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Hyperuricemia: The Silent Catalyst in Decongestion Management

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Disclosure

- Darya-Varia Laboratoria

OUTLINE

- Epidemiology and biological plausibility of Hyperuricemia (HUA) in CVD and HF
- Hyperuricemia Role in CV Risk/Disease and HF
- Management of Hyperuricemia in HF

Epidemiology HUA in CVD Patients

The prevalence of hyperuricemia in hypertensive patients is ranging from 20% to 40%.[1]

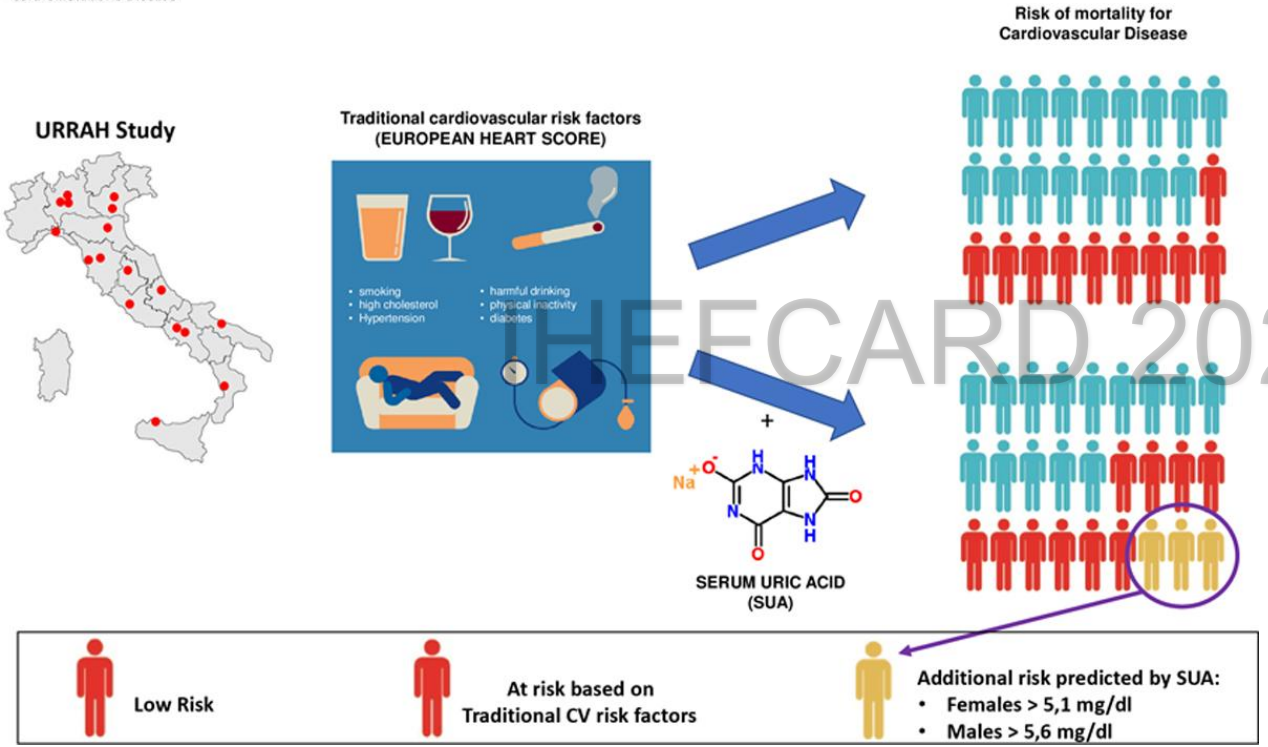
Hyperuricemia is found in 25% of individuals with untreated hypertension. The prevalence of hyperuricemia is higher in patients with more severe hypertension.[1]

A meta-analysis of 25 observational studies with 97,824 participants showed the risk of incident hypertension increased by **13% for every 1 mg/dl** increase in the uric acid level.[2]

In patients with HF, the prevalence of hyperuricemia: 30 to 60%.[3]

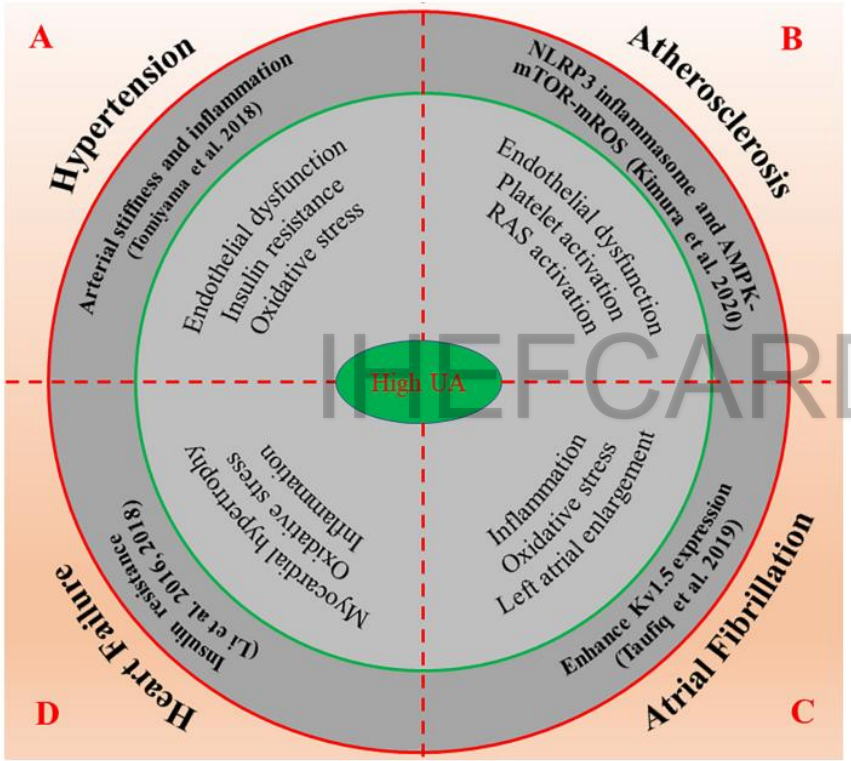
In patients with AF, the prevalence of hyperuricemia: 2.1%.[3]

1. *Giovanni Cimmino,Francesco Natale,Rosa Franzese,Mariarosaria Morello,Gisella Titolo,Noemi Mollo,Valentina Maria Caso,Paolo Golino,Plinio Cirillo,Uric acid in atherosclerosis and cardiovascular diseases: innocent bystander or ruthless killer?, Exploration of Musculoskeletal Diseases, 2, 3, (189-207), (2024).*
2. *Yuichi Saito, Atsushi Tanaka, Koichi Node, Yoshio Kobayashi, Uric acid and cardiovascular disease: A clinical review, Journal of Cardiology, Volume 78, Issue 1, 2021.*
3. *Hisatome I, Li P, Taufiq F, Maharani N, Kuwabara M, Ninomiya H, Bahrudin U. Hyperuricemia as a Risk Factor for Cardiovascular Diseases. Journal of Biomedicine and Translational Research [Online]. 2020 Dec;6(3):101-109. https://doi.org/10.14710/jbtr.v6i3.9383*



The optimal cut point for SUA to discriminate CVM status according to survival receiver operating characteristic curve analysis was **5.6 mg/dL** (95% CI, 4.99–6.21) in the entire population (Table 2). In women, the cut point providing the better discrimination for CVM was **5.1 mg/dL** (95% CI, 4.34–5.70), whereas in men, it was **5.6 mg/dL** (95% CI, 5.30–5.78)

Virdis A, Masi S, Casiglia E, Tikhonoff V, et al; from the Working Group on Uric Acid and Cardiovascular Risk of the Italian Society of Hypertension. Identification of the Uric Acid Thresholds Predicting an Increased Total and Cardiovascular Mortality Over 20 Years. Hypertension. 2020 Feb;75(2):302-308. doi: 10.1161/HYPERTENSIONAHA.119.13643. Epub 2019 Dec 9. PMID: 31813345.

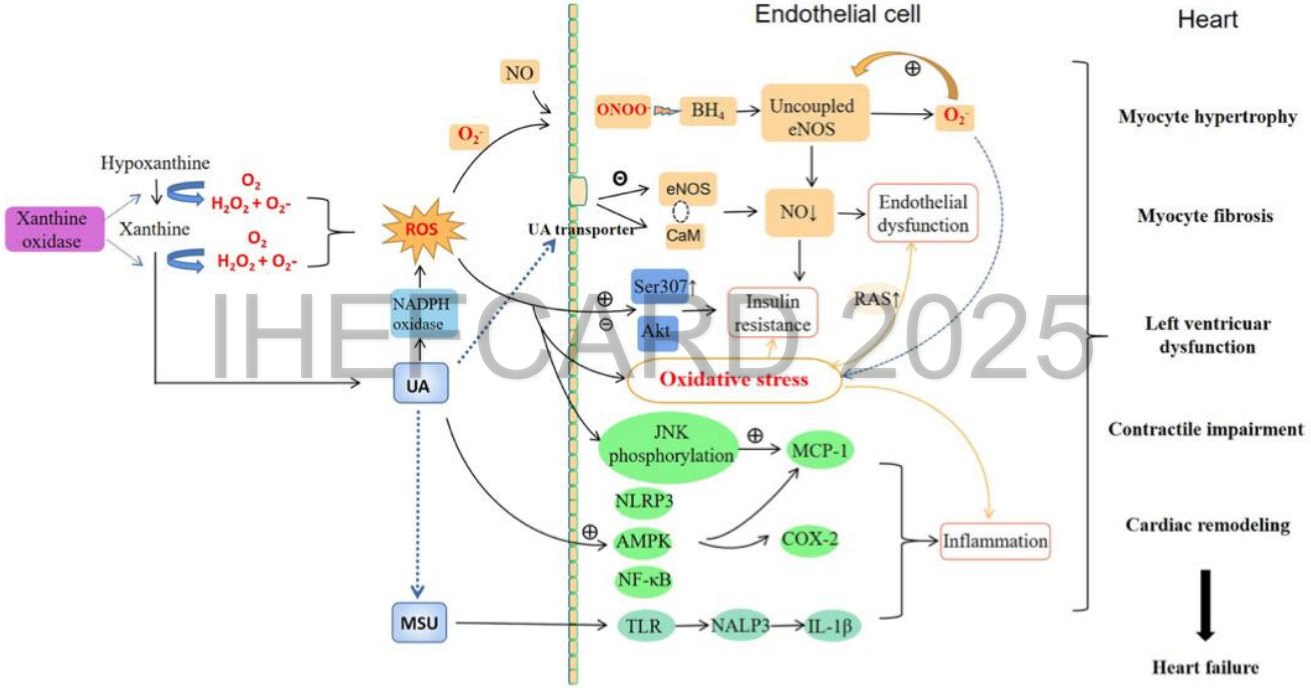


The possible molecular mechanisms of high UA promote the occurrence and development of cardiovascular diseases. High UA regulates numerous molecular signals such as inflammation, oxidative stress, insulin resistance, and endothelial dysfunction, thus affects the progression and prognosis of cardiovascular diseases including hypertension (A), atherosclerosis (B), atrial fibrillation (C) and heart failure (D).

AMPK, AMP-activated protein kinase; mROS, mitochondrial ROS; mTOR, mammalian target of rapamycin; NLRP3, nod-like receptor protein 3; RAS, renin-angiotensin system; UA, uric acid.

Yu W and Cheng J-D (2020) Uric Acid and Cardiovascular Disease: An Update From Molecular Mechanism to Clinical Perspective. Front. Pharmacol. 11:582680. doi: 10.3389/fphar.2020.582680

Potential Mechanisms of Hyperuricemia in Mediating HF



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Hiperuricemia in Heart Failure

Study	Study design	Population	No. of subjects	Main findings/ outcomes
Heart failure				
Pavlusova et al., 2019	Prospective	Acute HF	3610	Hyperuricemia was associated with unfavorable cardiovascular risk
Palazzuoli et al., 2017	Prospective	Acute HF	324	Hyperuricemia was the only independent predictor of HF hospitalization or death
Vaduganathan et al., 2014	Double-blind placebo RCT	Worsening chronic HF	3955	sUA is commonly elevated in patients hospitalized for worsening chronic HF
Huang et al., 2014	Meta-analysis	Chronic HF	427917	Elevated sUA is associated with an increased risk of incident HF and adverse outcomes in HF patients

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Hiperuricemia's Potential Impact on Decongestion in HF

- Hyperuricemia may be caused or aggravated by diuretic therapy
- Increase diuretic resistance
- Reduce renal function
- Increase inflammation lead to
- Increase oxidative stress

Yu W and Cheng J-D (2020) Uric Acid and Cardiovascular Disease: An Update From Molecular Mechanism to Clinical Perspective. Front. Pharmacol. 11:582680. doi: 10.3389/fphar.2020.582680

Should we treat HUA in HF?

How low should we get?

What choice of ULT should we give?

Population/Study (author)	Sample size	Design	Tested strategies	Comparator	Results
Hypertension					
Soletsky et al. [26]	60	DB, crossover	Allopurinol and probenecid	Placebo	In prehypertensive obese adolescents, urate-lowering therapy reduced clinic SBP (−10.1 vs. −10.2 vs. 1.7 mmHg, $p<0.001$)
Segal et al. [29]	110	DB	Allopurinol plus chlorthalidone	Placebo plus chlorthalidone	In hypertensive African-Americans, allopurinol non-significantly reduced clinic SBP (−3.4 vs. 0.8 mmHg, $p = 0.06$)
Ischemic stroke					
Higgins et al. [27]	80	DB	Allopurinol	Placebo	Allopurinol lowered central and brachial SBP and reduced carotid IMT progression
Type 1 DM					
PERL [33]	530	DB	Allopurinol	Placebo	Allopurinol did not delay GFR decline (between-group difference 0.001, 95% CI −1.9 to 1.9 ml/min/1.73 m^2)
CKD					
UPWARD [30]	65	DB	Topiroxostat	Placebo	Changes in eGFR were superior in the topiroxostat group (−0.2 vs. −4.0 ml/min/1.73 m^2, $p = 0.03$)
FEATHER [31]	441	DB	Febuxostat	Placebo	In CKD patients with hyperuricemia, febuxostat did not mitigate the decline in eGFR slope (0.23 vs. −0.47 ml/min/1.73 m^2 per year, $p = 0.1$)
CKD-FIX [32]	363	DB	Allopurinol	Placebo	The change in eGFR was not significantly different between the 2 groups (−3.33 vs. −3.23 ml/min/1.73 m^2, $p = 0.85$)
Heart failure					
Farquharson et al. [48]	11	DB, crossover	Allopurinol	Placebo	Allopurinol improved endothelial dysfunction assessed by forearm blood flow response to acetylcholine
OPT-CHF [50]	405	DB	Oxypurinol	Placebo	Clinical improvements including events and HF status did not differ between the 2 groups (45% vs. 43%, $p = 0.42$)
EXACT-HF [51]	253	DB	Allopurinol	Placebo	In hyperuricemic patients with HFrEF, allopurinol did not improve clinical status, exercise capacity, QOL, or LVEF
CAD					
Noman et al. [72]	65	DB, crossover	Allopurinol	Placebo	Allopurinol increased time to ST depression (median difference 43 s, 95% CI 31–58 s) and exercise time (difference 58 s, 95% CI 45–77 s)
Hyperuricemia/gout					
PRIZE [28]	483	Open-label	Febuxostat	Lifestyle modification	Mean% change of CCA-IMT in the febuxostat group was not significantly different (1.2% vs. 1.4%, $p = 0.83$)
FREED [71]	1070	Open-label	Febuxostat	Allopurinol (100 mg) allowed	Febuxostat was superior in the rate of composite cerebral, cardiovascular, and renal events (23.3% vs. 28.7%, $p = 0.02$)
CARES [69]	6190	DB	Febuxostat	Allopurinol	Non-inferiority of febuxostat was met ($p = 0.002$), though all-cause and CV mortality was significantly higher in the febuxostat group
FAST [70]	6128	Open-label	Febuxostat	Allopurinol	Non-inferiority of febuxostat was met ($p<0.001$) with no significant increase of risk of death

Urate, Blood Pressure, and Cardiovascular Disease

Evidence From Mendelian Randomization and Meta-Analysis of Clinical Trials

Dipender Gill, Alan C. Cameron, Stephen Burgess, Xue Li, Daniel J. Doherty, Ville Karhunen, Azmil H. Abdul-Rahim, Martin Taylor-Rowan, Verena Zuber, Philip S. Tsao, Derek Klarin, VA Million Veteran Program, Evangelos Evangelou, Paul Elliott, Scott M. Damrauer, Terence J. Quinn, Abbas Dehghan, Evropi Theodoratou,† Jesse Dawson,† Ioanna Tzoulaki†

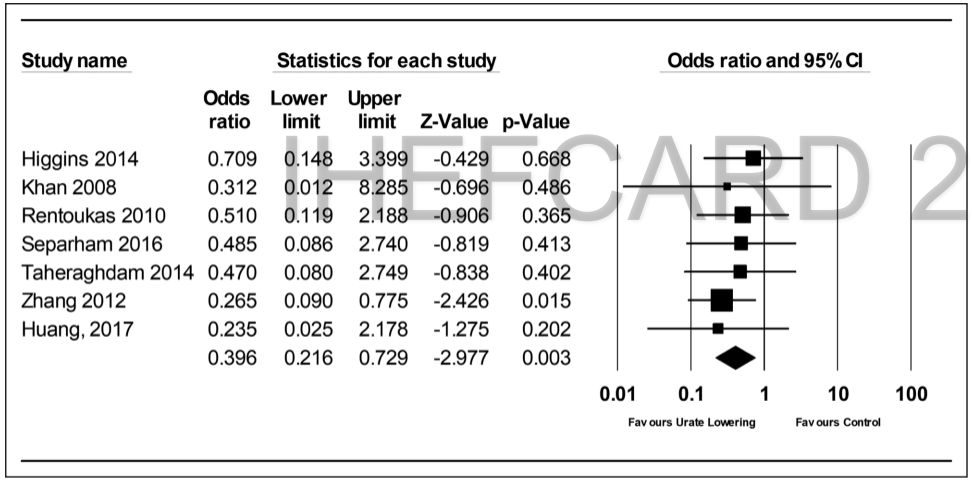

Figure 6. Forest plot of randomized controlled trial estimates for risk of major adverse cardiovascular events in patients with existing cardiovascular disease receiving urate-lowering therapy or placebo/no treatment.
I^2 heterogeneity statistic: 0%. A random-effects meta-analysis model was used.

Gill D, Cameron AC, et al. Urate, Blood Pressure, and Cardiovascular Disease: Evidence From Mendelian Randomization and Meta-Analysis of Clinical Trials. Hypertension. 2021 Feb;77(2):383-392. doi: 10.1161/HYPERTENSIONAHA.120.16547. Epub 2020 Dec 28. PMID: 33356394; PMCID: PMC7803439.

Uric acid Lowering Therapy (ULT)

- Currently, two potent classes of ULT medications are commonly used in clinical practice:
  - XOI (e.g., allopurinol, febuxostat)
  - Increasing UA excretion drugs (e.g., benzbromarone, probenecid)

Pathophysiological mechanisms	UA	ROS	Mechanism underlying beneficial effects of ULT
Oxidative stress	a. UA functions as a pro-oxidant in the hydrophobic intracellular environment (by generating ROS or stimulating NADPH oxidase) b. UA induces endothelial dysfunction-oxidative stress with an activation of the RAS	a. ROS interacts with NO to produce $ONOO^-$ and starts detrimental oxygen radical effects on endothelial cell b. ROS induces cardiac fibroblast proliferation and activates MMP and leads to cardic fibrosis and extracellular remodelling c. ROS depresses Ca^{2+} accumulation and Ca^{2+} ATPase of SR, and decreases cardiac contractility	Allopurinol has been reported to improve myocardial oxidative stress and attenuate cardiac fibrosis in cardiac diastolic dysfunction (42)
Endothelial dysfunction	a. UA induces oxidative stress, inflammation, or proliferation of VSMC, and reduces endothelial NO bioavailability b. UA attenuates eNOS activity and NO production or decreasing the interaction between eNOS and CaM or enhancing PKC-dependent eNOS phosphorylation	a. ROS-reduced $ONOO^-$ leads to lipid peroxidation and destroys endothelial membrane b. $ONOO^-$ causes eNOS uncoupling c. O_2^- induces endothelium injury directly and further promotes eNOS uncoupling d. ROS regulates canonical Wnt signaling and induces vascular endothelial dysfunction	Allopurinol had effects on endothelial function that significantly increased forearm blood flow response to acetylcholine (43)
Vascular inflammation	a. UA induces inflammation *via* NLRP3-inflammasome-mediated VSMC proliferation or AMPK and NF-κB signal pathways b. MSU activates NALP3 inflammasome and secrets IL-1β	ROS induces the phosphorylation of JNK, and contributes to the production of MCP-1 in macrophages	Febuxostat has been shown to control the formation of ROS and act against vascular inflammation promoted by oxidative stress (43)
LV dysfunction	a. UA-induced inflammation can reduce ability of the myocardium to contract and relax b. UA activates calpain-1 and ER stress and induces cardiomyocyte apoptosis, interstitial fibrosis and diastolic dysfunction	ROS leads to ventricular remodeling through a ET-1 pathway	Allopurinol diminished the ROS effects on myofilament Ca^{2+} sensitivity, contributing to the improvement of LV contractile function and efficiency
IR	a. UA reduces NO bioavailability and generation of mitochondrial oxidative stress to result in IR b. UA inhibits insulin-induced glucose uptake in H9c2 and primary cardiomyocytes	ROS plays a causal role in IR-related CV complications	Benzbromarone improved in IR index (41)

XO, xanthine oxidase; UA, urate acid; ROS, reactive oxygen species; ULT, uric acid lowering therapies; RAS, renin-angiotensin system; NO, nitric oxide; ONOO-, peroxynitrite; O2-, superoxide anion; MMP, matrix metalloproteinases; SR, sarcoplasmatic reticulum; VSMC, Vascular Smooth Muscle Cells; eNOS, endothelial nitric oxide synthase; CaM, calmodulin; PKC,

Study	Study design	Population	Mean follow-up	Treatment	Results	CV risk by treatment
Comparison between a XO inhibitor versus placebo						
Awsan Noman et al (55), (UK)	Randomized, double-blind, placebo-controlled, crossover study	Chronic stable angina	12-weeks	Allopurinol	Allopurinol prolonged the time to the total exercise time (58s median increase, p=0.0003), the time to angina (38s median increase, p=0.001), and ST-segment depression (43s median increase, p=0.0002)	Reduced
Li Wei et al (56), (Scotland)	Cohort study	Elderly (≥60 years old)	5-years	Allopurinol	High-dose (≥300 mg) allopurinol had reduced risk of CV events (adjusted HR 0.69,95%CI 0.50–0.94) and mortality (adjusted HR 0.75,95% CI 0.59–0.94)	Reduced
Lhanoo Gunawardhana et al (57), (USA)	Phase II, multicenter, placebo-controlled, double-blind proof-of-concept study	Gout	3-months	Febuxostat	Febuxostat lowered serum UA effectively and did not show an increased risk of CV complications	No difference
Comparison between XO inhibitors						
William B. White et al (58), (USA)	Multicenter, double-blind, noninferiority trial	Gout with CVD	32-months	Allopurinol *vs* Febuxostat	All-cause and CV mortality were higher in the febuxostat group than in the allopurinol group [HR for death from any cause, 1.22 (95% CI, 1.01 to 1.47); HR for CV death, 1.34 (95% CI, 1.03 to 1.73)].	Higher risk in febuxostat
Arrigo Francesco Giuseppe Cicero et al (59), (Italy)	Cohort study (prospective)	Elderly with CHF	5-years	Allopurinol *vs* Febuxostat	Febuxostat had a better CV outcome in patients treated with in comparison with allopurinol (The cumulative CV survival was 0.96 (95% CI 0.93–0.99) in febuxostat group and 0.89 (95% CI 0.84–0.93) in allopurinol group.	Lower risk in febuxostat
Isla S Mackenzie et al, (UK, Denmark (60), and Sweden)	Multicentre, prospective, open-label, non-inferiority trial	Elderly with Gout	4-years	Allopurinol *vs* Febuxostat	Febuxostat is non-inferior to allopurinol therapy about the primary cardiovascular endpoint, and it is not associated with an increased risk of death or serious adverse events compared with allopurinol.	No difference

XO, xanthine oxidase; CVD, cardio vascular disease; UA, urate acid; CHF, Congestive heart failure.

Elevated uric acid as a risk factor

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Dr. Federica Piani


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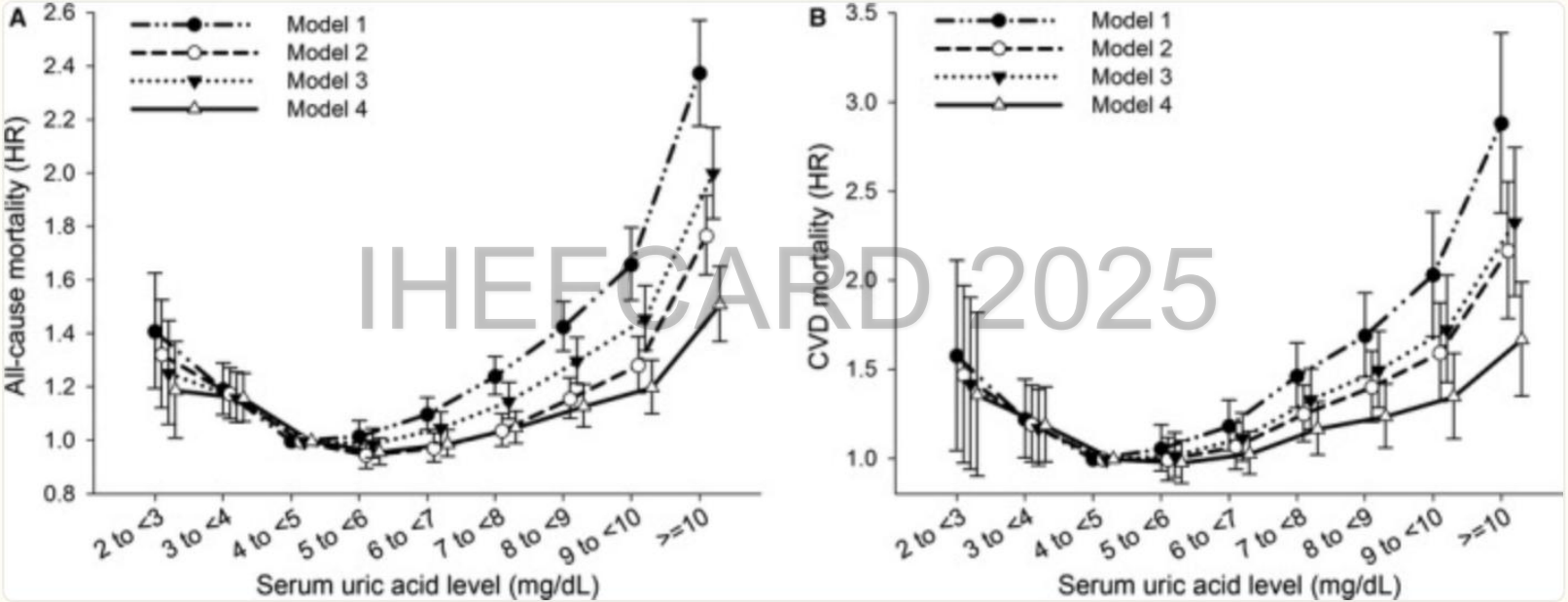
Hyperuricaemia is defined as SUA ≥6.0 mg/dL in women and ≥7.0 mg/dL in men [5]. From the discovery of hyperuricaemia as the cause of gout in the 19th century, several epidemiological and genetic studies have shown an association between high SUA levels and the incidence of several cardiovascular (CV) diseases and risk factors [6]. The treatment of hyperuricaemia is recommended for all symptomatic patients, namely those with gout, tophi, urate nephrolithiasis, or severe comorbidities [5]. The target for long-term SUA treatment is 6.0 mg/dL. Some studies suggest that people with asymptomatic hyperuricaemia should be treated only if their calculated CV risk at 10 years is high or very high, or if they have high SUA levels (>8 mg/dL). However, international guidelines/consensus documents recommend not to treat asymptomatic hyperuricaemia under any circumstances [5].



13.10 Gout and arthritis

Hyperuricemia is a common finding in patients with CHF with a prevalence up to 50%.[817,818] Hyperuricemia may be caused or aggravated by diuretic treatment and it is related to symptoms, exercise capacity, severity of diastolic dysfunction and long-term prognosis.[818,819] For every 1 mg/dL increase in serum uric acid levels the risk of all-cause mortality and of HF hospitalization increases by 4% and 28%, respectively.[820] Both febuxostat and allopurinol reduce uric acid levels. However, allopurinol was associated with a lower rate of all-cause death and CV death, compared with febuxostat, in a prospective, multicentre, double-blind, non-inferiority trial enrolling 6190 patients with gout and CV disease, 20% with HF, with a median follow-up of 32 months.[821] Allopurinol is therefore recommended as the first-choice urate-lowering drug in HF patients with no contraindication. There is no evidence that uric acid-lowering treatment has beneficial effects on LV function, symptoms or outcomes of patients with HF.[822–824]

With respect to treatment of acute gout attacks, non-steroidal anti-inflammatory drugs (NSAIDs) can worsen renal function and precipitate acute HF decompensation. Colchicine should be preferred as it is associated with less side effects.[825] However, it, too, should be used with caution in patients with severe renal dysfunction and is contraindicated in patients on dialysis. An increase in ventricular vulnerability was shown in experimental models.[826]

Take Home Messages

- Elevated serum uric acid level is associated with cardiovascular diseases such as hypertension, CKD, HF, and CAD, and is useful for risk stratification.
- Despite numerous investigations including Mendelian randomization studies, the causality is still controversial.
- The beneficial effect of uric acid-lowering treatment has been suggested on surrogate endpoints.
- The improvement in clinical outcomes need further studies, focusing on patients with elevated uric acid levels and high cardiovascular risks.

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

He Huang [1], Baotao Huang, Yulin Li, Yan Huang, Jing Li, Hongmei Yao, Xianchao Jing, Jianrong Chen, Ji Wang

Abstract

Aims: We aimed to perform a systematic review and meta-analysis to assess the association between serum uric acid and incident heart failure (HF)/prognosis of HF patients.

Methods and results: A systematic electronic literature search was conducted in Embase (Ovid SP, from 1974 to May 2013), Medline (Ovid SP, from 1946 to May 2013), and the Chinese Biomedical Literature Database (CBM, from 1978 to May 2013) to identify studies reporting on the association between serum uric acid and HF. Either a random effects model or a fixed effects model was used for pooling data. Five studies reporting on incident HF and 28 studies reporting on the adverse outcomes of HF patients were included. The results showed that hyperuricaemia was associated with an increased risk of incident HF [hazard ratio (HR) 1.65, 95% confidence interval (CI) 1.41-1.94], and the risk of all-cause mortality (HR 2.15, 95% CI 1.64-2.83), cardiovascular mortality (HR 1.45, 95% CI 1.18-1.78), and the composite of death or cardiac events (HR 1.39, 95% CI 1.18-1.63) in HF patients. 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), and the risk of all-cause mortality and the composite endpoint in HF patients increased by 4% (HR 1.04, 95% CI 1.02-1.06) and 28% (HR 1.28, 95% CI 0.97-1.70), respectively. Subgroup analyses supported the positive association between serum uric acid and HF.

Conclusions: Elevated serum uric acid is associated with an increased risk of incident HF and adverse outcomes in HF patients.