La goutte en 2023

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Hôpital Lariboisière, Paris

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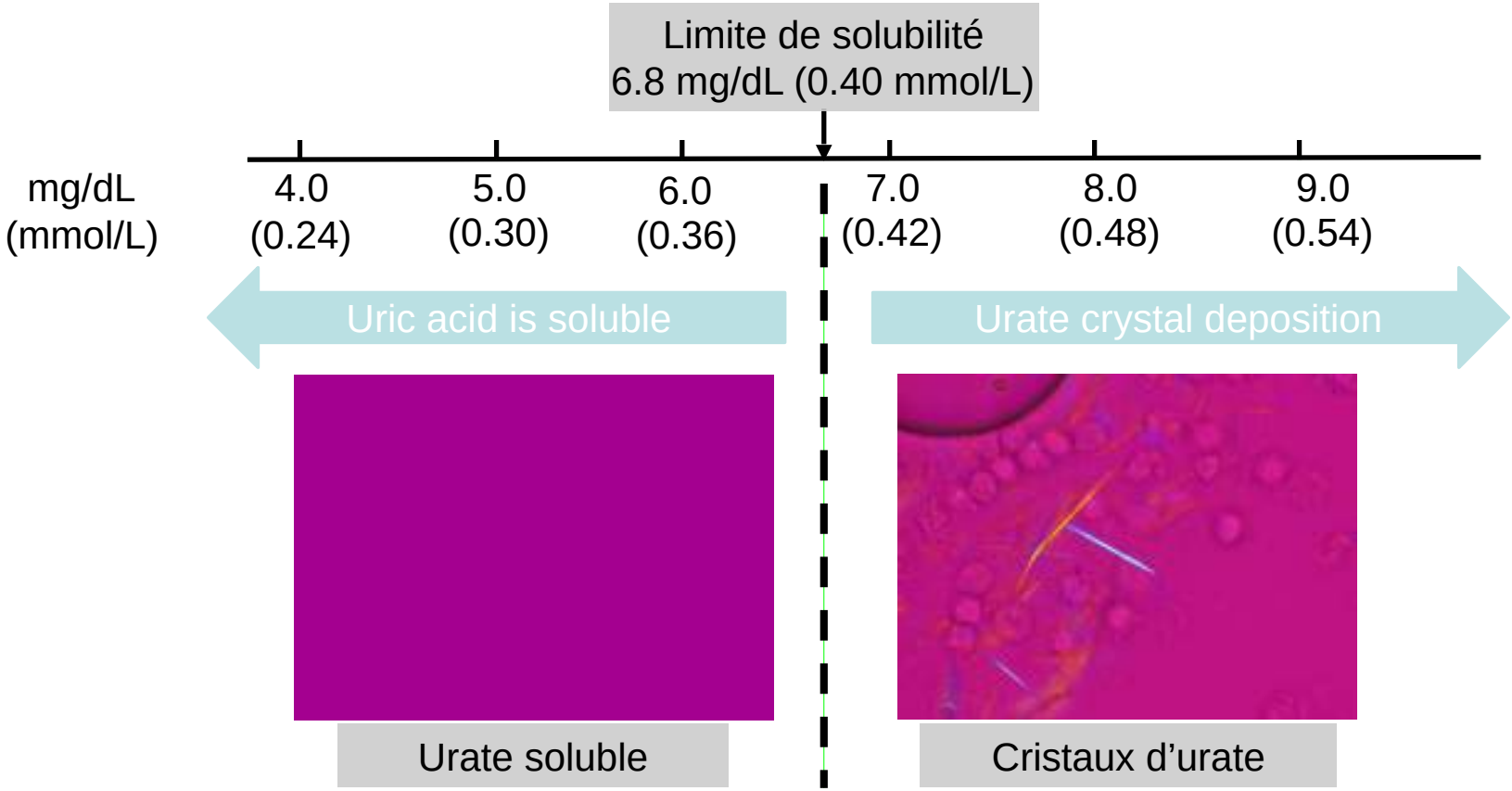
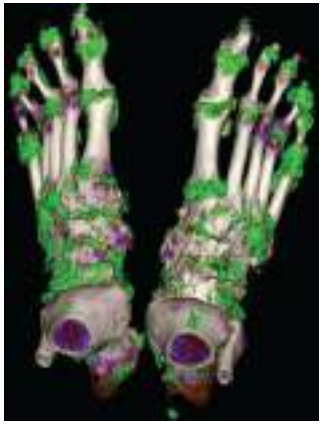
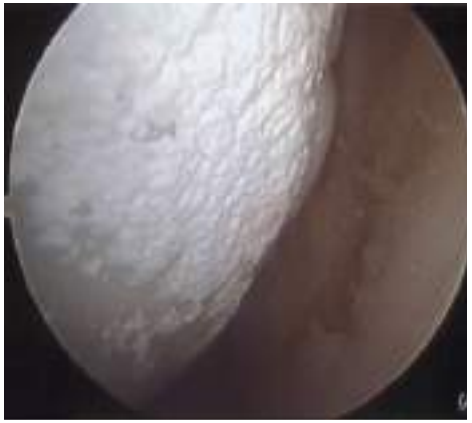
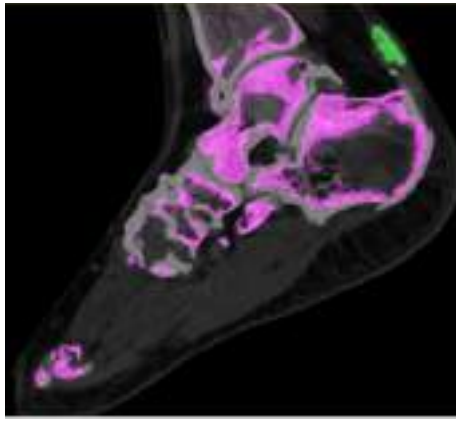
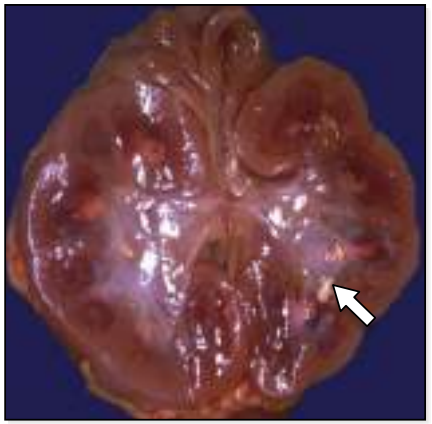
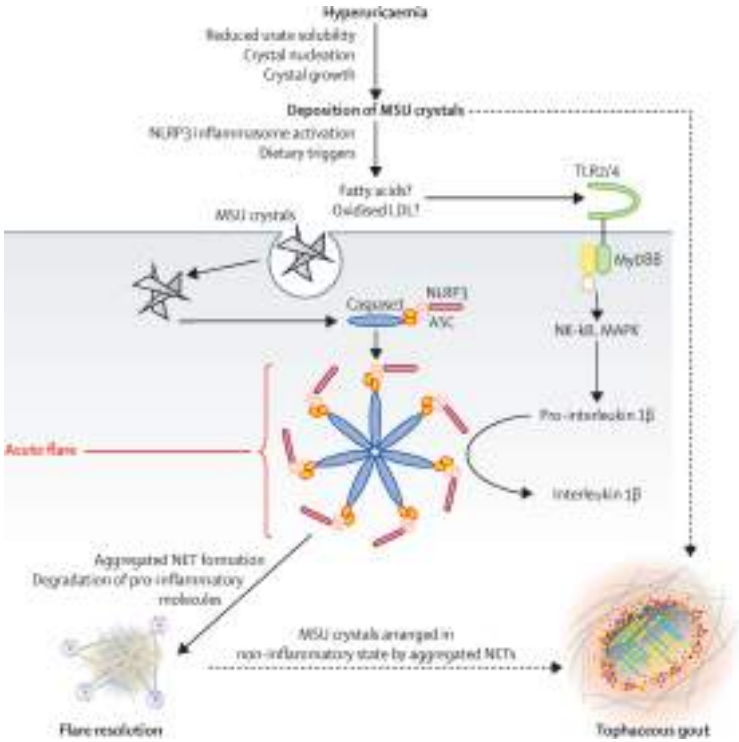
Bioscar U1132
Biologie de l'os et du cartilage

université PARIS DIDEROT PARIS 7

Conséquence du dépôt de cristaux d'urate de sodium lié à une hyperuricémie prolongée dans le sang




Hyperuricaemia
Reduced urate solubility
Crystal nucleation
Crystal growth
Deposition of MSU crystals
NLRP3 inflammasome activation
Dietary triggers
Fatty acids?
Oxidised LDL?
TLR2/4
MSU crystals
MyD88
Caspase1
NLRP3
ASC
NF-κB, MAPK
Pro-interleukin 1β
Acute flare
Interleukin 1β
Aggregated NET formation
Degradation of pro-inflammatory molecules
MSU crystals arranged in non-inflammatory state by aggregated NETs
Flare resolution
Tophaceous gout

Lancet 2016

Pourquoi l'uricémie est-elle proche du seuil de solubilité ?

PNAS

Evolutionary history and metabolic insights of ancient mammalian uricases

James T. Kratzer[A,B,1], Miguel A. Lanaspa[C,1], Michael N. Murphy[B,1], Christina Cicerchi[C], Christina L. Graves[B], Peter A. Tipton[B], Eric A. Ortlund[B,2], Richard J. Johnson[C,2], and Eric A. Gaucher[A,B,D,2]

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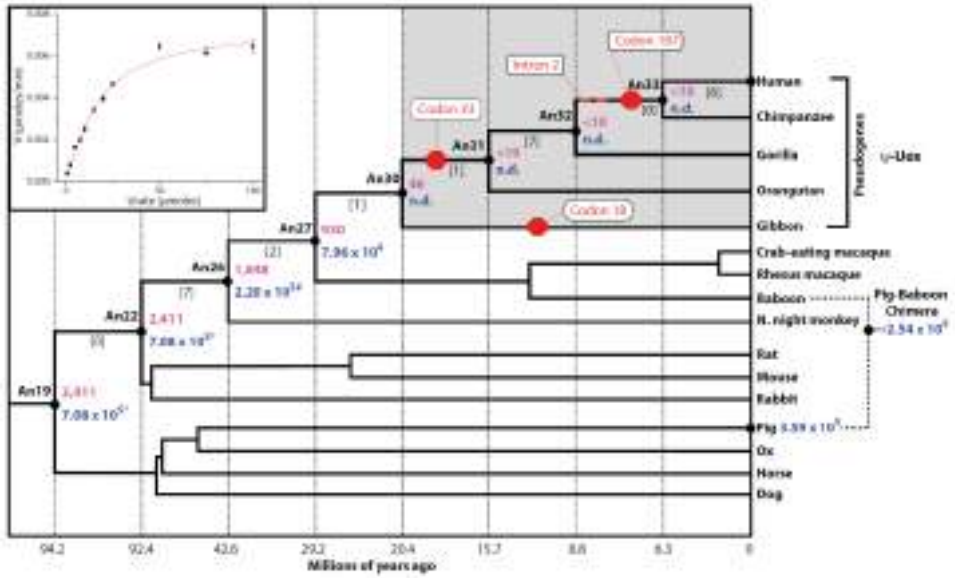
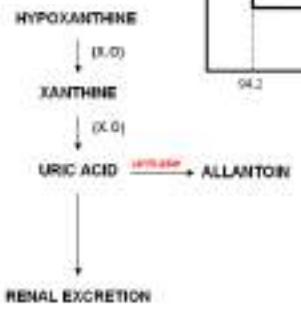
Edited by David M. Hillis, University of Texas at Austin, Austin, TX, and approved January 15, 2014 (received for review November 4, 2013)





Coevolution of URAT1 and Uricase during Primate Evolution: Implications for Serum Urate Homeostasis and Gout

Philip K. Tan,[*,1] Jennifer E. Farrar,[2] Eric A. Gaucher,[*,2,3] and Jeffrey N. Miner[1]

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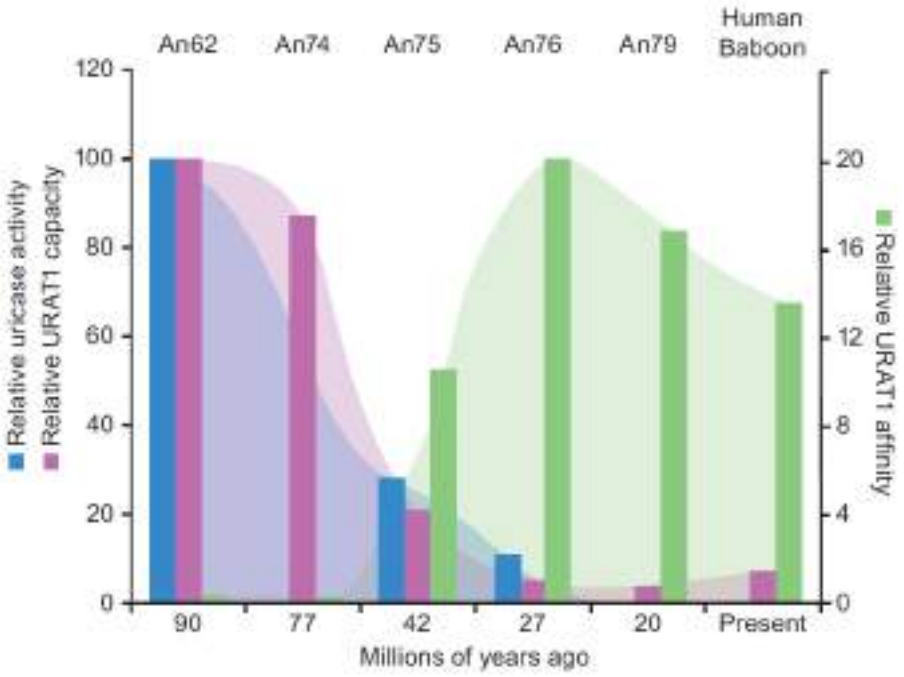
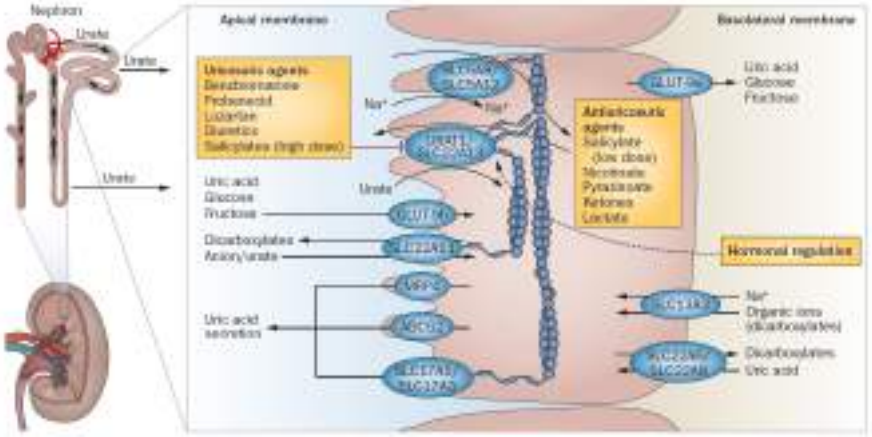
Associate editor: Connie Mulligan



Pourquoi l'uricémie s'élève t'elle ?: l'hérédité

Most of the genes that associated with serum uric acid levels or gout are involved in the renal urate-transport system



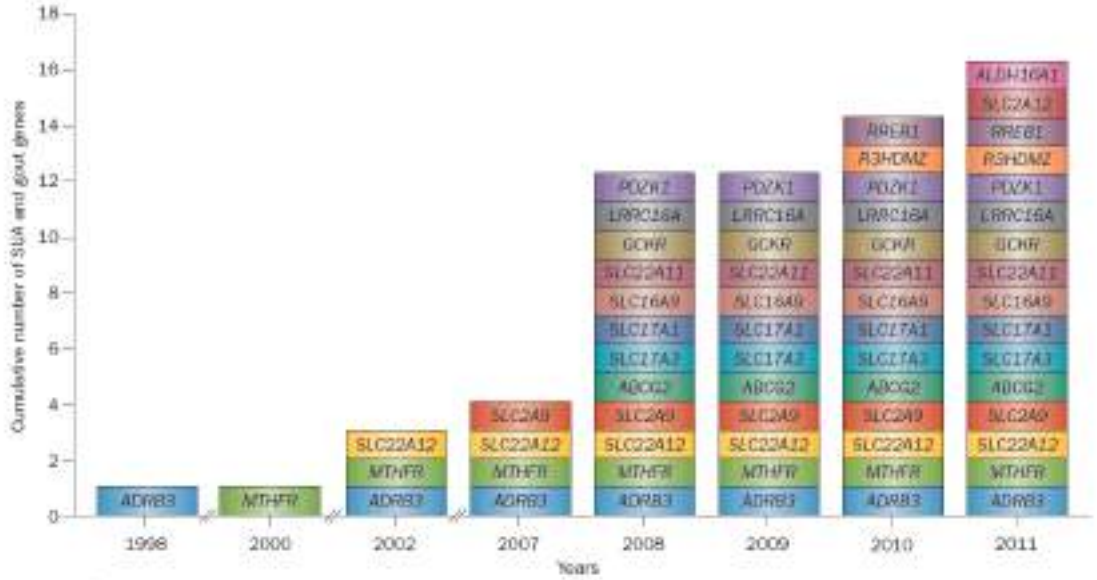


Figure 1 | Genetic variants implicated in the pathogenesis of hyperuricaemia or gout. Discovery timeline showing cumulative number of genes discovered from 2008–2011. Abbreviation: SUA, serum uric acid.

Nat. Rev. Rheumatol. 2012

Title: A genome-wide association analysis of 2,622,830 individuals reveals pathogenic pathways in gout

Tanya J. Major, Riku Takei, Hirotaka Matsuo, Megan P. Leask, Ruth K. Topless, Yuya Shirai, Zhiqiang Li, Murray J. Cadzow, Nicholas A. Sumpter, Marilyn E. Merriman, Amanda J. Phipps-Green, Mariana Urquiaga, Eric E. Kelley, Sara E. Lewis, Wen-H. Wei, Sally P.A. McCormick, Richard J. Reynolds, Kenneth G. Saag, Matthew J. Bixley, Tayana Padoan, Justin M. O'Sullivan, Lisa K. Stamp, Nicola Dalbeth, Abhishek Abhishek, Michael Doherty, Edward Roddy, Lennart T.H. Jacobsson, Melihа C. Kapetanovic, Ole Melander, Mariano Andrés, Fernando Pérez-Ruiz, Rosa Torres Jiménez, Timothy Radstake, Timothy L. Jansen, Matthijs Janssen, Leo A.B. Joosten, Tania O. Crişan, Fina Kurreeman, Tom W.J. Huizinga, René Toes, Frédéric Lioté, Pascal Richette, Thomas Bardin, E.A. Hang Kong, Tristan Pascart, Geraldine M. McCarthy, Laura Helbert, Blanka Stibůrková, Anne-K. Tausche, Till Uhlig, Véronique Vinet, Thibaud S. Boutin, Philip L. Riches, Stuart H. Ralston, Thomas M. MacDonald, Akiyoshi Nakayama, Tappei Takada, Masahiro Nakatochi, Seiko Shimizu, Yusuke Kawamura, Yu Toyoda, Hirofumi Nakaoka, Ken Yamamoto, Keiko Matsui, Noriyoshi Shimoniyi, Kimiyoshi Ichida, Chaeyoung Lee, Linda A. Bradbury, Matthew A. Brown, Philip C. Robinson, Russell R.C. Buchanan, Catherine L. Hill, Susan Lester, Malcolm D. Smith, Maureen Rischmueller, Hyon K. Choi, Eli A. Stahl, Jeff N. Miner, Daniel H. Solomon, Jing Cui, Kathleen M. Giacomini, Deanna J. Brackman, Eric M. Jorgenson, 23andMe Research Team, Wei Wang, Sagesh Shringarpure, Alexander So, Yukinori Okada, Chang-Gui Li, Yongyong Shi, Tony R. Merriman

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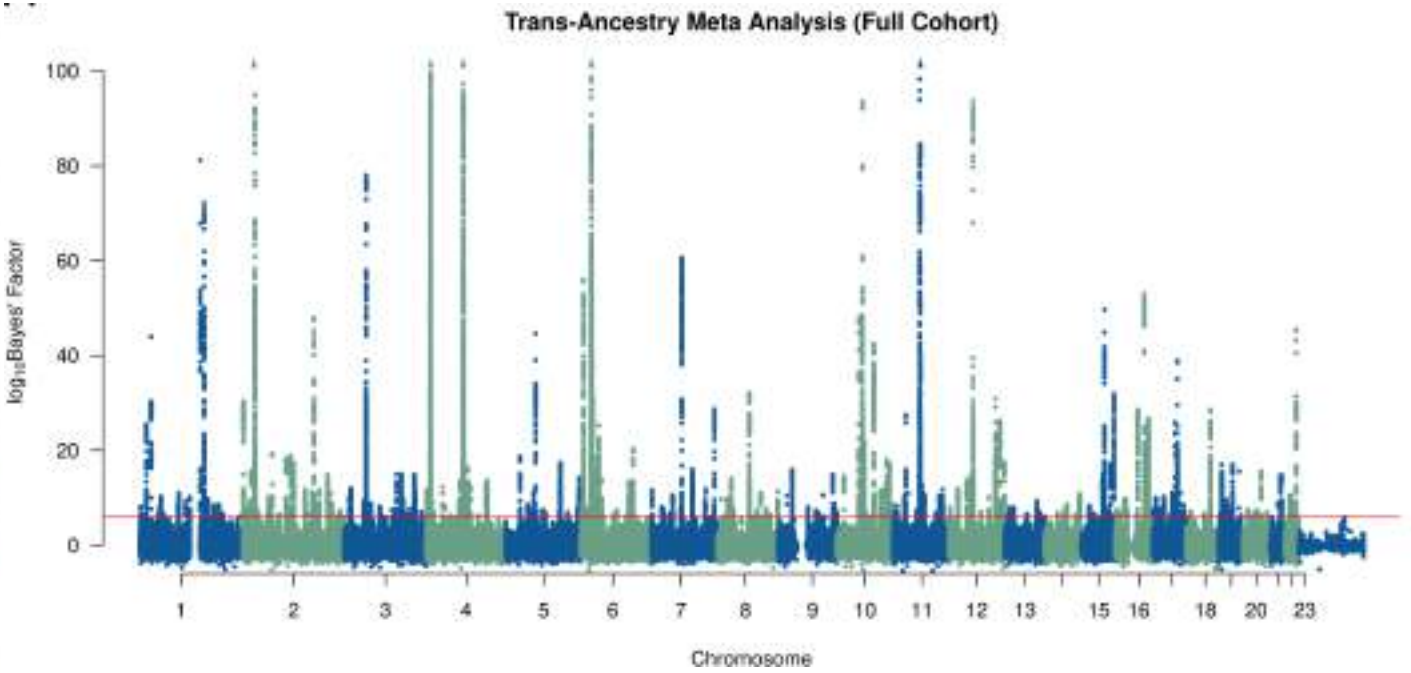
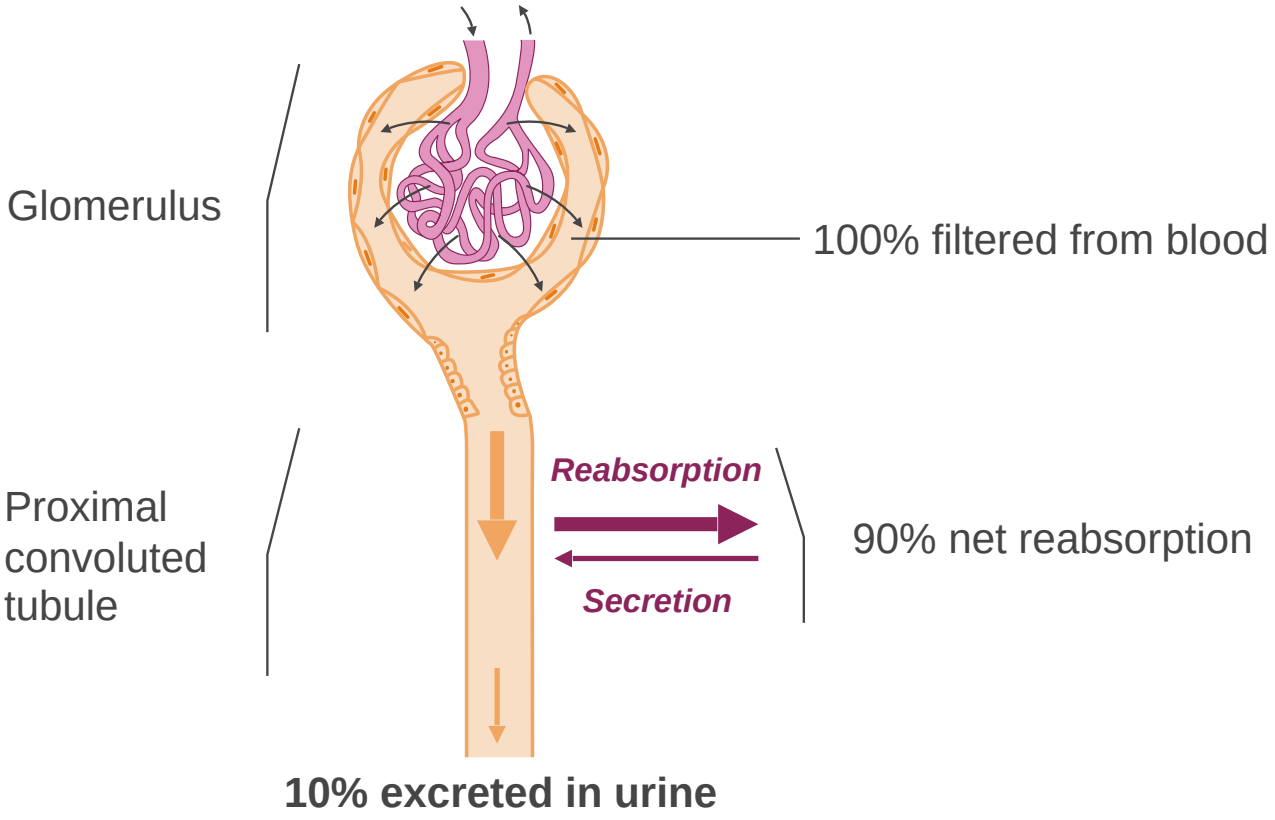


"Genetic study of 2.6M people, including 120K people with gout. We detect 385 loci and 560 genetically independent gout-associated variants (161 new loci in urate and gout)"

Nature genetics, submitted, 2022

Pourquoi l’uricémie s’élève t’elle ?: l’hérédité, l’I.Rénale, les diurétiques, l’obésité



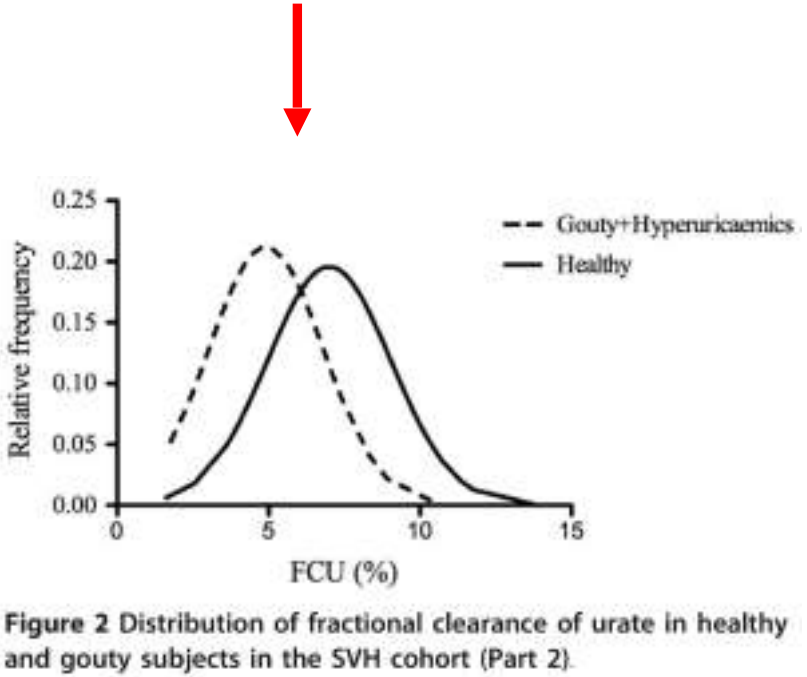


Figure 2 Distribution of fractional clearance of urate in healthy and gouty subjects in the SVH cohort (Part 2).

Goutte: une maladie d’origine rénale

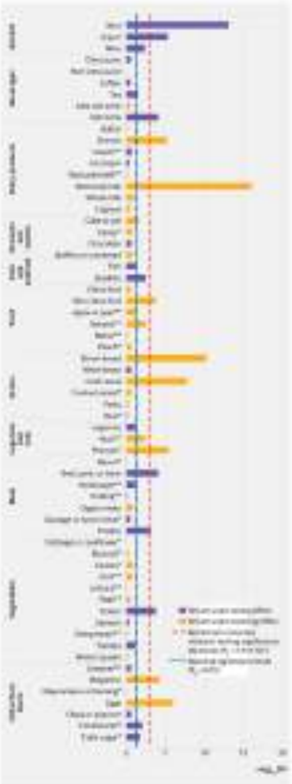
Alimentation versus Hérédité ?

BMJ 2018

RESEARCH

Evaluation of the diet wide contribution to serum urate levels: meta-analysis of population based cohorts

Tanya J Major,[1] Ruth K Topless,[1] Nicola Dalbeth,[2] Tony R Merriman[1]



- ✓ Three diet scores were inversely associated with serum urate levels
- ✓ A fourth was positively associated with raised serum urate levels
- ✓ Each explained ≤0.3% of variance in SUA levels

Table 2 | Percent variance in serum urate levels (µmol/L) explained by dietary and genetic factors in full, male, and female study cohorts

Diet, genetic score, and additional adjuster	Full cohort No	Full cohort β (95% CI)*	Full cohort P_{β}	Full cohort R^2 (%)†	Male cohort No	Male cohort β (95% CI)	Male cohort P_{β}	Male cohort R^2 (%)	Female cohort No	Female cohort β (95% CI)	Female cohort P_{β}	Female cohort R^2 (%)
Dietary effect												
Healthy Eating												
Unadjusted	16 759	−0.72 (−1.01 to −0.43)	<0.001	0.25	8413	−0.97 (−1.41 to −0.54)	<0.001	0.31	8346	−0.41 (−1.25 to 0.38)	0.30	0.07
Genetic risk score	12 362	−0.63 (−0.92 to [illegible])	<0.001	0.12	6109	−0.82 (−1.31 to −0.33)	<0.001	0.16	6053	−0.35 (−1.31 to 0.61)	0.48	0.05
DASH												
Unadjusted	16 731	−0.73 ([illegible])	<0.001	0.28	8402	−0.86 (−1.20 to −0.53)	<0.001	0.31	8329	−0.64 (−1.23 to −0.05)	0.03	0.17
Genetic risk score	12 139	−0.75 (−1.01 to [illegible])	<0.001	0.37	6100	−0.88 (−1.28 to −0.51)	<0.001	0.43	6039	−0.71 (−1.45 to 0.03)	0.06	0.25
Mediterranean												
Unadjusted	16 719	−0.34 ([illegible])	<0.001	0.05	8392	−0.58 (−1.05 to −0.11)	0.02	0.10	8327	−0.16 (−0.40 to 0.08)	0.19	0.03
Genetic risk score	12 13[illegible]	−0.54 ([illegible])	0.008	0.12	6093	−0.83 (−1.47 to −0.19)	0.01	0.23	6039	−0.26 (−0.84 to 0.28)	0.32	0.00
Data driven												
Unadjusted	16 652	0.57 (0.26 to 0.88)	<0.001	0.16	8354	0.62 (0.33 to 0.91)	<0.001	0.17	8298	0.53 (0.24 to 0.83)	<0.001	0.14
Genetic risk score	12 076	0.48 (0.25 to 0.71)	<0.001	0.08	6063	0.43 (0.10 to 0.76)	0.01	0.06	6005	0.54 (−0.18 to 1.27)	0.14	0.13
Genetic effect												
Genetic risk score												
Unadjusted	12 362	0.99 (0.93 to 1.05)	<0.001	7.85	6109	0.93 (0.84 to 1.01)	<0.001	5.80	6053	1.04 (0.97 to 1.12)	<0.001	10.55
Healthy Eating	12 362	0.99 (0.93 to 1.05)	<0.001	7.82	6109	0.93 (0.84 to 1.01)	<0.001	5.87	6053	1.04 (0.96 to 1.11)	<0.001	10.51
DASH	12 147	0.99 (0.93 to 1.05)	<0.001	7.85	6106	0.94 (0.84 to 1.03)	<0.001	5.91	6041	1.05 (0.96 to 1.13)	<0.001	10.55
Mediterranean	12 131	0.99 (0.93 to 1.05)	<0.001	7.80	6032	0.94 (0.84 to 1.03)	<0.001	5.93	6032	1.05 (0.97 to 1.13)	<0.001	10.53
Data driven	12 076	0.99 (0.93 to 1.05)	<0.001	7.84	6061	0.94 (0.84 to 1.03)	<0.001	5.89	6005	1.05 (0.97 to 1.13)	<0.001	10.53
Heritability estimate												
Unadjusted	12 362	NA	<0.001	23.9 (20.2 to 27.3)	6109	NA	<0.001	23.8 (16.4 to 31.3)	6053	NA	<0.001	40.3 (33.5 to 47.1)

DASH=Dietary Approaches to Stop Hypertension; Healthy Eating=based on the Harvard Healthy Eating Pyramid guidelines; NA=not applicable. 95% confidence interval given for the heritability estimate.

*Effect size reflecting the change in serum urate level (µmol/L) per one unit increase in diet score or genetic risk score.

SU heritability explained 23.9 % of variance in SUA levels

Conclusion: « In contrast with genetic contributions, diet explains very little variation in serum urate levels in the general

Clinical and epidemiological research

ARD 2018

CONCISE REPORT

Relationship between serum urate concentration and clinically evident incident gout: an individual participant data analysis

Nicola Dalbeth,[1] Amanda Phipps-Green,[2] Christopher Frampton,[3] Tuhina Neogi,[4] William J Taylor,[5] Tony R Merriman[2]

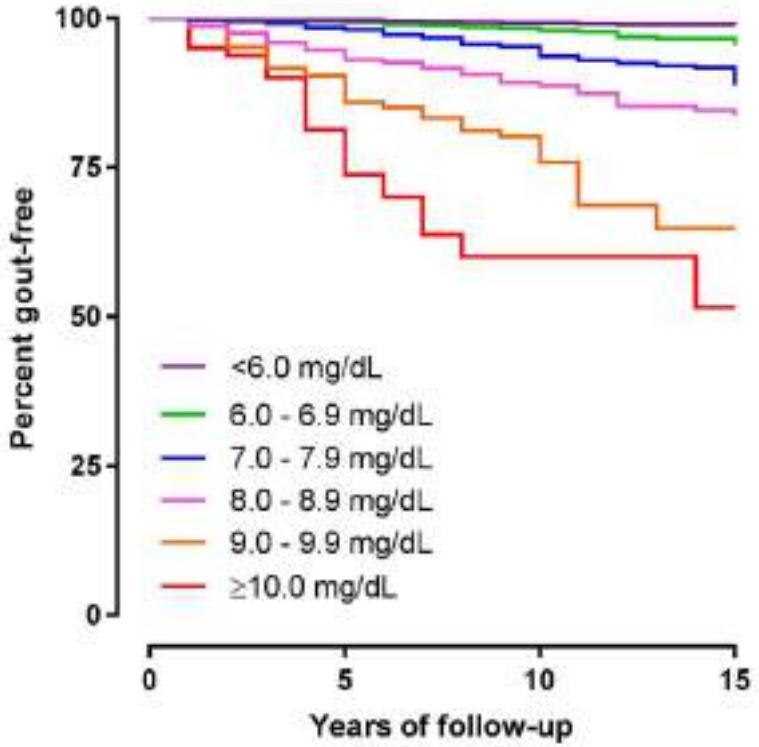
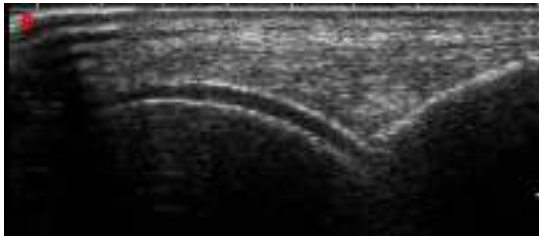


Figure 1 Kaplan-Meier plot showing the percentage of participants who were gout-free over the follow-up period, based on baseline serum urate categories in mg/dL.

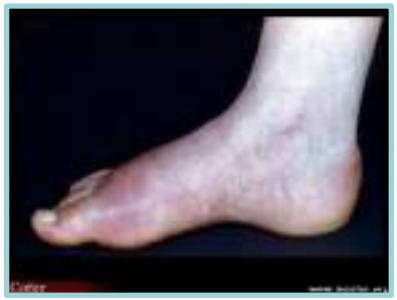
Continuum

Hyperuricémie asymptomatique

Dépots asymptomatiques

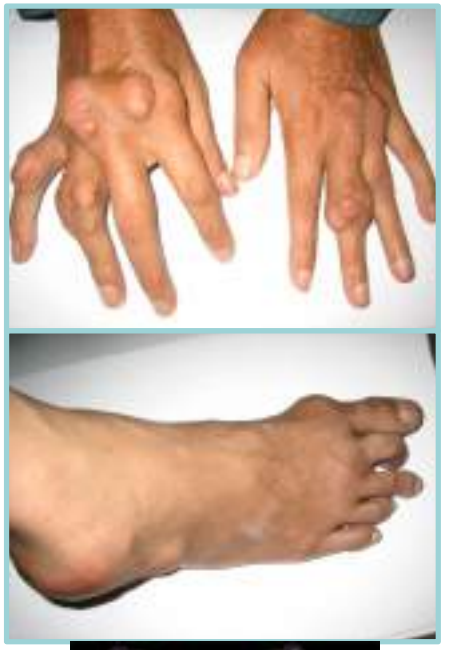


Accès aigu goutteux



IL-1 +++

Goutte sévère

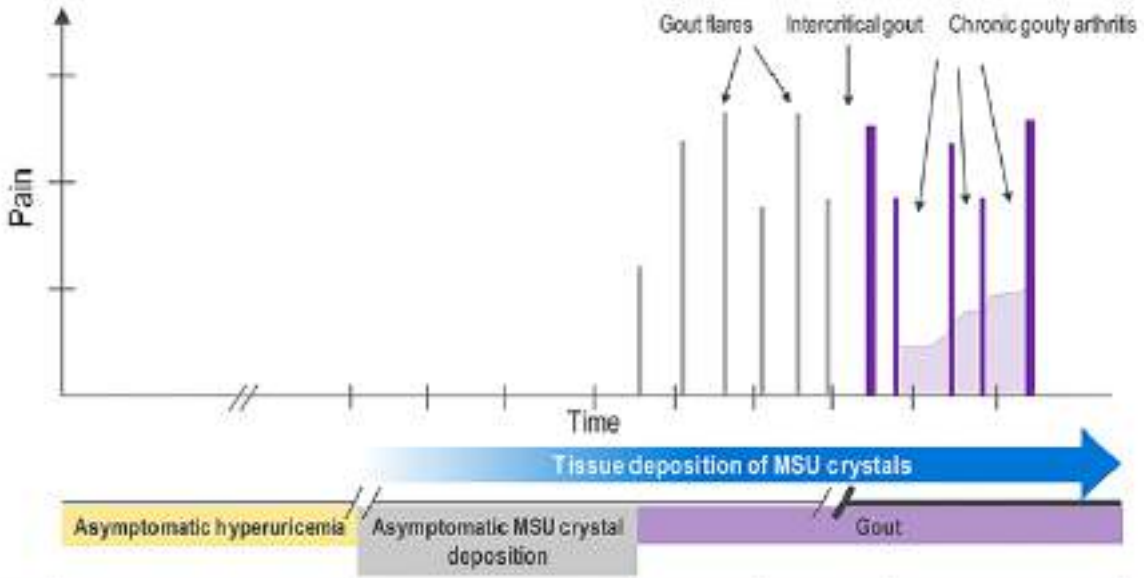


Eular Recommendation for the diagnosis of Gout (2020)

Table 1 Final set of eight recommendations for the diagnosis of gout

	Recommendations	Level of evidence	Grade of recommendation	Level of agreement
1	Search for crystals in synovial fluid or tophus aspirates is recommended in every person with suspected gout, because demonstration of MSU crystals allows a definitive diagnosis of gout.	2b	B	8.6±1.0
2	Gout should be considered in the diagnosis of any acute arthritis in an adult. When synovial fluid analysis is not feasible, a clinical diagnosis of gout is supported by the following suggestive features: monoarticular involvement of a foot (especially the first MTP) or ankle joint; previous similar acute arthritis episodes; rapid onset of severe pain and swelling (at its worst in <24 hours); erythema; male gender and associated cardiovascular diseases and hyperuricaemia. These features are highly suggestive but not specific for gout.	2b	B	8.6±0.8
3	It is strongly recommended that synovial fluid aspiration and examination for crystals is undertaken in any patient with undiagnosed inflammatory arthritis.	3	C	8.8±0.3
4	The diagnosis of gout should not be made on the presence of hyperuricaemia alone.	2a	B	8.9±0.2
5	When a clinical diagnosis of gout is uncertain and crystal identification is not possible, patients should be investigated by imaging to search for MSU crystal deposition and features of any alternative diagnosis.	1b	A	8.5±1.0
6	Plain radiographs are indicated to search for imaging evidence of MSU crystal deposition but have limited value for the diagnosis of gout flare. Ultrasound scanning can be more helpful in establishing a diagnosis in patients with suspected gout flare or chronic gouty arthritis by detection of tophi not evident on clinical examination, or a double contour sign at cartilage surfaces, which is highly specific for urate deposits in joints.	1b	A	8.2±0.9
7	Risk factors for chronic hyperuricaemia should be searched for in every person with gout, specifically: chronic kidney disease; overweight, medications (including diuretics, low-dose aspirin, cyclosporine, tacrolimus); consumption of excess alcohol (particularly beer and spirits), non-diet sodas, meat and shellfish.	1a	A	8.2±1.3
8	Systematic assessment for the presence of associated comorbidities in people with gout is recommended, including obesity, renal impairment, hypertension, ischaemic heart disease, heart failure, diabetes and dyslipidaemia.	1a	A	8.7±0.6

MSU, monosodium urate; MTP, metatarsophalangeal.

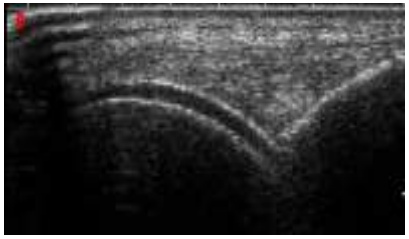


Diagnostic Tools	No MSU Crystal	MSU crystal deposition without symptoms of gout	Gout flares	Intercritical gout	Chronic gouty arthritis
Step 1: Search for MSU crystal*	-	+	+	+	+
Step 2: Clinical diagnosis**	-	-	+	+	+
Step 3: Imaging***	-	+	+	+	+

When a clinical diagnosis of gout is uncertain and crystal identification is not possible, patients should be investigated by imaging to search for MSU crystal deposition and features of any alternative diagnosis.

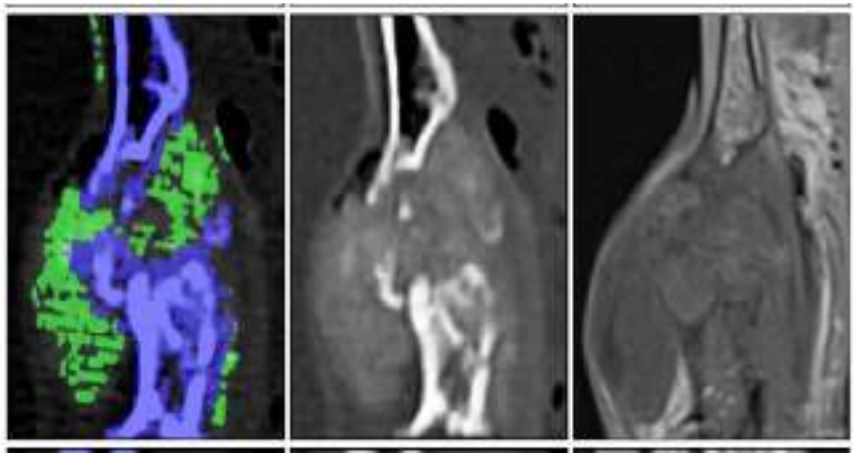
For patients with atypical clinical features and in whom crystal identification is not feasible, the task force recommends the use of conventional and/or advanced imaging techniques to help the physician diagnose gout.

UltraSound DECT Conventional CT MRI



The DC sign

overall US offers the best potential for diagnosing gout



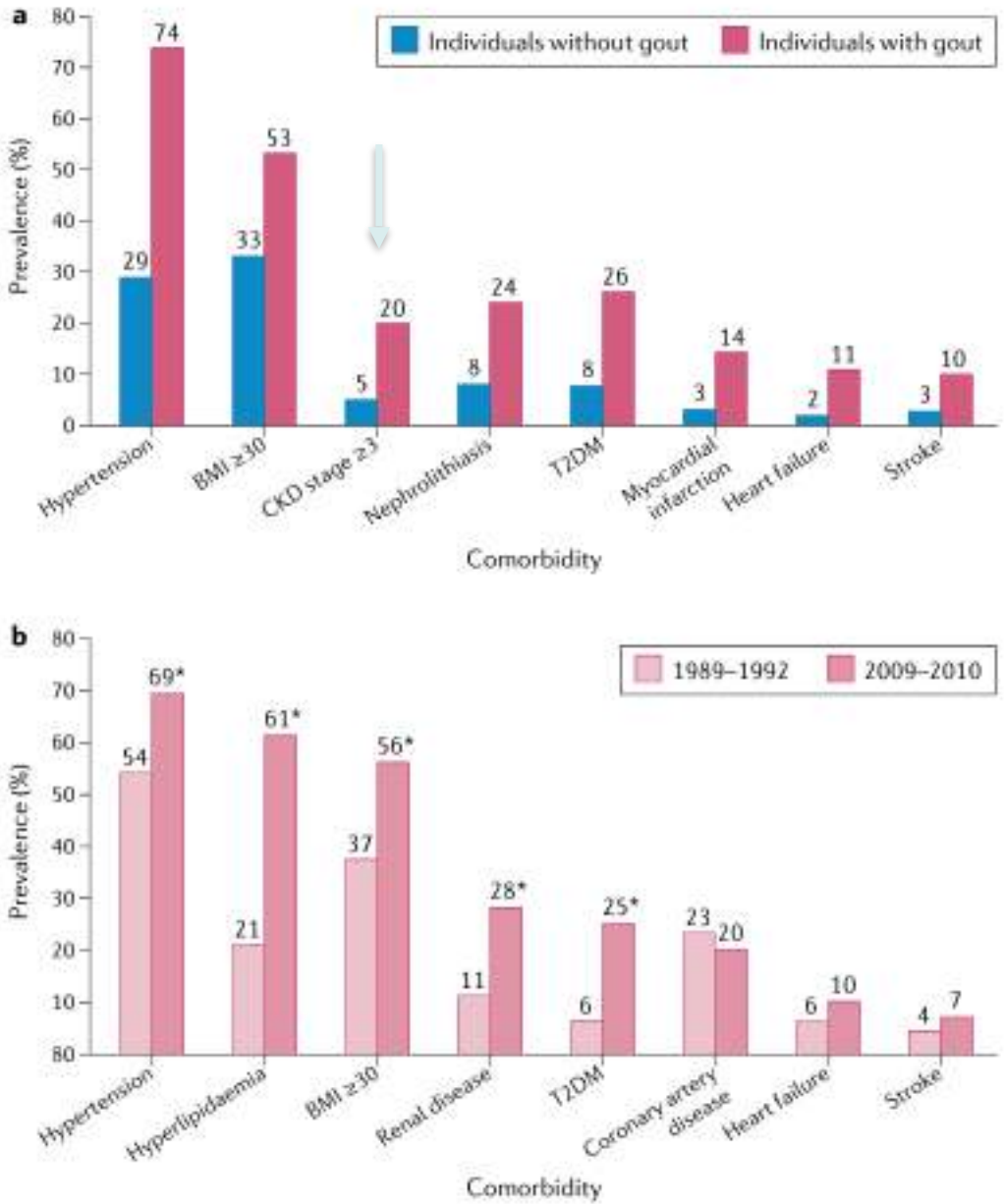
Chhana et al; ARD 2018

All can detect urate deposition, tophi and bone erosion

Excess comorbidities in gout: the causal paradigm and pleiotropic approaches to care

Hyon K. Choi[1,2,3,4]✉, Natalie McCormick[1,2,3,4] and Chio Yokose[1,2,3]

Nature Review Rheumatology
2022



Clinical and epidemiological research

OPEN ACCESS

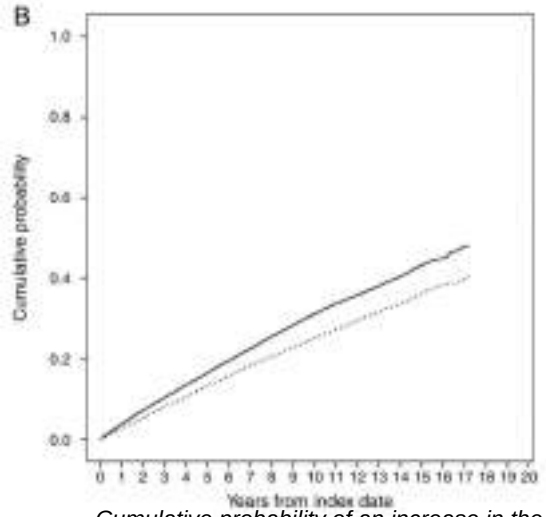
EXTENDED REPORT

Comorbidities in patients with gout prior to and following diagnosis: case-control study

Chang-Fu Kuo,[1,2] Matthew J Grainge,[3] Christian Mallen,[4] Weiya Zhang,[1] Michael Doherty[1]

There were 39 111 patients with incident gout and 39 111 matched controls identified from the UK Clinical Practice Research Data-link.

The risk of developing new comorbidity is higher in patients with incident gout than in the general population



Cumulative probability of an increase in the score of Charlson index in patients with incident gout (solid line) and matched controls (dotted line).

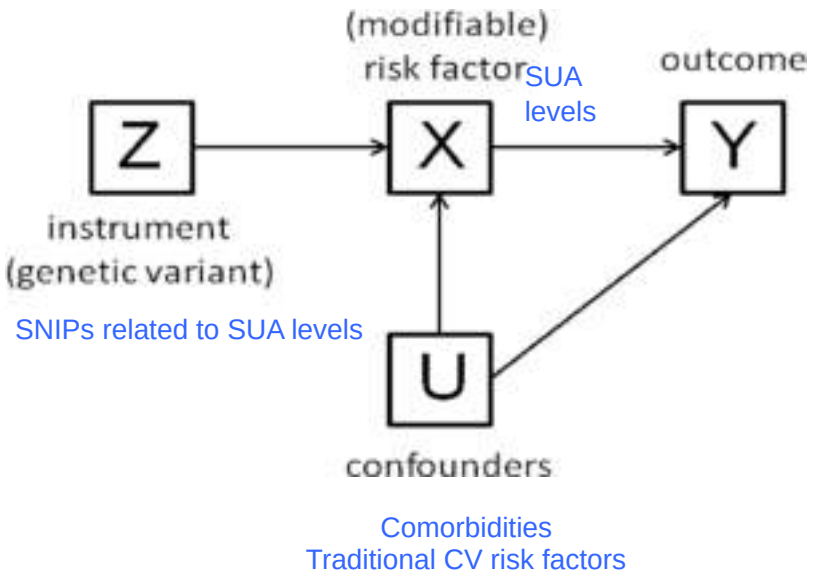
Table 2 Cumulative probability of comorbidity after diagnosis of gout

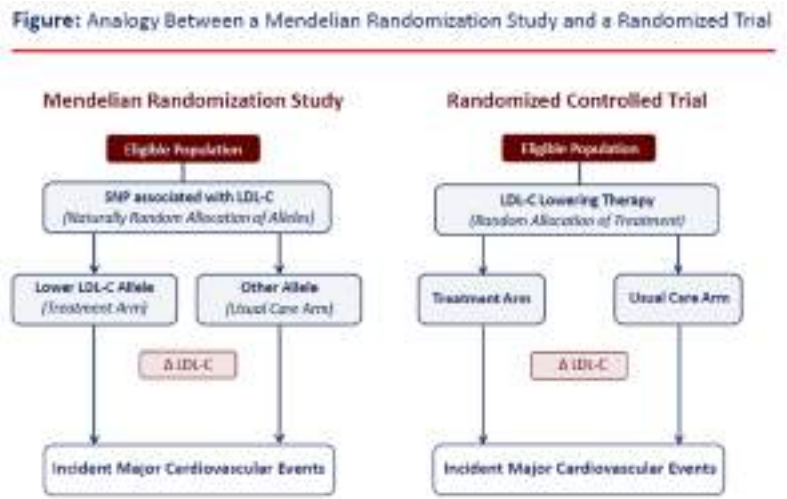
	Patients with incident gout					Controls					
	At diagnosis	1 year	2 years	5 years	10 years	At diagnosis	1 year	2 years	5 years	10 years	p Value
Charlson index ≥1	38.25	42.08	45.39	53.89	66.27	27.91	30.78	33.32	40.81	51.54	<0.001
Any increase in Charlson index	0	3.88	7.30	18.80	31.78	0	3.80	6.95	14.54	23.24	<0.001
Neoplasms											
Solid malignancy, leukaemia and lymphoma	5.35	6.47	7.70	11.84	19.44	4.48	5.54	6.56	10.27	16.76	<0.001
Metastatic solid tumours	0.14	0.28	0.51	1.65	2.88	0.16	0.33	0.49	0.97	1.88	0.266
Cardiovascular diseases											
Hypertension	34.81	38.46	41.58	49.62	58.64	18.70	21.28	23.85	33.50	39.19	<0.001
Cardiac arrhythmias	8.80	9.93	11.00	14.81	19.10	3.72	4.30	5.01	6.95	10.64	<0.001
Cerebrovascular disease	5.99	7.02	7.95	10.46	14.48	4.13	4.92	5.57	7.65	10.74	<0.001
Congestive heart failure	8.54	9.48	10.30	12.84	14.59	2.35	2.82	3.26	4.37	6.83	<0.001
Myocardial infarction	5.47	6.12	6.83	8.15	10.54	2.78	3.23	3.57	4.86	6.87	<0.001
Peripheral vascular disease	3.85	4.43	4.83	6.23	8.35	2.38	2.85	3.02	3.82	5.49	<0.001
Valvular heart disease	2.27	2.68	2.86	3.84	5.71	0.96	1.12	1.29	1.76	2.87	<0.001
Cerebrovascular diseases											
Urolithiasis	0.94	1.05	1.14	1.42	1.99	0.66	0.73	0.82	1.07	1.42	<0.001
Renal disease	3.85	4.28	5.30	8.59	12.51	0.54	0.76	1.07	2.22	4.84	<0.001

This suggests that gout increases the risk of developing comorbidities

Mendelian randomization studies

To reduce effects of potential confounders





To test the hypothesis that SUA levels are causally associated with comorbidities

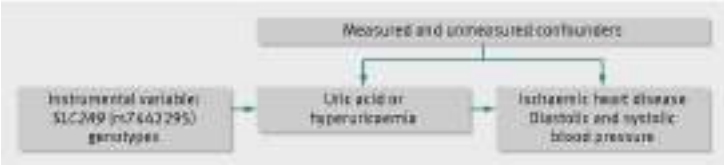
BMJ

RESEARCH

Data were collected from two large prospective cohort studies in Denmark (n=58 072 and 10 602 eligible participants, respectively)

Association of plasma uric acid with ischaemic heart disease and blood pressure: mendelian randomisation analysis of two large cohorts

OPEN ACCESS



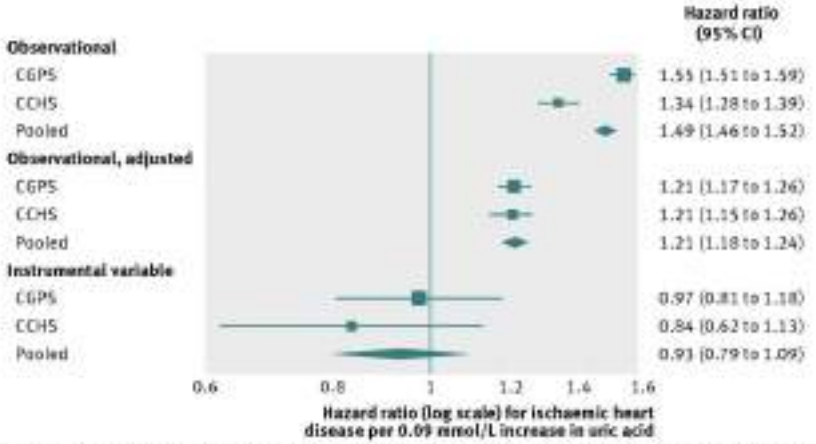


Fig 2 Forest plot showing observational and instrumental variable estimates of the effect of standardised urate on ischaemic heart disease. Observational adjusted estimates adjusted for age, sex, smoking, education, and income. CGPS=Copenhagen General Population Study; CCHS=Copenhagen City Heart Study; 0.09 mmol/L change in uric acid represents one standard deviation

Mendelian randomisation estimates found no evidence of causal effects of either uric acid or hyperuricaemia on risk of either ischaemic heart disease or raised blood pressure.

Excess comorbidities in gout: the causal paradigm and pleiotropic approaches to care

Hyon K. Choi[1,2,3,4]✉, Natalie McCormick[1,2,3,4] and Chio Yokose[1,2,3]

Nature Rheum, 2021

Pas de causalité entre uricémie et IR

Causalité « reverse » entre uricémie et CV

Table 1 | **Mendelian randomization studies assessing causal relationships between serum urate and CMR outcomes**

Outcome or exposure[a]	Significant studies (n)/total studies (n)[b]	Key studies		Refs
		Genetic instrument	Effect estimate or change in serum urate concentration[c]	
Serum urate as exposure				
Coronary artery disease	2(+)/13	7 non-pleiotropic variants[37]	OR 1.04; 95% CI 0.97–1.11; $P = 0.29$	[illegible]
Chronic kidney disease	1(−)/5	22 variants (outliers excluded)[38]	OR 0.99; 95% CI 0.91–1.07; $P = 0.74$	[illegible]
Glycaemic traits (fasting glucose, HbA_{1c})	0/4	16 non-pleiotropic variants[39]	FG: $\beta = 0.000$; 95% CI −0.021–0.021; $P > 0.99$	[illegible]
		17 non-pleiotropic variants[39]	HbA_{1c}: $\beta = 0.002$; 95% CI −0.012–0.016; $P = 0.79$	
Type 2 diabetes mellitus	0/6	14 non-pleiotropic variants[39]	OR 0.95; 95% CI 0.86–1.05; $P = 0.28$	[illegible]
Lipids	1(+)/7	*SLC2A9* variant[47]	TG: $\beta = 0.000$; 95% CI −0.001–0.001; $P = 0.99$	[illegible]
			HDL: $\beta = -0.011$; 95% CI −0.011–0.009; $P = 0.72$	
Insulin resistance or metabolic syndrome	0/7	29 variants (outliers excluded)[48]	FI: $\beta = 0.026$; 95% CI −0.011–0.062; $P = 0.17$	[illegible]
		SLC2A9 variant[48]	FI: $\beta = -0.005$; 95% CI −0.021–0.010; $P = 0.49$	
Adiposity	0/5	*SLC2A9* variant[49]	BMI: $\beta = -0.04$; 95% CI −0.25–0.16	[illegible]
Blood pressure or hypertension	5(4+; 1−)/12	*SLC2A9* variant[50]	SBP: $\beta = 0.061$; −0.053–0.597; $P = 0.10$	[illegible]
			DBP: $\beta = 0.092$; 95% CI −0.110–0.294; $P = 0.37$	
Ischaemic stroke	1/5	14 non-pleiotropic variants[50]	OR 0.99; 95% CI 0.88–1.12; $P = 0.93$	[illegible]
Serum urate as outcome				
Lipids	2/2	49 variants[51]	TG: 0.10; 95% CI 0.06–0.14; $P < 0.001$	[illegible]
		87 variants[51]	HDL: −0.09; 95% CI −0.012–0.05; $P < 0.001$	
Insulin resistance or metabolic syndrome	2/2	71 variants (outliers excluded)[48]	FI: 0.56; 95% CI 0.45–0.67; $P < 0.001$ per s.d.	[illegible]
Adiposity	4/4	3 variants: mapped to *FTO*, *MC4R*, *TMEM18* (REF.[7])	BMI: 0.51; 95% CI 0.34–0.67; per s.d.	[illegible]

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 25, 2020 VOL. 382 NO. 26

Serum Urate Lowering with Allopurinol and Kidney Function in Type 1 Diabetes

A. Dara, A.T. Gaweda, C. Spino, R. Pop-Busui, D.Z. Cherney, I. Lingvay, A. Parsa, P. Rossing, B.J. Sigal, M. Alkhalaf, R. Bannister, M.L. Carabenciov, J.P. Crandall, I.H. de Boer, T.G. Elliott, A.H. Goldfine, J.C. Haw, I.B. Hirsch, A.B. Katzel, G.M. Mauhs, J.B. McGill, M.E. Molitch, B.A. Perkins, S. Reddy, M. Prajapati, W.H. Roberts, S.E. Rosas, P. Sawicki, R.R. Toledo, G.E. Umpierrez, A. Walka, K.S. Weinstock, C. Wu, and M. Mauer, for the PERL Study Group*

ABSTRACT

BACKGROUND

Higher serum urate levels are associated with an increased risk of diabetic kidney disease. Lowering of the serum urate level with allopurinol may slow the decrease in the glomerular filtration rate (GFR) in persons with type 1 diabetes and early-to-moderate diabetic kidney disease.

METHODS

In a double-blind trial, we randomly assigned participants with type 1 diabetes, a serum urate level of at least 4.5 mg per deciliter, an estimated GFR of 40.0 to 99.9 ml per minute per 1.73 m² of body-surface area, and evidence of diabetic kidney disease to receive allopurinol or placebo. The primary outcome was the baseline-adjusted GFR, as measured with iohexol, after 3 years plus a 2-month washout period. Secondary outcomes included the decrease in the iohexol-based GFR per year and the urinary albumin excretion rate after washout. Safety was also assessed.

RESULTS

A total of 267 patients were assigned to receive allopurinol and 268 to receive placebo. The mean age was 51.1 years, the mean duration of diabetes 34.6 years, and the mean glycated hemoglobin level 8.2%. The mean baseline iohexol-based GFR was 68.7 ml per minute per 1.73 m² in the allopurinol group and 67.3 ml per minute per 1.73 m² in the placebo group. During the intervention period, the mean serum urate level decreased from 6.1 to 3.9 mg per deciliter with allopurinol and remained at 6.1 mg per deciliter with placebo. After washout, the between-group difference in the mean iohexol-based GFR was 0.084 ml per minute per 1.73 m² (95% confidence interval [CI], −1.8 to 1.9; P=0.96). The mean decrease in the iohexol-based GFR was −1.8 ml per minute per 1.73 m² per year with allopurinol and −2.5 ml per minute per 1.73 m² per year with placebo (between-group difference, −0.6 ml per minute per 1.73 m² per year; 95% CI, −1.5 to 0.4). The mean urinary albumin excretion rate after washout was 40% (95% CI, 8 to 80) higher with allopurinol than with placebo. The frequency of serious adverse events was similar in the two groups.

CONCLUSIONS

We found no evidence of clinically meaningful benefits of serum urate reduction with allopurinol on kidney outcomes among patients with type 1 diabetes and early-to-moderate diabetic kidney disease. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; PERL ClinicalTrials.gov number, NCT02017171.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Dara at the Section on Genetics and Epidemiology, Joslin Diabetes Center, 1 Joslin Pl., Boston, MA 02215, or at alexandra.dara@joslin.harvard.edu, or to Dr. Mauer at the Division of Pediatric Nephrology, 8th Fl., East Bldg., MB6B, 2450 Riverside Ave., Minneapolis, MN 55454, or at mauer002@umn.edu.

*The full list of the PERL Study Group members is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Dara, Gaweda, Spino, and Mauer contributed equally to this article.

N Engl J Med 2020;382:2099-108.
DOI: 10.1056/NEJMoa1914638

ORIGINAL ARTICLE

Effects of Allopurinol on the Progression of Chronic Kidney Disease

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The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Badve at the Renal and Metabolic Division, the George Institute for Global Health, Level 5, 1 King St., Newtown, NSW 2042, Australia, or at sbadve@georgeinstitute.org.au.

*A complete list of the CKD-FIX Study Investigators is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2020;382:2504-13.
DOI: 10.1056/NEJMoa1915833

ABSTRACT

BACKGROUND

Elevated serum urate levels are associated with progression of chronic kidney disease. Whether urate-lowering treatment with allopurinol can attenuate the decline of the estimated glomerular filtration rate (eGFR) in patients with chronic kidney disease who are at risk for progression is not known.

METHODS

In this randomized, controlled trial, we randomly assigned adults with stage 3 or 4 chronic kidney disease and no history of gout who had a urinary albumin:creatinine ratio of 265 or higher (with albumin measured in milligrams and creatinine in grams) or an eGFR decrease of at least 3.0 ml per minute per 1.73 m² of body-surface area in the preceding year to receive allopurinol (100 to 300 mg daily) or placebo. The primary outcome was the change in eGFR from randomization to week 104, calculated with the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.

RESULTS

Enrollment was stopped because of slow recruitment after 369 of 620 intended patients were randomly assigned to receive allopurinol (185 patients) or placebo (184 patients). Three patients per group withdrew immediately after randomization. The remaining 363 patients (mean eGFR, 31.7 ml per minute per 1.73 m²; median urine albumin:creatinine ratio, 716.9; mean serum urate level, 8.2 mg per deciliter) were included in the assessment of the primary outcome. The change in eGFR did not differ significantly between the allopurinol group and the placebo group (−3.33 ml per minute per 1.73 m² per year [95% confidence interval {CI}, −4.11 to −2.55] and −3.23 ml per minute per 1.73 m² per year [95% CI, −3.98 to −2.47], respectively; mean difference, −0.10 ml per minute per 1.73 m² per year [95% CI, −1.18 to 0.97]; P=0.85). Serious adverse events were reported in 84 of 182 patients (46%) in the allopurinol group and in 79 of 181 patients (44%) in the placebo group.

CONCLUSIONS

In patients with chronic kidney disease and a high risk of progression, urate-lowering treatment with allopurinol did not slow the decline in eGFR as compared with placebo. (Funded by the National Health and Medical Research Council of Australia and the Health Research Council of New Zealand; CKD-FIX Australian New Zealand Clinical Trials Registry number, ACTRN12611000791932.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Allopurinol on the Progression of Chronic Kidney Disease

Patients: CKD 3 et 4

Critère de jugement: Delta eGFR à 2 ans

Allopurinol: Titration 100 mg/mois pendant 3 mois.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Allopurinol (N=182)	Placebo (N=181)	Total (N=363)
Age — yr	62.3±12.6	62.6±12.9	62.4±12.7
Female sex — no. (%)	70 (38)	65 (36)	135 (37)
Race or ethnic group — no. (%)†			
White	143 (79)	129 (71)	272 (75)
Australian Aboriginal or Torres Strait Islander	2 (1)	2 (1)	4 (1)
New Zealand Maori	13 (7)	15 (8)	28 (8)
Asian	8 (4)	11 (6)	19 (5)
Other	16 (9)	24 (13)	40 (11)
Median body-mass index (IQR)‡	30 (26–36)	31 (27–35)	30 (26–36)
Blood pressure — mm Hg§			
Systolic	138.4±18.2	140.2±20.0	139.3±19.1
Diastolic	76.8±11.1	76.5±12.2	76.7±11.6
Primary cause of kidney disease — no. (%)			
Diabetic kidney disease	75 (41)	90 (50)	165 (45)
Nondiabetic kidney disease	107 (59)	91 (50)	198 (55)
Diabetes mellitus — no. (%)	104 (57)	106 (59)	210 (58)
Hypertension — no. (%)	171 (94)	173 (96)	344 (95)
Cardiovascular disease — no. (%)	58 (32)	64 (35)	122 (34)
SF-36 quality-of-life summary score¶	68.8±18.7	68.2±18.8	68.5±18.8
Receiving ACE inhibitor — no. (%)	71 (39)	75 (41)	146 (40)
Receiving ARB — no. (%)	63 (35)	67 (37)	130 (36)
eGFR — ml/min/1.73 m^2	31.6±11.7	31.9±12.4	31.7±12.0
Median urinary albumin:creatinine ratio (IQR)‖	716.9 (237.2–1947)	716.9 (246.0–1857)	716.9 (244.3–1857)
Serum urate — mg/dl**	8.2±1.8	8.2±1.7	8.2±1.8

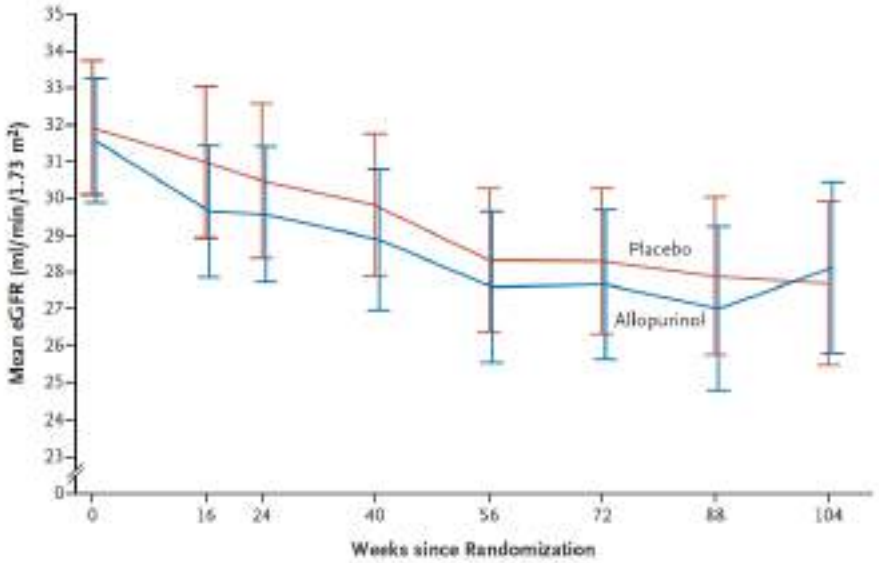


Figure 1. Effect of Allopurinol on Estimated Glomerular Filtration Rate (eGFR).
The effects of allopurinol and placebo on the eGFR are shown. I bars indicate 95% confidence intervals.

Lancet 2022; 400: 1195–205

Allopurinol versus usual care in UK patients with ischaemic heart disease (ALL-HEART): a multicentre, prospective, randomised, open-label, blinded-endpoint trial

Isla S Mackenzie, Christopher J Hawkey, Ian Ford, Nicola Greenlaw, Filippo Pigazzani, Amy Rogers, Allan D Struthers, Alan G Begg, Li Wei, Anthony J Avery, Jaspal S Taggar, Andrew Walker, Suzanne L Duce, Rebecca J Barr, Jennifer S Dumbleton, Evelien D Rooke, Jonathon N Townend, Lewis D Ritchie, Thomas M MacDonald, on behalf of the ALL-HEART Study Group*

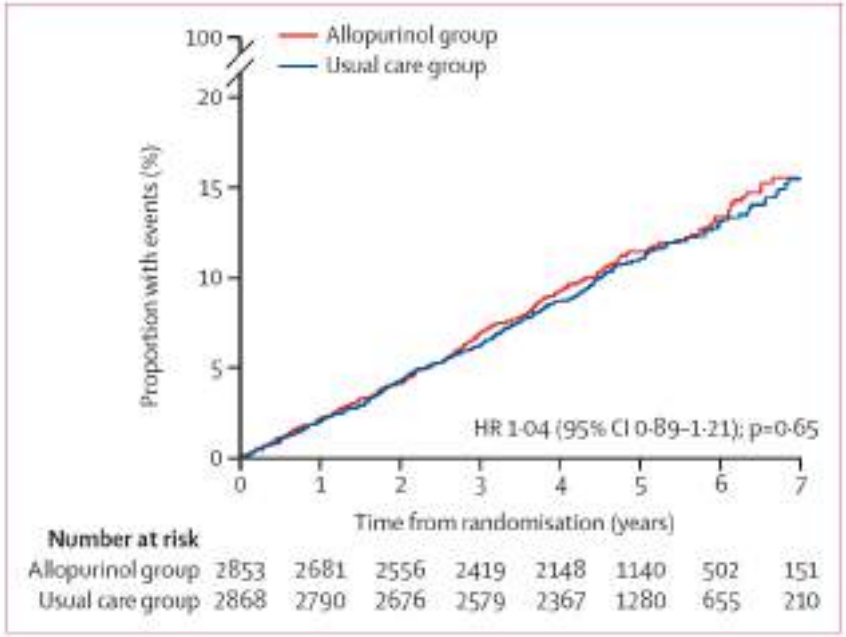
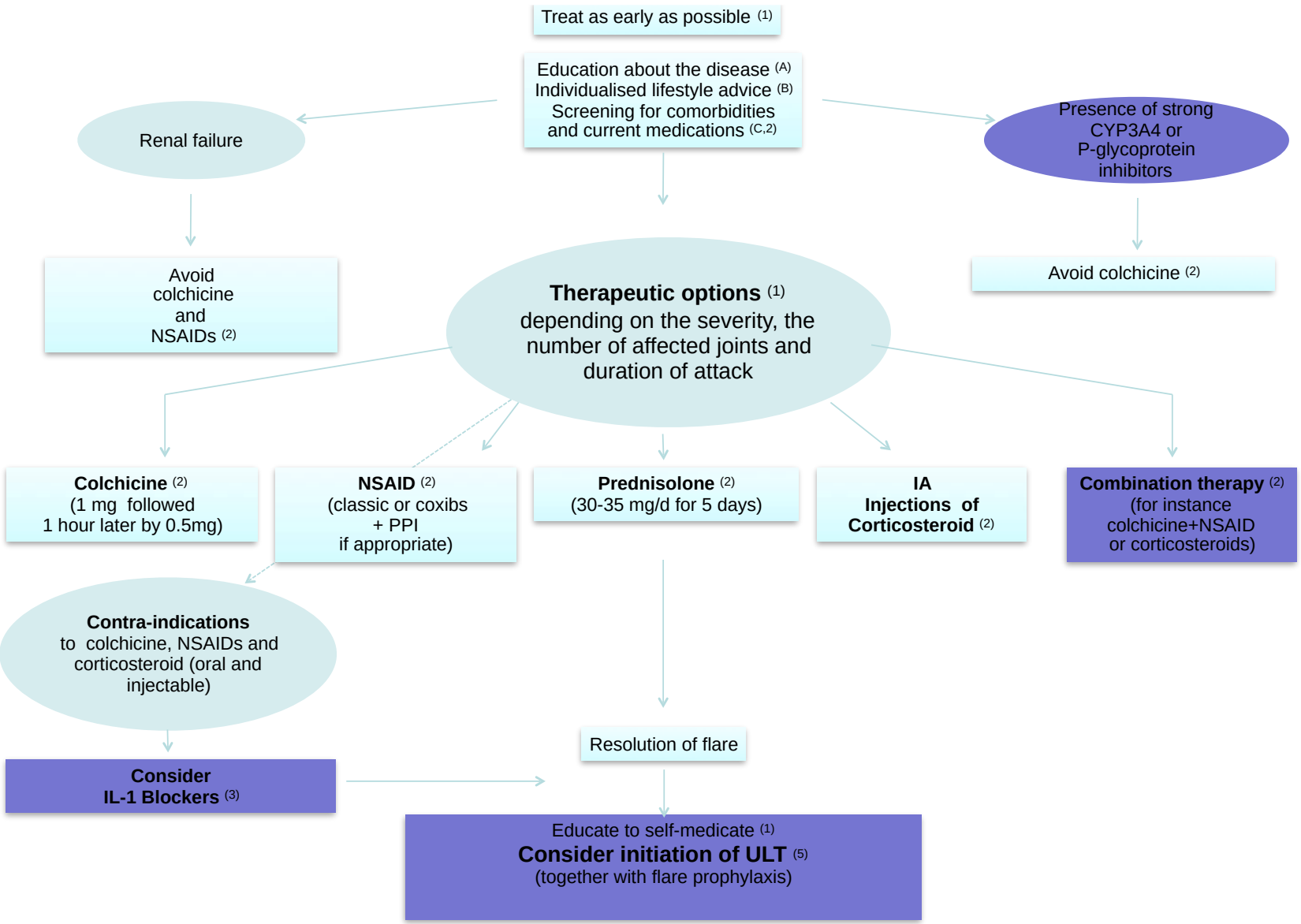


Figure 2: **Cumulative incidence functions for the primary composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death analysed in the modified intention-to-treat population**
The figure was adjusted for the competing risk of deaths not included in the endpoint. HR=hazard ratio.

EULAR RECOMMENDATION FOR THE MANAGEMENT OF FLARES IN PATIENTS WITH GOUT



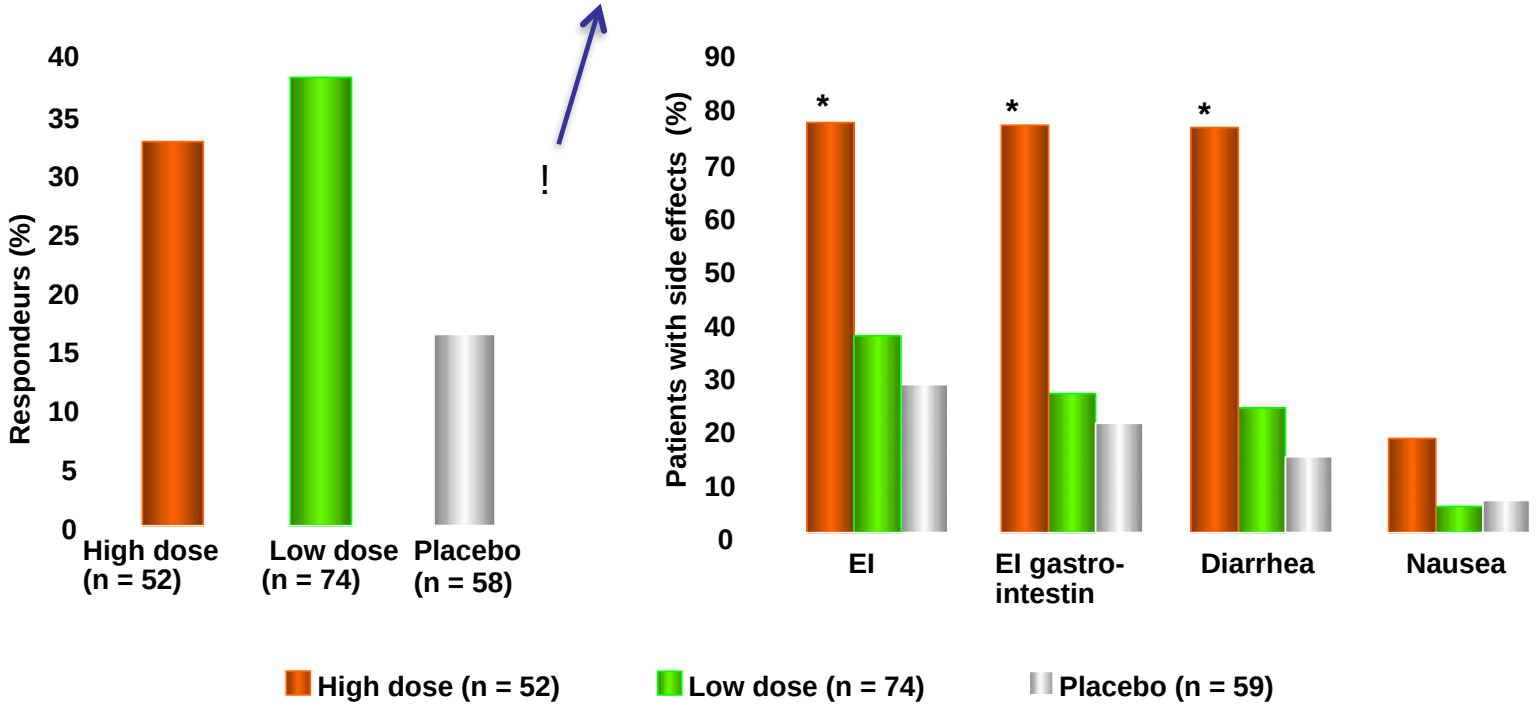
High Versus Low Dosing of Oral Colchicine for Early Acute Gout Flare

Twenty-Four–Hour Outcome of the First Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Comparison Colchicine Study

Une faible dose est efficace

RCT comparing 2 dosages given early (<12h), versus placebo. N= 180 patients
1.8 mg/d (1.2 + 0.6 1h after) is as efficient and better tolerated than 4.8 mg/d (1.2 + 0.6/h x 6)

Response to treatment: pain<50% **at 24h**



Terkeltaub et al Arthritis Rheum 2010

Colchicine: tolérance très variable d'un individu à l'autre

- Excrétion rénale: 20% de la clairance totale
- Pas éliminée par la dialyse

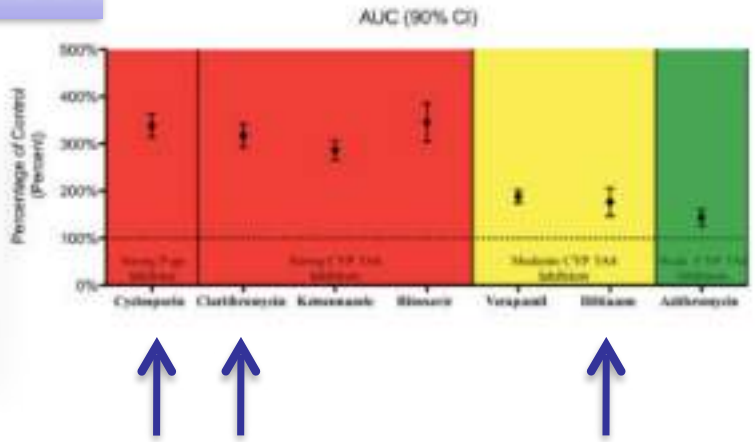
Novel Evidence-Based Colchicine Dose-Reduction Algorithm to Predict and Prevent Colchicine Toxicity in the Presence of Cytochrome P450 3A4/P-Glycoprotein Inhibitors

Robert A. Terkeltaub,[1] Daniel E. Furst,[2] Jennifer L. DiGiacinto,[3] Karin A. Kook,[3] and Matthew W. Davis[4]

AR 2011

3 facteurs de risque d'intolérance

1. ***Interactions médica.***
2. ***Insufficance hépatique***
3. ***Insufficance rénale***



➢ Cyclosporin
➢ Clarithromycin
➢ Diltiazem

Diminution de la posologie
Alternatives

OPEN ACCESS

CLINICAL SCIENCE

Open-label randomised pragmatic trial (CONTACT) comparing naproxen and low-dose colchicine for the treatment of gout flares in primary care

Edward Roddy ,[1,2] Kris Clarkson,[1,3] Milica Blagojevic-Bucknall ,[1,3] Rajnikant Mehta,[4] Raymond Oppong,[5] Anthony Avery,[6] Elaine M Hay,[1] Carl Heneghan,[7] Liz Hartshorne,[1,3] Julie Hooper,[8] Gemma Hughes,[1,3] Sue Jowett,[1,5] Martyn Lewis,[1,3] Paul Little,[8] Karen McCartney,[6] Kamal R Mahtani,[7] David Nunan,[7] Miriam Santer,[8] Sam Williams,[8] Christian D Mallen[1]

ARD 2020

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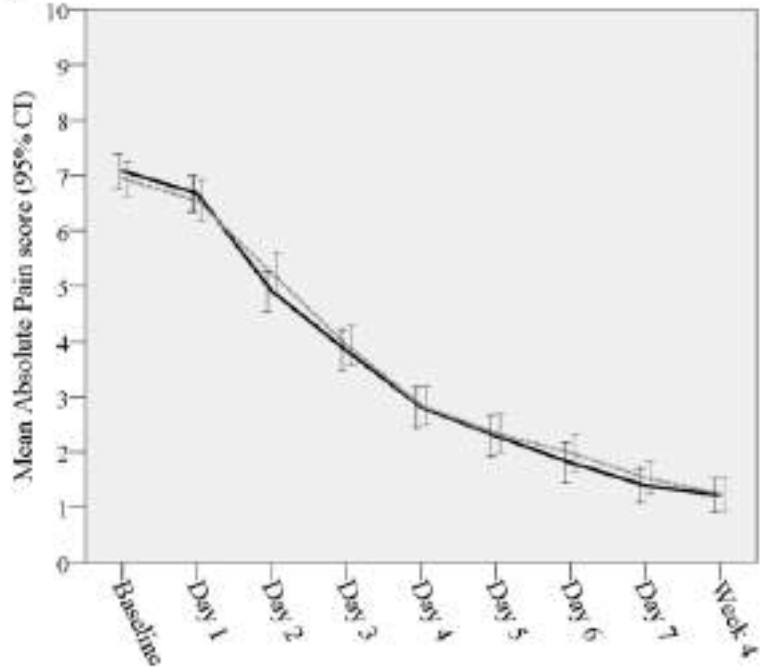

	Days 1–7		
	Naproxen	Colchicine	OR (95% CI) (p value)
	N (%)†	N (%)†	Complete case†
Nausea and/or vomiting	21 (14.0)	30 (20.5)	1.82 (0.96 to 3.46) (p=0.066)
Dyspepsia	20 (13.3)	20 (13.7)	0.89 (0.48 to 1.90) (p=0.95)
Abdominal pain	16 (10.7)	16 (11.0)	1.07 (0.51 to 2.25) (p=0.86)
Headache	16 (10.7)	30 (20.5)	2.38 (1.21 to 4.68) (p=0.012)
Constipation	29 (19.3)	7 (4.8)	0.20 (0.08 to 0.48) (p<0.001)
Diarrhoea	30 (20.0)	67 (45.9)	3.54 (2.10 to 5.99) (p<0.001)
Skin rash	3 (2.0)	3 (2.1)	1.13 (0.22 to 5.83) (p=0.88)
Any side effect(s)§	91 (60.7)	101 (69.2)	1.49¶ (0.92 to 2.43) (p=0.11)¶