Item number	Question	For yes	For partial yes/	Overall
1	Did the research question and inclusion	Population \boxtimes		Yes 🗵
	criteria for the review include the components of PICO?	Intervention 🛛		No 🗆
		Comparator group 🛛]	
		Outcome 🛛		
		(Optional/ recommended) Timeframe for follow-up \Box		
2	Did the report of the review contain an	a meta-analysis/synthesis plan, if appropriate, and 🛛	Review question(s) 🛛	Yes 🛛
	explicit statement that the review methods were established prior to the conduct of the	a plan for investigating causes of heterogeneity \boxtimes	A search strategy 🛛	Partial yes 🗆
	review and did the report justify any	a plan for investigating causes of heterogeneity \boxtimes	Inclusion/exclusion criteria	No 🗆
	significant deviations from the protocol?		A risk of bias assessment⊠	
3	Did the review authors explain their	For yes, the review should satisfy ONE of the following		Yes 🗆
	selection of the study designs for inclusion in the review?	Explanation for including only RCTs		No 🛛
	in the review.	OR explanation for including NRSI		
		OR explanation for including both RCTs and NSRI		
4	Did the review authors use a	For yes, should also have (all the following):	For partial yes (all the following):	Yes 🗆
	comprehensive literature search strategy?	Searched the references lists/ bibliographies of included studies \Box	Searched at least 2 databases (relevant to research question) \boxtimes	Partial yes 🛛
		Searched trial/ study registries 🛛	Provided key word and/or search strategy 🛛	No 🗆
		Included/ consulted content experts in the field	Justified publication restrictions (e.g. language)	
		Where relevant, searched for grey literature \Box		
		Conducted search within 24 months of completion of the review \boxtimes		
5	Did the review authors perform study	For yes, either ONE of the following:		Yes 🗵
	selection in duplicate?	At least two reviewers independently agreed on eligible studies and		No 🗆
		achieved consensus which studies to include \boxtimes		
		OR two reviewers selected a sample of eligible studies and achieved		
		good agreement (at least 80 percent), with reminder selected by one		
6		reviewer For yes, either ONE of the following:		
6		FOR yes, church OTNE of the following:		Yes 🗵

Supplementary Table S1. AMSTAR2 Critical appraisal of Chen et al. 2020

Item number	Question	For yes	For partial yes/	Overall
	Did the review authors perform data extraction in duplicate?	at least two reviewers achieved consensus on which data to extract from included studies \blacksquare		No 🗆
		OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.		
7	Did the review authors provide a list of	Justified and exclusion from the review of each potentially relevant	Provided a list of all potentially relevant studies	Yes 🗆
	excluded studies and justify the exclusions?	study 🗆	that were read in full-text form but excluded	Partial yes 🗆
	CACIUSIONS;		from the review	No 🛛
8	Did the review authors describe the	Described population in detail	Described populations	Yes 🗆
	included studies in adequate detail?	Described intervention in detail (including doses where relevant)	Described interventions	Partial yes 🛛
		Described comparator in detail (including doses where relevant) \Box	Described comparators 🛛	No 🗆
		Described study's setting 🛛	Described outcomes	
		Timeframe for follow-up	Described research designs 🛛	
9	Did the review authors use a satisfactory	Allocation sequence that was not truly random, and \boxtimes	unconcealed allocation, and \Box	Yes 🛛
	technique for assessing the risk of bias (RoB) in individual studies that were	Selection of the reported result from among multiple measurements	lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective	Partial yes 🗆
	included in the review?	or analyses of a specified outcome \boxtimes	outcomes such as all-cause mortality) \Box	No 🗆
10	Did the review authors report on the	Must have reported on the sources of funding for individual studies		Yes 🗆
	sources of funding for the studies included in the review?	included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies \Box		No 🛛
11	If meta-analysis was performed did the	The authors justified combining the data in a meta-analysis \boxtimes		Yes 🛛
	review authors use appropriate methods for statistical combination of results?	AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.		No 🗆
		AND investigated the causes of any heterogeneity \boxtimes		No meta-analysis conducted \Box
12	If meta-analysis was performed, did the	Included only low risk of bias RCTs 🛛		Yes 🛛
	review authors assess the potential impact of RoB in individual studies on the results	OR, if the pooled estimate was based on RCTs and/or NRSI at		No 🗆
	of the meta-analysis or other evidence synthesis?	variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.		No meta-analysis conducted \Box
13		Included only low risk of bias RCTs		Yes 🛛

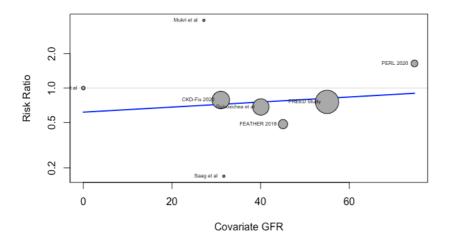
Item number	Question	For yes	For partial yes/	Overall
	Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results 🛛		No 🗆
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	There was no significant heterogeneity in the results ⊠ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review ⊠	-	Yes 🛛 No 🗆
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias ⊠		Yes ⊠ No □ No meta-analysis conducted □
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	The authors reported no competing interests OR \boxtimes The authors described their funding sources and how they managed potential conflicts of interest \boxtimes		Yes 🛛 No 🗆

Supplementary Table 32. Search Strates	
1 Hyperuricemia/	29 apazone.tw.
2 Uric Acid/	30 pegloticase/
3 hyperuric?emi*.tw.	31 pegloticase.tw.
4 ((uric acid or urate) adj	32 rasburicase/
3 (elevat* or high or raise* or rise or	33 rasburicase.tw.
rising)).tw. 5 1 or 2 or 3 or 4	
6 xanthine oxidase inhibitor/	34 urate oxidase/
7 xanthine oxidase inhibit*.tw.	35 urate oxidase.tw.
8 allopurinol/	36 uricase/
9 allopurinol.tw.	37 uricase.tw.
10 oxypurinol/	38 halofenate/
11 oxypurinol.tw.	39 halofenate.tw.
12 febuxostat/	40 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
	or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or
	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
	or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
13 febuxostat.tw.	41 randomized controlled trial.pt.
14 uricosuric agent/	42 controlled clinical trial.pt.
15 uricosuric agent.tw.	43 randomized.ab.
16 antigout agent/	44 placebo.ab.
17 antigout agent.tw	45 randomly.ab.
18 benzbromarone/	46 clinical trials as topic.sh.
19 benzbromarone.tw.	47 trial.ti.
20 probenecid/	48 41 or 42 or 43 or 44 or 45 or 46 or 47
21 probenecid.tw.	40 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
1	or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or
	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
	or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
22 sulfinpyrazone/	49 (5 or 40) and 48
23 sulfinpyrazone.tw.	50 exp Glomerular Filtration Rate/ or exp
	Kidney Function Tests/ or exp Creatinine/ or
	creatinine clearance.tw.
24 zoxazolamine/	51 exp Proteinuria/ or exp Albuminuria/ or
	microalbuminuria.tw.
25 zoxazolamine.tw.	52 exp Renal Dialysis/ or exp Renal
	Replacement Therapy/ or exp Kidney Failure,
	Chronic/ or exp Renal Insufficiency/ or exp Renal
	Insufficiency, Chronic/
26 azapropazone/	49 (5 or 40) and 48
27 azapropazone.tw.	53 exp Blood Pressure Determination/ or exp
	Hypertension/ or exp Blood Pressure/
28 apazone/	54 or/50-53
	55 (5 or 40) and 48 and 54

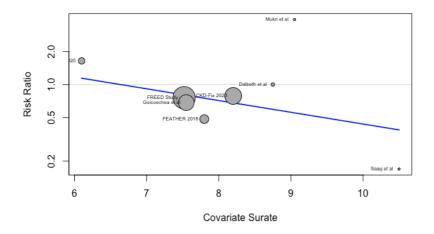
Supplementary Table S2: Search Strategy

Supplementary Figure S1: Sensitivity analysis of major adverse cardiovascular events (A and B) and eGFR (C and D)

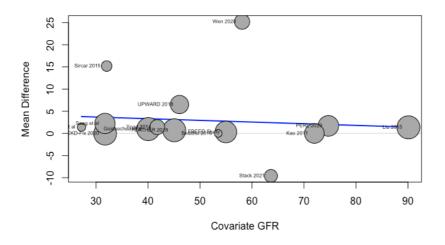
A. Impact of eGFR on Major adverse cardiovascular events



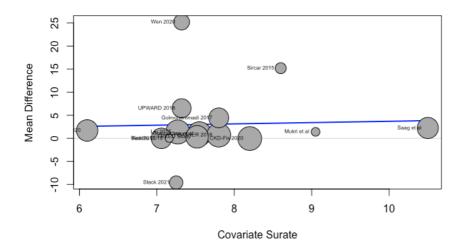
B. Impact of baseline serum urate on Major adverse cardiovascular events



C. Impact of baseline eGFR on eGFR change



D. Impact of baseline serum urate on eGFR change



Supplementary figure S2: Subgroup analysis of trial duration (A-D), hyperuricemia (E-I) and gout (J-M)

A. Trial duration effect on eGFR change

	Urate-lo	wering the	erapy	F	lacebo		0	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
6.5.1 < 12 months									
Shi 2012	7.4	62.9632	21	10.6	66.0094	19	0.1%	-3.20 [-43.28, 36.88]	• •
Beddhu 2016	-6	30.6	40	-6	38	40	0.4%	0.00 [-15.12, 15.12]	
Mukri 2018	0.2	29.5412	47	-1.2	39.8015	46	0.4%	1.40 [-12.87, 15.67]	
Stack 2021	-26.4	27.775	32	-3.36	23.662	28	0.5%	-23.04 [-36.06, -10.02]	←
Sircar 2015	6.4	32.6641	45	-8.8	23.1006	48	0.6%	15.20 [3.63, 26.77]	· · · · · ·
Yood 2014	-3.7637	18.7471	83	-5.184	15.552	20	1.3%	1.42 [-6.50, 9.34]	
Wen 2020	17	12.377	18	-8.2	11.785	20	1.4%	25.20 [17.49, 32.91]	
UPWARD 2018		10.8621	43		10.6327	22	2.6%	6.51 [1.01, 12.02]	
Kao 2011	0.2667	9.2	27	0.2667	7.3333	26	3.6%	0.00 [-4.47, 4.47]	
Subtotal (95% CI)			356			269	11.0%	3.73 [-4.25, 11.71]	
Heterogeneity: Tau ² = 1	110.04; Chi ²	= 53.85, 0	lf = 8 (P ⋅	< 0.00001	l); I ² = 859	6			
Test for overall effect: Z	Z = 0.92 (P =	= 0.36)							
6.5.2 ≥ 12 months									
Golmohammadi 2017	6.345594	18.3984	96	1.909	16.844	100	3.1%	4.44 [-0.51, 9.38]	<u> </u>
Saag 2016	0.5	14.1672	61	-1.74	4.99	32	4.4%	2.24 [-1.71, 6.19]	
PERL 2020	-4.7	21.8	267	-6.4	22.05	263	4.8%	1.70 [-2.03, 5.43]	
FREED Study	-0.37	22.2274	537	-0.69	23.6757	533	7.3%	0.32 [-2.43, 3.07]	
CKD-Fix Study	-1.665	5.333	182	-1.615	5.1136	181	15.5%	-0.05 [-1.12, 1.02]	+
FEATHER 2018	0.23	5.26	219	-0.47	4.48	222	16.4%	0.70 [-0.21, 1.61]	· · · · · · · · · · · · · · · · · · ·
Liu 2015	-0.2667	1.3	82	-1.6333	1.66667	70	18.4%	1.37 [0.89, 1.85]	-
Goicoechea 2015	-0.9286	0.22857	57	-1.9	0.71429	56	19.1%	0.97 [0.78, 1.17]	
Subtotal (95% CI)			1501			1457	89.0%	0.98 [0.66, 1.31]	•
Heterogeneity: Tau ² = (7 (P = 0.1)	25); $I^2 = 2$	2%				
Test for overall effect: 2	Z = 5.85 (P <	< 0.00001)							
Total (95% CI)			1857			1726	100.0%	1.41 [0.46, 2.36]	◆
Heterogeneity: $Tau^2 = 3$	1.21: Chi ² =	69.90. df =	= 16 (P <	0.00001)	$ ^2 = 77\%$				
Test for overall effect: 2									-20 -10 0 10 20
Test for subaroup diffe			= 1 (P =	(0.50) $I^2 =$	= 0%				Greater with urate-low Greater with placebo

B. Trial duration effect on Kidney Failure

	Urate-lowering th	ierapy	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
6.3.1 < 12 months							
Sircar 2015	6	45		48	10.0%		
Subtotal (95% CI)		45		48	10.0%	1.60 [0.48, 5.30]	
Total events	6		4				
Heterogeneity: Not ap	pplicable						
Test for overall effect	z = 0.77 (P = 0.44)						
6.3.2 ≥ 12 months							
CKD-Fix Study	82	182	72	181	29.8%	1.13 [0.89, 1.44]	
FEATHER 2018	8	219	13	222	15.1%	0.62 [0.26, 1.48]	
FREED Study	6	537	4	533	9.4%	1.49 [0.42, 5.25]	
Goicoechea 2015	9	57	24	56	19.1%	0.37 [0.19, 0.72]	
PERL 2020	13	267	11	263	16.6%		
Subtotal (95% CI)		1262		1255	90.0%	0.83 [0.50, 1.38]	•
Total events	118		124				
Heterogeneity: Tau ² =	= 0.20; Chi ² = 11.40	, df = 4 ((P = 0.02)); $ ^2 = 6$	55%		
Test for overall effect	z = 0.70 (P = 0.48)						
Total (95% CI)		1307		1303	100.0%	0.89 [0.56, 1.41]	•
Total events	124		128				
Heterogeneity: Tau ² =	= 0.17; Chi ² = 11.95	, df = 5 ((P = 0.04)); $I^2 = 5$	58%		0.01 0.1 1 10 100
Test for overall effect	z = 0.49 (P = 0.62)						Less with urate-lowering Less with placebo
Test for subgroup dif	fferences: Chi ² = 0.9	7, df = 1	(P = 0.3)	3), I ² =	0%		Less with drate-lowering Less with platebo

C. Trial duration effect on death

	Urate-lowering t	herapy	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
6.2.1 <12 months							
Mukri 2018	1	47	0	46	1.1%	2.94 [0.12, 70.30]	· · · · · ·
Subtotal (95% CI)		47		46	1.1%	2.94 [0.12, 70.30]	
Total events	1		0				
Heterogeneity: Not app	licable						
Test for overall effect: Z	Z = 0.67 (P = 0.51))					
6.2.2 ≥ 12 months							
CKD-Fix Study	11	182	6	181	11.4%	1.82 [0.69, 4.83]	
Dalbeth 2017	1	157	1	157	1.4%	1.00 [0.06, 15.85]	
FEATHER 2018	1	219	1	222	1.4%	1.01 [0.06, 16.10]	
FREED Study	25	537	26	533	37.6%	0.95 [0.56, 1.63]	_ _
Goicoechea 2015	17	57	19	56	37.0%	0.88 [0.51, 1.51]	
PERL 2020	10	267	4	263	8.2%	2.46 [0.78, 7.75]	
Saag 2016	1	63	2	32	1.9%	0.25 [0.02, 2.70]	
Subtotal (95% CI)		1482		1444	98.9%	1.05 [0.76, 1.46]	◆
Total events	66		59				
Heterogeneity: $Tau^2 = 0$	$0.00; Chi^2 = 5.32,$	df = 6 (P	= 0.50);	$I^2 = 09$	6		
Test for overall effect: 2	Z = 0.31 (P = 0.76))					
Total (95% CI)		1529		1490	100.0%	1.06 [0.77, 1.48]	◆
Total events	67		59				
Heterogeneity: $Tau^2 = 0$	$0.00; Chi^2 = 5.73,$	df = 7 (P	= 0.57;	$I^2 = 0$ %	6	H	
Test for overall effect: 2	Z = 0.37 (P = 0.71))					0.01 0.1 İ 10 1 Less with urate-lowering Less with placebo
Test for subgroup diffe	rences: $Chi^2 = 0.4$	0 $df = 1$	(P = 0.5)	3) $I^2 =$	0%		Less with urate-lowering Less with placebo

D. Trial duration effect on major adverse cardiovascular events

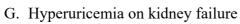
L L L L L L L L L L L L L L L L L L L	Jrate-lowering t	herapy	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
6.1.1 <12 months							
Goicoechea 2015	16	57	23	56	20.5%	0.68 [0.41, 1.15]	
Mukri 2018	4	47	1	46	1.7%	3.91 [0.45, 33.72]	
Subtotal (95% CI)		104		102	22.2%	1.20 [0.23, 6.13]	
Total events	20		24				
Heterogeneity: $Tau^2 = 0$.95; Chi ² = 2.49,	df = 1 (P	= 0.11);	$l^2 = 60$)%		
Test for overall effect: Z	= 0.22 (P = 0.83)	3)					
6.1.2 ≥ 12 months							
CKD-Fix Study	22	152	30	163	21.5%	0.79 [0.48, 1.30]	
Dalbeth 2017	6	157	6	157	5.9%	1.00 [0.33, 3.03]	
FEATHER 2018	12	219	21	222	13.5%	0.58 [0.29, 1.15]	
FREED Study	34	537	38	539	25.2%	0.90 [0.57, 1.40]	
PERL 2020	15	267	9	263	10.3%	1.64 [0.73, 3.69]	+
Saag 2016	1	63	3	32	1.6%	0.17 [0.02, 1.56]	
Subtotal (95% CI)		1395		1376	77.8%	0.85 [0.62, 1.16]	•
Total events	90		107				
Heterogeneity: $Tau^2 = 0$	0.03; Chi ² = 6.01,	df = 5 (P	= 0.31);	$ ^2 = 17$	7%		
Test for overall effect: Z	= 1.04 (P = 0.30)))					
Total (95% CI)		1499		1478	100.0%	0.83 [0.63, 1.10]	•
Total events	110		131				
Heterogeneity: $Tau^2 = 0$	0.03; Chi ² = 8.58,	df = 7 (P	= 0.28;	$l^2 = 18$	3%		
Test for overall effect: Z							0.01 0.1 i 10 100
Test for subgroup differ			(P = 0.6)	8), $1^2 =$	0%		Less with urate-lowering Less with placebo

E. Hyperuricaemia on MACE

U	Irate-lowering tl	nerapy	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.1.1 Not hyperuricemia	a						
CKD-Fix Study	22	152	30	163	21.5%	0.79 [0.48, 1.30]	
Goicoechea 2015	16	57	23	56	20.5%	0.68 [0.41, 1.15]	
PERL 2020	15	267	9	263	10.3%	1.64 [0.73, 3.69]	
Subtotal (95% CI)		476		482	52.2%	0.88 [0.56, 1.36]	◆
Total events	53		62				
Heterogeneity: $Tau^2 = 0$.	.06; $Chi^2 = 3.36$,	df = 2 (P	= 0.19);	$1^2 = 40$)%		
Test for overall effect: Z	= 0.59 (P = 0.56))					
3.1.2 Hyperuricemia							
Dalbeth 2017	6	157	6	157	5.9%	1.00 [0.33, 3.03]	
FEATHER 2018	12	219	21	222	13.5%	0.58 [0.29, 1.15]	
FREED Study	34	537	38	539	25.2%	0.90 [0.57, 1.40]	
Mukri 2018	4	47	1	46	1.7%	3.91 [0.45, 33.72]	
Saag 2016	1	63	3	32	1.6%	0.17 [0.02, 1.56]	
Subtotal (95% CI)		1023		996	47.8%	0.80 [0.50, 1.27]	◆
Total events	57		69				
Heterogeneity: $Tau^2 = 0$.	.07; $Chi^2 = 5.23$,	df = 4 (P	= 0.26);	$1^2 = 23$	3%		
Test for overall effect: Z	= 0.96 (P = 0.34))					
Total (95% CI)		1499		1478	100.0%	0.83 [0.63, 1.10]	•
Total events	110		131				
Heterogeneity: $Tau^2 = 0$.	.03; $Chi^2 = 8.58$,	df = 7 (P	= 0.28);	$l^2 = 18$	3%		0.01 0.1 1 10 10
Test for overall effect: Z	= 1.29 (P = 0.20))					0.01 0.1 1 10 10 Less with urate-lowering Less with placebo
Test for subgroup differe	ences: $Chi^2 = 0.0$	8. df = 1	(P = 0.7)	7), $ ^2 =$	0%		Less with drate-lowering Less with placebo

F. Hyperuricemia on Death

	Urate-lowering th	erapy	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
3.2.1 Not hyperurice	mia						
CKD-Fix Study	11	182	6	181	11.4%	1.82 [0.69, 4.83]	
Goicoechea 2015	17	57	19	56	37.0%	0.88 [0.51, 1.51]	_ _
PERL 2020	10	267	4	263	8.2%	2.46 [0.78, 7.75]	+
Subtotal (95% CI)		506		500	56.6%	1.37 [0.70, 2.66]	
Total events	38		29				
Heterogeneity: Tau ² =	= 0.16; Chi ² = 3.65, c	lf = 2 (P	= 0.16)	$1^2 = 4$	5%		
Test for overall effect	Z = 0.92 (P = 0.36)						
3.2.2 Hyperuricemia							
Dalbeth 2017	1	157	1	157	1.4%	1.00 [0.06, 15.85]	
FEATHER 2018	1	219	1	222	1.4%	1.01 [0.06, 16.10]	
FREED Study	25	537	26	533	37.6%	0.95 [0.56, 1.63]	- e
Mukri 2018	1	47	0	46	1.1%	2.94 [0.12, 70.30]	
Saag 2016	1	63	2	32	1.9%	0.25 [0.02, 2.70]	
Subtotal (95% CI)		1023		990	43.4%	0.93 [0.56, 1.53]	•
Total events	29		30				
Heterogeneity: Tau ² =	= 0.00; Chi ² = 1.68, c	lf = 4 (P	= 0.79)	$1^2 = 0^{\circ}$	6		
Test for overall effect	Z = 0.29 (P = 0.77)						
Total (95% CI)		1529		1490	100.0%	1.06 [0.77, 1.48]	
Total events	67		59				
Heterogeneity: Tau ² =	= 0.00; Chi ² $= 5.73$, c	lf = 7 (P	= 0.57)	$I^2 = 0$	6		0.01 0.1 1 10 100
Test for overall effect	Z = 0.37 (P = 0.71)						0.01 0.1 1 10 100 Less with urate-lowering Less with placebo
Test for subgroup dif	ferences: $Chi^2 = 0.84$	df = 1	(P = 0.3)	6), $I^2 =$	0%		Less with drate-lowering Less with platebo



~ 1	Urate-lowering th	nerapy	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
3.3.1 Not hyperuricer	nia						
CKD-Fix Study	82	182	72	181	29.8%	1.13 [0.89, 1.44]	+ -
Goicoechea 2015	9	57	24	56	19.1%	0.37 [0.19, 0.72]	_ _
PERL 2020 Subtotal (95% CI)	13	267 506	11	263 500	16.6% 65.5%		
Total events	104		107				
Heterogeneity: Tau ² = Test for overall effect:			- 0.007), 1 = 0	3070		
3.3.2 Hyperuricemia							
FEATHER 2018	8	219	13	222	15.1%	0.62 [0.26, 1.48]	
FREED Study	6	537	4	533	9.4%		
Sircar 2015	6	45	4	48	10.0%	1.60 [0.48, 5.30]	
Subtotal (95% CI)		801		803	34.5%	0.99 [0.52, 1.86]	•
Total events	20		21				
Heterogeneity: Tau ² = Test for overall effect:			= 0.35)	$I^2 = 69$	6		
Total (95% CI)		1307		1303	100.0%	0.89 [0.56, 1.41]	•
Total events Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diffe	Z = 0.49 (P = 0.62)	Ì					0.01 0.1 1 10 10 Less with urate-lowering Less with placebo

H. Hyperuricemia on yearly eGFR change

	Urate-lo	wering the	erapy	P	lacebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
3.5.1 Not hyperuricem	ia								
Yood 2014	-3.7637	18.7471	83	-5.184	15.552	20	1.3%	1.42 [-6.50, 9.34]	
Kao 2011	0.2667	9.2	27	0.2667	7.3333	26	3.6%	0.00 [-4.47, 4.47]	
PERL 2020	-4.7	21.8	267	-6.4	22.05	263	4.8%	1.70 [-2.03, 5.43]	
CKD-Fix Study	-1.665	5.333	182	-1.615	5.1136	181	15.5%	-0.05 [-1.12, 1.02]	+
Goicoechea 2015 Subtotal (95% CI)	-0.9286	0.22857	57 616	-1.9	0.71429	56 546	19.1% 44.4%	0.97 [0.78, 1.17] 0.94 [0.75, 1.13]	ī
Heterogeneity: Tau ² = 0 Test for overall effect: 2			4 (P = 0.	45); I ² = C	1%				
3.5.2 Hyperuricemia									
Shi 2012	7.4	62.9632	21	10.6	66.0094	19	0.1%	-3.20 [-43.28, 36.88]	· · · · · · · · · · · · · · · · · · ·
Beddhu 2016	-6	30.6	40	-6	38	40	0.4%	0.00 [-15.12, 15.12]	
Mukri 2018	0.2	29.5412	47	-1.2	39.8015	46	0.4%	1.40 [-12.87, 15.67]	
Stack 2021	-26.4	27.775	32	-3.36	23.662	28	0.5%	-23.04 [-36.06, -10.02]	←────
Sircar 2015	6.4	32.6641	45	-8.8	23.1006	48	0.6%	15.20 [3.63, 26.77]	
Wen 2020	17	12.377	18	-8.2	11.785	20	1.4%	25.20 [17.49, 32.91]	
UPWARD 2018	-0.3429	10.8621	43	-6.8571	10.6327	22	2.6%	6.51 [1.01, 12.02]	
Golmohammadi 2017	6.345594	18.3984	96	1.909	16.844	100	3.1%	4.44 [-0.51, 9.38]	
Saag 2016	0.5	14.1672	61	-1.74	4.99	32	4.4%	2.24 [-1.71, 6.19]	
FREED Study		22.2274	537		23.6757	533	7.3%	0.32 [-2.43, 3.07]	
FEATHER 2018	0.23	5.26	219	-0.47	4.48	222	16.4%	0.70 [-0.21, 1.61]	-
Liu 2015 Subtotal (95% CI)	-0.2667	1.3	82 1241	-1.6333	1.66667	70 1180	18.4% 55.6%	1.37 [0.89, 1.85] 3.03 [0.91, 5.15]	•
Heterogeneity: Tau ² = Test for overall effect: 2			= 11 (P <	0.00001)	; I ² = 83%				
Total (95% CI)			1857			1726	100.0%	1.41 [0.46, 2.36]	◆
Heterogeneity: Tau ² = Test for overall effect: Z Test for subgroup diffe	Z = 2.92 (P =	= 0.004)			,				-20 -10 0 10 Greater with urate-low Greater with placebo

I. Hyperuricemia on eGFR change

21	Disease 1.					0		Marrie Differences	New Difference
Charles and Carles and Street		owering th			Placebo	T I	M	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	20	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
3.8.1 Not hyperuricem									
CKD-Fix Study	-3.33	5.333			5.1817	181	11.5%		+
Goicoechea 2015	-6.5	9.86	57	-13.3	9.78	56	8.1%		
Kao 2011	0.2	6.9	27	0.2	5.5	26	8.5%	0.00 [-3.35, 3.35]	
PERL 2020	-14.1	18.12	267	-13	18.13	263	8.9%		
Subtotal (95% CI)			533			526	37.1%	1.17 [-1.64, 3.98]	•
Heterogeneity: $Tau^2 = 6$	5.16; Chi ² =	= 13.72, df	= 3 (P =	0.003);	$I^2 = 78\%$	6			
Test for overall effect: 2	Z = 0.82 (P	= 0.42)							
3.8.2 Hyperuricemia									
Beddhu 2016	-3.1	12.55	40	-3.6	14.25	40	5.3%	0.50 [-5.38, 6.38]	
FEATHER 2018	-0.1	12.86	219	-0.6	10.56	222	10.2%	0.50 [-1.70, 2.70]	
FREED Study	-0.37	22.23	537	-0.69	23.38	533	9.4%	0.32 [-2.41, 3.05]	
Golmohammadi 2017	6.45594	18.3984	96	1.909	16.844	100	6.3%	4.55 [-0.40, 9.49]	
Liu 2015	-0.8	13.98	82	-4.9	14.74	70	6.8%	4.10 [-0.49, 8.69]	— —
Shi 2012	3.7	25.45	21	5.3	26.73	19	1.1%	-1.60 [-17.82, 14.62]	
Sircar 2015	3.2	13.22	45	-4.4	9.07	48	6.7%	7.60 [2.96, 12.24]	
Stack 2021	-5.5	18.53	32	-0.7	18.84	28	2.8%	-4.80 [-14.28, 4.68]	
UPWARD 2018	-0.2	6.1738	43	-4	6.3152	22	8.7%	3.80 [0.58, 7.02]	
Wen 2020	8.5	8.05	18	-4.1	9.75	20	5.5%	12.60 [6.94, 18.26]	
Subtotal (95% CI)			1133			1102	62.9%	3.29 [0.83, 5.75]	◆
Heterogeneity: $Tau^2 = 9$	9.00; Chi ² =	= 27.20, df	= 9 (P =	0.001);	$I^2 = 67\%$	6			
Test for overall effect: Z	Z = 2.62 (P	= 0.009)							
Total (95% CI)			1666			1628	100.0%	2.50 [0.69, 4.31]	•
Heterogeneity: $Tau^2 = 3$	7.09: Chi ² =	= 48.43. df	= 13 (P -	< 0.000	$(01): ^2 =$	73%			
Test for overall effect: 2					/, •				-20 -10 0 10 20
Test for subgroup diffe			f = 1 (P -	- 0 27)	$1^2 - 10^3$	20/			Greater with urate-low Greater with placebo

Heterogenetity: $1aU^{-} = 7.0^{\circ}$; $ChT^{-} = 48.43$, dT = 13 (P < 0.00001); P = 73; Test for overall effect: Z = 2.71 (P = 0.007) Test for subgroup differences: $Chi^{2} = 1.24$, df = 1 (P = 0.27), $l^{2} = 19.3\%$

J. Effect of gout on MACE

	Urate-lowering t	herapy	Place	bo		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M–H, Random, 95% Cl		
2.1.1 No gout									
CKD-Fix Study	22	152	30	163	17.7%	0.79 [0.48, 1.30]			
FEATHER 2018	12	219	21	222	11.0%	0.58 [0.29, 1.15]			
FREED Study	93	357	87	302	38.9%	0.90 [0.70, 1.16]			
Goicoechea 2015	16	57	23	56	16.9%	0.68 [0.41, 1.15]			
Mukri 2018	4	47	1	46	1.3%	3.91 [0.45, 33.72]			
PERL 2020 Subtotal (95% CI)	15	267 1099	9	263 1052	8.3% 94.1%	1.64 [0.73, 3.69] 0.86 [0.66, 1.11]	•		
Heterogeneity: Tau ² = Test for overall effect			- 0.23),	1 - 2.	1 70				
2.1.2 Gout									
2.1.2 Gout Dalbeth 2017	6	157	6	157	4.7%	1.00 [0.33, 3.03]			
	6 1	157 63 220	6 3	157 32 189	4.7% 1.2% 5.9%	1.00 [0.33, 3.03] 0.17 [0.02, 1.56] 0.54 [0.10, 2.84]			
Dalbeth 2017 Saag 2016 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	1 7 = 0.78; Chi ² = 1.97,	63 220 df = 1 (P	3	32 189	1.2% 5.9%	0.17 [0.02, 1.56]			
Dalbeth 2017 Saag 2016	1 7 = 0.78; Chi ² = 1.97,	63 220 df = 1 (P	3	32 189 $ ^2 = 49$	1.2% 5.9%	0.17 [0.02, 1.56]			

K. Effect of gout on Death

Urate-lowering therapy			Place	bo		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI			
2.2.1 No gout										
CKD-Fix Study	11	182	6	181	18.3%	1.82 [0.69, 4.83]				
FEATHER 2018	1	219	1	222	2.3%	1.01 [0.06, 16.10]				
Goicoechea 2015	17	57	19	56	59.2%	0.88 [0.51, 1.51]				
Mukri 2018	1	47	0	46	1.7%	2.94 [0.12, 70.30]				
PERL 2020	10	267	4	263	13.2%	2.46 [0.78, 7.75]				
Subtotal (95% CI)		772		768	94.6%	1.20 [0.78, 1.84]	+			
Total events	40		30							
2.2.2 Gout Dalbeth 2017 Saag 2016 Subtotal (95% CI)	1 1	157 63 220	1 2		2.3% 3.1% 5.4%	1.00 [0.06, 15.85] 0.25 [0.02, 2.70] 0.45 [0.08, 2.73]				
Dalbeth 2017 Saag 2016	1 2 0.00; Chi ² = 0.55,	63 220 df = 1 (P	2	32 189	3.1% 5.4%	0.25 [0.02, 2.70]				
Dalbeth 2017 Saag 2016 Subtotal (95% CI) Total events Heterogeneity: Tau ² = C	1 2 0.00; Chi ² = 0.55,	63 220 df = 1 (P	2	32 189 $ ^2 = 0\%$	3.1% 5.4%	0.25 [0.02, 2.70]				

L. Effect of gout on yearly eGFR change

	Urate-lo	wering the	erapy	F	Placebo			Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
2.5.1 No gout											
Shi 2012	7.4	62.9632	21	10.6	66.0094	19	0.1%	-3.20 [-43.28, 36.88]	• • •		
Beddhu 2016	-6	30.6	40	-6	38	40	0.4%	0.00 [-15.12, 15.12]			
Mukri 2018	0.2	29.5412	47	-1.2	39.8015	46	0.4%	1.40 [-12.87, 15.67]			
Stack 2021	-26.4	27.775	32	-3.36	23.662	28	0.5%	-23.04 [-36.06, -10.02]	←────		
Sircar 2015	6.4	32.6641	45	-8.8	23.1006	48	0.6%	15.20 [3.63, 26.77]			
Golmohammadi 2017	6.345594	18.3984	96	1.909	16.844	100	3.1%	4.44 [-0.51, 9.38]			
(ao 2011	0.2667	9.2	27	0.2667	7.3333	26	3.6%	0.00 [-4.47, 4.47]			
PERL 2020	-4.7	21.8	267	-6.4	22.05	263	4.8%	1.70 [-2.03, 5.43]			
REED Study	-0.37	22.2274	537	-0.69	23.6757	533	7.3%	0.32 [-2.43, 3.07]			
CKD-Fix Study	-1.665	5.333	182	-1.615	5.1136	181	15.5%	-0.05 [-1.12, 1.02]	+		
EATHER 2018	0.23	5.26	219	-0.47	4.48	222	16.4%	0.70 [-0.21, 1.61]			
iu 2015.	-0.2667	1.3	82	-1.6333	1.66667	70	18.4%	1.37 [0.89, 1.85]	· · · · · · · · · · · · · · · · · · ·		
Goicoechea 2015	-0.9286	0.22857	57	-1.9	0.71429	56	19.1%	0.97 [0.78, 1.17]	•		
Subtotal (95% CI)			1652			1632	90.3%	0.87 [0.23, 1.51]	◆		
Heterogeneity: Tau ² =	0.36; Chi ² =	27.74, df =	= 12 (P =	0.006); I ²	= 57%						
Test for overall effect:	Z = 2.66 (P =	= 0.008)									
2.5.2 Gout											
Yood 2014	-3.7637	18.7471	83	-5.184	15.552	20	1.3%	1.42 [-6.50, 9.34]			
Ven 2020	17	12.377	18	-8.2	11.785	20	1.4%	25.20 [17.49, 32.91]			
JPWARD 2018	-0.3429	10.8621	43	-6.8571	10.6327	22	2.6%	6.51 [1.01, 12.02]			
Saag 2016	0.5	14.1672	61	-1.74	4.99	32	4.4%	2.24 [-1.71, 6.19]			
Subtotal (95% CI)			205			94	9.7%	8.59 [-0.62, 17.81]			
Heterogeneity: Tau ² =	77.83; Chi ² :	= 28.62, df	f = 3 (P <	0.00001)	; $I^2 = 90\%$						
Test for overall effect:	Z = 1.83 (P =	= 0.07)									
Total (95% CI)			1857			1726	100.0%	1.41 [0.46, 2.36]	•		
Heterogeneity: Tau ² =	1.21: Chi ² =	69.90. df =	= 16 (P <	0.00001)	$ ^2 = 77\%$				-+		
Test for overall effect:			(1 1		,. ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,				-20 -10 0 10 2 Greater with urate-low Greater with placebo		

M. Effect of gout on eGFR change

	Urate-le	owering the	erapy	F	Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.8.1 No Gout									
Beddhu 2016	-3.1	12.55	40	-3.6	14.25	40	5.3%	0.50 [-5.38, 6.38]	
CKD-Fix Study	-3.33	5.333	182	-3.23	5.1817	181	11.5%	-0.10 [-1.18, 0.98]	+
FEATHER 2018	-0.1	12.86	219	-0.6	10.56	222	10.2%	0.50 [-1.70, 2.70]	- -
FREED Study	-0.37	22.23	537	-0.69	23.38	533	9.4%	0.32 [-2.41, 3.05]	
Goicoechea 2015	-6.5	9.86	57	-13.3	9.78	56	8.1%	6.80 [3.18, 10.42]	
Golmohammadi 2017	6.45594	18.3984	96	1.909	16.844	100	6.3%	4.55 [-0.40, 9.49]	
Kao 2011	0.2	6.9	27	0.2	5.5	26	8.5%	0.00 [-3.35, 3.35]	 _
Liu 2015	-0.8	13.98	82	-4.9	14.74	70	6.8%	4.10 [-0.49, 8.69]	
PERL 2020	-14.1	18.12	267	-13	18.13	263	8.9%	-1.10 [-4.19, 1.99]	-+-
Shi 2012	3.7	25.45	21	5.3	26.73	19	1.1%	-1.60 [-17.82, 14.62]	
Sircar 2015	3.2	13.22	45	-4.4	9.07	48	6.7%	7.60 [2.96, 12.24]	
Stack 2021	-5.5	18.53	32	-0.7	18.84	28	2.8%	-4.80 [-14.28, 4.68]	
Subtotal (95% CI)			1605			1586	85.8%	1.63 [0.00, 3.27]	◆
Heterogeneity: Tau ² =	4.07; Chi2 :	= 28.89, df	= 11 (P =	= 0.002); $I^2 = 62$	2%			
Test for overall effect:	Z = 1.96 (P	= 0.05)							
2.8.2 Gout									
UPWARD 2018	-0.2	6.1738	43	-4	6.3152	22	8.7%	3.80 [0.58, 7.02]	
Wen 2020	8.5	8.05	18	-4.1	9.75	20	5.5%	12.60 [6.94, 18.26]	
Subtotal (95% CI)			61			42	14.2%	7.88 [-0.72, 16.48]	
Heterogeneity: Tau ² =	33.19; Chi ²	^e = 7.01, df	= 1 (P =	0.008);	$I^2 = 869$	6			
Test for overall effect:	Z = 1.80 (P	= 0.07)							
Total (95% CI)			1666			1628	100.0%	2.50 [0.69, 4.31]	•
Heterogeneity: Tau ² =	7.09: Chi ² :	= 48.43. df	= 13 (P ·	< 0.000	01): $I^2 =$	73%			
Test for overall effect:					/, •				
		i ² = 1.95, d							Greater with urate-low Greater with placebo