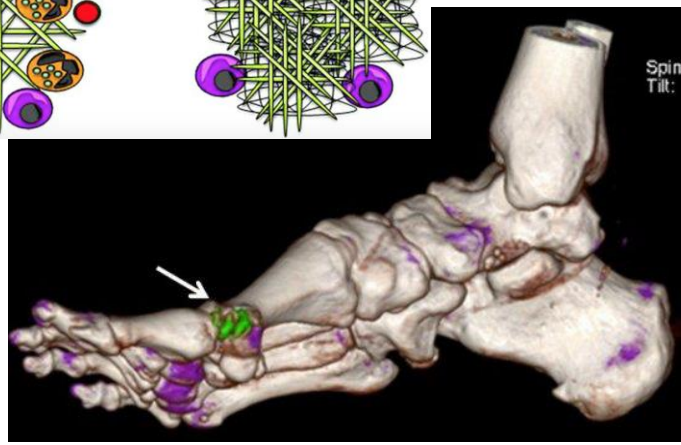
Giovambattista Desideri
UO Geriatria
Università dell'Aquila

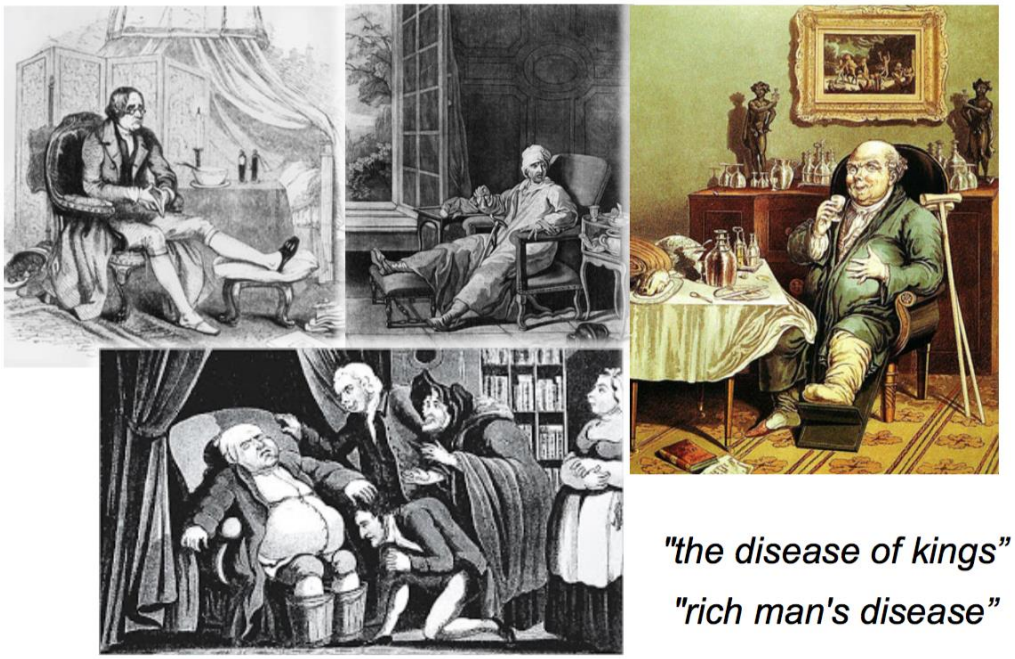
Gotta, iperuricemia e la gestione del paziente geriatrico: peculiarità cliniche terapeutiche



Gout: why an ancient disease is a modern day problem?

Epidemiology-Pathophysiology

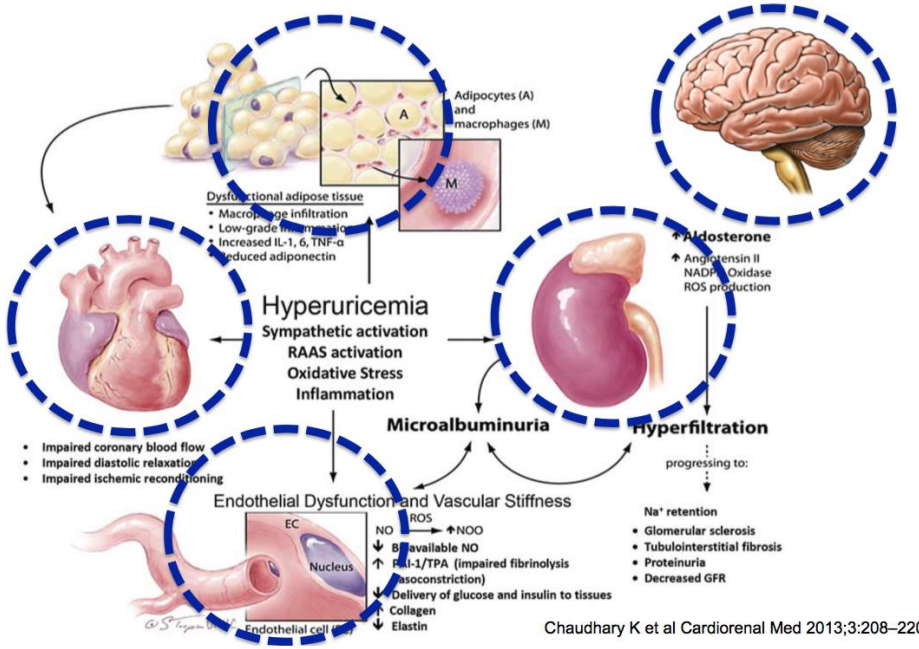
Gout: The Fashionable Disease



"the disease of kings"

"rich man's disease"

Hyperuricemia and Cardiorenal Metabolic Syndrome



Chaudhary K et al Cardiorenal Med 2013;3:208–220

Treatment

Why The Management of Gout in te Elderly is Really Challenging in the Modern Era?

- High prevalence
- Challenging Diagnosis
- Frequent coexistance of comorbidities
- Challenging therapeutic management

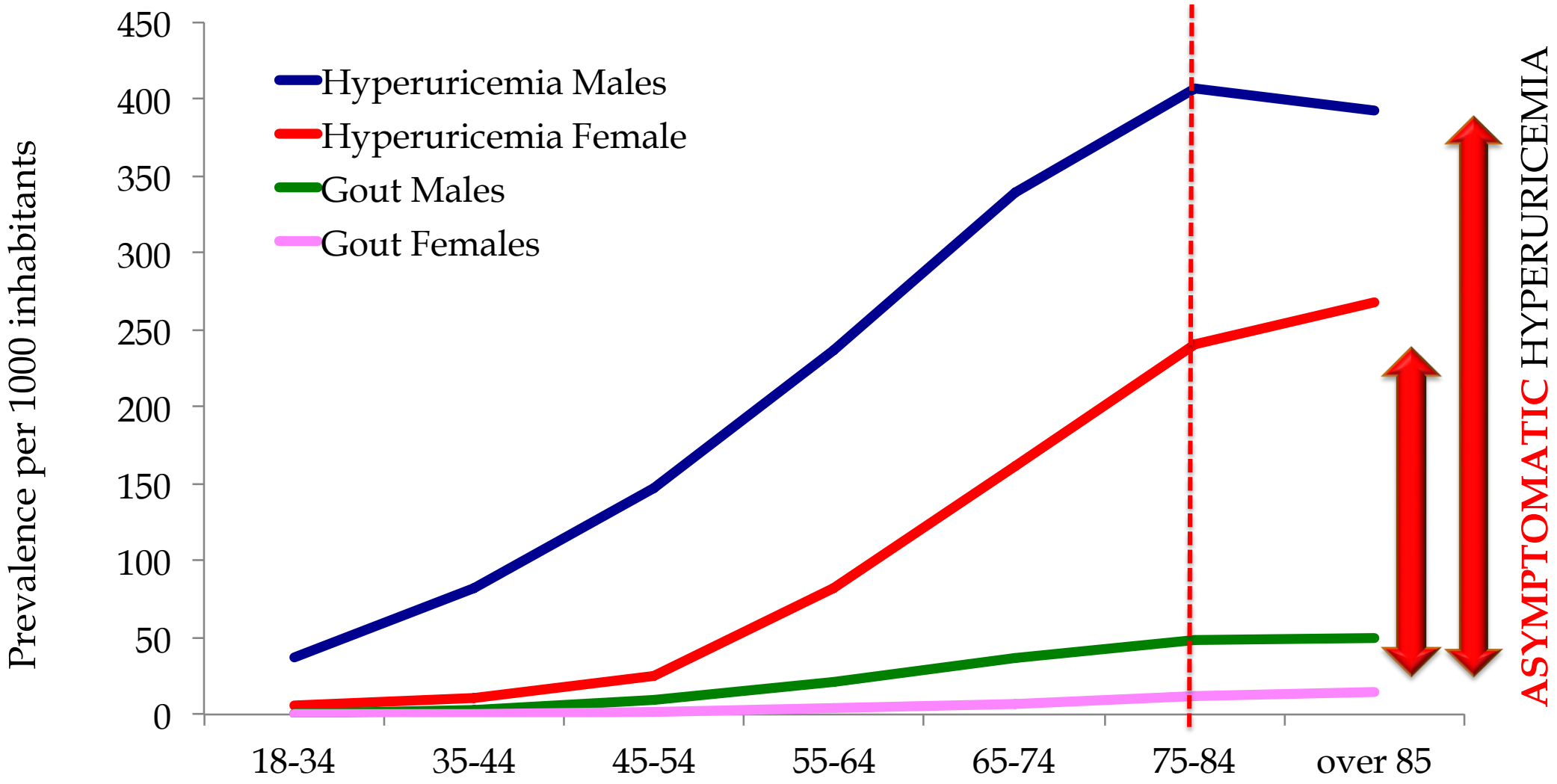
“The disease of the kings”
“The disease of the Popes”
“The disease of the riches”

“The common cold is well named – but the gout seems instantly to raise the patient’s social status“

(The London Times 1900)

“In keeping with the spirit of more democratic times, gout is becoming less upper-class and is now open to all … It is ridiculous that a man should be barred from enjoying gout because he went to the wrong school“ (Punch 1964)

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



Trifirò G, et al. Ann Rheum Dis (2011).

Why The Management of Gout in te Elderly is Really Challenging in the Modern Era?

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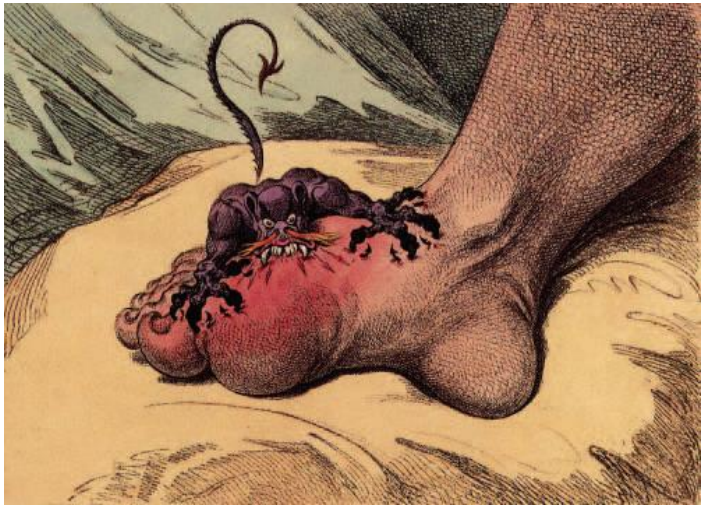
- Challenging Diagnosis
- Frequent coexistance of comorbidities
- Challenging therapeutic management

An accurate and colorful discription of a gout attack was elegantly written in 1683 by Dr. Thomas Sydenham who was himself a sufferer of gout:

"…The victim goes to bed and sleeps in good health. About 2 o'clock in the morning, he is awakened by a severe pain in the great toe; more rarely in the heel, ankle or instep.

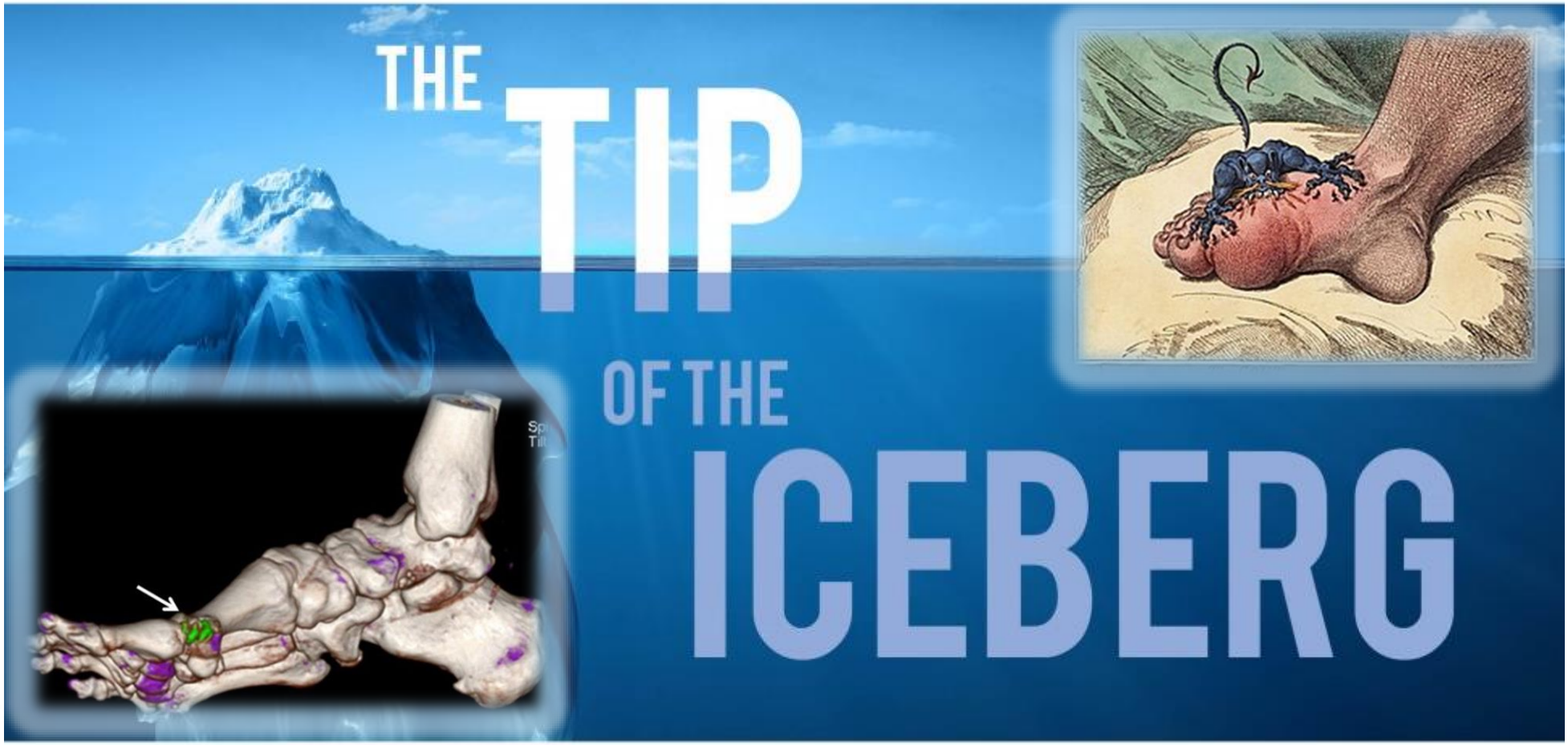
This pain is like that of a dislocation, and yet the parts feel as if cold water were poured over them. Then follows chills and shiver and a little fever. The pain which at first moderate becomes more intense. With its intensity the chills and shivers increase.

After a time this comes to a full height, accommodating itself to the bones and ligaments of the tarsus and metatarsus. Now it is a violent stretching and tearing of the ligaments– now it is a gnawing pain and now a pressure and tightening. So exquisite and lively meanwhile is the feeling of the part affected, that it cannot bear the weight of bedclothes nor the jar of a person walking in the room…."



'The Gout' by James Gillray (1799).

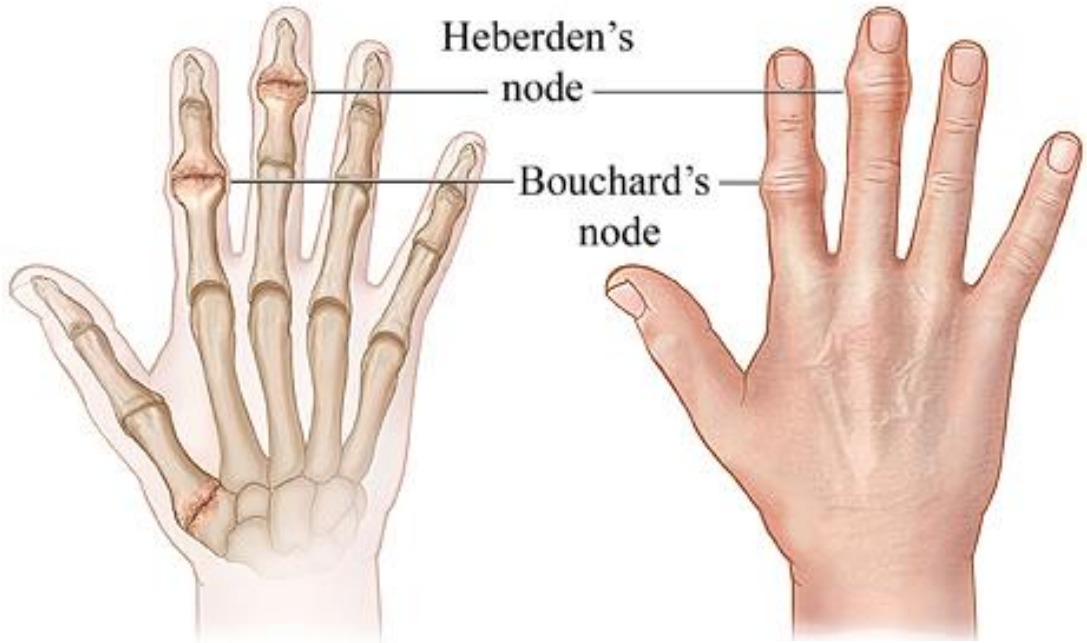
Gout flares and asymptomatic articular damage



Gout has often (a)tipical features

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

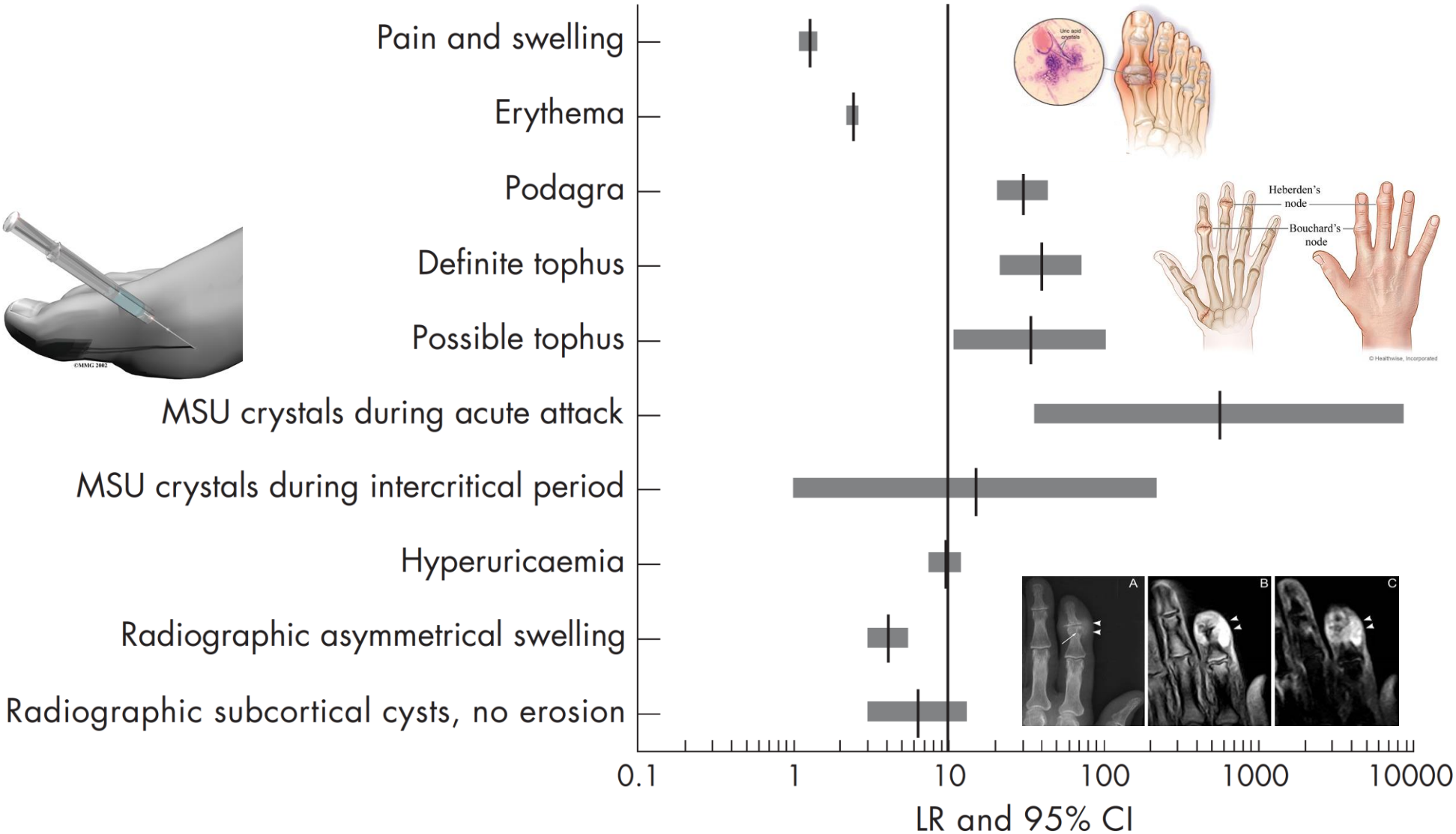
Gout can be mistaken for changes that are usually attributed to OA or RA



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

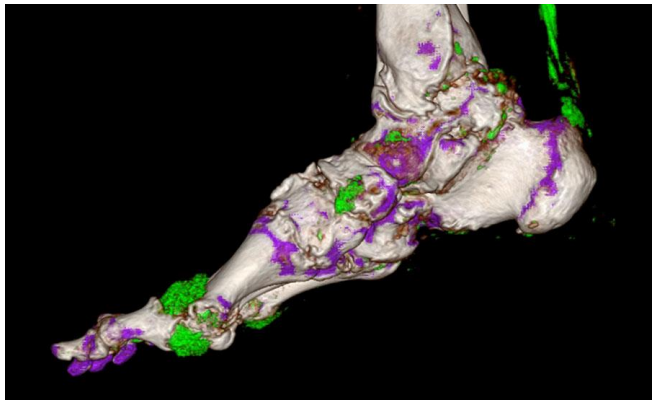
Tophi can supervene on Heberden's and Bouchard's nodes.

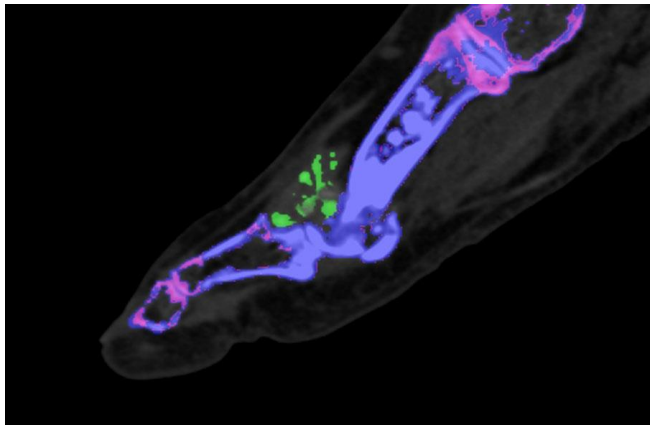
Likelyhood ratio for various features in the diagnosis of gout - EULAR

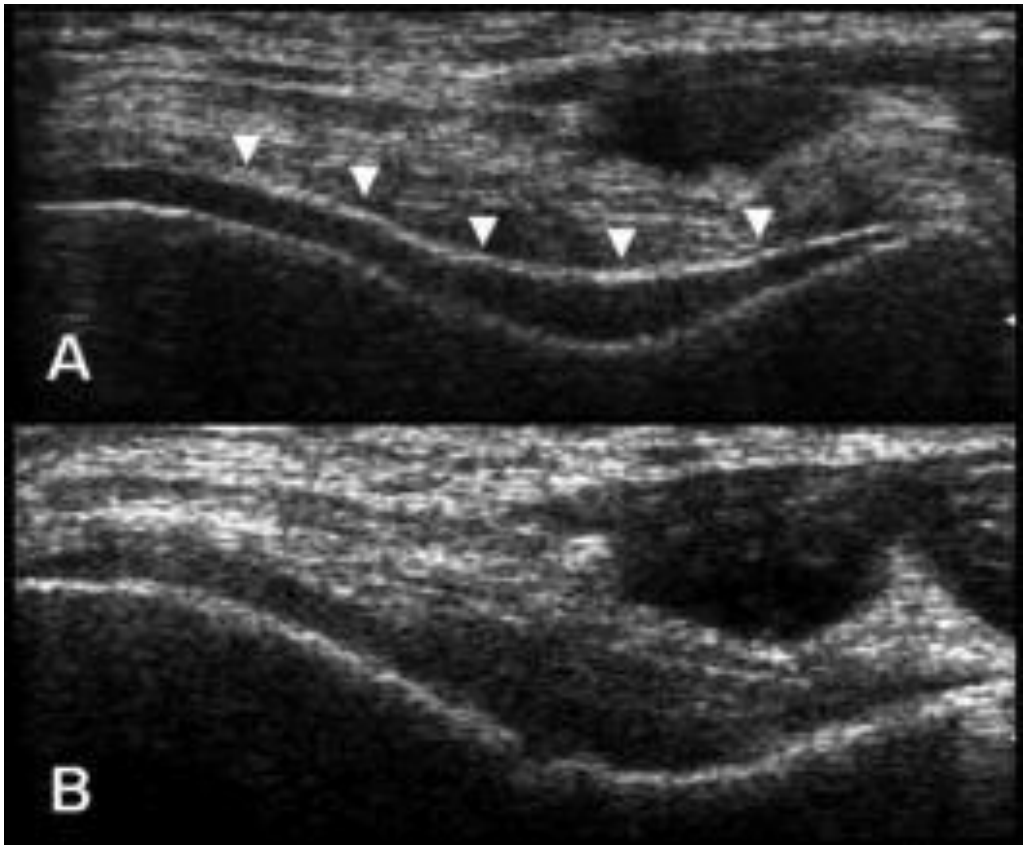


Ann Rheum Dis 2006;65:1301–1311

Asymptomatic articular damage in hyperuricemia





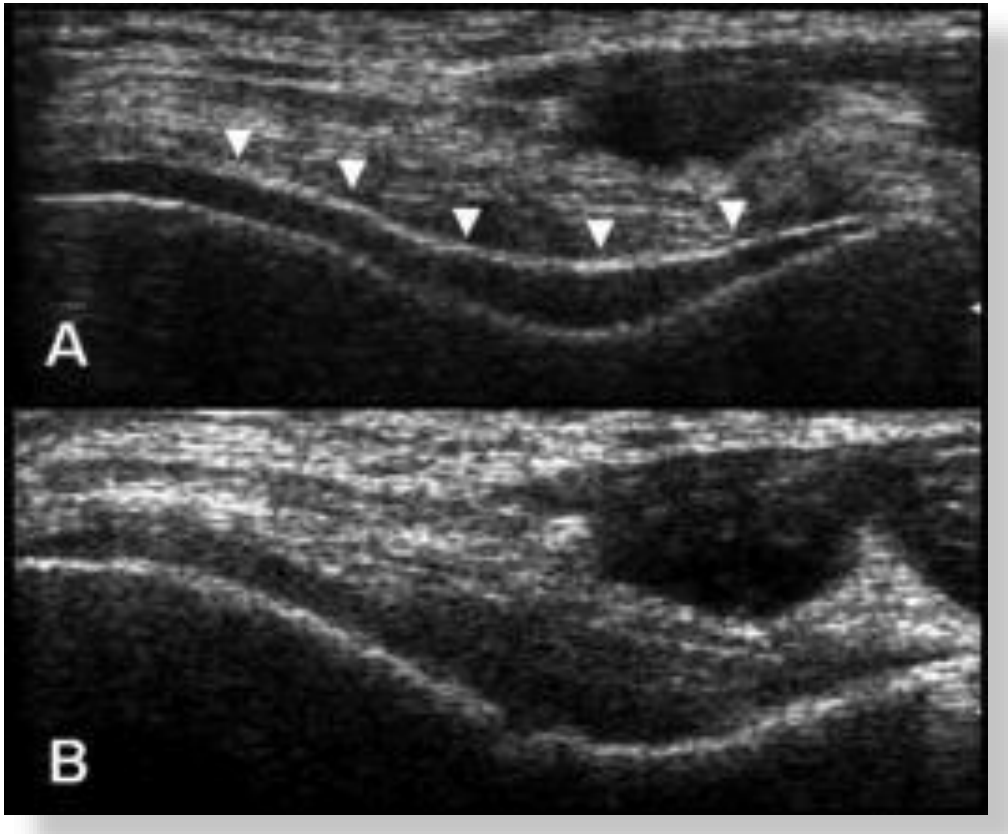


Musculoskeletal US can be able to visualize intraarticular crystal deposits with a characteristic hyperechoic enhancement of the outer surface of the hyaline cartilage, known as the “double contour sign.”

Asymptomatic articular damage in hyperuricemia

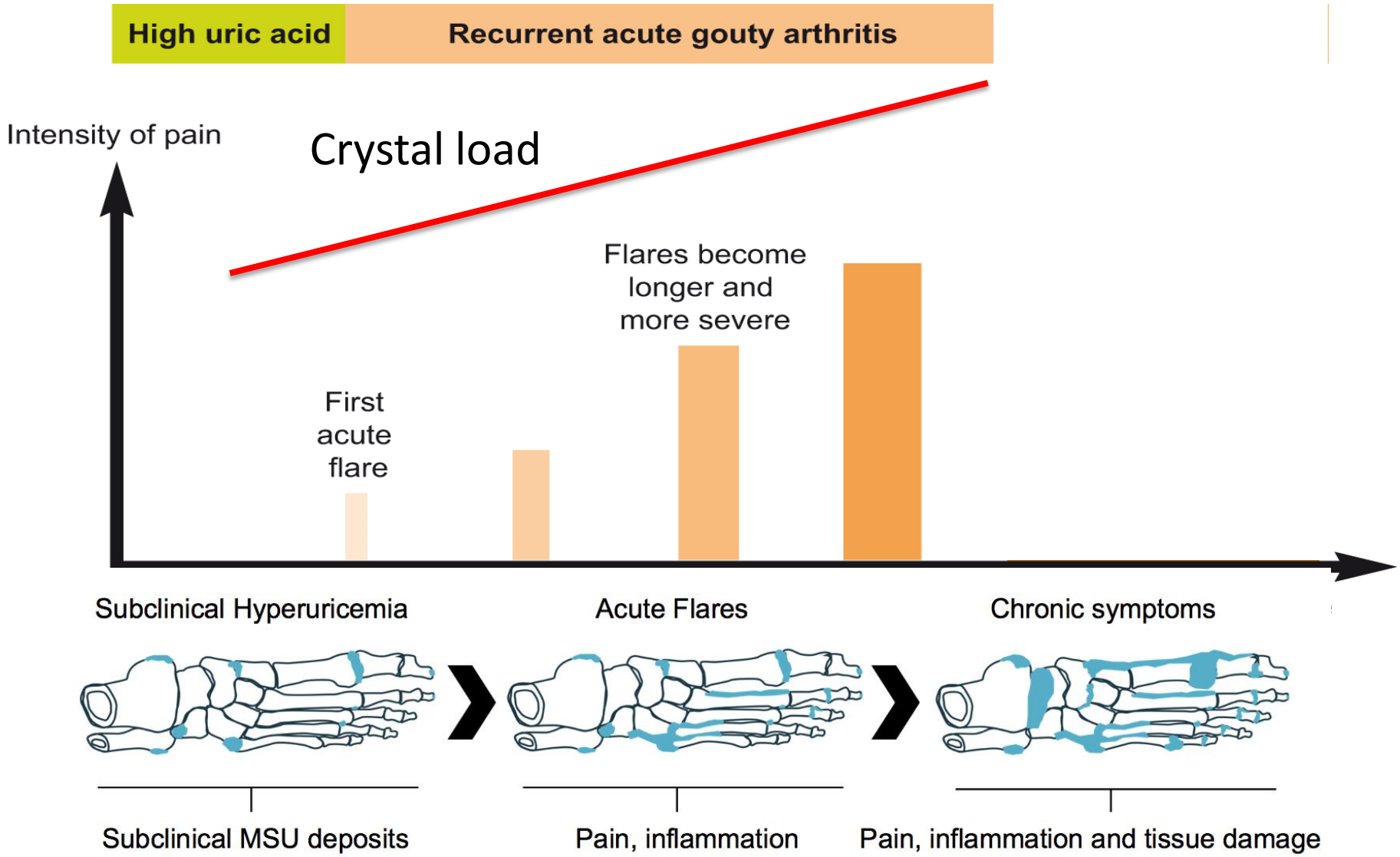
Anatomical site and US findings	Hyperuricemic (*n* = 100 joints)	Normouricemic (*n* = 104 joints)	*P* value
First MTP joint, *n* (%)			
Double contour sign	25 (25%)	0	<0.0001
Joint cavity widening (synovial fluid/ hypertrophy)	52 (52%)	25 (24%)	<0.0001
Power Doppler signal	0	0	NS
Bone erosion	12 (12%)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

Pineda et al. Arthritis Research & Therapy 2011.



Intra-articular crystal deposits in asymptomatic subjects with hyperuricaemia

Natural History of Gout: Crystal Load Worsens if Uricemia Remains high

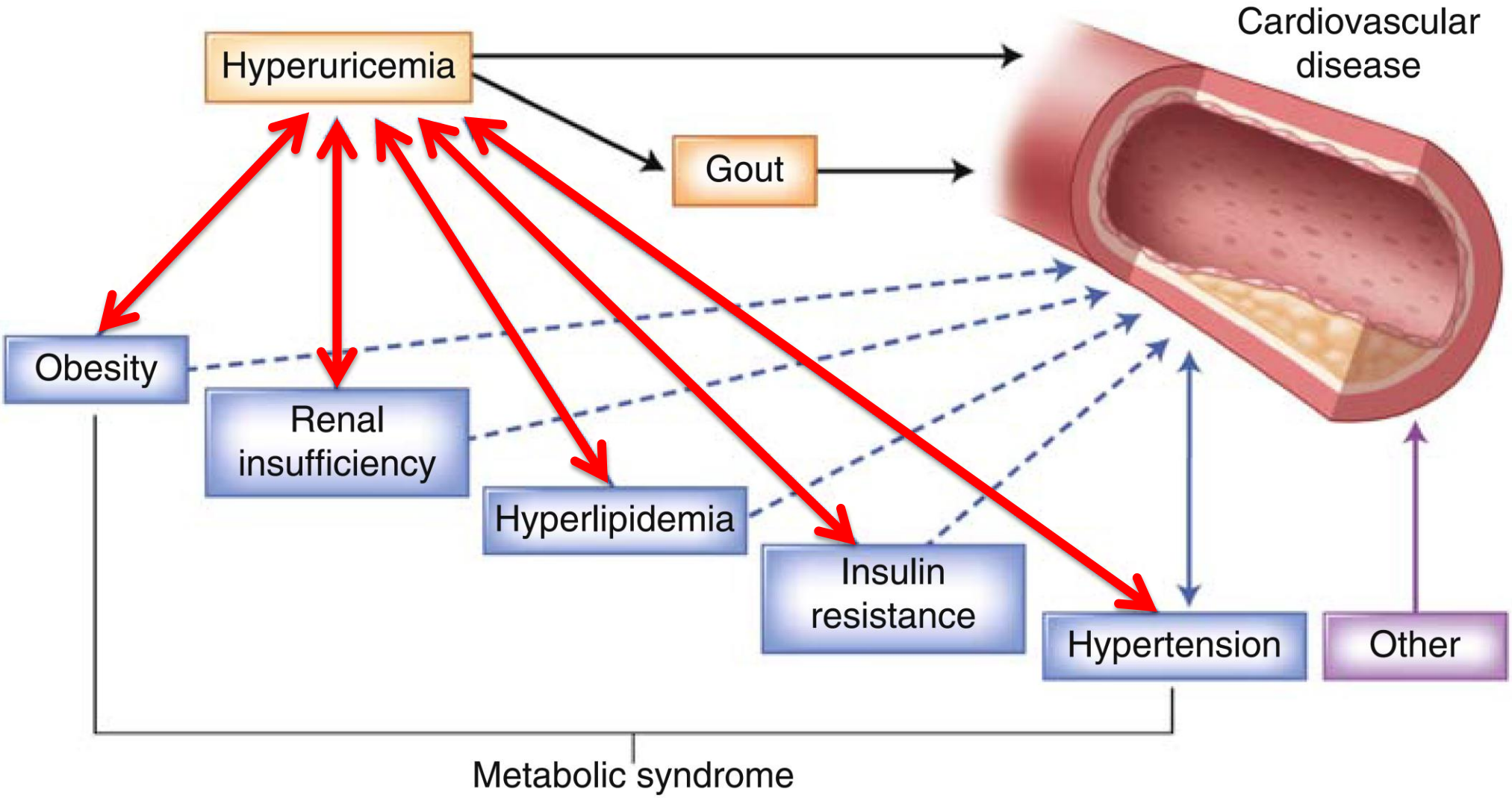


Adapted from "Gout. Risk Factors, Diagnosis and Treatment. Available on Internet: http://knol.google.com/k/gout

Why The Management of Gout in te Elderly is Really Challenging in the Modern Era?

- High prevalence
- Challenging Diagnosis
- **Frequent coexistance of comorbidities**
- Challenging therapeutic management

Gout, Hyperuricemia, and the Risk of Cardiovascular Disease: Cause and Effect?



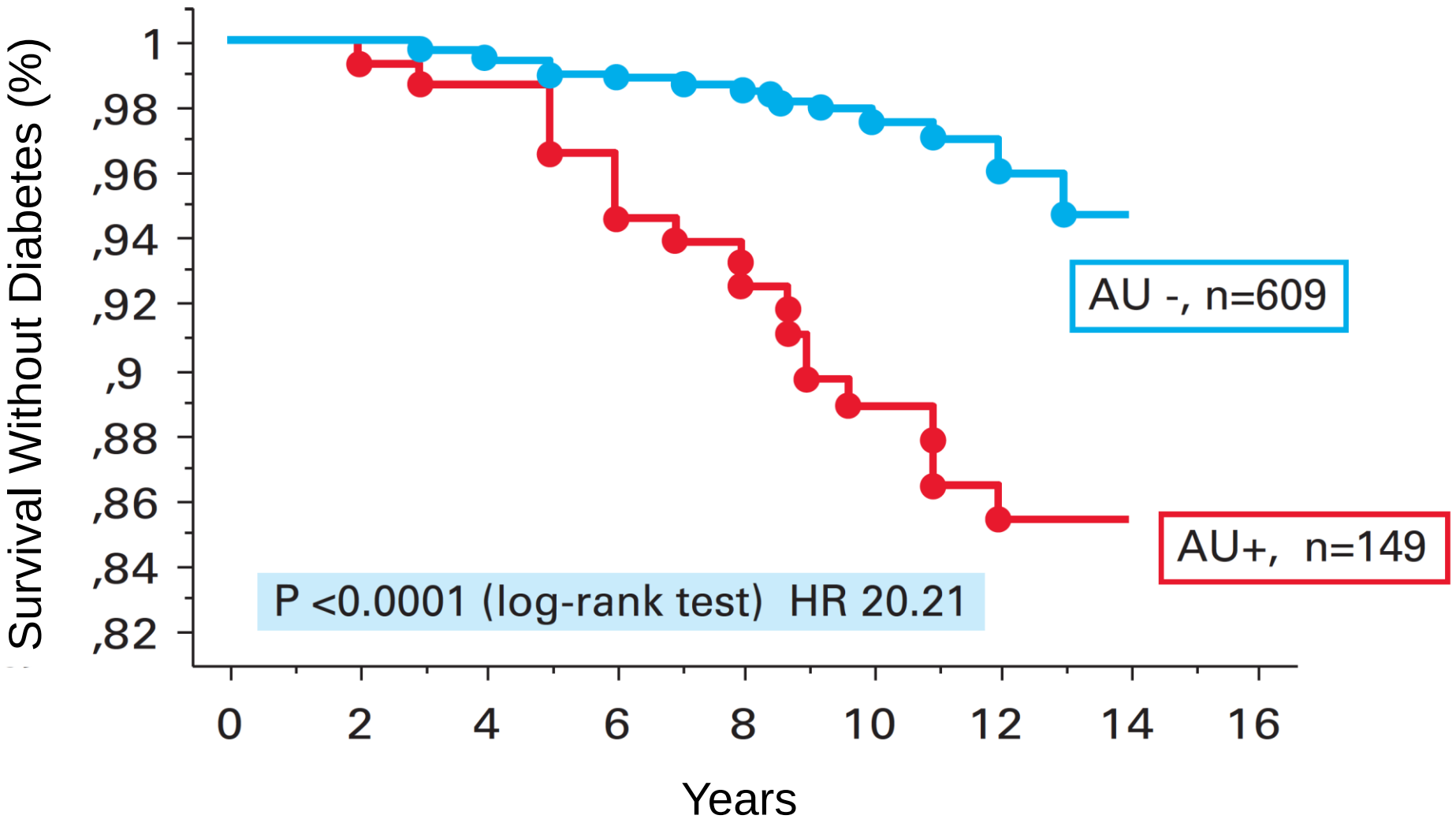
Shah A, et al. Curr Rheumatol Rep (2010) 12:118–124

Why having gout can mean you'll end up with heart disease..?
How one illness can be linked to another

Which came first?

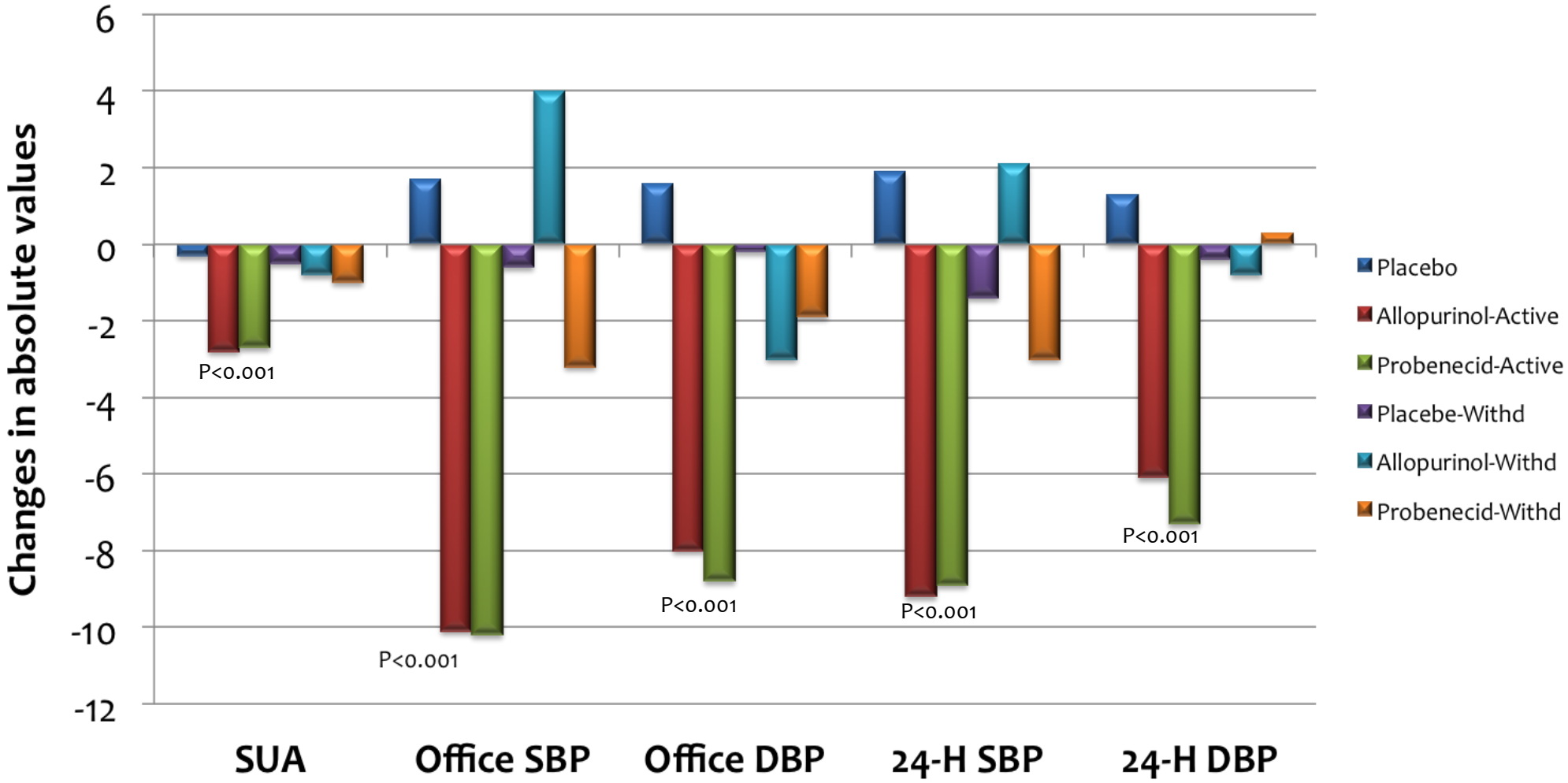
http://www.dailymail.co.uk

Serum Uric Acid Levels Predict New-Onset Type 2 Diabetes in Hospitalized Patients With Primary Hypertension: The MAGIC Study



Viazzi F et al. Diabetes Care. 2011; 34:126-8

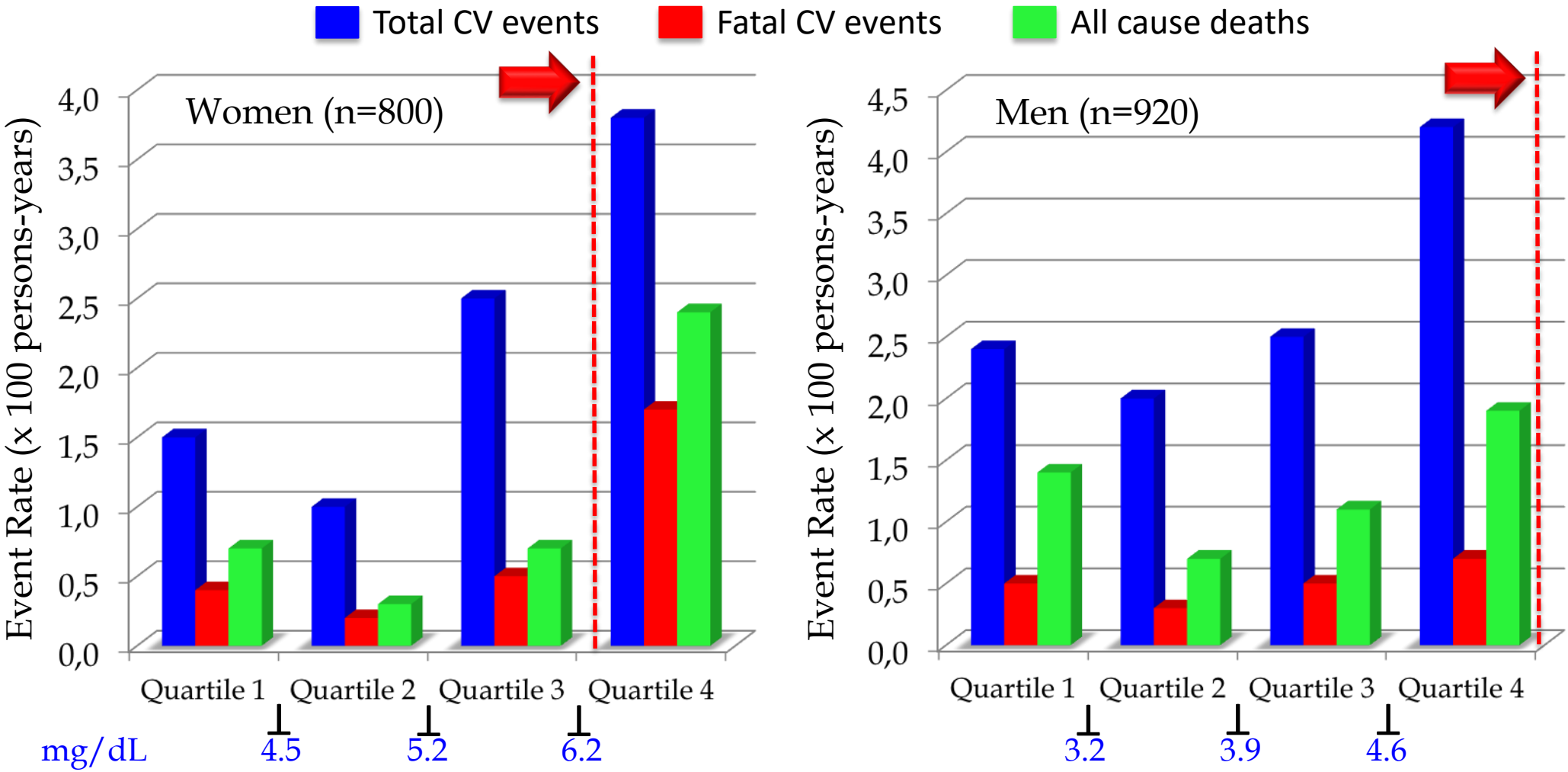
Changes in SUA, Systolic and diastolic BP in obese adolescent treated with Allopurinol and Probenecid



Soletsky B et al, Hypertension 2012

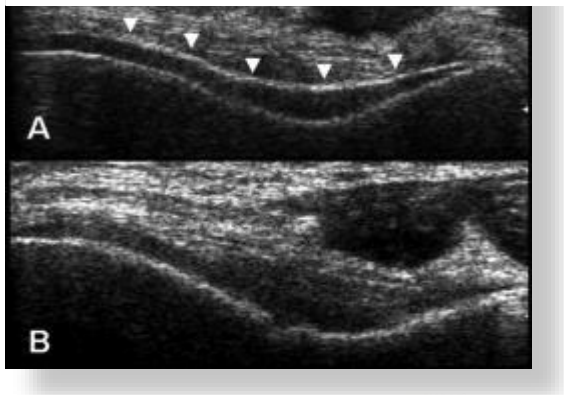
Relation Between Serum Uric Acid and Risk of CVD in Essential Hypertension: The PIUMA Study

1720 subjects with EH, untreated, screened for absence of cardiovascular disease, renal disease, cancer, and other important disease. Follow-up up to 12 years (mean, 4.0) were followed

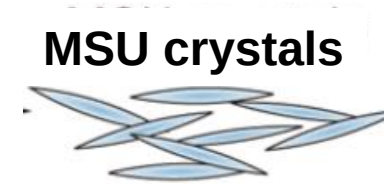


Verdecchia P et al. Hypertension. 2000;36:1072-1078.)

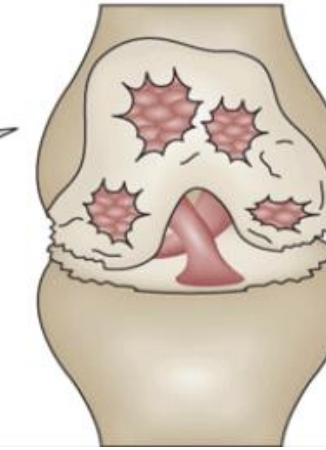
The pH-solubility relationships of uric acid and MSUM

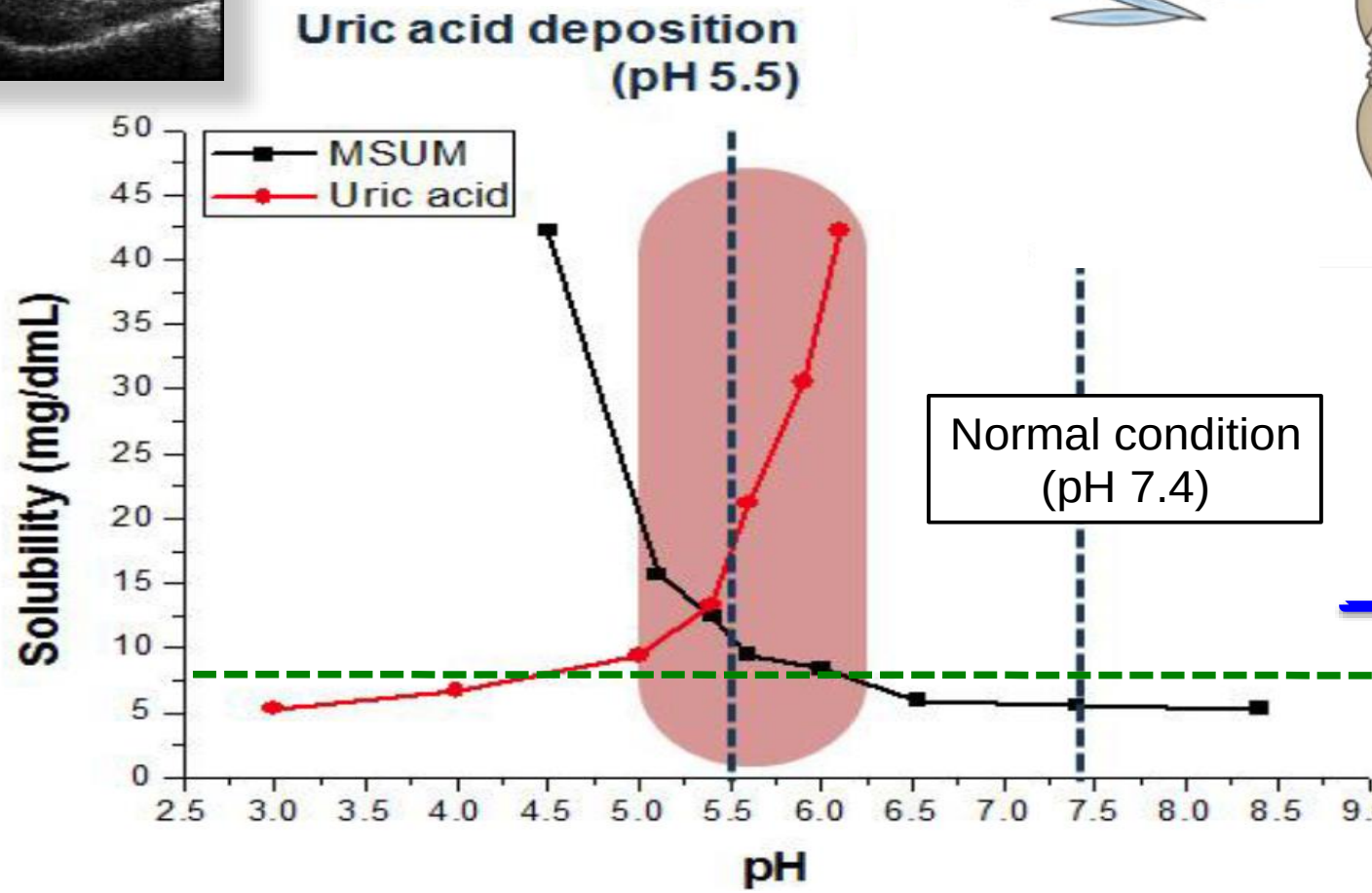


In normal condition (37° C, aqueous solution, pH 7.4) the solubility limit of MSU is reached when the urate concentration is about 6.4 mg/dL (384 □mmol/L)



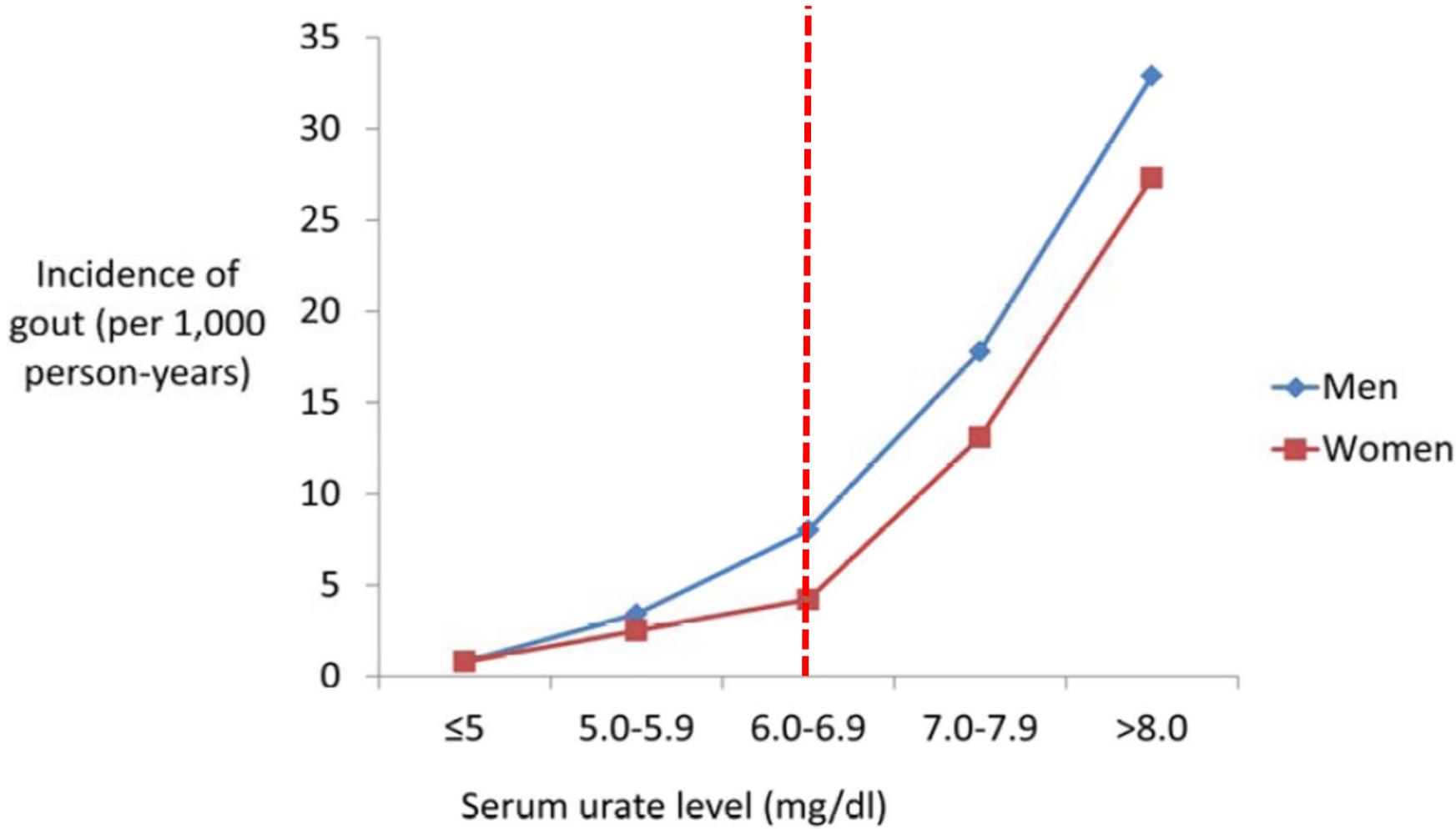
MSU crystals





Chih MH et al. CrystEngComm, 2016,18, 290-297

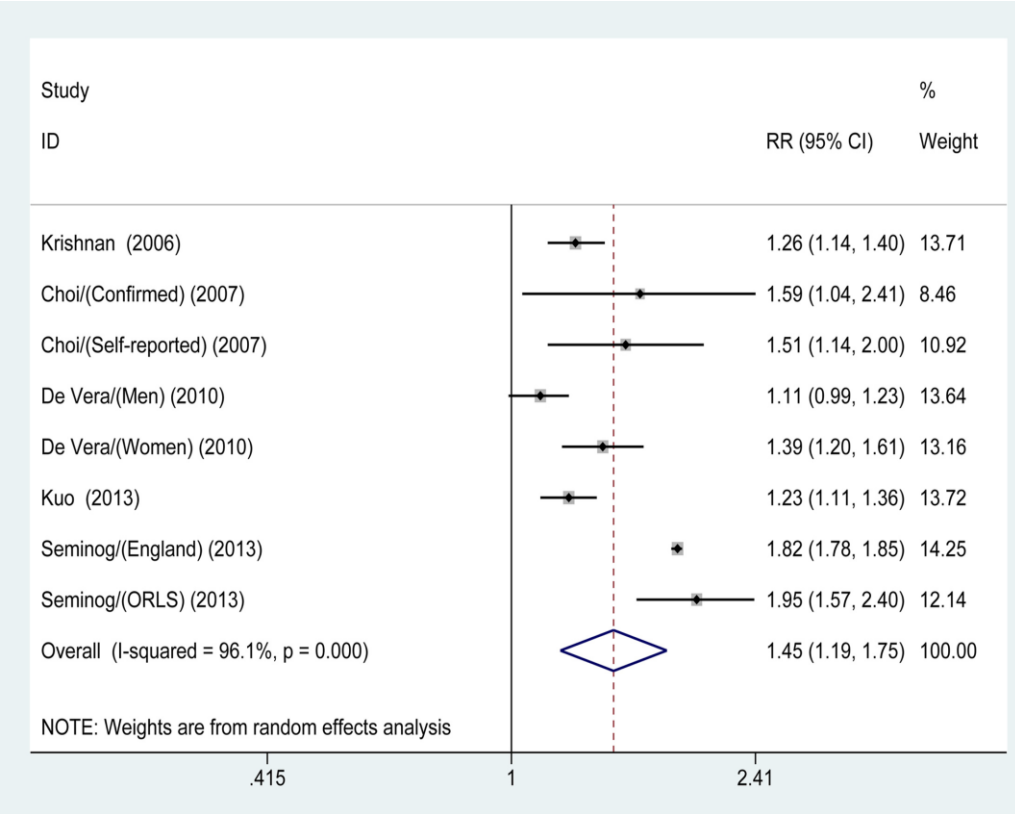
Relationship between serum uric acid levels and annual incidence of gout



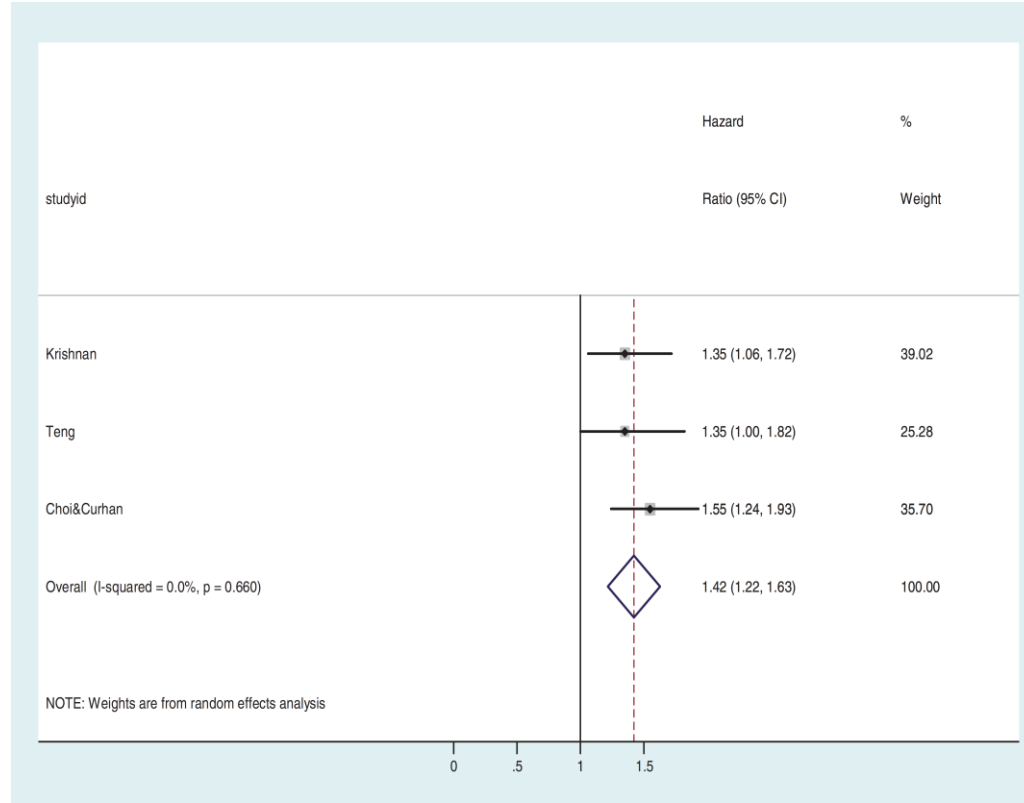
Bohle V et al. Arthritis Rheum 2010;62:1069-1076

Gout is associated with increased risk for cardiovascular events

Gout and Risk of Myocardial Infarction[1]

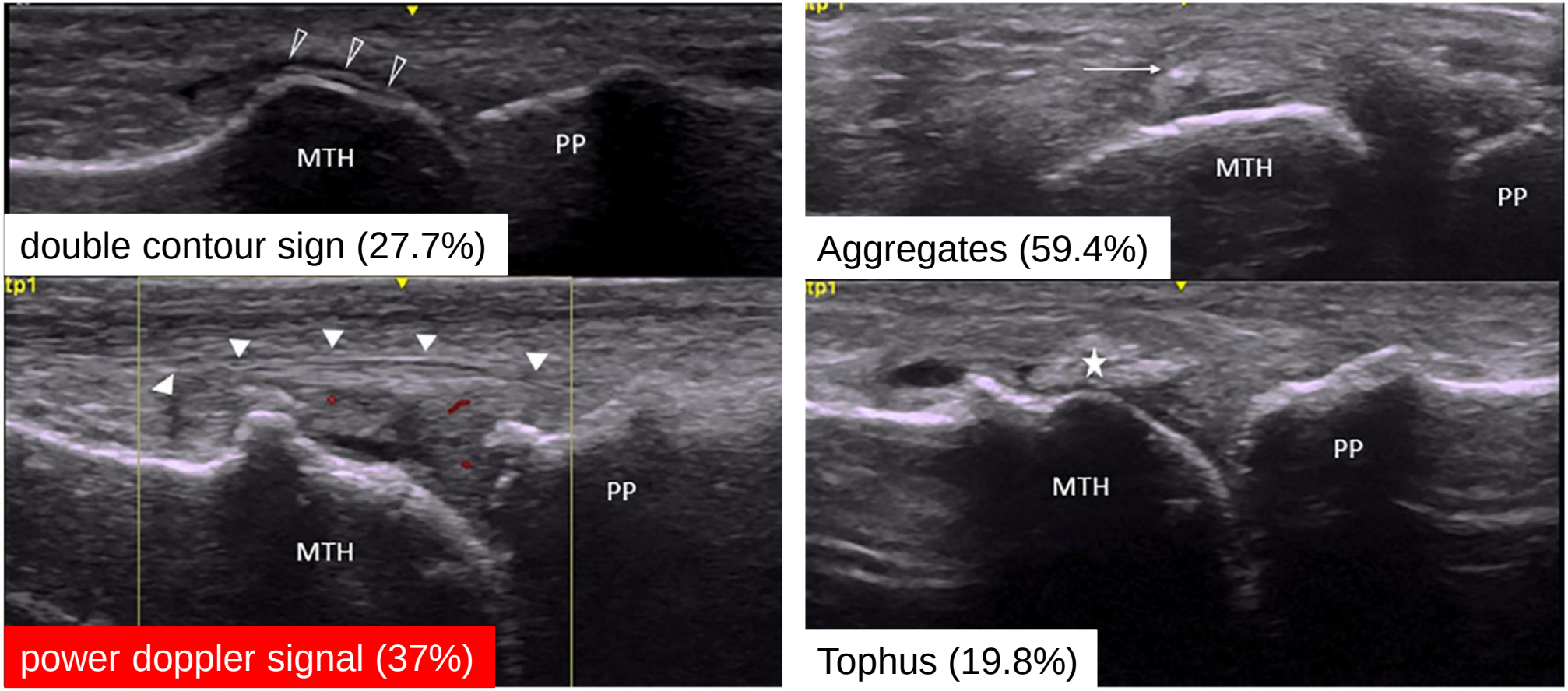


Gout and Mortality for CHD[2]



[1]Liu SC et al. PLoS One. 2015 Jul 31;10(7):e0134088. d
[2]Clarson LE et al. European Journal of Preventive Cardiology 2015, Vol. 22(3) 335-343

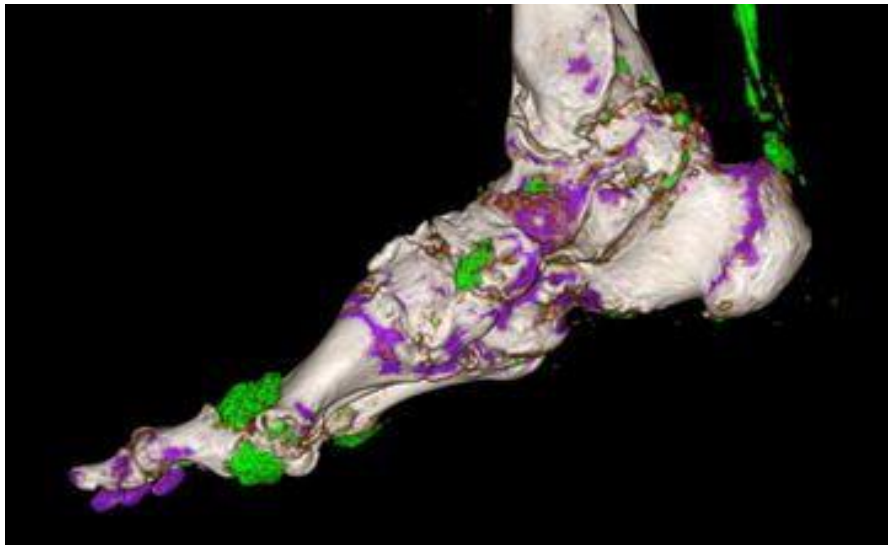
Ultrasonographic assessment of joint pathology in type 2 diabetes and hyperuricemia (60%) or gout (40%): The Fremantle Diabetes Study Phase II



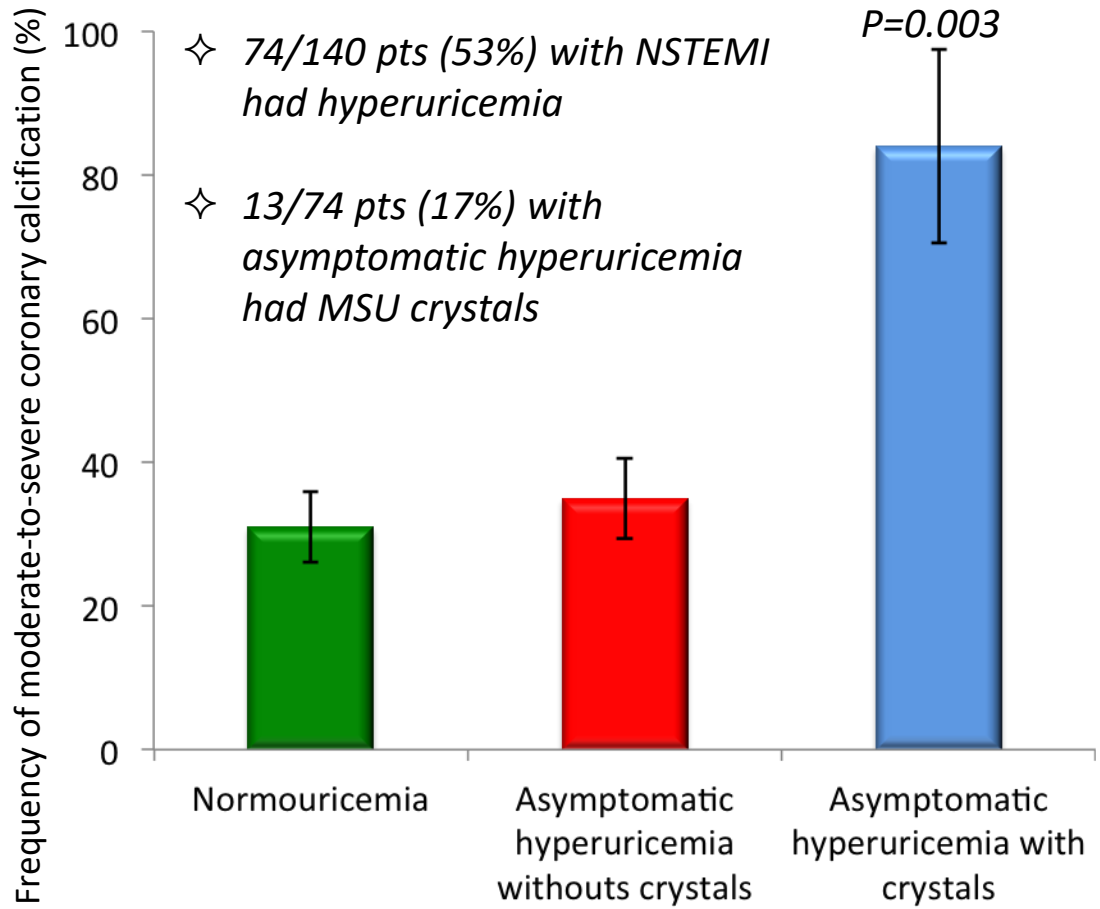
- A subset of 101 participants (mean age 70.4 years, 59.8% males, median diabetes duration 14.6 years) with hyperuricemia (fasting serum uric acid ≥0.42mmol/L),
- Joint inflammation and/or urate deposition were present in the majority of community-based patients with type 2 diabetes and hyperuricemia **regardless of whether there was a history of gout.**

Keen HI et al. **Journal of Diabetes and Its Complications 32 (2018) 400–405**

Subclinical Gout and Cardiovascular Disease



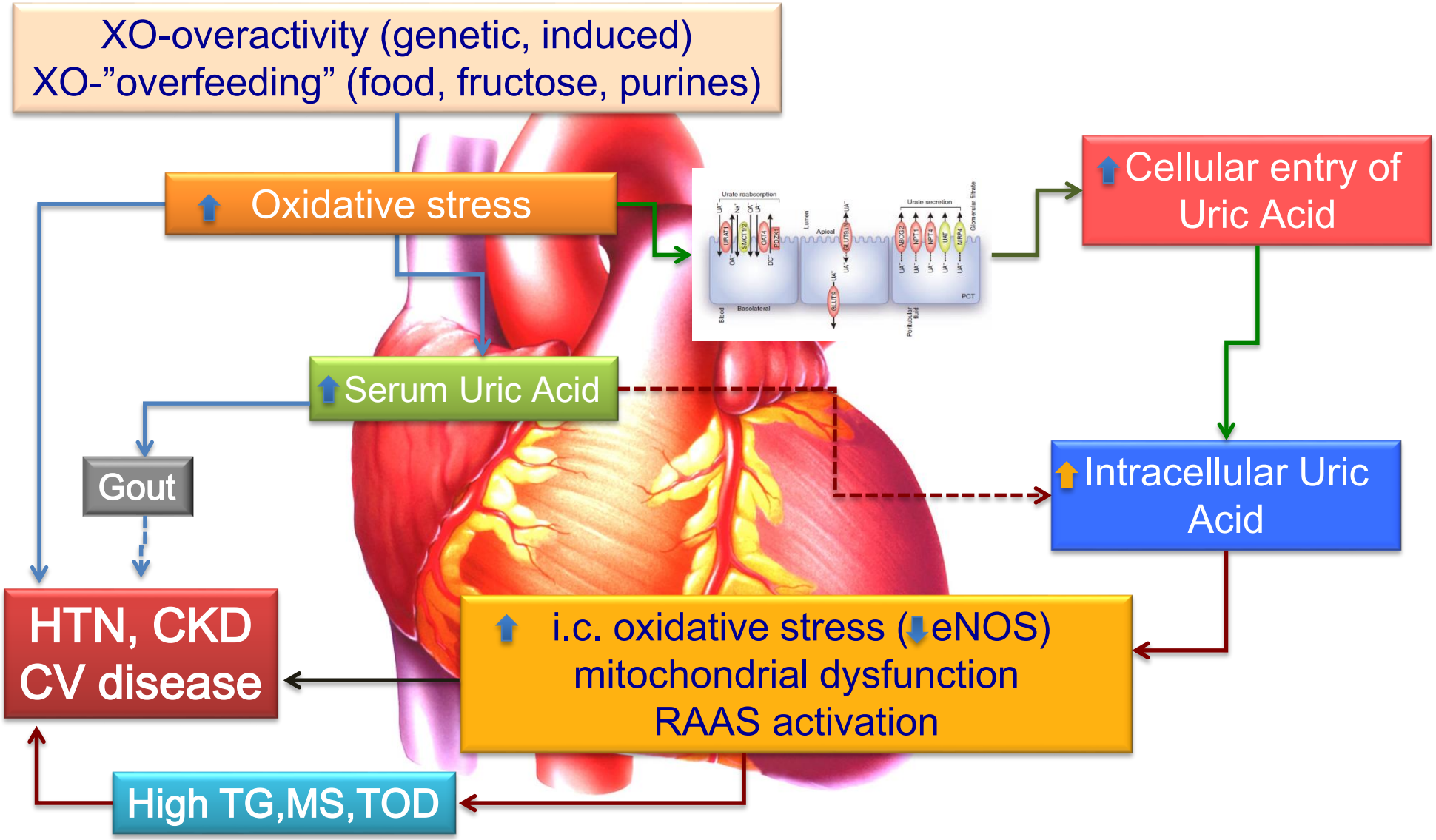
Silent MSU Crystal Deposits Are Associated With Severe Coronary Calcification in Asymptomatic Hyperuricemia (SUA >7 mg/dL)



Andrès M et al. ARTHR & RHEUM 2016:68 (6):1531–1539

SUA, oxidative stress and CV disease: a comprehensive hypothesis

Borghi C, Desideri G, Hypertension 2016



Hyperuricemia starts at 360 micromoles (6 mg/dL)

Journal of Hypertension 2015, 33:1729–1741

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-Ruiz[i], and Giuseppe Mancia[j]

European Review for Medical and Pharmacological Sciences 2014; 18: 1295-1306

Is it time to revise the normal range of serum uric acid levels?

G. DESIDERI[1], G. CASTALDO[2,3], A. LOMBARDI[4], M. MUSSAP[5], A. TESTA[6], R. PONTREMOLI[7], L. PUNZI[8], C. BORGHI[9]

Why The Management of Gout in te Elderly is Really Challenging in the Modern Era?

- High prevalence
- Challenging Diagnosis
- Frequent coexistance of comorbidities
- **Challenging therapeutic management**

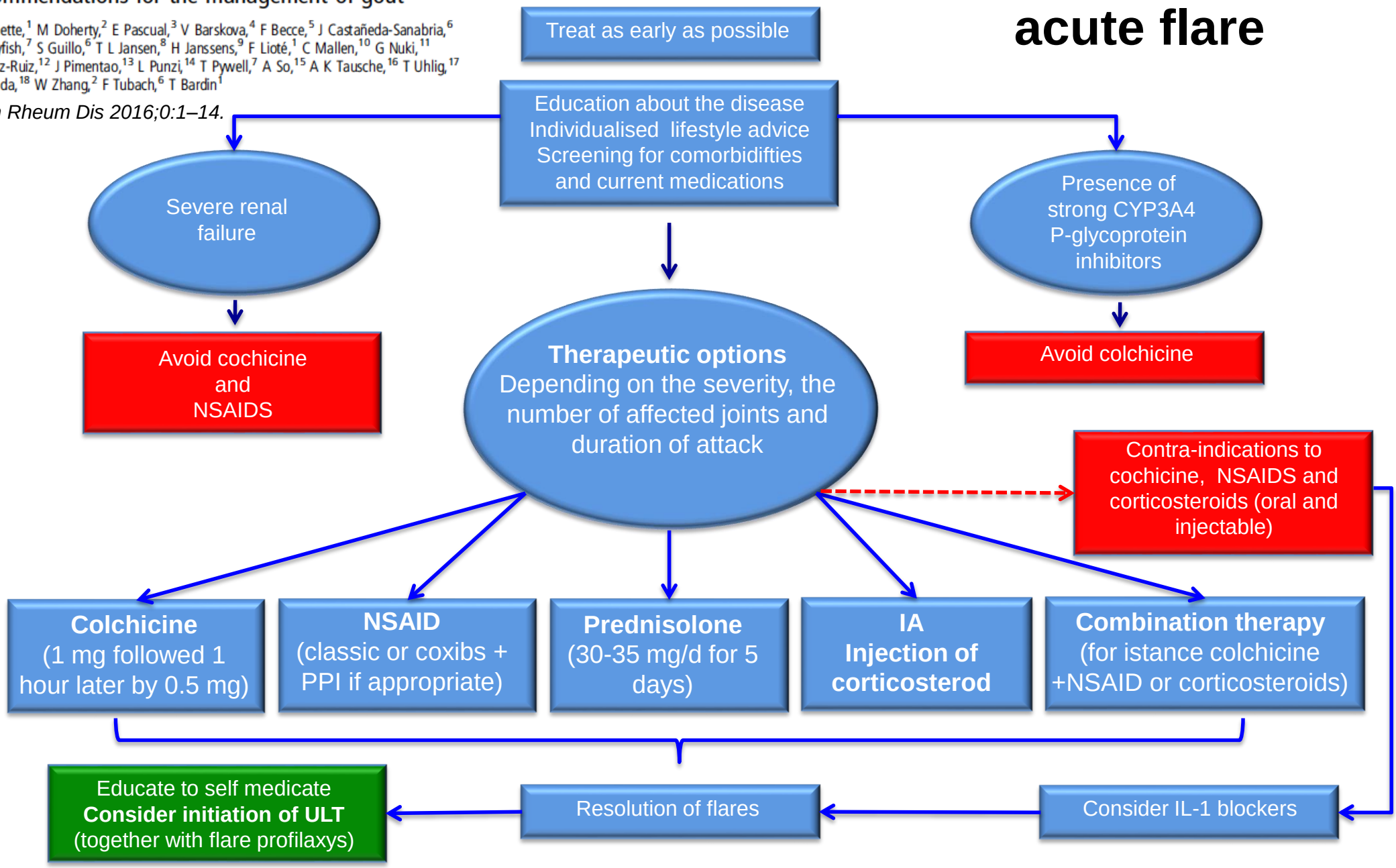
EXTENDED REPORT

2016 updated EULAR evidence-based recommendations for the management of gout

P Richette,[1] M Doherty,[2] E Pascual,[3] V Barskova,[4] F Becce,[5] J Castañeda-Sanabria,[6] M Coyfish,[7] S Guillo,[6] T L Jansen,[8] H Janssens,[9] F Lioté,[1] C Mallen,[10] G Nuki,[11] F Perez-Ruiz,[12] J Pimentao,[13] L Punzi,[14] T Pywell,[7] A So,[15] A K Tausche,[16] T Uhlig,[17] J Zavada,[18] W Zhang,[2] F Tubach,[6] T Bardin[1]

Ann Rheum Dis 2016;0:1–14.

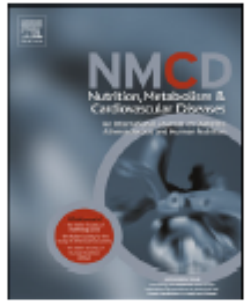
Management of acute flare



Nutrition, Metabolism & Cardiovascular Diseases (2016) 26, 951–961

ELSEVIER

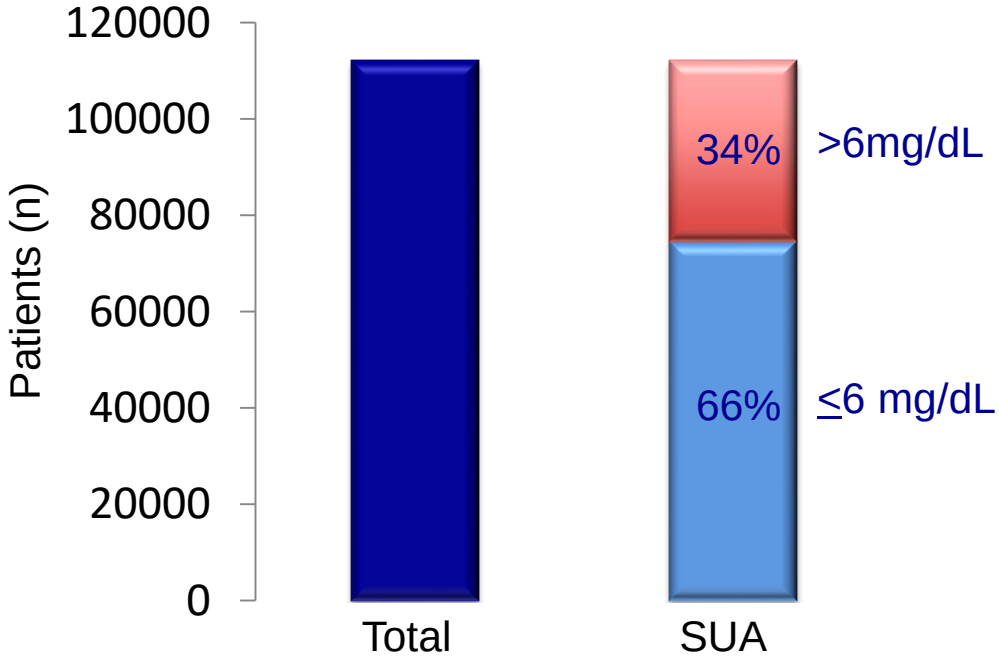
Serum Uric Acid Target < 6 mg/dL

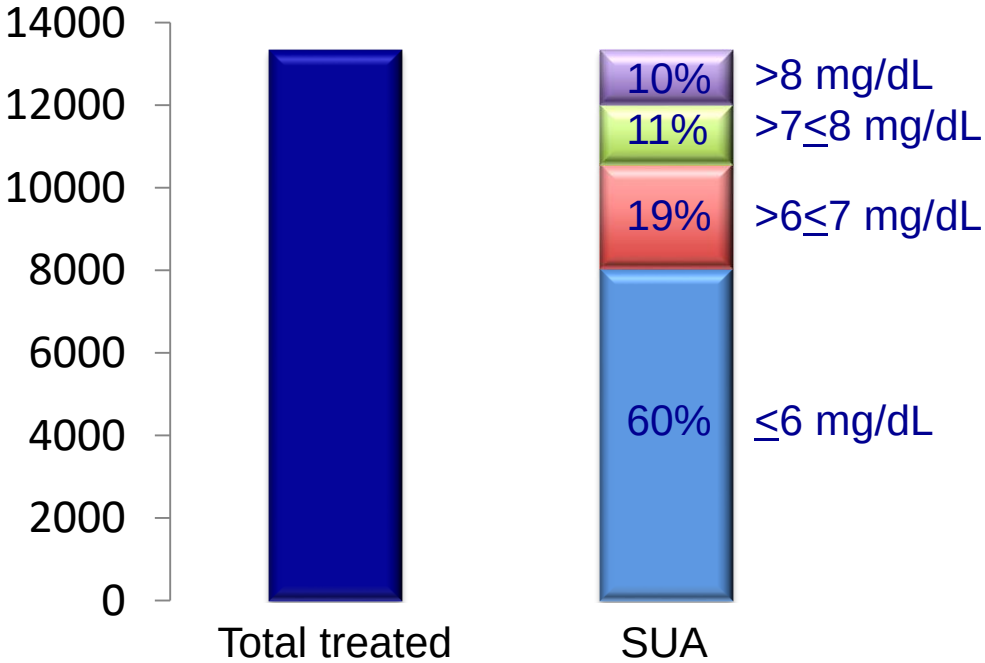


Hyperuricemia is associated with increased hospitalization risk and healthcare costs: Evidence from an administrative database in Italy

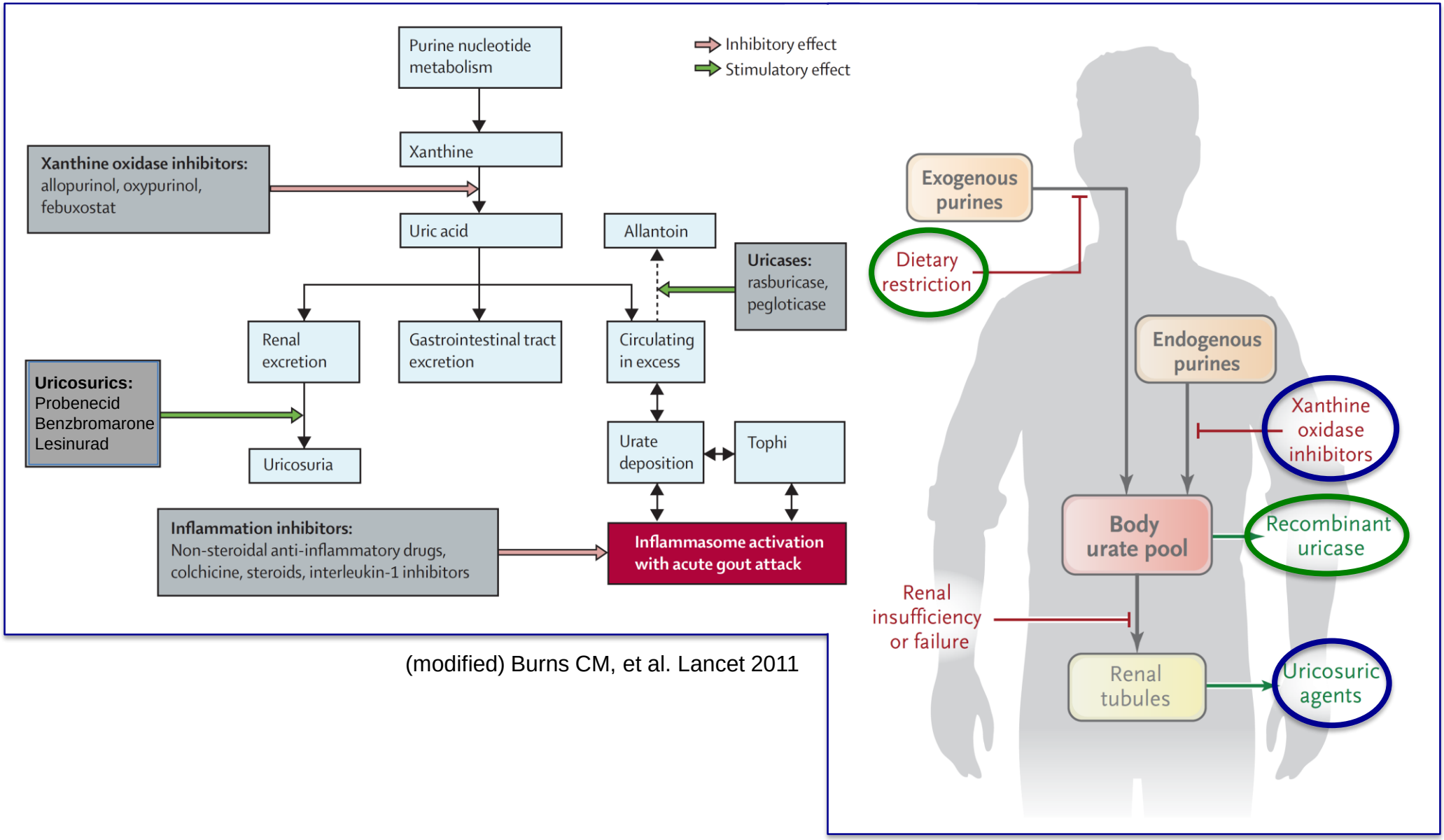
CrossMark

L. Degli Esposti [a,1], G. Desideri [b,*,1], S. Saragoni [a], S. Buda [a], R. Pontremoli [c], C. Borghi [d]





Gout therapeutics: new drugs for an old disease

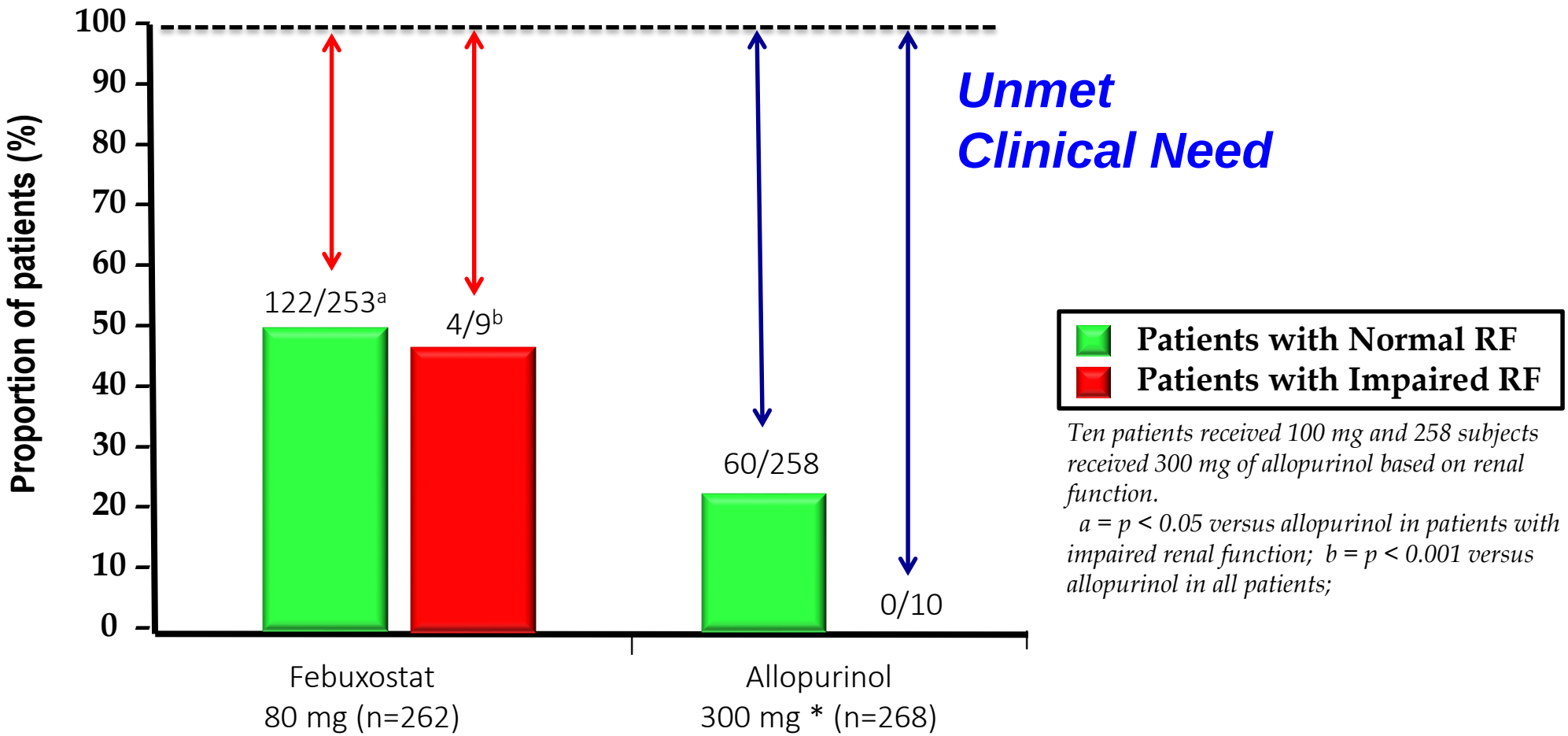


(modified) Burns CM, et al. Lancet 2011

Neogi T. N Eng J Med 2011;364:443-452

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)



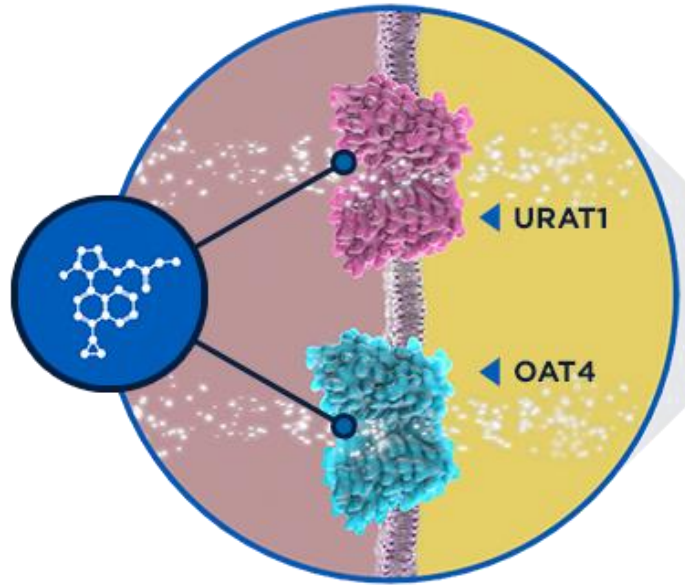
Ten patients received 100 mg and 258 subjects received 300 mg of allopurinol based on renal function.

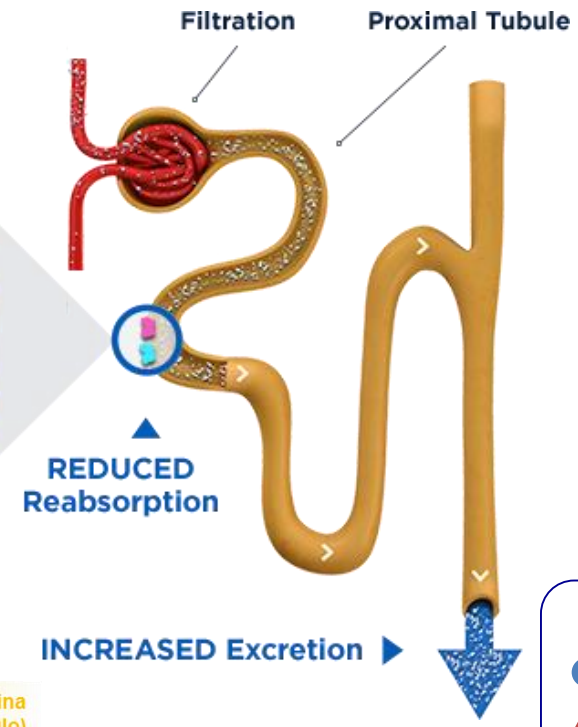
a = p < 0.05 versus allopurinol in patients with impaired renal function; b = p < 0.001 versus allopurinol in all patients;

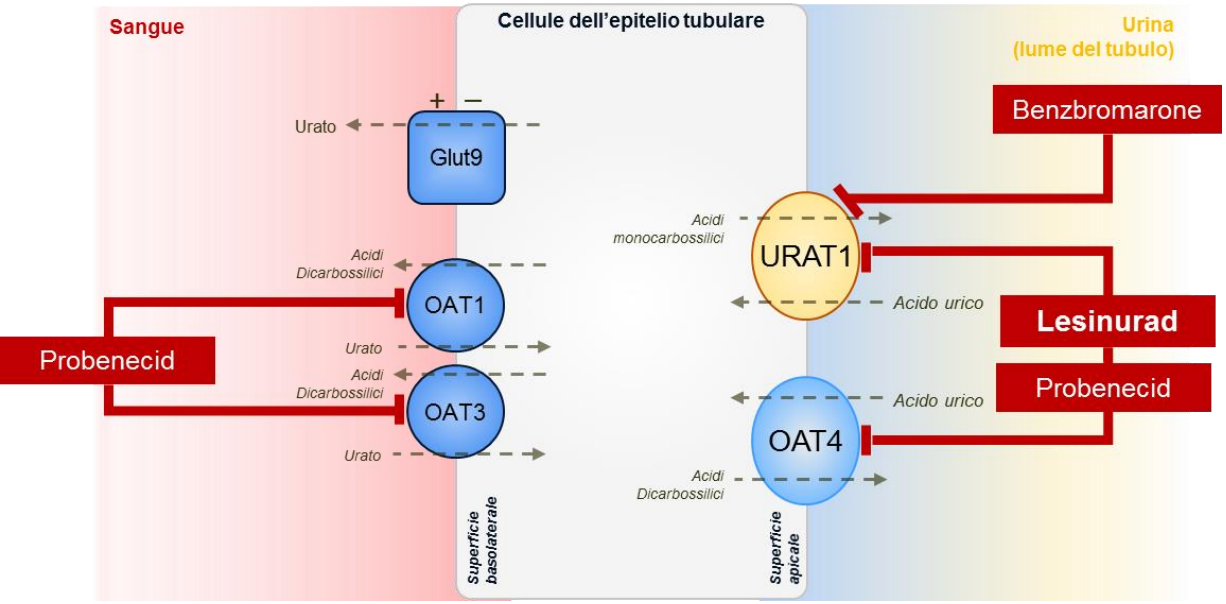
Becker MA et al. Arthritis Research & Therapy 2010; 12: R63.

Lesinurad reduces sUA by increasing renal excretion of UA

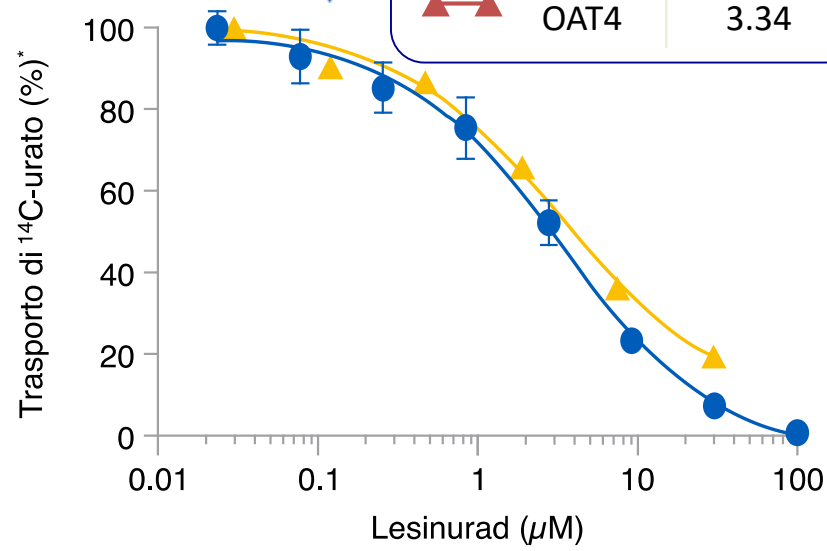
Lesinurad



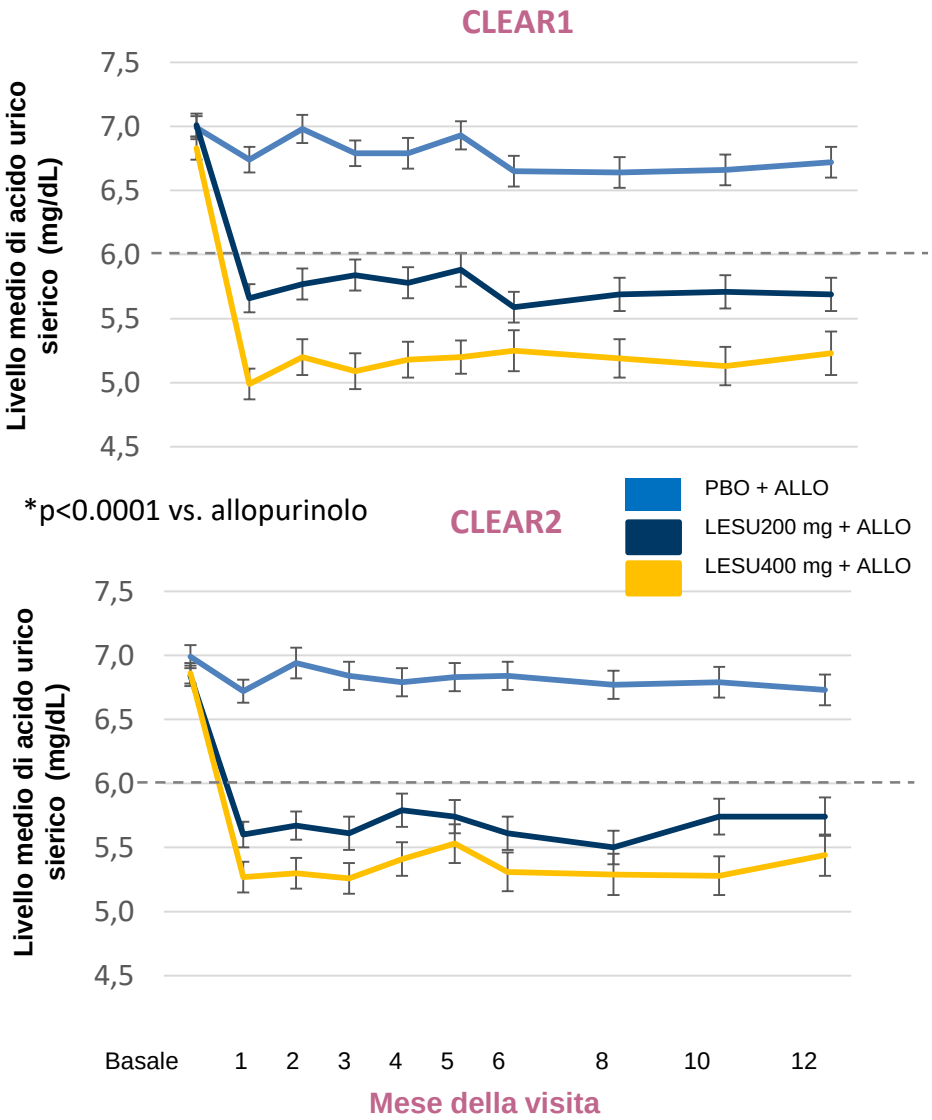




	IC_{50} (µM)
URAT1	3.36
OAT4	3.34

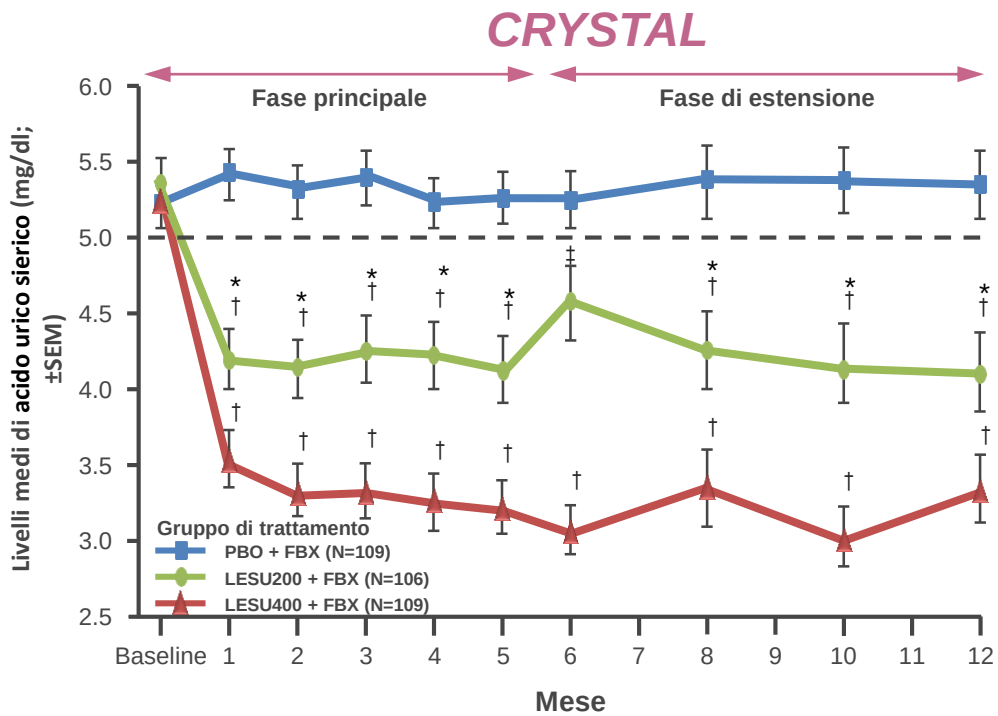


Superiore efficacia delle combinazione lesinurad+XO-I vs XO-I in monoterapia nel ridurre SUA



Saag KG, et al. Arthritis Rheumatol 2017;69:203–12.

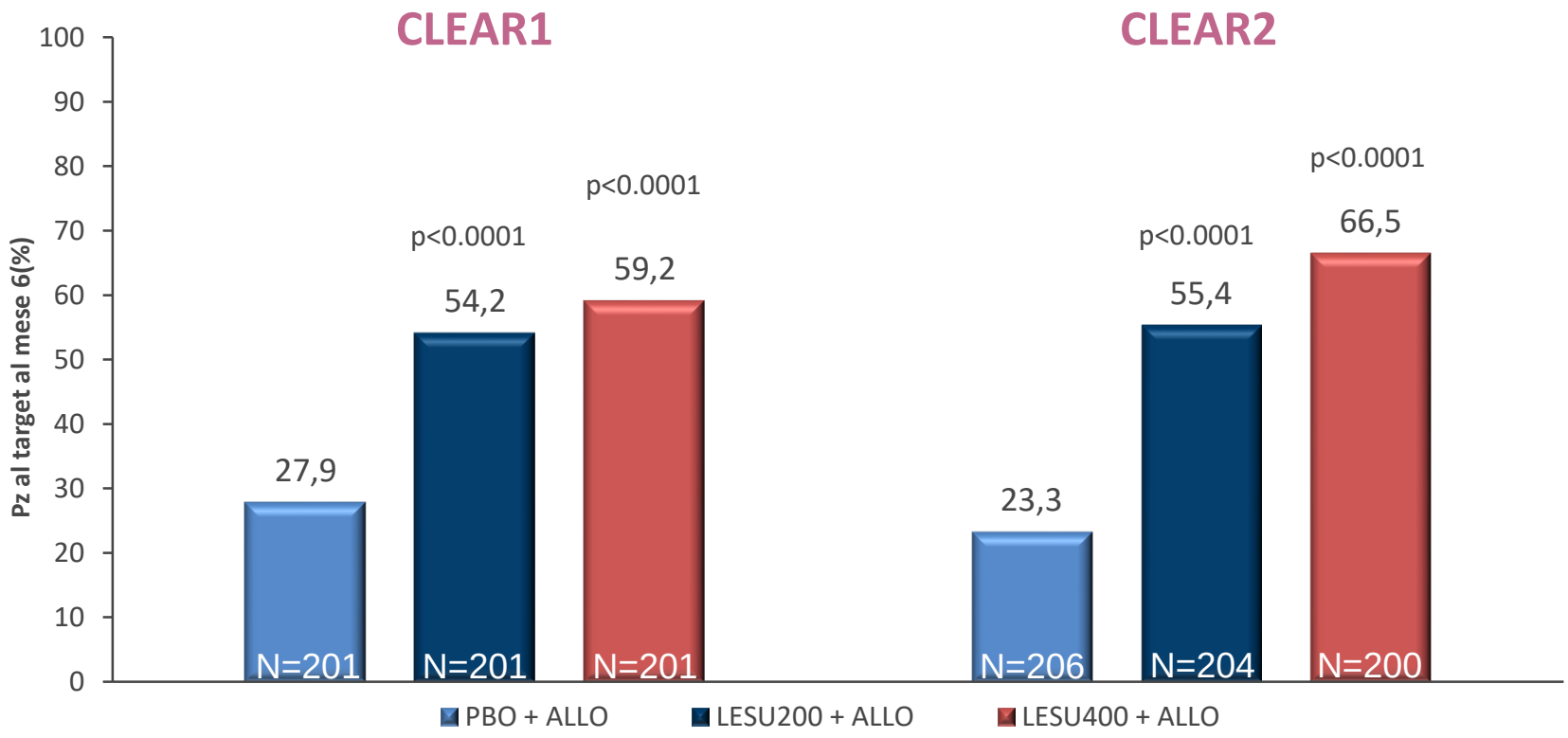
Bardin T, et al. Ann Rheum Dis 2016;76:811–20.



†p<0.0001 versus baseline; ‡p=0.0002 versus baseline. *p≤0.0281 LESU 200 + FBX vs PBO + FBX

Dalbeth N, et al. Arthritis Rheumatol. 2017 Sep;69(9):1903-1913

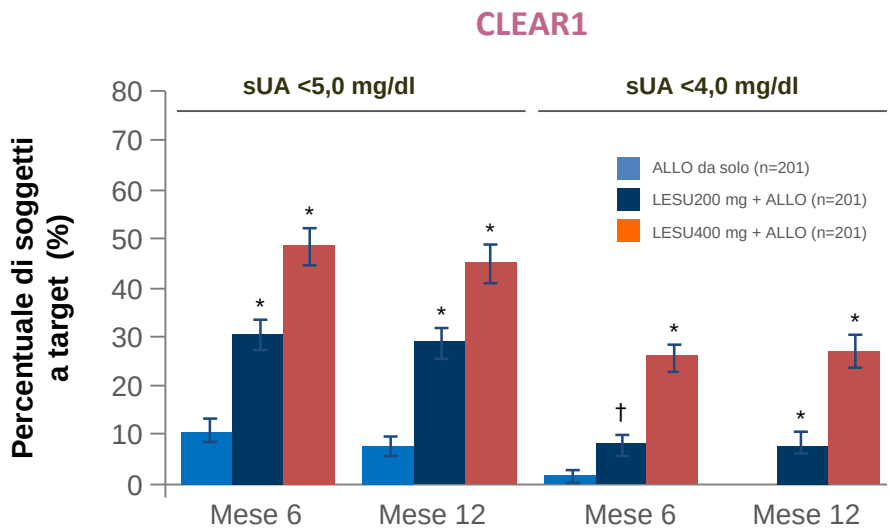
Superiore efficacia delle combinazione lesinurad+allopurinolo vs allopurinolo in monoterapia nel raggiungere SUA<6 mg/dL



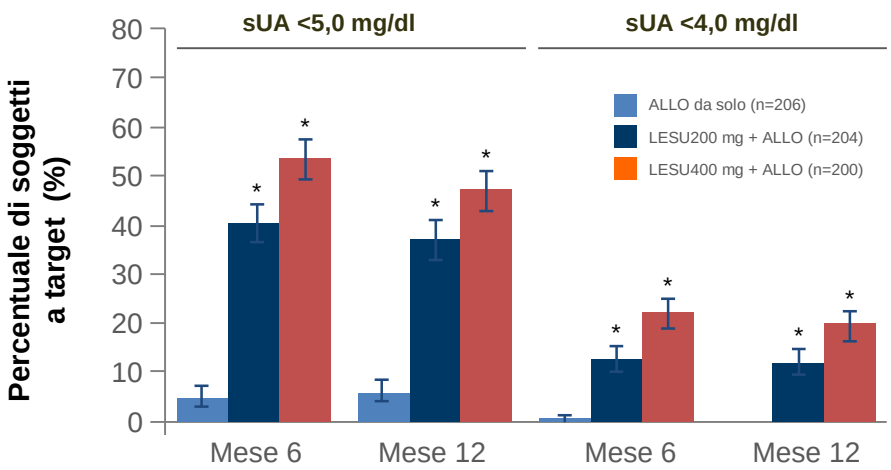
ALLO=allopurinolo; LESU=lesinurad; PBO=placebo Analisi NRI=non-responder imputation

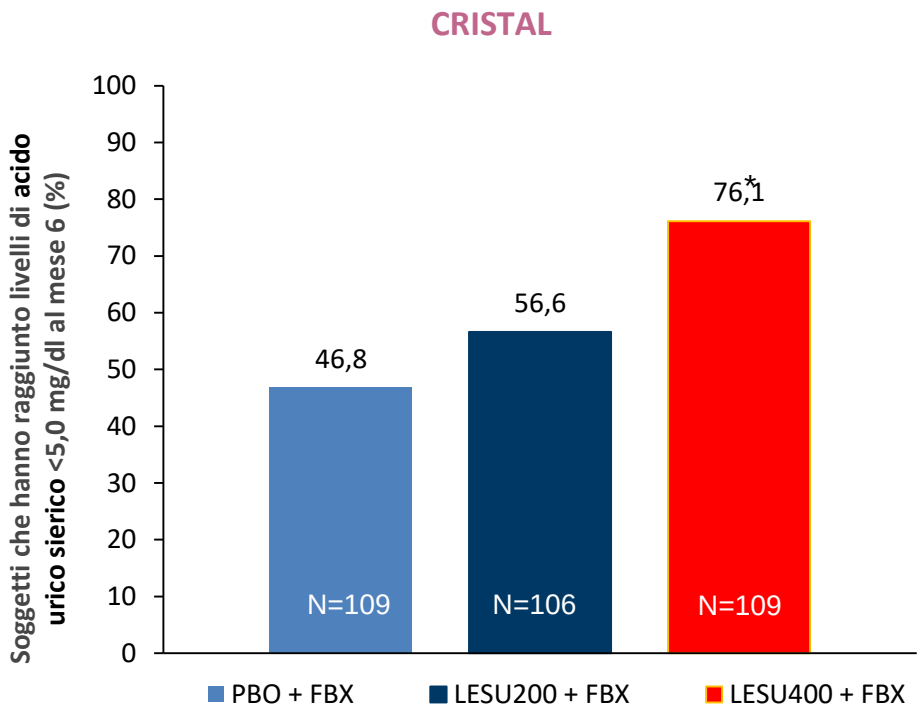
1. Saag KG, et al. Arthritis Rheumatol 2017;69:203–12. 2. Bardin T, et al. Ann Rheum Dis 2017;76:811–20.

Superiore efficacia delle combinazione lesinurad+XO-I vs XO-I in monoterapia nel raggiungere SUA <5 e <4 mg/dL



*p<0.0001 vs. allopurinolo da solo;
†p<0.01 vs. Allopurinoloda solo.





*p<0.0001 versus PBO + FBX;

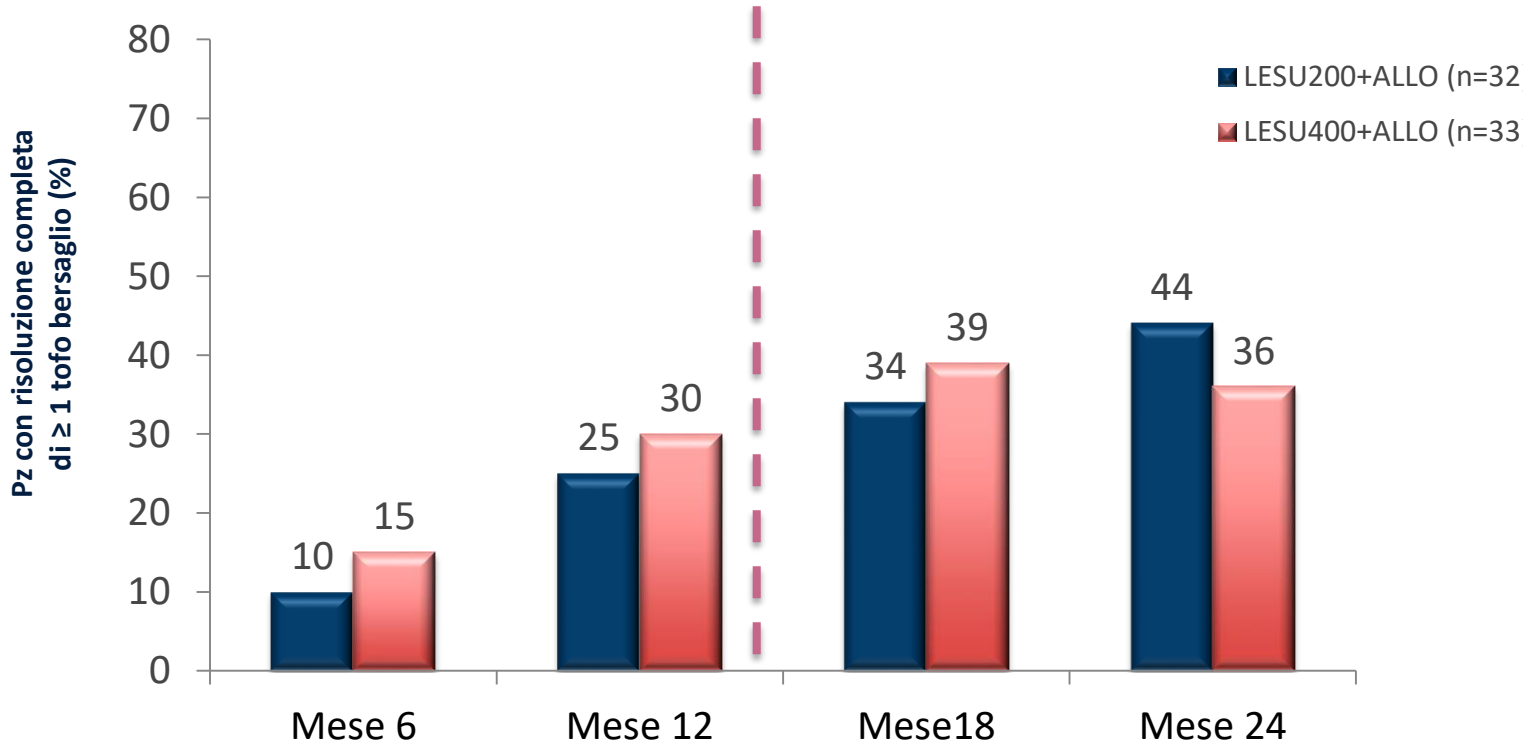
Saag KG, et al. Arthritis Rheumatol 2017;69:203–12.
Bardin T, et al. Ann Rheum Dis 2016;76:811–20.

Dalbeth N, et al. Arthritis Rheumatol. 2017 Sep;69(9):1903-1913

Superiore efficacia delle combinazione lesinurad+allopurinolo vs allopurinolo in monoterapia nell'indurre la risoluzione dei tofi

Incremento costante (fino al mese 12 dello studio di estensione) della % di pz trattati con Lesinurad 200 mg + allopurinolo* con risoluzione completa di almeno un tofo "bersaglio"

* Trattamento per 24 mesi continuativi

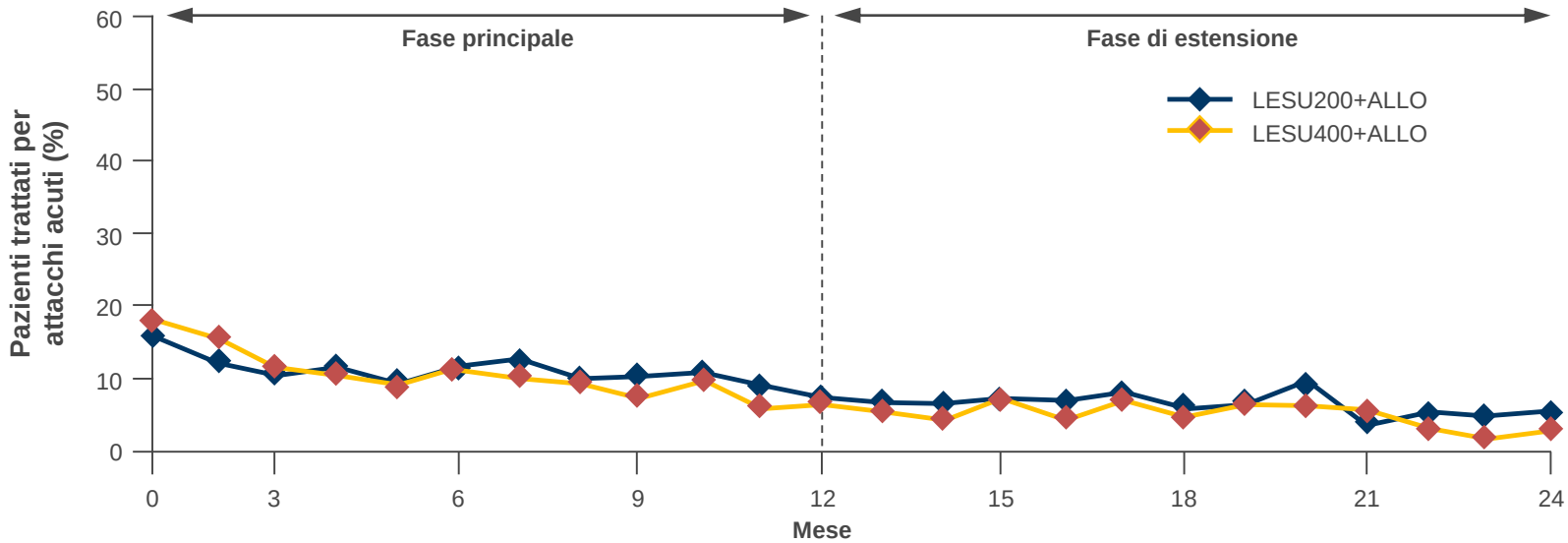


ALLO=allopurinolo; LESU=lesinurad.

Bardin T, *et al*. Presented at EULAR 2016. Poster 209.

Superiore efficacia delle combinazione lesinurad+allopurinolo vs allopurinolo in monoterapia nel ridurre gli attacchi acuti nel lungo termine

Per i soggetti che hanno ricevuto lesinurad + allopurinolo durante lo studio principale, la quota di pazienti che ha richiesto trattamento ha continuato a diminuire anche durante lo studio di estensione



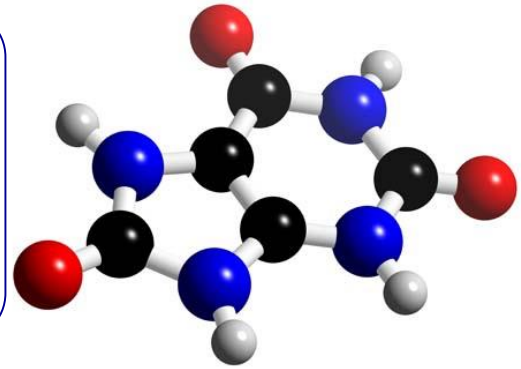
LESU200+ALLO	n=	239	239	219	196
LESU400+ALLO	n=	232	232	214	197

Bardin T, *et al*. Presented at EULAR 2016. Poster 209.

Uric Acid excretion/production balance

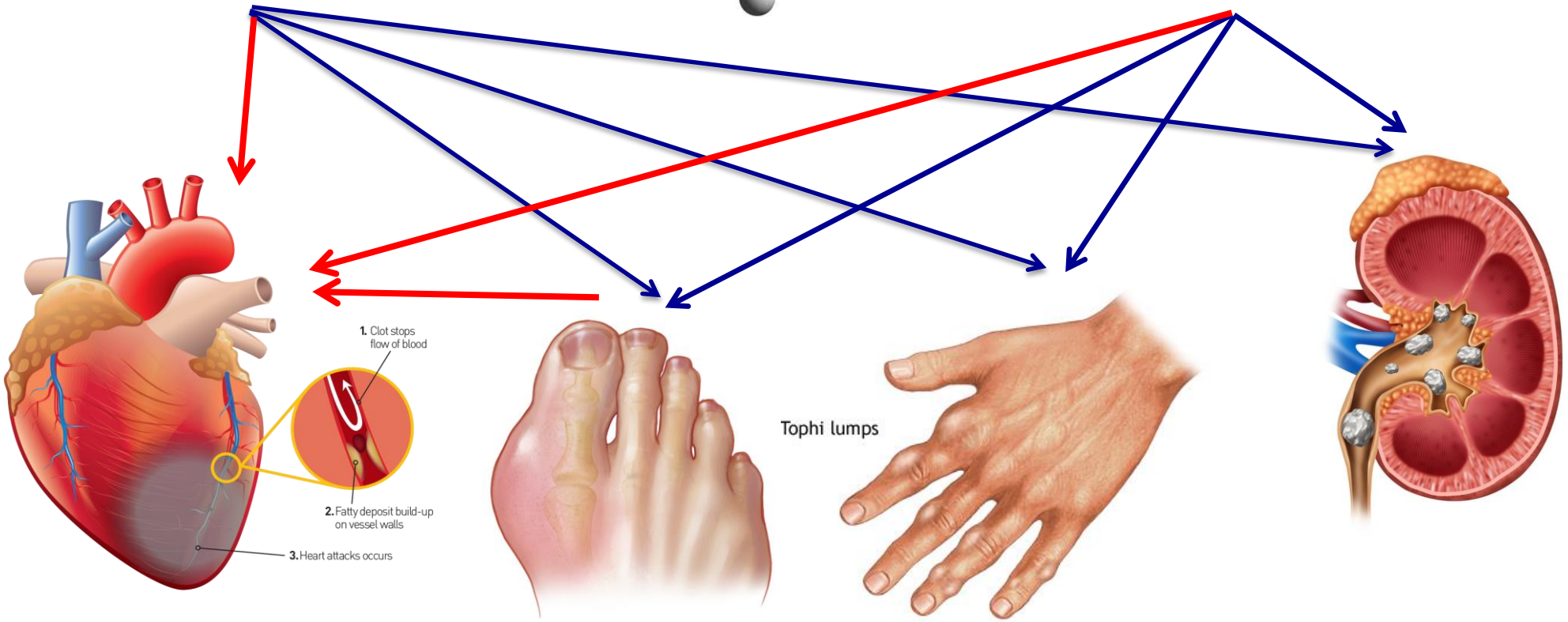
20% Iperproducers

XO overactivity (genetic, induced) or ”overfeeding” (food, fructose, purines)

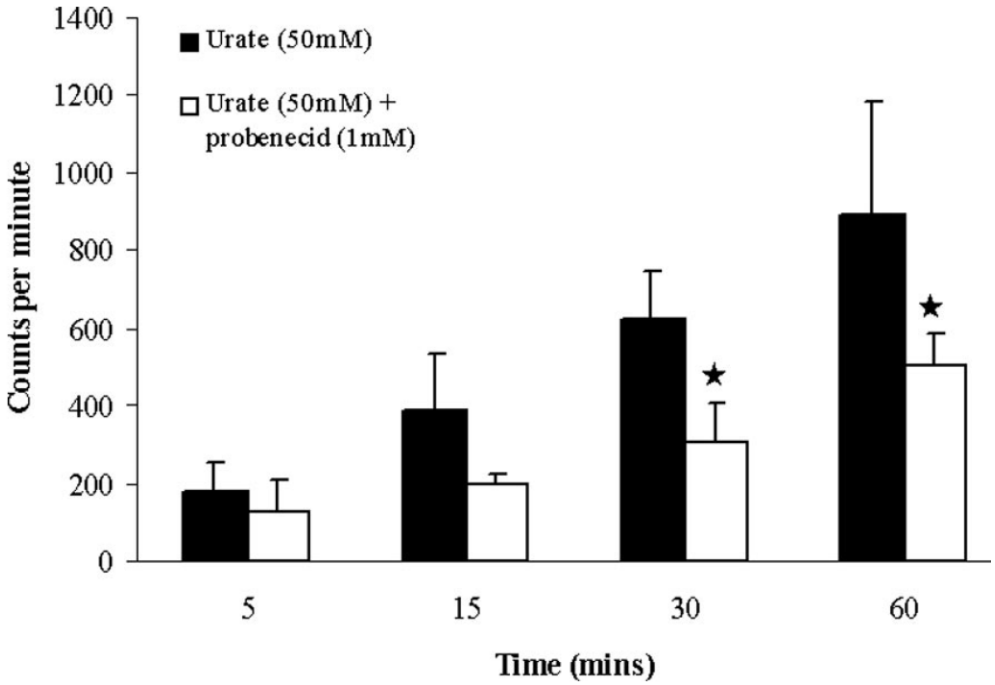


80% Underexcretors

(physiologically, low GFR, Diuretics)

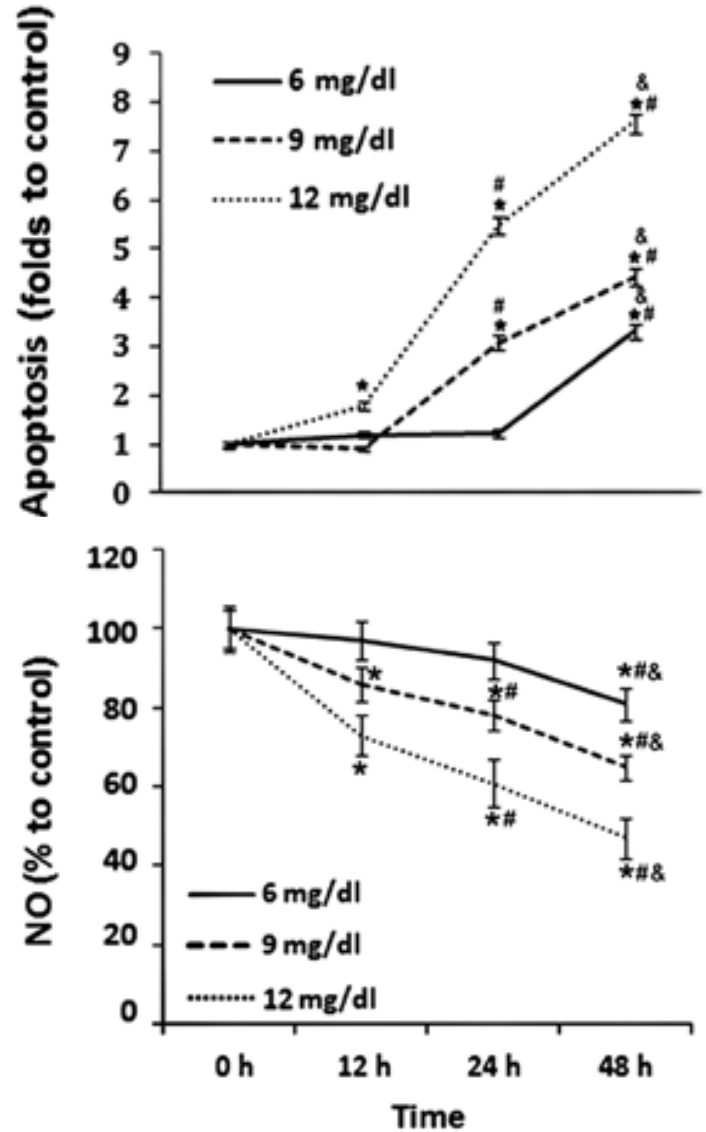


Human Vascular Smooth Muscle Cells Express a Urate Transporter



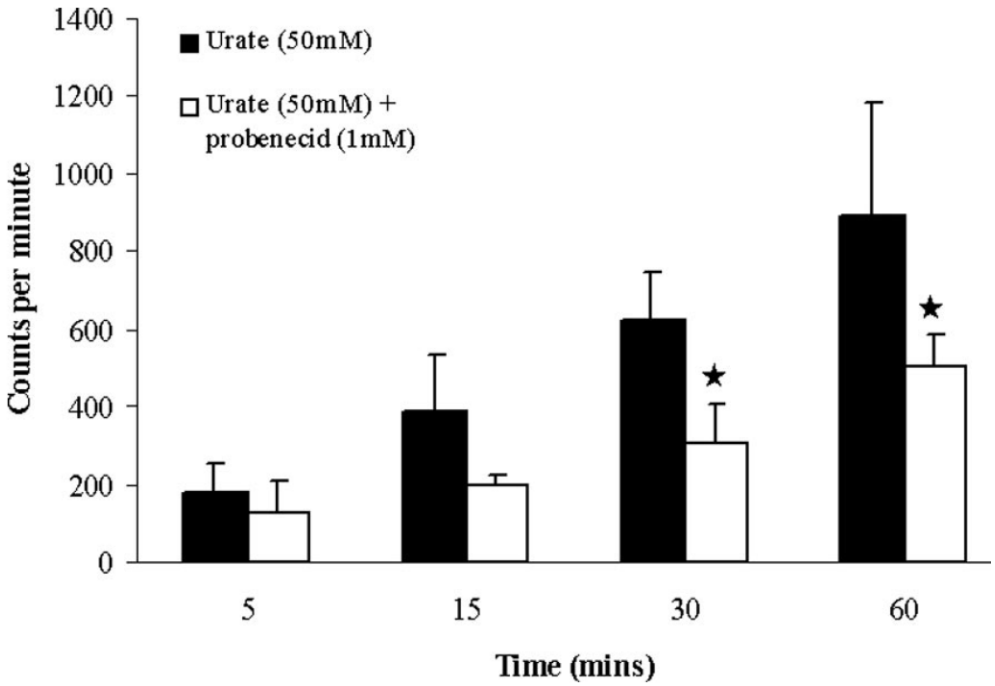
Price KL et al. J Am Soc Nephrol 17: 1791–1795, 2006.

UA iduces apoptosi and reduce NO in HUVECs



Li P et al. Int J Mol Med. 2016 Apr;37(4):989-97.

Human Vascular Smooth Muscle Cells Express a Urate Transporter



Price KL et al. J Am Soc Nephrol 17: 1791–1795, 2006.

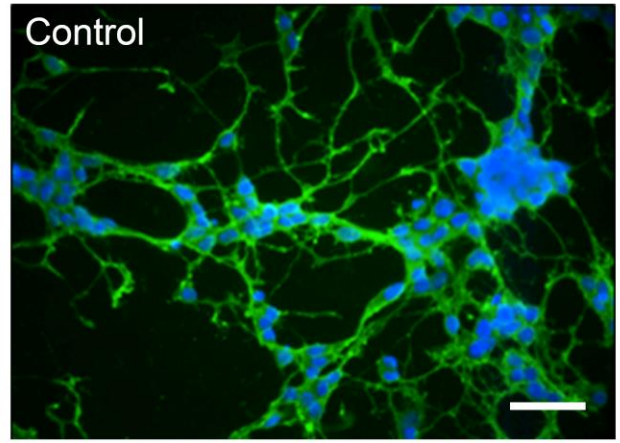
URAT1 Gene Polymorphisms Associated with Obesity and MS in Hypertension

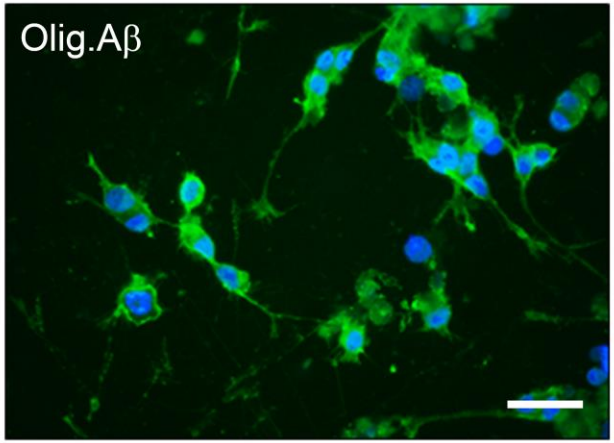
	A/A	A/T	T/T	p value
Caucasians (n = 234)	n = 28	n = 95	n = 111	
Age, years	52.60±1.67	52.04±0.98	50.68±0.82	0.44
Women, %	53.57	52.17	41.44	0.26
Serum uric acid, mg/dl	5.91±0.21	5.64±0.11	5.46±0.10	0.15
Triglycerides, mg/dl	168.54±18.16	152.04±10.02	134.12±9.19	0.17
HDL cholesterol, mg/dl	41.97±2.44	48.83±1.34	49.78±1.23	0.018
BMI	34.93±1.01	30.27±0.55	30.51±0.51	<0.0001
Waist circumference, cm	105.63±2.28	97.22±1.24	98.39±1.14	0.0033
African Americans (n = 166)	n = 121	n = 38	n = 7	
Age, years	48.55±7.89	48.0±8.65	49.0±11.46	0.92
Women, %	66.94	84.21	85.71	0.084
Serum uric acid, mg/dl	5.8±0.12	5.6±0.22	5.37±0.47	0.85
Triglycerides, mg/dl	108.75±8.16	107.83±14.75	100.7±32.2	0.97
HDL cholesterol, mg/dl	49.44±1.36	50.86±2.46	51.25±5.43	0.84
BMI	31.23±0.55	31.41±0.98	30.82±0.51	0.97
Waist circumference, cm	96.10±1.29	99.10±2.32	99.07±5.35	0.4888

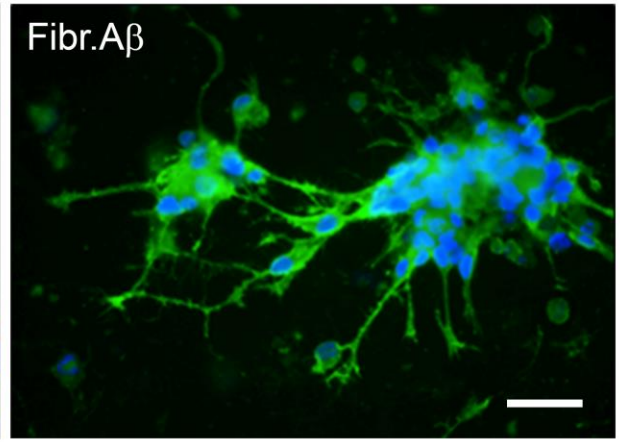
Data are expressed as means ± SD.

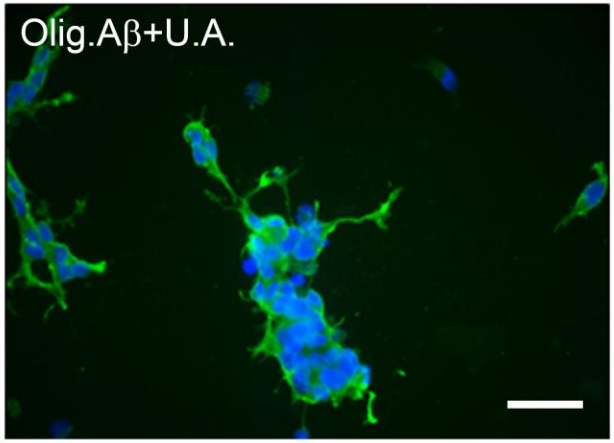
Shafiu M et al. Kidney Blood Press Res . 2012 ; 35(6): 477–482.

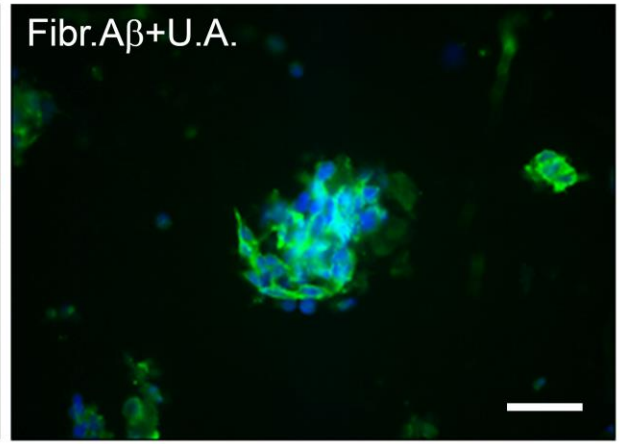
GAP-43

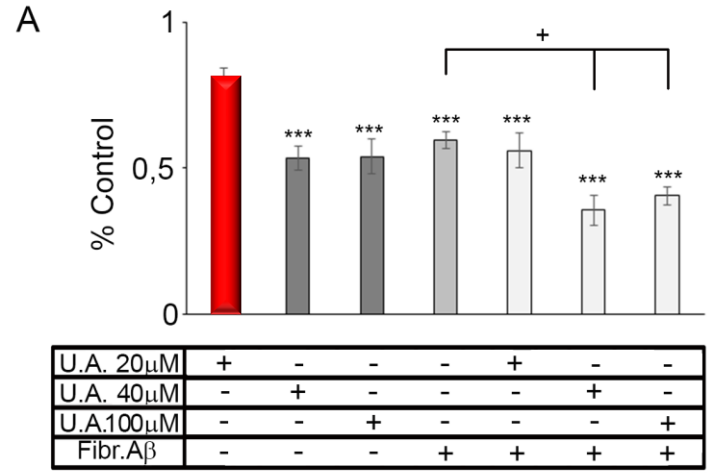


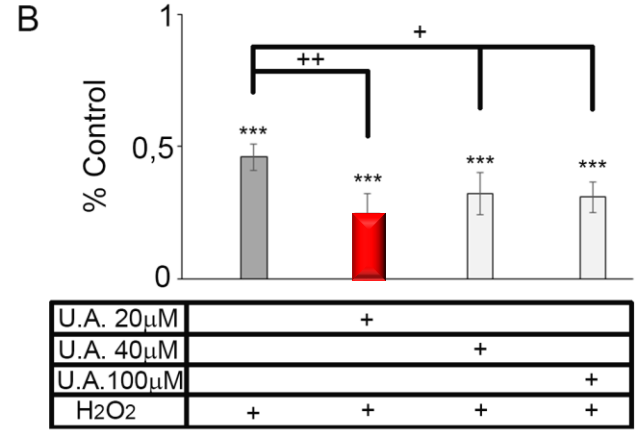


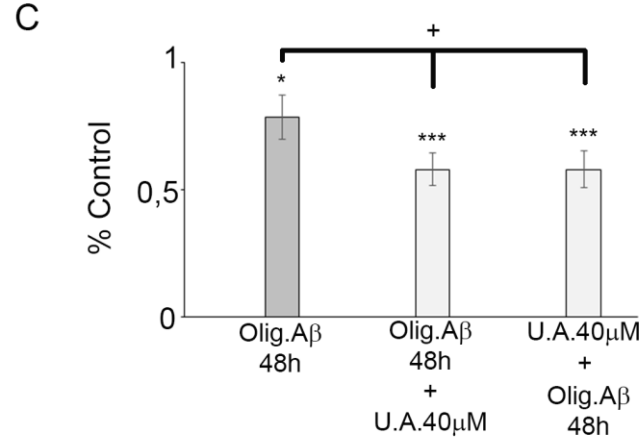












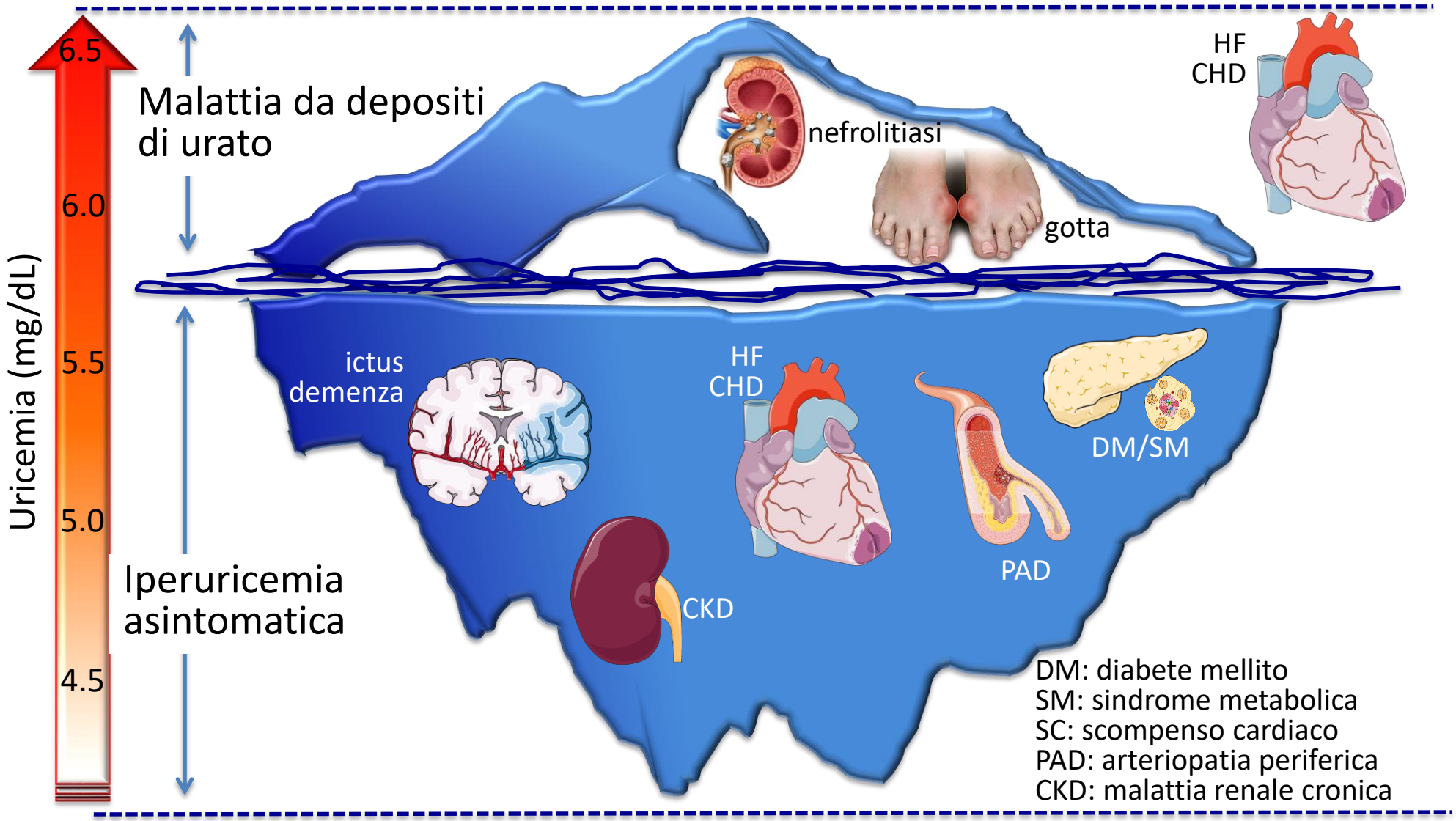
Desideri G et al. J. Cell. Physiol. 9999: 1–10, 2016.

The Geriatrician's Perspective

It is more important to know what sort of patient has a disease than to know what sort of disease a patient has

William Osler, 1892

Il mondo sommerso dell'iperuricemia con e senza depositi di urato



63° CONGRESSO NAZIONALE SIGG

PROGRAMMA DEFINITIVO

ROMA 28 novembre 01 dicembre 2018

Auditorium della Tecnica

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

Thank you