RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

4th Annual National Conference

September 21–23, 2023

Crystallizing the Latest Developments in Gout

Kris Giani, PA-C, Orthopedic Physicians Alaska, Wasilla AK

Jessica B. Michaud, PharmD, BCPS, Froedtert & the Medical College of Wisconsin, Milwaukee WI

Accreditation Statement

- All individuals in control of the content of continuing education activities provided by the Annenberg Center for Health Sciences at Eisenhower (ACHS) are required to disclose to the audience all relevant financial relationships related to the content of the presentation or enduring material. Full disclosure of all relevant financial relationships will be made in writing to the audience prior to the activity. All other staff at the Annenberg Center for Health Sciences at Eisenhower and RhAPP have no relationships to disclose.

Faculty Disclosures

- Kris Giani, PA-C:
  - Consultant: Abbvie
- Jessica Michaud, PharmD:
  - There are no financial relationships to disclose.

Objectives

- Differentiate gout from other types of crystal arthropathies
- Explain the role of pegloticase in gout
- Implement a plan for pegloticase that includes methotrexate
- Interpret literature on the cardiovascular risk related to gout and of allopurinol and febuxostat

Poll for the Attendees

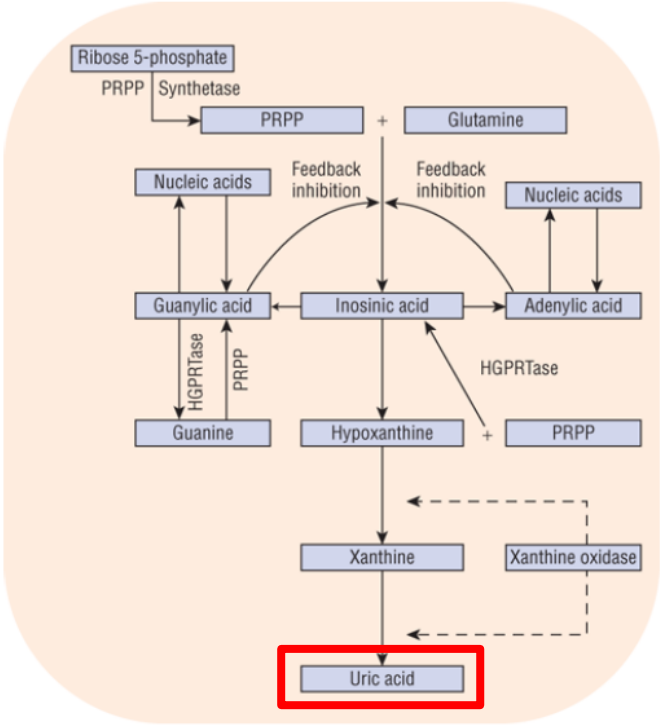
- How much experience do you have with gout?
  - 1: little to none → 4: a lot
- How much pegloticase have you used?
  - 1: none, 2: a few times, 3: many times, 4: a LOT
- Have you used a csDMARD with pegloticase?
  - Raise hand: yes

Epidemiology

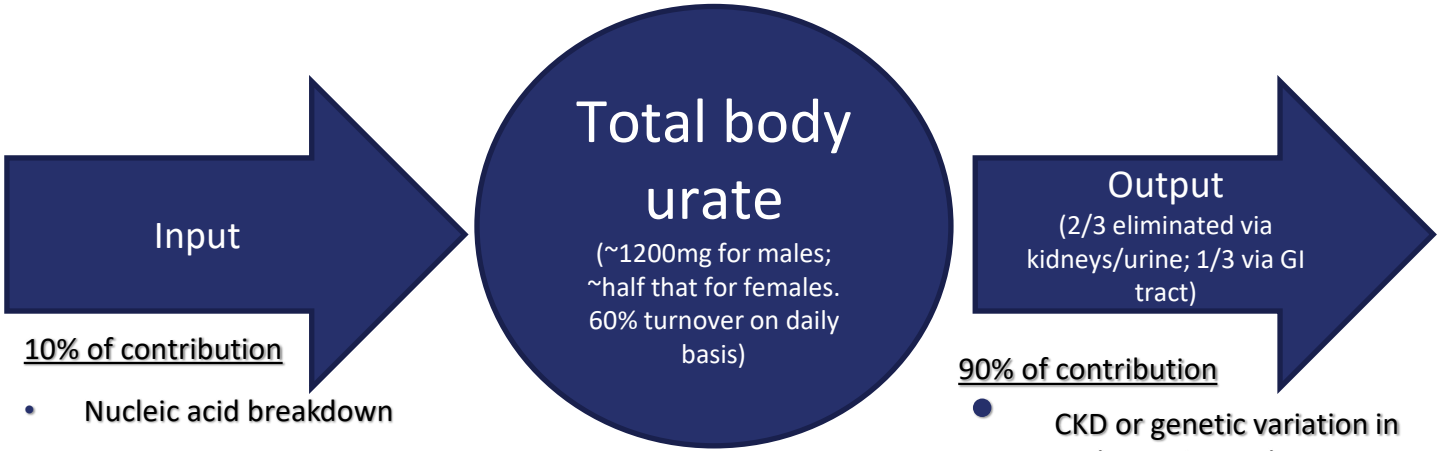
- Prevalence in the United States ~4% and increasing
- Risk factors
  - Non-modifiable
    - Age and gender (men overall but also at younger ages in men) (lower risk in premenopausal women due to↓ active renal reabsorptive urate transporters due to estrogen)
    - Race (racial and ethnic minorities, esp Black)
    - Genetics
  - Modifiable
    - Obesity
    - HTN
    - Dyslipidemia
    - Cardiovascular disease
    - Diabetes mellitus
    - CKD
    - Dietary factors
    - Alcohol
    - Medications altering urate balance

Pathophysiology

- Uric acid is the final waste product of nucleic acid (purine) breakdown
- Other mammals have uricase to further break down uric acid into allantoin
- Solubility threshold is <6.8 mg/dL



Pathophysiology



10% of contribution

- Nucleic acid breakdown
- Diet (red meat, organ meat, alcohol, seafood)
- Genetic defects in purine metabolism

90% of contribution

- CKD or genetic variation in reabsorptive and secretory urate transporters*
- Genetic defects in gut metabolism**
- Medications (eg thiazide or loop diuretics, calcineurin inhibitors)

FYI only

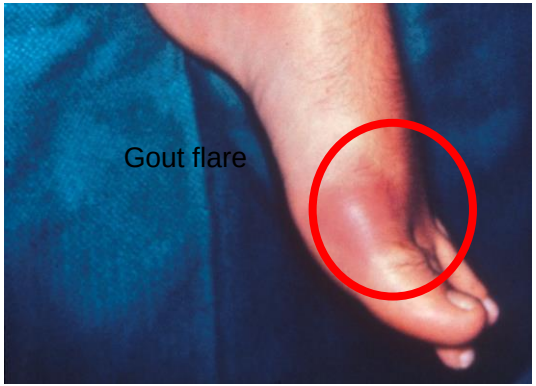
*~ 100% available for filtration, but only ~10% renal clearance due to:

- Reabsorption via urate-anion exchangers URAT1 (inhibited by losartan, fenofibrate, uricosurics) and OAT10 (inhibited by uricosurics), and others, then exits tubular cells via GLUT9
- Secretion via anion exchangers OAT1 and OAT3, and others

**Transportation into gut at least partly mediated by high-capacity urate efflux transporter ABCG2 (also expressed in proximal renal tubular epithelium), then degradation by colonic bacteria

Symptoms - Acute Gout Flare

- Severe joint pain – described as being on fire or being dislocated
- Rapid onset (6-12 hours), localized (85-90% single joint), inflammatory
- Self-limiting and may last from days to weeks (3-14 days)
- Most common joint is first metatarsophalangeal – "podagra"



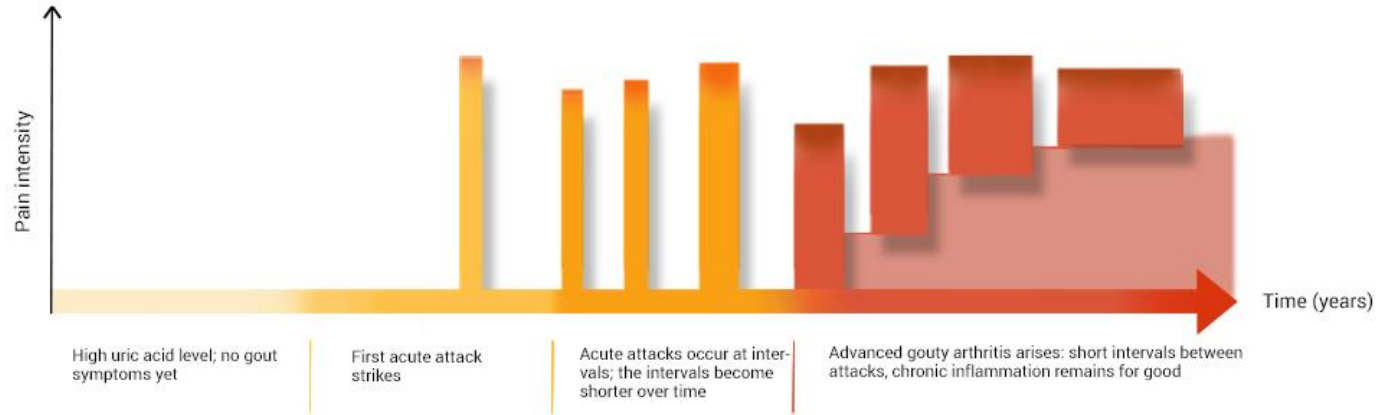
- Then in order: insteps, ankles, heels, knees, wrists, fingers, elbows

Disease Course

Asymptomatic hyperuricemia

Intercritical gout and recurrent gouty arthritis

Chronic tophaceous gout



http://www.periodicfevers.com/thescience/gout/

Diagnosis

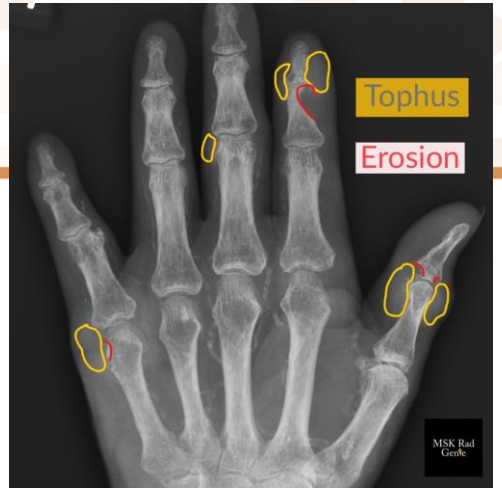
- Joint fluid aspiration – gold standard (“crystal-prove”)
  - Look for MSU crystals – confirms gout
  - Other crystals may be present, eg calcium pyrophosphate (CPP) → calcium pyrophosphate deposition disease (CPPD) or “pseudogout”
- Serum uric acid (SUA) should be measured and followed, however, it is **NOT** diagnostic
  - Uric acid can be higher or lower (usually lower) than usual during a flare

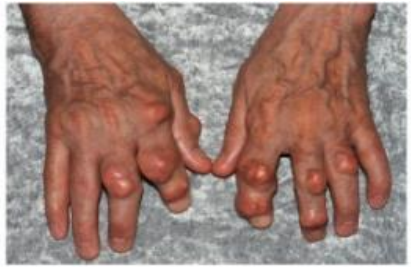
Why is This Important?

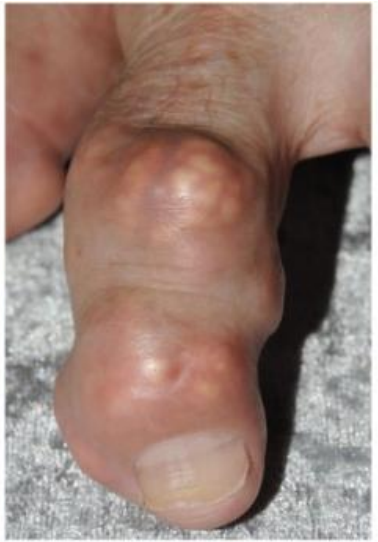
- Gout is NOT a disease of acute flares followed by full recovery of the involved joint!
- Gout is NOT a “self-inflicted” disease caused by food or alcohol → cannot be fully solved by diet changes
- Gout may be an independent risk factor for premature death
- Focus is often on treating flares, under-estimating gout’s impact on mobility, function, and quality of life

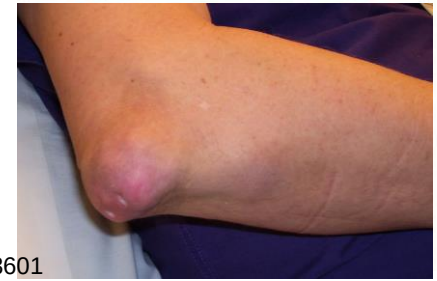
Why is This Important?

- Without treatment:
  - Flares
  - Joint damage
  - Tophi
  - Kidney stones (10-25%)
  - ?Urate nephropathy
- It can take months-years for crystals or tophi to dissolve









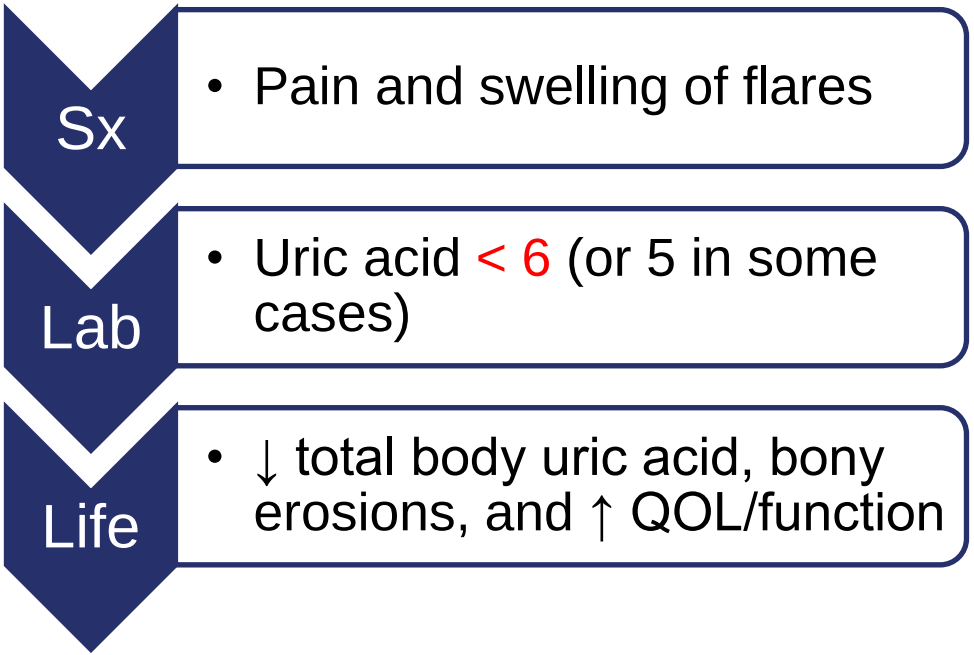
https://twitter.com/skeletalrad/status/1252670586528153601

TREATMENT

Guidelines

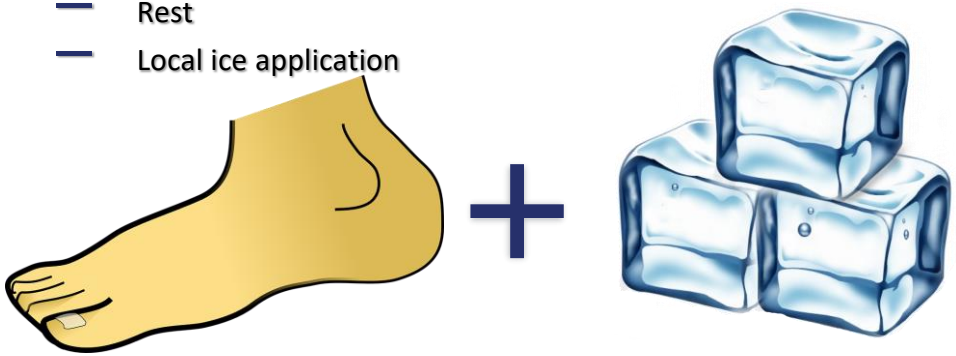
- American College of Rheumatology (ACR) 2020
- European Alliance of Associations for Rheumatology (EULAR) 2019

Goals of Treatment



Non-Pharmacologic Therapy

- For acute flares
  - Rest
  - Local ice application



- Diet and lifestyle changes (but estimated to result in only ~10-18% reduction in uric acid)
  - Avoid: organ meats, high-fructose corn syrup, excessive alcohol
  - Limit: meat, seafood, sugars (eg, naturally sweet fruit juices, desserts), salt
  - Weight loss

TREATMENT

ACUTE TREATMENT OF gout FLARES

Treatment of acute gout attack

Colchicine	• (+) soon after onset (esp 12hr) • (-) GFR < 30, liver insufficiency, CYP3A4/PGi
NSAID (any)	• (+) cost concerns • (-) HF, GI bleed, ↑ age, CKD, antithrombotic
Prednisone	• (+) CKD, cost concerns • (-) uncontrolled DM/HTN, GI bleed, infection, osteoporosis

Choose based on comorbidities and patient's experience re: efficacy/AEs

Colchicine

- MOA: Somewhat unknown. Thought to interfere with the system in WBCs that activates IL-1β. Also inhibits microtubules that are involved in activation and migration of neutrophils
- Dose for acute flares:
  - 1.2 mg, then 0.6 mg 1 hour later
    - May then start additional dosing of 0.6mg 1-2 times per day short-term (eg 2-5 days) if needed
  - Dose reductions required for CKD and drug interactions in certain cases

Colchicine

- Adverse effects:
  - Common: Nausea, diarrhea
  - Severe: myelosuppression, myotoxicity including rhabdomyolysis
- Drug interactions:
  - Colchicine is a substrate of both P-glycoprotein and CYP3A4 and may inhibit CYP3A4 to some degree
  - Fatal DDIs reported, esp if multiple interacting drugs, high colchicine dose, or CKD
  - Caution with statins (esp if competitive CYP3A4 substrates eg atorvastatin or simvastatin) due to additive risk of rhabdomyloysis

Corticosteroids

- Various oral dosing regimens are reasonable
  - Choose based on severity of flare, usual duration of flares, comorbidities, and patient's experience with efficacy/adverse effects
  - Examples
    - 40mg daily x 5 days
    - 30mg daily x 3 days, then 20mg daily x 3 days, then 10mg daily x 3 days
- Intra-articular steroid injections can also be done, but:
  - ≤ 2 joints involved
  - Patient must agree to have needle placed in painful joint (easier if already doing arthrocentesis)

TREATMENT

Urate-lowering Therapy (ult)

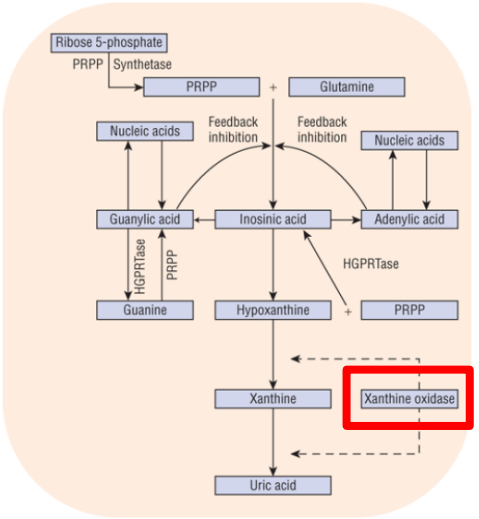
ULT Indications

Would you choose to take allopurinol long-term to prevent 2 severe gouty flares/year?

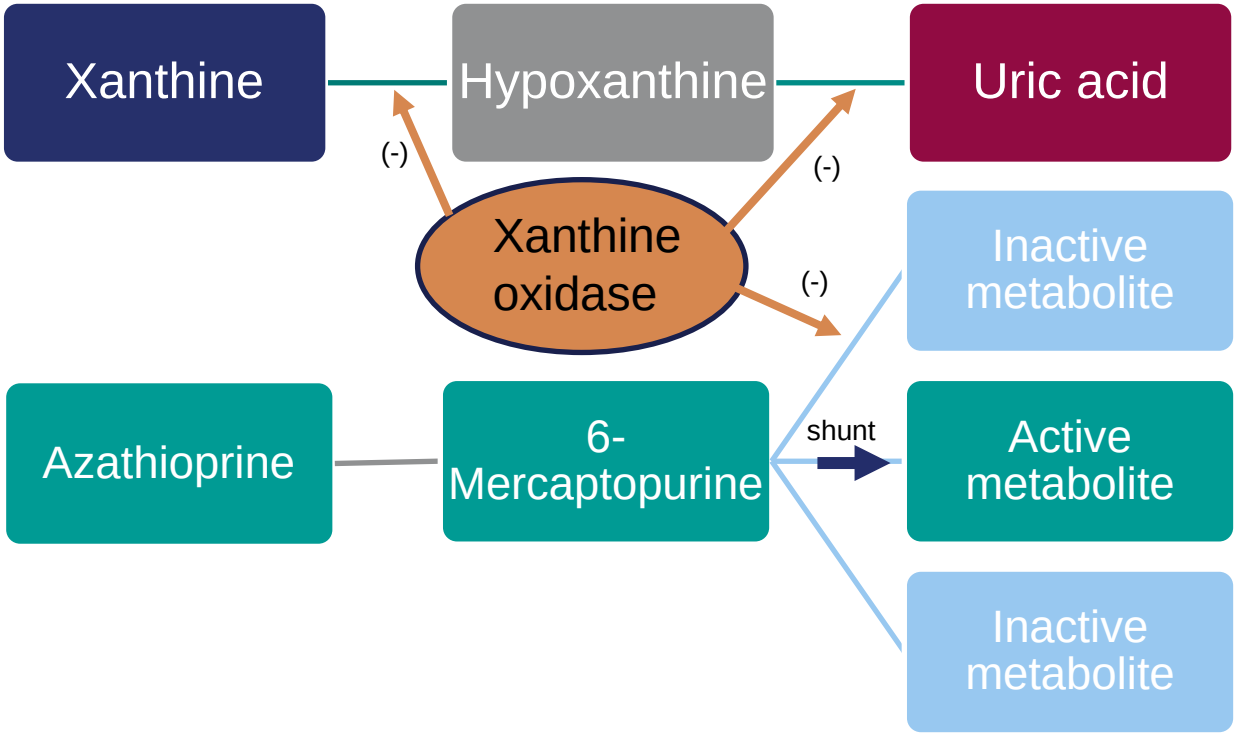
- Definitely
  - ≥ 1 subcutaneous tophi
  - Radiographic damage attributable to gout
  - Frequent (≥ 2 per year) or disabling flares
- Maybe
  - Infrequent (< 2 per year) flares
  - First flare with:
    - CKD stage ≥ 3 (reasoning: ↑ risk of gout progression and clinical tophi, acute flare tx options more limited, and may be added benefit to prevent CKD progression)
    - Uric acid > 9 mg/dL (reasoning: ↑ risk of gout progression), and/or
    - Urolithiasis (reasoning: ULT lowers 24-hour urinary uric acid excretion > placebo)

Xanthine Oxidase Inhibitors (XOIs)

- ↓ uric acid "production"
- Allopurinol
  - 1st line
  - Less expensive
  - Long history of use
  - Effective in vast majority
  - Risk of drug reaction with eosinophilia and systemic symptoms (DRESS)
- Febuxostat
  - Can be used if DRESS during allopurinol
  - Unclear cardiovascular risk vs allopurinol
  - Less renally metabolized
  - Simpler dose titration
  - More potent urate-lowering



XOIs – Drug Interaction



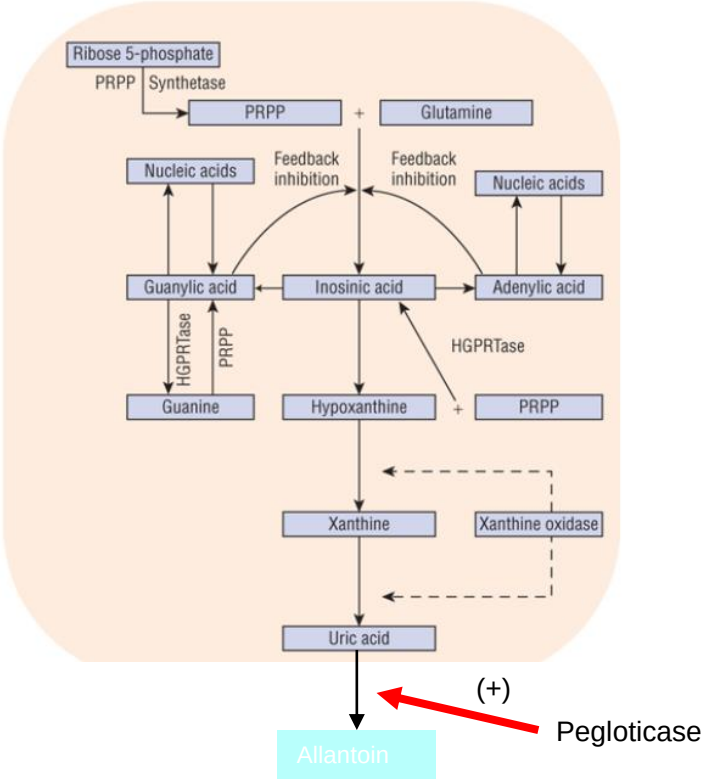
Allopurinol - AEs

- Adverse effects:
  - Common: GI
  - Severe: **severe cutaneous reactions (DRESS, toxic epidermal necrolysis, Stevens-Johnson)**, bone marrow suppression, hepatic toxicity
- DRESS (allopurinol hypersensitivity syndrome):
  - Rash (tell patients to stop the drug!), fever, AKI, hepatitis (↑ LFTs), eosinophilia
  - Very rare (0.1%) but mortality rate approaching 25%
  - ↑ risk in: CKD, HLA-B*5801, high initial dose
    - CKD: major active metabolite is oxypurinol, whose half-life is prolonged in CKD; oxypurinol has been implicated in allopurinol toxicity including DRESS
    - HLA-B*5801: check in Han Chinese, Korean, Thai, and African American patients, and if (+) do not use allopurinol
    - Low initial doses (≤ 100mg/day) reduce risk of DRESS

Probenecid

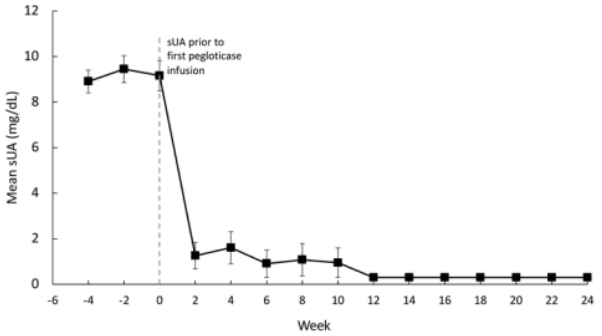
- MOA: uricosuric agent (=causes uricosuria), not a xanthine oxidase inhibitor
  - Acts by blocking the reabsorption of uric acid in the renal tubules
- Uses:
  - When XOIs can not be used or are not tolerated
  - In combination with XOIs when maximal doses do not achieve goal uric acid levels
- Relies on kidney to work → not likely to be effective in CrCl < 30 mL/min, no monotherapy if CrCl < 50
- Do not use in patients with a history of urinary stones
- Drinking plenty of water while on this medication will help to prevent stone formation

Pegloticase - MOA



Pegloticase

- Indicated as monotherapy for gout refractory to other therapies
- Dose: 8 mg IV infusion over 2 hours every 2 weeks
- Premedication with antihistamines and steroids required due to infusion reactions (relatively high risk of anaphylaxis)
- Anti-drug antibodies may cause lack of efficacy → uric acid will start to rise
  - Methotrexate or other immunosuppressants can/should be used concurrently to reduce risk
- Must monitor uric acid and stop if rises to > 6



Anti-Inflammatory Gout Flare Prophylaxis - Dosing

- Colchicine 0.6 mg po daily or BID (first-line due to more literature support)
  - Dose adjustments/avoid in CKD, liver insufficiency, drug interactions
- Low-dose NSAID (+ PPI), eg naproxen 250mg bid
- Prednisone 5mg daily

MIRROR RCT

Pegloticase and methotrexate

Objective

- To evaluate the safety, efficacy, pharmacokinetics and immunogenicity of Pegloticase with methotrexate administration versus placebo

Pegloticase and methotrexate

Methods

- Uncontrolled gout patient's with a serum urate ≥ 7
- Urate lowering therapy failure
- Presence of ongoing gout flaring symptoms
- ≥ 1 Tophus or ≥ 2 gout flares in 12 months

Pegloticase and methotrexate

- Patients were randomized 2:1 to 52 weeks of Pegloticase (8 mg biweekly) with either methotrexate 15 mg orally weekly or placebo.

Pegloticase and methotrexate

Primary endpoint

- Proportion of treatment responders during a 6-month timeframe
- Defined as: Serum urate <6 for ≥ 80% of visits throughout a 20-24 week trial

Pegloticase and methotrexate

Results

- 152 patients were randomized
- 100 patient's received Pegloticase plus methotrexate
- 52 patient's received Pegloticase plus placebo
- 71% of patients on methotrexate versus 38.5% of patients on placebo

Pegloticase and methotrexate

Conclusion

- Methotrexate coadministered increased pegloticase response rate over placebo 71% versus 38% during a 6-month trial with no increase in safety signals.
- Showed a higher treatment response rates
- Lower infusion reaction rates
- Lowered immunogenicity when Pegloticase was coadministered with methotrexate

RECIPE
Pegloticase and Mycophenolate

Objective

Evaluate mycophenolate mofetil immunogenicity and efficacy with use in Pegloticase infusions

Pegloticase and Mycophenolate

Methods

- Patients were randomized 3:1
- Receiving 1000 mg mycophenolate twice daily or placebo for 14 weeks respectively
- 2 weeks prior to receiving pegloticase infusions
- Receiving intravenous pegloticase 8 mg biweekly for 12 weeks
- With all patients receiving Pegloticase alone from week 12-24

Pegloticase and Mycophenolate

Primary endpoints

Proportion of patients who sustained serum urate level ≤ 6 at 12 weeks

Secondary endpoints

Included 24-week durability of the serum urate level ≤ 6

Pegloticase and Mycophenolate

Results

- At 12 weeks serum urate level of ≤ 6 was achieved in 86% of patients receiving mycophenolate versus 40% of patients in placebo arm
- At 24 weeks serum urate level ≤ 6 was achieved in 68% of patients receiving mycophenolate versus 30% of patients in placebo arm

Pegloticase and Mycophenolate

Conclusion

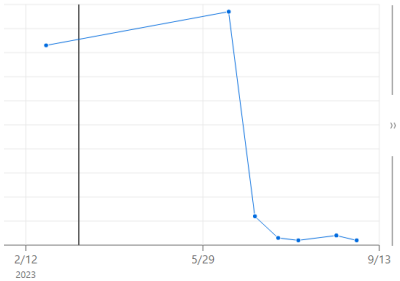
- Mycophenolate therapy with Pegloticase was well-tolerated
- Showed meaningful improvement in target serum urate levels of ≤ 6 at 12 and 24 weeks with decreased immunogenicity

Response rates of other immunomodulation cotherapy rates

- Pegloticase monotherapy: 42%
- Oral methotrexate 90%
- Subcutaneous methotrexate 78%
- Mycophenolate 86%
- Leflunomide 67%
- Azathioprine 64%
- As reported in the MIRROR RCT trial: Data from other clinical settings and open label trials.

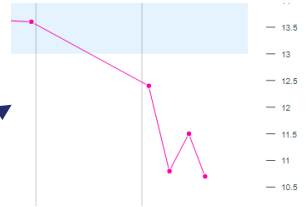
Pegloticase Patient Case #1

- FW 49yo Latino male, tophaceous (right elbow)
  - PMH: ischemic stroke, HTN, obesity (BMI 46), psoriasis, depression, anxiety
  - H/o intermittent allopurinol, then in 2021 started consistent allopurinol
  - Allopurinol titrated to 500mg/day → sUA 8.3
- Physician ordered pegloticase. Agree?
  - Loratadine 10mg, methylprednisolone 100mg IV, acetaminophen 1000mg
  - G6PD checked, negative
  - Continued prednisone 5mg daily prophylaxis
  - Methotrexate 15mg/week + folic acid starting 4 wk prior
    - CMP, CBC+diff 2 wk after starting methotrexate, then every 4 wk, no issue
  - Allopurinol d/c'ed 1 week prior to 1st pegloticase
  - As of 9/13, has received 6 doses, sUA checked within 4 days prior to each
  - Itchy throat, throat swelling, warm ears with 1st → discovered pre-meds error
  - Lots of patient ed, sUA reminders/stat orders, 4-5 gout flares



Pegloticase Patient Case #2

- NP 57yo white male, tophaceous gout, CLL
  - Enlarging/erupting tophi (right elbow, right heel, several DIPs s/p debulking surgery)
  - Intolerance to allopurinol (abdominal pain), rechallenges
  - Intolerance to febuxostat (abdominal pain, vision changes, memory issues, headache, “hangover”), “quite debilitating”, several rechallenges
  - Intolerance to probenecid (tinnitus, abdominal pain, dizziness)
  - 9 pegloticase infusions in 2015 with little change in sUA and “no noticeable change in tophi burden suggesting pre-formed antibodies (probably to PEG component)”
  - Rasburicase infusions 2015 for CLL associated with large swings of uric acid but did not improve gout flare severity or frequency/size of tophi
  - Has not tolerated losartan, fenofibrate
- Physician ordered pegloticase + methotrexate. Agree?
  - Continue prednisone 10mg daily, prn colchicine
  - Methotrexate 10mg/week barely tolerated (fatigue, anemia, sweating, tinnitus, headache), folic acid increased to 5mg/day, not titrated further
  - Pegloticase 1 infusion → no change to sUA, discontinued



References for CPPD, Gout, Pegloticase

• Nuki, G., Simkin, P.A. A concise history of gout and hyperuricemia and their treatment. Arthritis Res Ther 8 (Suppl 1), S1 (2006). https://doi.org/10.1186/ar1906

• Rosenthal AK. Pseudogout: Presentation, natural history, and associated conditions. In: Crystal-Induced Arthropathies: Gout, Pseudogout, and Apatite-Associated Syndromes, Wortmann RL, Schumacher HR Jr, Becker MA, Ryan LM (Eds), Taylor and Francis Group, New York 2006. p.99.

• Wilkins E, Dieppe P, Maddison P, EvisonG. Osteoarthritis and articular chondrocalcinosis in the elderly. Ann Rheum Dis. 1983 Jun;42(3):280-4. doi: 10.1136/ard.42.3.280. PMID: 6859960; PMCID: PMC1001132.

• Cipolletta E, Di Matteo A, Scanu A, Isidori M, Di Battista J, Punzi L, Grassi W, Filippucci E. Biologics in the treatment of calcium pyrophosphate deposition disease: a systematic literature review. Clin Exp Rheumatol. 2020 Sep-Oct;38(5):1001-1007. Epub 2020 Apr 28. PMID: 32359034

• Chen-Xu M, Yokose C, Rai SK, PillingerMH, Choi HK. Contemporary prevalence of gout and hyperuricemia in the United States and decadal trends: the National Health and Nutrition Examination Survey, 2007–2016. Arthritis Rheumatolgy2019;71:991–9.

• Rashid N, Coburn BW, Wu YL, Cheetham TC, Curtis JR, Saag KG, et al. Modifiable factors associated with allopurinol adherence and outcomes among patients with gout in an integrated healthcare system. J Rheumatolgy 2015;42:504–12.

• AbdellatifW, Ding J, Khorshed D, ShojaniaK, Nicolaou S. Unravelling the mysteries of gout by multimodality imaging.Semin Arthritis Rheum. 2020;50(3 suppl):S17-S23.

• Ahmad MI, Masood S, FurlanettoDM and Nicolaou S (2021) Urate Crystals; Beyond Joints. Front. Med. 8:649505. doi: 10.3389/fmed.2021.649505

• Young Hee Rho, Yanyan Zhu, YuqingZhang, Anthony M. Reginato, Hyon K. Choi, Risk factors for pseudogout in the general population, Rheumatology, Volume 51, Issue 11, November 2012, Pages 2070–2074, https://doi.org/10.1093/rheumatology/kes204

• Madhura A. Desai, Jeffrey J. Peterson, Hillary Warren Garner, and Mark J. Kransdorf. Clinical Utility of Dual-Energy CT for Evaluation of Tophaceous Gout. RadioGraphics 2011 31:5, 1365-1375

• Rosenthal AK. Basic calcium phosphate crystal-associated musculoskeletal syndromes: an update. CurrOpin Rheumatol. 2018 Mar;30(2):168-172. doi: 10.1097/BOR.0000000000000477. PMID: 29227255; PMCID: PMC6241512

CARES AND FAST TRIALS

CARES: cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular morbidities,
FAST: febuxostat versus allopurinol streamlined trial

Cardiovascular Implications: CARES

Population

- N = 6,190 in US, Canada, Mexico
- Inclusion: men ≥50 & women ≥55 yr, uncontrolled gout, **major CV disease**

Study Design

Results

Impact & Interpretation

N Engl J Med 2018;378(13):1200-1210 (CARES). CV: cardiovascular, MI: myocardial infarction, ULT: urate-lowering therapy.

Cardiovascular Implications: FAST

Population

- N = 6,128 in UK, Denmark, Sweden
- Inclusion: ≥ 60 yr taking allopurinol for gout, ≥1 **CV risk factor**

Study Design

Results

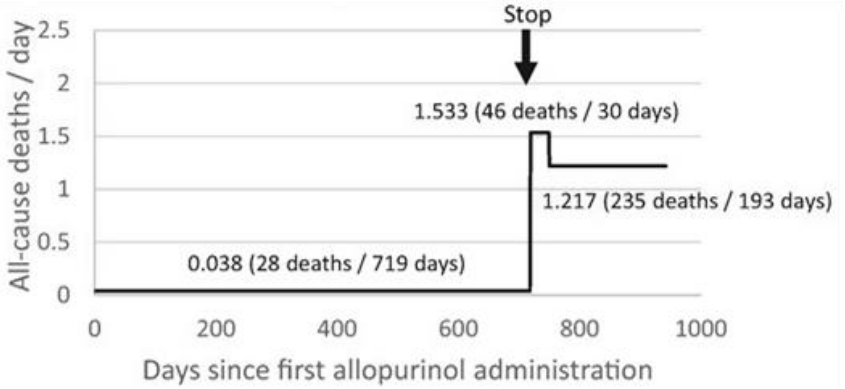
Lancet 2020;396(10264):1745-1757 (FAST). ACEi: ACE inhibitor, ACS: acute coronary syndrome, CHF: congestive heart failure

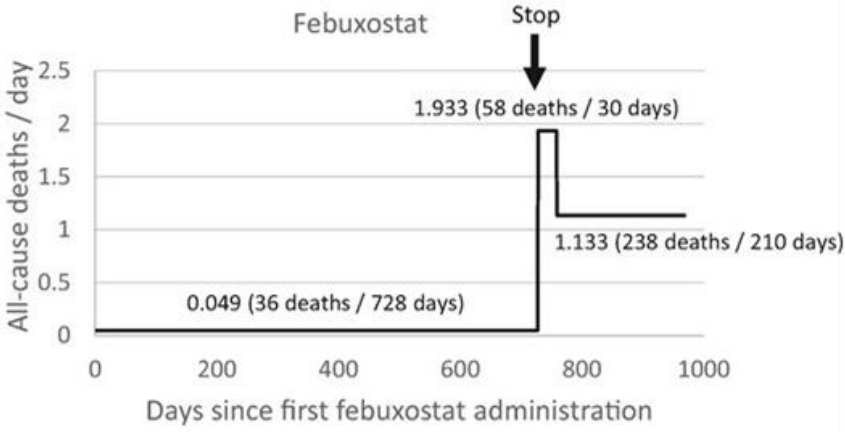
Cardiovascular Implications: CARES, FAST

Characteristic	CARES	FAST
CV disease	• CV disease history – 100% CV disease at baseline • Included HF of any severity	• CV disease risk factor(s) – 33% CV disease at baseline • NYHA Class III or IV HF excluded
Gout severity	• 21% prevalence of tophi • Included patients new to ULT	• 10% prevalence of tophi • Patients previously on allopurinol
Discontinuation	• 57% stopped febuxostat • 55% stopped allopurinol • 45% did not complete all study visits	• 32% stopped febuxostat • 17% stopped allopurinol • 6% withdrew

Discontinuation of ULT Affects CV Risk

- Reanalyses of CARES
- Eg study (at right) postulated MACE induced by rapid sUA changes

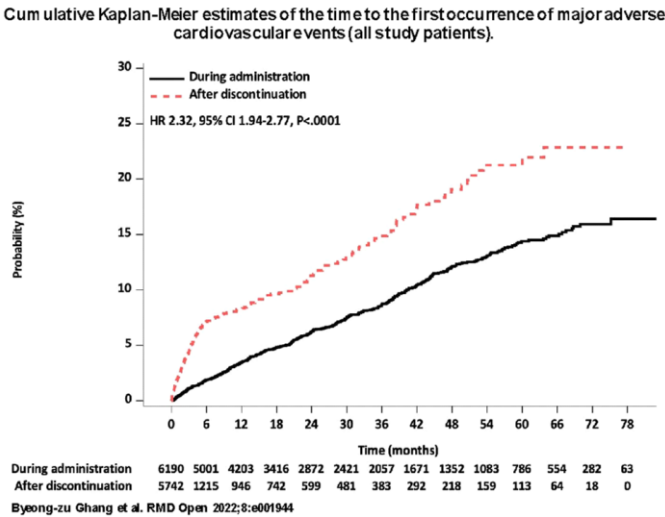




Rheumatol 2020;59(6):1439–1440. MACE: major adverse cardiovascular events.

Discontinuation of ULT Affects CV Risk

- Same authors reassess CARES
- HR 2.32 for MACE after d/c, vs during (p<0.0001)
- Changes in sUA*, age, and BMI associated with MACE after d/c
- Similar risk found in FAST (3X)

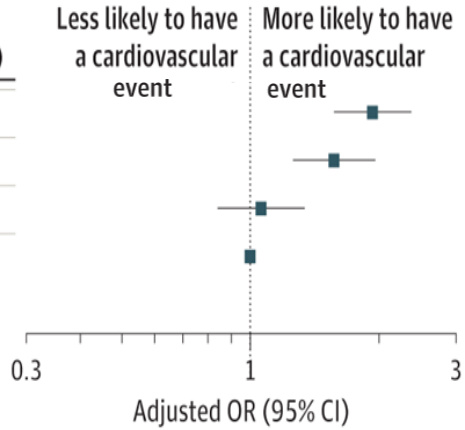


RMD Open 2022;8:e001944. HR: hazard ratio, BMI: body mass index, d/c: discontinuation. *per 1 mg/dL ↑ from baseline to last measurement before d/c.

Gout Flares May Affect CV Risk

- 2022 large database study: OR 1.9 for 0-60 days

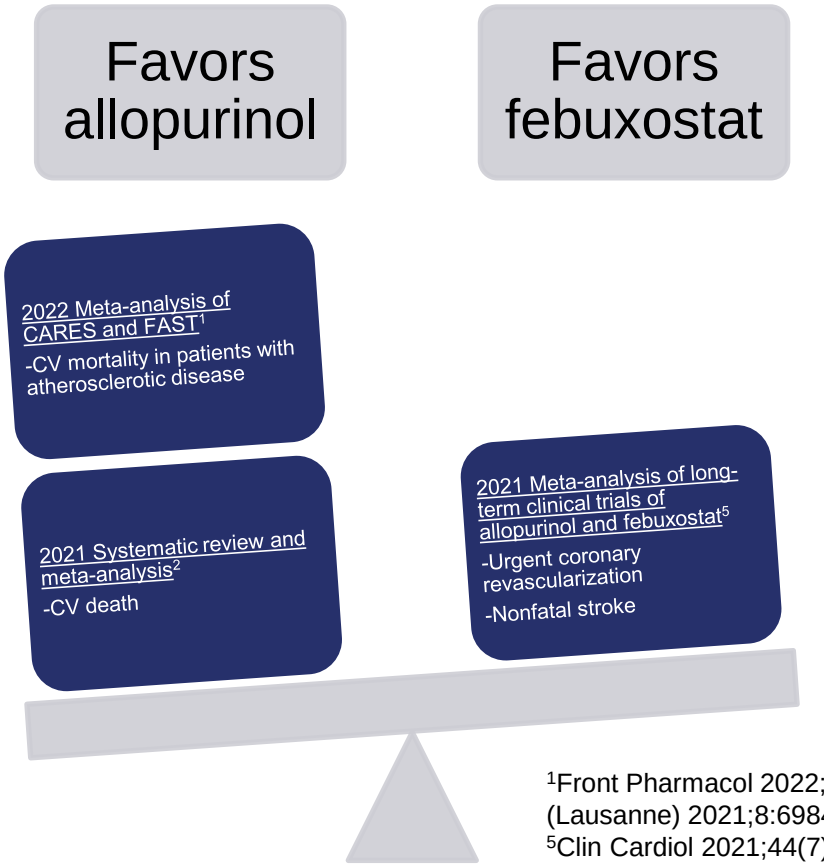
Gout flare exposure window, d[a]	No. (%) of participants: Cases[b] (N = 10 475)	Controls[c] (N = 52 099)	Unadjusted difference, % (95% CI)	Adjusted OR (95% CI)
0-60	204 (2.0)	743 (1.4)	0.5 (0.2 to 0.9)	1.93 (1.57 to 2.38)
61-120	170 (1.6)	628 (1.2)	0.4 (0.1 to 0.8)	1.57 (1.26 to 1.96)
121-180	148 (1.4)	662 (1.3)	0.1 (-0.2 to 0.5)	1.06 (0.84 to 1.34)
>180 d or no flare[e]	9953 (95.0)	50 066 (96.1)	-1.1 (-1.7 to -0.5)	1 [Reference]



Gout flare → Activation of NLRP-3 inflammasome → Neutrophil-rich inflammation (which is associated with atherosclerotic plaque instability and rupture)

JAMA 2022;328(5):440-450.

Post-CARES/FAST Trials



Neither favored

2022 Meta-analysis of CARES and FAST[1]
-MACE, CV mortality, all-cause mortality in all subjects

2021 Systematic review and meta-analysis[2]
-Major CV events

2021 Network meta-analysis[3]
-Adverse CV events

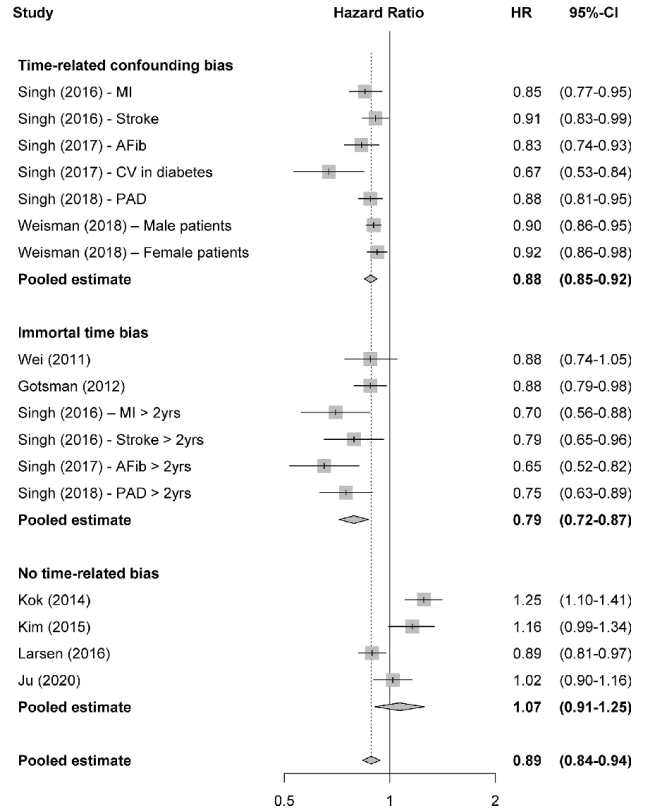
2022 arterial stiffness stable in both groups in patients with gout, elevated sUA, and ↑ CV risk[4]

2021 Meta-analysis of Long-Term Clinical Trials of Allopurinol and Febuxostat[5]
-Nonfatal MI
-CV death
-Death from any cause

[1]Front Pharmacol 2022;13:998441. [2]Ann Palliat Med 2021 Oct;10(10):10327-10337. [3]Front Med (Lausanne) 2021;8:698437. [4]Eur Heart J Cardiovasc Pharmacother 2022;8(3):236-242 (FORWARD). [5]Clin Cardiol 2021;44(7):907-916. 4

Studies of Allopurinol and CV Risk are Flawed

- Allopurinol has been found in some studies to ↓ CV risk
- Many of these studies are subject to time-related bias
- Studies that had no time-related bias were less likely to find a benefit



Arthritis Care Res (Hoboken) 2022 May;74(5):858-865.

Summary

CARES and FAST

Conflicting re: CV risk of allopurinol vs febuxostat

CV risk affected by

Discontinuation of ULT, which could have impacted CARES, and gout flares

Follow-up studies

Suggest similar or possibly better CV safety for allopurinol

CV RISK IN NON-GOUT POPULATION

Allopurinol Does not Affect CV Outcomes in Non-Gout Population

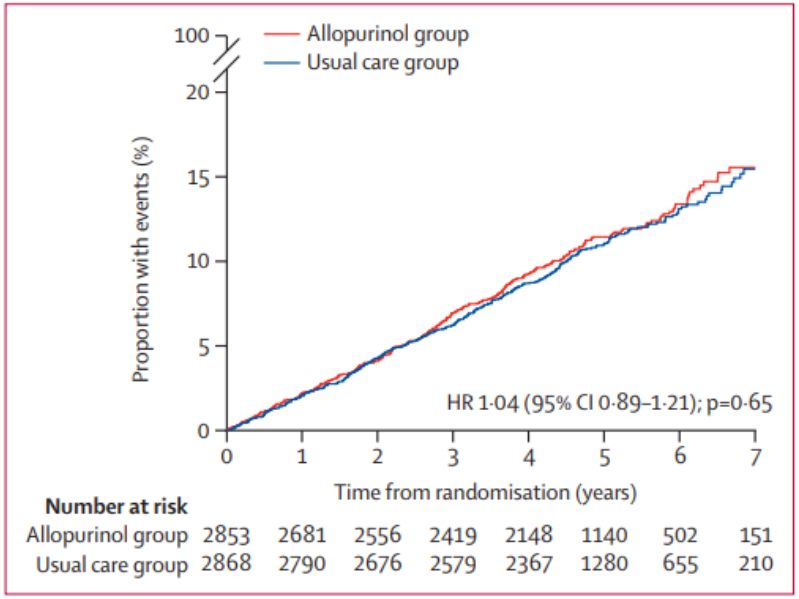


Figure 2: **Cumulative incidence functions for the primary composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death analysed in the modified intention-to-treat population**

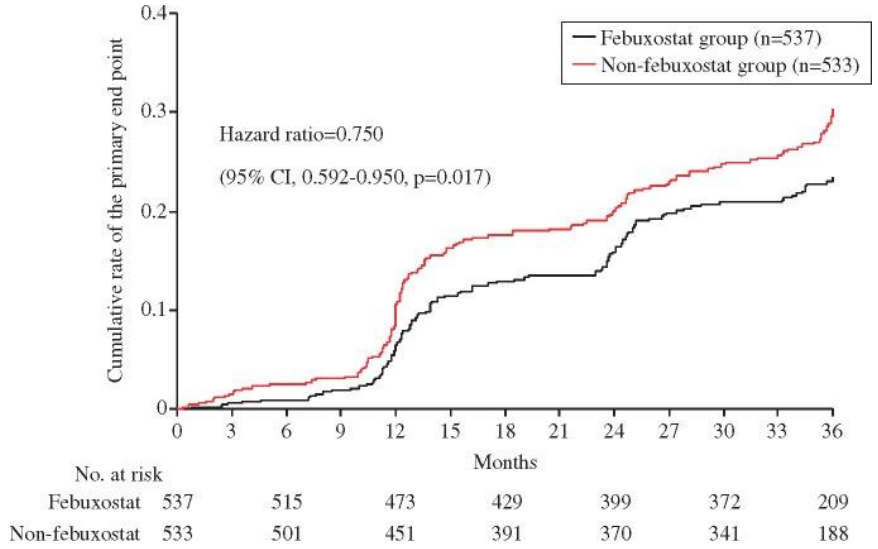
The figure was adjusted for the competing risk of deaths not included in the endpoint. HR=hazard ratio.

- Randomized, open-label, blinded-endpoint
- ≥60yr, ischemic heart disease, no gout
- Allopurinol up-titrated to 600mg daily (300mg daily in moderate CKD)

Lancet 2022;400:1195–205 (ALL-HEART).

Febuxostat Lowers Cerebral/Cardiorenal Outcome in Non-Gout Population

Fatal and non-fatal cerebral, CV, and renal events, and death other than cerebral or cardiorenal vascular disease



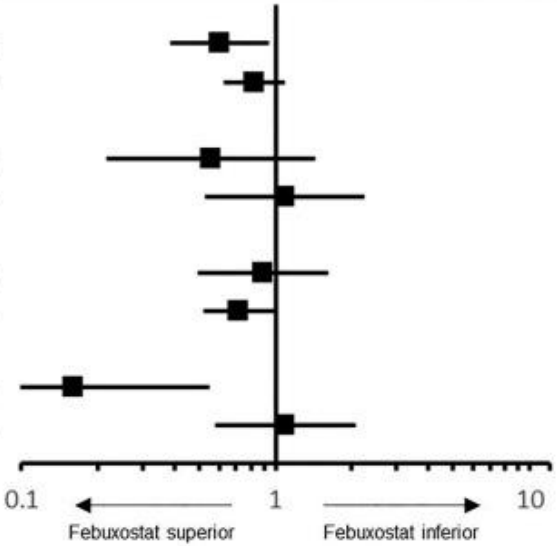
- Randomized, open-label, blinded-endpoint
- ≥65yr, sUA 7-9mg/dL, ≥1 RF for cerebral, CV, renal dz
- Febuxostat 40mg/day
- ↓ outcome driven by renal esp albuminuria
- No increase in CV events

Eur Heart J 2019;40(22):1778–1786 (FREED). RF: risk factor. Dz: disease.

Febuxostat Lowers CV Risk in Non-Gout Population with History of CV Disease

- Subgroup analysis of FREED study

		Febuxostat group n/N (%)	Non-febuxostat group n/N (%)	HR	95%CI	p	p for interaction
Primary endpoint							
CVD	Yes	34/115(29.6%)	46/119(38.7%)	0.601	(0.384-0.940)	0.026	0.227
	No	91/422(21.6%)	107/414(25.8%)	0.825	(0.624-1.091)	0.177	
Secondary hard endpoints							
CVD	Yes	7/115(6.1%)	12/119(10.1%)	0.555	(0.215-1.432)	0.223	0.293
	No	16/422(3.8%)	14/414(3.4%)	1.091	(0.531-2.242)	0.812	
Renal impairment							
CVD	Yes	22/115(19.1%)	22/119(18.5%)	0.896	(0.495-1.619)	0.715	0.613
	No	65/422(15.4%)	87/414(21.0%)	0.718	(0.520-0.990)	0.044	
Mortality analysis: all-cause death							
CVD	Yes	3/115(2.6%)	17/119(14.3%)	0.160	(0.047-0.547)	0.004	0.007
	No	20/422(4.7%)	18/414(4.3%)	1.091	(0.577-2.062)	0.790	



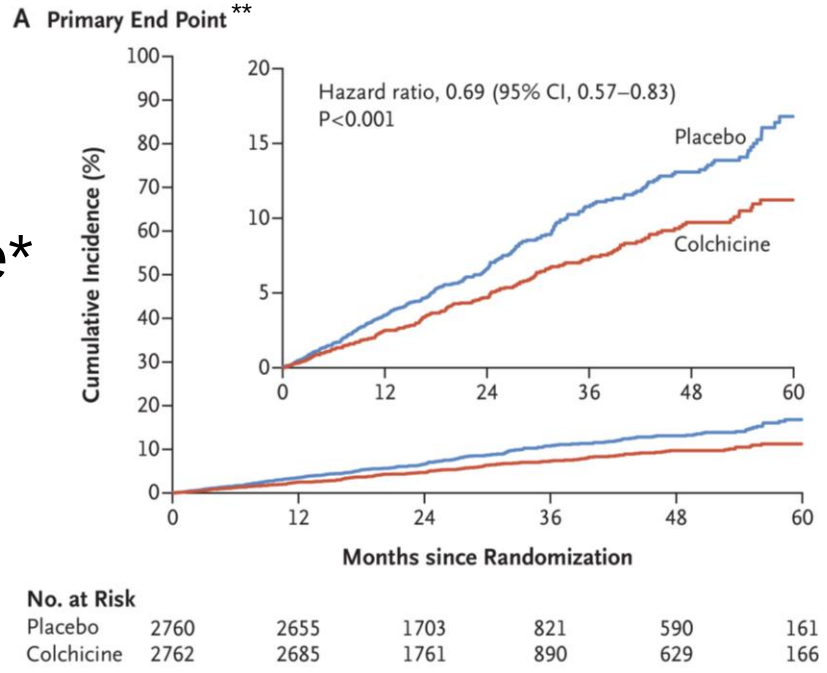
Int J Cardiol 2022;349:127-133.

Colchicine Approved for CV Risk Reduction

- Lodoco® 0.5 mg po daily
- Indication: ↓ risk of MI, stroke, coronary revascularization, and CV death in adult patients with established atherosclerotic disease or with multiple risk factors for CV disease

Colchicine Reduces CV Risk Irrespective of Gout

- Patients:
  - 35-82yo
  - Coronary artery disease*
  - GFR ≥ 50
  - 8% gout at baseline
- New gout in 1.4% colchicine vs 3.4% placebo



N Engl J Med 2020; 383:1838-1847 (LoDoCo2). *Evidence of coronary disease on invasive coronary angiography or CT angiography, or a coronary-artery calcium score of ≥ 400 Agatson units. **Composite of CV death, MI, ischemic stroke, ischemia-driven coronary revascularization.

Summary

Colchicine reduces CV risk in high-risk non-gout population

Allopurinol remains first-line ULT

Febuxostat use in patients with CVD should involve shared decision-making

Questions?