Hyperuricemia
Implications and Interventions

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Disclosures

- Financial relationships: None
- Off-label uses of drugs/devices: anakinra and canakinumab as investigational agents in the treatment of acute gout

Topics

- Hyperuricemia defined
- Consequences of hyperuricemia
- Hyperuricemia and hypertension, cardiovascular disease, and metabolic syndrome
- Interventions and outcomes, including controversies

Hyperuricemia – What and Why

- Humans lack uricase to break down uric acid
- Sustained hyperuricemia (≥7 mg/dL in men, ≥6 mg/dL in women) is associated with tissue deposition of uric acid and other metabolic effects
- Most often familial, involving polymorphisms is renal urate transport proteins

Hyperuricemia – Dietary Influences on Uric Acid Levels

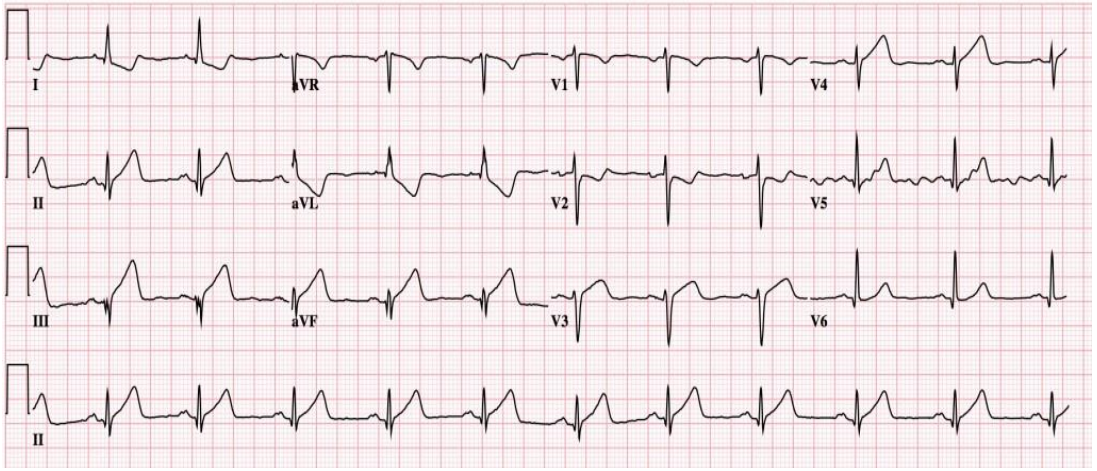
- Non-Western diet: 2-4 mg/dL (120-240 μM)
- Industrialized nations: 3-8 mg/dL
  - diets richer in purines and fructose (both of which generate urate)
  - greater alcohol intake
  - higher prevalence of factors that reduce kidney urate excretion (eg, insulin resistance, renal vasoconstriction associated with hypertension, and decreased kidney function)
  - interpopulation genetic differences

Complications of Hyperuricemia

- Confirmed
  - Gout
  - Nephrolithiasis
  - Uric acid nephropathy
- Emerging Data
  - Hypertension
  - Cardiovascular disease
  - Metabolic syndrome
- Still Controversial: Dementia

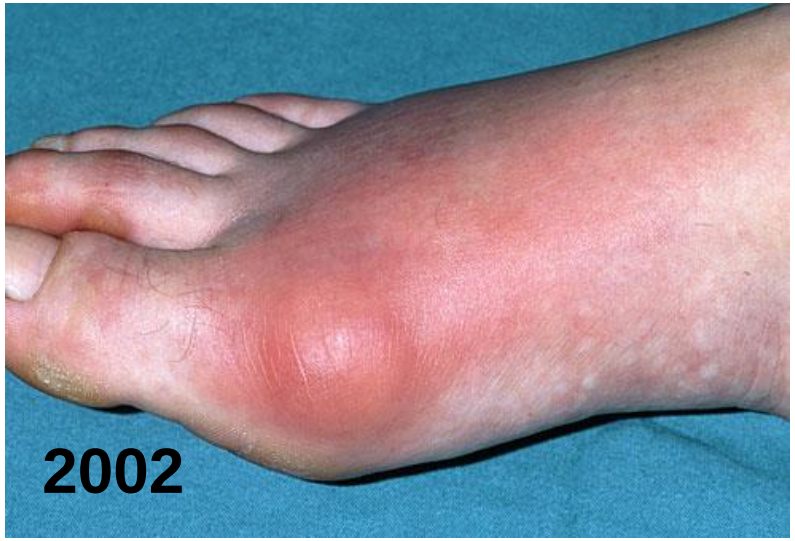
Case

- 70 year old Caucasian male – Consultation for sustained hyperuricemia
- First STEMI at age 54; three subsequent MIs; 3-vessel CABG at age 57
- Since then 15 coronary stent procedures
- Currently asymptomatic, exercising



Case

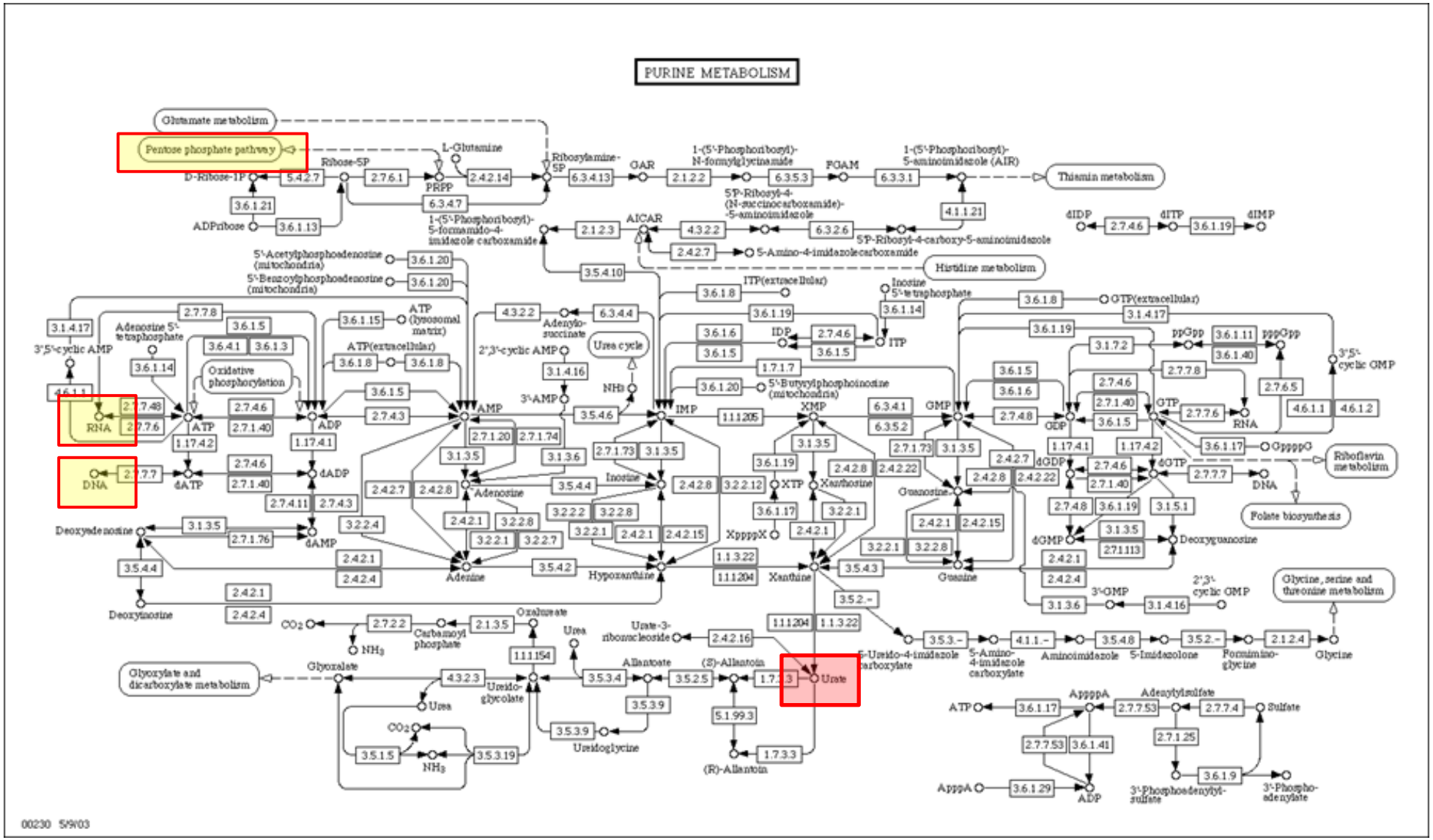
- Serum urate over last two years 8.2, 9.0, 8.8 mg/dL
- Recalls having 2 attacks of gout, last one 15 years ago, classic podagra and instep of right foot; none since then
- BP 136/84; no tophi. No arthritic changes.
- Labs: CBC and diff normal; Cr 1.3; Chol (total) 223, LDL 130, HDL 38, TG 230; hsCRP 22; HbA1c 6.3%; ESR 8 mm/h.



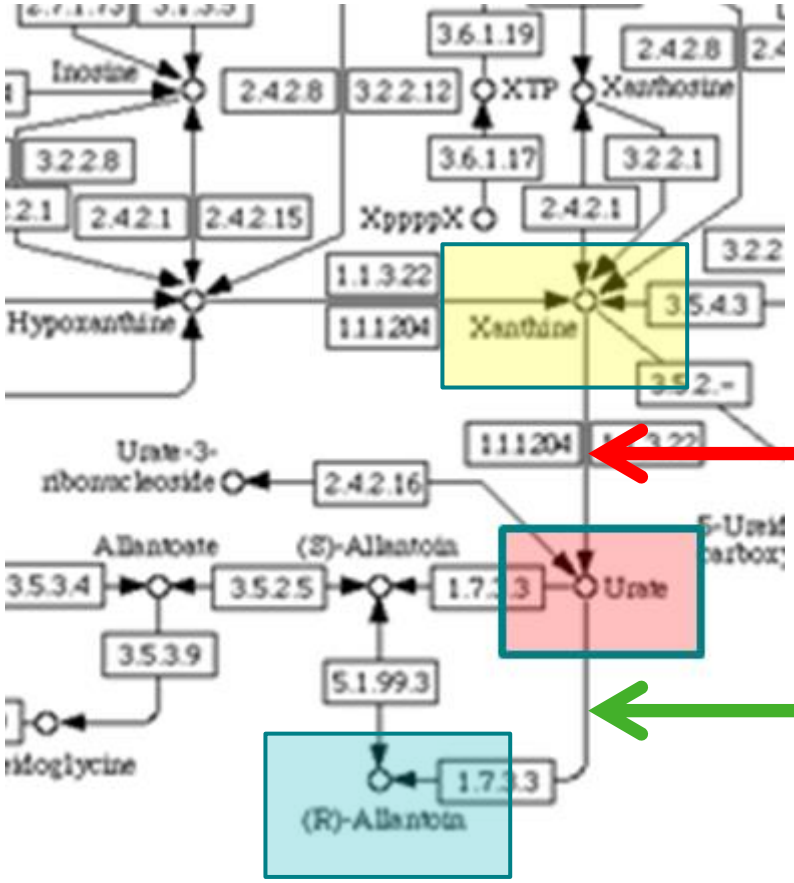
What would you do?

1. Advise dietary changes only to lower cardiac risk and serum uric acid
2. Add allopurinol 100 mg/d
3. Add allopurinol 300 mg/d
4. Add febuxostat 40 mg/d
5. Add probenecid 500 mg BID
6. Manage cardiac risk factors only

Purine Metabolism and the Entry Points to the Cycle



Purine Metabolism – Terminal Products



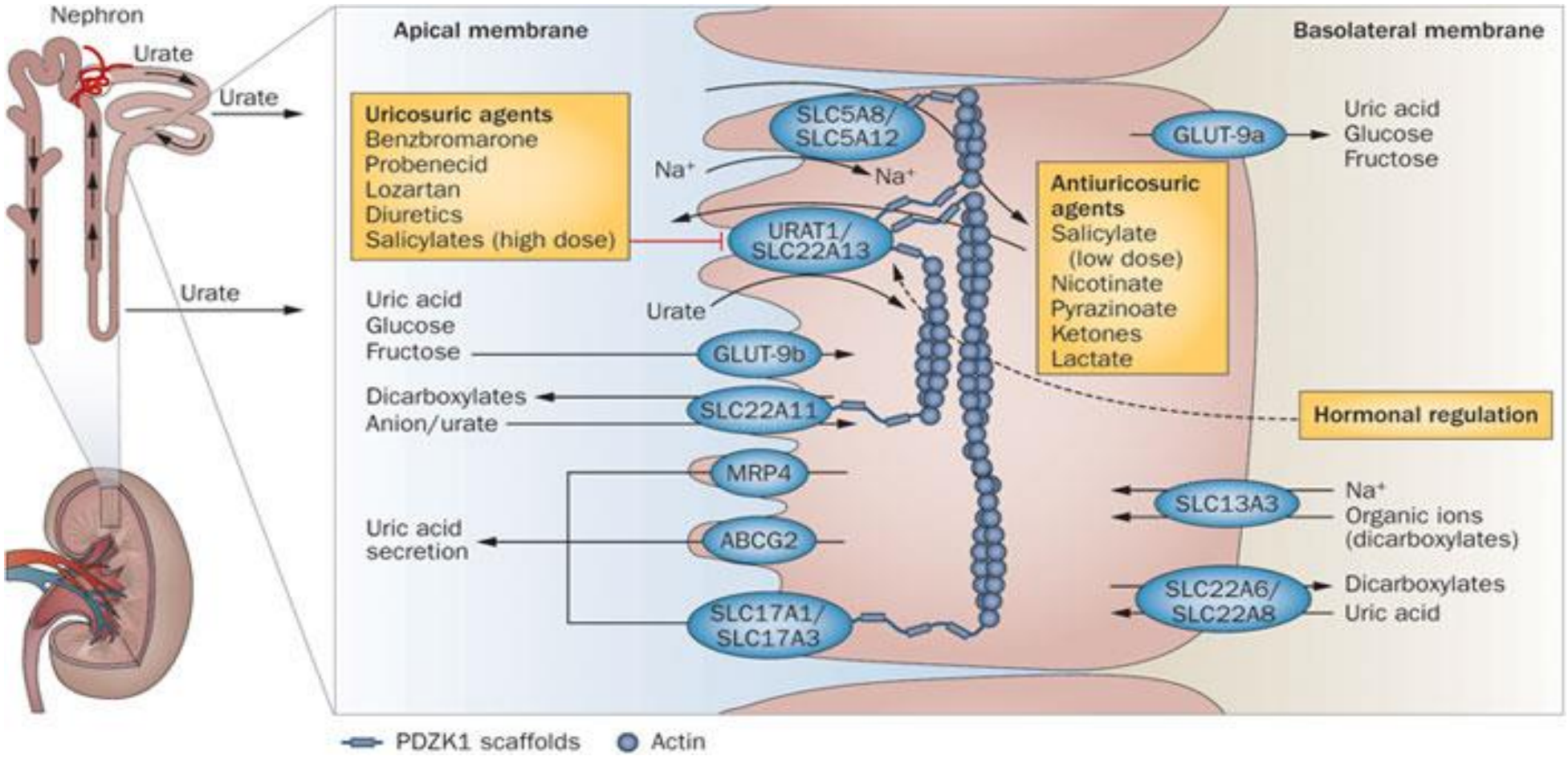
Xanthine oxidase

Inhibit:
Allopurinol
Febuxistat

Uricase

Supplement:
Pegloticase

Purine Metabolism – uric acid excretion



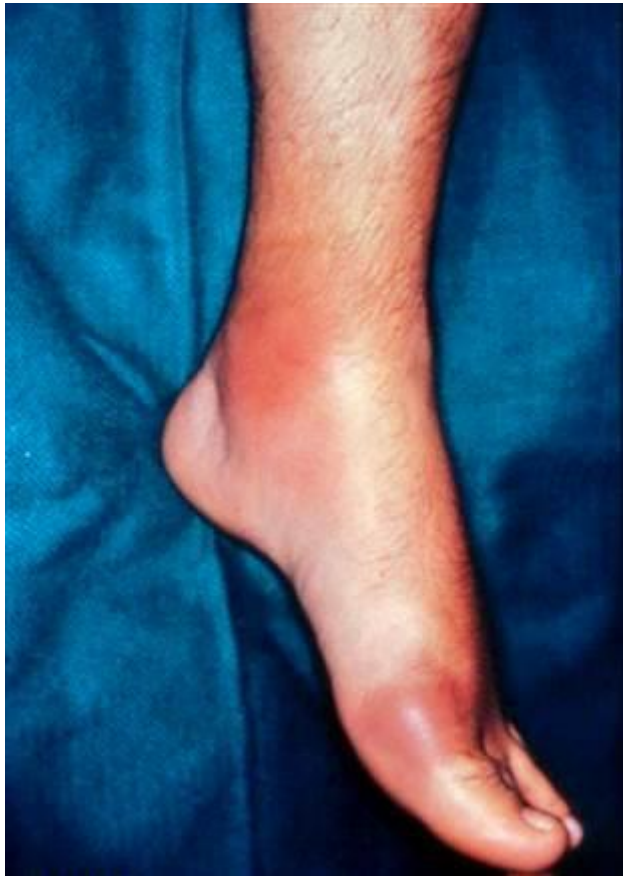
Reginato AM. Nat Rev Rheum 2012; 8(10):610-21.

Gout

- Gout prevalence increasing worldwide
- A disease of chronic urate accumulation; hence treatment should result in gradual urate elimination
- Treat-to-Target guidelines (American College of Rheumatology) vs. don’t treat to target (ACP)

Making the Diagnosis of Gout

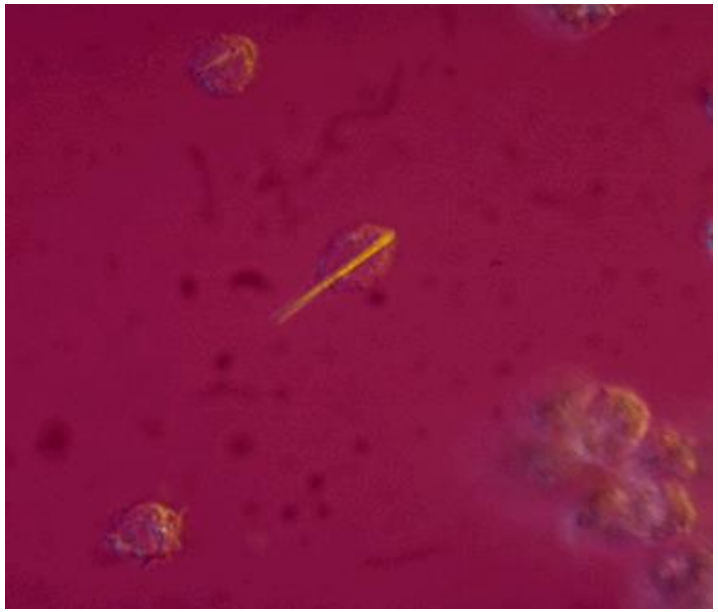
- **Helpful clinical features:**
  - monoarticular involvement of a foot (especially the first MTP) or ankle joint
  - previous similar acute arthritis episodes
  - rapid onset of severe pain and swelling (at its worst in <24 hours), resolution in 7-10 days
  - erythema
  - male gender
  - associated cardiovascular diseases and hyperuricemia
  - the diagnosis of gout should not be made on the presence of hyperuricemia alone

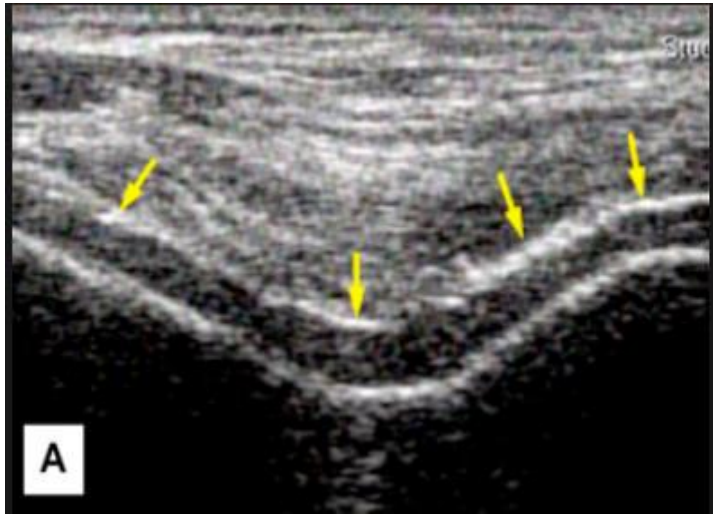


Adapted from Richette P, Doherty M, Pascual E, *et al. Ann Rheum Dis 2019.* doi: 10.1136/annrheumdis-2019-215315

Making the Diagnosis of Gout

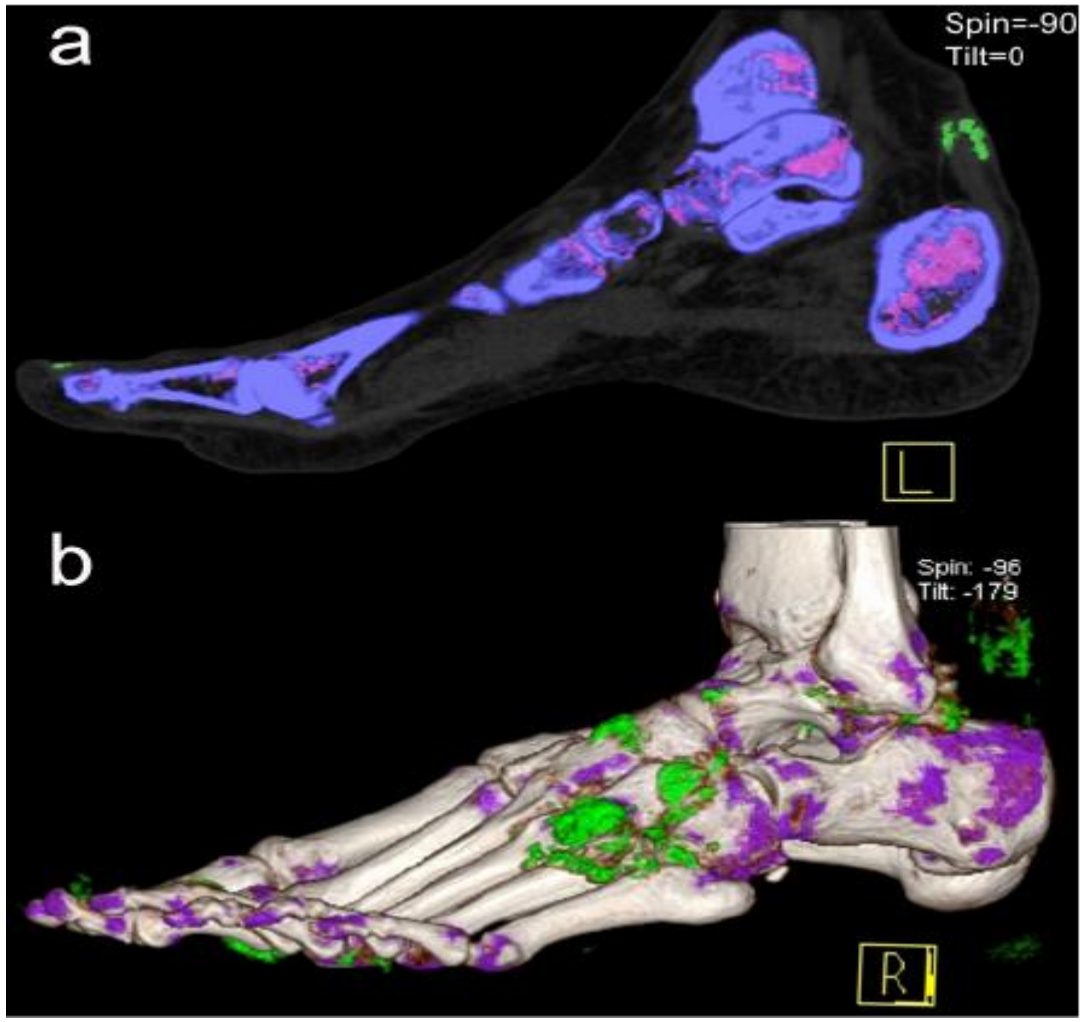
- **Pathology**: aspirate synovial fluid or tophus whenever possible; demonstration of MSU crystals allows a definitive diagnosis of gout.
- **Radiologic Imaging**
  - Plain radiographs can provide evidence of MSU crystal deposition but have limited value for the diagnosis of gout flare
  - Ultrasound can provide detection of tophi
  - Dual-energy CT scanning is a sensitive method to detect uric acid deposition

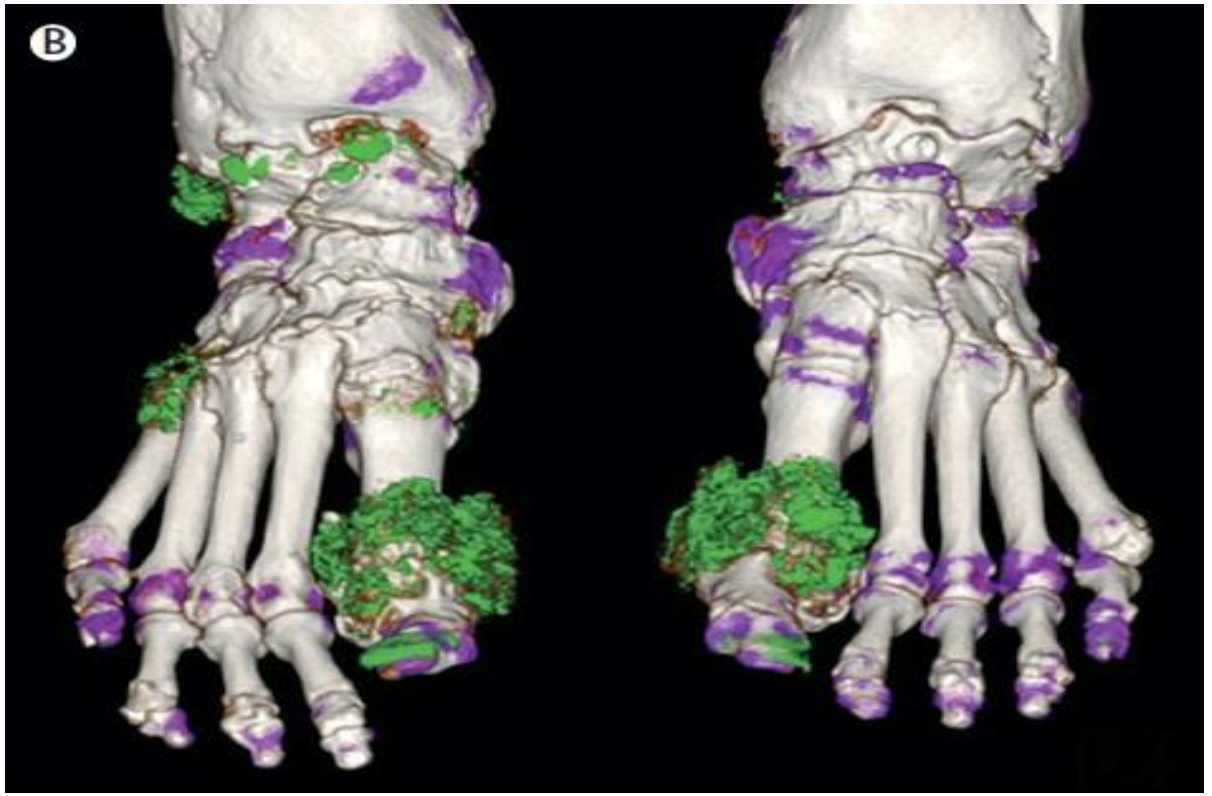




Adapted from Richette P, Doherty M, Pascual E, *et al. Ann Rheum Dis 2019.* doi: 10.1136/annrheumdis-2019-215315

Dual-energy CT (DECT) for urate deposition





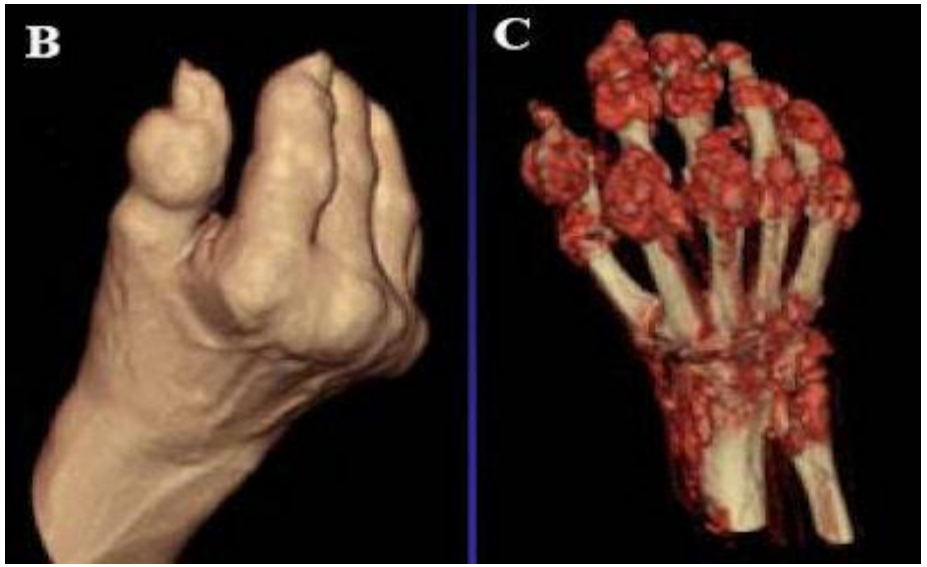
Additional Considerations in Gout Management

- **Risk factors for chronic hyperuricemia** should be searched for in every person with gout, specifically: chronic kidney disease; overweight, medications (including diuretics, low-dose aspirin, cyclosporine, tacrolimus); consumption of excess alcohol (particularly beer and spirits), non-diet sodas, meat and shellfish
- Systematic assessment for the presence of **associated comorbidities** in people with gout is recommended, including obesity, renal impairment, hypertension, ischemic heart disease, heart failure, diabetes and dyslipidemia.

Adapted from Richette P, Doherty M, Pascual E, *et al. Ann Rheum Dis 2019.* doi: 10.1136/annrheumdis-2019-215315

Gout is a disease of urate accumulation

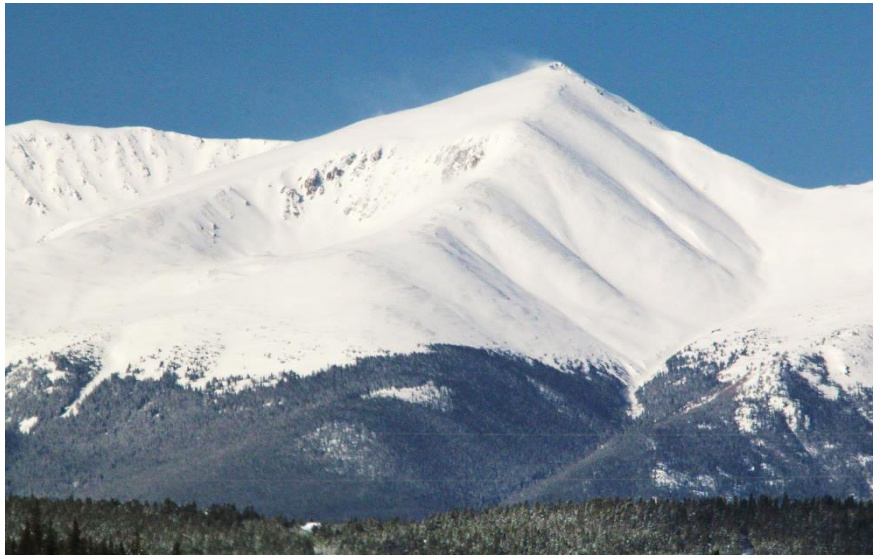
- Uric acid will begin to precipitate at a concentration of 6 mg/dL in water at 37°C and pH 7.4
- Lowering concentration leads to dissolution of crystals and decreased tissue burden of urate
- This is the basis of the treat-to-target goal of serum uric acid concentration [sUA] of 6.0 mg/dL, or ≤5.0 mg/dL in tophaceous disease



Neogi 2015; Richette 2016; Becker MA 2008

Chronic urate-lowering treatment

- **Begin allopurinol at 100 mg/d** in order to minimize chance of “initiation flare.” Cover with NSAIDs, colchicine, or glucocorticoids for 2-4 weeks
- **Titrate upwards** in 100 mg increments every 6 weeks to reach target uric acid concentration
- **Maximum daily dose is 800 mg/d –** allopurinol is frequently underdosed
- Hypersensitivity reactions very rare, but inform patient
- **Test HLA-B*5801** in Koreans, Japanese, Thai and Han Chinese, black populations (highest risk for Steven-Johnson syndrome)
- Higher risk of sensitivity reactions in CKD not confirmed
- Do not use allopurinol or febuxostat with azathioprine



Chronic urate-lowering treatment: other agents

- Febuxostat (Uloric®)
  - Start at 40 mg/d, increase to 80 mg/d
  - Some increased CV risk (White 2018)
- Probenecid – weak uricosuric; cannot use in GFR < 35
- Lesinurad (Zurampic®) – new uricosuric drug for allopurinol nonresponders, now discontinued in U.S. (low sales)
- Losartan: weak uricosuric effects

Febuxostat and increased cardiovascular mortality: the CARES Study

- CARES (Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout and Cardiovascular Disease)
- Prospective, double-blind, 320-center North American clinical trial
- 6,190 patients were randomized to febuxostat (Uloric) at 40-80 mg once daily or 200-600 mg of allopurinol once daily.
- Primary endpoint : composite of cardiovascular death, MI, stroke, and unstable angina resulting in urgent revascularization

White W et al. N Engl J Med. 2018 Mar 12. doi: 10.1056/NEJMoa1710895

Febuxostat and increased cardiovascular mortality: the CARES Study

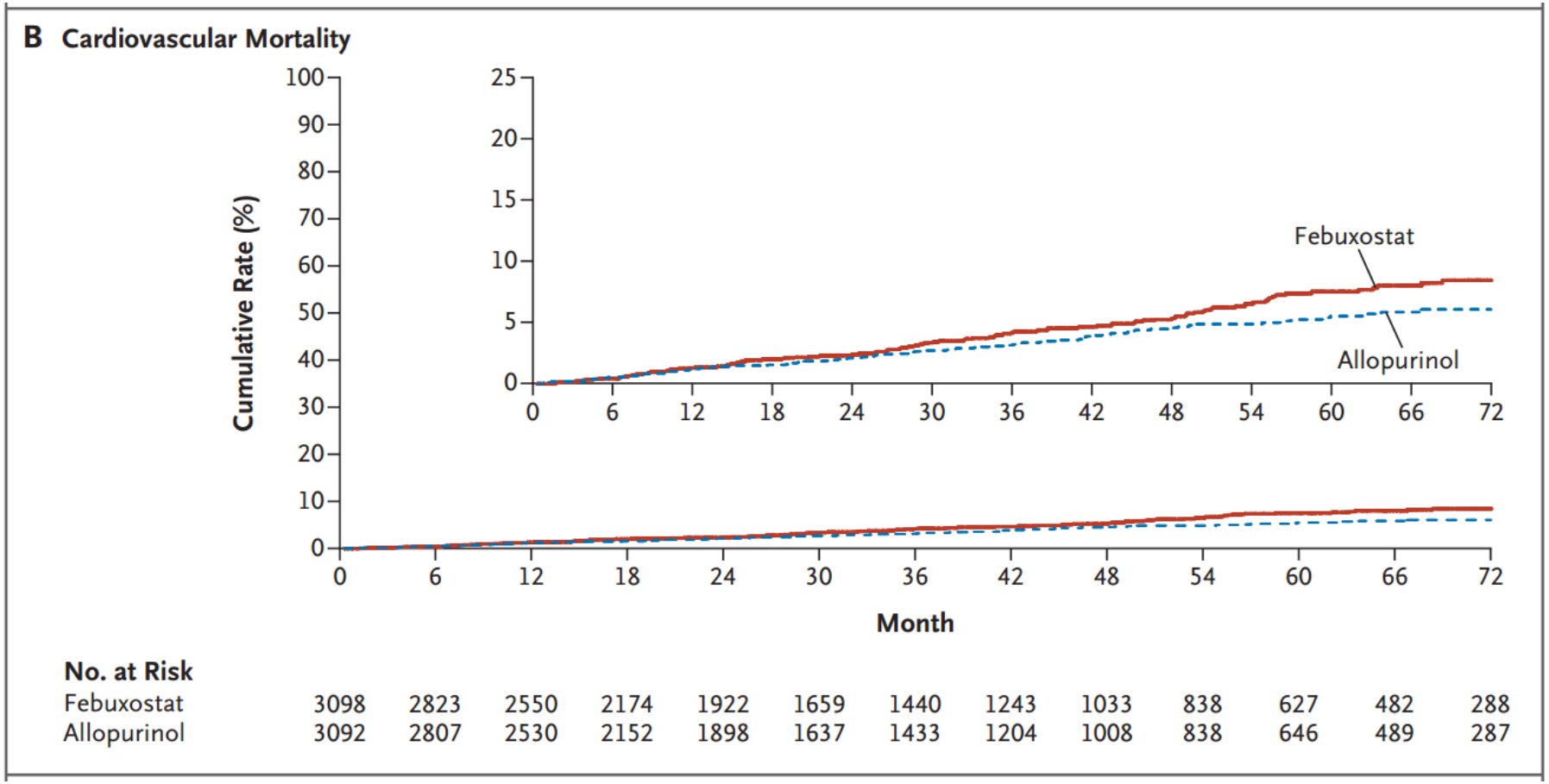
Table 3. Events That Occurred during Treatment or within 30 Days after Discontinuation of Treatment.*

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	242 (7.8)	238 (7.7)	1.00 (0.82–1.22)†	0.99
Secondary end points				
Cardiovascular death	62 (2.0)	41 (1.3)	1.49 (1.01–2.22)	0.047
Nonfatal myocardial infarction	93 (3.0)	106 (3.4)	0.87 (0.66–1.15)	0.32
Nonfatal stroke	59 (1.9)	62 (2.0)	0.94 (0.66–1.34)	0.72
Urgent revascularization for unstable angina	45 (1.5)	44 (1.4)	1.00 (0.66–1.52)	0.98
Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	205 (6.6)	200 (6.5)	1.01 (0.83–1.22)	0.93
Death from any cause	92 (3.0)	72 (2.3)	1.26 (0.93–1.72)	0.14

* This analysis was prespecified in the statistical analysis plan.
† The 97% confidence interval is provided here.

White W et al. N Engl J Med. 2018 Mar 12. doi: 10.1056/NEJMoa1710895

Febuxostat and increased cardiovascular mortality: the CARES Study



White W et al. N Engl J Med. 2018 Mar 12. doi: 10.1056/NEJMoa1710895

Febuxostat and increased cardiovascular mortality: the CARES Study

- Because of the high lost-to-follow-up rate, a private investigator was hired to look for missed deaths among study subjects. An extra 199 deaths were found. When those were added to the total, all-cause mortality in the febuxostat group was no longer significantly higher than allopurinol.
- Nonfatal MI, nonfatal stroke, and urgent revascularization due to unstable angina – were neutral or were less common with febuxostat
- Recommend caution, not contraindication

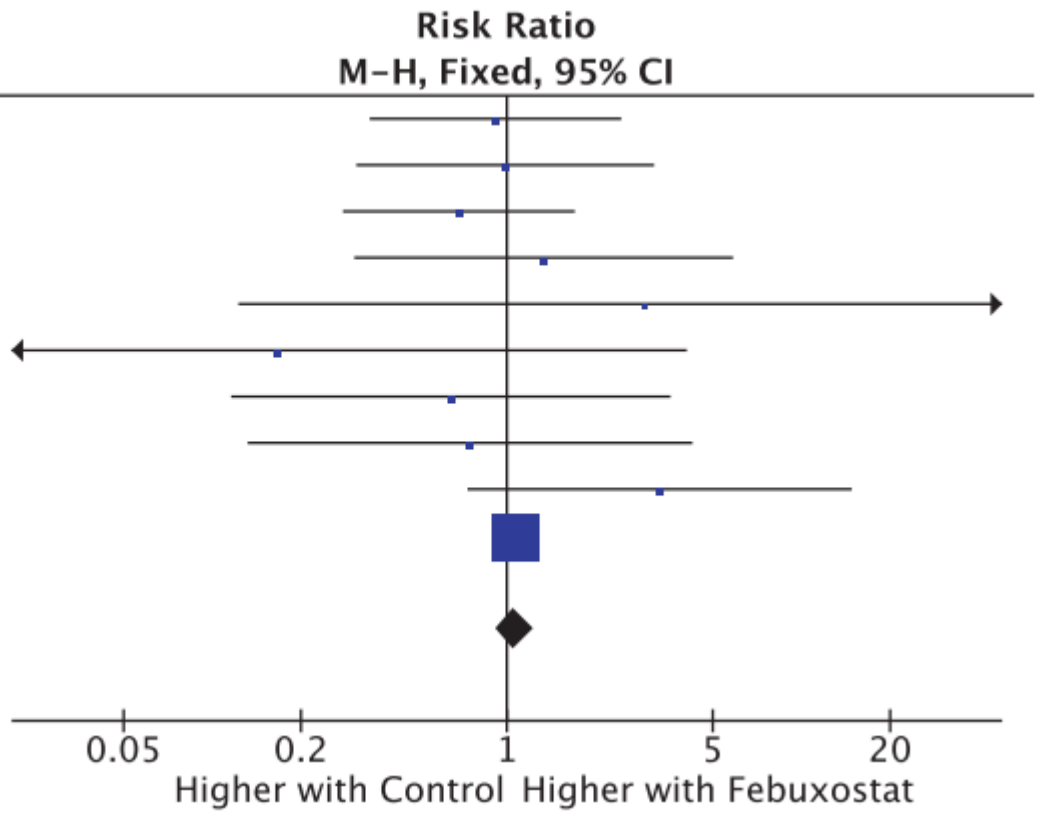
White W et al. N Engl J Med. 2018 Mar 12. doi: 10.1056/NEJMoa1710895

Independent meta-analysis

Study or Subgroup	Febuxostat Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Becker 2005	11	507	6	253	2.6%	0.91 [0.34, 2.45]
Becker 2009	32	994	3	92	1.8%	0.99 [0.31, 3.16]
Becker 2010	11	1513	8	756	3.4%	0.69 [0.28, 1.70]
Dalbeth 2017	4	157	3	157	1.0%	1.33 [0.30, 5.86]
Gunawardhana 2017	1	61	0	60	0.2%	2.95 [0.12, 71.05]
Huang 2014	0	344	1	172	0.6%	0.17 [0.01, 4.08]
Nakagomi 2015	2	31	3	30	1.0%	0.65 [0.12, 3.59]
Saag 2016	3	64	2	32	0.9%	0.75 [0.13, 4.27]
Schumacher 2008	11	670	2	402	0.8%	3.30 [0.74, 14.81]
White 2018	294	3098	274	3092	87.9%	1.07 [0.92, 1.25]
Total (95% CI)		**7439**		**5046**	**100.0%**	**1.06 [0.92, 1.23]**
Total events	369		302			

Heterogeneity: $Chi^2 = 5.44$, df = 9 (P = 0.79); $I^2 = 0\%$

Test for overall effect: Z = 0.81 (P = 0.42)

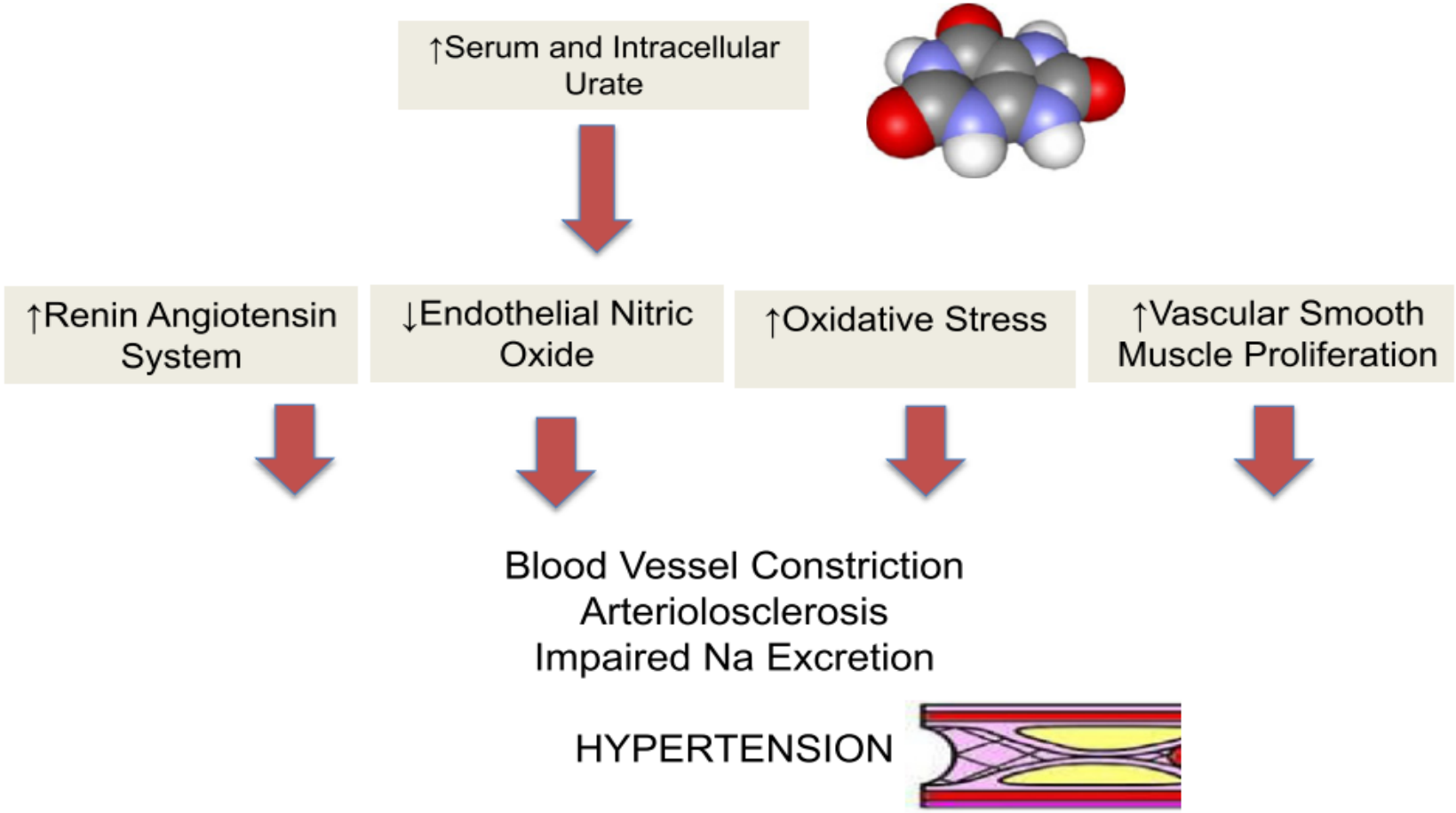


Cuenca JA et al. Int J Rheumatol. 2019 Feb 3;2019:1076189. doi: 10.1155/2019/1076189.

Biologic therapy in gout

- Treating acute inflammation: monoclonal antibody IL-1 inhibitors (not FDA approved)
  - Anakinra
  - Canakinumab
- Treating urate accumulation (severe tophaceous disease)
  - pegloticase (Krystexxa®)
  - rasburicase (Elitek®)

Hyperuricemia and hypertension: physiologic mechanisms



Johnson RJ et al. Am J Kidney Dis. 2018:1-15. Published online.

Epidemiologic data support an independent effect of hyperuricemia on hypertension

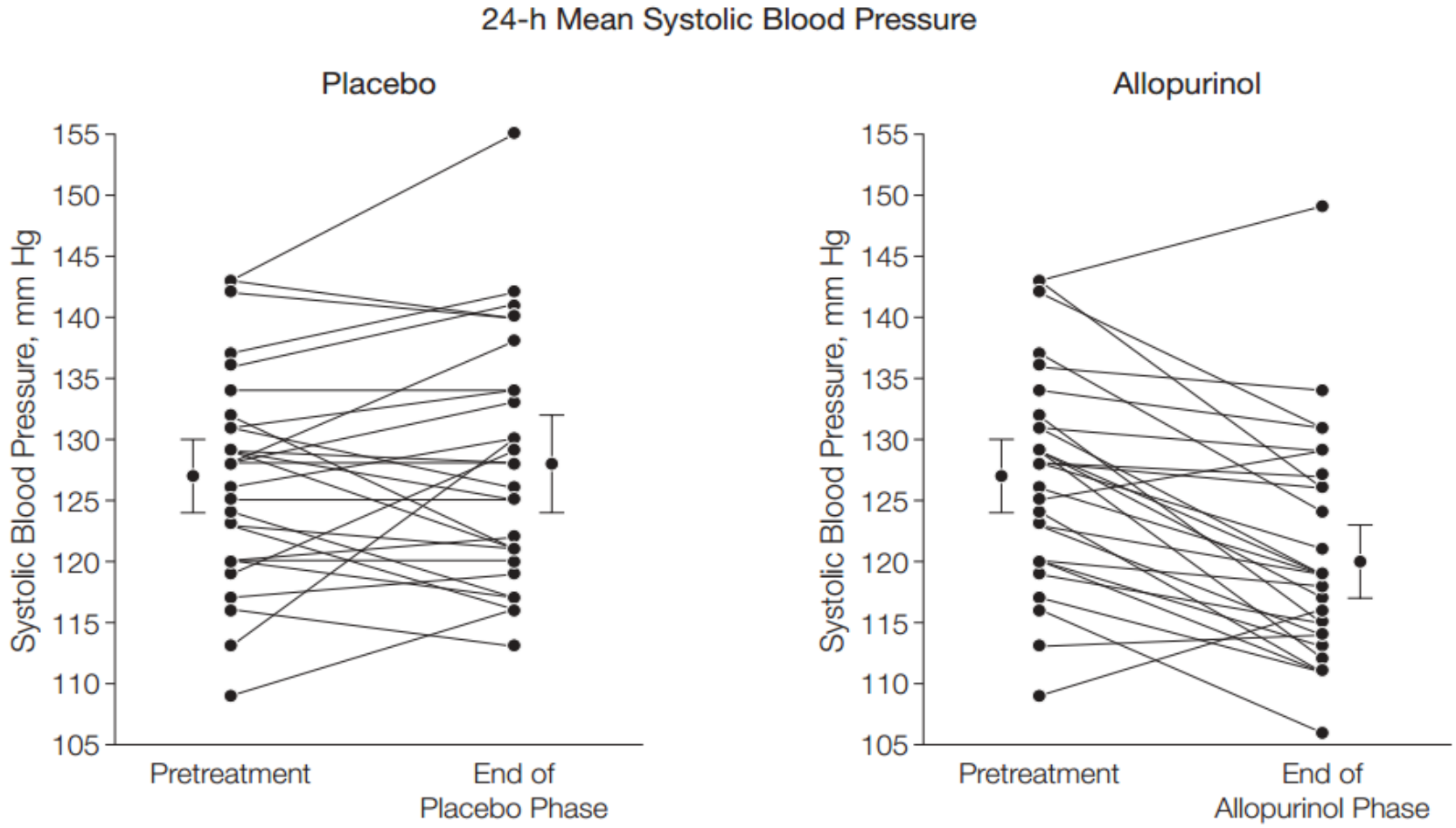
Table. Serum uric acid as a predictor of hypertension

Study	Population	Follow-up, y	Independent	Year	Reference
Israeli Heart Study	10 000 male participants	5	Not done	1972	112
Kaiser Permanente	2062 subjects	6	Yes	1990	113
University of Utah	1482 adults	7	Yes	1991	114
Olivetti Heart Study	619 male participants	12	Yes	1994	115
CARDIA study	5115 adults	10	Yes	1999	116
Osaka Health Survey	6356 males	10	Yes	2001	117
Hawaii-Los Angeles-Hiroshima	140 male participants	15	Yes	2001	118
Osaka Factory Study	433 male participants	5	Yes	2003	98
Osaka Health Survey	2310 male participants	6	Yes	2003	119
Okinawa	4489 adults	13	Yes	2004	120
Bogalusa Heart	679 children	11	Yes	2005	61
Framingham	3329 adults	4	Yes	2005	121
Normative Aging Study	2062 male participants	21	Yes	2006	122
ARIC	9104 adults	9	Yes	2006	123
Beaver Dam	2520 adults	10	Yes	2006	124
MRFIT	3073 men	6	Yes	2007	125
Health Professional Follow-up	750 men	18	No	2007	126
Nurses Health Study	1500 women	5	Yes	2009	127
China	7220 adults	4	Yes	2009	60
US	141 children	3	Yes	2009	128
Italy	1410 young adults	20	Yes	2010	129
GOCADAN	1078 adults	6	Yes	2012	130
NHANES Continuous	6036 adolescents	8	Yes	2012	71
Cardia	4752 adults	20	Men	2012	131

CARDIA, Coronary Artery Risk Development in Young Adults; *ARIC*, Atherosclerosis Risk in Communities Study; *MRFIT*, Multiple Risk Factor Intervention Trial; *GOCADAN*, Genetics of Coronary Artery Disease in Alaska Natives; *NHANES*, National Health and Nutrition Examination Survey.

Feig DI, et al. J Pediatr. 2013;162(5):896-902.

Allopurinol treatment reduces BP in hypertensive adolescents (crossover RCT)



Feig DI, Soletsky B, Johnson RJ.JAMA. 2008;300(8):924-932.

Allopurinol decreases SBP and carotid intimal thickness in post-stroke prehypertensive patients

Table 2 Primary and secondary outcome parameter results at 12 months

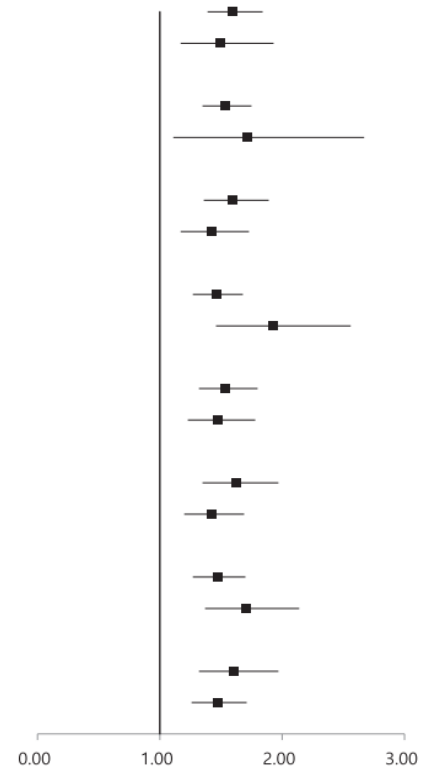
	Allopurinol group (n=34)	Placebo group (n=35)	Intergroup difference (95% CI)	p Value
Serum uric acid (mmol/L) (n, 34/34)†	−0.09 (0.07)	−0.01 (0.05)	−0.08 (−0.10 to −0.05)	<0.0001
Mean common carotid IMT (far wall), mm (n, 31/34)†	−0.02 (0.09)	0.08 (0.20)	−0.097 (−0.175 to −0.019)	0.02
Mean common carotid IMT (far wall), mm (sensitivity analysis) (n 31/34)†	−0.02 (0.09)	0.04 (0.11)	−0.057 (−0.108 to −0.006)	0.03
Mean maximum carotid IMT, mm (n 31/34)†	0.01 (0.15)	0.07 (SD 0.19)	−0.060 (−0.146 to 0.027)	0.17
Brachial systolic BP (mm Hg) (n, 30/30)†	−5.1	5.0	−9.9 (−17.3 to −2.4)	0.01
Brachial diastolic BP (mm Hg) (n, 30/30)	−1.9	0.5	−1.4 (−5.4, 2.5)	0.47
Mean central systolic BP, mm Hg (n, 30/27)†	−4.2 (13.3)	3.2 (11.0)	−6.6 (−13.0 to −0.3)	0.04
Mean central diastolic BP, mm Hg (n, 30/27)†	−3.5 (10.0)	0.4 (8.1)	−2.8 (−7.4 to 1.8)	0.23
Augmentation Index, % (n, 30/27)†	−1.6 (7.2)	2.40 (8.9)	−4.4 (−7.9 to −1.0)	0.01
Augmentation index @HR75, % (n, 30/26)†	−0.6 (6.5)	1.8 (9.1)	−3.0 (−6.6 to 0.6)	0.10
PAT RHI (0–6-month) (n, 28/25)†	−0.2 (1.0)	0.3 (0.8)	−0.2 (−0.6 to 0.2)	0.27
Combined recurrent TIA/stroke/MI	3 (7.5%)	4 (10.0%)	−2.5% (−14.9 to 9.9%)‡	0.69

Data are expressed as mean change at 12 months from baseline (SD). The intergroup difference is adjusted for baseline value of outcome and is expressed as allopurinol minus placebo value (with 95% CI). That is, a negative value represents a lower level of IMT progression with allopurinol treatment. Mean (SD) values are shown for continuous variables and n (%) for categorical variables.
†Shows number in allopurinol and placebo groups who provided data for outcomes with less than complete data.
‡Analysis by difference in two proportions.
MI, myocardial infarction; BP, blood pressure; PAT, peripheral arterial tonometry; RHI, reactive hyperaemia index; TIA, transient ischaemic attack.

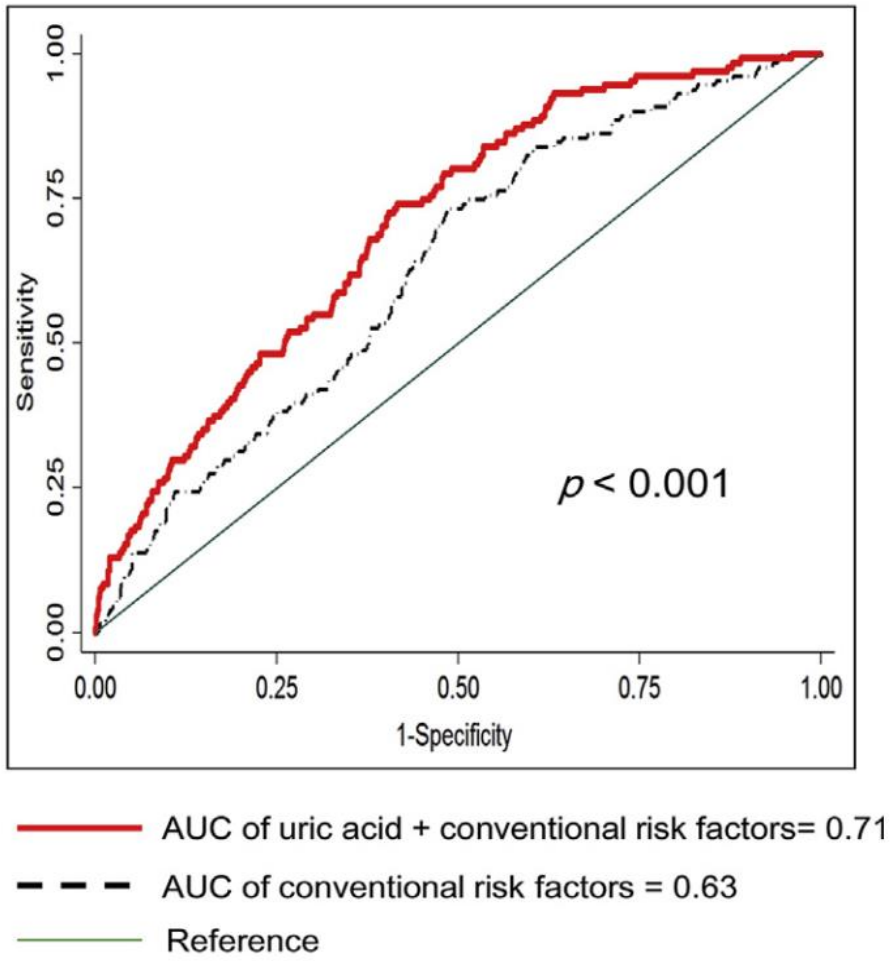
Higgins P et al. Heart 2014;100(14):1085-1092.

Elevated serum urate contributes to conventional cardiac risk factors to develop moderate coronary calcification

Variables	HR (95% CI) of SUA[#]	*p* for interaction
Age (year)		0.791
< 55	1.60 (1.39-1.84)	
≥ 55	1.50 (1.17-1.93)	
Sex		0.901
Male	1.54 (1.35-1.75)	
Female	1.72 (1.11-2.67)	
Diabetes		0.374
No	1.59 (1.36-1.89)	
Yes	1.43 (1.17-1.73)	
Current smoker		0.059
No	1.46 (1.27-1.68)	
Yes	1.93 (1.46-2.56)	
Hypertension		0.857
No	1.54 (1.32-1.80)	
Yes	1.48 (1.23-1.78)	
BMI (kg/m^2)		0.148
< 25	1.63 (1.35-1.97)	
≥ 25	1.43 (1.20-1.69)	
eGFR (mL/min/1.73 m^2)		0.394
60 ≤ eGFR < 90	1.47 (1.27-1.70)	
≥ 90	1.71 (1.37-2.14)	
CRP (mg/dL)		0.215
< median 0.07	1.61 (1.32-1.97)	
≥ median 0.07	1.47 (1.26-1.71)	



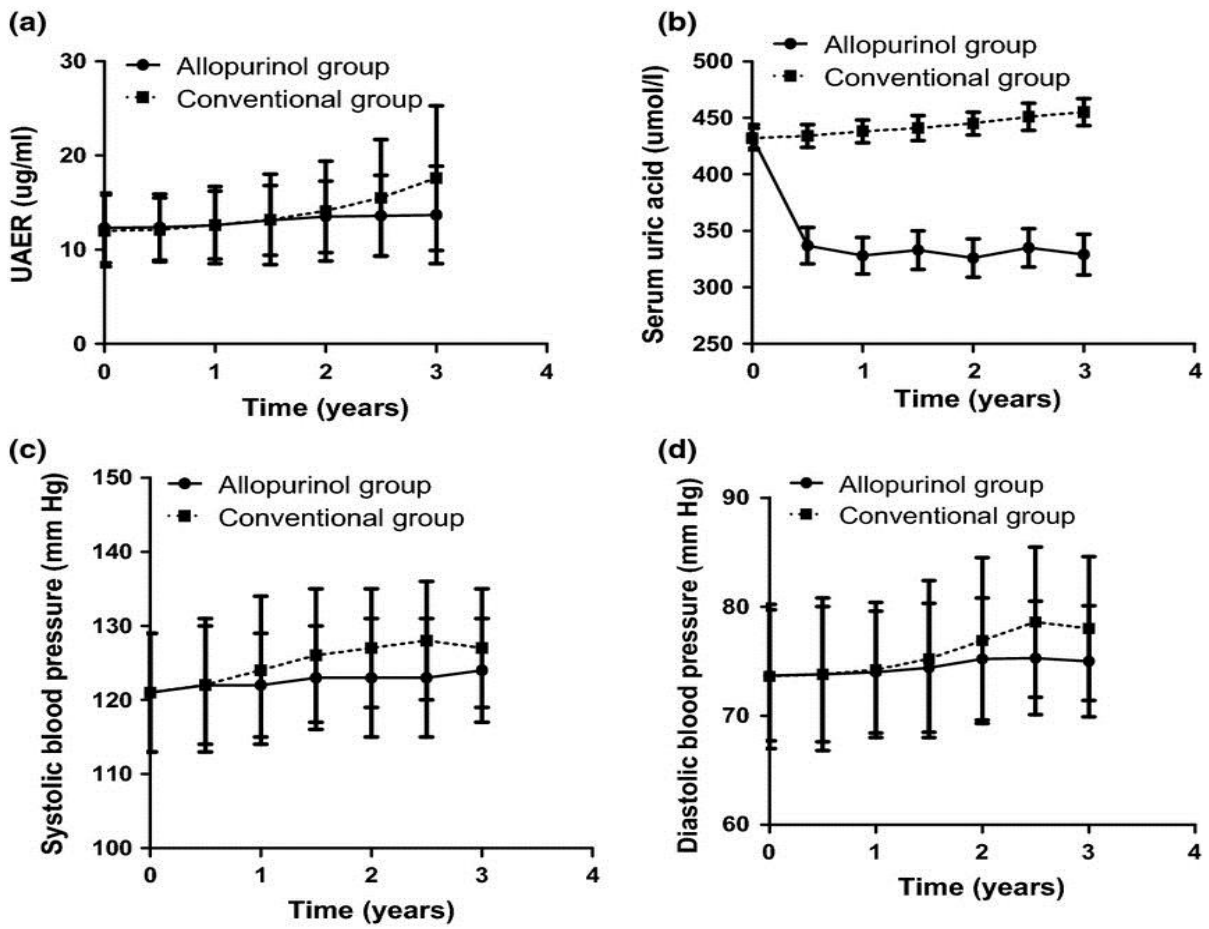
[#]Hazard ratio was measured according to every 1 mg/dL increase in serum uric acid as a continuous variable
SUA, serum uric acid; CAC, coronary artery calcification; BP, blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; ASCVD, atherosclerotic cardiovascular disease



J.E. Jun, et al. Atherosclerosis (2018), https://doi.org/10.1016/j.atherosclerosis.2018.02.014

Allopurinol stabilzes metabolic syndrome: a 3-year controlled trial in patients with T2DM (n=176)

- Intervention: allopurinol adjusted to maintain [sUA] below 6.0 mg/dL vs. placebo
- Usual antihypertensives (except losartan) and oral hypoglycemics maintained
- The allopurinol-treated group
  - Lower SBP and DBP
  - Less worsening of insulin resistance and serum triglyceride concentration
  - Lower albuminuria
  - Higher eGFR
  - Less new-onset diabetic nephropathy (defined as urine albumin excretion > 200µg/min (4.9% vs 10%)



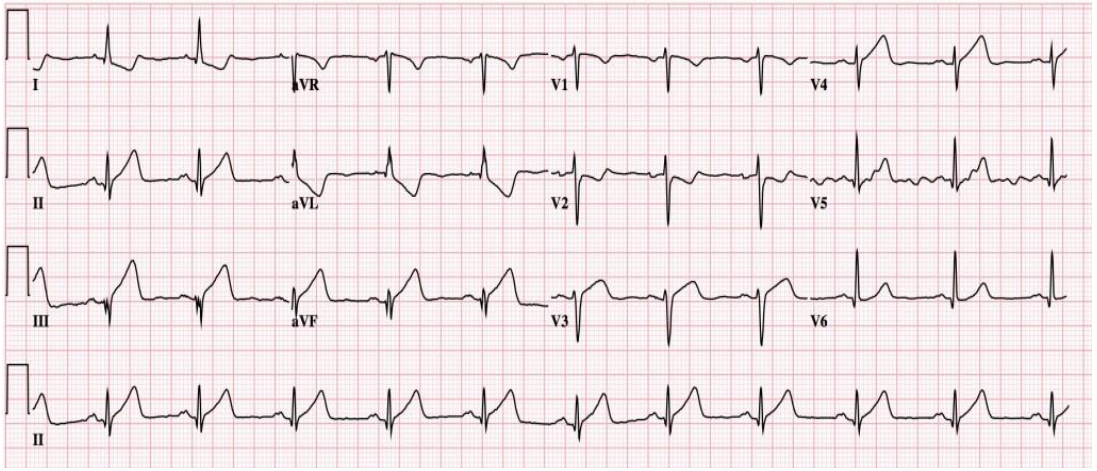
Liu P et al. Clinical Endo 2015; 83:475-482

Summary

- Hyperuricemia has wide ranging inflammatory and metabolic effects, with implications in arthritic, cardiovascular, and metabolic disease
- Available evidence suggests that intervention with urate-lowering drugs has positive benefits in the above domains
- Larger clinical trials and observational studies will be needed to confirm these benefits
- Febuxostat may have an independent, increased risk of cardiovascular disease compared to allopurinol

Case

- 70 year old Caucasian male – Consultation for sustained hyperuricemia
- First STEMI at age 54; three subsequent MIs; 3-vessel CABG at age 57
- Since then 15 coronary stent procedures
- Currently asymptomatic, exercising



What would you do?

1. Advise dietary changes only to lower cardiac risk and serum uric acid
2. Add allopurinol 100 mg/d
3. Add allopurinol 300 mg/d
4. Add febuxostat 40 mg/d
5. Add probenecid 500 mg BID
6. Manage cardiac risk factors only

Resolution of the case

- What would you do?
- My considerations
  - High risk for adverse cardiovascular outcomes
  - He’s had gout in the past, indicating that there is uric acid deposition
  - I’m pretty comfortable managing urate-lowering drugs
  - If he has another gout attack, he gets urate lowering drugs immediately
- My conclusion
  - I will treat his elevated uric acid level
  - I will stay away from febuxostat as a first-line agent but use it if necessary

Thank you

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