ADVANCES IN CARDIAC ARRHYTHMIAS
and
GREAT INNOVATIONS IN CARDIOLOGY

XXVI Giornate Cardiologiche Torinesi

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

UNIVERSITÀ DEGLI STUDI DI TORINO

From Caliper to Catheter

JMC JOINT MEETING OF CARDIOLOGY

Sebastiano MARRA MD,FESC

DIRECTOR
CARDIOVASCULAR and THORACIC DIPARTMENT

Chronic Ischemic Cardiomiopathy: RISK OF CARDIOVASCULAR DEATH AND URIC ACID

- NO CONFLITS OF INTEREST

Dr. Nathan Smith Davis

Am Medical Association, JAMA, 1897; 29:261-2

"High arterial tension in gout is due in part to uric acid or other toxic substances in the blood which increases the tonus of the renal arterioles"

Uric Acid

PURINE FOOD

200 mg

ENDOGENOUS SINTESYS

700 mg

TISSUE NUCLEIC AC.

100 mg

MISCIBLE POOL 1000 mg

ELIMINATION

RENAL 300-600 mg

INTESTINAL 100-200 mg

The " saturation point " of the miscible pool is 6.8 mg/dl at 37 C, pH 7.4.
With change of physical-chemical conditions already as low as 6.0 mg/dl

The Two Faces of Uric Acid

- **Uric acid highest anti-oxidant in blood**
- **Provide > 50% of total anti-oxidant**
- **Anti-oxidant effect complex**
  - **Doesn't react with some oxidants, e.g SO**
- **Effects in cardiovasc.disease?**
  - **Protective (compens) rxn vs primary cause**
  - **Acitivated by oxidative stress**
  - **Metab derangements - Cu++ & Fe++**

Hyperuricemia & Gout

Pathogenesis of hyperuricemia

10%

90%

Urate Overproduction		
Primary idiopathic	Myeloproliferative diseases	Rhabdomyolysis
HPRT deficiency	Polycythemia vera	Exercise
PRPP synthetase overactivity	Psoriasis	Alcohol
Hemolytic processes	Paget's disease	Obesity
Lymphoproliferative diseases	Glycogenosis III, V, and VII	Purine-rich diet
Decreased Uric Acid Excretion		
Primary idiopathic	Starvation ketosis	Drug ingestion
Renal insufficiency	Berylliosis	Salicylates (>2 g/d)
Polycystic kidney disease	Sarcoidosis	Diuretics
Diabetes insipidus	Lead intoxication	Alcohol
Hypertension	Hyperparathyroidism	Levodopa
Acidosis	Hypothyroidism	Ethambutol
Lactic acidosis	Toxemia of pregnancy	Pyrazinamide
Diabetic ketoacidosis	Bartter's syndrome	Nicotinic acid
	Down syndrome	Cyclosporine
Combined Mechanism		
Glucose-6-phosphatase deficiency	Fructose-1-phosphate aldolase deficiency	Alcohol
		Shock

Abbreviations: HPRT, hypoxanthine phosphoribosyltransferase; PRPP, phosphoribosylpyrophosphate.

...a...Metabolic Disease

Glycide metabolism disease (for ex. DM)

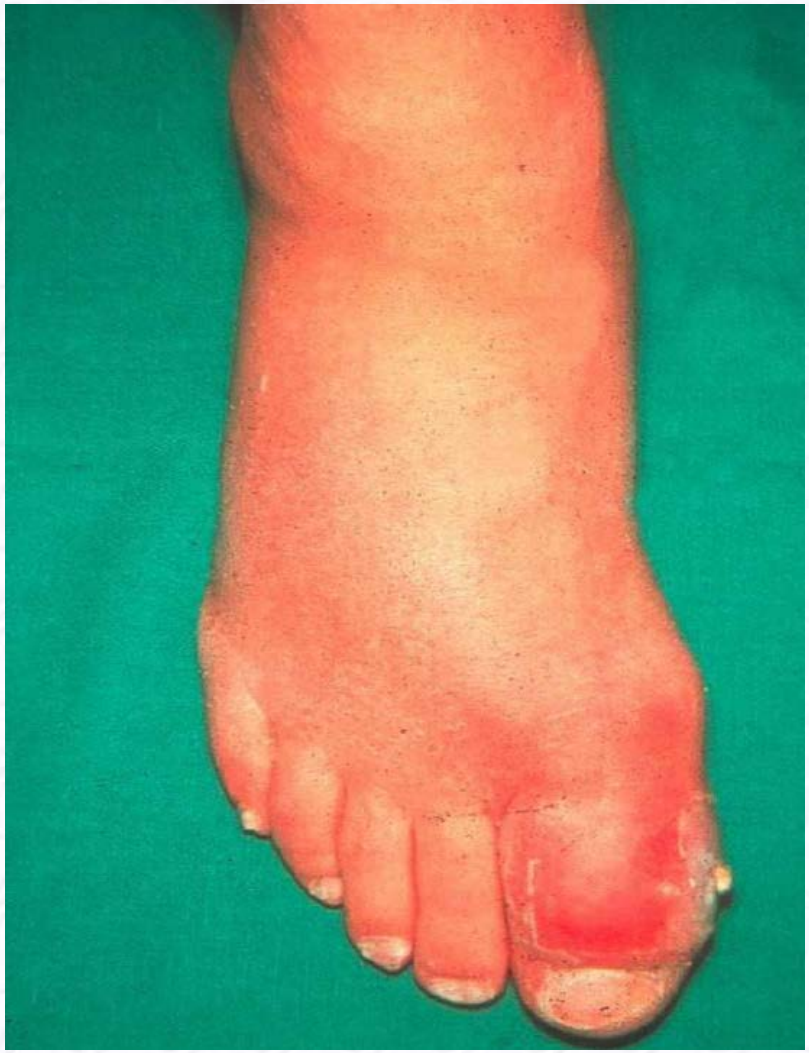
Lipidic metabolism disease (dyslipidemia)

Amino acids metabolism disease (aminoacidopathies)

Purinic metabolism disease (hyperuricemia and gout)

Energetic metabolism disease (obesity, thinness)

Gout



Prevalence has doubled the last 15 years

Why?

1) **Longevity - ↑ in DM / CHF**

2) **Iatrogenic – ASA & Diuretics**

3) **↑ HTN (1/3 of Americans)**

4) **↑ Caloric Intake (beer,wine,..)**

EPIDEMIOLOGY

Gout: most common form of inflammation arthritis in men > 40 y.o.

Prevalence of gout 2009-10 : 3.9%

- **12 million persons with Gout &S. Uric.Acid**
- **10 yr incr. of 45%**
- **> 80 yo, incr. 100%**
- **Uric acid levels have inc. signif. over last 80 yrs**

Inc. SUA is the most highly correlated lab value with the Metabolic Syndrome

Zhu Y, Pandya BJ, Choi HK. Prevalence of gout & hyperuricemia in the US general population: the National Health & Nutrition Exam Survey 2007-08. Arth. Rheum. 2011 Oct; 63 (10): 3136-41.

Italian Epidemiological Data: steady growth

Health Search data 2012:

Prevalence of gout

(assisted population ≥ 18 years old)

Perfect Storm

more severe & complex cases due to a convergence of factors

- **Prevalence of High BP**
- **Use of diuretics**
- **Use of ASA**
- **Obesity**
- **Inc. consumption of**
  - **Beer**
  - **Fructose**
  - **Corn syrup**

- **Inc. life expectancy**
- **Ability to keep pts alive with:**
  - **CAD**
  - **CHF**
  - **DM**
  - **CKD**
- **Lack of effective therapy**

Kuo CF, Yu KH, See LC, et al. Elevated risk of mortality among gout pts: a comparison with the national population in Taiwan. Joint Bone Spine. 2011 Dec;78(6):577-80.
Keenan RT, O'Brien WR, Lee KH, et al. Prevalence of contraindications & prescription of pharmacologic therapies fof gout. Am J Med. 2011 Feb;124(2):155-63.

Objectives

Review compelling data : hyperuricemia **&** its strong association with Hypertension, MI, Stroke , CKD

Reinforce an awareness that patients presenting with gout **should be evaluated** for other risk factors associated with CVD

Myth:

Gout is common among men but rare among women

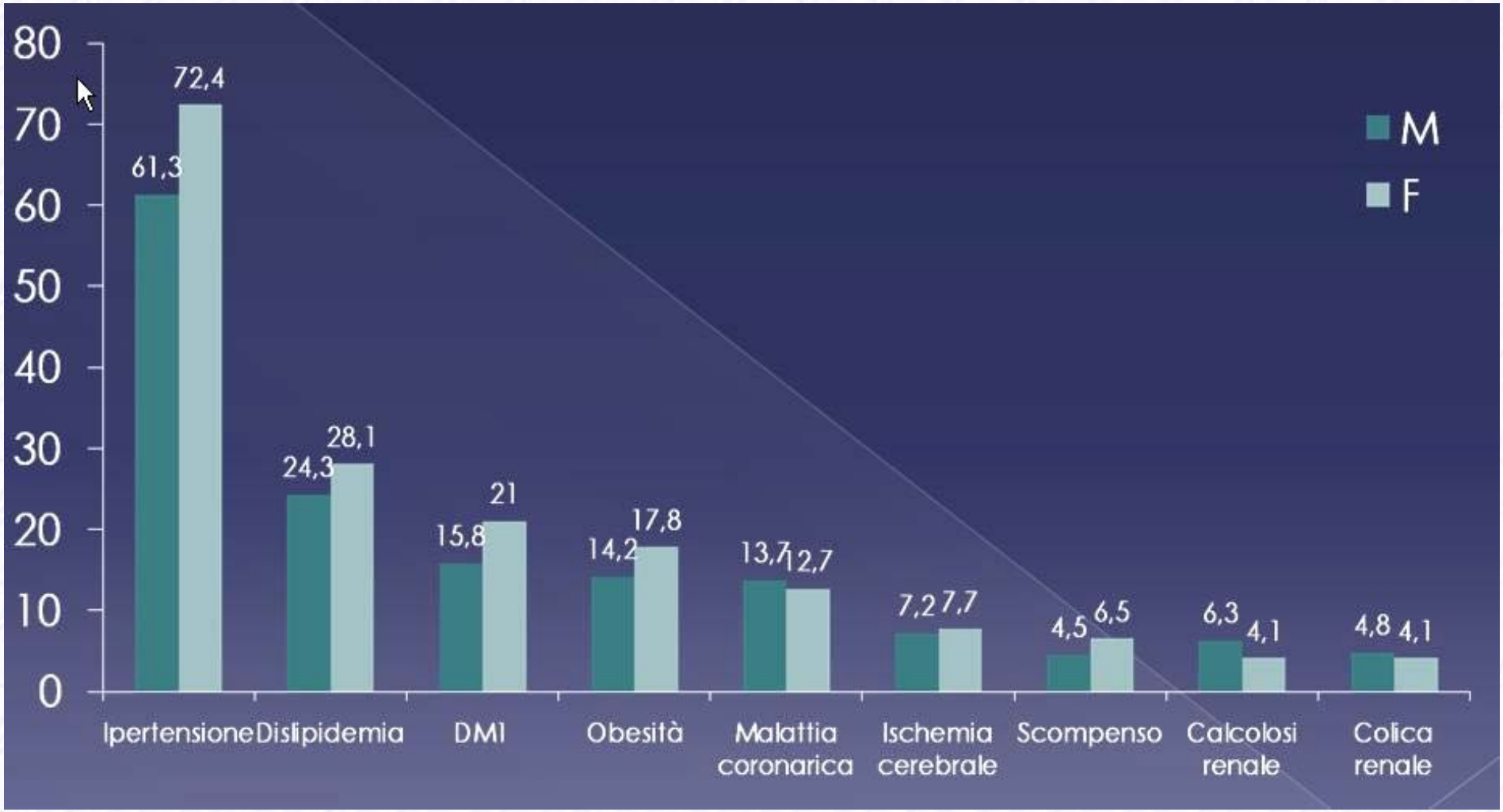
Reality

- **Increases substantially after menopause & rises with age**
- **In kidney, URAT1 responsible for reabsorbtion of uric acid from proximal tubule**
- **Estrogen has a direct effect on expression**

Enomoto et al. Nature. 2002; 417.

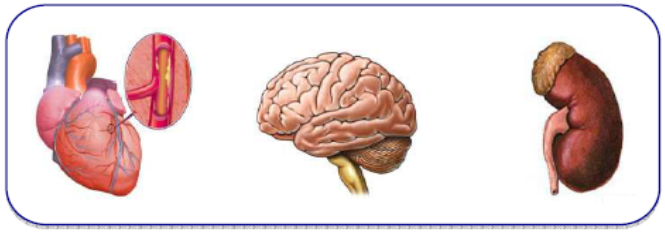
Gout and Co-morbidity

Stamp Lisa K and Chapman Peter T, Gout and its comorbidities: implications for therapy, Rheumatology (2013) 52 (1): 34-44.



progression

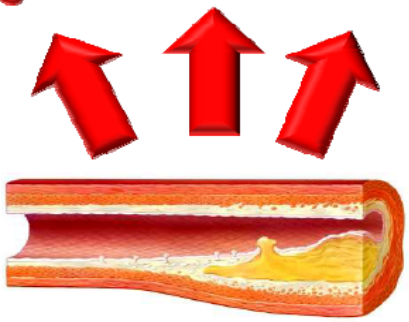
Myocardial infarction
Stroke
Cognitive decline
Proteinuria



Stroke CAD PAD

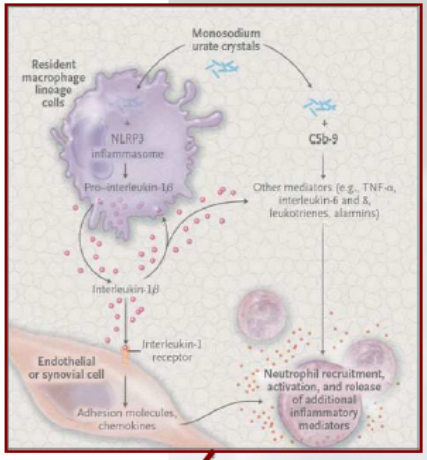
Atherosclerosi
LVH

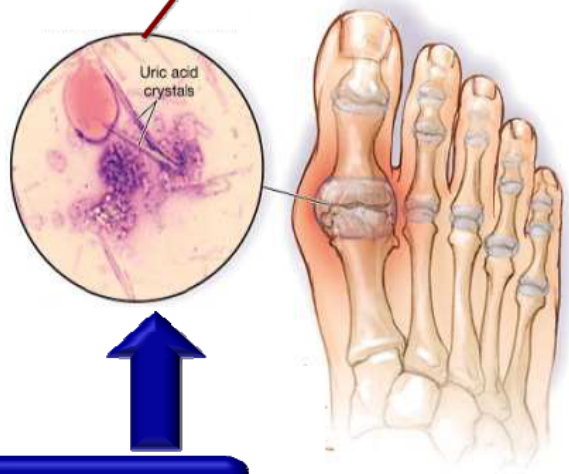
cardiovascular risk



CV risk factors

Heart failure
ESRD - Dementia





High Serum Uric Acid

How can I prove that Hyperuricemia is a risk factor for atherosclerosis?

- **Uric Acid pathologically assoc with vascular damage & inflammation**
- **Data that hyperuricemia is associated with CVD & premature death from MI & stroke**
- **Lowering uric acid levels is associated with a reduced risk**

SUA and relationship to Atherogenesis

The uric acid in soluble form can penetrate within the vascular smooth muscle cells and cause deleterious effects

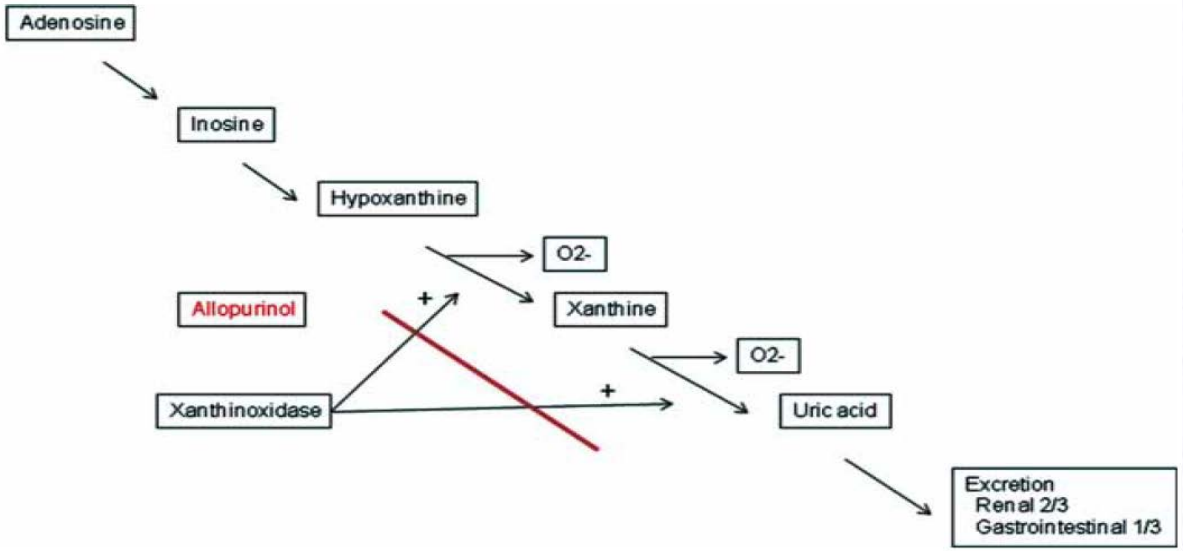
Uric acid is able to activate mitogenic factors of smooth muscle cell proliferation determining one of the characteristics of atherosclerosis

Corry DB et al, Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. J Hypertens 2008; 26(2):269-275

Uric acid intracellular also determines the formation of pro-inflammatory proteins and vasoconstrictors, including angiotensin II , and stimulates the production of different growth hormones , including the platelet-derived growth factor

Alderman MH, Iperuricemia e danno vascolare, Hot Topics in Cardiology 2008, 14: 7-14

Serum uric acid and cardiovascular disease



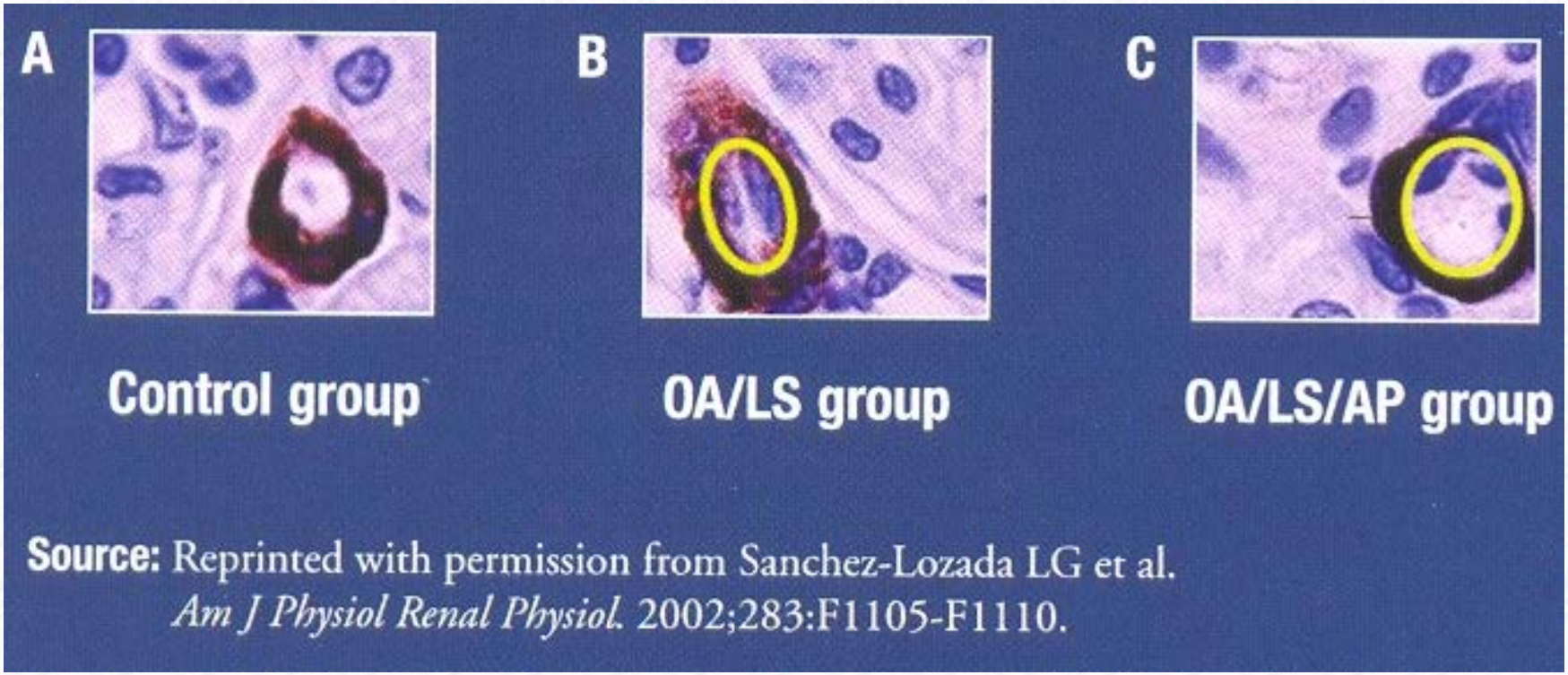
Conversion of hypoxanthine to uric acid is regulated by enzyme xanthine oxidoreductase (XO). Reactive oxygen species (ROS) are produced.

Major sources of XO are liver and small intestine, but are evidences for local production of XO by endothelium and myocardium.
XO is associated with enhanced oxidative stress.

XO activity is up-regulated in many cardiovascular diseases, such as myocardial ischemia, reperfusion injury, left ventricular remodeling after myocardial infarction and heart failure.

Mechanisms of vascular damage in gout & oxalosis:

Uncontrolled hyperuricemia results in afferent arteriole with thick wall & small lumen (B).
When urate normalized, arteriole thinner & the lumen larger (C).



Mechanisms of vascular damage in gout & oxalosis:

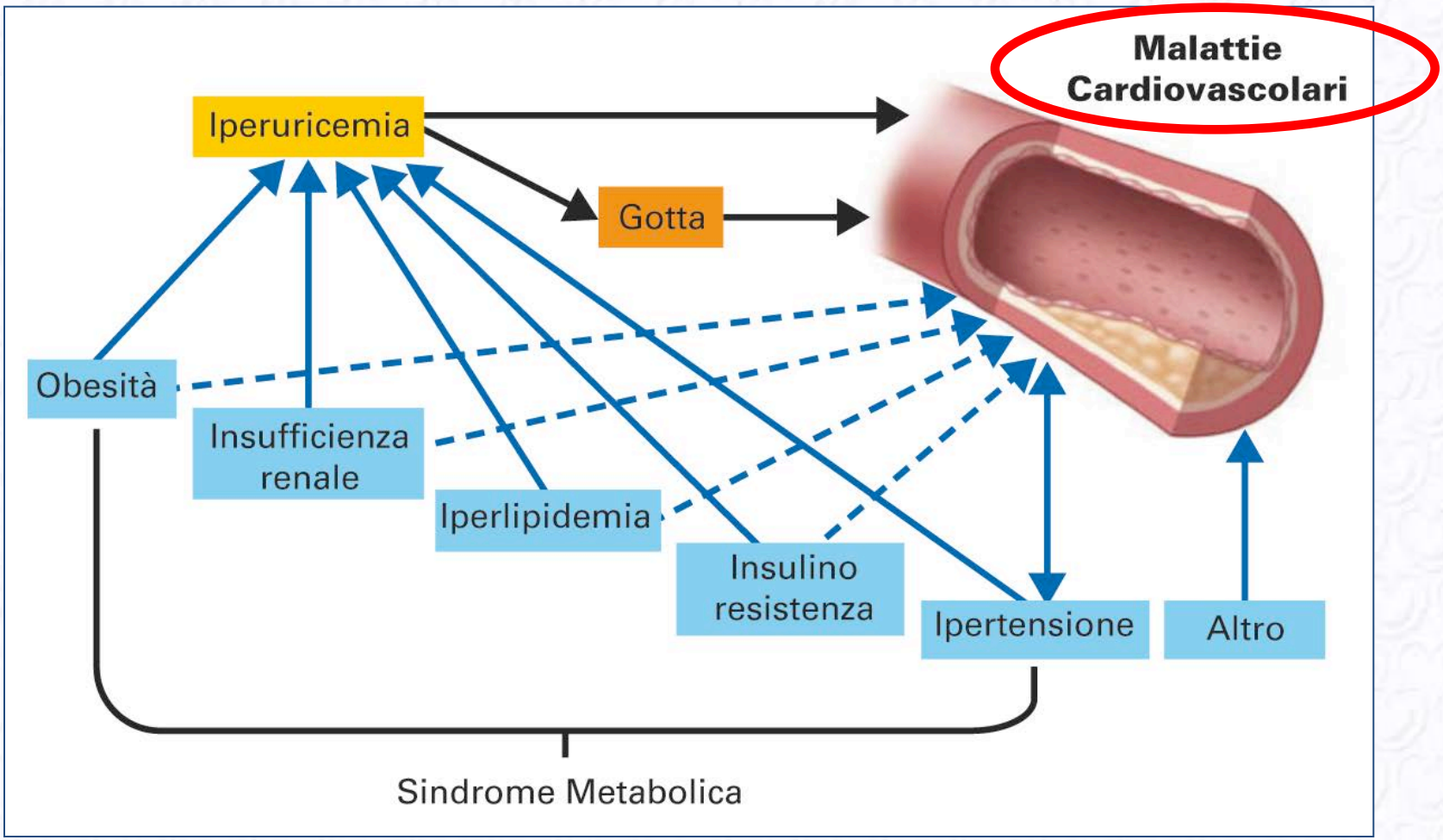
CRYSTAL INDUCED

GRANULOCYTE MEDIATED

ENDOTHELIAL INJURY

Boogaerts MA et al. Thromb Haemost. 1983 Aug 30;50(2):576-580.

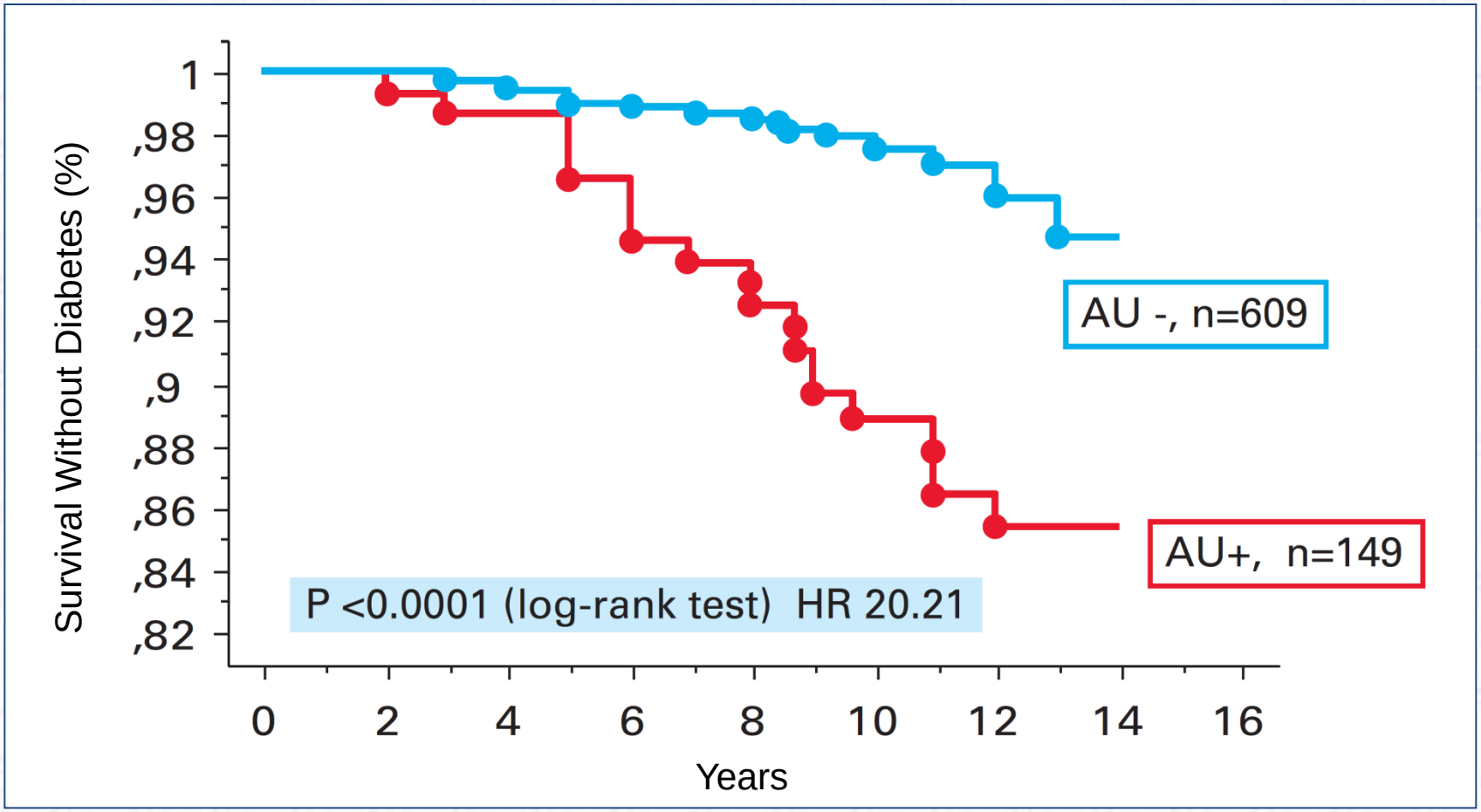
Gout, Hyperuricaemia and CVD: Cause or Consequences?



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

SUA and diabetes type 2

Circulating levels of uric acid predict the onset of diabetes type 2 in hospitalized patients with arterial hypertension: the MAGIC Study



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

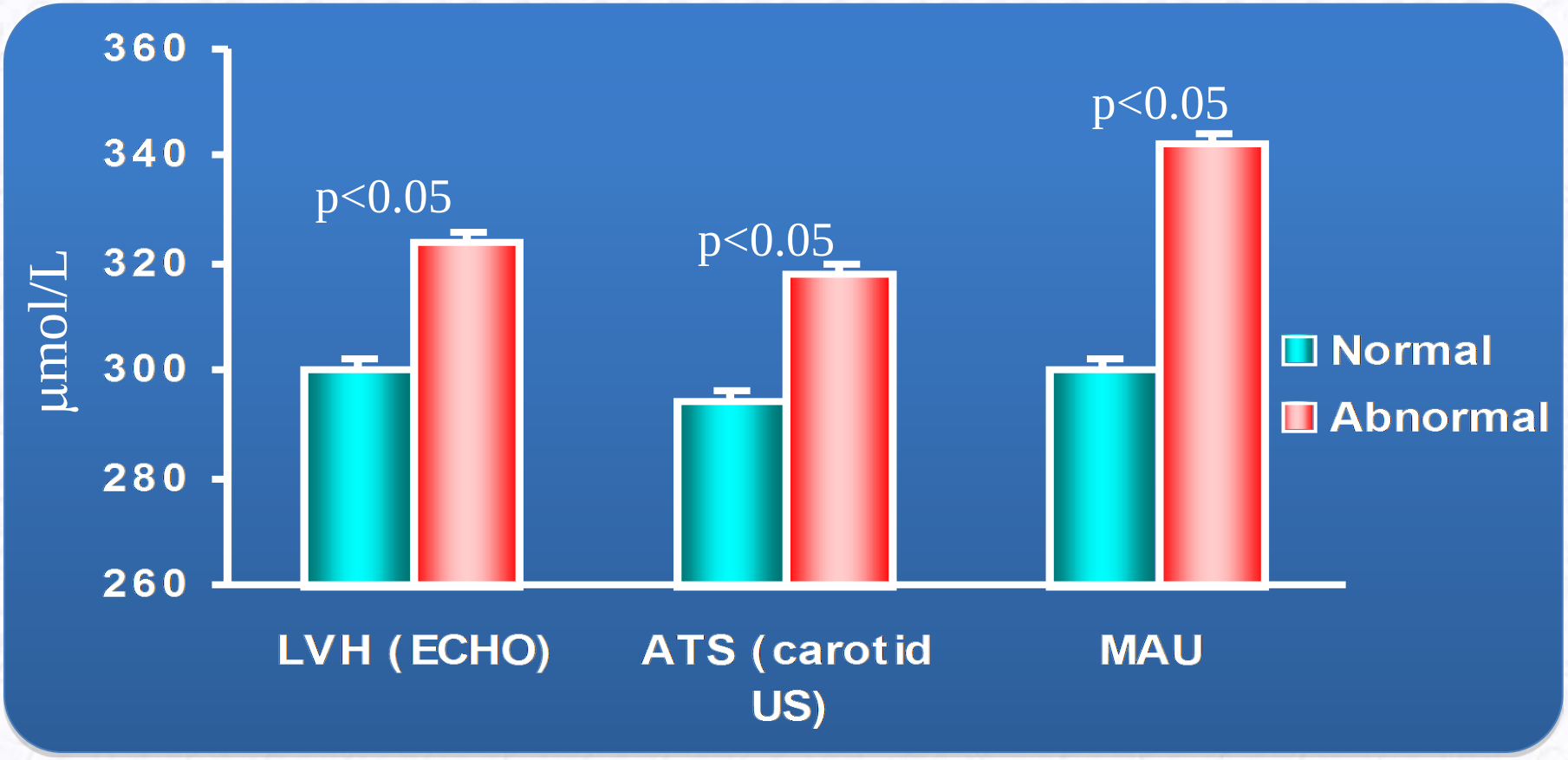
Is There a Pathogenetic Role for Uric Acid in Hypertension, Cardiovascular & Renal Disease?

- **SUA stimulates vascular smooth muscle cell proliferation & induces endothelial dysfunction**
- **SUA stimulates the production of cytokines from leukocytes & chemokines from vascular smooth muscle cells (TNF, IL-1, IL -6)**
- **Hyperuricemia activates circulating platelets**
- **Mild hyperuricemia inhibits the nitric oxide system in the kidney → vasoconstriction**

Johnson Richard J et al. Hypertension. 2003;41:1183
http://hyper.ahajournals. Org/cgi/content/full/41/6/1183

SUA and hypertension

Circulating levels of SUA and organ damage in hypertension



Viazzi F, et al. Hypertension 2005;45(5):991-6

SUA level is higher in patients with end-stage CHF

There are several mechanisms involved in hyperuricemia-induced heart failure.

The increased SUA production may be due to increased XO substrate (ATP breakdown to adenosine and hypoxanthine) and to the up-regulation and increase in XO activity.

When released from necrotic tissue, SUA can produce additional adverse effects on cardiovascular system and can mediate the immune response.

In heart failure hyperuricemia is a marker of XO activation.

SUA level and cardiovascular disease

Several studies have shown that the reduction in the SUA level may be associated with the reduction in cardiovascular morbidity and mortality.

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Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study

- **Compared losartan to atenolol for reduction in CV morbidity & mortality**
- **Losartan interferes with urate reabsorbtion**
- **>9000 pts w HBP & LVH followed for ~ 4.8 yrs**
- **Pts. generally not hyperuricemic on entry**
- **Baseline SUA found to be signif assoc with inc CV events**
- **Inc. SUA in atenolol gp signif > losartan gp (P<.0001)**
- **Estimated contribution of SUA to CV death, non-fatal & fatal MI, & fatal & non-fatal stroke was 29%**
- **Attenuating SUA reduces CV events in high risk gps**

Hoieggen A et al, Impact of serum uric acid on cardiovascular outcomes in LIFE study, Kidney Int. 2004;65:1041-1049.

GREACE Study

(Greek Atorvastatin and Coronary Heart Disease Evaluation)

ATHYROS VG, ELISAF M, PAPAGEOGIOU AA ET AL:
Effect of statins versus untreated diplipidemia on serum uric acid levels in patients with coronary heart disease: A subgroup analysis of the GREACE study
American Journal of Kidney Disease Vol. 43, Issue 4, pp 589-599 (April 2004)

1600 patients had normal Renal function (Creat. < 1.3mg/dl) and elevated S.U. Acid (> 7.1mg/dl) at baseline

8.2% reduction in SUA in treated patients compared to 3.3% ↑S.U. Acid in untreated patients

Cox multivariate analysis utilized revealing that S.U. Acid is an independent predictor of CHD recurrent events – recurrent events correlated significantly with SUA Levels

SUA is a Risk Factor for Myocardial Infarction & Stroke ?

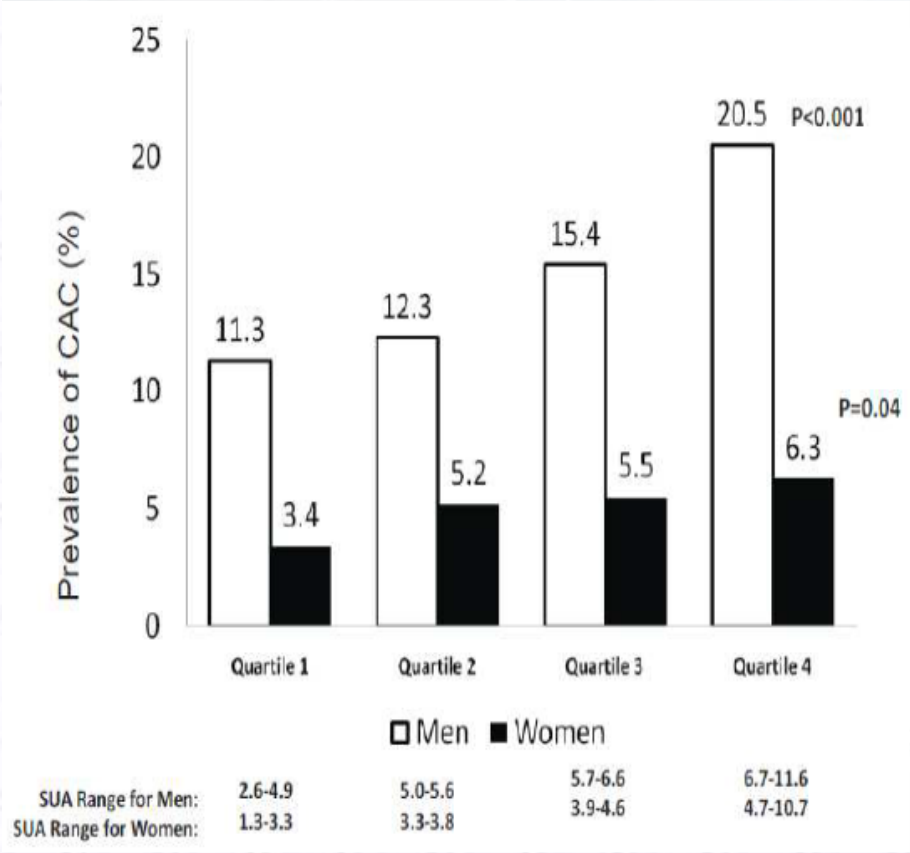
- 4385 participants in Rotterdam, 1990-1993 were >55 yoa, free from CVA & CHD
- Average f/u was 8.4 yrs
- Relationship betw SUA & risk of CVD is linear
- High SUA levels assoc with risk of MI & CVA
- Age & sex adjusted hazard ratios for highest vs lowest quintile of UA were
  - 1.68 CVD
  - 1.87 MI
  - 1.57 CVA

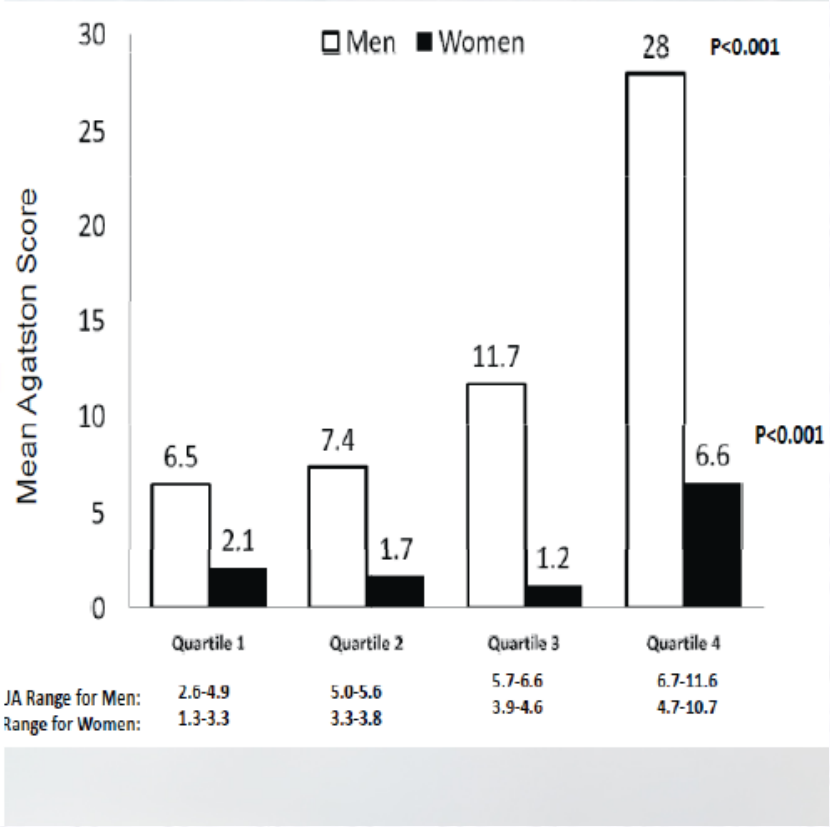
SUA is a strong risk factor for MI & stroke

Bos MJ et al. Stroke. 2006;37:1503-1507.

SUA : coronary calcium (Cardia Study)

2,498 participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study





Krishnan E et al, Arthritis Research & Therapy 2011; 13: 66-70

Am J Cardiol 2012;109:1260 –1265

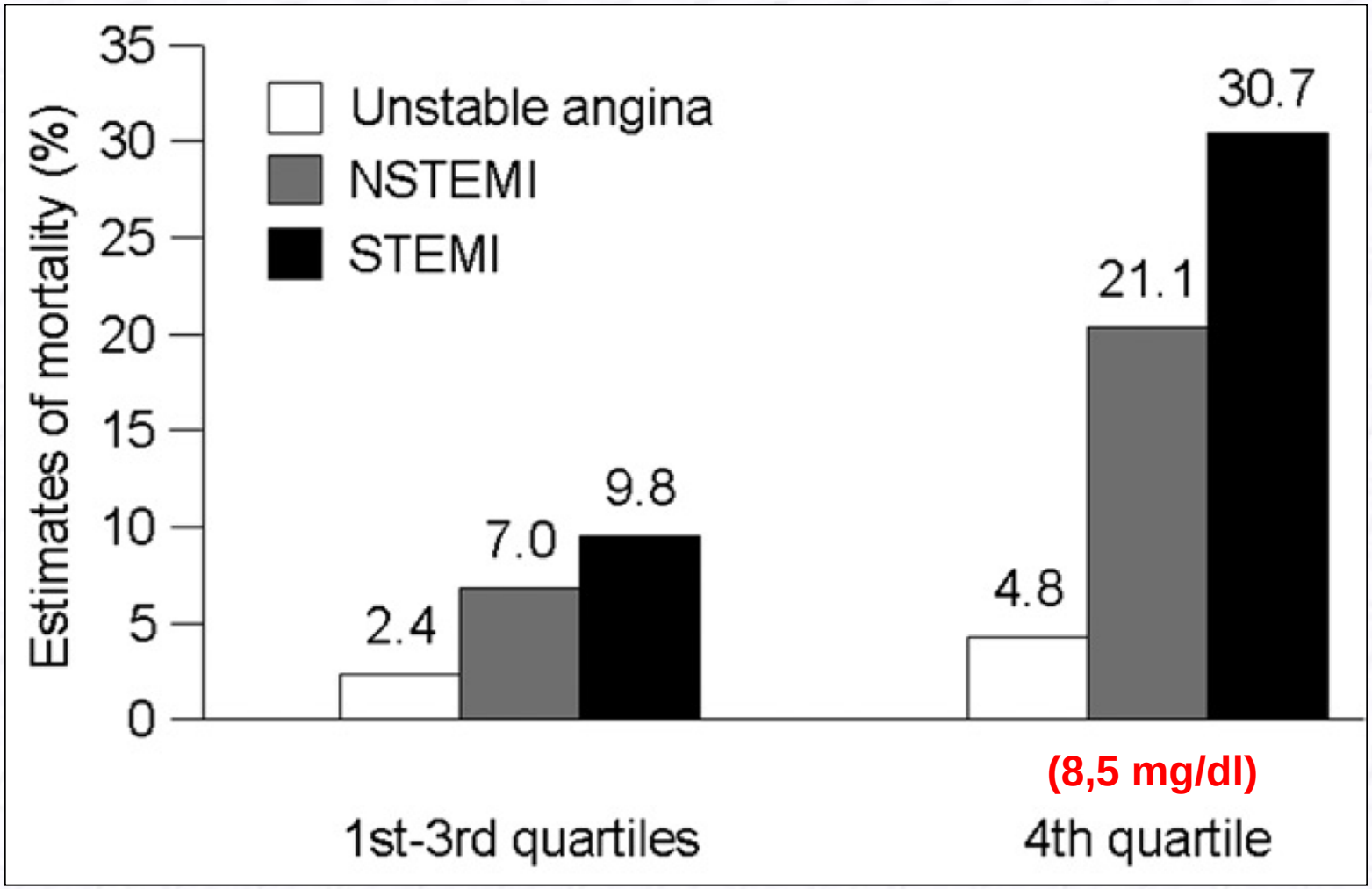
Prognostic Value of Uric Acid in Patients With Acute Coronary Syndromes

Gjin Ndrepepa, MD[a,*], Siegmund Braun, MD[a], Hans-Ullrich Haase, MD[b], Stefanie Schulz, MD[a], Sabine Ranftl, MD[a], Martin Hadamitzky, MD[a], Julinda Mehilli, MD[a], Albert Schömig, MD[a,b], and Adnan Kastrati, MD[a]

…elevated levels of uric acid are independent predictor of 1-year mortality across the whole spectrum of patients with acute coronary syndromes treated with percutaneuos coronary intervention.

SUA and CAD

Prognostic value of SUA in patients with acute coronary syndrome



Ndrepepa G et al, Am J Cardiol 2012;109:1260 –1265

FASI DEL DANNO BIOCHIMICO DA ISCHEMIA / RIPERFUSIONE

1 . IN ISCHEMIA

. Degradazione dell' ATP a IPOXANTINA
. Conversione della Xantina Deidrogenasi a XANTINA OSSIDASI ad opera del CALCIO

2 . ALLA RIPERFUSIONE

. Ossidazione della IPOXANTINA ad URATO con formazione di ROS (Anioe Superossido)

Uric acid for diagnosis and risk stratification in suspected myocardial infarction

Karin Wildi[*,1], Philip Haaf[*,1], Tobias Reichlin[†], Resat Acemoglu[*], Jeannine Schneider[*], Cathrin Balmelli[*], Beatrice Drexler[*], Raphael Twerenbold[*], Tamina Mosimann[*], Miriam Reiter[*], Mira Mueller[*], Susanne Ernst[‡], Paola Ballarino[§], Christa Zellweger[*], Berit Moehring[*], Carles Vilaplana[¶], Heike Freidank[**] and Christian Mueller[*]

[*]Department of Cardiology, University Hospital, Basel, Switzerland, [†]Brigham & Women´s Hospital, Boston, MA, USA, [‡]Department of Internal Medicine, Kantonsspital Olten, Olten, Switzerland, [§]Emergency Department, San Martino Hospital, Genova, Italia, [¶]Servicio de Laboratorios, Hospital del Mar—IMIM, Barcelona, Spain, [**]Laboratory Medicine, University Hospital, Basel, Switzerland

ABSTRACT

Background Hypoxia precedes cardiomyocyte necrosis in acute myocardial infarction (AMI). We therefore hypothesized that uric acid – as a marker of oxidative stress and hypoxia – might be useful in the early diagnosis and risk stratification of patients with suspected AMI.

Materials and methods In this prospective observational study, uric acid was measured at presentation in 892 consecutive patients presenting to the emergency department with suspected AMI. The final diagnosis was adjudicated by two independent cardiologists. Patients were followed 24 months regarding mortality. Primary outcome was the diagnosis of AMI, secondary outcome was short- and long-term mortality.

Results Uric acid at presentation was higher in patients with AMI than in patients without (372 μM vs. 336 μM; $P < 0{\cdot}001$). The diagnostic accuracy of uric acid for AMI as quantified by the area under the receiver operating characteristic curve (AUC) was 0·60 (95%CI 0·56–0·65). When added to cardiac troponin T (cTnT), uric acid significantly increased the AUC of cTnT from 0·89 (95%CI 0·85–0·93) to 0·92 (95%CI 0·89–0·95, $P = 0{\cdot}020$ for comparison). Cumulative 24-month mortality rates were 2·2% in the first, 5·4% in the second and the third and 15·6% in the fourth quartile of uric acid ($P < 0{\cdot}001$ for log-rank). Uric acid predicted 24-month mortality independently. Adding uric acid to TIMI and GRACE risk score improved their prognostic accuracy as shown by an integrated discrimination improvement of 0·04 ($P = 0{\cdot}007$) respective 0·02 ($P = 0{\cdot}021$).

Conclusions Uric acid, an inexpensive widely available biomarker, improves both the early diagnosis and risk stratification of patients with suspected AMI.

Keywords Acute coronary syndrome, chest pain, diagnosis, mortality, uric acid.

Eur J Clin Invest 2013; 43 (2): 174–182

Uric acid for diagnosis and risk stratification in suspected myocardial infarction

Eu J Clin Invest 2013; 42 (2): 174-182

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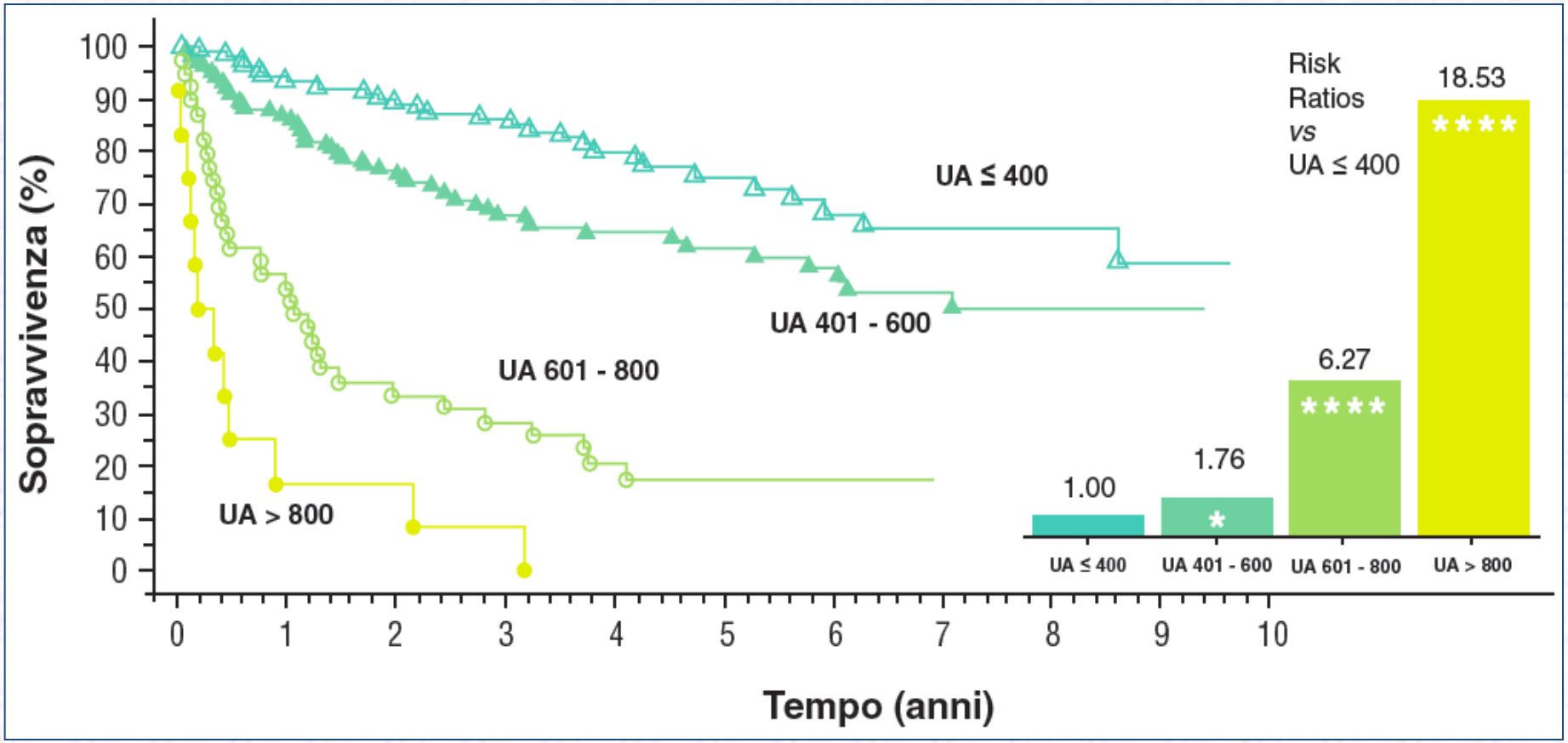
…ucid acid, an inexpensive widely avaible biomarker, improves both the early diagnosis and risk stratification of patients with suspected AMI.

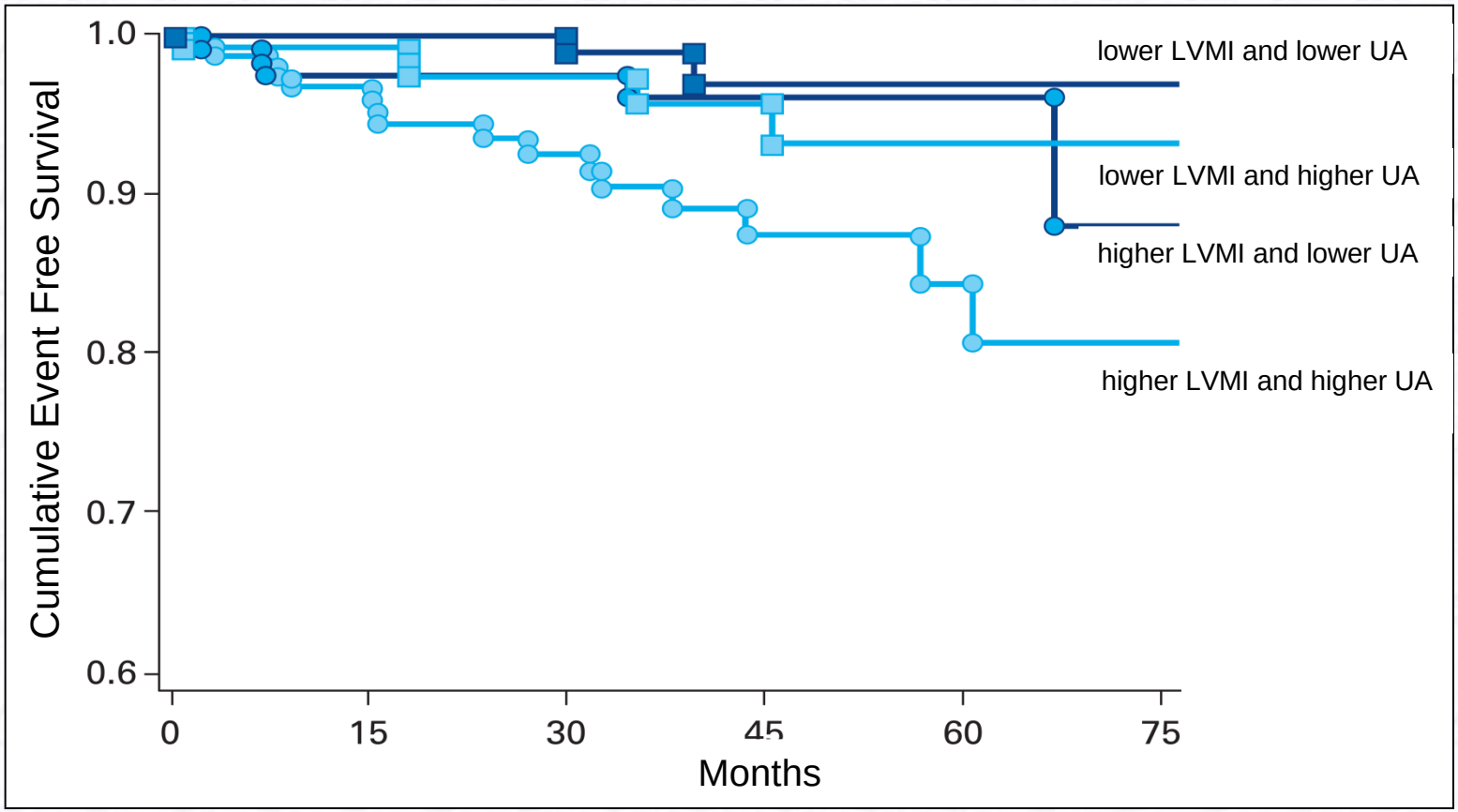
Survival Kaplan-Meier curves for distinct levels of SUA in patients with mild-to-moderate CHF



Anker SD et al. Circulation 2003; 107: 1991-97

SUA and CVD: survival

Cumulative event-free survival in CVD patients with and without organ damage in relation to circulating levels of SUA



Niskanen LK, et al. Arch Intern Med 2004; 164: 1546-1551
Feig DI, et al. N Engl J Med 2008; 359: 1811-1821

SUA and CVD: mortality

CRYSTAL ARTHRITIS (MH PILLINGER, SECTION EDITOR)

Curr Rheumatol Rep (2012) 14:195–203

Association Between Gout and All-Cause as well as Cardiovascular Mortality: A Systematic Review

Kathrin Lottmann · Xiaoyu Chen · Peter K. Schädlich

…CONCLUSION……

There was an independent association between gout and all-cause as well as cardiovascular mortality.

Knowing that patients with gout are at risk emphasized the need for adequate care.

SUA ...&...TREATMENT

Allopurinol and Oxypurinol are XO inhibitors which has been used to treat hyperuricemia.

The reducing the SUA level in HT with XO inhibitors lowers blood pressure in young with HT of recent onset.

In CHF allopurinol improves endothelial dysfunction, peripheral vasodilatator capacity and myocardial energy by reducing markers of oxidative stress

In OPT-CHF Study oxypurinol increased left ventricular ejection fraction and improved clinical outcome in CHF patients presenting with high SUA levels.

SUA and CVD: therapy

The target of the ipo-uricemic therapy :

Is to facilitate the dissolution of urate chrystals and to prevent the new making

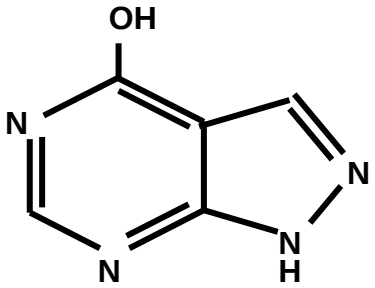
It's possible if we maintain serum uric acid levels under the monosodium urate saturation point

EULAR raccomandation 2011 (European League Against Reumathism)

Allopurinol - Febuxostat

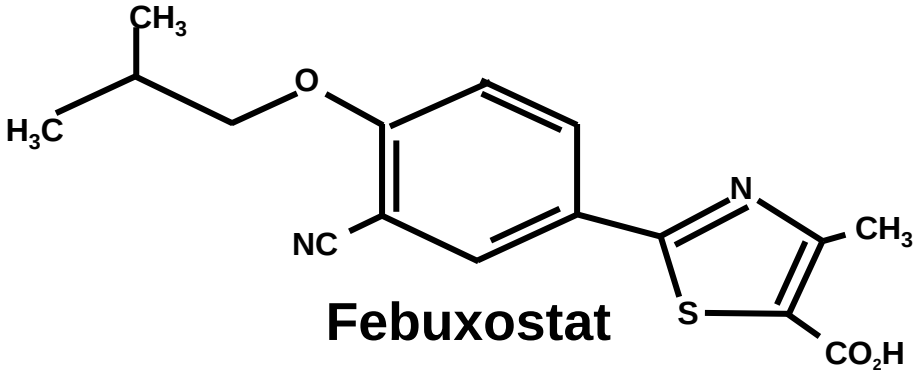
XO (xantino-ossidasi) inibitors

Purinic



Allopurinol

No purinic



Febuxostat

Un-selective (weak)

Reduced form

Hepatic elimination

Selective (powerful)

Oxidized form

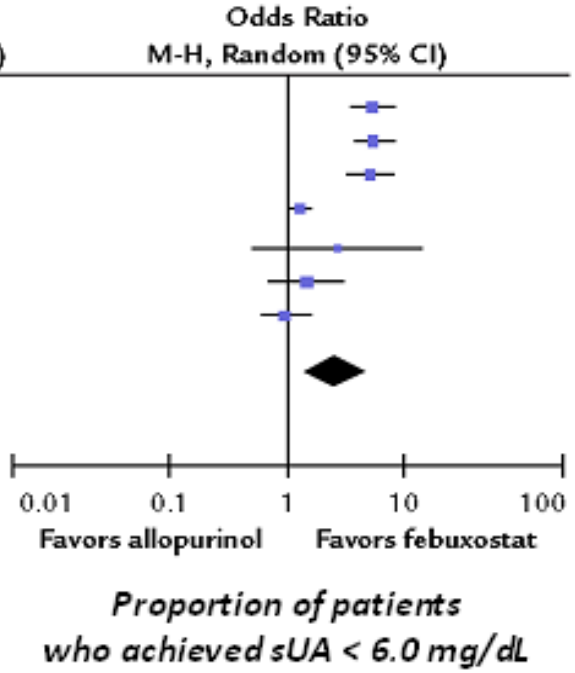
Renal/Epatic elimination

Febuxostat

Efficacy and Tolerability of Febuxostat in Hyperuricemic Patients With or Without Gout: A Systematic Review and Meta-Analysis

Study or Subgroup	Febuxostat Events	Total	Allopurinol Events	Total	Weight (%)	Odds Ratio M-H, Fixed (95% CI)
Becker (2005)[27]	378	491	88	242	15.6	5.85 (4.18–38.19)
Schumacher (2008)[21]	508	644	102	263	15.7	5.90 (4.32–8.05)
Becker (2009)*[28]	742	897	64	139	15.4	5.61 (3.85–8.17)
Becker (2010)[29]	849	1513	318	755	16.3	1.76 (1.47–2.10)
Kamatani (2011)[30]	16	20	11	20	7.9	3.27 (0.80–13.35)
Kamatani (2011)[31]	100	122	84	120	13.8	1.95 (1.06–3.57)
Fengchun Zhang (data on file)	155	307	67	157	15.3	1.37 (0.93–2.02)
Total (95% CI)		**3994**		**1696**	**100.0**	**3.14 (1.82–5.44)**
Total events	**2748**		**734**			

Heterogeneity: $\tau^2 = 0.47, \chi^2 = 94.79$, $df = 6$ ($P < 0.00001$); $I^2 = 94\%$
Test for overall effect: $Z = 4.09$ ($P < 0.0001$)



Clinical Therapeutics J, 2013; 35: 180-187

Take home message

Elevations of uric acid >6.0 mg/dl should be considered a "red flag" in those patients at risk for cardiovascular disease and should alert the clinician to strive to utilize a global risk reduction program in a team effort to reduce the complications of the atherogenic process resulting in the morbid – mortal outcomes of cardiovascular disease.

The higher circulating levels of uric acid (>6.0 mg/dl) are associated with an increased risk of cardiovascular morbidity and mortality, with a 20% increase in CVD risk for each standard deviation (95 mmol/l ≈ 1.6 mg/dL) with SUA increase, regardless of age, sex , traditional risk factors and medication use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and
GREAT INNOVATIONS IN CARDIOLOGY
XXVI Giornate Cardiologiche Torinesi
Directors
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Turin
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Thank you