Crystal arthritis: an overview

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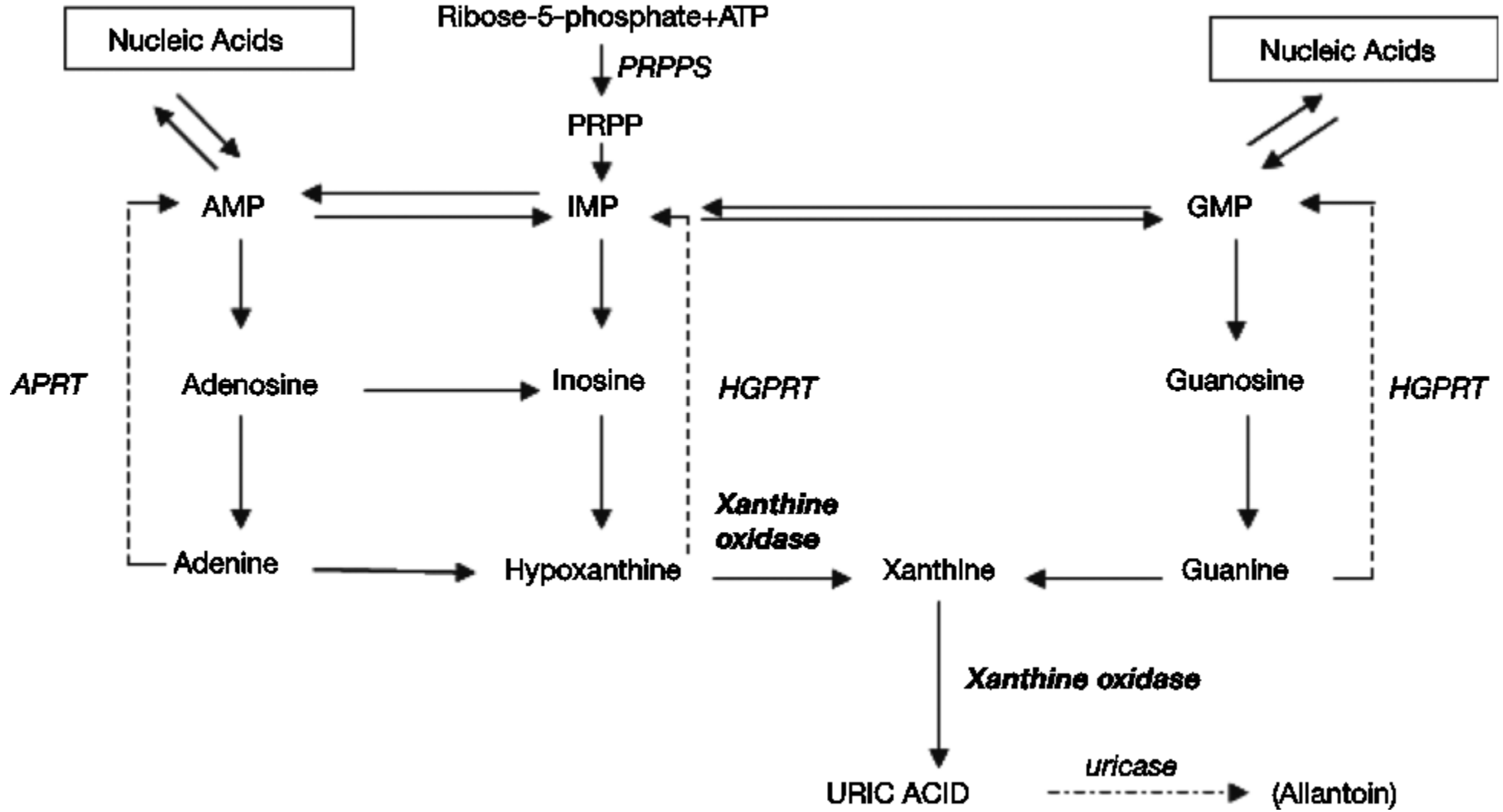
Objectives

- Purine metabolism and hyperuricemia
- Gout clinical features and its love for comorbidities
- Gout: acute phase treatments
- Current practice in the management of gout and CKD
- Current practice in the management of gout and cardiac disease
- What's new in gout?
- CPPD arthritis and latest EBM

The origin of gout

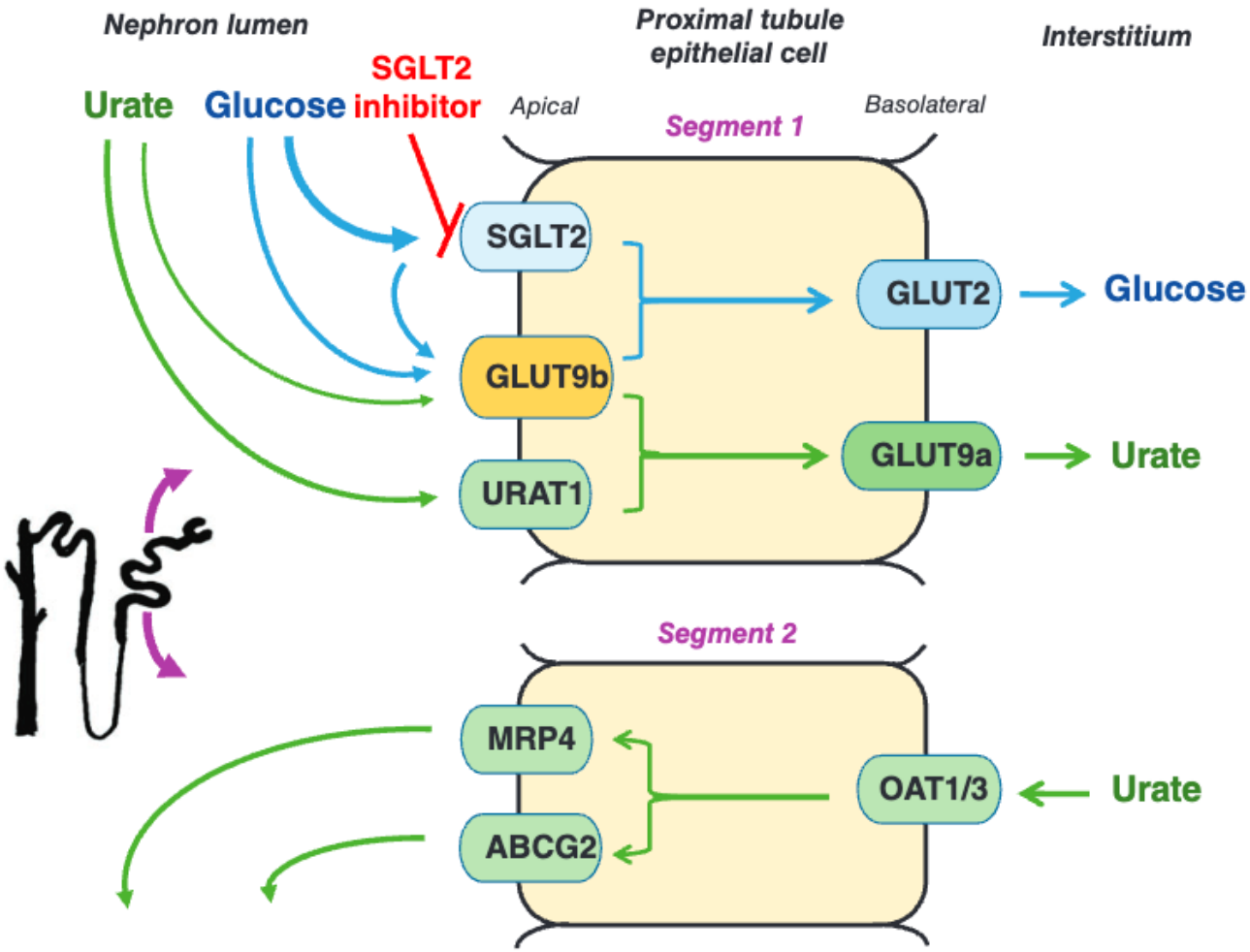
- Acute gout symptoms first recognized by the Egyptians in 2640 BC
- Described by the Greeks in 400 BC as Podagra (Pous = foot, agra = seizure)
- Believed that when there is disequilibrium in the 4 humours (black and yellow bile, phlegm, blood), one of these will drop or flow into the joint
- Gout derived from “Gutta” = drop


Nucleic Acids
Ribose-5-phosphate+ATP
PRPPS
PRPP
Nucleic Acids
AMP
IMP
GMP
APRT
Adenosine
Inosine
HGPRT
Guanosine
HGPRT
Xanthine oxidase
Adenine
Hypoxanthine
Xanthine
Guanine
Xanthine oxidase
uricase
URIC ACID
(Allantoin)

Causes of hyperuricemia

- Decreased fractional excretion via kidneys
- Increased ingestion – beer, fructose rich beverages
- Increased degradation – high cell turn over in psoriasis, haematological malignancy and their treatment
- Advancing age (women tend to get raised urate post menopause)
- Genetic mutations causing increased synthesis

- Local factors for MSU crystal deposition:
  - Osteoarthritis- cartilage damage exposes collagen fibres which may act as templates for epitaxial formation, prompting MSU crystal nucleation and growth
  - Colder temperature – MSU crystal formation in ear helix and distal joints



Schematic representation of renal tubular cell showing the location of organic anion transporters and direction of of uric acid transport

Bailey CJ. Diabetes Obes Metab. 2019 Jun;21(6):1291-1298

All about gout and diet

Bad guys

- Large epidemiological studies confirm the following to be associated with hyperuricemia and gout:
  - Higher levels of consumption of meat, seafood, sugar-sweetened soft drinks, fructose, alcohol (particularly beer)
  - Western dietary patterns (higher intake of red and processed meats, sugar-sweetened beverages, sweets, desserts, French fries and refined grains)

https://www.ukgoutsociety.org/docs/goutsociety-allaboutgoutanddiet-0113.pdf

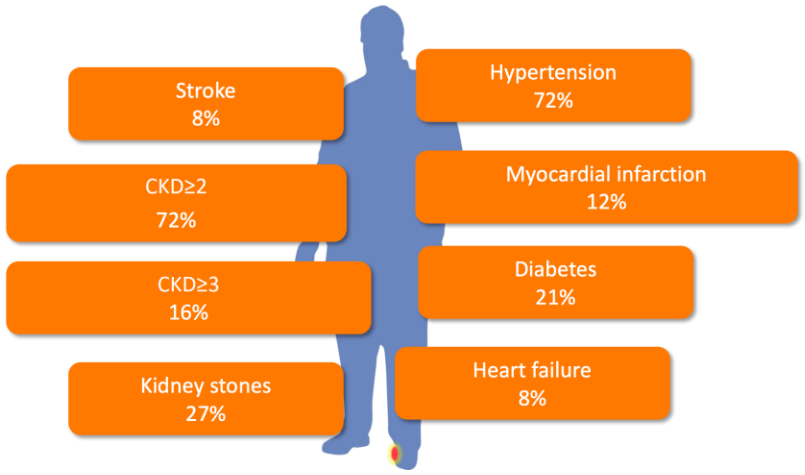
Good guys

Dairy products

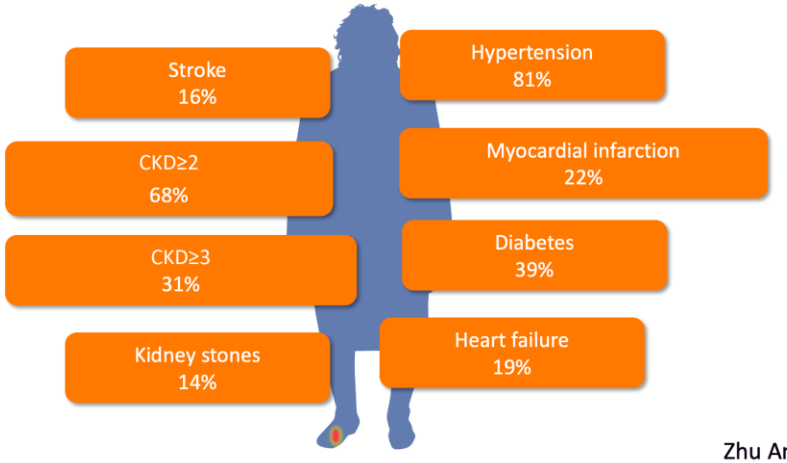
Coffee

Vitamin C

Men



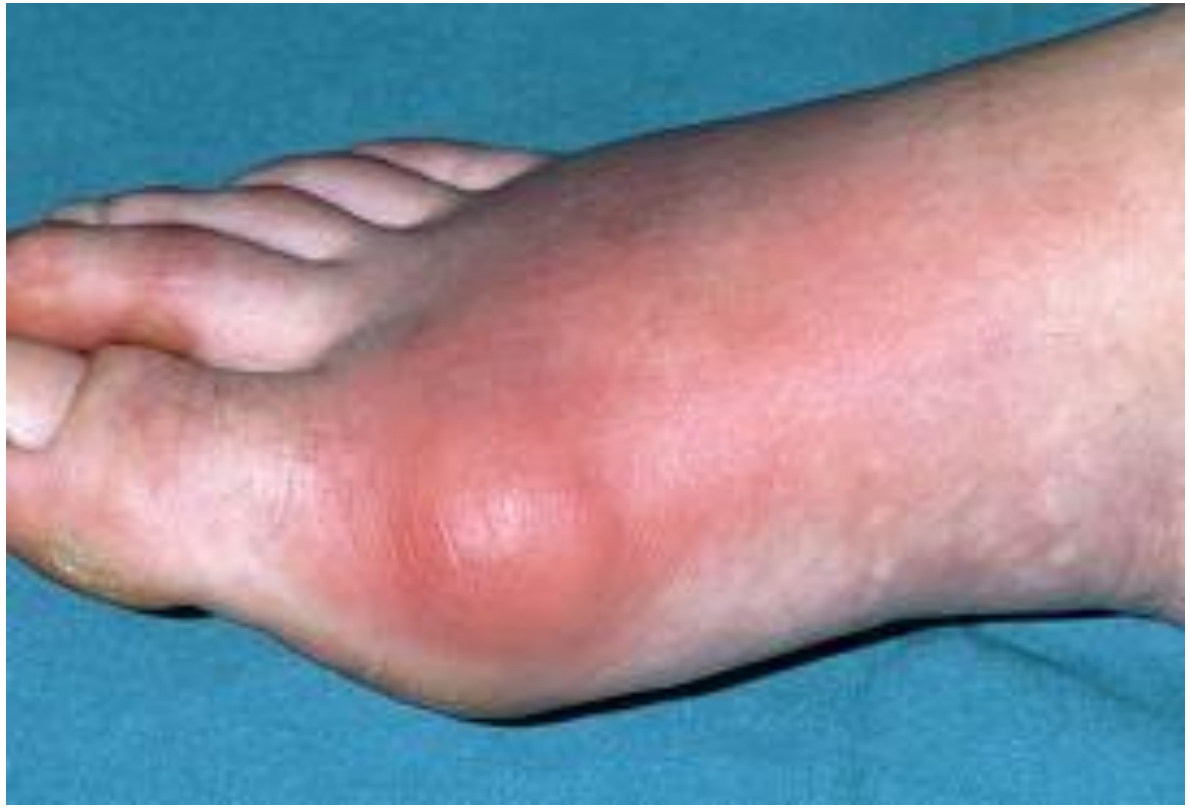
Women

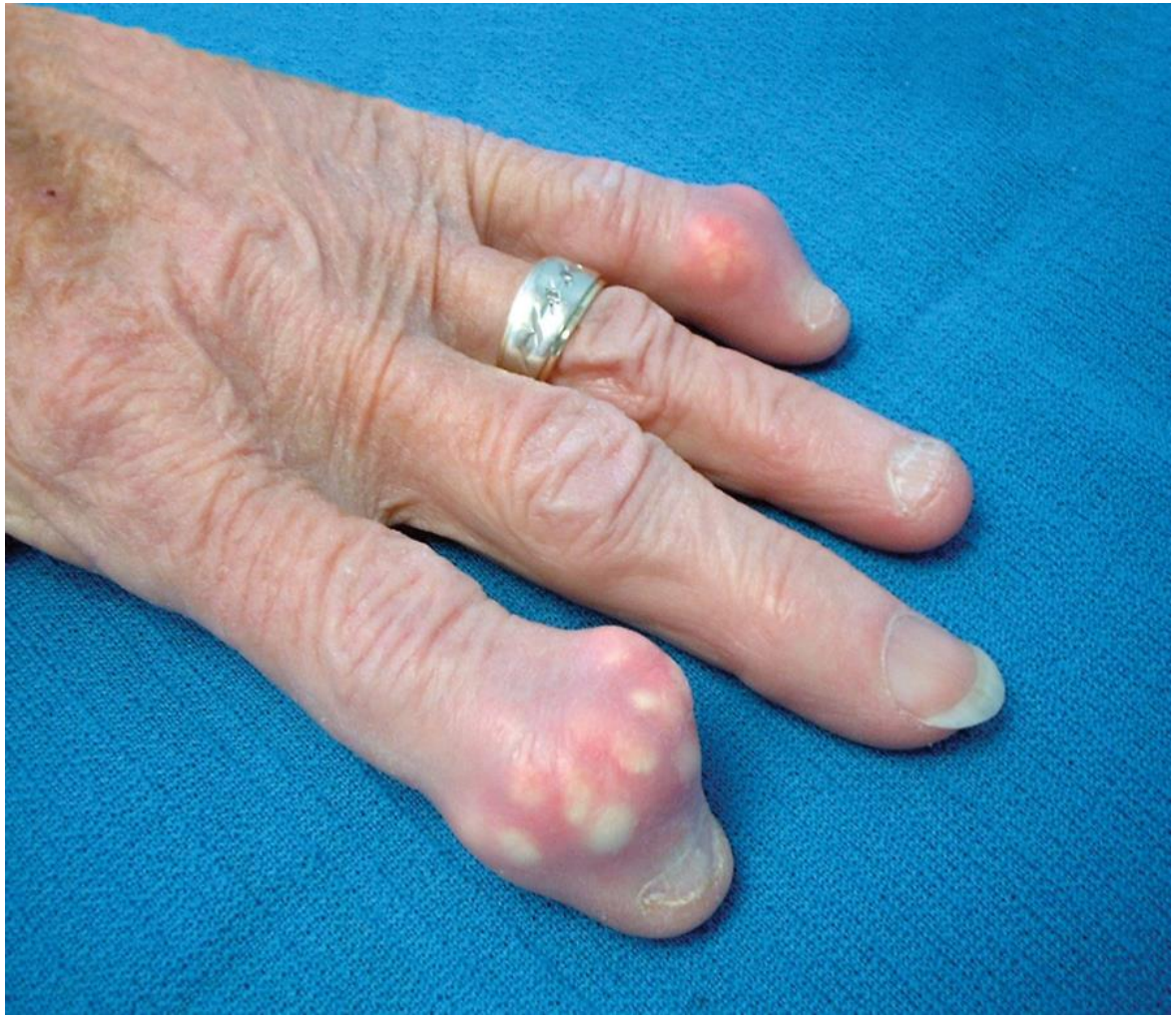


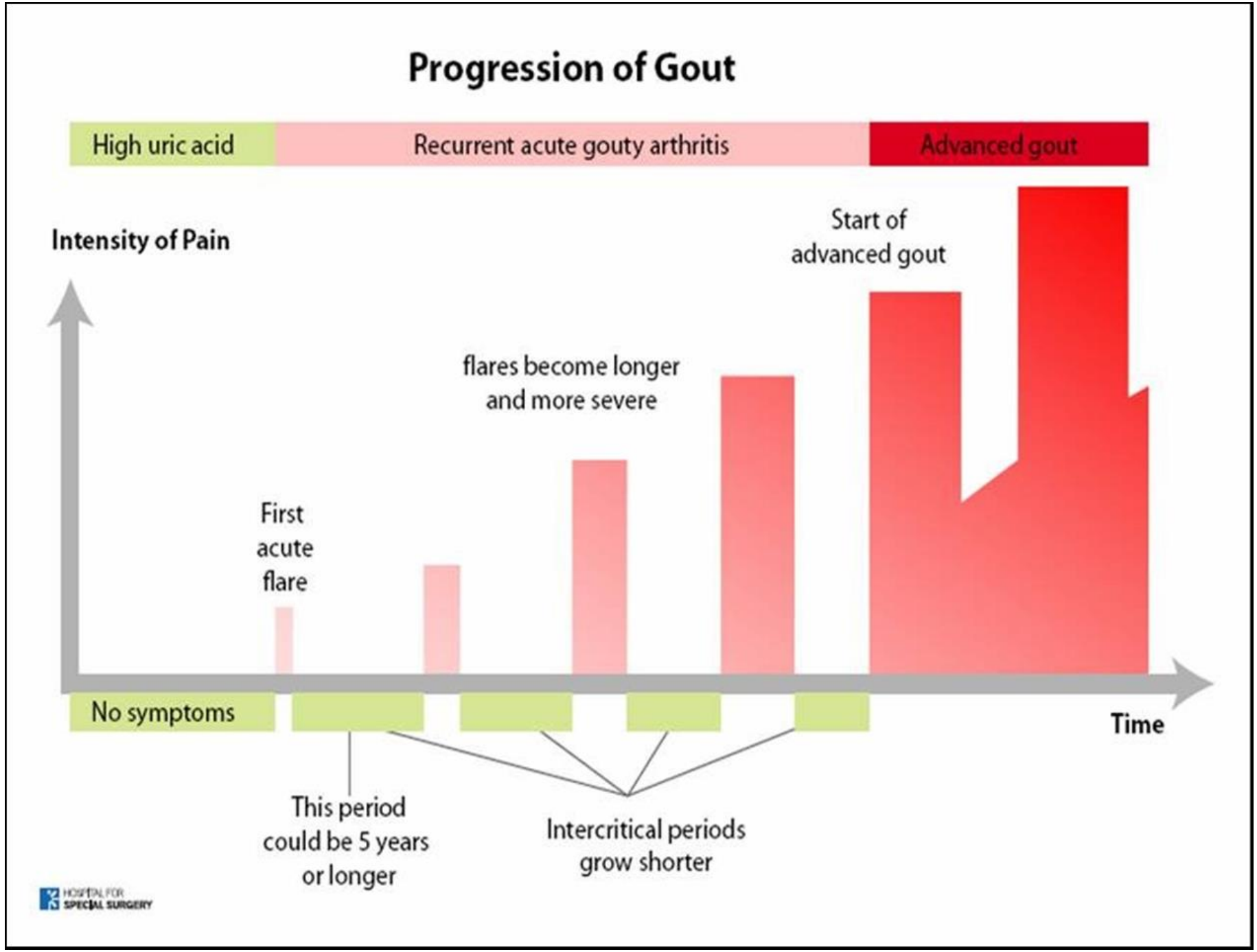
Zhu Am J Med 2012

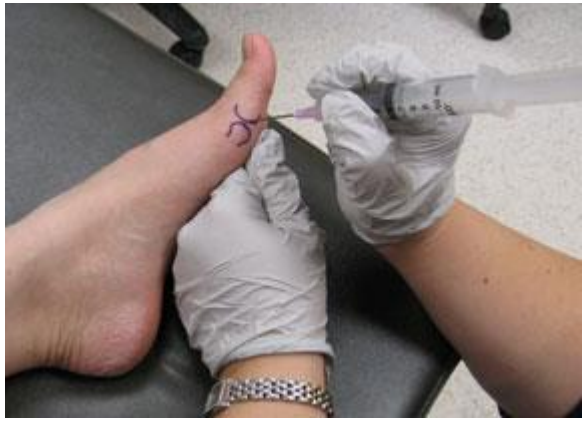
Trigger for acute gout?

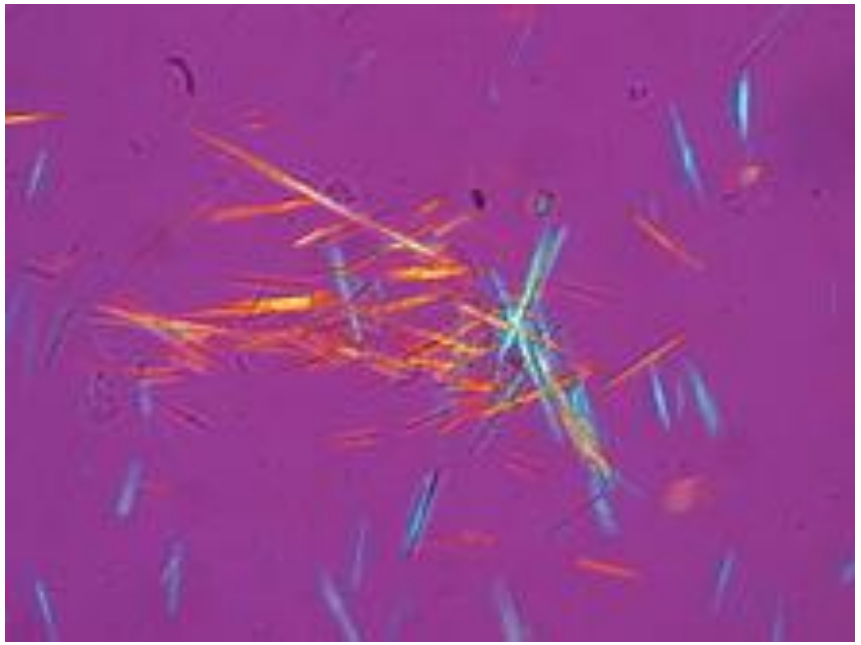
- Shedding of MSU crystals into the joint cavity from surrounding tissues
- Early in the development of the attack, MSU crystals activate monocytes and macrophages
- Influx of neutrophils into joint cavity
- Release of cytokines which promote inflammatory cascade
- MSU crystals activate NLRP3-inflammasome, a multimolecular intracellular complex that converts pro-interleukin (IL)-1 and pro-IL-18 into their active forms
- Attacks are self limiting ? MSU switch from producing pro to anti inflammatory cytokines






Progression of Gout
High uric acid
Recurrent acute gouty arthritis
Advanced gout
Intensity of Pain
Start of advanced gout
flares become longer and more severe
First acute flare
No symptoms
Time
This period could be 5 years or longer
Intercritical periods grow shorter
HOSPITAL FOR SPECIAL SURGERY





Negatively birefringent

Imaging in gout

US

Non-specific signs including synovitis, joint effusion, synovial hypertrophy and erosions

Highly specific (90%) signs: the double contour sign, tophus and aggregates

However DC can occur in CPPD as pseudo DC sign (calcifications maybe seen within the annular ligament but not the surface of the hyaline cartilage)

DECT

DECT relies on the combined attenuation properties of two X-ray beams of different energies projected at right angles

Difference in attenuation of the analyzed tissue allows for distinguishing urate and calcium in soft tissues surrounding bone

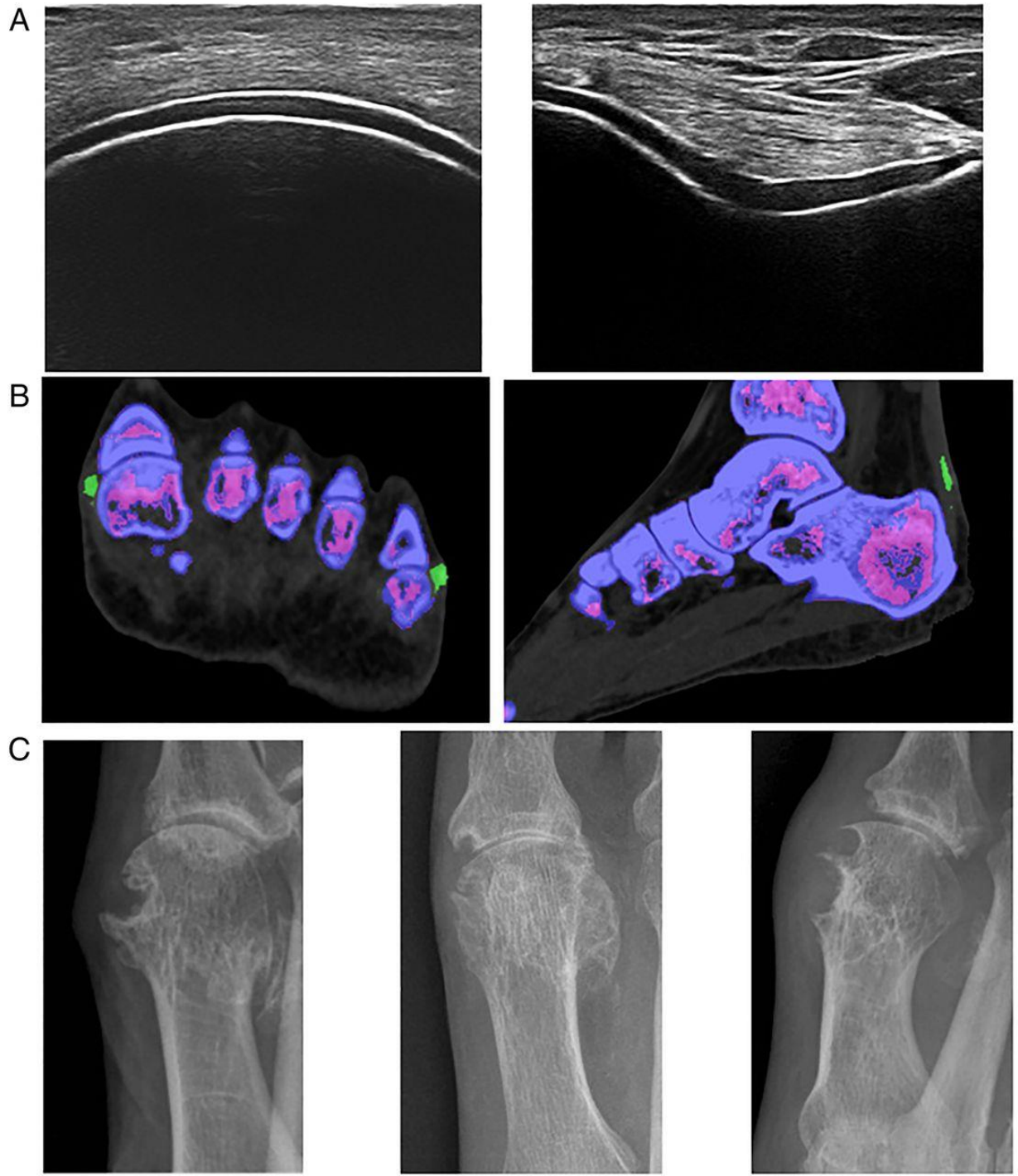
DECT allows color coded identification of MSU and CPP crystals in joints and soft tissues

Provides an automatic calculation of MSU crystal volume that could be useful for quantitative analysis

DECT detects all MSU crystal load but not DCS

Sensitivity lower in early disease (overall up to 97% sensitive and 95% specific)

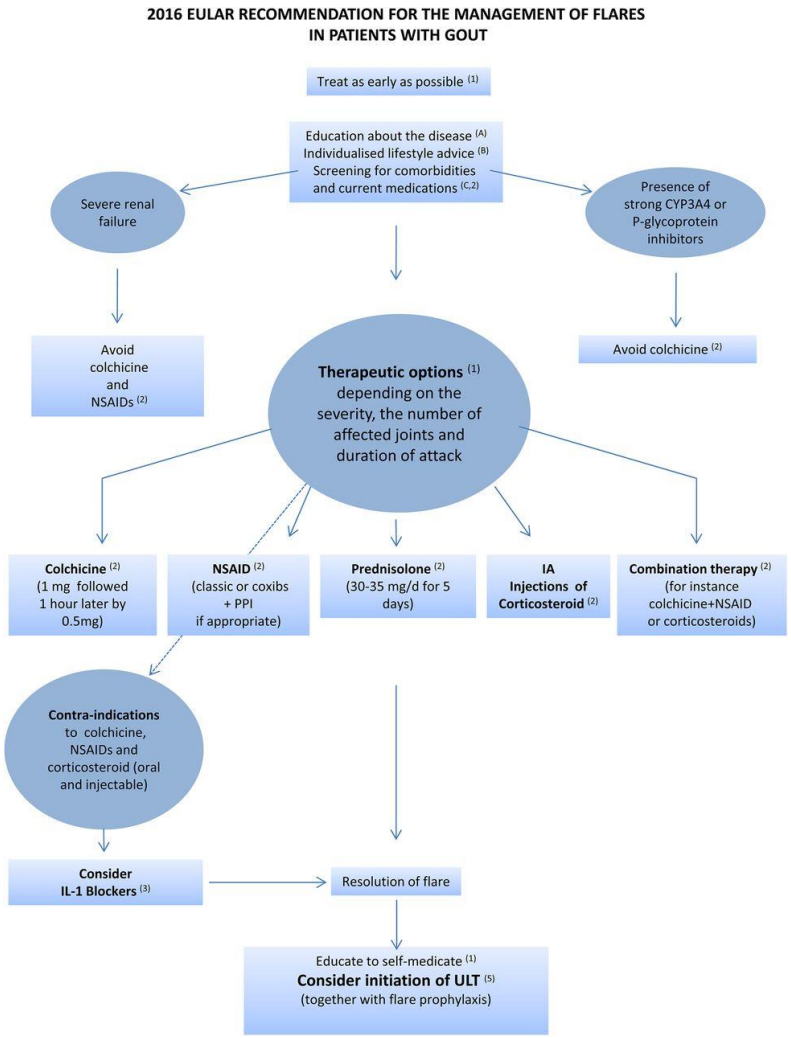
Possible correlation between MSU crystal burden and CV/ renal disease


A
B
C

Overarching principles of treatment

- Every person with gout should receive advice regarding lifestyle: Weight loss
  - Avoidance of alcohol (especially beer and spirits) and sugar-sweetened drinks
  - Excessive intake of meat and seafood
  - Low-fat dairy products should be encouraged
  - Regular exercise should be advised
- Systematically screened for associated comorbidities and cardiovascular risk factors:
  - renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidemia, hypertension, diabetes and smoking

Management of acute flare according to the European League Against Rheumatism recommendations.



P Richette et al. Ann Rheum Dis 2017;76:29-42

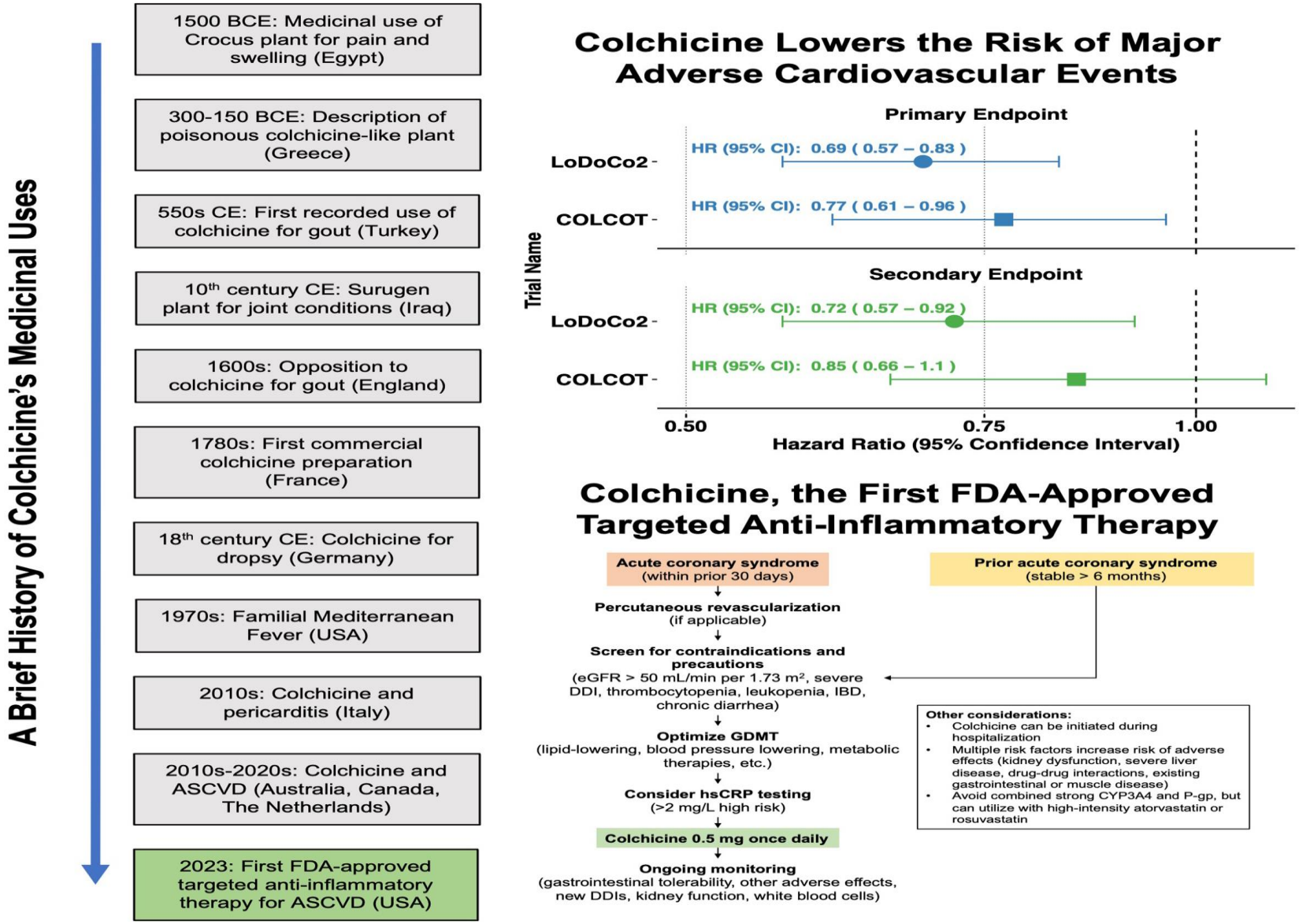
ARD

Treatment of acute gout in comorbidities

	CKD	CCF
NSAIDs	X	X
Colchicine	Renal dosing	FDA approved as first line
Steroids	Short course	Short course
Canakinumab	Reduced the risk of new flares compared with TA in pts with CKD stage 3 or worse	Superior to Triamcinolone in stable CAD
Anakinra	Higher half life in CKD, dose alt days <GFR 30	No adverse effects (no effect on cardiac function)

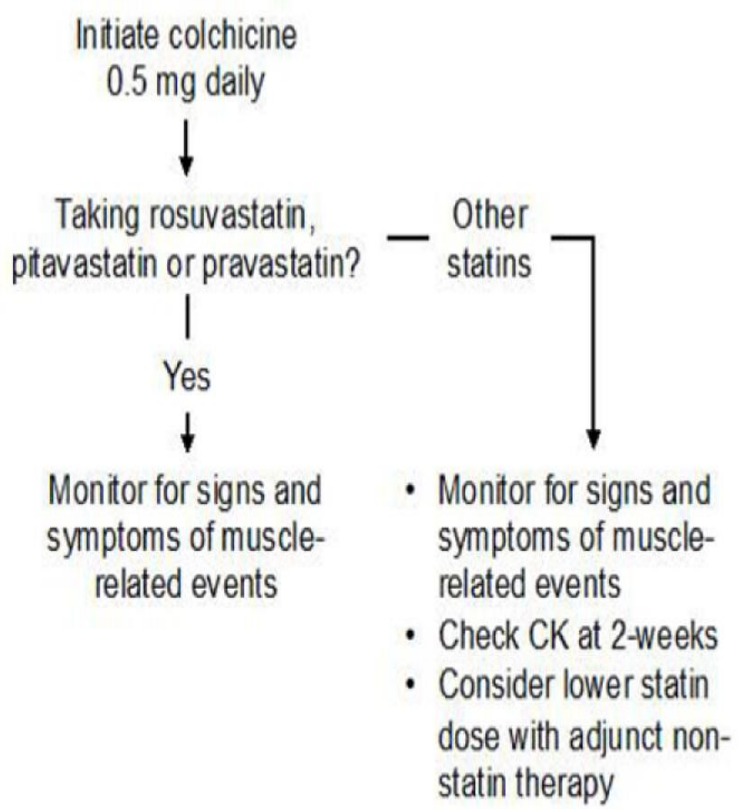
Colchicine half life x 2-3 in CKD
Colchicine is NOT removed by HD

McKenzie BJ, et al. Cochrane Database of Systematic Reviews 2021; CD006190. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022352s017lbl.pdf
Abdellatif AA, et al. Am J Ther 2014;21:523
Schlesinger N, et al. Ann Rheum Dis 2012;71:1839
Mouradjian MT, et al. Am J Cardiovasc Drugs 2020;20:431, Sunkureddi P, et al. Ann Rheum Dis. 2013;2013:447.
Mahfooz K et al. Med Sci (Basel). 2022 Dec 26;11(1):4



Leo F. Buckley. Arteriosclerosis, Thrombosis, and Vascular Biology. Colchicine's Role in Cardiovascular Disease Management, Volume: 44, Issue: 5, Pages: 1031-1041, DOI: (10.1161/ATVBAHA.124.319851)

Statin-Colchicine Drug-Drug Interaction



Other Colchicine Drug-Drug Interactions

Evaluate*:

- Potential severity and duration of drug-drug interaction
- Potential consequences of stopping colchicine
- Other risk factors for adverse events related to colchicine or interacting drug
- Availability of enhanced monitoring parameters for colchicine and interacting drug

DDI Severity	Duration of Concomitant Therapy: Short (≤14 days)	Duration of Concomitant Therapy: Intermediate-Long (>14 days)
Severe	Hold colchicine	• Stop colchicine and re-evaluate other ASCVD risk reduction options • Consider decreased colchicine dose (off-label, unstudied) or decreased dose of alternative therapy
Minor-Moderate	• Continue colchicine with enhanced monitoring • Can consider holding colchicine	Continue colchicine with enhanced monitoring

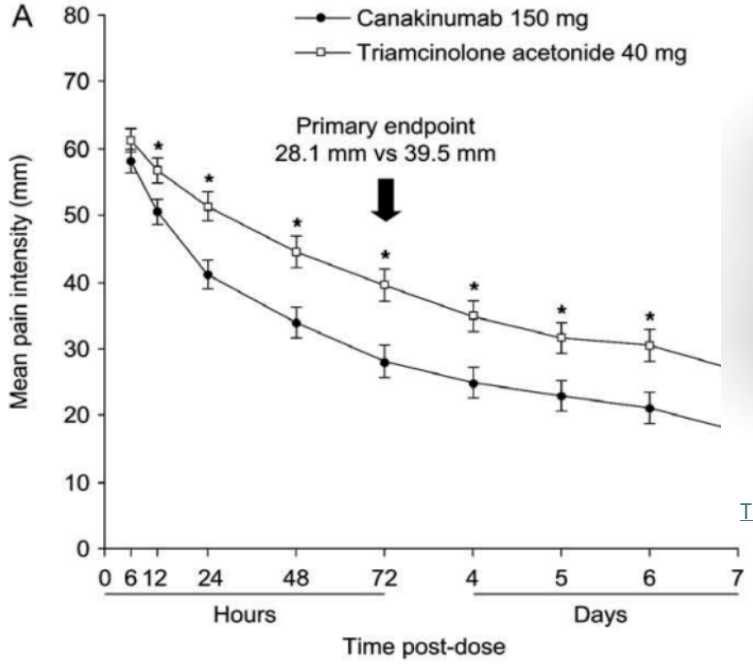
Leo F. Buckley. Arteriosclerosis, Thrombosis, and Vascular Biology. Colchicine's Role in Cardiovascular Disease Management, Volume: 44, Issue: 5, Pages: 1031-1041, DOI: (10.1161/ATVBAHA.124.319851)

Duration of prophylactic treatment

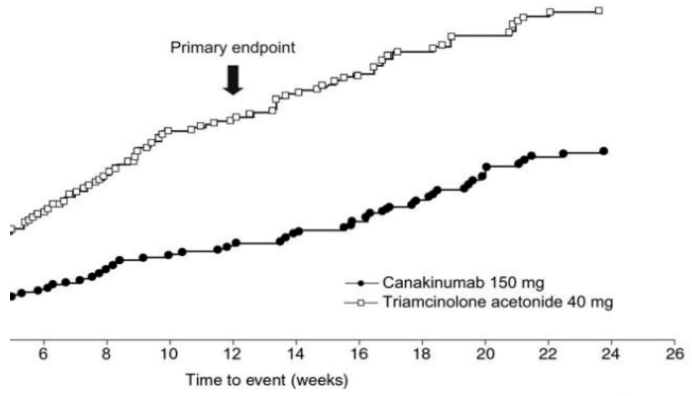
- From trials of febuxostat versus a fixed dose of allopurinol (300 mg) found that flare prophylaxis with low-dose colchicine (colchicine, 0.6 mg/day) or low-dose NSAID (naproxen, 250 mg twice daily) for up to 6 months appeared to provide greater benefit than flare prophylaxis for 8 weeks, with no increase in adverse events
- May however have to avoid NSAID depending on comoribidities
- May have to lower colchicine dose/ duration depending on CKD stage, DDI with p glycoprotein/ CYP3A4 inhibitors
- Case by case decision making

Canakinumab for treatment of acute gout flares

Gout flare treatment



Time to next gout flare



		Kaplan–Meier estimates		Cox's proportional hazard regression model		
Treatment	N	Flare probability over 24 weeks (95% CI)	Median time to new flare – days (95% CI)	Hazard ratio to triamcinolone acetonide 40 mg	95% CI	One-sided p-value
Canakinumab 150 mg s.c.	225	32.4 (26.2 – 39.5)	Not Est (Not Est – Not Est)	0.44	(0.32 – 0.60)	<0.0001
Triamcinolone acetonide 40 mg i.m.	229	56.0 (49.0 – 63.4)	131.0 (104.0 – Not Est)	–	–	–

Cox's proportional hazard regression model with treatment group and body mass index at baseline as covariates.
CI, confidence interval; i.m., intramuscular; Not Est, not estimable; s.c., subcutaneous.
Median time to new flare was not estimable in the canakinumab group because fewer than 50% of patients treated with canakinumab experienced their first flare.

Schlesinger *Ann Rheum Dis* 2012

Indications for ULT

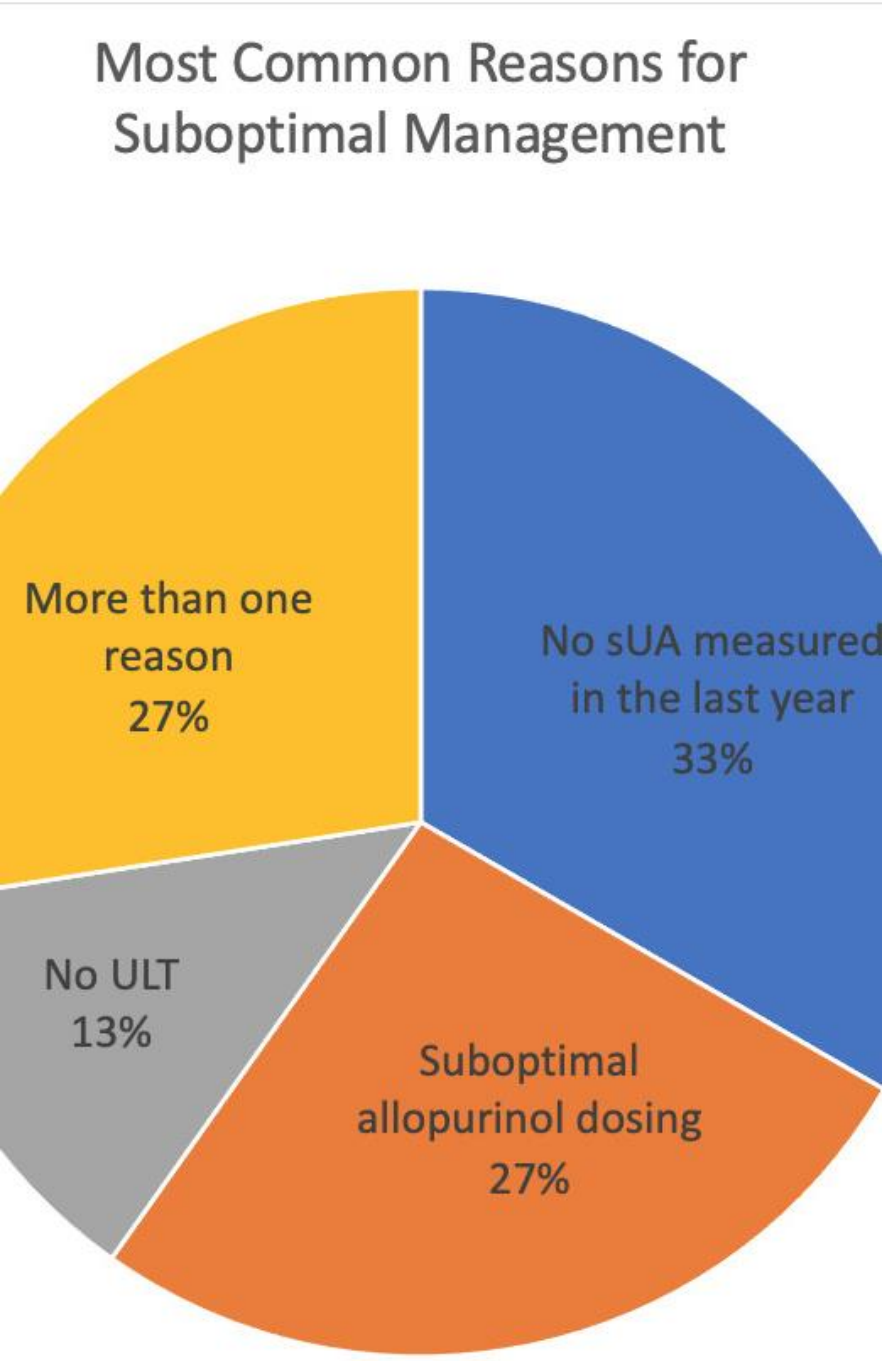
Recommendation	PICO question	Certainty of evidence
For patients with 1 or more subcutaneous tophi, we strongly recommend initiating ULT over no ULT.	1	High
For patients with radiographic damage (any modality) attributable to gout, we strongly recommend initiating ULT over no ULT.	2	Moderate
For patients 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 JD et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Care Res, 72: 744-760



Gout treatment in CKD: where are we now?

- 1 year retrospective analysis of EHR of a primary care centre
- ICD 10 codes for gout and CKD 3-5
- 121 care records manually reviewed for validity of diagnosis/investigations treatments. Benchmark: ACR 2020 guidelines for the management of gout
- 40% CKD 3, 35% CKD 4 and 25% CKD 5
- Average GFR 28.5
- Only 16% had optimal gout management as defined by ACR 2020 guidelines

Eder L, Leverenz D. Identifying and Addressing Suboptimal Urate Lowering Therapy in Gout Patients with Chronic Kidney Disease [abstract]. *Arthritis Rheumatol.* 2023; 75 (suppl 9).

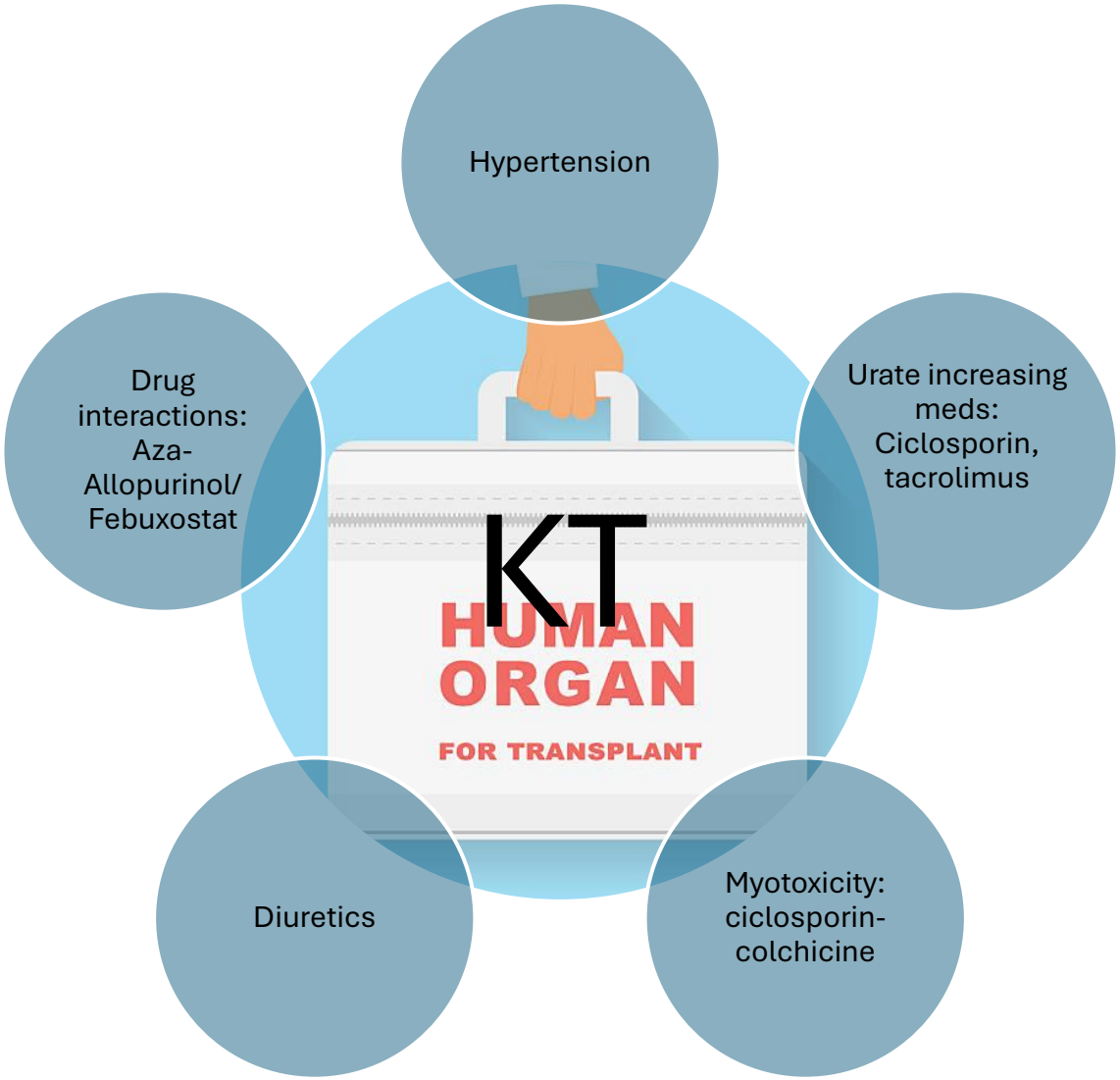
Case

68 year old female

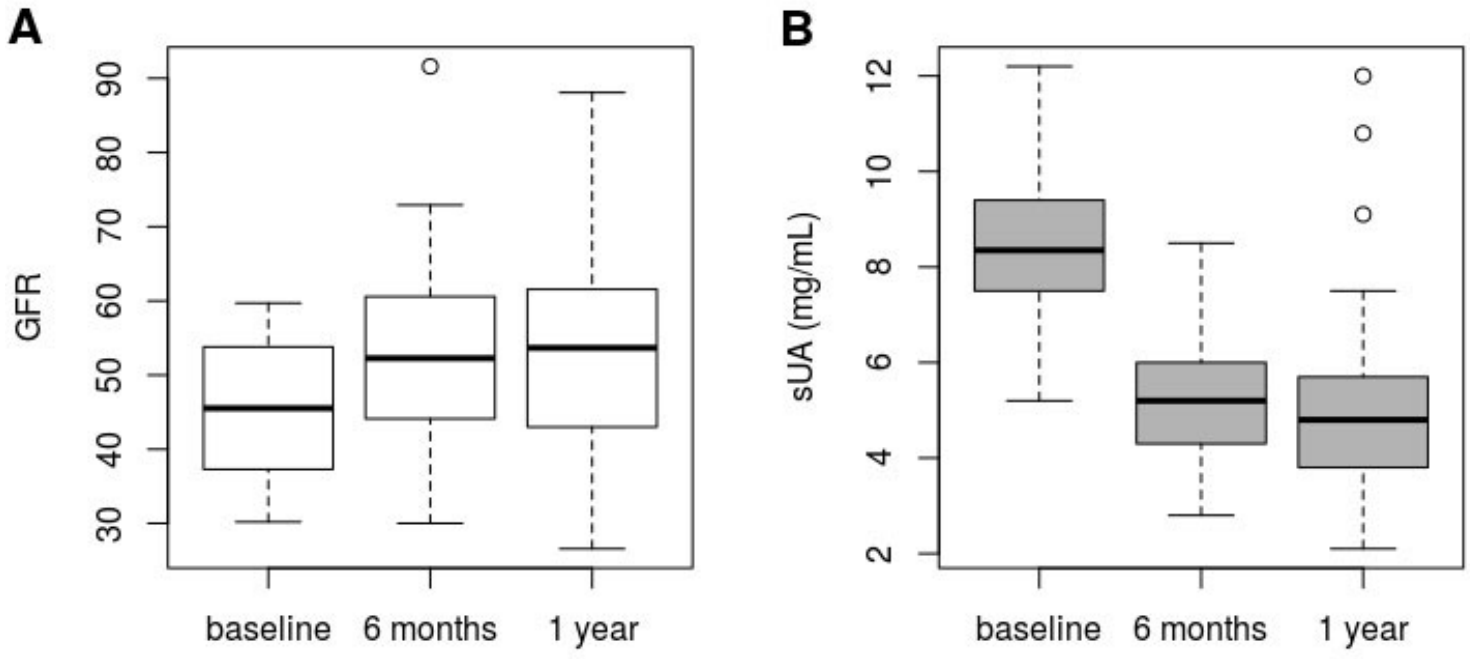
- Renal transplant 2000, hypertension
- Recurrent attacks affecting 1st MTPJs, knees, hands
- Tophi on hands
- SUA 596 µmol/L, eGFR 23 ml/min, creatinine 192 µmol/L

Current treatment:

- *azathioprine 75mg od*
- tacrolimus 1mg bd
- furosemide 80mg od
- losartan
- bisoprolol
- thyroxine
- ezetimibe
- alfacalcidol
- aspirin


Hypertension
Drug interactions: Aza-Allopurinol/ Febuxostat
Urate increasing meds: Ciclosporin, tacrolimus
KT
HUMAN ORGAN
FOR TRANSPLANT
Diuretics
Myotoxicity: ciclosporin-colchicine

T2T in gout has a renoprotective effect in moderate CKD



Randomized multi centre obs study 2014-2018

ACR/EULAR 2015 gout criteria and CKD 3 (CG calculation) GFR 30-59, treated with XOI, FU 6 and 12 months

KT/single kidney excluded

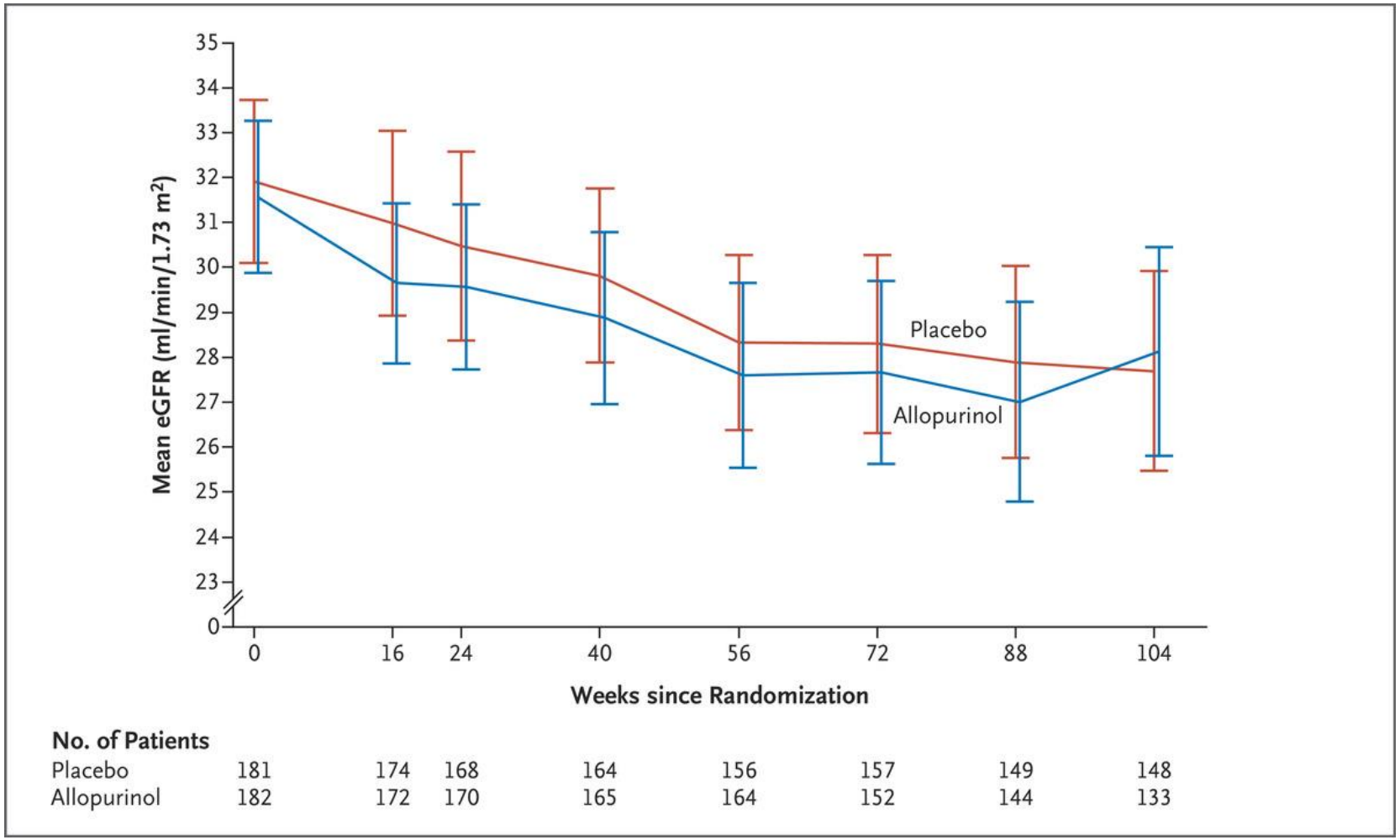
50 patients, Mean baseline sUA was 8.55±1.57 mg/dl and mean eGFR 45.52±9.21 ml/min/m2

Sig improvement in GFR in first 6 months, associated with an inverse relationship with SUA

Non smoker and males had higher GFRs, no difference b/w Febuxostat and Allopurinol

Calvo Aranda E et al. Arthritis Rheumatol. 2019; 71 (suppl 10).

Effect of Allopurinol on Estimated Glomerular Filtration Rate (eGFR) in asymptomatic hyperuricemia



SV Badve et al. N Engl J Med 2020;382:2504-2513.

The NEW ENGLAND JOURNAL of MEDICINE

Starting allopurinol in CKD

Stamp LK et al. Arthritis Rheum. 2012 Aug;64(8):2529-36

- The guidance is to start allopurinol 1.5 mg/ unit of EGFR (mL/min/1.73 m2)
- Cautious approach recommended

Estimated GFR, ml/minute/1.73 m^2	Allopurinol starting dosage
<5	50 mg/week
5–15	50 mg twice weekly
16–30	50 mg every 2 days
31–45	50 mg/day
46–60	50 mg and 100 mg on alternate days
61–90	100 mg/day
91–130	150 mg/day
>130	200 mg/day

Allopurinol maintenance dose by renal function

Creatinine clearance (ml/min)	Allopurinol (mg)
0	100m y 3 days
10	1 every 2 days
20	mg od
40	50mg od
60	g od
80	25
100	300mg
120	350mg od
140	400mg od

RISK FACTORS FOR AHS:

- Age
- Female gender
- Renal function
- Diuretic use
- Starting dose
- Recent initiation
- HLA–B*5801 genotype

Hande Am J Med 1984
Stamp Nat Rev Rheumatol 2015

HLA b5801

- HLA-B*58:01 can present the allopurinol metabolite, oxypurinol, directly to cytotoxic T cells without antigen processing
- T cell mediated cytotoxicity related to allopurinol or oxypurinol is restricted to carriers of HLA-B*58:01
- SCARs: drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis
- HLA B5801 allele is commoner in Chinese, Thai, and Korean patients
- This allele is 5 x commoner in African Americans compared to white and hispanic population
  - 3 x greater risk of SCAR in AA population compared to the others
- Screening advised in this population group
  - Reduced SCAR
  - Cost effective

- Negative predictive value of HLA-B*58:01 for allopurinol induced SCARs is 100%
- PPV is 2%
- Han Chinese people who carry HLA-B*58:01 have a much higher risk of developing allopurinol induced SCARs than those who do not carry the allele (OR 580.3; 95% confidence interval 34.4 to 9780.9; P<0.001

Ko TM et al. BMJ. 2015 Sep 23;351

Case

- 52 F, Familial hypercholesterolaemia, salivary and renal calculi (recurrent), hypertension, gout, fatty liver
- Multiple ADRs, including allopurinol previously
- DH: Fenofibrate, losartan
- sUA 544µmol/L, eGFR 52, γGT 144, ALT 92
- Freq of attack- once a year
- USS – calcific deposit at achilles tendon –tophi

What is the best treatment option here?

- Allopurinol desensitisation
- Febuxostat
- Probenecid
- Benzbromarone

Febuxostat in CKD

- Febuxostat is safe in GFR ≥ 15, and has no cross reactivity with allopurinol
- No dose adjustment needed for CrCl≥30mL/min
- As per FDA, restrict dose to 40 mg daily in for CrCl 15–29mL/min
- Limited data in advanced CKD, HD, transplant

Quilis N et al. Arthritis Rheumatol 2016;68:2563–4.
Saag KG et al. Arthritis Rheumatol 2016;68:2035–43.
Bardin T et al. Joint Bone Spine 2016;83:314–17.

Febuxostat in CVD: to prescribe or not?

- Conditional recommendation to use Febuxostat in those with CVD
- FDA-mandated CARES trial of febuxostat versus allopurinol:
  - there was no difference between the 2 arms in the primary composite CVD end point
  - Febuxostat, however, was associated with a higher risk of CVD-related death and all-cause mortality (driven by CVD deaths) compared with allopurinol
  - but there was no association with the other 3 secondary CVD outcomes (nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization for unstable angina)
  - Difficult to interpret due to high drop out rate and majority of deaths after ULT discontinuation
  - Lack of untreated control group, therefore no measure of absolute CVD risk with Febuxostat
  - FDA black box warning though…
- These results were not replicated in other studies:
  - Large observational study (recruitment not selected for CVD) did not show an increased risk of CVD or all-cause mortality associated with febuxostat compared with allopurinol using methods to address confounding by indication
  - A managed care database study demonstrated lower risk of any major CVD event among febuxostat initiators than allopurinol, though confounding by indication may not have been adequately addressed
  - EMA FAST trial: no signal similar to CARES but majority Caucasian older male population

White WB et al. N Engl J Med 2018;378:1200–10.
Zhang M et al. Circulation 2018;138: 1116–26.
Foody J et al. Am Health Drug Benefits 2017;10:393–401
Mackenzie I et al. The Lancet, Volume 396, Issue 10264, 1745 - 1757

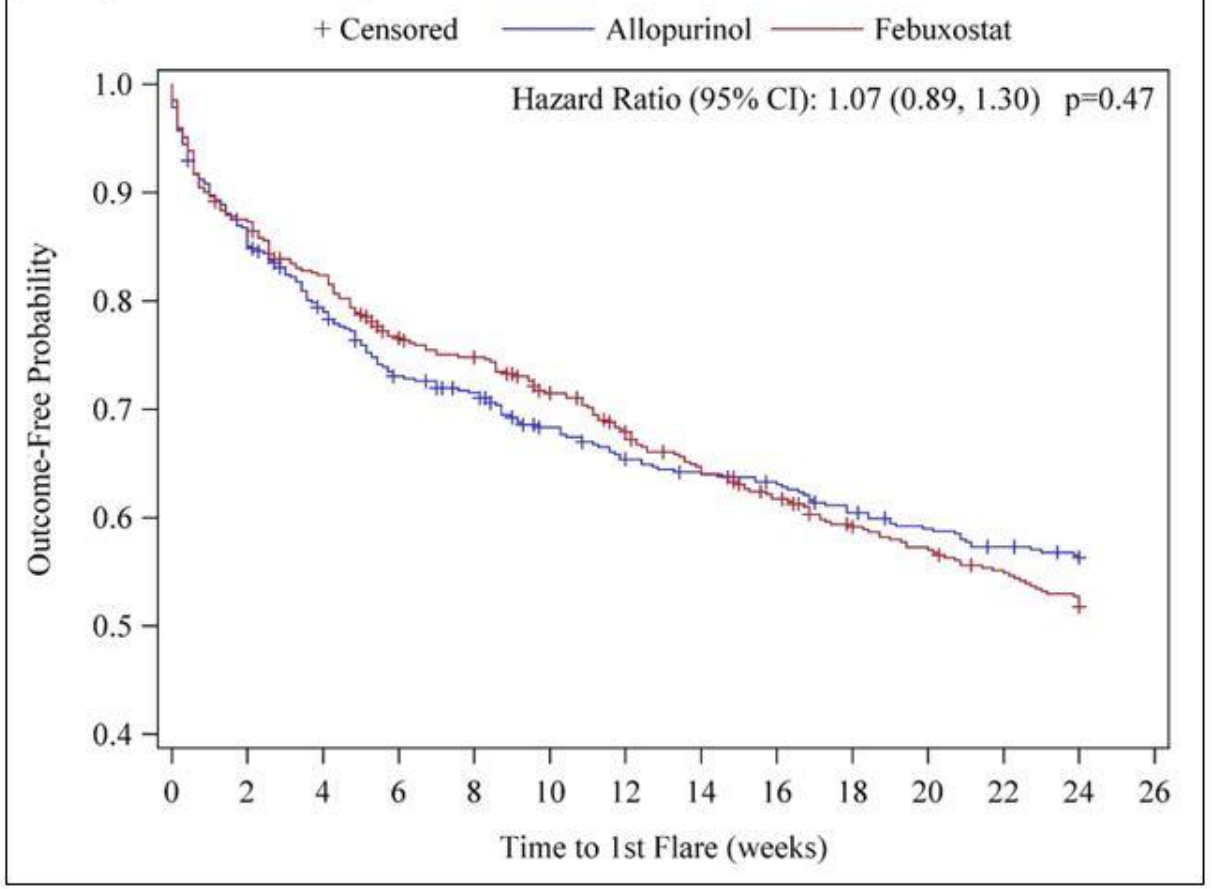
Gout Flares During the Initiation and Escalation of Treat-to-Target Urate Lowering Therapy: A Post-hoc Analysis of a Randomized Multicenter Comparative Effectiveness Trial

- No difference in flare risk between allopurinol and febuxostat during initiation and titration according to a treat-to-target management strategy
- No impact of what prophylaxis used or comorbidities

Risk factors for flare during Rx initiation/ escalation:

- Higher baseline sUA (aHR 1.09; 95% CI 1.01-1.18)
- Absence of tophi (aHR 0.70; 95% CI 0.54-0.91)

Figure 1: Time to first gout flare in patients receiving allopurinol vs. febuxostat (unadjusted HR shown)



*Patients censored at time of study withdrawal or death.

Barry A et al. https://de170d6b23836ee9498a-9e3cbe05dc55738dcbe22366a8963ae7.ssl.cf1.rackcdn.com/2531028-1079903-001.pdf ACR 2023

Case

56, M, hypertension, T2DM, tophaceous gout, prev excess alcohol intake

DH: losartan, amlodipine, metformin, febuxostat 120 mg, diclofenac PRN, prednisolone 10 mg for acute episodes

Previously had allopurinol 900 mg

sUA consistently >500 for the last decade

Freq of attack every 2-3 weeks

OE: Tophi dorsum foot, achilles tendon, olecranon bursae, PIPJs

What would you do?

Uricosuric drugs for Chronic gout

	Potency	eGFR ml/min	Mono/ combination therapy	Renal stones	Available	Monitor
Sulfinpyrazone 200-800mg	++	>30	Either	CI	Named pt	
Probenecid 500mg-2g	++	>30	Either	CI	Named pt	
Benzbromarone 50-200mg	+++	>20	Either	CI	Named pt	LFT
Lesinurad 200mg	++	>30	Combine with XOI		Withdrawn from market	

Pegloticase + MTX for chronic refractory gout: the MIRROR trial

- 12 month RCT of PEG (8mg bi weekly) + MTX (15 mg/OW) vs PEG +Placebo
- Inclusion: SUA > 7mg/dL at baseline/ ULT failure or intolerance/ > 2 flares/year, > 1 tophus, gouty arthropathy
- Exclusion: G6PD, MTX C/I, CKD 4-5
- 60% of MTX and 30% of placebo group met primary endpoint of SUA < 6 mg/dL
- 63% placebo and 23% MTX group met SUA discontinuation criteria (2 consecutive pre infusion SUA > 6 mg/dL after week 2)
- Of pts with tophi at baseline, 53.8% vs 31.0% had complete resolution of ≥1 tophus at Wk 52
- Similar safety profile b/w the two groups (with all AEs occurring by wk 24)

Botson J, saag k et al. *Arthritis Rheumatol.* 2022; 74 (suppl 9).

Hemodialysis

Ifudu O et al. Am J Kidney Dis. 1994;23(3):347–351
Guedes M et al. Am J Kidney Dis. 1994;23(3):347–351
Wright DF et al. Am J Kidney Dis. 1994;23(3):347–351
Arenas MD et al. Am J Kidney Dis. 1994;23(3):347–351

Gout flares and tophi decrease after initiation of HD, new cases of gout are rare if on HD

Another study reports prevalence of gout in HD – 13% in HD and 21% in PD

For those who continue allopurinol during HD, it is best dosed after HD because oxypurinol is dialyzable

SUA levels drop by 80% immediately after HD, remain below 6.8 mg/dL after final session of HD/week (results same for those on ULT and those who are not)

Therefore ? No need for ULT if on HD but this study only included patients on HD for on average 7 years and may not be generalizable to new HD starters/ higher SUA burden

PD

Most patients on PD have normal SUA

20 patients, of which only 2 patients remained hyperuricemic after median 20 months of PD

Whilst patients with ULT had lower mean SUA (4.2 mg/dL) cf those not on ULT (5.6 mg/dL, $p < 0.05$), both groups remained below hyperuricemia cut off

Continuous cyclic PD more effective than nocturnal intermittent PD

ULT may need to be continued on RRT if still having gout flares (due to meds: diuretics to help volume status) or if SUA >6 mg/dL.

Diez Lopez C et al. Am J Kidney Dis. 1994;23(3):347–351

Flare prophylaxis in CKD

Colchicine 0.6mg BID or QD can be continued for up to 6 months

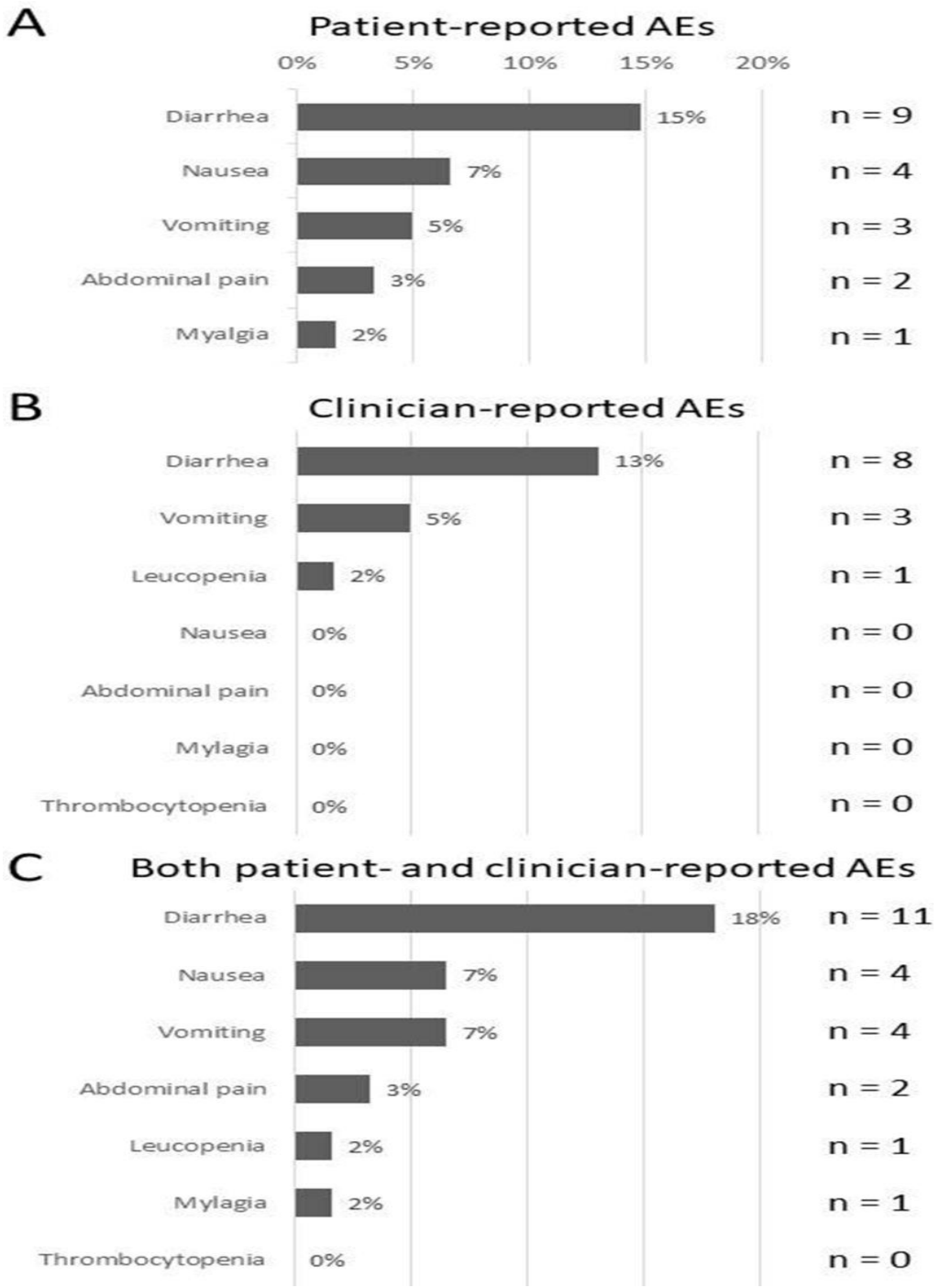
GFR >60 - no reduction in colchicine dose

GFR 30-60 – colchicine 0.6 mg QD

GFR< 30 –start 0.3 mg daily

GFR <10 - avoid

HD- 0.3 mg twice/weekly

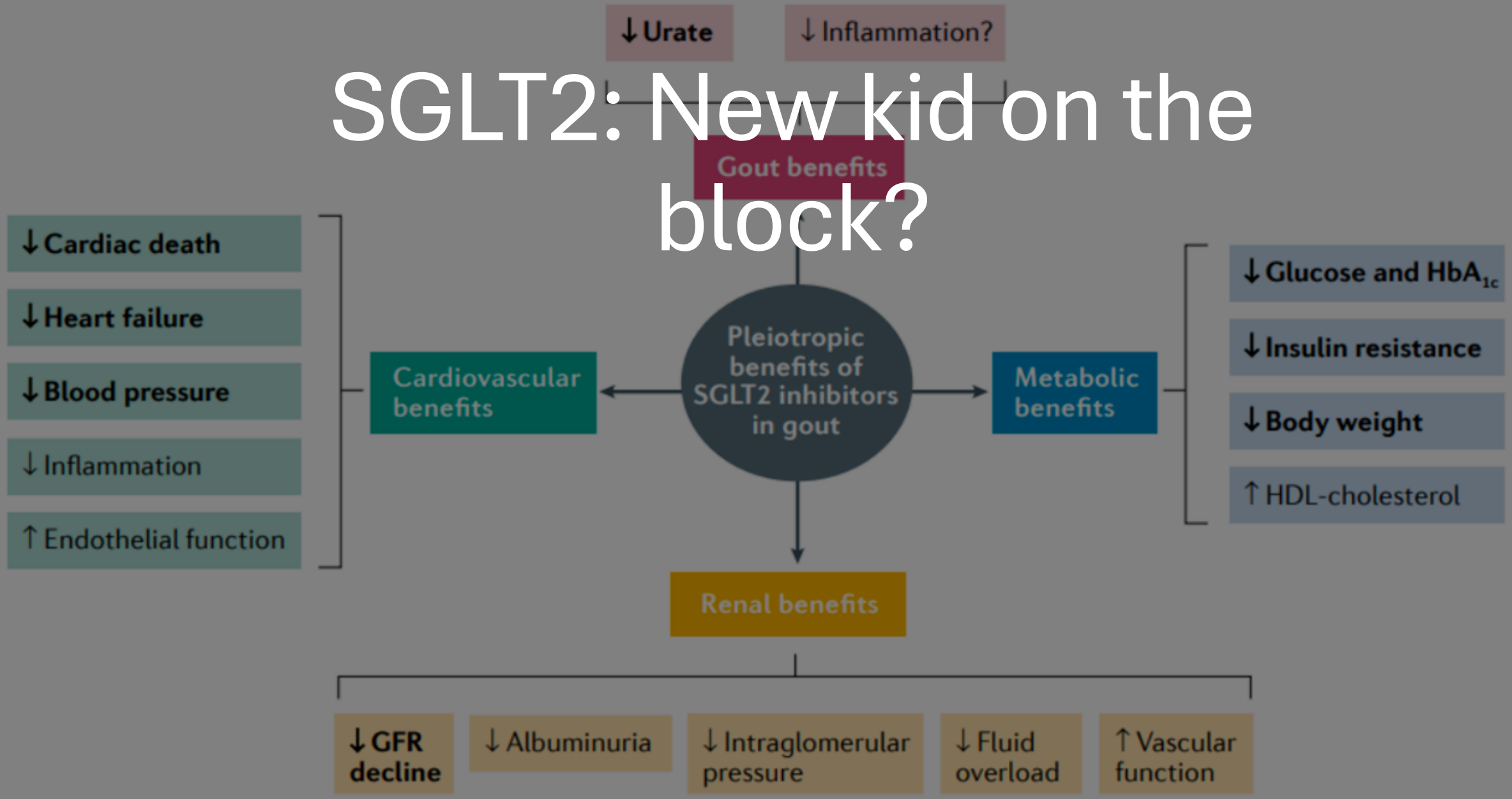


Wason et al. Arthritis Rheum 2011;63 (Suppl 10): 2581

Bausson J et al. RMD Open 2024;10:e003872. doi: 10.1136/rmdopen-2023-003872

Choi Nat Rev Rheumatol 2022

SGLT2: New kid on the block?



Management of Gout and CKD

Flare and Prophylaxis

Colchicine	• 0.3-0.6 mg orally every other day or twice weekly, depending on CKD stage and/or drug interactions • Avoid using in ESKD
NSAIDS	• Generally contraindicated in CKD except in very selected cases
Systemic Glucocorticoids	• Use cautiously in patients with comorbid diabetes or hypertension • Can worsen infectious risk
Anakinra (IL-1 Inhibitor)	• Dose every other day in patients with eGFR < 30 mL/min/1.73 m2 • Case studies report nonfatal infections with use

Urate-lowering Therapy

Allopurinol	• First-line agent, even in CKD • Start at ≤ 100 mg/day or ≤ 50 mg/day with CKD and titrate to serum urate levels of ≤ 6 mg/dL by increasing the dose incrementally every 2-5 weeks • Concern for allopurinol hypersensitivity syndrome
Febuxostat	• Start with ≤ 40 mg/day with subsequent titration to serum urate levels of ≤ 6 mg/dL by increasing the dose incrementally every 2 to 5 weeks • Conflicting data exists as to febuxostat increasing the risk of cardiovascular death
Uricosurics	• Generally contraindicated in CKD
Uricases	• Use in severe, refractory gout • Available data suggest similar efficacy and safety in those with and without CKD • May require concurrent use of immunomodulating drugs to reduce immunogenicity

Kannuthurai V et al. Kidney360. 2023 Sep 1;4(9):e1332-e1340

CPPD arthritis

- Calcium pyrophosphate (CPP) dihydrate crystals are commonly found in the joints of the elderly
- Also called pseudogout
- CPPD can also be secondary to a number of metabolic diseases

Definite associations	Possible associations
Hypophosphatasia	Gout
Primary hyperparathyroidism	Ochronosis
Familial hypercalciuric hypercalcaemia	Wilson’s disease
Haemochromatosis	Hypophosphataemic rickets
Hypomagnesaemia	Brachydactyly and epiphyseal dysplasias Acromegaly

CPPD pathophysiology

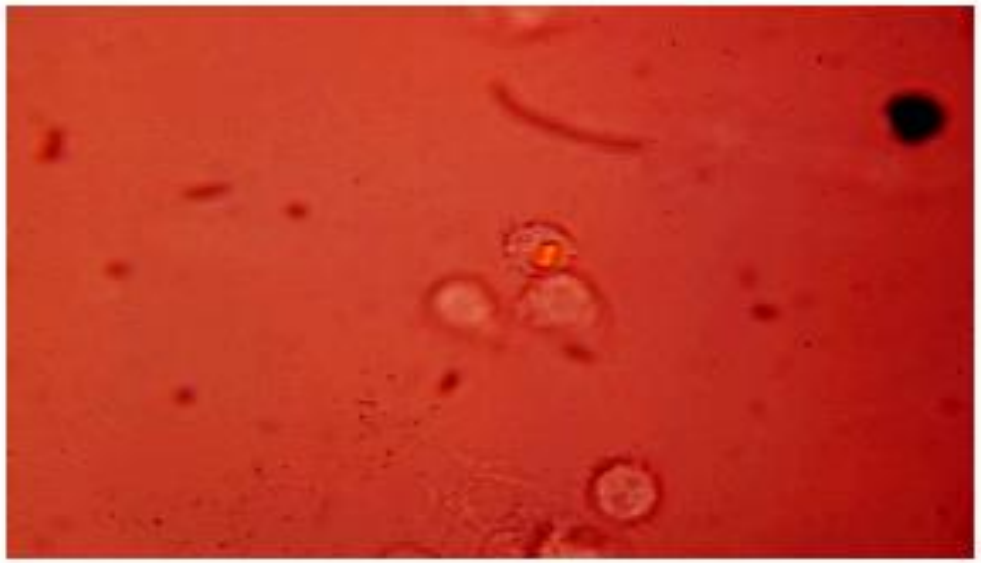
CPP deposits occur mainly in the mid-zone of articular cartilage and in fibrocartilage of joints and are believed to be due to a locally excessive (Ca × PP) product

Magnesium is a coenzyme to alkaline phosphatase and increases CPP solubility, explaining the link between CPPD and hypomagnesaemia

Hypercalcaemia due to familial primary hyperparathyroidism or hypocalciuric hypercalcaemia increases the (Ca × PPi) product

In addition cartilage damage is also likely to play a role in CPPD

Intracellular calcium pyrophosphate dihydrate crystal



A faintly yellow, positively birefringent, rhomboidal, intracellular crystal characteristic of calcium pyrophosphate dihydrate (CPP) is seen in the synovial fluid of a patient with acute CPP crystal arthritis (pseudogout) when viewed with compensated, polarized microscopy.

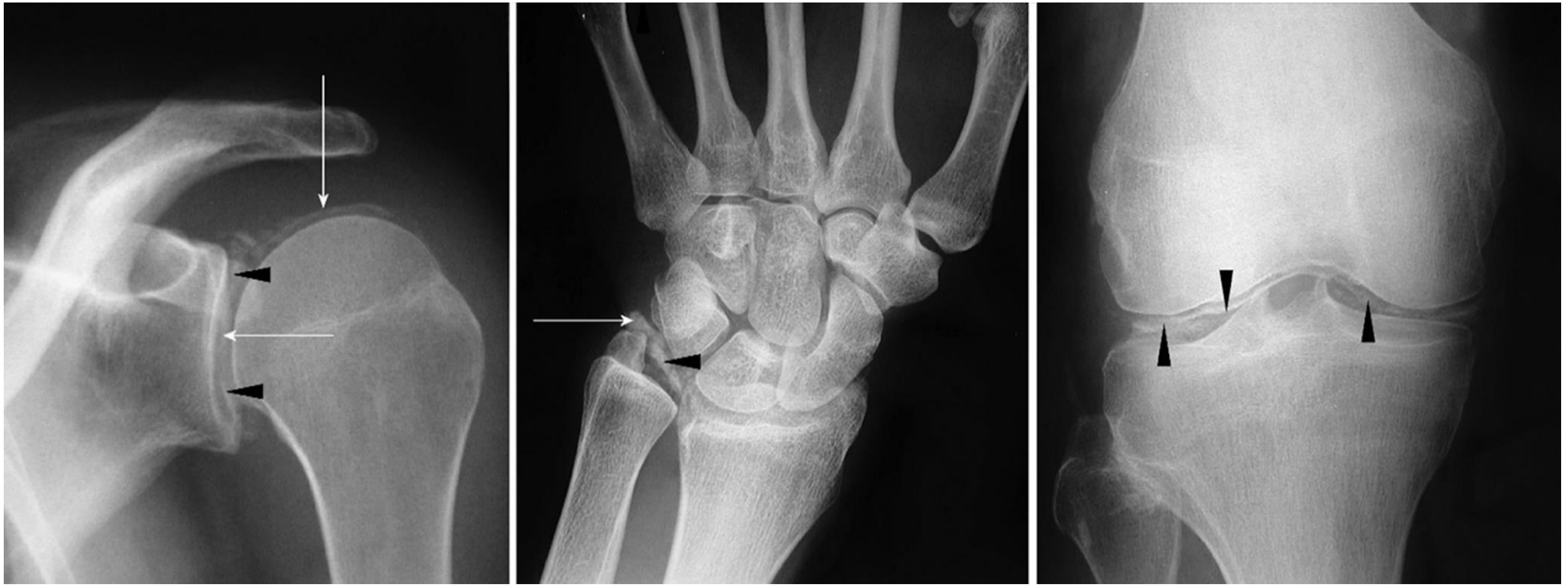
Image courtesy of Ralph Schumacher, MD.

UpToDate®

Slide courtesy UpToDate

Clinical features of CPPD

- Acute CPPD is self limiting synovitis (no long called pseudogout)
- Chronic CPPD – chronin inflam oligoarthritis or polyarthritis (consider as DD in RA and other chronic joint diseases)
- Spinal ankylosis, cord or nerve root compression may occur in spinal involvement
- Weakly positive birefringent rhomboid (or rod) shaped crystals

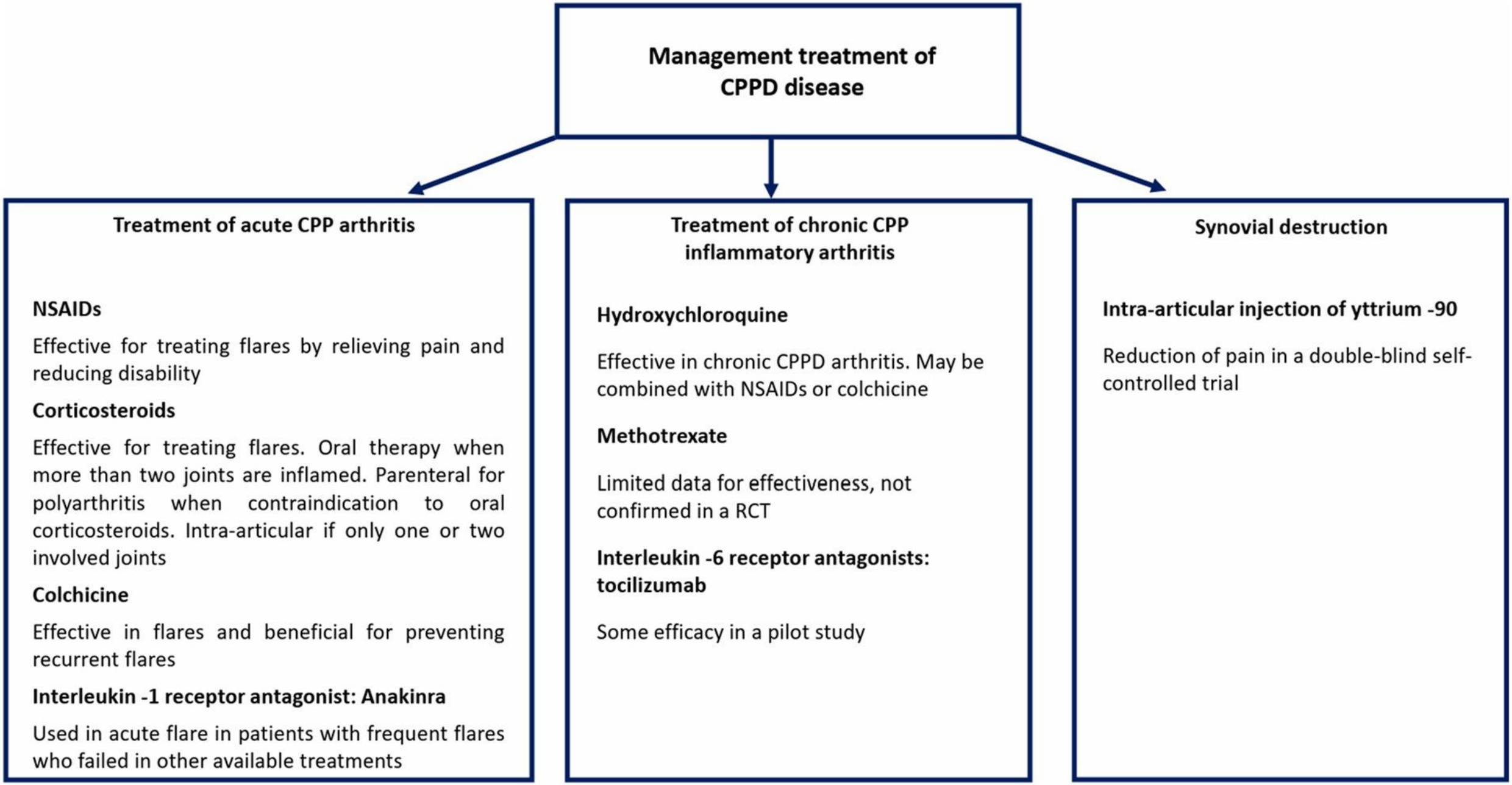


- XR shows calcification in the HC, FC, synovial membranes, joint capsules and tendons
- US- CPP crystals as thin hyperechoeic bands with HC and hyperechoeic sparkling spots in FC
- CT useful for CPPD in atlantooccipital joint or AA articulation (Crowned Dens syndrome)
- DECT- well defined linear or punctate calcifications within FC or HC, which are thinner and less dense (<300 hounsfield units) compared to cortical bone

Triggers for acute CPPD arthritis

- Trauma
- Intercurrent illness or surgery
- Bisphosphonate infusion
- Parathyroidectomy
- Joint lavage of the affected joint
- GCSF given in neutropenia
  - Process starts with formation of CPP crystals in the cartilage's pericellular matrix
  - Inorganic pyrophosphate derived from ATP plays a crucial role in CPPD
  - CPP crystals activate NLRP3 inflammasome and create NET triggering inflammation

- Important to distinguish CPPD from from chondrocalcinosis, which involves radiographic calcification in hyaline cartilage and fibrocartilage
- Presence of CC in 15% in those >60 years of age


Management treatment of CPPD disease
Treatment of acute CPP arthritis
NSAIDs
Effective for treating flares by relieving pain and reducing disability
Corticosteroids
Effective for treating flares. Oral therapy when more than two joints are inflamed. Parenteral for polyarthritis when contraindication to oral corticosteroids. Intra-articular if only one or two involved joints
Colchicine
Effective in flares and beneficial for preventing recurrent flares
Interleukin -1 receptor antagonist: Anakinra
Used in acute flare in patients with frequent flares who failed in other available treatments
Treatment of chronic CPP inflammatory arthritis
Hydroxychloroquine
Effective in chronic CPPD arthritis. May be combined with NSAIDs or colchicine
Methotrexate
Limited data for effectiveness, not confirmed in a RCT
Interleukin -6 receptor antagonists: tocilizumab
Some efficacy in a pilot study
Synovial destruction
Intra-articular injection of yttrium -90
Reduction of pain in a double-blind self-controlled trial

Side effects

- Colchicine:
  - GI
  - Reversible peripheral neuropathy
  - Cytopenia
  - Rhabdomyolysis
  - Myopathy
  - Liver failure
  - Avoid colchicine with drugs that inhibit CYP3A4 or membrane p glycoprotein
- Steroid:
  - BM
  - HTN
  - HF
- COLCHICORT trial: compared low dose colchicine with prednisone in acute CPPD.
  - Equivalent short term efficacy in alleviating joint pain at 24 h but different safety profiles as above

1.Pascart, Tristan et al. The Lancet Rheumatology, Volume 5, Issue 9, e523 - e531

Anakinra in CPPD arthritis

- IL1-Ra
- CPPD crystals induce the downregulation of natural IL-1Ra, leading to increased IL activity and pro inflam cytokines
- Typically a 3 day regimen has been used to treat acute flares
- If frequently recurrent or persistent arthritis, can give daily as maintenance therapy
- Mainly case reports and cohort studies as evidence base
  - A SR by Cipoletta et al: 74 CPPD patients who received anakinra for refractory disease (85%) or CI to other treatments (23%)
  - Clinical response (reduced TJC, SJC, VAS pain and CRP) in 81%

Cipoletta et al. Clin Exp Rheumatol. (2020) 38:1001–7

Treatment of chronic CPPD

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Chollet-Janin, A, Finckh, A, Dudler, J, and Guerne, P-A. Methotrexate as an alternative therapy for chronic calcium pyrophosphate deposition disease: an exploratory analysis. *Arthritis Rheum*. (2007) 56:688–92. doi: 10.1002/art.22389

Andres, M, Sivera, F, and Pascual, E. Methotrexate is an option for patients with refractory calcium pyrophosphate crystal arthritis. *J Clin Rheumatol*. (2012) 18:234–6. doi: 10.1097/RHU.0b013e3182611471

Finckh, A, Mc Carthy, GM, Madigan, A, Van Linthoudt, D, Weber, M, Neto, D, et al. Methotrexate in chronic-recurrent calcium pyrophosphate deposition disease: no significant effect in a randomized crossover trial. *Arthritis Res Ther*. (2014) 16:458. doi: 10.1186/s13075-014-0458-4

HCQ:

- One DBRCT of 36 patients
- Dose 100-400 mg daily
- RR (at least 30% reduction in TJ/SJ) was seen in 76% of the treatment vs 32% PBO group
- OLE- 85% who were given PBO and crossed over to HCQ achieved treatment response
- EULAR recommended

MTX:

- case series of 5-10 patients showed positive response, mean time to response 7.4 weeks (range 4-16 weeks)
- EULAR recommended
- However DBRCT of 26 patients had contrasting results
  - No diff in DAS, TJ/SJ, CRP, analgesia usage, no.of flares in 3 months or VAS pain between MTX and PBO

Other therapies

Latourte, A, Ea, HK, Frazier, A, Blanchard, A, Lioté, F, Marotte, H, et al. Tocilizumab in symptomatic calcium pyrophosphate deposition disease: a pilot study. *Ann Rheum Dis*. (2020) 79:1126–8
Adinolfi, A, Rumi, F, Carrara, G, Govoni, M, Frediani, B, Scirè, CA, et al. AB0862 efficacy and safety of US-guided injections of the knees with hyaluronic acid in patients affected by osteoarthritis associated to calcium pyrophosphate deposition disease: preliminary results. Ann Rheum Dis. (2019) 78:1899
Doherty, M, and Dieppe, PA. Double blind, placebo controlled trial of magnesium carbonate in chronic pyrophosphate arthropathy. Ann Rheum Dis. (1983) 42:106–7.

Tocilizumab: Open label pilot study of 11 patients	Sustained efficacy in global VAS at 10 months
Intraarticular glycosaminoglycan polysulfate	
Hyaluronic acid	
Synovial destruction- yttrium synovectomy	
Magnesium supplement	Regardless of baseline Mg DBPCT of 38 patients 30 mEq of magnesium carbonate daily for a period of 6 months Improvement in pain, TJ, SJ but ? PBO effect

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THANK YOU