SUPPLEMENTARY APPENDIX 8: Evidence Report

2020 American College of Rheumatology Guideline for the Management of Gout

Methods for the evidence synthesis

1. **Question generation**

With the assistance of a methodologist, the core team formulated 57 questions using the Patients, Intervention, Comparison, and Outcomes (PICO) framework, which were classified in 6 topics

1. Indications for ULT (5 questions)
2. Approaches to initiating ULT (7 questions)
3. Ongoing management of ULT in gout (18 questions)
4. Gout flares (10 questions)
5. Lifestyle in patients with gout (9 questions)
6. Lifestyle in patients with asymptomatic hyperuricemia (8 questions)

The core team formulated the questions considering relevant clinical problems, and chose the outcomes using a patient-centered perspective.

2. **Outcome prioritization**

The core team brainstormed about all the potentially relevant outcomes for decision-making, and prioritized those that were considered critical or important, relative to the other outcomes.[1]

For each outcome, the core team generated a hierarchy for the methods of measurement and reporting. In addition, they chose time points of measurement that would be the most informative.

3. **Eligibility criteria**

Eligibility criteria regarding patients, interventions, and comparators varied across questions, and matched the patients and interventions specified in each question. We included randomized clinical trials and any type of observational study that presented data relevant to the comparisons of interest. We only included studies published in full (in other words, we did not include studies published only as conference abstracts). We only included studies published in English language. We allowed departures from the eligibility criteria when- after study

selection- there was no evidence for specific questions, and the core team believed that case series, or studies conducted in slightly different populations would be useful to inform such questions.

4. Search for evidence

We conducted searches in Medline and Embase up to September 2018. A librarian created one search string for each of the electronic databases. The searches were sensitive, and targeted relevant evidence for all the questions. We did not limit by year of publication.

5. Study selection

Two reviewers screened all the references of potentially relevant articles, in duplicate and independently. In a first stage, reviewers used the tiles and abstracts to identify whether each article matched any of the patients, interventions, and type of studies of interest. A third reviewer resolved disagreements and finalized the list of studies selected for the second stage.

In a second stage, pairs of reviewers screened the full texts of all the potentially relevant articles, independently. For each article, they identified whether the study matched a population and comparison of interest, whether it was an eligible type of study, and whether it reported an outcome of interest. Studies that met all eligibility criteria were included. A third reviewer resolved disagreements when necessary. These first two stages were performed using the software DistillerSR.[2]

In a third stage, a reviewer read each of the included articles, and matched them to each of the questions. Studies could be matched to more than one question.

Finally, the core team reviewed the list of included studies per question, as well as the list of excluded studies, to ensure completeness of the body of evidence. For some questions for which there was no evidence, the core team suggested including specific studies that were considered as presenting relevant evidence.

6. Data abstraction and risk of bias assessment.

Reviewers underwent 1-2 rounds of calibration before conducting data abstraction and assessment of risk of bias.

For each study, we abstracted data regarding the population at baseline (inclusion and exclusion criteria, methods for diagnosing gout or asymptomatic hyperuricemia, age, sex, duration of gout, tophi, number of flares in the previous year, serum urate levels, and body mass index); the intervention and comparator (drug, regimen, cointerventions); and the outcomes.

For each outcome, we abstracted data according to the hierarchy of methods of measurement created by the core team. Thus, if a study reported the same outcome in more than one way (for example, serum urate as the proportion of people achieving serum urate < 6 mg/dL and as the mean change on serum urate levels from baseline), we only abstracted information for the method listed highest in the hierarchy (proportion of people achieving serum urate < 6 mg/dL).

We assessed risk of bias of randomized clinical trials using the Cochrane Risk of Bias tool.[3] We assessed risk of bias of observational studies using the ROBINS-I tool.[4]

7. Measures of effect

We used the risk ratio for dichotomous outcomes whenever randomized controlled trials or cohort studies were available. We only used the odds ratio when there were case-control studies or when the researchers only provided this information. For questions in which the rate of serious adverse events 0 in both arms, and this could not be analyzed as the risk ratio, we used the risk difference

We used the mean difference for continuous outcomes. Depending on the specific outcome and on the reporting of the studies, we used the mean difference at follow up (i.e. differences between the mean scores of each group at a specific time point) or the mean difference in change from baseline (i.e. differences between the mean change from baseline of each group at a specific time point). For questions in which researchers used different scales to measure the same outcome, we used the standardized mean difference.

We used hazard ratio when this was the only information provided by the researchers.

8. Data analysis

We combined the results of different studies through meta-analysis whenever possible. We used a frequentist framework, and random effects models when pooling results from different studies. We used fixed effects models when pooling data from different subgroups from the same study. We conducted meta-analyses using the software Revman.[5]

We used network meta-analysis (NMA) to include direct and indirect evidence to address two questions (Question 10 and question 32) in which there were more than two interventions of interest. We conducted network meta-analyses using a frequentist framework and a random-effects model. We used the package *netmeta* in the software R.[6]

9. Assessment of quality of the evidence

For each outcome, we assessed the quality of the evidence using GRADE.[7] GRADE classifies the quality of the evidence in 4 categories: high, moderate, low, or very low. For questions about the effect of interventions, bodies of evidence from randomized clinical trials start the assessment as high and observational studies start it as low. The quality of the evidence can be further reduced owing to serious or very serious concerns of risk of bias (limitations in study design), inconsistency, indirectness, imprecision, and publication bias.

For the evidence from NMA, in addition, we considered what source of evidence contributed to the network estimate the most (direct versus indirect), intransitivity issues when the estimates were calculated mostly based on indirect evidence, and incoherence between direct and indirect evidence.[8, 9]

The lowest level of evidence for the outcomes deemed critical to patients determined the quality of evidence for each PICO. On the basis of input from the patient panel and prior guidance from the GRADE working group, the panel made the following decisions. For any of the 3 critical outcomes, SU, gout flare or tophi, if moderate or high quality of evidence demonstrated improvement, we deemed this sufficient evidence to support the recommendation - and thus designated this outcome as critical. Evidence from the other two outcomes, being therefore unnecessary to support the decision, were designated as important but not critical. We rated quality of evidence using the highest level of evidence from any of the critical outcomes – thus, once one of the outcomes yielded moderate or high quality evidence, lower quality for the other outcomes did not lower the overall evidence quality.

10. Summaries of evidence

For each question, we created Evidence Profiles (EPs)[10] using the software GRADEpro.[11] EPs present a summary of the evidence per outcome, and contain information regarding the number of studies and people providing evidence, relative and absolute estimates of effect comparing the options, and assessment of the quality of the evidence.

Owing to the large amount of information originating from NMAs, EPs have not been implemented for these analyses. We summarized the information at the outcome level by using a novel approach that allows classifying interventions in categories according to their likelihood of being in groups from the most to the least efficacious for each outcome. The judgments that place interventions into categories are based on the presence and magnitude of the differences between pairwise comparisons, and the quality of the evidence.

1: Should ULT vs. No ULT be used in <u>patients with subcutaneous tophi</u> (with any number of gout flares)?

We found 1 study addressing this question, which was published in 3 different articles.[12-14] The researchers compared 2 regimens of pegloticase versus placebo, in a group of patients where the majority had tophi (65% to 75% depending on the group).
The evidence shows:

- Patients who receive ULT may have a higher probability of tophi resolution after 13 weeks than those who do not receive it.
- Patients who receive ULT probably have a higher probability of tophi resolution after 6 months than those who do not receive it.
- Patients who receive ULT probably have a lower mean number of tophi after 24 weeks than those who do not receive it.
- Patients who receive ULT probably have a higher mean of gout flares up to 3 months than those who do not receive it.
- There is probably no difference in the mean number of flares from 4 to 6 months between patients who receive ULT and those who do not receive it.
- Patients who receive ULT are more likely to achieve SUA levels 6 mg/dL at 6 months than those who do not receive ULT.
- Patients who receive ULT are likely to have a higher probability of an improvement in pain higher than a minimally important difference, at 25 weeks than those who do not receive it.
- Patients who receive ULT are likely to have a higher probability of an improvement in patient global assessment higher than a minimally important difference, at 25 weeks than those who do not receive it.
- Patients who receive ULT are likely to have a higher probability of an improvement in health-related quality of life higher than a minimally important difference, at 25 weeks than those who do not receive it.
- Patients who receive ULT experience a higher improvement in activity limitation at 25 weeks, than those who do not receive it.
- Patients who receive ULT probably experience more serious adverse events at 6 months than those who do not receive ULT.

The overall quality of the evidence is HIGH
When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is MODERATE

Note: The recommendation associated to this question may also be informed by the evidence in question 10. Studies included in that question were not performed in the subpopulation of interest, however.

Table 1: Evidence profile

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With No ULT	With ULT		Risk with No ULT	Risk difference with ULT
Tophus* (follow up: mean 13 weeks; assessed with: Patients with complete tophi resolution)											
123 (2 RCTs)	not serious	not serious	not serious	very serious [a]	none	⨁⨁◯◯ LOW	0/29 (0.0%)	14/94 (14.9%)	**RR 4.50** (0.61 to 33.09)	0 per 1,000	**140 more per 1,000** (10 more to 270 more)
Tophus (follow up: mean 6 months; assessed with: Patients with complete tophi resolution)**											
131 (2 RCTs)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	2/27 (7.4%)	32/104 (30.8%)	**RR 4.11** (1.05 to 16.12)	74 per 1,000	**230 more per 1,000** (4 more to 1,120 more)
Tophus (follow up: mean 24 weeks; assessed with: Mean tophi per patient)**											
142 (2 RCTs)	not serious	not serious	not serious	serious [d]	none	⨁⨁⨁◯ MODERATE	In one study, the mean number of tophi per patient was 3.7 in those who received pegloticase 8mg every two weeks, 3.6 in those who received pegloticase 8 mg every four weeks, and 4.0 in those who received placebo. Patients who received pegloticase 8 mg every two weeks had an average of 0.3 less tophi than those who received placebo; and patients who received pegloticase 8 mg every four weeks had an average of 0.4 less tophi than those who received placebo. A statistical analysis was not done due to lack of data.				

Gout flares* (follow up: range 1 months to 3 months; assessed with: Mean rate per patient)

212 (2 RCTs)	not serious	not serious	not serious	serious [e]	none	⨁⨁⨁◯ MODERATE	43	169	-	The mean gout flares** was **1.2** flares	MD **1.29 flares more** (0.7 more to 1.87 more)

Gout flares (follow up: range 4 months to 6 months; assessed with: Mean rate per patient)**

181 (2 RCTs)	not serious	not serious	not serious	serious [e]	none	⨁⨁⨁◯ MODERATE	43	138	-	The mean gout flares** was **1.3** flares	MD **0.19 flares fewer** (0.71 fewer to 0.33 more)

Serum urate (follow up: mean 6 months; assessed with: Patients with SUA <6mg/dL)**

212 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	0/43 (0.0%)	65/169 (38.5%)	**RR 9.13** (2.33 to 35.87)	0 per 1,000	**390 more per 1,000** (290 more to 490 more)

Pain* (follow up: mean 25 weeks; assessed with: Patients with improvement higher than minimally clinically important difference in Pain)

159 (2 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	14/37 (37.8%)	60/122 (49.2%)	**RR 1.30** (0.83 to 2.04)	378 per 1,000	**114 more per 1,000** (64 fewer to 394 more)

Patient Global Assessment* (follow up: mean 25 weeks; assessed with: Patients with improvement higher than minimally clinically important difference in Patient Global Assessment)

142 (2 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	10/35 (28.6%)	56/107 (52.3%)	**RR 1.83** (1.05 to 3.19)	286 per 1,000	**237 more per 1,000** (14 more to 626 more)

Health related quality of life* (follow up: mean 25 weeks; assessed with: Patients with improvement higher than minimally clinically important difference)

158 (2 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	11/38 (28.9%)	75/120 (62.5%)	**RR 2.14** (1.28 to 3.59)	289 per 1,000	**330 more per 1,000** (81 more to 750 more)

Activity Limitation* (follow up: mean 25 weeks; assessed with: mean change in Health Assessment Questionnaire-Disability Index score; Scale from: 0 to 3)

159 (2 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	37	122	-		MD **0.23 points lower** (0.38 lower to 0.08 lower)

Serious adverse events* (follow up: mean 6 months)

212 (2 RCTs)	not serious	not serious	not serious	serious [a]	none	⊕⊕⊕◯ MODERATE	5/43 (11.6%)	39/169 (23.1%)	**RR 1.99** (0.83 to 4.74)	116 per 1,000	**115 more per 1,000** (20 fewer to 435 more)

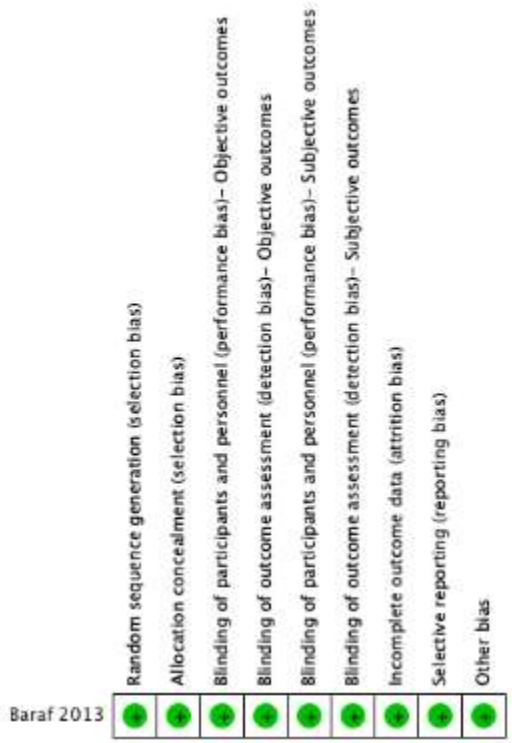
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

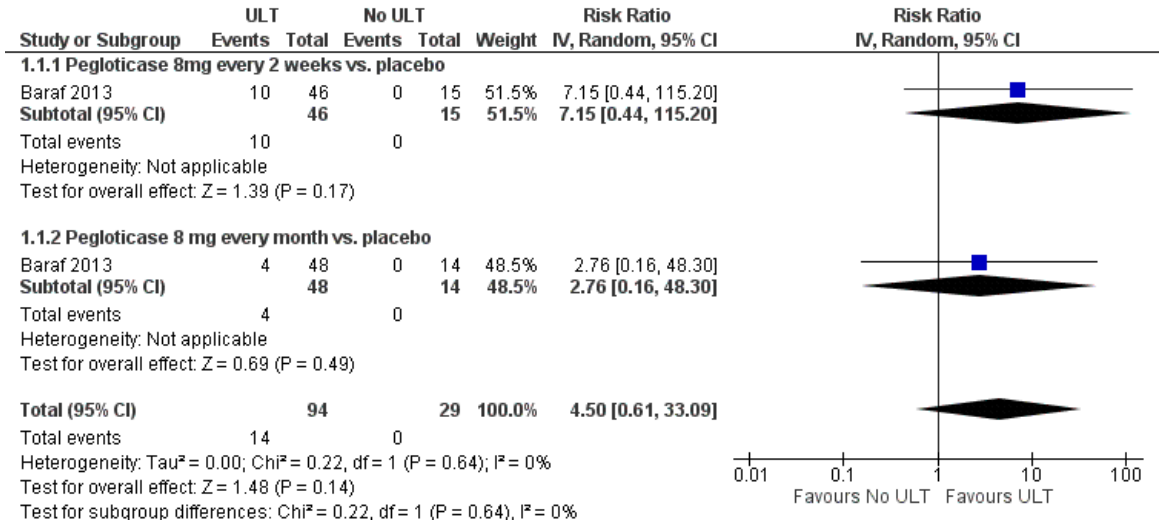
Explanations

a. The confidence interval suggests the possibility of important benefit as well as important harm. The number of participants included in the study, and the number of events are not large enough to make sound conclusions
c. The number of events and participants is not sufficient to make sound conclusions
d. The number of participants included in the study is not large enough to make sound conclusions
e. The confidence interval suggests the possibility of benefit and harm

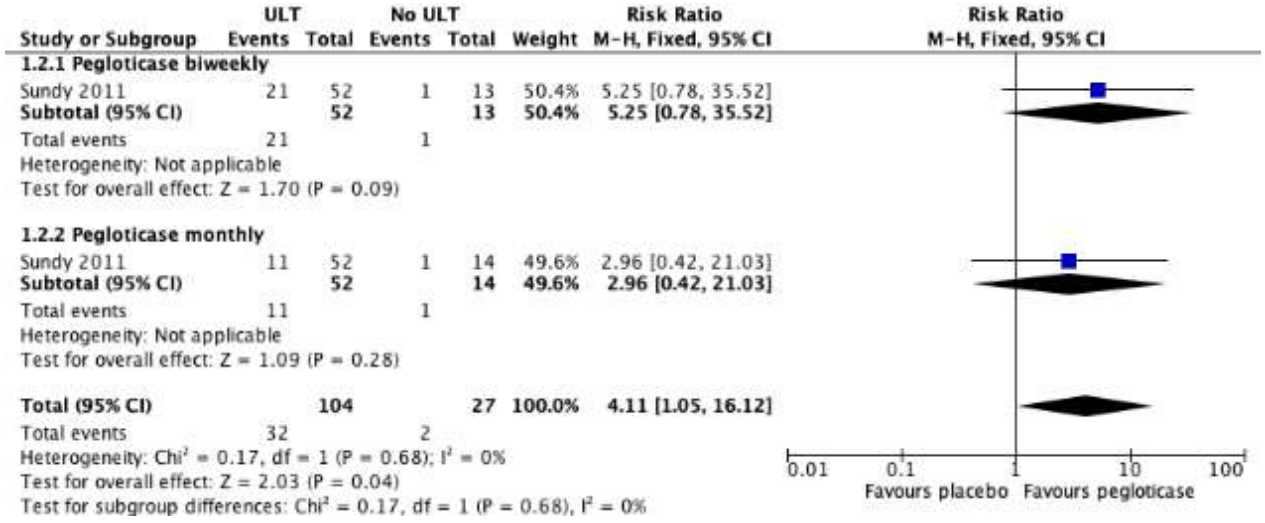
Outcome importance:
** Critical outcomes
* Important outcomes

Figure 1: Risk of bias assessment

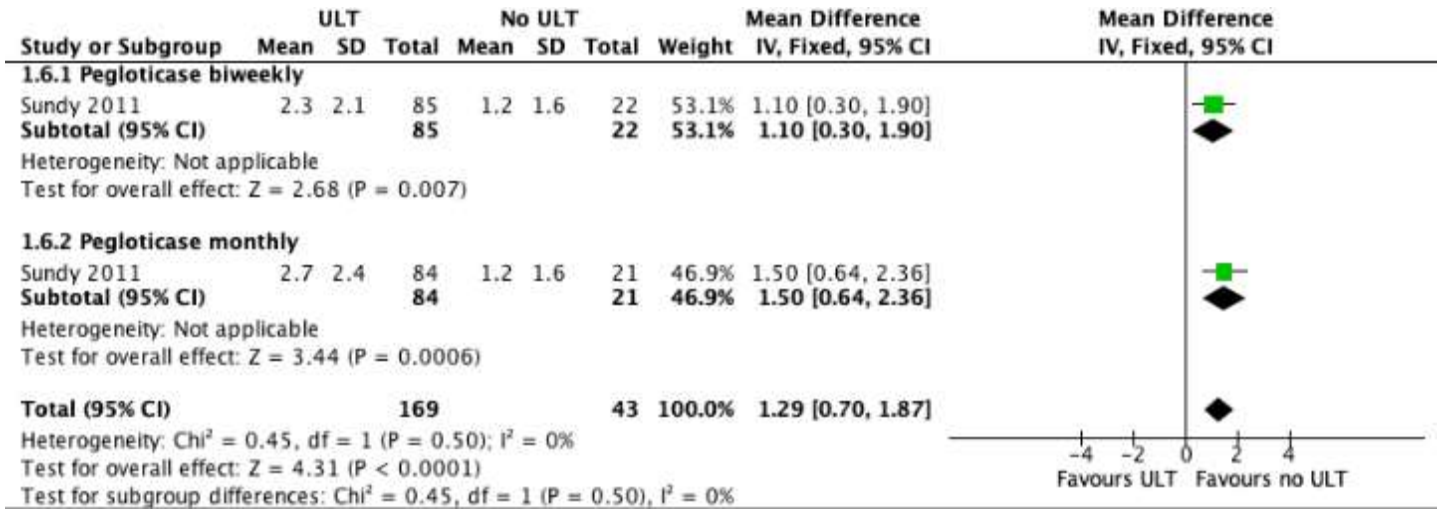




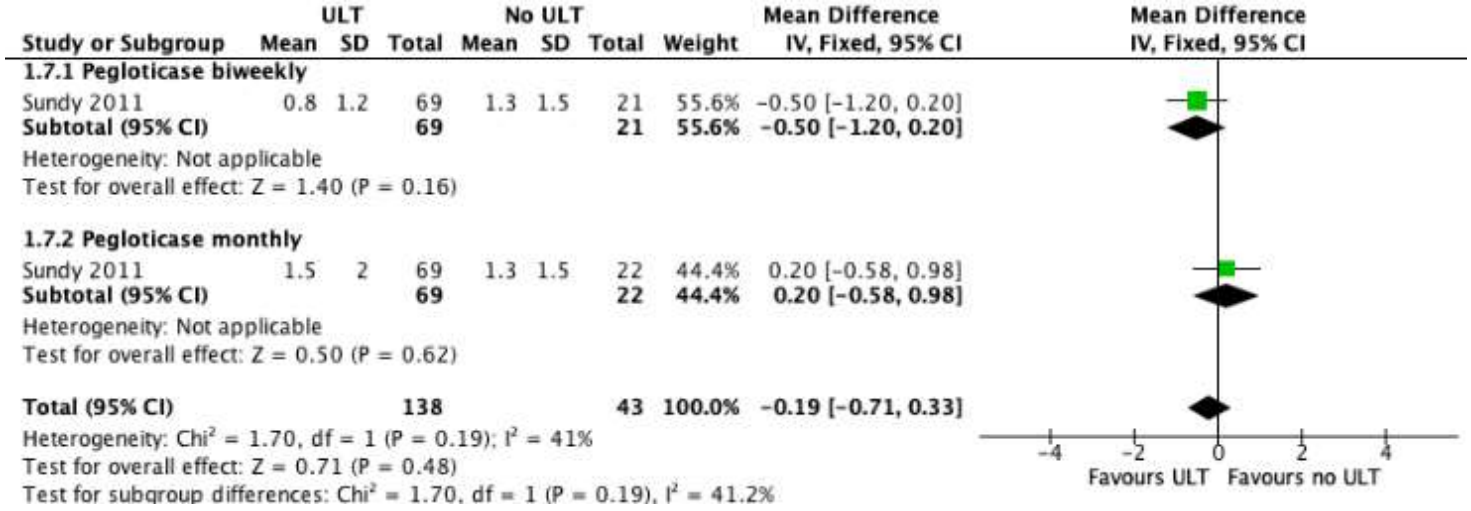
Forest plot of comparison: 1 ULT vs. No ULT, outcome: 1.1 Tophus complete resolution at 13 weeks (closest to 3 months).



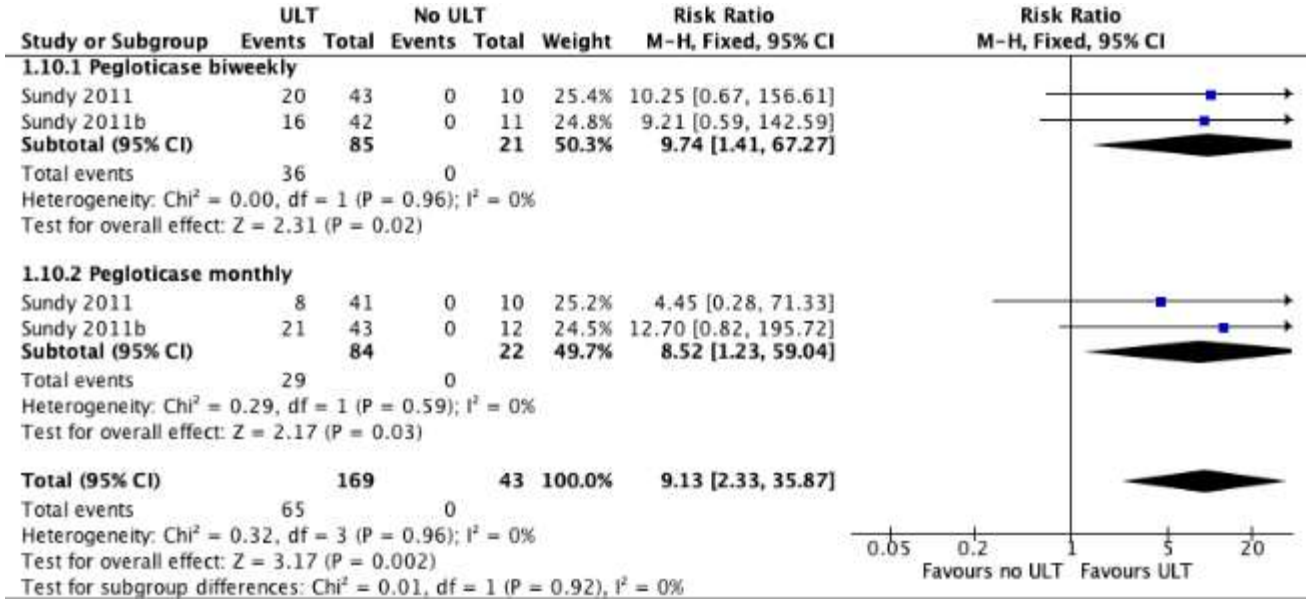
Forest plot of comparison: 1 ULT vs. No ULT, outcome: 1.2 Tophus complete resolution at 6 months.



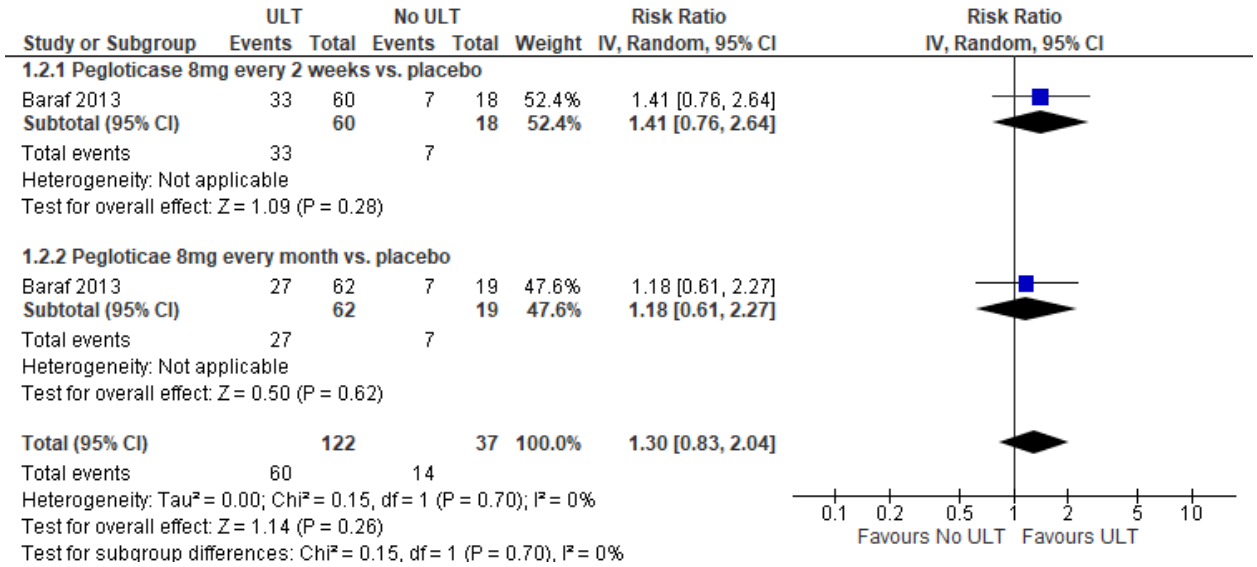
Forest plot of comparison: 1 ULT vs. No ULT, outcome: 1.3 Mean gout flares per patient from 1-3 months



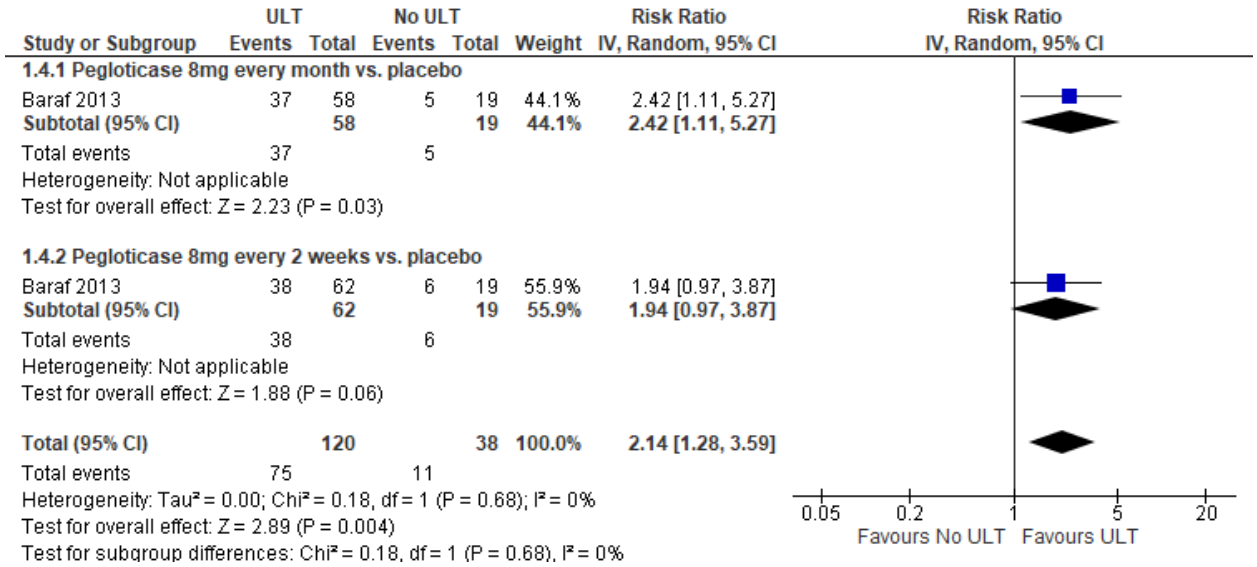
Forest plot of comparison: 1 ULT vs. No ULT, outcome: 1.4 Mean gout flares per patient from 4-6 months



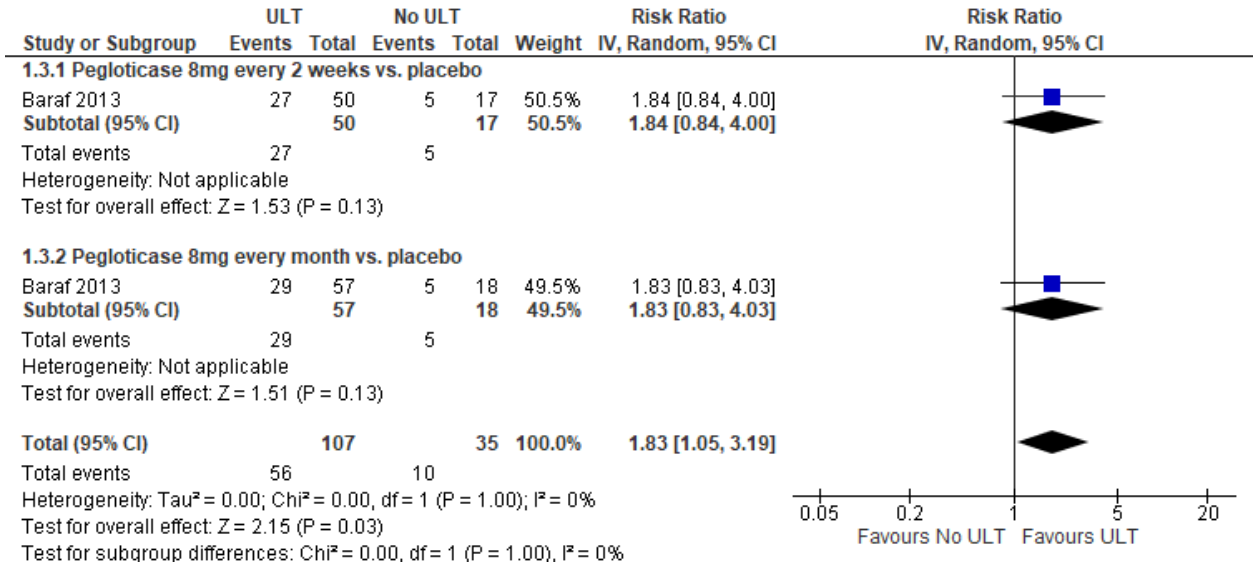
Forest plot of comparison: 1 ULT vs. No ULT, outcome: 1.5 Serum urate- proportion of patients with SUA<6.0mg/dL



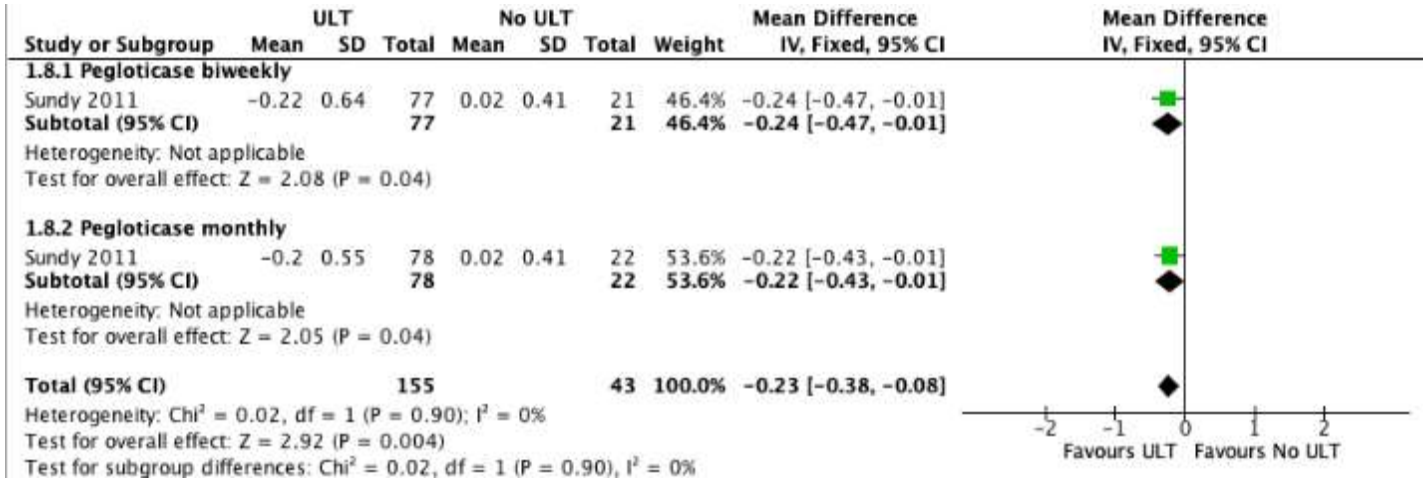
Forest plot of comparison: 1 ULT vs. No ULT, outcome: 1.6 Pain - Number of patients with minimally clinically important improvements from baseline pain at week 25.



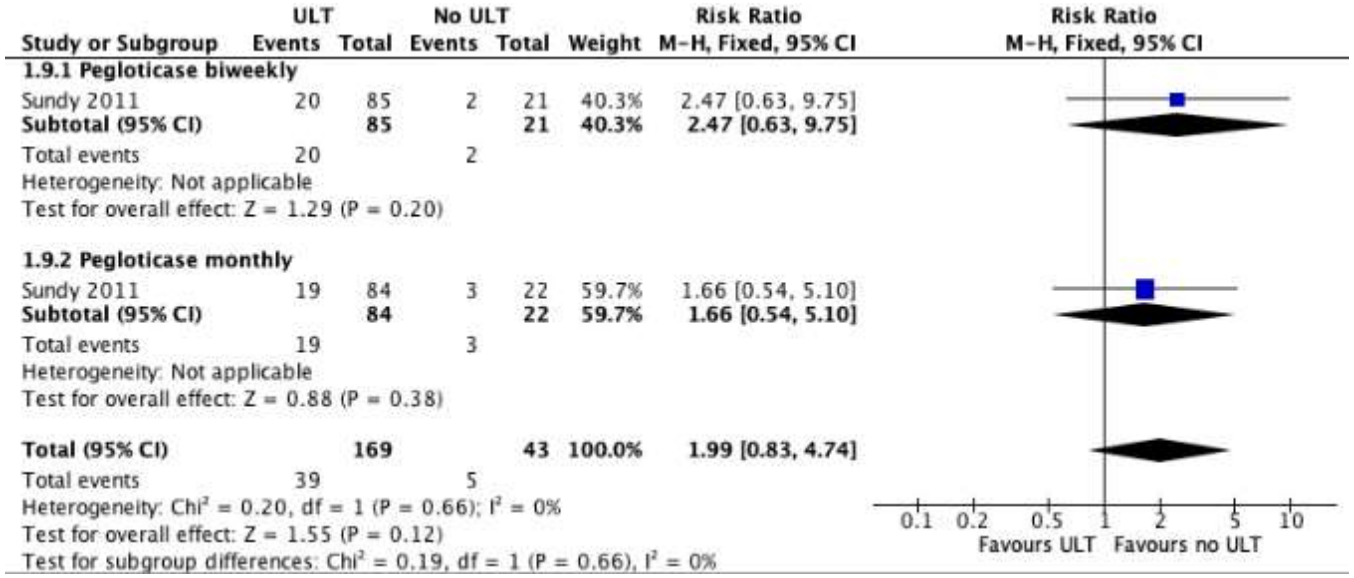
Forest plot of comparison: 1 ULT vs. No ULT, outcome: 1.7 Health related quality of life: number of patients with minimally clinically important improvements from baseline pain at week 25.



Forest plot of comparison: 1 ULT vs. No ULT, outcome: 1.8 Patient Global Assessment - Number of patients with minimally clinically important improvements from baseline pain at week 25.



Forest plot of comparison: 1 ULT vs. No ULT, outcome: 1.9 Mean change in activity limitation score up to 25 weeks.



Forest plot of comparison: 1 ULT vs. No ULT, outcome: 1.10 Serious adverse events up to 6 months.

2: Should ULT versus no ULT be used in patients with radiographic damage due to gout but no subcutaneous tophi on exam?

There were no studies addressing this question. The core team advised to use to information from PICO 10 to inform this recommendation, specifically the information regarding how different ULTs compare to placebo.

The evidence shows that patients with subcutaneous tophi:

- Who start any ULT are probably more likely to achieve serum urate levels <6 mg/dL than those who do not start ULT, up to 2 years
- Who start any ULT may not have a higher risk of any serious adverse events or cardiovascular adverse events than those who do not start ULT, up to 2 years
- Who start febuxostat are probably less likely to experience 1+ gout flares than those who do not start ULT, up to 2 years
- Who start febuxostat or febuxostat + lesinurad have a higher probability of experiencing 1+ gout flares than those who do not start ULT, in the first 3 months.
- Who start allopurinol may not have a different risk of gout flares than those who do not start ULT, in the first 3 months and up to 2 years
- Who start probenecid may not have a different risk of gout flares than those who do not start ULT, in the first 3 months
- Probably have a higher likelihood of achieving serum urate levels <6 mg/dL than those who do not start ULT, up to 2 years
- Who start pegloticase may have a different probability of tophi resolution than those who do not start ULT, up to 6 months

The overall quality of the evidence is MODERATE
When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is LOW

Table 1: Summary of information about ULT versus placebo from network meta-analysis from PICO 10

Treatment versus placebo	Critical outcomes			Important outcomes			Highest level among critical outcomes
	Flares longest follow up	Tophus	Serum urate	Flares up to 3 months	SAEs	SAEs- CV	
Allopurinol							MODERATE
Allopurinol + lesinurad							MODERATE
Fabuxostat							MODERATE
Febuxostat + lesinurad							MODERATE
Pegloticase							MODERATE
Probenecid							VERY LOW
	Better, moderate quality	Not different, moderate quality	Not different, low or very low quality	Worse,moderate quality			

3: Should ULT vs. No ULT be used in patients <u>without subcutaneous tophi and with frequent gout flares</u> (two or more/year)?

We found 1 study addressing this question.[15] The researchers enrolled 214 participants and compared the effects of lesinurad versus placebo. The participants' mean number of flares per year was 6, and 75% of them did not have tophi.
The evidence shows:

- Patients without subcutaneous tophi but with frequent gout flares (>=2/year) who receive ULT
    - Have a higher proportion reaching serum urate levels lower than 6 mg/dL is higher than in those who do not receive ULT, after 6 months.
    - May have a lower proportion experiencing 1 or more gout flares than in those who do not receive ULT, after 6 months.
    - May have higher proportion with serious adverse events overall, and renal serious adverse events than in those who do not receive ULT, up to 6 months.
    - May have little to no difference in the proportion with cardiovascular serious adverse events compared with those who do not receive ULT, up to 6 months.

The overall quality of the evidence is HIGH
When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is HIGH

Note: the recommendation associated to this question may also be indirectly informed by the evidence in question 10. The studies in that question, however, did not include the subpopulation of interest.

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With No urate lowering therapy	With Urate lowering therapy	Relative effect (95% CI)	Risk with No urate lowering therapy	Risk difference with Urate lowering therapy
Serum urate* (follow up: mean 6 months; assessed with: Patients with SUA less than 6.0 mg/dL)											
214 (1 RCT)	not serious [a]	not serious	not serious	serious [b]	none	⨁⨁⨁⨁ HIGH	2/107 (1.9%)	32/107 (29.9%)	**RR 16.00** (3.93 to 65.09)	19 per 1,000	**280 more per 1,000** (55 more to 1,198 more)
Gout flares (follow up: range 5 months to 6 months; assessed with: Patients with gout flares)**											
178 (1 RCT)	serious [c]	not serious	not serious	serious [d]	none	⨁⨁◯◯ LOW	14/94 (14.9%)	10/84 (11.9%)	**RR 0.80** (0.38 to 1.70)	149 per 1,000	**30 fewer per 1,000** (92 fewer to 104 more)
Serious Adverse Events* (follow up: mean 6 months; assessed with: Investigator determined serious treatment related adverse event)											
214 (1 RCT)	not serious [a]	not serious	not serious	very serious [d]	none	⨁⨁◯◯ LOW	4/107 (3.7%)	9/107 (8.4%)	**RR 2.25** (0.71 to 7.08)	37 per 1,000	**47 more per 1,000** (11 fewer to 227 more)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Serious adverse events (Renal)* (follow up: mean 6 months; assessed with: % of patients with sCr elevation ≥ 1.5 times)											
214 (1 RCT)	not serious [a]	not serious	not serious	very serious [d]	none	⨁⨁◯◯ LOW	0/107 (0.0%)	26/107 (24.3%)	**RR 53.00** (3.27 to 858.67)	0 per 1,000	**240 more per 1,000** (160 more to 330 more)
Serious adverse events (Renal)* (follow up: mean 6 months; assessed with: Nephrolithiasis)											
214 (1 RCT)	not serious [a]	not serious	not serious	very serious [d]	none	⨁⨁◯◯ LOW	0/107 (0.0%)	1/107 (0.9%)	**RR 3.00** (0.12 to 72.83)	0 per 1,000	**10 more per 1,000** (20 fewer to 30 more)
Serious adverse events (Cardiovascular)* (follow up: mean 6 months; assessed with: Composite cardiovascular event and stroke)											
214 (1 RCT)	not serious [a]	not serious	not serious	very serious [d]	none	⨁⨁◯◯ LOW	1/107 (0.9%)	1/107 (0.9%)	**RR 1.00** (0.06 to 15.78)	9 per 1,000	**0 fewer per 1,000** (9 fewer to 138 more)
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Evidence profile

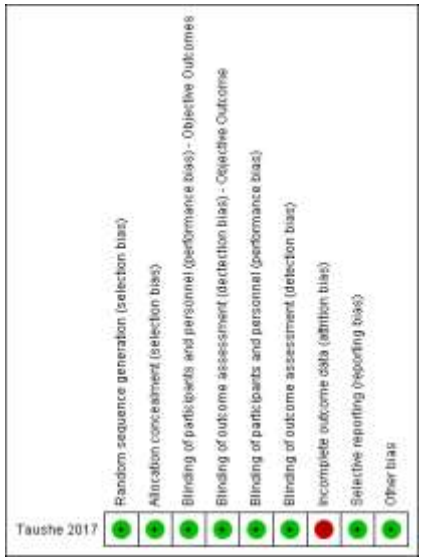
Certainty assessment							Summary of findings				
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events (hypersensitivity)* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

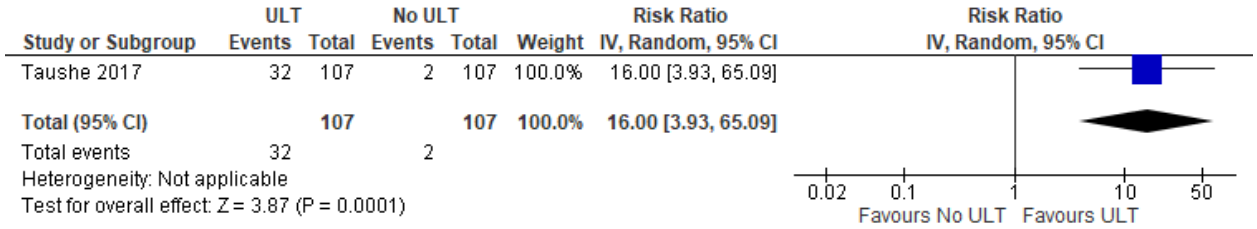
CI: Confidence interval; **RR:** Risk ratio

Explanations

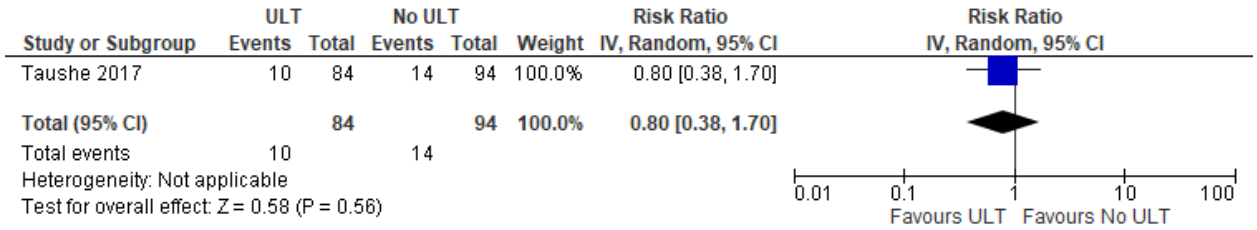
a. Even though there was high risk of attrition bias in this study, it did not affect this outcome
b. The number of participants and events is not sufficient to make sound conclusions, but the experts agreed that they are still confident in the presence of an effect
c. The study had a high risk of attrition bias
d. The confidence interval suggests the possibility of important benefit and important harm. The number of events and participants was not sufficient to make sound conclusions
Outcome importance:
** Critical Outcomes
* Important outcomes

Figure 1: Risk of bias assessment

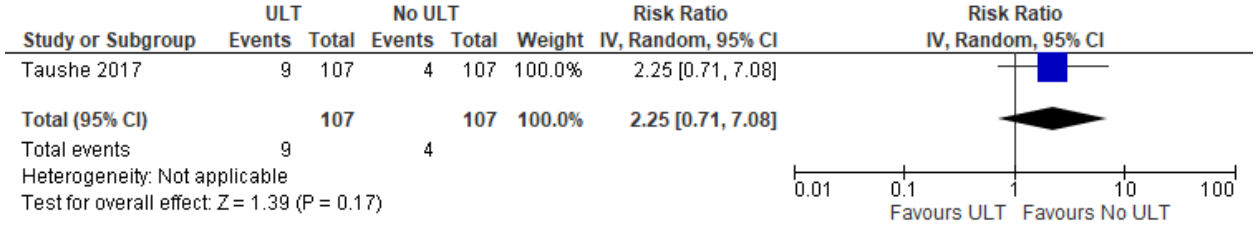




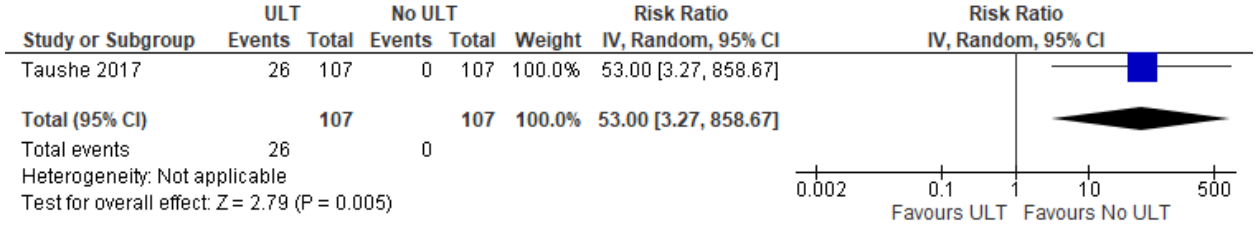
Forest plot of comparison: 1 ULT versus No ULT, outcome: 1.1 Percentage of patients with SUA <6.0 mg/dL at 6 months.



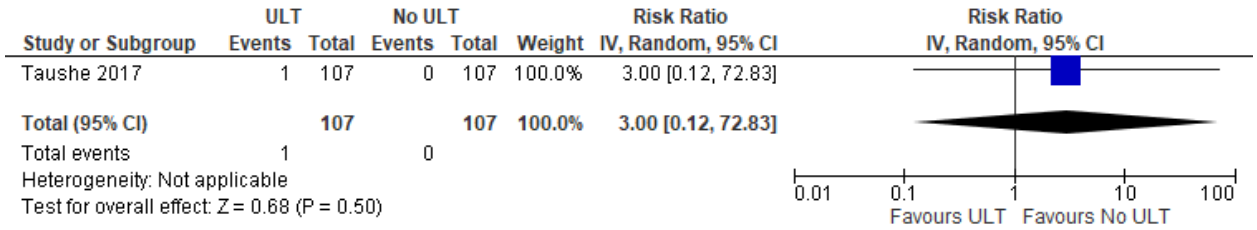
Forest plot of comparison: 1 ULT versus No ULT, outcome: 1.2 Percentage of patients with gout flare during month#6.



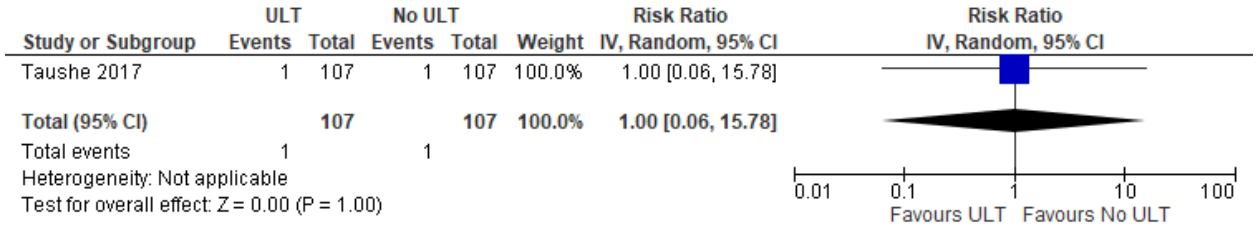
Forest plot of comparison: 1 ULT versus No ULT, outcome: 1.3 Serious Adverse Event



Forest plot of comparison: 1 ULT versus No ULT, outcome: 1.4 Serious AE (Renal) % of patients with sCr elevation ≥ 1.5 times.



Forest plot of comparison: 1 ULT versus No ULT, outcome: 1.5 Serious AE (Kidney Stones).



Forest plot of comparison: 1 ULT versus No ULT, outcome: 1.6 Serious AE (Cardiovascular).

4: Should Urate lowering therapy vs. No Urate lowering therapy be used in patients without tophi who have experienced more than one flare but have a low frequency (<2/year of flare)?

We found 1 study addressing this question.[16] The researchers enrolled 314 participants, and compared the effects of febuxostat versus placebo. To be eligible, participants could have had at most 1 gout flare in the preceding year. The proportion of participants with tophi was 12%.

The evidence shows:

- Patients without tophi who have experienced more than one flare but have a low frequency (<2/year of flare) who receive ULT:
    - are likely to have a higher probability of achieving serum urate levels <6 mg/dL than patients who do not receive ULTs, at 24 months.
    - are likely to have a lower probability of having at least 1 gout flares than patients who do not receive ULTs, up to 24 months.
    - may not have a different risk of any serious adverse events than those who do not receive ULT, up to 24 months.
    - may not have a different risk of cardiovascular serious adverse events than those who do not receive ULT, up to 24 months.

The overall quality of the evidence is MODERATE

When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is MODERATE

Note: the recommendation associated with this question may also be informed by the evidence presented in question 10. The studies included for that question, however, do not specify including the subpopulation of interest.

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With No Urate lowering therapy	With Urate lowering therapy	Relative effect (95% CI)	Risk with No Urate lowering therapy	Risk difference with Urate lowering therapy
Serum urate (follow up: mean 24 months; assessed with: Patients with SUA < 6.0 mg/dL **											
314 (1 RCT)	serious [a]	not serious	not serious	Not serious [b]	none	⨁⨁⨁◯ MODERATE	9/157 (5.7%)	99/157 (63.1%)	**RR 11.00** (5.77 to 20.98)	57 per 1,000	**573 more per 1,000** (273 more to 1,145 more)
Gout flares (follow up: mean 24 months; assessed with: Participants with at least one gout flare)											
314 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	65/157 (41.4%)	46/157 (29.3%)	**RR 0.71** (0.52 to 0.96)	414 per 1,000	**120 fewer per 1,000** (199 fewer to 17 fewer)
Serious Adverse Events* (follow up: mean 24 months)											
314 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	11/157 (7.0%)	13/157 (8.3%)	**RR 1.18** (0.55 to 2.56)	70 per 1,000	**13 more per 1,000** (32 fewer to 109 more)
Serious Adverse Event (Cardiovascular)* (follow up: mean 24 months)											
314 (1 RCT)	serious [a]	not serious	not serious	serious [b,c]	none	⨁⨁◯◯ LOW	2/157 (1.3%)	3/157 (1.9%)	**RR 1.50** (0.25 to 8.85)	13 per 1,000	**6 more per 1,000** (10 fewer to 100 more)

Table 1: Evidence profile

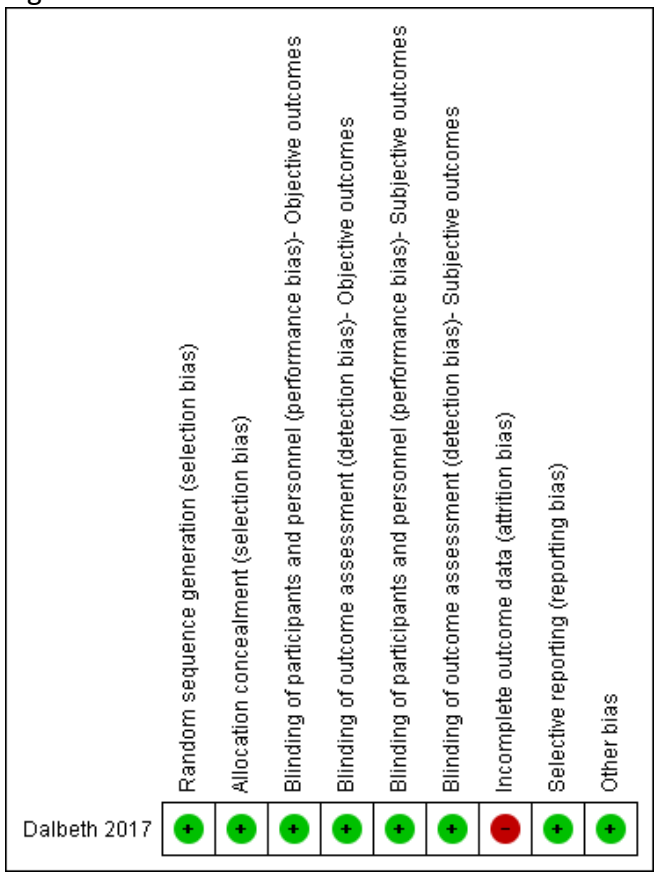
Certainty assessment							Summary of findings				
Pain - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient Global Assessment - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
HRQoL - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity Limitation - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse event (renal, kidney stones, hypersensitivity) - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

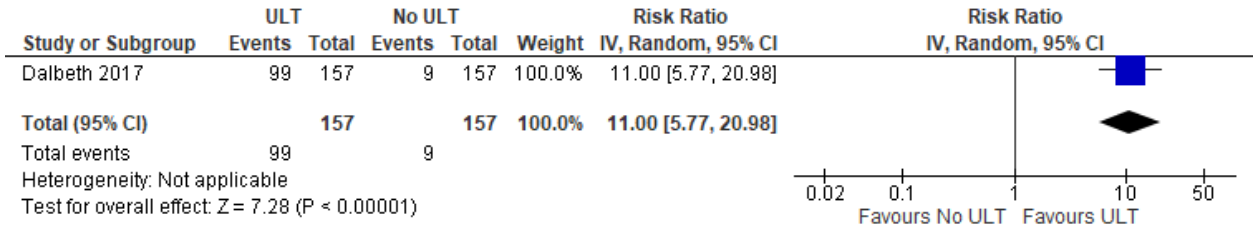
CI: Confidence interval; **RR:** Risk ratio

Explanations

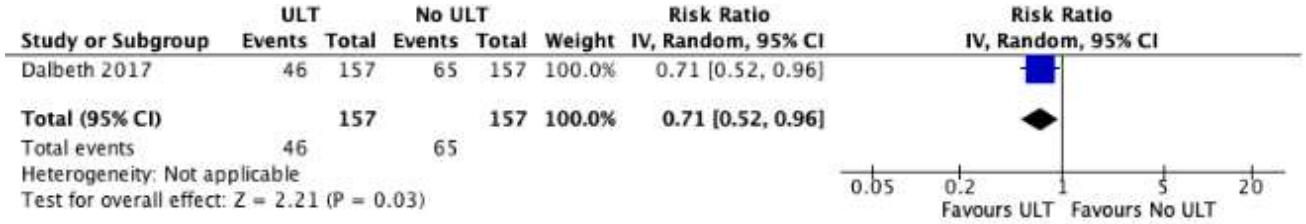
a. Almost half of the participants did not complete the trial
b. The total number of events and participants included in the analysis is insufficient to make sound conclusions, but the experts agreed that they are still confident in the presence of an effect
c. The confidence interval suggests the possibility of important benefit and important harm
Outcome importance:
** Critical outcomes
* Important outcomes

Figure 1: Risk of bias assessment

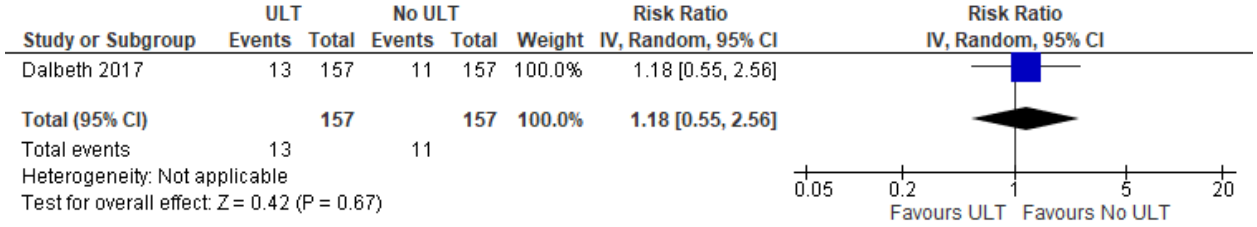




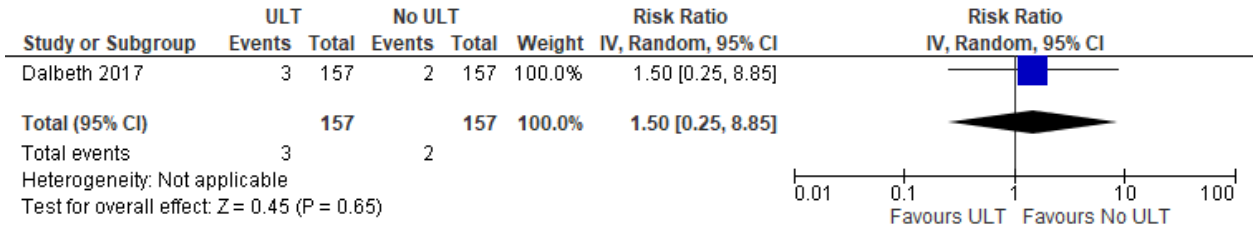
Forest plot of comparison: 1 ULT versus No ULT, outcome: 1.1 SUA < 6mg/dL at 24 months.



Forest plot of comparison: 1 ULT versus No ULT, outcome: 1.2 At least one gout flare within 24 months.



Forest plot of comparison: 1 ULT versus No ULT, outcome: 1.3 Serious Adverse Event at 24 months.



Forest plot of comparison: 1 ULT versus No ULT, outcome: 1.4 Serious Adverse Event (Cardiovascular) at 24 months.

5: Should ULT versus no ULT be used in patients without tophi who have experienced a single gout flare?

There were no studies addressing this question. The core team advised to use to information from PICO 10 to inform this recommendation, specifically the information regarding how different ULTs compare to placebo.

The evidence shows that patients with subcutaneous tophi:

- Who start any ULT are probably more likely to achieve serum urate levels <6 mg/dL than those who do not start ULT, up to 2 years
- Who start any ULT may not have a higher risk of any serious adverse events or cardiovascular adverse events than those who do not start ULT, up to 2 years
- Who start febuxostat are probably less likely to experience 1+ gout flares than those who do not start ULT, up to 2 years
- Who start febuxostat or febuxostat + lesinurad have a higher probability of experiencing 1+ gout flares than those who do not start ULT, in the first 3 months.
- Who start allopurinol may not have a different risk of gout flares than those who do not start ULT, in the first 3 months and up to 2 years
- Who start probenecid may not have a different risk of gout flares than those who do not start ULT, in the first 3 months
- Probably have a higher likelihood of achieving serum urate levels <6 mg/dL than those who do not start ULT, up to 2 years
  Who start pegloticase may not have a different probability of tophi resolution than those who do not start ULT, up to 2 years

The overall quality of the evidence is MODERATE
When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is LOW

Table 1: Summary of information about ULT versus placebo from network meta-analysis from PICO 10

Treatment versus placebo	Critical outcomes			Important outcomes			Highest level among critical outcomes
	Flares longest follow up	Tophus	Serum urate	Flares up to 3 months	SAEs	SAEs- CV	
Allopurinol							MODERATE
Allopurinol + lesinurad							MODERATE
Fabuxostat							MODERATE
Febuxostat + lesinurad							MODERATE
Pegloticase							MODERATE
Probenecid							VERY LOW
	Better, moderate quality	Not different, moderate quality	Not different, low or very low quality	Worse,moderate quality			

6: Should ULT be used during a gout flare vs. after a gout flare has resolved be used in patients diagnosed with gout?

We found 3 studies addressing this question.[17-19] Two of the studies were randomized clinical trials[18, 19] and one was an observational study.[17]
The evidence shows:

- Patients with gout who start ULT during a gout flare
    - May not have a different risk of gout flares than patients who start ULT after the flare has resolved, up to 3 months and 6 months; but we are very uncertain about this evidence
    - May not have a different risk of gout flares than patients who start ULT after the flare has resolved, up to 1 month
    - May experience gout flares of longer duration than patients who start ULT after the flare has resolved, up to 28 days
    - May not have a different probability of achieving serum urate levels <6 mg/dL than patients who start ULT after the flare has resolved, up to 6 months; but we are very uncertain about this evidence
    - Probably experience a higher reduction in serum urate levels than patients who start ULT after the flare has resolved up to 10 days
    - May not have a different risk of having tophi than patients who start ULT after the flare has resolved, up to 6 months; but we are very uncertain about this evidence
    - May not experience different pain levels than patients who start ULT after the flare has resolved, up to 10 days
    - May not have a different risk of serious adverse events than patients who start ULT after the flare has resolved, up to 30 days

The overall quality of the evidence is MODERATE
When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is VERY LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With after a gout flare has resolved	With ULT be used during a gout flare	Relative effect (95% CI)	Risk with after a gout flare has resolved	Risk difference with ULT be used during a gout flare
Gout flares* (follow up: range 8 weeks to 12 weeks; assessed with: proportion of participants with at least one flare)											
580 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	132/457 (28.9%)	38/123 (30.9%)	**OR 1.10** (0.71 to 1.70)	289 per 1,000	**20 more per 1,000** (65 fewer to 120 more)
Gout flares (follow up: mean 36 weeks; assessed with: proportion of participants with at least one flare)**											
580 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	42/457 (9.2%)	15/123 (12.2%)	**OR 1.37** (0.73 to 2.57)	92 per 1,000	**30 more per 1,000** (23 fewer to 115 more)
Gout flares* (follow up: mean 30 days; assessed with: proportion with flare in any joint)											
51 (1 RCT)	not serious	not serious	not serious	very serious [b]	none	⨁⨁◯◯ LOW	3/25 (12.0%)	2/26 (7.7%)	**RR 0.64** (0.12 to 3.52)	120 per 1,000	**43 fewer per 1,000** (106 fewer to 302 more)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Gout flares* (follow up: mean 28 days; assessed with: time from enrollment in study to resolution of acute gout attack (Intention to treat))											
35 (1 RCT)	serious [c]	not serious	not serious	serious [d]	none	⨁⨁◯◯ LOW	19	16	-	The mean gout flares** was **12.53** hours	MD **4.47 hours longer** (0.97 shorter to 9.91 longer)
Serum urate (follow up: mean 36 weeks; assessed with: participants with serum urate <6mg/dL)**											
580 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	300/457 (65.6%)	82/123 (66.7%)	**OR 1.05** (0.69 to 1.60)	656 per 1,000	**11 more per 1,000** (88 fewer to 97 more)
Serum urate (follow up: mean 10 days; assessed with: Mean change in Serum Urate level, mg/dL)**											
86 (2 RCTs)	serious [c]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	41	45	-	The mean serum urate** was **0.48** mg/dL	MD **2.83 mg/dL lower** (3.84 lower to 1.81 lower)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Tophi* (follow up: mean 36 weeks; assessed with: proportion with tophi at follow up)											
580 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	44/457 (9.6%)	11/123 (8.9%)	**OR 0.92** (0.46 to 1.84)	96 per 1,000	**7 fewer per 1,000** (50 fewer to 68 more)
Pain* (follow up: mean 10 days; assessed with: Visual analogue scale or numerical rating score (range 0-10))											
86 (2 RCTs)	serious [c]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	41	45	-	The mean pain* was **0.89**	MD **0.1 lower** (0.58 lower to 0.38 higher)
Serious adverse events* (follow up: mean 30 days; assessed with: Proportion with serious adverse event- death)											
51 (1 RCT)	not serious	not serious	not serious	very serious [b]	none	⨁⨁◯◯ LOW	0/25 (0.0%)	1/26 (3.8%)	**RR 2.89** (0.12 to 67.75)	0 per 1,000	**40 more per 1,000** (60 fewer to 140 more)
Serious adverse events* (follow up: mean 30 days; assessed with: Proportion with serious adverse event- hypersensitivity reaction)											
51 (1 RCT)	not serious	not serious	not serious	very serious [b]	none	⨁⨁◯◯ LOW	1/25 (4.0%)	0/26 (0.0%)	**RR 0.32** (0.01 to 7.53)	40 per 1,000	**27 fewer per 1,000** (40 fewer to 261 more)

Table 1: Evidence profile

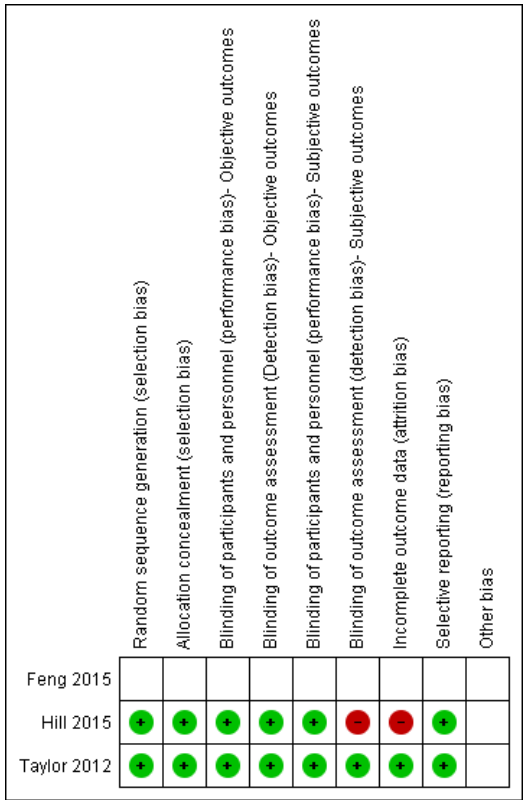
Certainty assessment							Summary of findings				
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity Limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health related quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient adherence* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

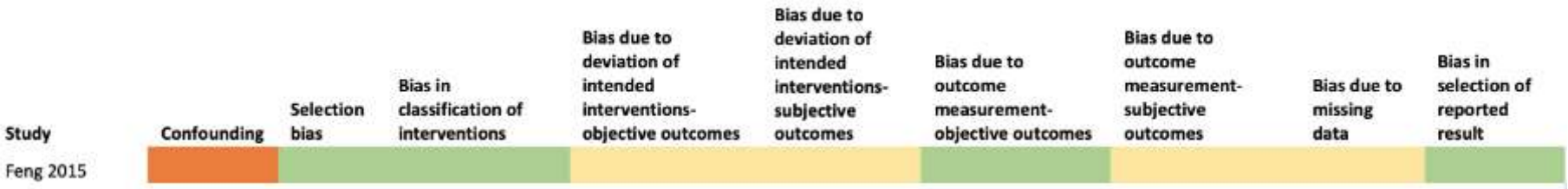
CI: Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio; **MD:** Mean difference

Explanations

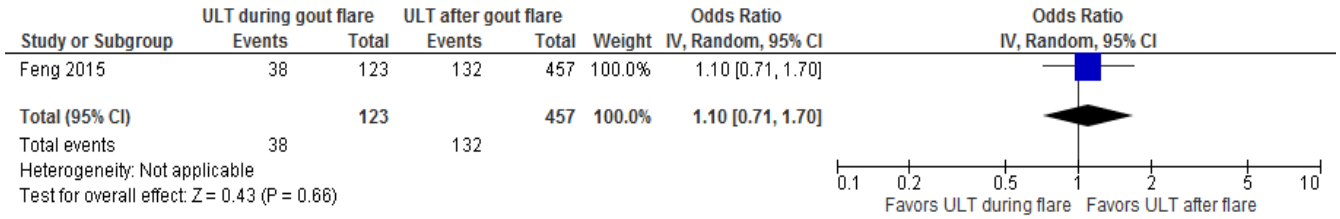
a. observational study with moderate risk of bias in multiple categories
b. Pooled estimate crosses null
c. RCT with several domains with high RoB
d. small sample sizes in each arm
Outcome importance
**Critical outcomes
* Important outcomes

Risk of bias assessment

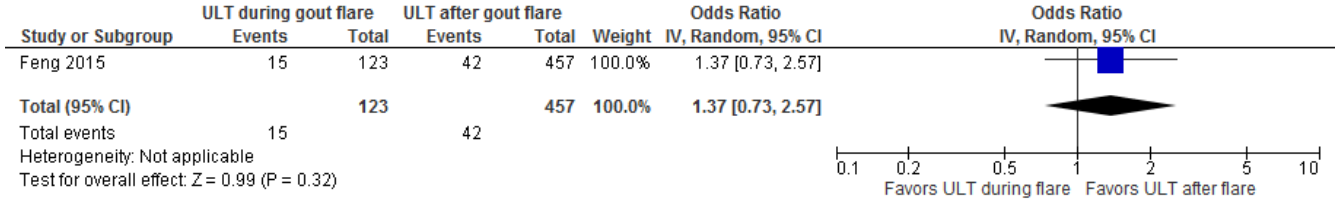




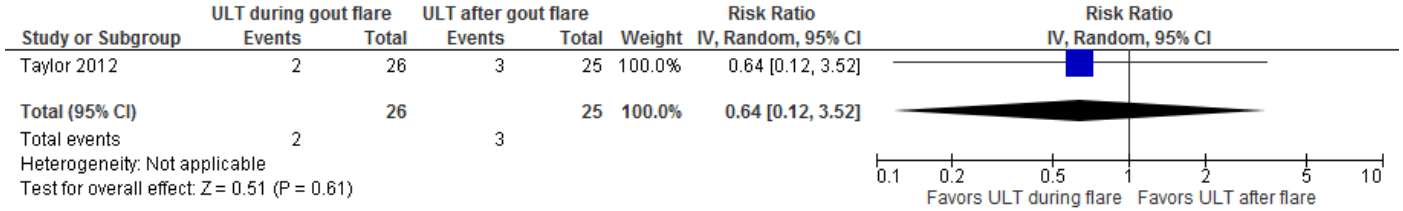
1.1 Forest plot of comparison: 1 ULT during flare vs after flare-OBS, outcome: 1.1 proportion of participants with at least one flare-8-12 weeks.



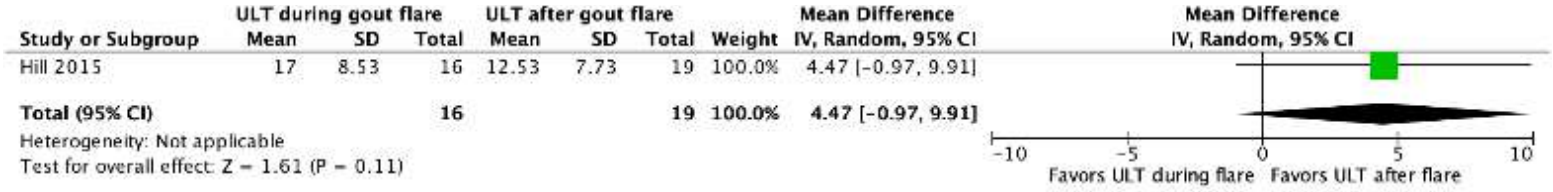
1.2 Forest plot of comparison: 1 ULT during flare vs after flare-OBS, outcome: 1.2 proportion of participants with at least one flare-36 weeks



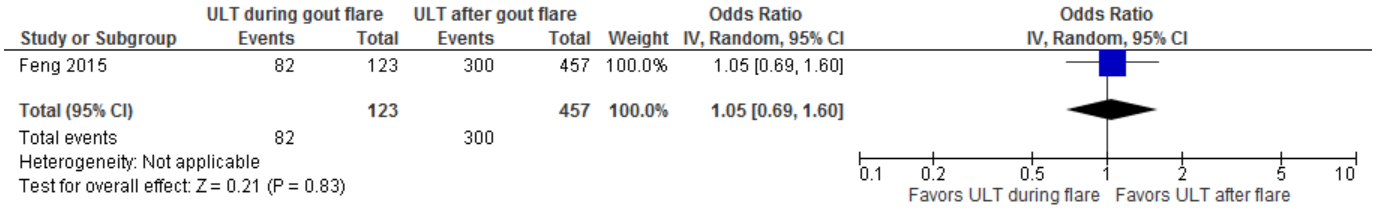
1.3 Forest plot of comparison: 1 ULT during flare vs after flare-RCT, outcome: 1.3 proportion with flare in any joint- 30 days.



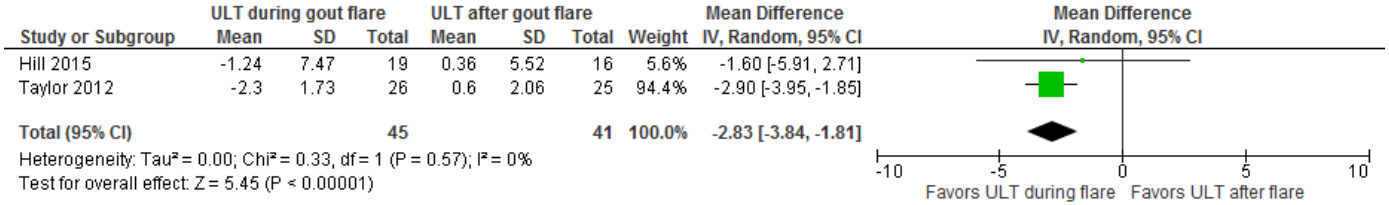
1.4 Forest plot of comparison: 1 ULT during flare vs after flare- RCT, outcome: 1.4 time from enrollment in study to resolution of acute gout attack (Intention to treat)- 28 days.



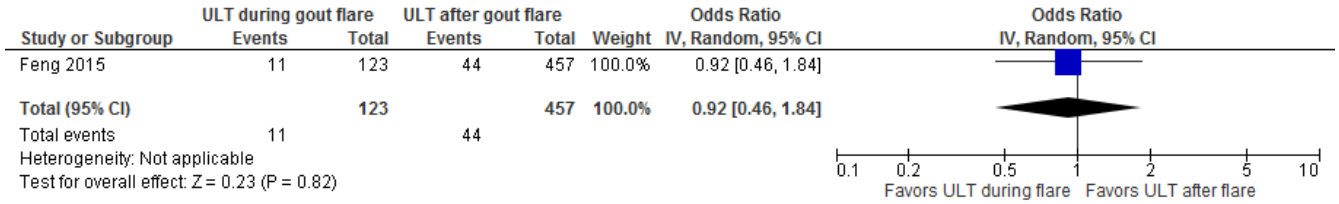
1.5 Forest plot of comparison: 1 ULT during flare vs after flare-OBS, outcome: 1.5 participants with serum urate <6mg/dL- 36 weeks.



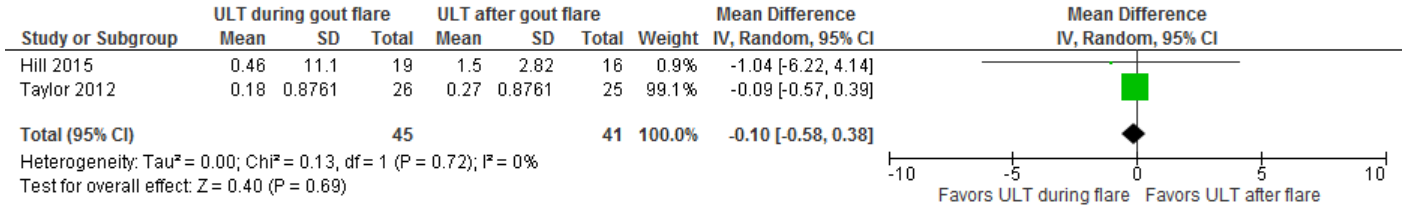
1.6 Forest plot of comparison: 1 ULT during flare vs after flare-RCT, outcome: 1.6 Mean change in Serum Urate level, mg/dL- 10 days.



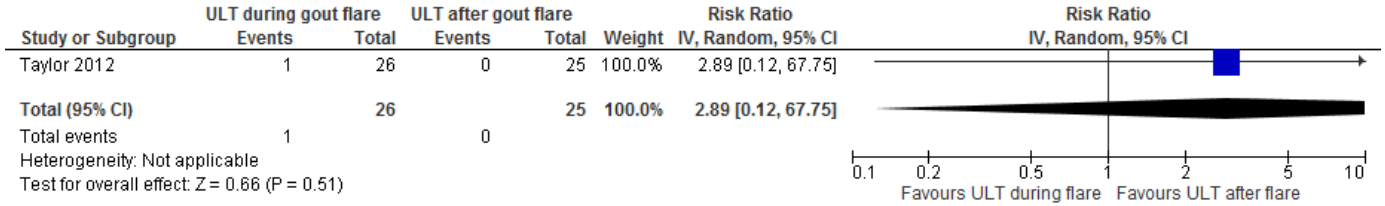
1.7 Forest plot of comparison: 1 ULT during flare vs after flare-OBS, outcome: 1.7 proportion with tophi at follow up- 36 weeks



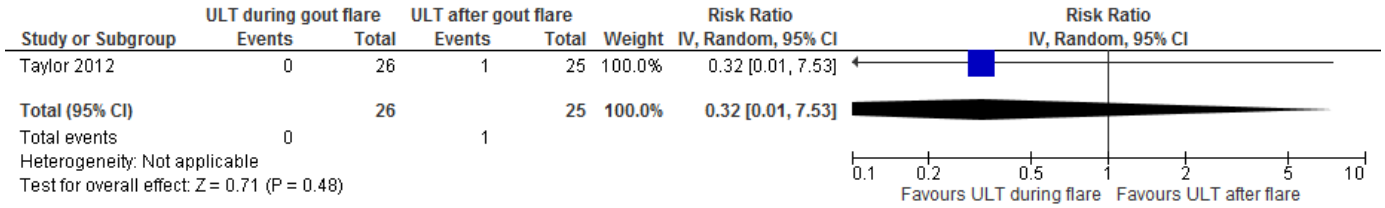
1.8 Forest plot of comparison: 1 ULT during flare vs after flare-RCT, outcome: 1.8 Pain- Visual analogue scale or numerical rating score (range 0-10)- 10 days.



1.9 Forest plot of comparison: 1 ULT during flare vs after flare- RCT, outcome: 1.9 Proportion with serious adverse event- death- 30 days.



1.10 Forest plot of comparison: 1 ULT during flare vs after flare- RCT, outcome: 1.10 Proportion with serious adverse event-hypersensitivity reaction- 30 days.



7: Should starting a low dose of the ULT agent and doing gradual dose escalation vs. starting the ULT at a higher dose be used in patients diagnosed with gout starting any ULT?

We did not find any studies addressing the question of interest directly. We found two studies that addressed a similar question, and the core team decided they could be used as relevant indirect evidence to address this question. In the first study,[20] researchers recruited 255 participants, who were assigned to start treatment with febuxostat at a dose of 10 mg/day, which was gradually increased to 40 mg/day; or to start treatment with febuxostat at a dose of 40 mg/day. In the second study,[21] researchers evaluated the relationship between the starting dose of allopurinol (starting at a dose higher than creatinine clearance based dose or starting at the same or a lower dose than creatinine clearance-based dose) and hypersensitivity syndrome.

The evidence shows:

- Patients who start ULT at a lower dose and undergo gradual dose escalation may be less likely to experience gout flares at 3 months, than patients who start the ULT at a higher dose.
- Patients who start ULT at a lower dose and undergo gradual dose escalation may have a lower mean number of flares up to 6 months, than patients who start the ULT at a higher dose; but we are very uncertain about this evidence (the quality of the evidence is very low).
- There are probably no differences in the proportion of patients who achieve serum urate levels <6mg/dL after 3 and 6 months, between patients who start ULT at a lower dose and undergo gradual dose escalation and those who start the ULT at a higher dose.
- There may be no differences in the proportion of patients with hypersensitivity reactions to febuxostat up to 24 weeks, between patients who start febuxostat at a lower dose and undergo gradual dose escalation and those who start the febuxostat at a higher dose.
- Patients who start allopurinol at a lower dose and undergo gradual dose escalation may be less likely to experience allopurinol hypersensitivity syndrome up to 30 days, than patients who start the allopurinol at a higher dose

The overall quality of the evidence is MODERATE

When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is VERY LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With starting the ULT at a higher dose	With starting a low dose of the ULT agent and doing gradual dose escalation	Relative effect (95% CI)	Risk with starting the ULT at a higher dose	Risk difference with starting a low dose of the ULT agent and doing gradual dose escalation
Gout flares* (follow up: mean 3 months; assessed with: patients with at least 1 flare)											
146 (1 RCT)	serious [a]	not serious	serious [b]	not serious	none	⨁⨁◯◯ LOW	18/50 (36.0%)	20/96 (20.8%)	**RR 0.58** (0.34 to 0.99)	360 per 1,000	**151 fewer per 1,000** (238 fewer to 4 fewer)
Gout flares (follow up: mean 6 months; assessed with: mean flare per patient)**											
21 (1 RCT)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	Starting low dose with stepwise increase had 1.20 flares/patient, starting at fixed high dose had 1.33 flares/patient. Difference is 0.13 flares/patient favoring starting low dose with stepwise increase				
Serum urate (follow up: mean 3 months; assessed with: patients with SUA<6 mg/dL)**											
132 (1 RCT)	not serious [d]	not serious	serious [b]	serious [e]	none	⨁⨁⨁◯ MODERATE	32/42 (76.2%)	62/90 (68.9%)	**RR 0.90** (0.73 to 1.13)	762 per 1,000	**76 fewer per 1,000** (206 fewer to 99 more)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Serum urate (follow up: mean 6 months; assessed with: patients with SUA<6 mg/dL)**											
115 (1 RCT)	not serious [d]	not serious	serious [b]	serious [e]	none	⨁⨁⨁◯ MODERATE	28/38 (73.7%)	58/77 (75.3%)	**RR 1.02** (0.81 to 1.29)	737 per 1,000	**15 more per 1,000** (140 fewer to 214 more)
Serious adverse events (follow up: mean 24 weeks; assessed with: reaction to febuxostat)**											
146 (1 RCT)	not serious [d]	not serious	serious [b]	serious [e]	none	⨁⨁◯◯ LOW	5/50 (10.0%)	7/96 (7.3%)	**RR 0.73** (0.24 to 2.18)	100 per 1,000	**27 fewer per 1,000** (76 fewer to 118 more)
Serious adverse events (follow up: mean 30 days; assessed with: Allopurinol hypersensitivity syndrome)**											
205 (1 observational study)	very serious [f]	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	23/41 (56.1%)	30/164 (18.3%)	**OR 0.18** (0.08 to 0.36)	561 per 1,000	**374 fewer per 1,000** (468 fewer to 246 fewer)
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Health-related quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient adherence* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. There was high risk of detection bias in the study. Trial was open label, which could have affected the reporting of flares
b. Febuxostat dose escalation was from 10mg to 40mg and starting at fixed higher dose was 40mg. High dose and low dose does not meet definition of high/low dose specified in PICO
c. Small number of total events, small sample size. Unlikely to meet Optimal information size.
d. The high risk of detection bias is unlikely to have affected this outcome
e. Results are not imprecise because we are rating the certainty that there are no important differences
f. This study had moderate risk of bias owing to serious confounding, moderate detection bias, and moderate incomplete outcome data bias
Outcome importance:
** Critical outcomes
* Important outcomes

Figure 1: Risk of bias assessment- RCTs

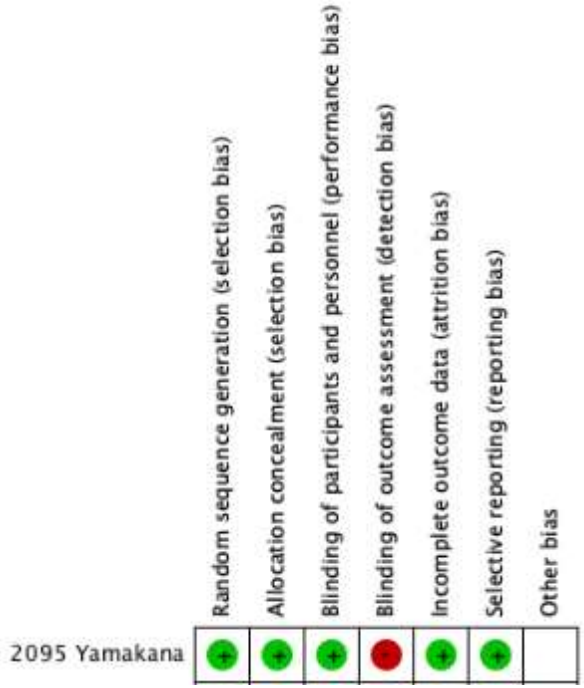
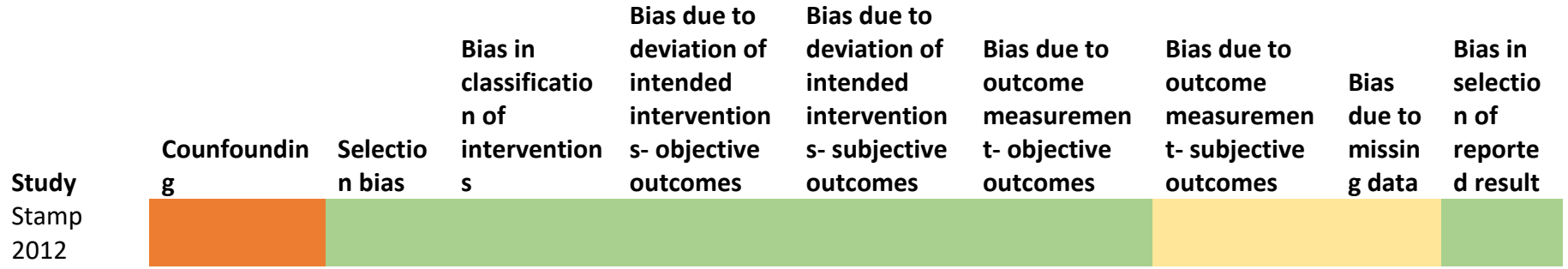


Figure 2: Risk of bias assessments- Observational studies

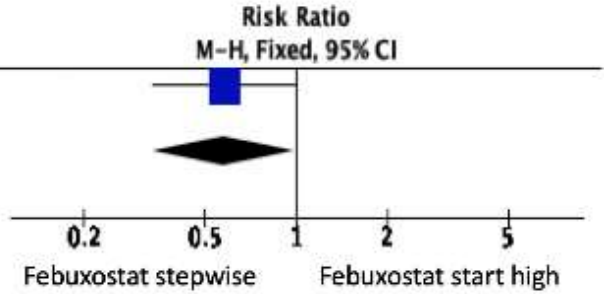


Figures: Data analyses

Febuxostat start low (10mg) with gradual dose escalation (stepwise) vs starting febuxostat at a higher dose (40mg) (start high), Gout flare, Patients with at least 1 gout flare, up to 3 months

Study or Subgroup	Febuxostat stepwise Events	Total	Febuxostat start high Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2095 Yamakana	20	96	18	50	100.0%	0.58 [0.34, 0.99]
Total (95% CI)		96		50	100.0%	0.58 [0.34, 0.99]
Total events	20		18			

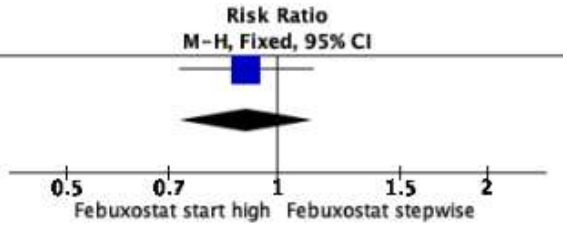
Heterogeneity: Not applicable
Test for overall effect: Z = 2.00 (P = 0.05)



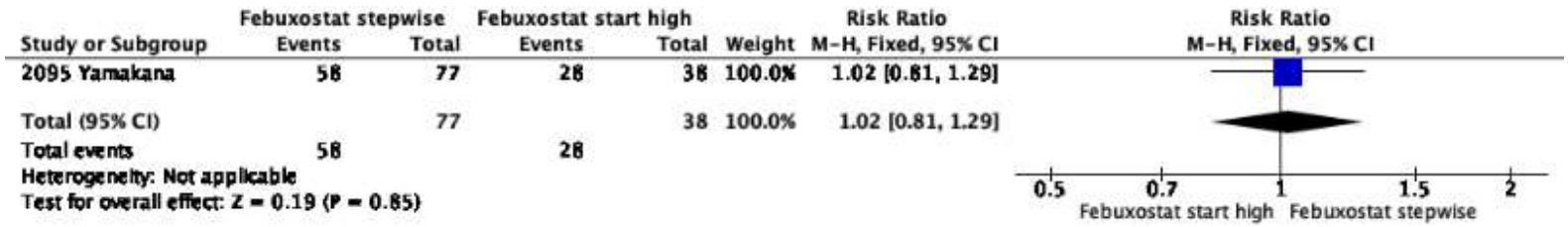
Febuxostat start low (10mg) with gradual dose escalation (stepwise) vs starting febuxostat at a higher dose (40mg) (start high), Serum urate, percentage of patients with SUA<6mg/dl, 3 months

Study or Subgroup	Febuxostat stepwise Events	Total	Febuxostat start high Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2095 Yamakana	62	90	32	42	100.0%	0.90 [0.73, 1.13]
Total (95% CI)		90		42	100.0%	0.90 [0.73, 1.13]
Total events	62		32			

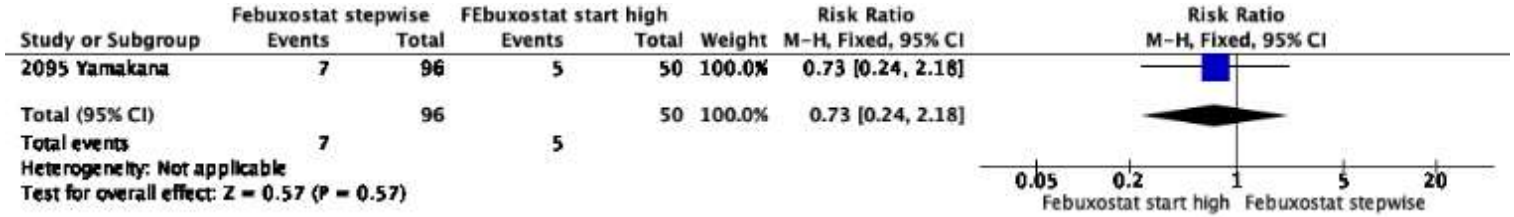
Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)



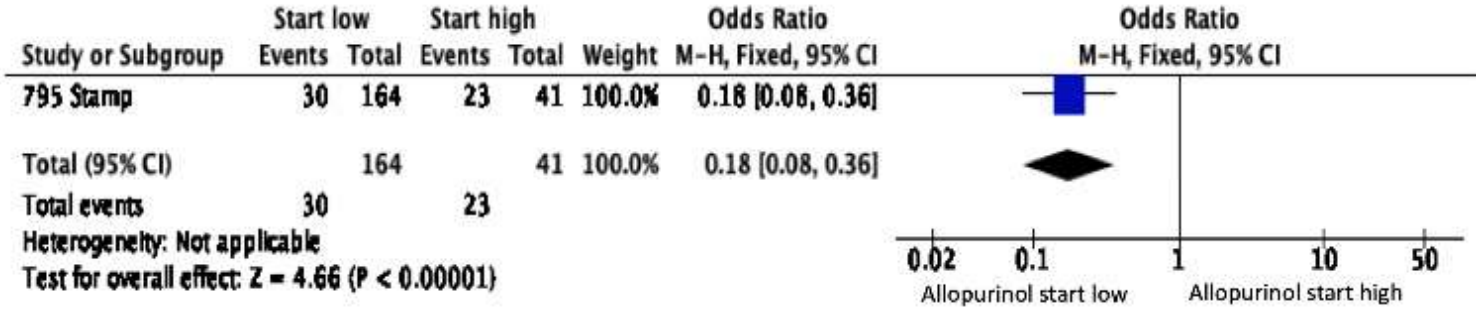
Febuxostat start low (10mg) with gradual dose escalation (stepwise) vs starting febuxostat at a higher dose (40mg) (start high), Serum urate, percentage of patients with SUA<6mg/dl, 6 months (longest follow up)



Febuxostat start low (10mg) with gradual dose escalation (stepwise) vs starting febuxostat at a higher dose (40mg) (start high), adverse events, patients with adverse reaction to febuxostat



Allopurinol start low vs start higher dose, allopurinol hypersensitivity



8: Should non-physician health care professional-augmented (e.g. nursing or pharmacy) package of care vs. usual care be used in patients with gout?

We found 3 studies addressing this question.[22-24] These were all randomized clinical trials.

The evidence shows:

- Patients with gout who receive a health-care professional-augmented package
    - May not have a different number of gout flares than patients who receive usual care, at 1 and 2 years
    - Probably have a lower risk of experiencing 2 or more flares than patients who receive usual care, at 2 years
    - May experience a higher rate of gout flares per patient years than patients who receive usual care, at 1 year
    - May not experience a different rate of gout flares per patient years than patients who receive usual care, at 2 years
    - Probably have a higher probability of achieving serum urate levels <6 mg/dL than patients who receive usual care, at 1 year
    - May have a higher probability of achieving serum urate levels <6 mg/dL than patients who receive usual care, at 2 years
    - Probably have smaller tophi than patients who receive usual care, at 2 years
    - Probably have better health-related quality of life than patients who receive usual care, at 2 years
    - May not experience different activity limitation than patients who receive usual care, at 2 years
    - Probably have better adherence to ULTs than patients who receive usual care, at 1 year
    - May not have a different risk of serious adverse events than patients who receive usual care, at 2 years

The overall quality of the evidence is MODERATE
When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With usual care	With non-physician health care professional-augmented (e.g. nursing or pharmacy) package of care	Relative effect (95% CI)	Risk with usual care	Risk difference with non-physician health care professional-augmented (e.g. nursing or pharmacy) package of care
Gout flares* (follow up: mean 1 year; assessed with: Number of gout flares)											
517 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	262	255	-	The mean gout flares** was **3.5**	MD **0.1 higher** (4.3 lower to 4.5 higher)
Gout flares (follow up: mean 2 years; assessed with: Number of gout flares)**											
517 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	262	255	-	The mean gout flares** was **2.4**	MD **0.9 lower** (3.67 lower to 1.87 higher)
Gout flares (follow up: 2 years; assessed with: People with 2 or more flares)**											
517 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	64/262 (24.4%)	21/255 (8.2%)	**RR 0.34** (0.21 to 0.56)	244 per 1,000	**161 fewer per 1,000** (193 fewer to 107 fewer)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Gout flares (assessed with: gout flare rates per 100 patient years)**											
77 (1 RCT)	serious [a]	not serious	not serious	serious	none	⨁⨁◯◯ LOW	40	37	-	The mean gout flares** was **68.7** flares/100 patient years	MD **13 flares/100 patient years higher** (3.07 higher to 22.93 higher)
Gout flares (follow up: range 18 months to 24 months; assessed with: gout flare rates per 100 patient years)**											
77 (1 RCT)	serious [a]	not serious	not serious	serious	none	⨁⨁◯◯ LOW	40	37	-	The mean gout flares** was **48.5** flares/ 100 patient years	MD **2.9 flares/ 100 patient years lower** (13.17 lower to 7.37 higher)
Serum urate (follow up: mean 12 weeks; assessed with: participants with serum urate <6mg/dL)**											
77 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	3/40 (7.5%)	15/37 (40.5%)	**RR 5.41** (1.70 to 17.18)	75 per 1,000	**331 more per 1,000** (53 more to 1,214 more)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Serum urate (follow up: range 6 months to 1 years; assessed with: Proportion with Serum Urate <6mg/dL)**											
2057 (3 RCTs)	seriou s [a]	serious	not serious	not serious	none	⨁⨁◯◯ LOW	191/108 4 (17.6%)	458/973 (47.1%)	**RR 2.68** (1.51 to 4.75)	176 per 1,000	**296 more per 1,000** (90 more to 661 more)
Tophi* (follow up: mean 2 years; assessed with: Diameter of largest tophus (mm))											
517 (1 RCT)	seriou s [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERAT E	262	255	-	The mean tophi* was **13.61** mm	MD **10.32 mm lower** (12.38 lower to 8.26 lower)
Health related quality of life* (follow up: 2 years; assessed with: Gout concern overall score)											
517 (1 RCT)	seriou s [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERAT E	262	255	-	The mean health related quality of life* was **53.52**	MD **16.08 lower** (20.56 lower to 11.6 lower)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Activity Limitation* (follow up: 12 months; assessed with: Health Assessment Questionnaire; Scale from: 0 (no disability) to 3 (totally independent))											
143 (1 RCT) 12 months	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	73	70	-	The mean activity Limitation * was **0.51**	MD **0.11 higher** (0.14 lower to 0.36 higher)
Serious adverse events* (follow up: mean 2 years; assessed with: Death)											
510 (1 RCT)	serious [a]	not serious	not serious	serious	none	⨁⨁◯◯ LOW	8/255 (3.1%)	2/255 (0.8%)	**RR 0.25** (0.05 to 1.17)	31 per 1,000	**24 fewer per 1,000** (30 fewer to 5 more)
Serious adverse events* (follow up: mean 2 years; assessed with: Cutaneous reaction)											
1463 (1 RCT)	serious [a]	not serious	not serious	serious	none	⨁⨁◯◯ LOW	1/782 (0.1%)	1/681 (0.1%)	**RR 1.15** (0.07 to 18.32)	1 per 1,000	**0 fewer per 1,000** (1 fewer to 22 more)
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

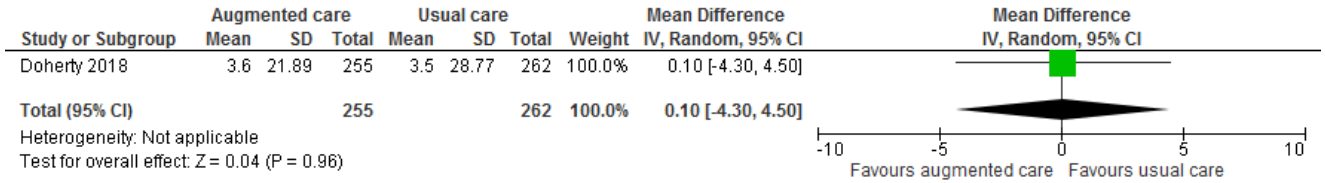
CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

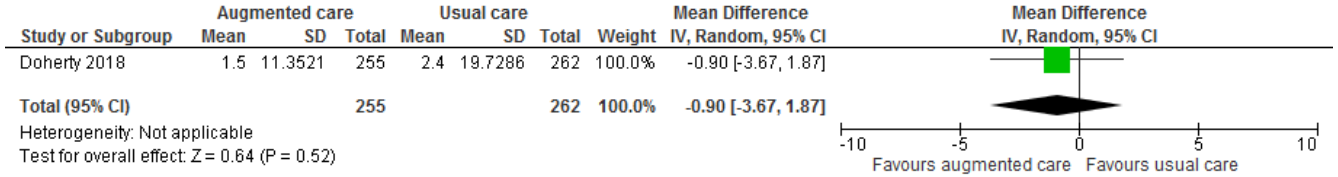
a. RCT with some domains with high ROB
b. diamond crosses the null line
c. Statistical but not clinical heterogeneity
Outcome importance
** Critical outcomes
* Important outcomes

Risk of bias assessment

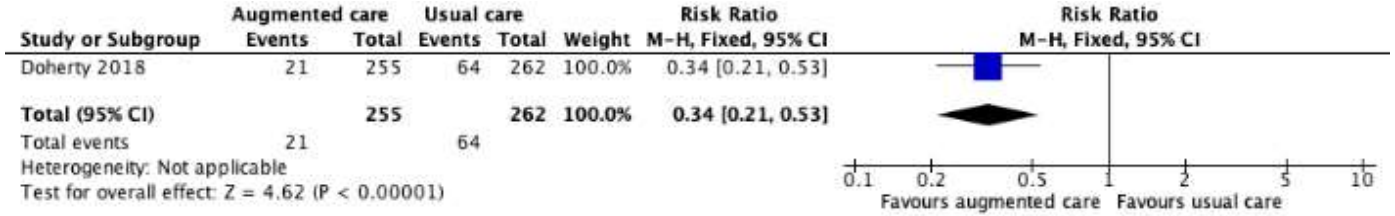
1.1 Forest plot of comparison: 1 Augmented care vs usual care, outcome: 1.1 Number of gout flares- mean- 1 year.



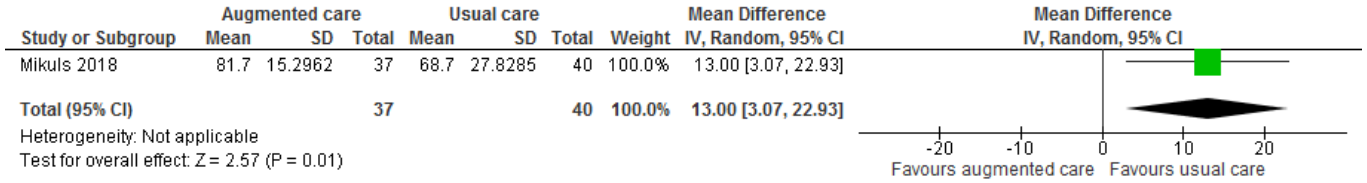
1.2 Forest plot of comparison: 1 Augmented care vs usual care, outcome: 1.2 Number of gout flares- mean- 2 year.



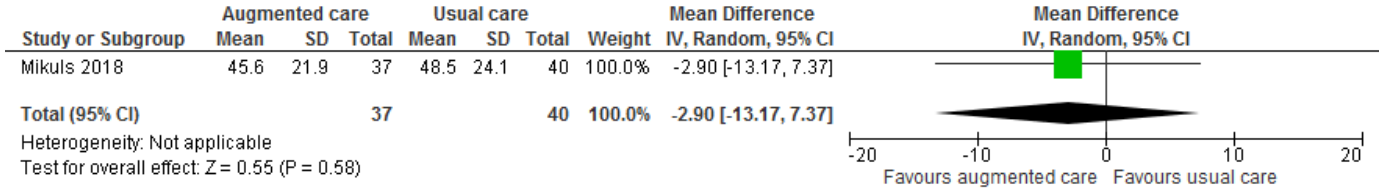
1.3 Forest plot of comparison: 1 Augmented care vs usual care, outcome: 1.3 Risk of 2+ flares- 2 year.



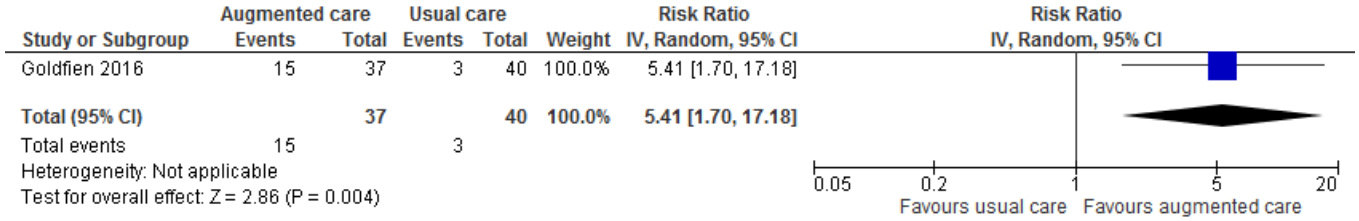
1.4 Forest plot of comparison: 1 Augmented care vs usual care, outcome: 1.4 gout flare rates per 100 patient years- 0-6 months.



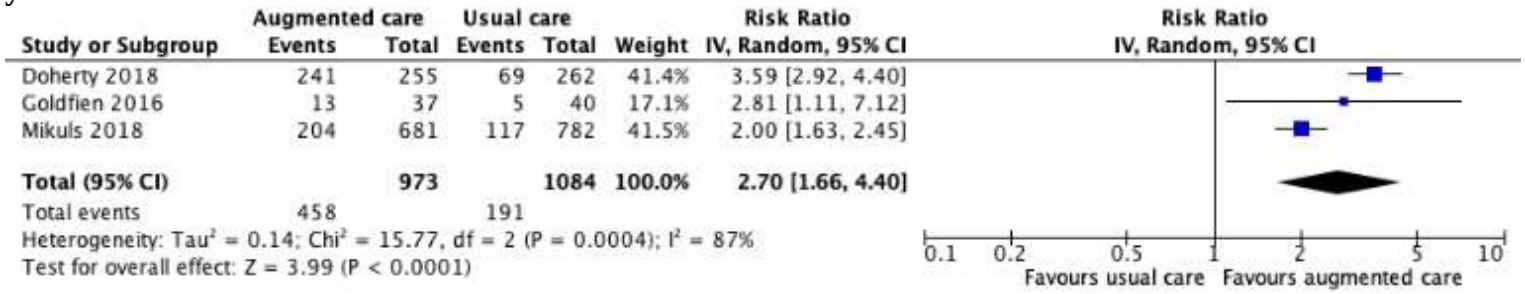
1.5 Forest plot of comparison: 1 Augmented care vs usual care, outcome: 1.5 gout flare rates per 100 patient years- >18-24 months.



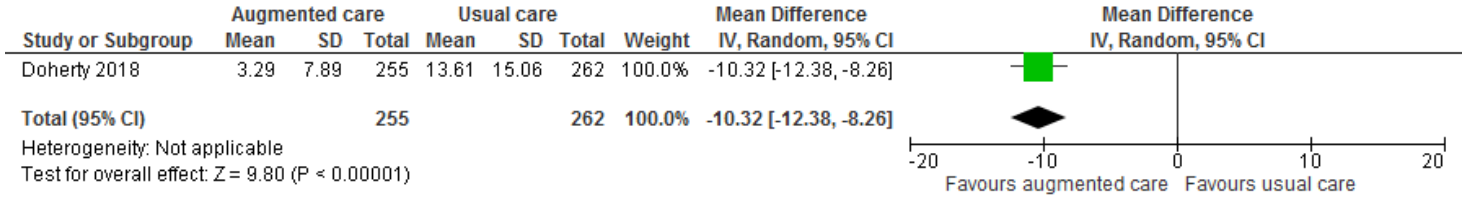
1.6 Forest plot of comparison: 1 Augmented care vs usual care, outcome: 1.6 participants with serum urate <6mg/dL- 12 weeks.



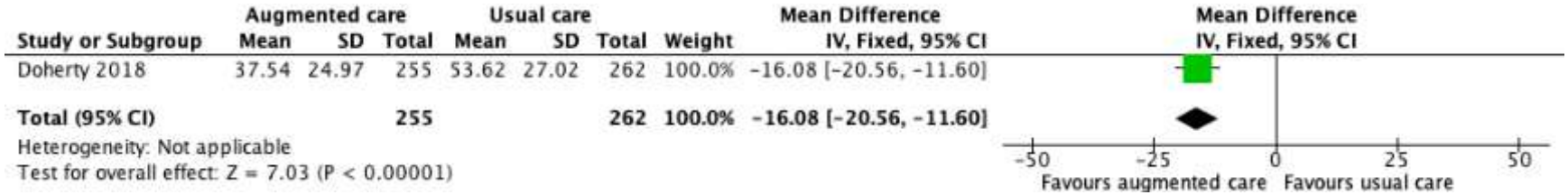
1.7 Forest plot of comparison: 1 Augmented care vs usual care, outcome: 1.7 Proportion with Serum Urate <6mg/dL- 6 months to 1 year.



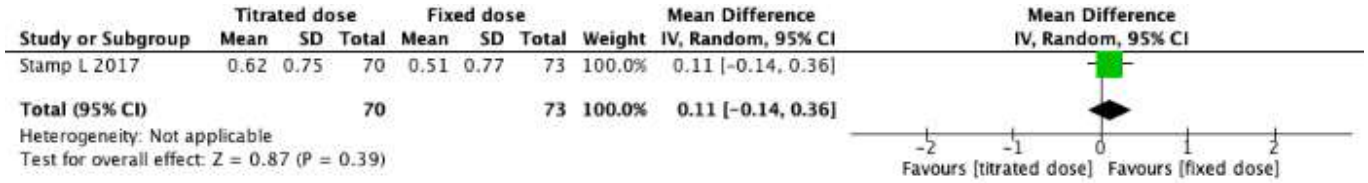
1.8 Forest plot of comparison: 1 Augmented care vs usual care, outcome: 1.8 Diameter of largest tophus (mm)- mean- 2 year.



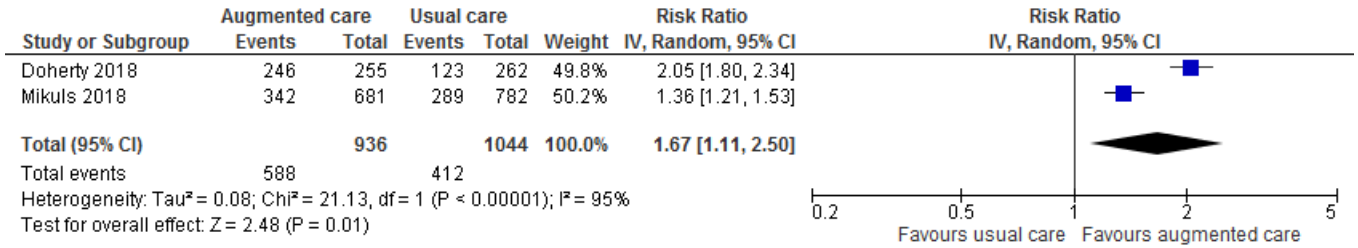
1.9 Forest plot of comparison: 1 Augmented care vs usual care, outcome 1.9: Health-related quality of life- gout concern score.



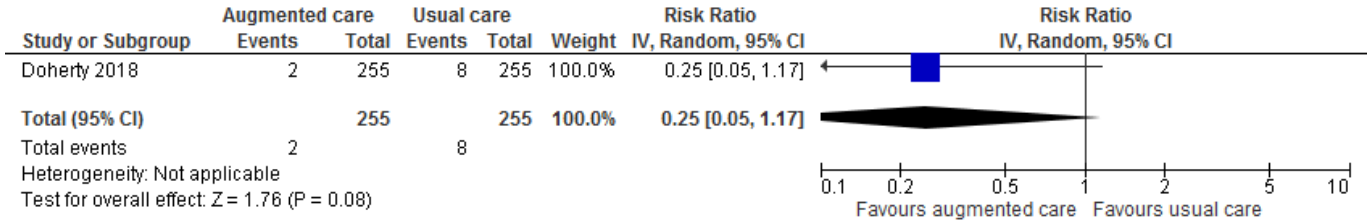
1.10 Forest plot of comparison: 1 Augmented care vs usual care -RCT, outcome: 1.10 Activity Limitation- Health Assessment Questionnaire- 12 month follow-up.



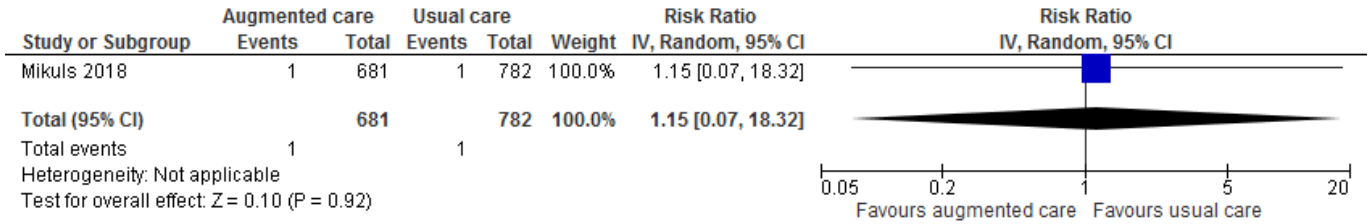
1.11 Forest plot of comparison: 1 Augmented care vs usual care, outcome: 1.11 Proportion of patients taking urate-lowering therapy- 1 year.



1.12 Forest plot of comparison: 1 Augmented care vs usual care, outcome: 1.12 Serious adverse event (death)- 2 years.



1.13 Forest plot of comparison: 1 Augmented care vs usual care, outcome: 1.13 Serious cutaneous reaction- 2 years.



9: Should Prophylaxis vs. No Prophylaxis be used in Patients with gout starting ULT?

We found 11 studies adressing this question.[20, 25-34] Eight of the studies were randomized clinical trials that compared prophylaxis versus no prophylaxis (placebo). Half of the trials compared colchicine versus no prophylaxis,[20, 25, 27, 28] and the other half compared rilonacept versus no prophylaxis.[26, 30, 31, 33] Two studies were observational studies that compared the colchicine versus no prophylaxis,[32, 34] and steroids versus no prophylaxis.[34] Another trial compared the effects of canakinumab and colchicine.[29]
The evidence shows:

- There were no important differences between the evidence from randomized clinical trials and observational studies for most outcomes, unless noted below.
- There were no important differences between colchicine and rilonacept, and between doses of rilonacept for most outcomes, unless noted below.
- Patients who receive prophylaxis:
    - probably have a lower risk of gout flares up to 3 months, than those who do not receive it.
    - probably have a lower mean number of flares up to 4 months, than those who do not receive it.
    - with canakinumab have a lower risk of gout flares up to 4 months than patients who receive prophylaxis with colchicine.
    - with canakinumab probably have no differences in the changes in serum urate up to 4 months compared with those who receive prophylaxis with colchicine.
    - probably experience fewer days of important pain than those who do not receive prophylaxis, up to 4 months.
    - may have no differences in patient adherence up to 3 months compared with those who do not.
    - may have no differences in the risk of any serious adverse events up to 6 months compared with those who do not.
    - with canakinumab probably have no differences in the risk of serious adverse events up to 4 months compared with those who receive prophylaxis with colchicine.
    - may have no differences in the risk of renal and hypersensitivity serious adverse events up to 5.5 months compared with those who do not.
- Randomized trials suggest that there may be no differences in the risk of cardiovascular adverse events up to 6 months, between patients who receive prophylaxis and those who do not. Observational studies suggest that patients who receive prophylaxis have a lower risk of primary cardiovascular events, but we are very uncdertain about that evidence.

The overall quality of the evidence is MODERATE
When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is MODERATE

Table 1: Evidence profile- Prophylaxis versus no prophylaxis, RCT Data

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With No Prophylaxis	With Prophylaxis	Relative effect (95% CI)	Risk with No Prophylaxis	Risk difference with Prophylaxis
Gout Flares (follow up: 3 months; assessed with: Proportion of Patients with 1 + Gout Flare)**											
1754 (6 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	338/605 (55.9%)	350/1149 (30.5%)	**RR 0.36** (0.27 to 0.48)	559 per 1,000	**358 fewer per 1,000** (408 fewer to 291 fewer)
Gout Flares (follow up: range 3 months to 4 months; assessed with: Mean Flares per Patient)**											
1886 (4 RCTs)	serious [b]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	533	1353	-	The mean gout Flares** was **1.29** flares/ patient/ month	MD **0.98 flares/ patient/ month lower** (1.22 lower to 0.74 lower)
Pain* (follow up: range 3 months to 4 months; assessed with: Number of Days per Patient with Pain with Severity Score of => 5 with 24 hour recall)											
568 (3 RCTs)	serious [g]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	200	368	-	The mean pain* was **2.02** days	MD **2 days lower** (2.77 lower to 1.24 lower)

Table 1: Evidence profile- Prophylaxis versus no prophylaxis, RCT Data

Certainty assessment							Summary of findings				
Adherence* (follow up: 4 months; assessed with: Proportion of Patients with > 80% Adherence)											
1563 (2 RCTs)	serious [h]	not serious	not serious	serious [i]	none	⨁⨁◯◯ LOW	380/412 (92.2%)	1063/1151 (92.4%)	**RR 1.05** (0.69 to 1.60)	922 per 1,000	**46 more per 1,000** (286 fewer to 553 more)
Adherence* (follow up: 4 months; assessed with: To Study Drug Injections)											
201 (1 RCT)	serious [j]	serious [k]	not serious	not serious [k]	none	⨁⨁◯◯ LOW	37/40 (92.5%)	148/161 (91.9%)	**RR 0.88** (0.16 to 4.77)	925 per 1,000	**111 fewer per 1,000** (777 fewer to 3,487 more)
Adherence* (follow up: 4 months; assessed with: Percentage of Study Drug Injections)											
83 (1 RCT)	serious [l]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	42	41	-	The mean adherence* was **92.4** %	MD **5.5 % higher** (0.81 higher to 10.19 higher)
Serious Adverse Events* (follow up: range 3 months to 5.5 months; assessed with: Diverse Definitions)											
2138 (6 RCTs)	serious [m]	serious [n]	not serious	not serious [d]	none	⨁⨁◯◯ LOW	47/1501 (3.1%)	24/637 (3.8%)	**RR 0.82** (0.50 to 1.35)	31 per 1,000	**6 fewer per 1,000** (16 fewer to 11 more)

Table 1: Evidence profile- Prophylaxis versus no prophylaxis, RCT Data

Certainty assessment							Summary of findings				
Cardiovascular Adverse Events* (follow up: range 4 months to 6 months; assessed with: Proportion of Patients with Stroke/Angina)											
366 (3 RCTs)	serious [o]	not serious	not serious	serious [p]	none	⨁⨁◯◯ LOW	1/143 (0.7%)	2/223 (0.9%)	**RR 1.18** (0.18 to 7.62)	7 per 1,000	**1 more per 1,000** (6 fewer to 46 more)
Renal Adverse Events* (follow up: 5.5 months; assessed with: Proportion of Patients with Alteration in Renal Function)											
83 (1 RCT)	serious [q]	not serious	not serious	serious [r]	none	⨁⨁◯◯ LOW	1/42 (2.4%)	0/41 (0.0%)	**RR 0.33** (0.01 to 8.42)	24 per 1,000	**16 fewer per 1,000** (24 fewer to 177 more)
Serious adverse events- Drug Hypersensitivity* (follow up: 3 months; assessed with: Number of Patients with Drug Hypersensitivity)											
107 (1 RCT)	serious [q]	not serious	not serious	serious [r]	none	⨁⨁◯◯ LOW	0/54 (0.0%)	1/53 (1.9%)	**RR 3.06** (0.13 to 73.37)	0 per 1,000	**20 more per 1,000** (30 fewer to 70 more)
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient Global Assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Evidence profile- Prophylaxis versus no prophylaxis, RCT Data

Certainty assessment							Summary of findings				
Health Related Quality of Life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity Limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Multiple included studies (3/6) with serious risk of bias. Remaining (3/6) with unclear risk in some domains.
b. None of the included studies was at low risk of bias
c. Studies with results on both sides of the graph, minimal overlap of confidence intervals
d. The inconsistency resulted in imprecision, so we rated down only one level for both
e. 2/6 included studies with serious risk of bias
f. One study with close to 20% weight is to the right of the plot, rest just to the left
g. 2/3 included studies with serious risk of bias
h. 2/2 included studies with unclear bias - one in selection and the other in performance/detection
i. Pooled estimate suggests the possibility of either of the interventions having higher adherence
j. One included study with unclear risk of selection bias (randomization and allocation)
k. Moderate inconsistency which resulted in imprecision. Rated down one level for both
l. One included study with serious risk of bias
m. 2/6 included studies with serious risk of bias. All others with at least 2 categories of unclear risk of bias
n. 3/6 studies with Mean Differences to the right of the graph and 3/6 studies with Mean Differences to the left of the graph
o. 2/3 studies with serious risk of bias
p. One study shows more risk with placebo, another shows more CV risk with prophylaxis
q. One included study with unclear risk of selection bias
r. Few events and participants included. CI suggests the possibility of appreciable benefit and appreciable harm
Outcome importance:
**Critical outcomes
* Important outcomes

Table 2: Evidence profile- Prophylaxis versus no prophylaxis, Observational studies data

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With No Prophylaxis	With Prophylaxis	Relative effect (95% CI)	Risk with No Prophylaxis	Risk difference with Prophylaxis
Gout Flares (follow up: 3 months; assessed with: Mean Flares per Patient per Month)**											
273 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	72	201	-	The mean gout Flares** was **1.72** flares/patient/month	MD **1.26 flares/patient/month lower** (1.69 lower to 0.82 lower)
Serious Adverse Events (follow up: 3 months; assessed with: Diverse definitions)**											
273 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	0/72 (0.0%)	0/201 (0.0%)	not estimable	0 per 1,000	**0 fewer per 1,000** (30 fewer to 30 more)
Cardiovascular Adverse Events (follow up: median 16.5 months; assessed with: Primary CV Events)**											
1788 (1 observational study)	serious [d]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	82/1002 (8.2%)	28/786 (3.6%)	**RR 0.41** (0.27 to 0.64)	82 per 1,000	**48 fewer per 1,000** (60 fewer to 29 fewer)
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 2: Evidence profile- Prophylaxis versus no prophylaxis, Observational studies data

Certainty assessment							Summary of findings				
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient Global Assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health Related Quality of Life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity Limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. One included study with moderate/serious risk of bias due to confounding, outcome bias
b. The CI suggests the possibility of no prophylaxis or prophylaxis being more effective for this outcome
d. One included study with serious risk of bias due to confounding, selection, outcome and missing data
Outcome importance:
**Critical outcomes
* Important outcomes

Table 3: Evidence profile Canakinumab versus Colchicine

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Colchicine	With Canakinumab	Relative effect (95% CI)	Risk with Colchicine	Risk difference with Canakinumab
Gout Flares (follow up: 4 months; assessed with: Proportion of Patients with 1 + Gout Flares)**											
207 (1 RCT)	not serious [a]	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	48/99 (48.5%)	18/108 (16.7%)	**RR 0.34** (0.21 to 0.54)	485 per 1,000	**320 fewer per 1,000** (383 fewer to 223 fewer)
Serious Adverse Events* (follow up: 6 months; assessed with: Any Serious Event)											
216 (1 RCT)	not serious [a]	not serious [a]	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	6/108 (5.6%)	6/108 (5.6%)	**RR 1.00** (0.33 to 3.00)	56 per 1,000	**0 fewer per 1,000** (37 fewer to 111 more)
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient Global Assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 3: Evidence profile Canakinumab versus Colchicine

Certainty assessment							Summary of findings				
Health Related Quality of Life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity Limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

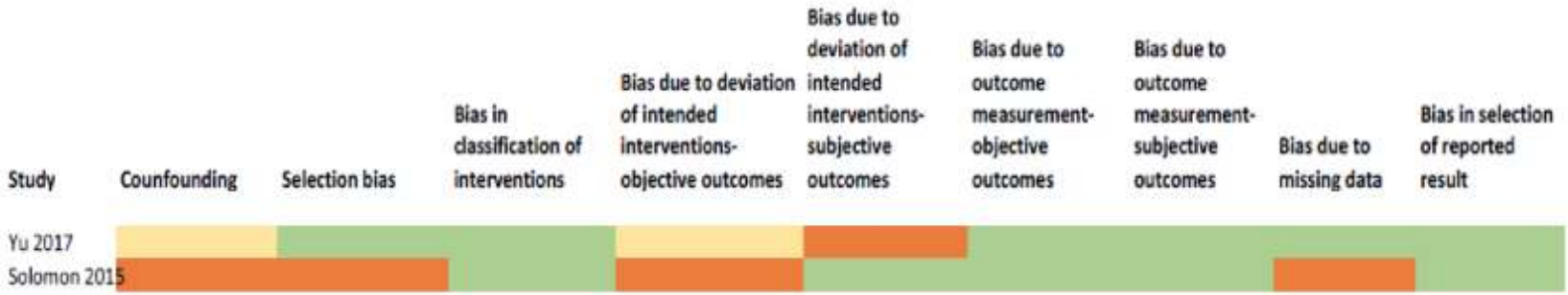
CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Risk of selective outcome reporting did not affect this outcome
b. One included study with serious risk of selective reporting
c. The CI suggests the possibility of increasing or decreasing the probability of adverse events
Outcome importance:
**Critical outcomes
* Important outcomes

Risk of Bias Summary – RCTs

Risk of Bias Summary – PICO 9, Observational Studies



Prophylaxis vs No Prophylaxis – RCT Data

Figure 1.1 – Gout Flares – Number with at least 1 gout flare at 3 – 4 months

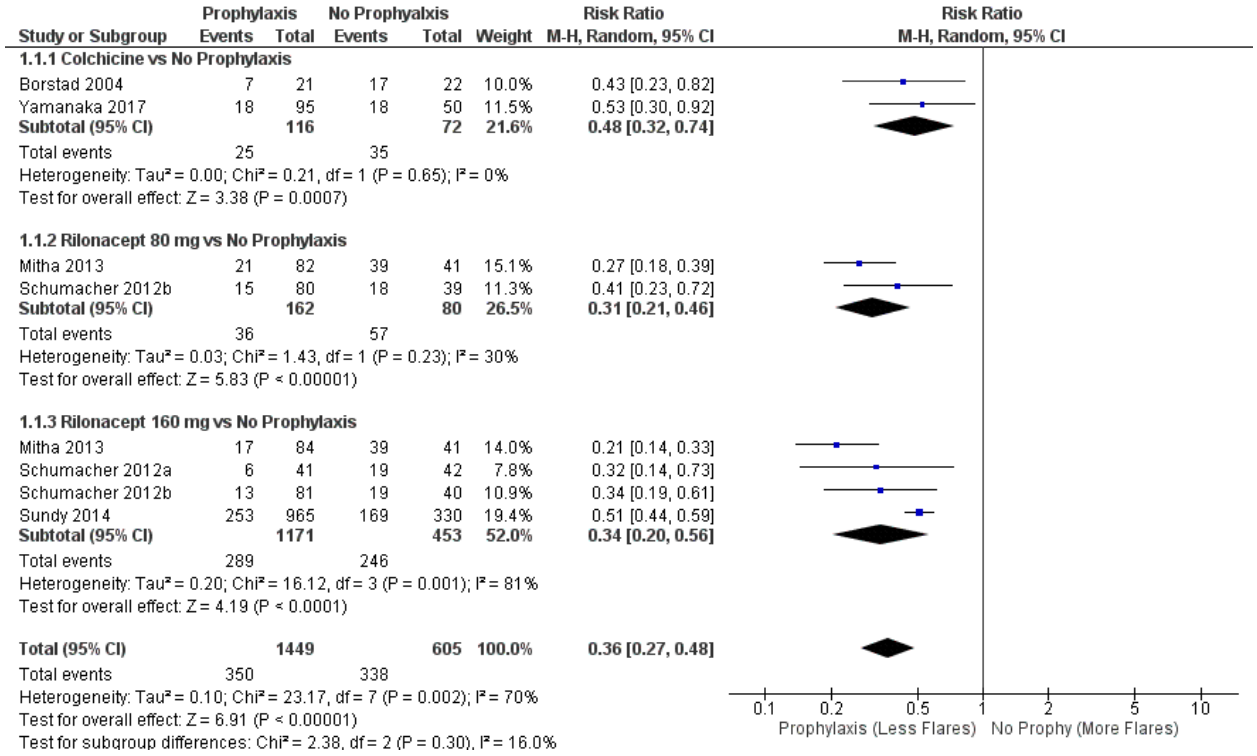


Figure 1.2 – Gout Flares – Mean Flares/Patient/Month at 3 – 4 months of study period

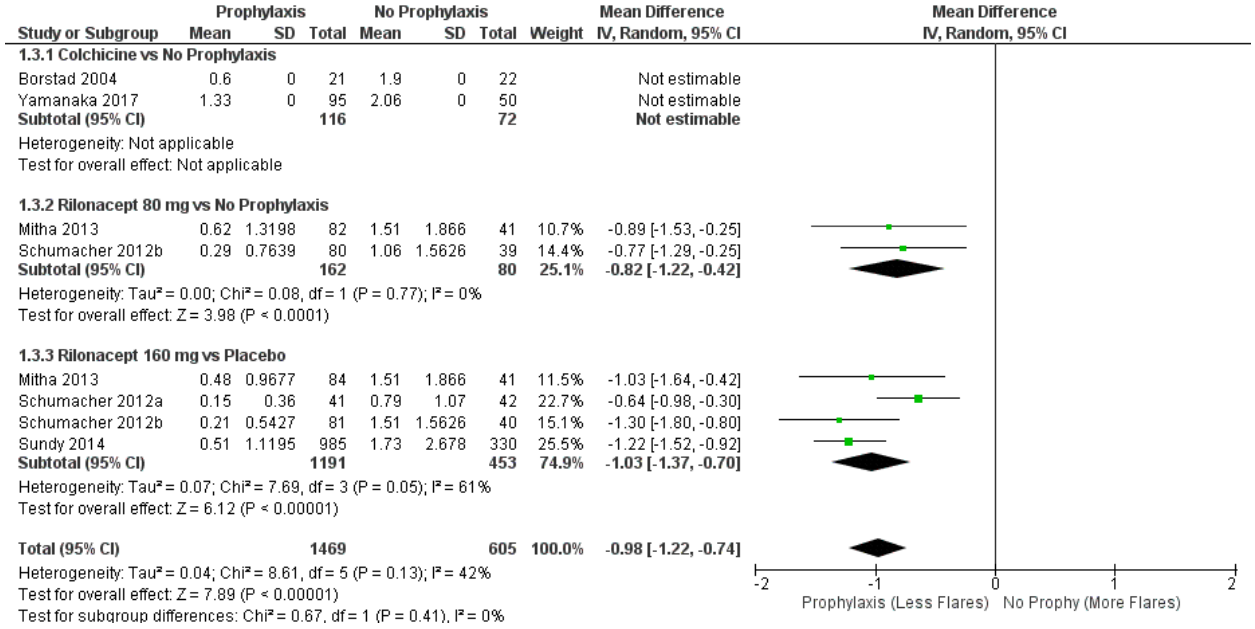


Figure 1.3 – Serum Urate < 6 mg/dL

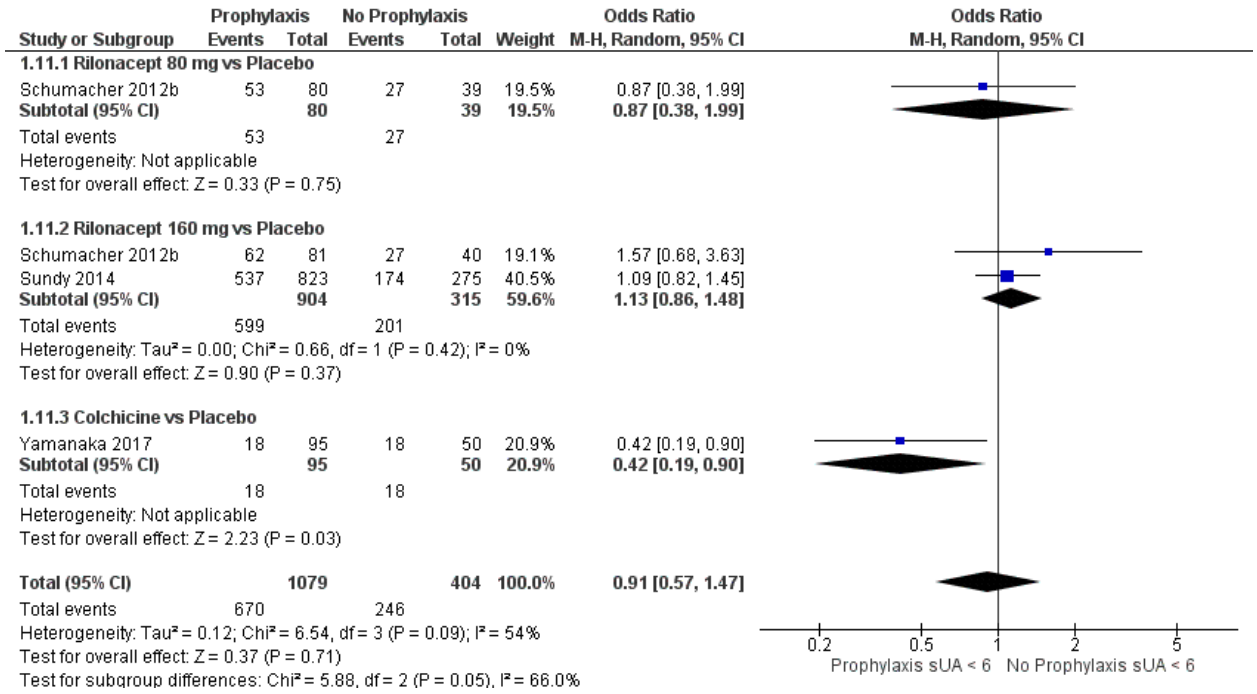


Figure 1.4 – Mean Change in Serum Urate

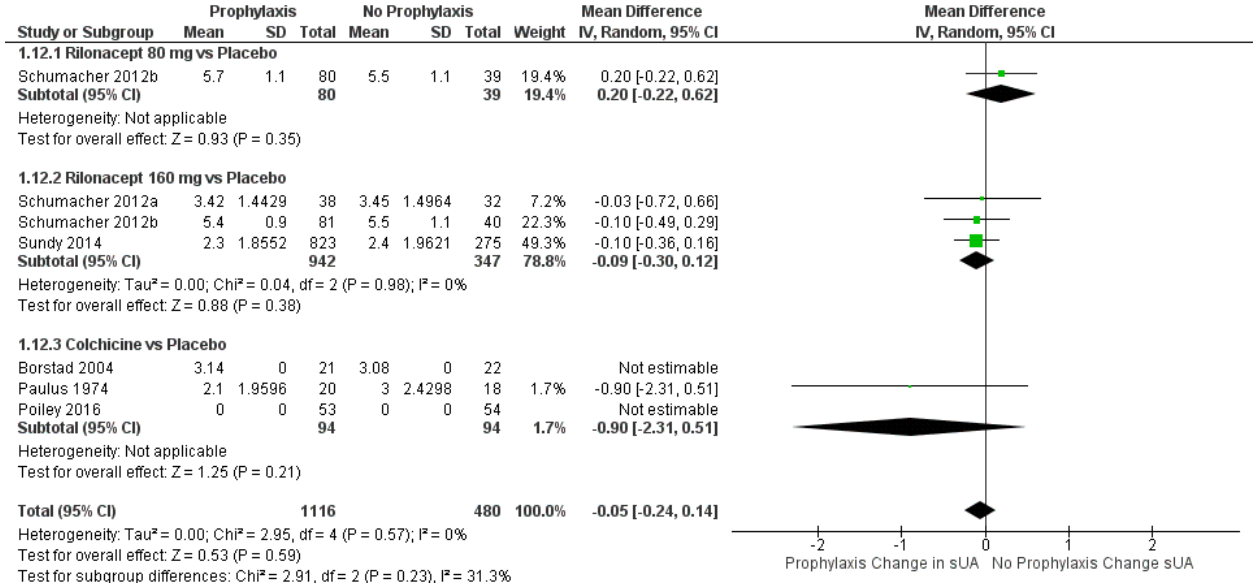


Figure 1.5 – Pain

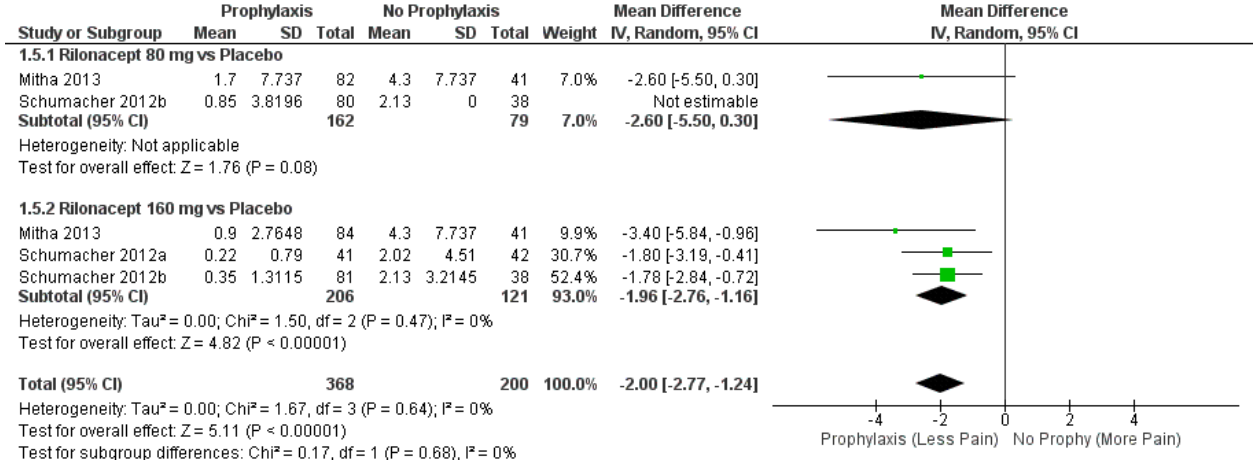


Figure 1.6 – Patient Adherence; Proportion with > 80% adherence

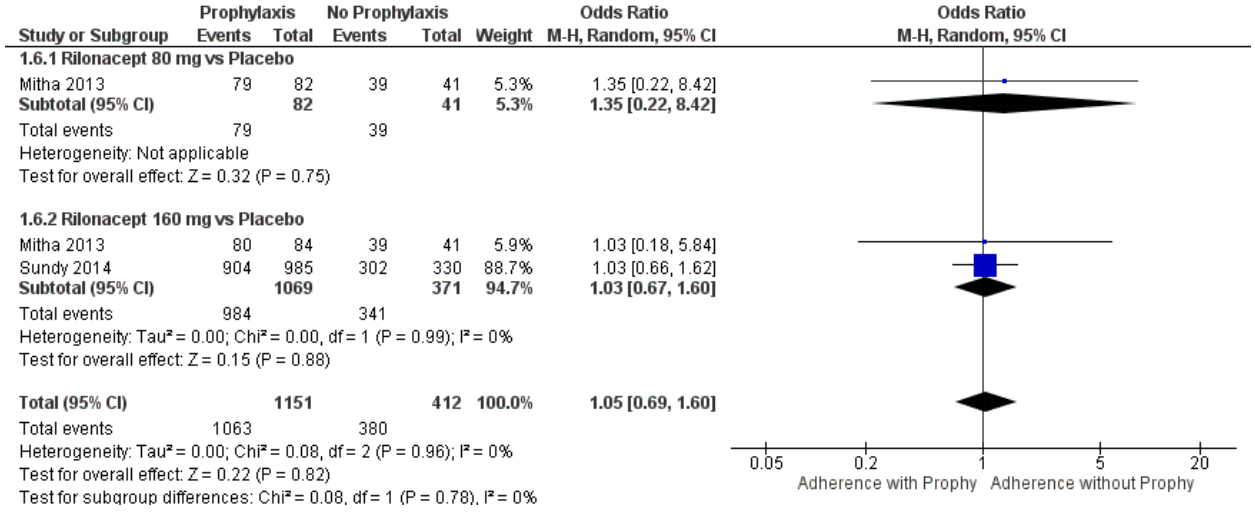


Figure 1.7 – Patient Adherence; Adherent to Study Drug Injections

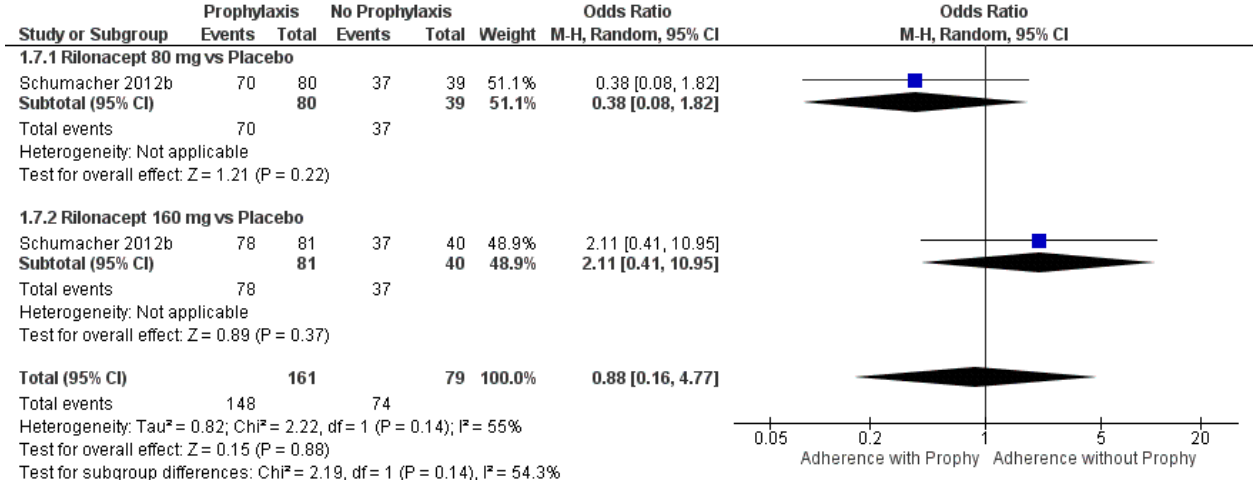


Figure 1.8 – Patient Adherence; % doses of Study Drug Injections

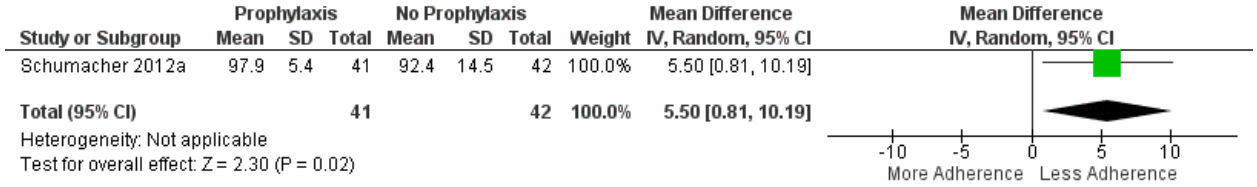


Figure 1.9 – Serious Adverse Events; Diverse Definitions

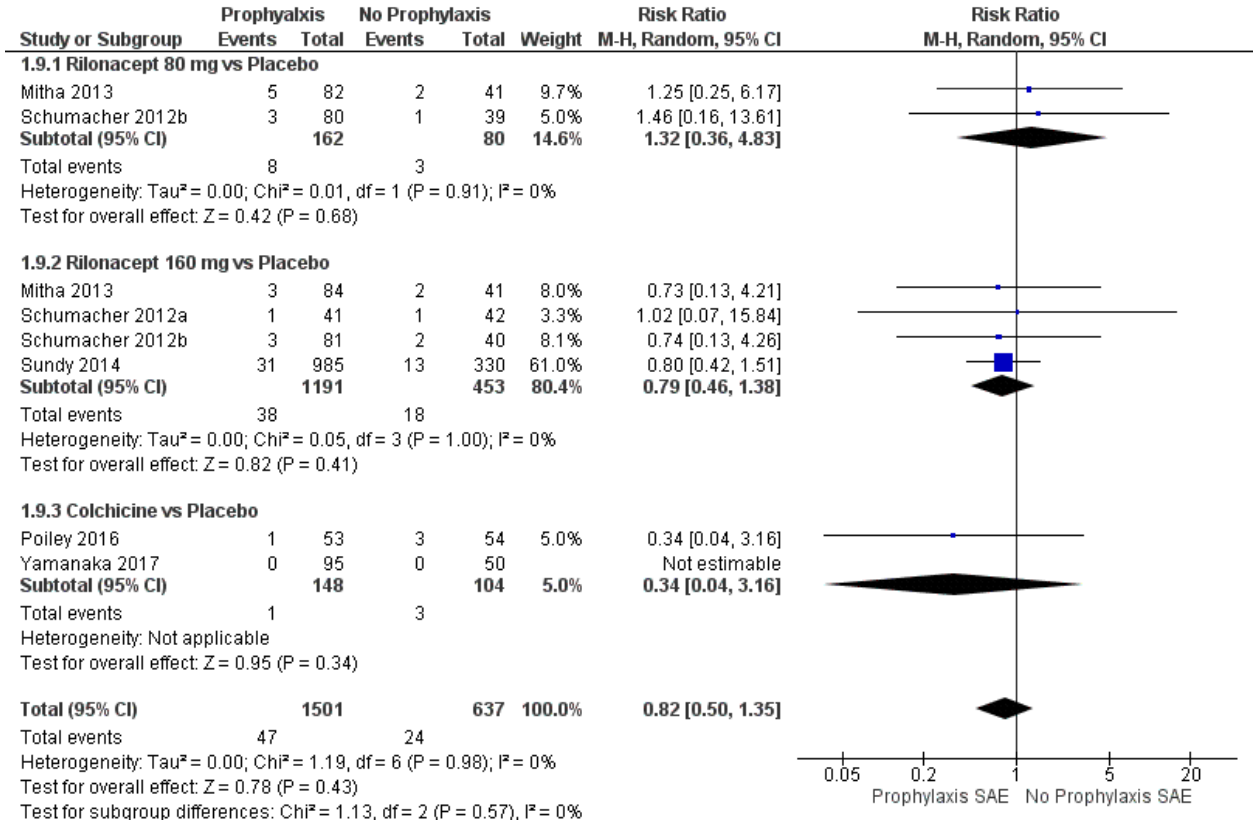


Figure 1.10 – Cardiovascular Adverse Events

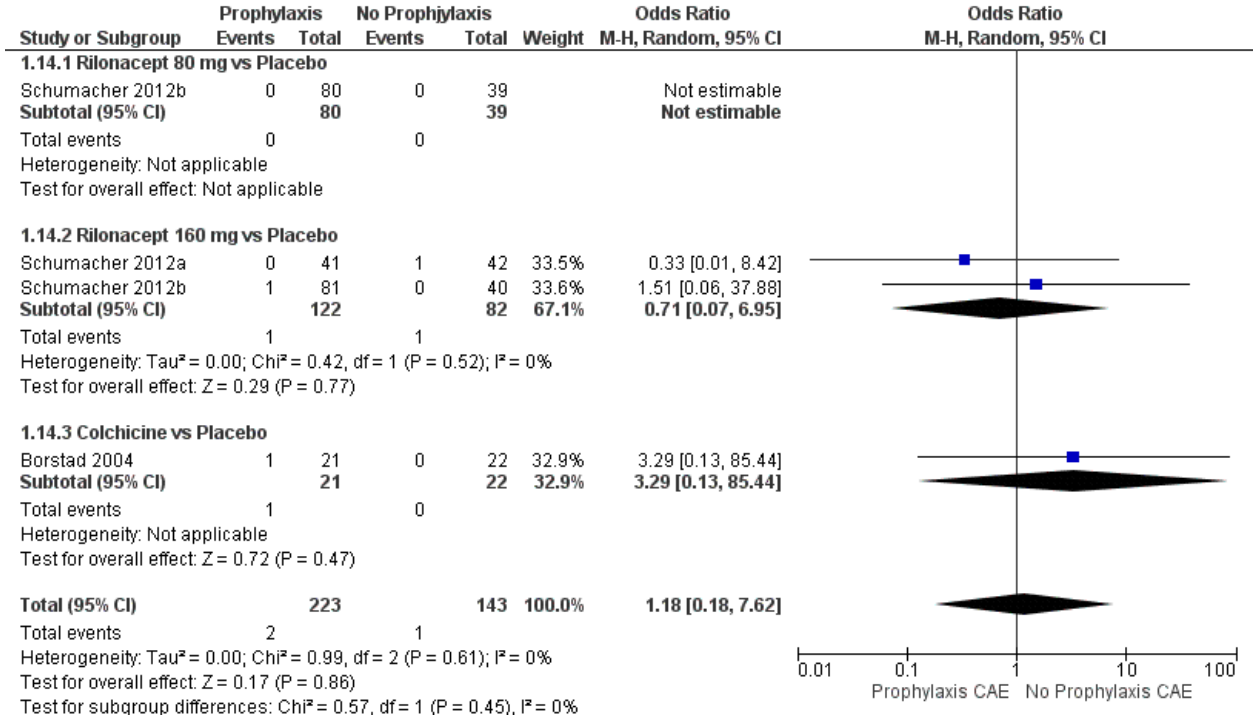


Figure 1.11 – Renal Adverse Events

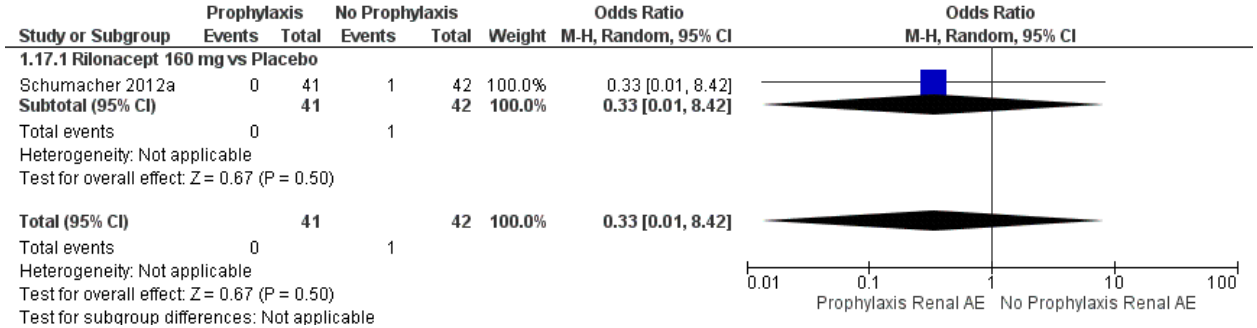
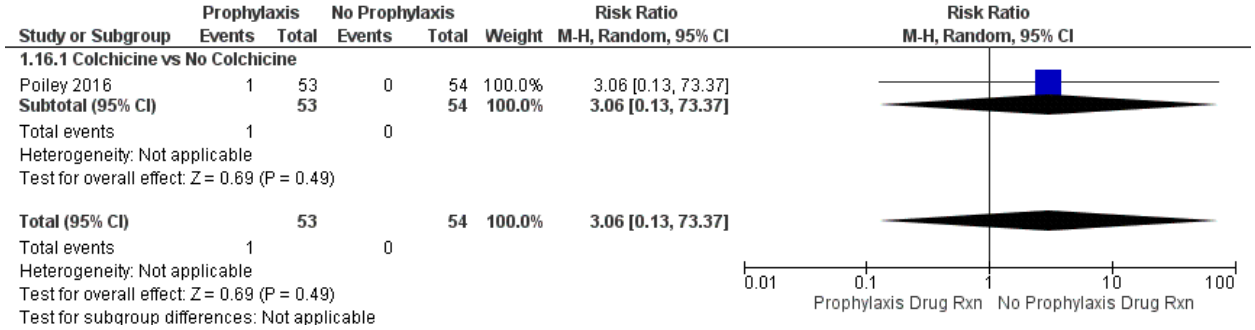


Figure 1.12 – Drug Hypersensitivity



Prophylaxis vs No Prophylaxis – Observational Data

Figure 2.1 – Mean Flares/Patient/Month

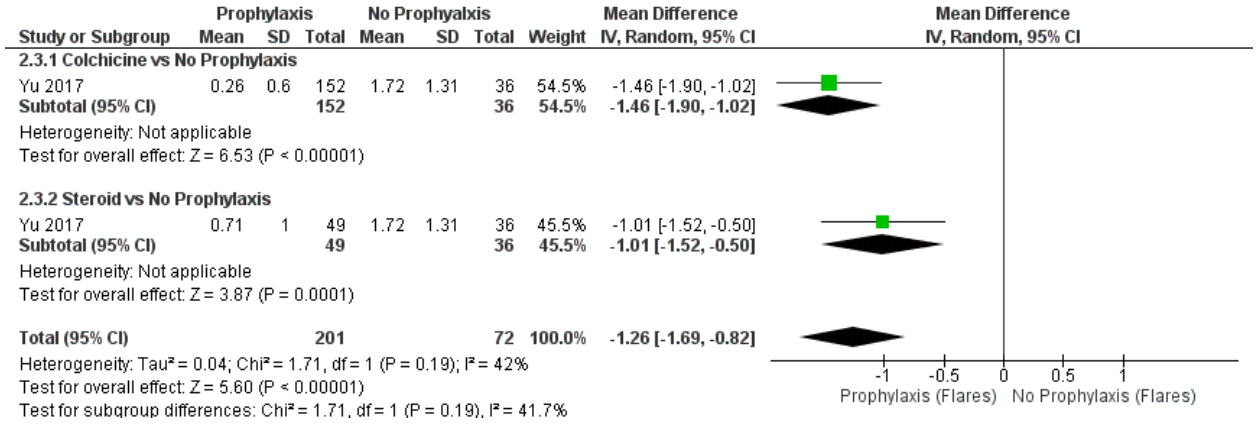


Figure 2.2 – Mean Change in SUA

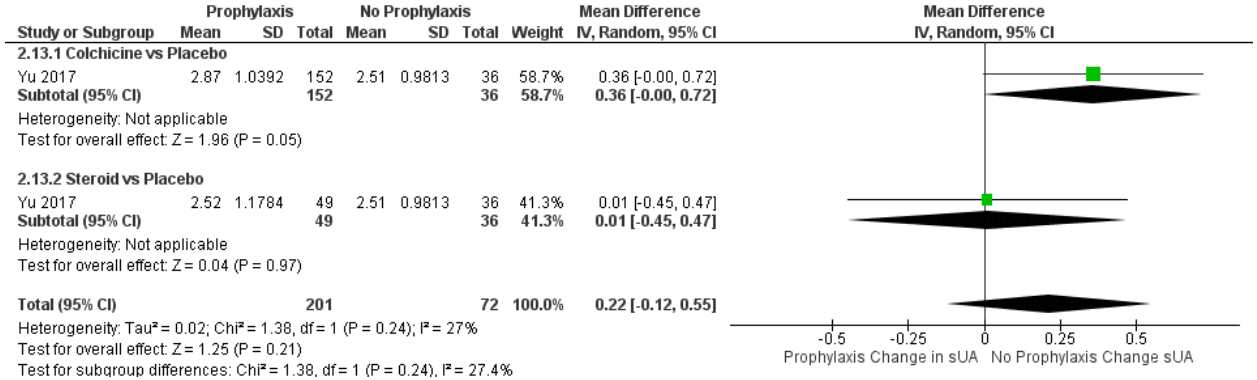


Figure 2.3 – Serious Adverse Events; Diverse Definitions

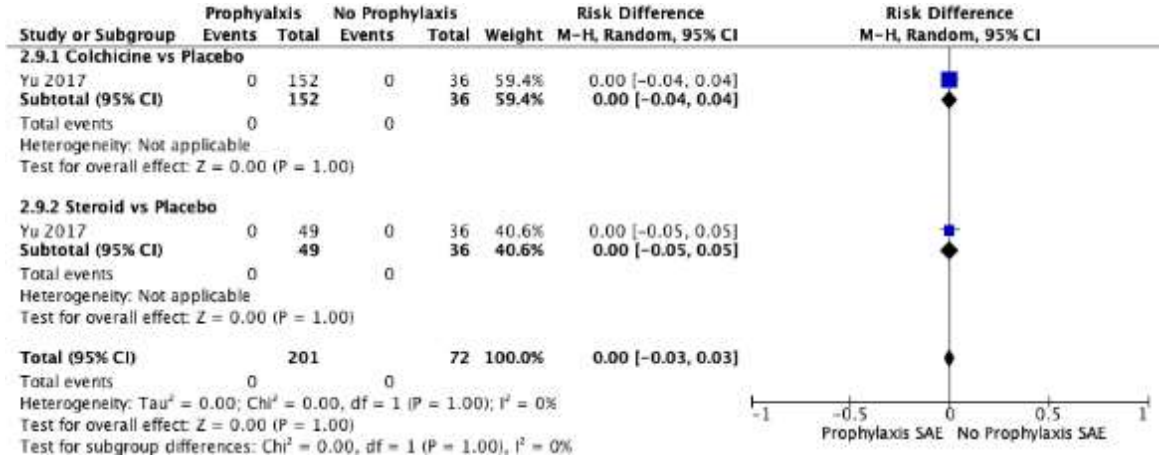
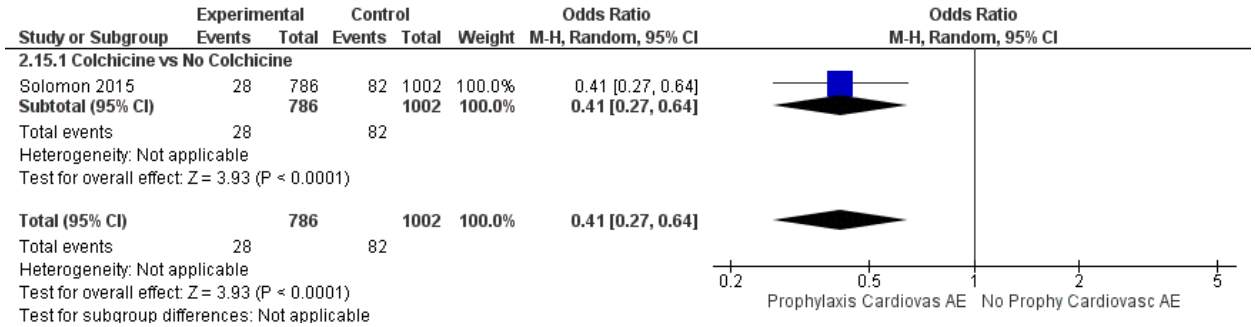


Figure 2.4 – Cardiovascular Adverse Events



Canakinumab vs Colchicine

Figure 3.1 – Gout Flares; Number with at least 1 gout flare

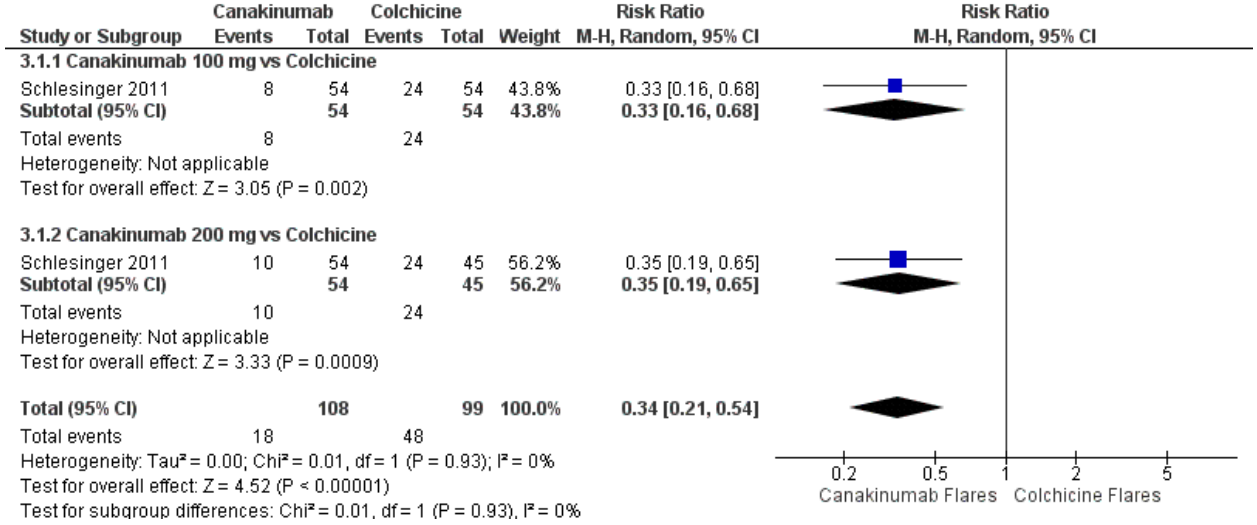
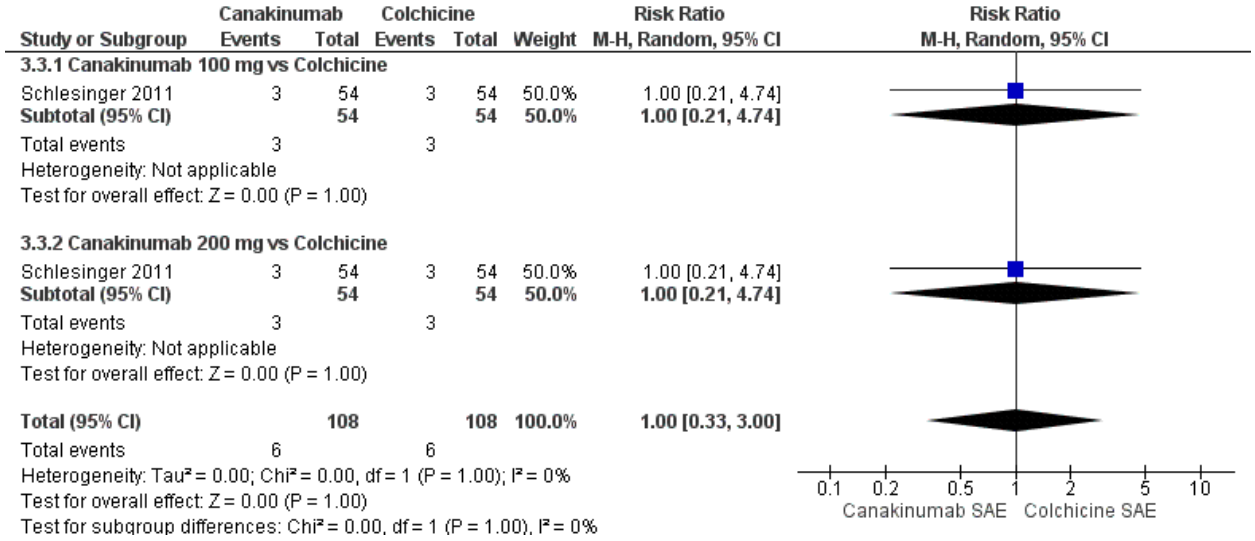


Figure 3.2 – Serious Adverse Events



10 Should we use allopurinol, febuxostat, probenecid, allopurinol/lesinurad 200mg combination, febuxostat/lesinurad 200mg combination, pegloticase, or no treatment in patients diagnosed with gout with an indication for ULT?

For this question, there was evidence from randomized clinical trials and observational studies. Evidence from randomized clinical trials was combined using network meta-analysis. The results from this analysis are presented in appendix X.

Evidence from observational studies

We found 10 observational studies addressing this question.[35-45] The studies provided information regarding 3 different comparisons. There were 5 studies comparing ULT vs no ULT.[35, 39, 40, 42, 45] These studies included information for patients who received only allopurinol,[35, 40] allopurinol or febuxostat,[39] and allopurinol, benzbromarone, or probenecid;[42] and compared their outcomes to patients who did not receive ULTs. This evidence is presented in Table 1. There were 4 studies comparing the effects of febuxostat with those of allopurinol.[36, 37, 43, 44] The studies compared doses from 40 to 80 mg of febuxostat, and 150 or 300 mg of allopurinol. The results described below apply to all doses, unless a specific dose is mentioned. This evidence is presented in Table 2. Finally, two studies compared the outcomes of patients receiving probenecid and allopurinol.[38, 41] One of the studies did not provide details regarding the doses,[41] whereas the other described that the median dose of probenecid was 500 mg per day, and the median dose of allopurinol was 176 mg/day.[38] This evidence is presented in Table 3.
The evidence shows:

- Patients who receive ULTs
    - May have a lower risk of gout flares than patients who do not receive ULT, up to 3 years; but we are very uncertain about this evidence
    - May have a higher reduction in serum urate levels than patients who do not receive ULT, up to 3 years; but we are very uncertain about this evidence
    - May have a lower risk of all-cause mortality than patients who do not receive ULT, up to 6 years; but we are very uncertain about this evidence
    - May have a higher risk of cardiovascular adverse events than patients who do not receive ULT, up to 1.5 years
    - May not have a different risk of cardiovascular adverse events than patients who do not receive ULT, up to 6 years; but we are very uncertain about this evidence
    - May have a lower risk of developing CKD3+ than patients who do not receive ULT, up to 4.5 years
- Patients who receive febuxostat

    - May have a higher risk of experiencing gout flares than patients who receive allopurinol, up to 8 months; but we are very uncertain about this evidence
    - 40 mg may not have a different change in serum urate levels than patients who receive allopurinol 300 mg, up to 12 weeks; but we are very uncertain about this evidence
    - 80 mg may experience a higher change in serum urate levels than patients who receive allopurinol 300 mg, up to 12 weeks; but we are very uncertain about this evidence
    - In a median dose of 45-55 mg may have a higher probability of achieving serum urate levels < 6 mg/dL than patients who receive allopurinol 150 mg
    - 80 mg may have a lower risk of hypersensitivity serious adverse events than patients who receive allopurinol 300 mg, up to 6 months; but we are very uncertain about this evidence
    - May not have a different risk of abnormal renal function than patients who receive allopurinol 300 mg, up to 6 months; but we are very uncertain about this evidence
    - 40 mg may have a lower risk of major cardiovascular events than patients who receive allopurinol 150 mg, up to 8 months; but we are very nuncertain about this evidence
- Patients who receive probenecid
    - May not have a different probability of achieving serum urate levels <6 mg/dL than patients who receive allopurinol, up to 29 months; but we are very uncertain about this evidence
    - May have a lower risk of experiencing serious adverse events (including cardiovascular events, stroke, coronary revascularization, and heart failure) than patients who receive allopurinol, up to 4 months
    - May have a lower risk of all-cause mortality than patients who receive allopurinol, up to 4 months

The overall qualiy of the evidence from obervational studies is VERY LOW
When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is VERY LOW

Table 1: Evidence profile- Urate lowering therapy compared to no urate lowering therapy in patients with gout

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no urate lowering therapy	With Urate lowering therapy	Relative effect (95% CI)	Risk with no urate lowering therapy	Risk difference with Urate lowering therapy
Gout flares (follow up: mean 3 years; assessed with: Participant with at least one gout flare)**											
267 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	22/35 (62.9%)	69/232 (29.7%)	**RR 0.47** (0.34 to 0.65)	629 per 1,000	**333 fewer per 1,000** (415 fewer to 220 fewer)
Serum urate (follow up: mean 3 years; assessed with: Mean change in serum urate)**											
267 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	35	232	-	The mean serum urate** was **0.21** mg/dL	MD **1.22 mg/dL lower** (1.83 lower to 0.61 lower)
Serious Adverse Events* (follow up: mean 6.5 years; assessed with: All-cause mortality)											
572 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	36/286 (12.6%)	17/286 (5.9%)	**RR 0.47** (0.27 to 0.82)	126 per 1,000	**67 fewer per 1,000** (92 fewer to 23 fewer)

Table 1: Evidence profile- Urate lowering therapy compared to no urate lowering therapy in patients with gout

Certainty assessment							Summary of findings				
Serious Adverse Events* (follow up: range 5.25 years to 6.5 years; assessed with: Cardiovascular mortality, cardiovascular event requiring hospitalization)											
5538 (2 observational studies)	serious [b]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	482/2769 (17.4%)	567/2769 (20.5%)	**RR 0.39** (0.03 to 5.15)	174 per 1,000	**106 fewer per 1,000** (169 fewer to 722 more)
Serious adverse events* (follow up: 1.5 years; assessed with: Composite of cardiovascular events)											
48216 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	628/24108 (2.6%)	788/24108 (3.3%)	**HR 1.16** (0.99 to 1.36)	26 per 1,000	**4 more per 1,000** (0 fewer to 9 more)
Serious adverse events* (follow up: median 4.5 years; assessed with: Risk of developing CKD 3+)											
9520 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	623/4760 (13.1%)	579/4760 (12.2%)	**HR 0.87** (0.77 to 0.98)	131 per 1,000	**16 fewer per 1,000** (from 28 fewer to 2 fewer)
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health related quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Evidence profile- Urate lowering therapy compared to no urate lowering therapy in patients with gout

Certainty assessment							Summary of findings				

Activity limitation* - not reported

-	-	-	-	-	-	-	-	-	-	-	-

Tophus - not reported

-	-	-	-	-	-	-	-	-	-	-	-

Serious adverse events (hypersensitivity reactions)* - not reported

-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **HR:** Hazard ratio

Explanations

a. Study at high risk of bias
b. One of the studies is at high risk of bias. This may be the cause of inconsistency and imprecision, so we rated down only one level for all
Outcome importance
** Critical outcomes
* Important outcomes

Table 2: Evidence profile- Febuxostat compared to allopurinol for patients diagnosed with gout

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With allopurinol 300 mg	With febuxostat	Relative effect (95% CI)	Risk with allopurinol 300 mg	Risk difference with febuxostat
Gout flares - Febuxostat 40 and 80 mg versus Allopurinol 150 or 300 mg (follow up: range 6 months to 8 months; assessed with: Percentage of patients with 1+ flares)**											
2516 (2 observational studies)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	471/2086 (22.6%)	123/430 (28.6%)	**RR 1.25** (1.05 to 1.48)	226 per 1,000	**56 more per 1,000** (11 more to 108 more)
Serum Urate - Febuxostat 40 mg versus Allopurinol 300 mg (follow up: 12 weeks; assessed with: Mean change from baseline)**											
60 (1 observational study)	serious [b]	not serious	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	30	30	-	The mean serum Urate** was **-2.82** mg/dL	MD **0.35 mg/dL lower** (1 lower to 0.3 higher)
Serum Urate - Febuxostat 80 mg versus Allopurinol 300 mg (follow up: 12 weeks; assessed with: Mean change from baseline)**											
60 (1 observational study)	serious [d]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	30	30	-	The mean serum Urate** was **-2.82 mg/dL**	MD **1.35 lower** (2 lower to 0.7 lower)

Table 2: Evidence profile- Febuxostat compared to allopurinol for patients diagnosed with gout

Certainty assessment							Summary of findings				
Serum Urate - Febuxostat 45-55mg (median) vs Allopurinol 150 mg (follow up: 6 months; assessed with: People with SUA <6 mg/dl)**											
14736 (2 observational studies)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	3843/12053 (31.9%)	1446/2683 (53.9%)	**RR 1.38** (1.29 to 1.46)	319 per 1,000	**121 more per 1,000** (92 more to 147 more)
Serious adverse Events, Hypersensitivity Reaction* - Febuxostat 80 mg versus Allopurinol 300 mg (follow up: mean 6 months; assessed with: number of events)											
60 (1 observational study)	serious [d]	not serious	not serious	serious [e]	none	⨁◯◯◯ VERY LOW	5/30 (16.7%)	1/30 (3.3%)	**RR 0.14** (0.02 to 0.82)	167 per 1,000	**143 fewer per 1,000** (163 fewer to 30 fewer)
Serious Adverse Events, Abnormal Renal Function* - Febuxostat 40 mg or 80 mg versus Allopurinol 300 mg (follow up: mean 6 months; assessed with: number of events)											
60 (1 observational study)	serious [f]	not serious	not serious	serious [g]	none	⨁◯◯◯ VERY LOW	1/30 (3.3%)	1/30 (3.3%)	**RR 0.81** (0.10 to 6.27)	33 per 1,000	**6 fewer per 1,000** (30 fewer to 176 more)
Serious adverse events, Any major CV event* - Febuxostat 40 mg versus Allopurinol 150 mg (follow up: range 7.5 months to 8.2 months; assessed with: Number of events (CAD, CVA or PVD))											
2426 (1 observational study)	serious [h]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	148/2056 (7.2%)	14/370 (3.8%)	**RR 0.53** (0.31 to 0.90)	72 per 1,000	**34 fewer per 1,000** (50 fewer to 7 fewer)

Table 2: Evidence profile- Febuxostat compared to allopurinol for patients diagnosed with gout

Certainty assessment							Summary of findings				
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health Related Quality of Life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity Limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Two trials contributed to the information about this outcome. Foody et al weighted highly (94.6%) and had issues with confounding and selection bias. Other trial had moderate bias in subjective component of deviation in intended interventions and outcome measurements.
b. Moderate bias in subjective component of deviation of intended interventions and measurement of outcomes.
c. Effect crosses midline and there were only 30 patients in each arm.
d. Moderate bias in subjective component of deviation of intended interventions and measurement of outcomes.
e. While the diamond does not cross midline, there are less than 150 events (only 10 events)
f. There was moderate bias in the subjective component of deviation of intended interventions and measurement of outcomes.
g. Effect crosses midline and there are <150 events
h. This trial had issues with selection and confounding bias
Outcome importance
** Critical outcomes
* Important outcomes

Table 3: Evidence profile- Probenecid compared to Allopurinol for patients with gout who have indication for ULT

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Allopurinol	With Probenecid	Relative effect (95% CI)	Risk with Allopurinol	Risk difference with Probenecid
Serum urate (follow up: mean 29 months; assessed with: Numer of patients with preindex sUA >6 (within 1 yr prior to initiation of ULT) and postindex sUA < 6 mg/dl)**											
155 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	36/147 (24.5%)	3/8 (37.5%)	**RR 1.53** (0.60 to 3.91)	245 per 1,000	**130 more per 1,000** (98 fewer to 713 more)
Serious adverse events- Cardiovascular events* (follow up: median 4 months; assessed with: Number of events, composite CV endpoint of hospitalization for MI or stroke for any length of stay)											
38888 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	1182/29166 (4.1%)	203/9722 (2.1%)	**RR 0.52** (0.44 to 0.60)	41 per 1,000	**19 fewer per 1,000** (23 fewer to 16 fewer)
Serious adverse events- Stroke* (follow up: median 4 months; assessed with: Number of events)											
38888 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	539/29166 (1.8%)	83/9722 (0.9%)	**RR 0.46** (0.37 to 0.58)	18 per 1,000	**10 fewer per 1,000** (12 fewer to 8 fewer)

Table 3: Evidence profile- Probenecid compared to Allopurinol for patients with gout who have indication for ULT

Certainty assessment							Summary of findings				
Serious adverse events- Coronary Revascularization* (follow up: median 4 months; assessed with: Number of events)											
38888 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	1033/29166 (3.5%)	213/9722 (2.2%)	**RR 0.62** (0.53 to 0.72)	35 per 1,000	**13 fewer per 1,000** (17 fewer to 10 fewer)
Serious adverse events- New Heart Failure* (follow up: median 4 months; assessed with: Number of events)											
28404 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	1421/21303 (6.7%)	289/7101 (4.1%)	**RR 0.61** (0.54 to 0.69)	67 per 1,000	**26 fewer per 1,000** (31 fewer to 21 fewer)
Serious adverse events- Exacerbation of Heart Failure* (follow up: median 4 months; assessed with: Number of events)											
10484 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	2627/7863 (33.4%)	590/2621 (22.5%)	**RR 0.67** (0.62 to 0.73)	334 per 1,000	**110 fewer per 1,000** (127 fewer to 90 fewer)

Table 3: Evidence profile- Probenecid compared to Allopurinol for patients with gout who have indication for ULT

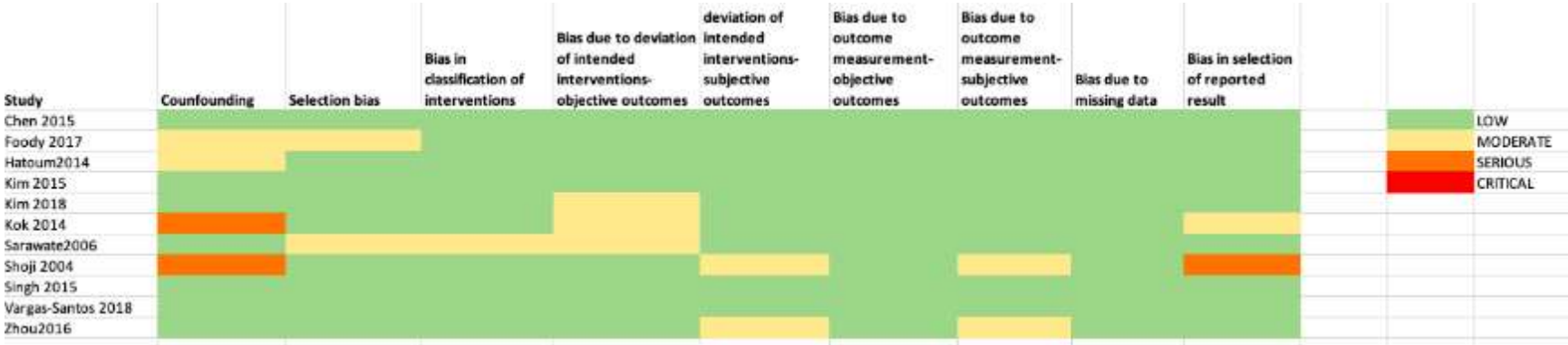
Certainty assessment							Summary of findings				
38888 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	1387/29166 (4.8%)	255/9722 (2.6%)	**RR 0.55** (0.48 to 0.63)	48 per 1,000	**21 fewer per 1,000** (25 fewer to 18 fewer)
Gout flares - not reported**											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health related quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio

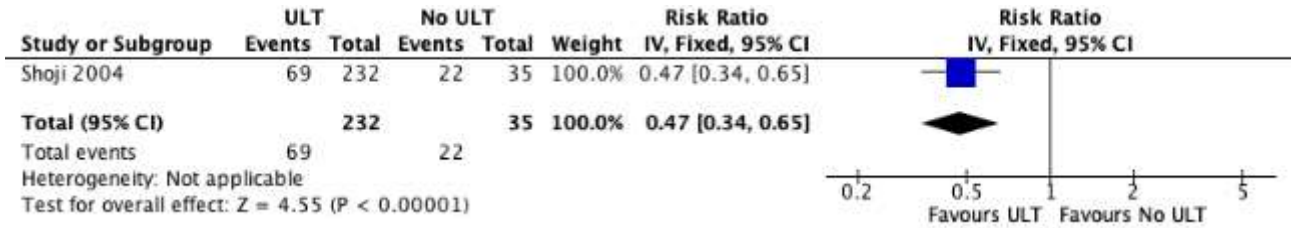
Explanations

a. There was selection bias, bias in the classification of interventions and deviation of intended outcomes
b. Effect crosses mid-line and there are <150 events
Outcome importance
** Critical outcomes
* Important outcomes

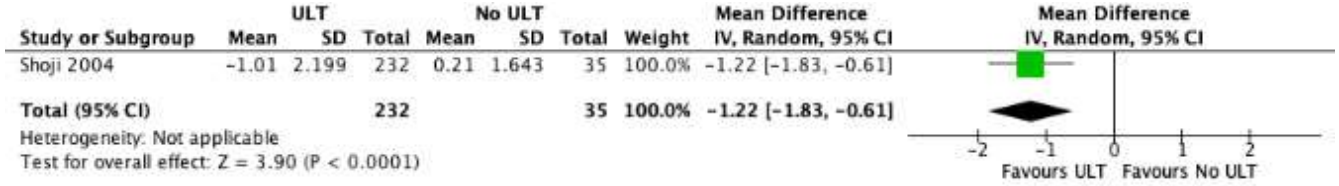
Risk of bias assessment



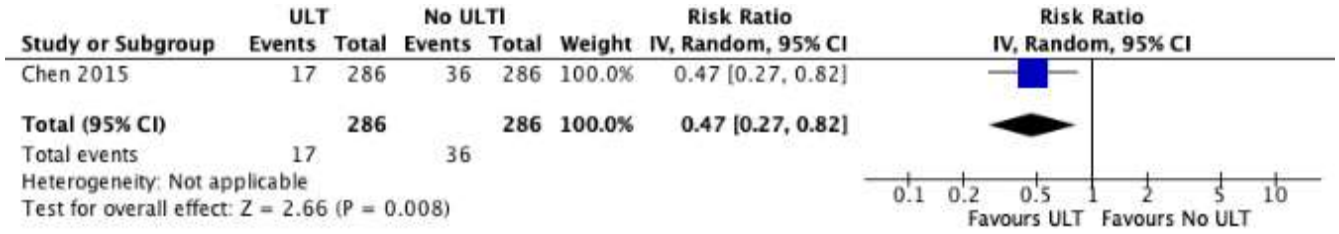
Comparison 1: ULT vs no ULT



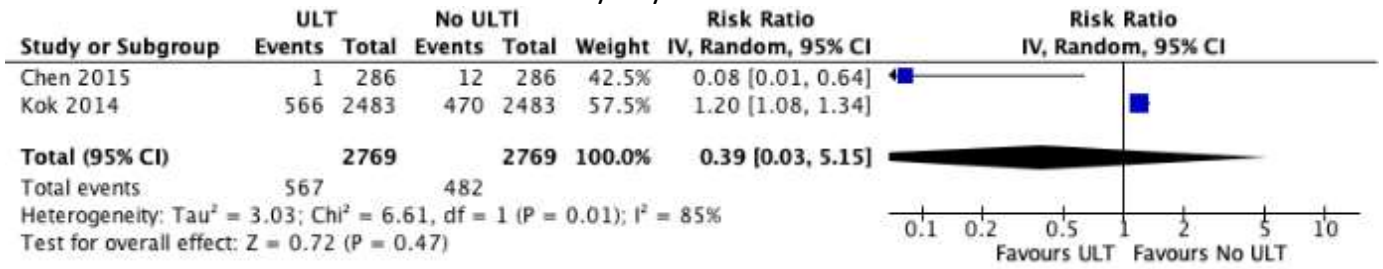
1.1 Gout flares (people with 1+ flares)- 3 years



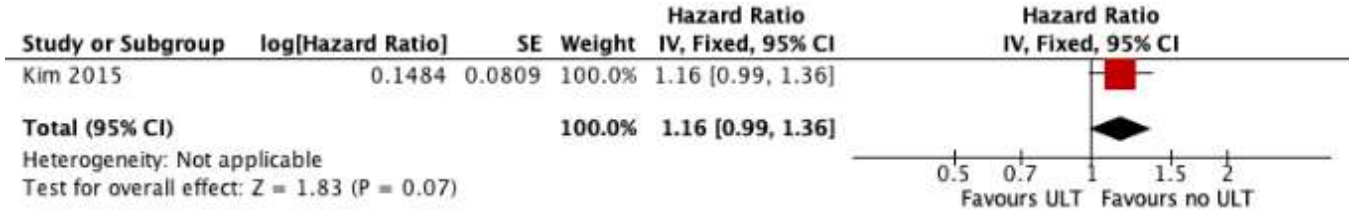
1.2 Serum urate (mean change from baseline)- 1 year



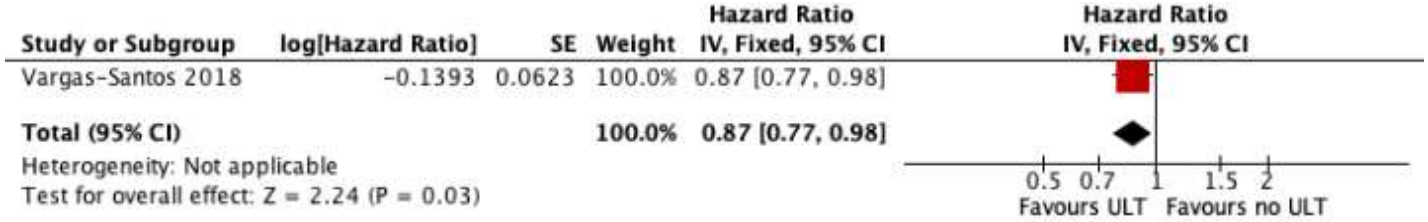
1.3 Serious adverse events- all-cause mortality- 6 years



1.4 Serious adverse events- cardiovascular events- 6 years

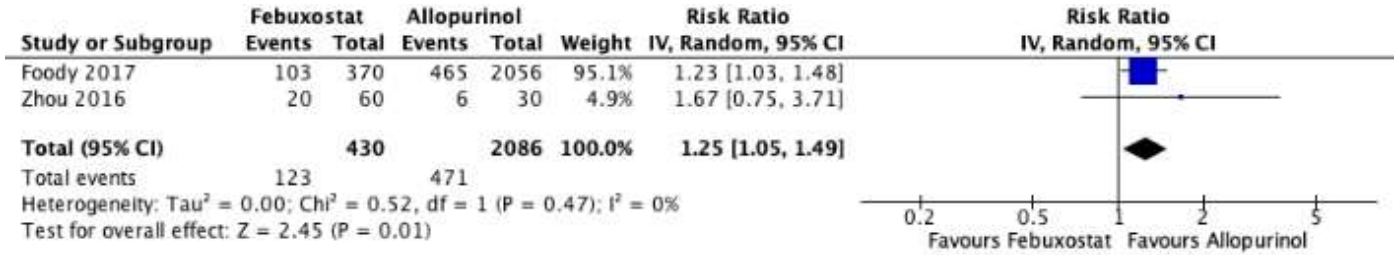


1.5 Serious adverse events- cardiovascular events 1.5 years/ person years

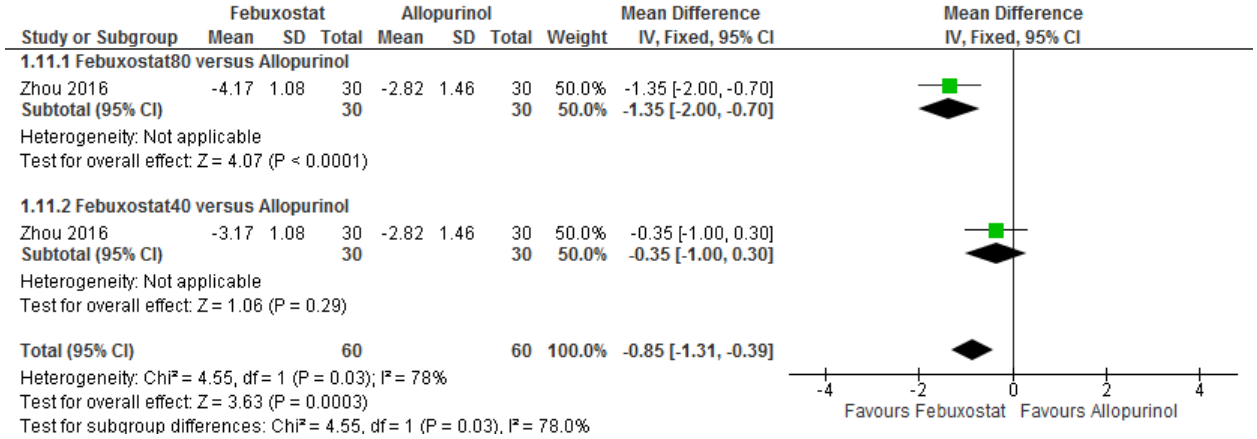


1.6 Serious adverse events: Risk of CKD3+

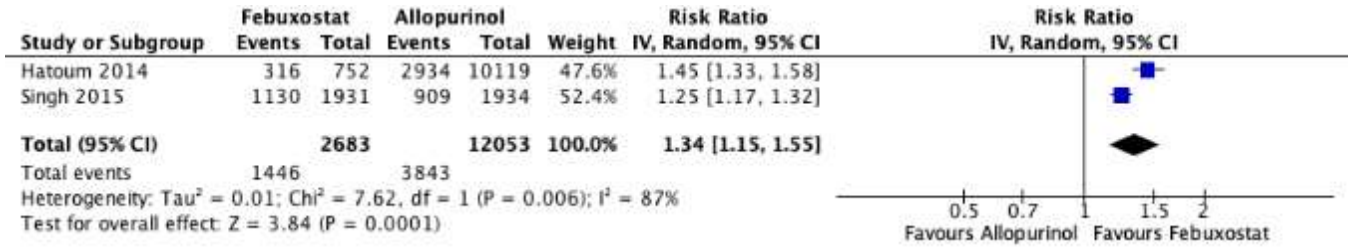
Comparison 2: Febuxostat versus allopurinol



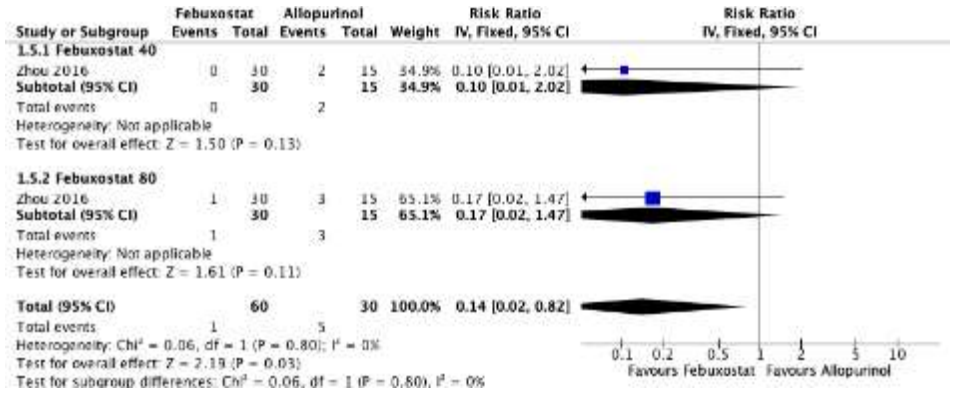
2.1 Patients with gout flares up to 8 months



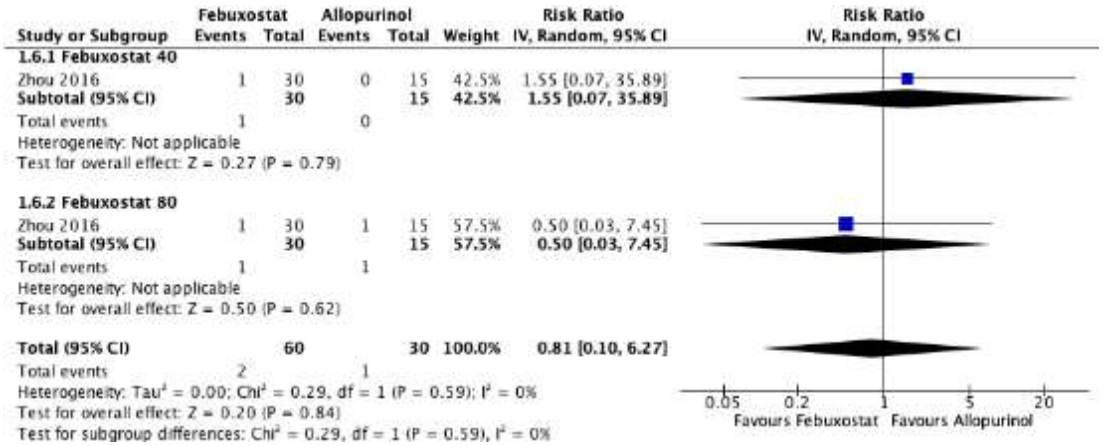
2.2 Serum urate- mean change up to 12 weeks



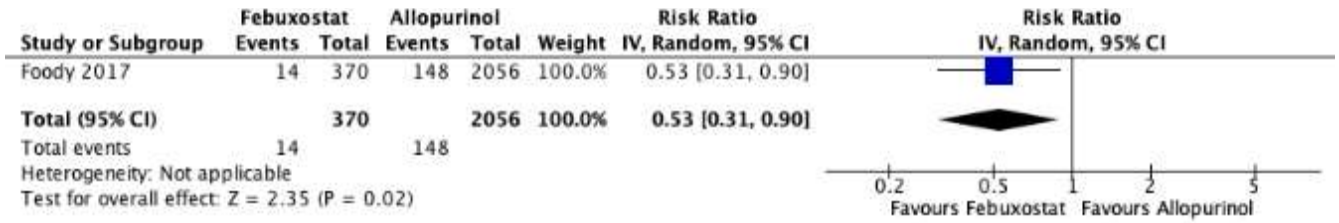
2.3 Serum Urate < 6 mg/dl at 6 months



2.4 Serious Adverse Events Hypersensitivity reactions - Febuxostat versus Allopurinol.

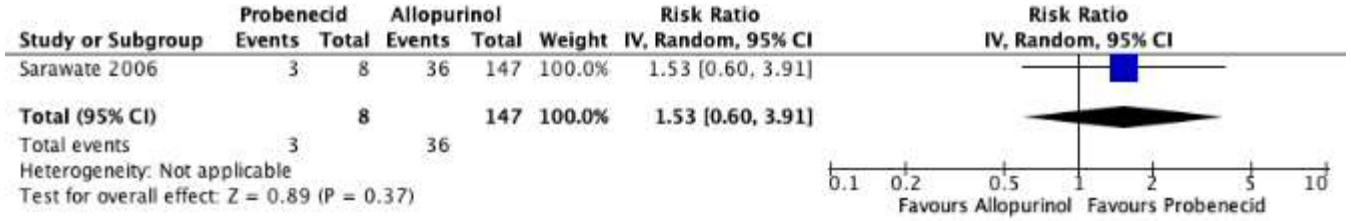


2.5 Serious Adverse Events Abnormal Renal Function - Febuxostat 40 or 80 versus Allopurinol.

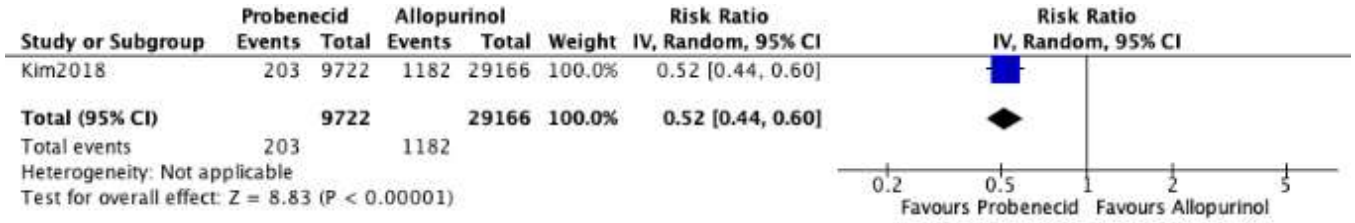


2.6 Serious adverse events, any major cardiovascular event up to 8 months

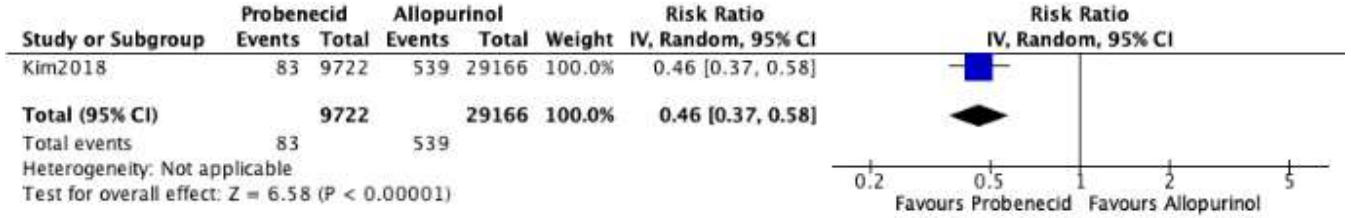
Comparison 3: Probenecid vs Allopurinol



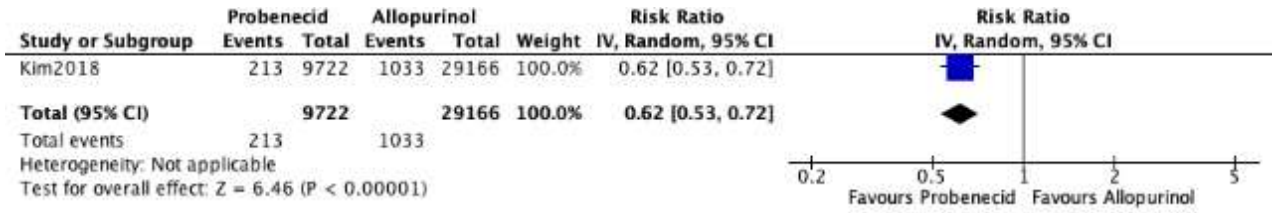
3.1 Forest plot of comparison: 2 Probenecid versus Allopurinol, outcome: 2.1 Number of patients with preindex sUA >6 (within 1 yr prior to initiation of ULT) and postindex sUA < 6 mg/dl.



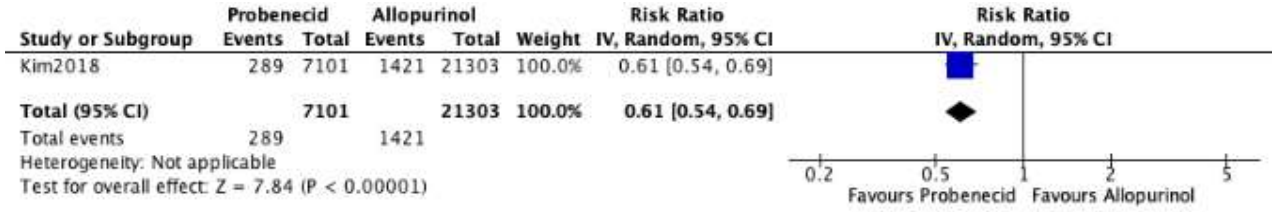
3.2 Forest plot of comparison: 2 Probenecid versus Allopurinol, outcome: 2.2 composite CV endpoint of hospitalization for MI or stroke for any length of stay.



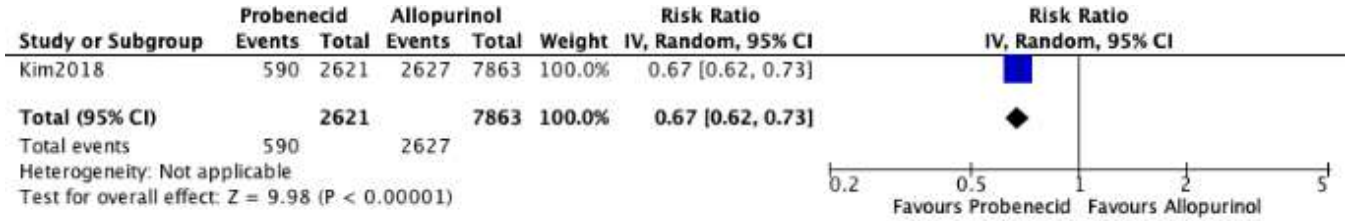
3.3 Forest plot of comparison: 2 Probenecid versus Allopurinol, outcome: 2.3 Stroke (based on ICD codes).



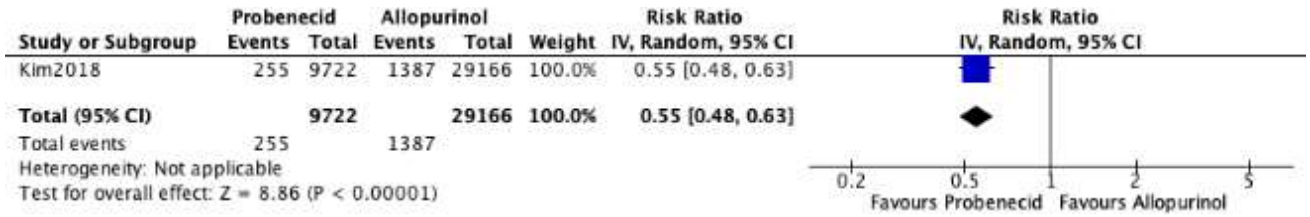
3.4 Forest plot of comparison: 2 Probenecid versus Allopurinol, outcome: 2.4 Coronary Revascularization (based on ICD codes).



3.5 Forest plot of comparison: 2 Probenecid versus Allopurinol, outcome: 2.5 New Heart Failure (based on ICD codes).



3.6 Forest plot of comparison: 2 Probenecid versus Allopurinol, outcome: 2.6 Exacerbation of Heart Failure (based on ICD codes).



2.7 Forest plot of comparison: 2 Probenecid versus Allopurinol, outcome: 2.7 All cause death.

11 Should we use allopurinol or febuxostat in patient with gout receiving hemodialysis who are starting an ULT?

The systematic review did not find any studies addressing this question.

12: Should HLA-B*5801 be tested and allopurinol be avoided if positive vs. HLA-B*5801 not be tested and allopurinol be started in all patients be used in patients diagnosed with gout starting allopurinol?

We found one observational study addressing this question.[46]

The evidence shows:

- Patients who undergo testing of HLA-B*5801 and in whom allopurinol is avoided if positive may have a lower risk of serious hypersensitivity adverse events up to 2 months than patients who do not undergo testing; but we are very uncertain about this evidence

The overall quality of the evidence is VERY LOW

When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is VERY LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With HLA-B*5801 not be tested and allopurinol be started in all patients	With HLA-B*5801 be tested and allopurinol be avoided if positive	Relative effect (95% CI)	Risk with HLA-B*5801 not be tested and allopurinol be started in all patients	Risk difference with HLA-B*5801 be tested and allopurinol be avoided if positive
Severe adverse events (follow up: mean 2 months; assessed with: Cutaneous reaction)**											
4346 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	7/2173 (0.3%)	0/2173 (0.0%)	**RR 0.07** (0.00 to 1.17)	3 per 1,000	**3 fewer per 1,000** (3 fewer to 1 more)
Gout flares* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Evidence profile

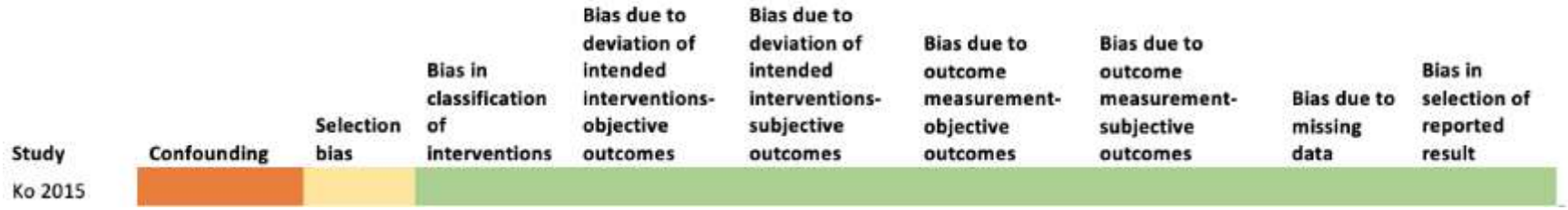
Certainty assessment							Summary of findings				
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health related quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serum urate* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient adherence* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio

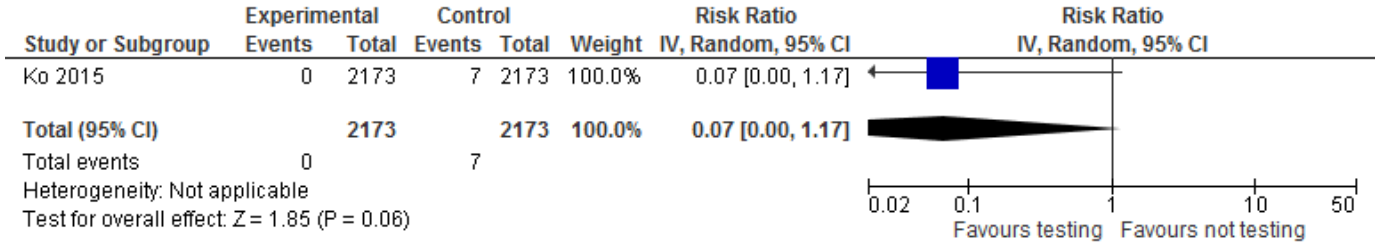
Explanations

a. observational study with serious risk of bias in certain domains
b. diamond crosses null threshold
Outcome importance
** Critical outcomes
* Important outcomes

Risk of bias assessment



1.1 Forest plot of comparison: 1 Testing vs not testing HLA B*5801-OBS, outcome: 1.1 Severe cutaneous events- 2 months.



13: Should dose titration while checking serum urate versus fixed ULT doses be used in gout patients on ULT (RCT data)?

We found 3 studies addressing this question.[22, 47, 48] The first study was a randomized clinical trial[47] in which researchers enrolled 183 participants, who were assigned to receive a dose of allopurinol that could be escalated based on serum urate levels or a fixed dose. Even though the researchers reported outcomes for an open label extension,[49] in which all patients received dose escalation, we only synthesized the data for the first 12 months, which is the data applicable to this question. The second study was a randomized clinical trial[22] in which 517 patients were allocated to receive a nurse-led care package, which could include ULT dose titration according to SUA levels, or usual care. The third study was an observational study in which researchers included 120 participants who received an increased dose of allopurinol or a maintenance dose of allopurinol.
The evidence shows:

- Patients who receive dose titration based on serum urate levels
    - May not have a different risk of gout flares than patients who receive fixed doses, at 3 months and 12 months
    - May not have a different mean number of flares than patients who receive fixed doses, at 12 months and 24 months
    - Probably have a lower risk of experiencing 2 or more flares than patients who receive fixed doses, at 24 months
    - Probably have a higher probability of achieving serum urate levels <6 mg/dL than patients who receive fixed doses, at 12 and 24 months
    - Probably experience lower levels of pain than patients who receive dose titration based on serum urate levels, at 12 months
    - May not have tophus of different size than patients who receive fixed doses, at 3 months and 12 months
    - Probably have smaller tophi at 12 and 24 months that patients who received fixed doses, as measured by regression of largest tophus.
    - May not experience different activity limitation than patients who receive fixed doses, at 12 months
    - Probably have better health related quality of life than patients who receive fixed doses, 24 months
    - May not experience any, cardiovascular, renal, or hypersensitivity serious adverse events than patients who receive fixed doses, at 12 months
- The evidence from observational studies agrees with that of randomized trials regarding adverse effects, and shows that there may be no differences in serum urate levels up to 4 years; but we are very uncertain about this evidence

The overall quality of the evidence is MODERATE
When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is MODERATE

Table 1: Evidence profile- ULT dose titration compared to fixed dose ULT while checking serum urate in gout patients on ULT (RCT data)

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With fixed dose ULT while checking serum urate	With ULT dose titration	Relative effect (95% CI)	Risk with fixed dose ULT while checking serum urate	Risk difference with ULT dose titration
Gout flares* (follow up: mean 3 months; assessed with: proportion of participants with at least 1 gout flare)											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	50/93 (53.8%)	44/90 (48.9%)	**RR 0.91** (0.69 to 1.21)	538 per 1,000	**48 fewer per 1,000** (167 fewer to 113 more)
Gout flares* (follow up: mean 12 months; assessed with: proportion of participants with at least 1 gout flare)											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	55/93 (59.1%)	49/90 (54.4%)	**RR 0.92** (0.71 to 1.19)	591 per 1,000	**47 fewer per 1,000** (172 fewer to 112 more)
Gout flares* (follow up: 12 months; assessed with: mean number of gout flares per patient)											

Table 1: Evidence profile- ULT dose titration compared to fixed dose ULT while checking serum urate in gout patients on ULT (RCT data)

Certainty assessment							Summary of findings				
517 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	262	255	-	The mean gout flares** was **3.5**	MD **0.1 higher** (4.38 lower to 4.58 higher)

Gout flares* (follow up: range 12-24 months; assessed with: mean number per patient)

517 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	262	255	-	The mean gout flares** was **2.4**	MD **0.9 lower** (4.02 lower to 2.22 higher)

Gout flares* (follow up: 2 years; assessed with: People with 2+ flares)

517 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	64/262 (24.4%)	21/255 (8.2%)	**RR 0.34** (0.21 to 0.53)	244 per 1,000	**161 fewer per 1,000** (193 fewer to 115 fewer)

Serum urate* (follow up: mean 12 months; assessed with: proportion of people with serum urate <6mg/dL)

700 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	99/355 (27.9%)	304/345 (88.1%)	**RR 2.82** (1.69 to 4.70)	279 per 1,000	**508 more per 1,000** (192 more to 1,032 more)

Table 1: Evidence profile- ULT dose titration compared to fixed dose ULT while checking serum urate in gout patients on ULT (RCT data)

Certainty assessment							Summary of findings				
Serum urate (follow up: 24 months; assessed with: proportion of people with serum urate <6mg/dL)**											
517 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	78/262 (29.8%)	242/255 (94.9%)	**RR 3.19** (2.64 to 3.85)	298 per 1,000	**652 more per 1,000** (488 more to 848 more)
Pain* (follow up: 12 months; assessed with: Visual analogue scale; Scale from: 0 to 10)											
183 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	93	90	-	The mean pain* was **2.04**	MD **0.11 lower** (0.2 lower to 0.02 lower)
Tophus* (follow up: 3 months; assessed with: Mean size in mm)											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	93	90	-	The mean tophus* was **11.8** mm	MD **0.9 mm lower** (3.32 lower to 1.52 higher)
Tophus* (follow up: 12 months; assessed with: Mean size in mm)											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	93	90	-	The mean tophus* was **9.7** mm	MD **1.8 mm lower** (4.2 lower to 0.6 higher)

Table 1: Evidence profile- ULT dose titration compared to fixed dose ULT while checking serum urate in gout patients on ULT (RCT data)

Certainty assessment							Summary of findings				
Tophus* (follow up: 12 months; assessed with: diameter of largest tophus in mm)											
517 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	262	255	-	The mean tophus* was **16.54** mm	MD **9.01 mm lower** (11.42 lower to 6.6 lower)
Tophus* (follow up: 24 months; assessed with: diameter of largest tophus in mm)											
517 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	262	255	-	The mean tophus* was **13.61** mm	MD **10.32 mm lower** (12.38 lower to 8.26 lower)
Activity Limitation* (follow up: 12 months; assessed with: Health Assessment Questionnaire; Scale from: 0 (no disability) to 3 (total dependence)); Scale from: 0 (no disability) to 3 (total dependence))											
143 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	73	70	-	The mean activity Limitation* was **0.51**	MD **0.11 higher** (0.14 lower to 0.36 higher)

Table 1: Evidence profile- ULT dose titration compared to fixed dose ULT while checking serum urate in gout patients on ULT (RCT data)

Certainty assessment							Summary of findings				
Health Related Quality of Life* (follow up: 24 months; assessed with: Gout impact scale: gout concern overall score)											
517 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	262	255	-	The mean health Related Quality of Life* was **53.62**	MD **16.08 lower** (20.56 lower to 11.6 lower)
Health Related Quality of Life* (follow up: 24 months; assessed with: Gout impact scale: unmet gout treatment need score)											
517 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	262	255	-	The mean health Related Quality of Life* was **33.61**	MD **12.68 lower** (15.76 lower to 9.6 lower)
Patient adherence* (follow up: 24 months; assessed with: proportion of patients taking ULT)											
517 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	147/262 (56.1%)	245/255 (96.1%)	**RR 1.71** (1.53 to 1.91)	561 per 1,000	**398 more per 1,000** (297 more to 511 more)

Table 1: Evidence profile- ULT dose titration compared to fixed dose ULT while checking serum urate in gout patients on ULT (RCT data)

Certainty assessment							Summary of findings				
Serious adverse events* (follow up: mean 12 months; assessed with: proportion with life threatening event that required hospital admission or resulted in death)											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	25/93 (26.9%)	22/90 (24.4%)	**RR 0.91** (0.55 to 1.49)	269 per 1,000	**24 fewer per 1,000** (121 fewer to 132 more)
Serious adverse events* (assessed with: death longest follow-up)											
700 (2 RCTs)	serious [a]	serious [c]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	13/355 (3.7%)	7/345 (2.0%)	**RR 0.56** (0.14 to 2.17)	37 per 1,000	**16 fewer per 1,000** (31 fewer to 43 more)
Serious adverse events, cardiovascular* (follow up: mean 12 months; assessed with: Proportion of people with CV events)											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	8/93 (8.6%)	11/90 (12.2%)	**RR 1.42** (0.60 to 3.37)	86 per 1,000	**36 more per 1,000** (34 fewer to 204 more)
Serious adverse events, renal* (follow up: mean 12 months; assessed with: Proportion of people with worsening kidney function)											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	5/93 (5.4%)	2/90 (2.2%)	**RR 0.41** (0.08 to 2.08)	54 per 1,000	**32 fewer per 1,000** (49 fewer to 58 more)

Table 1: Evidence profile- ULT dose titration compared to fixed dose ULT while checking serum urate in gout patients on ULT (RCT data)

Certainty assessment							Summary of findings				
Serious adverse events, hypersensitivity* (follow up: mean 12 months; assessed with: proportion of people with allopurinol hypersensitivity)											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	0/93 (0.0%)	0/90 (0.0%)	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Patient Global Assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. The risk of bias table indicated at least one category at high risk of bias.
b. The confidence interval crosses null.
c. Few events
**Critical outcomes
* Important outcomes

Table 2: Evidence profile- evidence from Observational studies

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With ULT dose titration while checking serum urate	With fixed ULT doses	Relative effect (95% CI)	Risk with ULT dose titration while checking serum urate	Risk difference with fixed ULT doses
Serum urate** (follow up: range 2.3 years to 3.7 years; assessed with: mean level mg/dL)											
120 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	52	68	-	The mean serum urate** was 6.72 mg/dL	MD 0.16 mg/dL lower (1.75 lower to 1.43 higher)
Serious adverse events** (follow up: range 2.3-3.7 years; assessed with: proportion with allopurinol reaction)											
120 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	3/52 (5.8%)	2/68 (2.9%)	**RR 0.51** (0.09 to 2.94)	58 per 1,000	28 fewer per 1,000 (53 fewer to 112 more)
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient Global Assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 2: Evidence profile- evidence from Observational studies

Certainty assessment							Summary of findings				

Health Related Quality of Life* - not reported

-	-	-	-	-	-	-	-	-	-	-	-

Activity Limitation* - not reported

-	-	-	-	-	-	-	-	-	-	-	-

Patient Adherence* - not reported

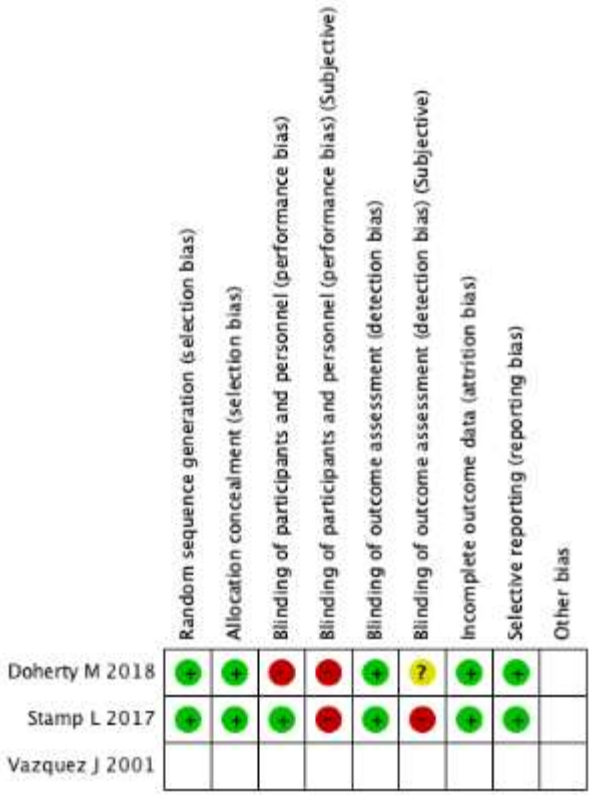
-	-	-	-	-	-	-	-	-	-	-	-

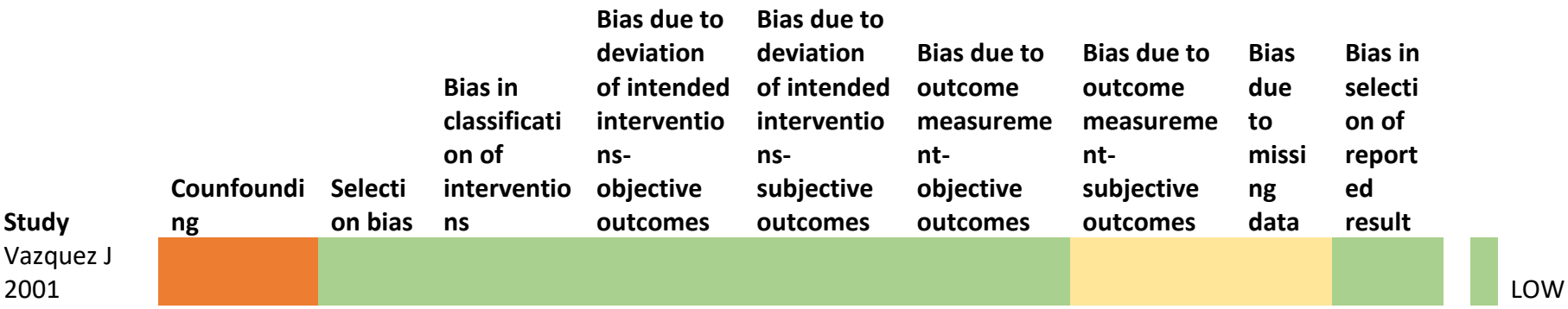
CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

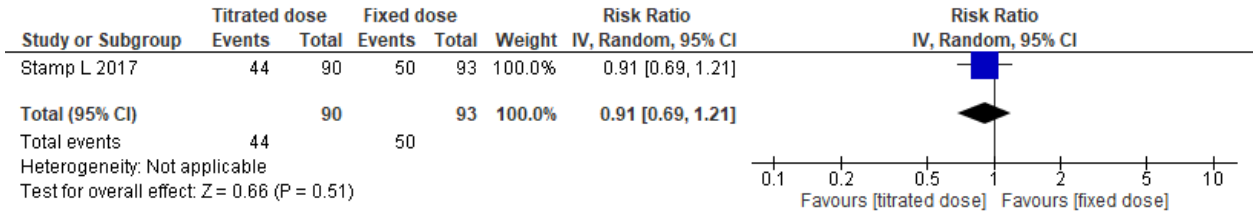
a. The study was at high risk of bias.
b. Confidence interval crosses the null
Outcome importance:
**Critical outcomes
* Important outcomes

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

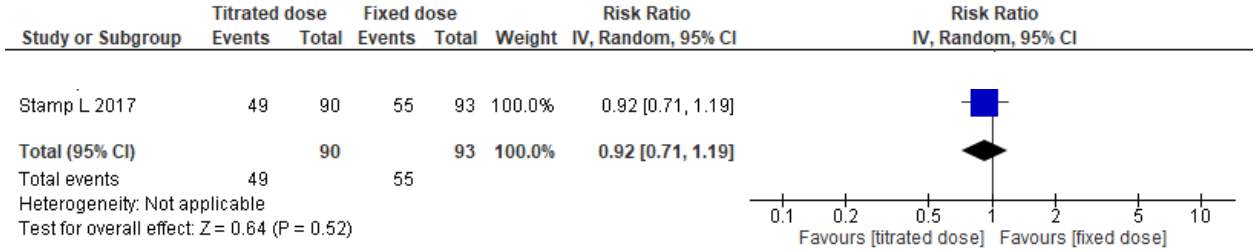



Study
Counfoundi ng
Selecti on bias
Bias in classificati on of interventio ns
Bias due to deviation of intended interventio ns- objective outcomes
Bias due to deviation of intended interventio ns- subjective outcomes
Bias due to outcome measureme nt- objective outcomes
Bias due to outcome measureme nt- subjective outcomes
Bias due to missi ng data
Bias in selecti on of report ed result
Vazquez J 2001
LOW

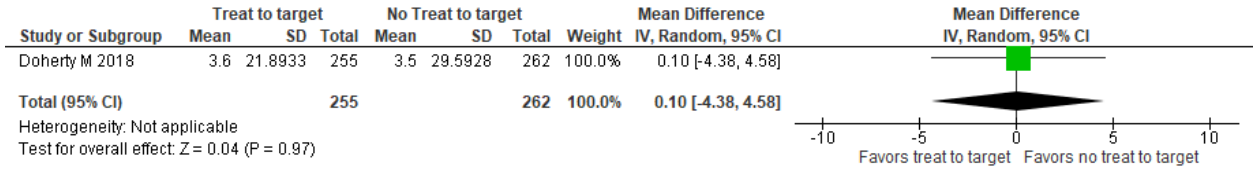
Forest plot of comparison 1 Dose titration versus fixed dose-RCT, outcome: 1.1 Gout flares- proportion of participants with at least 1 gout flare- 3 months.



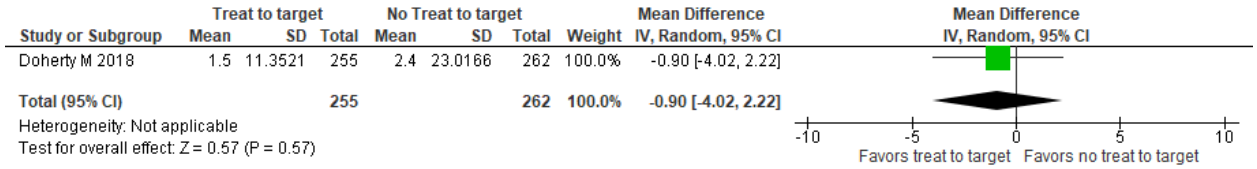
Forest plot of comparison 1 Dose titration versus fixed dose-RCT, outcome: 1.2 Gout flares- proportion of participants with at least 1 gout flare- 12 month follow-up.



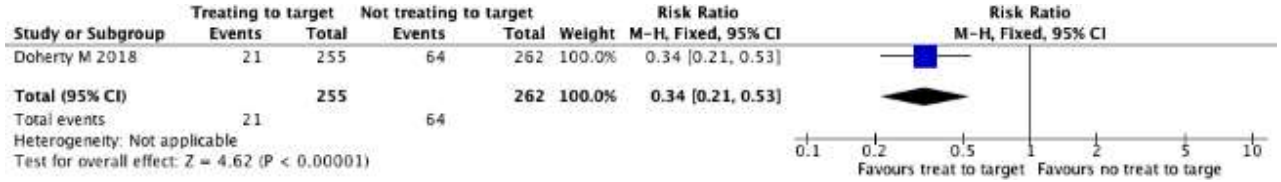
Forest plot of comparison 1 Dose titration versus fixed dose-RCT, outcome: 1.3 Gout flares: number at 12 month-follow-up.



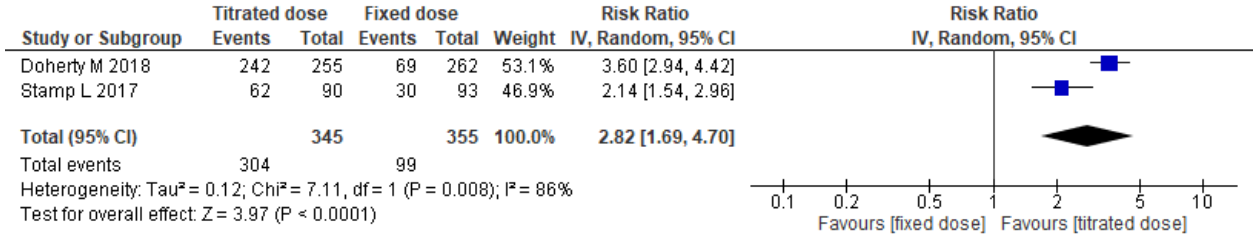
Forest plot of comparison 1 Dose titration versus fixed dose, outcome: 1.4 Gout flares: longest follow-up.



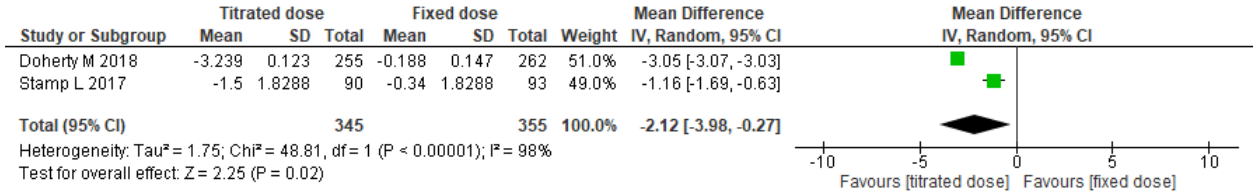
Forest plot of comparison 1 Dose titration versus fixed dose, outcome: 1.5 Gout flares, people with 2+ flares: longest follow-up.



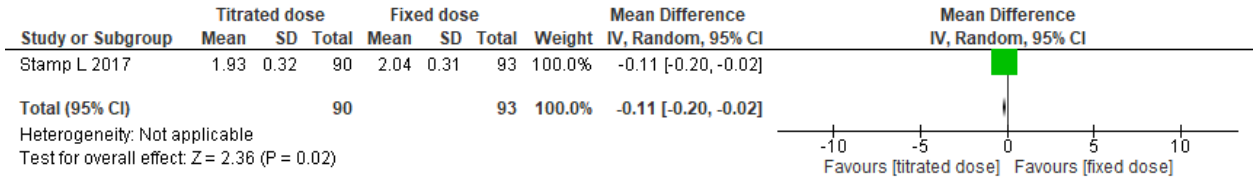
Forest plot of comparison 1 Dose titration versus fixed dose-RCT, outcome: 1.6 Proportion with serum urate <6mg/dL at 12 month follow-up.



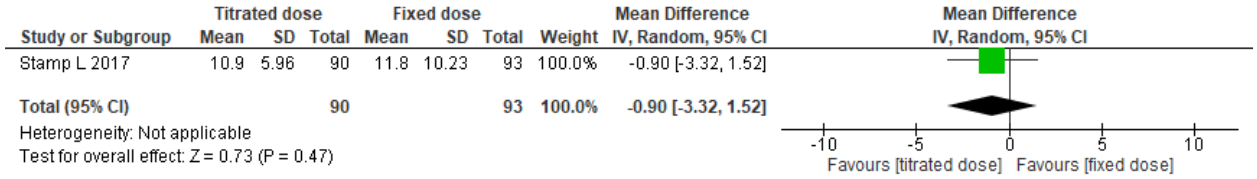
Forest plot of comparison 1 Dose titration versus fixed dose-RCT, outcome: 1.7 Serum urate, mean change 12 month follow-up mg/dL.



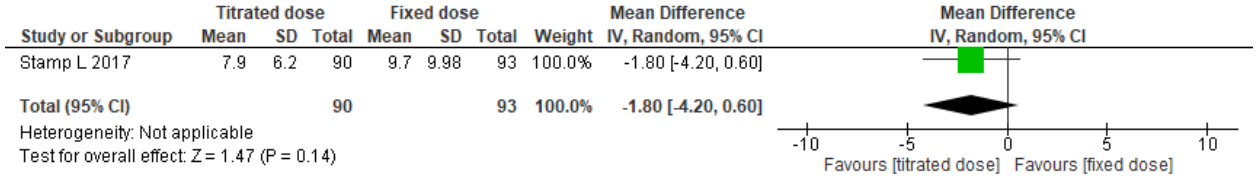
Forest plot of comparison 1 Dose titration versus fixed dose-RCT, outcome: 1.8 Pain- Visual analog scale. 12 month follow up- cm.



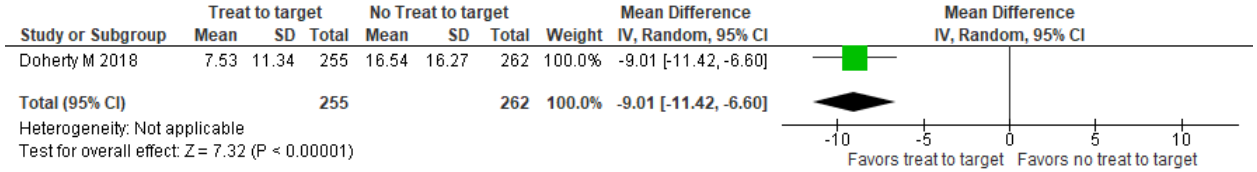
Forest plot of comparison: 1 Dose titration versus fixed dose-RCT, outcome: 1.9 Mean tophus size-3 month follow-up - mm.



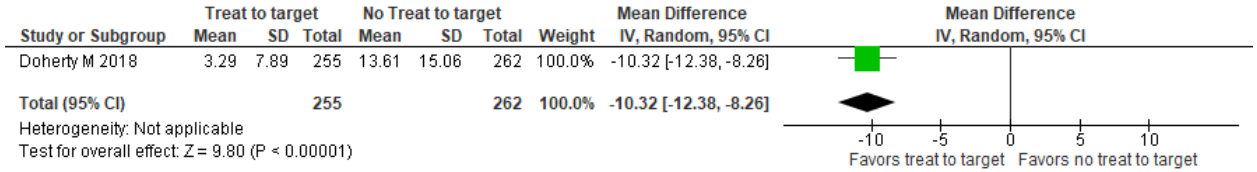
Forest plot of comparison 1 Dose titration versus fixed dose-RCT, outcome: 1.10 Mean tophus size-12 month follow-up - mm.



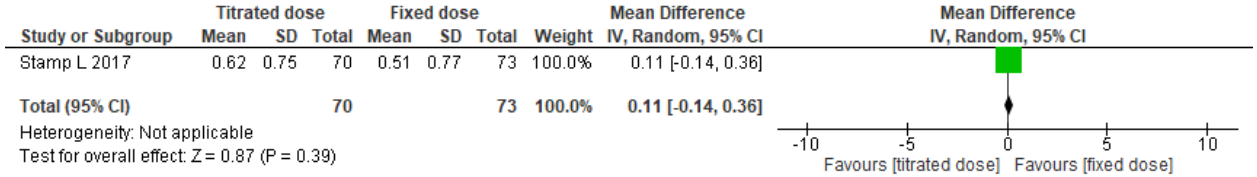
Forest plot of comparison 1 Dose titration versus fixed dose-RCT, outcome: 1.11 Tophus: diameter of largest tophus 12 month follow-up millimeters.



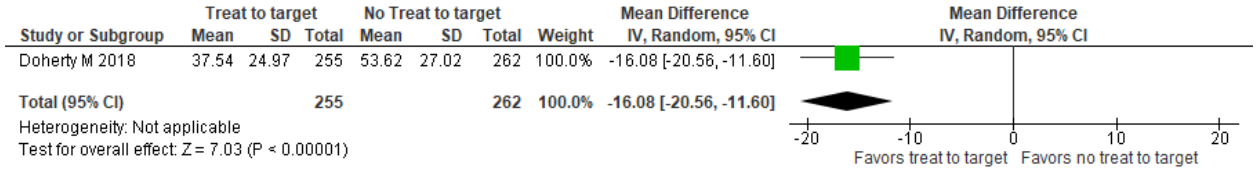
Forest plot of comparison 1 Nurse-led treat to target care vs general practitioner-led no treat to target care-RCT, outcome: 1.12 Tophus: diameter of largest tophus longest follow-up millimeters.



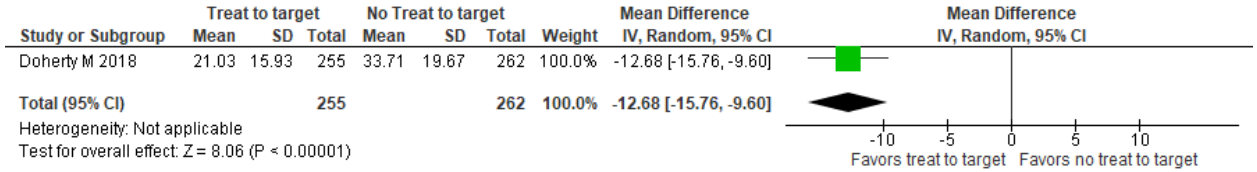
Forest plot of comparison 1 Dose titration versus fixed dose-RCT, outcome: 1.13 Activity Limitation- Health Assessment Questionnaire- 12 month follow-up.



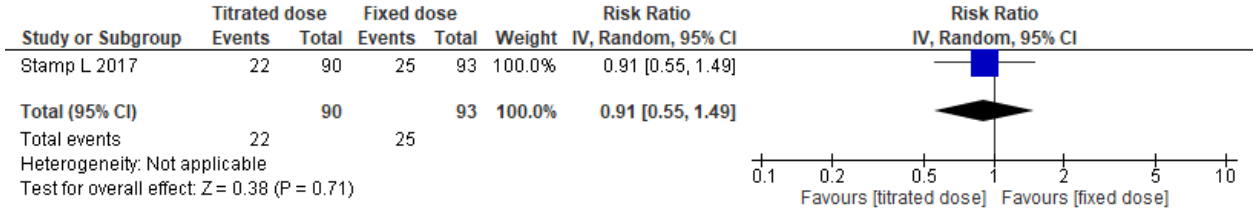
Forest plot of comparison 1 Nurse-led treat to target care vs general practitioner-led no treat to target care-RCT, outcome: 1.14 Health Related QOL: Gout impact scale: gout concern overall score longest follow-up.



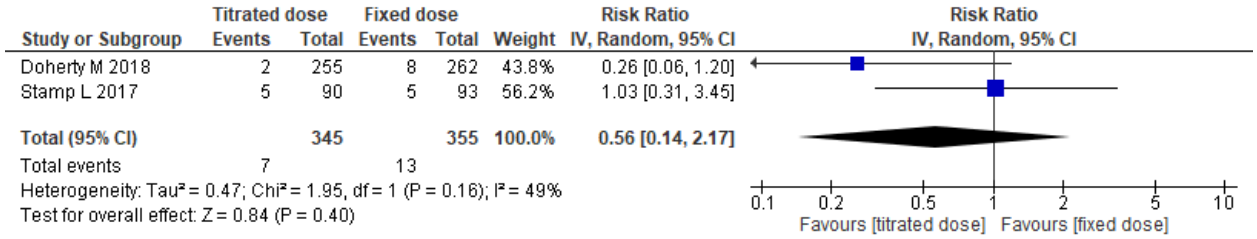
Forest plot of comparison 1 Nurse-led treat to target care vs general practitioner-led no treat to target care-RCT, outcome: 1.15 Health Related QOL: Gout impact scale: unmet gout treatment need score longest follow-up.



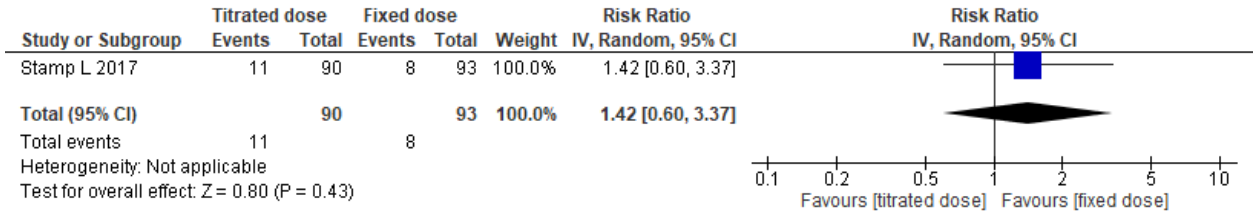
Forest plot of comparison 1 Dose titration versus fixed dose-RCT, outcome: 1.16 Serious adverse events: proportion with life threatening event that required hospital admission or resulted in death, longest follow-up



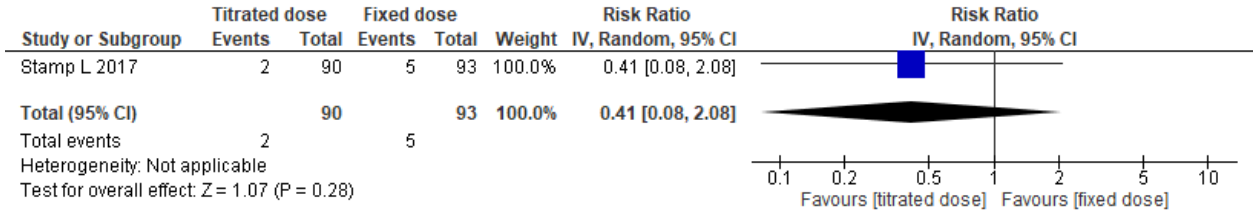
Forest plot of comparison 1 Dose titration versus fixed dose-RCT, outcome: 1.17 Serious adverse events: death, longest follow-up



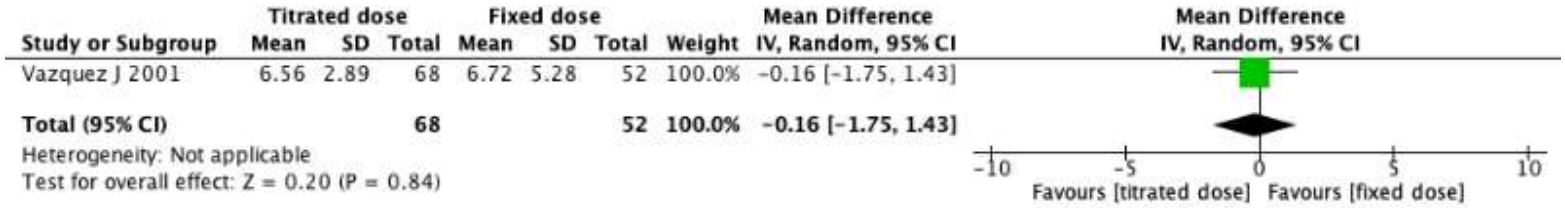
Forest plot of comparison 1 Dose titration versus fixed dose-RCT, outcome: 1.18 Serious adverse events: proportion of people with CV events, longest follow-up.



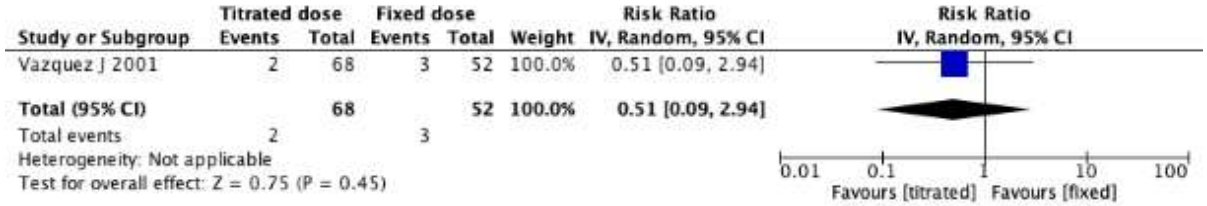
Forest plot of comparison 1 Dose titration versus fixed dose-RCT, outcome: 1.19 Serious adverse events: proportion of people with worsening kidney function, longest follow-up.



Forest plot of comparison 2 Dose titration versus fixed dose-observational, outcome: 2.1 Serum urate- mean longest follow-up mg/dL.



Forest plot of comparison 2 Dose titration versus fixed dose-observational, outcome: 2.2 Serious adverse events: proportion with allopurinol reaction, longest follow-up.



14: Should prescribing ULT to achieve serum urate <6mg/dL vs. not prescribing ULT to achieve serum urate <6mg/dL be used in patients with gout on ULT who are not in clinical remission?

We found one study addressing this question.[22] The researchers enrolled 517 participants and assigned them to receive nurse-led care with a treat to target approach, or usual care with their practitioner.

The evidence shows:

- Patients who receive a treat-to-target approach
    - May not have a different mean number of flares than participants who do not receive a treat-to-target approach, at 12 and 24 months
    - Probably have a lower risk of experiencing 2 or more flares than participants who do not receive a treat-to-target approach, at 24 months
    - Are more likely to achieve serum urate levels <6 mg/dL than participants who do not receive a treat-to-target approach, at 12 and 24 months
    - Have smaller tophus than participants who do not receive a treat-to-target approach, at 12 and 24 months
    - Probably have better health-related quality of life than participants who do not receive a treat-to-target approach, at 24 months
    - Probably have better patient adherence than participants who do not receive a treat-to-target approach at 24 months
    - Probably experience fewer adverse events than participants who do not receive a treat-to-target approach, up to 24 months

The overall quality of the evidence is HIGH

When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is HIGH

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With not prescribing ULT to achieve serum urate <6mg/dL	With prescribing ULT to achieve serum urate <6mg/dL	Relative effect (95% CI)	Risk with not prescribing ULT to achieve serum urate <6mg/dL	Risk difference with prescribing ULT to achieve serum urate <6mg/dL
Gout flares* (follow up: 12 months; assessed with: mean number per patient)											
517 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	262	255	-	The mean gout flares** was **3.5** flares	MD **0.1 flares higher** (4.38 lower to 4.58 higher)
Gout flares* (follow up: range 12 months to 24 months; assessed with: mean number per patient)											
517 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	262	255	-	The mean gout flares** was **2.4**	MD **0.9 lower** (4.02 lower to 2.22 higher)
Gout flares* (follow up: 2 years; assessed with: Patients with 2+ flares)											
517 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	21/255 (8.2%)	64/262 (24.4%)	**RR 0.34** (0.21 to 0.53)	82 per 1,000	**54 fewer per 1,000** (65 fewer to 39 fewer)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Serum urate (follow up: 12 months; assessed with: proportion of patients achieving mean serum urate <6mg/dL)**											
517 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	69/262 (26.3%)	242/255 (94.9%)	**RR 3.60** (2.94 to 4.42)	263 per 1,000	**685 more per 1,000** (511 more to 901 more)
Serum urate (follow up: 24 months; assessed with: proportion of patients achieving mean serum urate <6mg/dL)**											
517 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	78/262 (29.8%)	242/255 (94.9%)	**RR 3.19** (2.64 to 3.85)	298 per 1,000	**652 more per 1,000** (488 more to 848 more)
Tophus* (follow up: 12 months; assessed with: diameter of largest tophus in mm)											
517 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	262	255	-	The mean tophus* was **18.94** mm	MD **9.01 mm lower** (11.42 lower to 6.6 lower)
Tophus* (follow up: 24 months; assessed with: diameter of largest tophus)											
517 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	262	255	-	The mean tophus* was **13.61** mm	MD **10.32 mm lower** (12.38 lower to 8.26 lower)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Health Related Quality of Life* (follow up: 24 months; assessed with: Gout impact scale: gout concern overall score)											
517 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	262	255	-	The mean health Related Quality of Life* was **53.62**	MD **16.08 lower** (20.56 lower to 11.6 lower)
Health Related Quality of Life* (follow up: 24 months; assessed with: Gout impact scale: unmet gout treatment need score)											
517 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	262	255	-	The mean health Related Quality of Life* was **33.71**	MD **12.68 lower** (15.76 lower to 9.6 lower)
Patient adherence* (follow up: 24 months; assessed with: proportion of patients taking ULT)											
517 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	147/262 (56.1%)	245/255 (96.1%)	**RR 1.71** (1.53 to 1.91)	561 per 1,000	**398 more per 1,000** (297 more to 511 more)
Serious adverse events* (assessed with: death longest follow-up)											
517 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	8/262 (3.1%)	2/255 (0.8%)	**RR 0.26** (0.06 to 1.20)	31 per 1,000	**23 fewer per 1,000** (29 fewer to 6 more)

Table 1: Evidence profile

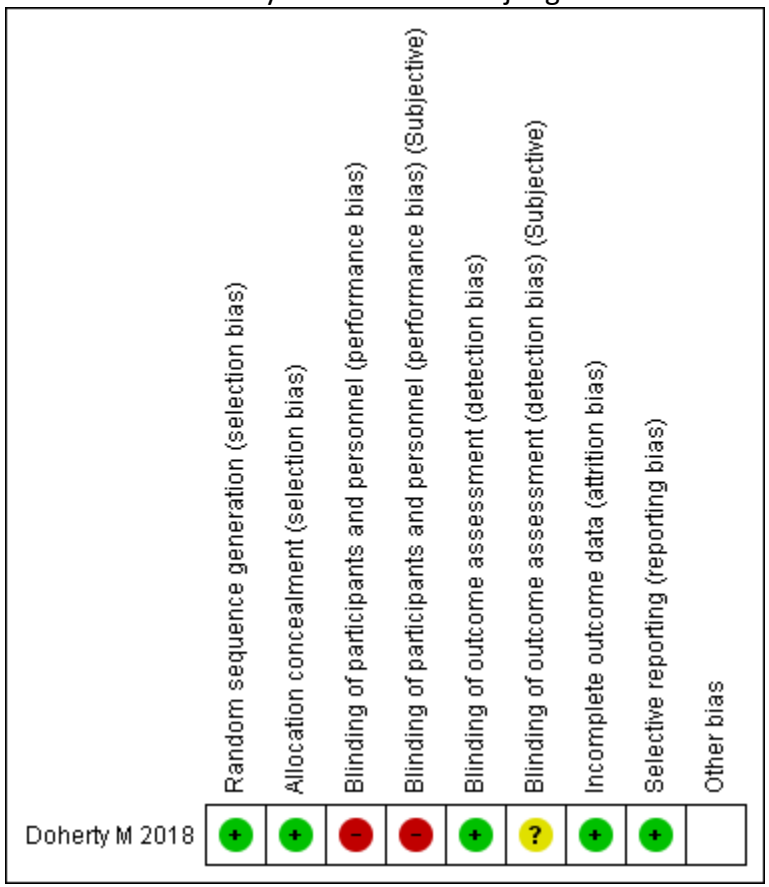
Certainty assessment							Summary of findings				
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient Global Assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity Limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

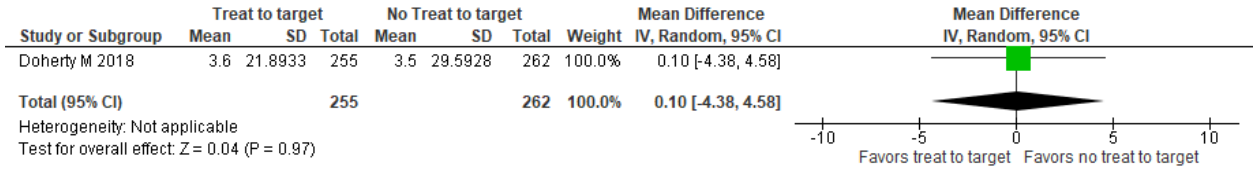
Explanations

a. The risk of bias table indicated that the trial was at high risk of bias in 2 categories.
b. The confidence interval value crosses the null.
Outcome importance:
**Critical outcomes
*Important outcomes

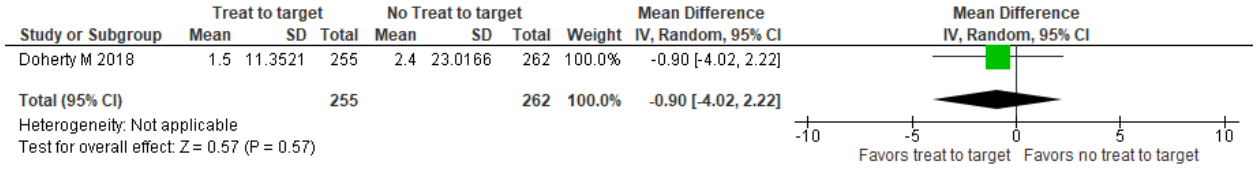
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Forest plot of comparison: 1 Nurse-led treat to target care vs general practitioner-led no treat to target care-RCT, outcome: 1.1 Gout flares: number at 12 month-follow-up.

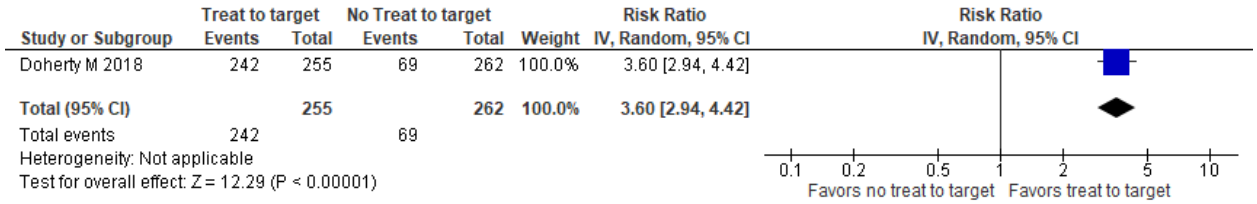


Forest plot of comparison: 1 Nurse-led treat to target care vs general practitioner-led no treat to target care-RCT, outcome: 1.2 Gout flares: longest follow-up.

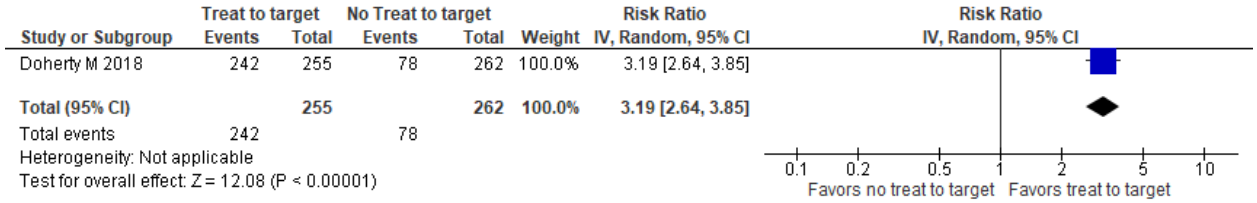


Forest plot of comparison: 1 Nurse-led treat to target care vs general practitioner-led no treat to target care-RCT, outcome: 1.3 Gout flares, people with flares: longest follow-up.

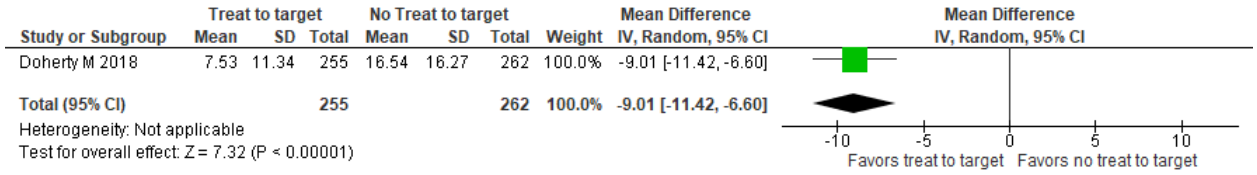
Forest plot of comparison: 1 Nurse-led treat to target care vs general practitioner-led no treat to target care-RCT, outcome: 1.4 Serum urate: proportion of patients achieving mean serum urate <6mg/dL 12 month follow-up.



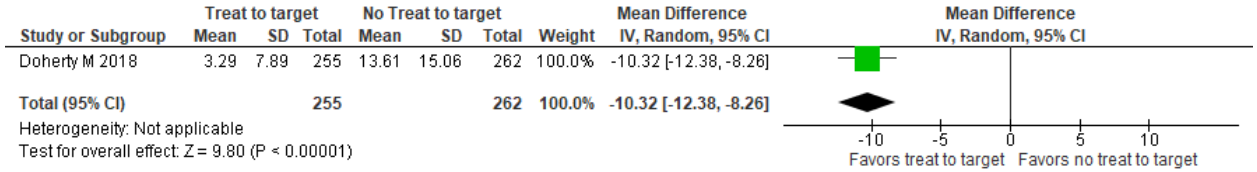
Forest plot of comparison: 1 Nurse-led treat to target care vs general practitioner-led no treat to target care-RCT, outcome: 1.5 Serum urate: proportion of patients achieving mean serum urate <6mg/dL longest follow-up.



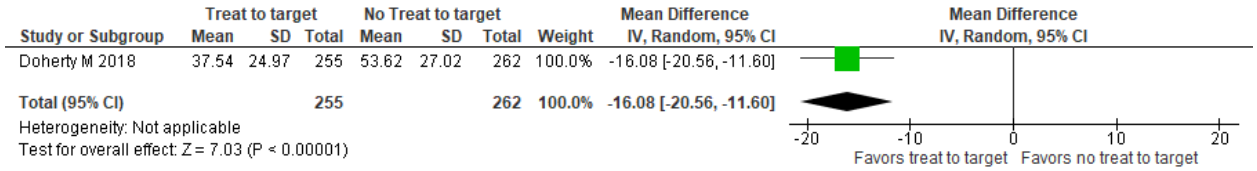
Forest plot of comparison: 1 Nurse-led treat to target care vs general practitioner-led no treat to target care-RCT, outcome: 1.6 Tophus: diameter of largest tophus 12 month follow-up millimeters.



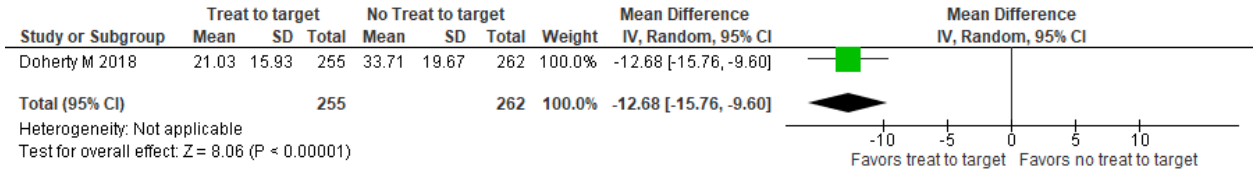
Forest plot of comparison: 1 Nurse-led treat to target care vs general practitioner-led no treat to target care-RCT, outcome: 1.7 Tophus: diameter of largest tophus longest follow-up millimeters.



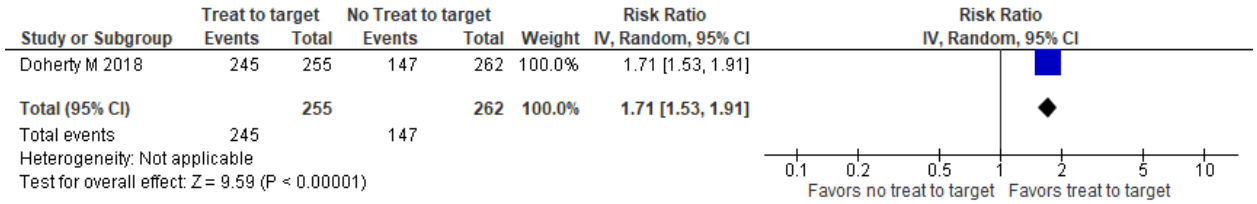
Forest plot of comparison: 1 Nurse-led treat to target care vs general practitioner-led no treat to target care-RCT, outcome: 1.8 Health Related QOL: Gout impact scale: gout concern overall score longest follow-up.



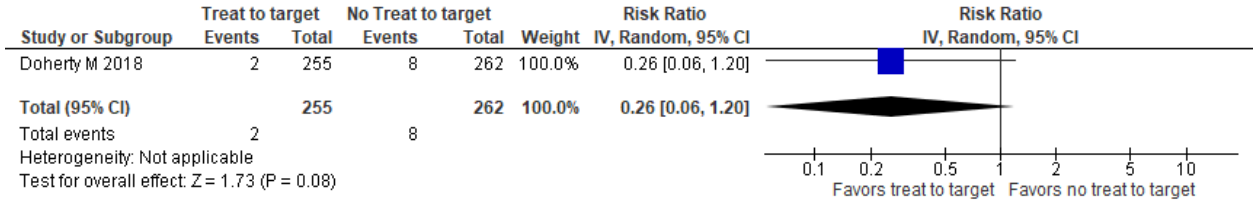
Forest plot of comparison: 1 Nurse-led treat to target care vs general practitioner-led no treat to target care-RCT, outcome: 1.9 Health Related QOL: Gout impact scale: unmet gout treatment need score longest follow-up.



Forest plot of comparison: 1 Nurse-led treat to target care vs general practitioner-led no treat to target care-RCT, outcome: 1.10 Patient adherence: proportion of patients taking ULT longest follow-up.



Forest plot of comparison: 1 Nurse-led treat to target care vs general practitioner-led no treat to target care-RCT, outcome: 1.11 Serious adverse events: Death, longest follow-up.



15 Should we prescribe ULT to achieve a serum urate target versus another in patients with gout on ULT who are in clinical remission?

The systematic review did not find any studies addressing this question

16 Should we check serum urate on a regular basis and make adjustments in ULT guided by serum urate concentrations or not check serum urate to guide future ULT use/ dosing in patients with gout on ULT for more than 2 years?

The systematic review did not find any studies addressing this question

17: Should fixed dose ULT vs. titrated ULT be used in patients with gout on ULT who have achieved serum urate target but still have sufficient inflammatory symptoms to warrant ULT re-evaluation?

We found one study addressing this question. This study was reported in 2 different articles.[47, 50] The researchers enrolled 183 participants, whose average number of gout flares per year was more than 3, and assigned them to receive a titrated dose of allopurinol or to continue with a fixed dose.

The evidence shows:

- Patients who have achieved serum urate target but still have sufficient inflammatory symptoms to warrant ULT re-evaluation, and subsequently receive dose titration of their ULT
    - May not have a different risk of gout flares at 3 and 12 months than do patients who receive fixed dose ULT
    - Are likely to have a higher probability to achieve serum urate levels <6 mg/dL at 12 months than do patients who receive fixed dose ULT
    - Are likely to experience less pain at 12 months than do patients who receive fixed dose ULT
    - May not have tophus of different size at 12 months than do patients who receive fixed dose ULT
    - May have not experience different activity limitation at 12 months than do patients who receive fixed dose ULT
    - May not experience any, cardiovascular, renal, or hypersensitivity adverse events at 12 months than do patients who receive fixed dose ULT

The overall quality of the evidence is MODERATE

When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With fixed dose ULT	With ULT dose titration	Relative effect (95% CI)	Risk with fixed dose ULT	Risk difference with ULT dose titration
Gout flares* (follow up: 3 months; assessed with: proportion of participants with at least 1 gout flare)											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	50/93 (53.8%)	44/90 (48.9%)	**RR 0.91** (0.69 to 1.21)	538 per 1,000	**48 fewer per 1,000** (167 fewer to 113 more)
Gout flares (follow up: 12 months; assessed with: proportion of participants with at least 1 gout flare)**											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	55/93 (59.1%)	49/90 (54.4%)	**RR 0.92** (0.71 to 1.19)	591 per 1,000	**47 fewer per 1,000** (172 fewer to 112 more)
Serum urate(follow up : 12 months; assessed with: Proportion with serum urate <6mg/dl)**											
183 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	30/93 (32.3%)	62/90 (68.9%)	**RR 2.14** (1.54 to 2.96)	323 per 1,000	**368 more per 1,000** (174 more to 632 more)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Pain (follow up: 12 months; assessed with: Visual analog scale; Scale from: 0 to 10)**											
183 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	93	90	-	The mean pain** was **2.04**	MD **0.11 lower** (0.2 lower to 0.02 lower)
Tophus* (follow up: 3 months; assessed with: Mean tophus size in mm)											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	93	90	-	The mean tophus* was **11.8** mm	MD **0.9 mm lower** (3.32 lower to 1.52 higher)
Tophus* (follow up: 12 months; assessed with: Mean tophus size in mm)											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	93	90	-	The mean tophus* was **9.7** mm	MD **1.8 mm lower** (4.2 lower to 0.6 higher)
Activity Limitation* (follow up: 12 months; assessed with: Health Assessment Questionnaire; Scale from: 0 (no disability) to 3 (totally independent))											
143 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	73	70	-	The mean activity Limitation* was **0.51**	MD **0.11 higher** (0.14 lower to 0.36 higher)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Serious adverse events* (follow up: 12 months; assessed with: proportion with life threatening event that required hospital admission or resulted in death)											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	25/93 (26.9%)	22/90 (24.4%)	**RR 0.91** (0.55 to 1.49)	269 per 1,000	**24 fewer per 1,000** (121 fewer to 132 more)
Serious adverse events* (follow up: 12 months; assessed with: proportion of people with CV events)											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	8/93 (8.6%)	11/90 (12.2%)	**RR 1.42** (0.60 to 3.37)	86 per 1,000	**36 more per 1,000** (34 fewer to 204 more)
Serious adverse events* (follow up: 12 months; assessed with: proportion of people with worsening kidney function)											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	5/93 (5.4%)	2/90 (2.2%)	**RR 0.41** (0.08 to 2.08)	54 per 1,000	**32 fewer per 1,000** (49 fewer to 58 more)
Serious adverse events* (follow up: 12 months; assessed with: proportion of people with allopurinol hypersensitivity)											
183 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	0/93 (0.0%)	0/90 (0.0%)	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

Table 1: Evidence profile

Certainty assessment							Summary of findings				

Patient Global Assessment* - not reported

-	-	-	-	-	-	-	-	-	-	-	-

Health Related Quality of life* - not reported

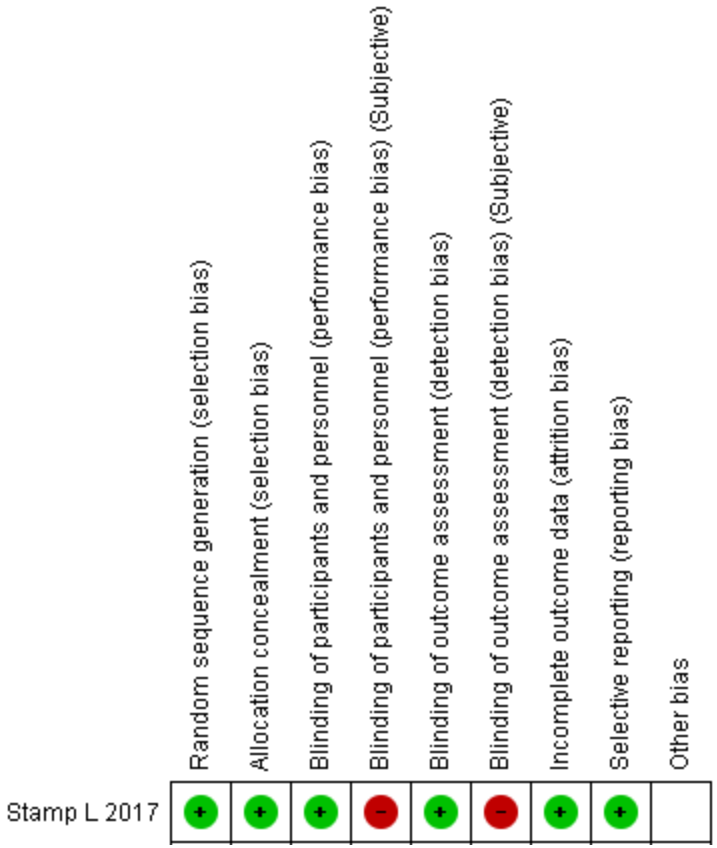
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

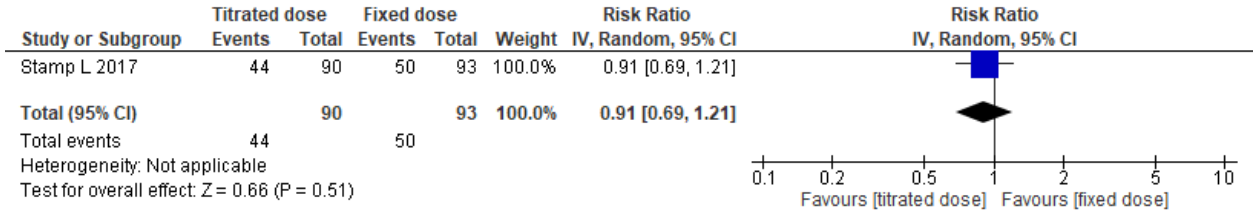
Explanations

a. The risk of bias table indicates high risk of bias in at least one category
b. Confidence interval crosses null.
Outcome importance:
** Critical outcomes
* Important outcomes

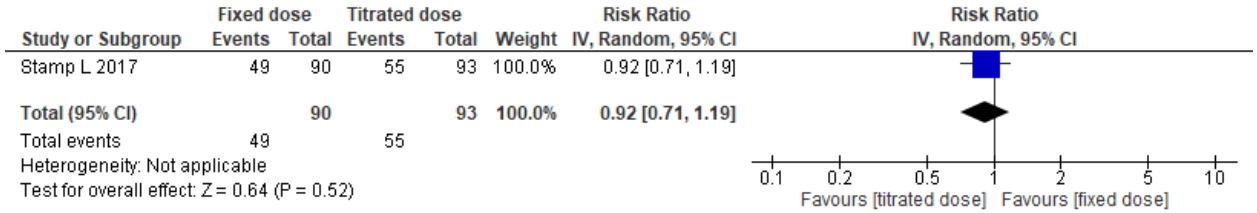
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



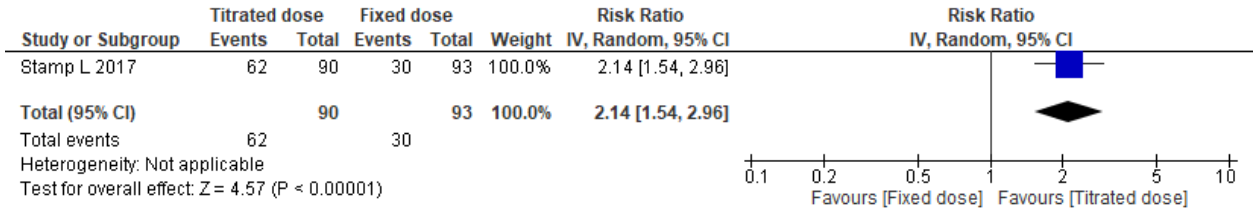
Forest plot of comparison: 1 Dose titration vs fixed dose-RCT, outcome: 1.1 Gout flares- proportion of participants with at least 1 gout flare- 3 months.



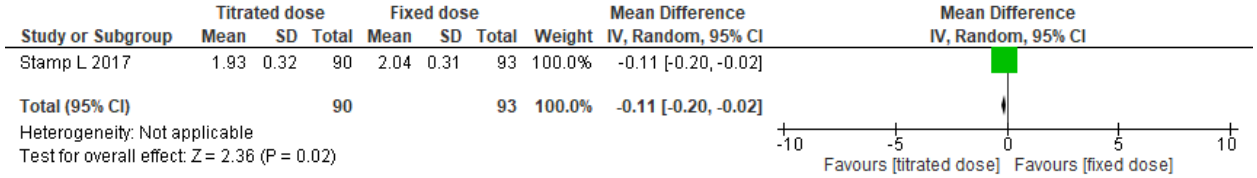
Forest plot of comparison: 1 Dose titration vs fixed dose -RCT, outcome: 1.2 Gout flares- proportion of participants with at least 1 gout flare- 12 month follow-up.



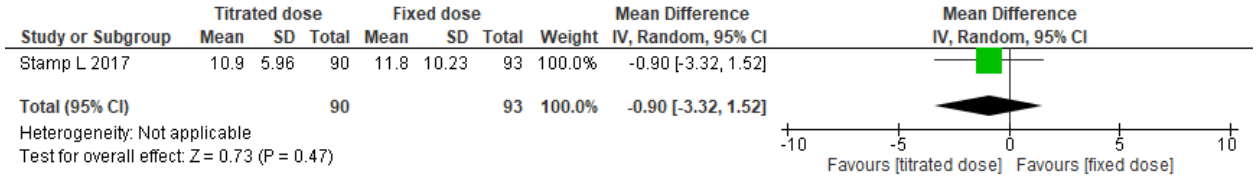
Forest plot of comparison: 1 Dose titration vs fixed dose -RCT, outcome: 1.3 Proportion with serum urate <6mg/dL at 12 month follow-up.



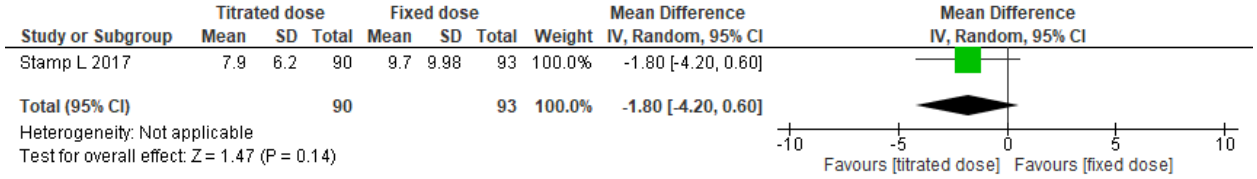
Forest plot of comparison: 1 Dose titration vs fixed dose -RCT, outcome: 1.4 Pain- Visual analog scale. 12 month follow up- cm.



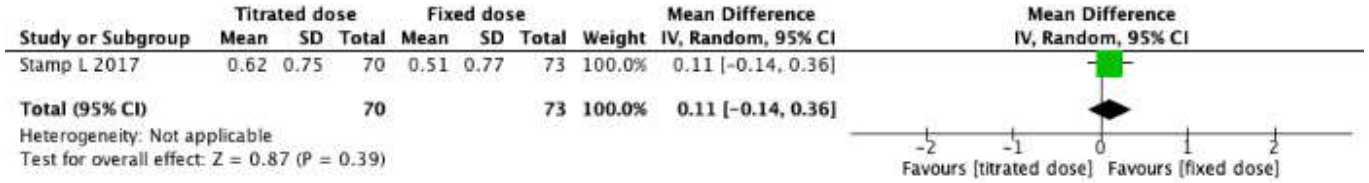
Forest plot of comparison: 1 Dose titration vs fixed dose -RCT, outcome: 1.5 Mean tophus size-3 month follow-up - cm.



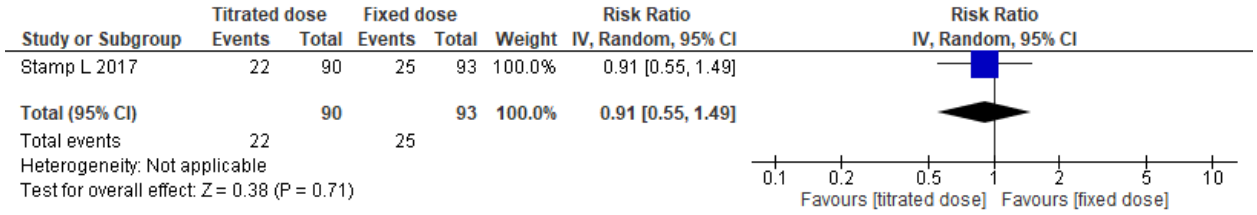
Forest plot of comparison: 1 Dose titration vs fixed dose -RCT, outcome: 1.6 Mean tophus size-12 month follow-up - cm.



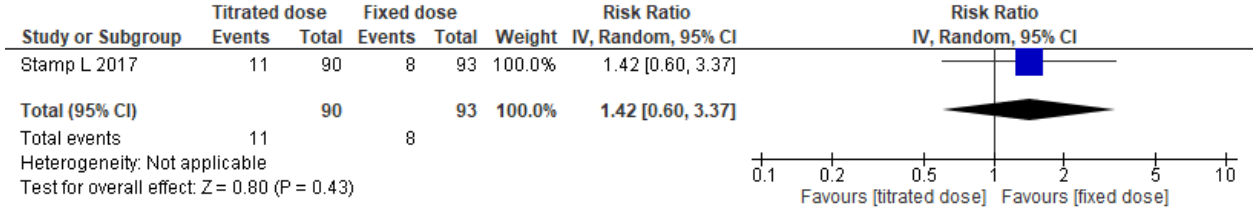
Forest plot of comparison: 1 Dose titration vs fixed dose -RCT, outcome: 1.7 Activity Limitation- Health Assessment Questionnaire- 12 month follow-up.



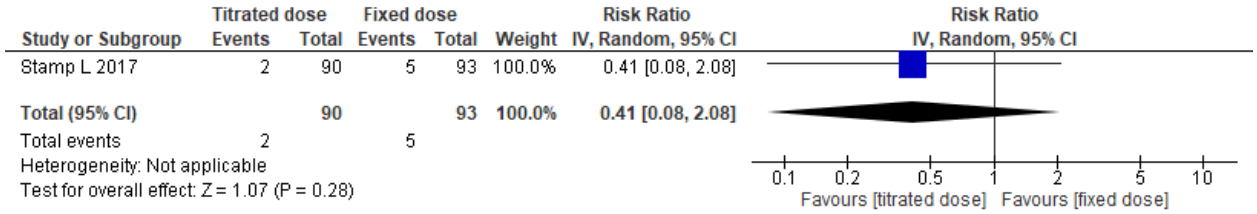
Forest plot of comparison: 1 Dose titration vs fixed dose -RCT, outcome: 1.8 Serious adverse events: proportion with life threatening event that required hospital admission or resulted in death.



Forest plot of comparison: 1 Dose titration vs fixed dose -RCT, outcome: 1.9 Serious adverse events: proportion of people with CV events.



Forest plot of comparison: 1 Dose titration vs fixed dose -RCT, outcome: 1.10 Serious adverse events: proportion of people with worsening kidney function.



18 Should we increase the ULT dose to achieve serum urate target or continue current ULT dose in patients with gout adherent to ULT who have not achieved serum urate target but have infrequent symptoms and no subcutaneous tophi?

The systematic review did not find any studies addressing this question

19: Should stopping ULT or reducing vs. continuing ULT be used for patients with gout on ULT, in clinical remission?

We did not find any studies addressing this question. The core team suggested to include a case series that addressed this question partially.[51] In this study, researchers provided information about the outcomes of 211 patients who had SUA levels<7 mg/dL, in whom treatment with ULT was withdrawn.

The evidence shows

- Patients in whom ULT was stopped
    - had a 38.9% risk of experiencing gout flares, after 27.5 weeks.
    - had an average SUA level of 8.7 mg/dL, after 27.5 weeks.
- We are very uncertain about the relative effects of stopping or reducing versus continuing ULT in patients with gout on ULT, in clinical remission.

The overall quality of the evidence is VERY LOW

When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is VERY LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With continuing ULT	With stopping ULT or reducing	Relative effect (95% CI)	Risk with continuing ULT	Risk difference with stopping ULT or reducing
Gout flares (follow up: median 27.5 months)**											
211 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	NA	82/211 (38.9%)	-	-	-
Serum urate (follow up: median 27.5 months; assessed with: Mean SUA level)**											
211 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	NA	8.7 mg/dL	-	-	-
Gout flares - not reported**											
-	-	-	-	-	-	-	-	-	-	-	-
Serum urate - not reported**											
-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health-Related Quality of Life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval

Explanations

a. This study did not have a control group, and thus we cannot know whether this outcome is different in patients who continued ULT

Outcome importance:

** Critical outcomes

* Important outcomes

Risk of bias assessment: There were no serious concerns about the risk of bias of the study itself. The quality of the evidence was rated down because of the inherent risk of bias when informing an intervention question using a case series.

20. Should relaxing serum urate target vs. continuing current serum urate target be used in patients with gout on ULT, in clinical remission?

We did not find any studies addressing this question. The core team suggested to include a case series that addressed this question partially.[51] In this study, researchers provided information about the outcomes of 211 patients who had SUA levels<7 mg/dL, in whom treatment with ULT was withdrawn.

The evidence shows

- Patients in whom ULT was stopped had
    - a 38.9% risk of experiencing gout flares, after 27.5 weeks.
    - an average SUA level of 8.7 mg/dL, after 27.5 weeks.
- We are very uncertain about the relative effects of relaxing serum urate target versus continuing current serum urate target in patients with gout on ULT, in clinical remission.

The overall quality of the evidence is VERY LOW

When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is VERY LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With continuing current serum urate target	With relaxing serum urate target	Relative effect (95% CI)	Risk with continuing current serum urate target	Risk difference with relaxing serum urate target
Gout flares (follow up: median 27.5 months)**											
211 (1 observational study)	serious [a]	not serious	serious [b]	not serious	none	⨁◯◯◯ VERY LOW	0/0	82/211 (38.9%)	-	-	-
Serum urate (follow up: median 27.5 months; assessed with: Mean SUA level)**											
211 (1 observational study)	serious [a]	not serious	serious [b]	not serious	none	⨁◯◯◯ VERY LOW	0	8.7 mg/dL	-	-	-
Gout flares - not reported**											
-	-	-	-	-	-	-	-	-	-	-	-
Serum urate - not reported**											
-	-	-	-	-	-	-	-	-	-	-	-
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health-Related Quality of Life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval

Explanations

a. This study did not have a control group, and thus we cannot know whether this outcome is different in patients who continued ULT
b. This study does not address any of the interventions of interest exactly
Outcome importance:
** Critical outcomes
* Important outcomes

Risk of bias assessment: There were no risk of bias concerns regarding the study itself as a case series. The concerns arise because this study, which has no comparison, is being used as evidence to inform an intervention question.

21 Which duration of intensive ULT therapy should we use in patients with gout on intensive ULT management?

The systematic review did not find any studies addressing this question

PICO 22: Should stopping and switching to an alternative ULT vs. continuing febuxostat be used in patient with gout on febuxostat with a history of cardiovascular disease or a new cardiovascular event?

We found 2 studies addressing this question.[36, 52] One was a randomized clinical trial[52] and another an observational study.[36] Both studies included patients who were on ULTs (not necessarily febuxostat), and assessed the effects of prescribing allopurinol (switching to an alternative ULT) or febuxostat (continuing febuxostat).

The evidence shows that patients who switch to an alternative ULT:

- Are probably more likely to achieve serum urate levels <6 mg/dL than patients who continue febuxostat, at 3 months
- Probably do not have a different likelihood of achieving serum urate levels <6 mg/dL than patients who continue febuxostat, at 72 months
- May have a lower probability of experiencing one or more flares than patients who continue febuxostat, up to 8 months; but we are very uncertain about this evidence
- Probably have a lower rate of gout flares per year than patients who continue febuxostat, up to 32 months.
- Probably have no different risk of experiencing cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to angina, than patients who continue febuxostat, up to 32 months.
- May have a higher risk of any major cardiovascular event than patients who continue febuxostat, up to 8 months; but we are very uncertain about this evidence.

The overall quality of the evidence is MODERATE

When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is MODERATE

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With continuing febuxostat	With stopping and switching to an alternative ULT	Relative effect (95% CI)	Risk with continuing febuxostat	Risk difference with stopping and switching to an alternative ULT
Serum urate (follow up: 3 months; assessed with: proportion of patients with SUA< 6 mg/dL)**											
5387 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	1975/2701 (73.1%)	1863/2686 (69.4%)	**RR 0.95** (0.92 to 0.98)	731 per 1,000	**37 fewer per 1,000** (from 58 fewer to 15 fewer)
Serum urate (follow up: 72 months; assessed with: proportion of patients with SUA< 6 mg/dL)**											
515 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	199/267 (74.5%)	186/248 (75.0%)	**RR 1.01** (0.91 to 1.11)	745 per 1,000	**7 more per 1,000** (from 67 fewer to 82 more)
Gout flares* (follow up: median 8 months; assessed with: Proportion of patients with 1+flares)											
2426 (1 observational study)	serious [b]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	103/370 (27.8%)	465/2056 (22.6%)	**RR 0.81** (0.68 to 0.98)	278 per 1,000	**53 fewer per 1,000** (from 89 fewer to 6 fewer)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Gout flares (follow up: median 32 months; assessed with: Rates of gout flares per patient/year)**											
(1 RCT) [c]	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	The rate of gout flares per patient/year was 0.63 in patients that received allopurinol and 0.68 in those who received febuxostat (difference: 0.05 more when continuing febuxostat; measure of effect not reported)				
Serious adverse events- Cardiovascular events (follow up: median 32 months; assessed with: Proportion of patients with CV death, nonfatal myocardial infarction, nonfatal stroke, and urgent revascularization due to angina)**											
6190 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	335/3098 (10.8%)	321/3092 (10.4%)	**RR 0.96** (0.83 to 1.11)	108 per 1,000	**4 fewer per 1,000** (from 18 fewer to 12 more)
Serious adverse events- Cardiovascular events (follow up: 8 months; assessed with: Any major CV event)**											
2426 (1 observational study)	serious [b]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	14/370 (3.8%)	148/2056 (7.2%)	**RR 1.90** (1.11 to 3.25)	38 per 1,000	**34 more per 1,000** (from 4 more to 85 more)
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health-related quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Trial was not judged at low risk of bias. Key domains are unclear risk of bias
b. The study was at moderate risk of bias
c. Number of patients that contributed to the results for this outcome are not reported
Outcome importance
**Critical outcomes
*Important outcomes

Figure 1: Risk of bias of included randomized trials

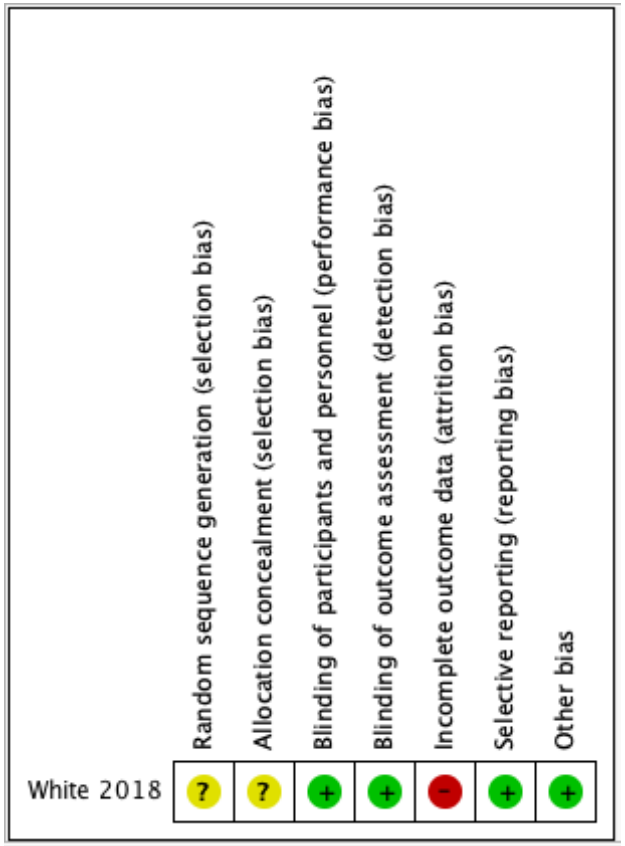


Figure 2: Risk of bias of included observational study

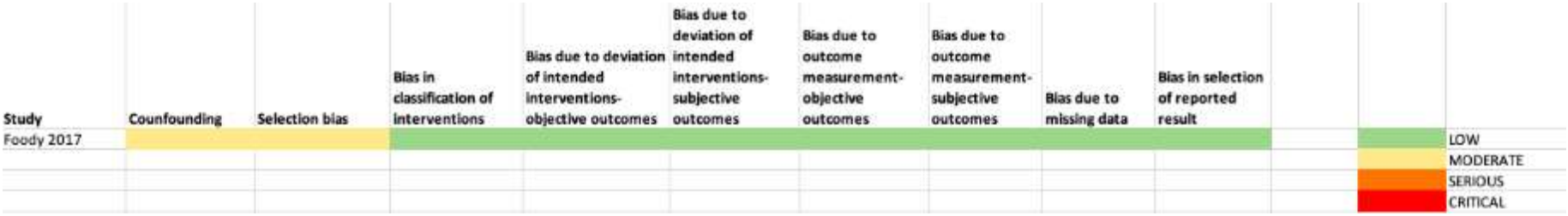


Figure 3: Stopping and switching versus continuing febuxostat; outcome: Serum urate levels <6 mg/dL at 3 months

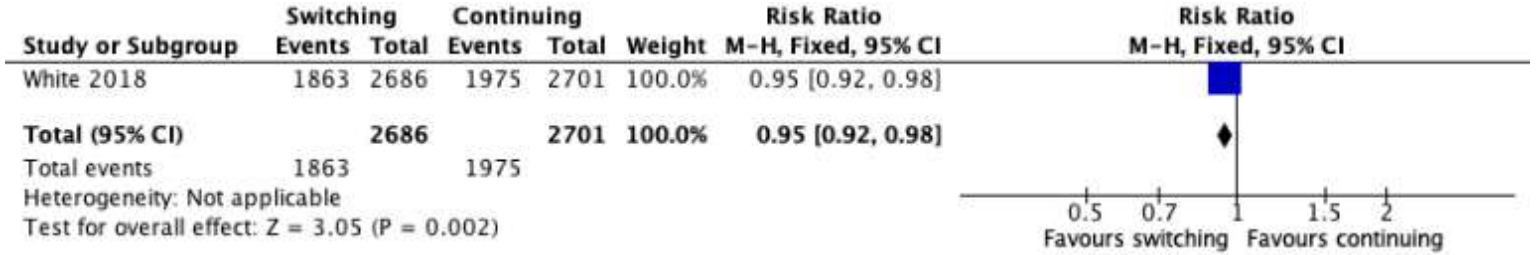


Figure 4: Stopping and switching versus continuing febuxostat; outcome: Serum urate levels <6 mg/dL at longest follow up (72 months)

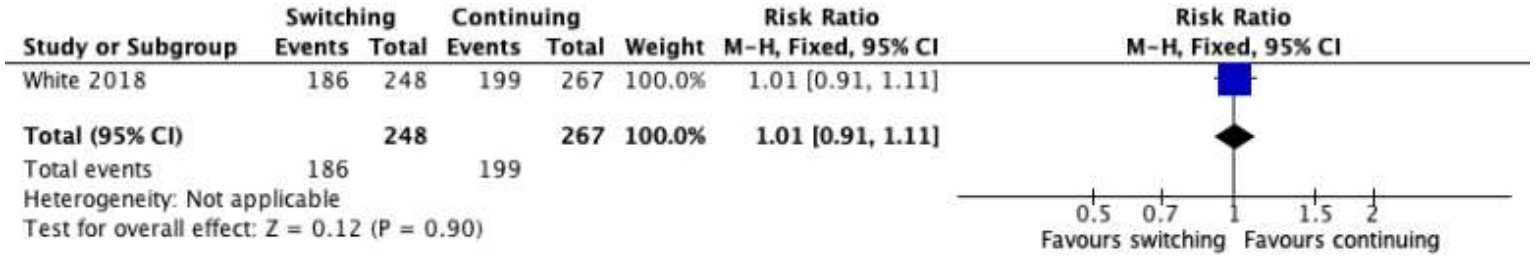


Figure 5: Stopping and switching versus continuing febuxostat; outcome: Gout flares at 8 months (proportion of patients with 1+ flares)

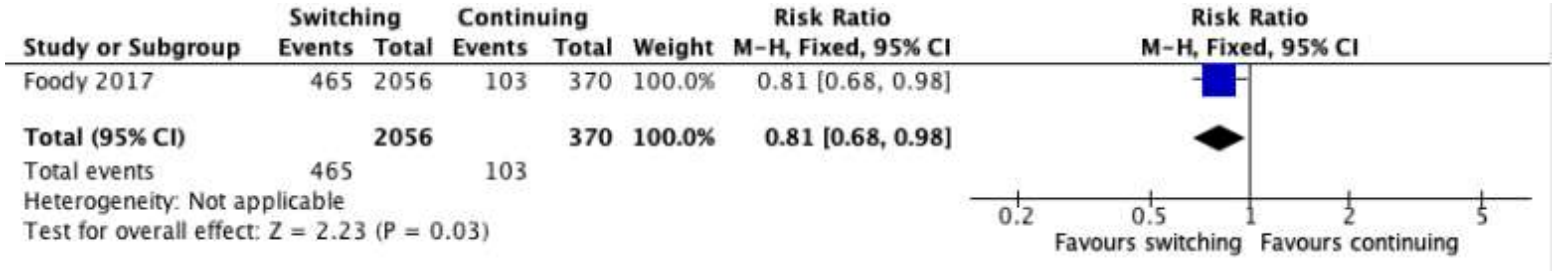


Figure 6: Stopping and switching versus continuing febuxostat; outcome: Serious adverse events- cardiovascular (32 months)

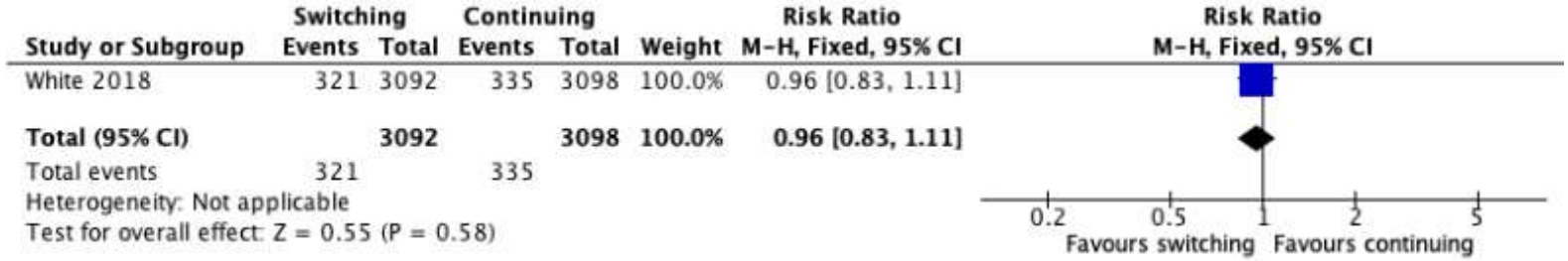
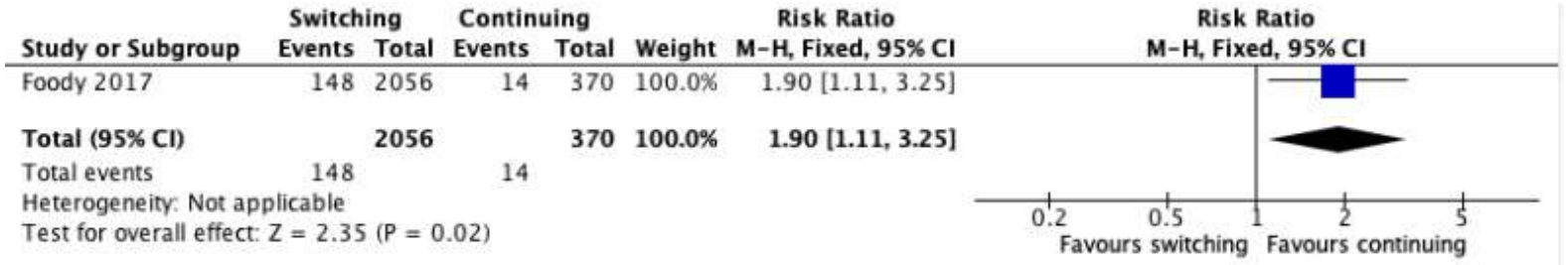


Figure 7: Stopping and switching versus continuing febuxostat; outcome: Serious adverse events- any major cardiovascular event (8 months)



23: Should Allopurinol desensitization vs. no desensitization be used in patients with gout who have experienced an allergic reaction to allopurinol and who cannot be treated with other oral ULT?

We did not find any studies addressing this question. The core team suggested two studies that could be used as indirect evidence to inform this question. The first study was a case series in which researchers provided information about the outcomes of 32 patients who underwent allopurinol desensitization.[53] The second study was a retrospective cohort study in which researchers compared the outcomes of a group of patients who underwent a fast desensitization protocol (5 days) and another who underwent a slow desensitization protocol (16 days).[54]

The evidence shows:

- The proportion of patients with serious adverse events (unable to tolerate allopurinol) may be 25%.
- There may be no difference in the risk of serious adverse events between patients who receive a slow desensitization protocol and those who receive a fast desensitization protocol.

The overall quality of the evidence is VERY LOW

When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is VERY LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no desensitization	With Allopurinol desensitization	Relative effect (95% CI)	Risk with no desensitization	Risk difference with Allopurinol desensitization
Serious adverse events (follow up: median 24 months; assessed with: allopurinol desensitization failure-unable to tolerate)**											
28 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW		7/28 (25.0%)	-	-	-
Serious adverse events (follow up: range 5 days to 16 days; assessed with: patients with breakthrough reactions; comparison: fast protocol versus slow protocol)**											
21 (1 observational study)	not serious	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	6/10 (60.0%)	4/11 (36.4%)	**RR 0.38** (0.07 to)	600 per 1,000	**372 fewer per 1,000** (558 fewer to 732 more)
Gout flares - not reported**											
-	-	-	-	-	-	-	-	-	-	-	-
Serum urate - not reported**											
-	-	-	-	-	-	-	-	-	-	-	-
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health related quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. There is no comparison, and thus it is not possible to know if there would be more adverse events without desensitization
b. The study does not address the exact comparison of interest
c. Very few events and patients included. The CI suggests the possibility of appreciable benefit and appreciable harm
Outcome importance:
**Critical outcomes
* Important outcomes

Figure 1: ROB assessment

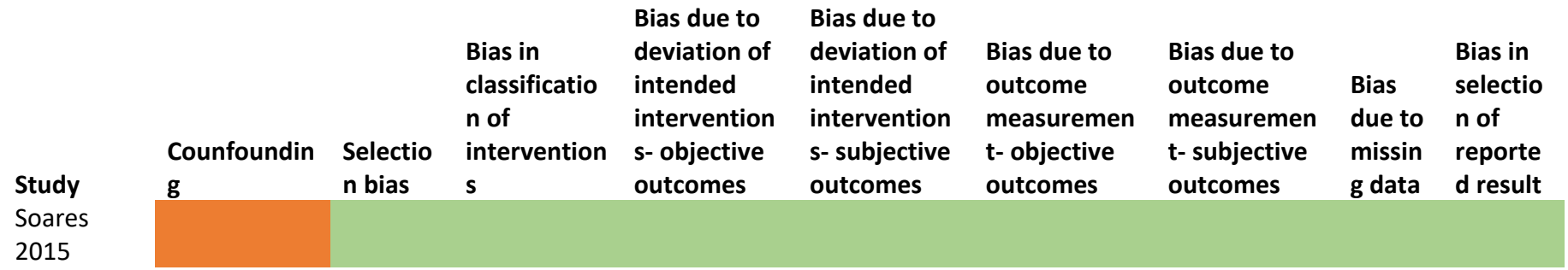
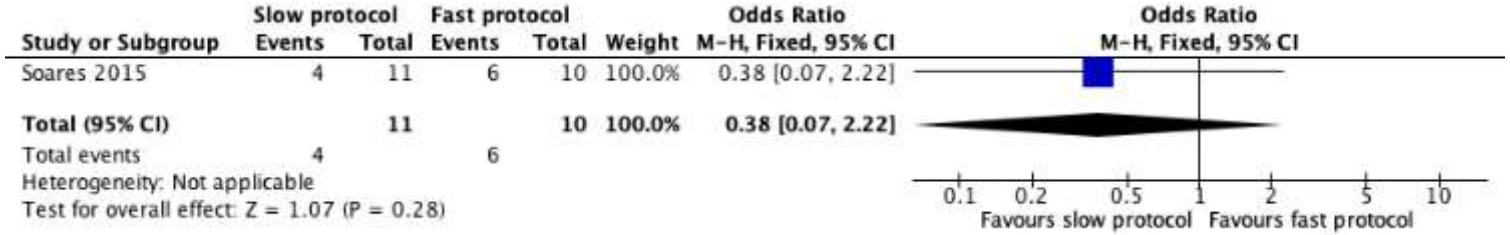


Figure 2: Allopurinol desensitization (slow protocol) vs no desensitization (fast protocol), Serious adverse events



24: Should switching a XOI for another XOI vs. adding a uricosuric agent be used in patients with gout on their first XOI monotherapy at maximum tolerated or FDA indicated dose who are not at serum urate target and/or have continued frequent gout flares or non-resolving subcutaneous tophi?

We found one study addressing this question.[55] This was an observational study in which researchers compared serum urate levels between patients receiving allopurinol who switched to febuxostat and patients who continued febuxostat.
The evidence shows:

- Patients with gout who are not at serum urate target or have continued frequent gout flares or non-resolving tophi who switch to another XOI
    - May be more likely to achieve serum urate levels <6 mg/dl than those who add an uricosuric, after 40 months; but we are very uncertain about this evidence
    - May experience a higher reduction of serum urate levels than those who add a uricosuric, after 40 months; but we are very uncertain about this evidence
    - May be more likely to achieve serum urate levels <5 mg/dl than those who add a uricosuric, after 40 months; but we are very uncertain about this evidence

The overall quality of the evidence is VERY LOW
When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is VERY LOW

In addition, the core team advised to use information from PICO 10, specifically that corresponding to comparisons between XOI alone versus XOI+ uricosuric. In each summary point below, we specify in brackets where the information is located in the file corresponding to PICO 10.
The evidence shows:

- Patients who receive allopurinol 300 mg
    - Probably do not have a different risk of gout flares in a 1-month period than patients who receive allopurinol 300+lesinurad 200, up to 13 months (Table 3, row 1)
    - Are less likely to achieve serum urate levels <6 mg/dL than patients who receive allopurinol 300+lesinurad 200, up to 24 months (Table 5, row 1)
    - May not have a different probability of tophus resolution than patients who receive allopurinol 300+lesinurad 200, up to 24 months (Table 9, row 1 in network comparisons)

- Probably do not have a different risk of serious adverse events than patients who receive allopurinol 300+lesinurad 200, up to 24 months (Table 12, row 1)
- Probably do not have a different risk of cardiovascular adverse events than patients who receive allopurinol 300+lesinurad 200, up to 32 months (Table 13, row 1)

The overall quality of the evidence is HIGH for this comparison, but it is MODERATE for the comparison of interest (switching versus adding)

When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is LOW

- Patients who receive febuxostat 80 mg
  - May not have a different risk of gout flares than patients who receive febuxostat+ lesinurad 200, up to 3 months (Table 2, row 29) and 13 months (in a 1-month period) (Table 3, row 15)
  - May not have a different probability of achieving serum urate levels <6 mg/dL than patients who receive febuxostat 80+lesinurad 200, up to 24 months (Table 5, row 69)
  - May not have a different probability of tophus resolution than patients who receive febuxostat+lesinurad 200, up to 24 months; but we are very uncertain about this evidence (Table 9, row 8 in network comparisons)
  - May not have a different risk of serious adverse events than patients who receive febuxostat 80+lesinurad 200, up to 24 months (Table 12, row 77)
  - May not have a different risk of serious adverse events than patients who receive febuxostat 80+lesinurad 200, up to 24 months; but we are very uncertain about this evidence (Table 13, row 47)

The overall quality of the evidence is LOW for this comparison, but it is very low for the comparison of interest (switching versus adding)

When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is VERY LOW

The evidence regarding febuxostat versus probenecid from the NMA is relevant

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With adding a uricosuric agent	With switching XOI to an alternate XOI	Relative effect (95% CI)	Risk with adding a uricosuric agent	Risk difference with switching XOI to an alternate XOI
Serum urate** (follow up: mean 40 months; assessed with: proportion achieving SUA<6 mg/dL)											
1723 (1 observational study)	serious [a]	not serious	serious [b]	not serious	none	⨁◯◯◯ VERY LOW	-/1278	-/445	OR 1.403 (1.166 to 1.687)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)
Serum urate** (follow up: mean 40 months; assessed with: change in mean SUA level, pre-index to post-index)											
1723 (1 observational study)	serious [a]	not serious	serious [b]	not serious	none	⨁◯◯◯ VERY LOW	1278	445	-	The mean serum urate** was **-0.36** mg/dL	MD **1.4 mg/dL higher** (1.18 higher to 1.62 higher)
Serum urate** (follow up: mean 40 months; assessed with: proportion achieving SUA<5 mg/dL)											
1723 (1 observational study)	serious [a]	not serious	serious [b]	not serious	none	⨁◯◯◯ VERY LOW	-/1278	-/445	OR 1.83 (1.51 to 2.21)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Gout flares** - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health-Related Quality of Life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse effects* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. The study has a moderate risk of bias

b. The study does not compare the exact options of interest, the relative effects may be different

Outcome importance:

** Critical outcomes

* Important outcomes

Risk of bias assessment:

Study	Counfounding	Selection bias	Bias in classification of interventions	Bias due to deviation of intended interventions-objective outcomes	Bias due to deviation of intended interventions-subjective outcomes	Bias due to outcome measurement-objective outcomes	Bias due to outcome measurement-subjective outcomes	Bias due to missing data	Bias in selection of reported result
Altan PICO 24									

Figure 1: Forest plot of comparison: 1 Adding or changing medications vs no change in medication, outcome: 1.2 serum urate, proportion achieving SUA<6 mg/dL, post index period (longest follow up).

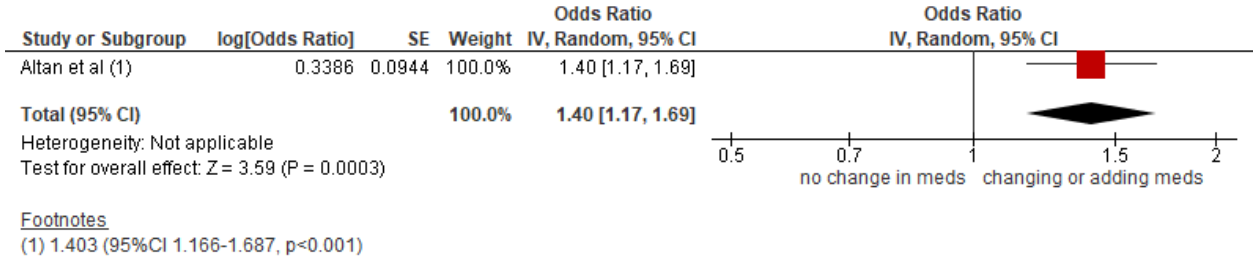


Figure 2: Forest plot of comparison: 1 Adding or changing medications vs no change in medications, outcome: 1.1 urate level, change in mean SUA level, pre-index to post-index, longest follow-up.

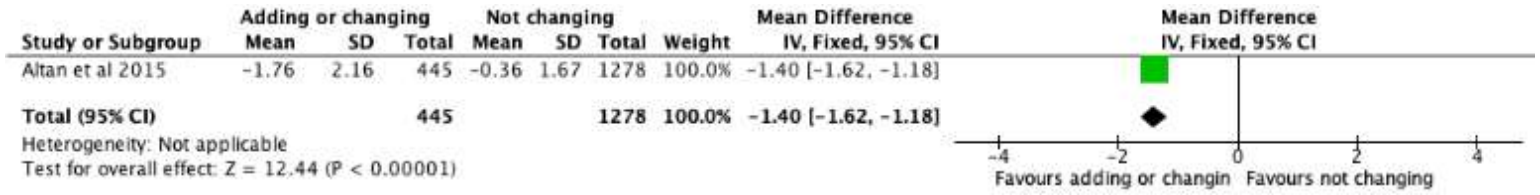
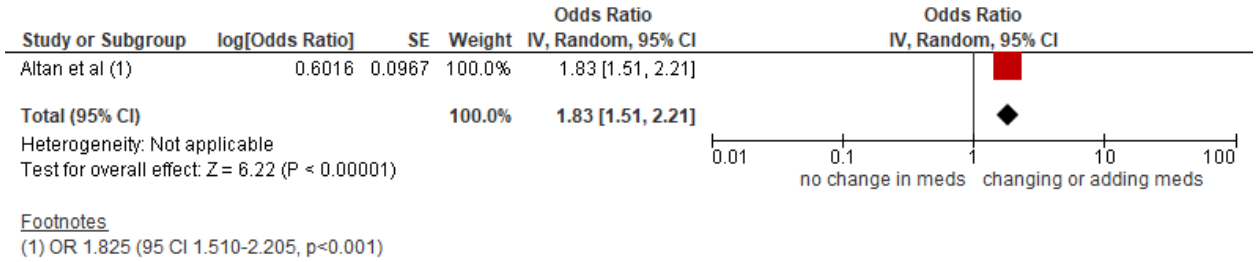


Figure 3: Forest plot of comparison: 1 Adding or changing medications vs no change in medication, outcome: 1.3 serum urate, proportion achieving SUA<5 mg/dL, post index period (longest follow up).



Footnotes
(1) OR 1.825 (95 CI 1.510-2.205, p<0.001)

25: Should we add a uricosuric or switch to uricosuric monotherapy in patients with gout on their second (maximum tolerated or FDA indicated dose) XOI agent who are not at serum urate target and/or have continued frequent gout flares or non-resolving subcutaneous tophi?

The systematic review did not find any studies addressing this question

26: Should we add an XOI or switch to lesinurad/ XOI in patients with gout on maximum probenecid monotherapy (e.g. XOI failure) who are not at serum urate target and/or have continued frequent flares or non-resolved subcutaneous tophi?

The systematic review did not find any studies addressing this question

PICO 27: Should we change to pegloticase versus continue current ULT in patients with gout in whom XOI, uricosurics, and other interventions failed to achieve serum urate target and/or have frequent gout flares or non-resolving subcutaneous tophi?

We did not find any studies addressing this question. The core team advised to inform this recommendation using the evidence from the recommendation question regarding ULT (PICO 10).

The evidence shows:

- Patients in whom XOI, uricosurics, and other interventions failed who receive biweekly pegloticase 8 mg
    - May not have a different probability of achieving serum urate <6 mg/dL than patients who receive allopurinol 300 mg, allopurinol 300 mg+ lesinurad 200 mg, febuxostat at any dose, or febuxostat 80 mg+ lesinurad 200 mg up to 24 months (Table 5, rows 2, 22, 24-31)
    - May not have a different probability of achieving serum urate <6 mg/dL than patients who receive monthly pegloticase up to 24 months (Table 5, row 32)
    - Probably have a higher probability of achieving serum urate <6 mg/dL than patients who receive placebo up to 24 months (Table 5, row 33)
    - May not have a different change in pain score than patients who receive monthly pegloticase or placebo at 6 months; but we are very uncertain about this evidence (Table 7)
    - Probably have a larger improvement in patient global assessment than patients who receive placebo, at 6 months (Table 8, row 1)
    - May not have a different improvement in patient global assessment than patients who receive monthly pegloticase, at 6 months (Table 8, row 3)
    - May not have a different probability of tophus resolution than patients who receive placebo, up to 24 months; but we are very uncertain about this evidence (Table 9, row 1)
    - Probably have a higher probability of tophus resolution than patients who receive monthly pegloticase, up to 24 months (Table 9, row 3)
    - Probably have a larger improvement in health-related quality of life than patients who receive placebo, at 6 months (Table 10, row 1)
    - May not have a different improvement in health-related quality of life than patients who receive monthly pegloticase (Table 10, row 3)
    - Probably have a larger improvement in activity limitation than patients who receive placebo, at 6 months (Table 11, row 1)
    - May not have a different improvement in activity limitation than patients who receive monthly pegloticase (Table 11, row 3)

    - May not have a different risk of serious adverse events than patients who receive allopurinol 300 mg, allopurinol 300 mg+ lesinurad 200 mg, febuxostat at any dose, febuxostat 80 mg+ lesinurad 200 mg, monthly pegloticase, probenecid 2 mg, or placebo, up to 24 months (Table 12, rows 2, 14, 26-36)
- Patients in whom XOI, uricosurics, and other interventions failed who receive monthly pegloticase 8 mg
    - May not have a different probability of achieving serum urate <6 mg/dL than patients who receive allopurinol 300 mg allopurinol 300 mg+ lesinurad 200 mg, febuxostat at any dose, febuxostat 80 mg+ lesinurad 200 mg up to 24 months (table 5, rows 11, 41, 49, 56, 62, 67, 71, 74, 76)
    - Probably have a higher probability of achieving serum urate <6 mg/dL than patients who receive placebo up to 24 months (Table 5, row 78)
    - May not have a different change in pain score than patients who receive placebo at 6 months; but we are very uncertain about this evidence (Table 7)
    - Probably have a larger improvement in patient global assessment than patients who receive placebo, at 6 months (Table 8, row 2)
    - May not have a different probability of tophus resolution than patients who receive placebo, up to 24 months (Table 9, row 2)
    - Probably have a larger improvement in health-related quality of life than patients who receive placebo, at 6 months (Table 10, row 2)
    - Probably have a larger improvement in activity limitation than patients who receive placebo, at 6 months (Table 11, row 2)
    - May not have a different risk of serious adverse events than patients who receive allopurinol 300 mg, allopurinol 300 mg+ lesinurad 200 mg, febuxostat at any dose, febuxostat 80 mg+ lesinurad 200 mg, probenecid 2 mg, or placebo, up to 24 months (Table 12, rows 11, 44, 53, 61, 68, 74, 79, 83, 86, 89, 90)

The overall quality of the evidence is MODERATE

When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is LOW

28: Should checking urinary acid vs. not checking urinary acid be used in patients with gout starting any uricosuric treatment?

We did not find any studies addressing this question. The core team suggested one article that could be included as indirect evidence.[56] The article provided information regarding levels of urinary uric acid in 216 patients who were starting treatment with benzbromarone, and their risk of developing nephrolithiasis.

The evidence shows the following

- We are very uncertain regarding the effect of checking urinary acid on nephrolithiasis in patients with gout starting any uricosuric treatment
- Patients with <20 mg/dL of undissociated urinary uric acid are likely to have a lower risk of nephrolithiasis than those with >20 mg/dL of undissociated urinary uric before starting treatment with uricosurics

The overall quality of the evidence is VERY LOW

When re-analyzed using the lowest level quality of evidence across all critical outcomes, the overall quality of the evidence is VERY LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With not checking urinary acid	With checking urinary acid	Relative effect (95% CI)	Risk with not checking urinary acid	Risk difference with checking urinary acid
Nephrolithiasis*- Comparison: < 20 mg/dL versus >20 mg/dL (follow up: mean 41 months; assessed with: undissociated urinary uric acid)											
216 (1 observational study)	not serious	not serious	serious [a]	not serious	none	⨁◯◯◯ VERY LOW	14/42 (33.3%)	7/174 (4.0%)	**RR 0.12** (0.05 to 0.28)	333 per 1,000	**293 fewer per 1,000** (317 fewer to 240 fewer)
Nephrolithiasis* (follow up: mean 41 months; assessed with: Risk of event per 1 unit increment in 24 hour urinary uric acid)											
211 (1 observational study) [b]	serious [c]	not serious	serious [a]	not serious	none	⨁◯◯◯ VERY LOW	[b]	-/211 [b]	**HR 1.003** (1.001 to 1.005)	0 per 1,000 [b]	**-- per 1,000** (-- to --)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Exposure: 24 hour urinary acid levels at baseline in patients with lithiasis (follow up: mean 41 months; assessed with: Comparison: patients with lithiasis versus patients without lithiasis)											
1118 (1 observational study)	not serious	not serious	serious [a]	not serious	none	⨁◯◯◯ VERY LOW	488	630	-	The mean exposure: 24 hour urinary acid levels at baseline in patients with lithiasis was **630** mg/day	MD **142 mg/day higher** (44.37 higher to 239.63 higher)

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio; **MD:** Mean difference

Explanations

a. This study is not addressing the question of interest directly. The levels of the exposure are being used as a surrogate to answer that question
b. Number of patients and outcome per group not reported. The study included a total of 211 participants
c. This is an unadjusted analysis. The adjusted analysis shows a lack of association between the urinary uric acid level and nephrolithiasis, but the estimates of such analysis are not reported

Outcome importance:
** Critical outcomes
* Important outcomes

Figure 1: Comparison: patients with undissociated urinary uric acid < 20 mg/dL versus >20 mg/dL. Outcome: nephrolithiasis

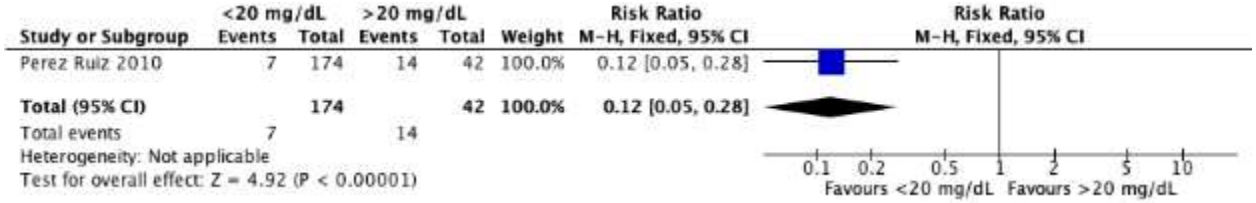
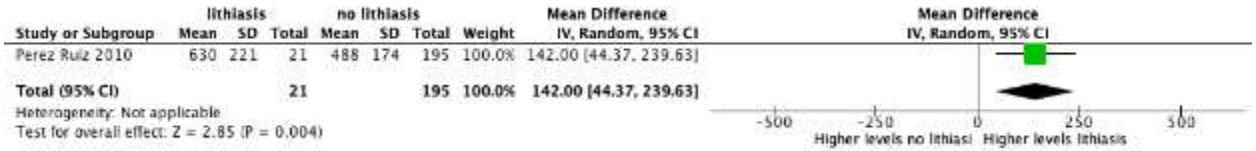


Figure 2: Comparison: patients with lithiasis versus without lithiasis. Outcome: 24- hour urinary uric acid (mg/day) at baseline



29: Should we alkalinize urine or not in patients on uricosuric treatment?

The systematic review did not find any studies addressing this question

30: Should we monitor urinary uric acid at regular intervals or not in patients on uricosuric treatment?

The systematic review did not find any studies addressing this question

31: Should Topical ice as adjuvant therapy vs. no ice as adjuvant therapy be used in patients experiencing a gout flare initiating anti-inflammatory treatment?

We found one study addressing this question.[57] The researchers enrolled 19 participants who were experiencing a gout flare, and assigned them to receive topical ice or not, in addition to their anti-inflammatory treatment.

The evidence shows:

- Patients who receive topical ice
    - May experience less pain, and a higher reduction in pain than patients who do not receive topical ice, after one week.
    - May not experience less joint swelling than patients who do not receive topical ice, after one week.
    - May not have a different risk of serious adverse events than patients who do not receive topical ice, up to one week.

The overall quality of the evidence is LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no ice as adjuvant therapy	With Topical ice as adjuvant therapy	Relative effect (95% CI)	Risk with no ice as adjuvant therapy	Risk difference with Topical ice as adjuvant therapy
Pain (follow up: 1 weeks; assessed with: Visual analog scale; Scale from: 0 to 10)**											
19 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	9	10	-	The mean pain** was **4.74** cm	MD **3.94 cm lower** (6.14 lower to 1.74 lower)
Pain (follow up: 1 weeks; assessed with: Reduction in visual analogue scale scores)**											
19 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	9	10	-	The mean pain** was **-4.42** cm	MD **3.33 cm lower** (5.84 lower to 0.82 lower)
Joint swelling* (follow up: 1 weeks; assessed with: Reduction in joint circumference in cm)											
19 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	9	10	-	The mean joint swelling* was **-3.83** cm	MD **2.07 cm lower** (5.7 lower to 1.56 higher)

Table 1: Evidence profile

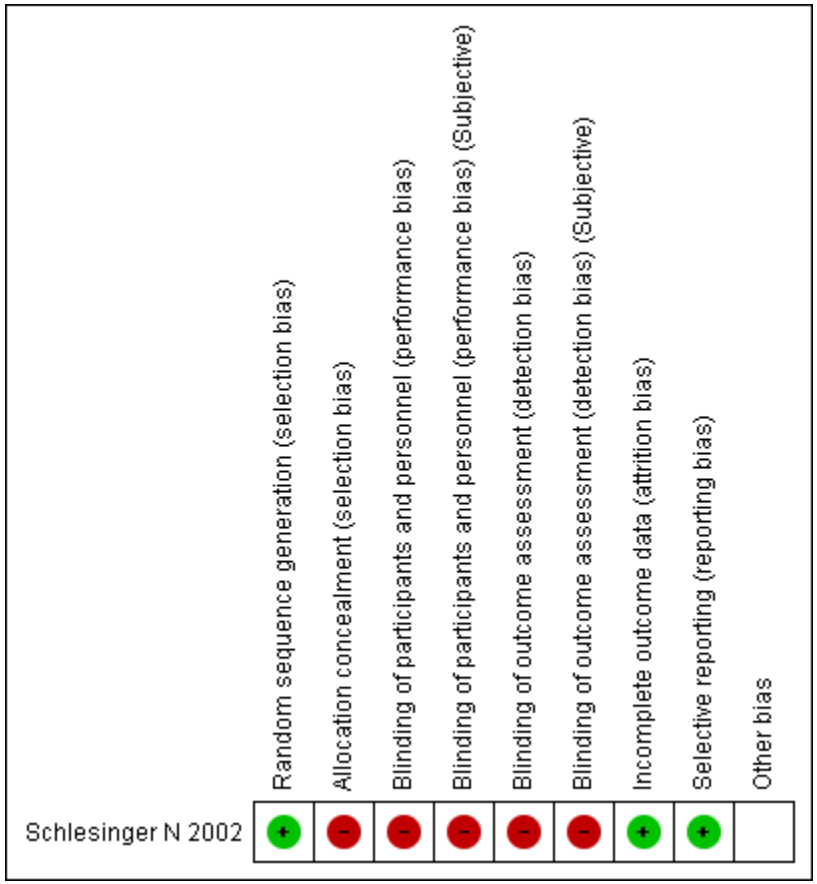
Certainty assessment							Summary of findings				
Serious adverse events (follow up: 1 weeks; assessed with: Proportion with serious adverse events)**											
19 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	0/9 (0.0%)	0/10 (0.0%)	not estimable	0 per 1,000	**0 fewer per 1,000** (180 fewer to 180 more)
Patient Global Assessment - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Joint Tenderness* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

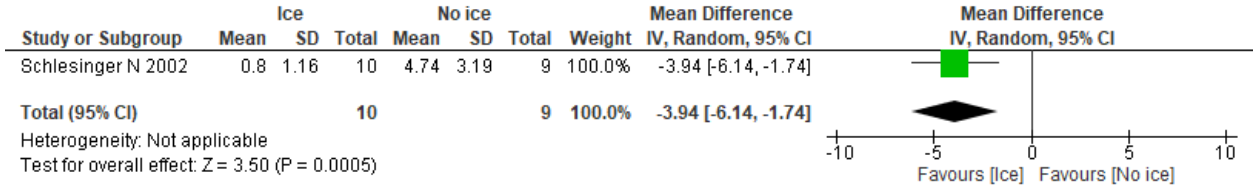
Explanations

a. At least one category in the risk of bias table with at least serious risk of bias.
b. Fewer than 200 people in the study.
Outcome importance:
**Critical outcomes
* Important outcomes

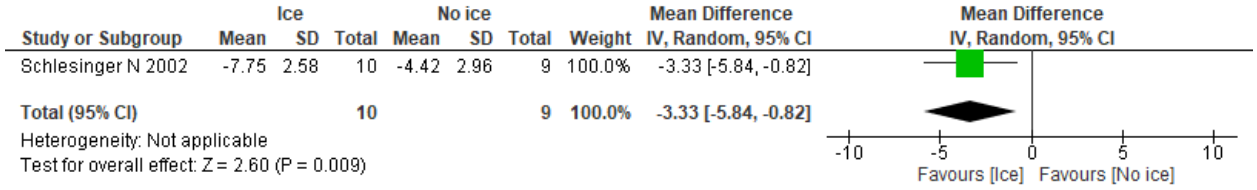
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



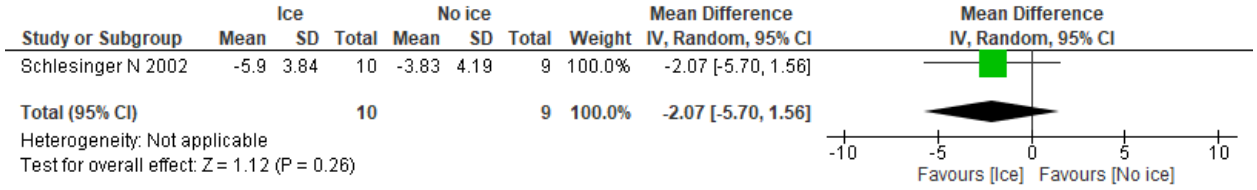
Forest plot of comparison: 1 Ice versus no ice-RCT, outcome: 1.1 Pain: Visual analog scale 1 week follow-up cm.



Forest plot of comparison: 1 Ice versus no ice-RCT, outcome: 1.2 Pain: mean reduction at 1 week, cm.



Forest plot of comparison: 1 Ice versus no ice-RCT, outcome: 1.3 Joint swelling: Reduction in joint circumference at 1 week, cm.



32: Should we use high-dose colchicine, low-dose colchicine, NSAIDs, systemic glucocorticoids, intra-articular glucocorticoids, ACTH, IL-1 inhibition, or no treatment in patients experiencing a gout flare?

Evidence from randomized clinical trials was combined using network meta-analysis. The results from this analysis are presented in appendix X.

33: Should IL-1 inhibition versus best-supportive analgesic therapy be used in patients experiencing a gout flare for whom anti-inflammatory therapies are poorly tolerated or contraindicated?

We found 4 articles relevant to answer this question.[58-61] The 4 articles reported the results from 3 different randomized clinical trials. The researchers compared canakinumab (IL-1 inhibition) versus triamcinolone acetonide (best supportive analgesic therapy). The trials included a small proportion of patients (22% in one trial and 30% in the other), whom the researchers described as "having contraindications or intolerance" or in whom NSAIDs were "poorly tolerated". Even though in one study the researchers used more than one dose of canakinumab, we only present data for the comparison between canakinumab 150 mg and triamcinolone acetonide 40 mg.

The evidence shows the following:

- Patients who receive canakinumab probably experience a higher pain reduction and a lower pain level in the most affected joint than those who receive triamcinolone acetonide, at 2 and 7 days.
- Patients who receive canakinumab are probably more likely to make a global assessment of good or very good/excellent than patients who receive triamcinolone acetonide, at 2 and 7 days.
- The risk of experiencing moderate or severe joint swelling may be lower in patients who receive canakinumab than in those who receive triamcinolone acetonide, at 2 and 7 days.
- The risk of experiencing moderate or severe joint tenderness is probably lower in patients who receive canakinumab than in those who receive triamcinolone acetonide, at 2 and 7 days.
- The risk of experiencing serious adverse events is probably higher in patients who receive canakinumab than in those who received triamcinolone.

The overall quality of the evidence is MODERATE

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With best supportive analgesic therapy	With IL-1 inhibition	Relative effect (95% CI)	Risk with best supportive analgesic therapy	Risk difference with IL-1 inhibition
Pain reduction (follow up: mean 3 days; assessed with: 100-mm VAS)**											
83 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	53	30	-	The mean pain reduction was **57.8** mm	MD **26.8 mm higher** (13.91 higher to 39.69 higher)
Pain reduction (follow up: mean 7 days; assessed with: 100-mm VAS)**											
68 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	43	25	-	The mean pain reduction was **74.8** mm	MD **17.9 mm higher** (6.98 higher to 28.82 higher)
Pain (follow up: mean 2 days; assessed with: Level in the most affected joint using a 100-mm VAS)**											
454 (2 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	229	225	-	The mean pain was **43** mm	MD **10.09 mm lower** (14.79 lower to 5.39 lower)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Pain (follow up: mean 7 days; assessed with: Level in the most affected joint using a 100-mm VAS)**											
454 (2 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	229	225	-	The mean pain was **15.5** mm	MD **7.18 mm lower** (11.63 lower to 2.73 lower)
Patient global assessment* (follow up: range 2 days to 3 days; assessed with: Assessed as good or very/good/excellent)											
537 (3 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	132/285 (46.3%)	161/252 (63.9%)	**RR 1.46** (1.21 to 1.76)	463 per 1,000	**213 more per 1,000** (97 more to 352 more)
Patient global assessment* (follow up: mean 7 days; assessed with: Assessed as good or very good/excellent)											
537 (3 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	161/285 (56.5%)	186/252 (73.8%)	**RR 1.32** (1.16 to 1.49)	565 per 1,000	**181 more per 1,000** (90 more to 277 more)
Joint swelling* (follow up: range 2 days to 3 days; assessed with: Patients with moderate/severe)											
537 (3 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	152/285 (53.3%)	125/252 (49.6%)	**RR 0.66** (0.26 to 1.70)	533 per 1,000	**181 fewer per 1,000** (395 fewer to 373 more)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Joint swelling* (follow up: mean 7 days; assessed with: Patients with moderate/severe)											
537 (3 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	44/285 (15.4%)	25/252 (9.9%)	**RR 0.55** (0.18 to 1.67)	154 per 1,000	**69 fewer per 1,000** (127 fewer to 103 more)
Joint tenderness* (follow up: range 2 days to 3 days; assessed with: Patients with moderate/severe)											
537 (3 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	60/285 (21.1%)	21/252 (8.3%)	**RR 0.40** (0.25 to 0.64)	211 per 1,000	**126 fewer per 1,000** (158 fewer to 76 fewer)
Joint tenderness* (follow up: mean 7 days; assessed with: Patients with moderate/severe)											
481 (3 RCTs) [c,d]	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	33/229 (14.4%) [c,d]	0/252 (0.0%) [c]	**OR 2.21** (1.50 to 3.25)	144 per 1,000 [c,d]	**127 more per 1,000** (58 more to 210 more)
Serious adverse events (follow up: mean 24 weeks; assessed with: Researchers definition)**											
539 (3 RCTs)	not serious	not serious	not serious [e]	serious [f]	none	⨁⨁⨁◯ MODERATE	8/286 (2.8%)	17/253 (6.7%)	**RR 2.26** (0.98 to 5.18)	28 per 1,000	**35 more per 1,000** (1 fewer to 117 more)

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. Only a small proportion of the participants included in the studies were classified as having poor tolerance or contraindication for anti-inflammatory treatments

b. The confidence interval shows that there is a possibility that switching to an alternative anti-inflammatory agent results in more benefit than adding or switching to IL-1 inhibition
c. The researchers do not report the number of patients with moderate/ severe joint tenderness in one of the studies.. They provided the OR instead
d. We calculated the proportion using the data from the one study where this information was provided
e. Even though only a small proportion of participants had poor tolerance or contraindication to anti-inflammatories, it is unlikely that SAEs are different if the majority of participants had this condition
f. The confidence interval shows that there switching to IL-1 could importantly increase SAEs, but also that the difference between the two approaches is not important

Outcome importance:
** Critical outcomes
* Important outcomes

Figure 1: Risk of bias

Figure 2: Pain reduction at 3 days

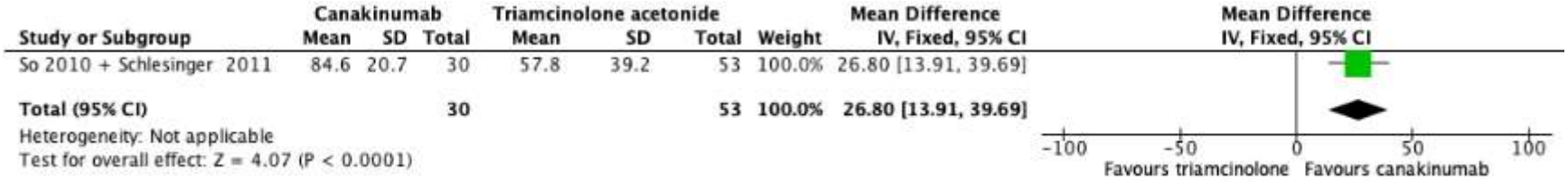


Figure 3: Pain reduction at 7 days

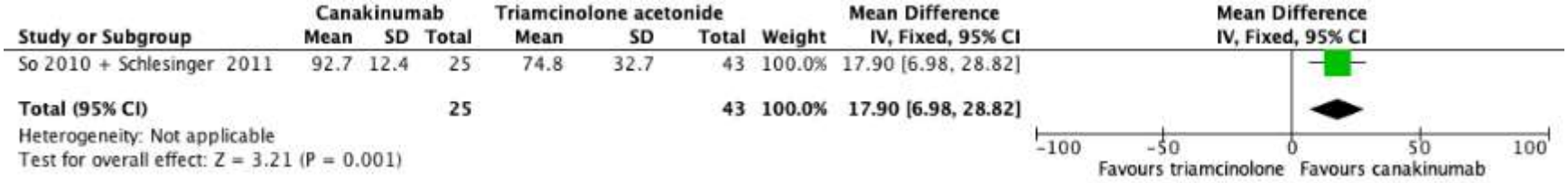


Figure 4: Pain in the most affected joint at day 2

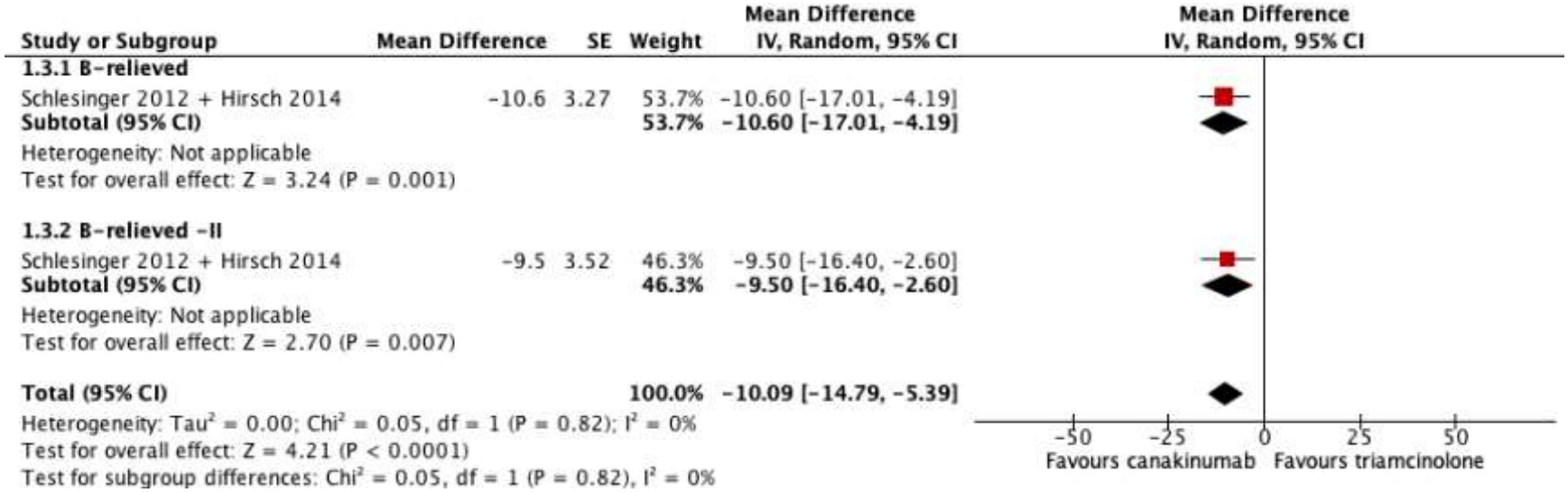


Figure 5: Pain in the most affected joint at day 7

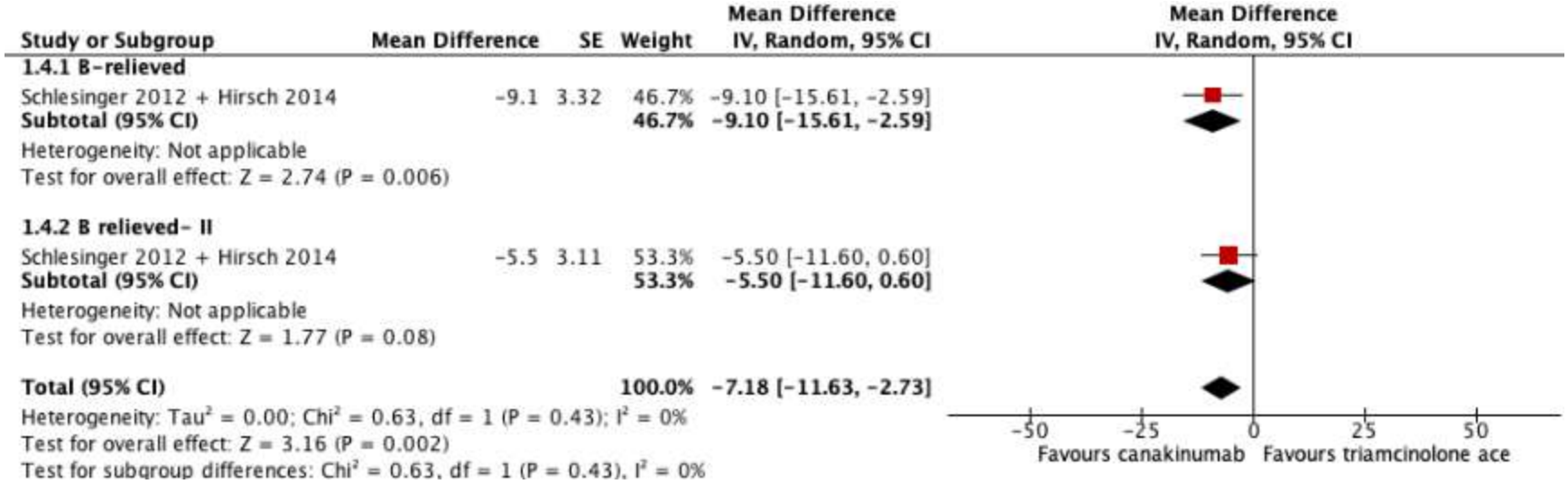


Figure 6: Patient global assessment at 2 to 3 days

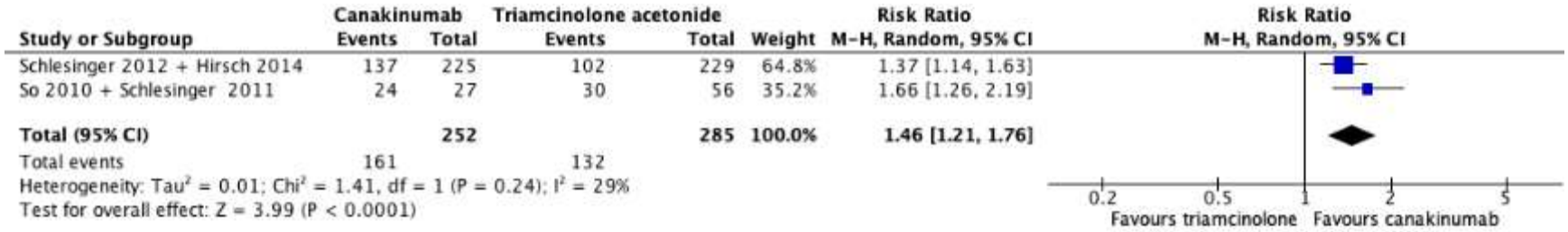


Figure 7: Patient global assessment at 7 days

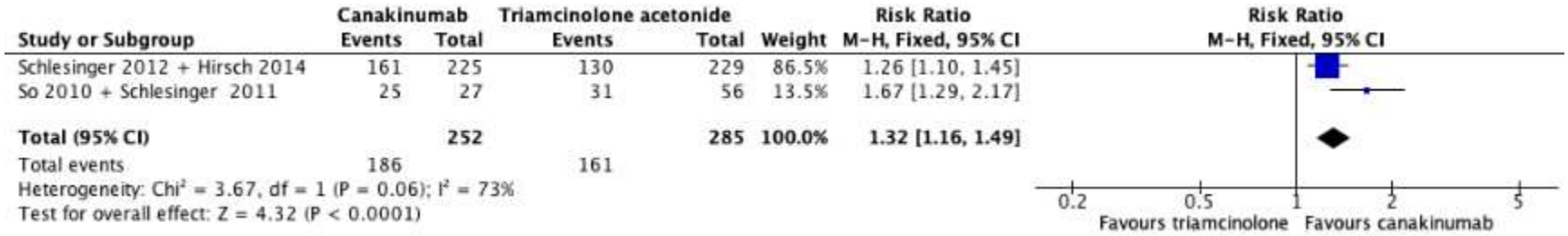


Figure 8: Joint swelling at day 2-3

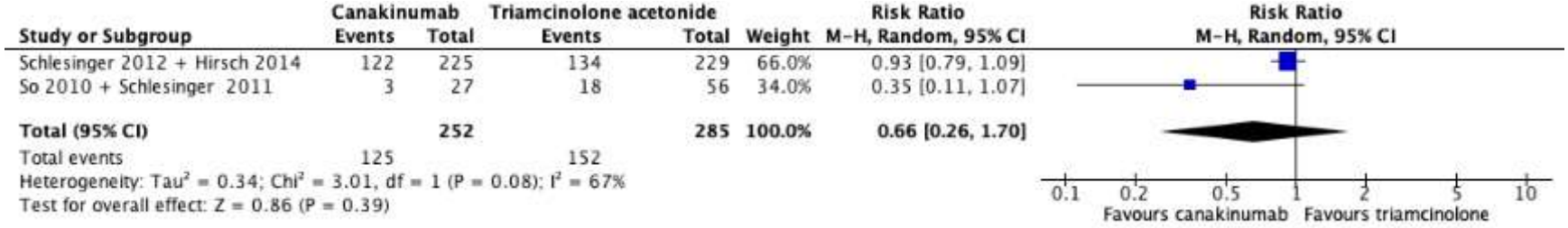


Figure 9: Joint swelling at day 7

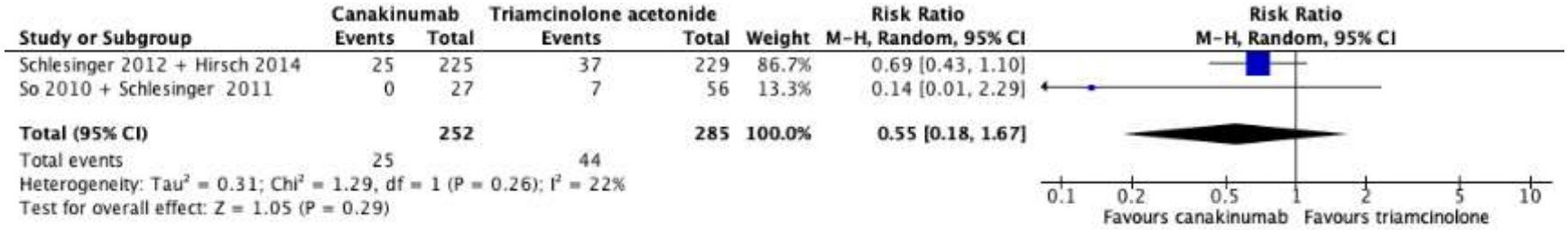


Figure 10: Joint tenderness at day 2-3

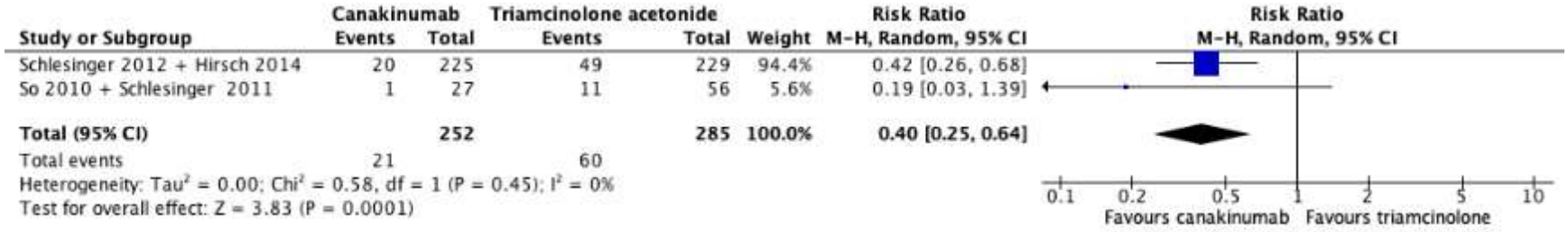


Figure 11: Joint tenderness at day 7

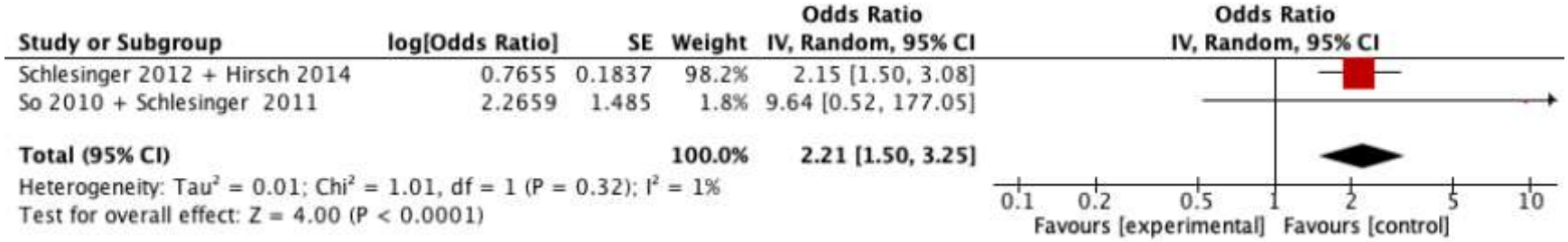
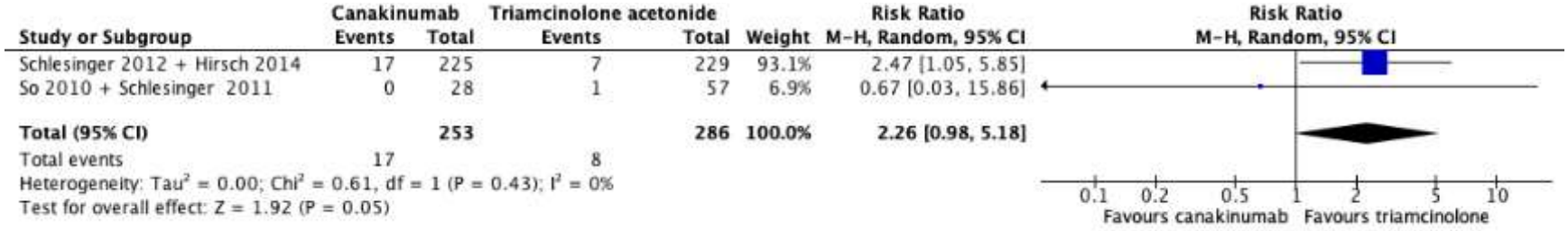


Figure 12- Serious adverse events



34: Should we switch to an alternative anti-inflammatory monotherapy or continue the same treatment in patients experiencing a gout flare and achieving a suboptimal treatment response after 36-48 hours?

The systematic review did not find any studies addressing this question

35: Should we add an additional anti-inflammatory agent or continue with the same treatment in patients experiencing a gout flare and achieving a suboptimal response after 36-48 hours?

The systematic review did not find any studies addressing this question

36: Should we switch to an alternative anti-inflammatory monotherapy or add an additional anti-inflammatory agent in patients experiencing a gout flare and achieving a suboptimal treatment response after 36-48 hours?

The systematic review did not find any studies addressing this question

37: Should switching to or adding IL-1 inhibition versus switching to an alternative anti-inflammatory agent be used in patients experiencing a gout flare and achieving suboptimal response after 36-48 hours?

We found 4 articles addressing this question.[58-61] The 4 articles reported the results from 3 different randomized clinical trials. The researchers compared canakinumab (switching to IL-1 inhibition) versus triamcinolone acetonide (alternative anti-inflammatory agent). The trials included mostly patients (72% in one trial and 90% in the other) who had achieved a suboptimal response, whom they described as "unresponsive to NSAIDs" or "with refractory disease". Even though in one study the researchers used more than one dose of canakinumab, we only present data for the comparison between canakinumab 150 mg and triamcinolone acetonide 40 mg.

The evidence shows:

- Patients who receive canakinumab experience a higher pain reduction and a lower pain level in the most affected joint than those who receive triamcinolone acetonide, at 2 and 7 days.
- Patients who receive canakinumab are more likely to make a global assessment of good or very good/excellent than patients who receive triamcinolone acetonide, at 2 and 7 days.
- The risk of experiencing moderate or severe joint swelling is probably lower in patients who receive canakinumab than in those who receive triamcinolone acetonide, at 2 and 7 days.
- The risk of experiencing moderate or severe joint tenderness is lower in patients who receive canakinumab than in those who receive triamcinolone acetonide, at 2 and 7 days.
- The risk of experiencing serious adverse events is higher in patients who receive canakinumab than in those who received triamcinolone.

The overall quality of the evidence is HIGH

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With switching to an alternative anti-inflammatory agent	With switching to or adding IL-1 inhibition	Relative effect (95% CI)	Risk with switching to an alternative anti-inflammatory agent	Risk difference with switching to or adding IL-1 inhibition
Pain reduction (follow up: mean 3 days; assessed with: 100-mm VAS)**											
83 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	53	30	-	The mean pain reduction was **57.8** mm	MD **26.8 mm higher** (13.91 higher to 39.69 higher)
Pain reduction (follow up: mean 7 days; assessed with: 100-mm VAS)**											
68 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	43	25	-	The mean pain reduction was **74.8** mm	MD **17.9 mm higher** (6.98 higher to 28.82 higher)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Pain (follow up: mean 2 days; assessed with: Level in the most affected joint using a 100-mm VAS)**											
454 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	229	225	-	The mean pain was **43** mm	MD **10.09 mm lower** (14.79 lower to 5.39 lower)
Pain (follow up: mean 7 days; assessed with: Level in the most affected joint using a 100-mm VAS)**											
454 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	229	225	-	The mean pain was **15.5** mm	MD **7.18 mm lower** (11.63 lower to 2.73 lower)
Patient global assessment* (follow up: range 2 days to 3 days; assessed with: Assessed as good or very/good/excellent)											
537 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	132/285 (46.3%)	161/252 (63.9%)	**RR 1.46** (1.21 to 1.76)	463 per 1,000	**213 more per 1,000** (97 more to 352 more)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Patient global assessment* (follow up: mean 7 days; assessed with: Assessed as good or very good/excellent)											
537 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	161/285 (56.5%)	186/252 (73.8%)	**RR 1.32** (1.16 to 1.49)	565 per 1,000	**181 more per 1,000** (90 more to 277 more)
Joint swelling* (follow up: range 2 days to 3 days; assessed with: Patients with moderate/severe)											
537 (3 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	152/285 (53.3%)	125/252 (49.6%)	**RR 0.66** (0.26 to 1.70)	533 per 1,000	**181 fewer per 1,000** (395 fewer to 373 more)
Joint swelling* (follow up: mean 7 days; assessed with: Patients with moderate/severe)											
537 (3 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	44/285 (15.4%)	25/252 (9.9%)	**RR 0.55** (0.18 to 1.67)	154 per 1,000	**69 fewer per 1,000** (127 fewer to 103 more)
Joint tenderness* (follow up: range 2 days to 3 days; assessed with: Patients with moderate/severe)											
537 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	60/285 (21.1%)	21/252 (8.3%)	**RR 0.40** (0.25 to 0.64)	211 per 1,000	**126 fewer per 1,000** (158 fewer to 76 fewer)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Joint tenderness* (follow up: mean 7 days; assessed with: Patients with moderate/severe)											
481 (3 RCTs) [b]	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	33/229 (14.4%) [b]	-/252 [b]	**OR 2.21** (1.50 to 3.25) [c]	144 per 1,000 [b]	**127 more per 1,000** (58 more to 210 more) [c]
Serious adverse events (follow up: mean 24 weeks; assessed with: Researchers definition)**											
539 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	8/286 (2.8%)	17/253 (6.7%)	**RR 2.26** (0.98 to 5.18)	28 per 1,000	**35 more per 1,000** (1 fewer to 117 more)

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. The confidence interval shows that there is a possibility that switching to an alternative anti-inflammatory agent results in more benefit than adding or switching to IL-1 inhibition
b. The researchers do not report the number of patients with moderate/ severe joint tenderness in one of the studies.. They provided the OR instead
c. We used the proportion from the study that provided the number of patients

Outcome importance:
** Critical outcomes
* Important outcomes

Figure 1: Risk of bias

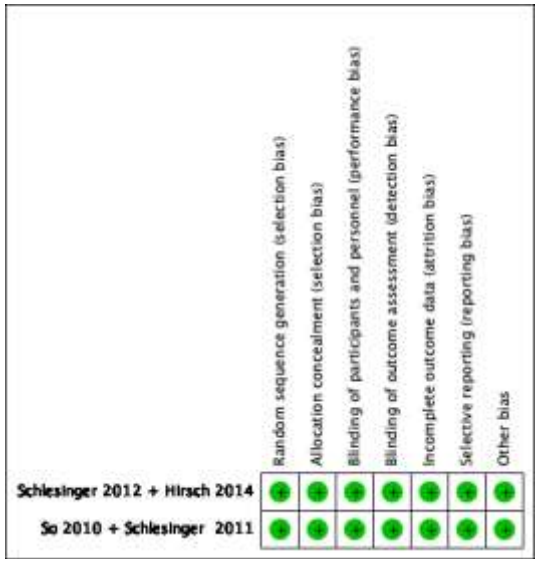


Figure 2: Pain reduction at 3 days

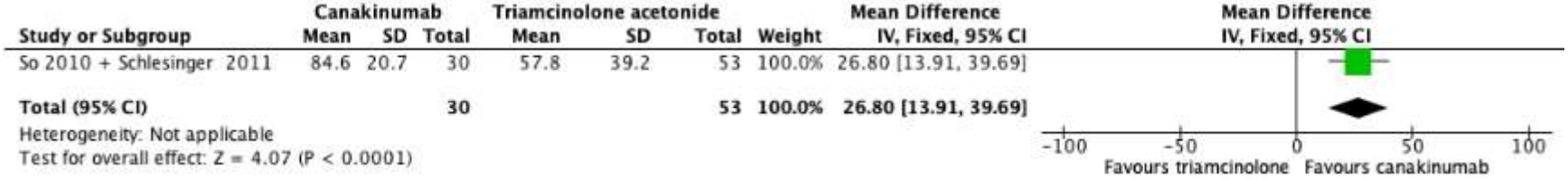


Figure 3: Pain reduction at 7 days

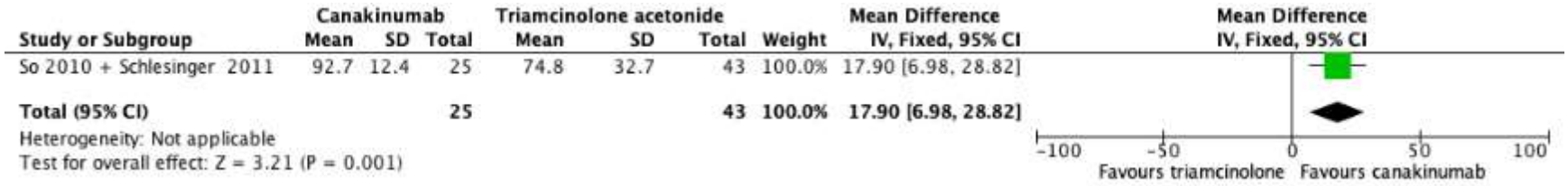


Figure 4: Pain in the most affected joint at day 2

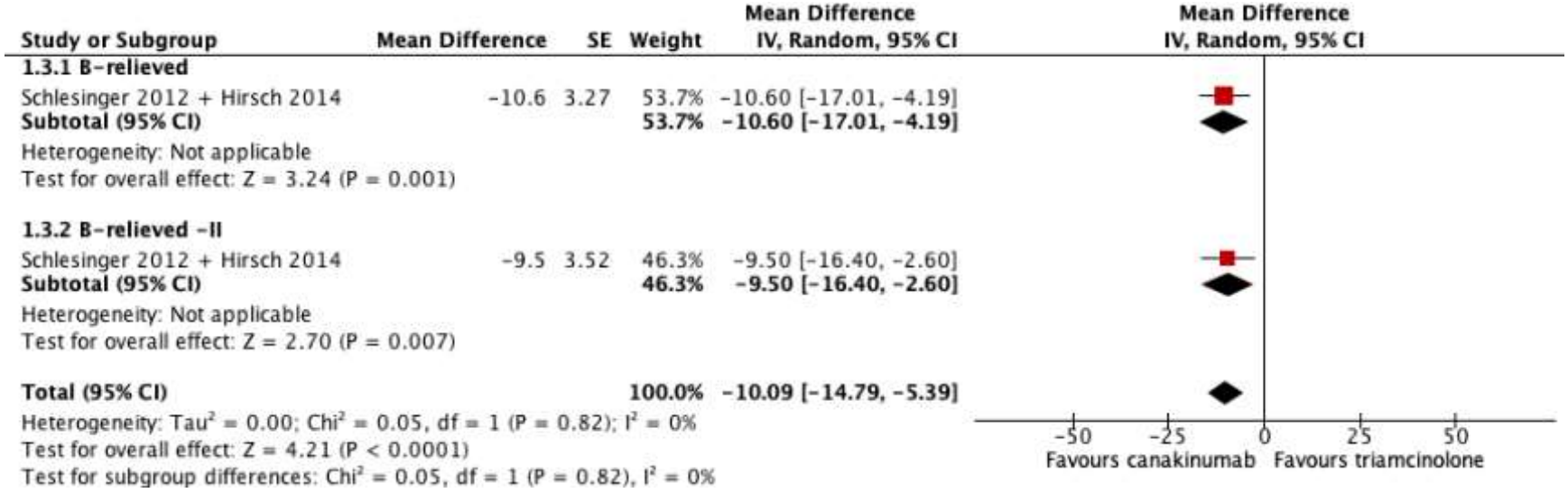


Figure 5: Pain in the most affected joint at day 7

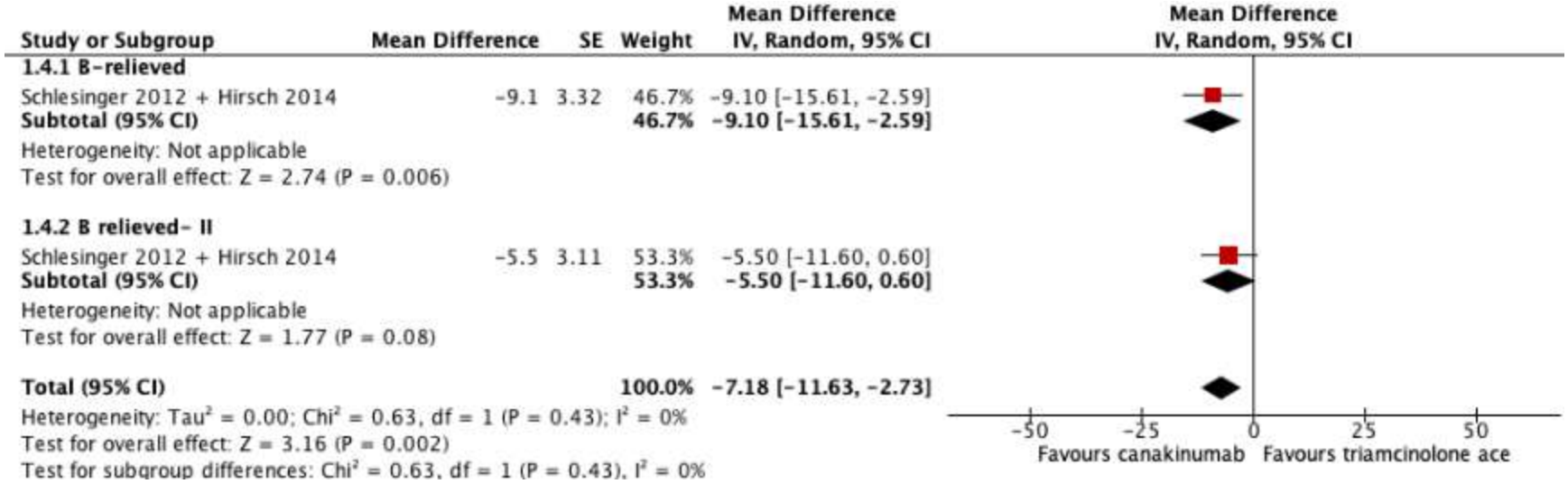


Figure 6: Patient global assessment at 2 to 3 days

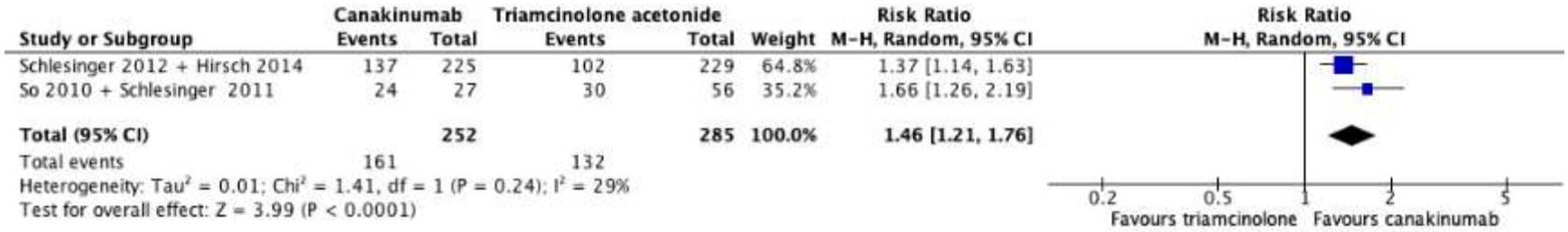


Figure 7: Patient global assessment at 7 days

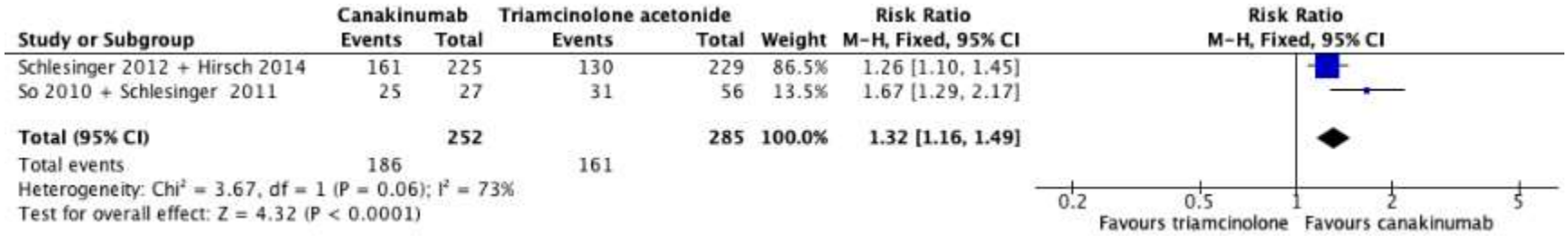


Figure 8: Joint swelling at day 2-3

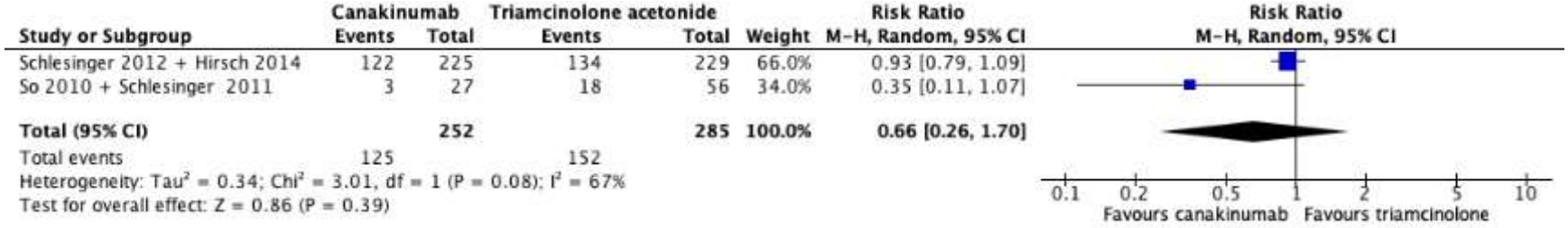


Figure 9: Joint swelling at day 7

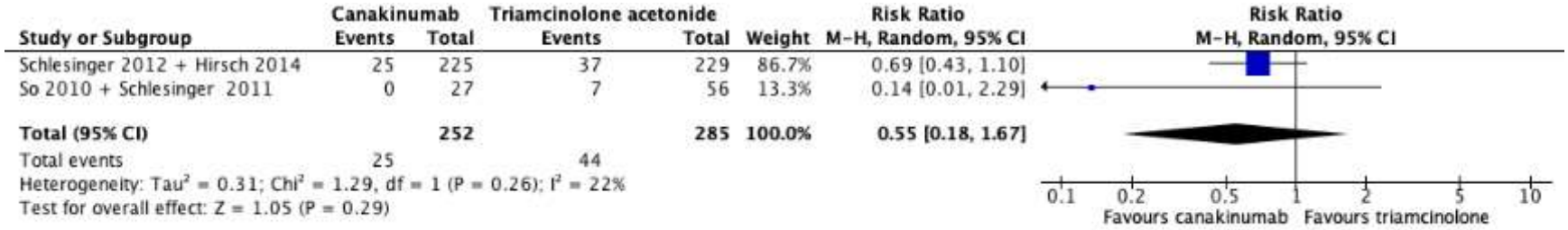


Figure 10: Joint tenderness at day 2-3

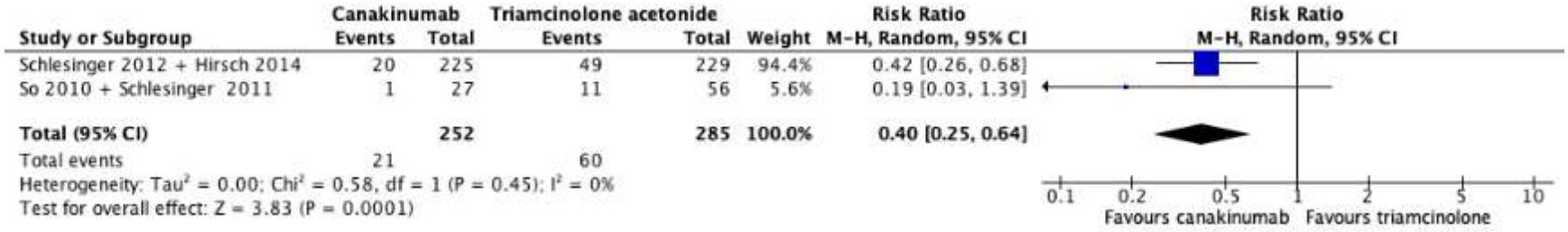


Figure 11: Joint tenderness at day 7

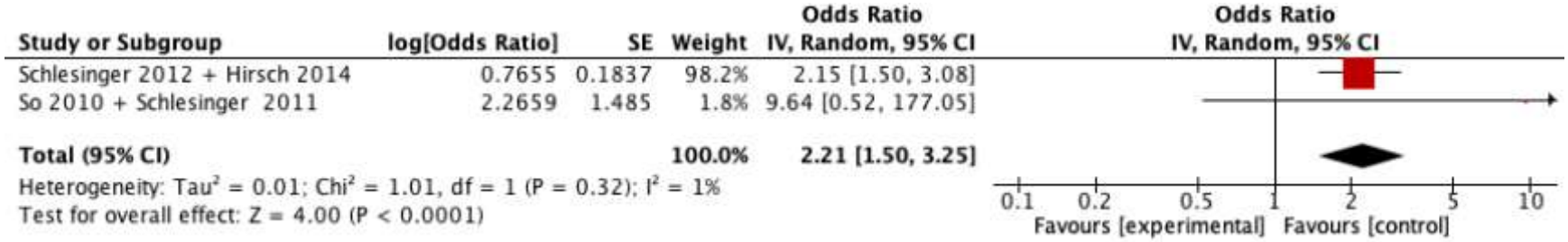
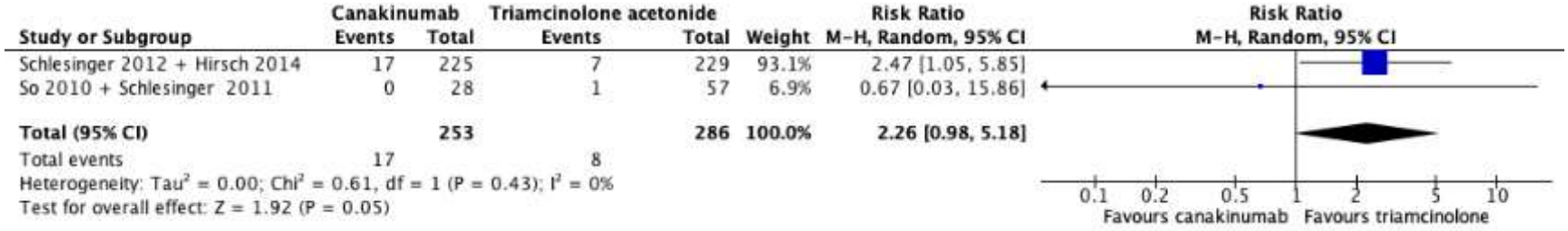


Figure 12- Serious adverse events



38: Should we add an additional anti-inflammatory agent or switch to/ add IL-1 inhibition in patients experiencing a gout flare and achieving suboptimal treatment response after 36-48 hours?

The systematic review did not find any studies addressing this question

40: Should we add an additional anti-inflammatory agent or use intra-articular glucocorticoids in patients experiencing a gout flare and achieving a suboptimal treatment response to an oral anti-inflammatory after 36-48 hours?

The systematic review did not find any studies addressing this question

41: Should limiting alcohol consumption vs. no limiting alcohol consumption be used in patients with gout?

We found 3 studies addressing this question, which were reported in 4 articles.[62-65] These were all observational studies.
The evidence shows:

- Patients who abstain from drinking alcohol or limit their alcohol consumption
    - May have lower levels of serum urate than those who do not, up to 6 months
    - May have a lower risk of gout flares than those who do not, up to 48 hours, but we are uncertain about this evidence
    - May have a lower risk of gout flares than those who do not, up to 6 months, but we are uncertain about this evidence

The overall quality of the evidence is LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no limiting alcohol consumption	With limiting alcohol consumption	Relative effect (95% CI)	Risk with no limiting alcohol consumption	Risk difference with limiting alcohol consumption
Serum urate (follow up: range 2 weeks to 6 months; assessed with: Mean level)**											
62 (2 observational studies)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	33	29	-	The mean serum urate** was **8.4** mg/dL	MD **1.61 mg/dL lower** (2.62 lower to 0.5 lower)
Gout flares (follow up: range 1 days to 2 days; assessed with: Risk of flares)**											
724 (2 observational studies)	serious [a]	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	-/724	-/724	**OR 0.66** (0.48 to 0.92)	Not reported	**Not estimable**
Gout flares (follow up: mean 6 months; assessed with: Risk of flares)**											
38 (1 observational study)	serious [a]	not serious	not serious	not serious [b]	none	⨁◯◯◯ VERY LOW	20/21 (95.2%)	5/17 (29.4%)	**OR 0.02** (0.00 to 0.20)	952 per 1,000	**660 fewer per 1,000** (890 fewer to 420 fewer)

Table 1: Evidence profile

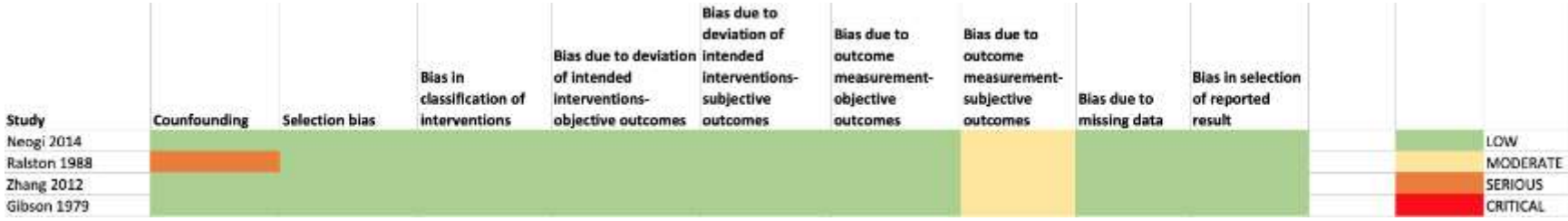
Certainty assessment							Summary of findings				
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health related Quality of Life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient acceptability* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious Adverse Events - not reported**											
-	-	-	-	-	-	-	-	-	-	-	-

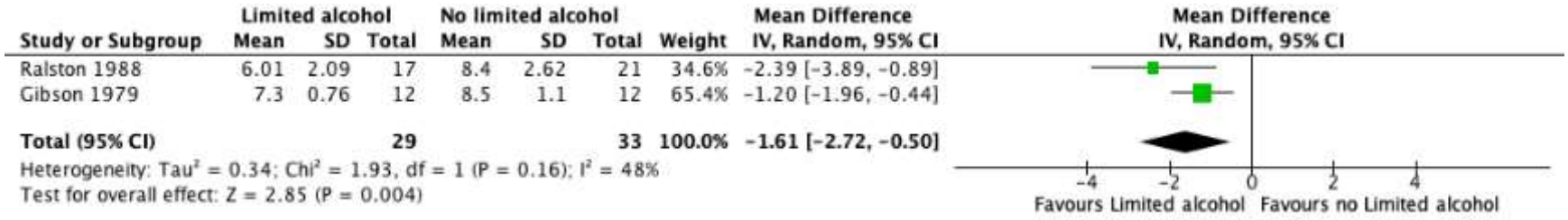
CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio, **NR:** Not reported

Explanations

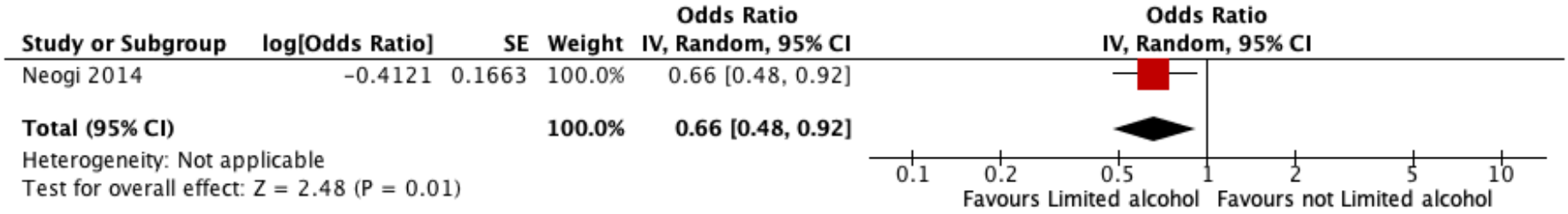
a. The studies do not suffer from any biases not accounted for in the rating
b. The experts are confident in the presence of an effect, regardless of the number of participants included
Outcome importance
**Critical outcomes
* Important outcomes

Risk of bias assessment

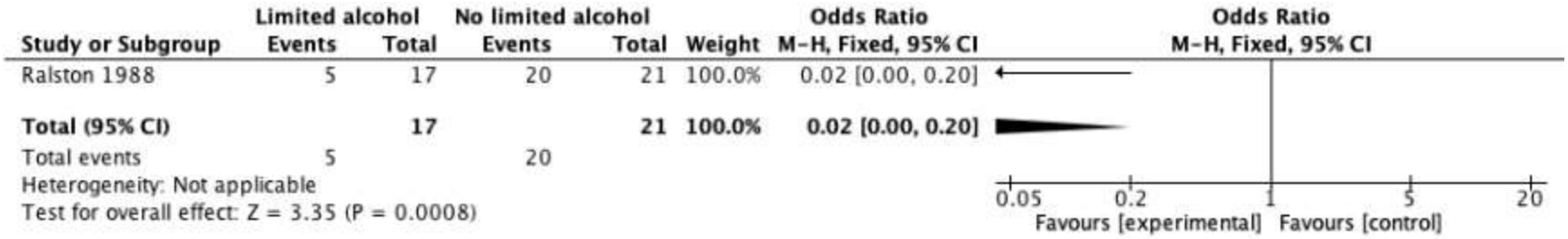




Forest plot of comparison: Abstaining or limiting alcohol vs no limiting alcohol consumption, outcome: 1.1 Serum urate change.



Forest plot of comparison: Abstaining or limiting alcohol vs no limiting alcohol consumption, outcome: 1.2 Risk of gout flares with limiting alcohol up to 48 hours



Forest plot of comparison: Abstaining or limiting alcohol vs no limiting alcohol consumption, outcome: 1.3 Risk of gout flares with limiting alcohol up to 6 months

42: Should Limited purine intake vs. no limited purine intake be used in patients with gout?

We found 2 studies addressing this question, which were reported in 3 articles.[63, 65, 66] One study was a small randomized clinical trial,[66] in which researchers enrolled 29 participants and assigned them to receive dietary advice about several nutrients, including purine. The other 2 studies were observational studies in which researchers assessed the occurrence of gout flares after consuming several nutrients, including purine.[63, 65]

The evidence shows:

- Patients with gout who are advised to limit their purine intake
    - May not have a different change in serum urate levels than patients who are not advised to do so, after 6 months.
    - May not have a different risk of gout flares than patients who are not advised to do so, after 6 months; but we are very uncertain about this evidence
    - May have a lower risk of gout flares than patients who are not advised to do so, up to 2 days.

The overall quality of the evidence is LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no limited purine intake	With Limited purine intake	Relative effect (95% CI)	Risk with no limited purine intake	Risk difference with Limited purine intake
Serum urate (follow up: mean 6 months; assessed with: Mean final level, mg/dL)**											
29 (1 RCT)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	15	14	-	The mean serum urate** was **-4.54** mg/dL	MD **0.5 mg/dL higher** (0.42 lower to 1.42 higher)
Gout flares (follow up: mean 6 months; assessed with: Patients with gout flares)**											
29 (1 RCT)	serious [a]	not serious	serious [b]	very serious [d]	none	⨁◯◯◯ VERY LOW	1/15 (6.7%)	2/14 (14.3%)	**RR 2.14** (0.22 to 21.10)	67 per 1,000	**76 more per 1,000** (52 fewer to 1,340 more)
Gout flares (follow up: range 24 hours to 2 days; assessed with: Patients with gout flares)**											
724 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	-/724	-/724	**OR 0.43** (0.34 to 0.53)	Not reported	**Not estimable**
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health related Quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious Adverse Events* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

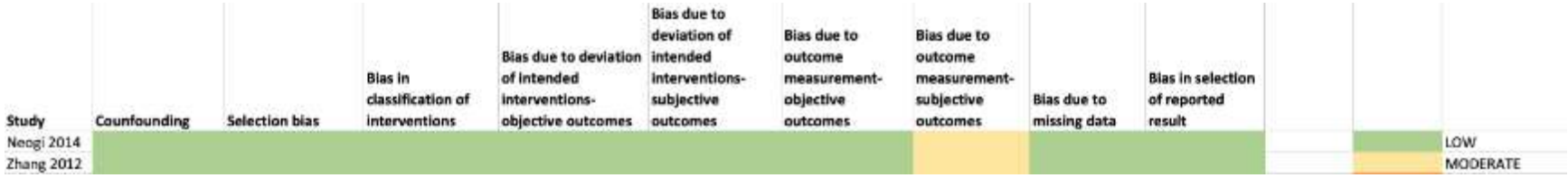
CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **OR:** Odds ratio

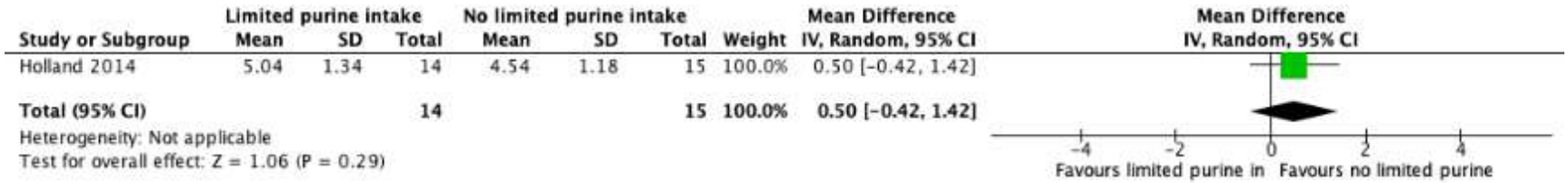
Explanations

a. Trial at high risk of bias
b. Intervention was composed of different strategies, so the effect of purines alone may be importantly different
c. Very small number of patients included in the trial
b. Wide CI crosses no-effect line and reflects important uncertainty. The number of participants and events is very small
Outcome importance:
**Critical outcomes
* Important outcomes

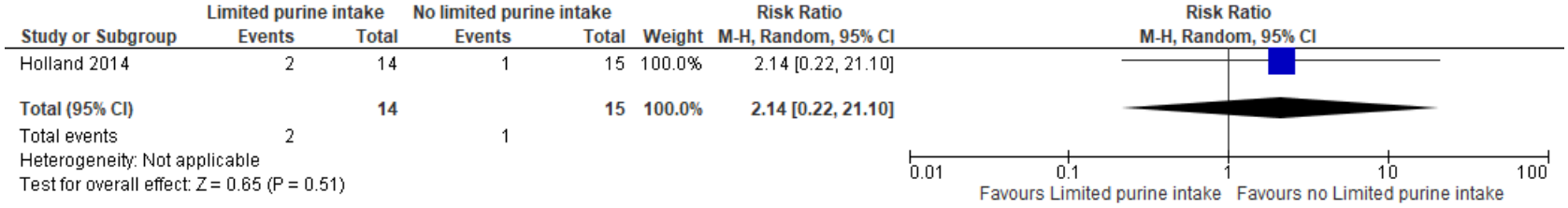
Risk of bias assessment, RCT:

Risk of bias assessment: observational studies

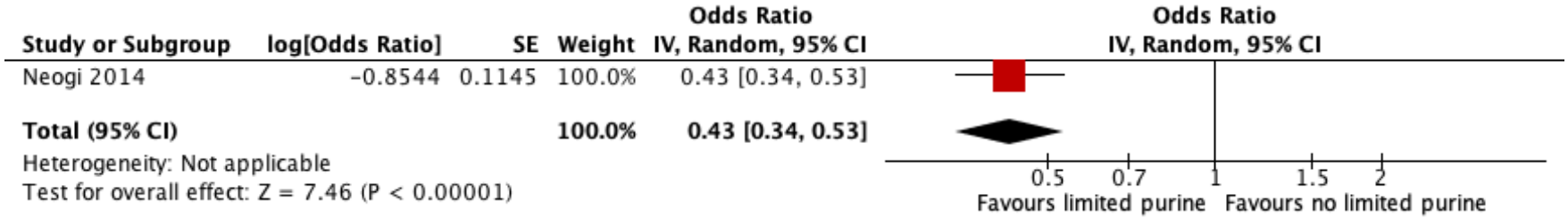




Forest plot of comparison: Limited purine intake vs no limited purine intake - RCT, outcome: 1.1 Serum urate level (final)



Forest plot of comparison: 1 Limited purine intake vs no limited purine intake - RCT, outcome: 1.2 Gout flares.



Forest plot of comparison: 1 Limited purine intake vs no limited purine intake, outcome: 1.3 Risk of gout flares with limited purine intake.

43: Should limiting or abstaining from high-fructose corn syrup or no limited intake of high-fructose corn syrup be used in patients with gout?

The systematic review did not find any studies addressing this question

44: Should Increase of dairy protein vs. no increase of dairy protein be used in patients with gout?

We found 3 studies addressing this question.[66-68] All the studies were randomized clinical trials.

The evidence shows

- Patients with gout who increase their dairy protein intake
    - Probably do not have different serum urate level changes than patients who do not increase their dairy protein intake, up to 6 months.
    - May not have a different risk of gout flares than patients who do not increase their dairy protein intake, up to 6 months.
    - Probably do not have a different frequency of gout flares than patients who do not increase their dairy protein intake, up to 3 months.
    - Probably do not experience different pain levels than patients who do not increase their dairy protein intake, up to 3 months.
    - Probably do not have a different risk of adverse events than patients who do not increase their dairy protein intake, up to 3 months.

The overall quality of the evidence is MODERATE

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no increase of dairy protein	With Increase of dairy protein	Relative effect (95% CI)	Risk with no increase of dairy protein	Risk difference with Increase of dairy protein
Serum urate (follow up: range 2 months to 6 months; assessed with: Mean change from baseline)**											
134 (3 RCTs)	not serious [a]	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	67	67	-	The mean serum urate** change was - **0.08** mg/dL	MD **0.12 mg/dL higher reduction** (0.48 higher to 0.25 lower)
Gout Flares (follow up: mean 6 months; assessed with: Patients with flares)**											
29 (1 RCT)	serious [c]	not serious	serious [d]	very serious [b]	none	⨁◯◯◯ VERY LOW	1/15 (6.7%)	2/14 (14.3%)	**RR 2.14** (0.22 to 21.10)	67 per 1,000	**76 more per 1,000** (52 fewer to 1,340 more)
Gout flares (follow up: mean 3 months; assessed with: Change in frequency)**											
80 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	40	40	-	The mean gout flares** was **- 0.74**	MD **0.24 higher** (0.26 lower to 0.74 higher)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Pain* (follow up: mean 3 months; assessed with: Mean change in 10-cm visual analogue scale; Scale from: 0 to 10)											
80 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	40	40	-	The mean pain* was **-0.77**	MD **0.35 lower** (1.44 lower to 0.75 higher)
Serious adverse events* (follow up: mean 3 months; assessed with: Patients with SAE)											
80 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	0/40 (0%)	3/40 (7.5%)	**RR 7.0** (0.37 to 131.28)	0 per 1,000	**70 more per 1,000** (20 fewer to 170 more)
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health related quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

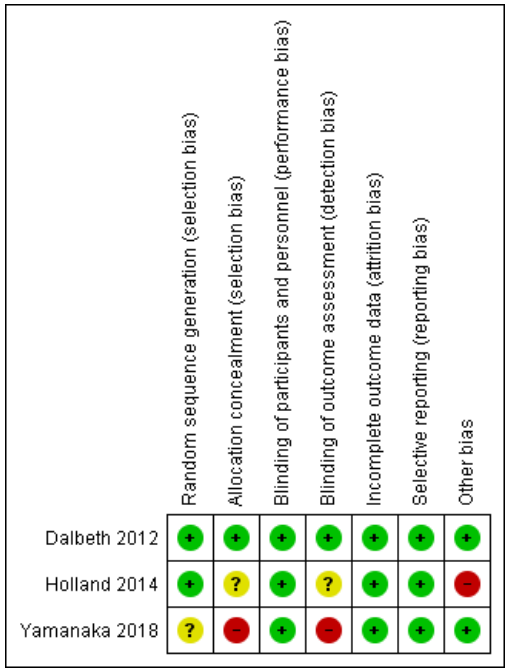
CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

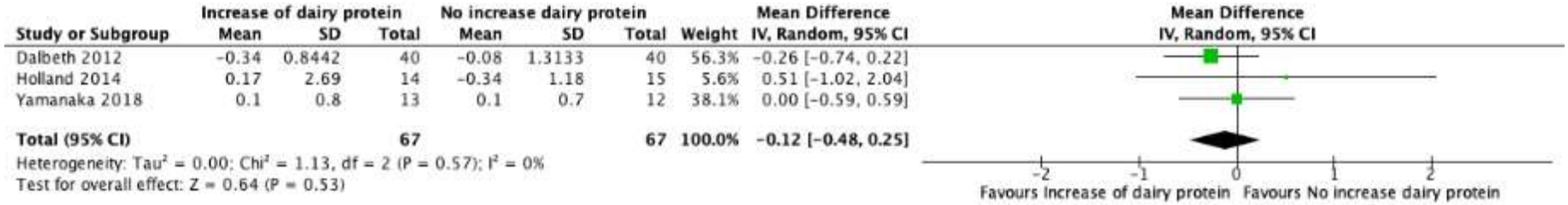
Explanations

a. Studies at high and low risk of bias show similar results

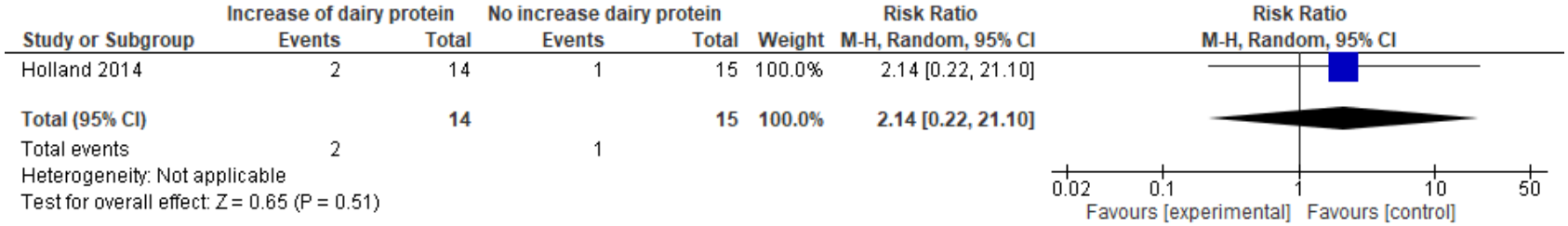
b. Wide CI crosses a no-effect line
c. Study at high risk of bias
d. Intervention was a mix of strategies, and effect of dairy alone may be impotantly different
Outcome importance
** Critical outcomes
* Important outcomes

Risk of bias assessment

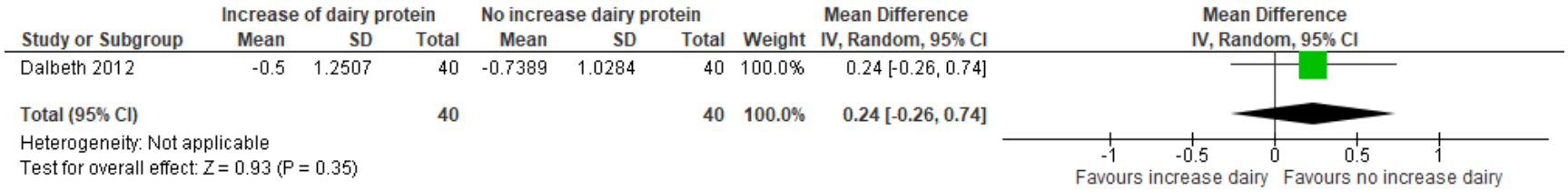




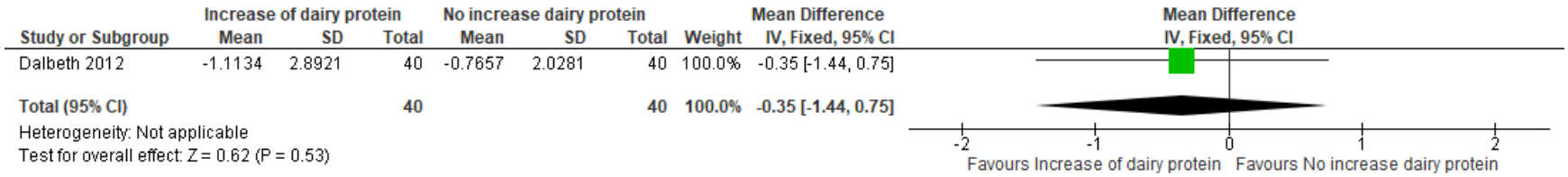
Forest plot of comparison: Increase of dairy protein vs no increase of dairy protein, outcome: 1.1 Serum urate level change.



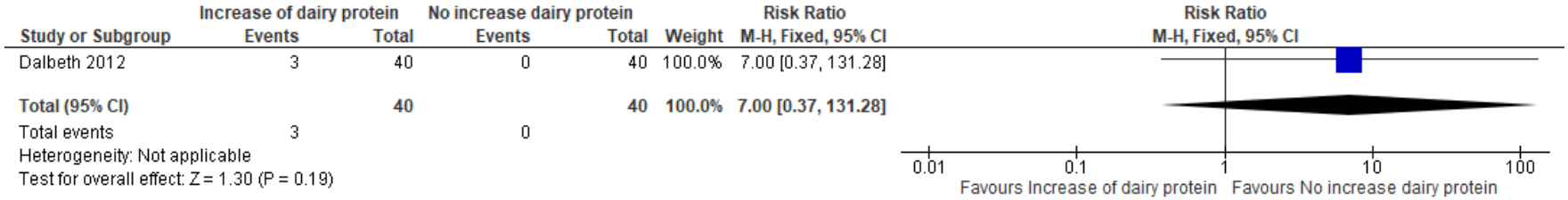
Forest plot of comparison: Increase of dairy protein vs no increase of dairy protein, outcome: 1.2 Flares.



Forest plot of comparison: Increase of dairy protein vs no increase of dairy protein, outcome: 1.3 Change in gout flare frequency.



Forest plot of comparison: Increase of dairy protein vs no increase of dairy protein, outcome: 1.4 Pain score change.



Forest plot of comparison: Increase of dairy protein vs no increase of dairy protein, outcome: 1.5 Serious adverse events.

45: Should the DASH diet versus any other diet be used in patients with gout?

We did not find any studies addressing this question. The core team advised to use evidence regarding patients with asymptomatic hyperuricemia to inform this recommendation question.

We found 3 articles addressing the question in patients with hyperuricemia.[69-71] The 3 articles were reports of subgroups of patients from a single randomized clinical trial in which researchers had assigned participants with hypertension to receive DASH diet or control diet. The control diet was described as a diet "typical of what many people in the United States eat";[72] the nutrient composition was[73]

- Potassium, magnesium and calcium at levels close to the 25th percentile of U.S. consumption
- Macronutrient profile and fiber according to average consumption

Within these reports, there was outcome data available for participants with hyperuricemia- which was the population of interest. Thus, we used the data from this subgroup of patients. The researchers categorized the information according to serum urate levels, which is what is presented in this report.
This body of evidence shows:

- Overall, patients with asymptomatic hyperuricemia (>6 mg/dL) who are advised to follow the DASH diet may have a reduction in serum urate levels 1 mg/dL higher than those who are advised to follow a control diet
- Patients with asymptomatic hyperuricemia and serum urate levels >7 mg/dL who are advised to follow the DASH diet may have a reduction in serum urate levels 1.3 mg/dL higher than those who are advised to follow a control diet
- Patients with asymptomatic hyperuricemia and serum urate levels between 6 and 8 mg/dL who are advised to follow the DASH diet may have a higher reduction in serum urate levels than those who are advised to follow a control diet
- Patients with asymptomatic hyperuricemia and serum urate levels > 8 mg/dL who are advised to follow the DASH diet may have a higher reduction in serum urate levels than those who are advised to follow a control diet

The overall quality of the evidence is LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With any other diet	With DASH diet	Relative effect (95% CI)	Risk with any other diet	Risk difference with DASH diet
Serum Urate* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA > 6mg/dL)											
24 (1 RCT)	not serious [a]	not serious	not serious	very serious [b]	none	⨁⨁◯◯ LOW	12	12	-	The mean serum Urate was 6.6 mg/dL	MD **1 mg/dL lower** (1.88 lower to 0.12 lower)
Serum Urate* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA > 7 mg/dL)											
8 (1 RCT) [c]	not serious	not serious	not serious	very serious [d]	none	⨁⨁◯◯ LOW	[c]	8 [c]	-	The mean serum Urate was **not reported**[c]	MD **1.29 mg/dL lower** (2.5 lower to 0.08 lower)
Serum Urate* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA >6 to 7 mg/dL)											
21 (1 RCT) [e]	not serious	not serious	not serious	very serious [f,g]	none	⨁⨁◯◯ LOW	[e]	21 [e]	-	The mean serum Urate was **not reported** [e]	MD **0.65 mg/dL higher** (0.43 lower to 1.73 higher)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Serum Urate* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA >7 to 8 mg/dL)											
17 (1 RCT) [h]	not serious	not serious	not serious	very serious [g,i]	none	⨁⨁◯◯ LOW	[h]	17 [h]	-	The mean serum Urate was **not reported** [h]	MD **0.28 mg/dL higher** (1.43 lower to 1.99 higher)
Serum Urate* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA > 8 mg/dL)											
18 (1 RCT) [j]	not serious	not serious	not serious	very serious [k]	none	⨁⨁◯◯ LOW	[j]	18 [j]	-	The mean serum Urate was **not reported** [j]	MD **1.02 mg/dL lower** (2.37 lower to 0.32 higher)
Serum urate* (follow up: mean 90 days; assessed with: patients with SUA <6mg/dL)											
12 (1 observational study)	serious [l]	not serious	not serious	serious [m]	none	⨁◯◯◯ VERY LOW	0/0	8/12 (66.7%)	-	-	-
Gout Flares - not reported**											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Health related quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient Acceptability* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Although there was no possibility of blinding, it is unlikely that this affected the outcome serum urate levels.
b. There were only 24 patients in total included in this analysis
c. There were a total of 8 patients. The researchers do not describe how many patients belonged to each group
d. There were only 8 patients in total included in this analysis
e. There were a total of 29 patients. The researchers do not describe how many patients belonged to each group
f. There were only 29 patients included in the analysis
g. The confidence interval shows the possibility of benefit or harm
h. There were a total of 17 patients. The researchers do not describe how many patients belonged to each group
i. There were only 17 patients included in the analysis
j. There were a total of 18 patients. The researchers do not describe how many patients belonged to each group
k. There were only 18 patients included in the analysis
l. The researchers do not provide results for a comparison group that was present
m. There are only 12 patients included in the analysis

Outcome importance:
** Critical outcomes
* Important outcomes

Figure 1: Risk of bias assessment

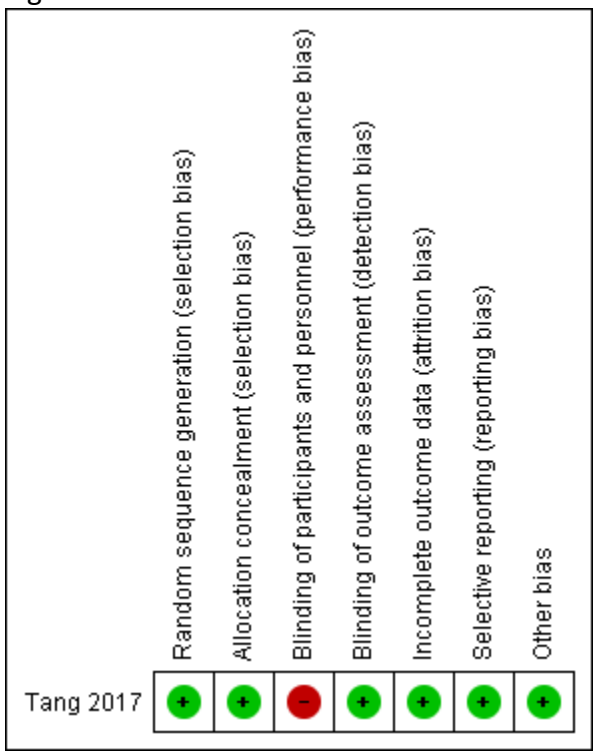
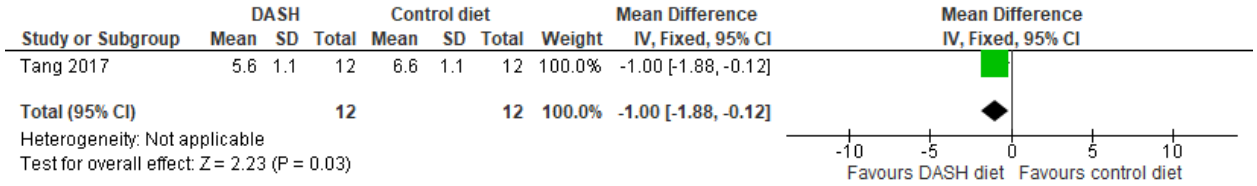


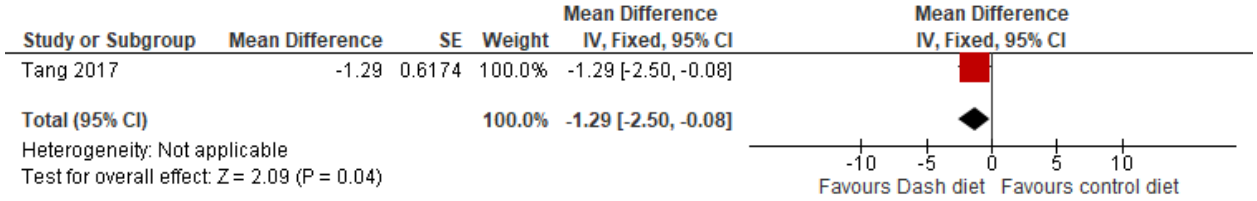
Figure 2: Forest plots

1. DASH diet vs no diet or any other diet, outcome:

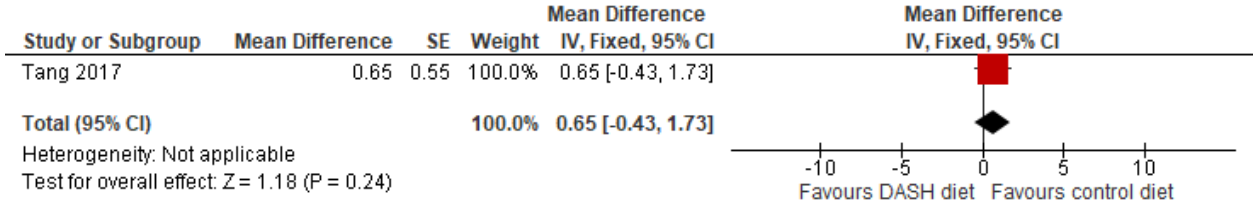
1.1 Serum Urate levels at 90 days in patients with >6 mg/dL.



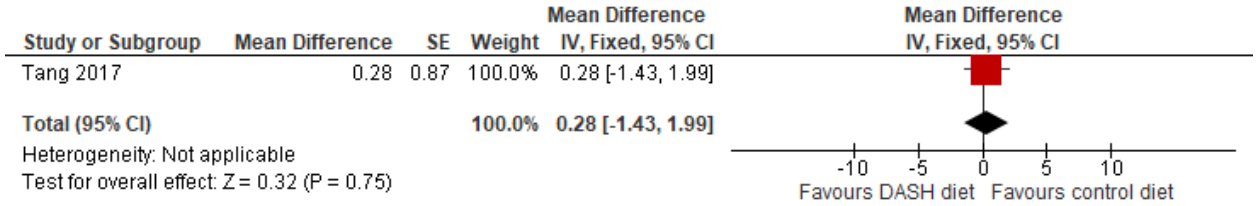
1.2 Serum urate levels at 90 days in patients with >7 mg/dL



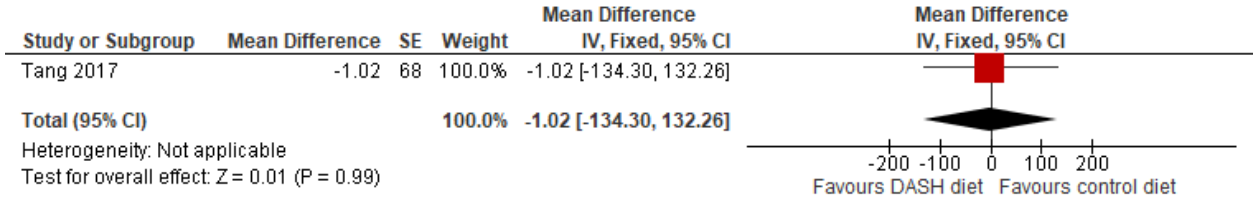
1.3 Serum urate levels at 90 days in patients with >6 to 7 mg/dL



1.4 Serum urate levels at 90 days in patients with >7 to 8 mg/dL



1.5 Serum urate levels at 90 days in patients with > 8 mg/dL



46: Should Weight loss vs. no weight loss be used in patients with gout?

We found 1 study addressing this question.[62] In this study, the researchers compared serum urate levels before and after a group of 11 patients lost weight. In addition, the core team determined that some of the studies included in a systematic review[74] may be useful to inform this question, even if the comparison presented in those studies was not specifically weight loss versus not, but instead BMI reduction,[75] bariatric surgery,[76, 77] or diet advice.[78] We included information (including outcome data about assessment of risk of bias) from those studies as it was reported by the authors of the systematic review.

The evidence shows:

- Patients who lose weight may have lower serum urate levels than patients who do not lose weight, after 2 months, but we are very uncertain about this evidence.
- There may be an increase in the number of patients who are at serum urate level <6 mg/dL after they undergo bariatric surgery or receive dietary advice up to 6 months, but we are very uncertain about this evidence.
- There may be no reduction in the risk of recurrent gout flares when the BMI decreases up to 12 months, but we are very uncertain about this evidence.
- There may be no differences or changes in the risk of gout flares with bariatric surgery up to 13 months, but we are very uncertain about this evidence.
- There may be a reduction in the median number of gout flares with dietary advice up to 4 months, but we are very uncertain about this evidence.

The overall quality of the evidence is VERY LOW

Note: The recommendation associated with this question can also be informed with the evidence from the recommendation question #55

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no weight loss	With Weight loss	Relative effect (95% CI)	Risk with no weight loss	Risk difference with Weight loss
Serum urate** (follow up: mean 2 months; assessed with: Mean level)											
22 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	11	11	-	The mean serum urate** was 7.8 mg/dL	MD 1.1 mg/dL lower (2.24 lower to 0.04 higher)
Serum urate** (follow up: 6 months; assessed with: Proportion of people with serum urate <6 mg/dL- Comparison: Before and after bariatric surgery)											
12 (1 observational study)	serious [b]	not serious	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	The absolute number of patients with raised SUA decreased 60%.				
Serum urate** (follow up: 4 months; assessed with: Proportion of people with serum urate <6 mg/dL- Comparison: before and after dietary advice)											
13 (1 observational study)	very serious [d]	not serious	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	The absolute number of patients with raised SUA decreased 50%				

Table 1: Evidence profile

Certainty assessment							Summary of findings
Gout flares** (timing of exposure: 12 months; assessed with: Risk of recurrent gout flares- Comparison: BMI reduction versus not)							
(1 observational study)	very serious [d]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	One study reported that there was no statistical association between people who reduced their BMI and those who did not. The OR (95% CI) was 0.94 (0.43 to 2.06) for people whose BMI decreased 3.6 to 5%, and 0.61 (0.32 to 1.16) for those whose BMI decreased more than 5% (reference: no change in BMI)
Gout flares** (follow up: range 6 months to 13 months; assessed with: Risk of gout flares. Comparison: Bariatric surgery versus not)							
167 (2 observational studies)	serious [b]	serious [e]	not serious	not serious	none	⨁◯◯◯ VERY LOW	One study reported that the risk of gout flares was lower (RR, 0.72; CI not reported) for patients who received bariatric surgery than for those who did not. Another study reported that 0 patients 1+ flares in 6 months before the surgery, whereas 3 patients had 1+ flares in 12 months after the surgery
Gout flares** (follow up: 4 months; assessed with: Median number of flares in 4 months- Comparison: Before and after dietary advice)							
13 (1 observational study)	very serious [d]	not serious	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	In one study, the median number of gout flares decreased from 2.1 to 0.6.
Pain* - not reported							
-	-	-	-	-	-	-	-
Tophus* - not reported							
-	-	-	-	-	-	-	-

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health related Quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

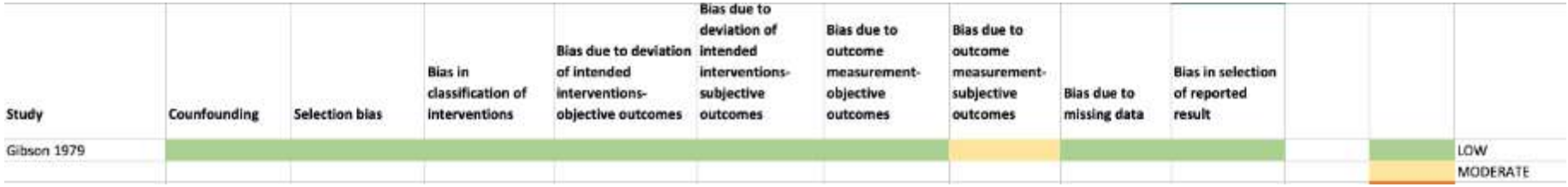
CI: Confidence interval; **MD:** Mean difference

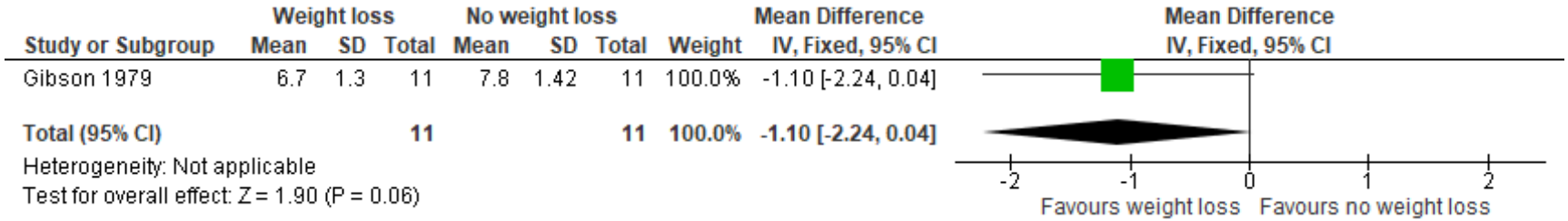
Explanations

a. small sample, CI crosses no effect line
b. Authors of the systematic review judged the study at serious risk of bias
c. Very small number of patients
d. Authors of the systematic review judged the study at very serious risk of bias
e. One study suggests benefits and the other is not so clear. Given the uncertainty, we decided to rate down one level for imprecision and inconsistency

Outcome importance:
** Critical outcomes
*Important outcomes

Risk of bias assessment





Forest plot of comparison: Weight loss vs no weight loss, outcome: 1.1 Serum urate level change.

47: Should changing or adding medications vs. no change in medication be used in patients with gout?

We found one study potentially addressing this question.[79] The researchers assessed the pharmacokinetic effects of febuxostat alone or in combination with verinurad. The core team determined that this study was not relevant to answer this question.

48: Should Vitamin C supplementation vs. no supplementation be used in patients with gout?

We found 2 studies addressing this question.[66, 80] Both studies were randomized clinical trials. In one trial,[66] researchers assessed the effects of dietary advice regarding several nutrients, including vitamin C. In the other trial, researchers compared the effects of adding vitamin C supplementation versus increasing the dose of allopurinol.[80]

The evidence shows:

- Patients with gout who receive vitamin C supplementation
    - May not have a different change in serum urate levels than patients who do not receive vitamin C supplementation, up to 6 months.
    - May have a lower change in serum urate levels than patients who receive allopurinol, up to 2 months
    - May not have a different risk of gout flares than patients who do not receive vitamin C supplementation, up to 6 months.

The overall quality of the evidence is LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no supplementation	With Vitamin C supplementation	Relative effect (95% CI)	Risk with no supplementation	Risk difference with Vitamin C supplementation
Serum urate (follow up: 6 months; assessed with: Mean change from baseline)**											
29 (1 RCT)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	15	14	-	The mean serum urate change** was **-0.34** mg/dL	MD **0.51 mg/dL higher reduction** (1.02 lower to 2.04 higher)
Serum urate (follow up: 2 months; assessed with: Mean change from baseline, mg/dL. Comparison: Vit C vs allopurinol)**											
40 (1 RCT)	serious [a]	not serious	serious [d]	not serious	none	⨁⨁◯◯ LOW	One study showed that the reduction on SUA levels was 0.24 mg/dL in patients who received Vit C and 1.98 mg/dL in those who received allopurinol. Measure of effect was not reported, but differences were statistically significant.				
Gout flares (follow up: mean 6 months; assessed with: patients with gout flares)**											
29 (1 RCT)	serious [a]	not serious	serious [b]	very serious [c]	none	⨁⨁◯◯ LOW	1/15 (6.7%)	2/14 (14.3%)	**RR 2.14** (0.22 to 21.10)	67 per 1,000	**76 more per 1,000** (from 52 fewer to 1,000 more)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health related quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

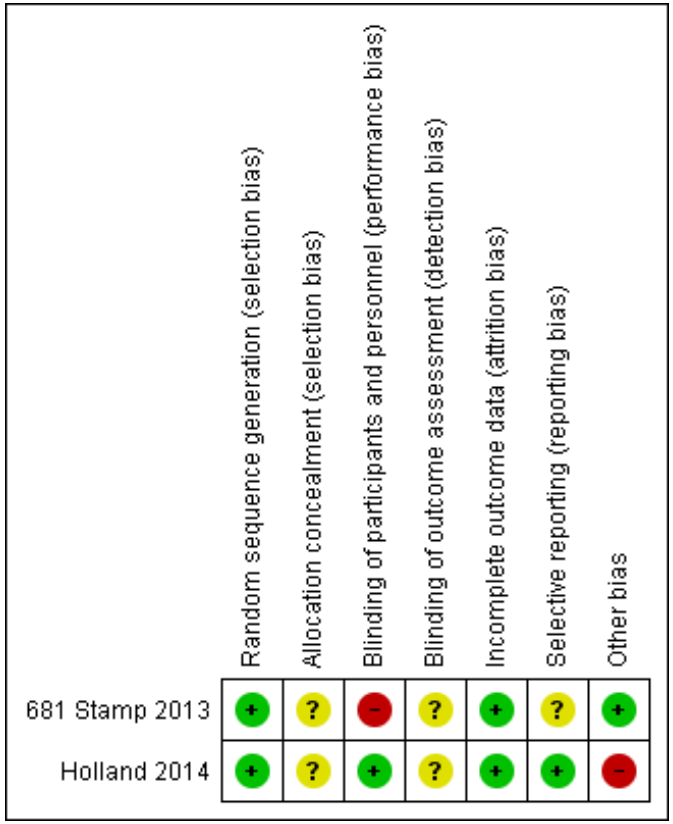
CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

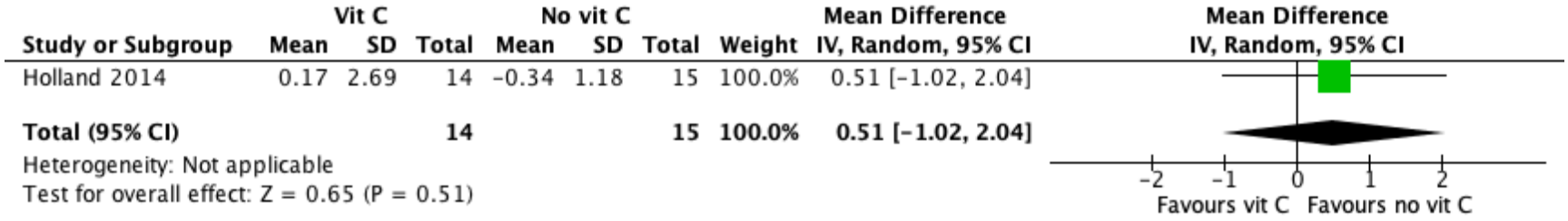
Explanations

a. None of the trials were at low risk of bias
b. Intervention was a mix of strategies, and effect of vitamin C alone may an effect importantly different
c. Small sample size, wide CI crosses no-effect line
d. Compares vit C versus allopurinol. Relative effect of Vit C vs placebo is likely to differ
Outcome importance
**Critical outcomes

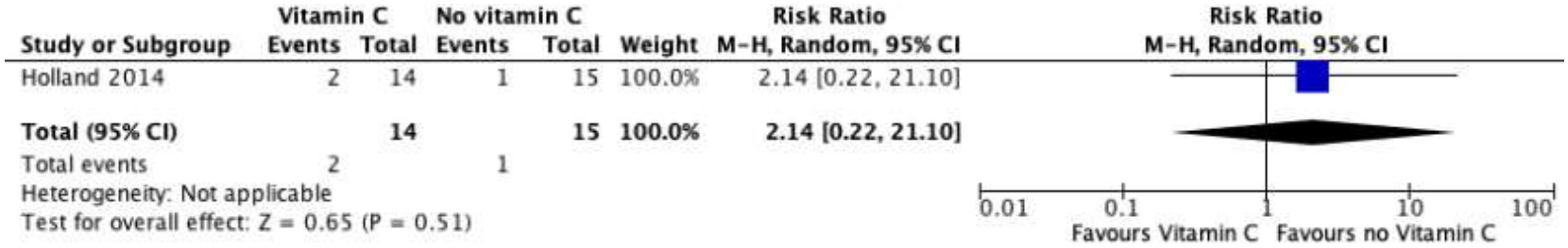
* Important outcomes

Risk of bias assessment





Forest plot of comparison: Vitamin C vs no supplementation, outcome: 1.1 Serum urate change.



Forest plot of comparison: 1 Vitamin C vs no supplementation, outcome: 1.2 Gout flares

49: Should Cherry extract intake vs. no cherry extract intake be used in patients with gout?

We found 2 studies addressing this question.[65, 66] The first study was a randomized clinical trial in which the researchers assessed the effects of dietary advice regarding several nutrients, including cherry intake.[66] The second study was an observational study in which researchers assessed gout flares after cherry consumption.[65]

The evidence shows:

- Patients with gout who receive cherry extract
    - May not have different serum urate level changes than patients who do not receive cherry extract, up to 6 months.
    - May not have a different risk of gout flares than patients who do not receive cherry extract, up to 6 months.
    - May have a lower risk of gout flares than patients who do not receive cherry extract, up to 2 days.

The overall quality of the evidence is LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no cherry extract intake	With Cherry extract intake	Relative effect (95% CI)	Risk with no cherry extract intake	Risk difference with Cherry extract intake
Serum urate (follow up: mean 6 months; assessed with: Mean change)**											
29 (1 RCT)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	15	14	-	The mean serum urate** was **-0.34** mg/dL	MD in change **0.51 mg/dL higher** (1.02 to 2.04 higher)
Gout flares (follow up: mean 6 months; assessed with: Patients with flares)**											
29 (1 RCT)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	1/15 (6.7%)	2/14 (14.3%)	**RR 2.14** (0.22 to 21.10)	67 per 1,000	**76 more per 1,000** (52 fewer to 1,340 more)
Gout flares (follow up: mean 2 days; assessed with: Patients with flares)**											
633 (1 observational study)	not serious	not serious	not serious	serious	none	⨁⨁◯◯ LOW	-/633	-/633	**OR 0.55** (0.30 to 1.01)	Not reported	**Not estimable**

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Pain* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient global assessment* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health related quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Activity limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **OR:** Odds ratio

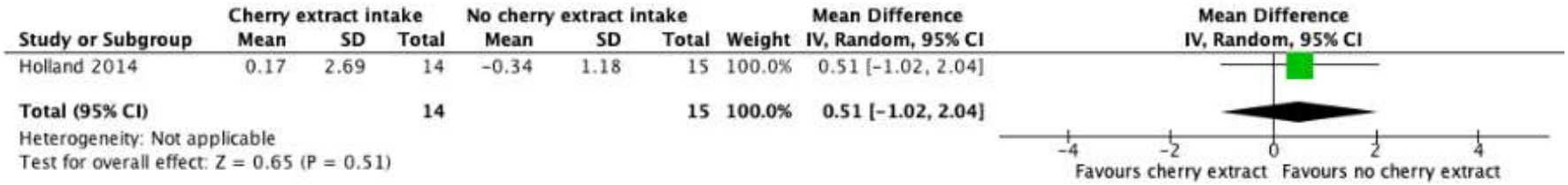
Explanations

a. The trial is at high risk of bias
b. Intervention was a mix of strategies, and effect of carries alone may be importantly different
c. Small sample size
Outcome importance:
** Critical outcomes
* Important outcomes

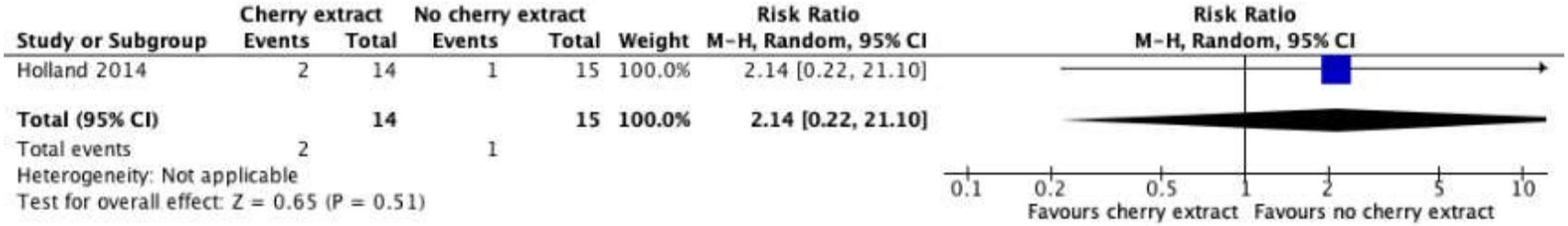
Risk of bias assessment- RCT

Risk of bias assessment- Observational study

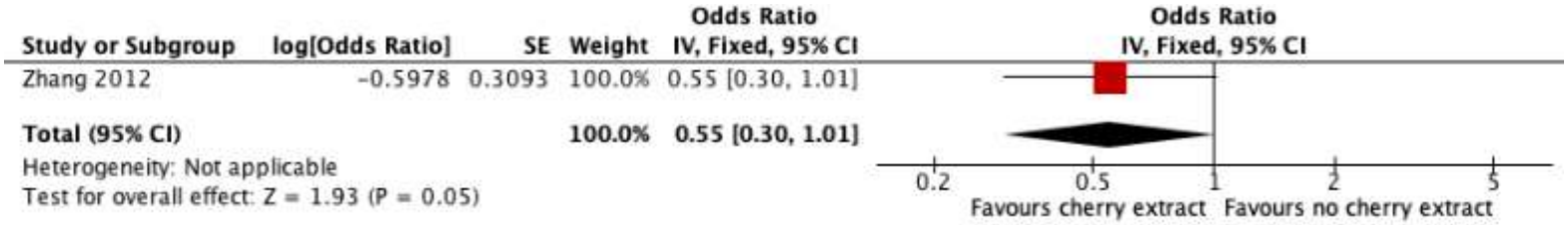
Study	Counfounding	Selection bias	Bias in classification of interventions	Bias due to deviation of intended interventions- objective outcomes	Bias due to deviation of intended interventions- subjective outcomes	Bias due to outcome measurement- objective outcomes	Bias due to outcome measurement- subjective outcomes	Bias due to missing data	Bias in selection of reported result			
Zhang 2012												LOW
												MODERATE



Forest plot of comparison: Cherry extract intake vs no cherry extract intake RCT, outcome: 1.1 Serum urate level change.



Forest plot of comparison: Cherry extract intake vs no cherry extract intake, outcome: 1.2 Gout flares.



Forest plot of comparison: Cherry extract intake vs no cherry extract intake RCT, outcome: 1.3 Risk of gout flares.

50: Should we use limiting or abstaining from alcohol intake or not limit intake of alcohol in patients with asymptomatic hyperuricemia?

The systematic review did not find any studies addressing this question

51: Should we use limiting purine intake or not in patient with asymptomatic hyperuricemia?

The systematic review did not find any studies addressing this question

52: Should we use limiting or abstaining from high-fructose corn syrup or no limited intake of high-fructose corn syrup in patients with asymptomatic hyperuricemia?

The systematic review did not find any studies addressing this question

53: Should we use increasing dairy protein intake or no increase in dairy intake in patients with asymptomatic hyperuricemia?

The systematic review did not find any studies addressing this question

54: Should the DASH diet versus any other diet be used in patients with hyperuricemia?

We found 3 articles addressing these questions.[69-71] The 3 articles were reports of subgroups of patients from a single randomized clinical trial in which researchers had assigned participants with hypertension to receive DASH diet or control diet. The control diet was described as a diet "typical of what many people in the United States eat";[72] the nutrient composition was[73]

- Potassium, magnesium and calcium at levels close to the 25th percentile of U.S. consumption
- Macronutrient profile and fiber according to average consumption

Within these reports, there was outcome data available for participants with hyperuricemia- which was the population of interest. Thus, we used the data from this subgroup of patients. The researchers categorized the information according to serum urate levels, which is what is presented in this report.

This body of evidence shows:

- Overall, patients with asymptomatic hyperuricemia (>6 mg/dL) who are advised to follow the DASH diet may have a reduction in serum urate levels 1 mg/dL higher than those who are advised to follow a control diet
- Patients with asymptomatic hyperuricemia and serum urate levels >7 mg/dL who are advised to follow the DASH diet may have a reduction in serum urate levels 1.3 mg/dL higher than those who are advised to follow a control diet
- Patients with asymptomatic hyperuricemia and serum urate levels between 6 and 8 mg/dL who are advised to follow the DASH diet may have a higher reduction in serum urate levels than those who are advised to follow a control diet
- Patients with asymptomatic hyperuricemia and serum urate levels > 8 mg/dL who are advised to follow the DASH diet may have a higher reduction in serum urate levels than those who are advised to follow a control diet

The overall quality of the evidence is LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With any other diet	With DASH diet	Relative effect (95% CI)	Risk with any other diet	Risk difference with DASH diet
Serum Urate* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA > 6mg/dL)											
24 (1 RCT)	not serious [a]	not serious	not serious	very serious [b]	none	⨁⨁◯◯ LOW	12	12	-	The mean serum Urate was 6.6 mg/dL	MD **1 mg/dL lower** (1.88 lower to 0.12 lower)
Serum Urate* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA > 7 mg/dL)											
8 (1 RCT) [c]	not serious	not serious	not serious	very serious [d]	none	⨁⨁◯◯ LOW	[c]	8 [c]	-	The mean serum Urate was **not reported**[c]	MD **1.29 mg/dL lower** (2.5 lower to 0.08 lower)
Serum Urate* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA >6 to 7 mg/dL)											
21 (1 RCT) [e]	not serious	not serious	not serious	very serious [f,g]	none	⨁⨁◯◯ LOW	[e]	21 [e]	-	The mean serum Urate was **not reported** [e]	MD **0.65 mg/dL higher** (0.43 lower to 1.73 higher)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Serum Urate* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA >7 to 8 mg/dL)											
17 (1 RCT) [h]	not serious	not serious	not serious	very serious [g,i]	none	⨁⨁◯◯ LOW	[h]	17 [h]	-	The mean serum Urate was **not reported** [h]	MD **0.28 mg/dL higher** (1.43 lower to 1.99 higher)
Serum Urate* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA > 8 mg/dL)											
18 (1 RCT) [j]	not serious	not serious	not serious	very serious [k]	none	⨁⨁◯◯ LOW	[j]	18 [j]	-	The mean serum Urate was **not reported** [j]	MD **1.02 mg/dL lower** (2.37 lower to 0.32 higher)
Serum urate* (follow up: mean 90 days; assessed with: patients with SUA <6mg/dL)											
12 (1 observational study)	serious [l]	not serious	not serious	serious [m]	none	⨁◯◯◯ VERY LOW	0/0	8/12 (66.7%)	-	-	-
Gout Flares - not reported**											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Health related quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Patient Acceptability* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Although there was no possibility of blinding, it is unlikely that this affected the outcome serum urate levels.
b. There were only 24 patients in total included in this analysis
c. There were a total of 8 patients. The researchers do not describe how many patients belonged to each group
d. There were only 8 patients in total included in this analysis
e. There were a total of 29 patients. The researchers do not describe how many patients belonged to each group
f. There were only 29 patients included in the analysis
g. The confidence interval shows the possibility of benefit or harm
h. There were a total of 17 patients. The researchers do not describe how many patients belonged to each group
i. There were only 17 patients included in the analysis
j. There were a total of 18 patients. The researchers do not describe how many patients belonged to each group
k. There were only 18 patients included in the analysis
l. The researchers do not provide results for a comparison group that was present
m. There are only 12 patients included in the analysis

Outcome importance:
** Critical outcomes
* Important outcomes

Figure 1: Risk of bias assessment

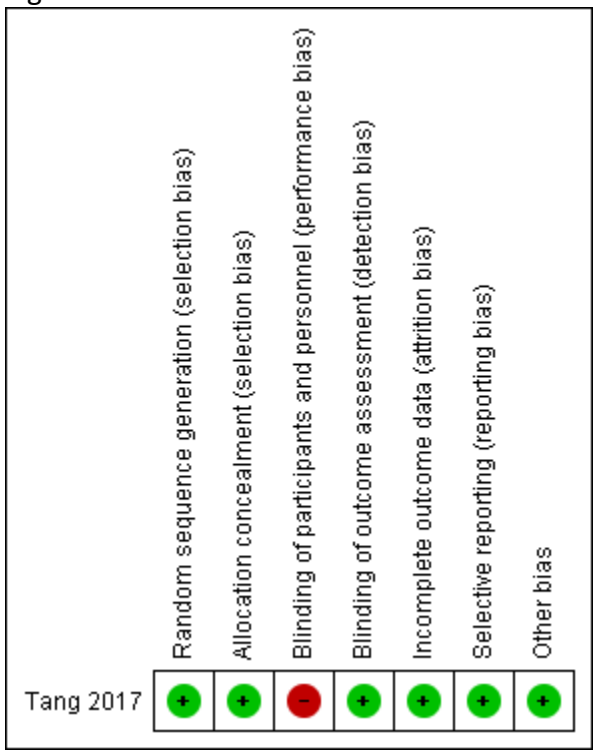
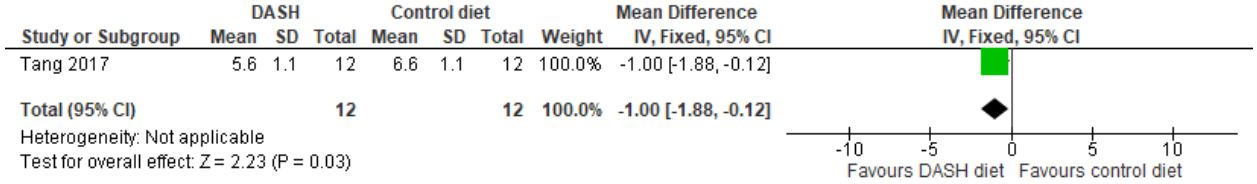


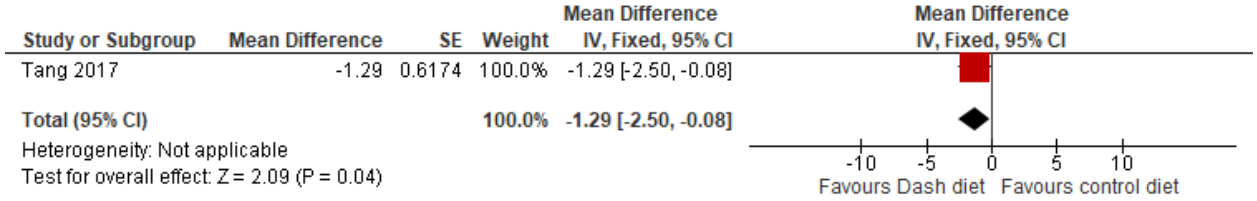
Figure 2: Forest plots

1. DASH diet vs no diet or any other diet, outcome:

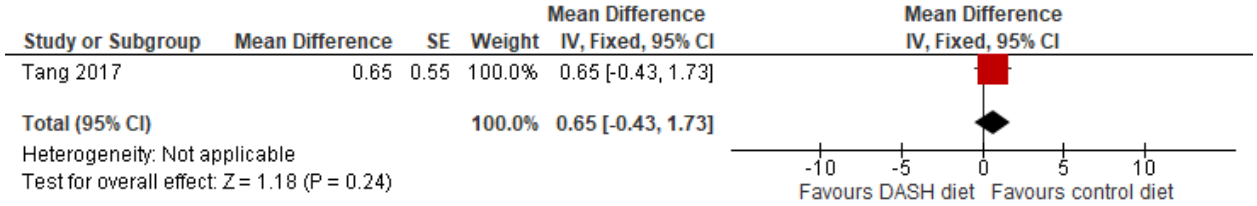
1.1 Serum Urate levels at 90 days in patients with >6 mg/dL.



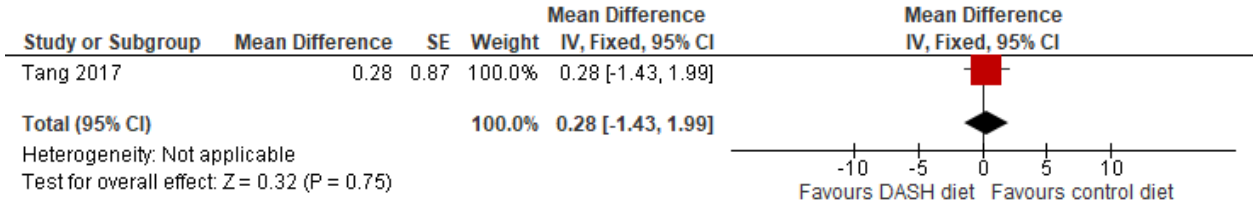
1.2 Serum urate levels at 90 days in patients with >7 mg/dL



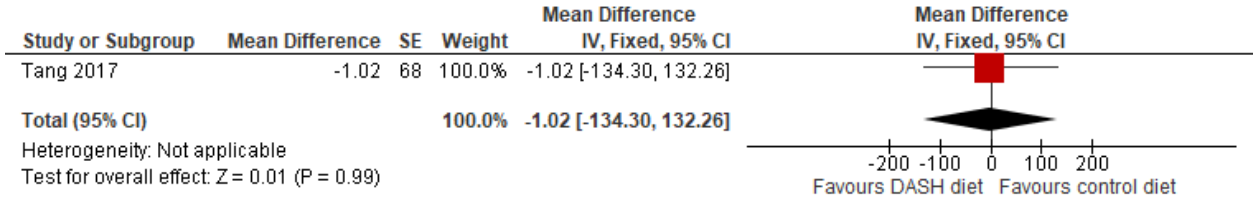
1.3 Serum urate levels at 90 days in patients with >6 to 7 mg/dL



1.4 Serum urate levels at 90 days in patients with >7 to 8 mg/dL



1.5 Serum urate levels at 90 days in patients with > 8 mg/dL



55. Should weight loss vs. no weight loss be used in patients with asymptomatic hyperuricemia?

We did not find any studies directly addressing this question. The core team suggested one article that could be included as indirect evidence.[74] The article was a systematic review in which authors assessed the effects of weight loss in overweight/ obese patients with gout. The authors included 10 studies (1 randomized clinical trial, and 9 observational studies). We used the data from meta-analyses and descriptive tables as reported by the authors of the systematic review.

The evidence shows that:

- Overall, we are very uncertain of the effects of weight loss in patients with asymptomatic hyperuricemia
- Patients with gout who lose weight may experience a reduction in the number of gout flares, but we are very uncertain about this effect
- There is inconsistency between comparative studies and single-arm studies regarding the effects of weight loss in serum urate levels. The former suggest that the proportion of people with serum urate levels <6 mg/dL decreases, and the later suggest that it increases. However, both bodies of evidence have very low quality.
- There is also inconsistency among the studies that assessed the relationship between weight loss and serum urate levels. Even though most suggest a decrease, a few suggest an increase.

The overall quality of the evidence is VERY LOW

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no weight loss	With weight loss	Relative effect (95% CI)	Risk with no weight loss	Risk difference with weight loss
Gout flares (follow up: range 13 months to 33 months; assessed with: Patients with 1+ flares- Comparative studies)**											
(2 observational studies) [a]	serious [b]	not serious	serious [c]	serious [d]	none	⨁◯◯◯ VERY LOW					Two studies reported a relative risk decrease in the risk of having 1 or more gout flares (RR 0.72 and 0.35). The reduction in weight in these studies was 31 kg and 3 kg, respectively.
Gout flares (follow up: range 4 months to 18 months; assessed with: Gout flares occurrence- Single arm studies)**											
(5 observational studies) [a]	serious [b]	not serious	serious [c]	serious [d]	none	⨁◯◯◯ VERY LOW					Studies that compare the number of flares between baseline and follow up show a reduction in the range of flares per patient (1-6 to 0-2) and the number of flares (71% fewer). Another study showed a dose-response relationship between BMI change and recurrent gout attacks. One study provides the number of flares between baseline and follow up without a comparison. One study shows that the proportion of people with 1+ flare increased at 18 months.
Serum Urate* (follow up: 32 months; assessed with: Proportion of people with SUA<6 mg/dL- Comparative study)											
191 (1 observational study)	not serious	not serious	serious [c]	serious [e]	none	⨁◯◯◯ VERY LOW	146/162 (90.1%)	27/29 (93.1%)	**OR 0.68** (0.15 to 3.11)	901 per 1,000	**40 fewer per 1,000** (323 fewer to 65 more)

Serum urate* (follow up: range 4 months to 18 months; assessed with: Proportion of people with SUA<6 mg/dL- Single arm studies)

(3 observational studies) [a]	very serious [f]	not serious	serious [c]	not serious	none	⨁◯◯◯ VERY LOW	Three studies showed that when participants lost weight, the proportion of them with SUA<6 mg/dL has an absolute increase that ranges from 46% through 54%. These participants lost an average of 3 through 34 kg.

Serum urate* (assessed with: Changes in serum urate levels (mg/dL)- longest follow up)

(8 observational studies) [a]	serious [b]	serious [g]	serious [c]	not serious	none	⨁◯◯◯ VERY LOW	The change in serum urate levels ranged from an average decrease of 2.8 mg/dL to an average increase of 0.5 mg/dL.

Serious adverse events* (follow up: 18 months; assessed with: Case series)

12 (1 observational study)	serious [b]	not serious	not serious	serious [h]	none	⨁◯◯◯ VERY LOW		0/12 (0.0%)	-	-	-

Tophus* - not reported

-	-	-	-	-	-	-	-	-	-	-	-

Health related quality of life* - not reported

-	-	-	-	-	-	-	-	-	-	-	-

Patient acceptability* - not reported

-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **OR:** Odds ratio

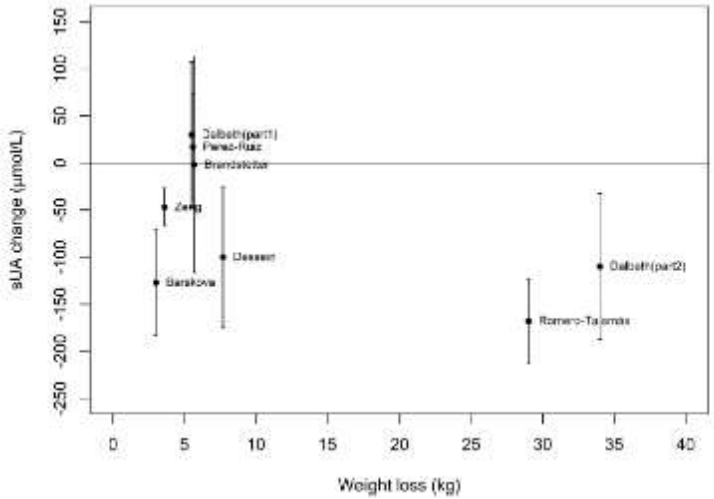
Explanations

a. Specific number of patients contributing this information is not reported
b. Studies judged at serious risk of bias by the systematic review authors
c. This study was done in patients with gout, not in patients with asymptomatic hyperuricemia. Relative effect of weight loss vs not is likely to differ
d. CIs are not provided but Optimal information size was not met
e. Confidence interval suggests the possibility of important benefit or important harm. Optimal information size not met.
f. The information to address this PICO comes from many single-arms studies (3/4) as opposed to comparative studies. The studies themselves were judged at serious risk of bias by the systematic review authors. Patients were compliant to ULT and thus most of them were at target at baseline
g. Some studies suggest that serum urate decreases with weight loss whereas others suggest it increases

h. Very small sample size- 12 patients

Outcome importance:
** Critical outcomes
* Important outcomes

Appendix 1: Figure- Relationship between average weight loss and SUA change in the studies that reported this outcome. Each study is presented with its corresponding 95% confidence interval. The figure belongs to the systematic review published by Nielsen et al.



56: Should adding or changing urate lowering therapy vs. no change in medications be used in patients with hyperuricemia?

We found one study potentially addressing this question.[79] This was a randomized trial assessing the pharmacokinetics of febuxostat in combination with verinurad or febuxostat alone, but the core team determined that this study was not relevant. In addition, the core team suggested to include evidence from a randomized clinical trial[81] in which researchers compared fenofibrate versus placebo in patients with diabetes (29% had hyperuricemia).

The evidence shows:

- Patients with asymptomatic hyperuricemia who add or change medications
    - Probably have a lower risk of gout flares than patients who do not change their medications, up to 5 years

The overall quality of the evidence is MODERATE

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no change in medications	With adding or changing urate lowering therapy	Relative effect (95% CI)	Risk with no change in medications	Risk difference with adding or changing urate lowering therapy
Gout flares (follow up: 5 years; assessed with: participants with at least 1 flare)**											
9795 (1 RCT)	not serious [a]	not serious	serious	not serious	none	⨁⨁⨁◯ MODERATE	151/4900 (3.1%)	81/4895 (1.7%)	**RR 0.54** (0.41 to 0.70)	31 per 1,000	**14 fewer per 1,000** (18 fewer to 9 fewer)
Serum urate- not reported**											
-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse events not reported**											
-	-	-	-	-	-	-	-	-	-	-	-
Tophus* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health related quality of life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

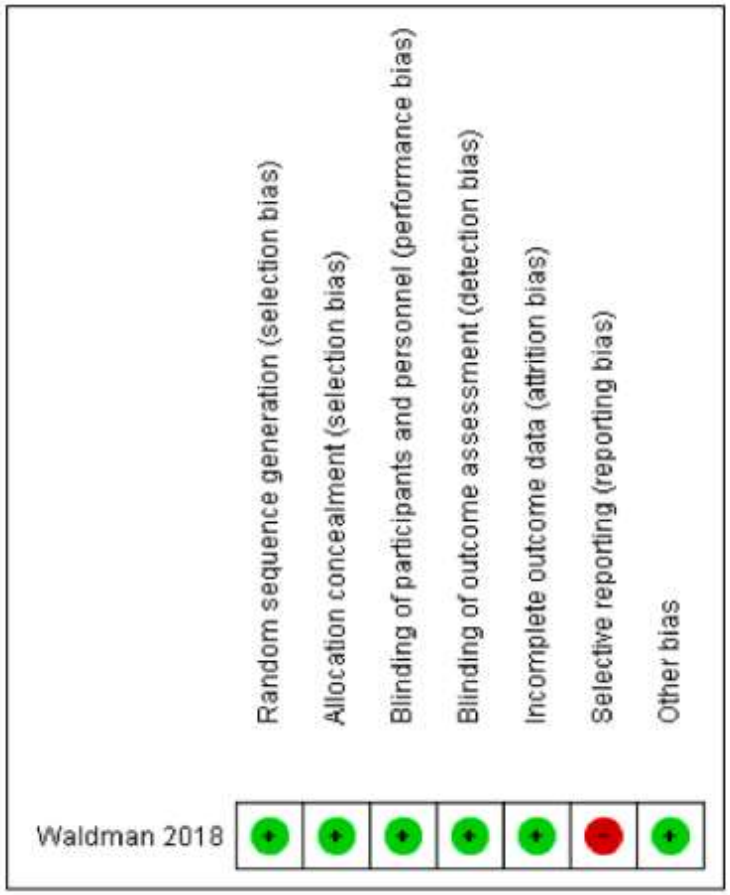
Table 1: Evidence profile

Certainty assessment							Summary of findings				
Patient acceptability* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

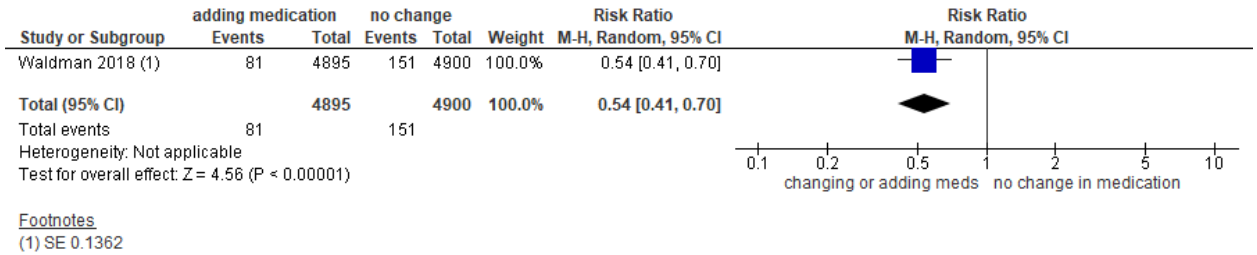
CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Risk of bias in this study did not affect this outcome
b. Study at high risk of bias
c. Very small sample size, rated down one level for imprecision and indirectness
d. Very small sample size and no events
Outcome importance:
** Critical outcomes
* Important outcomes



Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Forest plot of comparison: 1 Adding or changing urate lowering therapy vs no change in meds, outcome: 1.4 gout flares, participants with at least 1 flare, at 5 years (longest FU).

57: Should ULT vs. No ULT be used in patients with asymptomatic hyperuricemia?

We found 11 studies addressing this question.[20, 25-34, 82-92] Nine of the studies were randomized clinical trials[82, 83, 85, 86, 88-92] and two were observational studies.[84, 87] The studies compared either allopurinol [84-88, 90]or febuxostat[82, 83, 88, 89, 91, 92] to no treatment.

The evidence shows:

- Patients with asymptomatic hyperuricemia who receive ULT
    - Have a higher reduction in the SUA levels at 3 months, 6 months, and 3-5 years than patients who do not receive ULT.
    - Have a higher probability of achieving SUA levels <6mg/dL at 2 years, than patients who do not receive ULT.
    - Have a lower risk of gout flares up to 3 years than patients who do not receive ULT.
    - May not have a different risk of any adverse serious adverse events and cardiovascular serious adverse events, up to 2 years, than patients who do not receive ULT.
    - May not have a higher risk of all-cause mortality up to 6 months and 6 years than patients who do not receive ULT.
    - Probably do not have a different risk of hypersensitivity reactions than patients who do not receive ULT.
    - Probably do not have a change in renal function higher than those who do not receive ULT at 6 months, but do have a higher change at 3-5 years.

The overall quality of the evidence is HIGH

Table 1: Evidence profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With No ULT	With ULT	Relative effect (95% CI)	Risk with No ULT	Risk difference with ULT
Serum Urate level (follow up: 3 months; assessed with: change from baseline mg/dl)**											
216 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	89	127	-	The median Serum Urate level change** was **+1.01** mg/dL	MD **3.73 mg/dL higher reduction** (1.72 higher to 5.73 higher)
Serum Urate level (follow up: 6 months; assessed with: change from baseline mg/dl)**											
233 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	118	115	-	The mean Serum Urate level change** was **-0.1** mg/dL	MD **2.96 mg/dL higher reduction** (2.13 higher to 3.79 higher)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Serum Urate level (follow up: range 3 years to 5 years; assessed with: change from baseline mg/dl)**											
373 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	206	167	-	The mean Serum Urate level change** was +**0.05** mg/dL	MD **1.84 mg/dL higher reduction** (1.13 higher to 2.55 higher)
Serum Urate level (follow up: 108 weeks; assessed with: proportion of patients with SUA ≤6 mg/dl)**											
441 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	41/222 (18.5%)	212/219 (96.8%)	**RR 5.24** (3.97 to 6.92)	185 per 1,000	**783 more per 1,000** (549 more to 1,093 more)
Gout flares (follow up: 3 years; assessed with: proportion with gout flare)**											
617 (2 RCTs)	not serious	not serious	not serious	not serious [a]	none	⨁⨁⨁⨁ HIGH	15/310 (4.8%)	2/307 (0.7%)	**RR 0.16** (0.04 to 0.62)	48 per 1,000	**41 fewer per 1,000** (46 fewer to 18 fewer)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Serious adverse events- all* (follow up: range 24 weeks to 108 weeks; assessed with: proportion with SAEs)											
521 (2 RCTs)	not serious	serious [b]	not serious	serious [c]	none	⨁⨁◯◯ LOW	59/262 (22.5%)	63/259 (24.3%)	**RR 0.96** (0.50 to 1.85)	225 per 1,000	**9 fewer per 1,000** (113 fewer to 191 more)
Serious adverse events - Mortality* (follow up: 6 months; assessed with: proportion with all-cause mortality)											
93 (1 RCT)	not serious	serious [d]	not serious	serious [e]	none	⨁⨁◯◯ LOW	0/48 (0.0%)	0/45 (0.0%)	not estimable	0 per 1,000	**0 fewer per 1,000** (40 fewer to 40 more)
Serious adverse events - Mortality* (follow up: mean 6.3 years; assessed with: proportion of patients all-cause mortality)											
225 (1 observational study)	not serious	not serious	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	28/136 (20.6%)	19/89 (21.3%)	**RR 1.04** (0.62 to 1.74)	206 per 1,000	**8 more per 1,000** (78 fewer to 152 more)
Serious adverse events – Mortality* (assessed with: proportion with death/person-years)											
14254 (1 observational study) [f,g]	serious	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	1455/7127 (20.4%) [g]	723/7127 (10.1%) [f]	**HR 0.68** (0.62 to 0.74)	204 per 1,000 [g]	**60 fewer per 1,000** (72 fewer to 49 fewer)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Serious adverse events - Cardiovascular event* (follow up: range 6 months to 108 weeks; assessed with: proportion with CV event)											
534 (2 RCTs)	not serious	serious [h]	not serious	serious [c]	none	⨁⨁◯◯ LOW	7/270 (2.6%)	4/264 (1.5%)	**RR 0.58** (0.17 to 1.95)	26 per 1,000	**11 fewer per 1,000** (22 fewer to 25 more)
Serious adverse events – Cardiovascular event* (assessed with: proportion with CV event/person-years)											
14254 (1 observational study) [i,j]	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	1364/7127 (19.1%) [j]	792/7127 (11.1%) [i]	**HR 0.89** (0.81 to 0.97)	191 per 1,000 [j]	**19 fewer per 1,000** (33 fewer to 5 fewer)
Serious adverse events - Renal function* (follow up: 6 months; assessed with: change from baseline in mil/min)											
233 (3 RCTs)	not serious	not serious	not serious	serious	none	⨁⨁⨁◯ MODERATE	118	115	-	The mean serious adverse events - Renal function* was **-3.7** ml/m	MD **5.4 ml/m higher** (0.31 lower to 11.11 higher)

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Serious adverse events - Renal function* (follow up: range 3 years to 5 years; assessed with: change from baseline in ml/min)											
373 (2 RCTs)	not serious	serious [k]	not serious	not serious	none	⨁⨁⨁◯ MODERATE	206	167	-	The mean serious adverse events - Renal function* was **-7.95** ml/m	MD **6.54 ml/m higher** (1.74 higher to 11.34 higher)
Serious adverse events - Hypersensitivity* (follow up: 108 weeks; assessed with: proportion with hypersensitivity)											
531 (2 RCTs)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	11/252 (4.4%)	9/279 (3.2%)	**RR 0.73** (0.31 to 1.72)	44 per 1,000	**12 fewer per 1,000** (30 fewer to 31 more)
Tophus * - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health Related Quality of Life* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Evidence profile

Certainty assessment							Summary of findings				
Patient acceptability * - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanations

a. Low number of total events, but the experts were still confident about the presence of an effect
b. Discrepant point estimates between studies and high heterogeneity.
c. Confidence interval suggests the possibility of appreciable benefit and appreciable harm.
d. Unable to calculate point estimates due to absence of events.
e. Unable to calculate a pooled estimate due to lack of events.
f. The total person-years was 18272
g. The total person years was 30878
h. Unable to compare point estimates and CI due to low number of events.
i. The total person years was 18272
j. The total person years was 30878
k. Individual point estimates do not have overlapping CI, but pooled treatment effect is in the same direction
Outcome importance:
**Critical outcomes
* Important outcomes

Figure 1: Risk of bias of RCTs

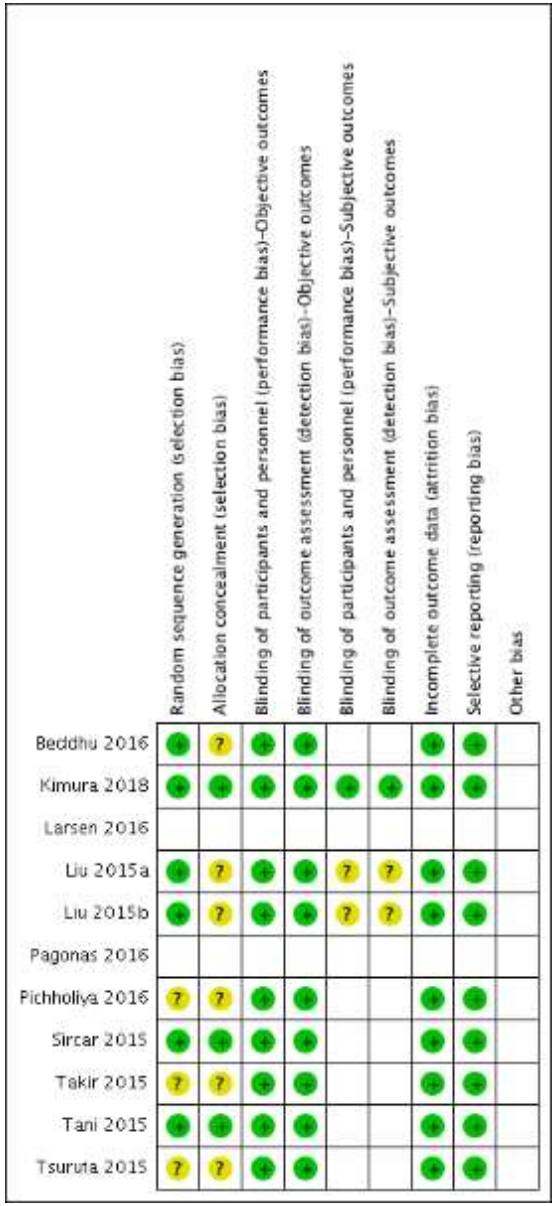
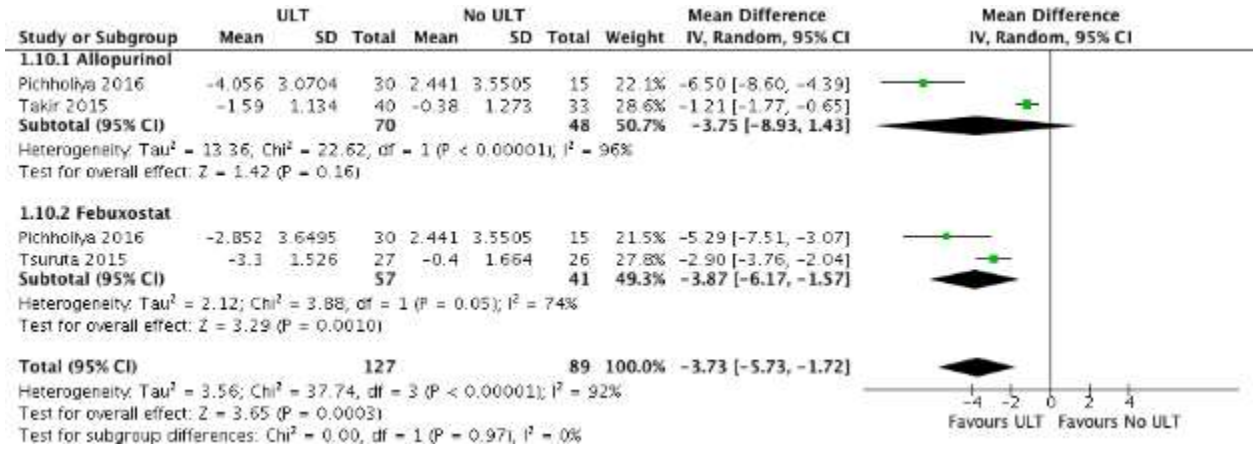


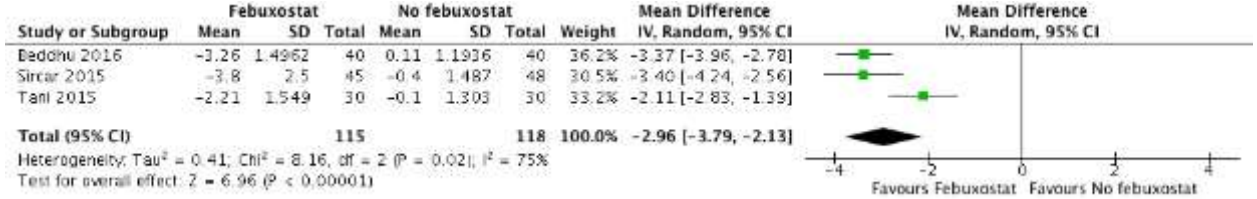
Figure 2: Risk of bias of observational studies

Study	Counfounding	Selection bias	Bias in classification of interventions	Bias due to deviation of intended interventions-objective outcomes	Bias due to deviation of intended interventions-subjective outcomes	Bias due to outcome measurement-objective outcomes	Bias due to outcome measurement-subjective outcomes	Bias due to missing data	Bias in selection of reported result
Pagonas 2016					N/A		N/A		
Larsen 2016					N/A		N/A		

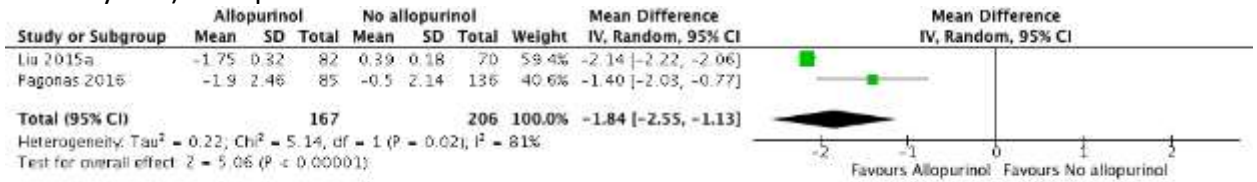
1. ULT vs no ULT for asymptomatic hyperuricemia, outcome: Serum Urate level - change from baseline mg/dl - shortest follow-up - Allopurinol & Febuxostat



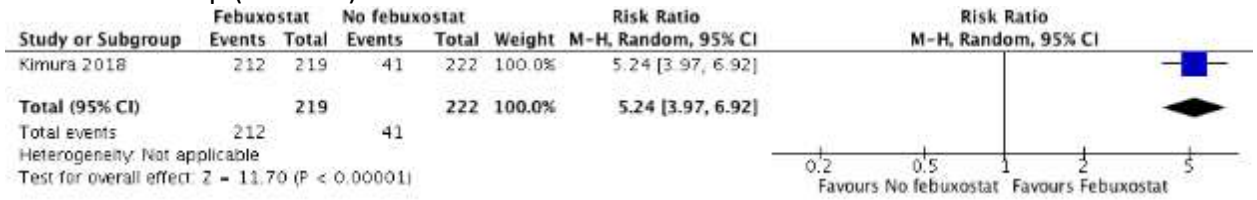
2. ULT vs no ULT for asymptomatic hyperuricemia, outcome: Serum Urate level - change from baseline mg/dl - longest follow-up (6 months) - Febuxostat.



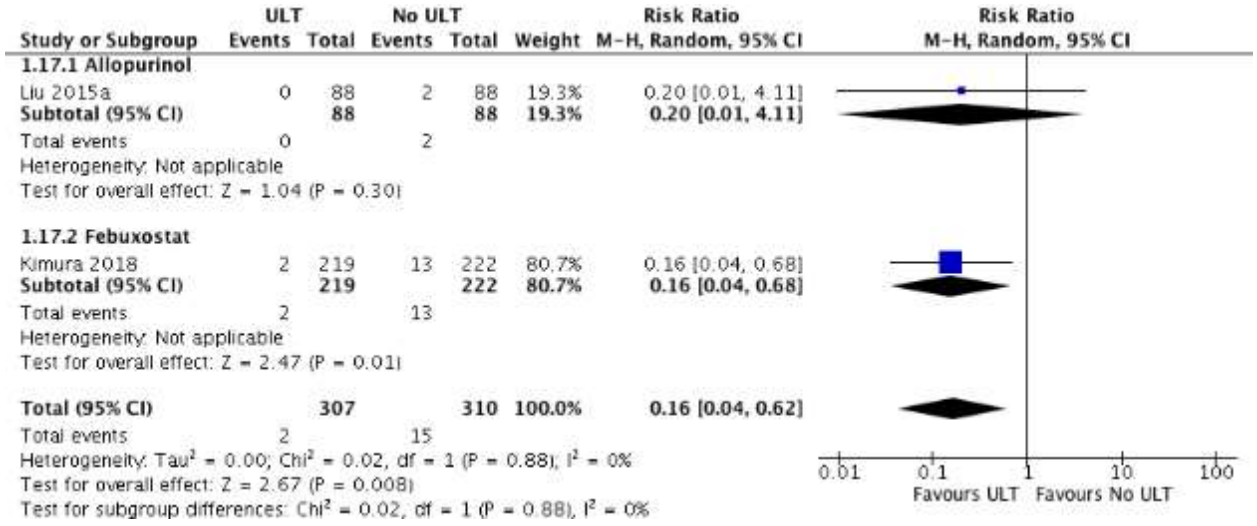
3. ULT vs no ULT for asymptomatic hyperuricemia, outcome: Serum Urate level - change from baseline mg/dl - longest follow-up (3-5 years) - Allopurinol.



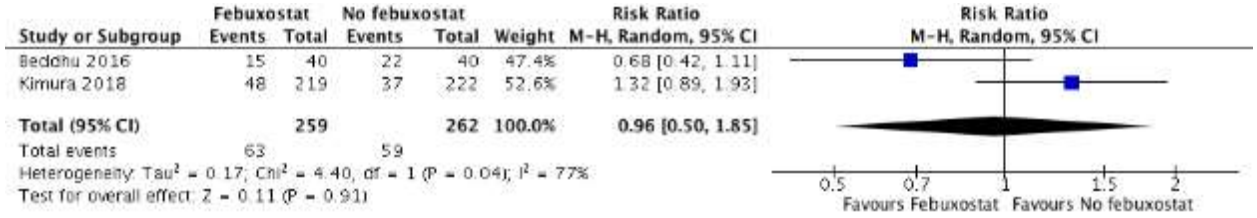
4. ULT vs no ULT for asymptomatic hyperuricemia, outcome: Serum Urate level - proportion of patients with SUA ≤6 mg/dl - longest follow-up (108 wks) - Febuxostat.



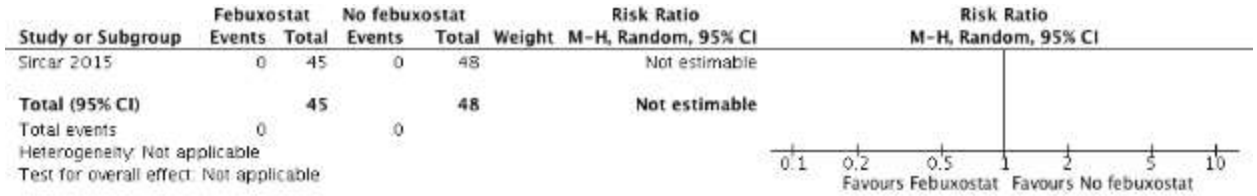
5. ULT vs no ULT for asymptomatic hyperuricemia, outcome: Gout flare - proportion with gout flare - longest follow-up - Allopurinol & Febuxostat



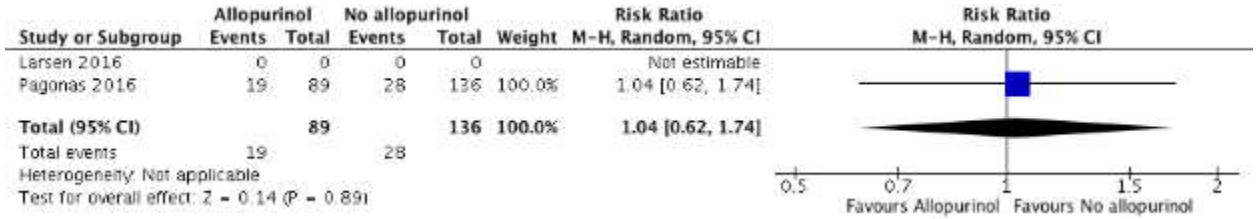
6. ULT vs no ULT for asymptomatic hyperuricemia, outcome: SAE - all SAEs - proportion with SAEs - longest follow-up (24-108 weeks) - Febuxostat.



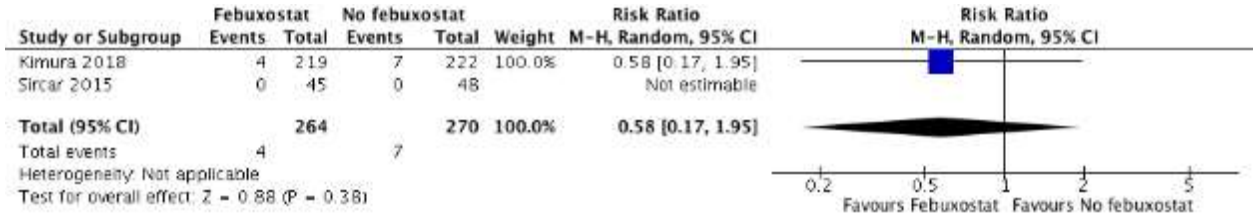
7. ULT vs no ULT for asymptomatic hyperuricemia, outcome: SAE - mortality – proportion with all-cause mortality – longest follow-up (6 months) - Febuxostat.



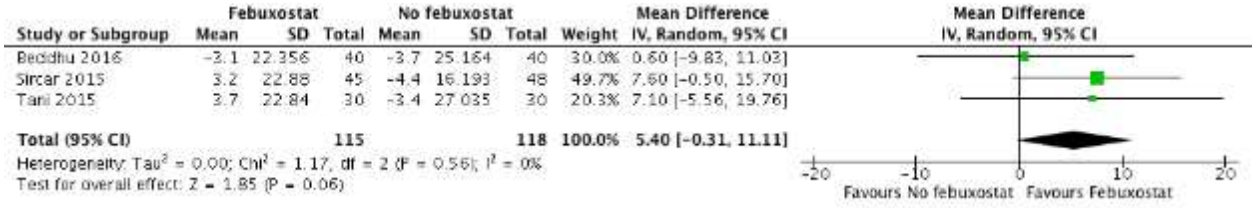
8. ULT vs no ULT for asymptomatic hyperuricemia, outcome: SAE - mortality - proportion of patients all-cause mortality - longest follow-up (6.3 years) - Allopurinol.



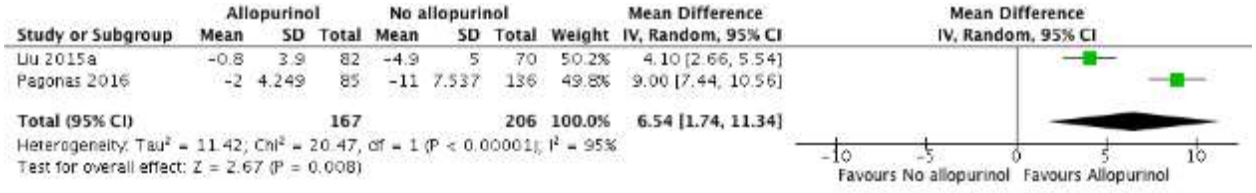
9. ULT vs no ULT for asymptomatic hyperuricemia, outcome: 1.15 SAE - CV event - proportion with CV event - longest follow-up (6 months - 108 weeks) - Febuxostat.



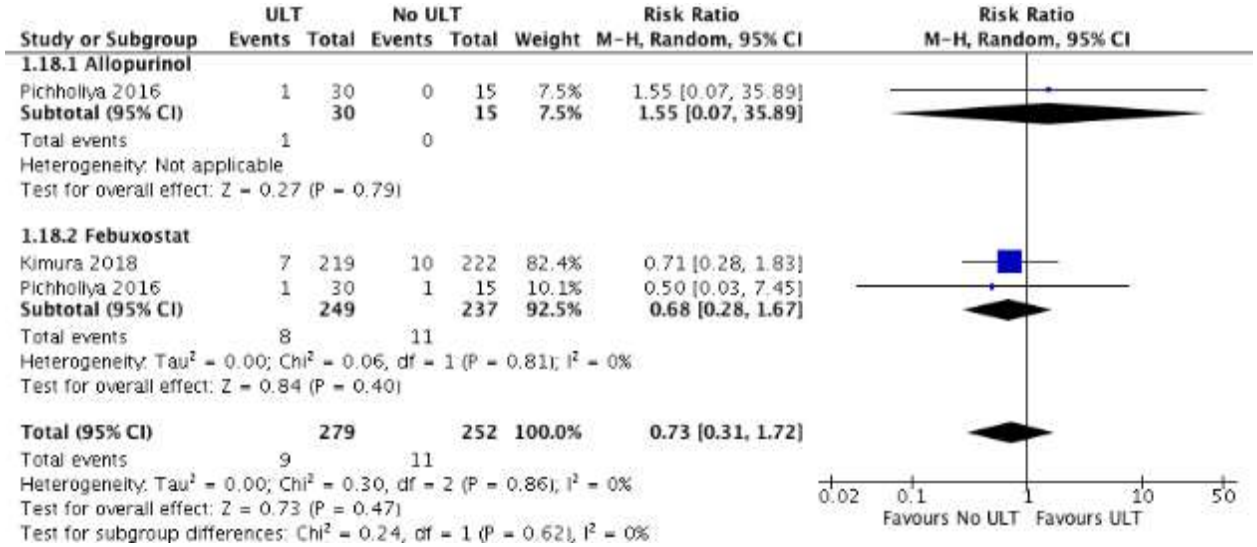
10. ULT vs no ULT for asymptomatic hyperuricemia, outcome: SAE - renal function - change from baseline in mil/min - longest follow-up (6 months) - Febuxostat.



11. ULT vs no ULT for asymptomatic hyperuricemia, outcome: SAE - renal function - change from baseline in ml/min - longest follow-up (3-5 years) - Allopurinol.



12. ULT vs no ULT for asymptomatic hyperuricemia, outcome: Hypersensitivity - proportion with hypersensitivity - longest follow-up - Allopurinol & Febuxostat.



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