Ορθη χρήση υποουριχαιμικών φαρμάκων και κολχικινης

ΘΑΝΟΣ ΚΟΥΤΡΟΥΜΠΑΣ

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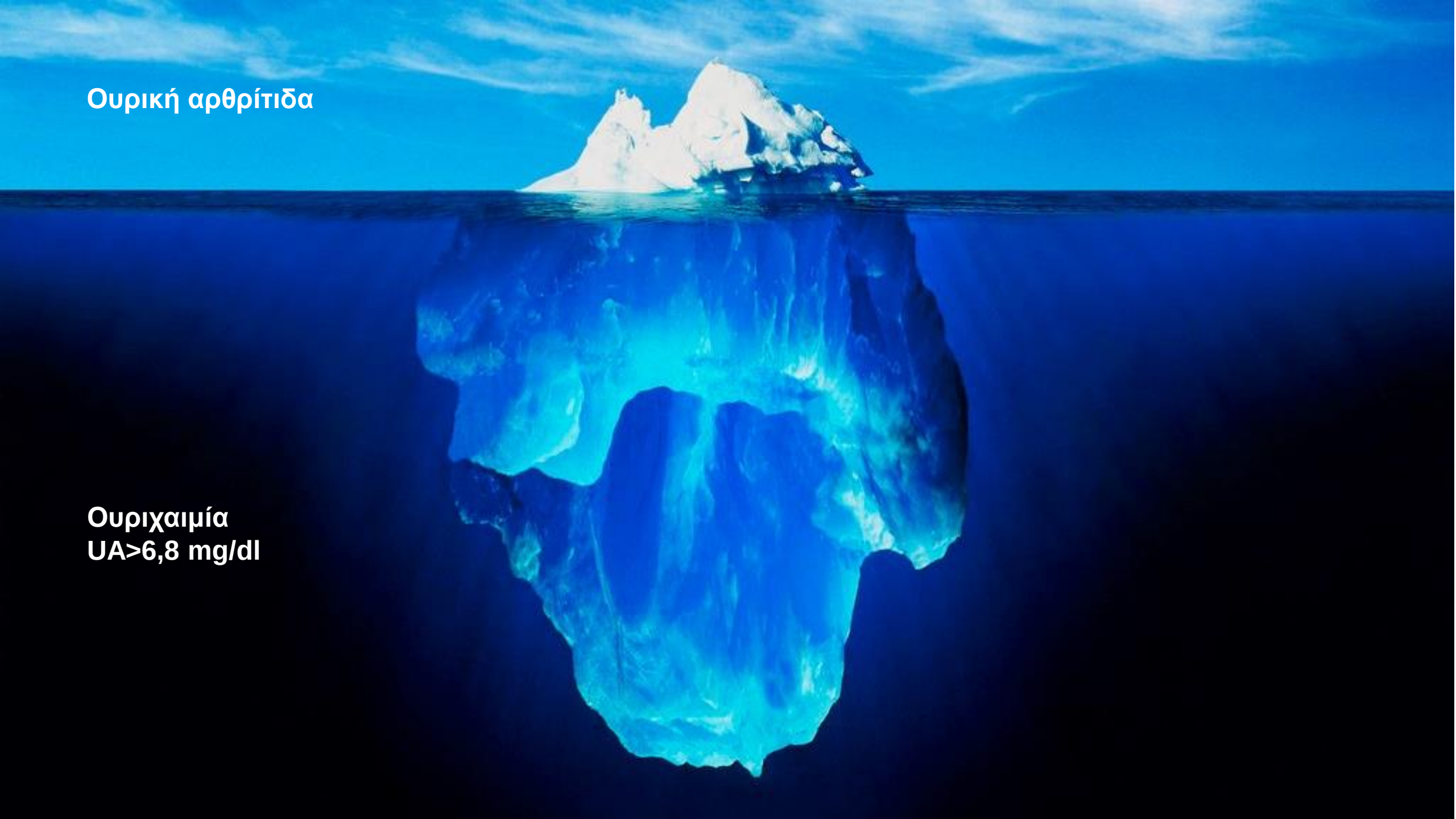
Σύγκρουση συμφερόντων

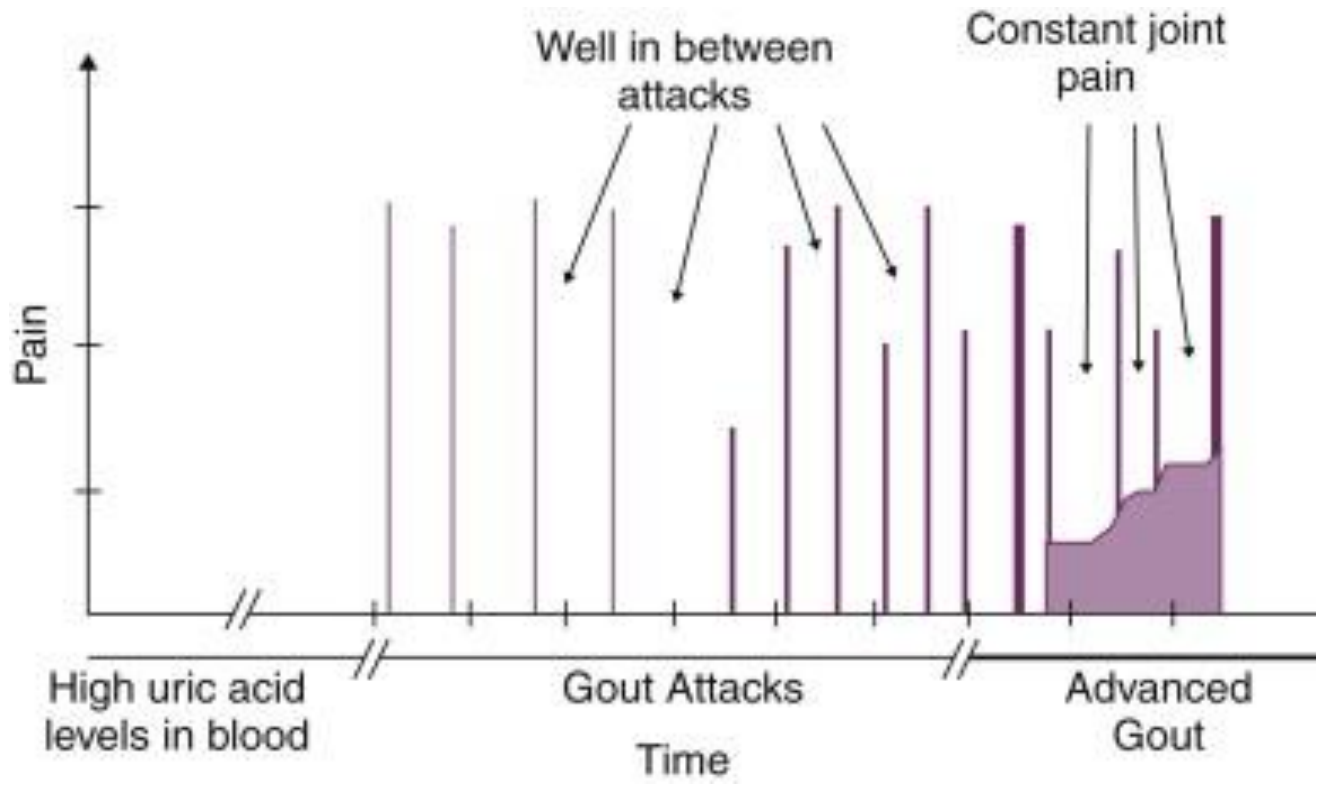
Καμία για την παρουσίαση αυτή

Τιμητική αμοιβή για εκπόνηση ομιλιών, ερευνητικών μελετών και συμβουλευτικών υπηρεσιών την τελευταία 2 ετία από τις εταιρείες:

AbbVie, Pfizer, Lilly, GSK.

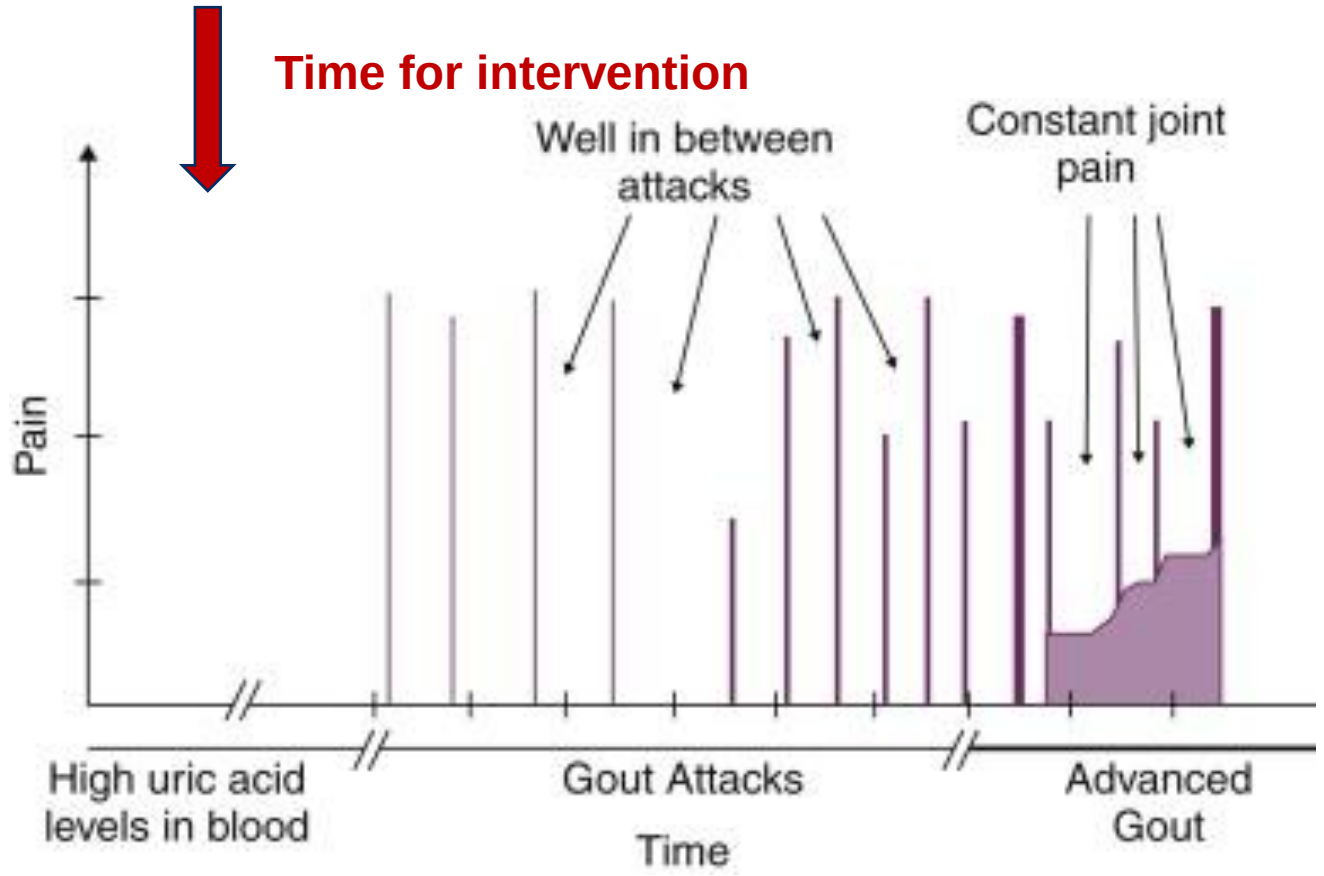

Ουρική αρθρίτιδα
Ουριχαιμία
UA>6,8 mg/dl

Gout: Natural history



Klippel et al, eds. Primer on the Rheumatic Diseases. 12th ed. Arthritis Foundation; 2001:313.)

Gout: Natural history



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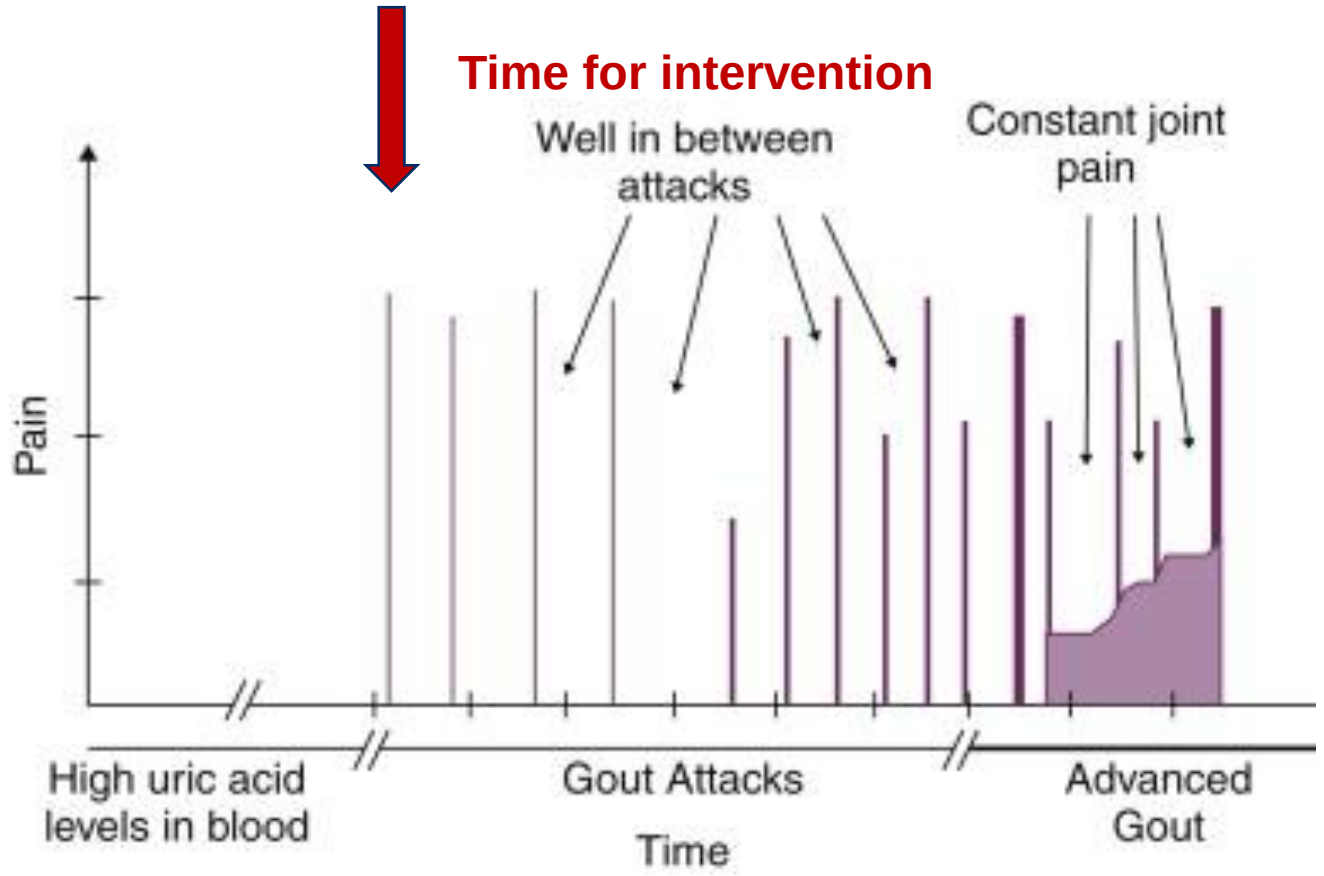
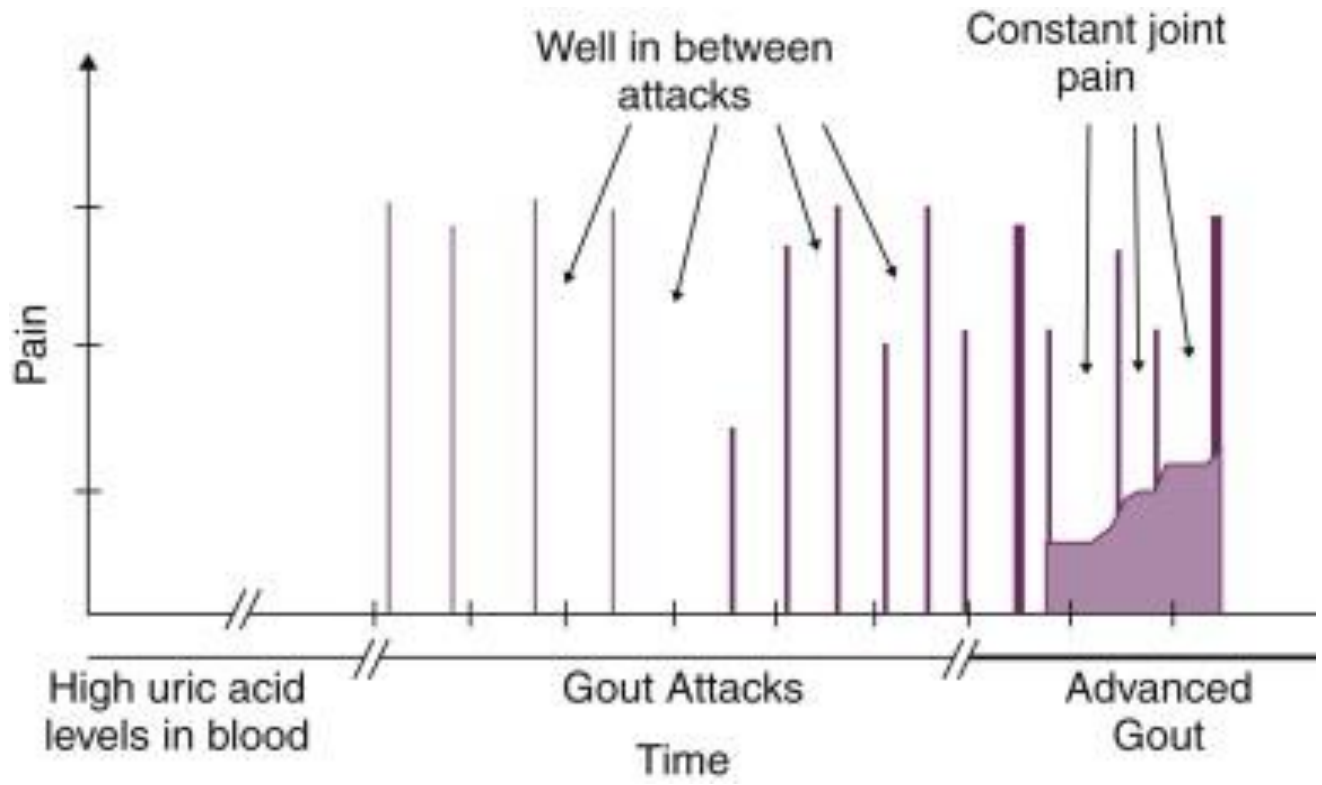
Gout: Natural history



Klippel et al, eds. Primer on the Rheumatic Diseases. 12th ed. Arthritis Foundation; 2001:313.)

Gout: Natural history

Time for intervention



Klippel et al, eds. Primer on the Rheumatic Diseases. 12th ed. Arthritis Foundation; 2001:313.)

Ποιά είναι η καλύτερη στιγμή παρέμβασης;

Ποιός είναι ο ιδανικός τρόπος παρέμβασης;

Ποιά η στρατηγική παρέμβασης;

Ποιοί οι στόχοι;

Ποιά η διάρκεια της παρέμβασης;

Treat-to-target or treat-to-symptom?

Isnt't it the same?

The rationale behind T2T in gout

Neogi and Mickuls, Ann Intern Med 2017

How early is "early intervention"?

OR

Should we treat asymptomatic hyperuricemia?

What do we expect to earn when we treat asymptomatic patients with hyperuricemia

Does ULT lower the risk of incident gout in asymptomatic hyperuricemia?

Incidence of gout

Febuxostat: 0,9 % (2/219)

Placebo: 5,9 % (13/222)

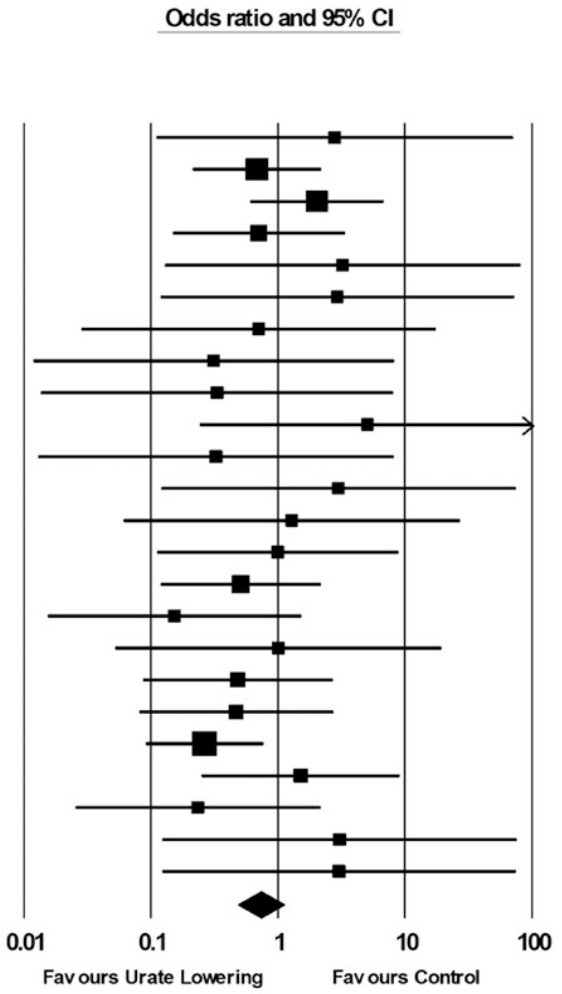
NNT for 3 years to prevent a single (incident) gout flare: 24

Kimura, Am J Kidney Dis 2018, FitzGerald, Arthritis Rheumatol 2020

What we *do* know

Forest plot of randomized controlled trial estimates for risk of major adverse cardiovascular events *in all patients* receiving urate-lowering therapy or placebo/no treatment.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Dickerson 2009	2.803	0.110	71.656	0.623	0.533
Givertz 2015	0.685	0.212	2.219	-0.630	0.528
Hare 2008	2.031	0.602	6.854	1.141	0.254
Higgins 2014	0.709	0.148	3.399	-0.429	0.668
Jalal 2016	3.234	0.128	81.791	0.712	0.476
Jarnerot 2000	2.938	0.118	73.033	0.658	0.511
Kamatani 2011 late phase 2	0.706	0.028	17.677	-0.212	0.832
Khan 2008	0.312	0.012	8.285	-0.696	0.486
Mao 2015	0.332	0.013	8.187	-0.674	0.500
NCT01078389 2014	5.064	0.241	106.341	1.044	0.296
NCT01350388 2016	0.325	0.013	8.222	-0.682	0.495
NCT01496469 2015	3.000	0.120	75.113	0.669	0.504
NCT02128490 / Gunawardhana 2016	1.288	0.061	27.378	0.162	0.871
NCT02139046 / Saag 2016	0.998	0.111	8.956	-0.002	0.998
Rentoukas 2010	0.510	0.119	2.188	-0.906	0.365
Saag 2016	0.153	0.015	1.539	-1.594	0.111
Schumacher 2008	1.006	0.052	19.591	0.004	0.997
Separham 2016	0.485	0.086	2.740	-0.819	0.413
Taheraghdam 2014	0.470	0.080	2.749	-0.838	0.402
Zhang 2012	0.265	0.090	0.775	-2.426	0.015
Dalbeth, 2017	1.510	0.249	9.161	0.448	0.654
Huang, 2017	0.235	0.025	2.178	-1.275	0.202
Mukri, 2018	3.061	0.122	76.949	0.680	0.497
Tausche, 2017	3.028	0.122	75.171	0.676	0.499
	0.725	0.482	1.091	-1.541	0.123



Gill, Hypertension 2020

What we *do* know

Forest plot of randomized controlled trial estimates for risk of major adverse cardiovascular events *in patients with existing cardiovascular disease* receiving urate-lowering therapy or placebo/no treatment.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Higgins 2014	0.709	0.148	3.399	-0.429	0.668
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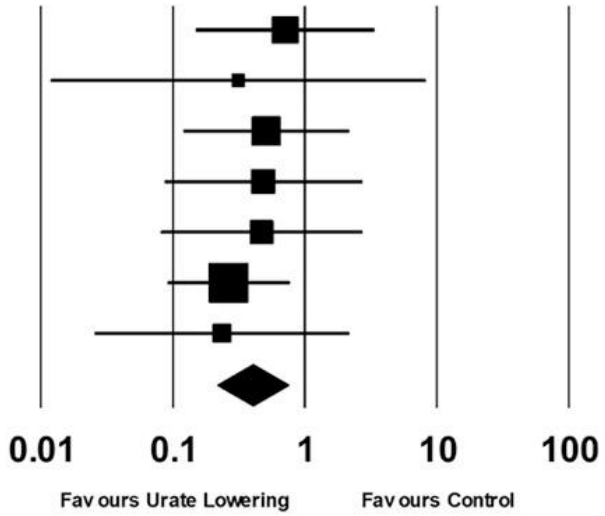
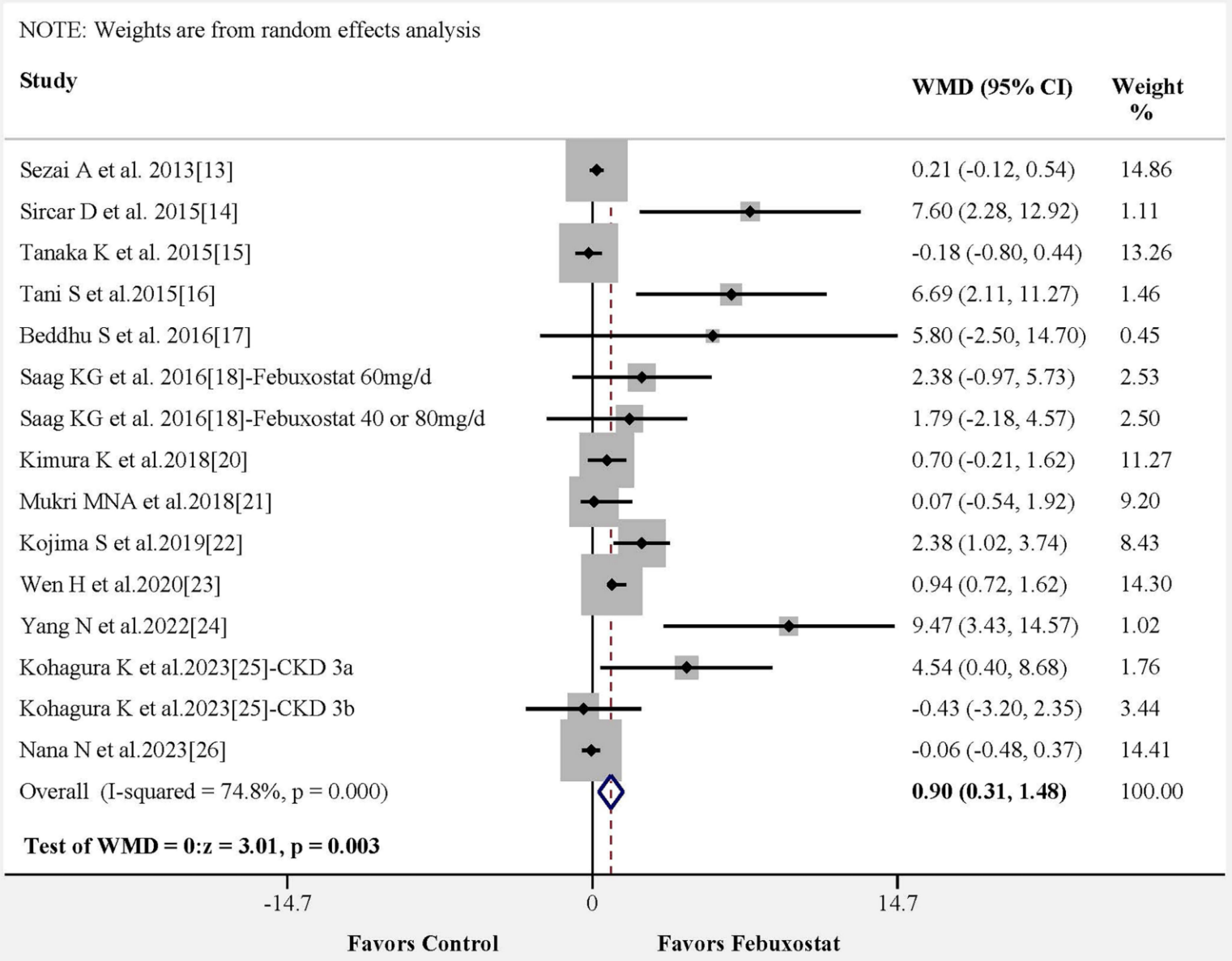
Taheraghdam 2014	0.470	0.080	2.749	-0.838	0.402
Zhang 2012	0.265	0.090	0.775	-2.426	0.015
Huang, 2017	0.235	0.025	2.178	-1.275	0.202
	0.396	0.216	0.729	-2.977	0.003



Gill, Hypertension 2020

What we *do* know

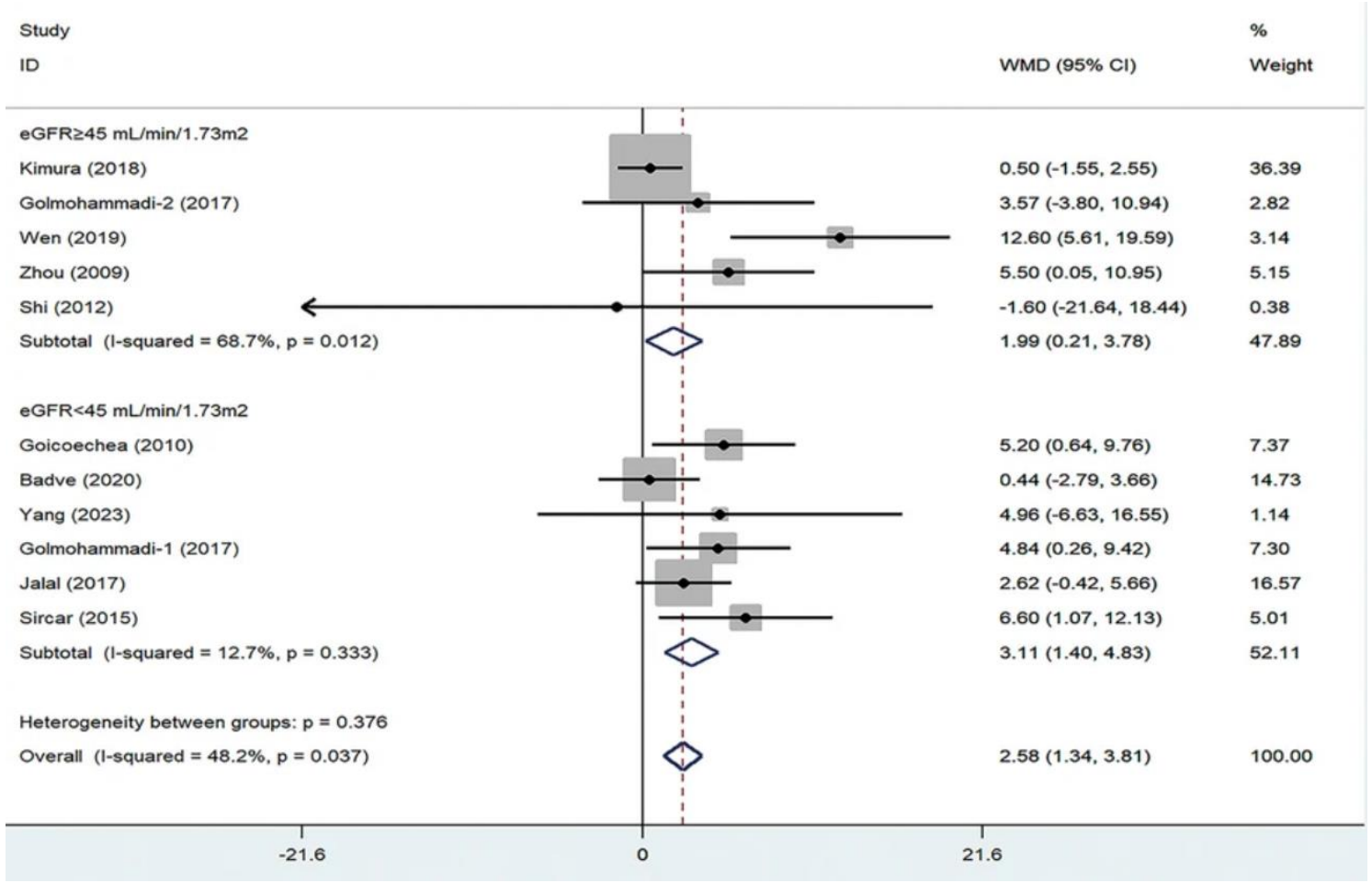
Mean difference (WMD) for eGFR associated with febuxostat from pooled studies.



Yang, Ann Med 2024

What we *do* know

Forest plot for the effect of ULT versus controls on the change in eGFR.



Luo, BMC Nephrol 2024

What we *don't* know

Who is at excess risk for CVD, renal or other complications?

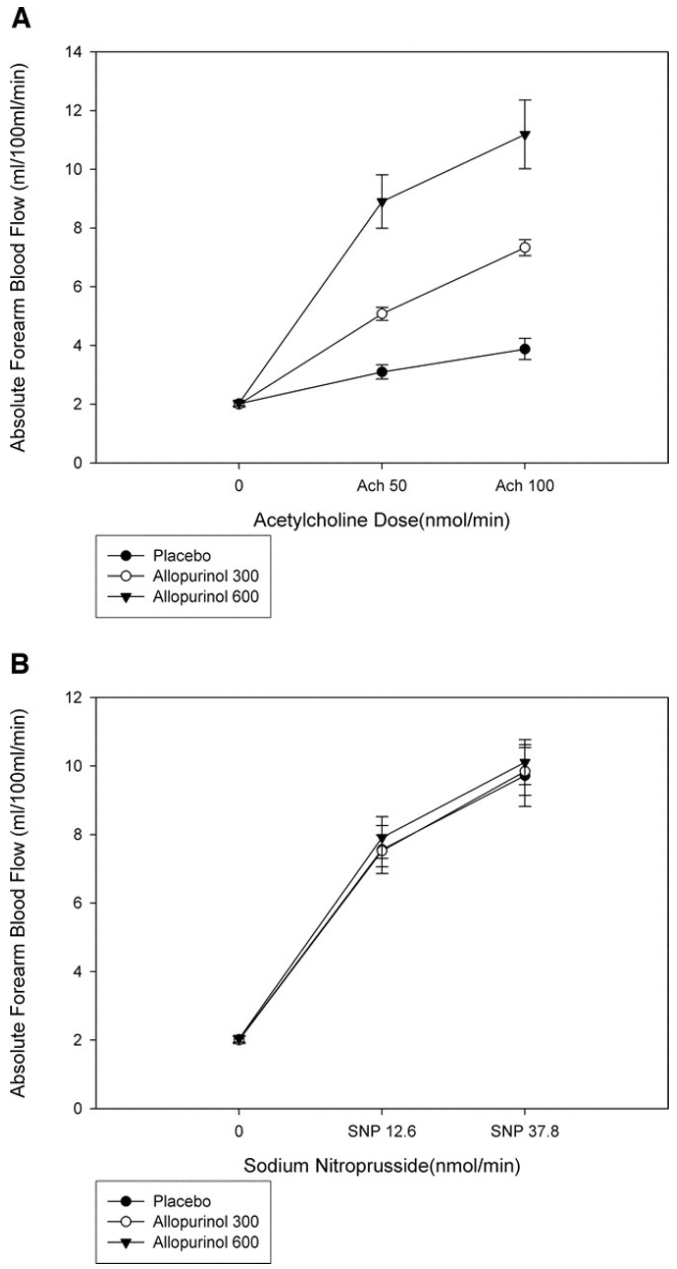
Does the addition of hypouricemic agents improve prognosis in the whole population with asymptomatic hyperuricemia, and selected high-risk populations?

In these patients, does the anticipated benefit outweigh the risk (eg possible CV risk associated with febuxostat)

What is the UA target level for primary (first event) or secondary (second event) prevention?

Dose-response effect of allopurinol in ameliorating CV risk?

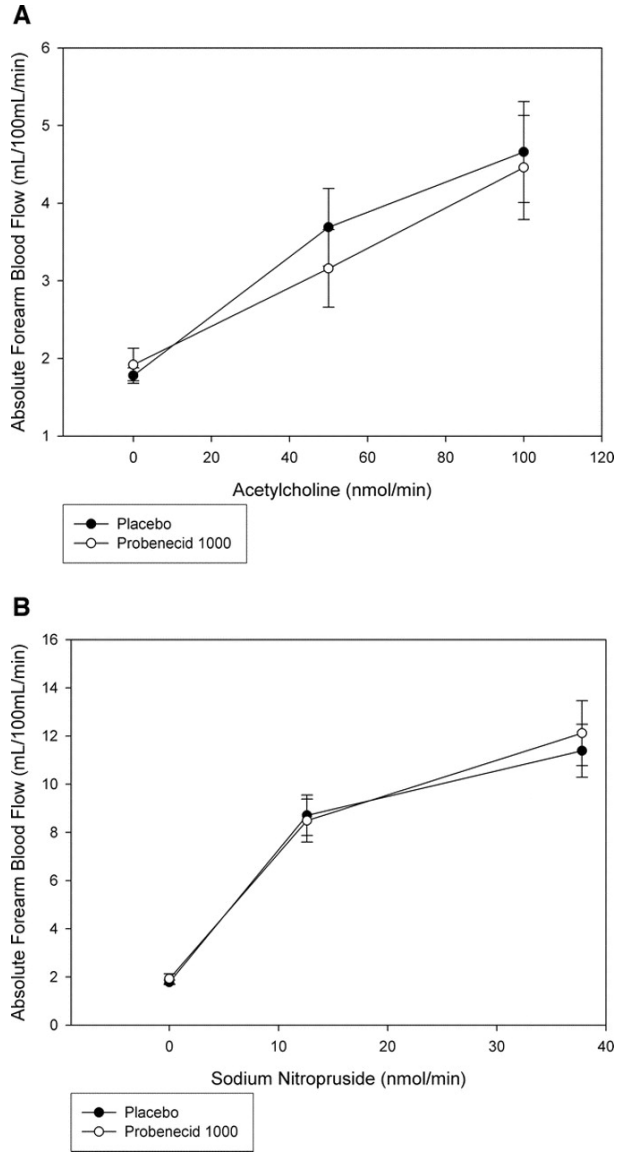
Allopurinol has a dose-related effect on Forearm Blood Flow, which is not mediated by uric acid reduction



George, Circulation 2006

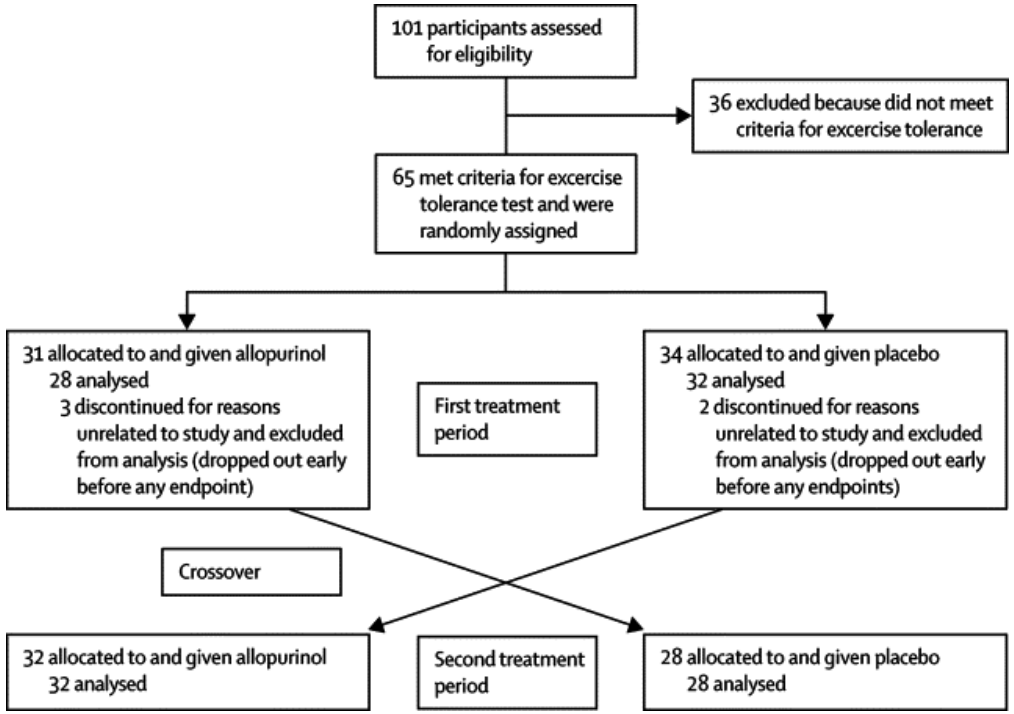
Dose-response effect of allopurinol in ameliorating CV risk?

Effect of 1000 mg of provenecid on forearm blood flow



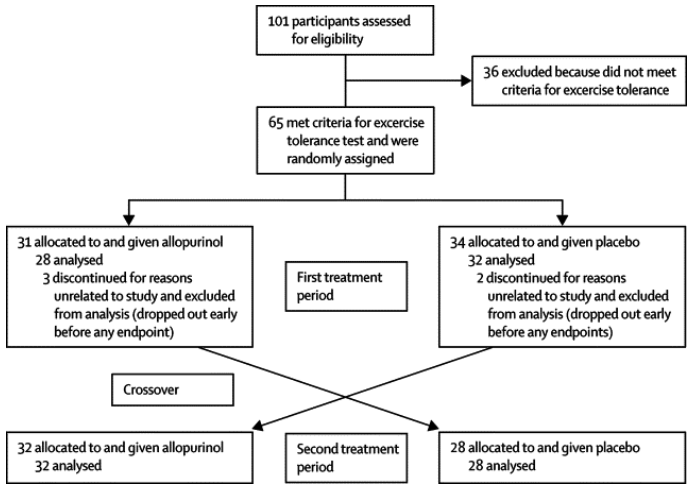
George, Circulation 2006

High dose allopurinol improves exercise time in patients with stable angina



Noman, Lancet 2010

High dose allopurinol improves exercise time in patients with stable angina



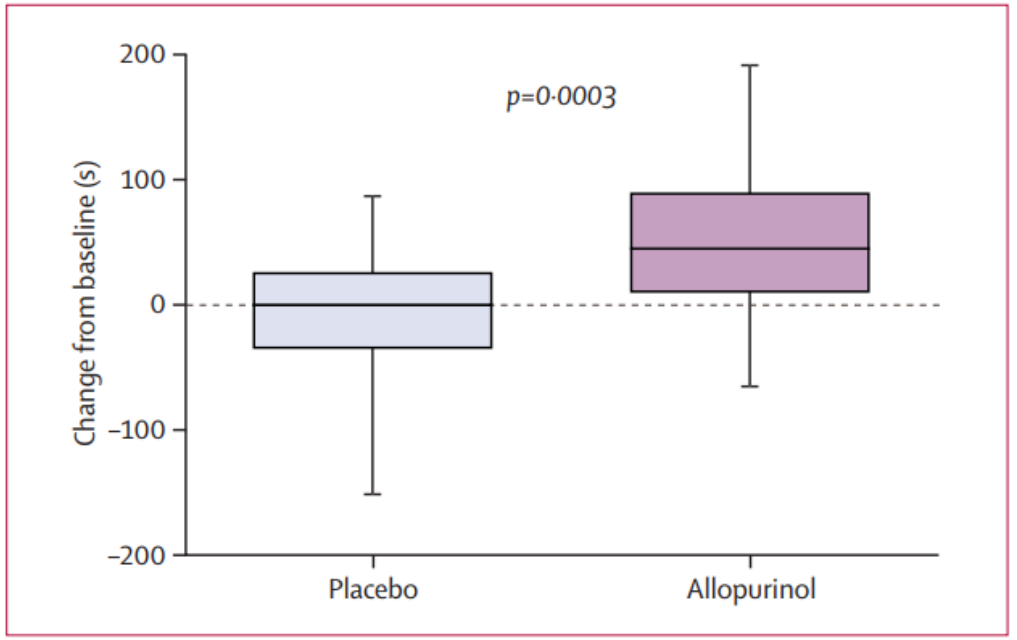
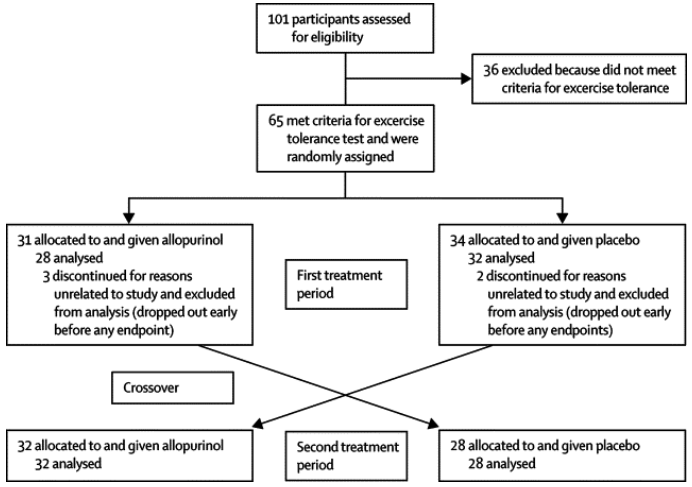


Figure 2: **Change in total exercise time from baseline**
Data are median (IQR).

Noman, Lancet 2010

High dose allopurinol improves exercise time in patients with stable angina



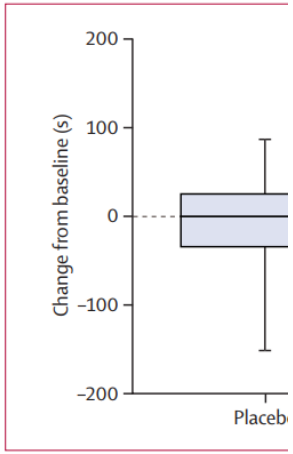


Figure 2: **Change in total exerci**
Data are median (IQR).

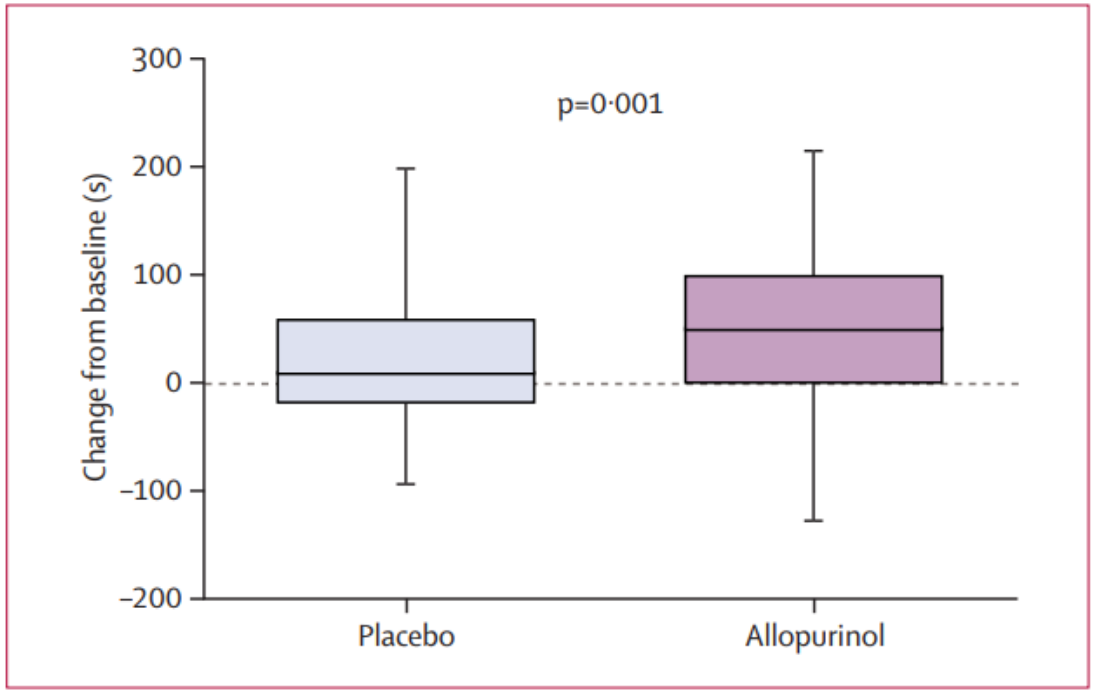
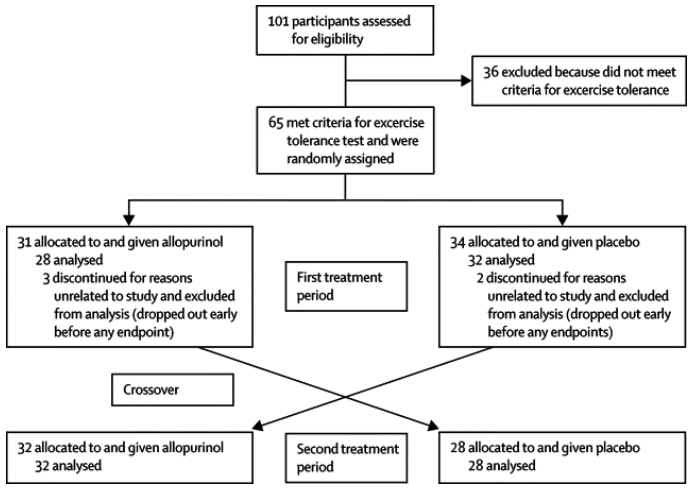


Figure 4: **Change in time to chest pain symptoms from baseline**
Data are median (IQR).

Noman, Lancet 2010

High dose allopurinol improves exercise time in patients with stable angina



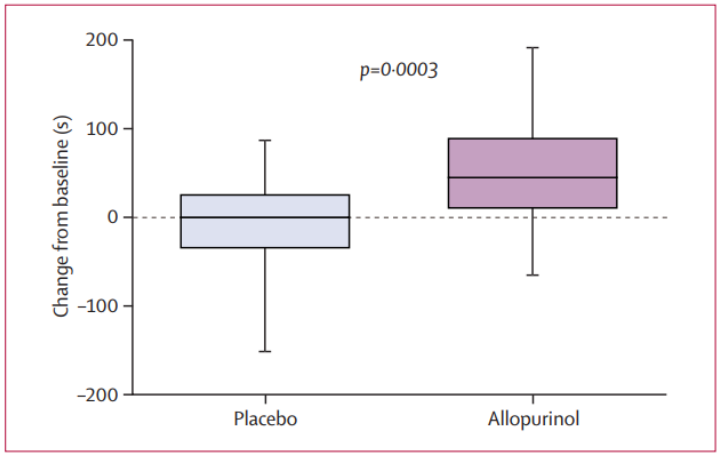


Figure 2: **Change in total exercise time from baseline**
Data are median (IQR).

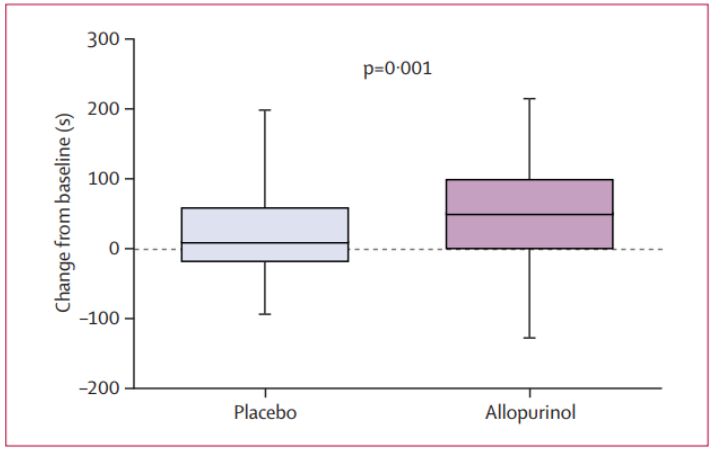


Figure 4: **Change in time to chest pain symptoms from baseline**
Data are median (IQR).

Noman, Lancet 2010

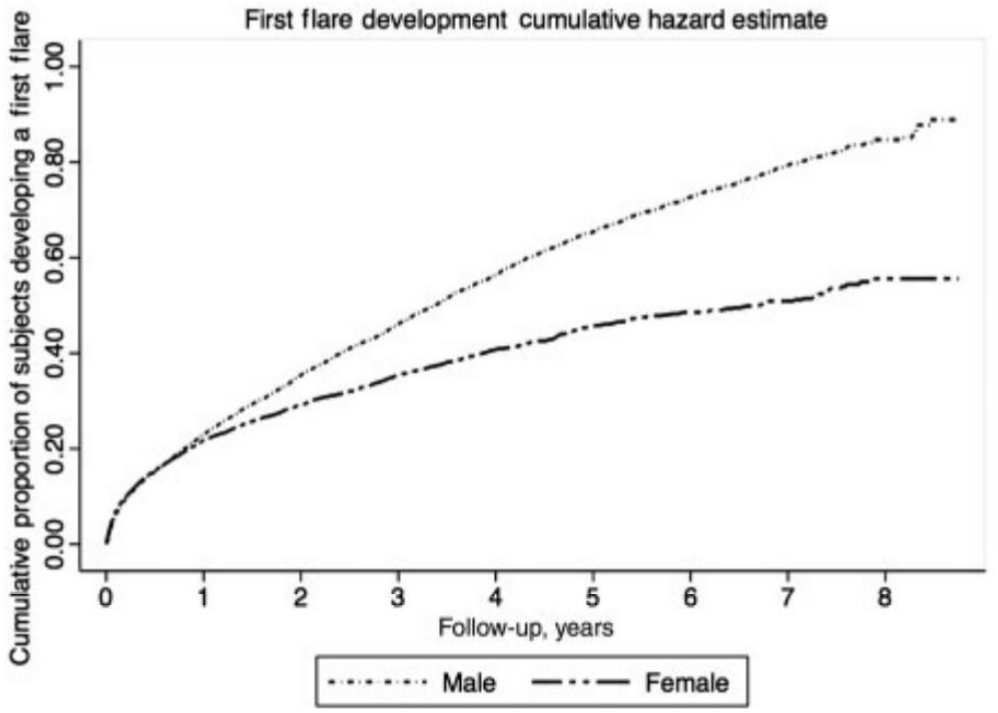
How early is "early intervention"?

OR

When is the right time for ULT?

Flare rates after a first gout diagnosis

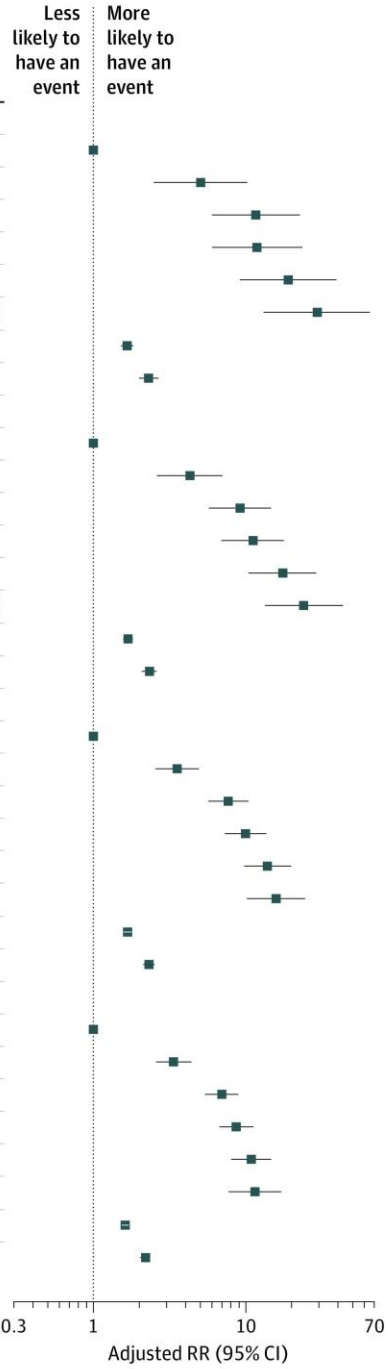
FIG. 2 Cumulative hazard estimates of first post-diagnosis flare stratified by sex.



Rothenbacher, Rheumatology 2011

Flare rates are associated with UA levels

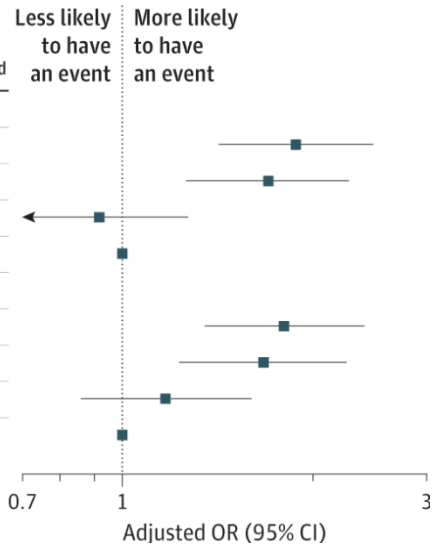
Serum urate, mg/dL	No. of patients with gout	Follow-up, person-years	No. of flares	Flares per 1000 person-years	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[a]	Extended adjusted RR (95% CI)[b]
1 Year							
<6	1057	1057	10	9.5	1 [Reference]	1 [Reference]	1.0 [Reference]
6.0-6.9	781	780	43	55.2	5.83 (2.89-11.75)	5.14 (2.54-10.41)	4.69 (2.29-9.62)
7.0-7.9	872	870	109	125.3	13.24 (6.84-25.62)	11.59 (5.96-22.54)	9.79 (4.90-19.53)
8.0-8.9	609	609	77	126.4	13.36 (6.80-26.23)	11.86 (6.01-23.38)	9.83 (4.84-19.96)
9.0-9.9	212	212	41	193.8	20.47 (9.92-42.21)	18.95 (9.17-39.19)	16.81 (7.85-35.98)
≥10	82	82	25	306.7	32.65 (14.64-72.82)	29.20 (13.07-65.20)	27.09 (11.59-63.30)
Per mg/dL	3613	3608	305	84.5	1.67 (1.54-1.82)	1.66 (1.52-1.80)	1.63 (1.48-1.80)
Per SD	3613	3608	305	84.5	2.31 (2.01-2.65)	2.27 (1.98-2.62)	2.22 (1.89-2.61)
2 Years							
<6	1057	2110	22	10.4	1 [Reference]	1 [Reference]	1.0 [Reference]
6.0-6.9	781	1554	79	50.8	4.87 (3.00-7.93)	4.39 (2.69-7.16)	4.09 (2.48-6.74)
7.0-7.9	872	1735	184	106.0	10.17 (6.44-16.04)	9.13 (5.76-14.46)	8.08 (4.99-13.09)
8.0-8.9	609	1217	155	127.3	12.21 (7.68-19.41)	11.09 (6.95-17.70)	9.71 (5.93-15.88)
9.0-9.9	212	421	81	192.3	18.42 (11.11-30.54)	17.39 (10.46-28.91)	15.75 (9.20-26.95)
≥10	82	162	44	272.4	26.34 (14.71-47.17)	24.05 (13.40-43.16)	23.17 (12.46-43.07)
Per mg/dL	3613	7200	565	78.5	1.68 (1.58-1.80)	1.67 (1.57-1.79)	1.65 (1.53-1.78)
Per SD	3613	7200	565	78.5	2.34 (2.10-2.60)	2.31 (2.08-2.57)	2.26 (2.00-2.55)
5 Years							
<6	1057	5230	58	11.1	1 [Reference]	1 [Reference]	1.0 [Reference]
6.0-6.9	781	3845	170	44.2	3.98 (2.89-5.48)	3.57 (2.59-4.92)	3.28 (2.36-4.57)
7.0-7.9	872	4299	407	94.7	8.53 (6.35-11.47)	7.66 (5.67-10.33)	6.74 (4.91-9.23)
8.0-8.9	609	3023	369	122.0	11.03 (8.16-14.93)	10.00 (7.36-13.57)	8.70 (6.29-12.03)
9.0-9.9	212	1041	172	165.2	14.88 (10.51-21.08)	13.84 (9.75-19.64)	12.27 (8.47-17.77)
≥10	82	397	76	191.4	17.42 (11.23-27.01)	15.77 (10.16-24.49)	15.05 (9.47-23.92)
Per mg/dL	3613	17836	1252	70.2	1.69 (1.61-1.78)	1.67 (1.59-1.76)	1.63 (1.54-1.73)
Per SD	3613	17836	1252	70.2	2.35 (2.17-2.55)	2.30 (2.12-2.50)	2.23 (2.03-2.44)
10 Years							
<6	1057	8833	94	10.6	1 [Reference]	1 [Reference]	1.0 [Reference]
6.0-6.9	781	6458	259	40.1	3.76 (2.90-4.87)	3.37 (2.60-4.39)	3.16 (2.41-4.13)
7.0-7.9	872	7260	595	82.0	7.69 (6.05-9.79)	6.93 (5.43-8.84)	6.20 (4.79-8.03)
8.0-8.9	609	5106	517	101.3	9.56 (7.46-12.25)	8.67 (6.74-11.14)	7.77 (5.94-10.15)
9.0-9.9	212	1756	220	125.3	11.68 (8.69-15.70)	10.81 (8.02-14.56)	9.80 (7.14-13.44)
≥10	82	663	88	132.8	12.66 (8.57-18.69)	11.42 (7.72-16.90)	11.26 (7.47-16.97)
Per mg/dL	3613	30076	1773	59.0	1.64 (1.57-1.71)	1.61 (1.54-1.68)	1.58 (1.50-1.66)
Per SD	3613	30076	1773	59.0	2.23 (2.08-2.40)	2.18 (2.02-2.34)	2.11 (1.95-2.28)



McCormick, JAMA 2024

A gout flare is associated with increased cardiovascular events

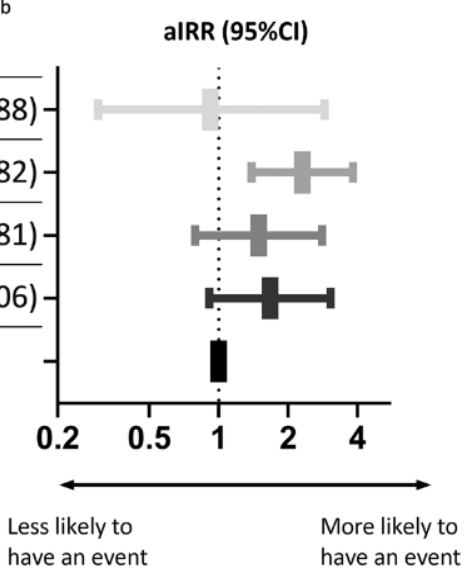
Gout flare exposure window, d[a]	No. (%) of participants: Cases[b] (N = 10 475)	Controls[c] (N = 52 099)	Unadjusted difference, % (95% CI)	Adjusted OR (95% CI)[d]
Acute myocardial infarction				
0-60	116 (2.0)	743 (1.4)	0.6 (0.1 to 1.0)	1.88 (1.42 to 2.49)
61-120	103 (1.8)	628 (1.2)	0.6 (0.1 to 1.0)	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]



CIPOLLETTA, JAMA 2022

Gout flares are associated with venous thromboembolism

Time period	Number of events [a]	Total follow-up time (person-days)	aIRR (95%CI) [b]
Induction period [c]	-/-	4,396	0.92 (0.30 to 2.88)
Flare date to day 30	16	9,376	2.31 (1.39 to 3.82)
Day 31-60	10	9,160	1.49 (0.79 to 2.81)
Day 61-90 days	11	9,057	1.67 (0.91 to 3.06)
Baseline period [d]	274	390,276	Reference



CIPOLLETTA, ARTHRITIS RHEUMATOL 2024

Who benefits from ULT?

When to initiate ULT?

Arthritis & Rheumatology
Vol. 72, No. 6, June 2020, pp 879–895
DOI 10.1002/art.41247

American College of Rheumatology
Empowering Rheumatology Professionals

ACR GUIDELINE FOR MANAGEMENT OF GOUT

2020 American College of Rheumatology Guideline for the Management of Gout

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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.

Which is the best ULT?

What are the options?

Xantine oxidase inhibitors (allopurinol, febuxostat)

Uricosurics (provenecid)

Pegloticase

Allopurinol: is it any good?

Adequate dosing is key

Predicted daily doses (*D*) of allopurinol to produce target plasma concentrations of urate (from substitution in equation 3*)

	6 mg/L	5 mg/L
Pre-treatment plasma urate (U_P, mmol l^{-1})	Predicted allopurinol dose (mg day^{-1}) to achieve EULAR target (U_T = 0.36 mmol l^{-1})	Predicted allopurinol dose (mg day^{-1}) to achieve BSR target (U_T = 0.30 mmol l^{-1})
11 mg/L		
10		
9,3		
8,4		
7,56		
0.65	405	775
0.6	335	665
0.55	265	554
0.5	195	443
0.45	126	332

*Equation 3: $D = ID_{50} \times (U_P - U_T)/(U_T - U_R)$.

BSR, British Society of Rheumatology; EULAR, European League Against Rheumatism; ID_{50}, dose of allopurinol that has reduced the inhibitable urate ($U_P - U_R$) by 50%; U_R, apparent resistant plasma concentration of urate; U_T, plasma concentration of urate during treatment with allopurinol.

Optimized values for U_R and ID_{50} (from Table 1) are 0.20 mmol l^{-1} and 226 mg, respectively.

Graham, Br J Clin Pharmacol 2013

Allopurinol: is it any good?

Adequate dosing is key

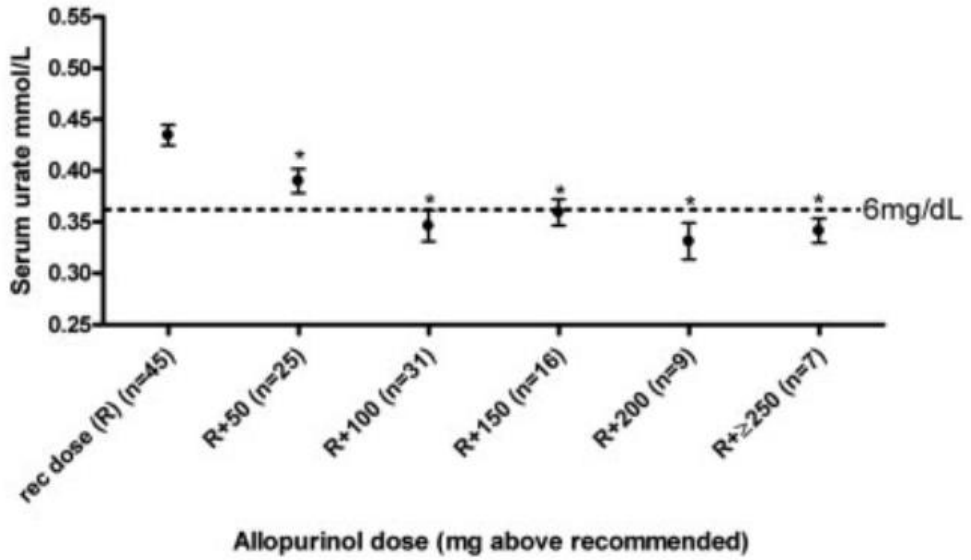


Figure 1. Mean ± SD serum urate concentrations in patients receiving the recommended (rec) dose of allopurinol and those receiving each dose increment above the recommended dose. R+50 = 50 mg greater than the recommended dose. * = $P < 0.0001$ versus baseline.

Stamp, Arthritis Rheum 2011

Febuxostat or allopurinol?

Meta-analysis of RCTs

Febuxostat 40 and 80 mg

Vs

Allopurinol 200-300 mg

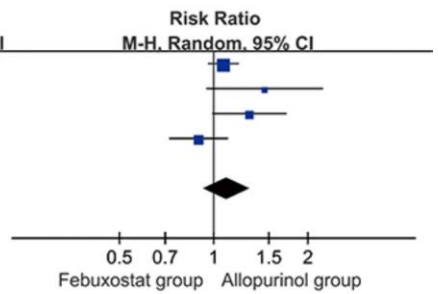
Feb 40 mg

Feb 80 mg

A

Study or Subgroup	Febuxostat group Events	Total	Allopurinol group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Becker 2010	342	757	318	756	39.9%	1.07 [0.96, 1.20]
Kamatani 2011	16	19	11	19	11.7%	1.45 [0.95, 2.24]
Xu 2015	72	160	55	159	21.3%	1.30 [0.99, 1.71]
Zhang 2019	81	181	92	184	27.0%	0.90 [0.72, 1.11]
Total (95% CI)		**1117**		**1118**	**100.0%**	**1.10 [0.93, 1.31]**
Total events	511		476			

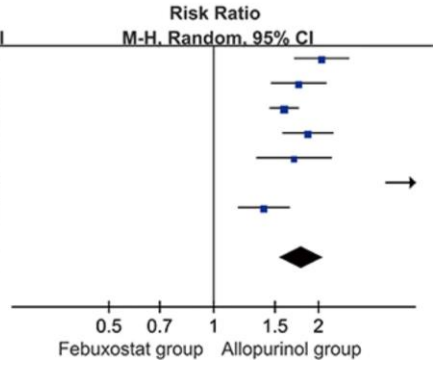
Heterogeneity: Tau² = 0.02; Chi² = 6.50, df = 3 (P = 0.09); I² = 54%
Test for overall effect: Z = 1.15 (P = 0.25)



B

Study or Subgroup	Febuxostat group Events	Total	Allopurinol group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Becker 2005	185	249	88	242	15.8%	2.04 [1.70, 2.45]
Becker 2009	501	620	64	139	15.8%	1.76 [1.46, 2.11]
Becker 2010	507	756	318	756	19.1%	1.59 [1.45, 1.76]
Schumacher 2008	183	253	102	263	16.4%	1.87 [1.57, 2.21]
Xu 2015	93	158	55	159	13.0%	1.70 [1.32, 2.19]
Yu 2016	44	54	7	54	3.6%	6.29 [3.11, 12.69]
Zhang 2019	131	188	92	184	16.2%	1.39 [1.17, 1.66]
Total (95% CI)		**2278**		**1797**	**100.0%**	**1.79 [1.55, 2.08]**
Total events	1644		726			

Heterogeneity: Tau² = 0.03; Chi² = 25.68, df = 6 (P = 0.0003); I² = 77%
Test for overall effect: Z = 7.76 (P < 0.00001)



Xie, BMC Pharmacol Toxicol 2023

Febuxostat or allopurinol?

RCT

Febuxostat 40 to 120 mg

Vs

Allopurinol 100-800 mg

Up titration & treat-to-target

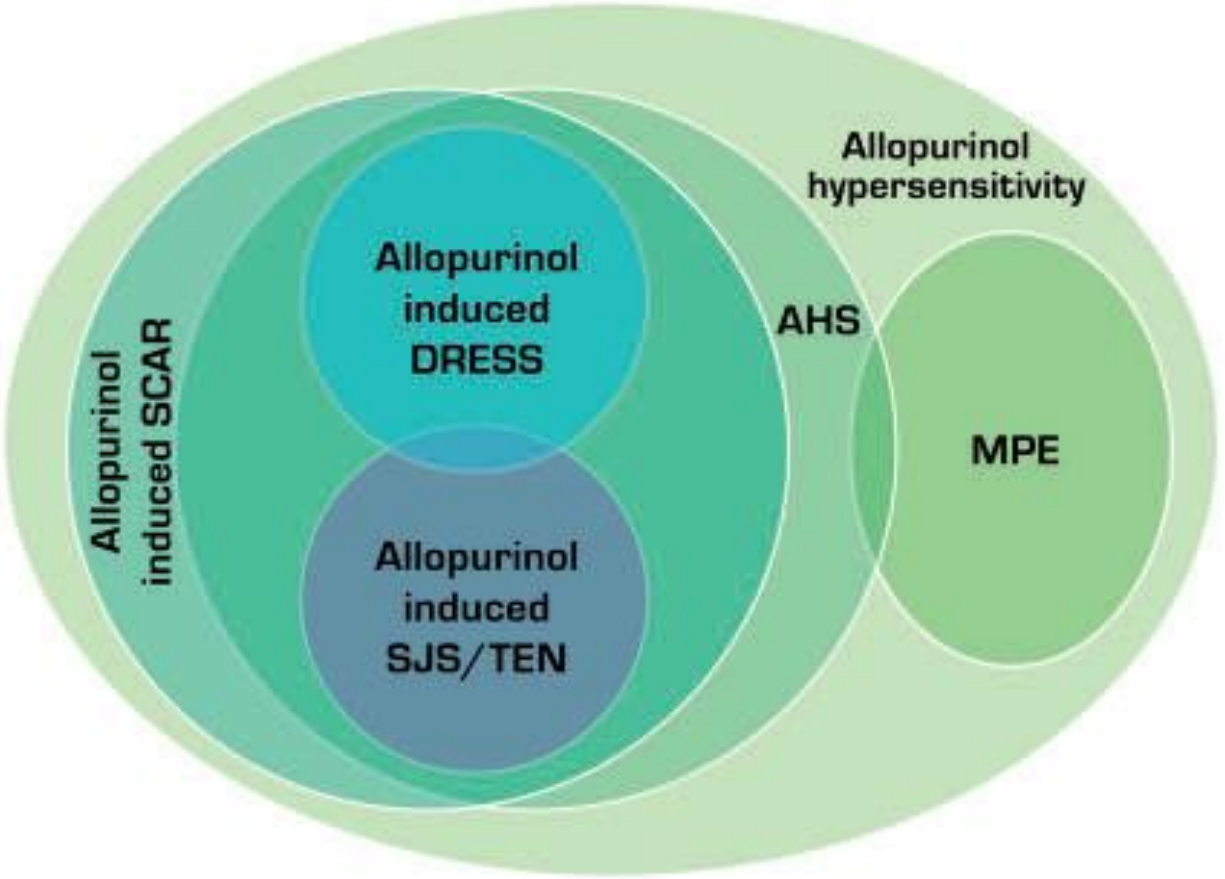
Table 2. Study Results.

End Point*	Allopurinol	Febuxostat	Risk Difference or Risk Ratio (95% CI)†
Primary			
≥1 gout flare in phase 3	36.5 (135/370)	43.5 (165/379)	−7 (−∞ to −1.2)
Secondary			
All study participants			
Serum urate in phase 2 < 6.0 mg/dl‡	81.1 (318/392)	78.4 (308/393)	1.04 (0.96 to 1.11)
Serum urate in phase 2 < 6.8 mg/dl‡	92.4 (362/392)	91.1 (358/393)	1.01 (0.97 to 1.06)

O'Dell, NEJM Evidence 2022

What are the costs and risks associated with allopurinol?

Hypersensitivity to allopurinol



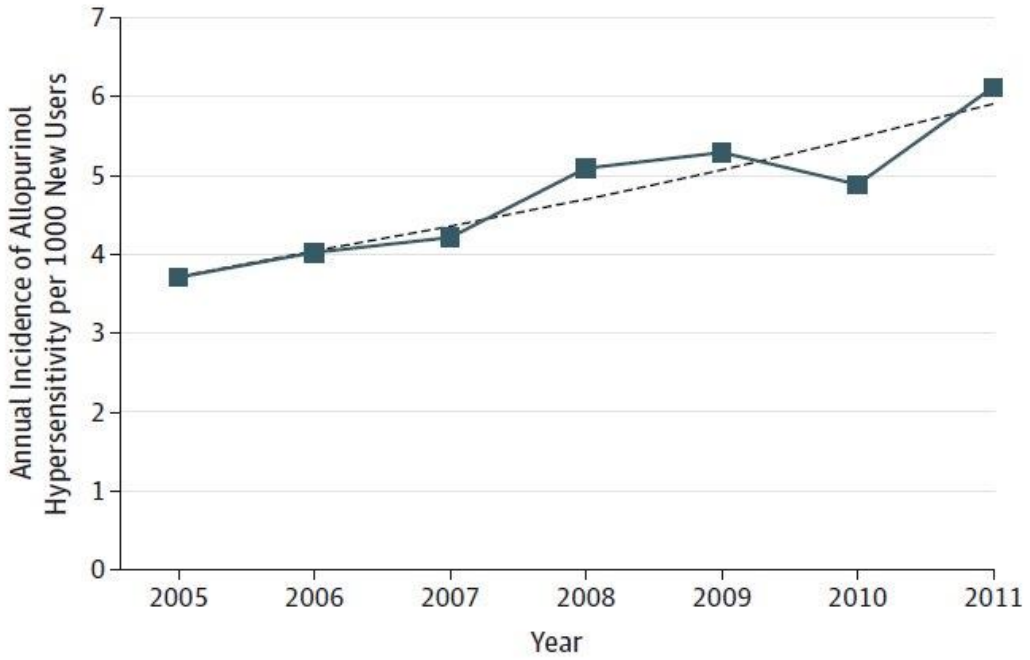
WHAT?

Stamp and BArclay, Rheumatology 2018

Hypersensitivity to allopurinol

HOW OFTEN?

Figure. Annual Incidence of Allopurinol Hypersensitivity in Taiwan



Yang, JAMA 2015

Hypersensitivity to allopurinol

HOW OFTEN?

Arthritis Care & Research
Vol. 65, No. 4, April 2013, pp 578–584
DOI 10.1002/acr.21817

ORIGINAL ARTICLE

Severe Cutaneous Reactions Requiring Hospitalization in Allopurinol Initiators: A Population-Based Cohort Study

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HOW OFTEN?

Hypersensitivity to allopurinol

WHO?

Yang, JAMA 2015

Table 3. Multivariable Logistic Regression Analysis of Risk Factors Associated With Allopurinol Hypersensitivity and Related Mortality

Variable	Odds Ratio (95% CI)			
	Allopurinol Hypersensitivity	*P* Value	Allopurinol Hypersensitivity–Related Mortality	*P* Value
Sex				
Male	1 [Reference]	NA	1 [Reference]	NA
Female	1.45 (1.35-1.56)	<.001	1.63 (1.28-2.08)	<.001
Age, y				
0-39	1 [Reference]	NA	1 [Reference]	NA
40-59	1.02 (0.91-1.14)	.74	1.03 (0.48-2.19)	.95
60-79	1.43 (1.27-1.61)	<.001	5.54 (2.84-10.80)	<.001
≥80	2.27 (1.97-2.60)	<.001	12.37 (6.24-24.53)	<.001
Initial allopurinol dosage, mg/d				
Low, ≤100	1 [Reference]	NA	1 [Reference]	NA
High, >100	1.27 (1.18-1.37)	<.001	1.07 (0.83-1.38)	.61
Antibiotics				
No	1 [Reference]	NA	1 [Reference]	NA
Yes	1.03 (0.77-1.38)	.83	0.93 (0.30-2.89)	.89
Antiepileptic drugs				
No	1 [Reference]	NA	NA	NA
Yes	0.48 (0.21-1.06)	.07	NA	NA
Thiazide diuretics				
No	1 [Reference]	NA	1 [Reference]	NA
Yes	1.02 (0.78-1.32)	.90	1.32 (0.67-2.57)	.42
Angiotensin-converting enzyme inhibitors				
No	1 [Reference]	NA	1 [Reference]	NA
Yes	0.88 (0.74-1.06)	.17	1.26 (0.80-2.01)	.32
With renal diseases				
No	1 [Reference]	NA	1 [Reference]	NA
Yes	1.49 (1.38-1.61)	<.001	2.20 (1.69-2.87)	<.001
With cardiovascular diseases				
No	1 [Reference]	NA	1 [Reference]	NA
Yes	1.13 (1.04-1.22)	.003	1.79 (1.39-2.30)	<.001
With diabetes mellitus				
No	1 [Reference]	NA	1 [Reference]	NA
Yes	0.92 (0.85-0.99)	.03	0.96 (0.74-1.25)	.75
With cancer				
No	1 [Reference]	NA	1 [Reference]	NA
Yes	0.97 (0.88-1.07)	.60	0.69 (0.49-0.97)	.03
Using allopurinol for asymptomatic hyperuricemia				
No	1 [Reference]	NA	1 [Reference]	NA
Yes	2.08 (1.94-2.24)	<.001	2.32 (1.79-3.01)	<.001

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What options are there for patients intolerable to allopurinol/febuxostat?

Is febuxostat suitable for patients with hypersensitivity to allopurinol?

9,1-14,9% of patients with cutaneous adverse reactions (CARs) to allopurinol, also developed CARs to febuxostat

Quilis, Ann Rheum Dis 2022, Bardin, Joint Bone Spine 2016, Bardin, abstr ACR 2014

Desensitization to allopurinol

Low evidence

Little experience

FitzGerald, Arthritis Rheumatol 2020

Uricosurics: provenecid

Start with a low dose: 500 mg once or twice daily

Up- titrate up to 2 gr daily

Not for patients with moderate-to-severe CKD (> or = st 3)

FitzGerald, Arthritis Rheumatol 2020

Pegloticase

PEGylated uricase

Biweekly infusions

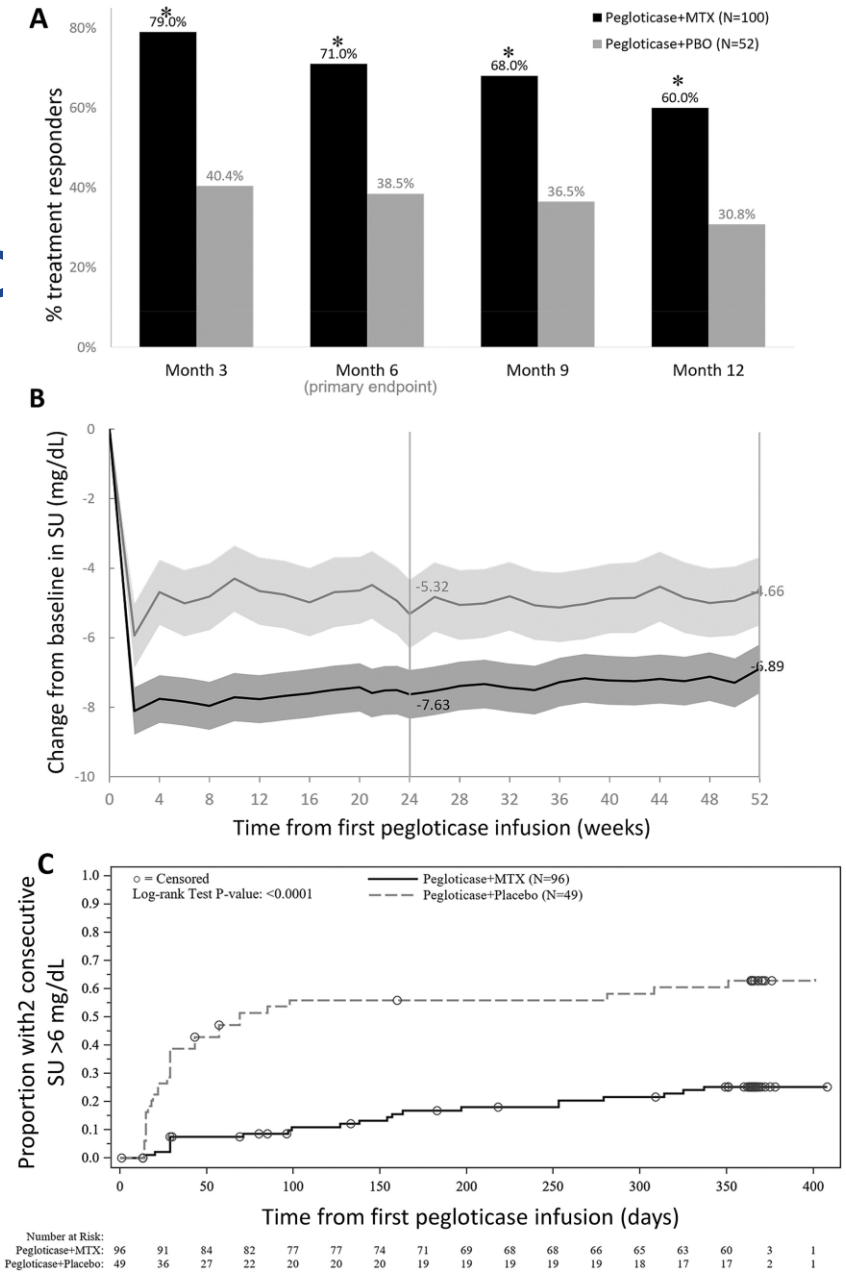
***Caution*:**

Allergic reactions and infusion related AEs common (25%)

Loss of efficacy due to anti-drug antibodies

Botson, Arthritis Rheumatol 2022

Pegloticase+MTX for uncontrolled gc



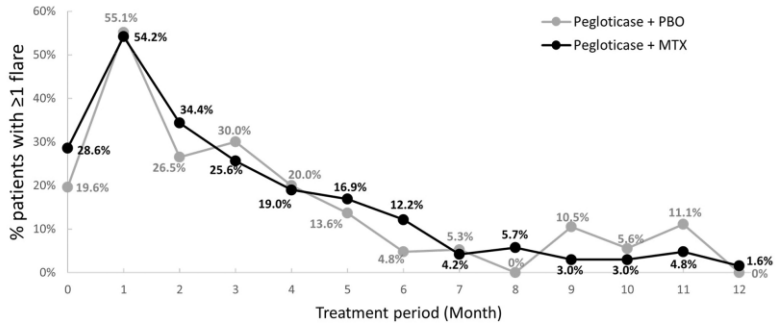
Botson, Arthritis Rheumatol 2022

Pegloticase+MTX of uncontrolled gou

A

Pegloticase + blinded MTX/PBO Treatment period	Pegloticase+MTX (N=96)	Pegloticase+PBO (N=49)
≥1 treatment-emergent AE, n (%)	81 (84.4%)	47 (95.9%)
Gout flare[a]	64 (66.7%)	35 (71.4%)
Musculoskeletal	24 (25.0%)	11 (22.4%)
Infection/infestation[a,b]	18 (18.8%)	9 (18.4%)
COVID-19 infection	9 (9.4%)	3 (6.1%)
Nervous system disorders[c]	15 (15.6%)	4 (8.2%)
Gastrointestinal disorder[b]	13 (13.5%)	9 (18.4%)
General disorders/administration site conditions[d]	12 (12.5%)	6 (12.2%)
Skin[b]	9 (9.4%)	7 (14.3%)
Respiratory/thoracic[b]	9 (9.4%)	2 (4.1%)
Cardiac disorder[a]	5 (5.2%)	0
Cardiac event[a]	1 (1.0%)	0
Infusion reaction[a]	3 (3.1%)	15 (30.6%)
Vascular disorders	2 (2.1%)	4 (8.2%)
Elevated LFTs[b]	2 (2.1%)	2 (4.1%)[f]
Anaphylaxis[a]	1 (1.0%)	0
≥1 Serious AE, n (%)	13 (13.5%)	5 (10.2%)
Infection[a,b,g]	3 (3.1%)	1 (2.0%)
Cardiac disorder	2 (2.1%)	0
Cardiac arrest[a]	1 (1.0%)	0
Mitral valve incompetence	1 (1.0%)	0
Infusion reaction[a]	1 (1.0%)	2 (4.1%)
Small intestine obstruction	1 (1.0%)	0
Anaphylaxis[a]	1 (1.0%)	0
Polymyalgia rheumatica	1 (1.0%)	0
Gunshot wound	1 (1.0%)	0
Rib Fracture	1 (1.0%)	0
Nephrolithiasis	1 (1.0%)	0
Pneumothorax	1 (1.0%)	0
Pulmonary embolism	1 (1.0%)	0
Syncope	0	1 (2.0%)
Non-cardiac chest pain	0	1 (2.0%)
Inappropriate ADH secretion	0	1 (2.0%)
Subdural hematoma	0	1 (2.0%)
Subarachnoid hemorrhage	0	1 (2.0%)
Facial bone fracture	0	1 (2.0%)
Failure to thrive	0	1 (2.0%)

B



Botson, Arthritis Rheumatol 2023

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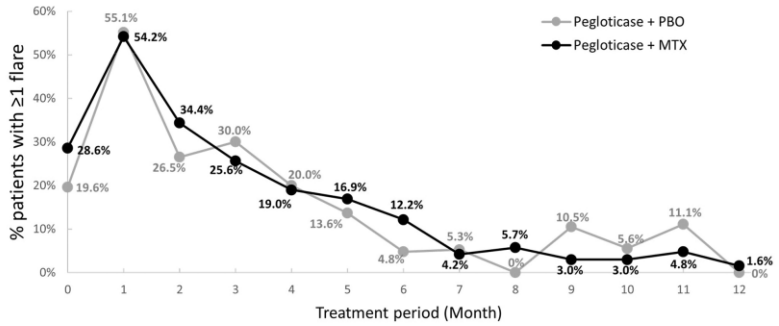
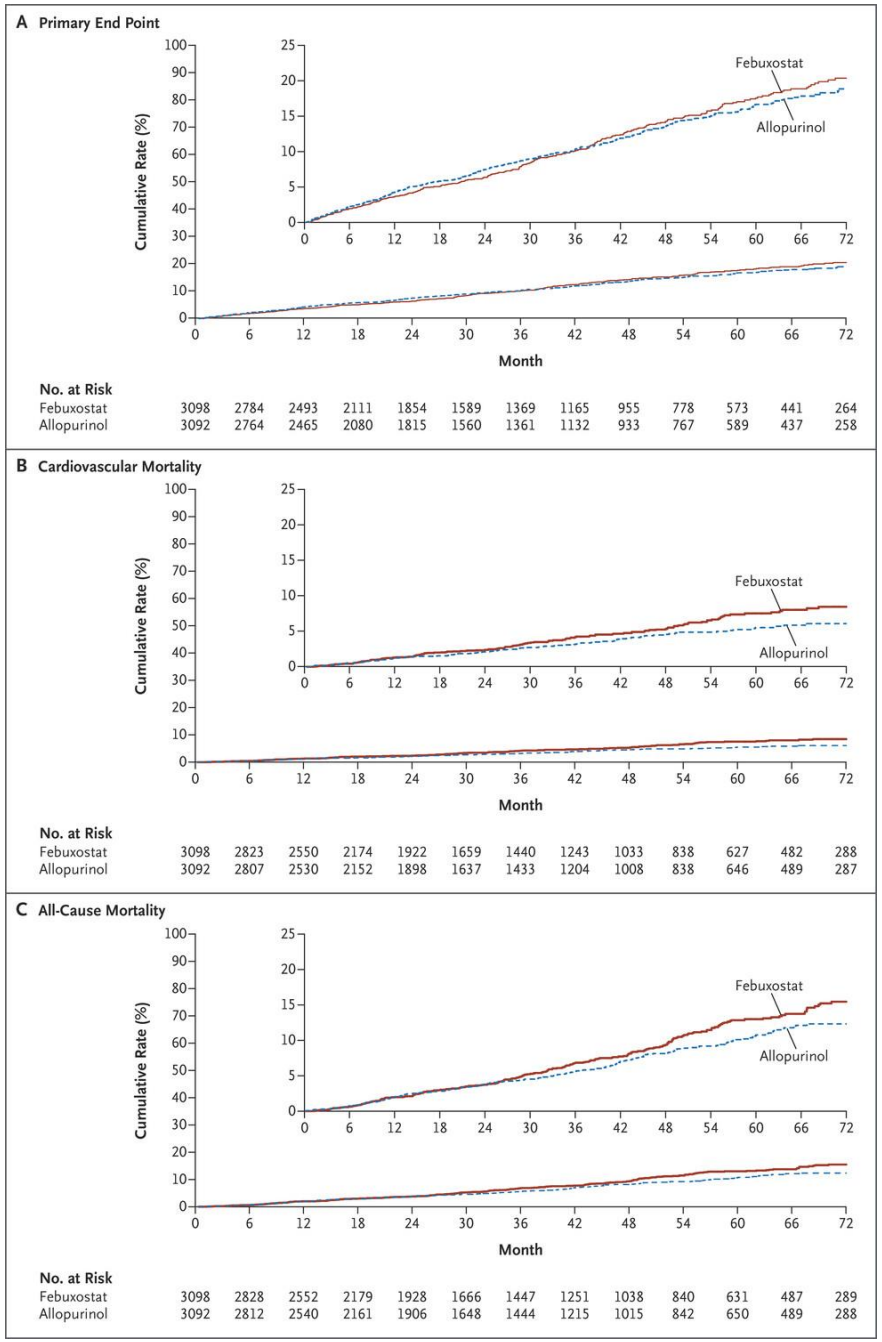
B



Botson, Arthritis Rheumatol 2023

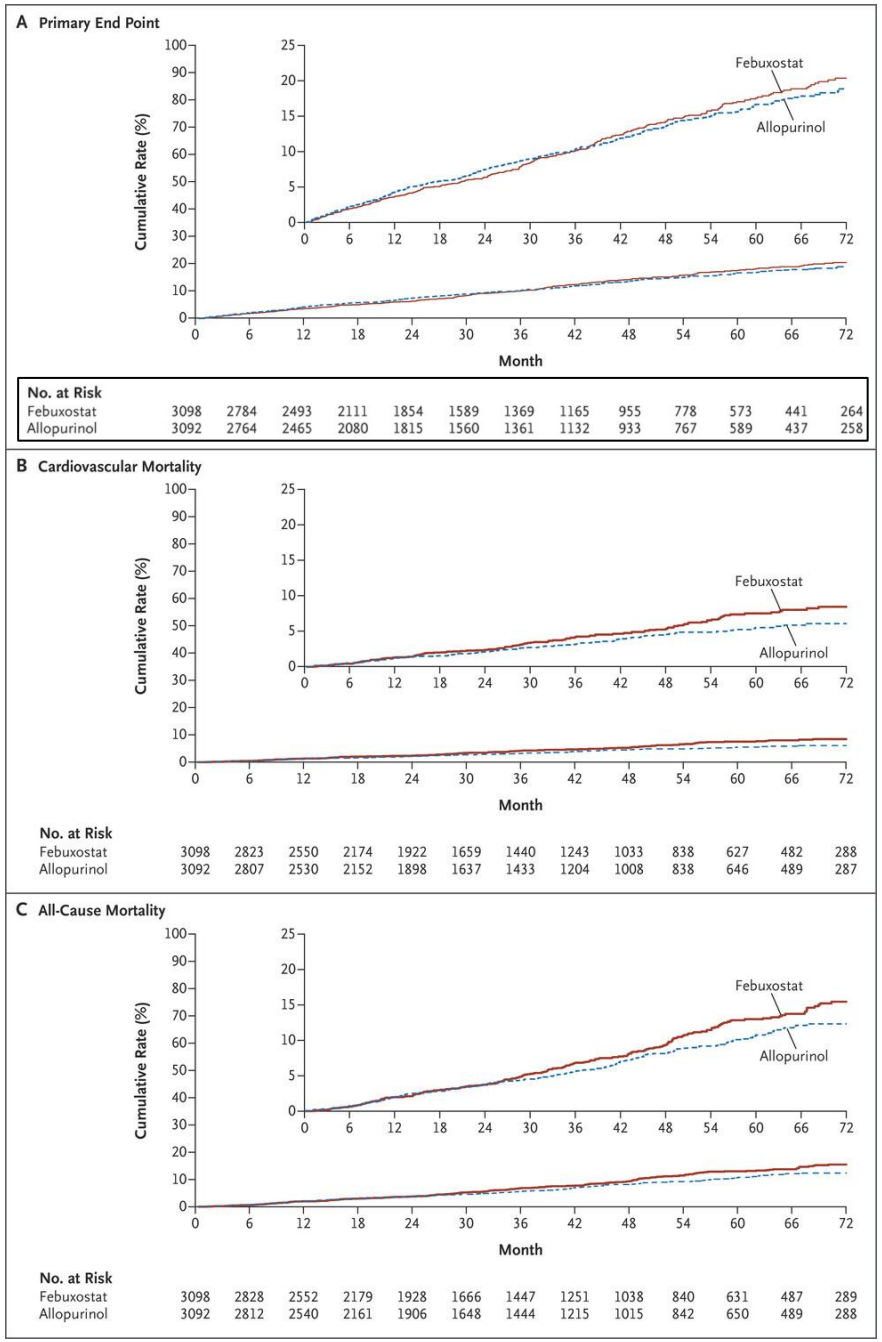
Is febuxostat OK for a patient with ischemic heart disease?

The CARES trial: CV safety of febuxostat vs allopurinol in patients with gout and CV risk factors



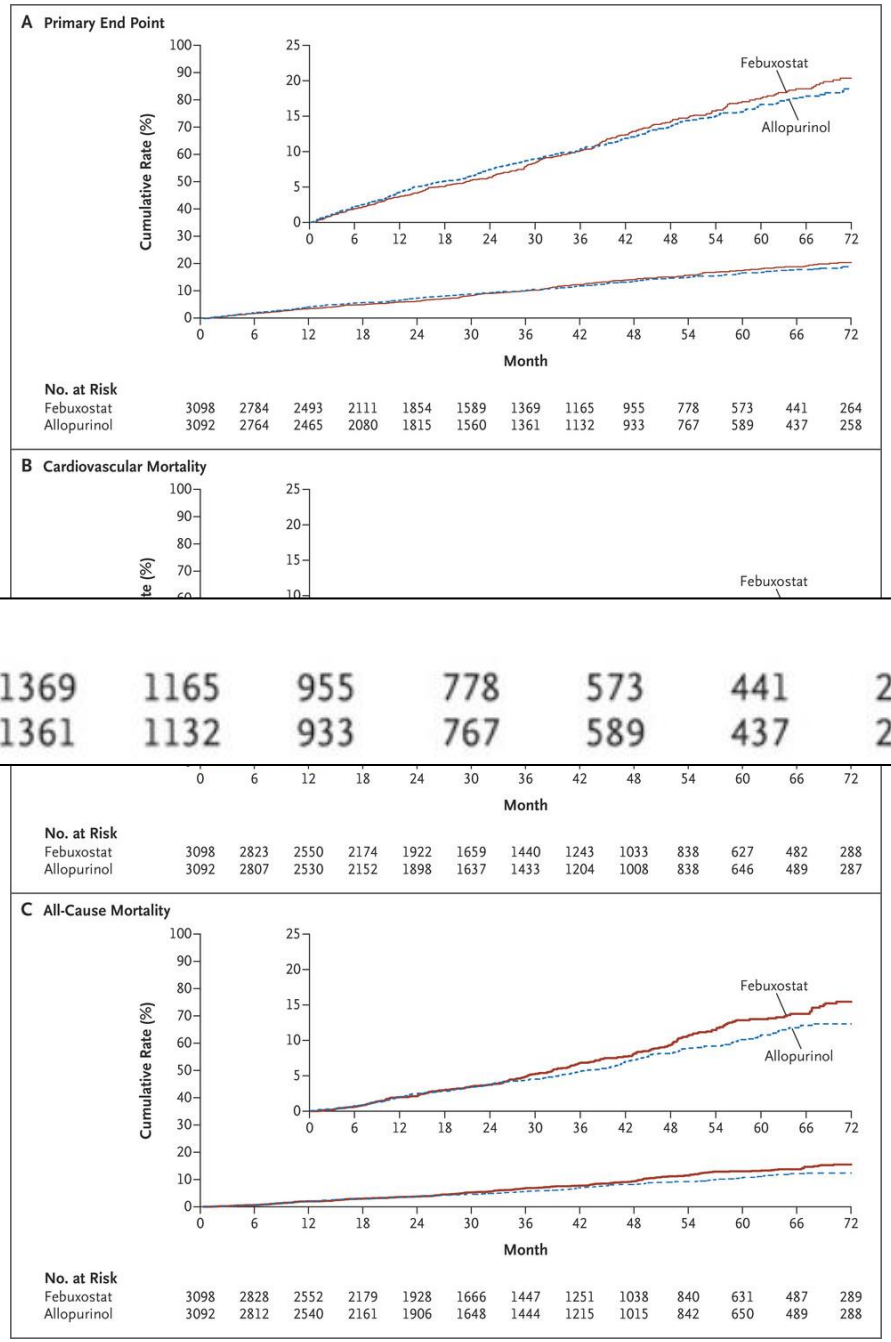
White, N Engl J Med 2018

The CARES trial: CV safety of febuxostat vs allopurinol in patients with gout and CV risk factors



White, N Engl J Med 2018

The CARES trial: CV safety of febuxostat vs allopurinol in patients with gout and CV risk factors



No. at Risk

Febuxostat	3098	2784	2493	2111	1854	1589	1369	1165	955	778	573	441	264
Allopurinol	3092	2764	2465	2080	1815	1560	1361	1132	933	767	589	437	258

High dropout rate (56,6%)

High percentage of patients lost to follow-up (45%)

White, N Engl J Med 2018

The CARES trial: CV safety of febuxostat vs allopurinol in patients with gout and CV risk factors

Most events occurred after treatment discontinuation

Table S12. All known deaths according to treatment status*

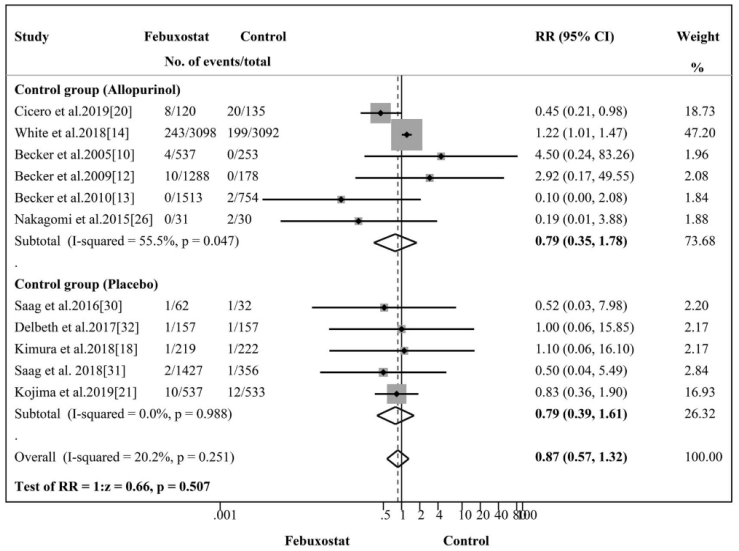
Analysis	Febuxostat (n = 3098)	Allopurinol (n = 3092)	Hazard Ratio for Febuxostat Group (95% CI)
All deaths, N (%)	332 (10.7)	309 (10.0)	1.09 (0.94, 1.28)
Time from randomization to death on treatment	36 (1.2)	28 (0.9)	1.27 (0.77, 2.08)
Time from randomization to death within 30 days after treatment	94 (3.0)	74 (2.4)	1.25 (0.92, 1.70)
Time from last dose of study medication to death	296 (9.6)	281 (9.1)	1.10 (0.93, 1.29)

* Additional deaths (non-adjudicated) were identified via a search company
Time from randomization to first occurrence of death from all causes were fitted using a COX proportional hazard model with factors including treatment and baseline renal function.

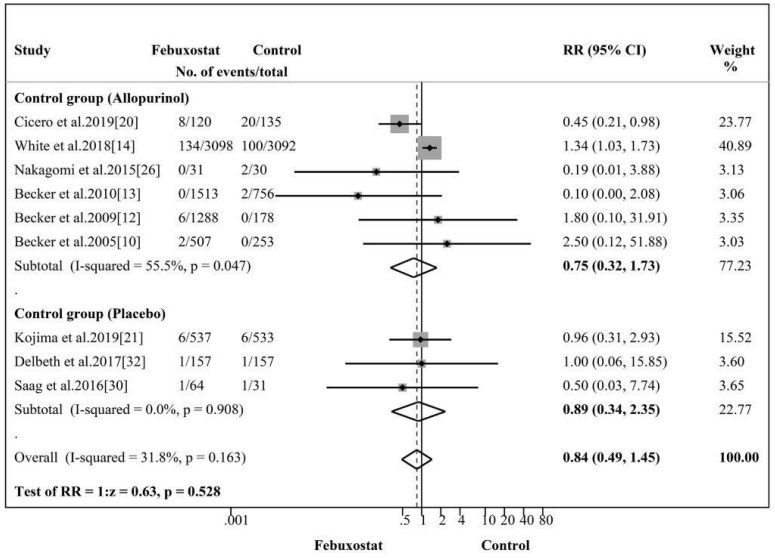
White, N Engl J Med 2018

CV safety of febuxostat in patients with gout

Meta-analysis of 20 RCTs



Outcome: all-cause mortality



Outcome: CVD death

Deng, J Rheumatol 2021

OK, ULT. But for how long?

Indefinitely, except...

Risk of gout recurrence after discontinuation of ULT (patients *without* tophi)

According to sUA levels after treatment cessation, following a 5-year treatment period

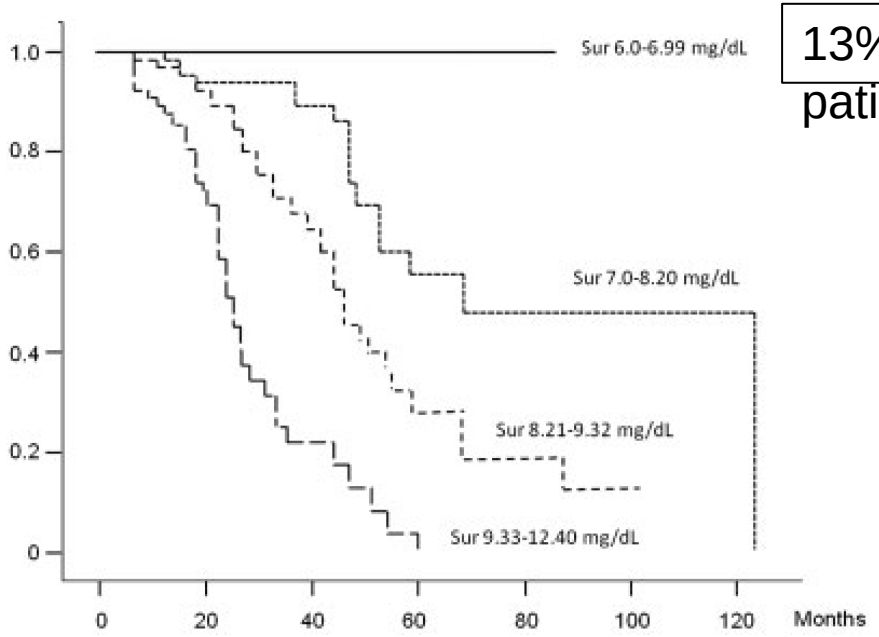


Figure 1. Survival function plot by serum urate (Sur) levels after withdrawal of urate-lowering therapy.

13% of patients

Perez-Ruiz, Arthritis Rheum 2011

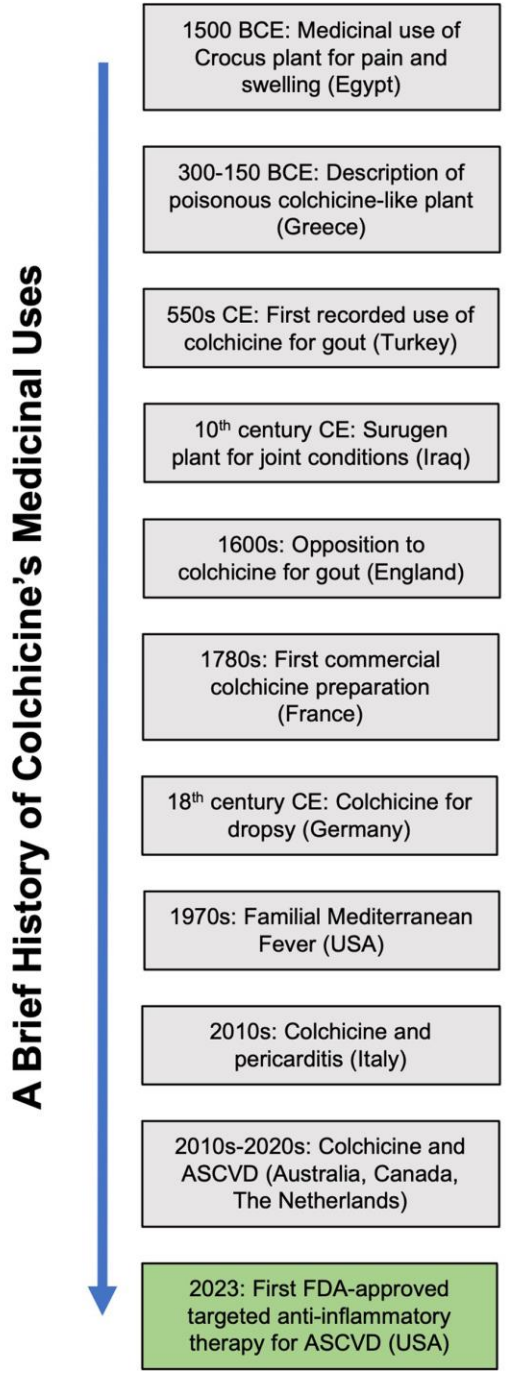
Colchicine

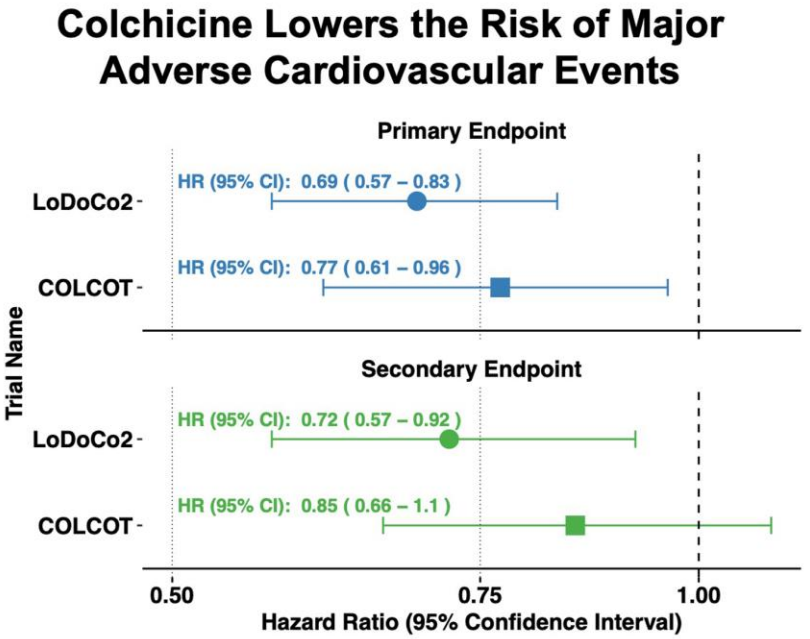
Who?

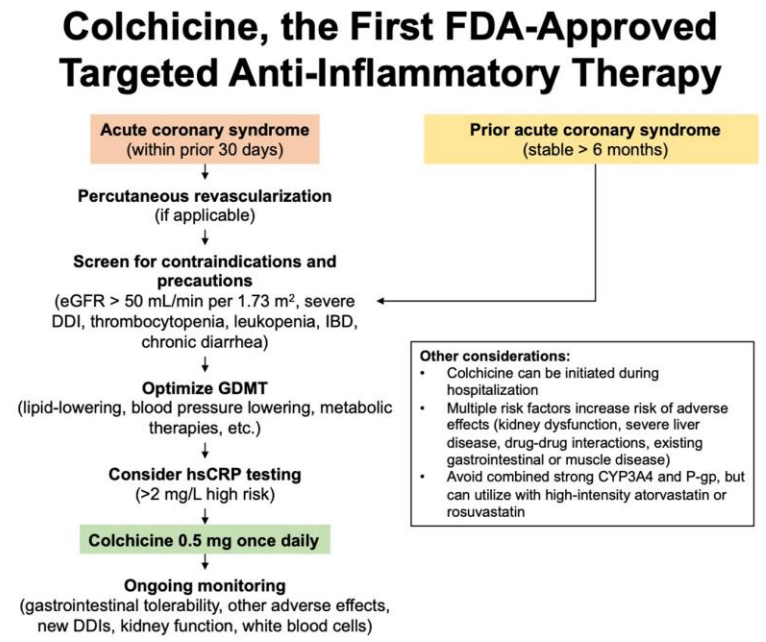
During the initial 24 h (12 h?) of an acute gout attack

For 3-6 months of the initiation and up-titration of ULT, as prophylaxis

Colchicine's Role in Cardiovascular Disease Management

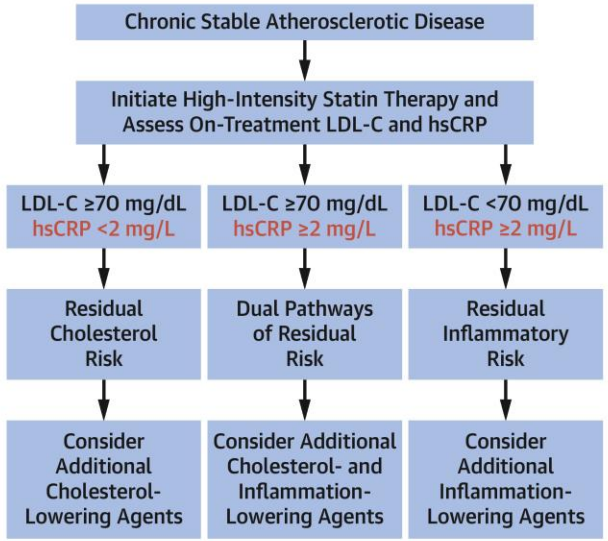


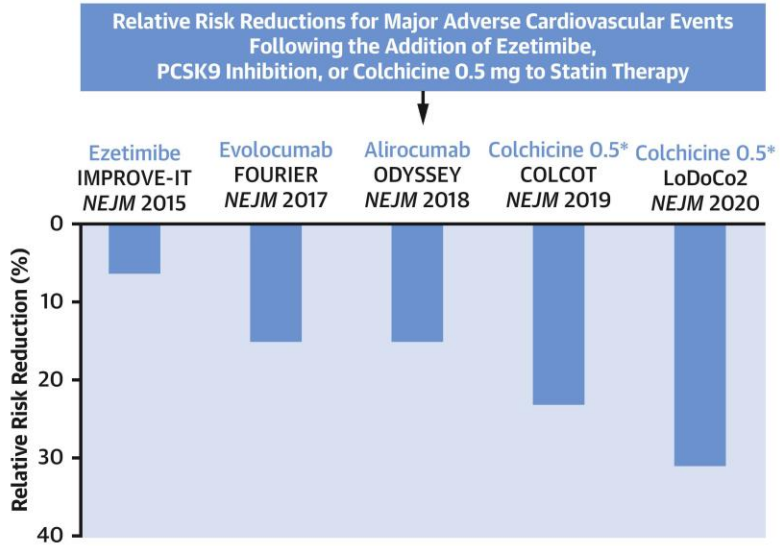




Buckley and Libby, Atheroscler, Thromb Vasc Biol 2024

CENTRAL ILLUSTRATION: Managing Residual Inflammatory Risk and Residual Cholesterol Risk in Stable Coronary Disease





Nelson K, et al. J Am Coll Cardiol. 2023;82(7):648-660.

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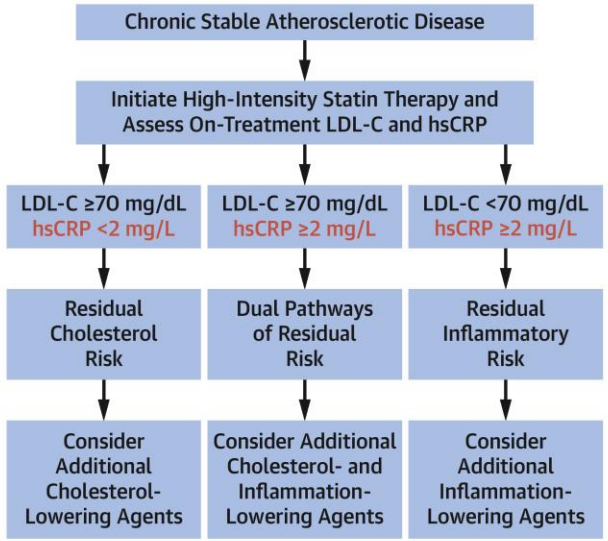

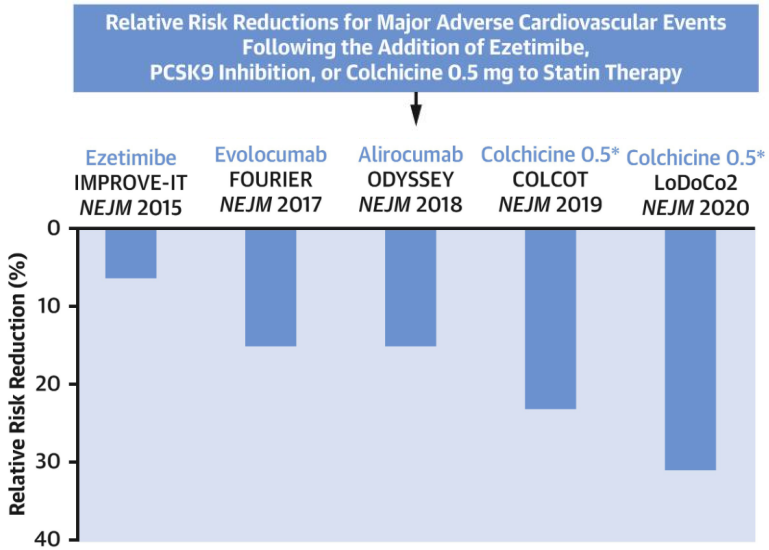

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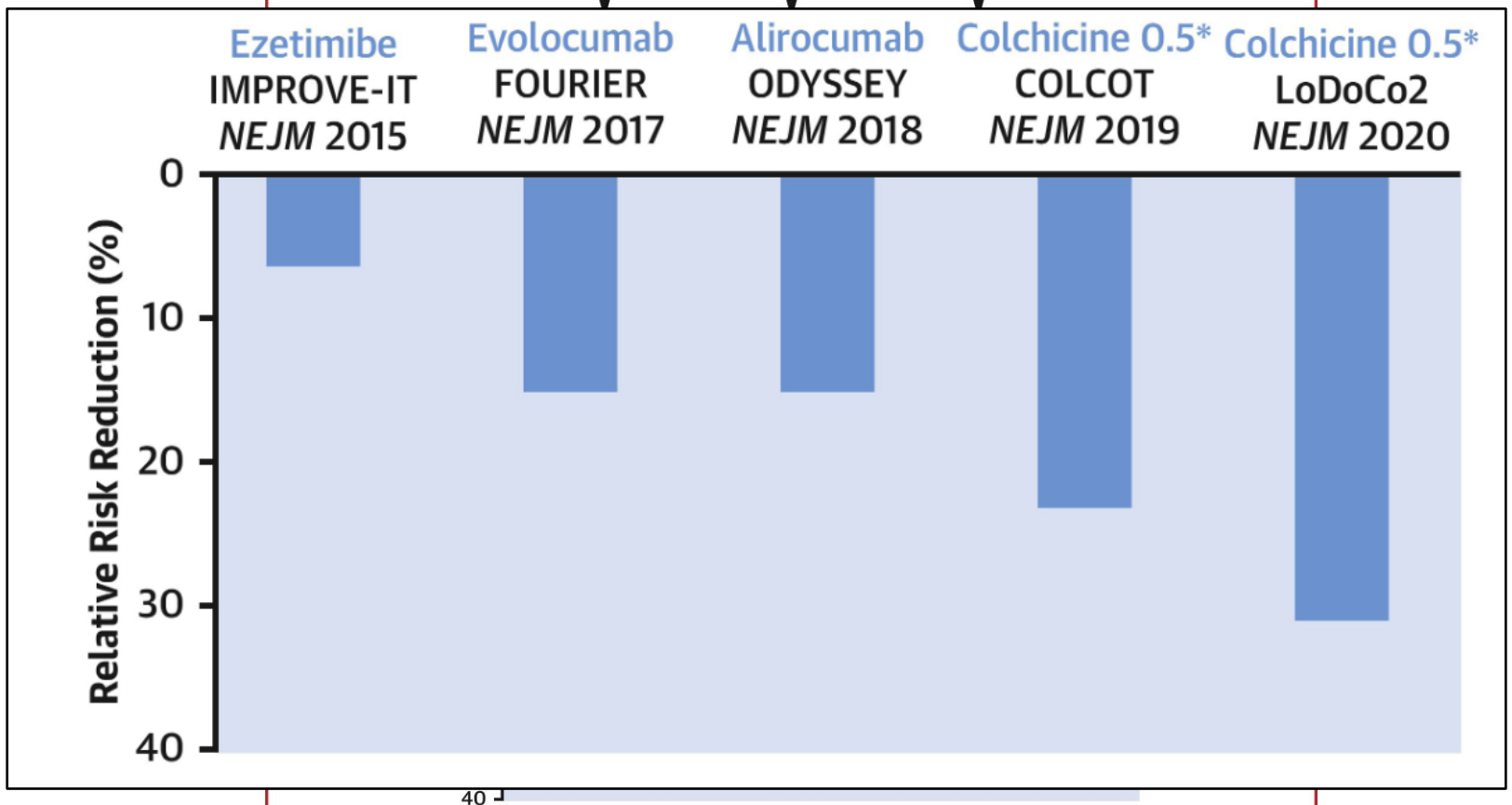

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How safe is colchicine?

REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Consensus Statement Regarding the Efficacy and Safety of Long-Term Low-Dose Colchicine in Gout and Cardiovascular Disease

Philip C. Robinson, MBChB, PhD,[a,b] Robert Terkeltaub, MD,[c] Michael H. Pillinger, MD,[d] Binita Shah, MD, MS,[e] Vangelis Karalis, PhD,[f] Eleni Karatza, PhD,[f] David Liew, MBBS,[g,h] Massimo Imazio, MD,[i] Jan H. Cornel, MD, PhD,[j] Peter L. Thompson, MBBS, MD,[k] Mark Nidorf, MBBS, MD[l]

Robinson, Am J Med 2023

How safe is colchicine?

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THE AMERICAN JOURNAL of MEDICINE®

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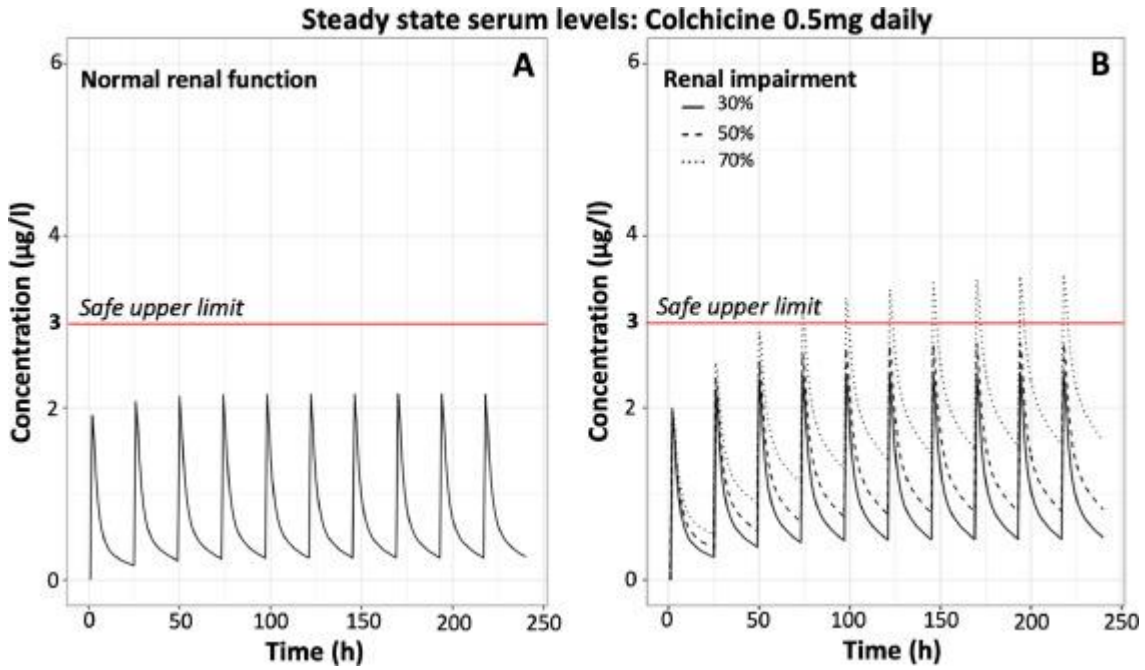
Philip C. Robins[a,b] ... MD,[d] Binita Shah, MD, MS,[e]
Vangelis Karalis ... MD,[i] Jan H. Cornel, MD, PhD,[j]
Peter L. Thomps

CLINICAL SIGNIFICANCE

- Long-term low-dose colchicine is effective for preventing gout flares and cardiovascular events in a wide range of patients.
- The clinical benefits of colchicine achieved at low dose do not sustain serum levels above the upper limit of safety in patients without advanced renal or liver disease or when used concomitantly with most medications.
- Long-term low-dose colchicine does not increase the risk of cancer, sepsis, cytopenia, or myotoxicity.

Robinson, Am J Med 2023

How safe is colchicine?



Robinson, Am J Med 2023

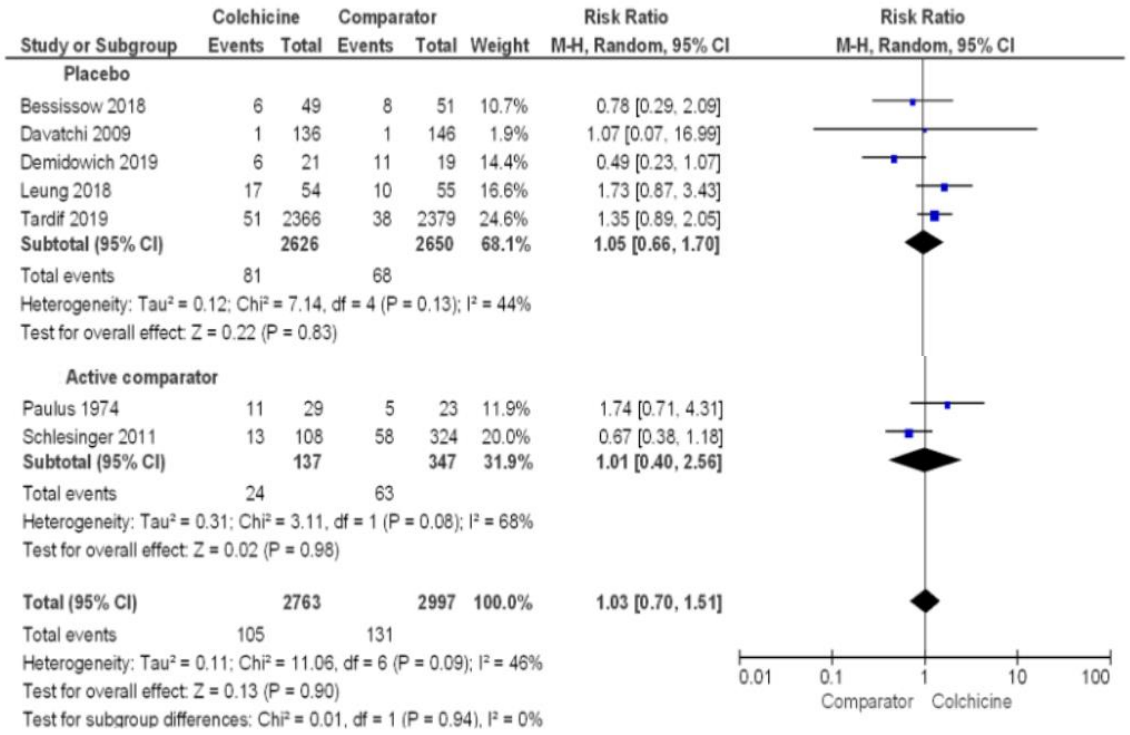
How safe is colchicine?

Table Safe Doses of Colchicine with Commonly Used Drugs That Affect Clearance of Colchicine

CYP3A4 Inhibitors	P-glycoprotein inhibitors	Safe Colchicine Use
Strong Clarithromycin Telithromycin Ketoconazole Voriconazole Fluconazole	Strong Clarithromycin Itraconazole Ketoconazole Voriconazole Fluconazole	Avoid concomitant use of colchicine at any dose because an overlap of therapy for short periods may be rarely toxic even in patients with normal renal function.[12,18–20]
Moderate Cyclosporine Ritonavir	Moderate HIV medications (Ritonavir)	Doses up to 0.5-0.6 mg daily are likely safe in patients with normal renal and liver function.[17,21] In patients with renal or liver failure avoid if possible or reduce colchicine dose to alternate day.
Mild Erythromycin Ciprofloxacin Cobicistat Imatinib Atorvastatin Grapefruit	Mild Diltiazem Verapamil Amiodarone Carvedilol Quinidine Ranolazine Erythromycin Simvastatin	Doses of 0.5-0.6 mg daily are safe without dose adjustment required in patients with normal renal or liver function.

Robinson, Am J Med 2023

Is colchicine immunosuppressive?



Study or Subgroup	Colchicine Events	Colchicine Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Random, 95% CI
Placebo						
Bessissow 2018	6	49	8	51	10.7%	0.78 [0.29, 2.09]
Davatchi 2009	1	136	1	146	1.9%	1.07 [0.07, 16.99]
Demidowich 2019	6	21	11	19	14.4%	0.49 [0.23, 1.07]
Leung 2018	17	54	10	55	16.6%	1.73 [0.87, 3.43]
Tardif 2019	51	2366	38	2379	24.6%	1.35 [0.89, 2.05]
Subtotal (95% CI)		**2626**		**2650**	**68.1%**	**1.05 [0.66, 1.70]**
Total events	81		68			
Heterogeneity: Tau² = 0.12; Chi² = 7.14, df = 4 (P = 0.13); I² = 44%						
Test for overall effect: Z = 0.22 (P = 0.83)						
Active comparator						
Paulus 1974	11	29	5	23	11.9%	1.74 [0.71, 4.31]
Schlesinger 2011	13	108	58	324	20.0%	0.67 [0.38, 1.18]
Subtotal (95% CI)		**137**		**347**	**31.9%**	**1.01 [0.40, 2.56]**
Total events	24		63			
Heterogeneity: Tau² = 0.31; Chi² = 3.11, df = 1 (P = 0.08); I² = 68%						
Test for overall effect: Z = 0.02 (P = 0.98)						
Total (95% CI)		**2763**		**2997**	**100.0%**	**1.03 [0.70, 1.51]**
Total events	105		131			
Heterogeneity: Tau² = 0.11; Chi² = 11.06, df = 6 (P = 0.09); I² = 46%						
Test for overall effect: Z = 0.13 (P = 0.90)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%						

Supplementary Figure 8. Forest plot showing estimated relative risk of infectious events during colchicine use compared to placebo and active comparator groups

Stewart, Arthritis Res Ther 2020


Drugs don't work in patients
who don't take them.
C. Everett Koop
quotefancy