TURIN,
October
25th-27th
2018
Starhotels
Majestic

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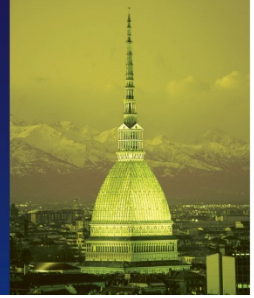
CARDIOLOGICHE
TORINESI



UNIVERSITÁ DEGLI STUDI DI TORINO

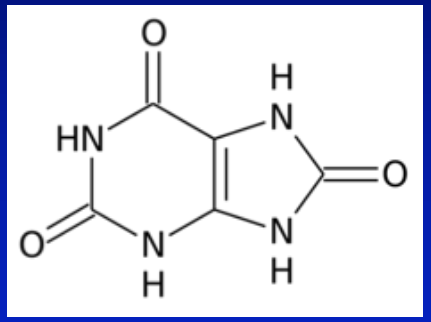
AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

How toxic is uric acid?

Elisabetta Toso, MD

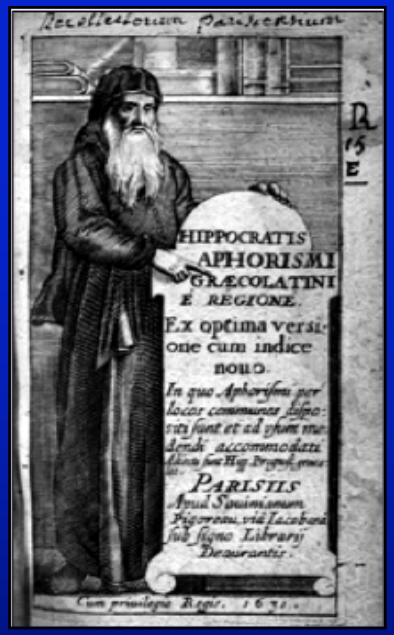
Città della Salute e della Scienza di Torino

Cardiology Division, University of Turin



Uric acid is a heterocyclic compound of carbon, nitrogen, oxygen and hydrogen. It is the ***end product of purine metabolism*** in humans. Uric acid monovalent sodium salt (urate) is soluble in plasma at pH 7.4, and ***at physiological concentrations acts as an antioxidant.***

Rheumatology 2010; 49: 2010-5.



Hyppocrathes

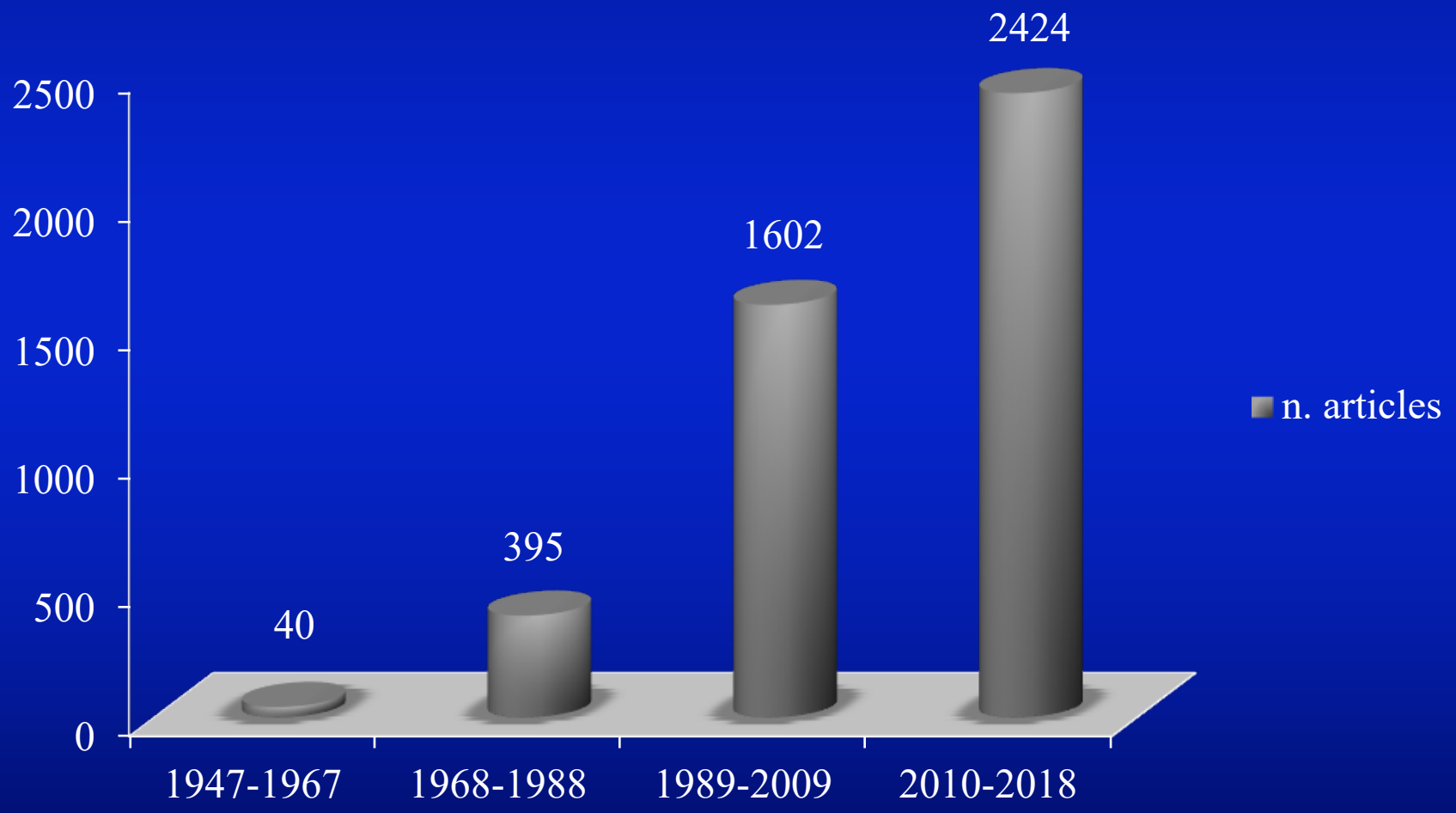
Antoni van Leuuwenhoek (1679)

«The aged man that coffers-up his gold / Is plagued with cramps and gouts and painful fits»

Shakespeare W.
"The rape of Lucrece" 1594

Acid Uric and Cardiovascular Diseases

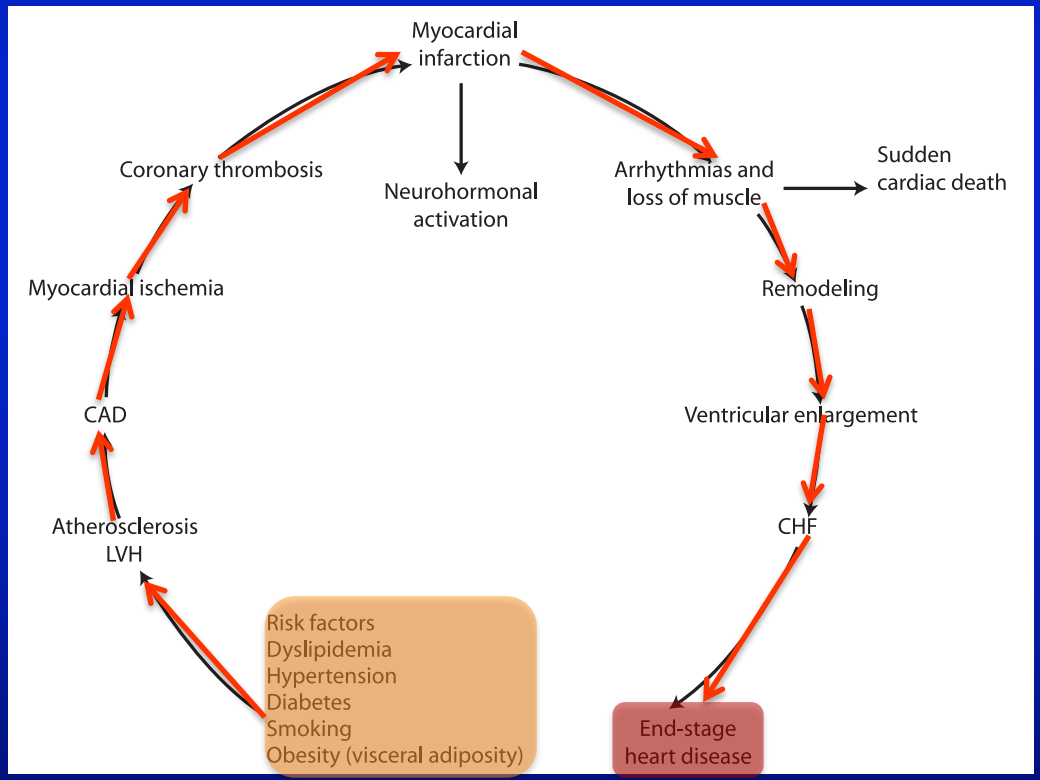
Trend of Publications on PubMed from 1947 to 2018



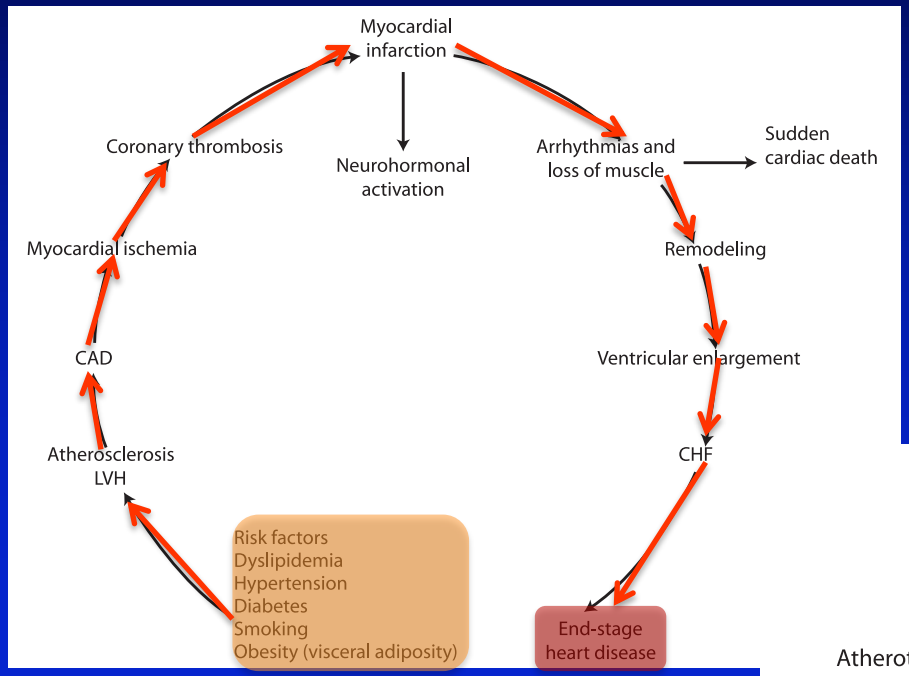
The Cardiovascular Disease Continuum Validated: Clinical Evidence of Improved Patient Outcomes

CVD Continuum:

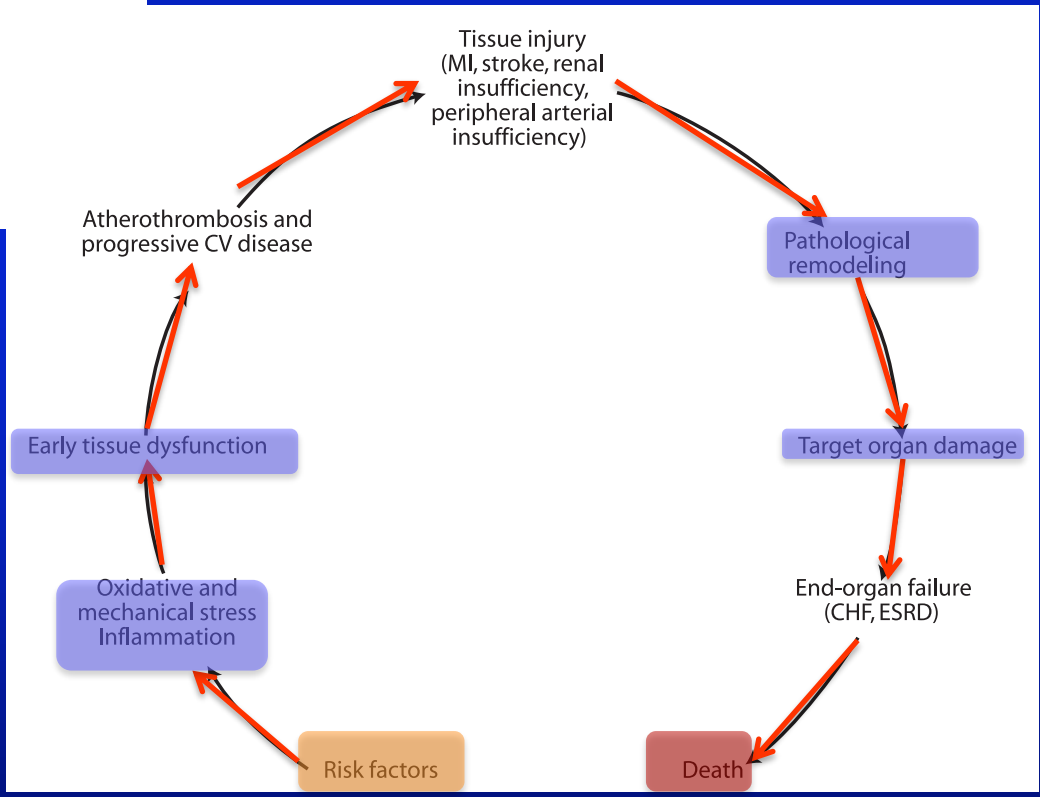
a chain of events initiated by a myriad of ***risk factors***, progressing through numerous physiological pathways and processes to the development of ***end-stage heart disease***



Dzau VJ. et al. Circulation. **2006;114:2850-2870.**



CV risk factors promote oxidative stress and cause endothelial dysfunction, initiating a cascade of events, including alterations in vasoactive mediators, inflammatory responses, and vascular remodeling, that culminates in target-organ pathology



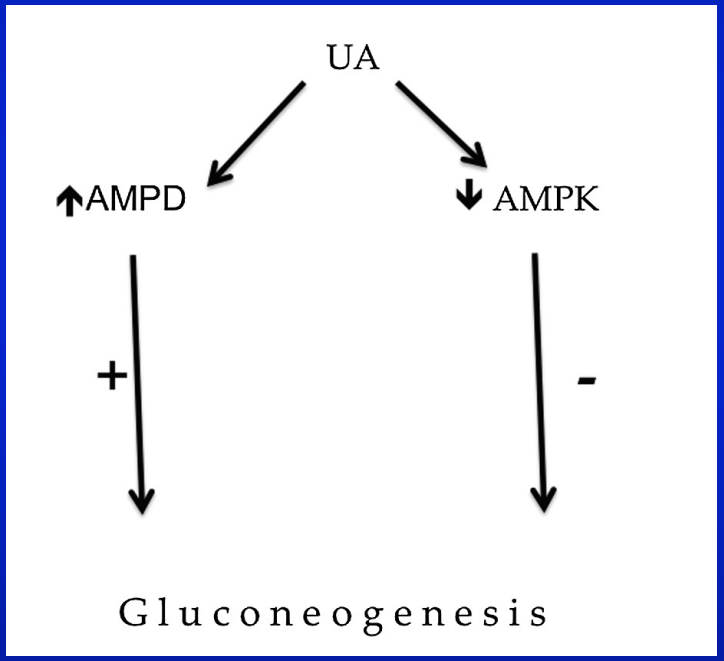
Dzau VJ. et al. Circulation. **2006;114:2850-2870.**

What is the role of Uric Acid in the CVD Continuum?

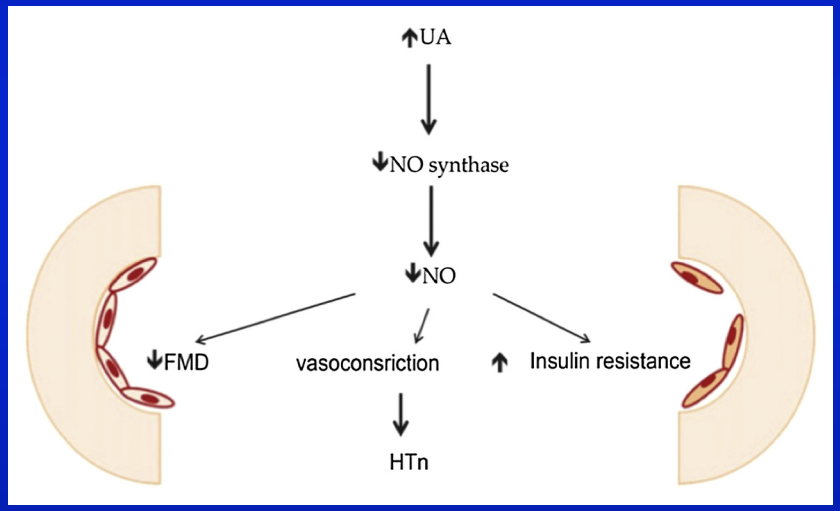
Uric acid in the pathogenesis of metabolic, renal, and cardiovascular diseases: A review

Usama A.A. Sharaf El Din [a,*], Mona M. Salem [b], Dina O. Abdulazim [c]

Hyperuricemia is an indipendent risk factor for insuline resistence and Type 2 DM

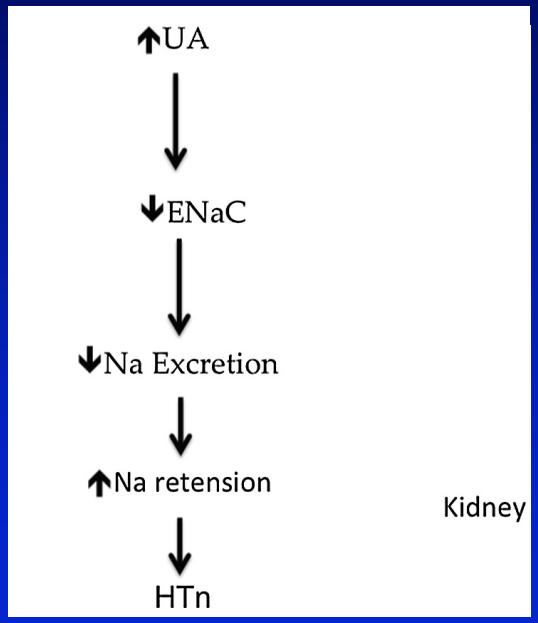


Intracellular UA stimulates adenosine monophosphate deydrogenase and AMPD stimulates hepatic gluconeogenesis



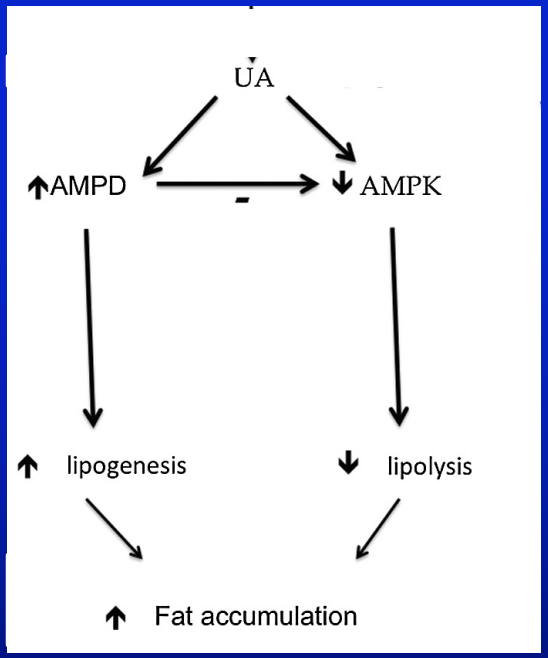
Hyperuricemia decreases endothelial NO synthase, causing an increased insuline resistence

Journal of Advanced Research 8 (2017) 537–548



Hyperuricemia induces the epithelial sodium channel in the distal nephron with consequent decrease in renal sodium excretion, increase in sodium retention and **Hypertension**

UA is an important factor underlying excess fat storcge. When AMPK activity is reduced, excess fat infiltration occurs; AMPD has opposing effect on lipogenesis and **hepatic steatosis**



Journal of Advanced Research 8 (2017) 537–548

Genetic contributors to serum uric acid levels in Mexicans and their effect on premature coronary artery disease.

Macias-Kauffer LR et al. Int J Cardiol. 2018

Relation of Elevated Serum Uric Acid Level to Endothelial Dysfunction in Patients with Acute Coronary Syndrome.

Saito Y. et al. J Atheroscler Thromb. 2018

Uric acid levels are associated with endothelial dysfunction and severity of coronary atherosclerosis during a first episode of acute coronary syndrome.

Gaubert M et al. Purinergic Signal. 2018

Hyperuricemia as a prognostic factor after acute coronary syndrome.

Lopez Pineda A. et al. Atherosclerosis. 2018

Prognostic impact of elevated serum uric acid levels on long-term outcomes in patients with chronic heart failure: A post-hoc analysis of the GISSI-HF.

Mantovani A. et al. Metabolism. 2018

Gu J. Serum uric acid is associated with incidence of heart failure with preserved ejection fraction and cardiovascular events in patients with arterial hypertension.

Gu J et al. J Clin Hypertens 2018

Serum uric acid as a potential marker for heart failure risk in men on antihypertensive treatment: The British Regional Heart Study.

Wannamethee SG. et al. Int J Cardiol. 2018.

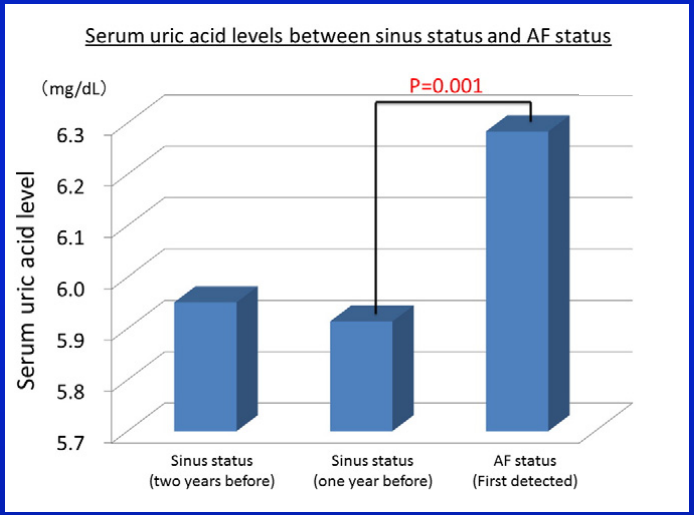
Prevalence of Hyperuricemia in Patients With Acute Heart Failure With Either Reduced or Preserved Ejection Fraction.

Palazzuoli A. et al. Am J Cardiol. 2017

Hyperuricemia is an independent competing risk factor for atrial fibrillation

49.292 subjects enrolled without cv risk factors (database Center for Preventive Medicine in Tokyo) mean age 42 y, 36% males

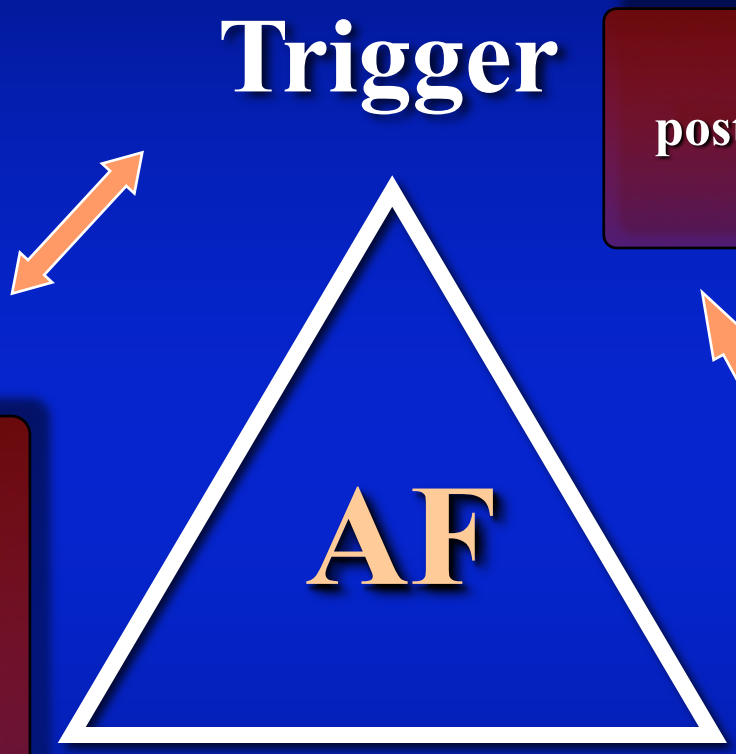
	Non-AF	AF	P
Number of subjects	49,231	61	<0.001
Age	41.9 ± 10.0	59.1 ± 11.0	<0.001
Male sex	36.1%	90.2%	<0.001
Height (cm)	163.6 ± 8.3	169.2 ± 7.3	<0.001
Weight (kg)	56.9 ± 10.5	67.0 ± 10.0	<0.001
Body mass index (kg/m^2)	21.1 ± 2.7	23.4 ± 2.8	<0.001
Systolic BP (mmHg)	110.1 ± 12.7	115.7 ± 2.8	0.001
Diastolic BP (mmHg)	68.3 ± 8.5	72.2 ± 7.9	<0.001
Pulse rate (bpm)	73.3 ± 10.3	76.1 ± 11.5	0.031
Smoking	33.9%	68.9%	<0.001
Drinking habits	62.0%	72.1%	0.084
% volume capacity (%)	110.2 ± 13.8	105.8 ± 16.9	0.011
FEV1/FVC (%)	82.3 ± 6.8	74.3 ± 7.4	<0.001
White blood cell (/μL)	5064 ± 1334	5298 ± 1521	0.171
Hemoglobin (g/dL)	13.4 ± 1.4	14.5 ± 1.1	<0.001
Total protein (g/dL)	7.05 ± 0.35	7.04 ± 0.42	0.860
Albumin (g/dL)	4.41 ± 0.22	4.26 ± 0.24	<0.001
Total bilirubin (mg/dL)	0.84 ± 0.31	0.97 ± 0.30	0.001
AST (U/L)	20.4 ± 8.3	25.1 ± 6.6	<0.001
ALT (U/L)	18.5 ± 13.8	23.7 ± 10.3	0.003
BUN (mg/dL)	12.7 ± 3.1	14.8 ± 3.0	<0.001
Serum creatinine (mg/dL)	0.69 ± 0.14	0.90 ± 0.12	<0.001
eGFR (mL/min/1.73m^2)	85.7 ± 14.6	76.9 ± 13.5	<0.001
Sodium (mEq/L)	141.3 ± 1.8	142.1 ± 1.7	0.001
Potassium (mEq/L)	4.08 ± 0.27	4.23 ± 0.27	<0.001
Chloride (mEq/L)	106.2 ± 1.8	106.2 ± 1.8	0.860
CRP (mg/dL)	0.12 ± 0.27	0.12 ± 0.09	0.999
Serum uric acid (mg/dL)	4.84 ± 1.26	6.26 ± 1.46	<0.001



Serum UA levels were analyzed over 3 years: **in AF UA was significantly higher than that in SR** (5.91 versus 6.28 mg/dL, p =0.001)

Masanari Kuwabara et al. Int Journal of Cardiol 231 (2017) 137–142

Mechanisms of AF

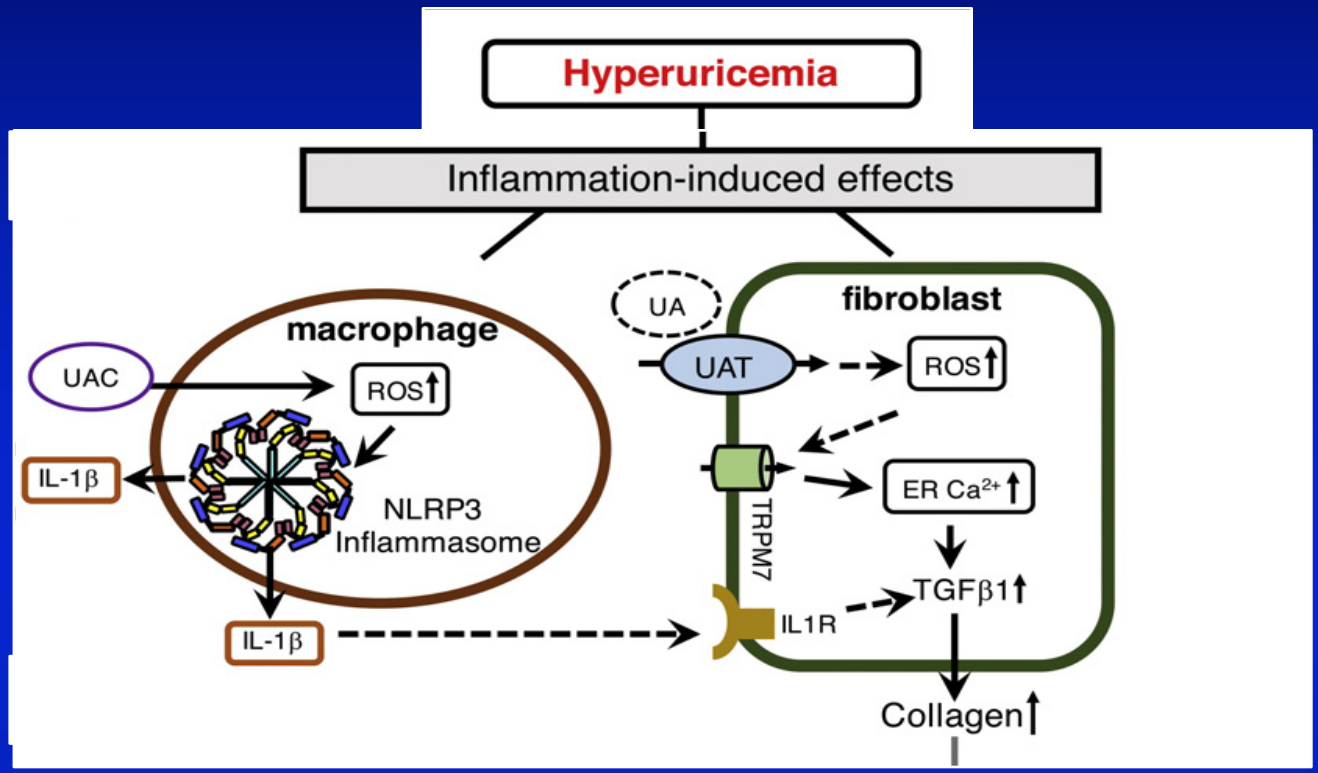


APC,
post-extrasystolic pause,
long-short cycle

Anatomical:
Atrial dilatation,
↑ deposition of collagen and
↑ fibrosis, Hypertrophy,

Electrophysiological:
Short ERP,
ERP dispersion,
lack of ERP rate adaptation
intraatrial conduction delay,
functional conduction block.

Vagal
Adrenergic

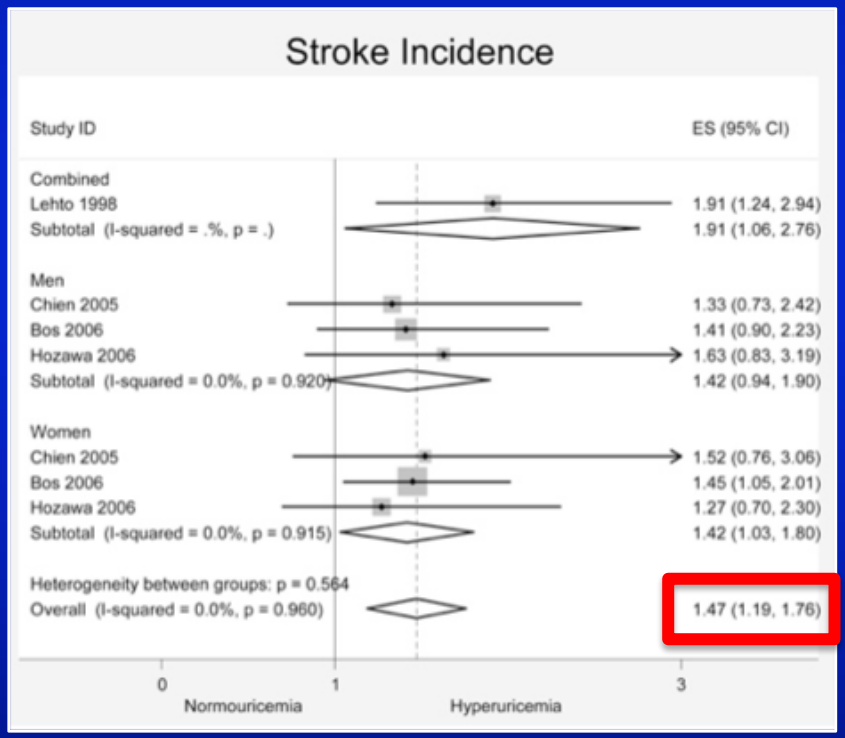


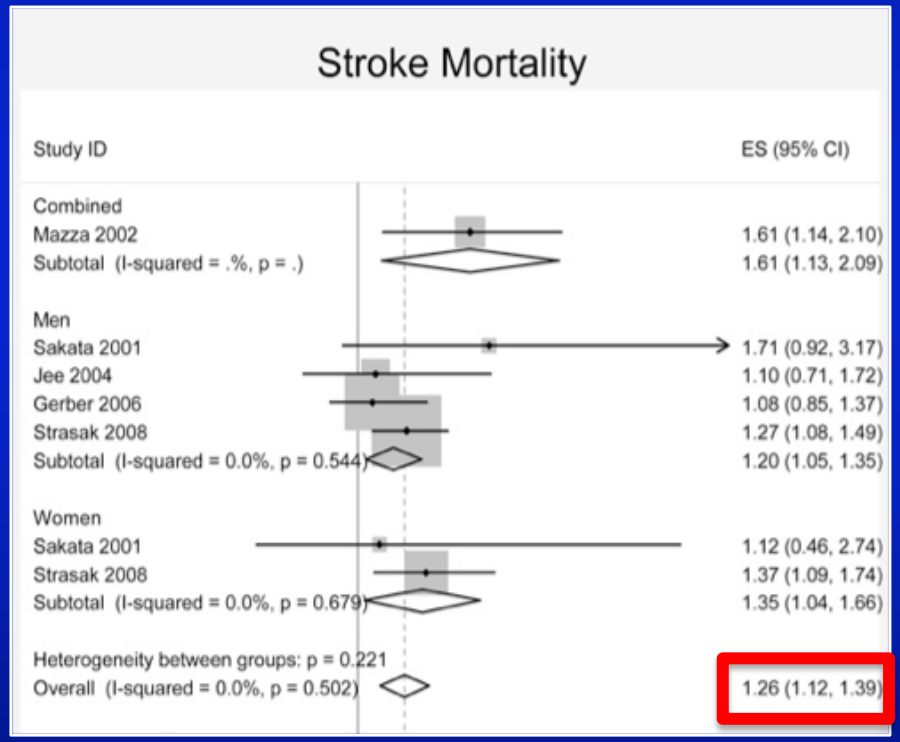
The macrophages can engulf uric acid crystal (UAC) → secretion of IL-1β → proliferation and differentiation of fibroblasts to myofibroblasts → production of cytokines, chemokines and TGFβ1 → increase collagen production and deposition → fibrosis → structural remodeling

International Journal of Cardiology 231 (2017) 177–178

Hyperuricemia and Risk of Stroke: A Systematic Review and Meta-analysis

16 prospective studies, 238.449 pts included

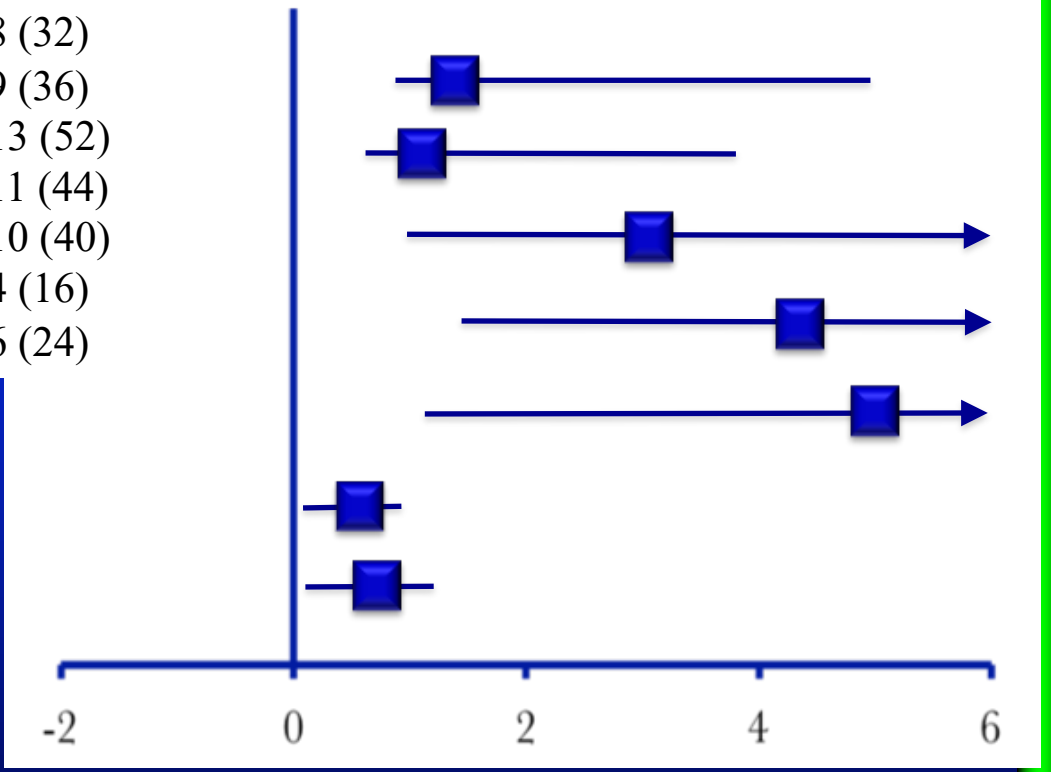




Seo Young Kim et al. Arthritis Rheum. 2009 61(7): 885–92

Serum Uric Acid and Cognitive Function in Community-Dwelling Older Adults

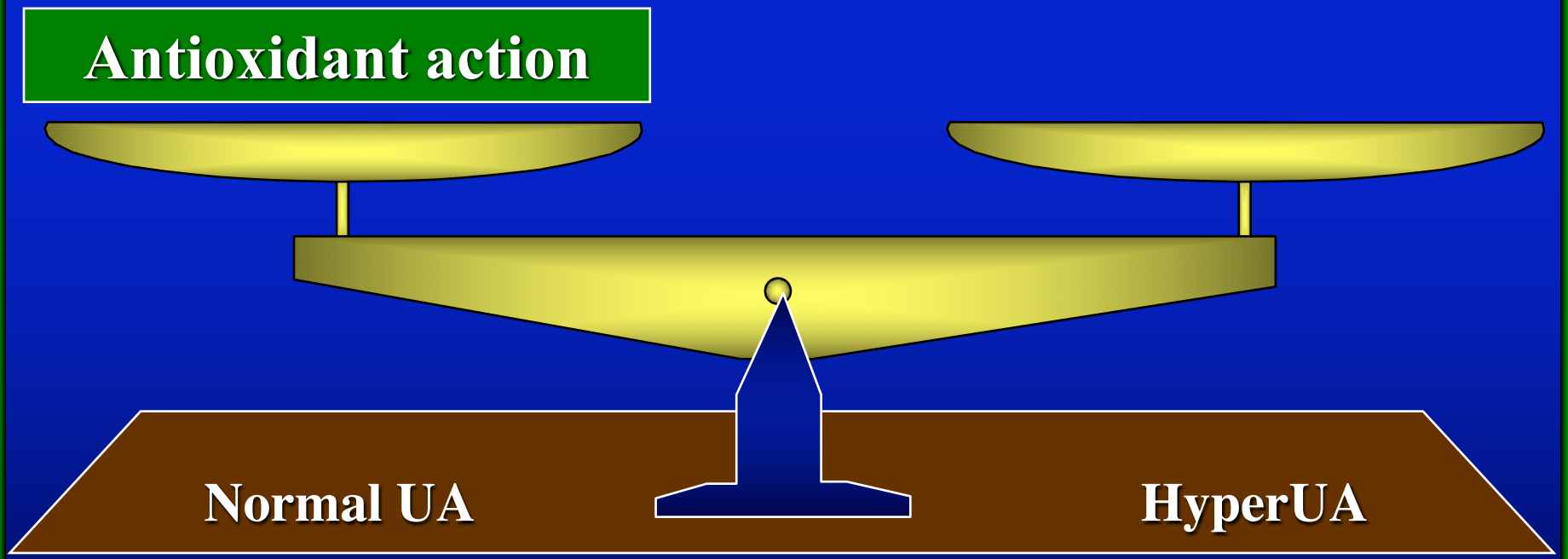
Cognitive domain	Number (%) in lowest quartile: low-moderate UA (n=71)	high UA (n=25)
General verba	16 (23)	8 (32)
General visuospatial	15 (21)	9 (36)
Processing speed *	11 (16)	13 (52)
Working memory **	13 (18)	11 (44)
Verbal memory ***	14 (20)	10 (40)
Visual memory	18 (25)	4 (16)
Verbal fluency	18 (25)	6 (24)



*p<0.001
**p<0.01
***p<0.05

Schretlen DJ, et al. Neurophychology, 2007; 21: 1, 136–140

How toxic is uric acid ?



How toxic is uric acid ?