

Il continuum cardio-nefrometabolico

La gestione del rischio cardio-nefro- metabolico: focus su acido urico e terapia con statine

Giovambattista Desideri

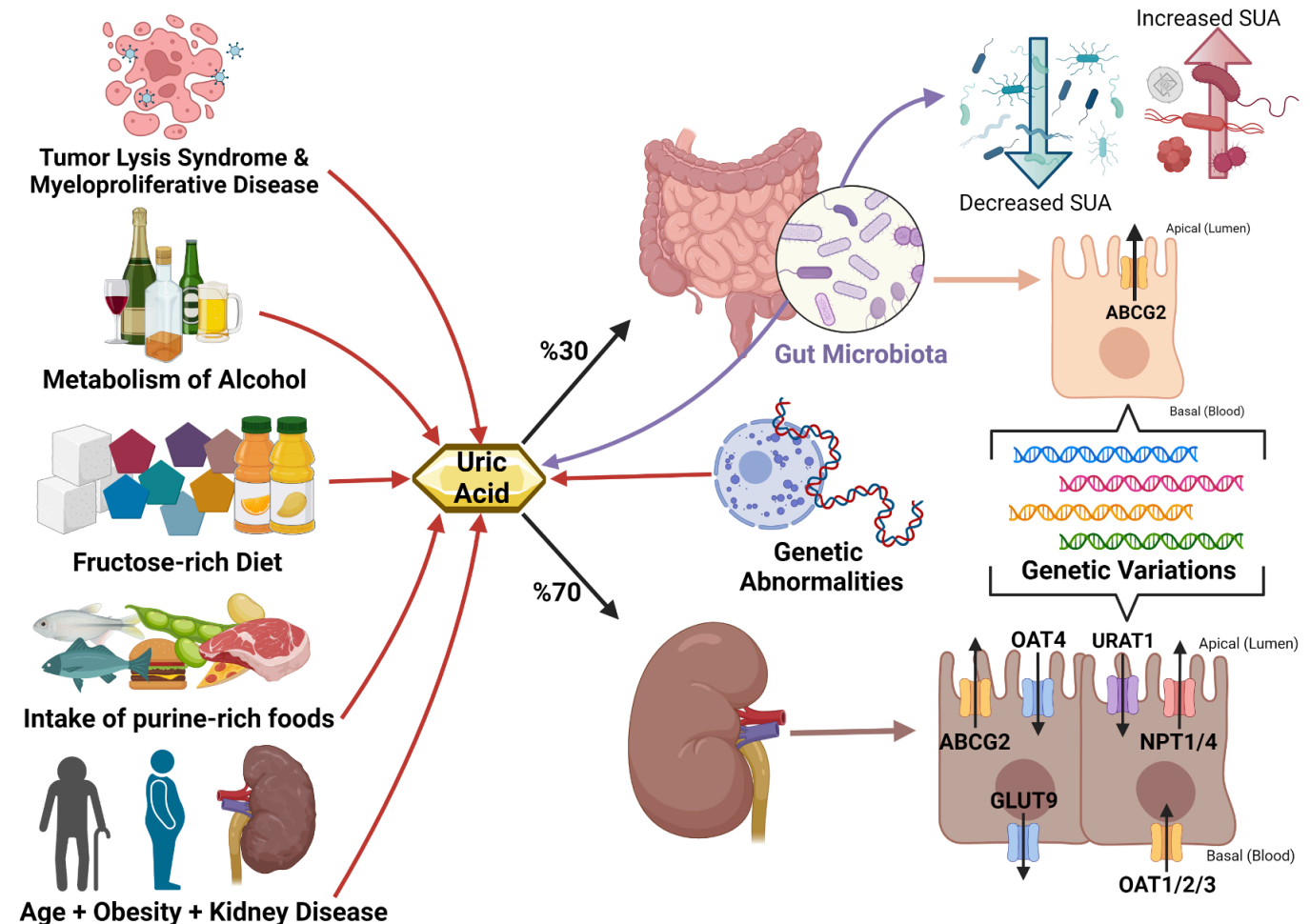


Introduction to the metabolic syndrome

Alberti G. *Eur Heart J (suppl)* 2005

The field moved forward significantly following the 1988 Banting Lecture given by Gerry Reaven.⁴ He described 'a cluster of risk factors for diabetes and cardiovascular disease' and named it 'Syndrome X'. His main contribution was the introduction of the concept of insulin resistance.

In 1989, Kaplan⁵ renamed the syndrome 'The Deadly Quartet' and in 1992 it was again renamed 'The Insulin Resistance Syndrome'.⁶ It is now agreed that the well-established term 'metabolic syndrome' remains the most usual description of this cluster of metabolic abnormalities.



Copur S et al. *Eur J Intern Med* 103 (2022) 4–12

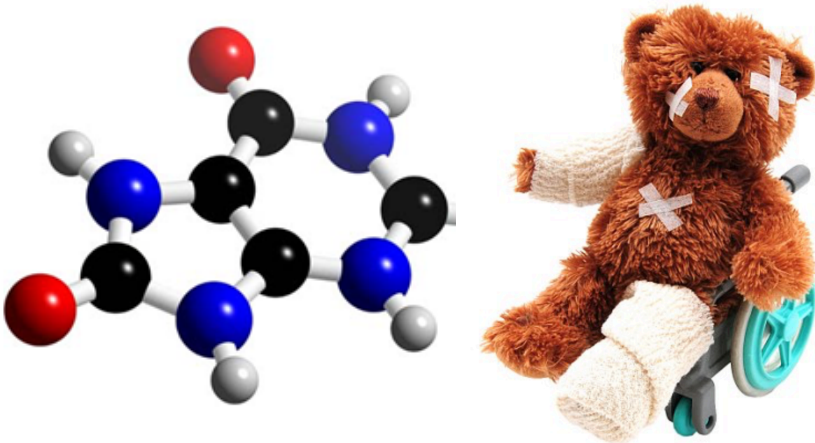
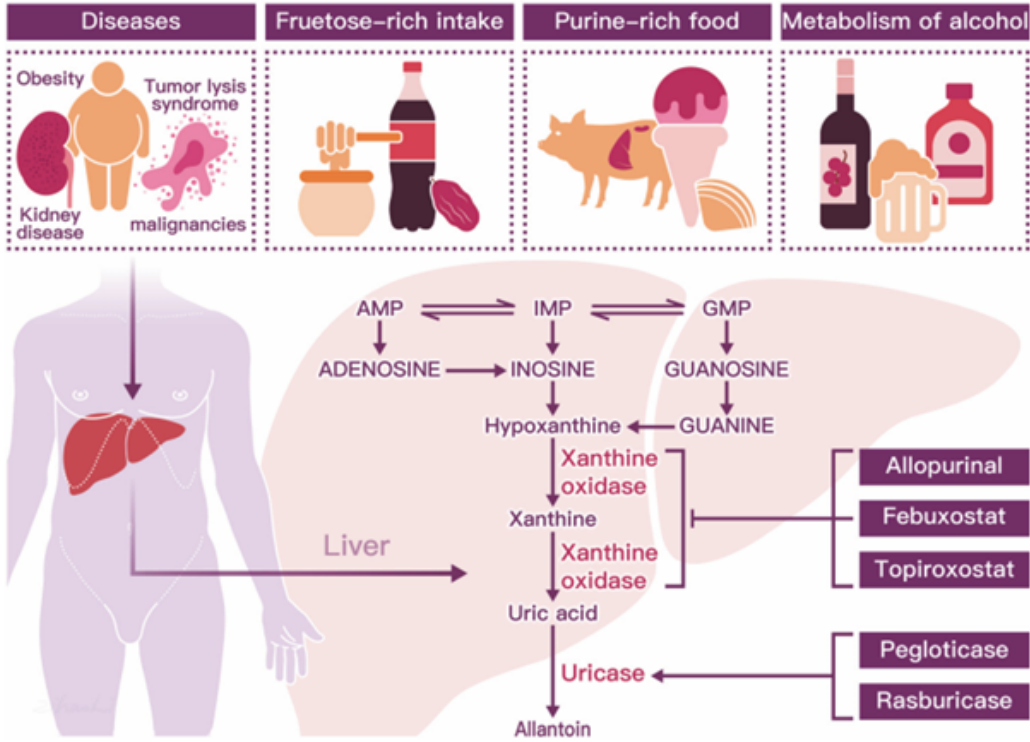
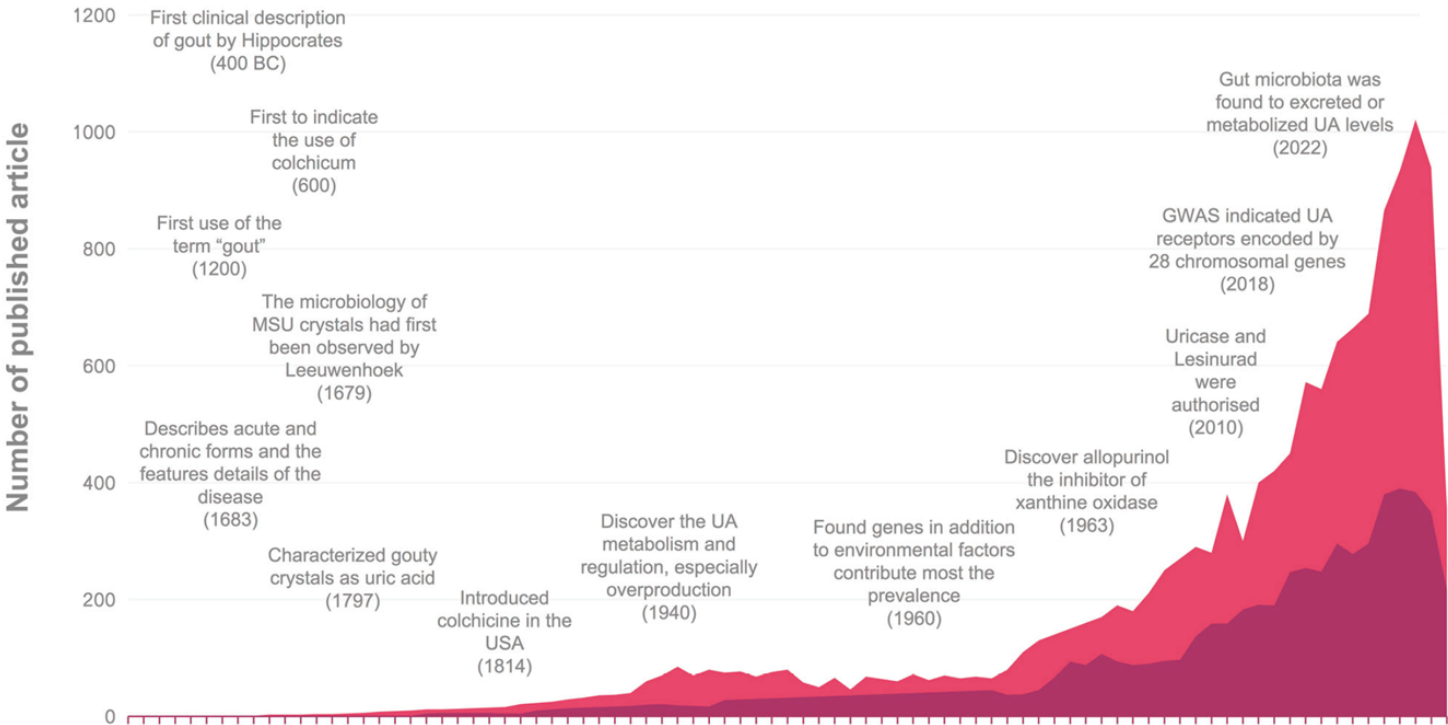


REVIEW ARTICLE OPEN

Hyperuricemia and its related diseases: mechanisms and advances in therapy

Lin Du^{1,2}, Yao Zong³, Haorui Li^{1,2}, Qiyue Wang^{1,2}, Lei Xie^{1,2}, Bo Yang^{1,2}, Yidan Pang⁴, Changqing Zhang⁴, Zhigang Zhong^{1,2} and Junjie Gao^{1,2,4}

Growth and Timescale of Hyperuricemia



SUA and drug treatment: what else?

DAPA-HF

Doherty KF et al, AHA 2021

PARADIGM-HF Study

Mogensen UM et al, Eur J Heart Fail 2017

SOCRATES-Reduced

Kramer F et al, Eur J Heart Fail 2020

LIFE Study/RENAAL Study

Hoiegggen A et al, Kindney Int, 2004

EMPAREG Study

Inzucchi S et al, Diab Care 2018

EMPEROR-PRESERVED Study

Anker S et al, New Engl J Med 2021

What they have in common?

Significant Improvement in clinical outcome

Significant decrease in S.Uric Acid

Poisoned by URIC ACID

URODONAL

has acquired a world-wide reputation. Thousands of doctors in all countries have prescribed this preparation, recognised by them as highly efficacious. Many scientific works and communications to learned societies testify to the great value of this now standard remedy. Analyses prove that Urodonal drains uric acid from the system, being thirty-seven times more active than lithia; this is why doctors prescribe it with confidence, sure of the mathematical results which it cannot fail to give them in all uricemic affections where the poison, URIC ACID, must be **eliminated from the organism**. No other dissolvent can be compared with Urodonal. It has the inestimable advantage of presenting no drawbacks of any kind, and is harmless and agreeable.

There are no toxic effects, no fatigue of the stomach, the kidneys, the heart or the brain, even with large doses.

Urodonal cleans the Kidneys, washes the liver, relieves stiff joints, and, by dissolving uric acid, assists nutrition and imparts vitality to the tissues.

Tortured by Pain

The Best and Only Cure for
RHEUMATISM. GOUT.
GRAVEL. CALCULI.
NEURALGIA.
SICK HEADACHE.
ARTERIO-SCLEROSIS.
SCIATICA. OBESITY.

He can only be relieved by

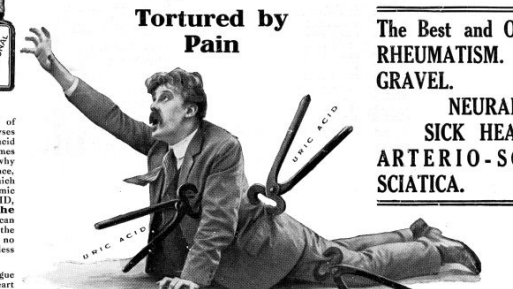
URODONAL

The One True Solvent for Uric Acid.

PREPARED AT CHATELAIN'S LABORATORIES, 2, RUE DE VALENCIENNES, PARIS.
British & Colonial Agents: **HEPPELL & CO., FOREIGN CHEMISTS, 164, PICCADILLY, W.**

A Full Explanatory Booklet on URODONAL, giving Doctors' Opinions, Report from the "Lancet" of its safety, and interesting points on how to maintain health, sent post free on application to the Agents—**HEPPELL & CO.**

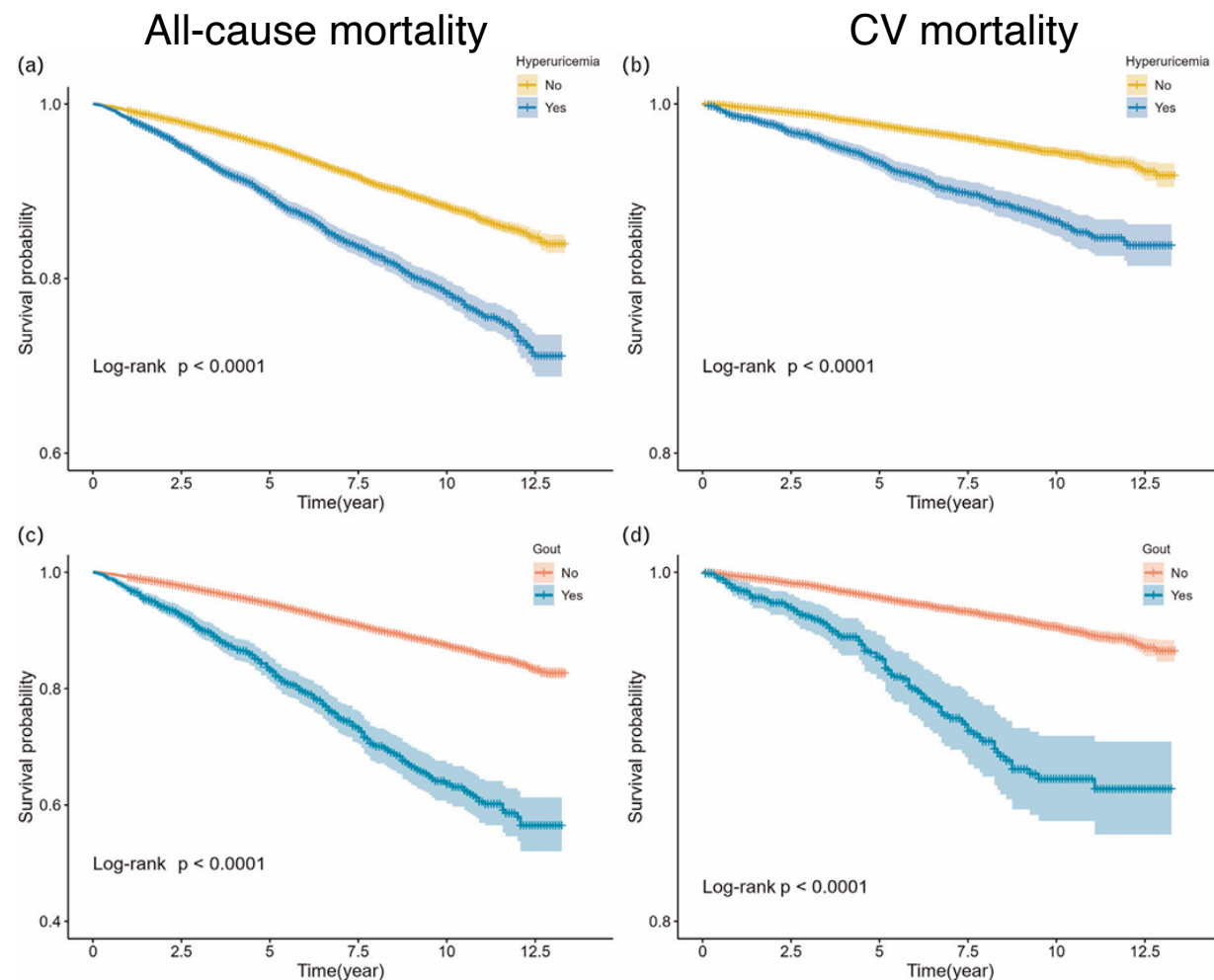
OF ALL CHEMISTS **6/-** or post free from **HEPPELL & CO.** Foreign Chemists, 164, Piccadilly, W.





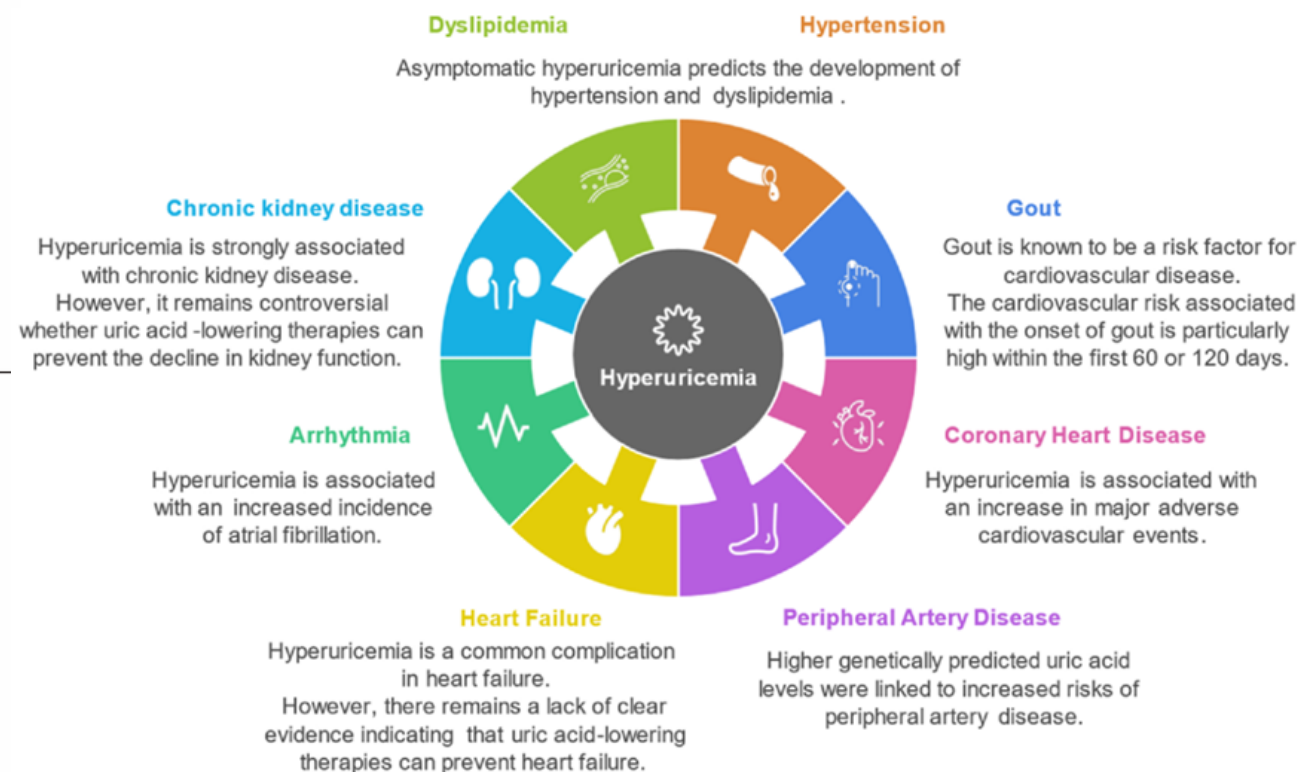
Hyperuricemia and gout enhanced the risk of long-term mortality in hypertension: insights from the National Health and Nutrition Examination Survey 2007–2018

Jinhang Che^{a,*}, Jin Tong^{b,*}, Xue Kuang^a, Caiyin Zheng^a, Na He^a, and Zengzhang Liu^a



Hyperuricemia, A new cardiovascular risk

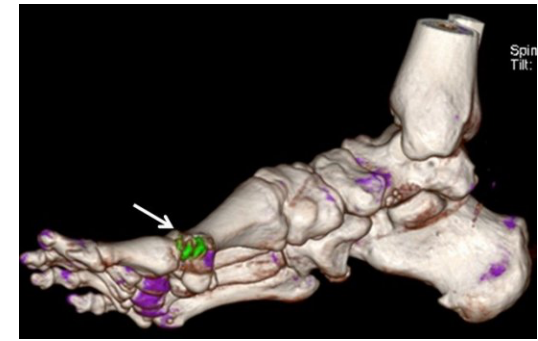
Masanari Kuwabara^{a,b,c,*}, Ichiro Hisatome^c, Ryusuke Ae^a, Koki Kosami^a, Yuhei Aoki^d, Ana Andres-Hernando^e, Mehmet Kanbay^f, Miguel A. Lanaspa^e



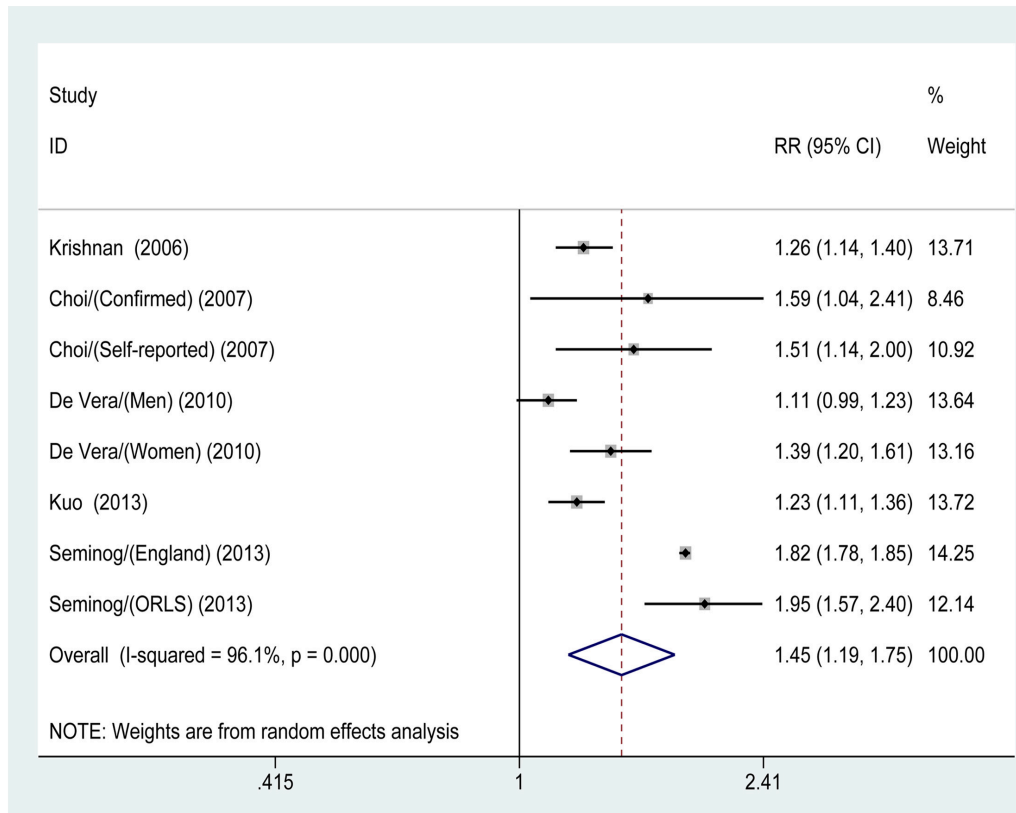




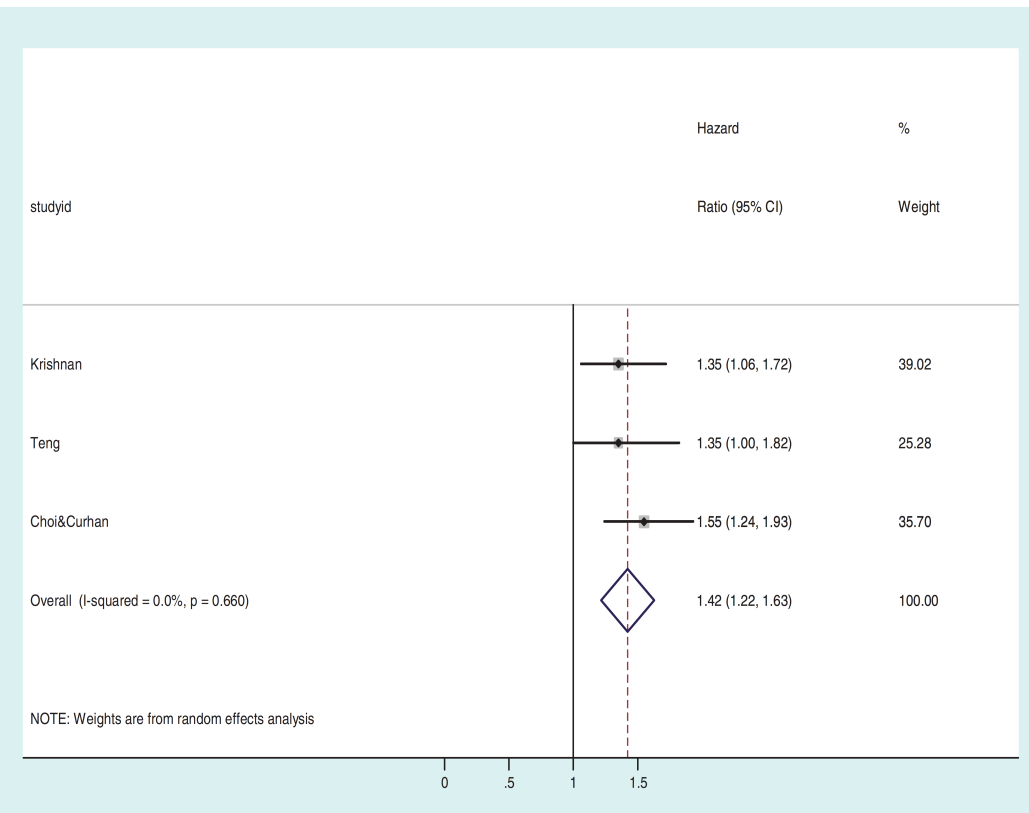
Gout is associated with increased risk for cardiovascular events



Gout and Risk of Myocardial Infarction¹



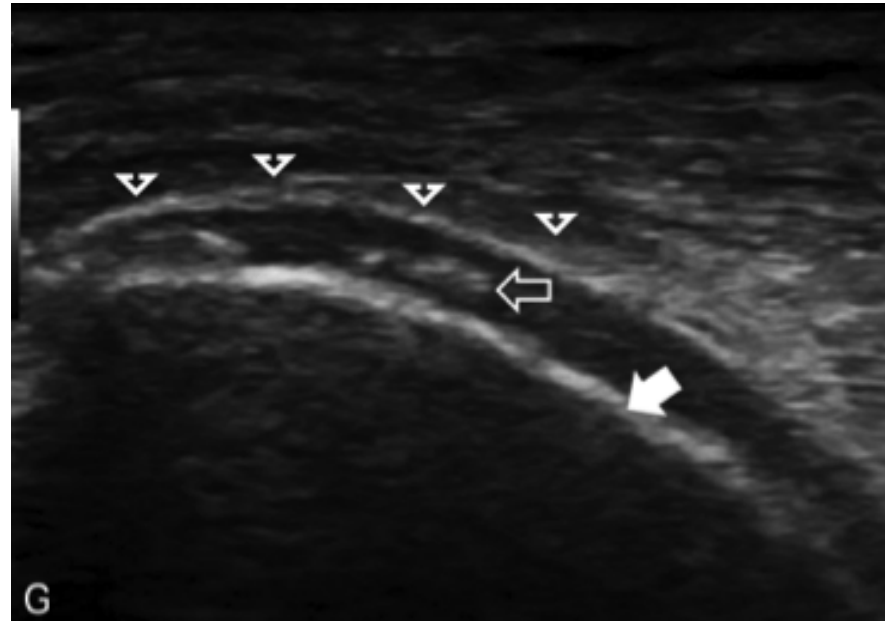
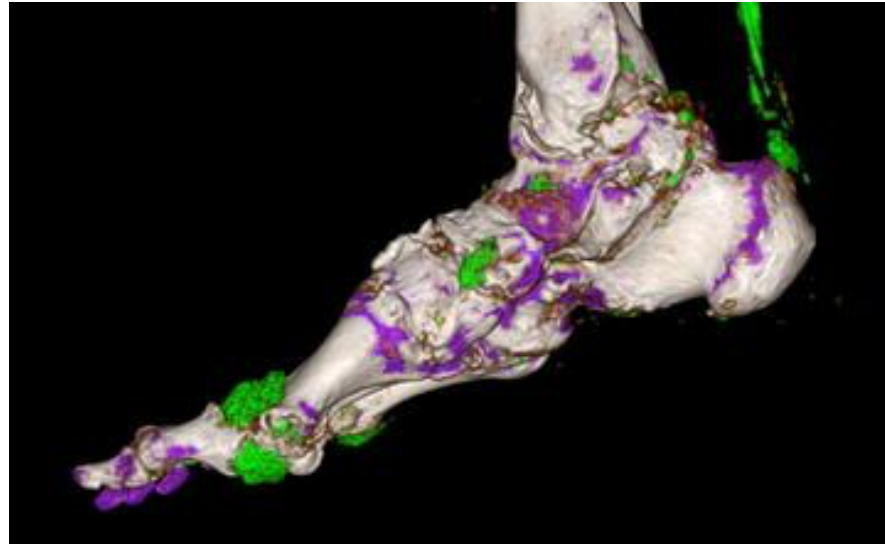
Gout and Mortality for CHD²



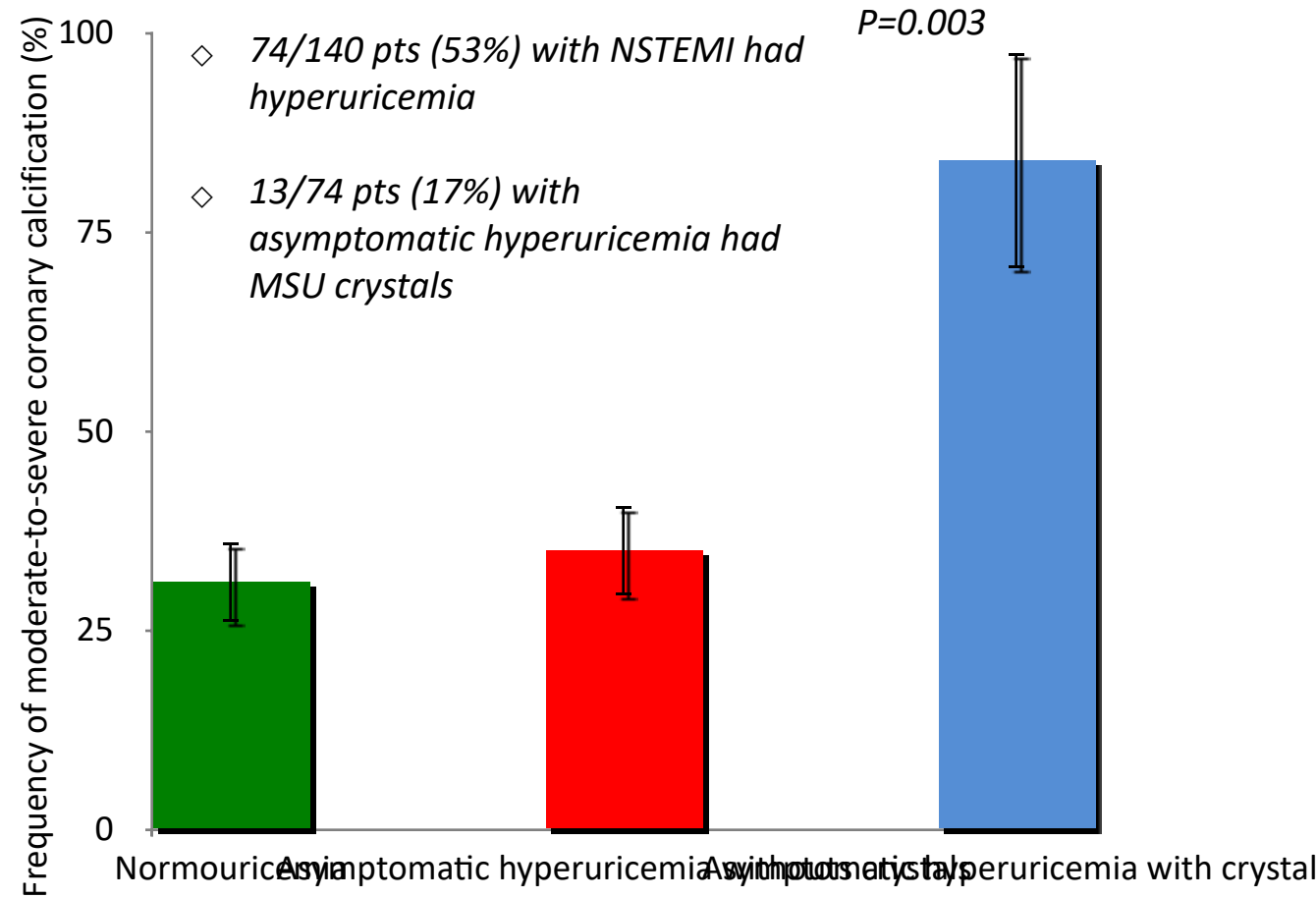
¹Liu SC et al. PLoS One. 2015 Jul 31;10(7):e0134088. d

²Clarson LE et al. European Journal of Preventive Cardiology 2015, Vol. 22(3) 335-343

Subclinical Gout and Cardiovascular Disease

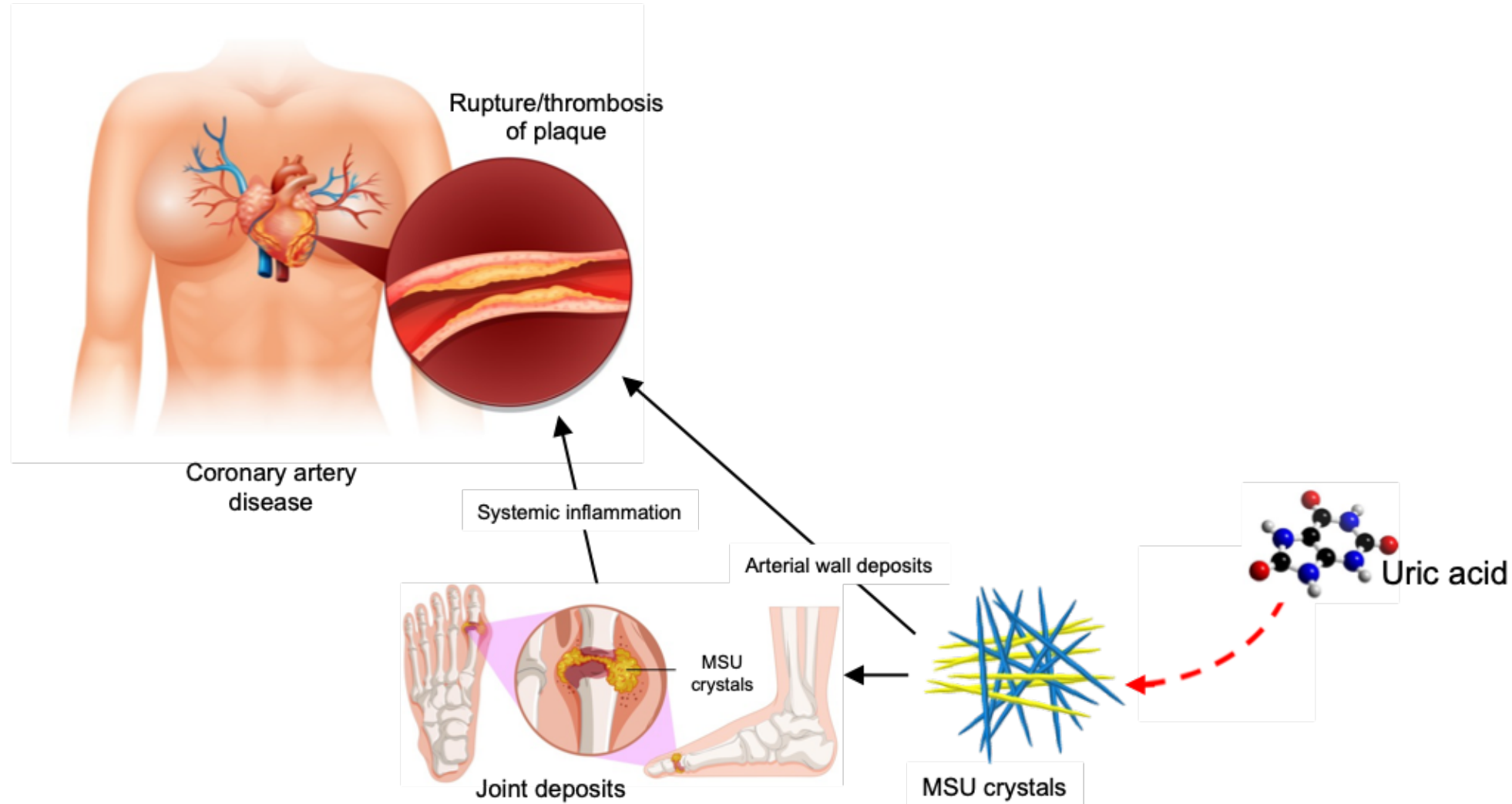


Silent MSU Crystal Deposits Are Associated
With Severe Coronary Calcification in
Asymptomatic Hyperuricemia (SUA >7 mg/dL)



Xanthine oxidase inhibition and cardiovascular protection: Don't shoot in the dark

Desideri G, Borghi C. Eur J Int Med 2023 (in press)



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

**Main determinants
of hyperuricemia**

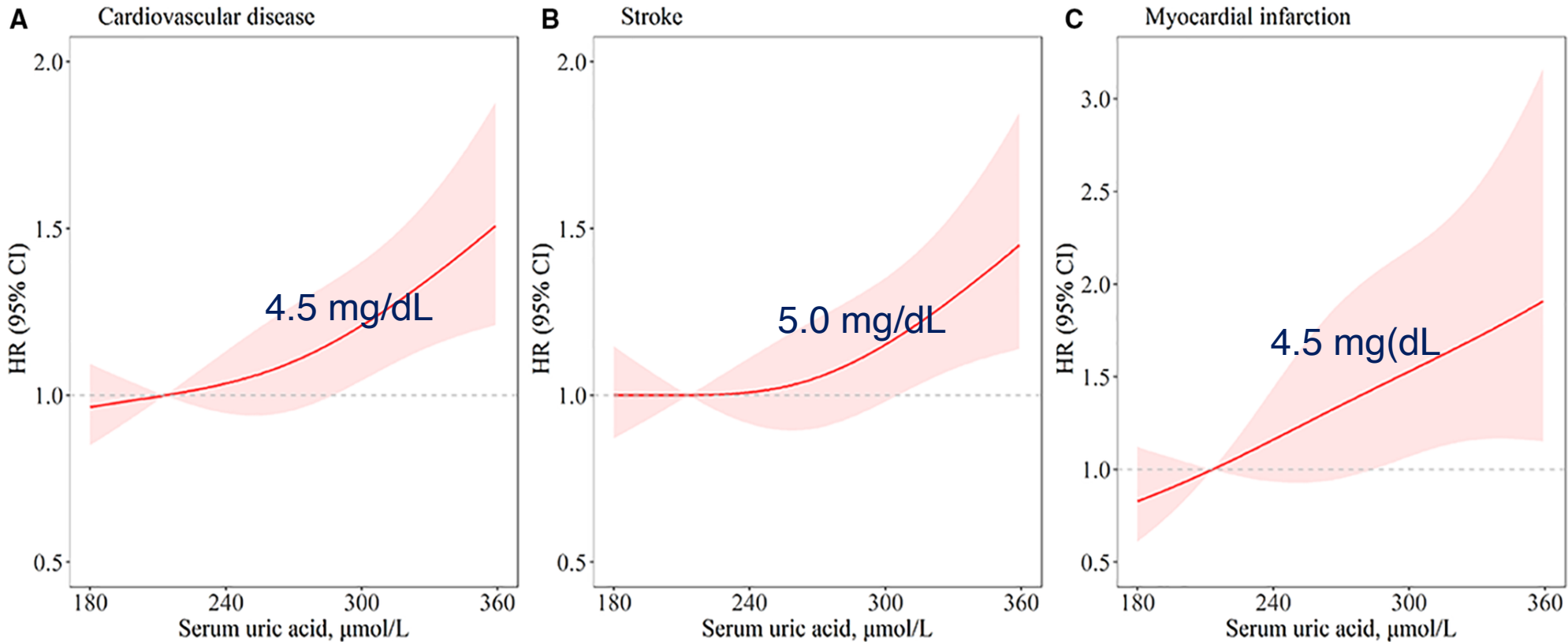
Impaired renal
handling (genetic,
chronic kidney
disease, diuretics)

ORIGINAL RESEARCH

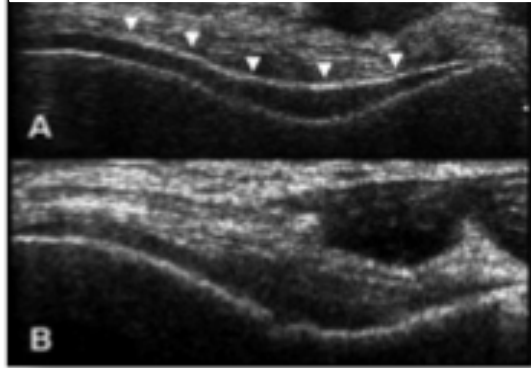
Association of Normal Serum Uric Acid Level and Cardiovascular Disease in People Without Risk Factors for Cardiac Diseases in China

Xue Tian, PhD; Penglian Wang, MD; Shuohua Chen, MD; Yijun Zhang, PhD; Xiaoli Zhang, BS; Qin Xu, PhD; Yanxia Luo, PhD; Shouling Wu, MD; Anxin Wang, PhD

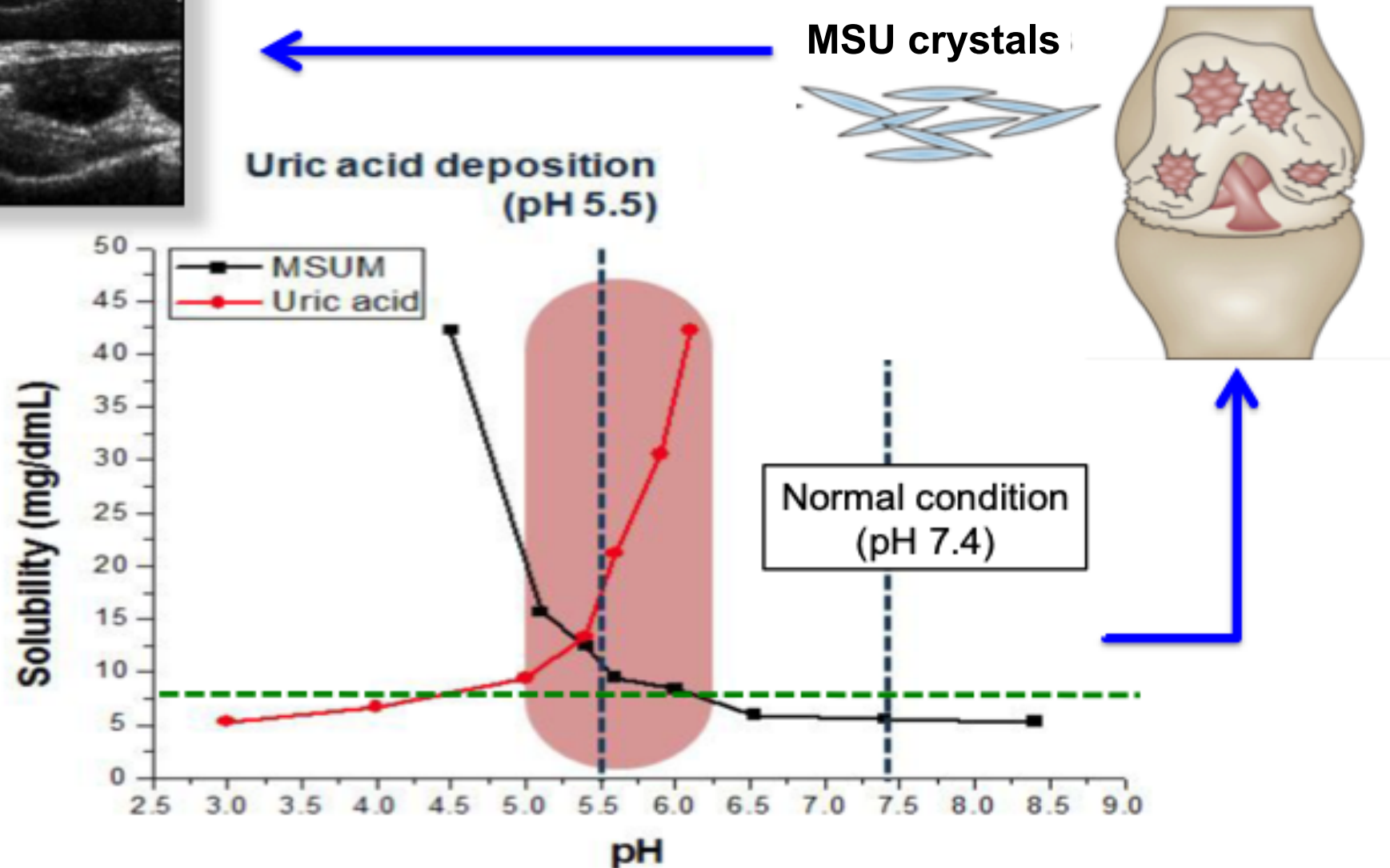
Serum Uric Acid Level and Cardiovascular Disease in People Without Risk Factors for Cardiac Diseases in China



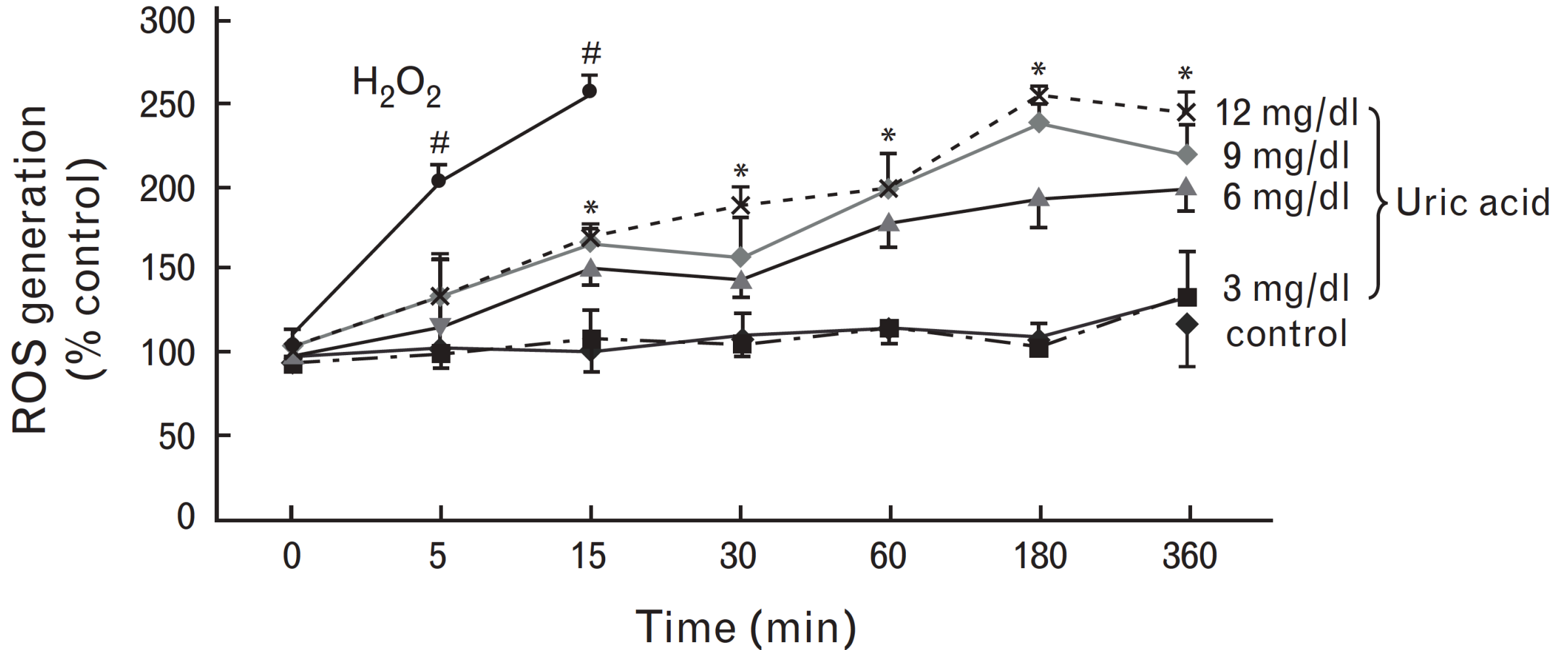
The pH-solubility relationships of uric acid and MSUM



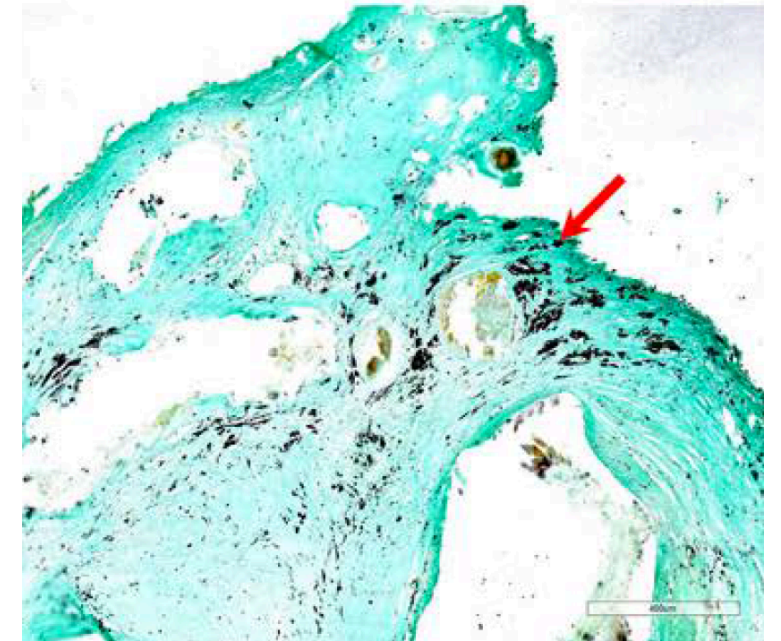
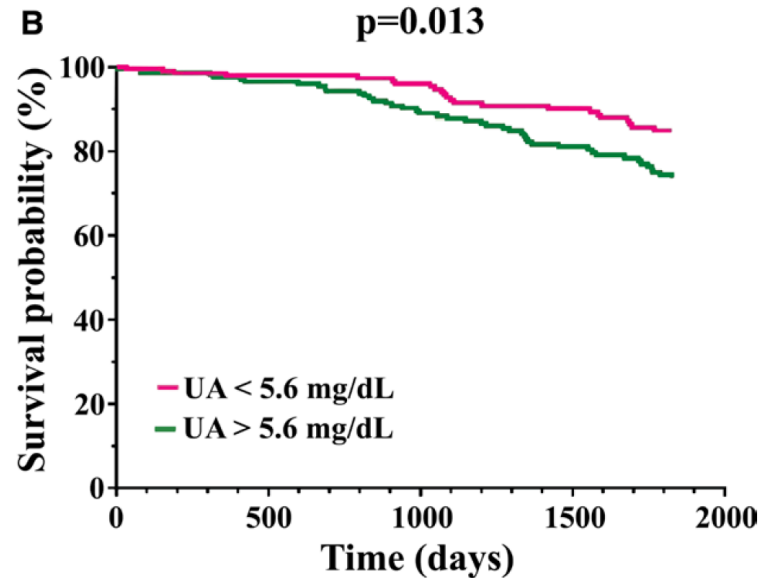
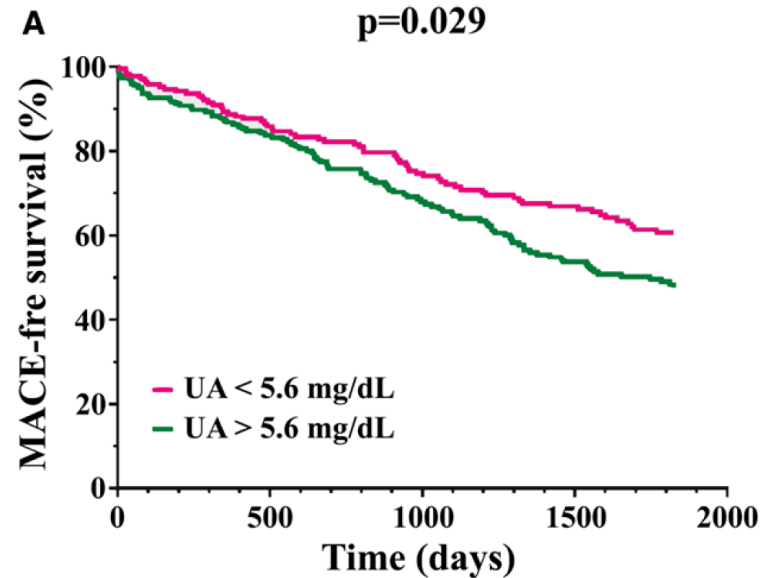
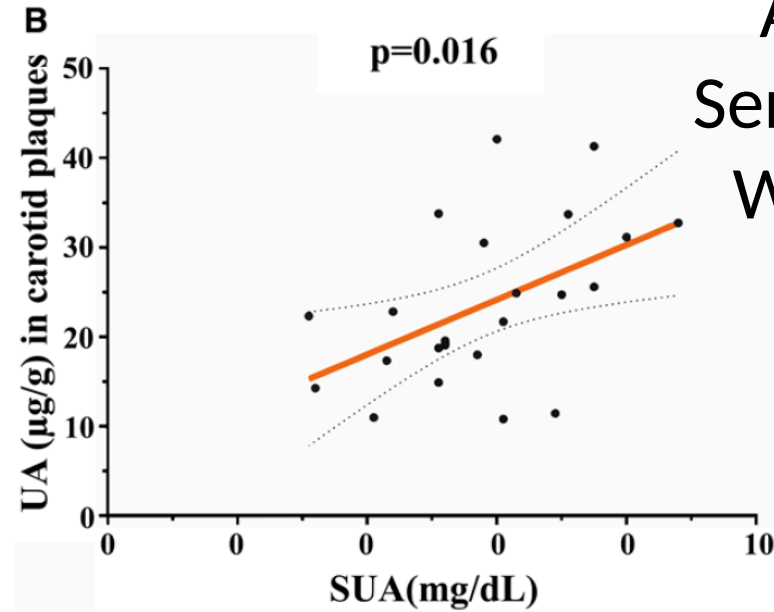
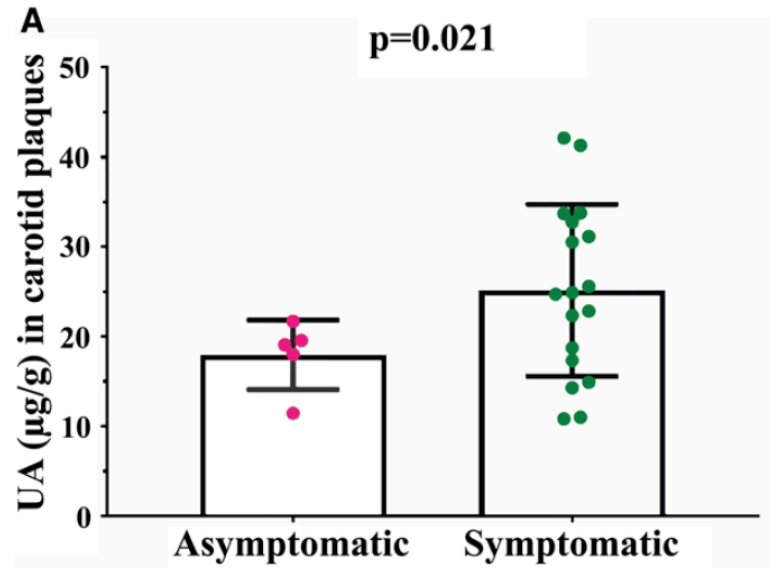
In normal condition (37°C, aqueous solution, pH 7.4) the solubility limit of MSU is reached when the urate concentration is about 6.4 mg/dL (384 μ mol/L)



Effect of uric acid on ROS generation in human umbilical vein endothelial cells.

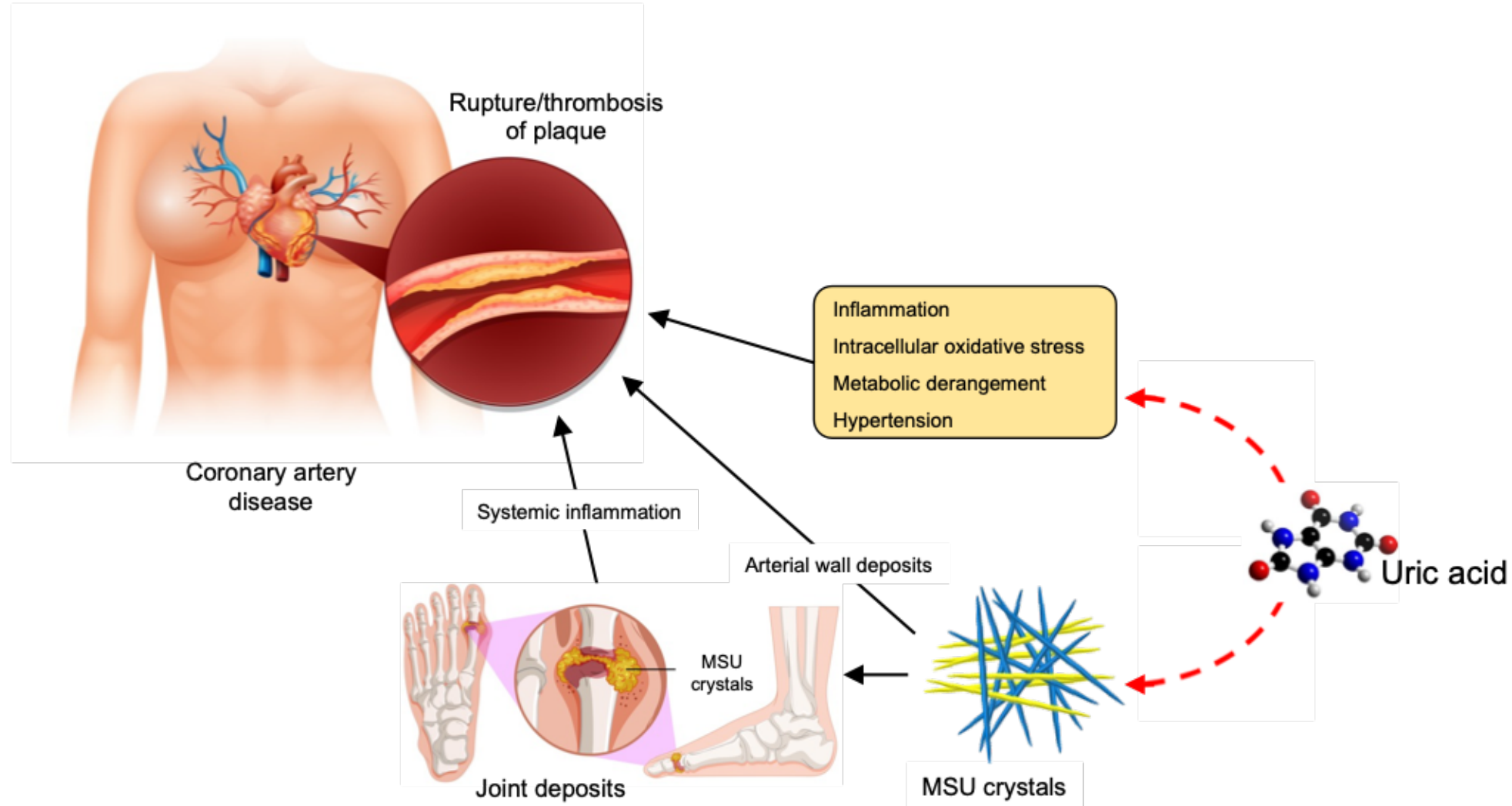


Uric Acid Expression in Carotid Atherosclerotic Plaque and Serum Uric Acid Are Associated With Cerebrovascular Events



Xanthine oxidase inhibition and cardiovascular protection: Don't shoot in the dark

Desideri G, Borghi C. Eur J Int Med 2023 (in press)

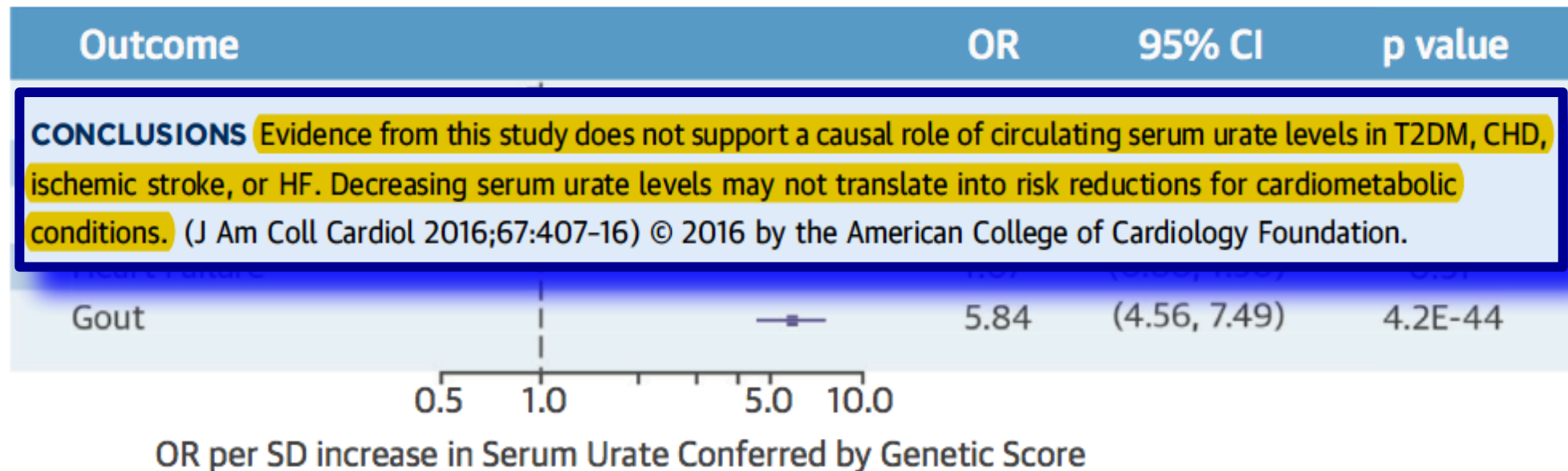


Causal Assessment of Serum Urate Levels in Cardiometabolic Diseases Through a Mendelian Randomization Study

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ISSN 0735-1097/\$36.00
<http://dx.doi.org/10.1016/j.jacc.2015.10.086>

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





Original article

Hyperuricaemia-associated all-cause mortality risk effect is increased by non-impaired kidney function – Is renal hyperuricaemia less dangerous?

Janis Timsans^{a,*}, Jenni Emilia Kauppi^b, Anne Mirjam Kerola^{a,c,d}, Tiina Maarit Lehto^c, Hannu Juhani Kautiainen^{d,f}, Markku Jaakko Kauppi^{a,d}

^a Department of Rheumatology, Pääjt-Häme Central Hospital, Lahti, Finland

^b Unit of Physiatry and Rehabilitation Medicine, Pääjt-Häme Central Hospital, Lahti, Finland

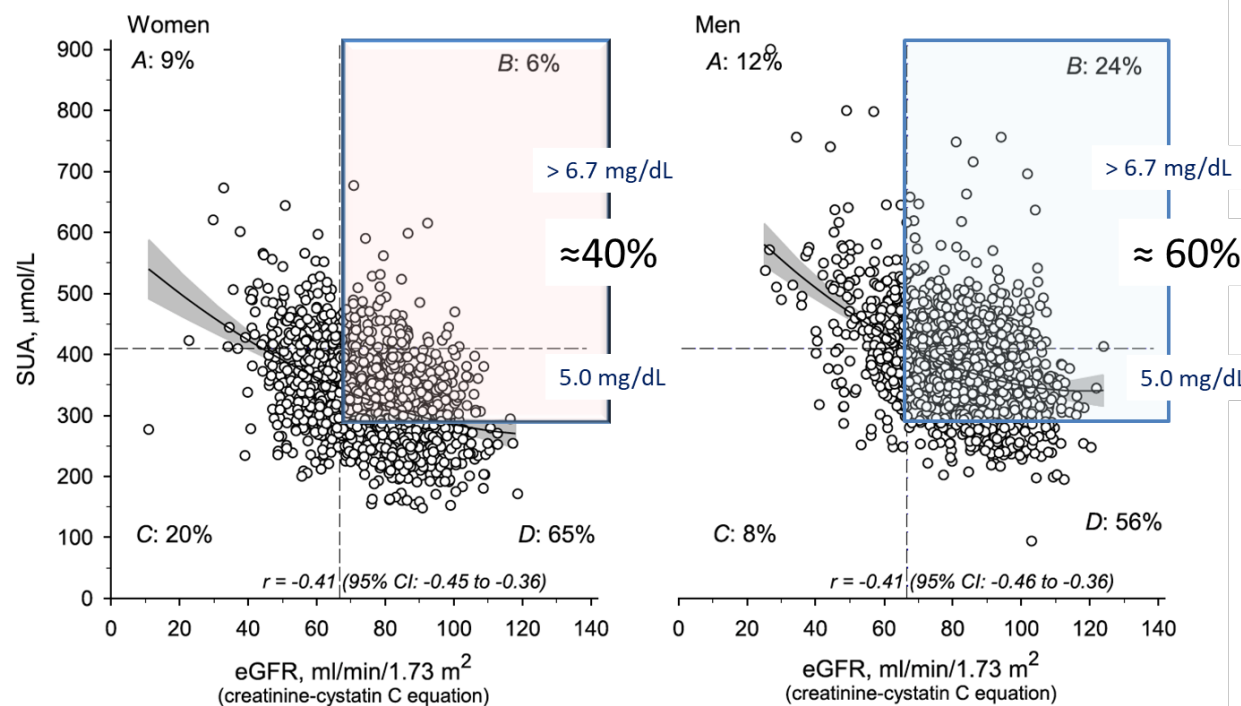
^c Inflammation Center, Rheumatology, Helsinki University Hospital, Helsinki, Finland

^d University of Helsinki, Helsinki, Finland

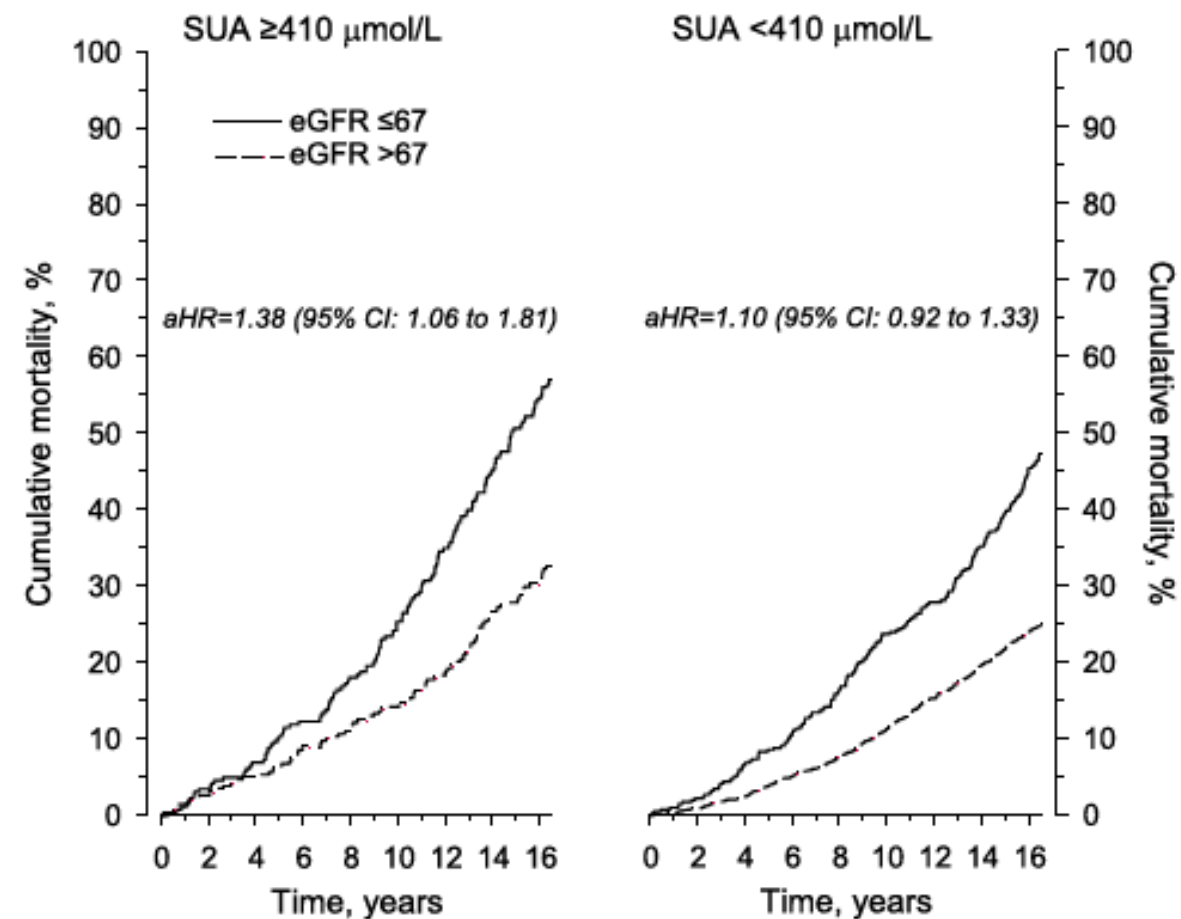
^e Department of Clinical Chemistry, Finlab Laboratoriot Oy, Lahti, Finland

^f Folkhälsan Research Center, Helsinki, Finland

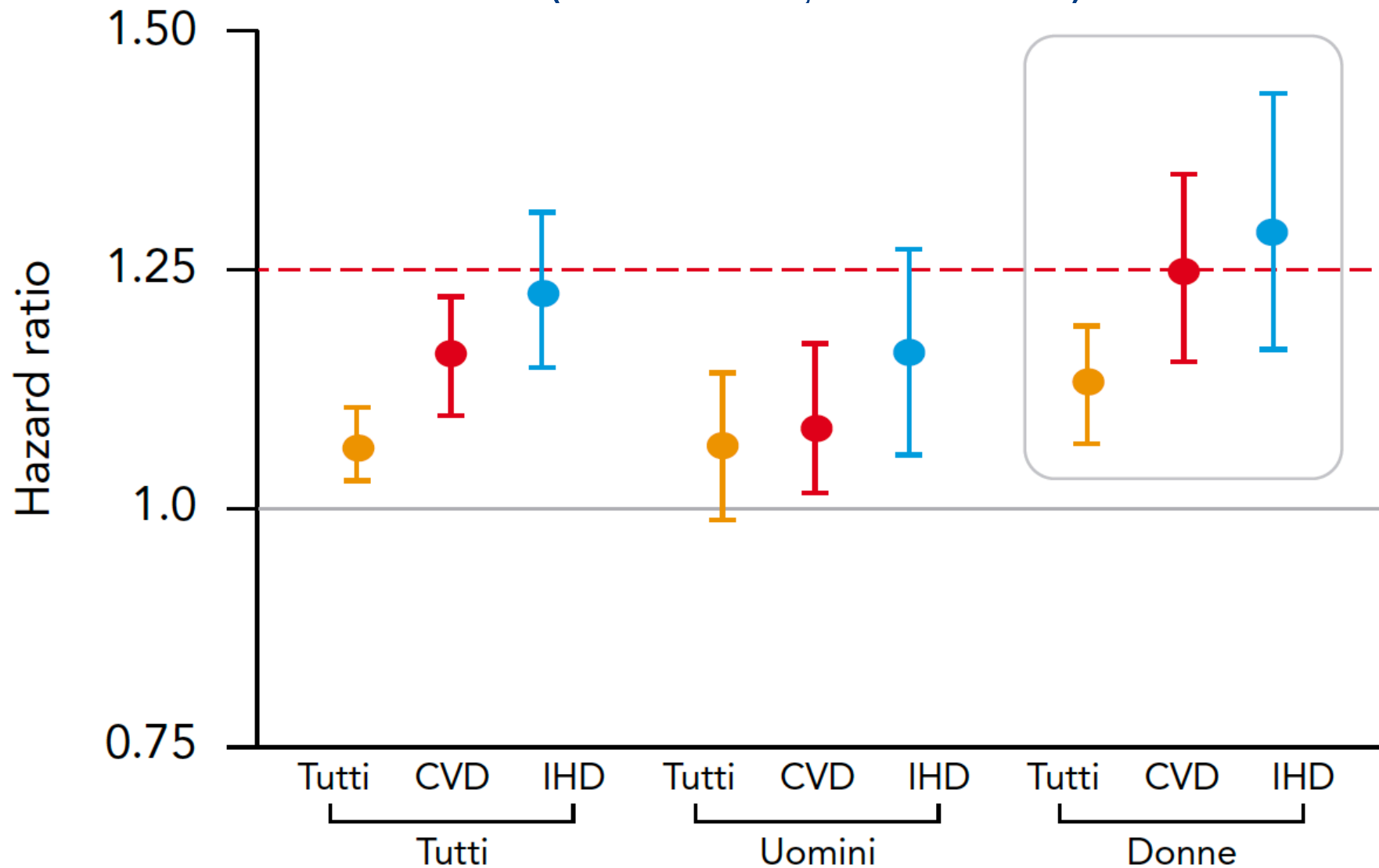
Relationship between SUA levels and eGFR in women and men



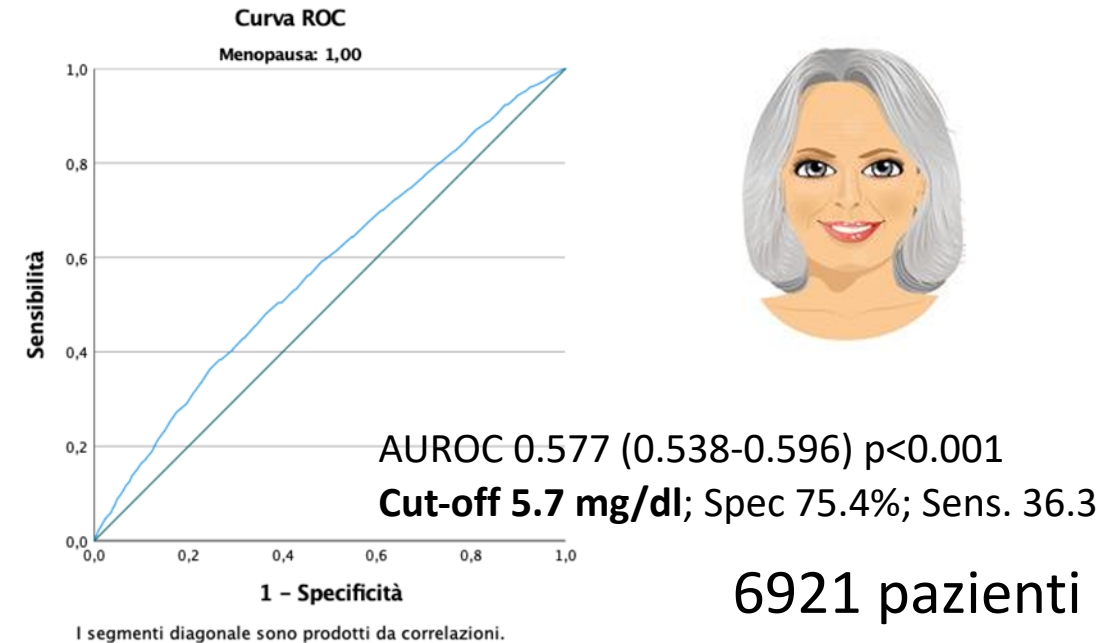
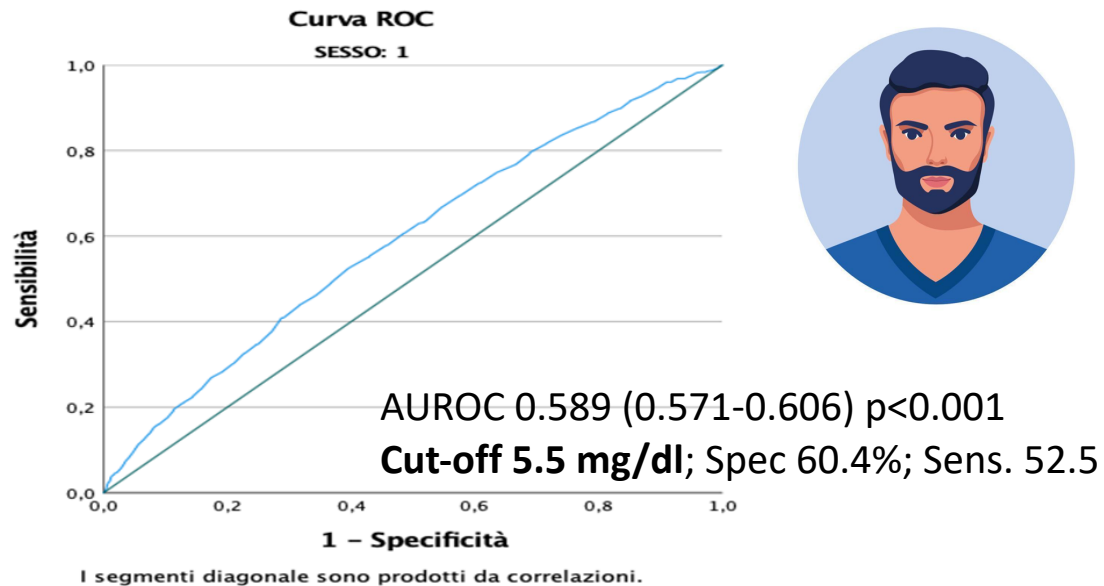
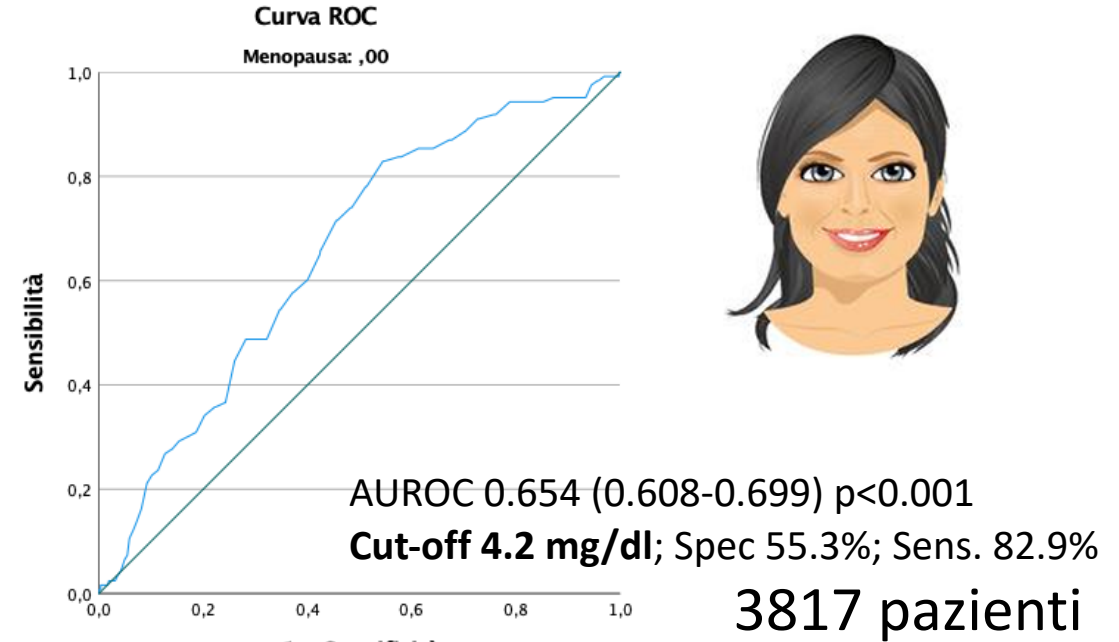
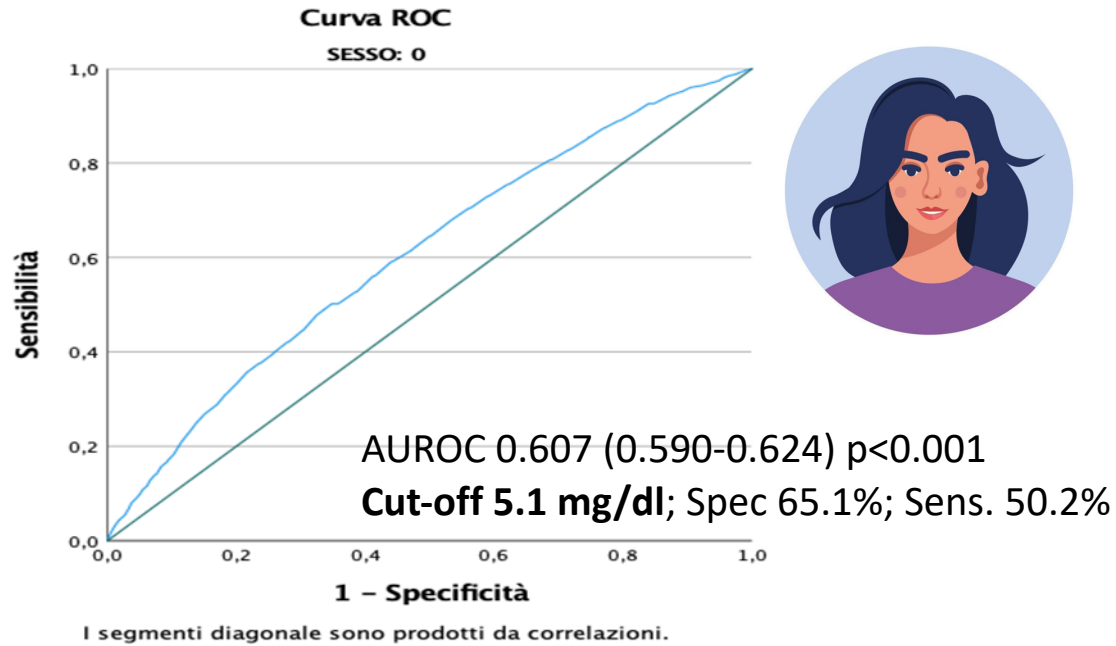
Difference between the crude cumulative all-cause mortality rate in 15-year period in individuals with preserved and reduced renal function in clearly hyperuricaemic and less hyperuricaemic/normouricaemic study subjects.



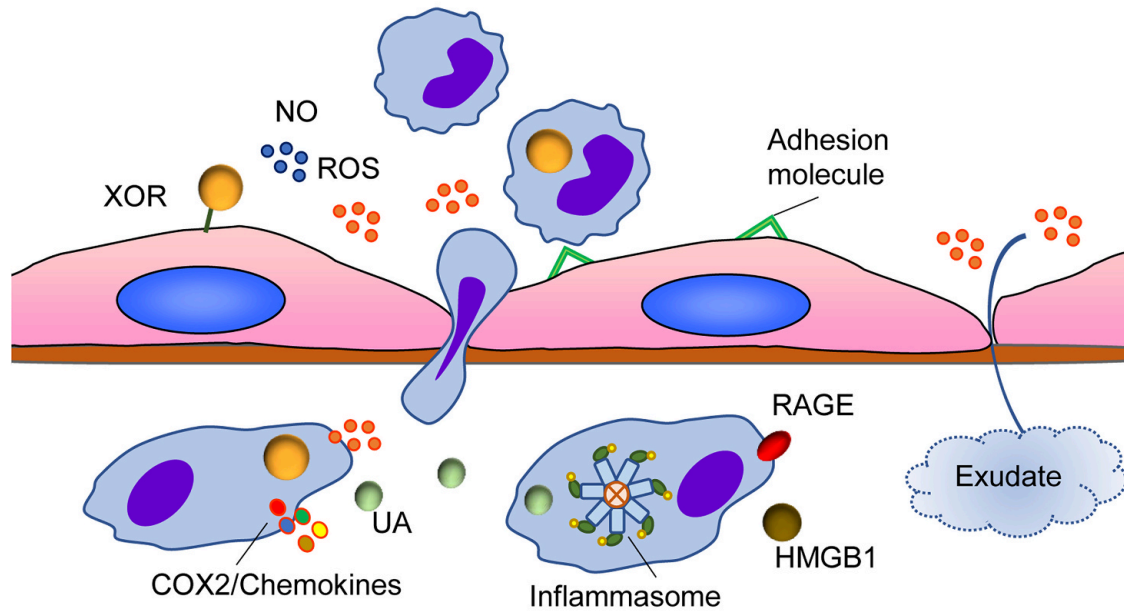
Hazard Ratios per la mortalità per tutte le cause, per malattie cardiovascolari (CVD) e per malattia coronarica (IHD) per ogni aumento dell'uricemia di 1 mg/dL (NHANES I, 1971-1992)



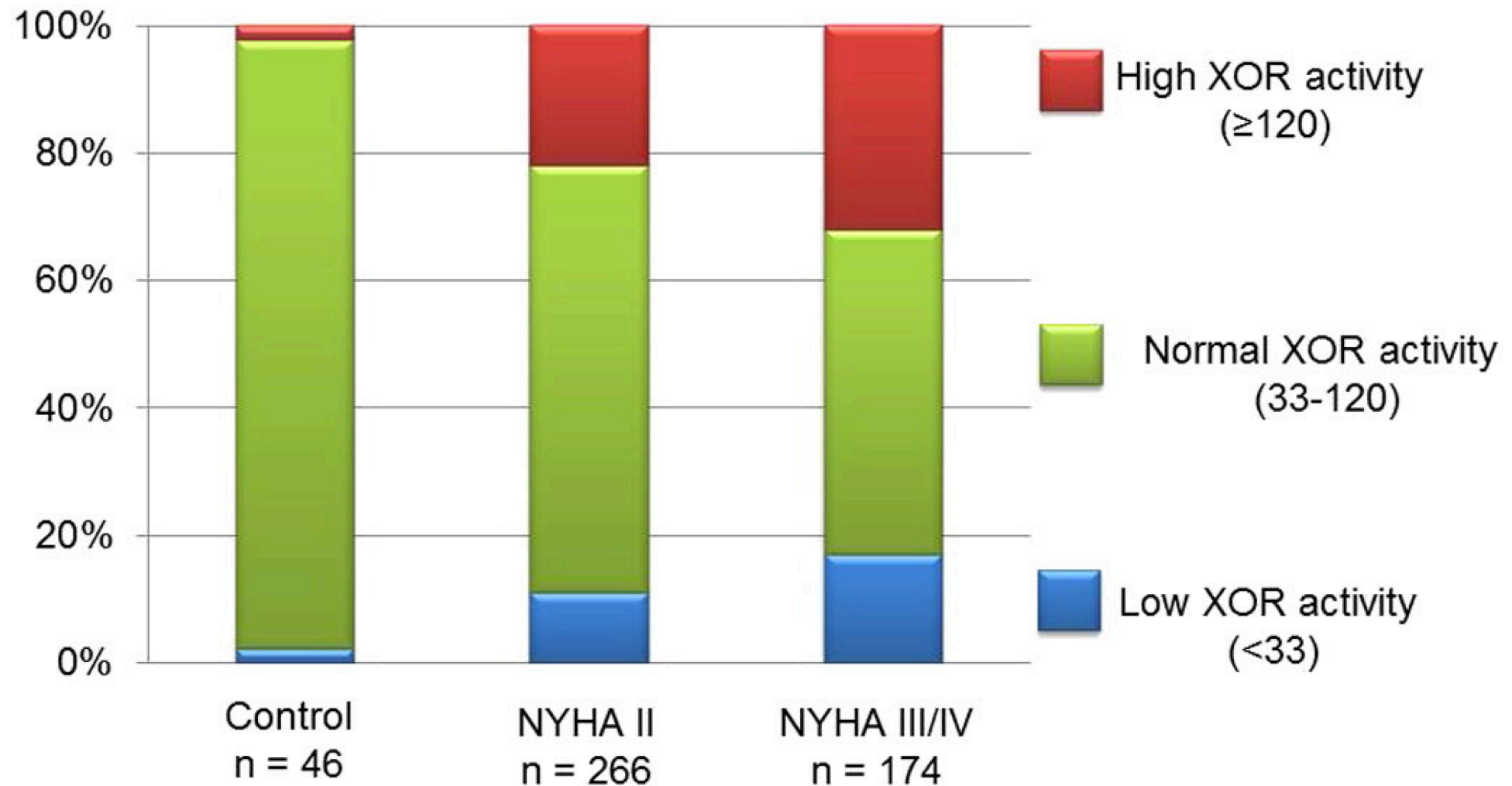
URRAH – 4P MACE (20243 pts)



Xanthine oxidoreductase: A leading actor in cardiovascular disease drama

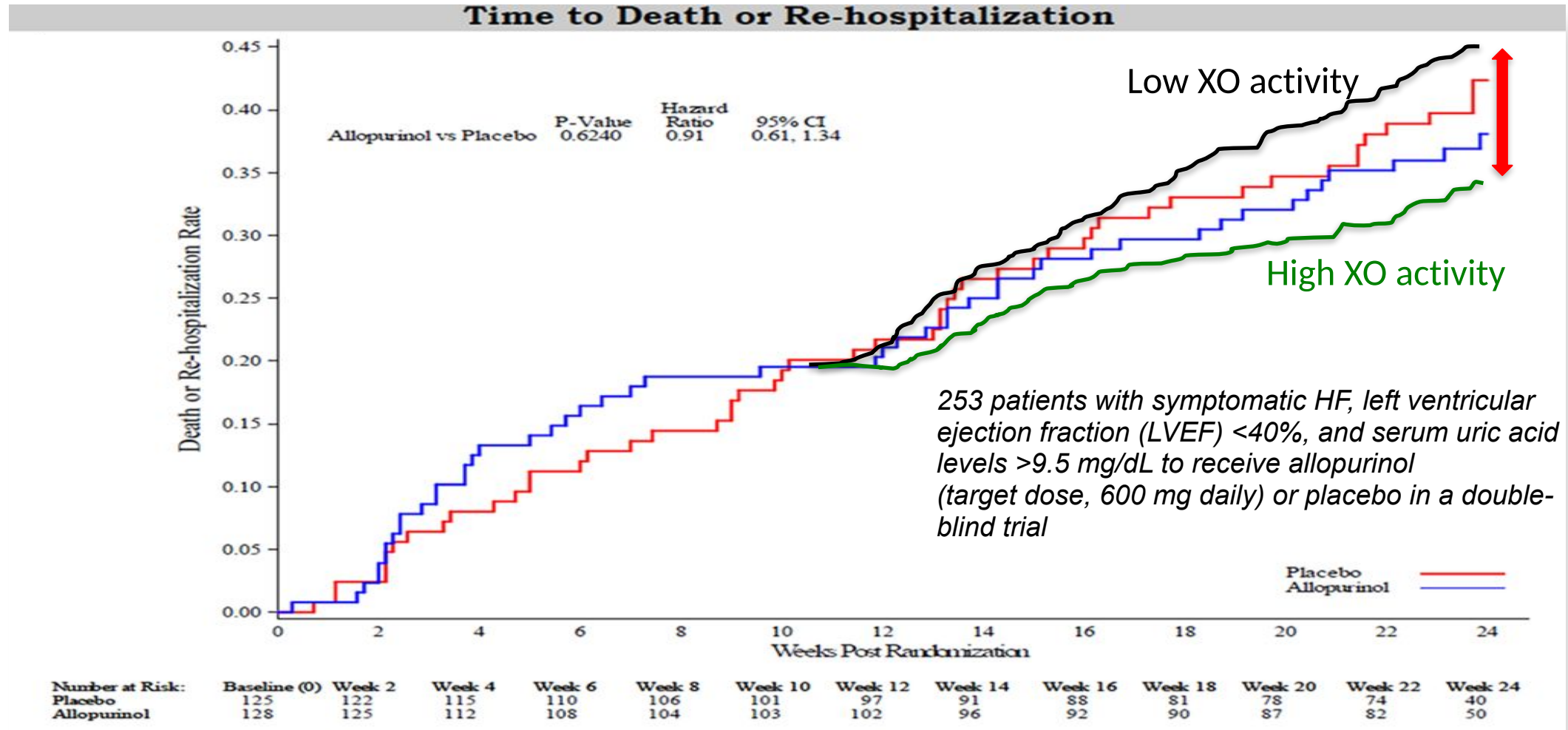


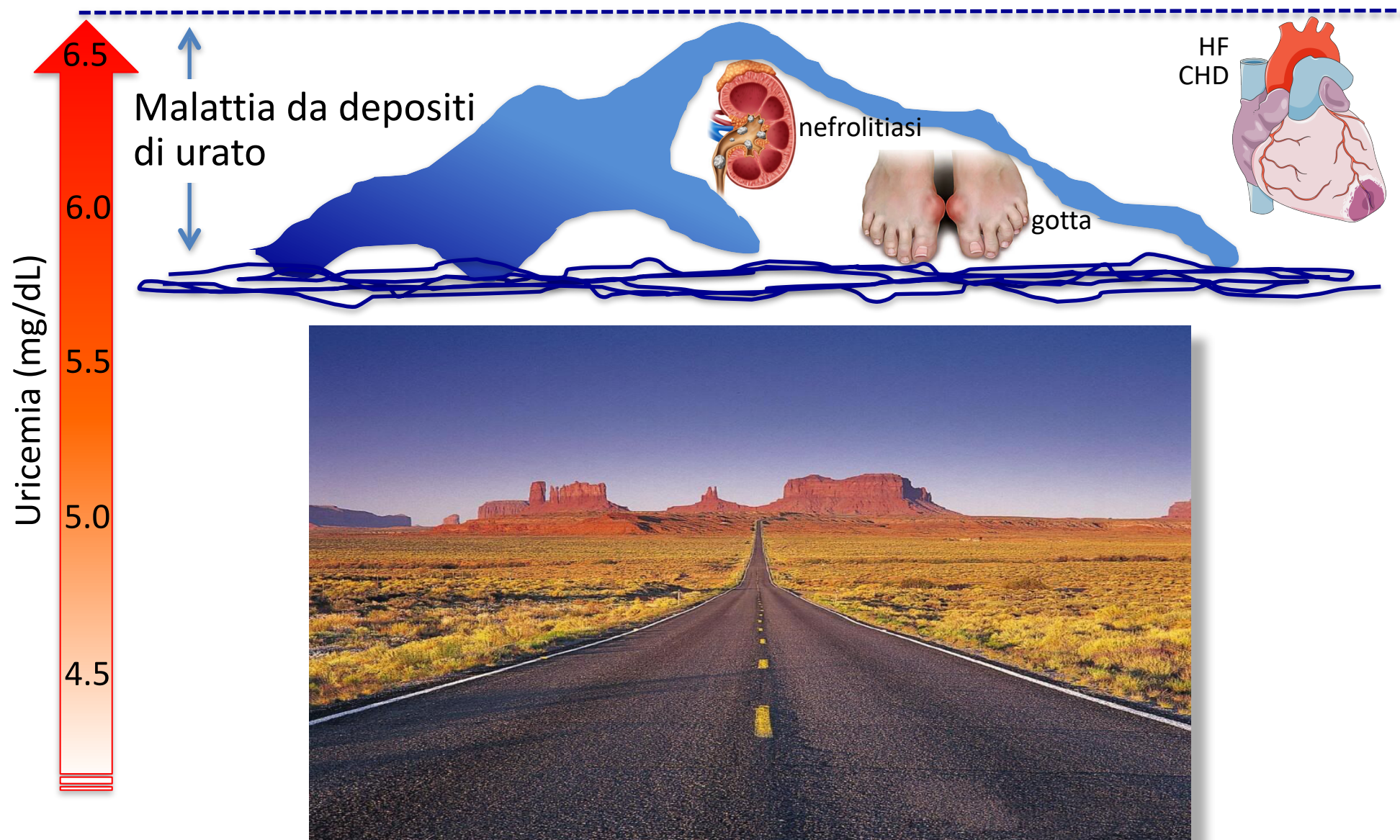
Association of plasma xanthine oxidoreductase activity with severity and clinical outcome in patients with chronic heart failure



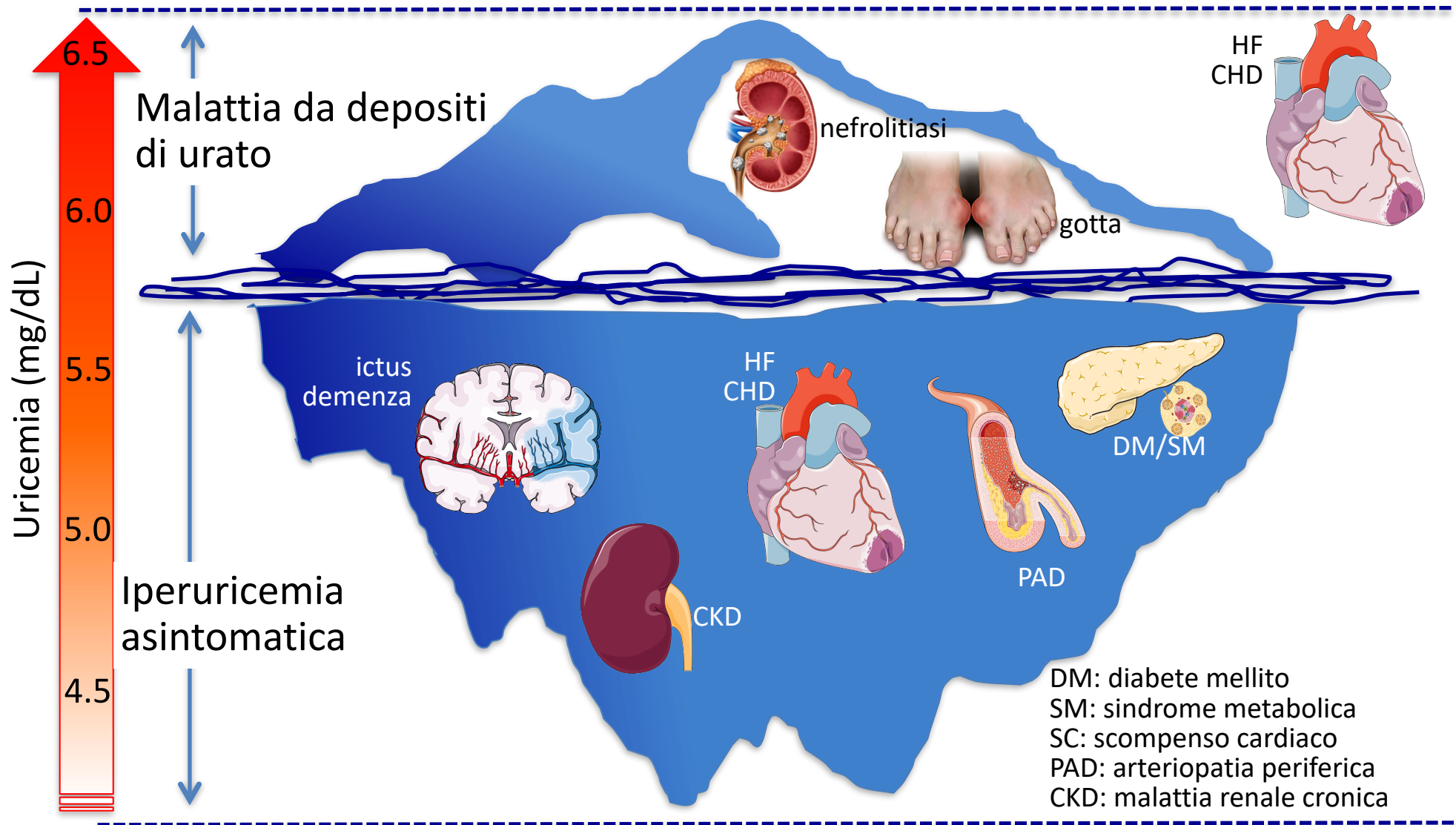
Effects of Xanthine Oxidase Inhibition in Hyperuricemic Heart Failure Patients

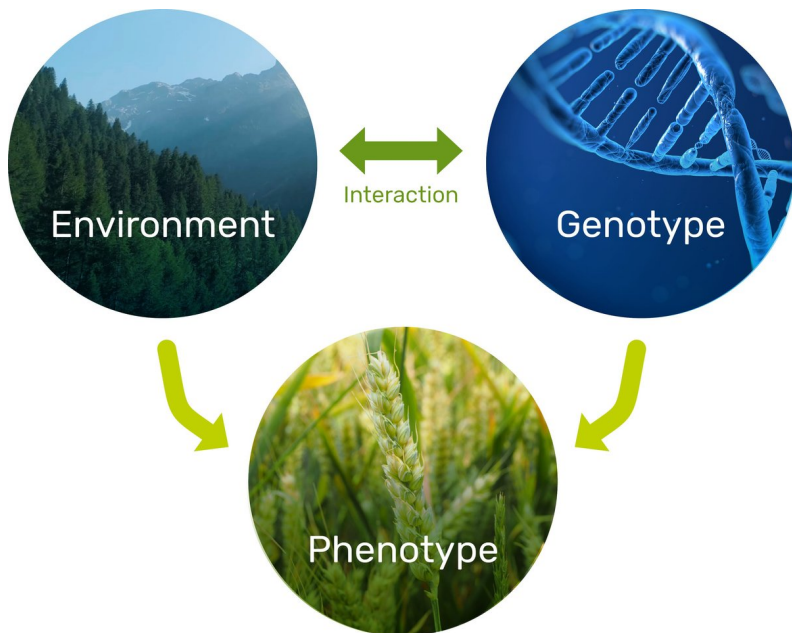
The Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) Study





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





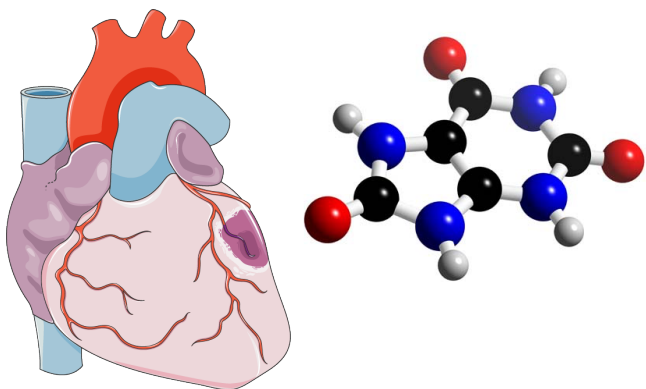
Le facce molteplici del fenotipo: il caso della uricemia



**Elevati livelli di
Ac.urico**
(geni & dieta)

Ridotta Escrezione > Produzione

Aumentata Produzione > Excrezione



↑ Riassorbimento tubulare
Deposito di urati
Infiammazione e danno vascolare

**Malattia
renale**

Gotta e complicanze



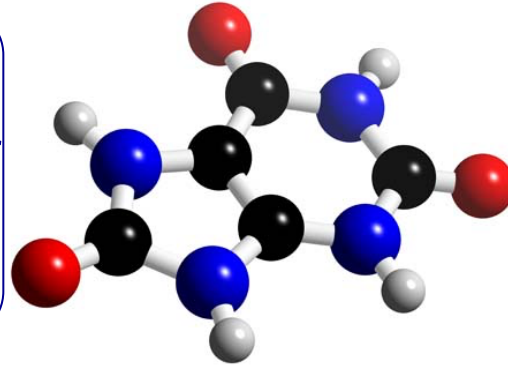
↑ Attività XO genetica
Stress Ossidativo
Danno vascolare

Malattia cardio-metabolica

Uric Acid excretion/production balance

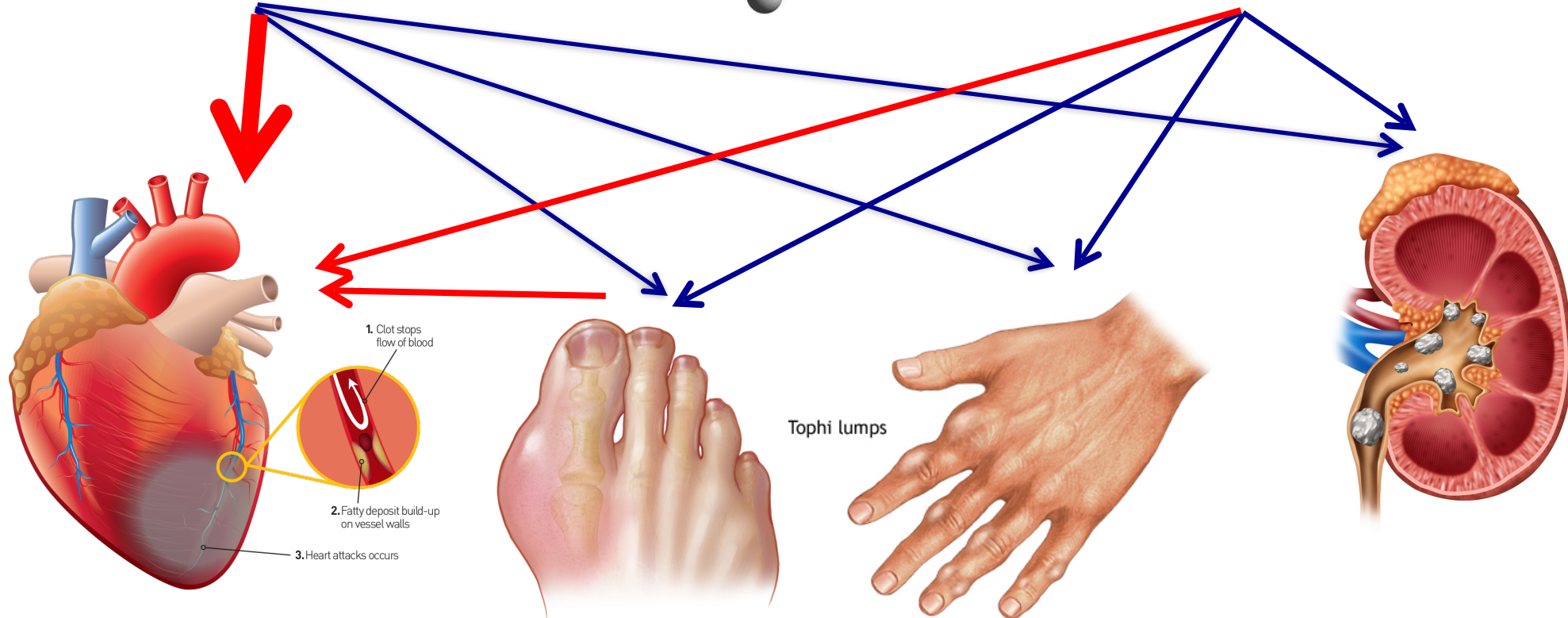
20% Iperproducers

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

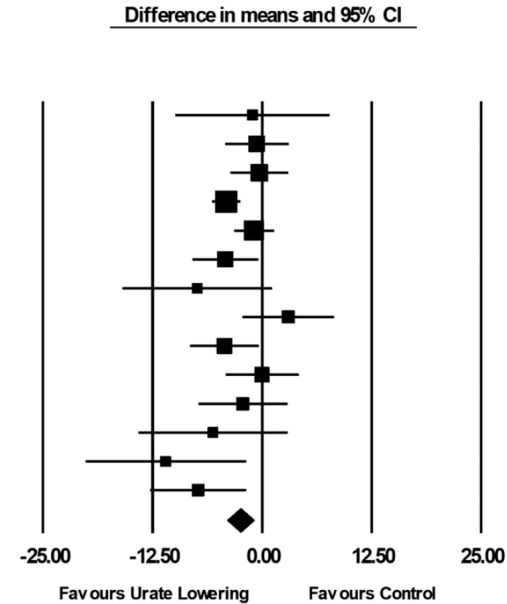


80% Underexcretors

(physiologically, low GFR,
Diuretics)



Studyname	Statistics for each study						p-Value
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	
Alshahawey, 2017	-1.100	4.521	20.441	-9.961	7.761	-0.243	0.808
Gingles, 2019	-0.590	1.886	3.556	-4.286	3.106	-0.313	0.754
Gunawhardana, 2017	-0.300	1.712	2.933	-3.656	3.056	-0.175	0.861
Kimura, 2018	-4.100	0.863	0.744	-5.791	-2.409	-4.753	0.000
McMullan, 2017	-0.900	1.199	1.437	-3.249	1.449	-0.751	0.453
Segal, 2015	-4.200	1.945	3.781	-8.011	-0.389	-2.160	0.031
Higgins, 2014	-7.400	4.380	19.181	-15.984	1.184	-1.690	0.091
Dogan, 2011	3.000	2.688	7.226	-2.269	8.269	1.116	0.264
Karbay, 2011	-4.300	2.027	4.110	-8.273	-0.327	-2.121	0.034
Goicoechea, 2010	0.000	2.153	4.635	-4.220	4.220	0.000	1.000
Momeni, 2010	-2.200	2.619	6.859	-7.333	2.933	-0.840	0.401
Khan, 2008	-5.600	4.368	19.076	-14.160	2.960	-1.282	0.200
Siu, 2006	-11.000	4.706	22.148	-20.224	-1.776	-2.337	0.019
Morgan, 2018	-7.300	2.828	7.998	-12.843	-1.757	-2.581	0.010
	-2.552	0.767	0.589	-4.056	-1.048	-3.326	0.001



MENDELIAN RANDOMIZATION

Urate, Blood Pressure, and Cardiovascular Disease

Evidence From Mendelian Randomization and Meta-Analysis of Clinical Trials

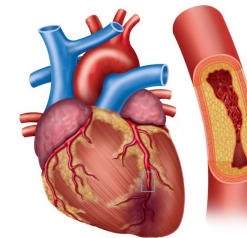
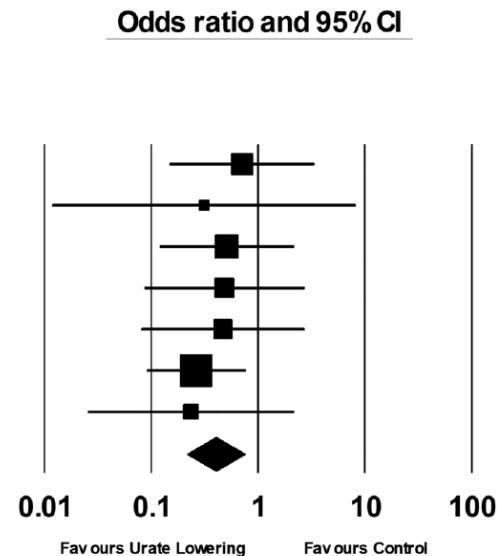
Dipender Gill¹; Alan C. Cameron²; Stephen Burgess, Xue Li, Daniel J. Doherty³, Ville Karhunen, Azmil H. Abdul-Rahim⁴, Martin Taylor-Rowan, Verena Zuber, Philip S. Tsao⁵, Derek Klarin⁶, VA Million Veteran Program, Evangelos Evangelou, Paul Elliott, Scott M. Damrauer⁷, Terence J. Quinn⁸, Abbas Dehghan, Evropi Theodoratou,† Jesse Dawson,† Ioanna Tzoulaki⁹†

Hypertension. 2021;77:383–392.

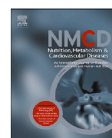


favorable effect of urate lowering therapy on systolic blood pressure

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Higgins 2014	0.709	0.148	3.399	-0.429	0.668
Khan 2008	0.312	0.012	8.285	-0.696	0.486
Rentoukas 2010	0.510	0.119	2.188	-0.906	0.365
Separham 2016	0.485	0.086	2.740	-0.819	0.413
Taheraghdam 2014	0.470	0.080	2.749	-0.838	0.402
Zhang 2012	0.265	0.090	0.775	-2.426	0.015
Huang, 2017	0.235	0.025	2.178	-1.275	0.202
	0.396	0.216	0.729	-2.977	0.003



favorable effect of urate lowering therapy on cardiovascular events in **those with previous cardiovascular disease**



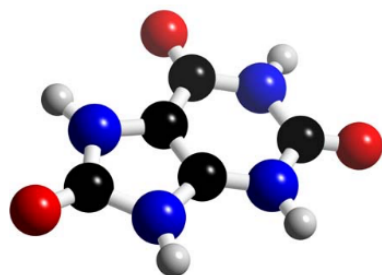
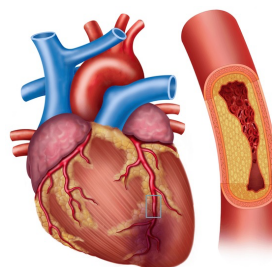
SYSTEMATIC REVIEWS AND META-ANALYSES

The net clinical benefits of febuxostat versus allopurinol in patients with gout or asymptomatic hyperuricemia – A systematic review and meta-analysis

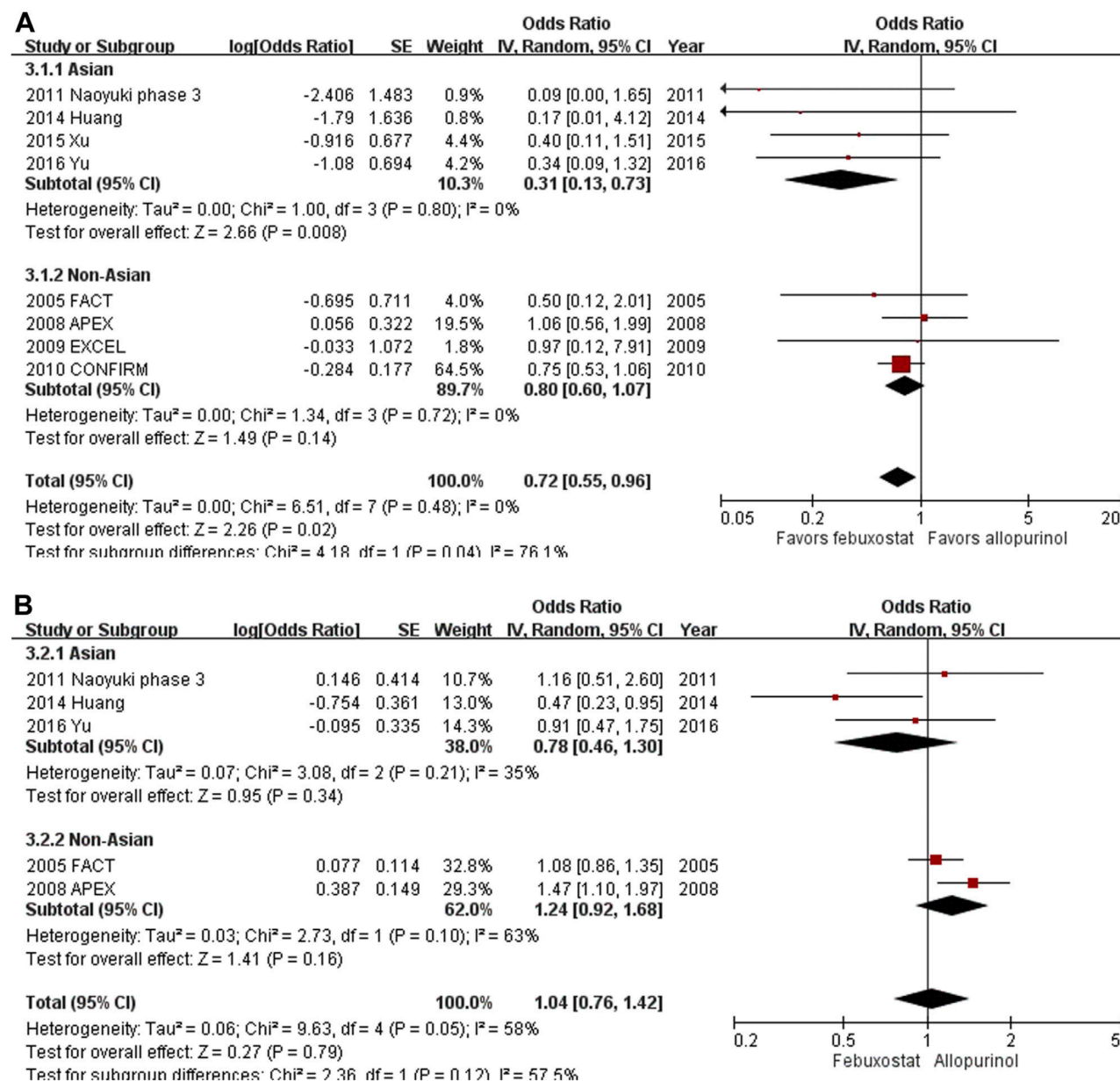
Cheng-Wei Liu^{a,b,c}, Wei-Cheng Chang^a, Chiao-Chin Lee^d, Wen-Yi Shau^c,
Fu-Shun Hsu^{c,e}, Man-Ling Wang^{c,f}, Tsung-Chih Chen^c, Chiao Lo^{c,g},
Juey-Jen Hwang^{h,i,*}



CV outcome



Gout outcome



FREED Study

Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDY

S. Kojima et al. *European Heart Journal* (2019) 40, 1778–1786

AIM



To compare the occurrence of cerebral, cardiovascular, and renal events in hyperuricaemic patients treated with **febuxostat vs** conventional therapy (lifestyle modification).

STUDY DESIGN



Multicentre
(141 hospitals
in Japan)



Prospective,
randomized,
open-label,
blinded endpoint



Follow-up
36 months



Intention-
to-treat
population

PRIMARY ENDPOINT

Composite endpoint:



Cerebrovascular disease



Cardiovascular disease



Renal impairment



Non-fatal coronary artery disease, heart failure requiring hospitalization, arteriosclerotic disease requiring treatment, atrial fibrillation



Death due to any cause

STUDY POPULATION



Elderly patients
with hyperuricaemia
(SUA >7.0 to ≤9.0 mg/dL)
at risk for cerebral,
cardiovascular, or
renal disease

Risk factors (≥1)

- ✓ Hypertension
- ✓ Type 2 diabetes
- ✓ Renal disease
- ✓ History of cerebral or cardiovascular disease

1070 patients
randomized

Febuxostat group
n = 537



Febuxostat
40 mg/day

Non-febuxostat group
n = 533



Conventional therapy
(lifestyle modification)

SECONDARY ENDPOINTS (individual components)

Cerebrovascular
disease



HR 1.271
(0.479–3.371)

Non-fatal
coronary artery
disease



HR 0.559
(0.167–1.869)

Heart failure
requiring
hospitalization



HR 0.699
(0.290–1.689)

Arteriosclerotic
disease requiring
treatment



HR 0.644
(0.107–3.873)

Renal
impairment



HR 0.745
(0.562–0.987)

Atrial
fibrillation



HR 1.320
(0.292–5.968)

EXPLORATORY ENDPOINTS

hs-CRP and NT-proBNP
(no significant difference
between groups)



HbA1c at 36 months
lower in febuxostat group



P = 0.024 and P = 0.035

CONCLUSION



In elderly hyperuricaemic patients at risk for cerebrovascular, cardiovascular, or renal disease, febuxostat significantly lowered serum uric acid levels and reduced the risk of the primary composite endpoint, mainly by decreasing renal impairment events.

Registration

ClinicalTrials.gov (NCT01984749)

SUA, serum uric acid; HR, hazard ratio; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide; HbA1c, glycated hemoglobin.

Introduction to the metabolic syndrome

Alberti G. *Eur Heart J (suppl)* 2005

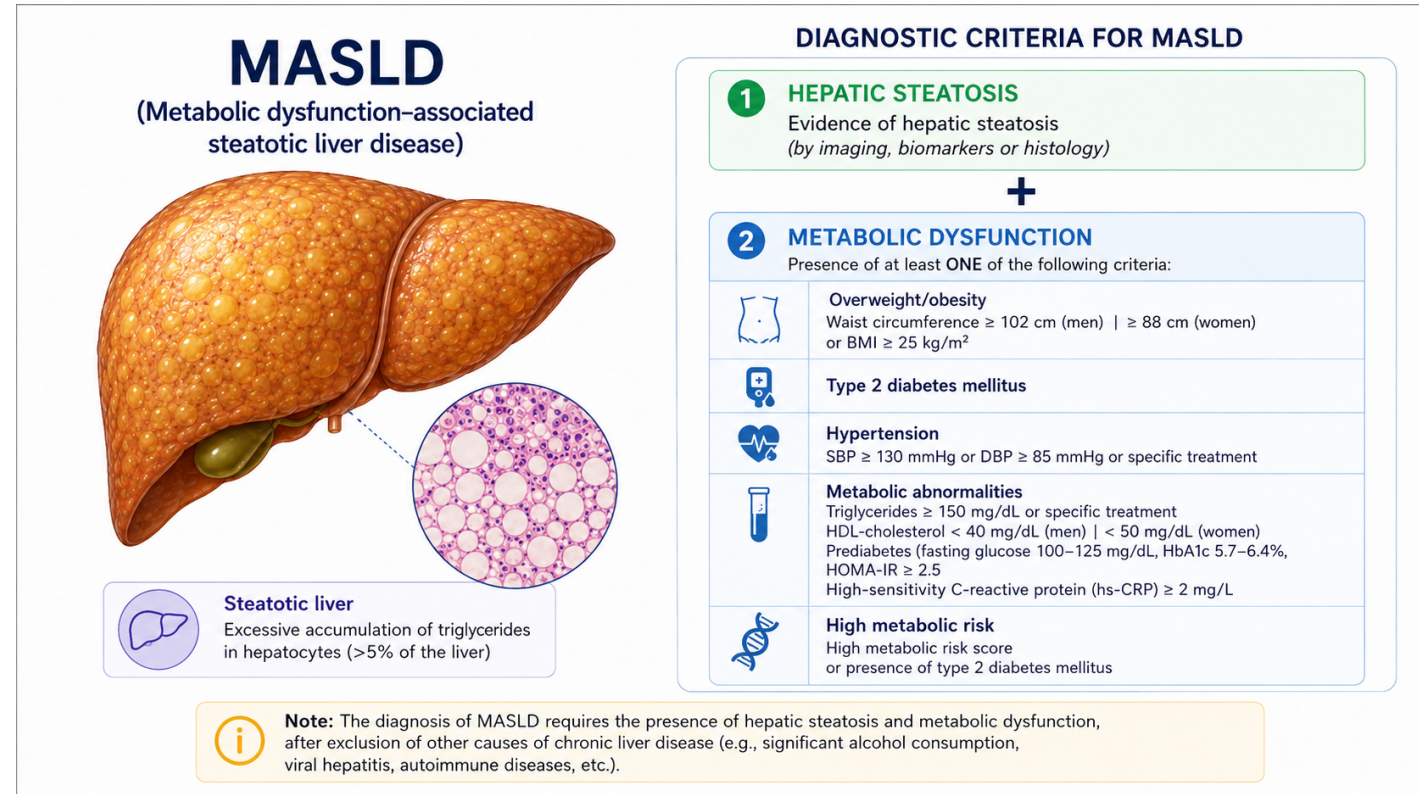
The metabolic syndrome has its origins in 1923 when Kylin¹ described a syndrome involving hypertension, hyperglycaemia and hyperuricaemia. In the 1940s Vague² wrote about abdominal obesity and fat distribution and its relation to diabetes and other disorders. Following this, in 1965 an abstract was presented at the European Association for the Study of Diabetes annual meeting by Avogaro and Crepaldi³ which again described a syndrome which comprised hypertension, hyperglycaemia, and obesity.

The field moved forward significantly following the 1988 Banting Lecture given by Gerry Reaven.⁴ He described 'a cluster of risk factors for diabetes and cardiovascular disease' and named it 'Syndrome X'. His main contribution was the introduction of the concept of insulin resistance.

In 1989, Kaplan⁵ renamed the syndrome 'The Deadly Quartet' and in 1992 it was again renamed 'The Insulin Resistance Syndrome'.⁶ It is now agreed that the well-established term 'metabolic syndrome' remains the most usual description of this cluster of metabolic abnormalities.

Uric Acid in MASLD

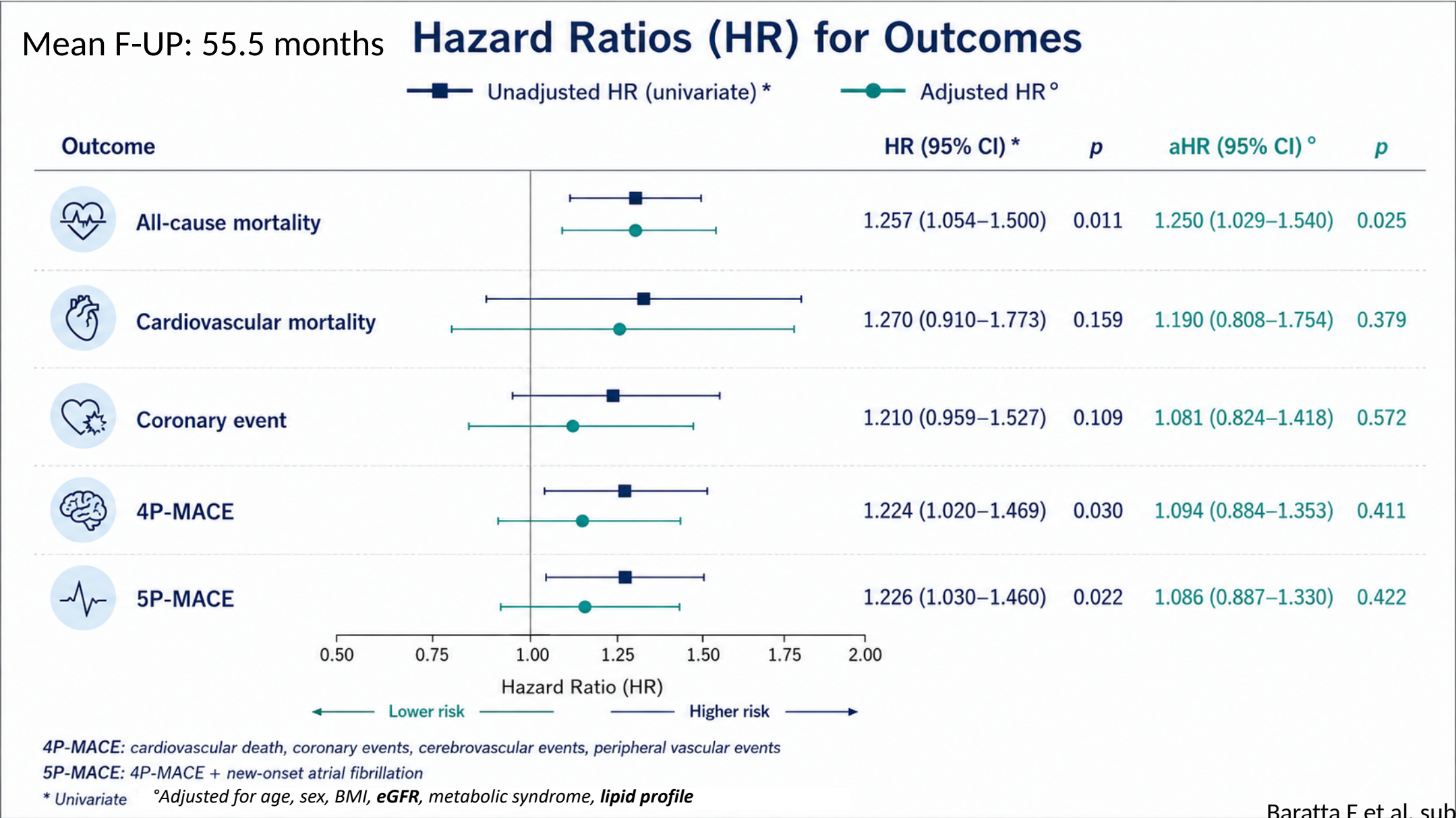
Biomarker, risk factor, target..other?



Baratta F et al. submitted



Does Uric Acid Dysmetabolism Predict Prognosis in Patients with Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD)?



Does Uric Acid Dysmetabolism Predict Prognosis in Patients with Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD)?



ANALYZED COHORT
1,018
patients



MASLD
832 patients
(81.7%)



CONTROLS
186 patients
(18.3%)

MAIN DIFFERENCES: MASLD vs CONTROLS



YOUNGER

Mean age (years)

55.4 vs **58.1**

p = 0.007



HIGHER METABOLIC BURDEN

Diabetes

28.1% vs 12.4%

Metabolic syndrome

59.1% vs 23.7%

TyG index

4.8 vs 4.6

all p < 0.001



MORE ATHEROGENIC LIPID PROFILE

HDL (mg/dL)

48.0 vs 56.6

Triglycerides (mg/dL)

155.6 vs 107.6

Remnant cholesterol (mg/dL)

29.4 vs 21.2

all p < 0.001



WORSE RENAL FUNCTION

eGFR (CKD-EPI)
(mL/min/1.73 m²)

88.6 vs **85.7**

p = 0.040



HIGHER URIC ACID

Uric acid (mg/dL)

5.9 vs **5.0**

p < 0.001



KEY MESSAGE

Patients with MASLD present a more unfavorable cardiometabolic profile and significantly higher uric acid levels compared with controls.



Data are expressed as mean ± SD or %. Comparisons between MASLD and controls.

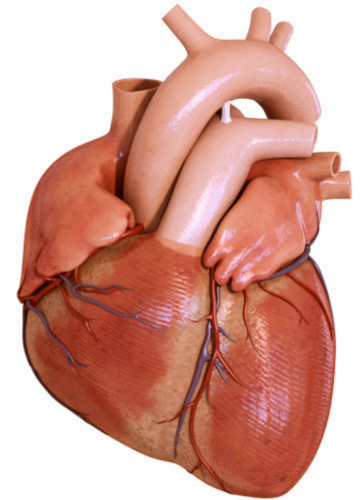
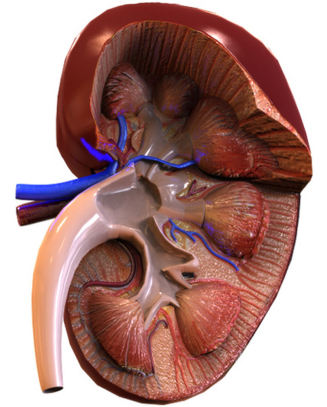
MASLD: Metabolic Dysfunction–Associated Steatotic Liver Disease; eGFR: estimated glomerular filtration rate.

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias



European Society
of Cardiology

European Heart Journal (2025) **00**, 1–20
<https://doi.org/10.1093/eurheartj/ehaf190>



Very high risk

People with any of the following:

- Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), chronic coronary syndromes, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque^a on coronary angiography or CT scan or on carotid or femoral ultrasound or markedly elevated CAC score by CT^b
- DM with target organ damage,^c or at least three major risk factors, or early onset of T1DM of long duration (>20 years)
- Severe CKD (eGFR <30 mL/min/1.73 m²)
- A calculated SCORE2 or SCORE2-OP ≥20% for 10 year risk of fatal or non-fatal CVD
- FH with ASCVD or with another major risk factor

High risk

People with any of the following:

- Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg
- Patients with FH without other major risk factors
- Patients with DM without target organ damage,^c with DM duration ≥10 years or another additional risk factor
- Moderate CKD (eGFR 30–59 mL/min/1.73 m²)
- A calculated SCORE2 or SCORE2-OP ≥10% and <20% for 10 year risk of fatal or non-fatal CVD

Moderate risk

People with any of the following:

- Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors
- Calculated SCORE2 or SCORE2-OP ≥2% and <10% for 10 year risk of fatal or non-fatal CVD

Low risk

- Calculated SCORE2 or SCORE2-OP <2% for 10 year risk of fatal or non-fatal CVD

“CKD-addon” to Incorporate Kidney Disease Measures Into the ESC SCORE2 Equation



Kidney Measures

eGFR (estimated glomerular filtration rate)
(mL/min/1.73m²) **35**

Urine Albumin to Creatinine Ratio (mg/g)
click on units to change between mg/g and mg/mmol
[Convert Urine Protein-Creatinine to Albumin-Creatinine](#) **200**

SCORE2 Variables

Age (40-85yrs) **60**

Gender **Male**

Systolic Blood Pressure (mmHg) **120**

Total Cholesterol (mg/dL)
click on units to change between mg/dL and mmol/L **200**

HDL Cholesterol (mg/dL)
click on units to change between mg/dL and mmol/L **40**

Smoking Status **Not Current Smoker**

Diabetes **No**

Predicted 10 year risk of cardiovascular disease

CKD Add-on is based on data from CKD-PC (Chronic Kidney Disease Prognosis Consortium)

Low risk countries	
Original SCORE2 5.1%	Original SCORE2 + CKD Add-on 15.7%
Medium risk countries	
Original SCORE2 6.5%	Original SCORE2 + CKD Add-on 19.6%
High risk countries	
Original SCORE2 6.8%	Original SCORE2 + CKD Add-on 20.4%
Very high risk countries	
Original SCORE2 12.0%	Original SCORE2 + CKD Add-on 34.1%

ESKD is for the few survivors!

- Older patients^a with CKD are 6 times more likely to die of CV disease than to advance to ESKD and dialysis^b



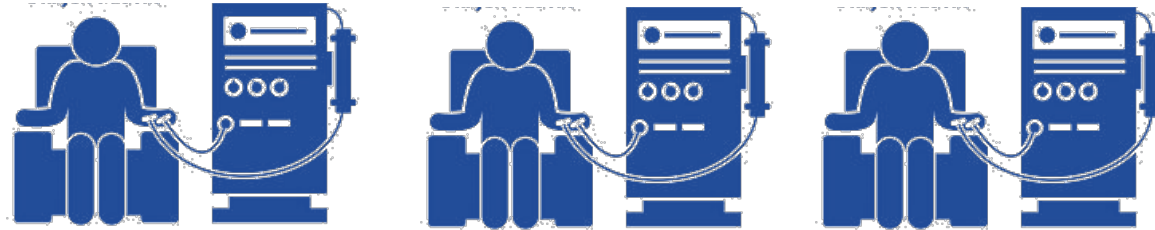
Deaths



26.6%

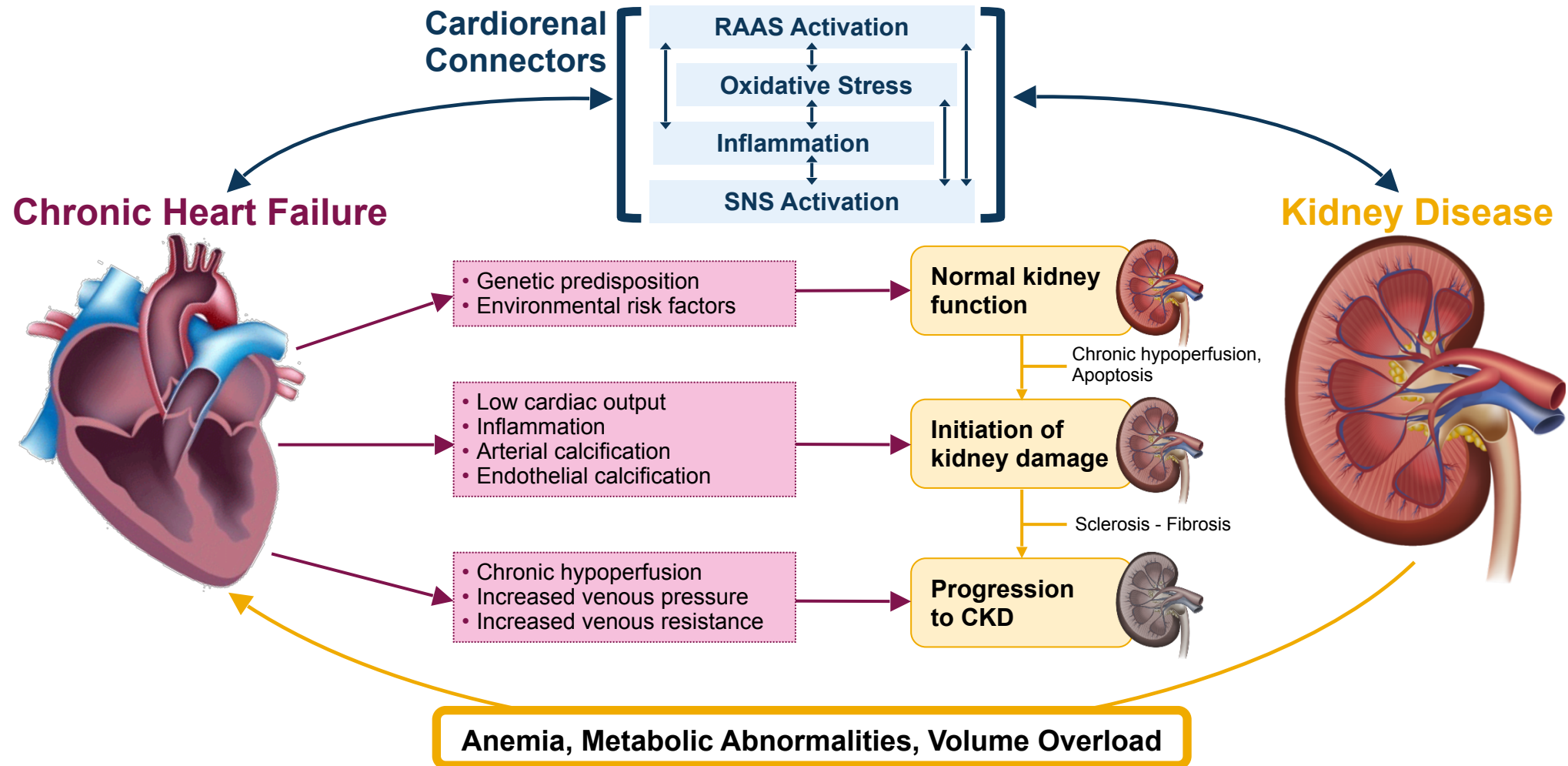


Survival to
ESKD/dialysis



4.7%

Close Association Between Cardiac and Kidney Pathophysiology^{1,2}



CKD = chronic kidney disease; CV = cardiovascular; RAAS = renin-angiotensin aldosterone system; SNS = sympathetic nervous system.

1. Adapted from Raina R et al. *Cardiol Res.* 2020;11:76-88; 2. Adapted from Yogasundaram H et al. *Can J Cardiol.* 2019;35:1208-1219; 3. Damman K et al. *J Am Coll Cardiol.* 2014;63:853-871; 4. Metra M et al. *Eur Heart J.* 2012;33:2135-2143.

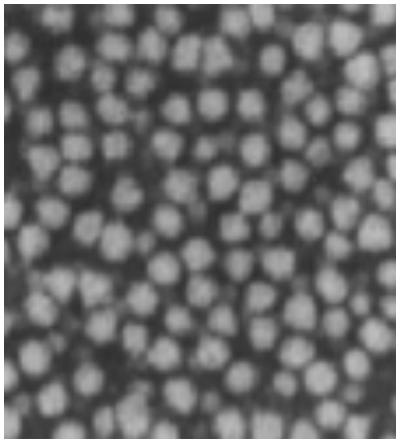
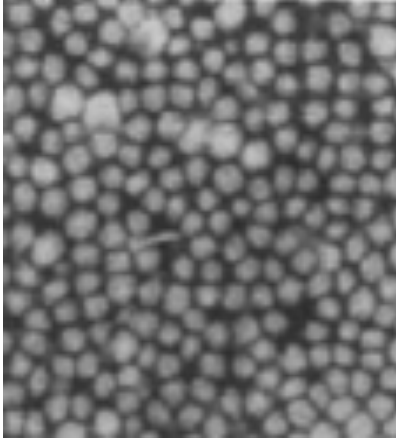
Lipid profile across CKD stages

	Nephrotic syndrome	CKD (stages 1–2)	CKD (stages 3–4)	HD	PD	KTR
Total Cholesterol	↑↑	=	=	= or ↓	↑	↑
LDL	↑↑	=	= or ↓	= or ↓	↑	↑
HDL	↓	↓	↓	↓	↓	= or ↓
Triglycerides	↑↑	↑↑	↑↑	= or ↑	↑↑	↑ or ↑↑

HD haemodialysis, *HDL* high-density lipoprotein cholesterol, *KTR* kidney transplant recipient, *LDL* low-density lipoprotein cholesterol, *PD* peritoneal dialysis

Pontremoli R et al.. Management of dyslipidaemia in patients with chronic kidney disease: a position paper endorsed by the Italian Society of Nephrology. *Journal of Nephrology*. 2020.

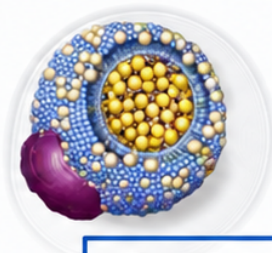
“Normal” LDL cholesterol levels: misleading information in CKD patient

	<u>Subject A</u> Control	<u>Subject B</u> CKD	
LDL-C= 119 mg/dl TG 113 mg/dL HDL 51 mg/dL Apo B= 93 mg/dl			LDL-C= 124 mg/dl TG 224 mg/dL HDL 48 mg/dL ↑Apo B= 112 mg/dl
LDL Mean diameter 273 Å	“Normal” LDL-C	“Normal” LDL-C ↑Small Dense LDL ↑Ox-LDL	LDL Mean diameter 233 Å

Risk of CHD



Lipoprotein phenotype ↑TG, ↓ HDL-C, ↑ sd LDL;
Apo B: Marker of circulating LDL particles



↑ CM remnants
↑ VLDL

- ↓ LPL activity
- ↓ LPL activators (apo CII and apo E)
- ↑ LPL inhibitors (apo CI and apo CIII)
- ↓ PPARα activity
- ↓ CM catabolism
- ↓ Receptor activity (LRP, LDLR)
- ↑ VLDL synthesis
- ↓ VLDL catabolism

↑ LDL
↑ LDL rich in TG
↑ Small and dense LDL
↑ Lipoprotein(a)

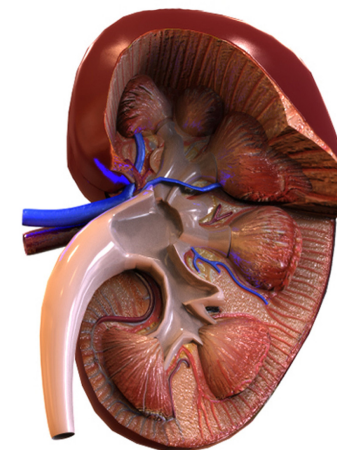


Altered LDL metabolism

- ↓ LDL receptor activity
- ↑ Reduced HMG-CoA reductase activity
- ↑ ACAT activity
- ↑ CETP activity
- ↑ Hepatic synthesis of Lipoprotein(a)

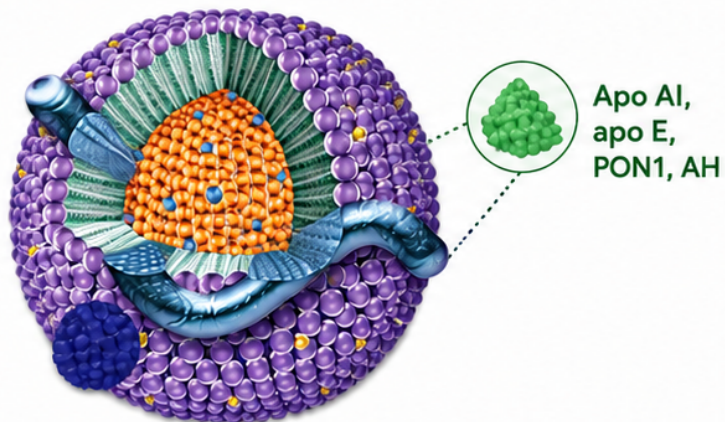
↓ HDL ↑ HDL rich in TG

- ↓ apo AI and apo AII synthesis
- ↓ LCAT activity
- ↑ ACAT activity
- ↑ CETP activity
- ↓ HDL maturation
- ↓ SR-B1 receptor activity



QUALITATIVE ALTERATIONS OF HDL IN CKD

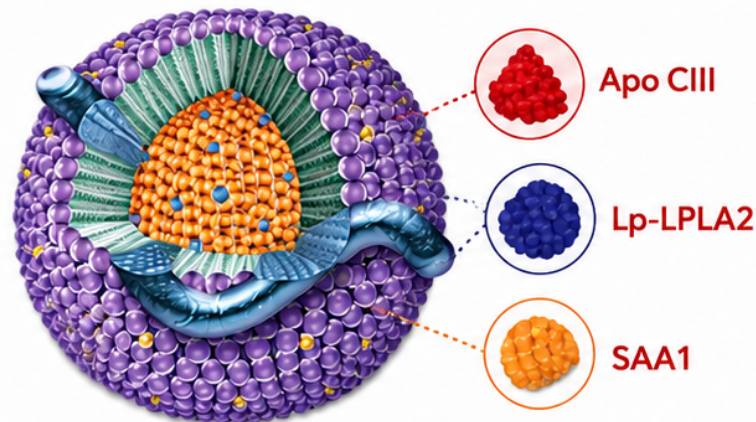
«FUNCTIONAL» HDL



- ↑ Cholesterol efflux
- ↓ Inflammation
- ↓ Thrombosis
- ↓ Oxidation

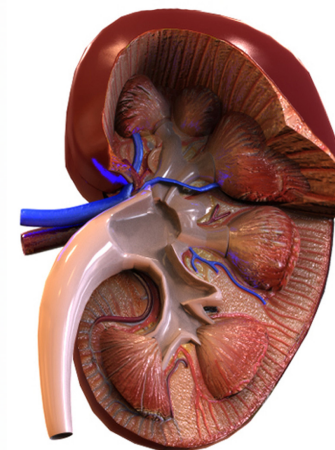
● Apo AI, apo E, PON1, AH

«DYSFUNCTIONAL» HDL



- ↓ Cholesterol efflux
- ↑ Inflammation
- ↑ Thrombosis
- ↑ Oxidation
- ↑ Asymmetric dimethylarginine

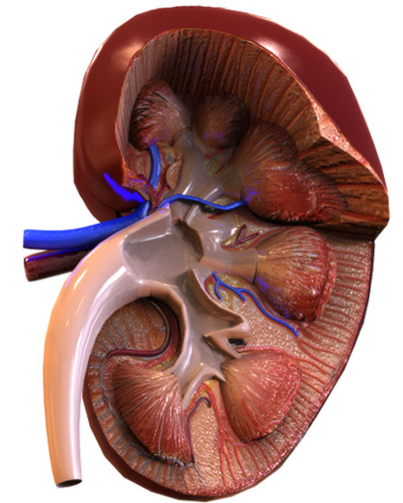
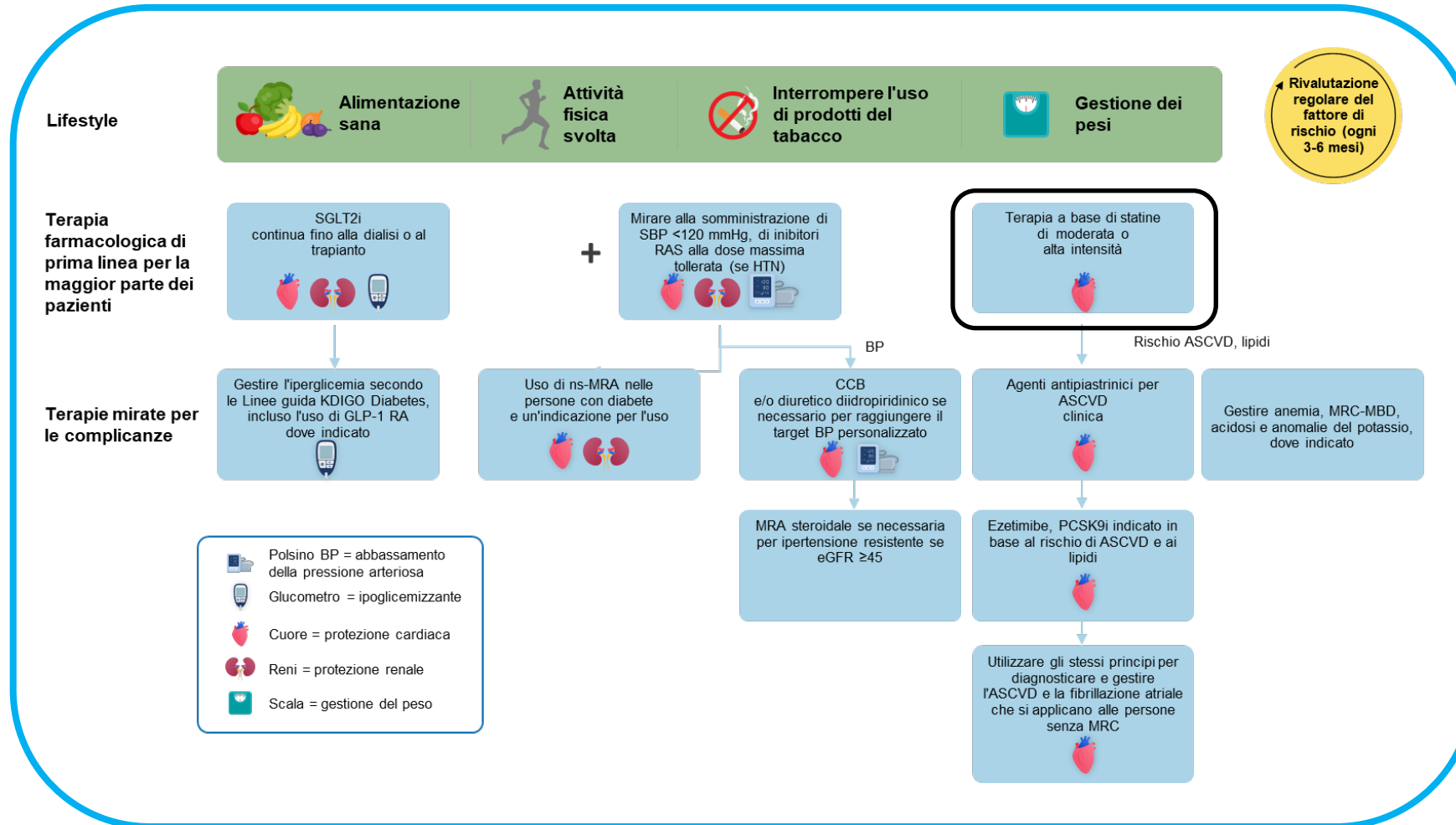
● Apo CIII, Lp-LPLA2, SAA1



In CKD, HDL undergoes qualitative alterations, shifting from **anti-atherogenic (functional)** to **pro-atherogenic (dysfunctional)**, contributing to increased cardiovascular risk.



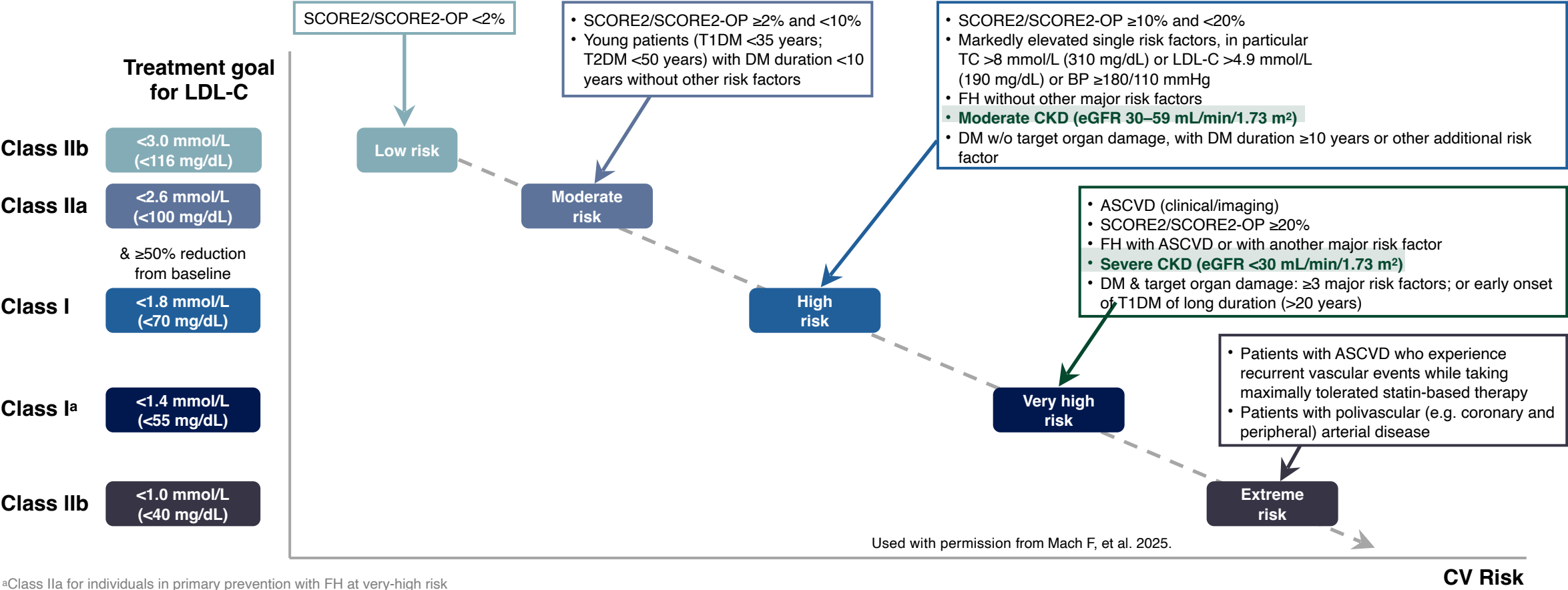
KDIGO 2024: valutazione e gestione della malattia renale cronica¹⁸



*Gli SGLT2i dovrebbero essere considerati (insieme a RAASi) come co-terapia di prima scelta nei pazienti con MRC.

SGLT2i: inibitori del cotrasportatore sodio-glucosio di tipo 2; **ACEi:** inibitori dell'enzima di conversione dell'angiotensina; **ARB:** bloccante del recettore dell'angiotensina; **SBP:** pressione arteriosa sistolica; **RAS:** sistema renina-angiotensina; **HTN:** ipertensione; **GLP-1 RA:** agonista del recettore del peptide-1 glucagon-like; **ns-MRA:** antagonista del recettore mineralcorticoide non steroideo; **CCB:** bloccante dei canali del calcio; **BP:** pressione sanguigna; **ASCVD:** malattia cardiovascolare aterosclerotica; **MRC-MBD:** malattia renale cronica-minerale e disturbo osseo; **MRA:** antagonista del recettore mineralcorticoide; **PCSK9i:** subtilisina della proproteina convertasi/inibitore della kexina di tipo 9; **eGFR:** velocità di filtrazione glomerulare stimata

2025 ESC/EAS Targets and risk groups





Management of dyslipidaemia in patients with chronic kidney disease: a position paper endorsed by the Italian Society of Nephrology

Roberto Pontremoli¹ · Vincenzo Bellizzi² · Stefano Bianchi³ · Roberto Bigazzi³ · Valeria Cernaro⁴ · Lucia Del Vecchio⁵ · Luca De Nicola⁶ · Giovanna Leoncini¹ · Francesca Mallamaci^{7,8} · Carmine Zoccali⁷ · Michele Buemi⁴

Received: 27 December 2019 / Accepted: 24 January 2020
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Consensus statement 1

Global CV risk management is a priority in CKD patients at all stages. **CKD is acknowledged as a coronary artery disease (CAD) risk equivalent** and complete assessment of lipid status (including total and HDL-cholesterol, triglycerides and LDL estimation) is mandatory to devise optimal therapeutic strategy.

Consensus statement 2

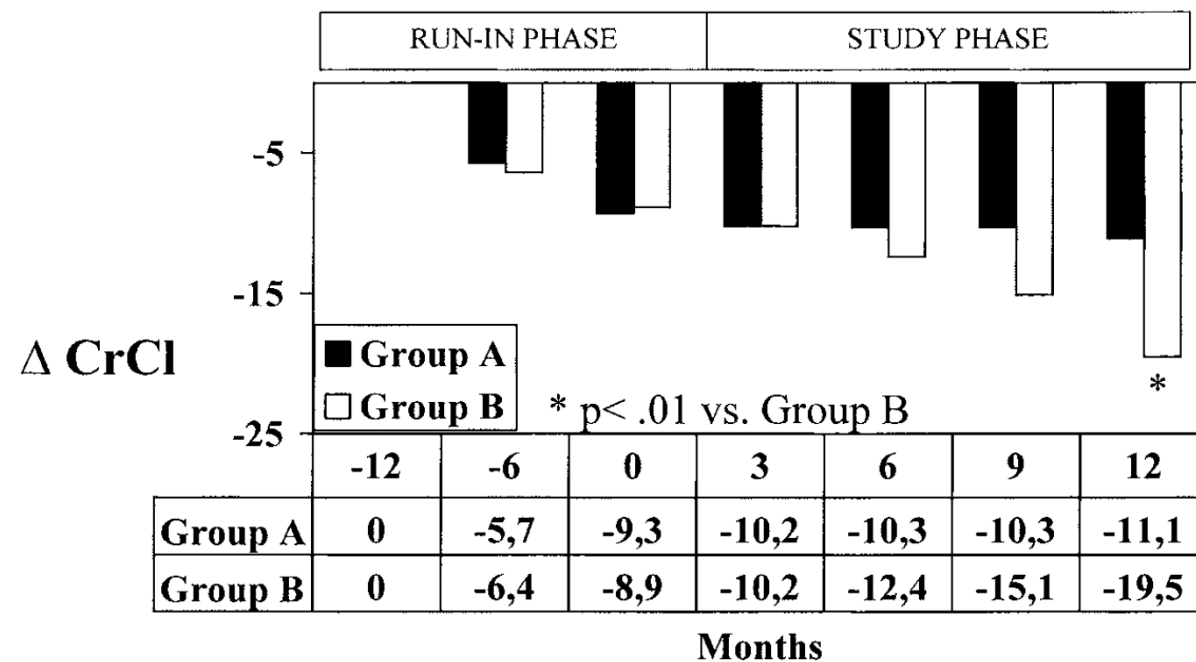
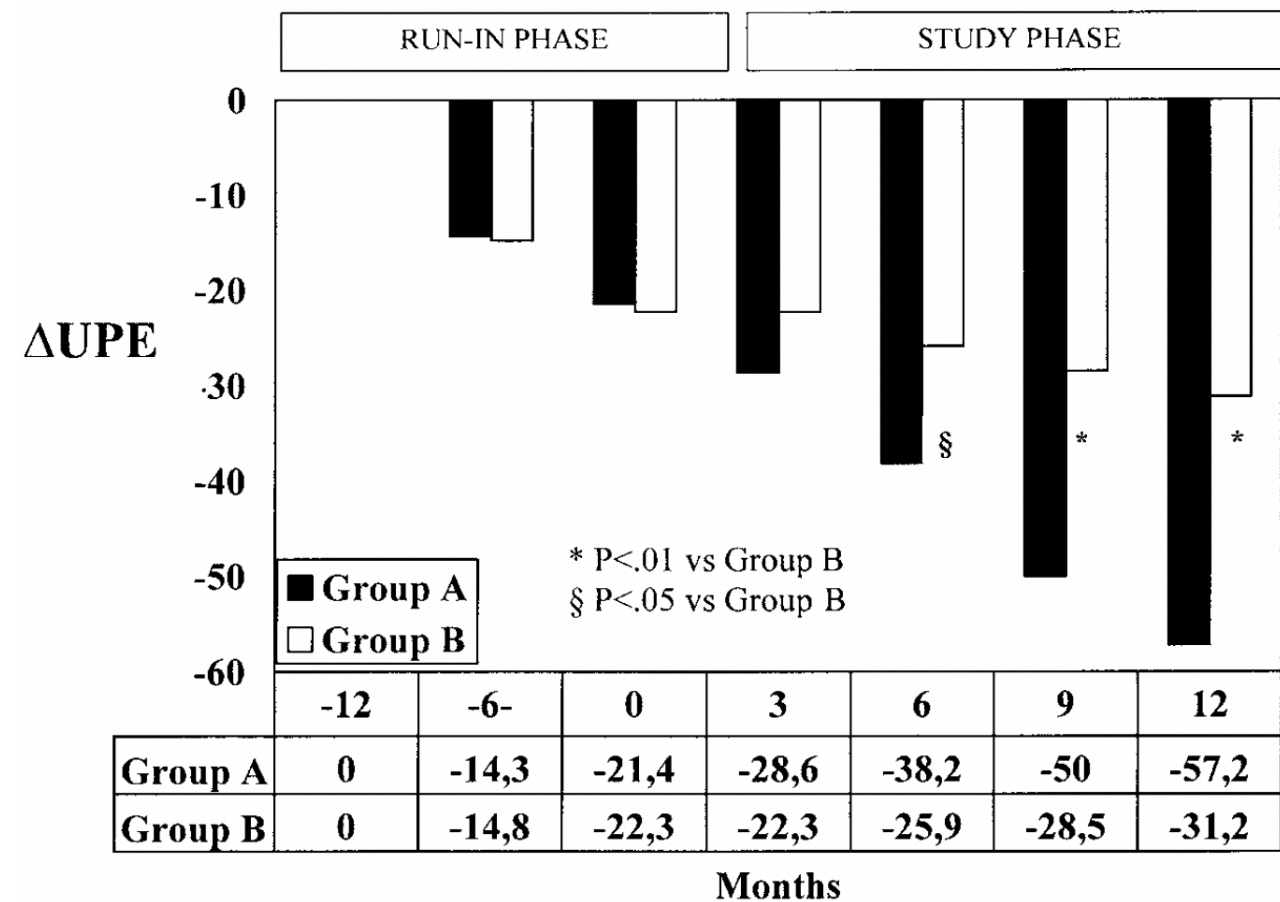
Therapeutic inertia is common in lipid management of CKD **patients. LDL reduction should be considered as the primary** target of therapy and pharmacologic intervention using statins with or without ezetimibe is recommended in all patients with stage 3–4 CKD irrespective of baseline values to achieve CV protection. **The effect of lipid-lowering treatment on proteinuria and renal** disease progression requires further evaluation.

Consensus statement 3

Patients with stage 3 CKD are considered to be at high risk and patients **with stage 4–5 CKD or on dialysis at very high risk**. In the **setting of non-dialysis CKD, goal of therapy is LDL <70 mg/dL** in high risk CKD patients and < 55 mg/dL in very high-risk patients.

A Controlled, Prospective Study of the Effects of Atorvastatin on Proteinuria and Progression of Kidney Disease

Stefano Bianchi, MD, Roberto Bigazzi, MD, Alberto Caiazza, MD, and Vito M. Campese, MD



Am J Kidney Dis 2003; 41:565-570.



Intensive Lipid Lowering with Atorvastatin 80 mg Improves Renal Function More Than 10 mg in Patients with Coronary Heart Disease

A Subanalysis of the Treating to New Targets (TNT) Study

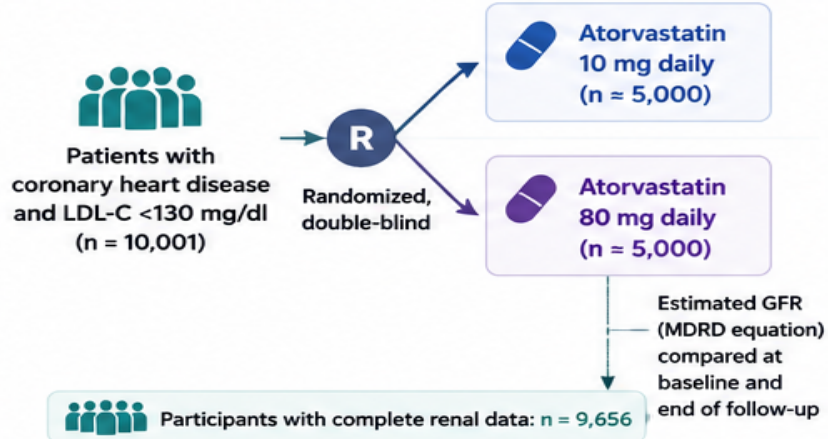
BACKGROUND & OBJECTIVES



Data suggest that atorvastatin may be nephroprotective.

This subanalysis of the TNT study investigated how intensive lipid lowering with 80 mg of atorvastatin affects renal function compared with 10 mg in patients with coronary heart disease.

DESIGN, SETTING, PARTICIPANTS & MEASUREMENTS



PRIMARY OUTCOME



Change in estimated GFR (ml/min per 1.73 m²) from baseline to end of follow-up

RESULTS

BASELINE

Atorvastatin 10 mg	Atorvastatin 80 mg
65.6 ± 11.4 ml/min per 1.73 m ²	65.0 ± 11.2 ml/min per 1.73 m ²

CHANGE IN ESTIMATED GFR (End of follow-up; median time 59.5 months)

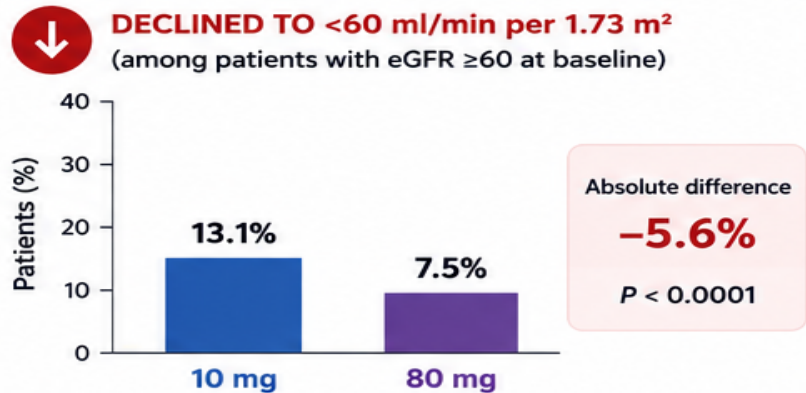
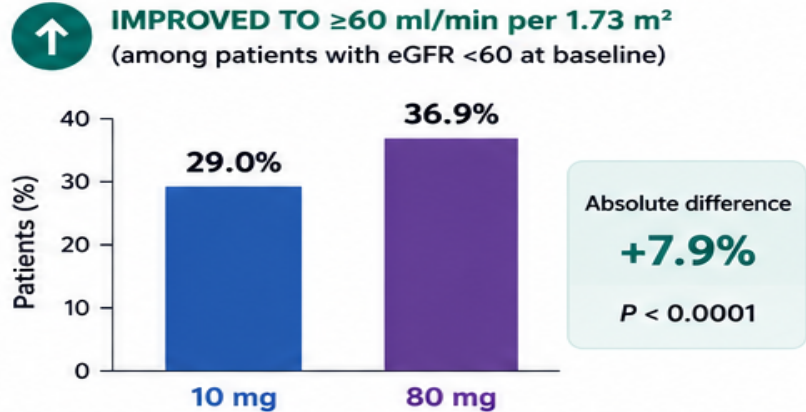
10 mg	80 mg
+3.5 ± 0.14 ml/min per 1.73 m ²	+5.2 ± 0.14 ml/min per 1.73 m ²

P < 0.0001
for treatment difference



In the 80-mg arm, estimated GFR improved to ≥60 ml/min per 1.73 m² in significantly more patients and declined to <60 ml/min per 1.73 m² in significantly fewer patients than in the 10-mg arm.

DISTRIBUTION OF ESTIMATED GFR AT FOLLOW-UP



CONCLUSIONS

The expected 5-year decline in renal function was not observed.

Estimated GFR improved in both treatment groups but was significantly greater with 80 mg than with 10 mg, suggesting this benefit may be dosage related.



PLANET I Trial: Different Renal Effects of High-Intensity Statins in Patients with Diabetes and Progressive Renal Disease



353 patients with type 1 or type 2 diabetes and proteinuria (UPCR 500–5000 mg/g) on stable ACEi/ARB therapy

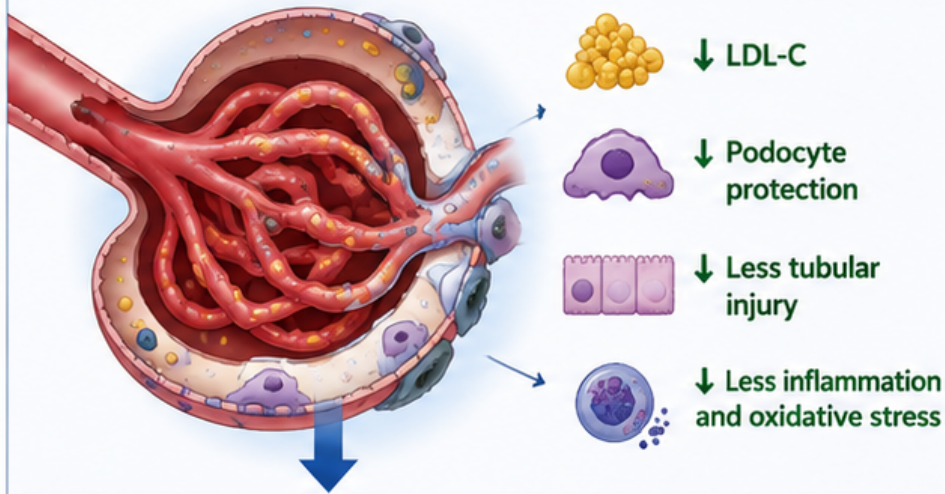


52 weeks randomised, double-blind



Primary endpoint: Change in UPCR from baseline to week 52

ATORVASTATIN 80 mg (n=111)



Proteinuria

↓ -13%

(UPCR ratio 0.87; p=0.033)



eGFR

Stable

(no decline)



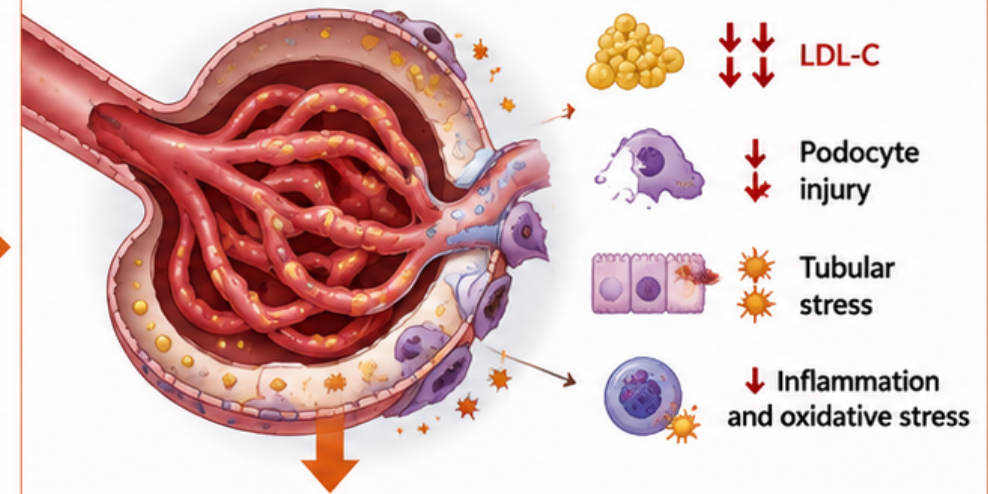
Renoprotection

EQUIVALENT
LIPID LOWERING



DIFFERENT
RENAL RESPONSE

ROSUVASTATIN 40 mg (n=124)



Proteinuria

↔

(UPCR ratio 0.96; p=0.53)



eGFR

↓ Decline

(significant fall)



More renal adverse events



Proteinuria

Only atorvastatin 80 mg significantly reduced proteinuria



Kidney function

eGFR preserved with atorvastatin
Declined with rosuvastatin



Clinical implication

Renoprotection is not a class effect of statins

Renal Effects of Atorvastatin vs Rosuvastatin in Proteinuric CKD

Combined Analysis of PLANET I (Diabetes) and PLANET II (Non-diabetes)

PLANET I

Patients with diabetes and proteinuria



Type 1 or type 2 diabetes
Proteinuria
(UPCR 500–5000 mg/g)
On stable ACEi/ARB
therapy



353 patients

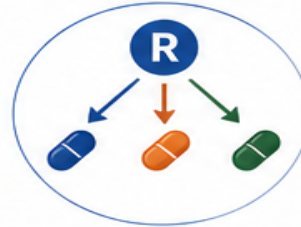
147 centres in 10 countries



52 weeks

Randomised,
double-blind,
parallel-group

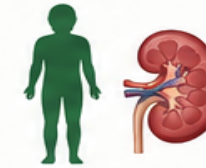
Design (both studies)



Primary endpoint:
Change in UPCR
from baseline to week 52

PLANET II

Patients without diabetes and proteinuria



Proteinuria
(UPCR 500–5000 mg/g)
On stable ACEi/ARB
therapy



237 patients

Similar design and locations



52 weeks

Randomised,
double-blind,
parallel-group



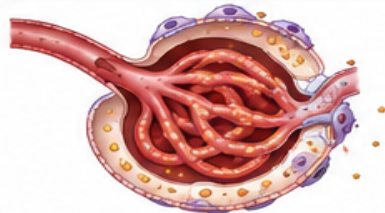
COMBINED POST-HOC ANALYSIS: PLANET I + PLANET II

Total N = 590 patients

To compare the renal effects of statins
in proteinuric CKD

Change in UPCR from Baseline to Week 52

ATORVASTATIN 80 mg

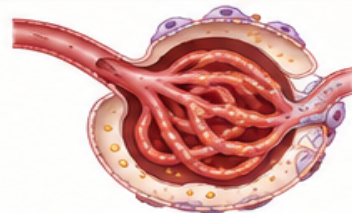


↓ **-13.6%**
(95% CI -20.9 to -5.7)

UPCR ratio
0.86

(95% CI 0.79–0.94)

ROSUVASTATIN 10 mg

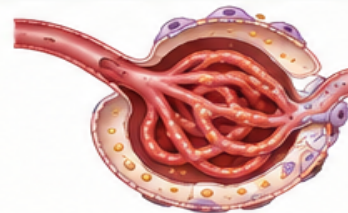


↓ **+1.9%**
(95% CI -9.6 to 14.3)

UPCR ratio
1.02

(95% CI 0.92–1.14)

ROSUVASTATIN 40 mg



↓ **-4.6%**
(95% CI -14.8 to 6.6)

UPCR ratio
0.95

(95% CI 0.86–1.05)

Between-group differences
(Atorvastatin 80 mg vs)

Rosuvastatin 10 mg
↓ **-15.6%**
(95% CI -28.3 to -0.5)
p = 0.043

Rosuvastatin 40 mg
↓ **-18.2%**
(95% CI -30.2 to -4.2)
p = 0.013

Other key findings

eGFR change (ml/min per 1.73 m²)



↓ **Atorvastatin 80 mg**
≈ Stable



↓ **Rosuvastatin 10 mg**
Slight decline



↓ **Rosuvastatin 40 mg**
Greater decline



Adverse events

Similar overall incidence
across groups



Renal adverse events

Lowest with atorvastatin
80 mg



CONCLUSION

In patients with proteinuric CKD, atorvastatin 80 mg reduced proteinuria significantly more than rosuvastatin 10 mg and rosuvastatin 40 mg, despite similar or greater LDL-C lowering with rosuvastatin.

Renoprotection is not a class effect of statins.

Association between statin treatment and outcome in relation to renal function in survivors of myocardial infarction

Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART): Period 2003-2006, n° 42814
pts in-hospital survivors of MI, no statin therapy on admission

- Hyperuricemia identifies patients at increased cardio-nephro-metabolic risk and is consistently associated with adverse cardiovascular and renal outcomes.
- Xanthine oxidase inhibition may represent a promising strategy for cardiovascular and renal protection beyond serum urate lowering.
- Chronic kidney disease markedly amplifies cardiovascular risk and should be considered a cardiovascular risk equivalent.
- Aggressive optimization of the lipid profile is a cornerstone of cardiovascular risk reduction in patients with CKD.
- Statins remain the foundation of lipid-lowering therapy in CKD, although their renoprotective effects appear to differ among individual agents.

