

Il controllo dell'iperuricemia con e/o senza deposito di urato: un “vecchio” nuovo fattore di rischio



PL. Temporelli

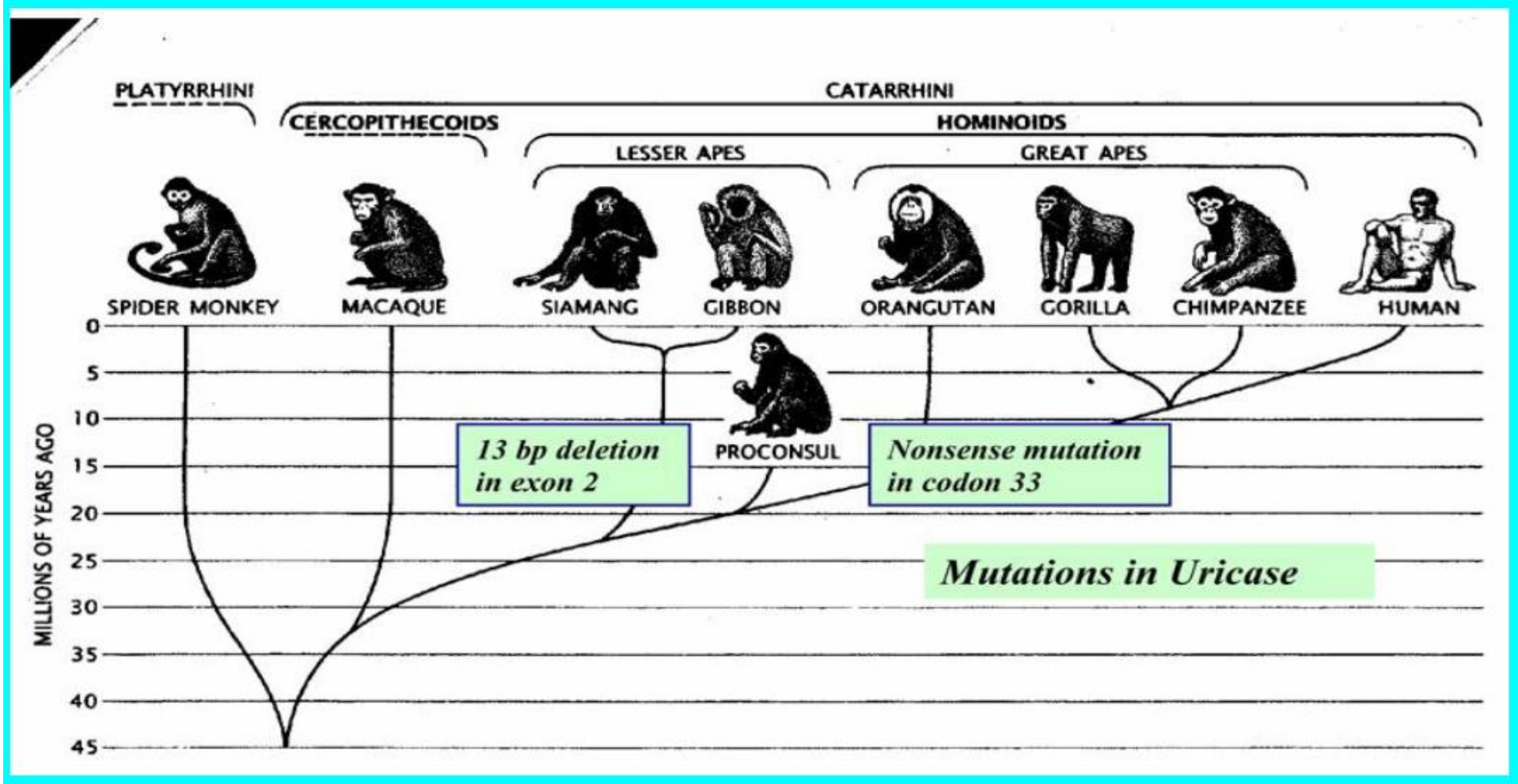
**Istituti Clinici Scientifici Maugeri, IRCCS
Divisione di Cardiologia Riabilitativa, Veruno**

Ogni verità passa attraverso 3 stadi:

- Primo: viene ridicolizzata
- Secondo: viene contrastata con violenza
- Terzo: viene accettata per la sua propria evidenza

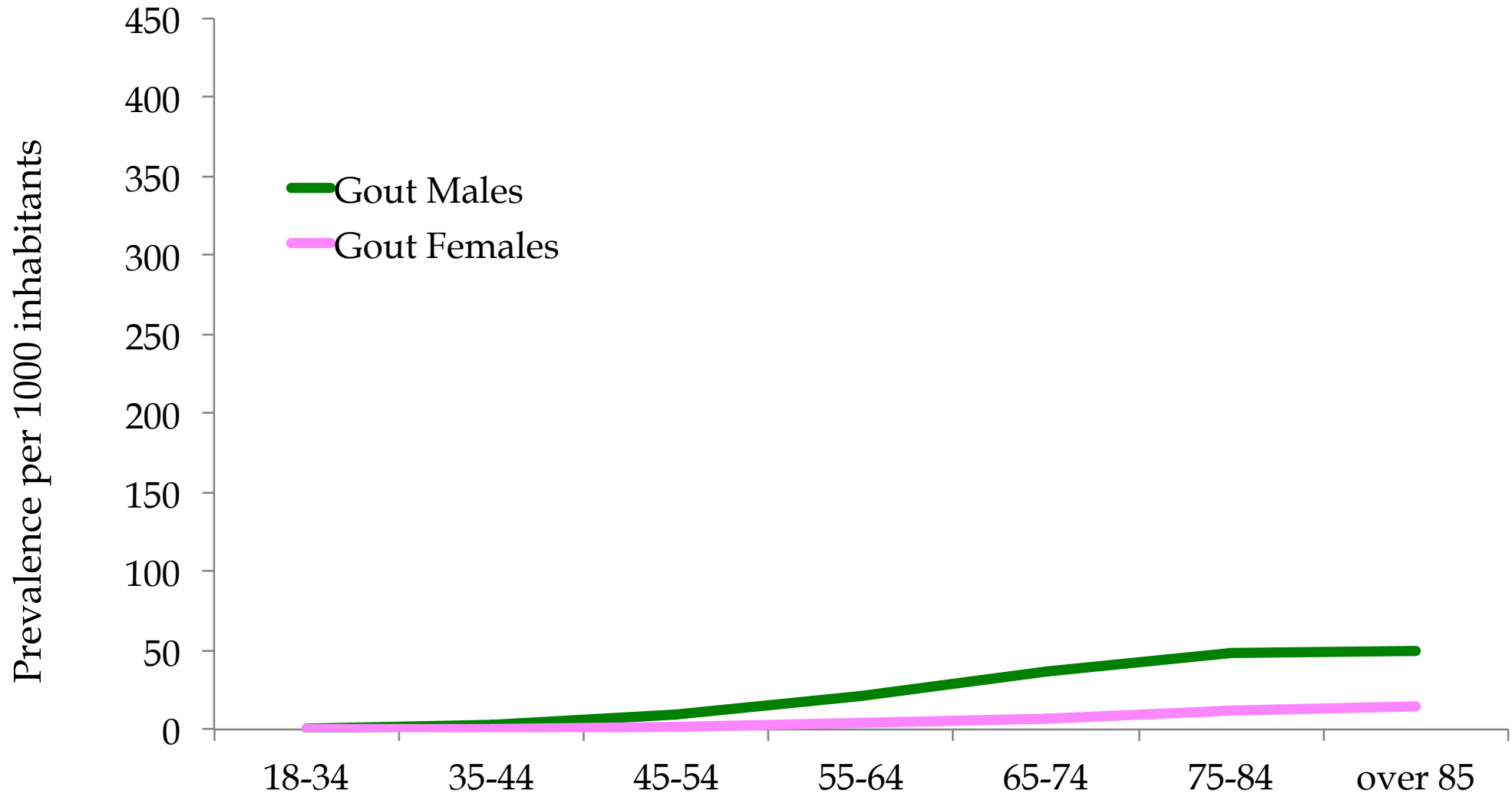
Arthur Schopenhauer (1788-1860)

Epidemiologia clinica dell'acido urico

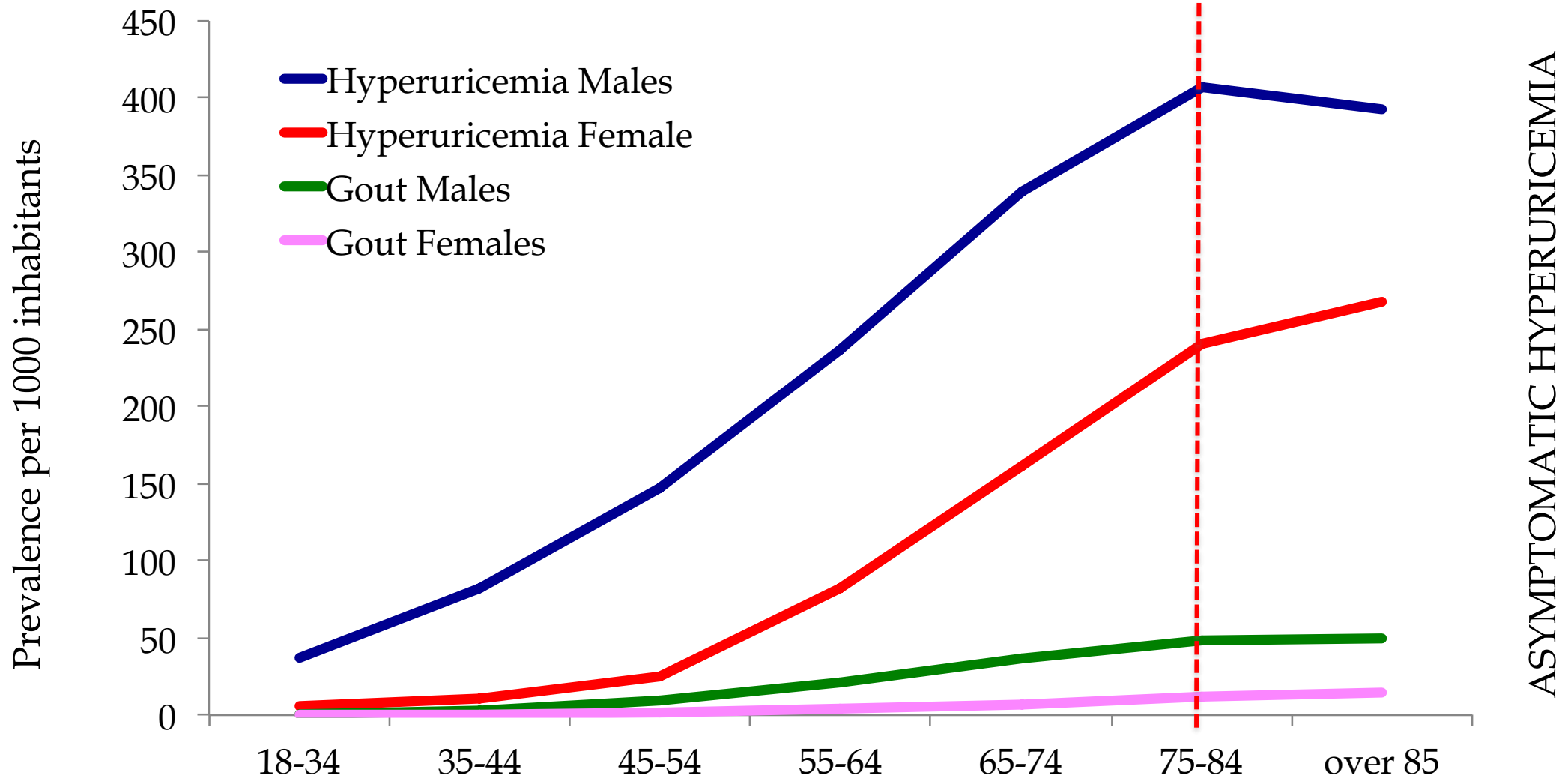


Circa 15 milioni di anni fa, un ominide nostro antenato subì una mutazione del gene dell'uricasi, l'enzima epatico che degrada l'acido urico in allantoina. Come conseguenza gli uomini e alcuni primati hanno livelli di uricemia più elevati degli altri mammiferi

Epidemiology of gout and hyperuricaemia (SUA >6 mg/dL) in Italy - 2009



Epidemiology of gout and hyperuricaemia (SUA >6 mg/dL) in Italy - 2009



Confronto della prevalenza della gotta e della iperuricemia in soggetti adulti US tra gli studi NHANES-III (1988-1994) e NHANES 2007-2008

	NHANES-III		NHANES 2007–2008		Difference
Prevalence of gout					
Unadjusted	2.7 (2.3, 3.0)	→	3.9 (3.3, 4.4)	→	1.2 (0.6, 1.9)
Age-adjusted	2.9 (2.5, 3.3)		3.9 (3.4, 4.5)	→	1.0 (0.4, 1.7)
Prevalence of hyperuricemia					
Unadjusted	18.2 (17.2, 19.3)	→	21.4 (19.7, 23.2)		3.2 (1.2, 5.2)
Age-adjusted	19.1 (18.1, 20.0)		21.5 (20.1, 23.0)	→	2.4 (0.7, 4.2)
Mean serum urate level, mg/dl					
Unadjusted	5.33 (5.29, 5.37)		5.48 (5.41, 5.55)		0.15 (0.07, 0.24)
Age-adjusted	5.36 (5.32, 5.40)		5.49 (5.44, 5.53)		0.13 (0.07, 0.18)

* Values are the percent (95% confidence interval). The data were adjusted for clusters and strata of the complex sample design of the National Health and Nutrition Examination Survey (NHANES) 2007–2008, with incorporation of sample weights.

**Acido urico solo
fattore di rischio CV
o anche target ?**

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.

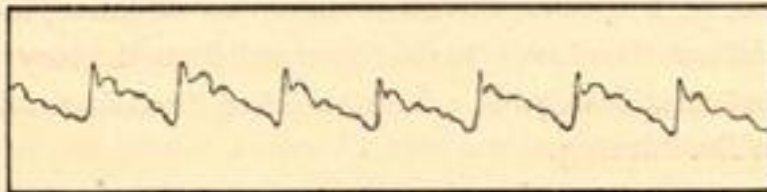
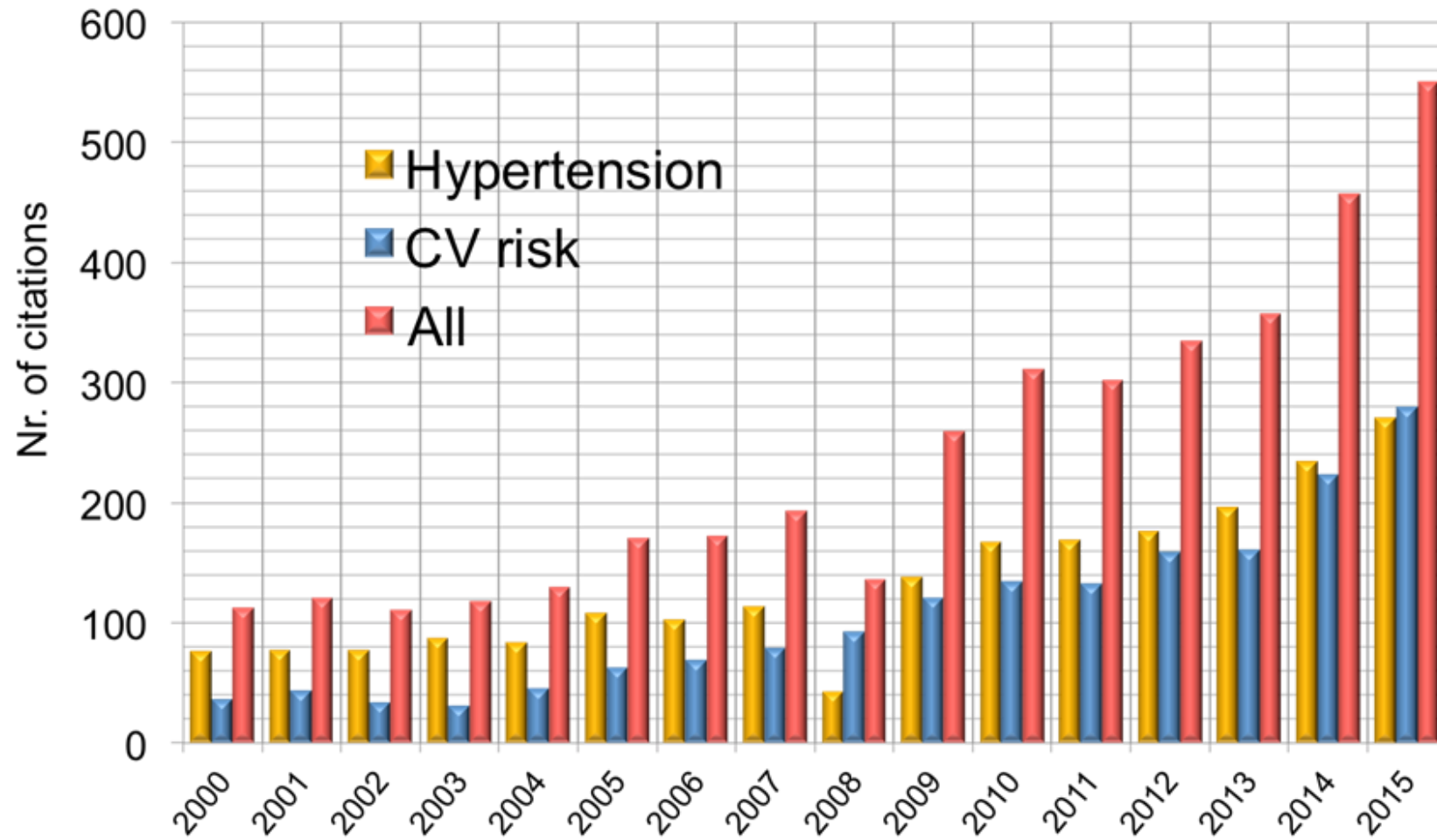


FIG. 14.—HIGH TENSION PULSE OF A URIC ACID HEADACHE. RATE 57.

Haig A: 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, edn 1. London: J & A Churchill; 1892.

Acido urico, ipertensione e rischio CV articoli citati in PubMed, 2015



Patologie cardiovascolari associate a livelli elevati di acido urico

- **Ipertensione e pre-ipertensione**
- **Malattia renale (compresa la ridotta percentuale di filtrazione glomerulare e la microalbuminuria)**
- **Sindrome metabolica** (compresa l'obesità addominale, l'ipertrigliceridemia, bassi livelli di colesterolo HDL, resistenza all'insulina, alterata tolleranza al glucosio, livello elevato di leptina)
- **Apnea ostruttiva notturna**
- **Malattia vascolare (carotidea, periferica, coronarica)**
- **Ictus e demenza vascolare**
- **Pre-eclampsia**
- **Markers dell'infiammazione** (proteina C reattiva, inibitore dell'attivatore del plasminogeno di tipo 1, molecola di adesione intracellulare solubile di tipo 1)
- **Disfunzione endoteliale**
- **Stress ossidativo**
- **Sesso e razza (donne in post-menopausa, razza nera)**
- **Fattori demografici (movimento dalle aree rurali a quelle urbanizzate, occidentalizzazione, immigrazione nei Paesi occidentali)**

SUA: Biological mechanisms of CV damage

Xantine oxidase generates uric acid and oxidants in settings of different stimulations (e.g. genetic, environmental, etc)



Endothelial Dysfunction and Impaired NO Production,

RAS (& AT₁ receptors) activation



Microvascular disease: renal and other vascular districts



Hypertension



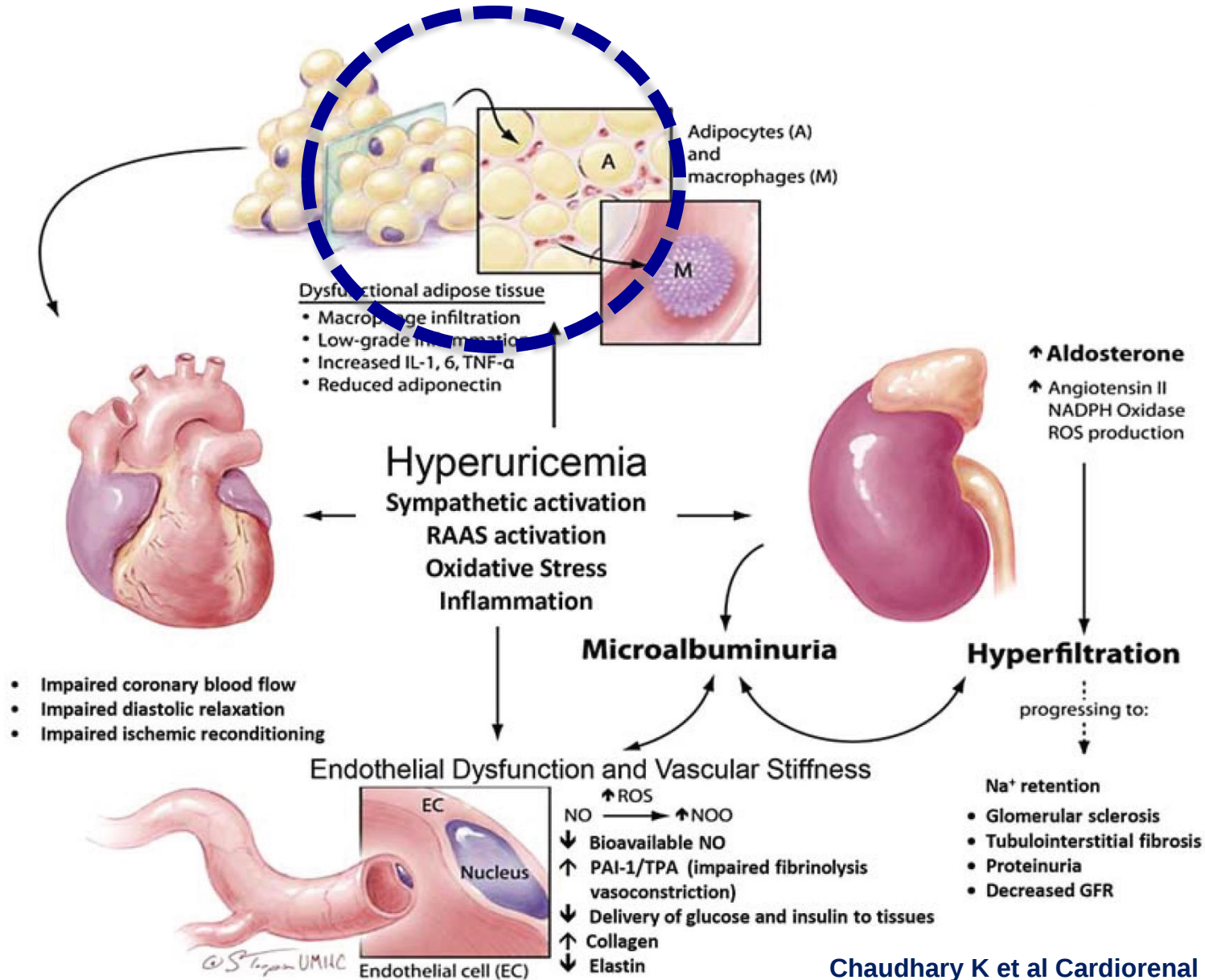
Renal/CV diseases

Farquharson CA *et al. Circulation.* 2002;106:221–226

Butler R *et al. Hypertension.* 2000;35:746–751

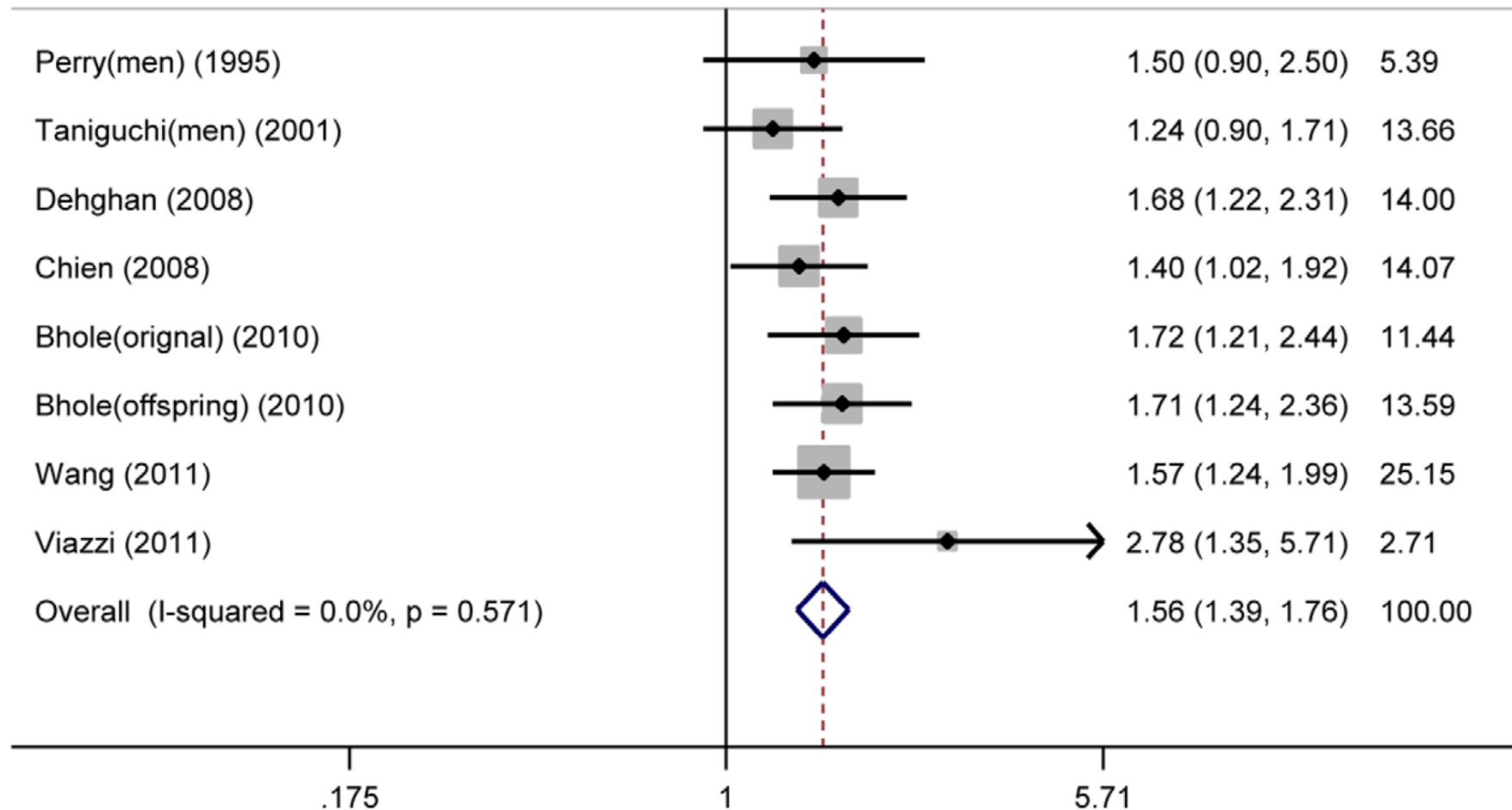
Johnson RJ *et al, Hypertension* 2005

Hyperuricemia and Cardiorenal Metabolic Syndrome



SUA and Increased Risk of Type 2 Diabetes: A Systemic Review and Meta-Analysis of Prospective Cohort Studies

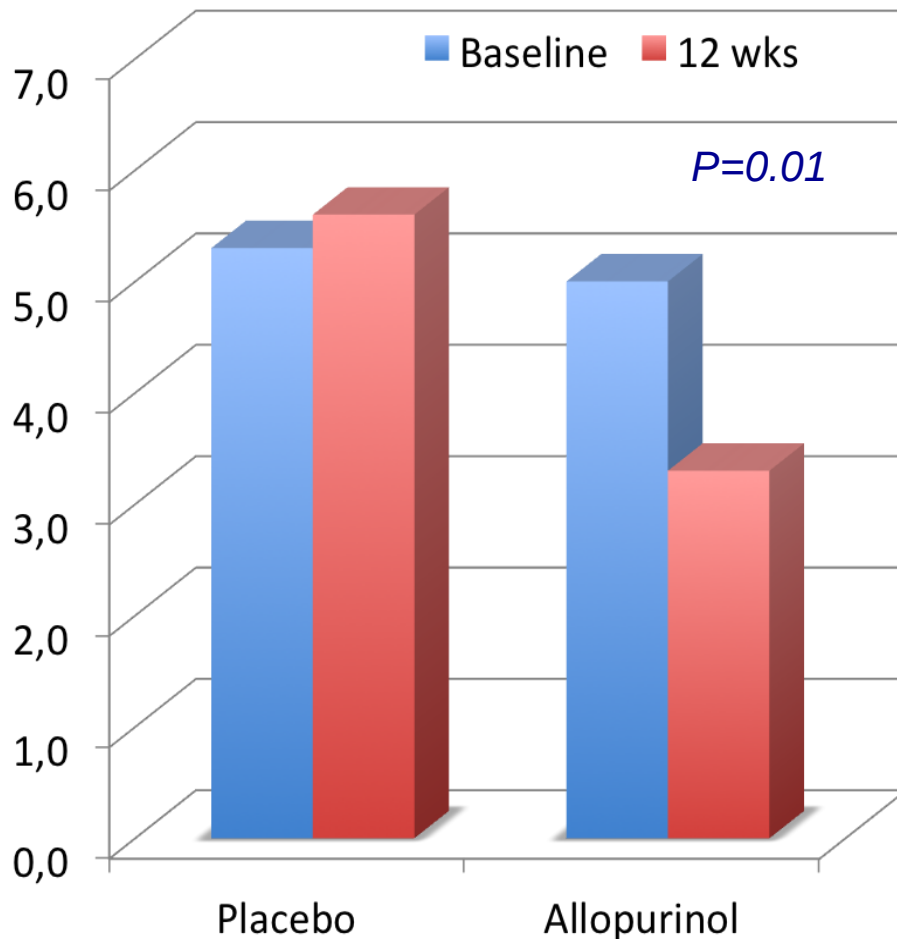
7 eligible articles derived from 8 prospective cohort studies, involving a total of 32016 participants and 2930 incident type 2 diabetes



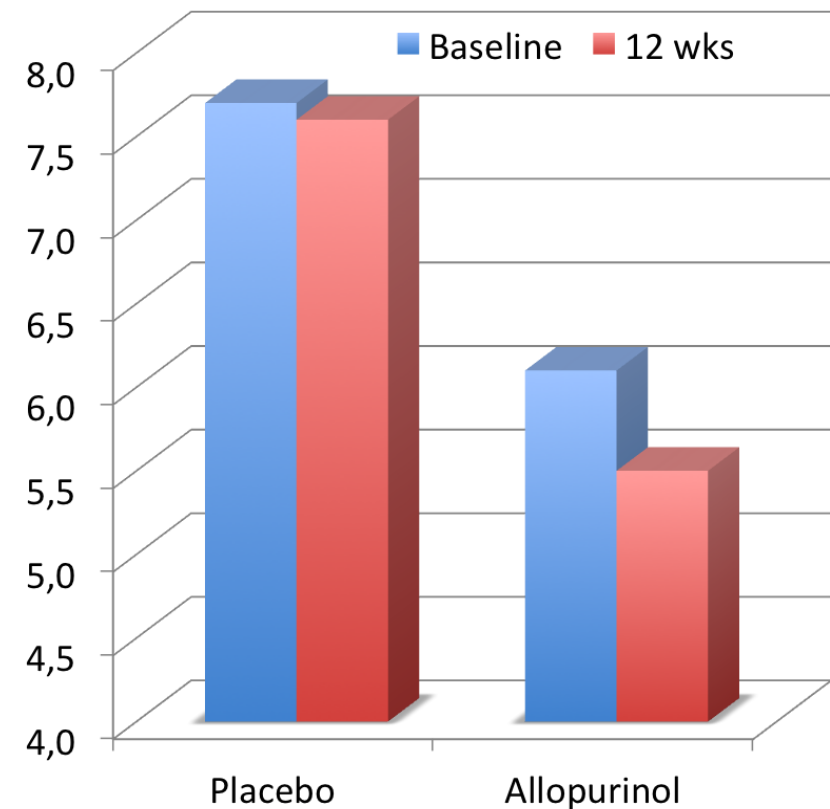
Effect of long-term and high-dose allopurinol therapy on HBA_{1c} in normotensive diabetic patients

100 diabetic normotensive pts randomized to **allopurinol (900 mg/die)** or placebo for 12 weeks.

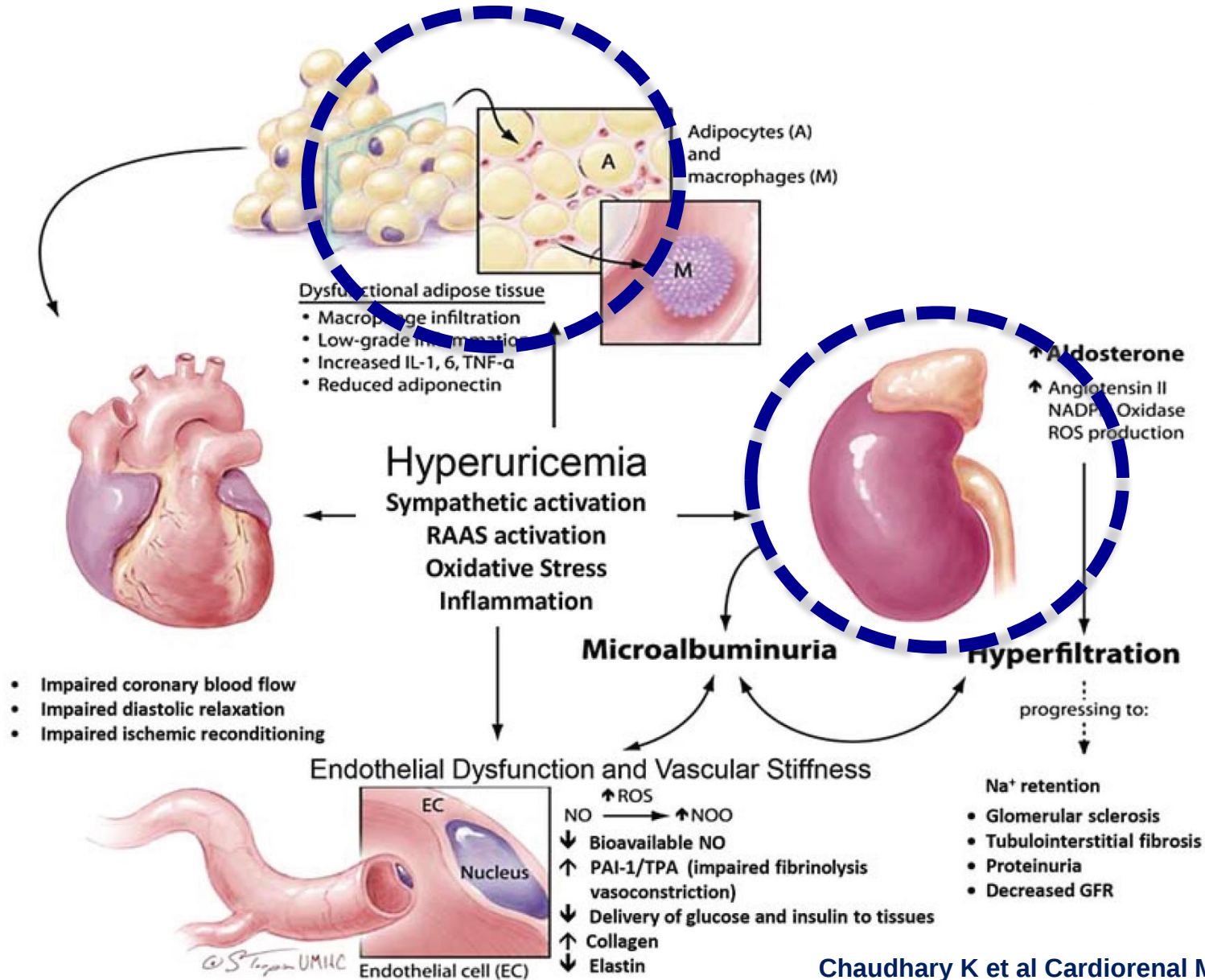
Uric acid (mg/dL)



HBA_{1c}



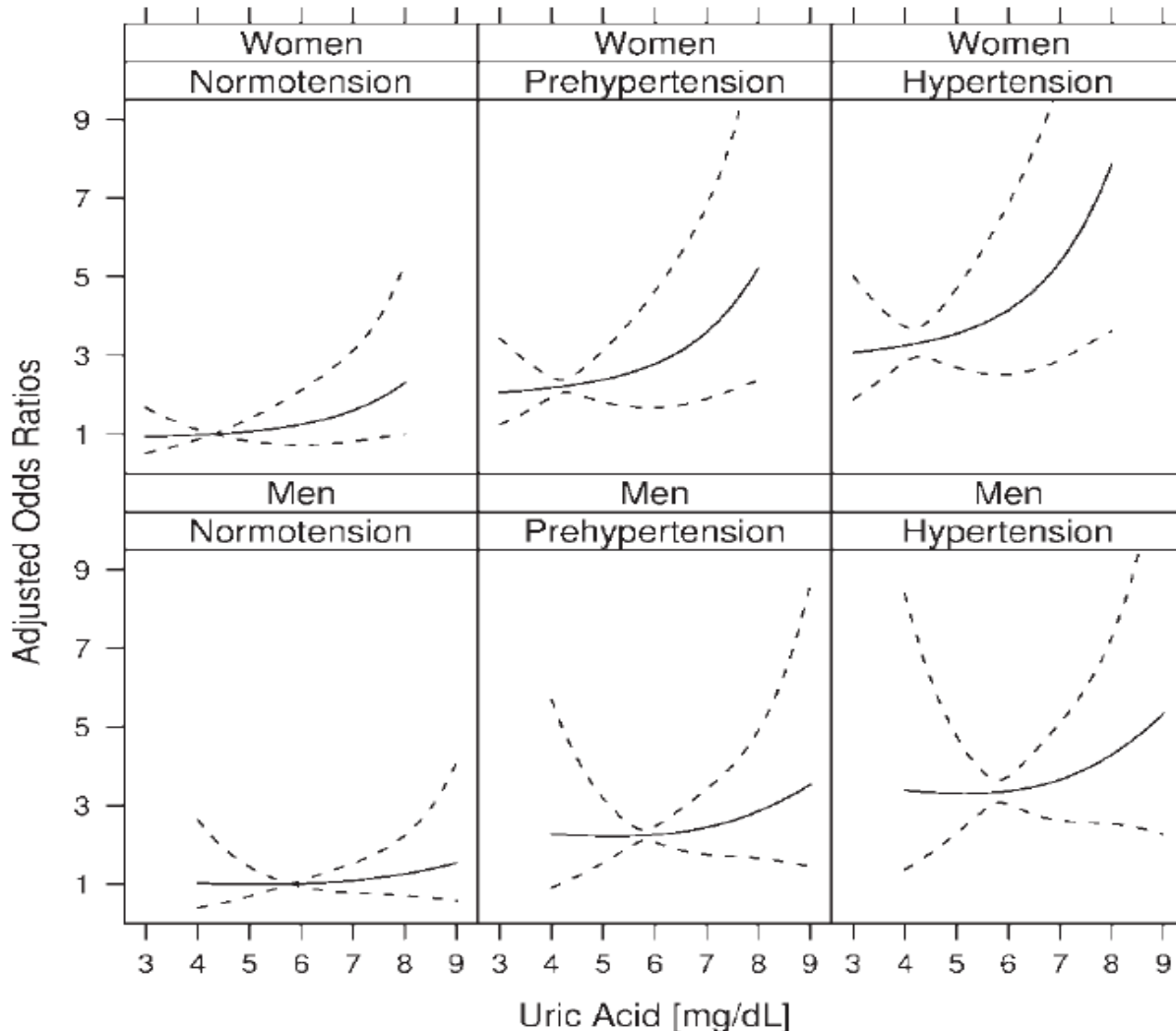
Hyperuricemia and Cardiorenal Metabolic Syndrome



Hyperuricemia Increases the Risk for Kidney Disease

n=21,475 **healthy volunteers** (Vienna health screening project);

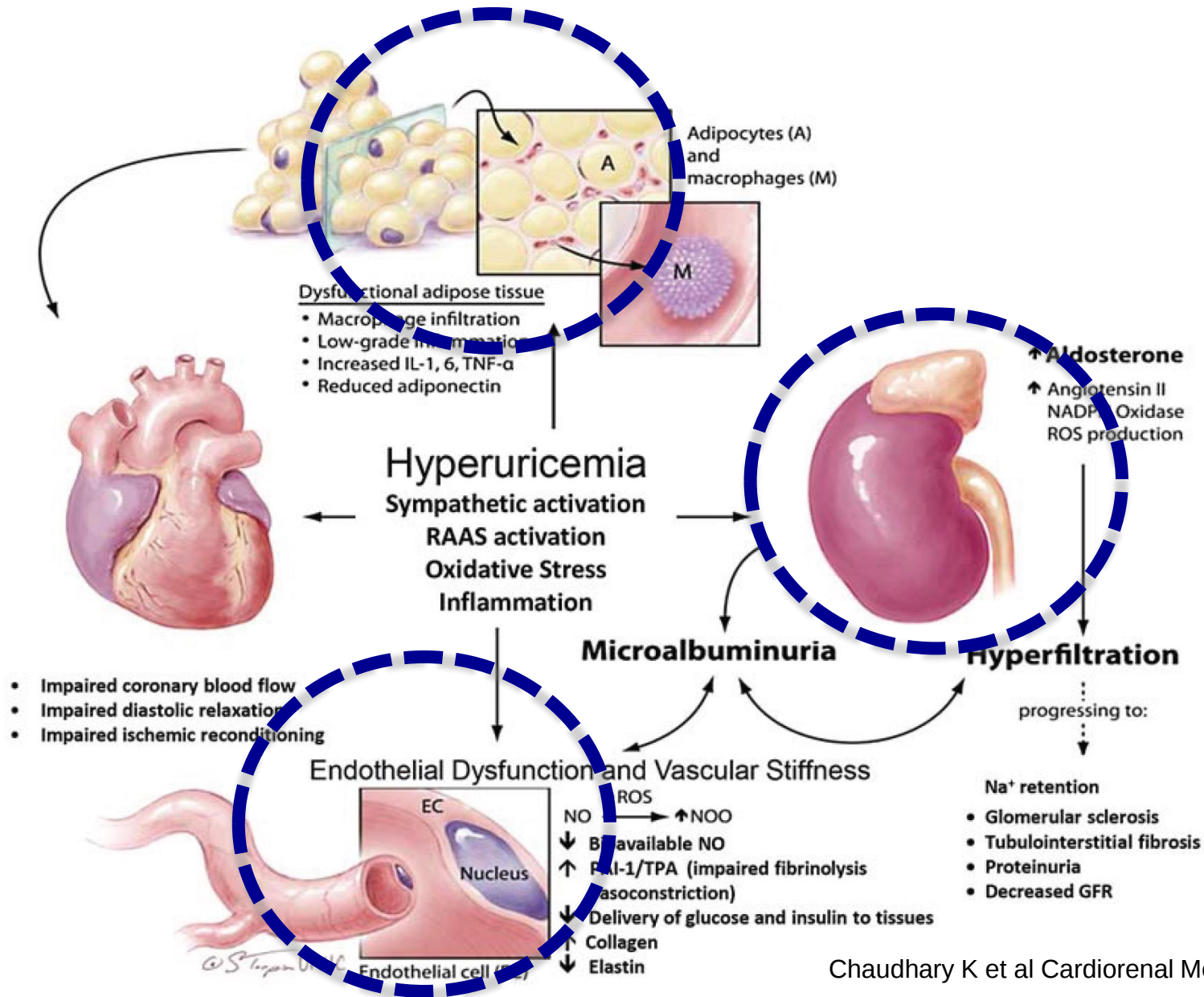
mean age 46 yrs; F-UP = 7 y; Development of Kidney Disease (eGFR-MDRD stage 3 CKD)



OR for stage 3 CKD depending on UA levels compared with mean UA levels (4.2 in females, 5.9 in men)

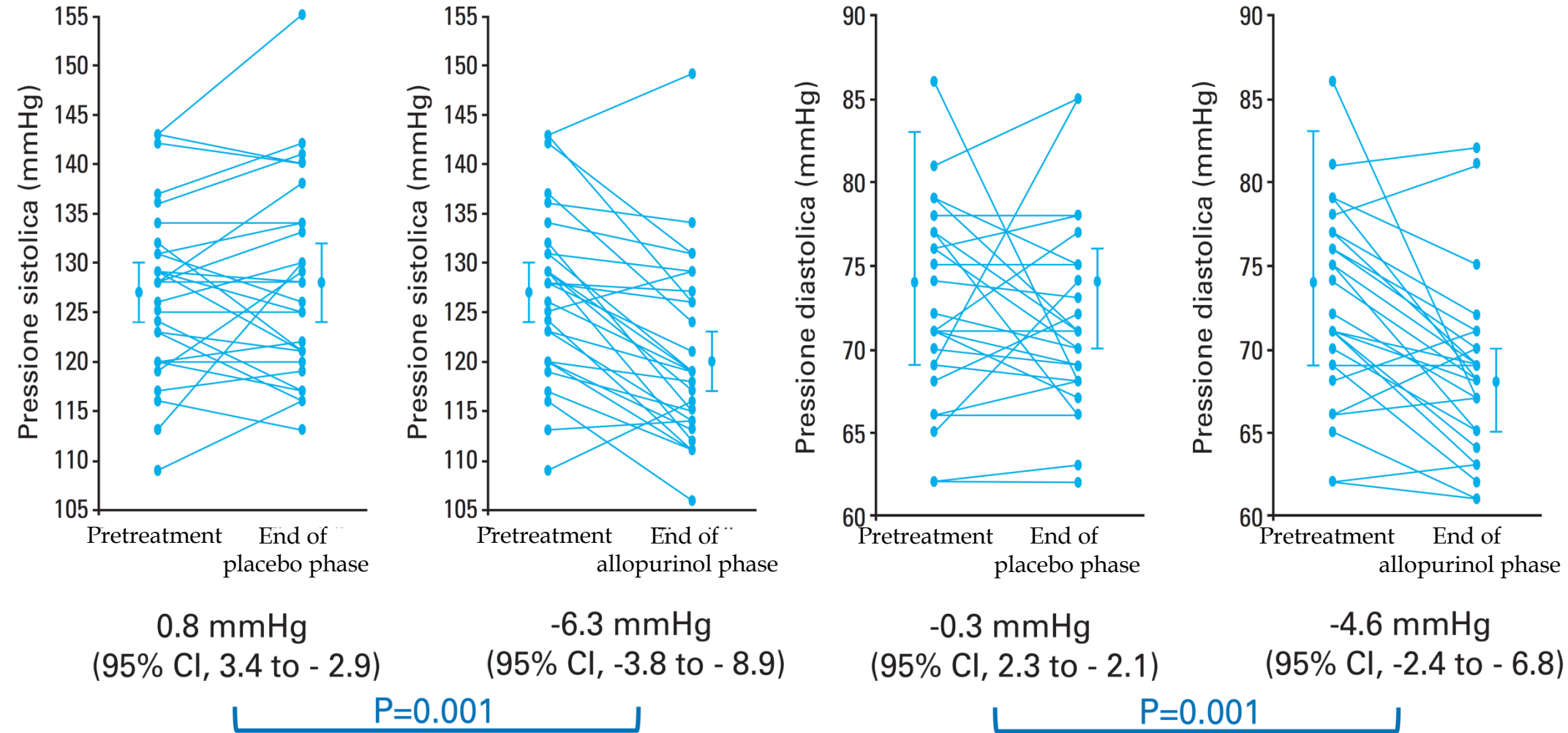
After adjustment for: **baseline eGFR**, gender, age, antihypertensive drugs, and components of the metabolic syndrome (waist circumference, HDL cholesterol, blood glucose, triglycerides, and BP)

Hyperuricemia and Cardiorenal Metabolic Syndrome

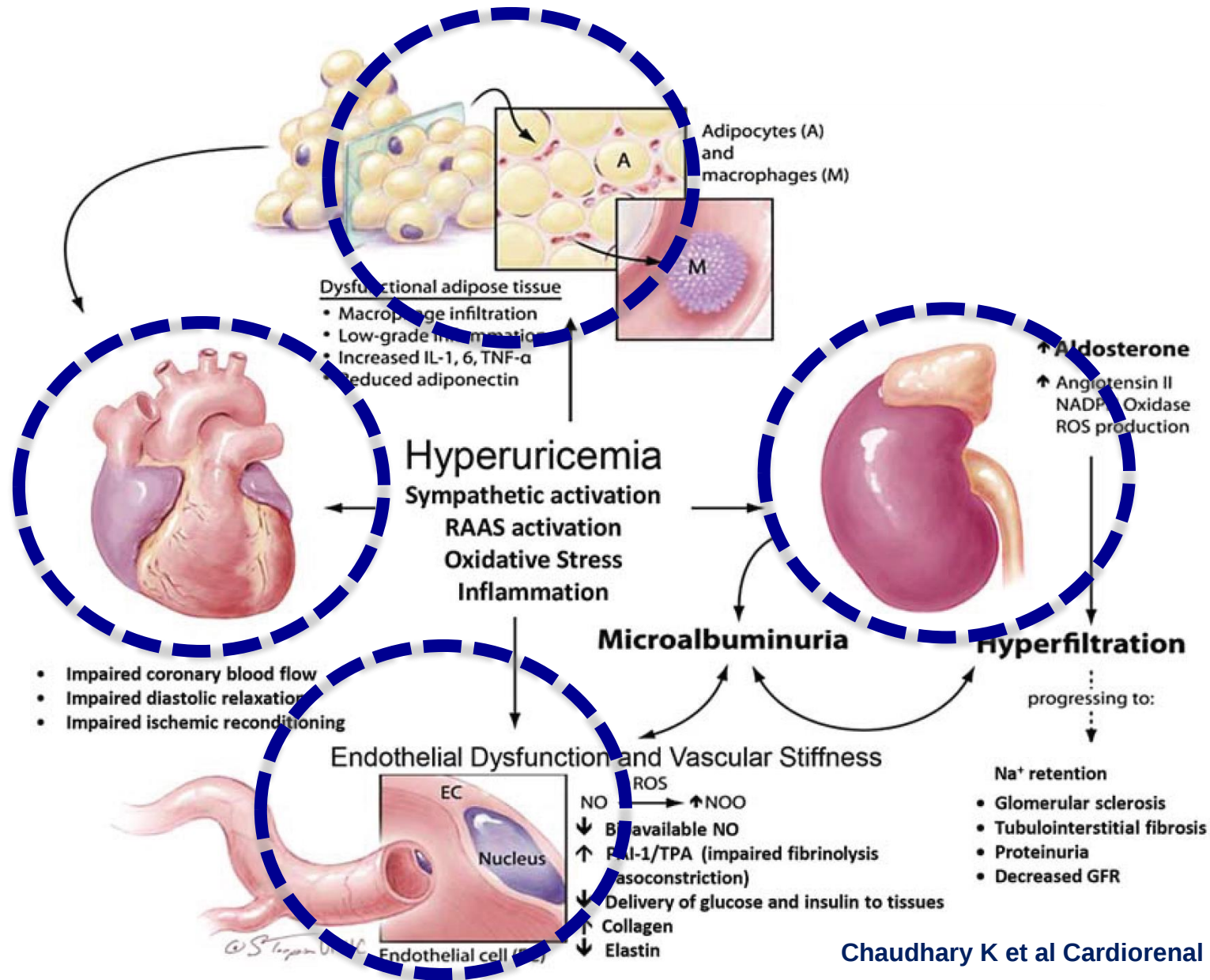


Effect of SUA Lowering on Blood Pressure of Adolescents With Essential Hypertension

pressione media delle 24 ore



Hyperuricemia and Cardiorenal Metabolic Syndrome

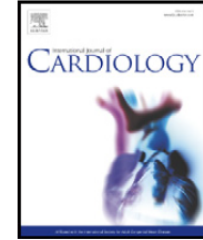




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journal homepage: www.elsevier.com/locate/ijcard



Serum uric acid on admission predicts in-hospital mortality in patients with acute coronary syndrome



Marco Magnoni^a, Martina Berteotti^a, Ferruccio Ceriotti^a, Vincenzo Mallia^a, Vittoria Vergani^a, Giovanni Peretto^a, Giulia Angeloni^b, Nicole Cristell^a, Attilio Maseri^c, Domenico Cianflone^{a,*,1}

^a IRCCS Ospedale San Raffaele and Università Vita-Salute San Raffaele, Milan, Italy

^b Department of Heart and Vessels, Careggi Hospital, University of Florence, Florence, Italy

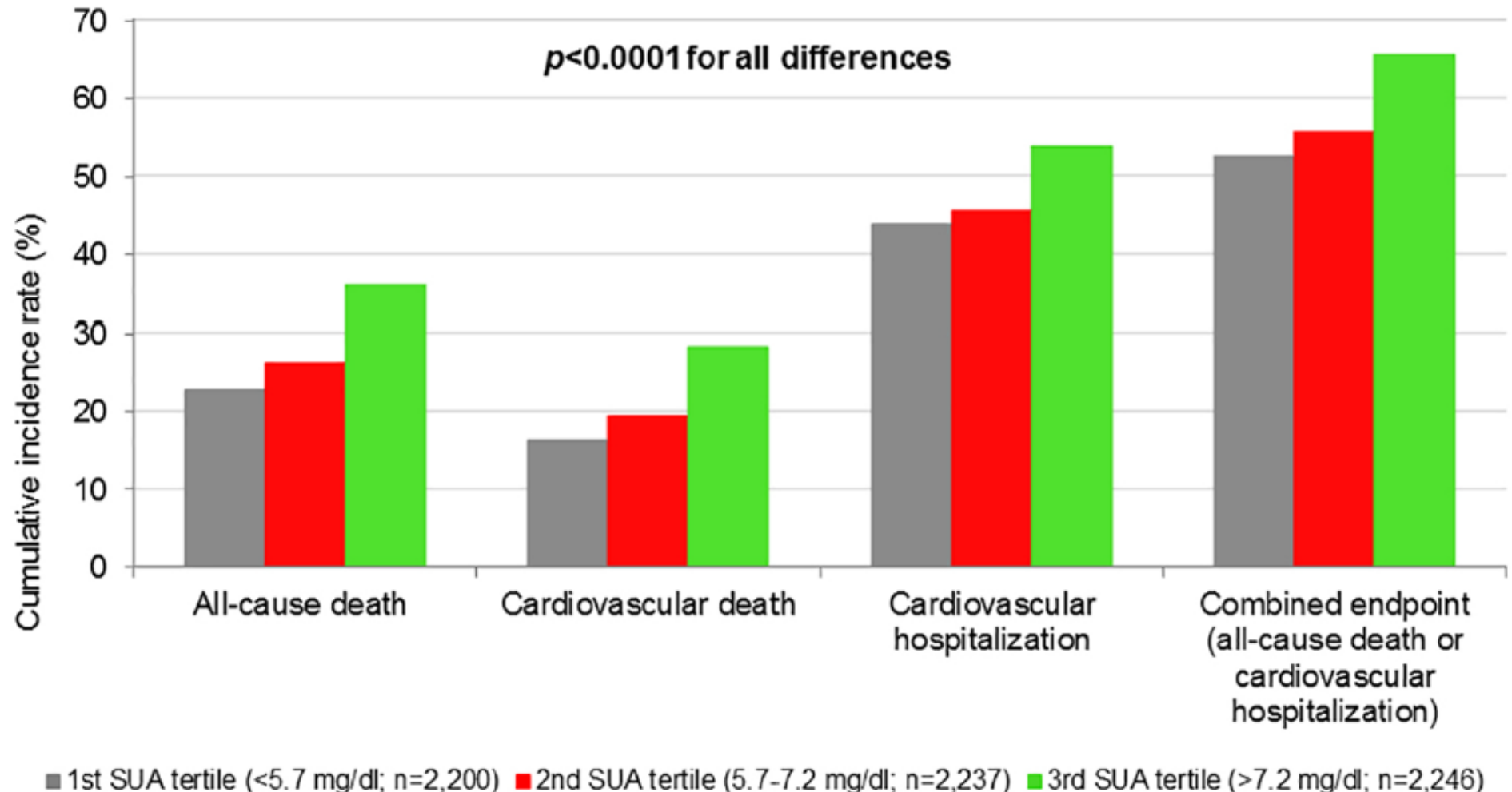
^c Heart Care Foundation Onlus, Florence, Italy

In patients with acute coronary syndrome, uricemia levels above the current international reference limit (6.0 mg/dl) were associated with in-hospital mortality, independently from ethnicity and renal function.

Uric acid and risk of heart failure: a systematic review and meta-analysis

- ✓ For every 1 mg/dL increase in serum uric acid, the odds of development of HF increased by 19% (HR 1.19, 95% CI 1.17–1.21)
- ✓ For every 1 mg/dL increase in serum uric acid, the risk of all-cause mortality increased by 4% (HR 1.04, 95% CI 1.02–1.06)

Prognostic Impact of Elevated Serum Uric Acid Levels on Long-Term Outcomes in Patients with CHF: A Post-Hoc Analysis of the GISSI-HF Trial



Hyperuricemia as an independent risk factor for major cardiovascular events: a 10-year cohort study from Southern Italy

Vincenzo Capuano^a, Federica Marchese^b, Rocco Capuano^a, Sergio Torre^a, Anna G. Iannone^a, Eduardo Capuano^a, Norman Lamaida^b, Matteo Sonderegger^a and Ernesto Capuano^a

J Cardiovasc Med 2017, 18:159–164

Characteristic	Uric acid >6 mg/dl	Uric acid <6 mg/dl	<i>P</i> -value
Age (years)	50 ± 15	49 ± 14	NS
BMI (kg/m ²)	29.7 ± 4.6	27.7 ± 4.8	0.000
SBP (mmHg)	138 ± 19	133 ± 20	0.003
DBP (mmHg)	85 ± 10	83 ± 10	0.048
Fasting plasma glucose (mg/dl)	109 ± 21.9	106.1 ± 32.1	NS
Total cholesterol (mg/dl)	214 ± 41	201 ± 42	0.000
HDL cholesterol (mg/dl)	41 ± 9	44 ± 11	0.001
LDL cholesterol (mg/dl)	134 ± 40	130 ± 38	NS
Triglycerides (mg/dl)	191 ± 111	133 ± 74	0.000
Fibrinogen (mg/dl)	279.2 ± 78.2	277.6 ± 75.2	NS
White blood cells (×10 ³ /μl)	6.9 ± 1.6	6.4 ± 1.7	0.002
Platelets (×10 ³ /μl)	208.9 ± 49.3	212.2 ± 53.2	NS
Fasting insulin (μIU/ml)	11.2 ± 8.3	10.6 ± 10.9	NS
HOMA-IR	3.1 ± 2.6	2.9 ± 4	NS
C3 (mg/dl)	113.6 ± 29.4	104.1 ± 33.1	0.002
Creatinine (mg/dl)	1.1 ± 0.4	0.9 ± 0.2	0.000

Hyperuricemia as an independent risk factor for major cardiovascular events: a 10-year cohort study from Southern Italy

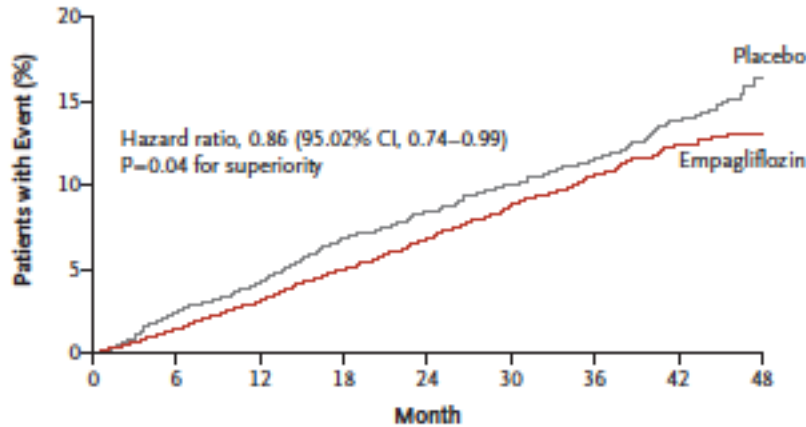
Vincenzo Capuano^a, Federica Marchese^b, Rocco Capuano^a, Sergio Torre^a, Anna G. Iannone^a, Eduardo Capuano^a, Norman Lamaida^b, Matteo Sonderegger^a and Ernesto Capuano^a

J Cardiovasc Med 2017, 18:159–164

- ✓ After the 10-year follow-up period, 135 out of 1175 patients reported at least one MACE, and the mean value of uric acid recorded at baseline in these patients was significantly higher than that in those without the presence of MACE (6.0 ± 4.8 and 4.6 ± 4.0 mg/dl, respectively; $P < 0.01$).
- ✓ Multivariate analysis adjusted for confounding variables showed that uric acid remained the independent variable ($\beta = 0.075$; $P = 0.04$).

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

A Primary Outcome

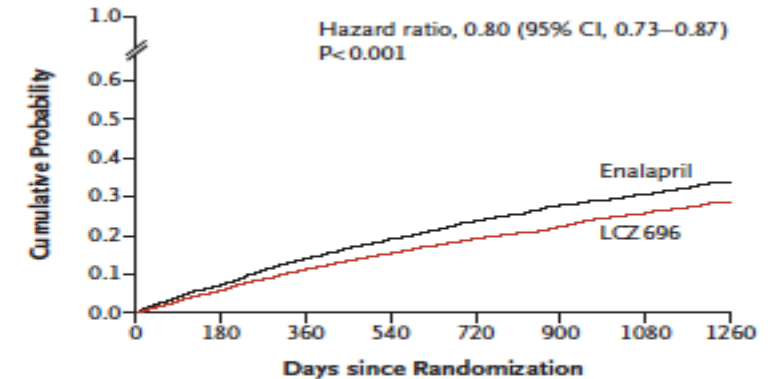


No. at Risk									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

that the mechanisms behind the cardiovascular benefits of empagliflozin are multidimensional²⁵ and possibly involve changes in arterial stiffness,^{26,27} cardiac function, and cardiac oxygen demand (in the absence of sympathetic-nerve activation),²⁶ as well as cardiorenal effects,^{21,26,28,29} reduction in albuminuria,^{20,30} reduction in uric acid,¹³⁻²⁰ and established effects on hyperglycemia, weight, visceral adiposity, and blood pressure.¹³⁻²⁰

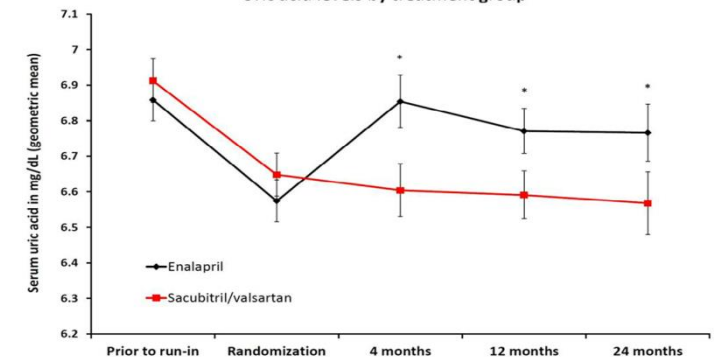
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

A Primary End Point

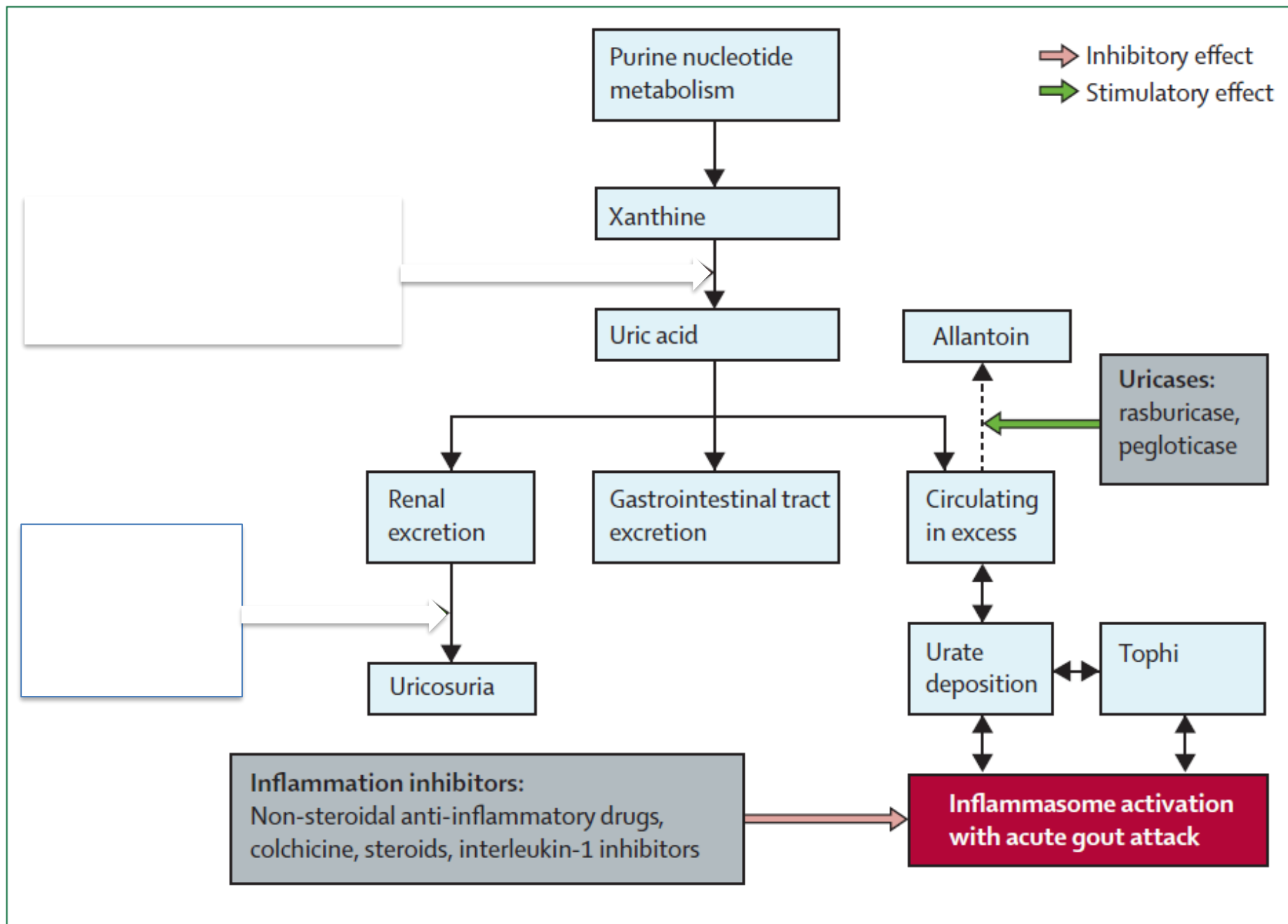


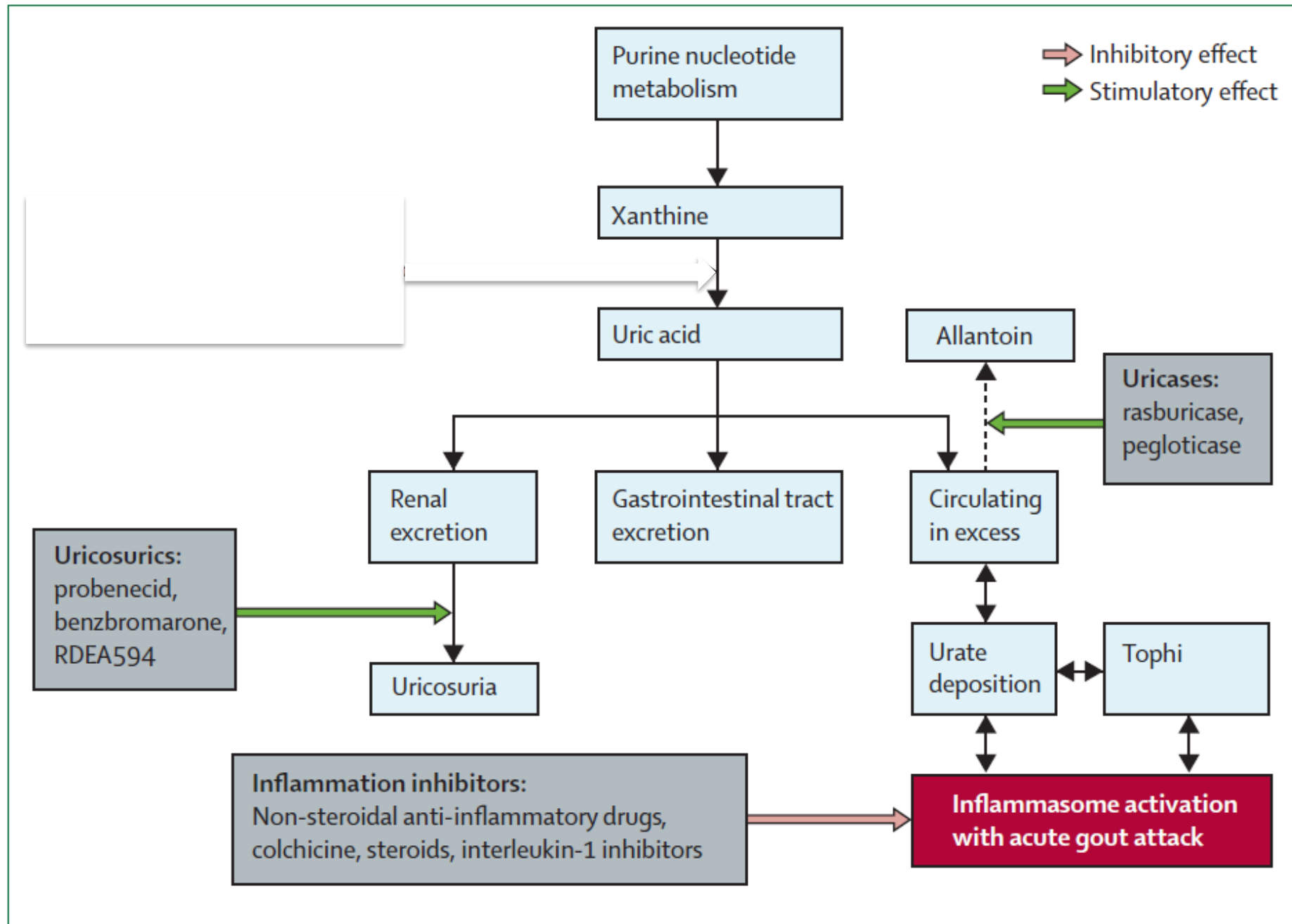
No. at Risk									
LCZ 696	4187	3922	3663	3018	2257	1544	896	249	
Enalapril	4212	3883	3579	2922	2123	1488	853	236	

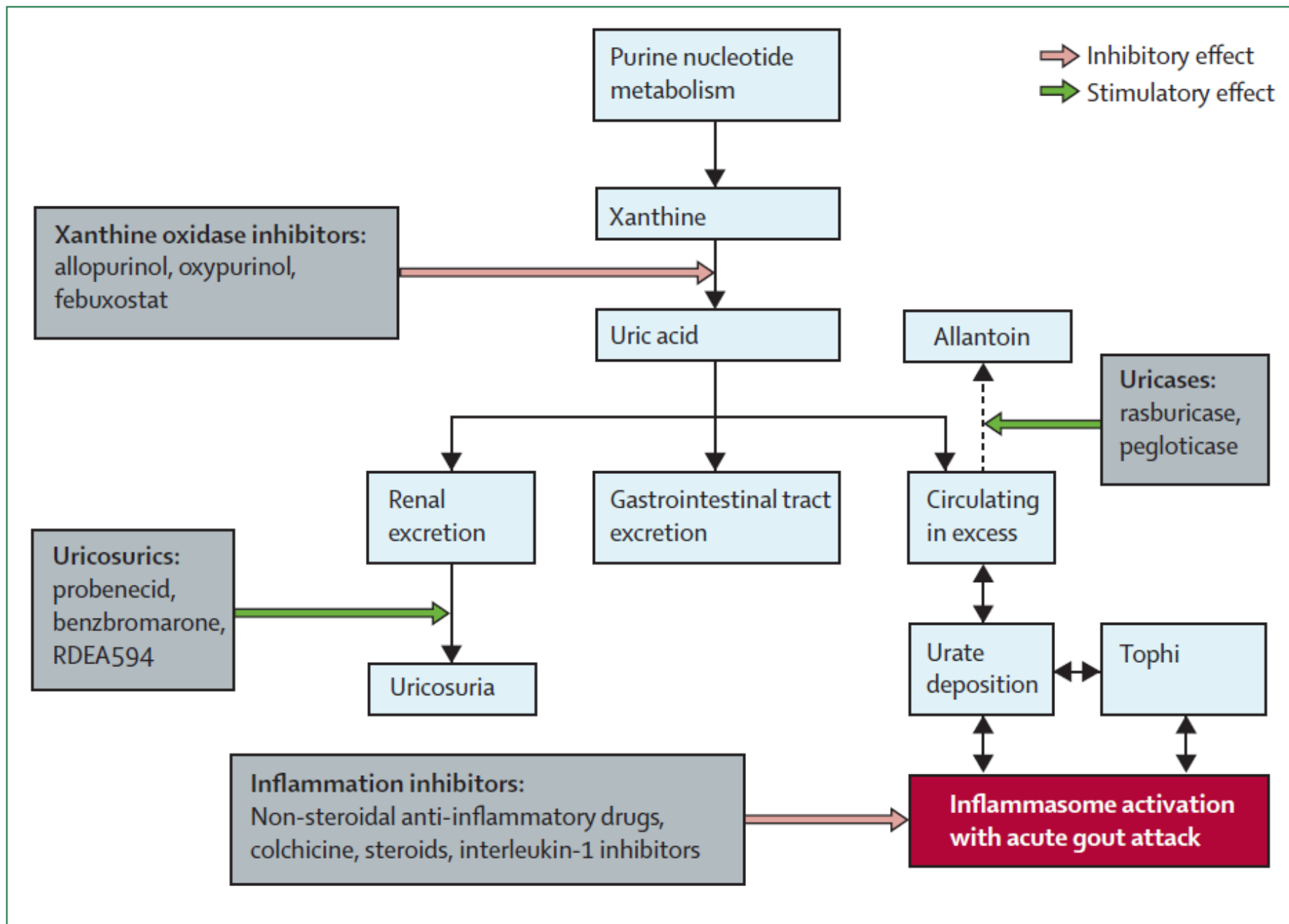
Uric acid levels by treatment group



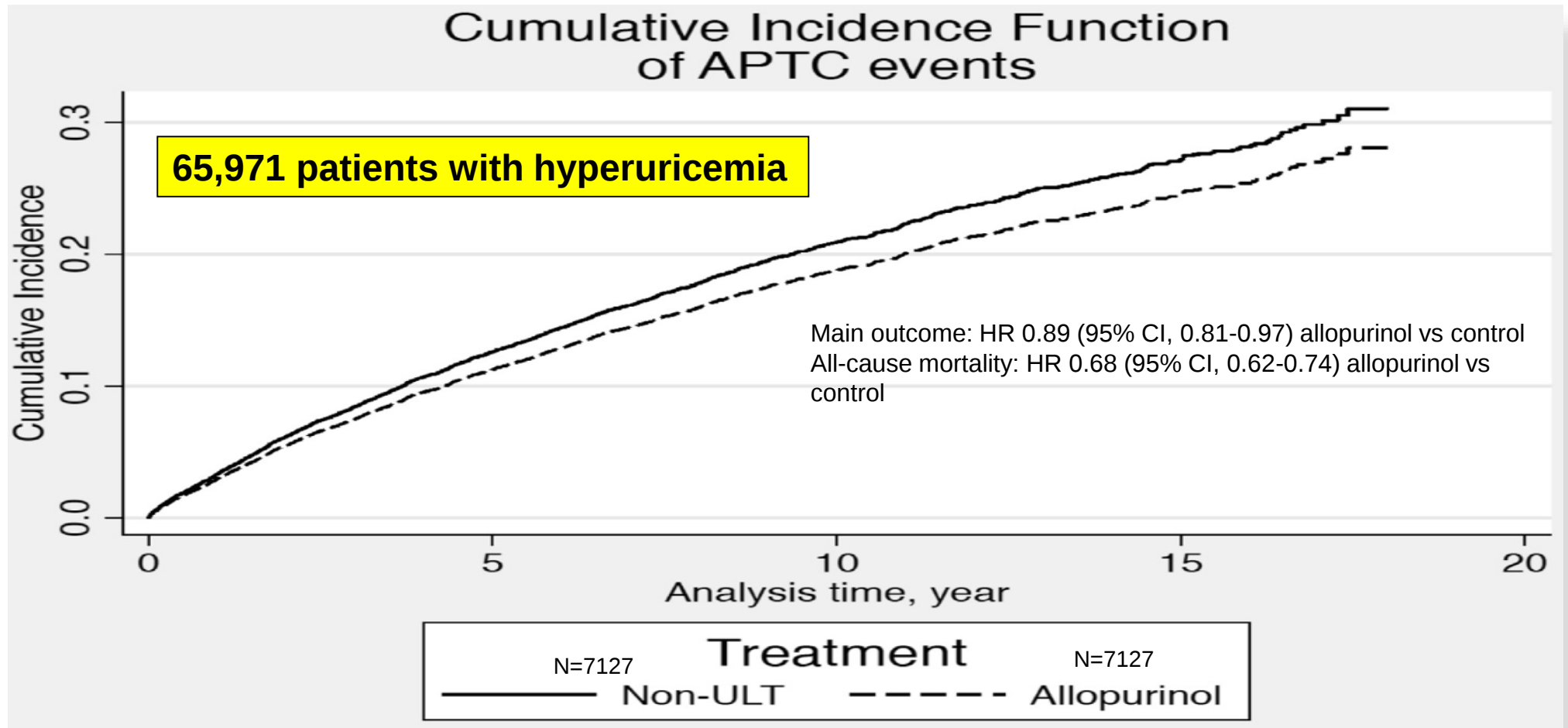
Acido urico e terapia ipouricemizzante







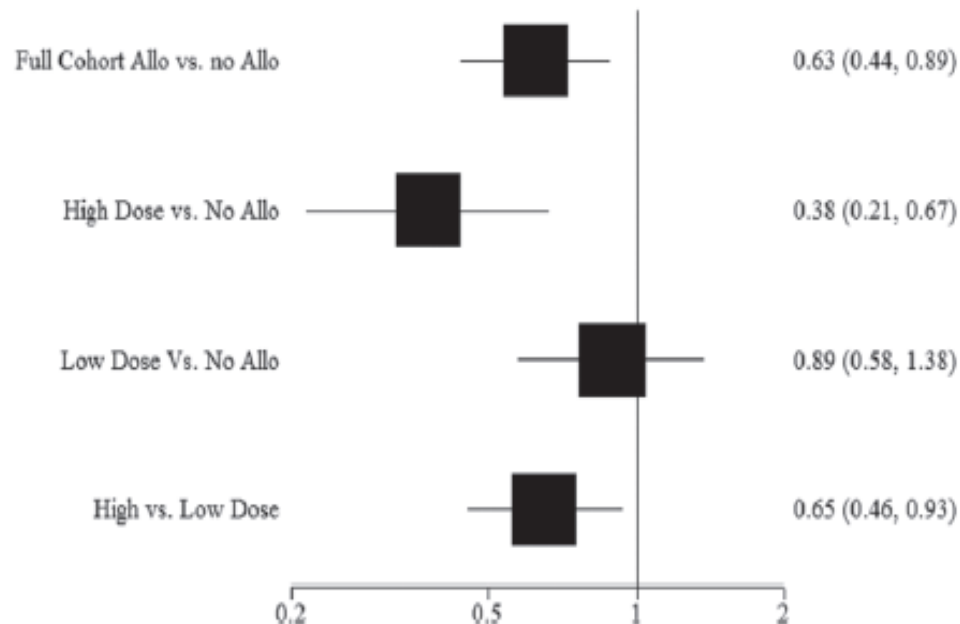
Effect of Allopurinol on Cardiovascular Outcomes in Hyperuricemic Patients: A (Danish) Cohort Study



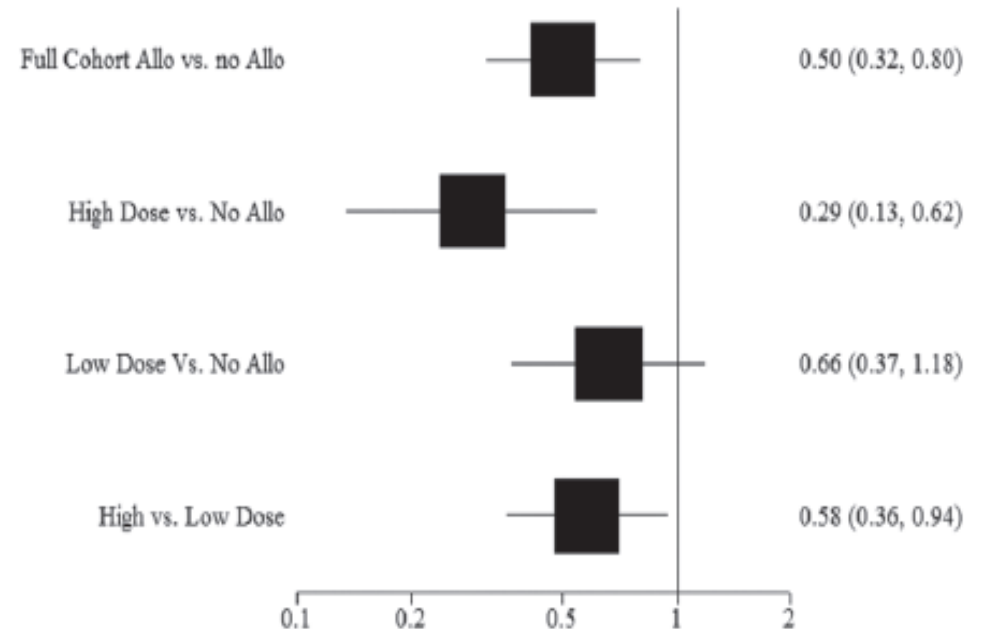
Allopurinol and Cardiovascular Outcomes in Adults With Hypertension

A total of 2032 allopurinol-exposed patients and 2032 matched nonexposed patients were studied: 10-year period

Risk of cardiac events



Risk of stroke

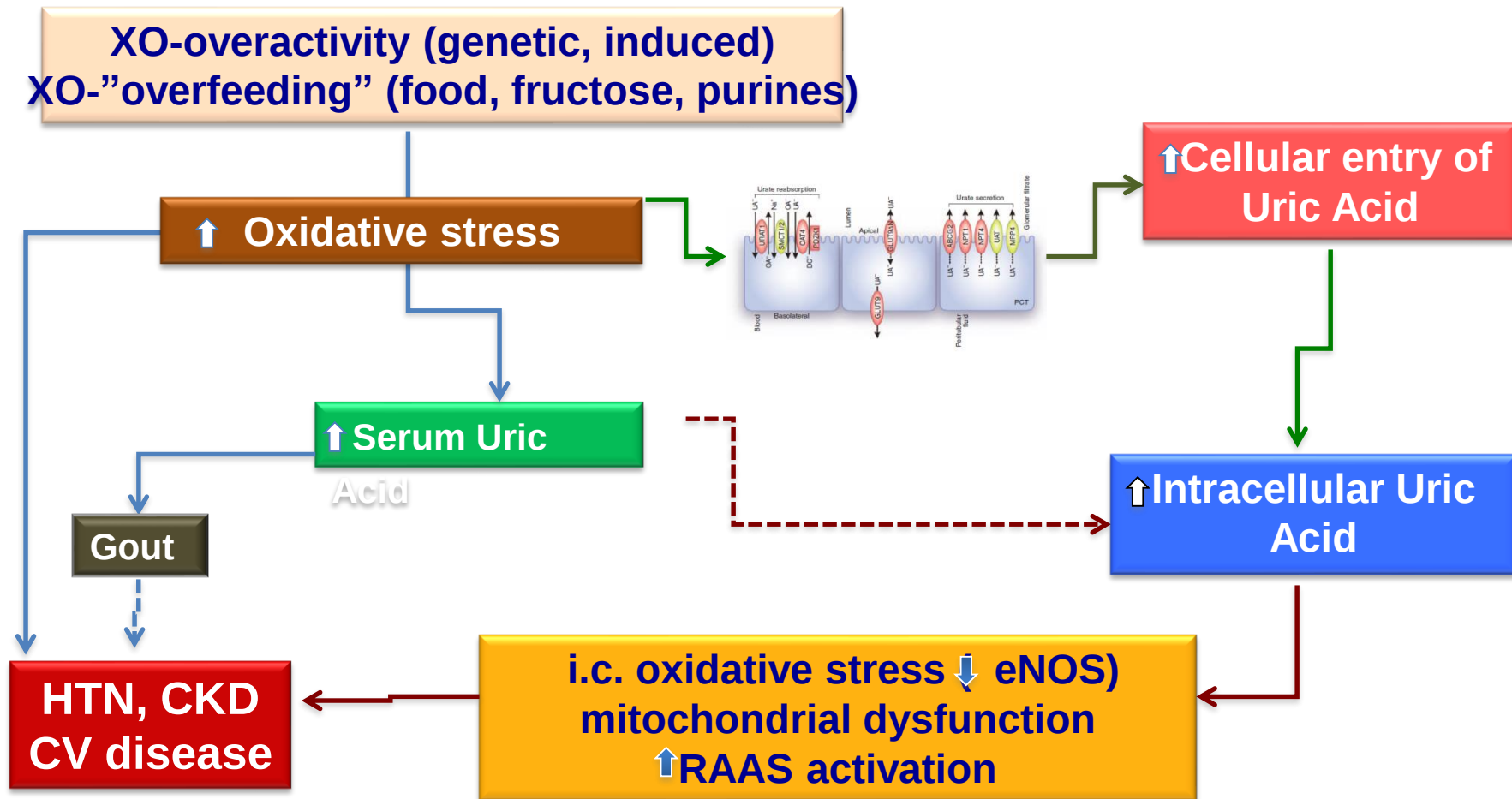


Xantine oxidasi inhibition – a novel therapy option in CVD ?

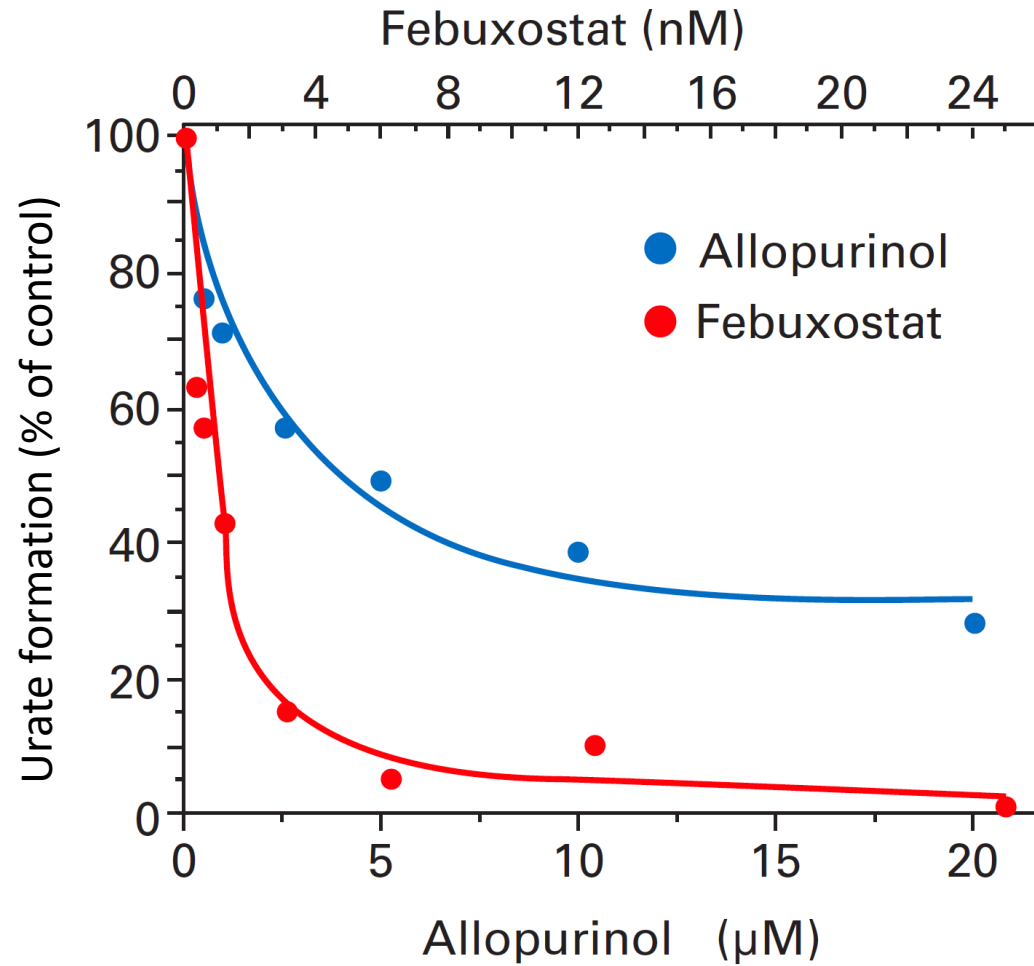
- ✓ The repeated positive results from proof of concept studies highlighted XO activity rather than UA as the true therapeutic target in HF
- ✓ By contrast, direct uric acid lowering without inhibition of xanthine oxidase failed to exert comparable beneficial effects as seen with XO inhibition

Urate-Lowering Drugs and Prevention of Cardiovascular Disease

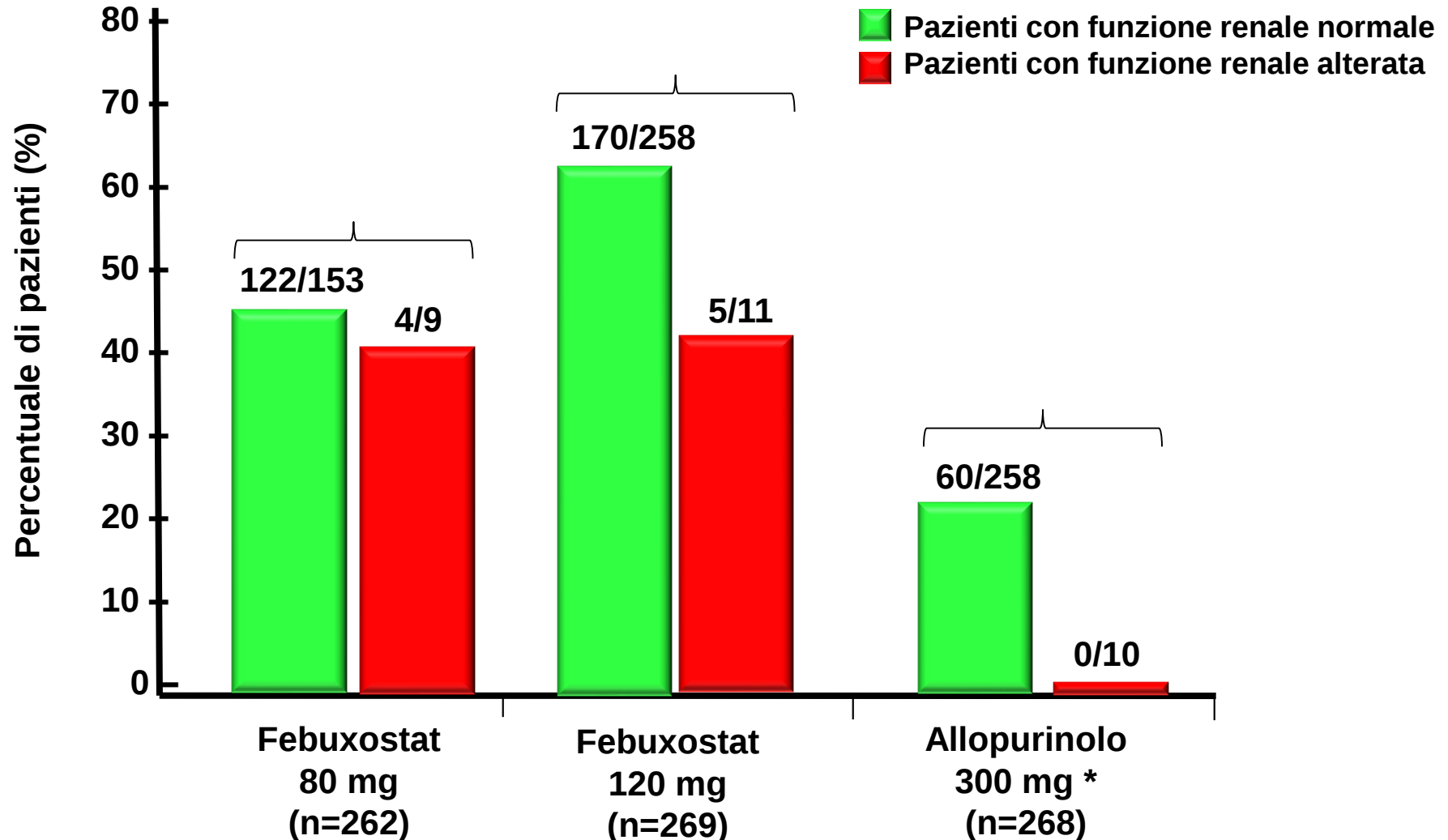
The Emerging Role of Xanthine Oxidase Inhibition



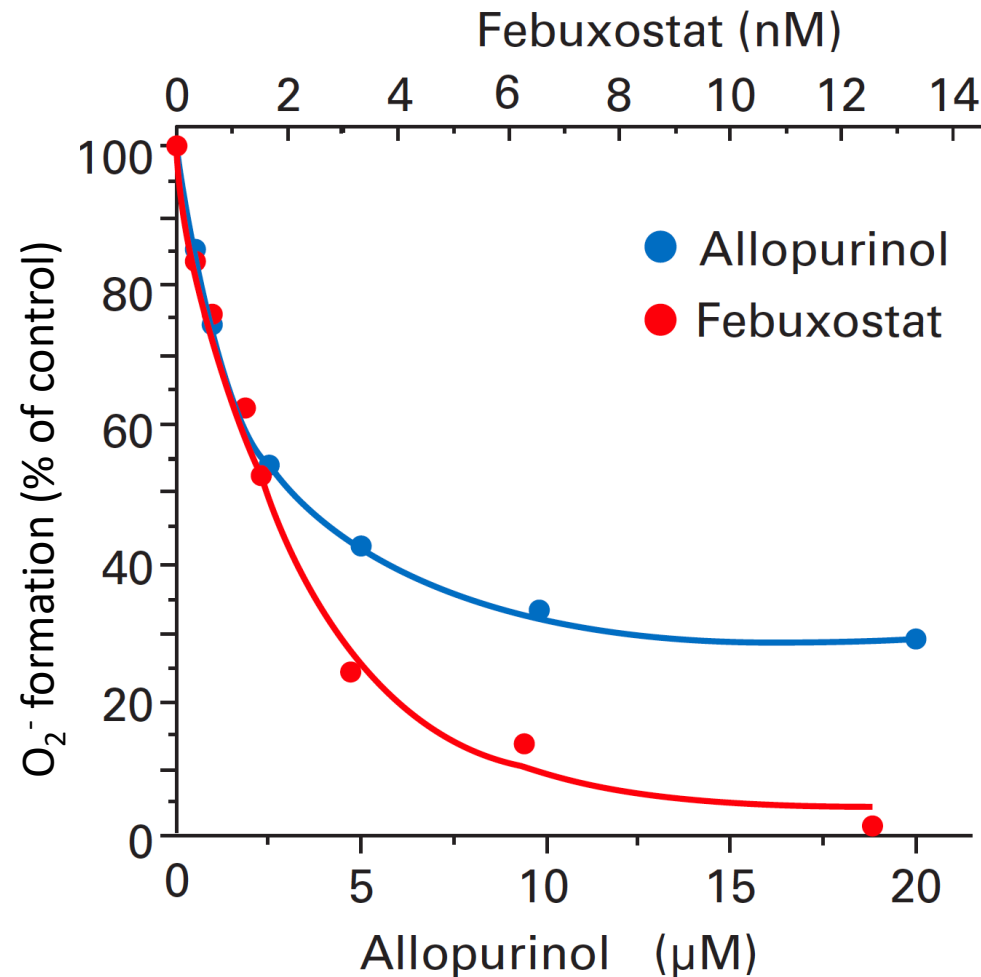
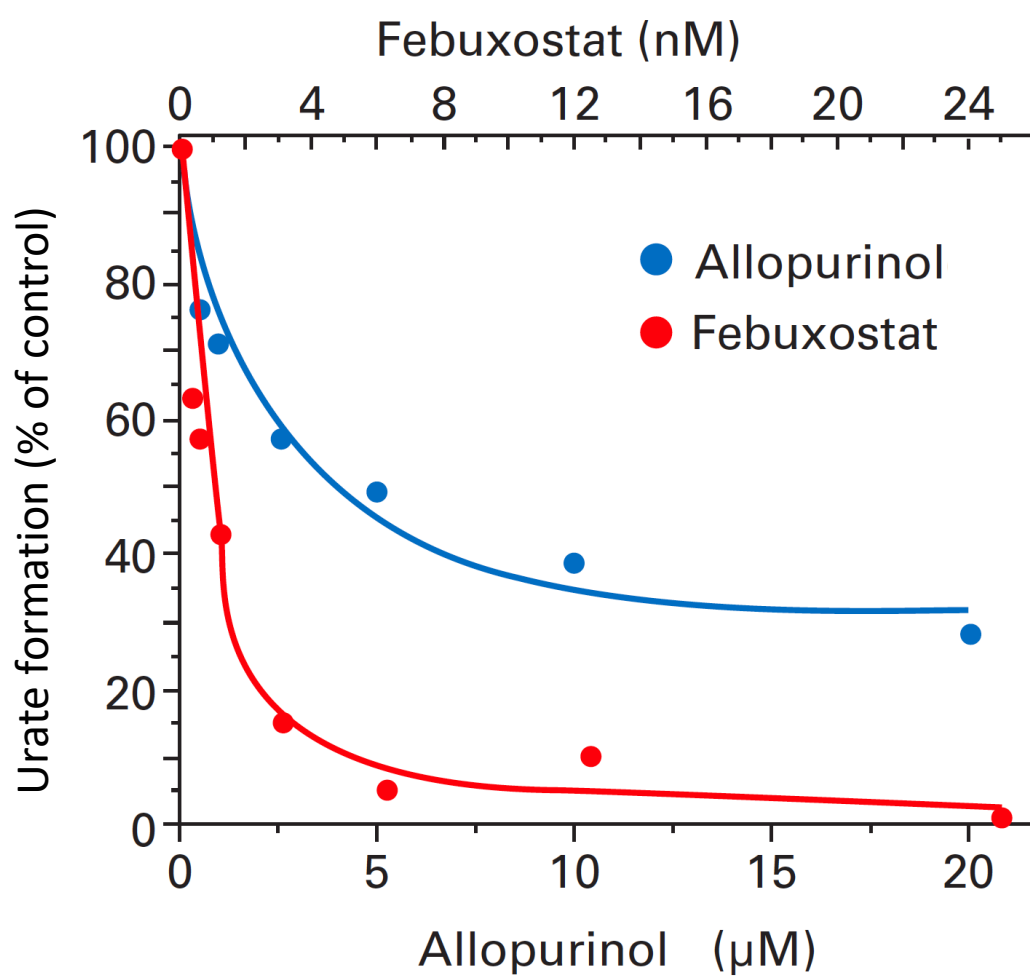
Febuxostat is more potent than allopurinol at inhibiting XO free in solution



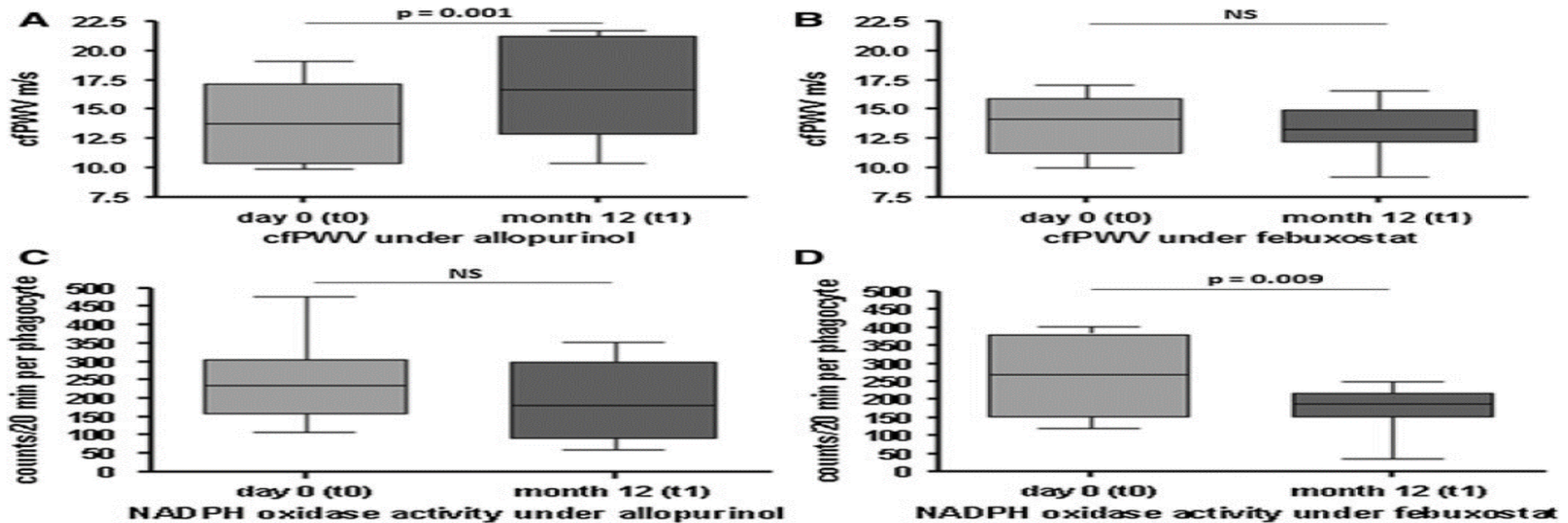
Acido urico e gotta: febuxostat vs allopurinolo. Studio CONFIRMS



Febuxostat is more potent than allopurinol at inhibiting XO free in solution



Urate-lowering therapy with febuxostat has superior effects on oxidative stress and pulse wave velocity in patients with severe chronic gout



Changes in PWV and oxidative stress in patients with gout treated with Allopurinol or Febuxostat

Take home message

- ✓ La riduzione della iperuricemia ha effetti clinici favorevoli che coinvolgono la prevenzione cardiovascolare
- ✓ Evidenze meccanicistiche identificano nella inibizione della XO la strategia più efficace per la riduzione della iperuricemia
- ✓ La selettività della inibizione della XO può giocare un ruolo primario nella gestione della iperuricemia in aggiunta e al di là degli effetti sulla uricemia

