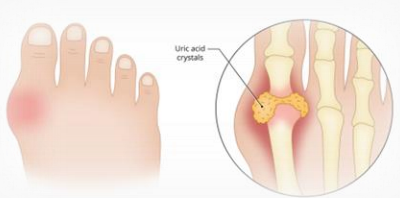
Νεφρός και ουρική νόσος



Χρήστος Πλέρος
Νεφρολόγος
Πανεπιστημιακό Γενικό Νοσοκομείο Ηρακλείου

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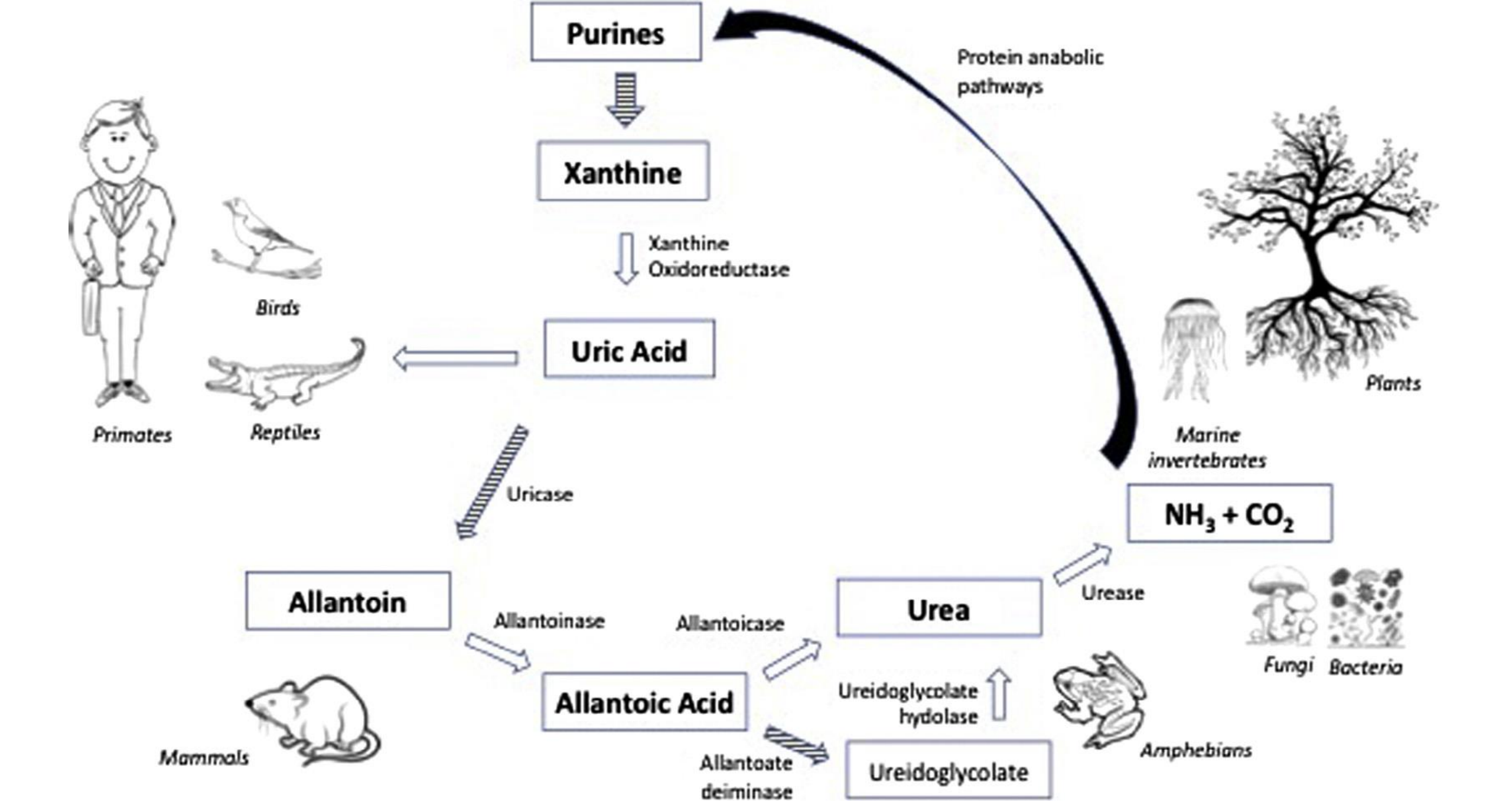
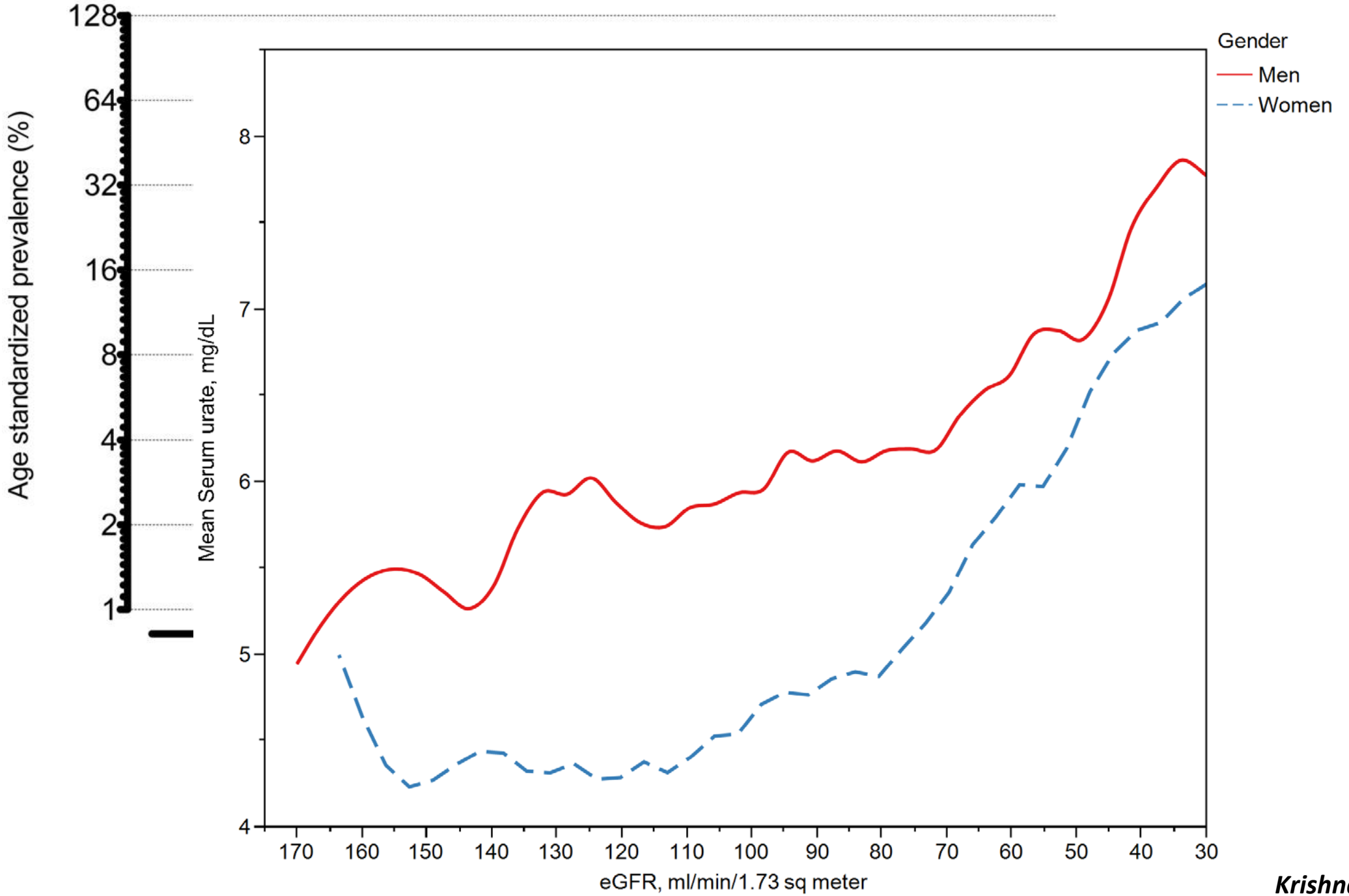


Barsoum & Khatib. J Adv Res 2017

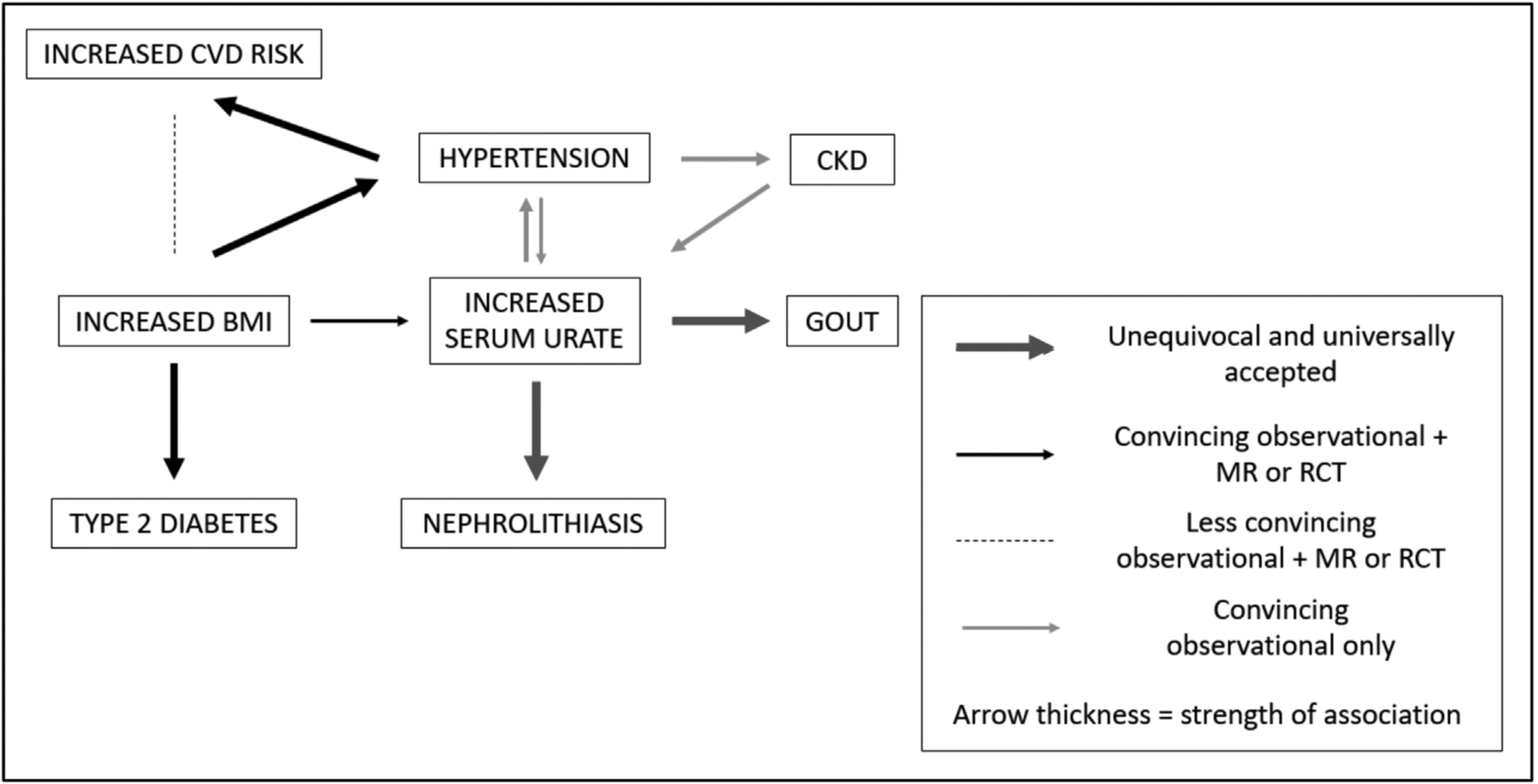
Table 1. Prevalence (%) of gout comorbidities in gout vs. nongout and hyperuricemia vs. nonhyperuricemia individuals

Comorbidity	Gout	Nongout	OR [95% CI]	Hyperuricemia	Nonhyperuricemia	OR [95% CI]
Hypertension	73.9%	28.9%	4.19 [2.75, 6.39]	49.7%	25.5%	2.60 [2.15, 3.14]
CKD ≥ stage 2	71.1%	42.1%	1.75 [1.23, 2.49]	61.4%	38.2%	2.33 [1.94, 2.80]
Obesity	53.3%	32.8%	2.35 [1.55, 3.57]	54.4%	27.6%	3.12 [2.43, 4.01]
Diabetes	25.7%	7.8%	2.36 [1.49, 3.73]	13.5%	7.1%	1.63 [1.13, 2.34]
Nephrolithiasis	23.8%	8.4%	2.10 [1.39, 3.18]	12.3%	8.3%	1.40 [1.07, 1.83]
CKD ≥ Stage 3	19.9%	5.2%	2.32 [1.65, 3.26]	14.8%	3.3%	3.96 [2.63, 5.97]
MI	14.4%	2.9%	2.37 [1.54, 3.65]	5.1%	2.8%	1.45 [1.12, 1.88]
Heart failure	11.2%	2.0%	2.68 [1.88, 3.83]	5.1%	1.6%	2.52 [1.58, 4.04]
Stroke	10.4%	2.9%	2.02 [0.98, 4.19]	5.7%	2.4%	1.74 [1.16, 2.59]

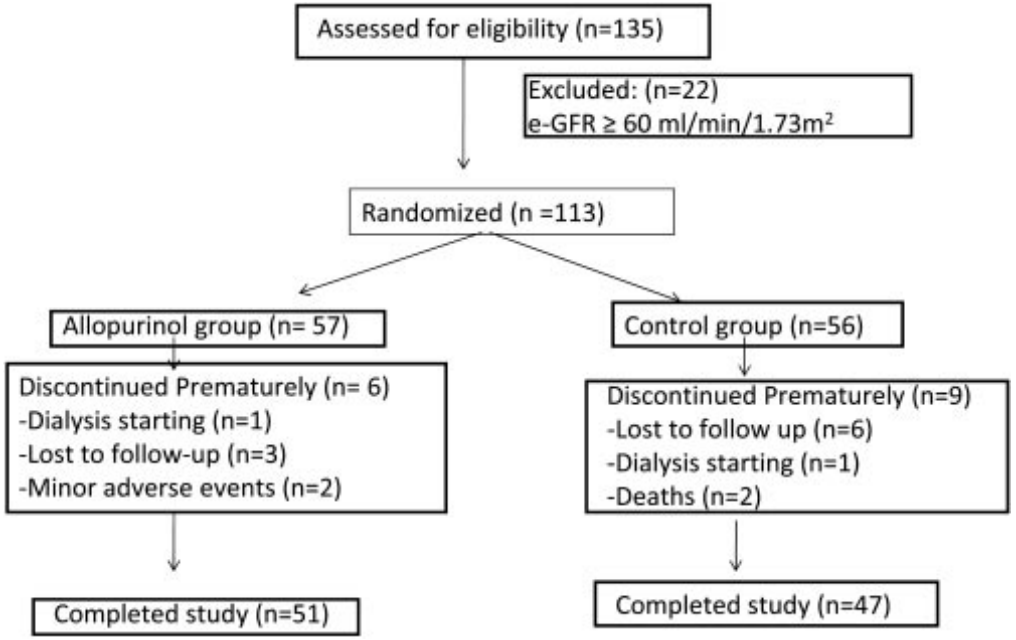
Zhu et al. Am J Med 2012

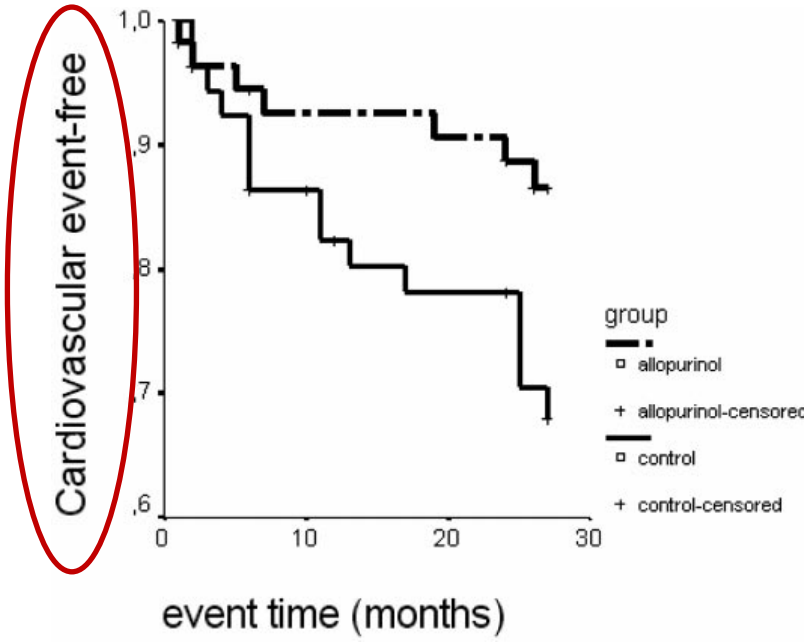


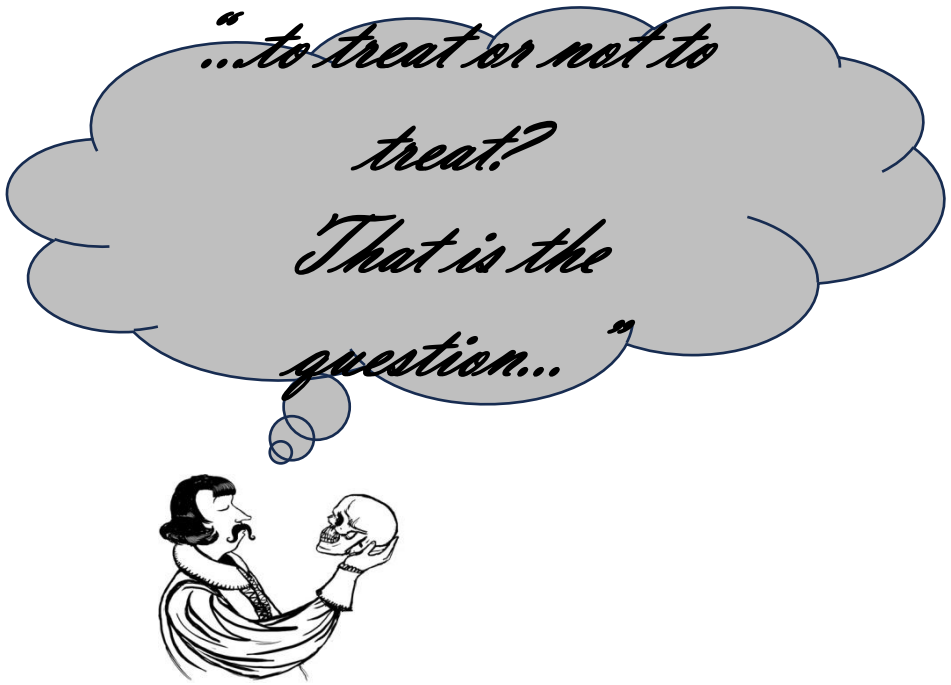
Krishnan E. PLoS One 2012

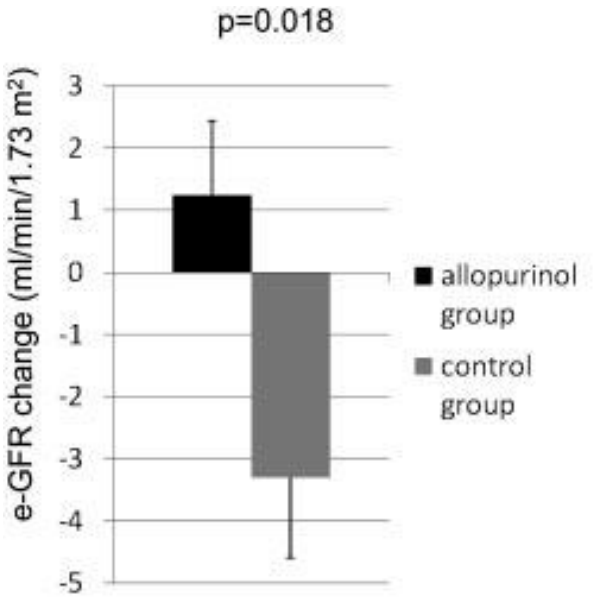


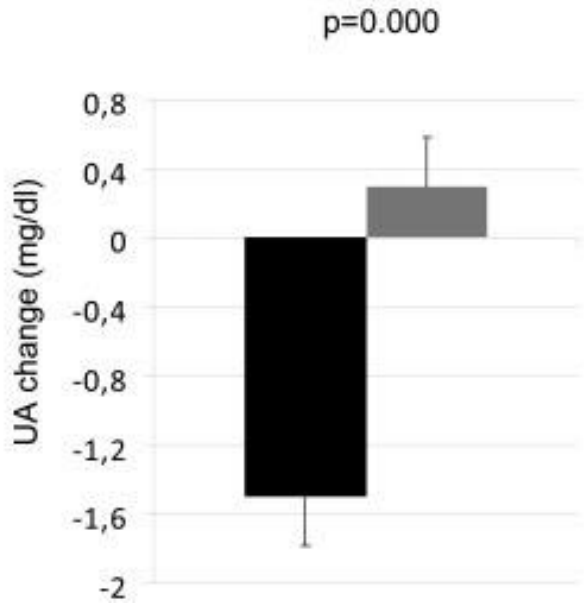
Sumpter et al. Curr Opin Rheumatol 2019











Goicoechea et al. Clin J Am Soc Nephrol 2010

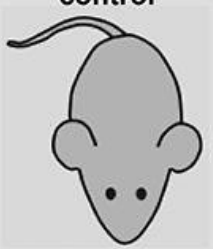
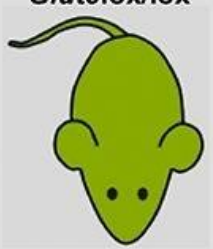
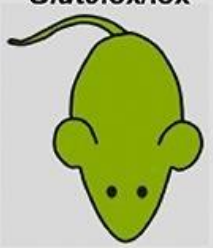
Only hyperuricemia with crystalluria but not asymptomatic hyperuricemia drives progression of chronic kidney disease

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

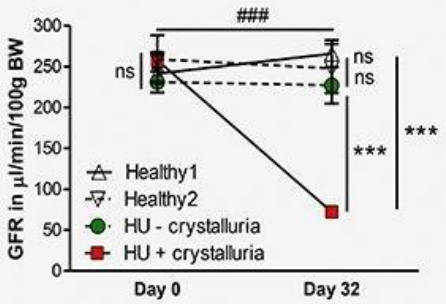
Methods

Mouse models:
- Aristolochic acid I-induced nephropathy
- Asymptomatic hyperuricemia without crystalluria
- Chronic uric acid crystal nephropathy with granulomatous nephritis

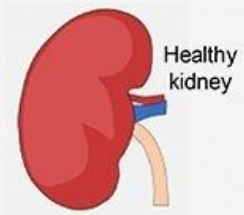
Serum uric acid

5.3±0.5 mg/dl	15.6±3.2 mg/dl	16.0±2.5 mg/dl
***Glut9*lox/lox control**	**Alb-creERT2; *Glut9*lox/lox**	**Alb-creERT2; *Glut9*lox/lox**
		
Urinary pH 6.9	Urinary pH 6.8	Urinary pH 5.2

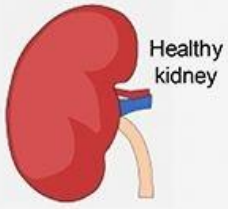
Results



Healthy



Asympt. hyperuricemia without crystalluria



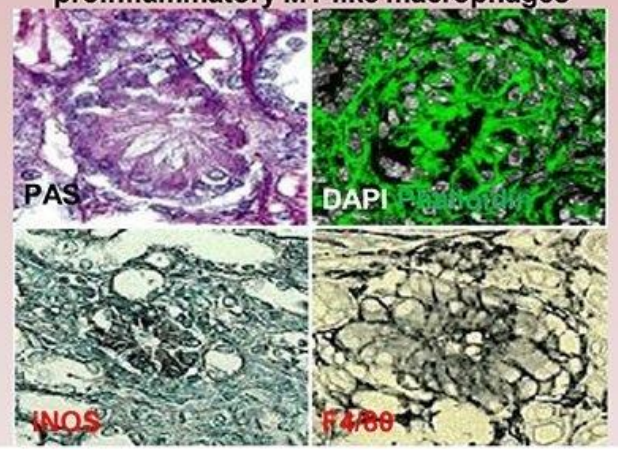
Hyperuricemia with crystalluria-induced CKD + granuloma formation

No impact of hyperuricemia (sUA 16 mg/dl) on pre-existing aristolochic acid I-induced nephropathy.

Conclusion

Asymptomatic hyperuricemia does not affect CKD progression unless uric acid crystallizes in the kidney, leading to tubular obstruction, inflammation, and interstitial fibrosis. Subsequently, uric acid crystal granulomas form, a process mediated by proinflammatory M1-like macrophages, and contribute to CKD progression.

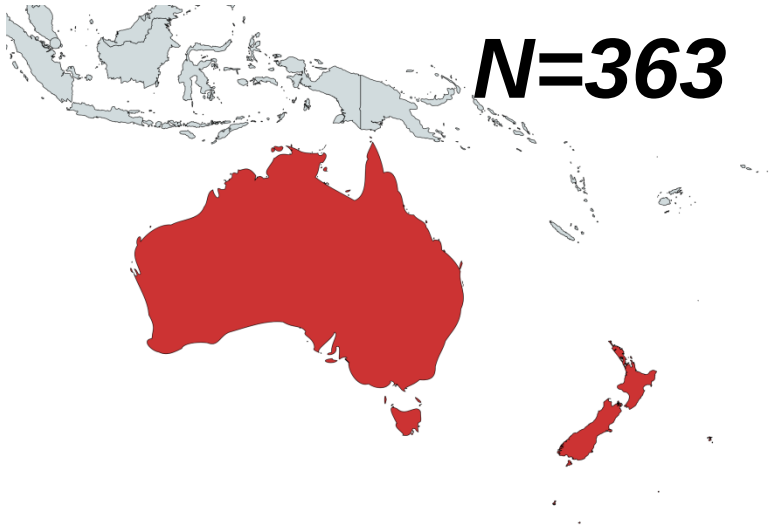
Uric acid crystal granulomas consist of proinflammatory M1-like macrophages



Sellmayr et al. 2020

The CKD-FIX trial

AKTN 10.02



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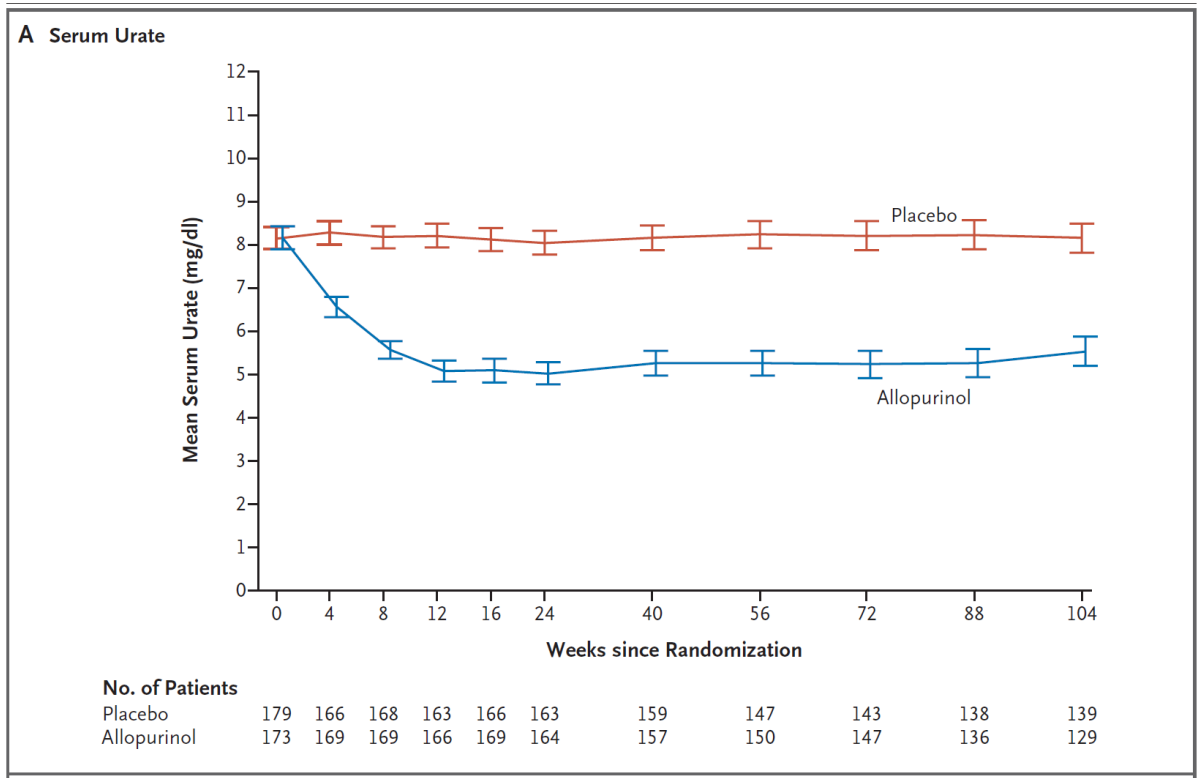
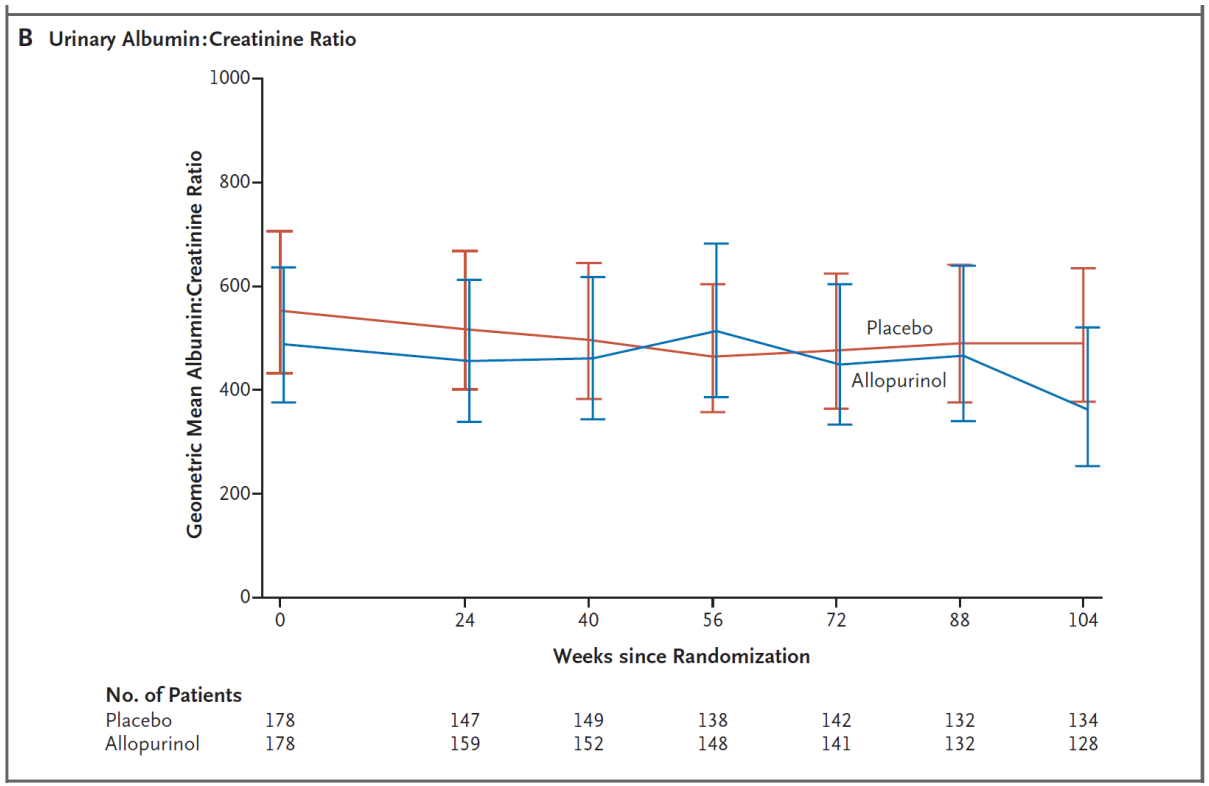
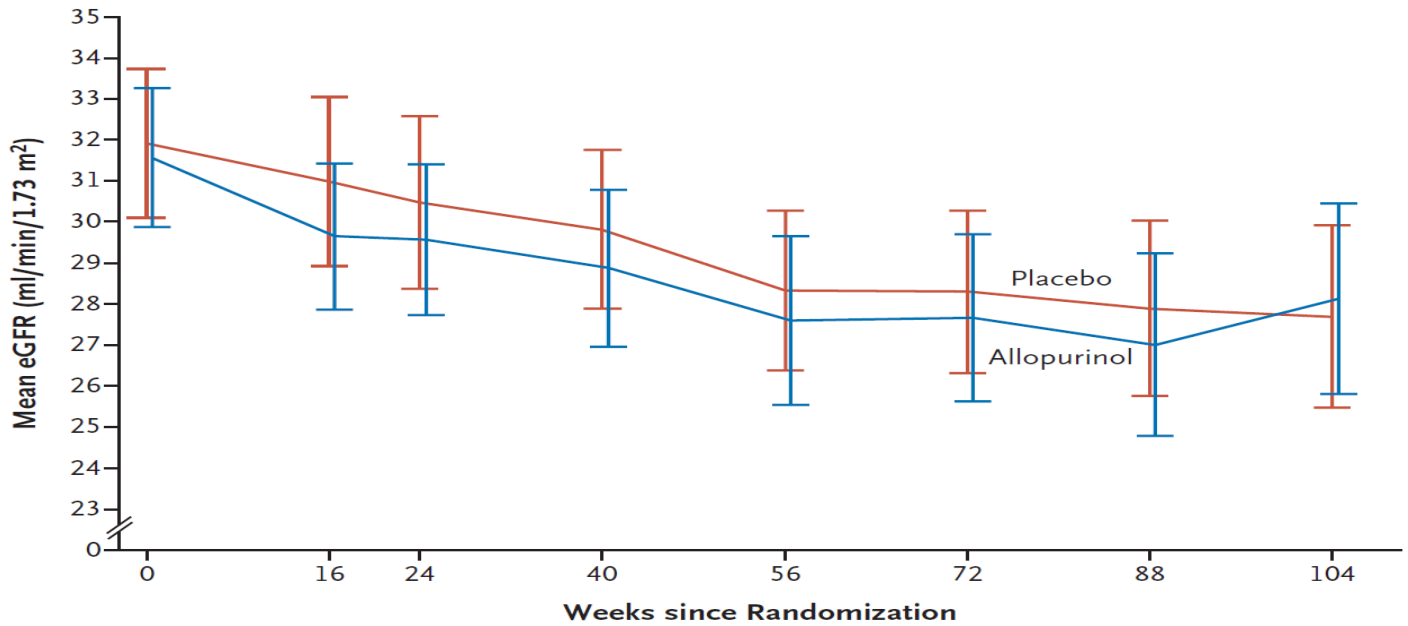




Badve et al. N Eng J Med 2020

The CKD-FIX AKTN 10.02 trial



No. of Patients							
Placebo	181	174	168	164	156	157	149	148
Allopurinol	182	172	170	165	164	152	144	133

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.

Badve et al. N Eng J Med 2020

CARI GUIDELINES

CARING FOR AUSTRALIANS & NEW ZEALANDERS WITH KIDNEY IMPAIRMENT

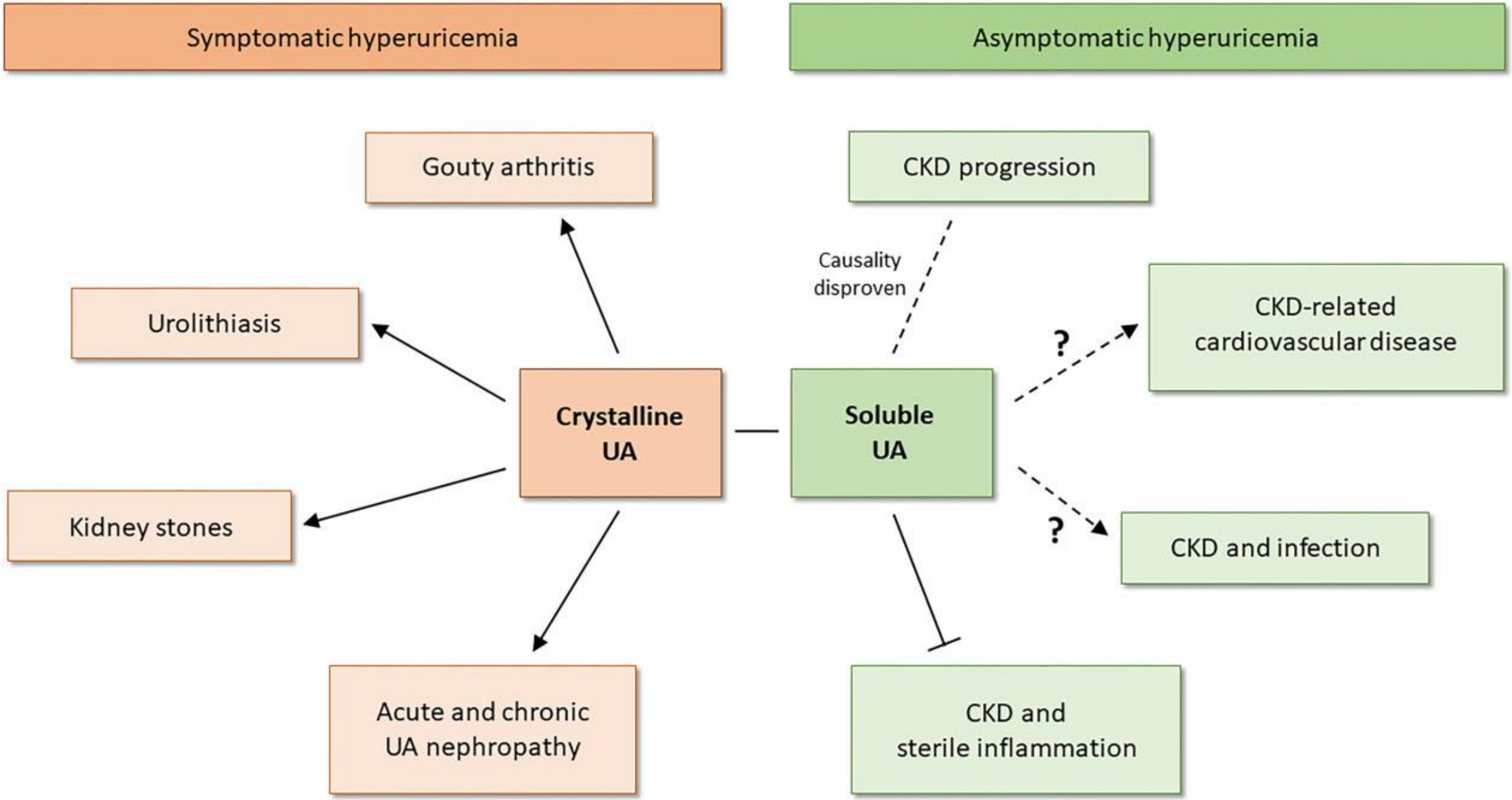
Clinical Question/ PICO

Population: Urate lowering-therapy for CKD

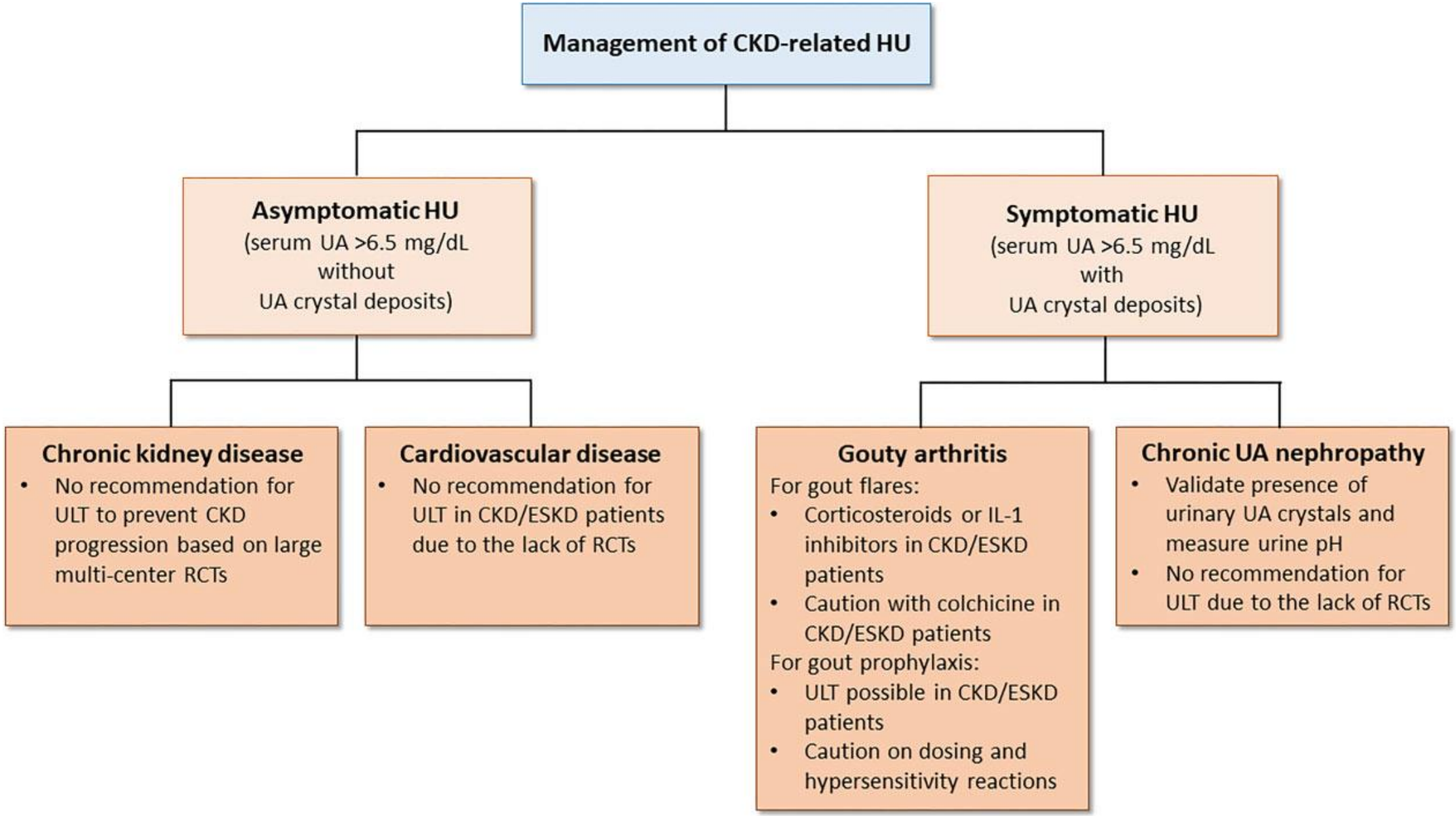
Intervention: Urate-lowering therapy

Comparator: Placebo / Standard of care / no treatment

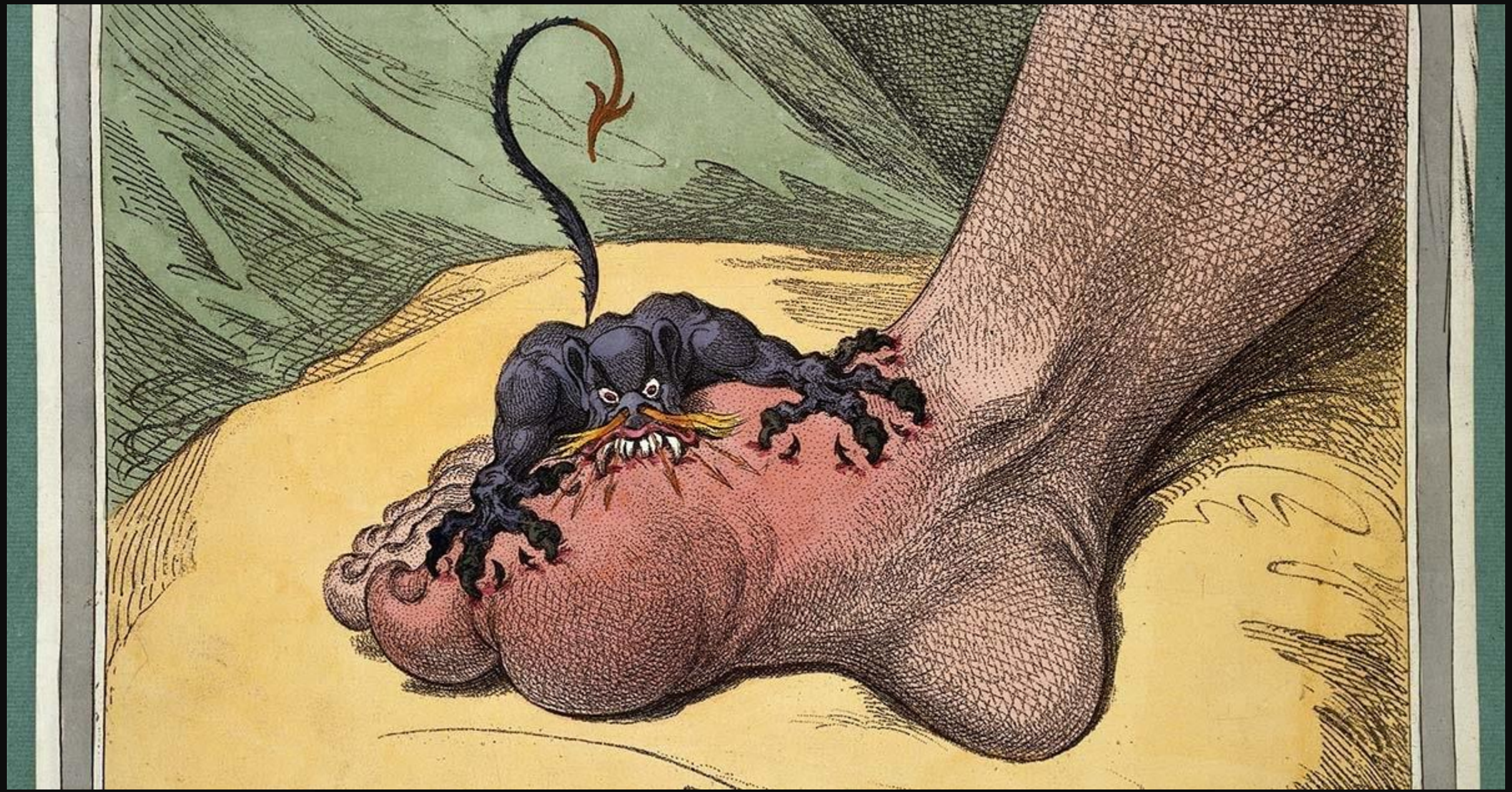
Outcome Timeframe	Study results and measurements	Comparator Placebo / Standard of care / no treatment	Intervention Urate-lowering therapy	Certainty of the Evidence (Quality of evidence)	Plain language summary
Major cardiovascular events	Relative risk 0.83 (CI 95% 0.63 – 1.1) Based on data from 2,977 patients in 8 studies. [1] (Randomized controlled) Follow up: Mean 32 months.	113 per 1000 Difference:	94 per 1000 **19 fewer per 1000** (CI 95% 42 fewer – 11 more)	Moderate Due to serious risk of bias [2]	Urate-lowering therapy probably has little or no difference on major cardiovascular events
Death	Relative risk 1.06 (CI 95% 0.77 – 1.48) Based on data from 3,019 patients in 8 studies. [3] (Randomized controlled) Follow up: Mean 32 months.	48 per 1000 Difference:	51 per 1000 **3 more per 1000** (CI 95% 11 fewer – 23 more)	Low Due to serious risk of bias, Due to serious imprecision [4]	Urate-lowering therapy may have little or no difference on death
Kidney failure	Relative risk 0.89 (CI 95% 0.56 – 1.41) Based on data from 2,610 patients in 6 studies. [5] (Randomized controlled)	2 per 1000 Difference:	2 per 1000 **0 fewer per 1000**	Low Due to serious risk of bias, Due to serious inconsistency [6]	Urate-lowering therapy may have little or no difference on kidney failure
Adverse events	Relative risk 1.03 (CI 95% 0.93 – 1.14) Based on data from 3,349 patients in 13 studies. [7] (Randomized controlled) Follow up: Mean 23 months.	402 per 1000 Difference:	414 per 1000 **12 more per 1000** (CI 95% 28 fewer – 56 more)	Moderate Due to serious risk of bias [8]	Urate-lowering therapy probably has little or no difference on adverse events
Annual eGFR	Based on data from: 3,583 patients in 17 studies. [9] (Randomized controlled) Follow up: Mean 22 months.	Difference:	**MD 1.37 higher** (CI 95% 0.48 higher – 2.26 higher)	Low Due to serious risk of bias, Due to serious inconsistency [10]	Urate-lowering therapy may increase change in eGFR per year slightly
Systolic blood pressure	Based on data from: 2,185 patients in 12 studies. [11] (Randomized controlled)	Difference:	**MD 3.45 lower** (CI 95% 6.1 lower – 0.8 lower)	Moderate Due to serious risk of bias [12]	Urate-lowering therapy probably improves systolic blood pressure
Diastolic blood pressure	Based on data from: 2,185 patients in 12 studies. [13] (Randomized controlled)	Difference:	**MD 2.02 lower** (CI 95% 3.25 lower – 0.78 lower)	Moderate Due to serious risk of bias [14]	Urate-lowering therapy probably improves diastolic blood pressure
Proteinuria	Based on data from: 110 patients in 2 studies. [15] (Randomized controlled)	Difference:	**MD 0.1 lower** (CI 95% 0.89 lower – 0.69 higher)	Low Due to serious risk of bias, Due to serious imprecision [16]	Urate-lowering therapy may have little or no effect on proteinuria

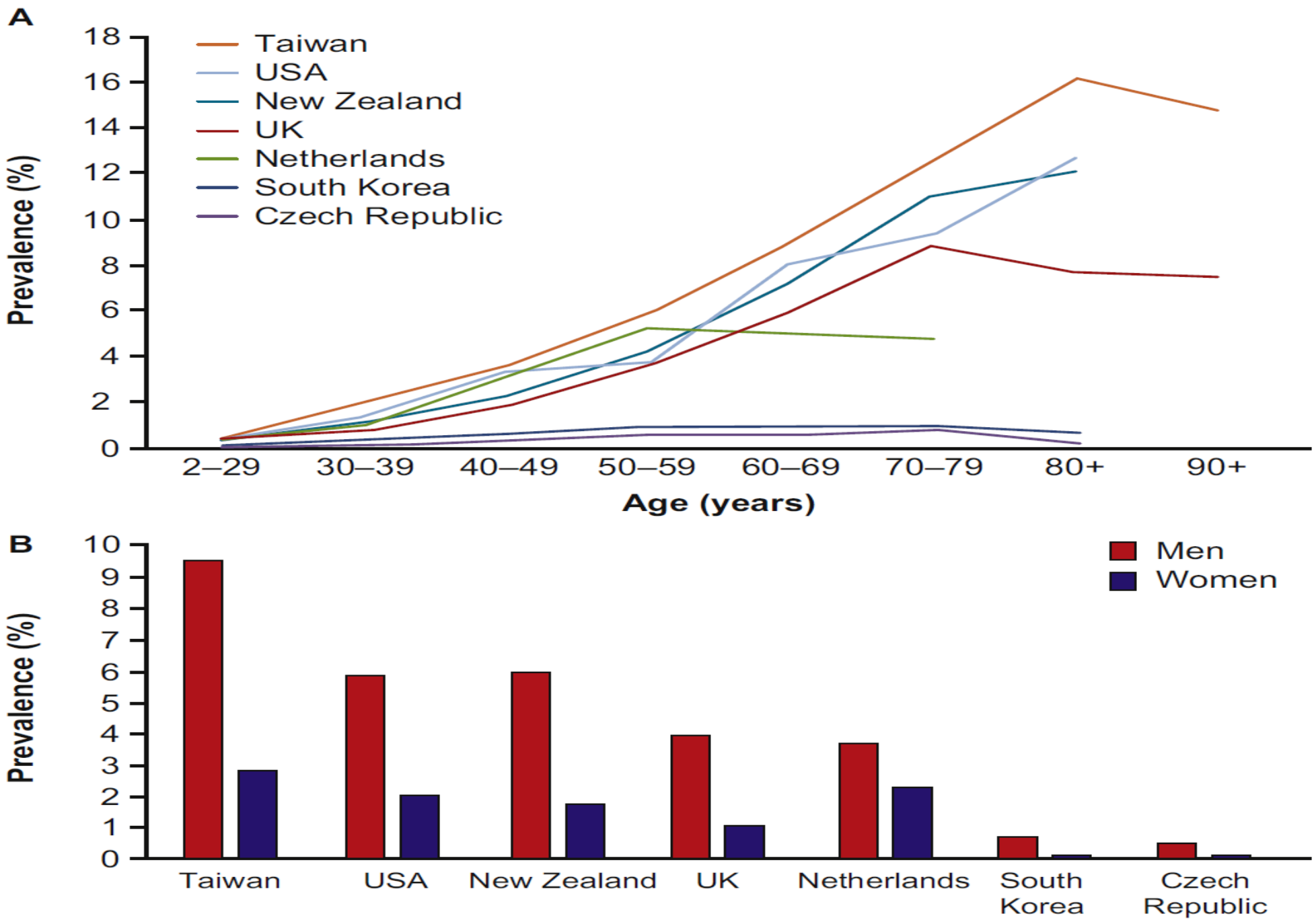


Anders et al. Clin Kidney J 2023



Anders et al. Clin Kidney J 2023





Singh & Gaffo. Semin Arthritis Rheum 2020

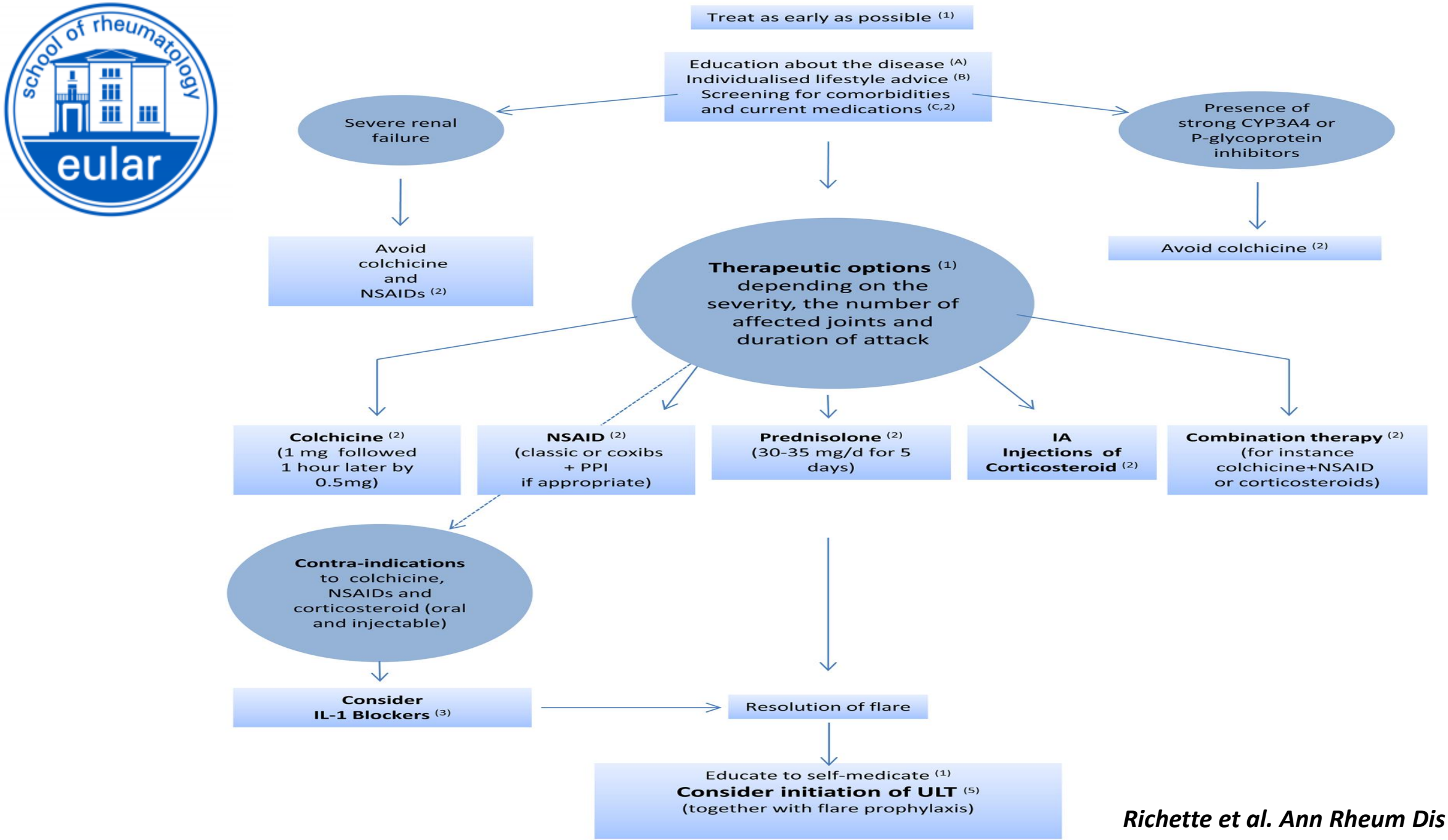
Table 1 Overarching principles and final set of 11 recommendations for the treatment of gout

	Overarching principles
A	Every person with gout should be fully informed about the pathophysiology of the disease, the existence of effective treatments, associated comorbidities and the principles of managing acute attacks and eliminating urate crystals through lifelong lowering of SUA level below a target level.
B	Every person with gout should receive advice regarding lifestyle: weight loss if appropriate and avoidance of alcohol (especially beer and spirits) and sugar-sweetened drinks, heavy meals and excessive intake of meat and seafood. Low-fat dairy products should be encouraged. Regular exercise should be advised.
C	Every person with gout should be systematically screened for associated comorbidities and cardiovascular risk factors, including renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidaemia, hypertension, diabetes and smoking, which should be addressed as an integral part of the management of gout.
	Final set of 11 recommendations
1	Acute flares of gout should be treated as early as possible. Fully informed patients should be educated to self-medicate at the first warning symptoms. The choice of drug (s) should be based on the presence of contraindications, the patient's previous experience with treatments, time of initiation after flare onset and the number and type of joint(s) involved.
2	Recommended first-line options for acute flares are colchicine (within 12 hours of flare onset) at a loading dose of 1 mg followed 1 hour later by 0.5 mg on day 1 and/or an NSAID (plus proton pump inhibitors if appropriate), oral corticosteroid (30–35 mg/day of equivalent prednisolone for 3–5 days) or articular aspiration and injection of corticosteroids. Colchicine and NSAIDs should be avoided in patients with severe renal impairment. Colchicine should not be given to patients receiving strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin or clarithromycin.
3	In patients with frequent flares and contraindications to colchicine, NSAIDs and corticosteroid (oral and injectable), IL-1 blockers should be considered for treating flares. Current infection is a contraindication to the use of IL-1 blockers. ULT should be adjusted to achieve the uricaemia target following an IL-1 blocker treatment for flare.
4	Prophylaxis against flares should be fully explained and discussed with the patient. Prophylaxis is recommended during the first 6 months of ULT. Recommended prophylactic treatment is colchicine, 0.5–1 mg/day, a dose that should be reduced in patients with renal impairment. In cases of renal impairment or statin treatment, patients and physicians should be aware of potential neurotoxicity and/or muscular toxicity with prophylactic colchicine. Co-prescription of colchicine with strong P-glycoprotein and/or CYP3A4 inhibitors should be avoided. If colchicine is not tolerated or is contraindicated, prophylaxis with NSAIDs at low dosage, if not contraindicated, should be considered.
5	ULT should be considered and discussed with every patient with a definite diagnosis of gout from the first presentation. ULT is indicated in all patients with recurrent flares, tophi, urate arthropathy and/or renal stones. Initiation of ULT is recommended close to the time of first diagnosis in patients presenting at a young age (<40 years) or with a very high SUA level (>8.0 mg/dL; 480 μmol/L) and/or comorbidities (renal impairment, hypertension, ischaemic heart disease, heart failure). Patients with gout should receive full information and be fully involved in decision-making concerning the use of ULT.
6	For patients on ULT, SUA level should be monitored and maintained to <6 mg/dL (360 μmol/L). A lower SUA target (<5 mg/dL; 300 μmol/L) to facilitate faster dissolution of crystals is recommended for patients with severe gout (tophi, chronic arthropathy, frequent attacks) until total crystal dissolution and resolution of gout. SUA level <3 mg/dL is not recommended in the long term.
7	All ULTs should be started at a low dose and then titrated upwards until the SUA target is reached. SUA <6 mg/dL (360 μmol/L) should be maintained lifelong.
8	In patients with normal kidney function, allopurinol is recommended for first-line ULT, starting at a low dose (100 mg/day) and increasing by 100 mg increments every 2–4 weeks if required, to reach the uricaemia target. If the SUA target cannot be reached by an appropriate dose of allopurinol, allopurinol should be switched to febuxostat or a uricosuric or combined with a uricosuric. Febuxostat or a uricosuric are also indicated if allopurinol cannot be tolerated.
9	In patients with renal impairment, the allopurinol maximum dosage should be adjusted to creatinine clearance. If the SUA target cannot be achieved at this dose, the patient should be switched to febuxostat or given benzbromarone with or without allopurinol, except in patients with estimated glomerular filtration rate <30 mL/min.
10	In patients with crystal-proven, severe debilitating chronic tophaceous gout and poor quality of life, in whom the SUA target cannot be reached with any other available drug at the maximal dosage (including combinations), pegloticase is indicated.
11	When gout occurs in a patient receiving loop or thiazide diuretics, substitute the diuretic if possible; for hypertension consider losartan or calcium channel blockers; for hyperlipidaemia, consider a statin or fenofibrate.

IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; SUA, serum uric acid; ULT, urate-lowering therapy.

Richette et al. Ann Rheum Dis 2017

2016 EULAR RECOMMENDATION FOR THE MANAGEMENT OF FLARES IN PATIENTS WITH GOUT

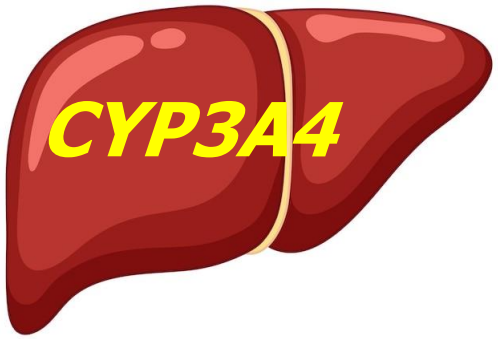


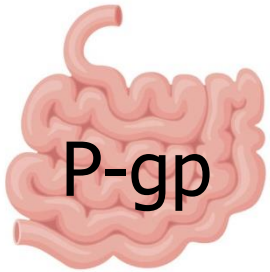
Richette et al. Ann Rheum Dis 2017

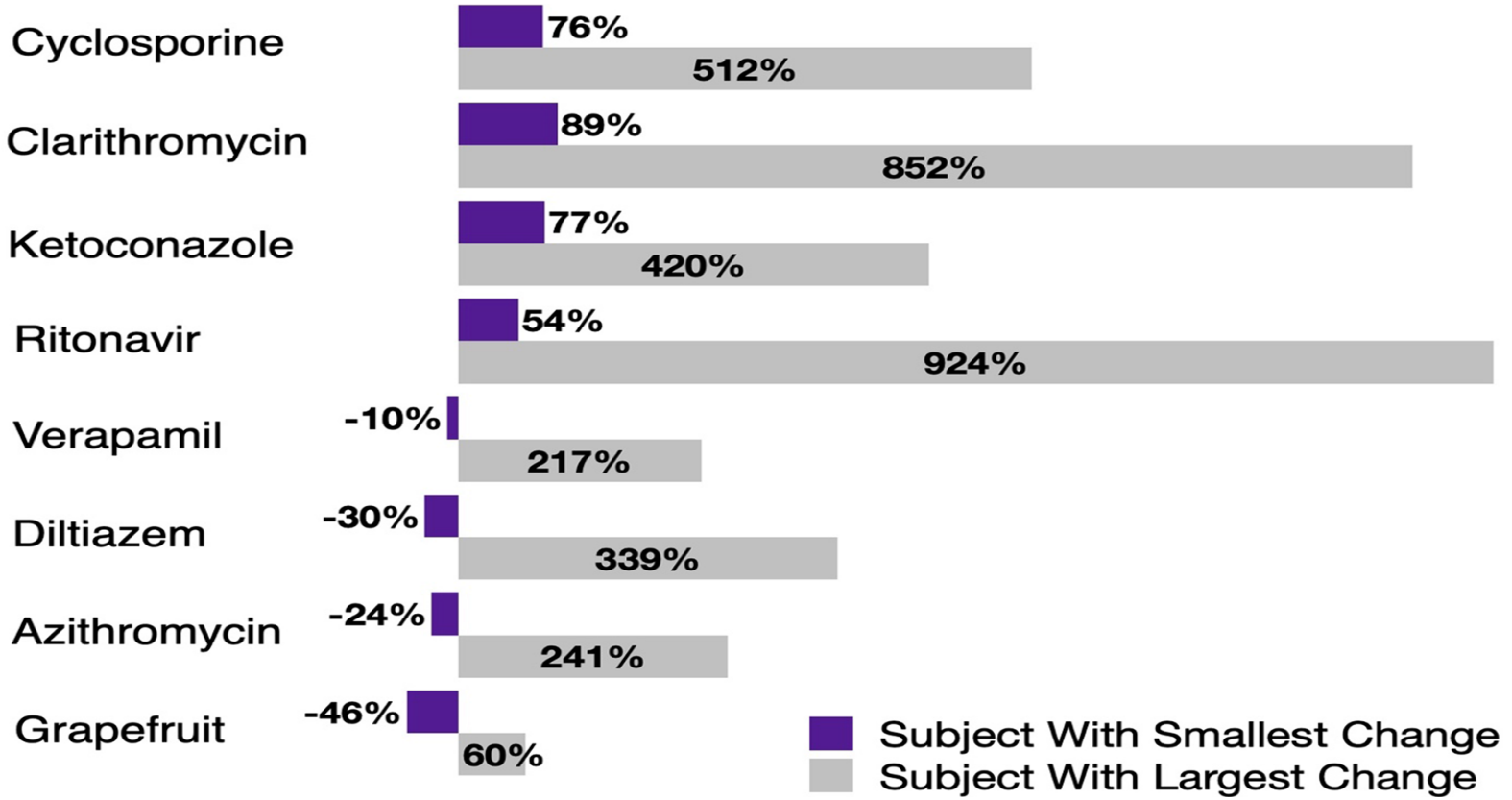
Table 1 Clinical findings of colchicine toxicity

Severity	Signs and symptoms
Mild	Gastrointestinal: diarrhea, nausea, vomiting, abdominal pain Miscellaneous: fatigue, lethargy, malaise, insomnia
Moderate	Neuromuscular: muscle pain, muscle weakness, paresthesias Hematologic: moderate neutropenia and/or moderate thrombocytopenia Respiratory: shortness of breath, cough Dermatologic: alopecia (usually late)
Severe/fatal	Neuromuscular: rhabdomyolysis, atonia, dark brown urine Hematologic: pancytopenia (infections, fever, bleeding) Multiorgan failure: renal failure, liver failure Cardiovascular: cardiac arrhythmias, cardiac failure, hypotension, cardiac arrest

<1%







Hansten et al. Drug Saf 2023

1 mg

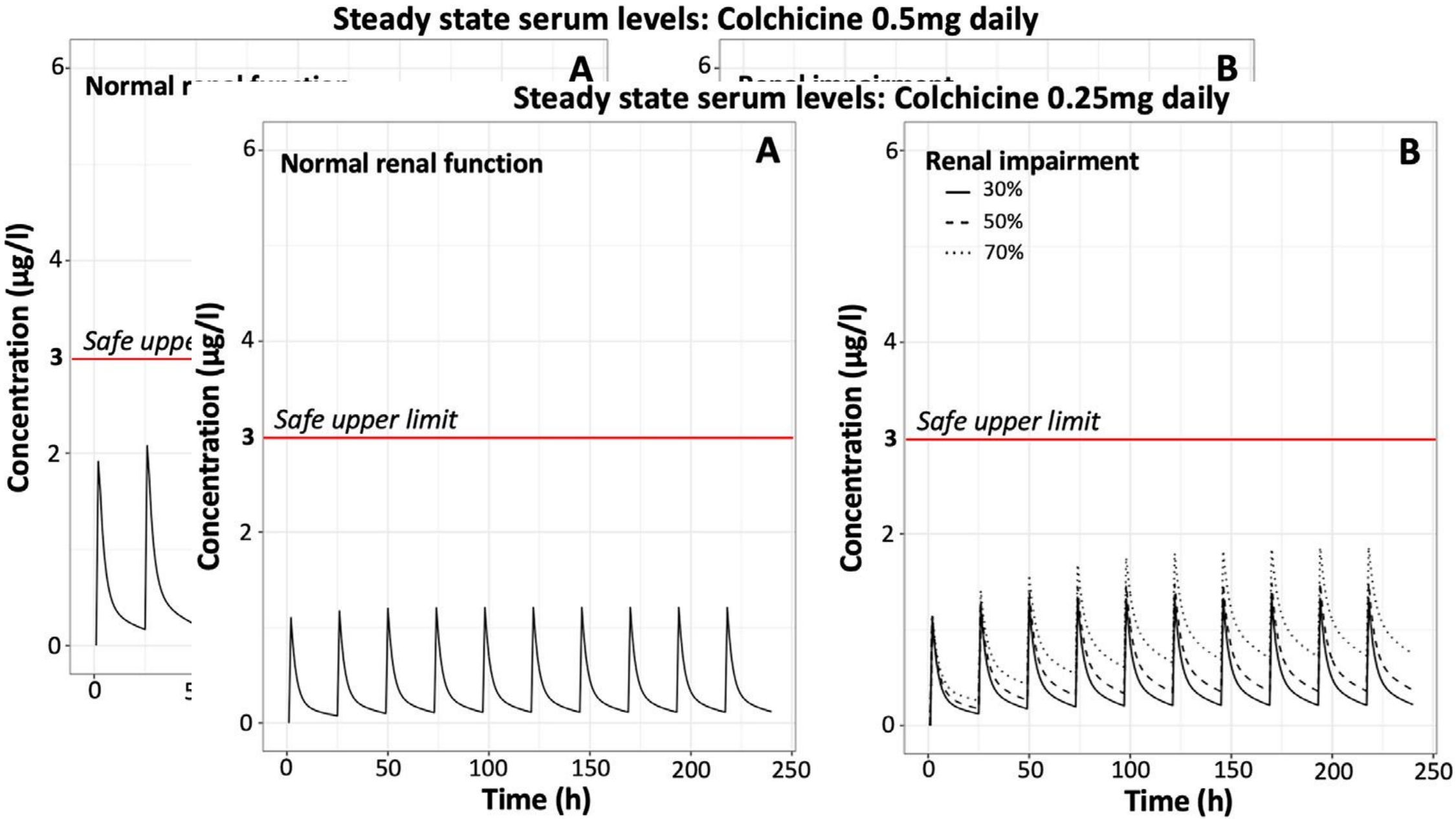
Table 1. Demographic features and eGFR of the groups

	Normal GFR N=6	Low GFR N=3	HD N=6	KTx recipients N=6	P
Age	34±4	39±9	42±6	40±6	NS
Gender (M/F)	5/1	2/1	4/2	5/1	NS
eGFR (ml/min)	110±10	25±11	Nil	73±13	<0.0001

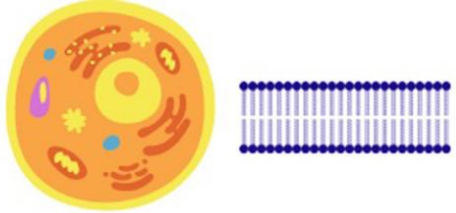
M: male, F: female, eGFR: estimated glomerular filtration rate, KTx: kidney transplantation, NS: not significant.

	Normal GFR N=6	Low GFR N=3	HD N=6	KTx recipients N=6	P
AUC_{0-24}(pmol.hour/ml)	5.3±1.6[a,b]	8.0±1.8	29.0±10.9[a,c]	16.9±6.1[b,c]	<0.001
Cmax (pmol/ml)	0.32±0.06[d,e]	0.49±0.15	1.49±0.44[d]	1.18±0.88[e]	0.008
Colchicine 0	**0**	**0**	**0**	**0**	
Colchicine 1	0.18±0.08[f]	0.27±0.04	1.15±0.54[f,g]	0.59±0.27[g]	0.001
Colchicine 2	0.24±0.10[h]	0.48±0.14	1.41±0.47[h]	0.96±0.95	0.016
Colchicine 4	0.30±0.07[i,j]	0.47±0.15	1.44±0.44[i,k]	0.81±0.23[j,k]	<0.001
Colchicine 8	0.23±0.06[l,m]	0.34±0.09 ***x1.5***	1.39±0.51[l,n] ***x7***	0.84±0.35[m,n] ***x4***	<0.001
Colchicine 24	0.18±0.08[o]	0.27±0.06	0.96±0.47[o]	0.51±0.30	0.004

Amanova et al. Clin Transplant 2014

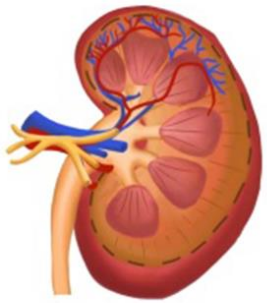


Robinson et al. Am J Med 2022



Phospholipids

Arachidonic acid
(Eicosanoid)



COX-1/COX-2

PGG_2

Peroxidase

PGH_2

Non Steroidal Anti Inflammatory Drug

PGE_2	PGI_2	$PGF_{2\alpha}$	TXA_2
Location: Glomeruli and collecting ducts **Functions:** - RAAS system modulator - Vasodilation - Increase Na+ and water excretion	**Location:** Glomerular mesangial cells, endothelial and podocytes **Functions:** - Arteriolar vasodilation - Decrease vasopressin - Increase Na+ excretion - Attenuate podocytes contraction	**Location:** Distal and collecting ducts **Functions:** - Promote Na+ and water excretion - Stimulate thiazide-sensitive Na-Cl cotransporter at distal tubules	**Location:** Glomeruli **Functions:** - Vasoconstriction - Podocytes contraction

Klomjit & Ungprasert. Eur J Intern Med 2022

At risk patients

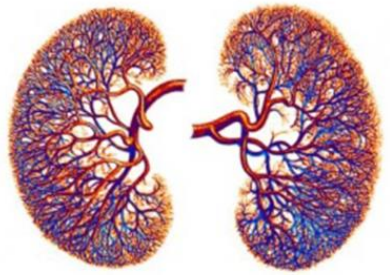
- Heart failure
- Liver failure
- Nephrotic syndrome
- Chronic kidney disease
- Older age
- Volume depletion
- Hypertension
- Diabetes
- Concomitant use of diuretic or RAASi
- Other nephrotoxic agents

Upregulated RAAS and vasoconstrictive mediators (ET-1 and NE)

PGs

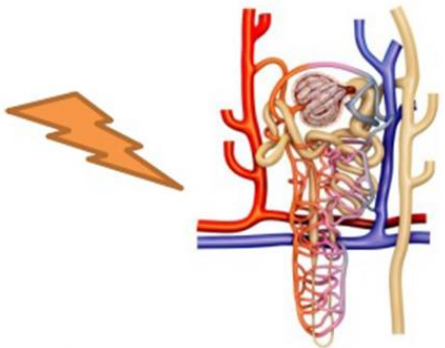
Maintain renal hemodynamics, blood flow and GFR

Renal vasoconstriction



NSAIDs

Unopposed vasoconstriction leading to ↓GFR and ↓ renal blood flow

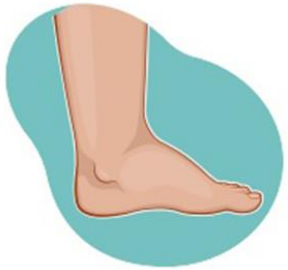


Ischemic kidney injury and acute tubular necrosis

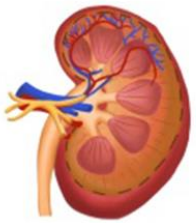
Non
Steroidal
Anti
Inflammatory
Drug

Klomjit & Ungprasert. Eur J Intern Med 2022

High risk patients

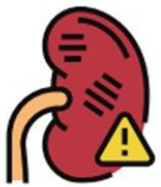


Edema: Na+ and Cl- retention



Acute kidney injury & papillary necrosis: Vasoconstriction

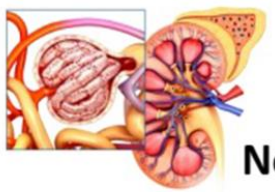
Hypertension: Vasoconstriction, Na+ and Cl- retention



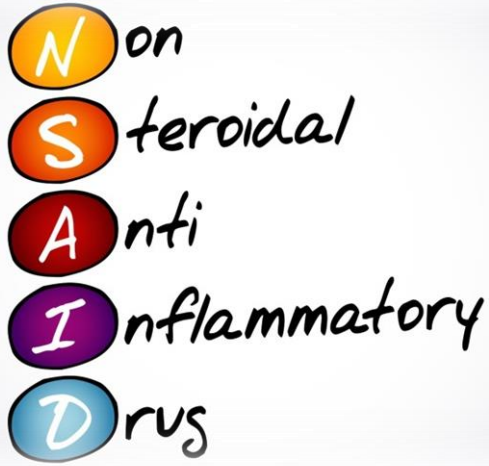
Acute interstitial nephritis: Allergic reaction

Hyponatremia: ↑ Vasopressin activities, SIADH

Hyperkalemia: ↓GFR, ↓ RAAS



Nephrotic syndrome (MCD,MN): Podocyte injury, immune process



Klomjit & Ungprasert. Eur J Intern Med 2022

	Acute or short-term use	Chronic use
GFR > 60	Acceptable Low risk of AIN	Acceptable Review need to continue regularly Monitor kidney function annually
GFR 30–59	Acceptable Low risk of AIN	Consider SDM with weighing of risks/benefits If used, review need to continue regularly Monitor kidney function
GFR < 30, not on dialysis	High risk of hemodynamic changes worsening kidney function (reversible) Low risk of AIN	Consider SDM with weighing of risks/benefits If used, review need to continue regularly Monitor kidney function
Hemodialysis	Acceptable	Acceptable Underlying risk of gastrointestinal bleeding higher in these patients
Peritoneal dialysis	Acceptable	Acceptable if no residual function In presence of residual function, consider SDM with weighing of risks/benefits Underlying risk of gastrointestinal bleeding higher in these patients

- ❑ **Monitoring για πιθανές επιπλοκές (ΑΠ, Cr, ηλεκτρολύτες, οίδημα)**
- ❑ **Συγχορήγηση PPI**
- ❑ **Αντένδειξη σε καταστάσεις stress (λοίμωξη, υπερογκαιμία, ΟΝΒ, υπογκαιμία, πρόσφατη αλλαγή αντιϋπερτασικής αγωγής κ.α.)**
- ❑ **Χαμηλές δόσεις – Μικρή διάρκεια θεραπείας**
- ❑ **Στενή παρακολούθηση του ασθενή**

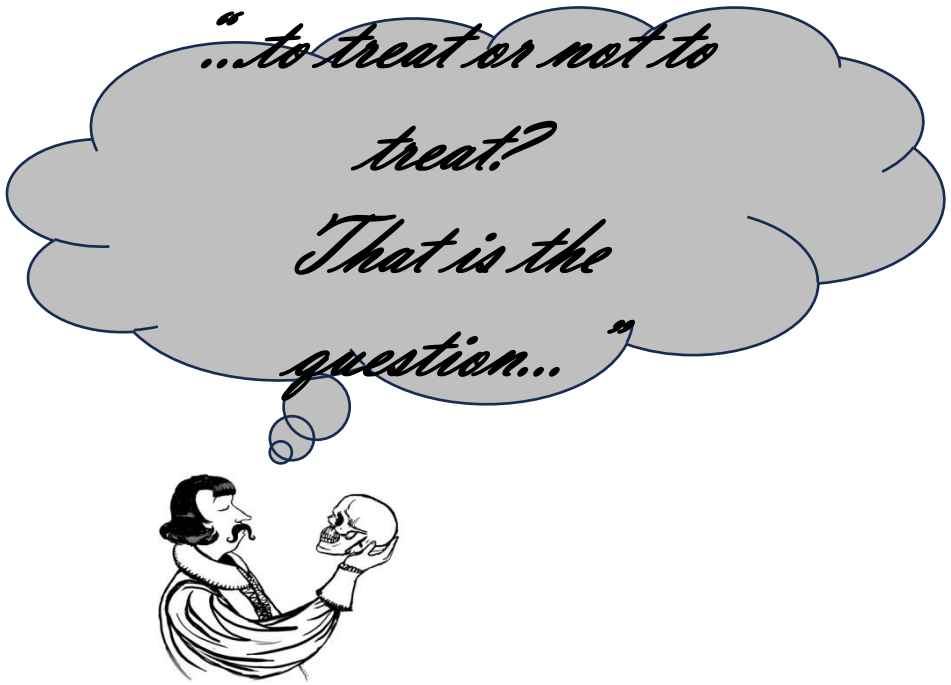
Sriperumbuduri & Hiremath
Curr Opin Nephrol Hypertens 2019

AMERICAN COLLEGE OF RHEUMATOLOGY

Initiating ULT is conditionally recommended *against* in patients with gout experiencing their first gout flare.

However, initiating ULT is conditionally recommended for patients with comorbid moderate-to-severe CKD (stage ≥3), SU concentration >9 mg/dl, or urolithiasis.

FitzGerald et al. Arthritis Rheumatol 2020



5. *ULT should be considered and discussed with every patient with a definite diagnosis of gout from the first presentation. ULT is indicated in all patients with recurrent flare (≥2/year), tophi, urate arthropathy and/or renal stones. Initiation of ULT is recommended close to the time of first diagnosis in patients presenting at a young age (<40 years), or with a very high SUA level (>8 mg/dL; 480 μmol/L) and/or comorbidities (renal impairment, hypertension, ischaemic heart disease, heart failure). Patients with gout should receive full information and be fully involved in decision-making concerning the use of ULT.*

Richette et al. Ann Rheum Dis 2017

febuxostat or a urico… …ot be tolerated.

9 In patients with renal … JA target cannot be achieved at this dose, the patient should be sw… …stimated glomerular filtration rate <30 mL/min.

10 In patients with cryst… …arget cannot be reached with any other available

TABLE III **Symptoms and … Life-Threatening…**

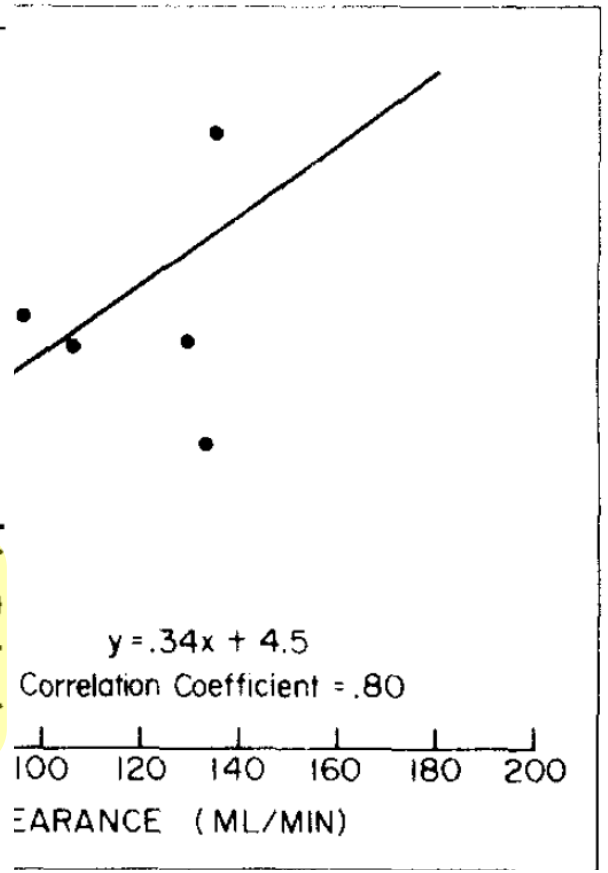
Symptoms	
Skin rash	
Hepatitis (SGOT >50 IU)	
Fever (>38.5°C)	
Leukocytosis (>10,000/mm^3)	
Eosinophilia (>450/mm^3)	
Worsening renal function	
(1.0 mg/dl increase in creatir…	
Death	
Associations	
Dose of allopurinol (mg per day)	
Duration of allopurinol therapy (…	
Renal insufficiency before allop…	
Concomitant diuretic therapy	

TABLE IV **Maintenance Doses of Allopurinol for Adults Based on Individual Creatinine Clearance Measurements**

Creatinine Clearance (ml per minute)	Maintenance Dose of Allopurinol
0	100 mg every three days
10	100 mg every two days
20	100 mg daily
40	150 mg daily
60	200 mg daily
80	250 mg daily
100	300 mg daily
120	350 mg daily
140	400 mg daily

This table is based on a standard maintenance dose of 300 mg per day of allopurinol for a patient with a creatinine clearance of 100 ml per minute. The suggested maintenance doses of allopurinol for patients with other creatinine clearances are based on the maintenance dose ratio, where:

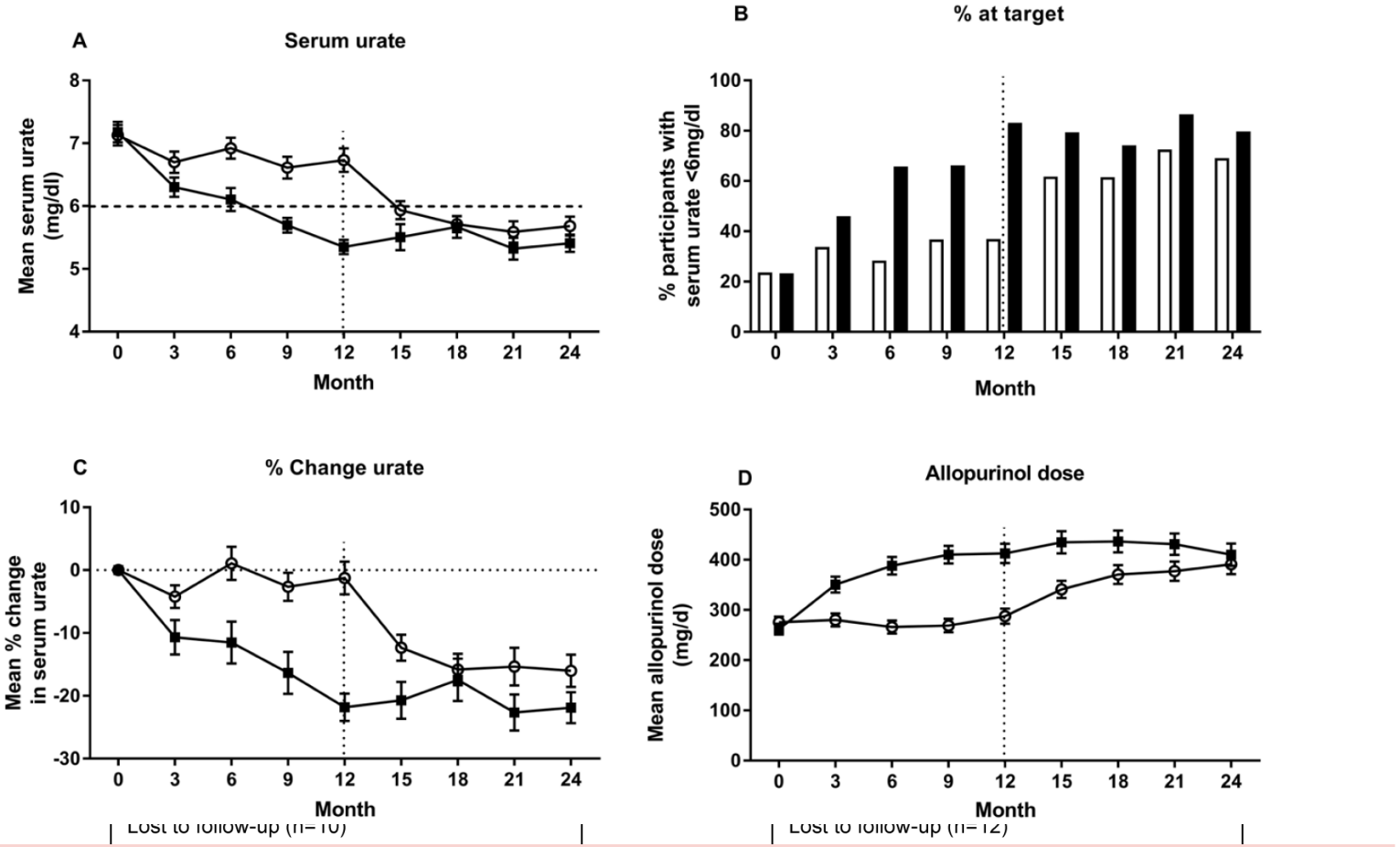
Renal insufficiency dose/Standard dose = Serum oxipurinol half-life oxipurinol at creatinine clearance of 100 ml per minute/Serum oxipurinol half-life oxipurinol in renal insufficiency



Hande et al. Am J Med 1984

Table 1 Participant baseline demographics and clinical features

Variable	Control (n=93)	Dose escalation (n=90)	All participants (n=183)
Age years*	60.9 (12.8)	59.5 (12.1)	60.2 (12.5)
Male, n (%)	78 (84%)	82 (91%)	160 (87.4%)
Ethnicity, n (%)			
NZ European	39 (42%)	37 (41%)	76 (41.5%)
Maori	22 (24%)	29 (32%)	51 (27.9%)
Pacific Island	27 (29%)	19 (21%)	46 (25.1%)
Asian	4 (4%)	5 (6%)	9 (4.9%)
Other	1 (1%)	0 (0%)	1 (1.1%)
Duration of gout (years)	17.9 (13.2)	16.5 (11.3)	17.2 (12.3)
Baseline serum urate mg/dL*	7.13 (1.6)	7.18 (1.6)	7.15 (1.6)
Creatinine (mg/dL)*	1.47 (1.02)	1.58 (0.11)	1.58 (1.02)
CrCL (mL/min)	60.3 (27.7)	60.1 (27.3)	60.2 (27.4)
Body mass index (kg/m^2)*	35.2 (7.4)	35.2 (7.9)	35.2 (7.7)
Flare frequency in the preceding year (median, IQR)	4 (1.3–11.8)	3 (1.0–5.3)	3 (1–8)
Baseline allopurinol dose mg/day†	275.8 (100–600)	261.9 (100–600)	269.0 (100–600)
Allopurinol dose mg/day n (%)			
100–200	31 (33.3%)	37 (41.1%)	68 (37.2%)
>200–300	50 (53.4%)	47 (52.2%)	97 (53%)
>300	12 (12.9%)	7 (7.7%)	19 (10.4%)
Presence of palpable tophi n (%)	46 (49%)	35 (39%)	81 (44.2%)
Coexisting conditions n (%)			
Obesity‡	70 (75%)	64 (71%)	134 (73.2%)
CrCL <60 mL/min	45 (48%)	50 (56%)	95 (51.9%)
CrCL <30 mL/min	14 (15%)	10 (11%)	24 (13.1%)



Lost to follow-up (n=10) | Lost to follow-up (n=12)

Allopurinol specific adverse events				
Allopurinol hypersensitivity syndrome	0	0	0	0
Rash	11 (12%)	8 (9%)	7 (7%)	4 (4%)
Pruritus	5 (5%)	10 (11%)	7 (7%)	4 (4%)
Nausea/vomiting	9 (10%)	6 (7%)	6 (6%)	5 (6%)
Abdominal pain	5 (5%)	6 (7%)	2 (2%)	3 (3%)

Stamp et al. Ann Rheum Dis 2017

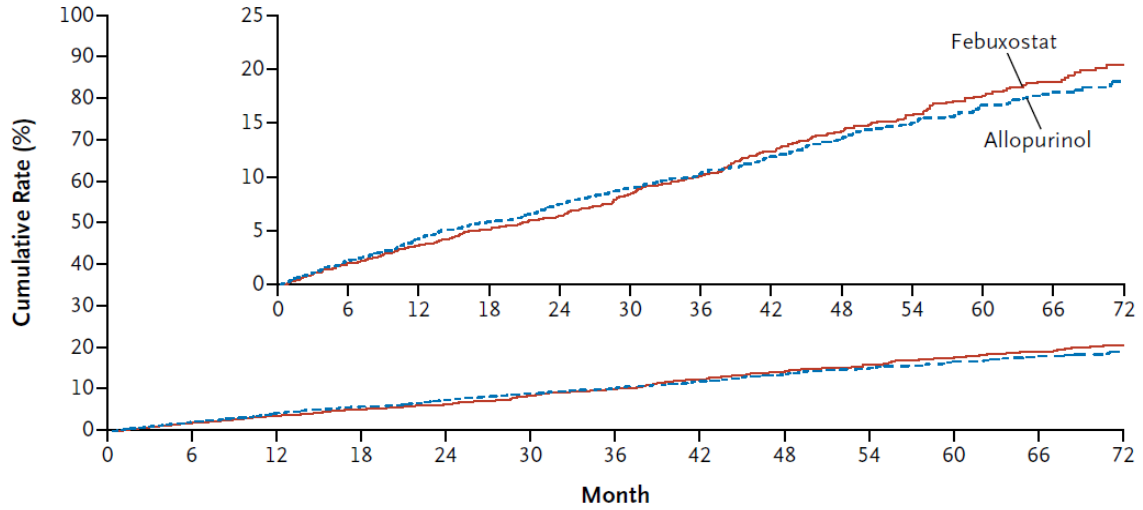
CARI GUIDELINES
CARING FOR AUSTRALIANS & NEW ZEALANDERS WITH KIDNEY IMPAIRMENT

Clinical Question/ PICO

Population: Urate lowering-therapy for CKD
Intervention: Urate-lowering therapy
Comparator: Placebo / Standard of care / no treatment

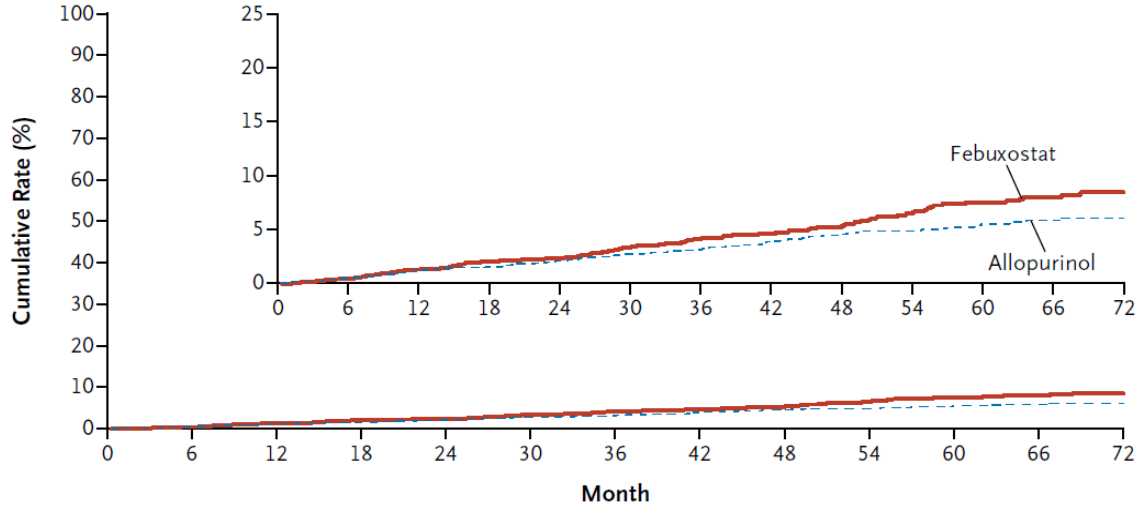
Outcome Timeframe	Study results and measurements	Comparator Placebo / Standard of care / no treatment	Intervention Urate-lowering therapy	Certainty of the Evidence (Quality of evidence)	Plain language summary
Major cardiovascular events	Relative risk 0.83 (CI 95% 0.63 – 1.1) Based on data from 2,977 patients in 8 studies. [1] (Randomized controlled) Follow up: Mean 32 months.	113 per 1000 Difference:	94 per 1000 **19 fewer per 1000** (CI 95% 42 fewer – 11 more)	Moderate Due to serious risk of bias [2]	Urate-lowering therapy probably has little or no difference on major cardiovascular events
Death	Relative risk 1.06 (CI 95% 0.77 – 1.48) Based on data from 3,019 patients in 8 studies. [3] (Randomized controlled) Follow up: Mean 32 months.	48 per 1000 Difference:	51 per 1000 **3 more per 1000** (CI 95% 11 fewer – 23 more)	Low Due to serious risk of bias, Due to serious imprecision [4]	Urate-lowering therapy may have little or no difference on death
Kidney failure	Relative risk 0.89 (CI 95% 0.56 – 1.41) Based on data from 2,610 patients in 6 studies. [5] (Randomized controlled)	2 per 1000 Difference:	2 per 1000 **0 fewer per 1000**	Low Due to serious risk of bias, Due to serious inconsistency [6]	Urate-lowering therapy may have little or no difference on kidney failure
Adverse events	Relative risk 1.03 (CI 95% 0.93 – 1.14) Based on data from 3,349 patients in 13 studies. [7] (Randomized controlled) Follow up: Mean 23 months.	402 per 1000 Difference:	414 per 1000 **12 more per 1000** (CI 95% 28 fewer – 56 more)	Moderate Due to serious risk of bias [8]	Urate-lowering therapy probably has little or no difference on adverse events
Annual eGFR	Based on data from: 3,583 patients in 17 studies. [9] (Randomized controlled) Follow up: Mean 22 months.	Difference:	**MD 1.37 higher** (CI 95% 0.48 higher – 2.26 higher)	Low Due to serious risk of bias, Due to serious inconsistency [10]	Urate-lowering therapy may increase change in eGFR per year slightly
Systolic blood pressure	Based on data from: 2,185 patients in 12 studies. [11] (Randomized controlled)	Difference:	**MD 3.45 lower** (CI 95% 6.1 lower – 0.8 lower)	Moderate Due to serious risk of bias [12]	Urate-lowering therapy probably improves systolic blood pressure
Diastolic blood pressure	Based on data from: 2,185 patients in 12 studies. [13] (Randomized controlled)	Difference:	**MD 2.02 lower** (CI 95% 3.25 lower – 0.78 lower)	Moderate Due to serious risk of bias [14]	Urate-lowering therapy probably improves diastolic blood pressure
Proteinuria	Based on data from: 110 patients in 2 studies. [15] (Randomized controlled)	Difference:	**MD 0.1 lower** (CI 95% 0.89 lower – 0.69 higher)	Low Due to serious risk of bias, Due to serious imprecision [16]	Urate-lowering therapy may have little or no effect on proteinuria

A Primary End Point



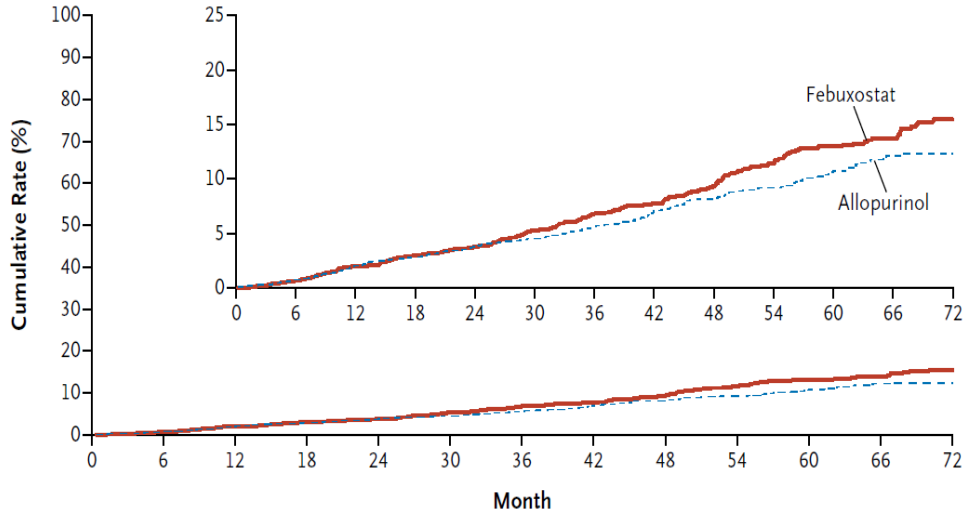
No. at Risk													
Febuxostat	3098	2784	2493	2111	1854	1589	1369	1165	955	778	573	441	264
Allopurinol	3092	2764	2465	2080	1815	1560	1361	1132	933	767	589	437	258

B Cardiovascular Mortality



No. at Risk													
Febuxostat	3098	2823	2550	2174	1922	1659	1440	1243	1033	838	627	482	288
Allopurinol	3092	2807	2530	2152	1898	1637	1433	1204	1008	838	646	489	287

C All-Cause Mortality

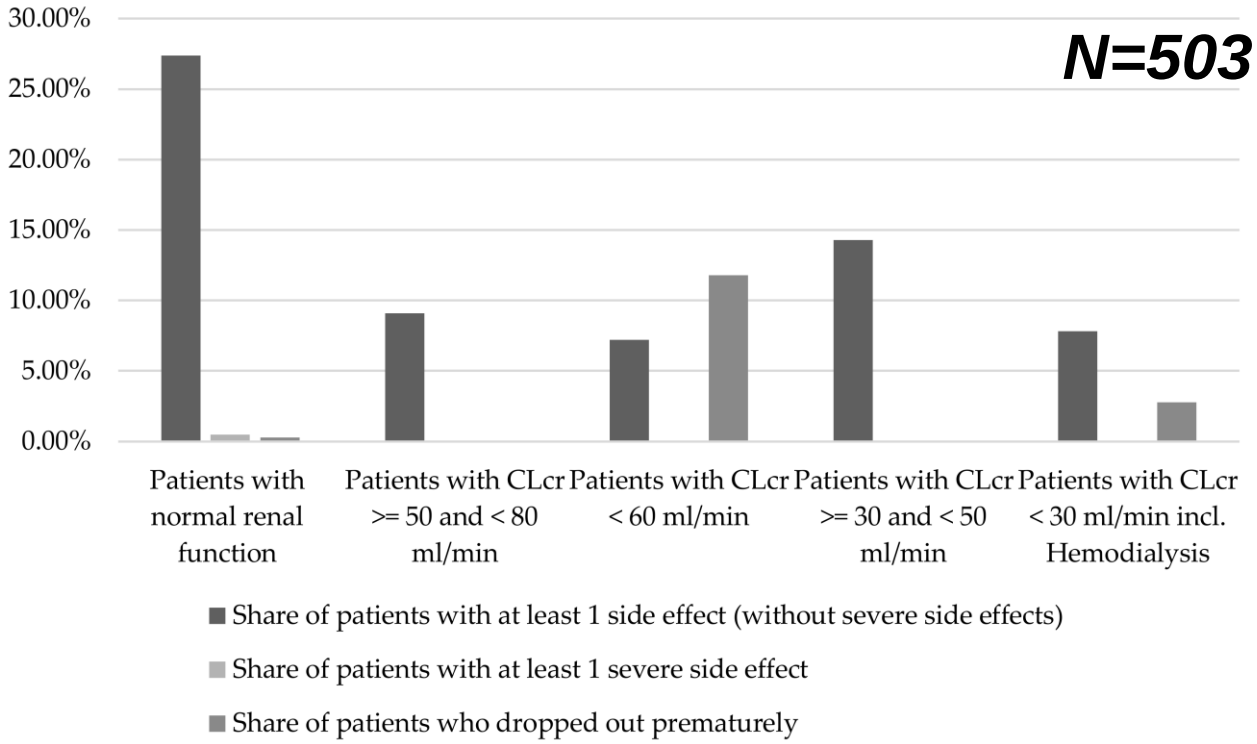


No. at Risk													
Febuxostat	3098	2828	2552	2179	1928	1666	1447	1251	1038	840	631	487	289
Allopurinol	3092	2812	2540	2161	1906	1648	1444	1215	1015	842	650	489	288

White et al. N Eng J Med 2018

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)

O' Dell et al. NEJM Evid 2022



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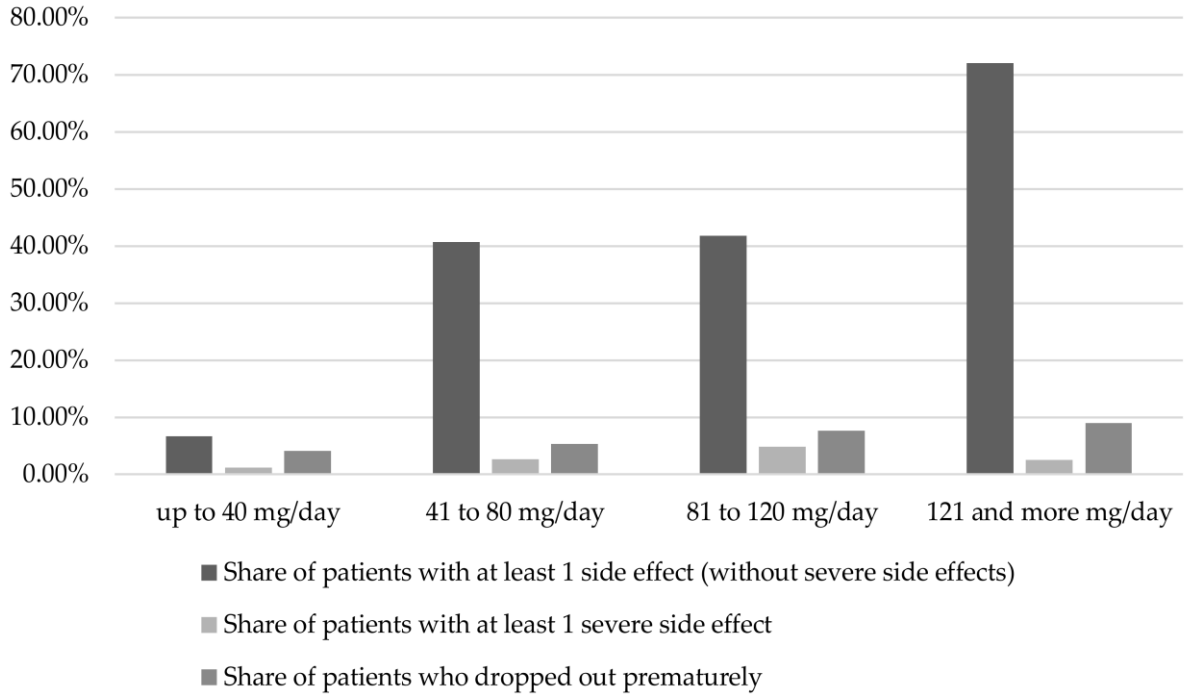
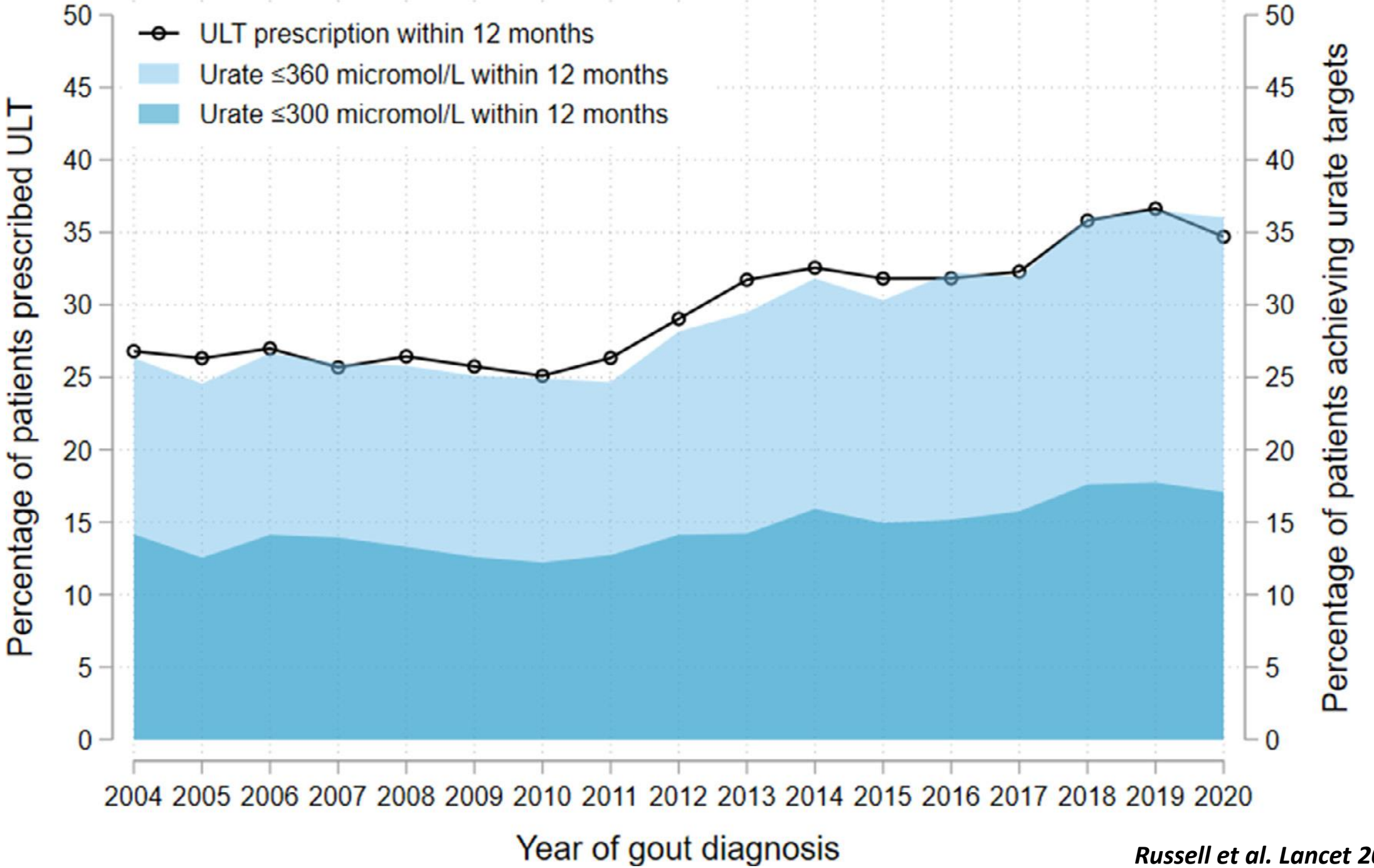


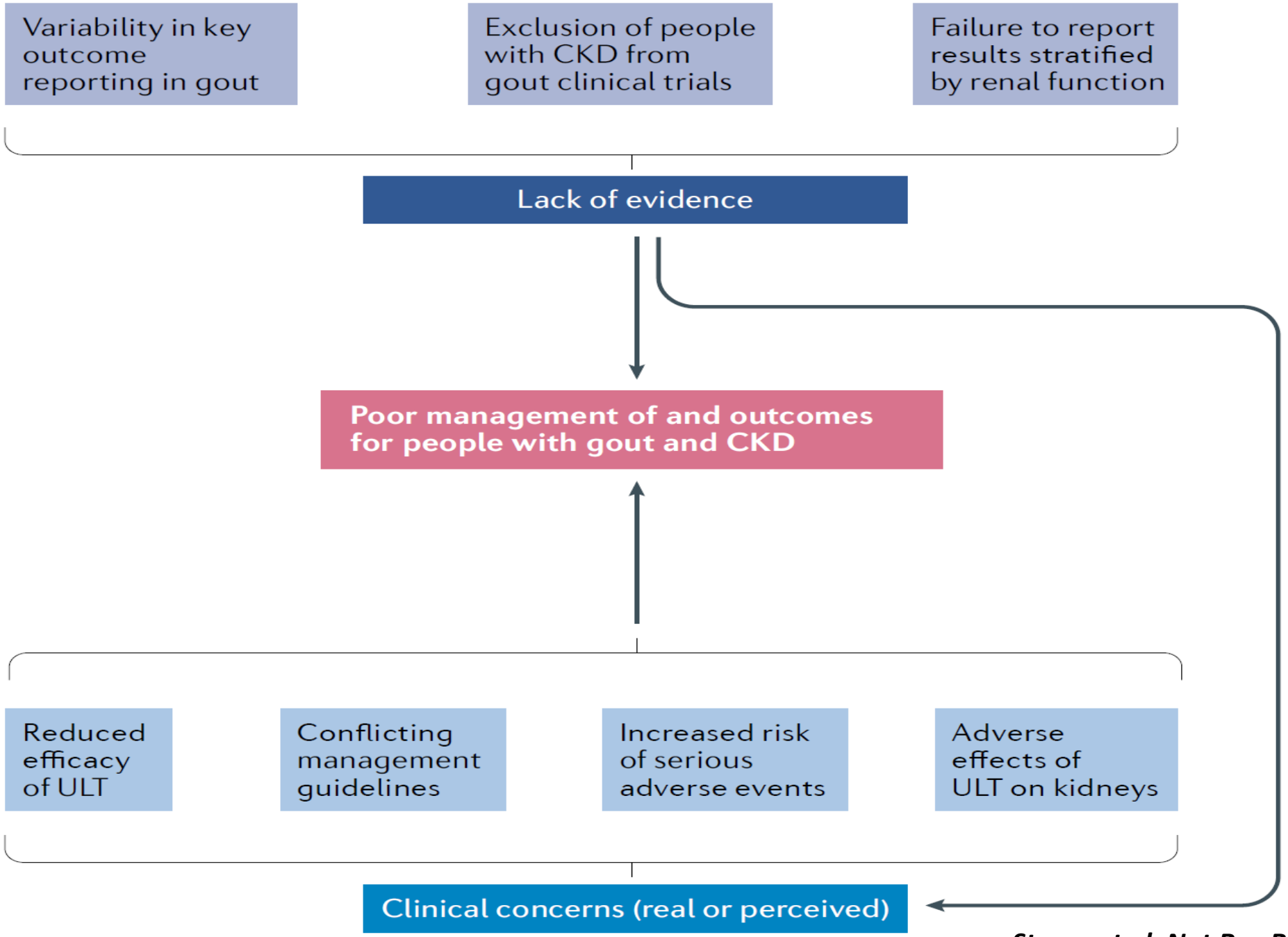
AMERICAN COLLEGE OF RHEUMATOLOGY

Starting treatment with low-dose allopurinol (≤100 mg/day and lower in patients with CKD [stage ≥3]) and febuxostat (≤40 mg/day) with subsequent dose titration over starting at a higher dose is strongly recommended.

Jordan & Gresser. Pharmaceuticals 2018



Russell et al. Lancet 2022



Stamp et al. Nat Rev Rheumatol 2021

Urate-Lowering Agents	Doses	Recommendations for CKD 3-5	Recommendations for CKD 5D (dialysis)
		XOIs[a]	
Allopurinol	Starting: 50-100 mg/d; maximal approved: 800 mg/d (900 mg/d in the UK)	$CL_{cr} \geq 30$ mL/min: start with ≤ 100 mg/d[18] $CL_{cr} < 30$ mL/min: start with 50 mg/d[18]	Intermittent HD: should be administered postdialysis,[26,27] start with 100 mg alternate days postdialysis Daily HD: additional 50% of dose may be required postdialysis Daily PD: start with 50 mg/d All types of RRT: uptitrate dose with 50-mg increments every 2-5 wk, measure serum urate predialysis
Febuxostat	Starting: 40 mg/d; maximal approved: 80 mg/d (120 mg/d in Europe)	Insufficient data for $CL_{cr} < 30$ mL/min	Despite some successful reports of dialysis patients using febuxostat up to 80 mg/d, this agent is not FDA approved for use in dialysis due to a lack of trials in this population[28-32]
		Uricosuric Agents[b]	
Benzbromarone[c]	Starting: 25-50 mg/d; maximal approved: 200 mg/d	Contraindicated if $CL_{cr} < 20$ mL/min	Contraindicated
Lesinurad[d]	Starting: 200 mg/d together with XOI; maximal approved: 200 mg/d	Contraindicated if $CL_{cr} < 45$ mL/min	Contraindicated
Probenecid	Starting: 250 mg twice daily; maximal approved: 2,000 mg/d	Not effective if $CL_{cr} \leq 30$ mL/min	Contraindicated
Sulfinpyrazone[c]	Starting: 50 mg twice daily; maximal approved: 800 mg/d	Not effective if $CL_{cr} \leq 30$ mL/min	Contraindicated
		Recombinant Uricase	
Pegloticase	Starting: 8 mg IV every 2 wk; maximal approved: 8 mg IV every 2 wk	No dose adjustment needed	No dose adjustment needed[33]

Vargas-Santos & Neogi. Am J Kidney Dis 2017

In a US population-based study, the prevalence of CKD (stage ≥2) in patients with SUA level ≥10 mg/dL (594.9 µmol/L) and in patients with gout was 86% and 53%, respectively. CKD appears to be a major risk factor for gout and, conversely, gout might cause renal dysfunction.[53] [54] The task force agreed that identifying CKD in patients with gout was of major importance because of the therapeutic implications, as discussed in items 1, 2, 4, 5, 8 and 9. Therefore, estimated glomerular filtration rate (eGFR) should be calculated at the time of diagnosis for CKD classification and monitored regularly in parallel with SUA measurement. This item also emphasises the need to search for other important associated comorbidities, especially coronary

Y: 50♂
W:80kg
H:180cm
Cr:1.35mg/dl

MDRD – eGFR: 55.9 mL/min/1.73m²

CKD-EPI – eGFR: 64 mL/min/1.73m²

Y: 50♂
W:50kg
H:160cm
Cr:1.35mg/dl

MDRD – eGFR: 55.9 mL/min/1.73m²

CKD-EPI – eGFR: 64 mL/min/1.73m²

Y: 35♂
W:105kg
H:190cm
Cr:1.45mg/dl

MDRD – eGFR: 55.4 mL/min/1.73m²

CKD-EPI – eGFR: 64 mL/min/1.73m²

eGFR Calculator

Glomerular filtration rate (GFR) is the best overall index of kidney function. Normal GFR varies according to age, sex, and body size, and declines with age. The National Kidney Foundation recommends using the CKD-EPI Creatinine Equation (2021) to estimate GFR. More information regarding this recommendation may be found here.

NKF and the American Society of Nephrology have convened a Task Force to focus on the use of race to estimate GFR. *Read more about the task force here.*

Serum Creatinine:		◉ mg/dL ○ µmol/L
Serum Cystatin C:		mg/L
Age:		Years
Gender:		◉ Male ○ Female
Standardized Assays:		◉ Yes ○ No ○ Not Sure
Adjust for body surface area:		○ Yes ◉ No ○ Not Sure

Calculate

Results

CKD-EPI creatinine equation (2021)		mL/min/1.73m^2

Calculators

Use our GFR calculators to estimate GFR for adults or children.

- eGFR Calculator
- Pediatric GFR Calculator
- Cockcroft-Gault formula *(use for drug research only)*
- Pediatric Chronic Kidney Disease Risk Calculator *(used by nephrologists and other healthcare providers only)*
- Kidney Failure Risk Equation
- eGFR Calculator App for iPhone/iPad
- FAQs About GFR Estimates

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Age:		Years
Gender:		◉ Male ○ Female
Standardized Assays:		◉ Yes ○ No ○ Not Sure
Adjust for body surface area:		◉ Yes ○ No ○ Not Sure
Height:		◉ Inches ○ Centimeters
Weight:		◉ Pounds ○ Kilograms

Calculate

Results

CKD-EPI creatinine equation (2021)		mL/min/1.73m^2

Calculators

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- Pediatric GFR Calculator
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- Pediatric Chronic Kidney Disease Risk Calculator *(used by nephrologists and other healthcare providers only)*
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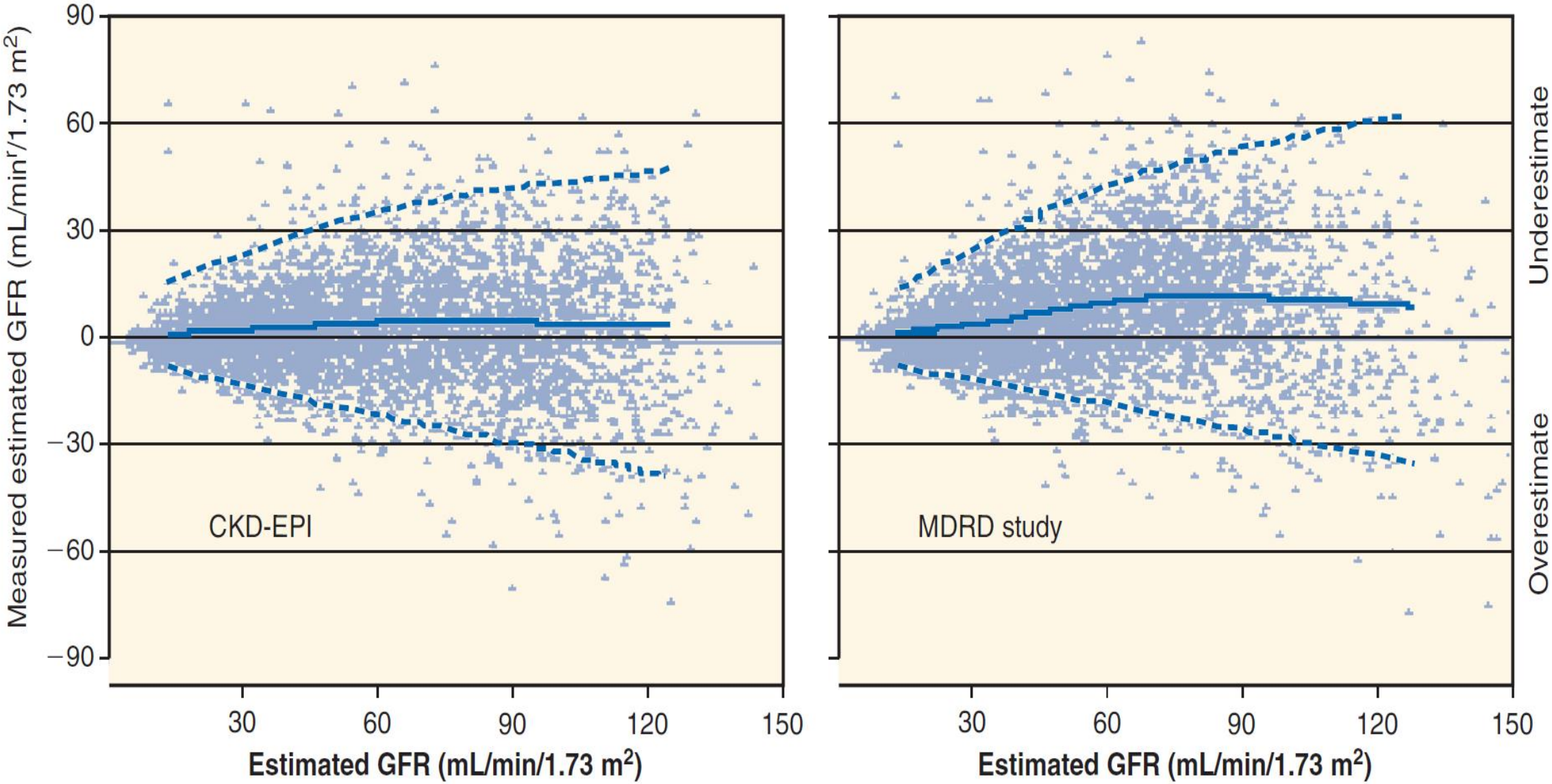
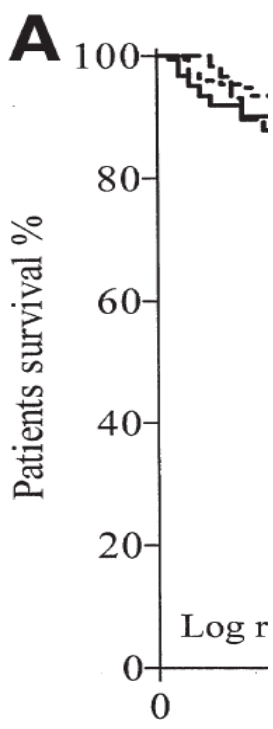


Levey et al. Ann Intern Med 2009



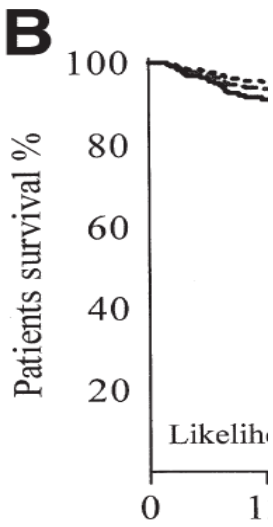
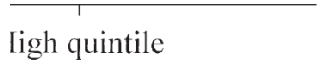


Table 2. Characteristics of Patients With CKD by Quintile of Serum Uric Acid Level

	Group I (quintile 1)	Group II (middle 3 quintiles)	Group III (quintile 5)	*P*
Sex (men/women)	24/38	117/56	44/15	<0.0001
Age (y)	54 ± 12	52 ± 12	53 ± 12	NS
Body mass index (kg/m^2)	25 ± 5	25 ± 4	25 ± 5	NS
Lean body mass index (kg/m^2)	15.9 ± 2.2	16.7 ± 2.2	16.7 ± 2.5	NS
Fat mass index (kg/m^2)	7.7 ± 4.0	7.2 ± 3.6	7.9 ± 3.8	NS
GFR (mL/min/1.73 m^2)	5.5 (1.9-10.4)	6.7 (1.8-13.7)	6.6 (0.8-14.3)	<0.05
CVD (%)	40	31	36	NS
Wasting (SGA >1) (%)	34	26	38	NS
CRP ≥10 mg/L (%)	32	33	46	NS
Diabetes mellitus (%)	27	31	34	NS
Serum albumin (g/dL)	3.3 ± 0.7	3.3 ± 0.6	3.5 ± 0.6	NS
Serum creatinine (mg/dL)	7.4 ± 2.2	8.2 ± 2.9	7.9 ± 3.0	<0.05
CRP (mg/L)	4.0 (0.2-118)	4.8 (0.2-218)	7.4 (0.2-163)	<0.05
IL-6 (pg/mL)	5.9 (1.1-35)	6.5 (1.1-48)	6.1 (0.7-45)	NS
TNF-α (pg/mL)	11 (5-70)	10 (3-206)	10 (3-28)	NS
Soluble intracellular adhesion molecule 1 (ng/mL)	251 (135-593)	238 (99-551)	271 (148-655)	<0.05
Hemoglobin (g/dL)	10.4 ± 1.5	10.4 ± 1.5	10.5 ± 1.3	NS
Phosphate (mg/dL)	5.3 ± 1.5	6.2 ± 1.9	6.5 ± 1.9	<0.01
Calcium (mg/dL)	10.4 ± 0.9	10.0 ± 1.1	9.9 ± 1.0	<0.05
Ca × P product (mg^2/dL^2)	55 ± 16	61 ± 19	63 ± 17	<0.05
Protein intake (normalized PNA; g/kg body weight/d)	0.69 ± 0.14	0.71 ± 0.17	0.71 ± 0.14	NS
Total cholesterol (mg/dL)	201 ± 50	205 ± 58	201 ± 62	NS
Triglycerides (mg/dL)	159 ± 62	186 ± 106	213 ± 142	<0.05
HDL cholesterol (mg/dL)	58 ± 27	50 ± 27	42 ± 15	<0.01
Apo A (mg/dL)	142 ± 37	131 ± 33	122 ± 27	<0.01
Apo B (mg/dL)	101 ± 31	106 ± 35	104 ± 33	NS
Hemoglobin A_{1c} (%)	5.1 ± 1.2	5.4 ± 1.6	5.2 ± 1.4	NS
Glucose (mg/dL)	113 ± 49	117 ± 63	119 ± 56	NS
Systolic blood pressure (mm Hg)	145 ± 22	155 ± 24	144 ± 26	<0.01
Diastolic blood pressure (mm Hg)	86 ± 12	90 ± 13	84 ± 14	<0.05



Suliman et al. Am J Kidney Dis 2006

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