#### **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 patients with subcutaneous tophi (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.

		Cert	ainty assess	ment				Sun	nmary of fi	indings	
Nº of	Risk					Overall	Study rates	event s (%)	Relative	Anticipat ef	ted absolute fects
participants (studies) Follow-up	of bias	Inconsistency	Indirectness	Imprecision	bias	certainty of evidence	With No ULT	With ULT	effect (95% CI)	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%)	<b>RR 4.50</b> (0.61 to 33.09)	0 per 1,000	<b>140 more</b> <b>per 1,000</b> (10 more to 270 more)
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### Tophus\*\* (follow up: mean 6 months; assessed with: Patients with complete tophi resolution)

131 (2 RCTs)	not serious	not serious	not serious	serious <sup>c</sup>	none	⊕⊕⊕⊖ MODERATE	2/27 (7.4%)	32/104 (30.8%)	<b>RR 4.11</b> (1.05 to 16.12)	74 per 1,000	<b>230 more</b> <b>per 1,000</b> (4 more to 1,120 more)
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### Tophus\*\* (follow up: mean 24 weeks; assessed with: Mean tophi per patient)

142 (2 RCTs)	not serious	not serious	not serious	serious <sup>d</sup>	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.
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### 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 <sup>e</sup>	none	⊕⊕⊕⊖ MODERATE	43	169	-	The mean gout flares** was <b>1.2</b> flares	MD <b>1.29</b> flares more (0.7 more to 1.87 more)
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### Gout flares\*\* (follow up: range 4 months to 6 months; assessed with: Mean rate per patient)

181 (2 RCTs)	not not serious	not serious	serious <sup>e</sup>	none	⊕⊕⊕⊖ MODERATE	43	138	-	The mean gout flares** was <b>1.3</b> flares	MD <b>0.19</b> flares fewer (0.71 fewer to 0.33 more)
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### 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	⊕⊕⊕⊕ нісн	0/43 (0.0%)	65/169 (38.5%)	<b>RR 9.13</b> (2.33 to 35.87)	0 per 1,000	<b>390 more</b> <b>per 1,000</b> (290 more to 490 more)
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## 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 <sup>a</sup>	none	⊕⊕⊕⊖ MODERATE	14/37 (37.8%)	60/122 (49.2%)	<b>RR 1.30</b> (0.83 to 2.04)	378 per 1,000	<b>114 more</b> <b>per 1,000</b> (64 fewer to 394 more)
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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 <sup>a</sup>	none	⊕⊕⊕⊖ MODERATE	10/35 (28.6%)	56/107 (52.3%)	<b>RR 1.83</b> (1.05 to 3.19)	286 per 1,000	<b>237 more</b> <b>per 1,000</b> (14 more to 626 more)
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# 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	⊕⊕⊕⊕ нісн	11/38 (28.9%)	75/120 (62.5%)	<b>RR 2.14</b> (1.28 to 3.59)	289 per 1,000	<b>330 more</b> <b>per 1,000</b> (81 more to 750 more)
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## 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	⊕⊕⊕⊕ нісн	37	122	-		MD <b>0.23</b> points lower (0.38 lower to 0.08 lower)
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### Serious adverse events\* (follow up: mean 6 months)

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

	ULT		No UI	LT		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl		IV, Random, 95% Cl	
1.1.1 Pegloticase 8m	ig every 2	week	s vs. plac	cebo					
Baraf 2013	10	46	0	15	51.5%	7.15 [0.44, 115.20]			
Subtotal (95% CI)		46		15	51.5%	7.15 [0.44, 115.20]			
Total events	10		0						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z=1.39 (	(P = 0.1	7)						
1.1.2 Pegloticase 8 n	ng every i	month	vs. place	bo					
Baraf 2013	4	48	0	14	48.5%	2.76 [0.16, 48.30]			
Subtotal (95% CI)		48		14	48.5%	2.76 [0.16, 48.30]			
Total events	4		0						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.69 (	(P = 0.4	19)						
Total (95% CI)		94		29	100.0%	4.50 [0.61, 33.09]			
Total events	14		0						
Heterogeneity: Tau² =	0.00; Chi	i² = 0.2	2, df = 1 (	(P = 0.6	4); l <sup>2</sup> = 09	б			100
Test for overall effect:	Z=1.48 (	(P = 0.1	4)				0.01	Eavours No LILT Eavours LILT	100
Test for subgroup diff	erences:	Chi <sup>z</sup> = I	0.22, df=	1 (P =	0.64), l <sup>2</sup> =	- 0%			

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

	ULT	<b>F</b>	No U	LT		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
1.2.1 Pegloticase biv	weekly								
Sundy 2011 Subtotal (95% CI)	21	52 52	1	13 13	50.4% 50.4%	5.25 [0.78, 35.52] 5.25 [0.78, 35.52]			
Total events	21		1						
Heterogeneity: Not ap	plicable								
Test for overall effect	Z = 1.70	(P = 0)	).09)						
1.2.2 Pegloticase mo	onthly							_	
Sundy 2011 Subtotal (95% CI)	11	52 52	1	14 14	49.6% 49.6%	2.96 [0.42, 21.03] 2.96 [0.42, 21.03]			
Total events	11		1						
Heterogeneity: Not ap	plicable								
Test for overall effect	: Z = 1.05	P = 0	).28)						
Total (95% CI)		104		27	100.0%	4.11 [1.05, 16.12]		-	
Total events	32		2						
Heterogeneity: Chi2 =	0.17, df	= 1 (P	= 0.68);	$J^2 = 09$	6		1 az		100
Test for overall effect	Z = 2.03	P = 0	).04)				0.01 0.1 Eawor	i 10 .	100
Test for subgroup diff	ferences:	Chi <sup>2</sup> =	0.17, df	= 1 (P)	= 0.68),	$l^2 = 0\%$	Favor	is placeou ravours pegioucase	

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

	ULT			No ULT				Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
1.6.1 Pegloticase biv	veekly										
Sundy 2011 Subtotal (95% CI)	2.3	2.1	85 85	1.2	1.6	22 22	53.1% 53.1%	1.10 [0.30, 1.90] 1.10 [0.30, 1.90]	-		
Heterogeneity: Not ap	plicable								10000		
Test for overall effect:	Z = 2.6	58 (P	= 0.00	7)							
1.6.2 Pegloticase mo	onthly										
Sundy 2011 Subtotal (95% CI)	2.7	2.4	84 84	1.2	1.6	21 21	46.9% 46.9%	1.50 [0.64, 2.36] 1.50 [0.64, 2.36]	*		
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 3.4	44 (P	= 0.00	06)							
Total (95% CI)			169			43	100.0%	1.29 [0.70, 1.87]	•		
Heterogeneity: Chi2 =	0.45, d	f = 1	(P = 0)	.50); I2	= 0%	ê.					
Test for overall effect:	Z = 4.3	31 (P	< 0.00	01)					Favours ULT Favours no ULT		
Test for subgroup diff	ferences	: Chi <sup>2</sup>	= 0.4	5. df =	1 (P =	= 0.50)	$1^2 = 0\%$		ravours der ravours no der		

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

	ULT	<b>F</b>	No U	LT		Risk Ratio	Risk Ratio
Study or Subgroup	<b>Events Total</b>		<b>Events Total</b>		Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.10.1 Pegloticase b	iweekly						100 C
Sundy 2011	20	43	0	10	25.4%	10.25 [0.67, 156.61]	
Sundy 2011b	16	42	0	11	24.8%	9.21 [0.59, 142.59]	
Subtotal (95% CI)		85		21	50.3%	9.74 [1.41, 67.27]	
Total events	36		0				
Heterogeneity: Chi2 =	0.00, df	= 1 (P)	= 0.96);	$1^2 = 0.9$	6		
Test for overall effect:	Z = 2.31	(P = 0)	0.02)				
1.10.2 Pegloticase m	onthly						
Sundy 2011	8	41	0	10	25.2%	4.45 [0.28, 71.33]	
Sundy 2011b	21	43	0	12	24.5%	12.70 [0.82, 195.72]	
Subtotal (95% CI)		84		22	49.7%	8.52 [1.23, 59.04]	
Total events	29		0				
Heterogeneity: Chi <sup>2</sup> =	0.29, df	= 1 (P)	= 0.59);	$1^2 = 0.9$	6		
Test for overall effect:	Z = 2.17	7 (P = 0)	0.03)				
Total (95% CI)		169		43	100.0%	9.13 [2.33, 35.87]	
Total events	65		0				
Heterogeneity: Chi2 =	0.32, df	= 3 (P)	= 0.96);	$1^2 = 09$	6		
Test for overall effect:	Z = 3.17	7 (P = 0)	0.002)				Eavours no III T Eavours III T
Test for subgroup diff	ferences:	$Chi^2 =$	0.01, df	= 1 (P	= 0.92),	$l^2 = 0\%$	ravours no der Fravours der

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

	ULT		No UI	LT		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.2.1 Pegloticase 8m	g every 2	week	s vs. plac	cebo			
Baraf 2013	33	60	7	18	52.4%	1.41 [0.76, 2.64]	
Subtotal (95% CI)		60		18	52.4%	1.41 [0.76, 2.64]	-
Total events	33		7				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=1.09 (	(P = 0.2	:8)				
1.2.2 Pegloticae 8mg	every mo	onth vs	, placeb	0			
Baraf 2013	27	62	7	19	47.6%	1.18 [0.61, 2.27]	
Subtotal (95% CI)		62		19	47.6%	1.18 [0.61, 2.27]	
Total events	27		7				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z= 0.50 (	(P = 0.6	2)				
Total (95% CI)		122		37	100.0%	1.30 [0.83, 2.04]	◆
Total events	60		14				
Heterogeneity: Tau² =	0.00; Chi	<b>r</b> = 0.19	5, df = 1 (	P = 0.7	0); I <sup>2</sup> = 09	6	
Test for overall effect:	Z = 1.14 (	(P = 0.2	(6)				Eavours No LILT Eavours LILT
Test for subgroup diff	erences: •	Chi <b>²</b> = I	0.15, df=	1 (P =	0.70), l <sup>2</sup> =	: 0%	

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.

	ULT		No ULT			Risk Ratio	<pre>k Ratio</pre>		
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Rand	om, 95% Cl	
1.4.1 Pegloticase 8m	g every m	nonth v	s. placel	00					
Baraf 2013 <b>Subtotal (95% CI)</b>	37	58 <mark>58</mark>	5	19 <b>19</b>	44.1% <b>44.1%</b>	2.42 [1.11, 5.27] <b>2.42 [1.11, 5.27]</b>			
Total events	37		5						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 2.23 (	P = 0.0	3)						
1.4.2 Pegloticase 8m	g every 2	weeks	s vs. plac	ebo					
Baraf 2013 <b>Subtotal (95% CI)</b>	38	62 62	6	19 <b>19</b>	55.9% <mark>55.9%</mark>	1.94 [0.97, 3.87] <b>1.94 [0.97, 3.87]</b>		-	
Total events	38		6						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z=1.88 (	P = 0.0	6)						
Total (95% CI)		120		38	100.0%	2.14 [1.28, 3.59]		•	
Total events	75		11						
Heterogeneity: Tau² =	0.00; Chi	<sup>2</sup> = 0.18	3, df = 1 (	P = 0.6	8); I <sup>2</sup> = 09	6			
Test for overall effect:	Z = 2.89 (	P = 0.0	04)				Eavours No LILT	Eavoure LILT	20
Test for subgroup diff	erences: (	Chi²=0	).18, df=	1 (P=	0.68), I <sup>z</sup> =	:0%	T avours NO OLI		

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.

	ULT		No UI	T		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% Cl	
1.3.1 Pegloticase 8m	g every 2	weeks	s vs. plac	ebo:						
Baraf 2013	27	50	5	17	50.5%	1.84 [0.84, 4.00]		-		
Subtotal (95% CI)		50		17	50.5%	1.84 [0.84, 4.00]		-		
Total events	27		5							
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z=1.53 (	P = 0.1	3)							
1.3.2 Pegloticase 8m	g every m	onth v	s. placel	00						
Baraf 2013	29	57	5	18	49.5%	1.83 [0.83, 4.03]		-	-	
Subtotal (95% CI)		57		18	49.5%	1.83 [0.83, 4.03]		-		
Total events	29		5							
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z=1.51 (	P = 0.1	3)							
Total (95% CI)		107		35	100.0%	1.83 [1.05, 3.19]			•	
Total events	56		10							
Heterogeneity: Tau² =	0.00; Chi	<sup>2</sup> = 0.00	), df = 1 (	P = 1.0	0); I <sup>z</sup> = 09	6	0.05		<u></u>	
Test for overall effect:	Z = 2.15 (	P = 0.0	3)				0.00	Eavours No ULT	Favours ULT	20
Test for subgroup diff	erences: (	Chi²=0	0.00, df=	1 (P =	1.00), I <sup>z</sup> =	:0%				

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.

	ULT			N	IO ULT	1		Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
1.8.1 Pegloticase biv	veekly										
Sundy 2011 Subtotal (95% CI)	-0.22	0.64	77	0.02	0.41	21 21	46.4% 46.4%	-0.24 [-0.47, -0.01] -0.24 [-0.47, -0.01]	-		
Heterogeneity: Not ap Test for overall effect:	plicable Z = 2.0	8 (P =	0.04)						1212		
1.8.2 Pegloticase mo	onthly										
Sundy 2011 Subtotal (95% CI)	-0.2	0.55	78 78	0.02	0.41	22 22	53.6% 53.6%	-0.22 [-0.43, -0.01] -0.22 [-0.43, -0.01]	*		
Heterogeneity: Not ap Test for overall effect:	plicable Z = 2.0	5 (P =	0.04)								
Total (95% CI)			155			43	100.0%	-0.23 [-0.38, -0.08]	•		
Heterogeneity: Chi <sup>2</sup> =	0.02, di	f = 1 (	P = 0.9	$(0); I^2 =$	0%			· · · · · · · · · · · · · · · · · · ·	<u> </u>		
Test for overall effect:	Z = 2.9	2 (P =	0.004	)					Favours ULT Favours No ULT		
Test for subgroup diff	erences:	Chi2 =	= 0.02,	df = 1	(P = 0)	.90), I <sup>2</sup>	= 0%				

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

	ULT	r i	No U	LT		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	<b>Events Total</b>		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.9.1 Pegloticase biv	weekly						
Sundy 2011 Subtotal (95% CI)	20	85 85	Z	21 21	40.3% 40.3%	2.47 [0.63, 9.75] 2.47 [0.63, 9.75]	
Total events	20		2				
Heterogeneity: Not ap	plicable						
Test for overall effect	Z = 1.29	P = 0	).20)				
1.9.2 Pegloticase mo	onthly						
Sundy 2011	19	84	3	22	59.7%	1.66 [0.54, 5.10]	
Subtotal (95% CI)		84		22	59.7%	1.66 [0.54, 5.10]	
Total events	19		3				
Heterogeneity: Not ap	plicable						
Test for overall effect	Z = 0.88	B (P = 0)	).38)				
Total (95% CI)		169		43	100.0%	1.99 [0.83, 4.74]	
Total events	39		5				
Heterogeneity: Chi <sup>2</sup> =	0.20, df	= 1 (P)	= 0.66);	$l^2 = 09$	6		
Test for overall effect	Z = 1.55	i (P = 0)	).12)				0.1 0.2 0.5 1 2 5 10 Eavours III T Eavours no III T
Test for subgroup dif	ferences:	Chi <sup>2</sup> =	0.19, df	= 1 (P)	= 0.66),	$l^2 = 0\%$	

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

	Critical outcom	es		Important outco	omes			
Treatment versus placebo	Flares longest follow up	Tophus	Serum urate	Flares up to 3 months	SAEs	SAEs- CV	Highest level among critical outcomes	
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				

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

### 3: Should ULT vs. No ULT be used in patients without subcutaneous tophi and with frequent gout flares (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.

		Certa	ainty assess		Summary of findings						
Nº of							Study event rates (%)			Anticipated absolute effects	
Nº or participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	overall certainty of evidence	With No urate lowering therapy	With Urate Iowering 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 <sup>b</sup>	none	⊕⊕⊕⊕ нісн	2/107 (1.9%)	32/107 (29.9%)	<b>RR 16.00</b> (3.93 to 65.09)	19 per 1,000	<b>280 more</b> <b>per 1,000</b> (55 more to 1,198 more)
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### 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 <sup>d</sup>	none	⊕⊕⊖⊖ Low	14/94 (14.9%)	10/84 (11.9%)	<b>RR 0.80</b> (0.38 to 1.70)	149 per 1,000	<b>30 fewer</b> <b>per 1,000</b> (92 fewer to 104 more)
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## Serious Adverse Events\* (follow up: mean 6 months; assessed with: Investigator determined serious treatment related adverse event)

$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	<b>47 more</b> <b>per 1,000</b> (11 fewer to 227 more)
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## Serious adverse events (Renal)\* (follow up: mean 6 months; assessed with: % of patients with sCr elevation $\geq$ 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%)	<b>RR 53.00</b> (3.27 to 858.67)	0 per 1,000	<b>240 more</b> <b>per 1,000</b> (160 more to 330 more)
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### Serious adverse events (Renal)\* (follow up: mean 6 months; assessed with: Nephrolithiasis )

214 (1 RCT)	not serious ª	not serious	not serious	very serious	none		0/107 (0.0%)	1/107 (0.9%)	<b>RR 3.00</b> (0.12 to 72.83)	0 per 1,000	<b>10 more</b> <b>per 1,000</b> (20 fewer to 30 more)
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## 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		1/107 (0.9%)	1/107 (0.9%)	<b>RR 1.00</b> (0.06 to 15.78)	9 per 1,000	<b>0 fewer</b> <b>per 1,000</b> (9 fewer to 138 more)
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**Pain\* - not reported** 

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### **Tophus\* - not reported**

|--|--|

Certainty	assessment
certainty	ussessment

Summary of findings

### Patient global assessment\* - not reported

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### Health-related quality of life\* - not reported

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### **Activity limitation\* - not reported**

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### Serious adverse events (hypersensitivity)\* - not reported

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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

austre 2017	Random sequence generati	Allocation concessment (sel-	Blinding of participants and	Bitnang of outcome assess	Blinding of participants and	Blinding of outcome assess	Incomplete outcome data (a	Selective reporting (reporting)	Other bias
	tion (selection bias)	(seid noilsei	personnel (performance bias) - Objective Outcome	sment (dectection bias) - Cojective Outconse	personnel (performance bias)	sment (detection bias)	atrition trias)	diseid g	

	ULT	ſ	No UI	T		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Taushe 2017	32	107	2	107	100.0%	16.00 [3.93, 65.09]	
Total (95% CI)		107		107	100.0%	16.00 [3.93, 65.09]	
Total events	32		2				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 3.87 (	(P = 0.0	)001)				0.02 0.1 1 10 50 Favours No ULT Favours ULT

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

	ULT		No UI	T		Risk Ratio		Risk Rat	tio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random,	95% CI	
Taushe 2017	10	84	14	94	100.0%	0.80 [0.38, 1.70]				
Total (95% CI)		84		94	100.0%	0.80 [0.38, 1.70]		-		
Total events	10		14							
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.58 (	(P = 0.5	56)				L 0.01	0.1 1 Favours ULT Fa	10 IVours No ULT	100

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

	ULT	ſ	No UI	T		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Taushe 2017	9	107	4	107	100.0%	2.25 [0.71, 7.08]	
Total (95% CI)		107		107	100.0%	2.25 [0.71, 7.08]	-
Total events	9		4				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.39 (	(P = 0.1	7)				0.01 0.1 1 10 100 Favours ULT Favours No ULT

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

	ULT		No UI	T		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% Cl	
Taushe 2017	26	107	0	107	100.0%	53.00 [3.27, 858.67]				
Total (95% CI)		107		107	100.0%	53.00 [3.27, 858.67]				
Total events	26		0							
Heterogeneity: Not ap Test for overall effect:	plicable Z = 2.79 (	(P = 0.0	105)				0.002	0.1 1 Favours ULT	10 Favours No ULT	500

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

	ULT	Г	No UI	T		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% Cl	
Taushe 2017	1	107	0	107	100.0%	3.00 [0.12, 72.83]				
Total (95% CI)		107		107	100.0%	3.00 [0.12, 72.83]				
Total events	1		0							
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.68 (	(P = 0.5	i0)				0.01 0	).1 Favours ULT	1 10 Favours No ULT	100

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

	ULT	-	No UI	LT		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% Cl	
Taushe 2017	1	107	1	107	100.0%	1.00 [0.06, 15.78]				
Total (95% CI)		107		107	100.0%	1.00 [0.06, 15.78]				
Total events	1		1							
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.00 (	(P = 1.0	)0)				L.01	0.1 Favours ULT	1 10 Favours No ULT	100

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.</li>
  - o 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.
  - o 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.

	Certainty assessment								Summary of findings					
							Study ev (१	ent rates ⁄₀)		Anticipat ef	ed absolute fects			
№ от participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	overall certainty of evidence	With No Urate Iowering therapy	With Urate Iowering 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 <sup>b</sup>	none	⊕⊕⊕⊖ MODERATE	9/157 (5.7%)	99/157 (63.1%)	<b>RR 11.00</b> (5.77 to 20.98)	57 per 1,000	<b>573 more</b> <b>per 1,000</b> (273 more to 1,145 more)
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### Gout flares\*\* (follow up: mean 24 months; assessed with: Participants with at least one gout flare)

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### Serious Adverse Events\* (follow up: mean 24 months)

314 (1 RCT)	serious not serious	not serious	serious <sup>c</sup>	none		11/157 (7.0%)	13/157 (8.3%)	<b>RR 1.18</b> (0.55 to 2.56)	70 per 1,000	<b>13 more</b> <b>per 1,000</b> (32 fewer to 109 more)
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### Serious Adverse Event (Cardiovascular)\* (follow up: mean 24 months)

314 (1 RCT)	serious ª	not serious	not serious	serious <sup>b,c</sup>	none		2/157 (1.3%)	3/157 (1.9%)	<b>RR 1.50</b> (0.25 to 8.85)	13 per 1,000	6 more per 1,000 (10 fewer to 100 more)
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		Cert	ainty assess		Summary of findings						
Pain - n	ot repo	orted									
-	-	-	-	-	-	-	-	-	-	-	-
Tophus	- not r	eported						· · · · · ·			
-	-	-	-	-	-	-	-	-	-	-	-
Patient	Global	Assessmer	nt - not re	ported				· · · · · ·			
-	-	-	-	-	-	-	-	-	-	-	-
HRQoL	- not re	eported				·					
-	-	-	-	-	-	-	-	-	-	-	-
Activity	Limita	tion - not r	eported								
-	-	-	-	-	-	-	-	-	-	-	-
Serious	advers	se event (re	enal, kidno	ey stones,	, hyperse	nsitivity	) - not r	eported	I	1	
	_	_	_	_	_	_	_	_		_	_

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

	ULT			LT		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Rand	om, 95% Cl		
Dalbeth 2017	99	157	9	157	100.0%	11.00 [5.77, 20.98]				-	
Total (95% CI)		157		157	100.0%	11.00 [5.77, 20.98]					
Total events	99		9								
Heterogeneity: Not ap Test for overall effect:	plicable Z = 7.28 (	(P < 0.0	)0001)				0.02	0.1 Favours No ULT	1 10 Favours ULT	I T	50

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

	ULT		No ULT		Risk Ratio			Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% Cl			
Dalbeth 2017	46	157	65	157	100.0%	0.71 [0.52, 0.96]						
Total (95% CI)		157		157	100.0%	0.71 [0.52, 0.96]		+				
Total events	46		65									
Heterogeneity: Not ap	plicable						0.05	0.2	ł	20		
Test for overall effect	: Z = 2.21	(P = 0)	0.03)				0.05	Favours ULT	Favours No I	ULT 20		

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

	ULT Study of Subgroup - Support - Tota					Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% Cl
Dalbeth 2017	13	157	11	157	100.0%	1.18 [0.55, 2.56]		
Total (95% CI)		157		157	100.0%	1.18 [0.55, 2.56]		-
Total events Heterogeneity: Not ap Test for overall effect:	13 oplicable Z = 0.42	(P = 0.6	11 )7)				0.05	0.2 1 5 20 Favours ULT Favours No ULT

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

	ULT Study of Subarray Frends Ta			LT		Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95	5% CI	
Dalbeth 2017	3	157	2	157	100.0%	1.50 [0.25, 8.85]				
Total (95% CI)		157		157	100.0%	1.50 [0.25, 8.85]				
Total events	3		2							
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.45 (	(P = 0.6	65)				L.01	0.1 1 Favours ULT Favo	10 Durs No ULT	100

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</li>
  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

	Critical outcom	es		Important outco			
Treatment versus placebo	Flares longest follow up	Tophus	Serum urate	Flares up to 3 months	SAEs	SAEs- CV	Highest level among critical outcomes
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			

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

### 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
  - o 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

		Cert	ainty assess		Sun	nmary of fi	ndings				
							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 <sup>b</sup>	none	⊕OOO VERY LOW	132/457 (28.9%)	38/123 (30.9%)	<b>OR 1.10</b> (0.71 to 1.70)	289 per 1,000	<b>20 more</b> <b>per 1,000</b> (65 fewer to 120 more)
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## 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 <sup>b</sup>	none	⊕OOO VERY LOW	42/457 (9.2%)	15/123 (12.2%)	<b>OR 1.37</b> (0.73 to 2.57)	92 per 1,000	<b>30 more</b> <b>per 1,000</b> (23 fewer to 115 more)
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### 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	none		3/25 (12.0%)	2/26 (7.7%)	<b>RR 0.64</b> (0.12 to 3.52)	120 per 1,000	<b>43 fewer</b> <b>per 1,000</b> (106 fewer to 302 more)
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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 <sup>d</sup>	none		19	16	-	The mean gout flares** was <b>12.53</b> hours	MD <b>4.47</b> hours longer (0.97 shorter to 9.91 longer)
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## 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 <sup>b</sup>	none	⊕OOO VERY LOW	300/457 (65.6%)	82/123 (66.7%)	<b>OR 1.05</b> (0.69 to 1.60)	656 per 1,000	<b>11 more</b> <b>per 1,000</b> (88 fewer to 97 more)
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## 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 <b>0.48</b> mg/dL	MD <b>2.83</b> mg/dL lower (3.84 lower to 1.81 lower)
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<b>Certainty assessmen</b>	t										
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#### 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 <sup>b</sup>	none	⊕OOO VERY LOW	44/457 (9.6%)	11/123 (8.9%)	<b>OR 0.92</b> (0.46 to 1.84)	96 per 1,000	<b>7 fewer</b> <b>per 1,000</b> (50 fewer to 68 more)
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## 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 <sup>b</sup>	none		41	45	-	The mean pain* was <b>0.89</b>	MD <b>0.1</b> lower (0.58 lower to 0.38 higher)
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## 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	none		0/25 (0.0%)	1/26 (3.8%)	<b>RR 2.89</b> (0.12 to 67.75)	0 per 1,000	<b>40 more</b> <b>per 1,000</b> (60 fewer to 140 more)
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## 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	none	⊕⊕⊖⊖ Low	1/25 (4.0%)	0/26 (0.0%)	<b>RR 0.32</b> (0.01 to 7.53)	40 per 1,000	<b>27 fewer</b> <b>per 1,000</b> (40 fewer to 261 more)
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### Table 1: Evidence profile

Certainty assessment
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Summary of findings

#### Patient global assessment\* - not reported

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### Activity Limitation\* - not reported

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### Health related quality of life\* - not reported

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### 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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)- Objective outcomes	Blinding of outcome assessment (Detection bias)- Objective outcomes	Blinding of participants and personnel (performance bias)- Subjective outcomes	Blinding of outcome assessment (detection bias)- Subjective outcomes	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	
Feng 2015										
Hill 2015	•	•	•	•	•	•		•		
Taylor 2012	•	•	•	•	•	•	•	•		

Study	Confounding	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
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#### 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.

	ULT during gout flare ULT after gout flar					Odds Ratio		Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI			IV, Rando	m, 95% C	1	
Feng 2015	38	123	132	457	100.0%	1.10 [0.71, 1.70]						
Total (95% CI)		123		457	100.0%	1.10 [0.71, 1.70]						
Total events	38		132									
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.43 (P = 0.6)	6)					⊢ 0.1	0.2 Favors ULT d	0.5 uring flare	Favors U	2 JLT after flar	10 10 10

### 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

	ULT during gou	t flare	ULT after go	ut flare		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Feng 2015	15	123	42	457	100.0%	1.37 [0.73, 2.57]	
Total (95% CI)		123		457	100.0%	1.37 [0.73, 2.57]	
Total events	15		42				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.99 (P = 0.32	2)					U.1 0.2 0.5 1 2 5 10 Favors ULT during flare Favors ULT after flare

#### 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.

	ULT during gout flare ULT after gout flare					Risk Ratio		Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Rand	om, 95% Cl			
Taylor 2012	2	26	3	25	100.0%	0.64 [0.12, 3.52]				_		
Total (95% CI)		26		25	100.0%	0.64 [0.12, 3.52]				-		
Total events	2		3									
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.51 (P = 0.61	1)					0.1 0.2 Favors U	0.5 ULT during flare	1 2 Favors ULT aff	5 ter flare	10	

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.

	ULT duri	ULT during gout flare ULT after gout flare						Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
Hill 2015	-1.24	7.47	19	0.36	5.52	16	5.6%	-1.60 [-5.91, 2.71]				
Taylor 2012	-2.3	1.73	26	0.6	2.06	25	94.4%	-2.90 [-3.95, -1.85]				
Total (95% CI)			45			41	100.0%	-2.83 [-3.84, -1.81]	◆			
Heterogeneity: Tau² = Test for overall effect: :	0.00; Chi² Z = 5.45 (P	= 0.33, d < 0.000	f = 1 (P = D1)	= 0.57); I²	= 0%				-10 -5 0 5 10 Favors ULT during flare Favors ULT after flare			

#### 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.

	ULT during gout flare ULT after gout flar				flare		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Hill 2015	0.46	11.1	19	1.5	2.82	16	0.9%	-1.04 [-6.22, 4.14]			
Taylor 2012	0.18	0.8761	26	0.27	0.8761	25	99.1%	-0.09 [-0.57, 0.39]	•		
Total (95% CI)			45			41	100.0%	-0.10 [-0.58, 0.38]	•		
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: .	0.00; Chi Z = 0.40 (	i <sup>z</sup> = 0.13, d (P = 0.69)	lf=1 (P=	= 0.72); i	²=0%				-10 -5 0 5 10 Favors ULT during flare Favors ULT after flare		

## **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.

	ULT during gout	t flare	ULT after goi	ut flare		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Taylor 2012	1	26	0	25	100.0%	2.89 [0.12, 67.75]	
Total (95% CI)		26		25	100.0%	2.89 [0.12, 67.75]	
Total events	1		0				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.66 (P = 0.51	)					0.1 0.2 0.5 1 2 5 10 Favours ULT during flare Favours ULT after flare

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

	ULT during gout flare ULT after gout flare					Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Taylor 2012	0	26	1	25	100.0%	0.32 [0.01, 7.53]	·
Total (95% CI)		26		25	100.0%	0.32 [0.01, 7.53]	
Total events	0		1				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.71 (P = 0.48	)					Favours ULT during flare Favours ULT after flare

## 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

		Cert	ainty assess	sment			Sumn	nary of fin	dings		
	Certainty assess				Study e (	vent 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 <sup>b</sup>	not serious	none		18/50 (36.0%)	20/96 (20.8%)	<b>RR 0.58</b> (0.34 to 0.99)	360 per 1,000	<b>151 fewer</b> <b>per 1,000</b> (238 fewer to 4 fewer)
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### Gout flares\*\* (follow up: mean 6 months; assessed with: mean flare per patient)

21 (1 RCT)	serious ª	not serious	serious <sup>b</sup>	serious <sup>c</sup>	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
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### Serum urate\*\* (follow up: mean 3 months; assessed with: patients with SUA<6 mg/dL)

132 (1 RCT)	not serious d	not serious	serious <sup>b</sup>	serious <sup>e</sup>	none	⊕⊕⊕⊖ MODERATE	32/42 (76.2%)	62/90 (68.9%)	<b>RR 0.90</b> (0.73 to 1.13)	762 per 1,000	<b>76 fewer</b> <b>per 1,000</b> (206 fewer to 99 more)
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#### **Certainty assessment**

#### Summary of findings

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

115 (1 RCT)	not not serious erious d	serious <sup>b</sup>	serious <sup>e</sup>	none	⊕⊕⊕⊖ MODERATE	28/38 (73.7%)	58/77 (75.3%)	<b>RR 1.02</b> (0.81 to 1.29)	737 per 1,000	<b>15 more</b> <b>per 1,000</b> (140 fewer to 214 more)
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#### Serious adverse events\*\* (follow up: mean 24 weeks; assessed with: reaction to febuxostat)

146 (1 RCT)	not serious d	not serious	serious <sup>b</sup>	serious <sup>e</sup>	none	⊕⊕⊖⊖ Low	5/50 (10.0%)	7/96 (7.3%)	<b>RR 0.73</b> (0.24 to 2.18)	100 per 1,000	<b>27 fewer</b> <b>per 1,000</b> (76 fewer to 118 more)
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#### 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%)	<b>OR 0.18</b> (0.08 to 0.36)	561 per 1,000	<b>374 fewer</b> <b>per 1,000</b> (468 fewer to 246 fewer)
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#### **Pain\* - not reported**

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### Tophus\* - not reported

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#### Patient global assessment\* - not reported

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### **Table 1: Evidence profile**

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Gentannity assessin	

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 2: Risk of bias assessments- Observational studies

Study	Counfoundin g	Selectio n bias	Bias in classificatio n of intervention s	Bias due to deviation of intended intervention s- objective outcomes	Bias due to deviation of intended intervention s- subjective outcomes	Bias due to outcome measuremen t- objective outcomes	Bias due to outcome measuremen t- subjective outcomes	Bias due to missin g data	Bias in selectio n of reporte d result
Stamp 2012									

#### 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



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

	Febuxostat st	epwise	Febuxostat sta	art high		<b>Risk Ratio</b>		R	sk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H,	Fixed, 95%	6 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 ap	plicable					8 <del>-</del>	0.5	0 7	-	15	-
Test for overall effect	z = 0.90 (P = 0)	).37)					Febu	xostat start h	igh Febux	ostat step	owise

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**

		Certa	ainty assess	Summary of findings							
							Study ev	Study event rates (%)		Anticipat ef	ted absolute fects
№ of participant s (studies) Follow-up	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Publicatio n bias	Overall certainty of evidence	With usual care	With non- physician health care professional -augmented (e.g. nursing or pharmacy) package of care	Relativ e 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)

## Gout flares\*\* (follow up: mean 2 years; assessed with: Number of gout flares)

517 (1 RCT)	seriou s <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	⊕⊕⊖⊖ Low	262	255	-	The mean gout flares** was <b>2.4</b>	MD <b>0.9</b> lower (3.67 lower to 1.87 higher)
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## Gout flares\*\* (follow up: 2 years; assessed with: People with 2 or more flares)

517 (1 RCT)	seriou s ª	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	64/262 (24.4%)	21/255 (8.2%)	<b>RR</b> <b>0.34</b> (0.21 to 0.56)	244 per 1,000	<b>161 fewer</b> <b>per 1,000</b> (193 fewer to 107 fewer)
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#### **Certainty assessment**

#### Summary of findings

### Gout flares\*\* (assessed with: gout flare rates per 100 patient years)

77 (1 RCT)	seriou s <sup>a</sup>	not serious	not serious	serious	none	⊕⊕⊖⊖ Low	40	37	-	The mean gout flares** was <b>68.7</b> flares/100 patient years	MD 13 flares/100 patient years higher (3.07 higher to 22.93 higher)
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## Gout flares\*\* (follow up: range 18 months to 24 months; assessed with: gout flare rates per 100 patient years)

77 (1 RCT)	seriou s ª	not serious	not serious	serious	none	⊕⊕⊖⊖ Low	40	37	_	The mean gout flares** was <b>48.5</b> flares/ 100 patient years	MD 2.9 flares/ 100 patient years lower (13.17 lower to 7.37 higher)
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## Serum urate\*\* (follow up: mean 12 weeks; assessed with: participants with serum urate <6mg/dL)

77 (1 RCT)	seriou s ª	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	3/40 (7.5%)	15/37 (40.5%)	<b>RR</b> <b>5.41</b> (1.70 to 17.18)	75 per 1,000	<b>331 more</b> <b>per 1,000</b> (53 more to 1,214 more)
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## Serum urate\*\* (follow up: range 6 months to 1 years; assessed with: Proportion with Serum Urate <6mg/dL)

2057 s (3 RCTs)	u serious	not serious	not serious	none		191/108 4 (17.6%)	458/973 (47.1%)	<b>RR</b> <b>2.68</b> (1.51 to 4.75)	176 per 1,000	<b>296 more</b> <b>per 1,000</b> (90 more to 661 more)
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## Tophi\* (follow up: mean 2 years; assessed with: Diameter of largest tophus (mm))

517 (1 RCT)	seriou S <sup>a</sup>	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	262	255	-	The mean tophi* was <b>13.61</b> mm	MD <b>10.32</b> <b>mm lower</b> (12.38 lower to 8.26 lower)
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## Health related quality of life\* (follow up: 2 years; assessed with: Gout concern overall score)

517 (1 RCT)	seriou s <sup>a</sup>	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	262	255	-	The mean health related quality of life* was <b>53.52</b>	MD <b>16.08</b> <b>lower</b> (20.56 lower to 11.6 lower)
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<b>Certainty assessment</b>	
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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	seriou s <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	⊕⊕⊖⊖ Low	73	70	-	The mean activity Limitation * was <b>0.51</b>	MD <b>0.11</b> higher (0.14 lower to 0.36 higher)
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## Serious adverse events\* (follow up: mean 2 years; assessed with: Death)

510 (1 RCT)	seriou not serious s <sup>a</sup>	not serious	serious	none	⊕⊕⊖⊖ Low	8/255 (3.1%)	2/255 (0.8%)	<b>RR</b> <b>0.25</b> (0.05 to 1.17)	31 per 1,000	<b>24 fewer</b> <b>per 1,000</b> (30 fewer to 5 more)
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## Serious adverse events\* (follow up: mean 2 years; assessed with: Cutaneous reaction)

1463 (1 RCT)	seriou n s ª	not serious	not serious	serious	none		1/782 (0.1%)	1/681 (0.1%)	<b>RR</b> <b>1.15</b> (0.07 to 18.32)	1 per 1,000	0 fewer per 1,000 (1 fewer to 22 more)
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### **Pain\* - not reported**

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## Patient global assessment\* - not reported

-	-	-	-	-	-	-	-	-	-	-	-
		NA									

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
<u>Outcome importance</u>
\*\* 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.

	Augmente	d care	Usual	care		<b>Risk Ratio</b>			Ris	k Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fi	xed, 95% CI		
Doherty 2018	21	255	64	262	100.0%	0.34 [0.21, 0.53]		1				
Total (95% CI)		255		262	100.0%	0.34 [0.21, 0.53]		-				
Total events	21		64									
Heterogeneity: Not ap	plicable						01	0.2	0'5	+ +	1	10
Test for overall effect	Z = 4.62 (P	< 0.00	001)				0.1 F	avours au	gmented car	e Favours usu	al care	10

#### 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.

	Augmente	d care	Usual	care		<b>Risk Ratio</b>		Ris	k Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Rand	om, 95% Cl
Doherty 2018	241	255	69	262	41.4%	3.59 [2.92, 4.40]			
Goldfien 2016	13	37	5	40	17.1%	2.81 [1.11, 7.12]			
Mikuls 2018	204	681	117	782	41.5%	2.00 [1.63, 2.45]			
Total (95% CI)		973		1084	100.0%	2.70 [1.66, 4.40]			-
Total events	458		191						
Heterogeneity: Tau2 =	= 0.14; Chi <sup>2</sup>	= 15.77	df = 2 (	P = 0.0	0004); l <sup>2</sup>	= 87%	0.1	0 0 0 0	1 1 1
Test for overall effect	: Z = 3.99 (P	< 0.000	01)				0.1	Favours usual car	Favours augmented care

#### 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.

	Augn	nented	care	Us	ual care	e		Mean Difference		Me	an Differe	nce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV,	Fixed, 95%	CI	
Doherty 2018	37.54	24.97	255	53.62	27.02	262	100.0%	-16.08 [-20.56, -11.60]		-			
Total (95% CI)			255			262	100.0%	-16.08 [-20.56, -11.60]		+			
Heterogeneity: Not ap	plicable								-50	-25		25	50
Test for overall effect	Z = 7.0	13 (P < 0)	0.0000	1)					Favor	urs augmented	care Favo	urs usual care	50

**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.

	Titra	ted de	ose	Fix	ed do:	se		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Stamp L 2017	0.62	0.75	70	0.51	0.77	73	100.0%	0.11 [-0.14, 0.36]	
Total (95% CI)			70			73	100.0%	0.11 [-0.14, 0.36]	+
Heterogeneity: Not ap	plicable							A STATISTICS AND A STAT	<u> </u>
Test for overall effect	: Z = 0.8	37 (P =	0.39)						Favours [titrated dose] Favours [fixed dose]

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

	Augmented	care	Usual o	care		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Rando	om, 95% Cl	
Doherty 2018	246	255	123	262	49.8%	2.05 [1.80, 2.34]				
Mikuls 2018	342	681	289	782	50.2%	1.36 [1.21, 1.53]			-	
Total (95% CI)		936		1044	100.0%	1.67 [1.11, 2.50]				
Total events	588		412							
Heterogeneity: Tau <sup>z</sup> =	0.08; Chi <b>ž</b> = 3	21.13, di	′=1 (P <	0.0000	1); I² = 95'	%		0.5		-
Test for overall effect:	Z = 2.48 (P =	0.01)					0.2	Favours usual care	Favours augmented care	0

#### 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.

	Augmented	care	Usual	care		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Rando	om, 95% Cl	
Mikuls 2018	1	681	1	782	100.0%	1.15 [0.07, 18.32]			
Total (95% CI)		681		782	100.0%	1.15 [0.07, 18.32]			
Total events	1		1						
Heterogeneity: Not ap Test for overall effect:	oplicable : Z = 0.10 (P = 0	0.92)					0.05 0.2 Favours augmented care	1 5 Favours usual care	20

### 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:
  - o 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.
  - o 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

		Certa	ainty assess	Summary of findings							
Nº of		<b>T</b>				Overall	Study even	t rates (%)	Dolotiv	Anticipated absolute effects	
participant s (studies) Follow-up	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Publicatio n bias	certainty of evidence	With No Prophylaxi S	With Prophylaxi S	e effect (95% CI)	Risk with No Prophylaxi S	Risk difference with Prophylaxi s

## Gout Flares\*\* (follow up: 3 months; assessed with: Proportion of Patients with 1 + Gout Flare)

1754 (6 RCTs)	seriou s <sup>a</sup>	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	338/605 (55.9%)	350/1149 (30.5%)	<b>RR</b> <b>0.36</b> (0.27 to 0.48)	559 per 1,000	<b>358 fewer</b> <b>per 1,000</b> (408 fewer to 291 fewer)
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## Gout Flares\*\* (follow up: range 3 months to 4 months; assessed with: Mean Flares per Patient)

1886 (4 RCTs)	seriou S <sup>b</sup>	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	533	1353	-	The mean gout Flares** was <b>1.29</b> flares/ patient/ month	MD 0.98 flares/ patient/ month lower (1.22 lower to 0.74 lower)
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## 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)	seriou s <sup>g</sup>	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	200	368	_	The mean pain* was <b>2.02</b> days	MD <b>2 days</b> lower (2.77 lower to 1.24 lower)
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Certainty assessment	Summary of findings
Adherence* (follow up: 4 months; assessed with: Proportio	on of Patients with > 80% Adherence)

	-					-					-
1563 (2 RCTs)	seriou s <sup>h</sup>	not serious	not serious	serious <sup>i</sup>	none	⊕⊕⊖⊖ Low	380/412 (92.2%)	1063/1151 (92.4%)	<b>RR</b> <b>1.05</b> (0.69 to 1.60)	922 per 1,000	<b>46 more</b> <b>per 1,000</b> (286 fewer to 553 more)

## Adherence\* (follow up: 4 months; assessed with: To Study Drug Injections)

201 (1 RCT)	seriou s <sup>j</sup>	serious <sup>k</sup>	not serious	not serious <sup>k</sup>	none	⊕⊕⊖⊖ <sub>Low</sub>	37/40 (92.5%)	148/161 (91.9%)	<b>RR</b> <b>0.88</b> (0.16 to 4.77)	925 per 1,000	<b>111 fewer</b> <b>per 1,000</b> (777 fewer to 3,487 more)
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## Adherence\* (follow up: 4 months; assessed with: Percentage of Study Drug Injections)

83 (1 RCT)	seriou s <sup>1</sup>	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	42	41	-	The mean adherence* was <b>92.4</b> %	MD <b>5.5 %</b> higher (0.81 higher to 10.19 higher)
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## Serious Adverse Events\* (follow up: range 3 months to 5.5 months; assessed with: Diverse Definitions)

Certainty assessment	Summary of findings
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## Cardiovascular Adverse Events\* (follow up: range 4 months to 6 months; assessed with: Proportion of Patients with Stroke/Angina)

366 (3 RCTs)	seriou not serious s °	not serious	serious <sup>p</sup>	none		1/143 (0.7%)	2/223 (0.9%)	<b>RR</b> <b>1.18</b> (0.18 to 7.62)	7 per 1,000	<b>1 more per</b> <b>1,000</b> (6 fewer to 46 more)
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## Renal Adverse Events\* (follow up: 5.5 months; assessed with: Proportion of Patients with Alteration in Renal Function)

83 (1 RCT)	seriou s <sup>q</sup>	not serious	not serious	serious <sup>r</sup>	none	⊕⊕⊖⊖ <sub>Low</sub>	1/42 (2.4%)	0/41 (0.0%)	<b>RR</b> <b>0.33</b> (0.01 to 8.42)	24 per 1,000	<b>16 fewer</b> <b>per 1,000</b> (24 fewer to 177 more)
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## Serious adverse events- Drug Hypersensitivity\* (follow up: 3 months; assessed with: Number of Patients with Drug Hypersensitivity)

107 (1 RCT)	seriou s <sup>q</sup>	not serious	not serious	serious <sup>r</sup>	none	0/54 (0.0%)	1/53 (1.9%)	<b>RR</b> <b>3.06</b> (0.13 to 73.37)	0 per 1,000	<b>20 more</b> <b>per 1,000</b> (30 fewer to 70 more)
								, 5.57 )		

## **Tophus\* - not reported**

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-	-	=	=	=	-	-	-	-	-	=	-

## Patient Global Assessment\* - not reported

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Certainty assessment	
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Summary of findings

### **Health Related Quality of Life\* - not reported**

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#### **Activity Limitation\* - not reported**

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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
- I. 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					
№ of participa nts (studies) Follow-up	Risk	Inconsiste ncy	Indirectne Impr ss o		Dublicati	Overall certaint		Study event rates (%)		Anticipated absolute effects		
	of bias			on	Publicati on bias	y of evidenc e	With No Prophyla xis	With Prophyla xis	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 observatio nal study)	serio not serious us <sup>a</sup>	not serious not serio	s none	⊕⊖⊖ ⊖ VERY LOW	72	201	-	The mean gout Flares** was <b>1.72</b> flares/patient/m onth	MD 1.26 flares/patient/m onth lower (1.69 lower to 0.82 lower)
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## Serious Adverse Events\*\* (follow up: 3 months; assessed with: Diverse definitions)

273 (1 observatio nal study)	serio us <sup>a</sup>	not serious	not serious	not serious	none	⊕⊖⊖ ⊖ VERY LOW	0/72 (0.0%)	0/201 (0.0%)	not estimab le	0 per 1,000	<b>0 fewer per 1,000</b> (30 fewer to 30 more)
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# Cardiovascular Adverse Events\*\* (follow up: median 16.5 months; assessed with: Primary CV Events)

1788 (1 observatio nal study)	serio us <sup>d</sup>	not serious	not serious	not serious	none	⊕⊖⊖ ⊖ VERY LOW	82/1002 (8.2%)	28/786 (3.6%)	<b>RR</b> 0.41 (0.27 to 0.64)	82 per 1,000	<b>48 fewer per</b> <b>1,000</b> (60 fewer to 29 fewer)
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## Pain\* - not reported

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		Certa	inty assess	sment			Summary of findings					
Tophus	* - no	ot reporte	d									
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Patient	Glob	al Assess	ment* -	not repo	rted							
Health	Relat	ed Quality	y of Life*	<sup>:</sup> - not re	ported							
-	-	-	-	-	-	-	-	-	-	-	-	
Activity	Activity Limitation* - not reported											
-	-	-	-	-	-	-	-	-	-	-	-	

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

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				
№ of participant s						Overall	Study eve	Study event rates (%)		Anticipated absolute effects	
participant s (studies) Follow-up	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Publicatio n bias	overall certainty of evidence	With Colchicin e	With Canakinuma b	e effect (95% CI)	Risk with Colchicin e	Risk difference with Canakinuma b

## Gout Flares\*\* (follow up: 4 months; assessed with: Proportion of Patients with 1 + Gout Flares)

207 (1 RCT)	not not serious seriou s <sup>a</sup>	not serious	not serious	none	⊕⊕⊕⊕ HIGH	48/99 (48.5%)	18/108 (16.7%)	<b>RR</b> <b>0.34</b> (0.21 to 0.54)	485 per 1,000	<b>320 fewer</b> <b>per 1,000</b> (383 fewer to 223 fewer)
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## Serious Adverse Events\* (follow up: 6 months; assessed with: Any Serious Event)

216 (1 RCT)	not seriou s ª	not serious <sup>a</sup>	not serious	serious <sup>c</sup>	none	⊕⊕⊕⊖ MODERAT E	6/108 (5.6%)	6/108 (5.6%)	<b>RR</b> <b>1.00</b> (0.33 to 3.00)	56 per 1,000	<b>0 fewer per</b> <b>1,000</b> (37 fewer to 111 more)
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## Pain\* - not reported

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**Tophus\* - not reported** 

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## Patient Global Assessment\* - not reported

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### Table 3: Evidence profile Canakinumab versus Colchicine

Certainty assessment	Summary of findings
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## Health Related Quality of Life\* - not reported

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### **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



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias) - Objective outcomes	Blinding of outcome assessment (detection bias) - Objective outcomes	Blinding of participants and personnel (performance bias) - Subjective outcomes	Blinding of outcome assessment (detection bias) - Subjective outcomes	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Borstad 2004	•	•	•	•	•	•	•	•	•
Mitha 2013	•	•	•	•	?	?	•	•	•
Paulus 1974	•	•	•	•	•	•	•	•	•
Poiley 2016	?	?	•	•	•	•	•	•	•
Schlesinger 2011	•	•	•	•	•	•	•	•	•
Schumacher 2012a	?	?	•	•	•	•	•	•	•
Schumacher 2012b	?	?	•	•	•	•	•	•	•
Solomon 2015									
Sundy 2014	•	•	•	•	?	?	•	•	•
Yamanaka 2017	•	•	•	•	•	•	•	•	•
Yu 2017									

#### 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

	Prophyl	axis	No Prophy	yalxis		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl			
1.1.1 Colchicine vs N	o Prophyla	ixis								
Borstad 2004	7	21	17	22	10.0%	0.43 [0.23, 0.82]				
Yamanaka 2017	18	95	18	50	11.5%	0.53 [0.30, 0.92]				
Subtotal (95% CI)		116		72	21.6%	0.48 [0.32, 0.74]				
Total events	25		35							
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 0.21,	df = 1 (P =	0.65); l²	= 0%					
Test for overall effect:	Z = 3.38 (F	P = 0.00	07)							
1.1.2 Rilonacept 80 m	ng vs No Pi	rophyla	xis							
Mitha 2013	21	82	39	41	15.1%	0.27 [0.18, 0.39]	<b>_</b>			
Schumacher 2012b	15	80	18	39	11.3%	0.41 [0.23, 0.72]	<b>_</b>			
Subtotal (95% Cl)		162		80	26.5%	0.31 [0.21, 0.46]	◆			
Total events	36		57							
Heterogeneity: Tau <sup>2</sup> =	0.03; Chi <sup>z</sup>	= 1.43,	df = 1 (P =	0.23); I <sup>z</sup>	= 30%					
Test for overall effect:	Z = 5.83 (F	° < 0.00	001)							
1.1.3 Rilonacept 160	mg vs No l	Prophyl	axis							
Mitha 2013	17	84	39	41	14.0%	0.21 [0.14, 0.33]	<b>_</b>			
Schumacher 2012a	6	41	19	42	7.8%	0.32 [0.14, 0.73]				
Schumacher 2012b	13	81	19	40	10.9%	0.34 [0.19, 0.61]				
Sundy 2014	253	965	169	330	19.4%	0.51 [0.44, 0.59]				
Subtotal (95% CI)		1171		453	<b>52.0</b> %	0.34 [0.20, 0.56]				
Total events	289		246							
Heterogeneity: Tau <sup>2</sup> =	0.20; Chi <sup>z</sup>	= 16.12	2, df = 3 (P =	= 0.001)	; I <b>²</b> = 81 %					
Test for overall effect:	Z = 4.19 (F	° < 0.00	01)							
Total (95% CI)		1449		605	100.0%	0.36 [0.27, 0.48]	◆			
Total events	350		338							
Heterogeneity: Tau <sup>2</sup> =	0.10; Chi <sup>2</sup>	= 23.17	7, df = 7 (P =	= 0.002)	; <b>I²</b> = 70%					
Test for overall effect:	Z = 6.91 (F	• < 0.00	001)		-		U.1 U.2 U.5 T Z 5 1U Pronhylavis (Less Elares) No Pronhy (More Elares)			
Test for subgroup diff	erences: C	>hi <b>²</b> = 2.	38. df = 2 (l	P = 0.30	), I <b>≃</b> = 16.0	)%	Trophylaxis (Less Fidles) Two Frophy (More Fidles)			
0.			-		-	/		-		
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	Pr	ophylaxis	5	No F	rophylax	cis		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
1.3.1 Colchicine vs N	o Prophy	/laxis								
Borstad 2004	0.6	0	21	1.9	0	22		Not estimable		
Yamanaka 2017	1.33	0	95	2.06	0	50		Not estimable		
Subtotal (95% CI)			116			72		Not estimable		
Heterogeneity: Not ap	plicable									
Test for overall effect:	Not app	licable								
132 Dilonacont 00 m	a ve No	Dronbuds	avie							
1.5.2 Kilonacept ou n	IQ VS NO	Propriya		4.54	4 000		40.70	0.0074.50 0.051		
Mitha 2013 Rehumeeher 2012h	0.62	1.3198	82	1.51	1.866	41	10.7%	-0.89 [-1.53, -0.25]		
Schumacher 2012b Subtotal (95% Cl)	0.29	0.7639	162	1.06	1.5626	39	14.4% 25.1%	-0.77 [-1.29, -0.25] -0.82 [-1.22, -0.42]		
Heterogeneity: Tau <sup>2</sup> =	0.00; CI	ni² = 0.08	. df = 1	(P = 0.7	7); <b>I</b> ² = 09	%				
Test for overall effect:	Z = 3.98	(P < 0.00	001)							
1.3.3 Rilonacept 160	ma vs P	lacebo								
Mitha 2013	n 48	0.9677	84	1.51	1 866	41	11.5%	-1 03 [-1 64 -0 42]		
Schumacher 2012a	0.15	0.0011	41	0.79	1.000	42	22.7%	-0.64 [-0.98 -0.30]	<b>_</b>	
Schumacher 2012b	0.21	0.5427	81	1.51	1.5626	40	15.1%	-1.30 [-1.80, -0.80]		
Sundy 2014	0.51	1.1195	985	1.73	2.678	330	25.5%	-1.22 [-1.52, -0.92]	_ <b></b>	
Subtotal (95% CI)			1191			453	74.9%	-1.03 [-1.37, -0.70]	◆	
Heterogeneity: Tau² =	0.07; CI	ni² = 7.69	, df = 3	(P = 0.0)	l5); l² = 61	1%				
Test for overall effect:	Z = 6.12	(P < 0.00	0001)							
Total (95% CI)			1469			605	100.0%	-0.98 [-1.22, -0.74]	•	
Heterogeneity: Tau <sup>2</sup> =	0.04: CI	ni² = 8.61	df = 5	(P = 0.1)	3); <b> ²</b> = 40					
Test for overall effect:	Z = 7.89	(P < 0.00	0001)		-/1/	•			-2 -1 0 1 2	
Testfor subgroup differences: Chi=0.67, df=1 (P=0.41), I=0% Prophylaxis (Less Flares) No Prophy (M										

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

# Figure 1.3 – Serum Urate < 6 mg/dL

	Prophyl	axis	No Prophy	/laxis		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.11.1 Rilonacept 80	mg vs Pla	cebo					
Schumacher 2012b <b>Subtotal (95% Cl)</b>	53	80 <b>80</b>	27	39 <b>39</b>	19.5% <b>19.5</b> %	0.87 (0.38, 1.99) <b>0.87 (0.38, 1.99)</b>	
Total events	53		27				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.33 (F	<sup>o</sup> = 0.75	)				
1.11.2 Rilonacept 160	) mg vs Pl	acebo					
Schumacher 2012b	62	81	27	40	19.1%	1.57 [0.68, 3.63]	
Sundy 2014	537	823	174	275	40.5%	1.09 [0.82, 1.45]	-
Subtotal (95% CI)		904		315	<b>59.6</b> %	1.13 [0.86, 1.48]	-
Total events	599		201				
Heterogeneity: Tau² =	0.00; Chi <sup>z</sup>	<sup>e</sup> = 0.66,	df = 1 (P =	0.42); I²	= 0%		
Test for overall effect:	Z = 0.90 (F	° = 0.37	)				
1.11.3 Colchicine vs F	Placebo						
Yamanaka 2017	18	95	18	50	20.9%	0.42 [0.19, 0.90]	
Subtotal (95% CI)		95		50	<b>20.9</b> %	0.42 [0.19, 0.90]	
Total events	18		18				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 2.23 (F	P = 0.03	)				
Total (95% CI)		1079		404	<b>100.0</b> %	0.91 [0.57, 1.47]	
Total events	670		246				
Heterogeneity: Tau² =	0.12; Chi <sup>z</sup>	= 6.54	df = 3 (P =				
Test for overall effect:	Z=0.37 (F	° = 0.71	)		Prophylaxis sUA < 6 No Prophylaxis sUA < 6		
Test for subgroup diff	erences: C	>hi² = 5.	88, df = 2 (F				

## Figure 1.4 – Mean Change in Serum Urate

Prophylax		Prophylaxis No Prophylaxis						Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl		
1.12.1 Rilonacept 80	mg vs P	lacebo									
Schumacher 2012b Subtotal (95% CI)	5.7	1.1	80 <b>80</b>	5.5	1.1	39 <b>39</b>	19.4% <b>19.4</b> %	0.20 [-0.22, 0.62] <b>0.20 [-0.22, 0.62]</b>			
Heterogeneity: Not ap	oplicable										
Test for overall effect:	Z = 0.93	(P = 0.35	5)								
1.12.2 Rilonacept 16	0 mg vs l	Placebo									
Schumacher 2012a	3.42	1.4429	38	3.45	1.4964	32	7.2%	-0.03 [-0.72, 0.66]			
Schumacher 2012b	5.4	0.9	81	5.5	1.1	40	22.3%	-0.10 [-0.49, 0.29]	<b>_</b>		
Sundy 2014	2.3	1.8552	823	2.4	1.9621	275	49.3%	-0.10 [-0.36, 0.16]			
Subtotal (95% CI)			942			347	78.8%	-0.09 [-0.30, 0.12]	◆		
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	= 0.00; Cł : Z = 0.88	ni² = 0.04, (P = 0.38	, df = 2 3)	(P = 0.9	98); I² = 0'	%					
1.12.3 Colchicine vs	Placebo										
Borstad 2004	3.14	0	21	3.08	0	22		Not estimable			
Paulus 1974	2.1	1.9596	20	3	2.4298	18	1.7%	-0.90 [-2.31, 0.51]			
Poiley 2016	0	0	53	0	0	54		Not estimable			
Subtotal (95% CI)			94			94	1.7%	-0.90 [-2.31, 0.51]			
Heterogeneity: Not ap	oplicable										
Test for overall effect:	Z=1.25	(P = 0.21	1)								
Total (95% CI)			1116			480	100.0%	-0.05 [-0.24, 0.14]	•		
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Cł	ni² = 2.95,	, df = 4	(P = 0.5)	57); I² = 0'	%		-			
Test for overall effect:	Z = 0.53	(P = 0.59	3)						-2 -1 U I 2 Prophylavis Change in sUA No Prophylavis Change sUA		
Test for subgroup diff	ferences	: Chi <sup>2</sup> = 2.	.91, df:	= 2 (P =	0.23), I <sup>z</sup> :	= 31.39	6		rispinians onlinge in som horrophynaxis offatige som		

# Figure 1.5 – Pain

	Pr	ophylaxis	axis No Prophylaxis					Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl		
1.5.1 Rilonacept 80 m	g vs Pla	icebo									
Mitha 2013	1.7	7.737	82	4.3	7.737	41	7.0%	-2.60 [-5.50, 0.30]			
Schumacher 2012b	0.85	3.8196	80	2.13	0	38		Not estimable			
Subtotal (95% CI)			162			79	7.0%	-2.60 [-5.50, 0.30]			
Heterogeneity: Not app	olicable										
Test for overall effect: 2	Z = 1.76	(P = 0.08	3)								
1.5.2 Rilonacept 160 r	ng vs P	lacebo									
Mitha 2013	0.9	2.7648	84	4.3	7.737	41	9.9%	-3.40 [-5.84, -0.96]			
Schumacher 2012a	0.22	0.79	41	2.02	4.51	42	30.7%	-1.80 [-3.19, -0.41]	<b>_</b>		
Schumacher 2012b	0.35	1.3115	81	2.13	3.2145	38	52.4%	-1.78 [-2.84, -0.72]	_ <b>_</b>		
Subtotal (95% CI)			206			121	<b>93.0</b> %	-1.96 [-2.76, -1.16]	◆		
Heterogeneity: Tau <sup>2</sup> =	0.00; Cł	ni² = 1.50	, df = 2	(P = 0.4)	7); I <sup>2</sup> = 0'	%					
Test for overall effect: 2	Z = 4.82	(P < 0.00	0001)								
Total (95% CI)			368			200	<b>100.0</b> %	-2.00 [-2.77, -1.24]	◆		
Heterogeneity: Tau <sup>2</sup> =	0.00; Cł	ni² = 1.67	, df = 3	(P = 0.6	i4); I <sup>2</sup> = 0 <sup>4</sup>	%		-			
Test for overall effect: 2	Z = 5.11	(P < 0.00	0001)						-4 -2 U Z 4 Pronbylavis (Loss Pain) No Pronby (Mora Pain)		
Test for subgroup diffe	rences	Chi <sup>2</sup> = 0	.17, df=	= 1 (P =	0.68), I <sup>z</sup> :	= 0%			FIOPHYIAXIS (LESS FAIL) INO FIOPHY (MOLE FAIL)		

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

	Prophyl	axis	No Prophy	/laxis		Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl		
1.6.1 Rilonacept 80 r	ng vs Plac	ebo:							
Mitha 2013	79	82	39	41	5.3%	1.35 [0.22, 8.42]			
Subtotal (95% CI)		82		41	5.3%	1.35 [0.22, 8.42]			
Total events	79		39						
Heterogeneity: Not ap	oplicable								
Test for overall effect:	: Z = 0.32 (	P = 0.79	5)						
1.6.2 Rilonacept 160	mg vs Pla	icebo							
Mitha 2013	80	84	39	41	5.9%	1.03 [0.18, 5.84]			
Sundy 2014	904	985	302	330	88.7%	1.03 [0.66, 1.62]			
Subtotal (95% CI)		1069		371	94.7%	1.03 [0.67, 1.60]	•		
Total events	984		341						
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi	<b>²</b> = 0.00	, df = 1 (P =	0.99); l²	'= 0%				
Test for overall effect	: Z = 0.15 (	P = 0.81	B)						
Total (95% CI)		1151		412	100.0%	1.05 [0.69, 1.60]	+		
Total events	1063		380						
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi	<b>z</b> = 0.08	, df = 2 (P =	0.96); P					
Test for overall effect:	Z = 0.22 (	P = 0.82	2)				Adherence with Prophy Adherence without Prophy		
Test for subgroup differences: Chi <sup>2</sup> = 0.08, df = 1 (P = 0.78), i <sup>2</sup> = 0%									

## Figure 1.7 – Patient Adherence; Adherent to Study Drug Injections

	Prophyl	axis	No Prophy	ylaxis		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.7.1 Rilonacept 80 m	ng vs Plac	ebo					
Schumacher 2012b Subtotal (95% Cl)	70	80 <b>80</b>	37	39 <b>39</b>	51.1% <b>51.1</b> %	0.38 [0.08, 1.82] <b>0.38 [0.08, 1.82]</b>	
Total events Heterogeneity: Not ap	70 plicable		37				
l est for overall effect:	Z = 1.21 (ł	P = 0.22	9				
1.7.2 Rilonacept 160	mg vs Pla	cebo					
Schumacher 2012b Subtotal (95% Cl)	78	81 <b>81</b>	37	40 <b>40</b>	48.9% <b>48.9</b> %	2.11 [0.41, 10.95] <b>2.11 [0.41, 10.95]</b>	
Total events Heterogeneity: Not ap	78 plicable		37				
Test for overall effect:	Z = 0.89 (F	P = 0.37	")				
Total (95% CI)		161		79	100.0%	0.88 [0.16, 4.77]	
Total events	148		74				
Heterogeneity: Tau <sup>2</sup> =	0.82; Chi <sup>a</sup>	²= 2.22,	df = 1 (P =	0.14); I <sup>z</sup>	= 55%		
Test for overall effect:	Z = 0.15 (ł	P = 0.88	))	Adherence with Pronby Adherence without Pronby			
Test for subgroup diff	erences: C	Chi <b>²</b> = 2.	19, df = 1 (F	Autorence with rophy. Autorence without rophy			

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

	Prophylaxis No Prophylaxis				xis		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Schumacher 2012a	97.9	5.4	41	92.4	14.5	42	100.0%	5.50 [0.81, 10.19]	
Total (95% CI)			41			42	100.0%	5.50 [0.81, 10.19]	
Heterogeneity: Not ap Test for overall effect: .	plicable Z = 2.30	(P = 0	).02)						-10 -5 0 5 10 More Adherence Less Adherence

## Figure 1.9 – Serious Adverse Events; Diverse Definitions

	Prophya	alxis	No Proph	ylaxis		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.9.1 Rilonacept 80 r	ng vs Plac	ebo					
Mitha 2013	5	82	2	41	9.7%	1.25 [0.25, 6.17]	
Schumacher 2012b	3	80	1	39	5.0%	1.46 [0.16, 13.61]	<b>-</b>
Subtotal (95% CI)		162		80	14.6%	1.32 [0.36, 4.83]	
Total events	8		3				
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi <sup>z</sup>	= 0.01	df = 1 (P =	0.91); l <sup>a</sup>	= 0%		
Test for overall effect	: Z = 0.42 (F	P = 0.68	3)				
4 4 4 5 7							
1.9.2 Rilonacept 160	mg vs Pla	cebo	-				
Mitha 2013	3	84	2	41	8.0%	0.73 [0.13, 4.21]	
Schumacher 2012a	1	41	1	42	3.3%	1.02 [0.07, 15.84]	
Schumacher 2012b	3	81	2	40	8.1%	0.74 [0.13, 4.26]	
Sundy 2014	31	985	13	330	61.0%	0.80 [0.42, 1.51]	
Subtotal (95% CI)		1191		453	80.4%	0.79 [0.46, 1.38]	-
Total events	38		18				
Heterogeneity: Tau*=	= 0.00; Chi <del>*</del>	·= 0.05,	, df = 3 (P =	1.00); P	= 0%		
l est for overall effect	: Z = 0.82 (F	2 = 0.41	)				
1.9.3 Colchicine vs P	Placebo						
Poilev 2016	1	53	3	54	5.0%	0.34 (0.04, 3.16)	
Yamanaka 2017	O	95	0	50		Not estimable	
Subtotal (95% CI)	-	148	-	104	5.0%	0.34 [0.04, 3.16]	
Total events	1		3				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 0.95 (F	P = 0.34	l)				
Total (95% CI)		1501		637	100.0%	0.82 [0.50, 1.35]	
Total events	47		24				
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi <sup>z</sup>	'= 1.19,	df = 6 (P =	0.98); l²	= 0%		
Test for overall effect	: Z = 0.78 (F	P = 0.43	3)				Pronbylaxis SAF No Pronbylaxis SAF
Test for subgroup dif	ferences: C	⊳hi² = 1.	Hophynaxia one Horrophynaxia one				

## Figure 1.10 – Cardiovascular Adverse Events

U	Prophyl	laxis	No Prophj	ylaxis		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.14.1 Rilonacept 80	mg vs Pla	cebo					
Schumacher 2012b Subtotal (95% CI)	0	80 <b>80</b>	0	39 <b>39</b>		Not estimable Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not applic	able					
1.14.2 Rilonacept 16	0 mg vs Pl	acebo					
Schumacher 2012a	0	41	1	42	33.5%	0.33 [0.01, 8.42]	
Schumacher 2012b	1	81	0	40	33.6%	1.51 [0.06, 37.88]	
Subtotal (95% CI)		122		82	67.1%	0.71 [0.07, 6.95]	
Total events	1		1				
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Chi <sup>a</sup>	²= 0.42,	df = 1 (P =	0.52); I²:	= 0%		
Test for overall effect:	Z = 0.29 (ł	P = 0.77	)				
1.14.3 Colchicine vs	Placebo						
Borstad 2004	1	21	0	22	32.9%	3.29 [0.13, 85.44]	
Subtotal (95% CI)		21		22	32.9%	3.29 [0.13, 85.44]	
Total events	1		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.72 (ł	P = 0.47	)				
Total (95% CI)		223		143	<b>100.0</b> %	1.18 [0.18, 7.62]	
Total events	2		1				
Heterogeneity: Tau² =	: 0.00; Chi <sup>a</sup>	² = 0.99,	df = 2 (P =	0.61); I²:	= 0%		
Test for overall effect:	Z = 0.17 (i	P = 0.86	i)				Prophylaxis CAF No Prophylaxis CAF
Test for subgroup diff	ferences: (	Chi <b>²</b> = 0.	57, df = 1 (F	P = 0.45	, I² = 0%		riophynaxia and niorrophynaxia and

## Figure 1.11 – Renal Adverse Events

-	Prophyl	axis	No Prophy	/laxis		Odds Ratio	Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl				
1.17.1 Rilonacept 160	) mg vs Pl	acebo									
Schumacher 2012a Subtotal (95% Cl)	0	41 41	1	42 42	100.0% <b>100.0</b> %	0.33 [0.01, 8.42] <b>0.33 [0.01, 8.42]</b>					
Total events Heterogeneity: Not ap	0 plicable		1								
Test for overall effect:	Z=0.67(F	P = 0.50	)								
Total (95% CI)		41		42	100.0%	0.33 [0.01, 8.42]					
Total events	0		1								
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 0.67 (F	P = 0.50	0				U.UT U.T T 10 100 Prophylaxie Panal AE No Prophylaxie Panal AE				
Test for subgroup diff	erences: N	lot appl	icable				FIOPHYLAXIS REHALAE IND FIOPHYLAXIS REHALAE				

# Figure 1.12 – Drug Hypersensitivity

	Prophyl	Prophylaxis		Prophylaxis		Prophylaxis		ophylaxis 🛛 No Proph		/laxis		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl						
1.16.1 Colchicine vs	No Colchi	cine											
Poiley 2016 Subtotal (95% CI)	1	53 53	0	54 54	100.0% <b>100.0</b> %	3.06 [0.13, 73.37] <b>3.06 [0.13, 73.37]</b>							
Total events Heterogeneity: Not ap Test for overall effect:	1 oplicable : Z = 0.69 (	P = 0.4	0 3)										
Total (95% CI)		53		54	100.0%	3.06 [0.13, 73.37]							
Total events Heterogeneity: Not ap Test for overall effect: Test for subgroup dif	1 oplicable : Z = 0.69 ( ferences: 1	P = 0.4! Not app	0 3) licable				0.01 0.1 1 10 100 Prophylaxis Drug Rxn No Prophylaxis Drug Rxn						

# Prophylaxis vs No Prophylaxis – Observational Data

#### Figure 2.1 – Mean Flares/Patient/Month Prophylaxis No Prophyalxis Mean Difference Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI 2.3.1 Colchicine vs No Prophylaxis 0.26 0.6 152 1.72 1.31 36 54.5% -1.46 [-1.90, -1.02] Yu 2017 Subtotal (95% CI) 36 54.5% -1.46 [-1.90, -1.02] 152 Heterogeneity: Not applicable Test for overall effect: Z = 6.53 (P < 0.00001) 2.3.2 Steroid vs No Prophylaxis Yu 2017 0.71 49 1.72 1.31 36 45.5% -1.01 [-1.52, -0.50] 1 Subtotal (95% CI) 49 36 45.5% 1.01 [-1.52, -0.50] Heterogeneity: Not applicable Test for overall effect: Z = 3.87 (P = 0.0001) Total (95% CI) 201 72 100.0% -1.26 [-1.69, -0.82] Heterogeneity: Tau<sup>2</sup> = 0.04; Chi<sup>2</sup> = 1.71, df = 1 (P = 0.19); l<sup>2</sup> = 42% -0.5 ó 0.5 -1 Test for overall effect: Z = 5.60 (P < 0.00001) Prophylaxis (Flares) No Prophylaxis (Flares) Test for subgroup differences: Chi<sup>2</sup> = 1.71, df = 1 (P = 0.19), l<sup>2</sup> = 41.7%

### Figure 2.2 – Mean Change in SUA

-	Prophylaxis			laxis No Prophylaxis				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
2.13.1 Colchicine vs	Placebo								
Yu 2017 Subtotal (95% CI)	2.87	1.0392	152 <b>152</b>	2.51	0.9813	36 <b>36</b>	58.7% <b>58.7</b> %	0.36 [-0.00, 0.72] <b>0.36 [-0.00, 0.72]</b>	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 1.98	6 (P = 0.0	5)						
2.13.2 Steroid vs Pla Yu 2017 Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect:	cebo 2.52 oplicable Z = 0.04	1.1784 (P = 0.9	49 <b>49</b> 7)	2.51	0.9813	36 <b>36</b>	41.3% 4 <b>1.3</b> %	0.01 [-0.45, 0.47] <b>0.01 [-0.45, 0.47]</b>	
Total (95% CI)			201			72	100.0%	0.22 [-0.12, 0.55]	
Heterogeneity: Tau <sup>2</sup> =	: 0.02; C	hi <sup>z</sup> = 1.38	, df = 1	(P = 0.3	24); I <sup>z</sup> = 2	7%		-	
Test for overall effect:	Z=1.25	5 (P = 0.2	1)				-0.5 -0.25 0 0.25 0.5 Pronhylavis Change in sUA No Pronhylavis Change sUA		
Test for subgroup diff	ferences	: Chi <sup>2</sup> = 1	.38, df	= 1 (P =	riophylaxis onlange in solve not rophylaxis onlange solv				

# Figure 2.3 – Serious Adverse Events; Diverse Definitions

	Prophy	aixis	No Proph	ylaxis		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.9.1 Colchicine vs P	lacebo				100000000000000000000000000000000000000		
Yu 2017 Subtotal (95% CI)	o	152 152	O	36 36	59.4% <b>59.4%</b>	0.00 [-0.04, 0.04] 0.00 [-0.04, 0.04]	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect	Z = 0.00	(P = 1)	.00)				
2.9.2 Steroid vs Place	ebo						
Yu 2017	0	49	0	36	40.6%	0.00 [-0.05, 0.05]	*
Subtotal (95% CI)		49		36	40.6%	0.00 [-0.05, 0.05]	•
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect	Z = 0.00	(P = 1	.00)				
Total (95% CI)		201		72	100.0%	0.00 [-0.03, 0.03]	•
Total events	0		0				
Heterogeneity: Tau <sup>2</sup> =	0.00; Ch	$  ^2 = 0.0$	00, df = 1	P = 1.0	$(0); 1^2 = 0$	8	to de la de d
Test for overall effect	Z = 0.00	(P = 1	.00)				-1 -0.5 0 0.5 1 Pronhulavir SAE No Pronhulavir SAE
Test for subgroup diff	ferences: (	$Chi^2 = 0$	).00, df = )	1 (P = 1)	$(00), 1^2 =$	0%	Propriyaxis SME INO Propriyaxis SME

## Figure 2.4 – Cardiovascular Adverse Events

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.15.1 Colchicine vs	No Colchic	ine					
Solomon 2015 Subtotal (95% Cl)	28	786 <b>786</b>	82	1002 <b>1002</b>	100.0% <b>100.0</b> %	0.41 [0.27, 0.64] <b>0.41 [0.27, 0.64]</b>	
Total events Heterogeneity: Not a Test for overall effect	28 pplicable : Z = 3.93 (F	P < 0.00	82 01)				
Total (95% CI)		786		1002	100.0%	0.41 [0.27, 0.64]	
Total events Heterogeneity: Not a Test for overall effect Test for subgroup dit	28 pplicable :: Z = 3.93 (F fferences: N	° < 0.00 lot appl	82 01) icable				0.2 0.5 1 2 5 Prophylaxis Cardiovas AE No Prophy Cardiovasc AE

# Canakinumab vs Colchicine

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

-				-			
	Canakini	imab	Colchie	cine		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.1.1 Canakinumab	100 mg vs (	Colchici	ne				
Schlesinger 2011	8	54	24	54	43.8%	0.33 [0.16, 0.68]	<b>_</b>
Subtotal (95% CI)		54		54	43.8%	0.33 [0.16, 0.68]	
Total events	8		24				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 3.05 (F	P = 0.002	?)				
3.1.2 Canakinumab	200 mg vs (	Colchici	ne				
Schlesinger 2011	10	54	24	45	56.2%	0.35 [0.19, 0.65]	<b></b>
Subtotal (95% CI)		54		45	56.2%	0.35 [0.19, 0.65]	
Total events	10		24				
Heterogeneity: Not a	pplicable						
Test for overall effect	:: Z = 3.33 (F	P = 0.000	9)				
Total (95% CI)		108		99	100.0%	0.34 [0.21, 0.54]	<b>•</b>
Total events	18		48				
Heterogeneity: Tau <sup>2</sup> :	= 0.00; Chi <sup>z</sup>	= 0.01, (	df = 1 (P :	= 0.93)	; I <b>²</b> = 0%	-	
Test for overall effect	: Z = 4.52 (F	° < 0.000	)01)				U.Z U.O I Z D Canakinumah Elaras Colchicina Elaras
Test for subaroup dit	fferences: C	;hi² = 0.0	1. df = 1	(P = 0.	93), <b>i²</b> = 0	%	Canakinumas nares continume nares

## Figure 3.2 – Serious Adverse Events

	Canakinu	ımab	Colchie	ine		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.3.1 Canakinumab 10	00 mg vs (	Colchici	ne				
Schlesinger 2011 Subtotal (95% Cl)	3	54 54	3	54 54	50.0% <b>50.0</b> %	1.00 [0.21, 4.74] <b>1.00 [0.21, 4.74</b> ]	•
Total events	3		3				
Heterogeneity: Not app	olicable						
Test for overall effect: 2	Z = 0.00 (F	<sup>e</sup> = 1.00)	)				
3.3.2 Canakinumab 20	00 mg vs (	Colchici	ne				
Schlesinger 2011 Subtotal (95% Cl)	3	54 54	3	54 54	50.0% 50.0%	1.00 [0.21, 4.74] 1.00 [0.21, 4.74]	
Total events	3		3		001070	100 [012 1, 11 1]	
Heterogeneity: Not app	olicable						
Test for overall effect: 2	Z = 0.00 (F	<sup>2</sup> = 1.00)	)				
Total (95% CI)		108		108	100.0%	1.00 [0.33, 3.00]	
Total events	6		6				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>z</sup>	= 0.00,	df = 1 (P :	= 1.00);	I² = 0%		
Test for overall effect: 2	Z = 0.00 (F	r = 1.00	)				U.1 U.2 U.5 1 2 5 1U Capakinumah SAE Calabiaina SAE
Test for subgroup diffe	erences: C	hi² = 0.0	00. df = 1	(P = 1.0	00), <b>i²</b> = 0'	%	Canakinumab SAE COICHICINE SAE

# 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</li>
  - 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
  - o 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 ev (१	ent rates ⁄⁄0)		Anticipate eff	ed absolute fects			
№ 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 <sup>a</sup>	not serious	not serious	not serious	none	⊕OOO VERY LOW	22/35 (62.9%)	69/232 (29.7%)	<b>RR 0.47</b> (0.34 to 0.65)	629 per 1,000	<b>333</b> <b>fewer per</b> <b>1,000</b> (415 fewer to 220 fewer)
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## Serum urate\*\* (follow up: mean 3 years; assessed with: Mean change in serum urate)

267 (1 observational study)	serious not s	erious not seriou	s not serious	none		35	232	-	The mean serum urate** was <b>0.21</b> mg/dL	MD <b>1.22</b> mg/dL lower (1.83 lower to 0.61 lower)
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## 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%)	<b>RR 0.47</b> (0.27 to 0.82)	126 per 1,000	<b>67 fewer</b> <b>per 1,000</b> (92 fewer to 23 fewer)
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# 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 <sup>b</sup>	not serious	not serious	not serious	none	⊕OOO VERY LOW	482/2769 (17.4%)	567/2769 (20.5%)	<b>RR 0.39</b> (0.03 to 5.15)	174 per 1,000	<b>106</b> <b>fewer per</b> <b>1,000</b> (169 fewer to 722 more)
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## 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		628/24108 (2.6%)	788/24108 (3.3%)	<b>HR 1.16</b> (0.99 to 1.36)	26 per 1,000	<b>4 more</b> <b>per 1,000</b> (0 fewer to 9 more)
--	----------------	-------------	-------------	-------------	------	--	---------------------	---------------------	-------------------------------	-----------------	---

## Serious adverse events\* (follow up: median 4.5 years; assessed with: Risk of developing CKD 3+)

9520 not (1 seriou observational study)	not serious s	not serious	not serious	none	⊕⊕⊖⊖ Low	623/4760 (13.1%)	579/4760 (12.2%)	<b>HR 0.87</b> (0.77 to 0.98)	131 per 1,000	<b>16 fewer</b> <b>per 1,000</b> (from 28 fewer to 2 fewer)
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## 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

# 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 observationa I studies)	seriou s <sup>a</sup>	not serious	not serious	not serious	none	⊕⊖⊖ O VERY LOW	471/2086 (22.6%)	123/430 (28.6%)	<b>RR 1.25</b> (1.05 to 1.48)	226 per 1,000	<b>56 more</b> <b>per 1,000</b> (11 more to 108 more)
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# Serum Urate\*\* - Febuxostat 40 mg versus Allopurinol 300 mg (follow up: 12 weeks; assessed with: Mean change from baseline)

60 (1 observationa I study)	seriou s <sup>b</sup>	not serious	not serious	serious <sup>c</sup>	none	⊕⊖⊖ ⊖ VERY LOW	30	30	-	The mean serum Urate** was <b>-2.82</b> mg/dL	MD 0.35 mg/dL lower (1 lower to 0.3 higher)
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# Serum Urate\*\* - Febuxostat 80 mg versus Allopurinol 300 mg (follow up: 12 weeks; assessed with: Mean change from baseline)

60 (1 observationa I study)	seriou s <sup>d</sup>	not serious	not serious	not serious	none	⊕⊖⊖ O VERY LOW	30	30	-	The mean serum Urate** was -2.82 mg/dL	MD <b>1.35</b> lower (2 lower to 0.7 lower)
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## Table 2: Evidence profile- Febuxostat compared to allopurinol for patients diagnosed with gout

Certainty assessment	Summary of findings
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# Serum Urate\*\* - Febuxostat 45-55mg (median) vs Allopurinol 150 mg (follow up: 6 months; assessed with: People with SUA <6 mg/dl)

14736 (2 observationa I studies)	not not seriou s	t serious not se	rious not serious	none	⊕⊕⊖O Low	3843/1205 3 (31.9%)	1446/2683 (53.9%)	<b>RR 1.38</b> (1.29 to 1.46)	319 per 1,000	<b>121 more</b> <b>per 1,000</b> (92 more to 147 more)
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Serious adverse Events, Hypersensitivity Reaction\* - Febuxostat 80 mg versus Allopurinol 300 mg (follow up: mean 6 months; assessed with: number of events)

I study) to 3 fewe	60 (1 observati I study	a seriou	not serious	not serious	serious <sup>e</sup>	none	⊕⊖⊖ ⊖ VERY LOW	5/30 (16.7%)	1/30 (3.3%)	<b>RR 0.14</b> (0.02 to 0.82)	167 per 1,000	<b>143 fewer</b> <b>per 1,000</b> (163 fewer to 30 fewer)
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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 observationa I study)	seriou s <sup>f</sup>	not serious	not serious	serious <sup>g</sup>	none	⊕⊖⊖ ⊖ VERY LOW	1/30 (3.3%)	1/30 (3.3%)	<b>RR 0.81</b> (0.10 to 6.27)	33 per 1,000	<b>6 fewer</b> <b>per 1,000</b> (30 fewer to 176 more)
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# 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 observationa l study)	seriou not seriou s <sup>h</sup>	not serious	not serious	none	⊕⊖⊖ ⊖ VERY LOW	148/2056 (7.2%)	14/370 (3.8%)	<b>RR 0.53</b> (0.31 to 0.90)	72 per 1,000	<b>34 fewer</b> <b>per 1,000</b> (50 fewer to 7 fewer)
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		Certa	ainty assess	ment				Summ	ary of fi	ndings	
Pain* - r	not rej	ported									
-	-	-	-	-	-	-	-	-	-	-	-
Tophus*	- not	reported									
-	-	-	-	-	-	-	-	-	-	-	-
Patient g	global	assessme	nt* - not r	eported							
-	-	-	-	-	-	-	-	-	-	-	-
Health R	elated	d Quality o	f Life* - n	ot reporte	ed						
-	-	-	-	-	-	-	-	-	-	-	-
	limita	tion* - not	tranartad	•	•					•	

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

#### ACLIVILY LIMILATION Ποι ιεροιτευ

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

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

		Certa	ainty assess	ment				Summ	ary of fi	ndings	
Nº of						Queroll	Study even	t rates (%)	Deletiv	Anticipate eff	d absolute ects
participant s (studies) Follow-up	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Publicatio n bias	certainty of evidence	With Allopurino I	With Probeneci d	e effect (95% CI)	Risk with Allopurino I	Risk difference with Probeneci d

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 observationa I study)	seriou s <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	⊕⊖⊖ ⊖ VERY LOW	36/147 (24.5%)	3/8 (37.5%)	<b>RR</b> <b>1.53</b> (0.60 to 3.91)	245 per 1,000	<b>130 more</b> <b>per 1,000</b> (98 fewer to 713 more)
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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 observationa I study)	not seriou s	not serious	not serious	not serious	none	⊕⊕⊖⊖ <sub>Low</sub>	1182/2916 6 (4.1%)	203/9722 (2.1%)	<b>RR</b> <b>0.52</b> (0.44 to 0.60)	41 per 1,000	<b>19 fewer</b> <b>per 1,000</b> (23 fewer to 16 fewer)
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## Serious adverse events- Stroke\* (follow up: median 4 months; assessed with: Number of events)

38888 (1 observationa I study)	not seriou s	not serious	not serious	not serious	none		539/29166 (1.8%)	83/9722 (0.9%)	<b>RR</b> <b>0.46</b> (0.37 to 0.58)	18 per 1,000	<b>10 fewer</b> <b>per 1,000</b> (12 fewer to 8 fewer)
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# 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)

# Serious adverse events- New Heart Failure\* (follow up: median 4 months; assessed with: Number of events)

# Serious adverse events- Exacerbation of Heart Failure\* (follow up: median 4 months; assessed with: Number of events)

10484 (1 observationa I study)	not seriou s	not serious	not serious	not serious	none	⊕⊕⊖O Low	2627/7863 (33.4%)	590/2621 (22.5%)	<b>RR</b> <b>0.67</b> (0.62 to 0.73)	334 per 1,000	<b>110 fewer</b> <b>per 1,000</b> (127 fewer to 90 fewer)
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# Table 3: Evidence profile- Probenecid compared to Allopurinol for patients with gout who have indication for ULT

# Serious adverse events- All cause mortality\* (follow up: median 4 months; assessed with: Number of events)

38888 not (1 seriou observationa s I study)	not serious	not serious	not serious	none	⊕⊕⊖⊖ Low	1387/2916 6 (4.8%)	255/9722 (2.6%)	<b>RR</b> <b>0.55</b> (0.48 to 0.63)	48 per 1,000	<b>21 fewer</b> <b>per 1,000</b> (25 fewer to 18 fewer)
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## Gout flares\*\* - not reported

|--|--|--|--|--|

## Tophus\* - not reported

											1
-	-	-	-	-	-	-	-	-	-	-	-

## Patient global assessment\* - not reported

Health related quality of life* - 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



### Comparison 1: ULT vs no ULT

	ULT		No U	LT		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	d, 95% CI	
Shoji 2004	69	232	22	35	100.0%	0.47 [0.34, 0.65]		-		
Total (95% CI)		232		35	100.0%	0.47 [0.34, 0.65]		-		
Total events	69		22							
Heterogeneity: Not ap	plicable						0'2	0'5	1 1	ł
Test for overall effect	Z = 4.55	5 (P < 0)	0.00001)				0.2	Favours ULT	Favours No UL	r

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

		ULT		B	No ULT			Mean Difference	Mean Differ	ence
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 9	5% CI
Shoji 2004	-1.01	2.199	232	0.21	1.643	35	100.0%	-1.22 [-1.83, -0.61]		
Total (95% CI)			232			35	100.0%	-1.22 [-1.83, -0.61]	-	
Heterogeneity: Not ap Test for overall effect	plicable : Z = 3.9	90 (P <	0.0001	)					-2 -1 0 Favours ULT Fav	1 2 ours No ULT

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



### 1.4 Serious adverse events- cardiovascular events- 6 years



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

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
Vargas-Santos 2018	-0.1393	0.0623	100.0%	0.87 [0.77, 0.98]	
Total (95% CI)			100.0%	0.87 [0.77, 0.98]	•
Heterogeneity: Not ap Test for overall effect:	plicable Z = 2.24 (P = 0.03)			<u> 1</u>	0.5 0.7 1 1.5 2 Favours ULT Favours no ULT

### 1.6 Serious adverse events: Risk of CKD3+

### **Comparison 2: Febuxostat versus allopurinol**

	Febuxostat Allopurinol					Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Foody 2017	103	370	465	2056	95.1%	1.23 [1.03, 1.48]	-
Zhou 2016	20	60	6	30	4.9%	1.67 [0.75, 3.71]	
Total (95% CI)		430		2086	100.0%	1.25 [1.05, 1.49]	+
Total events	123		471				
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Ch	$i^2 = 0.5$	52, df =	1 (P = 0)	).47); l <sup>2</sup> =	= 0% -	
Test for overall effect	Z = 2.45	(P = 0	.01)				Favours Febuxostat Favours Allopurinol

### 2.1 Patients with gout flares up to 8 months



2.2 Serum urate- mean change up to 12 weeks

	Febuxo	stat	at Allopurinol			Risk Ratio	Risk Ratio		
Study or Subgroup	<b>Events Total</b>		Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Hatoum 2014	316	752	2934	10119	47.6%	1.45 [1.33, 1.58]	1		
Singh 2015	1130	1931	909	1934	52.4%	1.25 [1.17, 1.32]			
Total (95% CI)		2683		12053	100.0%	1.34 [1.15, 1.55]	+		
Total events	1446		3843				2012/04		
Heterogeneity: Tau <sup>2</sup> =	= 0.01; Cł	$ni^2 = 7.6$	52, df =	1 (P = 0	.006); 12	- 87%			
Test for overall effect	Z = 3.84	(P = 0)	.0001)				Favours Allopurinol Favours Febuxostat		

2.3 Serum Urate < 6 mg/dl at 6 months



2.4 Serious Adverse Events Hypersensitivity reactions - Febuxostat versus Allopurinol.

	Febuxo	stat	Allopu	rinol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.6.1 Febuxostat 40							Service and a service of the service
Zhou 2016 Subtotal (95% CI)	1	30 30	0	15 15	42.5% 42.5%	1.55 [0.07, 35.89] 1.55 [0.07, 35.89]	
Fotal events	1		0				
Heterogeneity: Not app	plicable						
Test for overall effect:	Z = 0.27	(P = 0	.79)				
1.6.2 Febuxostat 80							272
Zhou 2016	1	30	1	15	57.5%	0.50 [0.03, 7.45]	
Subtotal (95% CI)		30		15	57.5%	0.50 [0.03, 7.45]	
Fotal events	1		1				
Heterogeneity: Not app	plicable						
Fest for overall effect:	Z = 0.50	(P = 0)	.62)				
Total (95% CI)		60		30	100.0%	0.81 [0.10, 6.27]	
Total events	2		1				N. 10
Heterogeneity: Tau <sup>4</sup> =	0.00; CP	$n^{2} = 0.1$	29. df =	1 (P = 0)	0.59); l <sup>2</sup> =	= 0%	the star is the star
Test for overall effect:	Z = 0.20	(P = 0	.84)				0.05 0.2 1 5 20
Test for subgroup diffe	erences:	$Chi^2 = 0$	.29. df :	= 1 (P =	0.59), P	i = 0%	Favours repuxosat Favours Allopunnoi

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

	Febuxo	stat	Allopu	rinol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Foody 2017	14	370	148	2056	100.0%	0.53 [0.31, 0.90]	
Total (95% CI)		370		2056	100.0%	0.53 [0.31, 0.90]	-
Total events	14		148				50 AT 50 50
Heterogeneity: Not ap	plicable					÷	
Test for overall effect	Z = 2.35	(P = 0	.02)				Favours Febuxostat Favours Allopurinol

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

### Comparison 3: Probenecid vs Allopurinol

	Probenecid		d Allopurinol			Risk Ratio			Ris	k Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI			IV, Ran	dom, 95% CI		
Sarawate 2006	3	8	36	147	100.0%	1.53 [0.60, 3.91]			12			
Total (95% CI)		8		147	100.0%	1.53 [0.60, 3.91]			-		-	
Total events	3		36							201		
Heterogeneity: Not ap	plicable						61	0,2	015	+ +	1	10
Test for overall effect	Z = 0.89	(P = 0)	.37)				0.1	Favou	irs Allopurin	ol Favours Pro	benecid	10

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.

	Proben	ecid	Allopurinol			Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Rando	m, 95% CI	
Kim2018	203	9722	1182	29166	100.0%	0.52 [0.44, 0.60]	87 <mark>-0</mark> 76		
Total (95% CI)		9722		29166	100.0%	0.52 [0.44, 0.60]	•		
Total events	203		1182						
Heterogeneity: Not ap	plicable					2	0,3 0,8	1 1 1	
Test for overall effect	Z = 8.83	8 (P < 0	.00001)				Favours Probenecid	Favours Allopurinol	

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.

	Proben	ecid	Allopu	rinol		Risk Ratio	Risk Ratio				
Study or Subgroup	Events Total		Events	Total	Weight	IV, Random, 95% CI	IV,	Random, 95% Cl	l		
Kim2018	83	9722	539	29166	100.0%	0.46 [0.37, 0.58]					
Total (95% CI)		9722		29166	100.0%	0.46 [0.37, 0.58]	+	4			
Total events	83		539								
Heterogeneity: Not ap	plicable						02 05		t t		
Test for overall effect	Z = 6.58	8 (P < 0	.00001)				Favours Prob	enecid Favours Å	llopurinol		

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

	Proben	ecid	Allopurinol			Risk Ratio		Risk Ratio				
Study or Subgroup	<b>Events Total</b>		Events	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% CI			
Kim2018	213	9722	1033	29166	100.0%	0.62 [0.53, 0.72]						
Total (95% CI)		9722		29166	100.0%	0.62 [0.53, 0.72]		+				
Total events	213		1033									
Heterogeneity: Not ap	plicable						12	0 5	1 1	<u> </u>		
Test for overall effect	Z = 6.48	5 (P < 0	.00001)				0.2	Favours Probenecid	Favours Allopur	inol		

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

	Proben	ecid	Allopurinol			<b>Risk Ratio</b>	Risk Ratio				
Study or Subgroup	<b>Events Total</b>		Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI				
Kim2018	289	7101	1421	21303	100.0%	0.61 [0.54, 0.69]					
Total (95% CI)		7101		21303	100.0%	0.61 [0.54, 0.69]	•				
Total events	289		1421								
Heterogeneity: Not ap Test for overall effect	plicable Z = 7.84	I (P < 0	.00001)				0.2 0.5 Favours Probenecid	1 2 5 Favours Allopurinol			

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

	Proben	ecid	Allopurinol			Risk Ratio		Risk	Ratio	
Study or Subgroup	<b>Events Total</b>		Events	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% Cl	
Kim2018	590	2621	2627	7863	100.0%	0.67 [0.62, 0.73]	1			
Total (95% CI)		2621		7863	100.0%	0.67 [0.62, 0.73]		٠		
Total events	590		2627							
Heterogeneity: Not ap	plicable						22	0 5	1	
Test for overall effect:	Z = 9.98	8 (P < 0	.00001)				0.2	Favours Probenecid	Favours Allopurinol	3

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

	Proben	Allopu	rinol		Risk Ratio	Risk Ratio				
Study or Subgroup	Events Total		Events	Total	Weight	IV, Random, 95% CI	IV, Rando	m, 95% Cl		
Kim2018	255	9722	1387	29166	100.0%	0.55 [0.48, 0.63]				
Total (95% Cl)		9722		29166	100.0%	0.55 [0.48, 0.63]	•			
Total events	255		1387				0.565			
Heterogeneity: Not ap	plicable					8	0/2 0/5	1 1		
Test for overall effect	Z = 8.86	5 (P < 0)	.00001)				Favours Probenecid	Favours Allopurinol		

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

		Certa	ainty assess	Summary of findings								
							Study even	t rates (%)		Anticipated absolute effects		
№ of participant s (studies) Follow-up	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Publicatio n bias	Overall certainty of evidence	With HLA- B*5801 not be tested and allopurino I be started in all patients	With HLA- B*5801 be tested and allopurino I be avoided if positive	Relativ e effect (95% CI)	Risk with HLA- B*5801 not be tested and allopurino I be started in all patients	Risk difference with HLA- B*5801 be tested and allopurino I be avoided if positive	

# Severe adverse events\*\* (follow up: mean 2 months; assessed with: Cutaneous reaction)

# Gout flares\* - not reported

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

Pain\* - not reported

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

## Tophus\* - not reported

-	-	-	-	-	_	-	-	-	-	-	-
											(

## Table 1: Evidence profile

Certainty assessment
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Summary of findings

# Patient global assessment\* - not reported

-	-	-	-	-	-	-	-	-	-	-	-		
Health re	Health related quality of life* - not reported												

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

## Activity limitation\* - not reported

|--|

## Serum urate\* - not reported

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# 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
 <u>Outcome importance</u>
 \*\* Critical outcomes
 \* Important outcomes

### **Risk of bias assessment**

Study	Confounding	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
Ko 2015					edinate resources	Contraction of the second second	Andrea and Andrea	an a fandan e	

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

	Experim	ental	Cont	rol		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI				
Ko 2015	0	2173	7	2173	100.0%	0.07 [0.00, 1.17]					
Total (95% CI)		2173		2173	100.0%	0.07 [0.00, 1.17]					
Total events	0		7								
Heterogeneity: Not ap Test for overall effect:	oplicable Z = 1.85 (F	P = 0.06	)				0.02 0.1 1 10 50 Favours testing Favours not testing				
#### 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.

The evidence shows:

- Patients who receive dose titration based on serum urate levels
  - o 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
  - o 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

		Cert	ainty assess	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 <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none		50/93 (53.8%)	44/90 (48.9%)	<b>RR 0.91</b> (0.69 to 1.21)	538 per 1,000	<b>48 fewer</b> <b>per 1,000</b> (167 fewer to 113 more)
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Gout flares\* (follow up: mean 12 months; assessed with: proportion of participants with at least 1 gout flare)

$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	<b>47 fewer</b> <b>per 1,000</b> (172 fewer to 112 more)
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Gout flares\* (follow up: 12 months; assessed with: mean number of gout flares per patient)

		Cert	ainty assess	Summary of findings							
517 (1 RCT)	serious ª	not serious	not serious	serious <sup>b</sup>	none	⊕⊕⊖⊖ Low	262	255	_	The mean gout flares** was <b>3.5</b>	MD <b>0.1</b> 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 <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	⊕⊕⊖⊖ Low	262	255	_	The mean gout flares** was <b>2.4</b>	MD <b>0.9</b> <b>lower</b> (4.02 lower to 2.22 higher)
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### 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%)	<b>RR 0.34</b> (0.21 to 0.53)	244 per 1,000	<b>161</b> <b>fewer per</b> <b>1,000</b> (193 fewer to 115 fewer)
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## 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%)	<b>RR 2.82</b> (1.69 to 4.70)	279 per 1,000	<b>508 more</b> <b>per 1,000</b> (192 more to 1,032 more)
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#### **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 <sup>a</sup>	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERATE	78/262 (29.8%)	242/255 (94.9%)	<b>RR 3.19</b> (2.64 to 3.85)	298 per 1,000	652 more per 1,000 (488 more to 848 more)
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### 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 <b>2.04</b>	MD <b>0.11</b> lower (0.2 lower to 0.02 lower)
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#### Tophus\* (follow up: 3 months; assessed with: Mean size in mm)

183 (1 RCT)	serious a	not serious	not serious	serious <sup>b</sup>	none	⊕⊕⊖⊖ Low	93	90	-	The mean tophus* was <b>11.8</b> mm	MD <b>0.9</b> mm lower (3.32 lower to 1.52 higher)
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#### Tophus\* (follow up: 12 months; assessed with: Mean size in mm)

183 (1 RCT)	serious ª	not serious	not serious	serious <sup>b</sup>	none		93	90	-	The mean tophus* was <b>9.7</b> mm	MD <b>1.8</b> <b>mm lower</b> (4.2 lower to 0.6 higher)
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Certainty assessment	Summary of findings
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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 <b>16.54</b> mm	MD <b>9.01</b> mm lower (11.42 lower to 6.6 lower)
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### 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 <b>13.61</b> mm	MD <b>10.32</b> <b>mm lower</b> (12.38 lower to 8.26 lower)
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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 <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	⊕⊕⊖⊖ Low	73	70	-	The mean activity Limitation* was <b>0.51</b>	MD <b>0.11</b> higher (0.14 lower to 0.36 higher)
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Cer	tain	TV I	as	ses	sm	ent

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 <b>53.62</b>	MD <b>16.08</b> <b>lower</b> (20.56 lower to 11.6 lower)
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## 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 <b>33.61</b>	MD <b>12.68</b> <b>lower</b> (15.76 lower to 9.6 lower)
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### 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%)	<b>RR 1.71</b> (1.53 to 1.91)	561 per 1,000	<b>398 more</b> <b>per 1,000</b> (297 more to 511 more)
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### 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)

more)
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### Serious adverse events\* (assessed with: death longest follow-up)

700 (2 RCTs)	serious ª	serious <sup>c</sup>	not serious	serious <sup>c</sup>	none	⊕OOO VERY LOW	13/355 (3.7%)	7/345 (2.0%)	<b>RR 0.56</b> (0.14 to 2.17)	37 per 1,000	<b>16 fewer</b> <b>per 1,000</b> (31 fewer to 43 more)
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## 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 <sup>b</sup>	none		8/93 (8.6%)	11/90 (12.2%)	<b>RR 1.42</b> (0.60 to 3.37)	86 per 1,000	<b>36 more</b> <b>per 1,000</b> (34 fewer to 204 more)
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## Serious adverse events, renal\* (follow up: mean 12 months; assessed with: Proportion of people with worsening kidney function)

183 (1 RCT)	serious not ser	ous not serious	serious <sup>b</sup>	none	⊕⊕⊖O Low	5/93 (5.4%)	2/90 (2.2%)	<b>RR 0.41</b> (0.08 to 2.08)	54 per 1,000	<b>32 fewer</b> <b>per 1,000</b> (49 fewer to 58 more)
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#### 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 <sup>b</sup>	none		0/93 (0.0%)	0/90 (0.0%)	not estimable	0 per 1,000	<b>0 fewer</b> <b>per 1,000</b> (0 fewer to 0 fewer)
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#### Patient Global Assessment\* - not reported

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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

		Certa	ainty assess	ment			Summary of findings					
							Study eve (%	ent rates >)		Anticipat ef	ed absolute fects	
№ 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	

### Table 2: Evidence profile- evidence from Observational studies

### Serum urate\*\* (follow up: range 2.3 years to 3.7 years; assessed with: mean level mg/dL)

120 (1 observational study)	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	⊕OOO 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)
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### Serious adverse events\*\* (follow up: range 2.3-3.7 years; assessed with: proportion with allopurinol reaction)

120 s (1 observational study)	serious ª	not serious	not serious	serious <sup>b</sup>	none	⊕OOO VERY LOW	3/52 (5.8%)	2/68 (2.9%)	<b>RR 0.51</b> (0.09 to 2.94)	58 per 1,000	28 fewer per 1,000 (53 fewer to 112 more)
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### Tophus\* - not reported

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											1
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											1
											1

#### Patient Global Assessment\* - not reported

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

#### Table 2: Evidence profile- evidence from Observational studies

Certa	ainty assessment	

Summary of findings

### Health Related Quality of Life\* - not reported

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### **Activity Limitation\* - not reported**

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#### **Patient Adherence\* - not reported**

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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.

CounfoundiStudyngVazquez J120011	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	LOW
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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.

	Titrated	dose	Fixed d	ose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Stamp L 2017	44	90	50	93	100.0%	0.91 [0.69, 1.21]	
Total (95% CI)		90		93	100.0%	0.91 [0.69, 1.21]	<b>•</b>
Total events	44		50				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.66 (F	P = 0.51	)				0.1 0.2 0.5 1 2 5 10 Favours [titrated dose] Favours [fixed dose]

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.

	Titrated dose Fixed dose					Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
							· ·
Stamp L 2017	49	90	55	93	100.0%	0.92 [0.71, 1.19]	-
Total (95% CI)		90		93	100.0%	0.92 [0.71, 1.19]	◆
Total events Heterogeneity: Not ap Test for overall effect:	49 plicable Z = 0.64 (F	P = 0.52	55				0.1 0.2 0.5 1 2 5 10 Favours [titrated dose]

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

	Tre	at to targ	et	No T	reat to tar	get		Mean Difference	Mean Difference					
Study or Subgroup	Mean	\$D	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI					
Doherty M 2018	3.6	21.8933	255	3.5	29.5928	262	100.0%	0.10 [-4.38, 4.58]						
Total (95% CI)	nlianhla		255			262	100.0%	0.10 [-4.38, 4.58]						
Test for overall effect:	Z = 0.04	+ (P = 0.97	)						-10 -5 0 5 10 Favors treat to target Favors no treat to target					

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

	Tre	at to targe	et	No T	reat to tar	get		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI
Doherty M 2018	1.5	11.3521	255	2.4	23.0166	262	100.0%	-0.90 [-4.02, 2.22]		
<b>Total (95% CI)</b> Heterogeneity: Not applicable Test for overall effect: Z = 0.57 (P = 0.57)			255 )			262	100.0%	-0.90 [-4.02, 2.22]	+ -10	-5 0 5 10 Favors treat to target

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

	Treating to	target	Not treating to	o target		Risk Ratio			Ri	sk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			- M-H, F	ixed, 95% C	1		
Doherty M 2018	21	255	64	262	100.0%	0.34 [0.21, 0.53]		_					
Total (95% CI)		255		262	100.0%	0.34 [0.21, 0.53]		-	-				
Total events	21		64										
Heterogeneity: Not ap Test for overall effect	plicable Z = 4.62 (P	< 0.0000	)1)				0.1	0.2 Favours	0.5 treat to targ	et Favours	no treat t	5 o targe	10

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.

	Titrated of	dose	Fixed d	ose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Doherty M 2018	242	255	69	262	53.1%	3.60 [2.94, 4.42]	
Stamp L 2017	62	90	30	93	46.9%	2.14 [1.54, 2.96]	<b>_</b>
Total (95% CI)		345		355	100.0%	2.82 [1.69, 4.70]	-
Total events	304		99				
Heterogeneity: Tau² = Test for overall effect:	0.12; Chi² Z = 3.97 (F	= 7.11, P < 0.00	df = 1 (P 01)	= 0.008	3); I <b>²</b> = 86°	%	0.1 0.2 0.5 1 2 5 10 Favours [fixed dose] Favours [titrated dose]

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

	Titra	ated dos	е	Fib	ed dose			Mean Difference	Mean Difference
Study or Subgroup	Mean SD Total Mean SD Total						Weight	IV, Random, 95% CI	IV, Random, 95% CI
Doherty M 2018	-3.239	0.123	255	-0.188	0.147	262	51.0%	-3.05 [-3.07, -3.03]	
Stamp L 2017	-1.5	1.8288	90	-0.34	1.8288	93	49.0%	-1.16 [-1.69, -0.63]	-
Total (95% CI)			345			355	100.0%	-2.12 [-3.98, -0.27]	•
Heterogeneity: Tau² =	1.75; Ch	ni² = 48.8	1, df = 1	1 (P ≤ 0.0	)0001); I <sup>2</sup>	'= 98%			
Test for overall effect:	Z= 2.25	(P = 0.02	2)						Favours [titrated dose] Favours [fixed dose]

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

	Titrated dose Fixed dose							Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Stamp L 2017	1.93	0.32	90	2.04	0.31	93	100.0%	-0.11 [-0.20, -0.02]	
<b>Total (95% CI)</b> Heterogeneity: Not ap	plicable	!	90			93	100.0%	-0.11 [-0.20, -0.02]	
Test for overall effect:	Z = 2.36	6 (P = 0	).02)						Favours [titrated dose] Favours [fixed dose]

#### 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.

	Titrated dose Fixed dose							Mean Difference	Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI					
Stamp L 2017	7.9	6.2	90	9.7	9.98	93	100.0%	-1.80 [-4.20, 0.60]						
Total (95% CI)			90			93	100.0%	-1.80 [-4.20, 0.60]						
Heterogeneity: Not ap Test for overall effect:	Z = 1.47	(P = 0	.14)						-10 -5 0 5 10 Favours [titrated dose] Favours [fixed dose]					

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.

	Titrated	dose	Fixed d	ose		Risk Ratio	Risk Ratio						
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI						
Stamp L 2017	11	90	8	93	100.0%	1.42 [0.60, 3.37]							
Total (95% CI)		90		93	100.0%	1.42 [0.60, 3.37]							
Total events	11		8										
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.80 (F	P = 0.43	)				0.1 0.2 0.5 1 2 5 Favours [titrated dose] Favours [fixed dose]	10					

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.

	Titra	ated de	ose	Fixed dose				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Vazquez J 2001	6.56	2.89	68	6.72	5.28	52	100.0%	-0.16 [-1.75, 1.43]	
Total (95% CI)			68			52	100.0%	-0.16 [-1.75, 1.43]	-
Heterogeneity: Not ap Test for overall effect	plicable :: Z = 0.2	20 (P =	0.84)						-10 -5 0 5 10 Favours [titrated dose] Favours [fixed dose]

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

	Titrated	dose	Fixed (	dose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Vazquez J 2001	2	68	3	52	100.0%	0.51 [0.09, 2.94]	
Total (95% CI)		68		52	100.0%	0.51 [0.09, 2.94]	
Total events	2		3				
Heterogeneity: Not ap	plicable						0.01 01 1 10 100
Test for overall effect	Z = 0.75	(P = 0.4)	45)				Favours [titrated] Favours [fixed]

### 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**

		Certa	ainty assess	Summary of findings								
							Study even	t rates (%)		Anticipated absolute effects		
№ of participant s (studies) Follow-up	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Publicatio n bias	Overall certainty of evidence	With not prescribin g ULT to achieve serum urate <6mg/dL	With prescribin g ULT to achieve serum urate <6mg/dL	Relativ e effect (95% CI)	Risk with not prescribin g ULT to achieve serum urate <6mg/dL	Risk difference with prescribin g ULT to achieve serum urate <6mg/dL	

### Gout flares\* (follow up: 12 months; assessed with: mean number per patient)

517 (1 RCT)	seriou s <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	⊕⊕⊖⊖ Low	262	255	-	The mean gout flares** was <b>3.5</b> flares	MD <b>0.1</b> flares higher (4.38 lower to 4.58 higher)
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### Gout flares\* (follow up: range 12 months to 24 months; assessed with: mean number per patient)

517 (1 RCT)	seriou not serious s <sup>a</sup>	not serious	serious <sup>b</sup>	none	⊕⊕⊖O Low	262	255	-	The mean gout flares** was <b>2.4</b>	MD <b>0.9</b> lower (4.02 lower to 2.22 higher)
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### Gout flares\* (follow up: 2 years; assessed with: Patients with 2+ flares)

517 (1 RCT)	seriou s <sup>a</sup>	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	21/255 (8.2%)	64/262 (24.4%)	<b>RR</b> <b>0.34</b> (0.21 to 0.53)	82 per 1,000	<b>54 fewer</b> <b>per 1,000</b> (65 fewer to 39 fewer)
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#### **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 seriou s	not serious	not serious	not serious	none	⊕⊕⊕⊕ нісн	69/262 (26.3%)	242/255 (94.9%)	<b>RR</b> <b>3.60</b> (2.94 to 4.42)	263 per 1,000	<b>685 more</b> <b>per 1,000</b> (511 more to 901 more)
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## Serum urate\*\* (follow up: 24 months; assessed with: proportion of patients achieving mean serum urate <6mg/dL)

517 (1 RCT)	not seriou s	not serious	not serious	not serious	none	⊕⊕⊕⊕ <sub>HIGH</sub>	78/262 (29.8%)	242/255 (94.9%)	<b>RR</b> <b>3.19</b> (2.64 to 3.85)	298 per 1,000	652 more per 1,000 (488 more to 848 more)
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### Tophus\* (follow up: 12 months; assessed with: diameter of largest tophus in mm)

517 (1 RCT)	not seriou s	not serious	not serious	not serious	none	⊕⊕⊕⊕ нісн	262	255	-	The mean tophus* was <b>18.94</b> mm	MD <b>9.01</b> <b>mm lower</b> (11.42 lower to 6.6 lower)
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#### Tophus\* (follow up: 24 months; assessed with: diameter of largest tophus)

517 (1 RCT)	not seriou s	not serious	not serious	not serious	none	⊕⊕⊕⊕ нісн	262	255	_	The mean tophus* was <b>13.61</b> mm	MD <b>10.32</b> <b>mm lower</b> (12.38 lower to 8.26 lower)
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#### **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)	seriou s <sup>a</sup>	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	262	255	-	The mean health Related Quality of Life* was <b>53.62</b>	MD <b>16.08</b> lower (20.56 lower to 11.6 lower)
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## Health Related Quality of Life\* (follow up: 24 months; assessed with: Gout impact scale: unmet gout treatment need score)

517 (1 RCT)	seriou s <sup>a</sup>	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	262	255	-	The mean health Related Quality of Life* was <b>33.71</b>	MD <b>12.68</b> lower (15.76 lower to 9.6 lower)
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#### Patient adherence\* (follow up: 24 months; assessed with: proportion of patients taking ULT)

517 (1 RCT)	seriou s <sup>a</sup>	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	147/262 (56.1%)	245/255 (96.1%)	<b>RR</b> <b>1.71</b> (1.53 to 1.91)	561 per 1,000	<b>398 more</b> <b>per 1,000</b> (297 more to 511 more)
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### Serious adverse events\* (assessed with: death longest follow-up)

517 (1 RCT)	not seriou s	not serious	not serious	serious <sup>b</sup>	none	⊕⊕⊕⊖ MODERAT E	8/262 (3.1%)	2/255 (0.8%)	<b>RR</b> <b>0.26</b> (0.06 to 1.20)	31 per 1,000	<b>23 fewer</b> <b>per 1,000</b> (29 fewer to 6 more)
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#### **Table 1: Evidence profile**

	Certainty assessment Pain* - not reported							Summ	ary of fi	ndings	
Pain* - r	not re	ported									
-	-	-	-	-	-	-	-	-	-	-	-

### Patient Global Assessment\* - not reported

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										, , ,	1

#### Activity Limitation\* - not reported

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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

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?

+

Doherty M 2018

+

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.

	Treat to target			No T	reat to tar	get		Mean Difference		Mean Differen	се	
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 959	% CI	
Doherty M 2018	3.6	21.8933	255	3.5	29.5928	262	100.0%	0.10 [-4.38, 4.58]				
Total (95% CI)			255			262	100.0%	0.10 [-4.38, 4.58]				
Test for overall effect:	Z = 0.04	+ (P = 0.97	)						-10 - Favors ti	5 0 reat to target Favor	5 rs no treat t	10 o target

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.

	Tre	at to targ	et	No Treat to target				Mean Difference		Mean D	ifference		
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI		IV, Rand	om, 95% Cl		
Doherty M 2018	1.5	11.3521	255	2.4	23.0166	262	100.0%	-0.90 [-4.02, 2.22]					
Total (95% CI) Heterogeneity: Not ap	plicable		255			262	100.0%	-0.90 [-4.02, 2.22]	+			<u> </u>	<del></del>
Test for overall effect:	Z = 0.57	' (P = 0.57	)						-10	-5 Favors treat to target	U Favors no t	5 reat to target	10

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.

	Treat to t	arget	No Treat to	target		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Doherty M 2018	242	255	69	262	100.0%	3.60 [2.94, 4.42]	
Total (95% CI)		255		262	100.0%	3.60 [2.94, 4.42]	•
Total events	242		69				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=12.29 (	P < 0.00	1001)				Favors no treat to target Favors treat to target

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.

	Treat to ta	arget	No Treat to	target		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Doherty M 2018	245	255	147	262	100.0%	1.71 [1.53, 1.91]	
Total (95% CI)		255		262	100.0%	1.71 [1.53, 1.91]	•
Total events	245		147				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=9.59 (P	< 0.000	101)				Favors no treat to target Favors treat to target

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
  - o 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
  - o 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
  - o 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 St								Summary of findings				
NO -6						0	Study ev	vent rates %)		Anticipate eff	ed absolute ects		
Nº or 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 <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none	⊕⊕⊖⊖ Low	50/93 (53.8%)	44/90 (48.9%)	<b>RR 0.91</b> (0.69 to 1.21)	538 per 1,000	<b>48 fewer</b> <b>per 1,000</b> (167 fewer to 113 more)
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## 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 <sup>b</sup>	none	⊕⊕⊖⊖ Low	55/93 (59.1%)	49/90 (54.4%)	<b>RR 0.92</b> (0.71 to 1.19)	591 per 1,000	<b>47 fewer</b> <b>per 1,000</b> (172 fewer to 112 more)
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### 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%)	<b>RR 2.14</b> (1.54 to 2.96)	323 per 1,000	<b>368 more</b> <b>per 1,000</b> (174 more to 632 more)
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#### **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 <b>2.04</b>	MD <b>0.11</b> <b>lower</b> (0.2 lower to 0.02 lower)
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#### Tophus\* (follow up: 3 months; assessed with: Mean tophus size in mm)

183 (1 RCT)	serious <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none		93	90	-	The mean tophus* was <b>11.8</b> mm	MD <b>0.9 mm</b> lower (3.32 lower to 1.52 higher)
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#### Tophus\* (follow up: 12 months; assessed with: Mean tophus size in mm)

183 (1 RCT)	serious ª	not serious	not serious	serious <sup>b</sup>	none		93	90	-	The mean tophus* was <b>9.7</b> mm	MD <b>1.8 mm</b> <b>lower</b> (4.2 lower to 0.6 higher)
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## 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 <sup>b</sup>	none		73	70	-	The mean activity Limitation* was <b>0.51</b>	MD <b>0.11</b> higher (0.14 lower to 0.36 higher)
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#### **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 not serious	not serious	serious <sup>b</sup>	none	⊕⊕⊖⊖ Low	25/93 (26.9%)	22/90 (24.4%)	<b>RR 0.91</b> (0.55 to 1.49)	269 per 1,000	<b>24 fewer</b> <b>per 1,000</b> (121 fewer to 132 more)
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# Serious adverse events\* (follow up: 12 months; assessed with: proportion of people with CV events)

183 (1 RCT)	serious	not serious	not serious	serious <sup>b</sup>	none		8/93 (8.6%)	11/90 (12.2%)	<b>RR 1.42</b> (0.60 to 3.37)	86 per 1,000	<b>36 more</b> <b>per 1,000</b> (34 fewer to 204 more)
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## 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 <sup>b</sup>	none		5/93 (5.4%)	2/90 (2.2%)	<b>RR 0.41</b> (0.08 to 2.08)	54 per 1,000	<b>32 fewer</b> <b>per 1,000</b> (49 fewer to 58 more)
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## 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 <sup>b</sup>	none		0/93 (0.0%)	0/90 (0.0%)	not estimable	0 per 1,000	<b>0 fewer</b> <b>per 1,000</b> (0 fewer to 0 fewer)
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#### **Table 1: Evidence profile**

Certainty assessment
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Summary of findings

#### Patient Global Assessment\* - not reported

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#### Health Related Quality of life\* - not reported

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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.

	Titrated	dose	Fixed d	ose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	CI IV, Random, 95% CI
Stamp L 2017	44	90	50	93	100.0%	0.91 [0.69, 1.21]	
Total (95% CI)		90		93	100.0%	0.91 [0.69, 1.21]	ı 🔶
Total events	44		50				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.66 (f	P = 0.51	)				0.1 0.2 0.5 1 2 5 10 Favours [titrated dose] Favours [titrated dose]

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.

	Titrated	Titrated dose Fixed dose				Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	CI IV, Random, 95% CI	
Stamp L 2017	62	90	30	93	100.0%	2.14 [1.54, 2.96]	6]	
Total (95% CI)		90		93	100.0%	2.14 [1.54, 2.96]	6] 🔶	
Total events	62		30					
Heterogeneity: Not ap Test for overall effect:	oplicable Z= 4.57 (F	P < 0.00	001)				0.1 0.2 0.5 1 2 5 10 Favours [Fixed dose] Favours [Titrated dose]	ĵ

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

	Titrated dose Fixed dose				е		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Stamp L 2017	1.93	0.32	90	2.04	0.31	93	100.0%	-0.11 [-0.20, -0.02]	•
Total (95% CI)			90			93	100.0%	-0.11 [-0.20, -0.02]	(
Heterogeneity: Not ap Test for overall effect:	plicable Z = 2.36	: 6 (P = 0	).02)						-10 -5 0 5 10 Favours [titrated dose] Favours [fixed dose]

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

	Titrated dose Fixed dose					е		Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI				
Stamp L 2017	10.9	5.96	90	11.8	10.23	93	100.0%	-0.90 [-3.32, 1.52]					
Total (95% CI)			90			93	100.0%	-0.90 [-3.32, 1.52]					
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.73	) (P = 0	).47)						-10 -5 0 5 10 Favours [titrated dose] Favours [fixed dose]				

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

	Titrated dose Fixed dose					е		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI				
Stamp L 2017	7.9	6.2	90	9.7	9.98	93	100.0%	-1.80 [-4.20, 0.60]				
Total (95% CI)			90			93	100.0%	-1.80 [-4.20, 0.60]				
Heterogeneity: Not ap Test for overall effect:	plicable Z=1.47	(P = 0	1.14)					-	10 -5 0 5 10 Favours [titrated dose] Favours [fixed dose]			

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

	Titra	ated do	ose	Fix	ed dos	ie		Mean Difference		Mei	an Differe	nce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Ra	andom, 95	% CI	
Stamp L 2017	0.62	0.75	70	0.51	0.77	73	100.0%	0.11 [-0.14, 0.36]			-		
Total (95% CI)			70			73	100.0%	0.11 [-0.14, 0.36]			+		
Heterogeneity: Not ap	plicable							n - no construction and construction - or	5	- 5-	-	- 1	-1
Test for overall effect	Z = 0.8	87 (P =	0.39)						-2 Favours	[titrated d	ose] Favo	urs (fixed	dose]

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.

	Titrated	dose	Fixed d	ose		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI				
Stamp L 2017	22	90	25	93	100.0%	0.91 [0.55, 1.49]					
Total (95% CI)		90		93	100.0%	0.91 [0.55, 1.49]	-				
Total events	22		25								
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.38 (F	P = 0.71	)				0.1 0.2 0.5 1 2 5 10 Favours [titrated dose] Favours [fixed dose]				

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
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		Certa	ainty assess	Summary of findings							
NO -6							Study event rates (%)			Anticipated absolute effects	
participant s (studies) Follow-up	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Publicatio n bias	Overall certainty of evidence	With continuin g ULT	With stopping ULT or reducin g	Relativ e effect (95% CI)	Risk with continuin g ULT	Risk differenc e with stopping ULT or reducing

# Gout flares\*\* (follow up: median 27.5 months)

211 (1 observationa I study)	seriou s <sup>a</sup>	not serious	not serious	not serious	none	⊕⊖⊖ ⊖ VERY LOW	NA	82/211 (38.9%)	-	-	-
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# Serum urate\*\* (follow up: median 27.5 months; assessed with: Mean SUA level)

211 (1 observationa	seriou s <sup>a</sup>	not serious	not serious	not serious	none	NA	8.7 mg/dL	-	-	-
T Study)										

# Gout flares\*\* - not reported

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

# Serum urate\*\* - not reported

-	_	-	-	-	_	_	-	-	_	_	-
											1 '

<b>Certainty assessment</b>
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Summary of findings

#### Pain\* - not reported

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#### Tophus\* - not reported

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## Patient global assessment\* - not reported

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#### Health-Related Quality of Life\* - not reported

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#### Activity limitation\* - not reported

|--|

#### Serious adverse events\* - not reported

-	-	-	-	-	-	-	-	-	-	-	-
CT. Confidonco											

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
  - o 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

		Certa	ainty assess	ment				Sumn	nary of f	indings	
							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	serious ª	not serious	serious <sup>b</sup>	not serious	none	0/0	82/211 (38.9%)	-	-	-
study)										

# Serum urate\*\* (follow up: median 27.5 months; assessed with: Mean SUA level)

# Gout flares\*\* - not reported

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

# Serum urate\*\* - not reported

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# Pain\* - not reported

-	-	-	-	-	-	-	_	-	-	-	-

		Cert	ainty assess	ment				Sumn	nary of f	indings	
Tophus*	- not r	eported									
-	-	-	-	-	-	-	-	-	-	-	-
Patient g	lobal a	ssessment*	- not repo	rted							
-	-	-	-	-	-	-	-	-	-	-	-
Health-Re	elated	Quality of Li	ife* - not re	eported							
-	-	-	-	-	-	-	-	-	-	-	-
Activity li	mitatio	on* - not re	ported								
-	-	-	-	-	-	-	-	-	-	-	-
Serious a	dverse	e events* - r	not reporte	d							

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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</li>
- 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

		Certa	ainty assess	ment				Summ	ary of fi	ndings	
				le series de la companya de la comp			Study even	t rates (%)		Anticipate eff	d absolute ects
№ of participant s (studies) Follow-up	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Publicatio n bias	Overall certainty of evidence	With continuin g febuxosta t	With stopping and switching to an alternativ e ULT	Relativ e effect (95% CI)	Risk with continuin g febuxosta t	Risk difference with stopping and switching to an alternativ e ULT

# Serum urate\*\* (follow up: 3 months; assessed with: proportion of patients with SUA< 6 mg/dL)

5387 (1 RCT)	seriou s ª	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	1975/2701 (73.1%)	1863/2686 (69.4%)	<b>RR 0.95</b> (0.92 to 0.98)	731 per 1,000	<b>37 fewer</b> <b>per 1,000</b> (from 58 fewer to 15 fewer)
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# Serum urate\*\* (follow up: 72 months; assessed with: proportion of patients with SUA< 6 mg/dL)

515 (1 RCT)	seriou s <sup>a</sup>	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	199/267 (74.5%)	186/248 (75.0%)	<b>RR 1.01</b> (0.91 to 1.11)	745 per 1,000	<b>7 more</b> <b>per 1,000</b> (from 67 fewer to 82 more)
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# Gout flares\* (follow up: median 8 months; assessed with: Proportion of patients with 1+flares)

2426 (1 observationa I study)	seriou s <sup>b</sup>	not serious	not serious	not serious	none		103/370 (27.8%)	465/2056 (22.6%)	<b>RR 0.81</b> (0.68 to 0.98)	278 per 1,000	<b>53 fewer</b> <b>per 1,000</b> (from 89 fewer to 6 fewer)
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#### **Certainty assessment**

#### Summary of findings

## Gout flares\*\* (follow up: median 32 months; assessed with: Rates of gout flares per patient/year)

E (difference: 0.05 more when continuing febuxostat; meas effect not reported)	(1 RCT) <sup>c</sup>	seriou s ª	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	The rate of gout flares per patient/year was 0.63 in patients the received allopurinol and 0.68 in those who received febuxostat (difference: 0.05 more when continuing febuxostat; measure effect not reported)
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# 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)	seriou s <sup>a</sup>	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERAT E	335/3098 (10.8%)	321/3092 (10.4%)	<b>RR 0.96</b> (0.83 to 1.11)	108 per 1,000	<b>4 fewer</b> <b>per 1,000</b> (from 18 fewer to 12 more)
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## Serious adverse events- Cardiovascular events\*\* (follow up: 8 months; assessed with: Any major CV event)

2426 (1 observationa I study)	seriou s <sup>b</sup>	not serious	not serious	not serious	none	14/370 (3.8%)	148/2056 (7.2%)	<b>RR 1.90</b> (1.11 to 3.25)	38 per 1,000	<b>34 more</b> <b>per 1,000</b> (from 4 more to 85 more)
										/

**Pain\* - not reported** 

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#### **Tophus\* - not reported**

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Certainty assessment	Summary of findings

#### Patient global assessment\* - not reported

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											1

# Health-related quality of life\* - not reported

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											1

# 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

	Switching Events Total		Continuing			Risk Ratio	Risk Ratio		
Study or Subgroup			Events	ivents Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI		
White 2018	1863	2686	1975	2701	100.0%	0.95 [0.92, 0.98]			
Total (95% CI)		2686		2701	100.0%	0.95 [0.92, 0.98]	•		
Total events	1863		1975				22		
Heterogeneity: Not ap	plicable					72.2	0 5 0 7 1 1 5	<del></del>	
Test for overall effect	Z = 3.05	5 (P = 0)	0.002)				Favours switching Favours co	ontinuing	

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

	Switching Events Total		Continuing			<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup			Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
White 2018	186	248	199	267	100.0%	1.01 [0.91, 1.11]	
Total (95% CI)		248		267	100.0%	1.01 [0.91, 1.11]	+
Total events	186		199				20 D D D D D D D D D D D D D D D D D D D
Heterogeneity: Not ap	plicable					3. <del>3</del>	
Test for overall effect	Z = 0.12	P = 0	).90)				Favours switching Favours continuing

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)

	Switch	ing	Contin	uing		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events Total		Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
White 2018	321	3092	335	3098	100.0%	0.96 [0.83, 1.11]	
Total (95% CI)		3092		3098	100.0%	0.96 [0.83, 1.11]	+
Total events	321		335				
Heterogeneity: Not ap	plicable						
Test for overall effect	Z = 0.55	5 (P = 0)	).58)				Favours switching Favours continuing

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

	Switch	ning	Continuing			<b>Risk Ratio</b>				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, F	ixed, 95% CI	
Foody 2017	148	2056	14	370	100.0%	1.90 [1.11, 3.25]				
Total (95% CI)		2056		370	100.0%	1.90 [1.11, 3.25]			-	
Total events	148		14							
Heterogeneity: Not ap	plicable					÷-	0 2	0.5	1 5	1
Test for overall effect:	Z = 2.35	5 (P = 0)	).02)				Fav	ours switchin	ng Favours continui	ing

# 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

		Certa	inty asses	sment			Summary of findings				
							Study even	t rates (%)		Anticipated at	solute effects
№ of participan ts (studies) Follow-up	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Publicati on bias	Overall certaint y of evidenc e	With no desensitizati on	With Allopurinol desensitizati on	Relativ e effect (95% CI)	Risk with no desensitizati on	Risk difference with Allopurinol desensitizati on

# Serious adverse events\*\* (follow up: median 24 months; assessed with: allopurinol desensitization failureunable to tolerate)

28 (1	seriou s <sup>a</sup>	not serious	not serious	not serious	none	⊕⊖⊖	7/28 (25.0%)	-	-	-
observatio nal study)						VERY LOW				

# 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 observatio nal study)	not seriou s	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	⊕⊖⊖ ⊖ VERY LOW	6/10 (60.0%)	4/11 (36.4%)	<b>RR</b> <b>0.38</b> (0.07 to )	600 per 1,000	<b>372 fewer</b> <b>per 1,000</b> (558 fewer to 732 more)
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# Gout flares\*\* - not reported

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# Serum urate\*\* - not reported

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# Pain\* - not reported

|--|--|

		Certa	inty assess	sment				Summa	ary of fi	ndings					
Patient g	global	assessme	nt* - not	reported											
-	-	-	-	-	-	-	-	-	-	-	-				
Health r	lealth related quality of life* - not reported														
-															
Activity	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 interestc. 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

Study	Counfoundin g	Selectio n bias	Bias in classificatio n of intervention s	Bias due to deviation of intended intervention s- objective outcomes	Bias due to deviation of intended intervention s- subjective outcomes	Bias due to outcome measuremen t- objective outcomes	Bias due to outcome measuremen t- subjective outcomes	Bias due to missin g data	Bias in selectio n of reporte d result
Soares 2015									

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

	Slow pro	otocol	Fast pro	tocol		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI
Soares 2015	4	11	6	10	100.0%	0.38 [0.07, 2.22]		
Total (95% CI)		11		10	100.0%	0.38 [0.07, 2.22]		
Total events	4		6					
Heterogeneity: Not ap	plicable							
Test for overall effect	Z = 1.07	(P = 0.2	28)				Favours slow protocol	Favours fast protocol

# 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)</li>
  - 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)</li>
  - 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

		Certa	ainty assess	ment				Summ	ary of fi	ndings	
							Study ev (१	ent rates %)		Anticipate effe	d absolute ects
№ 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 <sup>b</sup>	not serious	none	⊕OOO VERY LOW	-/1278	-/445	OR 1.403 (1.166 to 1.687)	0 per 1,000	<b>0 fewer</b> <b>per 1,000</b> (from 0 fewer to 0 fewer)
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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 <sup>b</sup>	not serious	none		1278	445	-	The mean serum urate** was <b>-0.36</b> mg/dL	MD <b>1.4</b> mg/dL higher (1.18 higher to 1.62 higher)
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Serum urate\*\* (follow up: mean 40 months; assessed with: proportion achieving SUA<5 mg/dL)

1723 (1 observational study)	serious not serious	serious <sup>b</sup>	not serious	none		-/1278	-/445	OR 1.83 (1.51 to 2.21)	0 per 1,000	<b>0 fewer</b> <b>per 1,000</b> (from 0 fewer to 0 fewer)
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		Certa	ainty assess		Summary of findings						
Gout flare	2S** -	not reported									
-	-	-	-	-	-	-	-	-	-	-	-
Pain* - no	ot repo	rted	I			1					11
-	-	-	-	-	-	-	-	-	-	-	-
Tophus*	- not re	eported									
-	-	-	-	-	-	-	-	-	-	-	-
Patient gl	obal as	ssessment*	- not report	ted							
-	-	-	-	-	-	-	-	-	-	-	-
Health-Re	elated (	Quality of Lif	e* - not re	ported							
-	-	-	-	-	-	-	-	-	-	-	-
Activity li	mitatio	n* - not rep	orted								
-	-	-	-	-	-	-	-	-	-	-	-
Serious a	dverse	effects* - n	ot reported								

ious auverse effects i not reporteu

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_	_	_	_	_	-	-	-		_	_	_

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

#### **Explanations**

a. The study has a moderate risk of biasb. The study does not compare the exact options of interest, the relative effects may be different

Outcome importance:

\*\* Critical outcomes

\* Important outcomes

Risk of bi	Risk of bias assessment:													
			Bias in classification of	Bias due to deviation of intended interventions-	Bias due to deviation of intended interventions- subjective	Bias due to outcome measurement- objective	Bias due to outcome measurement- subjective	Bias due to	Bias in selection of reported					
Study	Counfounding	Selection bias	interventions	objective outcomes	outcomes	outcomes	outcomes	missing data	result					
Altan PICO 24	4													

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.

	Adding or changing			Not changing				Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI					
Altan et al 2015	-1.76	2.16	445	-0.36	1.67	1278	100.0%	-1.40 [-1.62, -1.18]					
Total (95% CI)			445			1278	100.0%	-1.40 [-1.62, -1.18]		٠			
Heterogeneity: Not ap Test for overall effect:	plicable Z = 12.4	4 (P < 0.	00001)						-4 Favour:	-2 adding or char	o gin Favours	2 not changin	4

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).



# 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)</li>
  - 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)</li>
  - 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)</li>
  - 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

		Certa	ainty assess	Summary of findings							
№ of participants (studies) Follow-up							Study event rates (%)			Anticipat ef	ed absolute fects
	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)

observational study) 0.28) (317 fev 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) <sup>b</sup>	serious c	not serious	serious <sup>a</sup>	not serious	none	⊕OOO VERY LOW	b	-/211 <sup>b</sup>	<b>HR 1.003</b> (1.001 to 1.005)	0 per 1,000 <sup>b</sup>	per 1,000 ( to)
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**Certainty assessment** 

## 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 <sup>a</sup>	not serious	none		488	630	-	The mean exposure: 24 hour urinary acid levels at baseline in patients with lithiasis was <b>630</b> mg/day	MD <b>142</b> mg/day higher (44.37 higher to 239.63 higher)
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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?

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

### 31: Should Topical ice as adjuvant therapy vs. no ice as adjuvant therapy be used in patients experiencing a gout flare initiating antiinflammatory 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

		Certa	ainty assess	ment				Sum	mary of fi	ndings	
							Study ev (१	ent rates ⁄⁄0)		Anticipat ef	ed absolute fects
№ 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 <sup>a</sup>	not serious	not serious	serious <sup>b</sup>	none		9	10	-	The mean pain** was <b>4.74</b> cm	MD <b>3.94</b> <b>cm lower</b> (6.14 lower to 1.74 lower)
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## Pain\*\* (follow up: 1 weeks; assessed with: Reduction in visual analogue scale scores)

19 (1 RCT)	serious ª	not serious	not serious	serious <sup>b</sup>	none		9	10	-	The mean pain** was - <b>4.42</b> cm	MD <b>3.33</b> cm lower (5.84 lower to 0.82 lower)
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## Joint swelling\* (follow up: 1 weeks; assessed with: Reduction in joint circumference in cm)

19 (1 RCT)	serious ª	not serious	not serious	serious <sup>b</sup>	none		9	10	-	The mean joint swelling* was - <b>3.83</b> cm	MD <b>2.07</b> <b>cm lower</b> (5.7 lower to 1.56 higher)
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#### **Certainty assessment**

Summary of findings

# Serious adverse events\*\* (follow up: 1 weeks; assessed with: Proportion with serious adverse events)

### **Patient Global Assessment - not reported**

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### 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.

		lce		N	lo ice			Mean Difference		Mean Di	fference	
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI		IV, Rando	om, 95% Cl	
Schlesinger N 2002	0.8	1.16	10	4.74	3.19	9	100.0%	-3.94 [-6.14, -1.74]				
<b>Total (95% CI)</b> Heterogeneity: Not app Test for overall effect: 2	olicable Z = 3.50	(P = 0	<b>10</b> .0005)			9	100.0%	-3.94 [-6.14, -1.74]	<del> </del> -10	-5 Favours [lce]	0 5 Favours [No	10 10 D ice]

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

		lce		N	lo ice			Mean Difference		Mean Di	fference	
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% Cl	
Schlesinger N 2002	-7.75	2.58	10	-4.42	2.96	9	100.0%	-3.33 [-5.84, -0.82]				
Total (95% CI)			10			9	100.0%	-3.33 [-5.84, -0.82]				
Heterogeneity: Not app Test for overall effect: 2	olicable Z = 2.60	(P = 0	.009)						-10	-5 Favours [lce]	D 5 Favours (No i	10 ice]

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

		Ice		N	lo ice			Mean Difference		Mean	Differen	се	
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI		IV, Ran	dom, 95	% CI	
Schlesinger N 2002	-5.9	3.84	10	-3.83	4.19	9	100.0%	-2.07 [-5.70, 1.56]			+		
Total (95% CI)	liaabla		10			9	100.0%	-2.07 [-5.70, 1.56]					
Test for overall effect: 2	Z = 1.12	(P = 0	.26)						-1'0	-5 Favours (Ic	Ó e] Favor	5 urs (No ice)	1'0

# 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 antiinflammatory 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

		Certa	ainty assess	ment				Summ	ary of fi	ndings	
							Study eve (%	ent rates o)		Anticipate effe	d absolute ects
Nº of participant s (studies) Follow-up	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Publicatio n bias	Overall certainty of evidence	With best supportiv e analgesic therapy	With IL- 1 inhibitio n	Relativ e effect (95% CI)	Risk with best supportiv e analgesic therapy	Risk differenc e with IL- 1 inhibition

## Pain reduction\*\* (follow up: mean 3 days; assessed with: 100-mm VAS)

83 (1 RCT)	not seriou s	not serious	serious <sup>a</sup>	not serious	none	⊕⊕⊕⊖ MODERAT E	53	30	-	The mean pain reduction was <b>57.8</b> mm	MD <b>26.8</b> mm higher (13.91 higher to 39.69 higher)
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## Pain reduction\*\* (follow up: mean 7 days; assessed with: 100-mm VAS)

68 (1 RCT)	not seriou s	not serious	serious <sup>a</sup>	not serious	none	⊕⊕⊕⊖ MODERAT E	43	25	-	The mean pain reduction was <b>74.8</b> mm	MD <b>17.9</b> mm higher (6.98 higher to 28.82 higher)
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## Pain\*\* (follow up: mean 2 days; assessed with: Level in the most affected joint using a 100-mm VAS)

454 (2 RCTs)	not seriou s	not serious	serious <sup>a</sup>	not serious	none	⊕⊕⊕⊖ MODERAT E	229	225	-	The mean pain was <b>43</b> mm	MD <b>10.09</b> mm lower (14.79 lower to 5.39 lower)
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#### 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 not seriou s	t serious ser	erious ª	not serious	none	⊕⊕⊕⊖ MODERAT E	229	225	-	The mean pain was <b>15.5</b> mm	MD <b>7.18</b> mm lower (11.63 lower to 2.73 lower)
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# Patient global assessment\* (follow up: range 2 days to 3 days; assessed with: Assessed as good or very/good/excellent)

537 (3 RCTs)	not seriou s	not serious	serious <sup>a</sup>	not serious	none	⊕⊕⊕⊖ MODERAT E	132/285 (46.3%)	161/252 (63.9%)	<b>RR 1.46</b> (1.21 to 1.76)	463 per 1,000	<b>213 more</b> <b>per 1,000</b> (97 more to 352 more)
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# Patient global assessment\* (follow up: mean 7 days; assessed with: Assessed as good or very good/excellent)

537 (3 RCTs)	not seriou s	not serious	serious <sup>a</sup>	not serious	none	⊕⊕⊕⊖ MODERAT E	161/285 (56.5%)	186/252 (73.8%)	<b>RR 1.32</b> (1.16 to 1.49)	565 per 1,000	<b>181 more</b> <b>per 1,000</b> (90 more to 277 more)
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### Joint swelling\* (follow up: range 2 days to 3 days; assessed with: Patients with moderate/severe)

537 (3 RCTs)	not seriou s	not serious	serious <sup>a</sup>	serious <sup>b</sup>	none	⊕⊕⊖⊖ Low	152/285 (53.3%)	125/252 (49.6%)	<b>RR 0.66</b> (0.26 to 1.70)	533 per 1,000	<b>181</b> fewer per <b>1,000</b> (395 fewer to 373 more)
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#### **Certainty assessment**

### Summary of findings

#### Joint swelling\* (follow up: mean 7 days; assessed with: Patients with moderate/severe)

537 (3 RCTs)	not seriou s	not serious	serious <sup>a</sup>	serious <sup>b</sup>	none	⊕⊕⊖⊖ Low	44/285 (15.4%)	25/252 (9.9%)	<b>RR 0.55</b> (0.18 to 1.67)	154 per 1,000	<b>69 fewer</b> <b>per 1,000</b> (127 fewer to 103 more)
											more

#### Joint tenderness\* (follow up: range 2 days to 3 days; assessed with: Patients with moderate/severe)

537 (3 RCTs)	not seriou s	not serious	serious <sup>a</sup>	not serious	none	⊕⊕⊕⊖ MODERAT E	60/285 (21.1%)	21/252 (8.3%)	<b>RR 0.40</b> (0.25 to 0.64)	211 per 1,000	<b>126</b> <b>fewer per</b> <b>1,000</b> (158 fewer to 76 fewer)
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#### Joint tenderness\* (follow up: mean 7 days; assessed with: Patients with moderate/severe)

481 (3 RCTs) <sup>c,d</sup>	not seriou s	not serious	serious <sup>a</sup>	not serious	none	⊕⊕⊕⊖ MODERAT E	33/229 (14.4%) <sup>c,d</sup>	0/252 (0.0%) <sup>c</sup>	<b>OR 2.21</b> (1.50 to 3.25)	144 per 1,000 <sup>c,d</sup>	<b>127 more</b> <b>per 1,000</b> (58 more to 210 more)
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### Serious adverse events\*\* (follow up: mean 24 weeks; assessed with: Researchers definition)

539 (3 RCTs)	not no seriou s	ot serious	not serious <sup>e</sup>	serious <sup>f</sup>	none	⊕⊕⊕⊖ MODERAT E	8/286 (2.8%)	17/253 (6.7%)	<b>RR 2.26</b> (0.98 to 5.18)	28 per 1,000	<b>35 more</b> <b>per 1,000</b> (1 fewer to 117 more)
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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

	Cana	kinun	nab	Triamcino	lone acet	onide		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
So 2010 + Schlesinger 2011	92.7	12.4	25	74.8	32.7	43	100.0%	17.90 [6.98, 28.82]	I
Total (95% Cl)			25			43	100.0%	17.90 [6.98, 28.82]	i
Heterogeneity: Not applicable Test for overall effect: Z = 3.2	L (P = 0	.001)							-100 -50 0 50 100 Favours triamcinolone Favours canakinumab

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

	Canakin	umab	Triamcinolone ace	tonide		Risk Ratio		Ri	sk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Ra	ndom, 95% CI	
Schlesinger 2012 + Hirsch 2014	137	225	102	229	64.8%	1.37 [1.14, 1.63]		1.1	0.00	
So 2010 + Schlesinger 2011	24	27	30	56	35.2%	1.66 [1.26, 2.19]				
Total (95% CI)		252		285	100.0%	1.46 [1.21, 1.76]			+	
Total events	161		132							
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> =	= 1.41, df	= 1 (P =	= 0.24); l <sup>2</sup> = 29%				0.3	0.5		
Test for overall effect: Z = 3.99 (P	< 0.0001	)					Favo	urs triamcinolo	ne Favours cana	ikinumab

## Figure 7: Patient global assessment at 7 days

	Canakin	umab	Triamcinolone ad	cetonide		<b>Risk Ratio</b>		Ris	k Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, F	ixed, 95% CI	
Schlesinger 2012 + Hirsch 2014	161	225	130	229	86.5%	1.26 [1.10, 1.45]				
So 2010 + Schlesinger 2011	25	27	31	56	13.5%	1.67 [1.29, 2.17]				
Total (95% CI)		252		285	100.0%	1.32 [1.16, 1.49]			•	
Total events	186		161							
Heterogeneity: Chi <sup>2</sup> = 3.67, df =	1 (P = 0.06)	i); $l^2 = 7$	3%				0.2	0.5	4 4	ł
Test for overall effect: $Z = 4.32$ (F	< 0.0001	)					Fav	ours triamcinolo	Favours cana	kinumab

## Figure 8: Joint swelling at day 2-3

	Canakin	umab	Triamcinolone ace	tonide		Risk Ratio			Ri	sk Rati	0		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI			M-H, Ra	ndom,	95% CI		
Schlesinger 2012 + Hirsch 2014	122	225	134	229	66.0%	0.93 [0.79, 1.09]				-			
So 2010 + Schlesinger 2011	3	27	18	56	34.0%	0.35 [0.11, 1.07]	-			-			
Total (95% CI)		252		285	100.0%	0.66 [0.26, 1.70]		1			-		
Total events	125		152										
Heterogeneity: Tau <sup>2</sup> = 0.34; Chi <sup>2</sup>	= 3.01, df	= 1 (P =	$= 0.08$ ; $l^2 = 67\%$				-	012	015	+	- 1 -	<u> </u>	10
Test for overall effect: $Z = 0.86$ (P	9 = 0.39)						0.1	Favours	canakinum	ab Fav	ours triar	ncinolone	10

## Figure 9: Joint swelling at day 7

	Canakin	umab	Triamcinolone ace	tonide		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Schlesinger 2012 + Hirsch 2014	25	225	37	229	86.7%	0.69 [0.43, 1.10]	
So 2010 + Schlesinger 2011	0	27	7	56	13.3%	0.14 [0.01, 2.29]	· · · · · · · · · · · · · · · · · · ·
Total (95% CI)		252		285	100.0%	0.55 [0.18, 1.67]	
Total events	25		44				
Heterogeneity: Tau <sup>2</sup> = 0.31; Chi <sup>2</sup>	= 1.29, df	= 1 (P =	0.26); I <sup>2</sup> = 22%				
Test for overall effect: Z = 1.05 (P	e = 0.29)						Favours canakinumab Favours triamcinolone

## Figure 10: Joint tenderness at day 2-3

	Canakin	umab	Triamcinolone ace	tonide		Risk Ratio			Ris	k Ratio	6		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI			M-H, Ran	dom, 9	5% CI		
Schlesinger 2012 + Hirsch 2014	20	225	49	229	94.4%	0.42 [0.26, 0.68]							
So 2010 + Schlesinger 2011	1	27	11	56	5.6%	0.19 [0.03, 1.39]	•			-			
Total (95% CI)		252		285	100.0%	0.40 [0.25, 0.64]							
Total events	21		60										
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> =	= 0.58, df	= 1 (P =	$= 0.45$ ; $l^2 = 0\%$				01	0.2	0.5	+	-		10
Test for overall effect: Z = 3.83 (P	= 0.0001)	)					0.1	Favours	canakinuma	b Favo	urs trian	ncinolone	10

## Figure 11: Joint tenderness at day 7

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Odd IV, Rand	s Ratio om, 95% Cl
Schlesinger 2012 + Hirsch 2014	0.7655	0.1837	98.2%	2.15 [1.50, 3.08]		
So 2010 + Schlesinger 2011	2.2659	1.485	1.8%	9.64 [0.52, 177.05]		
Total (95% CI)			100.0%	2.21 [1.50, 3.25]		•
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup>	= 1.01, df = 1 (P =	0.32); 12	= 1%			1 1 1 1
Test for overall effect: $Z = 4.00$ (F	<i>P</i> < 0.0001)				Favours [experimental	Favours [control]

## Figure 12- Serious adverse events

	Canakin	umab	Triamcinolone acc	etonide		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Schlesinger 2012 + Hirsch 2014	17	225	7	229	93.1%	2.47 [1.05, 5.85]	
So 2010 + Schlesinger 2011	0	28	1	57	6.9%	0.67 [0.03, 15.86]	• • •
Total (95% CI)		253		286	100.0%	2.26 [0.98, 5.18]	
Total events	17		8				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup>	= 0.61, df	= 1 (P =	$= 0.43$ ; $l^2 = 0\%$				
Test for overall effect: Z = 1.92 (P	9 = 0.05)						Favours canakinumab Favours triamcinolone

# 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?

# 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?

# 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?

# 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

		Certa	ainty assess	sment				Summ	ary of fi	ndings	
							Study event	rates (%)		Anticipated effeo	absolute cts
№ of participant s (studies) Follow-up	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Publicatio n bias	Overall certainty of evidence	With switching to an alternative anti- inflammator y agent	With switchin g to or adding IL-1 inhibitio n	Relativ e effect (95% CI)	Risk with switching to an alternative anti- inflammator y agent	Risk differenc e with switchin g to or adding IL-1 inhibition

## Pain reduction\*\* (follow up: mean 3 days; assessed with: 100-mm VAS)

83 (1 RCT)	not seriou s	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	53	30	-	The mean pain reduction was <b>57.8</b> mm	MD <b>26.8</b> mm higher (13.91 higher to 39.69 higher)
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## Pain reduction\*\* (follow up: mean 7 days; assessed with: 100-mm VAS)

68 (1 RCT)	not seriou s	not serious	not serious	not serious	none	⊕⊕⊕⊕ нісн	43	25	_	The mean pain reduction was <b>74.8</b> mm	MD <b>17.9</b> mm higher (6.98 higher to 28.82 higher)
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Certainty assessment

### Pain\*\* (follow up: mean 2 days; assessed with: Level in the most affected joint using a 100-mm VAS)

454 (2 RCTs)	not seriou s	not serious	not serious	not serious	none	⊕⊕⊕⊕ нісн	229	225	-	The mean pain was <b>43</b> mm	MD <b>10.09</b> mm lower (14.79 lower to 5.39 lower)
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### Pain\*\* (follow up: mean 7 days; assessed with: Level in the most affected joint using a 100-mm VAS)

454 (2 RCTs)	not seriou s	not serious	not serious	not serious	none	⊕⊕⊕⊕ нісн	229	225	_	The mean pain was <b>15.5</b> mm	MD <b>7.18</b> mm lower (11.63 lower to 2.73 lower)
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# Patient global assessment\* (follow up: range 2 days to 3 days; assessed with: Assessed as good or very/good/excellent)

537 (3 RCTs)	not seriou s	not serious	not serious	not serious	none	⊕⊕⊕⊕ high	132/285 (46.3%)	161/252 (63.9%)	<b>RR</b> <b>1.46</b> (1.21 to 1.76)	463 per 1,000	<b>213</b> more per <b>1,000</b> (97 more to 352 more)
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#### 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 seriou s	not serious	not serious	not serious	none	⊕⊕⊕⊕ нісн	161/285 (56.5%)	186/252 (73.8%)	<b>RR</b> <b>1.32</b> (1.16 to 1.49)	565 per 1,000	<b>181</b> more per <b>1,000</b> (90 more to 277 more)
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#### Joint swelling\* (follow up: range 2 days to 3 days; assessed with: Patients with moderate/severe)

537 (3 RCTs)	not seriou s	not serious	not serious	serious <sup>a</sup>	none	⊕⊕⊕⊖ MODERAT E	152/285 (53.3%)	125/252 (49.6%)	<b>RR</b> <b>0.66</b> (0.26 to 1.70)	533 per 1,000	<b>181</b> <b>fewer</b> <b>per</b> <b>1,000</b> (395 fewer to 373 more)
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#### Joint swelling\* (follow up: mean 7 days; assessed with: Patients with moderate/severe)

537 (3 RCTs)	not not seriou s	serious	not serious	serious <sup>a</sup>	none	⊕⊕⊕⊖ MODERAT E	44/285 (15.4%)	25/252 (9.9%)	<b>RR</b> <b>0.55</b> (0.18 to 1.67)	154 per 1,000	<b>69 fewer</b> <b>per</b> <b>1,000</b> (127 fewer to 103 more)
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### Joint tenderness\* (follow up: range 2 days to 3 days; assessed with: Patients with moderate/severe)

537 (3 RCTs)	not seriou s	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	60/285 (21.1%)	21/252 (8.3%)	<b>RR</b> <b>0.40</b> (0.25 to 0.64)	211 per 1,000	<b>126</b> <b>fewer</b> <b>per</b> <b>1,000</b> (158 fewer to 76 fewer)
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		Certa	ainty assess	ment		Summary of findings						
Joint tenderness* (follow up: mean 7 days; assessed with: Patients with moderate/severe)												
481 (3 RCTs) ⁵	not seriou s	not serious	not serious	not serious	none	⊕⊕⊕⊕ нісн	33/229 (14.4%) <sup>ь</sup>	-/252 <sup>b</sup>	<b>OR</b> <b>2.21</b> (1.50 to 3.25) <sup>c</sup>	144 per 1,000 <sup>b</sup>	<b>127</b> more per <b>1,000</b> (58 more to 210 more) <sup>c</sup>	

#### Serious adverse events\*\* (follow up: mean 24 weeks; assessed with: Researchers definition)

539 (3 RCTs)	not n seriou s	not serious	not serious	not serious	none	⊕⊕⊕⊕ нісн	8/286 (2.8%)	17/253 (6.7%)	<b>RR</b> <b>2.26</b> (0.98 to 5.18)	28 per 1,000	<b>35 more</b> <b>per</b> <b>1,000</b> (1 fewer to 117 more)
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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

Schlesinger 2012 + Hirsch 2014							
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance blas	Blinding of outcome assessment (detection bias)	incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias

## Figure 2: Pain reduction at 3 days

	Cana	akinun	nab	Triamcino	lone acet	onide		Mean Difference		Mean [	Difference	
Study or Subgroup	Mean SD T		Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI	
So 2010 + Schlesinger 2011	84.6	20.7	30	57.8	39.2	53	100.0%	26.80 [13.91, 39.69]				
Total (95% CI)			30			53	100.0%	26.80 [13.91, 39.69]			+	
Heterogeneity: Not applicable Test for overall effect: $Z = 4.0$	7 (P < 0.	.0001)							-100	-50 Favours triamcinolon	0 50 Favours canakinur	100 nab

#### 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

	Canakinumab		Triamcinolone ace	tonide		Risk Ratio		Ri	sk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Ra	ndom, 95% CI	
Schlesinger 2012 + Hirsch 2014	137	225	102	229	64.8%	1.37 [1.14, 1.63]		1.1		
So 2010 + Schlesinger 2011	24	27	30	56	35.2%	1.66 [1.26, 2.19]				
Total (95% CI)		252		285	100.0%	1.46 [1.21, 1.76]			+	
Total events	161		132							
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> =	= 1.41, df	= 1 (P =	= 0.24); l <sup>2</sup> = 29%				0.2	0.5	+ +	
Test for overall effect: Z = 3.99 (P	< 0.0001	)					Favo	urs triamcinolo	ne Favours can	akinumab

## Figure 7: Patient global assessment at 7 days

	Canakin	umab	Triamcinolone ad	cetonide		<b>Risk Ratio</b>		Ris	k Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, F	ixed, 95% CI	
Schlesinger 2012 + Hirsch 2014	161	225	130	229	86.5%	1.26 [1.10, 1.45]				
So 2010 + Schlesinger 2011	25	27	31	56	13.5%	1.67 [1.29, 2.17]				
Total (95% CI)		252		285	100.0%	1.32 [1.16, 1.49]			•	
Total events	186		161							
Heterogeneity: Chi <sup>2</sup> = 3.67, df =	1 (P = 0.06)	i); $l^2 = 7$	3%				0.2	0.5	4 4	ł
Test for overall effect: $Z = 4.32$ (F	< 0.0001	)					Fav	ours triamcinolo	Favours cana	kinumab

## Figure 8: Joint swelling at day 2-3

	Canakin	umab	Triamcinolone ace	tonide		Risk Ratio			R	sk Rati	0		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI			M-H, Ra	indom,	95% CI		
Schlesinger 2012 + Hirsch 2014	122	225	134	229	66.0%	0.93 [0.79, 1.09]			1.	-			
So 2010 + Schlesinger 2011	3	27	18	56	34.0%	0.35 [0.11, 1.07]	-			-			
Total (95% CI)		252		285	100.0%	0.66 [0.26, 1.70]		1			-		
Total events	125		152										
Heterogeneity: Tau <sup>2</sup> = 0.34; Chi <sup>2</sup>	= 3.01, df	= 1 (P =	$0.08$ ; $l^2 = 67\%$				-	212	015	-	- 1 -	<u> </u>	10
Test for overall effect: $Z = 0.86$ (F	P = 0.39						0.1	Favours	canakinum	ab Fa	/ours triar	> ncinolone	10

## Figure 9: Joint swelling at day 7

	Canakin	umab	Triamcinolone ace	tonide		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Schlesinger 2012 + Hirsch 2014	25	225	37	229	86.7%	0.69 [0.43, 1.10]	
So 2010 + Schlesinger 2011	0	27	7	56	13.3%	0.14 [0.01, 2.29]	· · · · · · · · · · · · · · · · · · ·
Total (95% CI)		252		285	100.0%	0.55 [0.18, 1.67]	
Total events	25		44				
Heterogeneity: Tau <sup>2</sup> = 0.31; Chi <sup>2</sup>	= 1.29, df	= 1 (P =	0.26); I <sup>2</sup> = 22%				
Test for overall effect: Z = 1.05 (P	r = 0.29						Favours canakinumab Favours triamcinolone

## Figure 10: Joint tenderness at day 2-3

	Canakinumab		Triamcinolone acetonide			Risk Ratio		Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI					
Schlesinger 2012 + Hirsch 2014	20	225	49	229	94.4%	0.42 [0.26, 0.68]							
So 2010 + Schlesinger 2011	1	27	11	56	5.6%	0.19 [0.03, 1.39]	•			-			
Total (95% CI)		252		285	100.0%	0.40 [0.25, 0.64]							
Total events	21		60										
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.58, df = 1 (P = 0.45); l <sup>2</sup> = 0%							01	0.2	0.5	+	-	1	10
Test for overall effect: Z = 3.83 (P = 0.0001)							0.1	Favours	canakinuma	b Favo	urs triar	ncinolone	10

## Figure 11: Joint tenderness at day 7

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI					
Schlesinger 2012 + Hirsch 2014	0.7655	0.1837	98.2%	2.15 [1.50, 3.08]						
So 2010 + Schlesinger 2011	2.2659	1.485	1.8%	9.64 [0.52, 177.05]	1		+			
Total (95% CI)			100.0%	2.21 [1.50, 3.25]		•				
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup>	= 1.01, df = 1 (P =		1 1 1	10						
Test for overall effect: $Z = 4.00$ (P	< 0.0001)				Favours [experimenta	I] Favours [control]	10			

## Figure 12- Serious adverse events

	Canakin	umab	Triamcinolone acc	etonide		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Schlesinger 2012 + Hirsch 2014	17	225	7	229	93.1%	2.47 [1.05, 5.85]	
So 2010 + Schlesinger 2011	0	28	1	57	6.9%	0.67 [0.03, 15.86]	· · · · · · · · · · · · · · · · · · ·
Total (95% CI)		253		286	100.0%	2.26 [0.98, 5.18]	
Total events	17		8				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup>	= 0.61, df	= 1 (P =	$= 0.43$ ; $l^2 = 0\%$				
Test for overall effect: $Z = 1.92$ (P	9 = 0.05)						Favours canakinumab Favours triamcinolone

# 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?

# 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?

#### 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
		Certa	inty assess	sment			Summary of findings					
				li de la companya de			Study even	t rates (%)		Anticipate effe	d absolute ects	
№ of participant s (studies) Follow-up	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisio n	Publicatio n bias	Overall certaint y of evidenc e	With no limiting alcohol consumptio n	With limiting alcohol consumptio n	Relativ e effect (95% CI)	Risk with no limiting alcohol consumptio n	Risk difference with limiting alcohol consumptio n	

## Serum urate\*\* (follow up: range 2 weeks to 6 months; assessed with: Mean level)

62 (2 observation al studies)	not not serious seriou s	not serious n	not serious	none	⊕⊕⊖ O Low	33	29	-	The mean serum urate** was <b>8.4</b> mg/dL	MD <b>1.61</b> mg/dL lower (2.62 lower to 0.5 lower)
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## Gout flares\*\* (follow up: range 1 days to 2 days; assessed with: Risk of flares)

724 (2 observation al studies)	seriou s ª	not serious	not serious	not serious	none	⊕⊕⊖ O Low	-/724	-/724	<b>OR</b> <b>0.66</b> (0.48 to 0.92)	Not reported	Not estimable
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## Gout flares\*\* (follow up: mean 6 months; assessed with: Risk of flares)

38 (1 observation al study)	seriou s <sup>a</sup>	not serious	not serious	not serious <sup>b</sup>	none	⊕⊖⊖ ⊖ VERY LOW	20/21 (95.2%)	5/17 (29.4%)	OR 0.02 (0.00 to 0.20)	952 per 1,000	<b>660 fewer</b> <b>per 1,000</b> (890 fewer to 420 fewer)
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		Cert	ainty asses	sment	Summary of findings						
Pain* -	not re	eported									
-	-	-	-	-	-	-	-	-	-	-	-
Tophus	* - no	t reported	d	·	·	·		·	·		
-	-	-	-	-	-	-	-	-	-	-	-
Patient	globa	l assessm	nent* - no	t reporte	d	·		·	·		
-	-	-	-	-	-	-	-	-	-	-	-
Health	relate	d Quality	of Life* -	not repo	rted						
-	-	-	-	-	-	-	-	-	-	-	-
Activity	limita	ation* - n	ot reporte	ed	·	·		·	·		
-	-	-	-	-	-	-	-	-	-	-	-
				· •			•	•	1		1

#### **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	s assessmer	nt								
Study	Counfounding	Selection bias	Bias in classification of interventions	Bias due to deviation of intended interventions- objective outcomes	Bias due to deviation of n intended interventions- subjective outcomes	Bias due to outcome measurement- objective outcomes	Bias due to outcome measurement- subjective outcomes	Bias due to missing data	Blas in selection of reported result	
Neogi 2014										LOW
Ralston 1988										MODERATE
Zhang 2012										SERIOUS
Gibson 1979										CRITICAL

	Limit	ed alco	ohol	No limited alcohol				Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Ralston 1988	6.01	2.09	17	8.4	2.62	21	34.6%	-2.39 [-3.89, -0.89]		
Gibson 1979	7.3	0.76	12	8.5	1.1	12	65.4%	-1.20 [-1.96, -0.44]		
Total (95% CI)			29			33	100.0%	-1.61 [-2.72, -0.50]	-	
Heterogeneity: Tau <sup>2</sup> =	= 0.34; 0	$Chi^2 = 1$	1.93, df	= 1 (P =	= 0.16);	$ ^2 = 48$	%			
Test for overall effect	Z = 2.8	5 (P =	0.004)						Favours Limited alcohol Favours no Limited alcohol	

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

	Limited al	cohol	No limited a	Icohol		Odds Ratio	Odd	s Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fix	ed, 95% Cl	
Ralston 1988	5	17	20	21	100.0%	0.02 [0.00, 0.20]	·		
Total (95% CI)		17		21	100.0%	0.02 [0.00, 0.20]			
Total events	5		20						
Heterogeneity: Not ap	plicable						0.05 0.2	1	20
Test for overall effect	: Z = 3.35 (P	= 0.00	08)				Favours [experimental]	Favours [control]	20

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 purines, 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

		Cert	ainty assess	Summary of findings							
							Study ev (°	vent rates %)		Anticipat ef	ted absolute ffects
№ 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 <sup>b</sup>	serious <sup>c</sup>	none		15	14	-	The mean serum urate** was - <b>4.54</b> mg/dL	MD <b>0.5</b> mg/dL higher (0.42 lower to 1.42 higher)
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## Gout flares\*\* (follow up: mean 6 months; assessed with: Patients with gout flares)

29 (1 RCT)	serious <sup>a</sup>	not serious	serious <sup>b</sup>	very serious	none	⊕OOO VERY LOW	1/15 (6.7%)	2/14 (14.3%)	<b>RR 2.14</b> (0.22 to 21.10)	67 per 1,000	<b>76 more</b> <b>per 1,000</b> (52 fewer to 1,340 more)
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## 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	<b>OR 0.43</b> (0.34 to 0.53)	Not reported	Not estimable
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## Pain\* - not reported

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		Cert	ainty assess	ment				Sun	nmary of fi	ndings			
Tophus*	- not	reported											
-	-	-	-	-	-	-	-	-	-	-	-		
Patient g	Jobal	assessmen	t* - not re	eported									
-	-	-	-	-	-	-	-	-	-	-	-		
Health related Quality of life* - not reported													
-	-	-	-	-	-	-	-	-	-	-	-		
Activity	Activity limitation* - not reported												
-	-	-	-	-	-	-	-	-	-	-	-		
_		_		_									

#### Serious Adverse Events\* - not reported

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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

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	
Neogi 2014										LOW
Zhang 2012										MODERATE

	Limited	purine in	ntake	e No limited purine intake				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Holland 2014	5.04	1.34	14	4.54	1.18	15	100.0%	0.50 [-0.42, 1.42]	
Total (95% CI) 1		14			15	100.0%	0.50 [-0.42, 1.42]	-	
Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.06	P = 0.29	)					5	-4 -2 0 2 4 Favours limited purine in Favours no limited purine

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

	Limited purine i	ntake	No limited purine	e intake		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	om, 95% Cl		
Holland 2014	2	14	1	15	100.0%	2.14 [0.22, 21.10]					
Total (95% CI)		14		15	100.0%	2.14 [0.22, 21.10]					
Total events	2		1								
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.65 (P = 0.51	)					0.01	0.1 Favours Limited purine intake	1 Favours no Limited	) I purine intake	100

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

		Cert	ainty assess	ment				Sum	mary of fi	ndings	
№ of participants (studies) Follow-up							Study ev (°	vent rates %)		Anticipat ef	ted absolute ffects
№ 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 <sup>b</sup>	none	⊕⊕⊕⊖ MODERATE	67	67	-	The mean serum urate** change was - <b>0.08</b> mg/dL	MD <b>0.12</b> mg/dL higher reduction (0.48 higher to 0.25 lower)
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### Gout Flares\*\* (follow up: mean 6 months; assessed with: Patients with flares)

29 (1 RCT)	serious c	not serious	serious <sup>d</sup>	very serious	none	⊕OOO VERY LOW	1/15 (6.7%)	2/14 (14.3%)	<b>RR 2.14</b> (0.22 to 21.10)	67 per 1,000	<b>76 more</b> <b>per 1,000</b> (52 fewer to 1,340 more)
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## Gout flares\*\* (follow up: mean 3 months; assessed with: Change in frequency)

80 (1 RCT)	not serious	not serious	not serious	serious <sup>b</sup>	none	⊕⊕⊕⊖ MODERATE	40	40	-	The mean gout flares** was - <b>0.74</b>	MD <b>0.24</b> higher (0.26 lower to 0.74 higher)
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#### **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 <sup>b</sup>	none	⊕⊕⊕⊖ MODERATE	40	40	-	The mean pain* was - <b>0.77</b>	MD <b>0.35</b> <b>lower</b> (1.44 lower to 0.75 higher)
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#### Serious adverse events\* (follow up: mean 3 months; assessed with: Patients with SAE)

80 (1 RCT) s	not serious	not serious	not serious	serious <sup>b</sup>	none	⊕⊕⊕⊖ MODERATE	0/40 (0%)	3/40 (7.5%)	<b>RR 7.0</b> (0.37 to 131.28)	0 per 1,000	<b>70 more</b> <b>per 1,000</b> (20 fewer to 170 more)
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#### Tophus\* - not reported

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#### Patient global assessment\* - not reported

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#### Health related quality of life\* - not reported

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#### Activity limitation\* - not reported

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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



	Increase of dairy prote					otein		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	5D	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Dalbeth 2012	-0.34	0.8442	40	-0.08	1.3133	40	56.3%	-0.26 [-0.74, 0.22]	
Holland 2014	0.17	2.69	14	-0.34	1.18	15	5.6%	0.51 [-1.02, 2.04]	13
Yamanaka 2018	0.1	0.8	13	0.1	0.7	12	38.1%	0.00 [-0.59, 0.59]	
Total (95% CI)			67			67	100.0%	-0.12 [-0.48, 0.25]	+
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi2	= 1.13, df	f = 2 (P =	0.57); 12 =	= 0%			21	
Test for overall effect:	Z = 0.64 (	P = 0.53							Favours Increase of dairy protein Favours No increase dairy protein

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

	Increase of dairy p	orotein	No increase dairy	protein		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Holland 2014	2	14	1	15	100.0%	2.14 [0.22, 21.10]	
Total (95% CI)		14		15	100.0%	2.14 [0.22, 21.10]	
Total events	2		1				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.65 (P = 0.51)						0.02 0.1 1 10 50 Favours [experimental] Favours [control]

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

	Increase	of dairy pr	otein	No increase dairy protein				Mean Difference	Mean Difference
Study or Subgroup	Mean	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Dalbeth 2012	-0.5	1.2507	40	-0.7389	1.0284	40	100.0%	0.24 [-0.26, 0.74]	
Total (95% CI) Heterogeneity: Not app Test for overall effect: 2	plicable Z = 0.93 (P	40			40	100.0%	0.24 [-0.26, 0.74]	-1 -0.5 0 0.5 1 Favours increase dairy	

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

	Increase	of dairy p	rotein	No increa	ise dairy pr	otein		Mean Difference			Mean Di	fference		
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Fixed, 95% CI			IV, Fixed	I, 95% CI		
Dalbeth 2012	-1.1134	2.8921	40	-0.7657	2.0281	40	100.0%	-0.35 [-1.44, 0.75]	5]					
Total (95% CI)			40			40	100.0%	-0.35 [-1.44, 0.75]					1	
Heterogeneity: Not ap Test for overall effect:	piicable Z = 0.62 (P	= 0.53)							-2 Fave	ours Increas	l e of dairy protein	) Favours No inc	1 rease dairy protei	2 in

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 25<sup>th</sup> 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

		Certa	ainty assess	ment				Su	mmary of fi	ndings	
Nº of	<b>D</b> . 1	l		l.		Overall	Study ev	vent rates %)	5.1.1	Anticipat efi	ed absolute fects
participants (studies) Follow-up	of bias	Inconsistency	Indirectness	Imprecision	Publication bias	overall certainty of evidence	With any other diet	With DASH diet	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	none	⊕⊕⊖⊖ Low	12	12	-	The mean serum Urate was 6.6 mg/dL	MD <b>1</b> mg/dL lower (1.88 lower to 0.12 lower)
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# Serum Urate\* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA > 7 mg/dL)

8 (1 RCT) °	not serious	not serious	not serious	very serious d	none	⊕⊕⊖⊖ Low	с	8 <sup>c</sup>	-	The mean serum Urate was <b>not</b> reported <sup>c</sup>	MD 1.29 mg/dL lower (2.5 lower to 0.08 lower)
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# Serum Urate\* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA >6 to 7 mg/dL)

21	not	not serious	not serious	very serious	none		е	21 e	_	The mean	MD 0 65
(1 RCT) <sup>e</sup>	serious	not senous	not serious	f,g	none	$\Phi\PhiOO$		21		serum	mg/dL
、 <i>,</i>						LOW				Urate was	higher
										not	(0.43 lower
										reported	to 1.73
										e	higher)

#### **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) <sup>h</sup>	not serious	not serious	not serious	very serious <sub>g,i</sub>	none	⊕⊕⊖⊖ Low	h	17 <sup>h</sup>	-	The mean serum Urate was <b>not</b> reported h	MD <b>0.28</b> mg/dL higher (1.43 lower to 1.99 higher)
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# Serum Urate\* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA > 8 mg/dL)

18 (1 RCT) <sup>j</sup>	not serious	not serious	not serious	very serious <sup>k</sup>	none	⊕⊕⊖⊖ Low	j	18 <sup>j</sup>	-	The mean serum Urate was <b>not</b> reported	MD <b>1.02</b> mg/dL lower (2.37 lower to 0.32 higher)
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## Serum urate\* (follow up: mean 90 days; assessed with: patients with SUA <6mg/dL)

#### Gout Flares\*\* - not reported

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### **Tophus\*** - **not reported**

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**Certainty assessment** 

Summary of findings

#### Health related quality of life\* - not reported

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#### Serious adverse events\* - not reported

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-	-	-	-	-	=	-	-	-	=	-	=

#### Patient Acceptability\* - not reported

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**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

I. 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



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#### 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.

	D	ASH		Cont	trol di	et		Mean Difference	Mean Difference						
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Fixed, 95% CI			IV, Fix	ed, 95%	CI		
Tang 2017	5.6	1.1	12	6.6	1.1	12	100.0%	-1.00 [-1.88, -0.12]							
Total (95% CI)			12			12	100.0%	-1.00 [-1.88, -0.12]			_ ◄				
Heterogeneity: Not applicable Test for overall effect: Z = 2.23 (P = 0.03)								-	-'	0 Favours	-5 DASH die	้ t Favoเ	5 Jrs contr	10 ol diet	-

#### 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

				Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Tang 2017	0.65	0.55	100.0%	0.65 [-0.43, 1.73]	
Total (95% CI)			100.0%	0.65 [-0.43, 1.73]	◆
Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.18 (P = 0.24)				

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



				mean principlice	mean billerence
Study or Subgroup	Mean Difference	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Tang 2017	-1.02	68	100.0%	-1.02 [-134.30, 132.26]	
Total (95% CI)			100.0%	-1.02 [-134.30, 132.26]	
Heterogeneity: Not a Test for overall effect	oplicable : Z = 0.01 (P = 0.99)				-200 -100 0 100 200 Favours DASH diet Favours control diet

#### 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

		Cert	ainty assess		Summary of findings						
NO of							Study event rates (%)			Anticipated absolute effects	
n≌ or participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	overall certainty of evidence	With no weight loss	With Weight Ioss	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 <sup>a</sup>	none	⊕OOO 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)
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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 <sup>b</sup>	not serious	not serious	very serious c	none	⊕OOO VERY LOW	The absolute number of patients with raised SUA decreased 60%.
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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 <sup>c</sup>	none	⊕⊖⊖⊖ VERY LOW	The absolute number of patients with raised SUA decreased 50%
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#### **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)
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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 <sup>b</sup>	serious <sup>e</sup>	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
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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	⊕OOO VERY LOW	In one study, the median number of gout flares decreased from 2.1 to 0.6.
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Pain\* - not reported

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Tophus\* - not reported

Cer	taint	/ ass	essm	ent

Summary of findings

#### Patient global assessment\* - not reported

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											1
											1

## Health related Quality of life\* - not reported

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#### Activity limitation\* - not reported

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#### Serious adverse events\* - not reported

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#### 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



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

		Certa	inty asses	sment				Summa	ary of fi	findings		
NO of							Study even	t rates (%)		Anticipated at	osolute effects	
nº or participa nts (studies) Follow- up	Risk of bias	Inconsiste ncy	Indirectn ess	Imprecisi on	Publicati on bias	Overall certaint y of evidenc e	With no supplementat ion	With Vitamin C supplementat ion	Relati ve effect (95% CI)	Risk with no supplementat ion	Risk difference with Vitamin C supplementat ion	

## Serum urate\*\* (follow up: 6 months; assessed with: Mean change from baseline)

29 (1 RCT)	serio us ª	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	⊕⊖⊖ ⊖ VERY LOW	15	14	-	The mean serum urate change** was -0.34 mg/dL	MD <b>0.51</b> mg/dL higher reduction (1.02 lower to 2.04 higher)
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# Serum urate\*\* (follow up: 2 months; assessed with: Mean change from baseline, mg/dL. Comparison: Vit C vs allopurinol)

40 (1 RCT)	serio us ª	not serious	serious <sup>d</sup>	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.
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## Gout flares\*\* (follow up: mean 6 months; assessed with: patients with gout flares)

29 (1 RCT)	serio us ª	not serious	serious <sup>b</sup>	very serious <sup>c</sup>	none	⊕⊕⊖ ⊖ Low	1/15 (6.7%)	2/14 (14.3%)	<b>RR</b> 2.14 (0.22 to 21.10)	67 per 1,000	<b>76 more per</b> <b>1,000</b> (from 52 fewer to 1,000 more)
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Certai	ntv	asse	ssm	ent

Summary of findings

#### Pain\* - not reported

-	-	-	-	-	-	-	-	-	-	-	-			
Tophus	* - n	ot report	ed											
-	-	-	-	-	-	-	-	-	-	-	-			
Patient	glob	al assess	ment* -	not repo	orted									
-														
Health related quality of life* - not reported														
Activity limitation* - not reported														
-	-	-	-	-	-	-	-	-	-	-	-			
Sariaus			tak nat	roporto	.d	•	•							

#### Serious adverse events\* - not reported

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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



	Vit C			No vit C				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Holland 2014	0.17	2.69	14	-0.34	1.18	15	100.0%	0.51 [-1.02, 2.04]	
Total (95% CI) Heterogeneity: Not ap	plicable	5 (P -	14			15	100.0%	0.51 [-1.02, 2.04]	
rest for overall effect:	z = 0.0	55 (P =	0.51)						Favours vit C Favours no vit C

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

	Vitami	in C	No vitamin C			Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-	H, Random, 95% CI	
Holland 2014	2	14	1	15	100.0%	2.14 [0.22, 21.10]	-		8
Total (95% CI)		14		15	100.0%	2.14 [0.22, 21.10]			
Total events	2		1						
Heterogeneity: Not ap	plicable						0.01 0.1	1 10	100
Test for overall effect	Z = 0.65	6 (P = 0)	0.51)				Favours Vi	tamin C Favours no Vitami	n C

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

		Certa	ainty assess	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)

## Gout flares\*\* (follow up: mean 6 months; assessed with: Patients with flares)

29 so (1 RCT)	serious ª	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	⊕OOO VERY LOW	1/15 (6.7%)	2/14 (14.3%)	<b>RR 2.14</b> (0.22 to 21.10)	67 per 1,000	<b>76 more</b> <b>per 1,000</b> (52 fewer to 1,340 more)
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## Gout flares\*\* (follow up: mean 2 days; assessed with: Patients with flares)

633 (1 se observational study)	not not serious serious	not serious	serious	none		-/633	-/633	<b>OR 0.55</b> (0.30 to 1.01)	Not reported	Not estimable				
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		Certa	ainty assess		Summary of findings									
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Pain* - r	not rep	oorted												
-	-	-	-	-	-	-	-	-	-	-	-			
Tophus*	Tophus* - not reported													
-	-	-	-	-	-	-	-	-	-	-	-			
Patient global assessment* - not reported														
-	-	-	-	-	-	-	-	-	-	-	-			
Health re	elated	quality of	life* - not	reported										
-	-	-	-	-	-	-	-	_	-	-	-			
Activity	limitat	tion* - not	reported											
-														
Serious	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	Blas due to missing data	Bias in selection of reported result	
Zhang 2012	- ALA CALMAN DAVANCES						A CONTRACTOR OF	- 400 C 10 M 200 C 10 C	00.00000	LOW
							2			 MODERATE

	Cherry e	xtract in	take	No cherry	extract in	ntake		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Holland 2014	0.17	2.69	14	-0.34	1.18	15	100.0%	0.51 [-1.02, 2.04]	
Total (95% CI)			14			15	100.0%	0.51 [-1.02, 2.04]	
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.65	(P = 0.5)	1)						-4 -2 0 2 4 Favours cherry extract Favours no cherry extract

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

	Cherry e	xtract	No cherry	extract		Risk Ratio			Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl			M-H, Rand	om, 95% (	CI		
Holland 2014	2	14	1	15	100.0%	2.14 [0.22, 21.10]		-					
Total (95% CI)		14		15	100.0%	2.14 [0.22, 21.10]		_	_				
Total events	2		1										
Heterogeneity: Not ap	plicable						01	0 2	0.5	1 1		Ł	10
Test for overall effect	Z = 0.65	(P = 0.5)	51)				0.1	Favours	cherry extract	Favours r	no cherry	extrac	t

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

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% Cl
Zhang 2012	-0.5978	0.3093	100.0%	0.55 [0.30, 1.01]	
Total (95% CI)			100.0%	0.55 [0.30, 1.01]	
Heterogeneity: Not ap Test for overall effect	oplicable : Z = 1.93 (P = 0.0	5)		8	0.2 0.5 1 2 5 Favours cherry extract Favours no cherry extract

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?

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

# 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?

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

# 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 25<sup>th</sup> 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

		Certa	ainty assess	ment				Su	mmary of fi	ndings	
Nº of	Diele			l.		Overall	Study ev	vent rates %)	Deletion	Anticipat efi	ed absolute fects
participants (studies) Follow-up	of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With any other diet	With DASH diet	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	none	⊕⊕⊖⊖ Low	12	12	_	The mean serum Urate was 6.6 mg/dL	MD <b>1</b> mg/dL lower (1.88 lower to 0.12 lower)
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# Serum Urate\* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA > 7 mg/dL)

8 (1 RCT) °	not serious	not serious	not serious	very serious d	none	⊕⊕⊖⊖ Low	с	8 <sup>c</sup>	-	The mean serum Urate was <b>not</b> reported <sup>c</sup>	MD 1.29 mg/dL lower (2.5 lower to 0.08 lower)
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# Serum Urate\* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA >6 to 7 mg/dL)

Urate was high   not (0.43 lo   reported to 1.7   e high	21 (1 RCT) <sup>e</sup>	not serious	not serious	not serious	very serious	none		e	21 <sup>e</sup>	-	The mean serum Urate was not reported e	MD <b>0.65</b> mg/dL higher (0.43 lowe to 1.73 higher)
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### **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) <sup>h</sup>	not serious	not serious	not serious	very serious <sub>g,i</sub>	none	⊕⊕⊖⊖ Low	h	17 <sup>h</sup>	-	The mean serum Urate was <b>not</b> reported	MD <b>0.28</b> mg/dL higher (1.43 lower to 1.99 higher)
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# Serum Urate\* (follow up: mean 90 days; assessed with: serum urate level in patients with SUA > 8 mg/dL)

18 (1 RCT) <sup>j</sup>	not serious	not serious	not serious	very serious <sup>k</sup>	none	⊕⊕⊖O Low	j	18 <sup>j</sup>	-	The mean serum Urate was <b>not</b> reported	MD <b>1.02</b> mg/dL lower (2.37 lower to 0.32 higher)
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# Serum urate\* (follow up: mean 90 days; assessed with: patients with SUA <6mg/dL)

12 (1 observational study)	serious I	not serious	not serious	serious <sup>m</sup>	none	⊕OOO VERY LOW	0/0	8/12 (66.7%)	-	-	-
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# Gout Flares\*\* - not reported

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# **Tophus\*** - **not reported**

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**Certainty assessment** 

Summary of findings

#### Health related quality of life\* - not reported

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#### 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

I. 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

Tang 2017	
•	Random sequence generation (selection bias)
•	Allocation concealment (selection bias)
•	Blinding of participants and personnel (performance bias)
•	Blinding of outcome assessment (detection bias)
•	Incomplete outcome data (attrition bias)
•	Selective reporting (reporting bias)
•	Other bias

# 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.

	D	ASH		Cont	trol di	et		Mean Difference			Mean	Differen	се		
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Fixed, 95% CI			IV, Fix	ed, 95%	CI		
Tang 2017	5.6	1.1	12	6.6	1.1	12	100.0%	-1.00 [-1.88, -0.12]							
Total (95% CI)			12			12	100.0%	-1.00 [-1.88, -0.12]			_ ◄				
Heterogeneity: Not ap Test for overall effect:	Z = 2.23	) (P=	0.03)					-	-'	0 Favours	-5 DASH die	้ t Favoเ	5 Jrs contr	10 ol diet	-

#### 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

				Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Tang 2017	0.65	0.55	100.0%	0.65 [-0.43, 1.73]	
Total (95% CI)			100.0%	0.65 [-0.43, 1.73]	◆
Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.18 (P = 0.24)				

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



				mean principlice	mean billerence
Study or Subgroup	Mean Difference	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Tang 2017	-1.02	68	100.0%	-1.02 [-134.30, 132.26]	
Total (95% CI)			100.0%	-1.02 [-134.30, 132.26]	
Heterogeneity: Not a Test for overall effect	oplicable : Z = 0.01 (P = 0.99)				-200 -100 0 100 200 Favours DASH diet Favours control diet

### 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

Certainty assessment									Summar	y of finc	lings		
Nº of						Overall	Study ev (१	ent rates ⁄⁄0)	Delative	Antic	ticipated absolute effects		
participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	certainty of evidence	With no weight loss	With weight loss	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 <sup>b</sup>	not serious	serious <sup>c</sup>	serious <sup>d</sup>	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.
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# Gout flares\*\* (follow up: range 4 months to 18 months; assessed with: Gout flares occurrence- Single arm studies)

(5 observational studies) ª	serious <sup>b</sup>	not serious	serious <sup>c</sup>	serious <sup>d</sup>	none	⊕OOO 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.
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# Serum Urate\* (follow up: 32 months; assessed with: Proportion of people with SUA<6 mg/dL- Comparative study)

# 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 <sup>c</sup>	not serious	none	⊕OOO 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.
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# Serum urate\* (assessed with: Changes in serum urate levels (mg/dL)- longest follow up)

(8 observational studies) ª	serious <sup>b</sup>	serious <sup>g</sup>	serious <sup>c</sup>	not serious	none	⊕OOO 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.
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#### Serious adverse events\* (follow up: 18 months; assessed with: Case series)

12 (1 observational	serious <sup>b</sup>	not serious	not serious	serious <sup>h</sup>	none		0/12 (0.0%)	-	-	-
study)										

#### Tophus\* - not reported

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#### Health related quality of life\* - not reported

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#### Patient acceptability\* - not reported

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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

		Certa	ainty assess	Summary of findings							
							Study event rates (%)			Anticipated absolute effects	
№ of participant s (studies) Follow-up	Risk of bias	Inconsistenc y	Indirectnes s	Imprecisio n	Publicatio n bias	Overall certainty of evidence	With no change in medication s	With adding or changin g urate lowering therapy	Relativ e effect (95% CI)	Risk with no change in medication s	Risk differenc e with adding or changing urate lowering therapy

# Gout flares\*\* (follow up: 5 years; assessed with: participants with at least 1 flare)

9795 (1 RCT)	ot not serious	serious	not serious	none	⊕⊕⊕⊖ MODERAT E	151/4900 (3.1%)	81/4895 (1.7%)	<b>RR</b> <b>0.54</b> (0.41 to 0.70)	31 per 1,000	<b>14 fewer</b> <b>per 1,000</b> (18 fewer to 9 fewer)
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# Serum urate\*\*- not reported

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# Serious adverse events\*\* not reported

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

**Tophus\* - not reported** 

		-	-	-	-	-	-	-	-	-	-	-	-
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# Health related quality of life\* - not reported

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Certainty assessment	Summary of findings
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# **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.

	cation	no cha	nge		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Waldman 2018 (1)	81	4895	151	4900	100.0%	0.54 [0.41, 0.70]	
Total (95% CI)		4895		4900	100.0%	0.54 [0.41, 0.70]	◆
Total events	81		151				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=4.56 (P ≺ 0	.00001)					changing or adding meds no change in medication
Footnotes							
(1) SE 0.1362							

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

Certainty assessment						Summary of findings					
№ of participants (studies) Follow-up	Risk	Inconsistency	Indirectness		Publication bias bias evidence	Study eve (%	ent rates	Relative	Anticipate eff	Anticipated absolute effects	
	of bias			Imprecision		of evidence	With No ULT	With ULT	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)

# 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 <b>-0.1</b> mg/dL	MD 2.96 mg/dL higher reduction (2.13 higher to 3.79 higher)
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**Certainty assessment** 

# 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	⊕⊕⊕⊕ нісн	206	167	-	The mean Serum Urate level change** was + <b>0.05</b> mg/dL	MD <b>1.84</b> mg/dL higher reduction (1.13 higher to 2.55 higher)
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### Serum Urate level\*\* (follow up: 108 weeks; assessed with: proportion of patients with SUA $\leq 6$ mg/dl)

441 (1 RCT)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ high	41/222 (18.5%)	212/219 (96.8%)	<b>RR 5.24</b> (3.97 to 6.92)	185 per 1,000	<b>783 more</b> <b>per 1,000</b> (549 more to 1,093 more)
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# Gout flares\*\* (follow up: 3 years; assessed with: proportion with gout flare)

617 (2 RCTs)	not serious	not serious	not serious	not serious <sup>a</sup>	none	⊕⊕⊕⊕ нісн	15/310 (4.8%)	2/307 (0.7%)	<b>RR 0.16</b> (0.04 to 0.62)	48 per 1,000	<b>41 fewer</b> <b>per 1,000</b> (46 fewer to 18 fewer)
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#### **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	<sup>b</sup> not serious	serious <sup>c</sup>	none	⊕⊕⊖⊖ Low	59/262 (22.5%)	63/259 (24.3%)	<b>RR 0.96</b> (0.50 to 1.85)	225 per 1,000	<b>9 fewer</b> <b>per 1,000</b> (113 fewer to 191 more)
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# Serious adverse events - Mortality\* (follow up: 6 months; assessed with: proportion with all-cause mortality)

93 (1 RCT)	not serious	serious <sup>d</sup>	not serious	serious <sup>e</sup>	none	⊕⊕⊖O Low	0/48 (0.0%)	0/45 (0.0%)	not estimable	0 per 1,000	<b>0 fewer</b> <b>per 1,000</b> (40 fewer to 40 more)
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#### Serious adverse events - Mortality\* (follow up: mean 6.3 years; assessed with: proportion of patients allcause mortality)

225 (1 observational study)	not serious	not serious	not serious	serious <sup>c</sup>	none		28/136 (20.6%)	19/89 (21.3%)	<b>RR 1.04</b> (0.62 to 1.74)	206 per 1,000	8 more per 1,000 (78 fewer to 152 more)
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#### Serious adverse events – Mortality\* (assessed with: proportion with death/person-years)

14254 (1 observational study) <sup>f,g</sup>	serious	not serious	not serious	not serious	none		1455/7127 (20.4%) <sup>g</sup>	723/7127 (10.1%) <sup>f</sup>	<b>HR 0.68</b> (0.62 to 0.74)	204 per 1,000 <sup>g</sup>	<b>60 fewer</b> <b>per 1,000</b> (72 fewer to 49 fewer)
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### **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 <sup>h</sup>	not serious	serious <sup>c</sup>	none		7/270 (2.6%)	4/264 (1.5%)	<b>RR 0.58</b> (0.17 to 1.95)	26 per 1,000	<b>11 fewer</b> <b>per 1,000</b> (22 fewer to 25 more)
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### Serious adverse events – Cardiovascular event\* (assessed with: proportion with CV event/person-years)

14254 (1 observational study) <sup>i,j</sup>	not serious	not serious	not serious	not serious	none	⊕⊕⊖⊖ Low	1364/7127 (19.1%) <sup>j</sup>	792/7127 (11.1%) <sup>i</sup>	<b>HR 0.89</b> (0.81 to 0.97)	191 per 1,000 <sup>j</sup>	<b>19 fewer</b> <b>per 1,000</b> (33 fewer to 5 fewer)
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# 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 <b>-3.7</b> ml/m	MD <b>5.4</b> ml/m higher (0.31 lower to 11.11 higher)
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**Certainty assessment** 

# 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 <sup>k</sup>	not serious	not serious	none	⊕⊕⊕⊖ MODERATE	206	167	-	The mean serious adverse events - Renal function* was - <b>7.95</b> ml/m	MD <b>6.54</b> <b>ml/m</b> <b>higher</b> (1.74 higher to 11.34 higher)
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# Serious adverse events - Hypersensitivity\* (follow up: 108 weeks; assessed with: proportion with hypersensitivity)

531 (2 RCTs)	not serious	not serious	not serious	serious <sup>c</sup>	none	⊕⊕⊕⊖ MODERATE	11/252 (4.4%)	9/279 (3.2%)	<b>RR 0.73</b> (0.31 to 1.72)	44 per 1,000	<b>12 fewer</b> <b>per 1,000</b> (30 fewer to 31 more)
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Tophus \* - not reported

|--|--|--|--|--|--|

# Health Related Quality of Life\* - not reported

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**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

					Bias due to				
					deviation of	Bias due to	Bias due to		
				Bias due to deviation	intended	outcome	outcome		
				of intended	interventions-	measurement-	measurement-		<b>Bias in selection</b>
			<b>Bias in classification</b>	interventions-	subjective	objective	subjective	Bias due to	of reported
Study	Counfounding	Selection bias	of interventions	objective outcomes	outcomes	outcomes	outcomes	missing data	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

		ULT			No ULT			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	5D	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.10.1 Allopurinol									
Pichholiya 2016	-4.056	3.0704	30	2.441	3.5505	15	22.1%	-6.50 [-8.60, -4.39]	
Takir 2015	-159	1.134	40	-0.38	1.273	33	28.6%	-121[-1.77, -0.65]	-
Subtotal (95% CI)			70			48	50.7%	-3.75 [-8.93, 1.43]	
Heterogeneity: Tau <sup>2</sup> -	- 13 36; 0	:hi² - 22	62, df	- 1 (P -	< 0.0000	1); 12 =	96%		
Test for overall effect	Z = 1.42	(P = 0.1	6)	0.0000121068					
1.10.2 Febuxostat									
Pichholiya 2016	-2.852	3.6495	30	2.441	3.5505	15	21.5%	-5.29 [-7.51, -3.07]	
Tsuruta 2015	-3.3	1.526	27	-0.4	1.664	26	27.8%	-2.90 [-3.76, -2.04]	
Subtotal (95% CI)			57			41	49.3%	-3.87 [-6.17, -1.57]	-
Heterogeneity: Tau <sup>2</sup> =	= 2.12; Ch	12 = 3.88	3, df = 1	1 (F = 0	).05); l <sup>2</sup> =	74%			
Test for overall effect	: Z = 3.29	P = 0.0	010)						
Total (95% Cl)			127			89	100.0%	-3.73 [-5.73, -1.72]	•
Heterogeneity: Tau <sup>2</sup> -	- 3.56: Ch	12 = 37.7	4. df =	3 (P <	0.00001	$  1^2  = 5$	32%	13 년 월	- <u>ī</u> t   t
Test for overall effect	Z = 3.65	(P = 0.0	00031	5 M S	0.00000000	2011-212	1222		-4 -2 0 2 4
Test for subaroup diff	ferences:	$Chi^2 = 0$	00. df -	1 (P =	0.971 12	= 0%			Pavours ULI Favours No UL

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

	Fe	buxostat	£	No	febuxost	at		Mean Difference	Mean Di	Ifference
Study or Subgroup	Mean	5D	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Rando	m, 95% Cl
Beddhu 2016	-3.26	1.4962	40	0.11	1.1936	40	36.2%	-3.37 [-3.96, -2.78]		
Sircar 2015	-3.8	2.5	45	-0.4	1.487	48	30.5%	-3 40 [-4 24, -2 56]		
Tani 2015	-2.21	1.549	30	-0.1	1.303	30	33.2%	-2.11[-2.83, -1.39]		
Total (95% CI)			115			118	100.0%	-2.96 [-3.79, -2.13]	-	
Heterogeneity: Tau <sup>2</sup> =	0.41; 0	hi <sup>2</sup> = 8.1	6, cff =	2 (P =	0.02); 12	= 75%		54 - SA	4 5 7	4 4
Test for overall effect	Z = 6.9	6 (P < 0,	00001	1					Favours Febuxostat	Favours No febuxostat

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

	Alle	purin	ol	No a	lopuri	nol		Mean Difference	Mean Diffe	rence
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random,	95% CI
Liu 2015a	-1.75	0.32	82	0.39	0.18	70	59.4%	-2.14 [-2.22, -2.06]		N985-0600
Pagonas 2016	-1.9	2.46	85	-0.5	2.14	136	40.6%	-1.40 [-2.03, -0.77]		
Total (95% CI)			167			206	100.0%	-1.84 [-2.55, -1.13]	-	
Heterogeneity: Tau <sup>2</sup> -	0.22; 0	hi² =	5.14, d	f = 1 (P	= 0.0	21, 1 <sup>2</sup> =	81%		5 5 6	+ +
Test for overall effect	2 = 5.0	16 (P -c	0,000	01)					Favours Allopurinol Fa	wours No 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.

	Febuxe	ostat	No febu	costat		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Ra	andom, 95% Cl	172 42
Kimura 2018	212	219	41	222	100.0%	5.24 [3.97, 6.92]				
Total (95% CI)		219		222	100.0%	5.24 [3.97, 6.92]				-
Total events	212		41						0.05	
Heterogeneity Not ap	plicable					-	25	ate .	+ +	
Test for overall effect	Z = 11.7	70 (P <	0.00001)				Favours	No febuxos	stat Favours Febux	ostat

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



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

	Febuxo	stat	No febu	costat		Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	lom, 95% Cl
Beddhu 2016	15	40	22	40	47.4%	0.68 [0.42, 1.11]		-
Kimura 2018	48	219	37	222	52.6%	1 32 [0 89, 1 93]	<u> </u>	
Total (95% CI)		259		262	100.0%	0.96 [0.50, 1.85]		
Total events	63		59					
Heterogeneity: Tau2 -	0 17; Ch	1 <sup>2</sup> = 4.	40, $df = 1$	(P = 0.0	04); I <sup>2</sup> = 1	77%		1 12 1
Test for overall effect.	Z = 0.11	(P = 0	91)	-32	202		Favours Febuxostat	Favours No 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.

<b>Study or Subgroup</b> Larsen 2016 Pagonas 2016	Allopu	rinol	No allop	urinol		Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	ş	M-H, Random, 95% CI			
Larsen 2016	0	0	0	0		Not estimable		· · · · · · · · · · · · · · · · · · ·			
Pagonas 2016	19	89	28	136	100.0%	1.04 [0.62, 1.74]					
Total (95% CI)		89		136	100.0%	1.04 [0.62, 1.74]					
Total events	19		28								
Heterogeneity. Not ap	plicable								<del>1</del>		
Test for overall effect	Z = 0.14	(P = 0	891				0.5	Favours Allopurinol Favours No 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.

	Fe	ebuxosta	t	No	febuxost	at		Mean Difference	Mean D	Ifference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Rando	om, 95% CI	
Bedidhu 2016	-3.1	22.356	40	-3.7	25.164	40	30.0%	0.60 [-9.83, 11.03]			
Sircar 2015	3.Z	22.88	45	-4.4	16.193	48	49.7%	7.50 [-0.50, 15.70]			-
Tani 2015	3.7	22.84	30	-3.4	27 035	30	20.3%	7.10 [-5.56, 19.76]	10 <u>-</u>	•	
Total (95% CI)			115			118	100.0%	5.40 [-0.31, 11.11]			
Heterogeneity: Tau <sup>2</sup> =	. 0.00; )	$Chl^2 = 1.1$	17, df =	2 (F =	0.551; 12	= 0%			1. 1.	d d	1
Test for overall effect	Z = 1.8	85 (P = 0	.06)						Favours No febuxostat	Favours Febuxostat	20

# 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.

	All	opuring	ol .	No a	llopuri	lon		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Liu 2015a	-0.8	3.9	82	-4.9	5	70	50.2%	4.10 [2.66, 5.54]	
Pagonas 2016	-2	4.249	85	-11	7.537	136	49.8%	9.00 [7.44, 10.56]	
Total (95% CI)			167			206	100.0%	6.54 [1.74, 11.34]	
Heterogeneity: Tau <sup>2</sup> -	- 11.42;	Chi <sup>2</sup> =	20.47,	df = 1	(P < 0.0	00001)	1 <sup>2</sup> = 95%		to the destable
Test for overall effect	: Z = 2.6	57 (P =	0.008)						Favours No allopurinol Favours Allopurinol
## 12. ULT vs no ULT for asymptomatic hyperuricemia, outcome: Hypersensitivity - proportion with hypersensitivity - longest follow-up - Allopurinol & Febuxostat.

Study or Subgroup	ULT		No ULT		Risk Ratio		Risk Ratio	
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
1.18.1 Allopurinol								
Pichholiya 2016 Subtotal (95% CI)	1	30 30	0	15 15	7.5% 7.5%	1.55 [0.07, 35.89] 1.55 [0.07, 35.89]		
Total events	1		0					
Heterogeneity: Not ap	plicable							
Test for overall effect	Z = 0.27	7 (P = 0	0.791					
1.18.2 Febuxostat								
Kimura 2018	7	219	10	222	82.4%	0.71 [0.28, 1.83]		
Pichholiya 2016 Subtotal (95% CI)	1	30 249	1	15 237	10.1% 92.5%	0.50 [0.03, 7.45] 0.68 [0.28, 1.67]		
Total events	8		11					
Heterogeneity: Tau <sup>2</sup> -	0.00; Cł	ni <sup>2</sup> = 0.	06, df =	1 (P -	0.81); 12	- 0%		
Test for overall effect	Z = 0.84	4 (P = 0	0.40)					
Total (95% CI)		279		252	100.0%	0.73 [0.31, 1.72]	-	
Total events	9		11					
Heterogeneity, Tau <sup>2</sup> -	0.00; Cł	$ni^2 = 0.$	30, df =	2 (P =	0.86); 12	= 0%	las als de la	
Test for overall effect	Z = 0.73	P = 0	).471	an (460,556		0	.02 0.1 1 10 2	
Test for subgroup diff	ferences:	Chi <sup>2</sup> =	0.24. df	= 1 (P	= 0.621	$l^2 = 0\%$	ravours no oci Favours oci	

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