Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial

***Lancet* 2008; 371: 1854–60**

ORIGINAL RESEARCH

Annals of Internal Medicine

Oral Prednisolone in the Treatment of Acute Gout

A Pragmatic, Multicenter, Double-Blind, Randomized Trial

2016

120 patients with crystal-proven gout, randomised into 2 groups:

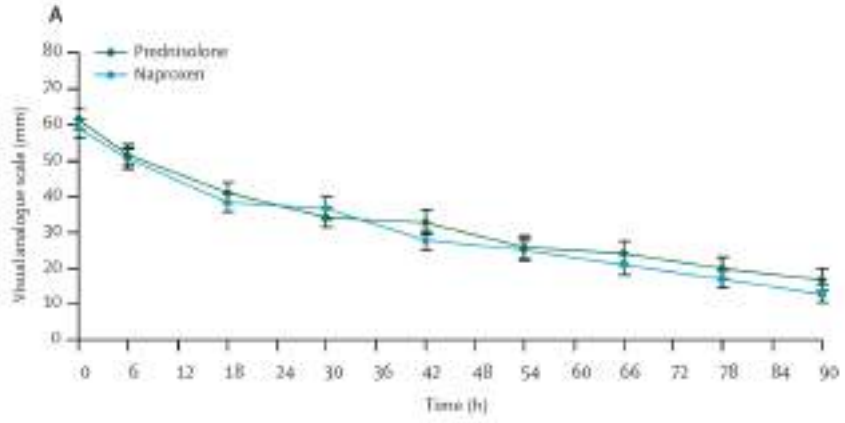
- Prednisone 35mg/d
- Naproxen 500 mg BID

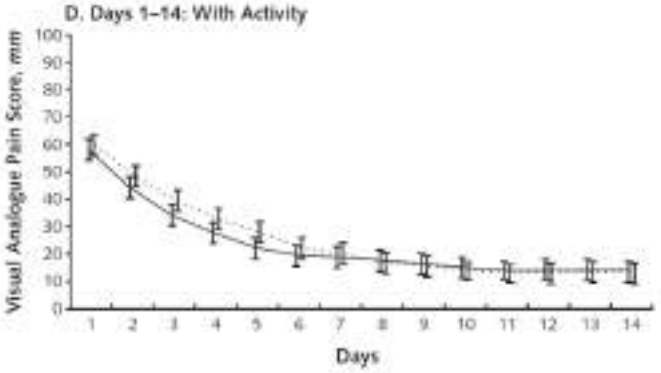
For 5 days

416 patients randomised into 2 groups:

- Prednisone 30mg/d
- Indomethacin 150 mg/d for 2 days, then 75 mg/d for 3 days

For 5 days

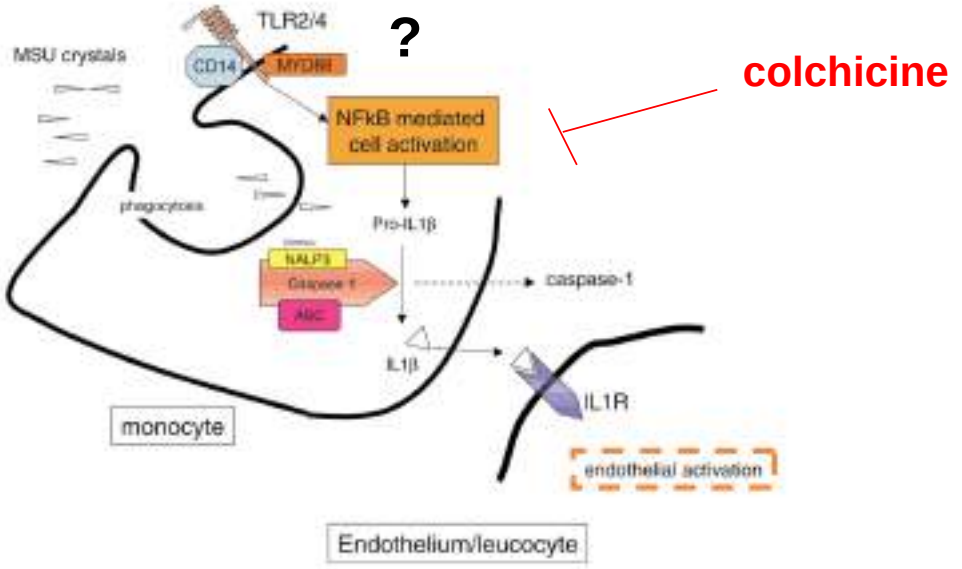


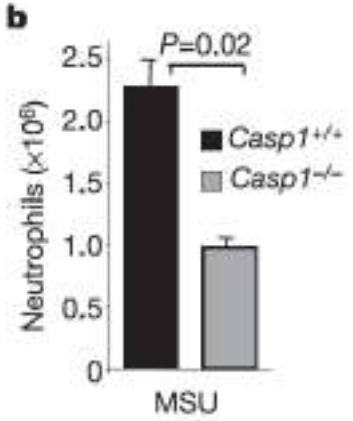


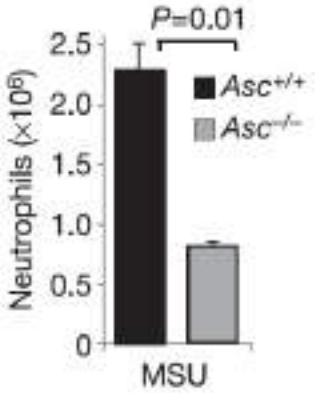
Similar safety profile

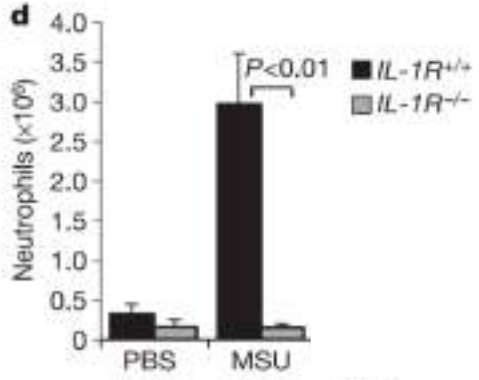
LETTERS

Gout-associated uric acid crystals activate the NALP3 inflammasome









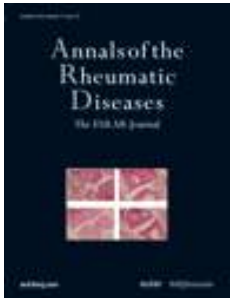
Martinon et al. Nature. 2006
Liu-Bryan et al, A&R 2005,52, 2936-46

EXTENDED REPORT

Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions

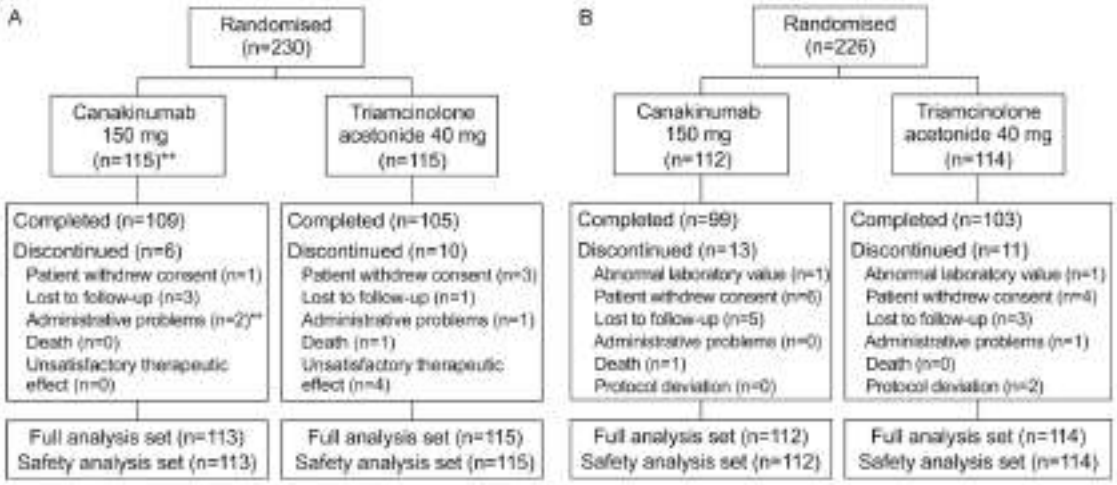
Naomi Schlesinger,[1] Rieke E Alten,[2] Thomas Bardin,[3] H Ralph Schumacher,[4] Mark Bloch,[5] Alberto Gimona,[6] Gerhard Krammer,[6] Valda Murphy,[6] Dominik Richard,[6] Alexander K So[7]

Canakinumab has been approved by the EMA for "the symptomatic treatment of frequent acute GFs in patients in whom NSAIDs and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate"



ARD 2012

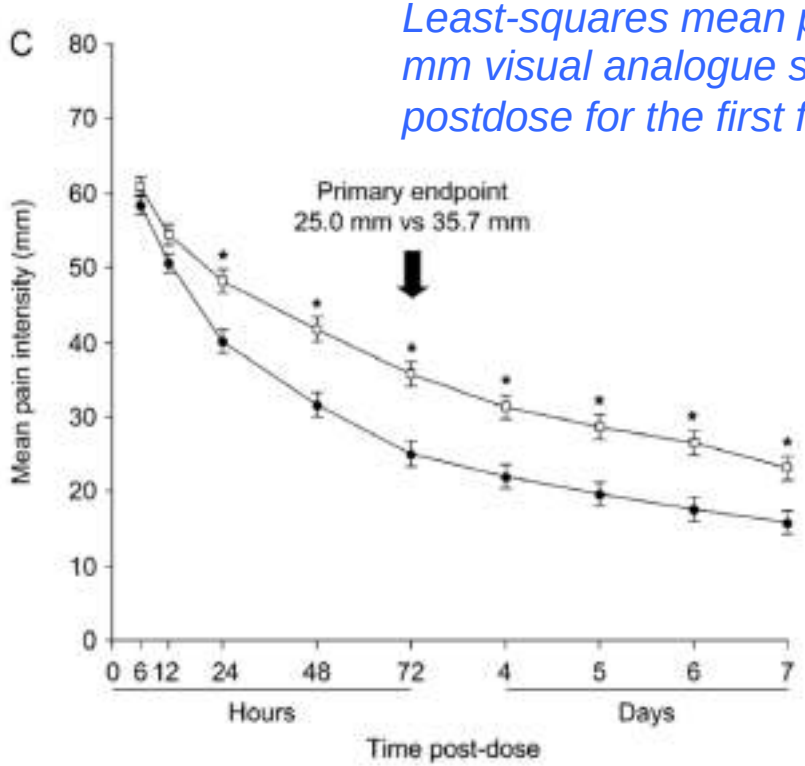
The primary objectives of the core studies were to demonstrate superiority of canakinumab 150 mg over TA 40 mg



**In β-RELIEVED, two patients randomised to canakinumab 150 mg were discontinued because randomisation errors resulted in them not receiving any study medication. These patients were not included in the safety or full analysis sets.

Two co-primary efficacy endpoints:
- Pain intensity (VAS score) in the most affected joint at 72 h post dose
- Time to first new flare over the first 12 weeks

Least-squares mean pain intensity (0–100 mm visual analogue scale) over 7 days postdose for the first flare



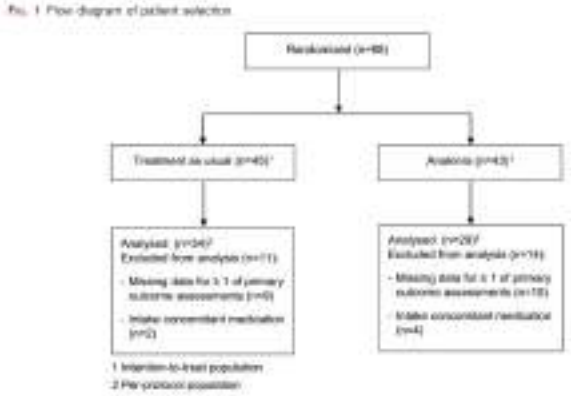
Time	Hours					Days			
	6	12	24	48	72†	4	5	6	7
Mean difference canakinumab vs triamcinolone acetonide,* mm	−2.4	−3.7	−8.1	−10.1	−10.7	−9.3	−9.0	−8.9	−7.3
95% confidence intervals	−6.1–1.2	−7.7–0.3	−12.5–−3.6	−14.8–−5.4	−15.4–−6.0	−13.8–−4.8	−13.5–−4.6	−13.4–−4.4	−11.8–−2.9
p value	0.187	0.069	0.0004	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	0.0013

RHEUMATOLOGY

Original article

Anakinra for the treatment of acute gout flares: a randomized, double-blind, placebo-controlled, active-comparator, non-inferiority trial

Carly A. Janssen[1], Martijn A. H. Oude Voshaar[1], Harald E. Vonkeman[1,2], Tim L. Th. A. Jansen[3], Matthijs Janssen[3,4], Marc R. Kok[5], Bea Radovits[6], Caroline van Durme[7], Hetty Baan[8] and Mart A. F. J. van de Laar[1,2]



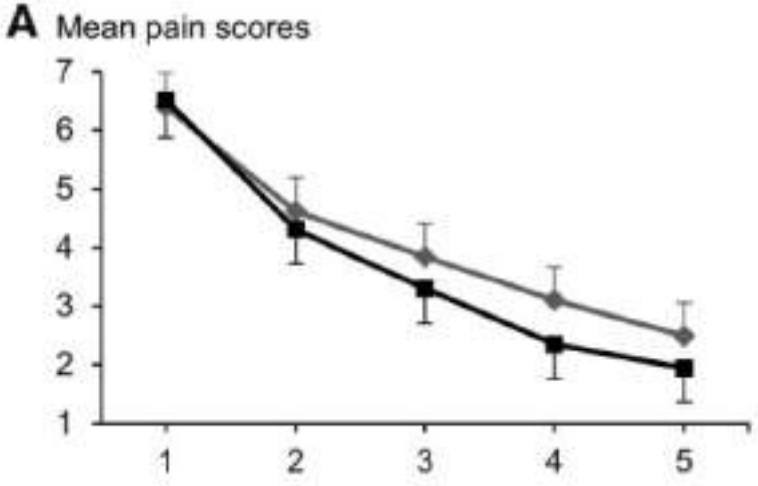
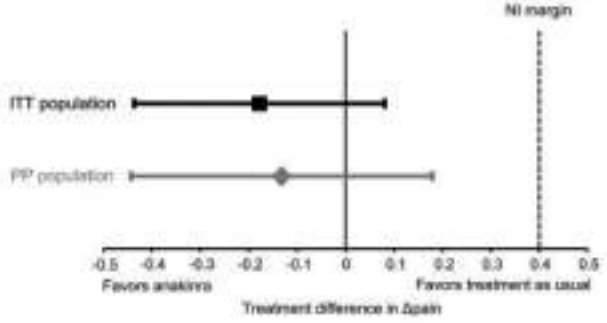


FIG. 2 The 95% CI for the estimated marginal mean difference in ΔPain between the treatment groups



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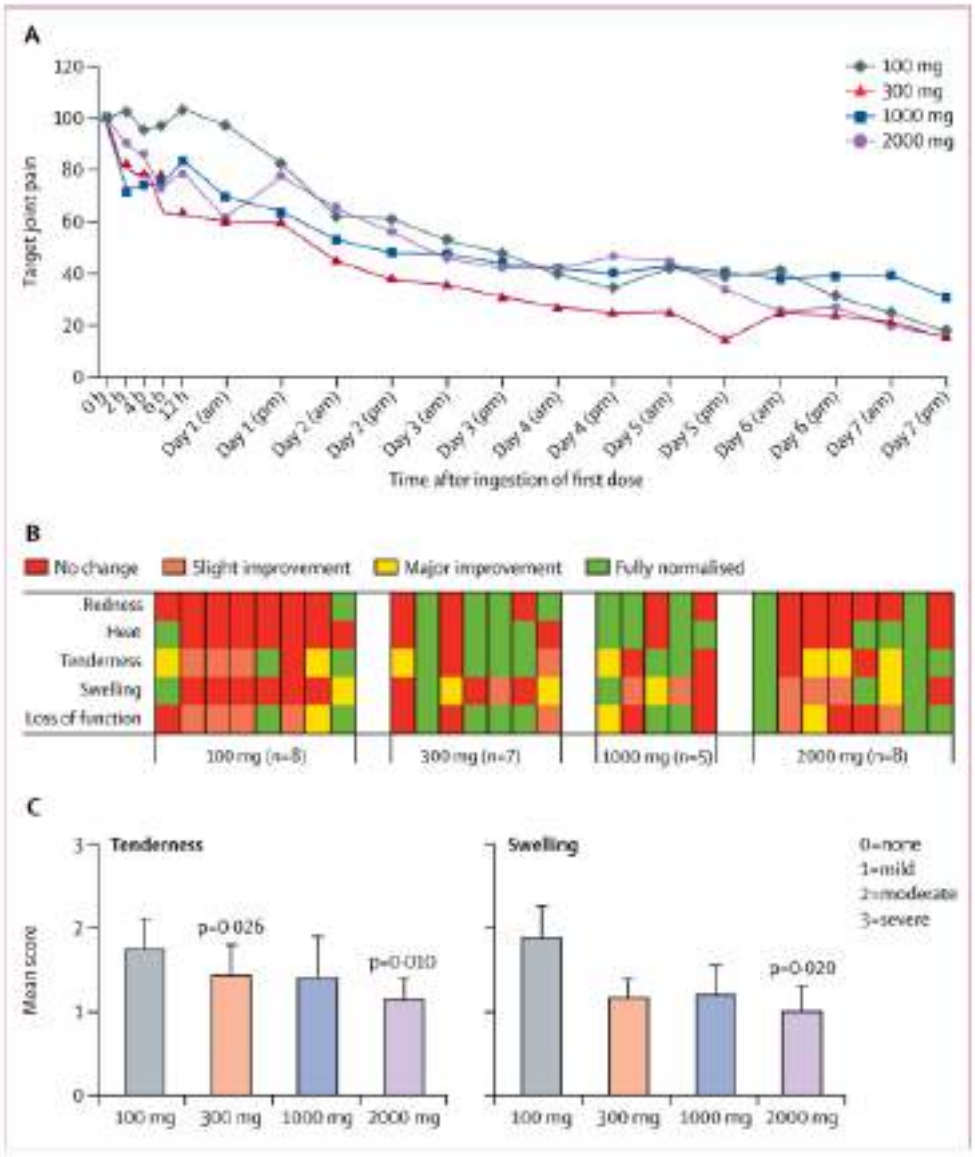
Lancet Rheumatol. 2020 May ; 2(5): e270–e280. doi:10.1016/s2665-9913(20)30065-5.

Dapansutrile, an oral selective NLRP3 inflammasome inhibitor, for treatment of gout flares: an open-label, dose-adaptive, proof-of-concept, phase 2a trial

Viola Klück[*], **Tim L Th A Jansen**[*], **Matthijs Janssen**, **Antoaneta Comarniceanu**, **Monique Efdé**, **Iesk W Tengesdal**, **Kiki Schraa**, **Maartje C P Cleophas**, **Curtis L Scribner**, **Damaris B Skouras**, **Carlo Marchetti**, **Charles A Dinarello**, **Leo A B Joosten**

Department of Internal Medicine, Radboud University Medical Center, Nijmegen, Netherlands (V Klück MD, K Schraa BSc, M C P Cleophas PhD, Prof C A Dinarello MD, Prof L A B Joosten PhD); Department of Rheumatology, VieCuri Medical Center, Venlo, Netherlands (T L Th A Jansen PhD, M Janssen PhD, A Comarniceanu MD, M Efdé MD); Olatec Therapeutics, New York, NY, USA (C L Scribner MD, D B Skouras MBA); Department of Medicine, University of Colorado, Aurora, CO, USA (I W Tengesdal MSc, C Marchetti PhD, Prof C A Dinarello); and Department of Medical Genetics, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania (Prof L A B Joosten)



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

Research

JAMA | Original Investigation

Association Between Gout Flare and Subsequent Cardiovascular Events Among Patients With Gout

Eduardo Cipolletta, MD; Laila J. Tata, PhD; Georgina Nakafero, PhD; Anthony J. Avery, MD; Mamas A. Mamas, PhD; Abhishek Abhishek, PhD

Figure 2. Association Between Cardiovascular Event and Recent Prior Gout Flare in a Nested Case-Control Study

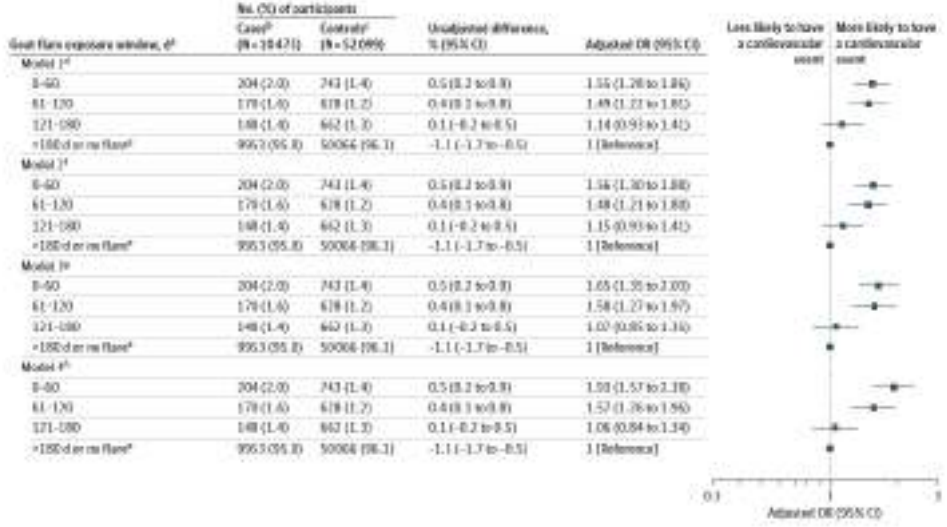
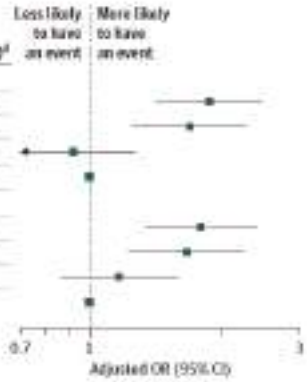


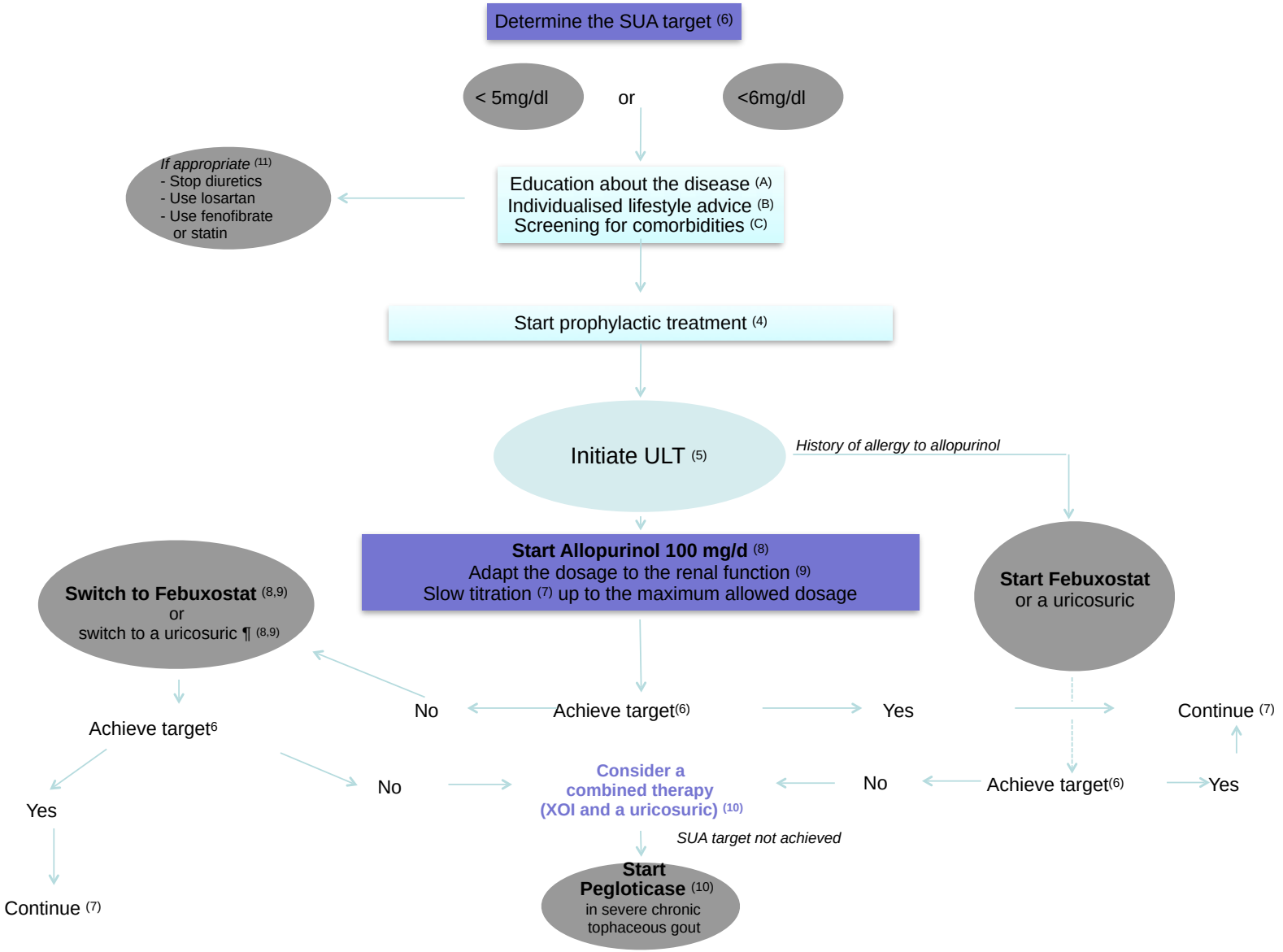
Figure 3. Association Between Acute Myocardial Infarction, Stroke, and Recent Prior Gout Flares in a Nested Case-Control Study

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]



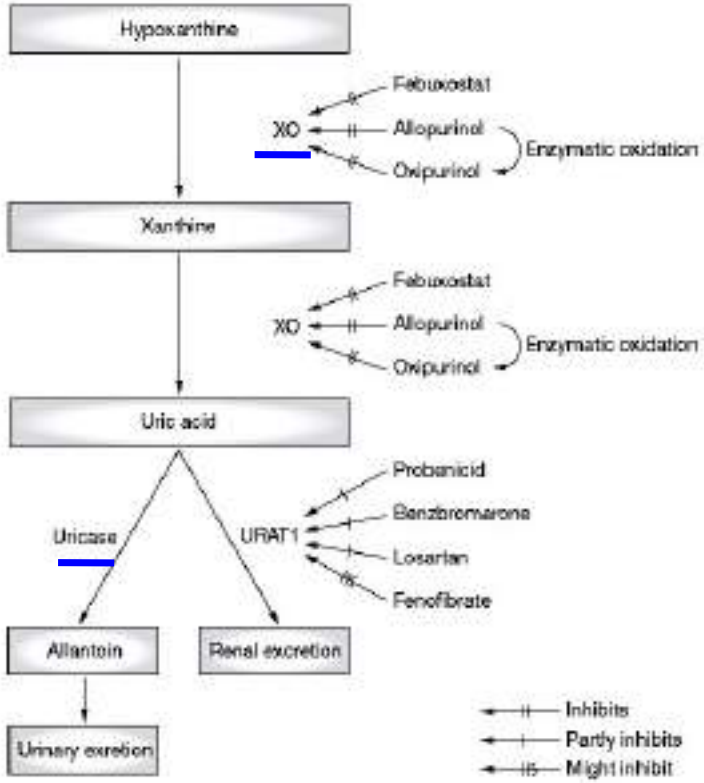
Les arthrites goutteuses exposent à un risque accru d'IDM et d AVC dans les 3-4 mois

EULAR RECOMMENDATION FOR THE MANAGEMENT OF HYPERURICEMIA IN PATIENTS WITH GOUT



Les TTT Hypouricémiants

- Inhibiteur de la XO
  - Allopurinol
  - Fébuxostat
- Uricosuriques
  - Probénécide
  - Benzbromarone
  - Fénofibrate
  - Losartan
- Pégloticase
- Rasburicase



ALLOPURINOL

Titration: 100 mg/j, augmentée tous les 15 j jusqu'à la cible: uricémie <360 mmol/L)

- *VIDAL: adaptation des doses selon la clairance de la créatinine*

Table 2 — Allopurinol dosing recommendations

Estimated creatinine clearance	Maintenance dosage
100 mL/min	300 mg/d
60 mL/min	200 mg/d
40 mL/min	150 mg/d
20 mL/min	100 mg/d
10 mL/min	100 mg q2d
0 mL/min	100 mg q3d

Data from Hande KR et al. Am J Med. 1984.[1]

→ Cible dans 50% des cas

≈ jamais à la cible

AR 2012

Starting Dose Is a Risk Factor for Allopurinol Hypersensitivity Syndrome

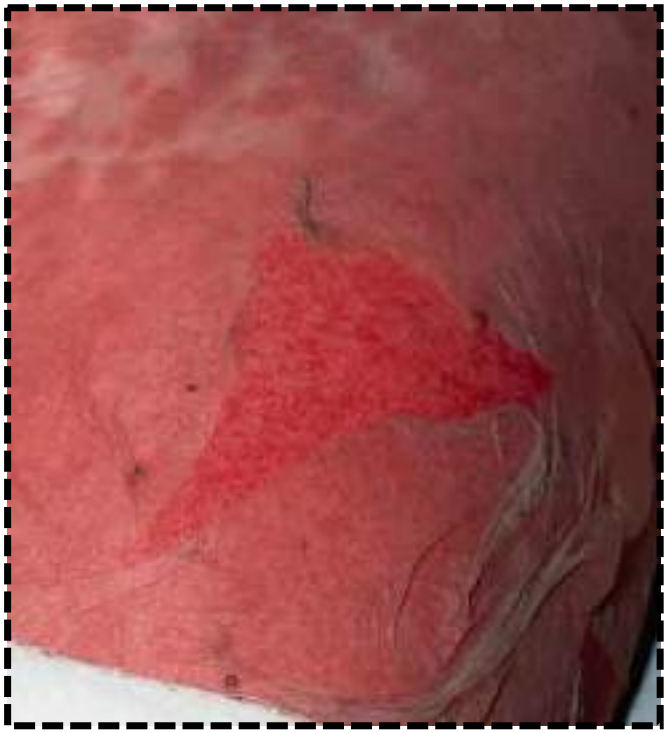
A Proposed Safe Starting Dose of Allopurinol

Lisa K. Stamp,[1] William J. Taylor,[2] Peter B. Jones,[3] Jo L. Dockerty,[4] Jill Drake,[1] Christopher Frampton,[1] and Nicola Dalbeth[5]

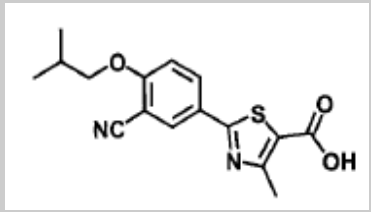
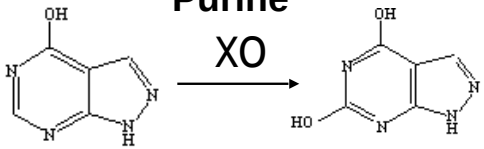
SEVERE ALLERGIC SKIN REACTION
(SJ, Lyell, DRESS syndrome)

Prevalence: 0.7/1 000
Mortality 20%

- **Dose in renal failure patients**
- **HLA*B-5801 in Asians**
- **Recent onset of allopurinol treatment**
- **Starting dose**



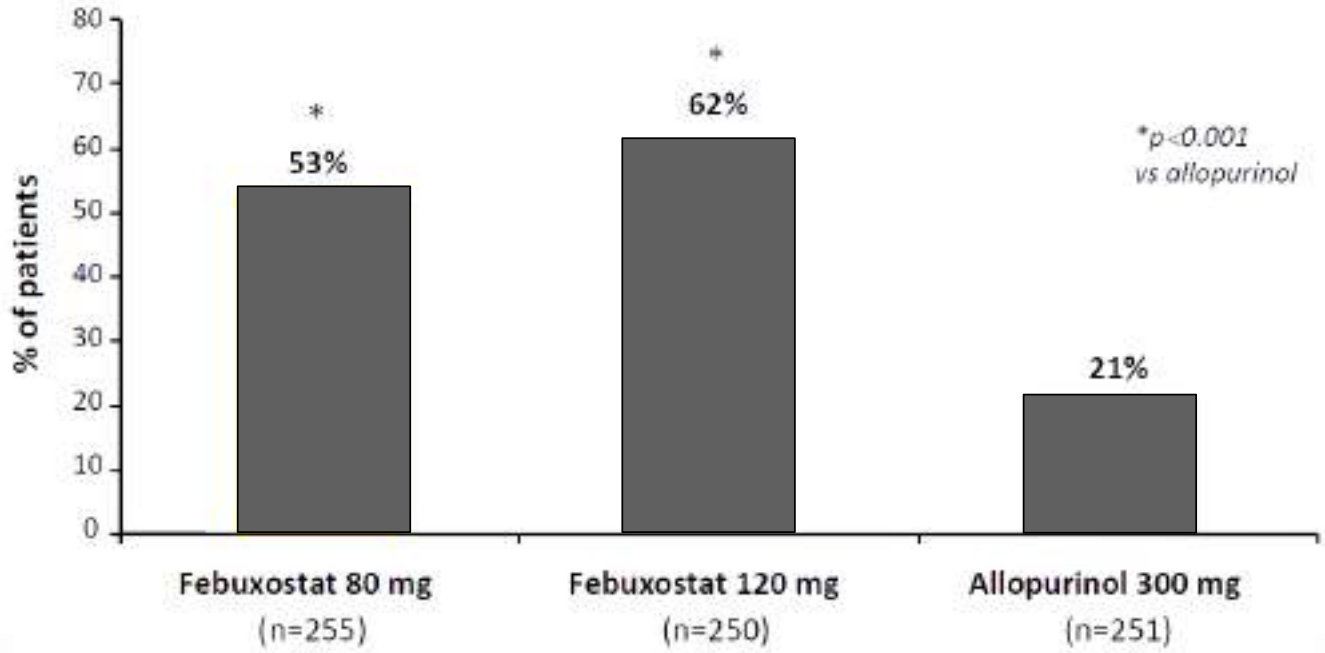
Febuxostat : selective XO inhibitor

	Febuxostat	Allopurinol (Oxypurinol)
Structure		
Inhibitor constant		
Ki (nM)	0.12 [1]	700 [5]
Ki' (nM)	0.9 [1]	0.54 [6]
Enzyme selectivity	Selective inhibitor of Xanthine Oxidase [2]	Non-selective inhibitor of Xanthine Oxidase [7-10]
Clearance	Extensively metabolized in the liver and excreted into urine and feces [3,4]	Mainly excreted into urine [11]
Half life (hr)	4.7 [4]	14-26 [12]

Pivotal trials: febuxostat is more effective in CKD patients (eGFR > 30) than allopurinol given at doses adjusted to creatinine clearance

FACT study (1 year)

proportion of subjects with last 3 sUA levels <6.0 mg/dl (<0.36 mmol/l)



ITT population: subjects with serum urate level ≥8.0 mg/dl on day -2.

Becker MA, et al. N Engl J Med 2005; 353:2450-2461.

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NEJM Evid. 2022 March ; 1(3): . doi:10.1056/evidoa2100028.

Comparative Effectiveness of Allopurinol and Febuxostat in Gout Management

James R. O'Dell, M.D.[1,2], Mary T. Brophy, M.D.[3,4], Michael H. Pillinger, M.D.[5,6], Tuhina Neogi, M.D., Ph.D.[7], Paul M. Palevsky, M.D.[8,9], Hongsheng Wu, Ph.D.[3,10], Anne Davis-Karim, Pharm.D.[11], Jeff A. Newcomb, B.S.[1,2], Ryan Ferguson, Sc.D.[3], David Pittman, B.E.[11], Grant W. Cannon, M.D.[12], Thomas Taylor, M.D.[13,14], Robert Terkeltaub, M.D.[15], Amy C. Cannella, M.D.[1,2], Bryant R. England, M.D.[1,2], Lindsay N. Helget, M.D.[1,2], Ted R. Mikuls, M.D.[1,2]

- *950 goutteux et SUA sup 6.8*
- *Etude de non infériorité: % de patients avec au moins 1 accès durant la phase 3*
- *Phase 1: titration avec cible à 6 mg/dl ou 5 mg/dl*
- *1/3 CKD 3*

TTT Prophylactique

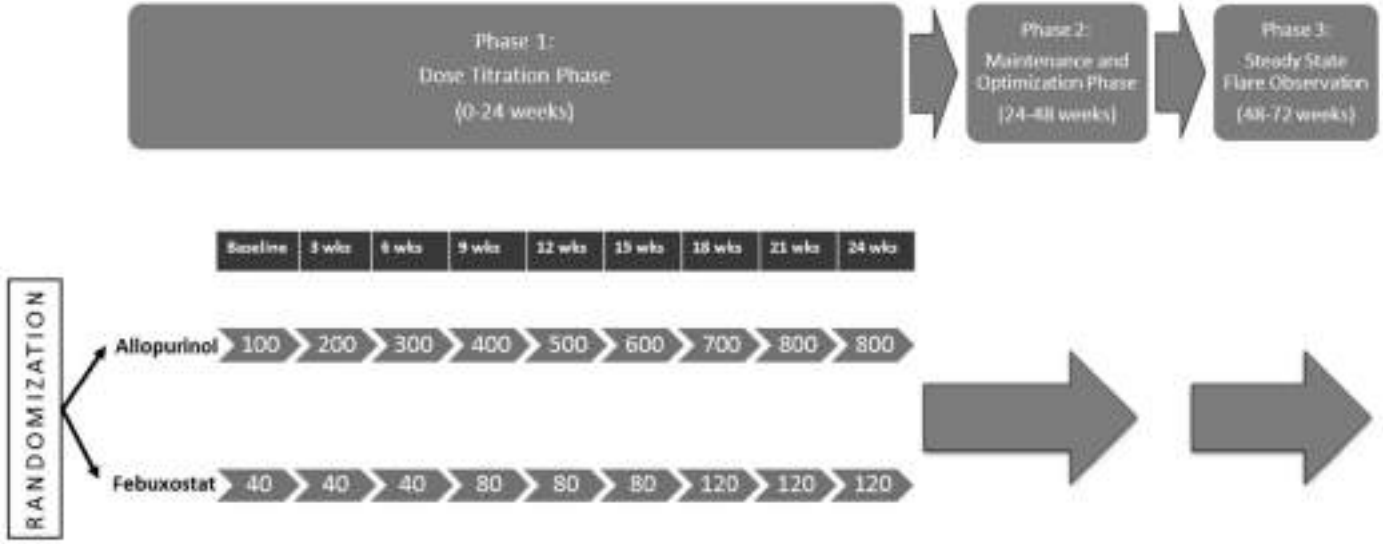


Table 2. Study Results.

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)
Serious adverse event	26.7 (125/468)	26.1 (123/472)	1.02 (0.83 to 1.27)
Early study termination	20.5 (96/468)	19.7 (93/472)	1.04 (0.81 to 1.34)
Rate of gout flares — events/person-years			
During whole study	1.73	1.97	0.88 (0.81 to 0.96)
During phase 1	2.09	2.25	0.93 (0.81 to 1.06)
During phase 2	1.60	1.59	1.00 (0.85 to 1.18)
During phase 3	1.48	2.02	0.73 (0.63 to 0.86)
Cardiovascular event§	8.1 (38/468)	6.8 (32/472)	1.20 (0.76 to 1.88)
C-reactive protein — mg/l¶	7.0 (12.3)	6.5 (11.3)	N/A
Serum creatinine — mg/dl¶	1.2 (0.4)	1.2 (0.4)	N/A
Serum urate in phase 2 — mg/dl‡	5.2 (1.2)	5.2 (1.3)	N/A
Serum urate at study end — mg/dl	5.1 (1.4)	5.3 (1.8)	N/A
Week 48 medication dosage — mg‖	400 (300–500)	40 (40–80)	N/A
Participants with stage 3 chronic kidney disease			
≥1 gout flares in phase 3	31.9 (44/138)	45.3 (63/139)	−13.4 (−∞ to −3.9)**
Serious adverse events	38.1 (69/181)	35.9 (61/170)	1.06 (0.81 to 1.40)
Serum urate < 6.0 mg/dl in phase 2‡	78.8 (119/151)	81.3 (117/144)	0.97 (0.87 to 1.09)
Serum urate < 6.8 mg/dl in phase 2‡	92.1 (139/151)	93.1 (134/144)	0.99 (0.93 to 1.06)

* Primary end point was assessed for 749 patients entering phase 3 ($P<0.001$). Values are presented as percentages (proportions) unless indicated otherwise.

† Risk differences (95% confidence intervals [CIs]) are presented for the primary end point, whereas risk ratios are presented for the secondary end points unless indicated otherwise. N/A indicates not applicable.

‡ Serum urate in phase 2 was defined as the mean concentration at weeks 36, 42, and 48; 46 (5.9%) at week 36, 144 (18.5%) at week 42, and 33 (4.2%) serum urate measurements are missing.

§ Table shows adjudicated cardiovascular events.

¶ Mean (SD) C-reactive protein and serum creatinine laboratory values were calculated from participants within the week 48 visit window.

‖ Values are presented as the median (interquartile range).

** This result is the risk difference. All other results below in this column are risk ratio results.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Colchicine in Patients with Chronic Coronary Disease

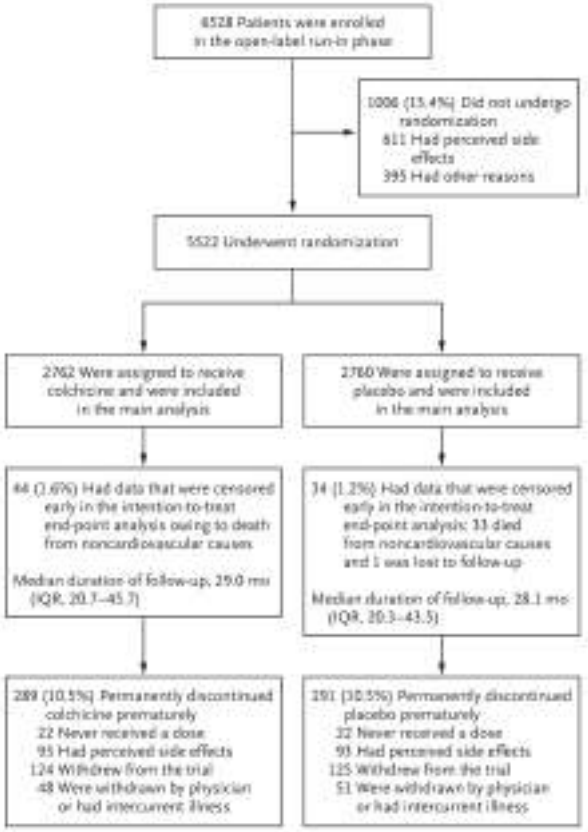
S.M. Nidorf, A.T.L. Fiolet, A. Mosterd, J.W. Eikelboom, A. Schut, T.S.J. Opstal, S.H.K. The, X.-F. Xu, M.A. Ireland, T. Lenderink, D. Latchem, P. Hoogslag, A. Jerzewski, P. Nierop, A. Whelan, R. Hendriks, H. Swart, J. Schaap, A.F.M. Kuijper, M.W.J. van Hessen, P. Saklani, I. Tan, A.G. Thompson, A. Morton, C. Judkins, W.A. Bax, M. Dirksen, M. Alings, G.J. Hankey, C.A. Budgeon, J.G.P. Tijssen, J.H. Cornel, and P.L. Thompson, for the LoDoCo2 Trial Investigators*

In a randomized, controlled, double-blind trial, we assigned patients with chronic coronary disease to receive 0.5 mg of colchicine once daily or matching placebo.

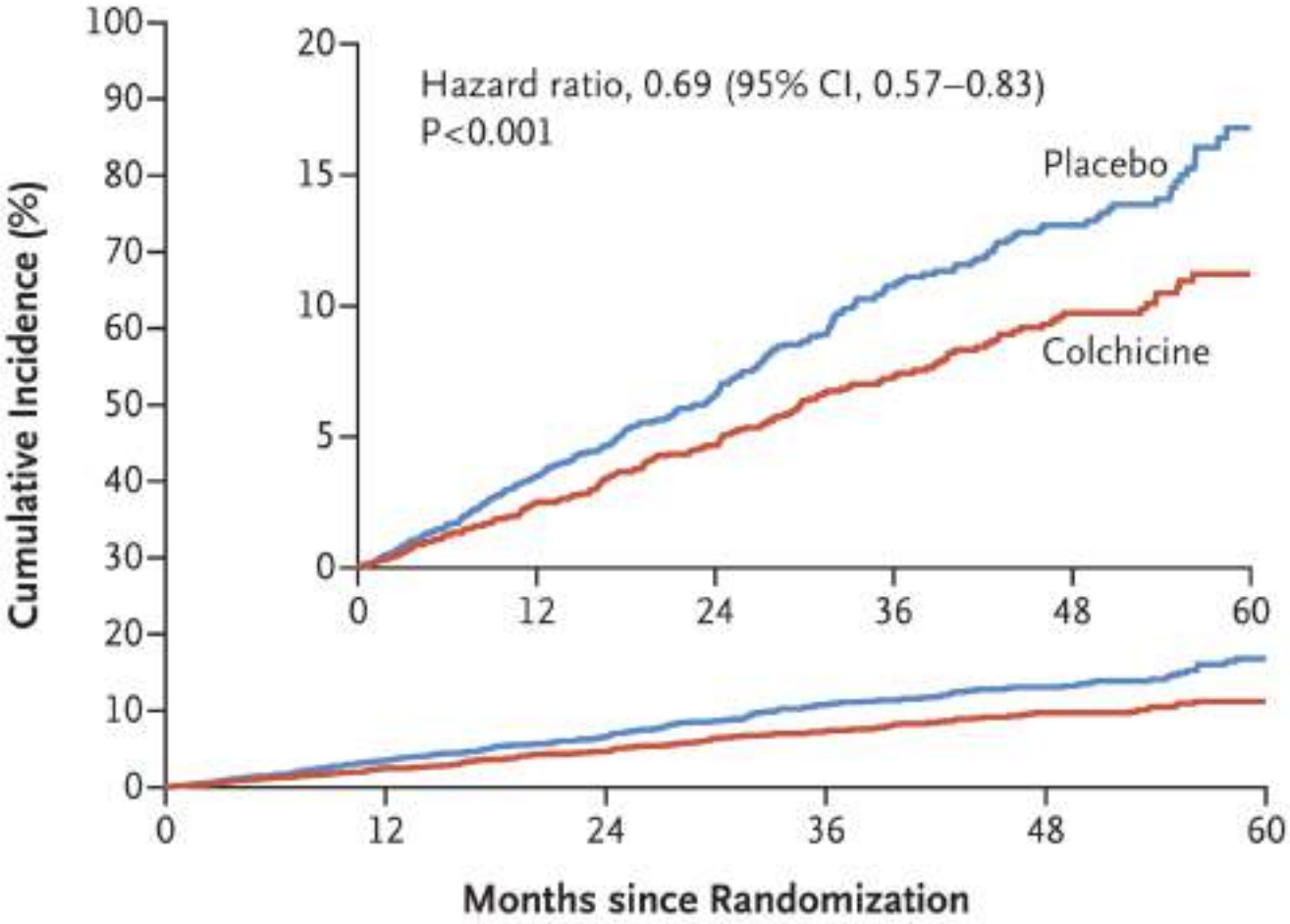
The primary end point was a composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization

Table 1. Characteristics of the Trial Patients at Baseline.*

Characteristic	Colchicine (N=2762)	Placebo (N=2760)
Age — yr	65.8±8.4	65.9±8.7
Female sex — no. (%)	457 (16.5)	389 (14.1)
Country — no. (%)		
Australia	951 (34.4)	953 (34.5)
The Netherlands	1811 (65.6)	1807 (65.5)
Current smoker — no. (%)†	318 (11.5)	330 (12.0)
Hypertension — no. (%)	1421 (51.4)	1387 (50.3)
Diabetes — no. (%)		
Patients receiving any treatment for diabetes	492 (17.8)	515 (18.7)
Patients dependent on insulin	140 (5.1)	147 (5.3)
Renal function — no. (%)‡		
Stage 1 or 2	2614 (94.6)	2602 (94.3)
Stage 3a	148 (5.4)	158 (5.7)
Prior acute coronary syndrome — no. (%)	2323 (84.1)	2335 (84.6)
Time since last acute coronary syndrome — no. (%)		
≤24 mo	751 (27.1)	726 (26.3)
>24 mo	1570 (56.8)	1609 (58.3)
Prior coronary revascularization — no. (%)	2301 (83.3)	2320 (84.1)
Coronary artery bypass grafting	319 (11.5)	392 (14.2)
Percutaneous coronary intervention	2100 (76.0)	2077 (75.3)
History of atrial fibrillation — no. (%)	352 (12.0)	317 (11.5)
History of gout — no. (%)	220 (8.0)	226 (8.2)



A Primary End Point



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

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Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

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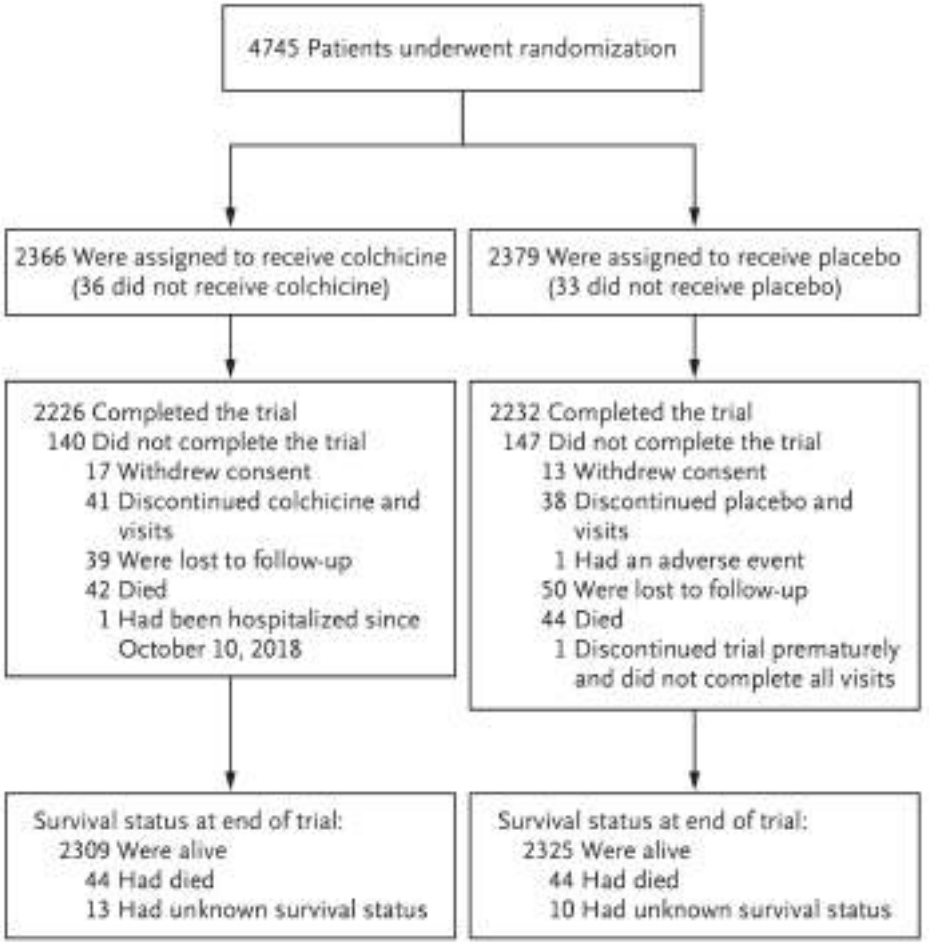
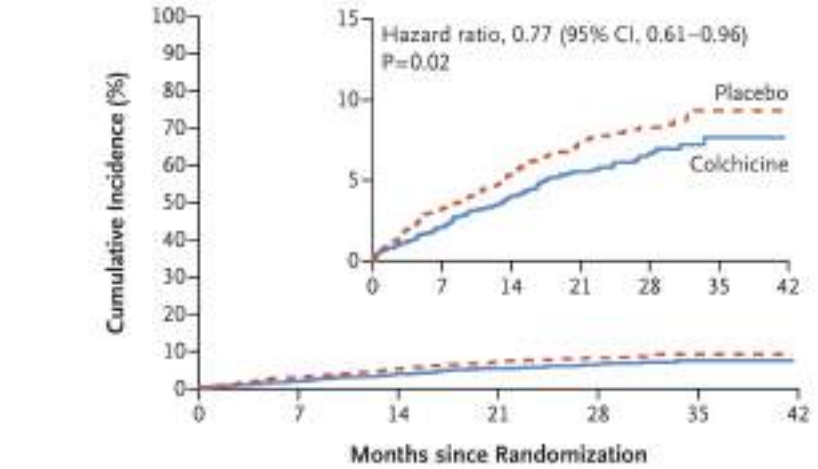
We performed a randomized, double-blind trial involving patients recruited within 30 days after a myocardial infarction.
The patients were randomly assigned to receive either low-dose colchicine (0.5 mg once daily) or placebo.
The primary efficacy end point was a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization.

Table 1. Characteristics of the Patients.*

Characteristic	Colchicine (N = 2366)	Placebo (N = 2379)
Age — yr	60.6±10.7	60.5±10.6
Female sex — no. (%)	472 (19.9)	437 (18.4)
White race — no./total no. (%)†	1350/1850 (73.0)	1329/1844 (72.1)
Body-mass index	28.2±4.8	28.4±4.7
Current smoking — no./total no. (%)	708/2366 (29.9)	708/2377 (29.8)
Hypertension — no. (%)	1185 (50.1)	1236 (52.0)
Diabetes — no. (%)	462 (19.5)	497 (20.9)
History of myocardial infarction — no. (%)	370 (15.6)	397 (16.7)
History of PCI — no. (%)	392 (16.6)	406 (17.1)
History of CABG — no. (%)	69 (2.9)	81 (3.4)
History of heart failure — no. (%)	48 (2.0)	42 (1.8)
History of stroke or TIA — no. (%)	55 (2.3)	67 (2.8)
Time from index myocardial infarction to randomization — days	13.4±10.2	13.5±10.1
PCI for index myocardial infarction — no./total no. (%)	2192/2364 (92.7)	2216/2375 (93.3)
Medication use — no. (%)		
Aspirin	2334 (98.6)	2352 (98.9)
Other antiplatelet agent	2310 (97.6)	2337 (98.2)
Statin	2339 (98.9)	2357 (99.1)
Beta-blocker	2116 (89.4)	2101 (88.3)





No. at Risk

Placebo	2379	2261	1854	1224	622	144	0
Colchicine	2366	2284	1868	1230	628	153	0

Table 2. Major Clinical End Points (Intention-to-Treat Population).*

End Point	Colchicine (N = 2366)	Placebo (N = 2379)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary composite end point	131 (5.5)	170 (7.1)	0.77 (0.61–0.96)	0.02†
Components of primary end point				
Death from cardiovascular causes	20 (0.8)	24 (1.0)	0.84 (0.46–1.52)	
Resuscitated cardiac arrest	5 (0.2)	6 (0.3)	0.83 (0.25–2.73)	
Myocardial infarction	89 (3.8)	98 (4.1)	0.91 (0.68–1.21)	
Stroke	5 (0.2)	19 (0.8)	0.26 (0.10–0.70)	
Urgent hospitalization for angina leading to revascularization	25 (1.1)	50 (2.1)	0.50 (0.31–0.81)	
Secondary composite end point‡	111 (4.7)	130 (5.5)	0.85 (0.66–1.10)	
Death	43 (1.8)	44 (1.8)	0.98 (0.64–1.49)	
Deep venous thrombosis or pulmonary embolus	10 (0.4)	7 (0.3)	1.43 (0.54–3.75)	
Atrial fibrillation	36 (1.5)	40 (1.7)	0.93 (0.59–1.46)	

ORIGINAL ARTICLE

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout

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ABSTRACT

BACKGROUND

Cardiovascular risk is increased in patients with gout. We compared cardiovascular outcomes associated with febuxostat, a nonpurine xanthine oxidase inhibitor, with those associated with allopurinol, a purine base analogue xanthine oxidase inhibitor, in patients with gout and cardiovascular disease.

METHODS

We conducted a multicenter, double-blind, noninferiority trial involving patients with gout and cardiovascular disease; patients were randomly assigned to receive febuxostat or allopurinol and were stratified according to kidney function. The trial had a prespecified noninferiority margin of 1.3 for the hazard ratio for the primary end point (a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or unstable angina with urgent revascularization).

RESULTS

In total, 6190 patients underwent randomization, received febuxostat or allopurinol, and were followed for a median of 32 months (maximum, 85 months). The trial regimen was discontinued in 56.6% of patients, and 45.0% discontinued follow-up. In the modified intention-to-treat analysis, a primary end-point event occurred in 335 patients (10.8%) in the febuxostat group and in 321 patients (10.4%) in the allopurinol group (hazard ratio, 1.03; upper limit of the one-sided 98.3% confidence interval [CI], 1.23; P=0.002 for noninferiority). All-cause and cardiovascular mortality were higher in the febuxostat group than in the allopurinol group (hazard ratio for death from any cause, 1.22 [95% CI, 1.01 to 1.47]; hazard ratio for cardiovascular death, 1.34 [95% CI, 1.03 to 1.73]). The results with regard to the primary end point and all-cause and cardiovascular mortality in the analysis of events that occurred while patients were being treated were similar to the results in the modified intention-to-treat analysis.

CONCLUSIONS

In patients with gout and major cardiovascular coexisting conditions, febuxostat was noninferior to allopurinol with respect to rates of adverse cardiovascular events. All-cause mortality and cardiovascular mortality were higher with febuxostat than with allopurinol. (Funded by Takeda Development Center Americas; CARES ClinicalTrials.gov number, NCT01101035.)

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*A complete list of the CARES investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 12, 2013, at NEJM.org.

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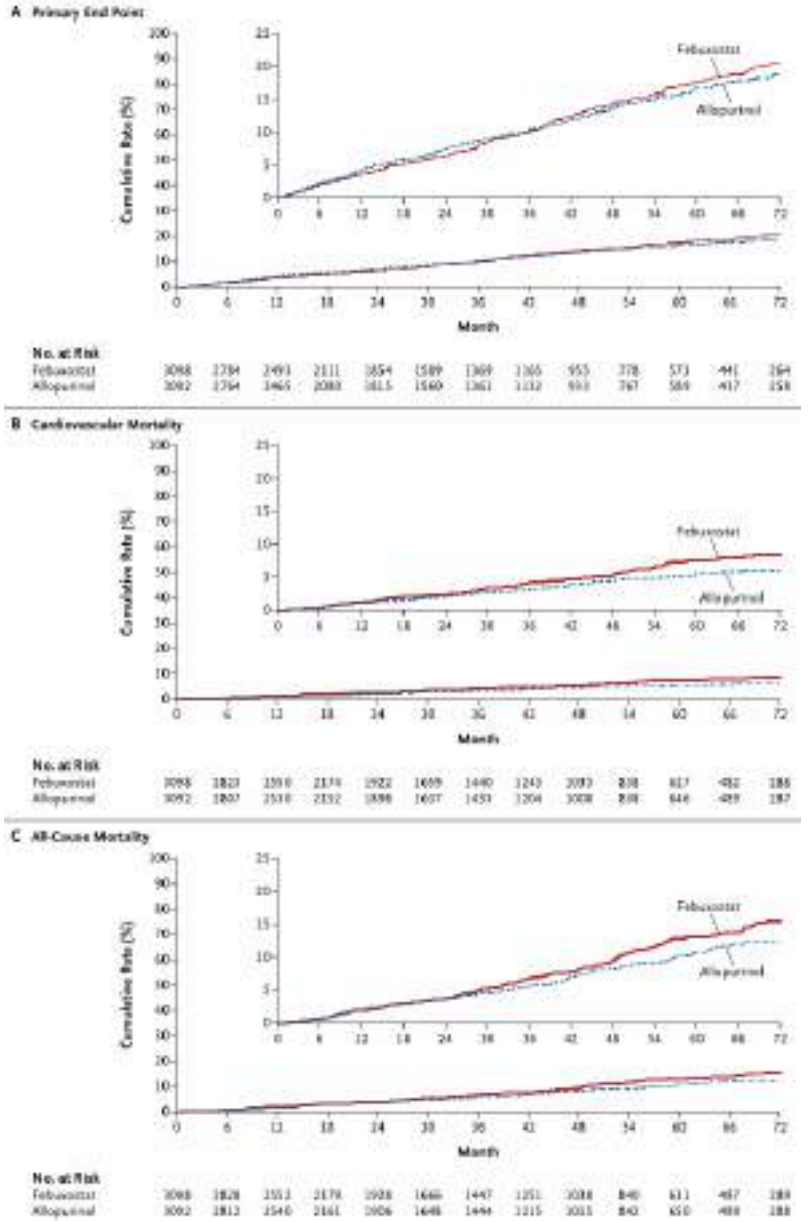
Febu: 40-80 mg
Allo : up to 600mg

Table 1. Baseline Characteristics of the Patients.^

Characteristic	Febuxostat (N=3098)	Allopurinol (N=3092)
Median age (interquartile range) — yr	64.0 (58–71)	65.0 (58–71)
Age ≥65 yr — no. (%)	1514 (48.9)	1586 (51.3)
Male sex — no. (%)	2604 (84.1)	2592 (83.8)
Duration of gout — yr	11.8±11.4	11.9±11.2
Baseline serum urate level — mg/dl	8.7±1.7	8.7±1.7
Presence of tophi — no. (%)	668 (21.6)	650 (21.0)
Median body weight (interquartile range) — kg	97.7 (84–113)	97.3 (84–113)
Body-mass index†	33.6±7.0	33.4±6.9
Race or ethnic group — no. (%)‡		
White	2160 (69.7)	2140 (69.2)
Black	552 (17.8)	593 (19.2)
Asian	92 (3.0)	96 (3.1)
American Indian or Alaska Native	262 (8.5)	234 (7.6)
Native Hawaiian or other Pacific Islander	15 (0.4)	14 (0.5)
Other	19 (0.6)	15 (0.5)
Cardiovascular risk factors and history — no. (%)		
Diabetes mellitus with small-vessel disease	1193 (38.5)	1213 (39.2)
Hypertension	2864 (92.4)	2851 (92.2)
Hyperlipidemia	2678 (86.4)	2702 (87.4)
Myocardial infarction	1197 (38.6)	1231 (39.8)
Hospitalization for unstable angina	855 (27.6)	869 (28.1)
Coronary revascularization	1129 (36.4)	1182 (38.2)
Cerebral revascularization	69 (2.2)	54 (1.7)
Congestive heart failure	622 (20.1)	631 (20.4)
Stroke	460 (14.8)	410 (13.3)
Peripheral vascular disease	412 (13.3)	375 (12.1)
Median estimated creatinine clearance — ml/min§		
Stage 1 or 2 chronic kidney disease	75.0	73.0
Stage 3 chronic kidney disease	46.0	46.0
Stage of chronic kidney disease — no./total no. (%)		
Stage 1 or 2	1456/3092 (47.1)	1459/3090 (47.2)
Stage 3	1636/3092 (52.9)	1631/3090 (52.8)

Table 2. **Major Safety End Points (Modified Intention-to-Treat Analysis).***

End Point	Febuxostat (N=3098)	Allopurinol (N=3092)	Hazard Ratio (95% CI)	P Value†
	no. of patients (%)			
Primary end point: composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to unstable angina	333 (10.8)	321 (10.4)	1.03 (0.87–1.23)‡	0.66 (0.002)
Secondary end points				
Cardiovascular death	134 (4.3)	100 (3.2)	1.34 (1.03–1.73)	0.03
Nonfatal myocardial infarction	111 (3.6)	118 (3.8)	0.93 (0.72–1.21)	0.61
Nonfatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73–1.41)	0.94
Urgent revascularization for unstable angina	49 (1.6)	56 (1.8)	0.86 (0.59–1.26)	0.44
Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	296 (9.6)	271 (8.8)	1.09 (0.92–1.28)	0.33
Death from any cause	243 (7.8)	199 (6.4)	1.22 (1.01–1.47)	0.04



2020

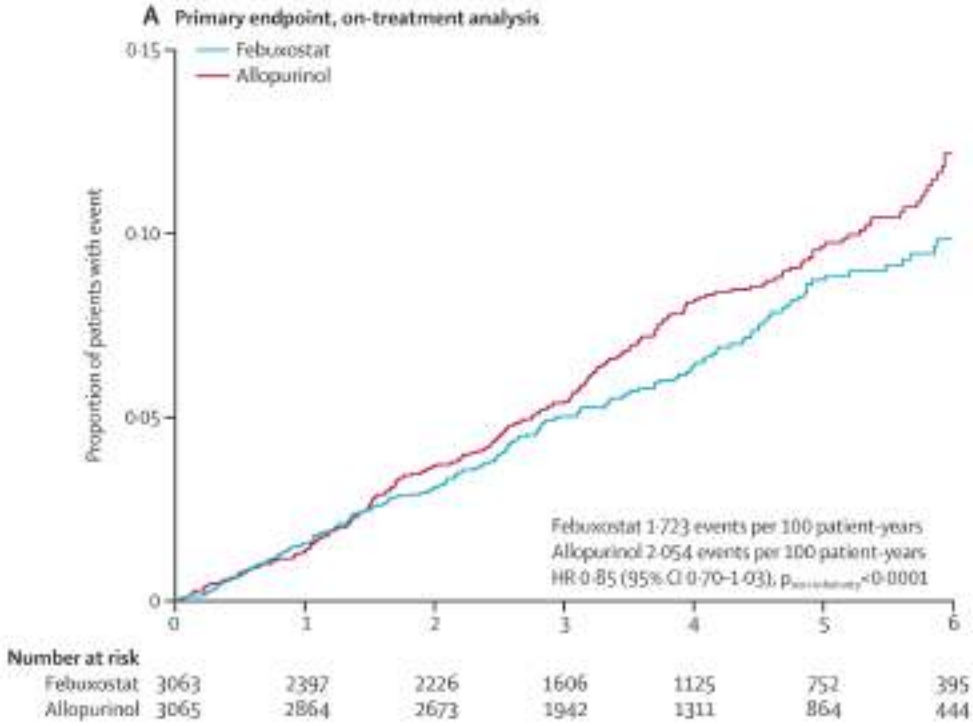
Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial

Iain S Mackenzie, Ian Ford, George Nuki, Jesper Hallas, Christopher J Hawkey, John Webster, Stuart H Ralston, Matthew Walters, Michele Robertson, Raffaele De Caterina, Evelyn Findlay, Fernando Perez-Ruiz, John J V McMurray, Thomas M MacDonald, on behalf of the FAST Study Group*

	Events				HR (95% CI)	$p_{non-inferiority}$	$p_{superiority}$
	Febuxostat (n=3091)		Allopurinol (n=3065)				
	Patients, n (%)	Rate per 100 patient-years	Patients, n (%)	Rate per 100 patient-years			
Primary endpoint (composite): cardiovascular death, hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome, or non-fatal stroke	256 (8·4%)	2·047	285 (9·3%)	2·295	0·89 (0·75–1·06)	<0·0001	0·185
Cardiovascular death	117 (3·8%)	0·933	122 (4·0%)	0·949	0·96 (0·74–1·23)	0·0088	0·730
Hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome	102 (3·3%)	0·808	110 (3·6%)	0·873	0·93 (0·71–1·21)	0·0067	0·573
Non-fatal stroke	80 (2·6%)	0·629	87 (2·8%)	0·687	0·92 (0·68–1·25)	0·013	0·591
All-cause death	222 (7·2%)	1·728	263 (8·6%)	2·045	0·84 (0·71–1·01)	<0·0001	0·063
Hospitalisation for heart failure	92 (3·0%)	0·724	102 (3·3%)	0·805	0·90 (0·68–1·19)	0·0047	0·441
Hospitalisation for unstable, new, or worsening angina	5 (0·2%)	0·039	12 (0·4%)	0·094	0·41 (0·14–1·16)	0·015	0·092
Hospitalisation for coronary revascularisation	87 (2·8%)	0·689	83 (2·7%)	0·656	1·05 (0·78–1·42)	0·080	0·761
Hospitalisation for cerebrovascular revascularisation	3 (0·1%)	0·023	8 (0·3%)	0·062	0·38 (0·10–1·42)	0·033	0·148
Hospitalisation for transient ischaemic attack	20 (0·7%)	0·156	25 (0·8%)	0·195	0·79 (0·44–1·42)	0·048	0·430
Hospitalisation for non-fatal cardiac arrest	5 (0·2%)	0·039	6 (0·2%)	0·047	0·84 (0·26–2·77)	0·238	0·779
Hospitalisation for venous and peripheral arterial vascular thrombotic event	36 (1·2%)	0·282	40 (1·3%)	0·313	0·90 (0·57–1·41)	0·054	0·640
Hospitalisation for arrhythmia with no evidence of ischaemia	74 (2·4%)	0·583	49 (1·6%)	0·385	1·51 (1·05–2·17)	0·796	0·024

Non-inferiority p values are based on a non-inferiority limit for the HR of 1·3, with the one-sided type I error rate set at 2·5%. The type I error rate was set at 5% for the superiority analyses. HRs were from Cox proportional hazards models adjusted for the stratification variable (previous cardiovascular events) and country. HR=hazard ratio.

Table 3: Primary and secondary outcomes in the intention-to-treat analysis



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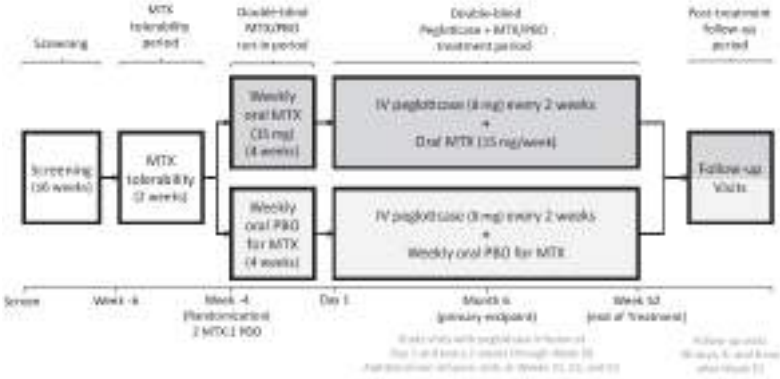
American College of Rheumatology
Empowering Rheumatology Professionals

A Randomized, Placebo-Controlled Study of Methotrexate to Increase Response Rates in Patients with Uncontrolled Gout Receiving Pegloticase: Primary Efficacy and Safety Findings

John K. Botson,[1] Kenneth Saag,[2] Jeff Peterson,[3] Naval Parikh,[4] Stephen Ong,[5] Dan La,[6] Karon LoCicero,[7] Katie Obermeyer,[8] Yan Xin,[8] Jason Chamberlain,[9] Brian LaMoreaux,[9] Supra Verma,[9] Stephen Sainati,[9] Suneet Grewal,[9] Amar Majhoo,[10] John R. P. Tesser,[11] and Michael E. Weinblatt[12]



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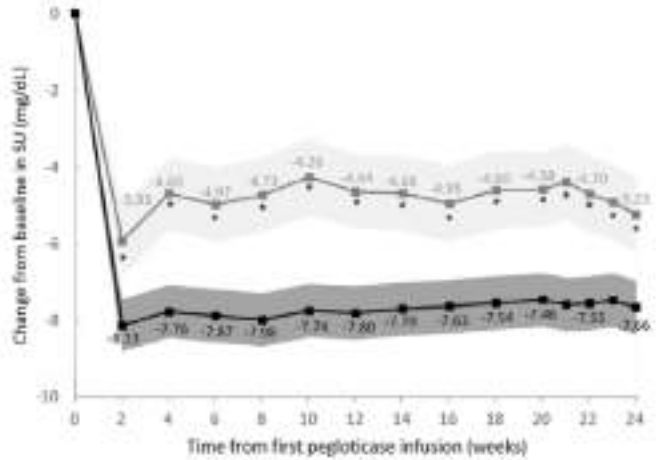


N, patients													
Pegloticase + PBO	52	52	46	39	37	32	42	34	31	27	27	31	35
Pegloticase + MTX	100	96	92	85	84	82	83	83	79	78	80	77	74

A

Treatment efficacy endpoints	Pegloticase + MTX	Pegloticase + PBO	Between group difference (95% CI)	p-value
ITT population	N = 100	N = 52		
6-month treatment responder*, n (%)	71 (71.0%)	20 (38.5%)	32.3% (16.3%, 48.3%)	<0.0001
3-month treatment responder, n (%)	79 (79.0%)	21 (40.4%)	38.3% (22.7%, 53.8%)	<0.0001
Overall treatment responder, n (%)	70 (70.0%)	20 (38.5%)	31.3% (15.2%, 47.3%)	0.0001
SU change from baseline†, LS mean±SE, mg/dL	-7.66 ± 0.358	-5.23 ± 0.507	-2.43 (-3.58, -1.27)	<0.0001
Complete resolution of ≥1 tophus‡, n/N (%)	18/52 (34.6%)	4/29 (13.8%)	20.8% (2.8%, 38.8%)	0.0434

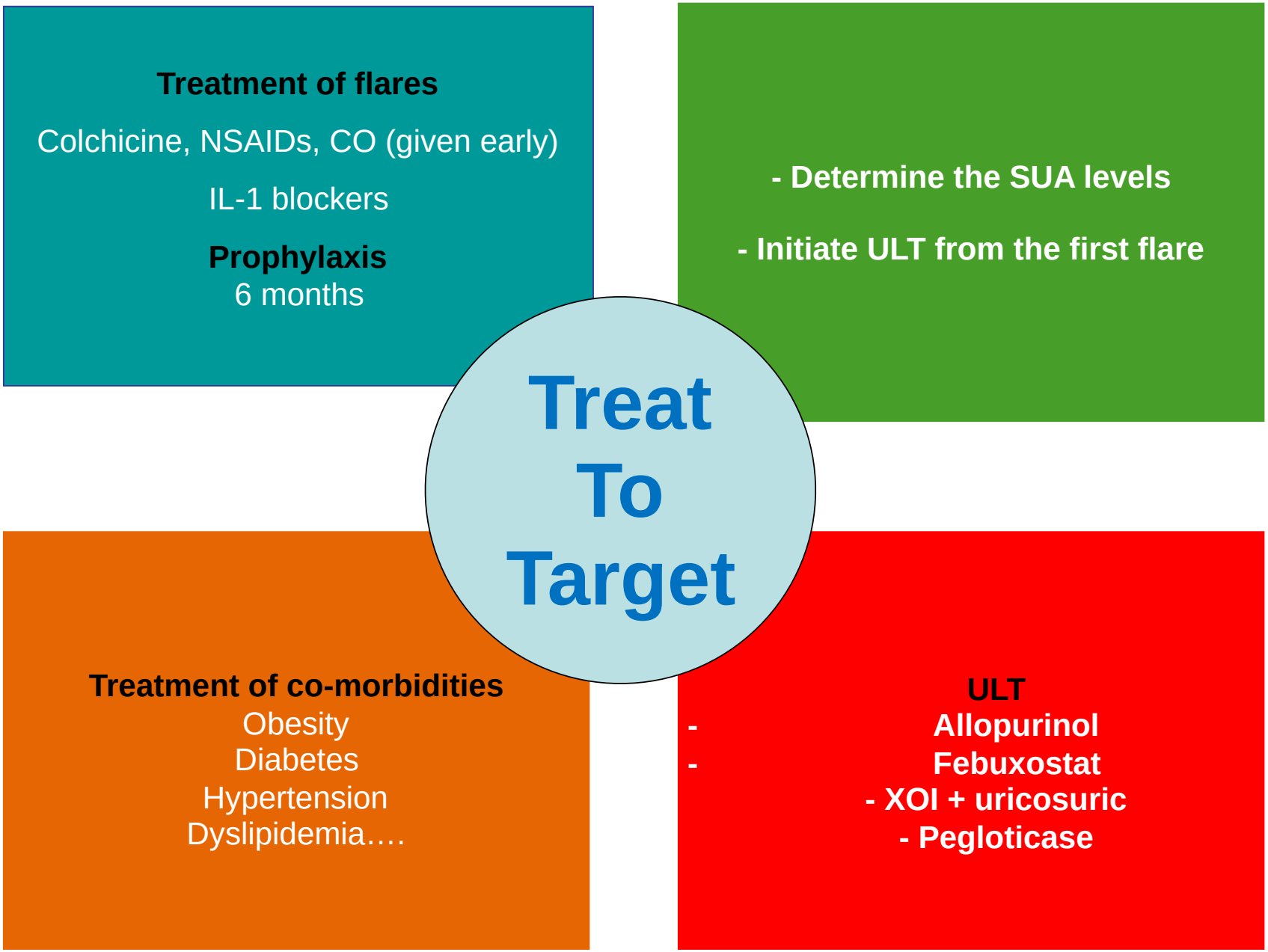
2018

Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial

Michael Doherty, Wendy Jenkins, Helen Richardson, Aliya Sarmanova, Abhishek Abhishek, Deborah Ashton, Christine Barclay, Sally Doherty, Lelia Duley, Rachael Hatton, Frances Rees, Matthew Stevenson, Weiya Zhang

	Nurse-led care (n=255)	Usual care (n=252)	Risk ratio (95% CI)
Serum urate concentration <360 μmol/L			
Baseline	22·35%	21·40%	1·04 (0·72–1·51)
1 year	94·75%	26·23%	3·59 (2·72–4·75)
2 years	94·88%	28·71%	3·30 (2·42–4·49)
p for trend within group	<0·0001	0·0752	–
Serum urate concentration <300 μmol/L			
Baseline	8·63%	10·24%	0·83 (0·48–1·46)
1 year	80·42%	12·75%	6·48 (4·48–9·36)
2 years	88·65%	12·46%	5·21 (3·81–7·13)
p for trend within group	<0·0001	0·0587	–
Taking urate-lowering therapy			
Baseline	26·81%	28·91%	1·02 (0·77–1·34)
1 year	96·70%	45·85%	2·46 (2·05–2·97)
2 years	94·38%	56·13%	1·73 (1·58–2·11)
p for trend within group	<0·0001	0·0051	–
Two or more flares			
Baseline	79·57%	79·77%	1·00 (0·85–1·21)
1 year	53·93%	33·81%	1·26 (1·05–1·77)
2 years	8·60%	14·29%	0·32 (0·18–0·57)
p for trend within group	<0·0001	<0·0001	–
Four or more flares			
Baseline	38·64%	35·11%	1·08 (0·82–1·44)
1 year	27·92%	20·75%	1·33 (0·92–1·93)
2 years	1·25%	12·55%	0·09 (0·02–0·36)
p for trend within group	<0·0001	<0·0001	–
Presence of tophi			
Baseline	11·73%	8·78%	1·56 (0·91–2·65)
1 year	7·85%	16·15%	0·53 (0·28–1·01)
2 years	3·85%	13·25%	0·21 (0·08–0·52)
p for trend within group	<0·0001	0·4146	–

Percentage and risk ratio values were estimated with multiple imputation with the assumption that data were missing at random.


Treatment of flares
Colchicine, NSAIDs, CO (given early)
IL-1 blockers
Prophylaxis
6 months
- Determine the SUA levels
- Initiate ULT from the first flare
Treat To Target
Treatment of co-morbidities
Obesity
Diabetes
Hypertension
Dyslipidemia….
ULT
- Allopurinol
- Febuxostat
- XOI + uricosuric
- Pegloticase