OUT WITH THE GOUT!
Updated Treatment Guidelines

Primary Care Update

02/13/2024

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Disclosures

- None

By the end of this talk, you should be able to:

1

Describe mechanisms of hyperuricemia and gouty arthritis

2

Recognize the risk factors and clinical stages of gout

3

Master treatment strategies for acute and chronic gout management

By the end of this talk, you should be able to:

1

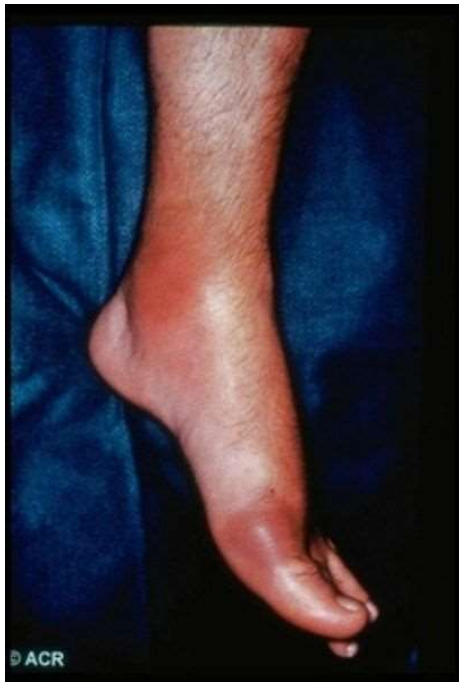
Describe mechanisms of hyperuricemia and gouty arthritis

Gout is the end-result of chronic hyperuricemia

Disorder of urate metabolism and elimination

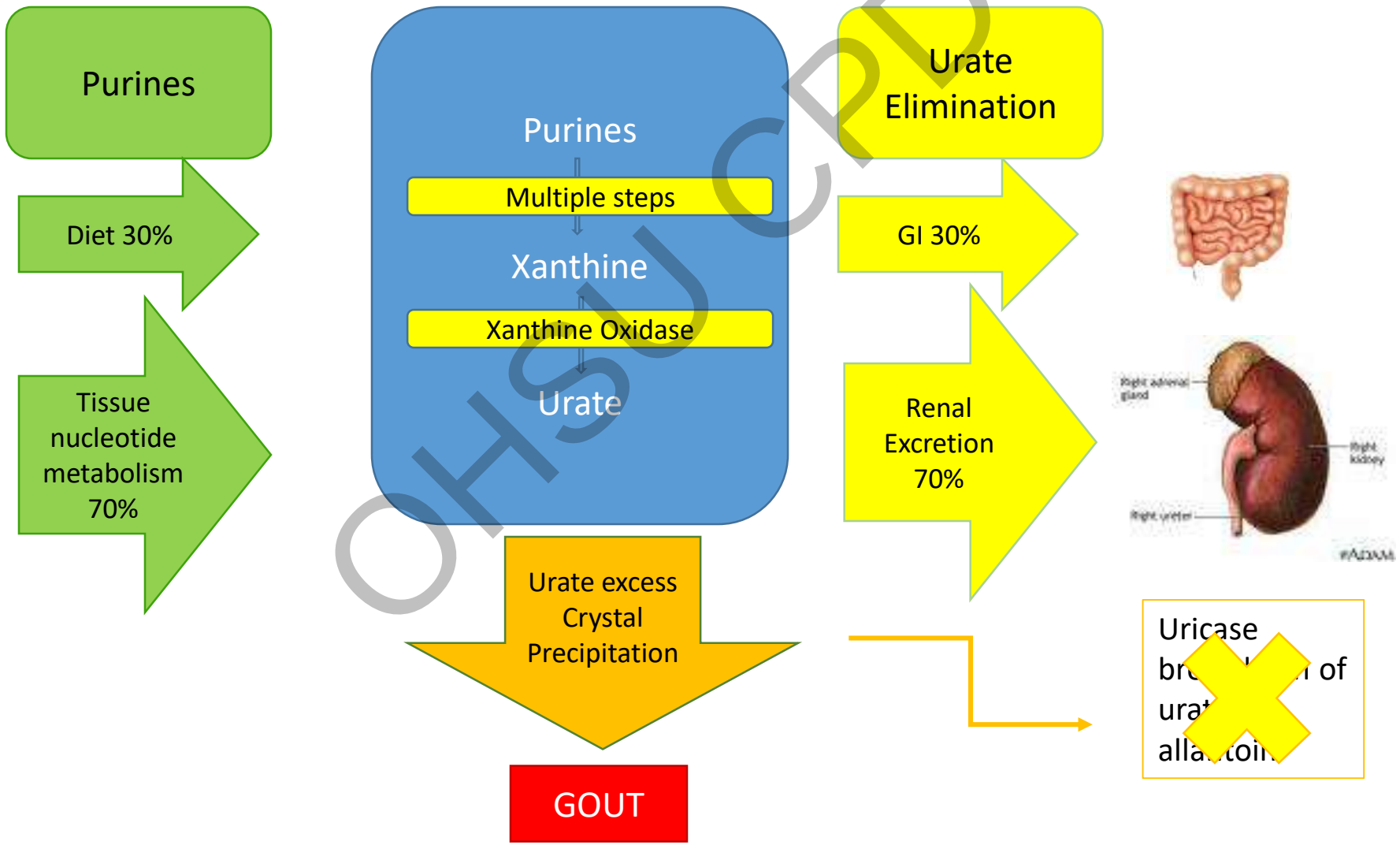
Hyperuricemia leading to uric acid deposition in tissues

Innate immune system activation (inflammasome)



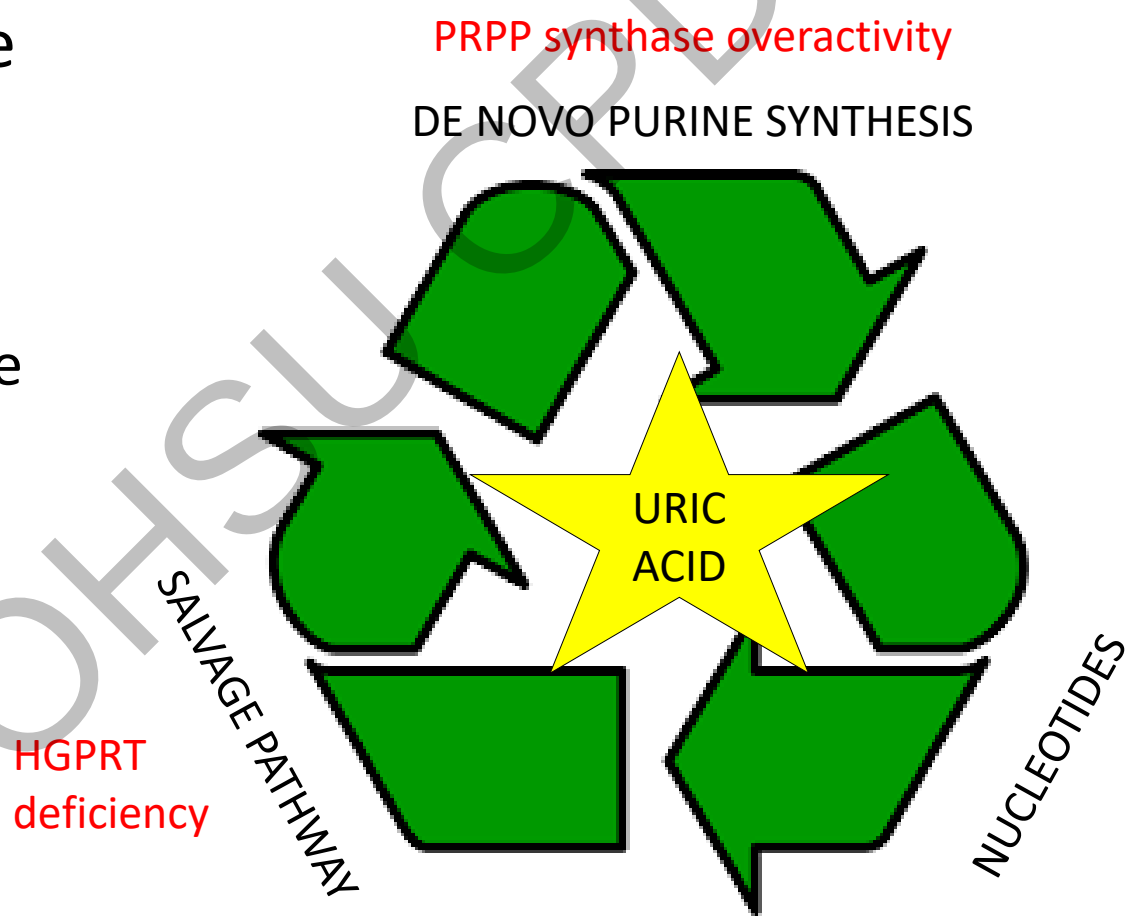
CLINICAL GOUT

Urate level depends on purine intake, metabolism, and elimination.



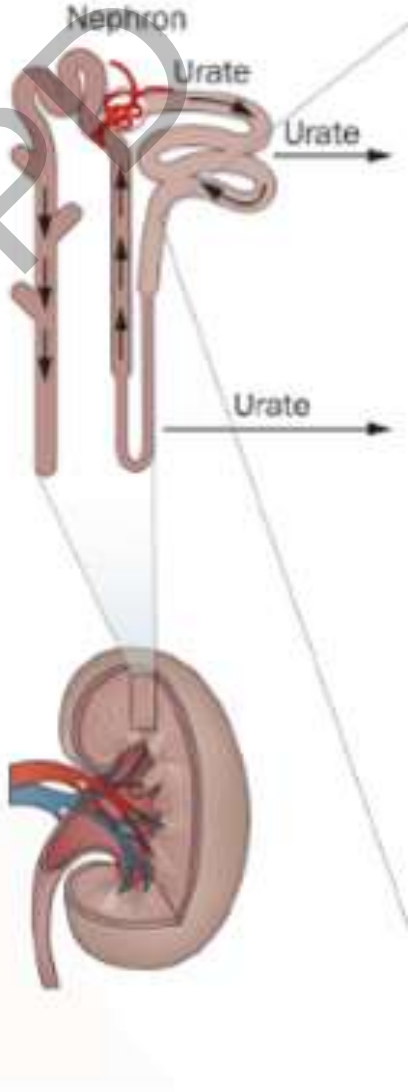
Why do people have hyperuricemia?

- The minority (10%) are overproducers
  - Inherited disorders of purine metabolism
  - High cell turnover state

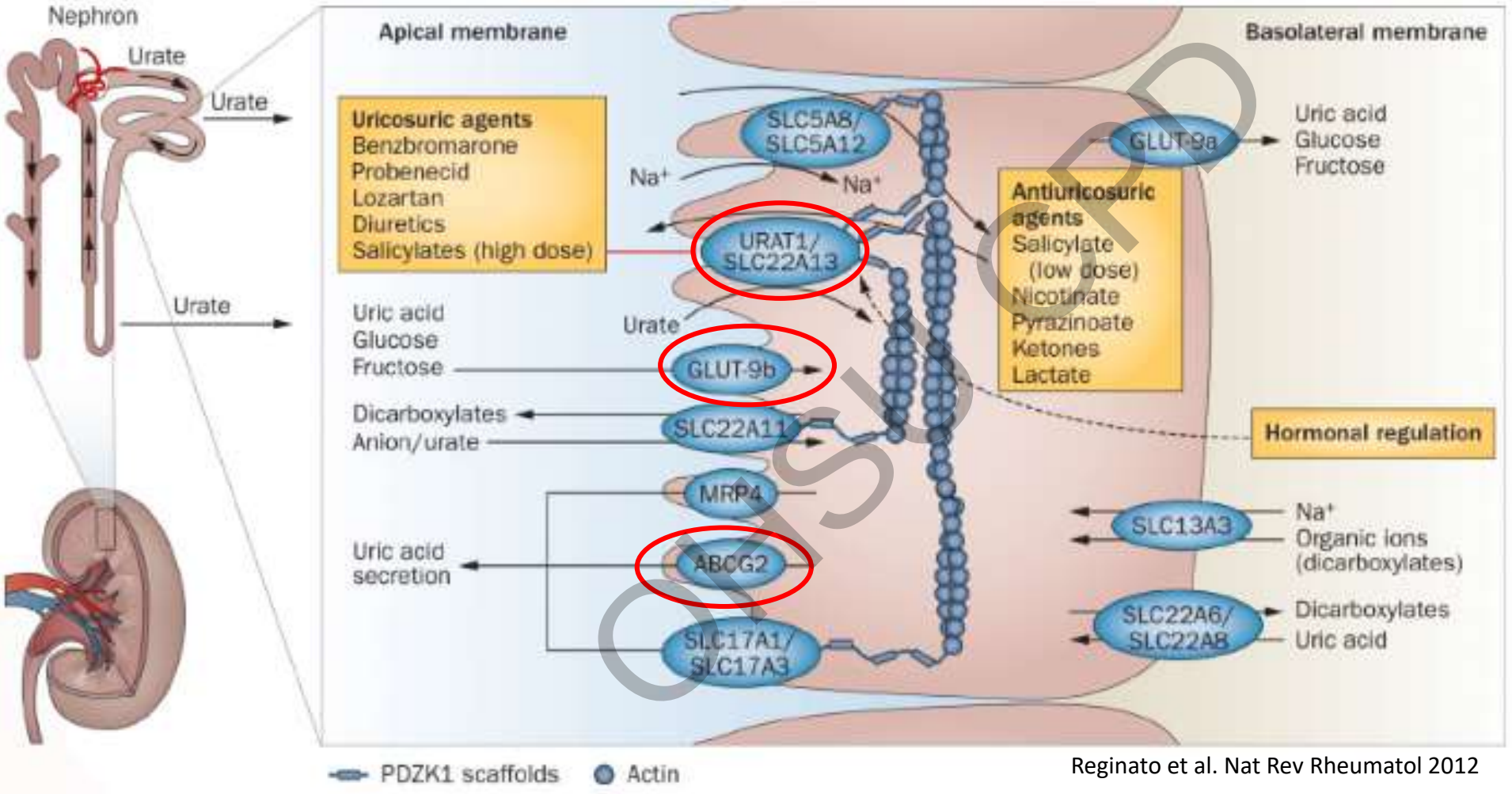


Why do people have hyperuricemia?

- The minority (10%) are overproducers (inherited disorders of purine metabolism or high cell turnover state)
- The vast majority (90%) of patients with hyperuricemia are urate under-excretors



Renal tubular excretion of urate



Reginato et al. Nat Rev Rheumatol 2012

Filtered 100%

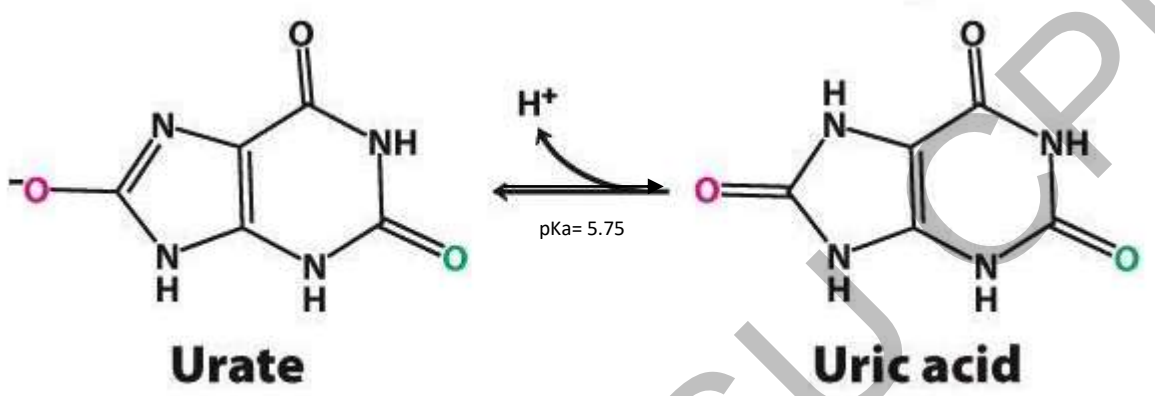
Pre secretory Reabsorption 99%

Secretion 50%

Post secretory Reabsorption 40%

Excretion 5-10%

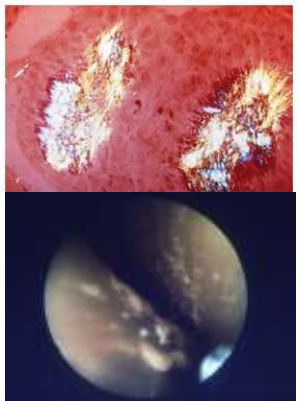
Uric acid is a weak organic acid which in body fluid exists mostly as soluble monosodium urate (50:1)



Urate + Na^+ + H^+ ⇌ Uric Acid

Low pH
Low temperature
≥6.8mg/dl

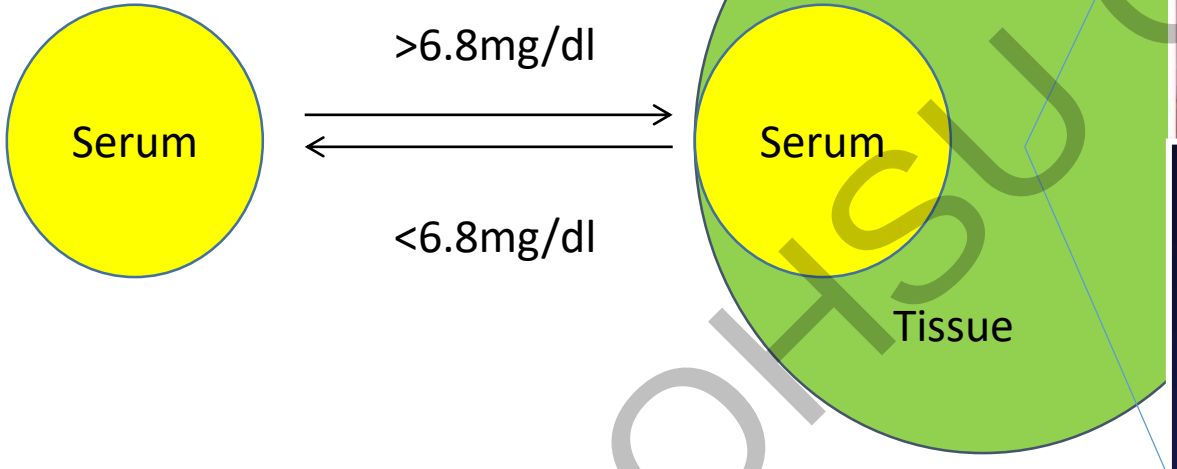
<6.8mg/dl

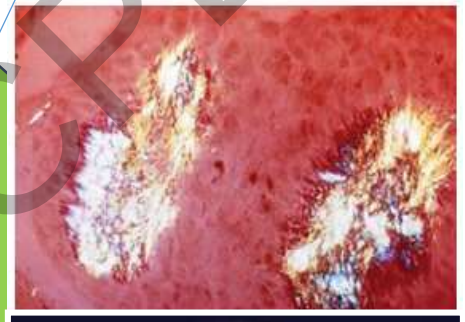


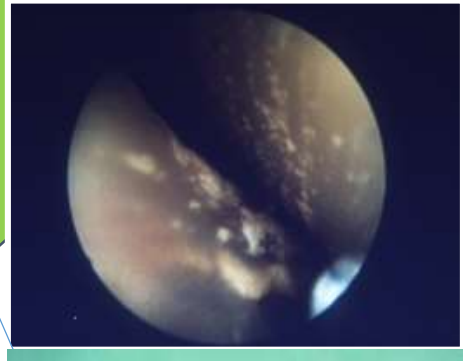
Monosodium Urate (MSU) → **Soluble in plasma**

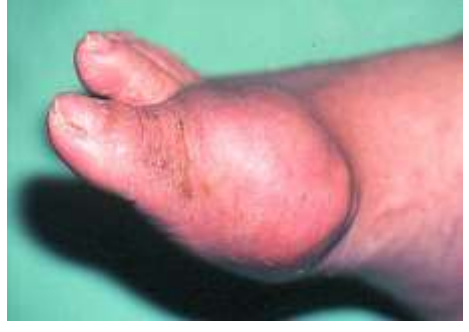
Uric Acid Crystals → **Insoluble, precipitates in tissues**

Gout is not a serum urate level disease but a urate deposition disease.

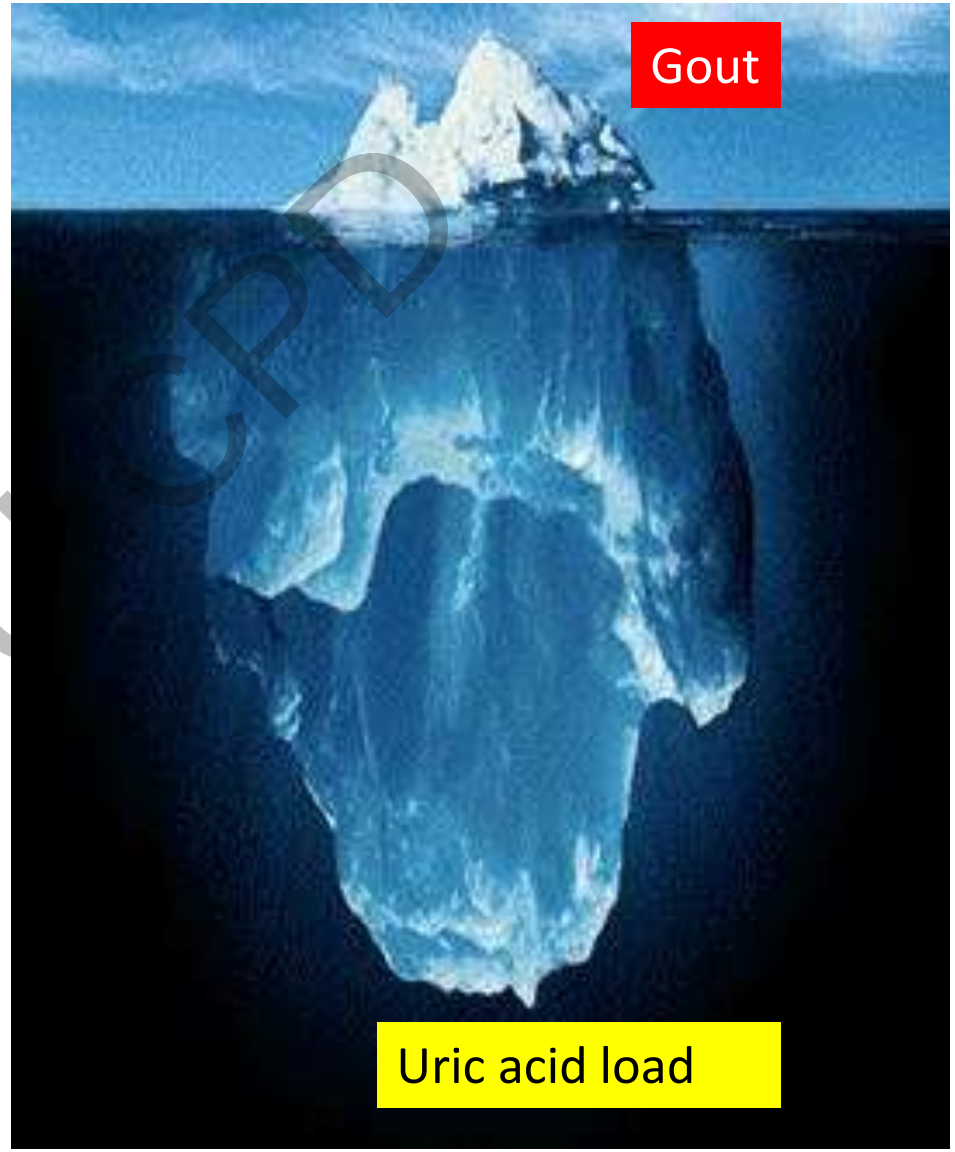






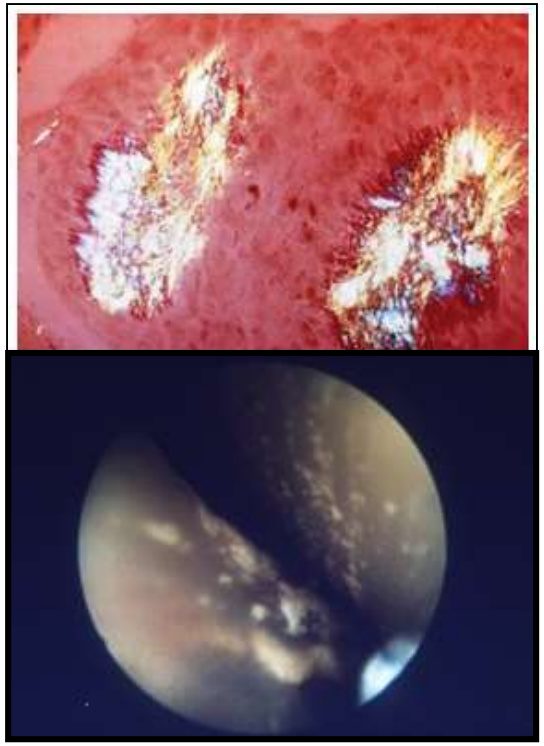


Gout is the tip of the hyperuricemia iceberg



What triggers the acute attack?

Walled off crystals
present in joints
in asymptomatic phase



Microtrauma, ΔsUA, dehydration, ΔpH

↓

Microcrystal shedding

↓

Naked MSU crystals
(IgG coating, C5 cleavage)

↓

Resident macrophages

↓

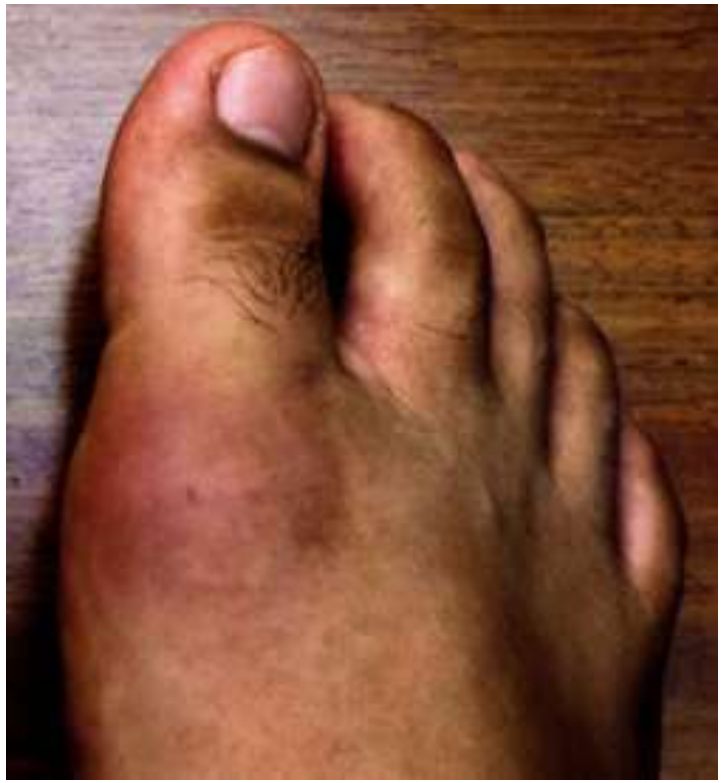
Cytokines (**IL1**, TNF, IL18, NO)

↓

Neutrophils

↓

Acute Inflammation



TGFβ, IL10, Apo B ↓

Resolution

Uric acid crystals

↓

Macrophages

↓

Danger signals

↓

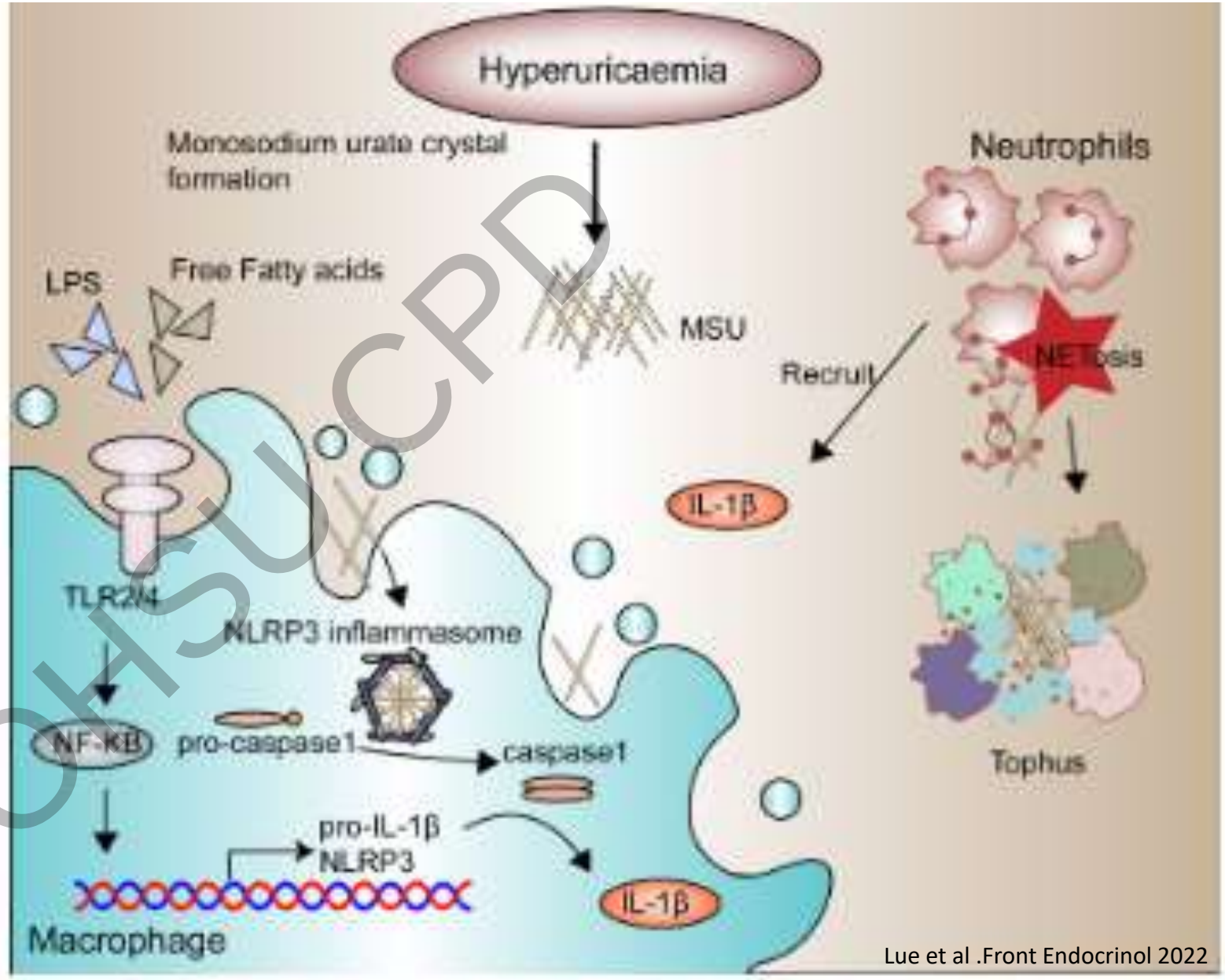
Innate immunity

↓

IL-1β release

↓

Neutrophil recruitment



Lue et al .Front Endocrinol 2022

By the end of this talk, you should be able to:

1

Describe mechanisms of hyperuricemia and gouty arthritis

2

Recognize the risk factors and clinical stages of gout

Gout prevalence has risen in both men & women

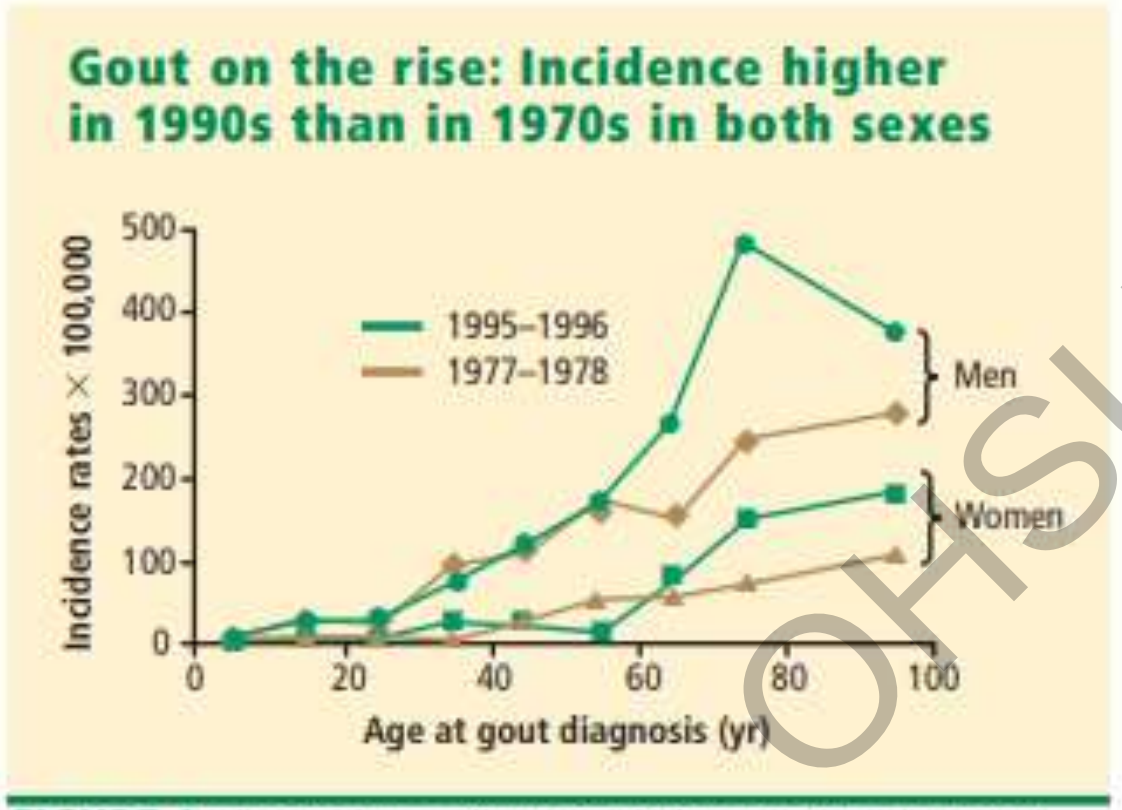


FIGURE 1. The incidence of gout in Rochester, Minn., in recent and remote 2-year periods according to age at diagnosis.

Reprinted, with permission, from *Journal of Rheumatology* (Arromdee E, et al. J Rheumatol 2002; 29:2403–2406).

- As of 2015-2016, Gout affects 3.9% of US adults (i.e. 9.2 million people)
  - 5.2% in men
  - 2.7% in women
- Most common form if inflammatory arthritis in men over age 40

Weaver A. Clev Clin J Med 2008 ; 75:S5
Zhu et al. Arth Rheum 2011; 3136-3141

Gout is more common in men, but women are at risk post menopause

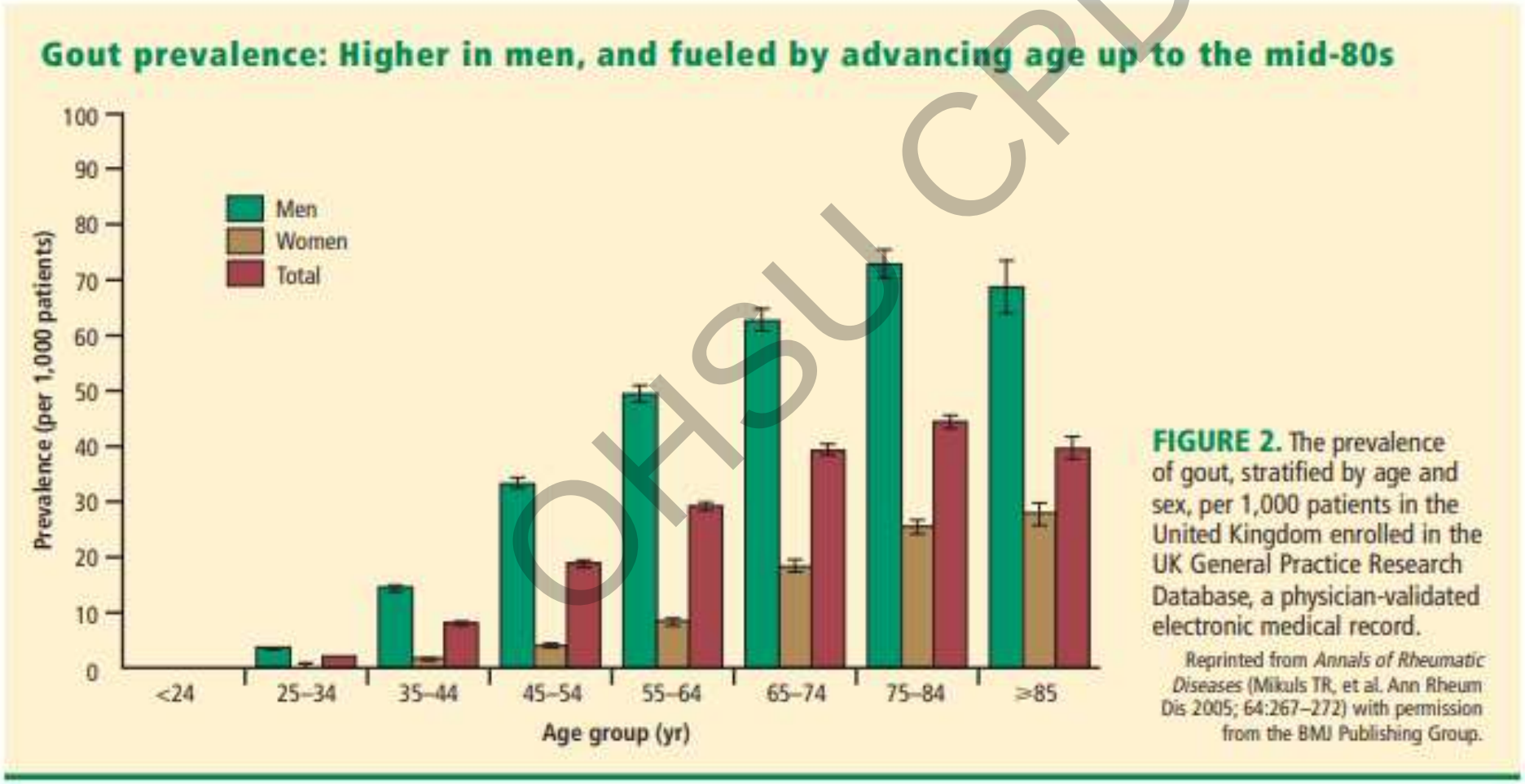


FIGURE 2. The prevalence of gout, stratified by age and sex, per 1,000 patients in the United Kingdom enrolled in the UK General Practice Research Database, a physician-validated electronic medical record.

Reprinted from *Annals of Rheumatic Diseases* (Mikuls TR, et al. Ann Rheum Dis 2005; 64:267–272) with permission from the BMJ Publishing Group.

Weaver A. Clev Clin J Med 2008 ; 75:S5

Risk factors for hyperuricemia and gout

Non-modifiable

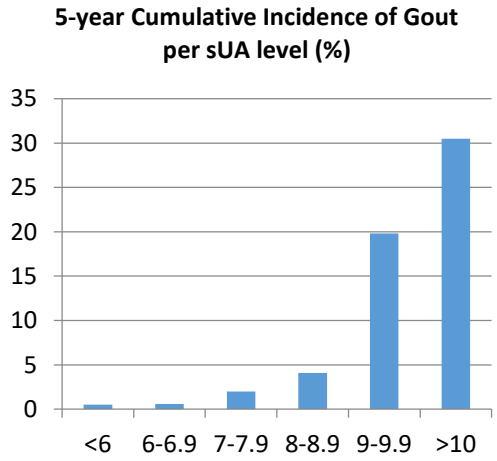
- Male sex
- Age
- Heredity
  - Urate tubular transporters: ABCG2
- High blood pressure
- Chronic kidney disease
- Transplant

Modifiable

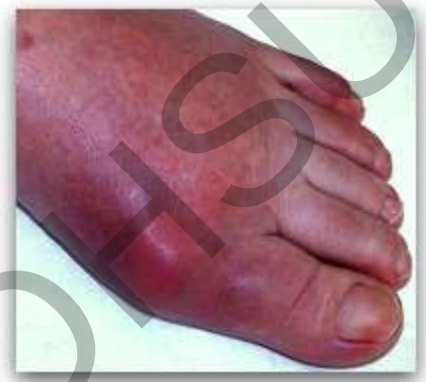
- Obesity
- Insulin resistance
- Metabolic syndrome
- Medications
- Alcohol Consumption
- Diet

Clinical Stages of Gout

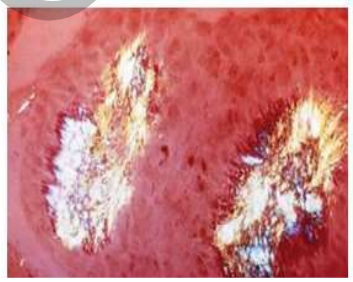
Asymptomatic hyperuricemia: Not all patients with hyperuricemia get gout

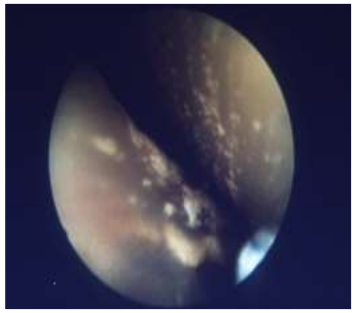


Acute gout:
Age at onset 30-40
Acute Monoarthritis
Peaks at 4-12 hours
Self-limited or easily treated
1MTP, foot, ankle, knee

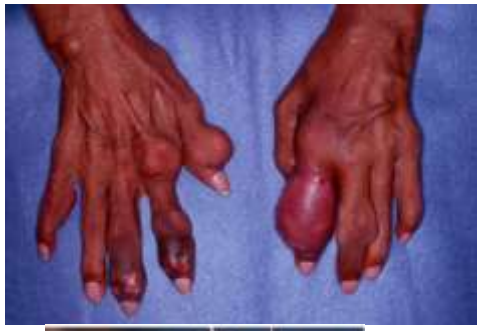


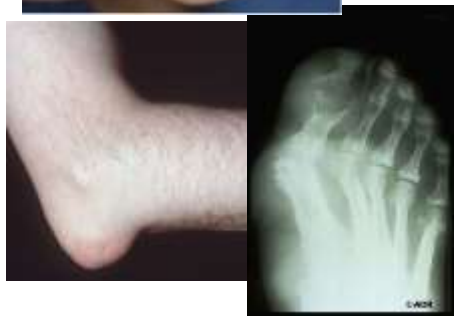
Intercritical:
Asymptomatic





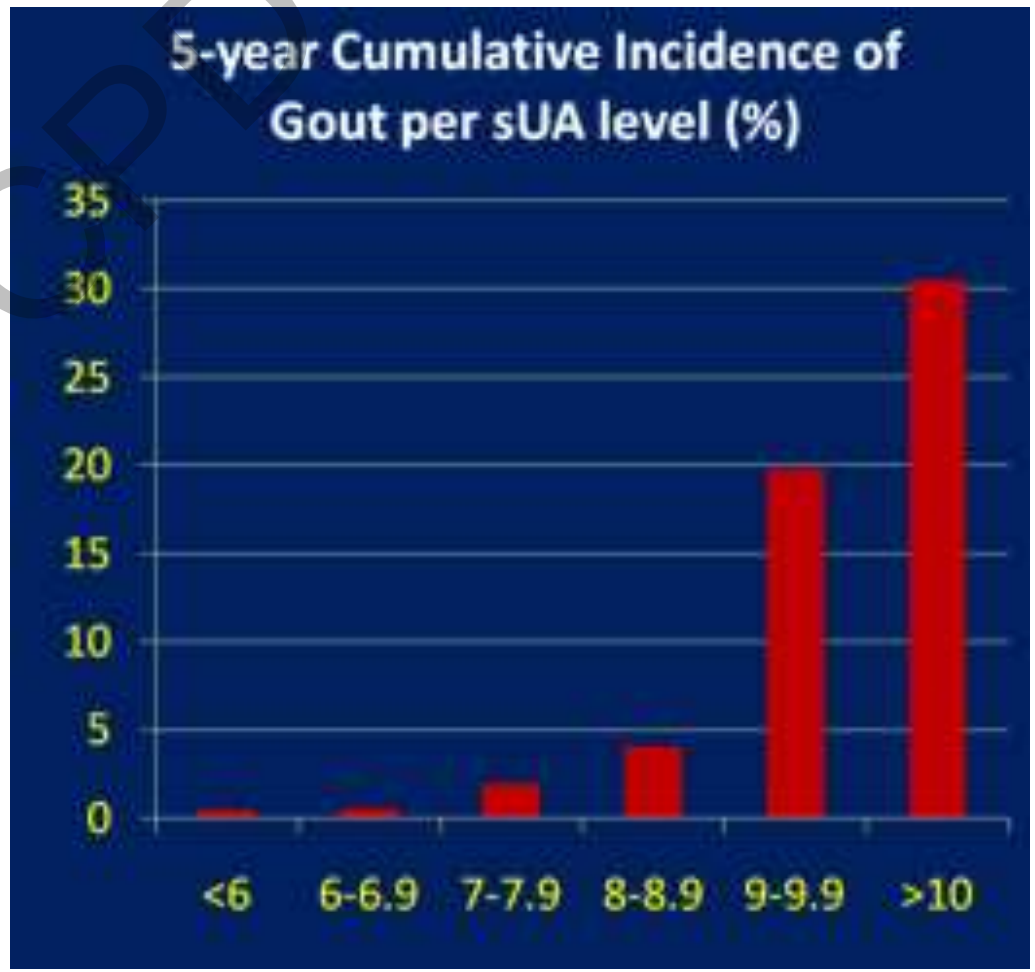
Advanced gout:
Multiple joints
Wrist, elbows, fingers
Prolonged episodes
Harder to treat
Tophi
Erosions





Hyperuricemia: Necessary but not sufficient

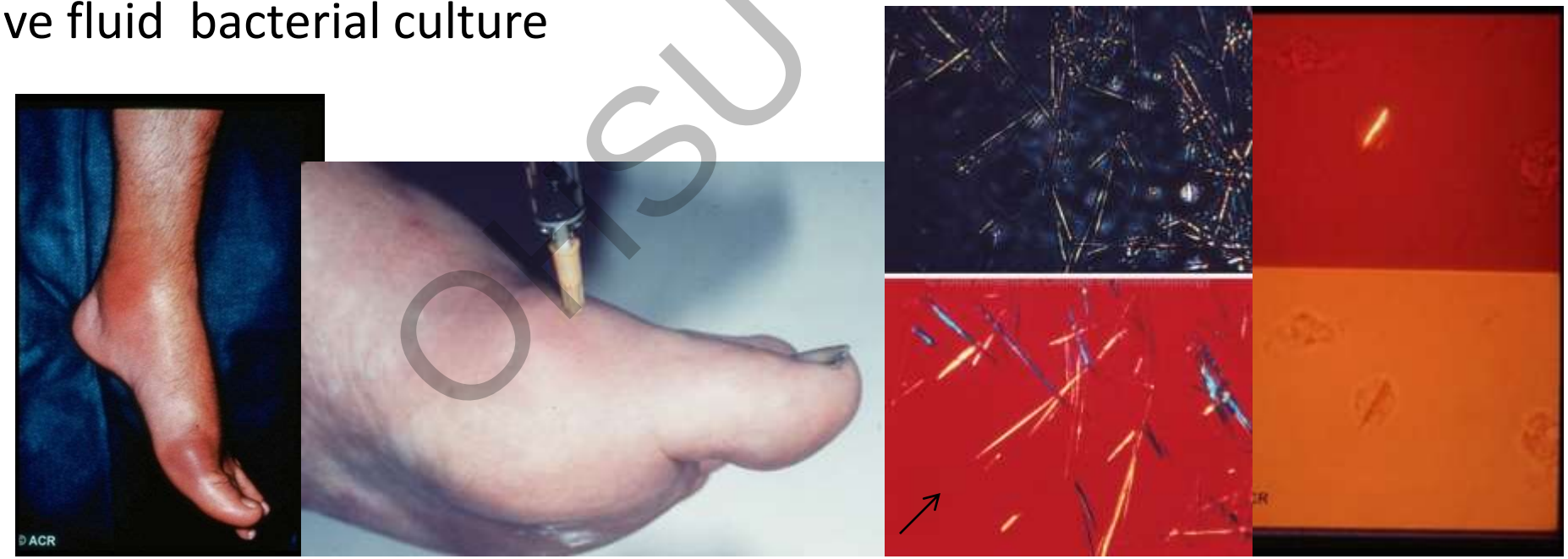
- sUA not helpful during an acute attack
  - Level may be normal during acute flare in up to 30%
  - Hyperuricemia ≠ gout
- sUA needed to monitor response to treatment



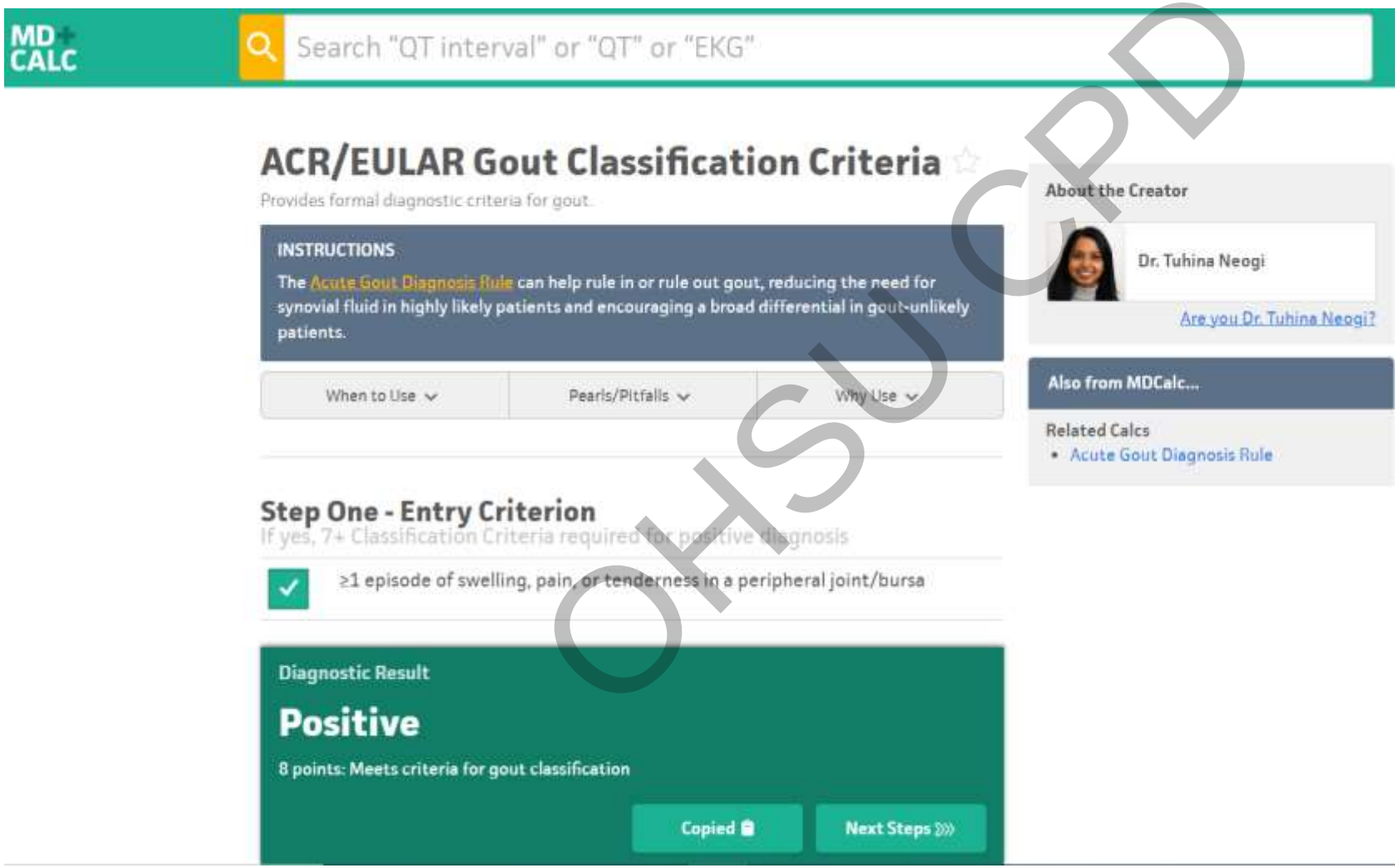
Rigby and Wood. *Clin Exp Rheumatol* 1994; 12:395
Campion et al, Normative Aging Study, *Am J Med*, 1987

Gout Diagnosis: Joint aspiration is the gold standard for a definitive diagnosis of gout

- Inflammatory fluid
  - Cell count: WBC >2000, neutrophil predominance
  - Polarized microscopy: Needle shaped, negatively birefringent, intra- and extra-cellular uric acid crystals
  - Negative fluid bacterial culture



Clinical Diagnosis of Gout



https://www.mdcalc.com/calc/2195/acr-eular-gout-classification-criteria

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Describe mechanisms of hyperuricemia and gouty arthritis

2

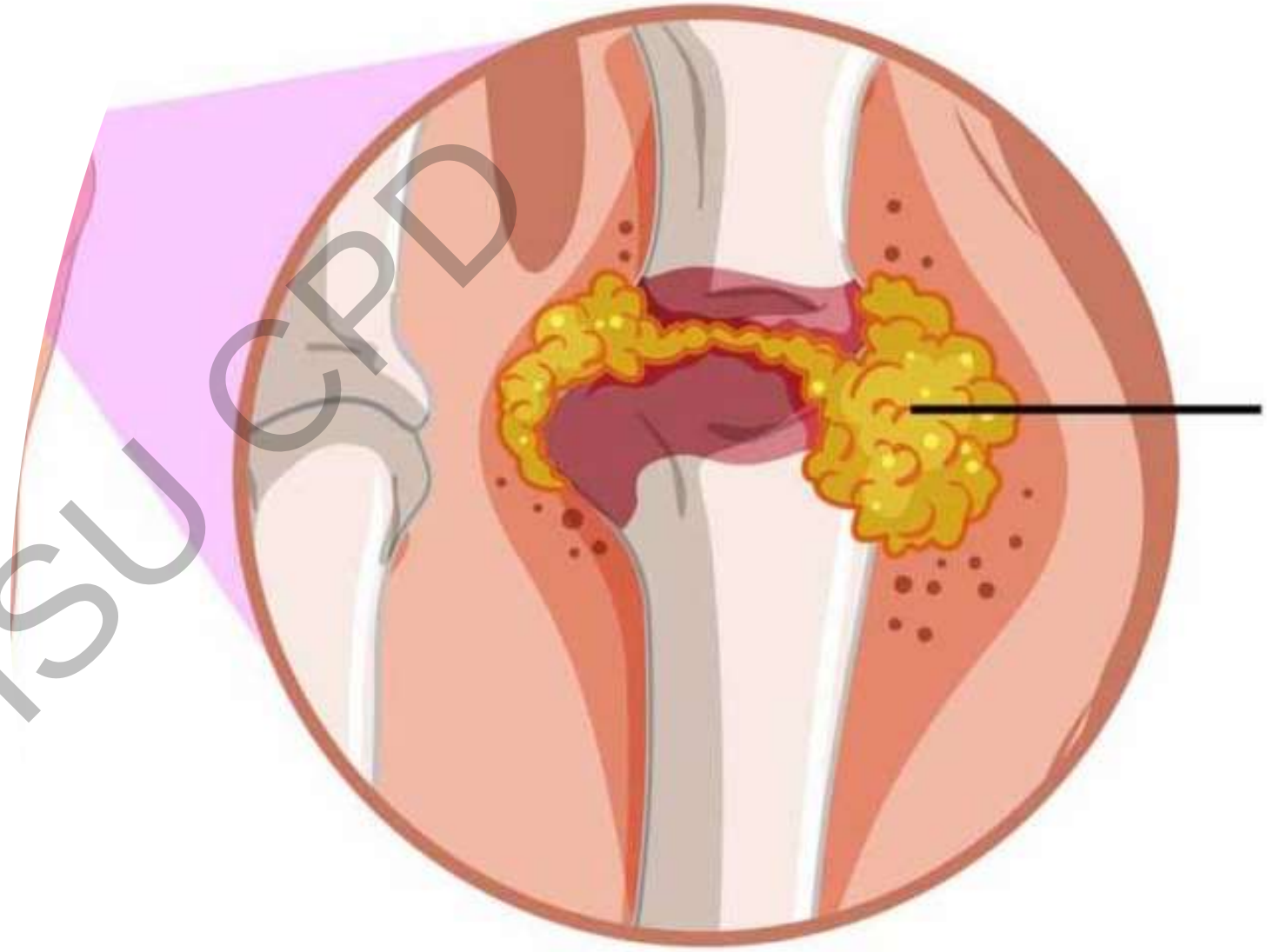
Recognize the risk factors and clinical stages of gout

3

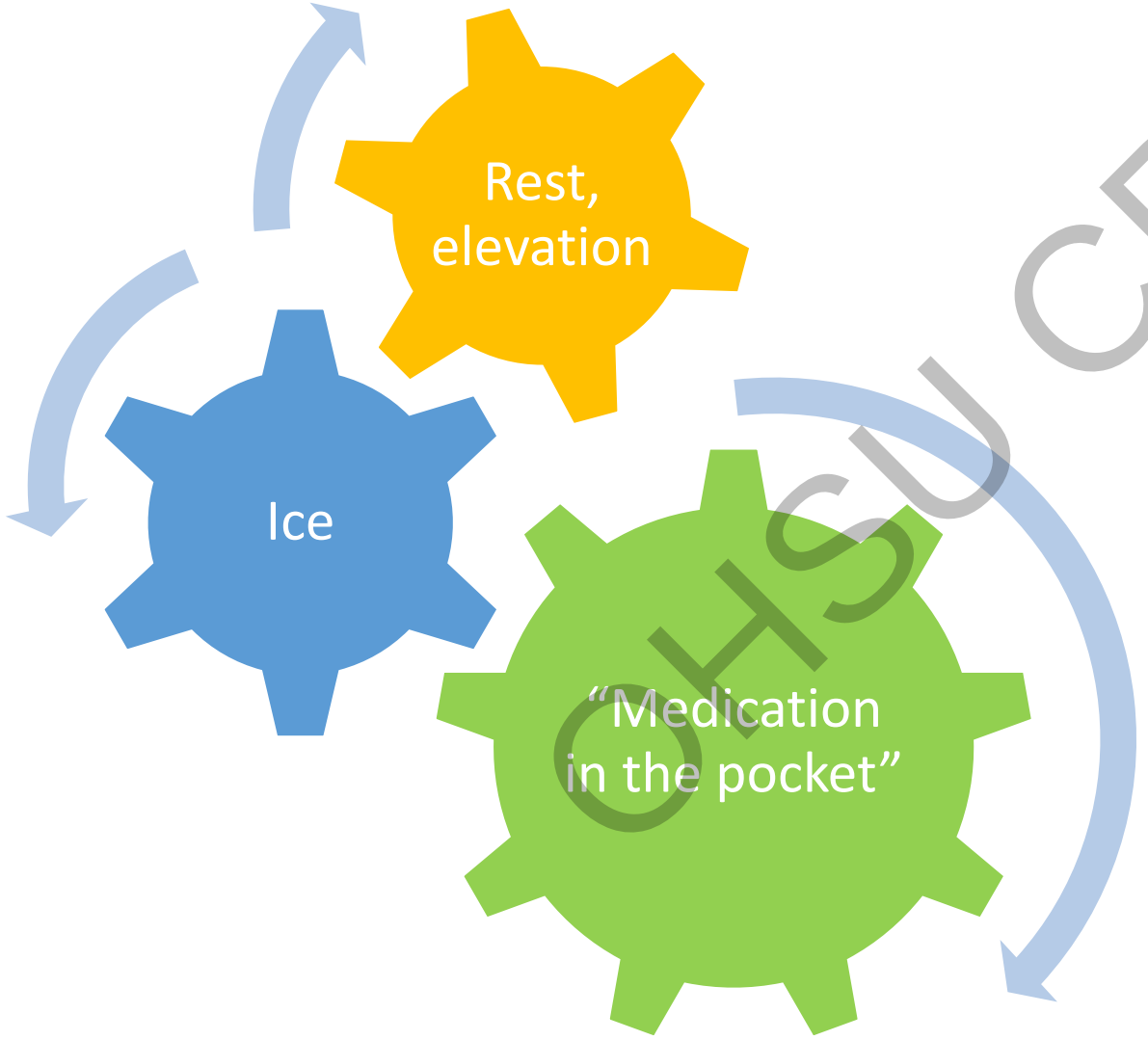
Master treatment strategies for acute and chronic gout management

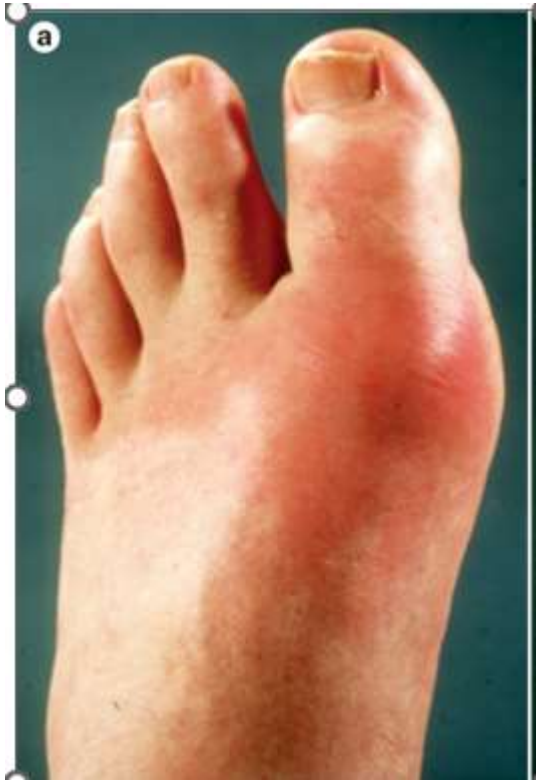
Goals of Gout Treatment

- Treat acute arthritis to relieve pain and restore function
- Prevent future attacks
- Prevent development of chronic advanced gout & permanent joint damage
- Patient education



Managing acute gout flares





Rees et al. Nat Rev Rheum. 2014; 10:271-83.

Fitzgerald et al. AC&R 2020 72(6):744-760

Acute Gout Treatment: Know the co-morbidities!

NSAIDs

If no contraindications
Full dose
5-7 days
(Avoid indomethacin in older individuals)

Colchicine 2+1

(0.6mg x2 then 0.6 mg x1, one hour later)

Steroids

If no DM, low risk of infection
(Prednisone 40mg, taper by 10 mg every 2-4 days)

IL-1 Inhibitors

(Inpatient, when all NSAIDs, colchicine, steroids contraindicated)

Colchicine

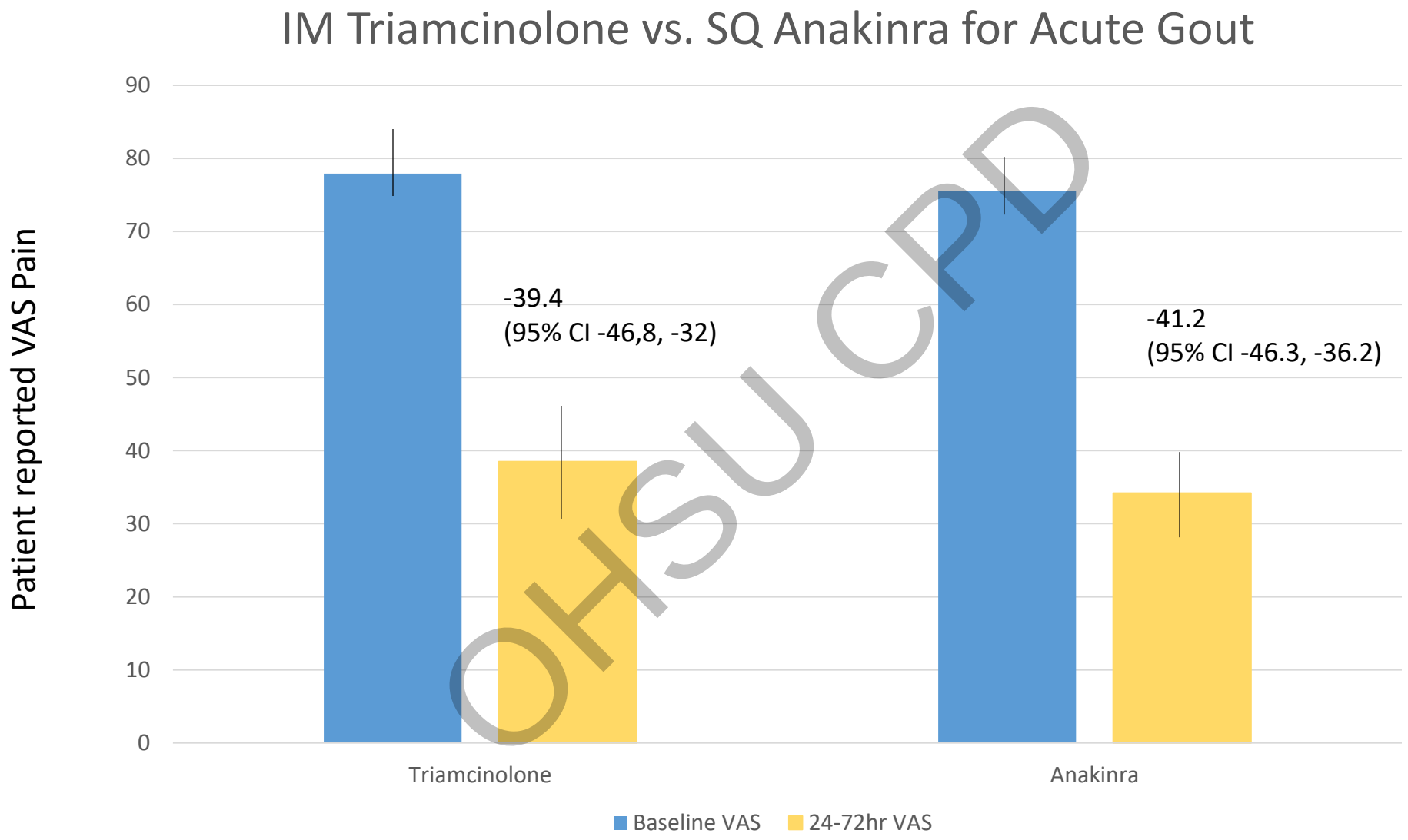
- How does it work?
  - Binds the microtubule ends and inhibits neutrophil chemotaxis, phagocytosis, & protein expression
  - Limits expression of adhesion molecules on leucocytes and endothelial cells
  - Attenuates the activation of the inflammasome
- Low dose is as good and less toxic than high dose

	1.8 mg	**4.8mg**	**placebo**
50% better at 24hrs	38%	32%	15%
Diarrhea	23%	73%	14%
Any GI s/e	45%	94%	28%

Terkeltaub et al. Arthritis Rheum. 2010 Apr;62(4):1060-8

- Drug-drug interactions, adjust for eGFR

IL-1 Blockade in Acute Gout: AnaGO Study

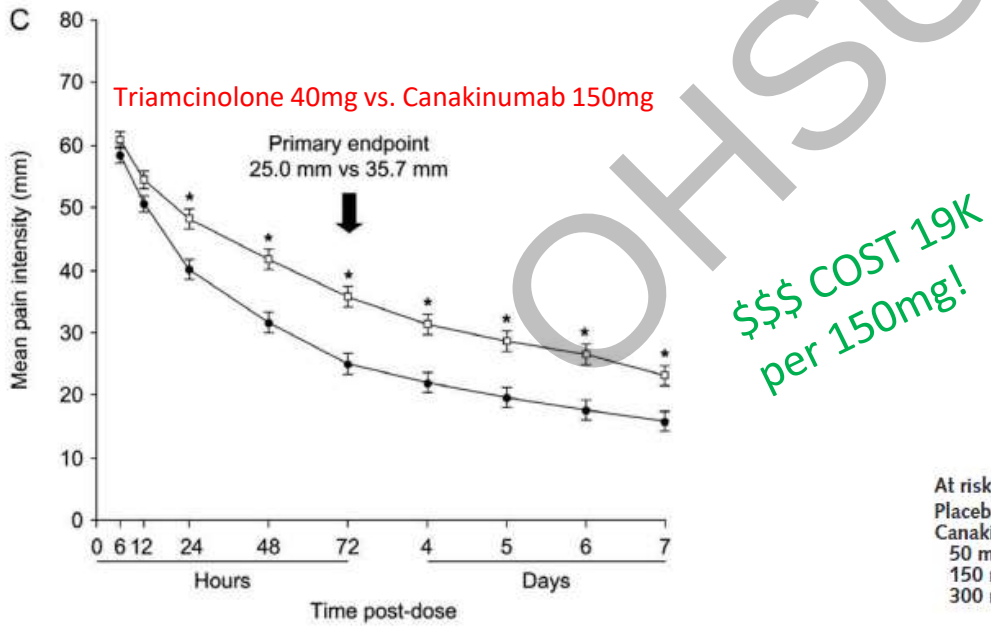


Difference in mean change -1.8 (95% CI -10.8, 7.1) for anakinra compared with triamcinolone (p 0.688)

Saag et al. A&R 2021. 73)8):1533-1542

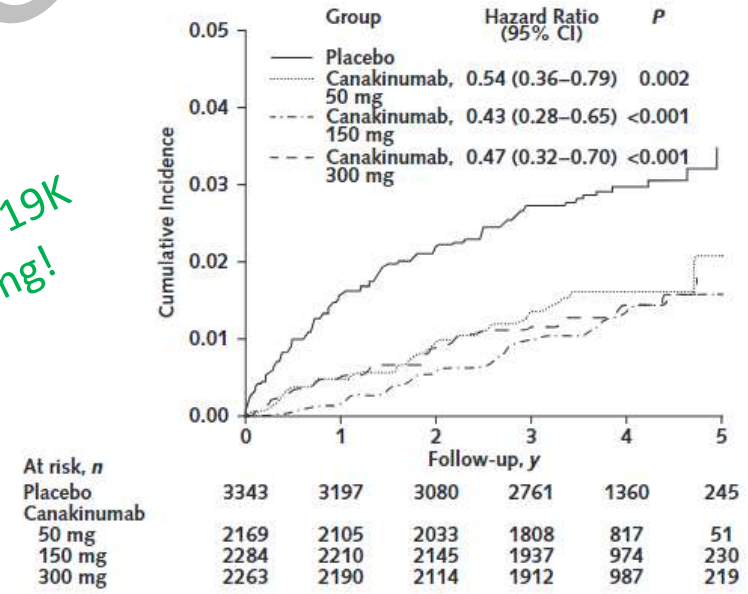
IL-1 Blockade in Gout Treatment: For those who have contraindications to traditional therapies

- Anakinra is not FDA approved, used off-label to treat acute gout
  - Recombinant IL-1 receptor antagonist: 100 mg SQ x 3-5 days
- Canakinumab is FDA approved
  - Anti-IL1-beta monoclonal antibody: 150 mg SQ q 12 weeks



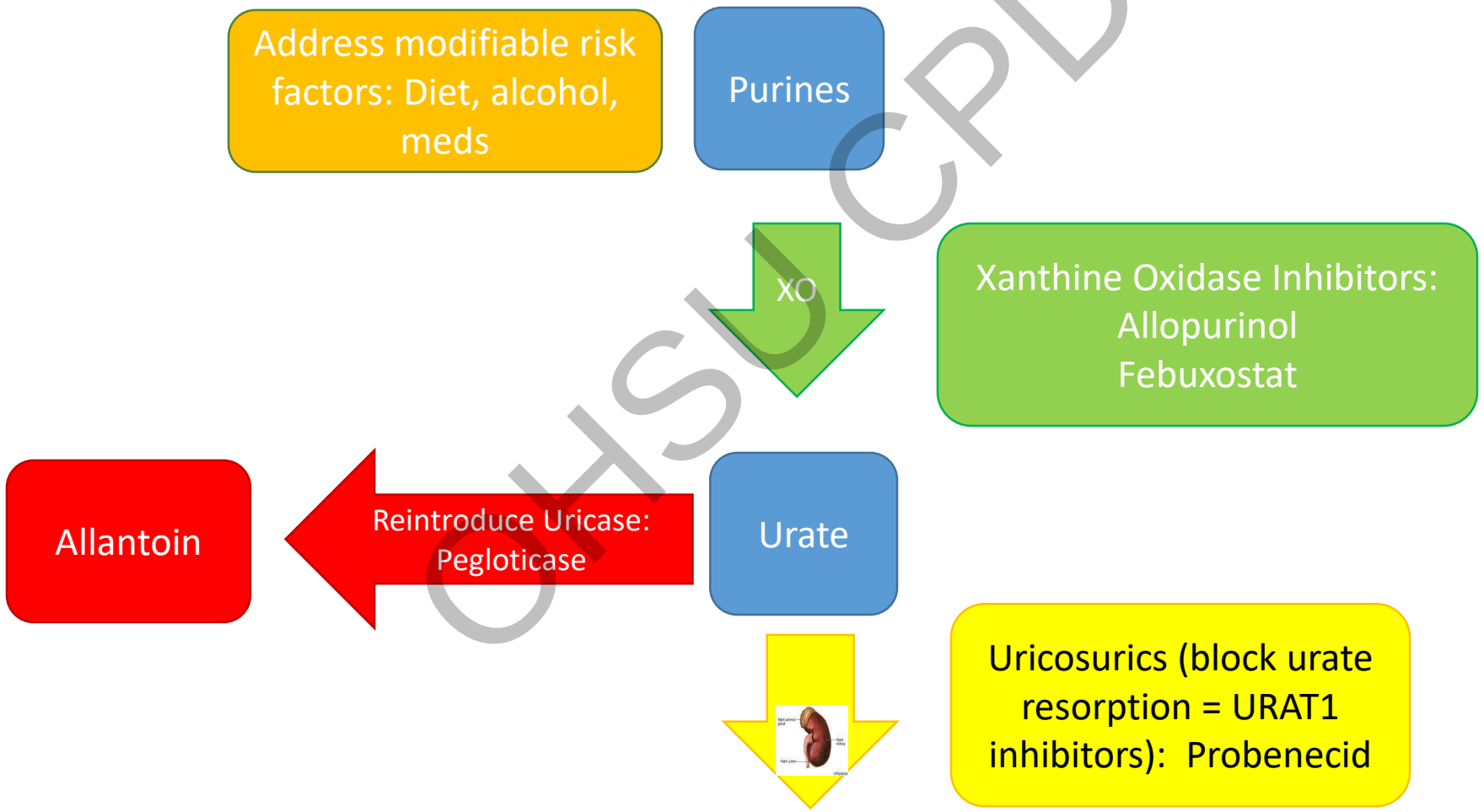
Schlesinger et al. ARD 2012

$$$ COST 19K per 150mg!



Solomon et al. ARD 2018

Targeting hyperuricemia to prevent flares is key!



American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis Care & Research
Vol. 72, No. 6, June 2020, pp 744–760
DOI 10.1002/acr.24180

ACR GUIDELINE FOR MANAGEMENT OF GOUT

2020 American College of Rheumatology Guideline for the Management of Gout

John D. FitzGerald,[1] Nicola Dalbeth,[2] Ted Mikuls,[3] Romina Brignardello-Petersen,[4] Gordon Guyatt,[4] Aryeh M. Abeles,[5] Allan C. Gelber,[6] Leslie R. Harrold,[7] Dinesh Khanna,[8] Charles King,[9] Gerald Levy,[10] Caryn Libbey,[11] David Mount,[12] Michael H. Pillinger,[5] Ann Rosenthal,[13] Jasvinder A. Singh,[14] James Edward Sims,[15] Benjamin J. Smith,[16] Neil S. Wenger,[17] Sangmee Sharon Bae,[17] Abhijeet Danve,[18] Puja P. Khanna,[19] Seoyoung C. Kim,[20] Aleksander Lenert,[21] Samuel Poon,[22] Anila Qasim,[4] Shiv T. Sehra,[23] Tarun Sudhir Kumar Sharma,[24] Michael Toprover,[5] Marat Turgunbaev,[25] Linan Zeng,[4] Mary Ann Zhang,[20] Amy S. Turner,[25] and Tuhina Neogi[11]

When to initiate Urate Lowering Therapy?

Table 1. Indications for pharmacologic urate-lowering therapy (ULT)*

Recommendation	PICO question	Certainty of evidence
For patients with 1 or more subcutaneous tophi, we strongly recommend initiating ULT over no ULT.	1	High
For patients with radiographic damage (any modality) attributable to gout, we strongly recommend initiating ULT over no ULT.	2	Moderate
For patients with frequent gout flares (≥2/year), we strongly recommend initiating ULT over no ULT.	3	High
For patients who have previously experienced >1 flare but have infrequent flares (<2/year), we conditionally recommend initiating ULT over no ULT.	4	Moderate
For patients experiencing their first flare, we conditionally recommend *against* initiating ULT over no ULT, with the following exceptions.	5	Moderate
For patients experiencing their first flare and CKD stage ≥3, SU >9 mg/dl, or urolithiasis, we conditionally recommend initiating ULT.	5	Very low
For patients with asymptomatic hyperuricemia (SU >6.8 mg/dl with no prior gout flares or subcutaneous tophi), we conditionally recommend *against* initiating any pharmacologic ULT (allopurinol, febuxostat, probenecid) over initiation of pharmacologic ULT.	57	High†

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes; CKD = chronic kidney disease; SU = serum urate.
† There is randomized clinical trial data to support the benefit that ULT lowers the proportion of patients who develop incident gout. However, based on the attributable risk, 24 patients would need to be treated for 3 years to prevent a single (incident) gout flare leading to the recommendation against initiating ULT in this patient group.

Fitzgerald et al. ACR Gout Guidelines 2020 AC&R

Starting Urate lowering Therapy

<u>STRONG</u> Recommendations to start ULT:

1. Tophus
2. Radiographic damage (any modality due to gout)
3. Frequent gout flares (≥ 2 per year)

Start lowest dose possible, reach target over weeks to months

T2T sUA < 6mg/dl

CONDITIONAL Recommendations to start ULT:

1. Previously experienced >1 flare, but less than 2 per year
2. First flare with Moderate-severe CKD (≥ Stage 3), sUA ≥ 9 mg/dl, or urolithiasis
3. Start as soon as possible

CONDITIONAL Recommendations AGAINST starting ULT:

1. First flare EVER
2. Asymptomatic hyperuricemia

Adapted from Cohen et a. Curr Rheumatol Rep 2021; 23(4)

Rationale for Treat-To-Target Strategy: sUA< 6

- Reducing detectable uric acid crystals in joints
  - Serial joint fluid aspiration
  - Serial imaging (ultrasound, dual energy CT)
- Lowering the likelihood of future gout flares
- Shrinking tophi
- Slowing down joint damage
  - Erosions by CT imaging

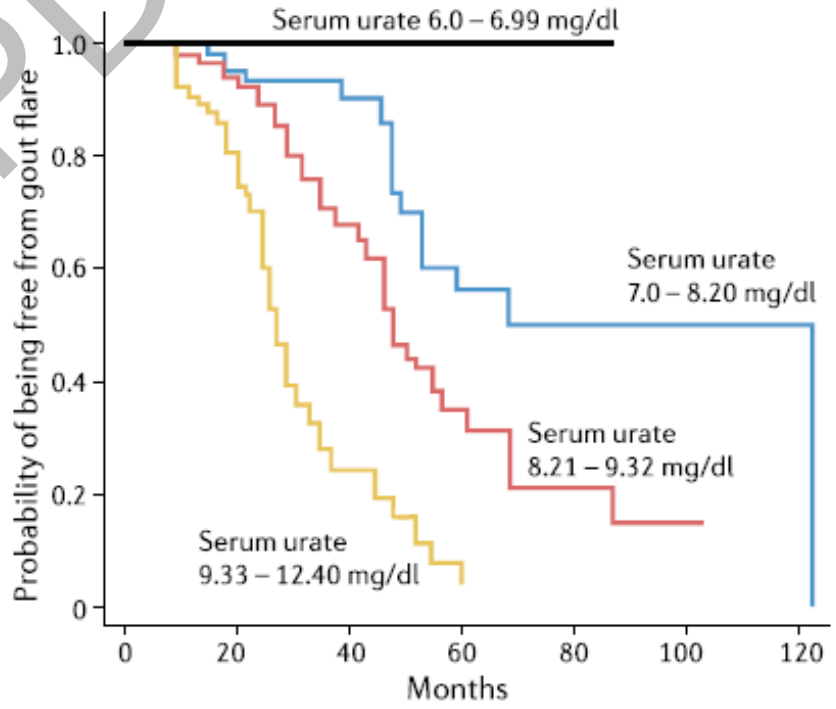


Fig. 2 | **Time to recurrence of gout flare after withdrawal of urate-lowering therapy.** Kaplan–Meier

Stamp & Dalbeth. Nature Rev Rheum 2022

Pearls in initiating urate lowering therapy

- Pick a urate lowering drug: start low, go slow
- Do not forget to concomitantly start an anti-inflammatory drug ("prophylactic therapy") to prevent gout flares as uric acid levels begin to drop
  - Colchicine 0.6mg daily or qod (consider drug-drug interactions, eGFR)
  - Low dose NSAID eg naproxen 500 mg daily
  - Low dose prednisone 5 mg/day
  - (Canakinumab)

Pearls in initiating urate lowering therapy

- Pick a urate lowering drug: start low, go slow
- Do not forget to concomitantly start an anti-inflammatory drug ("prophylactic therapy") to prevent gout flares as uric acid levels begin to drop
- Continue prophylactic therapy for 6 months after initiating urate lowering therapy, and for at least 12 weeks post achieving uric acid goal
- Check sUA level 2-4 weeks after each dose adjustment
- Target SUA level of < 6 mg/dl (if tophi, < 5mg/dl)

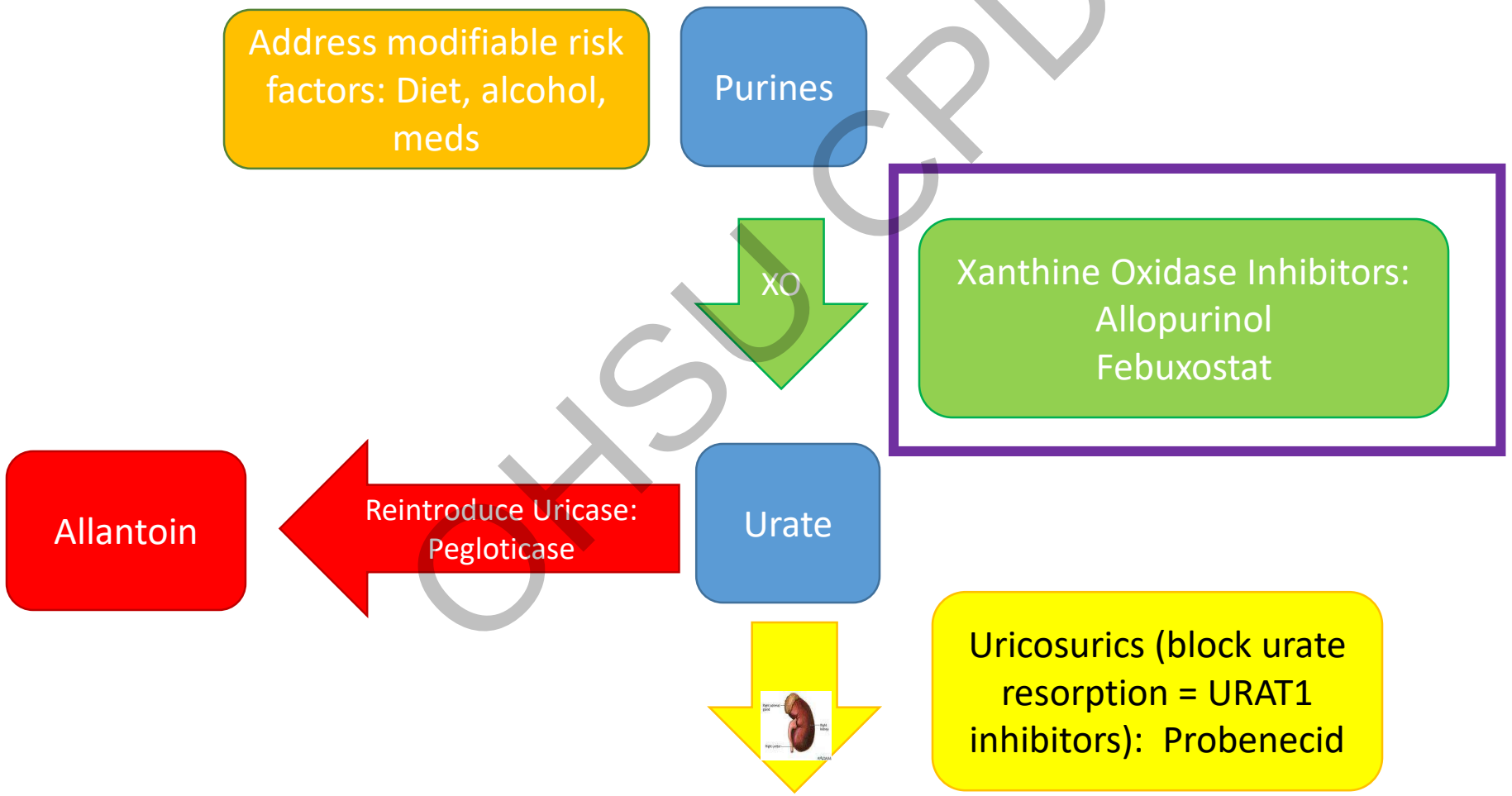
Pitfall

- Failure to start prophylactic anti-inflammatory drug together with urate lowering therapy

Pitfall

- Failure to titrate urate lowering therapy to target a sUA < 6 mg/dl

Targeting hyperuricemia to prevent flares is key!

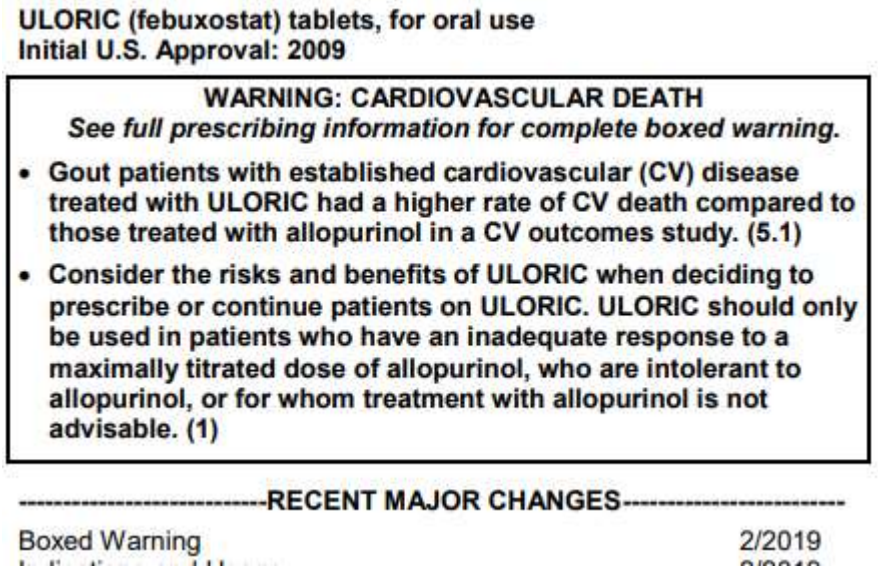


Allopurinol: First line Urate lowering Therapy

- Favored: Cheap, once a day
- Drug-drug interaction: Azathioprine and 6-MP (DO NOT USE)
- Screen for HLA-B5801 in Chinese, Thai, S Korean, African American
  - Do not use if HLA-B5801 allele is present
- Start low and go slow to reduce flare risk and hypersensitivity risk
  - If GFR>30: Start with 100 mg daily and titrate up by 100mg q 4 weeks
  - If GFR <30: Start with 50 mg daily and titrate up by 50 mg q 4 weeks
- Target sUA < 6mg/dl
  - If tophi, aim for < 5mg/dl
- Max FDA approved dose 800 mg/day
- Monitor for rash, pruritus, abnormal labs

Febuxostat: Second line Urate Lowering Therapy

- Less favored: Expensive, initial concern for increased CV events and mortality compared to allopurinol (black box warning)
  - CARES vs. FAST trials
- Drug-drug interaction: Azathioprine and 6-MP (DO NOT USE)
- OK to use if HLA-B5801 +
- Start 40 mg/day
  - Increase to 80 mg/day if sUA > 6 mg/dl after 2 weeks
- May cause GI side-effects, liver enzyme elevations



ULORIC (febuxostat) tablets, for oral use
Initial U.S. Approval: 2009

WARNING: CARDIOVASCULAR DEATH
See full prescribing information for complete boxed warning.

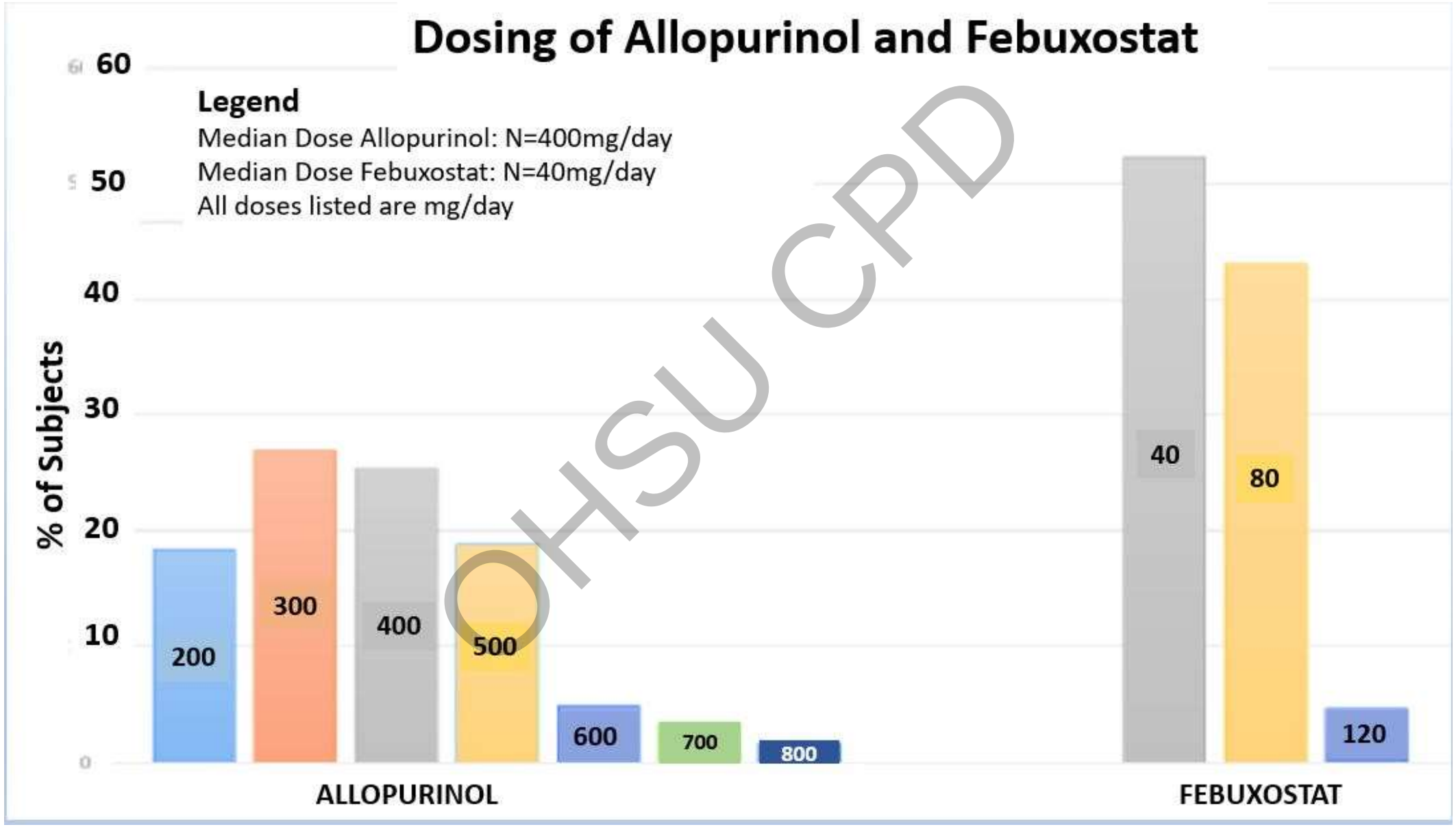
- **Gout patients with established cardiovascular (CV) disease treated with ULORIC had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study. (5.1)**
- **Consider the risks and benefits of ULORIC when deciding to prescribe or continue patients on ULORIC. ULORIC should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable. (1)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	2/2019

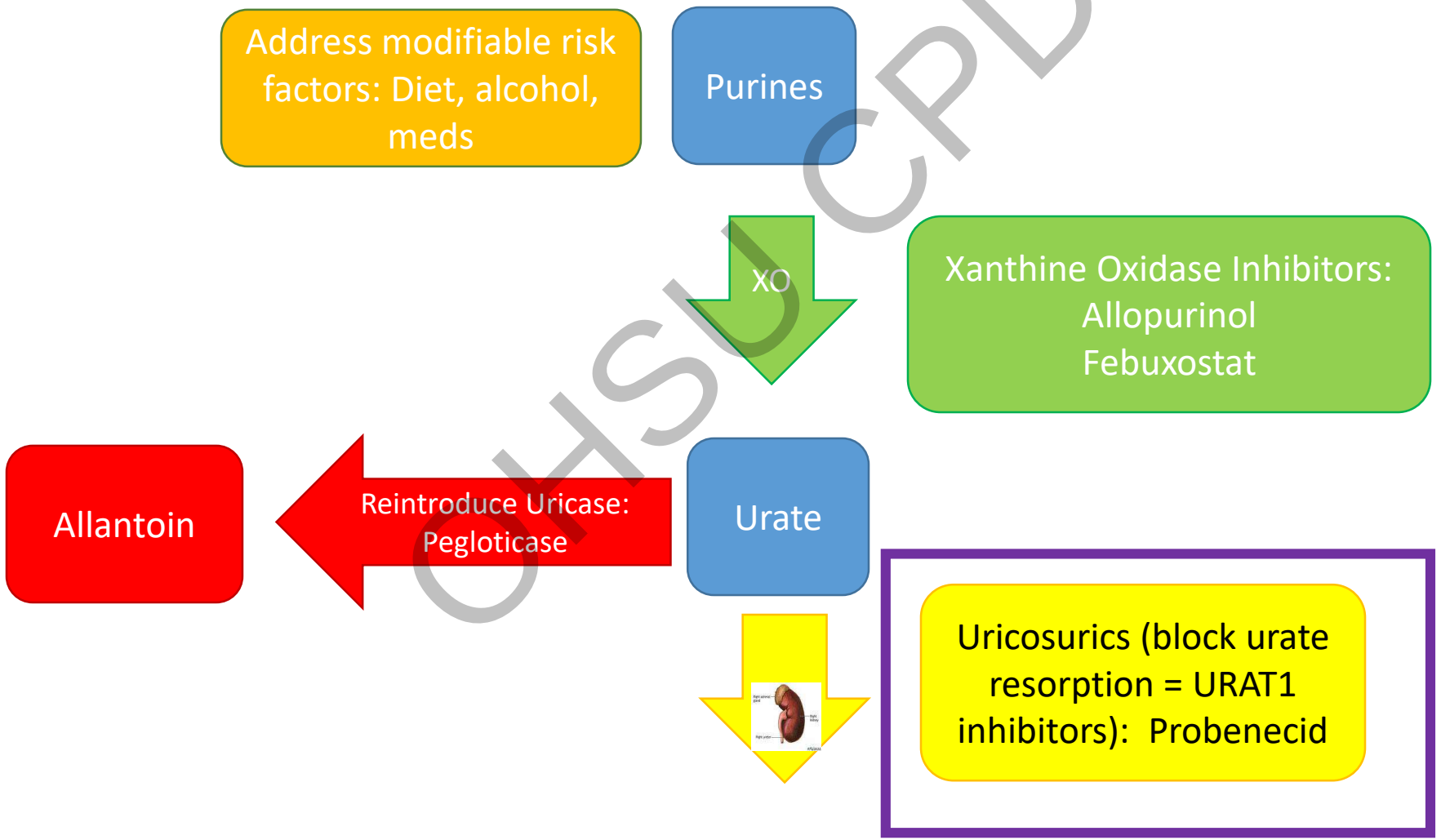
White et al. CARES Trial. NEJM 2018; Mackenzie et al. FAST Trial. Lancet 2020

STOP-Gout Trial: Allopurinol vs. Febuxostat



O'Dell et al. STOP_Gout. NEJM Evidence 2022

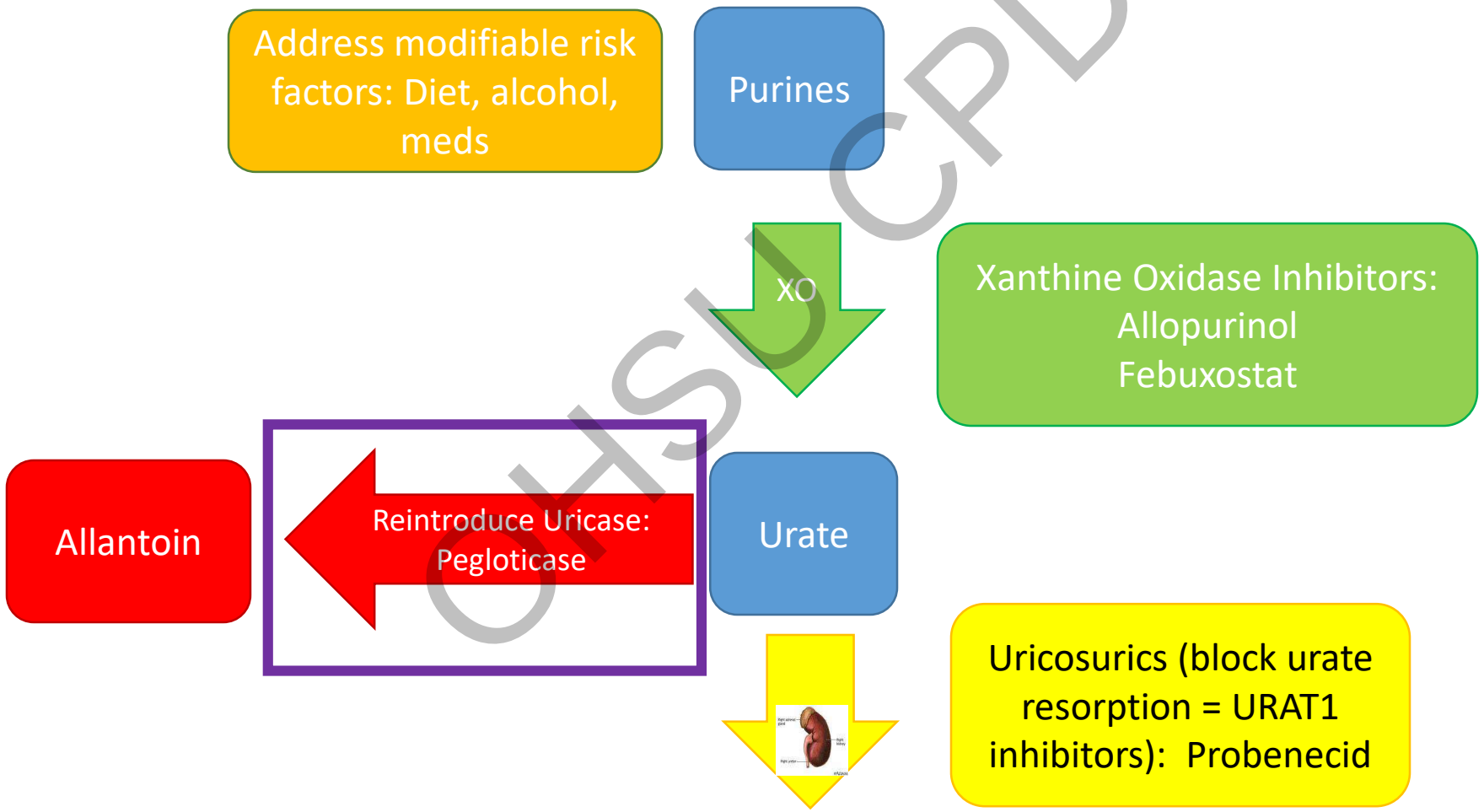
Targeting hyperuricemia to prevent flares is key!



Probenecid- Second line ULT

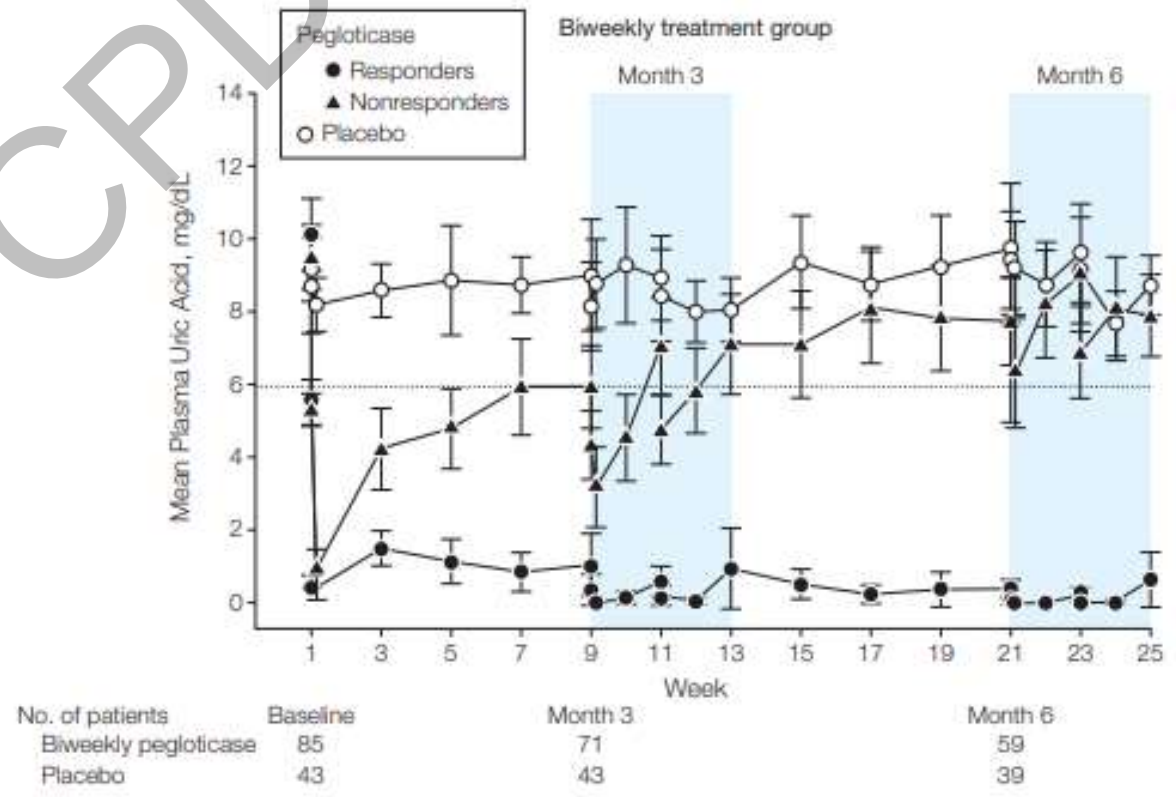
- URAT-1 inhibitor, so increases urinary excretion of uric acid
- Seems like we should use it in everyone then
- But… much less effective GFR <60 and…
  - BID dosing
  - Drug-drug interactions
  - Risk of nephrolithiasis (need to check baseline 24 hour urine uric acid excretion; not to be used if > 800 mg per 24 hours)
  - More expensive than allopurinol
- Can be combined with allopurinol or febuxostat

Targeting hyperuricemia to prevent flares is key!



Pegloticase

- Recombinant uricase
- Infusion, 8 mg every 2 weeks IV
- Uric acid drop dramatically to 0.5-1mg/dl and tophi will shrink
- High risk of allergic and anaphylactic reaction
  - Risk reduced by combining it with methotrexate or mycophenolate
- Expensive
- Reserved for severe, refractory, tophaceous gout
- May be used for 6-12 months then transition back to oral agent



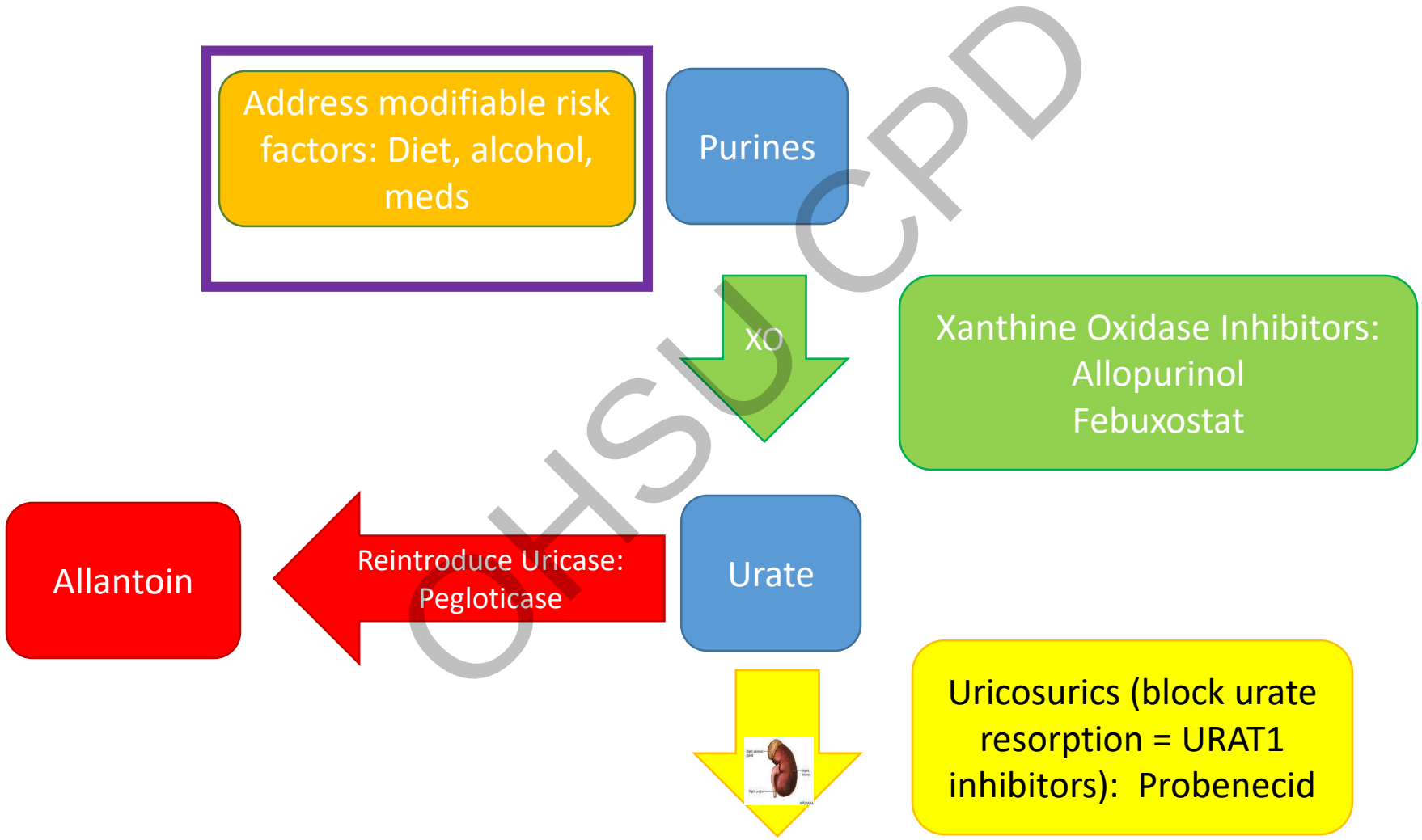
Sundy et al. JAMA, 2011

Dramatic resolution of tophus with pegloticase

70 yo man with 25 yr h/o gout and nephrolithiasis, allergic to allopurinol received 8mg IV q 2 weeks for 12 wks. Uric acid level fell from 9.3 to <0.1 and remain that low even 2 weeks post last infusion.

Baraf et al *A&R* 2008; 11:3632.

Targeting hyperuricemia to prevent flares is key!

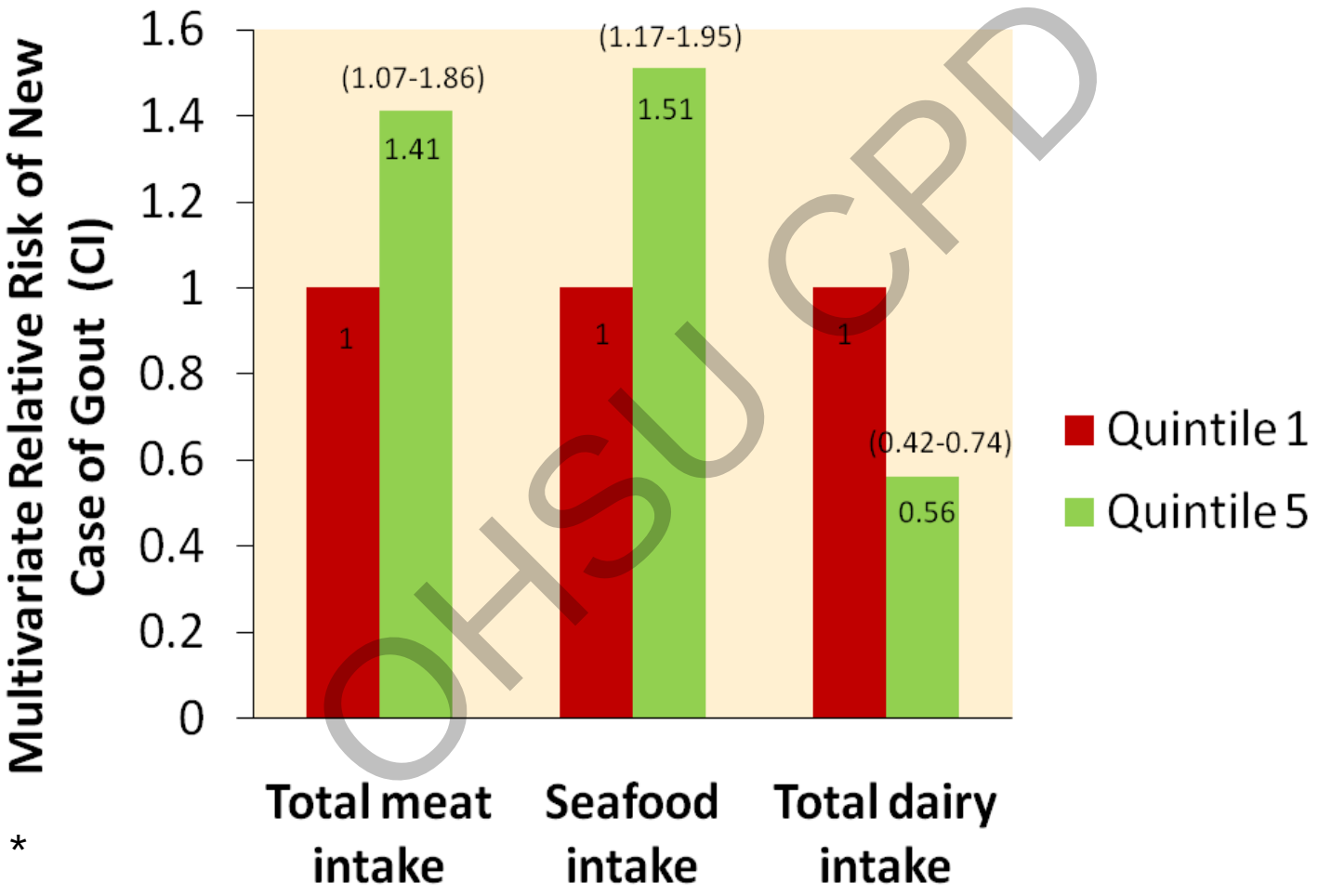


Diet and gout

- Reduce red meat (including organ meat)
- Reduce shellfish
- Reduce alcohol
- Reduce high fructose drinks and fruit juices
- Increase low fat milk and vegetables

Choi et al. Health Professionals Follow-Up Study *NEJM* 2004; 350:1093

High meat and seafood intake associated with gout risk



*

* Adjusted for age, total energy intake, body-mass index, use of diuretics, presence or absence of a history of hypertension,presence or absence of a history of renal failure, and intake of alcohol, fluid, total meats, seafood, purine-rich vegetables, and dairy products.

Choi et al. *NEJM* 2004; 350:1093

Beer and liquor but not wine associated with sUA level

- NHANES III
  - Relationship between sUA and alcohol
  - sUA difference <u>per EtOH serving per day</u>

Alcohol Type	Multivariate Δ sUA	CI	P for trend
Beer	0.46	0.32,0.60	<0.01
Liquor	0.29	0.14,0.45	<0.01
Wine	0.04	-0.2,0.11	0.6

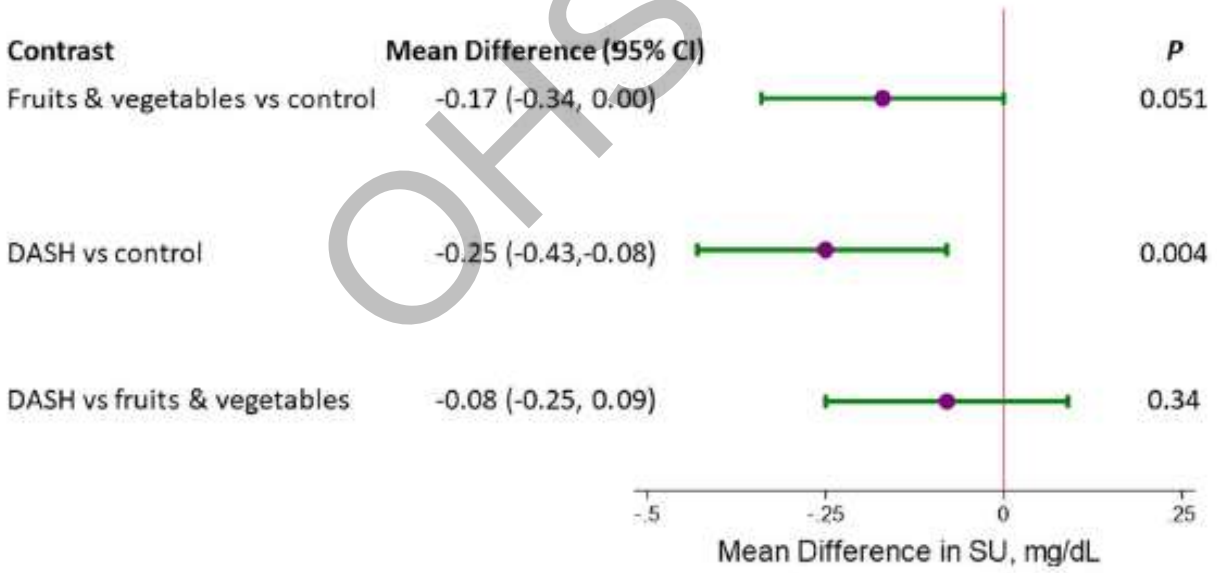
Choi and Curhan *Arth Care & Res* 2004 51:1023

American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis & Rheumatology
Vol. 73, No. 6, June 2021, pp 1014–1020
DOI 10.1002/art.41614

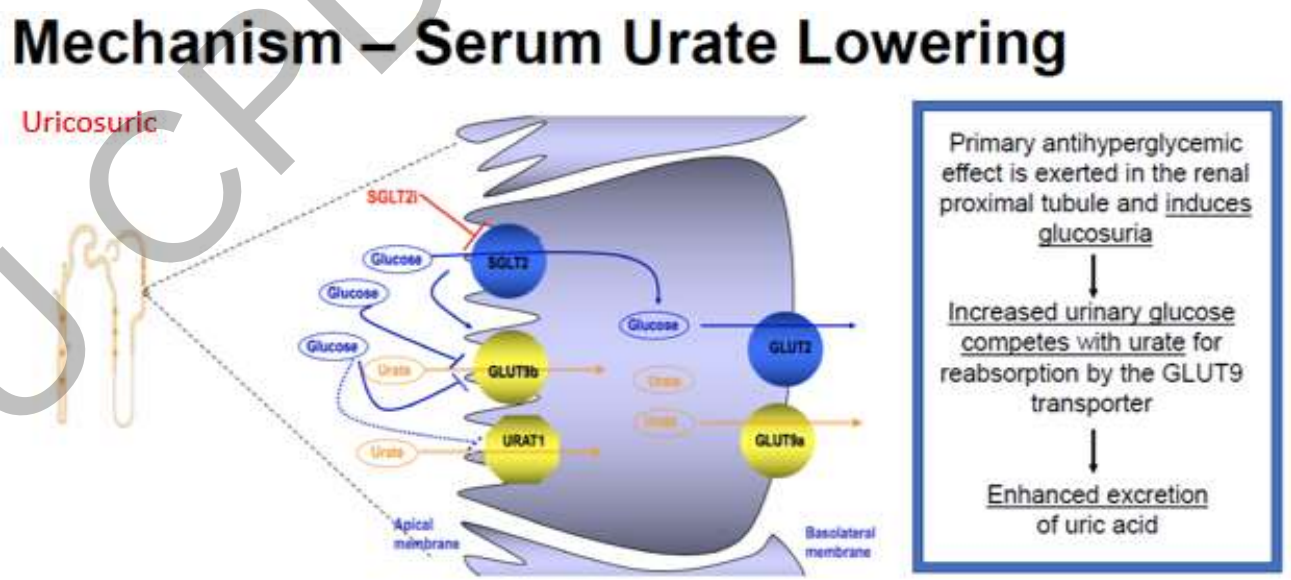
Effects of Dietary Patterns on Serum Urate: Results From a Randomized Trial of the Effects of Diet on Hypertension

Stephen P. Juraschek,[1] Chio Yokose,[2] Natalie McCormick,[2] Edgar R. Miller III,[3] Lawrence J. Appel,[3] and Hyon K. Choi[2]



Gout Comorbidities

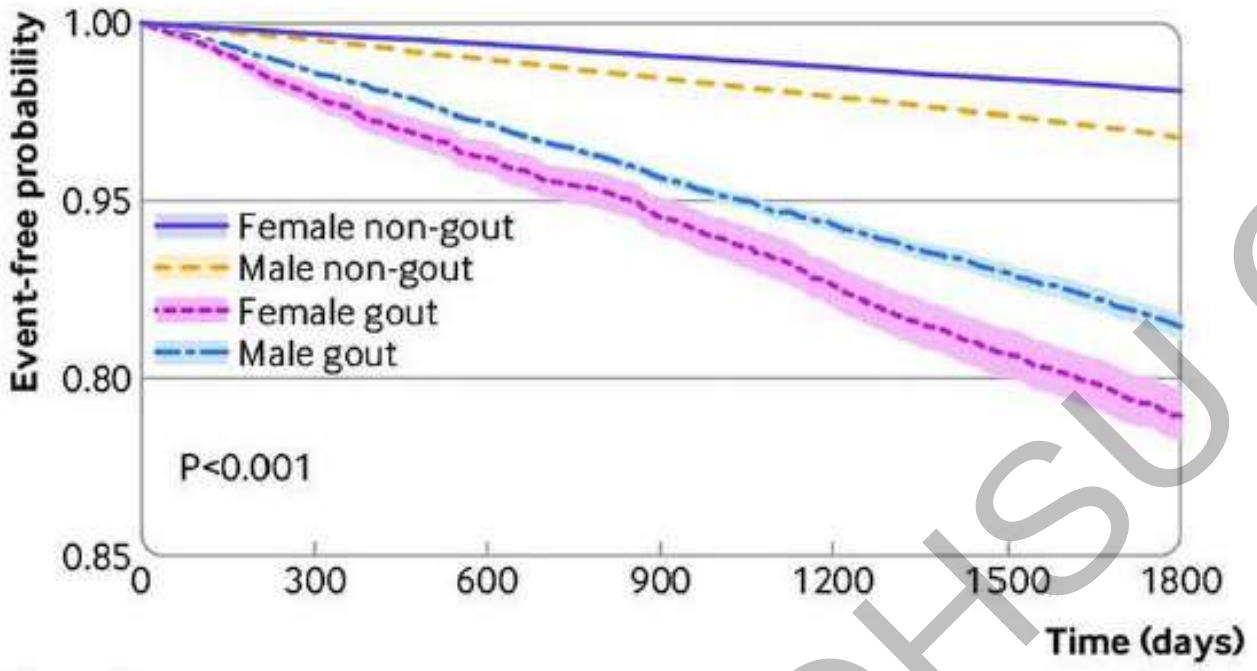
- Medication Management to help lower the sUA
  - Stop HCTZ if other agents for HTN ok
  - Losartan (not class effect of all ARBs)
  - Calcium channel blockers
  - Atorvastatin
  - Ok to continue low dose ASA
  - SGLT-2 inhibitors
- Be mindful of the increased CV risk associated with gout



Courtesy McCormick ACR Convergence 2023

CVD risk and the premature mortality gap

Gout is associated with increased risk of CV events



Study 1 million adults in NZ demonstrated lower event free probability of new onset CVD in gout vs. non-gout

Cai et al. BMJ 2022

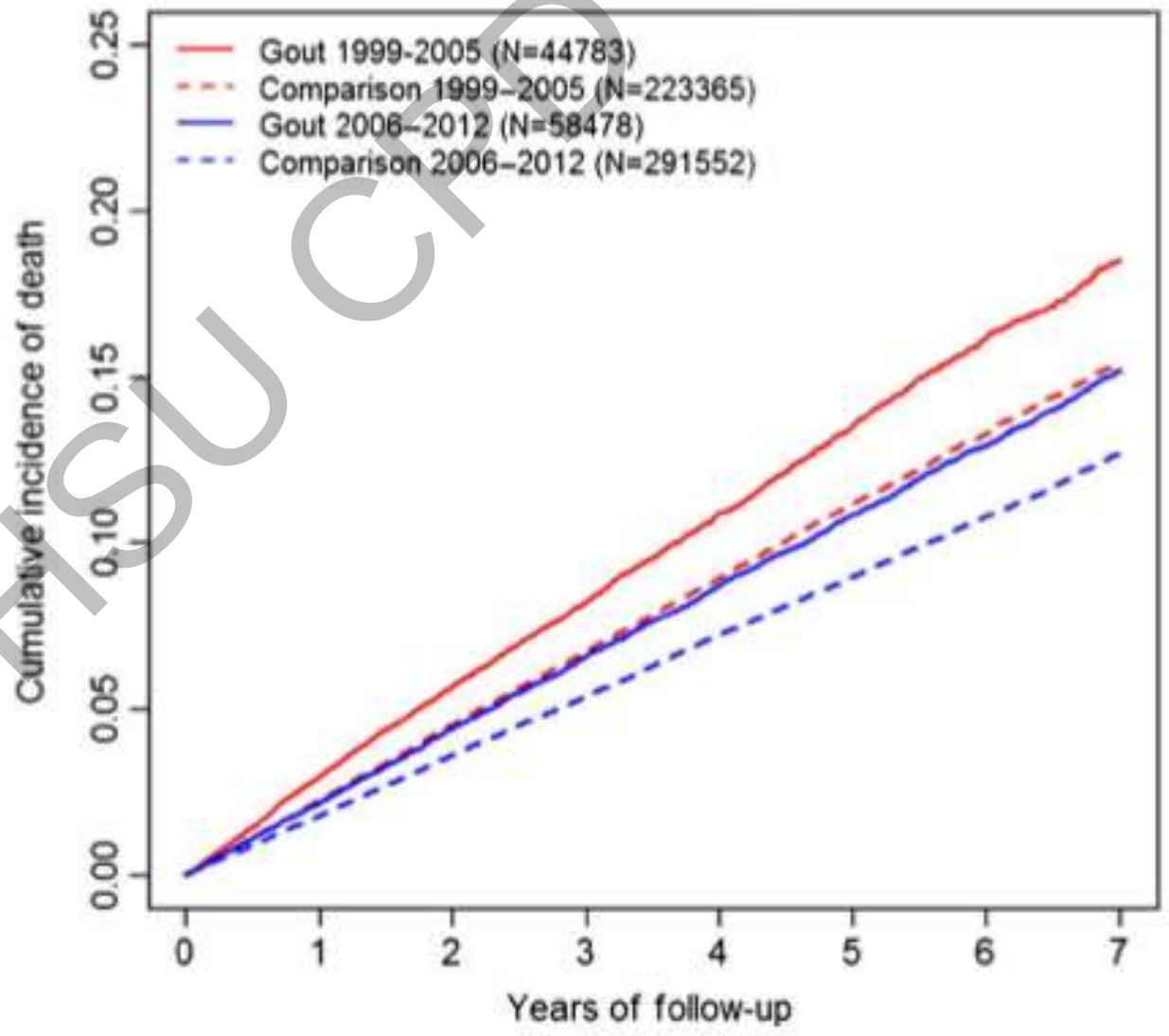
Gout associated with persistent increased mortality compared to no gout, despite advances in medical care

The increased CV risk is independent of:

- Hyperuricemia
- Traditional risk factors

Perhaps related to chronic inflammation?

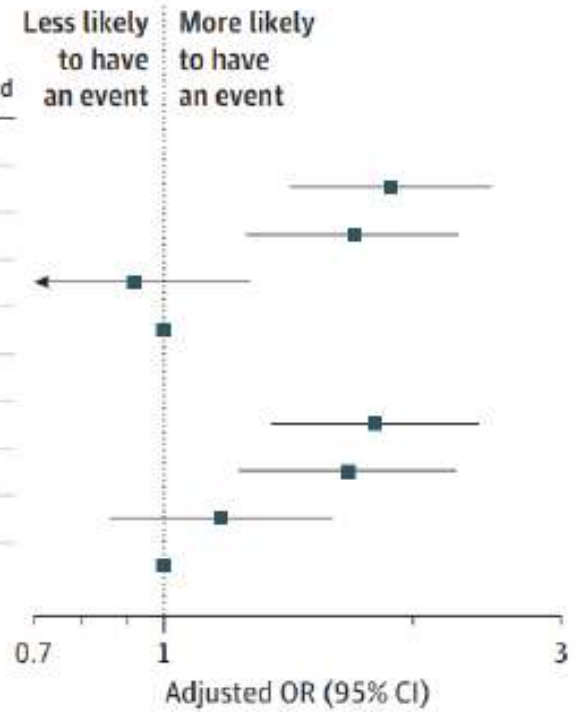
McCormick et al. ACR Convergence 2023 Plenary Abstract



Flares associated with greater risk of MI/stroke in subsequent 120 days…

Figure 3. Association Between Acute Myocardial Infarction, Stroke, and Recent Prior Gout Flares in a Nested Case-Control Study

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)[d]
Acute myocardial infarction				
0-60	116 (2.0)	743 (1.4)	0.6 (0.1 to 1.0)	1.88 (1.42 to 2.49)
61-120	103 (1.8)	628 (1.2)	0.6 (0.1 to 1.0)	1.70 (1.26 to 2.28)
121-180	77 (1.3)	662 (1.3)	0.1 (-0.3 to 0.5)	0.92 (0.67 to 1.27)
>180 d or no flare[e]	5489 (94.9)	50 066 (96.1)	-1.2 (-1.9 to -0.5)	1 [Reference]
Stroke				
0-60	102 (1.8)	743 (1.4)	0.4 (0.1 to 0.8)	1.80 (1.35 to 2.41)
61-120	88 (1.6)	628 (1.2)	0.4 (0.1 to 0.8)	1.67 (1.23 to 2.26)
121-180	81 (1.4)	662 (1.3)	0.2 (-0.2 to 0.6)	1.17 (0.86 to 1.60)
>180 d or no flare[e]	5354 (95.2)	50 066 (96.1)	-0.9 (-1.6 to -0.2)	1 [Reference]



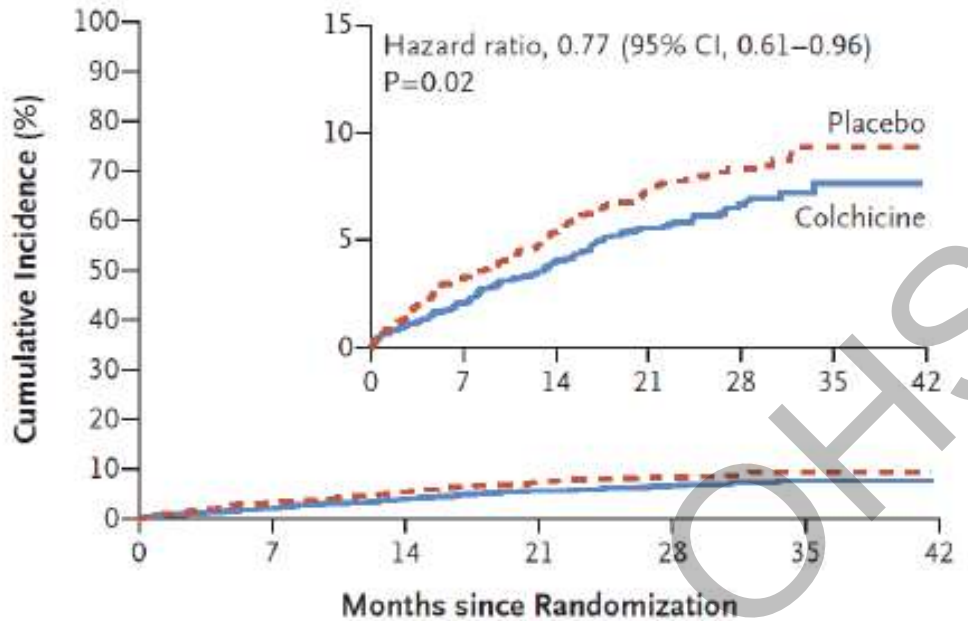
Nested case control study of patients with gout; those with MI/stroke vs those without, had greater odds of having had a gout flare in the period leading up to the index date

Cipolletta *JAMA* 2022

Cardiovascular benefits of low dose colchicine in the general population, similar benefits in gout?

Outcome: Cumulative Incidence Composite Major Adverse CV Events (MACE)

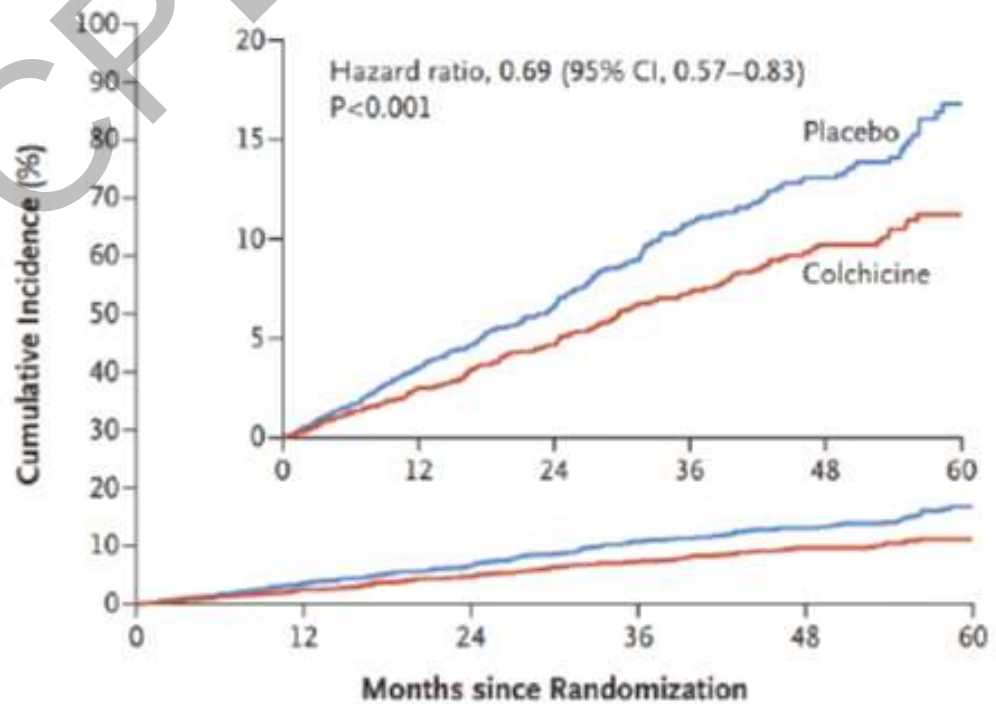
COLCOT-post MI population



No. at Risk							
Placebo	2379	2261	1854	1224	622	144	0
Colchicine	2366	2284	1868	1230	628	153	0

Tardif *NEJM* 2019

LoDoCo- stable CVD population

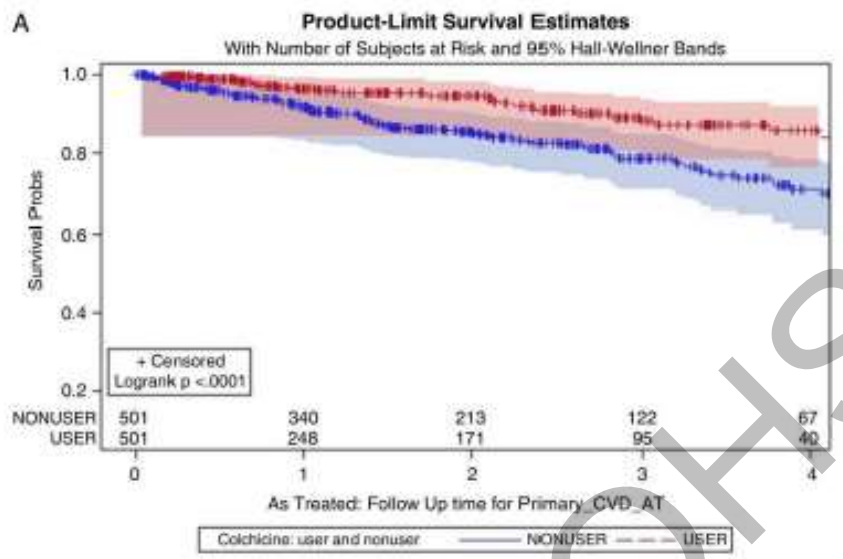


No. at Risk						
Placebo	2760	2655	1703	821	590	161
Colchicine	2762	2685	1761	890	629	166

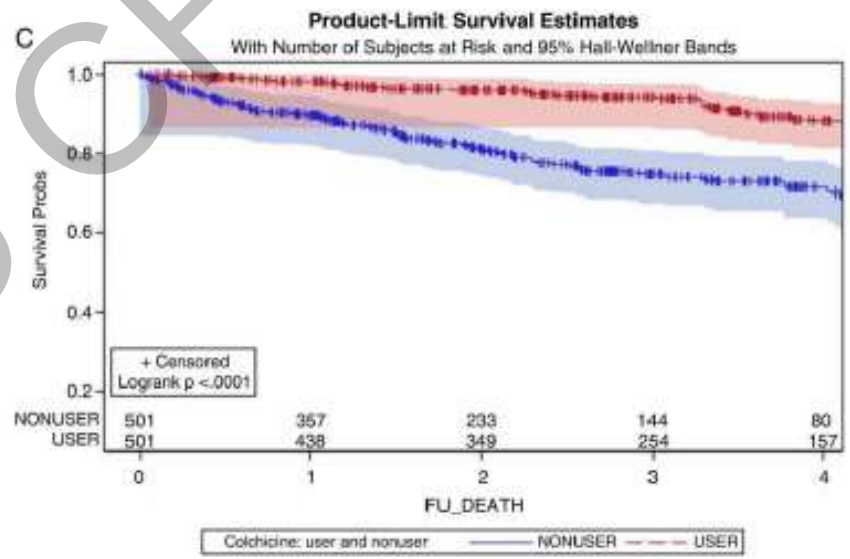
Nidorf *NEJM* 2020

Cardiovascular benefits of low dose colchicine in gout?

Composite of MI, stroke and TIA



All-cause mortality



Retrospective

Cohort study using electronic medical records linked with Medicare claims, matched 501 users with an equal number of non-users with a median follow-up of 16.5 months

Solomon *Ann Rheum Dis* 2016

Take Home Messages

- Educate patients about treatment goals
- Treat acute flare, but also manage hyperuricemia
- Don't stop urate lowering therapy
- Especially not in a flare
- Don't forget a prophylactic anti-inflammatory when starting ULT (~6 months or until sUA at target & no flares)
- Treat-to-target sUA <6 mg/dl
- Check a yearly sUA to ensure continued adherence

When to refer gout patients to rheumatology?

- Establishing diagnosis in atypical cases
- Managing refractory acute gouty arthritis
- Inability to reach target sUA despite titration of ULT
- Gout & CKD, where medication up-titration may be more challenging
- Adverse reactions to oral ULT and considering pegloticase

The Gout, cartoon by james Gillray (1799)

Origin of the gout, cartoon by Henry Bunbury (1786)

Questions?

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