Iperuricemia e rischio cardio-metabolico: nuove strategie di trattamento

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Dipartimento MESVA
Università degli Studi di L'Aquila

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

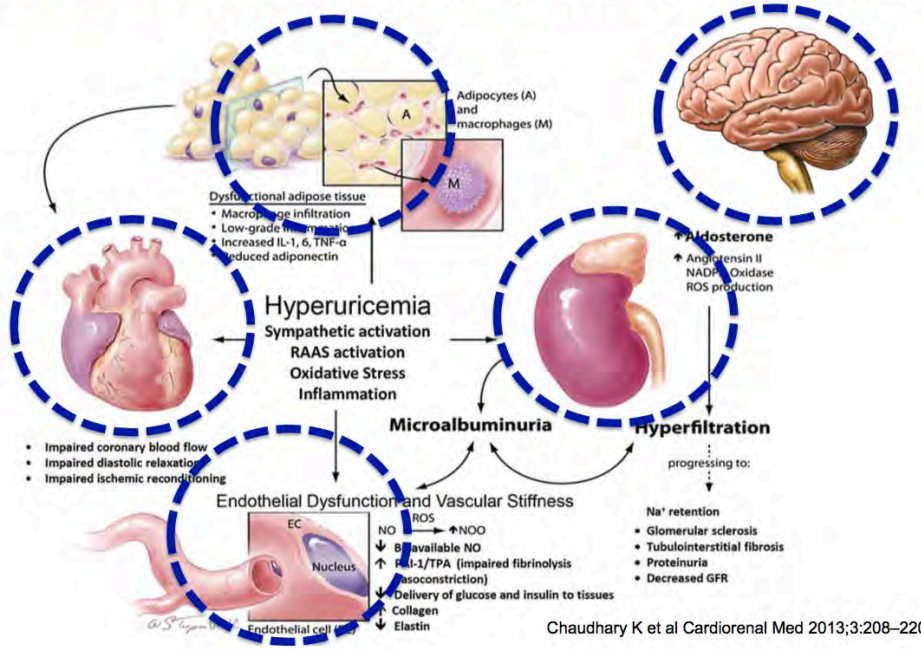
Epidemiology-Pathophysiology

Gout: The Fashionable Disease

"the disease of kings"

"rich man's disease"

Hyperuricemia and Cardiorenal Metabolic Syndrome



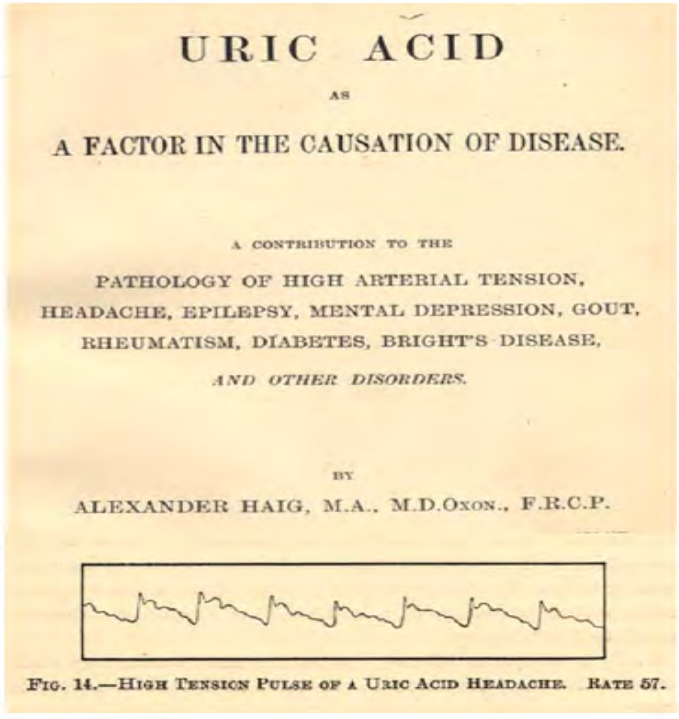
Chaudhary K et al Cardiorenal Med 2013;3:208–220

Treatment

ESC European Society of Cardiology
European Heart Journal (2018) 00, 1–98
doi:10.1093/eurheartj/ehy339

2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)



URIC ACID

AS

A FACTOR IN THE CAUSATION OF DISEASE.

A CONTRIBUTION TO THE

PATHOLOGY OF HIGH ARTERIAL TENSION, HEADACHE, EPILEPSY, MENTAL DEPRESSION, GOUT, RHEUMATISM, DIABETES, BRIGHT'S DISEASE, *AND OTHER DISORDERS.*

BY

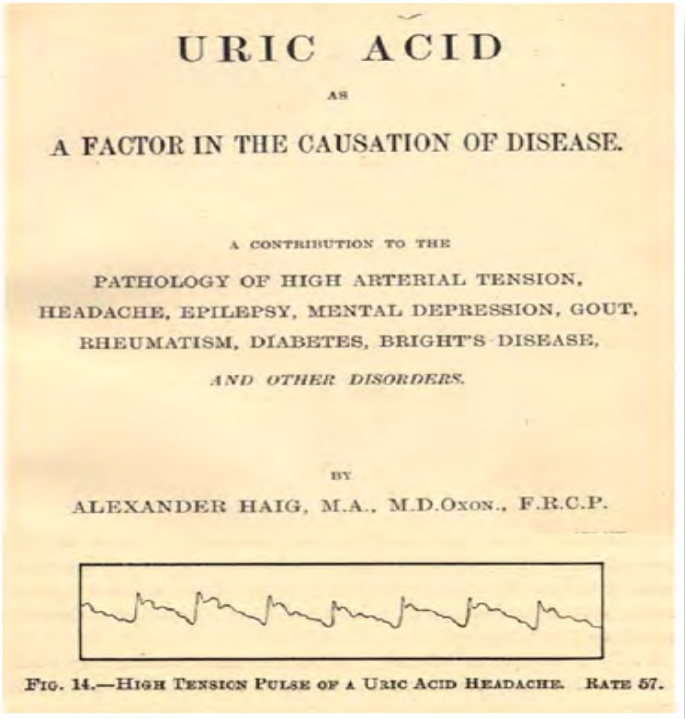
ALEXANDER HAIG, M.A., M.D.Oxon., F.R.C.P.

FIG. 14.—HIGH TENSION PULSE OF A URIC ACID HEADACHE. RATE 57.

Routine laboratory tests
Haemoglobin and/or haematocrit
Fasting blood glucose and glycated HbA_{1c}
Blood lipids: total cholesterol, LDL cholesterol, HDL cholesterol
Blood triglycerides
Blood potassium and sodium
Blood uric acid
Blood creatinine and eGFR
Blood liver function tests
Urine analysis: microscopic examination; urinary protein by dip-stick test or, ideally, albumin:creatinine ratio
12-lead ECG

2020 International Society of Hypertension Global Hypertension Practice Guidelines

Thomas Unger, Claudio Borghi, Fadi Charchar, Nadia A. Khan, Neil R. Poulter, Dorairaj Prabhakaran, Agustin Ramirez, Markus Schlaich, George S. Stergiou, Maciej Tomaszewski, Richard D. Wainford, Bryan Williams, Aletta E. Schutte



URIC ACID

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FIG. 14.—HIGH TENSION PULSE OF A URIC ACID HEADACHE. RATE 57.

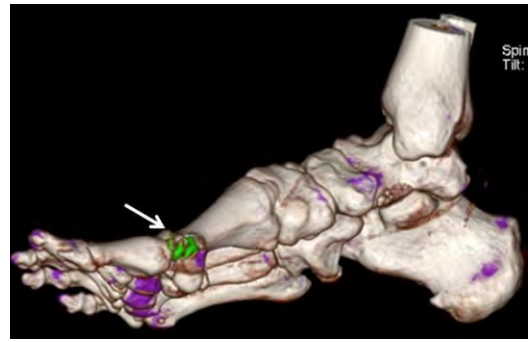
- **Carotid ultrasound:** Plaques (atherosclerosis), stenosis.
- **Kidneys/renal artery and adrenal imaging:** Ultrasound/renal artery Duplex; CT-/MR-angiography: renal parenchymal disease, renal artery stenosis, adrenal lesions, other abdominal pathology.
- **Fundoscopy:** Retinal changes, hemorrhages, papill-edema, tortuosity, nipping.
- **Brain CT/MRI:** Ischemic or hemorrhagic brain injury due to hypertension.

Functional Tests and Additional Laboratory Investigations

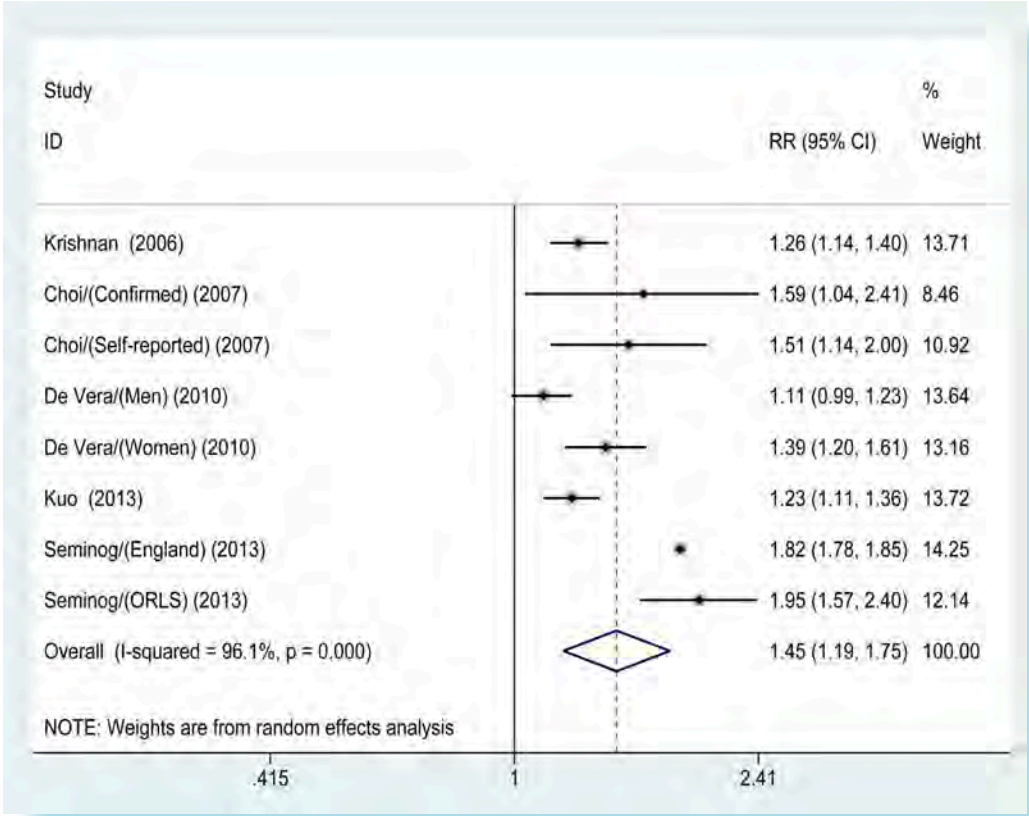
- **Ankle-brachial index:** Peripheral (lower extremity) artery disease.
- **Further testing for secondary hypertension if suspected:** Aldosterone-renin ratio, plasma free metanephrines, late-night salivary cortisol or other screening tests for cortisol excess.
- Urinary albumin/creatinine ratio
- Serum uric acid (s-UA) levels
- Liver function tests


Uricemia (mg/dL)
6.5
6.0
5.5
5.0
4.5
Malattia da depositi di urato
nefrolitiasi
gotta
START

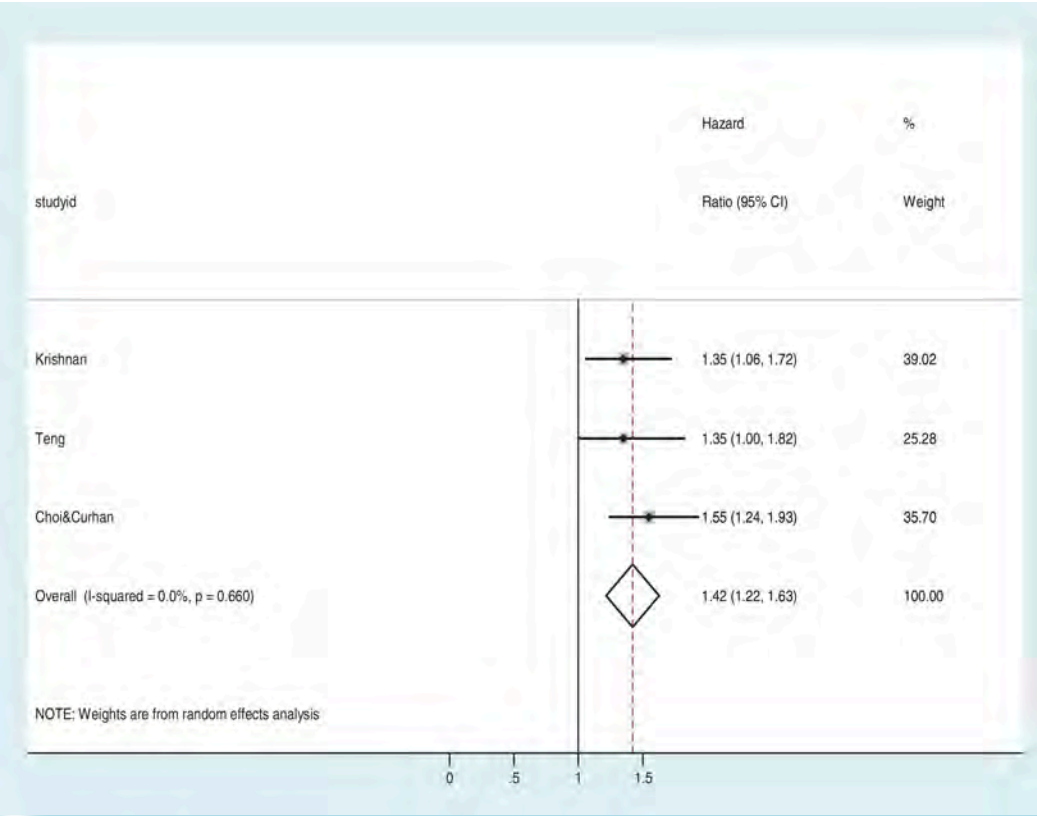
Gout is associated with increased risk for cardiovascular events



Gout and Risk of Myocardial Infarction[1]

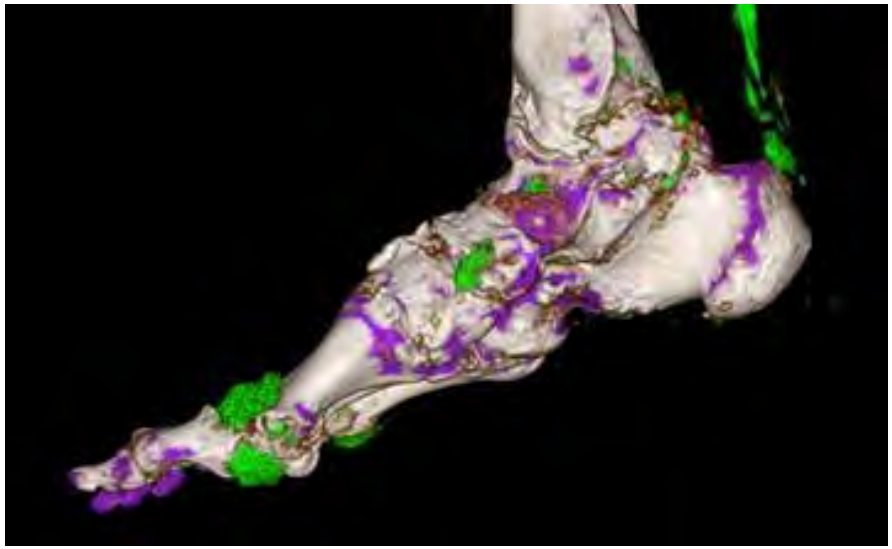


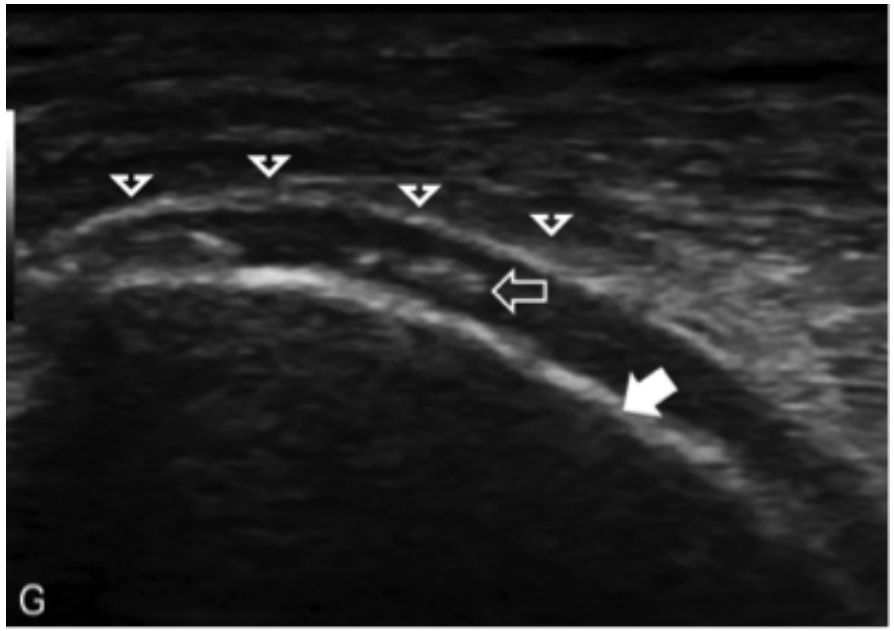
Gout and Mortality for CHD[2]



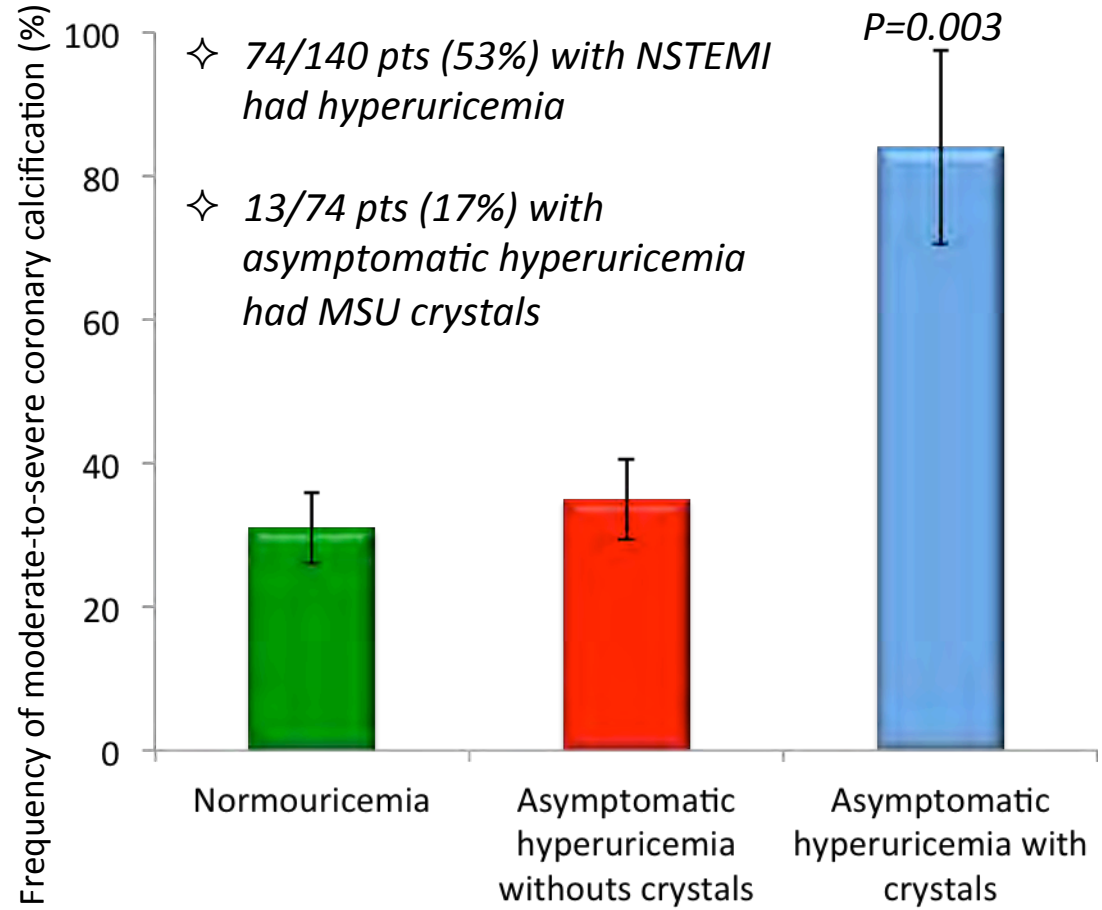
[1]Liu SC et al. PLoS One. 2015 Jul 31;10(7):e0134088. d
[2]Clarson LE et al. European Journal of Preventive Cardiology 2015, Vol. 22(3) 335-343

Subclinical Gout and Cardiovascular Disease





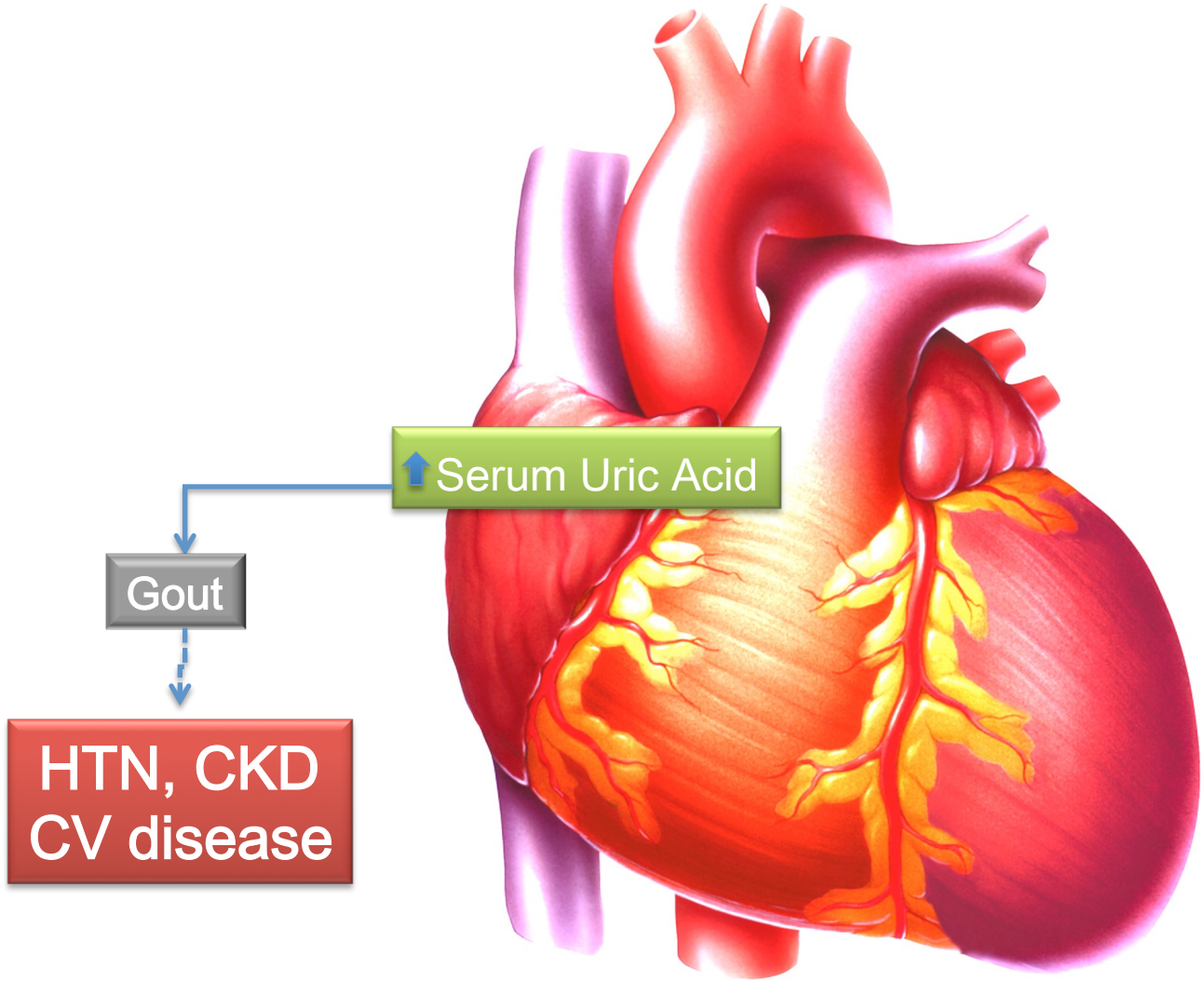
Silent MSU Crystal Deposits Are Associated With Severe Coronary Calcification in Asymptomatic Hyperuricemia (SUA >7 mg/dL)



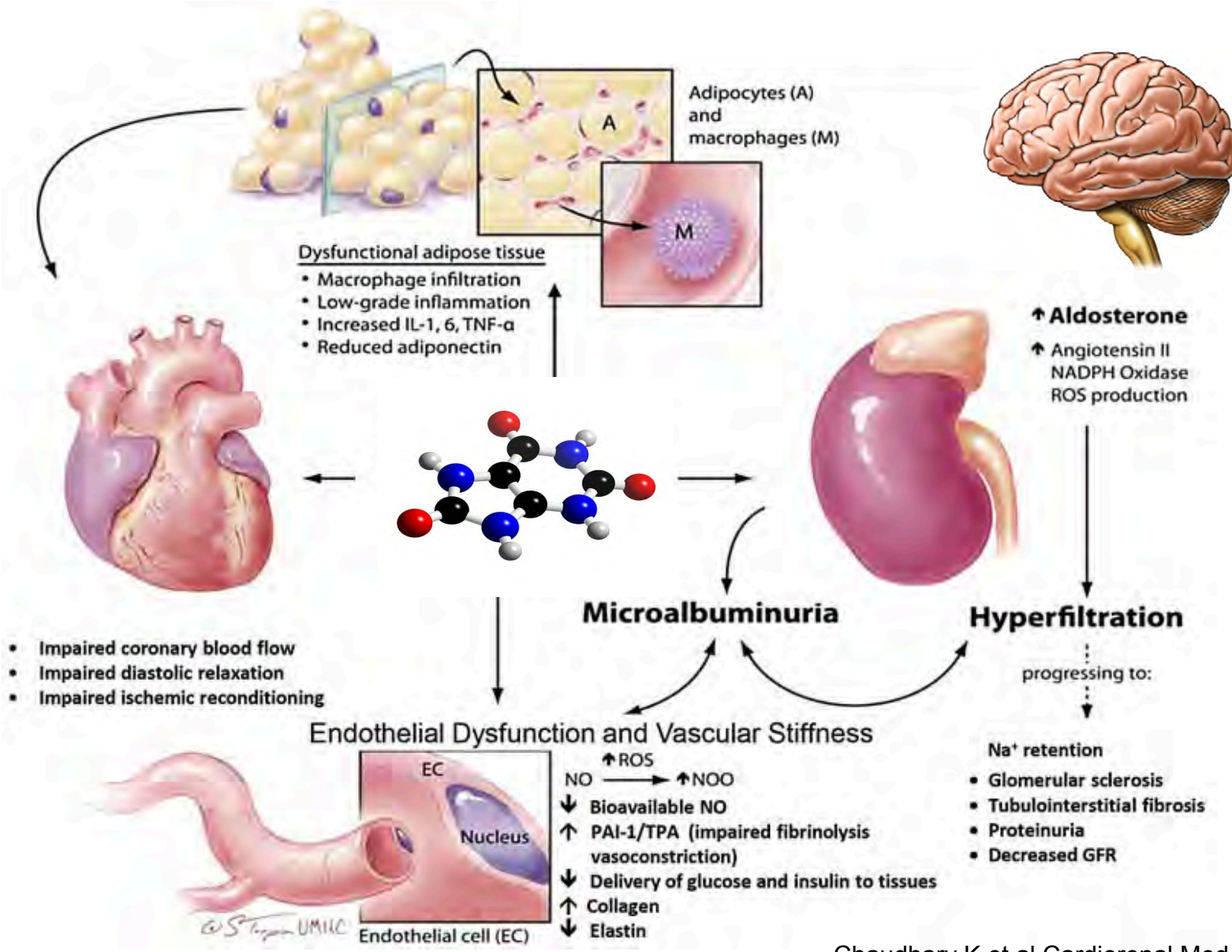
Andrès M et al. ARTHR & RHEUM 2016:68 (6):1531–1539

SUA, oxidative stress and CV disease: a comprehensive hypothesis

Borghi C, Desideri G, Hypertension 2016

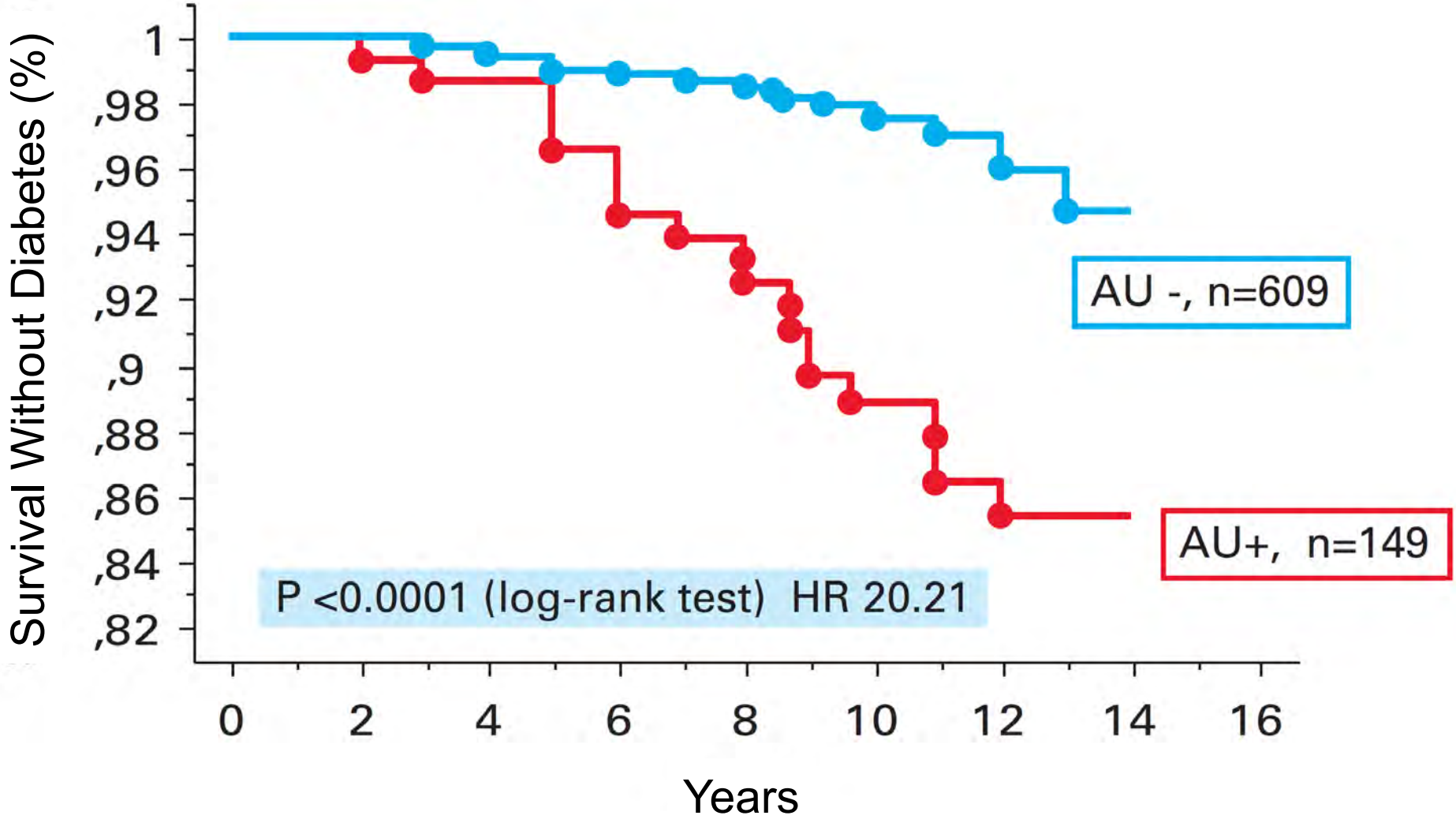


Uric Acid – Key Ingredient in the Recipe for Cardiorenal Metabolic Syndrome



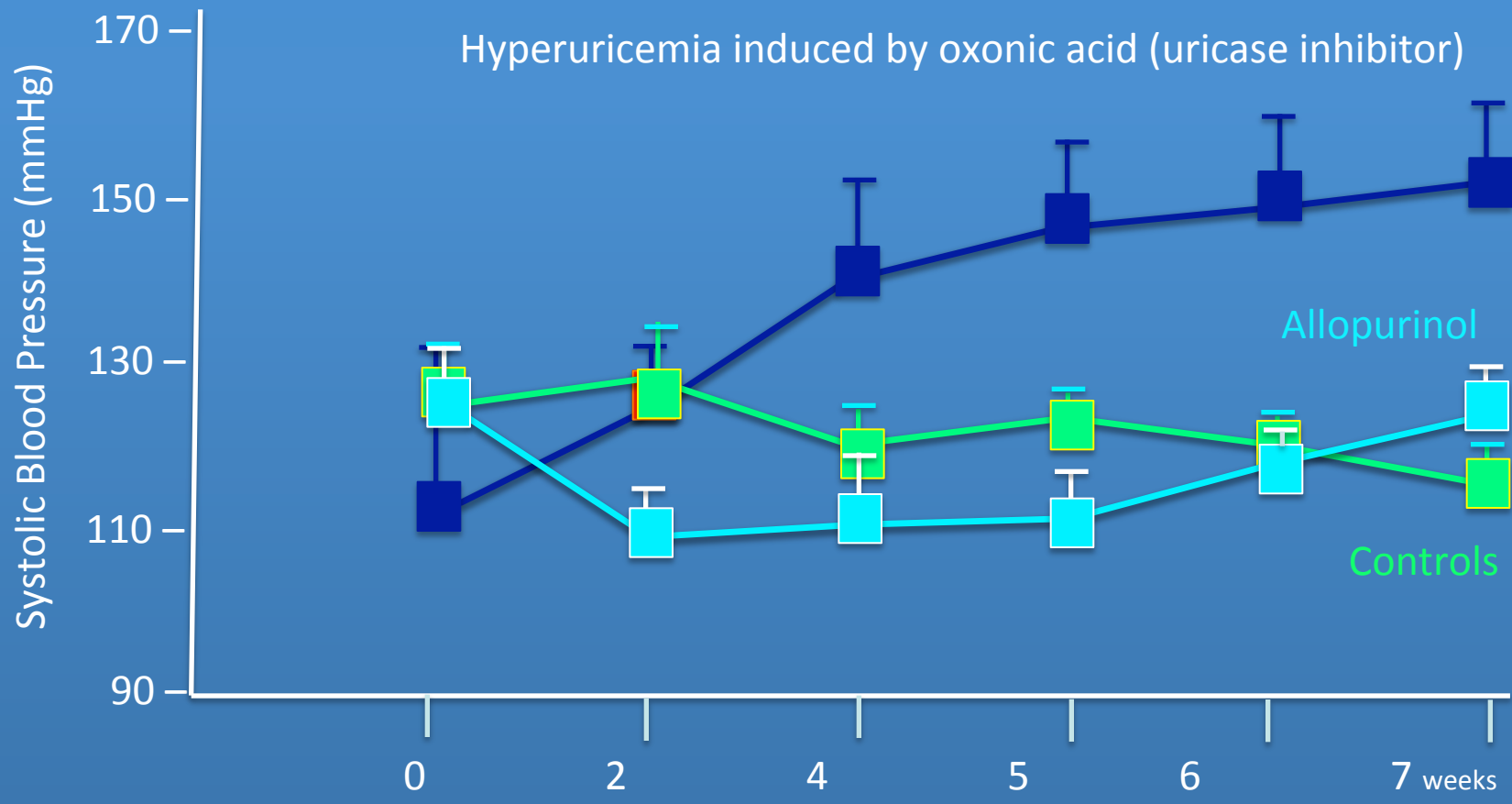
Chaudhary K et al Cardiorenal Med 2013;3:208–220

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

Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism



Mazzali M et al. Hypertension 2001, 38:1101-1106

Serum uric acid as a predictor of hypertension

Study	Population	Follow-up, y	Independent	Year
Israeli Heart Study	10 000 male participants	5	Not done	1972
Kaiser Permanente	2062 subjects	6	Yes	1990
University of Utah	1482 adults	7	Yes	1991
Olivetti Heart Study	619 male participants	12	Yes	1994
CARDIA study	5115 adults	10	Yes	1999
Osaka Health Survey	6356 males	10	Yes	2001
Hawaii-Los Angeles-Hiroshima	140 male participants	15	Yes	2001
Osaka Factory Study	433 male participants	5	Yes	2003
Osaka Health Survey	2310 male participants	6	Yes	2003
Okinawa	4489 adults	13	Yes	2004
Bogalusa Heart	679 children	11	Yes	2005
Framingham	3329 adults	4	Yes	2005
Normative Aging Study	2062 male participants	21	Yes	2006
ARIC	9104 adults	9	Yes	2006
Beaver Dam	2520 adults	10	Yes	2006
MRFIT	3073 men	6	Yes	2007
Health Professional Follow-up	750 men	18	No	2007
Nurses Health Study	1500 women	5	Yes	2009
China	7220 adults	4	Yes	2009
US	141 children	3	Yes	2009
Italy	1410 young adults	20	Yes	2010
GOCADAN	1078 adults	6	Yes	2012
NHANES Continuous	6036 adolescents	8	Yes	2012
Cardia	4752 adults	20	Men	2012

Feig J et al. J Pediatrics 2013

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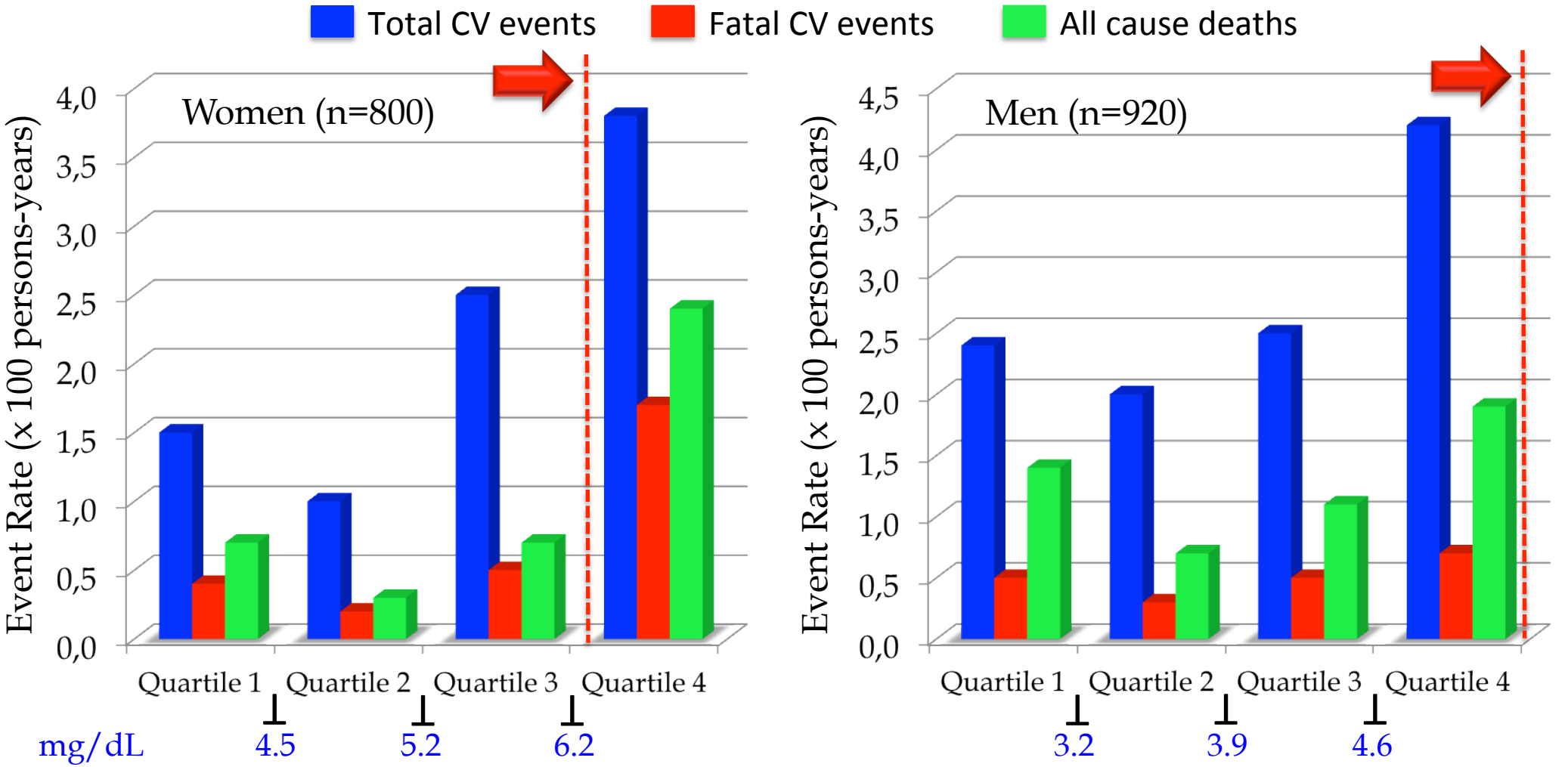
NHANES Continuous	6036 adolescents	8	Yes	2012
Cardia	4752 adults	20	Men	2012

Author	Patients (*n*)	Cut-off point	Follow-up	Adjusted risk ratio
Krishnan *et al.*, 2007 [24]	3073 Normotensive men, age 35–57 yrs, nondiabetic, without metabolic syndrome	>7.0 mg/dl	6 years	HR 1.81 (95% CI, 1.59–2.07)
Grayson *et al.*, 2011 [21]	55 607 Meta-analysis	1 SD higher serum uric acid	3 to 21.5 years	RR 1.13 (95% CI, 1.06–1.20)
Perlstein *et al.*, 2006 [25]	2062 Healthy men	>7.0 mg/dl	21.5 years	RR 1.1 (95% CI, 1.06–1.15)
Forman *et al.*, 2009 [26]	1496 Healthy women aged 32–52 yrs	>4.6 mg/dl	8 years	OR 1.89 (95% CI, 1.26–2.82).
Mellen *et al.*, 2006 [27]	9104 Healthy, mean (range) age 53.3 (45–64) yrs	>7.0 mg/dl	9 years	HR 1.1 (95% CI, 1.04–1.15)
Zhang *et al.*, 2009 [28]	7220 General population	5.7 (men)	4 years	RR 1.55 (95% CI, 1.10–2.19) for men
		4.8 (women)		RR 1.91 (95% CI, 1.12–3.25) for women
Shankar *et al.*, 2006 [29]	2520 General population	6.6 mg/dl	10 years	RR 1.65 (95% CI, 1.41–1.93)
Sundström *et al.*, 2005 [30]	3329 General population	1 SD increase in serum uric acid	4 years	OR 1.17 (95% CI, 1.02–1.33)
Bombelli *et al.*, 2014 [22]	2051 General population	1-mg/dl increase in serum uric acid	16 years	HR 1.34 (95% CI 1.06–1.70) home hypertension
				HR 1.29 (95% CI 1.05–1,70) ambulatory hypertension

Feig J et al. J Pediatrics 2013

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.)

High Blood Press Cardiovasc Prev
https://doi.org/10.1007/s40292-018-0250-7

ORIGINAL ARTICLE

Exploration into Uric and Cardiovascular Disease: Uric Acid Right for heArt Health (URRAH) Project, A Study Protocol for a Retrospective Observational Study

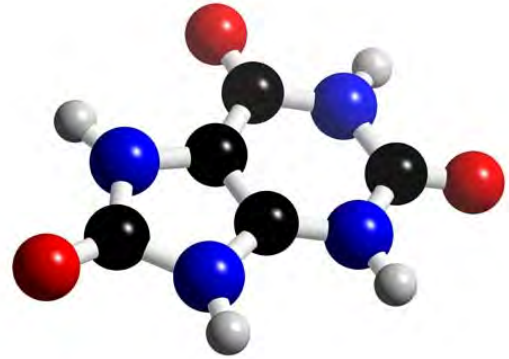
Giovambattista Desideri[1] · Agostino Virdis[2] · Edoardo Casiglia[3] · Claudio Borghi[4] · On behalf of the Working Group on Uric Acid and Cardiovascular Risk of the Italian Society of Hypertension

✧ Casiglia E, et al. J Hypertens. 2020;38(3):412-419

✧ Virdis A, et al Hypertension. 2020;75(2):302-308.

✧ Maloberti A, et al. High Blood Press Cardiovasc Prev. 2020 Apr;27(2): 121-128.

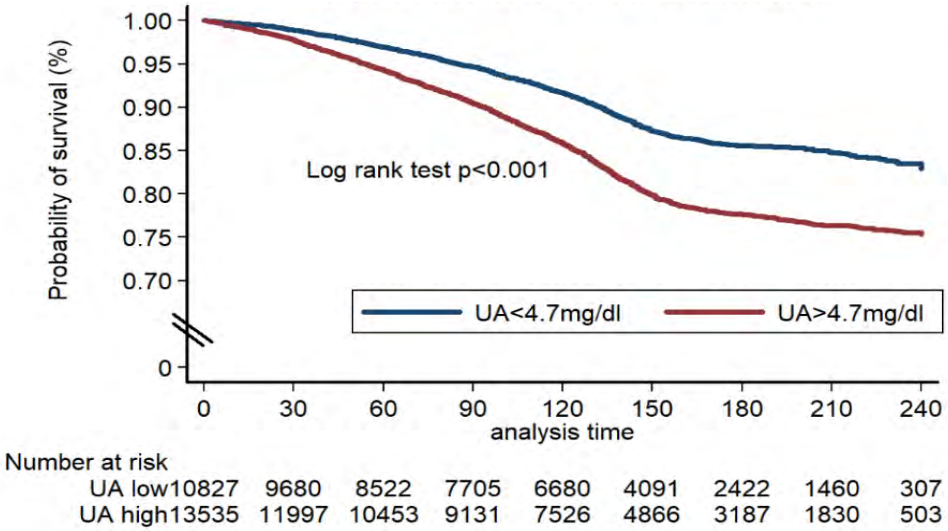
✧ Muiesan ML, et al . J Hypertens. 2020 Jul 15. doi: 10.1097/HJH. 0000000000002589..



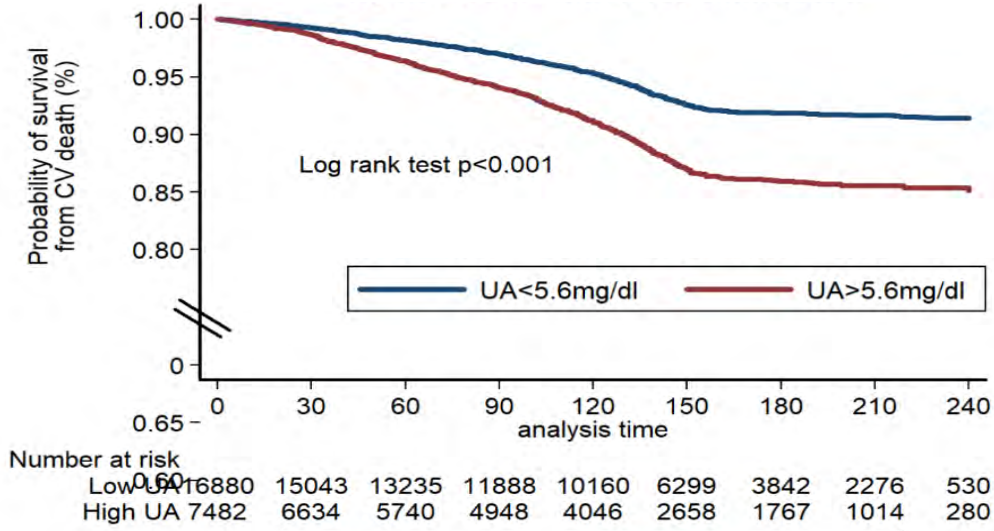
Identification of the uric acid thresholds predicting an increased total and cardiovascular mortality over 20 years

Kaplan-Meier survival estimates according to the identified thresholds

all-cause mortality – 4.7 mg/dL

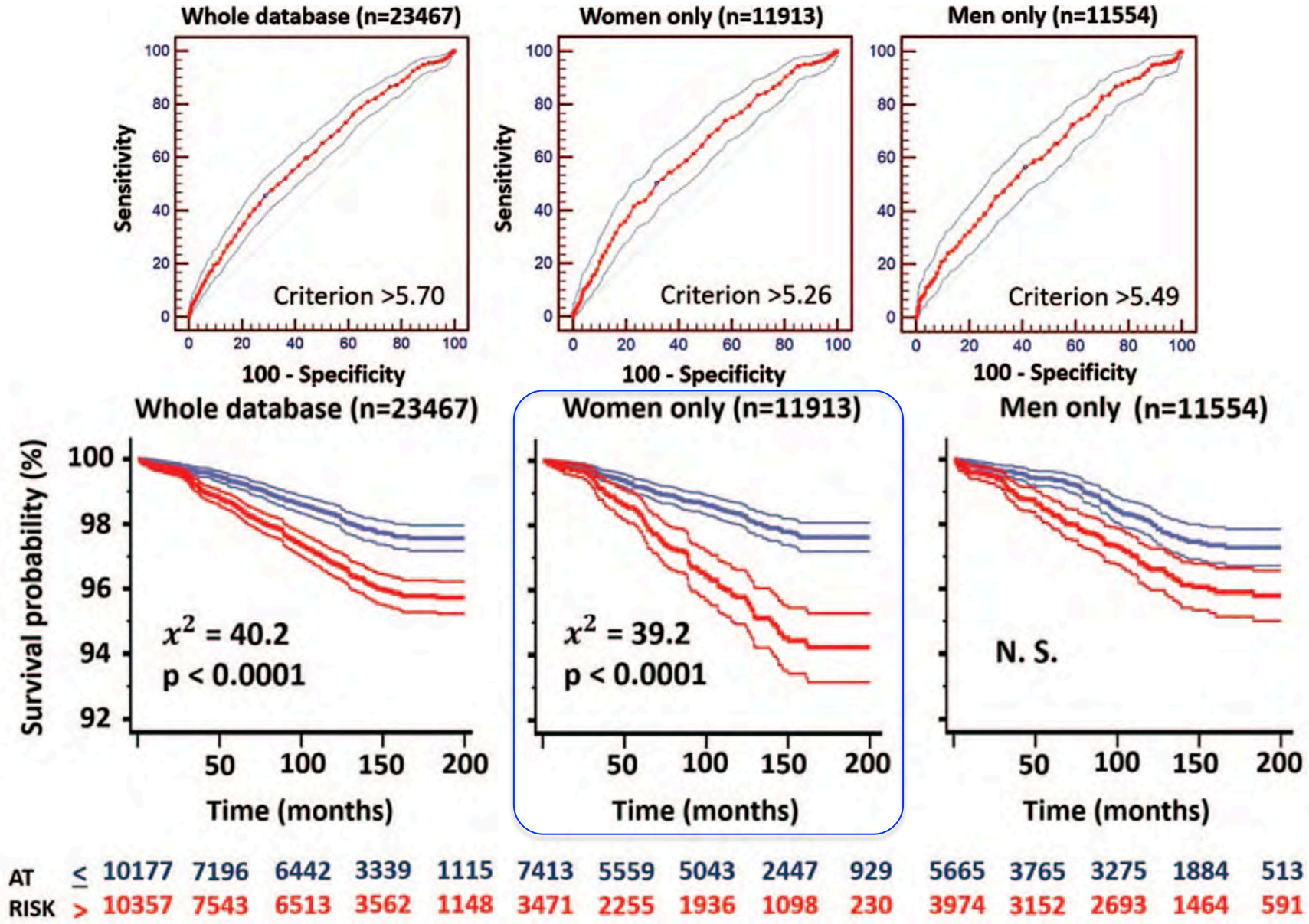


cardiovascular mortality – 5.6 mg/dL



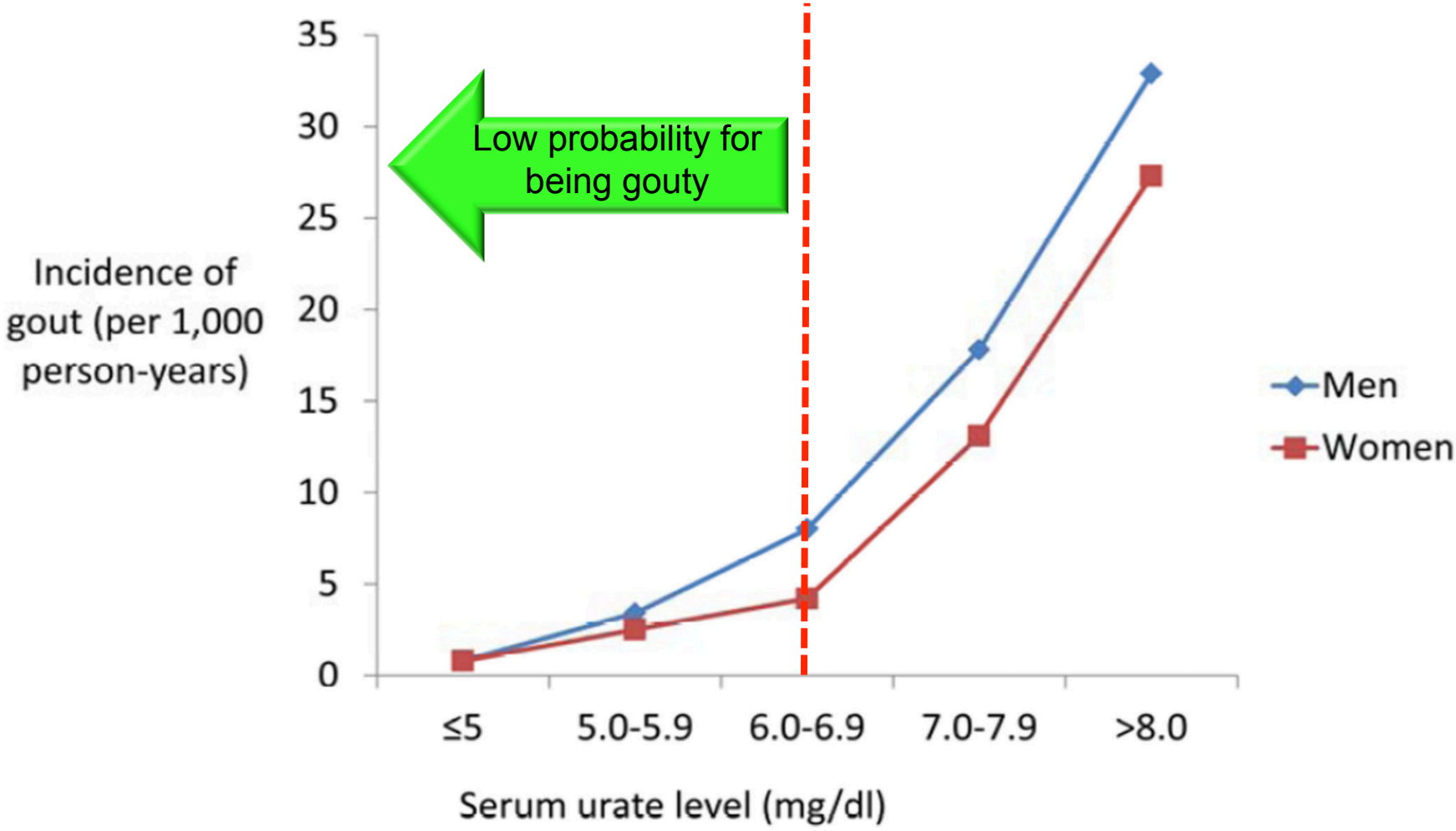
Virdis A et al. Hypertension in press

Serum uric acid and **fatal myocardial infarction**: detection of prognostic cut-off values:The URRAH (Uric Acid Right for Heart Health) study



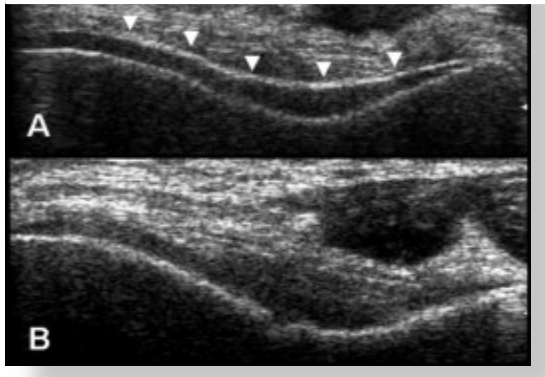
Casiglia E et al. J Hypertension 2019

Relationship between serum uric acid levels and annual incidence of gout



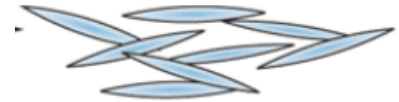
Bohle V et al. Arthritis Rheum 2010;62:1069-1076

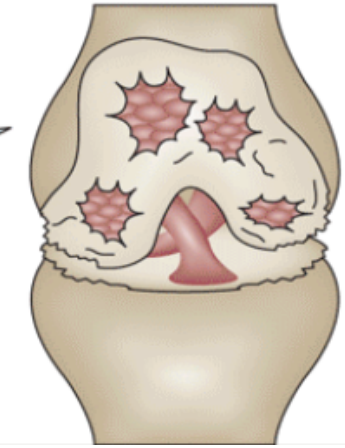
The pH-solubility relationships of uric acid and MSUM

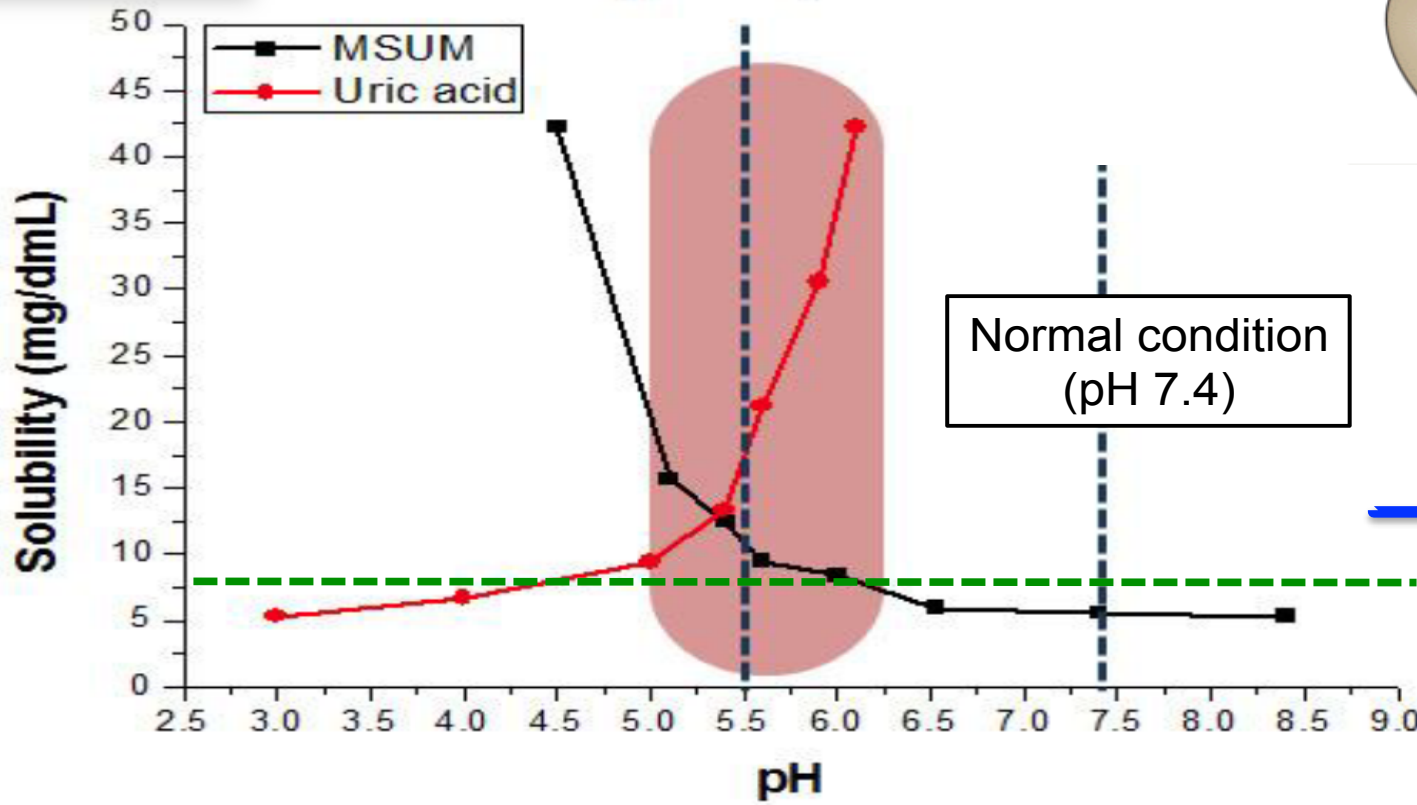


In normal condition (37°C, aqueous solution, pH 7.4) the solubility limit of MSU is reached when the urate concentration is about 6.4 mg/dL (384 mmol/L)

MSU crystals



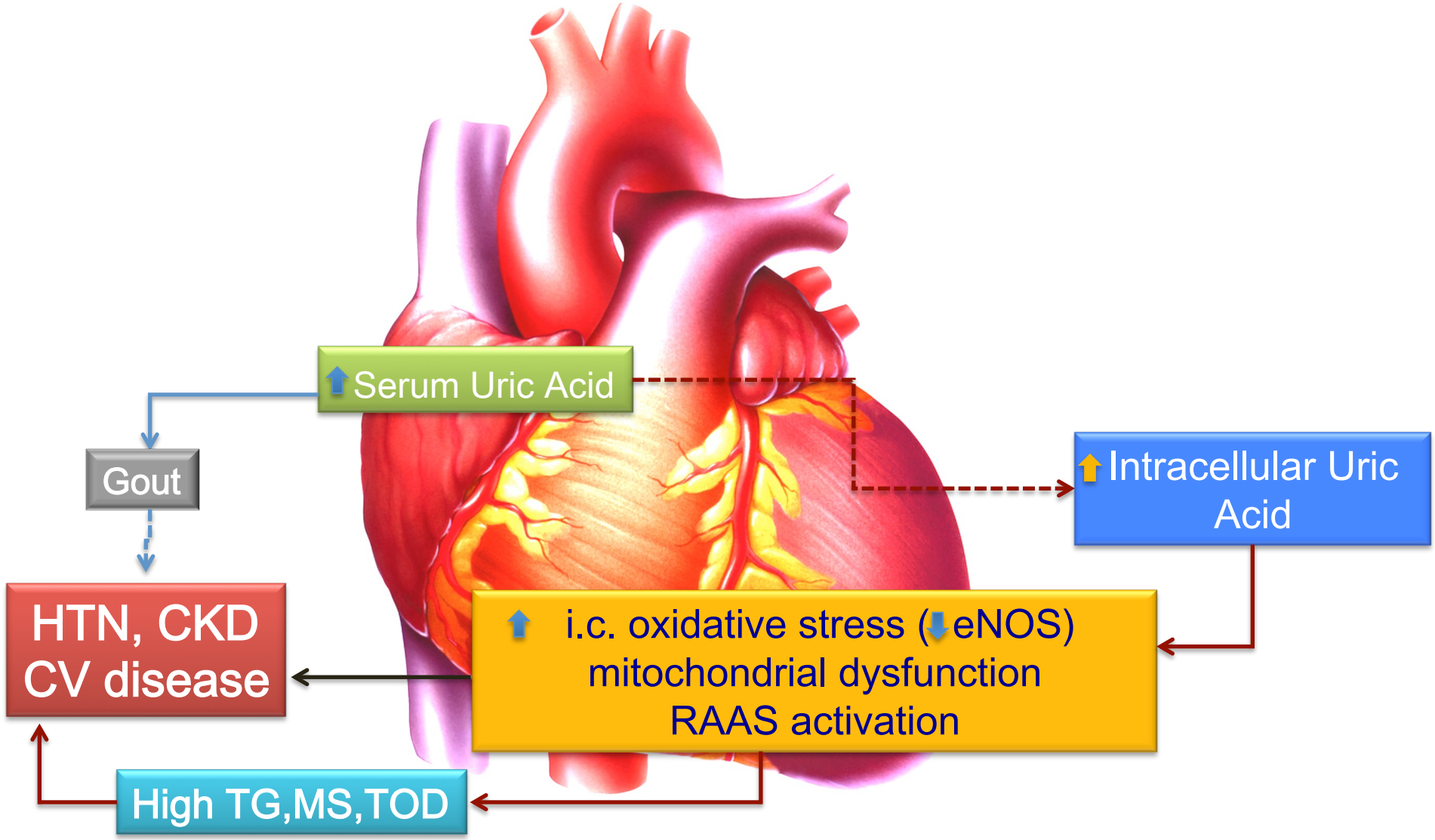




Chih MH et al. CrystEngComm, 2016,18, 290-297

SUA, oxidative stress and CV disease: a comprehensive hypothesis

Borghi C, Desideri G, Hypertension 2016



Causal Assessment of Serum Urate Levels in Cardiometabolic Diseases Through a Mendelian Randomization Study

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 67, NO. 4, 2016

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacc.2015.10.086

Urate Genetic Score: Association of Genetically Raised Urate With Cardiometabolic Outcomes

Outcome	OR	95% CI	p value
Type 2 Diabetes	0.95	(0.86, 1.05)	0.28
Coronary Heart Disease	1.02	(0.92, 1.12)	0.73
Ischemic Stroke	0.99	(0.88, 1.12)	0.93
Heart Failure	1.07	(0.88, 1.30)	0.51
Gout	5.84	(4.56, 7.49)	4.2E-44

OR per SD increase in Serum Urate Conferred by Genetic Score

Keenan T et al. J Am Coll Cardiol. 2016 Feb 2;67(4):407-16.

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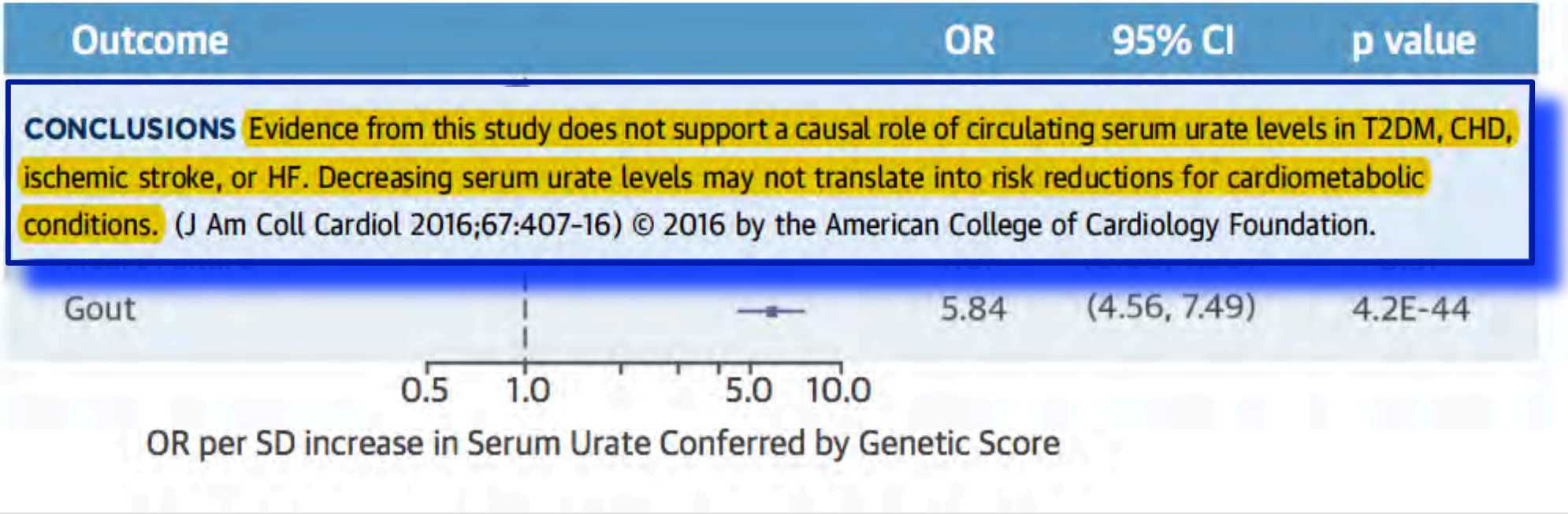
Urate Genetic Score: Association of Genetically Raised Urate With Cardiometabolic Outcomes

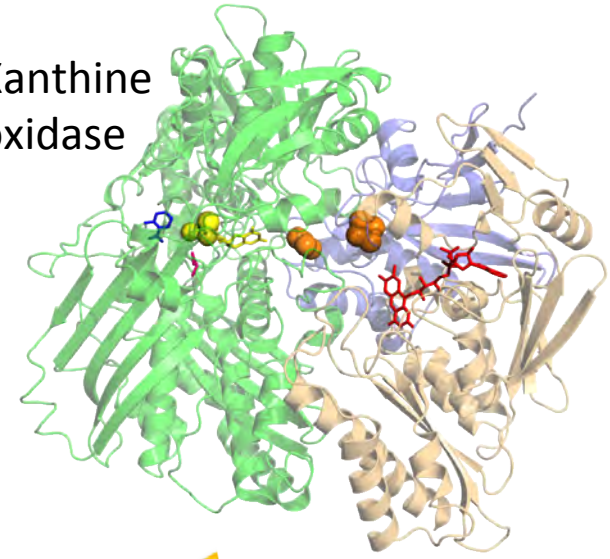
CONCLUSIONS Evidence from this study does not support a causal role of circulating serum urate levels in T2DM, CHD, ischemic stroke, or HF. Decreasing serum urate levels may not translate into risk reductions for cardiometabolic conditions. (J Am Coll Cardiol 2016;67:407-16) © 2016 by the American College of Cardiology Foundation.



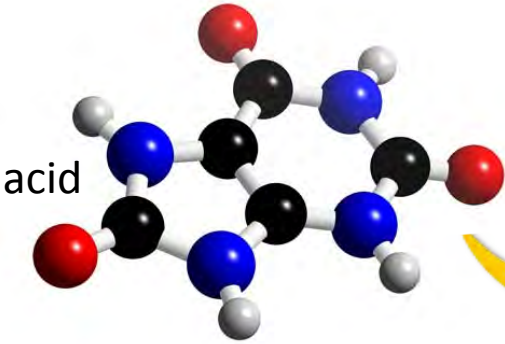
Keenan T et al. J Am Coll Cardiol. 2016 Feb 2;67(4):407-16.

Searching for the righ relationship between uric acid and CV diseases

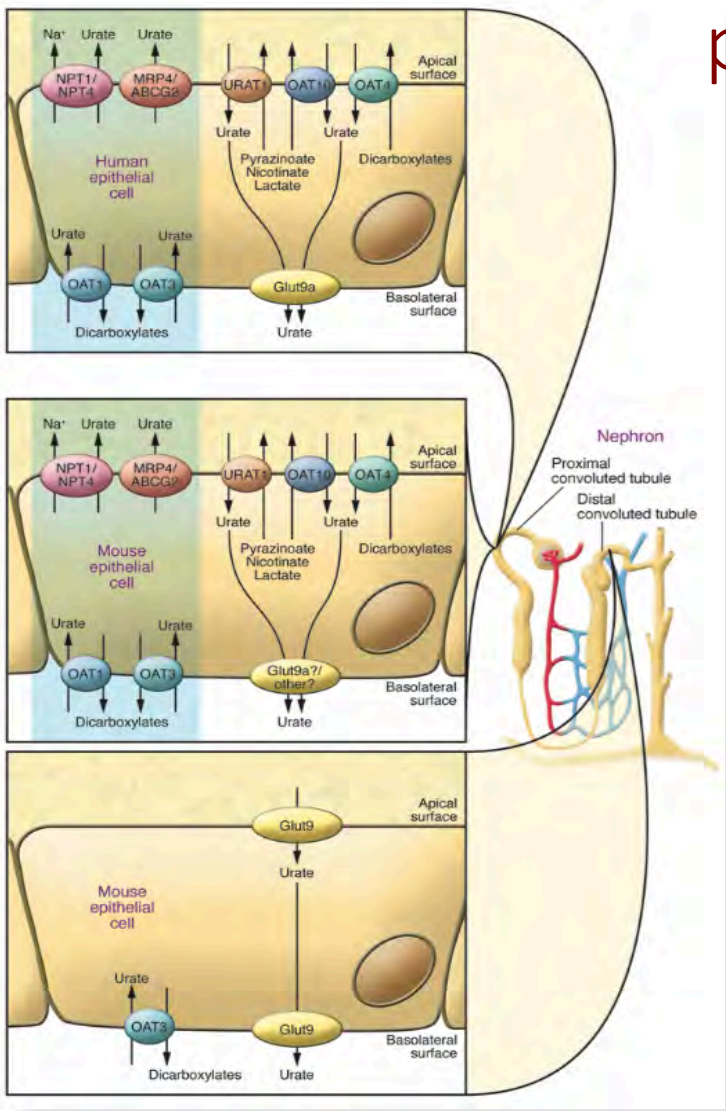
Xanthine oxidase

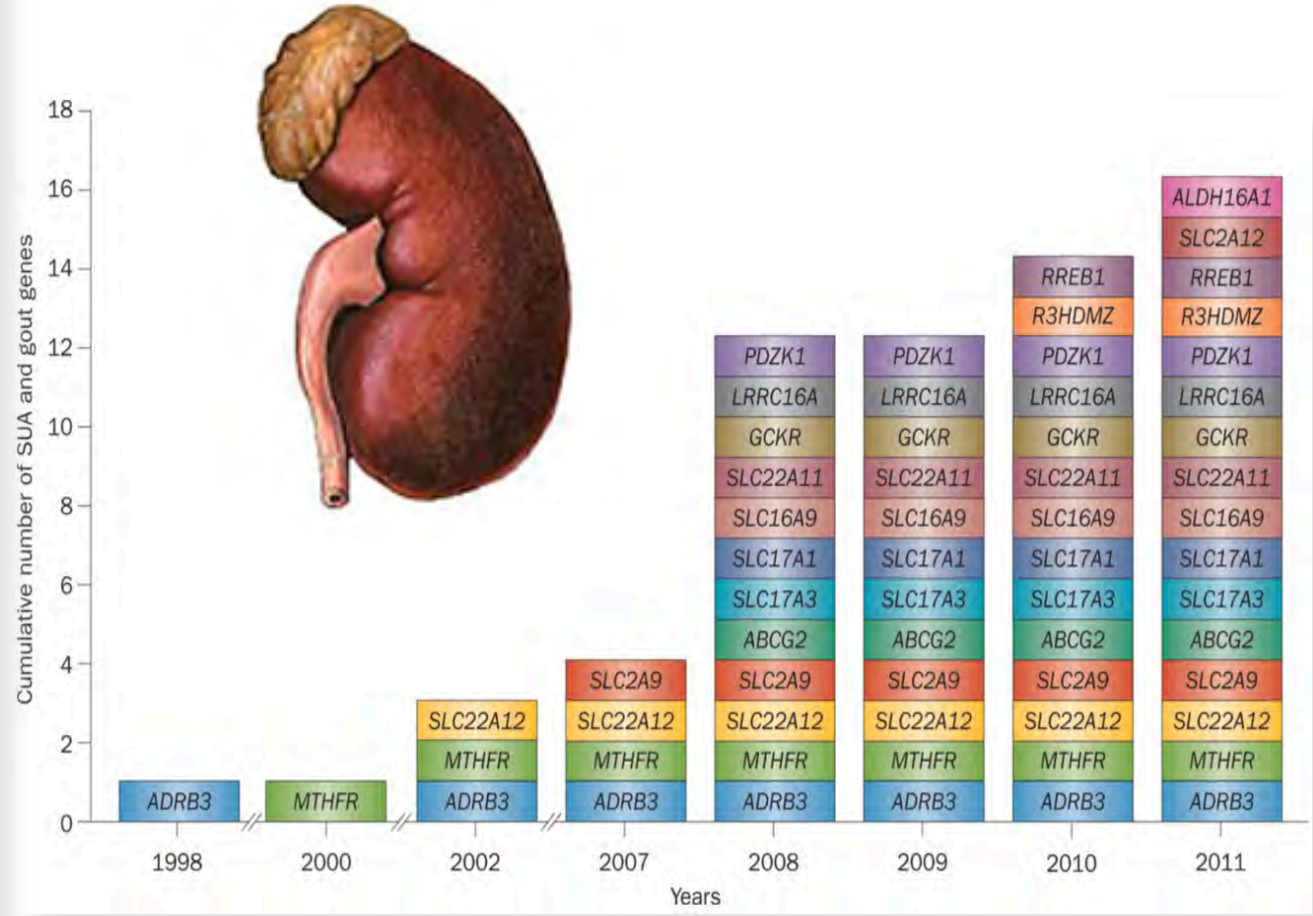


Uric acid



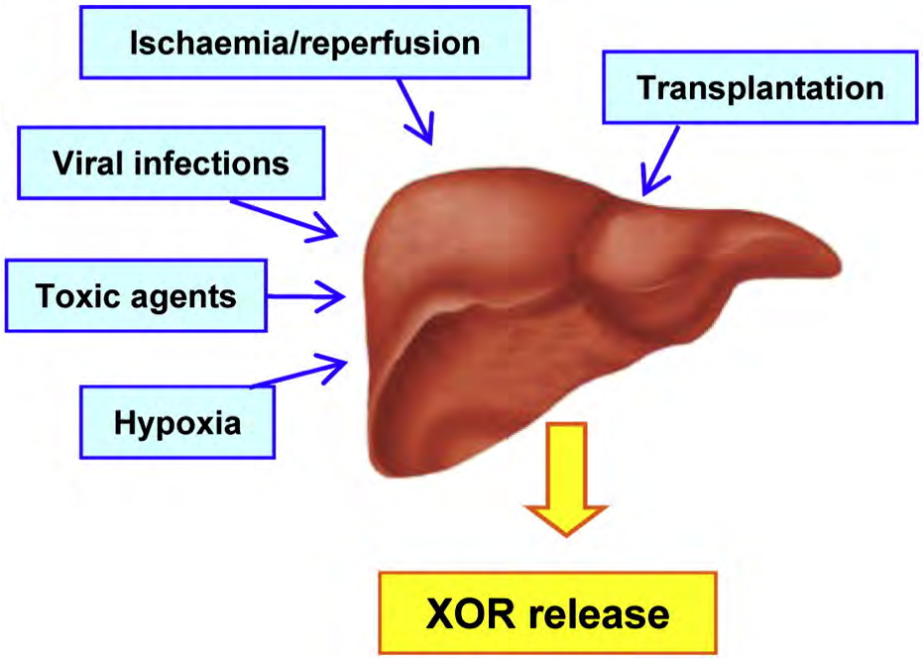
Genetic variants implicated in the pathogenesis of hyperuricaemia or gout

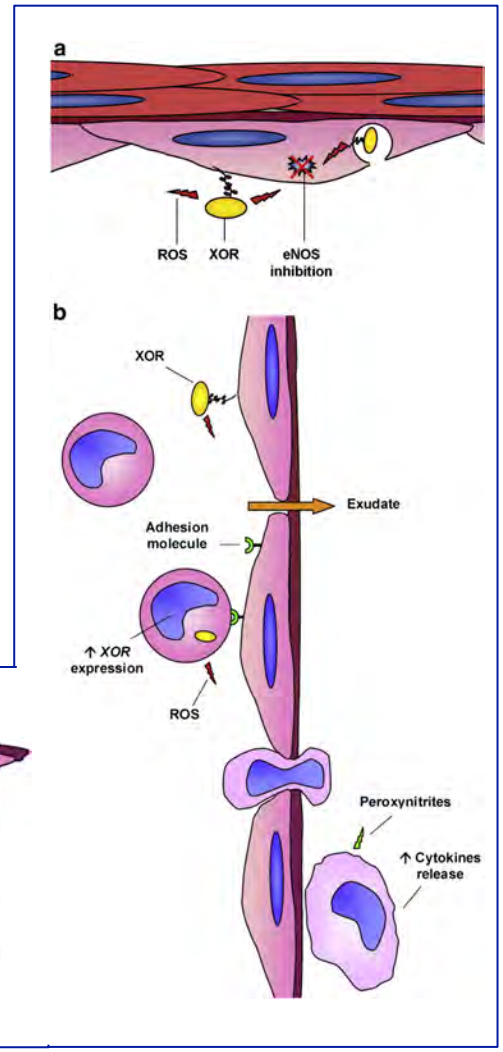


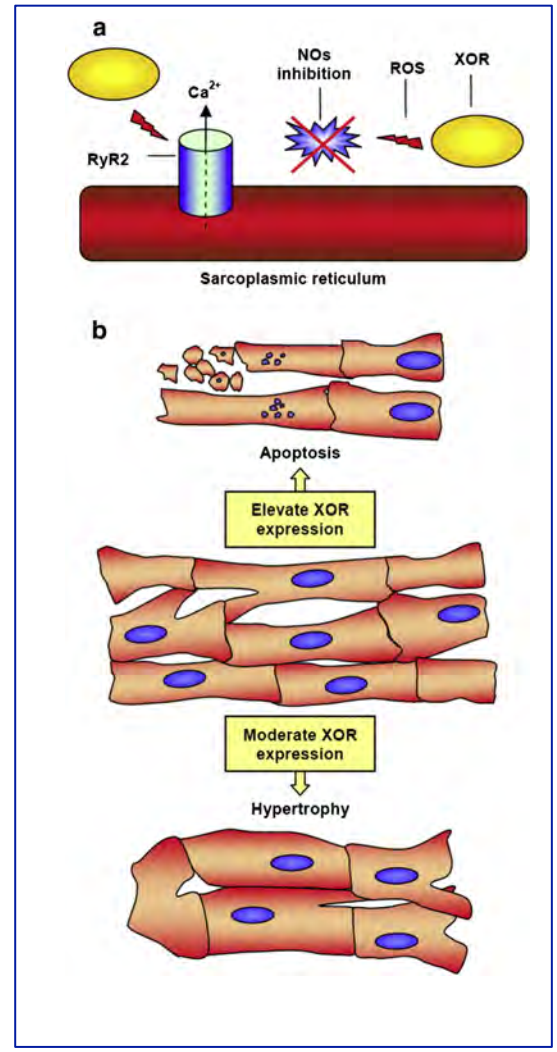


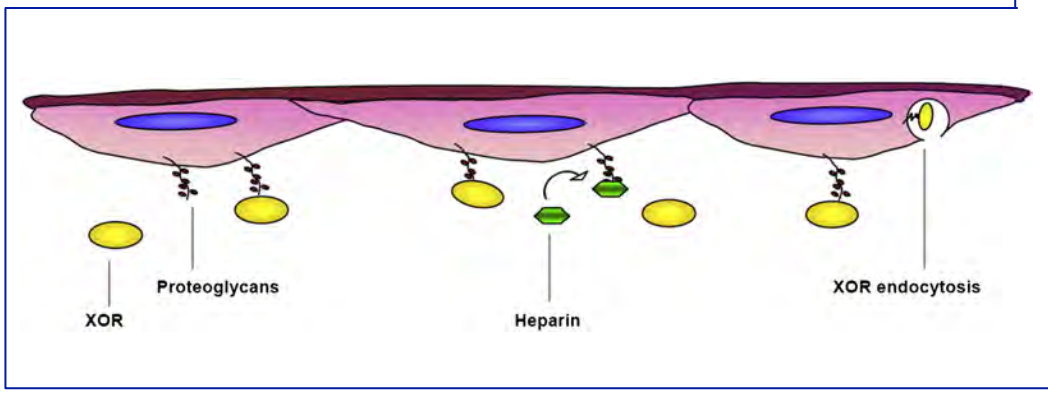
So A et al. J Clin Invest. 2010;120(6):1791–1799.
Reginato AM et al. Nat Rev Rheumatol. 2012 October ; 8(10): 610–621

Pathophysiology of circulating xanthine oxidoreductase: New emerging roles for a multi-tasking enzyme



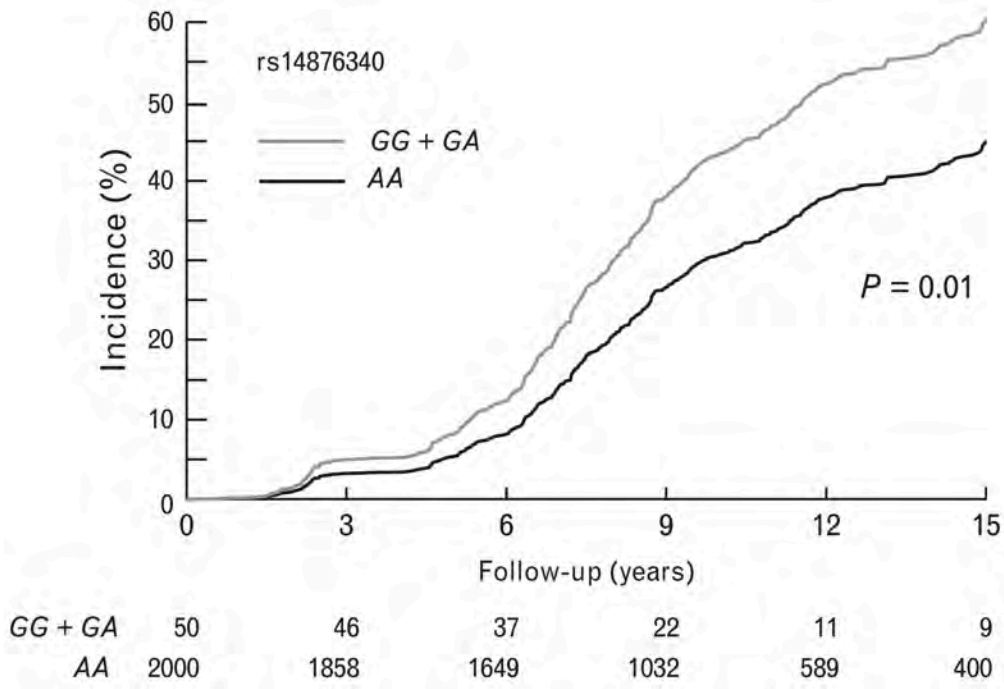


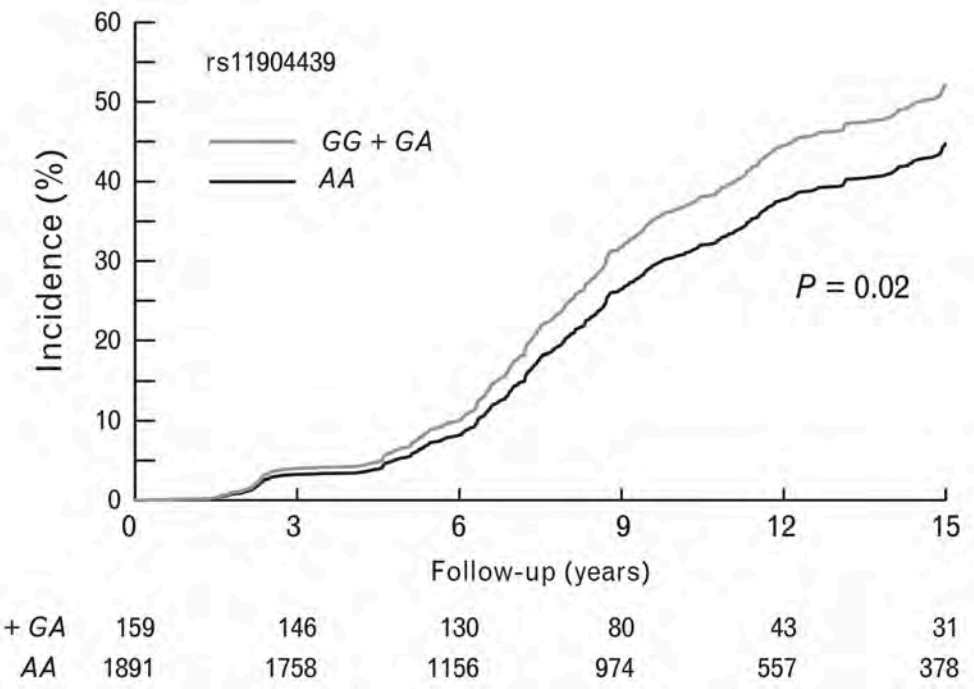




Battelli MG et al. Biochimica et Biophysica Acta 1842 (2014) 1502–1517

Xanthine oxidase gene variants and their association with blood pressure and incident hypertension

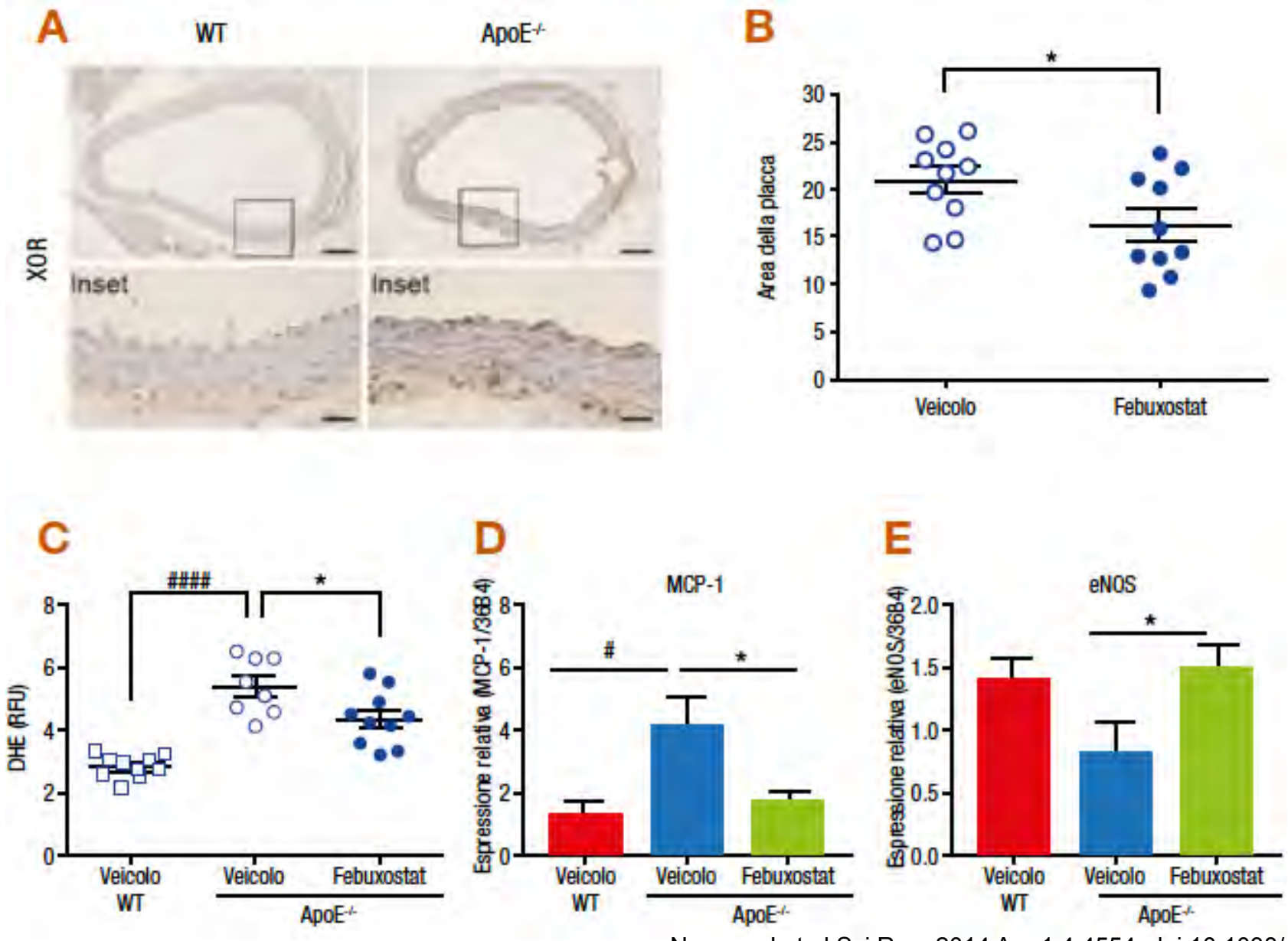




Variation in uric acid production, as captured by genetic variation in XOR, might be a predictor of changes in blood pressure and in the risk of hypertension

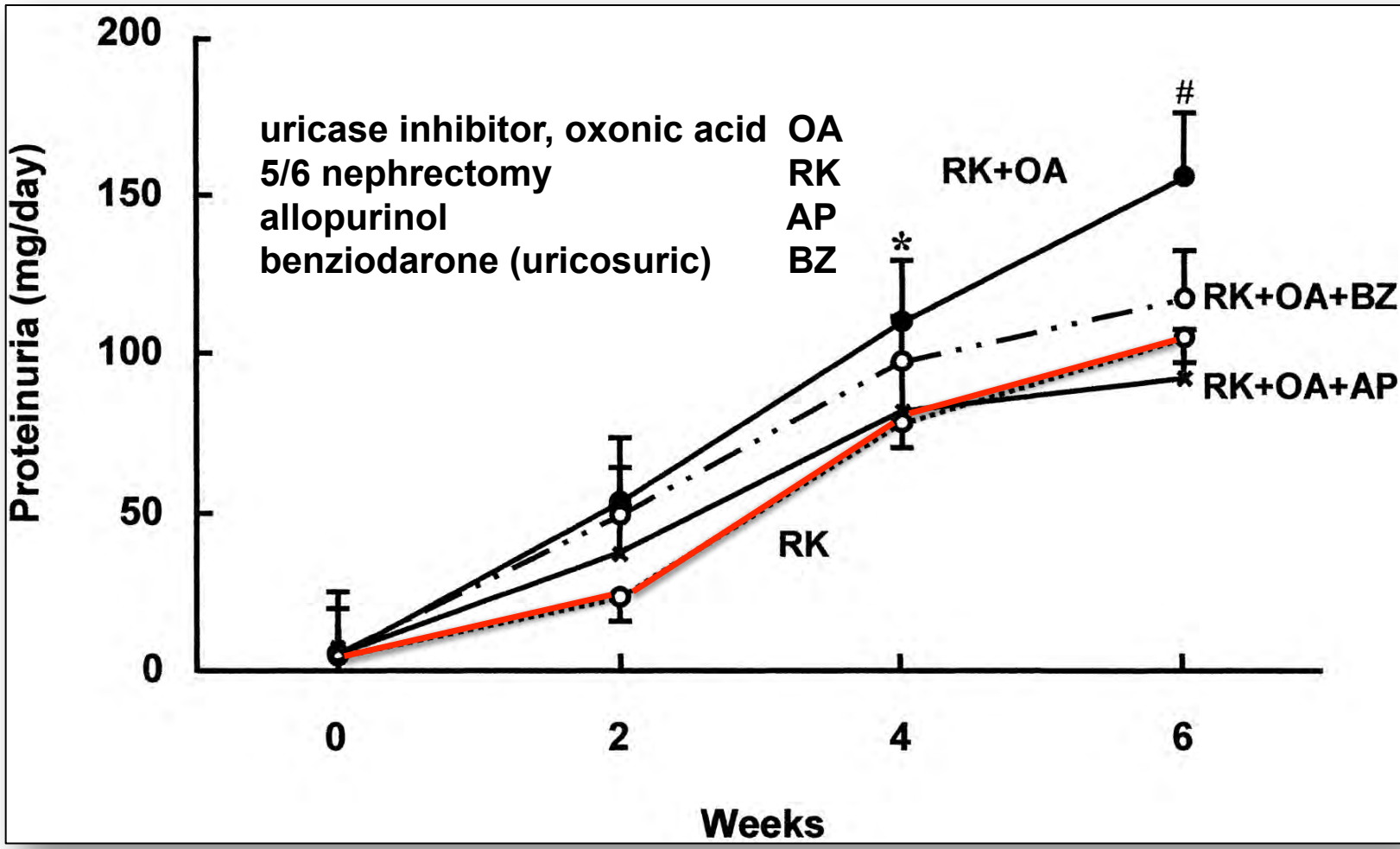
Scheepers LEJM et al. J Hypertens 2016;34:2147–2154

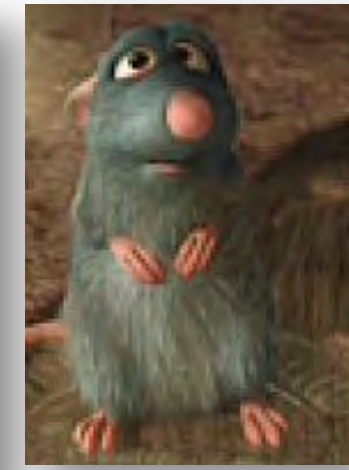
Inibizione della XO e protezione vascolare

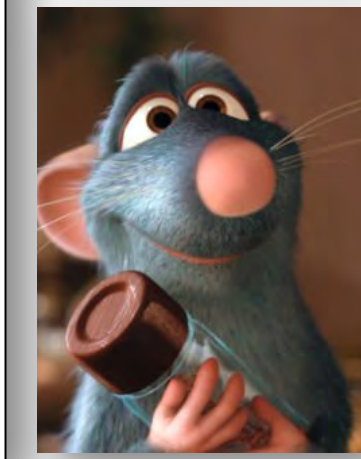


Nomura J et al Sci Rep. 2014 Apr 1;4:4554. doi:10.1038/srep04554

A Role for Uric Acid in the Progression of Renal Disease



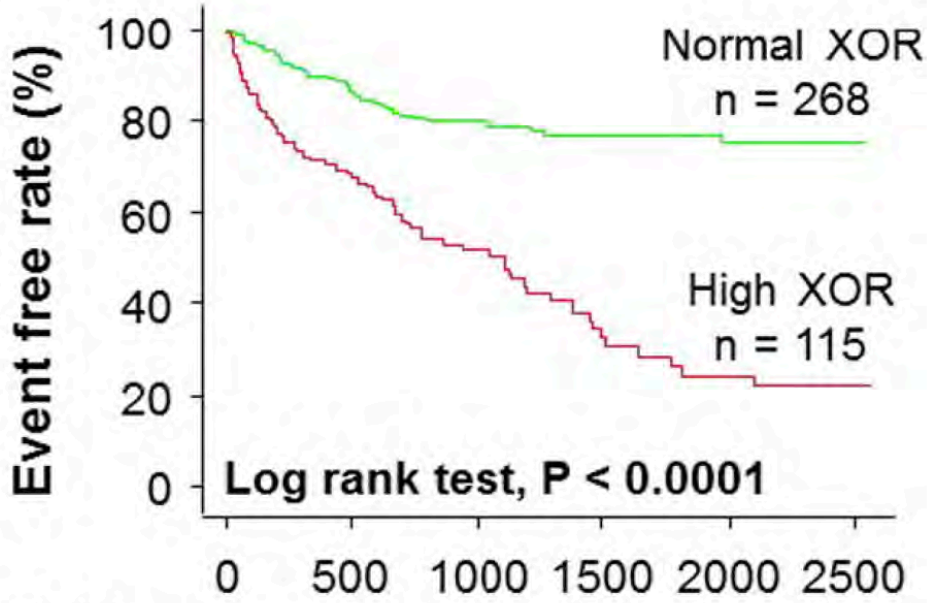




KANG et al. *JASN* 13: 2888-2897, 2002

Association of **high** plasma xanthine oxidoreductase activity with severity and clinical outcome in patients with chronic heart failure

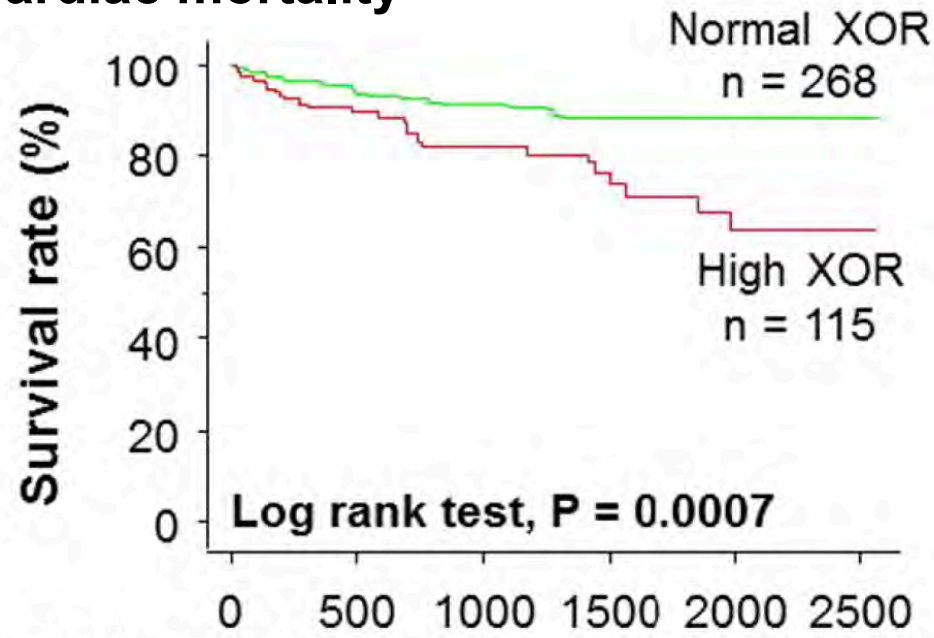
All cardiac event



No at risk

Normal XOR	0/268	38/202	51/124	55/69	56/49
High XOR	0/115	37/70	52/41	64/19	69/11

Cardiac mortality



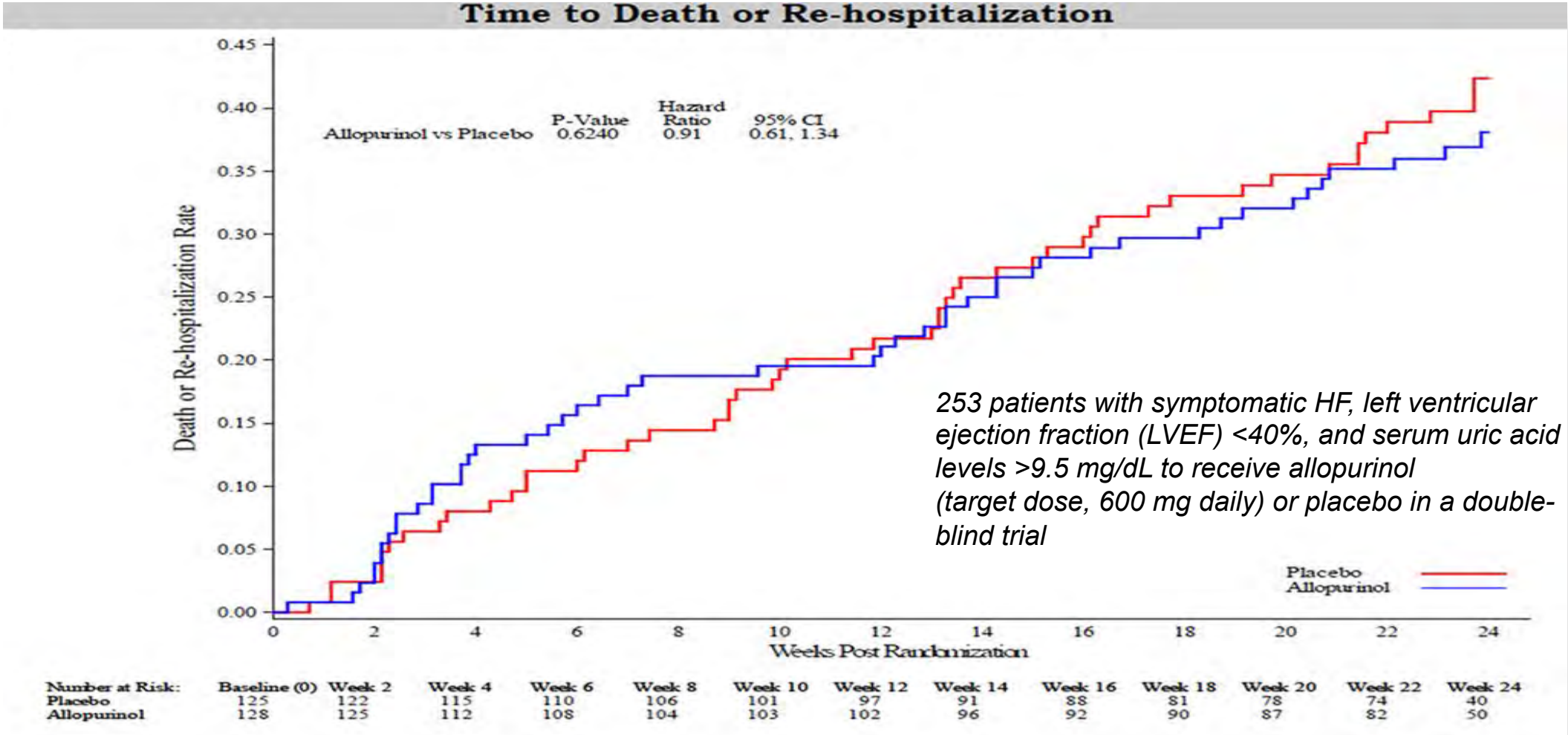
No at risk

Normal XOR	0/268	17/224	21/140	25/83	25/58
High XOR	0/115	12/83	18/54	21/31	25/19

Otaki Y et al. International Journal of Cardiology 228 (2017) 151–157

Effects of Xanthine Oxidase Inhibition in Hyperuricemic Heart Failure Patients

The Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) Study

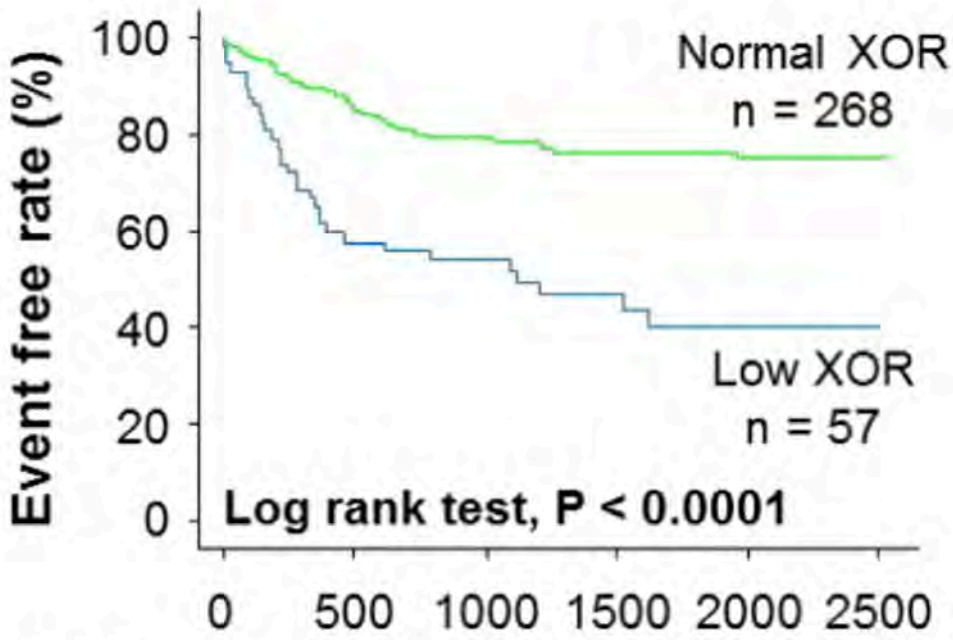


253 patients with symptomatic HF, left ventricular ejection fraction (LVEF) <40%, and serum uric acid levels >9.5 mg/dL to receive allopurinol (target dose, 600 mg daily) or placebo in a double-blind trial

Givertz MM et al. Circulation. 2015;131:1763-1

Association of **low** plasma xanthine oxidoreductase activity with severity and clinical outcome in patients with chronic heart failure

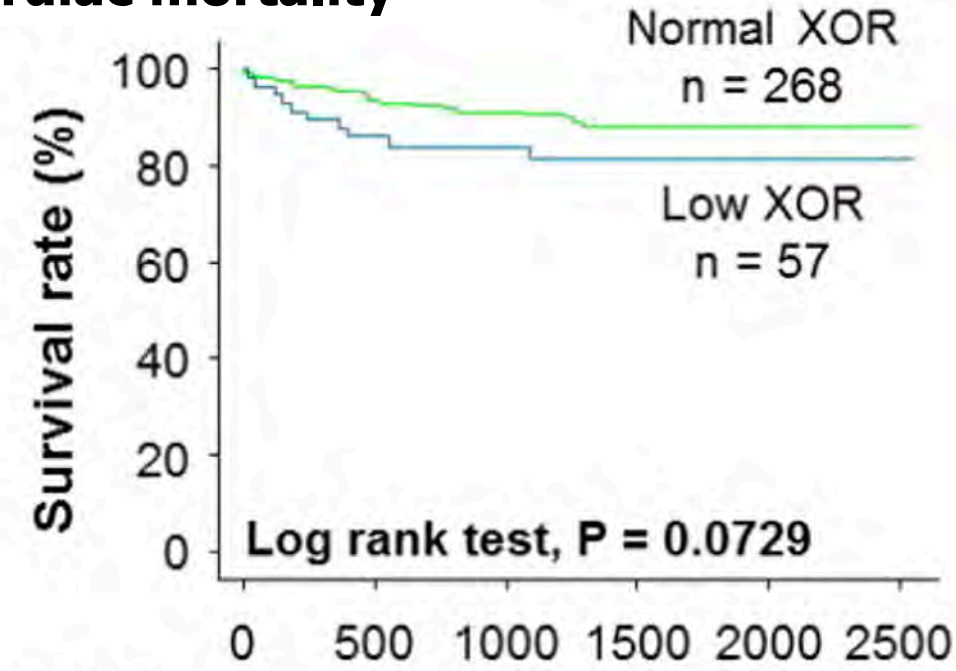
All cardiac event



No at risk

Normal XOR	0/268	38/202	51/124	55/69	56/49
Low XOR	0/57	24/32	26/26	29/14	31/9

Cardiac mortality

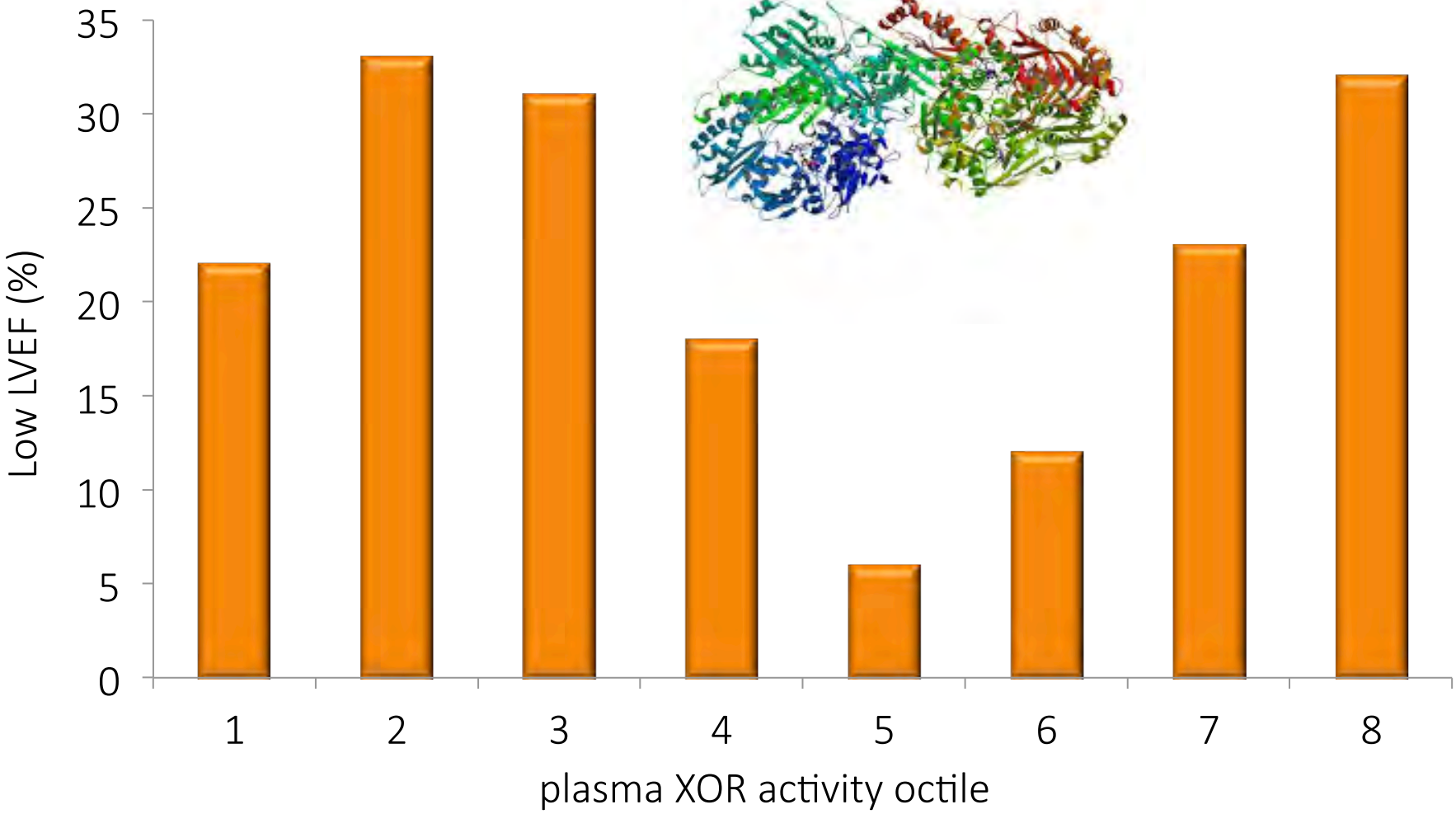


No at risk

Normal XOR	0/268	17/224	21/140	25/83	25/58
Low XOR	0/57	8/46	9/33	10/22	10/13

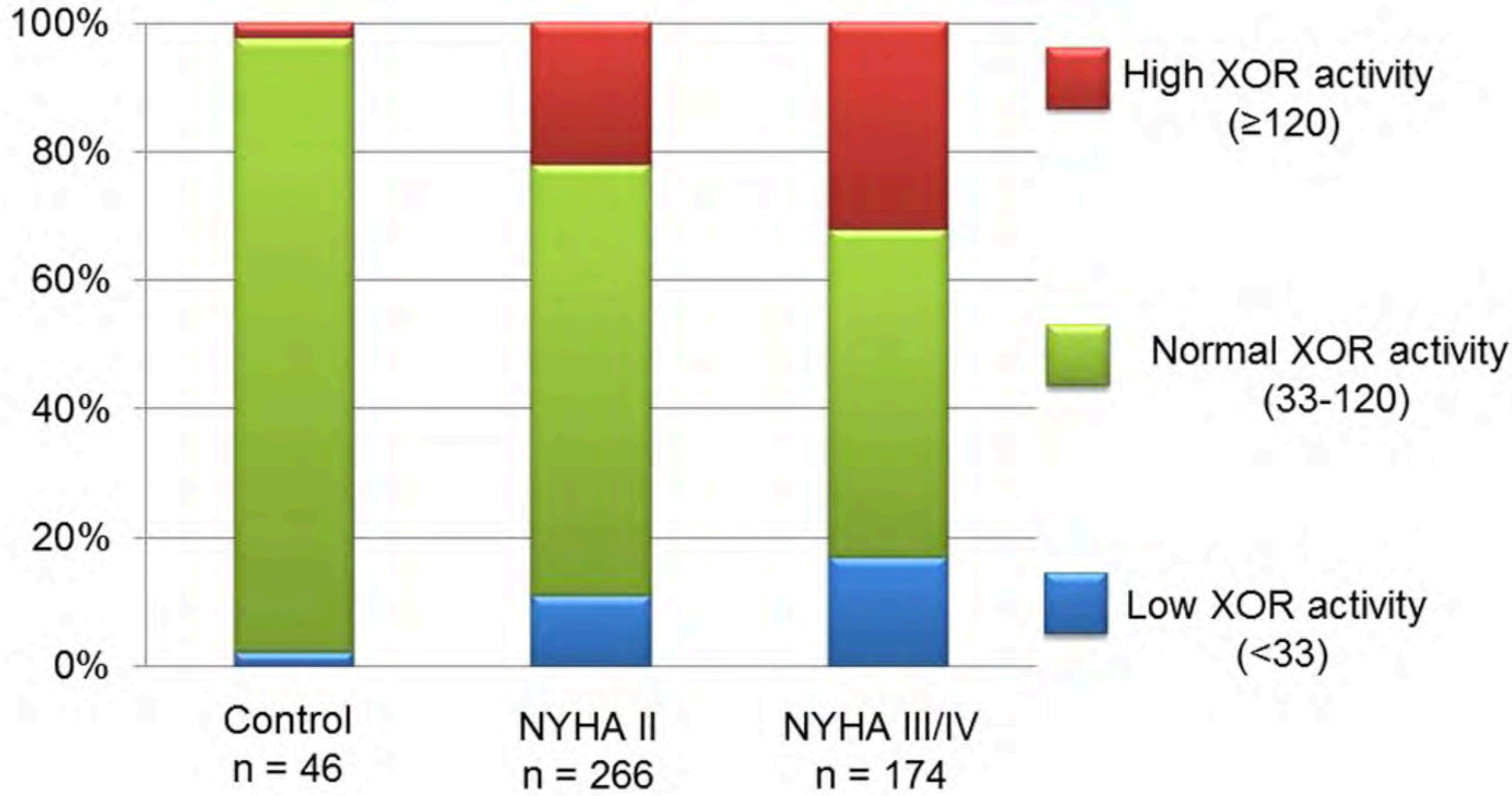
Otaki Y et al. International Journal of Cardiology 228 (2017) 151–157

Relationship between plasma xanthine oxidoreductase activity and LVEF among cardiac patients



Fujimura Y et al. PLoS ONE 12(8): e0182699.

Association of plasma xanthine oxidoreductase activity with severity and clinical outcome in patients with chronic heart failure



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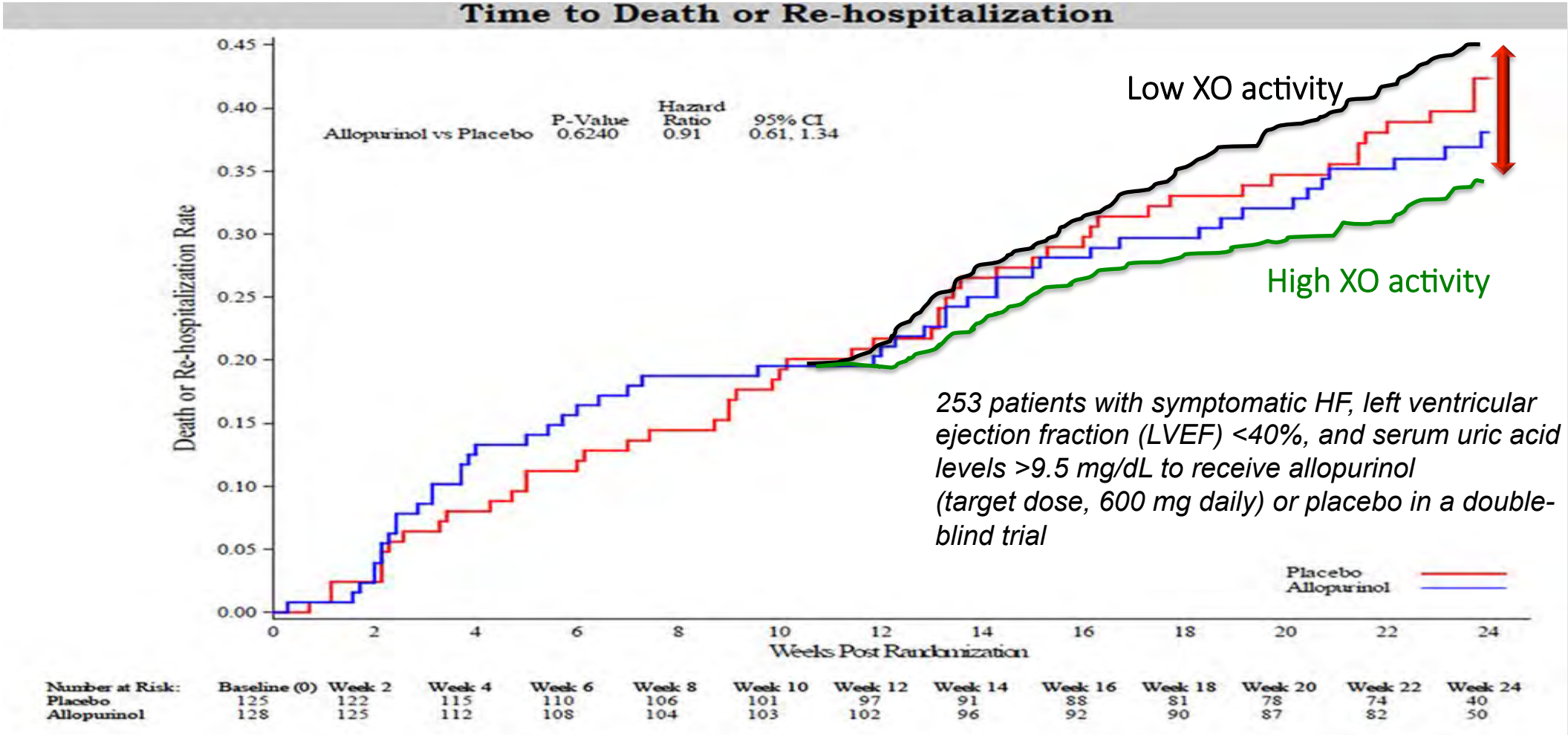
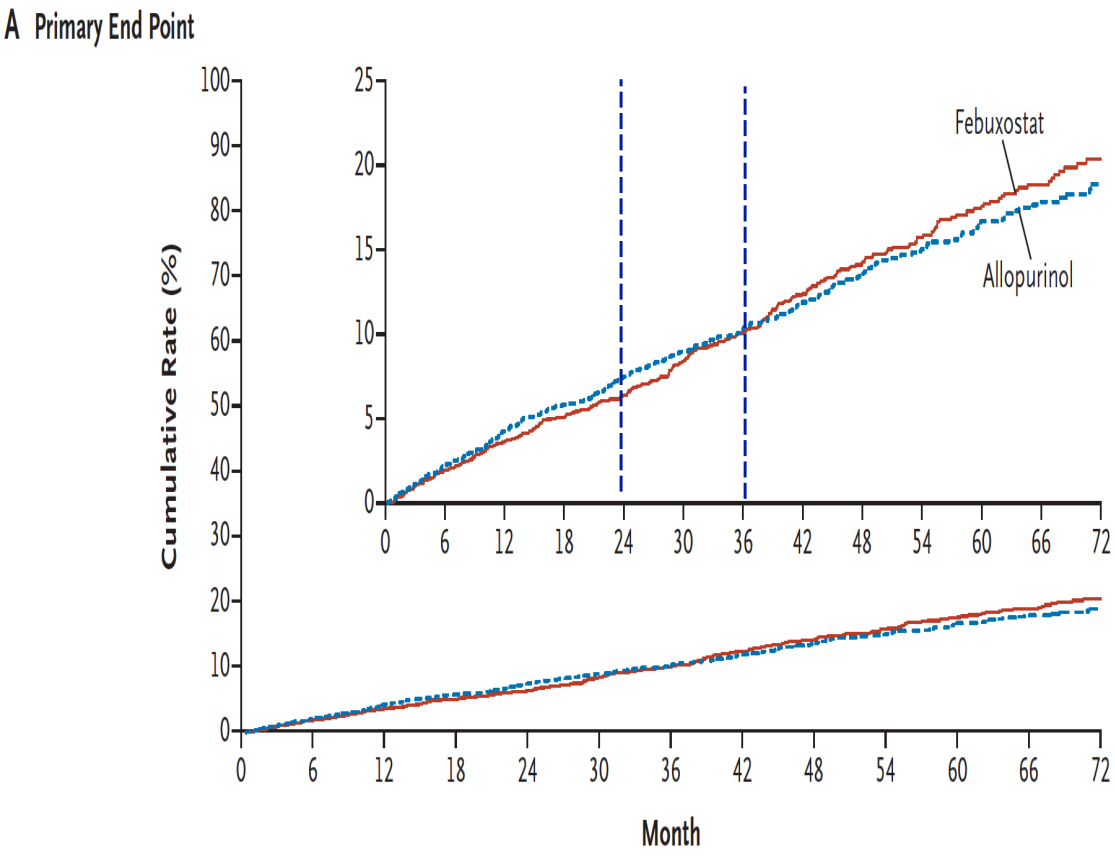
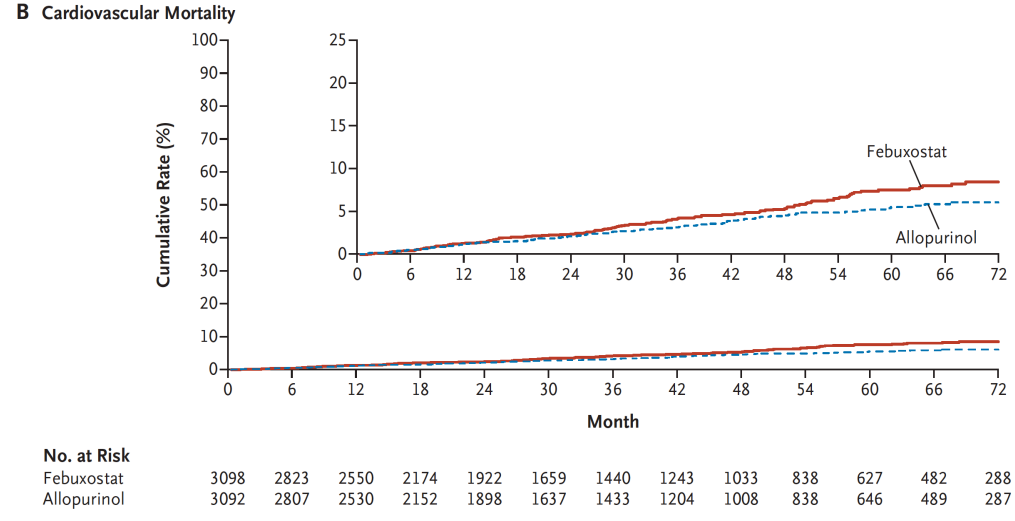


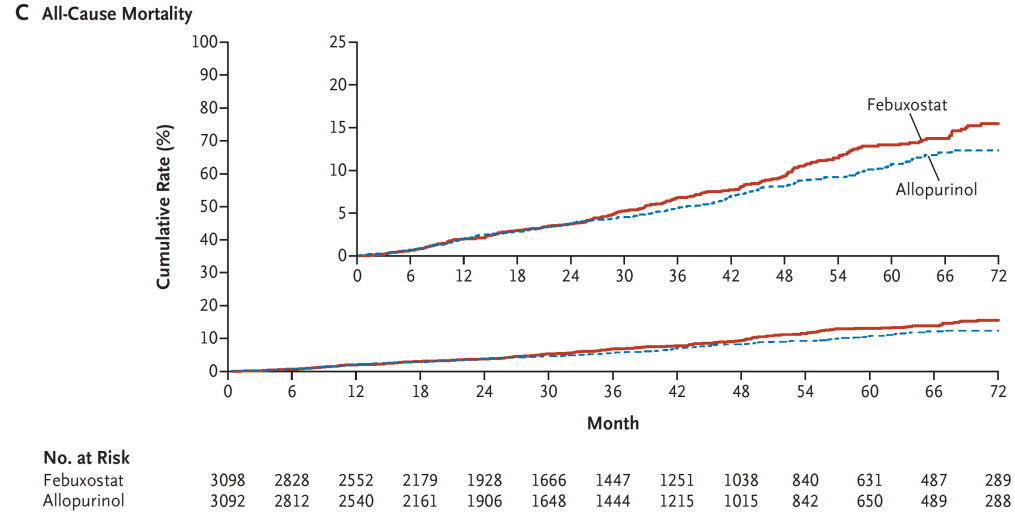
Givertz MM et al. Circulation. 2015;131:1763-1

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout

Primary end-point: a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or unstable angina with urgent revascularization







White WB et al. N Engl J Med. 2018 Mar 12.

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout

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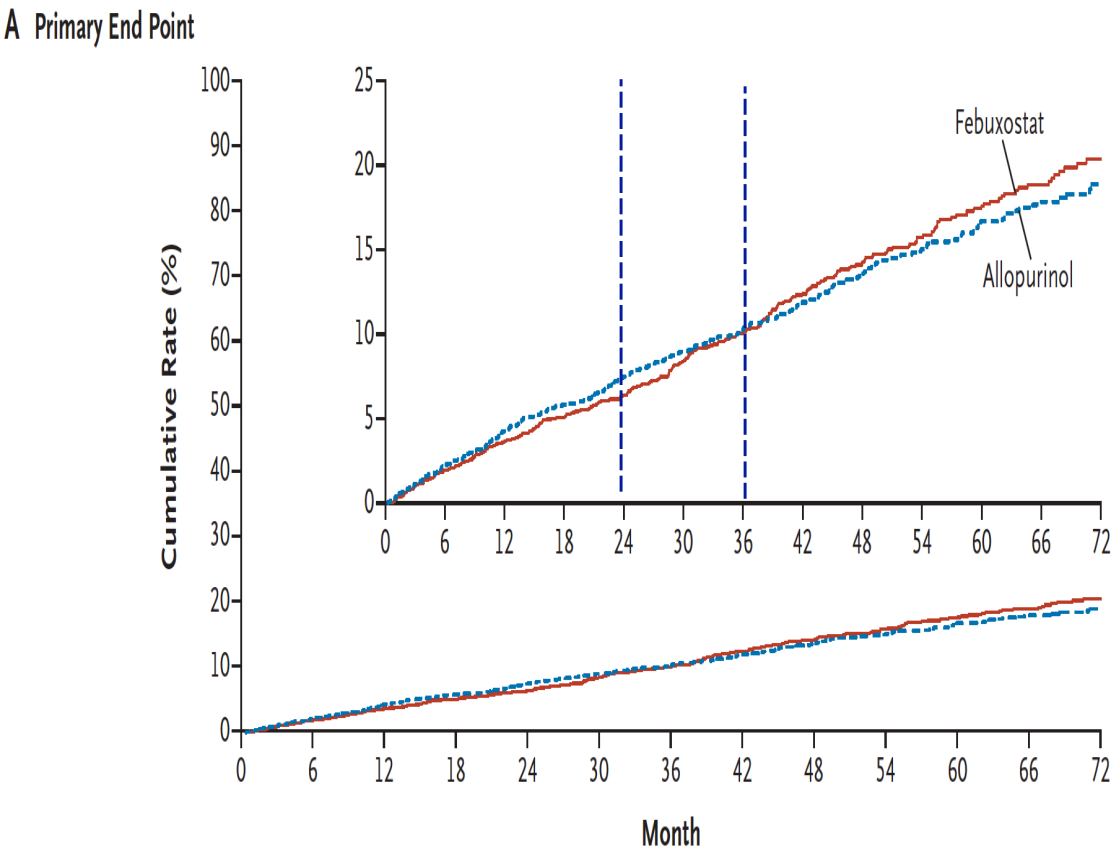

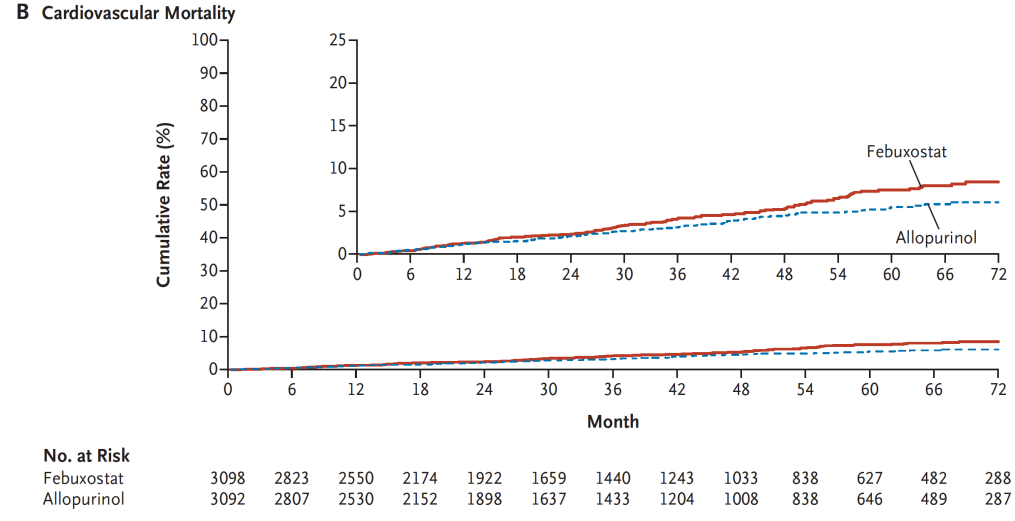

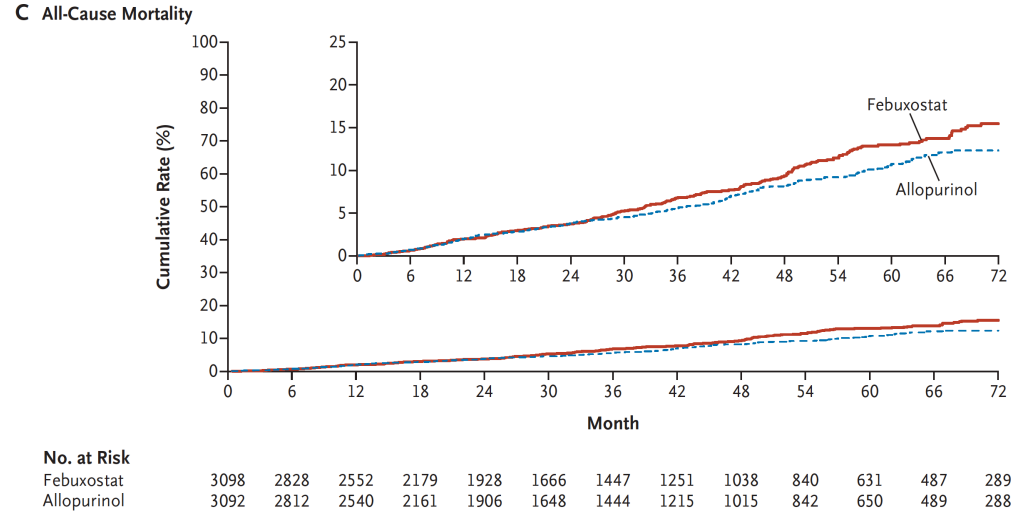

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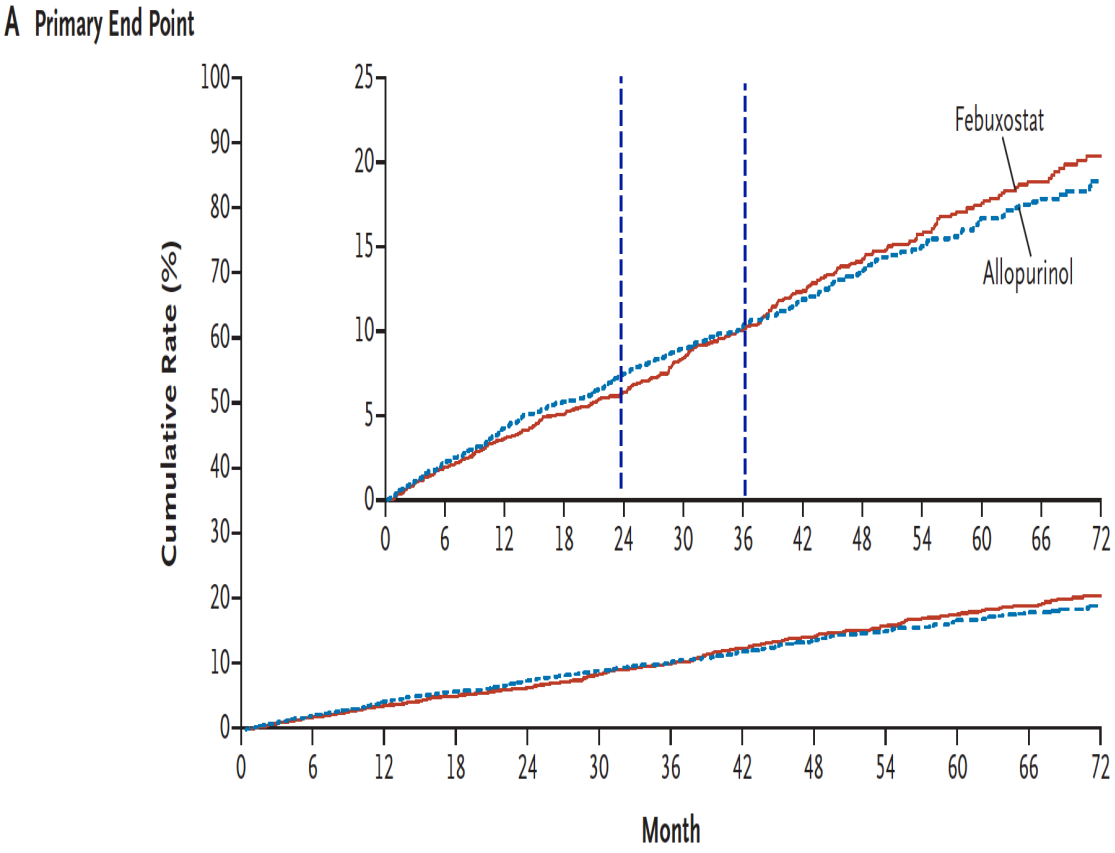
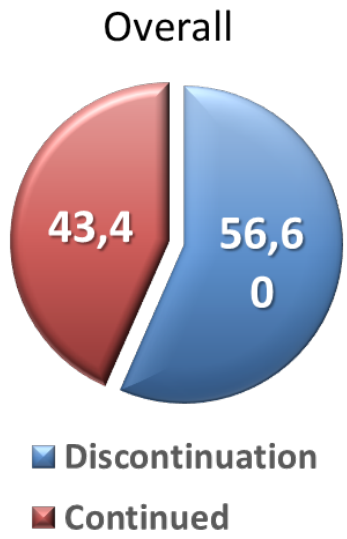
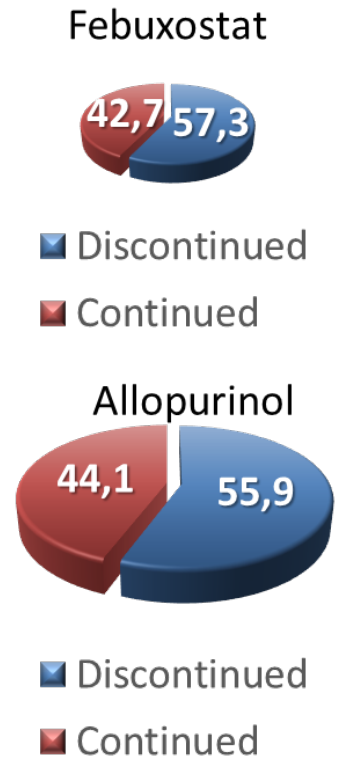
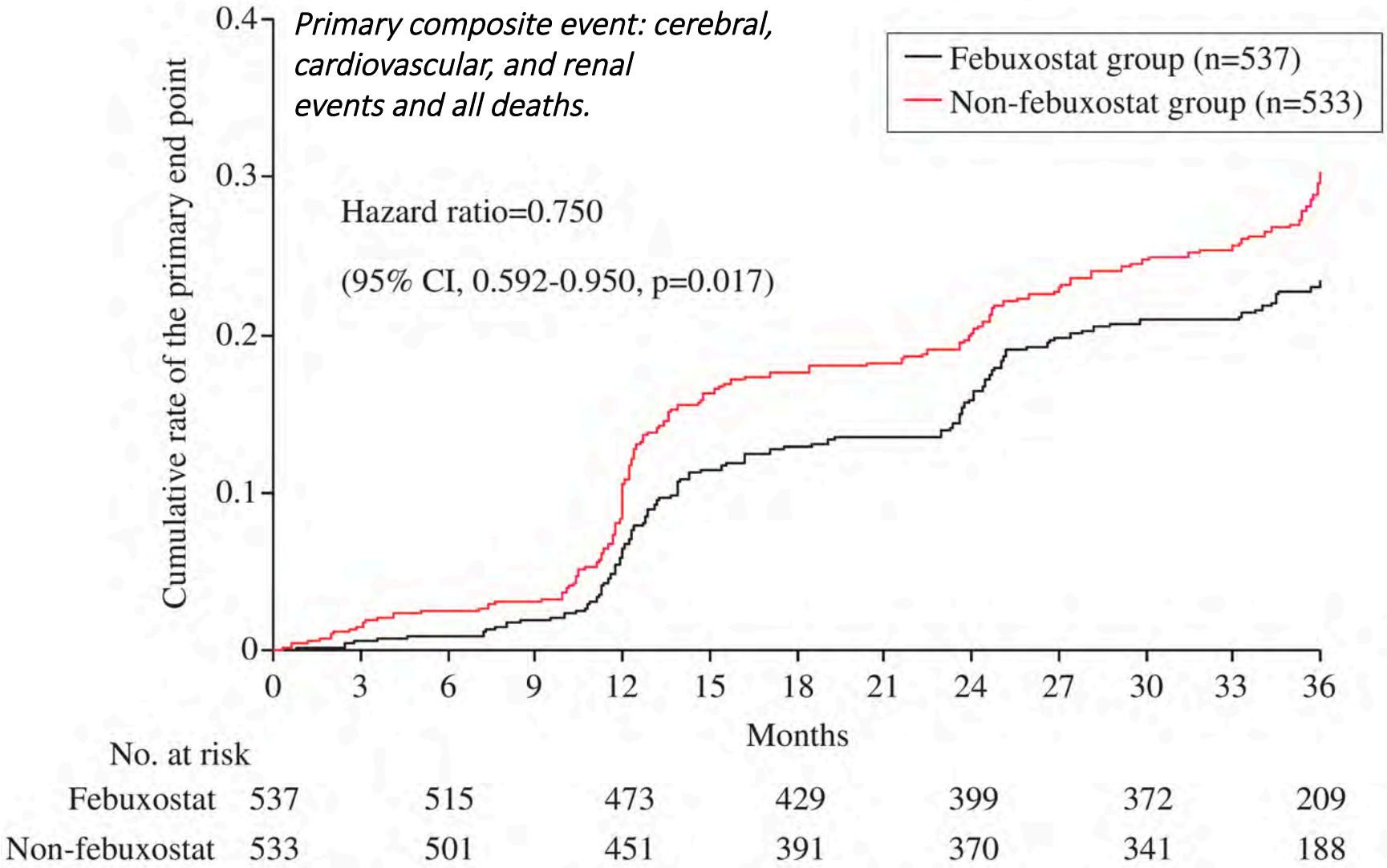






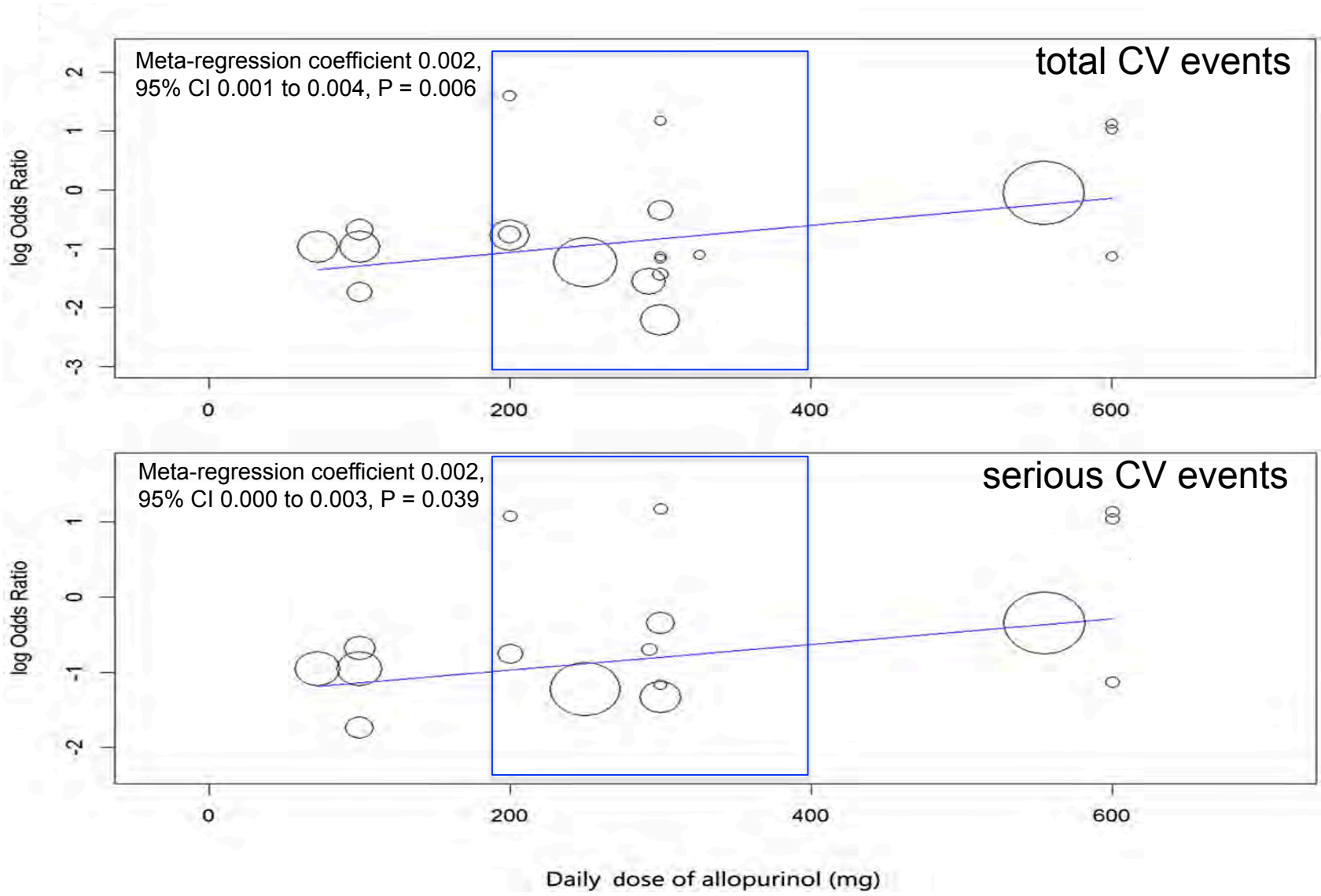
White WB et al. N Engl J Med. 2018 Mar 12.

Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion (FREED) StuDy



Kojima S et al. European Heart Journal (2019) 00, 1–10

Xanthine oxidase inhibitors for **prevention** of cardiovascular events: a systematic review and meta-analysis of RCT

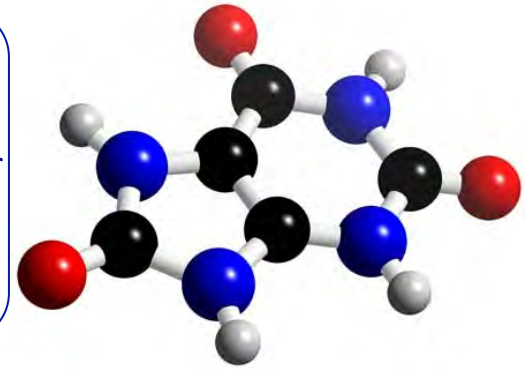


Bredemeier et al. BMC Cardiovascular Disorders (2018) 18:24

Uric Acid excretion/production balance

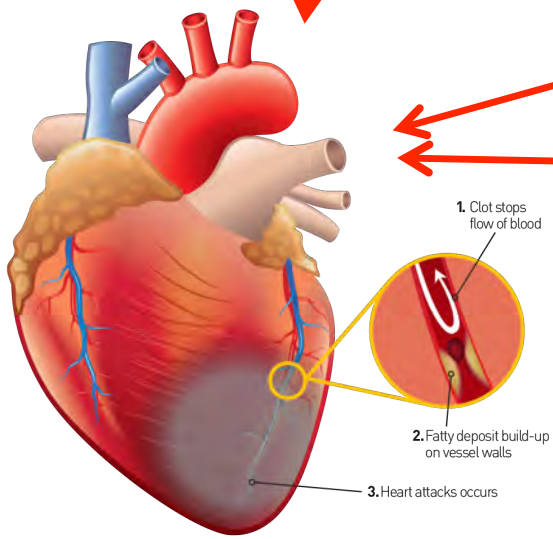
20% Iperproducers

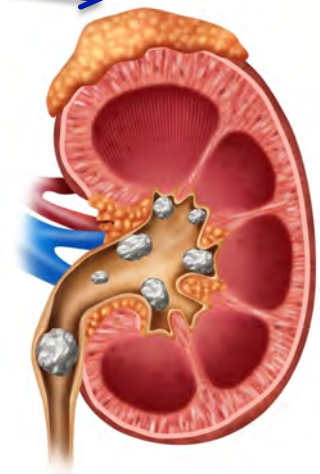
XO overactivity (genetic, induced) or ”overfeeding” (food, fructose, purines)

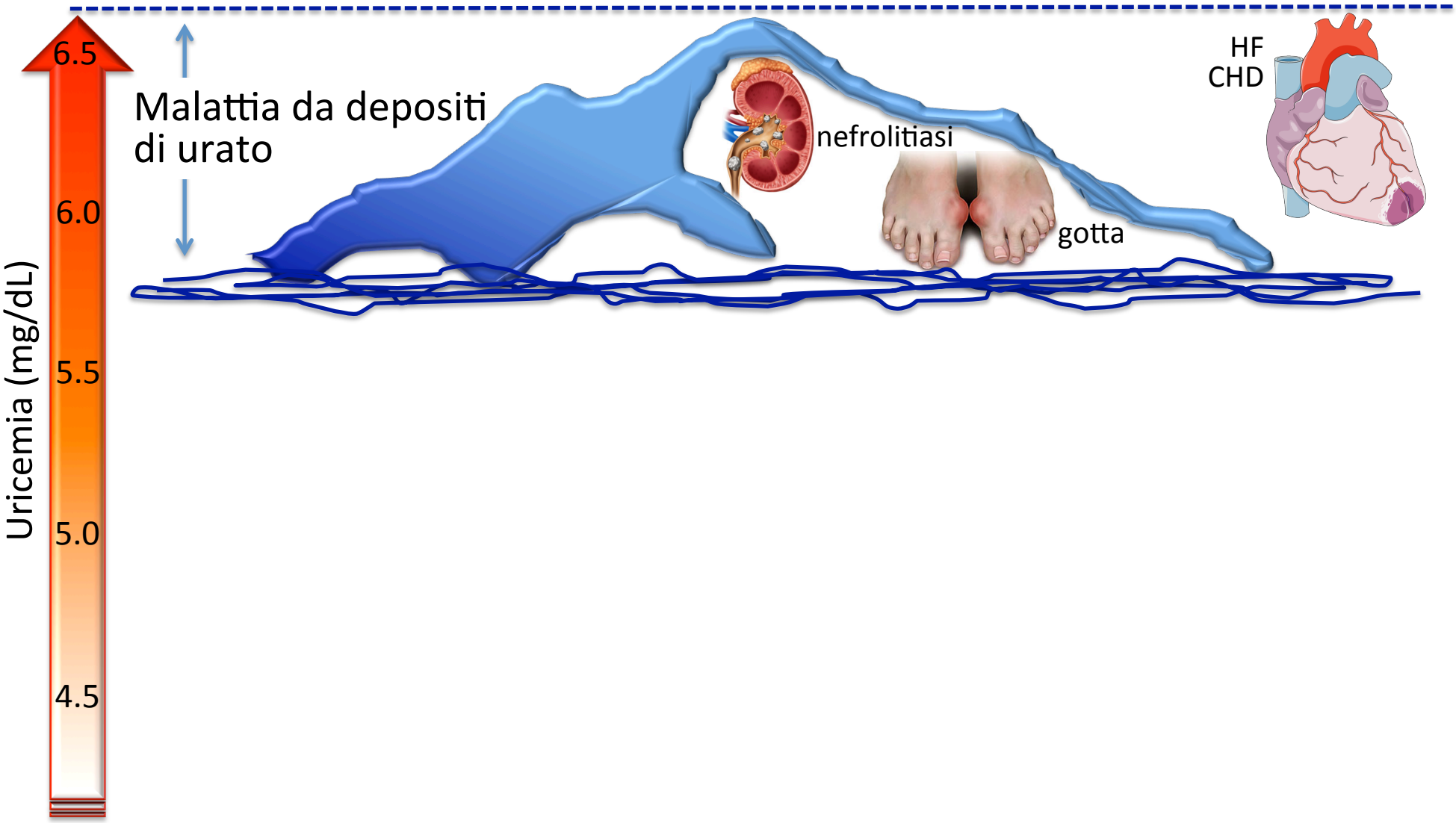


80% Underexcretors

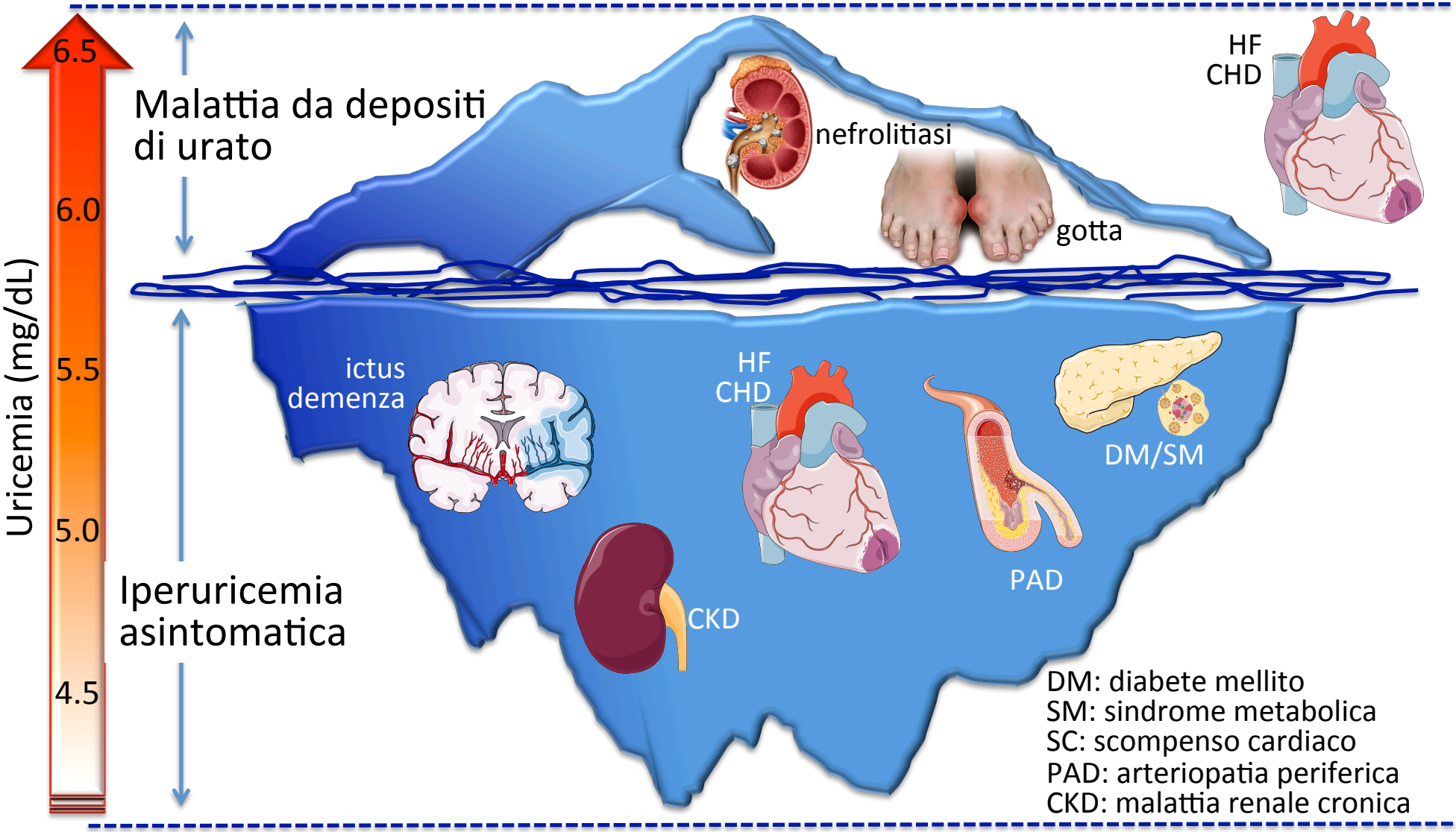
(physiologically, low GFR, Diuretics)



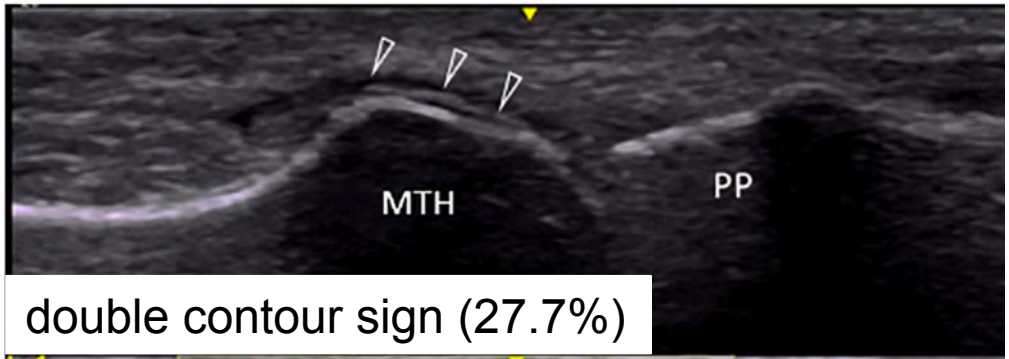



Uricemia (mg/dL)
6.5
6.0
5.5
5.0
4.5
Malattia da depositi di urato
nefrolitiasi
gotta
HF
CHD

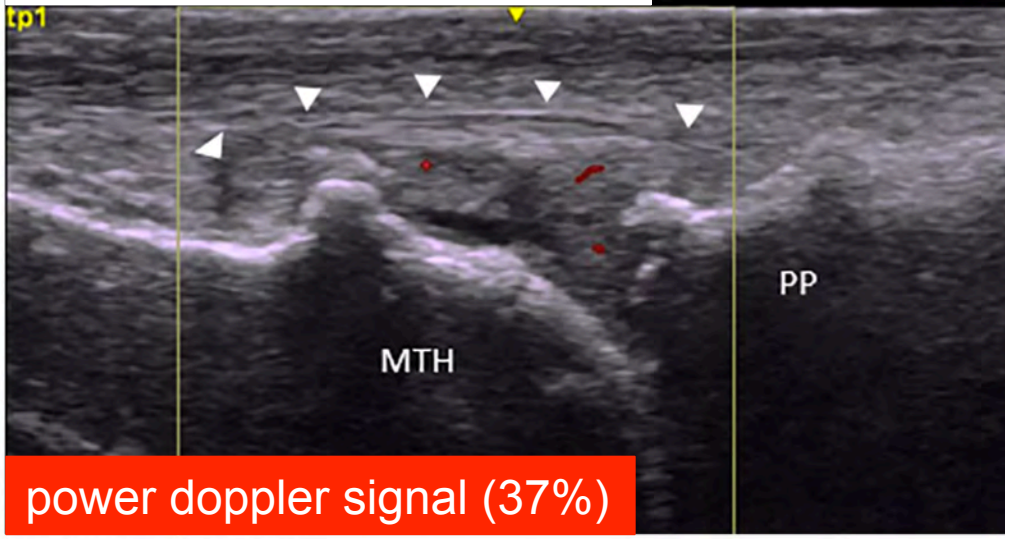
Il mondo sommerso dell'iperuricemia con e senza depositi di urato



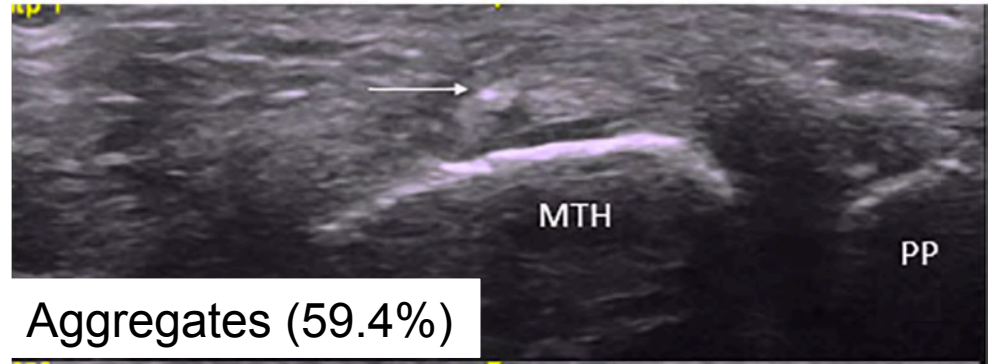
Ultrasonographic assessment of joint pathology in type 2 diabetes and hyperuricemia (60%) or gout (40%): The Fremantle Diabetes Study Phase II



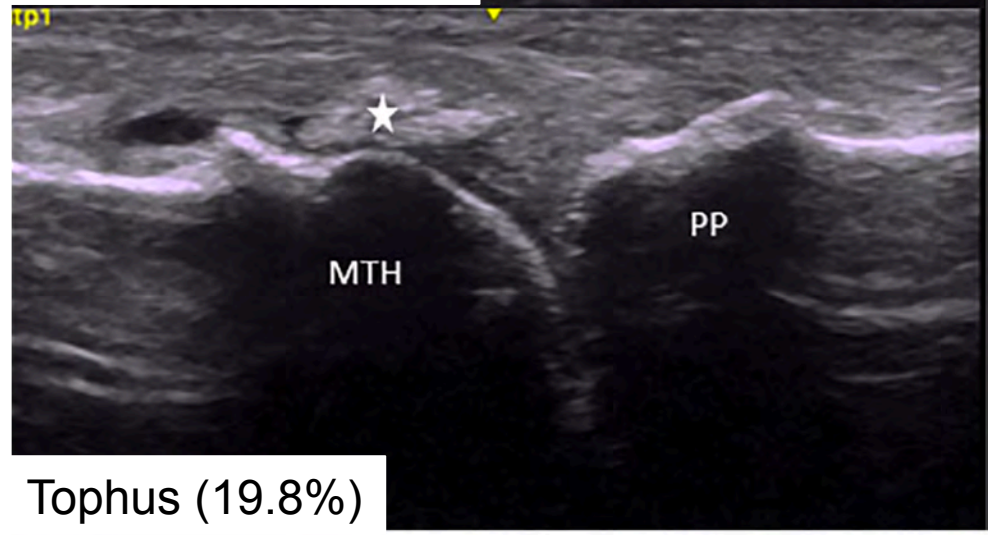
double contour sign (27.7%)



power doppler signal (37%)



Aggregates (59.4%)



Tophus (19.8%)

- 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.**

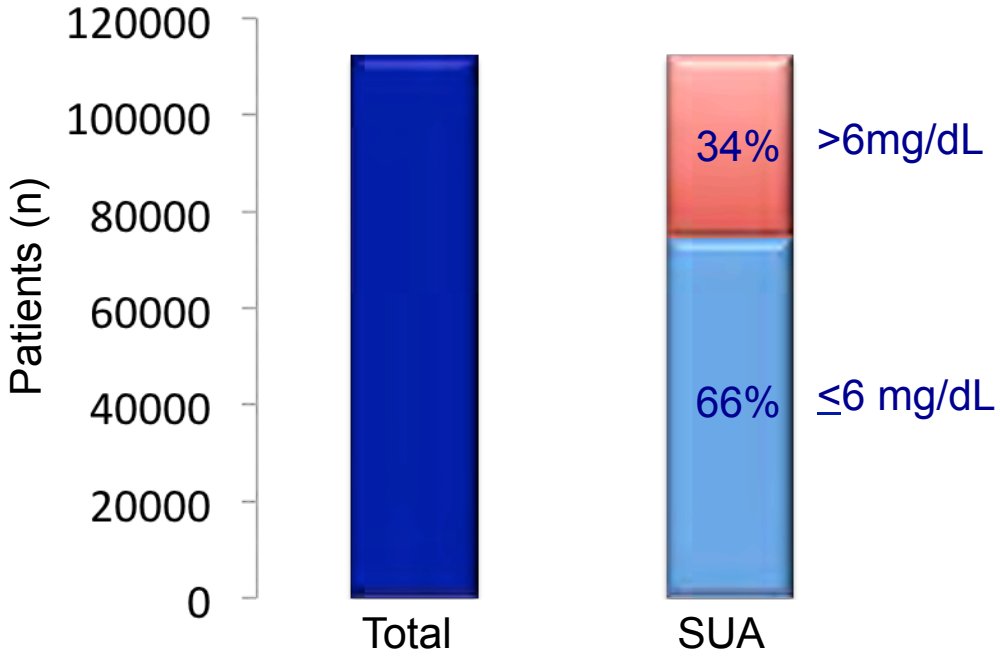
Keen HI et al. **Journal of Diabetes and Its Complications 32 (2018) 400–405**

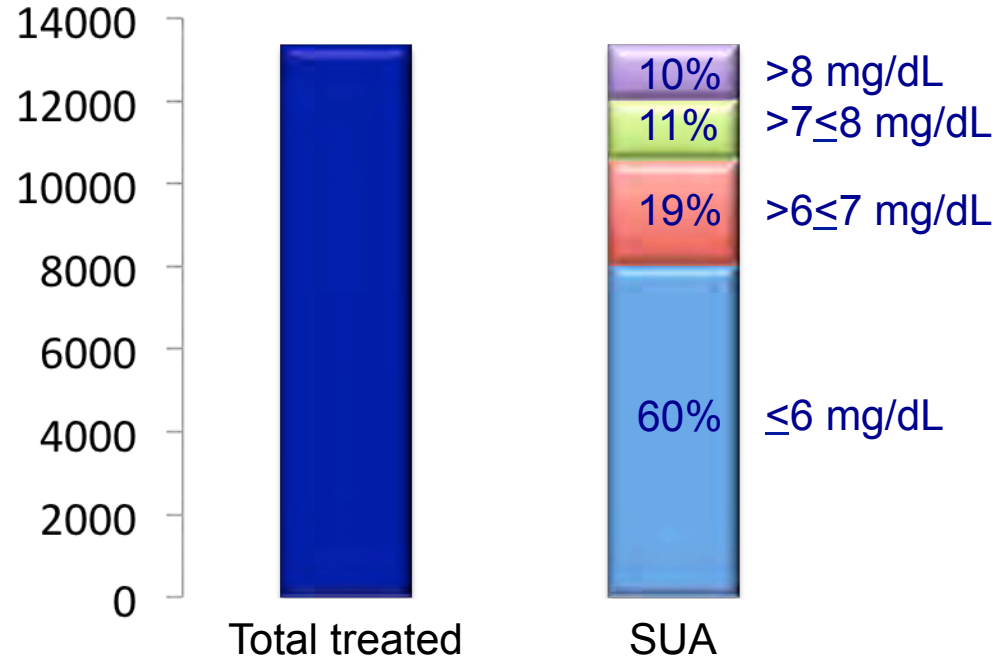
Nutrition, Metabolism & Cardiovascular Diseases (2016) 26, 951–961

Serum Uric Acid Target < 6 mg/dL

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

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





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

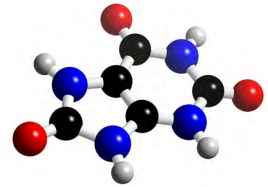
Claudio Borghi[a], Enrico Agabiti Rosei[b], Thomas Bardin[c,d,e], Jesse Dawson[f], Anna Dominiczak[f], Jan T. Kielstein[g], Athanasios J. Manolis[h], Fernando Perez-Ruiz[i], and Giuseppe Mancia[j]

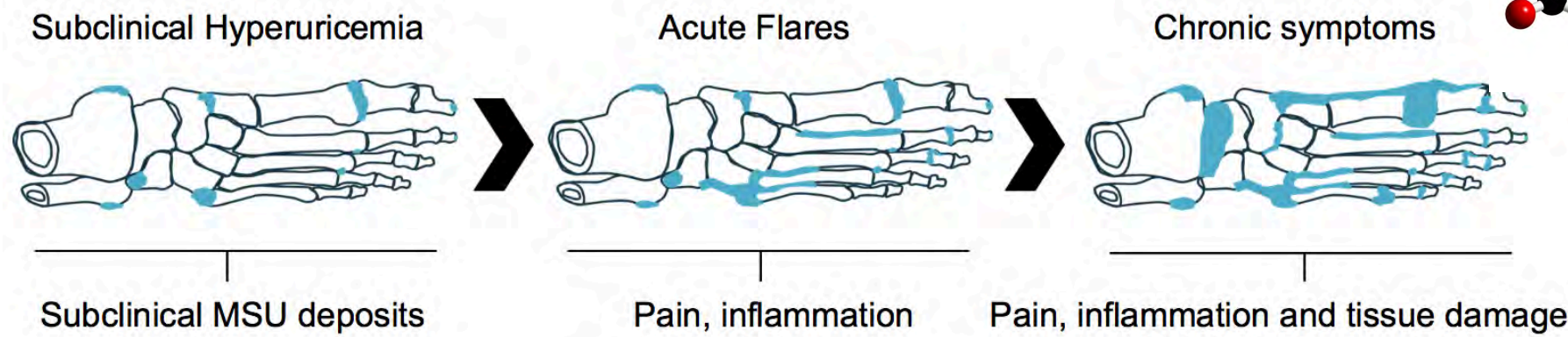
European Review for Medical and Pharmacological Sciences 2014; 18: 1295-1306

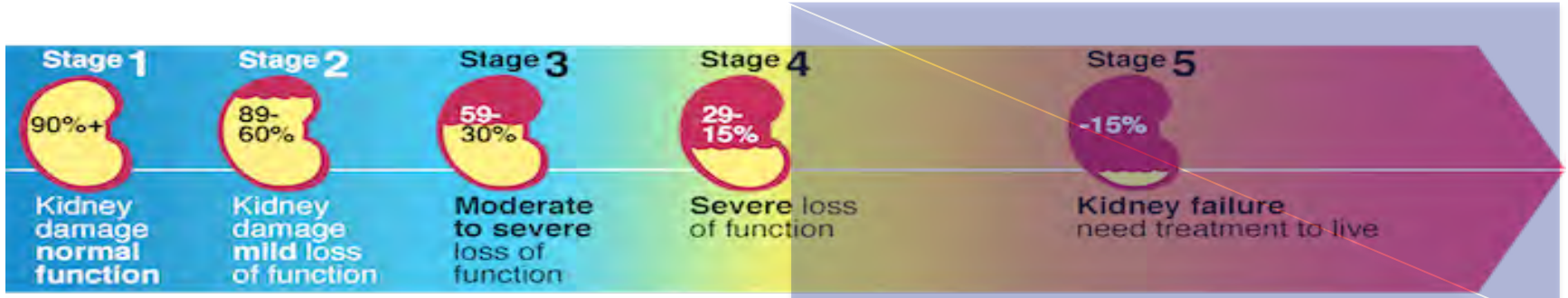
Is it time to revise the normal range of serum uric acid levels?

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]

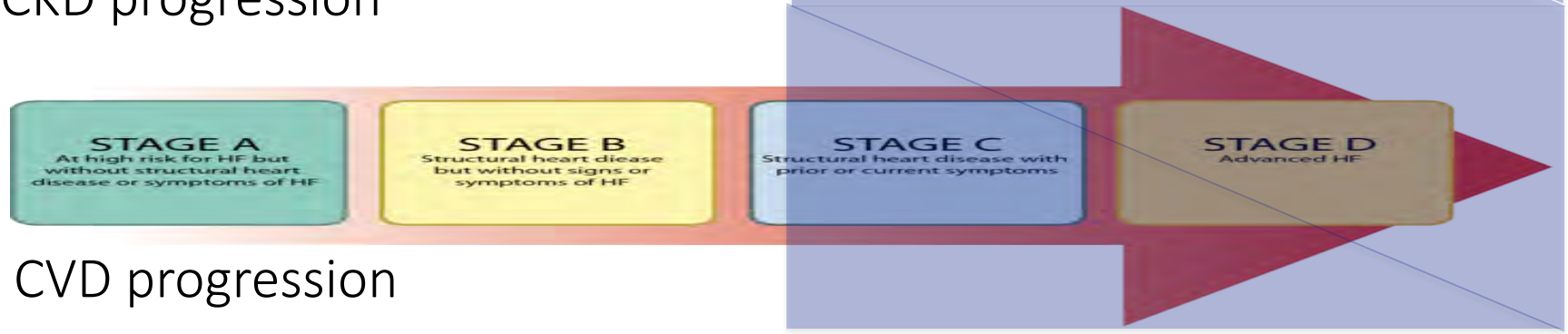
XO-inhibition: intervention area





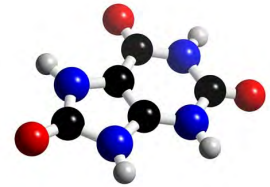


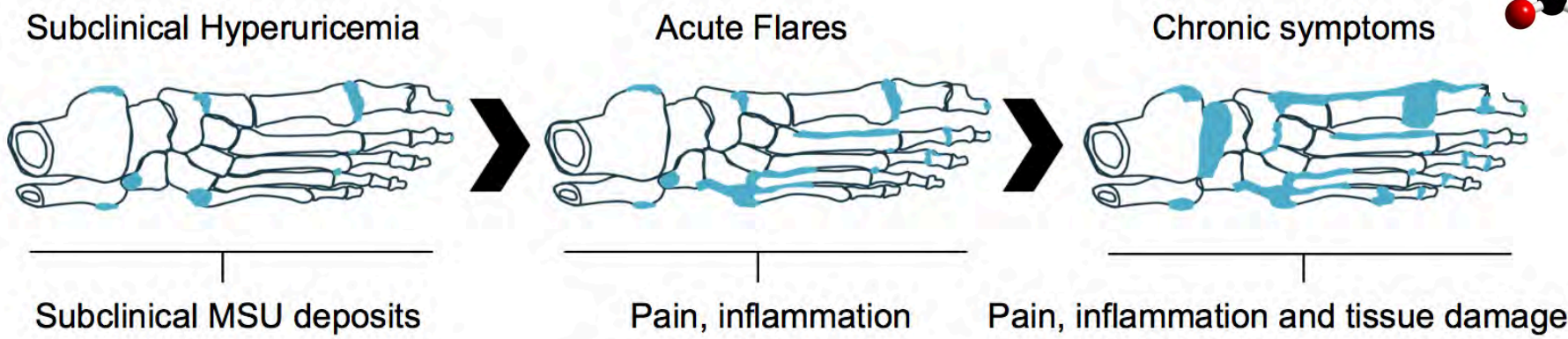
CKD progression



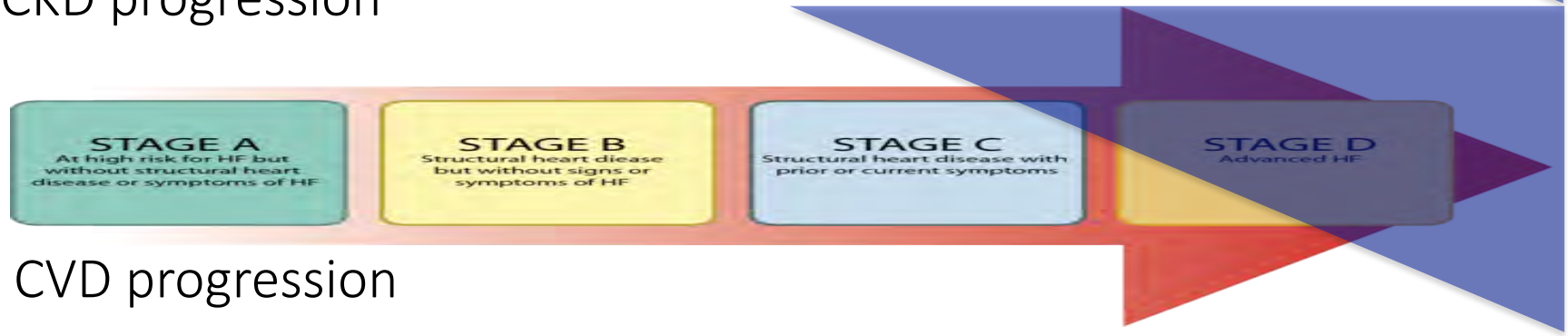
CVD progression

XO-inhibition: intervention area





CKD progression

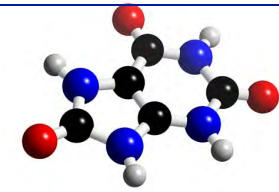


CVD progression

Conclusions

Pathophysiological mechanisms linking hyperuricemia with and/or withouts deposits to CVD (likely) include

- ✧ UA induced vascular dysfunction
- ✧ UA induced metabolic derangement
- ✧ XO overactivity (genetic, induced) or ”overfeeding” (food, fructose, purines)
- ✧ UA deposits induced “microinflammation”

Asymptomatic or…..  subclinical?

Mechanistic evidence identifies the **selective XO-inhibition** as the most effective strategy for the management of hyperuricemia in addition and beyond the effects on SUA