

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

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

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

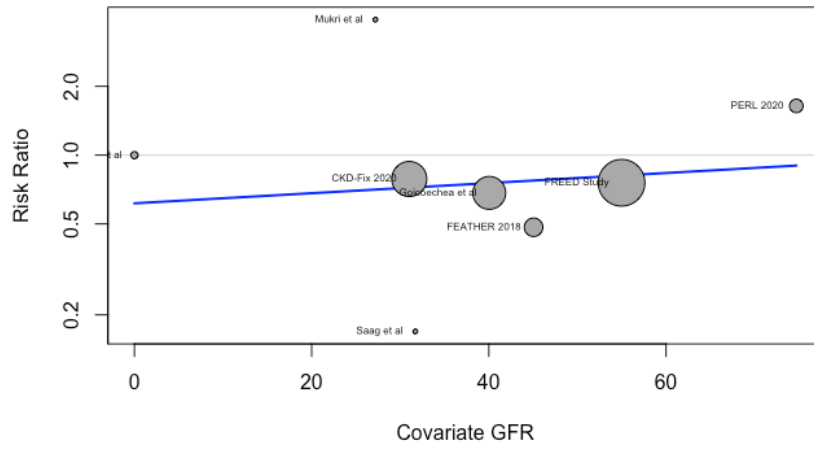
Item number	Question	For yes	For partial yes/	Overall
	Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	OR, if RCT's with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results <input checked="" type="checkbox"/>		No <input type="checkbox"/>
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 <input checked="" type="checkbox"/>		Yes <input checked="" type="checkbox"/>
		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 <input checked="" type="checkbox"/>		No <input type="checkbox"/>
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 <input checked="" type="checkbox"/>		Yes <input checked="" type="checkbox"/>
				No <input type="checkbox"/>
				No meta-analysis conducted <input type="checkbox"/>
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 <input checked="" type="checkbox"/>		Yes <input checked="" type="checkbox"/>
		The authors described their funding sources and how they managed potential conflicts of interest <input checked="" type="checkbox"/>		No <input type="checkbox"/>

Supplementary Table S2: Search Strategy

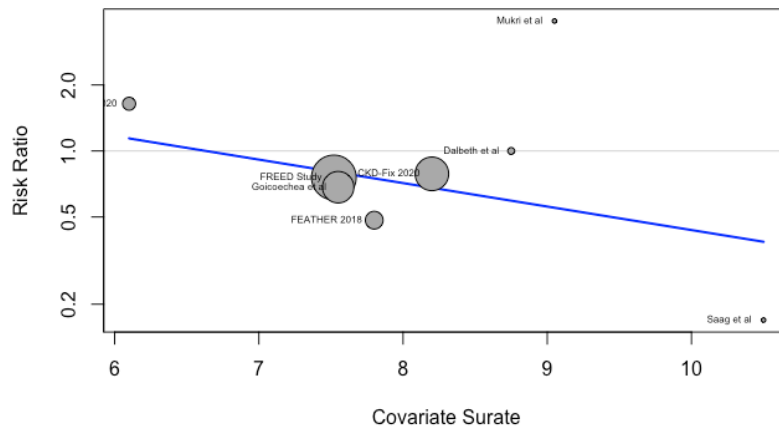
1	Hyperuricemia/	29	apazone.tw.
2	Uric Acid/	30	pegloticase/
3	hyperuric?emi*.tw.	31	pegloticase.tw.
4	((uric acid or urate) adj	32	rasburicase/
3	(elevat* or high or raise* or rise or rising)).tw. 5	33	rasburicase.tw.
6	xanthine oxidase inhibitor/	34	urate oxidase/
7	xanthine oxidase inhibit*.tw.	35	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 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 Figure S1: Sensitivity analysis of major adverse cardiovascular events (A and B) and eGFR (C and D)

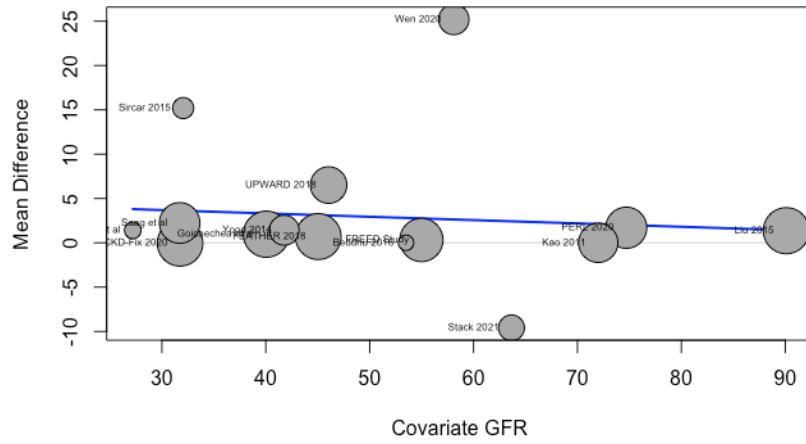
A. Impact of eGFR on Major adverse cardiovascular events



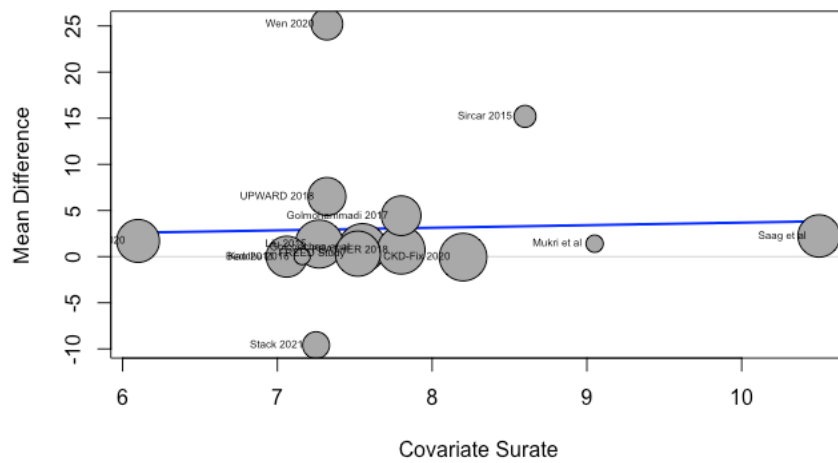
B. Impact of baseline serum urate on Major adverse cardiovascular events



C. Impact of baseline eGFR on eGFR change

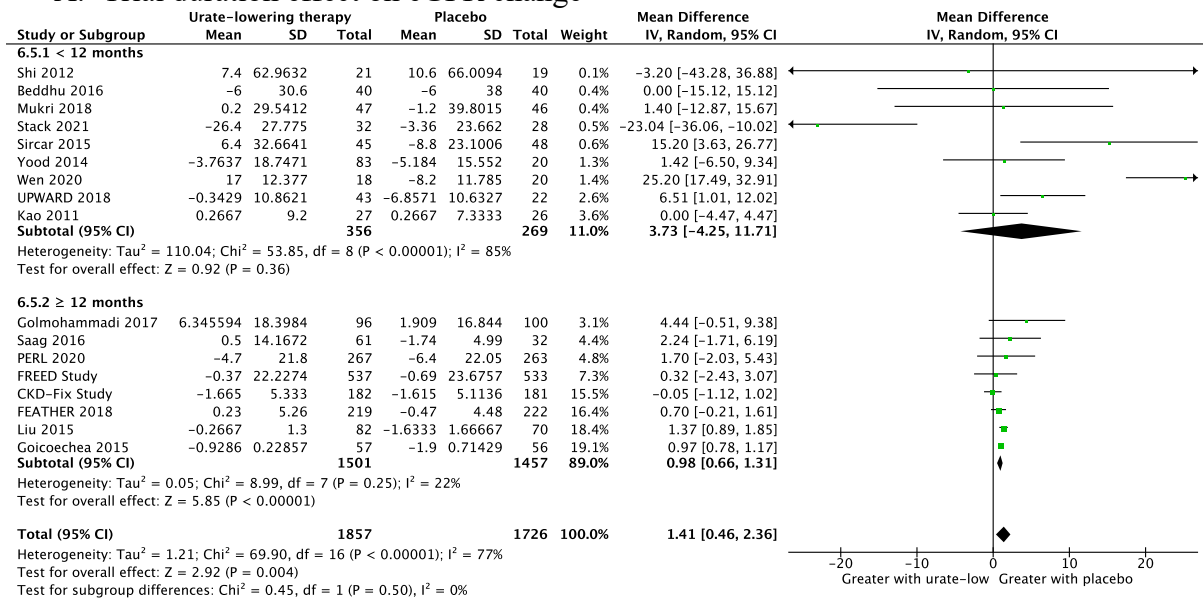


D. Impact of baseline serum urate on eGFR change

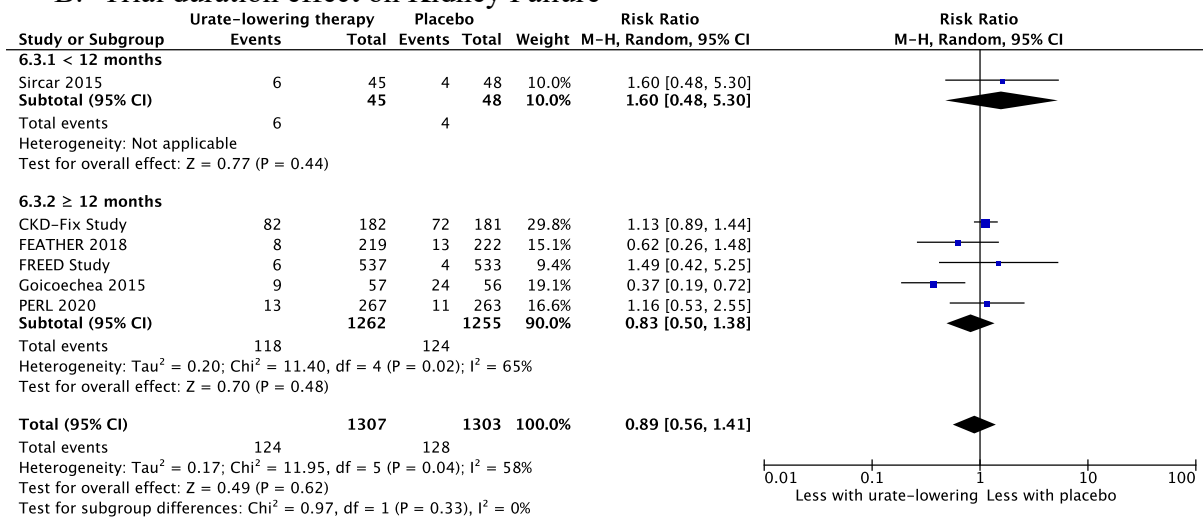


Supplementary figure S2: Subgroup analysis of trial duration (A-D), hyperuricemia (E-I) and gout (J-M)

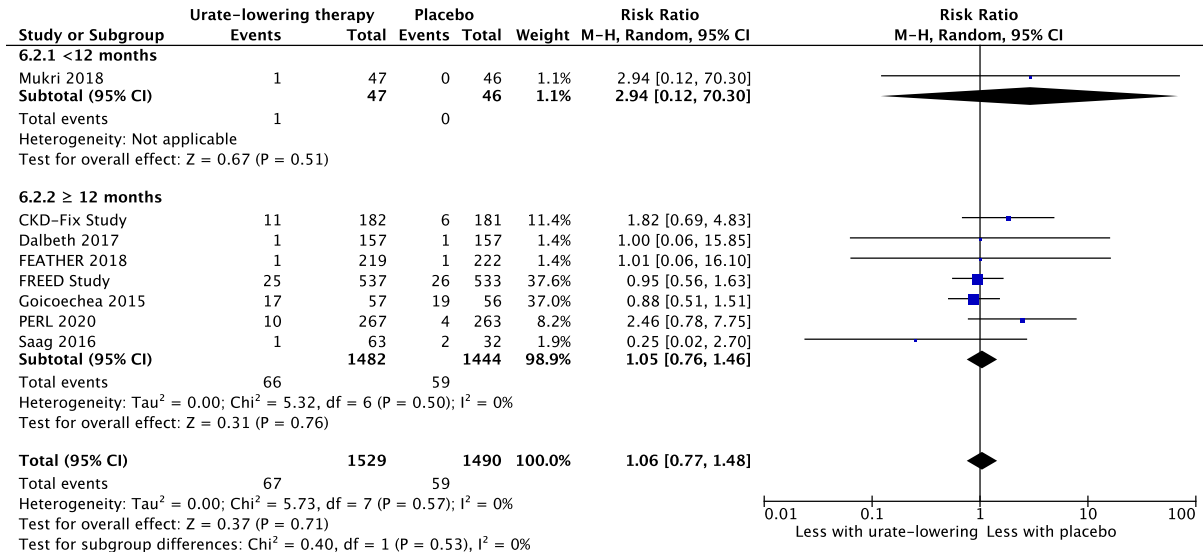
A. Trial duration effect on eGFR change



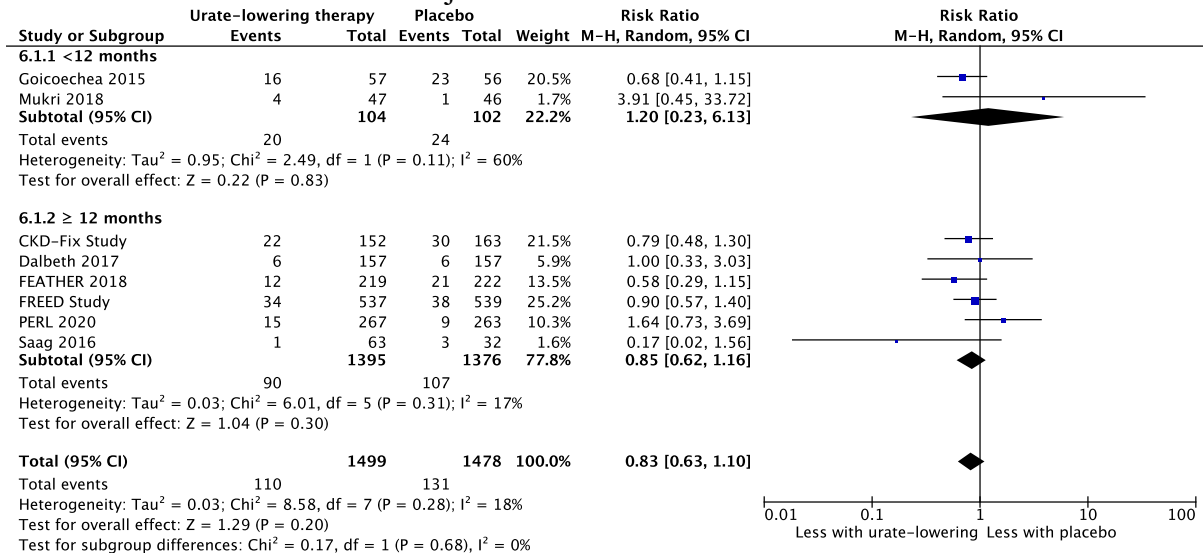
B. Trial duration effect on Kidney Failure



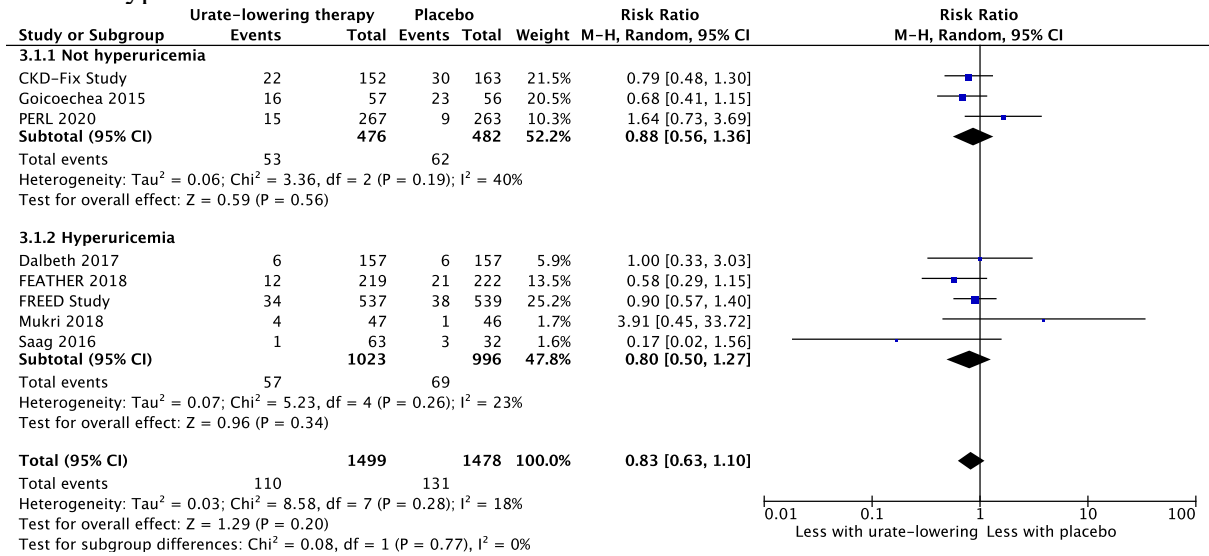
C. Trial duration effect on death



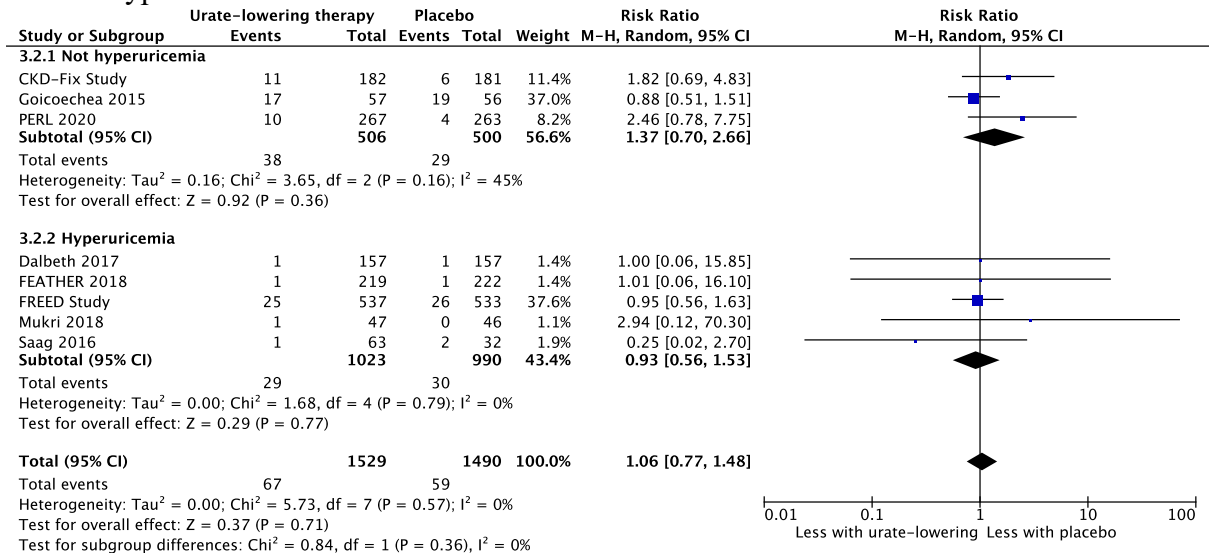
D. Trial duration effect on major adverse cardiovascular events



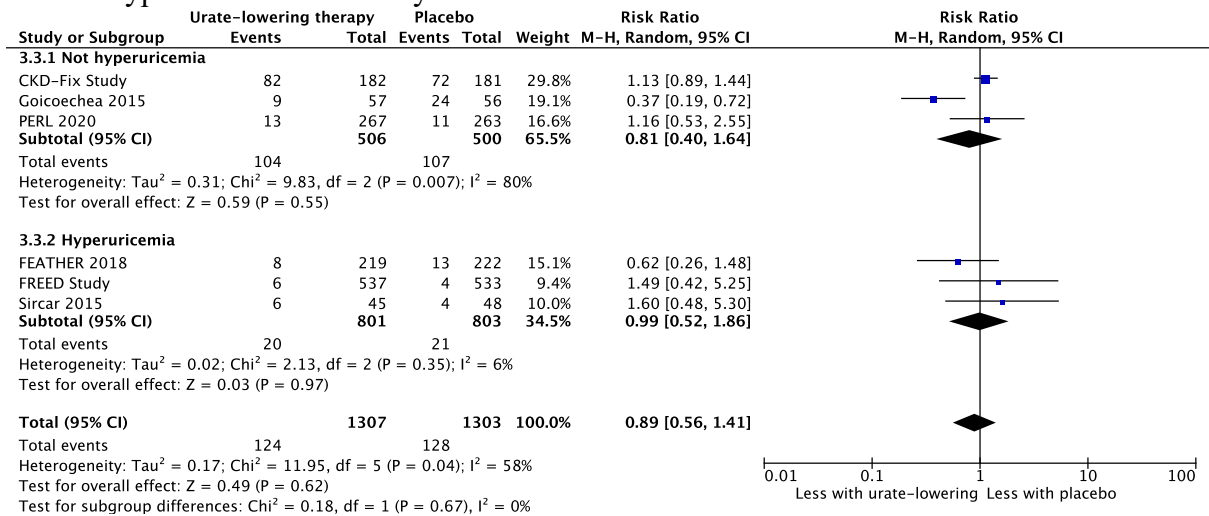
E. Hyperuricaemia on MACE



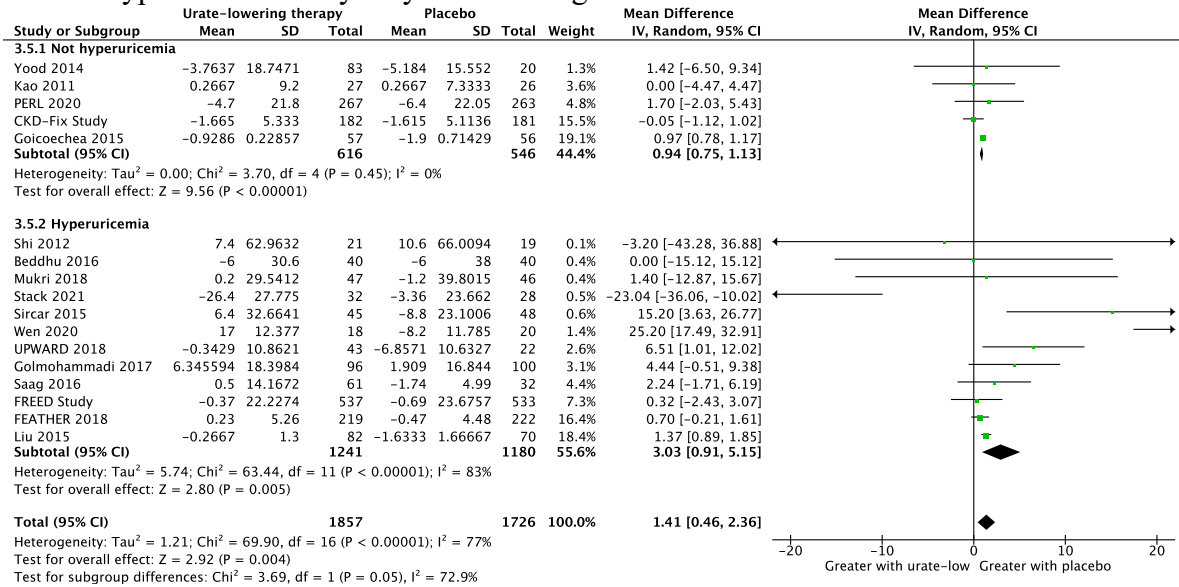
F. Hyperuricemia on Death



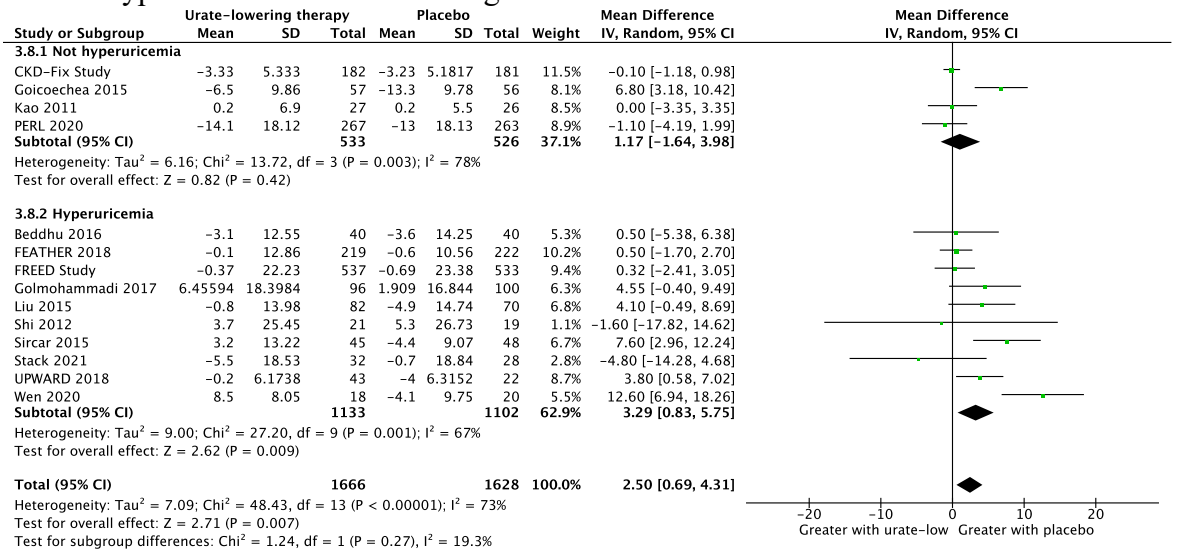
G. Hyperuricemia on kidney failure



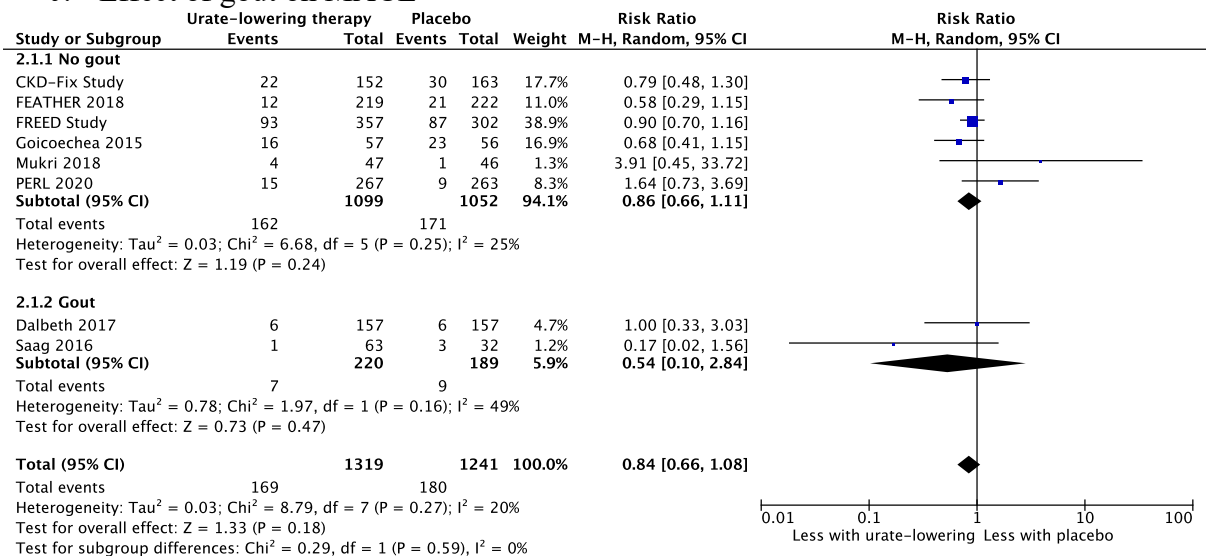
H. Hyperuricemia on yearly eGFR change



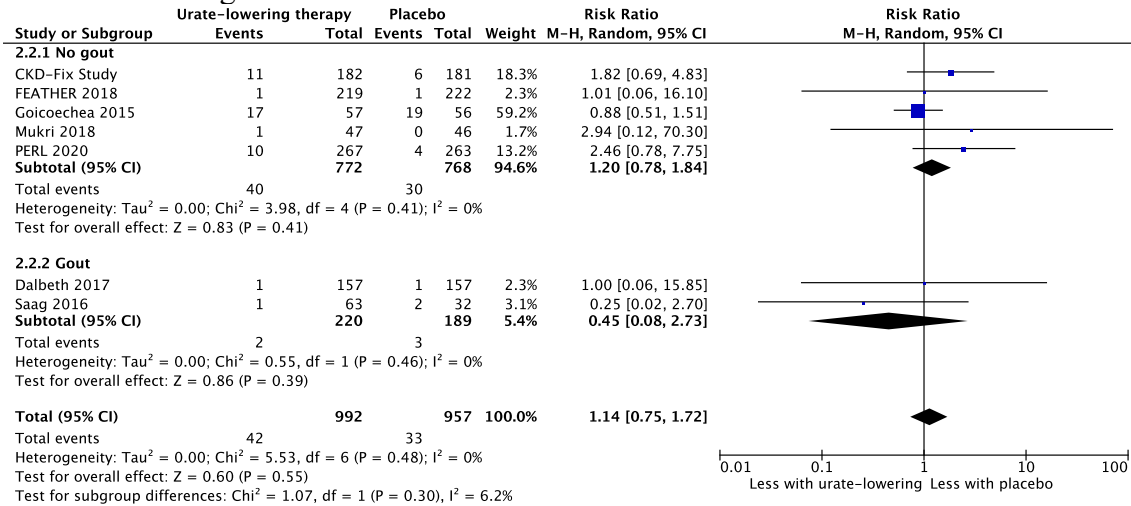
I. Hyperuricemia on eGFR change



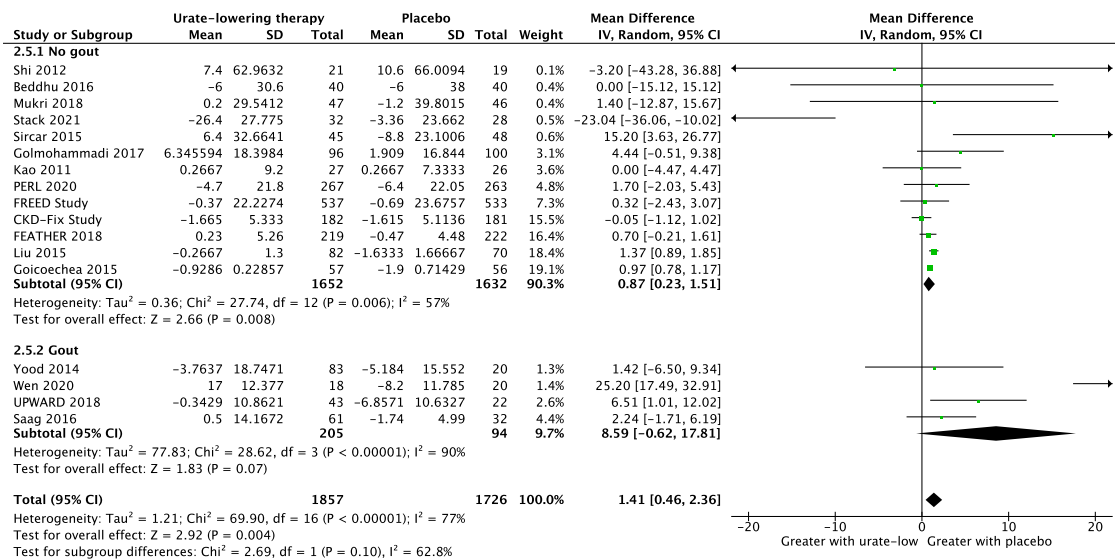
J. Effect of gout on MACE



K. Effect of gout on Death



L. Effect of gout on yearly eGFR change



M. Effect of gout on eGFR change

