



# AMERICAN COLLEGE OF RHEUMATOLOGY

EDUCATION • TREATMENT • RESEARCH

## American College Of Rheumatology Updated Guideline for the Management of Gout

*Project Plan – ~~October 2018~~ Updated March 2019*

### **PARTICIPANTS**

*(still being finalized)*

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**ORGANIZATIONAL LEADERSHIP AND SUPPORT**

This updated clinical practice guideline is being developed by the American College of Rheumatology (ACR) with funding by the ACR.

**BACKGROUND**

Gout is the most common inflammatory arthritis, affecting 4% of adults in the United States. While the pathophysiology is well-understood and effective treatments are available, the management of gout remains poor, with 70% experiencing recurrent flares, and a substantial proportion burdened by tophi, joint damage, and functional limitations.

**OBJECTIVES**

The objective of this project is to develop recommendations for the management of patients with gout. Specifically, we aim to develop recommendations for:

1. Indications for urate-lowering therapy.
2. Approaches to initiating urate-lowering therapy.
3. Ongoing management of urate-lowering therapy.
4. Management of gout flares.
5. Lifestyle factors in patients with gout.
6. Asymptomatic hyperuricemia.

Additionally, we will develop recommendations for each of the categories above for specific subgroups of patients as appropriate.

**METHODS**

*Identification of Studies*

Literature search strategies, based on PICO questions (Population/patients, Intervention, Comparator, and Outcomes; *see Appendix A*) will be developed by the research librarian, systematic literature review leader, and principal investigators, with input from the Core Team. The search strategies will be peer reviewed by another medical librarian using Peer Review of Electronic Search Strategies (PRESS) (1).



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37 Searches will be performed in OVID Medline (1946 +), Embase (1974 +), the Cochrane Library, and  
38 PubMed (mid-1960s +).

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40 The search strategies will be developed using the controlled vocabulary or thesauri language for each  
41 database: Medical Subject Headings (MeSH) for OVID Medline, PubMed and Cochrane Library; and  
42 Emtree terms for Embase. Text words will also be used in OVID Medline, PubMed, and Embase, and  
43 keyword/title/abstract words in the Cochrane Library.

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45 *Search Limits*

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47 Only English language articles will be retrieved.

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49 *Grey Literature*

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51 The websites of appropriate agencies, such as the Agency for Healthcare Research and Quality (AHRQ),  
52 will be searched for peer-reviewed reports not indexed by electronic databases.

53  
54 *Literature Search Update*

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56 Literature searches will be updated one month prior to the voting panel meeting to ensure  
57 completeness.

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59 *Inclusion/Exclusion Criteria*

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61 See PICO questions (*Appendix A*), which outline the defined patient population, interventions,  
62 comparators and outcomes.

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64 *Management of Studies and Data*

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66 References and abstracts will be imported into bibliographic management software (Reference  
67 Manager) (2), duplicates removed, and exported to Distiller SR, a web-based systematic review manager  
68 (3). Screening forms will be created in Distiller SR. Search results will be divided among reviewers, and  
69 two reviewers will screen each title/abstract, with disagreements at the title/abstract screening stage  
70 defaulting to inclusion for full manuscript review. Following the same dual review process,  
71 disagreements at the full manuscript screening stage will be discussed and adjudicated by the literature  
72 review leadership, if necessary.

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75 *Phases*

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77 1. A search for randomized controlled trials and observational studies about interventions aimed  
78 at the management of gout will be performed to determine existing studies covering outcomes  
79 of interest.

80 2. Additionally, recently published systematic reviews covering outcomes of interest will also be  
81 sought and used for reference cross-checking.

82 3. Data will be abstracted and evidence will be synthesized using RevMan (4) and GRADE Pro  
83 software (5), respectively.

84 4. Chosen studies will be assessed for risk of bias using modified versions of the Cochrane Risk of  
85 Bias tool (6) and the ROBINS-I (7).

86 5. The evidence will be synthesized and assessed at the outcome level within each question using  
87 the GRADE approach.

88

89 *GRADE Methodology*

90

91 GRADE methodology (8) will be used in this project to rate the certainty of evidence and facilitate  
92 development of recommendations. The certainty in the evidence (also known as “quality” of evidence)  
93 will be graded as high, moderate, low or very low. The strength of recommendations will be graded as  
94 strong or conditional. The strength of recommendations will not depend solely on the certainty in the  
95 evidence, but also on patient preferences and values, the balance between benefits and harms, and  
96 other important considerations when necessary (e.g., resources, feasibility, acceptability). A series of  
97 articles that describe the GRADE methodology can be found on the GRADE working group’s website:  
98 [www.gradeworkinggroup.org](http://www.gradeworkinggroup.org).

99

100 *Analysis and Synthesis*

101

102 The literature review team will appraise and synthesize data from included studies that address the  
103 PICO questions. Meta-analysis will be conducted to pool results across studies whenever possible. When  
104 not possible, a narrative synthesis of the results will be presented. An evidence summary, which  
105 includes the estimates of effects comparing the options and details regarding the assessment of the  
106 certainty of the evidence, will be prepared for each PICO question using GRADEprofiler (GRADEpro)  
107 software (5). The evidence summary will contain all of the outcomes (benefits and harms) considered  
108 important for formulating recommendations summarized across studies. For each outcome, the  
109 summary will present the relative effects comparing the options under consideration, the assumed and  
110 corresponding risk for comparators and interventions (95% CI), the risk difference, the number of



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111 participants/number of studies providing evidence for that outcome, and the certainty of the evidence  
112 (i.e., high, moderate, low or very low).

113  
114 The evidence summary will also document the overall certainty in the evidence for each critical and  
115 important outcome across studies and summarize the rationale of the GRADE criteria for rating down  
116 (risk of bias, inconsistency, indirectness, imprecision and publication bias), or rating up the certainty in a  
117 body of evidence (large magnitude of effect, dose-response gradient, and all plausible confounding that  
118 would reduce a demonstrated effect).

119  
120 *Development of Recommendation Statements*

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122 PICO questions will be revised to formulate recommendation statements. Using the evidence  
123 summaries, the voting panel, consisting of nine rheumatologists, one nephrologist, one physician  
124 assistant, one health services researcher, and two patient representatives (one still to be determined),  
125 will consider the drafted recommendation statements in two stages. The voting panel will first  
126 individually evaluate and vote on each drafted recommendation statement using the evidence  
127 summary. The initial votes are anonymous and used to determine where consensus (70% or greater  
128 agreement) exists on the drafted recommendation statements. The results of round 1 voting will  
129 determine the in person voting panel meeting agenda. At the face-to-face voting panel meeting, chaired  
130 by the co-principal investigators, the panelists will review results of all PICO round 1 votes, discuss the  
131 evidence in the context of their clinical experience and expertise to reach consensus on the final  
132 recommendations. The voting panel meeting discussions will be supported by the literature review  
133 leader, the GRADE expert, and selected members of the literature review team, who will attend the  
134 meeting to provide details about the evidence, as requested. Voting panel discussions and decisions will  
135 be informed by a separately convened patient panel, which will meet in the days before the voting panel  
136 meeting, to provide unique patient perspectives on the drafted recommendations based on their  
137 experiences and the available literature; the two patients on the voting panel will participate in the  
138 separate patient panel meeting.

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140 **PLANNED APPENDICES (AT MINIMUM)**

- 141  
142 A. Final literature search strategies  
143 B. Evidence summaries, including GRADE evidence profiles, for each PICO question

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148 **AUTHORSHIP**

149

150 Authorship of the guideline will include: co-principal investigators, Drs. John FitzGerald and Tuhina  
151 Neogi, as the lead authors and voting panel leaders; Dr. Romina Brignardello-Petersen, literature review  
152 leader; Drs. Ted Mikuls and Nicola Dalbeth, content experts; and Dr. Gordon Guyatt, GRADE expert.  
153 Members of the literature review team and voting panel will also be authors. The co-PIs will determine  
154 final authorship and order of authors, dependent on the efforts made by individuals throughout the  
155 guideline development process, using international authorship standards as guidance.

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157 **DISCLOSURES/CONFLICTS OF INTEREST**

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159 The ACR's disclosure and COI policies for guideline development will be followed for this project. These  
160 can be found in the ACR Guideline Manual on [this page of the ACR web site](#), under Policies &  
161 Procedures. *See Appendix B for participant disclosures.*

162

163 **REFERENCES**

164

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180 APPENDIX A – PICO Questions

181 **Best Practice Statements**

- 182 • Unless otherwise stated, prescribers should adhere to regulatory and labelling guidance.
- 183 • Patients starting any therapy for gout should be educated on the role of each therapy (e.g. anti-inflammatory for symptoms relief, urate lowering with purpose of reducing risk of gout attack or tophus burden), and for those starting ULT, the need for continuous use.
- 185 • Pertinent comorbidities (e.g., cardiovascular disease, hypertension, diabetes, renal insufficiency, nephrolithiasis) should be assessed in all patients with gout with appropriate management of the condition(s).

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190 **Definitions**

- 191 • ACTH: adrenocorticotrophic hormone
- 192 • Anti-IL1 therapy: anakinra, canakinumab, rilonacept
- 193 • Anti-inflammatory treatments for flare or prophylaxis: colchicine, NSAIDs, glucocorticoids (oral, parenteral or intra-articular), anti-IL-1 therapy
- 194 • Asymptomatic Hyperuricemia: individual with serum urate  $\geq 6.8$ mg/dL with no prior gout flares or subcutaneous tophi or imaging
- 195 • Chronic Kidney Disease Stage 3, Glomerular Filtration Rate  $< 60$  ml/min/1.73m<sup>2</sup>
- 196 • Clinical remission: no gout flares in the last 12 months AND no subcutaneous tophi
- 197 • Flare Frequency:
  - 200 ○ Infrequent gout flares ( $< 2$  per year) vs.
  - 201 ○ Frequent gout flares ( $\geq 2$  per year)
- 202 • Medications that impact serum urate levels:
  - 203 ○ Increase serum urate: hydrochlorothiazide, furosemide, low-dose ASA ( $\leq 325$ mg/d)
  - 204 ○ Decrease serum urate: losartan, fenofibrate
- 205 • Suboptimal Flare Treatment Response: Failure to achieve low pain score (e.g.  $\leq 2$  using a VAS scale of 0 to 10) OR failure to return to baseline pain score
- 206 • ULT (urate-lowering therapy): allopurinol, febuxostat, probenecid, lesinurad, pegloticase
  - 207 ○ Low dose ULT: Allopurinol  $\leq 150$  mg/day, Febuxostat  $\leq 40$  mg/day, Probenecid  $\leq 250$  mg twice daily
  - 208 ○ Intensive ULT: pegloticase **OR** serum urate target  $< 3$  mg/dL
- 209 • Subcutaneous tophus – A tophus that is detectable by physical examination.
- 210 • Imaging evidence of MSU crystal deposition - Findings that are highly suggestive of monosodium urate crystals on an imaging test (regardless if clinically palpable)
- 211 • Durability of ULT: Duration of ULT adherence. Lack of ULT abandonment.





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**Indications for urate-lowering therapy**

1. For patients with one or more subcutaneous tophi (with any number of gout flares), what is the impact of starting ULT compared with no ULT on gout flares, pain scores, tophus, patient global assessment, health related quality of life, activity limitation, joint damage, serum urate, changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse events (mild-moderate and serious)?
  - Does the relative impact differ across different ULT medications (allopurinol, febuxostat, probenecid, lesinurad, pegloticase)?
  - Does this differ in patients with radiographic damage vs. those without radiographic damage?
  - Do the effects differ in patients with tophi on advanced imaging (ultrasound, MRI, CT, or dual energy CT) but no subcutaneous tophi vs those with subcutaneous tophi?
  - People with CKD 3 or worse versus normal or mild CKD stages (1 or 2)?
2. For patients with radiographic damage (any modality) due to gout, but no subcutaneous tophi on exam (with any number of gout flares), what is the impact of starting ULT compared with no ULT on gout flares, pain scores, tophus, patient global assessment, health related quality of life, activity limitation, joint damage, serum urate, changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse events (mild-moderate and serious)?
  - Does the relative impact differ across different ULT medications (allopurinol, febuxostat, probenecid, lesinurad, pegloticase)?
  - People with CKD 3 or worse versus normal or mild CKD stages (1 or 2)?
3. For patients without subcutaneous tophi and with frequent gout flares (two or more gout flares/year), what is the impact of starting ULT compared with no ULT on gout flares, pain scores, tophus, patient global assessment, health related quality of life, activity limitation, joint damage, serum urate, changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse events (mild-moderate and serious)?
  - Does the relative impact differ across different ULT medications (allopurinol, febuxostat, probenecid, lesinurad, pegloticase)?
  - People with CKD 3 or worse versus normal or mild CKD stages (1 or 2)?
4. For patients without tophi who have previously experienced more than one flare but have had a low frequency < 2/year of flares, what is the impact of starting ULT compared with no ULT on gout flares, pain scores, tophus, patient global assessment, health related quality of life, activity limitation, joint damage, serum urate, changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse events (mild-moderate and serious)?





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- Does the relative impact differ across different ULT medications (allopurinol, febuxostat, probenecid, lesinurad, pegloticase)?
  - Do these effects differ in the following subgroups?
    - People with CKD 3 or worse versus normal or mild CKD stages (1 or 2)?
    - People with urolithiasis versus no urolithiasis?
    - People with cardiovascular disease versus no cardiovascular disease?
    - People with hypertension versus no hypertension?
    - People with marked hyperuricemia (SU > 9 mg/dl), versus SU ≤9mg/dL?
    - People with early onset disease (<30 in men, premenopausal women) versus those with later onset?
    - People with renal transplantation versus no renal transplantation?
5. For patients without tophi and who have experienced a single gout flare, what is the impact of starting ULT compared with no ULT on gout flares, pain scores, tophus, patient global assessment, health related quality of life, activity limitation, joint damage, serum urate, changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse events (mild-moderate and serious)?
- Does the relative impact differ across different ULT medications (allopurinol, febuxostat, probenecid, lesinurad, pegloticase)?
  - Do these effects differ in the following subgroups?
    - People with CKD 3 or worse versus normal or mild CKD stages (1 or 2)?
    - People with urolithiasis versus no urolithiasis?
    - People with cardiovascular disease versus no cardiovascular disease?
    - People with hypertension versus no hypertension?
    - People with marked hyperuricemia (SU > 9 mg/dl), versus SU ≤9mg/dL?
    - People with early onset disease (<30 in men, premenopausal women) versus those with later onset?
    - People with renal transplantation versus no renal transplantation?

278 **Approaches to Initiating urate lowering therapy (ULT)**

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6. For patients diagnosed with gout starting any ULT, what is the impact of starting ULT during a gout flare compared with starting ULT after the gout flare has resolved on: current gout flare severity, current gout flare duration, subsequent gout flares, pain scores, tophus, patient global assessment, serum urate, changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse events (mild-moderate and serious)?
- Does the relative impact differ across different ULT medications (allopurinol, febuxostat, probenecid, lesinurad, pegloticase)?



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- 287 7. For patients diagnosed with gout starting any ULT, what is the impact of starting a low dose of the  
288 ULT agent (e.g., allopurinol  $\leq$ 150mg, febuxostat  $\leq$ 40mg, probenecid 250mg bid) with gradual dose  
289 escalation compared with starting the ULT at a higher dose (e.g., allopurinol 300mg, febuxostat  
290 80mg, probenecid 1g bid) on: gout flares, pain scores, tophus, patient global assessment, health  
291 related quality of life, activity limitation, joint damage, serum urate, changes in gout flares or tophus  
292 as inferred by changes in serum urate, cost, adverse events (mild-moderate and serious), patient  
293 adherence, durability of ULT?
- 294 • Does the relative impact differ across different ULT medications (allopurinol, febuxostat,  
295 probenecid, lesinurad, pegloticase)?
- 296 8. For patients diagnosed with gout prescribed any ULT (allopurinol, febuxostat, probenecid, lesinurad,  
297 pegloticase), what is the impact of a non-physician health care professional-augmented (e.g.  
298 nursing or pharmacy) package of care compared with usual care on: gout flares, pain scores, tophus,  
299 patient global assessment, health related quality of life, activity limitation, joint damage, serum  
300 urate, changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse events  
301 (mild-moderate and serious) patient adherence, durability of ULT?
- 302 • Does the relative impact differ across different ULT medications (allopurinol, febuxostat,  
303 probenecid, lesinurad, pegloticase)?
- 304 9. ~~For patients diagnosed with gout starting any ULT (allopurinol, febuxostat, probenecid, lesinurad,  
305 pegloticase), what is the relative impact of concomitant anti-inflammatory prophylaxis therapy  
306 (colchicine, NSAIDs, prednisone/prednisolone, canakinumab, rilonacept, anakinra) compared with  
307 no anti-inflammatory prophylaxis on: gout flares, pain scores, tophus, patient global assessment,  
308 health related quality of life, activity limitation, joint damage, serum urate, changes in gout flares or  
309 tophus as inferred by changes in serum urate, cost, adverse events (mild-moderate and serious)  
310 patient adherence, durability of ULT? REVISED QUESTION (changed during literature review): For  
311 patients diagnosed with gout with an indication for ULT, what is the relative impact of starting  
312 allopurinol, febuxostat, probenecid, allopurinol/lesinurad 200mg combination, febuxostat/lesinurad  
313 200mg combination, pegloticase, or no treatment?~~
- 314 • Does the impact differ if the anti-inflammatory prophylaxis is continued for only three  
315 months, if continued for six months, or if continued until complete resolution of tophi and  
316 gout flares?
  - 317 • Does the relative impact differ across different ULT medications (allopurinol, febuxostat,  
318 probenecid, lesinurad, pegloticase)?
  - 319 • Does the relative impact of prophylaxis differ across different starting dosage levels of ULT  
320 (e.g., allopurinol  $\leq$ 150mg, febuxostat  $\leq$ 40mg, probenecid 250mg bid) with gradual dose  
321 escalation compared with starting the ULT at a higher dose (e.g., allopurinol 300mg,  
322 febuxostat 80mg, probenecid 1g bid)?



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- 323 10. ~~For patients diagnosed with gout starting ULT, what is the relative impact of starting allopurinol,~~  
324 ~~febuxostat, probenecid, allopurinol/lesinurad 200mg combination, febuxostat/lesinurad 200mg~~  
325 ~~combination, or pegloticase on: gout flares, pain scores, tophus, patient global assessment, health~~  
326 ~~related quality of life, activity limitation, joint damage, serum urate, changes in gout flares or tophus~~  
327 ~~as inferred by changes in serum urate, cost, adverse events (mild-moderate and serious)?~~ REVISED  
328 QUESTION (changed during literature review): For patients diagnosed with gout with an indication  
329 for ULT, what is the relative impact of starting allopurinol, febuxostat, probenecid,  
330 allopurinol/lesinurad 200mg combination, febuxostat/lesinurad 200mg combination, pegloticase, or  
331 no treatment?
- 332 • Do the effects differ in people in people with or without established cardiovascular disease,  
333 or in people in people with CKD 3 or worse versus normal or mild CKD stages (1 or 2)?
- 334 11. For patients diagnosed with gout receiving haemodialysis who are starting ULT, what is the impact  
335 of starting allopurinol compared with febuxostat on: gout flares, pain scores, tophus, patient global  
336 assessment, health related quality of life, activity limitation, joint damage, serum urate, changes in  
337 gout flares or tophus as inferred by changes in serum urate, cost, adverse events (mild-moderate  
338 and serious)?
- 339 12. For patients diagnosed with gout starting allopurinol, what is the impact of testing HLA-B\*5801 and  
340 avoiding allopurinol if positive result compared with not testing HLA-B\*5801 and starting allopurinol  
341 in all patients on: cost, adverse events (mild-moderate and serious)?
- 342 • Do the effects differ in people of African American ancestry versus people with Chinese,  
343 Thai, or Korean ancestry versus those with all other ancestries?
  - 344 • Do the effects differ in people with CKD 3 or worse versus normal or mild CKD stages (1 or  
345 2)?
  - 346 • Do the effects differ in people starting a low allopurinol dose (e.g.  $\leq 100$ mg) with gradual  
347 dose escalation vs. starting allopurinol at a higher dose (eg, 300mg)?

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349 **Ongoing Management of Urate-Lowering Therapy in patients with gout**

350  
351 **Definitions: Conceptual detail for ULT dosing for PICO 13**

352 ULT dosing is either a

- 353 – *Pre-specified ULT fixed dose* based on drug, dose and renal function: E.g. allopurinol 300  
354 mg, febuxostat 40 mg, probenecid 500 mg twice daily or allopurinol 200 mg (or lower),  
355 febuxostat 40 mg in patients with CKD > 3 **OR**
  - 356 – *Serum urate target specified ULT dose* where ULT dosing is guided by serial serum urate  
357 values measured after each change in dose
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- 359 13. For patients with gout on ULT, what is the relative impact of ULT dose titration and subsequent  
360 management guided by serial serum urate values compared with fixed, standard doses of ULT on:  
361 gout flares, pain scores, tophus, patient global assessment, health related quality of life, activity  
362 limitation, joint damage, serum urate, changes in gout flares or tophus as inferred by changes in  
363 serum urate, cost, adverse events (mild-moderate and serious), patient adherence, durability of  
364 ULT?
- 365 • Does the impact of dosing strategy differ by presence vs absence of comorbid disease (e.g.  
366 CKD 3 or worse or cardiovascular disease), frequency of gout flares, presence of  
367 subcutaneous tophi?
  - 368 • Specifically, could serum urate target dosing exceeding Hande dosing recommendations?
  - 369 • Does the impact differ by frequency of monitoring?
- 370 14. For patients with gout on ULT who are not in *clinical remission*, what is the relative impact of  
371 prescribing ULT to achieve a serum urate target of [INSERT VALUE] on: gout flares, pain scores,  
372 tophus, patient global assessment, health related quality of life, activity limitation, joint damage,  
373 serum urate, changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse  
374 events (mild-moderate and serious), patient adherence, durability of ULT?
- 375 < 6 mg/dL vs. ≥ 6mg/dL, OR  
376 < 5 mg/dL vs. ≥5mg/dL OR  
377 < 4 mg/dL vs. ≥4mg/dL OR  
378 < 3 mg/dL vs. ≥3mg/dL?
- 379
  - 380 • Does the impact differ by flare frequency, presence of subcutaneous tophi? (See below for  
381 patients in *clinical remission*.)
  - 382 • Does the impact differ by frequency of monitoring?
- 383 15. For patients with gout on ULT who are in *clinical remission*, what is the relative impact of prescribing  
384 ULT to achieve a serum urate target of [INSERT VALUE] on: gout flares, pain scores, tophus, patient  
385 global assessment, health related quality of life, activity limitation, joint damage, serum urate,  
386 changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse events (mild-  
387 moderate and serious), patient adherence, durability of ULT?
- 388 < 8 mg/dL vs. ≥ 8mg/dL, OR  
389 < 7 mg/dL vs. ≥ 7mg/dL, OR  
390 < 6.8 mg/dL vs. ≥ 6.8mg/dL, OR  
391 < 6 mg/dL vs. ≥ 6mg/dL?
- 392
  - 393 • Does the impact differ by duration of clinical remission (e.g., 1-year vs. 5-years)?
  - 394 • Does the impact differ by frequency of monitoring?



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- 395 16. For patients with gout on ULT > 2 years, what is the impact of checking serum urate on a regular  
396 schedule and making adjustments in ULT guided by serum urate concentration compared with not  
397 checking serum urate to guide future ULT use / dosing on: gout flares, pain scores, tophus, patient  
398 global assessment, health related quality of life, activity limitation, joint damage, serum urate,  
399 changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse events (mild-  
400 moderate and serious), patient adherence, and durability of ULT?
- 401 • Does the impact of checking vs. not checking differ by:
    - 402 • Frequency of monitoring (e.g., every 6 months vs. every 12 months)
    - 403 • Disease severity: presence or duration of clinical remission, flare frequency,  
404 presence of subcutaneous tophi
- 405 17. For patients with gout on ULT who have achieved serum urate target but still have sufficient  
406 inflammatory symptoms to warrant ULT re-evaluation (e.g.,  $\geq 2$  flares in the last 12-months), what is  
407 the impact of lowering serum urate target by an additional 1 mg/dL and dose escalating ULT to this  
408 target compared with not changing the serum urate target and making no change to ULT on: gout  
409 flares, pain scores, tophus, patient global assessment, health related quality of life, activity  
410 limitation, joint damage, serum urate, changes in gout flares or tophus as inferred by changes in  
411 serum urate, cost, adverse events (mild-moderate and serious)?
- 412 18. For patients with gout adherent to ULT who have not achieved serum urate target, but have  
413 *infrequent symptoms* (gout flares well controlled ( $\leq 1$  flare in last 6 months)) and no subcutaneous  
414 tophi, what is the impact of increasing ULT dose to achieve serum urate target compared with  
415 continuing current ULT dose on gout flares, pain scores, tophus, patient global assessment, health  
416 related quality of life, activity limitation, joint damage, serum urate, changes in gout flares or tophus  
417 as inferred by changes in serum urate, cost, adverse events (mild-moderate and serious)?
- 418 • Does this impact differ if patient is in 1-year or 5-year *clinical remission*?
- 419 19. For patients with gout on ULT in *clinical remission*, what is the impact of stopping or reducing ULT  
420 compared with continuing ULT on gout flares, pain scores, tophus, patient global assessment, health  
421 related quality of life, activity limitation, joint damage, serum urate, changes in gout flares or tophus  
422 as inferred by changes in serum urate, cost, adverse events (mild-moderate and serious)?
- 423 • Do these effects differ based on the sustainable serum urate level following ULT reduction  
424 or cessation off ULT or the duration of clinical remission (e.g. 1-year vs. 5-years)?
- 425 20. For patients with gout on ULT in clinical remission, what is the impact of relaxing the serum urate  
426 target compared with continuing current serum urate target on gout flares, pain scores, tophus,  
427 patient global assessment, health related quality of life, activity limitation, joint damage, serum  
428 urate, changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse events  
429 (mild-moderate and serious)?
- 430 • Do these effects differ based on the duration of clinical remission (e.g. 1-year vs. 5-years)?



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- 431 21. For patients with gout on *intensive ULT* management (e.g. ULT to achieve sUA < 3 mg/dL), what is  
432 the impact of the duration of intensive ULT therapy for [INSERT VALUE] on gout flares, tophus  
433 burden, neurotoxicity and cancer risk, mortality rates?  
434  
435 < 1 year vs.  $\geq$  1 year OR  
436 < 2 years vs.  $\geq$  2 years  
437
- 438 22. For patients with gout on febuxostat with a history of CVD or a new CV event, what is the impact of  
439 stopping and switching to an alternative ULT agent compared with continuing febuxostat after  
440 reviewing the risks and benefits of febuxostat with the patient on: gout flares, pain scores, tophus,  
441 patient global assessment, health related quality of life, activity limitation, joint damage, serum  
442 urate, changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse events  
443 (mild-moderate and serious)?
- 444 23. In patients with gout who have experienced an allergic response to allopurinol and who cannot be  
445 treated with other oral ULT, what is the impact of allopurinol desensitization on tolerability of  
446 allopurinol, adverse events, cost, and patient acceptability.  
447
- 448 *For patients not at serum urate target and the inflammatory symptoms of gout or tophi are poorly*  
449 *controlled:*  
450
- 451 24. For patients with gout on their first XO1 monotherapy at maximum tolerated or FDA indicated dose  
452 who are not at serum urate target and/or have continued frequent gout flares or non-resolving  
453 subcutaneous tophi, what is the impact of switching the first XO1 to an alternate XO1 agent  
454 compared with adding a uricosuric agent on: gout flares, pain scores, tophus, patient global  
455 assessment, health related quality of life, activity limitation, joint damage, serum urate, changes in  
456 gout flares or tophus as inferred by changes in serum urate, cost, adverse events (mild-moderate  
457 and serious)?
- 458 • Do these effects differ based on the presence of chronic kidney disease or the magnitude of  
459 hyperuricemia?
- 460 25. For patients with gout on second (maximum tolerated or FDA indicated dose) XO1 agent who are not  
461 at serum urate target and/or have continued frequent gout flares or non-resolving subcutaneous  
462 tophi, what is the impact of adding a uricosuric compared with switching to uricosuric monotherapy  
463 on: gout flares, pain scores, tophus, patient global assessment, health related quality of life, activity  
464 limitation, joint damage, serum urate, changes in gout flares or tophus as inferred by changes in  
465 serum urate, cost, adverse events (mild-moderate and serious)?
- 466 • Do these effects differ based on the presence of chronic kidney disease or the magnitude of  
467 hyperuricemia or 24 hour urate excretion?





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- 468 26. For patients with gout on (max) probenecid monotherapy (e.g. XO1 failure) who are not at serum  
469 urate target and/or have continued frequent flares or non-resolving subcutaneous tophi, what is the  
470 impact of adding XO1 compared with switching to lesinurad/XOI on gout flares, pain scores, tophus,  
471 patient global assessment, health related quality of life, activity limitation, joint damage, serum  
472 urate, changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse events  
473 (mild-moderate and serious)?
- 474 • Do these effects differ based on the presence of chronic kidney disease or the magnitude of  
475 hyperuricemia?
- 476 27. For patients with gout where XO1, uricosurics and other interventions failed to achieve serum urate  
477 target and have frequent gout flares or non-resolving subcutaneous tophi what is the impact of  
478 changing to pegloticase compared with continuing current ULT on: gout flares, pain scores, tophus,  
479 patient global assessment, health related quality of life, activity limitation, joint damage, serum  
480 urate, changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse events  
481 (mild-moderate and serious)?
- 482 • Does the impact differ by frequency or severity of symptoms or presence or severity of tophi  
483 affect recommendation?
- 484
- 485 *For patients considered for or on uricosuric treatment:*
- 486
- 487 28. Prior to starting any uricosuric treatment, what is the impact of checking urinary uric acid compared  
488 with not checking urinary uric acid on: nephrolithiasis?
- 489 • Does this recommendation differ for patients where uricosuric is to be added to XO1  
490 treatment compared with those who will receive uricosuric treatment alone?
- 491 29. For all patients on uricosuric treatment, what is the impact of alkalinizing urine compared with not  
492 doing so on: nephrolithiasis?
- 493 • Does this recommendation differ for patients where uricosuric is to be added to XO1  
494 treatment compared with those who will receive uricosuric treatment alone?
- 495 30. For all patients on uricosuric treatment, what is the impact of monitoring urinary uric acid at regular  
496 intervals while on therapy compared with not doing so on: nephrolithiasis?
- 497 • Does this recommendation differ for patients where uricosuric is to be added to XO1  
498 treatment compared with those who will receive uricosuric treatment alone?
- 499

500

501 **Gout Flares**

502

503 ***General Management of a Gout Flare***

504





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- 505 31. For patients experiencing a gout flare initiating anti-inflammatory treatment, what is the impact of  
506 using topical ice as an adjuvant treatment compared with no adjuvant treatment on: pain scores,  
507 patient global assessment, joint tenderness, activity limitation, adverse events (mild-moderate and  
508 serious)?
- 509 32. ~~For patients experiencing a gout flare, what is the relative impact of colchicine, NSAIDs, systemic~~  
510 ~~glucocorticoids (e.g. prednisone/prednisolone), intra-articular glucocorticoids, ACTH, or IL-1~~  
511 ~~inhibition on: pain scores, patient global assessment, joint tenderness, joint swelling, activity~~  
512 ~~limitation, cost, or adverse events (mild-moderate and serious)?~~ REVISED QUESTION (changed  
513 during literature review): For patients experiencing a gout flare, what is the relative impact of high  
514 dose colchicine, low dose colchicine, NSAIDs, systemic glucocorticoids (e.g.  
515 prednisone/prednisolone), intra-articular glucocorticoids, ACTH, IL-1 inhibition, or no treatment?
- 516 • Does the relative impact of these agents differ based on any of the following?
    - 517 ○ The number of joints involved
    - 518 ○ Pain levels
    - 519 ○ Duration of the flare at presentation
    - 520 ○ Duration of anti-inflammatory therapy
    - 521 ○ Ability to tolerate or take oral agents (e.g. NPO status)
    - 522 ○ Dose of the agent given
- 523 33. For patients experiencing a gout flare for whom anti-inflammatory therapies are poorly tolerated or  
524 contraindicated, what is the impact of IL-1 inhibition compared with no therapy (beyond supportive  
525 / analgesic treatment) on: pain scores, patient global assessment, joint tenderness, joint swelling,  
526 activity limitation, cost, or adverse events (mild-moderate and serious)?

527

528 ***Management in Patients with Suboptimal Treatment Responses after 36-48 hours***

529

- 530 34. For patients experiencing a gout flare and achieving a suboptimal treatment response after 36-48  
531 hours, what is the impact of switching to an alternative anti-inflammatory monotherapy compared  
532 with continuing the same treatment on: pain scores, patient global assessment, joint tenderness,  
533 joint swelling, activity limitation, cost, or adverse events (mild-moderate and serious)?
- 534 35. For patients experiencing a gout flare and achieving a suboptimal treatment response after 36-48  
535 hours, what is the impact of adding an additional anti-inflammatory agent (e.g. escalating to  
536 combination therapy) compared with continuing the same treatment on pain scores, patient global  
537 assessment, joint tenderness, joint swelling, activity limitation, cost, or adverse events (mild-  
538 moderate and serious)?
- 539 36. For patients experiencing a gout flare and achieving a suboptimal treatment response after 36-48  
540 hours, what is the impact of switching to an alternative anti-inflammatory monotherapy compared  
541 with adding an additional anti-inflammatory agent (e.g. escalating to combination therapy) on: pain



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- 542 scores, patient global assessment, joint tenderness, joint swelling, activity limitation, cost, or  
543 adverse events (mild-moderate and serious)?
- 544 37. For patients experiencing a gout flare and achieving a suboptimal treatment response after 36-48  
545 hours, what is the impact of switching to an alternative anti-inflammatory agent compared with  
546 switching to or adding IL-1 inhibition on: pain scores, patient global assessment, joint tenderness,  
547 joint swelling, activity limitation, cost, or adverse events (mild-moderate and serious)?
- 548 38. For patients experiencing a gout flare and achieving a suboptimal treatment response after 36-48  
549 hours, what is the impact of adding an additional anti-inflammatory agent (e.g. escalating to  
550 combination therapy) compared with switching to or adding IL-1 inhibition on: pain scores, patient  
551 global assessment, joint tenderness, joint swelling, activity limitation, cost, or adverse events (mild-  
552 moderate and serious)?
- 553 39. For patients experiencing a gout flare and achieving a suboptimal treatment response to an oral  
554 anti-inflammatory after 36-48 hours, what is the impact of switching to an alternative oral anti-  
555 inflammatory agent compared with the use of intra-articular glucocorticoids on: pain scores, patient  
556 global assessment, joint tenderness, joint swelling, activity limitation, cost, or adverse events (mild-  
557 moderate and serious)?
- 558 • Does the relative impact of these strategies differ by the number of joints involved (e.g.  
559 mono- or oligoarticular involvement vs. polyarticular involvement)?
- 560 40. For patients experiencing a gout flare and achieving a suboptimal treatment response to an oral  
561 anti-inflammatory after 36-48 hours, what is the impact of adding an additional anti-inflammatory  
562 agent (e.g. escalating to combination therapy) compared with the use of intra-articular  
563 glucocorticoids on pain scores, patient global assessment, joint tenderness, joint swelling, activity  
564 limitation, cost, or adverse events (mild-moderate and serious)?
- 565 • Does the relative impact of these strategies differ by the number of joints involved (e.g.  
566 mono- or oligoarticular involvement vs. polyarticular involvement)?

567  
568  
569 **Lifestyle factors in patients with gout**

570  
571 *For patients with gout, regardless of disease activity:*

- 572  
573 41. What is the impact of limiting or abstaining from alcohol intake compared with no limited intake of  
574 alcohol on: gout flares, pain scores, tophus, patient global assessment, health related quality of life,  
575 activity limitation, joint damage, serum urate, changes in gout flares or tophus as inferred by  
576 changes in serum urate, cost, adverse events (mild-moderate and serious), patient acceptability,  
577 QOL?
- 578 • Does the impact differ by flare frequency (frequent vs. infrequent)?



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- 579           • Does the impact differ by the type of alcohol?
- 580 42. What is the impact of limiting purine intake compared with no limited intake of purines on: gout
- 581 flares, pain scores, tophus, patient global assessment, health related quality of life, activity
- 582 limitation, joint damage, serum urate, changes in gout flares or tophus as inferred by changes in
- 583 serum urate, cost, adverse events (mild-moderate and serious), patient acceptability, QOL?
- 584           • Does the impact differ by flare frequency (frequent vs. infrequent)?
- 585 43. What is the impact of limiting or abstaining from high-fructose corn syrup (HFCS) compared with no
- 586 limited intake of HFCS on: gout flares, pain scores, tophus, patient global assessment, health related
- 587 quality of life, activity limitation, joint damage, serum urate, changes in gout flares or tophus as
- 588 inferred by changes in serum urate, cost, adverse events (mild-moderate and serious), patient
- 589 acceptability, QOL?
- 590           • Does the impact differ by flare frequency (frequent vs. infrequent)?
- 591 44. What is the impact of increasing dairy protein intake compared with no increase in dairy intake on:
- 592 gout flares, pain scores, tophus, patient global assessment, health related quality of life, activity
- 593 limitation, joint damage, serum urate, changes in gout flares or tophus as inferred by changes in
- 594 serum urate, cost, adverse events (mild-moderate and serious), patient acceptability, QOL?
- 595           • Does the impact differ by flare frequency (frequent vs. infrequent)?
- 596 45. What is the impact of following the DASH (Dietary Approaches to Stop Hypertension) diet compared
- 597 with no specific diet or any other diet on: gout flares, pain scores, tophus, patient global
- 598 assessment, health related quality of life, activity limitation, joint damage, serum urate, changes in
- 599 gout flares or tophus as inferred by changes in serum urate, cost, adverse events (mild-moderate
- 600 and serious), patient acceptability, QOL?
- 601           • Does the impact differ by flare frequency (frequent vs. infrequent)?
- 602 46. What is the impact of weight loss compared with no weight loss on: gout flares, pain scores, tophus,
- 603 patient global assessment, health related quality of life, activity limitation, joint damage, serum
- 604 urate, changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse events
- 605 (mild-moderate and serious), patient acceptability, QOL?
- 606           • Does the impact differ by flare frequency (frequent vs. infrequent)?
- 607 47. What is the impact of changing or adding medications that affect urate levels compared with no
- 608 change in medication on: gout flares, pain scores, tophus, patient global assessment, health related
- 609 quality of life, activity limitation, joint damage, serum urate, changes in gout flares or tophus as
- 610 inferred by changes in serum urate, cost, adverse events (mild-moderate and serious)?
- 611           • Does the impact differ by flare frequency (frequent vs. infrequent)?
- 612           • Does the impact differ by type of medication change?
- 613           • Does the impact differ by CKD?



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614 48. What is the impact of vitamin C supplementation compared with no supplementation on: gout  
615 flares, pain scores, tophus, patient global assessment, health related quality of life, activity  
616 limitation, joint damage, serum urate, changes in gout flares or tophus as inferred by changes in  
617 serum urate, cost, adverse events (mild-moderate and serious), patient acceptability, QOL?

618 • Does the impact differ by flare frequency (frequent vs. infrequent)?

619 49. What is the impact of cherry extract intake compared with no intake on: gout flares, pain scores,  
620 tophus, patient global assessment, health related quality of life, activity limitation, joint damage,  
621 serum urate, changes in gout flares or tophus as inferred by changes in serum urate, cost, adverse  
622 events (mild-moderate and serious), patient acceptability, QOL?

623 • Does the impact differ by flare frequency (frequent vs. infrequent)?

624 **Asymptomatic Hyperuricemia**

625

626 *For individuals with asymptomatic hyperuricemia:*

627

628 50. What is the impact of limiting or abstaining from alcohol intake compared with no limited intake of  
629 alcohol on: development of gout (flare, subcutaneous tophi), adverse events (mild-moderate and  
630 serious), patient acceptability, QOL?

631 Does the impact differ for:

632 • People with marked hyperuricemia (SU > 9 mg/dl), versus SU 6.8-≤9mg/dL?

633 • People with CKD 3 or worse versus stages 1 or 2 or no renal disease?

634 • People with urolithiasis versus no urolithiasis?

635 • People with cardiovascular disease versus no cardiovascular disease?

636 • People with hypertension versus no hypertension?

637 • People with renal transplantation versus no renal transplantation?

638 • People with radiographic gouty bone erosion?

639 • People with advanced imaging (US/DECT) evidence of MSU deposition?

640 • People with early onset hyperuricemia (<30 in men, premenopausal women) versus those  
641 with later onset?

642 51. What is the impact of limiting purine intake compared with no limited intake of purines on:

643 development of gout (flare, subcutaneous tophi), adverse events (mild-moderate and serious),  
644 patient acceptability, QOL?

645 Does the impact differ for:

646 • People with marked hyperuricemia (SU > 9 mg/dl), versus SU 6.8-≤9mg/dL?

647 • People with CKD 3 or worse versus stages 1 or 2 or no renal disease?

648 • People with urolithiasis versus no urolithiasis?

649 • People with cardiovascular disease versus no cardiovascular disease?



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- 650           • People with hypertension versus no hypertension?  
651           • People with renal transplantation versus no renal transplantation?  
652           • People with radiographic gouty bone erosion?  
653           • People with advanced imaging (US/DECT) evidence of MSU deposition?  
654           • Does the impact differ by type of source purine (e.g. animal vs. vegetable)?  
655 52. What is the impact of limiting or abstaining from high-fructose corn syrup (HFCS) compared with no  
656 limited intake of HFCS on: development of gout (flare, subcutaneous tophi), adverse events (mild-  
657 moderate and serious), patient acceptability, QOL?  
658 Does the impact differ for:  
659           • People with marked hyperuricemia (SU > 9 mg/dl), versus SU 6.8-≤9mg/dL?  
660           • People with CKD 3 or worse versus stages 1 or 2 or no renal disease?  
661           • People with urolithiasis versus no urolithiasis?  
662           • People with cardiovascular disease versus no cardiovascular disease?  
663           • People with hypertension versus no hypertension?  
664           • People with renal transplantation versus no renal transplantation?  
665           • People with radiographic gouty bone erosion?  
666           • People with advanced imaging (US/DECT) evidence of MSU deposition?  
667           • People with early onset hyperuricemia (<30 in men, premenopausal women) versus those  
668 with later onset?  
669 53. What is the impact of increasing dairy protein intake compared with no increase in dairy intake on:  
670 development of gout (flare, subcutaneous tophi), adverse events (mild-moderate and serious),  
671 patient acceptability, QOL?  
672 Does the impact differ for:  
673           • People with marked hyperuricemia (SU > 9 mg/dl), versus SU 6.8-≤9mg/dL?  
674           • People with CKD 3 or worse versus stages 1 or 2 or no renal disease?  
675           • People with urolithiasis versus no urolithiasis?  
676           • People with cardiovascular disease versus no cardiovascular disease?  
677           • People with hypertension versus no hypertension?  
678           • People with renal transplantation versus no renal transplantation?  
679           • People with radiographic gouty bone erosion?  
680           • People with advanced imaging (US/DECT) evidence of MSU deposition?  
681           • People with early onset hyperuricemia (<30 in men, premenopausal women) versus those  
682 with later onset?  
683 54. What is the impact of following the DASH (Dietary Approaches to Stop Hypertension) diet compared  
684 with no specific diet or any other diet on: development of gout (flare, subcutaneous tophi), adverse  
685 events (mild-moderate and serious), patient acceptability, QOL?



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686 Does the impact differ for:

- 687 • People with marked hyperuricemia (SU > 9 mg/dl), versus SU 6.8-≤9mg/dL?
- 688 • People with CKD 3 or worse versus stages 1 or 2 or no renal disease?
- 689 • People with urolithiasis versus no urolithiasis?
- 690 • People with cardiovascular disease versus no cardiovascular disease?
- 691 • People with hypertension versus no hypertension?
- 692 • People with renal transplantation versus no renal transplantation?
- 693 • People with radiographic gouty bone erosion?
- 694 • People with advanced imaging (US/DECT) evidence of MSU deposition?
- 695 • People with early onset hyperuricemia (<30 in men, premenopausal women) versus those
- 696 with later onset?

697 55. What is the impact of weight loss compared with no weight loss on: development of gout (flare,  
698 subcutaneous tophi), adverse events (mild-moderate and serious), patient acceptability, QOL?

699 Does the impact differ for:

- 700 • People with marked hyperuricemia (SU > 9 mg/dl), versus SU 6.8-≤9mg/dL?
- 701 • People with CKD 3 or worse versus stages 1 or 2 or no renal disease?
- 702 • People with urolithiasis versus no urolithiasis?
- 703 • People with cardiovascular disease versus no cardiovascular disease?
- 704 • People with hypertension versus no hypertension?
- 705 • People with renal transplantation versus no renal transplantation?
- 706 • People with radiographic gouty bone erosion?
- 707 • People with advanced imaging (US/DECT) evidence of MSU deposition?
- 708 • People with early onset hyperuricemia (<30 in men, premenopausal women) versus those
- 709 with later onset?

710 56. What is the impact of changing or adding medications that affect urate levels (such as losartan or  
711 fenofibrate) compared with no change in medication on: development of gout (flare, subcutaneous  
712 tophi), adverse events (mild-moderate and serious), patient acceptability, QOL?

713 Does the impact differ for:

- 714 • People with marked hyperuricemia (SU > 9 mg/dl), versus SU 6.8-≤9mg/dL?
- 715 • People with CKD 3 or worse versus stages 1 or 2 or no renal disease?
- 716 • People with urolithiasis versus no urolithiasis?
- 717 • People with cardiovascular disease versus no cardiovascular disease?
- 718 • People with hypertension versus no hypertension?
- 719 • People with renal transplantation versus no renal transplantation?
- 720 • People with radiographic gouty bone erosion?
- 721 • People with advanced imaging (US/DECT) evidence of MSU deposition?





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- 722           • People with early onset hyperuricemia (<30 in men, premenopausal women) versus those  
723           with later onset?
- 724 57. What is the impact of initiating any pharmacologic urate-lowering therapy (allopurinol, febuxostat,  
725           probenecid) compared with no initiation of pharmacologic ULT on: development of gout (flare,  
726           subcutaneous tophi), adverse events (mild-moderate and serious), patient acceptability, QOL?  
727           Does the impact differ for:
- 728           • People with marked hyperuricemia (SU > 9 mg/dl), versus SU 6.8-≤9mg/dL?  
729           • People with CKD 3 or worse versus stages 1 or 2 or no renal disease?  
730           • People with urolithiasis versus no urolithiasis?  
731           • People with cardiovascular disease versus no cardiovascular disease?  
732           • People with hypertension versus no hypertension?  
733           • People with renal transplantation versus no renal transplantation?  
734           • People with radiographic gouty bone erosion?  
735           • People with advanced imaging (US/DECT) evidence of MSU deposition?  
736           • People with early onset hyperuricemia (<30 in men, premenopausal women) versus those  
737           with later onset?  
738



