Ουρική αρθρίτιδα
Treat-to-target or treat-to-symptoms?

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Σύγκρουση συμφερόντων

Καμία για την συγκεκριμένη παρουσίαση

Την τελευταία διετία αμοιβή από τις εταιρείες

AbbVie, Pfizer, Elpen, UCB

Παρουσίαση περιστατικού

Άνδρας 62 ετών

BMI: 29

Ατομικό αναμνηστικό: Αρτηριακή υπέρταση (αΜΕΑ+υδροχλωροθειαζίδη), χοληστερολαιαμία (στατίνη)

1 κρίση αρθρίτιδας 1 ΜΤΦ πριν 8 χρόνια που πέρασε σε 5 μέρες με ΜΣΑΦ (πιθανότατα ουρικής αρθρίτιδας)

Παρουσίαση περιστατικού

Τώρα: οξεία αρθρίτιδα ΔΕ γόνατος με πυρετό μέχρι 38C.

Παρακέντηση- μικροσκόπηση: κρύσταλλοι ουρικού μονονατρίου

Καλλιέργεια: στείρα

ΤΚΕ= 85

CRP=92 mg/L

Ουρικό οξύ= 9,1 mg/dl

Παρουσίαση περιστατικού

- ΜΣΑΦ και κολχικίνη: ύφεση σε 2 μέρες.
- Εναρξη αλλοπουρινόλης 100 mg
- + κολχικίνης 0,5 mg
- Σε 1 μήνα ουρικό οξύ =8,6 mg

Παρουσίαση περιστατικού

- Αυξηση αλλοπουρινόλης 200 mg
- Συνέχιση κολχικίνης
- Σε 1 μήνα ουρικό οξύ =7,6 mg/dl

Παρουσίαση περιστατικού

- Αυξηση αλλοπουρινόλης 200 mg
  - Συνέχιση κολχικίνης
  - Σε 1 μήνα ουρικό οξύ =7,6 mg/dl

- Αυξηση αλλοπουρινόλης 300 mg
  - Συνέχιση κολχικίνης
  - Σε 1 μήνα ουρικό οξύ = 6,8 mg/dl

Παρουσίαση περιστατικού

3 Μήνες.

Διακοπή κολχικίνης

Μία κρίση στο μεγάλο δάκτυλο (ήπια)- υποχώρησε εν τη γεννέσει με λήψη 1 mg κολχικίνης για 2 μέρες

Παρουσίαση περιστατικού

Παραμενει ασυμπτωματικός

(μόνο ήπιες κρίσεις ανα 8-12 μήνες που υποχωρούν τάχιστα με λήψη κολχικίνης για 1-2 μέρες)

Ουρικό οξύ= 7-7,5 mg/dl

The controversy:

The recommendations:

- ACP insufficient data to propose a target level.
- Treat-to-symptoms

- ACR, EULAR treat-to-target with a target of UA of <6 mg/dl (or <5 mg/dl in severe cases)

Clinical trials in gout: What is the optimal end-point?

Two perspectives

Number of gout flares (Severity? Duration?)

Uric acid level as a surrogate marker for disease severity (evidence?)

The paradox: flare rates during the first 2 years of treatment

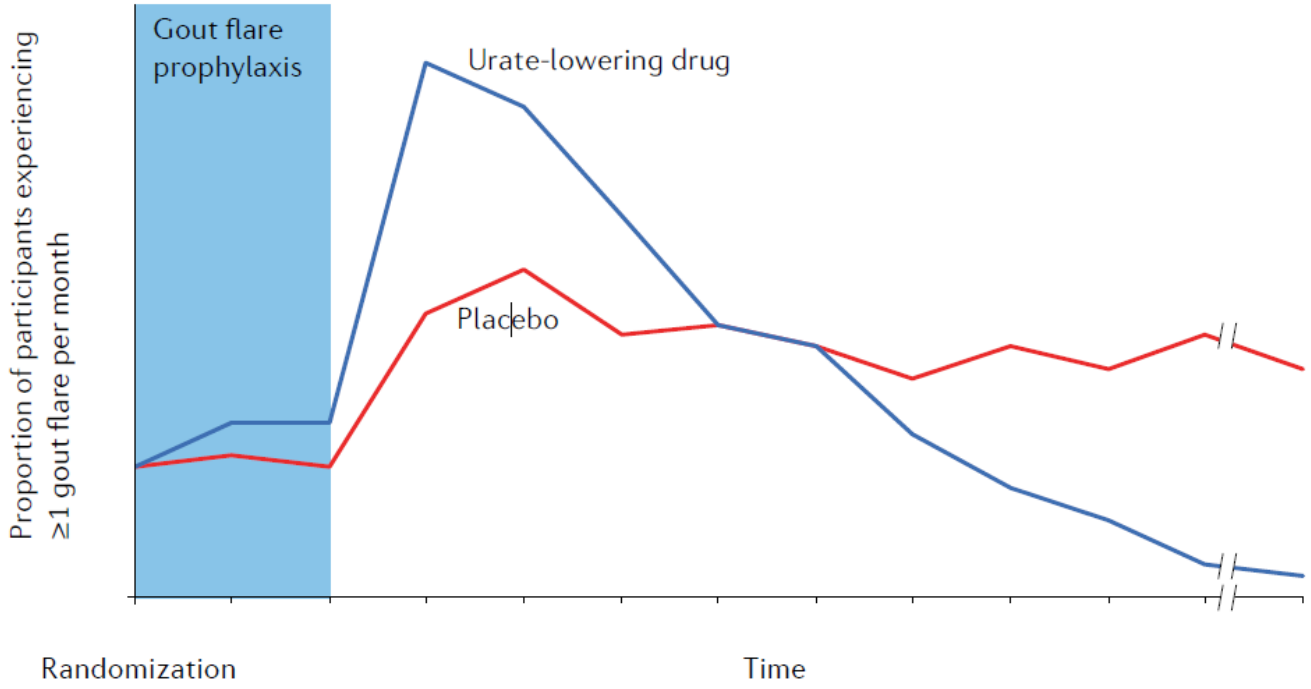


Fig. 1 | **Gout flare trends after initiation of a potent urate-lowering agent in a hypothetical placebo-controlled randomized controlled trial.** The risk of flares in the urate-lowering drug group increases after the initial anti-inflammatory prophylaxis phase of the trial (for example, 3 months) dissipates. This paradoxical worsening is followed by a substantially lower risk of flares over time. By contrast, the placebo group is expected to have a similar (or higher) level of flares over time, once the initial anti-inflammatory prophylaxis effect discontinues.

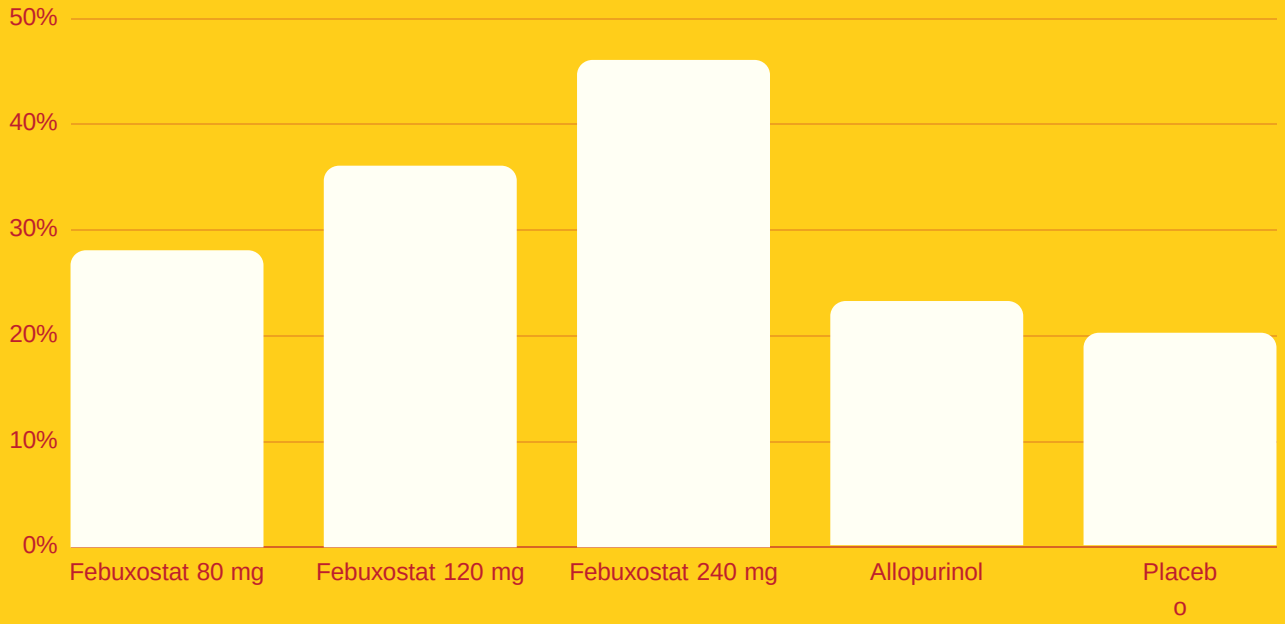
"Mobilization flares"

Common in the first months after ULT initiation

About 35-50% of the patients with, and 75% without anti-inflammatory prophylaxis

Choi, Nat Rev Rheumatol 2022, O'Dell, NEJM Evidence 2022

RATE OF FLARE DURING THE FIRST 8 WEEKS



Schumacher, Arthritis Care Res 2008

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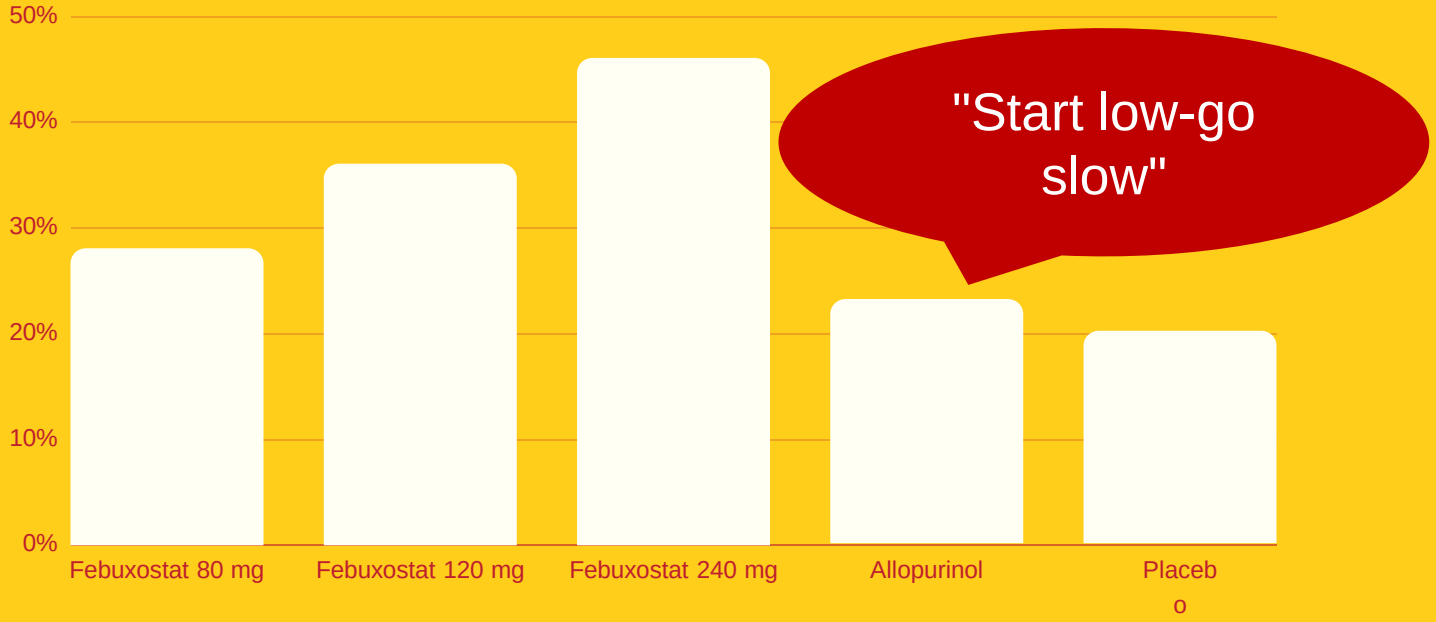
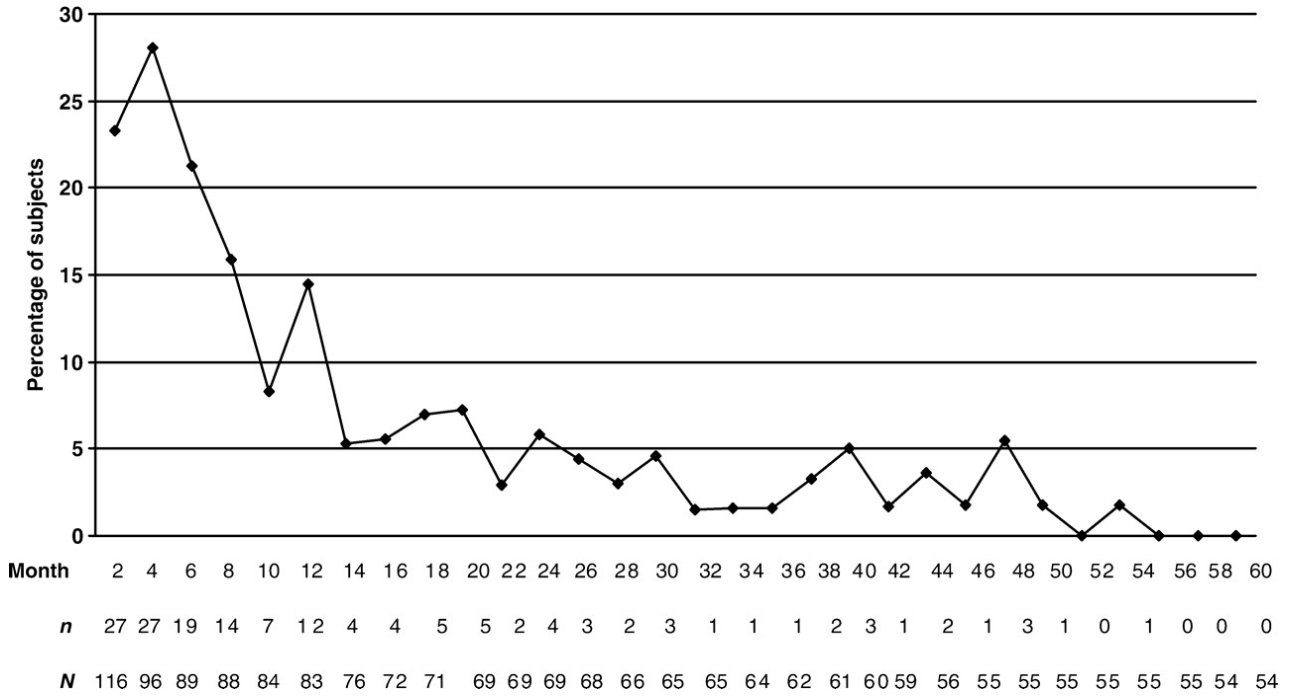


Schumacher, Arthritis Care Res 2008

Remission of gout flares under ULT (febuxostat) takes a long time



Percentage of subjects that required treatment for flares while they received maintenance dose. Time is with respect to duration of treatment with stable maintenance dose. Months are the end of time intervals and data points represent the total incidence of gout flares that required treatment during each 2-month interval. '*N*' represents the total number of subjects on a final stable dose of febuxostat for the duration designated and '*n*' is the total number of subjects that reported at least one gout flare that required treatment in the given time interval.

Schumacher, Rheumatology 2009

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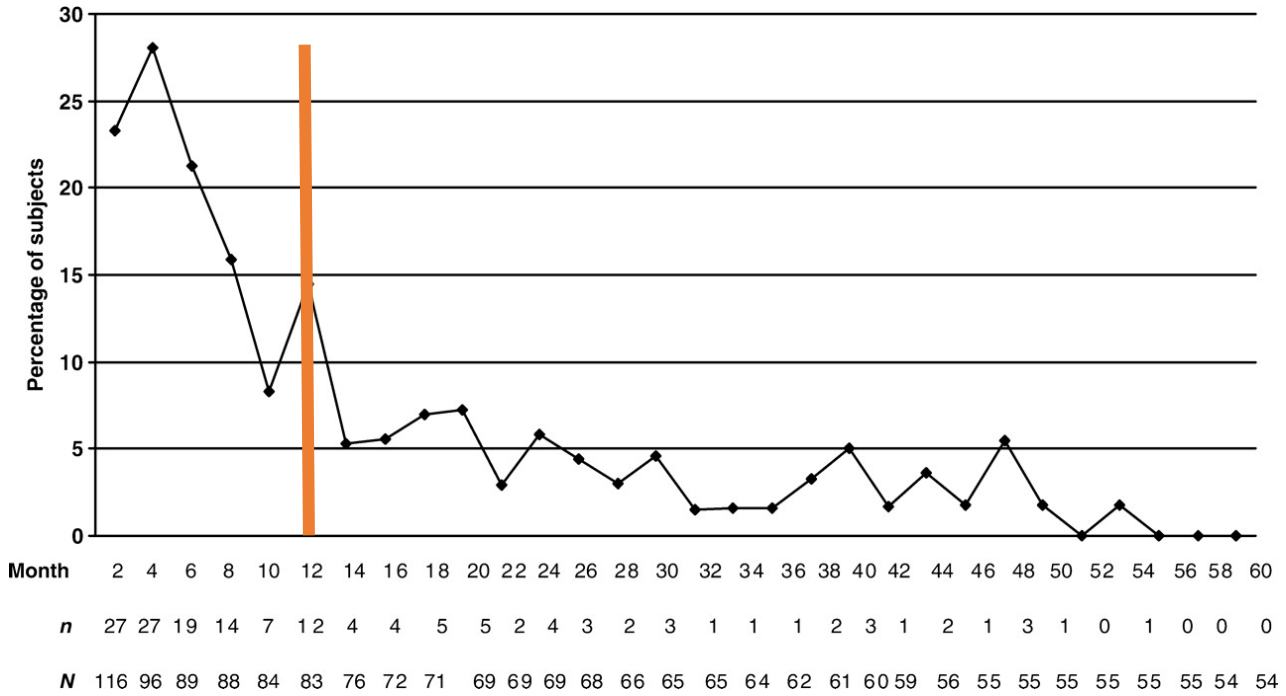

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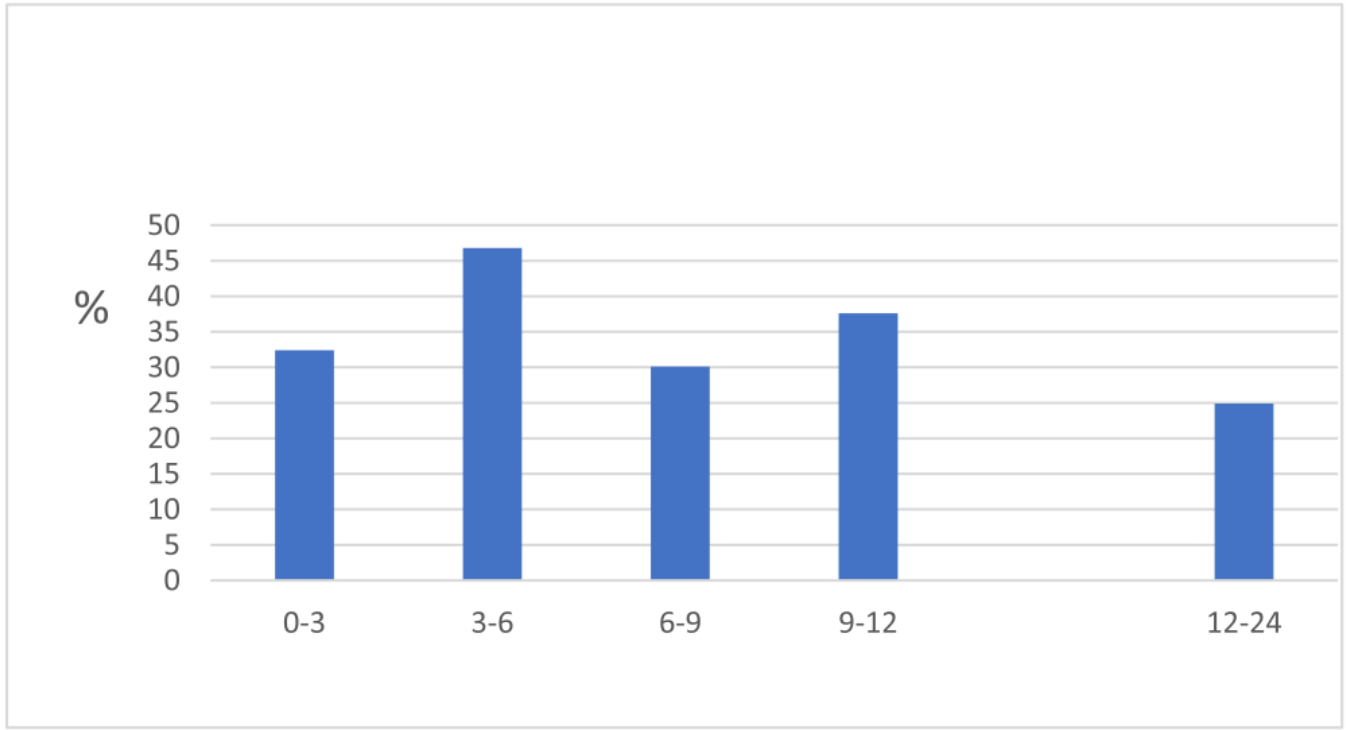
Schumacher, Rheumatology 2009

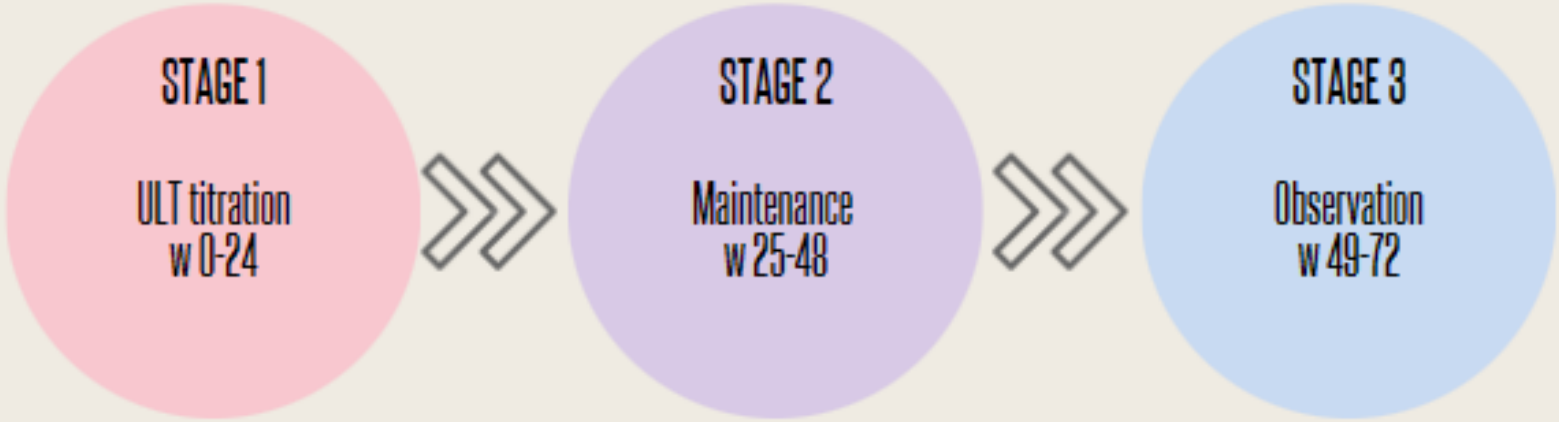
Flares are more common in the first year after initiation of ULT



Flare frequency during the 3 months periods in year 1 and in year 2 after treat-to-target ULT

Uhlig, Arthritis Res Ther 2022

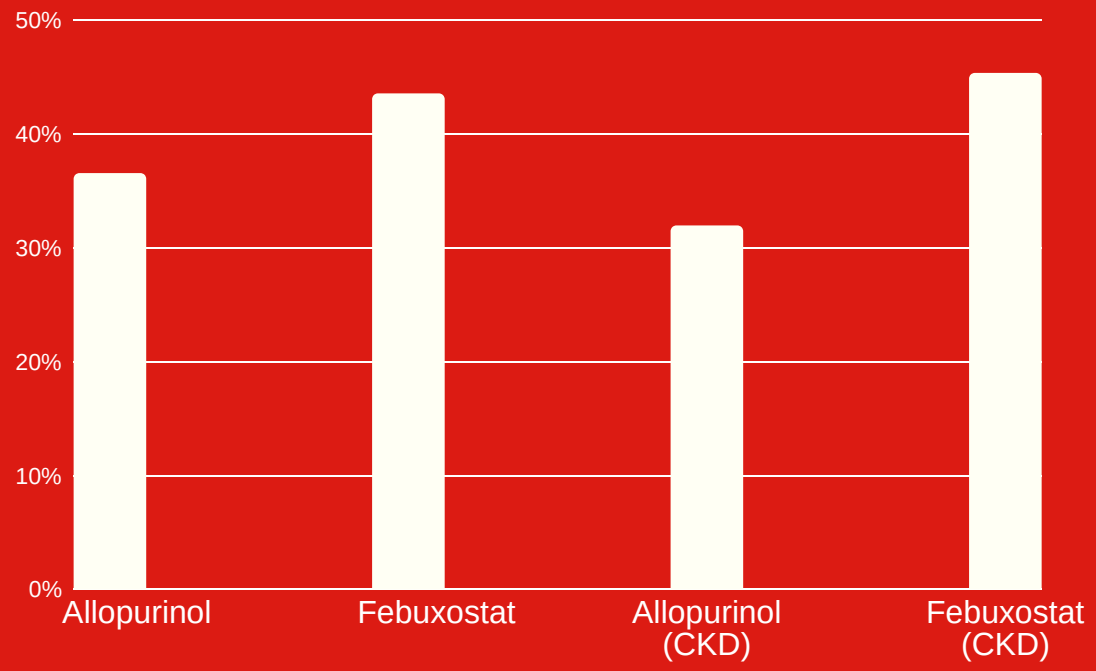
COMPARATIVE STUDY OF ALLOPURINOL VS FEBUXOSTAT



Stamp, NEJM Evidence 2022

PATIENTS WITH FLARE DURING PHASE 3

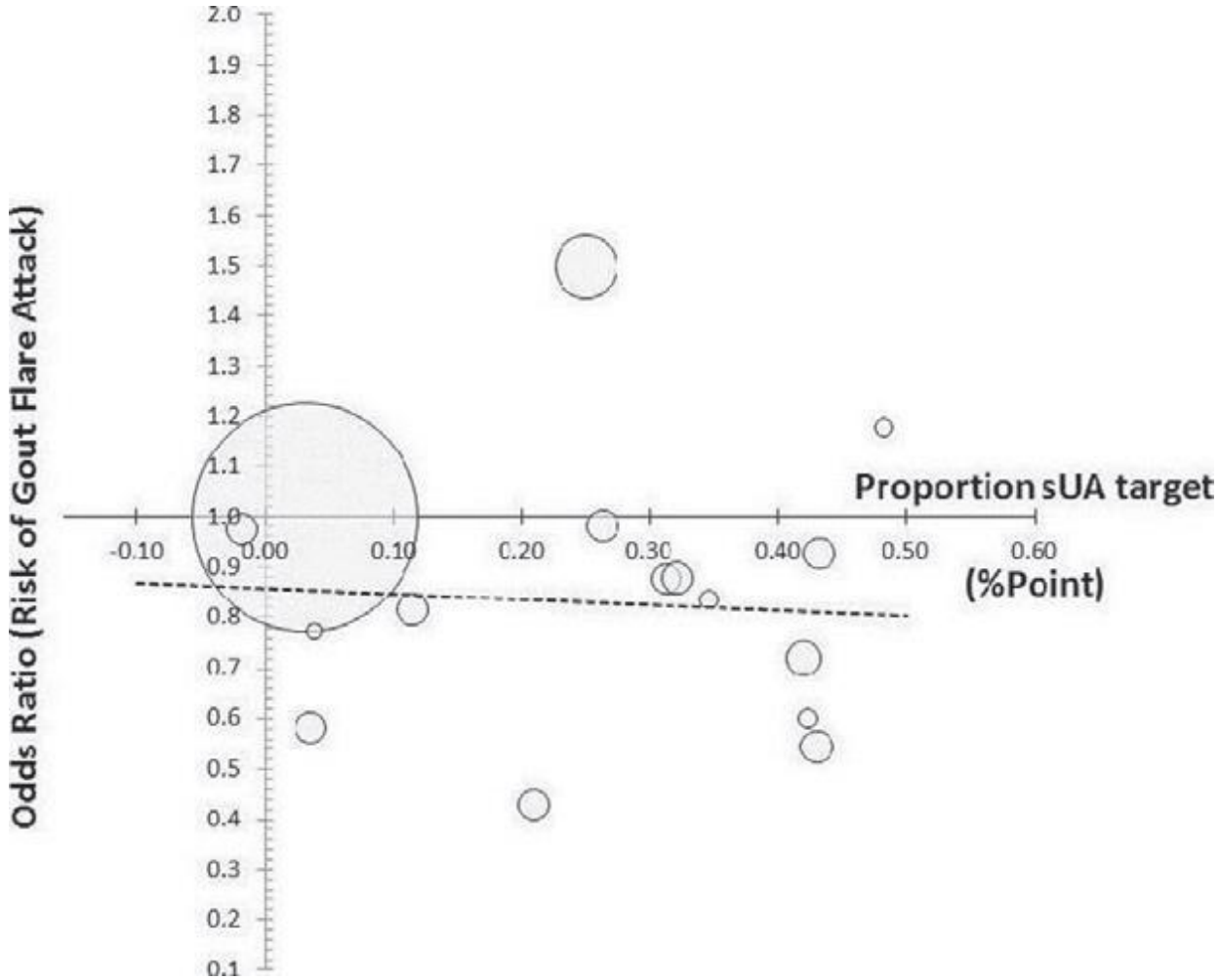
(Weeks 49-72)



STAMP, NEJM EVIDENCE 2022

Serum uric acid concentration as a surrogate marker for disease activity

Based on clinical trial data, a correlation between serum UA and flare rate *cannot* be confirmed



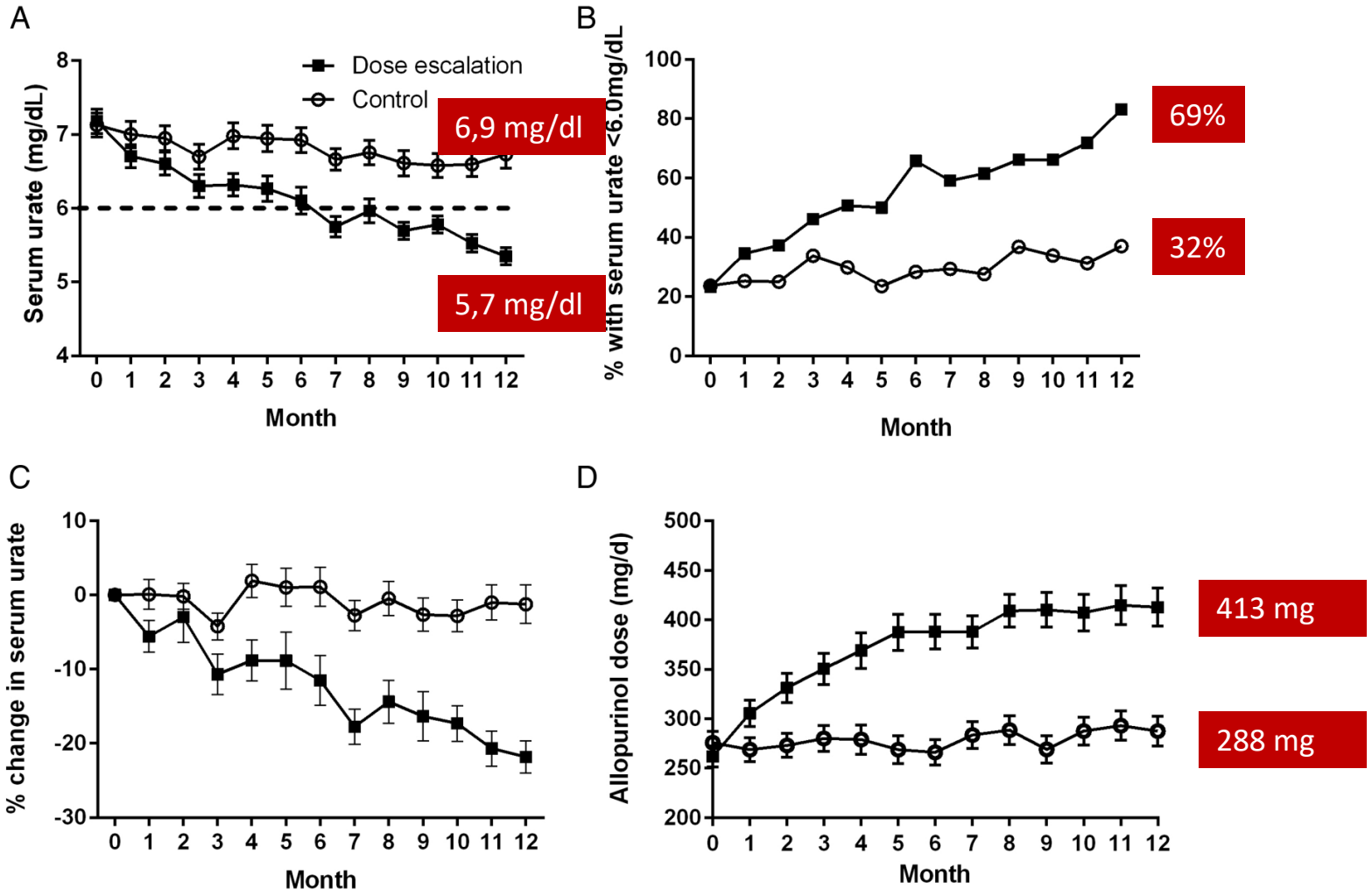
Stamp, Semin Arthritis Rheum 2018, Stamp, EULAR 2017, Abstr No OP0267

The rationale behind T2T in gout

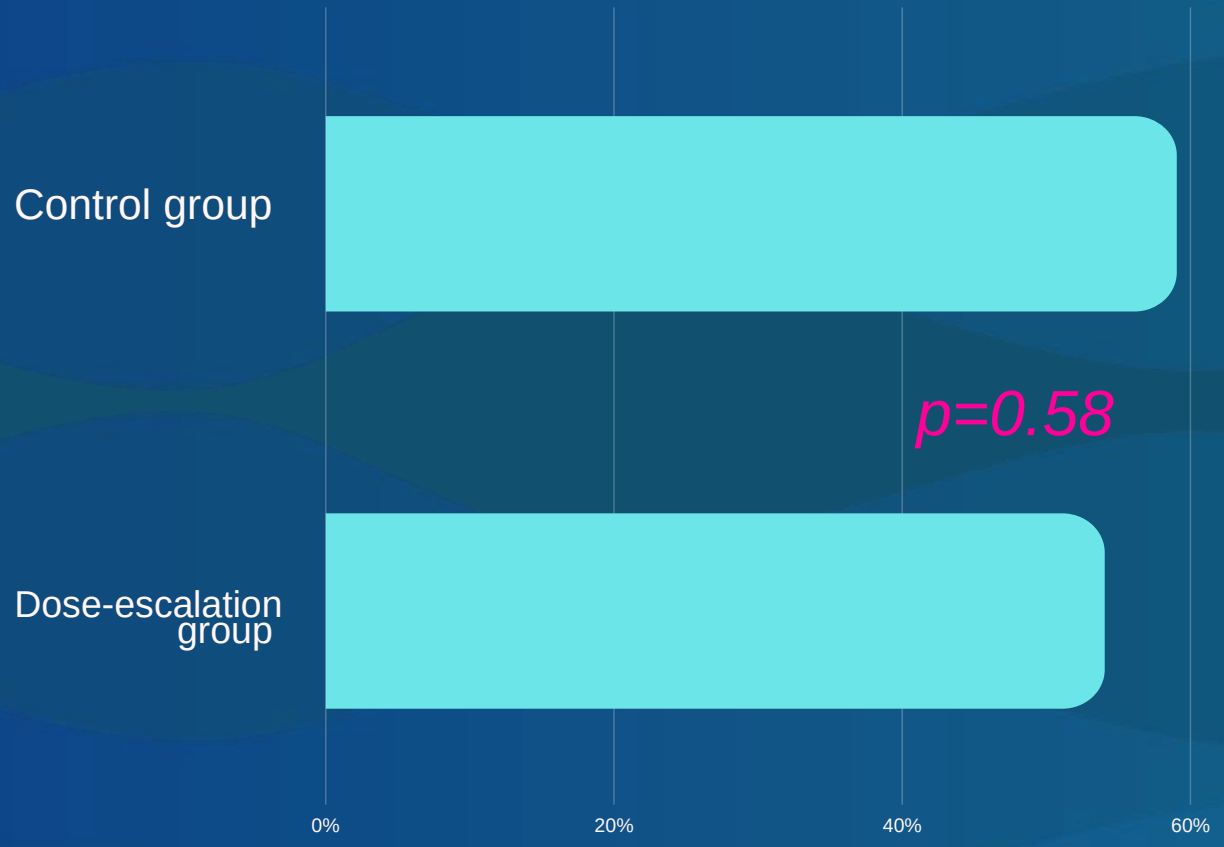
Neogi and Mickuls, Ann Intern Med 2017

T2T: *does* it matter?

Allopurinol dose-escalation vs fixed dose in patients with gout: an RCT



Stamp, Ann Rheum Dis 2016



ALLOPURINOL DOSE-ESCALATION VS FIXED DOSE IN PATIENTS WITH GOUT: AN RCT

Patients with at least one self-reported gout flare during the study period

Stamp, Ann Rheum Dis 2017

Allopurinol dose-escalation vs fixed dose in patients with gout: an RCT

Supplementary Table 2: Primary and secondary efficacy endpoints

Endpoint	Control	Dose escalation	P value
Primary endpoint			
Reduction in serum urate at final visit (mg/dl)	-0.34	-1.5	<0.001
Secondary endpoints			
Serum urate <6mg/dl at last 3 monthly visits n (%)	10/73 (14%)	42/71 (59%)	<0.001
Serum urate <6mg/dl at final visit n (%)	30 (32%)	62 (69%)	<0.001
Percentage change in serum urate from baseline to final visit mean (SE)	-3.3 (2.2)	-17.8 (2.3)	<0.001
HAQ mean (SE)	N=73	N=70	
Baseline	0.53 (0.07)	0.57 (0.07)	0.51
Month 12	0.51 (0.09)	0.62 (0.09	
Pain VAS mean (SE)			
Baseline	1.73 (0.27)	1.97 (0.27)	0.42
Month 12	2.04 (0.31)	1.93 (0.32)	
SJC mean (SE)			
Baseline	1.92 (0.60)	1.42 (0.60)	0.93
Month 12	1.58 (0.69)	1.01 (0.70)	
TJC mean (SE)			
Baseline	3.43 (0.78)	2.11 (0.79)	0.39
Month 12	2.07 (0.86)	1.73 (0.86)	

Stamp, Ann Rheum Dis 2017

Allopurinol dose-escalation vs fixed dose in patients with gout: an RCT

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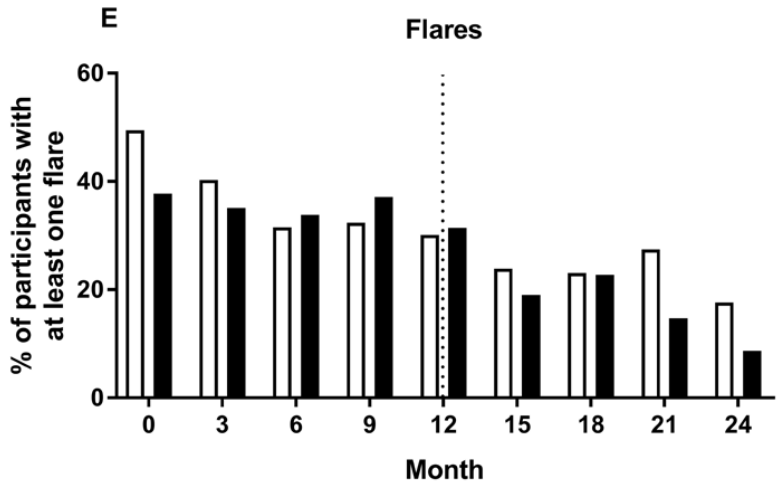
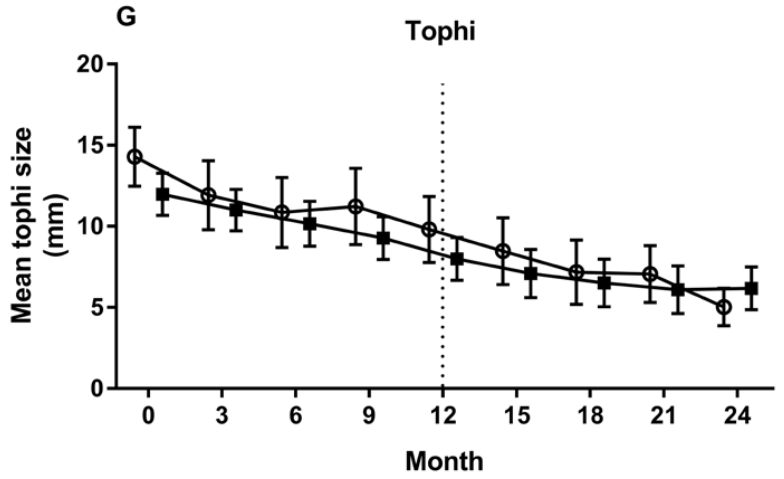
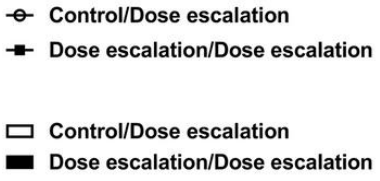
Stamp, Ann Rheum Dis 2017

OPEN-LABEL EXTENSION: YEAR 2

Flares during year 2: dose escalation to achieve a level of UA of <6 mg/dl vs stable dose allopurinol.







Stamp, Ann Rheum Dis 2017

T2T in gout: secondary analysis of responder and non-responder data from two RCTs

No (%) of patients with gout flare during months 12-24

	Serum urate responder	Serum urate non-responder	OR (95% CI) or mean difference between groups (95% CI)*	p value
Unadjusted				
Nottingham	n=290	n=227	..	..
Participants with gout flare	75 (26%)	148 (65%)	0·19 (0·13 to 0·27)	<0·0001
Number of gout flares	0·63 (0·05)	2·41 (0·10)	−1·78 (−2·0 to −1·55)	<0·0001
New Zealand	n=53	n=18	..	..
Participants with gout flare	16 (30%)	8 (44%)	0·54 (0·18 to 1·62)	0·27
Number of gout flares	0·81 (0·12)	1·0 (0·24)	−0·19 (−0·71 to 0·33)	0·48
Combined	n=343	n=245	..	..
Participants with gout flare	91 (27%)	156 (64%)	0·20 (0·15 to 0·29)	<0·0001
Number of gout flares	0·66 (0·04)	2·31 (0·10)	−1·64 (−1·85 to −1·44)	<0·0001
Adjusted†				
Nottingham	n=290	n=227	..	..
Participants with gout flare	75 (26%)	148 (65%)	0·18 (0·10 to 0·32)	<0·0001
Number of gout flares	0·55 (0·05)	2·17 (0·16)	−1·62 (−1·97 to −1·28)	<0·0001
New Zealand	n=53	n=18	..	..
Gout flare	16 (30%)	8 (44%)	0·53 (0·17 to 1·61)	0·26
Number of gout flares	0·86 (0·13)	1·06 (0·25)	−0·20 (−0·76 to 0·35)	0·47
Combined	n=343	n=245	..	..
Gout flare	91 (27%)	156 (64%)	0·22 (0·13 to 0·37)	<0·0001
Number of gout flares	0·61 (0·05)	1·94 (0·14)	−1·33 (−1·64 to −1·03)	<0·0001
Adjusted‡				
Nottingham	n=290	n=227	..	..
Gout flare	75 (26%)	148 (65%)	0·24 (0·12 to 0·47)	<0·0001
Number of gout flares	0·65 (0·06)	2·52 (0·22)	−1·88 (−2·34 to −1·41)	<0·0001
New Zealand	n=53	n=18	..	..
Gout flare	16 (30%)	8 (44%)	0·53 (0·17 to 1·62)	0·26
Number of gout flares	0·81 (0·13)	0·99 (0·24)	−0·18 (−0·70 to 0·34)	0·50
Combined	n=343	n=245	..	..
Gout flare	91 (27%)	156 (64%)	0·29 (0·17 to 0·51)	<0·0001
Number of gout flares	0·69 (0·06)	2·09 (0·17)	−1·41 (−1·77 to −1·04)	<0·0001

Data are n (%) or mean (SE). OR=odds ratio. *OR for primary outcome; mean difference for secondary outcome. †Adjusted for flare history (and randomised group for the Nottingham data). ‡Adjusted for flare history, baseline serum urate, and baseline tophi (and randomised group for Nottingham data).

Table 2: **Primary and secondary outcomes by serum urate responder status**

Stamp, Lancet Rheumatol 2022

T2T in gout: secondary analysis of responder and non-responder data from two RCTs

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Table 1: Baseline demographics and clinical features for the NZ (15) and Nottingham studies (14). Data are present as n (%) or mean (SD).

	SU Responder		SU Non-Responder	
Variable	Nottingham	NZ	Nottingham	NZ
	(n=290)	(n = 53)	(n=227)	(n = 18)
Serum urate baseline (mg/dL)	7.0 (1.8)	7.06 (1.46)	8.0 (1.2)	7.21 (1.49)
Serum urate month 12	4.3 (0.9)	5.18 (0.72)	7.7 (1.4)	5.75 (1.31)
Serum urate month 24	4.4 (1.2)	5.30 (1.01)	7.4 (1.7)	5.77 (1.50)
CrCL (mL/min)	72.1 (15.9)	57.7 (25.8)	69.2 (15.9)	67.7 (31.6)
Body mass index (kg/m^2)	29.5 (5.2)	34.8 (7.1)	30.2 (4.8)	37.2 (9.3)
Flare frequency in the preceding year	4.0 (4.8)	5.9 (11.8)	4.1 (4.9)	10.1 (17.1)
Tophus	36 (12.4%)	19 (36%)	22 (9.7%)	6 (34%)

Stamp, Lancet Rheumatol 2022

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Stamp, Lancet Rheumatol 2022

T2T: does it *really* matter?

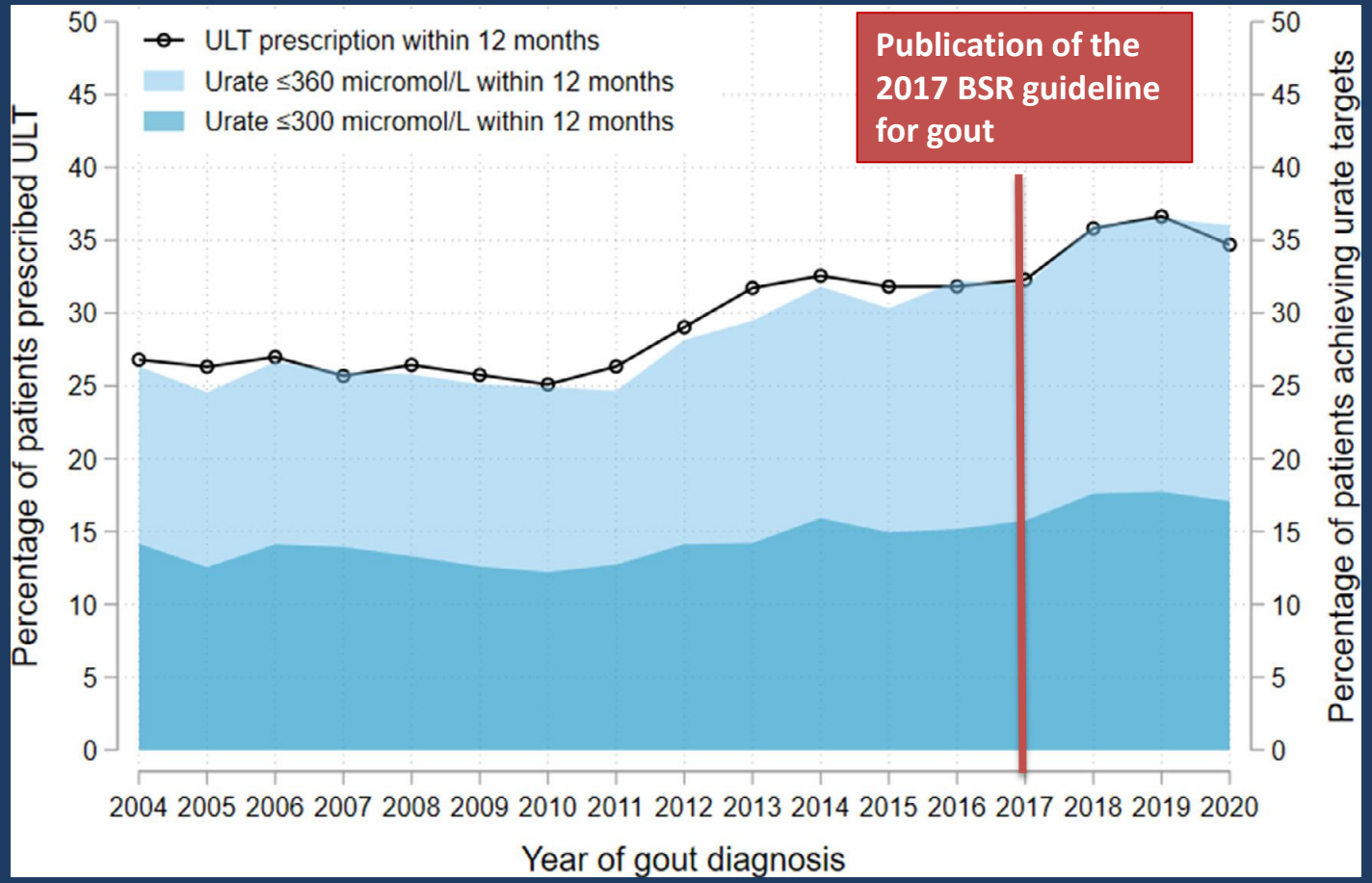
POOR ADHERENCE IN GOUT

ADHERENCE RATES: <0.8

ADHERENT PATIENTS: 10-46%

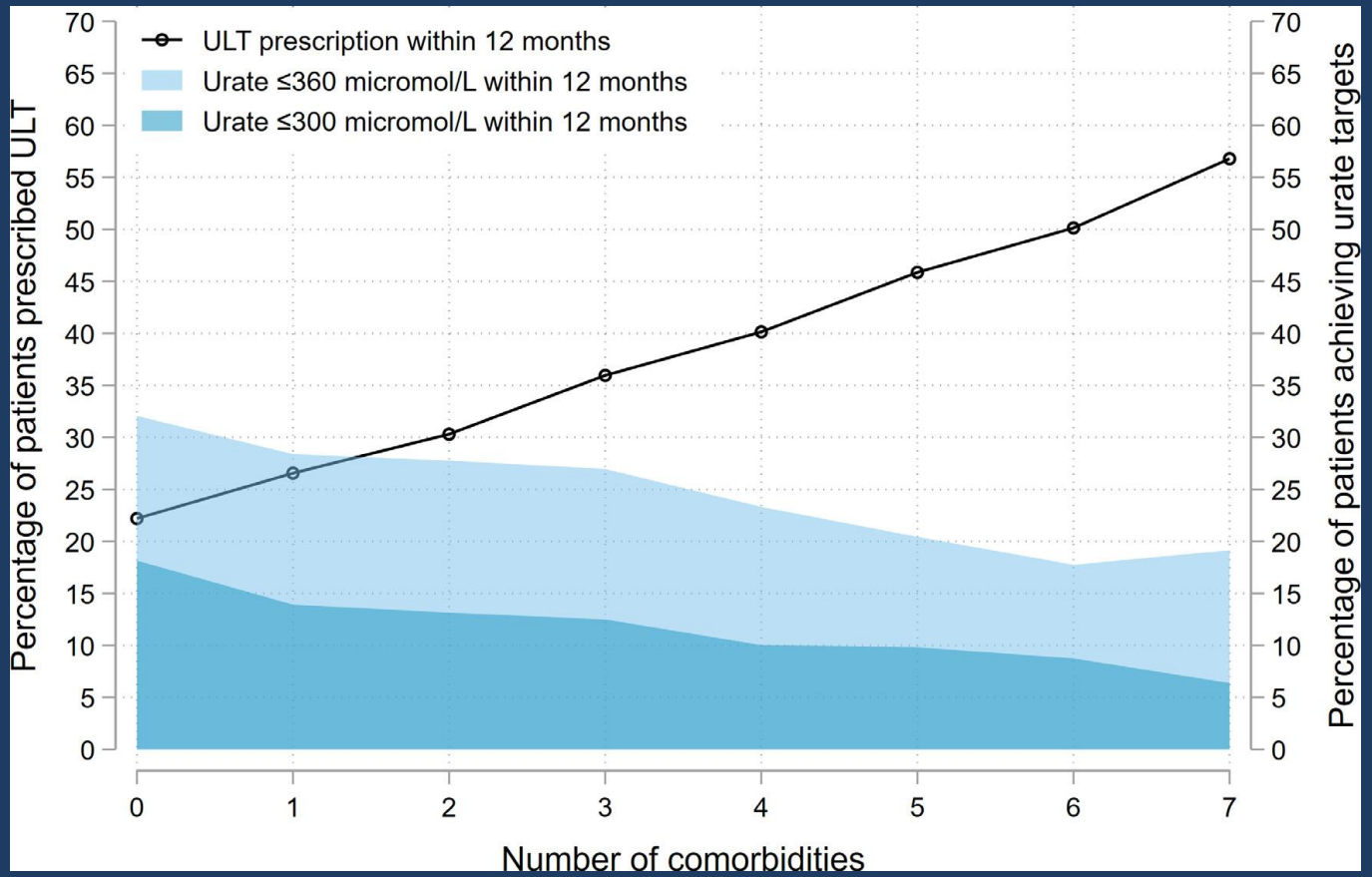
De Vera, Arthritis Care Res 2014

WHO IS DOING POORLY?



Russell, Lancet Regional Health 2022

WHO IS DOING POORLY?



Russell, Lancet Regional Health 2022

Optimizing adherence to allopurinol for gout

		Initiation	Implementation	Discontinuation
Nonintentional nonadherence		Not reported	✓ Reminder systems ✗ Forgetfulness	Not reported
Intentional nonadherence	**Belief allopurinol is/isn't effective**	✓ Trust in HCP[a] ✗ Preference for natural remedies	✓ Trust in HCP (warning they may initially experience an increase in gout flares) ✓ Experiencing decreased frequency of gout flares ✓ Experiencing minimal side effects on ULT ✓ Experiencing reduced impact of gout on daily life ✗ Continuing to experience gout flares ✗ Unsatisfactory interaction(s) with HCP	✓ Gout flares trigger return to allopurinol ✓ Trust in HCP triggers return to allopurinol ✗ Continuing to experience gout flares ✗ Switching ULT[b]
	Belief allopurinol is/isn't necessary	✓ Trust in HCP ✓ Prevention of gout flares ✓ Peer reinforcement ✗ Reluctance to start long-term prophylactic medication ✗ Preventative therapy seen as unnecessary ✗ Concern of side effects	✓ Trust in HCP ✓ Prevention of gout flares ✓ Peer reinforcement ✓ Trust in ULT ✓ Minimal concerns about long-term medications ✗ Infrequent gout flares ✗ Lack of immediate feedback to assess effectiveness of allopurinol	✓ Gout flares trigger return to allopurinol ✓ Trust in HCP triggers return to allopurinol ✗ Infrequent gout flares ✗ Identified dietary trigger for gout flares ✗ Concern of taking allopurinol long-term

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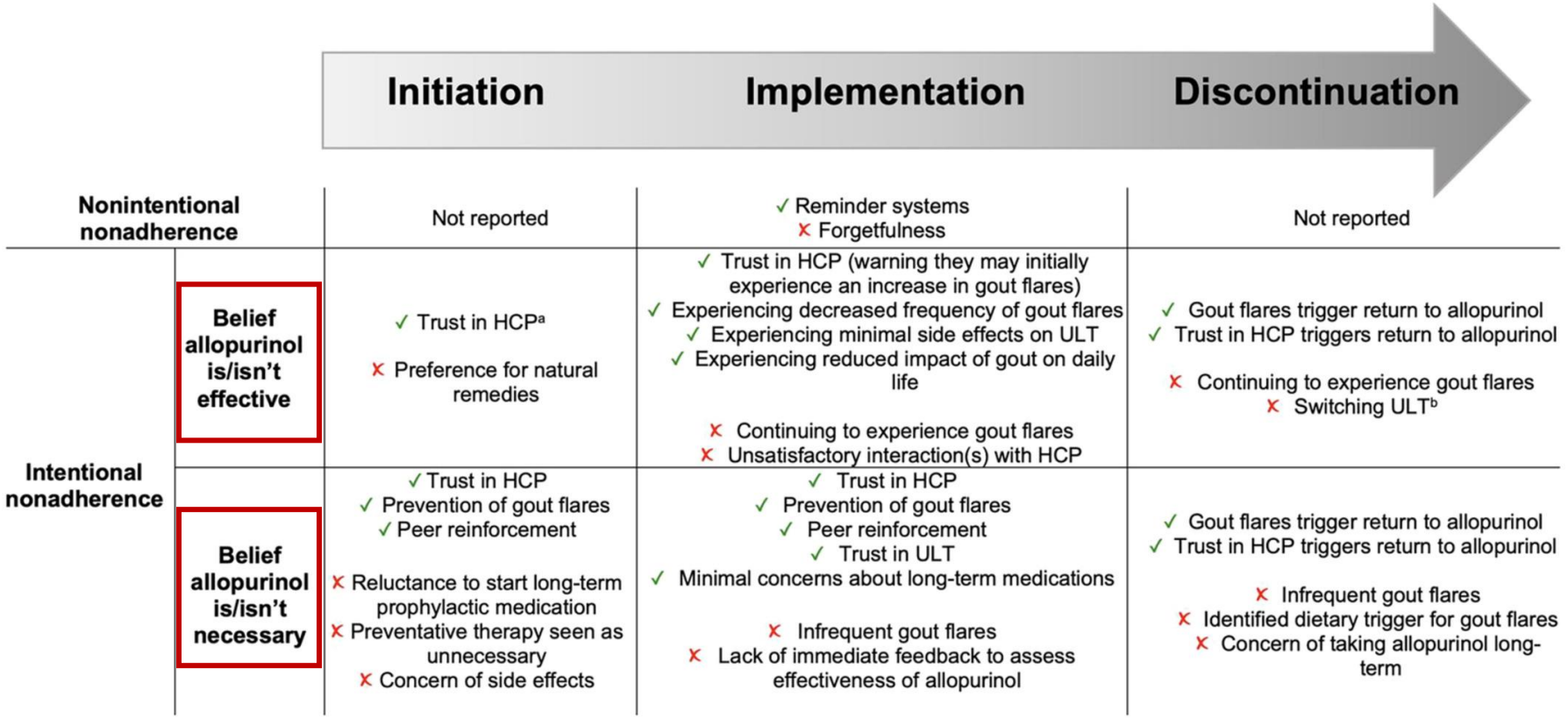
Optimizing adherence to allopurinol for gout



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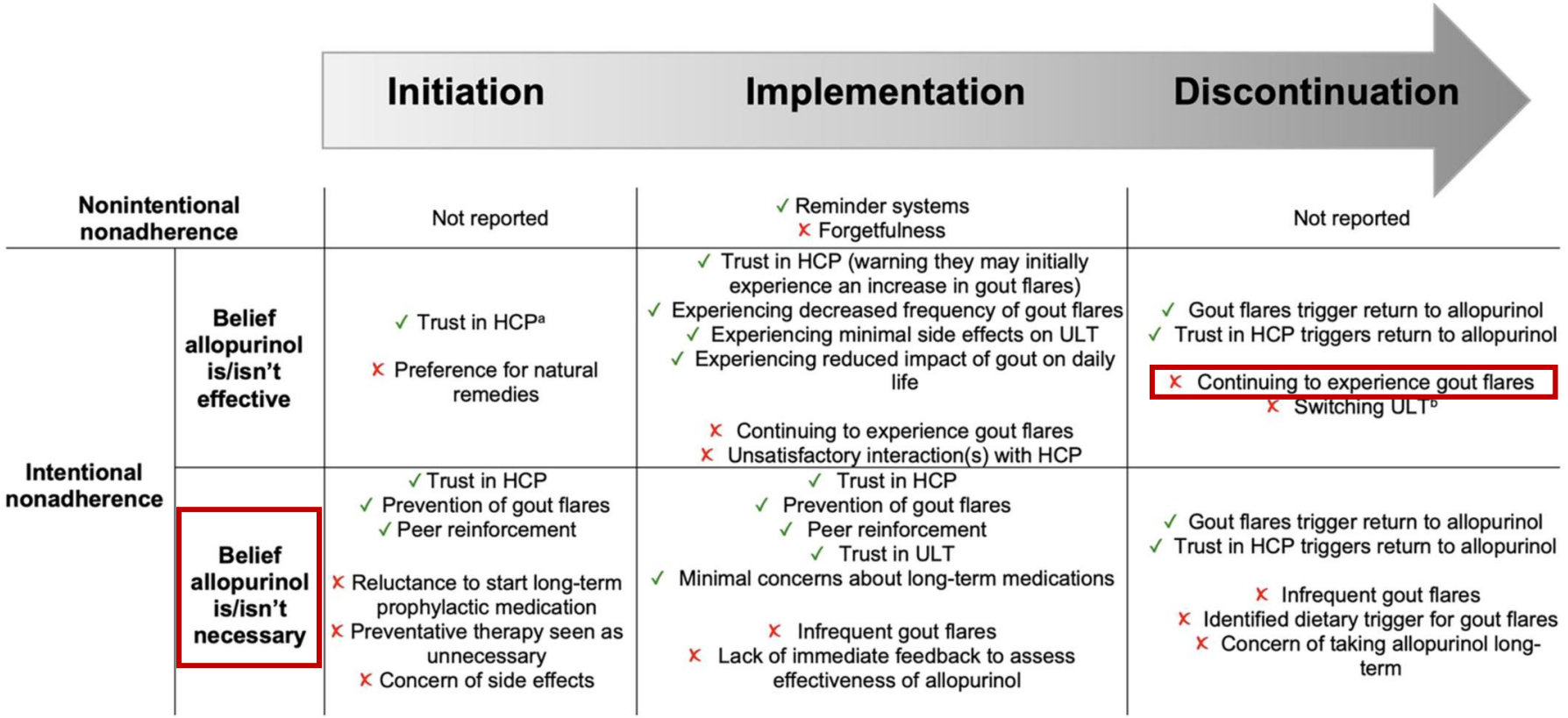

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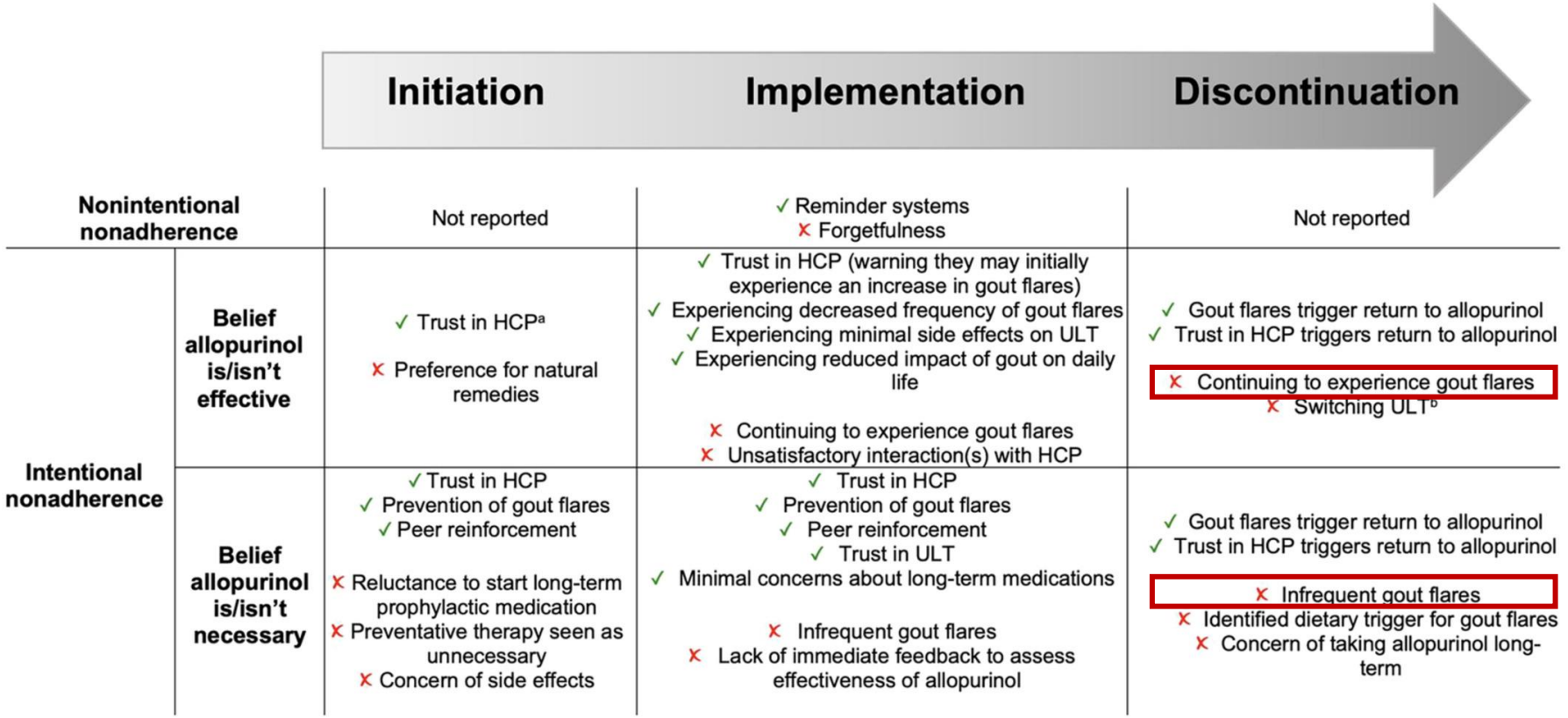

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Conclusions

Serum urate levels are the main pathophysiological culprit of gout

Higher urate levels correlate with gout flares

Lowering urate levels is associated with control of disease

However, the target level of urate remains controversial

We need better compliance