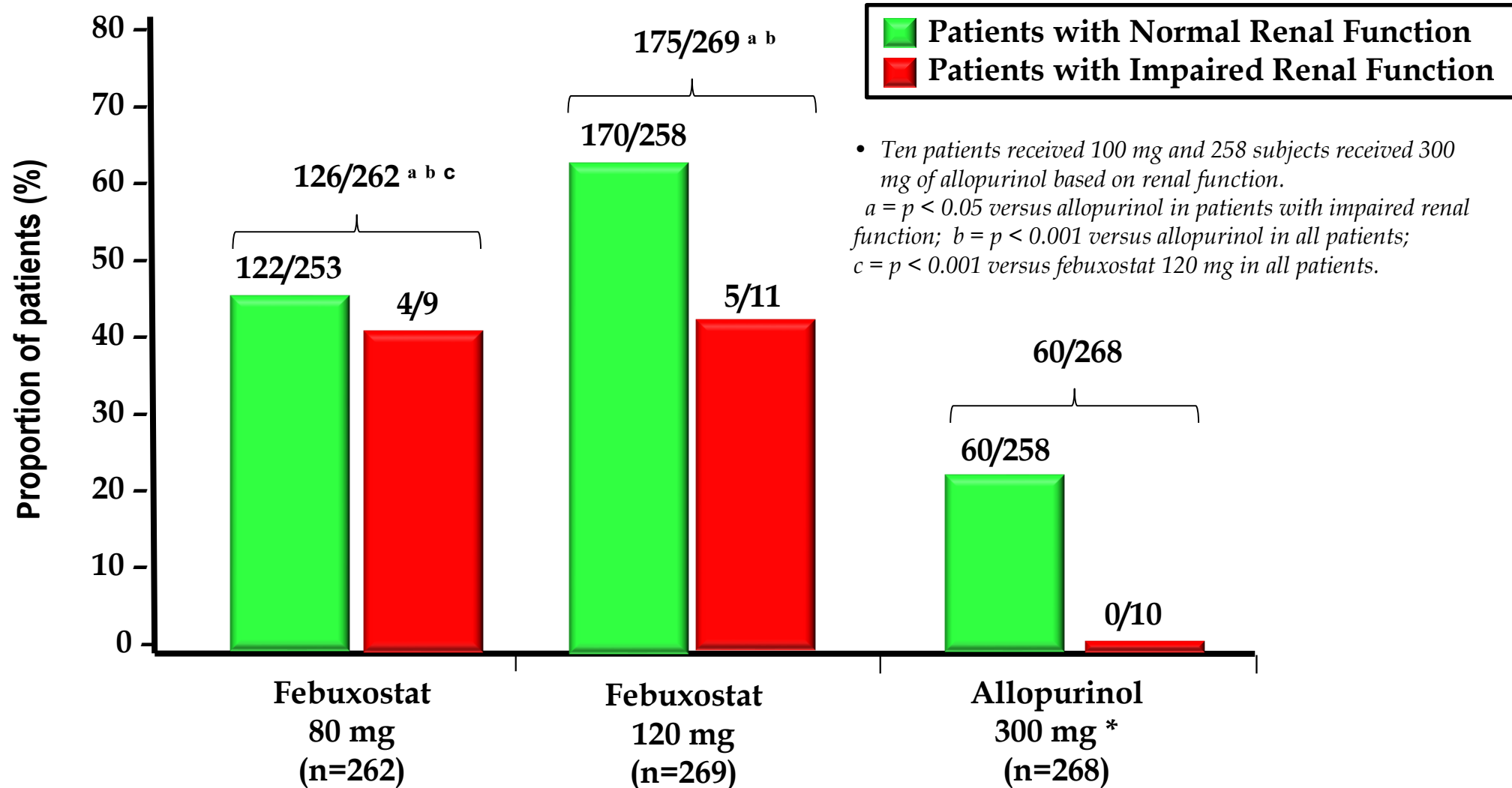
Italian Society of Rheumatology recommendations for the management of gout

M. Manara¹, A. Bortoluzzi², M. Favero³, I. Prevete⁴, C.A. Scirè¹,
G. Bianchi⁵, C. Borghi⁶, M.A. Cimmino⁷, G.M. D'Avola⁸, G. Desideri⁹,
G. Di Giacinto¹⁰, M. Govoni², W. Grassi¹¹, A. Lombardi¹², M. Marangella¹³,
M. Matucci Cerinic¹⁴, G. Medea¹⁵, R. Ramonda³, A. Spadaro¹⁶,
L. Punzi³, G. Minisola⁴

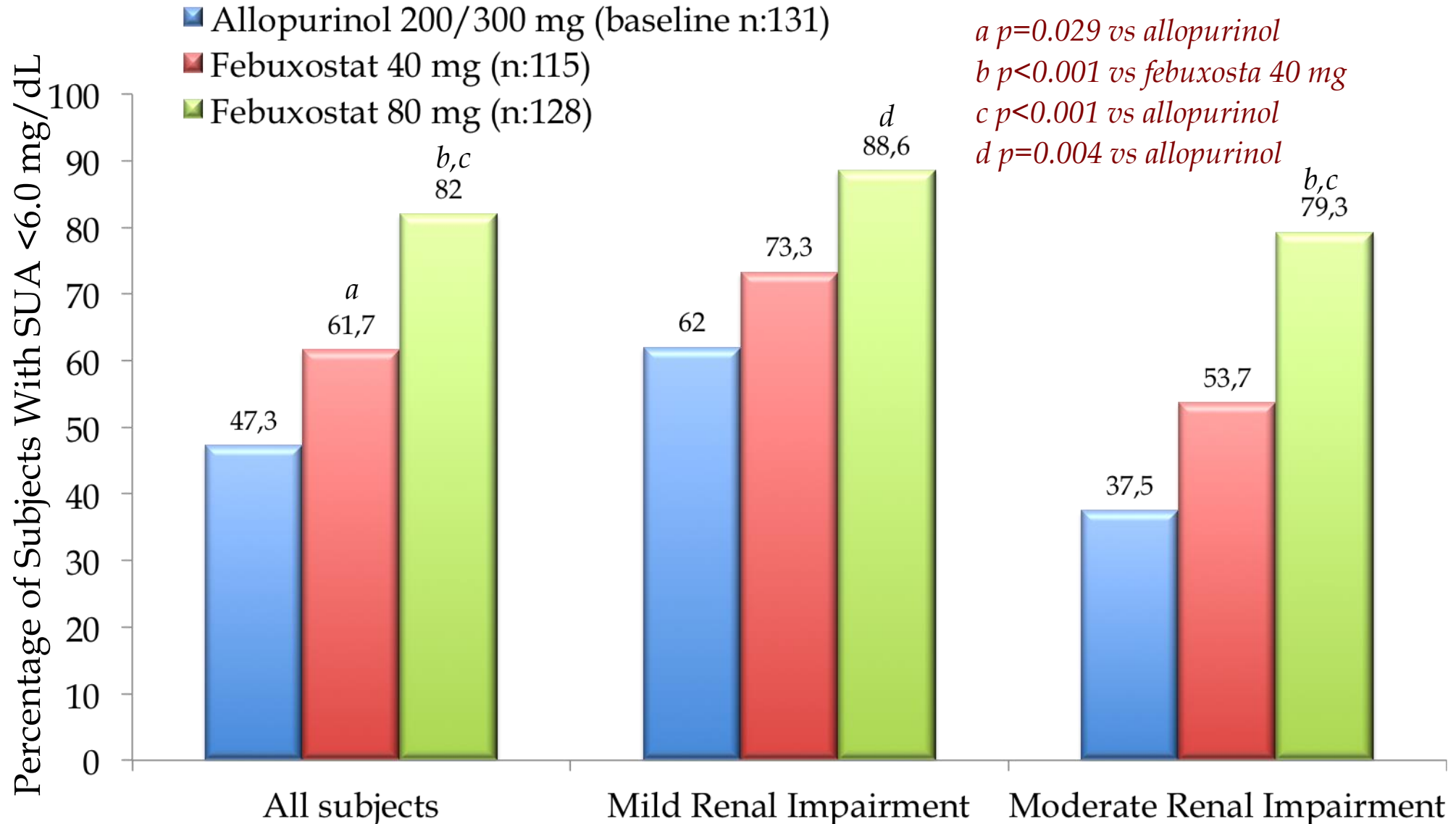
Febuxostat is an effective alternative to allopurinol which shows greater efficacy and minor adverse effects as urate lowering agent. Starting doses are to be low and increased if necessary. Strength of recommendation (95% CI): 82 (76, 89)

Allopurinol- and Placebo-Controlled, Efficacy Study of Febuxostat: APEX study

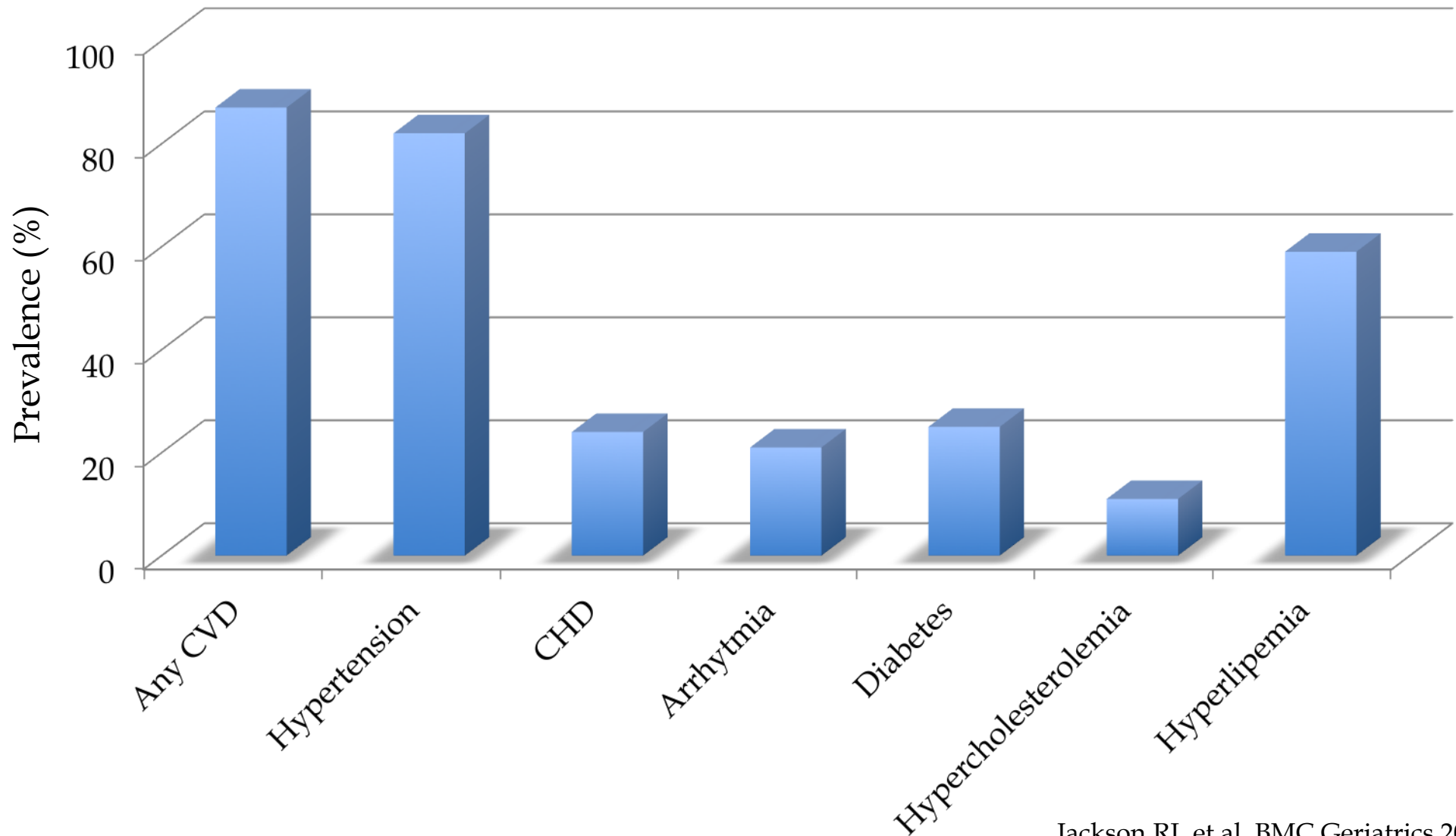
Subjects ($n = 1,072$) with serum urate level >8.0 mg/dL and gout and normal or impaired RF (creat. >1.5 to ≤ 2.0 mg/dl)



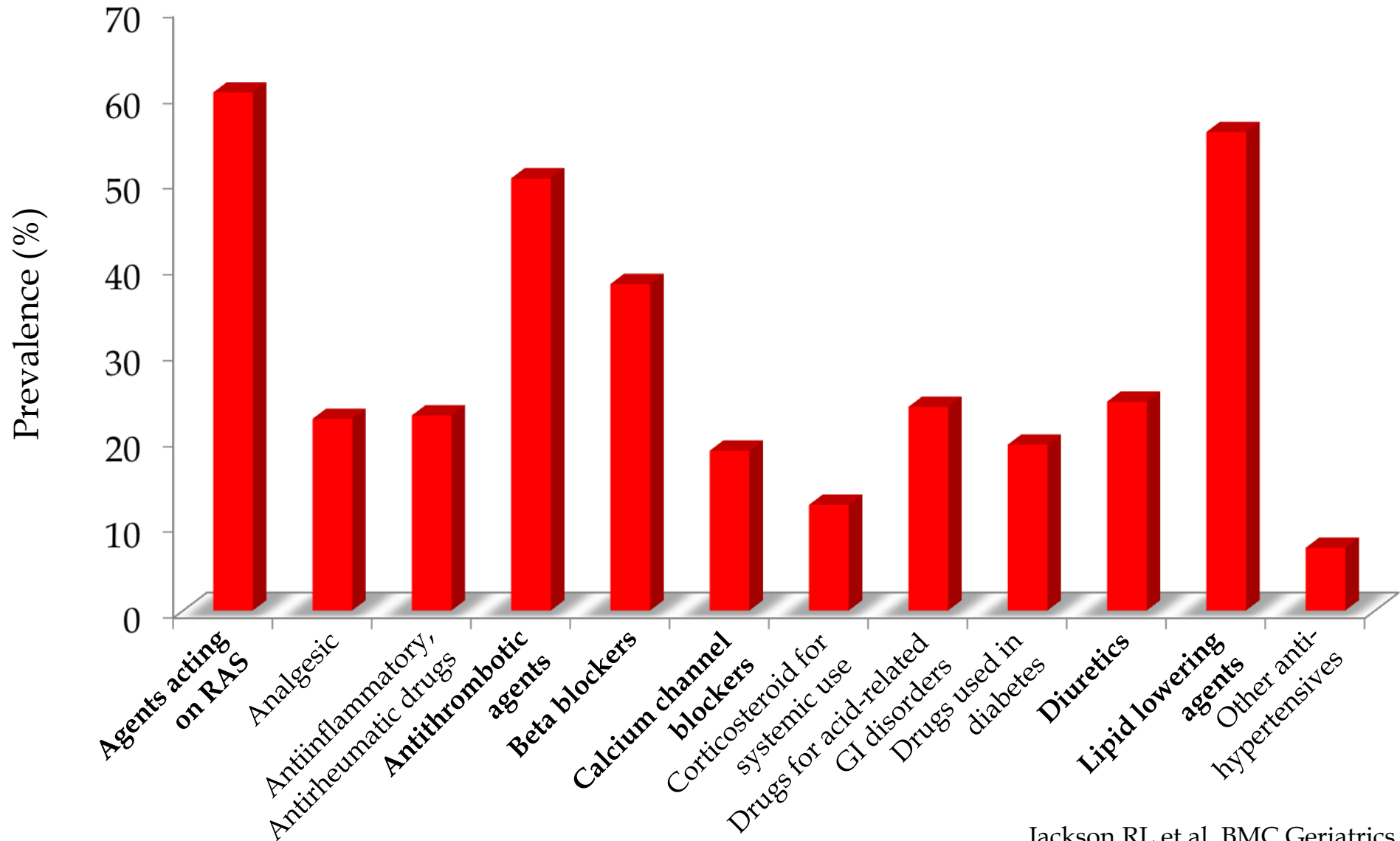
Efficacy and Safety of Febuxostat for Urate Lowering in Gout Patients ≥ 65 Years of Age



Elderly Subjects Often Have a Great Frequency of Comorbidities and Are Taking Multiple Drugs



Selected concomitant medication use among elderly subjects during the CONFIRMS trial



Serum uric acid and the risk of cardiovascular and renal disease

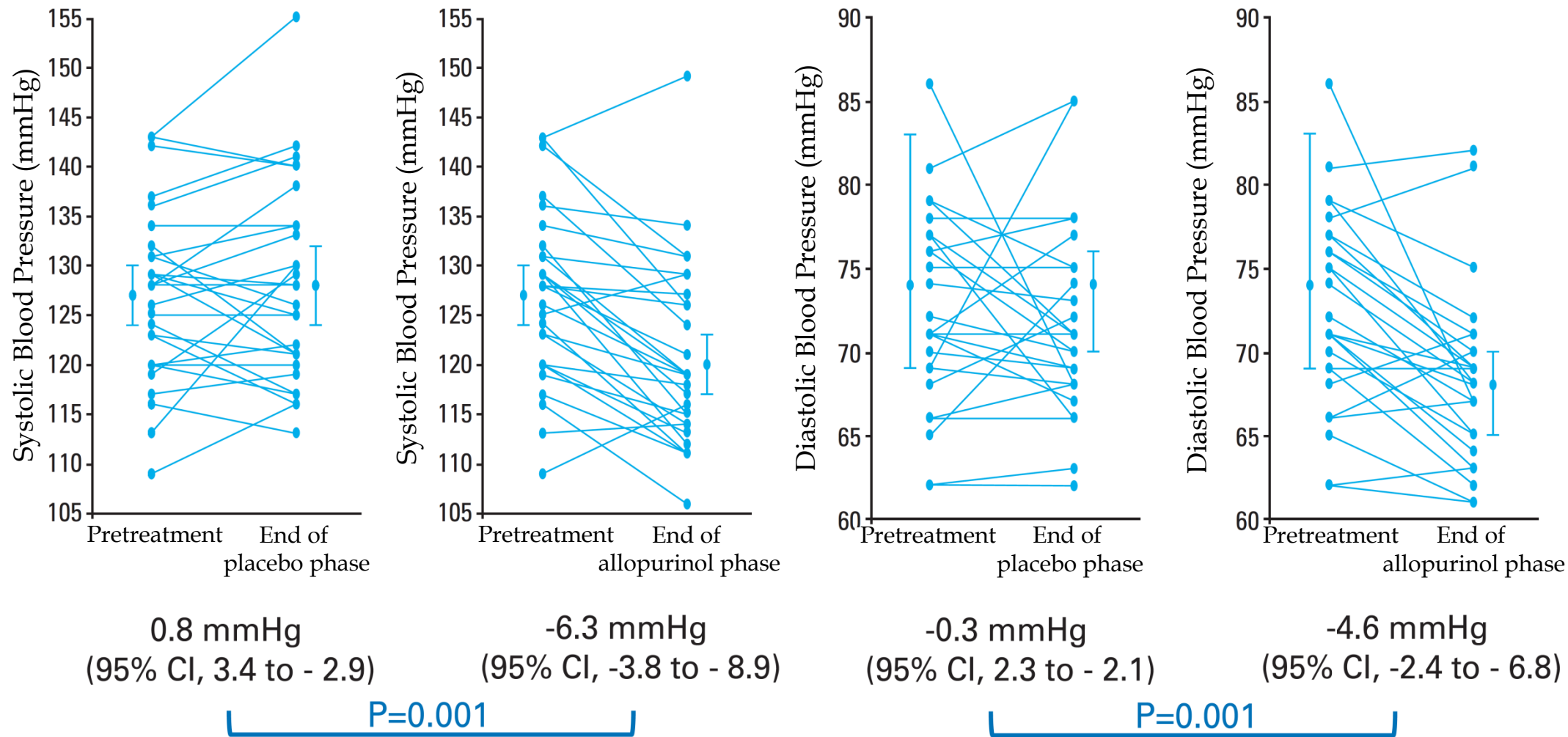
Claudio Borghi^a, Enrico Agabiti Rosei^b, Thomas Bardin^{c,d,e}, Jesse Dawson^f, Anna Dominiczak^f, Jan T. Kielstein^g, Athanasios J. Manolis^h, Fernando Perez-Ruizⁱ, and Giuseppe Mancia^j

IMPORTANT QUESTIONS

- ✧ What threshold should be adopted to define hyperuricemia?
- ✧ Is hyperuricemia an independent risk factor for cardiovascular disease?
- ✧ **Can we improve cardiovascular and renal outcomes by lowering sUA levels?**
- ✧ When should urate-lowering therapy be started?

Effect of Uric Acid Lowering on Blood Pressure of Adolescents With Newly Diagnosed Essential Hypertension

Mean 24 hour blood pressure

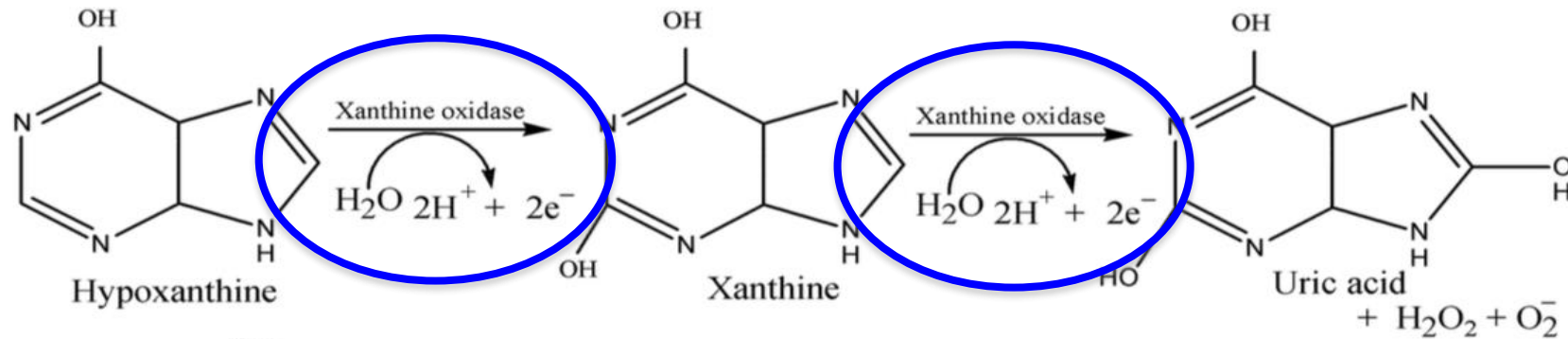


Comparison of randomized studies using xanthine oxidase inhibition in heart failure

Author	Heart failure Population	Xanthine oxidase inhibitor	Follow-up in weeks	Primary Outcome definition	Primary outcome result
Givertz et al. 2015	253 with SUA >9.5 mg/dl with one more high risk marker	Allopurinol 300-600 mg/day	24	Clinical status: Outcomes, medication change and patient global assessment.	13% improved in both allopurinol and placebo arms.
Greig et al. 2011	32 NYHA II-III	Allopurinol 300 mg/day	4	6-minute walk test and oxidative stress markers	No difference in 6-minute walk test and improved oxidative markers
Nasr et al. 2010	59 NYHA III-IV	Allopurinol 300 mg/day	36	Composite endpoint: Global cardiac function and mortality/ morbidity	Allopurinol did not improve composite endpoint
Hare et al. 2008	405 with a median SUA of 7.8 mg/dl and NYHA III-IV	Oxypurinol 600 mg/day	24	Clinical status: Outcomes, medication change, patient global assessment or NYHA	43% improved in the oxypurinol arm compared to 45% in the placebo arm. Improved primary outcome in patients with higher uric acid levels
Cingolani et al. 2006	60 NYHA II-III	Oxypurinol 600 mg/day	4	Ejection fraction	4.7+/- 2.6 % higher EF between oxypurinol and placebo arms
Gavin et al. 2005	50 NYHA II-III	Allopurinol 300 mg/day	12	Exercise stress test and 6 minute walk test	No difference in exercise performance with a decrease in plasma BNP.

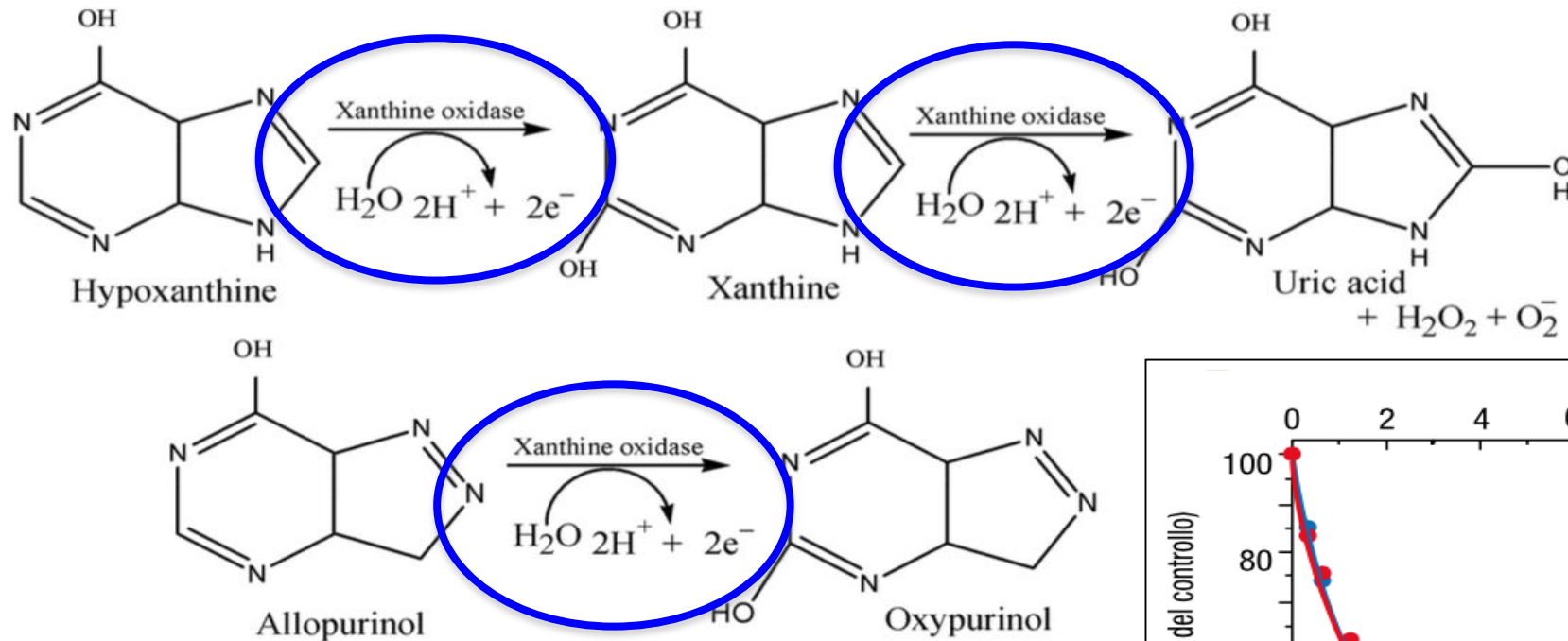
SUA: Serum uric acid, NYHA: New York Heart Association, EF: ejection fraction, BNP: Brain natriuretic peptide

Reaction scheme for the XO-mediated conversion of hypoxanthine to UA and suicide inhibitor allopurinol to the dead end inhibitor, oxypurinol



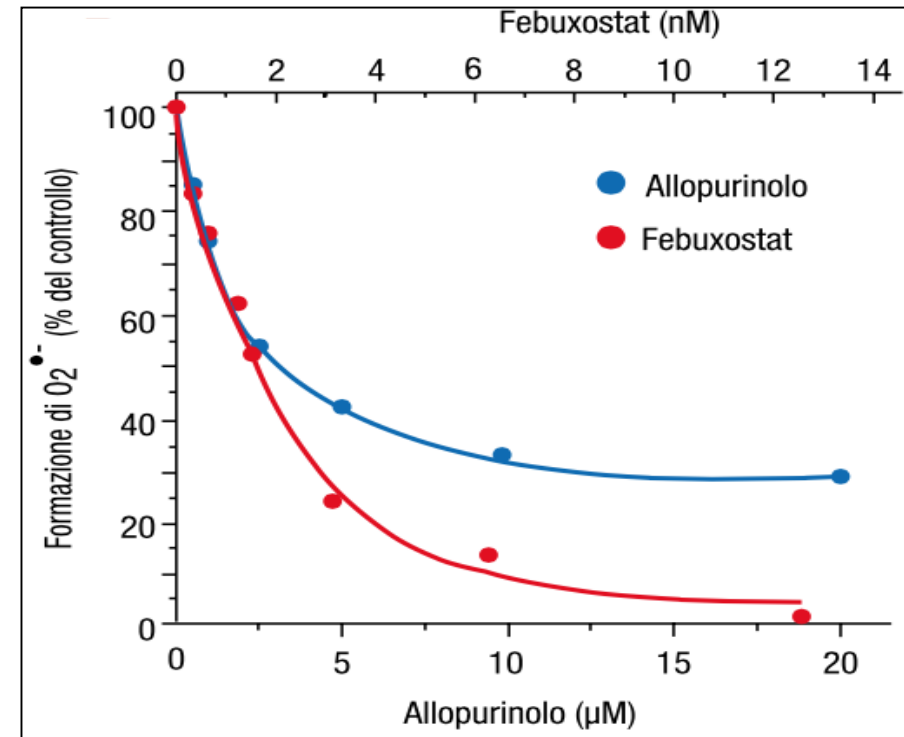
Allopurinol inhibits uric acid formation but produces ROS

Reaction scheme for the XO-□mediated conversion of hypoxanthine to UA and suicide inhibitor allopurinol to the dead□ end inhibitor, oxypurinol



Malik UZ et al. Free Radic Biol Med. 2011 Jul 1;51(1):179-84.

Allopurinol inhibits uric acid formation but produces ROS



Febuxostat: RCT with CV outcome

Trial	Drug	1° objective	Reference
BP control	Febuxostat vs. Allopurinol	Clinic and ABPM	NCT01701622
Coronary endothelial dysfunction	Febuxostat vs. Placebo	Coronary flow	NCT01763996
BP control	Febuxostat vs. Placebo	ABPM	NCT01496469
Exercise tolerance in chronic angina	Febuxostat vs. Placebo	Exercise test (ETT)	NCT01549977



ClinicalTrial.gov

Effect of febuxostat on renal function and CV damage in cardiac surgery patients

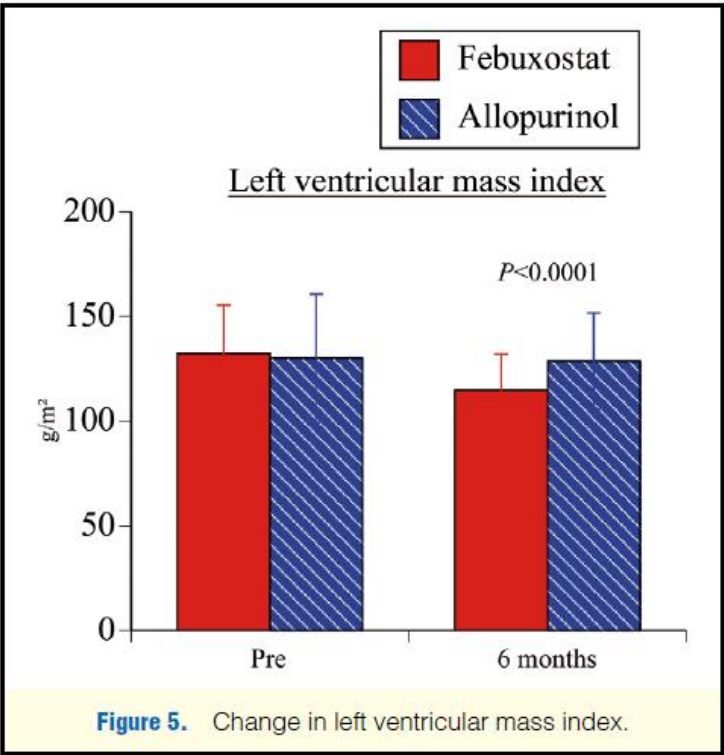
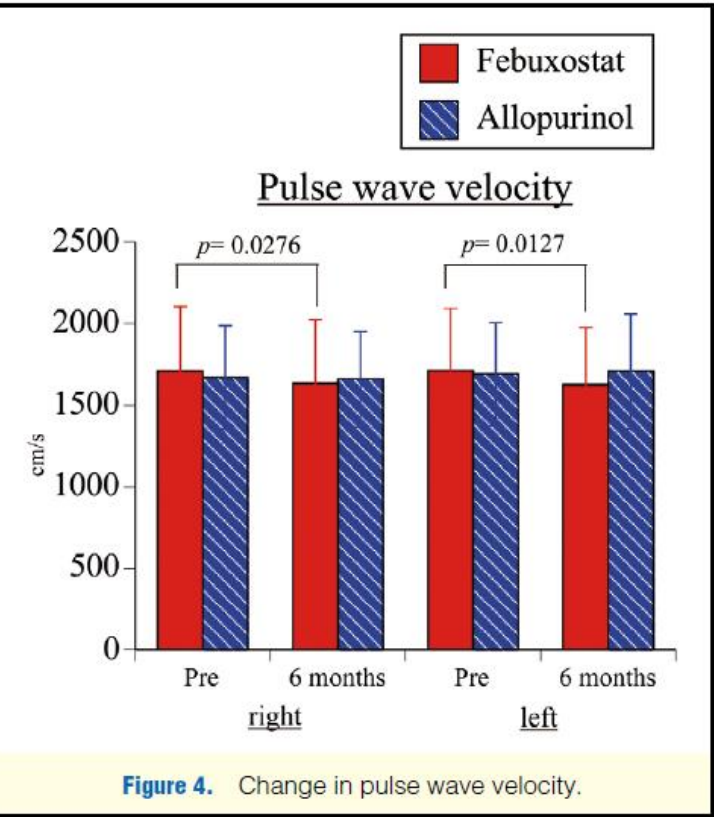
NU-FLASH Trial

Table 2. Changes in Renal Function and Lipid Parameters

	Before treatment	1 month	3 months	6 months
Serum creatinine				
Febuxostat	1.25±0.31	1.16±0.29*. [#]	1.14±0.29 [#]	1.14±0.30*. [#]
Allopurinol	1.24±0.35	1.27±0.42	1.24±0.40	1.26±0.39
eGFR				
Febuxostat	47.5±17.3	51.3±18.0 [#]	52.0±18.1 [#]	52.0±18.0 [#]
Allopurinol	48.5±16.6	48.3±17.8	49.6±17.9	48.3±17.1

Table 3. Changes in Other Parameters

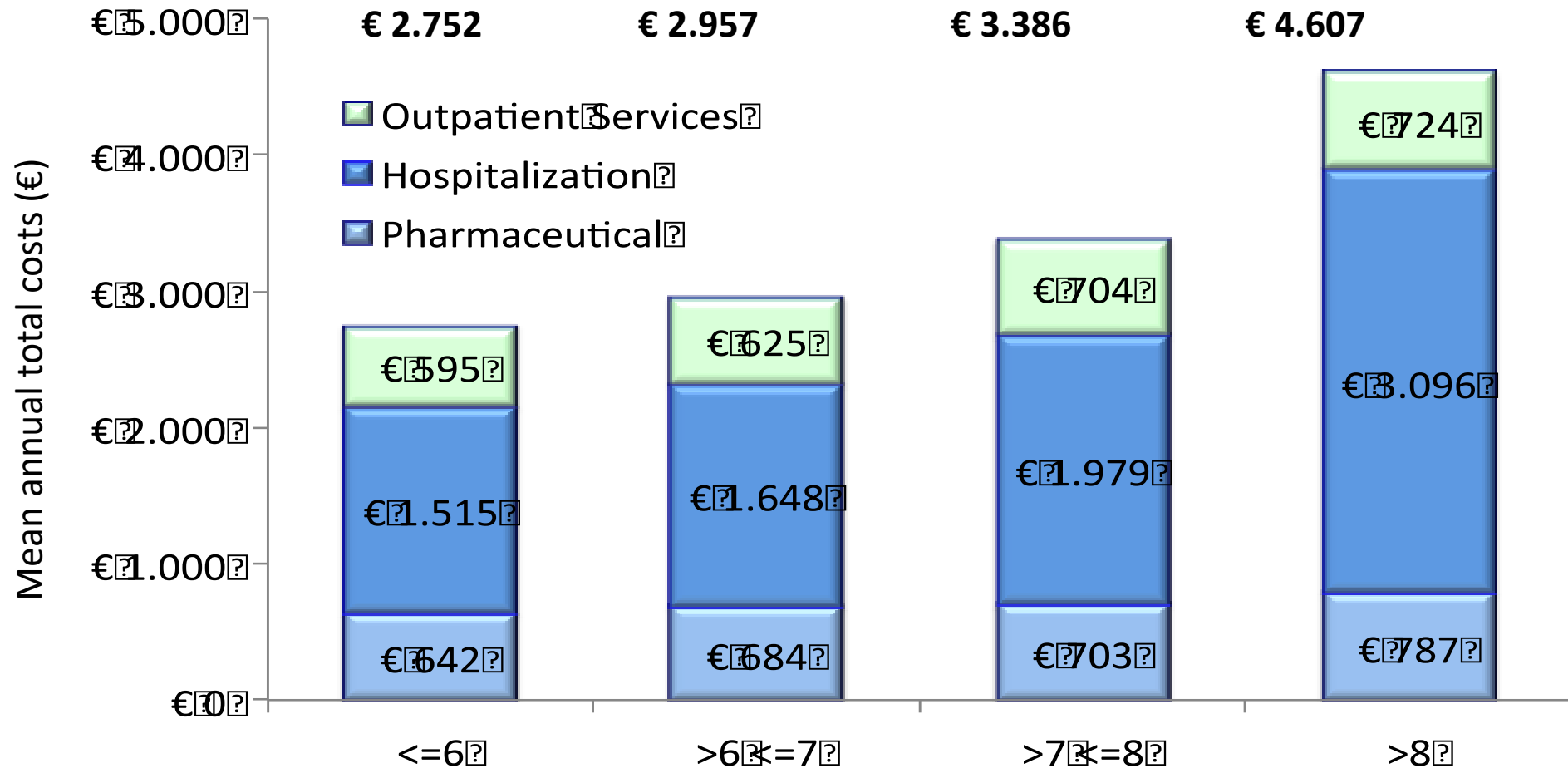
	Before treatment	3 months	6 months
Urinary albumin			
Febuxostat	144.5±371.9	77.0±216.2*	62.5±131.2*
Allopurinol	143.8±272.2	176.7±294.4	163.2±233.8



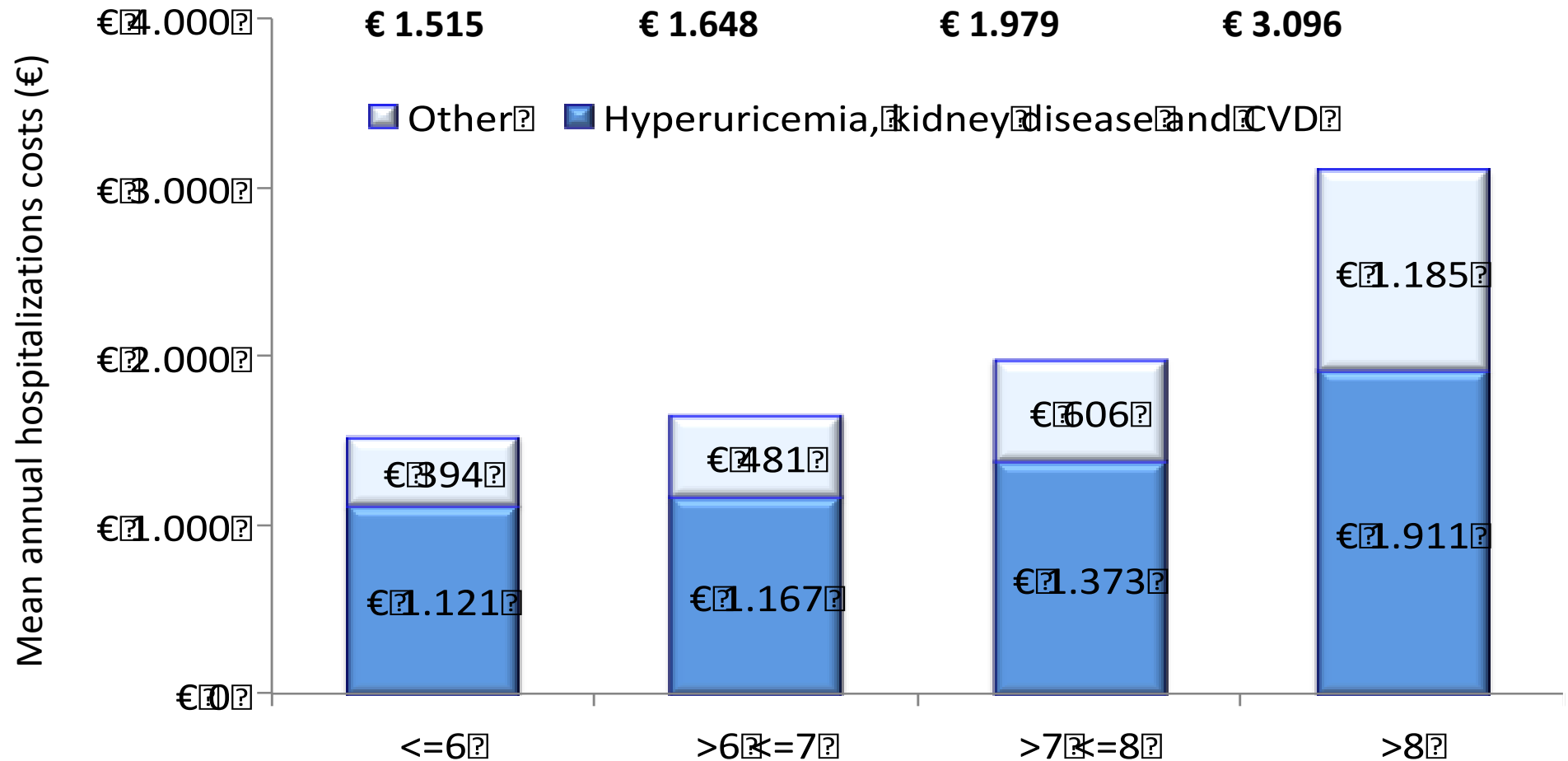
Febuxostat (80 mg)= 69 pz

Allopurinol (300 mg)= 70 pz

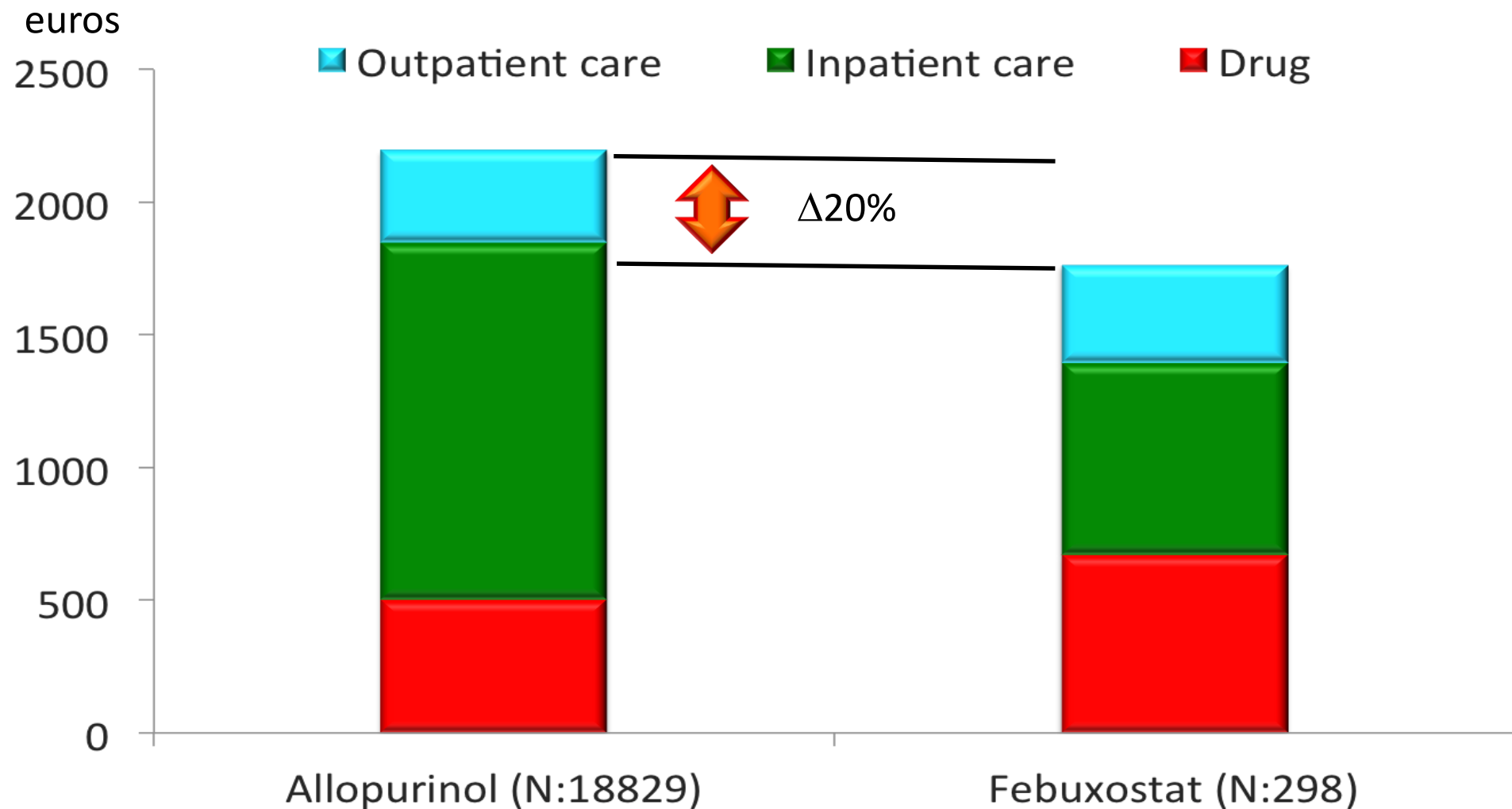
Total health care resource costs according to SUA levels



Total hospitalization costs according to SUA levels



Total health care resource costs during 6 months from index date according to ULT



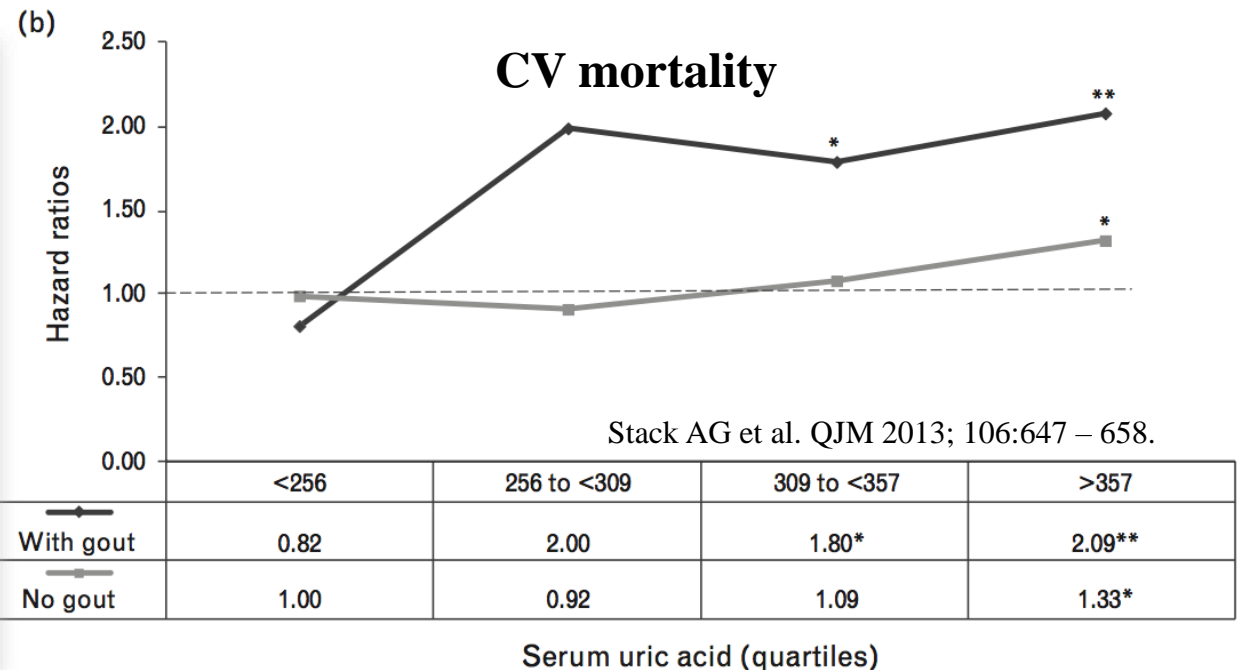
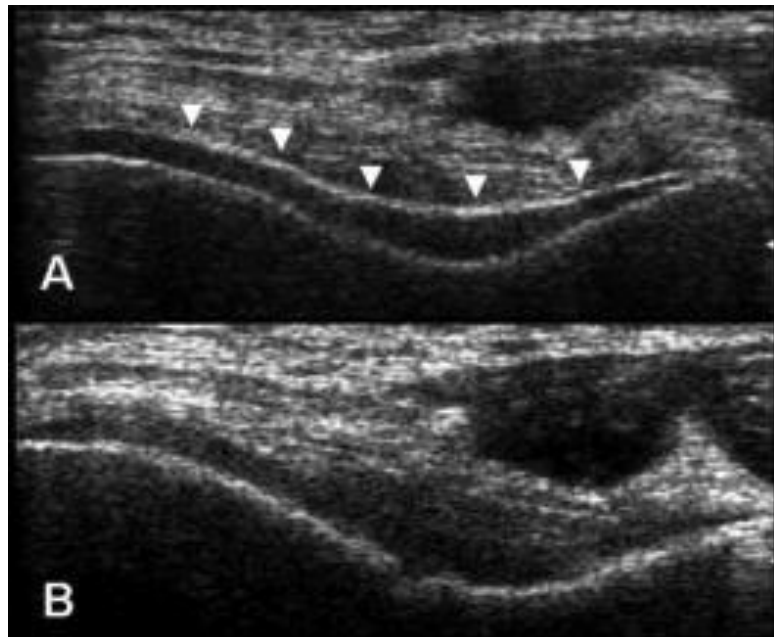
2014 EULAR recommendations on the management of gout



Recommendation 11: (ULT)

Median: 9; min: 8; max: 9

- All ULT should be started at a low dose and subsequently titrated upwards until the SUA target is reached. SUA below 6 mg/dl (360 μ mol/L) should be maintained lifelong.



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Iperuricemia cronica con e senza depositi di urato nell'anziano: specificità cliniche e terapeutiche

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