National Institute for Health and Care Excellence

Guideline version (Final)

Gout: diagnosis and management

[E] Evidence reviews for which people with gout should be offered a urate-lowering therapy

NICE guideline NG219

Evidence reviews underpinning recommendations 1.5.1 to 1.5.3 in the NICE guideline

June 2022

Final

National Institute for Health and Care Excellence

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1.1 Review question: Which people with gout should be offered a urate-lowering therapy such as a xanthine oxidase inhibitor, a uricosuric or a uricase?

1.1.1 Introduction

The main aim of treating gout is to minimize the likelihood of gout flares reoccurring. Urate-lowering therapy works by reducing the production of serum urate or increasing the excretion of serum urate. If gout is not treated this can result in more gout attacks causing severe pain, joint inflammation, the possibility of joint destruction, and negatively impact on physical, psychological and social function.

Urate-lowering therapy includes xanthine oxidase inhibitors, uricosuric and uricase medications. The use of urate-lowering therapy in current practice is not standardised.

This aim of this review is to identify which groups of people with gout are at higher risk of having flares or disabilities and more likely to benefit from taking urate-lowering therapy.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: Adults (18 years and older) with gout Strata: None Exclusion: people with calcium pyrophosphate crystal deposition, including pseudogout
Prognostic variables under consideration	Patient risk factors: • Flare frequency • Presence of tophi • Chronic gouty arthritis • Presence of any joint damage • Renal impairment (eGFR less than 60 ml/min) • history of urinary stones • Diuretic use • Young age of onset of primary gout • or a combination of the above
Confounding factors	Confounding factors that may be independently associated with prognostic variable:

	• Age • Gender Multivariate studies need to have adjusted for both of these prognostic variables.
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Frequency of flares • Health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures
Study design	• Prospective and retrospective cohort studies if all the key confounders have been accounted for in a multivariate analysis.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Three cohort studies included in this review[30-32] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3 to Table 7).

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Rashid 2015[30] Retrospective cohort study	n=8828 Patients were included if they received a prescription for a urate-lowering therapy (ULT) - allopurinol, febuxostat, or probenecid, during the study time period (January 2007–December 2010); the index date was defined as the patient's first ULT prescription identified during	Multivariable logistic regression models	Risk factor Diuretic use at baseline: 1-2 flares group: 2345 (48.5%), ≥3 flares group: 701 (55.1%) No flares group: 1331 (47.6%) Comparison No diuretic use at baseline: 1-2 flares group: 2453 (51.5%), ≥3 flares group: 549 (44.9%)	Confounders adjusted for: sex, age, race, Serum Uric Acid (sUA) levels, comorbidities, anti-inflammatory medications, diuretic use, and rheumatologist as a prescriber	Frequency of flares - patients with 1-2 flares during 12 months post index Frequency of flares - patients with ≥3 flares during 12 months post index Frequency of flares - patients with no flares during 12 months post index	None

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	the study time period. Patients had to be ≥18 years of age at time of index date and were required to have at least 12 months of Kaiser Permanente Southern California (SPSC) membership eligibility including drug benefits prior to their index date, index date, and 12 months post-index. Age – 1-2 flares group: <55 years old – 41% 55-64 years old – 28.5% ≥65 years old – 35.5% ≥3 flares group: <55 years old – 30.5% 55-64 years old – 22.2% ≥65 years old – 47.3		No flares group: 1449 (52.4%)			

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	no gout flares group: <55 years old – 34.2% 55-64 years old – 28.4% ≥65 years old – 37.2% Gender (M/F) – 7045/1783 Ethnicity: 1-2 flares group: Caucasian 42.7%, African-American 14.1%, Hispanic 19.3%, Asian/Pacific Islander 23.4 %, Other 0.5% ≥3 flares group, Caucasian 42.7%, African-American 14.1% , Hispanic 19.3%, Asian/Pacific islander 23.4 %, Other 0.5% no gout flares group: Caucasian					

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	42.7%, African-American 14.1% , Hispanic 19.3%, Asian/Pacific islander 23.4 %, Other 0.5% USA					
Rothenbacher 2011[31] Prospective cohort study	n=23857 Single cohort of patients aged 20-89 years diagnosed with incident gout between the years 2000 and 2007. Subjects with any prescription of anti-gout treatment or any Read code suggesting gout before the start date were subsequently excluded from the cohort and considered as prevalent patients. All patients with cancer before the start date were also	Multivariate analysis using Cox proportional hazard model	Risk factor: History of chronic kidney failure (n=880 (3.7%)) Comparison: No history of chronic kidney failure (n=22977 (96.3%)	HR adjusted for sex, age (at start date of follow-up), GP visits (1 year before first-ever diagnosis of gout), smoking, alcohol, BMI, IHD, hypertension, hyperlipidaemia, renal failure and diabetes. before first-ever diagnosis of gout).	Frequency of flares – 1 or more flares (mean follow-up 3.8 years)	None

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	excluded. Age – n (%): 20-49 years – 5211 (21.8%) 50-59 years – 4761 (20.1%) 60-69 years -5547 (23.3%) 70-79 years – 5533 (23.2% 80-89 years – 2805 (11.8%) Gender (M/F): 17358/7499 Ethnicity: not reported UK					
Scire 2013[32] Retrospective cohort study	N=446 Patients with a clinical diagnosis of gout from 30 rheumatology centres in Italy Age – mean years (SD): 63.9 (11.6)	Multivariate linear regression model	Risk factors 1 Presence of tophi (n=87) Comparison 1 No tophi (n=359) Risk factors 2 number of swollen joints (n=not reported) Median (IQR) 0 (0 to1)	Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment	SF36 physical component at 6 months; SF36 mental component at 6 months; HAQ-DI at 6 months.	None

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	Gender (M/F): 403/43 Ethnicity: not reported Italy		Comparison 2 number of swollen joints (n=not reported) Risk factors 2 number of tender joints (n=not reported) Median (IQR) 1 (0 to 3) Comparison 2 number of tender joints (n=not reported)			

See Appendix D for full evidence tables.

1.1.6 Summary of the prognostic evidence

Table 3: Clinical evidence summary: renal impairment - history of chronic renal failure

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Frequency of flares (1 or more flares)	n=23857	HIGH[a]	Adjusted HR 1.33 (1.20 to 1.47)b
a. Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Methods: multivariable analysis, confounders studied: sex; age (20-49, 50-59, 60-69, 70-79, 80-89 years); number of GP visits (0-4, 5-9, 10-19, >20 visits); smoking (non-smoker, smoker, former); alcohol consumption (none, 1-9, 10-24, 25-42, >42 U/week); BMI (categories in kg/m2:15-19, 20-24, 25-29, ≥30).			

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
b. Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes.			

Table 4: Clinical evidence summary: diuretics use

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
One to two flares	n=8828	HIGH[a]	Adjusted OR 1.19 (1.05 to 1.35)b
Over or equal to 3 flares	n=8828	HIGH[a]	Adjusted OR 1.23 (1.01 to 1.50)b
a. Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Methods: multivariable analysis, confounders studied: sex; age (20-49, 50-59, 60-69, 70-79, 80-89 years);number of GP visits (0-4, 5-9, 10-19, >20 visits); smoking (non-smoker, smoker, former); alcohol consumption (none, 1-9, 10-24, 25-42, >42 U/week); BMI (categories in kg/m2:15-19, 20-24, 25-29, ≥30); b. Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes.			

Table 5: Clinical evidence summary: presence of tophi

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
SF-36 physical component (presence of tophi) (higher is better)	N=446	HIGH[a]	Adjusted MD 3.2 lower (5.41 lower to 0.99 lower)c
SF-36 mental component (presence of tophi) (higher is better)	N=446	MODERATE[a,b]	Adjusted MD 1.26 higher (0.88 lower to 3.4 higher)c

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
HAQ-DI (presence of tophi) (lower is better)	N=446	HIGH[a]	Adjusted OR 1.92 (1.07 to 3.45)c

a Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Methods: multivariable analysis: Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment.

b Downgraded by 1 increment because the confidence interval crossed the null line

c. Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes.

Table 6: Clinical evidence summary: presence of any joint damage – number of swollen joints

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
SF-36 physical component (presence of any joint damage – number of swollen joints) (higher is better)	N=446	HIGH[a]	Adjusted MD 0.54 lower (0.79 lower to 0.29 lower)c
SF-36 mental component (presence of any joint damage – number of swollen joints) (higher is better)	N=446	MODERATEa[,b]	Adjusted MD 0.2 lower (0.45 lower to 0.05 higher)c
HAQ-DI (presence of any joint damage – number of swollen joints) (lower is better)	N=446	HIGH[a]	Adjusted OR 1.23 (1.13 to 1.34)c

a. Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Method: multivariable analysis adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment.

b. Downgraded by 1 increment because the confidence interval crossed the null line.

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
c. Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes.			

Table 7: Clinical evidence summary: presence of any joint damage – number of tender joints

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
SF-36 physical component (presence of any joint damage – number of tender joints) (higher is better)	N=446	HIGH[a]	Adjusted MD 0.39 lower (0.55 lower to 0.23 lower)b
SF-36 mental component (presence of any joint damage – number of tender joints) (higher is better)	N=446	HIGH[a]	Adjusted MD 0.24 lower (0.39 lower to 0.09 lower)b
HAQ-DI (presence of any joint damage – number of tender joints) (lower is better)	N=446	HIGH[a]	Adjusted OR 1.10 (1.06 to 1.14)b
a. Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Methods: multivariable analysis adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment. b. Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes.			

See Appendix F for full GRADE

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Economic model

A cost effectiveness analysis was not conducted for this review question due to a lack of appropriate data to sufficiently model the long-term outcomes and effects for which people should be offered ULT.

The committee, however, noted that the prescription of ULTs in current practice is sub-optimal. Therefore, a costing analysis was conducted to assess the differences in costs between current and future practice – incorporating the cost of an increased uptake in ULTs.

Costing analysis

The following set of calculations were conducted to aid the committee's consideration of cost effectiveness. The purpose of these calculations was to estimate the cost of current practice and the cost of future practice with increased uptake of ULT and a greater proportion of people on ULTs receiving febuxostat, and a treat-to-target management strategy – incorporating the cost of gout flares and ULT costs. Increased uptake of ULT will reduce the number of flares observed in the long run, but also result in higher ULT costs. Therefore, these calculations were undertaken to determine if an increase in uptake of ULT is cost effective.

The calculations are based on the outcomes reported in the nurse-led arm from the Doherty trial[12]. In these calculations it is assumed baseline values from the nurse-led arm reported in Doherty are reflective of current practice and two-year outcomes are reflective of future practice. The costing data inputs used in these calculations are based on costs calculated for Evidence review G. Detailed methodology and rationale of costing data inputs can therefore be found in Evidence review G.

Estimating the number of flares people observe in current and future practice

The Doherty trial[12] captures both an increase in people being prescribed ULT (39.61% in current practice compared to 96.10% in future practice), in addition to people in future practice being prescribed a treat-to-target regimen of ULT.

The Doherty trial[12] compares a treat-to-target management strategy with usual care – where the majority of people in the treat-to-target arm receive allopurinol. Because the recommendations made for this guideline will likely result in more people being prescribed febuxostat, we have calculated the cost of ULTs for future practice incorporating this change. More information on the costing of ULTs for these calculations can be found in the 'Total cost of ULT' section and in Table 10 and **Error! Reference source not found.**. Of note, the increased proportions of people receiving febuxostat in future practice will not affect the total number of flares people experience in future practice (compared to the outcomes reported in

Doherty), but only the cost of treatment. This is because these calculations assume people have already achieved target serum urate levels, in which case the differences in the number flares observed in the long run between allopurinol and febuxostat should be negligible.

The number of flares observed at baseline and for people receiving treat-to-target ULT at two years were reported in Doherty[12] (Figure 3). For our costing analysis, we assumed baseline values were representative of current practice and outcomes observed at two years were representative of future practice. The average number of flares people therefore experience in current practice and future practice are presented in **Error! Reference source not found.**.

Table 8: Total number of flares people experience at baseline and two years of treatment

Health state	Total number of flares per person[(a)]
Current practice (baseline)	4.2
Future practice (two years)	1.5

(a) Doherty trial[12] – Figure 3.

Total cost of gout flares for current and future practice

To calculate the total cost of gout flares for current and future practice the average number of flares per person were multiplied by the lowest and highest cost of a gout flare (which are calculated in Evidence review G). The cost of a gout flare was estimated using a combination of sources such as, NHS reference costs, the BNF and committee opinion. The lower cost of a gout flare assumes 1% of people receive treatment for their gout flare in hospital and the higher cost of a gout flare assumes 5% of people receive treatment for their gout flare in hospital. The total costs for gout flares in current and future practice are presented in Table 9.

Table 9: The total cost of gout flares for current practice and treatment at two years

	Average number of flares per person[(a)]	Cost of a gout flare (lower)[(b)]	Cost of a gout flare (higher)[(b)]	Total cost of gout flares (lower)	Total cost of gout flares (higher)
Current practice	4.2	£27.22	£55.64	£114.32	£233.69
Future practice	1.5			£40.83	£83.46

(a) See Table 8
(b) Obtained from calculations in Evidence review G

Total cost of ULT

The cost of ULT in current practice was estimated using the proportions of people receiving different doses of allopurinol in the Doherty[12] trial at baseline and the proportions of people receiving different doses of febuxostat received in the FAST trial[22]. Data from the FAST trial[22]

was used for the proportion of people receiving different doses of febuxostat because the proportion of people receiving different doses of febuxostat was not reported in the Doherty[12] trial. The cost allopurinol and febuxostat based on these proportions are presented in Table 10.

Table 10: Total cost for allopurinol and febuxostat current practice based on the Doherty trial weighting for allopurinol and FAST trial weighting for febuxostat

Drug	Cost per daily dose[(a)]	Total cost per year	Doherty and FAST trial weighting[(b)]	Cost[(c)]
Allopurinol 100mg	£0.04	£12.91	31.68%	£4.09
Allopurinol 200mg	£0.08	£25.81	18.81%	£4.86
Allopurinol 300mg	£0.06	£17.86	42.57%	£7.60
Allopurinol 400mg	£0.09	£30.76	6.93%	£2.13
Allopurinol 500mg	£0.13	£43.67	0.99%	£0.43
Allopurinol 600mg	£0.11	£35.72	0.00%	£0.00
Allopurinol 700mg	£0.15	£48.62	0.00%	£0.00
Allopurinol 800mg	£0.19	£61.53	0.00%	£0.00
Allopurinol 900mg	£0.17	£53.58	0.00%	£0.00
Febuxostat 80mg	£0.10	£31.68	97.50%	£30.88
Febuxostat 120mg	£0.87	£317.55	2.50%	£7.94
Total cost allopurinol				***£19.11***
Total cost febuxostat				***£38.82***

(a) Source: British National Formulary (BNF)[5]: Date accessed 18/02/2022

(b) In the Doherty trial[12] 0.99% of people received 500mg or more of allopurinol. It was assumed this 0.99% of people received 500mg of allopurinol

(c) Obtained by multiplying the yearly cost by the trial weighting

Based on the proportions presented in Table 10 the total cost for allopurinol and febuxostat was estimated and subsequently multiplied by the proportion of people receiving each ULT. For current practice it was assumed 97.8% of people were prescribed allopurinol and 2.2% of people were prescribed febuxostat. This was based on CPRD data which was sourced as part of the collaborative research project between NICE and the University of Edinburgh (Multimorbidity and clinical guidelines: using epidemiology to quantify the applicability of trial evidence to Inform guideline development)[16]. The total cost of ULT in current practice was therefore, £19.54 ([£19.11*97.8%] + [£38.82*2.2%]).

As in Evidence G, data from the FAST trial[22] was used to estimate the total cost for allopurinol and febuxostat in future practice. These calculations, however, differed to those in Evidence review G because the drugs costs associated with up-titrating (such as prophylaxis to mitigate the flare triggering effect associated with initiating ULT) were not included. We omitted this cost because data from the Doherty trial[12] for future practice was based on treatment at two years. At two years of treatment people would have already up titrated to their required dose of ULT to achieve target serum urate levels.

The total costs for allopurinol and febuxostat for future practice are presented in Table 11.

Table 11: Total cost for allopurinol and febuxostat in future practice based on the FAST trial weighting

Drug	Cost per daily dose[(a)]	Total cost per year	FAST trial weighting[(b)]	Cost[(c)]
Allopurinol 100mg	£0.04	£12.91	10.00%	£1.29
Allopurinol 200mg	£0.08	£25.81	23.30%	£6.01
Allopurinol 300mg	£0.06	£17.86	50.90%	£9.09
Allopurinol 400mg	£0.09	£30.76	11.90%	£3.66
Allopurinol 500mg	£0.13	£43.67	2.73%	£1.19
Allopurinol 600mg	£0.11	£35.72	0.43%	£0.15
Allopurinol 700mg	£0.15	£48.62	0.35%	£0.17
Allopurinol 800mg	£0.19	£61.53	0.23%	£0.14
Allopurinol 900mg	£0.17	£53.58	0.16%	£0.08
Febuxostat 80mg	£0.10	£31.68	97.50%	£30.88
Febuxostat 120mg	£0.87	£317.55	2.50%	£7.94
Total cost allopurinol				***£21.80***
Total cost febuxostat				***£38.82***

(d) Source: British National Formulary (BNF)[5]: Date accessed 18/02/2022
(e) FAST trial[22] data. 3.9% of people received a dose of 500mg or more. It was assumed 70% of the 3.9% of people received 500mg of allopurinol, 11% received 600mg, 9% received 700mg, 6% received 800mg, and 4% received 900mg
(f) Obtained by multiplying the yearly cost by the FAST trial[22] weighting

For the total cost of ULT in future practice it was assumed 50% of people received allopurinol and febuxostat. The total cost of ULT in future practice was therefore estimated as £30.31 ([£21.80*50%] + [£38.82*50%]).

Total cost of current and future practice

Total costs for current and future practice were calculated by adding the cost of gout flare (Table 9), to the cost of ULT multiplied by the proportion of people receiving ULT (in either current or future practice). The proportion of people receiving ULT in current and future practice was based on data from the Doherty trial[12] (where 39.61% of people received ULT in current practice [baseline] and 96.10% in future practice [at two years]). The results for the total costs of current and future are presented in Table 12.

Table 12: Total cost per person of current practice and future practice

	Total cost using the lowest cost of a gout flare	Total cost using the highest cost of a gout flare
Current practice	£122.07[(a)]	£241.43[(c)]
Future practice	£69.96[(b)]	£112.59[(d)]

(a) Calculated as The cost of a gout flare in current practice using the lowest cost of a gout flare scenario (Table 9 – £114.32) + Cost of ULTs in current practice (£19.54) multiplied by the proportion of people receiving ULTs in current practice (39.61%)
(b) Calculated as The cost of a gout flare in future practice using the lowest cost of a gout flare scenario (Table 9 – £40.83) + Cost of ULTs in future practice (£30.31) multiplied by the proportion of people receiving ULTs in future practice (96.10%)
(c) Calculated as The cost of a gout flare in current practice using the highest cost of a gout flare scenario (Table 9 – £233.69) + Cost of ULTs in current practice (£19.54) multiplied by the proportion of people receiving ULTs in current practice (39.61%)

(d) Calculated as The cost of a gout flare in future practice using the highest cost of a gout flare scenario (Table 9 – £112.59) + Cost of ULTs in future practice (£30.31) multiplied by the proportion of people receiving ULTs in future practice (96.10%)

As can be seen in Table 12, future practice is less costly than current practice. Although more people in future practice are prescribed ULT (96.10% compared to 39.61%) and more people in future practice are prescribed febuxostat (50% compared to 2.2%) – which is more costly than allopurinol. The increase in costs of ULT are offset by the reduction in costs associated with fewer flares observed in future practice (1.5 compared to 4.5), making future practice less costly. The increase in costs of ULT between current and future practice is £21.39 (£29.13 - £7.74). However, as demonstrated in Table 9, significant cost savings are observed due to the reduction in the number of flares.

Because the price of febuxostat was nearly double the price of allopurinol in future practice (Table 11), an additional calculation was conducted for future practice assuming all people received febuxostat (£38.82 for the cost of ULT, where 97.5% of people receive 80mg febuxostat and 2.5% of people receive 120mg febuxostat). Once again, it was assumed 96.10% of people would be prescribed ULT in future practice and 39.61% of people were prescribed ULT in current practice. In these calculations, future practice using the lowest cost of a gout flare cost £78.14 and future practice using the highest cost of a gout flare cost £120.77, which in both scenarios is still lower than the total cost of current practice presented in Table 12 (£122.07 and £241.43, respectively).

Additional scenario analyses

A number of additional calculations were undertaken to assess the impact of differing ULT costs on the results of the calculations.

Calculating the cost of ULT for future practice using the proportion of people receiving different doses of allopurinol and febuxostat from the Doherty and FORWARD trial

Highlighted in Evidence review G, the highest cost for ULT is when data from the Doherty trial[12] and FORWARD trial[11] are used for the proportions of people receiving different dosages of allopurinol and febuxostat. This higher cost is attributed to a greater number of people receiving higher doses of allopurinol and febuxostat (compared to the FAST trial[22]). Therefore, a sensitivity analysis was conducted to estimate the cost of ULT in future practice using the proportions of people receiving different foes of allopurinol and febuxostat form the Doherty[12] and FORWARD trial[11]. The total costs of allopurinol and febuxostat using these proportions are presented in Table 13.

Table 13: Total cost for allopurinol and febuxostat based on the Doherty and Forward trial weighting

Drug	Total cost per year	Doherty and FORWARD trial weighting	Cost
Allopurinol 100mg	£12.91	0.49%	£0.06
Allopurinol 200mg	£25.81	2.96%	£0.76
Allopurinol 300mg	£17.86	16.75%	£2.99
Allopurinol 400mg	£30.76	27.09%	£8.34
Allopurinol 500mg	£43.67	36.90%	£16.11
Allopurinol 600mg	£35.72	5.80%	£2.07
Allopurinol 700mg	£48.62	4.74%	£2.31
Allopurinol 800mg	£61.53	3.16%	£1.95
Allopurinol 900mg	£53.58	2.11%	£1.13
Febuxostat 80mg	£31.68	78.30%	£24.80
Febuxostat 120mg	£317.55	21.70%	£68.91

Drug	Total cost per year	Doherty and FORWARD trial weighting	Cost
Total cost allopurinol			***£35.72***
Total cost febuxostat			***£104.63***

In the Doherty trial 53% of people received a dose of 500mg or more. It was assumed 70% of the 53% of people received 500mg of allopurinol, 11% received 600mg, 9% received 700mg, 6% received 800mg, and 4% received 900mg (as in line with what was done for the costing calculations presented in Evidence Review G).

As before, for future practice it was assumed 50% of people received allopurinol and febuxostat. Total ULT costs for ULT in future practice were therefore estimated as £70.17 ([£35.72*50%] + [£104.63*50%]).

The cost of current practice was assumed to be the cost of current practice estimated for the base case – £19.54 (see section Total cost of ULT).

Once again for these set of calculations we assumed 39.61% were prescribed ULT in current practice and 96.10% were prescribed ULT in future practice. Using the costs of ULT highlighted above (£19.54 and £70.17) and multiplying these costs by the proportion of people receiving ULT in current and future practice, we obtained the total cost of ULT in current and future practice (£7.74 and £67.44 respectively). ULT was therefore £59.69 more expensive compared to current practice.

The result of this sensitivity analysis is presented in Table 14.

Table 14: Total cost of current practice and future practice using data from the FORWARD trial and Doherty trial

	Total cost using the lowest cost of a gout flare	Total cost using the highest cost of a gout flare
Current practice	£122.07	£241.07
Future practice	£108.27	£150.90

As shown in Table 14, when ULT costs are estimated based on the proportion of people receiving allopurinol and febuxostat from the FORWARD[11] and Doherty trial[12] future practice is still less costly than current practice.

In this scenario the differences in costs between future and current practice were lower compared to the base case analysis, £13.80 compared to £52.11 in the base case analysis using the lowest cost of a gout flare and £90.53 compared to £128.84 in the base case analysis for the highest cost of a gout flare. As anticipated, the smaller cost difference observed is due a higher proportion of people receiving higher doses of allopurinol and febuxostat.

Once again, we also ran these set of calculations where it was assumed, in future practice, all people received febuxostat based on the proportions observed in FORWARD trial[11] (Table 13 – £104.63 for the cost of ULT, where 78.30% of people receive 80mg febuxostat and 21.70% of people receive 120mg febuxostat). In this instance, the total cost of future practice using the lowest cost of a gout flare was £141.38 and the total cost using the highest cost of a gout flare was £184.01. Therefore, in this future practice was only cheaper when the highest cost of a gout flare was used.

Threshold calculations

In addition to the calculations above, further calculations were undertaken where it was assumed all people received a fixed dose of each respective dose of allopurinol and febuxostat in future practice (see Table 13 for dosages). These calculations were compared with the calculated costs of current practice (Table 12 and Table 14).

In all scenarios, apart from when all people received 120mg febuxostat, current practice was more expensive than future practice. When all people received 120mg febuxostat, and the lowest cost of a gout flare was used, the total cost of future practice was £346.00 compared to £122.07 in current practice. When using the highest cost of a gout flare, the cost of future practice was £399.63 compared to £241.43 in current practice. Future practice is more expensive when all people are prescribed 120mg febuxostat due to the higher costs associated with this drug dosage (£0.87).

Because future practice is more expensive when all people receive 120mg febuxostat, a threshold calculation was conducted to determine at what proportion of people receiving different doses of febuxostat (80mg or 120mg), does future practice become more expensive (assuming all people are prescribed febuxostat). The costs of current practice (Table 12 and Table 14) were compared with the calculated costs of future practice (using the highest and lowest cost of a gout flare) using iterations of 1% for the different doses for people receiving febuxostat (80mg or 120mg).

Using the lowest cost of a gout flare scenario current practice cost £122.07 and future practice became more expensive when 19% of people were prescribed 120mg febuxostat. Using the highest cost of a gout flare scenario, current practice cost £241.43 and future practice became more expensive when 47% of people were prescribed 120mg febuxostat.

Discussion

The committee acknowledged there would be additional costs associated with ULT in the first year of treatment which haven't been included in these calculations. For example, the cost of prophylaxis used when initiating and up titrating ULT, up titration costs in the form of GP and nurse time, and the cost of flares associated with the flare triggering effect which is observed when initiating and up titrating ULT. However, the committee highlighted the purpose of these calculations was to compare the costs of current practice and long-term future practice, illustrating that in the long-run, future practice is less costly compared to current practice.

The committee acknowledged that cost of treatment at one year could be significantly higher than current practice due to the increased uptake in ULTs and the flare triggering effect associated with initiating ULT. However, the committee emphasised the number flares observed in the long run is significantly less. The committee also noted that the number of flares people experience at two years is likely to remain relatively constant over a person's lifetime given good adherence to medication. Therefore, demonstrating treatment with ULT is cost saving long term. In addition, people will have a significantly improved quality of life as they will experience less frequent and severe flares.

1.1.9 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 15: Urate-lowering therapy costs

Resource	Cost per unit	Dosage
Allopurinol 100mg tablet	£0.04	100mg – 900mg per day
Allopurinol 300mg tablet	£0.05	

Resource	Cost per unit	Dosage
Febuxostat 80mg tablet	£0.09	80mg – 120mg per day
Febuxostat 120mg tablet	£0.87	

Source: British National Formulary, February 2022[5]

1.1.10 Evidence statements

Economic

- No relevant economic evaluations were identified.

1.1.11 The committee's discussion and interpretation of the evidence

The effectiveness of ULTs is addressed in Evidence Review G and recommendations have been made on prescribing ULTs.

1.1.11.1. The outcomes that matter most

The committee considered frequency of flares and health-related quality of life as the two most important outcomes for decision-making. The committee agreed that highlighting specific groups as being at higher risk of having flares or lower quality of life would help clinicians to identify people more likely to benefit from taking urate-lowering therapy.

1.1.11.2 The quality of the evidence

Three cohort studies evaluating which patient risk factors are associated with worse outcomes in terms of quality of life or frequency of flares were included in this review.

One cohort study evaluated the association between history of chronic renal failure and frequency of flares outcome. The quality of evidence was graded high. Another cohort study evaluated the association between diuretic use and frequency of flares (1 - 2 flares and ≥3 flares). The quality of evidence was high. One cohort study evaluated the association between presence of tophi, number of swollen joints, number of tender joints and quality of life outcomes: SF-36 (physical and mental components) and HAQ-DI. The quality of evidence ranged from moderate to high, the mental component of the SF-36 was downgraded due to imprecision. This was a very small study, with a short follow-up time (6 months) in comparison to the other studies (12 months and 3.8 years).

1.1.11.3 Benefits and harms

The committee agreed that although the quality ranged from moderate to high, the evidence was limited by the lack of studies and lack of clinical benefits for health-related quality of life. The evidence showed no clinical difference for SF-36 physical and mental components in relation to tophi, swollen joints, and presence of tender joints but the SF-36 is thought to be not particularly sensitive to change in musculoskeletal conditions, therefore the committee had less confidence in these results.

The evidence showed that gout flares are more likely in patients with a history of chronic renal failure (one or more flares) or in patients using diuretics (one to three or more flares). Furthermore, the evidence showed that presence of tophi, swollen joints and tender joints were associated with higher HAQ-DI score (more disability). The committee discussed that within current practice gout is not well managed and the people to whom ULT is offered is very variable. However, the committee agreed that the groups studied reflected the people who in their experience would be identified as benefiting from ULT.

People on diuretics are prone to significant hyperuricaemia and frequent flares owing to the effect of diuretics in reducing renal urate excretion. The committee noted people with CKD or on diuretics tend to have more flares than people with normal renal function due to reduced urate excretion leading to more severe hyperuricaemia and greater monosodium urate crystal formation. They agreed that people with multiple or troublesome flares with painful swollen joints are harder to treat. The committee discussed the debilitating effects that tophi and swollen joints can have and the major impact on quality of life. They noted that chronic gouty arthritis can lead to permanent joint damage and loss of range of motion in the joints. Overall, the committee agreed gout can lead to significant harms and therefore agreed ULT should be offered to people with multiple or troublesome flares, CKD stages 3 - 5, diuretic use, tophi and/or chronic gouty arthritis.

CPRD data provided by Guthrie et al.[16] found that only 31.8% of people with gout are being treated with ULT. The committee noted that there may be missed opportunities of not offering ULTs to people with gout early in their disease but acknowledged that there was a lack of evidence for this. However, they agreed as uptake of ULT was low it was important to take the opportunity to discuss the option of starting ULT with all people experiencing a first or subsequent gout flare. As part of the discussion, the committee agreed it was important to ensure that people understood ULT is a long-term treatment and would usually continue even when the target serum urate level is reached. Based on the evidence and their experience the committee agreed that urate-lowering therapy should be discussed and considered with all people experiencing a first or subsequent gout flare.

1.1.11.4 Cost effectiveness and resource use

No economic evidence was identified for this review question. Unit costs of treatment and estimates of projected costs for future practice assuming more people receive ULT were presented to aid to committee consideration of cost effectiveness.

The calculations assessed the cost differences between current and future practice assuming the proportion of people receiving ULT increases, and a greater proportion of people are prescribed febuxostat in future practice. The calculations incorporated the cost of ULTs and the cost of gout flares.

The calculations presented illustrated that future practice was less costly than current practice in the base case and most scenario analyses. The only two instances where future practice was more expensive was firstly, when the lowest cost of gout flare scenario was employed using the Doherty and FAST trial weighting and all people received febuxostat. The second scenario analysis when future practice was more expensive was when all people received 120mg febuxostat in future practice. An additional sensitivity analysis was therefore conducted to determine at what proportion of people receiving 120mg febuxostat (assuming all people receive febuxostat in future practice), does future practice become the more expensive strategy.

When the lowest cost of a gout flare scenario was used for current practice (costing £122.07), future practice became more expensive when 19% of people were prescribed 120mg febuxostat. When the highest cost of a gout flare scenario was used for current practice (costing £241.43), future practice became more expensive when 47% of people were prescribed 120mg febuxostat.

The committee were confident that no more than 47% of people would be prescribed 120mg of febuxostat in future practice. However, noted it was more plausible that more than 19% of people could be prescribed 120mg febuxostat in future practice.

In general, the committee acknowledged it would be very unlikely more than 30% of people would be prescribed 120mg febuxostat in future practice – and of note, when 31% of people were prescribed 120mg febuxostat in future practice the cost difference (using the lowest cost of a gout flare) observed between future and current practice was £26.14 (where future

practice is more expensive). The committee noted that if future practice was £26.14 more expensive, it is likely the QALY gains observed from the reduced number of flares experienced over time, would likely result in future practice being the most cost effective strategy.

In addition, the committee noted that the estimated cost of future practice used in this calculation assumed all other people received 80mg febuxostat. However, in reality, in future practice, a proportion of people would also receive allopurinol (with a high proportion of these people receiving lower doses of allopurinol) thus overestimating the total cost of future practice and subsequently the cost differences between current and future practice.

The committee also highlighted that because the calculations conducted estimated the costs of current and future practice at two years, they omitted the costs associated with initiating and up titrating ULT (such as, flares associated with up titrating ULT and prophylaxis). The committee acknowledged that the first year of treatment may be more expensive than current practice. However, emphasised that the calculations illustrated that future practice was cheaper compared to current practice in the long run. Future practice being less costly assumes that people receiving ULT remain at their target serum urate levels. However, the committee were confident that as a result of the recommendations made for this guideline a high proportion of people will remain at target serum urate levels. The committee accepted that target levels may deviate for short periods of time, but people will likely reobtain these due to improved information on gout and increased monitoring once people have achieved target serum urate levels.

The committee also noted that the clinical benefit for quality of life may not be fully captured in the included studies due to short follow up.

The committee discussed current practice regarding the prescription of ULTs, noting current practice is highly variable and uptake of ULTs is poor. Current best practice is to offer ULT for people who experience multiple flares, have CKD (stage 3 to 5), are receiving diuretic therapy, have tophi, or have chronic gouty arthritis. In addition, the committee also noted current best practice is to consider the option of ULT with a treat-to-target management strategy for people experiencing a first or subsequent flare. The committee made recommendations that are reflective of current best practice.

CPRD data analysed by Guthrie et al.[16] found that currently only 31.9% of people with gout are treated with ULT. However, the recommendations made as a result of this review question are likely to result in an increase in uptake of ULT. The committee noted it was difficult to accurately estimate what proportion of people will receive ULT as a result of the recommendations made. However, they noted it was unlikely more than 60%-70% of people with gout would be treated with ULT. This is because it may be a number of years until a person experiences a subsequent flare, and therefore the benefits of ULT may not outweigh the costs if ULT is initiated after an acute gout flare. In general, the decision to initiate ULT will be made by the person with gout and with help of a clinician to explain the benefits and harms of initiating ULT and assessing individual risks factors for subsequent flares and how frequent these may be.

Although the recommendations made as part of this review question will result in an increase in the number of people receiving ULT, the committee noted gout flares are costly to the NHS and have a significant impact on a person's quality of life. People experiencing gout flares may require a GP appointment to help manage their pain or seek help and advice. In addition, all people experiencing a gout flare will likely require a repeat prescription for their medication which will involve GP time and the cost of drugs prescribed (for example, NSAIDs, colchicine, and oral corticosteroids).

The committee also noted that if gout goes untreated without ULT for a long period of time people are at greater risk of experiencing tophi and long-term joint damage. If a person with gout develops tophi more aggressive and costly treatment with ULT is required to dissolve

the tophi and obtain target serum urate levels, in turn costing the NHS more money. Long-term joint damage will likely be highly costly for the NHS and have a severe negative impact on a person's quality of life. The committee also noted gout flares can be very painful and debilitating, noting it is unlikely someone experiencing a severe gout flare will be able to participate in their usual daily activities.

The recommendations made as a result of this review question are likely to result in a significant resource impact given the prevalence of gout and the current poor uptake of ULTs. However, as demonstrated by the calculations undertaken in this review, it is highly likely future practice with increased uptake of ULTs will be cost effective. Future practice was less costly in the majority of scenarios undertaken in the costing analysis and the committee were confident QALY gains would be greater in future practice. The committee did however acknowledge that a costing analysis is not as robust as a health economic model and therefore, made reference to additional evidence presented in Evidence review G – which showed treatment with ULT was cost effective compared to no treatment. In addition, the committee noted the evidence presented in Evidence review J which illustrated treat-to-target ULT was cost effective compared to usual care. Overall, the committee were therefore confident increased uptake of ULTs would be cost effective. The committee also acknowledged that future practice may even be the dominant strategy (less costly and more effective). However, the committee were not definitively able to conclude this due the associated limitations of drawing conclusions from costing analyses.

In general, the committee concluded these recommendations were important for improving the standards of care of the gout population. As a result of the recommendations made, treatment will become standardised whereby all people with gout will have the option to receive ULT if they wish to do so. The committee also emphasised treatment with ULT is highly likely to be cost effective (or even dominant) and improve people's quality of life with gout.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1 to 1.5.3.

1.1.13 References

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Appendices

Appendix A – Review protocol

Review protocol for which patients should be selected for urate-lowering therapy

ID	Field	Content
0.	PROSPERO registration number	CRD42021249992
1.	Review title	Which people with gout should be offered a urate-lowering therapy such as a xanthine oxidase inhibitor, a uricosuric or a uricase?
2.	Review question	Which people with gout should be offered a urate-lowering therapy such as a xanthine oxidase inhibitor, a uricosuric or a uricase?
3.	Objective	To determine which patient risk factors predict worse outcome in terms of quality of life or frequency of flares to inform who should be offered ULT
4.	Searches	The following databases (from inception) will be searched: • Embase • MEDLINE Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details) Searches will be restricted by: • English language studies • Human studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Gout (including people with gout and chronic kidney disease)
6.	Population	Inclusion: Adults (18 years and older) with gout Strata: None Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout

7.	Intervention/Exposure/Test	Patient risk factors: • Flare frequency • Presence of tophi • Chronic gouty arthritis • Presence of any joint damage • Renal impairment (eGFR less than 60 ml/min) • A history of urinary stones • Diuretic use • Young age of onset of primary gout • or a combination of the above
8.	Comparator/Reference standard/Confounding factors	Confounding factors that may be independently associated with prognostic variable: • Age • Gender Multivariate studies need to have adjusted for both of these prognostic variables.
9.	Types of study to be included	• Prospective and retrospective cohort studies if all the key confounders have been accounted for in a multivariate analysis. •
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. • Studies that do not adjust for the above confounding factors. • Studies with fewer than 10 participants per confounder
11.	Context	It is unknown whether all patients should receive ULT or not. To find out who will benefit most from ULT we need to establish which risk factors predict poor outcomes for the most important long-term patient outcomes, which was identified by the GC as quality of life and frequency of flares.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Frequency of flares • Health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the

		Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. The appropriate checklist for this review is Quality in Prognostic Studies (QUIPS) tool
16.	Strategy for data synthesis	• Pairwise meta-analyses will be conducted if the studies significantly match the protocol and adjust for relevant confounders, otherwise each study will be analysed separately. If used, pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.

		• A modified GRADEpro will be used to assess the quality of evidence for each risk factors, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • None.
18.	Type and method of review	☐ Intervention ☐ Diagnostic ☒ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	4th December 2020
22.	Anticipated completion date	13th June 2022
23.	Stage of review at time of this submission	Review stage / Started / Completed Preliminary searches: ☑ / ☑ Piloting of the study selection process: ☐ / ☐ Formal screening of search results against eligibility criteria: ☐ / ☐ Data extraction: ☐ / ☐

		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail managementofgout@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Gill Ritchie [Guideline lead] Julie Neilson [Senior systematic reviewer] Audrius Stonkus [Systematic reviewer] Alexandra Bonnon [Health economist] Amber Hernaman [Project manager] Joseph Runicles [Information specialist]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].		
29.	Other registration details	N/A		
30.	Reference/URL for published protocol	N/A		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:		

		• notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords		
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☒	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[26] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

	• OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2005 or later but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'. • Studies published before 2005 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

- Which people with gout should be offered a urate-lowering therapy such as a xanthine oxidase inhibitor, a uricosuric or a uricase?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[26]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using one or more of the following approaches:

- Population AND Study filter(s)

Table 16: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 06 July 2021	Observational studies Prognostic studies Exclusions (animal studies, letters, comments)
Embase (OVID)	1974 – 06 July 2021	Observational studies Prognostic studies Exclusions (animal studies, letters, comments)

Medline (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	podagra.ti,ab.
5.	pseudogout.ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/

19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	Limit 25 to English language
27.	Epidemiologic studies/
28.	Observational study/
29.	exp Cohort studies/
30.	(cohort adj (study or studies or analys* or data)).ti,ab.
31.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
32.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
33.	Controlled Before-After Studies/
34.	Historically Controlled Study/
35.	Interrupted Time Series Analysis/
36.	(before adj2 after adj2 (study or studies or data)).ti,ab.
37.	exp case control studies/
38.	case control*.ti,ab.
39.	Cross-sectional studies/
40.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
41.	or/27-40
42.	predict.ti.
43.	(validat* or rule*).ti,ab.
44.	(predict* and (outcome* or risk* or model*)).ti,ab.
45.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
46.	decision*.ti,ab. and Logistic models/
47.	(decision* and (model* or clinical*)).ti,ab.
48.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
49.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
50.	ROC curve/
51.	or/42-50
52.	26 and (41 or 51)

Embase (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	podagra.ti,ab.
5.	pseudogout.ti,ab.

6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	Limit 23 to English language
25.	Clinical study/
26.	Observational study/
27.	family study/
28.	longitudinal study/
29.	retrospective study/
30.	prospective study/
31.	cohort analysis/
32.	follow-up/
33.	cohort*.ti,ab.
34.	32 and 33
35.	(cohort adj (study or studies or analys* or data)).ti,ab.
36.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
37.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
38.	(before adj2 after adj2 (study or studies or data)).ti,ab.
39.	exp case control study/
40.	case control*.ti,ab.
41.	cross-sectional study/
42.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
43.	or/25-31,34-42
44.	predict.ti.
45.	(validat* or rule*).ti,ab.
46.	(predict* and (outcome* or risk* or model*)).ti,ab.
47.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.

48.	decision*.ti,ab. and Statistical model/
49.	(decision* and (model* or clinical*)).ti,ab.
50.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
51.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
52.	Receiver operating characteristic/
53.	or/44-52
54.	24 and (43 or 53)

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to a Gout population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updated after March 2018). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies and quality of life studies.

Table 17: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 14 June 2021 Quality of Life 1946 – 14 June 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments)
Embase	Health Economics 1 January 2014 – 14 June 2021 Quality of Life 1974 – 14 June 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments)
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	Uric Acid/
5.	uric acids*.ti,ab.
6.	(urate adj (crystal* or sodium or mono sodium)).ti,ab.

7.	hyperuricemia/
8.	(hyperuric* or hyper uric*).ti,ab.
9.	podagra.ti,ab.
10.	or/1-9
11.	letter/
12.	editorial/
13.	news/
14.	exp historical article/
15.	Anecdotes as Topic/
16.	comment/
17.	case report/
18.	(letter or comment*).ti.
19.	or/11-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animals/ not humans/
23.	exp Animals, Laboratory/
24.	exp Animal Experimentation/
25.	exp Models, Animal/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.
28.	or/21-27
29.	10 not 28
30.	limit 29 to English language
31.	Economics/
32.	Value of life/
33.	exp "Costs and Cost Analysis"/
34.	exp Economics, Hospital/
35.	exp Economics, Medical/
36.	Economics, Nursing/
37.	Economics, Pharmaceutical/
38.	exp "Fees and Charges"/
39.	exp Budgets/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.

46.	(value adj2 (money or monetary)).ti,ab.
47.	or/31-46
48.	quality-adjusted life years/
49.	sickness impact profile/
50.	(quality adj2 (wellbeing or well being)).ti,ab.
51.	sickness impact profile.ti,ab.
52.	disability adjusted life.ti,ab.
53.	(qal* or qtime* or qwb* or daly*).ti,ab.
54.	(euroqol* or eq5d* or eq 5*).ti,ab.
55.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
56.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
57.	(hui or hui1 or hui2 or hui3).ti,ab.
58.	(health* year* equivalent* or hye or hyes).ti,ab.
59.	discrete choice*.ti,ab.
60.	rosser.ti,ab.
61.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
62.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
63.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
64.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
65.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
66.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
67.	or/48-66
68.	30 and (47 or 67)

Embase (Ovid) search terms

1.	exp gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	exp uric acid/
5.	uric acid*.ti,ab.
6.	(urate adj (crystal* or sodium or mono sodium)).ti,ab.
7.	exp hyperuricemia/
8.	(hyperuric* or hyper uric*).ti,ab.
9.	podagra.ti,ab.
10.	or/1-9
11.	letter.pt. or letter/
12.	note.pt.
13.	editorial.pt.
14.	Case report/ or Case study/
15.	(letter or comment*).ti.
16.	or/11-15

17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animal/ not human/
20.	Nonhuman/
21.	exp Animal Experiment/
22.	exp Experimental animal/
23.	Animal model/
24.	exp Rodent/
25.	(rat or rats or mouse or mice).ti.
26.	or/18-25
27.	10 not 26
28.	limit 27 to English language
29.	health economics/
30.	exp economic evaluation/
31.	exp health care cost/
32.	exp fee/
33.	budget/
34.	funding/
35.	budget*.ti,ab.
36.	cost*.ti.
37.	(economic* or pharmaco?economic*).ti.
38.	(price* or pricing*).ti,ab.
39.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
40.	(financ* or fee or fees).ti,ab.
41.	(value adj2 (money or monetary)).ti,ab.
42.	or/29-41
43.	quality adjusted life year/
44.	"quality of life index"/
45.	short form 12/ or short form 20/ or short form 36/ or short form 8/
46.	sickness impact profile/
47.	(quality adj2 (wellbeing or well being)).ti,ab.
48.	sickness impact profile.ti,ab.
49.	disability adjusted life.ti,ab.
50.	(qal* or qtime* or qwb* or daly*).ti,ab.
51.	(euroqol* or eq5d* or eq 5*).ti,ab.
52.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
53.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
54.	(hui or hui1 or hui2 or hui3).ti,ab.
55.	(health* year* equivalent* or hye or hyes).ti,ab.
56.	discrete choice*.ti,ab.
57.	rosser.ti,ab.
58.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
59.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.

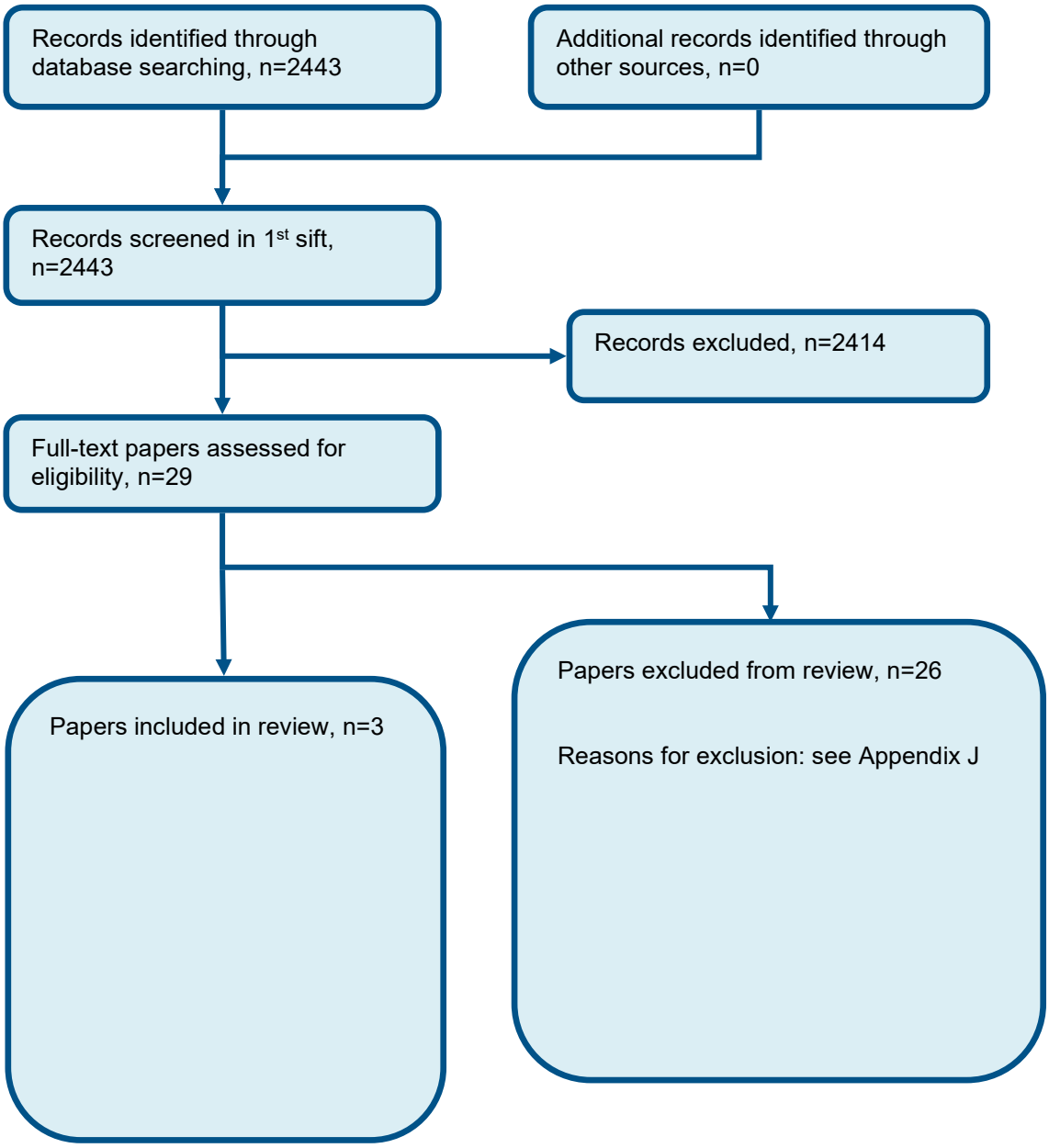
60.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
61.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
62.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
63.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
64.	or/43-63
65.	28 and (42 or 64)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Gout EXPLODE ALL TREES
#2.	(gout*)
#3.	(toph*)
#4.	MeSH DESCRIPTOR Uric Acid EXPLODE ALL TREES
#5.	(uric acid*)
#6.	((urate near (crystal* or sodium or mono sodium)))
#7.	MeSH DESCRIPTOR Hyperuricemia EXPLODE ALL TREES
#8.	((hyperuric* or hyper uric*))
#9.	(podagra)
#10.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of which people with gout should be offered a urate-lowering therapy such as a xanthine oxidase inhibitor, a uricosuric or a uricase?



Appendix D – Effectiveness evidence

Study	Rashid 2015[30]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=8828)
Countries and setting	Conducted in USA; Setting: 14 hospitals, 202 outpatient facilities, and a centralized laboratory
Line of therapy	Not applicable
Duration of study	January 1, 2007–December 31, 2010: 4 years
Method of assessment of guideline condition	Eligible patients were required to have two outpatient gout diagnoses [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 274.xx] ≥30 days apart or one inpatient gout diagnosis code in any position anytime during the study time period.
Stratum	Not applicable
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were included if they received a prescription for a ULT (allopurinol, febuxostat, or probenecid) during the study time period; the index date was defined as the patient's first ULT prescription identified during the study time period. Patients had to be ≥18 years of age at time of index date and were required to have at least 12 months of KPSC membership eligibility including drug benefits prior to their index date, index date, and 12 months post-index
Exclusion criteria	Patients were excluded if they had history of human immunodeficiency virus (HIV), a diagnosis code for chronic kidney disease (CKD) stage 5 or an estimated glomerular filtration rate (GFR) <15 ml/min/1.73 m2, history of dialysis, active cancer, current chemotherapy, or kidney stones/nephrolithiasis
Recruitment/selection of patients	Consecutive

Age, gender and ethnicity	Age: 1-2 flares group: <55 years old – 41%; 55-64 years old – 28.5%; ≥65 years old – 35.5% ≥3 flares group: <55 years old – 30.5%; 55-64 years old – 22.2%; ≥65 years old – 47.3. no gout flares group: <55 years old – 34.2%; 55-64 years old – 28.4%; ≥65 years old – 37.2% Ethnicity: 1-2 flares group: Caucasian 42.7%, African-American 14.1%, Hispanic 19.3%, Asian/Pacific Islander 23.4 %, Other 0.5% ≥3 flares group, Caucasian 42.7%, African-American 14.1%, Hispanic 19.3%, Asian/Pacific islander 23.4 %, Other 0.5% no gout flares group: Caucasian 42.7%, African-American 14.1%, Hispanic 19.3%, Asian/Pacific islander 23.4 %, Other 0.5%
Further population details	Previous treatment: At baseline - 1-2 flares group: NSAIDS 66.7%, Corticosteroids 30.1%, colchicine 52%, antihypertensives 71.8%, diuretics 48.5%, anti-hyperlipidemics45.5%, anti-diabetics 16.7%. ≥3 flares group: NSAIDS 67.1%, Corticosteroids 47.7%, colchicine 64.2%, antihypertensives 76.3%, diuretics 55.1%, anti-hyperlipidemics 46.5%, anti-diabetics 19.3% no gout flares group: NSAIDS 54.3%, Corticosteroids 16.2%, colchicine 33%, antihypertensives 74.8%, diuretics 47.6%, anti-hyperlipidemics 49.8%, anti-diabetics 19.9%
Indirectness of population	No indirectness
Interventions	(n=4377) Intervention 1: Diuretics use. Duration 12 months. Concurrent medication/care N/A Indirectness: No indirectness (n=4451) Intervention 2: No diuretics. Duration 12 months. Concurrent medication/care N/A
Funding	This study was supported by a research grant provided by Savient Pharmaceuticals, Inc. All authors do not have any other financial interests or potential conflict of interest with regards to the work.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Diuretics use versus no diuretics use	

Protocol outcome 1: frequency of flares - Actual outcome: 1-2 flares at 12 months post index; Group 1: 4798/8828, Group 2: 2780/8828; Adjusted OR 1.19 (1.05 to 1.35); Comments: multivariable analysis, confounders studied: sex; age (20-49, 50-59, 60-69, 70-79, 80-89 years);number of GP visits (0-4, 5-9, 10-19, >20 visits); smoking (non-smoker, smoker, former); alcohol consumption (none, 1-9, 10-24, 25-42, >42 U/week); BMI (categories in kg/m2:15-19, 20-24, 25-29, ≥30); Risk of bias: All domain - Low, Selection - Low, Blinding -Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: frequency of flares - Actual outcome: ≥3 flares at 12 months post index; Group 1: 1250/8828, Group 2: 2780/8828; Adjusted OR 1.233 (1.01 to 1.50); Comments: multivariable analysis, confounders studied: sex; age (20-49, 50-59, 60-69, 70-79, 80-89 years);number of GP visits (0-4, 5-9, 10-19, >20 visits); smoking (non-smoker, smoker, former); alcohol consumption (none, 1-9, 10-24, 25-42, >42 U/week); BMI (categories in kg/m2:15-19, 20-24, 25-29, ≥30); Risk of bias: All domain - Low, Selection - Low, Blinding -Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health-related quality of life at short (up to two weeks); Health-related quality of life

Study	Rothenbacher 2011[31]
Study type	Cohort study
Number of studies (number of participants)	1 (n=23857)
Countries and setting	Conducted in UK; Setting: primary care
Line of therapy	Not applicable
Duration of study	January 1, 2000–December 31, 2008: 9 years
Method of assessment of guideline condition	Unclear, not stated

Stratum	Not applicable
Subgroup analysis within study	Not applicable
Inclusion criteria	Cohort population with a first-ever diagnosis of gout recorded in the database using READ codes from January 2000 to December 2007 and who were between 20 and 89 years of age.
Exclusion criteria	Subjects with any prescription of anti-gout treatment or any code suggesting gout before the start date were subsequently excluded from the cohort and considered as prevalent patients. All patients with cancer before the start date were also excluded.
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age – mean (SD): 61.9 (14.5). Gender (M:F): 17358:6499. Ethnicity: not reported
Further population details	Previous treatment: no previous treatment
Indirectness of population	No indirectness
Interventions	(n=880) Intervention 1: Renal impairment – history of chronic kidney failure. Duration 8 years. Concurrent medication/care. Indirectness: No indirectness (n=22977) Intervention 2: Renal impairment – no history of chronic kidney failure. Duration 8 years. Concurrent medication/care: overall Allopurinol 3815 (16%), Colchicine 3245 (13.6%). Indirectness: No indirectness
Funding	The study was sponsored by Novartis Pharma AG
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Diuretics use versus no diuretics use	

Protocol outcome 1: frequency of flares - Actual outcome: 1 or more flares over 3.8 years of observation period; Group 1: 8806/23857, Group 2: 15051/23857; HR (95% CI)1.33 (1.20, 1.48). Comments: Multivariable analysis, confounders studied: sex; age (20-49, 50-59, 60-69, 70-79, 80-89 years);number of GP visits (0-4, 5-9, 10-19, >20 visits); smoking (non-smoker, smoker, former); alcohol consumption (none, 1-9, 10-24, 25-42, >42 U/week); BMI (categories in kg/m 2:15-19, 20-24, 25-29, ≥30); Risk of bias: All domain - Low, Selection - Low, Blinding -Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health-related quality of life at short (up to two weeks); Health-related quality of life

Study	**Scire 2013[32]**
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=446)
Countries and setting	Conducted in Italy; Setting: rheumatology clinics
Line of therapy	Not applicable
Duration of study	June 2011 and January 2012: 6 months
Method of assessment of guideline condition	Unclear, gout diagnosis confirmed by rheumatologists
Stratum	Not applicable
Subgroup analysis within study	Not applicable
Inclusion criteria	Clinical diagnosis of gout

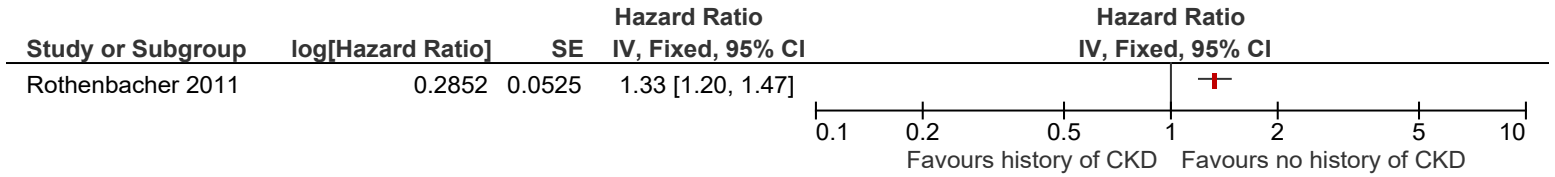
Exclusion criteria	Patients without gout
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age – mean (SD): 63.9 (11.6). Gender (M:F): 403:446. Ethnicity: not reported
Further population details	Previous treatment: overall at baseline: corticosteroids 125 (28%), NSAIDs or colchicine 189 (42.4%), Allopurinol 303 (67.9%), Febuxostat 60 (13.4%)
Indirectness of population	No indirectness
Interventions	(n=87) Intervention 1: Presence of tophi. Duration 6 months. Concurrent medication/care unclear not stated Indirectness: No indirectness (n=359) Comparison 1: No presence of tophi. Duration 6 months. Concurrent medication/care: unclear not stated. Indirectness: No indirectness (n=unclear) Intervention2: Presence of any joint damage – swollen joints. Duration 6 months. Concurrent medication/care: unclear not stated Indirectness: No indirectness n=unclear) Comparison 2: Presence of any joint damage – no swollen joints. Duration 6 months. Concurrent medication/care: unclear not stated. Indirectness: No indirectness (n=unclear) Intervention 3: Presence of any joint damage – tender joints. Duration 6 months. Concurrent medication/care: unclear not stated Indirectness: No indirectness n=unclear) Comparison 3: Presence of any joint damage – no tender joints. Duration 6 months. Concurrent medication/care: unclear not stated. Indirectness: No indirectness
Funding	Not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Diuretics use versus no diuretics use Protocol outcome 1: health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures: - Actual outcome: SF36 physical component; Group 1: unclear/446, Group 2: unclear/446; presence of tophi: adjusted MD -3.20 (-5.41, -0.99); number of swollen joints: adjusted MD -0.54 (-0.79, -0.29); number of tender joints: adjusted MD -0.39 (-0.55 to 0.23) Comments: N/A Risk of bias: All domain - Low, Selection - Low, Blinding -Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures - Actual outcome: SF36 mental component; Group 1: unclear/446, Group 2: unclear/446; presence of tophi: adjusted MD 1.26 (-0.88, 3.40); number of swollen joints: -0.2 (-0.45 to 0.04); number of tender joints: adjusted MD -0.24 (-0.39 to 0.09). Comments: N/A Risk of bias: All domain - Low, Selection - Low, Blinding -Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures - Actual outcome: HAQ-DI; Group 1: unclear/446, Group 2: unclear/446; presence of tophi: adjusted OR 1.92 (1.07 to 3.45); number of swollen joints: adjusted OR 1.23 (1.13 to 1.34); number of tender joints: adjusted OR 1.10 (1.06 to 1.14). Comments: N/A Risk of bias: All domain - Low, Selection - Low, Blinding -Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Frequency of flares

Appendix E – Forest plots

E.1 Renal impairment - history of chronic renal failure

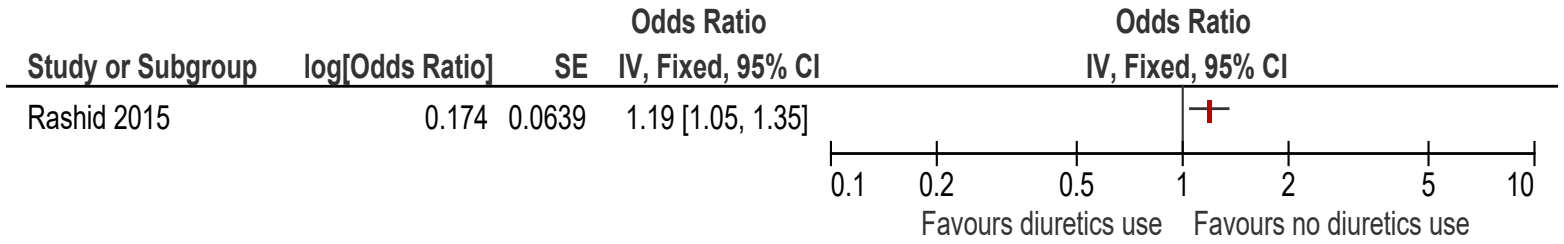
Figure 2: Frequency of flares (1 or more flares)[a]



[a] Hazard ratio was adjusted for sex, age (at start date of follow-up), GP visits (1 year before first-ever diagnosis of gout), smoking, alcohol, BMI, IHD, hypertension, hyperlipidaemia, renal failure and diabetes (anytime before first-ever diagnosis of gout).

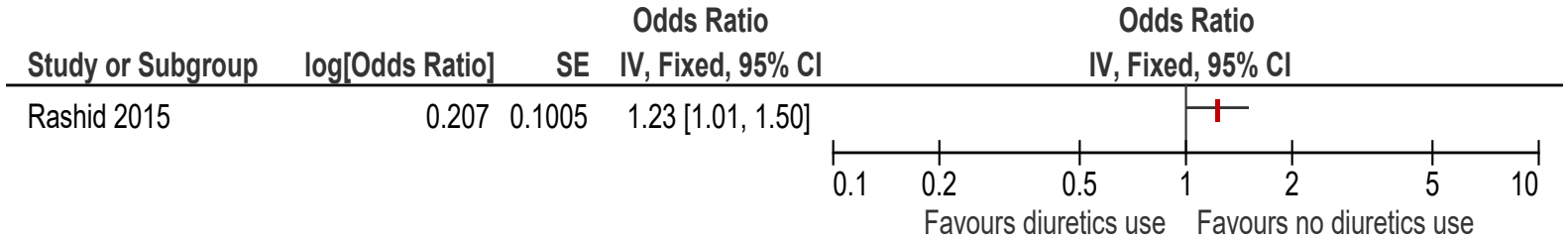
E.2 Diuretics use

Figure 3: Frequency of flares (1-2 flares)[a]



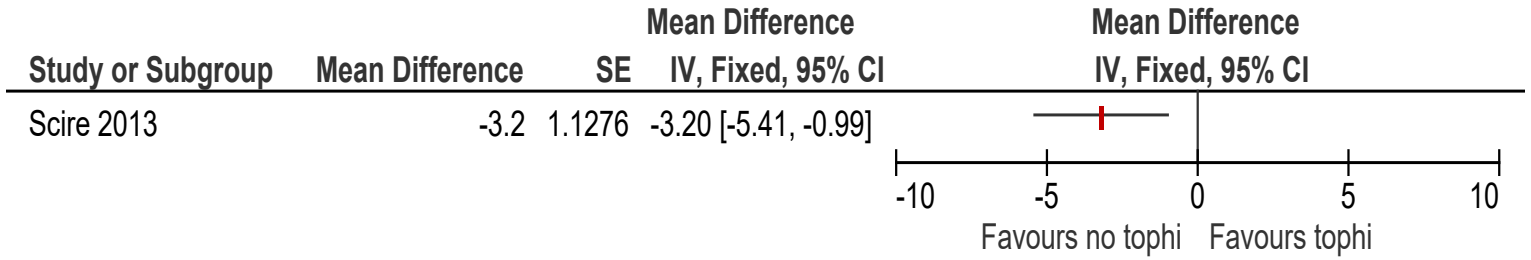
[a] Confounders adjusted for: sex, age, race, sUA levels, comorbidities, anti-inflammatory medications, diuretic use, and rheumatologist as a prescriber

Figure 4: Frequency of flares (≥3 flares)



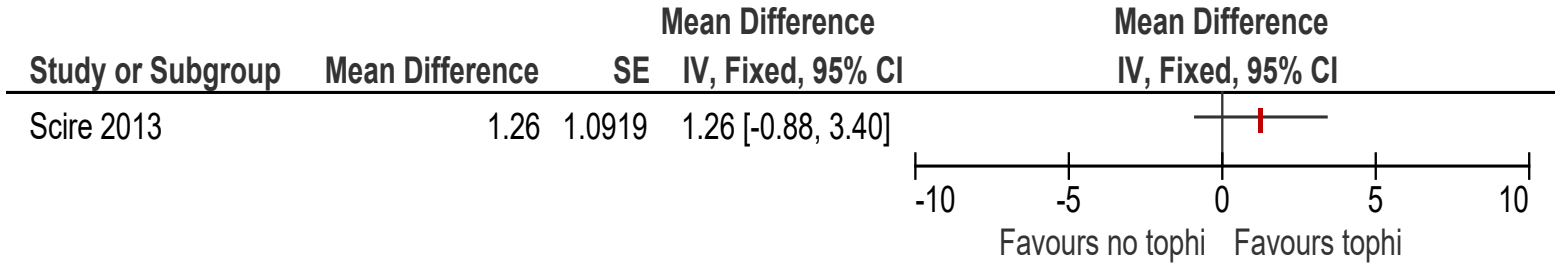
[a] Confounders adjusted for: sex, age, race, sUA levels, comorbidities, anti-inflammatory medications, diuretic use, and rheumatologist as a prescriber

Figure 5: SF 36 physical component



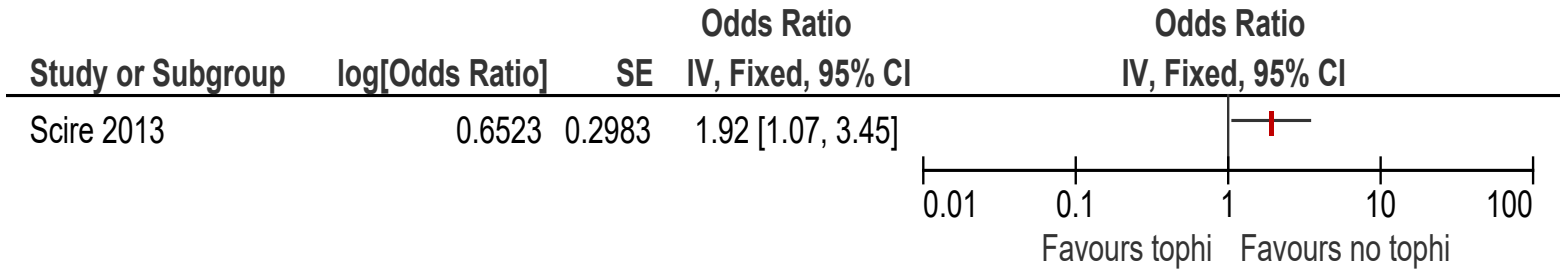
[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

Figure 6: SF 36 mental component



[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

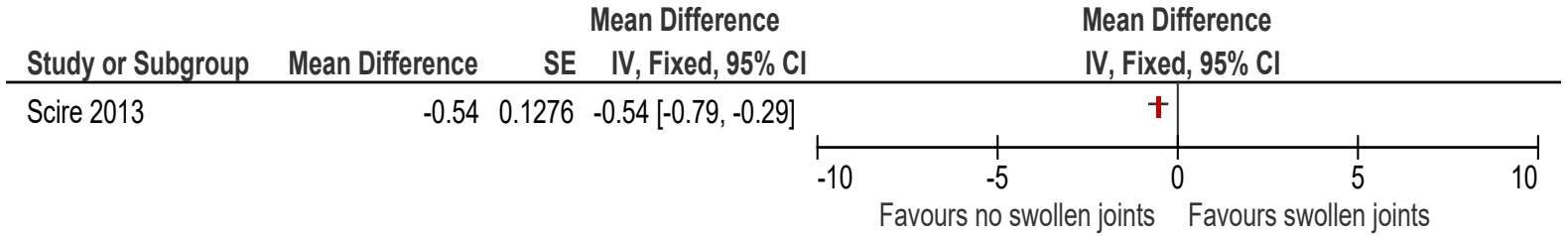
Figure 7: HAQ-DI



[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

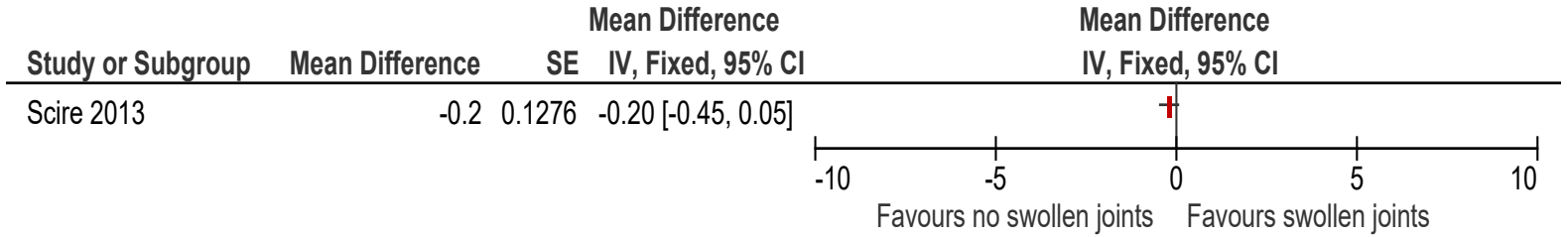
E.3 Presence of any joint damage – number of swollen joints

Figure 8: SF 36 physical component



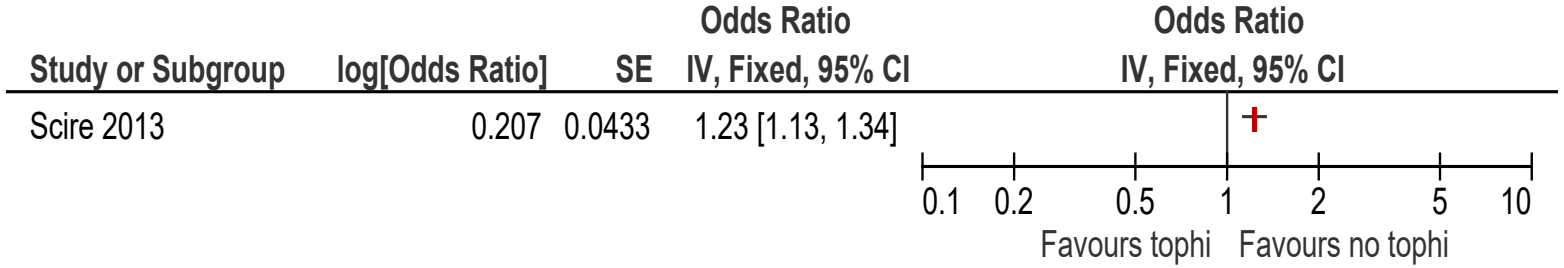
[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

Figure 9: SF 36 mental component



[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

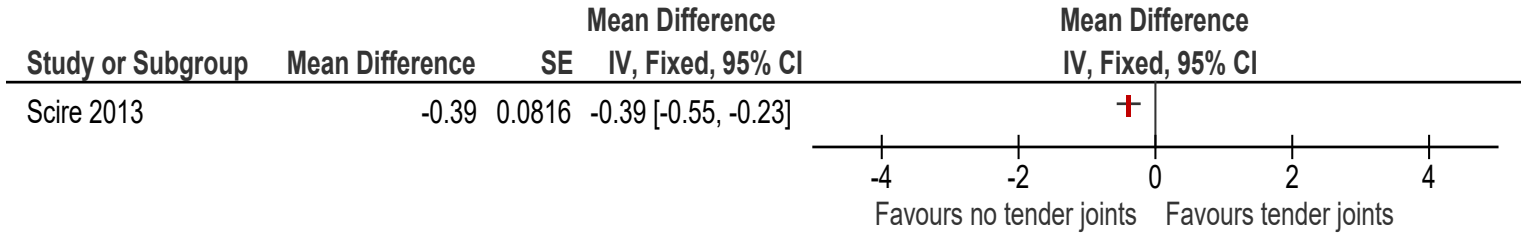
Figure 10: HAQ-DI



[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

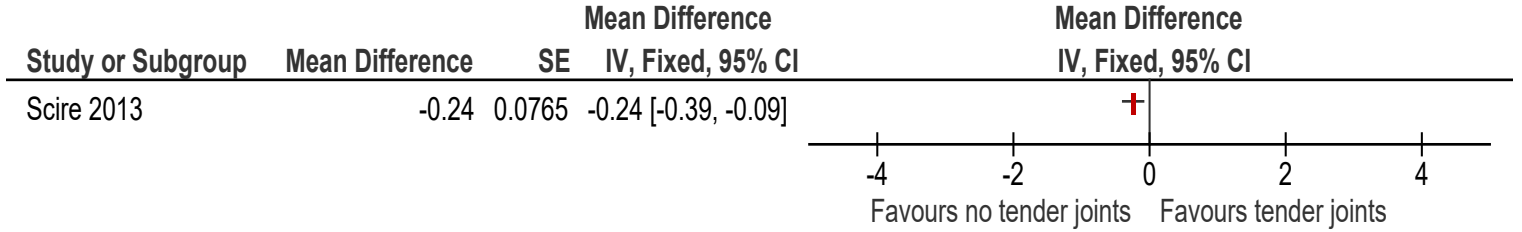
E.4 Presence of any joint damage – number of tender joints

Figure 11: SF 36 physical component



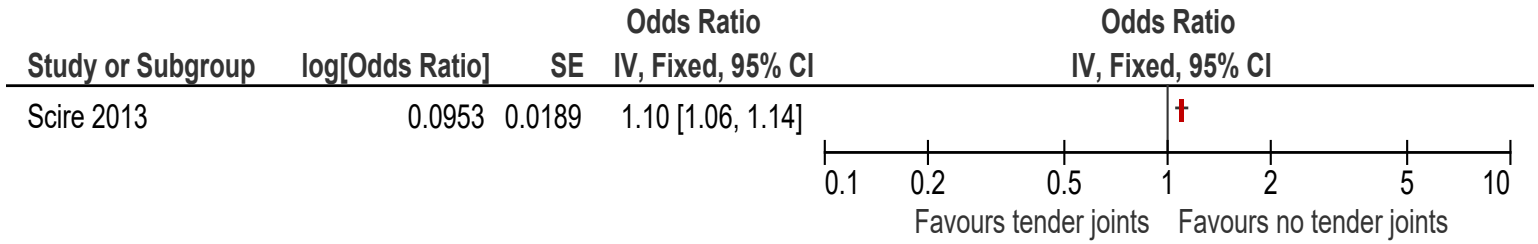
[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

Figure 12: SF 36 mental component



[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

Figure 13: HAQ-DI



[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

Appendix F – GRADE tables

Table 18: Clinical evidence profile: history of renal impairment versus no history of renal impairment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Renal impairment - history of renal failure	no history of renal failure	Relative (95% CI)	Absolute (95% CI)		
Frequency of flares (1 or more flares)												
1	observational studies	not serious[1]	not serious	not serious	not serious	none	-	-	**HR 1.33** (1.20 to 1.47)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

[1]. Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Methods: multivariable analysis adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment.

[2] Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes.

Table 19: Clinical evidence profile: diuretics use versus no diuretics use

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	diuretics use	no diuretic use	Relative (95% CI)	Absolute (95% CI)		
1-2 flares												
1	observational studies	not serious[1]	not serious	not serious	not serious	none	-	-	**OR 1.19** (1.05 to 1.35)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
>=3 flares												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	diuretics use	no diuretic use	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious[1]	not serious	not serious	not serious	none	-	-	**OR 1.23** (1.01 to 1.50)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

[1]. Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Methods: multivariable analysis adjusted for sex, age, race, sUA levels, comorbidities, anti-inflmmatory medications, diuretic use, and rheumatologist as a prescriber.

[2] Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes.

Table 20: Clinical evidence profile: presence of tophi versus no presence of tophi

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of tophi	no presence of tophi	Relative (95% CI)	Absolute (95% CI)		
SF36 physical component												
1	observational studies	not serious[1]	not serious	not serious	not serious	none	-	-	-	MD **3.2 lower** (5.41 lower to 0.99 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
SF36 mental component												
1	observational studies	not serious[1]	not serious	not serious	serious[2]	none	-	-	-	MD **1.26 higher** (0.88 lower to 3.4 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
HAQ-DI												
1	observational studies	not serious[1]	not serious	not serious	not serious	none	-	-	**OR 1.92** (1.07 to 3.45)	**2 fewer per 1,000** (from 3 fewer to 1 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

[1]. Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Methods: multivariable analysis adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment.

[2] Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes.

Table 21: Clinical evidence profile: swollen joints versus no swollen joints

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of any joint damage - number of swollen joints	no swollen joints	Relative (95% CI)	Absolute (95% CI)		
SF36 physical component												
1	observational studies	not serious	not serious	not serious	not serious	none	0	0	-	MD **0.54 lower** (0.79 lower to 0.29 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
SF36 mental component												
1	observational studies	not serious[1]	not serious	not serious	serious[2]	none	0	0	-	MD **0.2 lower** (0.45 lower to 0.05 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
HAQ-DI												
1	observational studies	not serious	not serious	not serious	not serious	none	-/0	-/0	**OR 1.23** (1.13 to 1.34)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

1 Method: multivariable analysis adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

2. Downgraded by 1 increment because the confidence interval crossed the null line

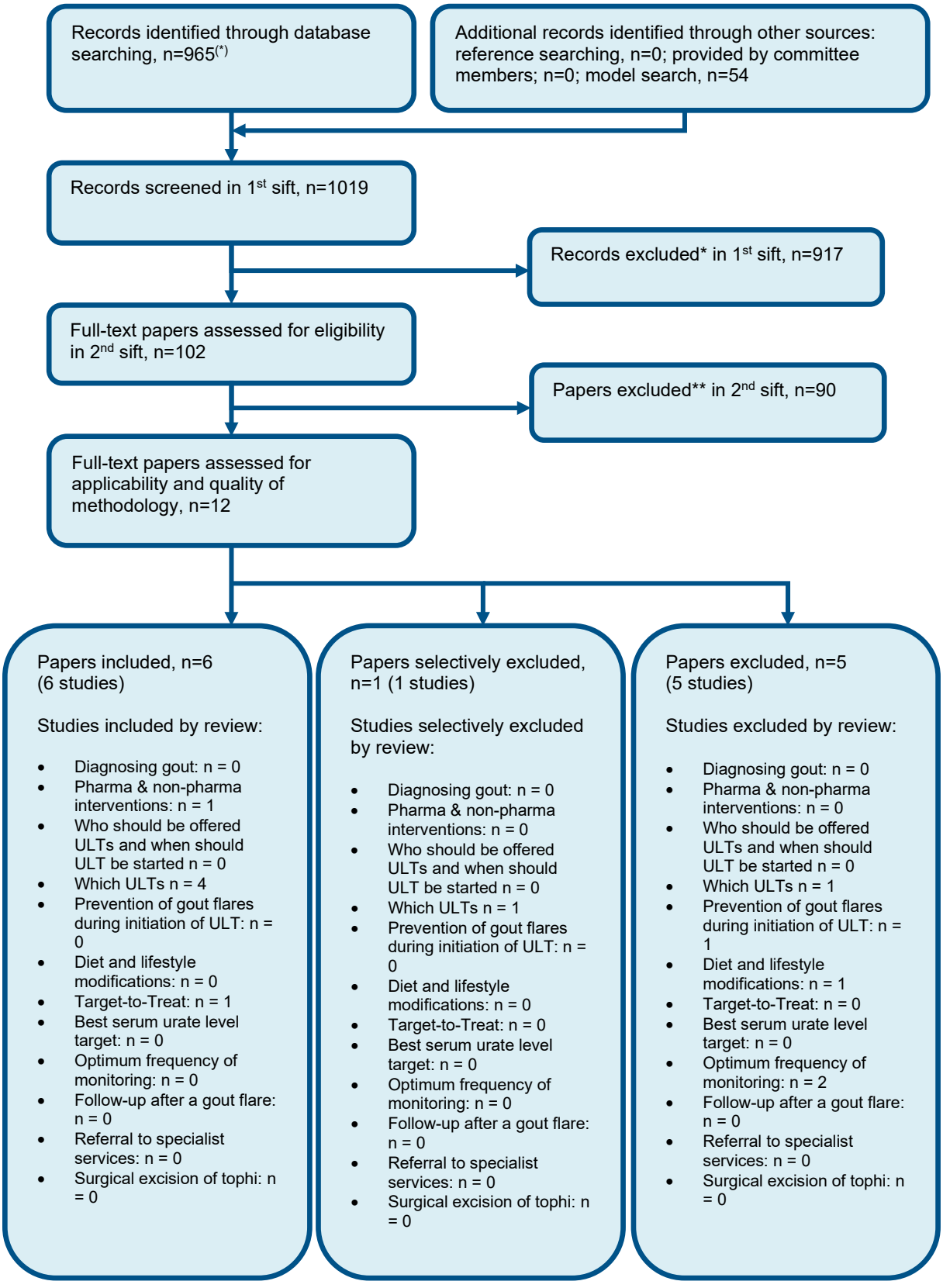
Table 22: Clinical evidence profile: tender joints versus no tender joints

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of any joint damage - number of tender joints	no tender joints	Relative (95% CI)	Absolute (95% CI)		
SF36 physical component												
1	observational studies	not serious[1]	not serious	not serious	not serious	none	0	0	-	MD **0.39 lower** (0.55 lower to 0.23 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
SF36 mental component												
1	observational studies	not serious[1]	not serious	not serious	not serious	none	0	0	-	MD **0.24 lower** (0.39 lower to 0.09 lower)	⨁⨁⨁ HIGH	CRITICAL
HAQ-DI												
1	observational studies	not serious[1]	not serious	not serious	not serious	none	-/0	-/0	**OR 1.10** (1.06 to 1.14)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

1 Methods: multivariable analysis adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

Appendix G – Economic evidence study selection

Figure 14: Flow chart of health economic study selection for the guideline



* excludes conference abstracts (n=280)

**Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

None.

Appendix I – Health economic model

No original economic modelling was undertaken for this review question.

Appendix J – Excluded studies

Clinical studies

Table 23: Studies excluded from the clinical review

Study	Exclusion reason
Abhishek 2016[2]	Incorrect study design - case-control study, cases comprised participants with >2 gout flares, controls <=2 gout flares, binary logistic regression
Abhishek 2017[1]	Incorrect study design - cross sectional study, bivariate logistic regression (adjusted for missing data), outcome - self-reported trigger of gout attacks
Alvarez-Nemegyei 2005[4]	Incorrect study design - cohort nested case-control study, patients with disability were compared to patients without disability
Avarado-de laBarrera 2020[3]	incorrect comparison - study aimed to determine the proportion of patients achieving SU target level of <6 for patients with non-severe gout and <5 mg/dL for patients with severe gout, as well as patients achieving remission after 5 years of follow-up, no multivariate analysis
Chandratre 2018[6]	Linear regression, to examine gout-related, comorbid and socio demographic characteristics associated with generic and disease specific HRQOL in gout, no multivariate analysis
Changchien 2015[7]	Incorrect comparison - primary endpoint was diagnosis of depressive disorders during follow-up in people with gout versus people without gout
Chapron 2019[8]	Incorrect study design/incorrect comparison - descriptive study of non-pharmacological management of gout. Secondary objective was to identify non-pharmacological management compliance among patients
Dalbeth 2013[9]	Incorrect comparison/analysis - factors independently associated with presence and number of tophi were analysed
Dalbeth 2018[10]	Incorrect comparison/analysis - dual energy CT assessed crystal deposition assessed crystal deposition in patients with gout treated with stable dose of allopurinol and investigated potential clinical determinants for crystal deposition. No multivariate analysis
Edwards 2011[13]	Incorrect comparison/analysis, the objective of this study was to assess how gout flares affect these activities in patients with chronic gout refractory to conventional therapy. No multivariate analysis. Nonrelevant outcomes
Fu 2017[15]	Incorrect study design - case-control study, survey was administered to gout patients and controls of gender-matched healthy individuals, study aimed to analyse prevalence of depression

Study	Exclusion reason
Fu 2018[14]	Incorrect study design - case-control study, study analysed risk factors for depression and anxiety in gout patients
Khanna 2011[20]	Incorrect comparison/analysis - before and after study, SF36 at baseline and SF36 at follow-up
Khanna 2012[19]	Incorrect comparison/analysis - association between QoL measures and frequency of gout flares, no multivariate analysis
Khanna 2015[21]	Incorrect comparison/analysis - mean scores of SF-12, for all patients and by gout status, no multivariate analysis
Khanna 2016[18]	Incorrect study design - cross-sectional study, no multivariate analysis
Mak 2009[23]	No relevant outcomes
Mitnala 2016[24]	Incorrect comparison/analysis - case-control study examined the clinical and genetic features of diuretic-associated gout, logistic regression of diuretic status with SLC2A9 , ABCG2 and SLC22A11 risk alleles
Pascart 2019[27]	Incorrect analysis/incorrect comparisons - study analysed variables associated with early onset group vs common gout group
Prior 2016[28]	Incorrect comparison/analysis/ no relevant outcomes - study aimed to determine the prevalence of depression and anxiety in gout, association between anxiety and depression and gout characteristics
Proudman 2019[29]	Incorrect comparison/analysis - prevalence study, no multivariate analysis
So 2011[33]	Incorrect analysis - multivariate analysis not adjusted for age and sex
Stewart 2018[36]	Incorrect analysis - stepwise linear regression
Taylor 2008[37]	Incorrect comparison/analysis - Rasch analysis was used to determine the internal validity of summated scores as a measure of physical disability, no multivariate analysis
Youssef 1995[38]	Incorrect population - included 42% patients without gout, no multivariate analysis
Zhang 2016[39]	Incorrect analysis - linear regression model for flare frequency and cumulative number of involved joints was used, factors analysed were onset age, duration and sUA, no multivariate analysis

Health Economic studies

None.