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URIC ACID and cardiovascular disease

CONSTANTINOS PANTOS

Conflict of interest

Research supported by MENARINI

Uric acid - General population

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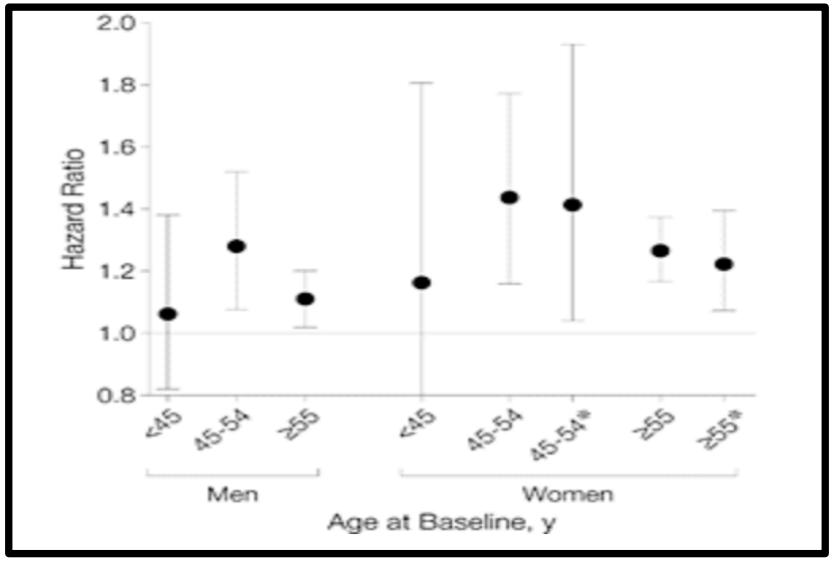
Serum Uric Acid and Cardiovascular Mortality

The NHANES I Epidemiologic Follow-up Study, 1971-1992

Jing Fang, MD; Michael H. Alderman, MD

Results



For both men and women, **the risk of increased serum uric acid levels for cardiovascular mortality was highest for those aged 45 to 54 years**. An increase of 59.48 µmol/L in serum uric acid level predicted an increase in cardiovascular mortality rate of 28% (95% CI, 1.08-1.52) in men and 43% (95% CI, 1.16-1.77) in women

JAMA. 2000;283(18):2404-2410.

Uric acid - General population

Serum Uric Acid and Cardiovascular Mortality

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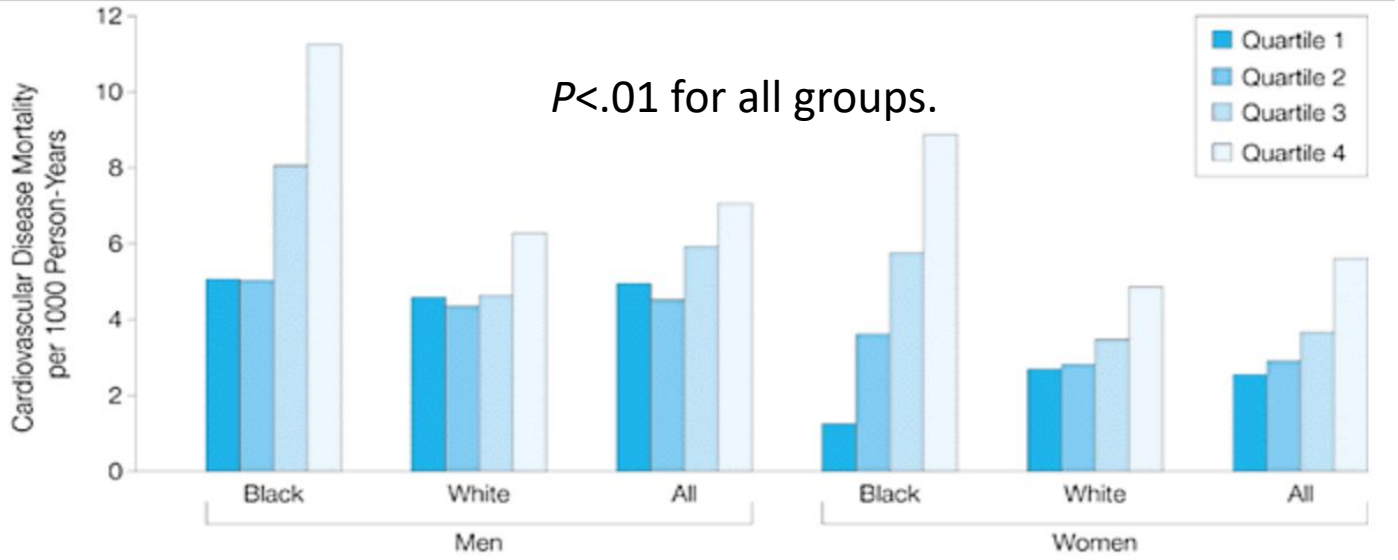


Age-adjusted cause-specific death rates for all races, as well as between races separately, revealed **that total cardiovascular mortality was highest in the highest serum uric acid level quartile for all subjects**, with the steepest rise in rates for black women

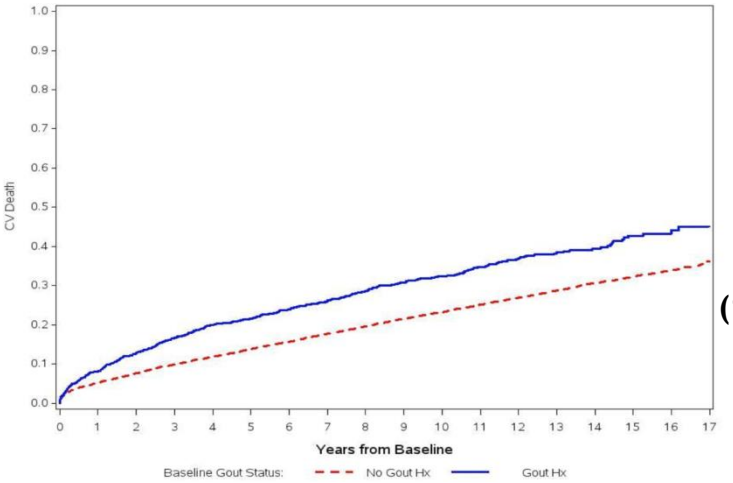
JAMA. 2000;283(18):2404-2410.

Uric acid - Coronary disease

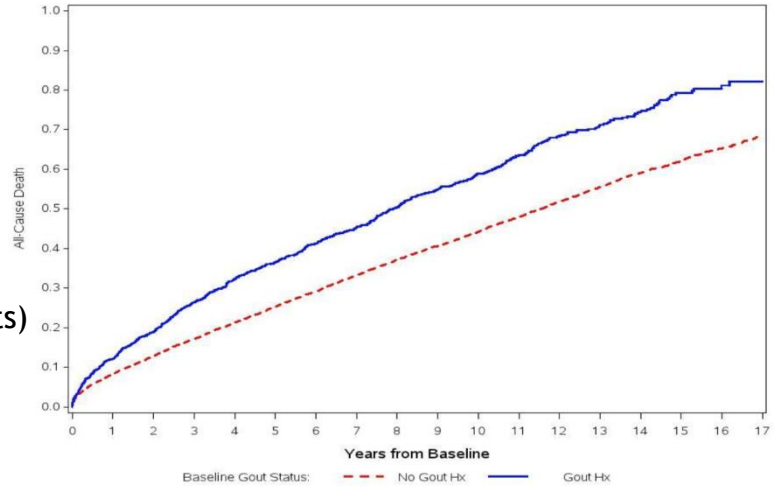
Association of Gout With Long-Term Cardiovascular Outcomes Among Patients With Obstructive Coronary Artery Disease

Retrospective data from the Duke Databank for Cardiovascular Disease

Cumulative Incidence Curves for CV and All cause death by Baseline Gout Status.



(17 201 patients)



- History of gout was related to <u>all-cause mortality</u> both before and after adjustment (adjusted HR [95% CI], 1.13 [1.05–1.23]; P=0.002;

- History of gout was related to other <u>cardiac death</u> (adjusted HR [95% CI], 1.23 [1.07–1.42]; P=0.003) and <u>noncardiac death</u> (adjusted HR [95% CI], 1.14 [1.02–1.28]; P=0.021) both before and after adjustment

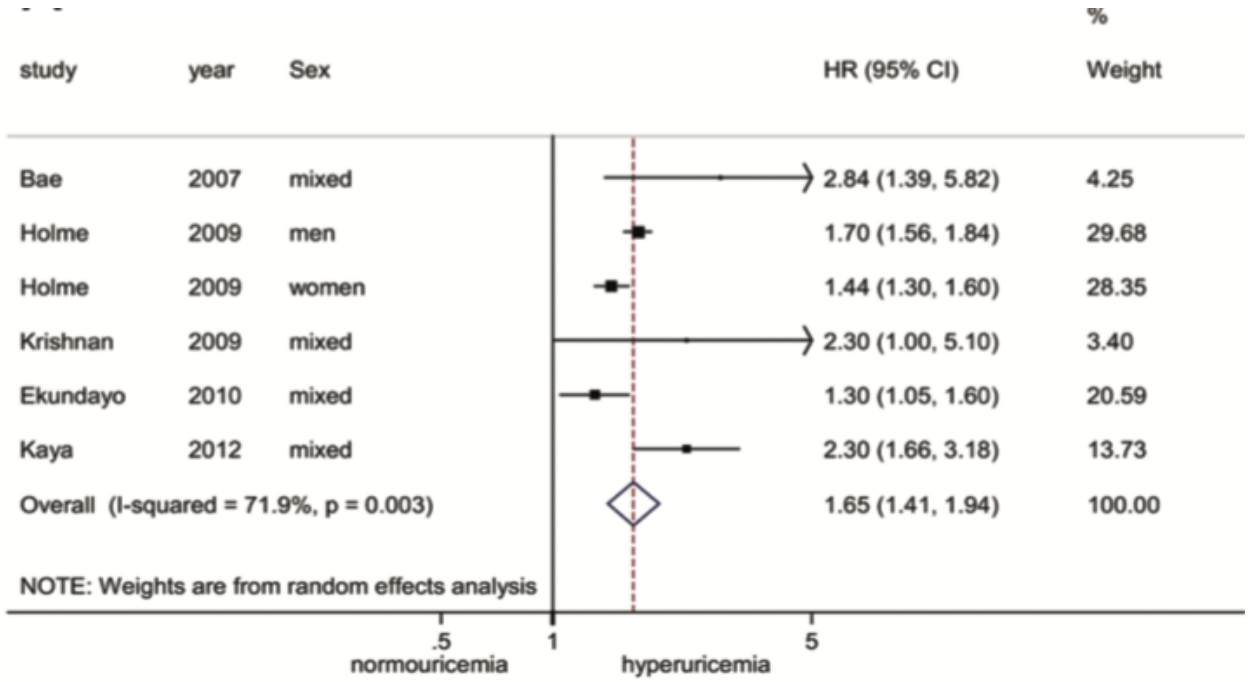
American Heart Association | American Stroke Association

Pagidipati NJ et al. J Am Heart Assoc. 2018;7:e009328.

Uric acid - Heart failure

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

Uric acid and the incidence of heart failure



Hyperuricaemia was associated with an increased risk of suffering from HF (HR 1.65, 95% CI 1.41 – 1.94)

H. Huang et al. European Journal of Heart Failure (2014) **16**, 15–24

Uric acid – Arterial hypertension

"People who are subject to this high blood pressure … frequently belong to gouty families, or have themselves suffered from the symptoms of this disease"

Frederick Mahomed.
Lancet i:400, 1879

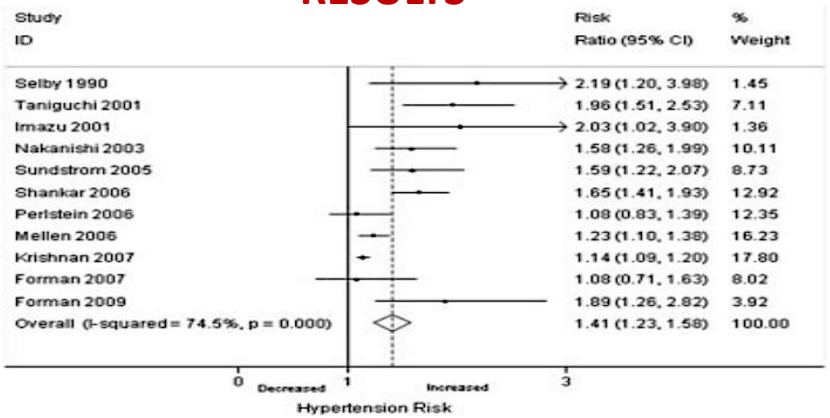
Uric acid – Arterial hypertension

Hyperuricemia and Incident Hypertension: A Systematic Review and Meta-Analysis

Arthritis Care & Research
Vol. 63, No. 1, January 2011, pp 102–110
2011, American College of Rheumatology

Grayson CP et al.

RESULTS



- Hyperuricemia was associated with **an increased risk for incident hypertension** (adjusted risk ratio [RR] 1.41, 95% confidenceinterval [95% CI] 1.23–1.58).
- For **a 1 mg/dl increase in uric acid level**, the pooled RR for incident hypertension after adjusting for potential confounding **was 1.13** (95% CI 1.06–1.20).
- These effects were significantly larger in **younger study populations** (P=0.02) and tended to be **larger in women** (P=0.059)

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URIC ACID: THE DOUBLE AGENT

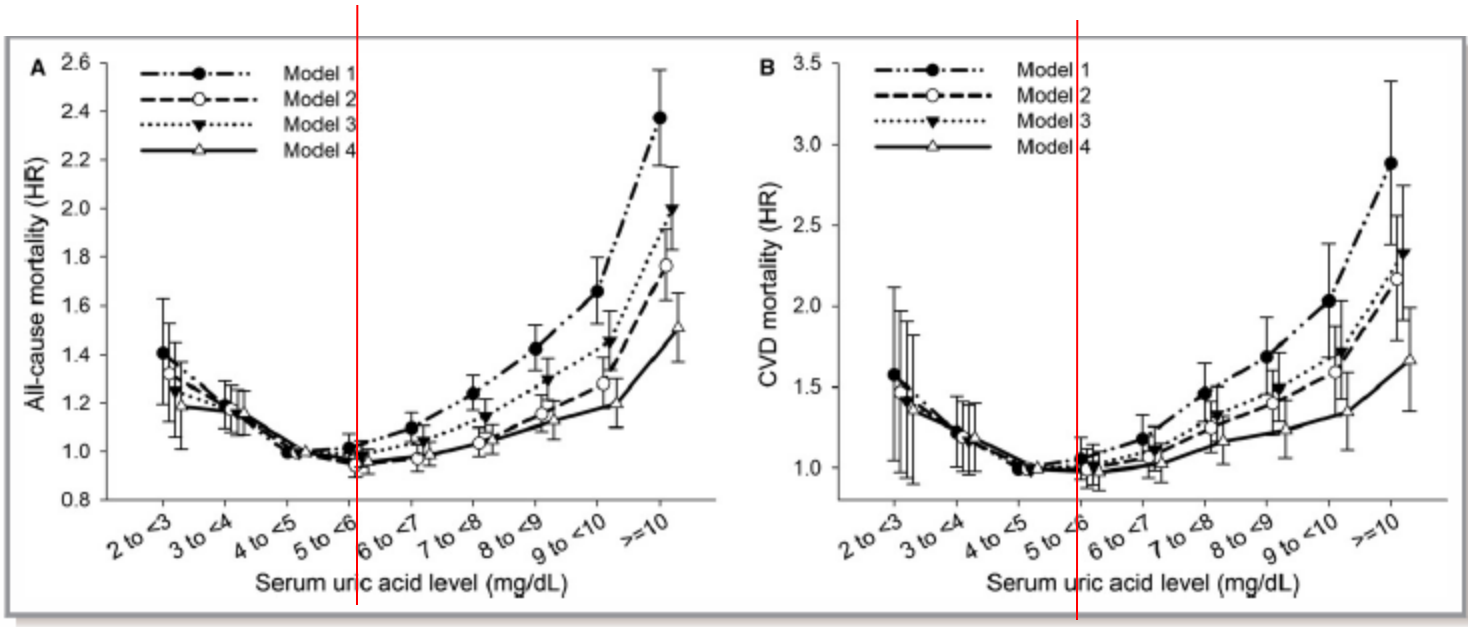
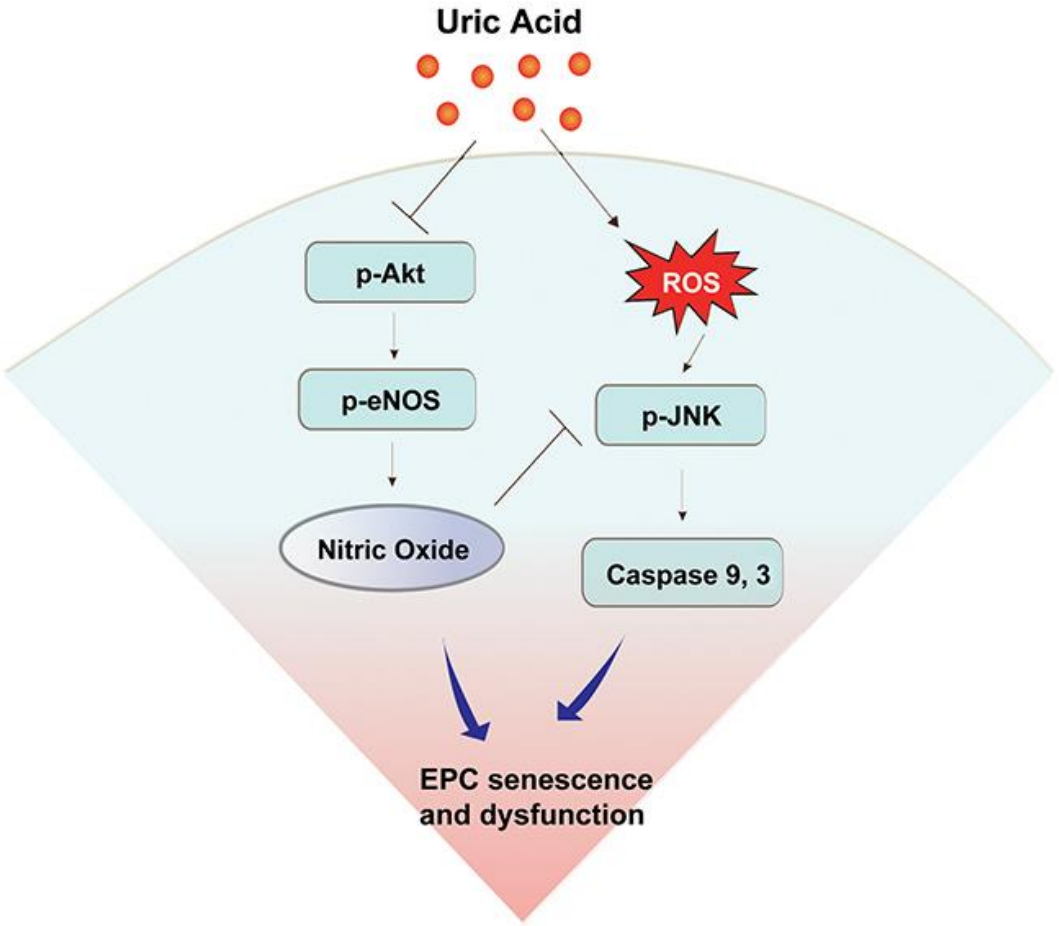
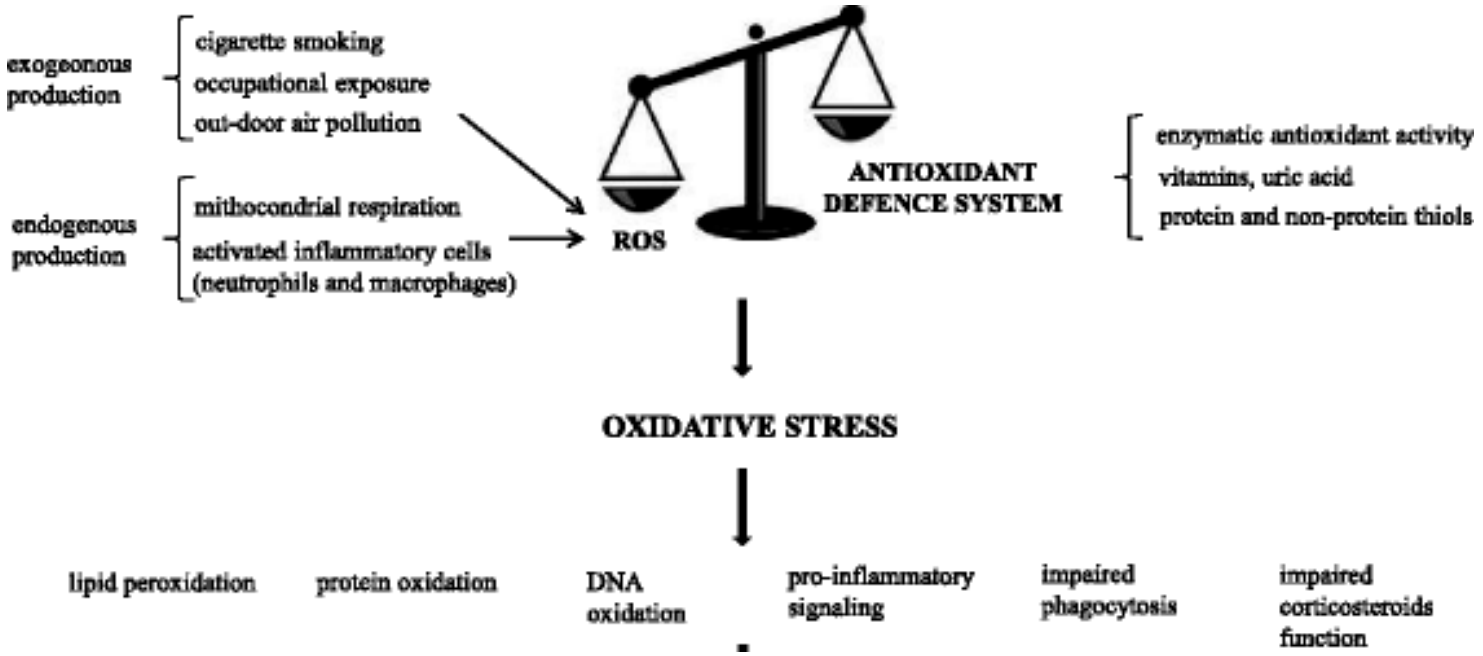


Figure 1. U-shaped association between serum uric acid level with (A) all-cause and (B) cardiovascular disease (CVD) mortality among 127 771 older people. Hazard ratios (HRs) (95% confidence intervals) of serum uric acid categories associated with (A) all-cause and (B) CVD mortality in Cox models are depicted. Model 1 was an unadjusted crude HR. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, smoking, alcohol consumption, body mass index, systolic blood pressure, and baseline comorbidities (hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, and cerebrovascular disease). Model 4 included covariates from model 3, as well as laboratory biochemical profiles. Serum uric acid category of 4 to <5 mg/dL served as reference.

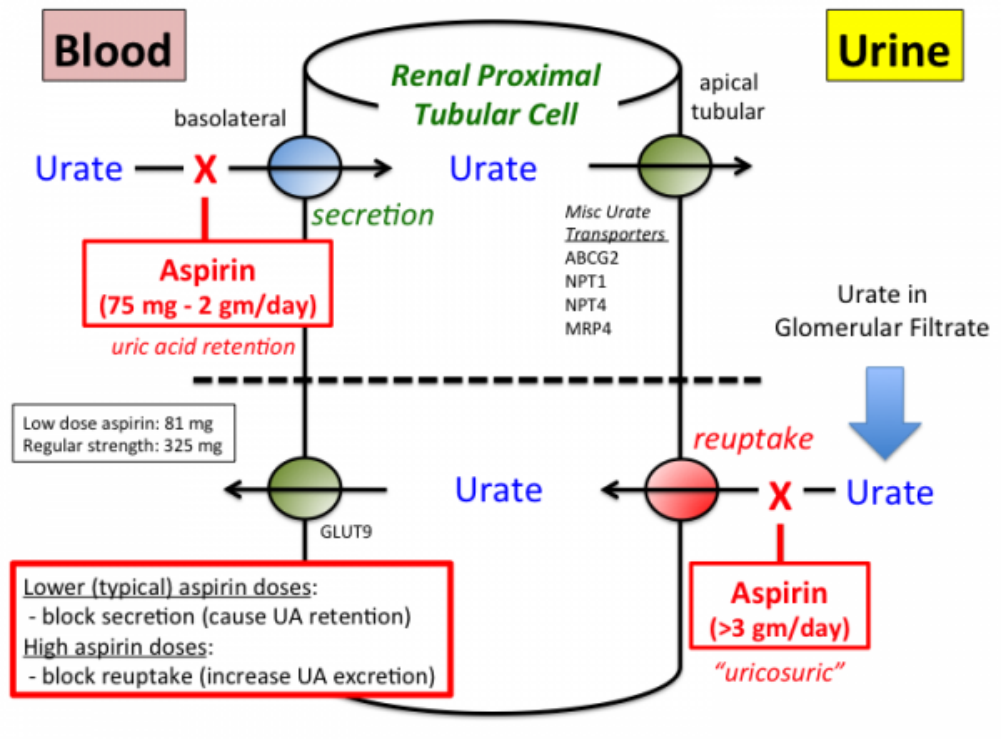
Uric acid induces damage through ROS: a concentration dependent effect



Uric acid protects against ROS : a concentration dependent effect



Uric acid and Aspirin



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The CARES study

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout

William B. White, M.D., Kenneth G. Saag, M.D., Michael A. Becker, M.D., Jeffrey S. Borer, M.D., Philip B. Gorelick, M.D., Andrew Whelton, M.D., Barbara Hunt, M.S., Majin Castillo, M.D., and Lhanoo Gunawardhana, M.D., Ph.D., for the CARES Investigators*

The CARES study

In total, 6190 patients underwent randomization, received febuxostat or allopurinol, and were followed for a median of 32 months (maximum, 85 months). The trial regimen was discontinued in 56.6% of patients, and 45.0% discontinued follow-up.

The CARES study

	Febuxostat (N = 3098)	Allopurinol (N = 3092)
Cardiovascular risk factors and history — no. (%)		
Diabetes mellitus with small-vessel disease	1193 (38.5)	1213 (39.2)
Hypertension	2864 (92.4)	2851 (92.2)
Hyperlipidemia	2678 (86.4)	2702 (87.4)
Myocardial infarction	1197 (38.6)	1231 (39.8)
Hospitalization for unstable angina	855 (27.6)	869 (28.1)
Coronary revascularization	1129 (36.4)	1182 (38.2)
Cerebral revascularization	69 (2.2)	54 (1.7)
Congestive heart failure	622 (20.1)	631 (20.4)
Stroke	460 (14.8)	410 (13.3)
Peripheral vascular disease	412 (13.3)	375 (12.1)

The CARES study

Uric acid serum levels

Baseline serum urate level — mg/dl	8.7±1.7	8.7±1.7
Presence of tophi — no. (%)	668 (21.6)	650 (21.0)

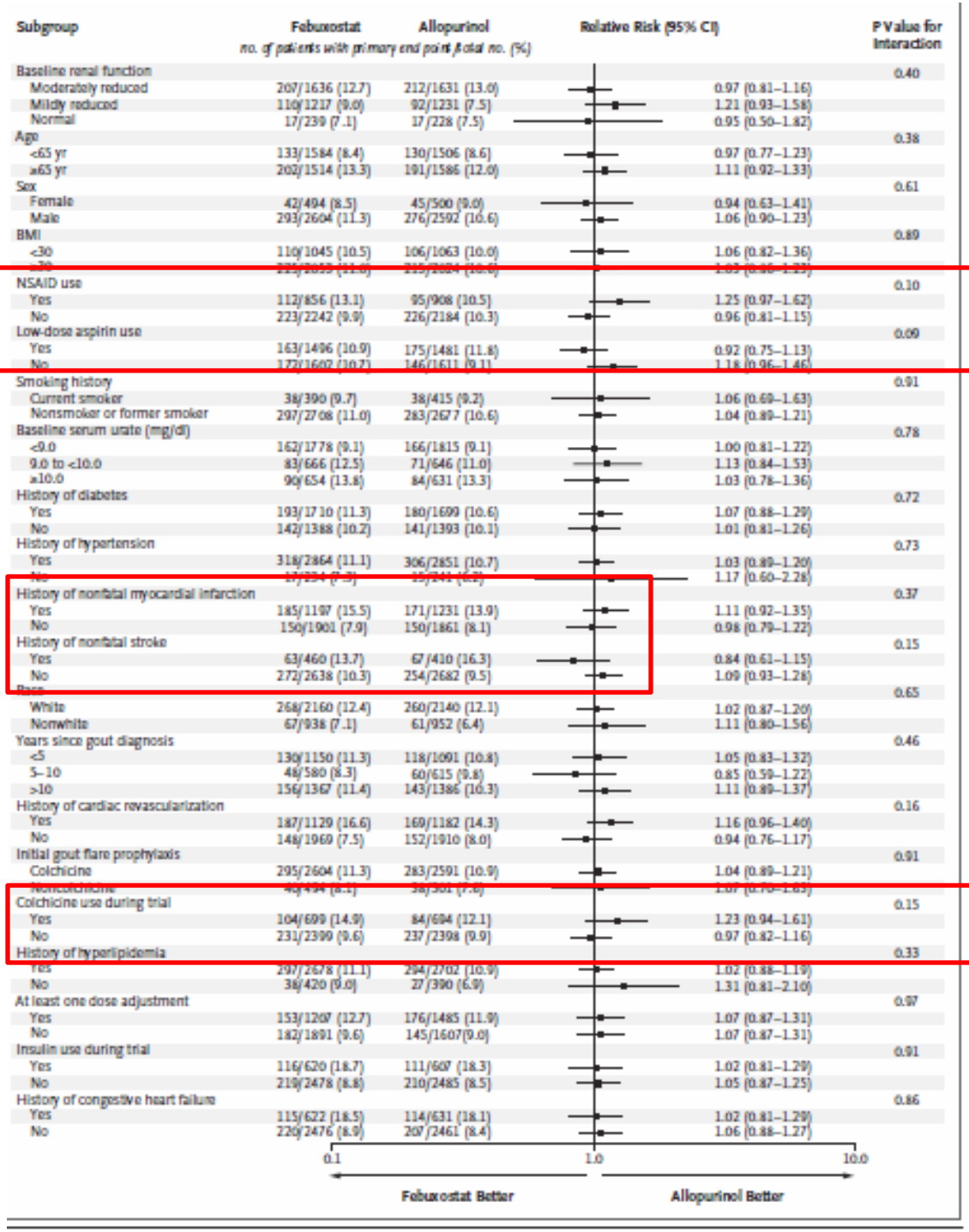
Table S4. Proportion of Patients with Serum Urate Levels < 6.0 mg/dl and < 5.0 mg/dl During the Trial

Visit	Febuxostat (n = 3098)	Allopurinol (n = 3092)	Febuxostat (n = 3098)	Allopurinol (n = 3092)
	< 6.0 mg/dl		< 5.0 mg/dl	
Week 2	1757/2892 (60.8%)	1456/2899 (50.2%)	978/2892 (33.8%)	549/2899 (18.9%)
Month 3	1975/2701 (73.1%)	1863/2686 (69.4%)	1156/2701 (42.8%)	716/2686 (26.7%)
Month 6	1823/2537 (71.9%)	1680/2530 (66.4%)	1113/2537 (43.9%)	717/2530 (28.3%)
Month 12	1544/2131 (72.5%)	1423/2152 (66.1%)	980/2131 (46.0%)	662/2152 (30.8%)
Month 18	1282/1775 (72.2%)	1194/1757 (68.0%)	839/1775 (47.3%)	571/1757 (32.5%)
Month 24	1159/1580 (73.4%)	1052/1557 (67.6%)	728/1580 (46.1%)	498/1557 (32.0%)
Month 36	836/1140 (73.3%)	776/1117 (69.5%)	566/1140 (49.6%)	378/1117 (33.8%)
Month 48	575/799 (72.0%)	567/782 (72.5%)	391/799 (48.9%)	296/782 (37.9%)
Month 60	387/511 (75.7%)	359/500 (71.8%)	277/511 (54.2%)	200/500 (40.0%)
Month 72	199/267 (74.5%)	186/248 (75.0%)	154/267 (57.7%)	109/248 (44.0%)

The CARES study

Table 2. Major Safety End Points (Modified Intention-to-Treat Analysis).*

End Point	Febuxostat (N=3098)	Allopurinol (N=3092)	Hazard Ratio (95% CI)	P Value†
	no. of patients (%)			
Primary end point: composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to unstable angina	335 (10.8)	321 (10.4)	1.03 (0.87–1.23)‡	0.66 (0.002)
Secondary end points				
Cardiovascular death	134 (4.3)	100 (3.2)	1.34 (1.03–1.73)	0.03
Nonfatal myocardial infarction	111 (3.6)	118 (3.8)	0.93 (0.72–1.21)	0.61
Nonfatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73–1.41)	0.94
Urgent revascularization for unstable angina	49 (1.6)	56 (1.8)	0.86 (0.59–1.26)	0.44
Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	296 (9.6)	271 (8.8)	1.09 (0.92–1.28)	0.33
Death from any cause	243 (7.8)	199 (6.4)	1.22 (1.01–1.47)	0.04


Subgroup
Febuxostat
Allopurinol
no. of patients with primary end point/total no. (%)
Relative Risk (95% CI)
P Value for Interaction
Baseline renal function
0.40
Moderately reduced
207/1636 (12.7)
212/1631 (13.0)
0.97 (0.81–1.16)
Mildly reduced
110/1217 (9.0)
92/1231 (7.5)
1.21 (0.93–1.58)
Normal
17/239 (7.1)
17/228 (7.5)
0.95 (0.50–1.82)
Age
0.38
<65 yr
133/1584 (8.4)
130/1506 (8.6)
0.97 (0.77–1.23)
≥65 yr
202/1514 (13.3)
191/1586 (12.0)
1.11 (0.92–1.33)
Sex
0.61
Female
42/494 (8.5)
45/500 (9.0)
0.94 (0.63–1.41)
Male
293/2604 (11.3)
276/2592 (10.6)
1.06 (0.90–1.23)
BMI
0.89
<30
110/1045 (10.5)
106/1063 (10.0)
1.06 (0.82–1.36)
≥30
225/2053 (11.0)
215/2084 (10.3)
1.05 (0.86–1.29)
NSAID use
0.10
Yes
112/856 (13.1)
95/908 (10.5)
1.25 (0.97–1.62)
No
223/2242 (9.9)
226/2184 (10.3)
0.96 (0.81–1.15)
Low-dose aspirin use
0.09
Yes
163/1496 (10.9)
175/1481 (11.8)
0.92 (0.75–1.13)
No
172/1602 (10.7)
146/1611 (9.1)
1.18 (0.96–1.46)
Smoking history
0.91
Current smoker
38/390 (9.7)
38/415 (9.2)
1.06 (0.69–1.63)
Nonsmoker or former smoker
297/2708 (11.0)
283/2677 (10.6)
1.04 (0.89–1.21)
Baseline serum urate (mg/dl)
0.78
<9.0
162/1778 (9.1)
166/1815 (9.1)
1.00 (0.81–1.22)
9.0 to <10.0
83/666 (12.5)
71/646 (11.0)
1.13 (0.84–1.53)
≥10.0
90/654 (13.8)
84/631 (13.3)
1.03 (0.78–1.36)
History of diabetes
0.72
Yes
193/1710 (11.3)
180/1699 (10.6)
1.07 (0.88–1.29)
No
142/1388 (10.2)
141/1393 (10.1)
1.01 (0.81–1.26)
History of hypertension
0.73
Yes
318/2864 (11.1)
306/2851 (10.7)
1.03 (0.89–1.20)
No
17/234 (7.3)
13/241 (5.4)
1.17 (0.60–2.28)
History of nonfatal myocardial infarction
0.37
Yes
185/1197 (15.5)
171/1231 (13.9)
1.11 (0.92–1.35)
No
150/1901 (7.9)
150/1861 (8.1)
0.98 (0.79–1.22)
History of nonfatal stroke
0.15
Yes
63/460 (13.7)
67/410 (16.3)
0.84 (0.61–1.15)
No
272/2638 (10.3)
254/2682 (9.5)
1.09 (0.93–1.28)
Race
0.65
White
268/2160 (12.4)
260/2140 (12.1)
1.02 (0.87–1.20)
Nonwhite
67/938 (7.1)
61/952 (6.4)
1.11 (0.80–1.56)
Years since gout diagnosis
0.46
<5
130/1150 (11.3)
118/1091 (10.8)
1.05 (0.83–1.32)
5–10
48/580 (8.3)
60/615 (9.8)
0.85 (0.59–1.22)
>10
156/1367 (11.4)
143/1386 (10.3)
1.11 (0.89–1.37)
History of cardiac revascularization
0.16
Yes
187/1129 (16.6)
169/1182 (14.3)
1.16 (0.96–1.40)
No
148/1969 (7.5)
152/1910 (8.0)
0.94 (0.76–1.17)
Initial gout flare prophylaxis
0.91
Colchicine
295/2604 (11.3)
283/2591 (10.9)
1.04 (0.89–1.21)
Noncolchicine
46/494 (9.1)
36/501 (7.2)
1.27 (0.79–2.03)
Colchicine use during trial
0.15
Yes
104/699 (14.9)
84/694 (12.1)
1.23 (0.94–1.61)
No
231/2399 (9.6)
237/2398 (9.9)
0.97 (0.82–1.16)
History of hyperlipidemia
0.33
Yes
297/2678 (11.1)
294/2702 (10.9)
1.02 (0.88–1.19)
No
38/420 (9.0)
27/390 (6.9)
1.31 (0.81–2.10)
At least one dose adjustment
0.97
Yes
153/1207 (12.7)
176/1485 (11.9)
1.07 (0.87–1.31)
No
182/1891 (9.6)
145/1607 (9.0)
1.07 (0.87–1.31)
Insulin use during trial
0.91
Yes
116/620 (18.7)
111/607 (18.3)
1.02 (0.81–1.29)
No
219/2478 (8.8)
210/2485 (8.5)
1.05 (0.87–1.25)
History of congestive heart failure
0.86
Yes
115/622 (18.5)
114/631 (18.1)
1.02 (0.81–1.29)
No
220/2476 (8.9)
207/2461 (8.4)
1.06 (0.88–1.27)
0.1
1.0
10.0
Febuxostat Better
Allopurinol Better

Other studies

Original article

doi:10.1093/rheumatology/kez189

Comparative cardiovascular risk of allopurinol *versus* febuxostat in patients with gout: a nation-wide cohort study

Eun Ha Kang [1], Hyon K. Choi[2], Anna Shin[1], Yun Jong Lee[1], Eun Bong Lee [3], Yeong Wook Song[3] and Seoyoung C. Kim[4,5]

Abstract

Objective. To compare cardiovascular (CV) risk among gout patients initiating allopurinol *vs* febuxostat.

Methods. Using 2002–2015 Korean National Health Insurance Service data for the entire Korean population, we conducted a cohort study on gout patients initiating allopurinol or febuxostat. The primary outcome was a composite CV endpoint of myocardial infarction, stroke/transient ischaemic attack, or coronary revascularization. Secondary outcomes were individual components of the primary outcome, and all-cause mortality. We used propensity score-matching with a 1:1 ratio for allopurinol and febuxostat initiators to control for confounding. Competing risk analyses were done for non-fatal outcomes accounting for deaths.

Results. We included 39 640 allopurinol initiators propensity score-matched on 9910 febuxostat initiators. The mean age was 59.1 years and 78.4% were male. The incidence rate per 100 person-years for the primary outcome was 1.89 for allopurinol and 1.84 for febuxostat initiators. The corresponding hazard ratio comparing allopurinol *vs* febuxostat initiators was 1.09 (95% CI: 0.90, 1.32). No significant difference was found for the secondary outcomes, including all-cause mortality (hazard ratio 0.96; 95% CI: 0.79, 1.16). Subgroup analyses limited to those at high CV risk and to equipotent-dose initiators (i.e. allopurinol ⩾300 mg/day *vs* febuxostat ⩾40 mg/day) showed similar results.

Conclusion. Overall, this large Korean population-based study suggests no difference in the risk of non-fatal CV events and all-cause mortality between allopurinol and febuxostat initiators. These findings are consistent with the recent US Medicare population study, although the current study population consisted of younger Asians.

Key words: gout, cardiovascular disease, allopurinol, febuxostat

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Conclusions

Uric acid is associated with cardiovascular disease

The uric acid U curve should be considered to interpret clinical data and the effects of lowering uric acid therapies